LONG-TERM OUTCOMES OF SECOND-LINE VS LATER-LINE ZANUBRUTINIB TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY MCL: AN UPDATED POOLED ANALYSIS

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INTRODUCTION

Zanubrutinib as an effective treatment option for mantle cell lymphoma (MCL) has been approved in the United States and China as monotherapy in patients with relapsed/refractory (R/R) MCL. We previously reported results of a pooled analysis of two zanubrutinib studies (BGB-3111-206 and BGB-3111-AU-003) with a median follow-up of 24.9 months, and showed numerically better progression free survival (PFS) and overall survival (OS) when zanubrutinib was administrated in the second line (with 1 prior line of therapy) compared with the later line (with >1 prior lines of therapy) for R/R MCL [1].

OBJECTIVES

Here, we present a longer follow-up (median 35.2 months) of the pooled data to compare long-term outcomes of second-line versus later-line of zanubrutinib treatment for R/R MCL patients.

METHOD

- This was a pooled analysis. Patient-level data were pooled for R/R MCL patients treated with zanubrutinib from a phase I study (BGB-3111-AU-003, NCT02343120) and a phase II study (BGB-3111-206, NCT03206970). The patients were divided into two groups based on the treatment line of zanubrutinib: the second-line and the later-line group. Inverse propensity score weighting method was used to balance the baseline covariates between the groups to mimic a randomized controlled trial [2].
- The primary outcome was OS. Secondary outcomes included PFS, PFS rate and OS rate at 12, 24 and 36 months, objective response rate (ORR) and duration of response (DOR). The safety profile in each arm was summarized.
- Survival probability was estimated by the Kaplan–Meier method. Cox proportional hazards model was used to compute hazard ratio (HR) and 95% confidence interval (CI) for PFS and OS. P value of less than 0.05 was considered to indicate statistical significance. However, hypothesis testing was not pre-stated.

RESULTS

Baseline characteristics

- A total of 112 patients with R/R MCL were pooled (79 in BGB-3111-206, 33 in BGB-3111-AU-003), among which 41 (36.6%) patients received zanubrutinib as second-line therapy and 71 (63.4%) patients as later-line.
- Before weighting, the second-line group had higher percentages of patients with age ≥65 years (46.3% vs 31.0%) and MIPI high risk scores (26.8% vs 18.3%), and lower percentages of patients with extra nodal disease (51.2% vs 64.8%) and blastoid subtype (2.4% vs 18.3%). After weighting, the baseline characteristics were balanced between the two groups (Table 1).

Table 1 Baseline characteristics in second-line group and later-line group before and after weighting

Characteristics	Before weighting		After weighting	
	Second-line therapy N=41	Later-line therapy N=71	Second-line therapy N=30	Later-line therapy N=61
Age, mean (SD) years	63.2 (11.3)	60.6 (9.0)	61.0 (10.2)	61.2 (9.9)
Age ≥65 years, n (%)	19 (46.3%)	22 (31.0%)	34%	35%
Males, n (%)	34 (82.9%)	52 (73.2%)	79%	77%
BMI, mean (SD)	25.4 (4.1)	24.7 (4.2)	24.7 (4.0)	24.8 (4.3)
ECOG PS >1, n (%)	2 (4.9%)	4 (5.6%)	3%	4%
Disease stage, n (%)				
I	2 (4.9%)	1 (1.4%)	4%	4%
II	2 (4.9%)	5 (7.0%)	5%	6%
III	4 (9.8%)	10 (14.1%)	18%	14%
IV	33 (80.5%)	55 (77.5%)	73%	76%
Blastoid variant, n (%)	1 (2.4%)	13 (18.3%)	2%	12%
Bulky disease*	13 (31.7%)	29 (40.8%)	41%	39%
Extra-nodal disease, n (%)	21 (51.2%)	46 (64.8%)	63%	62%
MIPI, n (%)				
Low risk	19 (46.3%)	36 (50.7%)	53%	49%
Intermediate risk	11 (26.8%)	22 (31.0%)	28%	30%
High risk	11 (26.8%)	13 (18.3%)	19%	21%
Refractory disease, n (%)	26 (63.4%)	48 (67.6%)	60%	71%

* Bulky disease defined as at least one lesion with longest diameter >5 cm.
ECOG PS, Eastern Cooperative Oncology Group performance status; MIPI, Mantle Cell Lymphoma International prognostic index; SD, standard deviation
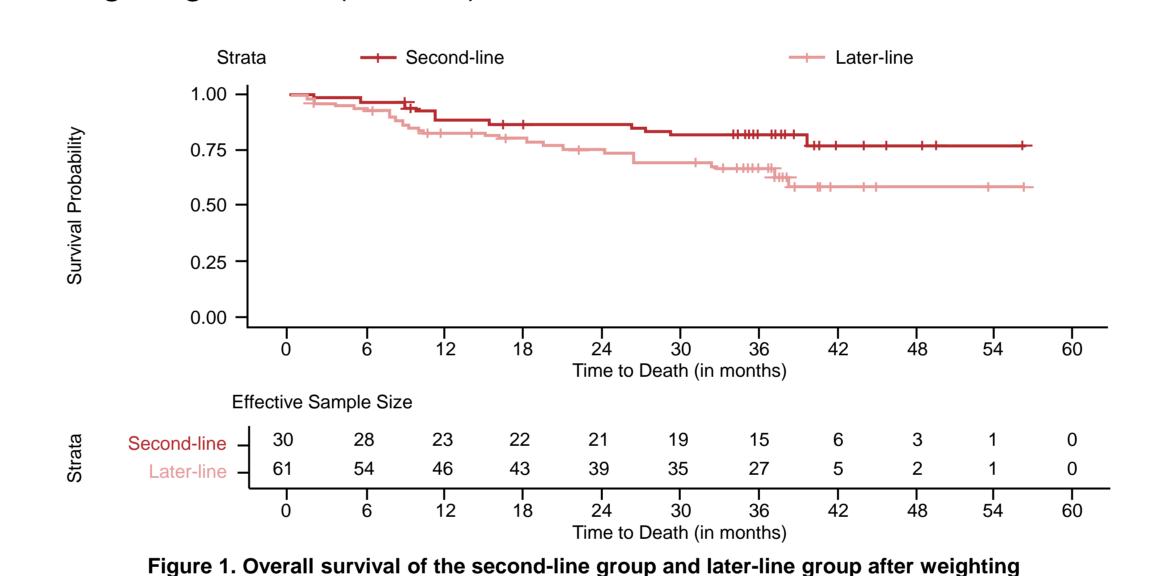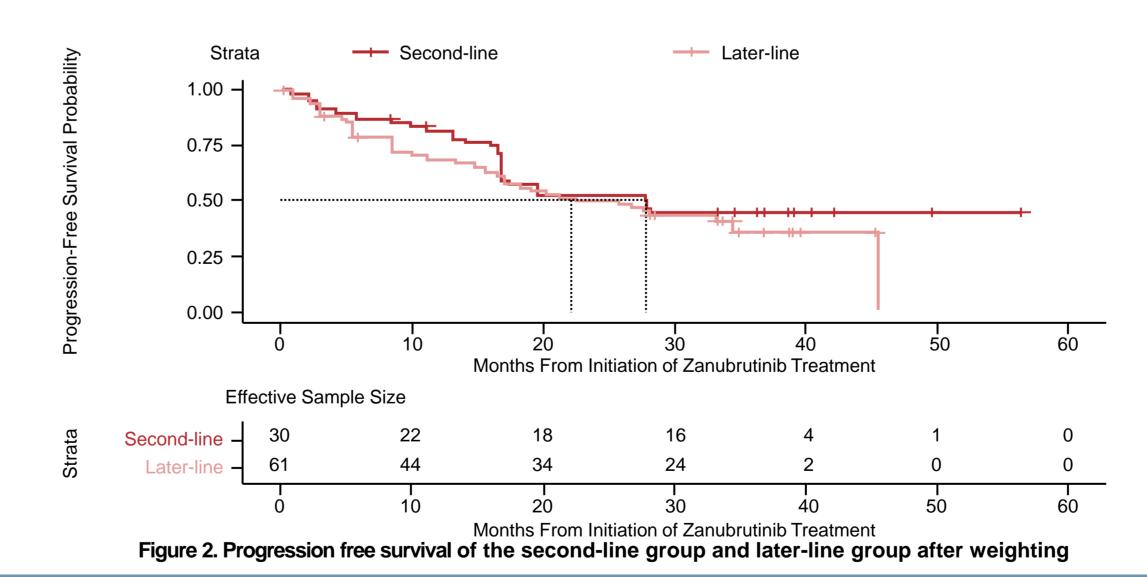
EFFICACY OUTCOMES

OS

- After weighting, with the median follow up of 37.0 months in the second-line group and 34.6 months in the later-line group, OS was statistically significantly improved in the second-line group versus the later-line group (median OS: NR vs NR; HR 0.459 [95% CI, 0.215-0.980], $p = 0.044$) (Figure 1 and Table 2).

- The 36-month OS rate was also numerically higher in the second-line group versus the later-line group (82.0% vs. 66.5%).
- OS in the original sample had the consistent results with the post-weighting results (Table 2).

PFS

- After weighting, PFS was similar between the second-line group and the later-line group (HR 0.78 [95% CI, 0.443-1.373], p = 0.389), with numerically longer median PFS in the second-line group versus the later-line group (27.8 vs 22.1 months) (Figure 2 and Table 2).
- The 36-month PFS rate was numerically higher in the second-line group versus the later-line group (44.8% vs. 35.4%).
- PFS in the original sample had the consistent results with the post-weighting results (Table 2).

Figure 1. Overall survival of the second-line group and later-line group after weighting

Figure 2. Progression free survival of the second-line group and later-line group after weighting

Response rate and duration

- ORR and DOR were similar between the second-line group and the later-line group (Table 2).

Table 2 Efficacy outcomes of second-line and later-line group before and after weighting

	Before weighting		After weighting	
	Second-line group (n=41)	Later-line group (n=71)	Second-line group (EES=30)	Later-line group (EES=61)
Median follow up, months	36.1	34.4	37.0	34.6
ORR, % (95% CI)	87.8 (73.7, 95.9)	83.1 (72.3, 91.0)	88.6 (73.8, 96.6)	85.7 (75.6, 92.8)
Median DOR, months (95% CI)	NR (14.7, NE)	30.6 (19.5, 43.1)	25.2 (14.1, NE)	25.1 (17.5, 43.0)
Median PFS, months (95% CI)	27.8 (16.8, NE)	25.8 (16.7, 45.5)	27.8 (16.8, NE)	22.1 (16.6, 45.5)
Median OS, months (95% CI)	NR (NE, NE)	NR (37.1, NE)	NR (NE, NE)	NR (38.2, NE)
PFS rate at, % (95% CI)				
12 months	77.3 (65.8, 91.5)	69.6 (59.8, 81.4)	81.6 (70.7, 94.5)	68.0 (57.2, 81.7)
24 months	53.3 (40.5, 71.9)	50.3 (40.1, 63.9)	52.4 (38.7, 74.3)	49.8 (39.1, 64.5)
36 months	45.3 (32.9, 64.4)	36.8 (26.8, 52.0)	44.8 (31.8, 66.9)	35.4 (25.0, 52.3)
OS rate at, % (95% CI)				
12 months	84.9 (74.8, 96.7)	79.9 (71.2, 89.9)	88.4 (79.8, 98.2)	82.6 (74.2, 92.1)
24 months	82.3 (71.7, 95.1)	72.1 (62.5, 83.7)	86.4 (77.2, 97.0)	75.2 (65.7, 86.6)
36 months	74.1 (62.0, 89.3)	62.4 (52.1, 75.5)	82.0 (71.7, 94.1)	66.5 (56.0, 79.5)

ORR, objective response rate; DOR, duration of response; PFS, progression free survival; OS, overall survival; CI, confidence interval; NR, not reached; NE, not estimable; ESS, effective sample size.

SAFETY

- The safety profile was similar between the two groups (all grade AEs: 95.1% vs 97.2%).
- Grade ≥3 AESI were rare in both the second-line and later-line groups (Table 3).

Table 3 Grade ≥3 AESI

Grade ≥3 AESI, %	All n=112	Before weighting		After weighting	
		Second-line group n=41	Later-line group n=71	Second-line group ESS=30	Later-line group ESS=61
Atrial fibrillation/flutter	2	2	1	1	2
Diarrhea	1	0	1	0	1
Hemorrhage	4	2	4	1	3
Hypertension	3	2	3	4	2

AESI: adverse event of special interest; ESS, effective sample size

CONCLUSIONS

The long-term follow-up further confirmed that zanubrutinib in the second-line treatment was significantly associated with prolonged OS compared with later-line treatment in patients with R/R MCL. Which suggested that earlier treatment with zanubrutinib is associated with better survival outcomes.

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