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MRD Continues to Prove Utility in Hematologic Malignancies

With expert opinions from:
Elias Jabbour, MD;
C. Ola Landergren, MD, PhD;
and more

MAIL TO:

EXECUTIVE EDITOR ELIAS JABBOUR, MD:
Highlighting Recent Research in AML

An official publication of
soho
society of hematologic oncology

NOW WITH LONG-TERM DATA[1,2]

BRUKINSA: MAKE A POWERFUL IMPACT WITH SUPERIOR EFFICACY IN CLL[3]

- **Superior PFS vs BR in 1L*[3,4]**
- **The only BTKi with superiority vs ibrutinib in 2L†[3,5]**
- **Sustained efficacy across lines of therapy[1,2]**
  ~4-year data in 1L and ~3-year data in 2L

*PFS was measured at 24 months at the initial analysis.[4]
†PFS and ORR. Median follow-up for PFS was 29.6 months at the initial analysis. Median follow-up for ORR was 24.7 months at the initial analysis.[5,6]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.8% of patients treated with BRUKINSA in clinical trials, with fatalities occurring in 0.2% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 32% 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 before and after 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. Grade 3 or higher infections occurred in 26% of patients, most commonly pneumonia (7.9%), with fatal infections occurring in 3.2% 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 (21%), thrombocytopenia (8%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA. Grade 4 neutropenia occurred in 10% of patients, and Grade 4 thrombocytopenia occurred in 2.5% 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. The most frequent second primary malignancy was non-melanoma skin cancers (8%), followed by other solid tumors in 7% of the patients (including melanoma in 1% of patients) and hematologic malignancies (0.7%). 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 4.4% of patients treated with BRUKINSA, including Grade 3 or higher cases in 1.9% 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 0.3% 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.

Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including BRUKINSA.

Evaluate bilirubin and transaminases at baseline and throughout treatment with BRUKINSA. For patients who develop abnormal liver tests after BRUKINSA, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold BRUKINSA. Upon confirmation of DILI, discontinue BRUKINSA.

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 (≥30%), including laboratory abnormalities, in patients who received BRUKINSA (N=1729) are decreased neutrophil count (51%), decreased platelet count (41%), upper respiratory tract infection (38%), hemorrhage (32%), and musculoskeletal pain (31%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is coadministered 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.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

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

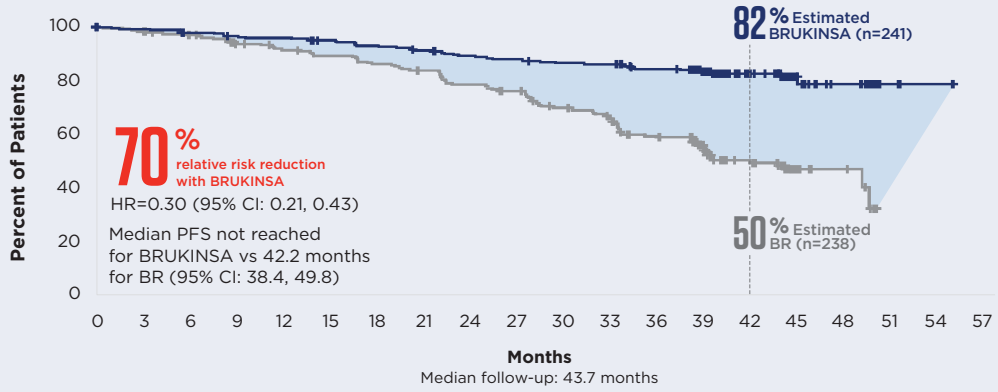
1L=first line; 2L=second line; BR=bendamustine+rituximab; BTKi=Bruton's tyrosine kinase inhibitor; CI=confidence interval; CLL=chronic lymphocytic leukemia; HR=hazard ratio; IRC=independent review committee; ITT=intent to treat; ORR=overall response rate; PFS=progression-free survival; SLL=small lymphocytic lymphoma.

1L: SEQUOIA

Superior PFS vs BR at initial analysis with sustained efficacy at ~4 years

Superior PFS vs BR (initial analysis; primary endpoint): **86%** estimated PFS at 24 months with BRUKINSA **vs 70%** with BR in patients without del(17p); HR=0.42 (95% CI: 0.28, 0.63); $p<0.0001$[‡§3,4]

Sustained PFS vs BR: patients without del(17p)[¶1]



No. of patients at risk

BRUKINSA	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0
BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0		

Consistent PFS benefit sustained over ~4 years in patients with del(17p)[1]

- 79% estimated PFS at 42 months in a BRUKINSA-only cohort (95% CI: 70.4, 85.9)[¶]

[‡]Median PFS was not reached in either arm; prespecified analysis assessed by IRC.[3,4]
[§]Median follow-up: 26.2 months.[4]
[¶]Exploratory analysis.

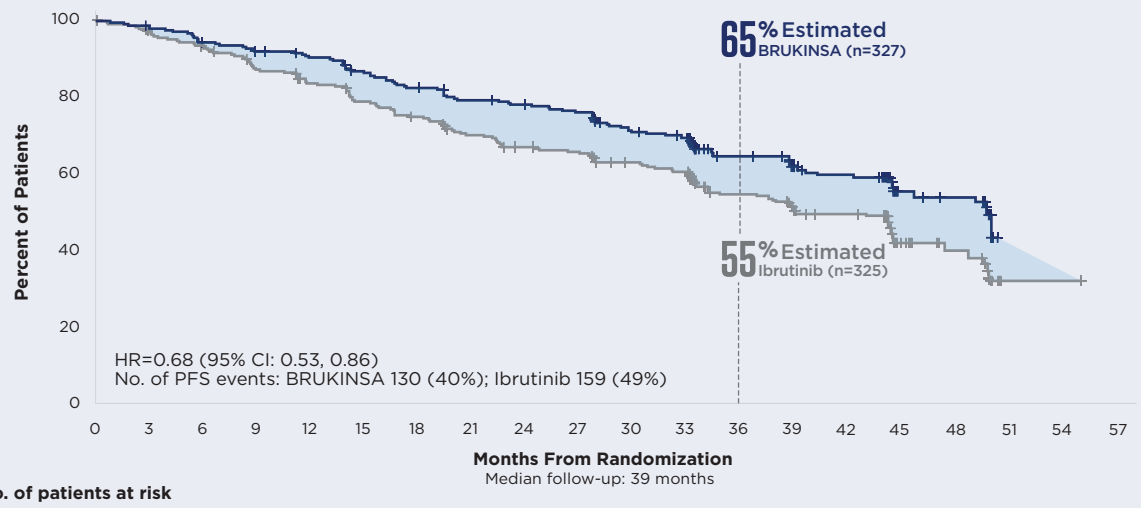
SEQUOIA was a global Phase 3, randomized, open-label, multicenter trial evaluating BRUKINSA vs BR in 479 patients with previously untreated CLL/SLL without del(17p). 110 patients with del(17p) were evaluated in a separate single-arm cohort and received BRUKINSA only. The primary endpoint was PFS per IRC in the ITT population in the BRUKINSA arm and the BR arm, with minimum 2-sided alpha of 0.05 for superiority.[3,4]

2L: ALPINE

Superior PFS vs ibrutinib at initial analysis with sustained efficacy at ~3 years

Superior PFS vs ibrutinib (initial analysis; secondary endpoint): **78%** estimated PFS at 24 months with BRUKINSA **vs 66%** with ibrutinib; HR=0.65 (95% CI: 0.49, 0.86); $p=0.0024$[#**3,5]

Sustained PFS vs ibrutinib: all-comer population[††2]



No. of patients at risk

BRUKINSA	327	315	302	295	287	272	258	247	242	236	217	206	151	124	118	42	38	0	0	0
Ibrutinib	325	305	293	273	258	242	229	212	200	194	182	171	116	92	88	28	22	1	1	0

Superior ORR vs ibrutinib (initial analysis; primary endpoint): **80%** with BRUKINSA (95% CI: 76.0, 85.0) **vs 73%** with ibrutinib (95% CI: 68.0, 78.0) (Median follow-up: 24.7 months; $p=0.0264$)[3,5,6]

[#]Prespecified analysis assessed by both IRC and investigator with similar results. Median PFS has not yet been reached with BRUKINSA vs 34 months with ibrutinib.[5]
[**]Median follow-up: 31 months.[3]
[††]Exploratory analysis.

ALPINE was a global Phase 3, randomized, open-label, multicenter trial evaluating BRUKINSA vs ibrutinib in 652 patients with relapsed/refractory CLL/SLL who received ≥1 prior systemic therapy. Statistical analysis for PFS and ORR was initially conducted for noninferiority. When noninferiority was met, superiority was tested.[3,5]

References: 1. Munir T, Shadman M, Robak T, et al. Zanubrutinib (zanu) vs bendamustine + rituximab (BR) in patients (pts) with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): extended follow-up of the SEQUOIA study. Poster presented at: European Hematology Association (EHA) 2023 Hybrid Congress; June 8-15, 2023. Abstract P639. **2.** Brown JR, Eichhorst B, Lamanna N, et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: American Society of Hematology (ASH) Annual Meeting and Exposition; December 9-12, 2023. **3.** BRUKINSA. Package insert. BeiGene USA, Inc.; 2024. **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. **5.** 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. **6.** Data on file. BeiGene USA, Inc.

SEE THE LONG-TERM DATA AT BRUKINSA.COM

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)]*.

1.5 Follicular Lymphoma

BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab, after two or more lines of systemic therapy.

This indication is approved under accelerated approval based on response rate and durability of response *[see Clinical Studies (14.5)]*. 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 hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.8% of patients treated with BRUKINSA in clinical trials, with fatalities occurring in 0.2% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 32% 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 before and after 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. Grade 3 or higher infections occurred in 26% of patients, most commonly pneumonia (7.9%), with fatal infections occurring in 3.2% 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 (21%), thrombocytopenia (8%), and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 10% of patients, and Grade 4 thrombocytopenia occurred in 2.5% 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. The most frequent second primary malignancy was non-melanoma skin cancers (8%), followed by other solid tumors in 7% of the patients (including melanoma in 1% of patients) and hematologic malignancies (0.7%). 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 4.4% of patients treated with BRUKINSA, including Grade 3 or higher cases in 1.9% 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 0.3% 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 Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including BRUKINSA.

Evaluate bilirubin and transaminases at baseline and throughout treatment with BRUKINSA. For patients who develop abnormal liver tests after BRUKINSA, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold BRUKINSA. Upon confirmation of DILI, discontinue BRUKINSA.

5.7 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)]*
- Hepatotoxicity, including DILI *[see Warnings and Precautions (5.6)]*

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 nine monotherapy and 2 combination clinical trials, administered at 160 mg twice daily in 1608 patients and at 320 mg once daily in 121 patients. Among these 1729 patients, the median duration of exposure was 27.6 months, 78% of patients were exposed for at least 12 months, and 60% of patients were exposed for at least 24 months.

In this pooled safety population, the most common adverse reactions (≥30%), including laboratory abnormalities, were neutrophil count decreased (51%), platelet count decreased (41%), upper respiratory tract infection (38%), hemorrhage (32%), and musculoskeletal pain (31%).

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 × 10^9/L and an absolute neutrophil count ≥1 × 10^9/L independent of growth factor support, hepatic enzymes ≤2.5 × upper limit of normal, total bilirubin ≤1.5 × ULN. The BGB-3111-AU-003 trial required a platelet count ≥50 × 10^9/L and an absolute neutrophil count ≥1 × 10^9/L independent of growth factor support, hepatic enzymes ≤3 × upper limit of normal, total bilirubin ≤1.5 × ULN. Both trials required a creatinine clearance (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 adverse reactions 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 × 10^9/L, platelet count ≥50 or ≥75 × 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 White, 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 trials 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, CLcr 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
Nausea	10	0	33	1.3
General disorders				
Fatigue[h]	14	1.3	21	1.8

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

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 (%)
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] Nonfasting 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
Pneumonia[b]	20*	8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[c]	38	2.7
Skin and subcutaneous tissue disorders		
Rash[d]	28	0
Bruising[e]	26	0.9
Vascular disorders		
Hemorrhage[f]	28	4.5
Hypertension[g]	11	5.4

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

System Organ Class Preferred Term	CLL/SLL with 17p Deletion BRUKINSA (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Neoplasms		
Second primary malignancy[h]	22[†]	6
Gastrointestinal disorders		
Diarrhea	18	0.9
Nausea	16	0
Constipation	15	0
Abdominal pain[g]	12	1.8
Respiratory, thoracic, and mediastinal disorders		
Cough[g]	18	0
Dyspnea[g]	13	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

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

System Organ Class Preferred Term	BRUKINSA (N=324)		Ibrutinib (N=324)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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	14	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
Nervous system disorders				
Dizziness[f]	10	0	7	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, postacute 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	23	0
Phosphate decreased	21	2.5	13	2.2
Calcium decreased	21	0.6	29	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.

Follicular Lymphoma

The safety of BRUKINSA in combination with obinutuzumab was evaluated in 143 adult patients with relapsed or refractory follicular lymphoma (FL) in study BGB-3111-212 (ROSEWOOD), a randomized, multicenter, open-label trial *[see Clinical Studies (14.5)]*. The trial required an absolute neutrophil count ≥1 × 10^9/L, platelet count ≥50 × 10^9/L, and CLcr ≥30 mL/min and excluded patients requiring a strong CYP3A inhibitor or inducer.

Patients were randomized to receive either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity plus obinutuzumab (n=143) or obinutuzumab monotherapy (n=71). Obinutuzumab was dosed at 1,000 mg intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks for up to 20 doses. At the discretion of the investigator, obinutuzumab was administered intravenously on Day 1 (100 mg) and on Day 2 (900 mg) of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1.

In patients who received BRUKINSA in combination with obinutuzumab, the median age was 63, 49% were female, 63% were White, and 21% were Asian. Most patients (97%) had an ECOG performance status of 0 to 1. The median duration of BRUKINSA treatment was 12 months, with 24% of patients treated for at least 2 years.

Serious adverse reactions occurred in 35% of patients who received BRUKINSA in combination with obinutuzumab. Serious adverse reactions in ≥5% of patients included pneumonia (11%) and COVID-19 (10%). Fatal adverse reactions occurred in 4.2% of patients, with the leading cause of death being COVID-19 (2.1%).

Adverse reactions led to permanent discontinuation of BRUKINSA in 17% of patients, dose reduction in 9%, and dose interruption in 40%. Adverse reactions leading to permanent discontinuation in ≥2% of patients were pneumonia, COVID-19, and second primary malignancy. The leading causes of BRUKINSA dosage modification (42% of all patients) were pneumonia, COVID-19, thrombocytopenia, and neutropenia.

Table 15 summarizes adverse reactions in BGB-3111-212.

Table 15: Adverse Reactions in ≥10% of Patients with Relapsed or Refractory FL Who Received BRUKINSA in Study BGB-3111-212

System Organ Class Preferred Term	BGB-3111-212			
	BRUKINSA + Obinutuzumab (N=143)		Obinutuzumab (N=71)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions				
Fatigue[a,b]	27	1.4	25	1.4
Pyrexia	13	0	20	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a,c]	22	3.5	23	1.4
Vascular disorders				
Hemorrhage[a,d]	20	1.4	10	1.4
Gastrointestinal disorders				
Diarrhea	18	2.8	17	1.4
Constipation	13	0	9	0
Abdominal pain[a]	11	2.1	11	0
Infections and infestations				
Upper respiratory tract infection[a,e]	17	2.8	10	0
Pneumonia[a,f,*]	15	13	11	7
COVID-19[a,*]	13	9	11	4.2
Herpes virus infection[g]	11	2.1	1.4	0
Urinary tract infection[h]	10	1.4	7	0
Respiratory, thoracic, and mediastinal disorders				
Cough[a]	14	0	14	0
Dyspnea[a,*]	11	2.1	13	0
Skin and subcutaneous tissue disorders				
Rash[a,i]	11	0	14	0

* Includes fatal outcomes: COVID-19 (3 patients), pneumonia (2 patients), dyspnea (1 patient).
[a] Includes multiple related terms.
[b] Fatigue: Fatigue, asthenia, and lethargy.
[c] Musculoskeletal pain: Back pain, musculoskeletal pain, musculoskeletal discomfort, noncardiac chest pain, neck pain, pain in extremity, myalgia, spinal pain, bone pain, arthralgia, and related terms.
[d] Hemorrhage: All terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[e] Upper respiratory tract infection: Upper respiratory tract infection, sinusitis, pharyngitis, laryngitis, rhinitis, nasopharyngitis, laryngopharyngitis, tonsillitis bacterial, and related terms.
[f] Pneumonia: Pneumonia, COVID-19 pneumonia, lung infiltration, lung consolidation, and related terms including specific types of infection.
[g] Herpes virus infection: Herpes viral infection, herpes zoster, herpes simplex, herpes simplex reactivation, varicella, and Epstein-Barr viremia.
[h] Urinary tract infection: Urinary tract infection, cystitis, pyelonephritis, and related terms.
[i] Rash: Rash, erythema, dermatitis, drug eruption, skin reaction, and related terms.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA in combination with obinutuzumab included bruising, edema, pruritus, petechiae, vomiting, headache, arthralgia, hypertension, sepsis, cardiac arrhythmias, renal insufficiency, febrile neutropenia, transaminase elevation, and pneumonitis.

Table 16: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received BRUKINSA in Study BGB-3111-212

Laboratory Abnormality[a]	BGB-3111-212			
	BRUKINSA + Obinutuzumab		Obinutuzumab	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Platelets decreased	65	11	43	11
Neutrophils decreased	47	17	42	14
Hemoglobin decreased	31	0.8	23	0
Lymphocytes decreased	30	11	51	25
Chemistry				
Glucose increased[b]	53	8	41	9
Alanine aminotransferase increased	23	0	28	0
Phosphate decreased	21	0.8	14	0

[a] The denominator used to calculate the rate was 122 in the BRUKINSA + obinutuzumab arm, and varied from 56 to 58 in the obinutuzumab 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] Nonfasting conditions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of BRUKINSA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hepatobiliary disorder: drug-induced liver injury

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7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 17: 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 CYP3A 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 postimplantation 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 of BRUKINSA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1729 patients with MCL, MZL, WM, CLL/SLL, and FL in clinical studies with BRUKINSA, 59% were ≥65 years of age, and 21% 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 (57% and 38%, respectively) than patients <65 years of age (51% and 29%, 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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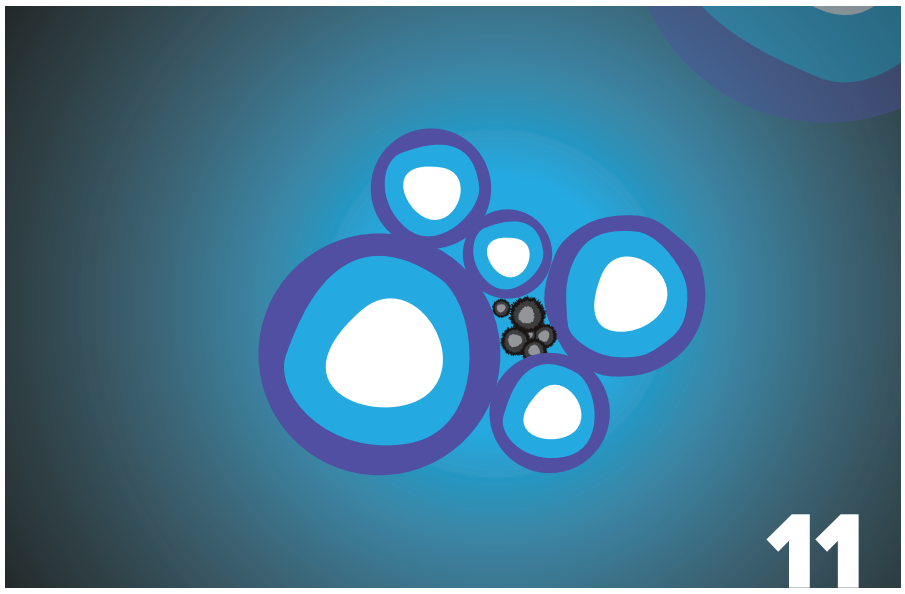

Status Update: MRD Continues to Prove Utility in Hematologic Malignancies

The interest in using quantitative tests to measure residual cancer cells—called measurable residual disease—continues to expand in the arena of hematologic malignancies.

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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 10–11, 2025
Highlights of ASH North America
New York, New York
Seattle, Washington

February 1, 2025
The Leukemia & Lymphoma Society Blood Cancer Conference–Northern California
San Francisco, California

February 3–7, 2025
Hematology & Medical Oncology Practice Updates and Board Review 2025, Mayo Clinic
Kapalua, Hawaii

February 6–8, 2025
EHA-EBMT 7th European CAR T-Cell Meeting
Strasbourg, France

February 7–9, 2025
European Society for Medical Oncology Summit Africa 2025
Cape Town, South Africa

February 12–15, 2025
2025 Tandem Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®
Honolulu, Hawaii

February 22, 2025
The Leukemia & Lymphoma Society Blood Cancer Conference–Florida
Orlando, Florida

February 27–March 2, 2025
29th Annual International Congress on Hematologic Malignancies®: Focus on Leukemias, Lymphomas, and Myeloma
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March 6–8, 2025
Japanese Society of Medical Oncology Annual Meeting
Kobe City, Japan

March 7–8, 2025
Annual Meeting of the International Extranodal Lymphoma Study Group
Stresa, Italy

March 7–9, 2025
AACR Special Conference in Cancer Research: Acute Lymphoblastic Leukemia
San Diego, California

March 12–15, 2025
Clinical Multidisciplinary Hematology & Oncology 19th Annual Review, Mayo Clinic
Scottsdale, Arizona

March 28–30, 2025
National Comprehensive Cancer Network 2025 Annual Conference
Orlando, Florida

April 11–12, 2025
European Society for Medical Oncology Summit Latin America 2025
Lima, Peru

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Matthew Lunning, DO, FACP

Matthew Lunning, DO, FACP, an Associate Professor in the Division of Hematology/Oncology at the University of Nebraska Medical Center, discusses his origins in clinical research, the rise of cellular therapy, and the parallels between teaching tennis and medicine.

Where did you grow up, and when did you know you wanted to be a physician?
I grew up in Mason City, Iowa, in a middle class family right next to the railroad, so I can sleep through anything. My mom, Marianne, has been an orthopedic nurse for 45 years at the same hospital on the same floor. I admired her loyalty and her willingness to lead when COVID-19 struck our city. I grew up idolizing my mom and spent my summers at our local community hospital playing catch with foam balls with the bedbound, postoperative patients. I'd always have to go and hide when the doctors came to round. I enjoyed the hospital environment growing up as a child.

Fittingly, one of my first jobs introducing me into health care was as a clinical research assistant at my local community cancer center. This role introduced me to the concept of clinical trials, which spurred my interest into oncology in general. Then I met **Gerald Marti, MD, PhD,** whose father had cancer. He has been very instrumental in my life. He worked at the National Institutes of Health and helped run a clinical flow cytometry lab back in the days when flow cytometry was in its infancy. He offered me a "quick trip" to work in his lab and help write a case report about mantle cell lymphoma. I spent two weeks in his lab from early morning to dark and got an understanding of what it meant to do clinical research and bench research. That two-week experience led to two summers of working in his lab at the Center for Biologic Evaluation and Research.

From that oncology experience in clinical research and further research focused on blood cancers, I knew that I wanted to do blood cancer research before I even matriculated into medical school. I tell people I've been a blood cancer researcher since I was 19.

Were there any other mentors who shaped your career path?
There's been a bunch along the way. Over time, you become a little piece of your mentor. It's like the 'antihorcrux,' to make a Harry Potter reference. You take on the good pieces of those mentors but still have you own core flare.

Peter Silberstein, MD, a community oncologist, gave me first access to patients. He was the first to have one-on-one discussions with me and test my knowledge to see if I could effectively communicate. From those days, I knew at the core of being a physician is being an effective and creative communicator. At a very young age, he gave me those opportunities through the lens of clinical trials, which was often foreign to patients and their family.

Dr. Marti opened my eyes to what it meant to work for the federal government and how the clinical research engine works on the other side from a device or technology standpoint. I got to see both community research and federal research at the age of 19. He also introduced me to writing with a goal to be published in peer-reviewed journals.

I also met **James Armitage, MD,** through a random phone call at the age of 19 from a clinical trial question. He asked me more about myself than I did about the clinical trial. My mind was blown about who this man was. I researched him endlessly on that new thing called the internet. I aspired to be like him and tried to mold my career path such that I would get to work with him. As a result, I went to the University of Nebraska Medical Center's internal medicine residency program. During my residency, I got the opportunity to work with him and be a principal investigator on a prospective clinical trial that looked at cardiac magnetic resonance imaging in lymphoma patients, a new technology at the time. It got me exposure to writing clinical trials from scratch, an important feat one should do at least once in their careers. I needed faculty support, and he was willing to be the mentor to put his stamp on—among others—in the institution. He helped low the fence and showed that residents can do prospective clinical research, too.

That experience helped navigate me to a hematology oncology fellowship at the Memorial Sloan Kettering Cancer Center in New York City, which I think is one of the best fellowships in the world. There, I met **Steve Horowitz, MD,** a T-cell lymphoma expert. He taught me not only how to conduct clinical trials, but how to do it in an efficient team environment where everyone knew the role. He also taught me how to work with industry sponsors through investigator-initiated trials and industry sponsored research. He allowed me to understand not only the interplay between FDA, sponsor, and principal investigators, but also gave me an introduction to understanding the financials of research and how to do it.

"I want to see the continued rise of cellular therapy, and I want to see it become more broadly accessible. Equity of opportunity is very important to me."

When I came back to Nebraska, I returned under Dr. Armitage's tutelage and the leadership of **Julie Vose, MD, MBA.** I have grown in my research career, but also through those individuals.

What advice would you give to younger physicians or trainees in the field?
Several people have helped me in my career, so I feel that it's necessary to pay it forward. I mentor both internally and externally. It's always important to have internal mentors, but it's almost as important to have external mentorship to help address different issues that come along the path to becoming a successful academic physician.

One piece of advice is that you have to be careful of saying "yes." Dr. Vose would harp on me when I had too many things on my academic plate. We all have that fear of missing out. You get an offer to do a review article, write an article, or see more patients. But everybody enters their career in different landscapes. Some enter their career taking over a patient panel for a physician who's either moving into retirement or moving on to a different institution for a different opportunity. Then, there's some who enter a career with zero patients and have to build. Understanding

Get to Know

the landscape you're coming into can provide different footing to how you grow. I believe it is incredibly important to walk before you run so you can excel clinically early in your career. If you don't have that clinical footing and clinical trust with yourself and your team, then you're always scrambling in the clinic.

This impacts you negatively in other aspects of your career, whether it's doing clinical research or the ability to sit down and understand clinical research operations. The first six months are getting your clinical footing, and the next six months are understanding your clinical research operations and how clinical trials work at the institution you work at. I came with a general understanding of how clinical trials work, but I wanted to understand how the machinery works, the parts within the machine, and the assembly line of coming up with a clinical trial idea, getting it approved, then reporting it out. I dug in deep and got my hands dirty in the clinical trial operations. I think that not a lot of investigators are educated along the way through residencies and fellowships on the conduct and operations of clinical research. That hamstrings them along their career.

Can you talk about your current clinical research?

One of my areas of major focus is cellular therapy. I consider myself a global ambassador for cellular therapy. I travel around the world talking about access issues to cellular therapy. Access remains one of the major issues to the implementation of the successes of cellular therapy in lymphoma and other hematologic malignancies and as it moves into solid tumor oncology through different mechanisms, whether it's [chimeric antigen receptor (CAR)] T-cell, bispecific T-cell engagers, tumor-infiltrating lymphocytes, or other forms of immunotherapy. Getting it right, right now, is imperative to future success.

How do we access those technologies for everybody, and not just those who can travel to the centers that have them? That's where the next revolution comes. Can we find technologies like allogeneic cellular therapies that are off the shelf and have broader applicability that can get more access because the toxicity profile may afford it? Off the shelf nature means that you don't have to have apheresis capabilities, biological processing facilities, or the chain of command capabilities constraints. We're learning through clinical trials and asking ourselves the question: "is this portable to a broader environment?"

There's also an explosion of opportunities happening in autoimmunity, which has become a hot topic within the cellular therapy world. Do you need autologous products? Should you be using autologous products in people with other underlying autoimmune disorders who have historically been excluded from clinical trials in earlier autologous CAR T-cell trials because of the concern for how their immune system inherently behaves versus leveraging that allogeneic aspect where you're using a single donor source or somebody else's immune system that's unperturbed by an underlying autoimmune condition? Can you get the same successes without the potential inherent risks of an autologous product?

Trying to do my part in answering some of those questions, I assisted in shepherding CAR-T into the autoimmune space here at the University of Nebraska. First in rheumatology, then moving into lupus, scleroderma, and myositis—classically uncommon and underserved research arenas that strike individuals within the prime of their lives. We often focus on cancer, but we also need to focus on other conditions like autoimmune conditions that lead to long-term quality of life issues that can be manifested as end-stage renal disease or another end-organ damage that we classically think is part of the natural history. Can we intervene into that natural history with cellular therapy? I think this will spread into other disorders like multiple sclerosis. We're building an infrastructure that exports my experience and my team's experience in cellular therapy to onboard those therapies to investigators who have never heard of cellular therapy, CAR T-cell, or natural killer cell research.

We're doing that through a gene and cellular therapy support service, where a cellular therapist and a cellular therapy research coordinator who have years of experience are supporting other research teams to onboard cellular therapies within their own discipline, whether it's lupus, multiple sclerosis, or cystic fibrosis. How can cellular therapy potentially impact those diseases in a way where you limit the risk not only to the subject, but to the institution that's trying to bring this powerful technology to a noncancer population?

When you hear scary words like neurotoxicity or cytokine release syndrome, those are things you want to have experienced individuals involved in the research team to help shepherd those technologies through focused areas and to eager people who want to learn. You want to educate, onboard, gain experience, then allow them to learn within a mentee/mentor role. That's something I've established with one of our rheumatologists, **Jennifer Medlin, MD.** We recently did the first allogeneic CAR T-cell in lupus in the world, which brought back the butterflies I had when I did my first CAR-T for hematologic malignancies at Nebraska. As a junior investigator, she understands that she has an amazing opportunity to lead this study while being supported in the shadows by a seasoned support team. It's very fulfilling to do, and I love seeing others succeed as my mentors have seen in me. It's fun to be there for them and watch them grow in confidence.

What do you hope to see in the field over the next 10 years?

I want to see the continued rise of cellular therapy, and I want to see it become more broadly accessible. Equity of opportunity is very important to me. How do we expand the therapeutic realm to not only bring safe cellular therapy products to those who want them, but to also expand the education on who truly is a CAR T-cell or cellular therapy-eligible patient? We see that in oncology, but we also see that as we move into nononcologic clinical trials.

Sometimes the most ill can't get access to them, so trying to find the sweet spot of where the risk-benefit is not only in oncology—as we drive forward earlier lines of therapy—but also outside of oncology through clinical trials. Finding cellular therapies that have broader applicability and access can only happen through clinical trials and broader education on the technology.

I travel across the world talking about access to this technology. I talk to people about how they dealt with access issues in different health systems, whether it's a private health care-based system like the United States, a national health care system like in England or Canada, or a hybrid system like in other Southeast Asian countries. A lot of them are still trying to get access to some of the therapies that we take for granted. They struggle to get rituximab. They want to learn about these key technologies, but they're still struggling to get certain therapeutics that I wouldn't blink an eye at thinking of getting. I've become humbled by some of the situations I hear about.

What hobbies or activities do you enjoy outside of work?

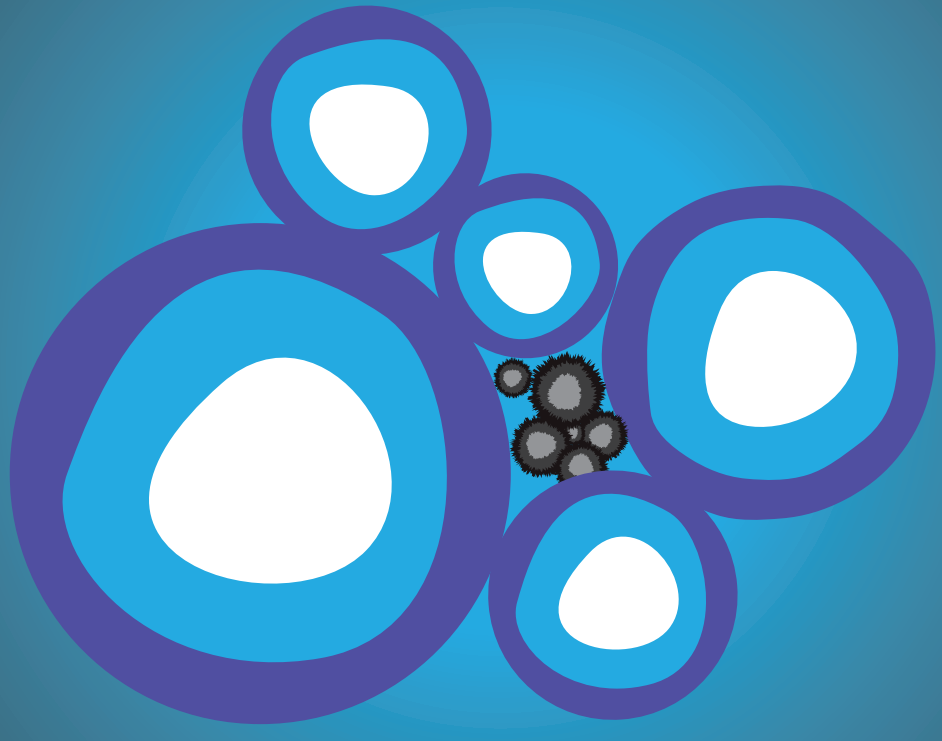
I really enjoyed teaching tennis to pay for my undergraduate and medical school education. I was given a gift of learning how to communicate and teach effectively through Dr. Steven Wilkinson, my tennis coach at Gustavus Adolphus College. His philosophy of "tennis and life" resonated with me and has stayed at my core. It was his ability to communicate with people one-on-one on something that may frustrate them, give them suggestions, and see them improve and succeed through a different approach. It was very complimentary to a life in medicine.

What would you do for a living if you weren't a doctor?

When I was trying to get into medical school, I was in Washington, DC, in Bethesda, Maryland, right by the National Naval Medical Center. I was one of those kids who grew up watching Top Gun over and over. If I couldn't get into medical school, I was going to try to be a naval officer because I'd have my bachelor's degree and apply to be a pilot. I was short and had the Tom Cruise build. I wanted to fly F-16s with my hair on fire having no piloting experience. I learned that you didn't need to have piloting experience, you just had to be a naval officer to apply. I finished my flight application for the Navy, but I got into medical school instead. Whenever I go to meetings in San Diego and we stay up in La Jolla, right by Miramar, I hear the F-16s shooting over the hotel. That could have been me!

Status Update: MRD Continues to Prove Utility in Hematologic Malignancies

By Leah Lawrence



The interest in using quantitative tests to measure residual cancer cells—called measurable residual disease (MRD)—continues to expand in the arena of hematologic malignancies. Tests to measure MRD take a "snapshot" of a patient's current status and provide clinicians with a yes or no answer to the question, "is disease still present in the body?" at a time when cancer cannot be detected using other traditional methods.

Applications of MRD vary depending on the disease state but can include providing prognostic information, acting as a measure of clinical efficacy, guiding therapeutic decisions, and serving as a clinical endpoint.

Blood Cancers Today spoke with experts in acute lymphoblastic leukemia (ALL), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL) for a status update on the use of MRD in each of these diseases.

Continued on page 12

In Focus

ALL Update

MRD is highly predictive and prognostic in ALL, explained **Elias Jabbour, MD, a** Professor of Medicine in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston.

"You cannot treat ALL if you do not measure and act on MRD," Dr. Jabbour said. "MRD is a critical part of management of ALL."

In its requirements for the diagnosis of ALL, the National Comprehensive Cancer Network (NCCN) guidelines include a "baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent" MRD analysis, and many of its treatment algorithms recommended therapy based on MRD status.[1]

There has been mounting evidence of the prognostic value of MRD in ALL, with much of the data for adult patients building on already-established evidence for pediatric populations.

For example, data from patients with ALL from two large transplant centers showed that detection of MRD even at a low level increased a patient's risk for post-transplant relapse. Any MRD detection post-transplant also increased the risk for relapse. In contrast, patients with undetectable MRD prior to transplant and through the first year of monitoring have excellent post-transplant outcomes.[2]

"You cannot treat ALL if you do not measure and act on MRD. MRD is a critical part of management of ALL."

—Elias Jabbour, MD, Professor of Medicine, University of Texas MD Anderson Cancer Center

Transplant-eligible patients who are MRD positive can receive blinatumomab prior to transplant. Blinatumomab was the first drug to receive US Food and Drug Administration (FDA) approval for the treatment of B-ALL.[3]

There is also early evidence that MRD status could predict relapse after chimeric antigen receptor (CAR) T-cell therapy in patients with B-ALL. Data from the pediatric and young adult populations showed that next-generation sequencing (NGS) MRD from bone marrow was highly predictive of relapse after tisagenlecleucel therapy, possibly enabling clinicians to consider additional treatment to prevent relapse.[4]

Dr. Jabbour and colleagues have presented results of a meta-analysis evaluating associations between MRD and long-term outcomes in Philadelphia chromosome-positive (Ph+) ALL. Study-level and individual patient data showed that deeper molecular response at end of induction yielded better long-term event-free survival (EFS) and overall survival (OS), that MRD-negative complete remission (CR) was associated with long-term EFS and OS, and that MRD-negative CR had a greater prognostic value than CR alone.[5]

"We are very close to considering MRD as a finite way to tailor therapy in ALL," Dr. Jabbour said.

There are still multiple methods for measuring MRD use—flow cytometry, polymerase chain reaction, or NGS—each with its own level of sensitivity. However, Dr. Jabbour said that he feels the field will soon adopt NGS as a standard of care. Currently, ClonoSEQ assay, an NGS-based test, is the only FDA-approved test for the measurement of MRD in ALL or MM.[6]

In ALL, the high sensitivity of NGS, which can measure to a depth of 10^{-6}, allows for measurement of MRD in peripheral blood. Studies have shown that there is concordance between blood and bone marrow assessment in adult patients.[7]

When clinicians choose to measure MRD by NGS, they must obtain the baseline patient-specific clonotype and then measure it again after induction therapy, consolidation therapy, and regularly throughout maintenance therapy.

"At my practice, I measure MRD every month until a patient becomes MRD negative," Dr. Jabbour said. "Once a patient is MRD negative, then I measure it every three months throughout treatment, and once treatment is finished, every three to six months for the first couple of years."

The use of MRD to guide therapeutic decisions is becoming more and more standard, Dr. Jabbour said.

"Eventually, with very effective therapy, the MRD response will trump the basic biologic features [of ALL]," Dr. Jabbour said. "The field is evolving and MRD assessment will carry a bigger and bigger weight moving forward."

Myeloma Update

The biggest recent advance in the use of MRD in MM is the April 2024 Oncologic Drugs Advisory Committee (ODAC) 12-0 vote in favor of using MRD as an early endpoint to support accelerated approval,[8] an achievement that was more than 15 years in the making according to **C. Ola Landergren, MD, PhD,** professor of Medicine, Chief of the Myeloma Division, and Co-Leader of the Translational and Clinical Oncology Program at the University of Miami Sylvester Comprehensive Cancer Center.

"Progression-free survival (PFS) is a surrogate endpoint for OS, and it is used for full approval of new drugs. But to have a surrogate endpoint you have to have strong correlations, and you have to have many datasets to prove your case with sufficient statistical power," Dr. Landgren explained. "We developed a model where we tested the hypothesis that MRD was reasonably likely to predict clinical benefit, which is the level of statistical evidence you need to have for an endpoint to qualify as an endpoint for accelerated approval."

The gathering of data and creation of this model began many years ago. When Dr. Landgren realized that while the drug companies had the data that might correlate MRD with clinical benefit and the FDA would review the data, a third party would be required to gather datasets from a wide range of classes of drugs and to develop statistical models designed to evaluate MRD as an early endpoint in MM.

This culminated in the publication of the EVIDENCE meta-analysis, which included eight phase II or III randomized studies of newly diagnosed MM and four studies of relapsed or refractory MM. Individual-level associations between 12-month MRD negativity and PFS yielded a global odds ratio of 4.02 for newly diagnosed disease and 7.67 for relapsed or refractory disease.[9]

These data, combined with similar data from the collaborative research group I2TEAMM (International Independent Team for Endpoint Approval of Myeloma MRD), led to the unanimous ODAC recommendation for the use of MRD as an early endpoint for accelerated approvals.

Dr. Landgren explained why this recommendation could be a big step forward.

"In a trial of MM, if you enroll 500 patients—which can take two years and then one year after the last patient is enrolled—you have MRD data for every patient," Dr. Landgren said. "However, you would have to wait more than 10 years for the dataset to mature (ie, to obtain sufficient statical power) for PFS outcomes."

This new evidence validates that MRD was able to predict PFS benefits.

"The deliverable is that you shrink those 12 years down to three," Dr. Landgren said. "This makes it attractive to develop drugs in a disease where otherwise–with traditional endpoints–it isn't because the patent would be almost over by the time the drug was approved."

Additionally, trials designed to cure patients with MM can have an answer about whether it works in less than three years—one to two years for enrollment and one year for MRD measurement.

Best of all, this approach can be adapted to other diseases, Dr. Landgren said.

In addition to its use as an early clinical endpoint, evidence continues to grow in support of using MRD to guide therapeutic decisions in patients with MM.

Results of the PERSEUS trial published earlier in 2024 compared bortezomib, lenalidomide, and dexamethasone (VRd) plus lenalidomide maintenance or VRd plus daratumumab (D-VRd) plus daratumumab and lenalidomide maintenance. After two years of maintenance, patients who were MRD-negative for at least 12 months could discontinue daratumumab; recurrence of MRD prompted the return to daratumumab maintenance.[10]

Taking it a step further, the MRD2STOP trial looked at complete discontinuation of maintenance therapy in patients with sustained multimodal MRD negativity. Results showed that maintenance

discontinuation resulted in a high rate of sustained MRD negativity and lack of disease progression.[11]

Dr. Landgren is also part of the ADVANCE study, which randomly assigned patients to eight cycles of carfilzomib, lenalidomide, and dexamethasone with or without daratumumab with autologous hematopoietic stem cell transplant offered to patients who remain MRD positive after eight cycles.[12] Results are expected in 2025.

"There is not yet a trial that has definitely proven that [measuring MRD] is the way to do it," Dr. Landgren said. "The reality is that it's also probably true for all other markers; we use serum protein electrophoresis (SPEP) or light chains, but there are very few randomized trials that formally have proven their use."

The biggest roadblock for increased use of MRD in MM is that it is measured using bone marrow biopsy, Dr. Landgren said. Blood-based techniques exist but have not yet been validated to fully replace bone marrow biopsies in myeloma.

"A blood-based MRD test for MM would very likely change the whole treatment field in the future," Dr. Landgren said. "I could see some patients going off therapy and being tested every few months. In other patients, the therapy will be stepped up or down based on the MRD results."

CLL Update

The utility of MRD measurement in CLL is not all that different than in ALL or MM, according to **Talal Hilal, MD,** a hematologist oncologist and bone marrow transplant physician at the Mayo Clinic in Phoenix, Arizona.

Similar to ALL and MM, MRD detection in CLL uses similar assays, with six or eight color flow cytometry detecting MRD to 10^{-4}, and the same NGS assay–ClonoSeq–detecting to 10^{-6}.

"One thing that makes MRD a little more versatile in CLL is that MRD can be easily tested in the peripheral blood as compared with ALL and MM, where it is still tested primarily from bone marrow samples," Dr. Hilal explained.

Within CLL though it remains to be seen if MRD is a surrogate endpoint for clinical outcomes. Recently, Dr. Hilal and colleagues published a meta-analysis looking at associations between MRD and PFS in CLL using data from 11 prospective clinical trials of targeted agents or obinutuzumab-based regimens.

Undetectable MRD measured at 10^{-4} was associated with significantly improved PFS (hazard ratio [HR]=0.28) compared with MRD positivity, with improved outcomes noted for patients treated in the firstline, relapsed or refractory setting, or in trials using time-limited therapy.[13]

Researchers from the German CLL Study Group presented a similar analysis using patient- and trial-level data to look at correlations between PFS and MRD, and confirmed a correlation of MRD status with PFS.[14]

"These data showed if you achieve undetectable MRD at 10^{-4} after time-limited therapy—whether chemoimmunotherapy or venetoclax-based treatment—your PFS is going to be better than someone who does not achieve that endpoint," Dr. Hilal said. "The hard part is understanding whether improving undetectable MRD rates can predict clinical benefit as defined by the FDA."

Dr. Hilal noted that some clinicians may be hesitant to use MRD in practice because progression of CLL does not always mean a patient needs more treatment. Instead, "it may be necessary to correlate undetectable MRD to something more clinically meaningful like time to next treatment and, if possible, OS," he said.

It also remains to be seen if MRD has clinical utility and if it can be used to guide therapeutic decisions.

In Dr. Hilal's practice, a patient being treated with time-limited venetoclax plus obinutuzumab will typically have MRD tested at one year and possibly at six months.

"I often don't do anything with the results though, which is sort of the issue," Dr. Hilal said. "It is just an extra data point that provides prognostic information. It doesn't change my approach to treatment."

However, researchers are looking to change that. In December 2023, results of the FLAIR study showed that MRD-directed ibrutinib plus venetoclax resulted in significantly better PFS compared with fludarabine, cyclophosphamide, and rituximab.[15] The duration of ibrutinib plus venetoclax was defined by MRD assessed in peripheral blood and bone marrow, and was double the time taken to achieve undetectable levels.

The phase III MAJIC study comparing acalabrutinib plus venetoclax versus venetoclax plus obinutuzumab will also use MRD to guide therapy duration.[16]

"If we can show in MAJIC that there is an improvement in PFS by extending the duration of therapy in someone who is MRD positive, then I think that is something people will start doing in practice," Dr. Hilal said.

In contrast to extending the duration of therapy, there are times when MRD is undetectable by the six month mark, Dr. Hilal added. However, little is known about using MRD to shorten the duration of treatment, and it is difficult to fund studies looking at shortening duration.

"Let's say though that a patient is having side effects from venetoclax and they are pushing through to get the maximum benefit. If they are MRD negative at six months, I would feel better about stopping therapy and would not push as hard as I would with someone who still has significant disease," Dr. Hilal said. This could also be a strategy used in older patients who do not tolerate the regimen, he noted.

Additional research is needed to establish best practices for the method and timing of MRD testing. The use of flow cytometry may have a bit more uptake, since the use of NGS for MRD requires sequencing at diagnosis, Dr. Hilal said.

Another unanswered question is whether the use of peripheral blood to measure MRD in CLL is adequate. MRD negativity in the blood does not always mean MRD negativity in the bone marrow, Dr. Hilal said. There is a correlation between the samples 90% of the time, but bone marrow remains the most sensitive method.

"When it comes to MRD practices, there is no standardization. That is true across many hematologic malignancies."

—Talal Hilal, MD, hematologist oncologist, Mayo Clinic, Phoenix, Arizona.

"When it comes to MRD practices, there is no standardization. That is true across many hematologic malignancies," Dr. Hilal said. "It varies by institution; Mayo Arizona may even do things different than Mayo Rochester."

Finally, Dr. Hilal said that there are ongoing discussions about the best upfront combination therapy for patients with CLL.

"There is a lot of argument in favor of targeted therapy with a Bruton tyrosine kinase and B-cell lymphoma 2 inhibitor, which is not currently FDA approved," Dr. Hilal said. "If we get that approval, that regimen will compete with time-limited therapy like venetoclax plus obinutuzumab. A lot of the argument for the use of one versus the other will hinge on differences in rates of MRD between those two strategies."

Clinicians may not have answers to many of these questions any time soon, Dr. Hilal noted. Nevertheless, MRD will continue to be a large part of the conversation whenever a novel therapy approval rolls out.

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

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Highlights From the **21ST INTERNATIONAL MYELOMA SOCIETY ANNUAL MEETING**

Triplet Combination Shows 'Promising' Safety, Efficacy in MM

Mezigdomide, tazemetostat, and dexamethasone demonstrated promising efficacy and safety in patients with relapsed or refractory multiple myeloma, according to preliminary data from the CA057-003 phase I/II trial.

The study was led by **Luciano Costa, MD,** of the University of Alabama at Birmingham, and presented at the 21st International Myeloma Society Annual Meeting in Rio de Janeiro, Brazil.

Luciano Costa, MD

Thirteen patients (median age, 67) were included in the study. All patients had progressive disease, an Eastern Cooperative Oncology Group performance status score ≤1, an absolute neutrophil count ≥1000/µL, and an estimated glomerular filtration rate ≥45 mL/min/1.73 m^2. The treatment regimen consisted of oral mezigdomide at three escalating doses (0.3, 0.6, and 1.0 mg) on days 1–21 of each 28-day cycle; oral tazemetostat (800 mg) twice daily on days 1–28; and oral dexamethasone (40 mg; 20 mg if ≥75 years of age) every week.

The primary endpoints of the study included defining the recommended phase II dose and dosing schedule as well as evaluating safety. Secondary objectives included assessing efficacy and pharmacokinetics. The median follow-up was 4.2 months.

Nine patients experienced grade 3 or 4 treatment-emergent adverse events (TEAEs). The most common hematological TEAEs were neutropenia (46.2%) and anemia (15.4%), while the most common grade 3 or 4 nonhematological TEAEs were infections (15.4%) and dyspnea (15.4%). There were no dose-limiting toxicities. Six (46.2%) patients continued treatment, and five discontinued due to progressive disease (one due to physician's decision, and one due to an AE). One death occurred due to pulmonary sepsis.

The overall response rate (ORR) was 53.8% (95% CI, 25.1–80.8), including one stringent complete response, two very good partial responses, and four partial responses. The median time to response was 0.95 months.

"[Mezigdomide] remained pharmacodynamically active, inducing Ikaros/Aiolos degradation and B-cell reduction with [tazemetostat] at all dose levels (greatest effect observed at [mezigdomide] 1.0 mg)," the researchers wrote.

Reference

Costa L, Popat R, Siegel D, et al. Mezigdomide (MEZI), tazemetostat (TAZ), and dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): preliminary results from the CA057-003 trial. Abstract #OA-29. Presented at the 21st International Myeloma Society Annual Meeting. September 25-28, 2024; Rio de Janeiro, Brazil.

Durcabtagene Autoleucel Demonstrates High Responses, Manageable Safety in MM

Durcabtagene autoleucel has shown high response rates and manageable safety in patients with relapsed or refractory MM in a recent interim analysis.

The phase II trial was led by **Andrew Spencer, MBBS,** of Alfred Health, and presented at the 21st International Myeloma Society Annual Meeting in Rio de Janeiro, Brazil.

Andrew Spencer, MBBS

A novel BCMA-directed chimeric antigen receptor (CAR) T-cell therapy, durcabtagene autoleucel is manufactured using the T-Charge™ platform that reduces manufacturing time to less than two days while preserving T-cell stemness.

Evaluating two target doses for the therapy, "[e]fficacy thus far has appeared comparable between doses, with a trend toward better safety at the 5^6 dose," the investigators wrote.

The open-label, single-arm, multicenter trial enrolled 161 adults who had received at least three prior lines of therapy. The 145 participants who received durcabtagene autoleucel infusion had a median age at enrollment of 61 years and were 63% male. A total of 111 infused patients received a target dose of 10e6 cells and 34 received a target dose of 5^6 cells.

The trial's efficacy analysis set was 62 patients with a median follow-up of 8.3 months. The set achieved an overall response rate (ORR) of 92%, which met the primary endpoint of the trial ($P<.001$). It also attained a complete response rate (CRR) of 53% and a six-month progression-free survival (PFS) probability of 82%.

The trial's full analysis set included all infused patients. The 107 patients who had follow-up of at least six months achieved an ORR of 97%, a CRR of 53%, and a six-month PFS probability of 86%.

All patients experienced at least one adverse event (AE). AEs of grade 3 or worse severity that affected at least 20% of patients were anemia, neutropenia, and thrombocytopenia.

Cytokine release syndrome (CRS) of any grade was experienced by 96% of patients; grade 3 or worse severity occurred in 6%. CRS had a median time to onset of eight days and median duration of four days. Immune effector cell-associated neurotoxicity syndrome (ICANS) affected 13% of patients and was grade 3 or worse severity in 4% of them. Ten percent of patients reported experiencing macrophage activation syndrome, hemophagocytic lymphohistiocytosis (HLH), or immune effector cell-associated HLH-like syndrome.

Of the 14 mortalities in the trial, four occurred within 30 days of infusion. Ten mortalities were due to AEs, nine of which were of patients who received the 10^6 cells target dose and five of which were due to infection. Four mortalities were due to MM progression, three of which were of patients who received the 10^6 cells target dose.

Reference

Spencer A, Raab MS, Iida S, et al. Interim phase 2 study results of durcabtagene autoleucel (PHE885), a T-Charge™ manufactured BCMA-directed CAR-T cell therapy in patients (pts) with r/r multiple myeloma (RRMM). Abstract #OA-12. Presented at the 21st International Myeloma Society Annual Meeting. September 25-28, 2024; Rio de Janeiro, Brazil.

Highlights From the **TWELFTH ANNUAL MEETING OF THE SOCIETY OF HEMATOLOGIC ONCOLOGY**

Pacritinib Superior to Best Available Therapy for Patients With Myelofibrosis, Thrombocytopenia, Anemia

Full-dose pacritinib is efficacious in terms of spleen volume reduction, symptoms, and transfusion response in patients with myelofibrosis with thrombocytopenia and anemia, according to a recent study.

The study was led by **Pankit Vachhani, MD,** of the O'Neal Comprehensive Cancer Center at the University of Alabama at Birmingham, and presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology in Houston, Texas.

Pankit Vachhani, MD

"Thrombocytopenia and anemia pose treatment challenges in myelofibrosis," wrote Dr. Vachhani and colleagues. "When these two cytopenias co-occur ('bicytopenia'), management becomes particularly challenging, and appropriate treatment selection is critical to optimize efficacy while minimizing myelosuppressive side effects."

The researchers presented data from the PERSIST-2 trial on spleen and symptom benefit in patients with moderate or severe bicytopenia at baseline (platelet count <100 × 10^9L and hemoglobin <10 g/dL) who were treated with pacritinib. Endpoints included spleen volume reduction (SVR) 35% or greater, total symptom score (TSS) reduction of at least 50%, Patient Global Impression of Change (PGIC), and transfusion independence response (TI-R).

Forty-six patients received pacritinib 200 mg twice daily, whereas 47 received best available therapy (BAT). Pacritinib demonstrated superiority to BAT for all endpoints. Twenty percent of patients in the pacritinib group had SVR 35% or greater, compared with 0% in the BAT group (P=.0054). This trend was also observed with TSS: 32.5% of patients in the pacritinib group had at least 50% TSS reduction, compared with 10.5% of patients in the BAT group (P=.0274). Thirty percent of patients on pacritinib had a PGIC response of "very much" or "much" improved at week 24, compared with 13.2% patients on BAT.

Twenty-seven patients on pacritinib and 36 on BAT received red blood cell transfusions at baseline. Of those patients, 26% on pacritinib and 8% on BAT achieved TI-R (P=.0838).

"Pacritinib at full dose demonstrates efficacy for spleen, symptoms, and transfusion response in patients with myelofibrosis and both thrombocytopenia and anemia," the researchers concluded.

Reference

Vachhani P, Gupta V, Palandri F, et al. Efficacy of pacritinib in patients with myelofibrosis who have both thrombocytopenia and anemia. #MPN-470. Presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology. September 4-7, 2024; Houston, Texas.

Talquetamab Plus Pomalidomide Achieves Effective Responses in Multiple Myeloma

The combination of talquetamab and pomalidomide induced rapid and deep responses in patients with relapsed or refractory multiple myeloma and two or more prior lines of therapy, according to data from the phase Ib MonumenTAL-2 trial.

Emma Searle, MD, of the Christie NHS Foundation Trust and the University of Manchester, presented the findings at the Society of Hematologic Oncology 2024 Annual Meeting in Houston, Texas.

Emma Searle, MD

Dr. Searle added that talquetamab and pomalidomide yielded robust responses across patient subgroups and had safety "consistent with the individual agents, with low rates of treatment discontinuation due to adverse events (AEs) and no evidence of additive hematologic/cytokine release syndrome (CRS) toxicities."

The analysis included 35 patients who received pomalidomide 2 mg daily alongside talquetamab at either 0.4 mg/kg once weekly (QW; n=16) or 0.8 mg/kg once every two weeks (Q2W; n=19).

Over a median follow-up of 15.0 months and 11.1 months in the QW and Q2W groups, respectively, the overall response rates were 93.8% and 84.2% and median times to first response were 1.7 months and 1.2 months, respectively. Median duration of response and progression-free survival were not reached.

Among all patients, the most common AEs were taste-related events (85.7%), infections (80%), and CRS (74.3% grade 1/2; one grade 3). Grade 3/4 AEs occurred in 91.4% of patients, most commonly neutropenia (54.3%), anemia (25.7%), infections (22.9%), and thrombocytopenia (20%). Nail toxicities occurred in 68.6% of patients, skin in 74.3%, and rash in 20%, most of which were grade 1/2 with none leading to discontinuation, the authors reported.

"The promising efficacy and manageable safety profile of talquetamab plus pomalidomide support talquetamab as a versatile combination partner," Dr. Searle and colleagues concluded.

Reference

Searle E, Quach H, Biran N, et al. Talquetamab (Tal), a GPRC5D×CD3 bispecific antibody (BsAb), in combination with pomalidomide (pom) in patients with relapsed/refractory multiple myeloma (RRMM): efficacy and safety results from the phase 1b MonumenTAL-2 study. Abstract #MM-349. Presented at the Society of Hematologic Oncology Annual Meeting; September 4-7, 2024; Houston, Texas.

Cytogenetic Analysis Reveals Lower Risk Profile in African American Patients With MDS

A retrospective study explored the cytogenetic profile of African American (AA) patients with myelodysplastic syndromes (MDS), which arise from clonal mutations in hematopoietic stem cells, leading to bone marrow dysplasia, ineffective hematopoiesis, and peripheral cytopenias.

Although cytogenetic abnormalities play a significant role in the prognosis and treatment of MDS, their incidence in the AA population remains understudied. This research, led by **Navneet Kaur, MD,** of the North Alabama Medical Center, was conducted in a community clinic in Brooklyn, New York. The researchers aimed to address this gap by analyzing cytogenetic data from AA patients with MDS.

Navneet Kaur, MD

The study included adult AA patients who presented to the cancer clinic between January 2012 and December 2023, focusing on those with available cytogenetic data. Of the 48 patients identified, 18 met the study's criteria. The group included 12 males (66.6%) and six females (33.3%), with a median age of 79 years (range, 51–95 years). The researchers collected data on complete blood counts, bone marrow biopsies, and cytogenetic results, which were categorized with the revised International Prognostic Scoring System (IPSS-R) into five risk groups: very low, low, intermediate, high, and very high.

Results showed that cytogenetic abnormalities were present in 22% of the AA patients, indicating that abnormal cytogenetics in this population are not more frequent than in the general MDS population, where the rate is around 45%. Most of the AA patients fell into lower IPSS-R risk categories, with seven patients (38%) classified as very low-risk, eight (44%) as low-risk, one (5%) as intermediate-risk, and two (11%) as very high-risk. None of the patients were categorized as high-risk. The average hemoglobin level among the patients was 10.166 ± 2.53 g/dL, with a mean absolute neutrophil count of 1.51 ± 0.759 × 10^9/L, and a mean platelet count of 114.72 ± 51.488 × 10^9/L.

The findings suggest that the frequency of abnormal cytogenetics among AA patients with MDS is similar to or lower than that in the general population, with a notable concentration in the lower-risk IPSS-R categories.

Reference

Kaur N, Biswas R, Ojha VS, et al. Incidence of cytogenetic abnormalities in myelodysplastic syndrome in the African American population: a decade-long single-center real-world experience. Abstract #MDS-398. Presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology. September 4-7, 2024; Houston, Texas.

IPSS-M Improves Accuracy of MDS Survival Projection

The Molecular International Prognostic Scoring System (IPSS-M) is more prognostically accurate in MDS compared to the Revised IPSS (IPSS-R), according to a study presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology in Houston, Texas.

"In cases of discrepant risk classification, IPSS-M significantly improved prognostic assessment, particularly for high-risk IPSS-R cases with a low-risk mutational profile," wrote **Habibe Kurt, MD,** of Brigham and Women's Hospital in Boston, Massachusetts, and colleagues.

Habibe Kurt, MD

The investigators in this single-institution study calculated IPSS-R and IPSS-M scores for a cohort of 123 patients with MDS. The cohort was 38% female and had a median age of 74 years.

Assessed with the IPSS-R, 2% of the cohort had very-low-risk disease, 33% had low-risk disease, 23% had intermediate-risk disease, 23% had high-risk disease, and 19% had very high-risk disease. The range of median overall survival (OS) rates was 4.6 years for patients with very low-risk or low-risk disease to 0.7 years for patients with very high-risk disease.

Assessed with the IPSS-M, 33% of the cohort had very low-risk or low-risk disease, 7% had moderate low-risk disease, 11% had moderate high-risk disease, 19% had high-risk disease, and 30% had very high-risk disease. The range of median OS rates was 4.6 years for patients with very low-risk or low-risk disease to 0.9 years for patients with very high-risk disease.

The investigators determined that the IPSS-M had superior OS discrimination compared with the IPSS-R based on a Cox model Harrell's C statistic of 0.77 calculated for the former versus 0.68 for the latter. They commented that the local assay they used to evaluate the performance of the IPSS-M projections lacked *KMT2A*^{PTD} in 61% of patients, but that this did not compromise the superiority they observed.

"Using commercially available [next-generation sequencing] panels, even without identifying *KMT2A*^{PTD}, IPSS-M provided greater prognostic accuracy than IPSS-R," Dr. Kurt and colleagues wrote.

The IPSS-R classified 71 patients in the cohort as having very low-risk, low-risk, or intermediate-risk MDS, and 24% of those patients were reclassified by the IPSS-M as having high-risk or very high-risk disease. The patients with reclassified disease had markedly worse two-year OS, calculated as 86% for IPSS-M low-risk disease and 42% for high-risk disease ($P<.001$).

The IPSS-R classified 52 patients in the cohort as having high-risk or very high-risk MDS, and 8% of those patients were reclassified by the IPSS-M as having very low-risk, low-risk, or moderate low-risk disease. The two-year OS rate calculated for the patients with reclassified disease was 100%.

Reference

Kurt H, Chergui A, Omer M, et al. Improved risk stratification of MDS patients with IPSS-M: A single-institution experience. Abstract #MDS-663. Presented at the Twelfth Annual Meeting of the Society of Hematologic Oncology. September 4-7, 2024; Houston, Texas.

Regulatory Actions

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

Supplemental BLA Submitted for MM Treatment Combination

A supplemental Biologics License Application (BLA) was submitted to the US Food and Drug Administration (FDA) for the approval of a new indication for daratumumab and hyaluronidase-fihj (DARZALEX FASPRO®) combined with D-VRd (bortezomib, lenalidomide, and dexamethasone) for transplant-ineligible, newly diagnosed multiple myeloma (MM), according to a press release by Johnson & Johnson, the manufacturer of the therapy. The combination was previously indicated for transplant-eligible patients.

The new indication is based on results from the phase II CEPHEUS study, which compared the efficacy and safety of D-VRd and VRd. A total of 60.9% of patients achieved measurable residual disease (MRD) negativity with D-VRd, compared to 39.4% of patients with VRd (odds ratio [OR], 2.37; 95% CI, 1.58-3.55; $P<.0001$). D-VRd also reduced the risk of progression or death by 43% (hazard ratio, 0.57; 95% CI, 0.41-0.79; $P<.0005$). The complete response rate was 81.2% for D-VRd and 61.6% for VRd ($P<.0001$).

The safety profile of D-VRd was consistent with the known safety profiles for daratumumab and hyaluronidase-fihj and VRd.

"The subcutaneous daratumumab-based quadruplet regimen has compelling efficacy characterized by deep, durable responses and reduced risk of disease progression in the frontline population of patients not undergoing transplant, supporting the potential of this quadruplet to become a new regimen in this treatment setting," **Saad Z. Usmani, MD, FACP,** Chief of Myeloma Service at the Memorial Sloan Kettering Cancer Center and study investigator, said in the press release.

NMPA in China Approves Supplemental BLA for Relma-Cel Immunotherapy Injection in MCL

The National Medical Products Administration (NMPA) in China has approved the supplemental Biologic License Application (BLA) for relmacabtagene autoleucel (relma-cel) injection to treat relapsed or refractory mantle cell lymphoma (MCL) in adult patients.

Relma-cel is under development by JW Therapeutics and marketed under the trade name Carteyva for its oncology indications. It is an anti-CD19 autologous chimeric antigen receptor T-cell immunotherapy and the first such agent to be approved in China for the relapsed or refractory MCL clinical setting.

The data supporting the supplemental BLA for relma-cel injection came from a single-arm, multicenter clinical study conducted in China where 59 adults with relapsed or refractory MCL received relma-cel infusion following lymphodepleting chemotherapy. An impressive best objective response rate of 81.36% and best complete response rate of 67.8% was observed. Regarding grade 3 or worse adverse effects in the study cohort, the incidence of cytokine release syndrome was 6.8% and neurotoxicity was 6.8%.

"We are delighted to have a product that can deliver meaningful efficacy in this disease, nearly 70% of patients with [relapsed or refractory] MCL have achieved complete remission after treatment with [relma-cel], and the overall safety data demonstrated that the treatment was generally well-tolerated," stated **Sophia Yang,** Senior Vice President and Head of Regulatory, Research & Development at JW Therapeutics, in a press release.

Asciminib Receives Accelerated Approval for Chronic Phase Ph+ CML

Asciminib (Scemblix®) was granted accelerated approval by the FDA for the treatment of newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP), according to a press release from Novartis, the manufacturer of the drug.

The approval is based on results of the phase III ASC4FIRST trial, which evaluated the efficacy of asciminib compared with imatinib alone and other investigator-selected tyrosine kinase inhibitors (TKIs) such as nilotinib, dasatinib, and bosutinib. Asciminib showed superior molecular response rates at week 48 compared to imatinib alone (69% vs 40%, respectively; 95% CI, $P<.001$) and compared to investigator-selected TKIs (68% vs 49%, respectively; 95% CI, $P<.001$).

The safety profile of asciminib was consistent with previous studies. The most common adverse events were musculoskeletal pain, rash, fatigue, upper respiratory tract infection, headache, abdominal pain, and diarrhea.

"While there are a range of effective TKIs currently available for newly diagnosed patients, clinicians frequently have had to weigh sacrificing either efficacy or tolerability," **Jorge Cortes, MD,** Director of the Georgia Cancer Center and study investigator, said in the press release. "In the first-of-its-kind ASC4FIRST trial, [asciminib] achieved impressive results across all three parameters of efficacy, safety, and tolerability versus all standard of care TKIs. This [asciminib] data has the potential to be practice changing."

Selinexor Approved in Thailand for Two Adult MM Indications

The Thailand Food and Drug Administration approved a New Drug Application (NDA) for commercialization of selinexor (XPOVIO®) to treat adult patients with previously treated MM, according to a press release from Antengene, the manufacturer of the drug.

The approval of selinexor was for two indications in this patient population. The first was in combination therapy with bortezomib and dexamethasone. The second was in combination with dexamethasone for disease refractory to two immunomodulatory agents, two proteasome inhibitors, and an anti-CD38 monoclonal antibody.

Selinexor has previously received NDA approvals for several indications in Australia, China, Hong Kong, Macau, Malaysia, Singapore, South Korea, and Taiwan, with a submitted NDA expected to be approved in Indonesia in the second half of 2024. It was also approved for health insurance coverage in Australia, China, Singapore, and South Korea.

"Leveraging the drug's novel mechanism of action, Antengene is currently developing multiple combination regimens of [selinexor] for the treatment of various indications including myelofibrosis, and endometrial cancer," Antengene stated in a press release.

Multiple clinical studies are currently underway in China to evaluate this agent for such indications, and three of these studies Antengene is conducting jointly with Karyopharm Therapeutics Inc.

Selinexor Approved for Third Malignancy Indication in South Korea

The South Korean Ministry of Food and Drug Safety approved a new supplemental NDA for use of selinexor in combination with bortezomib and dexamethasone to treat MM in adults who received at least one prior therapy.

This is the third indication for which selinexor has received regulatory approval in South Korea. The agent is already approved for use in combination with dexamethasone to treat adults with relapsed or refractory MM and as monotherapy for adults with relapsed or refractory diffuse large B-cell lymphoma.

"This recent approval for [selinexor] in South Korea will bring another innovative therapy to the clinical management of multiple myeloma patients in South Korea, benefiting countless patients and families," Antengene officials stated in a press release.

Editor's Picks

In each issue of Blood Cancers Today*, we take a closer look at a particular topic in hematologic malignancies. This month, Executive Editor* ***Elias Jabbour, MD,*** *Professor of Medicine in the Department of Leukemia at the University of Texas MD Anderson Center, highlights recent research in acute myeloid leukemia. Visit bloodcancerstoday.com to stay up to date on the latest news in each area of hematologic oncology.*

Elias Jabbour, MD

ACUTE MYELOID LEUKEMIA

Ivosidenib, Venetoclax, Plus Azacitidine Shows Promise in *IDH1*-Mutated Myeloid Malignancies

The triplet regimen ivosidenib and venetoclax plus azacitidine is effective and well-tolerated in patients with *IDH1*-mutated myeloid malignancies, according to a phase Ib/II study published in *Blood Cancer Discovery*.

This triplet "appears to overcome resistance mechanisms observed with single-agent [isocitrate dehydrogenase]-inhibitor use, with high [measurable residual disease (MRD)]-negative remission rates," wrote **Curtis A Lachowiez, MD,** of the University of Texas MD Anderson Cancer Center, and colleagues.

The study involved 31 patients in four cohorts who received ivosidenib plus venetoclax with or without azacitidine. The composite complete remission rate calculated for patients who received the triplet was 90%, which was higher than the 83% of patients who received the doublet ivosidenib plus venetoclax.

Why I chose this research:

"The combination of ivosidenib, venetoclax, and azacitidine appears safe and effective in patients with IDH1*-mutated malignancies and appears to overcome resistance mechanisms observed with single-agent IDH-inhibitor use. This combination induces high rates of MRD-negative remission."*

Sixteen patients had evaluable MRD, and 63% attained MRD-negative remission. MRD-negative rates were greater among the patients who received triplet therapy than in those who received the doublet, at 75% versus 50%, respectively (P=.60). However, this finding was not considered statistically significant.

Both the triplet and doublet were well-tolerated by patients, with 91% of the adverse events in the total study cohort being grade 1 or 2. The maximum tolerated dose was not reached.

The study's cytogenetic and molecular analysis findings demonstrated that "[p]atients with signaling gene mutations appeared to particularly benefit from the triplet regimen. Longitudinal single-cell proteogenomic analyses linked co-occurring mutations, antiapoptotic protein expression, and cell maturation to therapeutic sensitivity of IDH1-mutated clones," the investigators wrote.

Translational analyses in the study also identified several resistance mechanisms behind relapsed disease. The authors consider these mechanisms, such as mutations in signaling pathways, transcription factors, and tumor suppressor genes, to merit further investigation as potential avenues to manage treatment-resistant *IDH1*-mutated myeloid malignancies.

Reference

Lachowiez CA, Loghavi S, Zeng Z, et al. A phase Ib/II study of ivosidenib with venetoclax ± azacitidine in *IDH1*-mutated myeloid malignancies. *Blood Cancer Discov*. 2023;4(4):276-293. doi.org/10.1158/2643-3230.BCD-22-0205

Remission, Safety Favorable With Revumenib for *KMT2A*-Rearranged Acute Leukemia

Revumenib-targeted therapy produces favorable remission rates and is well-tolerated in patients with relapsed or refractory menin-lysine methyltransferase 2A-rearranged (*KMT2Ar*) acute leukemia. This was the interim analysis finding from the phase II portion of the international phase I/II AUGMENT-101 trial, reported in the *Journal of Clinical Oncology*.

"Treatment with the menin inhibitor revumenib provided clinical benefit and a low rate of discontinuation for [adverse events (AEs)] indicating a predictable safety profile," wrote **Ghayas C. Issa, MD,** of the MD Anderson Cancer Center, and colleagues.

Why I chose this research:

"Revumenib therapy induced an ORR of 63.2% with a complete remission (CR) plus CR with partial hematologic recovery rate of 22.8% in relapsed or refractory KMT2A*-rearranged acute leukemia. The intervention had a predictable safety profile with grade 3 or higher differentiation syndrome in 16% and QTc prolongation in 13.8% of patients."*

The trial enrolled 94 patients (median age, 37 years). All patients had relapsed or refractory *KMT2Ar* acute leukemia or acute myeloid leukemia (AML) with nucleophosmin 1 (*NPM1*) mutation. They received oral revumenib once every 12 hours, in 163 mg doses or 95 mg/m^2 if patient weight was less than 40 kg, as well as a cytochrome P450 inhibitor in 28-day cycles.

Efficacy was evaluable in 57 patients, all of whom had centrally confirmed *KMT2Ar* disease, and their overall response rate was 63.2%. Their rate of complete remission with partial hematologic recovery was 22.8%, which exceeded the null hypothesis of 10% (P=.0036). Among the 22 patients in whom measurable residual disease (MRD) could be evaluated, 15 had none detected.

The researchers evaluated safety results for all patients with confirmed *KMT2Ar* disease who underwent treatment. Regarding the prevalence of grade 3 or worse severity AEs, 37.2% experienced febrile neutropenia, 16.0% had differentiation syndrome, and 13.8% had QTc prolongation.

The separate trial cohort of patients with AML with *NPM1* mutation is ongoing.

Reference

Issa GC, Aldoss I, Thirman MJ, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). *J Clin Oncol.* 2024. doi:10.1200/JCO.24.00826

HemOnc Happenings

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

International Myeloma Society Presents Awards at 21st Annual Meeting

The International Myeloma Society (IMS) presented annual awards to three multiple myeloma (MM) clinicians and researchers during the 21st Annual Meeting held September 25-28 in Rio de Janeiro, Brazil.

Photos Courtesy of @Myeloma_Society on X

Waldenström Lifetime Achievement Award

Thierry Facon, MD, a Professor of Hematology in the Department of Hematology at Lille University Hospital, received the Waldenström Lifetime Achievement Award for his long-term research contributions to the field of MM.

Dr. Facon's recent research focuses on quadruplet therapy regimens for MM. He is also a founder, member, and administrator of the *Fondation Française pour la Recherche contre le Myélome et les Gammapathies,* which enables scientists and students to conduct research programs in laboratories in France or abroad, according to the European Multiple Myeloma Academy.

Since 1989, the award has honored the late Jan Waldenström (1906-1996), who the IMS describes as "a pioneer in treating blood cancers". Dr. Waldenström served as Professor of Practical Medicine at the University of Lund and Physician-in-Chief at Malmö General Hospital. He is known for creating "concepts of monoclonal and polyclonal hypergamma globulinemia as a term for malignant and for numerous infectious and inflammatory and autoimmune diseases," according to his biography at Lund University.

Past award recipients include **Sundar Jagannath, MD,** of the Icahn School of Medicine at Mount Sinai in 2023; **Peter Sonneveld, MD, PhD,** of the Erasmus University of Rotterdam in 2022; and **S. Vincent Rajkumar, MD,** of the Mayo Clinic in Rochester, Minnesota, in 2021.

Ken Anderson Basic and Translational Research Award

Hermann Einsele, MD, FRCP, a Professor of Internal Medicine and Director of the Department of Internal Medicine II at the University Hospital Würzburg, Germany, received the Ken Anderson Basic and Translational Research Award. Dr. Einsele's recent research focuses on chimeric antigen receptor T-cell therapy and immunotherapy for MM.

The award honors the contributions of **Ken Anderson, MD,** Program Director of the Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute, to translational MM research. His research is credited for identifying and validating targets in the tumor cell, leading to US Food and Drug Administration approval of novel targeted and immune MM therapies, according to his faculty profile at Dana-Farber.

"I am proud to receive the award named after Ken Anderson, who in the last four decades has focused his research in the lab and in the clinic on [MM]," Dr. Einsele said. "What always impressed me about Ken Anderson's work was that he always aimed to benefit the patients by not only improving the treatment of [MM], but also by making treatments better tolerable for patients to allow them to experience a good quality of life."

Past award recipients include **Hervé Avet-Loiseau, MD, PhD,** of the University Cancer Center of Toulouse in 2023; **Noopur Raje, MD,** of Massachusetts General Hospital in 2022; and **Paola Neri, PhD, MD,** of the University of Calgary in 2021.

Bart Barlogie Clinical Investigator Award

Sagar Lonial, MD, FACP, Chief Medical Officer of the Winship Cancer Institute of Emory University, received the Bart Barlogie Clinical Investigator Award for his outstanding research in MM. The award honors **Bart Barlogie, MD, PhD,** Professor of Medicine the Icahn School of Medicine at Mount Sinai.

Dr. Lonial's research interests include immuno-therapy, plasma cell disorders, and evaluating novel combinations in MM and lymphoma, according to his faculty profile at Emory University. He is also a lead member of the bone marrow transplantation team and clinical trials team.

"Receiving the Bart Barlogie Clinical Investigator Award is a tremendous honor given the huge number of contributions Dr. Barlogie made to the field," Dr. Lonial said. "I am grateful for all the support and guidance from our team as well as many in the global myeloma community who are constantly partnering together to make advances for our patients."

Dr. Barlogie introduced the multidrug regimen Total Therapy, the first curative therapy for MM, and founded the Winthrop P. Rockefeller Cancer Institute's University of Arkansas for Medical Sciences Myeloma Center Program in 1989.

Past award recipients include **Shaji Kumar, MD,** of the Mayo Clinic in Rochester, Minnesota, in 2023; **María-Victoria Mateos, MD, PhD,** of the University of Salamanca, Spain, in 2022; and **Saad Usmani, MD,** of the Memorial Sloan Kettering Cancer Center, New York, in 2021.

Immunotherapy Researcher Honored for 50 Years of Service at the NCI

Steven Rosenberg, MD, PhD

Steven Rosenberg, MD, PhD, received a milestone award for 50 years of service at the Center for Cancer Research National Cancer Institute (NCI) in Bethesda, Maryland. Since 1974, he has served as Chief of the Surgery Branch at the NCI after completing a residency training in surgery at the Peter Bent Brigham Hospital. He also serves as a Senior Investigator and Head of the Tumor Immunology Section at the NCI.

Dr. Rosenberg's areas of expertise include immunology and immunotherapy, tumor-infiltrating lymphocytes, T-cell receptors, and gene therapy. He is credited with pioneering the development of gene therapy and successfully inserting foreign genes into humans for the first time, according to the NCI.

He was also the first to determine that genetically engineered chimeric antigen receptor (CAR) T-cells are effective in treating B-cell malignancies. His studies on the adoptive transfer of genetically modified lymphocytes, utilizing CARs or conventional T-cell receptors, has also led to the regression of metastatic cancer in patients with lymphomas and solid cancers.

In addition to his roles at the NCI, Dr. Rosenberg serves as Professor of Surgery at the Uniformed Services University of Health Sciences and at the George Washington University School of Medicine and Health Sciences in Washington, DC, and a Professor in the Department of Laboratory Medicine at the Karolinska Institutet in Stockholm, Sweden.

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AML is a complex, multi-driver disease.[1]

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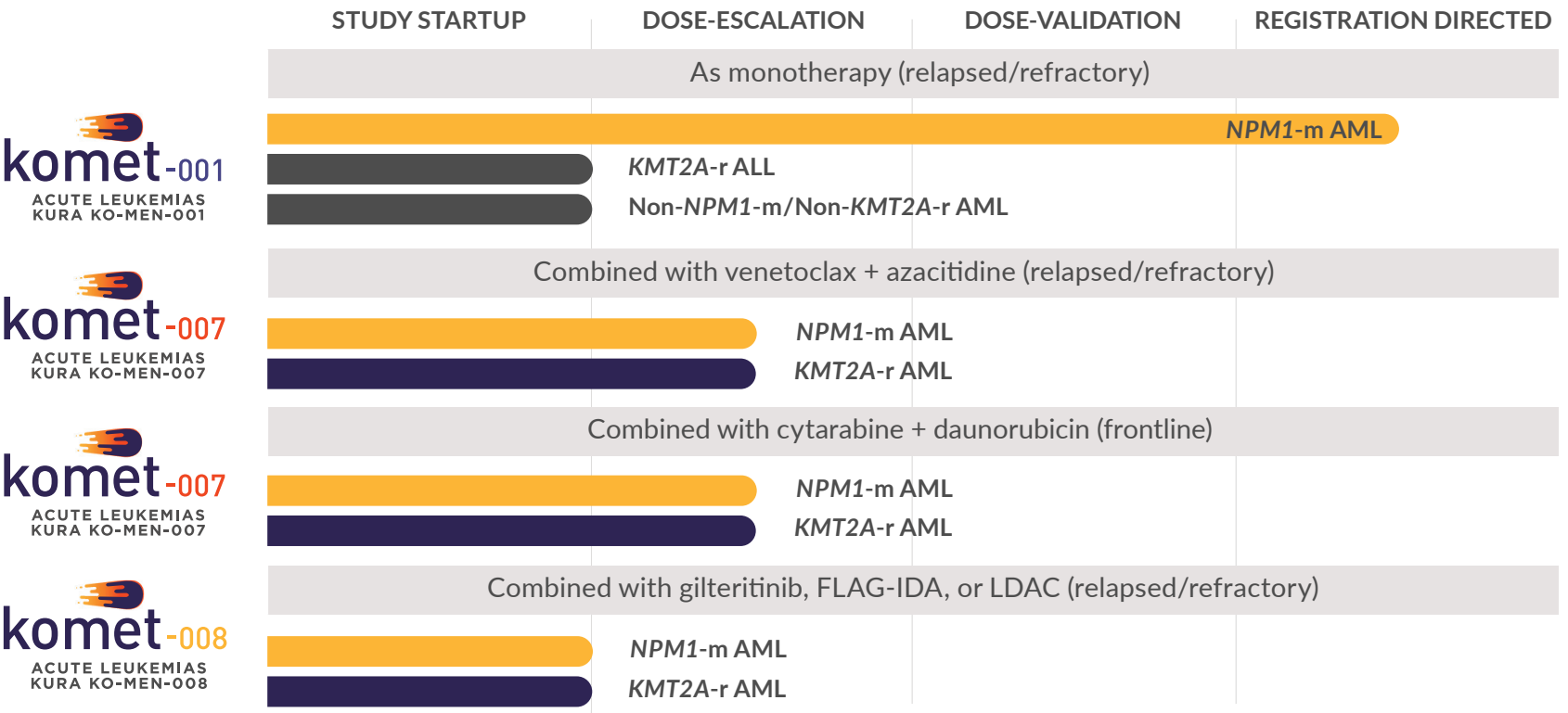
ZIFTOMENIB CLINICAL TRIALS FOR ACUTE LEUKEMIAS



Ziftomenib is an investigational drug candidate that has not received FDA approval.

Trial status as of June 2024.

AML, acute myeloid leukemia; FDA, US Food and Drug Administration; FLAG-IDA, fludarabine, cytarabine, granulocyte-colony stimulating factor, idarubicin; KMT2A, histone-lysine N-methyltransferase 2A gene; LDAC, low-dose cytarabine; -m, mutated; NPM1, nucleophosmin 1 gene; -r, rearranged.

1. Kumar CC. Genetic abnormalities and challenges in the treatment of acute myeloid leukemia. Genes Cancer [italics]. 2011;2(2):95-107. 2. Klossowski S, Miao H, Kempinska K, et al. Menin inhibitor MI-3454 induces remission in MLL1-rearranged and NPM1-mutated models of leukemia. *J Clin Invest*. 2020;130(2):981-997. 3. Prata PH, Bally C, Prebet T, et al. NPM1 mutation is not associated with prolonged complete remission in acute myeloid leukemia patients treated with hypomethylating agents. *Haematologica*. 2018;103(10):e455-e457. 4. Collins CT and Hess JL. *Curr Opin Hematol*. 2016;23(4): 354–361.

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