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RESEARCH ARTICLE

# Dismantling the Status Quo: Venetoclax in Mantle Cell Lymphoma

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ABSTRACT

Mantle cell lymphoma (MCL) is a rare B-cell non-Hodgkin lymphoma, and remains a clinically challenging disease entity, particularly in the relapsed setting where outcomes are poor. However, recent innovations in targeted therapeutics have expanded treatment options and demonstrate significant efficacy even in relapsed disease. MCL frequently harbours aberrations of apoptosis pathways including over-expression of the anti-apoptotic protein BCL2. Such aberrancy promotes and sustains lymphomagenesis, thus rendering MCL an attractive target for venetoclax, the highly specific, orally bioavailable inhibitor of BCL2. Pre-clinical and early clinical data of venetoclax monotherapy demonstrated high response rates in relapsed/refractory MCL, though the durability of response in high-risk patients appears modest. More recently, clinical trials deploying combination strategies that pair venetoclax with other novel agents have been undertaken, with some promising early data reported. In this article, we review the biological rationale for deploying venetoclax in MCL, as well as the emerging data from clinical trials of venetoclax monotherapy and novel combinations.

## Introduction

Mantle cell lymphoma (MCL) is a clinically heterogeneous and relatively uncommon B-cell non-Hodgkin lymphoma (NHL). [1] Since being recognised as a specific clinicopathological entity in 1992, our understanding of MCL pathobiology has deepened considerably, yielding improvements in patient management and outcomes. Aggressive cytarabine-based chemoimmunotherapy (CIT) approaches have achieved notable success for those suitable patients, but MCL remains largely incurable, and for those patients whose disease relapses and/or becomes refractory to CIT, treatment response rates are modest and survival outcomes sobering.[2–5] Furthermore, given that the median age of patients at MCL diagnosis is in the 7th-8th decade of life, many patients are not candidates for high-intensity CIT. Accordingly, there remains a significant unmet clinical need in MCL. The advent of novel targeted agents has reshaped the landscape of MCL management, with a number of agents demonstrating meaningful clinical activity, even among heavily pre-treated individuals. Amongst the most promising targeted therapies in MCL, is venetoclax, an orally bioavailable specific inhibitor of the anti-apoptotic regulatory protein, BCL2. In this article, we review the biological rationale for deploying venetoclax in MCL, as well as the emerging data from clinical trials of venetoclax monotherapy and novel combinations.

## Mantle Cell lymphoma

Mantle cell lymphoma accounts for approximately 3-10% of B-cell NHLs in the United States[6], and its incidence appears to be slightly lower in Asian countries.[7,8] Patients are diagnosed with MCL at a median age of approximately 67 years, and men are disproportionately affected at a ratio of 2:1.**[9]** Although a significant minority of patients present with clinically indolent disease that is appropriately observed without treatment until progression,[10] MCL remains a challenging entity to manage for most patients, and population based average survival ranges from 3-6 years.[11] Although the routine use of cytarabine-containing intensive CIT and consolidative high-dose therapy with autologous stem cell transplants (ASCT) have improved outcomes, the young and fit populations have been the principal beneficiaries of these advances, some of whom achieve durable remissions.[5,12–15] Until recently, older patients had a paucity of treatment options, especially in the relapsed or refractory setting.[16]

With rare exceptions, overexpression of the cell cycle regulator, Cyclin D1, is the pathophysiological hallmark of MCL. Most commonly, the t(11;14)(q13;q32) translocation juxtaposes the Cyclin D1 gene (*CCND1*) to the immunoglobulin heavy chain enhancer, inducing aberrantly constitutive Cyclin D1 overexpression that dysregulates cell cycle progression.[17] Cyclin D1, which is not expressed in normal B lymphocytes, engages and activates cyclin-dependent kinases 4 and 6, and the resultant complex thence phosphorylates and inactivates the retinoblastoma protein, negating its cell cycling repressive activity.[18] Beyond direct effects on cell cycle progression, Cyclin D1 has also been documented to impact DNA repair and perturb transcriptional processes that may also contribute to its oncogenic potential.[19–21] Rare cases that lack Cyclin D1 overexpression almost inevitably possess alternative mutations that upregulate other Cyclin D proteins such as Cyclin D2 or D3, producing an equivalent lymphomagenic phenotype.[22] However, whilst Cyclin D overexpression is a necessary primer for MCL development, it is not independently sufficient to transform cells. [17,23] A wide variety of recurrent secondary mutations have been detected in MCL, affecting numerous molecular pathways involved in DNA damage repair (such as *ATM* and *p53*), [24] the NF-KB transcription factor family,[25,26] chromatin modifiers and epigenetic regulators,[27] NOTCH pathway members,[28] the JAK/STAT signalling pathway,[29,30] the PI3/AKT/MTOR pathway,[31–33] the WNT pathway[32,34] and critically, apoptosis regulators. The anti-apoptotic protein BCL2 is overexpressed in the overwhelming majority of MCL cases, and chromosomal amplification of its gene locus (18q11-23) is found in up to a quarter of cases.[35,36] Further dysregulation of apoptosis in MCL can result from deletions of the pro-apoptotic BIM,[37] impaired BCL2 degradation,[38] augmented NF-KB activity,[38] Cyclin-D1 mediated sequestration of the pro-apoptotic BAX,[39] and overexpression of anti-apoptotic MCL1.[40,41] Recent innovations in molecular profiling technologies have informed the major therapeutic advances in MCL treatment, and the constellation of abnormalities involving apoptosis regulators led investigators to hypothesise that such abnormalities may prove an exploitable therapeutic vulnerability in MCL.

**Venetoclax**

Life requires death, and the orderly control of cell death is a critical and fundamental physiological process, required to maintain homeostasis in multicellular organisms. Broadly, cell death may be conceptualised as either programmed or non-programmed. Whilst non-programmed death is the product of unintended injury or pathology, physiologic programmed cell-death is the antithesis of chaos; orchestrated by exquisitely regulated and complex molecular programs. Apoptosis is the dominant programmed-cell death modality, and refers to a concatenation of highly regulated active intracellular events that culminate in the release of caspases and is characterised by cellular involution, organelle degradation, membranous blebbing and DNA fragmentation.[42] Apoptosis may be initiated by the death receptor-mediated extrinsic pathway, or the mitochondrial-mediated intrinsic pathway. The intrinsic pathway is controlled by the *BCL2* regulatory family, and cell fate is often determined by shifts in the delicately balanced and opposing activity of its constituent members.[43] Pro-apoptotic BH3-only proteins including BIM, BID, BAD, NOXA and PUMA, bind and activate mitochondrial pore-forming executioners BAX and BAK, which trigger mitochondrial outer membrane permeabilisation (MOMP). In opposition to this propensity are the pro-survival guardian proteins such as BCL2, BCL-$X_L$, BCL-W, BFL-1/A1 and MCL1, which inhibit apoptosis by binding and sequestering pro-apoptotic proteins.[44]

Hijacking and perturbation of apoptosis regulation is a powerful mechanism in the pursuit of malignant cellular immortality,[45] and upregulation of *BCL2* is a prevalent feature of non-Hodgkin lymphoma, including MCL. Malignant transformation is intrinsically associated with increased DNA damage and increased intracellular stress, and raising the apoptotic threshold can be critical to cancer cell survival, especially in haematological malignancies in which the cells of origin generally exhibit a more sensitive apoptotic threshold compared to many other cell types.[42,46] Additionally, beyond facilitating malignant transformation, disrupting apoptosis can also enhance resistance to cytotoxics or immunotherapies,[47] yet paradoxically, the advantage afforded to cells with corrupt apoptotic pathways can simultaneously be an indispensable addiction, and thus a leverageable therapeutic susceptibility.[48]

Intensive efforts to develop apoptosis modulating therapeutics yielded the first generation BH3 mimetic drug navitoclax. Binding to BCL2, BCL-$X_L$ and BCL-W, early clinical trials demonstrated navitoclax's activity in CLL and NHL.[49–51] However, the broader multitargeting activity within the BCL2 protein family ($K_I$ <1 nM for BCL2, BCL-$X_L$ and BCL-W) proved challenging, with the inhibitory effect on BCL-$X_L$ resulting in significant on-target thrombocytopenia, which curtailed dose escalation and therefore the clinical utility of navitoclax as a single agent.[49] Nonetheless, these early studies illustrated the potential of pro-apoptotic therapies, and structure-informed reverse engineering ultimately produced ABT-199, later re-named venetoclax. Venetoclax is a highly specific BH3 mimetic inhibitor of BCL2. Venetoclax' superior binding affinity displaces BH3 proteins bound to BCL2, freeing them to activate BAX and BAK, or inhibit other anti-apoptotic proteins, thereby facilitating apoptosis.[52] Venetoclax demonstrates high avidity binding to BCL2 ($K_I$ <0.01 nM), but markedly less predilection for BCL-$X_L$($K_I$ =48 nM) or BCL-W ($K_I$ =245 nM), and accordingly thrombocytopenia is not an on-target toxicity of the drug.[53] Orally bioavailable, venetoclax has a half-life of approximately 16-19 hours, with plasma concentrations that peak at 4-7hrs dependent on meal timing. Important to dosing and administration considerations, venetoclax requires a fed state for optimal absorption and is subject to CYP3A4 and CYP3A5 metabolism, with the associated potential for drug-drug interactions, as well as being a p-glycoprotein substrate.[54,55]

Early phase studies established venetoclax' safety and tolerability, and further trials have demonstrated dramatic clinical activity in a variety of haematological malignancies. The particular success of venetoclax in chronic lymphocytic leukaemia (CLL) and acute myeloid leukaemia (AML) has come to define new treatment paradigms in these entities and a variety of combinatorial approaches in a multitude of disease settings continue to be investigated.[56]

**Venetoclax in MCL**

***Preclinical data***

Initial preclinical studies of venetoclax demonstrated potent single-agent *in vitro* killing in an array of haematological cancer cell lines, including numerous MCL cell lines.[53] Furthermore, murine models of xenografted MCL tumours (Granta-519 cells) showed clinical response to

venetoclax in combination with bendamustine and rituximab (BR), with significant delay in tumour growth, as well a 50% complete response (CR) rate in mice receiving the triplet therapy. In contrast, no mouse achieved CR with BR alone.[53] Utilising an approach that would subsequently form the basis for a pivotal clinical trial, further *in vitro* studies demonstrated the synergistic activity of venetoclax with inhibitors of Bruton's tyrosine kinase (BTK), achieving strong induction of apoptosis in both cell lines and primary patient samples. [57] Further murine experiments also showed significant *in vivo* activity of venetoclax, including at bone marrow and central nervous system disease foci.[58] These data arise in the context of numerous other preclinical studies of venetoclax activity that established its utility in tumours that bear dysregulated apoptosis phenotypes, including aberrations of *TP53*,[59] thereby providing a cogent rationale for investigating venetoclax in clinical trials including MCL patients.

***Early clinical trial data***

The initial first-in-human phase 1 trial of venetoclax monotherapy in patients with relapsed/refractory non-Hodgkin lymphoma included 28 patients with MCL. These patients had received a median of 3 prior lines of therapy (range 1-7) and included 7 who had received a prior ASCT. The MCL cohort achieved an overall response rate (ORR) of 75%, with 21% attaining a complete response (CR). The median progression free survival (PFS) was 14 months, and the median duration of response for those who achieved a CR was 31.5 months.[60] Impressive though responses were, it is important to note that no MCL patient in this trial had previously received a BTK inhibitor, a relevant consideration given the emergence of this class of therapeutics as another breakthrough treatment in MCL. There are no prospectively collected data available to address this issue, but retrospective reports are sobering. Several published datasets demonstrate encouraging venetoclax response rates in the order of 40-53% for MCL patients previously exposed to BTK inhibitors; however, the durability of such responses is modest, with median PFS ranging from 3.2 months to 8 months.[61–63] Such results must be tempered against the retrospective nature of these studies, which have considerable variability in both the patient populations and whether venetoclax was deployed as a single agent or as part of a combination regimen; nonetheless the utility of venetoclax monotherapy in this setting appears modest. The performance of ibrutinib in relapsed/refractory MCL is comparable to venetoclax, with the phase 3 study demonstrating an ORR of 72% with CR rate of 19% and a median PFS of 14.6 months. [64] Whilst each representing remarkable innovation and progression, neither BTK nor BCL2 inhibition alone has demonstrated high rates of durable CR in the relapsed/refractory setting. However, combining these agents which target distinct pathophysiological mechanisms is an enticing strategy that has been the subject of several clinical trials.

***Venetoclax and ibrutinib***

Preclinical studies investigating a BCL2 and BTK dual targeting approach have consistently shown a synergistic effect. [38,57,65,66] Beyond targeting non-overlapping oncogenic pathways, some evidence suggests adding a BTK inhibitor could potentially circumvent MCL resistance to venetoclax due to upregulation of alternative anti-apoptotic proteins such as BCL-$X_L$. [67] This escape mechanism is at least partially dependent on the influence of the tumour microenvironment, and egress of MCL cells into the blood induced by ibrutinib potentially neutralises this protection, consequently restoring sensitivity of MCL to venetoclax. [68]

The AIM study is a phase 2 trial of venetoclax and ibrutinib in patients with relapsed/refractory MCL (n=23) or first line MCL in patients ineligible for cytotoxic chemotherapy (n=1). Designed to mitigate the risk of tumour lysis syndrome (TLS), which can be clinically important in MCL,[69] patients received a 4-week ibrutinib lead in (560mg daily) prior to commencing venetoclax ramp-up. Venetoclax was first initiated at 50mg daily with gradual escalation to 400mg daily, and combination therapy was continued until disease progression. A protocol revision modified the starting dose of venetoclax to 20mg daily after 2 cases of TLS, and dosing was permitted to increase to 800mg daily if CR had not been attained by week 16. The patient cohort was generally enriched with high-risk features, with a median age of 68 (range 47-81) years, 75% of patients had high-risk prognostic scores, 50% had *TP53* aberrations and participants had received a median of 2 prior lines of therapy (range 0-6). Overall, 17 patients (71%) achieved a disease response and all responders achieved CR as best response. Interestingly, high rates of minimal residual disease (MRD) clearance were achieved, with 67% MRD negativity by flow cytometry and 38% MRD negativity assessed by allele-specific

oligonucleotide polymerase chain reaction (ASO PCR). Among assessable patients achieving CR, 93% (14/15) were MRD negative by flow cytometry and 82% (9/11) were MRD negative by ASO PCR. At a median of 15.9 months follow-up, median PFS had not been reached, but 78% of responders were estimated to be progression free at 15 months.[70] Safety analysis showed that after the protocol amendment to adjust the venetoclax ramp up, no further cases of TLS occurred. Serious adverse events (SAEs) occurred in 58% of patients, the most common of which was diarrhoea, which was also the most common side effect overall. Neutropenia was the most frequent adverse event of grade 3 severity or higher, occurring in 33% of patients. A subsequent 3-year analysis of the AIM study revealed that the median time-to-progression (TTP) and duration of response (DOR) still had not been reached, but were estimated to be 74% and 60% at 30 months respectively. The median PFS was 29 months and median overall survival was 32 months.[71] Thus far, response rates and durability compare favourably to historical controls treated with either single agent ibrutinib or venetoclax. [60,72]

Building on this initial study, the SYMPATICO study is a phase 3, multinational, double-blind randomised controlled trial of venetoclax and ibrutinib vs ibrutinib and placebo in patients with relapsed/refractory MCL (NCT03112174). The trial also included a preceding open label, safety run-in (SRI) cohort, in which 21 patients were treated, and for whom data have been reported with a median follow-up of 31 months.[73] In contrast to AIM, patients on SYMPATICO receive both drugs from day 1 of the trial, with a five-week venetoclax ramp up, commencing at 20mg daily and increasing to 400mg daily. Patients received dual therapy for 2 years, then revert to ibrutinib monotherapy until disease progression. No clinical TLS events occurred during the safety run-in. One patient experienced laboratory TLS, but was able to continue treatment and ultimately reached full dose dual therapy. Whilst most AEs were low grade, significant infections of grade 3 or higher occurred in 8 patients (38%), with an equal number experiencing grade $\geq$ 3 diarrhoea or neutropenia. Comparable to the AIM data, the ORR was 81% with 62% achieving CR, and all patients with detectable MRD at baseline converted to MRD negativity. Median PFS and OS was 35 months.[73] The randomised component of SYMPATICO, as well as an open-label single-arm cohort of first line MCL patients are currently in progress and yet to report outcome data which are eagerly awaited.

Recently Portell and colleagues published results from their effort to further refine the dosing strategy of venetoclax plus ibrutinib, and mitigate the toxicity shown in AIM and the SYMPATICO SRI cohort; hypothesising that lowering the dose used in single-agent strategies might achieve a better balance between efficacy and toxicity.[74] In this trial, venetoclax was commenced first, with ibrutinib incorporated during the venetoclax dose ramp-up, and a continual reassessment method (CRM) was employed to identify the optimal combination of doses, from 6 different dose permutations. Venetoclax doses were at either 200mg or 400mg daily, and ibrutinib dosing ranged from 280-560mg daily. The CRM methodology allocates patients to dosing cohorts based on the efficacy and toxicity data obtained from preceding cohorts. In contrast to AIM and SYMPATICO, patients received treatment for 6 cycles of 28 days. Thirty-five patients with relapsed MCL were treated, and ultimately this method determined the optimal dosing levels to be 200mg daily of venetoclax and 420mg daily of ibrutinib. With this dose regimen, 16 patients demonstrated an ORR of 93.8% (15/16) and dose-limiting toxicity (DLT) rate of 6.2% (1/16). At this dose level, the only AE of grade $\geq$ 3 that occurred in more than one patient was neutropenia (grade 3 - 18.75%, grade 4 – 18.75%). For the study cohort overall, the ORR was 82.3%, with 42.4% CR. At a median duration of follow up of 26.7 months, the median PFS and OS for the whole cohort was estimated to be 10.7 months and 28.3 months respectively. Considering the optimal dosing arm in isolation, neither median PFS or OS had been reached with a median follow up of 22.9 months in this subgroup.[74] However, firm conclusions on response and survival rates should be made with caution in this study, given the fixed duration of therapy at only 6 cycles, variability in dosing and relatively small cohort size within dose levels. Additionally, the study selected for patients with lower risk MCL when compared to previous trials and those who had received a previous BTKi were excluded. Furthermore, the CRM technique precludes the capacity to match patient characteristics between dosing arms, introducing further uncertainty at analysis. Nonetheless, the study raises interesting and important questions of dosing optimisation that are worthy of further investigation, and the findings certainly suggest

efficacy and safety could be enhanced by dose modulation in combination regimens.

***Further combinations with venetoclax***

The tumour microenvironment (TME) plays a critical role in MCL as in other B cell malignancies, mediating lymphoma cell proliferation, maintenance and therapeutic sensitivity.[75,76] As stated, the concurrent use venetoclax and BTKi is, in part, predicated on depriving MCL cells of the haven bestowed by the tumour microenvironment. Prevalent within the TMI, CD40 signalling pathways strongly contribute to apoptosis resistance, principally by upregulation of BCL-$X_L$. CD40 stimulation appears to exert this affect via activation of NF-KB. [77,78] CD20 monoclonal antibodies, and particularly the type-2 CD20 antibody obinutuzumab, have previously been demonstrated to inhibit NF-KB signalling, and in pre-clinical models, this prompts down-regulation of BCL-$X_L$ and can thereby potentially overcome resistance to venetoclax.[79,80] Accordingly, adding a CD20 monoclonal antibody to venetoclax and ibrutinib was theorised to further combat resistance and enhance efficacy.

The OASIS clinical trial is a single-arm, multicentre, phase 1/2 study of the venetoclax/ibrutinib/obinutuzumab triplet in patients with either relapsed or untreated MCL.[81] The combination proved to be well tolerated, and the maximum tolerated dose (MTD) for venetoclax was not reached. Venetoclax was administered at 400mg daily in the subsequent expansion phase. Patients received standard obinutuzumab dosing (1g IV - cycle 1: Days 1, 8 and 15; cycles 1b-8: Day, cycles 9-23: every 2 months) and ibrutinib at 560mg daily. 24 patients with relapsed MCL received the triplet in Cohort B, and after 6 cycles the ORR was 75% with 67% of patients achieving CR (Cheson 99 criteria).[82] With a median follow-up of 17 months the 1-year PFS was 74.5% and 1-year OS was 87.5%. In Cohort B, 10 of 14 evaluable patients cleared their MRD (measured by ASO-PCR) at cycle 3, and a further patient achieved MRD negativity by the completion of cycle 6. Amongst the 15 treatment-naïve participants in Cohort C, the ORR by Cheson criteria after 6 cycles was 93% (14/15) and 80% were in CR. At median follow-up duration of 14 months, 1-year PFS and OS were 93.3% and 100% respectively. All MRD-evaluable Cohort C patients achieved MRD negativity by cycle 3, and sustained this depth of response at reassessment following cycle 6. Whilst no DLT occurred in any OASIS treatment group, the triple combination caused considerable toxicity. 75% of Cohort B and 53% of Cohort C patients experienced a grade 3 or higher AE, the most frequent being neutropenia and thrombocytopenia. One third of Cohort B patients and 2 Cohort C patients received <90% of planned therapy. OASIS is an undeniably small study, with few participants in each arm, and hence comparisons to AIM or other studies must be made judiciously; nonetheless the impressive rates of early MRD clearance in OASIS likely portends a favourable outcome. Longer follow-up and a larger study will likely be required to accurately assess the additive benefit of obinutuzumab with venetoclax/ibrutinib, but early data are indeed promising.

Based on similar theoretical underpinnings to OASIS, a further study in treatment naïve MCL deploys venetoclax combined with rituximab and the second generation covalent BTK inhibitor, acalabrutinib.[83] When delivered as monotherapy, second generation BTK inhibitors such as acalabrutinib and zanubrutinib appear to achieve higher response rates and longer PFS in relapsed/refractory MCL, hence the appeal of combinations utilising these agents.[84,85] Acalabrutinib was administered at 100mg BD from commencement and continued until disease progression or discontinuation. Patients received 375m/$m^2$ of rituximab on day 1 of 28-day cycles from cycle 1-6, followed by maintenance dosing every other cycle for a maximum of 24 cycles. Starting at cycle 2, venetoclax was ramped up to a maximum dose of 400mg daily. 21 patients were enrolled with 90% having stage IV disease, and 71% with intermediate or high risk MIPI scores. At the completion of cycle 6, the ORR was 100% with 90% of patients in CR by Lugano criteria,[86] and MRD negativity was documented for 75% of patients with evaluable samples. No DLTs were recorded and early survival data are expectedly robust. Longer duration follow-up of this cohort is also eagerly awaited, as the prospect of chemotherapy-free regimens in first line treatment is most appealing to patients and clinicians.

The immunomodulatory agent lenalidomide has modest single-agent activity in MCL,[87–89] but demonstrates greater efficacy when combined with other agents including rituximab, bortezomib, ibrutinib or cytotoxics.[90–94] The activity of combining venetoclax with R2 (Rituximab and

lenalidomide) in relapsed/refractory MCL is the subject of the VALERIA trial. [95] Several cohorts were recruited to study different dosing strategies; in 28-day cycles patients received either 15mg daily (D1-21) (cohorts A and Y) or 20mg daily (D1-21) (cohorts B and C) of lenalidomide, with venetoclax administered following ramp-up at 400mg daily (cohorts A and B), 600mg daily (cohort Y) or 800mg daily (cohort C). All patients received the same rituximab regimen, with the first dose of 375mg/m$^2$ intravenously, followed by regular subcutaneous injections. No DLT occurred in cohorts A or B, but 2/3 patients in cohort C (venetoclax 800mg daily) developed grade 3-4 infection. Cohort Y was tested with an intermediate dose of venetoclax (600mg daily) and the recommended phase 2 dose (RP2D) of venetoclax was established at 600mg daily. Only short duration follow-up (median of 5 months) data are available at present, but at the time of reporting, with 16 patients evaluable for efficacy, the ORR was 56% with 31.25% in CR. In this study, patients who achieve MRD negativity continue therapy for a further three months, and should they remain MRD negative, therapy is ceased. At the time of abstract publication, 4 patients had realised sustained MRD clearance, and therefore discontinued treatment. The feasibility of treatment discontinuation for deeply responsive patients is a critical question being investigated by this trial, and a possibility that has also been raised by findings from the AIM study, in which 4 patients who achieved MRD negativity remained in remission at least 18 months following treatment cessation.[71] Additionally, evidence from the MURANO trial in CLL demonstrates that deep responders in whom treatment is withdrawn may retain sensitivity to venetoclax at subsequent progression.[96] Further follow up of MCL patients in a comparable scenario is anticipated from AIM, VALERIA and other studies.

The activity of venetoclax in MCL is undisputed (summarised in Table 1), but long-term durability of response to single agent treatment in multiply relapsed patients, especially post BTKi is limited. Combinatorial regimens are likely to represent the future standard of care, and numerous such approaches are under active investigation. Many currently active trials employ different combinations of the aforementioned drugs with venetoclax. Additional, previously untested combinations are also being studied, pairing venetoclax with conventional chemotherapy (NCT03834688, NCT03710772, NCT03295240, NCT03872180), second or third generation BTK inhibitors (NCT03740529, NCT03824483, NCT04855695, NCT03946878, NCT02717624) or polatuzumab (NCT04659044).

Additionally, the heterogeneity of molecular abnormalities within and between MCL patients suggests that no single regimen may prove optimal for all patients. Indeed, the AIM data demonstrate that at least 20% of patients had disease that proved refractory to venetoclax/ibrutinib, and subsequent genetic analyses revealed strong correlations of treatment resistance to specific mutational profiles.[70,97] Further correlative biomarker studies are required to guide treatment selection, particularly in patients with adverse risk characteristics. Such studies may also inform effective means of countervailing resistance to venetoclax.

**MCL resistance to venetoclax**

Venetoclax represents a significant advance in cancer therapeutics, yet a substantial minority of MCL patients have disease which does not respond to it, and many initial responders will ultimately progress. A greater understanding of the causal mechanisms underpinning venetoclax resistance is essential to preventing or overcoming it. Accumulating evidence highlights relationships between resistance and upregulation of other *BCL2* family anti-apoptotic proteins, *BCL2* mutations that modify the venetoclax binding pocket, tumour microenvironmental mechanisms and abnormalities of *TP53*.

**Table 1:** Major trials of venetoclax in mantle cell lymphoma

| | Reference | Line of therapy | No of patients | Regimen | ORR | CR | Outcome | OS |
|---|---|---|---|---|---|---|---|---|
| | Davids et al | R/R | 28 | Venetoclax | 75% | 21% | mPFS: 14 months<br>mDOR in patients who achieved CR: 31.5 months | Median: not reached |
| **AIM** | Tam et al<br>Handunnetti et al | R/R 1L | 23<br>1 | Ven + ibrutinib | 71% | 71% | mPFS – 29 months<br>MRD clearance 67% (flow cytometry) 38% (ASO PCR) | Median: 32 months |
| **SYMAPTICO** | Wang et al | R/R* | 21 | Ven + ibrutinib vs ibrutinib + placebo | 81%* | 62%* | mPFS 35 Months*<br>MRD clearance 100% (in measurable patients) (flow cytometry) | Median: 35 months* |
| | Portell et al | R/R | 35 | Ven + ibrutinib<br>Note: various dose regimens | 82.3% (overall cohort)<br>93.75% (optimal dose cohort) | 42.4% (overall cohort)<br>40% (optimal dose cohort) | mPFS – overall cohort: 10.7 months<br>mPFS – optimal dose cohort): not reach | Median – overall cohort: 28.3 months<br>Median - optimal dose cohort: not reached |
| **OASIS** | Le Gouill et al | R/R 1L | 24<br>15 | Ven + ibrutinib + obinutuzumab | R/R: 75%<br>1L: 93% | R/R: 67%<br>1L: 80% | R/R: 1-yr PFS: 74.5%<br>mDOR: not reached<br>1L: 1-yr PFS: 93.3%<br>mDOR: not reached | R/R 1-yr: 87.5%<br>1L: 1-yr: 100% |
| | Wang et al | 1L | 21 | Ven + acalabrutinib + rituximab | 100% | 90% | 1-yr PFS: 89%<br>MRD clearance 75% (in measurable patients) (clonoSEQ assay) | 1-yr: 95% |
| **VALERIA** | Jerkeman et al | R/R | 16^ | Ven + rituximab + lenalidomide | 56% | 31.25% | mPFS: not reached<br>mDOR: not reached<br>Median follow-up: 5 months<br>MRD clearance: 83.3% (RTqPCR) | Median OS: not reached |

*Table 1: 1L* first-line, *CR* complete response, *MCL* mantle cell lymphoma, *DOR* median duration of response, *mDOR* median duration of response, *mPFS* median progression free survival, *MRD* measurable residual disease, *PFS* progression-free survival, *R/R* relapsed/refractory, *Ven* venetoclax, *Safety run-in cohort data available only, ^Patients evaluable for efficacy at time of reporting

As previously mentioned, upregulation of other anti-apoptotic proteins is a well-documented cause of acquired venetoclax resistance. Increased expression of BCL-$X_L$ and MCL1 is demonstrable in MCL cell lines that develop venetoclax tolerance following chronic exposure.[98] Comparable phenomena have also been documented in other lymphoma models and patient samples.[99,100] Further evidence reveals that mitochondrial metabolic pathway dysfunction accompanies and synergises with altered *BCL2* family expression to contribute to venetoclax resistance. [100] Consistent with these findings, previous studies have demonstrated the relative ineffectiveness of venetoclax against cells that principally depend on BCL-$X_L$ or MCL1 to counteract apoptosis.[101,102] However, increased reliance on alternative anti-apoptotic family members may prove exploitable, and such cases may respond to novel inhibitors of these proteins, potentially in combination with venetoclax. [100,103,104] Additionally, the understanding of the TME and its contribution to BCL-$X_L$/MCL1 upregulation has informed new drug combinations as explored in previous sections. Further evidence reveals that disturbance of the PI3K-AKT/mTOR signalling pathway can also

contribute to MCL1 upregulation and consequent venetoclax resistance. Again, this perturbation can be targeted by novel inhibitors, and recent pre-clinical data demonstrates that PIK-75, a PI3K/CDK9 dual inhibitor can overcome venetoclax resistance and impair MCL cell growth *in vitro* and *in vivo* via inhibition of PI3K-AKT signalling, thereby blocking MCL1 overexpression. [105]

Genomic interrogation of samples from AIM study participants revealed striking mutational profiles differentiating responders and non-responders. [97] All patients with disease harbouring mutations in *WHSC1*, *UBR5* and *MLL2* responded to therapy, as did the tumours in 12 of 13 patients with *ATM* mutations. In contrast, mutations in *NOTCH1*, *CCND1* and *SMARCA4* were found only in non-responders. Indeed, loss of chromosome 9q21.1-p24.3 and/or mutations of SWI-SNF chromatin remodelling complex components were strong predictors of poor response or refractoriness. [97] These results represent a clear rationale for leveraging genomic data to guide targeted therapies in MCL, as well as the capability to dynamically monitor for the emergence of resistant clones.

In patients with CLL, mutations in *BCL2* such as Gly101Val, Val156Asp and Asp103Glu that result in structural reconfiguration of the BH3 binding pocket have been documented to reduce venetoclax binding affinity and thus contribute to resistance.[106–108] Recently, *BCL2* Val156Asp and Asp103Glu variants have been detected for the first time in MCL, occurring in a patient previously treated with venetoclax. [109] It is therefore likely that acquired *BCL2* mutations represent a significant cause of venetoclax resistance in MCL, though further exploration is required.

Data exploring the mutational profile of MCL samples resistant to venetoclax are limited, but *SMARCA4* abnormalities have been reported in two studies,[62,97] and despite early enthusiasm that venetoclax activity might prove agnostic to *TP53* mutations, such abnormalities are consistently enriched in poor responders to venetoclax across disease entities.[62,110] Furthermore, it is likely that multiple, intersecting pathways of resistance conduce to venetoclax treatment failure, and this complexity will be challenging to decipher.

Novel agents and combinations with venetoclax may be able to overcome some of the aforementioned mechanisms of resistance, but further investigation is required to crystallise our understanding of these processes and inform future strategies.

**Conclusions**

The current standard approach to MCL remains heavily reliant upon intensive CIT, a strategy ill-suited to many patients with the disease. The proven activity of venetoclax in MCL is an important development as the arc of therapy bends toward individualised treatment plans. Whilst venetoclax monotherapy may not prove to be optimal for many patients, emerging data from venetoclax-based combination therapies offers exciting glimpses of deeper and more durable responses in both the untreated and relapsed/refractory populations. Critical to maximising the benefit of these combinations are correlative translational studies that explore resistance mechanisms, as despite progress in many patients, those with highly adverse risk features such as *TP53* pathway abnormalities continue to represent an ongoing and exigent area of need. Other acute questions pertain to sequencing and selection of novel agent combinations, survival effect in treatment naïve patients and the feasibility of treatment discontinuation for patients achieving MRD negativity. A multitude of active studies will address many of these queries and may well herald an exhilarating new era for MCL treatment.

**Conflict of interest statement**

JMLC has no conflicts to declare. MA is an employee of the Walter and Eliza Hall Institute which receives milestone payments in relation to venetoclax to which MA is entitled to a share. MA has also received honoraria from AstraZeneca, Janssen and Abbvie. JFS serves on advisory boards and has received research funding from Abbvie, Janssen, Roche and Celgene. JFS has received honoraria from Abbvie, Celgene and Roche and has served on an AstraZeneca advisory board.

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