Hematological Oncology

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SUPPLEMENT ARTICLE

Diagnosis and Management of Waldenstrom's Macroglobulinemia

Steven P. Treon[1,2] | Shayna Sarosiek[1,2] | Jorge J. Castillo[1,2]

[1]Bing Center for Waldenstrom's Macroglobulinemia, Dana Farber Cancer Institute, Boston, Massachusetts, USA | [2]Harvard Medical School, Boston, Massachusetts, USA

Correspondence: Steven P. Treon (steven_treon@dfci.harvard.edu)

Accepted: 22 March 2025

Funding: S.P.T. is supported by a Leukemia and Lymphoma Society Translational Research Grant, and a Legacy Award from the International Waldenstrom's Macroglobulinemia Foundation.

Keywords: BTK | CXCR4 | lymphoplasmacytic lymphoma | MYD88 | TP53 | Waldenström macroglobulinemia

ABSTRACT

Waldenström macroglobulinemia (WM) is an IgM secreting lymphoplasmacytic lymphoma. Mutations in MYD88 (95%–97%) and CXCR4 (30%–40%) are common in patients with WM. TP53 is also altered in up to 30% of WM patients, particularly those previously treated. Mutated MYD88 triggers the expression and activation of HCK that drives multiple pro-survival signaling cascades, including BTK. There are over 40 CXCR4 mutation types in WM. WM patients bearing nonsense CXCR4 variants can present with symptomatic hyperviscosity and show greater resistance to covalent BTK inhibitors (cBTK-i). The cBTK-i zanubrutinib shows greater response activity and/or improved progression-free survival in WM patients with wild-type MYD88, mutated CXCR4, or altered TP53. New or emerging options for patients progressing on c-BTKi include pirtobrutinib, BGB-16673, venetoclax, and sonrotoclax. Combinations of BTK inhibitors with chemoimmunotherapy and BCL2 antagonists have advanced. Algorithms for patients with treatment-naïve and previously treated WM based on genomics, disease characteristics, and co-morbidities are discussed.

1 | Introduction

Waldenström macroglobulinemia (WM) is a B-cell lymphoid neoplasm resulting from the accumulation of a clonal population of lymphocytes, lymphoplasmacytic cells, and plasma cells, which secrete a monoclonal IgM. WM corresponds to lymphoplasmacytic lymphoma (LPL) as defined in the International Consensus Classification of Mature Lymphoid Neoplasms, and the World Health Organization classification systems [1, 2]. Most cases of LPL are WM; < 5% of cases are IgA-secreting, IgG-secreting, or non-secreting LPL [2]. The key mutations in WM include MYD88, CXCR4, and TP53. Up to half of WM patients have loss of the long arm (q) of chromosome 6. Acquired BTK mutations are common in those patients who progress on BTK inhibitors. The importance of these mutations to the pathogenesis and management of WM is discussed below.

2 | MYD88 Mutations

Mutated MYD88 ($MYD88^{Mut}$) is found in 95%–97% of WM patients, nearly all of which are of the L265P variant [3–8]. AS-PCR is preferable for $MYD88^{L265P}$ detection since next-generation sequencing (NGS) may miss $MYD88^{L265P}$ in 35% of WM patients, particularly in those with a bone marrow (BM) disease burden of < 10% [9]. The signaling cascades triggered by $MYD88^{Mut}$ are exhibited in Figure 1, and are dependent on Hematopoetic Cell Kinase (HCK) BTK and IL-1 receptor-

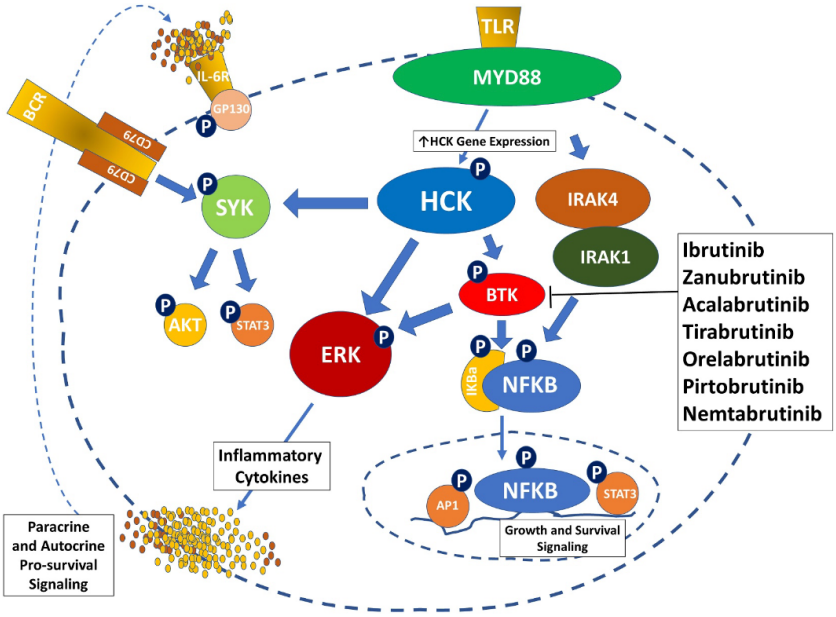

FIGURE 1 | Pro-survival signaling driven by mutated MYD88 signaling. Mutated MYD88 triggers gene expression of HCK, a SRC family member. HCK triggers BTK, SYK, and ERK1/2 signaling. BTK also triggers ERK1/2 as well as NFKB p65 mediated pro-survival signaling. IRAK4/IRAK1 are activated by mutated MYD88 through an HCK independent pathway and trigger, along with BTK, NFKB-mediated pro-survival signaling.

associated kinases (IRAKs) [10–16]. HCK activates BTK-dependent NFKB and ERK1/2 signaling, whilst IRAK1 and IRAK4 molecules trigger NFKB independent of BTK. Up to 5% of WM patients are MYD88 wild-type ($MYD88^{WT}$). Many of these patients carry NFKB-activating mutations distal to BTK signaling [17]. $MYD88^{WT}$ patients have a higher risk for disease transformation and show shorter overall survival (OS) [18, 19]. $MYD88^{Mut}$ status can also differentially impact outcomes with BTK inhibitors (discussed below). Current workshop guidelines recommend the determination of $MYD88^{Mut}$ status as part of the diagnostic workup by AS-PCR for the $MYD88^{L265P}$ variant. If negative, NGS may be used to identify any non-$MYD88^{L265P}$ variants [20].

3 | CXCR4 Mutations

$CXCR4^{Mut}$ are found in 30%–40% of WM patients [4, 21]. Over 40 CXCR4 nonsense and frameshift variants in the C-terminal domain have been identified in WM patients [4, 7, 22–25]. Nonsense ($CXCR4^{Mut/NS}$) variants such as $CXCR4^{S338X}$ cause truncation of the C-terminal regulatory domain while frameshift ($CXCR4^{Mut/FS}$) variants result from insertions or deletions [4, 21, 26, 27]. In response to CXCL12, $CXCR4^{Mut}$ triggers BTK, AKT, and ERK signaling, which promotes BM chemotaxis and ibrutinib-resistance [22–24]. CXCR4 antagonists such as plerixafor or ulocuplumab can sensitize $CXCR4^{Mut}$-expressing WM cells to ibrutinib [22–24].

$CXCR4^{Mut/NS}$ WM patients present with higher BM disease burden and serum IgM (sIgM) levels and are more likely to have symptomatic hyperviscosity. $CXCR4^{Mut}$ patients, particularly those with nonsense variants, may also have a shorter time to initial treatment versus those with either $CXCR4^{WT}$ or $CXCR4^{Mut/FS}$ [7, 26, 27]. One study also showed shorter OS in patients with $CXCR4^{Mut/NS}$ versus $CXCR4^{WT}$ or $CXCR4^{Mut/FS}$ [25]. $CXCR4^{Mut/NS}$ may also adversely impact treatment outcomes with BTK inhibitors versus $CXCR4^{WT}$ or $CXCR4^{Mut/FS}$ [28]. The importance of $CXCR4^{Mut}$ subtype on ibrutinib outcomes was evaluated in 180 symptomatic WM patients receiving ibrutinib. $CXCR4^{Mut/NS}$ was associated with lower major response rate (MRR) and shorter PFS versus those with $CXCR4^{Mut/FS}$ or $CXCR4^{WT}$ [28]. NGS may miss two-thirds of patients with $CXCR4^{Mut}$, particularly those with lower BM disease burden and clonality [29]. Newer NGS platforms may improve detection [25]. Current workshop guidelines recommend that $CXCR4^{Mut}$ status be considered part of the diagnostic workup by NGS, particularly in patients being considered for BTK inhibitor therapy [20].

4 | TP53 Alterations

Alterations in TP53 ($TP53^{Alt}$) occur in 5%–15% of treatment-naïve WM patients, including $TP53^{Mut}$ and 17p deletions [7, 30, 31]. The incidence of $TP53^{Alt}$ appears higher (25%–30%) in previously treated WM patients, most of whom received alkylators (85%) and/or nucleoside analogs (22%) [32]. $TP53^{Alt}$ WM patients show shorter OS and/or PFS with BTK inhibitors [30–32]. Current workshop guidelines recommend evaluating for $TP53^{Alt}$ at diagnosis and relapse using NGS as their presence

may guide treatment considerations [20]. As these studies have been qualitative, no cutoffs for $TP53^{Alt}$ have been established.

5 | Deletions in Chromosome 6q

Deletions in 6q (del6q) are present in up to half of WM patients at diagnosis and are almost always are heterozygous. 6q is of particular interest since important regulators of BTK (IBTK), MYD88/NFKB (TNFAIP3, HIVEP2, TRAF3IP2, IRAK1BP1), and regulators of apoptosis (FOXO3, BCLAF1, PERP) are located at this locus [33]. Serial whole exome sequencing identified homozygous deletions in 6q in WM patients progressing on ibrutinib, including evolution from heterozygous to homozygous loss of 6q at the time of progression [34].

6 | BTK Mutations

BTK^{Cys481} is the binding site for covalent BTK inhibitors (cBTK-i), including ibrutinib, zanubrutinib, acalabrutinib, orelabrutinib and tirabrutinib. BTK^{Cys481} variants are the most common mutations associated with acquired ibrutinib-resistance in WM patients [35]. Multiple clones bearing different BTK^{Cys481} mutations can occur within individual WM patients who progress on ibrutinib [35]. WM cells expressing the $BTK^{Cys481Ser}$ mutation show ibrutinib-resistance and re-activation of BTK-PLCγ2-ERK1/2 signaling [16]. Use of ERK1/2 inhibitors triggers apoptosis in $BTK^{Cys481Ser}$ expressing cells, and re-sensitization to ibrutinib [16]. Moreover, ERK1/2 re-activation is accompanied by IL-6 and IL-10 release which protects co-cultured wild-type BTK^{Cys481} WM cells from ibrutinib, demonstrating a paracrine means for propagating cBTK-i resistance [16].

7 | Genomics and Treatment Approach in WM

Figure 2 provides an algorithm for symptomatic, treatment-naïve WM patients based on underlying tumor genomics. The recommendations presented below considered recent consensus panel guidance [38]. For symptomatic treatment-naïve patients, chemoimmunotherapy with bendamustine and rituximab (Benda-R), dexamethasone, rituximab, and cyclophosphamide (DRC), as well as cBTK-i can be considered. For chemoimmunotherapy, Benda-R may offer an advantage over DRC since the former may offer deeper responses and longer PFS [40, 41].

For $MYD88^{Mut}$ only patients, using a cBTK-i may be appropriate to minimize the risk for acquired $TP53^{Alt}$. As all cBTK-i exhibit similar activity in $MYD88^{Mut}$ only patients, the choice should consider accessibility and adverse event profile, including risk for atrial fibrillation in patients at risk [38]. For $CXCR4^{Mut}$ patients requiring a rapid response, Benda-R or zanubrutinib are active options [36, 39, 42, 43]. Rituximab should be held in any rituximab-containing regimens, and plasmapheresis should be performed in those with symptomatic hyperviscosity. Rituximab should also be held in patients without symptomatic hyperviscosity and chemotherapy offered alone until the serum IgM levels are < 4000 mg/dL to avoid triggering a hyperviscosity crisis [38]. The median time to a major response was 2.8 months in $CXCR4^{Mut}$ WM patients receiving zanubrutinib in the ASPEN study, comparable to Benda-R [39]. Benda-R may be preferable

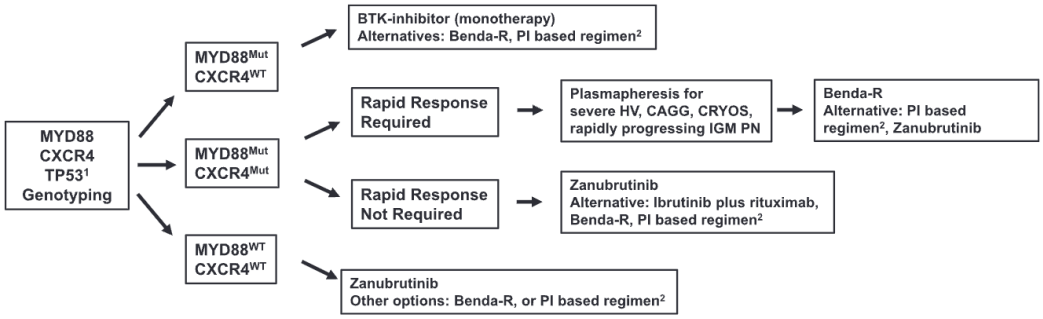

FIGURE 2 | Genomic based treatment algorithm for symptomatic, treatment Naïve patients with Waldenstrom macroglobulinemia. Clinicians should consult local regulatory approvals and guidelines for BTK inhibitor status and use in WM. The algorithm represents the authors' recommendations (see Treon et al. [36]) and their practice experiences in WM patients. Recommendations are intended for educational purposes. Rituximab should be held if chemoimmunotherapy is chosen until the serum IgM levels are < 4000 mg/dL to avoid triggering or exacerbating a hyperviscosity crisis. Benda-R can be considered for patients with bulky adenopathy or extramedullary disease. PI-based therapy or Benda-R can be considered for symptomatic amyloidosis with autologous stem cell transplantation as consolidation in select patients (see Merlini et al. [37]). Rituximab alone or with ibrutinib if $MYD88^{Mut}$ or Benda-R are options for patients with IgM demyelinating peripheral neuropathy depending on severity and pace of progression. Maintenance rituximab may be considered in patients > 65 years responding to chemoimmunotherapy with rituximab (see Buske et al. [38]). Rituximab, cyclophosphamide, and dexamethasone (RCD) is an option for chemoimmunotherapy if Benda-R is not accessible (see Buske et al. [38]). [1]Zanubrutinib may also be prioritized for those with TP53 alterations (see Tam et al. and Dimopoulos et al. [32, 39]). [2]Benda-R is preferable over PI-based regimens for those with bulky disease. Clinical trial options should always be considered. Benda, bendamustine; CAGG, cold agglutinins; CRYOS, cryoglobulinemia; HV, hyperviscosity; PI, proteasome-inhibitor; PN, peripheral neuropathy; R, rituximab.

in patients with bulky disease or symptomatic light chain amyloidosis [36, 38].

Zanubrutinib can also be considered in CXCR4^{Mut} patients who do not need rapid disease control since a shorter time to major response, deeper responses, and longer PFS were observed versus ibrutinib [39]. For MYD88^{WT} patients, zanubrutinib is favored for symptomatic, treatment-naïve patients since high response levels and long-term disease control can be achieved [39]. Benda-R and proteasome-inhibitor (PI) -based therapy are reasonable alternatives in CXCR4^{Mut} or MYD88^{WT} patients [38]. TP53^{Alt} status can be considered in positioning BTK inhibitors. Zanubrutinib is preferable for TP53^{Alt} WM patients given the ASPEN study findings showing higher levels of activity and long-term disease control versus ibrutinib [32, 39].

Figure 3 provides an algorithm for symptomatic, previously treated WM patients. The recommendations considered recent consensus panel guidance [43]. The consensus panel noted that biological age, co-morbidities and fitness, nature of relapse, patient preferences, hematopoietic reserve, and MYD88, CXCR4, and TP53 mutation status should be considered in treatment selection. For MYD88^{Mut} only patients who are refractory or in first relapse following initial chemoimmunotherapy, cBTK-i can be considered. As all cBTK-i exhibit similar response activity in MYD88^{Mut} only patients, the choice of agent should consider accessibility, disease morbidity, and adverse event profile in WM (summarized in Treon et al. [36]). For MYD88^{Mut}CXCR4^{Mut} patients who are refractory or in first relapse after initial chemoimmunotherapy, zanubrutinib may be preferable [36]. In MYD88^{WT} WM patients, zanubrutinib is preferable after initial chemoimmunotherapy [32, 39]. Zanubrutinib is also preferred for TP53^{Alt} WM patients, as noted above [32, 39].

Benda-R is preferable regardless of genomic subtype for WM patients who are refractory to initial cBTK-i therapy [36]. As discussed above, rituximab should be held in any rituximab-containing regimens, and plasmapheresis should be performed in those with symptomatic hyperviscosity. Rituximab should also be held in patients without symptomatic hyperviscosity and chemotherapy offered alone until the serum IgM levels are < 4000 mg/dL to avoid triggering a hyperviscosity crisis [38, 43]. For those progressing after initial cBTK-i response, options include Benda-R, PI-based therapy, venetoclax, or pirtobrutinib. Alkylator exposure should be avoided, particularly in patients < 70 years or with TP53^{Alt}. Venetoclax may be preferable for these patients since it is highly active in WM patients previously exposed to cBTK-i or with CXCR4^{Mut} disease [44, 45]. The activity of venetoclax in MYD88^{WT} or TP53^{Alt} WM patients remains to be clarified. Pirtobrutinib is an option post-cBTK-i therapy, though its activity in MYD88^{WT} or MYD88^{Mut}CXCR4^{Mut} patients is not known [46, 47]. Benda-R or PI-based regimens can also be considered for those progressing on a cBTK-i as these regimens appear active across all genomic subtypes [36, 42, 48]. Additional options in second or later relapse include reuse of chemotherapy if a response lasted for > 3 years, alternative chemoimmunotherapy, nucleoside analogs, or everolimus [38]. Clinical trials should also be prioritized in patients with relapsed disease.

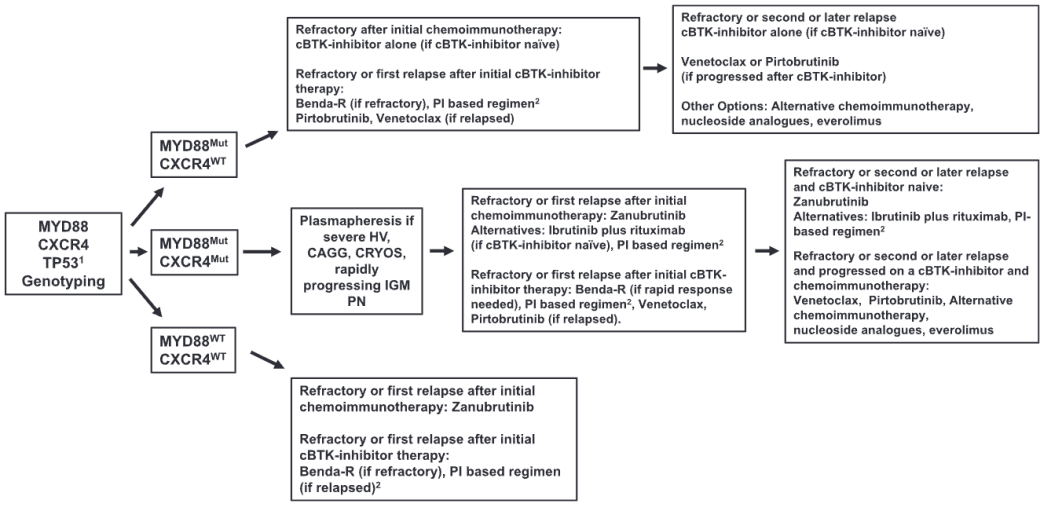

FIGURE 3 | Genomic based treatment algorithm for symptomatic, previously treated patients with Waldenstrom macroglobulinemia. Clinicians should consult local regulatory approvals and guidelines for BTK inhibitor status and use in WM. The algorithm represents the recommendations of the authors based on clinical trial data summarized in the text, consensus recommendations (see Treon et al. [36]), and their practice experiences in WM patients. Recommendations are intended for educational purposes. See also notations for Figure 2. Nucleoside analogs should be avoided in younger patients and candidates for autologous stem cell transplantation (ASCT). ASCT may be considered in patients with multiple relapses and chemosensitive disease, and those with systemic light chain amyloidosis for consolidation after PI or Benda-R therapy (see Merlini et al. [37]). [1]Zanubrutinib may also be prioritized for those with TP53 alterations (see Tam et al. and Dimopoulos et al. [32, 39]). [2]Benda-R is preferable over PI-based regimens for those with bulky disease. Clinical trial options should always be considered.

Benda-R is more suitable for WM patients with bulky extramedullary disease since data on BTK inhibitors in patients with bulky disease is limited. For WM patients with symptomatic light chain amyloidosis, consensus recommendations favor Benda-R or PI-based therapy followed by consolidation with high-dose chemotherapy and autologous stem cell transplant in suitable WM patients [37]. Covalent BTK-inhibitors are highly active and show durable responses in WM patients with CNS disease (Bing Neel Syndrome) [49–51].

8 | Emerging Treatment Options

Newer agents being developed for WM include the BTK degrader BGB-16673 and the BCL2 inhibitor sonrotoclax. In 27 heavily pre-treated WM patients (median prior therapies of 3), the overall and major response rates to single-agent BGB-16673 were 82% and 74% and were not impacted by MYD88, CXCR4 or TP53 mutation status [52]. 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. The efficacy of single-agent sonrotoclax has also been evaluated in a Phase 1 study in 19 previously treated WM patients. In this Phase 1 study, patients received 80, 160, and 320 mg daily. The overall and major response rates were 79% and 58% [53].

Combination studies are also underway with BTK and BCL2 inhibitors in WM. Zanubrutinib in combination with ixazomib and dexamethasone (ZID) is being investigated in a study in China (NCT04463953) and has shown high levels of response activity and good tolerance in symptomatic, treatment-naïve patients [54]. The overall, major, and VGPR/CR remission rates were 100%, 96%, and 46%, respectively. The median time to response was 2 months. Patients with mutations in *CXCR4* had similar VGPR/CR rates. The combination of Benda-R with acalabrutinib is being investigated in a multicenter (BRAWM Study) as first line therapy in WM [55]. Patients received 1 year of acalabrutinib along with 6 cycles of Benda-R. In a preliminary report, the major response rate was 100%, with 42% of patients achieving a VGPR/CR. Patients without CXCR4 mutations showed better VGPR/CR rates at cycle 12. The multicenter ZEBRA study has recently been initiated, and it will combine 15 months of zanubrutinib with four cycles of Benda-R (NCT06561347). The combination of pirtobrutinib with venetoclax is also being investigated in previously treated, symptomatic patients (NCT05734495) [56]. Patients receive 2 years of treatment in this study. The MRR was 87% in a preliminary report, with similar responses regardless of CXCR4 mutation status or previous covalent BTK inhibitor exposure. Combination studies with zanubrutinib and sonrotoclax are also contemplated in WM. The combination of acalabrutinib plus rituximab is also under investigation in patients with demyelinating neuropathy and concurrent IgM monoclonal gammopathy (NCT05065554). In Germany, the CZAR-1 study is investigating the efficacy and safety of carfilzomib in combination with ibrutinib versus ibrutinib alone in treatment-naïve and previously treated WM (NCT04263480). A second German study is also investigating the combination of Benda-R and ibrutinib (NCT03620903). 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).

Conflicts of Interest

S.P.T. received research funding, and/or consulting fees from Abbvie/Pharmacyclics Inc., Janssen Oncology Inc., Beigene Inc., Eli Lilly Pharmaceuticals, Bristol Myers Squibb, and Ono Pharmaceuticals. S.P.T. is a named inventor for MYD88 and CXCR4 testing for WM and has assigned all interests to his institution. J.J.C. received research funds from Abbvie, AstraZeneca, Beigene, Cellectar, LOXO, and Pharmacyclics and honoraria from Abbvie, Beigene, Cellectar, Janssen, Kite, LOXO, Mustang Bio, Nurix, and Pharmacyclics. S.S. received research funding and/or consulting fees from Beigene, Cellectar Biosciences, Astra Zeneca, and ADC Therapeutics.

Data Availability Statement

The manuscript represents a review. Citations for sources of data are provided.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/hon.70071.

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