Received: 10 February 2023 | Revised: 21 April 2023 | Accepted: 25 April 2023

DOI: 10.1002/hon.3172

WILEY

REVIEW

Unmet clinical needs in the use of zanubrutinib in malignant lymphomas (Waldenström macroglobulinemia, marginal zone lymphoma and mantle cell lymphoma): A consensus-based position paper from an ad hoc expert panel

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Abstract

Zanubrutinib has been approved for the treatment of patients with different lymphoproliferative disorders, and now represents a major breakthrough in the treatment of patients resistant or relapsing after the recommended therapies. Because few systematic studies or comparative randomized clinical trials have been conducted, optimal use of the drug in approved indications is challenging, and questions are emerging on its use in earlier stages of the disorders. This article presents the results of group discussion among an ad hoc constituted panel of experts aimed at identifying and addressing unmet clinical needs (UCNs) in the use of zanubrutinib in the lymphomas which have received the approval of use, specifically Waldenström macroglubulinemia, marginal zone lymphoma and mantle cell lymphoma. Key UCNs were selected according to the criterion of clinical relevance using the Delphi process. The panel produced recommendations and proposals for new studies for the management of the identified UCNs. These recommendations are intended for use not only by expert centers but above all by not experienced hematologists as well as general practitioners.

KEYWORDS
mantle cell lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia, zanubrutinib

1 | INTRODUCTION

Zanubrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (Bruton tyrosine kinase (BTK)) approved for the treatment of patients with different lymphoproliferative disorders. Zanubrutinib, like the other second generation BTK inhibitor acalabrutinib, was specifically designed to overcome the limitation of the first generation ibrutinib by delivering important and continuous inhibition on the BTKprotein thus optimizing bioavailability, half-life, and selectivity. This agent has been demonstrated to inhibit the proliferation of malignant B cells within a number of disease relevant tissues, and is currently being evaluated as a monotherapy and in combination with other therapies to treat various B-cell malignancies.[1,2]

The results of clinical trials have documented that zanubrutinb now represents a potential major breakthrough in the treatment of lymphoid malignancies. However, due to limited number of comparative randomized trials, uncertainties still remain on the optimal use of the drug even in approved indications. Moreover, new questions are emerging on the use of zanubrutinib monotherapy in disorders whose use is not approved, and in combination with other therapies.

The objective of this project is to identify and address unmet clinical needs (UCNs) and to produce recommendations for the management of zanubrutinib in malignant lymphomas, specifically Waldenström macroglobulinemia (WM), marginal zone lymphoma (MZL) and mantle cell lymphoma (MCL). A subsequent project dealing with chronic lymphocytic leukemia is also planned by this group of experts. These recommendations should inform practice of therapy with zanubrutinib and address the scientific questions.

2 | DESIGN AND METHODS

One chairman (PLZ) appointed a panel of 6 experts selected for their expertize in research and clinical practice of adult lymphoid malignancies, hereafter called the Panel. A clinician with expertize in clinical epidemiology (GB) assured the methodological appropriateness of the process. During an initial meeting, the Panel agreed on the areas of major concern in the use of zanubrutinib by generating and rank-ordering clinical key-questions using the criterion of clinical relevance, that is, impact on the management of patients and risk of inappropriateness, through a Delphi process.[3] The candidate key-questions that ranked highest formed the set of UCNs of the present document. In the follow-up of the project, a structured literature search for English-language publications was performed. Electronic data-bases such as MEDLINE, EMBASE, reviews including Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register were used. During a second meeting, the Panel examined the current state of knowledge regarding zanubrutinib therapy in the selected domains. Furthermore, three panelists drafted statements that addressed the identified UCNs. In a further phase of the project, the remaining panelists scored their agreement with those statements and provided suggestions for rephrasing. For exploiting this phase of the process, the Panel was convened and three virtual consensus meetings were held. The overall goals of the meetings were to reach a definite consensus over question-specific statements for which there was disagreement during a first-round postal phase. The nominal group technique was used by which participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote.[3]

3 | RESULTS

Although numerous UCNs in the domain of indication and management of zanubrutinib in malignant lymphomas were issued by the Panel (Supplemental Table S1), this review focuses only on some of the major outstanding challenges voted as the most relevant and urgent by the panelists.

3.1 | UCN1. Indication for zanubrutinib monotherapy use in patients with WM

Waldenström Macroglobulinemia (WM) is an indolent B-cell lymphoma characterized by the presence of IgM monoclonal gammopathy and bone marrow infiltrate of clonal lymphoplasmacytic cells.[4] More than 90% of patients present an activating mutation of *MYD88*.[5,6] *MYD88* ^{MUT} results in the downstream activation of nuclear factor-kappa B (NF-κB) through BTK and interleukin-1 receptor-associated kinases in the B-cell receptor pathway leading to unregulated cell survival, proliferation, and migration. Acquired *CXCR4* activating mutations in the C-terminal domain have been reported in 30%–40% of patients. *CXCR4*^{MUT} genotype consists of more than 30 different activating mutations, both frameshift and nonsense variants, which may lead to activation of the pro-survival factors AKT and ERK.

The presence or absence (wild-type, *WT*) of these mutations enabled the identification of three genetic subgroups: *MYD88*^{L265P}/*CXCR4*^{WT} (50%–60%), *MYD88*^{L265P}/*CXCR4*^{MUT} (30%–40%), and *MYD88*^{WT}/*CXCR4*^{WT} (5%–10%). These subgroups are characterized by different clinical presentation, treatment responses and survival.[7]

Treatment choice depends on patients and disease characteristics.[8,9] The optimal choice and sequence of therapies is uncertain considering that the majority of published studies are non-randomized, often phase II studies including both de novo and relapsed disease.

The identification of *MYD88* ^{MUT} with downstream BTK activation led to the strong rational of BTK inhibition as therapeutic approach.[10] In 2015, the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved ibrutinib, a first-generation BTK inhibitor (BTKi), for the treatment of WM.[11] Since ibrutinib's initial approval, more selective BTKis have been developed, including zanubrutinib approved by FDA and EMA for WM in 2021.[12]

3.1.1 | Therapy for refractory or relapsed WM patients

For patients with R/R disease after chemo-based treatment, although guidelines consider feasible to repeat or alternate rituximab-containing regimens after a prolonged progression free survival (PFS), in clinical practice the attitude is to administer BTKi as salvage therapy, to avoid chemotherapy short and long term toxicities.[9,13]

Clinical trials data of BTKi in R/R patients are summarized in Table 1. Ibrutinib monotherapy received FDA approval based on the results of a phase II study addressed to 63 pretreated patients (40% refractory, 2 median lines of prior therapy).[14] The extended 59 months follow-up of the pivotal study demonstrated an overall response rate (ORR) of 90.5% with major responses (MRs) of 79.4%. VGPRs rate increased over time reaching 30.2%. Despite the prolonged follow-up median PFS of the whole population was not achieved.

Ibrutinib monotherapy also showed to be effective in patients failing to achieve at least a minor response or in early relapse (<12 months) after their last rituximab-containing therapy (arm C phase 3 iNNOVATE trial).[15] Response rates were in line with those observed in the pivotal trial, PFS was shorter, median reached at 39 months.

Similar results were seen in the R/R $MYD88^{MUT}$ cohort of patients treated in the ibrutinib arm of the phase 3 randomized ASPEN trial (zanubrutinib vs. ibrutinib).[16] Although the ASPEN trial has now a follow-up of 44.4 months, results stratified according to disease status are reported only in the first analysis at 19.4 months. The ORR rate in the R/R setting resulted 94%, with a rate of complete remission (CR) plus very good partial remission ,VGPR of 20% and PR of 61%. Good quality of response rate may seem lower than that observed in the pivotal trial but we should consider the different studies follow-up. Time on treatment is important as quality of responses with BTKi tend to ameliorate over time.[16,17]

Efficacy of ibrutinib is strictly dependent on patients genotype (Table 2). $MYD88^{WT}$ represents a poor predictive feature with low rates of responses and very short PFS.[14] Although $CXCR4^{MUT}$ and $CXCR4^{WT}$ patients obtain similar ORs, the presence of $CXCR4^{MUT}$ is associated with lower MRs, slower response kinetic, and a significantly shorter median PFS. The significant poor prognostic role of $CXCR4^{MUT}$ has been also demonstrated in a large study including patients from a prospective single center database and from 2 clinical trials.[22]

The phase 3 iNNOVATE study comparing ibrutinib plus rituximab versus rituximab plus placebo demonstrated a number of

TABLE 1 Bruton tyrosine kinase (BTK) inhibitors clinical trials in refractory or relapsed patients with Waldenström macroglobulinemia.

Study	N° pts	ORR	CR + GVPR	PR	Median FU time	Outcomes
Ibrutinib						
Treon et al.[14]	63	90.5%	30.2%	49.2%	59 m	Median PFS NR 5 years PFS rate, 54%
Trotman et al.[15]	31	87%	29%	48%	58 m	Median PFS 39 m 60 m PFS rate 40%
Tam et al.[16,17]	81	94%	20%	61%	19.4 m	Median PFS NR 18 m PFS rate 82%
Ibrutinib + rituximab						
Buske et al.[18]	41	93%	34%	42%	50 m	Median PFS NR 54 m PFS rate 68%
Acalabrutinib						
Owen et al.[19]	92	95%	27%	57%	63.7 m	Median PFS: 67.5 m 66 m PFS rate 52%
Zanubrutinib						
Trotman et al.[20]	53	93.9%	51%	28.6%	36 m	Median PFS NR 36 m PFS rate 76.2%
An et al.[21]	43	76.7%	32.6%	37.2%	33 m	Median PFS NR 24 m PFS rate 60.5%
Tam et al.[16,17]	83	94%	29%	49%	19.4 m	Median PFS NR 18 m PFS rate 86%

Abbreviations: CR, complete remission; FU, follow-up; m, months; NR, not reached; ORR, overall response rate; PFS, progression free survival; VGPR, very good partial remission.

TABLE 2 Bruton tyrosine kinase (BTK) inhibitors treatment: Responses and outcome according to genotype in patients with Waldenström macroglobulinemia.

Study	Disease status	Genotype: N[a] pts	ORR	CR + GVPR	PR	Median time	Median FU	Outcomes
Ibrutinib								
Treon et al.[14]	R/R	*MYD88*^{MUT}/*CXCR4*^{WT}: 36	100%	47.2%	50%	MR: 1.8 m	59 m	Median PFS: NR. 5 years PFS 70%
		MYD88^{MUT}/*CXCR4*^{MUT}: 22	86.4%	9.1%	59.1%	MR: 4.7 m		Median PFS: 4.5 years 5 years PFS 38%
		MYD88^{WT}: 4	50%	0%	0	NA		Median PFS: 0.4 years
Trotman et al.[15]	R/R	*MYD88*^{MUT}/*CXCR4*^{WT}: 17	88%	41%	47%	MR: 1 m	58 m	Median PFS: NR
		MYD88^{MUT}/*CXCR4*^{MUT}: 7	86%	14%	57%	MR: 3.6 m		Median PFS: 18 m
		MYD88^{WT}: 1	0	0	0			PFS: 6 m
Tam et al.[16,17]	TN/RR	*MYD88*^{MUT}/*CXCR4*^{WT}: 72	94.4%	30.6%	54.1%	MR: 2.8 m; VGPR 11.3 m	44.1 m	Not reported
		MYD88^{MUT}/*CXCR4*^{MUT}: 20	95%	10%	55%	MR: 6.6 m; VGPR: 31.3 m		42 m PFS rate 49%
Castillo et al.[22]	TN/RR	*MYD88*^{MUT}/*CXCR4*^{WT}: 155	97%	35.7%	50%	NA	NA	Median PFS: NR. 5 years PFS rate 71%
		MYD88^{MUT}/*CXCR4*^{MUT}: 89	88%	16%	51%	NA		Median PFS: 4.4 years 5 years PFS rate 39%
Castillo et al.[23]	TN	*MYD88*^{MUT}/*CXCR4*^{WT}: 16	100%	44%	50%	MR:1.8 m	50.1 m	Median PFS: NR. 4 years PFS rate 92%
		MYD88^{MUT}/*CXCR4*^{MUT}: 14	100%	14%	64%	MR:7.3 m		Median PFS: NR. 4 years PFS rate 59%
Ibrutinib + Rituximab								
Buske et al.[18]	TN/RR	*MYD88*^{MUT}/*CXCR4*^{WT}: 32	94%	44%	38%	MR: 2 m	50 m	Median PFS: NR. 54 m PFS rate 79%
		MYD88^{MUT}/*CXCR4*^{MUT}: 26	100%	23%	54%	MR: 3 m		Median PFS: NR. 54 m PFS rate 63%
		MYD88^{WT}:11	82%	27%	45%	MR: 7 m		Median PFS: NR. 54 m PFS rate 70%
Acalabrutinib								
Owen et al.[19]	TN/RR	*MYD88*^{MUT} 36	94% 79%	11%	69%	Best response: 4.6 m[a]	27.4 m	NA
		MYD88^{WT} 14		0	64%			
Zanubrutinib								
Trotman et al.[20]	TN/RR	*MYD88*^{MUT}/*CXCR4*^{WT}: 39	97%	59%	28.2%	MR: 2.8 m[a]	36 m	Median PFS: NR.[a]
		MYD88^{MUT}/*CXCR4*^{MUT}: 11	100%	27.3%	63.6%			24 m PFS rate 91.5%[a]
		MYD88^{WT}: 8	100%	25%	37.5%			
An et al.[21]	R/R	*MYD88*^{MUT}/*CXCR4*^{WT}: 32	81.3%	40.6%	34.4%	NA	33 m	Median PFS NR. 24 m PFS rate 66.9%
		MYD88^{MUT}/*CXCR4*^{MUT}: 5	60%	0	60%			Median PFS NR. 24 m PFS rate 53.3%
		MYD88^{WT}: 6	66.7%	16.7	33.3			Median PFS NR. 24 m PFS rate 33.3%

TABLE 2 (Continued)

Study	Disease status	Genotype: N[a] pts	ORR	CR + GVPR	PR	Median time	Median FU	Outcomes
Tam et al.[16,17]	TN/RR	*MYD88*^{MUT}/ *CXCR4*^{WT}: 65	96.9%	44.6	38.5%	MR: 2.8 m; VGPR 6.5 m	44.1 m	NA
		MYD88^{MUT}/ *CXCR4*^{MUT}:33	90.9%	21.2	57.6%	MR: 3.4 m; VGPR: 11.1 m		Median PFS:NR. 42 m PFS rate 73.2%
Tam et al.[17]	TN/RR	*MYD88*^{WT}:28	80.4%	30.7%	34.6%	NA	42.9 m	Median PFS NR. 42 m PFS 53.8%

Abbreviations: m, months; MR, major response; NA, not available; NR, not reached; RR, relapsed/refractory; TN, treatment-naïve; VGPR, very good partial remission.

[a]Data reported for the whole population.

benefits in combining the BTKi with the MoAb.[18] The addition of MoAB to ibrutinib allows to overcome the predictive unfavorable outcome of genotype features.

The second generation BTKi acalabrutinib in monotherapy, similarly to ibrutinib, led to high ORs (95%) in 92 R/R patients with 27% reaching at least a VGPR. Median PFS was reached at 67.5 months. *CXCR4* status was not analyzed. As observed with ibrutinib, *MYD88*^{WT} patients showed lower OR rates (79% vs. 94%) and no CRs or VGPRs were recorded.[19,24]

No head-to-head studies addressed the role of acalabrutinib compared to the other BTKi in WM.

3.1.2 | Zanubruitnib in R/R patients

In the first trial (phase I/II) evaluating the role of zanubrutinib in WM, 53 among the 77 enrolled patients had been previously treated.[20] ORR obtained with zanubrutinib was high (93.9%) not different from the overall responses observed with ibrutinib and acalabrutinib. Major responses were seen in 79.6% R/R patients with a short median Time to response (TTR) of 2.8 months. Importantly the rate of at least VGPR was the highest observed with a BTKi treatment, 51% at 24 months. Responses increased during treatment, being 24.5% at 6 months and 38.8% at 12 months with evidence of a response plateau beginning approximately at 20 months. Zanubrutinib allowed to obtain a response in all *MYD88*^{WT} patients, with 25% reaching a good quality response. Despite MR rates being similar when patients were stratified according to *CXCR4*, deeper responses (≥VGPR) were observed in the subset of *CXCR4*^{WT} (59% vs. 27.3%).

Similar results with favorable VGPR or better (32.6%) were obtained after a median follow-up of 33 months in the phase 2 study enrolling Chinese patients only.[21] Again all mutation subgroups benefited from zanubrutinib with deeper responses seen in *MYD88*^{MUT}/*CXCR4*^{WT} patients.

Based on the deep responses of the phase I/II trial, the phase III randomized ASPEN trial, ibrutinib versus zanubrutinib, was designed with the primary objective of better CRs plus VGPRs in patients receiving the next generation BTKi. *MYD88*^{MUT} patients (cohort1) were randomized to receive one of the two inhibitors,[16,17] those *MYD88*^{WT} received zanubrutinib directly considering the poor outcome demonstrated with ibruitnib.[25]

The majority of patients enrolled in cohort 1 had R/R disease. At the first follow-up of 19.4 months the ORR, 94% for zanubrutinib and 94% for ibrutinib, as well as MRs (78% vs. 80% respectively) were similar in both arms. The primary objective of the study of a better quality of responses with zanubrutinib according to independent review committee (IRC) was not met ($p = 0.09$). The 18 months PFS was not different with the two BTKi (82% with ibrutinib and 86% with zanubrutinib).

The longer follow-up of the study at 44.1 months better clarifies the superiority and the meaningful clinical benefit of zanubrutinib. The investigator-assessed cumulative response increased over time in both treatment arms with CRs and VGPRs significantly higher for zanubrutinib at all time points, reaching 36.3% versus 25.3% at 44.1 months.[17] Importantly median time to achieve at least a VGPR was shorter for zanubrutinib, 6.7 months, when compared to the 16.6 months with ibrutinib. PFS rate at 42 months showed a hazard ratio favoring zanubrutinib HR (95% CI) 0.63 (0.36,1.12). With this longer follow-up the advantage of zanubrutinib treatment over ibrutinib in the high risk population of *CXCR4*^{MUT} patients is also more clear. In this group, zanubrutinib led to deeper (21.2% vs. 10%) and faster responses as well as better PFS (42 months PFS rate: 73.2% vs. 49%).

Zanubrutinib showed to be effective also in patients without *MYD8* ^{MUT} enrolled in cohort 2 of the ASPEN trial.[25] A high rate of patients, 65%, achieved MR with 30.7% of VGPRs and CRs. This result compares favorably with the MRs observed with acalabrutinib and ibrutinib. Furthermore zanubrutinib allowed to achieve prolonged PFS of 52.3% at 42 months.[21]

3.1.3 | Zanubrutinib in treatment naïve patients

The current commonly used frontline systemic treatments can be categorized as chemo-immunotherapy, PI-based therapy, BTKi-based therapy. Chemo-immunotherapy and proteasome inhibitor-based therapies offer time-limited durations of therapy with prolonged PFS and TTNT allowing a treatment-free period that can be beneficial for quality of life.[8,9,26]

BTKi have demonstrated significant clinical activity in first-line (Table 3) with a favorable tolerability, lower rate of cytopenias compared to chemo-immunotherapy and have the convenience of oral administration.

The phase 2 trial evaluating the role of ibrutinib in first line was addressed only in the setting of *MYD88*^{MUT} considering the poor outcome of *MYD88*^{WT} R/R patients treated with the BTKi.[23] All 30 enrolled patients achieved a response with MR rate of 87% and a 48 months PFS rate of 76%. As in the relapsed refractory setting, although less pronounced, patients with *CXCR4*^{MUT} showed lower rates of VGPR (14% vs. 44%; $p = 0.009$), longer time to achieve MR and a trend of shorter PFS (4-year PFS 59% vs. 92%; $p = 0.06$).

Although in the Innovate study a proportion of patients ($n = 68$) enrolled were TN the study was not powered to analyze outcomes according to treatment status.[18] Ibrutinib plus rituximab significantly improved 24 months PFS (84% compared to 59% of the placebo rituximab arm). In the whole population the combination allows to abrogate the inferior treatment response in *CXCR4*^{MUT} genotype and results in a short time to MR, 3 months, which compares favorably to the monotherapy trials.

In the phase 2 study of the second generation BTKi acalabrutinib a small number of patients ($n = 14$) were treated in first line.[19] None of the patients achieved CR, only 1 VGPR was recorded, with the majority obtaining PR (71%), the 66 months PFS resulted as 84%. Responses according to genotype were not reported.

As for the other BTK inhibitors data for zanubrutinib in front-line setting are currently limited. Overall 24 TN patients received zanubrutinib in the phase I/II study.[20] After 23.5 months treatment a high rate of early deep responses were observed (CR plus VGPR 33.3%). Importantly responses were observed across all *MYD88/CXCR4* genotypes. Considering that studies with BTKi demonstrated an improved quality of response with longer treatment duration, zanubrutinib results in the TN population compares favorably with those reported in ibrutinib trials despite the significantly longer treatment duration in the latter studies.

In the phase 3 randomized ASPEN study comparing zanubrutinib with ibrutinib in each arm 18% TN *MYD88*^{mut} patients were enrolled.[16] Patients outcomes according to disease status were analyzed on the first follow-up at 19.4 months. The ORR in both arms was similar. The difference in VGPR rate was not statistically significant between the two arms (p= not reached ,NR), although numerically more patients treated with zanubrutinib reached a VGPR (26% vs. 17%). The median time to MR in both arms was 2.8 months. The short follow-up does not allow to draw any conclusion on PFS and EFS outcomes.

It should be considered that there are no prospective data comparing BTKi with more conventional rituximab–chemotherapy approaches and only a limited number of patients were treated in BTKi clinical trials in first-line.[27] Based on this consideration EMA, differently from FDA, approved ibrutinib monotherapy or in

TABLE 3 Bruton tyrosine kinase (BTK) inhibitors clinical trials in treatment naive patients with Waldenström macroglobulinemia.

Study	N° pts	ORR	CR + GVPR	PR	Median FU time	Outcomes
Ibrutinib						
Castillo et al.[23]	30[a]	100%	30%	57%	50.1 m	Median PFS: NR 4 years PFS rate 76%
Tam et al.[16,17]	18[a]	89%	17%	50%	19.4 m	Median PFS: NR 18 m PFS rate 94%
Ibrutinib + rituximab						
Buske et al.[18]	34	91%	27%	50%	50 m	Median PFS: NR 54 m PFS rate 68%
Acalabrutinib						
Owen et al.[19]	14	93%	7%	71%	63.7 m	Median PFS: NR 66 m PFS rate 84%
Zanubrutinib						
Trotman et al.[20]	24	100%	33.3%	54.2%	23.5 m	Median PFS: NR 24 m PFS rate 91.5%
Tam et al.[16,17]	19[a]	95%	26%	47%	19.4 m	Median PFS: NR 18 m PFS rate 78%

Abbreviations: CR, complete remission; FU, follow-up; m, months; NR, not reached; ORR, overall response rate; PFS, progression free survival; VGPR, very good partial remission.

[a]Only *MYD88* mutated patients enrolled.

combination with rituximab, and zanubrutinib only for patients unsuitable for immuno-chemotherapy.

3.1.4 | Side effect risk evaluation

In Supplemental Table S2 are summarized patients disposition in treatment, cardiovascolar and bleeding events reported with ibrutinib, acalabrutinib, and zanubrutinib in WM clinical trials. Comparison of the AE between studies is difficult considering the different follow-up and enrolled patients characteristics.

The only study allowing a direct head-to-head comparison is the ASPEN randomized trial. Several AEs were statistically more frequent with ibrutinib than with zanubrutinib, including atrial fibrillation, hypertension, diarrhea, peripheral edema, muscle spasms, and pneumonia ($p < 0.05$ for all comparisons). In contrast, neutropenia occurred more frequently with zanubrutinib ($p < 0.05$). Although did not translate in an excess of infections. Pneumonia resulted higher in patient receiving ibruitinib (18.4% vs. 10.2%). Importantly zanubrutinib was associated with a lower risk of AEs leading to dose reduction (15.8% vs. 26.5%), treatment discontinuation (8.9% vesrsus 20.4%), or death (3.0% vs. 5.1%).[16,17]

4 | RECOMMENDATIONS AND PROPOSALS

According to NCCN and ESMO guidelines, BTK inhibitors are appropriate therapeutic options both in treatment naïve and refractory or relapsed patients with WM.

The Panel agreed on indicating zanubrutinib as the preferred BTK inhibitor in patients with WM.

The preferential decision was based on the evidence of numerically higher rates of VGPR and MR attainment at all time points with an HR of PFS at 44 months in favor of zanubrutinib. Moreover zanubrutinib, in patients with CXCR4 mutation, is associated with higher rates of VGPR and MR attainment, and a better 42 months PFS.

Zanubruitnib exerts a rapid response kinetics, shorter time to achieve a MR in CXCR4-mutated patients, and VGPR in both CXCR4-mutated and unmutated over ibrutinib. Although considerations from cross trial analysis have intrinsic limitations zanubruitnib is more effective in patients without MYD88 mutation.

Zanubrutinib should be considered preferable to ibrutinib also for its safety advantages, a higher rate of patients remain on zanubrutinib with a longer follow-up, with fewer events leading to treatment discontinuation and dose reductions. Treatment with zanubrutinib was associated with a lower rate of all grades of atrial fibrillation/flutter, hypertension, diarrhea and pneumonia.

The panel argued that there is no indication for further randomized studies comparing covalent BTKi given not only the proven efficacy of zanubruitnib but especially the better toxicity profile demonstrated.

4.1 | UCN2. Indication of use of zanubrutinib monotherapy in patients with MZL

Marginal zone lymphoma is an indolent B-cell lymphoma accounting for approximately 10% of non Hodgkin lymphomas. The incidence of MZL is 3–4/100.000 person/year and increases with age.[28] The WHO classification recognizes 3 different subtypes of MZL, namely extranodal MZL (70%) arising from the mucosa-associated lymphoma tissue, splenic MZL (20%) and nodal MZL (10%).[29] The role of chronic antigenic stimulation by bacterial or viral agents is crucial in the pathogenesis of MZL, as in gastric MZL associated with *Helicobacter pylori* infection or HCV-related splenic MZL. Though MZL is still an incurable disease, the overall survival is prolonged and even similar to age and sex matched general population in extranodal gastric MZL.[28] Due to incurability, the prolonged survival and advanced age of patients with MZL, an important goal of treatment is to minimize short and long-term toxicities.

The frontline treatment of MZL is highly variable, including antibiotic or antiviral treatment for infection-associated MZL (namely *Helicobacter pylori* eradication for gastric MZL and antiviral therapy in splenic MZL associated with HCV infection), local surgery or radiotherapy for localized extranodal or nodal MZL, and systemic treatment with anti-CD20 monoclonal antibody alone or combined with or chemotherapy in patients with advanced disease. Detailed description of efficacy and toxicity of these different treatment options are beyond the scope of this project and are described in the updated ESMO guidelines.[30–39]

For patients requiring systemic treatment, one of the major goals is to develop chemotherapy-free treatments able to reproduce the efficacy of chemo-immunotherapies, while avoiding chemotherapy-related toxicities in an often elderly patient population. Recent advances in understanding the biology of the disease have paved the way to chemo-free regimens with targeted agents, thus expanding the therapeutic armamentarium for MZL patients.

4.1.1 | BTK inhibitors therapy

The BTK inhibitor Ibrutinib has been the first drug specifically approved for R/R patients who had prior CD20 based anti-body therapy MZL, with an ORR of 53% (including 7% CR) and a median PFS of 14.2 months in the first analysis.[40] Responses deepened over time, leading to an increase of ORR and CR rates to 58% and 10% respectively in the final analysis, with a median follow-up of 33.1 months.[41] The most common AEss of treatment were anemia (14%), pneumonia (8%) and fatigue (6%). Among AEs events of interest, atrial fibrillation was reported in 6% of patients, all events being grade 1 or 2. Overall, 17% of patients discontinued treatment due to an AEs, a similar rate to that observed in in clinical trials that included patients with CLL.

The next-generation BTK inhibitor zanubrutinib has been recently evaluated in 68 patients with relapsed or refractory MZL

in the phase II trial MAGNOLIA.[42] The primary endpoint was the ORR determined by an IRC. With a median follow-up of 25.7 months, the ORR was 68.2% including a CR rate of 25.8%. The median PFS was NR and the 12 and 15 months- PFS rate was 82.5%. As compared with Ibrutinib, zanubrutinib yielded higher ORR and CR rates. A longer follow-up will show whether responses to zanubrutinib deepen over time as previously observed with ibrutinib.

More recently, in a phase II study including 40 patients with R/R MZL,[43] acalabrutinib was found to have activity, though ORR and CR rates as well as 12-month PFS rates seem lower than those reported with zanubrutinib.

The efficacy of BTK inhibitors in previously treated MZL patients is summarized in Table 4.

The role of BTK inhibitors in previously untreated patients with MZL is currently under investigation. The ongoing phase II trial MALIBU is evaluating the combination of rituximab and ibrutinib 560 mg/day for 6 cycles, followed by maintenance with ibrutinib for 1 year in untreated patients with MZL. A randomized phase III study is comparing the combination of rituximab and ibrutinib with rituximab and placebo (NCT04212013) in previously untreated patients with MZL. Similarly, the ongoing randomized phase III trial NCT05100862 is exploring the combination of zanubrutinib and rituximab in the frontline setting using the combination of lenalidomide and rituximab as control arm.

4.1.2 | Zanubrutinib safety

Regarding to the safety profile, zanubrutinib compares favorably with the first-in class BTK inhibitor Ibrutinib showing a lower rate of discontinuations due to AEs (6% vs. 17%) which is similar to that reported with the other second-generation BTKi, acalabrutinib (7%) (Supplemental Table S3). When the AEs of interest for this class of drugs,is considered in patients with MZL, the incidence of grade ≥3 cardiac events (atrial fibrillation/flutter and hypertension) is negligible for all the BTKi, though safety data are relatively more mature for ibrutinib only. The incidence of grade ≥3 neutropenia is higher with zanubrutinib and acalabrutinib as compared with Ibrutinib, however this does not translate in a higher incidence of grade ≥3 infections.

5 | RECOMMENDATIONS AND PROPOSALS

The analysis of efficacy and safety of BTK inhibitors in patients with relapsed or refractory MZL rely on cross-trial comparisons.

Despite this evidence limit, based on available data, the Panel agreed on indicating zanubrutinib as the preferred salvage treatment for R/R patients with MZL.

The preferred choice is based on the evidence that zanubrutinib compares favorably with other BTKi inhibitors as well as different

TABLE 4 Efficacy of Bruton tyrosine kinase (BTK) inhibitors in relapsed or refractory marginal zone lymphoma (MZL).

Reference	Trial phase	*N* of patients evaluable for response	Median follow-up (months)	ORR (%)	CR (%)	DOR (months)	Median PFS (months)	Median OS (months)
Ibrutinib								
Noy, Blood 2017[40]	II (PCYC1121)	60	19.4	48[a]	3[a]	Median not reached[a]	Median 14.2[a]	Median not reached
				53[b]	7[b]	Median 19.4[b]	Median 15[b]	Estimated 81% at 18 m
Noy, Blood Adv 2020[41]	II (PCYC1121 final analysis)	60	33.1	58[b]	10[b]	27.6	Median 15.7	Median not reached
								72% at 33 m
							32% at 33 m	
Zanubrutinib								
Opat, Clin Cancer Res 2021[42]	II (Magnolia)	66	15.7	68[a]	26	Median not estimable	Median not estimable	Median not estimable
				74[b]		93% at 12 m	82.5% at 12 m	95.3% at 12 m
Acalabrutinib								
Strati, BJH 2022[43]	II (ACE-LY-003)	40	13.3	53[b]	13	76% at 12m	Estimated 27.4	Median not reached
							67% at 12 m	91.4% at 12 m

[a]IRC.

[b]By investigator.

targeted therapies (rituximab-lenalidomide or PI3K inhibitors) both in terms of efficacy and safety.

Longer follow-up and real life studies with zanubrutinib are needed to confirm the better safety profile observed in the initial trial analysis.

The role of BTK inhibitors in previously untreated patients with MZL patients is currently under investigation. Pending these results, BTK inhibitors including zanubrutinib can not be recommended in previously untreated patients with MZL.

5.1 | UCN3. Indication of use of zanubrutinib monotherapy in patients with mantle cell lymphoma

Mantle cell lymphoma[44] represents 5%–7% of all lymphomas; it usually affects adults, with a median age at presentation between 60 and 70 years and a male prevalence. Mantle cell lymphoma has many heterogeneities that explain different clinical behaviors, responses to therapy and clinical outcomes. Apart from patients' related variables such as age, performance status, comorbidities and disease's parameters of diffusion (such as stage, extranodal involvement, LDH level), MCL displays pathological and genetic features associated with more aggressive course and bad prognosis. On these grounds it is important to distinguish the classic from the so-called blastoid/pleomorphic cytologic variant, quantify Ki-67 expression and identify some specific gene alterations (in particular, TP53 expression).

Despite new therapeutic approaches that significantly improved the quality of response and the outcome of MCL, this lymphoproliferative disorder is still considered an incurable disease with a clinical course characterized by relapses/progressions requiring subsequent salvage treatments.

In the last years the therapeutic landscape for patients with MCL has been enriched with the availability of new agents (i.e., BTK inhibitors, BCL-2 inhibitors, IMIDS), new antibodies (i.e., loncastuximab tesirine) and CAR-T cells.

5.1.1 | BTK inhibitor therapy

Ibrutinib was the first-in-class covalent irreversible BTK inhibitor that showed impressive activity in patients with MCL. In their pivotal phase 2 study (PCYC1104 trial), Wang et al.[45,46] reported the therapeutic activity and safety of Ibrutinib in 111 patients with R/R MCL. The median age of patients was 68 years (63% of patients were 65 years or more), bastoid/pleomorphic variant and bulky disease were present in 15% and 8%, respectively. The median number of previous therapies was 3 (range 1–5) with 45% of patients being refractory to the last treatment. Unfortunaltely, no data on Ki67 or TP53 mutation are available. Response criteria were based on CT evaluation according to the Cheson 2007 classification.[47] ORR and CR rates were 67% and 23%. Time to response (TTR) and to CR (TTCR) were 1.9 (range 1.4–13.7) and 5.5 (range 1.7–11.5) months, respectively. After a median follow-up of 26.7 months, the median PFS and OS were 13 and 22.5 months, respectively; the estimated 12 and 24-month PFS and the 12-month duration of response were 55%, 31% and 67%, respectively (Table 5). Subgroups analysis by baseline parameters and risk factors indicated more favorable outcomes for patients with less bulky tumors (CR, DOR, PFS, OS) and non refractory disease (PFS, OS). The median period of exposure to ibrutinib was 8.3 months.

Ibrutinib was compared with temsirolimus in a phase 3 study (RAY trial) reported by Dreyling et al.[48] and subsequently updated by Rule et al.[49] One hundred-thirty nine patients patients, with a median age of 67 years (62% with an age ≥65 years), were allocated to the ibrutinib arm. The percentage of patients with blastoid/pleomorphic variant and refractory disease were 12% and 26%, respectively. The median number of previous therapies was 2 (range 1–9) with 44 (31%) patients who received ≥3 prior therapies. No data regarding bulky disease, Ki67rate, and cases withTP53 mutation are available. In this study, the response criteria were based on the CT evaluation according to Cheson 2007. The ORR and CR were 77% and 23%, respectively. After a median follow up of 38.7 months, the median PFS was 15.6 months (higher in patients who received 1 vs. > 1 previous treatments) and the duration of response was higher in CR versus PR patients (35.6 vs. 12.1 months). The median period of exposure to ibrutinib was 14.4 months (range 1–24).

The results of these two studies in R/R with ibrutinib single agent led FDA and EMA to approve this agent in MCL and represented the background for the development of further studies which evaluated the use of ibrutinib in combination with standard chemotherapy or other biologic agents. Retrospective studies highlighted the activity of ibrutinib compared with other standard options for the treatment of R/R patients[56] and patients with central nervous system involvement.[57] These studies also highlighted some e limits of BTKi in MCL, either in term of activity and side effects. Despite a high ORR, the CR rate of ibrutinib and the median PFS are rather low, between 13 and 16 months with no evidence of plateau. Unfortunately in these studies the prognostic role of Ki67 and molecular biomarkers were not evaluated. However in a phase 2 study were ibrutinib was combined with rituximab[58] high Ki67 levels (>50%) were associated with lower ORR (50% vs. 100%), CR (17% vs. 54%) and median PFS (5.9 vs. NR).

Jekermen et al. investigated the combination of ibrutinib with lenalidomide and rituximab[59] in R/R patients with MCL. In this study the median PFS was adversely influenced by the presence of TP53 mutation (13 vs. 34 months). Similarly, in the SHINE trial[60] the significantly favorable impact of the addition of ibrutinib to front-line rituximab and bendamustine in terms of PFS appeared to be lost in those patients with TP53 mutation, blastoid or pleomorphic histologic subtypes, and bulky disease.

ACE-LY-004 was a phase 2 trial designed to evaluate the activity of acalabrutinib single agent a in R/R patients with MCL.[50,51,61] Baseline characteristics of the 124 patients included in the study were rather similar to those reported in the previous study with ibrutinib in terms of median age (68 years, range 61–75), rate of cases with blastoid/pleomorphic variant (21%) and bulky disease (8%)

TABLE 5 Clinical trials in mantle cell lymphoma (MCL): Patients characteristics, response rate and outcome.

References	Wang ML[45,46] PCYC1104 study	Dreyling M[48] Rule S[49] RAY study	Wang M[50,51] ACE-LY004 study	Tam C[52,53] BGB-3111-003 study	Song[54,55] BGB-3111-206 study
BTK inhibitor	Ibrutinib	Ibrutinib	Acalabrutinib	Zanubrutinib	Zanubrutinib
Phase of the study	2	3	2	1–2	2
Patients	111	139	124	32	86
Median age, years (range)	68 (40–84)	67	68 (61–75)	70 (42–86)	61 (34–75)
Patients ≥65 years	63%	62%	65%	75%	26%
Patients characteristics at baseline, *n* (%)					
MIPI low/intermediate/high	15/42/54 (48.6)	44/65/30 (21.5)	48/54/21 (16.9)	9/13/10 (31.2)	12/39/33 (38.3)
Blastoid/pleomorphic variant	17 (15)	16 (12)	26 (21)	2 (6.2)	12 (14)
Bulky disease (≥10 cm)	9 (8)	NA	10 (8)	3 (9.4)	7 (8.1)
Ki67 ≥ 30%	NA	NA	(Ki67 ≥ 50%) 32 (26)	NA	34 (39.5)
TP53 mutations	NA	NA	NA	NA	15 (27.8)
Median number prior therapies	3 (1–5)	2 (1–9)	2 (1–5)	1 (1–4)	2.0 (1–4)
≥3 prior therapies	61 (55)	44 (31)	28 (22.5)	NA	29 (33.7)
Refractory disease	50 (45)	36 (26)	30 (24)	8 (25)	45 (52.3)
Criteria for response evaluation	Cheson 2007	Cheson 2007	Lugano 2014	Cheson 2007	Lugano 2014
Overall response %	67	77	81	84.4	83.7
Subgroups analysis:					
MIPI low/intermediate versus high	73.3/66.7/66.7		81.3/90.7/57.1	77.8/92.3/80	(L + IvsH) 94.1 versus 69.7
Age ≥ 65	67 versus 68		83.8 versus 77.3	91.7 versus 62.5	59.1 versus 92.2
Blastoid/pleomorphic variant	70.6 versus 67		81 versus 81	100 versus 82.1	66.7 versus 86.8
Bulky disease (≥10 cm)	67 versus 67		90 versus 82	100 versus 82.8	71.4 versus 84.8
Ki67 ≥ 30%	NA		63 versus 89	NA	73.5 versus 92
TP53 mutations	NA		NA	NA	80 versus 89.7
≥3 prior therapies	60.7 versus 76		71.4 versus 83	88,9 versus 82.6	89.5 versus 72.4
Refractory disease	64 versus 70.5		80 versus 81.9	100 versus 81.8	82.2 versus 85.4
Complete response %	23	23	48	25	77.9
Bulky disease (≥10 cm)	11 versus 24				
Time to response (TTR months, range)	1.9 (1.4–13.7)	NA	1.9 (1.8–3.7)	2.8 (1.9–9.8)	2.7
Time to complete response (TTCR, months, range)	5.5 (1.7–11.5)	NA	3.4 (1.9–5.5)	5.5 (1.9–11.1)	2.9
Median follow up (months)	26.7	38.7	38.1	18.8	35.3
Median treatment duration (months, range)	8.3	14.4	17.5 (0.1–65.3)	15.4	27.6 (0.2–41)
Median PFS (months)	13	15.6	22	21.1	33
12-month PFS (%, range)	55	55	67	73	76
12-month DOR (%, range)	67	70	72	79	78
Median OS (months)	22.5	30.3	Not reached	26	Not reached

Abbreviation: NA, data not available.

but differed for the lower number of previous treatments (only 22.5% of patients received ≥3 lines of previous therapies) and a lower rate of patients with refractory disease (24%) (Table 5). Notably, response criteria of this study were based on PET evaluation according to the Lugano 2014 criteria.[52] The ORR and CR with acalabrutinib therapy were 81% and 48% (Table 5). ORR appeared not to be influenced by age, bulky disease, histologic variant, while resulted lower in those patients who had higher Ki67 rate and higher number of previous treatments. TP53 was not evaluated in this study. Time to response and time to complete response were 1.9 and 3.4 months, respectively. After a median follow up of 38.1 months, the median PFS was 22 months with a 12-month estimated PFS and DOR of 67% and 72%, respectively. The median time of exposure to acalabrutinib was 17.5 months (range 0.1–65.3).

BGB-3111-AU-003 is a phase 1–2 study that evaluated zanubrutinib in patients with R/R MCL. In the phase 1 of the study[53] no dose-limiting toxicities occurred in the dose escalation phase and the median BTK occupancy in peripheral blood mononuclear cells was >95% at all doses. Sustained complete (>95%) BTK occupancy in lymph node biopsy in specimens was more frequent with 160 mg twice daily than 320 mg once daily (89% vs. 50%; $p = 0.0342$). The results evaluating a subgroup analysis of 32 patients who received 320 mg daily of zanubrutinib were subsequently reported by Tam et al.[53] Main baseline characteristics of patients are summarize in Table 5. The median age was 70 years, blastoid/plemorphic variant and bulky disease were present in 2 (6.2%) and 3 patients (9.4%), respectively, and the median number of previous treatments was 1 (range 1–4) with 8 patients (25%) being refractoryto the last treatment. No data on TP53 mutation and Ki67 expression were reported. Response was assessed according to Cheson 2007 criteria.[47] ORR and CR were 84.4% and 25%. Time to response and TTCR were 2.8 months (range 1.9–9.8) and 5.5 months (1.9–11.1), respectively. Notably, zanubrutinib appeared to overcome unfavorable prognostic factor such as age, blastoid variant, bulky disease, previous treatments., After a median follow up of 18.8 months, the median PFS was 21 months with a 12-month-PFS and DOR of 73% and 79%, respectively.

Song et al[54,55] reported the results of a phase 2 study conducted in 86 Chinese R/R patients with MCL (BGB-3111-206) who received zanubrutinib monotherapy 160 mg BID up to 3 years. Compared with the previous described study, patients were younger (median age 61 years, range 34–75) with 22 patients (26%) being 65 years or more (Table 5) but showed more frequently refractory disease (52.3%). Blastoid/pleomorphic variant, bulky disease, kigh Ki67 expression and TP53 mutation were present in 14%, 8.1%, 39.5% and 27.8%, respectively. ORR, the primary endpoint of the study, was assessed by IRC using PET-based imaging according to the Lugano criteria 2014. Data of the initial publication were updated with longer follow-up in September 2020 61. ORR and CR were 83.7% and 77.9%, respectively with a median TTR and TTCR of 2.7 and 2.9 months. A lower ORR was registered in patients ≥65 years (59.1% vs. 92.2%), in those more heavily pretreated (89.5% vs. 72.4%) or with with blastoid/pleomorphic variant (66.7% vs. 86.8%), bulky disease (71.4% vs. 84.8%), Ki67 ≥ 30% (73.5% vs. 92%), TP53 mutation (80% vs. 89.7%) (18–19). After a median follow-up of 35.3 months, the median PFS was 33 months with an estimated 36-month PFS of 47.6%. PFS was similar in patients with or without refractory disease and blastoid histology. Patients with low MIPI-b score, <3 prior lines of therapy or wild-type TP53 had longer PFS. Median PFS resulted NR, and was 16.6 months for patients who achieved CR, and 2.6 months for those with PR or non responders (stable disease/progressive disease). Median OS was NR.

In conclusion, at present no randomized, head-to-head trials comparing BTK inhibitors inr MCL are available. The indirect comparison of studies in MCL with ibrutinib, acalabrutinib and zanubrutinib is limited by the several factors including different follow-up, clinical and biological characteristics of patients, criteria for response assessment (Cheson vs. Lugano criteria; PET vs. non PET based, clinical characteristics etc.).

Data for the single study with acalabrutinib indicates that the ORR seems to be higher (81%) to that observed with ibrutinib in the Wang pivotal trial (67%) where however the population of patients with MIPI high was higher (48.6% vs. 16.9%); and if we compare the results of ibrutinib of the RAY trial with the acalabrutinib trial (the population of patients with MIPI high in these 2 studies are superimposable) the ORR is similar (77% vs. 81%). The CR (48%) is much higher if compared to that registered in the 2 trials with ibrutinib; however in the acalabrutinib trial response evaluation was based on PET and not on CT and this may at least in part justify the difference. The median PFS appeared higher (22 months): since the population of the Ray trial and acalabrutib trial seem very similar as far as patients related and disease related prognostic factors, the increase of >6 months in median PFS (mPFS) can be considered a possibile indicator of higher therapeutic activity of acalabrutinib.

The characteristics of the patients included in the ibrutinib trials and in the trial by Song with zanubrutinib seems rather similar.

The study by Tam with zanubrutinib seems to include a less heavily pretreated but an older population. The study of Song has a lower rate of patients >65 years but a high rate of patients with refractory disease while MIPI, histologic variants, bulky disease were similar. ORR seems similar to that registered with acalabrutinib and higher to that observed with ibrutinib (nearly 84%). However in the study by Song study the response was evaluated according to the Lugano 2014 PET criteria. Similarly to the Wang acalabrutinib study, CR appeared to be much higher (48% vs. 77.9%) 55,56,60,61. This last study60,61 is the only one that evaluated TP53 mutation indicating a high therapeutic activity (ORR 80%) also in TP53 mutated patients.

However, ORR appeared lower in other high-risk subgroups of patients (older age, higher MIPI, elevated Ki-67, heavily pretreatment). However, data on the median PFS, 33 and 21 months, appeared impressive, and much higher than that observed with ibrutinib (13 and 15.5 months) but not superior to that recorded with acalabrutinib (22 months).

5.1.2 | Adverse events

No randomized studies comparing the efficacy of different BTKis have been performed. Cardiovascular and bleeding events in patients with MCL treated with BTK inhibitors are reported in Supplemental Table S4. Cardiovascolar complications appeared to be lower with second-generation BTKis[50–55,61] where severe cases of atrial fibrillation and hypertension were infrequent (Supplemental Table S5). In two single-arm trials with zanubrutinib, the rates of patients with grade ≥3 atrial fibrillation or hypertension were about 3% or less.[52–55] Headache, in the majority of case grade 1–2, was recorded more frequently with acalabrutinib[50,51] and and neutropenia with zanubrutinib.[54,55]

6 | RECOMMENDATIONS AND PROPOSALS

With the limit of the lack of head-to-head trials and an indirect comparison, in R/R patients with MCL zanubrutinb is associated with higher activity in terms of ORR, CR, and PFS. Moreover, high level of ORR can be achieved with zanubrutinib also in patients with TP53 mutation.

Low rates of severe atrial fibrillation and hypertension have been observed in two trials with zanubrutinib in R/R patients with MCL.

Based on the available evidence, the Panel agreed on indicating zanubrutinib as the best salvage treatment in patients with R/R MCL.

7 | CONCLUSIONS

The main aim of this endeavor is to optimize the use of zanubrutinib in malignant lymphomas that receivied the indication of use. Despite the paucity of high-level evidence on several important clinical issues, the Panel was able to reach a high degree of consensus. This consensus is a valid basis for clinical implementation of the recommendations given and for the design of new studies that may guide therapeutic decisions.

ACKNOWLEDGMENTS

Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST STATEMENT

Zinzani: Consultant (MSD, EUSAPharma, Novartis), Speakers bureau (Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, Astra Zeneca, Takeda, Roche, EUSAPharma, Kyowa Kirin, Novartis, Incyte, Beigene), Advisory board (Secura Bio, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, MSD, Astra Zeneca, Takeda, Roche, EUSAPharma, Kyowa Kirin, Novartis, ADC Therapeutics, Incyte, Beigene). Mauro: Advisory board (Janssen, Abbvie, Beigene, Astra Zeneca), Research support (Abbvie, Takeda). Tedeschi: Speakers bureau (Astra Zeneca, Abbvie, Beigene), Advisory board (Astra Zeneca, Abbvie, Beigene). Varettoni: Speakers bureau (Abbvie, Astra Zeneca, Beigene), Advisory board (Abbvie, Astra Zeneca, Beigene, Janssen). Zaja: Personal fees (Novartis, Amgen, Roche, Abbvie, Janssen, Takeda, BMS, Grifols, Argenx, Sobi, Beigene), Research support (Novartis, Amgen, Abbvie, Janssen), Fundings for educational projects (Janssen, Abbvie, Kyowa Kirin, Takeda, Beigene, Astra Zeneca). Barosi: no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PubMed at https://pubmed.ncbi.nlm.nih.gov/.

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/hon.3172.

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How to cite this article: Zinzani PL, Mauro FR, Tedeschi A, Varettoni M, Zaja F, Barosi G. Unmet clinical needs in the use of zanubrutinib in malignant lymphomas (Waldenström macroglobulinemia, marginal zone lymphoma and mantle cell lymphoma): a consensus-based position paper from an ad hoc expert panel. *Hematol Oncol*. 2023;41(5):795-808. https://doi.org/10.1002/hon.3172