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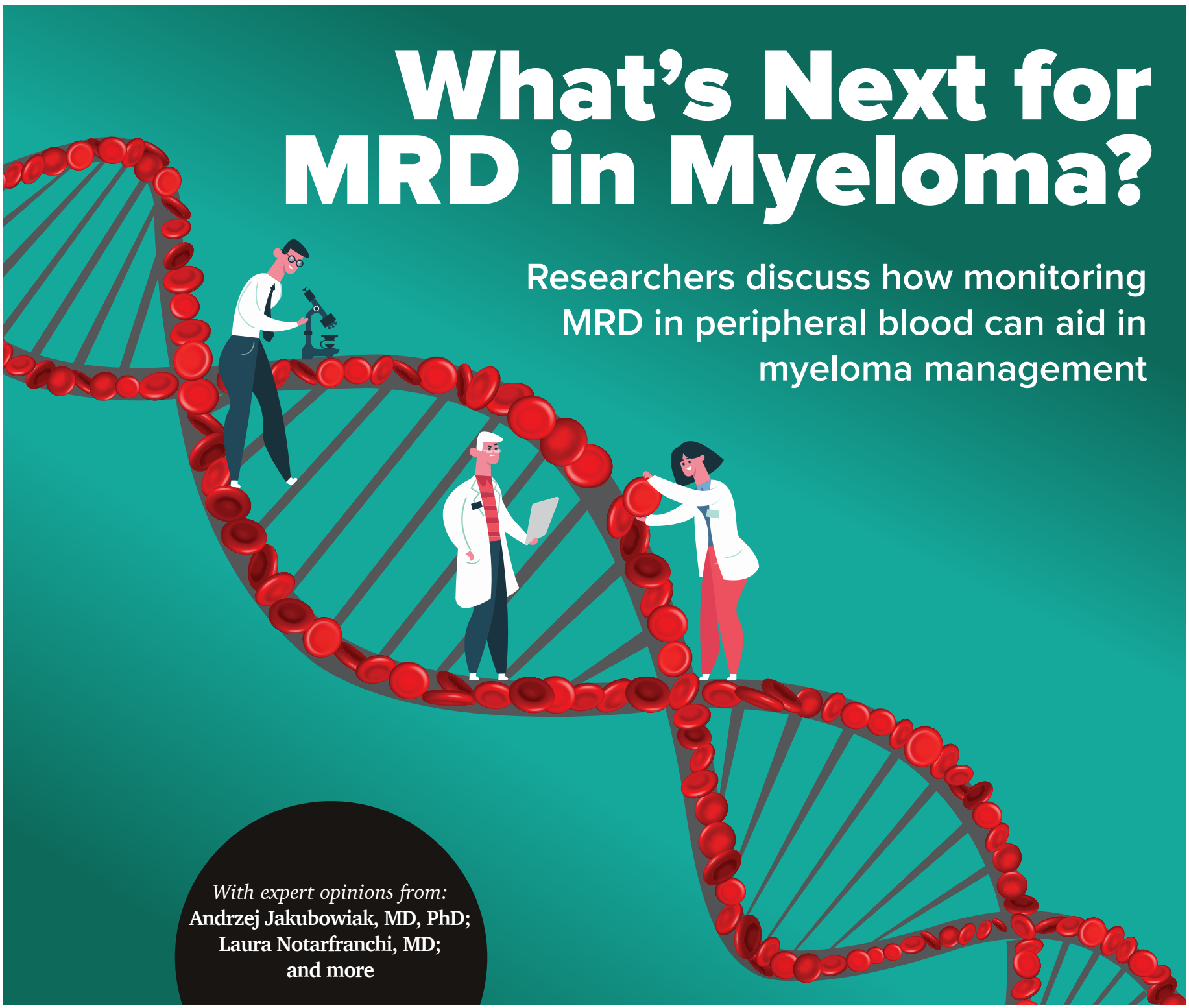

What’s Next for MRD in Myeloma?

Researchers discuss how monitoring MRD in peripheral blood can aid in myeloma management

With expert opinions from:
Andrzej Jakubowiak, MD, PhD; Laura Notarfranchi, MD; and more

MAIL TO:

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Polycythemia Vera Is More Than Hematocrit

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to find out why

PharmaEssentia™

Get to the Source of Polycythemia Vera[1]

Scan to discover how BESREMi targets PV at its source in the bone marrow[1]

INDICATION

BESREMi is indicated for the treatment of adults with polycythemia vera

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DISORDERS

Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy.

CONTRAINDICATIONS

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
- History or presence of active serious or untreated autoimmune disease
- Immunosuppressed transplant recipients

WARNINGS AND PRECAUTIONS

- Depression and Suicide: Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa-2b products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness.
  Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products. Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue BESREMi therapy.
- Endocrine Toxicity: These toxicities may include worsening hypothyroidism and hyperthyroidism. Do not use BESREMi in patients with active serious or untreated endocrine disorders associated with autoimmune disease. Evaluate thyroid function in patients who develop symptoms suggestive of thyroid disease during BESREMi therapy. Discontinue BESREMi in patients who develop endocrine disorders that cannot be adequately managed during treatment with BESREMi.
- Cardiovascular Toxicity: Toxicities may include cardiomyopathy, myocardial infarction, atrial fibrillation and coronary artery ischemia. Patients with a history of cardiovascular disorders should be closely monitored for cardiovascular toxicity during BESREMi therapy. Avoid use of BESREMi in patients with severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction.
- Decreased Peripheral Blood Counts: These toxicities may include thrombocytopenia (increasing the risk of bleeding), anemia, and leukopenia (increasing the risk of infection). Monitor complete blood counts at baseline, during titration and every 3-6 months during the maintenance phase. Monitor patients for signs and symptoms of infection or bleeding.
- Hypersensitivity Reactions: Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.
- Pancreatitis: Pancreatitis has occurred in 2.2% of patients receiving BESREMi. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever. Patients may experience elevated lipase, amylase, white blood cell count, or altered renal/hepatic function. Interrupt BESREMi treatment in patients with possible pancreatitis and evaluate promptly. Consider discontinuation of BESREMi in patients with confirmed pancreatitis.
- Colitis: Fatal and serious ulcerative or hemorrhagic/ischemic colitis have occurred in patients receiving interferon alfa products, some cases starting as early as 12 weeks after start of treatment. Symptoms may include abdominal pain, bloody diarrhea, and fever. Discontinue BESREMi in patients who develop these signs or symptoms. Colitis may resolve within 1 to 3 weeks of stopping treatment.
- Pulmonary Toxicity: Pulmonary toxicity may manifest as dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis. Some events have resulted in respiratory failure or death. Discontinue BESREMi in patients who develop pulmonary infiltrates or pulmonary function impairment.
- Ophthalmologic Toxicity: These toxicities may include severe eye disorders such as retinopathy, retinal hemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness. During BESREMi therapy, 23% of patients were identified with an eye disorder. Eyes disorders ≥5% included cataract (6%) and dry eye (5%). Advise patients to have eye examinations before and during BESREMi therapy, specifically in those patients with a retinopathy-associated disease such as diabetes mellitus or hypertension. Evaluate eye symptoms promptly. Discontinue BESREMi in patients who develop new or worsening eye disorders.
- Hyperlipidemia: Elevated triglycerides may result in pancreatitis. Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated. Consider discontinuation of BESREMi in patients with persistently, markedly elevated triglycerides.
- Hepatotoxicity: These toxicities may include increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and bilirubin. Liver enzyme elevations have also been reported in patients after long-term BESREMi therapy. Monitor liver enzymes and hepatic function at baseline and during BESREMi treatment. Discontinue BESREMi in patients who develop evidence of hepatic decompensation (characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage) during treatment.
- Renal Toxicity: Monitor serum creatinine at baseline and during therapy. Avoid use of BESREMi in patients with eGFR <30 mL/min. Discontinue BESREMi if severe renal impairment develops during treatment.
- Dental and Periodontal Toxicity: These toxicities may include dental and periodontal disorders, which may lead to loss of teeth. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with BESREMi. Patients should have good oral hygiene and regular dental examinations.
- Dermatologic Toxicity: These toxicities have included skin rash, pruritus, alopecia, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, and hyperhidrosis. Consider discontinuation of BESREMi if clinically significant dermatologic toxicity occurs.
- Driving and Operating Machinery: BESREMi may impact the ability to drive and use machinery. Patients should not drive or use heavy machinery until they know how BESREMi affects their abilities. Patients who experience dizziness, somnolence or hallucination during BESREMi therapy should avoid driving or using machinery.
- Embryo-Fetal Toxicity: Based on the mechanism of action, BESREMi can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended in females of reproductive potential prior to treatment with BESREMi. Advise females of reproductive potential to use an effective method of contraception during treatment with BESREMi and for at least 8 weeks after the final dose.

ADVERSE REACTIONS

The most common adverse reactions reported in > 40% of patients in the PEGINVERA study (n=51) were influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis, and musculoskeletal pain. In the pooled safety population (n=178), the most common adverse reactions greater than 10%, were liver enzyme elevations (20%), leukopenia (20%), thrombocytopenia (19%), arthralgia (13%), fatigue (12%), myalgia (11%), and influenza-like illness (11%).

DRUG INTERACTIONS

Patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs. Avoid use with myelosuppressive agents and monitor patients receiving the combination for effects of excessive myelosuppression. Avoid use with narcotics, hypnotics or sedatives and monitor patients receiving the combination for effects of excessive CNS toxicity.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on mechanism of action and the role of interferon alfa in pregnancy and fetal development, BESREMi may cause fetal harm and should be assumed to have abortifacient potential when administered to a pregnant woman. There are adverse effects on maternal and fetal outcomes associated with polycythemia vera in pregnancy. Advise pregnant women of the potential risk to a fetus.
- Lactation: There are no data on the presence of BESREMi in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children from BESREMi, advise women not to breastfeed during treatment and for 8 weeks after the final dose.
- Females of Reproductive Potential: BESREMi may cause embryo-fetal harm when administered to a pregnant woman. Pregnancy testing prior to BESREMi treatment is recommended for females of reproductive potential. Advise female patients of reproductive potential to use effective contraception during treatment with BESREMi and for at least 8 weeks after the final dose.
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
- Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent pages.

PV, polycythemia vera.

Reference: 1. Besremi. Package insert. PharmaEssentia Corporation; 2021.

BESREMi® (ropeginterferon alfa-2b-njft) INJECTION

PharmaEssentia™

US-BSRM-2200189 (v1.0) 01/2023

Brief Summary of Prescribing Information for BESREMi (ropeginterferon alfa-2b-njft)

BESREMi (ropeginterferon alfa-2b-njft) injection, for subcutaneous use

See package insert for full Prescribing Information

WARNING: RISK OF SERIOUS DISORDERS

Risk of Serious Disorders: Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy [*see Warnings and Precautions (5.1, 5,2, 5.3, 5.4) and Adverse Reactions (6.1)*].

1 INDICATIONS AND USAGE

BESREMi is indicated for the treatment of adults with polycythemia vera.

4 CONTRAINDICATIONS

BESREMi is contraindicated in patients with:

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
- History or presence of active serious or untreated autoimmune disease
- Immunosuppressed transplant recipients

5 WARNINGS AND PRECAUTIONS

5.1 Depression and Suicide

Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness. Serious neuropsychiatric reactions have been observed in 3% of patients treated with BESREMi during the clinical development program. Among the 178 patients in the clinical development program of BESREMi, 17 cases of depression, depressive symptoms, depressed mood, and listlessness occurred. Of these seventeen cases, 3.4% of the patients recovered with temporary drug interruption and 2.8% stopped BESREMi treatment.

Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products. BESREMi is contraindicated in patients with a history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt *[see Contraindications (4)]*.

Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue BESREMi therapy.

5.2 Endocrine Toxicity

Endocrine toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include worsening hypothyroidism and hyperthyroidism. Autoimmune thyroiditis and hyperglycemia, including new onset type 1 diabetes, have been reported in patients receiving interferon alfa-2b products. Eight cases of hyperthyroidism (4.5%), seven cases of hypothyroidism (3.9%) and five cases (2.8%) of autoimmune thyroiditis/thyroiditis occurred in the development program of BESREMi.

Do not use BESREMi in patients with active serious or untreated endocrine disorders associated with autoimmune disease *[Contraindications (4)]*. Evaluate thyroid function in patients who develop symptoms suggestive of thyroid disease during BESREMi therapy. Discontinue BESREMi in patients who develop endocrine disorders that cannot be adequately managed during treatment with BESREMi.

5.3 Cardiovascular Toxicity

Cardiovascular toxicity has occurred in patients receiving interferon alfa products, including BESREMi. Toxicities may include cardiomyopathy, myocardial infarction, atrial fibrillation and coronary artery ischemia *[see Adverse Reactions (6.1)]*. Patients with a history of cardiovascular disorders should be closely monitored for cardiovascular toxicity during BESREMi therapy. Avoid use of BESREMi in patients with severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction.

5.4 Decreased Peripheral Blood Counts

Decreased peripheral blood counts have occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include thrombocytopenia (increasing the risk of bleeding), anemia, and leukopenia (increasing the risk of infection). Thrombocytopenia of grade 3 (platelet counts <50,000 – 25,000/mm^3) or greater occurred in 2% of BESREMi-treated patients. Anemia of grade 3 (Hgb < 8 g/dL) or greater occurred in 1% of BESREMi-treated patients. Leukopenia of grade 3 (WBC counts <2,000 – 1,000/mm^3) or greater occurred in 2% of BESREMi-treated patients. Infection occurred in 48% of BESREMi-treated patients, while serious infections occurred in 8% of BESREMi-treated patients. Monitor complete blood counts at baseline, during titration and every 3-6 months during the maintenance phase. Monitor patients for signs and symptoms of infection or bleeding.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions have occurred in patients receiving interferon alfa products, including BESREMi. BESREMi is contraindicated in patients with hypersensitivity reactions to interferon products or any of the inactive ingredients in BESREMi *[see Contraindications (4)]*. Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.

5.6 Pancreatitis

Pancreatitis has occurred in patients receiving interferon alfa products, including BESREMi. Pancreatitis was reported in 2.2% of patients receiving BESREMi. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever. Patients may experience elevated lipase, amylase, white blood cell count, or altered renal/hepatic function. Interrupt BESREMi treatment in patients with possible pancreatitis and evaluate promptly. Consider discontinuation of BESREMi in patients with confirmed pancreatitis.

5.7 Colitis

Fatal and serious ulcerative or hemorrhagic/ischemic colitis have occurred in patients receiving interferon alfa products, some cases occurring as early as 12 weeks after start of treatment. Symptoms may include abdominal pain, bloody diarrhea, and fever. Discontinue BESREMi in patients who develop these signs or symptoms. Colitis may resolve within 1 to 3 weeks of stopping treatment.

5.8 Pulmonary Toxicity

Pulmonary toxicity has occurred in patients receiving interferon alfa products, including BESREMi. Pulmonary toxicity may manifest as dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis. Some events have resulted in respiratory failure or death. Discontinue BESREMi in patients who develop pulmonary infiltrates or pulmonary function impairment.

5.9 Ophthalmologic Toxicity

Ophthalmologic toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include severe eye disorders such as retinopathy, retinal hemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness. During BESREMi therapy, 23% of patients were identified with an eye disorder. Eyes disorders ≥5% included cataract (6%) and dry eye (5%). Advise patients to have eye examinations before and during BESREMi therapy, specifically in those patients with a retinopathy-associated disease such as diabetes mellitus or hypertension. Evaluate eye symptoms promptly. Discontinue BESREMi in patients who develop new or worsening eye disorders.

5.10 Hyperlipidemia

Hyperlipidemia has occurred in patients treated with interferon alfa products, including BESREMi. Hyperlipidemia, hypertriglyceridemia, or dyslipidemia occurred in 3% of patients receiving BESREMi. Elevated triglycerides may result in pancreatitis *[see Warnings and Precautions (5.6)]*. Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated. Consider discontinuation of BESREMi in patients with persistently, markedly elevated triglycerides.

5.11 Hepatotoxicity

Hepatotoxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Contraindications (4)]*.

Increases in serum ALT ≥3 times the upper limit of normal (ULN), AST ≥3 times the ULN, GGT ≥3 times the ULN, and bilirubin >2 times the ULN have been observed in patients treated with BESREMi.

In the clinical development program of BESREMi, 36 patients (20%) experienced liver enzyme elevations, 33 of whom had elevations of 1.25-5x ULN. Patients were able to resume BESREMi upon resolution of liver enzyme elevations. Liver enzyme elevations have also been reported in patients after long-term BESREMi therapy.

Monitor liver enzymes and hepatic function at baseline and during BESREMi treatment. Reduce BESREMi dosage by 50 mcg for increased AST/ALT/GGT then monitor AST/ALT/GGT weekly until the values return to baseline or grade 1 (ALT and AST < 3 x ULN if baseline was normal; 1.5 - 3 x baseline if baseline was abnormal, and GGT < 2.5 x ULN if baseline was normal; 2 - 2.5 x baseline if baseline was abnormal) *[see Dosage and Administration (2.3) in the full prescribing information]*. If toxicity does not improve, continue decreasing the BESREMi dose at biweekly intervals until recovery to grade 1. Hold if AST/ALT/GGT > 20 x ULN and consider permanent discontinuation if increased liver enzyme levels persist after four dose-reductions. Discontinue BESREMi in patients who develop evidence of hepatic decompensation (characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage) during treatment *[see Use in Specific Populations (8.7)]*.

5.12 Renal Toxicity

Renal toxicity has occurred in patients receiving interferon alfa products, including BESREMi. During BESREMi therapy, <1% of patients were reported to develop renal impairment and <1% of patients were reported to have toxic nephropathy. Monitor serum creatinine at baseline and during therapy. Avoid use of BESREMi in patients with eGFR <30 mL/min. Discontinue BESREMi if severe renal impairment develops during treatment *[see Use in Specific Populations (8.6)]*.

5.13 Dental and Periodontal Toxicity

Dental and periodontal toxicities may occur in patients receiving interferon alfa products, including BESREMi. These toxicities may include dental and periodontal disorders, which may lead to loss of teeth. In addition, dry mouth could have a damaging effect on teeth and oral mucous membranes during long-term treatment with BESREMi. Patients should have good oral hygiene and regular dental examinations.

5.14 Dermatologic Toxicity

Dermatologic toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities have included skin rash, pruritus, alopecia, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, and hyperhidrosis. Consider discontinuation of BESREMi if clinically significant dermatologic toxicity occurs.

5.15 Driving and Operating Machinery

BESREMi may impact the ability to drive and use machinery. Patients should not drive or use heavy machinery until they know how BESREMi affects their abilities. Patients who experience dizziness, somnolence or hallucination during BESREMi therapy should avoid driving or using machinery.

5.16 Embryo-Fetal Toxicity

Based on the mechanism of action, BESREMi can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full prescribing information and Use in Specific Populations (8.1)]*. Pregnancy testing is recommended in females of reproductive potential prior to treatment with BESREMi. Advise females of reproductive potential to use an effective method of contraception during treatment with BESREMi and for at least 8 weeks after the final dose *[see Dosage and Administration (2.1) in the full prescribing information and Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

- Depression and Suicide *[see Warnings and Precautions (5.1)]*
- Endocrine Toxicity *[see Warnings and Precautions (5.2)]*
- Cardiovascular Toxicity *[see Warnings and Precautions (5.3)]*
- Decreased Peripheral Blood Counts *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Pancreatitis *[see Warnings and Precautions (5.6)]*
- Colitis *[see Warnings and Precautions (5.7)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.8)]*
- Ophthalmologic Toxicity *[see Warnings and Precautions (5.9)]*
- Hyperlipidemia *[see Warnings and Precautions (5.10)]*
- Hepatotoxicity *[see Warnings and Precautions (5.11)]*
- Renal Toxicity *[see Warnings and Precautions (5.12)]*
- Dental and Periodontal Toxicity *[see Warnings and Precautions (5.13)]*
- Dermatologic Toxicity *[see Warnings and Precautions (5.14)]*
- Driving and Operating Machinery *[see Warnings and Precautions (5.15)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.16)]*

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 pooled safety population described in the Warnings and Precautions section reflects exposure to BESREMi as monotherapy for the treatment of polycythemia vera dosed every two to four weeks in 178 patients in two open-label trials [*PEGINVERA, PROUD/CONTINUATION PV*]. The mean age at baseline was 58.6 years (range 30-85 years), 88 (49.4%) women, 90 (50.6%) men, 177 (99%) Caucasian and 1 (1%) Asian. Among 178 patients who received BESREMi, 80% were exposed for 12 months or longer. The mean dose of BESREMi was 334 mcg SD ± 121 during the treatment period. In this pooled safety population, the most common adverse reactions greater than 10%, were liver enzyme elevations (20%), leukopenia (20%), thrombocytopenia (19%), arthralgia (13%), fatigue (12%), myalgia (11%), and influenza-like illness (11%).

The safety findings described below reflect exposure to BESREMi as monotherapy for the treatment of polycythemia vera in 51 patients in the PEGINVERA study *[see Clinical Studies (14) in the full prescribing information]*. Among the 51 patients receiving BESREMi, 71% were exposed for 12 months or longer, 63% were exposed for three years or longer, and 53% were exposed for greater than five years.

Serious adverse reactions were reported in 16% of patients in the PEGINVERA study. The most common serious adverse reactions observed during the study (≥ 4%) included urinary tract infection (8%), transient ischemic attack (6%) and depression (4%).

Adverse reactions requiring permanent discontinuation in >2% of patients who received BESREMi included depression (8%) arthralgia (4%), fatigue (4%), and general physical health deterioration (4%) In the PEGINVERA study, patients were not pre-screened for depression or anxiety disorders.

The most common adverse reactions reported in ≥10% of patients in the PEGINVERA study are listed in Table 2.

Table 2 Adverse Reactions in > 10% of Subjects with Polycythemia Vera in the PEGINVERA Study Over 7.5 Years.

Adverse Reactions*	BESREMi N=51 %
Influenza-like illness [a]	59
Arthralgia	47
Fatigue [b]	47
Pruritus	45
Nasopharyngitis [c]	43
Musculoskeletal pain [d]	41
Headache [e]	39
Diarrhea	33
Hyperhidrosis [f]	29
Nausea	28
Upper respiratory tract infection [g]	27
Local administration site reactions	26
Dizziness	22
Abdominal pain [h]	20
Depression	20
Sleep disorder [i]	20
Leukopenia	18
Decreased appetite	18
Alopecia	16
Edema [j]	16
Hypertension [k]	16
Muscle spasms	16
Neutropenia	16
Rash [l]	16
Transaminase elevations [m]	16
Urinary tract infection	16
Thrombocytopenia	12
Vertigo	12

*Adverse Reactions defined as all treatment emergent adverse events

Grouped Term Definitions
[a] Includes pyrexia, chills, and influenza-like illness.
[b] Includes asthenia, malaise, and fatigue.
[c] Includes pharyngitis and nasopharyngitis.
[d] Includes musculoskeletal pain, back pain, pain in extremity, bone pain, flank pain, and spinal pain.
[e] Includes headache, migraine, and head pain.
[f] Includes night sweats and hyperhidrosis.
[g] Includes upper respiratory tract infection, rhinitis, bronchitis, and respiratory tract infection.
[h] Includes abdominal pain upper, abdominal pain lower, and abdominal pain.
[i] Includes insomnia, sleep disorder, and abnormal dreams.
[j] Includes peripheral edema and generalized edema.
[k] Includes hypertension and hypertensive crisis.
[l] Includes rash, maculopapular rash, and pruritic rash.
[m] Includes transaminase increase, hepatic enzyme increase, GGT increase, AST increase, and ALT increase.

Clinically relevant adverse reactions in < 10% of patients include:
Cardiovascular System: Atrial fibrillation

6.2 Immunogenicity

As with all therapeutic proteins, there is 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 interferon alfa-2b products may be misleading.

The incidence of binding antibodies to ropeginterferon alfa-2b-njft was 1.4% (2/146) and they were observed as early as 8 weeks post-dosing. Among the patients who tested positive for binding antibodies, none developed neutralizing antibodies.

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

Certain proinflammatory cytokines, including interferons, can suppress CYP450 enzymes resulting in increased exposures of some CYP substrates *[see Clinical Pharmacology (12.3) in the full prescribing information].* Therefore, patients on BESREMi who are receiving concomitant drugs that are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs.

7.2 Myelosuppressive Agents

Concomitant use of BESREMi and myelosuppressive agents can produce additive myelosuppression. Avoid use and monitor patients receiving the combination for effects of excessive myelosuppression *[see Warnings and Precautions (5.4)].*

7.3 Narcotics, Hypnotics or Sedatives

Concomitant use of BESREMi and narcotics, hypnotics or sedatives can produce additive neuropsychiatric side effects. Avoid use and monitor patients receiving the combination for effects of excessive CNS toxicity *[see Warnings and Precautions (5.1)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available human data with BESREMi use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal studies assessing reproductive toxicity of BESREMi have not been conducted. Based on mechanism of action and the role of interferon alfa in pregnancy and fetal development, BESREMi may cause fetal harm and should be assumed to have abortifacient potential when administered to a pregnant woman. There are adverse effects on maternal and fetal outcomes associated with polycythemia vera in pregnancy *(see Clinical Considerations).* Advise pregnant women of the potential risk to a fetus.

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 is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Untreated polycythemia vera during pregnancy is associated with adverse maternal outcomes such as thrombosis and hemorrhage. Adverse pregnancy outcomes associated with polycythemia vera include increased risk for miscarriage.

8.2 Lactation

There are no data on the presence of BESREMi in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children from BESREMi, advise women not to breastfeed during treatment and for 8 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

BESREMi may cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Pregnancy testing prior to BESREMi treatment is recommended for females of reproductive potential.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BESREMi and for at least 8 weeks after the final dose.

Infertility

Females

Based on its mechanism of action, BESREMi can cause disruption of the menstrual cycle *[see Clinical Pharmacology (12.1) in the full prescribing information].* No animal fertility studies have been conducted with BESREMi.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of BESREMi did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

8.6 Renal Impairment

No dose adjustment is necessary in patients with estimated glomerular filtration rate (eGFR) ≥30 mL/min *[see Clinical Pharmacology (12.3) in the full prescribing information].* Avoid use of BESREMi in patients with eGFR <30 mL/min *[see Warnings and Precautions (5.12)].*

8.7 Hepatic Impairment

BESREMi is contraindicated in patients with hepatic impairment (Child-Pugh B or C) *[see Contraindications (4)].*

Increased liver enzyme levels have been observed in patients treated with BESREMi. When the increase in liver enzyme levels is progressive and persistent, reduce the dose of BESREMi. If the increase in liver enzymes is progressive and clinically significant despite dose-reduction, or if there is evidence of hepatic impairment (Child-Pugh B or C), discontinue BESREMi *[see Dosage and Administration (2.2) in the full prescribing information and Warnings and Precautions (5.11)].*

10 OVERDOSAGE

Overdosage of BESREMi may result in influenza-like symptoms or other adverse reactions. There is no antidote to BESREMi overdosage. In case of an overdose, frequently monitor signs and symptoms for adverse reactions.

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Calendar

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

August 17–19
Great Updates & Debates in Hematologic Malignancies
Westin Copley Place
Boston, Massachusetts

August 18–20
7th Annual Hematology & Oncology for NPs & PAs 2023
Mayo Clinic
Rochester, Minnesota

September 12–14
4th International Conference on Lymphocyte Engineering
Holiday Inn Munich – City Centre
Munich, Germany

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

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

September 29–October 1
Association of VA Hematology/Oncology 2023 Annual Meeting
Sheraton Grand Chicago Riverwalk
Chicago, Illinois

October 6–7
Acute and Chronic Leukemia: Practical Applications 2023 (Mayo Clinic Course)
Omni Orlando Resort at ChampionsGate
ChampionsGate, Florida

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

October 18–21
Lymphoma, Leukemia & Myeloma Congress
Sheraton New York Times Square Hotel
New York, New York

October 20–24
European Society of Medical Oncology Congress 2023
IFEMA Madrid
Madrid, Spain

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

November 2–3
15th International Congress on Myeloproliferative Neoplasms
New York Marriott at the Brooklyn Bridge
Brooklyn, New York

December 9–12
65th American Society of Hematology Annual Meeting and Exposition
San Diego Convention Center
San Diego, California

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

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

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SYROS

SELECT MDS AML

TAMIBAROTENE CLINICAL TRIALS

NOW ENROLLING

The SYROS SELECT trials are investigating **tamibarotene, a selective oral RARα agonist,** in certain patients with **HR-MDS** and **AML**

SCAN FOR TRIAL DETAILS & INQUIRIES

AML, acute myeloid leukemia; HR-MDS, higher-risk myelodysplastic syndrome; RARα, retinoic acid receptor alpha.
Tamibarotene is an investigational agent and is not approved for use in any indication in the U.S. or Europe.

Associate Editor's Message

Combination Therapy Promises to Leave Chemotherapy Behind

Elias Jabbour, MD
Associate Editor

As a leukemia expert, I'm fortunate to live in a time when we're making major progress. We can say with good confidence that the cure for acute lymphoblastic leukemia (ALL) will eventually happen in our lifetime. It's an exciting time because we have the tools to accomplish this goal, and we have ongoing trials that are already leading to very promising results.

One example is the treatment of Philadelphia chromosome (Ph)-positive ALL. Historically, Ph-positive ALL was a disease with a poor prognosis. Long-term survival rates were only 10%, and only those patients who were lucky enough to get a transplant had a long-term survival rate of 30%. Then, in the early 2000s we saw the approval of imatinib, the first tyrosine kinase inhibitor (TKI). TKI approval was revolutionary in the treatment of Ph-positive ALL and chronic myeloid leukemia (CML). When combined with chemotherapy, TKIs showed even better patient outcomes, and patients were able to undergo transplant in better shape when TKIs were administered early on.

As maintenance, post-transplant TKIs have proven to be extremely effective as well. Still, survival in the long run was limited to 50% with imatinib and second-generation TKIs.

There are several reasons why that is the case. First, we know the outcome is dependent on achieving a complete molecular remission (CMR). Second, we know resistance was driven by the emergence of certain mutations, among them *T315I,* that can drive resistance to the first- and second-generation TKIs. Third, despite the progress in transplantation, the treatment-related mortality remains non-negligible.

Therefore, in 2010 we hypothesized that if we can improve the CMR rate and suppress the emergence of the kinase domain *T315I* mutations, we can improve the outcome of this disease.

Ponatinib is a BCR-ABL inhibitor that was shown to be extremely effective in CML, more potent than other TKIs, and it can suppress the emergence of the *T315I* mutation. We designed a new regimen combining the hyper-CVAD chemotherapy backbone with ponatinib. With this combination, we've shown that we can improve both the three-month CMR rate and the six-year overall survival rate to 75%. We've also shown that patients who did not receive a transplant performed better than those who did. For the first time, we're questioning the role of transplant in this disease.

We then asked if we could identify the patients who may or may not need transplant. Since the three-month molecular response is an important milestone for transplant, we performed a landmark analysis at a different time point. The analysis showed that CMR at three months predicts for the best outcome regardless of the TKI a patient receives. However, even if a patient reaches CMR, approximately 25% of patients can relapse or progress.

The next step was to ask which patients are achieving CMR and not relapsing. In other words, can we triage patients by those who should go for transplant and those who should not? It turned out that patients who did receive ponatinib were able to achieve CMR and did not relapse.

Then, we aimed to reduce and eliminate the need for chemotherapy. Blinatumomab, a bispecific T-cell engager, has shown activity in relapsed or refractory disease. If it works and is better than chemotherapy, then why still go for chemotherapy? So, we designed a chemotherapy-free treatment, a combination of ponatinib and blinatumomab. We gave 12 doses of intrathecal chemotherapy to prevent any central nervous system disease.

By doing so, we've shown that most patients do respond well. In fact, the time to response is quite fast: patients achieved CMR within four weeks. The four-week CMR rate was 67%, and it was 88% at three months. We treated 60 patients, and our strategy involved no chemotherapy at all. Instead, we treated patients with immunotherapy and TKIs. The three-year survival rate is 95%. These are the best results ever obtained.

At the same time, ponatinib was compared with other TKIs in a randomized trial and has shown an improvement in outcomes and better responses when compared with imatinib. Ponatinib is a legitimate frontline therapy.

The combination of blinatumomab and ponatinib is a true chemotherapy-free regimen. What are the implications of such a regimen? Not only improving survival in our patients, but we know that intensive chemotherapy and transplant are problematic for a lot of them. Due to the complexity of our health care system and the complexity of ALL therapy, a lot of patients do not receive optimal care and therefore cannot sustain long-term therapy.

By offering a highly targeted finite therapy—five to six months with a three-year survival of 95%—we can have a major impact on our society. Patients can be cured and resume their normal life without any long-term toxicities.

In summary, we went from survival of 10% to 90% and from full-fledged chemotherapy and transplant to a chemotherapy-free, highly targeted regimen. This approach can serve as a model for how personalized therapy can improve the cure rate and the survival of our patients. We're very fortunate to have such therapy, and I hope that it will be confirmed and become the standard of care around the world.

Elias Jabbour, MD, *is a Professor in the Department of Leukemia at the MD Anderson Cancer Center.*

Loretta Nastoupil, MD

Dr. Nastoupil, an Associate Professor who serves as Director of the Lymphoma Outcomes Database, Section Chief of New Drug Development, and Deputy Chair of the Department of Lymphoma/Myeloma at the University of Texas MD Anderson Cancer Center, reflects on the experiences that led her to study disparities in lymphoma and the importance of representation in practice-changing trials.

Where did you grow up, and when did you know you wanted to be a physician?
I grew up in New Mexico as the oldest of three kids. Unfortunately, my grandfather and nearly all his siblings died of cancer. I thought that someone in our family needed to understand more about cancer.

What led you to specialize in lymphoma specifically?
When I was an undergraduate at Texas Tech, I was initially studying architecture, but I became intrigued by clinical lab science, so I switched my major.

What I found most interesting was looking at blood smears. To me, seeing leukemia or abnormal smears was intriguing. That's when I knew I wanted to be in the oncology field, and I was particularly interested in hematology. I ultimately became interested in lymphoma because I felt it bridged the gap between solid tumors and hematology.

Was there a mentor who shaped your path?
While I was doing my training at Emory University, Christopher Flowers, MD, MS, showed phenomenal clinical and communication skills. I wanted to emulate his knowledge base in lymphoma. I worked alongside him while I was at Emory, and he was pivotal in helping me get my career started at MD Anderson, where he is now my chair.

What led to your research on disparities in lymphoma?
I grew up in rural New Mexico where access to health care was a major challenge. I have a family history of folks with cancer who did not do well. For instance, my grandfather died of prostate cancer at 62. I had a niece who was diagnosed with anaplastic ependymoma. As a fellow, I helped coordinate getting her transferred out of the state because they didn't have the capacity at the time to handle her condition. She was 12 months old, and she had a large cerebellar mass that was causing hydrocephalus.

I was personally touched by growing up in an area where health care was sparse. When I moved to Atlanta, Georgia, as a fellow, that's when I saw the racial disparities emerge. Often, patients who are minorities or have a lower socioeconomic status can't access facilities that provide top-tier-type care, even if they live in a large metropolitan area.

When we started looking at lymphoma—where most patients can anticipate good outcomes, including a cure, as it pertains to diffuse large B-cell lymphoma—some of our Black patients were not achieving the same outcomes as our White patients.

When we looked at some of the life-changing therapies—like the incorporation of rituximab, which led to an overall survival advantage—the uptake in the Black community was much slower than in the White community. I'm continuing to work on understanding how to improve access and reduce barriers for our underserved populations.

"I was personally touched by growing up in an area where health care was sparse. When I moved to Atlanta, Georgia, as a fellow, that's when I saw the racial disparities emerge."

What can be done to address these disparities?
We need to make sure there's awareness, because if people are not aware, they're never going to start looking for solutions. However, sometimes we recognize that there's a disparity, and that's where we end.

How do we solve that problem from a societal standpoint, where often access to care is tied to the type of insurance you have? Are we getting good representation of minority patients on therapies that we think are going to be the most promising?

I've taken on the second part because it's something I can solve, but I still try to look at policy changes. I work at MD Anderson, and you could be critical of my choice, because I work in a center where we generally don't provide access to care for many patients who are underinsured. We do provide care to patients with Medicaid or Medicare, but in general, there are more favorable private insurances that we contract with.

If I look at the population of patients who are seen in our clinic, I ask if we do a good enough job of representing patients who are minorities, women, or older or younger adults in potentially practice-changing trials. I don't promote putting them in first-in-human studies, but if we have good phase II or randomized, phase III studies that we think are going to be practice-changing, our population should reflect the demographics of the patients we see in clinic.

We've implemented a patient navigator to discuss clinical trials using the language that patients are most comfortable with. We think it can be helpful to have someone who looks and talks like you describe why it's important to participate in clinical trials. We can get into understanding the barriers to participating and explore different grants that are potentially available to help soften the socioeconomic blow.

We're partnering with some of our sister institutions that are affiliated with the main campus of MD Anderson, such as UT San Antonio and Harris Health Lyndon B. Johnson Hospital, which is our county hospital. The practice-changing studies at those centers serve a larger minority population than we're able to serve here at the main campus of MD Anderson.

I've also been involved through the American Society of Clinical Oncology, which has a health disparities committee with several initiatives. Those initiatives involve bringing awareness to disparities, making sure that we're recruiting minority oncologists from the premedical stage through training and that our guidelines acknowledge where minorities are grossly underrepresented in large, practice-changing studies, and how that impacts generalizing these treatments.

I've been involved with this work at both the local and national levels. There's still a huge unmet need in terms of trying to get better health care delivered to communities that don't have the access that my patient population does.

How can clinical trials shape care and address disparities?
Clearly, I am biased—I'm a clinical investigator,

Get to Know

that's what I like to do—but I think there's potentially better care delivered to patients who are participating in trials.

You have many people looking in on those patients. Our primary objective is to look out for the safety of the patient. Often patients get access to some of the more novel treatments, which we think are better than the currently available standards of care, by participating in these studies.

Even in the last five years, new treatments have emerged, some of which are even better than what we had been using for decades. This progress is only possible through patients participating in clinical trials.

I want to do everything I can to ensure everyone has access to those trials, and that we get better representation on those studies of patients who reflect our general population. This diversity will allow us to have more confidence that results will generalize when these therapies are approved.

How do you hope to see lymphoma treatment evolve?

We still don't have good ways to personalize medicine. We have some rudimentary tools and clinical prognostic scores, but those are not too precise.

I'd like to see tumor profiling used to generate treatments that are more precise to the biology of a given patient's tumor. In chronic myeloid leukemia, for instance, identifying the translocation allowed the development of a pill that targets it. That disease was fatal for many patients, but it has become manageable nowadays.

If we can do a better job of tumor profiling and generate a score or signature that helps identify the most effective treatment for a given situation that would be major progress.

"I'm continuing to work on understanding how to improve access and reduce barriers for our underserved populations."

What do you enjoy doing outside of work?

In the wintertime, I love to snow ski. In the summertime, I love to hike. If I have any opportunity to be outside, you will find me there.

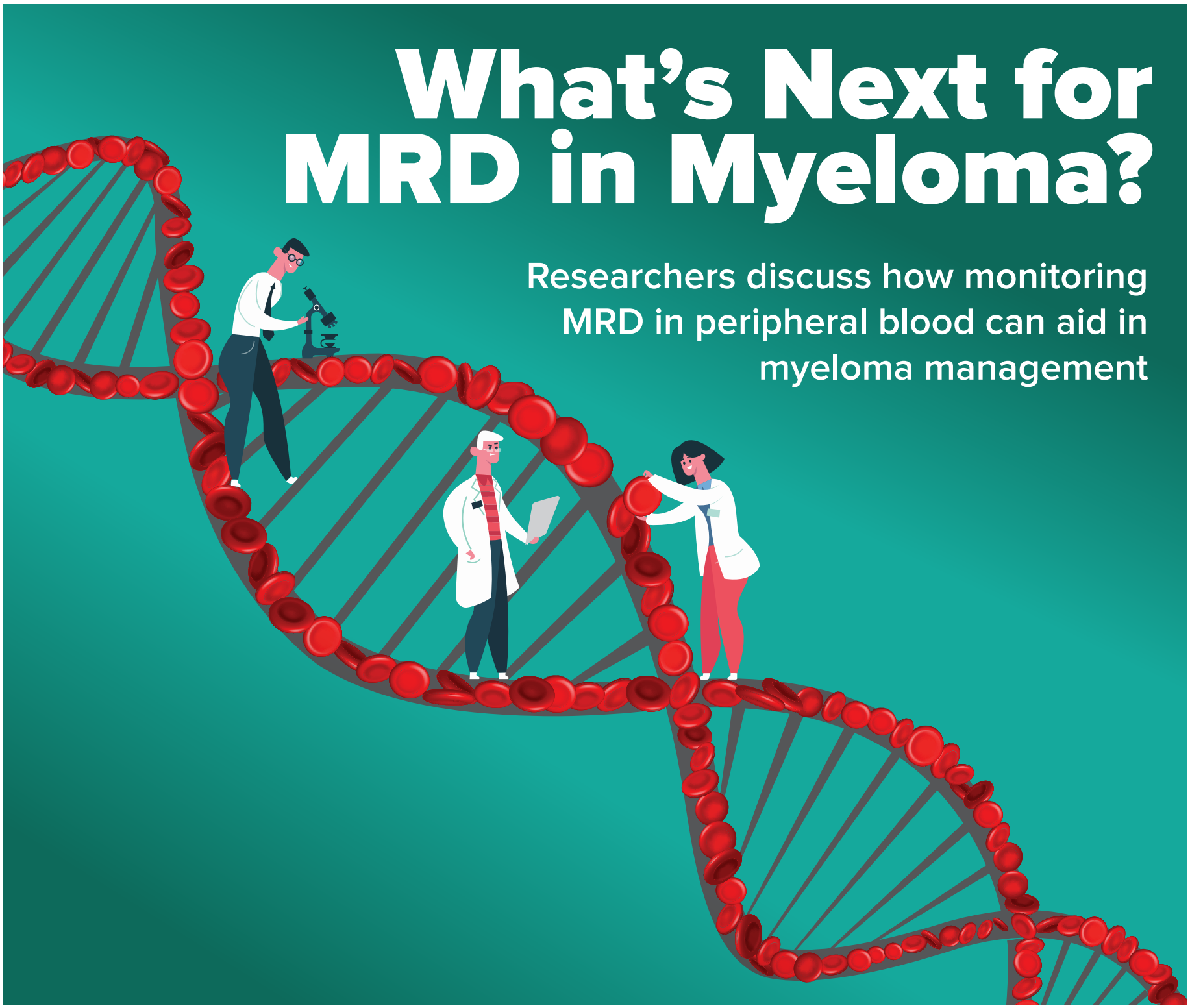
What is one thing people might be surprised to learn about you?

I have breast cancer myself. I've benefited from the system that I work in, but I'm passionate about the fact that we need to do a better job of improving communication to patients about the variety of treatment options and why it's not always clear which is the preferred option. It's important to avoid placing a lot of the decision burden on the patients, who sometimes feel woefully unprepared. That includes someone like me, who's an oncologist but spent most of her time in the hematology world.

Loretta Nastoupil, MD, *is an Associate Professor who serves as Director of the Lymphoma Outcomes Database, Section Chief of New Drug Development, and Deputy Chair of the Department of Lymphoma/Myeloma at the University of Texas MD Anderson Cancer Center.*

What's Next for MRD in Myeloma?

Researchers discuss how monitoring MRD in peripheral blood can aid in myeloma management



By Leah Lawrence

Current techniques to monitor measurable residual disease (MRD) in patients with multiple myeloma (MM) often test bone marrow aspirates, but the noninvasive nature of testing peripheral blood is drawing the interest of researchers.

MRD is one of the best available prognostic markers for patients with MM, according to **Bruno Paiva, PharmD, PhD,** Co-Director of the Flow Cytometry Platform and the Monoclonal Gammopathies Research Laboratory at the Clínica and CIMA Universidad de Navarra in Spain.

In 2016, the International Myeloma Working Group (IMWG) incorporated MRD measurement into its uniform response criteria to better identify responses that were deeper than what was traditionally defined as a complete response.[1] Current techniques to measure MRD most commonly test bone marrow aspirates.

However, there is growing interest in researching whether there are methods of measurement sensitive enough to assess MRD in the peripheral blood, a less invasive approach that could allow for more frequent monitoring.

"You have to keep in mind, though, that despite more than a decade of top-quality research into MRD in myeloma [measured in bone marrow], with several manuscripts reported by many different groups and pharmaceutical companies, all showing very reproducible, solid data, a lot of questions about the use of MRD remain," Dr. Paiva said.

"For MRD measurement in the blood, we are definitely only at the beginning, and, similar to bone marrow, I foresee a decade of intensive research prior to knowing how and when to use MRD in the blood."

Where Things Stand

Currently, it is not considered standard of care to check MRD in patients with MM, explained **Swathi Namburi, MD,** of the Swedish Cancer Institute in Seattle, Washington.

"There are reasons to check it and reasons not to check it," Dr. Namburi said. "I consider the patient's goals of care and what treatment plan they are eligible for to see if MRD testing should be incorporated into a typical diagnostic algorithm."

There is currently only one US Food and Drug

In Focus

Administration (FDA)-approved test to detect MRD in patients with myeloma: the next-generation, sequencing-based clonoSEQ assay, which measures MRD in bone marrow. Approved in 2018, the clonoSEQ assay is capable of detecting MRD at levels below one in 1 million cells or 10^{-6}.[2] The IMWG currently defines MRD negativity as the absence of clonal plasma cells at a minimum sensitivity of 10^{-5}.

The approval was based on data showing that MRD measured at the start of maintenance therapy was a strong prognostic indicator of progression-free survival (PFS) and overall survival (OS) in patients treated with lenalidomide, bortezomib, and dexamethasone. Patients with MRD negativity had a higher probability of prolonged PFS regardless of treatment approach.[3]

Although not FDA approved, other techniques of MRD assessment in bone marrow aspirate have been evaluated in clinical trials, including multiparametric flow cytometry (MFC),[4] allele-specific oligonucleotide quantitative polymerase chain reaction,[5] and, more recently, next-generation flow (NGF) cytometry.[6]

"[MRD] was a substantial addition to our understanding of how deeply patients can achieve response," said **Andrzej Jakubowiak, MD, PhD,** Director of the Myeloma Program at the University of Chicago Medical Center. "We have learned that of our patients who achieve a complete response, only a portion of those patients will be MRD-negative. Currently, up to 60% to 80% of patients can achieve MRD negativity with the standard sensitivity cutoff of 10^{-5}, but it may only be 40% to 50% with a cutoff of 10^{-6}."

"As peripheral blood testing gets better, I suspect that we will be looking to the marrow a lot less often." *—Swathi Namburi, MD*

A meta-analysis has established that MRD negativity in MM was associated with improved PFS and OS in both newly diagnosed and relapsed or recurrent disease, regardless of MRD sensitivity threshold, cytogenetic risk, method of MRD assessment, and depth of clinical response at the time of MRD measurement.[7]

"Outside of clinical trials, the use of MRD measurement is very physician-, practice-, or patient-dependent," said **Sarah Holstein, MD, PhD,** a Professor in the Division of Oncology and Hematology at the University of Nebraska Medical Center. "That is, in part, because MRD has not yet been formally defined as a surrogate endpoint for things like PFS or OS. In addition, it has not been clearly shown that basing treatment decisions of MRD status results in improved outcomes."

In 2020, the FDA finalized guidance on the use of MRD as a biomarker in clinical trials to support marketing approval of drugs and biological products. The guidance detailed that the relationship between MRD and clinical benefit needed to be demonstrated in multiple disease settings—relapsed, refractory, newly diagnosed, smoldering, nontransplant eligible—to establish MRD as a surrogate endpoint. The guidance also noted the potential issue that MRD assessed using MFC and next-generation sequencing (NGS) in the bone marrow is not able to detect extramedullary disease (EMD).[8]

The Potential of Blood

The ability to detect EMD could be one of the potential advantages for measuring MRD using peripheral blood, Dr. Paiva said.

"The blood could be more informative than the marrow because it would capture disease coming from different bone marrow sites—not just the one sampled—as well as extramedullary disease sites outside of the bone marrow," Dr. Paiva said. "This is particularly important in myeloma because the disease is characterized by heterogeneous bone marrow involvement and, less frequently, extramedullary involvement."

The other potential advantage is the noninvasive nature of testing peripheral blood.

"Bone marrow testing is very difficult for patients; they hate it," Dr. Jakubowiak said. "It is not sustainable to ask patients to undergo frequent MRD assessment in the bone marrow."

A method that allows for more frequent testing could potentially better capture MRD kinetics, which could be more informative not only from a prognostic point of view, but also to adjust treatment plans, he said.

The two main methods used for MRD assessment in bone marrow—NGS and NGF—can also be used in the blood; however, because tumor burden in the peripheral blood is lower than in the bone marrow, these methods produce many false-negative results.

For example, one study evaluating flow cytometry in the peripheral blood compared with the bone marrow showed that up to 40% of patients who were MRD-positive in bone marrow had undetectable circulating tumor plasma cells in paired blood samples.[9]

As a result, methods in development for measuring MRD in peripheral blood need to have increased sensitivity, and progress is being made in this area.

BloodFlow

Dr. Paiva together with **Laura Notarfranchi, MD,** of the Department of Medicine and Surgery at the University of Parma in Italy, and colleagues recently presented data on the use of a new technology they called BloodFlow.[10]

"The idea is to use NGF, developed by the EuroFlow Consortium, and to increase the sensitivity of the technique by integrating immunomagnetic microbeads targeting CD138 prior to NGF," Dr. Notarfranchi said.

The method requires a large sample of blood of about 50 mL, Dr. Notarfranchi said. These samples are then magnetically labeled and processed, and about 100-μL aliquots are enriched with circulating plasma cells and analyzed using NGF.

Dr. Notarfranchi and colleagues presented the results of an analysis comparing MRD assessment using BloodFlow with NGF in peripheral blood or bone marrow in 353 samples collected in different treatment scenarios. BloodFlow detected MRD in 9% of samples, with the lowest MRD level at 6×10^{-8}. Of the 33 samples that were MRD-positive with BloodFlow, more than half (58%) were MRD-negative using NGF. All MRD-negative cases on BloodFlow were also negative by NGF.

Concordance of samples was observed in 69% of double-negative samples and 9.5% of double-positive samples. Approximately 20% of samples were MRD-negative in bone marrow but positive in peripheral blood.

"BloodFlow showed a negative predictive value of 77% compared with NGF in marrow," Dr. Notarfranchi said, adding that they are working to increase the negative predictive value and reduce the number of false negatives in the blood compared with the marrow.

"This two-step process looks promising," Dr. Holstein said. "The recently presented work suggesting that they could detect levels as low as 6×10^{-8} is probably where we need to be to confidently say whether or not there are any abnormal plasma cells in the blood."

Mass Spectrometry

The other technique that has recently shown potential is the use of mass spectrometry as a method to detect the M protein, which is produced by the expanding plasma cell clone in monoclonal gammopathies.

"Mass spectrometry-based evaluation of MRD is, at the moment, at different phases of development," Dr. Jakubowiak said.

The Mayo Clinic has a commercially available form of mass spectrometry called matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) that is currently included in the IMWG's recommendations as an accepted method for screening for M proteins.[11]

A study comparing MALDI-TOF MS in peripheral blood with NGF in bone marrow in 71 patients with MM found concordance between methods for 62% of patients (44/71); eight patients were positive using both methods and 36 were negative for both. An additional 17 patients were detectable only by MALDI-TOF MS and 10 patients were detectable only by NGF.[12] The samples studied were not paired samples.

Another mass spectrometry method being explored is mass spectrometry with liquid chromatography (LC-MS). Dr. Jakubowiak and colleagues published the results of a phase II study analyzing the use of LC-MS, a method that may be more expensive than MALDI-TOF MS but offers increased sensitivity.

In the analysis, they compared mass spectrometry (both LC-MS and MALDI-TOF MS) in the peripheral blood with serum protein electrophoresis/immunofixation, positron emission tomography/computed tomography (PET/CT) imaging, MFC, and NGS in the bone marrow in 76 patients with newly diagnosed MM enrolled in a study of carfilzomib, lenalidomide, and dexamethasone (KRd). MALDI-TOF MS was at least as sensitive as MRD by NGS, with a limit of detection of less than 10^{-5} in the bone marrow.[13]

MRD assessment using LC-MS increased sensitivity. For some paired samples, LC-MS was superior to the current standard of MRD negativity, with a limit of detection less than 10^{-5} and was at least as sensitive as MRD by NGS, with a limit of detection less than 10^{-6}.

A more recent analysis comparing MRD assessment with MALDI-TOF MS and MS-LC in peripheral blood and NGS again showed that LC-MS could possibly exceed the sensitivity of MRD by NGS in the marrow, with a sensitivity threshold of 10^{-6}.[14]

"Mass spectrometry with or without liquid chromatography has limitations," Dr. Jakubowiak said. "With this technique—at least at the moment—there is a requirement to have earlier samples where the M protein is still present in reasonable abundance so you can identify the mass of M protein. You have to have that original sample to know that the original M protein is not detectable or substantially reduced."

Some patients with MM secrete M protein below a measurable quantity or have no detectable M protein at all.

Another potential limitation is a phenomenon where the M protein is relatively slow to disappear from the body, Dr. Jakubowiak said. "Mass spectrometry may be detecting a slowly clearing M protein that is otherwise no longer being produced."

Finding the right time for when mass spectrometry needs to be used requires further investigation.

Potential Applied Use

"It is going to be tricky to figure out how best to use this MRD data as far as clinical intervention goes," Dr. Namburi said. "This is not like acute leukemia. Patients with MM may have a long period of controlled disease that is MRD-positive, and we are waiting for a true relapse. Intervening too early may expose them to too much therapy without a proven survival benefit. Right now, this should only be done in a clinical trial setting."

How to best use MRD information has been, and continues to be, explored in a number of studies.

Earlier this year, Dr. Jakubowiak and colleagues published interim results of the phase III ATLAS trial, a comparison of KRd to lenalidomide alone as maintenance therapy after transplant.[15] As part of the risk-adapted, MRD-directed design, patients assigned to the triplet who had no detectable MRD at the 10^{-5} level after cycle 6 and had standard-risk cytogenetics were switched to lenalidomide maintenance at cycle 9. A post-hoc analysis showed a PFS benefit among those patients assigned to KRd who met criteria for de-escalation to maintenance lenalidomide alone.

"We based this strategy on previous results that had generated some preliminary information, and it still requires more validation, but this group of patients had the best outcomes of all patients in the trial," Dr. Jakubowiak said. "It showed the power of using MRD information for de-escalation of therapy to lower potential toxicity."

Similarly, the phase II MASTER trial used an MRD response-adapted approach in its analysis of daratumumab plus KRd induction followed by transplant and daratumumab-KRd consolidation. Patients who were MRD-negative at two landmark timepoints were allowed to discontinue treatment and be observed.[16]

"MRD negativity was high in this study, and they reported that people with standard-risk disease did very well," Dr. Jakubowiak said. "On the other hand, patients with high-risk disease who discontinued treatment had earlier progression of disease."

Recently presented results from the MRD2STOP trial also explored the use of multimodal MRD negativity for cessation of therapy after one year of maintenance. In MRD2STOP, for eligibility to discontinue maintenance therapy, MRD was assessed using the clonoSEQ method at the 10^{-6} level of sensitivity; however, the trial is also assessing the use of CD138-enriched bone marrow aspirates and clonoSEQ to achieve a sensitivity of 10^{-7} and both MALDI-TOF MS and LC-MS, as well as cell-free DNA.[17]

At a median follow-up of 14 months, five of 38 patients had MRD resurgence and two of these five had disease progression. Of the five who progressed, four had a positive MRD at baseline when tested for CD138-enriched samples at the higher, 10^{-7} sensitivity threshold, suggesting that patients who are MRD-positive at 10^{-7} sensitivity may be at increased risk for progression if they discontinue therapy.

There are also multiple other ongoing studies evaluating MRD-guided management of MM, including SWOG's DRAMMATIC trial that will evaluate maintenance lenalidomide with or without daratumumab/rHuPH20 post-transplant, with MRD used to direct therapy duration.[18]

"These trials should hopefully help us to look at an MRD-negative result and feel fairly confident about what to expect in terms of time until relapse," Dr. Namburi said. "That is what people want to know when they are dealing with this cancer. What do the next three years look like?"

Multimodal Future

Even with the increased sensitivity of the newer peripheral blood MRD technologies, it is likely that a thorough, accurate assessment of MRD will always include multiple modalities, including imaging, Dr. Paiva said.

"Imaging may not be as sensitive as classical MRD methods, but imaging is very important in a disease like myeloma," Dr. Paiva said. "PET/CT is more commonly used for evaluating treatment efficacy, and this may be complementary to MRD measured either in the marrow or, eventually, peripheral blood."

As it stands now, MRD measurement in peripheral blood is not ready to replace bone marrow aspiration, Dr. Notarfranchi said. "However, in the future, in particular settings such as during maintenance or follow-up, we may be able to reduce the number of bone marrow biopsies by integrating BloodFlow or other techniques."

"Bone marrow testing is very difficult for patients; they hate it. It is not sustainable to ask patients to undergo frequent MRD assessment in the bone marrow." *—Andrzej Jakubowiak, MD, PhD*

Dr. Namburi agreed, "As peripheral blood testing gets better, I suspect that we will be looking to the marrow a lot less often … maybe only a few times during the entire myeloma journey. We may be able to test the peripheral blood more routinely—depending on the phase of treatment—but still have defined timepoints where we feel compelled to check marrow."

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A New Era of Treatment for Patients with MCL?

Craig Portell, MD, an Associate Professor of Medicine at the University of Virginia, and **Tycel Phillips, MD,** a Clinical Associate Professor at the City of Hope in Duarte, California, discuss what the TRIANGLE study means for transplantation and treatment in general for patients with mantle cell lymphoma (MCL).

Transplant Versus Nontransplant

Dr. Portell: Autologous hematopoietic stem cell transplantation (AHSCT) consolidation after induction chemotherapy-induced remission has long been a standard of care in patients with MCL, and it has been shown to have survival advantages in the disease. Of course, transplant isn't appropriate for everyone, and most patients with MCL are not eligible for transplant due to age and comorbidities. For patients who are eligible, nonrandomized studies have mostly shown a benefit to transplant when the disease is treated aggressively during induction. The recently reported TRIANGLE study may question this paradigm; however, the study has only been presented, not published. Additional studies questioning the role of transplant are currently ongoing. While the field may move toward a nontransplant approach, as of today, transplant seems the most likely option to benefit our patients.


Craig Portell, MD

Dr. Phillips: The biggest argument for transplant has always been prolonging remission because the disease is incurable. Conversely, some people have argued the biggest strike against transplant is that none of the current studies have demonstrated a clear survival advantage for AHSCT in these patients. Given that fact, the current major question is whether we need transplant to achieve deep and durable remissions in this patient population. The availability of measurable residual disease (MRD) testing, which appears to be a more sensitive test than positron emission tomography/computed tomography, should allow us to evaluate this premise further in ongoing clinical trials.


Tycel Phillips, MD

The TRIANGLE study from the European MCL Network is one such trial. This study randomized patients to receive ibrutinib during the odd cycles of induction (R-CHOP cycles) and then for two years during maintenance in two of the study arms. One of the arms included AHSCT and the other did not. The third arm did not include ibrutinib during induction or maintenance but did consolidate it with AHSCT. The TRIANGLE trial seemed to indicate that the addition of ibrutinib alone in the frontline setting was better than transplant alone, and it appeared equivalent to the arm that included ibrutinib plus AHSCT. Given these findings, we are evaluating what appears to be a new treatment paradigm. Where exactly does this oral medication, the Bruton's tyrosine kinase (BTK) inhibitor, fit in the frontline setting for transplant-eligible patients? What does it mean for transplant given that we know transplant plus a BTK inhibitor doesn't appear to be any better than the BTK inhibitor with induction chemoimmunotherapy? The TRIANGLE study showed that transplant without a BTK inhibitor doesn't seem great, but there is still a lot to understand about the study's patient population. I think we are all looking forward to the final manuscript. As the TRIANGLE study matures, and if the curves remain superimposable over the next 48 months, the final nail in the coffin might be struck for autologous transplants for patients with MCL.

Death Knell for AHSCT?

Dr. Portell: The field is changing and evolving in front of our eyes. The TRIANGLE study gives us a lot of new insights into the role of transplant in MCL. The triple-arm design, a novel agent, a BTK inhibitor, with and without transplant as two of those arms, is very interesting. It suggests early on that the transplant may not be needed if given with a novel agent. Caveats abound, however, because the study was only presented at the American Society of Hematology Annual Meeting and Exposition. We need to see the final, peer-reviewed manuscript to really understand it.

There are also a lot of subtleties. First, the novel agent was ibrutinib, the first BTK inhibitor to the market and the only one available during the TRIANGLE study design, or at least it was the one that was furthest along in development. Over time, we now understand that ibrutinib is less safe than other second-generation BTK inhibitors. We don't feel comfortable giving ibrutinib to some patients but would feel comfortable giving the other second-generation BTK inhibitors. Can similar outcomes be identified with those second-generation BTK inhibitors? It's hard to know.

The second subtlety is that the researchers used ibrutinib during induction but only for 30 days in total. Is that important, or is it more that maintenance after finishing induction chemotherapy is important? From what I remember, the early portions of the survival curves would suggest that having the novel agent during induction may have prevented a few failures, but those data need to be evaluated more carefully.

Finally, over the course of the study, rituximab maintenance after transplant had been shown to have an overall survival advantage. Given this fact, half the patients received rituximab maintenance. While the TRIANGLE authors suggest there was no difference in outcomes, more details are needed to understand if BTK inhibitors and rituximab are truly needed. This is a particularly important point to consider given the immunosuppression one would see with the long-term treatment with BTK inhibitors and rituximab.

> **"Patients are essentially taking three to six months out of their lives to do the transplant process. If that time is something we can give back to them by not doing the transplant, with either equal or maybe even slightly worse outcomes, I would accept that."** *—Craig Portell, MD*

The TRIANGLE study is a potentially transformative study, but we really need to see it published before changing practice. Other ongoing studies are questioning whether transplant is needed. One of them is an Eastern Cooperative Oncology Group (ECOG) study, EA 4151, which is evaluating using next-generation

Point | Counterpoint

MRD testing to assess if a deeper remission than we can see on scans can supplant the need for high-dose chemotherapy with autologous stem cell rescue. I think the field is moving in the direction of eliminating transplant. Many of us question the need for transplant, but as of right now, autologous transplant consolidation would remain the standard of care for eligible patients with MCL.

Dr. Phillips: I do think Dr. Portell is quite correct about some of the intricacies of the TRIANGLE study. The data are immature, with only three years of follow-up, so none of us can confidently say that this change should alter our clinical practice, especially without a chance to fully evaluate the study manuscript. I will say that the field overall seems to be moving away from AHSCT. In addition to the TRIANGLE study, several other studies are introducing novel agents in the frontline setting, plus or minus the addition of some chemotherapy consolidation, and have not included AHSCT. These studies are ongoing and have shown good initial overall response rates and remissions, albeit in small sample sizes. These studies do lend some support to the idea that with the introduction of some of these novel treatments in the frontline setting, it is likely that we will be comfortable eliminating AHSCT, which, while quite safe for a majority of patients, does induce short-term complications in most patients and long-term complications in a few patients.

“I think it’s a good time for our patients. I think we’re going to be able to answer some very important questions about the needs of certain treatments.” *—Tycel Phillips, MD*

Treatment-induced myelodysplastic syndromes and secondary acute leukemia are the most concerning long-term complications related to this type of treatment. We do see some younger patients presenting with MCL, specifically in the transplant-eligible patient population. Preventing some of these secondary and late complications will be important, especially if we can continue to try to make this cancer a more chronic disease, with patients living longer and longer. I will concede to Dr. Portell that in a lot of these studies looking at novel treatments in the frontline setting, we do not have the long-term data like with autologous transplants.

Overall, I do think our field is heading firmly in the direction of eliminating AHSCT for most patients. There is an ECOG study that is randomizing AHSCT-eligible patients who are MRD-negative to transplant plus rituximab maintenance versus just rituximab maintenance. Those patients could have had a multitude of different induction regimens, some of which may not include any novel treatments.

If we can get an undetectable MRD test without transplant, that is important. Data have come out of Germany that show that an undetectable MRD test is an important endpoint to meet to have a long-term, progression-free survival (PFS). If we can avoid having to put a patient through a treatment like AHSCT, where they get high-dose chemotherapy and stem cell rescue and spend up to 14 or more days in a hospital, that is something we should do. Especially if that treatment is not adding a substantial PFS to our patient population.

To summarize, I think maturation of the TRIANGLE study is going to be very important, as are the results from the ECOG study. If those two studies demonstrate long-term remission without an AHSCT, then I think we can all agree that would be the end for AHSCT. Additionally, it would be nice if we had a study looking at a novel treatment regimen without chemotherapy versus a more traditional regimen, or even the transplant arm in the TRIANGLE study that included a novel treatment, to see if we need any of these cytotoxic agents during induction. To briefly touch on the “other” transplant, I don’t think any of these studies or others being evaluated will impact the use of allogeneic HSCT. I think allogeneic HSCT will still have a purpose because it is the only probable curative treatment option in MCL for the right patients. I think allogeneic HSCT should still be considered, but autologous stem cell rescue or AHSCT will be something we can mostly move away from.

Transplant as a Definitive Treatment?

Dr. Portell: What I would need to see, to clinch transplant as a definitive treatment option for patients with MCL or not, is these studies becoming negative or not showing much survival advantage. I completely agree with Dr. Phillips that transplant is toxic. It has a lot of problems from a quality-of-life perspective. Patients are essentially taking three to six months out of their lives to do the transplant process. If that time is something we can give back to them by not doing the transplant, with either equal or maybe even slightly worse outcomes, I would accept that. Maybe we accept a three-month-shorter PFS with novel agents without a transplant because, in theory, that’s the time we are taking away with transplant. It is a very safe procedure, but it takes a lot of effort to do and, as Dr. Phillips mentioned, has both short- and long-term toxicities.

Dr. Phillips: I think it’s a good time for our patients. I think we’re going to be able to answer some very important questions about the needs of certain treatments. Our goal is still maintaining overall survival because, again, we’re not getting rid of this cancer, but our patients are living longer with it, far longer than I think people would have imagined a decade ago. If we can do that and still maintain quality of life in our patients by eliminating certain things, or if we can have a more nuanced approach about who needs a transplant and who doesn’t, I think that will be better for all of us. Now, if you’re young and fit enough, you get a transplant. I think as we move along, these questions will be answered, and it will be better for all of us and for our patients, which is the most important thing.

Dr. Portell: I’m hopeful that we will eventually move away from the mindset of transplant-eligible versus transplant-ineligible during treatment decisions. Currently, even our induction chemotherapy choice is based on that mindset, particularly around the use of high-dose cytarabine. I can foresee a future, much like Dr. Phillips predicted, where novel agents alone, maybe biology-subset driven, will be used for all patients instead of intensive chemoimmunotherapy. With better treatments, we can eliminate the need to worry about transplant eligibility and its associated risks. Even induction chemotherapy can have significant problems, so finding safer and less toxic options is important.

Dr. Phillips: What we didn’t mention is the novel treatment ibrutinib, which was used in the TRIANGLE study. We’re not sure if we’re still going to have access to ibrutinib because its accelerated approval has been removed, and it is not clear what’s going to happen. As much as we like to extrapolate ibrutinib efficacy data to the other BTK inhibitors, that isn’t necessarily the case for insurance companies and the US Food and Drug Administration. We will have to take a guarded approach once those results are made available and if ibrutinib is indeed no longer available in the United States.

Dr. Portell: That is a very good point that further complicates the implementation of the TRIANGLE study.

To read about the TRIANGLE study, visit the *Blood Cancers Today* Mantle Cell Lymphoma Knowledge Hub.

PET-Adapted Therapy Linked with ‘Excellent’ PFS in Hodgkin Lymphoma

Take-aways:
- Patients with bulky stage I/II classic Hodgkin lymphoma who received ABVD underwent PET to determine if they should receive continued ABVD or escBEACOPP plus radiotherapy.
- Most patients were able to avoid escBEACOPP plus radiotherapy based on PET results.
- The estimated three-year PFS rate for all patients in the study was 92.3%.

Positron emission tomography (PET)-adapted therapy was associated with “excellent” progression-free survival (PFS) in patients with bulky stage I/II classic Hodgkin lymphoma, according to a recent study.

Ann LaCasce, MD, of the Dana Farber Cancer Institute, and colleagues conducted the research because patients with bulky stage I/II classic Hodgkin lymphoma are “typically treated with chemotherapy followed by radiation,” but “late effects associated with radiotherapy include increased risk of second cancer and cardiovascular disease.”

They hypothesized a PET-adapted strategy would be “effective and limit the use of mediastinal radiotherapy in this important and particularly high-risk group of patients in terms of late effects.”

Dr. LaCasce and colleagues evaluated the PET-adapted approach in patients with bulky early-stage classic Hodgkin lymphoma, omitting radiotherapy in patients who had interim PET-negative disease and intensifying treatment in those with PET-positive disease.

Phase II Trial Design and Patient Characteristics

The single-arm, phase II trial included patients with bulky disease, defined as a mass >10 cm or one-third of the maximum intrathoracic diameter on a chest x-ray. All patients received two cycles of full-dose doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by interim fluorodeoxyglucose PET (PET2). The patients underwent centrally reviewed PET on days 23 to 25 after the first day of cycle two.

Those who had a PET2-negative status, which the study’s authors defined as a score of one to three on the Deauville five-point scale, received four additional cycles of ABVD.

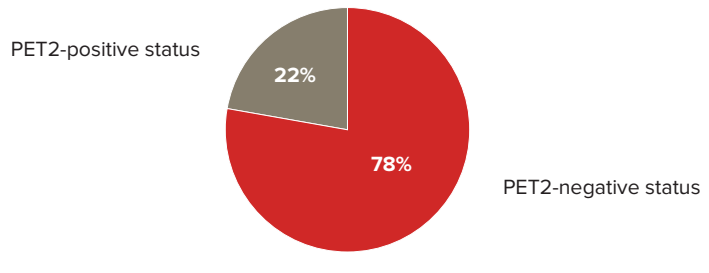
Patients who had a PET2-positive status received four cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escBEACOPP) followed by 30.6 gray involved-field radiation.

Patients received PET at the end of therapy and received computed tomography (CT) scans every three months for one year, every six months during years two and three, and then annually for a maximum of five years. The PET scans underwent central review by a member of an “expert team of PET-CT readers” with an “adjudicator from the same pool in the case of disagreement with the local physician,” Dr. LaCasce and colleagues wrote.

The study included 94 evaluable patients with a median age of 30 years (range, 18 to 58 years). A little more than half (53%) of patients were female. Nearly all (90%) patients had stage II disease, including 48 (51%) with stage IIB/IIBE disease.

The study’s primary endpoint was the three-year PFS rate. The study’s objectives were to maintain PFS in patients with a PET2-negative status without radiotherapy and improve PFS for patients with PET2-positive status by intensifying chemotherapy with consolidative radiotherapy.

FIGURE 1. Proportion of Patients with PET2-Positive or PET2-Negative Status



Patient Outcomes with PET-Adapted Approach

See **FIGURE 1** for PET2 results. Patients with a PET2-negative status had a three-year PFS rate of 93.1%, and those with a PET2-positive status had a three-year PFS rate of 89.7%. The estimated three-year PFS rate for all patients was 92.3% (95% CI, 87.0-98.0).

At a median follow-up of 60 months, seven PFS events, including five progressions and two deaths, occurred in the 73 patients with a PET2-negative status. There were two PFS events—both of which were progressions—in the 21 patients with a PET2-positive status.

When the researchers compared the PFS of patients with a PET2-positive status with those who had a PET2-negative status, the estimated hazard ratio was 1.03, which was significantly less than the null hypothesis of 4.1 (P=.04).

The three-year overall survival (OS) rate was 98.6% in those with a PET2-negative status and 94.4% in those with a PET2-positive status. The estimated three-year OS rate for all patients was 97.7% (95% CI, 94.7-100). See **TABLE 1** for information on complete response (CR) rates.

At a median follow-up of 69 months for survival, four patient deaths occurred, including one in a patient with a PET2-positive status.

TABLE 1. Proportion of Patients Who Achieved a CR

Patient groups	CR rate
Patients with PET2-positive status	76%
Patients with PET2-negative status	100%
All patients	95%

Nearly all (93%) patients who were evaluable for safety completed therapy per the study protocol, including 96% of those with a PET2-negative status and 91% of those with a PET2-positive status.

Neutropenia was the “predominant toxicity” reported by Dr. LaCasce and colleagues, as 9% of patients developed febrile neutropenia.

The researchers did not report any “unexpected” adverse events (AEs) in patients who received ABVD or escBEACOPP. No grade 5 AEs occurred.

Study Meets ‘Primary Goal’

Overall, patient outcomes were “excellent,” the researchers reported, but the study had several limitations, including its moderate size for a phase II study that did not randomize patients to receive standard therapy versus a PET-adapted approach. Furthermore, the sample of patients with a PET2-positive status after two cycles of ABVD was small, the researchers reported.

Despite the limitations, the study “met its primary goal” and has “important implications for clinical practice,” they wrote.

Future studies should evaluate novel agents in patients with early-stage disease, according to LaCasce and colleagues.

“The majority of patients with PET2-negative [status] remained disease-free without the need for high-dose chemotherapy with autologous stem cell transplant,” they concluded. “Future studies should focus on incorporating novel agents in early-stage patients who are unlikely to achieve durable remissions with chemotherapy alone and reduce exposure to regimens such as escBEACOPP, which may have a negative impact on fertility and bone marrow stem cells.”

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‘Dark Zone Signature’ Identifies DLBCL Subgroup with Poor Prognosis After R-CHOP

Take-aways:

- The double-hit signature characteristic of HGBCL-DH-*BCL2* can be found in GCB-DLBCL and Burkitt lymphoma.
- Based on these findings, the double-hit signature is now referred to as the dark zone signature.
- The dark zone signature refines the cell-of-origin classification and identifies a subgroup of patients with DLBCL who have a poor prognosis following R-CHOP.

The double-hit signature that was originally described as characteristic of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements (HGBCL-DH-*BCL2*) can be found in cases of germinal center B-cell-like (GCB) diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma, according to a recent study. The study’s authors have renamed the double-hit signature the dark zone signature based on these results.

Waleed Alduaij, MD, PhD, and **Brett Collinge,** a doctoral candidate, both of the University of British Columbia and the BC Cancer Centre for Lymphoid Cancer, and colleagues conducted the study and published its results in *Blood*.

Gene expression profiling dichotomizes most cases of DLBCL into two subgroups, GCB-DLBCL and activated B-cell-like (ABC)-DLBCL. Approximately 8% of DLBCL cases are reclassified as high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBCL-DH) based on the detection of these rearrangements.

The researchers previously described a “unifying gene expression signature” in HGBCL-DH-*BCL2*, which they translated into a digital gene expression profile-based assay. They found the double-hit signature extended beyond HGBCL-DH-*BCL2* to identify a subset of DLBCL tumors that lacked rearrangements of *MYC* and/or *BCL2*, with approximately 20% of those tumors harboring cryptic rearrangements.

Dr. Alduaij and colleagues designed the current study to assess “molecular determinants of real-world outcomes” in a population-based cohort of patients with DLBCL.

> **“These observations motivated us to rename the double-hit signature to the dark zone signature.”** *—Dr. Alduaij and colleagues*

Study Cohort

The study included all patients in British Columbia who were diagnosed between 2005 and 2010 with de novo DLBCL, not otherwise specified or HGBCL-DH with DLBCL morphology. A central pathology review confirmed the diagnosis in all available diagnostic biopsies and selected a representative area for tissue microarray construction. They excluded bone and bone marrow biopsies and biopsies with a surface area of <2 mm^2 from the analysis.

The researchers profiled evaluable biopsies with fluorescence in situ hybridization (FISH), immunohistochemistry, and digital gene expression profiling to assign the cell of origin and evaluate the double-hit signature.

The study included 1,149 patients, 902 of whom had an evaluable clinical diagnostic biopsy. Of the 902 evaluable biopsies, 649 were included on tissue microarray. Gene expression profile data were available for 804 patients, including 629 of the 866 patients who received R-CHOP.

GCB and unclassified tumors that were positive for the double-hit signature were assigned to the double-hit-signature-positive group. Tumors that were negative or indeterminate for the double-hit signature were assigned to the respective cell-of-origin subgroups.

Double-Hit Signature Expression Extends to Burkitt Lymphoma, GCB-DLBCL

Double-hit signature expression occurred in 12% of all tumors of DLBCL morphology. Of the tumors that were positive for the double-hit signature, 97% had a GCB cell of origin and 3% had an unclassified cell of origin.

HGBCL-DH-*BCL2* made up 38% of tumors with available FISH data that were positive for the double-hit signature. Of the tumors that were positive for the dark zone signature, the 62% that were negative for HGBCL-DH-*BCL2* by FISH were “associated with outcomes similar to HGBCL-DH-*BCL2*,” the researchers wrote.

All 55 cases of Burkitt lymphoma profiled were positive for the double-hit signature, while 21% of the 431 GCB-DLBCL cases were positive for the double-hit signature. The investigators noted that Burkitt lymphoma and GCB tumors that were positive for the double-hit signature “showed near-universal expression” of the germinal center marker CD10.

“Altogether, [the double-hit signature] identifies a group of aggressive B-cell lymphomas of [germinal center] origin with a common gene expression phenotype that reflects the [germinal center dark zone], extending beyond HGBCL-DH-*BCL2*,” Dr. Alduaij and colleagues wrote. “These observations motivated us to rename the [double-hit signature] to the ‘dark zone signature,’ and it will henceforth be referred to as such.”

Molecular Signatures Impact Real-world Outcomes in DLBCL

Among patients who had gene expression profiling data, 54% had a GCB cell-of-origin subtype, 36% had an ABC cell-of-origin subtype, and 11% had an unclassified cell-of-origin subtype.

In patients who received R-CHOP, the freedom from progression (FFP) was 14% higher and the overall survival (OS) was 12% higher in patients with GCB-DLBCL than in those with ABC-DLBCL.

When the dark zone signature was incorporated as a group, it “subsumed” 90 GCB cases and three unclassified cases, constituting 18% of all GCB-DLBCL and unclassified DLBCL.

Those who were positive for the dark zone signature had the worst outcomes, with a two-year FFP of 51% and a two-year OS of 57%. When patients with dark zone signatures were removed from the GCB-DLBCL group, the remaining patients had excellent outcomes, with a two-year FFP of 87% and a two-year OS of 89%, the study’s authors wrote.

In advanced-stage disease, those who were positive for the dark zone signature had “significantly inferior outcomes” compared with those with GCB-DLBCL, “in whom excellent outcomes were maintained with a two-year OS of 90%,” according to the study’s authors.

Patients who were positive for the dark zone signature and those who had ABC-DLBCL had significantly shorter diagnosis-to-treatment intervals than those with GCB-DLBCL.

“Taken together, [the dark zone signature] identifies a poor-prognosis DLBCL subgroup following R-CHOP, whereas excellent outcomes were observed with GCB-DLBCL lacking [the dark zone signature] expression,” they wrote.

The authors acknowledged that their study had several limitations, including a lack of adequate material in some cases and small sample sizes in rare molecular subgroups.

“Recognition of a [dark zone] signature refined the [cell-of-origin] classification by distinguishing patients within GCB-DLBCL with clinically relevant differences in outcomes and diagnosis-to-treatment times,” they concluded. “These findings may potentially improve patient selection for treatment intensification and clinical trial design in DLBCL.”

Reference

Alduaij W, Collinge BJ, Ben-Neriah S, et al. Molecular determinants of clinical outcomes in a real-world diffuse large B-cell lymphoma population. *Blood*. 2022. doi:10.1182/blood.2022018248

Regulatory Actions

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

EC Grants Approval to Lisocabtagene Maraleucel

The European Commission (EC) has granted approval to lisocabtagene maraleucel for relapsed or refractory large B-cell lymphoma (LBCL) after one prior therapy.

The EC approval covers the treatment of adult patients with diffuse LBCL, high-grade B-cell lymphoma, primary mediastinal LBCL, and follicular lymphoma grade 3B who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

The approval is based on results from the pivotal phase III TRANSFORM trial in which the drug demonstrated statistically significant and clinically meaningful improvements in the study's primary endpoint of event-free survival (EFS) and key secondary endpoints of complete responses (CR) and progression-free survival (PFS) compared with standard therapy, according to the manufacturer of the drug.

In the TRANSFORM study, lisocabtagene maraleucel increased median EFS more than four times compared with standard therapy (10.1 months vs 2.3 months) at the time of the prespecified interim analysis, with a median follow-up of 6.2 months. The primary analysis results were consistent with the interim analysis, with lisocabtagene maraleucel not reaching median EFS. Standard therapy had a median EFS of 2.4 months (median follow-up, 17.5 months). Lisocabtagene maraleucel resulted in a higher CR rate (73.9%) than standard therapy (43.5%). Median PFS was not reached with lisocabtagene maraleucel, and it was 6.2 months with standard therapy.

Source: Bristol Myers Squibb, May 2023

FDA to Review Additional Phase III Study Evaluating Synthetic Hypericin for CTCL

The FDA has received a request to initiate formal discussions, in the form of a Type A Meeting, regarding the design of a second phase III pivotal study evaluating synthetic hypericin in the treatment of early-stage cutaneous T-cell lymphoma (CTCL).

The proposed second phase III study comes in the wake of the recently published phase III FLASH trial, in which a total of 16% of the patients with stage IA, IB, or IIA CTCL receiving synthetic hypericin achieved at least a 50% reduction in their lesions compared with 4% of patients in the placebo group at eight weeks ($P=.04$) during the first treatment cycle, which was the primary endpoint. The FLASH trial also found the synthetic hypericin treatment to be safe and well tolerated.

Hypericin sodium is a novel photodynamic therapy that utilizes visible light for activation. It is topically applied to skin lesions, taken up by malignant T cells, and then activated by visible light 24 hours later. Photoactivated hypericin has demonstrated significant antiproliferative effects on activated normal human lymphoid cells and inhibited growth of malignant T cells isolated from patients with CTCL. The treatment approach avoids the risk of secondary malignancies inherent with the frequently employed DNA-damaging drugs and other phototherapies that are dependent on ultraviolet exposure, according to the manufacturer.

Source: Soligenix, April 2023

FDA Accepts BLA for Luspatercept-aamt as Treatment of Anemia in MDS

The US Food and Drug Administration (FDA) has accepted the supplemental Biologics License Application (BLA) for luspatercept-aamt to expand the current indication of the drug to include treatment of anemia without previous use of erythropoiesis-stimulating agents (ESAs) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require red blood cell (RBC) transfusions. The FDA has set a target action date of August 28, 2023.

The Type II Variation Application was accepted by the European Medicines Agency (EMA) as well. Both regulatory agencies based their decisions on results from the phase III COMMANDS study. In that trial, luspatercept-aamt demonstrated a statistically significant and clinically meaningful improvement compared with an ESA in red blood cell transfusion independence (RBC-TI) in the first-line treatment of adult patients with very low-, low-, or intermediate-risk MDS who require RBC transfusions.

Safety results in the trial were consistent with the safety profile of luspatercept-aamt for the treatment of anemia in adult patients with low-risk MDS who require regular RBC transfusions as observed in previous clinical trials.

The primary endpoint evaluated in the COMMANDS study is RBC-TI for 12 weeks, with a mean hemoglobin increase ≥1.5 g/dL. Key secondary endpoints include RBC-TI for 24 weeks, RBC-TI for ≥12 weeks, and erythroid response of at least eight weeks during weeks 1 through 24 of the study.

Luspatercept-aamt, a first-in-class therapeutic option, promotes late-stage RBC maturation in animal models.

Source: Bristol Myers Squibb, May 2023

Regulatory Applications Filed for Earlier Use of Idecabtagene Vicleucel

The FDA has accepted a supplemental BLA for idecabtagene vicleucel for earlier use in adults with triple class-exposed relapsed or refractory multiple myeloma (MM). The FDA has set a target action date of December 16, 2023.

The EMA also validated the Type II Variation Application for idecabtagene vicleucel. The validation of the application confirms the submission is complete and initiates the procedure and scientific assessment, the manufacturer of the drug reported.

A supplemental New Drug Application was also accepted by Japan's Ministry of Health, Labour, and Welfare.

The applications are based on interim results from the phase III KarMMa-3 trial, a randomized, controlled study designed to evaluate a chimeric antigen receptor (CAR) T-cell therapy in patients with triple class-exposed relapsed or refractory MM. For these patients, treatment options are limited, as they become triple class-exposed in earlier lines of therapy.

In the trial, researchers evaluated the therapy in patients who had received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Interim results showed that idecabtagene vicleucel significantly reduced the risk of disease progression or death versus standard regimens. The toxicity profile of the CAR T-cell therapy was consistent with previous studies.

"Positive results from our phase [III] KarMMa-3 study demonstrate a significant clinical benefit of [idecabtagene vicleucel] across lines of care in triple class-exposed [MM]," said **Steve Bernstein, MD,** Chief Medical Officer of 2seventy bio.

Idecabtagene vicleucel works by recognizing and binding to BCMA on the surface of MM cells, leading to CAR T-cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Source: Bristol Myers Squibb and 2seventy bio, April 2023

This article discusses the current state of the art in the treatment of polycythemia vera. The following material is reproduced from "SOHO State of the Art Updates and Next Questions: Polycythemia Vera: Is It Time to Rethink Treatment?" published in the February 2023 issue of Clinical Lymphoma, Myeloma & Leukemia. *The article was written by Barbara Mora, PhD, and Francesco Passamonti, MD.*

Are Traditional Treatments Falling Short in Polycythemia Vera?

Polycythemia vera (PV) is the most frequent of the Philadelphia-negative myeloproliferative neoplasms (MPNs). Median age at PV diagnosis is approximately 65 years old, with a higher prevalence in males. The incidence rate of PV has been estimated at 1.57 per 100,000 person-years (p-y) between 2002 and 2016.

PV is characterized by excessive myeloid cell production, mostly secondary to mutations in the *JAK2* gene. The consequent hyperactivation of the JAK-STAT pathway drives the typical PV phenotype. Clinically, PV is characterized by pruritus, microvascular disturbances, and constitutional symptoms. In the long term, what impacts an outcome is the increased risk of thrombotic events (TEs) and evolution into post-PV myelofibrosis (PPV-MF) or blast phase.

PPV-MF diagnosis should be confirmed by a bone marrow evaluation and cytogenetics, as they have prognostic relevance. Practicing physicians should be aware that the incidence rate of TEs is 2.3% p-y after transformation, with a suggested protective role of ongoing cytoreductive treatment (CT).

Treatment Indications and Rationale in 2022

Patients who report TEs have a significantly reduced overall survival compared with those who do not experience these complications. The main aim of treatment is preventing thrombotic complications given that approximately one-third of contemporary patients with PV die for vascular reasons. Standard therapy includes phlebotomies to maintain hematocrit (Hct) below 45% and low-dose aspirin (if not contraindicated).

Patients should be distinguished as at high risk (HR) of thrombosis if they are older than 60 years of age or had a previous TE, and at low risk (LR) in the absence of both factors. For HR patients, CT should be added. Patients conventionally defined as LR should start CT if they have confirmed leukocytosis, symptomatic progressive splenomegaly not related to PPV-MF evolution, or intolerance to phlebotomies. Recent studies have shown a correlation with thrombosis, mainly at arterial sites, and persistently high cardiovascular risk, but the decision to start CT in these otherwise LR cases should be made after all preventive measures have been implemented.

Patients who report a venous TE (including splanchnic vein thrombosis) also require systemic anticoagulation, with retrospective data suggesting a similar protective role for vitamin K antagonists and direct oral anticoagulants.

First-line Treatments in HR PV

Hydroxyurea and interferons (IFNs) are the first-line CT options for PV, as defined by international guidelines. Hydroxyurea is preferred in most countries, because conventional IFNs are burdened by numerous side effects, including flu-like symptoms and psychiatric and autoimmune disorders.

In one study, hydroxyurea did not appear to prevent recurrence of venous events after splanchnic vein thrombosis. Nevertheless, the authors suggest adding CT in the setting of splanchnic vein thrombosis if blood counts are permissive. Pegylated forms of IFNs (PEG-IFNs) have been developed to improve tolerability through less frequent administrations compared with conventional IFNs. Available evidence suggests that there could be a clinical benefit from first-line PEG-IFN if it is continued for the long term, and in instances when it is not necessary to reach complete hematologic response (CHR) quickly.

Resistance or Intolerance to Hydroxyurea

Approximately 15% to 30% of patients with PV develop resistance or intolerance to hydroxyurea, as specified in the 2010 European LeukemiaNet definitions (**TABLE 1**), with a discontinuation rate of the therapy estimated to be around 4.1% p-y. The most recent LeukemiaNet recommendations strongly suggest switching from hydroxyurea to another CT in case of intolerance, together with the development of nonmelanoma skin cancers or thrombotic-hemorrhagic events. The choice of a second-line CT should be based on the patient's age and preferences, in addition to the current evidence on alternative treatments.

To date, ruxolitinib and IFNs are the available options for patients who initially underwent hydroxyurea. Two prospective, randomized studies,

TABLE 1. 2010 European LeukemiaNet Definitions of Intolerance or Resistance to Hydroxyurea

Intolerance definitions
Neutrophil count <400×10^9/L or platelets <100×10^9/L or hemoglobin <10 g/dL at the lowest hydroxyurea dose required to achieve a complete or partial clinico-hematological response
Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any hydroxyurea dose
Resistance definitions
Need for phlebotomy to keep Hct <45% after three months of hydroxyurea at least 2 g/day
Uncontrolled myeloproliferation (eg, platelets >400×10^9/L and white blood cell count >10×10^9/L) after three months of hydroxyurea at least 2 g/day
Failure to reduce massive (≥10 cm from the left costal margin) splenomegaly by >50% by palpation, or failure to completely relieve symptoms related to splenomegaly after three months of hydroxyurea at least 2 g/day

Two recent phase III trials compared PEG-IFN-α2a with standard of care (mainly hydroxyurea) in PV. In the MPD-RC 112 trial, the PEG-IFN cohort achieved Hct control without phlebotomies at 12 months at a significantly higher rate (65% vs 43%). In the PROUD PV trial, after six years of follow-up, those patients treated with ropeginterferon (ropeg-IFN) obtained a significantly higher percentage of CHR (55% vs 35%).

Based on these encouraging results, the authors recommend considering PEG-IFNs in young patients, females of reproductive age, and patients without critical and recent vascular events or massive splenomegaly. A careful screening for psychiatric and autoimmune disorders should be performed before first administration.

The ongoing MITHRIDATE trial is comparing the JAK1/2 inhibitor ruxolitinib versus the best available therapy (IFNs or hydroxyurea) in treatment-naïve, not resistant, or intolerant PV subjects, with the primary endpoint of event-free survival, including occurrence of major TEs.

RESPONSE and RESPONSE-2, evaluated ruxolitinib in PV patients resistant or intolerant to hydroxyurea and in need of phlebotomies, with (RESPONSE) or without (RESPONSE-2) splenomegaly. In the RESPONSE trial, Hct control was reached in 60% of ruxolitinib-treated patients versus 20% in the control arm, with a 35% reduction in spleen volume achieved in 38% versus 1% of patients, respectively. In the RESPONSE-2 study, Hct control was reached in 62.2% of the ruxolitinib-treated patients versus 18.7% in the control arm.

Based on available evidence, ruxolitinib appears to be effective as a second-line therapy, particularly in improving Hct or splenomegaly and in terms of thrombotic risk reduction. It is necessary to keep monitoring patients for the development of nonmelanoma skin cancers while receiving ruxolitinib. Data on PEG-IFNs are limited in terms of late events and safety; however, their indications could be similar to the first-line setting. Finally, patients who are nonresponsive to available treatments should be evaluated for inclusion in clinical trials, when available.

Continued on next page

Venetoclax Plus Obinutuzumab Superior to Chemoimmunotherapy in CLL

The combination of venetoclax and the anti-CD20 monoclonal antibody obinutuzumab with or without ibrutinib outperformed chemotherapy in patients with chronic lymphocytic leukemia (CLL), according to a phase III study.

"Venetoclax [plus] obinutuzumab with or without ibrutinib was superior to chemoimmunotherapy as first-line treatment in fit patients with CLL," the authors, led by **Barbara Eichhorst, MD,** of the University Hospital of Cologne in Germany, wrote.[1]

The large-scale, phase III GAIA/CLL13 trial was conducted across nine European countries and Israel. It enrolled 920 fit patients with CLL who did not have *TP53* mutations. Patients were randomly assigned to four groups (**TABLE 1**).

TABLE 1. Number of Patients Assigned to Each Treatment

Treatment group	Total patients
Chemoimmunotherapy	229
Venetoclax plus rituximab	237
Venetoclax plus obinutuzumab	229
Venetoclax, obinutuzumab, and ibrutinib	231

Patients received either six cycles of chemoimmunotherapy or 12 cycles of venetoclax in combination with either rituximab, obinutuzumab, or obinutuzumab and ibrutinib. The primary endpoints of the study were undetectable measurable residual disease (MRD; sensitivity, $<10^{-4}$), as assessed by flow cytometry in peripheral blood at month 15, and progression-free survival (PFS).

Dr. Eichhorst and colleagues reported that at month 15, the percentage of patients with undetectable MRD was higher in the venetoclax plus obinutuzumab group and in the venetoclax plus obinutuzumab and ibrutinib group than in the chemoimmunotherapy group, but it was not significantly higher in the venetoclax plus rituximab group (see **TABLE 2**).

TABLE 2. Undetectable MRD at Month 15

Treatment group	Percentage of patients with undetectable MRD at month 15	97.5% CI	*P* value
Chemoimmunotherapy	52.0%	44.4-59.5	N/A
Venetoclax plus rituximab	57.0%	49.5-64.2	0.32
Venetoclax plus obinutuzumab	86.5%	80.6-91.1	<.001
Venetoclax, obinutuzumab, and ibrutinib	92.2%	87.3-95.7	<.001

Grade 3 and 4 infections were more common with chemoimmunotherapy (18.5%) and in the venetoclax, obinutuzumab, and ibrutinib arm (21.2%) than in the venetoclax plus rituximab arm (10.5%) or the venetoclax plus obinutuzumab arm (13.2%), Dr. Eichhorst and colleagues reported. See **TABLE 3** for the three-year PFS by treatment group.

TABLE 3. Three-Year PFS by Treatment Group

Treatment group	Three-year PFS rate	Hazard ratio (vs chemoimmunotherapy)	*P* value
Venetoclax, obinutuzumab, and ibrutinib	90.5%	0.32 (97.5% CI, 0.19- 0.54)	<.001
Venetoclax plus obinutuzumab	87.7%	0.42 (97.5% CI, 0.26- 0.68)	<.001
Venetoclax plus rituximab	80.8%	0.79 (97.5% CI, 0.53-1.18)	.18
Chemoimmunotherapy	75.5%	N/A	N/A

In all four groups, the treatment was temporary, in contrast to earlier studies that continued either venetoclax or ibrutinib, which prolongs exposure to side effects, dramatically increases the costs, and inevitably results in development of resistance, the authors reported in the press release.

"This study shows that with clever temporary and safe combinations, you can allow patients to be treatment-free in the long-term, with a much lower chance of developing resistance," **Arnon Kater, MD, PhD,** a Professor of Hematology at Amsterdam UMC and Chair of the HOVON CLL study group, said in a press release.[2]

Kater added that it might be possible to stop the combination therapy earlier than after one year.

"We now want to investigate this," Kater said. "This not only reduces side effects, but also health care costs."

This study was partially funded by AbbVie.

References

1. Eichhorst B, Niemann CU, Kater AP, et al. First-line venetoclax combinations in chronic lymphocytic leukemia. *N Engl J Med.* 2023;388(19):1739-1754. doi:10.1056/NEJMoa2213093

2. Combination therapy outperforms chemotherapy in patients with chronic lymphocytic leukaemia. EurekAlert. May 10, 2023. Accessed May 16, 2023. https://www.eurekalert.org/news-releases/988803

State of the Art from previous page

Should Cytoreduction Be Given to Patients with LR PV?

There is ongoing discussion as to the therapeutic paradigm for "confirmed" patients with LR PV who have been demonstrated to be at increased thrombotic risk compared with the general population, with a rate of 2% p-y. Periodic phlebotomies, with consequent Hct fluctuations and their ineffectiveness in treating leukocytosis, may not be sufficient to prevent vascular events.

Even though Hct control is often used as a surrogate endpoint of a reduced thrombosis risk, actual years of follow-up and number of patients under study are not enough to prove a protective vascular effect of ropeg-IFN-α2b in LR patients.

"One might hypothesize its administration in LR young cases if signs of hypermyeloproliferation or uncontrolled symptoms are present, or for curbing the need [for] and side effects of frequent [phlebotomies]," Drs. Mora and Passamonti wrote.

Considerations for Treatment Approaches

Current treatment approaches in PV include PEG-IFNs besides hydroxyurea for the first line and ruxolitinib for the second line, with some patients potentially also receiving PEG-IFN treatments in the latter setting.

The effect of ruxolitinib treatment on thrombosis has been documented. While a benefit of delaying PPV-MF progression is not evident with ruxolitinib, this is most likely due to the need for longer observation.

The use of ropeg-IFN is safe, and it exerts an important effect on the *JAK2* clone, whose significance requires a longer follow-up. Finally, low-dose aspirin continues to be important in PV.

"Additional efforts to understand disease progression are needed," the authors concluded.

Knowledge Hubs

In each issue of Blood Cancers Today*, we will take a closer look at a particular topic in hematologic malignancies. This month, we feature news in myelodysplastic syndromes and mantle cell lymphoma. Visit* BloodCancersToday.com *to view all of our Knowledge Hubs and stay up to date on the latest news in each area of hematologic oncology.*

MDS

Triplet Shows 'Encouraging Activity' in Patients with AML, Prior MDS

Eprenetapopt and venetoclax plus azacitidine had an "acceptable safety profile" as a frontline treatment for patients with *TP53*-mutated acute myeloid leukemia (AML), including patients with prior myelodysplastic syndromes (MDS), according to a phase I study.

Guillermo Garcia-Manero, MD, of the MD Anderson Cancer Center, and colleagues conducted the study and published its results in *The Lancet Haematology*.

The purpose of the open-label, dose-finding study was to evaluate the combination of eprenetapopt and venetoclax plus or minus azacitidine in patients with *TP53*-mutated AML. Eprenetapopt, also known as APR-246, is a first-in-class, small-molecule p53 reactivator.

Dr. Garcia-Manero and colleagues conducted the study at eight academic research hospitals in the United States, enrolling patients with treatment-naïve AML who were at least 18 years old and had at least one pathogenic *TP53* mutation. In dose-finding cohort one, patients received previous therapy with hypomethylating agents (HMAs) for MDS. In dose-finding cohort two, patients did not have previous use of HMAs.

Why I picked this article:

Kristen Pettit, MD

"Eprenetapopt (APR-246), a novel TP53 *reactivating agent, in combination with azacitidine and venetoclax showed promising safety and efficacy in this phase I study in patients with AML, including those patients with prior MDS."*

All patients received 28-day treatment cycles. In cohort one, patients received intravenous eprenetapopt 4.5 g/day on days one through four and oral venetoclax 400 mg/day on days one through 28. Patients in cohort two also received subcutaneous or intravenous azacitidine 75 mg/m^2 on days one through seven. The expansion portion of the study proceeded with patients enrolled in cohort two. The study's primary endpoints were safety in all cohorts and complete responses in the expansion cohort.

The study's investigators enrolled 49 patients across both cohorts, with six patients initially enrolled in each. However, after the researchers observed no dose-limiting toxicities, they expanded cohort two to enroll an additional 37 patients. The median patient age was 67 years, 49% of patients were female, and 82% were White.

The median length of follow-up was 9.5 months at data cutoff. The overall response rate in patients who received eprenetapopt and venetoclax plus azacitidine was 64%, while the complete response rate was 38%.

The researchers did not report any dose-limiting toxicities and determined the recommended phase II dose for the combination would be eprenetapopt 4.5 g/day on days one through four. The most common adverse events (AEs) of grade 3 or higher were febrile neutropenia, occurring in 47% of patients; thrombocytopenia, occurring in 37%; leukopenia, occurring in 25%; and anemia, occurring in 22%. Treatment-related serious AEs were reported in 27% of patients, including one treatment-related death from sepsis.

"Eprenetapopt and venetoclax with azacitidine had an acceptable safety profile and encouraging activity, supporting further frontline evaluation of this combination in the treatment of *TP53*-mutated acute myeloid leukemia," Dr. Garcia-Manero and colleagues concluded.

Reference

Garcia-Manero G, Goldberg AD, Winer ES, et al. Eprenetapopt combined with venetoclax and azacitidine in *TP53*-mutated acute myeloid leukaemia: a phase 1, dose-finding and expansion study. *Lancet Haematol.* 2023;10(4):e272-e283. doi:10.1016/s2352-3026(22)00403-3

MCL

PRMT5 Identified as Potential Target in MCL

A new study suggests a rationale for targeting PRMT5 in patients with relapsed or refractory mantle cell lymphoma (MCL) who have high mutation burdens.

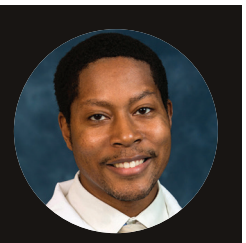
Yuxuan Che and **Yang Liu, PhD,** of the MD Anderson Cancer Center, and colleagues conducted the research and published their findings in *Blood Cancer Journal*.

They conducted the study because "recurrent relapses and therapy resistance" are "constant challenges" for treating patients with MCL, especially those who have somatic mutations in *ATM* and *TP53*. Those somatic mutations are "accumulated as therapy resistance emerges and the disease progresses," which is consistent with the researchers' OncoPrint results showing that *ATM* and *TP53* alterations were "most frequent" in relapsed or refractory MCL, they wrote.

The study showed PRMT5 was upregulated in relapsed or refractory MCL, which "predicted a poor prognosis," according to the authors. Furthermore, PRMT5 inhibitors "displayed profound antitumor effects" in murine models of MCL with mutated *ATM* and/or *TP53*, or those that were refractory to CD19-targeted chimeric antigen receptor T-cell therapy.

Genetic knockout of *PRMT5* "robustly inhibited" tumor growth in vivo, according to the study's authors.

Why I picked this article:



Tycel Phillips, MD

"Treatment of relapsed or refractory MCL remains difficult given the rapid proliferation and resistance to approved therapies. This study, while preliminary, hints at the role of PRMT5 as an effective target in MCL and suggests it might have potential to be combined with other agents that might impact DNA repair mechanisms."

"Co-targeting PRMT5 and ATR or CDK4 by using their inhibitors showed synergistic antitumor effects both in vitro and in vivo," they concluded. "Our results have provided a rational combination therapeutic strategy targeting multiple PRMT5-coordinated, tumor-promoting processes for the treatment of [relapsed or refractory] MCL with high mutation burdens."

Reference

Che Y, Liu Y, Yao Y, et al. Exploiting PRMT5 as a target for combination therapy in mantle cell lymphoma characterized by frequent *ATM* and *TP53* mutations. *Blood Cancer J.* 2023;13(1):27. doi:10.1038/s41408-023-00799-6

Clinical Trial Updates

Blood Cancers Today *shares clinical trials currently enrolling patients*

CPX-351 and Glasdegib for Newly Diagnosed AML with MDS-Related Changes or Therapy-Related AML

This phase II, single-arm, open-label clinical trial is evaluating the efficacy of CPX-351 in combination with glasdegib in patients who have acute myeloid leukemia (AML) with myelodysplastic syndromes (MDS)-related changes or therapy-related AML. The study's primary endpoint is the percentage of participants with event-free survival at six months. It is estimated to include 30 participants. The study's secondary endpoints include the percentage of grade 3-5 adverse events (AEs), the overall response rate, durability of response, overall survival of patients who received the combination of CPX-351 and glasdegib, time to normal hematopoiesis as assessed by laboratory studies, and the number of patients who go on to receive an allogeneic hematopoietic stem cell transplant.

Principal investigator: **Deepa Jeyakumar, MD**
Treatment agents: CPX-351, glasdegib
NCT04231851

A Phase I Study of YTB323 in CLL/SLL, DLBCL, and ALL

This first-in-human study is enrolling an estimated 225 patients. It will evaluate the feasibility, safety, and preliminary antitumor efficacy of YTB323, an autologous CD19-directed chimeric antigen receptor (CAR) T-cell therapy. YTB323 will be investigated in combination with ibrutinib in adults with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and as a single agent in adults with diffuse large B-cell lymphoma (DLBCL) or acute lymphoblastic leukemia (ALL).

The study's primary endpoints include the incidence and nature of dose-limiting toxicities and the incidence and severity of AEs and serious AEs, including changes in laboratory values, electrocardiogram, and vital signs. The study's other primary endpoints include the tolerability of ibrutinib dose modifications in the CLL/SLL arm and the manufacturing success of the CAR-T therapy, as measured by the number of patients who were infused with the planned target dose.

Principal investigator: **Nitin Jain, MD**
Treatment agents: YTB323, ibrutinib
NCT03960840

A Phase III Study of Acalabrutinib Plus R-CHOP in Previously Untreated DLBCL

In this phase III, randomized, double-blind, placebo-controlled study, researchers are evaluating adding acalabrutinib to R-CHOP in adults aged 70 years and younger with previously untreated nongerminal center DLBCL. All patients will receive standard R-CHOP chemotherapy and will be randomly assigned to also receive either acalabrutinib or a placebo. The study is enrolling an estimated 600 patients, and the primary endpoint is progression-free survival per the Lugano Classification.

To be eligible for this study, patients must be newly diagnosed with nongerminal center DLBCL. Other criteria include not receiving prior treatment for their cancer, and patients must be able to walk and do routine activities for more than half of their normal waking hours.

Principal investigator: **Paul Hamlin, MD**
Treatment agents: Acalabrutinib, R-CHOP
NCT04529772

Phase III Trial of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Therapy in Newly Diagnosed MM

This phase III trial is evaluating the conversion rate to measurable residual disease (MRD) negativity following the addition of daratumumab to lenalidomide relative to lenalidomide alone when administered as maintenance treatment. The study includes patients with newly diagnosed multiple myeloma (MM) who have not previously received anti-CD38 treatment and are MRD positive, as determined by next-generation sequencing (NGS) at screening, following high-dose therapy and autologous hematopoietic stem cell transplant.

The study's primary endpoint is the percentage of participants who are MRD-negative per NGS from baseline to 12 months after maintenance treatment.

Study director: **Janssen Research & Development, LLC**
Treatment agents: Daratumumab, lenalidomide alone
NCT03901963

Phase I Study of CB-5339 for Recurrent or Persistent AML or MDS

This phase I study is aiming to find the highest dose of the investigational drug CB-5339 that can be given safely in patients with recurrent or persistent AML or MDS. CB-5339 blocks the valosin-containing protein/p97 and is taken orally.

To be eligible for this study, patients must be aged 18 years or older and have recurrent or persistent AML or high-risk MDS, and at least two weeks should have passed since the completion of prior treatment and receipt of CB-5339. Patients must be able to walk and partake in routine activities for more than half of their normal waking hours.

Principal investigator: **Eytan M. Stein, MD**
Treatment agent: CB-5339
NCT04402541

Phase I Study of Ruxolitinib Plus Abemaciclib in Myelofibrosis

A phase I, dose-escalation trial evaluating the safety of ruxolitinib plus abemaciclib is now enrolling certain patients who have primary or secondary myelofibrosis.

The trial will enroll patients with intermediate-1, intermediate-2, or high-risk disease who require treatment and had an "inadequate response" to ruxolitinib.

The trial will follow a 3+3 dose-escalation design. Patients will receive increasing doses of abemaciclib and stable doses of ruxolitinib 10 mg or 15 mg twice daily.

The study's primary endpoint is to determine the maximum tolerated dose of ruxolitinib plus abemaciclib. Its secondary endpoints include measures of efficacy.

Principal investigator: **Raajit Rampal, MD, PhD**
Treatment agents: Ruxolitinib, abemaciclib
NCT05714072

Do you know of a clinical trial that's currently enrolling patients with hematologic malignancies? Tweet @Blood_Cancers to help spread the word.

HemOnc Happenings

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

Highest ASCO Honor Awarded to SOHO Co-Founder

Hagop M. Kantarjian, MD, FASCO, of the University of Texas MD Anderson Cancer Center, has received the David Karnofsky Memorial Award from the American Society of Clinical Oncology (ASCO), which is the society's highest honor.

Hagop M. Kantarjian, MD, FASCO

"Throughout a remarkable career, Dr. Kantarjian has contributed immensely to our mission of ending cancer. He not only advanced new treatments and furthered our knowledge of leukemia, but his leadership has inspired so many in the MD Anderson community," said **Peter WT Pisters, MD,** President of MD Anderson. "We congratulate Hagop on this exceptional achievement, and we thank him for the countless lives he has saved around the world."

Dr. Kantarjian, who co-founded the Society of Hematologic Oncology (SOHO) in 2012, serves as the Chair of the Department of Leukemia and currently holds the Samsung Distinguished University Chair in Cancer Medicine at the MD Anderson Cancer Center.

ASCO officials said in an announcement that Dr. Kantarjian is known for his practice-changing clinical-translational research in leukemia.

"In the past four decades, his research has transformed some standards of care and dramatically improved survival in several leukemia subtypes, including chronic myeloid leukemia, acute myeloid leukemia, myelodysplastic syndrome, and acute lymphocytic leukemia," according to ASCO.

Dr. Kantarjian has published more than 2,200 peer-reviewed manuscripts and more than 100 chapters, with an H-index of 203. He created the MD Anderson Leukemia Fellowship in 2000 and is "passionately involved in mentoring and education," ASCO officials said.

Dr. Kantarjian also has dedicated his career to the training and mentoring of clinicians and researchers focused on leukemia research and patient care, many of whom now provide exceptional treatment at institutions worldwide. These relationships have broadened Kantarjian's impact in the field and helped to extend knowledge far beyond the walls of MD Anderson.

He is a nonresident fellow in health care at the Rice Baker Institute and has "written extensively on important health care issues in cancer, including high cancer drug prices, the importance of universal equitable health care, health care safety nets and health care as a human right, drug shortages, the value of the Affordable Care Act, and others," according to the ASCO press release.

"Dr. Kantarjian's long list of accomplishments and groundbreaking discoveries are a testament to his lifelong commitment to impactful cancer research and patient care," said **Giulio Draetta, MD, PhD,** Chief Scientific Officer at MD Anderson. "As a community that strives to deliver cancer breakthroughs every day, we are immensely proud of him for receiving this well-deserved honor from ASCO."

Sources: ASCO, March 2023; University of Texas MD Anderson Cancer Center, April 2023

AACR Honors Clinicians, Researchers in Hematologic Oncology

The American Association for Cancer Research (AACR) honored several researchers and clinicians in the field of hematologic oncology during its annual meeting, which was held April 14-19, 2023, in Orlando, Florida.

Riccardo Dalla-Favera, MD, FAACR, of Columbia University, received the AACR Award for Outstanding Achievement in Blood Cancer Research.

Riccardo Dalla-Favera, MD, FAACR

"This award recognizes an individual on the basis of their meritorious achievements and contributions to any aspect of blood cancer research," AACR officials said in a news release.

Dr. Dalla-Favera, a Fellow of the AACR Academy, is being recognized for his "fundamental discoveries dedicated to characterizing the genetic drivers of human B-cell lymphomas and for uncovering new avenues for cancer prevention and therapy that have been routinely exploited clinically to diagnose and determine novel therapeutic strategies for B-cell lymphoma," according to the release.

Melissa Hudson, MD, of St. Jude Children's Research Hospital, received the AACR-Joseph H. Burchenal Award for Outstanding Achievement in Clinical Cancer Research.

Melissa Hudson, MD

She is being recognized for her "unrivaled clinical research involving hematological malignancies affecting children, adolescents, and young adults that has led to the establishment of the St. Jude Lifetime Cohort Study," AACR officials said. "This ongoing study catalogues comprehensive clinical data from over 6,000 five-year survivors of pediatric cancer, information that continues to be translated into practice-changing guidelines for pediatric cancer survivors."

Jun Yang, PhD, also of St. Jude Children's Research Hospital, received the AACR-Waun Ki Hong Award for Outstanding Achievement in Translational and Clinical Cancer Research.

Jun Yang, PhD

Dr. Yang is being recognized for his "inspiring contributions to genomic studies dedicated to analyzing therapeutic response rates in multiethnic pediatric acute lymphoblastic leukemia patient populations, which have resulted in the identification of a large number of genomic loci responsible for driving therapeutic response variability," according to the news release. "These findings are now being leveraged to predict treatment efficacy and toxicity in pediatric cancer populations."

The "award recognizes a worthy cancer researcher who has conducted highly meritorious translational and clinical cancer research anywhere in the world and who has not yet reached 51 years of age at the time of the award presentation," AACR officials said.

AACR also honored two researchers in the field of hematologic oncology in its AACR NextGen Stars program, which "provides an exciting opportunity to increase the visibility of early-career scientists at the AACR Annual Meeting and to support their professional development and advancement," organizers said.

Courtney Jones, PhD, and **Anastasia Tikhonova, PhD,** were both named AACR NextGen Stars. Dr. Jones gave a presentation titled "Targeting polyamine metabolism in acute myeloid leukemia stem cells" during the 2023 AACR Annual Meeting. Dr. Tikhonova gave a presentation titled "Dissecting immune microenvironment of T-cell acute lymphoblastic leukemia."

Courtney Jones, PhD

Anastasia Tikhonova, PhD

Drs. Jones and Tikhonova are both scientists at the Princess Margaret Cancer Centre and Assistant Professors at the University of Toronto.

Source: AACR, April 2023

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society of hematologic oncology

Faculty Speakers

SOHO 2023 will feature 145 internationally recognized experts presenting the latest findings in the field. Attend SOHO 2023 and participate in interactive exchanges and various engagement experiences with the experts! Go to **soho.click/program**.

Register Today

We are privileged to invite you to register for the Society of Hematologic Oncology Eleventh Annual Meeting (SOHO 2023) scheduled as a hybrid event on **September 6-9, 2023** at the GRB Convention Center in Houston, Texas. Register at **soho.click/2023**.

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