TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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How Can We Challenge the Status Quo in Myeloma Research?

With expert opinions from:
Sagar Lonial, MD, FACP;
Sikander Ailawadhi, MD;
and more

MAIL TO:

ASSOCIATE EDITOR
ELIAS JABBOUR, MD

SOHO Elevates the Global Dialogue on Hematologic Oncology

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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October 3–6
5th SOHO Italy Annual Conference
A. Roma Lifestyle Hotel
Rome, Italy

October 6–7
Acute and Chronic Leukemias: Practical Applications 2023 (Mayo Clinic Course)
Orlando World Center Marriott
Orlando, Florida

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

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

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

November 1
SOHO Highlights 2023: State of the Art and 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 9–12
65th American Society of Hematology Annual Meeting and Exposition
San Diego Convention Center
San Diego, California

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

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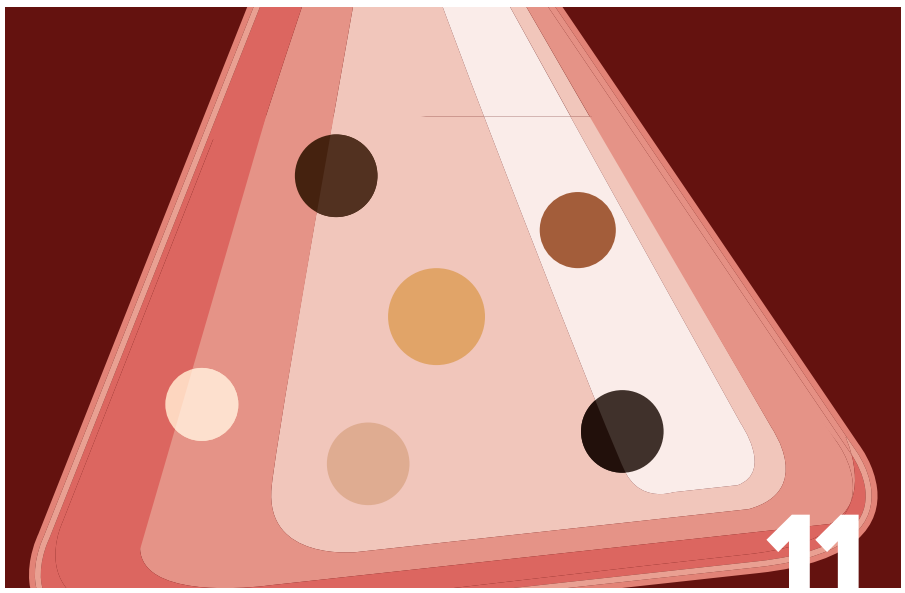

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About the Society of Hematologic Oncology
The Society of Hematologic Oncology was established as a nonprofit corporation in 2012 with aims to promote worldwide research, education, prevention, clinical studies, and optimal patient care in all aspects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

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SOHO Elevates the Global Dialogue on Hematologic Oncology

Elias Jabbour, MD
Associate Editor

September is always an exciting time for members of the Society of Hematologic Oncology (SOHO). The month brings the annual meeting in Houston, Texas. It is an amazing forum to hear updates in leukemia, lymphoma, myeloma, and transplant, while allowing for the flow of ideas and collaboration among colleagues. From my perspective, the meeting's sole focus on hematologic malignancies and the absence of parallel sessions set it apart from other conferences, making it one of the best meetings in the world.

I have long appreciated SOHO's mission to educate and elevate the standard of education, promote health care excellence, and deliver the best care to patients around the world. As SOHO members, we can actively help achieve these goals by holding smaller meetings in different countries and regions. Recognizing that only a few privileged individuals can attend the annual meeting in Houston—which reflects the inequality in who can access that education—our solution is to bring the knowledge right to the doorsteps of clinicians and researchers worldwide.

As a board member of SOHO Italy and SOHO Turkey, it has been very satisfying for me to see chapters emerge in new regions. Throughout the years, I have seen interest from local partners in different regions in holding meetings in their own countries and tailoring the content according to their region's needs.

This year, following the Eleventh Annual Meeting, regional meetings will take place around the world, including an event held by the new Middle East and North Africa (MENA) Chapter that I'm proud to have initiated. The first official MENA meeting holds personal significance for me as I hail from Lebanon, and we are thrilled to host the chapter's inaugural meeting at the Lebanese National Library in Beirut on September 29-30, 2023.

This meeting will gather world-class faculty from across the globe, some joining virtually, to educate local attendees from Iraq, Syria, Jordan, Lebanon, Egypt, Morocco, Algeria, Tunisia, and beyond. It's a major opportunity to share the knowledge we gain from the annual meeting in Houston with those who live in these regions, collaborating with local experts to deliver essential science and knowledge.

For the MENA Chapter, this is only the initial step in a long-term collaboration with SOHO to take up the Society's mission to educate clinicians worldwide. As a SOHO ambassador, it is personally fulfilling to witness the creation of our own local meeting, and to have a direct role in mentoring clinicians in the region.

Of course, other SOHO regional meetings will be taking place worldwide, from Italy to the Gulf region. All of these initiatives align with our values of enhancing knowledge and patient care. Beyond these directives, regional meetings build a network of collaboration, nurturing rising stars in research and health care. These efforts are vital and ensure excellence and support in our medical pursuits.

Establishing collaboration and disseminating knowledge are at the heart of our mission. We're turning the tables, bringing education to the regions. It's about inclusion, gathering outstanding minds to exchange ideas and information. This purpose, fundamental from the beginning, guides us forward.

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

Get to Know

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

Catherine Coombs, MD

Dr. Coombs, an Associate Professor in the Division of Hematology/Oncology at the University of California, Irvine (UCI) School of Medicine, discusses her journey into oncology, what it's like to broach both the lymphoid and myeloid worlds, and a unique skill she's lucky to have.

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

I grew up in the Cincinnati, Ohio, area. I decided to be a physician a bit later than most. I went to college as an economics major but switched to a premed major in my first semester of college. I completed the premed requirements but ended up going to graduate school for chemistry instead since I still wasn't 100% sure on the decision to pursue a career in medicine, which is such a huge decision. Although I was in a doctoral program for chemistry, I was still thinking about medicine in the back of my mind.

Ultimately, I decided I wanted to do medicine. I took the Medical College Admission Test while I was in graduate school and switched from the doctoral program to get a master's degree. I enrolled at the University of Cincinnati, which is where I was also in graduate school, as an early-decision medical student. I never looked back after that.

Medicine was never at the forefront of my mind, but once I started thinking about it early in college, it seemed to be a great career because I liked science and interacting with people. It's a career that melds those two things, and you can fulfill an academic mission, which is another aspiration of mine.

What led you to specialize in hematologic oncology?

When I decided I was interested in medicine, I was always going to specialize in cancer. I didn't have doctors in my family, but I had a lot of family members who had cancer and went through that experience. I admired their oncologists because it's a uniquely challenging type of medicine that seemed both interesting and rewarding to me.

I primarily had solid tumors in my family, so I was thinking about treating solid tumors. However, my second-year pathology class led me into the blood cancer realm because I completely fell in love with looking at blood cells under the microscope. That path was cemented during my intern year at Duke University Medical Center. I was interested in research, so I did interviews with faculty members for research projects. I met with **Mark Lanasa, MD, PhD,** who became my earliest mentor in hematologic oncology. He led the chronic lymphocytic leukemia (CLL) program at Duke. Under his guidance, I conducted a few research projects that were an extremely gratifying experience.

I realized patients with CLL are the best patients to have in terms of my goals as an oncologist. I wanted to be able to have long-term, meaningful, and fulfilling relationships with patients, and it's great to have treatments that are successful. Treating CLL has been a great career so far. I'm glad I was led in that direction early on.

After Duke, I did my fellowship at Memorial Sloan Kettering Cancer Center (MSKCC) from 2013 to 2016. At that time, they didn't have a faculty member who was highly focused on CLL, so I shifted to myeloid malignancies. My clinical mentor was **Martin Tallman, MD,** and I worked in translational research under my other mentor, **Ross Levine, MD,** who continues to be a huge advocate for my career.

When I took my first faculty position at the University of North Carolina (UNC), they were looking for a CLL-focused faculty member. That's when I hopped back into the CLL realm after doing myeloid and clonal hematopoiesis work at MSKCC. I still do a bit of that. Long-term, my main clinical hat is CLL, but I am in the minority of CLL docs given that I broach both the lymphoid and myeloid worlds.

You can't overstate the importance of mentors. The most important thing to me is supporting people regardless of whether their career meshes with yours. Dr. Levine is a primarily lab-based scientist, and I thought I wanted to do that when I went into fellowship. However, I realized I wanted to be a clinician and do research. It can be tough to figure out how to broach those two aspects of medicine, but it's great to have people who support your long-term goals.

Can you speak about your experiences so far and what you're looking forward to?

After six years at UNC, I moved to California. Had I not gotten married, I probably never would have left North Carolina. I loved it there. I loved the institution and my colleagues, but my husband is from Southern California, and we have a young son, so it was a good decision for our family to move closer to relatives. It was a great move for my life, but it has been an interesting experience to have a built a huge CLL practice and then completely start over.

I love my colleagues at UCI, and I am in the process of building a clinic essentially from scratch. It offers many opportunities, but it is also a challenge to begin the process of developing new relationships with referring community doctors and getting to know my all of the new patients that I am seeing after having known my prior patients for years. It was an emotional process for me to leave UNC because

"Patients give me ideas of where the knowledge gaps are in our modern practices."

I consider my patients as family, and I think about them often (though I know they are and will continue to be in great hands there!). UCI has been less busy clinically so far, but I know that won't last too long.

Prior to UCI, you established a clinic at UNC that focused on clonal hematopoiesis and clonal cytopenias. What was your experience in that clinic?

My research as a fellow at MSKCC focused on determining the implications of clonal hematopoiesis in the setting of advanced solid tumors. We found that having clonal hematopoiesis (with high burden clones) led to shortened cancer-specific survival.

I think it's important to understand the role of these mutations and counsel patients, so I opened the clinic at UNC in 2019. Seeing CHIP/CCUS primarily involves counseling because we don't have any known interventions to change the natural history of these mutations. However, we can counsel patients as far as what their risks are, whether there is a risk for developing leukemia in the future, cardiovascular risk, or other emerging associations.

I'm not a proponent of checking for these mutations broadly outside the context of a clinical trial because it creates anxiety to know about them. However, they can be picked up when we're not looking for them, and it's good for patients to talk to someone who knows what it means for their health. I still see these types of patients at UCI, though it is not my primary research focus anymore.

How does your work in the clinic inform your research?

I think it was **Steve Schuster, MD,** who said, "My clinic is my lab." You see situations that you wouldn't think about otherwise because patients present so uniquely. They give you ideas. You realize there are many situations where there are no data.

Get to Know

Patients give me ideas of where the knowledge gaps are in our current practices. They help me take things back to my own research projects, whether that's developing a clinical trial or coming up with a real-world research question.

I always want to do better for our patients. It's natural to ask, "What is the right thing to do in this situation based on the knowledge we have?"

How have you seen treatment for CLL evolve throughout your career?

I graduated medical school in 2010. When I was a resident, it was primarily chemotherapy-based treatments, but ibrutinib was just coming into the clinic—obviously first in the clinical trial setting—but then it subsequently received US Food and Drug Administration approval in 2013, which is when I started fellowship. I saw the end of the chemoimmunotherapy days.

As an attending, treatment has been primarily based on targeted novel agents, which is phenomenal because chemotherapy works but has severe toxicities that can be permanent. Not to say these novel agents don't have side effects, but for the most part, patients are living longer and their cancers are staying in remission longer. There is better progression-free survival and overall survival without the need for cytotoxic chemotherapy.

Things are continuing to change, though. When novel agents are first introduced, they're used as continuous treat-to-progression therapies. However, with the introduction of venetoclax—and the future being venetoclax and Bruton's tyrosine kinase (BTK) inhibitor combinations—I think we're going see a lot more time-limited therapies as opposed to indefinite treatments. There are other novel classes coming out that I'm also excited about, like the noncovalent BTK inhibitors or agents that are even more futuristic, like chimeric antigen receptor T-cell therapy, BTK degraders, and bispecific antibodies. The options have expanded. The future is bright for patients due to these developments.

What are your plans for future research?

I've been involved with the development of pirtobrutinib. I enrolled a good number of patients to the phase I/II BRUIN trial while I was at UNC. In the future, there is work to develop that drug further in multiple phase III trials. At UCI, I'm participating in the phase III trial of venetoclax with rituximab, with or without pirtobrutinib. There are several other phase III trials of pirtobrutinib that I'm also involved with in some capacity, and I've been excited to join the SWOG working group for CLL. I have also been working on developing an investigator-initiated trial, which is a huge undertaking. I also still participate in real-world CLL research projects.

How do you like to spend your time outside of work?

My two favorite things are animals and nature. I am an avid hiker, and I like being out West because the weather is much more pleasant. There are so many beautiful places to go hiking, and you can do it year-round. The past five years, I have hiked to the bottom of the Grand Canyon at least once annually, though my favorite place to hike is definitely Utah (especially Zion National Park).

As far as animals go, I sadly had to rehome my seven chickens in North Carolina. I'm hoping once we buy a house, I can reestablish a new coop and flock because I love being a chicken owner. We also have two dogs. I love taking my son to the zoo and the aquarium—both the San Diego Zoo and aquarium are amazing. My son got his love of animals from me, so we love seeing what all of Southern California has to offer.

Do you have a skill, hobby, or interest that readers might be surprised to learn about?

I don't know anyone who's as good at finding four-leaf clovers as I am. I look down, and even when I'm not looking for one, I find four-leaf clovers. I used to keep a little laminated book of all the ones I found, and then it just became too many.

Catherine Coombs, MD, *is an Associate Professor in the Division of Hematology/Oncology at the UCI School of Medicine.*

How Can We Challenge the Status Quo in Myeloma Research?

Researchers and clinicians are attempting to increase access to and enrollment in clinical trials to better reflect the population of patients with multiple myeloma (MM).

By Leah Lawrence

The lack of information from underrepresented populations in clinical trials of MM has significant implications for current clinical knowledge. The drivers of disparities in MM clinical trial enrollment are multifactorial. Regardless, disparities create a knowledge gap related to the effectiveness and safety of treatments for these patient populations.

"Without data from diverse groups, it becomes challenging to develop personalized treatment approaches and tailor interventions to address the unique needs of underrepresented patients," said **Manshi R. Shah, MD,** an Assistant Professor of Medicine at Rutgers Cancer Institute of New Jersey. "Consequently, clinical decision-making may be biased toward the majority of populations, leading to disparities in care and outcomes."

Age-adjusted death rates from MM are estimated to have decreased by an average of 1.3% each year from 2011 to 2020.[1] These gains are likely due, at least in part, to the approvals and combinations of classes of drugs like proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies that have transformed the treatment of MM.

"It is important to keep in mind that although numbers have improved for everybody—the number of patients getting novel drugs, the number of patients getting to transplant, duration of treatment, survival—these underrepresented groups always lag behind," said **Sikander Ailawadhi, MD,** a Professor of Medicine at the Mayo Clinic in Jacksonville, Florida. "There is never the same magnitude of improvement or benefit because these disparities exist."

Who Is Underrepresented?

When underrepresented populations are discussed in MM, racial and ethnic minorities are often the first groups to come up.

Recent data from the Surveillance, Epidemiology, and End Results Program estimated that per 100,000 individuals, there would be 15.8 new cases of MM among Black patients compared with less than half that number (6.9 cases) among White patients.[2] Additionally, Black patients are more likely to have precursor conditions like monoclonal gammopathies of undetermined significance (MGUS) compared with White patients.[3]

Despite those finding, Black patients are less likely to get triplet therapy, transplant, and chimeric antigen receptor T-cell therapy,[4] and they have a myeloma mortality rate that is twice that of White patients with MM.[5]

The Hispanic community is another racial/ethnic minority group where disparities related to MM are seen, pointed out **Shahzad Raza, MD,** a hematology specialist with the Cleveland Clinic. For example, one recent study found that MM-related in-hospital mortality is increased in Hispanic patients compared with non-Hispanic White and non-Hispanic Black patients.[6] Hispanic patients may also have delayed initiation of treatment with bortezomib and low utilization of stem cell transplant.[7]

Both Black and Hispanic patients are underrepresented in global MM clinical trials. A pooled analysis of data from trials submitted to the US Food and Drug Administration supporting

approval of MM therapies from 2006 to 2019 showed that Black patients comprised only 4% of the dataset. Hispanic patients also comprised just 4%.[8]

Certain racial/ethnic groups are not the only underrepresented populations in MM clinical trials. Another underrepresented group in the United States is elderly patients. MM occurs mostly in individuals aged 60 years or older, and the average age at diagnosis is 70.[9] However, an analysis of data from therapeutic trials from 2000 to 2016 showed that the median age of trial participants was 62 years and 66% of participants were younger than 65.[10]

Additionally, patients diagnosed with MM at ages younger than 65 years have improved survival rates compared with those aged 65 years or older.

"No matter your race or ethnicity, your age, or whether you are in a rural or urban environment, if you don't have access to primary care or other health care screenings, you are more likely to be diagnosed later in the disease course than someone with regular appointments where a provider runs a CBC or chemistry." *— Sagar Lonial, MD, FACP*

Almost 70% of younger adults are alive at five years compared with 40% of older adults. Little progress has been made in terms of excess mortality in patients older than 75 years of age.[11]

Individuals from rural geographic locations may also be underrepresented. Looking across cancer types, an analysis of 44 SWOG phase III or phase II/III treatment trials from 1986 to 2012 showed that less than one-fifth of enrolled participants were from rural locations.[12]

Finally, patients with advanced organ dysfunction or other comorbidities are also underrepresented.

"For example, 20% of myeloma patients show up with advanced kidney dysfunction, and they are never included in trials," Dr. Ailawadhi said.

These patients are often excluded from trials whether or not there is knowledge of the "metabolic pathways and excretory routes on the investigational drug."[13] When these patients are excluded, trial enrollment will likely favor younger patients.

Barriers to Care

Access to care is a major challenge for underrepresented patients with MM, according to Dr. Shah.

"Financial barriers, lack of health insurance, geographical constraints, transportation issues, and limited availability of specialized health care providers in certain areas hinder these patients from accessing the necessary care," Dr. Shah said. "Additionally, cultural and language barriers may further complicate communication and understanding, reducing the chances of receiving optimal treatment and support."

According to **Louis Williams, MD,** a hematologist at the Cleveland Clinic, good comparative data about barriers to care for MM beyond what is highly generalizable are lacking.

To try to find out more, Dr. Williams and colleagues have begun an initiative to interview members of the Black community who decide to enroll in trials and those who do not.

"We are trying to be a bit more precise about what positive practices are driving enrollment," Dr. Williams said. "There are a lot of studies of societal barriers and economic barriers, but very rarely are these [studies] translated into factors that drive patient decisions."

Instead, Dr. Williams and colleagues are trying to focus on what he called "translational disparities research" to identify actions to bring to the bedside.

Similarly, Dr. Ailawadhi and colleagues recently conducted a survey study of approximately 500 patients with cancer who were seen at the Mayo Clinic in Jacksonville. Patients were asked for their thoughts about clinical trials.

"We noticed that the number one difference was awareness about clinical trials," Dr. Ailawadhi said. "[Black] patients had significantly lower awareness."

Dr. Ailawadhi pointed out that this lack of awareness was found even in a population of patients who had sought out care at a large cancer center, indicating a different mindset or level of health care literacy.

"Now think about patients in rural Iowa or those who go to smaller community centers. The opportunities, awareness, and information [are] going to be even less there," Dr. Ailawadhi said. "This is a clear challenge for our already very demanding practices."

Clinicians have to be thinking about the right trial at the right time, present the information nicely, and make time to answer patients' questions, he said.

Even if awareness is increased and a wider variety of patients are offered enrollment on a clinical trial, the cards may still be stacked against certain populations.

"Eligibility criteria in trials may disproportionately exclude certain populations, especially the Black population, who at diagnosis may have a higher burden of disease and, therefore, more evidence of organ dysfunction, which further limits their representation and potentially exacerbates disparities in research findings," Dr. Shah said.

One recent study found that inclusion parameters that determine who can and cannot be enrolled may be disproportionately excluding minority patients. Black patients (25%) and patients from "other" (24%) racial subgroups had higher ineligibility rates compared with White (17%) and Asian (12%) patients.[14] Specifically, Black patients more often failed to meet hematologic lab criteria and treatment-related criteria.

Barriers to effective care often begin long before a patient may be approached for clinical trial enrollment.

"No matter your race or ethnicity, your age, or whether you are in a rural or urban environment, if you don't have access to primary care or other health care screenings, you are more likely to be diagnosed later in the disease course than someone with regular appointments where a provider runs a [complete blood count (CBC)] or chemistry," said **Sagar Lonial, MD, FACP,** a Professor and Chair in the Department of Hematology and Medical Oncology at Emory University School of Medicine and Chief Medical Officer at Winship Cancer Institute of Emory University.

What Is Being Done

Increased emphasis on diversity and inclusion in clinical trials, community engagement, and education programs; culturally tailored interventions; and collaborations with community organizations have helped improve representation and access to care.

The myeloma program at Emory has focused on partnering closely with physician colleagues around the state, partnerships the institute has been building for 20 years, Dr. Lonial said.

"Treatment plans we recommend can often be given locally, and anything that can only be done by us here, we keep here," Dr. Lonial said. "That kind of partnership is why our clinical trial enrollment is 30%."

More specifically, 34% of MM clinical trial participants at Winship Cancer Institute are Black. A survey study examining this high rate of enrollment found that scores on the Trust in Medical Research and Human Connection surveys were significantly higher than in national surveys. In their discussion of these findings, the study's researchers wrote that "the high correlation between trust and human connection among our study population may suggest that a way to increase trust levels of [Black] patients is to increase human connection, or the feeling of being heard and valued by the provider."[15]

At the Mayo Clinic in Jacksonville, Dr. Ailawadhi said that approximately two-thirds of all patients seen in the myeloma clinic are enrolled on clinical trials.

"My concept is if patients come to us, we have to offer them a clinical trial if they are in need of a change of treatment," Dr. Ailawadhi said. "It is ultimately up to the patient to decide to go on trial, but I believe if we present trials and make a case for trials, patients are not against participating."

Offering all patients access to trials is especially important, he said, as studies have shown that when given equal access, outcomes for Black patients are at least as good as if not superior to those of White patients.[16,17]

Some efforts to better include underrepresented racial/ethnic groups are not only looking to increase access to all MM trials but also designing trials specifically for those populations.

In 2022, researchers at the City of Hope in Duarte, California, announced that they were "casting a wide net" to reach patients with smoldering MM—specifically Black patients—for enrollment in a trial looking at leflunomide, an older rheumatoid arthritis drug. The trial will compare outcomes in Black and White patients but will look beyond skin color and examine participants' neighborhood, social structure, experiences of discrimination, and ancestry. To recruit for the trial, a multiethnic advisory council spearheaded outreach in communities with large Black populations and used culturally responsive educational materials.[18]

Dr. Williams mentioned both the PROMISE and SMRT trials as examples of studies designed at least in part to answer questions related to these specific patient populations.

PROMISE was designed to determine clinical/genomic alterations present in patients with MGUS or smoldering MM who are at high risk for developing MM, particularly Black individuals with or without a family history of MM.[19] The SMRT study is looking at racial differences in smoldering MM. Researchers at Memorial Sloan Kettering Cancer Center and New York University will study biomarkers and genomic sequencing to see how the transformation into MM differs in people of European or African descent.[20]

Cooperative study groups and industry sponsors are also trying to address how inclusion criteria can be broadened to incorporate a wider population of patients on clinical trials.

Some trials are beginning to allow for benign ethnic neutropenia, a condition where people of African descent may have genetically lower white blood cell counts. A National Cancer Institute-sponsored trial of belantamab mafodotin combined with carfilzomib, pomalidomide, and dexamethasone for relapsed or recurrent MM requires an absolute neutrophil count of at least 1, except in the case of benign ethnic neutropenia where it can be 0.75.[21]

The recently activated SWOG S2209 trial has modified inclusion criteria that will, for example, allow patients with any kidney dysfunction (outside of dialysis). Clinical trials typically demand a hemoglobin level above 8 g/dL, but this trial has been modified to 7 g/dL and allows for a platelet count as low as 50,000 and neutrophils above 0.75 instead of 1. The study is also allowing the use of growth factor and transfusion if cytopenias are considered secondary to bone marrow involvement in MM.

"In these patients, the counts are low because of the disease, but we often say if your counts are low you can't go on trial," Dr. AIlawadhi said. "Instead, we are saying if the disease is causing it, you can get help. We don't want a patient to not go on a trial because they have a lot of disease. I want to put them on the trial [precisely] because of that."

The study will also include patient-reported outcome measures in English and Spanish.[22]

In addition, Dr. Ailawadhi said SWOG 2209 will allow up to one cycle of treatment to be done in the community. He and others credit this type of change in access to the rapid adoption of telemedicine seen in response to the COVID-19 pandemic.

"There is a light at the end of the tunnel in that studies have shown that outcomes are not different between these populations," Dr. Ailawadhi said. "The biggest issue we have to keep working toward is equal and increased access."

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

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What Is the Best Strategy for Frontline Venetoclax Plus Obinutuzumab in CLL?

Othman Al-Sawaf, MD, a hematologist and oncologist at the University of Cologne in Germany, and **Nicole Lamanna, MD,** a Professor of Medicine at the Columbia University Medical Center, debate whether frontline venetoclax plus obinutuzumab should be limited to 12 cycles or extended to a longer duration for patients with chronic lymphocytic leukemia (CLL).

Fixed-Duration Combination Shows 'Sustained Efficacy' in CLL

By Dr. Al-Sawaf

To set the scene, in the phase III CLL14 trial, we explored the combination of venetoclax plus obinutuzumab in patients with previously untreated CLL. The study focused on patients with elderly onset CLL. They received 12 cycles of treatment, and all patients stopped therapy regardless of the response. It was a novel approach because we did not use chemotherapy. We started with the B-cell lymphoma 2 (BCL2) inhibitor venetoclax, which patients received for all 12 cycles. We also gave six cycles of obinutuzumab, a potent type two CD20-directed monoclonal antibody that was previously shown to be more active than rituximab in CLL.


Othman Al-Sawaf, MD

We compared this time-limited combination with 12 cycles of chlorambucil plus obinutuzumab. At the time, that combination was—at least in Europe—the standard of care for patients with elderly onset CLL. The study met its primary endpoint, which was showing superior progression-free survival (PFS) with venetoclax plus obinutuzumab compared with chlorambucil plus obinutuzumab.

In the latest follow-ups, we saw a sustained efficacy with this approach, as many patients are still in remission after finishing 12 cycles of venetoclax plus obinutuzumab. This finding demonstrates patients maintain their remissions in most cases, even without continuous exposure to an active regimen.

We also found that there are certain clinically relevant subgroups of patients who had a poor outcome even with a targeted approach. We noticed that patients with high-risk disease—for instance, *TP53* aberrations—had a shorter PFS than patients without *TP53* aberrations. In that sense, the *TP53* status is an independent prognostic factor in patients who receive venetoclax plus obinutuzumab.

Interestingly, the same also applies to *IGHV* mutation status, as unmutated *IGHV* is also associated with a shorter PFS in the context of fixed-duration venetoclax plus obinutuzumab.

However, the conclusions we can make as clinicians are always a bit dependent on the patients. In principle, we see there is activity and there is disease control with this time-limited approach in all patients. For instance, even the patients who have high-risk disease benefit from several years of treatment-free remission, even though their outcomes are worse than those of the patients who have a wild-type *TP53* status.

Clinically, the regimen is active across all subgroups. Therefore, in principle, any patient can be offered this approach, especially now that we have other datasets. For instance, in CLL13, we focused on patients who were younger and fitter. In that study, the fixed-duration treatment with venetoclax plus obinutuzumab was also superior to more intensive chemoimmunotherapy with fludarabine plus cyclophosphamide and rituximab or bendamustine plus rituximab.

This result demonstrates that in patients who are young and fit—as well as in patients who are elderly and unfit—the fixed-duration treatment approach with a BCL2 inhibitor and a CD20-directed monoclonal antibody is quite active in previously untreated CLL.

Whether continuous treatment or treating beyond 12 cycles is beneficial for patients is still an open question in my view. We need more data. Particularly, we need to explore measurable residual disease (MRD)-guided approaches that show us whether treating patients for longer than 12 cycles based on their MRD status might be beneficial.

We also need to explore whether patients who are on continuous treatment up front—for instance, on continuous therapy with a Bruton's tyrosine kinase (BTK) inhibitor—have similar or different outcomes compared with those receiving venetoclax plus obinutuzumab.

For now, based on the data we have, we can only make indirect comparisons across different trials, which of course comes with a lot of caveats. In general, from a clinical perspective, I think we can say that most patients with CLL can be at least considered for a fixed-duration approach with venetoclax plus obinutuzumab.

More Data Needed on Fixed-Duration Strategy, Especially in High-Risk CLL

By Dr. Lamanna

Obviously, these are excellent data from CLL14. I don't think any of us are completely surprised by the improvement in PFS with venetoclax plus obinutuzumab over chlorambucil plus obinutuzumab. With many different therapies, we've shown this time and time again. This outcome shows that patients now can have increased efficacy and receive a long-term benefit from time-limited approaches such as venetoclax plus obinutuzumab.


Nicole Lamanna, MD

We're all trying to figure out how to answer some interesting questions this approach has raised. Patients who receive this combination do have deep remissions and undetectable MRD levels. However, as Dr. Al-Sawaf and many others have shown, certain subpopulations—such as the high-risk patients with *TP53* aberrations—have a PFS rate of approximately 40%, which is distinctly different from the PFS rate of approximately 60% in the rest of the patients.

There is no doubt that there might be ways to

"Whether continuous treatment or treating beyond 12 cycles is beneficial for patients is still an open question." *—Othman Al-Sawaf, MD*

improve upon these time-limited approaches. Whether venetoclax plus obinutuzumab for 12 months is a completely optimal duration remains one question. Another question is about using this specific type of therapy versus other time-limited approaches involving either a BCL2 inhibitor plus a BTK inhibitor or an oral-oral time-limited therapy. If the duration or approach can be improved upon for patients with complex or high-risk disease, I think that remains another unanswered question. Hopefully, some of the other ongoing clinical trials looking at these different nuances will be able to answer that question for us.

"CLL14 is an excellent study; it's an excellent time-limited approach. However, I don't think it is the end-all strategy in terms of venetoclax plus obinutuzumab." *—Nicole Lamanna, MD*

The CLL14 trial has demonstrated the importance of MRD. We're all learning about how to translate MRD data into practical usage for patients and community physicians. There is a lot of work to be done here. We're trying to figure out for the future—and for all the clinical trials that are currently going on—how we can make it mainstream and standardize both the use of MRD and MRD testing itself in a practical sense. There is no doubt that the dynamics of MRD are influenced not only by the depth, but by the acceleration of the regrowth in high-risk disease. In this particular study, the patients who had MRD greater than 10^{-4} did not do as well with their overall survival or PFS compared with patients who had MRD 10^{-6} and better. I think we're going to learn more from these studies that incorporate MRD testing.

There are a lot of things to consider when deciding whether the optimal duration is 12 months for venetoclax plus obinutuzumab and if that approach is the best for everybody. There are trials evaluating extending that duration with consolidation. Whether that is going to work is questionable, because some patients, even with continuous treatment, may still regrow on treatment. That may show that they are truly resistant and don't need further therapy. However, I think there might be better ways to optimize a time-limited approach, particularly in patients with higher-risk disease.

Overall, CLL14 is an excellent study, and the combination of venetoclax plus obinutuzumab is an excellent time-limited approach for many patients. However, I don't think venetoclax-obinutuzumab is the only optimal time-limited strategy. I think we can fine-tune the approach in certain individuals and perhaps make it even better than what we have currently.

Pretransplant MRD Status in Blood Linked with Post-HSCT Survival, Relapse in AML

Take-aways:

- DNA sequencing can be used to identify residual *FLT3*-ITD or *NPM1* variants in the blood of adults with AML who are in their first remission before allogeneic HSCT.
- The persistence of *FLT3*-ITD or *NPM1* variants in pretransplant blood samples was associated with an increased post-HSCT relapse rate.
- Patients with persistent variants in pretransplant blood samples had significantly lower post-HSCT survival rates than those who did not.

Persistent *FLT3* internal tandem duplication (ITD) or *NPM1* variants in pretransplant blood samples from patients with acute myeloid leukemia (AML) who were in their first remission were associated with "increased relapse and worse survival," according to a recent study.

Laura Dillon, PhD, of the National Heart, Lung, and Blood Institute at the National Institutes of Health, and colleagues conducted the Pre-MEASURE study because there is "currently no standard" for testing measurable residual disease (MRD) in AML.

For example, flow cytometry is "commonly used" for MRD testing in AML, but "concerns have been raised about lack of interlaboratory standardization, leading to potentially limited prognostic value in decentralized settings," Dr. Dillon and colleagues wrote.

Due to the lack of a standard testing method, Dr. Dillon and colleagues used targeted deep DNA sequencing to test the hypothesis that detecting "specific residual AML-associated variants" in the blood of patients who are in their first remission prior to allogeneic hematopoietic stem cell transplantation (HSCT) would be "associated with higher rates of relapse and mortality after transplant."

Retrospective Study Tests Pretransplant Blood Samples From Patients with AML

The retrospective, observational study included adults who received their first allogeneic HSCT during their first remission between 2013 and 2019. Dr. Dillon and colleagues performed targeted DNA sequencing on banked pretransplant blood samples from the patients, who had AML associated with variants in *FLT3, NPM1, IDH1, IDH2,* or *KIT*. They defined MRD-positive results as those showing a variant allele fraction of 0.01% or higher.

The researchers analyzed 1,075 patients, identifying 822 patients who had *FLT3*-ITD, mutated *NPM1,* or both. The median patient age was 57.1 years, 54% of patients were female, and 84% were White. The researchers grouped patients into a discovery cohort that included those who received a transplant between 2013 and 2017 (n=371) and a validation cohort that included those who received a transplant between 2018 and 2019 (n=451).

The gene combinations used for next-generation sequencing (NGS) were determined by the discovery cohort and validated in the validation cohort. The study's primary outcomes were overall survival (OS) and relapse rates.

Persistent Variants Before Transplant Linked with Post-HSCT Relapse, Survival Outcomes

In the discovery cohort, pretransplant remission blood samples from 64 patients (17.3%) showed persistent *FLT3*-ITD, mutated *NPM1,* or both.

The three-year relapse rate was 59% in patients with persistent variants, significantly higher than the rate of 24% in those who did not have persistent variants (hazard ratio [HR], 3.71; 95% CI, 2.55-5.41; $P<.001$). The three-year OS rate was significantly lower in patients with persistent variants (34%) than in those without persistent variants (66%; HR, 2.60; 95% CI, 1.85-3.65; $P<.001$). See **TABLE 1** for information on three-year relapse-free survival (RFS) rates in the discovery cohort.

In the validation cohort, pretransplant remission blood samples from 78 patients (17.3%) showed persistent *FLT3*-ITD, mutated *NPM1,* or both.

Patients with persistent variants had a three-year relapse rate of 68%, significantly higher than the rate of 21% in those who did not have persistent variants (HR, 4.32; 95% CI, 2.98-6.26; $P<.001$). Patients with persistent variants had a three-year survival rate of 39%, significantly lower than the rate of 63% in patients who did not have persistent variants (HR, 2.43; 95% CI, 1.71-3.45; $P<.001$). See **TABLE 2** for information on three-year RFS rates in the validation cohort.

While persistent variants were associated with "higher rates of relapse and worse survival," this issue was "partially mitigated" in younger patients who received high-intensity myeloablative conditioning (three-year relapse rate, 53% vs 78%; HR, 1.97; 95% CI, 1.03-3.75; $P=.04$), according to Dr. Dillon and colleagues.

TABLE 1. RFS Rates by Pretransplant Variant Status in the Discovery Cohort

Pretransplant variant status	Three-year RFS rate
Patients with persistent variants	27%
Patients without persistent variants	59%

TABLE 2. RFS Rates by Pretransplant Variant Status in the Validation Cohort

Pretransplant variant status	Three-year RFS rate
Patients with persistent variants	19%
Patients without persistent variants	59%

Identifying Differential Risk

The authors outlined several limitations of the study, noting that it is "unknown" how results from bone marrow samples would differ from the results they found in blood samples.

Dr. Dillon and colleagues also did not have access to pretransplant flow cytometry MRD testing data from patients and could not evaluate if the NGS results would be consistent with those results. They noted that it is "unknown how these results apply to others who did not undergo transplant" and only around 10% of patients studied received maintenance therapy.

However, despite the study's limitations, its results showed NGS MRD testing on pretransplant blood samples from the first remission in patients who have AML with *FLT3*-ITD, *NPM1* mutations, or both "could identify differential risk between individuals otherwise placed in the same baseline risk classification."

"Among patients with [AML] in first remission prior to allogeneic hematopoietic cell transplant, the persistence of *FLT3* internal tandem duplication or *NPM1* variants in the blood at an allele fraction of 0.01% or higher was associated with increased relapse and worse survival compared with those without these variants," Dr. Dillon and colleagues concluded. "Further study is needed to determine whether routine DNA-sequencing testing for residual variants can improve outcomes for patients with [AML]."

Reference

Dillon LW, Gui G, Page KM, et al. DNA sequencing to detect residual disease in adults with acute myeloid leukemia prior to hematopoietic cell transplant. *JAMA*. 2023;329(9):745-755. doi:10.1001/jama.2023.1363

Menin Inhibitor Shows Activity in Acute Leukemias

Take-aways:

- Revumenib was associated with "promising" results in patients with AML who had a *KMT2A* rearrangement or *NPM1* mutation.
- No responses occurred in the patients who did not have a *KMT2A* rearrangement or *NPM1* mutation.
- The first-in-human study of revumenib demonstrated that inhibition is a therapeutic strategy for AML with *KMT2A* rearrangement or *NPM1* mutation.

A first-in-human, phase I clinical trial showed the menin inhibitor revumenib was associated with "promising antileukemic activity leading to deep and sustained remission" in certain patients with relapsed or refractory acute leukemia.

Ghayas Issa, MD, of the University of Texas MD Anderson Cancer Center, and colleagues conducted the trial evaluating revumenib, which is a potent, selective oral inhibitor of interaction between menin and the *KMT2A* protein. The interaction between menin and *KMT2A*, an epigenetic regulator, is a "dependence" in acute leukemias caused by rearrangement of *KMT2A* or a mutation in the *NPM1* gene, according to the study's authors.

KMT2A rearrangements, which can occur in approximately 10% of acute leukemias, have an "adverse prognosis," and *NPM1* mutations, which occur in up to 30% of cases, are the "most common genetic alteration in acute myeloid leukemia," Dr. Issa and colleagues wrote. However, there are "no targeted therapies specifically approved" for acute leukemia with *KMT2A* rearrangement or mutated *NPM1*.

Phase I Trial Design and Patient Characteristics

The phase I trial tested revumenib in 60 adults and eight children with relapsed or refractory acute leukemia. Adults had a median age of 50.5 years, while children had a median age of 2.5 years.

Most patients (82%) had acute myeloid leukemia (AML), 16% had acute lymphoblastic leukemia (ALL), and 2% had mixed-phenotype acute leukemia. Approximately two-thirds (68%) of patients had *KMT2A* rearrangements, 21% had mutated *NPM1*, and 12% had neither *KMT2A* rearrangements nor *NPM1* mutations.

The patients were "heavily pretreated" and had a median of four previous lines of therapy, with 46% relapsing after receiving an allogeneic hematopoietic stem cell transplantation (HSCT), according to the study's authors.

Responses to Revumenib Treatment

Complete remission (CR) or CR with partial hematologic recovery occurred in 30% of the 60 patients who were evaluable. Of those patients, 78% had undetectable measurable residual disease, as assessed by multiparameter flow cytometry. The median time to CR or CR with partial hematologic recovery was 1.9 months.

"Although imaging assessment was not mandated on study, responses were notably seen in both bone marrow and extramedullary sites in two of six evaluable patients with extramedullary leukemia at enrollment," Dr. Issa and colleagues wrote.

In patients who achieved CR or CR with partial hematologic recovery, the median duration of response was 9.1 months (95% CI, 2.7 to not reached) at a median follow-up of 11.9 months. The median overall survival was seven months (95% CI, 4.3-11.6) in the efficacy population, regardless of remission status, at a median follow-up of 14.3 months (95% CI, 10.6-16.7).

Furthermore, 12 patients received allogeneic HSCT as consolidation following their response to revumenib. Of those patients, nine were in remission at the time of data cutoff, seven of whom were in remission for more than six months.

Most patients (84%) who had *KMT2A* rearrangement and achieved morphologic remission after the first cycle of revumenib "retained the detectable fusions causing *KMT2A* [rearrangement] during concomitant cytogenetic analyses," the study's authors wrote, noting that "most patients later had clearance of these *KMT2A* rearrangements with subsequent cycles of therapy."

Patients with *KMT2A* rearrangement who achieved morphologic clearance of myeloblasts had a 64% complete cytogenetic response rate, with a median time to achieving cytogenetic CR of 1.9 months (range, 0.9-2.8 months).

No responses occurred in the eight patients who did not have a *KMT2A* rearrangement or *NPM1* mutation, which was "consistent with the preclinical hypothesis regarding the efficacy of menin inhibition in patients with *NPM1* mutations or *KMT2A* [rearrangement]," Dr. Issa and colleagues wrote.

The authors also conducted an exploratory descriptive analysis to evaluate responses by leukemia lineage and patient age, finding morphologic remission occurred in four of the eight (50%) children and in 28 of the 52 (54%) adults. See **TABLE 3** for a summary of responses by leukemia lineage.

TABLE 3. Morphologic Remission Rates by Leukemia Lineage Type

Type of leukemia	Patients achieving morphologic remission
AML	55%
ALL	40%

Menin Inhibition Established as a Therapeutic Strategy

Nearly all (99%) of the 68 patients who received treatment had an adverse event (AE) during treatment, with a treatment-related AE of any grade occurring in 78% of patients.

However, the therapy was associated with a "low frequency" of grade 3 or higher treatment-related AEs, Dr. Issa and colleagues wrote. See **TABLE 4** for information on treatment-emergent AEs of grade 3 or higher. Asymptomatic prolongation of the QT interval on electrocardiography was the only dose-limiting toxicity.

TABLE 4. Most Frequent Treatment-Emergent AEs of Grade 3 or Higher

Type of AE	Prevalence
Febrile neutropenia	31%
Thrombocytopenia	19%
Sepsis	18%

While treating patients who have relapsed or refractory acute leukemia with *KMT2A* rearrangement is "challenging," with low rates of CR with incomplete count recovery after two lines of therapy, the menin inhibitor has the "potential to address these unmet needs," the authors wrote.

The data from the first-in-human study "establish menin inhibition as a therapeutic strategy for susceptible" acute leukemia subtypes, according to the study's authors.

"In children and adults with highly refractory acute leukemia with *KMT2A* [rearrangement] or *NPM1* mutation, menin inhibition with revumenib monotherapy was associated with promising antileukemic activity leading to deep and sustained remission," Dr. Issa and colleagues concluded.

This study was funded by Syndax Pharmaceuticals.

Reference

Issa GC, Aldoss I, DiPersio J, et al. The menin inhibitor revumenib in *KMT2A*-rearranged or *NPM1*-mutant leukaemia. *Nature*. 2023. doi:10.1038/s41586-023-05812-3

Regulatory Actions

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

US FDA Grants Accelerated Approval to Talquetamab for Relapsed, Refractory Multiple Myeloma

The US Food and Drug Administration (FDA) has granted accelerated approval to talquetamab-tgvs (TALVEY) for adults 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 antibody.

This indication is approved under accelerated approval based on the response rate and durability of response. Continued approval for this indication is "contingent upon verification and description of clinical benefit in confirmatory trials," according to a news release from Janssen Pharmaceutical Companies of Johnson & Johnson, the manufacturer.

Talquetamab-tgvs is a T-cell-engaging bispecific antibody that binds to CD3 and GPRC5D. It is approved as a weekly or biweekly subcutaneous injection after an initial step-up phase.

The bispecific antibody was evaluated in the MonumenTAL-1 study, which included patients who had received at least four prior lines of therapy and who were not exposed to prior T-cell redirection therapy. The study also included 32 patients who were exposed to prior bispecific antibody or chimeric antigen receptor (CAR) T-cell therapy and had received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

"The clinically meaningful efficacy and safety profile observed with talquetamab in heavily pretreated patients in this clinical trial, which included patients treated with prior BCMA-targeted bispecific or CAR T-cell therapy, has been notable," **Ajai Chari, MD,** Director of the Multiple Myeloma Program and a Professor of Clinical Medicine at the University of California, San Francisco, said in the release. "Patients at this stage of disease have a poor prognosis. Talquetamab as a first-in-class therapy is a new option for patients with this difficult-to-treat blood cancer."

The safety profile includes a boxed warning for cytokine release syndrome and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome.

Source: PR Newswire, August 2023

FDA Approves Quizartinib Plus Chemotherapy for Newly Diagnosed *FLT3*-ITD AML

Quizartinib (VANFLYTA) has been approved by the FDA in combination with cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy.

The approval is for the treatment of adults with newly diagnosed acute myeloid leukemia (AML) who have *FLT3*-ITD internal tandem duplication (ITD) as detected by an FDA-approved test, according to a news release from Daiichi Sankyo, the manufacturer of the drug.

The FDA approval of quizartinib is based on results from the QuANTUM-First trial, which were published in *The Lancet*. The trial included patients who had newly diagnosed *FLT3*-ITD AML. It showed a 22% reduction in the risk of death compared with standard chemotherapy alone in patients who received quizartinib plus standard cytarabine and anthracycline induction, standard cytarabine consolidation, and continued maintenance monotherapy following consolidation. Investigators evaluated the safety of quizartinib in 265 patients who received it once daily in the trial.

Quizartinib is approved with a boxed warning for QT prolongation, torsades de pointes, and cardiac arrest. Quizartinib will be available only through a restricted program called the VANFLYTA Risk Evaluation and Mitigation Strategy, according to the news release. The drug will be available by prescription in the coming weeks, officials said.

Source: BusinessWire, July 2023

Conditional Marketing Authorization Recommended for Epcoritamab in Relapsed, Refractory DLBCL

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use issued a positive opinion recommending conditional marketing authorization for epcoritamab (TEPKINLY) monotherapy in adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The application for the approval of epcoritamab, a subcutaneous bispecific antibody, is based on results from the phase I/II EPCORE NHL-1 trial, which was conducted by **Catherine Thieblemont, MD, PhD,** of the Hôpital Saint-Louis Assistance-Publique-Hopitaux de Paris, and colleagues.

The open-label, multicenter trial evaluated the preliminary efficacy and safety of epcoritamab in patients with relapsed, progressive, or refractory CD20-positive mature B-cell non-Hodgkin lymphoma, including DLBCL. The overall response rate, which was the primary endpoint of the study, was 63.1%. Cytokine release syndrome was the most common treatment-emergent adverse event.

The final European Commission decision on this indication for epcoritamab is expected later this year, according to a news release from AbbVie, the manufacturer of the drug.

"Subcutaneous epcoritamab could become a promising treatment option for the DLBCL community, and I look forward to the European Commission's final decision," Dr. Thieblemont said in the release.

Source: AbbVie, July 2023

FDA Grants Fast Track Designation to Selinexor in Myelofibrosis Treatment

The FDA has granted Fast Track Designation to the development program of selinexor for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-essential thrombocythemia myelofibrosis, and post-polycythemia vera myelofibrosis.

In June 2023, Karyopharm, the manufacturer of the drug, initiated a pivotal phase III clinical trial, XPORT-MF-034, to assess the efficacy and safety of selinexor 60 mg once a week in combination with ruxolitinib in Janus kinase inhibitor-naïve patients with myelofibrosis. The results presented at the 2023 ASCO® Annual Meeting showed that selinexor plus ruxolitinib was effective in certain subgroups of patients with myelofibrosis.

Source: PR Newswire

EMA Approves Clinical Trial Application for Allogeneic CAR-T

The EMA has approved a Clinical Trial Application for AVC-201 in relapsed or refractory AML and other CD123-positive hematologic malignancies.

AVC-201 is a CRISPR-engineered allogeneic switchable CAR T-cell therapy candidate.

The open-label, phase I study will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AVC-201. It will be conducted at multiple sites in Germany and will include up to 35 patients.

Source: PR Newswire, August 2023

This article discusses the current state of the art in the treatment of classic Hodkin lymphoma (HL). The following material is reproduced from "SOHO State of the Art Updates and Next Questions: From Biology to Therapy: Progress in Hodgkin Lymphoma," published in the June 2023 issue of Clinical Lymphoma, Myeloma & Leukemia. *The article was written by Karan Chohan, MD, and Stephen Ansell, MD.*

Novel Targeted Therapies Shift the Treatment Paradigm in Hodgkin Lymphoma

Single-cell analysis has shed new light on the unique biology of classic HL, expanding the current understanding of its tumor microenvironment (TME) and immune cell interactions. HL subtypes are characterized by a unique TME and cytokine composition.

Over the past two decades, the HL treatment paradigm has shifted toward novel targeted therapies, which have now been incorporated into both the frontline and relapsed or refractory settings, and numerous novel agents are currently under investigation. These novel therapies include immune checkpoint inhibitors; antibody-drug conjugates (ADCs), such as brentuximab vedotin (BV); bispecific antibodies; and chimeric antigen receptor (CAR) T-cell therapies.

Emerging Checkpoint Inhibitor Therapies

While several PD-1 inhibitors have been investigated in HL, the most robust data currently exist for nivolumab and pembrolizumab. Anti-PD-1 antibodies have demonstrated exceptional efficacy in the relapsed or refractory setting and, recently, in the frontline setting. Furthermore, combination regimens of anti-PD-1 antibodies with other targeted agents, such as BV, and combination chemotherapies have demonstrated encouraging outcomes.

The field of immunotherapy in classic HL is now incorporating the use of newer PD-1 inhibitors, which include sintilimab, tislelizumab, penpulimab, zimberelimab, and camrelizumab. These agents have demonstrated promising efficacy, with immune-related adverse events being the predominant safety concern.

ADCs: BV, Camidanlumab Tesirine

Studies have investigated the utility of BV in all aspects of HL treatment within many combination regimens. In the frontline setting, the addition of BV in combination with AVD (BV-AVD) has demonstrated improvement over the traditional ABVD regimen. BV has exhibited a favorable safety profile, but toxicities associated with the treatment include peripheral neuropathy, pneumonitis, and neutropenia.

Initial phase I investigations for another ADC, camidanlumab tesirine, assessed the drug in both HL and non-Hodgkin lymphoma (NHL) in the relapsed or refractory setting. Among 77 patients with classic HL, including 74% with prior BV and checkpoint inhibitor therapy, an overall response rate (ORR) of 71% was reported.

Bispecific Antibodies

A handful of bispecifics are under investigation in classic HL.

AFM13, a CD30×CD16A bispecific, targets CD30 on HRS cells and CD16A on macrophages and NK cells. Modest response rates have been associated with AFM13 monotherapy. Furthermore, the combination regimen of AFM13 and pembrolizumab demonstrated an improved ORR (83%) in a phase lb study, but the contribution of AFM13 in this regimen was unclear. A phase I/II study is currently underway utilizing modified allogeneic umbilical cord blood-derived NK cells combined with AFM13 (AFM13-NK). The results of 30 patients (28 HL, 2 NHL) with double refractory CD30-positive lymphoma were recently presented at the 2022 American Society of Hematology (ASH) Annual Meeting and Exposition, and an excellent ORR of 97% with a complete response (CR) rate of 63% was observed among patients treated.

Additional bispecifics currently under investigation for the treatment of HL include MGD024, a CD123×CD3 bispecific, and AZD7789, a monovalent bispecific. Overall, the bispecific antibody field is readily evolving.

"CAR T-cell therapy has the potential to serve an important role in the treatment of relapsed or refractory disease."

CAR T-Cell Therapies

There is limited literature assessing CAR-T for the treatment of HL. The results of two trials assessing novel CAR-T constructs, HSP-CAR30 and CAR30.CAR-EBVST, were presented at ASH 2022.

An alternative CAR target may be CD123. In preclinical studies, anti-CD123 CAR-T therapy has demonstrated the ability to eradicate HL in mouse xenograft models. Checkpoint inhibitors may additionally offer an important combination regimen with CAR-T therapies in HL to help make the TME more favorable and result in an improved antitumor response. Although further investigation is needed, CAR T-cell therapy has the potential to serve an important role in the treatment of relapsed or refractory disease, especially post-BV and PD-1 inhibitor failure.

Pathway-Directed Therapies

Multiple agents have emerged that seek to address altered pathways in HRS cells and the TME. In patients with relapsed or refractory HL, ruxolitinib has demonstrated a modest efficacy profile, with the more recent phase II, open-label, multicenter trial, JeRiCHO, showing an ORR of 17% and a median progression-free survival (PFS) of 3.6 months in 12 patients.

PI3K and mTOR inhibitors are additional targeted therapies that have been investigated. ldelalisib, a PI3K inhibitor that demonstrated promising preclinical activity, was assessed in 25 patients with relapsed or refractory HL in a phase II trial. This single-agent regimen resulted in an ORR of 20% with a median PFS of 2.3 months. Given the initial promising preclinical data on the mTOR inhibitor everolimus, a phase II trial was conducted in patients with relapsed or refractory HL. Efficacy outcomes with everolimus monotherapy 10 mg/d were adequate, with a phase II study demonstrating an ORR of 46% with a 9% CR rate in 57 enrolled patients.

Many of these single-agent therapies targeting altered pathways demonstrated only modest efficacy outcomes. In an effort to target multiple dysregulated pathways, the phase I/II EVITA study is investigating everolimus plus itacitinib. Results presented at ASH 2020 demonstrated that among 15 patients with relapsed or refractory HL, all having received previous BV or PD-1 inhibitor therapy, the phase I/II ORR was 79% with a CR rate of 14% and a median PFS of 3.8 months, representing improved efficacy over the monotherapy regimens.

Novel Agents Demonstrate Encouraging Activity

Novel agents have demonstrated encouraging activity in classic HL, confirming that the use of agents that target tumor cells or the TME are promising strategies to improve patient outcomes. Investigation into understanding which drugs should be used in combination and the sequence of therapy administration will be exceedingly important to continue improving outcomes for patients. Additionally, promising ongoing studies that assess chemotherapy-free approaches for frontline and salvage treatment may lead to improved patient outcomes, especially if treatment is more tolerable and results in a deeper sustained response.

Knowledge Hubs

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. This month, we feature news across our Knowledge Hubs, including mantle cell lymphoma and myelofibrosis.*

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MANTLE CELL LYMPHOMA

Can Allogeneic HSCT Be Curative for *TP53*-Mutated MCL?

Allogeneic hematopoietic stem cell transplantation (HSCT) "can be curative" in patients with mantle cell lymphoma (MCL), including those with *TP53* mutations, according to a recent study.

The researchers conducted the study because patients with *TP53*-mutated disease "have poor outcomes with standard approaches." They previously reported that allogeneic HSCT "achieved durable remissions" in patients with MCL, but follow-up among patients with *TP53* mutations was "limited."

The overall cohort included 36 patients, with 13 patients having a *TP53* mutation. The median follow-up for the entire cohort was 10.8 years, while it was 4.2 years for the subset of patients with mutated *TP53*.

The estimated 10-year overall survival (OS) rate was 56% for the overall cohort and 59% for patients with mutated *TP53*. In patients with *TP53*-mutated disease, no relapses were reported more than six months after allogeneic HSCT. However, survival after a post-transplant relapse was "poor," with a median survival of 2.1 years, according to the researchers.

"These data confirm that [allogeneic HSCT] can be curative in MCL, including patients with *TP53*-mutated disease, and should be considered for earlier utilization in this subgroup for whom conventional chemoimmunotherapy is ineffective," they concluded.

Why I chose this article: *"This study supports that allogeneic transplant remains likely the only curative option for patients with MCL, and it can provide durable remissions in those with* TP53 *mutations. The follow-up in this group is shorter than in the group of patients without a known* TP53 *mutation, limiting the ability to evaluate fully if this treatment is potentially curative."*

Tycel Phillips, MD

Reference

Lew TE, Cliff ERS, Dickinson M, et al. Allogeneic stem cell transplantation achieves long-term remissions in mantle cell lymphoma, including in *TP53*-mutated disease. *Leuk Lymphoma.* 2023. doi:10.1080/10428194.2023.2241095

MYELOFIBROSIS

Should a BET Inhibitor Be Added to JAK Inhibitor Therapy for Myelofibrosis?

Pelabresib plus ruxolitinib showed "potentially higher efficacy" than Janus kinase (JAK) inhibitor monotherapy in patients with myelofibrosis who were JAK-inhibitor naïve, according to a recent study.

Vikas Gupta, MD, of the Princess Margaret Cancer Centre, and colleagues conducted the study because preclinical data "indicate that combining JAK and bromodomain and extraterminal domain (BET) inhibition leads to overlapping effects" in myelofibrosis.

For example, the oral BET inhibitor pelabresib plus ruxolitinib showed improvement in spleen volume reduction and total symptom score reduction from baseline in patients with myelofibrosis in the phase II MANIFEST study, the study's authors noted.

Dr. Gupta and colleagues performed an unanchored, matching-adjusted, indirect comparison analysis among multiple clinical trials. They used this approach to adjust for differences between studies and allow for a comparison between outcomes from arm three of the MANIFEST trial and outcomes from the COMFORT-I, COMFORT-II, SIMPLIFY-1, and JAKARTA trials.

Arm three of the MANIFEST trial evaluated pelabresib with ruxolitinib in patients with myelofibrosis who were JAK-inhibitor naïve. COMFORT-I and COMFORT-II evaluated ruxolitinib in patients with myelofibrosis who were JAK-inhibitor naïve. SIMPLIFY-1 evaluated ruxolitinib and momelotinib in patients with myelofibrosis who were JAK-inhibitor naïve, and JAKARTA evaluated fedratinib in patients with myelofibrosis who were JAK-inhibitor naïve.

Dr. Gupta and colleagues compared outcomes, including spleen volume reduction of at least 35% (SVR35), total symptom score (TSS), and TSS with a reduction of at least 50% (TSS50) among the trials.

In arm three of the phase II MANIFEST study, patients with intermediate- or high-risk myelofibrosis who had not previously received a JAK inhibitor had an SVR35 rate of 68% and a TSS50 rate of 56%. The researchers found response rate ratios of at least one for pelabresib with ruxolitinib versus all comparators (ruxolitinib, momelotinib, or fedratinib monotherapy) for SVR35 and TSS50 at week 24. They noted that TSS improvements were reported as early as week 12 and were durable.

"These results indicate that pelabresib with ruxolitinib may have a potentially higher efficacy than JAK [inhibitor] monotherapy in JAK [inhibitor]-treatment-naïve [myelofibrosis]," the study's authors concluded.

Why I chose this article: *"This analysis provides context for the results of the arm three portion of the phase II MANIFEST trial, which evaluated combining the pan-BET inhibitor pelabresib and ruxolitinib in patients with JAK2-inhibitor-naïve myelofibrosis. The response rate ratios were >1 in each cross-trial comparison for spleen reduction and symptom improvement, favoring the combination of pelabresib and ruxolitinib. The ongoing phase III MANIFEST-2 results projected to be released later in 2023 are eagerly awaited."*

John Mascarenhas, MD

Reference

Gupta V, Mascarenhas JO, Kremyanskaya M, et al. Matching-adjusted indirect comparison of pelabresib/ruxolitinib combination vs JAKi monotherapy in myelofibrosis. *Blood Adv.* 2023. doi:10.1182/bloodadvances.2023010628

HemOnc Happenings

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

Dr. Poplack Receives ASCO Excellence in Teaching Award

David Poplack, MD, has received the 2023 Excellence in Teaching Award from the American Society of Clinical Oncology (ASCO). Dr. Poplack is the Director of the Global Hematology Oncology Pediatric Excellence program and Associate Director at Texas Children's Cancer and Hematology Center. He is also a Professor in the Hematology and Oncology Section of the Department of Pediatrics at Baylor College of Medicine.

David Poplack, MD

"It is an honor to receive this award from ASCO," Dr. Poplack said in a statement. "I am a lifelong proponent of the importance of education, especially within pediatric oncology, and I am so proud of what the next generation of pediatric oncology researchers and physicians is already accomplishing."

The Excellence in Teaching Award honors his "outstanding ability to expand trainees' patient connection and communication skills, broaden their vision of patient-physician interaction and stimulate their personal and professional growth," officials said in a news release.

Dr. Poplack has authored over 370 publications and has served on national and international committees, including panel appointments at the National Institutes of Health, the US Food and Drug Administration (FDA), and the Institute of Medicine. He was appointed to the National Cancer Institute's Board of Scientific Counselors. In 2016, he received the American Society of Pediatric Hematology-Oncology Distinguished Career Award.

Source: Texas Children's Hospital, June 2023

CLL Society Announces 2023 Young Investigator Award

Andres Chang, MD, PhD, of the Winship Cancer Institute of Emory University, has received the Chronic Lymphocytic Leukemia (CLL) Society Young Investigator award.

Andres Chang, MD, PhD

The purpose of the CLL Society's Young Investigator Award is to "provide emerging scientists who are early in their careers with substantive grants that will help to grow and develop a new generation of researchers who are committed to solving the unmet needs of the disease," according to a news release from the society.

Dr. Chang is originally from Guatemala and gained his doctorate at the University of Kentucky before completing his internal medicine residency and hematology-oncology fellowship training at the Emory University School of Medicine. He joined the faculty of Emory University and is studying the immune response to the COVID-19 vaccine in patients with CLL and small lymphocytic leukemia.

Source: CLL Society, July 2023

Hematologic Oncologists to Receive ASH 2023 Honorific Awards

The American Society of Hematology (ASH) will recognize multiple hematologic oncologists with Honorific Awards during the 65th ASH Annual Meeting and Exposition, which will be held December 9-12, 2023, in San Diego, California.

William Dameshek Prize

Omar Abdel-Wahab, MD, of the Memorial Sloan Kettering Cancer Center, will be recognized with the William Dameshek Prize for his "trailblazing research characterizing the genetic mutations that drive blood cancers," according to an announcement from ASH.

Omar Abdel-Wahab, MD

Dr. Abdel-Wahab's work has focused on understanding how underlying recurrent mutations in the RNA-splicing mechanism can lead to the development of myelodysplastic syndromes and leukemia.

"This discovery has paved the way for the development of multiple drugs targeting RNA-splicing activity, currently in the early phases of clinical development," ASH officials said. "Additionally, his research has played a pivotal role in securing the [FDA's] approval of the first targeted therapies for patients with rare blood cancers known as systemic histiocytic neoplasms."

E. Donnall Thomas Lecture and Prize

Katy Rezvani, MD, PhD, a physician-scientist and "renowned transplant immunology expert" at the University of Texas MD Anderson Cancer Center, will receive the E. Donnall Thomas Lecture and Prize for her "groundbreaking contributions to cancer research," according to the announcement.

Katy Rezvani, MD, PhD

She leads a laboratory at the MD Anderson Cancer Center that investigates cell therapies.

"Dr. Rezvani has become a leader in developing immunotherapeutic strategies by genetically modifying natural killer cells derived from umbilical cord blood," ASH officials said. "This technology shows promise in treating a variety of cancer types, including myeloid malignancies and solid tumors. By overcoming challenges encountered with autologous [chimeric antigen receptor] T cells, this paradigm-shifting approach has the potential to reduce toxicity, lower the cost of therapy, and increase patient access to potentially life-saving cancer immunotherapies."

Mentor Award

Hematologic oncologists **Stephen Sallan, MD,** of the Dana-Farber Cancer Institute, and **Helen Heslop, MD, DSc,** of the Baylor College of Medicine, will each be honored with the ASH Mentor Award.

"For Dr. Sallan, mentorship remains the most rewarding aspect of his career. He has mentored hundreds of individuals throughout his career who have gone on to become leading investigators in hematology and oncology," officials said in the announcement. "His motivation to mentor others stems from the early impressions his own mentors made on him, encouraging him to push the boundaries of cancer medicine while remembering to find joy in his work and to always pass it forward."

Stephen Sallan, MD

Helen Heslop, MD, DSc

Dr. Sallan, who has researched and treated acute lymphoblastic leukemia for several decades, has been "widely recognized not only for providing his mentees with unparalleled scholarly opportunities but also for actively and selflessly promoting his mentees and propelling them to the next stages of their careers," according to the announcement.

Dr. Heslop is a "highly respected mentor who is known for her inclusivity and commitment to helping her mentees advance in their careers," ASH officials said.

Her primary research focus is developing adoptive immunotherapies. Dr. Heslop has also worked to improve hematopoietic stem cell transplantation and other cancer therapies.

"She is an exceptional physician-scientist who has made significant and lasting contributions to the field of hematology," according to the announcement. "One of her remarkable achievements is her ability to nurture a diverse group of mentees, including female physician-scientists and individuals from backgrounds historically underrepresented in hematology."

Source: ASH, June 2023

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society of hematologic oncology

SOHO HIGHLIGHTS

STATE OF THE ART & NEXT QUESTIONS

November 1, 2023 | Virtual Event Venue

Benefits of SOHO Highlights

- Discussion of the most important data presented at SOHO 2023 [State of the Art] as well as what to expect in the near-term [Next Questions]
- Participate in 10 minutes of Live Q&A with each Leading Authority in the Field
- SOHO Members may register for FREE* at:

https://soho.click/HL

*If you are not a SOHO Member, you may join the society for FREE at https://soho.click/join.