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Novel Agents in Mantle Cell Lymphoma

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Abstract

Mantle cell lymphoma is a mature B cell neoplasm constituting 5–7% of all non-Hodgkin lymphoma. Overall prognosis with current therapeutics remains poor, thus numerous novel agents are currently under investigation. In this review we focus on early phase trials that have demonstrated promise in mantle cell. Constitutive activation of signaling components downstream of the B cell receptor play an important role in the pathobiology of mantle cell lymphoma. Targeting of this signaling pathway has become a focus with specific agents under development including inhibitors of spleen tyrosine kinase, phosphoinositide-3-kinase and Bruton's tyrosine kinase. Promising data also supports further development of BH-3 mimetics, a crucial component of anti-apoptotic signaling. Histone deacetylase inhibitors have an established role in cutaneous T cell lymphoma and are now under investigation in mantle cell lymphoma as well. With further understanding of cellular signaling, the armamentarium of treatment options will be enhanced, with the hope of improving the prognosis of this disease.

Keywords

Mantle Cell Lymphoma; Novel Agents; B cell receptor

Introduction

Mantle Cell Lymphoma (MCL) is a mature B cell neoplasm first described in 1994 that constitutes 5–7% of all non-Hodgkin Lymphoma. This disease is characterized by the overexpression of cyclin D1 as a result of the translocation of t(11:14)(q13;q32). (1) MCL can be viewed as an incurable disease. Historically, survival at the time of diagnosis was estimated to be 3–5 years, however recent data suggest that patients can live greater than seven years.

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The authors report no relevant conflict of interest.

The standard of care has previously focused on aggressive upfront systemic chemotherapy with the option of autologous transplant, but recent literature has raised the question of an initial conservative approach with observation. Despite improved survival data in the younger population, therapy for the elderly or refractory/relapsed patient remains limited, and the prognosis quite poor. The role of proteasome inhibition and immunomodulatory therapy are well established, here we focus on novel agents recently identified as having a role in the treatment of mantle cell lymphoma.

At the crux of newer agents in MCL lie alterations of the B cell receptor (BCR). In normal B cell activation, initial antigen binding activates the SRC-family kinase LYN as depicted in figure 1. Spleen tyrosine kinase (SYK) is then activated via phosphorylation and autophosphorylation. (2) Once activated through association with B cell linker protein (BLNK), SYK facilitates downstream activation of Bruton tyrosine kinase (BTK) and subsequently phospholipase C γ 2 (PLC- γ 2), in addition to activating phosphoinositide 3-kinase (PI3K). Downstream from these signaling molecules, second messenger activation generates release of intracellular calcium and activated protein kinase C, ultimately activating various transcription factors including NF- κ B. (2) Other key downstream targets include mammalian target of rapamycin (mTOR) and AKT.

Current research in MCL indicates that BCR signal components are constitutively activated contributing to tumor proliferation and survival. (3) Modulation of this pathway has shown great promise in mantle cell, particularly in the otherwise refractory patient. A number of agents have been developed as logical targets for induction of apoptosis and will be addressed below, also highlighted in tables 1 and 2.

Spleen Tyrosine Kinase

Syk is a crucial component of the BCR pathway. It was first described in B lymphocytes, but is expressed in many cells including epithelial, fibroblasts, hepatocytes, and vascular smooth muscle cells. (4) Once recruited to the BCR complex, Syk is phosphorylated at which time it can activate several downstream targets including BLNK and PLC γ . Work in knockout mice reveal those that are Syk deficient have impaired lymphocyte development at the pre-pro B cell stage.

Experiments in four established mantle cell lines demonstrated elevated phosphorylated Syk protein levels. These cell lines were treated with a Syk inhibitor, piceatannol, and one cell line was found to have 80% cell growth arrest at 12.5 μ mol/liter.(5) Of note, cell growth was less impaired in those mantle cell lines that had lower levels of Syk expression.

Fostamatinib disodium (R788) is a prodrug of R406, a potent and selective inhibitor of spleen tyrosine kinase that is available in oral formulation. A phase 1 and 2 clinical trial of fostamatinib in non-Hodgkin lymphoma and chronic lymphocytic leukemia enrolled patients with relapsed or refractory disease over a one year period beginning in February 2007. (6) The phase 1 portion consisted of two cohorts who were sequentially assigned to receive doses of either 200 mg PO twice daily or 250 mg PO twice daily. Thirteen patients in total were enrolled in the cohorts of phase 1, (3 of which were mantle cell lymphoma) with a median age of 74.

In phase 2, patients were assigned to groups based on histology and each received fostamatinib disodium twice daily. A total of 63 patients were enrolled in the phase 2 portion, 9 with mantle cell lymphoma at a dose of 200 mg twice daily. Grade 3/4 neutropenia and anemia were the most common adverse events seen in 18% and 7% of patients respectively. Dose limiting toxicity was thought to be anemia, neutropenia, and thrombocytopenia.

Of the 9 mantle cell patients in the phase 2 portion, 1 achieved a partial response and 4 demonstrated stable disease. The average progression free survival was 3.8 months and the median time to response was 57 days. This initial trial evaluating a Syk inhibitor was the first to demonstrate the promise of BCR signaling inhibition in B cell malignancies including patients with heavily pretreated mantle cell lymphoma.

Bruton's Tyrosine Kinase

BTK, a member of the Tec family, has an established role in BCR signaling. BTK is activated by kinases Blk, Lyn, and Fyn and then activates PLC γ which subsequently leads to Ca²⁺ activation of NF- κ B and MAP kinase pathways. NF- κ B and MAP kinase are both vital to cell survival, thus a logical target of promoting cell death. (7)

Previously recognized to play a role in B lymphocyte development, mutations of BTK in humans leads to an inherited disorder, X-linked agammaglobulinemia. This particular disorder is defined by severe B cell-specific defects that manifest via significantly decreased levels of immunoglobulin production and the lack of peripheral B cells. BTK has been identified as an essential kinase in activated B cell subtype of diffuse large B-cell lymphoma where a BTK inhibitor promoted apoptosis *in vitro*. (8) Agents designed to inhibit this kinase are currently being tested.

PCI-32765 is a Cys-481 selective and potent orally available BTK inhibitor. PCI-32765 inhibits phosphorylation of Phospholipase-C γ in addition to downstream phosphorylation of Erk. A study using PCI-32765 in canine lymphoma models was developed to test the inhibition of BCR-signaling in lymphoma. (7) PCI-32765 was dosed orally, and inhibition of BTK was monitored *in vivo*. In five dogs, a single administration of PCI-32765 was sufficient to fully occupy BTK in both peripheral blood and in malignant tumor for 24 hours. Eight dogs in total were treated, a partial response was observed in three and three others demonstrated stable disease.

In humans subjects, Phase I trials evaluating PCI-32765 are underway. Fowler et al conducted a phase I study of PCI-32765 in patients with relapsed/refractory B-cell malignancies. (9) Patients were treated with escalating doses over 6 cohorts starting with 1.25 mg/kg/day then escalating to 2.5, 5.0, 8.3, 8.3 and 12.5 mg/kg/day. Of the 47 patients enrolled on study 20 (43%) achieved an objective response (OR) including 3 complete remissions (CR) and 17 partial remissions (PR). Fourteen of 47 patients have been on study for > 6 months with 8/14 achieving a (PR) and 6/14 with stable disease.

With regard to mantle cell patients, 3/4 demonstrated an objective response, 2 with a complete response and 1 with a partial response. The responses were independent of pre-treatment variables including performance status, lactate dehydrogenase and overall disease burden. Grade 3 toxicities were observed in 9/47 (19%) patients. Five patients had to discontinue treatment for reasons including grade 3 neutropenia, grade 3 hypersensitivity, and grade 3 small bowel obstruction. There have been no treatment related deaths reported and there is no evidence of cumulative hematologic toxicity.

A phase II trial is currently underway investigating PCI-32765 using 560 mg daily in patients with relapsed or refractory mantle cell lymphoma with two separate arms; one including patients previously treated with bortezomib and the other in bortezomib naïve patients.

Other BTK inhibitors have been developed and are currently being investigated in B cell malignancies. AVL-292 is a more selective inhibitor of BTK compared to PCI-32765, by preventing BTK autophosphorylation and phosphorylation of the substrate without

inhibiting upstream kinases Lyn or Syk. Similarities between the two agents include their daily oral administration. A phase 1B trial with AVL-292 is enrolling in relapsed refractory non-Hodgkin lymphoma.

Phosphoinositide 3-kinase

Many human cancers contain mutations in the cellular signaling pathway leading to over activation of PI3K. The PI3K signaling pathway has been proven to play a significant role in the development of human malignancies particularly those of B cell origin and specifically mantle cell lymphoma. PI3K is an enzyme that acts on the plasma membranes phospholipids and has been identified as a critical mediator in B-cell activation and differentiation. (10)

In hematologic malignancies, activation of this pathway results in constitutive B cell receptor activation; pathway activation appears to be mediated by Class 1 isoforms (α , β , δ , γ). The P110 δ isoform is expressed in cells of hematologic origin, predominately in leukocytes. (11) Pharmacologic inhibition of the P110 δ isoform has demonstrated its role in signaling through the normal B cell receptor in addition to demonstrating early signs of significant efficacy in B cell malignancies. (11)

CAL-101 is a specific potent oral inhibitor of the P110 δ isoform that decreases cellular viability by inhibiting PI3K. *In-vitro* studies in CLL reveal that in addition to causing cell death through disruption of intracellular signaling, CAL-101 impairs crosstalk between leukemic cells and the microenvironment. The resulting impairment in chemokine receptor function leads to diminished leukemia cell chemotaxis. (12)

In vitro, primary leukemic cells from 134 patients and 5 controls were tested for response to CAL-101. (11) Increased sensitivity to CAL-101 was seen in > than 20% of B cell acute lymphoblastic leukemia and only 3% of myeloid samples. The control samples showed no sensitivity to CAL-101. With regards to PIK3 signaling, 5 out of 5 mantle cell lines expressed constitutive levels of pAKT that were reduced by administration CAL-101. By inhibiting the PIK3 pathway vital signals for cell survival are lost thereby resulting in apoptosis. In taking this model forward, CAL-101 is being investigated at the phase I and II levels.

Kahl and colleagues conducted a large phase 1 trial of CAL 101 in individuals with relapsed or refractory hematologic malignancies. (13) Patients were enrolled at progressively higher doses with CAL-101 administered orally once or twice daily for 28 days for up to 12 cycles. Doses ranged from 50 mg twice daily to 350 mg BID. Tumor response was measured using standard criteria without the addition of PET/CT. Of the 55 patients enrolled, 18 had mantle cell lymphoma, 72 % previously received bortezomib. Objective responses were observed in 73% (8/11) and 40% (2/5) of MCL patients with relapsed and refractory disease respectively. However, the median duration of response was a modest 3 months. Correlative studies demonstrated plasma drug concentrations of chemokines CCL 22 and CCL 17 were elevated at baseline and decreased following administration of CAL-101.

An ongoing phase 1 trial is investigating the safety of CAL-101 combined with rituximab and/or bendamustine in patients with relapsed or refractory B-cell lymphoma. (14) CAL-101 is being administered at 100 mg BID in 28 days cycles with rituximab 375 mg/m² weekly for 8 weeks or bendamustine 90 mg/2 on the first two days of each cycle for 6 cycles. Although mantle cell patients are not specified, preliminary results demonstrate that of the three patients with non-Hodgkin lymphoma two had a partial response (1 each in the CAL-101 + rituximab group and CAL -101 + bendamustine group) and 1 a complete response from the CAL-101+ bendamustine group.

Other PI3K inhibitors are currently being developed in B cell malignancies, some of which inhibit additional PI3K isoforms in addition to delta. Give the objective response rates with CAL-101, combination studies are being planned in MCL

AKT

Downstream from PI3K, activated AKT targets important regulator signals of the cell cycle leading to apoptosis and protein translation. (15) As an antiapoptotic factor, inhibition of AKT is a logical intracellular target for therapy. Small oral potent AKT inhibitors are being developed including MK-2206. This drug has been tested in heavily pretreated patients with solid tumor and hematologic malignancies. (16) Based on this safety data and the importance of signaling through the PI3K-mTOR-AKT pathway in lymphoma early phase trials are underway in patients with relapsed or refractory disease, including those with mantle cell histology.

Protein Kinase C

Downstream from Syk is Protein Kinase C β (PKC β) the major isoform of PKC involved in BCR signaling. PKC β is a modulator of angiogenic activity of vascular endothelial growth factor (VEGF). (17) Elevated levels of VEGF receptor are associated with a poor prognosis in mantle cell lymphoma.

Enzastaurin is a selective inhibitor of PKC β , and in preclinical models has induced apoptosis in diffuse large B cell lines. To test its efficacy in mantle cell lymphoma, a phase II trial of enzastaurin was initiated enrolling 60 patients. (18) The drug was given orally once daily for 28 days per cycle up to six cycles. 22 patients were free from progression for 3 cycles and 6 of the 22 were free from progression for 6 months, however no objective responses were reported. The most common toxicities were fatigue and diarrhea; there were no grade 4 toxicities.

Janus-Associated Kinase

The Janus Kinase-2 pathway plays a vital role in the propagation of the malignant hematologic cell. (17) Western blotting of MCL lines have shown that phosphorylated STAT3 (ser 737) is constitutively activated (19) contributing to malignant cell proliferation via deregulated protein expression. (20) Furthermore, STAT 3 induces tumor angiogenesis, thus a potential target for inhibition. STAT proteins are often phosphorylated by Janus-associated kinase (JAK) providing rationale for the investigation of JAK inhibitors.

INCB16562 is a small molecule JAK1/JAK2 inhibitor recently tested on a panel of lymphoma cell lines (n=17) which included mantle cell lymphoma. (21) Cells were incubated with INCB1656 2 for up to 72 hours with subsequent evaluation of cell viability. IC50 values ranged from 1–9 μ M with DLBCL lines being the most sensitive. The bcl-2 family proteins Bcl-xl and MCL-1 were both downregulated in the most sensitive cell lines after treatment with INCB16562. Furthermore, INCB16562 was found to be synergistic with bcl-2 inhibition, suggesting promise for future combination studies.

BCL-2 Family

The inhibition of programmed cell death is essential in the pathogenesis of the malignant cell. In MCL, bcl-2 is constitutively overexpressed leading to the inhibition of apoptosis. (22) The bcl-2 family of proteins (of which includes BH-3) are key regulators of apoptosis, including those which potentiate cell survival and proteins that promote cell death. When activated, the BH-3 proteins lead to a cascade of signals and eventual cell death. (23)

Inhibitors of this pathway have been developed including the molecule Obataclax (GX15-070), a BH-3 mimetic. GX15-070 was tested in 5 mantle cell lines and produced cell death at various rates. GX15-070 was also tested in conjunction with bortezomib and synergistic apoptosis was observed. (23)

A second BH-3 mimetic, ABT-737 selectively binds to bcl-2 and bcl-xl displacing BH-3 from bcl-2 or bcl-xl leading to the activation of downstream caspases. The compound was tested *in vitro* with MCL lines. (24) Cell death was observed in 4 of 10 cell lines with ABT-737. Genetic testing revealed that amplification of chromosome 18q21, causing overexpression of bcl-2, was present in the four sensitive cell lines.

Another bcl-2 family inhibitor, ABT-263, is a potent orally bioavailable BH-3 mimetic that has also been evaluated in the pre-clinical setting. The *in vivo* properties of ABT-263 were tested in aggressive xenograft models of mantle cell lymphoma in combination with rituximab. Dosed at 100 mg/kg PO for 17 days, treatment with ABT-263 resulted in 44% tumor growth inhibition. (25) ABT-263 was also tested alone and in combination with R-CHOP in a GRANTA-519 xenograft MCL model. Single agent treatment with ABT-263 for 21 days resulted in 40% growth inhibition compared to R-CHOP alone which invoked 68% tumor growth inhibition with 20% complete responses. When ABT-263 was combined with R-CHOP, complete tumor response was seen in all animals without evidence of re-growth in 4 of 9 tumors. (25) Toxicity includes a rapid but reversible thrombocytopenia. Based on these results further studies in patients with relapsed/refractory lymphoma are in progress.

Novel antibodies

The role of rituximab has well been established in mantle cell lymphoma. Given this success, new antibodies targeting CD 20, CD 22, CD 40 and CD 74 have been developed and are in various stages of clinical development. These are highlighted in table 2.

Ofatumumab is a new human antibody that binds to the epitope of CD20 with a greater avidity than rituximab. (26) Preclinical work in CLL demonstrated that ofatumumab produced *in vitro* cell death more effectively than rituximab. (27) A phase I/II trial evaluating ofatumumab in 40 patients with relapsed / refractory follicular lymphoma at doses of 300 mg, 500 mg, 700 mg, and 1000 mg revealed responses in 63%, 33%, 20%, and 50% respectively. Furthermore, in 14 patients who had been previously treated with rituximab, the response rate was 64%. (28) Given these results, as well as previous results targeting CD 20 in MCL, four phase I/II trials investigating ofatumumab in combination are now recruiting MCL patients.

Another antibody currently being investigated is dacetuzumab, a humanized anti CD-40 monoclonal antibody. CD 40 is a type 1 transmembrane protein that is expressed on dendritic cells, activated B lymphocytes and activated monocytes. (29) CD-40 is also expressed on many malignancies of B-cell origin including non-Hodgkin lymphoma, multiple myeloma and chronic lymphocytic leukemia. In a phase 1 dose escalation study, dacetuzumab was administered in several cohorts to patients with lymphoma. Of the 10 mantle cell patients 1 achieved a partial response. (29)

Other antibodies undergoing investigation in MCL include milatuzumab. This compound is a fully humanized anti CD 74 antibody, found to exert its effect as a signaling molecule and survival receptors in the maturation of B cells through activation of the PI3K/Akt and NF- κ B pathways. Milatuzumab has been studied in combination with rituximab in mantle cell lines resulting in improved cell survival when compared to controls. (30)

Histone Deacetylase

The epigenetic modulation of gene expression is a crucial component of cellular biology. In the normal cell, DNA is packaged into an organized nucleosome that is composed of a strand of DNA wound around eight histone proteins. (31) The amino acid residues on the histone tails are modified by post –translational acetylation, methylation, and phosphorylation. As a result, the accessibility of transcription factors to gene promoters is increased. On the contrary, deacetylation, demethylation and dephosphorylation of histone decreases the accessibility of transcriptions factors to the promoter region. Histone deacetylases (HDAC) control the removal of lysine residues leading to hypoacetylation of histone gene promoters and subsequent inhibition of DNA transcription. At least 18 human HDACs have been identified varying in function and substrate. Knockout mice that are deficient in class I HDAC die in the perinatal setting. HDACs also play a role in the balance of pro and antiapoptotic proteins. Malignant cells have a high level of expression of HDAC resulting in hypoacetylation of histone. Inhibition of HDACs thus leads to cell cycle arrest followed by apoptosis. Furthermore, inhibition of HDAC leads to decreased expression of vascular endothelial growth factor. (31)

Given the above, development of HDAC inhibitors has become a promising area of advancement within the realm of oncology. These agents achieve their desired effect by binding to a critical Zn²⁺ ion required for catalytic function of the HDAC enzyme. (31) Each inhibitor has varying action with regard to potency and affinity for substrate. They are divided into 4 groups and more than 10 have been tested in clinical trials. (32) Vorinostat was the first HDAC inhibitor to reach the market, approved for cutaneous T-cell lymphoma in 2006.

In a phase II clinical trial, Kirschbaum et al investigated the efficacy of vorinostat in patients with refractory lymphoma. Nine MCL patients were included, and although none achieved a measurable response, one patient demonstrated stable disease for 26 months. (33) The most common grade 3 and 4 toxicities were myelosuppression and fatigue.

Yazbeck et al investigated the combination of a mTOR inhibitor in combination with vorinostat in MCL lines. (34) Results from their study suggest that temsirolimus works via autophagy, (the degradation of long-lived proteins) and vorinostat via apoptosis. In combination with temsirolimus, small concentrations of vorinostat activated the caspase pathway leading to apoptosis. (34) Inhibition of ERK phosphorylation was seen without reducing levels of bcl-2. Observed *in vitro* synergy may warrant further clinical investigation of this combination.

Panobinostat (LBH589), a pan-histone deacetylase inhibitor, was combined with everolimus in a phase I/II trial of patients with relapsed non-Hodgkin lymphoma. A total of 12 patients were enrolled, 2 of which had MCL. At 20 mg, grade 3 and 4 toxicities included thrombocytopenia (45%) and fatigue (18%) with one death on study possibly secondary to a pulmonary embolus. 10 of 11 patients that were evaluated had documented tumor reduction ranging from 31–63% with changes of cytokines levels including VEGF, IL-10 and IL-13. Based on these results, this dose level was recommended for phase II evaluation.

Aurora Kinase

The aurora kinases are a family of mitotic serine/threonine protein kinase that play a role in regulating the mitotic phase of the cell cycle. Three aurora homologues have been identified. Aurora A is involved in centrosome maturation and separation while Aurora B & C are essential for chromosomal separation. (35) Inhibition of Aurora A in tumor cells leads to a delay in mitotic entry leading to G2/M cell cycle arrest. Tissue microarray analysis has

demonstrated that Aurora kinase A & B are over expressed in mantle cell patients. Furthermore, over-expression is associated with a poor prognosis. There are at least twelve Aurora inhibitors that are currently being developed including those specific to the A & B isoform and pan Aurora inhibitors.

Alisertib (MLN8237) is an ATP-competitive oral inhibitor of Aurora A phosphorylation and histone-H3 phosphorylation leading to apoptosis. In mantle cell lines, MLN8237 decreased protein levels of Aurora A to a greater extent than Aurora B. (35) When studied in combination with docetaxel (microtubule targeting agent) in a SCID mouse xenograft model of MCL, significant tumor growth inhibition was seen compared to control.

In a phase II study of MLN8237 in 48 NHL patients including 13 with mantle cell lymphoma, 1 CR, 2 PRs and 6 patients with stable disease were observed. (36) The most common adverse events included neutropenia (73%) fatigue (60%) and diarrhea (56%). Further combinations are being investigated in B cell NHL, including mantle cell lymphoma.

Cyclin Dependent Kinase

Mantle cell lymphoma is characterized by increased expression of cyclin D1 secondary to the translocation between the IgH and BCL-1 genes. Cyclin D1, in conjunction with the cyclin dependent kinases CDK 4 and CDK 6, regulates the transition of the cell from G1 to S. The constitutive expression of cyclin D1 is thought to accelerate the progression of lymphoma through the G1/S checkpoint of the cell cycle. (37)

Flavopiridol is a synthetic pan-CDK 1 inhibitor that decreases both cyclin D1 and cyclin D3 leading to cell arrest of the G1 phase of the cell cycle. When tested in mantle cell lines, flavopiridol induced apoptosis via down regulation of cyclin D1 and inhibition of CDK 4.

At the phase I level, flavopiridol was tested in combination with rituximab and fludarabine in patient with B cell malignancies. (38) 10 of 38 patients had MCL, 7 of which achieved a complete response and 1 a partial response. The median progression free survival in mantle cell patients was 21.9 months. Substantial myelosuppression was noted with the combination.

Poly (ADP-ribose) polymerases

Poly (ADP-ribose) polymerases (PARPs) are a family of enzymes involved in DNA repair, transcriptional regulation, protein degradation, spindle maintenance and apoptosis. (39) PARPs bind to site of DNA breaks and facilitate DNA repair via base excision repair and non-homologous end joining. A number of PARP inhibitors have been developed and are currently under investigation in phase I trials. Veliparib (ABT-888) is a potent, novel PARP inhibitor. In a phase 0 study, patients with advanced malignancies (including non-Hodgkin lymphoma) were treated with ABT-888 and found to have decreased PARP levels after a single dose. (39) In vivo studies of MCL mouse models treated with olaparib, a PARP inhibitor, resulted in a significant reduction of tumor in the bone marrow and a trend towards spleen size reduction in 8 mice. (40) Consequently, combinations incorporating PARP inhibitors are being investigated in mantle cell lymphoma.

Conclusion

Progress in the treatment of MCL may depend on the development of small molecules. It is clear from pre-clinical and early phase trials that clinical efficacy can be achieved with targeted inhibition of constitutively activated pathways. Future efforts should be focused on

novel agent development, and combinations of targeted therapies. With this in mind, it is reasonable to believe that based on the more favorable side effect profile, Bendamustine may be a better platform for combination with novel agents when compared to CHOP or Hyper-CVAD, a strategy being tested in the cooperative group setting. Having demonstrated feasibility with bendamustine, the incorporation of agents targeting BCR signaling will likely be a focus of future clinical trials. Furthermore, ongoing laboratory work suggests that combining multiple agents targeting relevant signaling pathways in MCL may lead to clinically significant combinations that do not include chemotherapy. As we obtain an enhanced understanding of these pathways and the complicated cellular interactions, drug development will continue to become increasingly targeted, ultimately improving the prognosis of mantle cell lymphoma.

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Figure 1.

Key signaling pathways in relation to the B-cell receptor. Novel agents labeled in red are depicted at their particular focus of inhibition.

Table 1

Novel Agents in various stages of clinical development within Mantle Cell Lymphoma.

TARGET	DRUGS	PHASE OF CLINICAL DEVELOPMENT
Spleen Tyrosine Kinase	Fostamatinib	Phase II
Bruton's tyrosine Kinase	PCI-32765, AVL-292	Phase II
PI3K	CAL-101, SAR245409	Phase II
HDAC	Vorinostat, Randepsin, Panobinostat	Phase II
Cyclin D1	Flavopiridol	Phase II
Janus-Associated Kinase	INCB16562	Phase I
Protein Kinase C	Enzastaurin	Phase II
PARP	ABT-888, CEP-9722, BMN 673	Phase I
AKT	MK 2206	Phase II
Aurora Kinase	MLN 8237, AT9283	Phase I
Bcl-2 family	GX15-070, ABT-737, ABT 263	Phase I

Table 2

Monoclonal Antibodies in various stages of clinical development within Mantle Cell Lymphoma.

Antibody Target	Drug	Phase of Clinical Development
CD 20	Ofatumumab, Veltizumab	Phase II
CD 27	CDY-1127	Phase II
CD 40	Dacetuzumab	Phase I
CD 74	Milatumzumab	Phase I