ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib Versus Ibrutinib in Patients With Waldenström Macroglobulinemia

Paula Marlton[1], Ramon Garcia-Sanz[2], Stephen Opat[3], Shirley D'Sa[4], Wojciech Jurczak[5], Hui Peng Lee[6], Gavin Cull[7], Roger G. Owen[8], Bjorn E. Wahlin[9], Alessandra Tedeschi[10], Jorge J. Castillo[11], Tanya Siddiqi[12], Christian Buske[13], Veronique Leblond[14], Wai Y. Chan[15], Jingjing Schneider[15], Aileen Cohen[15], Meletios Dimopoulos[16], Constantine S. Tam[17,18]

[1]Princess Alexandra Hospital, University of Queensland Brisbane, QLD, Australia; [2]Hospital Universitario de Salamanca, Salamanca, Spain; [3]Monash Health, Monash University, Clayton, VIC, Australia; [4]Centre for Waldenström's Macroglobulinemia and Associated Disorders, University College London Hospital Foundation Trust, London, UK; [5]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland; [6]Flinders Medical Centre, Adelaide, SA, Australia; [7]Sir Charles Gairdner Hospital, University of Western Australia Perth, WA, Australia; [8]St. James University Hospital, Leeds, UK; [9]Karolinska Universitetssjukhuset and Karolinska Institutet, Stockholm, Sweden; [10]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [11]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [12]City Of Hope National Medical Center, Duarte, CA, USA; [13]CCC Ulm - Universitätsklinikum Ulm, Ulm, Baden-Württemberg, Germany; [14]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [15]BeiGene USA, Inc., San Mateo, CA, USA; [16]National and Kapodistrian University of Athens, Athens, Greece; [17]The Alfred Hospital, Melbourne, VIC, Australia; [18]Monash University, Clayton, VIC, Australia

INTRODUCTION

- Zanubrutinib is a potent, selective, and irreversible next-generation Bruton tyrosine kinase (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; zanubrutinib has high selectivity for BTK and minimal off-target inhibition of tyrosine-protein kinase TEC and epidermal growth factor receptor (EGFR) family kinases[1]
- Favorable drug interaction properties allow zanubrutinib to be coadministered with strong or moderate cytochrome P450 3A (CYP3A) inhibitors (eg, antifungals) at a reduced dose, 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 myeloid differentiation primary response gene 88 mutant (*MYD88*^{MUT}) Waldenström macroglobulinemia (WM); primary endpoint was the complete response or very good partial response (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 adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03

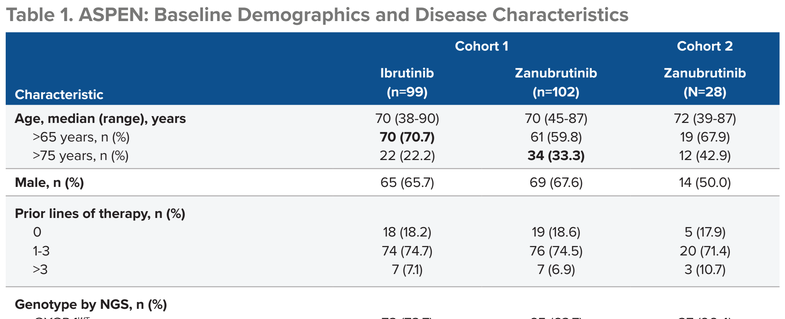
Exploratory Objectives

- To evaluate the efficacy and safety of zanubrutinib in patients with *MYD88* wild-type (*MYD88*^{WT}) WM and the efficacy of zanubrutinib vs ibrutinib according to C-X-C motif chemokine receptor 4 (*CXCR4*) 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.
BID, twice daily; BTK, Bruton tyrosine kinase; *CXCR4*, C-X-C chemokine receptor 4 gene; MUT, mutant; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; QD, once daily; R, randomization; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia; WT, wild type.

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 (limit of detection [LOD], 0.5%)[7,8] and detects all mutations in the region encompassing Ala260-Pro278, 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* warts, hypogammaglobulinemia, infections, and myelokathexis (*CXCR4*^{WHIM}) mutation was performed at screening; randomization in cohort 1 was stratified according to *CXCR4* mutation status (*CXCR4*^{WHIM} vs *CXCR4*^{WT}/missing; LOD, 10%-15%)
- *CXCR4* mutation status was assessed retrospectively by next-generation sequencing (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 National Comprehensive Cancer Network (NCCN®) WM guidelines and modified Owen criteria[10] as assessed by the independent review committee (primary analysis) and the investigator
- Efficacy endpoints: response rates (CR+VGPR, major and overall responses), duration of response, time to response, time to next treatment, progression-free survival (PFS), and overall survival (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 levels ≤110 g/L, which were higher in the zanubrutinib arm (**Table 1**)
- In cohort 2, 42.9% of patients were >75 years of age

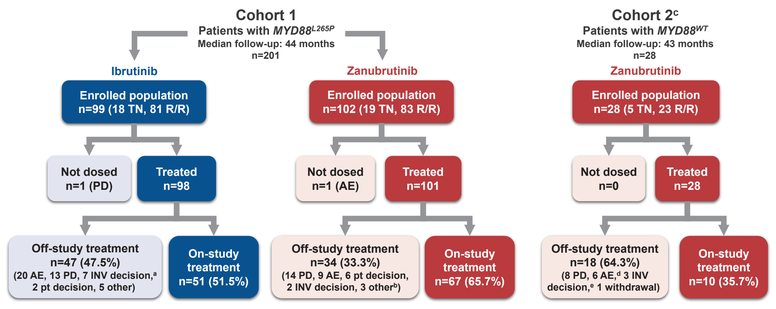
Table 1. ASPEN: Baseline Demographics and Disease Characteristics

Characteristic	Cohort 1 Ibrutinib (n=99)	Cohort 1 Zanubrutinib (n=102)	Cohort 2 Zanubrutinib (N=28)
Age, median (range), years	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)
Male, n (%)	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
IPSS for 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 level ≤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 values indicate >10% difference between arms in cohort 1.
CXCR4, C-X-C motif chemokine receptor 4 gene; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; MUT, mutant; NGS, next-generation sequencing; WM, Waldenström macroglobulinemia; WT, wild type.

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

Figure 2. Patient Disposition



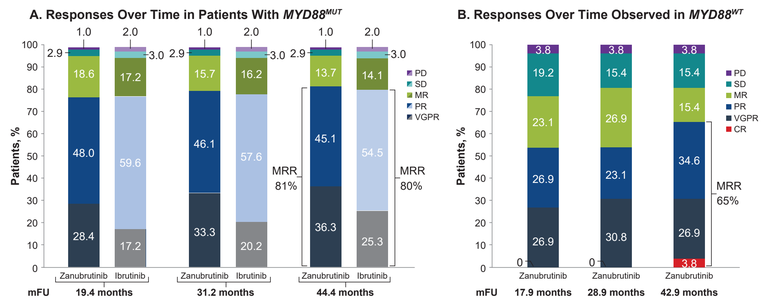
Data cutoff: 31 October 2021.
[a]One case related to COVID-19. [b]Radiotherapy for endometrial adenocarcinoma; patient started other anticancer therapy (rectal cancer); unwitnessed death (prior hospitalization for heart failure exacerbation but death not due to AE per site and no other information available). [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.
AE, adverse event; COVID-19, coronavirus disease of 2019; INV, investigator; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; R/R, relapsed/refractory; TN, treatment-naive; WT, wild type.

RESULTS (CONT)

Efficacy

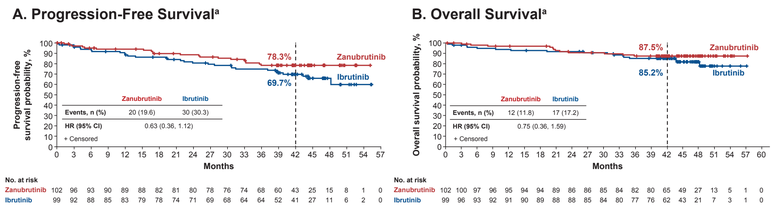
- In cohort 1, the investigator-assessed cumulative response rate increased over time in both treatment arms (**Figure 3A**)
  - No CRs were observed in cohort 1; the response rate of CR+VGPR was numerically higher at all time points with zanubrutinib compared with ibrutinib
  - At 44.4 months of median follow-up, CR+VGPR rates by investigator were 36.3% (zanubrutinib) vs 25.3% (ibrutinib)
- Median time to CR+VGPR was shorter with zanubrutinib (6.7 months [range, 1.9-42.0]) than ibrutinib (16.6 months [range, 2.0-49.9])
- Event-free rate for the duration of CR+VGPR at 24 months was higher with zanubrutinib (90.6% [range, 73.6-96.9]) than 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



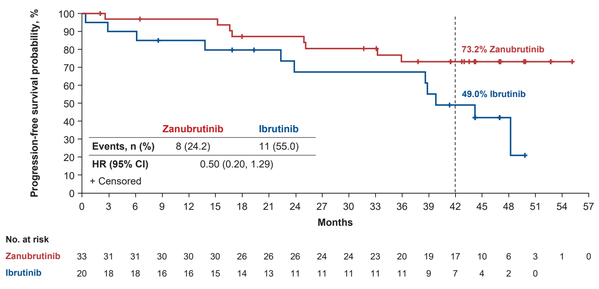
Data cutoff: 31 October 2021.
CR, complete response; mFU, median follow-up; MR, minimal response; MRR, major response rate; MUT, mutant; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response; WT wild type.

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



Data cutoff: 31 October 2021.
[a]By investigator assessment.
ITT, intent to treat.

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



Data cutoff: 31 October 2021.
CXCR4, C-X-C motif chemokine receptor 4 gene; MUT, mutant.

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

Data cutoff: 31 October 2021. **Bold** values indicate >10% difference between arms.
[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.
CXCR4, C-X-C motif chemokine receptor 4 gene; MUT, mutant; NGS, next-generation sequencing; VGPR, very good partial response; WT, wild type.

Long-Term Safety and Tolerability

- Zanubrutinib had fewer AEs leading to death, treatment discontinuations, and dose reductions than ibrutinib (**Table 3** and **Figure 6**)
  - The most common AEs that led to discontinuation were cardiac disorder and infection (4% each) with ibrutinib and 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 in 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)

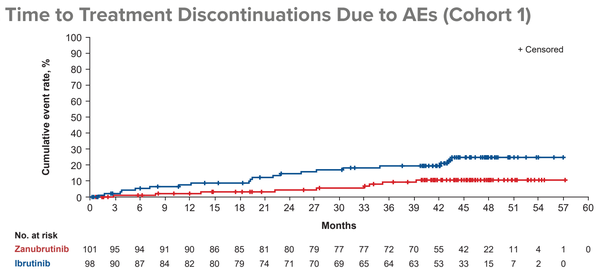
Data cutoff: 31 October 2021.
[a]Cardiac failure acute, death (unexplained), pneumonia, sepsis (n=2). [b]Cardiomegaly (cardiac arrest after plasmapheresis), metastatic malignant melanoma, subdural hematoma (after a fall). [c]Cardiac arrest, COVID-19 infection, lymphoma transformation. [d]Cardiac disorders (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).
AE, adverse event; COVID-19, coronavirus disease of 2019.

Table 4. Most Common AEs (Cohort 1)

AEs, n (%)[a]	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[b]	**28 (28.6)**[b]	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[b]	**21 (21.4)**[b]	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[b]	**18 (18.4)**[b]	5 (5.0)	**10 (10.2)**[b]	1 (1.0)
Syncope	8 (8.2)	5 (5.0)	6 (6.1)	5 (5.0)

Data cutoff: 31 October 2021. **Bold** values indicate rate of AEs with ≥10% (all grades) or ≥5% (Grade ≥3) difference between arms.
[a]Preferred terms by Medical Dictionary for Regulatory Activities v24.0, excluding cytopenia and cytopenias, are reported in **Table 5**.
[b]Descriptive purposes only; 1-sided *P*<.025 in rate difference in all grades and/or Grade ≥3.
AE, adverse event.

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



Data cutoff: 31 October 2021.
AE, adverse event.

Table 5. AEs of Interest in Cohort 1

AEs, n (%)[a]	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[b]	**25 (25.5)**	15 (14.9)	**20 (20.4)**[b]	10 (9.9)
Atrial fibrillation/flutter[b]	**23 (23.5)**[b]	8 (7.9)	**8 (8.2)**[b]	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia[b,c]	20 (20.4)	**35 (34.7)**[b]	10 (10.2)	**24 (23.8)**[b]
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)

Data cutoff: 31 October 2021. **Bold** values indicate rate of AEs with ≥10% (all grades) or ≥5% (Grade ≥3) difference between arms.
[a]AE categories (grouped terms) of preferred terms by Medical Dictionary for Regulatory Activities v24.0. [b]Descriptive purposes only; 1-sided *P*<.025 in rate difference in all grades and/or Grade ≥3. [c]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
AE, adverse event.

Figure 7A. Time to AEs of Interest (Cohort 1)

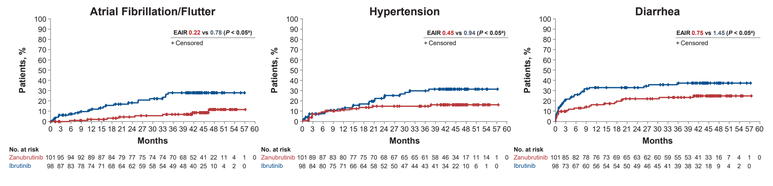
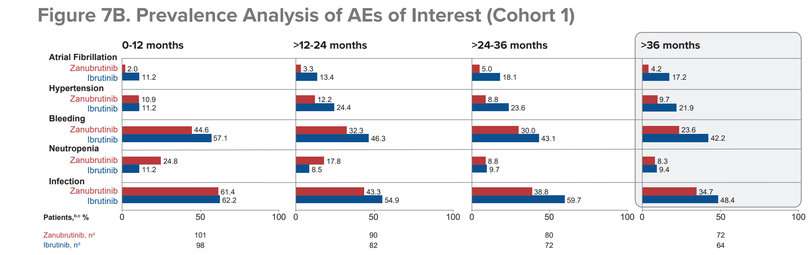


Figure 7B. Prevalence Analysis of AEs of Interest (Cohort 1)



Data cutoff: 31 October 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.
AE, adverse event; EAIR, exposure-adjusted incidence rate (persons per 100 person-months).

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 were still receiving 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 than ibrutinib
  - Fewer AEs leading to treatment discontinuations, 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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DISCLOSURES

PM: consulting at Roche, Janssen-Cilag, Novartis, AbbVie, Astellas Pharma, Pfizer, BeiGene, Jazz Pharmaceuticals, Gilead Sciences; honoraria from Roche, AbbVie
RGS: consulting at Janssen; travel expense from Janssen, Takeda; royalties from BIOMED 2 primers; honoraria from Janssen, Takeda, Amgen, BeiGene, Novartis, Astellas Pharma; research funding from Gilead Sciences, Incyte, Astellas Pharma
SO: honoraria from AbbVie, BeiGene, AstraZeneca, Bristol Myers Squibb, CSL Behring, Gilead, Janssen, Merck, Roche, Takeda; consulting at 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
SD: honoraria from Janssen, BeiGene, Sanofi; consulting at Janssen, BeiGene, Sanofi; speakers bureau at Janssen; expert testimony at Janssen; travel with BeiGene, Janssen
WJ: consulting at AstraZeneca, BeiGene, Janssen, Loxo Oncology, Sandoz, Roche; research funding at AbbVie, Astra Zeneca, Bayer, BeiGene, Celltrion, Celgene, Debiopharm, Epizyme, Incyte, Janssen, Loxo Oncology, Merck, Mei Pharma, MorphoSys, Novo Nordisk, Roche, Sandoz, Takeda, TG Therapeutics
GC: research funding at BeiGene
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VL: consulting at BeiGene, Janssen, AstraZeneca, Lilly, AbbVie; speakers bureau at BeiGene, AstraZeneca, AbbVie; travel with AbbVie, AstraZeneca, Roche Pharma AG, BeiGene, Amgen, Janssen Oncology, AbbVie, MSD Oncology, Lilly
WC: employment with BeiGene; stock with BeiGene, Bristol Myers Squibb
JS, AC: employment and stock with BeiGene
MD: consulting with Amgen, Janssen-Cilag, Takeda, Bristol Myers Squibb, BeiGene; honoraria with Amgen, Takeda, Janssen-Cilag, Bristol Myers Squibb, BeiGene
CST: research funding at Janssen, AbbVie, BeiGene; honoraria at Janssen, AbbVie, BeiGene, Loxo Oncology, Novartis
HL: nothing to disclose

CORRESPONDENCE

Paula.Marlton@health.qld.gov.au

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