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Health-Related Quality of Life in Patients With Waldenström Macroglobulinemia (WM) Treated With Zanubrutinib vs Ibrutinib: Results From the Phase 3 ASPEN Trial Long-term Follow-Up

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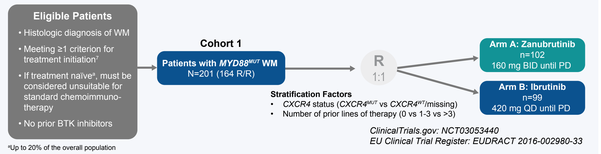
INTRODUCTION

- BTK inhibitors have changed the therapeutic landscape for patients with Waldenström macroglobulinemia (WM) over the last decade and are considered preferred options for first and later lines of treatment[1]
  - Ibrutinib, the first-in-class BTK inhibitor, has been associated with off-target kinase inhibition that contributes to AEs such as atrial fibrillation and bleeding, which can lead to early treatment discontinuation[2,3] that could negatively impact patients' health-related quality of life (HRQoL)
  - Zanubrutinib is a potent and irreversible next-generation BTK inhibitor designed with improved selectivity for BTK to minimize off-target effects and toxicities[3]
- ASPEN (NCT03053440), an open-label, multicenter, randomized phase 3 study of adult patients with WM, compared outcomes associated with zanubrutinib vs ibrutinib therapy in patients with WM[4-6] (**Figure 1**)
  - Patients aged ≥18 years diagnosed with R/R WM or treatment-naïve WM deemed unsuitable for chemotherapy were included in the trial
  - Patients with activating mutations in *MYD88* (Cohort 1) were randomized 1:1 to receive zanubrutinib 160 mg orally BID or ibrutinib 420 mg orally QD until disease progression or intolerance[4]
  - Primary[5] and long-term analyses[6] demonstrated that zanubrutinib had an improved safety/tolerability profile vs ibrutinib and provides deep, early, and durable responses in patients with WM regardless of prior treatment or *CXCR4* and *MYD88* mutational statuses
- The current analysis, performed at the end of the study (last patient visit June 21, 2021), evaluated HRQoL exploratory endpoints among Cohort 1 patients for both the ITT population and for patients achieving a CR or VGPR by Cycle 25

METHODS

Figure 1. ASPEN Study Design (Cohort 1)



*Up to 20% of the overall population

- HRQoL was assessed via patient-reported outcome (PRO) data collected using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30[8]) and the EuroQoL-5 dimension-5 level visual analog scale (EQ-5D-5L VAS[9]) at baseline (Cycle 1, day 1), every 3 cycles up to Cycle 13, and every 6 cycles until disease progression, death, or withdrawal of consent; 1 cycle constituted 28 days
  - Descriptive analysis was performed for all measured PROs
- In alignment with typical manifestations of disease and treatment-related AEs, key PRO endpoints included global health status (GHS)/QoL, physical and role functioning, and symptoms of fatigue, diarrhea, and nausea/vomiting, as measured by the EORTC QLQ-C30
- A linear mixed model for repeated measures (MMRM) analysis assessed differences between treatment arms for PRO endpoints at 4 key clinical cycles (Cycles 4, 7, 13, and 25), which were determined from regulatory recommendations, literature review, and expert opinions
  - The model included repeated measurements of PRO endpoints up to Cycle 25 as the dependent variable, with the baseline PRO score and treatment arm by time-point interaction as covariates; an unstructured covariance matrix was used
  - A clinically meaningful treatment difference was defined as ≥5 points difference from baseline; descriptive *P*-values were 2-sided and nominal

RESULTS

- In the ITT population (zanubrutinib, n=102; ibrutinib, n=99), baseline demographics and disease characteristics were balanced between arms, except more patients in the zanubrutinib arm were >75 years, had *CXCR4* mutations (by next-generation sequencing), and had hemoglobin levels ≤110 g/L[5,6]
- More patients (>10% difference) in the ibrutinib vs zanubrutinib arm experienced the following AEs (by PT): diarrhea (36.7% vs 22.8%), muscle spasms (28.6% vs 11.9%), atrial fibrillation (21.4% vs 6.9%), and pneumonia (21.4% vs 5.0%); more patients in the zanubrutinib vs ibrutinib arm experienced neutropenia (29.7% vs 16.3%)
- Compliance rates for PRO instruments were high across all key cycles (zanubrutinib 92%–96%; ibrutinib 84%–95%)

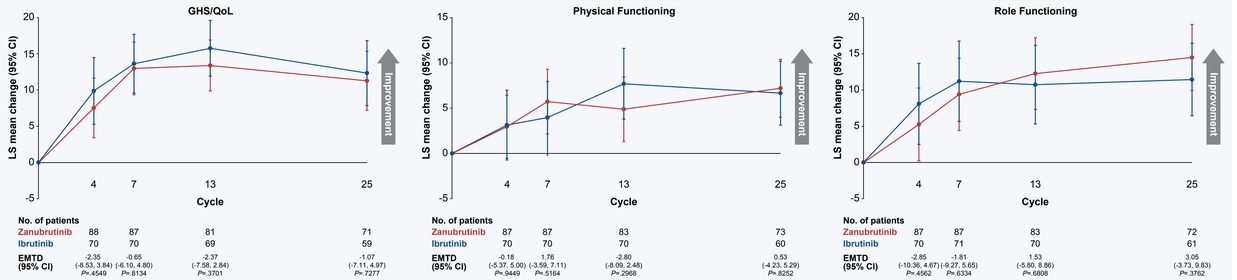
EORTC QLQ-C30 – MMRM Analysis (ITT Population)

- Changes in PROs from baseline for the ITT population are shown in **Figures 2 and 3**
- Diarrhea and nausea/vomiting symptom scores were stable from baseline through all key clinical cycles in the zanubrutinib arm, whereas patients receiving ibrutinib experienced initial worsening of diarrhea and nausea/vomiting from baseline
  - Treatment differences for diarrhea and nausea/vomiting were clinically meaningful at Cycle 4
- In other key PRO endpoints, both arms experienced improvements and differences between the 2 arms were not significant

EORTC QLQ-C30 – MMRM Analysis (CR + VGPR by Cycle 25 Population)

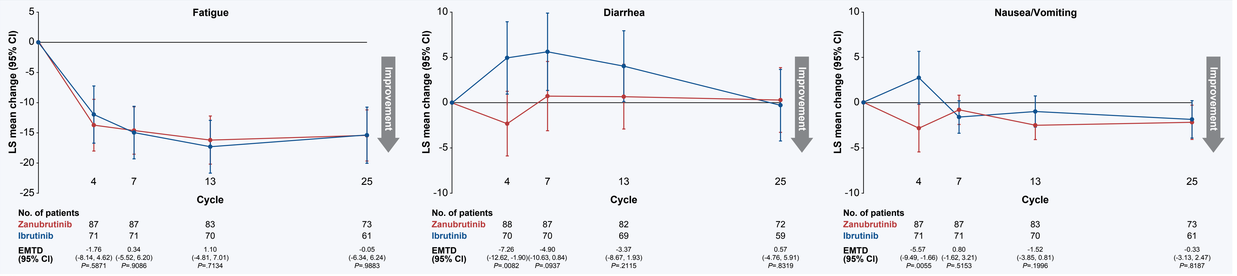
- At a median follow-up of 48.3 months, CR was not achieved in either arm; however, the VGPR rate was higher among patients receiving zanubrutinib vs ibrutinib (38.2% vs 25.3%, *P*=0.0374)
  - Median time to VGPR was shorter in patients receiving zanubrutinib (8.3 months) vs ibrutinib (16.6 months)
- For patients who achieved VGPR by Cycle 25 (zanubrutinib: n=31; ibrutinib: n=17), changes in PROs from baseline are shown in **Figures 4 and 5**
- In general, patients receiving zanubrutinib experienced greater functional and symptomatic improvements than patients receiving ibrutinib
- Treatment differences for diarrhea and nausea/vomiting were clinically meaningful by Cycle 4; differences for physical functioning and fatigue were clinically meaningful at Cycle 7 and again at Cycle 25

Figure 2. LS Mean Change From Baseline in GHS/QoL and Functional Scores (ITT Population)



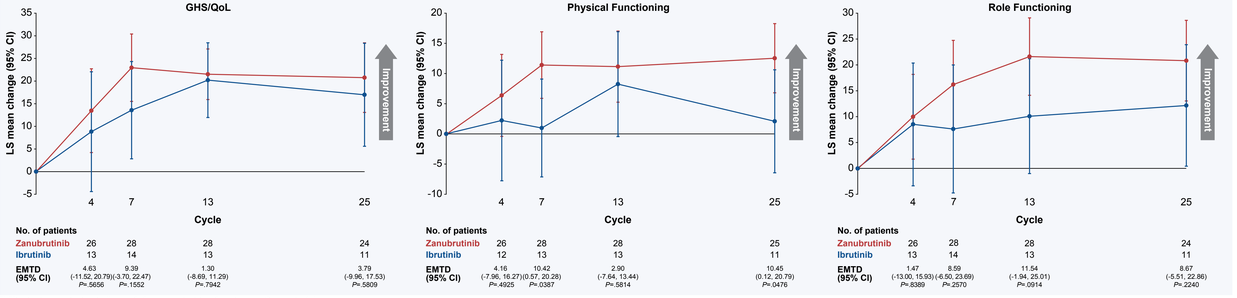
EMTD, estimated mean treatment difference; GHS, global health status; LS, least squares; QoL, quality of life.

Figure 3. LS Mean Change From Baseline in Symptom Scores (ITT Population)



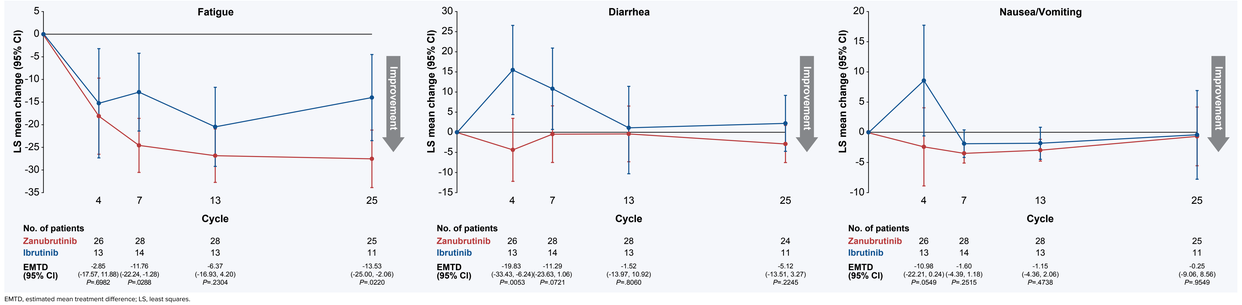
EMTD, estimated mean treatment difference; LS, least squares.

Figure 4. LS Mean Change From Baseline in GHS/QoL and Functional Scores (VGPR by Cycle 25 Population)



EMTD, estimated mean treatment difference; GHS, global health status; LS, least squares; QoL, quality of life.

Figure 5. LS Mean Change From Baseline in Symptom Scores (VGPR by Cycle 25 Population)



EMTD, estimated mean treatment difference; LS, least squares.

CONCLUSIONS

- In the ASPEN trial, treatment with zanubrutinib was associated with greater improvements in HRQoL vs ibrutinib in patients with WM and *MYD88* mutations
  - In earlier cycles of treatment, clinically meaningful differences were observed in diarrhea and nausea/vomiting in the ITT population and among patients who achieved VGPR by Cycle 25
  - In patients who achieved VGPR by Cycle 25, clinically meaningful differences in physical functioning and fatigue were achieved in early-term treatment and continued to the end of treatment
- The improved HRQoL seen with zanubrutinib among patients who achieved VGPR by Cycle 25 is consistent with the shorter median time to VGPR in the zanubrutinib arm and suggests that when disease is controlled to a similar extent, patients fare better in overall HRQoL when treated with zanubrutinib vs ibrutinib
- Given the improved long-term safety of zanubrutinib vs ibrutinib and deep, early, durable responses in patients in the ASPEN trial, the HRQoL results support the use of zanubrutinib as an effective option for BTK-inhibitor therapy in patients with WM

EQ-5D-5L VAS – Descriptive Analysis

- For the ITT (**Table 1**) and VGPR by Cycle 25 (**Table 2**) populations, mean change from baseline increased in the zanubrutinib and ibrutinib arms through Cycle 13; improvements from baseline were consistently greater in the zanubrutinib arm

Table 1. Mean (SD) Change From Baseline in EQ-5D-5L VAS (ITT Population)

	Zanubrutinib (n=102)			Ibrutinib (n=99)		
	n	Mean (SD)	Change from baseline[a], mean (SD)	n	Mean (SD)	Change from baseline[a], mean (SD)
Baseline	61	64.9 (16.84)		62	68.4 (17.04)	
Cycle 4	72	75.3 (15.48)	9.3 (16.82)	61	75.2 (15.85)	7.1 (17.55)
Cycle 7	82	76.4 (16.02)	10.5 (16.06)	73	77.4 (16.58)	8.7 (15.82)
Cycle 13	83	79.8 (14.09)	13.7 (14.66)	78	78.5 (17.95)	9.0 (17.90)
Cycle 25	73	79.2 (14.87)	11.6 (15.98)	66	77.4 (16.35)	10.1 (16.44)

[a]Among patients who also completed the questionnaire at baseline: zanubrutinib, n=53, 53, 49, and 45 and ibrutinib, n=50, 52, 53, and 45 at Cycles 4, 7, 13, and 25, respectively.

Table 2. Mean (SD) Change From Baseline in EQ-5D-5L VAS (VGPR by Cycle 25 Population)

	Zanubrutinib (n=31)			Ibrutinib (n=17)		
	n	Mean (SD)	Change from baseline[a], mean (SD)	n	Mean (SD)	Change from baseline[a], mean (SD)
Baseline	16	64.8 (15.77)		12	65.8 (17.94)	
Cycle 4	20	80.6 (14.43)	13.0 (10.99)	14	69.9 (18.83)	8.5 (18.16)
Cycle 7	28	79.3 (13.10)	14.6 (14.18)	16	69.8 (21.57)	8.8 (18.90)
Cycle 13	29	82.4 (13.52)	17.6 (14.07)	16	74.2 (19.88)	11.2 (20.50)
Cycle 25	26	83.5 (13.35)	15.7 (10.26)	13	71.0 (16.44)	7.1 (18.58)

[a]Among patients who also completed the questionnaire at baseline: zanubrutinib n=15, 16, 16, and 15 and ibrutinib n=11, 11, 12, and 10 at Cycles 4, 7, 13, and 25, respectively.

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DISCLOSURES

AT: consulting, advisory, speakers' bureau role with AbbVie, AstraZeneca, BeiGene, Janssen. **CST:** honoraria from AbbVie, BeiGene, Janssen. **RGO:** honoraria from AstraZeneca, BeiGene, Janssen-Cilag; consulting/advisory role with BeiGene, Janssen-Cilag. **CB:** honoraria from AbbVie, BeiGene, Celltrion, Gilead Sciences, Incyte, Janssen, MorphoSys, Novartis, Pfizer, Regeneron, Roche/Genentech; consulting/advisory role with AbbVie, BeiGene, Celltrion, Gilead Sciences, Incyte, Janssen, MorphoSys, Novartis, Pfizer, Regeneron, Roche; speakers' bureau role with AbbVie, BeiGene, Celltrion, Gilead Sciences, Janssen, Pfizer, Roche; research funding from Amgen, Celltrion, Janssen, MSD, Pfizer, Roche/Genentech. **VL:** honoraria from AbbVie, Amgen, AstraZeneca, BeiGene, Eli Lilly and Company, Janssen Oncology, MSD Oncology, Roche Pharma AG; consulting/advisory role with AbbVie, AstraZeneca, BeiGene, Eli Lilly and Company, Janssen; speaker's bureau role with AbbVie, AstraZeneca, BeiGene; travel, accommodations, expenses from AbbVie. **MD:** honoraria from Amgen, BeiGene, Bristol Myers Squibb, Janssen-Cilag, Takeda; consulting/advisory role with Amgen, BeiGene, Bristol Myers Squibb, Janssen-Cilag, Takeda. **RGS:** honoraria from Amgen, BeiGene, Janssen, Novartis, Takeda; consulting/advisory role with Janssen; research funding from Gilead Sciences, Incyte; patents, royalties, other intellectual property with BIOMED-2 primers; travel, accommodations, expenses from Janssen, Takeda; other relationship with Spanish Society of Hematology. **JJC:** consulting/advisory role with AbbVie/Pharmacyclics, BeiGene, Cellectar, Janssen, Roche/Genentech; institutional research funding from AbbVie, AstraZeneca, BeiGene, Janssen, Pharmacyclics, TG Therapeutics. **JT:** research funding from BeiGene, Celgene, Janssen-Cilag, Pharmacyclics, Roche/Genentech, Takeda; travel, accommodations, expenses from Roche/Genentech. **SPT:** consulting/advisory role with BeiGene, Bristol Myers Squibb, Janssen, Pharmacyclics, X4 Pharmaceuticals; research funding from AbbVie, BeiGene, Bristol Myers Squibb, Eli Lilly and Company, Pharmacyclics, X4 Pharmaceuticals; patents, royalties, other intellectual property (institutional, no personal income) related to the use of *MYD88* and *CXCR4* testing; travel, accommodations, expenses from Janssen Oncology; other relationship with BeiGene, Janssen, Pharmacyclics. **KY, BT, HA:** employment with BeiGene. **SP, JS, GB:** employment, equity with BeiGene. **AC:** employment, equity, travel expenses with BeiGene. **WYC:** employment with BeiGene; equity with BeiGene, Bristol Myers Squibb.

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