TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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October 2023

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FDA Approves Momelotinib in Patients with Myelofibrosis Plus Anemia
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Glofitamab Offers High Complete Response Rates for Relapsed or Refractory MCL
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HeMonitor Study Shows Noninvasive Hemoglobin Measurement Is 'Feasible' in Heme Malignancies
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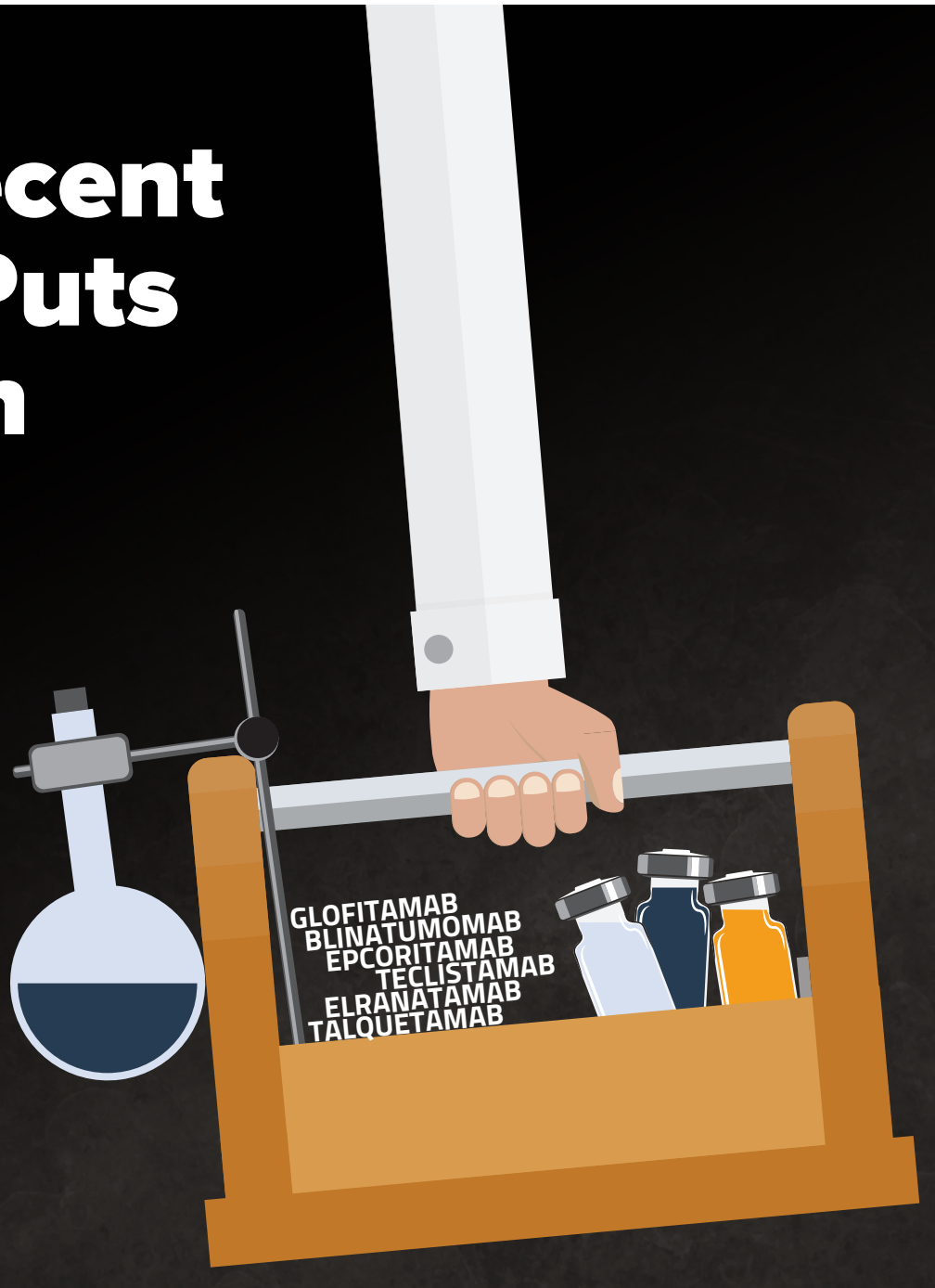
String of Recent Approvals Puts Spotlight on Bispecifics

Here's what they add to the treatment toolbox for hematologic malignancies



With expert opinions from:
Elias Jabbour, MD;
Ajay Nooka, MD, MPH;
and more

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ASSOCIATE EDITOR
KAMI MADDOCKS, MD

A Season of Change

An official publication of

soho
society of hematologic oncology

SUPERIOR EFFICACY IN CLL[1,2]

Superior PFS vs BR in 1L and superior PFS and ORR vs ibrutinib in 2L

ROBUST EFFICACY IN WM[1,3]

~4-year head-to-head data vs ibrutinib

CONSISTENT SAFETY[1-4]

Low rates of cardiac events, including atrial fibrillation/flutter

Explore the data at BRUKINSA.com

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage, including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%) and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥30% of patients who received BRUKINSA (N=1550) included decreased neutrophil count (42%), upper respiratory tract infection (39%), decreased platelet count (34%), hemorrhage (30%), and musculoskeletal pain (30%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

INDICATIONS

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
- Waldenström's macroglobulinemia (WM)

Please see full Prescribing Information including Patient Information.

1L=first line; 2L=second line; BR=bendamustine+rituximab; CLL=chronic lymphocytic leukemia; ORR=overall response rate; PFS=progression-free survival; WM=Waldenström's macroglobulinemia.

References: 1. BRUKINSA. Package insert. BeiGene, Ltd; 2023. **2.** Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(4):319-332. **3.** Tam CS, Garcia-Sanz R, Opat S, et al. ASPEN: long-term follow-up results of a phase 3 randomized trial of zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia. Poster presented at: American Society of Clinical Oncology (ASCO) 2022 Annual Meeting; June 3-7, 2022. Abstract 7521. **4.** Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2022;23(8):1031-1043.

Brukinsa® zanubrutinib 80 mg capsules

BRIEF SUMMARY OF PRESCRIBING INFORMATION
FOR BRUKINSA® (zanubrutinib)
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.2)]*.

1.3 Marginal Zone Lymphoma

BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti–CD20-based regimen.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

BRUKINSA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.4)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre and post surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%), and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.4)]*. Treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately *[see Dosage and Administration (2.4)]*, and consider the risks and benefits of continued BRUKINSA treatment.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single-agent in nine clinical trials, administered at 160 mg twice daily in 1445 patients and at 320 mg once daily in 105 patients. Among these 1550 patients, the median duration of exposure was 26 months, 80% of patients were exposed for at least 12 months, and 58% of patients were exposed for at least 24 months.

In this pooled safety population, the most common adverse reactions (≥30%), including laboratory abnormalities, included neutrophil count decreased (42%), upper respiratory tract infection (39%), platelet count decreased (34%), hemorrhage (30%), and musculoskeletal pain (30%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count ≥75 x 10^9/L and an absolute neutrophil count ≥1 x 10^9/L independent of growth factor support, hepatic enzymes ≤2.5 x upper limit of normal, total bilirubin ≤1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥50 x 10^9/L and an absolute neutrophil count ≥1 x 10^9/L independent of growth factor support, hepatic enzymes ≤3 x upper limit of normal, total bilirubin ≤1.5 x ULN. Both trials required a CLcr ≥30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection, and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer, and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Infections and infestations	Upper respiratory tract infection[a]	39	0
	Pneumonia[b]	15	10[c]
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rash[d]	36	0
	Bruising[e]	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage[f]	11	3.4[c]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[g]	14	3.4
Respiratory, thoracic and mediastinal disorders	Cough	12	0

[a] Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral.
[b] Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral.
[c] Includes fatal adverse reaction.
[d] Rash includes all related terms containing rash.
[e] Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.
[f] Hemorrhage includes all related terms containing hemorrhage, hematoma.
[g] Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.

Other clinically significant adverse reactions that occurred in <10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), and headache (4.2%).

Table 4: Selected Laboratory Abnormalities[a] (>20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	45	20
Lymphocytosis[b]	41	16
Platelets decreased	40	7
Hemoglobin decreased	27	6
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

[a] Based on laboratory measurements.
[b] Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Waldenström's Macroglobulinemia (WM)

The safety of BRUKINSA was investigated in two cohorts of Study BGB-3111-302 (ASPEN). Cohort 1 included 199 patients with MYD88 mutation (*MYD88^{MUT}*) WM, randomized to and treated with either BRUKINSA (101 patients) or ibrutinib (98 patients). The trial also included a non-randomized arm, Cohort 2, with 26 wild type MYD88 (*MYD88^{WT}*) WM patients and 2 patients with unknown MYD88 status *[see Clinical Studies (14.2)]*.

Among patients who received BRUKINSA, 93% were exposed for 6 months or longer, and 89% were exposed for greater than 1 year.

In Cohort 1 of the ASPEN study safety population (N=101), the median age of patients who received BRUKINSA was 70 years (45-87 years old); 67% were male, 86% were White, 4% were Asian and 10% were not reported (unknown race). In Cohort 2 of the ASPEN study safety population (N=28), the median age of patients who received BRUKINSA was 72 (39-87 years old); 50% were male, 96% were White and 4% were not reported (unknown race).

In Cohort 1, serious adverse reactions occurred in 44% of patients who received BRUKINSA. Serious adverse reactions in >2% of patients included influenza (3%), pneumonia (4%), neutropenia and neutrophil count decreased (3%), hemorrhage (4%), pyrexia (3%), and febrile neutropenia (3%). In Cohort 2, serious adverse reactions occurred in 39% of patients. Serious adverse reactions in >2 patients included pneumonia (14%).

Permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 2% of patients in Cohort 1 and included hemorrhage (1 patient), neutropenia and neutrophil count decreased (1 patient); in Cohort 2, permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 7% of patients and included subdural hemorrhage (1 patient) and diarrhea (1 patient).

Dosage interruptions of BRUKINSA due to an adverse reaction occurred in 32% of patients in Cohort 1 and in 29% in Cohort 2. Adverse reactions which required dosage interruption in >2% of patients included neutropenia, vomiting, hemorrhage, thrombocytopenia, and pneumonia in Cohort 1. Adverse reactions leading to dosage interruption in >2 patients in Cohort 2 included pneumonia and pyrexia.

Dose reductions of BRUKINSA due to an adverse reaction occurred in 11% of patients in Cohort 1 and in 7% in Cohort 2. Adverse reactions which required dose reductions in >2% of patients included neutropenia in Cohort 1. Adverse reaction leading to dose reduction occurred in 2 patients in Cohort 2 (each with one event: diarrhea and pneumonia).

Table 5 summarizes the adverse reactions in Cohort 1 in ASPEN.

Table 5: Adverse Reactions (≥10%) Occurring in Patients with WM Who Received BRUKINSA in Cohort 1

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[a]	44	0	40	2
	Pneumonia[b]	12	4	26	10
	Urinary tract infection	11	0	13	2
Gastrointestinal disorders	Diarrhea	22	3	34	2
	Nausea	18	0	13	1
	Constipation	16	0	7	0
	Vomiting	12	0	14	1
General disorders	Fatigue[c]	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising[d]	20	0	34	0
	Rash[e]	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[f]	45	9	39	1
	Muscle spasms	10	0	28	1
Nervous system disorders	Headache	18	1	14	1
	Dizziness	13	1	12	0
Respiratory, thoracic and mediastinal disorders	Cough	16	0	18	0
	Dyspnea	14	0	7	0
Vascular disorders	Hemorrhage[g]	42	4	43	9
	Hypertension	14	9	19	14

[a] Upper respiratory tract infection includes upper respiratory tract infection, laryngitis, nasopharyngitis, sinusitis, rhinitis, viral upper respiratory tract infection, pharyngitis, rhinovirus infection, upper respiratory tract congestion.
[b] Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.
[c] Fatigue includes asthenia, fatigue, lethargy.
[d] Bruising includes all related terms containing bruise, contusion, or ecchymosis.
[e] Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatoses, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, skin toxicity.
[f] Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis, musculoskeletal discomfort.
[g] Hemorrhage includes epistaxis, hematuria, conjunctival hemorrhage, hematoma, rectal hemorrhage, periorbital hemorrhage, mouth hemorrhage, post procedural hemorrhage, hemoptysis, skin hemorrhage, hemorrhoidal hemorrhage, ear hemorrhage, eye hemorrhage, hemorrhagic diathesis, periorbital hematoma, subdural hemorrhage, wound hemorrhage, gastric hemorrhage, lower gastrointestinal hemorrhage, spontaneous hematoma, traumatic hematoma, traumatic intracranial hemorrhage, tumor hemorrhage, retinal hemorrhage, hematochezia, diarrhea hemorrhagic, hemorrhage, melena, post-procedural hematoma, subdural hematoma, anal hemorrhage, hemorrhagic disorder, pericardial hemorrhage, postmenopausal hemorrhage, stoma site hemorrhage, subarachnoid hemorrhage.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included localized infection, atrial fibrillation or atrial flutter, and hematuria.

Table 6 summarizes the laboratory abnormalities in ASPEN.

Table 6: Select Laboratory Abnormalities[a] (≥20%) that Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[b]		Ibrutinib[b]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
Chemistry abnormalities				
Glucose increased	45	2.3	33	2.3
Creatinine increased	31	1	21	1
Calcium decreased	27	2	26	0
Potassium increased	24	2	12	0
Phosphate decreased	20	3.1	18	0
Urate increased	16	3.2	34	6
Bilirubin increased	12	1	33	1

[a] Based on laboratory measurements.
[b] The denominator used to calculate the rate varied from 86 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

Marginal Zone Lymphoma

The safety of BRUKINSA was evaluated in 88 patients with previously treated MZL in two single-arm clinical studies, BGB-3111-214 and BGB-3111-AU-003 *[see Clinical Studies (14.3)]*. The trials required an absolute neutrophil count ≥1 x 10^9/L, platelet count ≥50 or ≥75 x 10^9/L and adequate hepatic function and excluded patients requiring a strong CYP3A inhibitor or inducer. Patients received BRUKINSA 160 mg twice daily (97%) or 320 mg once daily (3%). The median age in both studies combined was 70 years (range: 37 to 95), 52% were male, 64% were Caucasian and 19% were Asian. Most patients (92%) had an ECOG performance status of 0 to 1. Eighty percent received BRUKINSA for 6 months or longer, and 67% received treatment for more than one year.

Two fatal adverse reactions (2.3%) occurred within 30 days of the last dose of BRUKINSA, including myocardial infarction and a Covid-19–related death.

Serious adverse reactions occurred in 40% of patients. The most frequent serious adverse reactions were pyrexia (8%) and pneumonia (7%).

Adverse reactions lead to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%. The leading cause of dose modification was respiratory tract infections (13%).

Table 7 summarizes selected adverse reactions in BGB-3111-214 and BGB-3111-AU-003.

Table 7: Adverse Reactions Occurring in ≥10% Patients with MZL Who Received BRUKINSA

Body System	Adverse Reaction	BRUKINSA (N=88)	
		All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[a]	26	3.4
	Urinary tract infection[b]	11	2.3
	Pneumonia[c,d]	10	6
Gastrointestinal disorders	Diarrhea[e]	25	3.4
	Abdominal pain[f]	14	2.3
	Nausea	13	0
Skin and subcutaneous tissue disorders	Bruising[g]	24	0
	Rash[h]	21	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[i]	27	1.1
Vascular disorders	Hemorrhage[j]	23	1.1
General disorders	Fatigue[k]	21	2.3
Respiratory, thoracic and mediastinal disorders	Cough[l]	10	0

[a] Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, tonsillitis, rhinitis, viral upper respiratory tract infection.
[b] Urinary tract infection includes urinary tract infection, cystitis, Escherichia urinary tract infection, pyelonephritis, cystitis.
[c] Pneumonia includes COVID-19 pneumonia, pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, organizing pneumonia.
[d] Includes 2 fatalities from COVID-19 pneumonia.
[e] Diarrhea includes diarrhea and diarrhea hemorrhagic.
[f] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort.
[g] Bruising includes contusion, ecchymosis, increased tendency to bruise, post procedural contusion.
[h] Rash includes rash, rash maculo-papular, rash pruritic, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug reaction with eosinophilia and systemic symptoms, erythema, photosensitivity reaction, rash erythematous, rash papular, seborrheic dermatitis.
[i] Musculoskeletal pain includes back pain, arthralgia, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal chest pain, bone pain, musculoskeletal discomfort, neck pain.
[j] Hemorrhage includes epistaxis, hematuria, hemorrhoidal hemorrhage, hematoma, hemoptysis, conjunctival hemorrhage, diarrhea hemorrhagic, hemorrhage urinary tract, mouth hemorrhage, pulmonary hematoma, subcutaneous hematoma, gingival bleeding, melena, upper gastrointestinal hemorrhage.
[k] Fatigue includes fatigue, lethargy, asthenia.
[l] Cough includes cough and productive cough.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included peripheral neuropathy, second primary malignancies, dizziness, edema, headache, petechiae, purpura, and atrial fibrillation or flutter.

Table 8 summarizes select laboratory abnormalities.

Table 8: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with MZL

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	43	15
Platelets decreased	33	10
Lymphocytes decreased	32	8
Hemoglobin decreased	26	6
Chemistry abnormalities		
Glucose increased	54	4.6
Creatinine increased	34	1.1
Phosphate decreased	27	2.3
Calcium decreased	23	0
ALT increased	22	1.1

[a] The denominator used to calculate the rate varied from 87 to 88 based on the number of patients with a baseline value and at least one post-treatment value.

Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The safety data described below reflect exposure to BRUKINSA (160 mg twice daily) in 675 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (14.4)]*. The trial required patients to be unsuitable for fludarabine, cyclophosphamide, and rituximab (FCR) therapy defined as age ≥65 years, or age 18 to <65 years with either a total Cumulative Illness Rating Scale (CIRS) >6, creatinine clearance 30 to 69 mL/min, or history of serious or frequent infections. The trial excluded patients with AST or ALT ≥2 times the upper limit of normal (ULN) or bilirubin ≥3 times (ULN) and patients requiring a strong CYP3A inhibitor or inducer.

SEQUOIA

The safety of BRUKINSA monotherapy in patients with previously untreated CLL/SLL was evaluated in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. Patients without deletion of chromosome 17p13.1 (17p deletion) (Cohort 1) received either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity (n=240) or bendamustine plus rituximab (BR) for 6 cycles (n=227). Bendamustine was dosed at 90 mg/m^2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m^2 on day 1 of Cycle 1 and 500 mg/m^2 on day 1 of Cycles 2 to 6.

Additionally, the same BRUKINSA regimen was evaluated in 111 patients with previously untreated CLL/SLL with 17p deletion in a non-randomized single arm (Cohort 2).

Randomized cohort: Previously untreated CLL/SLL without 17p deletion

In patients with previously untreated CLL/SLL without 17p deletion, the median age was 70, 62% were male, 89% were White, 2% were Asian, and 2% were Black. Most patients (93%) had an ECOG performance status of 0 to 1.

The median duration of exposure to BRUKINSA was 26 months, with 71% exposed for more than 2 years.

Serious adverse reactions occurred in 36% of patients who received BRUKINSA. Serious adverse reactions that occurred in ≥5% of patients were COVID-19, pneumonia, and second primary malignancy (5% each). Fatal adverse reactions occurred in 11 (4.6%) patients with the leading cause of death being COVID-19 (2.1%).

Adverse reactions led to permanent discontinuation of BRUKINSA in 8% of patients, dose reduction in 8%, and dose interruption in 46%. The most common adverse reactions leading to permanent discontinuation were second primary malignancy and COVID-19. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and hemorrhage.

Table 9 summarizes select adverse reactions in this randomized cohort.

Table 9: Adverse Reactions in ≥10% Patients with Previously Untreated CLL/SLL Without 17p Deletion in SEQUOIA

System Organ Class Preferred Term	CLL/SLL without 17p deletion			
	BRUKINSA (N=240)		BR (N=227)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a]	33	1.7	17	0.4
Infections and infestations				
Upper respiratory tract infection[b]	28	1.3	15	0.9
Pneumonia[c]	13*	5	8†	4
Vascular disorders				
Hemorrhage[d]	27*	4	4	0.4
Hypertension[e]	14	7	5	2.6
Skin and subcutaneous tissue disorders				
Rash[f]	24	1.3	30	5
Bruising[g]	24	0	2.6	0
Respiratory, thoracic and mediastinal disorders				
Cough[e]	15	0	10	0
Gastrointestinal disorders				
Diarrhea	14	0.8	12†	0.9
Constipation	10	0.4	18	0.0
Nausea	10	0	33	1.3
General disorders				
Fatigue[h]	14	1.3	21	1.8
Neoplasms				
Second primary malignancy[i]	13*	6	1.3	0.4
Nervous system disorders				
Headache[e]	12	0	8	0
Dizziness[j]	11	0.8	5	0

* Includes 3 fatal outcomes.
† Includes 2 fatal outcomes.
[a] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, musculoskeletal discomfort, bone pain.
[b] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, laryngitis, tonsillitis and upper respiratory tract inflammation, and related terms.
[c] Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.
[d] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[e] Includes multiple similar adverse reaction terms.
[f] Rash: Rash, dermatitis, drug eruption, and related terms.
[g] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[h] Fatigue: fatigue, asthenia, and lethargy
[i] Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including lung, renal, genitourinary, breast, ovarian, and rectal), and chronic myeloid leukemia.
[j] Dizziness: dizziness and vertigo.

Other clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included COVID-19 (9%), edema (8%), abdominal pain (8%), urinary tract infection (7%), and atrial fibrillation or flutter (3.3%).

Table 10 summarizes select laboratory abnormalities in this cohort.

Table 10: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA		BR	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	37	15	80	53
Hemoglobin decreased	29	2.5	66	8
Platelets decreased	27	1.7	61	11
Leukocytes increased	21[b]	21	0.4	0.4
Chemistry abnormalities				
Glucose increased[c]	55	7	67	10
Creatinine increased	22	0.8	18	0.4
Magnesium increased	22	0	14	0.4
Alanine aminotransferase increased	21	2.1	23	2.2

[a] The denominator used to calculate the rate was 239 in the BRUKINSA arm and 227 in the BR arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.
[b] Lymphocytes increased in 15%.
[c] Non-fasting conditions.

Single-arm cohort: Previously untreated CLL/SLL and 17p deletion

In 111 patients with previously untreated, 17p del CLL/SLL, the median age was 70, 71% were male, 95% were White, and 1% were Asian. Most patients (87%) had an ECOG performance status of 0 to 1. The median duration of exposure to BRUKINSA was 30 months.

Fatal adverse reactions occurred in 3 (2.7%) patients, including pneumonia, renal insufficiency, and aortic dissection (1 patient each).

Serious adverse reactions occurred in 41% of patients treated with BRUKINSA. Serious adverse reactions reported in ≥5% of patients were pneumonia (8%) and second primary malignancy (7%).

Adverse reactions led to treatment discontinuation in 5% of patients, dose reduction in 5%, and dose interruption in 51%. The leading causes of dose modification (≥5% of all patients) were pneumonia, neutropenia, second primary malignancy, and diarrhea.

Table 11 summarizes select adverse reactions in this cohort.

Table 11: Adverse Reactions in ≥10% of Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

System Organ Class Preferred Term	CLL/SLL with 17p Deletion	
	BRUKINSA (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations		
Upper respiratory tract infection[a]	38	0.0
Pneumonia[b]	20*	8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[c]	38	2.7
Skin and subcutaneous tissue disorders		
Rash[d]	28	0.0
Bruising[e]	26	0.9
Vascular disorders		
Hemorrhage[f]	28	4.5
Hypertension[g]	11	5.4
Neoplasms		
Second primary malignancy[h]	22†	6
Gastrointestinal disorders		
Diarrhea	18	0.9
Nausea	16	0.0
Constipation	15	0.0
Abdominal pain[g]	12	1.8
Respiratory, thoracic and mediastinal disorders		
Cough[g]	18	0.0
Dyspnea[g]	13	0.0
General disorders and administration site conditions		
Fatigue[i]	14	0.9
Nervous system disorders		
Headache	11	1.8

* Includes 1 fatal outcome.
† Includes non-melanoma skin cancer in 13%.
[a] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, upper respiratory tract inflammation, viral upper respiratory tract infection, and related terms.
[b] Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, and related terms including specific types of infection.
[c] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, bone pain.
[d] Rash: Rash, dermatitis, toxic skin eruption, and related terms.
[e] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[f] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[g] Includes multiple similar adverse reaction terms.
[h] Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including bladder, lung, renal, breast, prostate, ovarian, pelvis, and ureter), and malignant melanoma.
[i] Fatigue: fatigue, asthenia, and lethargy.

Clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included urinary tract infection (8%), edema (7%), atrial fibrillation or flutter (4.5%), and COVID-19 (3.6%).

Table 12 summarizes select laboratory abnormalities in this cohort.

Table 12: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	42	19[b]
Hemoglobin decreased	26	3.6
Platelets decreased	23	0.9
Chemistry abnormalities		
Glucose increased[c]	52	6
Magnesium increased	31	0
Creatinine increased	27	0.9

[a] The denominator used to calculate the rate varied from 110 to 111 based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.
[b] Grade 4, 9%.
[c] Non-fasting conditions.

ALPINE

The safety of BRUKINSA monotherapy was evaluated in patients with previously treated CLL/SLL in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. In ALPINE, 324 patients received BRUKINSA monotherapy, 160 mg orally twice daily and 324 patients received ibrutinib monotherapy, 420 mg orally daily until disease progression or unacceptable toxicity.

In ALPINE, the median duration of exposure was 24 months for BRUKINSA. Adverse reactions leading to death in the BRUKINSA arm occurred in 24 (7%) patients. Adverse reactions leading to death that occurred in >1% of patients were pneumonia (2.8%) and COVID-19 infection (1.9%).

One hundred and four patients in the BRUKINSA arm (32%) reported ≥1 serious adverse reaction. Serious adverse reactions occurring in ≥5% of patients were pneumonia (10%), COVID-19 (7%), and second primary malignancies (5%).

Adverse reactions led to treatment discontinuation in 13% of patients, dose reduction in 11%, and dose interruption in 42%. The leading cause of treatment discontinuation was pneumonia. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and neutropenia.

Table 13 summarizes select adverse reactions in ALPINE.

Table 13: Adverse Reactions in ≥10% of Patients with Relapsed or Refractory CLL/SLL Who Received BRUKINSA in ALPINE

System Organ Class Preferred Term	BRUKINSA (N=324)		Ibrutinib (N=324)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Upper respiratory tract infection[a]	27	1.2	22	1.2
Pneumonia[b]	18*	9	19†	11
COVID-19[c]	14*	7	10†	4.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[d]	26	0.6	28	0.6
Vascular disorders				
Hemorrhage[e]	24*	2.5	26†	3.7
Hypertension[f]	19	13	20	13
Skin and subcutaneous tissue disorders				
Rash[g]	20	1.2	21	0.9
Bruising[h]	16	0.0	14	0.0
Gastrointestinal disorders				
Diarrhea	14	1.5	22	0.9
General disorders				
Fatigue[i]	13	0.9	14	0.9
Respiratory, thoracic and mediastinal disorders				
Cough[f]	11	0.3	11	0.0
Nervous system disorders				
Dizziness[f]	10	0.0	7	0.0

* Includes fatal outcomes: pneumonia (9 patients), COVID-19 (8 patients), and hemorrhage (1 patient).
† Includes fatal outcomes: pneumonia (10 patients), COVID-19 (9 patients), and hemorrhage (2 patients).
[a] Upper respiratory tract infection: upper respiratory tract infection, sinusitis, pharyngitis, rhinitis, nasopharyngitis, laryngitis, tonsillitis, and related terms.
[b] Pneumonia: Pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.
[c] COVID-19: COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, SARS-CoV-2 test positive.
[d] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, bone pain, and musculoskeletal discomfort.
[e] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[f] Includes multiple similar adverse reaction terms.
[g] Rash: Rash, Dermatitis, and related terms.
[h] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[i] Fatigue: asthenia, fatigue, lethargy.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included urinary tract infection (9%), supraventricular arrhythmias (9%) including atrial fibrillation or flutter (4.6%), abdominal pain (8%), headache (8%), pruritus (6.2%), constipation (5.9%), and edema (4.6%).

Table 14 summarizes select laboratory abnormalities in ALPINE.

Table 14: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received BRUKINSA in ALPINE

Laboratory Abnormality[a]	BRUKINSA		Ibrutinib	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	43	15	33	16
Hemoglobin decreased	28	4	32	3.7
Lymphocytes increased	24	19	26	19
Platelets decreased	22	4	24	3.4
Chemistry abnormalities				
Glucose increased	52	5	29	2.8
Creatinine increased	26	0.0	23	0.0
Phosphate decreased	21	2.5	13	2.2
Calcium decreased	21	0.6	29	0.0

[a] The denominator used to calculate the rate was 321 in the BRUKINSA arm, and varied from 320 to 321 in the ibrutinib arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 15: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when coadministered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid coadministration of BRUKINSA with strong CYP3A inducers *[see Dosage and Administration (2.3)]*. • Avoid coadministration of BRUKINSA with moderate CYP3A4 inducers *[see Dosage and Administration (2.3)]*. If these inducers cannot be avoided, increase BRUKINSA dosage to 320 mg twice daily *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

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

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2 or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre and postnatal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g., cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for 1 week following the last dose of BRUKINSA. 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 men to avoid fathering a child while receiving BRUKINSA and for 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1550 patients with MCL, MZL, WM, and CLL/SLL in clinical studies with BRUKINSA, 61% were ≥65 years of age, and 22% were ≥75 years of age. Patients ≥65 years of age had numerically higher rates of Grade 3 or higher adverse reactions and serious adverse reactions (63% and 47%, respectively) than patients <65 years of age (57% and 36%, respectively). No overall differences in effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥15 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

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SOHO Highlights 2023: State of the Art & Next Questions
Virtual

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

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

November 2–4
European Hematology Association-Specialized Working Group Scientific Meeting on MDS/MPN/AML
Budapest Novotel City
and Congress Center
Budapest, Hungary

November 10–11
ASTCT/EBMT 6th International Conference on Relapse After Transplant and Cellular Therapy
Sheraton Universal Hotel
Los Angeles, California

December 1–3
European Society for Medical Oncology (ESMO) Asia Congress 2023
Suntec Singapore Convention
and Exhibition Centre
Singapore

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

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

February 2–4, 2024
Clinical Hematology & Oncology 2024 Conference
Hyatt Regency La Jolla at Aventine
San Diego, California

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

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

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

Associate Editor's Message

A Season of Change

Kami Maddocks, MD
Associate Editor

The season of fall is upon us. Fall is considered a time to let go, accept change, make room for new things, thrive, and grow. The practice of medicine, in many ways, can cycle like the seasons do, with scientific discovery challenging our standards and creating opportunities to replace less effective or more toxic therapies with novel treatments.

The time preceding annual scientific meetings is filled with intrigue and excitement. There is the anticipation of practice-changing data to be presented, counterpoints to be debated, and the resulting scientific exchange that moves the field forward. It also serves as a time to reflect on significant advances in the treatment of hematologic malignancies.

As I prepared slides on "Emerging Novel Agents in Mantle Cell Lymphoma" for the Eleventh Annual Meeting of the Society of Hematology Oncology, I reflected on the last decade of treatment advances for mantle cell lymphoma (MCL), from the accelerated approval of the first oral targeted therapy to the recent withdrawal of the US Food and Drug Administration (FDA) indication for that same therapy.

Ibrutinib, a first-in-class Bruton's tyrosine kinase inhibitor (BTKi), received accelerated approval for the treatment of relapsed or refractory MCL in November 2013. Without a doubt, ibrutinib changed the treatment landscape for patients with relapsed or refractory MCL. The efficacy of ibrutinib in B-cell malignancies was shown in early-phase clinical trials during my hematology/oncology fellowship. The promising efficacy of ibrutinib in various B-cell malignancies resulted in trials evaluating ibrutinib alone or in combination with other agents, and our institution offered several such trials. As an early-career clinical investigator, I was very fortunate to practice in a time that afforded the opportunity to offer patients an effective new therapy. It was a humbling experience when a sick, symptomatic patient with a poor prognosis had rapid improvement of disease burden and symptoms. At the same time, I will never forget the faces and stories of less fortunate patients deemed ineligible for these trials—patients who may have had access to a life-saving treatment if they were diagnosed a year later.

As more patients received ibrutinib therapy, serious adverse events emerged, including bleeding and atrial fibrillation. Clinical trials with acalabrutinib were pursued. As a second-generation BTKi, acalabrutinib is more selective for BTK, resulting in less "off-target" kinase inhibition, which is hypothesized to result in an improved safety profile. Acalabrutinib received accelerated approval for relapsed or refractory MCL in October 2017. Another second-generation BTKi, zanubrutinib, received accelerated approval in November 2019.

While no randomized trials have been conducted in MCL with the various BTKis, clinical trial data suggested similar efficacy but improved safety profiles with the second-generation BTKis, including a lower incidence of cardiac events and bleeding. Those findings were confirmed by randomized trials in other B-cell malignancies. With time, more physicians were electing to treat patients with subsequent BTKis.

Most patients with MCL respond to treatment with BTKis, but nearly all develop resistance. Numerous clinical trials have been conducted to improve outcomes evaluating doublet and triplet combinations in the relapsed setting along with efforts to move BTKis into the frontline setting. Naturally, with ibrutinib being the first available and approved BTKi, the bulk of existing clinical trial data includes ibrutinib.

Resistance to BTKis in MCL is not fully elucidated, with activation of bypass pathways and acquired mutations playing a role. Sequencing approved covalent BTKis (cBTKis) at progression is not effective; however, the first-in-class noncovalent BTKi, pirtobrutinib, demonstrated durable efficacy in patients who progress on prior cBTKi treatment. Pirtobrutinib received accelerated approval in February 2023, offering an effective therapy for select patients with MCL who progress on a cBTKi, including patients unable to receive chimeric antigen receptor (CAR) T-cell therapy and patients who require treatment to bridge to CAR-T. The ongoing phase III BRUIN321 trial randomizes patients with BTKi-naive MCL to pirtobrutinib versus investigator's choice cBTKi.

In April 2023, almost a decade after the accelerated approval of ibrutinib for relapsed MCL, the indication in MCL was voluntarily withdrawn. This decision was based on results of the randomized, phase III, confirmatory study, the SHINE trial, that evaluated ibrutinib in combination with chemoimmunotherapy plus rituximab maintenance in frontline treatment of older patients with MCL. This trial showed the addition of ibrutinib prolonged progression-free survival (the primary endpoint of the study), but not overall survival, and it resulted in increased toxicity, including deaths. The life cycle for ibrutinib in treating MCL had come to an end.

The news of the withdrawal of ibrutinib initially came as a surprise. Like most physicians, I had transitioned to treating patients with alternative BTKis. However, I felt uncertainty for patients currently on trials being treated with ibrutinib-containing regimens. I pondered the resulting impact if the SYMPATICO trial concludes that ibrutinib plus venetoclax is superior to ibrutinib alone. Further, so much excitement surrounded the recently reported TRIANGLE study, which showed the benefit of ibrutinib in the frontline treatment of younger patients with MCL, including suggesting a potential end to autologous hematopoietic stem cell transplantation.

Over time, the treatment paradigm for MCL has transformed from the sole use of chemoimmunotherapy to the availability of less effective targeted therapies to currently available, highly effective targeted agents and immunotherapies. It is my belief the future treatment of MCL will eliminate chemotherapy, despite the current lack of FDA approval for frontline BTKis. Without a doubt, ibrutinib was a novel therapy that saved the lives of patients with MCL.

How fortunate for patients that in just under 10 years we were able to "let go" of a therapy that revolutionized treatment for a disease because science led us to a better approach. And how remarkable it is to have the honor of being a physician who can offer new treatments to patients.

Scan the QR code to catch up on the SOHO 2023 on-demand content

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

Eleventh Annual Meeting of SOHO Is Largest in Society's History

The Eleventh Annual Meeting of the Society of Hematologic Oncology (SOHO) was held in Houston, Texas, September 6 through 9, 2023, bringing together clinicians and researchers for a comprehensive showcase of the latest research in hematologic oncology.

With more than 2,500 registrants attending in person or online, the meeting was the largest ever.

Jennifer Brown, MD, PhD, who served as the 2022-2023 SOHO President, said the annual meeting has "grown considerably over time." The attendance for this year's meeting was larger "than any other year since it was established in 2012." She added the meeting featured 180 presentations, with more than 150 speakers presenting at 14 general sessions across the spectrum of blood cancers.

"As a Society, we are a dedicated group of academicians, clinicians, research scientists, and related specialists who are committed to advancing efforts in research and treatment," she said during the opening ceremony. "We accomplish part of this mission through the exchange of scientific information. We believe that every member of the Society plays a valuable role in reaching this goal."

She also shared why she chose personalized medicine as the theme for the 2023 meeting.

"As our understanding of the underlying mechanisms of these malignancies [becomes better], we improve our ability to predict which treatments will work best for specific patients," Dr. Brown said. "The ultimate goal of personalized therapy is to improve outcomes by designing patient-specific plans rather than one size fits all."

Dr. Brown highlighted SOHO's monthly publication, *Blood Cancers Today,* as well as SOHO's partnership with DocMatter, a global medical community platform that SOHO members can use for in-depth clinical conversations.

Dr. Brown also spoke about the SOHO Ambassador Program.

"In an effort to increase geographical diversity and promote international understanding among hematologic oncology experts from different parts of the world, SOHO created the SOHO Ambassador Program," she said. "Each member of the program acts as an ambassador for the Society in their respective country."

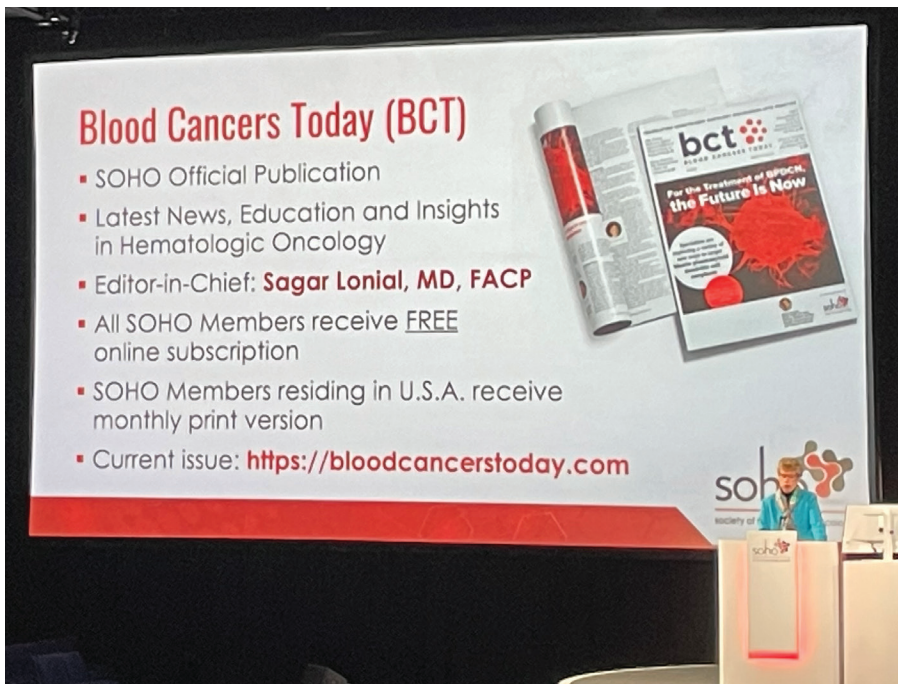
On the final day of the meeting, Dr. Brown welcomed the 2023-2024 SOHO President, **Guillermo Garcia-Manero, MD, PhD,** who said he was honored to be chosen for the role in an interview with *Blood Cancers Today.*

"I'm not someone who plans or thinks, 'In five years, I want to be the president of SOHO,'" he said. "Often, opportunities happen unexpectedly, so when I was nominated for the position, I said, 'Yes, absolutely, I would love to do this.' I'm honored that I was selected."

More than **2,500** attendees from **38 countries** were represented at the **Eleventh Annual Meeting of SOHO**

Scan the QR code to learn more about SOHO-DocMatter

Scan the QR code to read more about the SOHO Ambassador Program



Dr. Jennifer Brown highlights *Blood Cancers Today* during the opening session at the Eleventh Annual Meeting of SOHO. Courtesy photo.

Dr. Jennifer Brown hands off the SOHO presidency to Dr. Guillermo Garcia-Manero. (Photo courtesy of Barry Smith/SOHO.)

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Get to Know

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

Jerald Radich, MD

Dr. Radich, a Professor in the Translational Science and Therapeutics Division and the Kurt Enslein Endowed Chair at Fred Hutchinson Cancer Center, reflects on lessons in cowboy medicine, the genetics of luck, and a serendipitous meeting that impacted care for patients with chronic myeloid leukemia (CML) around the world.

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

I grew up in Sonoma, California, which was then a small town of about 3,000 people. I lived there for most of my childhood and then moved to Santa Rosa. I'm a small-town guy. My dad is from an immigrant family that came from Yugoslavia. My mom was a "*Grapes of Wrath* Okie" child, moving slowly from Oklahoma to California while living in government camps and picking crops. My sister was the first on either side of the family to get any college education. I was the first to do any graduate education.

I was sick a lot as a kid. I had a pretty visceral feeling for what physicians could do. I thought a career caring for people would be good. I liked the idea of doing something empathetic as a career.

The work I do now was never contemplated as a career for anyone I knew when I was growing up, especially me. Like many vaguely coordinated kids, I grew up thinking about playing sports, but I too soon discovered that my night vision was never going to allow me to do that (eg, the curveball). It was clear that using my head was my way to make a living.

During college, medicine was part of the picture, but I wasn't that intrigued by science at the time. I was into literature and fiction writing. It's ironic because you can say that what I do now is mostly fiction writing. We think it's fact now, but 20 years from now, anyone who bothers to read it will say, "What were they thinking?"

Along the line, I became interested in molecular biology and evolution. I went to graduate school for epidemiology and became more interested in medicine. Medicine was a place where I could do science-based work with empathy as the bedrock.

What led you to specialize in hematologic oncology?

I knew I wanted to do academic medicine, but it was difficult to decide on the specialty because I liked pulmonary intensive care, infectious disease, and nephrology. I liked oncology because of the basic science.

It seemed like oncology was where everything came together. Oncology was dealing with life and death. There wasn't a lot of gray area. Oncology was the distillation of all the intense medicine that I liked. Empathy is the touchstone because most things weren't going to work out well and you had to be both a scientist and a priest.

By the time I got out of medical school, I knew I wanted to do oncology. The question was whether I wanted to do pediatric or adult oncology. I interviewed for residencies in both, and I couldn't make up my mind. I filled up both match lists, had two FedEx envelopes ready, and I flipped a coin. I dropped one envelope in the mailbox and one in the trash. Internal medicine it was.

Was there a particular mentor who shaped your path in medicine?

When I was an early second-year resident, I got an elective at the Fred Hutchinson Cancer Center. That was in the 1980s, when bone marrow transplant was in its early days, and Fred Hutch was where it was happening. It was the most amazing place because things were going on there that were not happening anywhere else.

Every day was something new, something that people hadn't seen before. It was wild. It was like cowboy medicine. We were doing our best, but we were seeing things that people hadn't described before. It was quite a thing—full of invention, excitement, and an emotional roller coaster. At the end of that rotation, I said, "That's what I am going to do."

E. Donnall Thomas, MD, who won the 1990 Nobel Prize in Physiology or Medicine,* was the boss. He was a character to try to emulate because he was a stoic, west Texan gent. He had a singular sense of purpose, an intensely curious and active mind, and an interesting and dry sense of humor. When he started doing bone marrow transplantation, many people thought he was way out there, but he stuck with it and got the Nobel Prize. There was a cool determination that he had about doing things in a stepwise way. He was calm but driven. He was an excellent role model. You just didn't want to disappoint Don.

"We invented the concept of major molecular remission, which we defined as a three-log decrease in *BCR-ABL1* from diagnosis. It was an ad hoc analysis of the IRIS data, and we made up the term for the *New England Journal of Medicine* paper, but I don't think any of us really expected it to stick."

What led to your interest in diagnostics and studying what you've referred to as the "genetics of luck"?

My dad was good with his hands. He was drafted by the St. Louis Cardinals but chose to join the US Army Air Corps. He was a flight engineer on B24s flying over the hump into China during World War II. He was good at MacGyvering things on the fly. At home, what he couldn't do, he built. When I went to look at labs during the start of my fellowship, I admit that rather than being interested in biology alone, I was interested in what we could do mechanically to ask our questions.

The lab I worked in had the first polymerase chain reaction (PCR) machine in Seattle, and I broke the first PCR machine in Seattle about eight hours later. I was interested in making things up and designing new assays because it was fun. Eventually, that's

**The prize was awarded jointly to Joseph E. Murray and E. Donnall Thomas.*

what got me into diagnostics. It was looking at ways to detect disease when everyone else couldn't see it—the so-called minimal residual disease then—and building a better mousetrap to be able to find a needle in the haystack, that leukemia cell in a background of normal cells.

In one of the first grants I submitted, I wrote something like, "We think if we develop PCR methods to reliably predict relapse, that can be used to define therapies and pharmaceutical endpoints for trials." That was pure unvarnished grantsmanship, and darned if that didn't turn out to be what happened. It sounded good at the time, and I probably thought it could happen, but I never could have guessed how far and deep the concept of residual disease would catch on.

You were part of a team that helped to establish the international scale for *BCR-ABL1* testing and you worked to develop the first automated assay for *BCR-ABL1*. What was that process like?

The person who pushed standardization the most was my colleague **Susan Brandford, PhD,** of the University of Adelaide. She did the lion's share of work. We began using *BCR-ABL1* testing in the IRIS trial, which was the first international study of imatinib, the first tyrosine kinase inhibitor in CML. We found that by testing peripheral blood for *BCR-ABL1* at the end of 12 months, you could tell who would do well farther on. From that, the field took off. We invented the concept of major molecular remission (MMR), which we defined as a three-log decrease in *BCR-ABL1* from diagnosis. It was an ad hoc analysis of the IRIS data, and we made up the term for the *New England Journal of Medicine* paper, but I don't think any of us really expected it to stick. As it turns out, when people started doing retrospective analysis on all their phase II studies, the MMR concept worked in predicting the long-term success of imatinib.

Sue led the rest of us to design an international scale for *BCR-ABL1* testing. It allowed all labs to be set to the same standard so we could compare *BCR-ABL1* levels from lab to lab, trial to trial. Each lab had a dummy variable that they would multiply their value by to get to this international scale. The main advantage is we were able to—for the first time—change the natural history of how pharmaceutical trials are done. Subsequent CML trials with the new inhibitors used MMR at 12 months as one of the primary endpoints, changing five- to 10-year overall survival studies to very quick molecular endpoint trials.

The story behind developing the automated cartridges for testing is filled with twists. The story involves The Max Foundation in Seattle, founded and led by **Pat Garcia-Gonzalez.** Her son, Max, died because they couldn't find a bone marrow transplant donor for him (this was before the introduction of imatinib). She started the foundation as an outreach, education, and support organization for patients with CML in low-resource countries, starting in Central and South America.

Once imatinib was approved, she went to Novartis, the manufacturer of the drug. They came to an agreement that if Garcia-Gonzalez could diagnose patients with CML in a place in the world where they didn't have the drug, they would give that patient the drug for life.

A volunteer from The Max Foundation was setting up their computer system and Pat was lamenting that she had these patients in Central America who she believed had had CML, but she couldn't prove it. She couldn't test them, as no local facilities could even do the most basic of diagnostic tests. The volunteer told her to come speak with me.

Dr. Gerald Radich training for a Obliteride century ride. Courtesy photo.

It turns out that volunteer was a patient who had CML , and I had transplanted him 10 years before. He and I kept in touch. From that, we started doing testing for CML, first in patients from El Salvador. They would get us blood samples, we tested the samples, and patients would receive the drug if they had CML.

We then tried to partner with the foundation to set up labs in various countries, which turned out to be difficult because many places didn't have reliable electricity and you can't get the reagents into the labs. We needed another way to test.

Around that time, Cepheid approached me about cartridge assays. At the time they were a company testing for bioterrorism pathogens, starting after the anthrax attack in 2001. One of their main technologists came to work in my lab for three years, and we developed a cartridge assay for *BCR-ABL1*. That was cool, but what's even cooler is at about the same time, Cepheid developed cartridge assays for tuberculosis, HIV, and other diseases. The World Health Organization backed them and started paying to place Cepheid machines in the field all over the world. We were able to piggyback on that. Cepheid donated cartridges to The Max Foundation to provide access to CML testing around the globe.

The Max Foundation now takes care of about 60,000 to 80,000 patients with CML worldwide. They receive free treatment and testing. If you look at those patients, they have the same lifespan as newly diagnosed patients in Seattle. This is a remarkable arc of a story that arose from luck and happenstance.

What are your favorite hobbies and activities outside of work?

I play almost any sport with a ball, road bike, and I ran a lot before a recent knee replacement. Besides work, my perfect day would be having an exercise trifecta where I bike, play tennis, and go play golf.

Is there a skill, hobby, or experience you've had that people might be surprised to know about?

I am a minister of the Universal Life Church and have done around a dozen weddings. The most curious wedding was an impromptu one. I was at a wedding where the minister never showed up, so I officiated an Amish wedding in front of 200 people on the fly. Talk about luck.

***Jerald Radich, MD,** is a Professor in the Translational Science and Therapeutics Division and the Kurt Enslein Endowed Chair at the Fred Hutchinson Cancer Center.*

No Simple Solutions: Oncology Drug Shortage Persists

Limited supplies of common treatments for blood cancers are creating a ripple effect across the field

By Cecilia Brown

Critical drugs used to treat cancer are in short supply in the United States and around the world. The shortage touches all aspects of hematologic oncology, from common chemotherapy regimens to transplantation, cellular therapy, and clinical trials. While the reasons behind the shortage are complex, one thing is painfully clear.

"It is not exactly a black and white situation, but it is definitely affecting patient care," said **Marcos de Lima, MD,** Director of the Blood and Bone Marrow Transplant and Cellular Therapy Program at the Ohio State University Comprehensive Cancer Center–James Cancer Hospital and Solove Research Institute.

As the oncology drug shortage persists, many are grappling with its impact and trying to find solutions for patients. However, without a clear-cut solution or end in sight, the situation can feel precarious at times.

"A key issue is uncertainty," **Erin R. Fox, PharmD, MHA, BCPS, FASHP,** Associate Chief Pharmacy Officer of Shared Services at the University of Utah Health and an Adjunct Professor at the University of Utah College of Pharmacy, said in a statement to *Blood Cancers Today*. "Allocations mean that providers can only access products in small amounts week to week. This helps ensure fair access, but because the amounts are uncertain, clinicians don't know if there will be enough product available in three to four weeks for a patient's next treatment."

The list of drug shortages from the US Food and Drug Administration (FDA) included multiple oncology drugs, including numerous agents used to treat blood cancers, as of August 2023.[1] Of particular concern for many, are the shortages of carboplatin and cisplatin, which are used as single agents and in combinations to treat a variety of cancers.

"In addition to treatment, they're also used within clinical trials, so in terms of both clinical care and research in the oncology space, this shortage of cisplatin and carboplatin has a dramatic impact," said **Alyssa Schatz, MSW,** Senior Director of Policy and Advocacy for the National Comprehensive Cancer Network (NCCN).

Beyond these two well-known chemotherapy agents, several other key drugs used to treat blood cancers are also on the FDA list of shortages. These drugs include injectable azacitidine, methotrexate

injections and tablets, injectable cladribine, injectable cytarabine, injectable dacarbazine, and injectable fludarabine phosphate.[1]

The shortage of fludarabine phosphate, which is often used with busulfan or melphalan in conditioning regimens for patients undergoing allogeneic hematopoietic stem cell transplant (HSCT), represents an additional challenge in the transplant process.[2] Even drugs associated with chemotherapy, such as palifermin, are in shortage.[1]

"[Palifermin] helps prevent a complication of high-dose chemotherapy called mucositis and inflammation of the mouth and esophagus," Dr. de Lima said. "It has simply disappeared. Supposedly, we should see it again toward the end of this year. I'm still waiting. This is one you cannot find."

How Does the Oncology Drug Shortage Impact Patients, Clinical Trials?

With multiple drugs in shortage, the effect can be felt throughout the entire field of oncology. "The ongoing shortages of common generic chemotherapy agents such as cisplatin, carboplatin, and methotrexate are challenging for health systems and providers," Dr. Fox said.

In terms of hematologic oncology, Dr. de Lima pointed to the impact on transplant and cellular therapies, which often require the use of regimens based upon drugs that are currently in short supply.

"Basically, folks are having to resort to drugs that are less studied or were deemed inferior back in the late 1990s and early 2000s," he said. "There are cousins of fludarabine that were not used simply because they were deemed inferior way back when. People are having to improvise a little bit to compensate."

The shortage of fludarabine, which is used in reduced-intensity conditioning regimens for HSCT, has a major impact on certain patients.

"The fastest growing segment in transplant today is people above 60 and 65 years of age, and fludarabine is a backbone of this preparation," he said.

In terms of fludarabine, Dr. de Lima noted his institution was "lucky" because it "had a large supply" of the drug. However, the shortage still had an impact.

"We had to limit its use for a while by prioritizing transplants, but at other institutions I know people have been struggling a lot," he said.

Another group of patients who are particularly impacted are those preparing to receive chimeric antigen receptor (CAR) T cells because a lymphodepletion regimen involving fludarabine is used "almost universally" in this setting, Dr. de Lima said.

"The regimens without fludarabine are considered not so good," he explained. "I know that several places had to improvise as well for CAR-T cells. There are alternatives, but … some of them are not listed, some insurance [providers] may look at them and say, 'What are you doing? This is not a priority approval.'"

The NCCN Drugs & Biologics Compendium—a reference containing over 500 entries for drugs across the oncology space—is a resource that can help providers identify alternatives to drugs that are currently in short supply.[3] It can help clinicians navigate potential options by providing "authoritative, scientifically derived information designed to support decision-making about the appropriate use of drugs and biologics in patients with cancer," according to information from the NCCN.[3]

Dr. de Lima and Schatz both pointed to the NCCN Guidelines, which the NCCN Drugs & Biologics Compendium is based upon, as a resource to help negotiate with insurers. However, they both emphasized that there still can be challenges in terms of insurance approval for alternatives.

"The good news is that there are safe alternatives in many cases in times of a drug shortage," Schatz said. "But one thing that we are concerned about at NCCN is that a lack of guidance and clarification from payers may cause harmful delays in care when those alternatives aren't covered quickly."

"Basically, folks are having to resort to drugs that are less studied or were deemed inferior back in the late 1990s and early 2000s." *—Marcos de Lima, MD*

While it can be difficult to find a suitable alternative that is covered by insurance for patients who are treated in a more routine setting, clinical trials face additional challenges. The protocols for many clinical trials have strict requirements about the exact drugs and sequencing used in the trial. For example, a clinical trial might prescribe fludarabine, cyclophosphamide, and CAR-T cells as a specific treatment sequence.

In certain settings, institutions might prioritize the clinical trial, "because with clinical trials, you don't have an option," Dr. de Lima said. However, "other places had to either slow down or shut down those studies for a while because they didn't have the drug available," he added.

The delay or halt of clinical trials impacts not only individual patients, but the overall advancement of hematologic oncology research and treatment.

"I think [the shortage] potentially affected both trials in cell therapy and bone marrow transplants that were very prescriptive and didn't have alternatives written down on the actual protocol," Dr. de Lima said.

Can the 'Heart of the Issue' Be Addressed?

Market considerations and the economics surrounding generic drugs play a key role in the shortage. Schatz said she believes "the heart of this issue is a market problem." Although it may seem paradoxical, she explained that "low drug prices are actually a key driver of this shortage" because companies that manufacture generic versions of brand-name drugs operate on a "razor-thin margin," which "means any interruption or delay in manufacturing could create a ripple effect throughout the market."

The economics of the situation create a challenge that is difficult for any single entity to address.

"That razor-thin operating margin demands that these generics plants operate near capacity, and it also reduces the number of manufacturers in the market that are making generics," Schatz said. "So then when a crisis occurs and a manufacturer is closed, the system doesn't have the capacity to ramp up and address that with additional supply."

The FDA can do certain things to prevent and resolve drug shortages, such as expedite reviews of new production lines or material sources to increase production, extend product expiration dates if it is safe to do so, and import medicines if they meet safety and effectiveness criteria, according to its website.[4]

However, the FDA cannot require a pharmaceutical company to make a drug, "even if it is a medically necessary drug," officials said.[4] Additionally, the FDA cannot require a company to make more of a drug or change how much of and to whom the drug is distributed.

The FDA does require companies to notify it about "manufacturing interruptions or product discontinuances and create a risk-management plan for their product supply chain," and it emphasized that "early notification from drug companies of any issue that could lead to a potential disruption in supply is critical to preventing or lessening the impact of drug shortages."[4]

Schatz shared her insights on the current FDA response to the situation.

"The FDA has been importing drugs during the shortage," Schatz said. "Appropriately, they have also been implementing enhanced quality and safety measures to ensure that those drugs that are being imported in are safe."

However, she emphasized that importing drugs is a "short-term response" to the issue, noting that "there are many other stakeholders [who] are also coming together collaboratively to begin working on long-term solutions, because drug shortages are not a new development."

The big-picture, long-term solutions will need to be multipronged efforts involving numerous entities.

Continued on page 19

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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.

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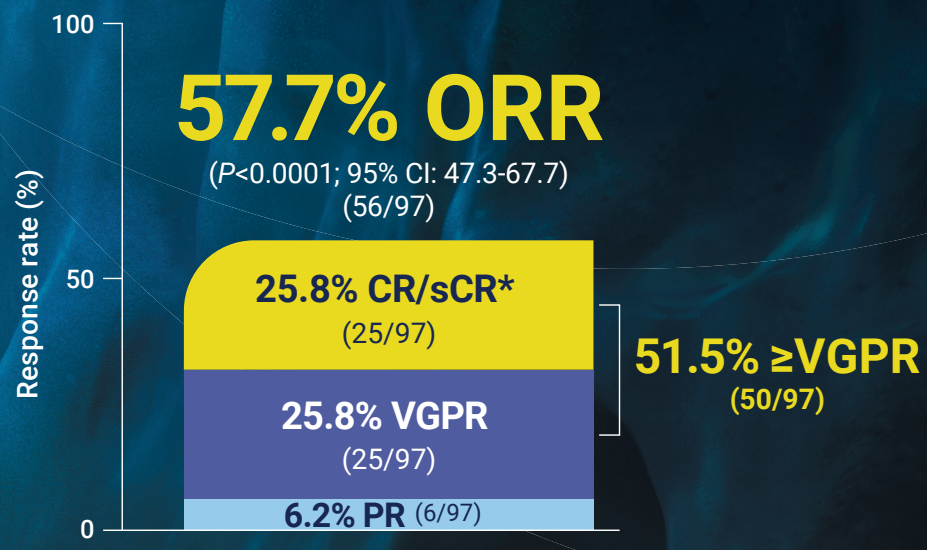

- Median follow-up was 10.2 months; range 0.2-20.1 months
- Among responding patients, the DoR rate at 9 months was 82.3%

- 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.

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- 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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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

Revised August 2023

Manufactured by:
Pfizer Inc.
NY, NY 10001
US License No. 2001

PP-E1A-USA-0423

Field Dispatch

Continued from page 13

"The good news is both the White House and Congress are looking at this issue," Schatz said. "Our convening stakeholders are seeking public comment and working on this with an appropriate sense of urgency. There are multiple proposals looking to tackle this right now. [The Centers for Medicare & Medicaid Services] has also put forth their own proposal around reimbursement for a buffer stock of medicines. There are some market-based reforms in Congress. There are a variety of proposals and people coming together to try to address it, both in the short term and in the long term."

Beyond action at a federal level, multiple medical societies—such as the American Society of Hematology, the American Society of Clinical Oncology, and the American Society of Transplantation and Cellular Therapy—are "taking a role" to negotiate on behalf of clinicians and patients, Dr. de Lima said.

As patients, clinicians, health care systems, and medical societies await larger solutions, the effects of the shortage continue to be felt throughout the country. However, multiple entities are working together to maintain and manage supplies. For example, the City of Hope has worked with a team to address the situation.

"Through our active participation with the Alliance of Dedicated Cancer Centers Pharmacy Leadership Group, we have been engaged with the FDA regarding this matter to procure these important medicines for our patients during this very challenging time," City of Hope officials said in a statement to *Blood Cancers Today*. "We are managing our current supply at hand through a dedicated team of integrated staff across our national cancer care system and have been able to provide the very best care possible for our patients."

However, not every patient receives care at a comprehensive cancer center in the United States, and the impact of the shortage extends far beyond national borders.

"Outside of the [United States], our colleagues in developing countries are not seeing any of these drugs because the little bit that remains is coming to us and possibly to Europe," Dr. de Lima said. "In places where the power, the money, and the volumes are not so high, they ran out of these drugs months ago. It's much worse than here."

"The heart of this issue is a market problem." *—Alyssa Schatz, MSW*

The situation also extends far beyond the present moment, as drug shortages have occurred in the past. For example, an FDA report showed a peak of 251 new drug shortages during 2011, compared with 49 new shortages in 2022.[5] The FDA listed 181 current or resolved drug shortages on its website as of August 2023.[1]

"Although the number of new drug shortages has declined since 2011 as a result of work by many groups, including [the] FDA, shortages continue to pose a real challenge to public health, particularly when the shortage has involved a critical drug to treat cancer, to provide parenteral nutrition, or to address other serious medical conditions, such as a shortage of antibiotics," FDA officials wrote in the report.[5] "In the past year, [the] FDA has seen manufacturers in the United States and abroad continue to experience quality issues as well as struggle with capacity constraints."

"A key issue is uncertainty. Allocations mean that providers can only access products in small amounts week to week."

—Erin R. Fox, PharmD, MHA, BCPS, FASHP

The FDA report emphasized the importance of continuing to develop and implement solutions that focus on preventing future shortages. Specifically, it outlined needs that "require ongoing work to be fully addressed," which include the need to "gain better insight into the supply chain" and the need to "increase the resilience of the supply chain."[5]

Others outside of the FDA have echoed these needs. For example, Dr. de Lima noted one "potential solution" to the supply chain issue is to look at cheaper manufacturing of generic medications outside the United States. However, he said there are several caveats and challenges with this approach, such as intellectual property considerations.

"The question, as always, is quality assurance and the legalities of this, [and] that's where the FDA comes in," he said.

Schatz spoke about addressing the situation from multiple angles.

"We potentially need some market interventions to address preventing shortages as well as predicting when shortages are more likely to occur so that we can prepare for that response," she said.

In terms of gaining insights into the supply chain, Schatz emphasized the importance of developing informatics infrastructure to "help us understand when a shortage occurs, what supply we have, and how we can allocate that [supply] in a way that is going to mitigate harm as much as possible."

That effort will require many entities to combine their resources and information.

"We have data in a variety of places, and we need all [the] different stakeholders to come together so that we can have a more centralized system to understand risk, opportunities to prepare and intervene, and also opportunities to mitigate harm when a shortage does occur," she said.

While the situation and solutions at hand are both complex and may require broad, high-level efforts from many stakeholders, individuals can still make a difference. Dr. de Lima and Schatz both emphasized the importance of making patient and clinician voices heard amid the drug shortage.

"I think that the first step is to make sure that people listen to us," Dr. de Lima said.

Schatz urged people affected by the shortage to call their elected officials about the situation.

"Patients need to know that their voice really matters," she said. "I've been doing policy and advocacy work for my entire career, and I can tell you that when someone who is personally impacted shares their story, it helps to change minds and create a sense of urgency."

Overall, the combined efforts of individuals, health care systems, manufacturers, government, and other institutions will be critical to addressing this shortage, as well as preventing future shortages.

"These [shortages] have happened before, and if we don't implement long-term sustainable solutions, they will happen again," Schatz said. "But they're not inevitable, and we can come together to address these issues."

***Cecilia Brown** is an Associate Editor for* Blood Cancers Today.

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In Focus

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

String of Recent Approvals Puts Spotlight on Bispecifics

Here's what they add to the treatment toolbox for hematologic malignancies

By Leah Lawrence

Many of the recent new drug approvals for patients with hematologic malignancies are providing novel options for these diseases and shifting the treatment landscape away from existing standards of care. One of the drug classes that has seen a myriad of US Food and Drug Administration (FDA) approvals is bispecific antibodies, drugs composed of two monoclonal antibodies engineered to bind to two different antigens or two different epitopes on the same antigen.

The first FDA-approved T cell-engaging bispecific antibody was blinatumomab, which was given accelerated approval for the treatment of Philadelphia (Ph) chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in 2014.[1]

Since then, blinatumomab has gained full approval for this indication and expanded its indications into other disease settings. In 2023, blinatumomab is just one of many bispecific antibodies available to treat hematologic malignancies.

Blood Cancers Today recently spoke with some experts involved in the studies of these drugs to explore how they gained approval and how they will be incorporated into the real-world treatment of these conditions.

Blinatumomab

Almost a decade after receiving its first FDA approval, blinatumomab received full FDA approval for measurable residual disease (MRD)-positive B-cell precursor ALL in June.[2] Blinatumomab was granted accelerated approval for this indication in 2018,[3] in addition to full approval for relapsed or refractory ALL in adults and children with Ph-negative and Ph-positive disease in 2017.[4]

"A majority of patients with ALL relapse after multiagent frontline therapy, and this relapse is driven by some persistent disease called MRD," said **Elias Jabbour, MD,** a Professor of Medicine at the University of Texas MD Anderson Cancer Center. "Historically, patients with persistent disease or those [who have] MRD had a survival of about 12 months on average."

This most recent indication is designed to target that MRD. Initially, blinatumomab was tested in a small German study of 20 patients with ALL and MRD persistence that showed the drug to be effective, with 16 of 20 patients becoming MRD-negative after treatment.[5]

That study prompted the pivotal phase III BLAST trial, which treated patients with ALL in first or second complete remission (CR) with MRD measured at 10^{-3} with blinatumomab; 78% of patients achieved MRD negativity. Median overall survival (OS) was 36.5 months.[6]

Blinatumomab was also granted marketing authorization in the European Union based on these results.[7]

The FDA's full approval, which came in 2023, was granted with additional data from two trials. The Children's Oncology Group ALL1331 study of blinatumomab in children, adolescents, and young adults showed no significant difference in disease-free survival (DFS) or OS between blinatumomab and standard chemotherapy overall, but it did show significant improvement in DFS and OS in 72.7% of patients with bone marrow and extramedullary relapse treated with blinatumomab.[8] Study 20120215 showed that blinatumomab significantly improved event-free survival compared with conventional chemotherapy in pediatric patients with high-risk B-cell ALL at first relapse.[9]

"This is the first and only FDA-approved drug for MRD-positive disease," Dr. Jabbour said.

Real-world data support the uptake and use of blinatumomab for patients with MRD-positive ALL. The retrospective, observational NEUF study out of Europe looked at blinatumomab in patients with CR with MRD-positive disease measured at 10^{-4}. Data showed that 93% of patients with Ph-negative disease and 64% with Ph-positive disease achieved an MRD response; median OS was not reached.[10] Dr. Jabbour and colleagues confirmed the efficacy of blinatumomab in patients with MRD-positive B-cell ALL (defined as 10^{-4}) with an MRD conversion rate of 73% and a three-year OS rate of 67%.[11]

"Giving blinatumomab for MRD at 10^{-4} is considered off-label use," Dr. Jabbour clarified. "The approval is at 10^{-3} so payers may limit use to the label, which could be problematic."

Amgen is currently providing a Humanitarian Access Program that will donate blinatumomab to pediatric patients at designated hospitals in India and Pakistan,[12] and research is being done to help develop a model that can be used to support the implementation of blinatumomab in low- and middle-income countries.[13]

> **"Being the first to market means that people may be more comfortable using teclistamab. That is always an advantage, even though both drugs are very effective."**
>
> *—Carolina Schinke, MD*

Glofitamab and Epcoritamab

In back-to-back accelerated approvals in May and June, the FDA added two more bispecific antibodies to the armamentarium for B-cell lymphoma.

Epcoritamab-bysp—often referred to as "epco"—was approved for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified.[14] The drug is not yet approved in the European Union but did receive a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use.[15]

Epcoritamab, a CD20-directed CD3 T-cell engager, was granted approval based on EPCORE NHL-1, a single-arm trial of 148 patients with relapsed or refractory DLBCL with two or more prior lines of therapy. The overall response rate (ORR) was 61%, with 38% of patients achieving CR. With a median follow-up of 9.8 months, the estimated median duration of response was 15.6 months.[14]

"The follow-up is still short, so time will tell if the durable remissions plateau, like what we have seen with CAR T-cell therapy in DLBCL, or if patients relapse and need another treatment," said **Tycel Phillips, MD,** an Associate Professor at the City of Hope Comprehensive Cancer Center in Duarte, California.

According to Dr. Phillips, the full approval of epcoritamab will be tied to results of several randomized trials comparing the drug with standard-of-care regimens. He did acknowledge that the standard-of-care arms will be harder to accrue to in the United States.

"It is going to take some time to see how this drug plays out in nontrial patients," Dr. Phillips said. "I suspect we may see some decline in efficacy reported because, more than likely, a lot of patients will be post-CAR T-cell therapy. I suspect that this will occur because: (a) in the trial they had a lower CR rate of 28% versus 38%, and (b) a lot of the patients who will get this drug initially would not have qualified for the trial."

Clinicians unfamiliar with epcoritamab should be aware that patients may experience cytokine release syndrome (CRS) with the third dose. The drug is administered subcutaneously and given with step-up dosing in cycle one (0.16 mg on day one, 0.8 mg on day eight, and 48 mg on days 15 and 22). The FDA advised that patients be hospitalized for 24 hours after the much larger cycle one, day 15 dosage of 48 mg.

It also remains to be seen how epcoritamab ultimately will be sequenced, Dr. Phillips said, because currently, CAR T-cell therapy is curative and has an OS benefit in the second-line setting, so epcoritamab for now will be reserved for patients in the third-line or later setting.

This approach could change as more data emerge about durability of response to bispecific antibodies in this patient population, he acknowledged, given that bispecifics likely will have a larger reach than CAR-T once the drugs are adopted by community physicians. Additionally, with several trials looking at bispecifics in frontline DLBCL, we may have to rethink the current discussion about how to sequence bispecifics and CAR T-cell therapy.

Another CD20-directed CD3 T-cell engager, glofitamab, was approved in Canada in March

and received accelerated approval by the FDA in July.[16,17] The approvals were based on the single-arm NP30179 trial, which included 132 patients, 20% of whom had DLBCL arising from follicular lymphoma. The ORR was 56%, with 43% of patients achieving CR. With a median follow-up of 11.6 months, the estimated median duration of response was 18.4 months.[17]

"This is very clinically significant in this patient cohort and not really achievable with other drugs out there, with the exception of CAR T-cell therapy," said **Michael Dickinson, MBBS,** of the Peter MacCallum Cancer Centre in Melbourne, Australia.

In Australia, glofitamab has been approved by the Therapeutic Goods Administration but is not funded by the national insurer. Glofitamab is available through clinical trials, Dr. Dickinson said.

Real-world data on glofitamab are sparse as it has only just come to market.

"I would say, though, that the hematology community is broadly very persuaded that as a class of agents bispecific antibodies are highly active in DLBCL," Dr. Dickinson said. "Glofitamab and similar drugs are the most potent antilymphoma single agents we have seen for years and years."

The STARGLO study is evaluating glofitamab in combination with gemcitabine and oxaliplatin compared with rituximab, gemcitabine, and oxaliplatin. There are also plans to explore glofitamab in combination with Pola-R-CHP for frontline therapy in DLBCL.

Like epcoritamab, glofitamab is also associated with CRS, with 70% of patients on the NP30179 trial experiencing any grade CRS. Also given with a step-up dosing schedule (2.5 mg on day eight of cycle one and 10 mg on day 15 of cycle one), then 30 mg on day one of each subsequent cycle for a maximum of 12 cycles, patients should be hospitalized for the first dose and the second dose if any CRS occurs with the 2.5-mg dose.

"With glofitamab, another thing to understand as compared with epcoritamab is the intravenous delivery and single dose of obinutuzumab as prophylaxis against CRS," Dr. Dickinson said. "Although it doesn't sound intuitive, the key thing to understand is that the corticosteroid load as prophylaxis against CRS is lower than other bispecific antibodies and the number of visits to the hospital is lower."

Additionally, glofitamab has been developed as a fixed-course treatment.

"The philosophical view is that patients like to see a horizon for their anticancer treatment," Dr. Dickinson said. "For me as a clinician, that is very attractive."

The Myeloma Bispecifics

In August, talquetamab-tgvs—a bispecific antibody directed against CD3 and GPRC5D—received FDA accelerated approval and European Commission Conditional Marketing Authorization for patients with relapsed or refractory multiple myeloma (MM) who have had at least four prior lines of therapy.[18,19] These approvals were based on data from the phase I/II MonumenTAL-1 study.

Carolina Schinke, MD, an Associate Professor of Medicine at the Myeloma Center at the University of Arkansas for Medical Sciences, and colleagues participated in the phase II portion of the trial that treated patients with subcutaneous talquetamab 0.8 mg/kg biweekly or 0.4 mg/kg weekly with step-up dosing.[20] Updated results showed an ORR of 71.7% in patients treated with the 0.8-mg/kg dose, with 60.7% achieving very good partial response (VGPR). With the 0.4-mg/kg dose, the ORR was 74.1% with a VGPR rate of 59.4%.

"With a median follow-up of nearly one year, the median duration of response was not reached in the 0.8-mg/kg biweekly group," Dr. Schinke said. "This is quite impressive for a single agent in this very heavily pretreated population."

It is too soon to know how this drug will be used in the clinic, for most patients will likely have already had BCMA-directed therapy before going to talquetamab. At the time of the interview, Dr. Schinke said most centers likely did not even have access to talquetamab yet.

"The greatest use of elranatamab will hopefully be in the community and not in academic centers."

—Ajay Nooka, MD, MPH

"There is a lot of regulatory and administrative work that needs to be completed before it can start being administered. We anticipate being able to start [using] it in the next two to three weeks," Dr. Schinke said when she spoke to *Blood Cancers Today*.

It also remains to be seen how talquetamab will be incorporated with other MM treatments, including the CD3×BCMA-targeting bispecific antibody teclistamab. Granted accelerated approval for relapsed or refractory MM in October 2022,[21] teclistamab has been in the hands of clinicians for about seven or eight months longer than talquetamab, Dr. Schinke noted.

"Being the first to market means that people may be more comfortable using teclistamab," Dr. Schinke said. "That is always an advantage, even though both drugs are very effective."

Teclistamab was approved based on results of the MajesTEC-1 study that yielded an ORR of 63.0%, with 39.4% of patients having CR or better and 26.7% with MRD-negative disease.[22] Long-term follow-up data showed 43% of patients with CR or better, a median PFS of 12.5 months, and a median OS of 21.9 months.[23]

"What we will want to know in the future is which to use first and how to use them sequentially," Dr. Schinke said. Those answers will depend, at least in part, on the side effect profile, she said.

Talquetamab has a unique adverse event (AE): dysgeusia, or loss of taste.

"It is quite unique in that no other drugs for myeloma have that side effect," Dr. Schinke said. "It is not life-threatening—most patients are able to eat—but the fact that they can't taste food has an impact on life quality."

Anecdotally, Dr. Schinke said she has had patients start talquetamab and because of the impressive response tolerated the dysgeusia, but once they were on it longer and were in remission, the side effect became more bothersome.

"As a clinician, if you already have a patient who is quite skinny and they have to start this drug that could have the potential for weight loss, you may not choose talquetamab," Dr. Schinke said.

With teclistamab, high rates of infection were seen in clinical trials. In MajesTEC-1, more than three-quarters of patients experienced infection, with 44.8% of infections being grade 3 or 4.

"We did not see that high rate of infection with talquetamab," Dr. Schinke said. "In this case, if you have a patient already prone to infection, you might be more careful about using teclistamab and opt for talquetamab."

Real-world data on the use of teclistamab are already underway, Dr. Schinke said, particularly looking at prophylactic methods to mitigate risk of infection.

Additionally, because the two drugs have different targets, studies are also looking at the feasibility of combining teclistamab and talquetamab. RedirecTT-1 combined teclistamab and talquetamab in 63 patients with relapsed or refractory MM. In all evaluable patients, the ORR was 84%, with a CR rate of 34%. At the established phase II dose, the ORR was 92%. Encouragingly, the ORR in patients with extramedullary disease was 73%.[24]

Clinicians administering the drugs should be familiar with the possibility of CRS seen with these two drugs.

"Despite lower rates and less severity than what is seen with CAR T-cell therapy, clinicians have to know that CRS can occur, and patients need to be monitored," Dr. Schinke said. "Step-up dosing for talquetamab is used, with the first dose given in-hospital before transitioning to an outpatient setting."

Elranatamab

Talquetamab was not the only bispecific antibody approved for myeloma in August. Elranatamab-bcmm was also granted an accelerated approval for adults with relapsed or refractory MM who have had at least four prior lines of therapy and prior treatment, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[25] Like teclistamab, elranatamab is also a CD3×BCMA-targeting compound.

"Both teclistamab and elranatamab are BCMA-targeting, and both are approved for the same indication," said **Ajay Nooka, MD, MPH,** a Professor and Director of the Myeloma Program in the Department of Hematology and Medical Oncology at Emory University School of Medicine.

Elranatamab was approved based on results of the single-arm MagnetisMM-3 study that measured the drug's efficacy in patients naive

to prior BCMA-directed therapy or those with at least four prior lines. The ORR was 61%, with an 84% probability of maintaining response at nine months.[26]

According to Dr. Nooka, elranatamab has a similar AE profile to teclistamab, including risk for CRS, neurotoxicity, infection, and cytopenia. The main difference between the two relates to the Risk Evaluation and Mitigation Strategy.

With the administration of teclistamab, given at 0.06 mg/kg on day one, 0.3 mg/kg on day four, and 1.5 mg/kg on day seven, it is recommended that patients be hospitalized for 48 hours after administration of all doses within the step-up dosing schedule.

The step-up dosing of elranatamab is 12 mg on day one, then 32 mg on day four, followed by the first treatment dose of 76 mg on day eight. Hospitalization is required for 48 hours after the first dose and 24 hours after the second dose.

"The third dose—or target dose—can be given as an outpatient," Dr. Nooka said.

Looking to the future, Dr. Nooka expects that administration of elranatamab will only get safer as clinicians continue to learn how to better mitigate CRS, neurotoxicity, and infections.

"The greatest use of elranatamab will hopefully be in the community and not in academic centers," Dr. Nooka said. "We want to be able to treat these patients nearer to home with their local oncologist. We need to put our effort into learning how to do that in a safer way."

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

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Regulatory Actions

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

FDA Approves Luspatercept as Frontline Treatment for Anemia in Lower-Risk MDS

The US Food and Drug Administration (FDA) has approved luspatercept-aamt (Reblozyl) for the treatment of anemia without previous erythropoiesis-stimulating agent (ESA) use in adults with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.

The expanded indication to the frontline setting is based on interim results from the pivotal phase III COMMANDS trial, in which luspatercept-aamt demonstrated "superior efficacy of concurrent RBC transfusion independence and hemoglobin increase compared [with] epoetin alfa, an ESA, regardless of ring sideroblast status," according to a news release from Bristol Myers Squibb, the manufacturer of the drug.

The phase III COMMANDS trial showed 58.5% of patients receiving luspatercept-aamt achieved the primary endpoint of RBC transfusion independence for at least 12 weeks with a mean hemoglobin increase of at least 1.5 g/dL within the first 24 weeks, while only 31.2% of patients receiving epoetin alfa did ($P<.0001$). The most common (>10%) adverse reactions were diarrhea, fatigue, hypertension, peripheral edema, nausea, and dyspnea.

"For patients with lower-risk MDS, current standard therapies, including ESAs, have provided limited benefit in controlling anemia, with only one in three patients responding for a duration of six to 18 months," said **Guillermo Garcia-Manero, MD,** lead investigator and Chief of the Section of Myelodysplastic Syndromes at the University of Texas MD Anderson Cancer Center, in a statement.

"Results from the COMMANDS study showed nearly twice as many patients treated with Reblozyl achieved transfusion independence of at least 12 weeks and concurrent hemoglobin increase compared [with] epoetin alfa. Today's approval represents an important advancement for patients with lower-risk MDS."

Results from the COMMANDS study were featured as part of the press program at the American Society of Clinical Oncology Annual Meeting and in a plenary session at the European Hematology Association Congress.

Officials said the drug is being developed and commercialized through a global collaboration with Merck.

Source: Bristol Myers Squibb, August 2023

Tagraxofusp Granted Orphan Drug Designation to Treat BPDCN

The Japanese Ministry of Health, Labor and Welfare (MHLW) granted orphan drug designation to tagraxofusp for the indication of blastic plasmacytoid dendritic cell neoplasm (BPDCN). Tagraxofusp was approved only for patients with BPDCN.

Japan's MHLW grants orphan drug designation to treatments designed for fewer than 50,000 patients, especially when there is a significant medical necessity. This designation has the potential to reduce the time needed for regulatory approval in Japan by several months, facilitating quicker patient access to these treatments.

Tagraxofusp is a fusion protein that combines interleukin 3 (IL-3) with diphtheria toxin. This fusion protein effectively eliminates cultured pDCs by attaching to their IL-3 receptors, enabling it to enter the cells and subsequently obstruct their protein synthesis.

Tagraxofusp is being manufactured by Nippon Shinyaku Co, Ltd in Japan, development partners to the Menarini Group and Stemline Therapeutics, Inc. Currently, Nippon Shinyaku is conducting a phase I/II clinical trial.

Source: Business Wire, August 2023

EC Grants Marketing Authorization to JZP458 for ALL, LBL

The European Commission (EC) has granted marketing authorization to JZP458 (Enrylaze) for use as a component of a multiagent chemotherapeutic regimen for certain patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL).

The marketing authorization is for adults and children one month and older who developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase, according to a news release from Jazz Pharmaceuticals, the manufacturer of JZP458.

JZP458, which is approved in the United States and Canada, is a new *Erwinia*-derived asparaginase developed using a next-generation recombinant technology with a safety profile "consistent with that of other asparaginase preparations," according to the news release.

The treatment can be administered by intravenous infusion and intramuscular injection and is dosed on alternate days or on a Monday, Wednesday, and Friday dosing schedule.

The marketing authorization follows the positive opinion issued in July 2023 by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use.

The EC approval is based on data from a phase II/III trial conducted in collaboration with the Children's Oncology Group in 228 pediatric and adult patients with ALL and LBL who developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase.

The EC approval extends to all European Union Member States, as well as Iceland, Norway, and Liechtenstein.

Source: Jazz Pharmaceuticals, September 2023

FDA Approves Momelotinib in Patients with Myelofibrosis Plus Anemia

Momelotinib (Ojjaara) has been approved by the FDA for the treatment of intermediate- or high-risk myelofibrosis, including primary myelofibrosis or secondary myelofibrosis (post-polycythemia vera and post-essential thrombocythemia), in adults with anemia.

The FDA approval is for use in myelofibrosis patients with anemia regardless of prior myelofibrosis therapy. Nearly all patients with myelofibrosis are estimated to develop anemia over the course of the disease, and over 30% will discontinue treatment due to anemia, according to GSK, the manufacturer of the drug.

The FDA approval of momelotinib is supported by data from the pivotal MOMENTUM study and a subpopulation of adult patients with anemia from the SIMPLIFY-1 phase III trial.

Source: Business Wire, September 2023

EMA Validates Imetelstat Marketing Authorization Application for Lower-Risk MDS Treatment

The EMA has validated the Marketing Authorization Application for imetelstat, a first-in-class investigational telomerase inhibitor, for the treatment of transfusion-dependent anemia in patients with lower-risk MDS.

The application is based on results from the IMerge phase III trial, which was a randomized, double-blind, placebo-controlled study evaluating imetelstat in patients with heavily transfusion-dependent, non-del(5q), lower-risk MDS who relapsed or were refractory to ESAs.

Source: Business Wire, September 2023

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

First-line Selinexor, Ruxolitinib Shows Ongoing Promise for Myelofibrosis

Selinexor plus ruxolitinib continues to demonstrate rapid, deep, and sustained spleen responses in patients with myelofibrosis, according to updated data from the phase I XPORT-MF-034 trial.

Previous data from the phase I study supported the use of selinexor 60 mg plus ruxolitinib for a phase III trial of the combination. **Haris Ali, MD,** of the City of Hope Comprehensive Cancer Center, presented updated data on the 60-mg cohort of the study, as well as a subgroup analysis, at the Eleventh Annual Meeting of SOHO.

In the open-label, phase I study, patients with treatment-naive myelofibrosis received selinexor 40 mg and 60 mg once weekly plus ruxolitinib. As of April 10, 2023, 14 patients had received the selinexor 60-mg dose; of these, 36% were female.

At week 12, 83% of the efficacy-evaluable population (10 of 12 patients), and 71% of the intent-to-treat population (10 of 14 patients) achieved a spleen reduction volume (SVR) of 35%. By week 24, these rates had increased to 92% and 79%, respectively.

At any time, an SVR of 35% was observed in 100% of the efficacy-evaluable population and 86% of the intent-to-treat population.

The rates of SVR of 35% occurred consistently in male and female patients, and at different ruxolitinib starting doses.

Robust symptom improvements were also observed. By week 24, 78% of the efficacy-evaluable population and 58% of the intent-to-treat population had achieved a 50% or greater reduction in their total symptom score.

"In the future, selinexor in combination with ruxolitinib may become a novel, first-line treatment for patients with [myelofibrosis]," the researchers concluded.

Reference

Ali H, Kishtagari A, Maher K, et al. Selinexor plus ruxolitinib in JAK inhibitor (JAKi) treatment-naïve patients with myelofibrosis: updated results and subgroup analyses from XPORT-MF-034. Abstract MPN-336. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

HeMonitor Study Shows Noninvasive Hemoglobin Measurement Is 'Feasible' in Heme Malignancies

The proof-of-concept HeMonitor study showed that noninvasive hemoglobin measurement is "feasible," according to machine-learning data presented at the Eleventh Annual Meeting of SOHO.

Anne Kubasch, MD, of Leipzig University Hospital, and colleagues conducted the noninterventional, prospective-exploratory HeMonitor study to develop a noninvasive hemoglobin level prediction model based on photographs of the ocular conjunctiva and fingernails using machine learning.

They recruited two cohorts of patients, one that included patients with hematological malignancies who were undergoing regular hemoglobin measurements (n=373) and a second cohort that included volunteer healthy blood donors (n=188).

Dr. Kubasch and colleagues took photographs of the ocular conjunctiva and fingernails under laboratory conditions and gathered patient clinical data along with an invasively determined hemoglobin level that they measured the same day. They used this information to develop the training and testing dataset. The researchers then trained a Bayesian ridge regression model using the scikit-learn Python framework, with the laboratory-derived hemoglobin measure as the target feature.

With the implemented approach, the researchers reported a mean hemoglobin deviation of 1.32 mmol/L when using photographs of conjunctiva compared with invasive hemoglobin measurement methods. They reported a mean hemoglobin deviation of 1.62 mmol/L when using photographs of fingernails compared with invasive hemoglobin measurement methods.

When they used photographs from conjunctiva in combination with photos of fingernails in a sequential prediction pipeline, the mean hemoglobin deviation was 1.42 mmol/L. However, there was "lower accuracy in patients below the anemia threshold (7.4 mmol/L), with frequent deviations of 4 mmol/L," according to the study's authors.

The proof-of-concept study showed that noninvasive hemoglobin measurement is "feasible," but there were several limitations, according to the researchers.

"The main limitations of our results are lower accuracy in severely anemic patients and thus currently limited clinical applicability," Dr. Kubasch and colleagues wrote. "Validation of our [machine-learning] model is currently ongoing within a larger, prospective study. Overall, by providing a way to monitor [hemoglobin] levels regularly at home, these measurements can contribute to better management of anemia and more personalized cancer care."

Reference

Hefner S, Oeser A, Klötzer C, et al. HeMonitor: machine learning-based noninvasive estimation of hemoglobin (Hb) value in patients with hematological malignancies. Abstract MDS 337. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

Glofitamab Offers High CR Rates for Relapsed or Refractory MCL

Patients with relapsed or refractory mantle cell lymphoma (MCL) may benefit from glofitamab monotherapy, according to research presented at the Eleventh Annual Meeting of SOHO.

A multinational research team led by presenter **Tycel Philips, MD,** of the City of Hope in Duarte, California, shared phase I/II trial results that showed a 73% complete response (CR) rate, with manageable safety issues, from the use of glofitamab.

After obinutuzumab pretreatment was administered seven days before in doses of 1,000 mg or 2,000 mg, intravenous glofitamab was then administered with step-up dosing on days eight (2.5 mg) and 15 (10 mg) of cycle one. Next, the target dose was given over 21-day cycles (16 mg or 30 mg after

obinutuzumab 1,000 mg or 30 mg after obinutuzumab 2,000 mg).

Of the 37 patients who had received glofitamab as of March 14, 2022, 16 received obinutuzumab 1,000-mg pretreatment and 21 received obinutuzumab 2,000-mg treatment. In addition, 91.9% of patients had Ann Arbor stage III/IV disease.

The patients had a median of three prior lines of therapy, with a range of one to five. Furthermore, 24 (64.9%) had received prior Bruton's tyrosine kinase inhibitor (BTKi) therapy, and 33 (89.2%) were refractory to any prior therapy.

The overall response rate was 83.8%, and the CR rate was 73.0% after the median follow-up of eight months. The median time of CR was 51 days, and the duration was 10 months. A total of 74.1% of CRs were ongoing at the data cutoff, according to the researchers.

As for adverse events (AEs), the most common was cytokine release syndrome (CRS), which occurred in 75.7% of patients but with a lower incidence (66.7%) in the group of patients who received obinutuzumab 2,000 mg.

However, all CRS events were deemed to be manageable and mainly low-grade; 17 patients were given tocilizumab, and 29.7% of the events were grade 1 and 29.7% were grade 2. No patients discontinued treatment because of AEs.

"Fixed-duration glofitamab monotherapy induced high, durable CR rates in patients with [relapsed or refractory] MCL, including those with prior BTKi therapy. CRS events were manageable and mostly low-grade," the authors wrote.

There were 10 deaths, but none were related to the study treatment, according to the researchers.

Reference

Philips T, Dickinson M, Morschhauser F, et al. Glofitamab monotherapy induces high complete response rates in patients with heavily pretreated relapsed or refractory mantle cell lymphoma. Abstract MCL-467. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

REVIVE Trial Shows Rusfertide Provides Hematocrit Control in Polycythemia Vera

Rusfertide is "highly effective" in patients with polycythemia vera (PV) who were receiving therapeutic phlebotomies with or without cytoreductive therapy, according to investigators of the REVIVE trial.

Naveen Pemmaraju, MD, of the University of Texas MD Anderson Cancer Center, and colleagues presented data from the randomized withdrawal phase of the study at the Eleventh Annual Meeting of SOHO.

The trial consists of three stages. In part one of the study, which was the first 28 weeks, the researchers adjusted the dose of rusfertide individually to control hematocrit <45%. Part two of the study, which was weeks 29 through 41, was the blinded, randomized withdrawal phase. Dr. Pemmaraju and colleagues randomized 53 patients to continue receiving rusfertide treatment (n=26) or matching placebo (n=26) during part two. Part three is a three-year, open-label extension.

To be eligible for the study, patients needed to receive at least three therapeutic phlebotomies with or without concurrent cytoreductive therapy in the 28 weeks prior to enrollment.

The researchers defined patients as responders in part two if they had hematocrit control without therapeutic phlebotomy eligibility, no therapeutic phlebotomy, and completed 12 weeks of treatment. A need for therapeutic phlebotomy was triggered by hematocrit of at least 45% and at least 3% higher than week 29 prerandomization hematocrit, hematocrit above 48%, or at least a 5% increase in hematocrit compared with week 29 hematocrit.

The response rate was 69.2% for patients receiving rusfertide in part two, while it was 18.5% for those receiving placebo (P=.0003). Rusfertide showed "superior efficacy relative to placebo" in patients receiving therapeutic phlebotomy alone (P=.02) and in those receiving therapeutic phlebotomy plus cytoreductive therapy (P=.02), according to Dr. Pemmaraju and colleagues.

Furthermore, rusfertide significantly improved maintenance of response, absence of the need for therapeutic phlebotomy, and persistent hematocrit control compared with placebo (P<.0001). It was also "well tolerated," as 83% of treatment-emergent AEs (TEAEs) were grade 1 or 2 and 17% were grade 3. No TEAEs of grade 4 or 5 were reported. The most common TEAEs were localized grade 1 or grade 2 injection site reactions.

"The REVIVE study demonstrated that rusfertide is highly effective in patients with PV receiving [therapeutic phlebotomy] with or without [cytoreductive therapy]. Rusfertide is well tolerated and produces sustained and durable [hematocrit] control," Dr. Pemmaraju and colleagues concluded.

Reference

Pemmaraju N, Kremyanskaya M, Kuykendall A, et al. Targeted therapy of uncontrolled erythrocytosis in polycythemia vera with the hepcidin mimetic, rusfertide: blinded randomized withdrawal results of the phase 2 REVIVE study. Abstract MPN-541. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

Mosunetuzumab Showed Durable Responses for Relapsed or Refractory Follicular Lymphoma

Updated data from a pivotal phase II study of the bispecific antibody mosunetuzumab in relapsed or refractory follicular lymphoma demonstrated that the durable responses previously seen with the drug continued to be observed with longer follow-up.

Loretta Nastoupil, MD, of the University of Texas MD Anderson Cancer Center, and colleagues presented data with a 28.3-month median follow-up as a poster presentation during the Eleventh Annual Meeting of SOHO.[1]

The single-arm, multicenter study included 90 patients with grade 1-3a follicular lymphoma who had received two or more prior lines of therapy. Intravenous mosunetuzumab was given using step-up dosing in cycle one, with patients receiving eight cycles if they achieved a CR by cycle eight or 17 cycles if they achieved partial response or stable disease by cycle eight.

In December 2022, mosunetuzumab received FDA accelerated approval for relapsed or refractory follicular lymphoma after two or more lines of therapy. The approval was based on initial results of this study, with an objective response rate (ORR) of 80% and a CR rate of 60%. With a median follow-up of 14.9 months among responders, the estimated median duration of response was 22.8 months.[2]

As of July 8, 2022, the investigator-based ORR was 78% with a CR rate of 60%. The median progression-free survival (PFS) was 24 months with mosunetuzumab compared with 12 months with the last prior therapy. The 24-month PFS was 48% with mosunetuzumab.

Median duration of response, median duration of CR, and time to next therapy with mosunetuzumab were not reached.

CRS occurred in 44% of patients but was mostly grade 1 or 2. No new CRS events or other fatal, serious, or grade 3 or worse AEs were reported since the previous analysis.

References

1. Barlett NL, Sehn LH, Matasar M, et al. Mosunetuzumab monotherapy demonstrates durable efficacy with a manageable safety profile in patients with relapsed/refractory follicular lymphoma who received ≥2 prior therapies: updated results from a pivotal phase II study. Abstract IBCL-458. Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology; September 6-9, 2023; Houston, Texas.

2. FDA grants accelerated approval to mosunetuzumab-axgb for relapsed or refractory follicular lymphoma. US Food and Drug Administration. December 22, 2022. Accessed September 22, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mosunetuzumab-axgb-relapsed-or-refractory-follicular-lymphoma

SOHO 2023 Edition

SOHO Announces Poster Award Winners at Eleventh Annual Meeting

Of the 500-plus posters that were displayed on the first night of the Eleventh Annual Meeting of the Society of Hematologic Oncology (SOHO), eight posters received awards from the Society during a ceremony held Wednesday evening.

In first place was the poster titled "TRANSCEND FL: Phase II Study Results of Lisocabtagene Maraleucel (Liso-Cel) in Patients with R/R Follicular Lymphoma (FL)," which was presented by **Loretta Nastoupil, MD,** of the University of Texas MD Anderson Cancer Center, and colleagues.

The second-place poster award went to "Idecabtagene Vicleucel (Ide-Cel) Versus Standard Regimens in Patients with Triple-Class-Exposed (TCE) Relapsed and Refractory Multiple Myeloma (RRMM): KarMMa-3, a Phase III Randomized Controlled Trial (RCT)," which was presented by **Natalie Callander, MD,** of the University of Wisconsin Carbone Cancer Center, and colleagues.

The third-place poster award went to the poster titled "First Report of PhALLCON: A Phase 3 Study Comparing Ponatinib Versus Imatinib in Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphocytic Leukemia," which was presented by **Elias Jabbour, MD,** of the MD Anderson Cancer Center, and colleagues.

The following posters received honorable distinctions:

- "Continuous Transfusion Independence with Imetelstat in Heavily Transfused Non-del(5q) Lower-Risk Myelodysplastic Neoplasms Relapsed/Refractory/Ineligible for Erythropoiesis-Stimulating Agents in IMerge Phase III," which was presented by **Faye Feller, MD,** of the Geron Corporation, and colleagues

- "Impact of Allogeneic Hematopoietic Cell Transplantation (allo-HCT) in First Complete Remission (CR1) in Addition to FLT3 Inhibition with Quizartinib in Acute Myeloid Leukemia (AML) with *FLT3*-Internal Tandem Duplication (*FLT3*-ITD): Results From the QuANTUM-First Trial," which was presented by **Richard Schlenk, MD,** of the Heidelberg University Hospital and German Cancer Research Center, and colleagues

- "Longer Follow-up Reaffirms Subcutaneous Epcoritamab Induces Deep and Durable Complete Remissions in Patients with Relapsed/Refractory Large B-cell Lymphoma: Updated Results From the Pivotal EPCORE NHL-1 Trial," which was presented by **Yasmin Karimi, MD,** of the University of Michigan Comprehensive Cancer Center, and colleagues

- "Activity, Tolerability, and Resistance Profile of the Menin Inhibitor Ziftomenib in Adults with Relapsed/Refractory *NPM1*-Mutated AML," which was presented by **Harry Erba MD, PhD,** of the Duke Cancer Institute, and colleagues

- "Addition of Navitoclax to Ruxolitinib for Myelofibrosis Patients with Relapsed/Refractory Disease and Suboptimal Response to Ruxolitinib Monotherapy: REFINE Cohort 1 Dose Escalation and Expansion," which was presented by **Naveen Pemmaraju, MD,** of the MD Anderson Cancer Center, and colleagues

At left, Loretta Nastoupil, MD, receives the first-place poster award for her poster on TRANSCEND FL from SOHO President Jennifer Brown, MD, PhD, during the poster awards session at the Eleventh Annual Meeting of SOHO. (All photos courtesy of Barry Smith/SOHO.)

Elias Jabbour, MD, presents during the acute lymphocytic leukemia session.

Attendees at the poster session.

HemOnc Happenings

Dr. Kantarjian Honored with SOHO Freireich Award

At right, Hagop Kantarjian, MD, receives the Emil Freireich Distinguished Pioneer Award from Sagar Lonial, MD, FACP.

Hagop Kantarjian, MD, Professor and Chair in the Department of Leukemia at the MD Anderson Cancer Center, was honored with the Emil Freireich Distinguished Pioneer Award during the Eleventh Annual Meeting of SOHO in Houston, Texas.

It is the society's "most prestigious award" and "serves to honor those [who] have been pioneers in their work and made a notable impact worthy of high regard and recognition by their peers," according to SOHO.

Dr. Kantarjian, who has authored over 2,000 peer-reviewed publications, focuses on translational-clinical developmental therapeutics in leukemia. His research and collaborations were the basis for the US Food and Drug Administration approvals of more than 20 drugs to treat leukemia, according to his biography from the MD Anderson Cancer Center.

In addition to his roles as Professor and Chair in the Department of Leukemia, Dr. Kantarjian also serves as Associate Vice President for Global Academic Programs and is the Samsung Distinguished University Chair in Cancer Medicine at the MD Anderson Cancer Center.

Dr. Kantarjian is an active SOHO member, serving as Secretary on the SOHO Board of Directors and as Chair of its Steering and Scientific committees. He has served the Society for 10 years.

The award is named for the late **Emil Freireich, MD,** who was a founding member of SOHO in 2012 and was elected in 2013 as SOHO's first president. His "direction in creating the first worldwide society dedicated to hematologic oncology was integral to the mission of SOHO," according to the Society.

Source: SOHO, September 2023

Jorge Cortes, MD, Receives Michael J. Keating Award at SOHO Annual Meeting

At left, Jorge Cortes, MD, is presented with the Michael J. Keating Award by Hagop Kantarjian, MD.

Dr. Cortes, who serves as Director of the Georgia Cancer Center in Augusta, was honored with the Michael J. Keating Award from SOHO during a plenary session at the Society's annual meeting.

Dr. Cortes reflected on how he felt about receiving the award.

"It is particularly meaningful to me because it is in honor of Dr. Keating," Dr. Cortes told *Blood Cancers Today*. "Dr. Keating was a giant in hematologic malignancies research [and] patient care. As a resident, I was reading his papers and learning from him from a distance. I was in Mexico in those days. When I came to the [United States] and I started working with him, he was always so generous with his time and his knowledge."

The award recognizes a SOHO member who has significantly contributed to the advancement of cancer treatment and research in the field of hematologic oncology. Dr. Cortes is an active member of the SOHO Education and Scientific committees and has served the Society for a decade.

He was previously at the MD Anderson Cancer Center for 27 years, where he was a Professor of Medicine and an internist. Additionally, he served multiple roles in the Department of Leukemia and the Division of Cancer Medicine at MD Anderson.

The award was created in honor of **Michael J. Keating, MD,** a founding member of the Society and a "major contributor to the field of leukemia research and treatment," according to SOHO. Dr. Keating served as SOHO's president in 2017 and has held positions on SOHO's Seering and Education committees and its Board of Directors.

"I always admired him so much, so receiving an award that carries his name with everything he did to advance knowledge, research, and patient care in hematologic malignancies really has a particular value for me and is something that I cherish," Dr. Cortes told *Blood Cancers Today*.

Source: SOHO, September 2023

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MMLJRNA220006 September 2023
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