Outcomes of Relapsed/Refractory MCL Patients Treated with Zanubrutinib Monotherapy in the Second Line and in Later Lines: A Pooled Analysis from 2 Studies

Abstract EP1169

Keshu Zhou, MD,[1] Dehui Zou, MD,[2] Jianfeng Zhou, PhD,[3] Jianda Hu, PhD,[4] Haiyan Yang, PhD,[5] Huilai Zhang, MD, PhD,[6] Jie Ji, MD,[7] Wei Xu, MD, PhD,[8] Jie Jin, PhD,[9] Fangfang Lv, MD,[10] Ru Feng, MD,[11] Sujun Gao, PhD,[12] Daobin Zhou, MD,[13] Constantine S. Tam, MBBS (Hons), MD, FRACP, FRCPA,[14] David Simpson, MBChB, FRACP, FRCPA,[15] Michael Wang, MD,[16] Tycel J. Phillips, MD,[17] Stephen Opat, MBBS (Hons), FRACP, FRCPA,[18] Huafei Lu, PhD,[19] Zhiyue Huang, PhD,[19] Yuqin Song, MD, PhD[20]

[1]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China. [2]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China. [3]Tongji Hospital, Tongji Medical College, Wuhan, China. [4]Fujian Medical University Union Hospital, Fuzhou, China. [5]Zhejiang Cancer Hospital, Hangzhou, China. [6]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China. [7]West China Hospital of Sichuan University, Chengdu, China. [8]The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China. [9]The First Affiliated Hospital, Zhejiang University College of Medicine, Hangzhou, China. [10]Fudan University Shanghai Cancer Center, Shanghai, China. [11]Nanfang Hospital of Southern Medical University, Guangzhou, China. [12]The First Hospital of Jilin University, Changchun, China. [13]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China. [14]Peter MacCallum Cancer Centre, St. Vincent's Hospital, University of Melbourne, Melbourne, Victoria, Australia. [15]North Shore Hospital, Auckland, New Zealand. [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [17]University of Michigan, Ann Arbor, Michigan, USA. [18]Monash Health, Monash University, Clayton, Victoria, Australia. [19]BeiGene (Beijing) Co., Ltd., Beijing, China. [20]Peking University Cancer Hospital & Institute (Beijing Cancer Hospital), Beijing, China.

INTRODUCTION

- Zanubrutinib is a highly specific, potent BTK inhibitor with minimal off-target inhibition of other kinases such as EGFR, JAK3, TEC, ITK, and others [1]
- Zanubrutinib has showed complete and sustained 24-hour BTK occupancy in both blood and lymph node biopsies from patients treated at 160 mg twice daily and is associated with durable responses in patients with non-Hodgkin lymphoma including mantle cell lymphoma (MCL) [2, 3]
- In a phase 2 study conducted in patients with relapsed/refractory (R/R) MCL, treatment with zanubrutinib results in an overall response rate (ORR) of 84%, with a complete response rate (CRR) of 78%, and median progression free survival (PFS) is not reached [3]
- We present the pooled analysis to compare the outcomes of zanubrutinib treatment for R/R MCL patients in the 2nd line with those in later lines after confounding is controlled

METHODS

- Our analysis was based on pooled data including R/R MCL patients treated with zanubrutinib in a phase 1 study (ClinicalTrials. gov NCT02343120) and a phase 2 study (ClinicalTrials. gov NCT03206970), corresponding median study follow-up 18.3 and 18.4 months (**Table 1**)
- Response to treatment was assessed per the Lugano classification [4]; PET scans were optional in NCT02343120 but required in NCT03206970
- Only patients with no missing baseline covariates (age, sex, BMI, ECOG, disease stage, blastoid variant, MIPI, bulky disease, extra nodal and bone marrow involvement) were pooled. One patient in NCT03206970 was excluded due to unconfirmed MCL
- Within the above defined dataset, 41 R/R MCL patients received second line treatment with zanubrutinib and 71 R/R MCL patients received treatment with zanubrutinib in later lines
- To balance the baseline covariates between groups and mimic a randomized controlled trail, inverse propensity score weighing was used [5]. In such design, R/R MCL patients who needed to receive 2nd line therapy were randomized into two arms: Arm A treated with zanubrutinib in the 2nd line and Arm B treated with any anti-cancer therapies other than BTK inhibitors and followed by zanubrutinib in later lines

Table 1. Sample Sizes by Studies and Groups in the Pooled Analysis

	Original Sample [a]			Weighted Sample [b]		
	MCL patients with 1 prior line of therapy	MCL patients with >1 prior lines of therapy	Total	Arm A	Arm B	Total
NCT02343120	20	17	37	18	12	25
NCT03206970	25	61	86	14	49	61
Total	45	78	123	26	59	83

Notes: [a] In which ten patients were excluded due to missing baseline covariates and one due to unconfirmed MCL for analysis. [b] Effective sample sizes were calculated by Kish's formula and reported. After weighting, Arm A consisted of 28.7% and 71.3% patients from NCT02343120 and NCT03206970 respectively, while Arm B consisted of 22.0% and 78.0% patients from patients from NCT02343120 and NCT03206970 respectively.

- The efficacy endpoints of zanubrutinib in the two arms were examined, including CRR, ORR, PFS and overall survival (OS). The difference between arms in CRR and ORR was investigated by logistic regression, and the difference between arms in time-to-event endpoints by the Cox proportional hazards model
- The difference between arms was adjusted by studies, involving the difference in race (Asian vs. non-Asian) and response assessment (PET and CT) due to different study designs
- The landmark analysis of duration of response (DOR), PFS and OS at 12 months was reported for the whole population as well as the subpopulation of complete responders in Arm A
- The safety profile in each arm was summarized

RESULTS

- The effective sample sizes of the weighted sample were reported in **Table 1**. The median follow-up time was 19.1 vs. 18.4 months for Arm A vs. Arm B; the median follow-up time was 18.9 months for the total weighted sample
- In the weighted sample, all baseline covariates were balanced between groups (**Table 2**) and the prevalence of prior medication use in each group was preserved (**Table 3**)
- 43.9%, 42.7% and 13.4% of the patients in Arm B were patients treated with zanubrutinib in the 3rd, 4th and ≥ 5th lines

Table 2. Summary of Baseline Covariates before and after Weighting

Baseline Covariates	Before Weighting			After Weighting		
	MCL patients with 1 prior line of therapy	MCL patients with >1 prior lines of therapy	Mean. Diff., (Var. Ratio) [a]	Arm A	Arm B	Mean. Diff., (Var. Ratio) [a]
Age, mean (SD)	63.95 (11.45)	60.17 (8.8)	0.37 (1.69)	60.94 (10.3)	61.25 (10.0)	-0.03 (1.01)
Sex, male	80%	75%	0.06	75%	75%	-0.01
BMI, mean (SD)	25.69 (4.05)	24.51 (4.22)	0.28 (0.92)	24.36 (3.96)	24.76 (4.18)	-0.10 (0.90)
ECOG, > 0	34%	34%	0.00	32%	31%	0.01
Disease Stage, I	5%	1%	0.03	3%	3%	0.00
Disease Stage, II	7%	5%	-0.02	4%	6%	-0.02
Disease Stage, III	10%	14%	-0.04	19%	14%	0.05
Disease Stage, IV	80%	77%	0.03	74%	77%	-0.03
Blastoid Variant, yes	2%	18%	-0.16	2%	12%	-0.10
MIPI, mean (SD)	5.84 (0.61)	5.70 (0.57)	0.24 (1.15)	5.70 (0.57)	5.73 (0.57)	-0.06 (1.01)
Bulky [b], yes	7%	8%	-0.01	6%	8%	-0.01
Extra Nodal, yes	51%	65%	-0.14	66%	62%	0.04
Bone Marrow Involvement, yes	51%	52%	-0.01	54%	52%	0.02

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; LDi, longest transverse diameter of a lesion; SD, standard deviation.
Notes: The listed baseline covariates were used to create a propensity score model along with the prior medication use in Table 3. [a] For continuous variables (age, BMI and MIPI), standardized mean difference was used. The balance criteria for a continuous variable was (i) the standardized mean difference was no more than 0.1 and (ii) the ratio of variances was between 0.67 and 1.5. The balance criteria for a discrete variable was that the absolute mean difference was no more than 0.1. [b] Bulky disease was defined as LDi > 10 cm.

Table 3. Summary of Prior Medication Use before and after Weighting

Prior Medication Use	Before Weighting		After Weighting	
	MCL patients with 1 prior line of therapy	MCL patients with >1 prior lines of therapy	Arm A	Arm B
(R) CHOP / (R) CHOEP / (R) CHOP-like	76%	86%	76%	88%
Rituximab or Rituximab Containing	80%	79%	74%	80%
Hyper CVAD or Hyper-CVAD-like	12%	21%	9%	19%
Lenalidomide	0%	14%	0%	15%
Bortezomib	2%	10%	1%	10%
Autologous Stem Cell Transplantation	2%	13%	2%	12%

Abbreviations: Hyper CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine; (R) CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; (R) CHOEP, rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone.
Note: The propensity score modeling was designed to keep the original prevalence of prior medication use preserved after weighting.

- CRR of zanubrutinib treatment was significantly higher in Arm A, compared to Arm B (74.6% vs 61.1%); **see Figure 1**. The adjusted odds of achieving complete response when treated with zanubrutinib in the 2nd line were 3.4 times as high as in later lines (p-value=0.03)
- ORR of zanubrutinib treatment was numerically higher in Arm A, compared to Arm B (90.7% vs 83.5%); **see Figure 1**. The adjusted odds of achieving overall response when treated with zanubrutinib in the 2nd line were 1.9 times as high as in later lines (p-value=0.29)

Figure 1: Best Overall Response of Zanubrutinib after Weighting

- The DOR rates at 6 and 12 months from first overall response, PFS rates and OS rates at 6 and 12 months from zanubrutinib treatment initiation were higher in Arm A (**Table 4**)

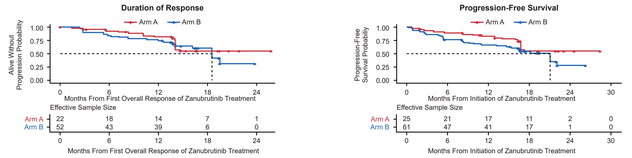
Table 4: Summary of DOR, PFS and OS after Weighting

	Weighted Pooled Sample		
	Arm A	Arm B	Total
DOR Rate at, % (95% CI) [a]			
6 Months	92.3 (84.1, 100)	83.6 (73.9, 95.0)	86.9 (80.3, 94.1)
12 Months	81.8 (70.4, 95.6)	74.7 (63.8, 88.1)	77.4 (69.3, 86.5)
PFS Rate at, % (95% CI) [a]			
6 Months	89.0 (80.6, 98.6)	76.2 (66.2, 88.2)	80.9 (73.8, 88.6)
12 Months	82.5 (71.7, 95.2)	66.4 (55.6, 80.1)	72.3 (64.3, 81.3)
OS Rate at, % (95% CI) [a]			
6 Months	96.2 (91.0, 100)	92.1 (86.5, 98.0)	93.6 (89.1, 98.3)
12 Months	87.5 (78.1, 98.5)	83.6 (75.7, 92.6)	85.0 (78.5, 92.2)

Abbreviations: CI, confidence interval; DOR, duration of response; OS, overall survival; PFS, progression-free survival.
Notes: [a] The DOR rates, PFS rates and OS rate at 6 months and 12 months were calculated by the Kaplan-Meier method with 95% CI constructed by the Greenwood's formula.

- The Kaplan-Meier curves of DOR and PFS of each arm were presented in **Figure 2**

Figure 2: Duration of Response and Progression-Free Survival after Weighting



- In Arm A, efficacy of zanubrutinib treatment was better in complete responders in terms of DOR rates, PFS rates and OS rates at 12 months (**Table 5**)

Table 5: Summary of DOR, PFS and OS by CR and PR in Arm A

	CR	PR
DOR Rate at 12 Months, % (95% CI) [a]	91.3 (81.9, 100)	36.7 (19.8, 80.1)
PFS Rate at 12 Months, % (95% CI) [a]	93.1 (84.2, 100)	64.8 (43.5, 100)
OS Rate at 12 Months, % (95% CI) [a]	93.1 (84.4, 100)	78.7 (58.8, 100)

Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; PFS, progression free survival; OS, overall survival; PR, partial response.
Notes: [a] The DOR rate, PFS rate and OS rate at 12 months were calculated by the Kaplan-Meier method with 95% CI constructed by the Greenwood's formula.

- In general, safety profile of zanubrutinib treatment in Arm A was also better in extent of exposure and adverse events, especially in adverse events of special interest including diarrhea, major hemorrhage and atrial fibrillation/flutter (**Table 6**)

Table 6: Summary of Extent of Exposure and Adverse Events after Weighting

		Arm A	Arm B	Total
Extent of Exposure	Duration of Treatment, (Month)	16.4	13.8	14.8
	Dose Reduction Due to AE, %	0.0	2.4	1.5
	Dose Interruption Due to AE, %	4.4	10.0	8.0
	Dose Modification Due to AE, %	4.4	10.0	8.0
	Treatment Discontinuation, %	40.4	52.0	47.8
	Due to AE	10.8	11.2	11.0
	Due to PD	29.7	36.9	34.3
	Due to Withdrawal	0.0	2.6	1.7
	Due to Investigators	0.0	1.3	0.8
Adverse Events [a]	At Least One AE, %	96.1	98.2	97.4
	At Least One ≥ Grade 3 AE, %	45.1	42.2	43.3
	At Least One AE Leading to Death, %	2.4	9.1	6.7
	At Least One SAE, %	35.9	25.2	29.1
	At Least One AESI [b], %	82.3	85.9	84.6
	Diarrhea	**15.5**	**24.4**	**21.2**
	Hypertension	12.1	10.9	11.3
	Major Hemorrhage	**1.1**	**6.4**	**4.5**
	Atrial Fibrillation/Flutter	**1.1**	**3.8**	**2.8**

Abbreviations: AE, adverse events; AESI, adverse events of special interest; PD, progressive diseases; SAE, serious AE.
Notes: [a] Adverse event grades were evaluated based on NCI-CTCAE Version 4.03. [b] AESI included haemorrhage (including minor bleeding such as contusion and petechiae), major haemorrhage, atrial fibrillation and flutter, hypertension, second primary malignancies, tumor lysis syndrome, infection and cytopenias.

CONCLUSIONS

- By inverse propensity score weighting, imbalance in baseline characteristics between groups with different prior lines of therapy was adjusted
- Zanubrutinib administered in the second line rather than in later lines led to a higher CRR
- When treated with zanubrutinib in the second line, MCL patients with deep responses had durable disease control
- Zanubrutinib was well tolerated with low rates of discontinuation due to AE in both arms; and rates of bleeding and atrial fibrillation/flutter were lower for second line use

REFERENCES

1. Guo Y et al. *J Med Chem*. 2019; 62: 7923-7940. 2. Tam CS, et al. *Blood*. 2019; 134: 851-859. 3. Song Y, et al. ICML 2019, Abstract #15 4.Cheson BD, et al. *J Clin Oncol*. 2014; 32: 3059-3068. 5. Austin PC. *Multivariate Behav Res*. 2011; 46: 399-424.

DISCLOSURES

KZ, DZ, JZ, JH, HY, HZ, JJ, WX, JJ, FL, RF, SG, DZ and **YS**: no relevant financial relationship to disclose. **CST:** honoraria from BeiGene, Janssen and AbbVie; consulting or advisory role with BeiGene, Janssen and AbbVie; research funding from BeiGene, Janssen and AbbVie. **DS:** employment and stock and other ownership interests with BeiGene; honoraria from AbbVie, Janssen, Roche; consulting or advisory role with Janssen and AbbVie; research funding from BeiGene, Amgen, AbbVie, Roche, Celgene, MSD, Acerta Pharma, Pharmacyclics, Sanofi and GSK; travel, accommodations and expenses from AbbVie. **MW:** stock or other ownership from MoreHealth; honoraria from Pharmacyclics, Janssen, AstraZeneca, OMI, Targeted Oncology, OncLive; consulting or advisory role with Pharmacyclics, Celgene, Janssen, AstraZeneca, MoreHealth, Pulse Biosciences, Nobel Insights, Guidepoint Global, Kite Pharma, Juno, Loxo Oncology; research funding from Pharmacyclics, Janssen, AstraZeneca, Kite Pharma, Juno, Celgene, Loxo Oncology, VelosBio, Verastem; travel, accommodations and expenses from Janssen, Pharmacyclics, Celgene, OMI, Kite Pharma, AstraZeneca. **TP:** honoraria from Fava Oncology; consulting or advisory role with Pharmacyclics, Celgene, Genentech, Gilead, Seattle Genetics, Curis and Bayer; research funding from Abbvie, Bayer and Incyte. **SO:** honoraria from AbbVie, Roche, AstraZeneca, Merck, Gilead, Janssen, Novartis; consulting or advisory role with AbbVie, Roche, AstraZeneca, Merck, Gilead, Novartis, Janssen; research funding from BeiGene, Roche, AstraZeneca, Janssen, Merck, Amgen, Epizyme. **HL** and **ZH:** employment and stock ownership with BeiGene

ACKNOWLEDGMENTS

We thank the investigators, site support staff, and especially the patients for participating in this study. This study was sponsored by BeiGene