

The ASPEN Trial

The only Head-to-Head Phase 3 Trial of BTK Inhibitors in Waldenström's macroglobulinemia (WM)

Waldenström's macroglobulinemia (WM) is a rare, incurable blood cancer found in the bone marrow. In the United States and Canada, the incidence rate of WM is about five cases per million people per year. Bruton's tyrosine kinase (BTK) inhibition has emerged as a promising strategy for treating WM, particularly in patients with MYD88 gene mutations.^{1,2}

BRUKINSA® (zanubrutinib) is a highly selective BTK inhibitor designed to provide deep and durable response.^{3,4}

I. WHAT IS THE ASPEN TRIAL?

The ASPEN Trial is a pivotal Phase 3 randomized, open-label, multicenter study evaluating BRUKINSA compared to ibrutinib in patients with relapsed/refractory or treatment-naïve Waldenström's macroglobulinemia (WM).^{3,4}

ASPEN was the first randomized Phase 3 study comparing two BTK inhibitors in any indication and is the largest prospective randomized Phase 3 study in WM.^{3,4}

2. TRIAL DESIGN^{4,5}

COHORT 1

201 PATIENTS WITH MYD88 MUTATION

ARM A:

102 patients, randomized to receive BRUKINSA **160 mg twice daily**

83

RELAPSED/
REFRACTORY
PATIENTS

19

TREATMENT
NAÏVE
PATIENTS

ARM B:

99 patients, randomized to receive ibrutinib **420 mg once daily**

81

RELAPSED/
REFRACTORY
PATIENTS

18

TREATMENT
NAÏVE
PATIENTS

COHORT 2

28 PATIENTS WITH MYD88 WILD-TYPE OR MUTATION UNKNOWN

ARM C:

non-randomized, all patients to receive **BRUKINSA 160 mg twice daily**; previous trials showed poor responses to ibrutinib therapy for patients with these mutations

Primary Efficacy Endpoint: Proportion of participants achieving a very good partial response (VGPR) in Cohort 1 as assessed by an independent review committee per modified Sixth International Workshop on Waldenström's Macroglobulinemia (IWWM-6) response criteria (Trean 2015).⁴

3. RESULTS

Although the trial did not achieve statistical significance for the primary efficacy endpoint, BRUKINSA was associated with a numerically higher VGPR rate. No patient in either arm achieved a CR.^{3,4}



ARM A³
28.4%

CR + VGPR
95% CI [20-38]



ARM B³
19.2%

CR + VGPR
95% CI [12-28]

p=0.092

Data cut-off, August 31, 2019;
19.4 months median follow-up



BRUKINSA demonstrated fewer AEs leading to treatment discontinuation, as well as lower frequency of atrial fibrillation and flutter or major bleeding, compared to ibrutinib.^{3,4}

	ARM A ³	ARM B ³
AEs ≥Grade 3 / Grade 5	58.4%/1.0%	63.3%/4.1%
AEs leading to discontinuation	4.1%	9.2%
Atrial fibrillation/flutter	2.0%/0%	15.3%/4.1%
Hypertension	10.9%/5.9%	17.3%/12.2%
Major bleeding*	5.9%/5.9%	9.2%/8.2%
Neutropenia**	29.7% /19.8%	13.3%/8.2%

Data cut-off, August 31, 2019; 19.4 months median follow-up.

*Includes grade >3 hemorrhage and central nervous system bleeding of any grade.

**Includes the Medical Dictionary for Regulatory Activities-preferred term "neutrophil count decreased" in 1 and 4 patients in the ibrutinib and zanubrutinib arms, respectively.

The most common (reported in >20% of patients) AEs among BRUKINSA patients were neutropenia (29.7%), upper respiratory infection (24%), and diarrhea (20.8%). Overall, 40% of BRUKINSA patients experienced >1 serious AE.⁴ The most common serious AEs for BRUKINSA were neutropenia (3 patients), febrile neutropenia (3), influenza (3), pyrexia (2), sepsis (2), pleural effusion (2), anemia (2), lower respiratory tract infection (2), thrombocytopenia (2) and basal cell carcinoma (2).⁴

BRUKINSA is approved by the U.S. Food and Drug Administration (FDA) and Health Canada for the treatment of adult patients with WM.

DOSING AND ADMINISTRATION

The recommended dose of BRUKINSA is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity. BRUKINSA capsules can be taken with or without food.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 3.0% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients treated with BRUKINSA monotherapy. Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 28% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred. Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.



Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (28%), thrombocytopenia (11%) and anemia (7%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 4% of patients. Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Secondary Primary Malignancies

Second primary malignancies have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (4%), melanoma (1.4%), and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter were reported in 2.8% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events of atrial fibrillation and atrial flutter were reported in 0.8% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity

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

Adverse reactions

The most common adverse reactions in > 20% of patients who received BRUKINSA were neutrophil count decreased (56%), upper respiratory tract infection (49%), platelet count decreased (44%), rash (35%), hemorrhage (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), bruising (25%), diarrhea (23%), pneumonia (22%), and cough (21%).

Drug Interactions

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

CYP3A Inducers: Avoid coadministration with moderate or strong CYP3A inducers.

Specific Populations

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

Please see full U.S. Prescribing Information at www.beigene.com/PDF/BRUKINSAUSPI.pdf and Patient Information at www.beigene.com/PDF/BRUKINSAUSPPI.pdf.

¹Treon, et al. Genomic landscape of Waldenström Macroglobulinemia and Its Impact on Treatment Strategies. *Journal of Clinical Oncology*. February 2020. 38:1198-1208.

²Waldenström's Macroglobulinemia Foundation of Canada. Newly Diagnosed. Accessed February 2021. Available at <https://www.wmfca.ca/about-wm/newly-diagnosed/>.

³Tam, et al. ASPEN: Results of a Phase 3 Randomized Trial of Zanubrutinib versus Ibrutinib for Patients with Waldenström Macroglobulinemia (WM). Presented at the American Society of Clinical Oncology, May 2020.

⁴Tam, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. October 2020. 136(18): 2038-2050.

⁵Dimopoulos, et al. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. *Blood Advances*. December 2020. 4(23): 6009-6018.

