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Aziz Nazha, MD;
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and more

MAIL TO:

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Jerald Radich, MD
With guest editor
Jacob Appelbaum, MD, PhD

Is 'Inflamodulation' What's Missing From AML Immunotherapy?

An official publication of
soho
society of hematologic oncology

BCL-2=B-cell lymphoma 2; ERK=extracellular-signal–regulated kinase; JAK/STAT=Janus kinase signal transducer and activator of transcription; MAPK=mitogen-activated protein kinase; MEK=MAPK/ERK kinase; MF=myelofibrosis; PI3K=phosphoinositide 3-kinase; RAF=rapidly accelerated fibrosarcoma.

References: 1. Pettit K et al. *Curr Hematol Malig Rep*. 2017;12(6):611-624. **2.** Schieber M et al. *Blood Cancer J.* 2019;9(9):74. **3.** Santos FPS et al. *Hematol Oncol Clin North Am*. 2012;26(5):1083-1099. **4.** Gleitz HFE et al. *HemaSphere*. 2019;3(S2):142-145.

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MFTAKESHOLD

Beyond the surface of symptoms

MYELOFIBROSIS TIGHTENS ITS GRIP

MULTIPLE PATHWAYS DRIVE myelofibrosis progression[1,2]

Pathways include JAK/STAT, BCL-2 family, epigenetic regulators, PI3K, and RAF/MEK/ERK (MAPK)[1,2]

Targeting the downstream signaling may still permit **malignant stem cells to evade apoptosis** and the **disease to progress**[2,3]

Additional pathways allow the **continued survival of malignant clones driving the progression of the underlying disease**[3,4]

EXPLORE THE PATHWAYS CONTRIBUTING TO DISEASE PROGRESSION

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December 1–3
European Society for Medical Oncology (ESMO) Asia Congress 2023
Singapore

December 6–8
ESMO Immuno-Oncology Congress 2023
Geneva, Switzerland

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

February 2–4, 2024
Clinical Hematology & Oncology 2024 Conference
San Diego, California

February 22–24, 2024
Japanese Society of Medical Oncology Annual Meeting
Nagoya, Japan

February 29–March 3, 2024
28th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma
Miami Beach, Florida

March 4–6, 2024
American Association for Cancer Research Blood Cancer Discovery Symposium
Boston, Massachusetts

April 3–6, 2024
2024 American Society of Pediatric Hematology/Oncology Conference
Seattle, Washington

April 3–6, 2024
2024 Hematology/Oncology Pharmacy Association Annual Conference
Tampa, Florida

April 5–7, 2024
National Comprehensive Cancer Network 2024 Annual Conference
Orlando, Florida

April 5–10, 2024
American Association for Cancer Research Annual Meeting 2024
San Diego, California

April 12–14, 2024
9th Translational Research Conference
Budapest, Hungary

MARK YOUR CALENDARS
SEPTEMBER 4–7, 2024
2024 SOHO Annual Meeting
George R. Brown Convention Center
Houston, Texas

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When Will AI Be Ready for Prime Time in Blood Cancers?

In today's era of accelerating innovation, artificial intelligence (AI), driven by advances in machine learning, has become a ubiquitous presence in our lives. As the technology continues to make inroads in the field of hematologic oncology, experts anticipate that eventually AI will be used at every step of the patient journey and may even help ease clinician burnout, but first there are quite a few obstacles to overcome.

News

GET TO KNOW

Sarah Tasian, MD

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

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REZUROCK®
(belumosudil) tablets

An innovative way to treat ***cGVHD***[1-3]

For patients with cGVHD aged ≥12 years after failure of any 2 prior lines of systemic therapy, help them[1-3]

ROCK ON

INDICATION

REZUROCK® (belumosudil) is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Embryo-Fetal Toxicity:** Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose

Adverse Reactions

- The most common (≥ 20%) adverse reactions, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension
- Permanent discontinuation of REZUROCK due to adverse reactions occurred in 18% of patients. The adverse reactions which resulted in permanent discontinuation of REZUROCK in > 3% of patients included nausea (4%). Adverse reactions leading to dose interruption occurred in 29% of patients. The adverse reactions leading to dose interruption in ≥ 2% were infections (11%), diarrhea (4%), and asthenia, dyspnea, hemorrhage, hypotension, liver function test abnormal, nausea, pyrexia, edema, and renal failure with (2% each)
- Monitor total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at least monthly

Drug Interactions

- **Strong CYP3A Inducers:** Coadministration of REZUROCK with strong CYP3A inducers decreases belumosudil exposure, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with strong CYP3A inducers
- **Proton Pump Inhibitors:** Coadministration of REZUROCK with proton pump inhibitors decreases belumosudil exposure, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with proton pump inhibitors

Use in Specific Populations

- **Pregnancy:** Based on findings from animal studies and the mechanism of action, REZUROCK can cause fetal harm when administered to pregnant women. There are no available human data on REZUROCK use in pregnant women to evaluate for a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to the fetus

75% ORR[1,a,b]

(95% CI, 63-85; *P*<.0001)[1,4]

PRIMARY END POINT[1]

Clinically and statistically significant responses with the 200-mg once-daily dose of REZUROCK in a **real-world demographic**[c] of patients with cGVHD in the ROCKstar study.[1,4]

The ROCKstar study was an open-label phase 2 study comparing REZUROCK 200 mg once daily (n=66)[d] with REZUROCK 200 mg twice daily (n=66) in patients with cGVHD aged ≥12 years who received 2 to 5 prior lines of systemic therapy.[5]

- **Once-daily oral medication that targets both inflammation and fibrosis** through selective ROCK2 inhibition[1-3]
- **There was no death or new systemic therapy initiation in 62%** (95% CI, 46-74) of responders[b] (n=49) ≥1 year since response[1]
- **Clinically meaningful improvements in QOL were reported by 52% of patients**[e] (≥7-point reduction in LSS[f] summary score), based on an exploratory analysis of LSS data[1]
- **CS and CNI dose reductions** were experienced by 64% (n=42) and 42% (n=10) of patients, respectively[5,6]
- **Well-established safety profile** across 2 clinical studies[1]

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AE, adverse event; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CNI, calcineurin inhibitor; CR, complete response; CS, corticosteroid; ECP, extracorporeal photopheresis; FDA, US Food and Drug Administration; LSS, Lee Symptom Scale; NIH, National Institutes of Health; ORR, overall response rate; PPI, proton pump inhibitor; PR, partial response; QOL, quality of life; ROCK2, rho-associated coiled-coil-containing protein kinase-2.

[a]Proportion of patients who achieved CR or PR according to the 2014 NIH cGVHD Consensus Criteria in the 200-mg once-daily arm.[1]
[b]Based on a final analysis by the FDA (n=65).
[c]ROCKstar study select baseline patient characteristics (200-mg once-daily arm): median age of 53 years (range, 21-77); male, n=42 (64%); median of 3 prior lines of systemic therapy; median of 25 months (range, 2-162) from cGVHD diagnosis to enrollment; median prednisone-equivalent dose at enrollment of 0.20 mg/kg/d (range, 0.03-0.95); concomitant PPI use, n=33 (50%); ≥4 organs involved, n=33 (50%); previous aGVHD, n=42 (64%); refractory to prior line of systemic therapy, n=44 (79%)[g]; NIH-defined disease severity: n=46 (70%) severe, n=18 (27%) moderate, n=2 (3%) mild. Prior systemic therapies included corticosteroids (prednisone), n=65 (99%); tacrolimus, n=40 (61%); ECP, n=31 (47%); ibrutinib, n=22 (33%); and ruxolitinib, n=20 (30%).[5,6]
[d]The final FDA interpretation of the ROCKstar study omitted 1 patient from the REZUROCK 200-mg once-daily arm. As a result, there are minor differences between the ROCKstar publication, where n=66, and the Prescribing Information, where n=65.
[e]Through cycle 7 day 1.[1]
[f]The LSS is a 30-item, 7-subscale symptom scale and QOL measurement tool that evaluates the AEs of cGVHD in the categories of skin, vitality, lung, nutritional status, psychological functioning, eye and mouth.[7]
[g]Denominator excludes patients with unknown status.[1]

IMPORTANT SAFETY INFORMATION (cont)

Use in Specific Populations (cont)

- **Lactation:** There are no data available on the presence of belumosudil or its metabolites in human milk or the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions from belumosudil in the breastfed child, advise lactating women not to breastfeed during treatment with REZUROCK and for at least one week after the last dose
- **Pediatric Use:** The safety and effectiveness of REZUROCK have been established in pediatric patients 12 years and older. The safety and effectiveness of REZUROCK in pediatric patients less than 12 years old have not been established
- **Geriatric Use:** Of the 186 patients with chronic GVHD in clinical studies of REZUROCK, 26% were 65 years and older. No clinically meaningful differences in safety or effectiveness of REZUROCK were observed in comparison to younger patients
- **Renal and Hepatic Impairment:** Treatment with REZUROCK has not been studied in patients with pre-existing severe renal or hepatic impairment. For patients with pre-existing severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with REZUROCK

You are encouraged to report side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call **1-800-FDA-1088**. You may also contact Kadmon Pharmaceuticals, LLC, at **1-877-377-7862** to report side effects.

References: 1. REZUROCK. Package insert. Kadmon Pharmaceuticals, LLC; 2022. **2.** Zanin-Zhorov A, Weiss JM, Nyuydzefe MS, et al. Selective oral ROCK2 inhibitor down-regulates IL-21 and IL-17 secretion in human T cells via STAT3-dependent mechanism. *Proc Natl Acad Sci USA*. 2014;111(47):16814-16819. doi:10.1073/pnas.1414189111 **3.** Flynn R, Paz K, Du J, et al. Targeted Rho-associated kinase 2 inhibition suppresses murine and human chronic GVHD through a Stat3-dependent mechanism. *Blood*. 2016;127(17):2144-2154. doi:10.1182/blood-2015-10-678706 **4.** Data on file 1. Kadmon Pharmaceuticals, LLC; 2021. **5.** Cutler C, Lee SJ, Arai S, et al; on behalf of the ROCKstar Study Investigators. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. *Blood*. 2021;138(22):2278-2289. doi:10.1182/blood.2021012021 **6.** Data on file 2. Kadmon Pharmaceuticals, LLC; 2021. **7.** Lee SJ, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2002;8(8):444-452. doi:10.1053/bbmt.2002.v8.pm12234170

Please see Brief Summary of Prescribing Information on adjacent pages.

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MAT-US-2203323-v2.0-04/2023

REZUROCK® (belumosudil) tablets, for oral use **Rx Only**

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

REZUROCK is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of REZUROCK is 200 mg given orally once daily until progression of chronic GVHD that requires new systemic therapy.

Instruct the patient on the following:

- Swallow REZUROCK tablets whole. Do not cut, crush, or chew tablets.
- Take REZUROCK with a meal at approximately the same time each day *[see Clinical Pharmacology (12.3) in the full prescribing information]*.
- If a dose of REZUROCK is missed, instruct the patient to not take extra doses to make up the missed dose.

Treatment with REZUROCK has not been studied in patients with pre-existing severe renal or hepatic impairment. For patients with pre-existing severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with REZUROCK *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

2.2 Dose Modifications for Adverse Reactions

Monitor total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at least monthly.

Modify the REZUROCK dosage for adverse reactions as per **Table 1**.

Table 1: Recommended Dosage Modifications for REZUROCK for Adverse Reactions

Adverse Reaction	Severity*	REZUROCK Dosage Modifications
Hepatotoxicity *[see Adverse Reactions (6.1)]*	Grade 3 AST or ALT (5x to 20x ULN) or Grade 2 bilirubin (1.5x to 3x ULN)	Hold REZUROCK until recovery of bilirubin, AST and ALT to Grade 0–1, then resume REZUROCK at the recommended dose.
	Grade 4 AST or ALT (more than 20x ULN) or Grade ≥3 bilirubin (more than 3x ULN)	Discontinue REZUROCK permanently.
Other adverse reactions *[see Adverse Reactions (6.1)]*	Grade 3	Hold REZUROCK until recovery to Grade 0–1, then resume REZUROCK at the recommended dose level.
	Grade 4	Discontinue REZUROCK permanently.

*Based on CTCAE v 4.03

2.3 Dosage Modification Due to Drug Interactions

Strong CYP3A Inducers

Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with strong CYP3A inducers *[see Drug Interactions (7.1)]*.

Proton Pump Inhibitors

Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with proton pump inhibitors *[see Drug Interactions (7.1)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of belumosudil to pregnant rats and rabbits during the period organogenesis caused adverse developmental outcomes including embryo-fetal mortality and malformations at maternal exposures (AUC) less than those in patients at the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1) in the full prescribing information]*.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

Chronic Graft versus Host Disease

In two clinical trials (Study KD025-213 and Study KD025-208), 83 adult patients with chronic GVHD were treated with REZUROCK 200 mg once daily *[see Clinical Studies (14.1) in the full prescribing information]*. The median duration of treatment was 9.2 months (range 0.5 to 44.7 months).

Fatal adverse reaction was reported in one patient with severe nausea, vomiting, diarrhea and multi-organ failure.

Permanent discontinuation of REZUROCK due to adverse reactions occurred in 18% of patients. The adverse reactions which resulted in permanent discontinuation of REZUROCK in >3% of patients included nausea (4%). Adverse reactions leading to dose interruption occurred in 29% of patients. The adverse reactions leading to dose interruption in ≥2% were infections (11%), diarrhea (4%), and asthenia, dyspnea, hemorrhage, hypotension, liver function test abnormal, nausea, pyrexia, edema, and renal failure with (2% each).

The most common (≥20%) adverse reactions, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension.

Table 2 summarizes the nonlaboratory adverse reactions.

Table 2: Nonlaboratory Adverse Reactions in ≥10% Patients with Chronic GVHD Treated with REZUROCK

Adverse Reaction	REZUROCK 200 mg once daily (N=83)	
	All Grades (%)	Grades 3–4 (%)
Infections and infestations		
Infection (pathogen not specified)*	53	16
Viral infection†	19	4
Bacterial infection‡	16	4
General disorders and administration site conditions		
Asthenia§	46	4
Edema¶	27	1
Pyrexia	18	1

Table 2: Nonlaboratory Adverse Reactions in ≥10% Patients with Chronic GVHD Treated with REZUROCK (continued)

Adverse Reaction	REZUROCK 200 mg once daily (N=83)	
	All Grades (%)	Grades 3–4 (%)
Gastrointestinal		
Nausea#	42	4
Diarrhea	35	5
Abdominal painÞ	22	1
Dysphagia	16	0
Respiratory, thoracic and mediastinal		
Dyspneaß	33	5
Coughà	30	0
Nasal congestion	12	0
Vascular		
Hemorrhageè	23	5
Hypertension	21	7
Musculoskeletal and connective tissue		
Musculoskeletal painð	22	4
Muscle spasm	17	0
Arthralgia	15	2
Nervous system		
Headacheø	21	0
Metabolism and nutrition		
Decreased appetite	17	1
Skin and subcutaneous		
Rashý	12	0
Pruritus£	11	0

*infection with an unspecified pathogen includes acute sinusitis, device related infection, ear infection, folliculitis, gastroenteritis, gastrointestinal infection, hordeolum, infectious colitis, lung infection, skin infection, tooth infection, urinary tract infection, wound infection, upper respiratory tract infection, pneumonia, conjunctivitis, sinusitis, respiratory tract infection, bronchitis, sepsis, septic shock.
†includes influenza, rhinovirus infection, gastroenteritis viral, viral upper respiratory tract infection, bronchitis viral, Epstein-Barr viremia, Epstein-Barr virus infection, parainfluenzae virus infection, Varicella zoster virus infection, viral infection.
‡includes cellulitis, Helicobacter infection, Staphylococcal bacteremia, catheter site cellulitis, Clostridium difficile colitis, Escherichia urinary tract infection, gastroenteritis Escherichia coli, Pseudomonas infection, urinary tract infection bacterial.
§includes fatigue, asthenia, malaise.
¶includes edema peripheral, generalized edema, face edema, localized edema, edema.
#includes nausea, vomiting.
Þincludes abdominal pain, abdominal pain upper, abdominal pain lower.
ßincludes dyspnea, dyspnea exertional, apnea, orthopnea, sleep apnea syndrome.
àincludes cough, productive cough.
èincludes contusion, hematoma, epistaxis, increased tendency to bruise, conjunctival hemorrhage, hematochezia, mouth hemorrhage, catheter site hemorrhage, hematuria, hemothorax, purpura.
ðincludes pain in extremity, back pain, flank pain, limb discomfort, musculoskeletal chest pain, neck pain, musculoskeletal pain.
øincludes headache, migraine.
ýincludes rash, rash maculo-papular, rash erythematous, rash generalized, dermatitis exfoliative.
£includes pruritus, pruritus generalized.

Table 3 summarizes the laboratory abnormalities in REZUROCK.

Table 3: Selected Laboratory Abnormalities in Patients with Chronic GVHD Treated with REZUROCK

	REZUROCK 200 mg once daily		
	Grade 0–1 Baseline	Grade 2–4 Max Post	Grade 3–4 Max Post
Parameter	**(N)**	**(%)**	**(%)**
Chemistry			
Phosphate decreased	76	28	7
Gamma Glutamyl Transferase increased	47	21	11
Calcium decreased	82	12	1
Alkaline Phosphatase increased	80	9	0
Potassium increased	82	7	1
Alanine Aminotransferase increased	83	7	2
Creatinine increased	83	4	0
Hematology			
Lymphocytes decreased	62	29	13
Hemoglobin decreased	79	11	1
Platelets decreased	82	10	5
Neutrophil Count decreased	83	8	4

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on REZUROCK

Strong CYP3A Inducers

Coadministration of REZUROCK with strong CYP3A inducers decreases belumosudil exposure *[see Clinical Pharmacology (12.3) in the full prescribing information]*, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK when coadministered with strong CYP3A inducers *[see Dosage and Administration (2.3)]*.

Proton Pump Inhibitors

Coadministration of REZUROCK with proton pump inhibitors decreases belumosudil exposure *[see Clinical Pharmacology (12.3) in the full prescribing information]*, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK when coadministered with proton pump inhibitors *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action *[see Clinical Pharmacology (12.1) in the full prescribing information]*, REZUROCK can cause fetal harm when administered to pregnant women. There are no available human data on REZUROCK use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of belumosudil to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and embryo-fetal malformations at maternal exposures (AUC) approximately ≥3- (rat) and ≥0.07 (rabbit) times the human exposure (AUC) at the recommended dose (see Animal data). Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal data

Embryo-fetal development studies were conducted in rats with administration of belumosudil to pregnant animals during the period of organogenesis at oral doses of 25, 50, 150, and 300 mg/kg/day in a pilot study and doses of 15, 50, and 150 mg/kg/day in a pivotal study. In the pilot study, maternal toxicity and embryo-fetal developmental effects were observed. Maternal toxicity (reduced body weight gain) occurred at 150 and 300 mg/kg/day doses. Increased post-implantation loss occurred at 50 and 300 mg/kg/day. Fetal-malformations were observed at ≥50 mg/kg/day and included absence of anus and tail, omphalocele, and dome shaped head. The exposure (AUC) at 50 mg/kg/day in rats is approximately 3 times the human exposure at the recommended dose of 200 mg.

In an embryo-fetal developmental study in rabbits, pregnant animals administered oral doses of belumosudil at 50, 125, and 225 mg/kg/day during the period of organogenesis resulted in maternal toxicity and embryo-fetal developmental effects. Maternal toxicity (body weight loss and mortality) was observed at doses ≥125 mg/kg/day. Embryo-fetal effects were observed at doses ≥50 mg/kg/day and included spontaneous abortion, increased post-implantation loss, decreased percentage of live fetuses, malformations, and decreased fetal body weight. Malformations included those in the tail (short), ribs (branched, fused or deformed), sternebrae (fused), and neural arches (fused, misaligned, and deformed). The exposure (AUC) at 50 mg/kg/day in rabbits is approximately 0.07 times the human exposure at the recommended dose of 200 mg.

8.2 Lactation

Risk Summary

There are no data available on the presence of belumosudil or its metabolites in human milk or the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions from belumosudil in the breastfed child, advise lactating women not to breastfeed during treatment with REZUROCK and for at least one week after the last dose.

8.3 Females and Males of Reproductive Potential

REZUROCK can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with REZUROCK.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose of REZUROCK. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for at least one week after the last dose of REZUROCK.

Infertility

Females

Based on findings from rats, REZUROCK may impair female fertility. The effect on fertility is reversible *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

Males

Based on findings from rats and dogs, REZUROCK may impair male fertility. The effects on fertility are reversible *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.4 Pediatric Use

The safety and effectiveness of REZUROCK have been established in pediatric patients 12 years and older. Use of REZUROCK in this age group is supported by evidence from adequate and well-controlled studies of REZUROCK in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of drug substance, that the exposure of drug substance is expected to be similar between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients.

The safety and effectiveness of REZUROCK in pediatric patients less than 12 years old have not been established.

8.5 Geriatric Use

Of the 186 patients with chronic GVHD in clinical studies of REZUROCK, 26% were 65 years and older. No clinically meaningful differences in safety or effectiveness of REZUROCK were observed in comparison to younger patients.

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Is 'Inflamodulation' What's Missing From AML Immunotherapy?

Jerald Radich, MD
Associate Editor

Jacob Appelbaum, MD, PhD
Guest Editor

While many patients diagnosed with acute myeloid leukemia (AML) respond to initial treatment, relapse remains the major obstacle to cure. The application of chemotherapy to relapsed AML is unlikely to yield long-term responses, so alternative modalities are sorely needed. Hematopoietic stem cell transplant (HSCT), the only curative therapy for relapsed AML, relies on the combination of high-dose chemotherapy and the graft-versus-leukemia (GVL) effect. T-cell activation is a critical feature of GVL and appears to restore long-lasting tumor immune surveillance in a variety of otherwise fatal hematologic malignancies. Unfortunately, the often short-term clinical activity observed in trials of T-cell-activating therapies suggests that T-cell activation alone is insufficient to recreate the lasting antitumor immunity that characterizes successful GVL.

A growing number of studies suggest the inflammatory milieu created by AML drives AML progression and directly limits T-cell antitumor reactivity. This new understanding is driving the development of a new generation of immunotherapies that incorporates "inflamodulation" to combat or reverse the immunomodulatory effects of the AML inflammatory environment.

The Critical Role of T Cells in GVL

The foundational role T cells play in support of the clinical activity of HSCT is clear.[1] The additional infusion of T cells in the context of donor lymphocyte infusion can rescue failed HSCTs, while depleting grafts of T cells increases the risk of relapse.[2] These data are buttressed by the ability to isolate donor-derived, leukemia-reactive, activated cytotoxic T lymphocytes from patients after HSCT capable of eliminating leukemic stem cells.[3,4] Together, these experiments suggested that if only T cells could be sufficiently activated, anti-AML tumor surveillance could be restored and lead to durable cures without the side effects of transplant. Efforts to engineer leukemia-specific T-cell activation were attempts to make good on this promise.

The immune environment of AML opposes these efforts. At diagnosis and relapse, endogenous T cells within patients with AML are reactive to tumor antigens but exert ineffective immune responses.[5] In some ways, this is tautology: if immune surveillance were effective, AML would not manifest in the first place. Nonetheless, identification of leukemia-reactive T-cell receptor (TCR) clones[6-8] and high-dimensional mapping of T-cell states[9,10] from leukemic and post-treatment bone marrow samples has allowed the identification of mechanisms that stifle effective immune responses. More broadly, transcriptional profiling of large patient cohorts suggests that approximately 25% of patients with AML exhibit immune states that modulate patient outcomes.[11-14] These include proliferation of regulatory T cells[15] and accumulation of exhausted[16-18] or anergic[19] cytotoxic T lymphocytes, some of which may be reversible,[5] suggesting an avenue to therapeutic intervention. Efforts to modulate this immune inflammatory environment for therapeutic effect are called "inflamodulation."

Three approaches to synthetic leukemia-specific T-cell activation in patients are now maturing: (1) multispecific T-cell-activating antibodies, (2) transgenic delivery of engineered TCRs and chimeric antigen receptors (CARs), and (3) immune checkpoint blockade. The first two of these technologies share the strategy of providing synthetic antigenic signaling, while the third removes negative signals that suppress responses already present.

The clinical experience of flotetuzumab (MGD006) in a phase I/II trial supports the claim that T-cell activation alone is insufficient to induce lasting remissions in most patients.[20] While expression of CD123 was required for trial entry, the overall rate of complete remission (CR) or CR with incomplete hematologic recovery was only 18% following treatment with an optimized drug dosing scheme. However, remission was more likely in patients with bone marrow transcriptional gene signatures associated with neutrophil and macrophage infiltration and interferon (IFN)-γ production, even in patients with the usually dire *TP53* mutations.[21] These data support that combining T-cell activation with the proper inflammatory milieu is a requirement for producing the long-term remissions observed following transplant with hoped-for frequencies.

Evaluation of CARs targeting CD33,[22,23] CD123,[24,25] CLL1,[26] CD7,[27] FLT3,[28] and other antigens seems to further undermine claims that the root cause of failure is the lack of a suitable target antigen. Constructs targeting each of these antigens produce T-cell activation in vitro and in preclinical models but have not yet demonstrated clinical activity. As a result, it seems that only B-cell malignancies, including lymphocytic leukemia, lymphomas, and myeloma exhibit the proper environment to sustain long-term tumor immune surveillance following synthetic T-cell activation.

New Approaches to Immune-Environmental Engineering

"Immunotherapists" have recognized that T-cell activation alone is insufficient to overcome the powerful immune-suppressive effects of AML. As a result, novel classes of immune-active therapies that attempt to either reverse the effects of the inflammatory AML microenvironment or supply missing signals that sustain T-cell survival and antitumor activity are being evaluated.

Inflamodulation is increasingly recognized as a successful strategy for treating myeloproliferative neoplasms. The high frequency of *JAK2* mutations and the clinical activity

of JAK 2 inhibitors have led some investigators to explore combinations of JAK2 inhibition with AML-type therapies. Small studies have found the doublet combination of ruxolitinib with hypomethylating agents is seemingly rarely effective for the treatment of relapsed or refractory patients.[29,30] Nonetheless, while *JAK2* mutations are infrequent among patients with AML, activation of down stream JAK2 targets, such as STAT3, is common.[31] Thus, more specific and potent T-cell-activating strategies will be needed.

Super-charged T cells are coming, and the modularity of CAR designs leads these adoptive cell therapies to the forefront of inflamodulatory testing. Incorporating a secreted anti-IL6 antibody into the CAR design not only eliminated neurotoxicity and made cytokine release syndrome a rare or limited event, but also maintained high response rates (90% among the acute lymphocytic leukemia cohort).[32] Incorporation of secreted IL15 may provide both pro-survival and anti-immunosuppressive signals, thereby reversing the effects of myeloid-derived suppressor cells,[33] which are increased in AML.[34] Secreted IL15,[35] membrane-bound IL15,[36] and injected IL15-polymer conjugates[37] are therefore being explored.

While cytokines create a pro-survival milieu, a super-charged receptor "engine" may break through environmental limitations of T-cell responses. Traditional CAR designs contain CD3 and 4-1BB signaling domains, and "strapping on" additional signaling domains like CD40 may boost antigenic signals, while activation of MYD88 may favorably tune metabolism.[38] The number of these studies and their rapid pace suggest CAR technology is an ideal model and platform for evaluating the signals needed to generate lasting GVL.

Attempts to simultaneously limit inflammation and enhance T-cell reactivity may be generalized through modulation of IFNγ. In the case of flotetuzumab, IFNγ production is a strong marker of T-cell activity and balances antihost with antileukemic allo-reactivity;[39,40] therefore, modulating IFNγ is a promising strategy to boost GVL and antileukemic responses.[41] Boosting IL18 signaling is one novel and promising strategy. A potent soluble inducer of IFNγ, IL18 activity can be supplemented by providing a synthetic decoy-resistant IL18 (DR18),[42] while simultaneously removing exhausted T cells via administration of cyclophosphamide following haploidentical transplants[43] or providing memory cells through infusion of donor lymphocytes. It is uncertain whether this strategy seeking to supercharge GVL can be translated to clinical testing without undue toxicity.

The Best Weed Suppression Is a Healthy Crop

The inflammatory environment produced by AML not only limits T-cell antitumor surveillance but also drives disease progression. Working in zebrafish models of clonal hematopoiesis of indeterminant potential (CHIP), the laboratory of Lenard Zon[44] showed that inflammatory signals elaborated by CHIP clones limited the growth of normal hematopoietic stem cells (HSCs). Genetic evaluation of preleukemic CHIP clones revealed evolved resistance to inflammatory signals. These findings suggested a positive feedback loop in which preleukemic clones and leukemic stem cells are simultaneously a source of and resistant to inflammatory signals, setting up an environment that maintains an advantage for AML cells over residual normal HSCs.

Expression of genes responsive to inflammatory signaling is predictive of chemotherapy resistance[45] and improves risk stratification.[46] Nearly half of AMLs are enriched in expression of genes associated with inflammation.[47] In one study, mechanistic interrogations using short hairpin RNA (shRNA) screens found that mediators of inflammatory signaling were standout targets,[47] with hits converging on *MYB* and *SPI/PU.1,* which function as "master switches" linking monocytic differentiation with inflammatory signaling.[48] Additional shRNA screens also targeted an unstudied gene, *IRF2BP2,* which, upon investigation, similarly functions to repress inflammatory signaling. Findings that *IRF2BP2* knockdown restored sensitivity to TNFα and IL1β and promoted AML apoptosis confirm the generalized model and have since been supported by a growing number of studies, wherein resistance to inflammatory signals is a critical component of the AML microenvironment.

Attempts to synthetically engineer the positive lasting immune activation seen during GVL following HSCT without graft-versus-host disease is a worthy, if incompletely realized, goal. Is therapeutic modulation of the AML inflammatory microenvironment the missing key to engineering GVL-like AML responses? Such "inflamodulation" is an underexplored area of clinical research and tempting to pursue. The next wave of immunotherapies will be the first to explore applications of this new understanding.

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Editorial

Blood Cancers Today *invites leading experts in hematologic oncology to its editorial pages*

Questions on the Treatment of Patients with Lower-Risk MDS

Guillermo Garcia-Manero, MD

The results of two major randomized clinical trials for patients with anemia and lower-risk myelodysplastic syndromes (LR-MDS) were presented in 2023.[1,2] These results are expanding the treatment armamentarium for this patient population; therefore, it is timely to discuss contemporary issues regarding the management of LR-MDS. In this short review, I discuss how we classify and prognosticate patients with LR-MDS, the incorporation of luspatercept in the front-line treatment of anemia in LR-MDS, emerging data in MDS with deletion 5q (del5q), the development of oral hypomethylating agents (HMAs), and a potential role for hematopoietic stem cell transplantation (HSCT). I also briefly mention some investigational approaches for this disease.

Guillermo Garcia-Manero, MD

What Is Lower-Risk MDS?

The classification of LR-MDS has changed as better and more modern prognostic classifications have been developed. With the International Prognostic Scoring System (IPSS),[3] patients with LR-MDS included those with low- and intermediate-1-risk disease. This definition is more complex when using the IPSS-R[4] since its intermediate subgroup includes patients with diverse prognosis. Most clinical trials divide patients into groups of those who have more or less than 3.5 points, thus including patients with very low, low, and some intermediate risk. This concept is being challenged by the recently proposed IPSS-M classification.[5] This system incorporates next-generation sequencing results into the IPSS-R system, dividing patients into six different subsets. Using IPSS-M, patients with lower-risk disease are defined as those with very low-, low-, or moderately low-risk disease. Of importance, when comparing IPSS-R with IPSS-M at the individual patient level, prognosis usually worsens once molecular data are added. Therefore, a significant fraction of patients with LR-MDS by IPSS-R could be considered higher-risk (HR)-MDS when using IPSS-M. Some of these patients could be transfusion independent (TI) with no excess blasts but with expected poor prognosis. The question is whether they should be considered candidates for disease-modifying therapy, including HSCT.

Another important development is the identification of patients with clonal hematopoiesis of indeterminate potential/clonal cytopenia of unknown significance (CCUS). A recent classification,[6] the clonal hematopoiesis risk score (CHRS), allows for the prognostication of these groups of individuals. Although most individuals with CCUS will never need any therapy, it is possible that those patients with high-risk disease by CHRS could be candidates for some type of intervention. This approach is being explored in clinical trials.

To summarize, the incorporation of molecular data is modifying our definition of LR-MDS.

A 2023 Treatment Approach to Anemia in LR-MDS

Anemia is one of the most common manifestations of LR-MDS. It results in major toxicities for patients and requires significant resources. Anemia in LR-MDS has been traditionally mitigated with erythropoietin-stimulating agents (ESAs). This class of drugs has been the standard for several decades but was never formally studied in the United States in randomized trials. In 2020, luspatercept, a TGF-ß modulator, was shown to be superior against placebo in the second line for patients with refractory anemia with ring sideroblasts.[7] These patients are frequently characterized by the presence of mutations in the *SF3B1* gene. Based on these results and the mild toxicity profile of this agent, researchers designed the COMMANDS study,[1] and those results were recently published.[7] In this study, patients with refractory anemia with ring sideroblasts (RS+) and those without (RS−) with LR-MDS requiring transfusion of red cells who had not received prior therapy, including ESAs, were randomized to either luspatercept or darbopoetin alpha. Using an intent-to-treat analysis, the response rate was 58% for luspatercept versus 31% for ESA. In addition, the duration of response was significantly longer in the luspatercept arm. Response was defined as achieving transfusion independence, as well as an increment of hemoglobin of at least 1.5 g/dL.

When looking at different subsets of patients, luspatercept was superior in all subgroups (RS+, low and high transfusion burden, *SF3B1* mutated and unmutated, high and low erythropoietin [EPO] levels) except for the RS− subset where the response rate was lower but the duration of response longer with luspatercept. These results have created some controversy. For patients with RS+ disease or an EPO level over 200, the results of luspatercept are clearly superior, but for those patients with RS− disease it could be argued that either an ESA or luspatercept could be considered as a first-line option.

Should We Consider Treatment of TI Patients with LR-MDS?

The standard of care is to restrict any intervention to transfusion-dependent (TD) patients or those with symptomatic anemia. This approach is being challenged by recent data from the SINTRA-REV trial. In this study, patients with TI LR-MDS with del5q were randomized to two years of lenalidomide 5 mg daily versus placebo. Patients treated with low-dose lenalidomide remained TI for a significantly longer period compared with placebo. Over 90% of the patients in the lenalidomide arm achieved a cytogenetic response. Therefore, it is possible that this group of patients could also have longer survival than those in the placebo arm. These data suggest that early intervention is justified in TI patients if we have access to effective, safe agents in specific subsets of patients. Several clinical trials are currently being developed for TI patients.

Is There a Role for HMAs in LR-MDS?

We have access to three HMAs for MDS in the United States, azacitidine, decitabine, and the more recently developed oral agent decitabine/cedazuridine.[8] All of these agents are approved for most patients with MDS, including LR-MDS. That said, no prospective, randomized study using these agents has evaluated their role specifically in LR-MDS. A randomized study of CC-486 (oral azacitidine) failed to show improvement in survival in LR-MDS.[9] Recent data from the MD Anderson Cancer Center and studies with oral decitabine/cedazuridine that have been presented further support the common use of this class of agents in LR-MDS.[10] The development of other oral HMAs, such as ASTX030 or CC-486 could transform the care of these patients.

What About Stem Cell Transplant in LR-MDS?

In general, HSCT is not considered for patients with LR-MDS[11] because the early mortality and toxicities associated with HSCT offset any potential survival benefit. This concept could be challenged by the incorporation of the IPSS-M risk score worsening the predicted survival of some patients with LR-MDS, but it needs to be studied in a prospective, systematic fashion. Some of these patients could be considered for HSCT. Other examples include those with HMA failure and potentially those with clonal evolution or poor risk molecular features such as *EZH2* or *p53* mutations.

What Is Next?

It is of interest that we are witnessing significant progress in LR-MDS instead of HR-MDS, where several combination studies have failed to demonstrate improved outcomes.[12] In 2023, in addition to the results of the COMMANDS trial,[1] we saw the results of the IMERGE study[2] with imetelstat versus placebo in second-line LR-MDS patients with TD anemia. This agent perturbs telomerase activity. The results of this trial are currently being reviewed by the US Food and Drug Administration and may constitute another agent for our patients. In addition, several studies targeting *SF3B1*, IRAK, or IL-1, among others, are being evaluated in LR-MDS. Finally, we need to study agents targeting thrombocytopenia.

Editorial

TABLE. 2023 Treatment Algorithm for LR-MDS

Entity	First line	Second line
Del(5q) MDS, isolated anemia	Lenalidomide	ESA, HMA, allogeneic HSCT
Isolated anemia, very low-risk features	ESA, luspatercept	HMA, lenalidomide, allogeneic HSCT
RARS post-ESA	Luspatercept	HMA, lenalidomide, allogeneic HSCT
Other lower-risk MDS (bilineal cytopenia)	HMA	Allogeneic HSCT

In the **TABLE**, I propose a potential treatment approach for patients with LR-MDS. Areas of importance include combination studies to further improve results with luspatercept, further studies in TI populations, targeting of HR-CCUS, and better understanding of the role of HSCT in LR-MDS. Perhaps in the future, we will be able to write that the goals of therapy in LR-MDS are prevention of MDS when treating CCUS, or improvement of survival instead of just symptom and cytopenia control.

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Get to Know

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

Sarah Tasian, MD

Dr. Tasian, an Associate Professor of Pediatrics at the University of Pennsylvania School of Medicine and Chief of the Hematologic Malignancies Program and the Joshua Kahan Endowed Chair in Pediatric Leukemia Research at the Children's Hospital of Philadelphia (CHOP), discusses the path that took her to the best job in the world, silver linings along the way, and how unexpected lessons from patients can shape the future of medicine.

Where did you grow up and when did you know you were interested in medicine?

I spent most of my childhood in Houston, Texas. I decided around the age of 11 that I wanted to be a doctor, and I knew from an early age that I wanted to work in pediatrics. My mother was a teacher and head of a school, so all my summer jobs somehow involved working with children. In high school, I had a deep interest in science, which coalesced with my joy in working with children into the idea of pediatric medicine. During my first year of medical school, I was absolutely fascinated by oncology and thought this was a perfect marriage of scientific investigation and personally meaningful clinical medicine.

What led you to specialize in pediatric hematologic oncology?

The pediatrics aspect came from my upbringing being proximal to schools and children. I coached children on the summer league swim team and volunteered at camps. My worst summer job was selling scratchy plaid Catholic school uniforms. During my undergraduate education at the University of Notre Dame, I returned home to Houston to work in a neonatology basic science research lab at the Baylor College of Medicine. There, I had my first taste of doing pediatric-specific biomedical research, and it was exciting and impactful.

The oncology aspect came from recognizing all the opportunities for life-long scientific learning. During my training, I also saw how career paths in oncology could unfold in many ways. The ability to do research that could translate scientific discoveries into better clinical treatments for patients with life-threatening diseases quickly became a critical goal for me as I embarked upon my own career development.

I was fortunate to receive outstanding training in primary care during my pediatrics residency at Seattle Children's Hospital, although my interest was always in subspecialty care in hematology-oncology. We have incredible relationships with our patients that are deep and long. In pediatric oncology, we end up doing a lot of primary care for our patients along the way, and I remain so grateful for my Seattle training now as a subspecialist. I was so lucky to further that mentality during my pediatric hematology-oncology fellowship training at the University of California, San Francisco (UCSF), when I finally reached my long-set goal of becoming a pediatric oncologist.

> **"We are so grateful to the children and their families for donating their cells and participating in research."**

Was there a particular mentor or group of mentors who shaped your career path?

I was incredibly lucky to have amazing female physician-scientist mentors early in my career. I met one of them when I took a year out of medical school to work in a research lab at the National Institutes of Health (NIH)/National Cancer Institute in the Pediatric Oncology Branch through the Howard Hughes Medical Institute NIH Research Scholars program. During 2001 and 2002, I worked in the laboratory of **Crystal Mackall, MD,** who was relatively early in her own career at that time. I was amazed at her ability to care for patients with multiple-relapsed cancers on phase I clinical trials at the NIH while running a busy basic science research laboratory. Crystal and I have stayed in touch for over 20 years and have collaborated during the past several years via shared research pursuits. It has been so exciting to see her tremendous career trajectory and continued role modeling as a world-renowned cancer immunotherapist. She is now the Director of the Cancer Immunotherapy Program at Stanford University. She continues to be a wonderful mentor, scientific colleague, and friend.

Another truly impactful mentor is **Mignon Loh, MD,** who was my postdoctoral research fellowship mentor in pediatric hematology-oncology at UCSF. She is now the Division Chief at Seattle Children's Hospital and an internationally recognized expert in childhood leukemias. I first met Dr. Loh in 2006 when I was a pediatrics resident interviewing for fellowship. I thought immediately, "This is absolutely with whom I want to work and to be my mentor if I come here!"

This was a case of clouds having silver linings. I decided to go to UCSF for my fellowship because my then-boyfriend/fiancé—now husband—was training at UCSF for his urology residency. After being apart for many years during our training, amongst several time zones and two countries, we wanted to be in the same city. I might not have chosen UCSF had it not been for our personal circumstances, but I truly think it was the best thing that ever happened to me in my career, particularly in terms of joining Dr. Loh's lab. Now, 15-plus years later, Mignon remains my "forever mentor." She is a clinical research collaborator in her role as the Children's Oncology Group ALL Committee chair, a laboratory collaborator in several childhood leukemia research projects, and a close and trusted friend. In reflecting back upon these formative early years when I was young and just starting out, it is amazing to realize the longevity of these and other career mentors and life mentors. I have never forgotten the power of this gift and their investment in me.

You use an approach in your research program that has been described as bench-to-bedside, and bedside-back-to-bench. Can you speak about that phrase and how it informs your work?

I have always been interested in late-stage translational research, doing research at the bench with patient samples in our quest to unravel high-risk leukemia biology and discover how to disrupt it. The clinical medicine that I do and the care of children with high-risk leukemias and lymphomas is tied intimately to my research program in the laboratory and in early-phase clinical trials. In all these domains, we are trying to discover the Achilles heels of high-risk childhood leukemias and learn

Continued on page 19

NOW APPROVED

ELREXFIO™
(elranatamab-bcmm)
INJECTION FOR SUBCUTANEOUS USE | 44 mg/1.1 mL 76 mg/1.9 mL

In the treatment of relapsed or refractory multiple myeloma (RRMM)

DEEP RESPONSE IN SIGHT

Deep response defined as ≥VGPR.[1]

ELREXFIO is an off-the-shelf BCMA-directed bispecific immunotherapy indicated for the treatment of adult patients with RRMM who have received at least four prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.[2]

This accelerated approval is based on response rate and durability of response. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).[2]

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving ELREXFIO. Initiate treatment with ELREXFIO step-up dosing to reduce risk of CRS. Withhold ELREXFIO until CRS resolves or permanently discontinue based on severity.

Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) and serious and life-threatening reactions, can occur in patients receiving ELREXFIO. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment. Withhold ELREXFIO until the neurologic toxicity resolves or permanently discontinue based on severity.

Because of the risk of CRS and neurologic toxicity, including ICANS, ELREXFIO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ELREXFIO REMS.

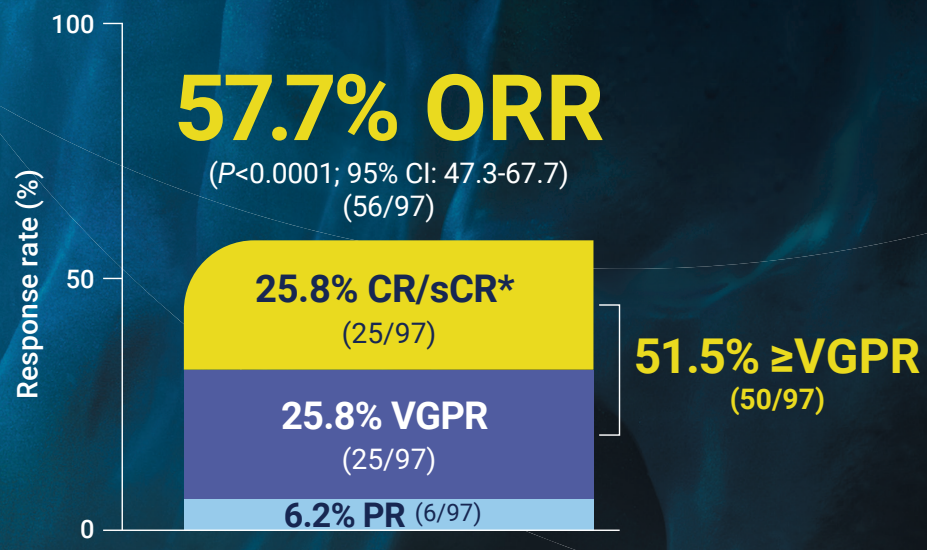
Cytokine Release Syndrome (CRS): ELREXFIO can cause CRS, including life-threatening or fatal reactions. In the clinical trial, CRS occurred in 58% of patients who received ELREXFIO at the recommended dose, with Grade 1 CRS in 44% of patients, Grade 2 CRS in 14% of patients, and Grade 3 CRS in 0.5% of patients. Recurrent CRS occurred in 13% of patients. Most patients experienced CRS after the first step-up dose (43%) or the second step-up dose (19%), with 7% of patients having CRS after the first treatment dose and 1.6% of patients after a subsequent dose. The median time to onset of CRS was 2 (range: 1-9) days after the most recent dose, with a median duration of 2 (range: 1-19) days.

Clinical signs and symptoms of CRS may include, but are not limited to, fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes.

Initiate therapy according to the ELREXFIO step-up dosing schedule to reduce risk of CRS and monitor patients following administration of ELREXFIO accordingly. Administer pretreatment medications prior to each dose in the step-up dosing schedule to reduce risk of CRS.

Delivered deep and durable responses[2,3]

The majority of BCMA-naïve patients who had ≥4 prior lines of therapy achieved an objective response (primary endpoint)



- Median follow-up was 10.2 months; range 0.2-20.1 months
- Among responding patients, the DoR rate at 9 months was 82.3%

- The most common adverse reactions (≥20%) were CRS (58%), fatigue (43%), injection-site reaction (37%), diarrhea (36%), upper respiratory tract infection (34%), musculoskeletal pain (34%), pneumonia (32%), decreased appetite (26%), rash (25%), cough (24%), nausea (22%), and pyrexia (21%)[2,†]
- The most common Grade 3/4 laboratory abnormalities (≥30%) were decreased lymphocytes (84%), decreased neutrophils (51%), decreased hemoglobin (43%), decreased white blood cells (40%), and decreased platelets (32%)[2,†]

*CR was achieved by 13.4% (13/97) of patients and sCR was achieved by 12.4% (12/97) of patients.[3]

†Safety population was comprised of the 183 patients (those with and without prior BCMA-directed therapy) who received the recommended step-up doses of 12 mg (Day 1) and 32 mg (Day 4).[2]

Study design: MagnetisMM-3 was an open-label, single-arm, non-randomized, multicenter, Phase 2 study in 187 adult patients with RRMM refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb. Of these patients, 183 received the recommended dosing regimen, and after 2 step-up doses of ELREXFIO, received 76 mg once weekly for Weeks 2 through 24, reduced to once every 2 weeks if a partial response or better was achieved and maintained for ≥2 months. The primary endpoint was ORR as assessed by BICR per IMWG criteria.[2,3]

IMPORTANT SAFETY INFORMATION (CONT'D)

Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, evaluate patients immediately for hospitalization. Manage CRS according to the recommendations and consider further management per current practice guidelines. Withhold or permanently discontinue ELREXFIO (elranatamab-bcmm) based on severity.

Neurologic Toxicity Including ICANS: ELREXFIO can cause serious or life-threatening neurologic toxicity, including ICANS.

In the clinical trial, neurologic toxicity occurred in 59% of patients who received ELREXFIO at the recommended dose, with Grade 3 or 4 neurologic toxicity occurring in 7% of patients. Neurologic toxicities included headache (18%), encephalopathy (15%), motor dysfunction (13%), sensory neuropathy (13%), and Guillain-Barré Syndrome (0.5%).

In the clinical trial, ICANS occurred in 3.3% of patients who received ELREXFIO at the recommended dose. Most patients had ICANS after the first step-up dose (2.7%), 1 (0.5%) patient had ICANS after the second step-up dose, and 1 (0.5%) patient had ICANS after subsequent dose(s). Recurrent ICANS occurred in 1.1% of patients. The median time to onset was 3 (range: 1-4) days after the most recent dose, with a median duration of 2 (range: 1-18) days. The most frequent clinical manifestations of ICANS included a depressed level of consciousness and Grade 1 or Grade 2 immune effector cell-associated encephalopathy (ICE) scores. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Counsel patients to seek medical attention should signs or symptoms of neurologic toxicity occur. Monitor patients for signs and symptoms of neurologic toxicities during treatment with ELREXFIO. At the first sign of neurologic toxicity, including ICANS, evaluate and treat patients immediately based on severity. Withhold or permanently discontinue ELREXFIO based on severity per recommendations and consider further management per current practice guidelines.

Due to the potential for neurologic toxicity, including ICANS, patients receiving ELREXFIO are at risk of depressed level of consciousness. Advise patients not to drive or operate heavy or potentially dangerous machinery for 48 hours after completing each of the 2 step-up doses and the first treatment dose within the ELREXFIO step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until symptoms resolve.

REMS: ELREXFIO is available only through a restricted program under a REMS called the ELREXFIO REMS because of the risks of CRS and neurologic toxicity, including ICANS.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.

Off-the-shelf, subcutaneous administration[2]

- Offers the convenience of a ready-to-use, single-dose vial, and no weight-based dosing
- Initiated with a step-up dosing schedule (Days 1, 4, and 8), then given once weekly
  - Due to the risk of CRS, patients should be hospitalized for 48 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose
- Weekly dosing should transition to every 2 weeks in patients who have received at least 24 weeks of treatment and achieved a partial response or better and maintained this response for at least 2 months

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ELREXFIO™
(elranatamab-bcmm)
INJECTION FOR SUBCUTANEOUS USE | 44 mg/1.1 mL 76 mg/1.9 mL

After Week 24

QW to Q2W DOSING

in responding patients[2]

LEARN MORE AT
ELREXFIOhcp.com

IMPORTANT SAFETY INFORMATION (CONT'D)

Hepatotoxicity: ELREXFIO can cause hepatotoxicity. In the clinical trial, elevated ALT occurred in 36% of patients, with Grade 3 or 4 ALT elevation occurring in 3.8%; elevated AST occurred in 40% of patients, with Grade 3 or 4 AST elevation occurring in 6%. Grade 3 or 4 total bilirubin elevations occurred in 0.5% of patients. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold ELREXFIO or consider permanent discontinuation of ELREXFIO based on severity.

Infections: ELREXFIO can cause severe, life-threatening, or fatal infections. In the clinical trial, in patients who received ELREXFIO at the recommended dose, serious infections, including opportunistic infections, occurred in 42% of patients, with Grade 3 or 4 infections in 31% and fatal infections in 7%. The most common serious infections reported (≥5%) were pneumonia and sepsis.

Do not initiate treatment with ELREXFIO in patients with active infections. Monitor patients for signs and symptoms of infection prior to and during treatment with ELREXFIO and treat appropriately. Withhold or permanently discontinue ELREXFIO based on severity. Administer prophylactic antimicrobial and antiviral medications according to current practice guidelines. Consider treatment with subcutaneous or intravenous immunoglobulin (IVIG) as appropriate.

Neutropenia: ELREXFIO can cause neutropenia and febrile neutropenia. In patients who received ELREXFIO at the recommended dose in the clinical trial, decreased neutrophils occurred in 62% of patients, with Grade 3 or 4 decreased neutrophils in 51%. Febrile neutropenia occurred in 2.2% of patients.

Monitor complete blood cell counts at baseline and periodically during treatment. Provide supportive care according to current practice guidelines. Monitor patients with neutropenia for signs of infection. Withhold ELREXFIO based on severity.

Embryo-Fetal Toxicity: Based on its mechanism of action, ELREXFIO may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ELREXFIO and for 4 months after the last dose.

Adverse Reactions: In patients who received ELREXFIO, the most common adverse reactions (incidence ≥20%) were CRS, fatigue, injection-site reaction, diarrhea, upper respiratory tract infection, musculoskeletal pain, pneumonia, decreased appetite, rash, cough, nausea, and pyrexia. The most common Grade 3 or 4 laboratory abnormalities (≥30%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased white blood cells, and decreased platelets.

INDICATION AND USAGE

ELREXFIO is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

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

BCMA=B-cell maturation antigen; BICR=Blinded Independent Central Review; CD=cluster of differentiation; CR=complete response; CRS=cytokine release syndrome; DoR=duration of response; IMiD=immunomodulatory drug; IMWG=International Myeloma Working Group; mAb=monoclonal antibody; ORR=objective response rate; PI=proteasome inhibitor; PR=partial response; QW=once weekly; Q2W=once every 2 weeks; sCR=stringent complete response; VGPR=very good partial response.

References: 1. Harousseau J-L, Avet-Loiseau H, Attal M, et al. Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: long-term analysis of the IFM 99-02 and 99-04 trials. *J Clin Oncol*. 2009;27:5720-5726. doi:10.1200/JCO.2008.21.1060
2. ELREXFIO Prescribing Information. New York, NY: Pfizer Inc. **3.** Data on file. Pfizer Inc., New York, NY.

Brief Summary of Prescribing Information

ELREXFIO (elranatamab-bcmm) injection, for subcutaneous use

Initial US Approval: 2023

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

- **Cytokine Release Syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving ELREXFIO. Initiate treatment with ELREXFIO step-up dosing schedule to reduce the risk of CRS. Withhold ELREXFIO until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration in Full Prescribing Information, Warnings and Precautions]*.**
- **Neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and serious and life-threatening reactions, can occur in patients receiving ELREXFIO. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment. Withhold ELREXFIO until the neurologic toxicity resolves or permanently discontinue based on severity *[see Dosage and Administration in Full Prescribing Information, Warnings and Precautions]*.**
- **Because of the risk of CRS and neurologic toxicity, including ICANS, ELREXFIO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ELREXFIO REMS *[see Warnings and Precautions]*.**

INDICATION AND USAGE

ELREXFIO is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

This indication is approved under accelerated approval based on response rate and durability of response *[see Clinical Studies]*. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome (CRS): ELREXFIO can cause CRS, including life-threatening or fatal reactions *[see Adverse Reactions]*.

In the clinical trial, CRS occurred in 58% of patients who received ELREXFIO at the recommended dosing schedule *[see Dosage and Administration in Full Prescribing Information]*, with Grade 1 CRS in 44% of patients, Grade 2 CRS in 14% of patients, and Grade 3 CRS in 0.5% of patients. Recurrent CRS occurred in 13% of patients. Most patients experienced CRS after the first step-up dose (43%) or the second step-up dose (19%), with 7% of patients having CRS after the first treatment dose and 1.6% of patients after a subsequent dose. The median time to onset of CRS was 2 (range: 1 to 9) days after the most recent dose, with a median duration of 2 (range: 1 to 19) days.

Clinical signs and symptoms of CRS may include, but are not limited to, fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes.

Initiate therapy according to the ELREXFIO step-up dosing schedule to reduce risk of CRS and monitor patients following administration of ELREXFIO accordingly *[see Dosage and Administration in Full Prescribing Information]*. Administer pre-treatment medications prior to each dose in the step-up dosing schedule to reduce risk of CRS *[see Dosage and Administration in Full Prescribing Information]*.

Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, evaluate patients immediately for hospitalization. Manage CRS according to the recommendations and consider further management per current practice guidelines. Withhold or permanently discontinue ELREXFIO based on severity *[see Dosage and Administration in Full Prescribing Information]*.

ELREXFIO is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

Neurologic Toxicity, Including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS): ELREXFIO can cause serious or life-threatening neurologic toxicity, including ICANS *[see Adverse Reactions]*.

In the clinical trial, neurologic toxicity occurred in 59% of patients who received ELREXFIO at the recommended dosing schedule *[see Dosage and Administration in Full Prescribing Information]*, with Grade 3 or 4 neurologic toxicity occurring in 7% of patients. Neurologic toxicities included headache (18%), encephalopathy (15%), motor dysfunction (13%), sensory neuropathy (13%), and Guillain-Barré Syndrome (0.5%).

In the clinical trial, ICANS occurred in 3.3% of patients who received ELREXFIO at the recommended dosing schedule *[see Dosage and Administration in Full Prescribing Information]*. Most patients had ICANS after the first step-up dose (2.7%), 1 (0.5%) patient had ICANS after the second step-up dose and 1 (0.5%) patient had ICANS after subsequent dose(s). Recurrent ICANS occurred in 1.1% of patients. The median time to onset was 3 (range: 1 to 4) days after the most recent dose, with a median duration of 2 (range: 1 to 18) days. The most frequent clinical manifestations of ICANS included a depressed level of consciousness and Grade 1 or Grade 2 Immune Effector Cell-Associated Encephalopathy (ICE) scores. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Counsel patients to seek medical attention should signs or symptoms of neurologic toxicity occur. Monitor patients for signs and symptoms of neurologic toxicities during treatment with ELREXFIO. At the first sign of neurologic toxicity, including ICANS, evaluate and treat patients immediately based on severity. Withhold or permanently discontinue ELREXFIO based on severity per recommendations *[see Dosage and Administration in Full Prescribing Information]* and consider further management per current practice guidelines.

Due to the potential for neurologic toxicity including ICANS, patients receiving ELREXFIO are at risk of depressed level of consciousness. Advise patients not to drive or operate heavy or potentially dangerous machinery during the ELREXFIO step-up dosing schedule and for 48 hours after completing each of the 2 step-up doses and the first treatment dose within the ELREXFIO step-up dosing schedule and in the event of new onset of any neurological toxicity symptoms until symptoms resolve *[see Dosage and Administration in Full Prescribing Information]*.

ELREXFIO is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

ELREXFIO REMS: ELREXFIO is available only through a restricted program under a REMS called the ELREXFIO REMS because of the risks of CRS and neurologic toxicity, including ICANS *[see Warnings and Precautions]*.

Notable requirements of the ELREXFIO REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Prescribers must counsel patients receiving ELREXFIO about the risk of CRS and neurologic toxicity, including ICANS, and provide patients with ELREXFIO Patient Wallet Card.
- Pharmacies and healthcare settings that dispense ELREXFIO must be certified with the ELREXFIO REMS program and must verify prescribers are certified through the ELREXFIO REMS program.
- Wholesalers and distributers must only distribute ELREXFIO to certified pharmacies or healthcare settings.

Further information about the ELREXFIO REMS program is available at www.ELREXFIOREMS.com or by telephone at 1-844-923-7845.

Infections: ELREXFIO can cause severe, life-threatening, or fatal infections. In the clinical trial, in patients who received ELREXFIO according to the recommended dosing schedule, serious infections, including opportunistic infections, occurred in 42% of patients, with Grade 3 or 4 infections in 31%, and fatal infections in 7%. The most common serious infections reported (≥5%) were pneumonia and sepsis *[see Adverse Reactions]*.

Do not initiate treatment with ELREXFIO in patients with active infections. Monitor patients for signs and symptoms of infection prior to and during treatment with ELREXFIO and treat appropriately. Withhold or permanently discontinue ELREXFIO based on severity *[see Dosage and Administration in Full Prescribing Information]*. Administer prophylactic antimicrobial and anti-viral medications according to current practice guidelines. Consider treatment with subcutaneous or intravenous immunoglobulin (IVIG) as appropriate.

Neutropenia: ELREXFIO can cause neutropenia and febrile neutropenia. In patients who received ELREXFIO at the recommended dose in the clinical trial, decreased neutrophils occurred in 62% of patients, with Grade 3 or 4 decreased neutrophils in 51%. Febrile neutropenia occurred in 2.2% of patients *[see Adverse Reactions]*.

Monitor complete blood cell counts at baseline and periodically during treatment. Provide supportive care according to current practice guidelines. Monitor patients with neutropenia for signs of infection. Withhold ELREXFIO based on severity *[see Dosage and Administration in Full Prescribing Information]*.

Hepatotoxicity: ELREXFIO can cause hepatotoxicity. In the clinical trial, elevated ALT occurred in 36% of patients, with Grade 3 or 4 ALT elevation occurring in 3.8%; elevated AST occurred in 40% of patients, with Grade 3 or 4 AST elevation occurring in 6%. Grade 3 or 4 total bilirubin elevations occurred in 0.5% of patients *[see Adverse Reactions]*. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold ELREXFIO or consider permanent discontinuation of ELREXFIO based on severity *[see Dosage and Administration in Full Prescribing Information]*.

Embryo-Fetal Toxicity: Based on its mechanism of action, ELREXFIO may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ELREXFIO and for 4 months after the last dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions]*.
- Neurologic Toxicity, Including ICANS *[see Warnings and Precautions]*.
- Infections *[see Warnings and Precautions]*.
- Neutropenia *[see Warnings and Precautions]*.
- Hepatotoxicity *[see Warnings and Precautions]*.

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

Relapsed/Refractory Multiple Myeloma

MagnetisMM-3

The safety of ELREXFIO was evaluated in MagnetisMM-3 *[see Clinical Studies in Full Prescribing Information]*. The safety population described (n = 183) includes patients who received the recommended dosage regimen of 12 mg subcutaneously on Day 1, 32 mg on Day 4, and 76 mg once weekly starting on Day 8. Among patients who received ELREXFIO, 42% were exposed for 6 months or longer and 9% were exposed for one year or longer.

The median age of patients who received ELREXFIO was 68 years (range: 36 to 88 years); 48% were female; 61% were White, 10% were Hispanic/Latino, 9% were Asian, and 6% were Black or African American.

Serious adverse reactions occurred in 68% of patients who received ELREXFIO at the recommended dosing schedule. Serious adverse reactions in >2% of patients included pneumonia (25%), sepsis (13%), CRS (13%), upper respiratory tract infection (4.4%), acute kidney injury (3.8%), urinary tract infection (3.3%), COVID-19 (3.3%), encephalopathy (3.3%), pyrexia (2.2%), and febrile neutropenia (2.2%). Fatal adverse reactions occurred in 10% of patients including pneumonia (3.3%), sepsis (2.7%), acute respiratory distress syndrome (0.5%), cardio-respiratory arrest (0.5%), cardiogenic shock (0.5%), cardiopulmonary failure (0.5%), COVID-19 (0.5%), failure to thrive (0.5%), and pulmonary embolism (0.5%).

Permanent discontinuations of ELREXFIO due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of ELREXFIO in >2% of patients included septic shock (2.2%).

Dosage interruptions of ELREXFIO due to an adverse reaction occurred in 73% of patients. Adverse reactions which resulted in dose interruptions of ELREXFIO in >5% of patients included neutropenia, COVID-19, upper respiratory tract infection, pneumonia, thrombocytopenia, and anemia.

The most common adverse reactions (≥20%) were CRS, fatigue, injection site reaction, diarrhea, upper respiratory tract infection, musculoskeletal pain, pneumonia, decreased appetite, rash, cough, nausea, and pyrexia. The most common Grade 3 to 4 laboratory abnormalities (≥30%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased white blood cells, and decreased platelets.

Table 1 summarizes adverse reactions in MagnetisMM-3.

Table 1. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Multiple Myeloma Who Received ELREXFIO in MagnetisMM-3

System Organ Class Preferred Term	ELREXFIO (N = 183)	
	All Grades (%)	Grade 3 or 4 (%)
Immune system disorders		
Cytokine release syndrome	58	0.5[#]
Hypogammaglobulinemia[*]	13	2.2[#]
General disorders and site administration conditions		
Fatigue[*]	43	6[#]
Injection site reaction[*]	37	0
Pyrexia	21	2.7[#]
Edema[*]	18	1.1[#]
Gastrointestinal disorders		
Diarrhea	36	1.1[#]
Nausea	22	0
Constipation	15	0
Vomiting	14	0
Infections		
Upper respiratory tract infection[*]	34	4.9
Pneumonia[a]	32	19

System Organ Class Preferred Term	ELREXFIO (N = 183)	
Sepsis[b]	15	11
Urinary tract infection[*]	12	4.4[#]
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[*]	34	2.7[#]
Metabolism and nutrition disorders		
Decreased appetite	26	1.1[#]
Skin and Subcutaneous Tissue disorders		
Rash[c]	25	0
Dry skin	13	0
Skin exfoliation[*]	10	0
Respiratory, thoracic and mediastinal disorders		
Cough[*]	24	0
Dyspnea[*]	15	3.3[#]
Nervous system disorders		
Headache	18	0.5
Encephalopathy[d]	15	2.7
Sensory neuropathy[e]	13	0.5[#]
Motor dysfunction[f]	13	2.2[#]
Cardiac disorders		
Cardiac arrhythmia[*]	16	2.2
Vascular disorders		
Hemorrhage[*]	13	1.6
Psychiatric disorders		
Insomnia	13	0
Injury, poisoning and procedural complications		
Fall	10	0.5[#]

Adverse reactions were graded based on CTCAE Version 5.0, with the exception of CRS, which was graded based on the ASTCT 2019 criteria.

* Includes other related terms.

\# Only grade 3 adverse reactions occurred.

a. Pneumonia includes COVID-19 pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia influenzal, pneumonia pseudomonal, pneumonia viral.

b. Sepsis includes bacteremia, device related bacteremia, device related sepsis, escherichia bacteremia, escherichia sepsis, klebsiella sepsis, pseudomonal sepsis, sepsis, septic shock, staphylococcal bacteremia, staphylococcal sepsis, streptococcal sepsis, urosepsis.

c. Rash includes erythema, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash pustular, symmetrical drug-related intertriginous and flexural exanthema.

d. Encephalopathy includes agitation, altered state of consciousness, cognitive disorder, confusional state, delirium, depressed level of consciousness, disorientation, hallucination, lethargy, memory impairment, mental status changes, metabolic encephalopathy, somnolence, toxic encephalopathy.

e. Sensory neuropathy includes burning sensation, dysesthesia, hypoesthesia, neuropathy peripheral, paresthesia, parosmia, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, sensory loss.

f. Motor dysfunction includes ataxia, balance disorder, gait disturbance, motor dysfunction, muscle contracture, muscle spasms, muscular weakness, peripheral motor neuropathy, peroneal nerve palsy, tremor.

Clinically relevant adverse reactions in <10% of patients who received ELREXFIO included ICANS, febrile neutropenia, Guillain-Barré Syndrome, abdominal pain, acute kidney injury, COVID-19, cardiac failure, congestion, and thrombosis.

Table 2 summarizes laboratory abnormalities in MagnetisMM-3.

Table 2. Select Laboratory Abnormalities (≥30%) That Worsened from Baseline in Patients with Relapsed or Refractory Multiple Myeloma Who Received ELREXFIO in MagnetisMM-3[a]

Laboratory Abnormality	ELREXFIO[b]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocyte count decreased	91	84
White blood cell decreased	69	40
Hemoglobin decreased	68	43
Neutrophil count decreased	62	51
Platelet count decreased	61	32
Chemistry		
Albumin decreased	55	6
AST increase	40	6
Creatinine increased	38	3.3
Potassium decreased	36	8
ALT increase	36	3.8
Alkaline phosphatase increased	34	1.1
Creatinine clearance decreased	32	10

a. Laboratory tests were graded according to NCI-CTCAE Version 5.0.

b. The denominator used to calculate the rate varied from 181 to 183 based on the number of patients with a baseline value and at least one post-treatment value.

DRUG INTERACTIONS

For certain CYP substrates, minimal changes in the concentration may lead to serious adverse reactions. Monitor for toxicity or drug concentrations of such CYP substrates when co-administered with ELREXFIO.

ELREXFIO causes release of cytokines *[see Clinical Pharmacology in Full Prescribing Information]* that may suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of ELREXFIO on Day 1 and up to 14 days after the 32 mg dose on Day 4 and during and after CRS *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy:

Risk Summary

Based on the mechanism of action, ELREXFIO may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology in Full Prescribing Information]*. There are no available data on the use of ELREXFIO in pregnant women to evaluate for a drug associated risk. No animal reproductive or developmental toxicity studies have been conducted with ELREXFIO. Elranatamab-bcmm causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. In addition, based on the finding of B-cell depletion in non-pregnant animals, elranatamab-bcmm can cause B-cell lymphocytopenia in infants exposed to elranatamab-bcmm in-utero. Human immunoglobulin (IgG) is known to cross the placenta after the first trimester of pregnancy; therefore, elranatamab-bcmm has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

ELREXFIO is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with ELREXFIO should be considered.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation:

Risk Summary

There are no data on the presence of elranatamab-bcmm in human milk, the effects on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk.

Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with ELREXFIO and for 4 months after the last dose.

Females and Males of Reproductive Potential:

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

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with ELREXFIO.

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of ELREXFIO.

Pediatric Use: The safety and effectiveness of ELREXFIO in pediatric patients have not been established.

Geriatric Use: Of the 183 patients with relapsed or refractory multiple myeloma treated with ELREXFIO in MagnetisMM-3 at the recommended dosage, 62% were 65 years of age or older, and 19% were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients 65-74 years of age compared to younger patients. Clinical studies did not include sufficient numbers of patients 75 years of age or older to determine whether they respond differently from younger patients.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

CRS: Discuss the signs and symptoms associated with CRS, including fever, hypoxia, chills, hypotension, tachycardia, and elevated liver enzymes. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of CRS. Advise patients that they will be hospitalized for 48 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose *[see Dosage and Administration in Full Prescribing Information, Warnings and Precautions]*.

Neurologic Toxicity, Including ICANS: Discuss the signs and symptoms associated with neurologic toxicity, including ICANS, including headache, encephalopathy, motor dysfunction, sensory neuropathy, and Guillain-Barré Syndrome. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of neurologic toxicity. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after administration of each of the 2 step-up doses and the first treatment dose within the ELREXFIO step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves *[see Dosage and Administration in Full Prescribing Information, Warnings and Precautions]*.

ELREXFIO REMS: ELREXFIO is available only through a restricted program called ELREXFIO REMS. Inform patients that they will be given an ELREXFIO Patient Wallet Card that they should carry with them at all times and show to all of their healthcare providers. This card describes signs and symptoms of CRS and neurologic toxicity, including ICANS which, if experienced, should prompt the patient to immediately seek medical attention *[see Warnings and Precautions]*.

Infections: Discuss the signs and symptoms of infection *[see Dosage and Administration in Full Prescribing Information, Warnings and Precautions]*.

Neutropenia: Discuss the signs and symptoms associated with neutropenia and febrile neutropenia *[see Dosage and Administration in Full Prescribing Information, Warnings and Precautions]*.

Hepatotoxicity: Advise patients that liver enzyme elevations may occur and that they should report symptoms that may indicate liver toxicity, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential to use effective contraception during treatment with ELREXFIO and for 4 months after the last dose *[see Warnings and Precautions, Use in Specific Populations]*.

Lactation: Advise women not to breastfeed during treatment with ELREXFIO and for 4 months after the last dose *[see Use in Specific Populations]*.

Rx only

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Get to Know

Continued from page 13

new ways of attacking these heels with targeted therapies.

The children who have a higher risk of relapse with conventional therapies—but we do not yet understand why—are the ones who especially inspire our work in the lab. We are quite fortunate to have access to primary patient samples that are invaluable resources for our studies in the lab. We are so grateful to the children and their families for donating their cells and participating in research.

It is tremendously important to advance promising precision medicine treatments identified in the research lab to children as quickly as possible. What inspires me most about the environment at CHOP is that it is not just about making scientific discoveries in the laboratory, it is about translating those advances to the clinic and turning knowledge gained into new therapeutic opportunities for children.

Patients treated with new therapies in early-phase clinical trials teach us lessons that we never could have predicted from test tubes, cell lines, or mice. Being able to study blood and bone marrow samples from children with high-risk leukemias back in the lab via bedside-back-to-bench studies helps us to further fine-tune our biologic and therapeutic understanding.

What are you working on right now?

We remain most excited about and focused upon conquering challenges in "boutique" high-risk genetic subtypes of leukemia in children. As clinicians, we have been lucky to cure many patients with B-cell acute lymphoblastic leukemia (B-ALL) with conventional chemotherapy. However, for those who do not achieve remission and those who relapse, some of the most exciting advances right now are in immunotherapies.

We have also been working diligently for over a decade on the problem of acute myeloid leukemia (AML), which is not nearly as curable in children with conventional chemotherapies. Overcoming chemotherapy resistance with new precision medicine strategies is one of the biggest problems that we are studying in both the laboratory and the clinical trial domain. Developing successful targeted inhibitors or antibody-based or cellular immunotherapies has been much more difficult in the AML space. We are probably five to seven years behind where we would love to be based upon the inspiring successes that we have witnessed in pediatric B-ALL.

How have you seen treatment for pediatric ALL and AML evolve?

I am humbled by the ability of pediatric oncologists to connect generously and share knowledge regarding research discoveries to help patients find the right treatment or clinical trial. Most of us practice at academic institutions and are extremely collaborative by nature. The focus on team science within pediatric oncology is incredibly powerful, and I truly believe that is in part how we have made so many advances nationally and internationally.

Children who were diagnosed with ALL or AML in the 1960s or early 1970s had a survival rate close to zero. It is through pediatric oncology consortia-based clinical trials that we have been able to advance cure rates to upward of 85% to 90% for children with ALL and 65% to 70% for children with AML in modern times. We have also learned together about maximizing supportive care and reducing toxicity for our patients so they can go on to live long and healthy lives after treatment. This collaborative focus on the holistic cure of children is a truly special aspect of pediatric oncology.

In 2023, we still face many challenges in curing all children with leukemia. As aforementioned, relapsed AML represents a persistent unmet medical need. We know that we are at a maximal asymptote in terms of chemotherapy intensity for these children and are thus working to integrate the tremendous knowledge gained in recent years regarding AML-associated genetic alterations and their prognostic significance with alternative treatment approaches. We have recently made progress in this domain via opening several pediatric-specific phase I clinical trials of exciting new targeted inhibitors or immunotherapies for relapsed or refractory AML. Another and more nuanced challenge in pediatric leukemia is successfully reducing chemotherapy intensity and associated toxicity for children who have particularly favorable-risk B-ALL, as we are learning that they are highly curable with far less therapy.

"The focus on team science within pediatric oncology is incredibly powerful, and I truly believe that is in part how we have made so many advances nationally and internationally."

What do you hope to see happen in the field?

I hope we can address some of these needs and questions more efficiently through the power of team science and participating in innovative clinical trials. I remain hopeful that we will be able to improve cure rates during the next five to 10 years, particularly for children with the highest risk of relapse and the leukemias that are hardest to treat with conventional chemotherapies. I am particularly hopeful that we can credential some of these new targeted therapies not just in the relapsed space, but also bring them forward to children with newly diagnosed leukemias with relevant genetics or biology.

What does your work in pediatric oncology mean to you?

As a pediatric oncologist and physician-scientist, I am lucky to have the best job in the world. We wear many different hats in medicine and science that provide a diversity of experiences, and it is the relationships that we have with our patients and their families that are truly inspiring. These children center us and keep us laser-focused on our shared scientific and clinical mission, particularly when things do not go as well as hoped. As a mother, I also have tremendous compassion for the hardships and sacrifices that our families endure in pursuit of successful cancer treatment for their children. I strive to care for them with the same level of excellence that I would expect for my own children.

Can you speak about the value of mentorship?

It is critically important to be paired with a mentor who is a good fit for you personally and professionally. I have learned along the way that you can also receive different mentoring components from different people, and the sum is often greater than the parts. It is so important to have someone who is a champion of young people, is generous with their time and creating opportunities, and will focus a bit selflessly on getting the young person to the next stage of their career development.

Because of the tremendous support that I received in my training and still receive from lifelong mentors, I have made it my mission to pay it forward through my own deliberate mentoring of our trainees and young faculty members, especially female physician-scientists. I hope to create for them similar exciting opportunities for their career development that I was so fortunate to have.

What are some of your favorite hobbies and activities outside of work?

I love to travel with my family, anywhere and everywhere! We have been lucky to enjoy many fantastic adventures together throughout the world. I have also been quite fortunate to travel to some amazing places with wonderful colleagues through our international collaborations in pediatric oncology.

Besides traveling, I love to read, run, visit art museums, needlepoint, brush up on foreign languages (I am learning Dutch now), and indulge in a bit of "gourmet fashion" shopping. My husband is a pediatric urologist at CHOP and the University of Pennsylvania and a clinical researcher/epidemiologist in pediatric kidney stone disease. Despite our busy work/home life as a dual professional couple, he and I enjoy spending as much time as possible with our two wonderful school-age boys, who are enormous football (soccer) fanatics and begrudgingly practice their cello and viola daily because their mother makes them.

Is there a skill you have that people might be surprised to learn about?

I was a competitive water polo player in high school and college (hole defense is tough!), which I suspect that most of my colleagues do not know about me. I also took five years of Latin, which I have found incredibly helpful in medicine, as well as in reading inscriptions on ancient statues while on holiday in Rome.

Sarah Tasian, MD, *is Chief of the Hematologic Malignancies Program and the Joshua Kahan Endowed Chair in Pediatric Leukemia at Children's Hospital of Philadelphia.*

In Focus

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

When Will AI Be Ready for Prime Time in Blood Cancers?

By Leah Sherwood

In today's era of accelerating innovation, artificial intelligence (AI), driven by advances in machine learning, has become a ubiquitous presence in our lives. It seems like every time we turn on the news or browse the web, there's a new AI-related story in the headlines.

So, what does AI bring to the field of hematologic oncology? The answer lies in its potential to revolutionize the way we approach the diagnosis, treatment, and understanding of blood-related cancers.[1,2]

"I think that we'll see it eventually at every stage of the patient's journey, starting from diagnosis to treatment to relapse to quality of life after the treatment or survivorship," said **Roni Shouval, MD, PhD,** a physician-scientist at Memorial Sloan Kettering Cancer Center in New York City. "At every time point, there may be an application for AI."

Dr. Shouval's choice of the words "eventually" and "may" reflects the hesitancy that is typical among researchers in the field. It is clear that the full potential of AI in hematologic oncology has yet to be realized, despite all the hype.

"When it comes to machine learning and AI, you have to separate the hype from where the value is—because there is value," said **Aziz Nazha, MD,** Global Head of Incyte's AI Innovations Institute. "But I think sometimes the hype overtakes the value. Once you focus too much on the hype, then it becomes a problem when the expectation of the technology is not getting realized, and then people become skeptical."

Making Inroads in the Field of Hematology

As AI continues to make inroads in the field of hematology, its usefulness is most evident in diagnostics, where it serves as a complementary tool rather than a replacement for physicians. The technology has the ability to significantly enhance both the speed and accuracy of diagnostics, and even to distinguish rare blood cancers that pose challenges to hematopathologists.[3]

"Hematology in general, especially malignant hematology, is such a unique field where you have several technologies," Dr. Nazha observed. "You have imaging flow cytometry and clinical and laboratory data, so you have multimodality data to make the diagnosis, and that's a great use case for machine learning."

The interpretation of pathology assays, including bone marrow smears and peripheral blood smears, is one of the first direct implementations of the technology in the field, according to Dr. Shouval.

"The concept is that you can help these labor-intensive, experience-based tasks by AI augmenting the ability of the pathologist to accurately perform these tests and do it at large scale," Dr. Shouval said. "The computers don't get tired, and you can at least try to program them to have less bias."

Another area of application is in the diagnosis of myelodysplastic syndromes (MDS), which are particularly challenging due to their close resemblance to other myeloid malignancies. In some instances, the only definitive differentiation can be achieved through a bone marrow biopsy, Dr. Nazha said.

To overcome this diagnostic challenge, Dr. Nazha and colleagues developed a machine learning model capable of distinguishing MDS from other myeloid diseases solely by analyzing complete blood counts (CBC), differentials, and next-generation, targeted, deep-sequencing data.[4]

This type of CBC model is only one of the many potential approaches to diagnosing MDS, Dr. Nazha said.

"For example, you can use computer vision to look at cells in bone marrow biopsy and say these are malignant or dysplastic cells," he noted. "Or you could use the clinical lab data in the structure notes from the pathology report to build a model to predict the disease diagnosis."

Diagnosis is just the first in a chain of potential clinical applications for AI. Other applications include prognosis and determining the next step in a patient's treatment.

"The right treatment at the right time can sometimes be challenging in cancer in general and certainly in hematologic malignancies," Dr. Nazha said.

Clinicians might use AI to decide whether to proceed with a transplant or to determine the appropriate intensity of chemotherapy.

"You could use machine learning to try to build models to predict response or resistance to chemo[therapy] and to understand the variables that impact that response and resistance," Dr. Nazha said.

However, Dr. Shouval cautioned that, at present, there is not yet much actual clinical utility for models that try to predict outcomes and make treatment or clinical trial recommendations.

"One, many of these models have not been validated externally, so you can't really run them on your own data safely," Dr. Shouval said. "Second, a lot of them still suffer from relatively low predictive performance. And third, because there's so much variation in the different populations that we treat, it's sometimes hard to extrapolate one model from one population to the other because of this variance. That's why in order to really incorporate these models, we need good validation sets and collaboration."

Far From Perfect

While AI holds tremendous promise, it's currently far from a panacea in the field. There are hurdles to overcome, such as data privacy concerns, the need for robust validation of AI models, a lack of qualified personnel, and the requirement for large and diverse datasets to train these models effectively. Moreover, integrating AI seamlessly into clinical practice and ensuring that it consistently benefits patients are ongoing challenges.

"I think one of the challenges for running or developing robust prediction models or diagnostic models in medicine is access to large datasets," said Dr. Shouval. "When you look at the algorithms that are currently used, the deep-learning algorithms, the large language models [LLMs], the ones that are used by ChatGPT and others, these need billions of samples to learn from."

Dr. Shouval believes that, given the challenges related to accessing large datasets and the limited representation of patients in pharmaceutical companies' clinical trials, the future of AI and machine learning in hematologic oncology lies in academia and collaborative centers.

"It's a challenge for pharmaceutical companies because they don't have the full spectrum of patients in their clinical trials; it's a selective group that's not reflective of what's out there in the real world," he said. "To actually train machine learning models or AI models, you need to learn from variation. So having larger datasets that are not siloed at one institution or with one company is a great advantage."

The field also has a talent challenge, which further hinders the progress of the technology, according to Dr. Nazha.

"We as physicians are not trained to understand machine learning and AI," he said. "The data scientists, on the other hand, approach the data in health care similar to banking and other types of data, which we all know is completely different. This data is messy, [there are] a lot of missing data. Sometimes you have a smaller patient population. So, there are a lot of intrinsic challenges to be addressed."

"The computers don't get tired, and you can at least try to program them to have less bias." *—Roni Shouval, MD, PhD*

As a step toward addressing the talent issue, Dr. Nazha developed a course called "No Code - Low Code Machine Learning For Healthcare," which is available at no cost on AI4healthcare.org.

Even if someone is qualified to build an AI model, a more important task is to identify the right clinical question to be answered by the model.

"I've seen multiple models built where the answer to the question we're trying to answer is useless, clinically not meaningful," Dr. Nazha said. "Because you can build a model, you can publish it, but nobody can use it, or nobody can derive benefit from it."

This point about the primacy of problems over models was echoed by Dr. Shouval, who in addition to his medical degree holds a doctoral degree in computer science.

"I never think first of the algorithm and then the problem; I always have a clinical problem in mind, and then I try to apply the best tool," he said. "Sometimes it's machine learning, sometimes it's not. I always look at machine learning just as another tool, just as a means to get to a certain aim and not as a goal in itself."

The opaqueness of machine learning models is also a major limitation, Dr. Shouval said.

"A lot of [models] are what we call black-box models, where we don't understand the rationale

behind a certain prediction or diagnosis," he said. "It may be important in medicine for sure, and sometimes for diagnosis, [but] we need to understand what the rationale is, and sometimes it helps us to criticize the prediction or classification."

Elevating Patient Voices

At the 64th American Society of Hematology Annual Meeting and Exposition, a study was presented that used natural language processing (NLP) and machine learning to shed light on the needs, anxieties, and general sentiments of patients with multiple myeloma (MM) and their caregivers.[5]

"We do a lot of real-world research to understand patients' unmet needs and how they are doing after receiving a treatment," said **Dee Lin, PharmD,** an Associate Director in the Department of Real World Value & Evidence, Oncology, at Janssen Scientific Affairs, LLC, who was the lead author on the study.

"When it comes to machine learning and AI, you have to separate the hype from where the value is." *—Aziz Nazha, MD*

NLP is a subfield of AI that has been around since the 1950s. Today, it is used to extract meanings, relationships, sentiments, and other insights from the vast amounts of free-form text available online or in private databases.

Even though NLP is old school by AI standards, it has proved useful for analyzing the text we all generate when we turn to the internet to connect with others, especially when we are sick. These online conversations on blogs, social media, and patient forums provide valuable real-world data for clinicians and researchers, immersing them in the lives of patients and their caregivers.

Lin cited a number of advantages of this kind of empirical text-mining over traditional methodologies.

"When we think about traditional patient surveys or interviews, [they're] often guided and highly structured by the researchers, who already have research questions in mind," she said. "A lot of times patient voices captured in the survey could have been narrowed down [or] filtered by the research questions. And then there are other biases, like the responses are not spontaneous, or there might be recall bias, response bias, and selection bias."

Social media and patient forum data, in contrast, are unstructured, organic, spontaneous, and more focused on what patients are interested in instead of what researchers are interested in. "It's more organic and patient initiated," Lin said.

In the study, the researchers analyzed close to 20,000 posts where patients and their caregivers openly discussed their experiences. They used machine learning tools to run analytics on any tags in the data and to supplement their list of prespecified keywords with alternative synonyms and misspellings to ensure that all relevant posts were captured. They then used NLP tools to classify the posts into specific categories based on topic, sentiment, emotion, and other attributes.

From this research, Lin and colleagues identified a number of areas of unmet patient needs, including access to new treatment options, financial support, living conditions, and caregiver burden.

Patients have varying unmet needs and concerns depending on where they are in their disease journey, Lin explained. Early-stage patients with MM often care more about the risk of side effects, choosing among treatment options, and impacts on quality of life, while those further along may focus more on duration of response and lack of treatment options.

One interesting takeaway from the study was the fact that there were zero mentions of bispecific antibodies in the patient and caregiver posts.

"At the time of the study (May 2020 to June 2022), there was no [US Food and Drug Administration (FDA)]-approved bispecific therapy in the market, so it's understandable if the physicians don't talk about it," she explained. "However, not finding any discussion online potentially indicates there might be a lack of awareness of new therapies in development, so there are definitely some education opportunities there."

Since the study concluded, the FDA has issued approvals to the company's two recent bispecific antibodies, teclistamab and talquetamab, for the treatment of relapsed or refractory MM.[6,7]

Lin pointed out that current value frameworks for medical therapies tend to be focused heavily on efficacy, safety, and cost, but research like hers may help bring patient needs and experiences to the table for a more comprehensive evaluation of the therapies.

"In the current value framework of oncology therapies, patient voices are not sufficiently represented. One of the reasons being it's just in general difficult to quantify," Lin explained. "But now, with new technology and the advancement in data, we can use these innovative methods and data sources to create a domain for patient voices and drive the value of innovative therapy beyond those traditional outcomes, which will really help us elevate patient-centered care."

Lend Me Your Ear, ChatGPT

Patients have been turning to the web for medical self-education, for better or worse, for more than 25 years.[8] What is new today, however, is the use of LLM chatbots to access medical information, a development that raises questions about the quality and accuracy of the information.

In a research letter published in *JAMA Oncology* in August 2023, scientists described how they asked ChatGPT questions about treatments for breast, lung, and prostate cancer and then evaluated the quality of its answers.[9] Specifically, three board-certified oncologists reviewed each of the chatbot's answers and compared them against the recommendations in the National Comprehensive Cancer Network (NCCN) guidelines from 2021.

The good news is that ChatGPT proffered at least one of the gold-standard NCCN recommendations for 102 of 104 (98%) prompts. More worryingly, however, one-third of treatments recommended by the chatbot were at least partially nonconcordant with NCCN guidelines, and 13 of 104 (12.5%) outputs contained "hallucinations" (ie, therapies that were not part of any recommended treatment).

The senior author on the paper, **Danielle Bitterman, MD,** a radiation oncologist and NLP researcher at the Dana-Farber Cancer Institute/Brigham and Women's Hospital and Harvard Medical School, said that the results were to be expected.

"It was disappointing that [ChatGPT] included so many wrong recommendations, but we didn't expect it to meet the high bar of providing clinical recommendations," Dr. Bitterman said. "The challenge lies in the way it provides information. Unless you have a deep understanding of the subject or access to medical guidelines, it's challenging to distinguish between the right and wrong responses. This is a feature of the fact that it's a chatbot, trained to provide responses that sound fluent and make superficial sense."

Dr. Bitterman also noted that the chatbot generated different responses to slightly reworded questions, explaining "that's also a challenge that needs to be addressed before [chatbots] are ready to be a reliable source of information for people."

In a nutshell, chatbots are not yet reliable for medical advice, and people should not seek medical care based on them, said **Shan Chen,** a doctoral candidate in the Artificial Intelligence in Medicine Program at Harvard Medical School and the first of author of the study.

"There's a lot of potential behind it, but there's a lot of work to do to make sure it's actually safe in really sensitive settings like legal or medical settings," he said.

Chen said that he had been following the progress of language models for some time, but the release of ChatGPT-3 really changed the game because it made these models widely accessible to people who seem to enjoy chatting with the chatbots.

"There's a study published from the University of California, San Diego,[10] which suggests these bots are more empathetic, which is another quality that is really hard to measure," he said. "But they're not factual—that's a problem."

On the flip side, using chatbots in health care to manage inbox messages can alleviate doctors' burnout and stress.[11] Chatbots can help sort messages and speed up reply times for critical messages, making health care communication faster, more streamlined, and possibly more empathetic.

"Building a really safe chatbot for the health care system will be an interesting direction," Chen said.

The Future: LLMs for Drug Discovery?

The usefulness of LLMs like ChatGPT extends beyond their abilities to ease burnout among clinicians or provide patients with an empathetic ear; the technology is positioned to speed up drug discovery and development.[12]

"Today, to take a drug from target to phase one, it's about five years on average," Dr. Nazha explained. "Then to take it from phase one to approval, which is what we call IND to NDA, that's a

minimum [of] five to seven years too. Total, you are talking about 10 years. If you shorten that to about seven years that's a long time in drug development."

Dr. Shouval predicts that the technology behind ChatGPT will be harnessed to generate or develop drugs or compounds, or novel combinations thereof, based on analogizing from previous experience.

"You could tell ChatGPT this agent is effective against target A, how about target B?" Dr. Shouval said. "You learn different compounds, different chemical structures, what works and what doesn't, and then develop new interventions or drugs based on that. This is one of the major promises I see with LLM models like ChatGPT. But again, this is going to require a huge amount of data to train and create useful models."

He added that this type of technology is "changing the world now, and it's going to change the way we practice."

Despite existing limitations and what may be perceived as disappointments, Dr. Bitterman sees a promising future for AI in the field.

"I'm very optimistic about the future of AI and in health care," Dr. Bitterman said. "I think there's incredible potential for AI to help people manage information and create new insights. We can start using all the data we've been collecting on patients for so long to improve people's health."

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

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Regulatory Actions

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

FDA Approves Bosutinib for Chronic Phase Ph-Positive CML in Pediatric Patients

The US Food and Drug Administration (FDA) has approved bosutinib (Bosulif) for pediatric patients one year of age and older who have chronic phase Philadelphia chromosome (Ph)-positive chronic myeloid leukemia (CML) that is newly diagnosed or resistant or intolerant to prior therapy.

The FDA also announced it approved a new capsule dosage form of bosutinib that is available in strengths of 50 mg and 100 mg.

The BCHILD trial evaluated the efficacy of bosutinib in pediatric patients with newly diagnosed, resistant, or intolerant chronic phase Ph-positive CML. The major efficacy outcome measures of the BCHILD trial included major cytogenetic response, complete cytogenetic response, and major molecular response (MMR).

In pediatric patients with newly diagnosed chronic phase Ph-positive CML, the major cytogenetic response rate was 76.2% and the complete cytogenetic response rate was 71.4%. The MMR rate was 28.6%.

In pediatric patients with resistant or intolerant chronic phase Ph-positive CML, the major cytogenetic response rate was 82.1%, and the complete cytogenetic response rate was 78.6%. The MMR rate was 50%.

The recommended dose for pediatric patients with newly diagnosed chronic phase Ph-positive CML is bosutinib 300 mg/m^2 orally once daily with food. The recommended dose for pediatric patients with resistant or intolerant chronic phase Ph-positive CML is bosutinib 400 mg/m^2 orally once daily with food. For patients who are unable to swallow capsules, the contents of the capsules can be mixed with applesauce or yogurt.

This application was granted priority review and Orphan Drug Designation, according to the FDA.

EMA Committee Recommends Approval of Zanubrutinib for Follicular Lymphoma

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) released a statement recommending the approval of zanubrutinib (Brukinsa), a Bruton's tyrosine kinase inhibitor, in combination with obinutuzumab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two previous lines of therapy.

The CHMP recommendation was based on positive findings from the phase II ROSEWOOD study and the phase Ib BGB-3111-GA101-001 study. ROSEWOOD included 217 patients with relapsed or refractory FL who received either zanubrutinib plus obinutuzumab or obinutuzumab alone. Over a median follow-up of approximately 20 months, the zanubrutinib arm achieved an overall response rate (ORR) of 69.0% compared with 45.8% in the obinutuzumab arm (P=.0012). The combination was generally well-tolerated, and safety results were consistent with previous studies for both therapies, according to a press release from BeiGene, the developer of zanubrutinib.

Currently, zanubrutinib is approved in the European Union (EU) for chronic lymphocytic leukemia and small lymphocytic lymphoma, marginal zone lymphoma, and Waldenström macroglobulinemia. It also holds various approvals in the United States, China, Great Britain, Canada, Australia, South Korea, and Switzerland, with ongoing development for additional indications.

Following the positive CHMP recommendation, the European Commission (EC) will review the marketing authorization for FL. If approved, the indication will apply to the 27 member states of the EU, Iceland, and Norway.

BeiGene has similar applications for the FL indication under review in the United States, China, Canada, Switzerland, and the United Kingdom.

Fatal Reaction in Lacutamab Clinical Trial Leads to FDA Partial Hold

The FDA placed a partial clinical hold on the Investigational New Drug application for lacutamab following one fatal case of hemophagocytic lymphohistiocytosis (HLH) reported in the clinical trial program.

Lacutamab is a first-in-class, anti-KIR3DL2, humanized, cytotoxicity-inducing antibody undergoing evaluation for the treatment of patients with cutaneous T-cell lymphoma (CTCL) and peripheral TCL. It was granted EMA PRIME and FDA Fast Track designations for patients with relapsed or refractory Sézary syndrome who have received at least two prior lines of therapy, as well as Orphan Drug Designation for CTCL.

The developer of lacutamab, Innate Pharma S.A., announced it would pause new patient enrollment into its ongoing phase II CTCL (TELLOMAK) and phase Ib peripheral T-cell lymphoma (PTCL; IPH4102-102) studies and would take steps to meet requests from the FDA, including HLH risk mitigation and management strategies.

The company noted that the TELLOMAK and PTCL studies have already completed their planned enrollment of 170 and 20 patients, respectively, and stated it did not predict delays in the publication of final data from TELLOMAK and preliminary data from the futility interim analysis of the PTCL study, both planned for the fourth quarter in 2023. The PTCL study would then proceed to the next phase with 20 additional patients, and all patients demonstrating a clinical benefit on lacutamab would be able to continue treatment after updating their consent.

EC Grants Conditional Marketing Authorization to Epcoritamab for DLBCL

The EC has granted conditional marketing authorization to epcoritamab (Tepkinly) as a monotherapy for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The subcutaneous T-cell-engaging bispecific antibody is now approved for the treatment of this patient population in the EU, as well as Liechtenstein, Norway, and Iceland, according to an announcement from Genmab, the manufacturer of the drug.

This conditional approval is supported by data from the pivotal EPCORE NHL-1 trial. The single-arm, phase I/II trial evaluated the preliminary efficacy and safety of epcoritamab. It included 139 patients with DLBCL who showed an ORR of 62%, with a complete response rate of 39%. The median duration of response was 15.5 months.

FDA Approves Ivosidenib Treatment for Relapsed or Refractory MDS

The FDA approved the use of ivosidenib (Tibsovo) for adult patients with relapsed or refractory myelodysplastic syndromes (MDS) with a susceptible *IDH1* mutation.

The approval was based on the open-label, single-arm, multicenter AG120-C-001 trial, which included 18 adult patients with relapsed or refractory MDS with an *IDH1* mutation.

Patients received ivosidenib orally at a starting dose of 500 mg daily for 28-day cycles until disease progression, unacceptable toxicity, or hematopoietic stem cell transplantation (median treatment duration, 9.3 months).

Of nine patients dependent on red blood cell (RBC) and/or platelet transfusions at baseline, six (67%) became RBC and platelet transfusion independent during any 56-day post baseline period. Meanwhile, of nine patients independent of both RBC and platelet transfusions at baseline, seven (78%) remained transfusion independent during any 56-day post baseline period.

The most common adverse reactions included gastrointestinal toxicities (diarrhea, constipation, mucositis, and nausea), arthralgia, fatigue, cough, myalgia, and rash, which were similar to common adverse reactions observed with ivosidenib monotherapy for acute myeloid leukemia. Ivosidenib may also cause QTc prolongation.

Highlights from the **11TH ANNUAL MEETING OF THE SOCIETY OF HEMATOLOGIC ONCOLOGY (SOHO)**

COMMANDS Biomarker Analysis Explores Luspatercept Mechanism in LR-MDS

Results from a biomarker analysis of the phase III COMMANDS study provide "novel insights" that "mechanistically differentiate the superior clinical benefit of luspatercept" from epoetin alfa in patients with low-risk myelodysplastic syndromes (LR-MDS), according to investigators.

Uwe Platzbecker, MD, of the University Hospital in Leipzig, and colleagues presented the research during the Eleventh Annual Meeting of SOHO in Houston, Texas.

The COMMANDS trial compared the efficacy and safety of luspatercept with epoetin alfa in patients with LR-MDS who were naïve to erythropoiesis-stimulating agents. It showed that 58.5% of patients receiving luspatercept achieved red blood cell transfusion independence for at least 12 weeks with a mean hemoglobin increase of at least 1.5 g/dL during weeks one through 24, while 31.2% of patients receiving epoetin alfa achieved this outcome.

Due to these results, Dr. Platzbecker and colleagues aimed to differentiate the mechanism of action of luspatercept from epoetin alfa and "determine its correlation with primary endpoint achievement."

They performed cytomorphology assessments on bone marrow aspirates at baseline, week 24, and week 48. The researchers measured complete blood count and reticulocytes in peripheral blood. They used bulk RNA sequencing on bone marrow mononuclear cells and used the enzyme-linked immunosorbent assay to measure serum ERFE, GDF11, hepcidin, and GDF15.

In patients who received luspatercept, erythroid precursors increased from baseline to week 24 (P=.031000) and week 48 (P=.000017), as did reticulocytes (P<.000100). In patients who received epoetin alfa, erythroid precursors increased from baseline to week 24 (P=.0017), but there was no change reported in reticulocytes.

At week 48, there was a "sustained increase" in erythroid precursors and reticulocytes in patients who received luspatercept (P<.001), but not in patients who received epoetin alfa (P=.056 and P=.670, respectively).

There was an increase in median ERFE levels at week 24 in patients who received luspatercept (7.2 vs 10.1 ng/mL; P<.05) and in those who received epoetin alfa (9.1 vs 10.4 ng/mL; P=not significant). There was also an increase in median GDF15 levels at week 24 in patients who received luspatercept (5.0 vs 7.0 ng/mL) and in those who received epoetin alfa (4.5 vs 5.4 ng/mL).

A gene set enrichment analysis on bone marrow mononuclear cells showed that enrichment of early, middle, and late erythroid precursor genes at baseline "favored response to luspatercept," while enrichment of middle and late erythroid precursor genes was "unfavorable" for epoetin alfa. The researchers also found that luspatercept downregulated TGFβ, interleukin-6, apoptosis, and spliceosome pathways.

"Compared with [epoetin alfa], response to luspatercept increased [erythroid precursors] and reticulocytes over 48 weeks with concomitant hemoglobin increase," Dr. Platzbecker and colleagues concluded. "Unlike [epoetin alfa], luspatercept acts on different erythroid stages, leading to expansion and maturation of [erythroid precursors], for superior clinical benefit. These novel insights mechanistically differentiate the superior clinical benefit of luspatercept in patients with LR-MDS from [epoetin alfa]."

Reference

Platzbecker U, Hayati S, Ahsan A, et al. Luspatercept restores effective erythropoiesis and provides superior and sustained clinical benefit versus epoetin alfa (EA): biomarker analysis from the phase III COMMANDS study. Abstract MDS-071. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

Is Outpatient Administration of Liso-Cel Cost-efficient for Patients with CLL?

Outpatient administration of lisocabtagene maraleucel (liso-cel) "may be a cost-efficient option" in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), according to a study presented during the Eleventh Annual Meeting of SOHO.

November McGarvey, PhD, of BluePath Solutions, and colleagues conducted the research because while patients receiving chimeric antigen receptor (CAR) T-cell therapy are "generally treated in the inpatient setting, opportunities for outpatient administration to reduce costs exist." However, health care resource utilization and monitoring costs after a patient receives CAR-T "may differ" by the site of care, they wrote.

The researchers aimed to estimate the one-year postinfusion health care resource utilization and costs by site of care among 108 patients with relapsed or refractory CLL who received liso-cel in the TRANSCEND trial.

Dr. McGarvey and colleagues analyzed individual patient-level case report forms from TRANSCEND that included details about health care resource utilization in the year following CAR-T infusion. The health care resource utilization cost categories included facility, diagnostics, procedures, and medications but excluded liso-cel acquisition costs. The researchers sourced unit costs from public databases and the literature and calculated the costs for each health care resource utilization category, adjusted to US $2,023.

They classified patients as receiving inpatient care if they had an overnight hospital stay and classified those who were discharged the same day of liso-cel infusion as receiving outpatient care. The researchers stratified all outcomes by site of care and month.

Dr. McGarvey and colleagues found that 87% of patients received inpatient care, while 13% received outpatient care. The mean age of those receiving inpatient care was 64.2 years, while the mean age of those receiving outpatient care was 65.1 years. The researchers reported that 16.0% of those receiving inpatient care had a stay in the intensive care unit (ICU), while 7.1% receiving outpatient care had an ICU stay. The median total hospital length of stay was 18 days for those receiving inpatient administration, and it was 14 days for those receiving outpatient administration.

Nearly all patients received antibiotics (inpatient, 98.9%; outpatient, 92.9%) and most received tocilizumab (inpatient, 69.1%; outpatient, 57.1%) and corticosteroids (inpatient, 67.0%; outpatient, 42.9%).

The estimated median one-year total postinfusion monitoring costs were $82,382 for those receiving inpatient administration and $38,398 for those receiving outpatient administration.

The researchers found that facility costs were the "primary cost driver." The inpatient facility costs

were $27,752, making up 34% of the total costs for patients receiving inpatient administration. The outpatient facility costs were $20,043, making up 52% of the total costs for those receiving outpatient administration. Most of the median total one-year costs occurred in the first month after infusion, with a median of $48,527 for those receiving inpatient administration and $28,778 for those receiving outpatient administration.

"Despite the small sample size of outpatients, these findings suggest that outpatient administration of liso-cel in patients with [relapsed or refractory] CLL may be a cost-efficient option due to the lower total one-year postinfusion costs and reduced [health care resource utilization] versus inpatients," Dr. McGarvey and colleagues concluded.

Reference

McGarvey N, Lee A, Imanak K, et al. Post-infusion monitoring costs and health care resource utilization (HCRU) by site of care (SOC) in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) receiving lisocabtagene maraleucel (liso-cel) treatment in the TRANSCEND CLL 004 (TRANSCEND) study. Abstract CT-105. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

Study Finds High Economic Burden in Patients with MPNs

Patients with myeloproliferative neoplasms (MPNs) such as polycythemia vera, essential thrombocythemia, and myelofibrosis face a high economic burden, according to a study presented at the Eleventh Annual Meeting of SOHO.

Researchers conducted the study to measure short- and long-term disability work loss in patients with MPNs, as well as direct and indirect costs for employees with MPNs.

The retrospective, cohort study used the MarketScan administration claims databases to identify 10,711 employees aged 18 to 64 years with at least one MPN diagnosis of myelofibrosis (n=173), polycythemia vera (n=4,477), or essential thrombocythemia (n=6,061) between 2009 and 2019. All patients had continuous plan enrollment six months before diagnosis and 12 months after diagnosis. The matched control cohort included patients who did not have MPNs, acute myeloid leukemia, or MDS who met the same enrollment criteria as the cohort of patients with myelofibrosis, polycythemia vera, or essential thrombocythemia.

The researchers found that the total direct health care costs were significantly higher among the cohorts of patients with myelofibrosis, polycythemia vera, or essential thrombocythemia compared with the matched control cohort of those who did not have MPNs (all $P<.001$). Patients with myelofibrosis had the largest mean cost difference, facing total direct health care costs that were $67,456 higher than the matched control cohort. Patients with essential thrombocythemia had total direct health care costs that were $22,279 higher than the matched control cohort, while those with polycythemia vera had costs that were $10,970 higher.

The cohorts of patients with myelofibrosis, polycythemia vera, or essential thrombocythemia had significantly higher percentages of patients with short-term disability claims, as well as a larger number of short-term disability work days lost and higher short-term disability-associated indirect costs than the matched control cohort.

Patients with myelofibrosis had an 8.1% higher chance of filing a short-term disability claim, while those with essential thrombocythemia had a 7.5% higher chance, and those with polycythemia vera had a 3.3% higher chance.

Patients with polycythemia vera or essential thrombocythemia who had thrombotic events were more likely to have an inpatient hospital stay and had higher all-cause total health care costs, as well as higher numbers of lost work days related to short-term disability and higher indirect costs related to short-term disability (all $P<.05$). The results were "consistent but less pronounced" for long-term disability claims, according to the study's authors.

"Economic burden was high among employed MPN patients," the researchers concluded. "Patients with [polycythemia vera, essential thrombocythemia, or myelofibrosis] were significantly more likely to take disability leave and had higher direct/indirect costs [versus] matched controls. [Thrombotic events] significantly impacted health care costs and [short-term disability] leave for [polycythemia vera or essential thrombocythemia] patients [versus] controls."

Reference

Yu J, Jerry M, Nelson J, et al. Direct and indirect costs for patients with myeloproliferative neoplasms (MPNs). Abstract MPN-531. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

Enrollment Underway for Phase II Study of Oral HMA Plus Magrolimab in MDS

The phase II ASTX727-10 study evaluating the combination of a hypomethylating agent (HMA) plus magrolimab in patients with intermediate- to very high-risk MDS has begun enrollment, according to a poster presentation at the Eleventh Annual Meeting of SOHO.

Amer Zeidan, MBBS, MHS, of Yale University, and colleagues are conducting the study to assess if using oral decitabine/cedazuridine in combination with magrolimab may "provide the benefits of combination therapy without the significant burden of parenteral therapy."

The primary aim of the phase II study is to evaluate the safety and efficacy of the combination treatment in patients who have intermediate- to very high-risk MDS per the MDS International Prognostic Scoring System–Revised (IPSS-R). The secondary aims of the study include evaluating the pharmacokinetic profiles of oral decitabine/cedazuridine and magrolimab, other clinical efficacy data on the combination, and safety and efficacy in prespecified subgroups of patients.

Dr. Zeidan and colleagues began enrolling patients in April 2023. To be eligible for the single-arm, open-label study, patients must meet certain criteria. Patients must have previously untreated MDS with <20% bone marrow blasts, as well as an Eastern Cooperative Oncology Group performance status score ≤2, and be willing to undergo red blood cell transfusions to achieve a hemoglobin level of >9 gm/dl at the start of study treatment, "per protocol parameters, and as clinically necessary," according to Dr. Zeidan and colleagues.

Key exclusion criteria include "significant medical issues," creatinine clearance <50 ml/min, immediate eligibility for hematopoietic stem cell transplant, secondary MDS, or MDS/myeloproliferative neoplasm overlap syndromes, the researchers wrote.

"Tolerability of the combination regimen will be confirmed in the first six to 18 subjects with dose and/or dosing decreases identified during this assessment applied to the entire study," Dr. Zedian and colleagues wrote.

Reference

Zeidan A, Mosher K, Souza S, et al. Phase 2 study of oral decitabine/cedazuridine in combination with magrolimab for previously untreated subjects with intermediate to very high-risk myelodysplastic syndromes (MDS). Abstract MDS-622. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

How Prevalent Are Financial, Time Toxicity in Patients with Multiple Myeloma?

Financial toxicity occurred in nearly 25% of patients with multiple myeloma (MM) and 39% experienced time toxicity, according to research presented at the 20th IMS Annual Meeting.

Rahul Banerjee, MD, of the Fred Hutchinson Cancer Center, and colleagues conducted the cross-sectional survey of 576 patients with MM who received autologous hematopoietic stem cell transplantation (AHSCT) at one institution in the United States. The survey included the validated FACIT-COST (Functional Assessment of Chronic Illness Therapy–Comprehensive Score for Financial Toxicity) inventory of financial toxicity, questions about financial fragility, as well as questions about symptoms and the frequency and nature of health care interactions.

The researchers defined financial toxicity as a FACIT-COST score in the lowest quartile, which was 25 or less. They defined time toxicity as MM-related health care interactions—including telehealth and phone calls—that averaged at least once a week, or in-person MM-related interactions that averaged at least once a month, with each interaction requiring at least four hours away from home, including transit time.

Of the 576 eligible patients who received the survey, 205 (36%) completed it. Most patients (62%) who completed the survey were on maintenance therapy, 22% were on observation, and 16% were on treatment for relapsed MM. The median patient age was 68 years, with a median of three years since AHSCT.

The median FACIT-COST score was 31 (interquartile range, 25 to 37). A total of 24% of patients had financial toxicity, 39% had time toxicity, and 12% had financial toxicity and time toxicity.

Nearly one-third (32%) of patients on maintenance therapy reported financial toxicity. Financial toxicity was reported by 26% of patients on observation and 23% of those with relapsed MM.

Financial toxicity was associated with increased anxiety, depression, and fatigue ($P<.01$ in all cases) in univariate analyses. It was also associated with "skipping essential items/medications and financial fragility," according to Dr. Banerjee and colleagues. Younger age (odds ratio [OR], 1.09; $P=.01$) and income below $50,000 (OR, 3.43; $P<.01$) were both predictors of financial toxicity in multivariate analyses.

Nearly all (87%) patients with relapsed MM reported time toxicity. Time toxicity was reported by 35% of patients on maintenance and by 11% of those on observation.

In the patients experiencing time toxicity, 58% reported any-type MM interactions occurring at least once a week, with 25% reporting in-person MM visits with long transit times occurring at least once a month and 16% reporting both.

Time toxicity was associated with increased fatigue in a univariate analysis ($P=.01$). Multivariate analyses showed the only predictor of time toxicity was relapsed disease status (OR, 8.85; $P<.01$).

"[Financial toxicity] was associated with increased symptom burden and financial fragility, and better support of out-of-pocket costs through post-[AHSCT] maintenance and relapse may be helpful," Dr. Banerjee and colleagues concluded. "[Time toxicity] was reported by over a third of [patients] on maintenance, and de-escalation of low-yield monitoring during this phase of survivorship should be considered."

Reference

Banerjee R, et al. Financial toxicity and time toxicity among patients with multiple myeloma. Abstract P-452. Presented at the 20th International Myeloma Society Annual Meeting. September 27-30, 2023; Athens, Greece.

What Are the Real-world Outcomes in Multiple Myeloma After Triple-Class Exposure?

There are "limited treatment options" for patients with MM who have triple-class exposure, as these patients are "often re-treated with the same therapies or therapies in the same classes," according to a real-world study presented at the 20th IMS Annual Meeting.

Rafael Fonseca, MD, of the Mayo Clinic, and colleagues conducted the study because patients with triple-class exposure to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies "have particularly high unmet needs."

Dr. Fonseca and colleagues used the Komodo Healthcare Map, which is a US claims dataset, to identify patients who began a subsequent line of therapy after triple-class exposure between July 3, 2019, and December 31, 2020.

The researchers followed patients until death, the last claim, or the end of the study period on June 30, 2021. The primary analysis included patients who received a subsequent line of therapy after triple-class exposure. The researchers also analyzed patients who had four or more previous lines of therapy. The index date was defined as the line of therapy start date after each exposure.

The study included 1,704 patients with triple-class exposure, including 1,072 who had four-plus previous lines of therapy. In patients with triple-class exposure, the mean number of prior lines of therapy before the index date was 3.9, while it was 4.7 in patients who had triple-class exposure with four-plus previous lines of therapy.

Nearly all patients with triple-class exposure previously received daratumumab (99.9%), as well as lenalidomide (85.6%) and bortezomib (84.2%) before the index date. In patients who had triple-class exposure with four-plus previous lines of therapy, nearly all had prior exposure to daratumumab (99.8%), as well as lenalidomide (86.4%) and bortezomib (83%) before the index date.

The most common treatments after triple-class exposure were pomalidomide-based regimens, used in 36.0% of patients, followed by daratumumab-based regimens in 35.0% and carfilzomib-based regimens in 33.7%. In patients who had triple-class exposure with four-plus previous lines of therapy, pomalidomide- and carfilzomib-based regimens were the most common therapies after triple-class exposure, each used in 33.8% of patients. Daratumumab-based regimens were used in 30.5% of patients.

At the regimen level, daratumumab and pomalidomide plus or minus dexamethasone was the most common regimen after the index date, used in 8.0% of patients with triple-class exposure and in 6.7% of those who were triple-class exposed with four-plus prior lines of therapy.

The median time to treatment discontinuation or death was 5.8 months in patients with triple-class exposure and 5.1 months in patients who were triple-class exposed with four-plus prior lines of therapy. The median time to next treatment or death was 8.4 months in patients with triple-class exposure and 7.1 months in patients who were triple-class exposed with four-plus prior lines of therapy.

"These findings demonstrate that in the real world, patients have limited treatment options after [triple-class exposure] and are often re-treated with the same therapies or therapies in the same classes," the researchers concluded. "Patients who were [triple-class exposed] discontinued treatment and moved on to next treatment shortly after initial treatment. These outcomes were even shorter for those with [four-plus previous lines]."

Reference

Fonseca R, et al. Real-world treatment patterns and clinical outcomes among patients with triple-class exposed (TCE) multiple myeloma (MM). Abstract P-257. Presented at the 20th International Myeloma Society Annual Meeting. September 27-30, 2023; Athens, Greece.

HemOnc Happenings

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

Hematologic Oncologists Receive Awards From Doris Duke Foundation

Multiple hematologic oncologists have received awards from the Doris Duke Foundation that "will provide mentored research funding and time protection to early-career physician-scientists to advance clinically significant research," according to an announcement from the foundation.

Hermioni Amonoo, MD, MPP, MPH, of the Brigham and Women's Hospital, received an award for a project titled "A Virtual Reality Psychosocial Intervention (BMT-VR) for Patients Undergoing Bone Marrow Transplantation – A Randomized Clinical Trial."

Hermioni Amonoo, MD, MPP, MPH

Anand Bhagwat, MD, PhD, of the Children's Hospital of Philadelphia, received an award for a project titled "Understanding the Role of Cytokine Release Syndrome in CAR T-Cell Therapy for Acute Myeloid Leukemia."

Anand Bhagwat, MD, PhD

Robert Stanley, MD, PhD, of the Memorial Sloan Kettering Cancer Center, received an award for a project titled "Synthetic Introns for Therapeutic Targeting of Myeloid Blood Cancers."

Robert Stanley, MD, PhD

Kaoru Takasaki, MD, of the Children's Hospital of Philadelphia, received an award for a project titled "Dissecting the Interaction of Trisomy 21, GATA1s and STAG2 Mutations in DS Leukemogenesis."

Kaoru Takasaki, MD

"This year's awardees are addressing critical issues that are impacting the health of patients across the United States and beyond," said Sindy Escobar Alvarez, Director for Medical Research at the Doris Duke Foundation, in a news release. "We are proud to support their important contributions, and we cannot wait to see what this group of physician-scientists will accomplish."

Drs. June, Sadelain to Receive 2024 Breakthrough Prize in Life Sciences for CAR-T

Carl June, MD, and **Michel Sadelain, MD, PhD,** will be honored with a 2024 Breakthrough Prize in Life Sciences for the development of chimeric antigen receptor (CAR) T cells.

Carl June, MD

The Breakthrough Prize honors an "esteemed group of the world's most brilliant minds for impactful scientific discoveries, including a subset responsible for substantial progress in the understanding and treatment of major diseases," according to organizers.

Michel Sadelain, MD, PhD

Drs. June and Sadelain were named laureates for the Breakthrough Prize in Life Sciences because "CAR T cells have remarkable rates of success against liquid cancers, including types of leukemia, lymphoma, and myeloma," and "for some patients, the tumors have been entirely eradicated and have not returned, years after treatment," organizers said in a news release.

Dr. June, of the Perelman School of Medicine at the University of Pennsylvania, and Dr. Sadelain, of the Memorial Sloan Kettering Cancer Center, will be honored with other laureates during the Breakthrough Prize ceremony scheduled for April 13, 2024, in Los Angeles, California.

IMS Honors Myeloma Physicians, Researchers at Annual Meeting

The International Myeloma Society (IMS) honored three hematologic oncologists with awards during the 20th IMS Annual Meeting.

Sundar Jagannath, MD, received the Waldenström Lifetime Achievement Award, which is "given to a researcher in recognition of their outstanding long-term contributions to the myeloma field," according to IMS.

Dr. Jagannath, who is a Professor of Medicine at the Mount Sinai School of Medicine, serves as Director of the Myeloma Center of Excellence at Mount Sinai Hospital. IMS officials highlighted his contributions to multiple myeloma treatment and research.

"Dr. Jagannath is being honored for his seminal contributions to the field of myeloma," IMS officials said in an announcement. "He has been a pioneer in transplantation, novel drugs, [chimeric antigen receptor T-cell] therapy, and [bispecific T-cell engagers]. He has established premier myeloma programs in the United States and mentored the next generation of leaders in the field."

Hervé Avet-Loiseau, MD, PhD, received the Ken Anderson Basic and Translational Research Award, which is "given to an investigator in recognition of excellence in translational research in the myeloma field," according to IMS.

Dr. Avet-Loiseau is a Professor of Hematology and serves as Head of the Laboratory for Genomics in Myeloma at the University Hospital Center of Toulouse.

"Dr. Avet-Loiseau is a world leader in genetic risk assessment," IMS officials said in the announcement. "He has defined high-risk disease and led the development of cytogenetic and [fluorescence in situ hybridization]-based classification of the disease. He has also led [next-generation sequencing]-assessed [measurable residual disease] assessment."

Shaji Kumar, MD, received the Bart Barlogie Clinical Investigator Award, which is "given to an investigator in recognition of excellence in research in the myeloma field," according to IMS.

Dr. Kumar is the Mark and Judy Mullins Professor of Hematologic Malignancies at the Mayo Clinic.

"Dr. Kumar has conducted groundbreaking original studies, which include research on survival benchmarks, new drug lab studies and trials, staging systems, and response criteria," IMS officials said in the announcement.

Sundar Jagannath, MD, receives the Waldenström Lifetime Achievement Award. (All photos courtesy of Todd Buchanan.)

Hervé Avet-Loiseau, MD, PhD, is shown with the Ken Anderson Basic and Translational Research Award.

Shaji Kumar, MD, is pictured with the Bart Barlogie Clinical Investigator Award.

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society of hematologic oncology

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HISTORY OF THE SOCIETY OF HEMATOLOGIC ONCOLOGY

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

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

GLOBAL REACH

SOHO represents physicians and other health care professionals from all corners of the world. The SOHO global network supports and is supported by nearly 8,000 members from 122 countries, who are leading vital efforts to further treatments for patients with hematologic malignancies. The society is an organization that focuses on learning and educational excellence, and promotes diversity and inclusion.

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