Inhibition of Constitutive NF-κB Activation in Mantle Cell Lymphoma B Cells Leads to Induction of Cell Cycle Arrest and Apoptosis

Lan V. Pham, Archito T. Tamayo, Linda C. Yoshimura, Piao Lo and Richard J. Ford

*J Immunol* 2003; 171:88-95; 
doi: 10.4049/jimmunol.171.1.88
http://www.jimmunol.org/content/171/1/88

**References**
This article cites 56 articles, 25 of which you can access for free at: 
http://www.jimmunol.org/content/171/1/88.full#ref-list-1

**Subscription**
Information about subscribing to *The Journal of Immunology* is online at: 
http://jimmunol.org/subscription

**Permissions**
Submit copyright permission requests at: 
http://www.aai.org/About/Publications/JI/copyright.html

**Email Alerts**
Receive free email-alerts when new articles cite this article. Sign up at: 
http://jimmunol.org/alerts
Inhibition of Constitutive NF-κB Activation in Mantle Cell Lymphoma B Cells Leads to Induction of Cell Cycle Arrest and Apoptosis

Lan V. Pham, Archito T. Tamayo, Linda C. Yoshimura, Piao Lo, and Richard J. Ford

Constitutive activation of the NF-κB has been documented to be involved in the pathogenesis of many human malignancies, including hemopoietic neoplasms. In this study, we examined the status of NF-κB in two non-Hodgkin’s lymphoma cell lines derived from mantle cell lymphoma (MCL) samples and in patient MCL biopsy specimens by EMSA and confocal microscopic analysis. We observed that NF-κB is constitutively activated in both the MCL cell lines and in the MCL patient biopsy cells. Since NF-κB has been shown to play an important role in a variety of cellular processes, including cell cycle regulation and apoptosis, targeting the NF-κB pathways for therapy may represent a rational approach in this malignancy. In the MCL cell lines, inhibition of constitutive NF-κB by the proteasome inhibitor PS-341 or a specific pIgBα inhibitor, BAY 11-7082, led to cell cycle arrest in G1 and rapid induction of apoptosis. Apoptosis was associated with the down-regulation of bcl-2 family members bcl-xL and bfl/A1, and the activation of caspase 3, that mediates bcl-2 cleavage, resulting in the release of cytochrome c from the mitochondria. PS-341 or BAY 11-induced G1 cell cycle arrest was associated with the inhibition of cyclin D1 expression, a molecular genetic marker of MCL. These studies suggest that constitutive NF-κB expression plays a key role in the growth and survival of MCL cells, and that PS-341 and BAY 11 may be useful therapeutic agents for MCL, a lymphoma that is refractory to most current chemotherapy regimens. The Journal of Immunology, 2003, 171: 88–95.

Mantle cell lymphoma (MCL) is an aggressive, recently recognized histotype of B cell non-Hodgkin’s lymphoma (NHL-B), a heterogeneous group of human lymphoid neoplasms that are showing a significant increase in incidence in the United States over the last three decades (1, 2). MCL is characterized cytogenetically by the presence of a nonrandom chromosomal abnormality, the translocation t(11;14)(q13;q32). This translocation results in overexpression of cyclin D1 (bcl-1, PRAD1), a member of the cyclin D family of nuclear proteins, that are involved in cell cycle control of G1 progression and G1-S transition (3, 4). Although MCL has been thought to represent only a relatively small percentage of NHL, there is some indication that the incidence or recognition of MCL is currently rising in the United States, where it remains the most therapeutically resistant of the NHL-B (5). The reason for the resistance of MCL to current chemotherapy and bone marrow transplantation protocols is not clear, since MCL due primarily to its small cell histiotype was previously considered to be a low to intermediate grade NHL-B in earlier lymphoma classifications. It is now clear, however, that MCL is in fact an aggressive NHL-B, as indicated in the recent WHO classification (6). The resistance of MCL to current chemotherapy regimens indicates that new therapeutic approaches to MCL are clearly needed.

NF-κB, a centrally important transcription factor involved in immune and inflammatory cellular responses affecting both cell growth and survival, appears to be pivotally involved in the pathogenesis of aggressive lymphoid malignancies (7). In mammalian cells, the NF-κB family consists of five members, c-rel, p65 (Rel A), Rel B, p50/p105 (NF-κB1), and p52/p100 (NF-κB2), that can form various hetero- or homodimers (8). Normally, NF-κB is transcriptionally inactive in the cytoplasm of most cells because it is bound to its cytoplasmic inhibitor IκBα. Upon stimulation with proinflammatory cytokines, such as TNF-α or IL-1, IκBα protein is phosphorylated, ubiquitinated, and subsequently degraded by the proteasome. This process exposes the previously masked nuclear localization signal of NF-κB that upon proteolysis of IκBα allows NF-κB to translocate into the nucleus and subsequently activate the expression of important target genes involved in cell growth, survival, adhesion, etc. (9, 10).

Proteasome inhibitors have recently emerged as an interesting and potentially new group of chemotherapeutic agents for a variety of human cancers, including breast, prostate, and lung carcinomas, that function, in part, by stabilizing the IκBα protein and, finally, inhibiting NF-κB activation (11–13). More recently, a series of dipeptide boronic acid analog proteasome inhibitors that specifically inhibit the chymotryptic enzyme activity of the proteasome have been synthesized (14, 15). One of these, PS-341, is a low molecular weight, water-soluble dipeptide that targets the chymotryptic site in the 20S proteasome. Recent reports have shown that PS-341 inhibits tumor cell growth by inhibiting NF-κB activation, particularly in tumors constitutively expressing this pivotal transcription factor (16, 17). PS-341 is currently undergoing clinical trials as a therapeutic agent for several human cancers in which preliminary studies have been promising (18, 19). In this study, we have used PS-341 to target the possible modulation of NF-κB in MCL cells. Although the proteasome inhibitor PS-341 is capable...
of inhibiting NF-κB activation, it also has a variety of other activities, since the proteasome is an enzymatic structure that degrades many important proteins, particularly protooncogenes and cell cycle regulators in the cell (20, 21). To examine specific effects of NF-κB down-regulation on MCL cell growth and survival, we have used a specific inhibitor of IkB phosphorylation, BAY 11-7082 (BAY 11), an organic compound that selectively inhibits the TNF-α-inducible phosphorylation of IkB (22).

In this study, we demonstrate that NF-κB is constitutively active in MCL cell lines as well as in primary MCL cells. Inactivating NF-κB in the MCL cell lines with the proteasome inhibitor PS-341 or the plxBa inhibitor BAY 11 blocks MCL cell growth, leading to tumor cell death. Our studies show that PS-341 or BAY 11 inhibits MCL tumor cell growth through two important control mechanisms: cell cycle arrest and induction of cell death, both of which involve inhibition of constitutive NF-κB activation. We also used a dominant-negative (DN) form of IkBα to transfect into MCL cells to determine whether all of the observed effects of PS-341 or BAY 11 treatments of MCL can be attributed to NF-κB inhibition. Our findings suggest that constitutive NF-κB activation plays a key role in the survival of MCL cells and that PS-341 and BAY 11 may be useful future therapeutic agents for clinical trials in MCL.

Materials and Methods
Cells and reagents
Human MCL cell lines (Mino and DB (sp53)) were established from patient biopsy samples as previously described (23, 24). The Molt-4 T cell leukemia cell line (American Type Culture Collection, Manassas, VA) and the Hodgkin’s lymphoma cell line (L-428; courtesy of Dr. V. Diehl, University of Cologne, Cologne, Germany) were cultured in RPMI 1640 (Life Technologies, Rockville, MD) containing 10% FCS (HyClone Laboratories, Logan, UT). Fresh biopsy-derived MCL cells were obtained from biopsy specimens from our Tissue Procurement and Banking core facility. Lymphoma cells were enriched by SRBC rosetting, followed by “Rosette Sep” and contained 98% CD20+ and <1% CD3+ T cells by flow cytometry.

Ab reagents and materials
The following Abs were used: bcl-xL, Bcl-2/A1, bcl-2, bax, cyclin (D1, D2, and D3), p27, p21, NF-κB p50, p52, p65, Rel-B, and c-rel, IkBα (Santa Cruz Biotechnology, Santa Cruz, CA); bcl-2 and p50 (Upstate Biotechnology, Lake Placid, NY); and phospho-IkBα (New England Biolabs, Beverly, MA). The proteasome inhibitor PS-341 was kindly supplied by Dr. J. Adams (Millennium, Cambridge, MA). The IkBα inhibitor BAY 11-7082 was purchased from Calbiochem (San Diego, CA). The following kits were used: caspase 3 (Calbiochem), 20S proteasome (Boston Biochem, Cambridge, MA), and D3), p27, p21, NF-κB induction of IκBα and contained 98% CD20+ and <1% CD3+ T cells by flow cytometry.

Transfection
Transient transfections of MCL cells with pCMV-IκBα or pCMV-IκBoM (Clontech Laboratories) were conducted using the “Nucleofector” protocol from AMAXA Biosystems (Cologne, Germany). MCL cells (5 x 10⁶) were suspended in 100 µl of Nucleofector T solution with 15 µg of plasmid DNA and then electroporated using program O-17. Cells were transferred to 2.5 ml of medium containing 15% FCS and harvested 24 h after transfection. For transfection efficiency, MCL cells were cotransfected with green fluorescent protein and analyzed by flow cytometry. The transfection efficiency ranges between 30 and 40% for each experiment.

Results
Constitutive NF-κB activation in MCL
Because NF-κB plays an important role in regulating cell growth and cell viability in many tumors, including other aggressive NHLs, such as diffuse large B cell lymphomas, we determined its biochemical status in MCL. Fig. 1A shows that in Mino and DB cell lines, and in primary MCL cells, NF-κB is constitutively activated by EMSA analysis. When analyzed by Western blotting, the nuclear proteins of MCL cells contain all of the NF-κB components (p50, p52, p65, c-rel, and reIβ) (Fig. 1B). Confocal microscopic analysis indicates that p50 and p65 are expressed in the nucleus of Mino and DB MCL cells and that in some areas they are colocalized (Fig. 1C). A supershift EMSA assay using specific Rel family Abs indicates that the p50, p65, and c-rel subunits of NF-κB are expressed and bound to DNA in MCL cells, while p52 and reIβ do not show binding (Fig. 2A). Because the NF-κB complex pattern observed in patient MCL cells is slightly different from that of the MCL cell lines, we performed a supershift assay on a representative MCL patient biopsy sample. As indicated in Fig. 2B, MCL patient cells, like the MCL cell lines, also expressed p50, p65, and c-rel but not p52 and reIβ. However, there was an unidentified additional band present in the patient cells that did not appear in the cell lines.

Effects of PS-341 and BAY 11 on constitutive NF-κB activation in MCL cells
To ascertain whether PS-341 and BAY 11 have an effect on NF-κB components expressed in MCL cells, we performed EMSA with...
nuclear extracts from PS-341-treated or BAY 11-treated Mino cells. NF-κB DNA-binding activity gradually declined between 6 and 12 h after the addition of PS-341 and was barely detectable at 24 h (Fig. 3A). PS-341 blocked IkBα degradation, resulting in the accumulation of p65IkBα after 3 and 6 h of treatment (Fig. 3B). However, there was little pIkBα present after 12 h of PS-341 treatment. PS-341 treatment also inhibited IkBα protein expression in a time-dependent manner (Fig. 3B). BAY 11 inhibits NF-κB DNA-binding activity after 6 and 20 h of treatment (Fig. 3A) and also blocks IkBα phosphorylation (Fig. 3B). Confocal microscopic analysis indicates that after PS-341 or BAY 11 treatment, the p50 and p65 components of NF-κB are prevented from translocating to the nucleus; i.e., consistent with the NF-κB inhibition observed by EMSA (Fig. 3C).

**Inhibition of MCL cell growth by PS-341 or BAY 11**

To evaluate the effects of PS-341 and BAY 11 on MCL cell growth, proliferation assays were performed in vitro on two MCL cell lines (Mino and DB). Both PS-341 (Fig. 4A) and BAY 11 (Fig. 4B) inhibited cell proliferation in Mino and DB MCL cell lines in a dose-dependent response. The sensitivity to PS-341 and BAY 11 was very similar in the two MCL cell lines. More importantly, PS-341, at doses above 25 nM, and BAY 11, at doses above 5 μM, completely inhibited MCL growth, as evidenced by low or virtually no tritiated thymidine uptake (Fig. 4, A and B). PS-341 and BAY 11 had significantly more growth inhibitory activity on the MCL cells than the other well-known biotherapeutic agents, with known negative growth effects on lymphoid tumor cells, including TGF-β (Fig. 4C) and IFN-α (Fig. 4D). These results suggest that even though Mino and DB MCL cells are relatively refractory to other common biotherapeutic agents, they are sensitive to the inhibitory effect of PS-341 or BAY 11. To demonstrate differing roles of these inhibitors on the proteasome, we subjected cell lysates from PS-341-treated and BAY 11-treated Mino cells to a 20S proteasome proteolysis assay. As shown in Fig. 4E, the proteasome activity was substantially inhibited (>50%) after 3 h of PS-341 treatment and was completely inactive after 6 h of treatment, whereas BAY 11 treatment did not affect the proteasome activity.

**Effects of PS-341 or BAY 11 on the cell cycle in MCL cells**

One likely target of cellular growth inhibitory activity of PS-341 or BAY 11 involves the cell cycle, where NF-κB has been shown to play a key role in cell cycle regulation. As shown in Fig. 5A, both PS-341- and BAY 11-treated MCL cells in vitro accumulated in the G0-G1 phase of the cell cycle. Because cyclin D1 is ectopically upregulated in MCL and involved in the early stage of the G1 phase of the cell cycle, we evaluated the effects of PS-341 or BAY 11 in modulating the ectopic expression of cyclin D1 in MCL cells. Fig. 5B shows that cyclin D1 gradually decreased in a time-dependent manner with PS-341 or BAY 11 treatments, whereas cyclin D2 was not affected by BAY 11 treatment but progressively increased for 12 h after PS-341 treatment and then leveled off for the next 12 h. We further explored the cell cycle effects of PS-341 and BAY 11 on later G1 cell cycle components. PS-341 treatment up-regulated the cyclin-dependent kinase inhibitor p21\(^{waf1}\) during the first 6 h of treatment, but was barely detectable at 12 and 24 h.
PS-341- or BAY 11-induced apoptosis in MCL cells involves bcl-xL and bfl/A1 inhibition and bcl-2 cleavage

We next determined whether PS-341 or BAY 11 treatment in MCL cells involves bcl-2 family proteins in the induction of apoptosis. As shown in Fig. 7A, PS-341 or BAY 11 treatment of Mino cells down-regulated the protein expression of bcl-xL and bfl/A1. We also evaluated two other members of the bcl-2 family proteins: bcl-2, an apoptosis antagonist, and bax, an apoptosis agonist. Interestingly, PS-341 or BAY 11 treatment in Mino cells cleaves the bcl-2 protein from a 29-kDa product to a 22-kDa product, suggesting that these agents may induce apoptosis by inactivating the cell death antagonist or by producing a proapoptotic form of bcl-2 (Fig. 7A). Bax protein expression increased as treatment of PS-341 duration increased, whereas BAY 11 has little or no effect on bax.

Previous reports have demonstrated that bcl-2 cleavage in apoptotic cells is due to caspase 3 activation (27, 28). To test this possibility in our system, we used caspase inhibitors to block PS-341-induced bcl-2 cleavage. Pretreatment with caspase 3 inhibitor (DEVD) but not the caspase 1 inhibitor (VAD) or the calpain inhibitor (N-acetyl-leucinyl-leucinyl-norleucinal-H) blocks PS-341-induced bcl-2 cleavage (Fig. 7B). Using cell fractionation studies, we show that upon PS-341 treatment, bcl-2 is cleaved within the mitochondria (Fig. 7C). PS-341 treatment also releases cytochrome c from the mitochondria into the cytoplasm (Fig. 7C). Caspase 3 inhibitor (DEVD) treatment before PS-341 treatment blocked bcl-2 cleavage in the mitochondria, partially inhibited the release of cytochrome c from the mitochondria (Fig. 7D), and partially inhibited PS-341-induced apoptosis (Fig. 7E).

Inhibition of constitutive NF-κB by the dominant-negative IκBα

Next, we wished to determine whether the specific inhibition of NF-κB is sufficient to block cell growth in MCL cells. The super-repressor form of IκBα (pCMV-IκBα) or pCMV-IκBαM, when overexpressed, binds to NF-κB and prevents it from translocating to the nucleus. Unlike pCMV-IκBα, pCMV-IκBαM binds to NF-κB but cannot be phosphorylated on the basis of alanine substitution for serines 32 and 36 as dominant negative, thereby blocking the NF-κB signaling pathway (29). As shown in Fig. 8A, transient transfection of the DN-IκBα in Mino MCL cells suppresses...
constitutive NF-κB expression. Suppression of NF-κB by the DN-ικBαM also leads to inhibition of MCL cell viability (Fig. 8B). These results suggest that NF-κB inhibition is linked to the anti-proliferative effects in MCL cells.

Effects of PS-341 or BAY 11 treatment in primary biopsy-derived MCL cells

To this point, we have established that the transcription factor NF-κB is an important factor in cell survival in MCL cell lines. Next, we examined the effect of PS-341 or BAY 11 on NF-κB expression and apoptosis on primary MCL cells. As shown in Fig. 9A, PS-341 or BAY 11 treatment suppresses constitutive NF-κB expression in T cell-depleted primary MCL cells derived from two patients (patients 1 and 2). Control and treated cells were also examined for apoptosis by annexin/propidium iodide staining and flow cytometric analysis. As shown in Fig. 9B, the apoptotic cell population increased from 30% (control) to 87 and 57% after PS-341 and BAY 11 treatments, respectively, in patient 1 and from 42% (control) to 86 and 78% after PS-341 and BAY 11 treatments, respectively, in patient 2. These results demonstrate that both of these NF-κB inhibitors, PS-341 and BAY 11, are effective not only in MCL cells from cell lines but also effective in primary MCL cells.

Discussion

In addition to MCL, constitutive activation of NF-κB has been demonstrated in a variety of other human malignancies, including pancreatic cancer, colon cancer, breast cancer, T cell leukemia, Hodgkin’s lymphoma, and large B cell, NHL-B (30–34). In this study, we demonstrate that MCL cells from two established cell lines and from freshly obtained MCL patient specimens constitutively express activated NF-κB (Fig. 1A). The molecular basis of constitutive NF-κB activation in many malignant cells is still unclear, but the constitutive expression of NF-κB is virtually always associated with the parallel constitutive expression of another important transcription factor, AP-1, that together are thought to mediate neoplastic transformation in a number of experimental oncogenesis systems (35). These findings suggest that constitutive activation of NF-κB and AP-1 in aggressive B cell neoplasms could be important participants in whatever the oncogenic event(s) are that result in malignant transformation in these tumors. Our studies also suggest that constitutive activation of NF-κB may also serve as a surrogate marker for malignancy in MCL (as well as in the other B cell malignancies that display this activity), which may be valuable in assessing the effectiveness of potential therapeutic agents. Recently, we have shown that in another aggressive NHL-B, diffuse large B cell lymphoma, that “ectopic” expression of CD154 by the lymphoma cells initiated NF-κB activation through an anchored CD40 signalosome in cell membrane lipid
rafts (34). Our preliminary data have shown that MCL cells may also use similar mechanism(s) for NF-κB activation (L. V. Pham, A. T. Tamayo, L. C. Yoshimura, R. J. Ford, et al., manuscript in preparation). Constitutive NF-κB activation in MCL cells is of particular importance because it implies that the cells use NF-κB for constant cycling through the cell cycle and to maintain MCL cell survival through antiapoptotic members of the bcl-2 family. Our finding that agents with known inhibitory effects targeting NF-κB inhibit the growth of MCL cells in vitro suggests that inhibition of NF-κB can alter continuous neoplastic cell cycling as well as MCL tumor cell survival.

Our data show that NF-κB inactivation with the proteasome inhibitor PS-341 or the pIκBα inhibitor BAY 11 leads to G1 cell cycle arrest in MCL cells. The impaired cell cycle progression following NF-κB inactivation was associated with the reduction of cyclin D1, but not cyclin D2 or D3. In MCL cells, cyclin D1 (bcl-1, PRAD 1) is a well-described protooncogene product, occurring as a result of gene dysregulation, and enforced overexpression due to t(11;14) chromosomal translocation. This nonrandom chromosomal anomaly is considered by most clinicians and investigators as the molecular signature of this B cell lymphoma (36). The t(11;14) translocation places the cyclin D1 gene under the control of the strong heterologous Ig H chain (IgH) enhancer, presumably resulting in unrestrained production of cyclin D1 protein (37). Cyclin D1 is also, however, a target gene of the transcription factor NF-κB(38) that under the constitutive activation of NF-κB is maintained in the expressed state. In MCL cells, ectopic cyclin D1 is overexpressed, as normal lymphocytes usually express cyclins D2 and/or D3 (but not D1), that are required for G1 traversal, in concert with cyclin-dependent kinases 4 and 6, resulting in the phosphorylation of Rb before subsequent entry into S phase (39).

It has been unclear however whether in MCL overexpressed cyclin D1 plays a direct or facilitative role in driving (or even streamlining) G1 traversal by possibly replacing cyclin D2 and/or D3, as has been previously hypothesized (40). Alternatively, it has been argued that cyclin D1 is accompanied by a down-regulation in cyclin D3 and is not related to the proliferative activity of the MCL cells (41). Our studies however indicate that the expression of ectopic cyclin D1 is actually involved cell cycle progression and that its expression in MCL as a result of t(11;14), is down-regulated by
Both PS-341 and Bay 11, resulting in G1 arrest. The cyclin-dependent kinase inhibitors p21<sup>sup</sup> and p27<sup>sup</sup> are substrates of the proteasome that accumulates after proteasomal inhibition (42, 43). Large B cell lymphomas and MCL cells generally show low levels of p21 and p27 due to rapid proteasomal degradation (44). Consistent with these findings, we have shown that both p21 and p27 proteins are up-regulated after PS-341 treatments, whereas, both p21 and p27 proteins are not affected by Bay 11 treatments. These results suggest that NF-κB inhibition-mediated G1 cell cycle arrest may not be involved with the cyclin-dependent kinase inhibitors p21 or p27.

A number of reports have demonstrated that NF-κB activation can maintain tumor cell viability and that inhibiting NF-κB activity alone can be sufficient to induce cell death (45–47). PS-341 and Bay 11 were recently reported to induce apoptosis via NF-κB inhibition in a variety of tumor cells (22, 48). In MCL cells, PS-341 and Bay 11 appear to affect cell viability indirectly not only by inhibiting bcl-2 family members, including bfl1/A1 and bcl-x<sub>L</sub>, that are regulated at the transcriptional level by NF-κB (49–51), but also through its activity in the mitochondria involving bcl-2 cleavage and cytochrome c release. This result suggests that initiation of caspase 3 activation appears as a result of bcl-x<sub>L</sub> and bfl1/A1 down-regulation, because either can suppress cytochrome c release (52).

A recent study suggested that PS-341 treatment of cells from another human B cell neoplasm, multiple myeloma, appears to produce apoptosis without affecting bcl-2 or bax (53). In MCL, however, we show that PS-341 or BAY 11 cleaves the 29-kDa bcl-2 protein to a 22-kDa product by activating caspase 3. Our studies agree with previous studies that bcl-2 can be cleaved by caspase 3 activation, transforming it from an antiapoptotic protein to a proapoptotic protein (27, 28). How the bcl-2 protein functions as a proapoptotic protein is still unknown. One possibility is that the BH4 domain of bcl-2 stabilizes a voltage-dependent anion channel in the mitochondria, preventing the release of cytochrome c, a critical molecule that binds to Apaf1 and caspase 9 to form an apotosome that leads to the activation of caspase 3 and, subsequently, to apoptosis (54). Another possibility is that when the BH4 domain is cleaved, the 22-kDa product of bcl-2 may heterodimerize with bax or allow bax to homodimerize to release cytochrome c, as both bcl-2 and bax are capable of creating pores in an artificial membrane (55). The cleaving of bcl-2 seems to be an amplification mechanism for facilitating the apoptotic pathway in MCL cells, as bcl-2 cleavage occurs only late in apoptosis.

The expression of NF-κB as well as the effect of the proteasome inhibitor PS-341 or pIκBα inhibitor BAY 11 have not yet been established in MCL. This is the first demonstration that NF-κB is constitutively active in MCL cells and that either PS-341 or BAY 11, two NF-κB inhibitory agents, can suppress NF-κB expression and induce apoptosis, both in MCL cell lines and in primary MCL cells. In fact, Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies has been conducted and has shown promising results, especially against refractory multiple myeloma and NHL (56).

In summary, this study describes an important aberrant signaling pathway involved with constitutive activation of NF-κB that maintains the growth and survival of MCL cells in vitro. This study also explores the antitumor mechanism(s) of PS-341 and BAY 11, that theoretically should target and affect the NF-κB pathway, and provides supporting evidence indicating that these agents (or other agents with similar mechanisms of action) may also be useful as potential therapeutic agents for MCL.

References


