Review Article

Venetoclax for the treatment of mantle cell lymphoma

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Abstract: While the last decade has seen an explosion in improved therapies for mantle cell lymphoma (MCL), the outlook for patients with relapsed or refractory MCL (R/R MCL) remains poor, especially for those who are older with comorbidities or harbour dysfunction in the TP53 pathway. MCL is one of the B cell malignancies in which there is a high frequency of BCL2 overexpression, and the selective BCL2 inhibitor venetoclax has shown particular promise in the treatment of patients with R/R MCL. As a single agent, the drug is associated with a close to 80% response rate in early phase studies. However, secondary progression due to the development of resistance remains a limiting factor in the usefulness of this agent. Preclinical data have driven the push to combine venetoclax with other novel agents, particularly the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib. This therapeutic combination has increased the rate of complete remissions to over 60% and provides a promising route to meaningful long-term disease control with non-chemotherapy-based treatment.

Keywords: Venetoclax (ABT-199); mantle cell lymphoma (MCL); BCL2; BH3 mimetics

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Introduction

Mantle cell lymphoma (MCL) is an uncommon subtype of B-cell non-Hodgkin lymphoma (NHL) with an incidence of approximately 0.5 cases per 100,000 person-years in the United States and Europe (1). While up to 30% of patients with MCL may have an initially indolent clinical course (2,3), in the majority, MCL displays more aggressive behaviour and often requires treatment soon after diagnosis. Until recently, patients with relapsed or refractory (R/R) disease after chemoimmunotherapy had limited treatment options, and MCL to this day bears one of the poorest prognoses of all lymphomas (4-6).

As a key regulator of apoptosis, the pro-survival protein BCL2 was first implicated in the pathogenesis of follicular lymphoma (FL) in 1984 (7,8). Since then, BCL2 has been recognised to be involved in many other B-cell NHLs, including chronic lymphocytic leukaemia (CLL) (9) and MCL (10), and to be a promoter not only of cancer development (11), but also of resistance to chemotherapy (12). The identification of apoptotic avoidance as a hallmark of cancer (13) sparked the recognition that therapies designed to restore the capacity of cancer cells to undergo apoptosis could be effective in the treatment of malignancies that depend on the derangement of the normal apoptotic machinery for their survival.

BH3 mimetics are small molecules that mimic the action of naturally-occurring BH3-only proteins, the endogenous antagonists of BCL2 and other pro-survival family members. Venetoclax (ABT-199) is a BH3 mimetic that directly and specifically inhibits BCL2 (14,15), restoring the ability of cancer cells with BCL2 overexpression to

undergo apoptosis. Venetoclax has shown promising results in clinical trials, particularly when used against CLL and MCL (15,16). In this review, we discuss the pre-clinical and early-phase clinical data supporting the use of venetoclax in MCL and review the next steps in the clinical application of this novel targeted therapy to improve outcomes for MCL patients.

A primer on apoptosis and the history of BCL2 targeted therapy

In multicellular organisms, programmed cell death is essential for the elimination of unwanted, infected, or otherwise damaged cells (17,18). The major mode of programmed cell death is apoptosis, a highly regulated process characterised by shrinkage of the nucleus and cytoplasm, and encasement of cellular contents within apoptotic bodies surrounded by plasma membrane that are ultimately cleared by nearby phagocytes (19). Apoptosis is terminally mediated by a family of proteases called caspases that have a cysteine at their active site and cleave target proteins at specific aspartic acids (20). Apoptotic signals activate initiator caspases, which then cleave and activate executioner caspases, which in turn cleave specific target proteins, such as nuclear lamins, leading to cellular destruction.

Initiator caspases are activated by one of two independent but convergent pathways: (I) the death receptor-mediated pathway (also called the extrinsic pathway); or (II) the mitochondrial pathway (also called the intrinsic pathway) (21,22). The death receptor-mediated pathway is activated when death receptor ligands from the tumour necrosis factor (TNF) family, such as FAS ligand and TNF, bind to their cognate death receptors on the plasma membrane, resulting in activation of the initiator caspase called caspase 8 (23).

In haematological malignancies, such as MCL, however, it is the mitochondrial pathway that is more commonly perturbed. The mitochondrial pathway is regulated by members of the BCL2 family of proteins, which can be divided into three functionally and structurally distinct groups: (I) BH3-only proteins (BIM, PUMA, tBID, BAD, and NOXA), which initiate apoptosis in response to stress signals; (II) their specific pro-survival BCL2 family protein partners (BCL2, BCL-X_L, BCL-W, MCL1, and BFL1/A1); and (III) pro-apoptotic effector proteins (BAX and BAK) (24).

Under normal physiological conditions, in untransformed mature B cells, pro-survival BCL2 family proteins bind to the pro-apoptotic effector proteins BAX and BAK, preventing them from forming oligomers that would otherwise permeabilise the outer membrane of the mitochondria and activate a cascade of reactions culminating in apoptotic cell death. A diverse range of cytotoxic stress signals, such as DNA damage and growth factor deprivation, cause transcriptional and post-translational induction of the BH3-only proteins, which carry out their pro-apoptotic function either by neutralising their specific pro-survival BCL2 family protein partners, thus enabling the oligomerisation of BAX and BAK on the mitochondrial outer membrane; or by directly activating these pro-apoptotic effector proteins. The oligomerisation of BAX and BAK triggers the release of a number of apoptogenic factors into the cytosol, including cytochrome c, which binds to the scaffold protein APAF1, resulting in the formation of the apoptosome (25,26). The apoptosome activates an initiator caspase called caspase 9, which in turn activates the executioner caspases 3, 6, and 7 (20), resulting in apoptotic cell death.

Derangements in the normal apoptotic machinery can render a cell resistant to apoptotic signals and contribute to oncogenesis. For example, the development of the majority of FL depends on a translocation between the long arm of chromosome 18 and the long arm of chromosome 14, which juxtaposes the *BCL2* gene with the immunoglobulin heavy chain (IgH) locus, resulting in deregulated expression of BCL2 (7,8). Since many cytotoxic therapies induce apoptosis by activating BH3-only proteins, elevated levels of BCL2 also contribute to therapy resistance (27). Paradoxically, however, some cells that overexpress BCL2 become dependent on or 'addicted to' BCL2 for survival, making them exquisitely sensitive to BCL2 inhibition, and thus, in a sense, 'primed for death' (28).

The discovery of BCL2 addiction in certain cancers stimulated the development of small molecules that mimic the action of BH3-only proteins such as BIM in neutralising BCL2. The most advanced of such BH3 mimetics is venetoclax (ABT-199), developed by structure-informed reverse engineering of navitoclax, a first-generation BH3 mimetic that binds to BCL2, BCL-X_L, and BCL-W with high affinity (K_i <1 nM for all) (29). In a phase I study, navitoclax was found to induce a partial response in 35% (9/26) of patients with relapsed or refractory CLL (R/R CLL), including those with adverse prognostic features, such as fludarabine-refractory disease, bulky adenopathy, and del(17p) CLL (30). In a separate phase I study of navitoclax in patients with a range of NHL, a partial response in 22% (10/46) of patients, with a median PFS

of 16 months, was observed (31). However, predictable thrombocytopenia due to on-target antagonism of BCL-X_L, the pro-survival protein critical for maintenance of platelet viability, limited the ability to escalate the dose of navitoclax and precluded its broad clinical application (32).

Venetoclax was the first BCL2-selective BH3 mimetic to be developed. In pre-clinical studies, venetoclax demonstrated a sub-nanomolar binding affinity for BCL2 (K_i <0.010 nM) with three orders of magnitude less avidity for BCL-X_L (K_i =48 nM) or BCL-W (K_i =245 nM) (14). Correspondingly, venetoclax showed the absence of any effects on platelets in contrast to navitoclax, enabling higher circulating concentrations of the drug to be achieved without dose-limiting thrombocytopenia. Venetoclax is currently approved in the US for use as monotherapy or in combination with rituximab in patients with CLL or small lymphocytic lymphoma (SLL), with or without del(17p), who have received at least one prior therapy, as well as for use in combination with azacitidine, decitabine or low-dose cytarabine in patients with newly diagnosed acute myeloid leukaemia (AML) who are aged 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy. The potential to add venetoclax to the armamentarium against NHLs, including DLBCL, MCL, and FL, is being explored.

MCL: opportunities for targeted therapy

MCL constitutes 6–8% of all NHLs (33,34). The median age at diagnosis is 68 years and three-quarters of patients are male (35). While there is a small subgroup of patients whose disease progresses slowly, in the majority of patients, MCL manifests as an aggressive disease, and stage III/IV disease is typically present at the time of diagnosis (36). Despite the introduction of aggressive multi-agent chemoimmunotherapeutic approaches, MCL continues to have one of the poorest prognoses of all lymphomas, with a median overall survival (OS) of approximately 3 years (37). The outcome is especially poor for patients who are older with comorbidities or who harbour aberrations in the TP53 pathway (38-43). While there have been incremental improvements in patient outcome with intensified chemotherapeutic approaches, such as the inclusion of high-dose therapy and autologous haemopoietic stem cell transplantation (HSCT), the treatment of refractory or relapsed MCL (R/R MCL) remains a challenge, and until recently patients with R/R MCL had few effective therapeutic options.

The genetic hallmark of MCL is the t(11;14)(q13;q32) translocation, which places the cyclin D1 gene (*CCND1*) at chromosome 11q13 in close proximity to the IgH heavy chain locus at chromosome 14q32, leading to overexpression of cyclin D1, a protein that is not normally expressed B cells. This genetic alteration facilitates the deregulation of the cell cycle at the G1-S phase transition by promoting the inactivation of retinoblastoma 1 (RB1) and degradation of p27. However, although cyclin D1 overexpression appears to be the oncogenic driver in the overwhelming majority of MCL cases, the failure of transgenic mice overexpressing cyclin D1 to develop B cell lymphoma suggests that cyclin D1 overexpression alone is insufficient to cause transformation of normal B cells (44). In addition to dysregulated cell cycle progression, MCL cells also demonstrate aberrations in the DNA damage response pathway and the cell survival pathway (45). BCL2 is commonly upregulated in MCL, with up to 93% of biopsies from MCL patients exhibiting high expression of BCL2 (16), and gain of 18q11-q23, the region where the BCL2 gene is located, seen in 11–26% of MCL patients (46,47). Homozygous deletions of BIM predisposing to avoidance of apoptosis have also been identified in MCL cell lines (48). Furthermore, high level of MCL1 expression in MCL has been associated with inferior outcomes (49). Hence, targeting apoptosis as a novel approach to treating high-risk MCL has long been an attractive option.

Several putative BCL2 inhibitors have been tested in MCL, including oblimersen and obatoclax, with modest clinical efficacy (50,51). However, these agents do not meet the criteria for a true BCL2 inhibitor (52). It was only with the emergence of navitoclax and subsequently venetoclax that testing of true BCL2 inhibitors for the treatment of MCL could commence.

Pre-clinical results of venetoclax to treat MCL

Given BCL2 overexpression is a feature in many cases of MCL, as it is in a number of other haematological malignancies, MCL cells are predicted to show a degree of BCL2 addiction, leading to heightened sensitivity to BCL2 inhibition. *In vitro* studies demonstrated the ability of venetoclax to induce apoptosis in a range of haematological cancer cell lines that depend on BCL2 for survival, including DLBCL, FL, and MCL (14). Sensitivity to venetoclax was directly correlated with BCL2 expression level, with NHL cell lines harbouring BCL2 gains, BCL2 amplifications, or the t(14;18) translocation

demonstrating increased sensitivity to venetoclax compared to cell lines without these genetic features (14). In mice bearing established MCL tumours, venetoclax was shown to enhance the tumour growth delay (TGD) induced by combination therapy with bendamustine and rituximab (BR), and cause a complete response (CR) in 50% of mice, whereas no mice achieved a CR after treatment with BR alone. The regimen was well-tolerated in mice with no overt signs of toxicity and no significant weight loss (14).

In the setting of CLL, venetoclax has demonstrated promising results in cases harbouring TP53 aberrations in the form of either del(17p) or mutation in the *TP53* gene (15), which, as in MCL, are known to be associated with inferior outcomes after standard chemoimmunotherapy (53,54). Despite confirmed loss of TP53, normal murine nodal B cells, human B lymphoblast cell lines, and primary CLL cells demonstrated the same sensitivity *in vitro* to the induction of apoptosis by venetoclax in comparison to cells with normal TP53 function. In addition, no difference was observed in baseline mitochondrial priming or degree of BCL2 dependence between CLL samples with or without TP53 dysfunction. Consistent with *in vitro* findings, TP53 status failed to predict the depth of compartmental responses to venetoclax in patients with CLL. Based on impressive response rates, venetoclax has been approved for CLL cases with TP53 aberrations. Taken together, these findings provide a rational basis for the use of venetoclax in the treatment of MCL, particularly those difficult cases harbouring TP53 dysfunction.

Early phase clinical results of venetoclax to treat MCL

In a phase I first-in-human study of venetoclax in patients with R/R CLL or NHL, impressive activity was observed in CLL, MCL, and Waldenström's macroglobulinemia (WM) (16,55,56). In the NHL cohort of the study, patients with R/R MCL demonstrated an overall response rate (ORR) of 75% (21/28) and a CR rate of 21% (6/28). The median PFS was 14 months, with only one progression amongst the six complete responders (16). The responses were more durable amongst patients who achieved CR than among those whose best response was partial remission (PR) (16).

The maximum tolerated dose (MTD) of venetoclax was not reached in the phase I trial in patients with NHL, but two dose-limiting toxicities occurred at a dose of 600 mg of venetoclax: one grade 4 neutropenia in a patient with Richter transformation diffuse large B cell lymphoma (DLBCL-RT), and one grade 3 febrile neutropenia in a patient with DLBCL (16). The recommended phase 2 dose (RPTD) was therefore determined by investigators to be 800 mg for MCL on the basis of significant activity at this dose and risk of incremental toxicity with dose escalation above this level (16). Of the 106 patients enrolled, three patients with bulky disease (maximal lymph node diameter >10 cm) demonstrated biochemical changes meeting the Cairo-Bishop criteria for laboratory tumour lysis syndrome (TLS) (16,57). In all three patients, the laboratory changes settled promptly with TLS treatment without the need for dose interruption (16). Subsequent experience with venetoclax in MCL suggests that TLS may be more prevalent and potentially fatal in this setting, leading to revised recommendations for dose escalation (58).

None of the patients treated in the phase I first-in-human trial of venetoclax monotherapy in NHL had received prior therapy with a BTK inhibitor (BTKi). Unfortunately, in an analysis of outcomes among 20 patients treated with venetoclax monotherapy after failure of BTKi, the results are less encouraging with an ORR of 53% and CR rate of 35%. This translates to a median PFS of only 3.2 months with a median OS of 9.4 months and median duration of response of 8.1 months. Among those who responded to venetoclax, however, the PFS was significantly improved (P=0.042) with the median PFS not reached (59).

Despite the ability of venetoclax to induce high rates of durable remission in cases of previously treated CLL, relapse occurs in the majority of patients, with the median response duration in CLL patients harbouring del(17p) receiving venetoclax monotherapy being 33.2 months (60). Analysis of paired pre-venetoclax and progression samples from 15 patients with CLL progression identified a novel Gly101Val mutation in BCL2, appearing in 7 patients at disease progression, but not at treatment initiation (61). Surface plasmon resonance (SPR) assays revealed that the Gly101Val mutation reduced the binding affinity of venetoclax to BCL2 180-fold, thereby compromising the ability of venetoclax to displace pro-apoptotic proteins, such as BIM, BAX and BAK, from BCL2 and conferring acquired resistance both *in vitro* and *in vivo* (61). A search is currently underway for similar mutations in MCL.

Ibrutinib is an oral covalent inhibitor of Bruton's tyrosine kinase (BTK), an essential component of the B cell receptor (BCR) signalling pathway, which has shown high clinical efficacy across a range of B cell cancers including CLL and MCL (62,63). In a phase 2 study of ibrutinib monotherapy in 111 patients with R/R MCL, an ORR of

68% (75/111), with a CR of 21% (23/111) and a median PFS of 13.9 months (62), was observed. A phase 3 trial demonstrated an ORR of 72%, with a CR of 19% and a median PFS of 14.6 months (64). Despite the significant efficacy of ibrutinib in MCL, primary resistance is seen in one-third of patients and acquired resistance seems to be universal. In CLL and WM, BTK mutations that reduce the binding affinity of ibrutinib for BTK, resulting in transient rather than irreversible inhibition, and PLCG2 mutations that enable the activation of the BCR signalling cascade despite loss of BTK function, are commonly associated with acquired resistance to ibrutinib (65-68). In contrast, BTK and PLCG2 mutations are rarely seen in MCL patients who are resistant to ibrutinib therapy (64,69-72). Instead, primary resistance to ibrutinib in MCL is thought to arise due to mutations in the NF-κB pathway, including nonsense mutations in TRAF2 and deletions of TRAF3, which result in activation of the alternative NF-κB pathway, and activating CARD11 mutations that lead to constitutive activation of NF-κB signalling (71). Given that MCL patients who experience ibrutinib failure are known to have poor outcomes and exhibit poor response to salvage chemotherapy (73,74), ibrutinib monotherapy is unlikely to represent a cure for all patients (75).

Since venetoclax and ibrutinib target distinct, presumably non-overlapping, survival pathways, the combination of the two agents is anticipated to provide added benefit (76-78). Cell cytotoxicity assays in five separate MCL cell lines confirmed strong synergistic effects of the ibrutinib-venetoclax combination. Testing with primary MCL cells from two cases of recurrent MCL that displayed varying responses to single agents also demonstrated robust synergy of apoptosis induction (77). Interestingly, ibrutinib-induced dephosphorylation of BTK and AKT, which is known to be associated with survival and proliferation of malignant B cells, was enhanced upon co-treatment with venetoclax. Dual therapy also resulted in downregulation of at least one, often two, pro-survival BCL2 family proteins as well as augmentation of mitochondrial membrane depolarisation and poly(ADP-ribose) polymerase (PARP) cleavage, suggesting caspase activation.

In addition to intrinsic abnormalities, such as overexpression of cyclin D1 and BCL2, extrinsic signalling from the tumour microenvironment is believed to be important for MCL growth, survival, and drug resistance, as it is in other B cell malignancies (79,80). Previously, CLL cells cultured on CD40L-expressing fibroblasts in the presence of IL-4 to mimic the lymph node microenvironment were shown to upregulate BCL-X_L and BFL2/A1, resulting in an approximately 1,000-fold resistance to ABT-737 (81). In a different *in vitro* lymph node model of CLL, co-stimulation of primary CLL cells with CD40 and IL-4 resulted in full resistance to high-dose venetoclax through upregulation of BCL-X_L (82). These results were subsequently recapitulated in both MCL cell lines and primary MCL cells. Specifically, it was shown that peripheral blood MCL cells, which express a low level of BCL-X_L and are highly sensitive to venetoclax, exhibit an increase in BCL-X_L protein level upon CD40 stimulation, and silencing of BCL-X_L can overcome venetoclax resistance induced by CD40 stimulation (83). Previous studies suggest the involvement of the NF-κB signalling pathway in CD40-dependent BCL-X_L upregulation (84). Mechanistically, ibrutinib disrupts BCR- and chemokine-mediated adhesion of MCL cell lines to the tumour microenvironment, resulting in egress of malignant cells into the peripheral blood (85). The capacity of ibrutinib to drive MCL cells out of the protective microenvironment of lymph nodes and bone marrow, combined with the demonstration of decreased BCL-X_L expression and increased venetoclax sensitivity in peripheral blood MCL cells, serves as a possible mechanistic explanation for the synergy observed with use of venetoclax and ibrutinib in combination.

Given the strong pre-clinical rationale, the combination of venetoclax and ibrutinib is currently being investigated in several clinical trials internationally (NCT02471391, NCT02558816, NCT03295240, NCT02419560) for use in R/R MCL. The first study to be completed is the ABT-199 and Ibrutinib in Mantle Cell Lymphoma (AIM) study (NCT02471391). AIM is an open-label, single-group, phase 2 study of daily oral ibrutinib and venetoclax in 24 patients with either R/R MCL (23 patients) or previously untreated MCL who could not undergo cytotoxic chemotherapy (1 patient). The study schema incorporates 4 weeks of single-agent ibrutinib induction at a dose of 560 mg per day prior to starting venetoclax, so as to reduce the tumour burden and decrease the risk of TLS. Patients then received venetoclax according to a dosing schedule that started at 50 mg per day and increased weekly in a stepwise fashion to 100 mg per day, then to 200 mg per day, and finally to 400 mg per day. Two cases of TLS occurred at the initial starting dose of venetoclax (50 mg daily), leading to revision of the schedule to commence venetoclax at 20 mg daily. No further TLS cases were encountered at the 20 mg starting dose of venetoclax.

In this study of 24 patients with MCL, the median age was 68 years, meaning that many of the patients would not have been suitable for intensified therapy for their condition (86). Among the 23 patients who had received prior therapy for MCL, the median number of previous treatments was two with a range from none to six. Twelve patients had evidence of TP53 aberration in the form of del(17p), a TP53 mutation, or both, and 23 had either an intermediate or a high-risk MCL International Prognostic Index (MIPI) score (86). The primary end point of the study was the CR rate at week 16, which was 42% according to computed tomography (CT) and 62% as assessed by positron-emission tomography (PET). The CR rate measured by CT was higher than the historical result of 9% achieved with ibrutinib after 16 weeks of treatment, potentially implying improved efficacy. Absence of minimal residual disease (MRD) in bone marrow, as assessed by flow cytometry, was recorded in 67% (16/24) of patients, and in blood, as assessed by ASO-PCR, in 38% (86). The ORR at week 16 was 71% (17/24), with a CR of 62% (15/24). The estimated rate of PFS was 57% at 18 months (86). The potential superiority of combination therapy to ibrutinib monotherapy is being tested further in a new phase 3 study comparing ibrutinib to the venetoclax-ibrutinib combination in R/R MCL (NCT03112174).

Despite the potential revealed by the AIM study of ibrutinib plus venetoclax to bring durable CRs to patients with R/R MCL, it is nevertheless important to note that over 20% of patients enrolled in the AIM study exhibited primary resistance to the combination therapy, and a further 10% relapsed following initial response with acquired resistance (86). Genomic characterisation of the clinical cohort revealed clear differences in the mutational profiles between responders and non-responders to combination therapy with ibrutinib and venetoclax (87). Mutations in ATM were present in most patients who achieved CR, and chromosome 9q21.1-p24,3 loss and/or mutations in components of the SWI-SNF chromatin-remodelling complex were present in all patients with primary resistance and two-thirds of patients with relapsed disease. The ability to characterise these genomic determinants of treatment response in real-time using circulating tumour DNA (ctDNA) testing was subsequently revealed. Together, these findings establish a molecular rationale to guide patient selection for ibrutinib plus venetoclax, and provide a means by which treatment response and emerging resistance could be dynamically monitored in the clinic. In addition, functional modelling showed that impairment of the SWI-SNF complex resulted in transcriptional upregulation of BCL-X_L, leading to the hypothesis that selective BCL-X_L inhibitors might produce a synergistic effect when used in combination with venetoclax and ibrutinib in patients with the resistance phenotype as identified by ctDNA testing (87).

Previously, anti-CD20 monoclonal antibodies have been shown to be able to counteract resistance to venetoclax induced by microenvironmental signals through inhibition of the NF-κB axis, resulting in downregulation of BCL-X_L (88,89). In an *ex vivo* coculture model for primary MCL cells, the type II anti-CD20 monoclonal antibody obinutuzumab, but not the type I anti-CD20 monoclonal antibody rituximab, demonstrated the capacity to counteract NF-κB-induced upregulation of BCL-X_L, and thus the consequent loss of mitochondrial priming and sensitivity to venetoclax (90). This is consistent with previous studies showing enhanced direct and immune effector cell-mediated B-cell cytotoxicity in lymphoid tissue treated with obinutuzumab compared with rituximab (91,92). Given that the synergy observed with ibrutinib plus venetoclax is at least in part due to the ability of ibrutinib to indirectly mediate down-modulation of BCL-X_L upon egress of MCL cells into the peripheral blood, these results predict that use of venetoclax with obinutuzumab, in addition to ibrutinib, may lead to improved clinical responses. Obinutuzumab has already demonstrated promising clinical activity as a single agent in MCL (93), and in contrast to bortezomib, is associated with limited *in vivo* adverse effects due to its specificity for B cells. The *in vivo* efficacy of venetoclax-ibrutinib-obinutuzumab triple therapy is currently being explored in the ongoing Obinutuzumab, GDC-0199 Plus Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma Patients (OAsIs) trial (NCT02558816) (94).

As exemplified by trials of the venetoclax-ibrutinib combination, while venetoclax monotherapy has substantial clinical efficacy in MCL, better results can clearly be obtained through use of this therapy in combination with other agents. The ideal partner drugs that optimise clinical response and minimise dose-limiting toxicity are yet to be fully elucidated and the sequencing of such therapies is also an area that requires more robust clinical data. In diseases such as FL and DLBCL, where the results of venetoclax monotherapy are inferior, venetoclax has already been tested in combination with chemoimmunotherapy in multiple clinical trials (NCT03064876, NCT03036904, NCT02187861). In an effort to improve on already impressive results in MCL, it is likely that future studies will build on venetoclax with or without ibrutinib in

combination with immunotherapy and standard cytotoxic chemotherapy.

Conclusions

MCL is a subtype of NHL characterised by rapid clinical progression and poor response to current therapeutic protocols. While the introduction of high-dose chemoimmunotherapy with autologous stem cell transplantation has led to significant improvements in the outcome among younger fitter patients, the treatment of elderly patients, patients with R/R MCL, and patients with TP53 aberrations remains an ongoing area of unmet need, highlighting the need for new individualised therapeutic approaches. Venetoclax, while a promising new agent in the armamentarium to treat MCL, is unlikely to be the answer for all patients due to limited PFS or the development of secondary resistance. Combination therapy with ibrutinib increases the depth of clinical response and may be associated with longer duration of PFS. Whether this can be further improved by the addition of monoclonal antibodies remains an open question. Ultimately, understanding the reasons for the development of resistance will help to identify patients who are candidates for intensified therapy and may suggest additional rationally targeted approaches for managing this difficult and needy group of patients.

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Footnote

Conflicts of Interest: MA Anderson, AW Roberts and DC Huang are employees of Walter and Eliza Hall Institute and are potentially eligible for royalty payments in relation to the sale of venetoclax. The other authors have no conflicts of interest to declare.

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