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Insights from the 12th International Workshop on Waldenstrom's Macroglobulinemia

The 12th International Workshop on Waldenstrom's Macroglobulinemia (IWWM-12) was held on October 17-19, 2024 in Prague, Czech Republic. IWWM-12 was organized by Dr. Jeffrey Matous (Colorado Blood Institute, Denver Co, USA); Dr. Christian Buske (University of Ulm, Ulm, Germany); Christopher Patterson (Dana Farber Cancer Institute, Boston MA, USA); and Steve Treon (Dana Farber Cancer Institute, Boston MA, USA). The workshop attracted over 600 physicians and scientists representing 33 countries (Figure 1). There were many new important insights offered on the underlying biology and management of IgM secreting lymphoplasmacytic lymphoma (LPL) represented by the diagnosis of WM, as well as the less understood non-IgM secreting LPL. Abstracts for the highlighted presentations below, as well as those of other investigators can be found at www.waldenstromsworkshop.org

Molecular studies identify at least two subsets of WM

While mutated *MYD88* occurs in 95-97% of WM patients, evidence for the existence of distinct subtypes within this patient population has been accruing. Among the key biological revelations at IWWM-12 was the identification of at least two subtypes of MYD88 mutated WM by multi-omic studies. By combining multi-omics and pseudotime derived tumor evolution, Hunter and colleagues reported the existence of three subtypes of WM including an "Early WM" which corresponded to smoldering WM, and B-cell like (BCL) and plasma cell like (PCL) subtype with distinct clinicopathological and genomic differences. Patients with Early WM concentrated with early pseudo-time values with intermediate expression of subtype associated genes, which appeared to evolve to either BCL or PCL subtypes. Those WM patients with BCL subtype showed higher expression of mutated CXCR4 (80% vs. 7%); CD79B (9% vs. 3%); amplifications of chromosome 18q (16% vs. 2%); and cell surface expression of CD5 (18% vs. 6%) in comparison to PCL subtyped WM patients. Conversely, WM patients with the PCL subtype showed higher expression of mutated NOTCH1 (9.5% vs. 1.1%); EP300 (18% vs. 5%); amplified chromosome 6p (18% vs. 3%); deleted chromosome 6q (46% vs 28%); and chromosome 17p (10% vs. 0%). WM patients with PCL subtype were more likely to express CD10 (12% vs. 1%); and to have higher bone marrow disease involvement (70% vs. 40%). Using single-cell multi-omics, Gagler et al identified two distinct subtypes of MYD88 mutated WM: Memory B-cell-like (MBC-like) and a Plasma cell-like (PC-like). The MBC-like subtype showed a blockade in differentiation at the memory B-cell stage, while the PC-like subtype showed partial differentiation towards a plasma cell. Among their key findings were that mutations in *CXCR4*, *NIK* and *ARID1A* mutations were prevalent in the MBC-like subtype while chromosome 6q deletions occurred in the PC-like subtype. The authors also reported that the differentiation block was driven by *SBPI1* and *SPIB* in MBC-Like, and by *FOXO1* along with *IRF4* in the PC-Like WM cluster. Distinct mutations, transcriptional and epigenomic features were also highlighted by Gagler and colleagues in these two *MYD88 mutated* WM subsets.

The identification of WM subtypes may be important for pursuing a more personalized treatment approach for WM. The expression of mutated *CXCR4* which is enriched in MBC-like WM is known to impact outcomes with BTK-inhibitors. However, changes in signaling that accompany disease evolution from early to symptomatic WM are also likely to impact outcomes to targeted therapies as suggested by Hunter et al. Therefore, both the evolutionary state using pseudotime analysis and subtype identification of WM will be of interest as predictive tools in future clinical trials. Molecular subtyping also offers the possibility for better prognostic and predictive testing, as well as development of more individualized treatment approaches for WM.

Evolution of the immune microenvironment from asymptomatic to symptomatic WM

An important highlight of IWWM-12 was the study reported by Sklavenitis-Pistofidis et al on immune dysregulation associated with disease evolution in WM. Using single-cell RNA-sequencing, they demonstrated that patients with asymptomatic WM already demonstrated extensive immune dysregulation with disease-specific immune hallmarks. Asymptomatic WM patient T and NK cells showed systemic hypo-responsiveness to interferon which improved following interferon administration. Notably, the proportion of Tregs also increased with disease progression from smoldering/IGM MGUS to symptomatic WM. The authors commented on the use of immune profiling for better patient risk stratification and potentially selecting patients who may benefit from early treatment for preventing disease progression.

Expanding our knowledge of mutated MYD88 and CXCR4 signaling and its vulnerabilities

The potential to abrogate mutated MYD88 signaling was further recognized at IWWM-12. Mutated MYD88 triggers a broad network of pro-survival signaling (Figure 2). At the center of mutated MYD88's signaling hub is the upregulation of the SRC family member hematopoetic cell kinase (HCK), which is transcriptionally upregulated and activated by mutated MYD88. HCK in turn triggers

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Figure 1. Attendees at the 12th International Workshop on Waldenstrom's Macroglobulinemia in Prague, The Czech Republic.

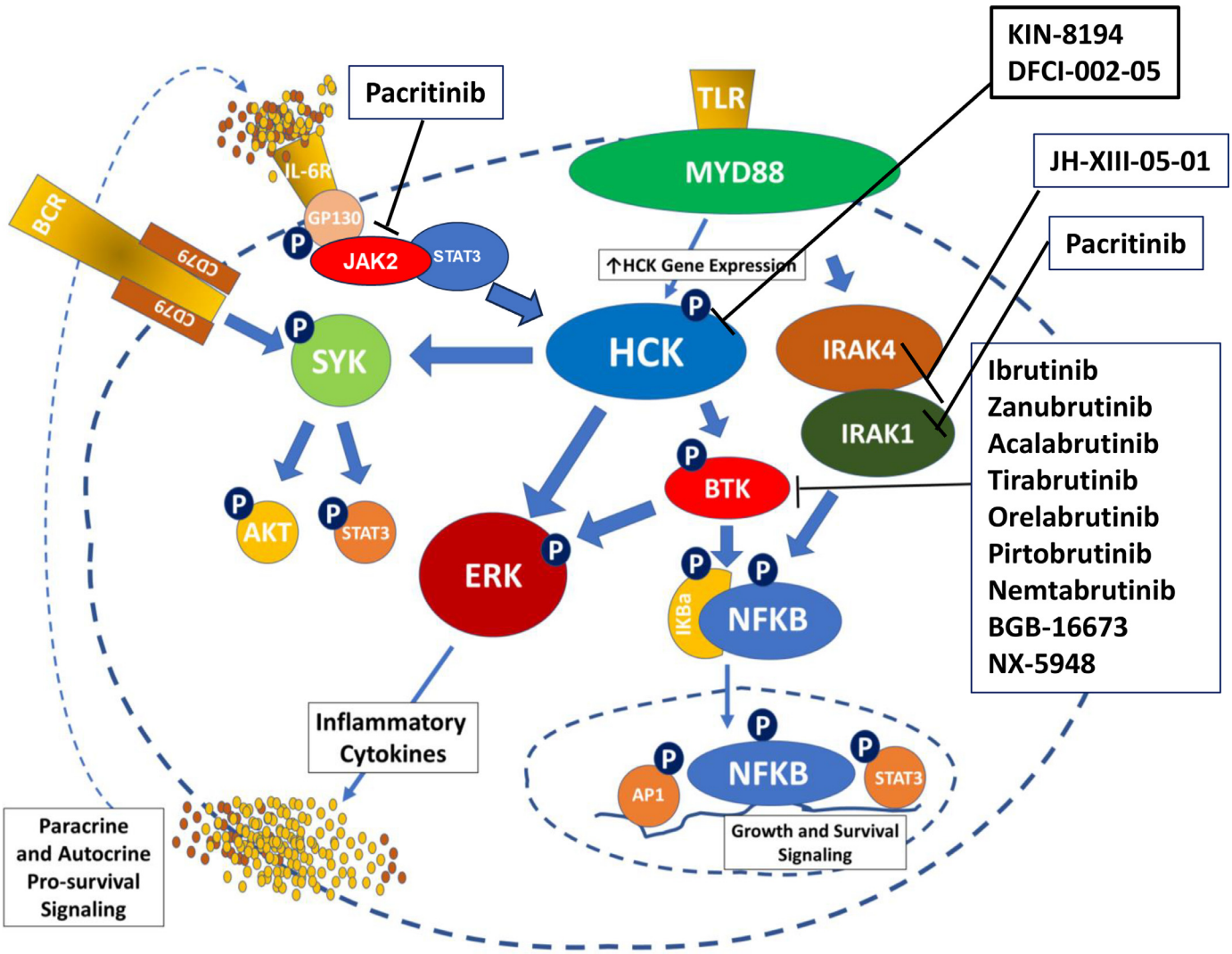

Figure 2. Pro-survival signaling hubs for mutated MYD88 and opportunities for targeted therapeutics.

BTK, BCR/SYK and ERK1/2. The identification of BTK as a downstream pro-survival molecule of $MYD88^{Mut}$ supported development of BTK-inhibitors and FDA/EMA approval of ibrutinib and zanubrutinib for WM. In Japan, tirabrutinib was approved for the treatment of WM. While BTK-inhibitors are highly active in WM with overall response rates of 80-90%, complete responses are rare and the median progression-free survival is 4-6 years. The intrinsic resistance to BTK-inhibition may be related to alternative NFKB pro-survival signaling by IRAK4 and IRAK1. IRAK4 triggers IRAK1 in response to $MYD88^{Mut}$ and both trigger NFKB pro-survival signaling. To address intrinsic resistance, Buhrlage et al developed IRAK-kinase inhibitors and degraders. At IWWM-12, they reported on the development of the development and characterization of a novel bifunctional proteolysis targeting chimera (PROTAC) JH-XIII-05-1 that showed potent IRAK4 and IRAK1 kinase inhibition and target degradation and was highly active in *MYD88* mutated B-cell lymphoma cells alone and in combination with BTK- and BCL2- inhibitors.

Hatcher et al presented data at IWWM-12 on the development of two highly potent and selective bifunctional HCK/BTK PROTACs that showed potent target kinase inhibition and protein degradation, as well as anti-proliferative and/or apoptotic activity in lymphoma cells engineered to express mutated BTK^{Cys481}. Both PROTACs showed robust bioavailability and degradation of HCK and BTK in murine TMD8 xenograft models as well as potent tumor suppression. Their studies provided a framework for advancing bifunctional HCK/BTK PROTACs for treating *MYD88* mutated lymphomas, including covalent BTK-inhibitor resistant disease carrying BTK^{Cys481} mutations.

Another relevant presentation to abrogating mutated MYD88 signaling was presented by Liu et al, on the repurposing of pacritinib to treat WM. Pacritinib, an FDA-approved kinase inhibitor for myelofibrosis, targets crucial signaling pathways associated with mutated MYD88 signaling, including IRAK1, JAK2, and SRC (a homolog of HCK). Pacritinib effectively targeted mutated MYD88 pro-survival signaling pathways and showed superior apoptotic activity in *MYD88* mutated WM and ABC DLBCL cells over covalent BTK-inhibitors. Pacritinib also showed robust synergistic interactions with BTK and BCL-2 inhibitors and overcame covalent BTK-inhibitor resistance associated with mutated $BTK^{Cys481Ser}$ both *in vitro* and *in vivo* in a TMD8 BTK Cys 481 mutated xenograft murine model. Our studies provide a framework for the investigation of pacritinib in MYD88-mutated lymphomas. Based on these findings, a phase II clinical trial investigating pacritinib in relapsed/refractory WM has been initiated by Sarosiek et al.

Expanding the Treatment Options for Symptomatic Treatment Naïve WM Patients

Bendamustine and rituximab (Benda-R), rituximab, cyclophosphamide and dexamethasone (RCD) and BTK-inhibitors have emerged common frontline options for symptomatic treatment-naïve WM. There has been no prospective study comparing these three regimens. At IWWM-12, Abeykoon and colleagues presented a retrospective study comparing outcomes of symptomatic, treatment-naïve MYD88 mutated WM patients who received either ibrutinib or Benda-R. While the findings of this study showed deeper response attainment with Benda-R, there was no difference in 6 year progression free or overall survival. Autore and colleagues presented their multi-center observational study from the Fondazione Italiana Linfomi (FIL) group on outcomes following frontline therapy with either Benda-R or RCD. Two hundred forty-five and 116 WM patients received either Benda-R or RCD in this study. A higher overall (93% vs 79%), VGPR/CR (44% vs. 19%), and four-year progression free survival (80% vs. 60%) was observed in this study in those receiving Benda-R vs. RCD, respectively. However, more patients on Benda-R required dose reduction for toxicity.

LeBlond and colleagues presented the long-term findings of a single arm study of Benda-R in symptomatic treatment-naïve patients. The study conducted by the French Innovative Leukemia Organization (FILO) administered six cycles of Benda-R. Notable in this study were long term toxicities that included persistent cytopenias in ghalf of patients, as well as second malignancies in 18% of 69 patients. Three cases of myelodysplastic syndrome that evolved into acute myelogenous leukemia in two patients were observed with a median follow-up of 66 months.

The long-term findings from several trials with BTK-inhibitors were also reported at IWWM-12. Dimopoulos et al reported on the long-term findings for the prospective ASPEN clinical trial which compared ibrutinib to zanubrutinib among MYD88 mutated patients in Cohort 1. In as well a second arm (Cohort 2) evaluated Zanubrutinib alone in MYD88 wild-type patients. The efficacy outcomes at 44 months were comparable with overall response rates of 95% and 94% for zanubrutinib and ibrutinib, though more patients attained a VGPR on zanubrutinib (36%) versus ibrutinib (25%). While progression free survival did not show a statistical difference between the arms for all comers in Cohort 1, those patients who were CXCR4 mutated showed deeper responses and superior progression free survival (73% vs. 49%) on zanubrutinib versus ibrutinib, respectively. Importantly, patients on Cohort 2 with MYD88 wild-type disease who received zanubrutinib showed a major response rate of 65%, which is notable since no major responses were observed in the pivotal trial with ibrutinib in the pivotal trial. Importantly, a significantly lower risk of atrial fibrillation and hypertension were observed for patients on zanubrutinib in Cohort 1; conversely while the risk of grade 3 neutropenia was higher with zanubrutinib, there was no increased infection risk.

Castillo and colleagues presented the long-term follow-up of a combination study of ibrutinib and venetoclax in symptomatic, treatment-naïve WM. The study was intended to assess the efficacy and safety of time limited therapy, with two years of planned therapy. The study was prematurely terminated due to the high incidence of ventricular arrythmias (9%), that included two grade 5 events. With a median time on treatment of 10.2 months, a follow-up on durability for therapy was presented. With a median follow-up of 36 months, the progression free survival was 51%. *CXCR4* mutation status, time on therapy $\geq$12 months, and VGPR attainment at end of treatment did not impact progression free survival after EOT. No treatment-emergent events, especially arrhythmia, were observed after treatment stopped. The relatively inferior progression free survival at 36 months compared to continuous ibrutinib alone suggests that a longer duration of combined BTK- and BCL2- inhibitor may be required to achieve comparable responses as continuous ibrutinib since the median on time treatment was 10 months in this study. Importantly, the combination of ibrutinib and venetoclax is not recommended given its high risk of ventricular arrythmias. Other BTK-inhibitors with less risk of ventricular arrhythmias are being contemplated. A study combining zanubrutinib and the novel BCL2 inhibitor sonrotoclax has recently been advanced in treatment-naïve WM patients.

An important study which may pave the way for a new time limited treatment approach for symptomatic treatment-naïve WM was the BRAWM study presentation by Berenstein et al. In this Canadian cooperative study, patients received 6 cycles of Benda-R along with one year of acalabrutinib. All patients on this study achieved a major response, including 18% who attained a complete response. At 18 months, 23% of patients had minimal residual disease (MRD) negative disease. While the importance of MRD remains to be clarified, utilizing MRD as a surrogate may be important to future trials attempting to establish its surrogacy as an end point for clinical trial in lieu of progression free or overall sur-

vival akin to efforts in multiple myeloma as presented in a keynote lecture by Ken Anderson at IWWM-12. Indeed, Varettoni et al presented data at IWWM-12 on the importance of molecular remission defined by quantitative MYD88 L265P mutation analysis of bone marrow samples by digital droplet PCR assay. Their study carried out as part of the Italian FIL-BIOWM study that assessed patients who received Benda-R or DRC showed that MRD attainment significantly correlated with improved progression free survival.

Yi and colleagues also presented preliminary data on the combination of zanubrutinib and Benda-R (ZBR) in symptomatic, newly diagnosed patients with WM. Patients on this study received 6 cycles of Benda-R overlapping with one year of zanubrutinib. The major response rate was 95%, with 65% of patients achieving a VGPR or better. By flow cytometry, MRD was achieved in half of evaluated patients. A multicenter Harvard based study of zanubrutinib and Benda-R (ZEBRA) was also presented at IWWM-12 in which patients will receive four cycles of Benda-R overlapping with 15 months of zanubrutinib (NCT06561347). In comparison to the BRAWM and ZBR studies, the ZEBRA trial is designed to minimize alkylator exposure by administering 4 versus 6 cycles of Benda-R, which is commonly used in WM patients in North America. Outcomes of this trial are awaited.

Buske et al presented data from the European Consortium for WM (ECWM-2) trial which evaluated the combination of bortezomib, ibrutinib and rituximab in symptomatic, treatment-naïve WM. Patients received induction with 6 cycles of bortezomib and rituximab along with continuous ibrutinib, followed by maintenance rituximab every 2 months for 1 year with continuous ibrutinib, then ibrutinib alone until study end or halt due to toxicity. Fifty-three WM patients were recruited to this study, which at 30 months following treatment start achieved overall and major response rates of 95% and 86%, respectively. Impressively, with a median follow-up of 37 months, no patient has progressed.

Expanding the Treatment Options for Previously Treated WM patients

Palomba and colleagues presented an update of a study of single agent of the non-covalent BTK-inhibitor pirtobrutinib in previously treated WM patients that included 63 patients who previously received a covalent BTK-inhibitor. Unfortunately, it was not known how many of these patients resistant to a prior covalent BTK-inhibitor prior to receiving pirtobrutinib. The overall and major response rates for all 80 study patients were 80% and 71%, respectively. Depth of response was impacted by prior treatment status with a covalent BTK-inhibitor. The major and VGPR response rates were 67% and 24% for those who received a prior covalent BTK-inhibitor. By comparison, the major and VGPR response rates were 88% and 35% for those who were treatment-naïve to a BTK-inhibitor prior to starting pirtobrutinib. Nonetheless, the activity of pirtobrutinib in those who did in fact receive a prior BTK-inhibitor is impressive. The median progression free survival for all patients in this study was 22 months. Castillo and colleagues presented data on the combination of pirtobrutinib and venetoclax in relapsed or refractory WM patients. The major response rate was 87% among 16 previously treated patiuents, with similar responses regardless of CXCR4 mutation status or previous covalent BTK inhibitor exposure.

The findings from several agents under investigation for previously treated WM were also presented at IWWM-12 and included the BTK degraders BGB-16673, NX-5948, and the BCL2 inhibitor sonrotoclax. Seymour et al presented findings on the activity of BGB-16673 in 27 heavily pre-treated WM patients. The overall and major response rates to BGB-16673 were 82% and 74% and were not impacted by MYD88, CXCR4 or TP53 mutation status. Responses were observed in patients carrying BTK mutations associated with acquired resistance to covalent (BTK^{Cys481}) and non-covalent (BTK^{Leu528}) BTK inhibitors. Treatment was well tolerated, and no episodes of atrial fibrillation were observed. O'Connor et al presented data on 13 heavily pretreated WM patients. A steady decrease in serum IgM levels was observed among treated patients with ongoing response evaluation.

Matous et al presented findings on the efficacy of single-agent sonrotoclax from an ongoing study in 20 previously treated WM patients. Patients received 80, 160 and 320 mg a day in the reported study. Among the 19 evaluable patients, the overall and major response rates were 79% and 58%. Response evaluation is ongoing.

Buske and colleagues also provided an update on the CZAR-1 study which is investigating the efficacy and safety of carfilzomib in combination with ibrutinib versus ibrutinib alone in treatment-naïve and previously treated WM (NCT04263480). Immunotherapies targeting WM are also advancing. A clinical trial with the antibody drug conjugate locastuximab tesirine that targets CD19 is enrolling WM patients with symptomatic, previously treated WM (NCT05190705). A study with the CD3/CD20 bispecific antibody epcoritamab has also been initiated in symptomatic previously treated WM (NCT06510491). Results from these trials are awaited. Important to advancing the development of cellular therapies for WM was the keynote lecture by Adrian Wiestner on the role of BTK-inhibitors as potential therapeutics for enhancing efficacy and ameliorating cytokine release syndrome.

Consensus Guidance on the Management of WM and non-IgM Lymphoplasmacytic Lymphoma related morbidities

As part of IWWM-12, six groups of experts were empaneled to provide guidance on important areas of management for WM, and non-IgM lymphoplasmacytic lymphoma (LPL). Consensus Panel 1 led by Drs. Shirley D'Sa and Efstathios Kastritis [1] developed consensus recommendations on the management of patients with IgM and WM related neuropathy. Consensus Panel 2 led by Drs. Shayna Sarosiek and Monique Minnema [2] provided consensus guidance on the management of Bing-Neel Syndrome in patients with WM. Consensus Panel 3 led by Drs. Prashant Kapoor and Marie Jose Kersten [3] advised on the identification and management of WM patients with high-risk disease. Consensus Panel 4 led by Drs. Alessandra Tedeschi and Ramon Garcia Sanz [4] oversaw the first consensus panel ever devoted to the management of non-IgM LPL, which constitutes about 5% of all LPL cases, the rest made up by WM. Consensus Panel 5 led by Drs. Jorge Castillo and Lia Palomba [5] provided much needed direction on the management of WM patients with intolerance or resistance to covalent BTK-inhibitors. Finally, Drs. Eric Durot and Ranjana Advani [6] led Consensus Panel 6 which provided consensus guidance on the diagnosis and management of transformed WM. The IWWM-12 consensus panel reports can be found in this edition of Seminars in Hematology and are for educational purposes and should not be construed as offering specific medical advice for patients.

Declaration of Competing Interest

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