EFFICACY AND SAFETY OF ZANUBRUTINIB VERSUS RITUXIMAB-BASED CHEMOIMMUNOTHERAPY IN WALDENSTRÖM MACROGLOBULINEMIA (WM): MATCHING-ADJUSTED INDIRECT COMPARISONS

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Background

- Waldenström macroglobulinemia (WM) is a rare, indolent B-cell lymphoma, commonly treated with rituximab-based regimens or Bruton tyrosine kinase inhibitors (BTKi)
- In February 2021, the US FDA accepted a supplemental new drug application for zanubrutinib, an orally administered BTKi, for the treatment of adults with WM, based on the results of a phase 3 ASPEN trial (NCT03053440) in patients who have received ≥1 prior therapy or as first-line treatment for patients unsuitable for chemo-immunotherapy
- However, there is a lack of randomized trials directly comparing zanubrutinib with chemoimmunotherapies

Objectives

- This study aimed to indirectly compare zanubrutinib with bendamustine-rituximab (BR) and with dexamethasone-rituximab-cyclophosphamide (DRC), the most commonly administered chemoimmunotherapy regimens

Methods

- Two single-arm studies identified in a systematic literature review (conducted in September 2020) were included in the indirect treatment comparison: Tedeschi et al. for BR[1] and Dimopoulos et al. / Kastritis et al. for DRC[2,3]
- Using the algorithm proposed by Signorovitch et al.[4], matching-adjusted indirect comparisons (MAICs) were conducted to re-weight the individual data of 102 WM patients (83 relapsed/refractory [R/R] and 19 treatment-naïve [TN] unsuitable for chemoimmunotherapy) treated with zanubrutinib in the ASPEN trial (NCT03053440) so that the weighted average baseline characteristics of zanubrutinib patients could match those of 71 R/R patients treated with BR, and 72 TN patients treated with DRC separately
- Matching variables for MAIC with BR included age, prior lines of therapy, serum IgM level, International Prognostic Scoring System for WM score (IPSSWM), and extramedullary disease (EMD); and for MAIC with DRC included age, platelet count, hemoglobin level, and EMD
- For baseline patient characteristics and safety outcomes, summary mean estimates were extracted from comparator trial publications wherever available
- For survival outcomes, Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) of comparators were digitized to re-create patient-level data
- Comparisons of survival and adverse event incidence between treatments were conducted using Cox proportional-hazard models and modified Poisson models

Results

- After matching, the baseline characteristics were well balanced for each of the treatment comparisons ***(Table 1** and **Table 2)***
- Compared to DRC, zanubrutinib was associated with ***(Table 3)***
  - Longer PFS (*HR [95%CI]:* 0.39 [0.18-0.82] and 0.35 [0.14-0.86] pre- and post-matching, respectively)
  - Longer OS (*HR [95%CI]:* 0.56 [0.20-1.53] and 0.47 [0.14-1.62] pre- and post-matching, respectively)
  - Higher incidences of neutropenia (*RR [95%CI]:* 1.63 [0.71-3.77] and 1.47 [0.58-3.74] pre- and post-matching, respectively)
- Compared to BR, zanubrutinib was associated with ***(Table 3)***
  - Longer PFS (*HR [95%CI]:* 0.32 [0.15-0.69] and 0.37 [0.15-0.91] pre- and post-matching, respectively)
  - Longer OS (*HR [95%CI]:* 0.31 [0.12-0.80] and 0.29 [0.10-0.85] pre- and post-matching, respectively)
  - Lower incidence of neutropenia (*RR [95%CI]:* 0.45 [0.26-0.78], and 0.50 [0.27-0.91] pre- and post-matching, respectively)
  - Lower incidence of pneumonia (*RR [95%CI]:* 0.18 [0.02-1.55], and 0.26 [0.03-2.28] pre-and post-matching, respectively)

Abbreviations: HR = hazard ratio; RR = risk ratio; 95% CI = 95% confidence interval

Table 1. Baseline characteristics before and after adjustment for ASPEN zanubrutinib arm vs BR population

Baseline Characteristics	Patients, %		
	Zanubrutinib, Unadjusted n=102	BR n=71	Zanubrutinib, Adjusted n_{eff}=50
Age ≤72 years	57.8	50.0	50.0
0-2 prior lines of therapy	79.4	50.0	50.0
IgM ≤38.15 g/L	63.7	50.0	50.0
IPSSWM score, intermediate risk	37.3	30.4	30.4
IPSSWM score, high risk	46.1	48.2	48.2
Presence of extramedullary disease: either splenomegaly or adenopathy (by investigator)	61.8	42.3	42.3

Abbreviations: BR = bendamustine rituximab; IgM = Immunoglobulin M; IPSSWM = International Prognostic Scoring System for Waldenström macroglobulinemia; n_{eff}= effective sample size

Table 2. Baseline characteristics before and after adjustment for ASPEN zanubrutinib arm vs DRC population

Baseline Characteristics	Patients, %		
	Zanubrutinib, Unadjusted n=102	DRC n=72	Zanubrutinib, Adjusted n_{eff}=53
Age ≤65 years	40.2	37.5	37.5
Age 65-≤69 years	6.9	12.5	12.5
Age >69 years	52.9	50.0	50.0
Platelet count <100 ×109/L	11.8	4.2	4.2
Hemoglobin <100 g/L	47.1	56.9	56.9
Presence of extramedullary disease: lymphadenopathy (by investigator)	59.8	38.9	38.9
Presence of extramedullary disease: splenomegaly (by investigator)	15.7	31.9	31.9

Abbreviations: DRC = dexamethasone, rituximab, and cyclophosphamide; n_{eff} = effective sample size

Table 3. Survival and adverse event incidence of zanubrutinib vs BR/DRC pre- and post-matching adjustments

Outcomes	Zanubrutinib vs DRC			Zanubrutinib vs BR	
	Zanubrutinib pre-matching (N=102)	Zanubrutinib post-matching DRC (n_{eff}= 53)	DRC (N=72)	Zanubrutinib post-matching BR (n_{eff}=50)	BR (N=71)
PFS, 12-mo rate, %	94	92	85	94	79
PFS, 24-mo rate, %	85	90	68	81	59
OS, 12-mo rate, %	97	95	92	98	87
OS, 24-mo rate, %	90	94	85	88	77
Anaemia, %	5.0	4.2	NR	3.6	NR
Hypertension, %	5.9	3.1	NR	9.5	NR
Neutropenia, %	15.8	14.3	9.7	17.5	35.2
Pneumonia, %	1.0	0.6	NR	1.5	5.6
Thrombocytopenia, %	5.9	4.4	0.0	5.2	NR

Abbreviations: BR = bendamustine-rituximab; DRC = dexamethasone-rituximab-cyclophosphamide; mo = month; n_{eff} = effective sample size; NR = not reported; OS = overall survival; PFS = progression-free survival

Conclusions

Zanubrutinib demonstrated **longer PFS than DRC,**
and **longer PFS and OS and lower incidence of neutropenia than BR** in WM, both before and after matching adjustments

Discussions

Limitations

- The differences in patient populations (a mixed population for zanubrutinib [81% R/R and 19% TN unsuitable for chemoimmunotherapy] versus 100% TN [suitable for chemoimmunotherapy] population for DRC and 100% R/R population for BR) might have led to an underestimation of the relative clinical benefit of zanubrutinib compared with DRC and a potential bias for the comparison of zanubrutinib to BR
- It is rarely possible to completely adjust for all unobserved or unreported baseline patient characteristics, which is a general limitation of a MAIC. Despite that, the outcome comparison was conducted before and after matching adjustment, which consistently showed the survival benefit of zanubrutinib compared with the comparators

References

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