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Report of consensus panel 2 from the 11th international workshop on Waldenström's macroglobulinemia on the management of relapsed or refractory WM patients ☆

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ABSTRACT

The consensus panel 2 (CP2) of the 11th International Workshop on Waldenström's macroglobulinemia (IWWM-11) has reviewed and incorporated current data to update the recommendations for treatment approaches in patients with relapsed or refractory WM (RRWM). The key recommendations from IWWM-11 CP2 include: (1) Chemoimmunotherapy (CIT) and/or a covalent Bruton tyrosine kinase (cBTKi) strategies are important options; their use should reflect the prior upfront strategy and are subject to their availability. (2) In selecting treatment, biological age, co-morbidities and fitness are important; nature of relapse, disease phenotype and WM-related complications, patient preferences and hematopoietic reserve are also critical factors while the composition of the BM disease and mutational status (*MYD88*, *CXCR4*, *TP53*) should also be noted. (3) The trigger for initiating treatment in RRWM should utilize knowledge of patients' prior disease characteristics to avoid unnecessary delays. (4) Risk factors for cBTKi related toxicities (cardiovascular dysfunction, bleeding risk and concurrent medication) should be addressed when choosing cBTKi. Mutational status (*MYD88*, *CXCR4*) may influence the cBTKi efficacy, and the role of TP53

☆ Ana, here are the reports for Consensus Panel 2. All authors have approved their submission. COIs were confirmed.

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disruptions requires further study) in the event of cBTKi failure dose intensity could be up titrated subject to toxicities. Options after BTKi failure include CIT with a non-cross-reactive regimen to one previously used CIT, addition of anti-CD20 antibody to BTKi, switching to a newer cBTKi or non-covalent BTKi, proteasome inhibitors, BCL-2 inhibitors, and new anti-CD20 combinations are additional options. Clinical trial participation should be encouraged for all patients with RRWM.

Introduction

At the 11th International Workshop on Waldenström's macroglobulinemia (IWWM-11) held in Madrid in 2022, 7 consensus panels were convened to address current challenges in diagnosis and management. Consensus panel 2 (CP2) was appointed to formulate a roadmap for managing patients with relapsed or refractory WM (RRWM). The need to update previous recommendations comes from newly available data since the last recommendations from the 10th IWWM in New York, USA (October 2018) [1]. Several phase 2 and some phase 3 studies have provided new data and treatment options that could positively influence the management of treatment-naïve (TN) and RRWM.

Covalent BTKi

Updates on the efficacy of the first-generation covalent Bruton tyrosine kinase inhibitor (cBTKi) ibrutinib have confirmed its long-term efficacy with or without rituximab in RRWM, and as monotherapy in rituximab-refractory patients [2,3]. Longer follow up from these and other studies in the real-world setting has revealed the challenges associated with BTKi therapy in terms of toxicity and as a continuous therapy.

Data on next-generation cBTKi, acalabrutinib and zanubrutinib in RRWM have expanded and gained traction with longer follow-up. Acalabrutinib was evaluated in a phase 2 study, which enrolled 106 patients, of which 92 had RRWM [4]. After a median follow-up of 27.4 months, 93% of these patients achieved a response with 23 (25%) patients discontinuing treatment. Acalabrutinib's toxicity profile has nuances relative to ibrutinib, including neutropenia and infections (grade 3-4 in 16% and in 7% respectively), atrial fibrillation (AF) (grade 3-4 in one (1%) patient) and bleeding (grade 3-4 in three (3%) patients) and notable headache of limited duration (21-55% of grade 1-2 severity) [5].

Zanubrutinib was evaluated in a phase 1/2 study in 77 patients with 24 TN and 53 RRWM patients. At a median follow-up of 36.0 months in the RRWM cohort, major responses were seen in 79.6%, within a median of 2.8 months; responses improved with continuing therapy with a plateau after 20 months [6]. Among RRWM, 16 discontinued the study drug, 7 for adverse events (AEs) and 7 for progressive disease (PD). Adverse events of interest included contusion/bruising (all grade 1, in 32.5%), neutropenia (18.2%), major hemorrhage (3.9%), atrial fibrillation/flutter (in 5.2%, but grade 3 in 1 patient only), and grade 3 diarrhea (2.6%).

In the phase 3 randomized ASPEN study, zanubrutinib was compared to ibrutinib in patients with TNWM or RRWM [7]. All patients had *MYD88*^{L265P} disease. Notably, the study's primary end point of the study was the attainment of very good partial response (VGPR) *and* complete response (CR). Among 199 treated patients, 164 had RRWM and 81 received Ibrutinib and 83 zanubrutinib. VGPR rate was 28% for those receiving zanubrutinib, and 19% for those receiving ibrutinib; there were no CRs in either arm. In the RRWM group, VGPR rate was 29% for zanubrutinib and 20% for ibrutinib. The overall response rate (ORR; 94% and 95% for zanubrutinib and ibrutinib) and major response rate (MRR; 78% and 81% respectively) were similar in RRWM. At 18 months, 87% and 86% of the responders were progression-free respectively. An update of ASPEN with 43-month follow-up was presented in the IWWM-11. At 44.4 months, the VGPR rate had increased to 36.3 % vs 25.3 % (for zanubrutinib vs ibrutinib respectively, in the whole population), also with a shorter median time to VGPR (6.7 vs 16.6 months) and higher event-free rate for the duration of CR + VGPR at 24 months (90.6% vs 79.3%). At 42 months, 87.5% vs 85.0 % patients were alive, and 78.3% vs 69.7% were progression-free and although median PFS or OS have not yet been reached, the hazard ratios favored zanubrutinib (HR for PFS was 0.63 and for OS was 0.75) though are not statistically significant at this time. Notably, 66% vs 52% of patients remained on treatment. Subgroup analysis showed that patients harboring *CXCR4* mutations might benefit more from zanubrutinib versus ibrutinib (VGPR 21.2% vs 10%, MRR 78.8% vs 65.0%, time to major response 3.4 vs 6.6 months, with 73% vs 49% remaining progression-free at 42 months with an HR for progression or death of 0.50).

ASPEN revealed potential safety advantages of zanubrutinib over ibrutinib, which remained consistent over time [8]. Thus, zanubrutinib-treated patients had lower cumulative incidences of atrial fibrillation, diarrhea, hypertension, muscle spasms, and pneumonia, and fewer AEs leading to death, treatment discontinuations, or dose reductions. Exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension were lower with zanubrutinib versus ibrutinib (7.9 % vs 23.5 % and 14.9 % vs 25.5 %, respectively). Neutropenia was more common with zanubrutinib (any grade, 34.7% vs 20.4%), although infection rates were similar (grade 3/4 events were 21.8% vs 27.6%).

An additional cohort of the ASPEN study included patients lacking *MYD88* mutations or with unknown mutational status [9]. Among 28 patients, 26 had centrally confirmed *MYD88*^{WT} and 23 had RRWM. At the initial report after a median follow-up of 18 months, 27% (7/26) *MYD88*^{WT} patients had achieved a VGPR, 50% a major response with PFS and OS rates of 68% and 88% respectively. At 42.9 months of follow-up, reported at IWWM-11, one patient had achieved CR and major responses increased to 65 %, with PFS and OS rates at 53.8% and 83.9%, respectively.

A biomarker companion study of ASPEN provided new data regarding the efficacy of cBTKi therapy in the context of the genetic characteristics [10]. The study included next-generation sequencing (NGS) results from 190 patients with *MYD88*^{MUT} (98 on zanubrutinib; 92 on ibrutinib) and 20 with *MYD88*^{WT} (Zanubrutinib only). *CXCR4* mutations were found in 25.7 %, *TP53* in 24.8 %, *ARID1A* in 15.2 % and *TERT* in 9.1 %. Importantly, *TP53* mutations were far more common in previously treated patients. *TERT* mutations were detected only in patients with *MYD88*$^{MUT.}$ *ARID1A* and *TP53* mutations were more commonly associated with *CXCR4* mutations. Among *MYD88*^{MUT} patients, mutations in *CXCR4*, *TP53*, and *TERT* were associated with a trend for lower rates of ≥VGPR or major responses, longer median time to response and shorter PFS (more pronounced for *TP53* mutations, HR, 2.15; $P = 0.011$).

There were also differences between ibrutinib and zanubrutinib: patients with *MYD88*^{MUT} and *CXCR4*^{NS} treated with ibrutinib showed lower VGPR (15.4 % vs 30.6 %), MRR (53.8 % vs 84.7 %) and 42-month PFS rate (43.5 % vs 57.1 %, $P = 0.017$) than those with *CXCR4*^{WT}; in the zanubrutinib arm VGPR rate was also lower (14.3 % vs 44.6%) but MRR (85.7 % vs 83.1 %) and PFS (66.7 % vs 81.3 %,

$P = 0.598$) were not significantly affected. For the small cohort of patients with *CXCR4*^{FS} mutations zanubrutinib (n = 19) was associated with a higher VGPR rate compared to ibrutinib (n = 7) (26.3 % vs 0 %, $P = 0.06$). Patients with *TP53*^{MUT} treated with ibrutinib had reduced VGPR (13.6 % vs 30.0 %), MRR (63.6 % vs 85.7 %) and PFS (57.9 % vs 72.1 %, $P = 0.027$) compared to *TP53* wild-type, while in the zanubrutinib arm no significant differences were seen [(VGPR [34.6 % vs 37.5 %], MRR [80.8 % vs 81.9 %] and 42-month PFS [62.0 % vs 84.6 %, $P = 0.120$]); thus, it seemed that in *TP53*^{MUT} patients the VGPR was significantly higher for zanubrutinib vs ibrutinib (34.6 % vs 13.6 %, $P < 0.05$). *TERT* mutations also impacted treatment outcome in the ASPEN Biomarker Analysis [10]. In both arms, the presence of the *TERT* mutation was associated with a lower MRR. In the zanubrutinib (n = 10) vs ibrutinib (n = 9) arms the MRR for *TERT*^{MUT} was 70% vs 44.4% respectively. By comparison, *TERT*^{WT} patients showed MRR of 83% vs 84.3% respectively. At 42 months, in the *TERT*^{MUT} groups, PFS was 37.5% vs 74% in the Zanubrutinib vs Ibrutinib arms [10]. Ongoing follow up in higher numbers of patients is needed going forwards.

Orelabrutinib is a novel cBTKi [11]. Data were presented in IWWM-11 from a phase 2 study of orelabrutinib in 66 patients with RRWM; 83 % were *MYD88*^{MUT} / *CXCR4*^{WT}. The major response rate was 80.9 %, ORR was 89.4 % (21.3 % VGPR, 59.6 % PR, 8.5 % minor response). Among patients with *MYD88*^{MUT}, MRR was 84.6 % in *CXCR4*^{WT}, and 100% in *CXCR4*^{MUT} but only 25.0 % in *MYD88*^{WT}. Twelve-month duration of response (DoR), PFS and OS were 88.8%, 85.1%, and 93.6%, respectively. The most common grade 3-4 AEs were neutropenia (8.5%) and thrombocytopenia (6.4 %) and one death because of hepatitis B reactivation occurred.

Tirabrutinib is another second-generation, highly selective covalent BTKi [12]. Updated results of a phase 2 study of tirabrutinib monotherapy in WM were presented at IWWM-11. A total of 27 patients (TN = 18; RRWM = 9) were included, most of whom (n = 22) had a *MYD88*^{MUT} / *CXCR4*^{WT} genotype. MRR was 88.9 % in RRWM (94.4 % in TN) and median time to MRR was 2.1 months (1.9 for TN) while the 2-year PFS was 88.9% (vs 94.4% for TN) and OS was 100%. The most common AEs with tirabrutinib were rash (44.4 %), neutropenia (30%) and nasopharyngitis (26%), bleeding (30%) while atrial fibrillation occurred in two patients (7.5%).

Non-covalent BTKi

cBTKi treatment can be limited by progressive intolerance caused by off-target inhibition of other kinases and the acquisition of resistance mutations, including *BTK*^{Cys481} mutations that may result in disease progression. Pirtobrutinib and nemtabrutinib are non-covalent (reversible) BTKi. Compared to cBTKi, they have similar in vivo efficacy in wild-type *BTK* and superior efficacy in *BTK*^{Cys481} in xenograft models and in other B-cell malignancies, including in patients with disease resistant to covalent BTK inhibitors.

Pirtobrutinib was evaluated in the Phase 1/2 BRUIN study which included RRWM [13]. A subset analysis (n = 78) was presented at ASH in 2022 [14], including 66 RRWM. Of the 61 patients who received ≥1 prior BTKi, 40 (66%) discontinued prior BTKi therapy due to disease progression. The MRR for the 72 response-evaluable patients was 68% including 17 VGPRs (24%) and 32 PRs (44%). At a median response follow-up time of 7.7 months, the median DoR among the 49 responding patients was not reached. In the subset of 55 response-evaluable patients who had received ≥1 prior BTKi, the MRR was 64% (including 13 VGPRs (24%) and 22 PRs (40%). In this BTKi-pretreated subset, the median DoR was not reached (95% CI, 8-NE) and the 6-month estimated DoR rate was 83% (95% CI, 60-93). In the subset of 60 response-evaluable patients who had received chemotherapy and anti-CD20 antibody, the major response rate was 68% (95% CI, 55-80), including 13 VGPRs (22%) and 28 PRs (47%). In the subset of 44 response-evaluable patients who had received chemotherapy and anti-CD20 antibody + BTKi, the major response rate was 64% (95% CI, 48-78), including 9 VGPRs (21%) and 19 PRs (43%). In the safety cohort of all pirtobrutinib treated patients with B-cell malignancies (n = 725), the most frequent TEAEs, regardless of attribution, were fatigue (26%, n = 191), diarrhea (22%, n = 160), and contusion (19%, n = 138). The most frequent Grade ≥3 TEAE was neutropenia (20%, n = 143). Importantly, low rates of Grade ≥3 TEAEs of hypertension (3%, n = 20), hemorrhage (2%, n = 16), and atrial fibrillation/flutter (1%, n = 7) were observed. Overall, 15 (2%) patients discontinued due to a treatment-related AE.

The relative efficacy and safety profiles of the various BTKi remain under investigation. Some data were presented at IWWM-11 on the safety and efficacy of zanubrutinib in patients intolerant to ibrutinib (n = 57) or acalabrutinib (n = 10) and subsequently published [15]. Most intolerance events (81 [70%] of 115 for ibrutinib; 15 [83%] of 18 for acalabrutinib) did not recur with zanubrutinib. Of the recurring events, 7 (21%) of 34 ibrutinib intolerance events and 2 (67%) of 3 acalabrutinib intolerance events recurred at the same severity with zanubrutinib; 27 (79%) ibrutinib intolerance events and 1 (33%) acalabrutinib intolerance event recurred at a lower severity with zanubrutinib. No events recurred at higher severity. No grade 4 intolerance events recurred. Table 1 summarizes the potential advantages and disadvantages of the various BTKi and highlights important caveats.

BCL-2 inhibitors

Venetoclax is a highly selective BCL-2 inhibitor, designed to counter the pro-survival signaling conferred by overexpression of *BCL2*. Following a phase 1 study demonstrating activity [16], a phase 2 study was performed in RRWM (n = 32; 16 had prior BTKi treatment, all were *MYD88*^{MUT}, and 17 *CXCR4*^{MUT}). The response rates were high (ORR: 84%, MRR: 81%, VGPR: 19%) using fixed duration venetoclax monotherapy [17]. A substantial proportion of patients, including responders progressed within 12 months after completing 24-months of therapy. While there has been no experience with combinations of BTK and BCL2 inhibitors in RRWM, a phase 2 study evaluated a 2-year combination of venetoclax with ibrutinib in 45 (of 50 planned) TN patients with WM [18]. Again, there were high response rates (MRR 93%; VGPR 40%), however, an unexpectedly high rate of ventricular arrhythmias found in 9% of the study population prompted premature closure of this study, and cessation of the treatment in all cases.

Proteasome inhibitors

Since the first-in-class proteasome inhibitor (PI), bortezomib was shown to have a high overall response rate in RRWM [19], further studies of bortezomib combinations have confirmed robust outcomes regarding efficacy [19,20]. Subcutaneous administration of bortezomib appears to ameliorate the incidence of treatment-induced peripheral neuropathy [21].

Carfilzomib is a next generation PI which was examined in TN patients [22] and showed an ORR 87% and MRR 68% but there are limited further data. In TN patients, the oral PI ixazomib as part of a triplet with dexamethasone and rituximab showed an ORR of 96% [23]. A combination of fixed duration ixazomib with intravenous then subcutaneous rituximab and dexamethasone was also investigated in 59 RRWM patients by the HOVON/ECWM groups and showed an ORR of 71% after 8 cycles of therapy [23]. Treatment delays due to hematological toxicity (n = 6), infusion-related reactions to rituximab (n = 2) neurotoxicity (n = 5) and other toxicities (n = 21) were observed in the safety analysis. Ibrutinib in combination with ixazomib in 21 patients with TN and RRWM was

Table 1
BTK inhibitors: potential benefits and drawbacks of different agents.

Class of therapy	Potential benefits	Potential drawbacks	Unknowns/ Caveats
Covalent BTK inhibitors			
Ibrutinib	• High ORR and MRR • Rapid responses • Durable responses	• Continuous therapy • Ineffective in genuine MYD88^{WT} • Adverse events due to off-target effects: cardiac arrhythmias, hypertension, bleeding, GI toxicity • Development of Cys481 mutations leading to resistance	• IR superiority in MYD88^{WT} not clear due to poor sensitivity of molecular methodology in iNNOVATE • Role of Ibrutinib combinations in improving efficacy/ enabling fixed duration remain under investigation
Acalabrutinib	• ORR 93% MRR 78% (n = 92 RRWM) • Lower rates of AF than Ibrutinib in CLL	• Continuous therapy • Neutropenia rate 16% • Headache is a notable AE	• No longer being developed for WM
Zarubrutinib (vs Ibrutinib-ASPEN)	• MRR 77 VS 78% VGPR 28 VS 19% [n = 164 RRWM) • VGPR/CR rate of 36 vs 22% in MYD88^{WT} (Cohort 2; n = 23 RRWM) • In CXCR4^{FS} mutations cohort [19 vs 7] zanubrutinib had higher VGPR+CR rate compared to ibrutinib (26.3% vs 0; $P = 0.06$) • In TP53^{MUT} patients the VQPR significantly higher for zanubrutinib vs ibrutinib (34.6% us. 13.6%, $P < 0.05$} • Lower rates of AF (8% vs 24%), hypertension (15% vs 26%) • Lower rates of discontinuation due to AEs [9% vs 19%) • AEs leading to discontinuation of ibrutinib or acalabrutinib may not recur with zanubrutinib or if they do, the severity is less than with original BTKi	• Continuous therapy • No CRs • Patients with TERT^{MUT} had lower VGPR (11.1 % vs 27.7 %) and MRR (44.4 % vs 84.3 %) but comparable PFS (74.0 % vs 68.4 %, $P = 0.304$) vs TERT^{MUT} in the ibrutinib arm but in the zanubrutinib arm VGPR was lower (10.0 % vs 39.8 %} and the significantly reduced PFS [37.5 % vs 83.4 %, $P = 0.001$). • Neutropenia more frequent (3-2 vs 1S%) • AF/flutter (8%), hypertension (15%) is not absent	• Resistance mutations are becoming evident
Orelabrutinib	• ORR 89.4%, MRR 80.9%, VGPR 59.6% (n = 66)	• Grade 3 AEs of neutropenia (8.5%), thrombocytopenia (6.4%), pneumonia (4%)	
Tirabrutinib	• MRR 88.9% in RRWM (n = 9)	• AEs include rash, leukopenia, nasopharyngitis	• Japan only
Non-covalent BTK inhibitors			
Pirtobrutinib	• High response rates (MRR: 6S%; CR+VGPR: 24%) in BRUIN (n = 66 RRWM who had discontinued covalent BTKi due to relapse [67%] or intolerance [33%]) • Shows efficacy in MYD88^{WT}, BTK^{C481S}, BTK^{C481R} mutated patients	• Limited follow up • Not currently approved for WM • Most frequent Grade >3 TEAE was neutropenia (20%)	• Superiority over covalent BTKi remains to be established

reported at ASH 2022 [24] demonstrating ORR 76%, VGPR 24% and PR 52% and median time to progression of 26 months. The safety analysis revealed anemia (81%), fatigue (76%), nausea (67%) and thrombocytopenia (52%) as the most common AEs. Table 2 summarizes the potential advantages and disadvantages of the various agents and highlights important caveats.

Consensus panel deliberations

What are the preferable treatments for relapsed or refractory, symptomatic WM patients?

The preferred treatment for relapsed or refractory (RR) WM depends on the upfront strategy, which in most cases is chemoimmunotherapy (CIT) and/or a covalent BTKi (cBTKi). Upfront therapy varies in different countries according to local guidelines and reimbursement arrangements. Clinical trial options should be offered to all patients if available. The duration of response (DoR) to prior treatment should be considered. Prolonged DoR (>3 years) following CIT might enable consideration of further CIT with non-cross-reactive agents. If prior therapy comprised a cBTKi only, then CIT would be a reasonable consideration at relapse. If patients develop RR WM following CIT *and* cBTKi, then other options include non-covalent BTKi (eg, pirtobrutinib), novel ant-CD20 monoclonal antibodies, BCL-2 inhibitors (eg, venetoclax) or more intensive CIT regimens. Younger, fitter patients may be considered suitable for an autologous stem cell transplant (ASCT) if they have failed both CIT and cBTKi, especially if clinical trials or other novel agents are limited. However, patients being considered for ASCT should have chemosensitive disease [25].

What patient characteristics should guide use of therapy in relapsed or refractory, symptomatic WM patients?

Biological age, co-morbidities, fitness and accessibility are important factors in selecting treatment choices. The phenotypic behavior of the disease at the outset, including any attendant WM complications at diagnosis (eg, hyperviscosity syndrome (HVS), acquired clotting factor deficiencies) may recur at relapse and influence treatment choice.

Patients who have previously experienced HVS may need plasma exchange if there are risk factors such as IgM>40 g/L and/or presence of a cryoglobulin. Incorporating anti-CD20 therapy may need to be deferred until chemotherapy effect has been established and the IgM level is <40g/L.

Table 2
Other targeted therapies: potential benefits and drawbacks.

	Potential benefits	Potential drawbacks	Unknowns/Caveats
BCL-2 inhibitors			
Venetoclax	• Phase 2 study with 24-month fixed-duration therapy: ORR 84% MRR 81% VGPR 19% (n = 32, 16 previous BTKI, all MYD88^{MUT}, 17 CXCR4^{MUT})	• No CRs • Significant progression within 6 months of completing 24 months- suggesting continuous therapy required • Phase 2 study of fixed-duration venetoclax with ibrutinib: (n = 45 TN patients) closed prematurely due to unexpected fatal ventricular tachycardias	• Potential for combination of (other) BCL-2 inhibitors with (other) BTKi: studies on hold
Proteasome inhibitors			
Bortezomib	• ORR 80%, PR 60% using monotherapy (RRWM) • CyBorD regimen (n = 11 RRWM): ORR 93%, MRR 53% • Real world data of Bortezomib-containing therapy (n = 32 RRWM): ORR 88%, median TTNT 66 months. Neuropathy Grade 1-2 in 24%; no treatment cessation due to AEs. Major responses comparable in BTKi-failures vs no BTKi	• Monotherapy study: Treatment emergent neuropathy (30%) (grade 2: n = l, grade 3: n = 2] • CyBordD study: Grade 3-4toxicities requiring dose changes/delajys included neuropathy (26%), cytopenia (20%), and bacteraemia (7%).	• Unclear where bortezomib fits in
Carfilzomib	• CaRD is a study in TN patients (n-33): ORR 87%, MRR 68%	• Limited data outside of trials	• Potential for cardiopulmonary toxicity
Ixazomib	• Fixed-duration Ixazomib + SC flat dose Rituximab + Dexamethasone (n = 59 RRWM): ORR 71%, VGPR 14%, PR 37% • Phase 2 study of combination of ibrutinib with ixazomib (n = 21 TN and RRWM): VGPR 24% PR 52%	• Hovon study: hematological toxicity (n = 6), infusion-related reactions to rituximab (n = 2) neurotoxicity (n = 5) and other toxicities (n = 21) • The safety analysis of the combination study: anaemia (81%), fatigue (76%), nausea (67%) and thrombocytopenia (52%) were the most common AEs.	

Patient preference is important and is aided by a detailed explanation of the differences between limited duration options (CIT) vs long-term continuous therapies (BTKi). The nature of relapse (rapid vs more gradual vs high-grade transformation) will influence the treatment choice, as will the level of hematopoietic reserve; limited reserve due to high BM disease burden will need caution with doses of CIT. The composition of the BM disease (lymphoid / plasmacytic balance) should be noted. If there is a minor response or worse, and the bone marrow burden is dominated by plasma cells, there may be a rationale for selecting proteasome inhibitors ahead of BTKi. The pre-existence or development of special clinical situations (eg, peripheral neuropathy, BNS, cryoglobulinemia, AL amyloidosis) should be identified and influence treatment accordingly.

Should criteria for initiating treatment be applied to newly diagnosed WM also be used in relapsed WM?

The criteria for initiating treatment are similar at presentation and relapse. Still, knowledge of the patient's past presentation should be employed to avoid unnecessary delays in treatment initiation at relapse. Previous toxicities (emesis, cytopenias, infections) and newly acquired co-morbidities should be mitigated using active pharmacological strategies, cross-specialty input and supportive measures.

As in the TN setting, the presence of functional iron deficiency could be mitigated by administration of intravenous iron; if this corrects the anemia and improves well-being, the urgency to commence treatment may be tempered.

What patient characteristics should guide choice of a BTK-inhibitor in relapsed or refractory, symptomatic WM patients?

Prior exposure to CIT influences repeated use, depending on the intensity of previous treatment, the DoR and ongoing toxicities (especially BM insufficiency and immunosuppression). If there are unremitted prior CIT-related toxicities such as cytopenias or hypogammaglobulinaemia / recurrent infections, use of further CIT over a BTKi is not desirable.

Relapse following previous cBTKi raises the possibility of using an alternative cBTKi or non-cBTKi. Data are immature regarding the best way to address this. Treatment availability per country and patient as well as physician choice may enable switching between agents with close attention regarding AE of special interest (AESI).

Risk factors for AESI should be actively sought prior to commencement of BTKi, in particular cardiovascular dysfunction (uncontrolled or unstable cardiac arrhythmias), bleeding risk (inherent or iatrogenic) and concurrent medication with CYP3A4 inducers/inhibitors. These should be addressed with cross-specialty input and mitigated where possible to safely administer cBTKi.

Mutational status (*MYD88*, *CXCR4*) may influence the effectiveness of cBTKi overall and some more than others. At IWWM-11 an update of the ASPEN randomized trial showed that zanubrutinib as a single agent showed deeper response activity and better PFS in *CXCR4*^{MUT} patients that included both treatment-naïve and previously treated WM patients·[7,27] Zanubrutinib was also active in *MYD88*^{WT} patients included as a separate single arm of the ASPEN study with a major response of 65%, whereas no major responses were observed with ibrutinib monotherapy [10,28]. *TP53* mutations were also more prevalent in previously treated patients included on ASPEN study. The emerging role of the altered *TP53* pathway deserves further study but cannot guide one choice over another at this time.

Which therapies should be recommended for patients failing or who are intolerant to covalent BTK-inhibitors?

Failure of cBTKi depends on the dose intensity achieved; if there was dose-reduction for toxicities, a trial of a higher

dose could be attempted in the first instance; if disease control is regained with tolerable side effects, this may suffice for a time.

CIT is an option in the setting of cBTKi-failure if there was no recent or prior CIT use. A non-cross-reactive regimen could be employed if prior CIT was used at this stage. The number of cycles (4 vs 6) should be tailored to the patient's immune function and marrow reserve. If the cBTKi was administered as a monotherapy, anti-CD20 antibody therapy could be added, subject to local rules.

Loss of disease control by cBTKi may be a feature of *MYD88*/*CXCR4* mutational status. There are data to suggest that zanubrutinib is effective in *MYD88*^{WT}, and more active over ibrutinib in *CXCR4*^{MUT} cases [7]; switching from ibrutinib to zanubrutinib is an option in *MYD88*^{WT} or *CXCR4*^{MUT} cases if response is lacklustre. The acquisition of resistance mutations in *BTK*^{Cys481} or PLCγ2 genes may occur in the cBTKi setting and may be overcome by non-cBTKi. There are no data to suggest switchover from one cBTKi to another if acquired resistance occurs.

Proteasome inhibitors (PI) could be considered for cBTKi failures as well [21]. Caution should be exercised for use of PIs in patients with peripheral neuropathy, and or neuropathy sparing PI such as carfilzomib could be considered. The availability of other options such as BCL-2 inhibitors, new anti-CD20 combinations (such as obinutuzumab with and without idelalisib) are country-specific. Clinical trial options should be considered and prioritized (ie, CAR-T-cell therapy, Iopofisine 131, loncastuximab, etc.).

Additional questions submitted to consensus panel from the audience at IWWM-11

What are the financial and access considerations if recommended drugs and tests are not approved or available?

CIT is effective in WM so has utility where BTKi or other targeted therapies are unavailable. Various guidelines describe the approach to using CIT and these should be followed. In younger fitter patients, the option of intensification after salvage therapy and consolidation with an ASCT could be considered on a case-by-case basis in the setting of chemosensitive disease.

Where cBTKI are available, different countries have differing rules for prescription. Accordingly, CIT and cBTKi should be used in a judicious sequence based on availability and best fit for the patient. Clinical trials may be an option but may require patients to travel to other centers.

Is it appropriate to use rituximab with BTK-inhibitors in the relapsed or refractory setting? Is it appropriate to use rituximab with CIT in the relapsed or refractory setting?

Anti-CD20 therapy is intrinsic to the treatment of B cell lymphomas, but its benefit in the relapsed setting may be questionable as a single agent if relapse occurs within 1 year of rituximab-based therapy. Using anti-CD20 therapy runs the risk of prolonged B cell immunosuppression and hypogammaglobulinemia, so the decision of adding rituximab to cBTKi should be made on a case-by-case basis and may be particularly important for those patients with wild-type *MYD88* and mutated *CXCR4*. The iNNOVATE study showed superiority across clinical outcomes regardless of *MYD88*/ *CXCR4* mutational status (although patients with *CXCR4*^{MUT} had shorter PFS), prior treatment or key patient characteristics. [2] However, the comparator was placebo and rituximab, so data on the benefit of adding rituximab to ibrutinib monotherapy are limited. Anti-CD20 therapy may have limited use at relapse if the bone marrow is devoid of CD20+ cells.

How should early relapsing patients be handled, ie, those with increasing IgM, but who have no signs or symptoms of progression or with slowly progressing signs or symptoms of disease?

In general, the criteria for initiating treatment are similar at presentation and relapse. Patients with biochemical progression but no clinical signs or symptoms should be followed up closely, keeping in mind the clinical behavior of their disease at the outset so that expected complications are prevented. Potential options should be considered, including clinical trial options that may be available. When treatment is required, restaging should include a bone marrow assessment and molecular analysis commensurate with local policies. *MYD88*, *CXCR4* and *TP53* status are encouraged as disruptions of these genes may enable a more tailored approach to therapy. Repeat imaging may also need to be considered prior to next therapy depending on signs/symptoms at progression.

Are there any management differences between relapsing vs refractory patients? What about patients considered to have inadequate response?

In patients who are relapsing after first line of therapy or who are refractory (defined as no response to treatment or who relapse within 6 months of the initial therapy), there are many options available. Second line treatment would therefore be expected to induce a clinically significant response. This might comprise relapse or being treatment refractory after CIT or cBTKi with the options as discussed above, including re-treatment with previously successful regimens. Nonetheless, treatment of subsequent relapse(s) tends to become less successful over time as resistance develops. Resistance mechanisms in CIT are likely to be overcome by cBTKi. Resistance to cBTKi has been addressed above. As patients become progressively refractory to different treatment modalities, ongoing choices should be selective for options that present a novel biological challenge for the disease, preferably within clinical trials. In parallel, refractoriness should be acted on without delay to preserve immune and bone marrow function. Attention should be paid to bone marrow reserve and treatment intensity moderated accordingly.

Some patients may have clinical improvement and restored well-being despite a minor or stable disease response as defined by the IWWM response criteria. It is important to revisit the treatment goals for the patient as a deep categorical response is not always necessary. In the case of clinical benefit, treatment may be continued and completed, followed by observation of the patient.

Should the immune function of the patient be considered in the choice of therapy?

There is mounting evidence from real-world data of vulnerability to infections in the setting of targeted therapies in indolent B cell lymphomas [26–28]. There are insufficient data to recommend systematic approaches to immune surveillance and adaptation of therapy or supportive care. Local prophylactic policies should be adopted and consideration of opportunistic infections in relevant situations. Hypogammaglobulinaemia could merit immunoglobulin replacement according to local policies. Antifungal prophylaxis may be needed in special situations such as prolonged concurrent use of steroids.

How should treatments be sequenced?

The sequencing of therapies at relapse depends on the initial treatment approach, which varies in different countries depending on the availability and reimbursement of the medicines. The duration of response, the safety profile and new clinical or co-morbid developments in the patient will also influence the sequencing of therapies. There are no robust data to advise on treatment sequencing. The opportunity to avail of a novel agent

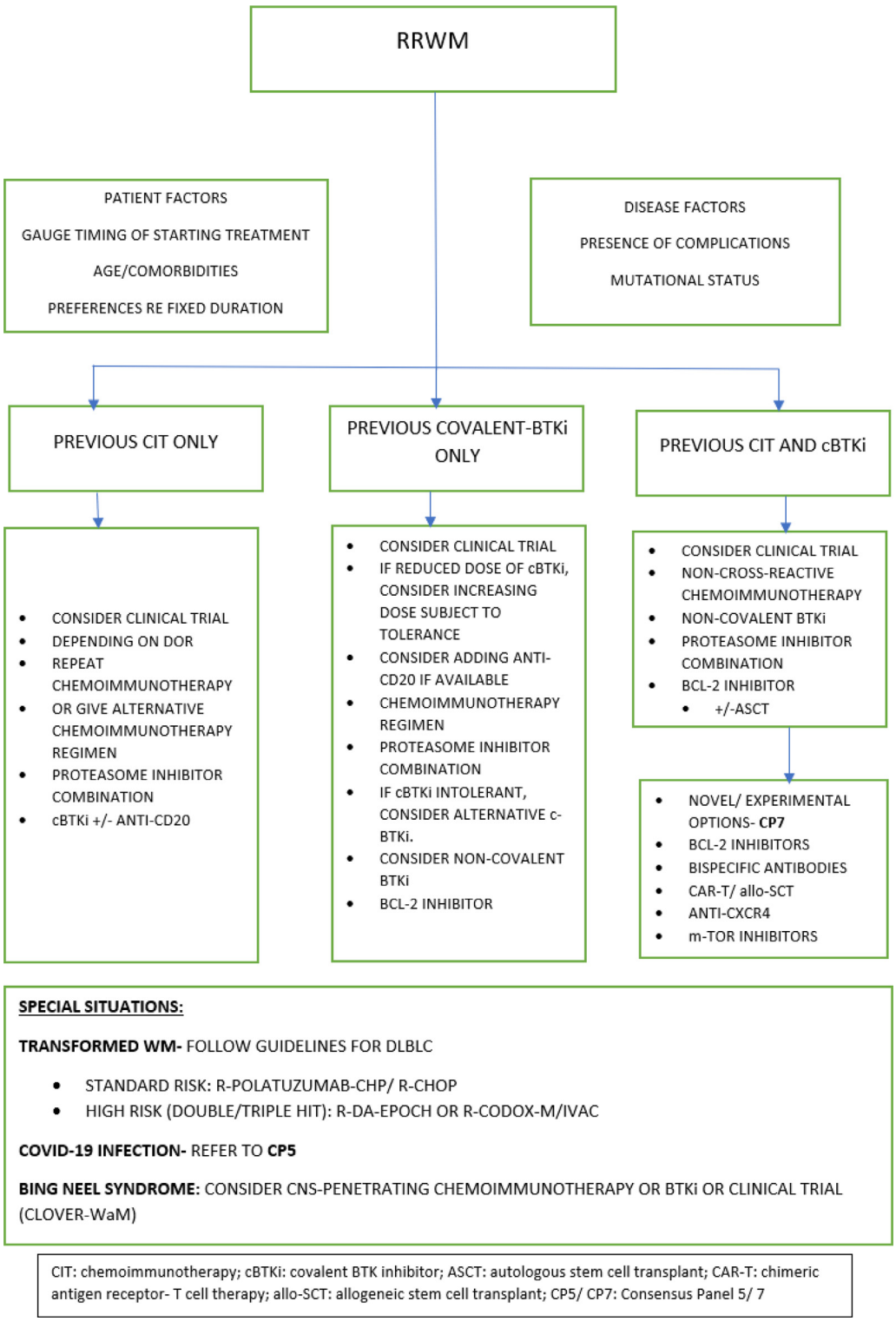

Fig. 1. Treatment algorithm in relapsed/ refractory Waldenström macroglobulinemia.

as part of a clinical trial may alter the sequence of therapies and should be considered. Figure 1 shows an algorithm for guidance.

What are the appropriate "bridging" strategies when coming off BTK-inhibitors?

A withdrawal syndrome is well recognised when BTKi are interrupted or discontinued [32]. This may be minimized by co-administration of corticosteroids as per existing treatment guidelines. Care is needed when bridging to a clinical trial as there are predefined limits on bridging therapies and use of corticosteroids. Thus, in the context of a clinical trial a prospective plan for appropriate bridging should be discussed and agreed in good time to enable smooth transition to the clinical trial. See also recommendations from consensus panel 1 in this edition of Seminars in Hematology.

How does use of molecular diagnostic testing, including MYD88, CXCR4, TP53 *determine treatment selection and should testing for these mutations be repeated at time of relapse or in the presence of refractory disease?*

The composition of the BM disease (lymphoid / plasmacytic balance) and mutational status (*MYD88*, *CXCR4*, *TP53*) should be noted at relapse. *MYD88* status is needed at diagnosis only as it will remain intrinsic to the disease, but *CXCR4* and *TP53* disruptions may develop with disease evolution. In centres that perform these studies, it is desirable to screen for these genetic alterations prior to therapy, bearing in mind the sensitivity and specificity of the techniques. In cases where the relapse is aggressive and demonstrating rapidly evolving refractoriness, acquisition of molecular data may assist in directing the selection of therapy, in discussion within an expert forum. The optimal frequency of molecular analysis is unclear as there are limited data to direct treatment selection. See also recommendations from CP3 in this edition of Seminars in Hematology.

How should prognostic factors be incorporated for treatment recommendations?

The revised IPSSWM was published in 2019 [29] to reflect more contemporary rituximab-based CIT and PI-based therapy as part of primary treatment but did not incorporate cBTKi treatment due to limited use in the cohort. Neither were cytogenetic nor molecular data incorporated. A sub-group of patients with a very poor prognosis was identified by the rIPSSWM, who should be targeted for new, innovative strategies via clinical trials.

How is transformed WM best managed? Is there a role for continuing BTK-inhibitors? Should they be offered alongside chemoimmunotherapy?

Treatment of transformed WM should follow the approved strategy employed in DLBCL. In some countries, polatuzumab has been approved first line for DLBCL (and transformed disease) as per the POLARIX trial [30]. As such, many consider the new standard of care for first-line patients to be R-Pola-CHP if available, or R-CHOP for standard risk. For high risk patients (*MYC*/ *BCL2* +/- *BCL6*: double and triple hit), R-DA-EPOCH or R-CODOX-M/IVAC might be considered [31]. There are ongoing trials with acalabrutinib with R-CHOP in both *de novo* DLBCL and Richter's, but the data are not mature yet. R-Benda-Pola may be used, if available, for the second or third line as a bridge to allogeneic stem cell transplantation (alloSCT) or CAR-T-cell therapy, when this option is available. Therapy options should be stratified by line of therapy and include all possible regimens, ie, mTOR inhibitors, ASCTs.

How do co-occurring myelodysplasia (MDS), or CHiPs influence management of RRWM?

Clonal hematopoesis (CHiP) in WM has been reported in 14% of patients with WM and associates with a greater likelihood of progression from IgM MGUS or smoldering WM to symptomatic disease but it was not associated with worse overall survival [32]. CHiP is also associated with an increased risk of myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) in WM though longer follow-up and prospective studies are needed to determine which patients with WM and CHiP have the highest risk of developing a secondary myeloid malignancy.

Discuss secondary malignancy risks as part of therapeutic recommendations

Refer to section on MDS and CHiPs above. See also recommendations from consensus panel 1 in this edition of Seminars in Hematology.

How does COVID-19 infection impact on choosing treatments?

See recommendations from consensus panels 1 and 5 in this edition of Seminars in Hematology.

What is the role for allogeneic stem cell transplantation in RRWM?

Data on the use of allo-SCT in WM reflect the era predating the use of BTKi and *MYD88*/*CXCR4* mutational status [33–35]. Consequently, it is not possible to make recommendations for this treatment outside of clinical trials or in specific cases in patients who have exhausted all other therapies but have a sufficient performance status and are in a state of remission at the time of transplant.

What is the role for CAR-T or Bispecifics in RRWM?

Data for CAR-T and Bispecific T-cell engagers are limited in WM [36]. A small series showed that CAR-T therapy targeting CD-19 demonstrated early tolerability and efficacy in patients with multiply relapsed and refractory WM [37]. Trials are underway and should be considered in RRWM. These therapies outside of a clinical trial cannot be recommended at this time. Consideration of patients with RRWM for participation in trials of T-cell engaging therapies or CAR-T cells therapies should be encouraged when appropriate.

Is there a right time to stop treatment and offer palliative care?

Survival of WM patients has improved significantly over time in both older and especially younger patients. Disease specific survival has improved incrementally in patients $\geq$ 65 years from 5.2 years in the 1960-1977 era to 12 years in the 1996-2013 era; the impact of novel therapies remains to be determined [38]. Despite remarkable progress in therapies for RRWM, early involvement by Palliative Care colleagues is encouraged to enable physicians to aid their patients in making appropriate choices [39].

Authors' Contributions

SD, EK, JM, RGS, JSM, and SPT prepared, reviewed and submitted key questions for consensus panel 2 (CP2). Questions were reviewed in an open general assembly by attendants of IWWM-11, and additional questions for CP2 deliberations were formulated and submitted. SD wrote the first draft of CP2 responses, and draft was reviewed and modified by EK, JM, RGS, JSM, and SPT. Final draft was submitted to CP2 general panel for review and commentary. CP2 general panel was composed of individuals with experience in the care of WM patients who attended IWWM-11 and volunteered to be on CP2 panel.

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JVM has served on advisory committee's for Pharmacyclics, Janssen and BeiGene.

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JSM declares participation on advisory boards and consulting services, on behalf of my Institution, for Abbvie, Amgen, BMS, Celgene, GSK, Haemalogix, Janssen-Cilag, Karyopharm, MSD, Novartis, Pfizer, Takeda, Regeneron, Roche, Sanofi, and SecuraBio.

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