TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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With expert opinions from:
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Charles Bennett, MD, PhD;
and more

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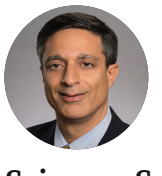

EDITOR-IN-CHIEF
SAGAR LONIAL, MD, FACP

Science, Serendipity, and the Intentional Life

An official publication of

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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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News

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Irene Ghobrial, MD

Dr. Ghobrial, of the Dana-Farber Cancer Institute, discusses how she entered the field of smoldering myeloma and the racial gap in myeloma research, treatment, and diagnosis.
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The Society of Hematologic Oncology was established as a nonprofit corporation in 2012 with aims to promote worldwide research, education, prevention, clinical studies, and optimal patient care in all aspects of hematologic malignancies and related disorders. The Society's global network supports and is supported by members from more than 110 countries, who are leading the vital efforts to further treatments for those afflicted by these diseases.

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Calendar

January 12–13
Highlights of ASH in North America
Seattle, Washington

January 20
2024 Leukemia & Lymphoma Society Blood Cancer Conference
Fort Lauderdale, Florida

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

February 19–20
22nd World Hematology Congress
London, United Kingdom

February 21–24
2024 Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR
San Antonio, Texas

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

February 29–March 3
28th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma
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March 4–6
American Association for Cancer Research (AACR) Blood Cancer Discovery Symposium
Boston, Massachusetts

March 8–9
Annual Meeting of the International Extranodal Lymphoma Study Group
Stresa, Italy

April 3–6
2024 American Society of Pediatric Hematology/Oncology Conference
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April 3–6
2024 Hematology/Oncology Pharmacy Association Annual Conference
Tampa, Florida

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

April 5–10
AACR Annual Meeting 2024
San Diego, California

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

Science, Serendipity, and the Intentional Life

Sagar Lonial, MD, FACP
Editor-in-Chief

As a philosophy major back in college, I recall spending hours in class debating the state of our collective future as viewed through the lens of the centuries-old argument on fatalism versus free will. Do we actually control our destiny, or was everything predetermined after the creation of the universe millions of years ago? Is it possible that, despite what we think our independent decisions are, the world, our fate, and the future are already decided?

As we wrap up another year, these are heady questions that are perhaps too esoteric for us to consider as the days get shorter and colder, but I am going to ask you to reflect on them, nonetheless. You see, while I attribute some of my greatest moments to serendipity (meeting my wife and switching my focus to myeloma after planning to be a leukemia doctor, to name a couple), I have to believe that we all have some impact on where our lives go, whom we meet, and our direction. There are obvious tragic events that innocent bystanders are inadvertently harmed by (mass shootings and the wars in the Middle East and Ukraine are examples). The other side of the coin suggests that there is no destiny, that we all make our way, and that good luck is just a consequence of hard work—there is no luck and no serendipity at all. This doesn't seem very satisfying either.

At this point, the reader is probably wondering where this is all going and why there is such philosophical blather in this December blood cancer publication. Here is the link: as I look over the past 10 issues of *Blood Cancers Today,* what strikes me the most is the enormous amount of purpose, intentionality, and hard work our community has brought to bear on the topic of often fatal blood cancers. This isn't just good luck or fate; this is a concentrated and curated global team effort to make a difference. We wouldn't have things like CAR-T or T-cell engagers, antibody-drug conjugates, and so many molecularly driven, targeted therapies in blood cancers if we didn't do all this work together. This doesn't mean that many trialists or scientists didn't have their "Eureka" moment (recall the serendipity of Archimedes in the bathtub). The inspiration of a new target or mechanism of action requires hard work and perseverance, and bringing something novel and life-changing to the public eye requires doing the work such that this new target will become a therapy that can impact patients all over the world. This is not chance, fate, or good luck; this is hard work, sometimes disappointing work, sometimes failed work. And yet we keep trying, keep testing, keep designing trials, keep on. Perhaps more daunting than the postman's creed (neither rain, nor sleet, nor snow…), for we know that if we don't succeed, if we don't keep trying, there are many lives that depend upon us in the balance.

So, as we close 2023, which began with saying goodbye to two long years of COVID isolation, fear, and hesitancy (vaccine or otherwise), it feels like we are all back, at full speed ahead, meeting in person, presenting great data, and doing the work that draws us together and to our field. To all those who wrote or edited or helped at BCT this past year, thank you, we couldn't be here without your tireless efforts. For all of you who are part of the movement, THANK YOU for your hard work, perseverance, and commitment to those we all serve. Take a few weeks to rest and relax with family and friends, and then get ready for a great 2024 together. With sweat and toil, and some serendipity, we will continue to make great strides in our work, and hopefully for the benefit of our patients.

Sagar Lonial, MD, FACP, *is Chair and Professor in the Department of Hematology and Medical Oncology, the Anne and Bernard Gray Family Chair in Cancer, and Chief Medical Officer of Winship Cancer Institute at Emory University School of Medicine in Atlanta, Georgia.*

2023 Year in Review

2023 Brings Advancements in Acute, Chronic Leukemias

Elias Jabbour, MD
Associate Editor
MD Anderson Cancer Center

The year 2023 marks a year filled with novel treatment options for patients with hematologic malignancies.

In acute lymphoblastic leukemia (ALL), we have transformed a once dire diagnosis into one where patients have a substantial chance at long-term survival. For younger patients, the early integration of immunotherapy, through pivotal or randomized trials, has demonstrated its role in significantly improving survival rates. Today, in adult patients, the long-term survival rate is approaching 80%, which is very close to what we obtain in the pediatric setting.

In Ph-positive ALL, we are combining tyrosine kinase inhibitors (TKIs) with immunotherapy treatments such as blinatumomab. The promising outcomes of this combination have been published this year and further updates will be presented at the American Society of Hematology (ASH) Annual Meeting. The three-year survival rate is 90%, which is phenomenal.

In older patients, we are performing well. Additionally, we've made progress in five-year survival, now at 40% to 50%, a significant increase from the historical 10%, owing to the upfront integration of immunotherapy. This approach is being tested in a forward-looking manner, and we're eagerly awaiting the results of randomized trials to confirm and further improve outcomes.

One of the novel treatment options we gained this year is subcutaneous blinatumomab, which produced very good results in an early-stage trial. The responses are overwhelmingly positive, with high measurable residual disease negativity. The hope is to administer subcutaneous blinatumomab upfront in all patients with ALL.

Therefore, in the realm of ALL treatment, there are numerous discoveries and novelties on the horizon—stay tuned for further updates.

In acute myeloid leukemia (AML), the addition of venetoclax to chemotherapy has already led to survival of 70% in younger patients, which is very good. In older patients, we are building on the backbone of a hypomethylating agent (HMA) and venetoclax together.

We are building on that approach with a triplet therapy consisting of cladribine, low-dose cytarabine, and venetoclax, which has shown very positive outcomes. This regimen is enabling patients to undergo transplantation with a survival rate of 70%—a significant advancement.

In fact, rather than a single disease, AML is a spectrum of diseases. Therefore, in treating AML, it's crucial to identify specific targets to improve treatment outcomes. Over the past year, we've witnessed the emergence of new IDH1 and IDH2 inhibitors, as well as targeted therapies that home in on CD123 and other antigens.

In AML, we are witnessing advancements akin to those in ALL, though not yet at the same level. It's important to highlight that a significant breakthrough in acute leukemia treatment has been the development of menin inhibitors. They have shown promise for patients with *KMT2A*-rearranged disease or *NPM1* mutations who did not respond to previous therapies. Currently, these patients are experiencing positive responses, and there is optimism for even further improvement in outcomes. Therefore, menin inhibitors are certainly worth watching in the evolving landscape of leukemia treatment.

I think we can say chronic lymphocytic leukemia (CLL) is a curable disease. We're already using B-cell lymphoma 2 inhibitors and Bruton's tyrosine kinase inhibitors in CLL treatment. We are using the combination of these agents in younger patients in particular, with the aim of offering a finite therapy with higher rates of molecular remission and long-term cure.

As for chronic myeloid leukemia, we have at our disposal novel TKIs for both initial and relapse treatment phases. Notably, agents like asciminib, an allosteric inhibitor, and ponatinib are expanding our treatment armamentarium. Additionally, a variety of other novel agents are currently under investigation. Among them, olvermbatinib is showing very promising activity, with meaningful responses in patients with ponatinib-resistant disease.

In 2023, we saw data with luspatercept in newly diagnosed low-risk myelodysplastic syndromes (MDS) presented at the 2023 ASCO® Annual Meeting and the European Hematology Association 2023 Congress. These data from a randomized, phase III trial led to the approval of luspatercept in the frontline indication for lower-risk, transfusion-dependent patients.

We've also seen data from the IMERGE randomized trial in the relapse practice setting with randomization to either imetelstat or standard of care. Imetelstat, which is a telomerase inhibitor, has shown activity, and we are awaiting the approval of this drug, too, in the near future.

In high-risk MDS, magrolimab, a CD47 antibody, unfortunately did not succeed, but we're eagerly awaiting the combination of HMA/venetoclax trials and hoping for a positive result to further improve outcomes.

In myelofibrosis, we've seen the approval of novel agents. Today, we have two new drugs that can overcome complications of thrombocytopenia and anemias: pacritinib and momelotinib, respectively. These drugs have opened the door for new combinations in myelofibrosis to further improve patient outcomes.

In conclusion, we are very fortunate to have these treatment options that improve patient outcomes available today. I look forward to what 2024 will bring.

2023 ASH Abstract Excitement

Kami Maddocks, MD
Associate Editor
Ohio State University

My mid-year highlight included so many exciting approvals and data presentations in the treatment of lymphoma that occurred through July 2023, so I have to say that the highlight of the second half of 2023 was reading through the ASH abstracts and seeing the BOVen study data for the frontline treatment of mantle cell lymphoma. I look forward to the full data presentation.

Rapid Integration of Immunotherapies for the Treatment of Multiple Myeloma

Thomas Martin, MD
Associate Editor
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There are now five novel immunotherapies approved for use in patients with relapsed or refractory multiple myeloma (MM) who have received at least four prior lines of therapy (PLT), including two chimeric antigen receptor (CAR) T-cell therapies, two bispecific antibodies (BsAb) targeting BCMA, and one BsAb targeting the cell surface protein GPRC5D. These agents have, in general, shown overall response rates (ORRs) of >60% and progression-free survival and overall survival (OS) rates of >12 months and >18 months, respectively, greatly eclipsing all other therapies previously tested in these heavily pretreated patients. Thus, there is a great deal of interest in identifying the best agents and optimal sequence for these therapies. Which should come first, CAR-T or BsAb? And which should be targeted, BCMA or GPRC5D? The choice may be different depending on the individual patient. In addition, there are numerous trials investigating these and other agents in earlier lines of therapy (eg, frontline therapy, maintenance therapy, and patients who have received 1 to 3 PLT). Many anticipate that CAR-T will replace autologous transplant as part of frontline therapy and that BsAb therapy may be most effective as maintenance therapy or for early relapse. Undoubtedly, the next five years will bring many changes to the MM treatment landscape, with immunotherapies dominating the scene and improvements in OS and potential cure being the end goal.

Good Winter Reading

Jerald Radich, MD
Associate Editor
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I don't know about you, gentle readers, but for me, it is hard to think about personal highlights in a year with so many global lowlights. But I'll weigh in on a highlight from my friend and colleague Fred Appelbaum, MD, who published *Living Medicine,* a history of the development of bone marrow transplantation. It prominently features my first boss, E. Donnall Thomas, MD, who won the Nobel Prize for his major contribution to transplant medicine in 1990. It's a lively read about hard thinking, hard work, compassion, and persistence. For those of you who didn't have the pleasure and honor of knowing Don, I'm sorry, but this is your chance to get to know him through Fred's great read.

Immunotherapy Comes of Age for LBCL

Laurie Sehn, MD, MPH
Associate Editor
BC Cancer Centre for
Lymphoid Cancer

This year, the era of immunotherapy for large B-cell lymphoma (LBCL) has most certainly come of age. While the potential of CAR T-cell therapy had already been recognized, sufficient long-term follow-up has enabled the term "curative" to be applied. ZUMA-1 evaluated the benefit of the CD19-directed CAR T-cell therapy axicabtagene ciloleucel (axi-cel) in patients with LBCL who had received at least two prior lines of therapy. With a median follow-up of 63.1 months, five-year event-free survival and OS were 30.3% and 42.6%, respectively, demonstrating sustained remission in a substantial proportion of patients (*Blood*. 2023;141[19]:2307-2315. doi:10.1182/blood.2022018893). In addition, longer follow-up from ZUMA-7, which compared second-line axi-cel to the standard-of-care approach of salvage therapy and autologous stem cell transplantation in refractory and early-relapsing patients with LBCL, demonstrated an improvement in OS for the CAR T-cell therapy arm (*N Engl J Med*. 2023;389[2]:148-157. doi:10.1056/NEJMoa2301665). This finding strongly supports a shift in the treatment paradigm, establishing CAR T-cell therapy as the preferred approach for high-risk patients in the second-line setting. While CAR T-cell therapy has firmly established itself as an integral therapy for relapsed or refractory LBCL with curative potential, maturing data on the value of bispecific antibodies have led to the approval of several agents in 2023. Glofitamab and epcoritamab are CD20×CD3-targeted bispecific antibodies designed to bring T cells in proximity with BCL to ignite a T-cell response. Both received approval from the US Food and Drug Administration this year for the treatment of LBCL after at least two prior lines of therapy based on pivotal phase II data in highly refractory patient populations, one-third of which had been exposed to CAR T-cell therapy (*N Engl J Med*. 2022;387[24]:2220-2231. doi:10.1056/NEJMoa2206913; *J Clin Oncol.* 2023;41[12]:2238-2247. doi:10.1200/JCO.22.01725). These studies demonstrated ORRs of greater than 50% and complete response rates of approximately 40%, with many responding patients achieving durable benefit. While longer follow-up will be required to ascertain the curative potential of bispecific antibodies, numerous ongoing combination trials in earlier lines of therapy will undoubtedly serve to further establish their role.

Get to Know

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

Irene Ghobrial, MD

Dr. Ghobrial, of the Dana-Farber Cancer Institute, discusses how she entered the field of smoldering myeloma, the PCROWD and PROMISE studies, and the racial gap in myeloma research, treatment, and diagnosis.

Where did you grow up and when did you know you wanted to be a physician-scientist?
I'm from Egypt originally, but I grew up in Nigeria. I lived there for 13 years before I moved back to Cairo. My parents are both physicians; my mom is a hematopathologist, and my dad is a cardiologist. For a long time, I did not want to be a physician. Then, as I was going through the process of applying to universities, I realized I was interested in biology, science, and medicine after all. I applied reluctantly, but I think it was one of the best decisions of my life. Immediately after, I knew I wanted to come to the United States to expand my knowledge and reach a different skill level.

I finished medical school in Cairo, went to Canada for a quick observership, and then came to the United States for my residency fellowship. That residency was mainly through the Detroit Medical Center and it was all clinical, so I wasn't exposed to research. I did a short rotation in immunology with a lab at the Mayo Clinic. There, I learned to do Western blots and similar processes. I remember once at 3 am running six gels simultaneously. They were leaking, and I was stressed out. I said, "This is as bad as the intensive care unit [ICU] rotations we have in medicine." My colleagues laughed and said, "How could this be as bad as being in the ICU all night?"

The work was exhilarating and stressful, but the best part was asking questions and answering them myself. In medicine, we see patients. We're taught to do our differential, to do this or that, to give this medicine. But you can never say, "Let me actually ask the question and answer it myself," which is the part of research I love. I never truly trained as a PhD, although I would have loved to. Instead, I learned science as I was doing it. I'm still learning every day from my postdocs and everyone I work with.

Were there any particular mentors who shaped your career path?
You can't really become who you are unless you have amazing mentors. My mom was my first mentor. She's a strong woman who really wanted to excel in everything. She had a PhD when she was living in Egypt, and that's very rare. She's a clinician. She raised four girls, and she never made us think we were any different than boys.

Sometimes you have to go out and find your mentors. They won't come to you. I had great mentors during residency and fellowship. **Morie Gertz, MD; Rafael Fonseca, MD;** and **Robert Kyle, MD**—who started the whole world of monoclonal gammopathy of unknown significance (MGUS) and smoldering myeloma—shaped my career. They got me into myeloma and sparked my love for the field.

I also credit **Rob Soiffer, MD**. I'm a full professor, at a point in my career where a mentor may not be necessary, and yet I go to him all the time, even with the smallest things. It's a lifetime mentorship. Even a full professor needs someone to talk to, to ask for advice, to look to for an answer to the question, "Am I doing the right thing?"

"Early detection and interception are critical for changing the way we think of cancer. There's nothing good about metastatic disease in any cancer. Myeloma is the perfect model of a cancer that you can detect early and intercept."

I would also say my husband; he's just amazing to believe in me. He believes I can succeed despite everything, and that's special.

How did you become interested in hematologic oncology, MGUS, and smoldering multiple myeloma?
I started my training with a fellowship at the Mayo Clinic. Thanks to Dr. Kyle, myeloma is a very strong field of study at Mayo. He really created the whole program. He is also an amazing person. He takes the time to explain things and always tells us to take care of the patients and put them first.

Drs. Gertz and Fonseca gave me the strength of understanding I needed to be a good clinician and scientist. They also taught me how to write grants and mentor new people. I still talk to them both; they are lifetime mentors.

I got into this field because of the passion Drs. Kyle, Gertz, and Fonseca have for myeloma. They're also the reason I like myeloma so much.

Can you explain the PCROWD and PROMISE studies and what's next for your research?
PCROWD sought to better understand the precursor conditions rather than waiting for MGUS and smoldering myeloma to develop. At the molecular level, what is the mechanism of disease progression? How can we define who will progress and who will not? Dr. Kyle defined it at the clinical and epidemiological levels, but there's so much more to understand.

We didn't have samples, and we didn't see enough patients at Dana-Farber to create cohorts and longitudinal follow-up. We established the Center for Prevention of Progression (now called the Center for Early Detection and Interception of Blood Cancers) and started seeing patients with MGUS and smoldering myeloma. Now, patients from the United States and around the world come to see us. We have expanded into CHIP, monoclonal B-cell lymphocytosis, and other disciplines. We have cardiologists, neurologists, and social workers on staff. We have developed multiple clinical trials, including a chimeric antigen receptor T-cell trial for smoldering myeloma that is actively recruiting.

For tissue banking, because you need the samples to ask those questions, we said, "Instead of waiting for patients to come to Dana-Farber, let's have it available for them everywhere." We put it online. Patients can click a link on a website, we send them a kit, and they send us their blood samples and clinical data. More than 3,000 patients follow us on MGUS

and smoldering myeloma, and we have over 10,000 samples in the bank. We've been able to perform single-cell RNA sequencing on over 500 samples and whole genome sequencing on hundreds. It's amazing what patients can do. They can drive research. They can ask the questions we are sometimes afraid to ask. I love collaborating directly with patients.

PROMISE came along because of a Stand Up to Cancer Dream Team application. We asked, "Instead of waiting for people to have MGUS and smoldering myeloma and then diagnosing them, can we screen for it? If you're at risk, especially if you're a Black patient, why are you at risk?" We screen only people who are at risk, so this is not a nationwide study where we're screening the general population.

PROMISE is helping us build an understanding of epidemiology, biology, and genetic variants. It opened the door for so many things, and it continues to open the door, because we have amazing collaborations. We expanded to South Africa and are hoping to expand to Kenya, Rwanda, and other countries. PROMISE brings communities together. It facilitates talking to people and understanding how we can overcome racial barriers. I never thought I would do global health, but I am, and it's wonderful.

What do you hope to see happen in this field and line of research in the next decade?

Early detection and interception are critical for changing the way we think of cancer. There's nothing good about metastatic disease in any cancer. Myeloma is the perfect model of a cancer that you can detect early and intercept. You can understand all those steps and use them as a footprint for getting into other cancers in the future.

If we can make it in myeloma, if we can prove that you can change survival, then it can be done in other cancers that might be harder to detect than just a simple blood sample with a monoclonal protein. We're very lucky to have some tools that can be useful. It's harder in other cancers. You can't detect it early, or you can't find the evidence of it.

I'd love to see us work on equity and diversity. We all say it, but we need to do it. Myeloma is much more common in Black individuals, but we don't know why. We haven't really done in-depth germline assessments. We don't know how the immune system of a Black patient compares with the immune system of a White patient or patients of other races. We don't know how to close the gap in treatment. Black patients are diagnosed much later than White patients, and we need to change that.

"In medicine, we see patients. We're taught to do our differential, to do this or that, to give this medicine. But you can never say, 'Let me actually ask the question and answer it myself,' which is the part of research I love."

What inspiration or recommendations would you give to younger physicians or trainees in the field?

First, think of what you want. Your own vision is critical. A lot of young faculty members are given a lot of ideas, and they don't have the time to think or ask themselves, "What do I want in five and 10 years?" They'll hear, "Oh, write this book chapter. Write this review. Do this clinical trial." They will get bombarded and need to learn early on to say, "No, I will focus on this question," and hopefully their mentorship committee will help them. Then, every step is a building block toward that goal.

Second, dream big. Don't let things limit what you want to do. Think of big ideas, talk to people outside of your community. Mentors may not be in the same area or at the same university. Working with others is important when you're trying to make a really big dream happen.

Third is a thing I haven't done, which is find work-life balance. I think it's critical these days to learn that it's okay to stop, think a little bit, take time off, and recharge rather than the "go, go, go" that I do.

What hobbies or activities do you enjoy outside of work?

I love to learn and try new things. I've taken a lot of hiking trips—I've done Kilimanjaro, I did Mount Fuji with my daughter, and I'm hoping to do Machu Picchu. I'm a horrible hiker, and I'm scared of heights, but I enjoy those trips because they alter your life. You spend seven days hiking, no TV, no phone, nothing. You really learn to appreciate life and understand the person you're hiking with.

I also love running. I've done the Boston Marathon and the New York Marathon, and I'm hoping to do a few others. I'm learning Spanish. I'm trying to learn dancing with my husband. I love traveling because I want to learn about other cultures and see the world. I would not mind learning anything and everything if I can.

Irene Ghobrial, MD, *is a Professor at the Dana-Farber Cancer Institute and Harvard Medical School.*

In Focus

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

Why Are Generic Cancer Drugs Out of Reach for Many Patients?

By Leah Lawrence

An estimated nine out of 10 prescriptions filled in the United States are for generic drugs,[1] yet access to generic drugs is still out of reach for many patients with cancer, including those with hematological malignancies.

Despite the unprecedented approval of novel therapeutics to treat cancer, "there are still a lot of generic drugs that are widely used in oncology," said **S. Vincent Rajkumar, MD,** the Edward W. and Betty Knight Scripps Professor of Medicine at the Mayo Clinic in Rochester, Minnesota. "For many cancers, [generics] are the backbone of treatment."

Whether due to availability or price, many patients with cancer may not be getting access to the off-brand drugs they need, either because certain long-standing generic drugs are in short supply or because patent strategies, product hopping, or litigation delay prevent new entries from coming to market.

"These two things exactly reflect the complexity of our drug supply at this moment," said **Mariana Socal, MD, PhD,** an Assistant Scientist in the Department of Health Policy and Management at Johns Hopkins Bloomberg School of Public Health.

"The complexity is that we have very expensive drugs that are expensive because of strategies that have successfully been used to avoid generic competition," Dr. Socal said. "And, simultaneously, we have very cheap drugs that have been successful in promoting generic competitors but are often not attractive to manufacturers who often leave the market or don't invest in good manufacturing practices."

According to Dr. Socal, the way this complexity is playing out in the oncology specialty is emblematic of the issue, and patients and the health care system are paying the cost.

Why Short Supply

In September, the White House issued a statement in response to a current shortage of 15 cancer drugs due to manufacturing and supply chain issues.[2] The statement specifically mentioned a nearly halving of the supply of three essential cancer drugs: cisplatin, carboplatin, and methotrexate (both methotrexate and cisplatin are used in some formulation to treat certain blood cancers).

The White House statement mentioned several steps being taken by the US Food and Drug Administration (FDA) to improve supply. Among them, the FDA has worked with manufacturers to increase capacity and bring back companies that stopped producing generics. In addition, the FDA has allowed for the importation of some generic cisplatin from a facility outside of the United States.

In an interview with *The Cancer Letter* earlier this year, **Richard Pazdur, MD,** Director of the FDA Oncology Center of Excellence and Acting Director of the Office of Oncologic Diseases, outlined some of the underlying causes of these drug shortages.[3] The most recent shortage of cisplatin was a result of quality issues at a single company's manufacturing facility in India, which caused a "ripple effect" leading to increased demand for the cisplatin alternative carboplatin, resulting in manufacturing challenges to meet demand for carboplatin as well.

"One of the FDA's main jobs is to patrol what they allow on the market and what is sold in the [US] market," said **George Tidmarsh, MD, PhD,** an Adjunct Professor at Stanford University. "The FDA found manufacturing deficiencies at the generic [cisplatin] manufacturer and tightened its standards, and with relatively few suppliers, that led to the drug being in short supply."

Similar issues have occurred with the manufacturing of methotrexate.

Many generics have only a small number of manufacturers because there are not large incentives to produce these drugs.

"In the typical generics cycle there is a rush to get the generic to market because the first one to market gets a period of exclusivity, up to 180 days in some cases; the others have to wait," Dr. Tidmarsh explained. "In the [United States] it is like the wild west. If you make a generic you have multiple manufacturers battling on price, and if you have bundling—although technically illegal—that drives the price down so much that making the generic may no longer be profitable."

A study looking at the flow of money through the pharmaceutical distribution system compared gross profit margins for branded manufacturers with generic manufacturers. In the branded market, gross margins are highest for the manufacturer (76.3%) and lower for the wholesaler (1.0%), the pharmacy (3.5%), the pharmacy benefit manager (PBM; 2.0%), and the insurer (22.2%). In contrast, in the generic market the gross margins are still highest for the manufacturer (49.8%) but are, at a minimum, quadrupled for others in the supply chain, including the pharmacy (42.7%), the wholesaler (18.5%), and the PBM (8.0%).[4]

In many European countries the government has

regulatory authority over drug prices, Dr. Tidmarsh said. The government and manufacturer agree on a reasonable price for a generic that is not burdensome to the consumer, and it can be fairly profitable.

In the United States, some of the supply issues are related to manufacturers, but they are not the only ones at fault, Dr. Socal said. Another underlying issue is that more than 90% of prescription drugs in the United States are distributed through just three wholesalers—AmerisourceBergen, Cardinal Health, and the McKesson Corporation.[5]

"Evidence shows that once you hit four or five manufacturers there is a sweet spot where competition really starts and begins to successfully bring down prices," Dr. Socal said. "The problem is we have purchasers who decide which manufacturers to buy from."

If these three wholesalers tell a company they will buy 10% or 20% from them, there is no incentive for the manufacturer to produce more of the drug than is needed to cover its assigned percentage, Dr. Socal explained.

This was seen when there was a nationwide shortage of injectables. One manufacturer went down, and the others could not ramp up production fast enough to supply what was needed.

"They did not have incentive to have redundant capacity," Dr. Socal said. "Why pay for the cost of redundant manufacturing capacity if you have a contract that outlines all you are going to ever sell over the course of a year?"

Old Problem, New Solutions?

Shortages of essential drugs are not new, said Dr. Tidmarsh, who described it as a "whack-a-mole" problem.

"As soon as people are motivated to action—because you are incensed that a child is suffering and can't get methotrexate, which is curative in leukemia—you ramp up all efforts to produce it, and then all of a sudden a supply of methotrexate appears," Dr. Tidmarsh said. "You sort of forget about it for a while, until the supply is gone again."

The same is true with other drugs, he said.

Solutions won't be simple. The US House Subcommittee on Health was recently at odds about the best way forward, with proposals ranging from suspending additional inflationary rebates for certain sterile injectables at risk of shortage, requiring the Center for Medicare and Medicaid Innovation to create a market-based pricing reimbursement policy, or awarding market exclusivity for drugs submitting shelf-life extension studies.[6]

A proposal from the Brookings Institution put forth a combination of "push" incentives designed to improve manufacturing infrastructure and "pull" incentives that would reward hospitals for taking steps to prevent shortages before they occur.[7]

In a recent study,[8] **Charles Bennett, MD, PhD,** the Frank P. and Josie M. Professor of Clinical Pharmacy and Outcomes Sciences at the University of South Carolina and an Affiliate Investigator with the Arnold Ventures Drug Access and Affordability Program at the Johns Hopkins Bloomberg School of Public Health, and colleagues proposed viewing the availability of these drugs as a public health imperative and including them in the United States' Strategic National Stockpile (SNS). The SNS is a national repository of antibiotics, chemical antidotes, antitoxins, life-support medications, intravenous administration supplies, airway maintenance supplies, and medical and surgical items that are stored for public health emergencies, such as following an anthrax dirty bomb, nuclear reactor explosion, hurricane, or COVID-19, for example.[9]

"The idea is to identify strategies to address this problem that do not require legislation to be passed or new things to be funded or authorized," Dr. Bennett said. "We want to work, if possible, within an existing framework."

Another possible solution is rewarding manufacturers that have no manufacturing quality issues, Dr. Socal said.

"If you are a hospital and have three products to choose from, you often have no information to go on except for price," Dr. Socal said. "If products had quality metrics, those could be used to justify a slightly more expensive price and would help hospitals make informed purchases."

"I can start patients on generic lenalidomide, and payments are slightly lower for a month or two, but then the generics hit their sales maximum, and there is no more generic drug available; then I have to prescribe Revlimid." *—S. Vincent Rajkumar, MD*

Blocking Competition

The second way patients may have insufficient access to generics is due to barriers that exist for delaying or blocking the release of generic or biosimilar versions of many novel targeted therapies as they move off patent.

Issues with patent strategies are not new in oncology. One of the first "blockbuster" targeted therapies for hematologic malignancies was the Bcr-Abl tyrosine kinase inhibitor (TKI) imatinib (Gleevec). Imatinib changed the outlook for chronic myeloid leukemia (CML), returning patients to an almost normal functional lifespan, but patients are on the drug for years.

Imatinib was first approved for CML in 2001,[10] when its introductory price was more than $26,000 per year.[11] More than 20 years later, it is still used as a frontline option for CML. The drug's initial patent was set to expire in May 2013, but the manufacturer was able to use a variety of patent extensions to extend its patent period to July 2015.

"One of the barriers that exists is that companies will generally have challenges in place at the end of a drug's patent designed to try to prolong patent life," Dr. Rajkumar said.

In this case, secondary patents filed on imatinib were designed to again extend its exclusivity to November 2019; however, generic manufacturer Sun Pharmaceuticals challenged those patents, and a confidential "pay-for-delay" agreement between Novartis and Sun Pharmaceuticals, the first generic company to receive FDA approval for a generic formulation of imatinib, delayed Sun's release of the generic an additional six months after the patent's expiration in exchange for an undisclosed amount of funds from Novartis.[12] In February 2016, Sun's generic formulation of imatinib became available in the US market. When the drug initially came to market, it was priced similarly to its brand-name predecessor (about $140K per year vs $146K per year), although prior to marketing initiation, Sun had announced that it would price its generic at 30% lower than the price of Gleevec, the branded imatinib formulation.[12]

The generic imatinib can now be bought for about $50 per month, but that does not mean that is the price insurance companies are paying and, therefore, what the patients are paying.[13,14] The price set by the manufacturer does not always dictate the cost; it is only the first price in the supply chain path.

In a 2022 commentary published in *The Lancet Haematology,* **Hagop Kantarjian, MD,** and colleagues discussed the issue: "It is generally accepted that… the price of generic drugs is substantially reduced once four to five generic options are available. This basis is reflected in the wholesale acquisition cost of the imatinib generics. However, the average wholesale price of imatinib remained high despite the availability of 12 formulations."

Dr. Kantarjian and colleagues cited an example of one generic imatinib that has a wholesale acquisition cost of about $6,900 but an average wholesale price of $131,200.[15]

A similarly frustrating situation has occurred with the long-anticipated generic form of lenalidomide, according to **Giada Bianchi, MD,** an Assistant Professor at Harvard Medical School.

"In multiple myeloma, lenalidomide is frequently used throughout induction and maintenance," Dr. Bianchi said. "Patients often receive it early on and may stay on it for several years, if not decades."

Lenalidomide was first approved in 2005.[16] According to Dr. Bianchi, there was great anticipation of the generic form of lenalidomide as a way of possibly offsetting some of the burden that patients and their families bear related to the cost of treatment.

In Focus

However, it took 17 years for a generic form of lenalidomide to be marketed in the United States, and this availability is "volume-limited" until 2026.[17]

Several generic manufacturers were forced to reach legal agreements with Celgene, the manufacturer of branded lenalidomide, as a result of patent litigation related to the submission of the abbreviated new drug application (ANDA) for a generic version of Revlimid (lenalidomide capsules) in the United States, which Celgene alleged infringed on Bristol Myers Squibb's patented, proprietary Risk Evaluation and Mitigation System (REMS) called RevAssist, as well as patents on lenalidomide itself, violating the Hatch-Waxman Act. According to Dr. Bennett, the manufacturer of Revlimid currently has 27 patents for lenalidomide. Four are for Active Pharmaceutical Ingredients, five are for product-related parts of the drug, and the rest are for the REMS distribution program.

The undisclosed "pay-for-delay" settlement allowed seven generic manufacturers to sell generic lenalidomide at restricted volumes, "described as a mid-single-digit percentage" of the brand name's monthly volume until 2026 in exchange for an undisclosed amount of payment to each generic manufacturer.[12,18]

What Does That Mean for Patient Access?

"I can start patients on generic lenalidomide, and payments are slightly lower for a month or two, but then the generics hit their sales maximum, and there is no more generic drug available; then I have to prescribe Revlimid," Dr. Rajkumar said. "This is very different from what is happening in Europe, Canada, or the United Kingdom. There, once a generic drug is available, prices fall, and the generic takes over market share. In almost all other countries, lenalidomide costs about $100 per month. In the United States, Revlimid is $17,000 a month."

Additionally, because the generic manufacturers have a limited market share available, they have no incentive to lower the price of the generic because the patented drug still controls 80% of the market, Dr. Rajkumar said.

Barriers to Use of Available Generics

Even once generics are available, there may be barriers to their uptake, including perceptions about safety and efficacy.

"The FDA can approve a generic that is equivalent to the original patented product, but it is in the FDA's authority to decide what kind of evidence is needed to show the product's equivalence," Dr. Rajkumar said.

Dr. Bianchi said that clinicians often have a sense of comfort using drugs they are familiar with, and in good faith tend to believe that the generic form will work similarly to the drug that was proven in clinical trials.

Among the FDA's requirements are that generics have the same active ingredient as the brand-name drug and show evidence that this active ingredient is the same; that the generic drug is the same strength, the same type of product (eg, tablet or injectable), and the same route of administration; that it has acceptable inactive ingredients; and that it is manufactured under the same strict standards as the brand name.[19]

"It is certainly possible that some side effects or allergic reactions could be triggered by additives that are present in a generic drug but are not contained in the formulary drug," Dr. Bianchi said. "If that happens and can be clearly documented, then a note needs to be added to the prescription to ensure patients are only dispensed the nongeneric form of drug."

However, in a review article published in *The Lancet Oncology* in 2016, Dr. Bennett and colleagues reported that no safety outbreaks among generic oncology drugs had been reported in developed countries.[20]

In general, Dr. Rajkumar believes that there is trust in the generic formulations.

Another barrier to increased use of generic drugs in oncology is the rapid pace of innovation. By the time one novel therapy comes off patent, another "second-generation" form of the drug could have taken its place.

"The complexity is that we have very expensive drugs that are expensive because of strategies that have successfully been used to avoid generic competition. Simultaneously, we have very cheap drugs that have been successful in promoting generic competitors but are often not attractive to manufacturers." *—Mariana Socal, MD, PhD*

Second-generation TKIs dasatinib, nilotinib, and bosutinib are considered more potent than imatinib and are active against imatinib-resistant CML.

"It is important to have thought-leaders speak up and say that you can get the same survival paying $500 or $600 a year for imatinib, and there is no reason to spend more on something like nilotinib or dasatinib," Dr. Rajkumar said.

Instead of trials looking at whether nilotinib produces better progression-free survival than imatinib, researchers need to examine whether using nilotinib after generic imatinib stops working still captures the whole benefit, Dr. Rajkumar said.

"The real trial isn't nilotinib versus imatinib, it is imatinib followed by nilotinib versus imatinib," Dr. Rajkumar said. "If you give 10 years of generic imatinib and then have to use nilotinib, which could be a generic form by that time, do you still capture the whole benefit? Is the benefit of a few months achieved by giving nilotinib early worth the cost paid?"

Newer formulations of a drug that provide some benefit compared with the original—even if it is marginal—fall into another strategy used to avoid generic entry called product hopping or evergreening. Product hopping may occur when a company reformulates their brand-name drug and encourages physicians to prescribe the new formulation. In some cases, the old drug formulation is removed from the market.[21]

The manufacturer of pembrolizumab, Merck, is currently looking to patent a new subcutaneous formulation of the drug. Patents on pembrolizumab are set to expire in 2028.[22] Although a subcutaneous version of the drug may be preferred by patients looking to avoid long intravenous infusions, it could also be more complicated to dose.[23] Currently being studied in clinical trials, if the subcutaneous formulation is effective, it could replace the intravenous version of the drug—and any biosimilars developed after the patent expires. Merck is just one of a handful of manufacturers looking to develop subcutaneous formulations of immune checkpoint inhibitors.

Other strategies for delaying generic competition include authorized generics produced by the brand company, pay-for-delay tactics where the brand company pays the generic competitor to delay entry, litigation efforts, or simply buying out the generic competitors.[17]

Potential Solutions

Similar to the generic drug shortage issue, there is no one solution that will stimulate healthy competition in the generic and biosimilar markets.

Widely, there is a push to regulate the cost of drugs in the United States at large. The Inflation Reduction Act was one step toward this goal. The act will require companies that raise their drug prices faster than the rate of inflation to pay Medicare a rebate. Additionally, it authorizes Medicare to negotiate directly with drug manufacturers to lower the price of 10 single-source drugs identified in a list that was disseminated on September 1, 2023.[24,25]

Dr. Bennett said, "only one cancer drug, Imbruvica, is included in this list of 10 drugs, and the negotiated price will not go into effect until 2026."

The Mark Cuban Cost Plus Drug Company is attempting to disrupt the status quo by selling certain drugs directly to patients with a prescription. On its website, the company admits to marking up the drug 15% plus a small pharmacy fee to cover costs.[26] However, Dr. Bennett noted, "only seven oral generic oncology drugs are sold by Cost Plus Drug—abiraterone, anastrozole, imatinib (100 mg and 400 mg), letrozole, methotrexate, and tamoxifen."

"The only catch is that patients are going to have to pay cash and are not able to use insurance," Dr. Rajkumar said. Though if patients have high-deductible insurance plans, the out-of-pocket cost savings may be worth it. "This shows that even in cases where lower-priced generic alternatives exist, that does not mean that the patient will be able to access [them]."

Dr. Rajkumar also supported an idea put forth by **Aaron Kesselheim, MD, JD, MPH,** of Harvard University, that supports the FDA offering reciprocal approval to generics approved in Europe or Canada and a so-called single-window pathway for approving generic medicines for use in multiple countries.[27]

There are also calls to reform patent laws that are used to exploit the system, although Dr. Socal said patent reform is likely to be "very difficult." The Initiative for Medicines, Access, and Knowledge recently published data showing that, on average, 74 patents are granted on each of America's 10 top-selling drugs, and about two-thirds of these patent applications were filed after the drug was approved by the FDA.[28]

"Major pharmaceutical companies have significant financial incentive to delay the inevitable competition in the market once the primary patents expire. Drugmakers prepare for these looming patent expirations by filing or amassing hundreds of patents ('patent thickets')," the report's authors wrote. "The strategy of securing additional patents extends their monopoly power far beyond the 20 years of patent protection intended under the law for an invention."

There are also calls for the FDA to establish a clear time window for generic entry and to streamline the review of ANDAs for generics, biosimilars, or new drugs that rely on research from an existing reference drug.

"The House Oversight Committee report in 2021 stated that the 14 largest drug companies in the world spend more on 'enriching investors and executives than on research and development,'" Dr. Bennett said. He added that the report concluded that Congress engages in five specific actions: "allow Medicare negotiation; restrain price increases and cap out-of-pocket costs; address anticompetitive practices on patents and targeting providers to prescribe patented drugs instead of generics; address anticompetitive 'pay-for-delay' agreements; and ensure transparency of research and development costs and support innovative research."

Dr. Bennet noted that "the 2022 Inflation Reduction Act has begun to address two of these recommendations: Medicare price negotiation and restraining price increases."

The system poses a complex challenge, with multiple factors involved, according to Dr. Rajkumar.

"These are things that need congressional, legislative, [and] regulatory type changes to enable the public to have access to these lower-cost generic drugs," he said.

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

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Regulatory Actions

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

FDA Accepts Lisocabtagene Maraleucel for Priority Review for CLL, SLL

The US Food and Drug Administration (FDA) has accepted for priority review the supplemental Biologics License Application for lisocabtagene maraleucel (Breyanzi) to expand its current indication to include the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who received a prior Bruton's tyrosine kinase inhibitor (BTKi) and B-cell lymphoma 2 inhibitor (BCL2i).

Lisocabtagene maraleucel is a CD19-directed chimeric antigen receptor (CAR) T-cell therapy with a 4-1BB co-stimulatory domain, which enhances the expansion and persistence of the CAR T cells. It is made from a patient's own T cells, which are collected and genetically reengineered to become CAR T cells that are delivered via infusion as a one-time treatment, according to the manufacturer of the drug.

The application was based on results from the primary analysis of the pivotal phase I/II, open-label, single-arm, multicenter TRANSCEND CLL 004 study, which were presented in an oral presentation during the 2023 ASCO® Annual Meeting in June. TRANSCEND CLL 004 is the first pivotal multicenter study to show clinical benefit with a CD19-directed CAR T-cell therapy in patients with relapsed or refractory CLL after progression following treatment with a BTKi and BCL2i.

The FDA assigned a target action date of March 14, 2024.

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

Quizartinib (VANFLYTA) has been approved in the European Union (EU) for use in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib single-agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukemia (AML) that is *FLT3*-ITD positive.

Quizartinib is the first *FLT3* inhibitor approved in the EU specifically for the treatment of patients with newly diagnosed *FLT3*-ITD-positive AML, which represents approximately 25% to 30% of all new AML cases, according to a press release from the manufacturer of the drug.

The authorization by the European Commission (EC) 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 during the trial.

"This approval of VANFLYTA represents an important advancement for frontline treatment of patients with *FLT3*-ITD-positive acute myeloid leukemia, an aggressive and historically difficult-to-treat subtype," said **Richard Schlenk, MD,** a Professor and Head of the Trial Center of the National Center of Tumour Diseases at Heidelberg University Hospital and German Cancer Research Center. "VANFLYTA is a potent and selective *FLT3* inhibitor that significantly improved overall survival when added to standard chemotherapy, and it will be a valuable treatment option for newly diagnosed *FLT3*-ITD-positive AML."

FDA Grants Orphan Designation to Drug Candidate for Oral GVHD

The FDA has granted Orphan Drug Designation to the drug candidate LP-310, designed for the treatment of oral graft-versus-host disease (GVHD).

LP-310 liposomal tacrolimus is a proprietary oral rinse formulation of LP-10, which was previously granted Orphan Drug Designation by the FDA, according to Lipella Pharmaceuticals, the manufacturer of both LP-310 and LP-10.

The FDA recently cleared a phase IIa clinical trial to evaluate the safety and efficacy of LP-310 in patients with symptomatic oral lichen planus, which currently has no FDA-approved treatment.

"GVHD occurs when donor immune cells attack the recipient's body tissues after an allogeneic tissue or bone marrow transplant," **Michael Chancellor, MD,** Chief Medical Officer at Lipella, said. "GVHD affects approximately 30,000 Americans, and oral GVHD contributes significantly to morbidity in cancer survivors. Morbidity of oral GVHD encompasses significant oral pain and discomfort, making it difficult for patients to eat, drink, and speak. In addition, the risk of oral cavity infection, fibrosis, and even oral cancer increases. Oral GVHD affects patients' quality of life and is a great unmet need in cancer survivors."

China NMPA Grants Approval to Inaticabtagene Autoleucel for B-Cell ALL

The China National Medical Products Administration (NMPA) has granted market approval for inaticabtagene autoleucel (CNCT 19), an investigational cell therapy, for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (B-cell ALL) in China.

Inaticabtagene autoleucel, a CD19 CAR T-cell therapy investigational cell therapy product from the manufacturer Juventas, has a unique CD19 scFv (HI19a) structure.

The drug has demonstrated a high level of efficacy, with durable remissions, and a substantially improved safety profile with reduced CAR-T-related toxicities in a pivotal clinical study for the treatment of adults with relapsed or refractory B-cell ALL, according to a press release from CASI Pharmaceuticals, a partner of Juventas.

The approval is based on the clinical results from a single-arm, multicenter, pivotal study of 39 adult patients with relapsed or refractory B-cell ALL in China. The 9.3-month follow-up data demonstrated very high durable response, an overall response rate of 82.1%, and a complete response rate of 66.7% within three months of infusion. Median duration of response was not reached. The safety profile showed decreased severity of CAR-T-related adverse events in patients with relapsed or refractory B-cell ALL.

Highlights from the **2023 INTERNATIONAL CONGRESS ON MYELOPROLIFERATIVE NEOPLASMS**

A Characterization of Strokes in Veterans with Myeloproliferative Neoplasms

Based on data from the US Department of Veterans Affairs, myeloproliferative neoplasms (MPN) are not frequently the cause of ischemic or hemorrhagic strokes in veterans with MPN; however, a recent analysis supported ongoing surveillance for MPN and identification of potential driver mutations after a diagnosis of stroke.

The authors, led by **Natasha Mathur, MD,** of the George Washington University Hospital in the District of Columbia, added that "there is a strong association of MPN and stroke."

The researchers noted their findings also supported "consideration for dual antiplatelet therapy for MPN patients with cardiovascular risk factors to prevent ischemic stroke and having a multidisciplinary discussion between neurology and hematology."

The authors analyzed 586,555 veterans from Illinois in the Veterans Affairs Informatics and Computing Infrastructure database. Using *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes, they identified ischemic strokes in 237 patients with MPN and 15,221 of those without and hemorrhagic strokes in 26 patients with MPN and 1,567 in those without.

Reportedly, MPN was associated with ischemic stroke (odds ratio [OR], 3.52; 95% CI, 3.08-4.03; $P<.0001$) and hemorrhagic stroke (OR, 3.54; 95% CI, 2.40-5.23; $P<.0001$). There was no difference in age at stroke diagnosis between patients with and without MPN; however, patients with MPN and ischemic stroke had higher rates of hypertension, smoking, and heart failure versus those without MPN.

Additionally, many ischemic strokes were diagnosed either more than three months prior to MPN diagnosis (n=115; 48.5%) or more than five years following MPN diagnosis (n=98; 41.4%).

Comparatively, the majority of hemorrhagic stroke diagnoses in veterans with MPN were more than three months before (n=14; 53.8%) and within three months of MPN diagnosis (n=7; 26.9%). Finally, among MPN cases with stroke, ischemic strokes had a recurrence rate of 45.18%, while hemorrhagic strokes recurred 40.00% of the time.

Reference

Mathur N, Tiu A, McKinnell Z, et al. Clinical characteristics and outcomes of veterans with myeloproliferative neoplasms who developed ischemic or hemorrhagic stroke. Abstract 112. Presented at the 15th International Congress on Myeloproliferative Neoplasms; November 2-3, 2023; Brooklyn, New York.

Developing a Pathomics Imaging Technique to Assess Bone Marrow in MPN

Among patients with BRC-ABL-negative MPN, such as polycythemia vera (PV) and myelofibrosis, bone marrow (BM) evaluation is necessary for differentiating and classifying malignancies, according to a pilot study.

The study's researchers, led by **Spencer Krichevsky,** of Stony Brook University in New York, sought to develop a deep learning (DL) technique that could estimate BM cellularity, characterize segmented nuclei, and identify variations in the BM microenvironment without the need for biopsies.

"[DL]-based pathomics and classical image analysis appear useful in segmenting nucleated cells, fat cells, and evaluable BM regions and characterizing the cellular features of the BM tissue microenvironment," the researchers wrote.

Researchers used morphology- and color-based models to differentiate trabecular bone, evaluable BM regions, and adipose tissue, which allowed them to estimate the ratio of hematopoietic cells to fat and derive the proportion of segmented cell nuclei within evaluable BM regions to assess nucleated cell density as a proxy for cellularity.

Whole slide images of BM biopsies with stained hematoxylin and eosin and respective clinical and pathological data were obtained from 54 patients with PV at a university center in the United States. Among the 54 patients, 17% were newly diagnosed, 61% were pretreated, and 17% were relapsed.

Comparing three DL algorithms in addition to their tissue-based approach, the authors reported U-Net (r=0.7; intraclass correlation coefficient [ICC]=0.6) and HistoCartography (r=0.7; ICC=0.5) algorithm estimations exhibited moderate agreement with hematopathology reports, while CellPose (r=0.2; ICC=0.2) and the tissue-based approach (r=0.2; ICC=0.0) had poorer agreement with BM reports.

Ultimately, the authors hoped to develop an image analysis strategy that expedited BM evaluation in order to eventually improve phenotyping of MPNs and other hematologic malignancies.

Reference

Krichevsky S, Abu-Zeinah G, Ouseph M, et al. Development of pathomics image analysis tools to quantify bone marrow cellularity in myeloproliferative neoplasms. Abstract 138. Presented at the 15th International Congress on Myeloproliferative Neoplasms; November 2-3, 2023; Brooklyn, New York.

Secondary Malignancies Observed After Rusfertide Exposure

Across five open-label, phase II studies on rusfertide plus concurrent therapies, nine cases of secondary malignancies were reported among 169 total patients who received treatment, representing an incidence rate of 5.3%. The highest rate of malignancies was observed in patients with PV (6.6%).

The study reviewed seven patients with malignancies following rusfertide therapy out of 70 patients (10%) with PV in the REVIVE trial. The median time from rusfertide initiation to diagnoses of malignancies in these patients was 234 days (range, 50-798 days).

Five out of the seven patients had a prior history of cutaneous malignancy prior to rusfertide exposure, and the remaining two had undiagnosed premalignant or pre-existing lesions in their medical history, according to the researchers.

The most common malignancy was nonmelanoma skin cancer (NMSC) in six patients, and two of the seven patients were diagnosed with stage I melanoma (one patient had concurrent NMSC and stage I melanoma). Additionally, acute myeloid leukemia developed in one patient with NMSC and a prior history of melanoma and thyroid cancer.

"The potential relationship, if any, between rusfertide exposure and development of malignancies is being evaluated in patients with PV in the randomized, placebo-controlled, phase III study VERIFY (NCT05210790) that is enrolling patients in Europe, North America, and other regions," the researchers wrote.

Reference

Pemmaraju N, Kremyanskaya M, Kuykendall A, et al. Summary of malignancies observed across 5 phase 2 open label clinical trials of the hepcidin mimetic rusfertide. Abstract 136. Presented at the15th International Congress on Myeloproliferative Neoplasms; November 2-3, 2023; Brooklyn, New York.

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, MPN, MDS, acute lymphoblastic leukemia, and acute myeloid leukemia.*

Visit BloodCancersToday.com *to view all of our Knowledge Hubs and stay up to date on the latest news in each area of hematologic oncology.*

MPN

Pelabresib Plus Ruxolitinib Is a Promising Treatment Regimen for Myelofibrosis

The combination of pelabresib plus ruxolitinib demonstrated significant clinical activity and disease-modifying potential without treatment-limiting toxicity in patients with myelofibrosis (MF), and an ongoing phase III study is expected to provide definitive efficacy results.

Raajit Rampal, MD, PhD, of the Memorial Sloan Kettering Cancer Center in New York, initiated the phase III MANIFEST-2 trial based on "compelling data" from arm three of the ongoing phase II MANIFEST study, which is currently evaluating the doublet therapy regimen in JAK inhibitor treatment-naïve patients with MF.

The double-blind, phase III study randomly stratified 431 patients by Dynamic International Prognostic Scoring System risk category (Int-1 vs Int-2 vs High), platelet count (>200 × 109/L vs 100-200 × 109/L), and spleen volume (≥1,800 cm^3 vs <1,800 cm^3). Patients received either pelabresib at 125 mg to 175 mg or a placebo once daily for 14 days, followed by a seven-day break, plus ruxolitinib at 5 mg to 25 mg twice daily for all 21 days of the cycle.

The primary endpoint is ≥35% reduction in spleen volume from baseline (SVR35) at week 24. Secondary endpoints include ≥50% reduction in Total Symptom Score (TSS50), percentage change in TSS, safety, pharmacokinetics, changes in bone marrow fibrosis, progression-free survival (PFS), overall survival (OS), conversion from transfusion dependence to independence, and rate of red blood cell transfusion for weeks 1 to 24.

In arm three of MANIFEST, 68% of 84 patients reported SVR35 and 56% reported TSS50 at 24 weeks. As for MANIFEST-2, a primary analysis after the last patient reaches the 24-week endpoint will be presented at the 65th ASH Annual Meeting & Exposition, December 9-12, 2023.

"Primary results from the pivotal phase III MANIFEST-2 trial…may have the potential to influence the MF treatment paradigm," researchers concluded. "MANIFEST-2 will also provide important insights in assessing the benefits of starting treatment at an earlier stage of the disease."

Why I chose this research:

John Mascarenhas, MD

"The MANIFEST-2 trial will explore the importance of starting combination therapy earlier in the disease course by enrolling intermediate-1-risk patients. The results of this trial are highly anticipated and have the potential to change the treatment paradigm, particularly if the durability of response is maintained and PFS and OS are favorable and balanced, with potential for added clinical and financial toxicity."

Reference

Rampal R, Grosicki S, Chraniuk D, et al. Pelabresib in combination with ruxolitinib for Janus kinase inhibitor treatment-naïve patients with myelofibrosis: results of the MANIFEST-2 randomized, double-blind, phase III study. Abstract #628. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

MANTLE CELL LYMPHOMA

Alternating Cytarabine in R-CHOP Induction Therapy Seems Marginal for Elderly Patients

Elderly patients with mantle cell lymphoma (MCL) did not exhibit efficacy or safety differences when undergoing induction therapy with R-CHOP versus R-CHOP alternating with rituximab, cytarabine, and dexamethasone (R-HAD), but maintenance therapy with rituximab plus lenalidomide (R2) significantly improved PFS versus rituximab alone, based on results from the MCL-R2 Elderly trial.

However, lead author, **Vincent Ribrag, MD,** of the Gustave Roussy Institute of Cancer in Villejuif, France, and contributors noted that the two maintenance therapies had no difference in OS, and the R2 group had increased toxicities.

The study randomized 620 patients between the induction regimens and subsequently randomized 495 patients between the maintenance regimens. The cohort had a median age of 71 years, was 69% male, and 85% had stage IV disease, 47% had intermediate-risk disease, and 46% had high-risk disease based on MCL International Prognostic Index criteria.

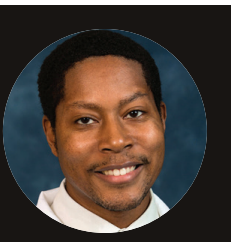
Both regimens were similar at the end of induction therapy. The overall response rate in the R-CHOP arm was 88% versus 86% in the R-CHOP plus R-HAD arm, and both arms had a complete response (CR) rate of 33%. Likewise, the R-CHOP and R-CHOP plus R-HAD arms had a PFS rate of 70.6% and 66.8% (P=.28), respectively, and an OS rate of 83.0% and 83.0% (P=.92), respectively, by the data cutoff date.

After a median follow-up of 4.2 years of maintenance therapy, the four-year PFS was 60.9% in the R2 arm versus 42.9% in the rituximab monotherapy arm (P=.0002); however, the R2 arm had more recurring adverse events (AEs) of grade 3 or higher, including neutropenia (50.8% vs 19.2%), respiratory tract infection (6.3% vs 0.8%), and skin cancer (5.9% vs 3.2%).

At two years, the OS rates were 87.6% with R2 and 85.1% with rituximab alone. Lastly, researchers noted 46% of patients in the R2 arm required at least one lenalidomide dose reduction.

Overall, the findings suggested that R-CHOP induction therapy alternating with intermediate doses of a cytarabine-containing regimen was comparable with R-CHOP alone in elderly patients with MCL.

Why I chose this research:



Tycel Phillips, MD

"Initial results with the induction regimen do not indicate a benefit to escalation of R-CHOP with cytarabine. Given the age of the patients enrolled, this could be related to tolerance of induction or due to the dose (1 gm) of cytarabine used, which is lower than that utilized in younger patients. The study adds evidence to the use of R2 for maintenance in patients with MCL but at a cost (toxicity). Given that this was an elderly study, it is possible that the toxicity/tolerance would be improved in a younger patient population, or that benefits could be seen with a lower dose of lenalidomide as compared with what was used during the trial."

Reference

Ribrag V, Safar V, Kluin-Nelemans H, et al. Induction and maintenance therapy in elderly patients with mantle cell lymphoma: double-randomized MCL R2 Elderly clinical trial by the European Mantle Cell Lymphoma Network. Abstract #979. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

ACUTE MYELOID LEUKEMIA

Sabatolimab Immunotherapy Promising in Patients with AML

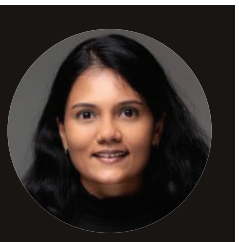
Sabatolimab monotherapy showed promising efficacy in a study of adult patients with acute myeloid leukemia (AML) who are in hematological CR with positive measurable residual disease (MRD+) after allogeneic stem cell transplantation.

Led by **Robert Zeiser, MD,** of the University of Freiburg in Germany, the study reported preliminary data from a safety run-in of the novel immunotherapy sabatolimab at two dose levels: 400 mg or 800 mg intravenous (IV) every four weeks. Twenty-one patients (10 at 400 mg and 11 at 800 mg) were enrolled.

The primary endpoint was incidence of treatment-emergent dose-limiting toxicity (DLT), including acute graft-versus-host disease (GVHD) and chronic GVHD during the first two cycles.

One DLT of grade 3 myocarditis occurred after the first infusion of sabatolimab 800 mg. Sixteen patients experienced AEs, with eight patients experiencing grade 3 or higher AEs such as neutropenia and thrombocytopenia. Two patients at 400 mg experienced serious AEs after the DLT observation period (>3 cycles), and two patients at 800 mg experienced serious AEs during the DLT period.

Why I chose this research:



Sangeetha Venugopal, MD

"In the STIMULUS-AML2 [study]...the primary endpoint was incidence of treatment-emergent DLT, including acute and chronic GVHD during the first two cycles. [Twenty-one] patients were enrolled in the safety run-in (10 at 400 mg; 11 at 800 mg). Importantly, there were no cases of GVHD or any immune-related AEs commonly seen with checkpoint inhibitors. Dose expansion at 800 mg is ongoing."

At the data cutoff, seven patients continued treatment and were in CR (three at 400 mg and four at 800 mg), while 14 patients discontinued treatment due to disease relapse (seven at 400 mg and seven at 800 mg). Five deaths occurred at 400 mg due to AML.

At 400 mg, two patients received 14 cycles of treatment and one patient received 15 cycles. Seven patients relapsed, including two patients after cycle one, two patients after cycle two, and one patient each after cycles three, four, and seven.

At 800 mg, one patient received five cycles, one patient received six cycles, and two patients received seven cycles. Five patients relapsed, including one patient after cycle one, two patients after cycle two, one patient after cycle three, and one patient after cycle five.

Overall, researchers found that sabatolimab at 400 mg and 800 mg was well tolerated, as cytopenias occurred at low rates and there were no reported cases of GVHD or any immune-related AEs commonly seen with checkpoint inhibitors.

Reference

Zeisler R, Devillier R, Mico M, et al. TIM-3 Inhibitor sabatolimab for patients with acute myeloid leukemia (AML) with measurable residual disease (MRD) detected after allogeneic stem cell transplantation (AlloSCT): Preliminary findings from the phase Ib/II STIMULUS-AML2 study. Abstract #59. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

MDS

Risk Factors for Patients With CK-MDS Undergoing Allogeneic HSCT

A recent study published in the *British Journal of Haematology* aimed to identify risk factors for patients with complex karyotype myelodysplastic syndrome (CK-MDS) undergoing allogeneic hematopoietic stem cell transplantation (HSCT).

Researchers discovered that several factors were "significantly associated with OS." These include the following characteristics: older age, male sex, poor hematopoietic cell transplant comorbidity, red blood cell transfusion requirement, platelet transfusion requirement, not-complete remission, a high number of karyotype abnormalities, and monosomal karyotype.

The multivariable analysis included 691 patients with CK-MDS who received their first allogeneic HSCT. The three-year OS of allogeneic HSCT, estimated using the Kaplan-Meier method, was determined to be 29.8% in patients with CK-MDS. Prognostic factors were identified using a Cox proportional hazards model.

Why I chose this research:

Kristen Pettit, MD

"Outcomes for those with CK-MDS who undergo allogeneic HSCT are relatively poor but variable. This study identified several risk factors for worse OS in this patient population."

Reference

Shimomura Y, Komukai S, Kitamura T, et al. The prognosis and risk factors for patients with complex karyotype myelodysplastic syndrome undergoing allogeneic haematopoietic stem cell transplantation. *Br J Haematol*. 2023. doi:10.1111/bjh.19139

ACUTE LYMPHOBLASTIC LEUKEMIA

Combination Treatment Is Tolerable in *BCR-ABL1*-Positive ALL, Blast Phase CML

Asciminib in combination with dasatinib and prednisone is feasible and tolerable in adult patients with *BCR-ABL1*-positive acute lymphoblastic leukemia (ALL) and blast phase chronic myeloid leukemia (CML), according to an investigator-initiated, phase I study.

The study evaluated the maximum tolerated dose and recommended phase II dose of asciminib with dasatinib and prednisone.

Fourteen patients received dasatinib 140 mg/day and prednisone 60 mg/m^2/day of prednisone on days one through 24, while asciminib was administered in escalating doses in a 3+3 design (DL1: 40 mg; DL2: 80 mg; DL3: 160 mg). Two patients at DL3 developed grade 3 amylase elevation, and one patient at DL3 developed grade 3 lipase elevations.

Because dose-limiting toxicity (DLT) was experienced at DL3, the study deescalated to DL2, and four additional patients enrolled at DL2 without experiencing a DLT. Therefore, asciminib at 80 mg/day was determined to be the recommended phase II dose.

"High rates of molecular response and bridging to transplant highlight encouraging preliminary activity," researchers concluded.

Why I chose this research:

Elias Jabbour, MD

"This trial examined the efficacy of combining a TKI, specifically the allosteric inhibitor of BCR-ABL1 *asciminib, with prednisone. The future direction of this trial is to integrate the therapeutic benefits of blinatumomab into this combination therapy."*

Reference

Luskin M, Murakami M, Keating J, et al. A phase I study of asciminib (ABL001) in combination with dasatinib and prednisone for BCR-ABL1-positive ALL and blast phase CML in adults. Abstract #965. Presented at the 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California.

2023 Top Stories

The top stories of 2023 from Blood Cancers Today *feature several articles on lymphoma and myelodysplastic syndromes (MDS), demonstrating how progress in the knowledge and treatment of these conditions is ongoing and significant.*

These are the top five most read articles published by *Blood Cancers Today*.

1

CAR-T Versus Bispecific Antibodies in Multiple Myeloma: Which Is the Better Option for Patients?

This year saw two US Food and Drug Administration approvals for the treatment of multiple myeloma (MM), elranatamab and talquetamab, both bispecific antibodies. Associate Editor **Thomas Martin, MD,** of the University of California Helen Diller Cancer Center, debates **Saad Usmani, MD,** of the Memorial Sloan Kettering Cancer Center, over which is the superior therapy when it comes to treating patients with MM: chimeric antigen receptor (CAR) T cells or bispecific antibodies.


Features
Point | Counterpoint
CAR-T Versus Bispecific Antibodies in Multiple Myeloma: Which Is the Better Option for Patients?
CAR T-Cell Therapy: Best Option for Patients
Bispecifics Will Overtake CAR T Cells in Myeloma Treatment

2

An Unclear Path: What's the Best Route After CAR-T Failure in B-Cell Lymphoma?

In an era of multiple treatment options, clinicians face the complex decision of determining the optimal sequence of therapies for diseases such as aggressive B-cell lymphoma, where durable complete responses are rare. These challenging outcomes underscore the urgent need for tailored treatment approaches for this group of patients. Current guidelines fall short of establishing a clear standard of care. Associate Editor **Kami Maddocks, MD,** of the Ohio State University, and others offer insights and analysis in this comprehensive feature.

3

Prognostic Tools Need Updates to Recognize High-Risk Features in Lower-Risk MDS

The presence of high-risk features in ostensibly low-risk cases presents a dilemma, as current prognostic scoring systems for MDS may not capture key variables that impact risk and treatment outcomes in patients with lower-risk MDS.

Amy DeZern, MD, MHS, and **William Brian Dalton, MD, PhD,** of the Sidney Kimmel Comprehensive Cancer Center and the Johns Hopkins University School of Medicine, respectively, argue for the pivotal recognition of high-risk characteristics within lower-risk MDS in a perspective published in *Expert Review of Hematology*.

Management of lower-risk disease is "generally conservative," and "underestimating the risk of progression may miss the optimal time to initiate more aggressive treatments," they wrote in the article.

4

The Post-POLARIX Trial Era: Polatuzumab Vedotin Shifts DLBCL Treatment

Coming in at number four on the list is not a written piece but a podcast episode from The HemOnc Pulse. In it, **Jonathan Friedberg, MD, MMSc,** a hematologic oncologist at the University of Rochester Medicine's Wilmot Cancer Institute, joins host **Chadi Nabhan, MD, MBA, FACP,** to discuss the subtle but important shift in the treatment landscape of diffuse large B-cell lymphoma (DLBCL) in the post-POLARIX trial era.

"I think that this was a robustly done randomized, placebo-controlled trial that showed a small but clinically significant benefit as far as progression-free survival in patients with an [International Prognostic Index] score of two and above [in] large B-cell lymphoma," he said during the episode. Scan to listen to the episode.

5

Is It Time for a Unified Approach to MDS?

Blood Cancers Today goes on a quest to figure out if the World Health Organization and the International Consensus Classification MDS classifications are really all that different after all. Spoiler alert: they are not.

HemOnc Happenings

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

Jerald Radich, MD, Honored with 2023 iCMLf Rowley Prize

Jerald Radich, MD, Director of the Radich Laboratory and the Molecular Oncology Laboratory at the Fred Hutchinson Cancer Center in Seattle, was recently awarded the 2023 International Chronic Myeloid Leukemia Foundation (iCMLf) Rowley Prize for his pioneering research on the molecular genetics of chronic myeloid leukemia (CML).

Jerald Radich, MD

According to the iCMLf website, "The Rowley Prize is awarded to celebrate people who have made outstanding lifetime contributions to the understanding of the biology of CML."

Dr. Radich's work explores genetic signals of treatment response, progression, and relapse, and what he dubs the "the biology of luck" to understand how specific genetic variants influence treatment response and outcomes. Radich and his team at the Fred Hutchinson Cancer Center also develop methods for improving the detection and treatment of chronic and acute myeloid leukemias.

"I am honored and humbled by receiving the Rowley Prize," Dr. Radich told iCMLf. "To be included in the company of past winners, under the name of the miraculous Janet Rowley, strains my belief and comprehension. I cannot adequately enough thank those who have given me this award and those in my lab who have actually done the work."

The award's namesake, the late Janet Rowley, was a "cancer genetics pioneer" who discovered that specific chromosomal changes caused certain types of leukemia, according to the University of Chicago where she served as the Blum-Riese Distinguished Service Professor of Medicine in the molecular genetics and cell biology and human genetics departments. The Rowley Prize was first awarded in 2009 to Brian Druker, MD.

Dr. Radich earned his medical degree from the University of California Davis School of Medicine, where he took an elective at the Fred Hutchinson Cancer Center as a second-year resident in the 1980s and conducted a fellowship in 1990. Today, the Radich Laboratory is credited as "one of the first to document that monitoring levels of the BCR::ABL1 fusion mRNA can be used to detect [measurable] residual disease and to predict relapse before CML cells can be detected by previously standard tests," according to iCMLf.

Dr. Radich's current research projects focus on clonal evolution in CML using highly sensitive genetic tests to characterize time-dependent changes in various leukemia cases. He is also studying outlier responses in CML and acute myeloid leukemia to understand the genetic pathways responsible for response versus refractory disease and relapse.

Source: iCMLf; University of Chicago, November 2023

ASH Presents Awards During Annual Meeting

Omar Abdel-Wahab, MD, of the Memorial Sloan Kettering Cancer Center in New York, and **Stephen Sallan, MD,** of the Dana-Farber Cancer Institute in Boston, received Honorific Awards at the 2023 American Society of Hematology (ASH) Annual Meeting and Exposition, which was held December 9-12.

Omar Abdel-Wahab, MD

Stephan Sallan, MD

The awards recognize "exemplary hematologists who have made significant contributions to the field," according to a press release by the organization.

Dr. Abdel-Wahab received the William Dameshek Prize for his research characterizing the genetic mutations that drive blood cancers. Dr. Abdel-Wahab's work focuses on understanding mutations in the RNA splicing mechanism leading to the development of myelodysplastic syndromes and leukemia. His research was also pivotal to the US Food and Drug Administration approval of the first targeted therapies for patients with systemic histiocytic neoplasms. Named after the late **William Dameshek, MD,** former President of ASH, the award has been presented since 1974 to an early- or mid-career individual (50 years of age or younger) who has made recent outstanding contributions to the understanding of hematology.

William Dameshek, MD

Dr. Sallan received one of two Mentor Awards for his mentorship to hundreds of individuals who have advanced into leading investigator roles in hematology and oncology. Inspired by his own mentors as he began his journey into pediatric hematology 50 years ago, Dr. Sallan shared his passion and provided his mentees with scholarly opportunities to promote them to the next stages of their careers.

"For Dr. Sallan, mentorship remains the most rewarding aspect of his career," according to the press release. The award is based on the training experiences and success of the nominee's mentees rather than the mentor's own career achievements. Since 2006, two Mentor Awards have been distributed at the ASH Annual Meeting and Exposition: the Basic Science Award, which Dr. Sallan received, and the Clinical Investigator Award. ASH President, **Robert Brodsky, MD,** of the Johns Hopkins University School of Medicine, reflected on this year's Honorific Awards. "Each of these individuals has left a lasting mark on our field. Their unwavering dedication to the betterment of patient care, research, and education in classical and malignant hematology has significantly enhanced the lives of those afflicted with blood disorders," he said in the press release.

Robert Brodsky, MD

Source: ASH, November 2023

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

Send the details to editor@bloodcancerstoday.com

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HISTORY OF THE SOCIETY OF HEMATOLOGIC ONCOLOGY

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

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

GLOBAL REACH

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