Trends in Cancer Research
Vol. 10, 2014

Review

The lymphoma misfit: a review of mantle cell lymphoma

Tycel Phillips*, Jessica Mercer and Moshe Talpaz
University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48103, USA.

ABSTRACT

Mantle cell lymphoma (MCL) is a B-cell neoplasm that comprises about 5 percent of all non-Hodgkin lymphoma (NHL) cases diagnosed yearly. It is characterized by distinct morphological, immunophenotypic, genetic and clinical features. MCL cells typically express CD5, CD43, CD19, CD20 and an IgM or IgD immunoglobulin on the cell surface, although some CD5-negative cases have been reported. Translocation (11;14) is present in approximately 95% of MCL cases and confirms the diagnosis in the majority of patients. Several other genetic abnormalities are also relatively common in this disease. The number of abnormalities present increases with time and appears to correlate with resistance to conventional therapies. Clinically most patients will present at diagnosis with advanced stage disease (stage III or IV), and will require some form of therapy within the first year of diagnosis. The advent of more modern regimens, which typically include consolidation with autologous stem cell transplantation, have markedly improved response rates. Nevertheless, the disease remains incurable and the current estimate of survival is 5-10 years after diagnosis. New small molecule inhibitors that target specific proteins and/or pathways that are essential to the survival and proliferative advantage of the malignant cell are showing promise in clinical trials and may allow therapy to be tailored to the patient's disease, including individual mutations. While the future appears bright for this once dismal disease, much work remains before this goal can be reached.

*Corresponding author: tycelp@med.umich.edu

KEYWORDS: mantle cell lymphoma, genomic abnormalities, young/fit patients, elderly patients, chemotherapy, small molecule inhibitors

1. Introduction

Mantle cell lymphoma (MCL) is a B-cell neoplasm that comprises ~5-6% of all non-Hodgkin lymphoma (NHL) cases diagnosed yearly [1]. The disease typically occurs in older patients (median age at diagnosis is 65), affects Caucasians twice as frequently as African Americans and has a strong male predominance. The malignant cell is thought to originate from a naïve pre-germinal center B-cell. Originally, classification of this disease fell under several subtypes of an indolent lymphoma until 1992, when the subtypes were united under the name mantle cell lymphoma at a consensus conference [2]. Classifying this lymphoma was difficult because the disease shares features of both indolent and aggressive lymphomas. Similar to indolent lymphomas, MCL cells are typically small and cleaved. However, the clinical behavior and outcome of this lymphoma resembles aggressive lymphoma, with most patients presenting with bone marrow, GI, and/or diffuse nodal involvement at diagnosis. Historically, the disease is incurable and the duration of remission obtained with treatment is short. Survival rates have improved over the last several decades, reaching the current estimate of 5-10 years after diagnosis. Here we will review the characteristic genetic abnormalities, diagnosis, prognostication, clinical course, and treatment for this complex disease.

2. Genomic abnormalities

Several genetic abnormalities characterize MCL. These mutations occur in genes that regulate cell

cycle, DNA damage, and cell survival and proliferation pathways. The number of genetic abnormalities appears to increase as the disease becomes more resistant to traditional chemotherapy. Here will we review several of the genomic changes that are known to occur in MCL.

2.1. Cyclin D1

The translocation (11;14), a pathognomonic feature of MCL [3, 4], relocates BCL-1 locus from 11q13 next to an enhancer region on the Ig heavy gene locus on 14q32. his rearrangement leads to deregulated PRAD1, which in turn over-activates cyclin D1. The exact role that the (11;14) translocation plays in the pathogenesis of MCL is unclear, as increased expression of cyclin D1 *in vitro* is not sufficient to induce malignant transformation. The *CCND1* gene consists of 5 exons, which can be alternatively spliced to create 2 major isoforms, *cyclin D1a* and *D1b*. The *cyclin D1b* isoform is shorter, more stable and the more common isoform in non-MCL tumors. Its presence is associated with an inferior clinical course. The *D1a* isoform is 4.5 kb in length, with a coding region of only 882 bp. The majority of this mRNA is a 3´ untranslated region (UTR), which contains mRNA destabilizing elements, that limits the transcript half-life and levels of cyclin D1 protein expression [5-9]. Some MCL patients harbor deletions and point mutations in this gene that shorten the 3´UTR of *cyclin D1a* mRNA. The shorter transcript is more stable than the full-length version and does not contain the binding site for microRNAs miR15/16, so these microRNAs cannot bind and inhibit the translation of *cyclin D1* mRNA. Clinically this truncation leads to a more aggressive phenotype [10]. Cyclin D1 functions by forming complexes with cyclin-dependent kinase 4 or 6 (CDK 4/6). In the nucleus the cyclin D1/CDK 4/6 complex phosphorylates the retinoblastoma tumor suppressor protein (Rb). Hyper-phosphorylated Rb releases E2F, allowing E2F to activate *cyclin E* transcription and promote cell cycle progression [11-13]. The cyclin D1-CDK4 complex can also sequester p27Kip1 and p21Waf1/Cip1 away from cyclin E-CDK2, further facilitating the G1/S transition. Increased CDK 4/6 activity can result from the homozygous deletion of *CDKN2A*, encoding the CDK4/6-selective inhibitor p16INK4A or through the amplification of *BMI-1*, which leads to overexpression of a transcriptional repressor of the *CDKN2A* locus [14-21]. In the cytoplasm cyclin D1 is polyubiquitinated by the E3 ligase, SKp1-Cul1-F box protein, and degraded through the proteasome. Recently mutations in UBR5, which encodes an E3 ligase, were detected in 18% of MCL tumor [22]. While the impact of this is not known, mutations in this gene in solid tumors have been linked to increased nuclear retention of cyclin D1.

2.2. SOX 11

The transcription factor SRY (sex-determining region Y)-box 11 (SOX 11) is expressed during fetal development and is important in organogenesis. It is not typically expressed in normal B-cells but is expressed in 90-95% of MCL patients. Its expression is rare in other lymphoma subtypes and so it can be used to discriminate the few MCL cases that are negative for cyclin D1. The clinical significance of SOX 11 expression in MCL has been widely debated. Several publications have linked absence of SOX 11 expression to a more aggressive clinical course, while others have linked its absence to a more favorable indolent course. Notably, most of the aggressive cases lacking SOX 11 expression harbored a concomitant p53 mutation. While invariably more research is needed to clarify this discrepancy, recent work [23-25] linked SOX 11 expression to the regulation of PAX5, which in MCL helps block terminal differentiation of B-cells. The authors speculate that SOX 11 contributes to tumor development by altering the terminal B-cell differentiator program of MCL.

2.3. *NOTCH1*

The *NOTCH* pathway is a highly conserved signaling system that enables communication between adjacent cells. It functions in a variety of physiological processes such as cell proliferation, death, and differentiation. The *NOTCH1* receptor is cleaved by γ-secretase, releasing an active intracellular portion that migrates to the nucleus and activates transcription of downstream targets. Dysregulation of *NOTCH1* has been linked to oncogenesis in several malignancies, and mutations in the *NOTCH1* gene have been best described in T-cell acute lymphoblastic leukemia and more recently in B-cell chronic lymphocytic leukemia. Truncating mutations in the PEST domain of

NOTCH1 have been identified in up to 12% of MCL cases. These mutations lead to increased activation of *NOTCH1* signaling through impaired degradation of the protein's intracellular component. *NOTCH1* mutations may have prognostic significance as MCL patients with this mutation had an inferior overall survival [26].

2.4. *ATM/p53*

Ataxia telangiectasia mutated (ATM) is a serine/ threonine protein kinase that plays a key role in the cellular response to DNA double-stranded breaks (DSBs) [27, 28]. It is also required for telomere maintenance and for processing the physiological DNA strand breaks that occur during meiosis and immune system maturation. DNA damage induces auto-phosphorylation of ATM, thereby activating its kinase activity. ATM phosphorylates several substrates involved in cell cycle arrest, DNA repair and apoptosis including p53, breast-cancer-associated 1 (BRCA1), p53-binding protein 1 and the checkpoint kinase2 [27-30]. Loss of ATM function, which occurs in 40-75% of patients with MCL has not been associated with a change in prognosis. Tumor suppressor protein *p53* binds its recognition site in DNA and stimulates transcription of hundreds of target genes, including $p21^{WAF1/CIP1}$. The p21 protein inhibits cyclin-dependent kinases (cdks), leading to cell cycle arrest. Loss of functional *p53* occurs in up to 30-40% of MCL cases, either through point mutation or deletion, and is most common in the blastic variant of MCL. This genetic abnormality has been associated with significant decline in overall survival.

2.5. JAK/Stats

The Janus kinase (JAK) and signal transducer and activator of transcription (Stat) signaling pathway mediates cellular responses to a number of cytokines and growth factors. Upon ligand binding, the cytokine receptors associated with JAKs undergo conformational changes that allow JAK trans-phosphorylation. The activated JAKs then phosphorylate multiple targets including cytokine receptors and Stats [31-37]. Phosphorylated Stat3 (pStat3) is highly oncogenic, as it leads to increased cell proliferation and survival through the up-regulation of c-myc, Cyclin D1, Bcl-X_L and other anti-apoptotic proteins [38-41]. Stat3 up-regulates transcription of cytokines IL-6 and 10, which in turn activates Stat3, creating a positive feedback loop. High expression of pStat3 has been noted in MCL and has been linked to tumor growth and chemotherapy resistance [20, 42, 43].

2.6. B-cell receptor (BCR)

Normal B-cells are under selective pressure to express non-autoreactive and functional B-cell receptors (BCRs). Murine lymphoid cells with ablated BCR expression undergo apoptosis [44, 45]. Activation of BCR triggers downstream signaling pathways that are crucial for the survival of normal mature B-cells. Upon antigen binding, the B-cell receptor initiates signaling by inducing Src-family kinases to phosphorylate tyrosine residues in ITAM domains of CD79A (Ig-alpha) and CD79B (Ig-beta). Upon this phosphorylation, Syk, another tyrosine kinase, is recruited and activated by binding to the ITAM motifs. This triggers downstream signaling that involves the Bruton tyrosine kinase (BTK), with subsequent activation of adaptor proteins, including phosphatidylinositol 3 kinase (PI3K) and phospholipase C gamma 2 (PLCγ2). Activation of PI3K results in recruitment and activation of the serine/threonine kinase AKT (PI3K/AKT pathway), while PLCγ2 activation leads to release of intracellular Ca^{2+} and activation of protein kinase C (PKC). PKC signaling proceeds with activation of the MAPK pathway (MEK/ERK) and phosphorylation of CARD11, with recruitment of BCL10 and MALT1 into a complex denominated CBM. This complex activates I Kappa B kinase (IKK), resulting in activation of NF kappa beta, increased transcription of anti-apoptotic proteins and promotion of cell survival [46]. B-cell lymphomas also depend on BCR signaling, and express BCR on their surface, albeit at different levels. Also, translocations into Ig-loci, frequent genetic hallmarks of lymphomas, virtually always occur in the non-productively rearranged immunoglobulin (Ig) gene loci. This suggests that translocations that disrupt expression of the BCR (i.e. coded by the productively rearranged Ig) would be incompatible with malignant cell survival. In addition, multiple proteins downstream of the BCR (e.g., Syk, BTK, and P13K) have increased activity in different B cell neoplasms, promoting malignant cell survival and proliferation [47-49]. Blockade of some of the key downstream effectors may halt the pro-survival machinery.

2.7. PI3K/AKT/mTOR

The phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway plays a critical role in cellular proliferation and survival. High levels of activated AKT, mTOR, and their downstream targets have been identified in MCL patients [50-52]. PI3K belongs to the PIK3CA family of kinases and is located within the cytosol. Following external signals from IGF1, B-cell receptor (BCR) engagement or other external signals, PI3K recruits Akt to the cell membrane where it is phosphorylated. A second phosphorylation on the mTORC2 complex stabilizes Akt [53]. Akt next phosphorylates the tuberous sclerosis complex (TSC1 and TSC2) [54, 55] which releases the negative inhibition of a small protein, Rheb. Rheb causes mTOR to form a complex with a series of scaffold proteins, including mTORC1 and mTORC2. mTORC1 is responsible for many of the growth functions attributed to the mTOR pathway; however inhibition of mTORC1 leads to increased mTORC2 phosphorylation and subsequent hyper-stimuation of Akt. This suggests that mTORC2 may play a more important role in the malignant potential of the mTOR pathway than what was originally considered [56]. The entire pathway is under proximal negative control by the tumor suppressor gene, PTEN, which blocks PI3K signaling and whose dysfunction has also been noted in patients with MCL.

3. Diagnosis

The malignant B-cell that is characteristic of MCL expresses CD5, CD43, CD19, CD20 and an IgM or IgD immunoglobulin on the cell surface, although some CD5-negative cases have been reported. Negativity for CD23 distinguishes MCL from chronic lymphocytic leukemia. Approximately 95% of MCL patients carry translocation (11;14) (q13;q32), which confirms the diagnosis. This translocation leads to abnormal expression and activity of the cell cycle protein cyclin D1, which is not expressed in normal B-cells. In the remaining 5% of cases that are negative for cyclin D1, detection of the neural transcription factor SOX 11 can clinch the diagnosis [57, 58]. Several studies have shown that the majority of the cyclin D1-negative samples abnormally express cyclin D2 or D3 [59-62], suggesting that expression of one cyclin D family member is required for the development of MCL. Testing for the other cyclin D proteins is not yet standard practice. Lastly, most MCL patients will have peripheral blood involvement at the time of diagnosis, and some patients will even present with a leukemic variant of the disease [63].

4. Clinical course

MCL exhibits the worst features of aggressive and indolent lymphomas. Similar to aggressive lymphomas, most patients will present at diagnosis with advanced stage disease (stage III or IV), and will require some form of therapy within the first year of diagnosis [64, 65]. Furthermore, remissions in between therapies are typically very short, which is characteristic of indolent lymphomas. The advent of more modern regimens, which typically include consolidation with autologous stem cell transplantation, have markedly improved response rates; however, most patients succumb to their disease within 5 years of diagnosis. A small subset of patients (10-15%) will present with an indolent form of MCL that may not require treatment at diagnosis. These patients survive for years without therapy and typically have an overall survival that far exceeds 5 years. Identifying this patient cohort early on has proven to be very difficult. Several studies have tested different diagnostic criteria to distinguish these patients, including exam results (e.g., splenomegaly, leukocytosis with circulating MCL, and absence of adenopathy at diagnosis), histologic findings (e.g., low ki-67 expression and mantle zone pattern), and/or genetic changes (e.g., mutation of the IGH variable region and presence/absence of SOX 11) [66-75]. SOX 11 expression correlated most strongly with clinical outcome, but like the other factors, it cannot definitely identify patients with indolent MCL [24, 42, 66]. Currently, most patients receive therapy at diagnosis regardless of risk classification, and this approach will likely continue until more research supports a watch and wait approach in asymptomatic patients with MCL.

5. What's in a score?

Development of a prognostic scoring system to stratify newly diagnosed MCL patients into risk

categories has proven challenging. Both the internal prognostic index (IPI) and the follicular lymphoma international prognostic index (FLIPI) failed to adequately stratify all patients [76]. The MCL international prognostic index (MIPI) was developed in 2008 to overcome the limitations of the IPI and FLIPI; its ability to appropriately prognosticate patients with MCL has been confirmed in multiple studies [77-91] including a recent European study that evaluated over 900 patients [92]. However, the MIPI in its current iteration is not an ideal scoring system. Several studies have challenged the prognostic relevance of the MIPI in MCL patients [93-96] and unlike the IPI or FLIPI, the MIPI score is difficult to calculate without the assistance of an electronic device.

6. Treatment

6.1. Young/fit patients

There has never been a consensus on how to treat newly diagnosed MCL patients; even today a standard for front-line treatment does not exist. Some of the difficulty has stemmed from poor understanding of the disease classification in addition to the lack of durable and effective treatments regimens. During the early days of chemotherapy, MCL patients were classified and treated as other indolent lymphomas. Regimens evolved from chlorambucil/prednisone to more modern regimens such as cyclophosphamide/ vincristine/prednisone and CHOP (cyclophosphamide/adriamycin/ vincristine/prednisone). Probably the most significant leap during the chemotherapy era was the utilization of high-dose chemotherapy followed by autologous stem cell transplantation [97]. Another key finding was the clinical benefit of including high-dose cytarabine (HiDAC) in the induction regimen [98-102]. Regimens that have utilized these components such as the Nordic regimen and R-Hyper-CVAD have increased survival rates from a median of just over two years to five years or more. In fact, some studies have reported long-term survival rates of ten years or more, albeit most of the cases were not typical MCL patients. For example, most patients enrolled in studies evaluating an aggressive induction chemotherapy regimen followed by autologous stem cell transplant were at least a decade younger than the median age of MCL patients at diagnosis [84, 103-108]. Based on these studies, an R-CHOP–like regimen alternating with HiDAC followed by a consolidative autologous stem cell transplant is recommended for young, fit patients.

The future for R-Hyper-CVAD in this disease is unclear, although it is the only regimen that has impressive survival data without the utilization of autologous stem cell transplantation. The multicenter SWOG and Italian group trials evaluating rituximab plus Hyper-CVAD alternating with high-dose methotrexate and cytarabine resulted in lower than expected response rates, high toxicity rates, and a high dropout rate [81, 109]. Additionally, the current Intergroup study (SWOG 1106) evaluating bendamustine-rituximab (BR) vs. R-Hyper-CVAD has closed the Hyper-CVAD arm due to toxicity.

With the recent introduction of effective and well tolerated oral targeted agents, the role and timing of transplantation in MCL patients has been widely debated, similar to what has played out in the myeloma arena. Allogeneic hematopoietic stem cell transplant (allo-HCT) is widely considered to be the only curative approach in MCL; yet with its high treatment related mortality and even higher morbidity it has a very narrow therapeutic index. Allo-HCT is typically reserved for young, very fit patients who have relapsed after frontline therapy and consolidative autologous transplant. Data from 202 patients with refractory MCL who underwent allo-HCT, collected by the Center for International Blood & Marrow Transplant Research, demonstrated a non-relapse rate of 43-47%, progression free survival (PFS) of 20-25%, and an overall survival (OS) of 25-30%. Additionally no difference in outcome was noted between the groups that received a myeloablative conditioning regimen vs. a reduced intensity/non-myeloablative regimen [110].

6.2. Elderly/unfit patients

Given that the median age of diagnosis of patients with MCL is 65, it is not surprising that many patients are not ideal candidates for intense chemotherapy regimens or eligible for consolidative autologous stem cell transplantation. Most elderly or unfit patients have historically been treated with R-CHOP-like regimens and achieved poor responses by today's standards. The poor response rate to R-CHOP may be due to the limited utility of an anthracycline in MCL, similar to the experience

with indolent NHL subtypes [111]. Still, R-CHOP alone was frequently given until a recent study by Rummel *et al*. demonstrated non-inferiority of bendamustine-rituximab (BR) compared with R-CHOP in indolent lymphomas and MCL. Specifically, the PFS of MCL patients treated with BR was greater than 12-months, with less treatment-related toxicity reported [112]. The benefit of BR vs. R-CHOP was confirmed in the subsequent BRIGHT study [113]. Thus, BR will likely be the front-line treatment of choice for elderly and unfit MCL patients who are treated outside of a clinical study.

6.3. Depth of response

Evaluation of disease response currently is limited to imaging (either computed tomography and/or positron emission tomography), morphologic evaluation of bone marrow, or endoscopy at the conclusion of therapy. Minimal residual disease (MRD) during therapy is not standardly performed in any lymphoma, because testing has not been standardized nor is it widely available. In addition, the long term benefit of attaining MRD status is still in question. A recent clinical trial demonstrated a disease-free survival benefit in patients who were MRD-negative after induction therapy and in patients who remained MRD-negative at least a year after transplant [105, 114]. Thus, attainment of MRD negativity after induction and consolidation may be an important prognostic marker, but this will need to be validated in future studies. We will also need to determine if MRD negativity results in any long-term benefits, as the study reported only short-term follow-up data. Further, when a patient inevitably becomes MRD-positive, is there a role for medical intervention and if so, how aggressive should it be? Lastly, we will need to standardize the methodology for evaluating MRD, including sample type (peripheral blood vs. marrow) and timing of sample collection before this modality can be implemented in standard clinical practice.

6.4. Maintenance

Maintenance therapy is increasingly used in MCL, and its benefit is much less controversial than when used in indolent lymphomas because of the aggressive nature of MCL at relapse. While clinical studies are currently evaluating several targeted therapies as maintenance agents, the only agent that has been proven to be effective in this setting is rituximab (R). The MCL Elderly Trial compared R-CHOP to R-fludarabine plus cyclophosphamide (R-FC) in patients older than 60, and responding patients were further randomized to maintenance R once every 2 months vs. maintenance interferon alpha given three times per week. In this study, maintenance R improved OS and PFS when given after R-CHOP [115]. Additional support for the utility of maintenance R comes from a small U.S. study that evaluated maintenance R given once weekly for four consecutive weeks every 6 months for a total of two years in which the median PFS was reported to be 37 months [116].

6.5. Targeted agents

Over the last several years, several drugs have been approved for MCL, and others are showing promise in completed and ongoing clinical trials. Most if not all of these treatments are small-molecule agents that target specific molecular targets and/or pathways that are essential to the survival and proliferative advantage of the malignant cell.

6.5.1. Bortezomib

Bortezomib (Velcade, PS-341) is a first-in-class proteasome inhibitor that was approved for treatment of relapsed/refractory MCL patients following at least one prior therapy based on the results of the Phase II PINNACLE trial. The overall response rate (ORR) was 33%, including 8% complete response (CR)/unconfirmed CR (CRu), a median duration of response (DOR) of 9.2 months, and median time to progression (TTP) of 6.2 months [117]. After a median follow-up of 26.4 months, patients demonstrated a TTP of 6.7 months, a median time to next therapy (TTNT) of 7.4 months, and median OS of 23.5 months. In responding patients, the median TTP was 12.4 months, DOR was 9.2 months, median TTNT was 14.3 months, and median OS was 35.4 months, while in the 8% that achieved a CR, TTP and DOR were not reached, and median OS was 36.0 months. The one-year survival rate was 69% overall and 91% in responding patients [118].

6.5.2. Lenalidomide

Lenalidomide (Revlimid, CC-5013) is a potent immunomodulatory derivative of thalidomide that

was initially approved for treatment of patients with multiple myeloma and myelodysplastic syndrome with a 5q-deletion. Because its efficacy was demonstrated in pre-clinical lymphoma models [119-121], lenalidomide was further explored in patients with relapsed/refractory disease. Results from two clinical studies (NHL-002 and -003) demonstrated some encouraging response rates, especially in patients with MCL [122-125]. The study that followed, MCL-001 (EMERGE), administered single agent lenalidomide dosed at 25 mg, days 1-21 of a 28 day cycle to patients with relapsed/refractory MCL. The study enrolled a total of 134 patients, who on average were heavily pretreated, with a median age of 67. The drug was relatively well tolerated and led to an ORR of 28% with a rapid time-to-response and a median DOR of 16.6 months [126]. Based on these results, lenalidomide was approved for patients with MCL who have relapsed or progressed after two prior therapies, one of which must include bortezomib.

6.5.3. Ibrutinib

BTK is a cytoplasmic tyrosine kinase with a well-defined role in BCR signaling that is important in B lymphocyte development, differentiation, and signaling. BTK is a member of the Tec family of kinases. Activation of BTK triggers a cascade of signaling events that culminates in the generation of calcium mobilization and fluxes, cytoskeletal rearrangements, and transcriptional regulation of NF-kB and nuclear factor of activated T-cells [127-133]. Ibrutinib (Imbruvica, PCI-32765) is a first-in-class selective, irreversible small-molecule inhibitor of BTK. *In vitro* studies have shown that ibrutinib binds covalently to cysteine-481 in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity at sub-nanomolar levels [134]. In cellular signal transduction assays with the B-cell lymphoma cell line DOHH2, ibrutinib inhibited autophosphorylation of BTK, phosphorylation of BTK's physiological substrate, PLCγ2, and phosphorylation of downstream ERK. Ibrutinib has been demonstrated to be effective at doses of 420 and 560 mg daily in several subtypes of NHL including MCL [135-137]. In the initial phase I study, seven of the nine enrolled MCL patients had an objective response to treatment, with three CRs reported [138]. Results from completed phase II studies indicate that most adverse events were grade 1 or 2, and included diarrhea, fatigue, bleeding and nausea, while cytopenias were uncommon [135-137]. The agent was approved in 2013 for relapsed/refractory MCL patients who have received at least one prior line of therapy. This approval was based on a phase II study of ibrutinib that enrolled 111 patients into two groups (bortezomib refractory vs. bortezomib naïve) [136]. The ORR was 68%, including 21% CRs, and prior treatment with bortezomib had no effect on RR. After a median follow-up of just over one year, the median DOR was 17.5 months, the estimated median PFS was 13.9 months, and the median OS was not reached. The estimated rate of OS was 58% at 18 months [136].

6.5.4. Idelalisib/IPI-145

Gene expression studies have implicated over-activity of the PI3K/AKT signaling pathway in the pathogenesis of MCL [50]. Constitutive activation of this pathway was found in cases of classic and blastoid MCL [50, 52], and Akt inhibition down-regulated cyclin D1 levels. Idelalisib (CAL-101, GS-1101) is an orally bioavailable inhibitor of the delta isoform of PI3K, which is expressed in a large percentage of B-cell lymphomas. The phase I study of idelalisib enrolled 40 patients with relapsed/refractory MCL who had received a median of 4 prior therapies. The median duration of idelalisib treatment was 3.5 months and the most common grade 3/4 adverse events (AEs) were diarrhea, nausea and transaminitis. ORR was 40% with CR in 2 patients, a median DOR of 2.7 months, median PFS of 3.7 months, and 1-year PFS of 22% [139]. Another oral inhibitor, IPI-145 targets the delta and gamma isoforms of PI3K and is currently being evaluated in relapsed/refractory aggressive B and T cell lymphomas. An early analysis of this study reported responses in 2/3 of the evaluable MCL patients enrolled [140]. Additionally, studies utilizing inhibitors of this signaling pathway either in combination with other agents or as single agents are ongoing as noted in recent ASCO abstracts [141, 142] and on clinical trials.gov.

6.5.5. Temsirolimus/Everolimus

mTOR is a downstream signaling molecule in the BCR/PI3K/AKT pathway that regulates mRNA

translation and cyclin D1 expression. Inhibition of AKT or mTOR can result in cell cycle arrest in MCL cells, as well as decreased expression of cyclin D1 [50]. Temsirolimus (Torisel, CCI-779) and Everolimus (Zortress, RAD001) are allosteric inhibitors of mTORC1, administered intravenously and orally respectively. Both agents are FDA approved for the treatment of renal cell carcinoma. Several clinical trials have explored the effectiveness of both agents for treatment of relapsed and refractory MCL with encouraging results, especially for temsirolimus, although toxicity was a concern with both agents [143-148]. The initial phase II trial treated MCL patients with temsirolimus dosed at 250 mg weekly and reported an ORR of 38%, but the majority of patients required dose reductions. A high hematologic toxicity rate of 71% was reported, with thrombocytopenia being the most common abnormality [145]. A second study evaluating this agent in MCL utilized a lower dose of temsirolimus and demonstrated an improved toxicity profile without a reduction in efficacy (ORR of 41%) [143]. A phase III study in relapsed/refractory MCL patients further evaluated two dosing regimens of temsirolimus vs. investigator's choice; the temsirolimus regimens were 175 mg weekly for three weeks followed by 75 mg weekly (175/75), or 175 mg weekly for three weeks followed by 25 mg weekly (175/25). The study concluded that temsirolimus dosed at 175/75 significantly improved PFS and RR as compared to investigator's choice [144]. A study evaluating temsirolimus dosed at 25 mg weekly in combination with standard dose rituximab, given every week for the 1st cycle then on day 1 only of subsequent cycles, demonstrated a CR rate of 19% and a ORR of 63% in the relapsed setting [149]. The other rapamycin analog, everolimus, was initially evaluated in a phase II study of patients with relapsed/refractory MCL. In this study, the RR to everolimus was 30% overall and 32% in patients with MCL [148]. Another study (PILLAR-1) evaluated single-agent everolimus in 58 MCL patients who were either refractory or intolerant to bortezomib and reported an ORR of 8.6%, PFS of 5.2 months, a median TTP of 6.7 months and an OS of 16.9 months. Approximately 70% of patients experienced grade 3/4 non-hematologic AEs, of which, infection, abdominal pain and fatigue were the most common. Grade 3/4 hematologic toxicities were common as well [147]. A third study (SAKK 36/06) evaluated single-agent everolimus in 36 patients with relapsed/refractory MCL who had received a maximum of three prior lines of therapy. This study reported an ORR of 20%, 2 CRs, and reduced rates of non-hematologic grade 3/4 toxicities compared to previous studies [146].

6.5.6. LEE011 and PD0332991

LEE011 and PD0332991 are both orally bioavailable, highly specific CDK4/6 inhibitors that are being evaluated in early phase clinical studies. The initial study of PD0332991 in patients with relapsed MCL demonstrated an ORR of 18% with the most common AEs reported being anemia, thrombocytopenia and fatigue [150]. A phase I study that enrolled patients with advanced solid tumors and lymphomas demonstrated similar safety profiles for LEE011 and PD0332991. Expansion cohorts are ongoing to further evaluate efficacy [151].

6.5.7. HDAC inhibitors

HDAC inhibitors (HDACi) regulate oncogenesis by modulating transcription of oncogenes and tumor suppressor genes. Vorinostat (suberoylanilide hydroxamic acid) is an orally bioavailable synthetic hydroxamic acid class HDACi that is currently approved for the treatment of advanced cutaneous T-cell lymphoma. The drug was evaluated in a phase II study [152] of relapsed/refractory indolent lymphoma patients including patients with MCL. There were no formal responses in the nine patients with MCL [153]. A phase II trial evaluated the oral pan-HDACi abexinostat (PCI-24781) in relapsed follicular and mantle cell lymphoma and demonstrated an ORR of 27% with a PFS of approximately 4 months [154]. Several pre-clinical trials have demonstrated efficacy of HDACi given in combination with targeted and cytotoxic agents, and clinical studies of these combinations are ongoing [155, 156].

6.5.8. Anti-apoptotic agents

Several agents targeting pro-survival proteins have been studied in lymphoma, and the new selective Bcl-2 inhibitor ABT-199 (GDC-0199) has shown the most promise thus far. The phase I study demonstrated an ORR of 100% in the eight MCL patients enrolled. Further studies evaluating

this agent in MCL and other lymphoid malignancies are ongoing. The pan-BH3 mimetics Obatoclax (GX15-070) and Navitoclax (ABT-263) have been or are currently being evaluated in several clinical studies [157, 158]. Both agents may have limited utility, however, due to drug-induced thrombocytopenia caused by inhibition of Bcl-$X_{L.}$

6.5.9. Other agents

Several other agents are being investigated as potential treatment options for patients with MCL. These include inhibitors of the NOTCH pathway, foregoing the γ-secretase inhibitors due to dose-limiting GI toxicity, in favor of more specific anti-NOTCH antibodies. B-cell activating factor (BAFF), a pro-survival TNF family member, promotes survival in B-cell malignancies, and studies of BAFF-neutralizing antibodies in mice support the therapeutic potential of this target in lymphoma. Additional agents being evaluated clinically include small molecular inhibitors of poly (ADP-ribose) polymerase 1 (PARP-1), the JAK/Stat pathway, Syk, PCKβ and heat shock proteins.

7. Conclusion

The outlook for patients with MCL has improved remarkably. Previously, survival rates for patients with MCL were bleak, but now long-term survival is a possibility. This has resulted, at least in part, from research over the last decade focused on the biologic and molecular drivers of MCL. The information that emerged from these studies has informed prognostic modeling and treatment strategies for MCL. Additionally, several new and promising targeted therapies have expanded our treatment armamentarium. Implementing these tools into clinical practice has steadily improved the quality of life for MCL patients. Although this success is encouraging, the disease remains incurable for the majority of patients. Thus, more research on the genetic alterations, deregulated signaling pathways and their triggering elements in MCL is needed to reach the ultimate goal of curing the disease.

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

REFERENCES

1. Swerdlow, S. H. 2008, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Presented at the IARC, Lyon (unpublished).
2. Banks, P. M., Chan, J., Cleary, M. L., Delsol, G., De Wolf-Peeters, C., Gatter, K., Grogan, T. M., Harris, N. L., Isaacson, P. G., Jaffe, E. S., Mason, D., Pileri, S., Ralfkiaer, E., Stein, H. and Warnke, R. A. 1992, Am. J. Surg. Pathol., 16(7), 637-640.
3. Jares, P., Colomer, D. and Campo, E. 2007, Nat. Rev. Cancer, 7(10), 750-762.
4. Welzel, N., Le, T., Marculescu, R., Mitterbauer, G., Chott, A., Pott, C., Kneba, M., Du, M. Q., Kusec, R., Drach, J., Raderer, M., Mannhalter, C., Lechner, K., Nadel, B. and Jaeger, U. 2001, Cancer Res., 61(4), 1629-1636.
5. de Boer, C. J., Schuuring, E., Dreef, E., Peters, G., Bartek, J., Kluin, P. M. and van Krieken, J. H. 1995, Blood, 86(7), 2715-2723.
6. de Boer, C. J., van Krieken, J. H., Kluin-Nelemans, H. C., Kluin, P. M. and Schuuring, E. 1995, Oncogene, 10(9), 1833-1840.
7. Lebwohl, D. E., Muise-Helmericks, R., Sepp-Lorenzino, L., Serve, S., Timaul, M., Bol, R., Borgen, P. and Rosen, N. 1994, Oncogene, 9(7), 1925-1929.
8. Lin, S., Wang, W., Wilson, G. M., Yang, X., Brewer, G., Holbrook, N. J. and Gorospe, M. 2000, Mol. Cell. Biol., 20(21), 7903-7913.
9. Rimokh, R., Berger, F., Bastard, C., Klein, B., French, M., Archimbaud, E., Rouault, J. P., Santa Lucia, B., Duret, L., Vuillaume, M., Coiffier, B., Bryon, P. and Magaud, J. P. 1994, Blood, 83(12), 3689-3696.
10. Wiestner, A., Tehrani, M., Chiorazzi, M., Wright, G., Gibellini, F., Nakayama, K., Liu, H., Rosenwald, A., Muller-Hermelink, H. K., Ott, G., Chan, W. C., Greiner, T. C., Weisenburger, D. D., Vose, J., Armitage, J. O.,

Gascoyne, R. D., Connors, J. M., Campo, E., Montserrat, E., Bosch, F., Smeland, E. B., Kvaloy, S., Holte, H., Delabie, J., Fisher, R. I., Grogan, T. M., Miller, T. P., Wilson, W. H., Jaffe, E. S. and Staudt, L. M. 2007, Blood, 109(11), 4599-4606.

11. Hunter, T. and Pines, J. 1994, Cell, 79(4), 573-582.
12. Sherr, C. J. 1996, Science, 274(5293), 1672-1677.
13. Sherr, C. J. and McCormick, F. 2002, Cancer Cell, 2(2), 103-112.
14. Hernandez, L., Bea, S., Pinyol, M., Ott, G., Katzenberger, T., Rosenwald, A., Bosch, F., Lopez-Guillermo, A., Delabie, J., Colomer, D., Montserrat, E. and Campo, E. 2005, Cancer Res., 65(6), 2199-2206.
15. Pinyol, M., Bea, S., Pla, L., Ribrag, V., Bosq, J., Rosenwald, A., Campo, E. and Jares, P. 2007, Blood, 109(12), 5422-5429.
16. Bea, S., Tort, F., Pinyol, M., Puig, X., Hernandez, L., Hernandez, S., Fernandez, P. L., van Lohuizen, M., Colomer, D. and Campo, E. 2001, Cancer Res., 61(6), 2409-2412.
17. Dreyling, M. H., Bullinger, L., Ott, G., Stilgenbauer, S., Muller-Hermelink, H. K., Bentz, M., Hiddemann, W. and Dohner, H. 1997, Cancer Res., 57(20), 4608-4614.
18. Gronbaek, K., Nedergaard, T., Andersen, M. K., thor Straten, P., Guldberg, P., Moller, P., Zeuthen, J., Ebbe Hansen, N., Hou-Jensen, K. and Ralfkiaer, E. 1998, Leukemia, 12(8), 1266-1271.
19. Jacobs, J. J., Kieboom, K., Marino, S., DePinho, R. A. and van Lohuizen, M. 1999, Nature, 397(6715), 164-168.
20. Lai, R., Rassidakis, G. Z., Medeiros, L. J., Leventaki, V., Keating, M. and McDonnell, T. J. 2003, J. Pathol., 199(1), 84-89.
21. Pinyol, M., Hernandez, L., Cazorla, M., Balbin, M., Jares, P., Fernandez, P. L., Montserrat, E., Cardesa, A., Lopez-Otin, C. and Campo, E. 1997, Blood, 89(1), 272-280.
22. Meissner, B., Kridel, R., Lim, R. S., Rogic, S., Tse, K., Scott, D. W., Moore, R., Mungall, A. J., Marra, M. A., Connors, J. M., Steidl, C. and Gascoyne, R. D. 2013, Blood, 121(16), 3161-3164.
23. Navarro, A., Clot, G., Prieto, M., Royo, C., Vegliante, M. C., Amador, V., Hartmann, E., Salaverria, I., Bea, S., Martin-Subero, J. I., Rosenwald, A., Ott, G., Wiestner, A., Wilson, W. H., Campo, E. and Hernandez, L. 2013, Clin. Cancer Res., 19(12), 3121-3129.
24. Navarro, A., Clot, G., Royo, C., Jares, P., Hadzidimitriou, A., Agathangelidis, A., Bikos, V., Darzentas, N., Papadaki, T., Salaverria, I., Pinyol, M., Puig, X., Palomero, J., Vegliante, M. C., Amador, V., Martinez-Trillos, A., Stefancikova, L., Wiestner, A., Wilson, W., Pott, C., Calasanz, M. J., Trim, N., Erber, W., Sander, B., Ott, G., Rosenwald, A., Colomer, D., Gine, E., Siebert, R., Lopez-Guillermo, A., Stamatopoulos, K., Bea, S. and Campo, E. 2012, Cancer Res., 72(20), 5307-5316.
25. Vegliante, M. C., Palomero, J., Perez-Galan, P., Roue, G., Castellano, G., Navarro, A., Clot, G., Moros, A., Suarez-Cisneros, H., Bea, S., Hernandez, L., Enjuanes, A., Jares, P., Villamor, N., Colomer, D., Martin-Subero, J. I., Campo, E. and Amador, V. 2013, Blood, 121(12), 2175-2185.
26. Kridel, R., Meissner, B., Rogic, S., Boyle, M., Telenius, A., Woolcock, B., Gunawardana, J., Jenkins, C., Cochrane, C., Ben-Neriah, S., Tan, K., Morin, R. D., Opat, S., Sehn, L. H., Connors, J. M., Marra, M. A., Weng, A. P., Steidl, C. and Gascoyne, R. D. 2012, Blood, 119(9), 1963-1971.
27. Shiloh, Y. 2003, Cell Cycle, 2(2), 116-117.
28. Shiloh, Y. 2003, Nat. Rev. Cancer, 3(3), 155-168.
29. Kastan, M. B. and Lim, D. S. 2000, Nat. Rev. Mol. Cell Biol., 1(3), 179-186.
30. Kastan, M. B. and Lim, D. S., Kim, S. T., Xu, B. and Canman, C. 2000, Cold Spring Harb. Symp. Quant. Biol., 65, 521-526.
31. Bowman, T., Garcia, R., Turkson, J. and Jove, R. 2000, Oncogene, 19(21), 2474-2488.
32. Catlett-Falcone, R., Dalton, W. S. and Jove, R. 1999, Curr. Opin. Oncol., 11(6), 490-496.
33. Garcia, R. and Jove, R. 1998, J. Biomed. Sci., 5(2), 79-85.
34. Quintas-Cardama, A., Vaddi, K., Liu, P., Manshouri, T., Li, J., Scherle, P. A., Caulder, E., Wen, X., Li, Y., Waeltz, P., Rupar, M., Burn, T., Lo, Y., Kelley, J., Covington, M.,

Shepard, S., Rodgers, J. D., Haley, P., Kantarjian, H., Fridman, J. S. and Verstovsek, S. 2010, Blood, 115(15), 3109-3117.
35. Turkson, J. and Jove, R. 2000, Oncogene, 19(56), 6613-6626.
36. Verstovsek, S., Kantarjian, H., Mesa, R. A., Pardanani, A. D., Cortes-Franco, J., Thomas, D. A., Estrov, Z., Fridman, J. S., Bradley, E. C., Erickson-Viitanen, S., Vaddi, K., Levy, R. and Tefferi, A. 2010, N. Engl. J. Med., 363(12), 1117-1127.
37. Verstovsek, S., Mesa, R. A., Gotlib, J., Levy, R. S., Gupta, V., DiPersio, J. F., Catalano, J. V., Deininger, M., Miller, C., Silver, R. T., Talpaz, M., Winton, E. F., Harvey, J. H., Arcasoy Jr., M. O., Hexner, E., Lyons, R. M., Paquette, R., Raza, A., Vaddi, K., Erickson-Viitanen, S., Koumenis, I. L., Sun, W., Sandor, V. and Kantarjian, H. M. 2012, N. Engl. J. Med., 366(9), 799-807.
38. Benkhart, E. M., Siedlar, M., Wedel, A., Werner, T. and Ziegler-Heitbrock, H. W. 2000, J. Immunol., 165(3), 1612-1617.
39. Darnell Jr., J. E. 1997, Science, 277(5332), 1630-1635.
40. Grad, J. M., Zeng, X. R. and Boise, L. H. 2000, Curr. Opin. Oncol., 12(6), 543-549.
41. Sinibaldi, D., Wharton, W., Turkson, J., Bowman, T., Pledger, W. J. and Jove, R. 2000, Oncogene, 19(48), 5419-5427.
42. Jares, P., Colomer, D. and Campo, E. 2012, J. Clin. Invest., 122(10), 3416-3423.
43. Zhang, L., Yang, J., Qian, J., Li, H., Romaguera, J. E., Kwak, L. W., Wang, M. and Yi, Q. 2012, Blood, 120(18), 3783-3792.
44. Mohamed, A. J., Yu, L., Backesjo, C. M., Vargas, L., Faryal, R., Aints, A., Christensson, B., Berglof, A., Vihinen, M., Nore, B. F. and Smith, C. I. 2009, Immunol. Rev., 228(1), 58-73.
45. Reeder, C. B. and Ansell, S. M. 2011, Blood, 117(5), 1453-1462.
46. Woyach, J. A., Johnson, A. J. and Byrd, J. C. 2012, Blood, 120(6), 1175-1184.
47. Fais, F., Ghiotto, F., Hashimoto, S., Sellars, B., Valetto, A., Allen, S. L., Schulman, P., Vinciguerra, V. P., Rai, K., Rassenti, L. Z., Kipps, T. J., Dighiero, G., Schroeder, H. W., Ferrarini Jr., M. and Chiorazzi, N. 1998, J. Clin. Invest., 102(8), 1515-1525.
48. Farinha, P. and Gascoyne, R. D. 2005, J. Clin. Oncol., 23(26), 6370-6378.
49. Seiffert, M., Dietrich, S., Jethwa, A., Glimm, H., Lichter, P. and Zenz, T. 2012, Leuk. Lymphoma, 53(6), 1023-1031.
50. Dal Col, J., Zancai, P., Terrin, L., Guidoboni, M., Ponzoni, M., Pavan, A., Spina, M., Bergamin, S., Rizzo, S., Tirelli, U., De Rossi, A., Doglioni, C. and Dolcetti, R. 2008, Blood, 111(10), 5142-5151.
51. Rizzatti, E. G., Falcao, R. P., Panepucci, R. A., Proto-Siqueira, R., Anselmo-Lima, W. T., Okamoto, O. K. and Zago, M. A. 2005, Br. J. Haematol., 130(4), 516-526.
52. Rudelius, M., Pittaluga, S., Nishizuka, S., Pham, T. H., Fend, F., Jaffe, E. S., Quintanilla-Martinez, L. and Raffeld, M. 2006, Blood, 108(5), 1668-1676.
53. Sarbassov, D. D., Guertin, D. A., Ali, S. M. and Sabatini, D. M. 2005, Science, 307(5712), 1098-1101.
54. Davies, M. A. 2011, J. Clin. Oncol., 29(35), 4715-4717.
55. Guertin, D. A. and Sabatini, D. M. 2007, Cancer Cell, 12(1), 9-22.
56. Smith, S. M. 2012, In: Best Practice & Research Clinical Haematology, J. Friedberg (Ed.), Vol. 25, pp. 175-183.
57. Seto, M. 2013, Blood, 121(8), 1249-1250.
58. Zeng, W., Fu, K., Quintanilla-Fend, L., Lim, M., Ondrejka, S. and Hsi, E. D. 2012, Am. J. Surg. Pathol., 36(2), 214-219.
59. Fu, K., Weisenburger, D. D., Greiner, T. C., Dave, S., Wright, G., Rosenwald, A., Chiorazzi, M., Iqbal, J., Gesk, S., Siebert, R., De Jong, D., Jaffe, E. S., Wilson, W. H., Delabie, J., Ott, G., Dave, B. J., Sanger, W. G., Smith, L. M., Rimsza, L., Braziel, R. M., Muller-Hermelink, H. K., Campo, E., Gascoyne, R. D., Staudt, L. M., Chan, W. C. and Lymphoma/Leukemia Molecular Profiling Project. 2005, Blood, 106(13), 4315-4321.
60. Gesk, S., Klapper, W., Martin-Subero, J. I., Nagel, I., Harder, L., Fu, K., Bernd, H. W., Weisenburger, D. D., Parwaresch, R. and Siebert, R. 2006, Blood, 108(3), 1109-1110.
61. Herens, C., Lambert, F., Quintanilla-Martinez, L., Bisig, B., Deusings, C. and de Leval, L. 2008, Blood, 111(3), 1745-1746.

62. Mozos, A., Royo, C., Hartmann, E., De Jong, D., Baro, C., Valera, A., Fu, K., Weisenburger, D. D., Delabie, J., Chuang, S. S., Jaffe, E. S., Ruiz-Marcellan, C., Dave, S., Rimsza, L., Braziel, R., Gascoyne, R. D., Sole, F., Lopez-Guillermo, A., Colomer, D., Staudt, L. M., Rosenwald, A., Ott, G., Jares, P. and Campo, E. 2009, Haematologica, 94(11), 1555-1562.
63. Ferrer, A., Salaverria, I., Bosch, F., Villamor, N., Rozman, M., Bea, S., Gine, E., Lopez-Guillermo, A., Campo, E. and Montserrat, E. 2007, Cancer, 109(12), 2473-2480.
64. Eve, H. E., Furtado, M. V., Hamon, M. D. and Rule, S. A. 2009, J. Clin. Oncol., 27(32), e189-191.
65. Martin, P., Chadburn, A., Christos, P., Weil, K., Furman, R. R., Ruan, J., Elstrom, R., Niesvizky, R., Ely, S., Diliberto, M., Melnick, A., Knowles, D. M., Chen-Kiang, S., Coleman, M. and Leonard, J. P. 2009, J. Clin. Oncol., 27(8), 1209-1213.
66. Del Giudice, I., Messina, M., Chiaretti, S., Santangelo, S., Tavolaro, S., De Propris, M. S., Nanni, M., Pescarmona, E., Mancini, F., Pulsoni, A., Martelli, M., Di Rocco, A., Finolezzi, E., Paoloni, F., Mauro, F. R., Cuneo, A., Guarini, A. and Foa, R. 2012, Br. J. Haematol., 156(5), 601-611.
67. Fernandez, V., Salamero, O., Espinet, B., Sole, F., Royo, C., Navarro, A., Camacho, F., Bea, S., Hartmann, E., Amador, V., Hernandez, L., Agostinelli, C., Sargent, R. L., Rozman, M., Aymerich, M., Colomer, D., Villamor, N., Swerdlow, S. H., Pileri, S. A., Bosch, F., Piris, M. A., Montserrat, E., Ott, G., Rosenwald, A., Lopez-Guillermo, A., Jares, P., Serrano, S. and Campo, E. 2010, Cancer Res., 70(4), 1408-1418.
68. Leitch, H. A., Gascoyne, R. D., Chhanabhai, M., Voss, N. J., Klasa, R. and Connors, J. M. 2003, Ann. Oncol., 14(10), 1555-1561.
69. Majlis, A., Pugh, W. C., Rodriguez, M. A., Benedict, W. F. and Cabanillas, F. 1997, J. Clin. Oncol., 15(4), 1664-1671.
70. Nygren, L., Baumgartner Wennerholm, S., Klimkowska, M., Christensson, B., Kimby, E. and Sander, B. 2012, Blood, 119(18), 4215-4223.
71. Ondrejka, S. L., Lai, R., Smith, S. D. and Hsi, E. D. 2011, Haematologica, 96(8), 1121-1127.
72. Orchard, J., Garand, R., Davis, Z., Babbage, G., Sahota, S., Matutes, E., Catovsky, D., Thomas, P. W., Avet-Loiseau, H. and Oscier, D. 2003, Blood, 101(12), 4975-4981.
73. Royo, C., Navarro, A., Clot, G., Salaverria, I., Gine, E., Jares, P., Colomer, D., Wiestner, A., Wilson, W. H., Vegliante, M. C., Fernandez, V., Hartmann, E. M., Trim, N., Erber, W. N., Swerdlow, S. H., Klapper, W., Dyer, M. J., Vargas-Pabon, M., Ott, G., Rosenwald, A., Siebert, R., Lopez-Guillermo, A., Campo, E. and Bea, S. 2012, Leukemia, 26(8), 1895-1898.
74. Rule, S. A., Poplar, S., Evans, P. A., O'Connor, S. J. and Owen, R. G. 2011, J. Clin. Oncol., 29(15), e437-439.
75. Tiemann, M., Schrader, C., Klapper, W., Dreyling, M. H., Campo, E., Norton, A., Berger, F., Kluin, P., Ott, G., Pileri, S., Pedrinis, E., Feller, A. C., Merz, H., Janssen, D., Hansmann, M. L., Krieken, H., Moller, P., Stein, H., Unterhalt, M., Hiddemann, W., Parwaresch, R. and European Mantle Cell Lymphoma Network. 2005, Br. J. Haematol., 131(1), 29-38.
76. Hoster, E., Dreyling, M., Klapper, W., Gisselbrecht, C., van Hoof, A., Kluin-Nelemans, H. C., Pfreundschuh, M., Reiser, M., Metzner, B., Einsele, H., Peter, N., Jung, W., Wormann, B., Ludwig, W. D., Duhrsen, U., Eimermacher, H., Wandt, H., Hasford, J., Hiddemann, W., Unterhalt, M., German Low Grade Lymphoma Study Group (GLSG) and the European Mantle Cell Lymphoma Network. 2008, Blood, 111(2), 558-565.
77. Budde, L. E., Guthrie, K. A., Till, B. G., Press, O. W., Chauncey, T. R., Pagel, J. M., Petersdorf, S. H., Bensinger, W. I., Holmberg, L. A., Shustov, A. R., Green, D. J., Maloney, D. G. and Gopal, A. K. 2011, J. Clin. Oncol., 29(22), 3023-3029.
78. Chang, J. E., Peterson, C., Choi, S., Eickhoff, J. C., Kim, K., Yang, D. T., Gilbert, L. A., Rogers, E. S., Werndli, J. E., Huie, M. S., McFarland, T. A., Volk, M., Blank, J., Callander, N. S., Longo, W. L. and Kahl, B. S. 2011, Br. J. Haematol., 155(2), 190-197.

79. Damon, L. E., Johnson, J. L., Niedzwiecki, D., Cheson, B. D., Hurd, D. D., Bartlett, N. L., Lacasce, A. S., Blum, K. A., Byrd, J. C., Kelly, M., Stock, W., Linker, C. A. and Canellos, G. P. 2009, J. Clin. Oncol., 27(36), 6101-6108.
80. Geisler, C. H., Kolstad, A., Laurell, A., Raty, R., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Boesen, A. M., Nilsson-Ehle, H., Kuittinen, O., Lauritzsen, G. F., Ralfkiaer, E., Ehinger, M., Sundstrom, C., Delabie, J., Karjalainen-Lindsberg, M. L., Brown, P., Elonen, E. and Nordic Lymphoma Group. 2010, Blood, 115(8), 1530-1533.
81. Merli, F., Luminari, S., Ilariucci, F., Petrini, M., Visco, C., Ambrosetti, A., Stelitano, C., Caracciolo, F., Di Renzo, N., Angrilli, F., Carella, A. M., Capodanno, I., Barbolini, E., Galimberti, S. and Federico, M. 2012, Br. J. Haematol., 156(3), 346-353.
82. Peterlin, P., Leux, C., Gastinne, T., Roland, V., Mahe, B., Dubruille, V., Delaunay, J., Chevallier, P., Guillaume, T., Blin, N., Ayari, S., Clavert, A., Mohty, M., Dousset, C., Milpied, N., Harousseau, J. L., Moreau, P., Wuilleme, S., Moreau, A. and Le Gouill, S. 2012, Transplantation, 94(3), 295-301.
83. Raty, R., Honkanen, T., Jantunen, E., Jyrkkio, S., Karjalainen-Lindsberg, M. L., Kuittinen, O., Lehto, M., Mikkola, M., Poikonen, E., Rauhala, A., Rimpilainen, J., Rasanen, A., Siitonen, S., Suominen, M., Vapaatalo, M. and Elonen, E. 2012, Leuk. Lymphoma, 53(10), 1920-1928.
84. Romaguera, J. E., Fayad, L. E., Feng, L., Hartig, K., Weaver, P., Rodriguez, M. A., Hagemeister, F. B., Pro, B., McLaughlin, P., Younes, A., Samaniego, F., Goy, A., Cabanillas, F., Kantarjian, H., Kwak, L. and Wang, M. 2010, Br. J. Haematol., 150(2), 200-208.
85. Ruan, J., Martin, P., Furman, R. R., Lee, S. M., Cheung, K., Vose, J. M., Lacasce, A., Morrison, J., Elstrom, R., Ely, S., Chadburn, A., Cesarman, E., Coleman, M. and Leonard, J. P. 2011, J. Clin. Oncol., 29(6), 690-697.
86. Salek, D., Vesela, P., Boudova, L., Janikova, A., Klener, P., Vokurka, S., Jankovska, M., Pytlik, R., Belada, D., Pirnos, J., Moulis, M., Kodet, R., Michal, M., Janousova, E., Muzik, J., Mayer, J. and Trneny, M. 2014, Leuk. Lymphoma, 55(4), 802-810.
87. Smith, S. D., Hsi, E., Bolwell, B., Pohlman, B., Dean, R., Effinger, M., Maggiotto, A. and Sweetenham, J. 2010, Am. J. Hematol., 85(6), 454-456.
88. Spurgeon, S. E., Pindyck, T., Okada, C., Chen, Y., Chen, Z., Mater, E., Abbi, K. and Epner, E. M. 2011, Leuk. Lymphoma, 52(8), 1488-1494.
89. Todorovic, M., Balint, B., Andjelic, B., Stanisavljevic, D., Kurtovic, N. K., Radisavljevic, Z. and Mihaljevic, B. 2012, Med. Oncol., 29(3), 2212-2219.
90. van de Schans, S. A., Janssen-Heijnen, M. L., Nijziel, M. R., Steyerberg, E. W. and van Spronsen, D. J. 2010, Haematologica, 95(9), 1503-1509.
91. Ying, Z. T., Zheng, W., Wang, X. P., Xie, Y., Tu, M. F., Lin, N. J., Ping, L. Y., Liu, W. P., Deng, L. J., Zhang, C., Zhu, J. and Song, Y. Q. 2012, Chin. J. Cancer, 31(7), 348-353.
92. Hoster, E., Klapper, W., Hermine, O., Kluin-Nelemans, H. C., Walewski, J., van Hoof, A., Trneny, M., Geisler, C. H., Di Raimondo, F., Szymczyk, M., Stilgenbauer, S., Thieblemont, C., Hallek, M., Forstpointner, R., Pott, C., Ribrag, V., Doorduijn, J., Hiddemann, W., Dreyling, M. H. and Unterhalt, M. 2014, J. Clin. Oncol., 32(13), 1338-1346.
93. Eve, H. E., Gambell, J., Smith, P., Qian, W. and Rule, S. A. 2009, Leuk. Lymphoma, 50(10), 1709-1711.
94. Mato, A. 2010, J. Clin. Oncol., 28(Suppl.), Abstract 8092.
95. Schaffel, R., Hedvat, C. V., Teruya-Feldstein, J., Persky, D., Maragulia, J., Lin, D., Portlock, C. S., Moskowitz, C. H. and Zelenetz, A. D. 2010, Ann. Oncol., 21(1), 133-139.
96. van 't Veer, M. B., de Jong, D., MacKenzie, M., Kluin-Nelemans, H. C., van Oers, M. H., Zijlstra, J., Hagenbeek, A. and van Putten, W. L. 2009, Br. J. Haematol., 144(4), 524-530.
97. Herrmann, A., Hoster, E., Zwingers, T., Brittinger, G., Engelhard, M., Meusers, P., Reiser, M., Forstpointner, R., Metzner, B., Peter, N., Wormann, B., Trumper, L.,

Pfreundschuh, M., Einsele, H., Hiddemann, W., Unterhalt, M. and Dreyling, M. 2009, J. Clin. Oncol., 27(4), 511-518.

98. de Guibert, S., Jaccard, A., Bernard, M., Turlure, P., Bordessoule, D. and Lamy, T. 2006, Haematologica, 91(3), 425-426.
99. Khouri, I. F., Romaguera, J., Kantarjian, H., Palmer, J. L., Pugh, W. C., Korbling, M., Hagemeister, F., Samuels, B., Rodriguez, A., Giralt, S., Younes, A., Przepiorka, D., Claxton, D., Cabanillas, F. and Champlin, R. 1998, J. Clin. Oncol., 16(12), 3803-3809.
100. Lefrere, F., Delmer, A., Levy, V., Delarue, R., Varet, B. and Hermine, O. 2004, Haematologica, 89(10), 1275-1276.
101. Romaguera, J. E., Fayad, L., Rodriguez, M. A., Broglio, K. R., Hagemeister, F. B., Pro, B., McLaughlin, P., Younes, A., Samaniego, F., Goy, A., Sarris, A. H., Dang, N. H., Wang, M., Beasley, V., Medeiros, L. J., Katz, R. L., Gagneja, H., Samuels, B. I., Smith, T. L. and Cabanillas, F. F. 2005, J. Clin. Oncol., 23(28), 7013-7023.
102. Romaguera, J. E., Khouri, I. F., Kantarjian, H. M., Hagemeister, F. B., Rodriguez, M. A., McLaughlin, P., Sarris, A. H., Younes, A., Rodriguez, J. and Cabanillas, F. 2000, Leuk. Lymphoma, 39(1-2), 77-85.
103. Ganti, A. K., Bierman, P. J., Lynch, J. C., Bociek, R. G., Vose, J. M. and Armitage, J. O. 2005, Ann. Oncol., 16(4), 618-624.
104. Geisler, C. H., Kolstad, A., Laurell, A., Andersen, N. S., Pedersen, L. B., Jerkeman, M., Eriksson, M., Nordstrom, M., Kimby, E., Boesen, A. M., Kuittinen, O., Lauritzsen, G. F., Nilsson-Ehle, H., Ralfkiaer, E., Akerman, M., Ehinger, M., Sundstrom, C., Langholm, R., Delabie, J., Karjalainen-Lindsberg, M. L., Brown, P. and Elonen, E. for the Nordic Lymphoma Group. 2008, Blood, 112(7), 2687-2693.
105. Le Gouill, S., Callanan, M., Macintyre, E., Delfau-Larue, M. H., Bodet-Milin, C., Meignan, M., Moreau, A., Travers-Glehen, A., Béné, M., Haouin, C., Gressin, R., Casasnovas, R., Ribrag, V., Damaj, G., Gyan, E., Oberic, L., Bouabdallah, K., Thieblemont, C. and Hermine, O. 2012, In: Proceedings of the 54th ASH Annual Meeting and Exposition; Dec 8-11; Atlanta, GA: Blood, 120, Abstract 152.
106. Hermine, O., Hoster, E., Walewski. J., Ribrag, V., Brousse, N., Thieblemont, C., Bouabdallah, R., Stilgenbauer, S., Feugier, P., Forstpointner, R., Haioun, C., Kneba, M., Hänel, M., Casasnovas, R., Finke, J., Hallek, M., Wandt, H., Bosly, A., Klapper, W., Gisselbrecht, C., Coiffier, B., Hiddemann, W., Unterhalt, M. and Dreyling, M. H. 2010, In: Proceedings of the 52nd ASH Annual Meeting and Exposition; Dec 4-7; Orlando, FL: Blood, 116, Abstract 110.
107. LaCasce, A., Vandergrift, J. L., Rodriguez, M. A., Crosby, A. L., Lepisto, E. M., Czuczman, M. S., Nademanee A. P., Blayney, D. W., Gordon, L. I., Millenson, M., Vanderplas, A., Abel, G. A., Zelenetz, A. D. and Friedberg, J. W. 2009, In: Proceedings of the 51st ASH Annual Meeting and Exposition; Dec 5-8; New Orleans, LA: Blood, 114, Abstract 403.
108. Pott, C., Hoster, E., Beldjord, K., Macintyre, E. A., Böttcher, S., Asnafi, V., Siebert, R., Plonquet, A., Callet-Bauchut, E., Ribrag, V., Klapper, W., Berger, F., Unterhalt, M., Kneba, M., Hiddemann, W., Dreyling, M. H., Hermine, O. and Delfau, M. 2010, In: Proceedings of the 52nd ASH Annual Meeting and Exposition; Dec 4-7; Orlando, FL: Blood, 116(21), Abstract 965.
109. Bernstein, S. H., Epner, E., Unger, J. M., Leblanc, M., Cebula, E., Burack, R., Rimsza, L., Miller, T. P. and Fisher, R. I. 2013, Ann. Oncol., 24(6), 1587-1593.
110. Hamadani, M., Saber, W., Ahn, K. W., Carreras, J., Cairo, M. S., Fenske, T. S., Gale, R. P., Gibson, J., Hale, G. A., Hari, P. N., Hsu, J. W., Inwards, D. J., Kamble, R. T., Klein, A., Maharaj, D., Marks, D. I., Rizzieri, D. A., Savani, B. N., Schouten, H. C., Waller, E. K., Wirk, B. and Lazarus, H. M. 2013, Biol. Blood Marrow Transplant., 19(4), 625-631.
111. Meusers, P., Engelhard, M., Bartels, H., Binder, T., Fulle, H. H., Gorg, K., Gunzer, U., Havemann, K., Kayser, W., König, E., König, H. J., Kuse, R., Löffler, H., Ludwig, W.-D., Mainzer, K., Martin, H., Pralle, H., Schoppe, W. D., Staiger, H. J., Theml, H., Zurborn, K. H., Zwingers, Th., Lennert, K., and Brittinger, G. 1989, Hematol. Oncol., 7(5), 365-380.

112. Rummel, M. J., Niederle, N., Maschmeyer, G., Banat, G. A., von Grunhagen, U., Losem, C., Kofahl-Krause, D., Heil, G., Welslau, M., Balser, C., Kaiser, U., Weidmann, E., Durk, H., Ballo, H., Stauch, M., Roller, F., Barth, J., Hoelzer, D., Hinke, A., Brugger, W. L. and Study Group Indolent Lymphomas (StiL). 2013, Lancet, 381(9873), 1203-1210.
113. Flinn, I. W., van der Jagt, R., Kahl, B. S., Wood, P., Hawkins, T. E., Macdonald, D., Hertzberg, M., Kwan, Y. L., Simpson, D., Craig, M., Kolibaba, K., Issa, S., Clementi, R., Hallman, D. M., Munteanu, M., Chen, L. and Burke, J. M. 2014, Blood, 123(19), 2944-2952.
114. Williams, M. E. 2013, Hematology Am. Soc. Hematol. Educ. Program, 2013, 568-574.
115. Kluin-Nelemans, H. C., Hoster, E., Hermine, O., Walewski, J., Trneny, M., Geisler, C. H., Stilgenbauer, S., Thieblemont, C., Vehling-Kaiser, U., Doorduijn, J. K., Coiffier, B., Forstpointner, R., Tilly, H., Kanz, L., Feugier, P., Szymczyk, M., Hallek, M., Kremers, S., Lepeu, G., Sanhes, L., Zijlstra, J. M., Bouabdallah, R., Lugtenburg, P. J., Macro, M., Pfreundschuh, M., Prochazka, V., Di Raimondo, F., Ribrag, V., Uppenkamp, M., Andre, M., Klapper, W., Hiddemann, W., Unterhalt, M. and Dreyling, M. H. 2012, N. Engl. J. Med., 367(6), 520-531.
116. Kenkre, V. P., Long, W. L., Eickhoff, J. C., Blank, J. H., McFarland, T. A., Bottner, W., Rezazedeh, H., Werndli, J. E., Bailey, H. H. and Kahl, B. S. 2011, Leuk. Lymphoma, 52(9), 1675-1680.
117. Fisher, R. I., Bernstein, S. H., Kahl, B. S., Djulbegovic, B., Robertson, M. J., de Vos, S., Epner, E., Krishnan, A., Leonard, J. P., Lonial, S., Stadtmauer, E. A., O'Connor, O. A., Shi, H., Boral, A. L. and Goy, A. 2006, J. Clin. Oncol., 24(30), 4867-4874.
118. Goy, A., Bernstein, S. H., Kahl, B. S., Djulbegovic, B., Robertson, M. J., de Vos, S., Epner, E., Krishnan, A., Leonard, J. P., Lonial, S., Nasta, S., O'Connor, O. A., Shi, H., Boral, A. L. and Fisher, R. I. 2009, Ann. Oncol., 20(3), 520-525.
119. Qian, Z., Zhang, L., Cai, Z., Sun, L., Wang, H., Yi, Q. and Wang, M. 2011, Leuk. Res., 35(3), 380-386.
120. Wu, L., Adams, M., Carter, T., Chen, R., Muller, G., Stirling, D., Schafer, P. and Bartlett, J. B. 2008, Clin. Cancer Res., 14(14), 4650-4657.
121. Zhang, L., Qian, Z., Cai, Z., Sun, L., Wang, H., Bartlett, J. B., Yi, Q. and Wang, M. 2009, Am. J. Hematol., 84(9), 553-559.
122. Habermann, T. M., Lossos, I. S., Justice, G., Vose, J. M., Wiernik, P. H., McBride, K., Wride, K., Ervin-Haynes, A., Takeshita, K., Pietronigro, D., Zeldis, J. B. and Tuscano, J. M. 2009, Br. J. Haematol., 145(3), 344-349.
123. Wiernik, P. H., Lossos, I. S., Tuscano, J. M., Justice, G., Vose, J. M., Cole, C. E., Lam, W., McBride, K., Wride, K., Pietronigro, D., Takeshita, K., Ervin-Haynes, A., Zeldis, J. B. and Habermann, T. M. 2008, J. Clin. Oncol., 26(30), 4952-4957.
124. Witzig, T. E., Vose, J. M., Zinzani, P. L., Reeder, C. B., Buckstein, R., Polikoff, J. A., Bouabdallah, R., Haioun, C., Tilly, H., Guo, P., Pietronigro, D., Ervin-Haynes, A. L. and Czuczman, M. S. 2011, Ann. Oncol., 22(7), 1622-1627.
125. Zinzani, P. L., Vose, J. M., Czuczman, M. S., Reeder, C., Haioun, C., Polikoff, J., Tilly, H., Pietronigro, D., Ervin-Haynes, A., Li, J. and Witzig, T. E. 2012, In: Proceedings of the 54th ASH Annual Meeting and Exposition; Dec 8-11; Atlanta, GA: Blood, Abstract 2738.
126. Goy, A., Sinha, R., Williams, M. E., Kalayoglu Besisik, S., Drach, J., Ramchandren, R., Zhang, L., Cicero, S., Fu, T. and Witzig, T. E. 2013, J. Clin. Oncol., 31(29), 3688-3695.
127. Bajpai, U. D., Zhang, K., Teutsch, M., Sen, R. and Wortis, H. H. 2000, J. Exp. Med., 191(10), 1735-1744.
128. Fluckiger, A. C., Li, Z., Kato, R. M., Wahl, M. I., Ochs, H. D., Longnecker, R., Kinet, J. P., Witte, O. N., Scharenberg, A. M. and Rawlings, D. J. 1998, EMBO J., 17(7), 1973-1985.
129. Jiang, A., Craxton, A., Kurosaki, T. and Clark, E. A. 1998, J. Exp. Med., 188(7), 1297-1306.
130. Petro, J. B., Rahman, S. M., Ballard, D. W. and Khan, W. N. 2000, J. Exp. Med., 191(10), 1745-1754.

131. Takata, M. and Kurosaki, T. 1996, J. Exp. Med., 184(1), 31-40.
132. Tomlinson, M. G., Woods, D. B., McMahon, M., Wahl, M. I., Witte, O. N., Kurosaki, T., Bolen, J. B. and Johnston, J. A. 2001, BMC Immunol., 2, 4.
133. Uckun, F. M., Waddick, K. G., Mahajan, S., Jun, X., Takata, M., Bolen, J. and Kurosaki, T. 1996, Science, 273(5278), 1096-1100.
134. Pan, Z., Scheerens, H., Li, S. J., Schultz, B. E., Sprengeler, P. A., Burrill, L. C., Mendonca, R. V., Sweeney, M. D., Scott, K. C., Grothaus, P. G., Jeffery, D. A., Spoerke, J. M., Honigberg, L. A., Young, P. R., Dalrymple, S. A. and Palmer, J. T. 2007, ChemMedChem., 2(1), 58-61.
135. Gilles A. Salles, Ajay K. Gopal, Peter Martin, Robert Marcus, Georg Hess, Pier Luigi Zinzani, Tahamtan Ahmadi, Sen Hong Zhuang and Ronald Levy. 2013, In: Proceedings of the 2013 ASCO Annual Meeting; May 31st – June 4th; Chicago, IL: JCO 2013, Vol. 31, No 15_suppl (May 20 Supplement), Abstract TPS8614.
136. Wang, M. L., Rule, S., Martin, P., Goy, A., Auer, R., Kahl, B. S., Jurczak, W., Advani, R. H., Romaguera, J. E., Williams, M. E., Barrientos, J. C., Chmielowska, E., Radford, J., Stilgenbauer, S., Dreyling, M., Jedrzejczak, W. W., Johnson, P., Spurgeon, S. E., Li, L., Zhang, L., Newberry, K., Ou, Z., Cheng, N., Fang, B., McGreivy, J., Clow, F., Buggy, J. J., Chang, B. Y., Beaupre, D. M., Kunkel, L. A. and Blum, K. A. 2013, N. Engl. J. Med., 369(6), 507-516.
137. Wilson, W. H., Gerecitano, J. F., Goy, A., de Vos, S., Kenkre, V. P., Barr, P. M., Blum, K. A., Shustov, A. R., Advani, R. H., Lih, J., Williams, M., Schmitz, R., Yang, Y., Pittaluga, S., Wright, G., Kunkel, L. A., McGreivy, J., Balasubramanian, S., Cheng, M., Moussa, D., Buggy, J. J. and Staudt, L. M. 2012, In: Proceedings of the 54th ASH Annual Meeting and Exposition; Dec 8-11; Atlanta, GA: Blood, Abstract 686.
138. Advani, R. H., Buggy, J. J., Sharman, J. P., Smith, S. M., Boyd, T. E., Grant, B., Kolibaba, K. S., Furman, R. R., Rodriguez, S., Chang, B. Y., Sukbuntherng, J., Izumi, R., Hamdy, A., Hedrick, E. and Fowler, N. H. 2013, J. Clin. Oncol., 31(1), 88-94.
139. Kahl, B. S., Spurgeon, S. E., Furman, R. R., Flinn, I. W., Coutre, S. E., Brown, J. R., Benson, D. M., Byrd, J. C., Peterman, S., Cho, Y., Yu, A., Godfrey, W. R. and Wagner-Johnston, N. D. 2014, Blood, 123(22), 3398-3405.
140. Patel, M. R., Kahl, B., Horwitz, S. H., Younes, A., Foss, F. M., Oki, Y., Sweeney, J., Allen, K., Faia, K., Kelly, P. F. and Flinn, I. 2013, In: Proceedings of the 2013 ASCO Annual Meeting; May 31st – June 4th; Chicago, IL: JCO 2013, Vol. 31, No 15_suppl (May 20 Supplement), Abstract 7070.
141. Leonard, J., Wagner-Johnston, N. D., Coutre, S. E., Flinn, I., Schreeder, M. T., Fowler, N. H., Sharman, J. P., Boccia, R. V., Barrientos, J. C., Rai, K. R., Boyd, T. E., Furman, R. R., Holes, L., Johnson, D. M., Kim, Y., Dansey, R. D., Godfrey, W. R. and De Vos, S. 2013, In: Proceedings of the 2013 ASCO Annual Meeting; May 31st – June 4th; Chicago, IL: JCO 2013, Vol. 31, No 15_suppl (May 20 Supplement), Abstract 8500.
142. Wagner-Johnston, N. D., De Vos, S., Leonard, J., Sharman, J. P., Schreeder, M. T., Boccia, R. V., Barrientos, J. C., Coutre, S. E., Flinn, I., Boyd, T. E., Holes, L., Johnson, D. M., Kim, Y., Dansey, R. D., Godfrey, W. R. and Fowler, N. H. 2013, In: Proceedings of the 2013 ASCO Annual Meeting; May 31st – June 4th; Chicago, IL: JCO 2013, Vol. 31, No 15_suppl (May 20 Supplement), Abstract 8501.
143. Ansell, S. M., Inwards, D. J., Rowland, K. M., Flynn Jr., P. J., Morton, R. F., Moore, D. F., Kaufmann Jr., S. H., Ghobrial, I., Kurtin, P. J., Maurer, M., Allmer, C. and Witzig, T. E. 2008, Cancer, 113(3), 508-514.
144. Hess, G., Herbrecht, R., Romaguera, J., Verhoef, G., Crump, M., Gisselbrecht, C., Laurell, A., Offner, F., Strahs, A., Berkenblit, A., Hanushevsky, O., Clancy, J., Hewes, B., Moore, L. and Coiffier, B. 2009, J. Clin. Oncol., 27(23), 3822-3829.
145. Witzig, T. E., Geyer, S. M., Ghobrial, I., Inwards, D. J., Fonseca, R., Kurtin, P., Ansell, S. M., Luyun, R., Flynn, P. J., Morton, R. F., Dakhil, S. R., Gross, H. and Kaufmann, S. H. 2005, J. Clin. Oncol., 23(23), 5347-5356.

146. Renner, C., Zinzani, P. L., Gressin, R., Klingbiel, D., Dietrich, P. Y., Hitz, F., Bargetzi, M., Mingrone, W., Martinelli, G., Trojan, A., Bouabdallah, K., Lohri, A., Gyan, E., Biaggi, C., Cogliatti, S., Bertoni, F., Ghielmini, M., Brauchli, P. and Ketterer, N. 2012, Haematologica, 97(7), 1085-1091.
147. Wang, M., Popplewell, L., Collins Jr., R. H., Winter, J. N., Goy, A., Robeva, A., Pirotta, N., Fan, J., Klimovsky, J. and O'Connor, O. A. 2012, In: Proceedings of the 54th ASH Annual Meeting and Exposition; Dec 8-11; Atlanta, GA: Blood, Abstract 2751.
148. Witzig, T. E., Reeder, C. B., LaPlant, B. R., Gupta, M., Johnston, P. B., Micallef, I. N., Porrata, L. F., Ansell, S. M., Colgan, J. P., Jacobsen, E. D., Ghobrial, I. M. and Habermann, T. M. 2011, Leukemia, 25(2), 341-347.
149. Ansell, S. M., Tang, H., Kurtin, P. J., Koenig, P. A., Inwards, D. J., Shah, K., Ziesmer, S. C., Feldman, A. L., Rao, R., Gupta, M., Erlichman, C. and Witzig, T. E. 2011, Lancet Oncol., 12(4), 361-368.
150. Leonard, J. P., LaCasce, A. S., Smith, M. R., Noy, A., Chirieac, L. R., Rodig, S. J., Yu, J. Q., Vallabhajosula, S., Schoder, H., English, P., Neuberg, D. S., Martin, P., Millenson, M. M., Ely, S. A., Courtney, R., Shaik, N., Wilner, K. D., Randolph, S., van den Abbeele, A. D., Chen-Kiang, S. Y., Yap, J. T. and Shapiro, G. I. 2012, Blood, 119(20), 4597-4607.
151. Infante, J. R., Shapiro, G., Witteveen, P., Gerecitano, J. F., Ribrag, V., Chugh, R., Issa, I., Chakraborty, A., Matano, A., Zhao, X., Parasuraman, S. and Cassier, P. 2014, In: Proceedings of the 2013 ASCO Annual Meeting; May 30th – June 3rd; Chicago, IL: JCO 2014, Vol. 32, No 15_suppl (May 20 Supplement), Abstract 2528.
152. Paoluzzi, L., Scotto, L., Marchi, E., Zain, J., Seshan, V. E. and O'Connor, O. A. 2010, Clin. Cancer Res., 16(2), 554-565.
153. Kirschbaum, M., Frankel, P., Popplewell, L., Zain, J., Delioukina, M., Pullarkat, V., Matsuoka, D., Pulone, B., Rotter, A. J., Espinoza-Delgado, I., Nademanee, A., Forman, S. J., Gandara, D. and Newman, E. 2011, J. Clin. Oncol., 29(9), 1198-1203.
154. Evens, A. M., Vose, J. M., Harb, W. A., Gordon, L. I., Langdon, R., Grant, B., Sprague, J., Plasencia, C., Sirisawad, M., Yue, J., Luan, Y., Siek, A., Zhou, L., Balasubramanian, S. and Bartlett, N. L. 2012, In: Proceedings of the 54th ASH Annual Meeting and Exposition; Dec 8-11; Atlanta, GA: Blood, 120, Abstract 55.
155. Dasmahapatra, G., Lembersky, D., Son, M. P., Attkisson, E., Dent, P., Fisher, R. I., Friedberg, J. W. and Grant, S. 2011, Mol. Cancer Ther., 10(9), 1686-1697.
156. O'Connor, O. A., Marchi, E., Zullo, K., Scotto, L., Amengual, J. E., Fuligni, F., Zinzani, P. L., Pileri, S. A. and Piccaluga, P. P. 2013, In: Proceedings of the 55th ASH Annual Meeting and Exposition; Dec 7-10; New Orleans, LA: Blood, 122, Abstract 646.
157. Goy, A., Hernandez-Ilzaliturri, F. J., Kahl, B., Ford, P., Protomastro, E. and Berger, M. 2014, Leuk. Lymphoma, 55(12), 2761-8158.
158. Wilson, W. H., O'Connor, O. A., Czuczman, M. S., LaCasce, A. S., Gerecitano, J. F., Leonard, J. P., Tulpule, A., Dunleavy, K., Xiong, H., Chiu, Y. L, Cui, Y., Busman, T., Elmore, S. W., Rosenberg, S. H., Krivoshik, A. P., Enschede, S. H. and Humerickhouse, R. A. 2010, Lancet Oncol., 11(12), 1149-1159.