ASH

2022 Annual Meeting

HIGHLIGHTS FROM THE
64TH AMERICAN SOCIETY OF HEMATOLOGY (ASH)
ANNUAL MEETING & EXPOSITION

DECEMBER 10–13, 2022 | NEW ORLEANS, LA.

APPROVED FOR ADULT PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA (WM)[1]

24-hour inhibition of BTK was maintained at 100% in PBMCs and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.[1,2]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration 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) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci 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 (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% 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 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection, and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias
Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

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

The most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients who received BRUKINSA (N=847) included decreased neutrophil count (54%), upper respiratory tract infection (47%), decreased platelet count (41%), hemorrhage (35%), decreased lymphocyte count (31%), rash (31%) 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 co-administration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid co-administration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

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

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

THE BTK INHIBITOR THAT DELIVERS POWERFUL AND CONSISTENT RESPONSES

BRUKINSA® (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with Waldenström's macroglobulinemia.

BRUKINSA vs **Ibrutinib**

The first and only head-to-head trial of BTK inhibitors in WM

A global, randomized Phase 3 trial in WM across a range of patients*[1]

- Treatment-naïve
- Relapsed/refractory
- *MYD88^{MUT} (CXCR4^{WT}, CXCR4^{WHIM})*
- *MYD88^{WT}*

Powerful Responses Across WM Patients

While the primary endpoint of superiority did not reach statistical significance, numerically higher VGPR/CR rates were achieved in the BRUKINSA treatment arm.[1]

All patients[1]

IWWM-6 criteria†
(Cohort 1)

BRUKINSA (n=102)	Ibrutinib (n=99)
78% VGPR+PR‡	**78%** VGPR+PR
(95% CI: 68, 85)	(95% CI: 68, 86)
16% VGPR‡	**7%** VGPR
62% PR	**71%** PR

All patients[1]

Modified IWWM-6 criteria†
(Cohort 1)

BRUKINSA (n=102)	Ibrutinib (n=99)
78% VGPR+PR‡	**78%** VGPR+PR
(95% CI: 68, 85)	(95% CI: 68, 86)
28% VGPR‡	**19%** VGPR
49% PR	**59%** PR

Median follow-up time was 19.4 months.[3]

The prespecified efficacy outcome measure of VGPR/CR was assessed by IRC.[1]

Safety in WM is consistent with the established BRUKINSA profile[1]

Serious adverse reactions, including fatal events, have occurred with BRUKINSA, including hemorrhage, infections, cytopenias, second primary malignancies, and cardiac arrhythmias. The most common adverse reactions (≥30%) include neutrophil count decreased, upper respiratory tract infection, platelet count decreased, hemorrhage, lymphocyte count decreased, rash, and musculoskeletal pain.

*Patients were enrolled from the United States, Europe, and Australia/New Zealand.
†IWWM-6 criteria (Owen et al, 2013) requires complete resolution of extramedullary disease (EMD) if present at baseline for VGPR to be assessed. Modified IWWM-6 criteria (Treon, 2015) requires a reduction in EMD if present at baseline for VGPR to be assessed.[4,5]
‡There were no CRs in either treatment arm.

BTK=Bruton's tyrosine kinase; CI=confidence interval; CR=complete response; IRC=independent review committee; IWWM-6=6th International Workshop on Waldenström's Macroglobulinemia; MUT=mutated; ORR=overall response rate; PBMCs=peripheral blood mononuclear cells; PR=partial response; VGPR=very good partial response; WHIM=WHIM syndrome-like somatic mutation; WT=wild type.

References: 1. BRUKINSA. Package insert. BeiGene, Ltd; 2021. **2.** Tam C, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859. **3.** Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-2050. **4.** Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinemia: update from the VIth International Workshop. *Br J Haematol*. 2013;160(2):171-176. **5.** Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2015;126(6):721-732.

Brukinsa® zanubrutinib 80mg capsules

LEARN MORE AT **BRUKINSA.com**

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).

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.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have 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 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade, excluding purpura and petechiae, occurred in 35% of patients.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration 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) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci 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 (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% 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 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate *[see Dosage and Administration (2.4)]*.

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 in seven clinical trials, administered as a single agent at 160 mg twice daily in 730 patients, at 320 mg once daily in 105 patients, and at 40 mg to 160 mg once daily (0.125 to 0.5 times the recommended dosage) in 12 patients. Among 847 patients receiving BRUKINSA, 73% were exposed for at least 1 year, 57% were exposed for at least 2 years and 26% were exposed for at least 3 years.

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients included neutrophil count decreased (54%), upper respiratory tract infection (47%), platelet count decreased (41%), hemorrhage (35%), lymphocyte count decreased (31%), rash (31%) 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 %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased	25	5
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection¶	39	0
	Pneumonia§	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rashǁ	36	0
	Bruising*	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage†	11	3.4^
Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

^ Includes fatal adverse reaction.
* Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.
† Hemorrhage includes all related terms containing hemorrhage, hematoma.
‡ Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.
§ 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.
ǁ Rash includes all related terms containing rash.
¶ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral.

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%), hyperuricemia (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities* (> 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
Platelets decreased	40	7
Hemoglobin decreased	27	6
Lymphocytosis†	41	16
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

* Based on laboratory measurements.
† 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¶	44	0	40	2
	Pneumonia§	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 and administration site conditions	Fatigue#	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising*	20	0	34	0
	Rashǁ	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	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†	42	4	43	9
	Hypertension	14	9	19	14

* Bruising includes all related terms containing "bruise," "contusion," or "ecchymosis."
† 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.
# Fatigue includes asthenia, fatigue, lethargy.
‡ Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis, musculoskeletal discomfort.
§ Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.
ǁ Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatosis, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, skin toxicity.
¶ 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.

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* (≥ 20%) That Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[1]		Ibrutinib[1]	
	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				
Bilirubin increased	12	1.0	33	1.0
Calcium decreased	27	2.0	26	0
Creatinine increased	31	1.0	21	1.0
Glucose increased	45	2.3	33	2.3
Potassium increased	24	2.0	12	0
Urate increased	16	3.2	34	6
Phosphate decreased	20	3.1	18	0

* Based on laboratory measurements.
[1] 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 infections[a]	26	3.4
	Urinary tract infection[b]	11	2.3
	Pneumonia[c†]	10	6
Gastrointestinal disorders	Diarrhea[d]	25	3.4
	Abdominal pain[e]	14	2.3
	Nausea	13	0
Skin and subcutaneous tissue disorders	Bruising[f]	24	0
	Rash[g]	21	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[h]	27	1.1
Vascular disorders	Hemorrhage[i]	23	1.1
General disorders	Fatigue[j]	21	2.3
Respiratory, thoracic and mediastinal disorders	Cough[k]	10	0

* Includes 2 fatal events of COVID-19 pneumonia.
[a] Upper respiratory tract infections 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] Diarrhea includes diarrhea and diarrhea hemorrhagic.
[e] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort.
[f] Bruising includes contusion, ecchymosis, increased tendency to bruise, post procedural contusion.
[g] 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.
[h] Musculoskeletal pain includes back pain, arthralgia, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal chest pain, bone pain, musculoskeletal discomfort, neck pain.
[i] 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.
[j] Fatigue includes fatigue, lethargy, asthenia.
[k] 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 selected laboratory abnormalities.

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

Laboratory Abnormality[1]	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

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.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 9: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration 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 co-administered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration 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 co-administration of BRUKINSA with moderate or strong CYP3A inducers *[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 post-natal 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

Pregnancy Testing

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

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. 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 847 patients in clinical studies with BRUKINSA, 53% were ≥ 65 years of age, and 20% were ≥ 75 years of age. No overall differences in safety or 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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HIGHLIGHTS FROM THE 64TH AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING & EXPOSITION

DECEMBER 10–13, 2022

NEW ORLEANS, LA.

The meeting offered a comprehensive educational experience about hematologic topics and included thousands of scientific abstracts highlighting the latest findings in the field. These pages contain a snapshot of the important research that came out of the meeting.

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Final Analysis Finds Zanubrutinib Is Effective and Safe Long-Term in Patients with MZL

RESEARCH SHOWED THAT zanubrutinib continued to be effective against marginal zone lymphoma (MZL) even after two-year follow-up. The treatment led to high response rates and durable disease control, and the drug was generally well tolerated.

"Advanced-stage MZL is generally considered incurable, characterized by periods of remission and relapse," wrote the authors, led by Stephen Opat, of Monash Health and Monash University, in Clayton, Victoria, Australia. The Phase 2 MAGNOLIA study explored whether the next-generation Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib is safe and effective against relapsed/refractory MZL. Initial results from the multicenter trial led to the drug's accelerated approval by the FDA and Health Canada in patients with relapsed/refractory MZL. In this final analysis, the researchers examined whether zanubrutinib continued to be effective in the long term.

A total of 68 patients enrolled in the trial (median age, 70 years; range, 37–95 years). They received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Patients were permitted to also receive long-term antiplatelets and anticoagulants.

At a median follow-up of 28 months (range, 1.6–32.9 months) and a median treatment duration of 24.2 months (range, 0.9–32.9 months), 66 patients were evaluable. An independent review committee evaluated positron emission tomography or computed tomography results and applied the Lugano criteria to assess overall response rate (ORR) and secondary outcomes. ORR was 68%, and responses occurred in all MZL subtypes. At the two-year mark, more than 70% of patients were alive or progression-free.

At the end of the study, 46% of patients entered a long-term extension study. The others discontinued treatment due to disease progression (n=24; 35%), adverse events (n=5; 7%), or need for other medications that are prohibited with zanubrutinib (n=2; 3%). One patient withdrew consent.

The most common treatment-related adverse events were bruising (23.5%), diarrhea (22.1%), constipation (17.6%), arthralgia (14.7%), pyrexia (14.7%), upper respiratory tract infection (13.2%), abdominal pain (11.8%), and back pain (11.8%). Five patients (7.4%) died from adverse events not related to treatment, including COVID-19 pneumonia, acute myeloid leukemia (AML), myocardial infarction, and septic encephalopathy.

REFERENCE

Opat S, Tedeschi A, Hu B, et al. Long-term efficacy and safety of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma: final analysis of the MAGNOLIA (BGB-3111-214) trial. Abstract #234. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Study Assesses How IPSS-M Would Change Decision-Making in Clinical Practice

THE INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS) is an important tool to determine prognosis in adult patients with primary, untreated myelodysplastic syndromes (MDS).

A revised version, the IPSS-R, uses a more detailed approach, involving five disease factors:

1. Blasts
2. Cytogenetics
3. Hemoglobin
4. Platelet count
5. Absolute neutrophil count.

Another revision has been proposed—the IPSS-M, which would incorporate next-generation sequencing (NGS) to include molecular data, in addition to the clinical variables. Researchers presented a study that assessed how the IPSS-M would affect prognosis and decision-making in practice.

"Since some of the genes included in the IPSS-M are unfrequently mutated in MDS and, therefore, not commonly assessed in routine diagnostic laboratories, we aimed to analyze the applicability of the new IPSS-M in a 'real-life' setting," wrote the authors, led by Sandra Novoa Jáuregui, MD, of the Department of Hematology at the University Hospital Vall d'Hebron and the Experimental Hematology Unit at Vall d'Hebron Institute of Oncology in Barcelona, Spain. "According to our cohort of MDS patients, the proportion of cases who might benefit from the re-stratification according to the IPSS-M, in terms of potential differences in clinical management, is lower than initially expected."

The researchers collected retrospective data from their institutional database on clinical, cytogenetic, and molecular variables of 126 patients with MDS who had molecular information available at the time of diagnosis. The data, from 2018 to 2022, included 27 out of 32 genes included in the IPSS-M.

The team then classified each patient with the IPSS-R and the IPSS-M and compared how the two results would affect risk stratification and decision-making. With IPSS-M, 54 of the patients (42.9%) would have been reclassified into a different risk category. The reclassification would have changed treatment decision-making in 22 patients (17.4%). Specifically, 15 patients (11.9%) would have been upgraded, and seven (5.6%) would have been downgraded. Finally, 12 patients (9.5%) would have been managed differently per the institution's treatment protocol.

REFERENCE

Jáuregui SN, Palomo L, Pérez A, et al. IPSS-M applicability and clinical impact in decision-making process in real-life clinical practice. Abstract #3096. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

U-Shaped Pattern to Costs of Care for Hematological Malignancies

A STUDY ASSESSED phase-specific costs of care in hematologic malignancies. The researchers found that mean total costs were lowest in the pre-diagnosis and follow-up phases of care and highest during initial treatment and end-of-life care. Inpatient care was the most significant driver of costs throughout the continuum of care.

"Hematological malignancies contribute a significant economic burden to health care systems," wrote the authors, led by Judy Truong, MD, of the University of Toronto, in North York, Ontario, Canada. The "U-shaped" pattern they discovered may help health care systems and payers "allocate appropriate resources throughout the different phases of cancer care for hematological malignancies, with particular focus on improving access to palliative care at the end of life."

The researchers collected data from 2003 to 2014 from the Ontario Cancer Registry, the Cancer Care Ontario database, and other administrative health care databases. The data covered 35,556 patients (55% male; median age at diagnosis, 64 years) with a variety of hematologic malignancies. The researchers then assessed health system costs and resource utilization for four phases of care:

1. Before diagnosis (90 days prior).
2. Initial treatment (from diagnosis to six months after).
3. Follow-up (end of treatment to the beginning of end-of-life care).
4. End of life (final six months of life for patients who died).

The researchers also examined costs by disease type. Costs were highest during initial treatment and end-of-life care among patients with AML or acute lymphocytic leukemia. Costs were lower among patients with follicular lymphoma or chronic lymphocytic leukemia (CLL).

Furthermore, inpatient care was the most significant driver of costs throughout the continuum of care. The second most significant was cancer treatment medication.

REFERENCE

Truong J, Seung SJ, Dharma C, et al. Phase-specific costs of care in hematological malignancies in Ontario, Canada. Abstract #894. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Trial Does Not Support Antifungal Prophylaxis with Venetoclax-Based Treatment for AML

A STUDY DOES not support the routine use of antifungal treatment to prevent invasive fungal infections (IFIs) in patients with AML receiving venetoclax-based low-intensity treatment combinations due to ineligibility for intensive chemotherapy.

"These combinations can be associated with prolonged cytopenias, in particular neutropenia. IFIs remain a major cause of morbidity and mortality in patients with AML, but their incidence and impact on patients treated with venetoclax-based low-intensity approach are uncertain," wrote the authors, led by Galia Stemer, MD, of the Hematology Institute at Galilee Medical Center in Nahariya, Israel, and the Bar Ilan Faculty of Medicine in Zefat, Israel.

As part of the REVIVE study, the researchers assessed many factors related to venetoclax efficacy and toxicity, as well as patient selection. The current analysis examined real-world patterns of IFIs and antifungal prophylaxis in 189 patients newly diagnosed with AML who were treated with venetoclax combinations at 12 medical centers in Israel from August 2019 to April 2022. The study found that 23 patients (12.1%) received 25 preventive antifungal treatments (fluconazole, 18; voriconazole, 6; posaconazole, 1) and that those patients were more likely to be treated in the outpatient setting.

IFI incidence was low in the overall patient sample (n=17; 9%). The incidence was not much lower among patients who received antifungal prophylaxis (n=4/23; 17%) compared to those who did not receive preventive treatment (n=13/166; 8%). Furthermore, the study found no significant differences between groups in:

- Adverse events that led to treatment discontinuation (n=4, or 17%, in the prophylaxis group vs. n=31, or 19%, in the no-prophylaxis group).
- 30-day mortality (n=1, or 4.3%, in the prophylaxis group vs. n=8, or 5%, in the no-prophylaxis group).
- Complete remission rates (61% in the prophylaxis group vs. 54% in the no-prophylaxis group).
- One-year overall survival (OS) rates (51% in the prophylaxis group vs. 39% in the no-prophylaxis group).

REFERENCE

Stemer G, Wolach O, Levi I, et al. Utilization of antifungal prophylaxis and treatment for newly diagnosed AML patients treated with venetoclax based regimens in routine clinical practice – a prospective analysis from the Revive Study. Abstract #2743. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Study Supports Switch to Zanubrutinib for B-Cell Malignancies Intolerant to Acalabrutinib

RESULTS OF A STUDY indicate that patients with B-cell malignancies who cannot tolerate acalabrutinib can achieve clinical benefit by switching to zanubrutinib.

"BTK inhibitors are a mainstay of treatment for B-cell malignancies; however, their use can be limited by adverse events, many of which are potentially caused by off-target inhibition of other tyrosine kinases," wrote the authors, led by Mazyar Shadman, MD, of the Fred Hutchinson Cancer Research Center in Seattle, Wash. "The next-generation BTK inhibitor zanubrutinib was designed to maximize tolerability by minimizing off-target binding."

The ongoing Phase 2 study initially established the tolerability of zanubrutinib in patients who were intolerant to ibrutinib and/or acalabrutinib. This more recent analysis explored the efficacy of zanubrutinib, as well as longer-term safety, in patients who could not continue acalabrutinib. The patient sample included those with CLL/small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia (WM), mantle cell lymphoma (MCL), or MZL.

The analysis included 17 patients (median age, 74 years; range, 51–87 years). On acalabrutinib, they had experienced 28 treatment-related adverse events, including arthralgia (n=4), myalgia (n=4), headache (n=4), hemorrhage (n=2), and fatigue (n=2). They received zanubrutinib 160 mg twice daily or 320 mg once daily, with a median treatment duration of 9.2 months (range, 0.5–20.9 months). Then the researchers evaluated them for response every three weeks, with median follow-up of 10.4 months (range, 1.1–20.9 months).

At the final time of analysis, 12 patients had remained on treatment, and five discontinued: two due to adverse events (myalgia and diarrhea at the same grade as that which occurred with acalabrutinib), and one due to progressive disease. Eleven patients (65%) did not experience any recurrent intolerance. Seven adverse events did occur (one at a lower grade than before and six at the same grade). Two patients who previously had pain in the extremities and atrial fibrillation did not experience those adverse events on zanubrutinib. Of the 14 patients evaluable for the efficacy analysis, 13 (93%) achieved at least stable disease, and nine (64%) had a deeper response. Enrollment and follow-up analyses continue.

REFERENCE

Shadman M, Flinn IW, Kingsley EC, et al. Zanubrutinib in acalabrutinib-intolerant patients with B-cell malignancies. Abstract #1587. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

COVID-19 Changes Care Utilization Among Veterans with Multiple Myeloma

THE COVID-19 PANDEMIC significantly decreased in-person medical care and laboratory testing in veterans with multiple myeloma (MM), but it did not affect prescriptions for oral MM treatments or inpatient admissions, according to a study.

A group of researchers collected data from electronic medical records from the Veterans Health Administration (VA) to analyze MM care utilization during the first year of the pandemic, as medical care quickly shifted to virtual platforms. The sample included 3,679 veterans receiving oral medications for MM in the VA system in all 50 states. The median age was 72 years; 67% of the veterans were white, and 31% were Black.

The researchers compared several factors between the pre-lockdown period (June 2019 to February 2020) and the post-lockdown period (April 2020 to December 2020). They found that:

- Outpatient visits (n=93,455) were 93% in-person before the lockdown and dropped to 68% afterward, shifting largely to email, phone, or telehealth.
- The number of oral MM medications that were prescribed and filled did not change significantly between the two time periods (ixazomib, lenalidomide, and pomalidomide; n=37,388 prescriptions).
- Laboratory tests (n=326,415) dropped significantly. Specifically, patients had 1,106 fewer creatinine tests, 1,096 fewer hemoglobin tests, and 98 fewer serum protein electrophoresis tests. Free light chain ratio testing did not appear to be affected.
- Monthly number of inpatient admissions (n=2,857) did not significantly change pre- to post-lockdown.

"The impact on clinical outcomes as a result of increasing virtual care in MM remain to be fully assessed, although the lack of major observed shifts in outpatient scripts and inpatient admissions is encouraging," wrote the authors, led by Christopher T. Su, MD, MPH, of the University of Michigan in Ann Arbor.

REFERENCE

Su CT, Jason Chen J, Sussman J, et al. Shifts in multiple myeloma care utilization of veterans in the COVID-19 era: interrupted time series analysis of Veterans Health Administration data. Abstract #3531. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Race, Ethnicity, and Racism Associated with Adverse Physical and Mental Health Outcomes in Cancer Survivors

A STUDY ADDS TO the evidence that historically marginalized racial and ethnic groups experience disparities in physical and mental health outcomes. The researchers said their data indicate that non-Hispanic Black and Hispanic cancer survivors may benefit from interventions that assess and improve sleep and mental health.

"Cancer survivors are at risk for adverse mental and physical health outcomes. However, it is not well understood how these outcomes may be differentially experienced according to an individual's race and/or ethnicity," wrote the authors, led by Kristine Karvonen, MD, of the Department of Pediatrics in the Division of Hematology/Oncology at the University of Washington School of Medicine, and the Palliative Care and Resilience Program at Seattle Children's Research Institute, both in Seattle. The team sought to evaluate ways race, ethnicity, and experiences of racism were associated with mental and physical health in a cancer care setting.

The team extracted data from the Behavioral Risk Factor Surveillance System database on 48,200 cancer survivors from records between 2014 to 2020. They then evaluated associations between (a) race, ethnicity, and effects of perceived racism with (b) adverse psychosocial outcomes, including:

- Activity limitations
- Days of poor mental or physical health
- Depression
- Inadequate sleep.

According to the results, cancer survivors who were non-Hispanic Black, Hispanic, American Indian, Alaska Native, Native Hawaiian, or Pacific Islander were more likely than non-Hispanic white counterparts to have at least one adverse outcome. Specifically, non-Hispanic Black survivors and Hispanic survivors were more likely to report inadequate sleep. In addition, non-Hispanic Black survivors also reported poor mental health more frequently but were less likely to be diagnosed with depression than non-Hispanic white survivors.

The data did not include many reports of distress related to experienced racism, but when it was reported, it was associated with a high burden of adverse health outcomes. Specifically, 32% to 59% of survivors who experienced perceived racism also reported at least one of the studied adverse health outcomes. The authors suggested that health care providers should be more careful to assess non-Hispanic Black and Hispanic cancer survivors for issues with sleep and mental health and offer interventions.

REFERENCE

Karvonen K, Balay-Dustrude E, Do A, et al. Race, ethnicity and experienced racism are associated with adverse physical and mental health outcomes among cancer survivors. Abstract #382. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

APPs Establish and Grow a Walk-In Clinic for Outpatient Management of VTE

A STUDY SUPPORTS outpatient care for most patients with venous thromboembolism (VTE). The researchers described an outpatient model they developed for an advanced practice provider (APP)-led clinic for patients newly diagnosed with VTE.

"There is hesitancy among some health care providers to manage patients with these high-risk acute conditions, on high-risk medications, without close and reliable follow-up, ... and the financial complications associated with appropriate anticoagulation further complicate management," wrote the authors, led by Cassiopeia Frank, PA-C, of the Division of Hematology at the University of North Carolina in Hillsborough.

To address these issues, they developed a "Walk-In Deep Vein Thrombosis (DVT) Clinic," which reserves appointments for patients newly diagnosed with VTE. Patients can be referred by any provider affiliated with the health system via a phone line or pager open during business hours or via the emergency department (ED) after hours. A physician assistant or nurse practitioner sees each patient with oversight from a hematologist, providing education and counseling on diagnosis and anticoagulation therapy. The APP also evaluates each patient for risk factors that may have contributed to the thrombotic event. Each patient leaves with a plan for follow-up and access to a health care provider to discuss bleeding complications, anticoagulation management before surgical procedures, and other questions. The clinic also has a pharmacist available to address drug interactions, medication access, patient questions, and more.

The researchers offered data on a group of 229 evaluable patients who visited the walk-in clinic during its first two years. The walk-in clinic grew quickly, seeing 84 patients the first year and 150 the second year. In the first year, 72% of the patients came from ED referrals. In the second year, 59% of referrals were from the ED. This demonstrates that

more referrals are now coming from medical and surgical specialists rather than the ED, which is one of the clinic's goals. In addition, more African American and Hispanic patients are visiting the clinic.

> **SINCE ITS INCEPTION, THE [CLINIC] HAS GROWN IN UTILIZATION, DIVERSITY OF REFERRALS, AND DIVERSITY OF PATIENTS SERVED.**

The median time to an appointment was four days in the first year, and that rose to five days in the second year. Therefore, the clinic has hired an additional APP. Notably, appointments have identified problems in 19 cases (13%), such as dose errors and misdiagnosis. They have also addressed patients' need for financial assistance, which occurred in 10% to 13% of patients.

"Since its inception, the APP-led 'DVT Walk-In Clinic' has grown in utilization, diversity of referrals, and diversity of patients served, with new focus on patient education tools and expanding access," the researchers concluded.

REFERENCE

Frank C, Key NS, Mooberry MJ, et al. Establishment and utilization of an advanced practice provider–led clinic for newly diagnosed venous thromboembolism. Abstract #3517. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Certain Mutations May be Associated with Disease Progression in B-Cell Malignancies

A RECENT EXPLORATORY analysis indicates that cell cycle, DNA damage, and *NOTCH1* pathway genes were frequently mutated in patients with B-cell malignancies who were part of the BGB-3111-215 study exploring use of zanubrutinib. In addition, patients with the mutations were more likely to have progressive disease.

"Targeting BTK to inhibit B-cell receptor signaling is an effective way to treat B-cell malignancies. However, some patients have experienced toxicities to BTK inhibitors ibrutinib and acalabrutinib, which lead to dose reduction or treatment discontinuation," wrote the authors, led by Linlin Xu, of BeiGene in Beijing, China, and San Mateo, California. As part of the ongoing Phase 2 BGB-3111-215 study, the researchers are exploring the safety and efficacy of the next-generation BTK inhibitor zanubrutinib in patients with B-cell malignancies who discontinued ibrutinib and/or acalabrutinib due to intolerance.

The current analysis explored gene mutation profiles to elucidate possible relationships among gene mutations, treatment response, and treatment intolerance. The patient sample (N=63) included those with CLL (n=41), WM (n=10), SLL (n=6), MCL (n=3), or MZL (n=3).

The researchers collected peripheral blood from all patients before zanubrutinib treatment. Using NGS, the team found that the most common mutations at baseline were *TP53* (31.7%), *SF3B1* (22.2%), *ATM* (17.5%), *NOTCH1* (17.5%), *CHEK2* (14.3%), and *KRAS* (12.7%). The 10 patients who experienced disease progression (eight with CLL, one with SLL, and one with MCL) had a significantly increased frequency of certain mutations: *TP53* (60%), *ATM* (50%), *SF3B1* (50%), *RB1* (40%), *SETD2* (40%), and *CDKN2A* (30%). The authors said their findings suggest that those baseline mutations may be associated with resistance to zanubrutinib.

REFERENCE

Xu L, Shadman M, Ponakala A, et al. Genomic characterization of patients in phase 2 study of zanubrutinib in BTK inhibitor-intolerant patients with relapsed/refractory B-cell malignancies. Abstract #4176. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Patients with Bleeding Disorders May Have Greater Need for Reproductive Health Care

A STUDY HIGHLIGHTED the importance of high-quality reproductive health care in patients with bleeding disorders. The study found higher rates of emergency contraception and medical and surgical abortions in this patient population than in the general population, as well as a trend toward more delayed or excessive hemorrhage after induced or spontaneous abortions and ectopic pregnancies.

The retrospective study used 2007 to 2022 data from the TriNetX Research Network, which contains health records from 66 U.S. health care organizations. Cases were included if they were female; aged 10 to 45 years; and had hemophilia A or B, were hemophilia A or B carriers, or had von Willebrand disease.

The researchers compared that cohort (n=19,733) to similar patients without a bleeding disorder (n=23,923,130). They used International Statistical Classification of Diseases and Related Health Problems codes to identify abortions, related bleeding complications, medical terminations with misoprostol/mifepristone, ectopic pregnancies, molar pregnancies, and other reproductive health factors.

The prevalence of all of those factors was significantly higher in patients who had a bleeding disorders than in controls. Specifically, among patients with a bleeding disorder:

- 9.8% had some form of documented abortion (either induced, spontaneous, or missed) compared to 1.8% of controls.
- 0.4% had a medication-induced abortion compared to 0.1% of controls.
- 2.5% had an abortion procedure compared to 0.6% of controls.
- 1.8% had an ectopic pregnancy compared to 0.3% of controls.
- 0.4% had a molar pregnancy compared to 0.1% of controls.
- 0.2% had delayed or excessive hemorrhage after one of those events compared to 0% of controls.
- 0.4% used emergency contraception compared to 0.2% of controls.

The researchers plan to continue their analyses to explore other outcomes. "A prospective registry to establish bleeding outcomes resulting from reproductive health-related procedures is urgently needed," wrote the researchers, led by Divyaswathi Citla Sridhar, MD, of Arkansas Children's Hospital, University of Arkansas for Medical Sciences, in Little Rock.

REFERENCE

Sridhar DC, Sidonio RF Jr., Ahuja S, et al. Reproductive health needs in patients with bleeding disorders. Abstract #3563. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Delirium Increases Health Care Utilization in Patients Undergoing HSCT

A STUDY FOUND that a large proportion of patients undergoing hematopoietic stem cell transplantation (HSCT) experienced delirium during their index hospitalization and that delirium was associated with longer length of stay and higher likelihood of antipsychotic medication use.

Delirium is common in hospitalized patients in general, and it is associated with poorer outcomes in other patient populations. The authors, led by Netana H. Markovitz, MD, of the Beth Israel Deaconess Medical Center and Massachusetts General Hospital, both in Boston, sought to learn more about delirium's effects, specifically in HSCT patients.

> **THE STUDY FOUND THAT HSCT-RELATED DELIRIUM WAS ASSOCIATED WITH LONGER HOSPITAL LENGTH OF STAY.**

"[Delirium is] often reversible with prompt diagnosis and appropriate management," they noted. "Our findings underscore the need to better identify patients at risk for delirium and assess for and manage delirium in patients undergoing HSCT since it negatively impacts health care utilization in this population."

The authors retrospectively reviewed 502 patients who were admitted for allogeneic or autologous HSCT at one of two Boston hospitals from April 2016 to April 2021. The patients' median age was 62 years, and 59% were male. After identifying patients they believed to have delirium, the researchers explored associations between delirium and health care utilization, after controlling for sociodemographic and clinical factors.

They discovered that 42% of the patients had indications of delirium during their index hospitalization for HSCT. The rates were similar between allogeneic (44%) and autologous (39%) HSCT. Of the entire sample, 257 patients (51%) were prescribed antipsychotic medications. However,

among the patients the researchers deemed to be delirious, 72 (34%) were not prescribed antipsychotics. The study also found that delirium was associated with longer hospital length of stay. Patients with delirium had more psychiatric consultations but not palliative care consultations as compared to patients without delirium.

REFERENCE

Markovitz NH, El-Jawahri A, Dale C, et al. Delirium and healthcare utilization in patients undergoing hematopoietic stem cell transplantation. Abstract #3633. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Controlling the Costs of Severe Aplastic Anemia

HEMATOLOGIC EMERGENCIES associated with severe aplastic anemia are potentially life-threatening and create an economic burden on health systems. A group of researchers offered insights from a systematic literature review regarding the economic implications of the disease. The team explored cost drivers and cost variations to inform future cost control.

The team searched MEDLINE, the Cumulative Index to Nursing and Allied Health Literature, Scopus, Web of Science, National Health Service Economic Evaluation Database, and the National Health Service Health Technology Assessment Database. They sought studies reporting estimates of direct, indirect, and total costs of severe aplastic anemia. They did not limit the results by study type, language, geography, or time.

The researchers selected 11 studies for final analysis—four from the United States and one each from Brazil, China, France, Germany, Mexico, South Africa, and Sweden. After adjusting costs to 2021 U.S. dollars, they found that the mean monthly direct costs per patient varied widely, from $430 to $40,107. Among those aged 21 years or younger, the mean cost was $18,029 (range, $979–$23,351). Costs tended to be lower among older adults.

Key cost drivers were prescription medications. However, medications also appeared to reduce hospitalizations, outpatient costs, and the need for rescue medications. None of the studies reported indirect costs.

"To the best of our knowledge, no study has systematically reviewed the literature for estimates pertaining to the economic impact of severe aplastic anemia. Available evidence on the costs of illness of the disease is extremely limited and considerably heterogenous in terms of geographical territories," wrote the authors, led by Christos Papagiannopoulos, of CTI Clinical Trial and Consulting Services in Stockholm, Sweden. They encouraged further research so that health care institutions and payers can improve management of this patient population and better control costs.

REFERENCE

Papagiannopoulos C, Ordoño MS, Gonçalves E, et al. Severe aplastic anemia: a systematic literature review on costs of illness. Abstract #4837. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Long-Term Outcomes of Second-Line Versus Later-Line Zanubrutinib in MCL

LONG-TERM FOLLOW-UP data confirm that second-line zanubrutinib treatment increased OS compared with later-line zanubrutinib treatment in patients with relapsed or refractory MCL.

Zanubrutinib, a BTK inhibitor, was recently approved for several uses in B-cell malignancies, including as monotherapy in relapsed or refractory MCL. Recent pooled analyses with a median follow-up of 24.9 months have shown that the medication provided better progression-free survival (PFS) and OS when administered as a second-line treatment rather than later in the treatment continuum. In the current analysis, Yuqin Song, MD, of the Peking University Cancer Hospital and Institute in Beijing, China, and colleagues examined survival at longer-term follow-up—35.2 months.

The analysis included 112 patients: 41 (37%) who received zanubrutinib as second-line treatment and had a median follow-up of 60.07 months and 71 (63%) who received it as later-line therapy and received a median follow-up of 34.37 months. OS was better in the second-line group, to a statistically significant level, but neither group reached median OS. Median PFS was similar between groups but slightly longer in the second-line group (27.8 months vs. 22.1 months).

Finally, zanubrutinib continued to be well tolerated, and no new safety issues arose with longer-term follow-up.

REFERENCE

Song Y, Zhou K, Zou D, et al. Long-term outcomes of second-line vs later-line zanubrutinib treatment in patients with relapsed/refractory MCL: an updated pooled analysis. Abstract #2894. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Mean Cost of CAR T-Cell Therapy Tops Half-Million Dollars per Patient

COSTS ASSOCIATED WITH chimeric antigen receptor (CAR) T-cell therapy in patients with relapsed or refractory large B-cell lymphoma (LBCL) average a half-million dollars per patient, according to an analysis. The authors encouraged health care institutions and payers to consider the data, along with the logistical challenges and long-term results of the therapy, as they make treatment decisions.

"Despite its association with promising clinical outcomes, CAR T-cell therapy may not be a feasible treatment option for some patients," wrote the authors, led by Kalatu R. Davies, PhD, of AbbVie, Inc., in North Chicago, Ill. "Because of long manufacturing times, patients often require bridging therapy prior to CAR-T, and a subset of patients die on bridging therapy without ever receiving CAR-T. Furthermore, more than half of patients relapse within one year of receiving CAR-T therapy." The researchers conducted the cost analysis to help systems understand the economic burden of this therapy.

> **"THE MEAN TOTAL COST PER PATIENT FROM 30 DAYS PRIOR TO 90 DAYS AFTER CAR T-CELL INFUSION WAS $511,139."**

The researchers analyzed health care resource utilization and all-cause health care costs from 30 days prior to CAR T-cell therapy through 90 days after CAR T-cell therapy in patients with diffuse LBCL (DLBCL) or primary mediastinal LBCL (PMBCL) who were treated between October 2017 and March 2021. The study used data from the Market Scan administrative claims database and reported costs in 2021 U.S. dollars.

A total of 106 patients were included in the analysis: 92 with DLBCL and 14 with PMBCL. Their mean age was 55 years, and 59% were male. Most patients (n=78; 74%) had at least five outpatient hospital visits in the 30 days before CAR T-cell therapy. Most received the therapy as inpatients (n=92; 87%), with a median length of stay of 18.4 days (standard deviation [SD], 11.3) at a mean cost of $341,217 (SD, $245,564). One important driver of cost was that 41 patients (45%) were admitted to the intensive care unit.

In the 90 days after CAR T-cell therapy, most patients (n=92; 87%) had at least five outpatient visits, and 30 patients (28%) required inpatient admission, with a mean length of stay of 12 days (SD, 12.44) at a mean cost of $83,952 (SD, $105,961). The mean total cost per patient from 30 days prior to 90 days after CAR T-cell infusion was $511,139 (SD, $293,631).

"While CAR-T therapy may be a treatment option as LBCL patients progress, patients face a considerable clinical and economic burden," the authors concluded. "These findings underscore the need for an accessible, off-the-shelf, and efficacious therapeutic option for LBCL patients."

REFERENCE

Davies KR, Kamalakar R, Yu J, et al. Health care resource utilization and costs of CAR T therapy in patients with large B-cell lymphoma: a retrospective US claims database analysis. Abstract #2215. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Quality-Improvement Initiative Addresses Racial Disparities in Acute Leukemia

A QUALITY-IMPROVEMENT initiative identified and addressed specific racial disparities that are barriers to care for patients with acute leukemia. The authors said the most significant inequities were related to access to care, shared decision-making, and enrollment in clinical trials.

"Racial disparities in acute leukemias ... have persisted for decades due to multi-level etiologies. To ensure that equitable care is delivered, health care professionals must be aware of potential systemic disparities and gaps in personalized treatment planning, shared decision-making, clinical trial enrollment, and treatment delivery among patient populations ... and identify potential opportunities to overcome ongoing disparities and gaps," wrote the authors, led by Manali I. Patel, of Stanford University in Palo Alto, Calif.

The initiative surveyed the hematology/oncology health care providers and patients (52 Black, 32 Hispanic, and 10 white) at two community oncology practices in the summer of 2021. The program also held small-group sessions with the health care providers to review the survey data, reflect on their own practices, and develop strategies to overcome barriers.

The biggest challenges according to providers and patients was "feeling confident in their treatment plan" and "identifying goals of treatment." Most providers (57%) did not believe there were any problems with "difficulty getting the best care because of race or ethnic background," but about half (48%) of Black patients identified that as a problem.

Regarding shared decision-making, providers reported "not enough time" (43%) and "patient resistance" (10%) as the biggest barriers, whereas Black patients (58%) cited "a lack of understanding about what the care team is saying," and Hispanic (65%) and white (78%) patients cited "trusting their care team to make the best decisions."

Although the providers (86%) believed they often or always discuss clinical trial enrollment with eligible patients, 38% of patients said they had no recollection of those discussions. When asked what area needed most improvement, Black patients (64%) identified insurance and financial counseling. Hispanic patients (55%) sought interpreters and translated educational materials. White patients (63%) wanted more education about treatment options, expectations, and prognosis.

The health care providers plan to address some of the challenges by expanding access to clinical trials, providing translated materials or interpreters, helping patients find ways to cover the costs of care, and better documenting quality of life.

REFERENCE

Patel MI, Ascensao JL, Gurska L, et al. Addressing racial disparities to advance quality care for adults with acute leukemia: a health equity-focused quality improvement program. Abstract #2233. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.

Potential Biomarkers Predict Response to Zanubrutinib and Tislelizumab Combination

DATA MAY INDICATE specific factors that can predict response or resistance to zanubrutinib and tislelizumab combination therapy in patients with DLBCL.

Frontline therapies for DLBCL are effective in many patients with the condition, but many others are refractory to treatment or relapse after standard therapy. Recently, the combination of zanubrutinib and tislelizumab has been effective in patients with B-cell malignancies. Jiaoyan Lyu, of BeiGene Co., Ltd., in Beijing, China, and colleagues sought to analyze whether certain biomarkers can predict response or resistance to zanubrutinib and tislelizumab combination therapy.

The researchers analyzed samples from 24 patients. Patients with *PD-L1* gene alteration appeared to have a higher ORR and higher complete response rate (CRR) than patients without the alteration. In addition, those with PD-L1-positive tumor cells had higher ORR and CRR. Those who responded to treatment tended to have higher mRNA levels of *CD3D, HLA-DRA,* and *LAG3*, which the authors wrote might indicate an inflamed tumor microenvironment.

> **"A HIGH MRNA LEVEL OF *REL* OR MUTATIONS IN *TP53* MAY CONTRIBUTE TO RESISTANCE OF ZANUBRUTINIB AND TISLELIZUMAB COMBINATION THERAPY."**

On the other hand, the research also identified some factors associated with inferior response or nonresponse: high mRNA levels of *REL*; mutations in tumor suppressor gene *TP53*; and more mutations in genes that affect immune evasion, epigenetic modifications, and cell survival than responders. The authors hypothesized that this indicates complex resistance mechanisms in nonresponders.

"Patients with *PD-L1* gene amplification, PD-L1-positive tumor cells, and high mRNA levels of *CD3D, HLA-DRA,* and *LAG3* in baseline tumor tissue may be more responsive to zanubrutinib and tislelizumab combination therapy," the authors wrote. "A high mRNA level of *REL* or mutations in *TP53* may contribute to resistance of zanubrutinib and tislelizumab combination therapy." However, the researchers cautioned that the results should be interpreted with caution because of the limited sample size.

REFERENCE

Jiaoyan Lyu J, Ma X, Huang R, et al. Biomarker analysis of zanubrutinib and tislelizumab combination therapy in patients with relapsed/refractory B-cell malignancies. Abstract #1529. Presented at the 64th American Society of Hematology Annual Meeting & Exposition, Dec. 10–13, 2022; New Orleans, La.