

Indirect Comparisons of Efficacy of Zanubrutinib versus Orelabrutinib in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma or Relapsed or Refractory Mantle Cell Lymphoma

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Objectives

- Two next-generation Bruton tyrosine kinase inhibitors, zanubrutinib and orelabrutinib, are approved in China for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or mantle cell lymphoma (MCL) who have received at least one prior therapy.
- In the absence of head-to-head studies comparing zanubrutinib versus orelabrutinib, we conducted two indirect comparisons to estimate the efficacy of zanubrutinib versus orelabrutinib in patients with relapsed or refractory (R/R) CLL/SLL or R/R MCL.

Methods

R/R CLL/SLL patients:

- An unanchored matching-adjusted indirect comparison (MAIC)^[1] was performed in patients with R/R CLL/SLL.
- Individual patient data from zanubrutinib trial (BGB-3111-205 [n=91])^[2] were adjusted to match the aggregate baseline characteristics reported in orelabrutinib trial (ICP-CL-00103 [n=80])^[3,4].
- The baseline characteristics to be matched in MAIC included all available prognostic factors and effect modifiers that were reviewed by clinical experts, including age, sex, Eastern Cooperative Oncology Group performance status, bulky disease, del (17p) or TP53 mutation, del (11q), IGHV mutation, Trisomy 12, prior lines of treatment.

R/R MCL patients:

- A naïve comparison was performed in patients with R/R MCL due to the different response assessment methodology between zanubrutinib trial (all by PET-CT in BGB-3111-206 [n=86])^[5] and orelabrutinib trial (28 patients by PET-CT and 78 patients by CT in ICP-CL-00102 [n=106])^[6].

Efficacy outcomes:

- Overall response rate (ORR)
- Progression free survival (PFS)

Results

» R/R CLL/SLL patients «

Baseline characteristics

- Compared with ICP-CL-00103 study, patients in BGB-3111-205 had higher percentage of IGHV unmutated, del (17p) or TP53 mutation, and lower percentage of age <65 years (Table 1).
- After matching, the baseline characteristics were balanced between orelabrutinib versus zanubrutinib.

Table 1 Baseline characteristics of orelabrutinib versus zanubrutinib in patients with R/R CLL/SLL					
Characteristics	ICP-CL-00103		BGB-3111-205		
	Orelabrutinib (N=80)	P value	Before matching		P value
			Zanubrutinib (N=85)*	Zanubrutinib (ESS=66)	
Age <65 years, %	72	0.45	66	72	1
Male, %	64	0.52	58	64	1
ECOG PS ≥1	94	0.65	96	94	1
Bulky disease LD ≥5 cm, %	42	1	42	42	1
Del(17p) or TP53 mutation, %	22	0.75	26	23	1
Del(11q), %	24	0.83	21	24	1
IGHV unmutated, %	41	0.07	56	41	1
Trisomy 12, %	19	0.85	21	19	1
Prior lines of treatment <2, %	54	0.80	51	54	1

ECOG PS, Eastern Cooperative Oncology Group performance status; LD, longest diameter; ESS, effective sample size. *One SLL patient with Ann-Arbor stage Phase 1 and five CLL patients with Binet stage A were excluded from BGB-3111-205 to match the population of ICP-CL-00103.

Efficacy

Response rates

- After matching, ORR assessed by IRC was comparable between zanubrutinib versus orelabrutinib^[3] (Table 2).

Table 2 Best responses by IRC after matching of zanubrutinib versus orelabrutinib			
	Zanubrutinib ESS=66	Orelabrutinib N = 80	Risk difference
Median follow up time, months	34	25.6	
ORR, % (95% CI)	86.6 (77.5, 93.0)	92.5 (84.4, 97.2)	-5.9 (-15.8, 3.8)
CR ^a , % (95% CI)	5.7 (1.8, 13.0)	16.3 (8.9, 26.2)	-10.5 (-20.9, -1.1)
PR ^a , % (95% CI)	80.9 (70.9, 88.6)	66.4 (54.8, 76.4)	14.7 (1.2, 27.9)

IRC, independent review committee; ORR, overall response rate; CR, complete response; PR, partial response; ESS, effective sample size. *CR included CR and CR with incomplete bone marrow recovery (CRI). No patient was CRI in zanubrutinib, and 1.3% of patients were CRI in orelabrutinib. ^aPR included PR and PR with lymphocytosis.

- After matching, ORR assessed by investigator was also similar between zanubrutinib versus orelabrutinib^[4] (90.1% vs. 93.8%; risk difference, -3.7% [95% CI: -12.8%, 5.2%]).

Survival outcomes

- For survival outcomes assessed by IRC, zanubrutinib had higher PFS rate and favorable PFS compared with orelabrutinib^[3] before and after matching (Figure 1 and Table 3).

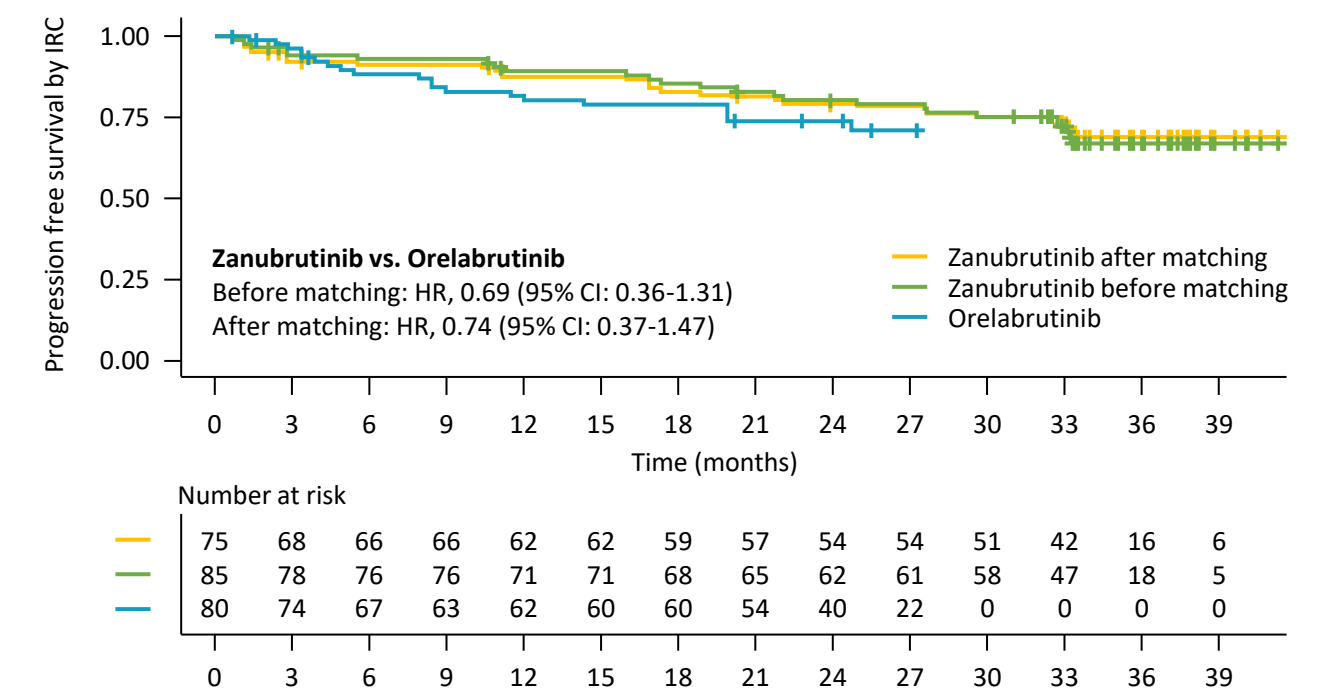


Table 3 Survival outcomes by IRC before and after matching of zanubrutinib versus orelabrutinib			
	Zanubrutinib	Orelabrutinib	HR (95% CI)
Median follow up time, months	34	25.6	
18-month PFS rate, % (95% CI)			
Before matching	85.4 (75.6, 91.4)	78.7 (75.6, 86.6)	
After matching	82.9 (70.5, 90.4)	78.7 (75.6, 86.6)	
PFS, median (95% CI) months			
Before matching	NR	NR	0.69 (0.36-1.31)
After matching	NR	NR	0.74 (0.37-1.47)

IRC, independent review committee; PFS, progression free survival; NR, not reached.

- We also evaluated the survival outcomes assessed by investigator.
- With the median follow up of 34 months in zanubrutinib and 33 months in orelabrutinib^[4], zanubrutinib showed favorable PFS compared with orelabrutinib after matching, with a higher 30-month PFS rate (73.6% vs. 69.7%).

» R/R MCL patients «

Baseline characteristics

- In R/R MCL patients, due to the different response assessment methodology between zanubrutinib trial (all by PET-CT) and orelabrutinib trial (only 28 out of 106 patients by PET-CT), herein, we reported the unadjusted naïve comparison results (Table 4).

Table 4 Baseline characteristics of orelabrutinib versus zanubrutinib in patients with R/R MCL			
	ICP-CL-00102	BGB-3111-206	P value
	Orelabrutinib (N=106)	Zanubrutinib (N=86)	
Age <65 years, %	72	74	0.80
Male, %	79	78	0.96
ECOG PS ≥1	54	30	<0.01
Bulky disease LD ≥5 cm, %	39	45	0.43
Bone marrow involvement, %	41	45	0.60
Stage III-IV, %	94	91	0.49
Prior lines of treatment ≥2, %	55	71	0.03

ECOG PS, Eastern Cooperative Oncology Group performance status; LD, longest diameter

Efficacy

Response rates

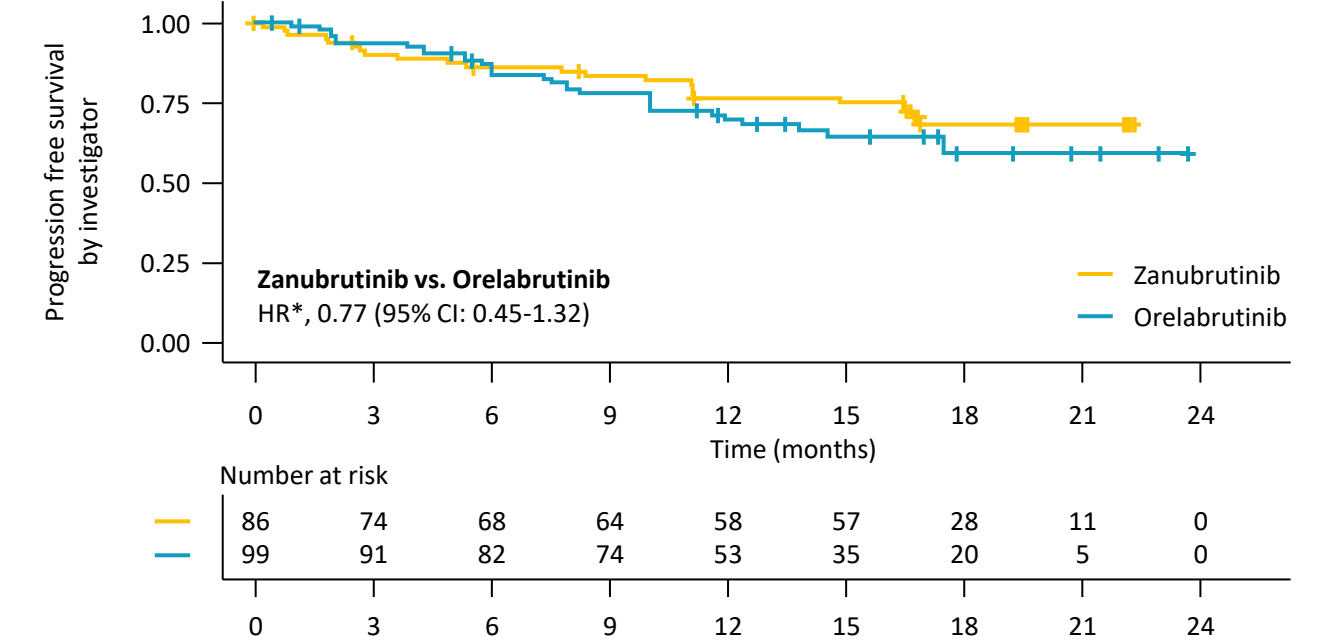
- ORR was similar between zanubrutinib versus orelabrutinib.
- CR rate was significantly higher in zanubrutinib compared with orelabrutinib.

Table 5 Best responses of zanubrutinib versus orelabrutinib			
% (95% CI)	Zanubrutinib* N = 86	Orelabrutinib* N = 99	Risk difference
ORR	83.7 (74.2, 90.8)	87.9 (79.8, 93.6)	-4.2 (-14.8, 6.0)**
CR	77.9 (67.7, 86.1)	42.9 (24.5, 62.8) [†]	35.0 (14.5, 53.7)
		34.3 (25.0, 43.8)	
PR	5.8 (1.9, 13.0)	53.5 (43.8, 63.5)	-48.0 (-58.1, -36.7)**

ORR, overall response rate; CR, complete response; PR, partial response. *Response evaluations were based on PET-CT. Efficacy analyses included patients who received at least one dose of zanubrutinib (n=86). [†]Response evaluations were based on CT. Efficacy analyses included 99 evaluable patients, 7 patients were not evaluable due to protocol violation, adverse event or dropped out before first assessment. [†]CR was evaluated based on PET-CT (n=28). **The response assessment methodology are different between trials, the risk difference of ORR and PR are descriptive and for reference only.

Survival outcomes

- PFS was favorable in zanubrutinib compared with orelabrutinib (HR, 0.77 [95% CI: 0.45-1.32]) (Figure 2 and Table 6).



*The response assessment methodology are different between trials; the HR is descriptive and for reference only.

Table 6 Survival outcomes by investigator of zanubrutinib versus orelabrutinib			
	Zanubrutinib	Orelabrutinib	HR (95% CI)
Median follow up time, months	18.4	16.4	
6-month PFS rate, % (95% CI)	86.7 (77.2, 92.4)	84.9 (76.1, 90.6)	
12-month PFS rate, % (95% CI)	77.5 (66.6, 85.2)	70.8 (60.5, 78.9)	
PFS, median (95% CI) months	NR	NR (17.3, NR)	0.77 (0.45-1.32)*

PFS, progression free survival; NR, not reached. *The response assessment methodology are different between trials; the HR is descriptive and for reference only.

Conclusions

- For R/R CLL/SLL patients, in this MAIC-based comparative efficacy assessment, zanubrutinib demonstrated a comparable ORR but more favorable PFS compared with orelabrutinib.
- For R/R MCL patients, based on naïve comparison, zanubrutinib showed a higher CR rate and favorable PFS compared with orelabrutinib.

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Contributions

All authors contributed to the data interpretation, writing and review of the abstract, and provided final approval of the submitted version.

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