ASPEN: Long-term follow-up results of a phase 3 randomized trial of zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia

Session SCO 01
Lymphomas

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BACKGROUND

- Zanubrutinib is a potent, selective, and irreversible next-generation BTK inhibitor designed to maximize BTK occupancy and minimize inhibition of off-target kinases[1]
- Zanubrutinib has demonstrated a complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes[2]
- Zanubrutinib has shown equipotency against BTK compared with ibrutinib.[1] Zanubrutinib has high selectivity for BTK and minimal off-target inhibition of TEC- and EGFR-family kinases[1]
- Favorable drug interaction properties allow zanubrutinib to be co-administered with strong or moderate CYP3A inhibitors (eg, antifungals) at a reduced dose, plus proton pump inhibitors, acid-reducing agents, and antithrombotic agents[3,4]

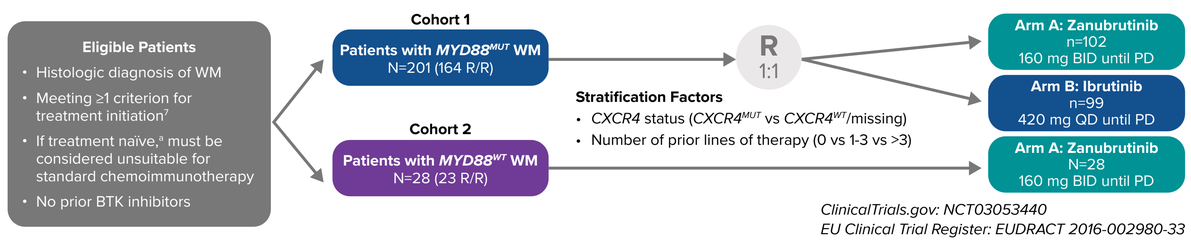
OBJECTIVES

- **Primary Objective:** To compare the efficacy of zanubrutinib vs ibrutinib in patients with activating *MYD88*^{MUT} WM; primary endpoint was the CR+VGPR rate
- **Secondary Objectives:** To further compare the efficacy, clinical benefit, and antilymphoma effects of zanubrutinib vs ibrutinib, and to evaluate safety and tolerability of zanubrutinib vs ibrutinib as measured by the incidence, timing, and severity of treatment-emergent AEs according to NCI CTCAE v4.03
- **Exploratory Objectives:** To evaluate the efficacy and safety of zanubrutinib in patients with *MYD88*^{WT} WM and the efficacy of zanubrutinib vs ibrutinib according to *CXCR4* gene mutation in patients with *MYD88*^{MUT} WM

METHODS

- ASPEN is an open-label, multicenter, randomized phase 3 study of zanubrutinib vs ibrutinib in patients with WM (**Figure 1**)

Figure 1: ASPEN Study Design: Zanubrutinib vs Ibrutinib in WM[5,6]



ClinicalTrials.gov: NCT03053440
EU Clinical Trial Register: EUDRACT 2016-002980-33

[a]Up to 20% of the overall population.

Cohort Assignments

- Bone marrow *MYD88* and *CXCR4* mutations were assessed centrally at study entry (NeoGenomics Laboratory, Aliso Viejo)[8,9]
  - The *MYD88*^{MUT} assay includes a wild-type allele-blocking approach (LOD, 0.5%)[7,8] and detects all mutations in the region encompassing amino acid Alanine^{260}-Proline^{278}, which includes the predominant mutation in WM, *MYD88*^{L265P}
  - Patients were assigned to cohort 1 (*MYD88*^{MUT}; randomized) or exploratory cohort 2 (*MYD88*^{WT} or *MYD88* unknown; nonrandomized)

CXCR4 Mutation Detection

- Standard polymerase chain reaction/bidirectional Sanger sequencing assay to detect *CXCR4*^{WHIM} mutation was performed at screening. Randomization in cohort 1 was stratified according to *CXCR4* mutation status (*CXCR*^{WHIM} vs *CXCR*^{WT}/missing; LOD, 10%-15%)
- *CXCR4* mutation status was assessed retrospectively by NGS using residual DNA samples or duplicate bone marrow biopsy sample (LOD, 0.25%)[7-9]

Response Assessments

- Responses were assessed according to response criteria in the NCCN® WM guidelines and modified Owen criteria[9] as assessed by the independent review committee (primary analysis) and by the investigator
- Efficacy endpoints: response rates (CR+VGPR, major and overall responses), duration of response, time to response, time to next treatment, PFS, and OS

RESULTS

- Both arms in cohort 1 were balanced except for patients aged >75 years, patients with *CXCR4*^{MUT} by NGS, and patients with hemoglobin ≤110 g/L, which were higher on the zanubrutinib arm (**Table 1**)
- In cohort 2, patients aged >75 years were more frequent (42.9%)

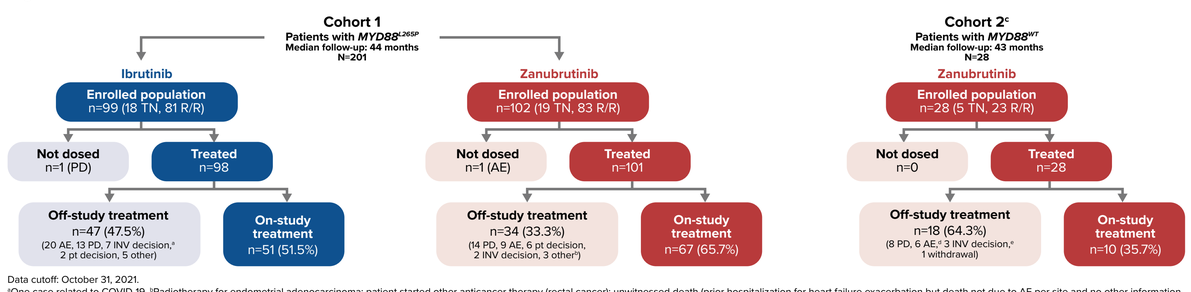
Table 1: ASPEN: Baseline Demographics and Disease Characteristics

Characteristics	Cohort 1 Ibrutinib (n=99)	Cohort 1 Zanubrutinib (n=102)	Cohort 2 Zanubrutinib (N=28)
Age, years median (range)	70 (38-90)	70 (45-87)	72 (39-87)
>65 years, n (%)	**70 (70.7)**	61 (59.8)	19 (67.9)
>75 years, n (%)	22 (22.2)	**34 (33.3)**	12 (42.9)
Sex, n (%)			
Male	65 (65.7)	69 (67.6)	14 (50.0)
Prior lines of therapy, n (%)			
0	18 (18.2)	19 (18.6)	5 (17.9)
1-3	74 (74.7)	76 (74.5)	20 (71.4)
>3	7 (7.1)	7 (6.9)	3 (10.7)
Genotype by NGS, n (%)			
CXCR4^{WT}	72 (72.7)	65 (63.7)	27 (96.4)
CXCR4^{MUT}	20 (20.2)	**33 (32.4)**	1 (3.6)
Unknown	7 (7.1)	4 (3.9)	0 (0.0)
IPSS WM, n (%)			
Low	13 (13.1)	17 (16.7)	5 (17.9)
Intermediate	42 (42.4)	38 (37.3)	11 (39.3)
High	44 (44.4)	47 (46.1)	12 (42.9)
Hemoglobin ≤110 g/L, n (%)	53 (53.5)	**67 (65.7)**	15 (53.6)
Baseline IgM (g/L, central lab), median (range)	34.2 (2.4-108.0)	31.8 (5.8-86.9)	28.5 (5.6-73.4)
Bone marrow involvement (%), median (range)	60 (0-90)	60 (0-90)	22.5 (0-50)
Extramedullary disease by investigator, n (%)	66 (66.7)	63 (61.8)	16 (57.1)

Bold text indicates >10% difference between arms in cohort 1..

- In cohort 1, 51 (51.5%) patients treated with ibrutinib and 67 (65.7%) patients treated with zanubrutinib remained in the study (**Figure 2**); main reasons for discontinuation were PD (n=14 and n=13) and AEs (n=9 and n=20) for zanubrutinib and ibrutinib, respectively
- In cohort 2, 10 (35.7%) patients treated with zanubrutinib remained in the study; main reasons for discontinuation were progressive disease (n=8) and AEs (n=6)

Figure 2: Patient Disposition

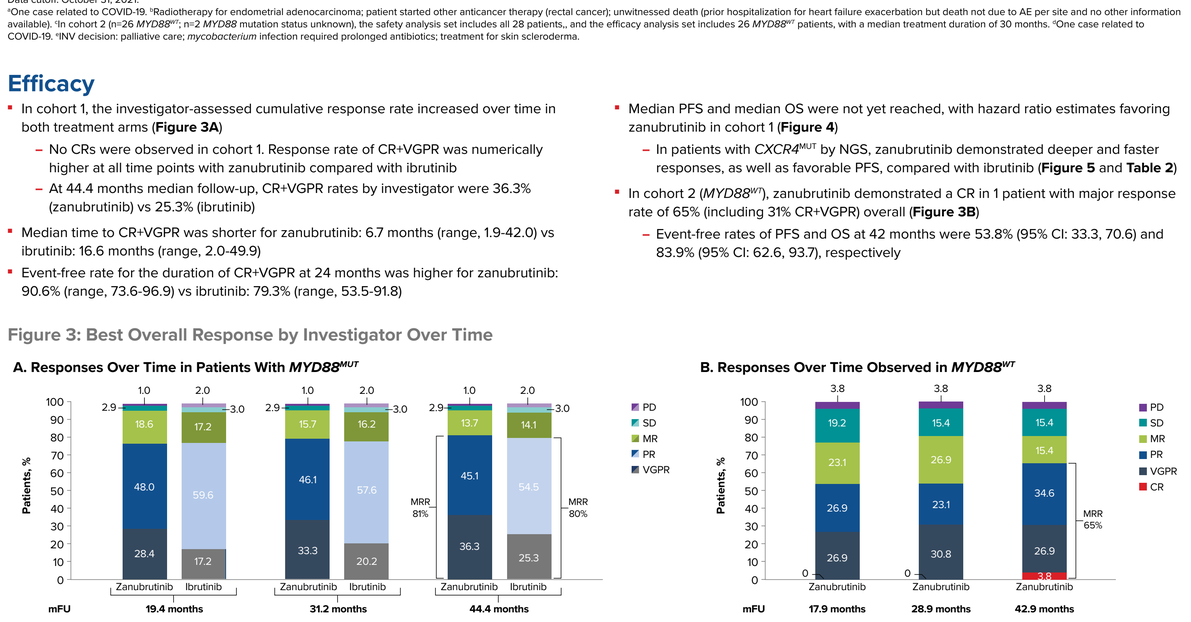


Data cutoff: October 31, 2021.
[a]One case related to COVID-19. [b]Radiotherapy for endometrial adenocarcinoma; patient started other anticancer therapy (rectal cancer); unwitnessed death (prior hospitalization for heart failure exacerbation but death not due to AE per site and no other information available). [c]In cohort 2 (n=26 *MYD88*^{WT}; n=2 *MYD88* mutation status unknown), the safety analysis set includes all 28 patients,, and the efficacy analysis set includes 26 *MYD88*^{WT} patients, with a median treatment duration of 30 months. [d]One case related to COVID-19. [e]INV decision: palliative care; *mycobacterium* infection required prolonged antibiotics; treatment for skin scleroderma.

Efficacy

- In cohort 1, the investigator-assessed cumulative response rate increased over time in both treatment arms (**Figure 3A**)
  - No CRs were observed in cohort 1. Response rate of CR+VGPR was numerically higher at all time points with zanubrutinib compared with ibrutinib
  - At 44.4 months median follow-up, CR+VGPR rates by investigator were 36.3% (zanubrutinib) vs 25.3% (ibrutinib)
- Median time to CR+VGPR was shorter for zanubrutinib: 6.7 months (range, 1.9-42.0) vs ibrutinib: 16.6 months (range, 2.0-49.9)
- Event-free rate for the duration of CR+VGPR at 24 months was higher for zanubrutinib: 90.6% (range, 73.6-96.9) vs ibrutinib: 79.3% (range, 53.5-91.8)
- Median PFS and median OS were not yet reached, with hazard ratio estimates favoring zanubrutinib in cohort 1 (**Figure 4**)
  - In patients with *CXCR4*^{MUT} by NGS, zanubrutinib demonstrated deeper and faster responses, as well as favorable PFS, compared with ibrutinib (**Figure 5** and **Table 2**)
- In cohort 2 (*MYD88*^{WT}), zanubrutinib demonstrated a CR in 1 patient with major response rate of 65% (including 31% CR+VGPR) overall (**Figure 3B**)
  - Event-free rates of PFS and OS at 42 months were 53.8% (95% CI: 33.3, 70.6) and 83.9% (95% CI: 62.6, 93.7), respectively

Figure 3: Best Overall Response by Investigator Over Time



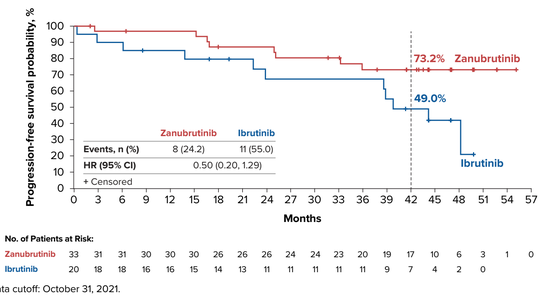
Data cutoff: October 31, 2021.

Figure 4: Progression-Free and Overall Survivals in ITT population (Cohort 1)

Data cutoff: October 31, 2021.
[a]By investigator assessment.

RESULTS (cont.)

Figure 5. Progression-Free Survival in Patients With *CXCR4*^{MUT}



Data cutoff: October 31, 2021.

Table 2: Response Assessment by *CXCR4* Status[a]

	CXCR4^{MUT} Ibrutinib (n=20)	CXCR4^{MUT} Zanubrutinib (n=33)	CXCR4^{WT} Ibrutinib (n=72)	CXCR4^{WT} Zanubrutinib (n=65)
VGPR or better	2 (10.0)	**7 (21.2)**	22 (30.6)	**29 (44.6)**
Major response	13 (65.0)	**26 (78.8)**	61 (84.7)	54 (83.1)
Overall response	19 (95.0)	30 (90.9)	68 (94.4)	63 (96.9)
Time to major response, median (months)	6.6	3.4	2.8	2.8
Time to VGPR, median (months)	31.3	11.1	11.3	6.5

Bold text indicates >10% difference between arms. Data cutoff: October 31, 2021.
[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.

Long-Term Safety and Tolerability

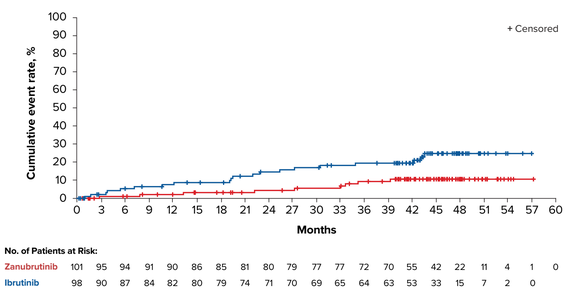
- Zanubrutinib when compared with ibrutinib had fewer AEs leading to death, treatment discontinuation, and dose reduction (**Table 3** and **Figure 6**)
  - Most common AEs that led to discontinuation were cardiac disorder and infection (4% each) with ibrutinib vs second malignancy (4%) with zanubrutinib (**Table 3**)
- The profile of AEs of interest favored zanubrutinib compared with ibrutinib (**Table 4**, **Table 5**, and **Figure 7**)
  - The prevalence of atrial fibrillation, hypertension, and bleeding were lower in the zanubrutinib arm at all time intervals
  - Neutropenia occurred early, and prevalence decreased over time for patients receiving zanubrutinib
  - Prevalence of infection decreased over time and to a greater extent in the zanubrutinib arm
- A similar safety profile for zanubrutinib in cohort 1 was observed in cohort 2

Table 3: Overall Safety Summary

Category, n (%)	Cohort 1 Ibrutinib (n=98)	Cohort 1 Zanubrutinib (n=101)	Cohort 2 Zanubrutinib (N=28)
Patients with ≥1 AE	98 (100.0)	100 (99.0)	26 (92.9)
Grade ≥3	71 (72.4)	75 (74.3)	20 (71.4)
Serious	49 (50.0)	57 (56.4)	14 (50.0)
AE leading to death	5 (5.1)[a]	3 (3.0)[b]	3 (10.7)[c]
AE leading to treatment discontinuation	20 (20.4)[d]	9 (8.9)[e]	6 (21.4)[f]
AE leading to dose reduction	26 (26.5)	16 (15.8)	2 (7.1)
AE leading to dose held	62 (63.3)	63 (62.4)	18 (64.3)
COVID-19–related AE	4 (4.1)	4 (4.0)	2 (7.1)

Data cutoff: October 31, 2021.
[a]Cardiac failure acute, death (unexplained), pneumonia, sepsis (n=2). [b]Cardiomegaly (cardiac arrest after plasmapheresis), metastatic malignant melanoma, subdural hematoma (after a fall). [c]Cardiac arrest, COVID-19 infection, lymphoma transformation. [d]Cardiac disorders (n=4, includes 2 due to atrial fibrillation), infection and infestations (n=4, pneumonia and sepsis, 2 each), respiratory, thoracic and mediastinal disorders (n=3), second malignancy (n=3), blood and lymphatic system disorders (n=2), renal and urinary disorders (n=1), death of unknown cause (n=1), drug-induced liver injury (n=1), hepatitis (n=1). [e]Second malignancy (n=4, includes breast cancer, metastatic melanoma, multiple myeloma, and myelodysplastic syndrome, 1 each), cardiomegaly (n=1), drug-induced liver injury (n=1), neutropenia (n=1), subdural hemorrhage (n=1), worsening of chronic kidney disease (n=1). [f]Cardiac arrest, COVID-19 infection, diarrhea, hepatitis B infection, squamous cell carcinoma of lung, subdural hemorrhage (after a fall).

Figure 6: Time to Treatment Discontinuations Due to AEs (Cohort 1)



Data cutoff: October 31, 2021.

Table 4. Most Common AEs (Cohort 1)

AEs,[a] n (%)	All grades (≥20%) Ibrutinib (n=98)	All grades (≥20%) Zanubrutinib (n=101)	Grade ≥3 (≥5%) Ibrutinib (n=98)	Grade ≥3 (≥5%) Zanubrutinib (n=101)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Upper respiratory tract infection	32 (32.7)	33 (32.7)	1 (1.0)	0
Muscle spasms*	**28 (28.6)***	12 (11.9)	1 (1.0)	0
Contusion	27 (27.6)	19 (18.8)	0	0
Arthralgia	24 (24.5)	24 (23.8)	0	3 (3.0)
Hypertension	24 (24.5)	15 (14.9)	**19 (19.4)**	10 (9.9)
Peripheral edema	21 (21.4)	18 (17.8)	0	0
Epistaxis	21 (21.4)	17 (16.8)	0	1 (1.0)
Atrial fibrillation*	**21 (21.4)***	7 (6.9)	6 (6.1)[b]	2 (2.0)
Cough	20 (20.4)	19 (18.8)	0	0
Fatigue	19 (19.4)	26 (25.7)	1 (1.0)	1 (1.0)
Pneumonia*	**18 (18.4)***	5 (5.0)	**10 (10.2)***	1 (1.0)
Syncope	8 (8.2)	5 (5.0)	6 (6.1)	5 (5.0)

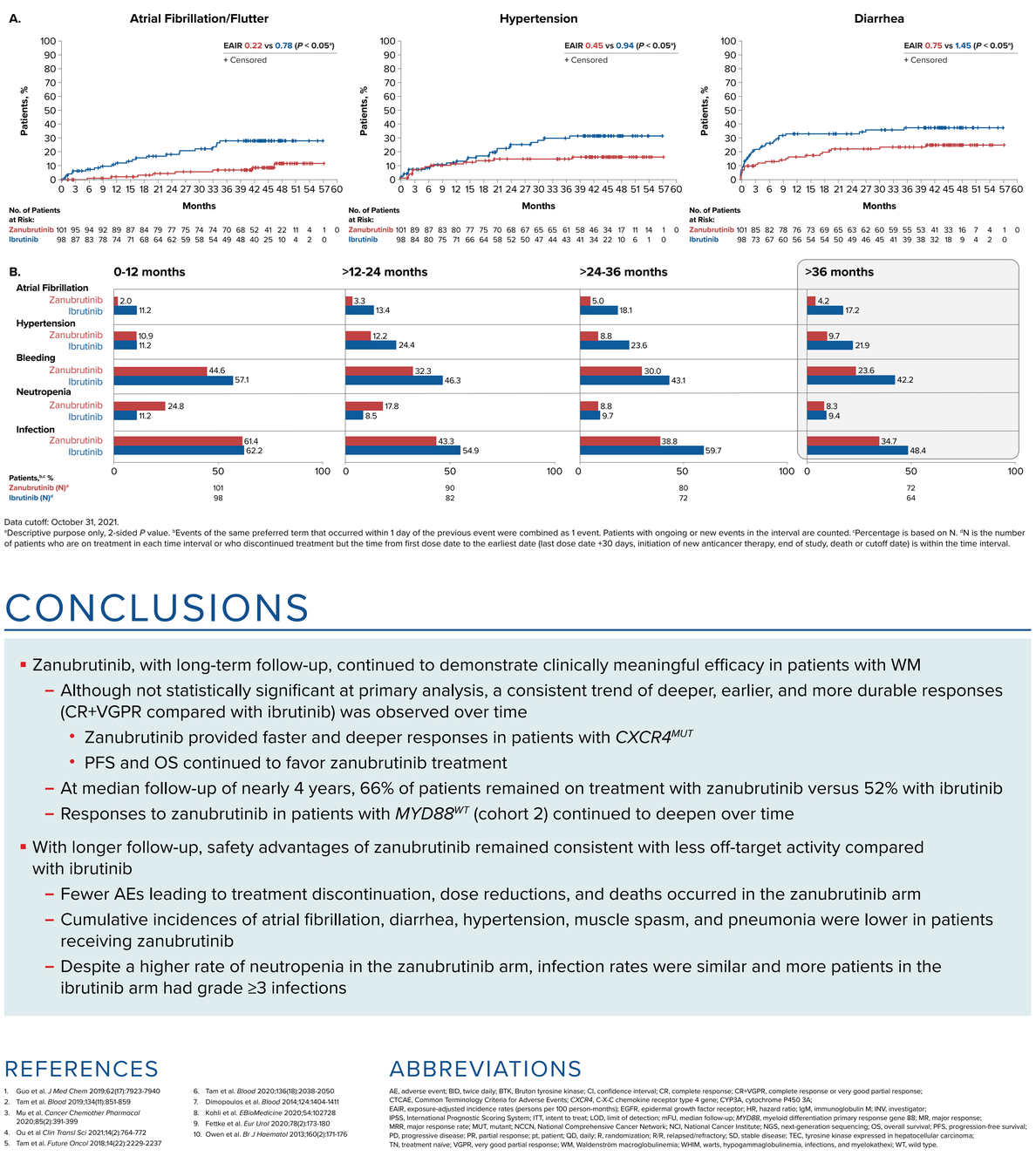
Bold text indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms.
Data cutoff: October 31, 2021. *Descriptive purposes only, 1-sided $P < 0.025$ in rate difference in all grades and/or grade ≥3.
[a]Preferred terms by Medical Dictionary for Regulatory Activities v24.0, excluding cytopenia; cytopenias are reported in **Table 5**.

Table 5: AEs of Interest in Cohort 1

AEs,[a] n (%)	All grades Ibrutinib (n=98)	All grades Zanubrutinib (n=101)	Grade ≥3 Ibrutinib (n=98)	Grade ≥3 Zanubrutinib (n=101)
Infection	78 (79.6)	80 (79.2)	**27 (27.6)**	22 (21.8)
Bleeding	61 (62.2)	56 (55.4)	10 (10.2)	9 (8.9)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Hypertension*	**25 (25.5)**	15 (14.9)	**20 (20.4)***	10 (9.9)
Atrial fibrillation/ flutter*	**23 (23.5)***	8 (7.9)	**8 (8.2)***	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia*[b]	20 (20.4)	**35 (34.7)***	10 (10.2)	**24 (23.8)***
Thrombocytopenia	17 (17.3)	17 (16.8)	6 (6.1)	11 (10.9)
Second primary malignancy/ nonskin cancers	17 (17.3)/ 6 (6.1)	17 (16.8)/ 6 (5.9)	3 (3.1)/ 3 (3.1)	6 (5.9)/ 4 (4.0)

Bold text indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms.
Data cutoff: October 31, 2021. *Descriptive purposes only, 1-sided P < 0.025 in rate difference in all grades and/or grade ≥3.
[a]AE categories (grouped terms) of preferred terms by Medical Dictionary for Regulatory Activities v24.0. [b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.

Figure 7: (A) Time to and (B) Prevalence Analysis for AEs of Interest (Cohort 1)



Data cutoff: October 31, 2021.
[a]Descriptive purpose only, 2-sided *P* value. [b]Events of the same preferred term that occurred within 1 day of the previous event were combined as 1 event. Patients with ongoing or new events in the interval are counted. [c]Percentage is based on N. [d]N is the number of patients who are on treatment in each time interval or who discontinued treatment but the time from first dose date to the earliest date (last dose date +30 days, initiation of new anticancer therapy, end of study, death or cutoff date) is within the time interval.

CONCLUSIONS

- Zanubrutinib, with long-term follow-up, continued to demonstrate clinically meaningful efficacy in patients with WM
  - Although not statistically significant at primary analysis, a consistent trend of deeper, earlier, and more durable responses (CR+VGPR compared with ibrutinib) was observed over time
    - Zanubrutinib provided faster and deeper responses in patients with *CXCR4*^{MUT}
    - PFS and OS continued to favor zanubrutinib treatment
  - At median follow-up of nearly 4 years, 66% of patients remained on treatment with zanubrutinib versus 52% with ibrutinib
  - Responses to zanubrutinib in patients with *MYD88*^{WT} (cohort 2) continued to deepen over time
- With longer follow-up, safety advantages of zanubrutinib remained consistent with less off-target activity compared with ibrutinib
  - Fewer AEs leading to treatment discontinuation, dose reductions, and deaths occurred in the zanubrutinib arm
  - Cumulative incidences of atrial fibrillation, diarrhea, hypertension, muscle spasm, and pneumonia were lower in patients receiving zanubrutinib
  - Despite a higher rate of neutropenia in the zanubrutinib arm, infection rates were similar and more patients in the ibrutinib arm had grade ≥3 infections

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ABBREVIATIONS

AE, adverse event; BID, twice daily; BTK, Bruton tyrosine kinase; CI, confidence interval; CR, complete response; CR+VGPR, complete response or very good partial response; CTCAE, Common Terminology Criteria for Adverse Events; *CXCR4*, C-X-C chemokine receptor type 4 gene; CYP3A, cytochrome P450 3A; EAIR, exposure-adjusted incidence rates (persons per 100 person-months); EGFR, epidermal growth factor receptor; HR, hazard ratio; IgM, immunoglobulin M; INV, investigator; IPSS, International Prognostic Scoring System; ITT, intent to treat; LOD, limit of detection; mFU, median follow-up; *MYD88*, myeloid differentiation primary response gene 88; MR, major response; MRR, major response rate; MUT, mutant; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; pt, patient; QD, daily; R, randomization; R/R, relapsed/refractory; SD, stable disease; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TN, treatment naive; VGPR, very good partial response; WM, Waldenström macroglobulinemia; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexi; WT, wild type.

DISCLOSURES

VL: honoraria from Roche, Amgen, BeiGene, Janssen, AstraZeneca, AbbVie; consulting with BeiGene, AstraZeneca, Lilly; speakers' bureau with AstraZeneca, BeiGene; travel support from AstraZeneca
CST: honoraria from Janssen, AbbVie, BeiGene, Loxo Oncology, Novartis; research funding from Janssen, AbbVie, BeiGene
RGS: grants or contracts with Gilead, Astellas; royalties or licenses with IVS; consulting with Janssen, Incyte, BeiGene; honoraria from Millennium/Takeda, Janssen, Incyte, Amgen, BeiGene, AstraZeneca, Pfizer; travel support from Janssen, Gilead, Sociedad Española de Hematologia y Hemoterapia (SEHH)
SO: honoraria from AbbVie, BeiGene, AstraZeneca, Bristol Myers Squibb, CSL Behring, Gilead, Janssen, Merck, Roche, Takeda; consulting with AbbVie, BeiGene, AstraZeneca, Bristol Myers Squibb, CSL Behring, Gilead, Janssen, Merck, Roche, Takeda; research funding from AbbVie, AstraZeneca, BeiGene, CSL Behring, Gilead, Janssen, Merck, Pharmacyclics, Roche, Takeda
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GC: research funding from BeiGene
RGO: honoraria from Janssen, Celgene; consulting with Janssen; travel support from Janssen
PM: consulting with BeiGene, Janssen, AstraZeneca, AbbVie, Roche, Astellas, Novartis, Gilead, IQVIA, Otsuka; honoraria from Janssen, AbbVie, Roche; participation on a data safety monitoring board or advisory board with ALLG
BEW: research funding from Roche, Incyte
AT: consulting with AbbVie, AstraZeneca, BeiGene, Janssen; speakers' bureau with AbbVie, Janssen, AstraZeneca, BeiGene
JJC: research funding from AbbVie, AstraZeneca, BeiGene, Pharmacyclics, TG Therapeutics; consulting with AbbVie, BeiGene, Cellectar, Janssen, Pharmacyclics, Roche
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CB: honoraria from Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead, Celltrion, MorphoSys, Regeneron; consulting with Gilead, Janssen, Roche, Pfizer, BeiGene, Celltrion, AbbVie, Incyte, Regeneron, MorphoSys, Novartis; speakers' bureau with Roche, Janssen, BeiGene, Celltrion, AbbVie, Pfizer, Gilead; research funding from Roche/Genentech, Janssen, Celltrion, MSD, Pfizer, Amgen
WYC: employment and stocks with BeiGene; stocks with Bristol Myers Squibb
MD: honoraria from Amgen, Bristol Myers Squibb, Janssen, Takeda, BeiGene
JJS, SP, AC: employment and stocks with BeiGene
HPL: nothing to disclose

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