Bruton Tyrosine Kinase Inhibitors for the Treatment of Mantle Cell Lymphoma: Review of Current Evidence and Future Directions

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Abstract: Mantle cell lymphoma (MCL) is a heterogeneous and uncommon non-Hodgkin lymphoma that affects predominantly older patients and often is associated with an aggressive clinical course. MCL relies upon B-cell receptor signaling through Bruton tyrosine kinase (BTK); therefore, the development of the BTK inhibitors ibrutinib and acalabrutinib represents a therapeutic breakthrough. In this review, we provide a summary of the efficacy and safety data from the landmark trials of single-agent ibrutinib and acalabrutinib that led to US Food and Drug Administration approval of these agents for patients with relapsed or refractory MCL. Toxicities of interest observed with ibrutinib include bleeding, atrial fibrillation, and increased risk for infection. The selectivity of acalabrutinib for BTK is greater than that of ibrutinib, which mitigates the risk for certain off-target toxicities, including atrial fibrillation; however, these toxicities, along with frequent headaches, still occur. Ongoing clinical trials are investigating both alternate BTK inhibitors and BTK inhibitors in combination with chemo-immunotherapy or other targeted agents in an effort to enhance the depth and duration of response. Trials to evaluate the use of these agents in the frontline setting are emerging and are likely to build upon the success of BTK inhibitors in patients with MCL.

Introduction

Mantle cell lymphoma (MCL) is a rare non-Hodgkin lymphoma (NHL) characterized by a translocation of *CCND1* on chromosome 11q13 with the *IGH* promoter on chromosome 14q32. This results in the upregulation of cyclin D1, which in complex with CDK4 and CDK6 leads to proliferation via the dysregulation of G1 to S cell cycle arrest. Although MCL accounts for fewer than 10% of all cases of NHL, the incidence appears to have increased in recent decades.[1,2] Challenges that arise in the treatment of MCL include an often aggressive clinical course, with options for intensive therapies limited by patient age and comorbidities; the median age at diagnosis is 68

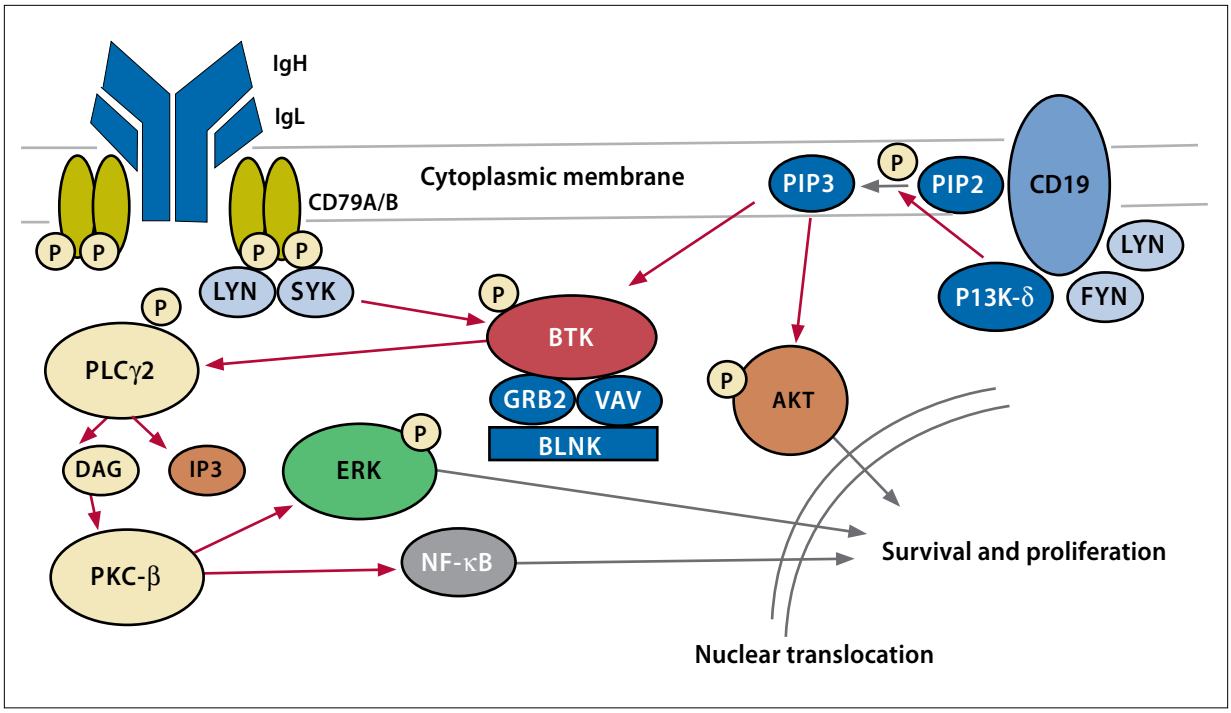

Figure. In the B-cell antigen receptor signaling pathway, stimulation of the immunoglobulin M B-cell receptor results in phosphorylation of the intracellular domain of CD79A and CD79B. This results in the recruitment and phosphorylation of SYK and LYN, which in turn lead to the recruitment and phosphorylation of BTK. BTK is bound to scaffolding protein, including BLNK. PI3K phosphorylates PIP2 to PIP3, thereby activating the AKT signaling pathway and promoting BTK signaling. Phosphorylated BTK phosphorylates PLCγ2, which in turn activates PKC-β. This then leads to downstream activation of ERK/MAPK and degradation of IκB-α, followed by the release of NF-κB. Together, these processes result in survival and proliferation of the malignant B cell.

BLNK, B-cell linker protein; BTK, Bruton tyrosine kinase; DAG, diacyl-glycerol; ERK, extracellular signal-regulated kinase, also known as mitogen-activated protein kinase (MAPK); GRB2, growth factor receptor-bound protein 2; IgH, immunoglobulin heavy; IgL, immunoglobulin light; IκB-α, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IP3, inositol triphosphate; NF-κB, nuclear factor–κB; PI3Kδ, phosphoinositide 3-kinase delta; PIP2, phosphatidylinositol bisphosphate; PIP3, phosphatidylinositol triphosphate; PKC-β, protein kinase C beta; PLCγ2, phospholipase C gamma 2; SYK, spleen tyrosine kinase.

years.[1] Although intensive frontline treatment strategies result in a median event-free survival of more than 7 years in younger patients, these therapies typically are not curative, with late relapses occurring at extended follow-up.[3]

Bruton Tyrosine Kinase

Bruton tyrosine kinase (BTK) is a Tec family tyrosine kinase that is integral to proximal B-cell receptor (BCR) signaling via the phosphorylation of phospholipase C gamma 2 (PLCγ2), which leads to the activation of multiple downstream pathways that include nuclear factor–κB (NF-κB) and mitogen-activated protein kinase (MAPK; Figure). Germline mutations in *BTK* cause the arrest of B-cell maturation, leading to low serum immunoglobulin levels (defined as the immunodeficiency syndrome X-linked agammaglobulinemia).[4] Dependence on constitutive BCR signaling is a common feature of multiple B-cell malignancies, including MCL.[5-9] The BTK inhibitor ibrutinib has been shown in preclinical models of B-cell malignancies, including MCL, to have therapeutic activity via inhibition of downstream BCR signaling, leading to cell death and inhibition of cell migration and proliferation.[10-13] A phase 1 trial of ibrutinib in patients with relapsed or refractory (R/R) B-cell malignancies demonstrated objective responses across multiple B-cell malignancies, including MCL, supporting further clinical development and providing proof of principle for the therapeutic potential of small-molecule BTK inhibitors.[14]

Approved BTK Inhibitors in Mantle Cell Lymphoma

Ibrutinib

The US Food and Drug Administration (FDA) granted accelerated approval to ibrutinib (Imbruvica,

Pharmacyclics/Janssen) as a single agent, dosed orally at 560 mg daily, for patients with previously treated MCL. Approval was based on results of the phase 2 open-label PCYC-1104-CA trial (Safety and Efficacy of PCI-32765 in Participants With Relapsed/Refractory Mantle Cell Lymphoma).[15] A total of 115 patients with previously treated MCL were enrolled, with 111 patients receiving at least 1 dose of therapy. The median age of the patients was 68 years, the median number of prior therapies was 3, and the disease of nearly half of the patients had been refractory to their last prior therapy. A total of 86% of cases were considered intermediate- or high-risk according to the simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score.[16] The overall response rate (ORR) was 68% and included a 21% rate of complete response (CR). Common toxicities of any grade included diarrhea (50%), fatigue (40%), nausea (30%), and decreased appetite (20%). Grade 3 or 4 hematologic events included neutropenia (11%), anemia (10%), and thrombocytopenia (11%). Bleeding events included subdural hematoma in 4 patients, and 5 patients had grade 3 bleeding events. With extended follow-up, median progression-free survival (PFS) was 13 months, median duration of response (DOR) was 17.5 months, and median overall survival (OS) was 22.5 months.[17] A subsequent phase 3 international trial called MCL3001 (Study of Ibrutinib [a Bruton's Tyrosine Kinase Inhibitor], Versus Temsirolimus in Patients With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy) included 280 patients randomly assigned to either ibrutinib or the mammalian target of rapamycin (mTOR) inhibitor temsirolimus. Ibrutinib resulted in superior PFS (14.6 vs 6.2 months) and ORR (72% vs 40%) compared with temsirolimus.[18] Efficacy data pooled from 370 patients enrolled in 3 open-label trials of ibrutinib for previously treated MCL (PCYC-1104-CA, MCL2001, and MCL3001) showed a median PFS of 13 months and median OS of 25 months (Table 1).[19] The patients who received ibrutinib as second-line treatment had a longer median PFS (28 vs 10 months) and longer OS (not reached vs 23 months) than did those who received the agent in later lines of therapy. The subset of patients who received ibrutinib as second-line treatment and had chemosensitive disease appeared to fare particularly well, with a CR rate of 47%, an ORR of 87%, and median PFS of 58 months.[20] Conversely, although the total numbers were small, patients with known *TP53* mutations had an ORR of 55%, with a median PFS of 4 months and a median OS of 10 months. With extended follow-up, therapy-associated toxicities included pneumonia in 12.7% of patients and atrial fibrillation in 6.2% of patients.

Toxicities of interest that were more common in the patients treated with ibrutinib included bleeding, cardiac arrhythmia, arthralgia, hypertension, and opportunistic infection. An increased incidence of atrial fibrillation has been observed in prospective trials of ibrutinib in multiple disease types, with an incidence of 6.5% reported in a pooled analysis of 1505 patients treated with ibrutinib at a median follow-up of 16.6 months.[21] Although the incidence of atrial fibrillation appears to be highest within the first 6 months after the start of therapy, an increasing incidence has been reported with extended exposure (estimated incidence of >10% with extended follow-up).[21,22] In addition to atrial arrhythmia, recent reports suggest an association between ibrutinib and ventricular arrhythmia.[23,24] Increased susceptibility to infection, including fungal and other opportunistic infection, has been observed in patients treated with ibrutinib, with the risk highest in the first 6 months of therapy.[25-30] Although B-cell inhibition contributes in part to the infectious risk, the mechanism of increased susceptibility to *Aspergillus fumigatus* infection appears to be due primarily to inhibition of the macrophage response as a BTK-dependent effect.[31] Serious bleeding events have been seen in patients on ibrutinib monotherapy, and early reports of major bleeding in patients receiving concomitant warfarin anticoagulation led to the exclusion of patients on warfarin from subsequent ibrutinib trials.[18,32] A recent meta-analysis found a higher overall incidence of bleeding but not major bleeding events with ibrutinib monotherapy than with alternate treatments.[33]

Although uncommon, central nervous system (CNS) involvement can occur in MCL. Patients with CNS involvement were excluded from the landmark trials of ibrutinib in MCL, but ibrutinib displays CNS penetration, and responses have been reported in case series of patients treated with ibrutinib for CNS relapse of MCL.[34,35]

Acalabrutinib

Acalabrutinib (Calquence, AstraZeneca), like ibrutinib, is a small-molecule irreversible BTK inhibitor. Compared with ibrutinib, acalabrutinib displays less off-target kinase inhibition of epidermal growth factor receptor (EGFR), tyrosine kinase expressed in hepatocellular carcinoma (TEC), and interleukin 2–inducible T-cell kinase (ITK).[36,37] Given that off-target kinase inhibition may contribute to specific toxicities seen in patients treated with ibrutinib, such as atrial fibrillation and diarrhea, acalabrutinib was investigated as an alternative BTK inhibitor. In the phase 2 ACE-LY-004 study (An Open-label, Phase 2 Study of ACP-196 in Subjects With Mantle Cell Lymphoma), 124 patients with R/R MCL were treated with acalabrutinib at a dose of 100 mg administered orally twice daily until disease

Table 1. Summary of Reported Trials of BTK Inhibitors in Mantle Cell Lymphoma

Agent	Study Name	Patients, No.	ORR, %	CR, %	Median PFS, mo	Median OS, mo	Most Common AEs	AEs of Interest
Ibrutinib[19]	PCYC-1104-CA, MCL-2001, MCL-3001	370	66	20	13	25	Diarrhea (40%), fatigue (35%), nausea (22%)	Grade ≥3 AF (5%), grade ≥3 bleeding (5%)
Acalabrutinib[38]	ACE-LY-004	124	81	40	NR, 67% at 12 mo	87% at 12 mo	Headache (38%), diarrhea (31%), fatigue (27%), myalgia (21%)	No AF reported, grade ≥3 bleeding (1%)
Zanubrutinib[57]	AU-003	43 (5 TN)	90	20	18	Not reported	Diarrhea (30%), bruising (30%), URI (28%)	AF (5%), major hemorrhage (7%)
Zanubrutinib[56]	BGB-3111-206	86	84	59	NR	NR	Neutropenia (31%), URI (29%), rash (29%)	No AF, major hemorrhage (1%)
Ibrutinib + rituximab[62,63]	NCI-2013-01304	50	88	44	43	NR	Fatigue (94%), diarrhea (78%), myalgia (68%), nausea (54%), mucositis (54%)	Grade ≥3 AF (12%), grade ≥3 bleeding (6%)
Ibrutinib, lenalidomide, rituximab[78]	PHILEMON	43	76	56	16	22	Gastrointestinal (68%), rash (56%), fatigue (56%), infection (36%)	AF (2%), grade ≥3 infection (18%)
Ibrutinib + venetoclax[71]	AIM Study	24 (1 TN)	71	71	NR	NR	Diarrhea (83%), nausea/vomiting (71%), GERD (38%)	Grade ≥3 bleeding (4%), grade ≥3 AF (8%), TLS (8%)
Ibrutinib + palbociclib[82]	NCI-2014-01202	20	67	44	NR	NR	Diarrhea (50%), fatigue (44%), rash (39%), bruising (17%)	Grade ≥3 rash (10%), no AF

AE, adverse event; AF, atrial fibrillation; CR, complete response; GERD, gastroesophageal reflux disease; mo, months; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TLS, tumor lysis syndrome; TN, treatment-naive; URI, upper respiratory tract infection.

progression or discontinuation owing to toxicity.[38] Enrolled patients had a median age of 68 years and a median of 2 prior therapies, and 24% had disease refractory to the last therapy used. The simplified MIPI score indicated high risk in 17% of the patients and intermediate risk in 44%. Toxicities seen with treatment included headache in 38%, diarrhea in 31%, fatigue in 27%, and myalgia in 21%. Grade 3 or higher toxicities, which were primarily hematologic and occurred in a minority of patients, included neutropenia (10%) and anemia (9%). Bleeding of any grade was seen in 31% of patients, including 1 patient with a grade 3 gastrointestinal bleeding event, and no cases of atrial fibrillation were reported. The ORR was 81% for all patients and included a CR rate of 40%. After a median follow-up of 15.2 months, the median PFS and OS had not been reached (12-month PFS, 67%; OS, 87%). On the basis of results from this trial, acalabrutinib received accelerated FDA approval on October 31, 2017, becoming the second approved BTK inhibitor available for the treatment of R/R MCL. In a recent report of extended follow-up, median PFS was 19.5 months, with a median DOR of 25.7 months.[39] Grade 3 bleeding occurred in 2% of patients and atrial fibrillation occurred in 3% of patients, including grade 3 atrial fibrillation in 1%. It remains to be seen if the frequency of these toxicities will increase as more patients are treated with acalabrutinib. A currently ongoing phase 3 study called ACE-CL-006 (Elevate CLL R/R: Study of Acalabrutinib Versus Ibrutinib in Previously Treated Subjects With High Risk Chronic Lymphocytic Leukemia; NCT02477696) is comparing acalabrutinib with ibrutinib as monotherapy for chronic lymphocytic leukemia, and results from this study

will help to provide a better characterization of differences between the toxicity profiles of the 2 agents. Currently, acalabrutinib may be a preferred option for patients with bleeding or cardiac risk factors.

Lymphocytosis

In early-phase clinical trials of ibrutinib in MCL, lymphocytosis was noted in patients who were otherwise responding to treatment.[14] The circulating lymphocytes that arise during BTK inhibitor therapy have been characterized as CD5+ and CD19+, with expression of Ki67, pERK, and CXCR4 decreased compared with expression in circulating MCL cells seen before BTK inhibitor treatment. The lymphocytosis is thought to result from a disruption in chemokine signaling between MCL cells and stromal cells, leading to the release of MCL cells into the peripheral circulation.[40] Baseline marrow involvement by MCL is associated with a greater degree of lymphocytosis, suggesting that disruption in stromal signaling in the bone marrow in particular contributes to treatment-related lymphocytosis.[41] Therapy-related lymphocytosis resolves over time and is not associated with an adverse response to therapy.[16]

Progression Following BTK Inhibitor Therapy

Both acalabrutinib and ibrutinib inhibit BTK by binding covalently to cysteine 481 within the adenosine triphosphate (ATP)–binding pocket of BTK. In chronic lymphocytic leukemia, 2 genetic mechanisms of acquired resistance to BTK inhibitors have been well characterized: a mutation leading to a cysteine-to-serine substitution within the ATP binding site of BTK (C481S) and downstream activating mutations within *PLCG2*.[42-45] Although C481S has been described in patients with MCL at the time of progression following BTK inhibitor therapy, it is seen in only a minority of cases, and *PLCG2* mutations have not been characterized in MCL.[46-48] Alterations in *TP53* may mediate progression in many cases, with a recent series showing deleterious mutations or loss of heterozygosity in *TP53* in a high proportion of patients with available biopsy specimens at the time of progression during BTK inhibitor therapy.[48] Patients who discontinue BTK inhibitors fare poorly overall with current therapies; retrospective series have shown a median OS of only 3 to 9 months for patients who discontinue ibrutinib owing to progression, with a response rate to the next line of therapy ranging from 26% to 32%.[47-49] This problem represents an unmet clinical need, and patients whose disease progresses while they are on BTK inhibitor therapy should strongly consider clinical trial enrollment when available, including trials investigating chimeric antigen receptor T-cell (CAR-T) therapy or other adoptive immunotherapy approaches. Outside clinical trial enrollment, the treatment for patients with disease progression on BTK inhibitors should be individualized on the basis of patient and disease characteristics, including prior chemosensitivity. Options for patients with chemoresistant disease include a chemotherapy-free regimen of dexamethasone, rituximab (Rituxan, Genentech/Biogen), lenalidomide (Revlimid, Celgene), and bortezomib (Velcade, Millennium/Takeda Oncology), which had encouraging activity in a small series of patients with ibrutinib resistance[50]; or venetoclax (Venclexta, AbbVie/Genentech), which, although not FDA-approved for MCL, had promising single-agent activity in an early-phase study.[51] Referral for consideration of hematopoietic cell transplant is advised for patients with disease progression on BTK inhibitors who achieve a response to salvage therapies.

Future Directions

Alternate BTK Inhibitors

Although acalabrutinib and ibrutinib are currently the only FDA-approved BTK inhibitors, alternative BTK inhibitors for MCL and other lymphoid malignancies are currently in clinical development. BTK inhibitors are separated into 2 categories: covalent, irreversible BTK inhibitors, which include ibrutinib and acalabrutinib, and noncovalent, reversible inhibitors. Covalent, irreversible inhibitors that are in development but are not currently FDA-approved include tirabrutinib (ONO/GS-4059) and zanubrutinib (BGB-3111), both of which demonstrate greater selectivity for BTK relative to other Tec family kinases than that of ibrutinib.[52,53] Tirabrutinib was studied in a phase 1 dose-escalation study, with clinical activity seen in multiple B-cell malignancies. A dose of 480 mg daily was established as the maximum tolerated dose, and an objective response to therapy was achieved in 11 of 12 patients with MCL treated across dose levels.[54]

Phase 1 and 2 studies of zanubrutinib established that a dose of 160 mg twice daily achieves greater than 99% lymph node and peripheral blood BTK occupancy, providing relevant nodal pharmacokinetic data not currently available with other BTK inhibitors[55] Two phase 2 studies of zanubrutinib in patients with MCL have been recently reported. Song and colleagues reported an ORR of 84%, including a CR rate of 59%, in a Chinese population assessed by positron emission tomography (PET) with a median follow-up of 36 weeks.[56] In a separate study, Tam and colleagues reported an ORR of 90%, including a CR rate of 20% and a median PFS of 18 months, with disease assessment performed primarily by computed tomography (CT; Table 1).[57] The discrepancy between the CR rates in these phase 2 studies may in part

have been caused by the differing imaging modalities (CT vs PET) employed for response assessment. Toxicities in both studies were similar to those observed with other BTK inhibitors and included diarrhea, bleeding or petechiae, and rash, although the incidence of minor bleeding or purpura (30% vs 4.7%) and of grade 3 or higher major hemorrhage (7.0% vs 1.2%) reported in the study by Tam and colleagues was higher than that reported by Song and colleagues. Fatal therapy-emergent adverse events were seen in 4.7% of patients in the study by Song and colleagues, including 1 case of cerebral hemorrhage.

Noncovalent, reversible BTK inhibitors inhibit BTK without interacting with Cys481 in the ATP binding site and thus are expected to be unaffected by C481S mutations.[58-60] Selective noncovalent BTK inhibitors such as SNS-062 and LOXO-305 exhibit minimal off-target inhibition of other Tec family kinases, potentially limiting off-target toxicities, whereas nonselective noncovalent BTK inhibitors such as ARQ-531 offer the potential benefit of inhibiting downstream signaling kinases in addition to BTK, thus potentially retaining activity in cases with downstream mutations in *PLCG2*.[61] Noncovalent BTK inhibitors are currently in early stages of clinical development, and their role in the treatment of MCL and other B-cell malignancies remains to be seen.

Combination Therapy for Relapsed and Refractory Disease

CD20-directed monoclonal antibodies. Although the addition of monoclonal antibodies targeting CD20 offers a clear benefit in conjunction with traditional cytotoxic chemotherapy, whether the addition of rituximab or other CD20-directed monoclonal antibodies improves upon the single-agent efficacy of BTK inhibitors in MCL is unclear. The combination of ibrutinib and rituximab (IR) was studied in a single-center phase 2 trial of patients with R/R MCL.[62] Baseline patient characteristics included a median of 3 prior lines of therapy, a high-risk simplified MIPI score in 12% of patients and an intermediate-risk score in 44%, and disease refractory to the most recent therapy in 70% of patients. Toxicities were similar to those seen in studies of single-agent ibrutinib and included diarrhea in 78%, myalgia in 68%, and vomiting in 32% of patients. An ORR of 88% was seen, with a CR rate of 44%. With extended follow-up, the median PFS was 43 months and the rate of CR improved to 59%.[63] Although the rates of CR and PFS with IR compare favorably with results from prior phase 2 and 3 studies of single-agent ibrutinib, a randomized trial is needed to compare these regimens directly.

Chemo-immunotherapy. The regimen of bendamustine and rituximab (BR) has a high ORR in R/R MCL,[64,65] and the combination of BR with BTK inhibitor therapy has been shown to be feasible at standard dosing. Ibrutinib in combination with BR was evaluated in a phase 1/1b study at our institution, which determined a maximum tolerated dose of 560 mg of ibrutinib with standard dosing of bendamustine at 90 mg/m^2.[66] Of 17 patients with MCL treated with the combination regimen across dose levels, an ORR of 94%, including a CR rate of 76%, was seen. Hematologic toxicities included grade 4 neutropenia in 21% of patients. Nonhematologic toxicities of grade 3 or higher included rash in 25% and infection in 8%, with 2 deaths occurring during treatment. More recently, results from a phase 2 study of acalabrutinib at 100 mg twice daily in combination with BR in patients with either previously untreated or R/R MCL were presented and demonstrated similarly encouraging activity, including an ORR of 94% and a CR rate of 72%.[67] Toxicities in the previously untreated cohort included grade 3 pneumonia in 11% of patients, and 3 deaths occurred during treatment. In the R/R cohort, toxicities included grade 3 diarrhea and pneumonia in 10% of patients. Together, these studies demonstrate clinical activity with an acceptable safety profile when BR is combined with ibrutinib or acalabrutinib, and these combinations may represent a particularly promising approach in the frontline setting.

BCL-2 inhibition. Venetoclax is an oral BH3 mimetic that directly inhibits the anti-apoptotic protein BCL-2, thereby provoking apoptotic cell death in malignant B cells.[68] Venetoclax is active as a single agent in MCL; in a phase 1 study of venetoclax in hematologic malignancies, an ORR of 75%, including a CR rate of 21%, was seen across all dose levels in patients with R/R MCL.[51] With extended follow-up, the median PFS was 11.3 months, with a median DOR of 15.7 months in responders. Preclinical MCL models demonstrate synergistic activity when venetoclax is combined with BTK inhibitors, providing a rationale for combination therapy.[69,70] In the phase 2 AIM study (ABT-199 & Ibrutinib in Mantle Cell Lymphoma), 24 patients with MCL, including 23 patients with R/R disease, were treated with ibrutinib in combination with venetoclax.[71] The study was designed with 4 weeks of ibrutinib monotherapy initially to mitigate the risk for tumor lysis syndrome (TLS); venetoclax was started on week 5 in a ramp-up dosing strategy. The protocol was amended to lower the starting dose of venetoclax to 20 mg after 2 cases of TLS were observed with a 50-mg starting dose, and no further episodes of TLS occurred with the modified ramp-up dosing to a final dose of 800 mg daily. Toxicities associated with the combination regimen included gastrointestinal toxicity (diarrhea in 83%, including grade 3 in 12%; nausea in 71%, including grade 3 in 10%, reported to decrease

Table 2. Selected Ongoing Trials of BTK Inhibitor–Based Combination Therapy for Mantle Cell Lymphoma

Setting	BTK Inhibitor	Combination Partner	Phase	Patients, No.	Identifier
Frontline, pt ≥65 y	Ibrutinib	BR	3	522	NCT01776840
Frontline, pt ≥65 y	Acalabrutinib	BR	3	546	NCT02972840
Frontline, pt ≤65 y	Ibrutinib	R-CHOP/R-DHAP ± ASCT	3	870	NCT02858258
Frontline, pt ≤65 y	Ibrutinib	Rituximab, followed by R-hyper-CVAD consolidation	2	131	NCT02427620
Frontline, pt ≥66 y	Ibrutinib	Rituximab and lenalidomide	2	40	NCT03232307
Frontline, pt ≤65 y	Acalabrutinib	BR/CR	2	15	NCT03623373
Frontline, pt ≥60 y	Ibrutinib	Rituximab	3	400	EudraCT: 2015-000832-13
R/R	Ibrutinib	Venetoclax	3	287	NCT03112174
R/R	Ibrutinib	Obinutuzumab and venetoclax	2	24	NCT02558816
R/R	Ibrutinib	Palbociclib	2	61	NCT03478514
R/R	Ibrutinib	Bortezomib	1/2	73	NCT02356458
R/R	Ibrutinib	Bortezomib	2	35	NCT03617484
R/R	Ibrutinib	Ixazomib	1/2	84	NCT03323151
R/R	Tirabrutinib	Idelalisib, entospletinib, and obinutuzumab	1b	197	NCT02457598
R/R	Zanubrutinib	Obinutuzumab	2	210	NCT03332017
R/R	Zanubrutinib	BGB-A317	2	125	NCT02795182

ASCT, autologous stem cell transplant; BR, bendamustine and rituximab; CR, cytarabine and rituximab; pt, patients; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-hyper-CVAD, rituximab combined with cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine; R/R, relapsed/refractory; y, years.

in most patients with ongoing therapy); rash (29%); mucositis (29%); bleeding (54%, including grade 3 in 4%); and hematologic toxicity (grade ≥3 neutropenia in 33%, anemia in 12%, and thrombocytopenia in 17%), with 29% of patients requiring growth factor support. Other serious adverse events included atrial fibrillation in 2 patients and pleural effusion in 2 patients. During treatment, 2 fatal adverse events occurred, including 1 death caused by a malignant otitis externa and 1 death caused by heart failure in a patient with the prior onset of atrial fibrillation during study therapy. The investigators determined that both of these deaths were not directly related to the combination therapy regimen.

Although the combination regimen appeared to be associated with greater toxicity than either ibrutinib or venetoclax as single agents in other studies, encouraging response rates were seen in a high-risk MCL patient population. An ORR of 71% was seen, with all responding patients achieving a CR as determined by PET as best response to therapy. Of the patients who achieved a CR, minimal residual disease (MRD) assessment was available for a subset, with 14 of 15 evaluable patients testing negative for MRD by flow cytometry and 9 of 11 evaluable patients testing negative by polymerase chain reaction for allele-specific oligonucleotide. The CR rate compares favorably with that in studies of ibrutinib monotherapy, and it is notable that 75% of enrolled patients were classified as high-risk by MIPI and 50% of patients harbored somatic mutations in *TP53*, which is associated with a poor response to intensive treatment regimens.[72-74] The 5 patients who failed to respond to combination therapy were found to have a genetic basis for perturbation in the SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin modeling complex owing to either copy loss or mutations within *SMARCA4* and mutations or deletions within *ARID2*.[75] In vitro studies by the same group demonstrated that SMARCA4 knockdown led to increased expression of the anti-apoptotic protein Bcl-xL, potentially mediated by decreased chromatin accessibility of the Bcl-xL repressor *ATF3*. Bcl-xL is not inhibited by venetoclax, and thus in vitro SMARCA4 knockdown led to resistance to the combination of venetoclax and ibrutinib. This suggests that a subset of patients who have MCL with these specific genetic

alterations are less likely to benefit from the combination of ibrutinib and venetoclax. A phase 3 randomized controlled trial called SYMPATICO (Study of Ibrutinib Combined With Venetoclax in Subjects With Mantle Cell Lymphoma; NCT03112174) is currently under way that is comparing the combination of ibrutinib and venetoclax vs ibrutinib and placebo to further evaluate the utility of this combination regimen in MCL (Table 2). Although the depth of response in terms of rate of both CR and MRD negativity in responding patients is promising with the combination of venetoclax and ibrutinib, the ORR is similar to that seen with single-agent therapy. Results from the randomized phase 3 trial are needed to determine whether this translates into improvement in DOR with the combination.

Immunomodulatory drugs. Lenalidomide plus rituximab is an active regimen in both untreated and R/R MCL[76,77] and was recently studied in combination with ibrutinib in patients with R/R MCL in the phase 2 PHILEMON study (A Trial of Ibrutinib, Lenalidomide and Rituximab for Patients With Relapsed/Refractory Mantle Cell Lymphoma).[78] A greater number of grade 3 or higher toxicities were seen with this regimen than with ibrutinib monotherapy; these included grade 3 or higher rash (14%), infection (26%), gastrointestinal toxicity (12%), neutropenia (38%), and thrombocytopenia (14%), with 3 treatment-related deaths. The ORR was 76%, with a CR rate of 56% and a median PFS of 16 months. Given the increased toxicity without clear improvement in durable remissions, the benefit of this combination may be limited; however, the response rate in patients with a *TP53* mutation was similar to that seen in the entire patient population, suggesting a potential role for the combination in this subset of patients, who fare poorly with chemo-immunotherapy.

CDK4/6 inhibitors. As previously discussed, a hallmark of MCL is cell cycle dysregulation driven by upregulation of cyclin D1, which complexes with CDK4 and CDK6 to promote cell cycle progression from G1 to S phase. Highly selective inhibitors of CDK4/6 have been developed,[79] and single-agent activity was observed in a phase 2 trial of 17 patients who had relapsed MCL treated with the CDK4/6 inhibitor palbociclib (Ibrance, Pfizer), with 1 patient achieving a CR and 2 patients achieving a partial response (PR), in addition to 7 patients with stable disease.[80] Preclinical models have demonstrated enhanced susceptibility to targeted agents during cell cycle arrest when CDK4/6 is targeted in MCL, providing a rationale for combining CDK4/6 and BTK inhibitors.[46,81] The combination of ibrutinib and palbociclib was studied in a phase 1 study enrolling 20 patients with relapsed MCL. The combination was relatively well tolerated, aside from grade 3 rash that led to discontinuation in 2 patients, and a 77% ORR was seen, including a CR in 44%.[82] At the time of preliminary presentation, the PFS and DOR for this phase 1 trial had not been reached, and a multicenter phase 2 trial (NCT078514) is currently under way to evaluate the efficacy of this combination regimen further.

Other combinations. Other combinations of targeted agents and BTK inhibitors are currently under investigation. These include combinations with phosphoinositide 3-kinase (PI3K) inhibitors (NCT02795182, NCT02457598), the selective nuclear export inhibitor selinexor (NCT02303392), and the SYK inhibitor entospletinib (NCT02457598). CAR-T constructs targeting CD19 have established efficacy in the treatment of R/R acute lymphoblastic leukemia and diffuse large B-cell lymphoma, and this class of therapies is currently being investigated in MCL. In preclinical MCL models, ibrutinib enhances the efficacy of CD19-directed CAR-T therapy, and this approach is being investigated in a pilot study (NCT02640209).[83]

Frontline combination therapy. Given the activity of BTK inhibitors in R/R MCL, research is ongoing to determine their role in frontline therapy. Today, frontline treatment decisions for patients with newly diagnosed MCL are based on patient fitness and the ability to tolerate intensive chemo-immunotherapy and/or autologous stem cell transplant (ASCT). When intensive frontline treatment approaches are unsuitable for patients, including most patients older than 65 years, less intensive combination chemo-immunotherapy regimens are generally preferred. Of these less intensive regimens, BR as frontline treatment has been shown to provide superior PFS, with a favorable side effect profile in comparison with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); thus, BR is widely used in older, previously untreated patients.[84,85] As previously discussed, the combination of BR with ibrutinib or acalabrutinib has been shown to be feasible, and randomized phase 3 trials in previously untreated patients aged 65 years and older are studying BR in combination with ibrutinib (SHINE [A Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Given in Combination With Bendamustine and Rituximab in Patients With Newly Diagnosed Mantle Cell Lymphoma]; NCT01776840) or acalabrutinib (ACE-LY-308 [A Study of Bendamustine and Rituximab Alone Versus in Combination With Acalabrutinib in Subjects With Previously Untreated Mantle Cell Lymphoma]; NCT02972840). Alternatively, a phase 2/3 randomized study is currently evaluating a chemotherapy-free approach

in untreated patients 60 years of age or older, comparing IR with chemo-immunotherapy (either R-CHOP or BR) followed by rituximab maintenance (ENRICH [Randomised, Open Label Study of Rituximab/Ibrutinib vs Rituximab/Chemotherapy in Older Patients With Untreated Mantle Cell Lymphoma]; EudraCT Number 2015-000832-13).

Among younger patients with previously untreated MCL, the addition of cytarabine to induction therapy before ASCT improves PFS, and the addition of maintenance rituximab after transplant improves both PFS and OS.[86,87] Multiple groups are currently investigating strategies to incorporate BTK inhibitors into frontline induction and maintenance therapies for younger patients with the hope of further extending DOR and allowing the intensity of frontline treatment to be decreased (Table 2). The 3-arm phase 3 TRIANGLE study (ASCT After a Rituximab/Ibrutinib/Ara-c Containing Induction in Generalized Mantle Cell Lymphoma; EudraCT Number 2014-001363-12; NCT02858258) is currently under way. This study is enrolling younger patients with MCL to compare R-CHOP plus ibrutinib alternating with rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) followed by ibrutinib maintenance with ASCT (arm A+I) or without ASCT (arm I) vs R-CHOP alternating with R-DHAP followed by ASCT (control arm). The 3-arm design of this study will make it possible to evaluate whether ibrutinib adds benefit to intensive frontline therapy, and also whether ASCT may be omitted in younger patients in the rituximab and BTK inhibitor era. A separate, ongoing, single-center phase 2 study is investigating IR induction therapy followed by 4 cycles of rituximab with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine (R-hyper-CVAD) consolidation. Preliminary results from this study were presented and demonstrated an ORR of 100% with a CR rate of 72% following IR induction therapy in the first 36 patients enrolled.[88] Further follow-up is needed to better establish the efficacy and toxicities of this treatment approach, but the response rate to the chemotherapy-free IR induction in younger untreated patients is notable, supporting further investigation of strategies to limit the intensity of chemotherapy in younger patients in the era of novel targeted agents. Finally, alternative intensive combination regimens are also being studied, with a pilot study under way to evaluate the safety and feasibility of the combination of acalabrutinib with BR alternating with rituximab and cytarabine (NCT03623373). Thus, although chemo-immunotherapy with or without consolidative ASCT followed by maintenance rituximab is currently the mainstay of the frontline treatment in MCL, this treatment paradigm may rapidly change as results from ongoing studies of ibrutinib- or acalabrutinib-based frontline combination regimens emerge.

Conclusions

The BTK inhibitors acalabrutinib and ibrutinib are highly active as single agents in patients with R/R MCL and have become preferred options at first relapse in the majority of patients. Objective responses are seen in more than two-thirds of patients when R/R MCL is treated with ibrutinib or acalabrutinib, and outcomes are better in patients receiving BTK inhibitors as second-line therapy than in more heavily pretreated patients. Although single-agent BTK inhibitors have changed the therapy landscape for R/R MCL, outcomes for patients whose disease progresses while they are taking these agents remain poor. Several ongoing clinical trials are attempting to improve the duration of response to BTK inhibitors without creating unacceptable toxicity through the use of rational combination therapies. Despite combination approaches, approximately 25% of patients exhibit primary resistance to BTK inhibitors, and identifying these patients also remains a priority. Further research is ongoing to determine the role of BTK inhibitor–based combination therapy in the frontline setting and to identify biomarkers predictive of response to therapy. As these agents become incorporated into approaches to frontline therapy, it will become even more important to understand mechanisms of resistance to develop effective treatment strategies for patients with disease progression on BTK inhibitor therapy.

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