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Translocation t(11;14) and BCL2-inhibition in multiple myeloma

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ABSTRACT:

Multiple myeloma is an increasingly treatable disease with improved survival, yet characterized by multiple subclones that drive heterogeneity and variable clinical outcomes between patients. A biomarker driven approach can help tailor treatment and improve patient outcomes. Translocation t(11;14), a primary cytogenetic abnormality present in 15-20% of myeloma patients at diagnosis, is currently the most prominent targetable lesion in myeloma. In the era of induction with proteasome inhibitor and/or immunomodulatory drugs, t(11;14) has been associated with poorer outcomes compared to other standard-risk subgroups, with shorter progression-free and overall survival. The presence of t(11;14) in myeloma cells confers increased dependence on the pro-survival BCL2 protein, thus driving its ability to evade apoptosis, and is the main biomarker predicting response to BCL2-inhibitors. This review will examine the pathogenesis and prognostic significance of t(11;14) in myeloma and the impact of concurrent high-risk cytogenetics, the mechanism of action of BCL2-inhibitors, cumulative evidence supporting its use, and proposed mechanisms of resistance. The review will also present potential future directions regarding BCL2-inhibitor based regimens and how best to position these drugs to optimize patient outcomes.

REVIEW ARTICLE – MAIN TEXT:

INTRODUCTION

Multiple myeloma (MM) is an incurable hematological malignancy. Recent advances, particularly in immune therapies (e.g. bispecific antibody-T cell engagers and chimeric antigen T-cell receptor therapy) and small molecules (e.g. BCL2-inhibitors, cereblon E3 ligase modulators), have significantly improved progression free survival (PFS) and overall survival (OS). However, the treatment of MM remains challenging due to the significant heterogeneity, with variable treatment responses both between patients and across successive relapses. This has driven efforts to identify specific molecular targets in MM to allow for a biomarker driven treatment approach.[1] Currently, the only targetable lesion in MM is the t(11;14) translocation. Although not classified as a high-risk lesion in the revised International Staging System (R-ISS)[2] for MM or the new International Myeloma Society (IMS) and International Myeloma Working Group (IMWG) Consensus Genomic Staging of high-risk MM[3], growing evidence supports that patients with t(11;14) have poorer outcomes compared to standard-risk patients, with lower response to immunomodulatory drugs (IMiD), proteasome inhibitors (PI) and novel therapeutics – representing a population of unmet clinical need.[4-8] MM cells with t(11;14) overexpress the pro-survival BCL2 protein, which makes it particularly susceptible to treatment with BCL2-inhibitors (BCL2i). This sensitivity has been confirmed in preclinical models, and demonstrated in clinical practice;[9-17] however, no BCL2i are yet to receive regulatory approval for the treatment of myeloma.

This review delves into the prognostic implications of t(11;14) and the pathogenesis of BCL2 dependence. It also explores the current evidence supporting BCL2i treatment in this subpopulation of patients as well as potential mechanisms of resistance, and in doing so informs our direction for future development of BCL2i-based regimens.

TRANSLOCATION t(11;14) IN MULTIPLE MYELOMA

Chromosomal abnormalities play a critical role in plasma cell clonal evolution and drive disease emergence and progression. Genetic profiling is important in the risk stratification and

prognostication of MM patients; it informs our treatment algorithm as clinicians and allows for risk-adapted treatment. Chromosomal abnormalities in MM are classified into primary or secondary abnormalities. Primary abnormalities, usually translocations (e.g. t(4;14), t(11;14), t(14;16)) or trisomies, are present at diagnosis (i.e. initiating lesions), while secondary abnormalities such as del(17p) and 1q gain/amplification (1q+) usually occur at disease relapse.

Incidence of t(11;14) in multiple myeloma

Primary aberrant IgH rearrangement occurs in 60% of MM, of which t(11;14) is the most common.[18] Historically, t(11;14) was thought to occur in only a small subset of patients, with a quoted incidence of 5% based on conventional karyotyping. However, conventional karyotyping has lower sensitivity due to low plasma cell proliferation.[19, 20] With the use of interphase and cytoplasmic Fluorescence In Situ Hybridization (FISH) testing, t(11;14) has been found to occur in 15-20% of MM patients.[21, 22] In primary plasma cell leukemia, the incidence of t(11;14) is even higher, up to nearly 50%.[23-25] Higher prevalence of t(11;14) has also been reported in African American patients,[26, 27] although a more recent large prospective cohort study analyzing data from the Connect MM Registry demonstrated similar prevalence of t(11;14) by race.[28]

In some laboratories, the standard CG/FISH panel does not automatically include t(11;14) testing, resulting in under-reporting. However, given the known poorer prognosis of these patients as well as the targetable nature of this translocation, t(11;14) is now increasingly being incorporated as part of the diagnostic panel in patients with suspected MM. While CG/FISH testing is the standard method of detection for t(11;14), micro single nucleotide polymorphisms (SNP)-array or next-generation sequencing (NGS) can also be used, although these tests are not as easily accessible. In countries where NGS testing is accessible, this is potentially a more cost-effective method of biomarker testing.

Pathogenesis of t(11;14) and BCL2-dependence in multiple myeloma

The survival of MM cells with t(11;14) is driven by its ability to evade cellular apoptosis. This ability is underpinned by overexpression of the pro-survival BCL2-protein. To understand the pathogenesis of t(11;14) MM, we first need to appreciate the critical role that the BCL2 family of proteins play in regulating the intrinsic pathway of apoptosis and cell survival.

The BCL2-network consists of three functional subfamilies, that is, the anti-apoptotic / pro-survival members (e.g. BCL2, MCL1, BCL-XL), pro-apoptotic members (BAX and BAK), and BH3-only members (e.g. BIM, BID, BAD, NOXA).[29] Anti-apoptotic BCL2-proteins maintain cellular viability via inhibition of BAX and BAK. In response to physiological stressors, expression of BH3-only proteins is increased; these proteins bind pro-survival BCL2-proteins thus allowing for BAX/BAK-driven apoptosis (Figure 1A). In myeloma cells, the presence of t(11;14) confers an increase dependence on BCL2, with high levels of expression compared to the other anti-apoptotic proteins, BCL-XL and MCL1.[30] This dysregulated balance of pro-survival and pro-apoptotic proteins drives ongoing MM cell survival (Figure 1B).

Our understanding of this mitochondrial pathway of life-death has led to the development of small molecules that mimic BH3-only proteins. BH3-mimetics bind tightly to pro-survival BCL2-proteins, and inhibit their ability to bind to BAX/BAK (Figure 1C). Cancer cells that are particularly reliant on BCL2 are highly sensitive to these drugs. Venetoclax is a first-in-class oral BCL2-selective BH3-mimetic that has demonstrated efficacy in the treatment of various hematological malignancies such as acute myeloid leukaemia (AML) and chronic lymphocytic leukaemia (CLL) and has received approval in the treatment of these conditions.

In the MM space, a preclinical study by Touzeau et al[9] confirmed that myeloma cell lines with CCND1 translocation were the most sensitive to venetoclax, with a high BCL2/MCL-ratio being the most powerful biomarker for predicting sensitivity to venetoclax. This has successfully translated into clinical practice with multiple studies demonstrating the efficacy of venetoclax, as well as second generation BCL2i, in the treatment of RRMM patients with t(11;14).[10-17, 31, 32]

It is important to note however, that BCL2-protein overexpression with high BCL2/BCL-XL or BCL2/MCL1 ratio is not synonymous with the presence of t(11;14). This was demonstrated by De Ramon et al.[33] in an analysis of 120 NDMM patients treated on the PETHEMA/GEM2012 study. Quantification of BCL2-family protein expression was performed on patient samples using capillary nanoimmunoassay. While t(11;14) patients had significantly higher BCL2/BCL-XL ratios compared to non-t(11;14) patients, some patients with other CG abnormalities expressed a higher ratio compared to those of the third quartile of the t(11;14) cohort. Certainly, the efficacy of venetoclax has also been demonstrated in non-t(11;14) myeloma with high BCL2 expression in both in vitro and clinical studies.[33-35] This suggests that quantification of BCL2-protein expression could potentially be a better and more inclusive biomarker predicting response to BCL2i therapy, rather than relying solely on the presence of t(11;14). BCL2-protein expression in MM patients have been analysed via RNA

sequencing, immunohistochemistry, and flow cytometry.[35-38] There is yet, however, to be a standardised method of BCL2 quantification, thus making t(11;14) translocation the main biomarker for response to BCL2i currently.

Prognostic implications of t(11;14) in multiple myeloma

Based on the R-ISS staging system[2] and the recently published IMS/IMWG Consensus Genomic Staging of high-risk MM,[3] isolated t(11;14) is still considered a standard-risk lesion. However, there is now growing consensus that t(11;14) does confer inferior prognosis, with poorer outcomes compared to other standard-risk subgroups.

Several studies have reported on the impact of t(11;14) on patient outcomes.[4-8, 21, 22, 28, 39] Results of clinical studies on NDMM patients treated with conventional chemotherapy concluded t(11;14) to be a neutral genetic lesion.[21, 22] However, studies in the era of induction with immunomodulatory drugs (IMiD) and/or proteasome inhibitors (PI) demonstrate that patients with t(11;14) and no other HRCA have shorter PFS, OS and time to next treatment (TTNT).[4-8] Table 1 provides a detailed summary of these studies.

In the largest study to date investigating t(11;14) patients, Bal et al[6] compared a total of 5581 patients across five cohorts: del(17p) versus HRCA versus chromosome 1 (chr(1)) abnormality versus t(11;14) with no high-risk lesions versus non-t(11;14). This robust study provided a nuanced analysis of not just the significance of t(11;14), but also provided insight into its behavior in the presence of other CG abnormalities. Patients with t(11;14) had shorter PFS compared to the non-t(11;14) group, but longer PFS compared to the other three groups. There was no difference in PFS or OS between the t(11;14) and non-t(11;14) group who had combination IMiD and PI induction. Survival in t(11;14) patients with concomitant chr(1) abnormalities were similar. However, patients with t(11;14) and del(17p) had worse OS compared to patients with del(17p) without IgH translocations (34 months vs 47 months, $p<0.01$), suggestive of a "double-hit" phenomenon. This is consistent with the findings of a retrospective study at Mayo Clinic of 795 NDMM patients where the presence of concurrent del(17p) (10.7%) and ISS Stage III were predictive of reduced OS in the t(11;14) cohort.[5]

One study in the era of IMiD and/or PI induction has reported t(11;14) to be a neutral prognostic factor. The Connect MM registry was a large prospective study that showed that the presence of t(11;14) had no impact on PFS or OS, regardless of the type of induction therapy.[28] Authors concluded that concurrent CG abnormalities were more important to consider when evaluating the

prognostic impact of t(11;14). It is important to note however, that only a third of patients in this study had combination IMiD and PI induction.

The study that is most applicable to current clinical practice is that of a retrospective study by Kaufman et al[8] of 1000 NDMM patients who all had induction with combination IMiD and PI (lenalidomide-bortezomib-dexamethasone). Patients with t(11;14) had lower rates of very good partial response or better (≥VGPR) post induction (49.5% vs 76.3%, p<0.001), and shorter median PFS (51 months vs 75 months, p<0.001) compared to those with standard risk CG. This difference was even more marked in patients who did not receive maintenance therapy. The impact of t(11;14) on outcomes in patients who underwent autologous stem cell transplant (ASCT) at MD Anderson has been evaluated in a retrospective study, where two thirds of patients received induction with either IMiD and/or PI agents.[4] Patients with t(11;14) had shorter PFS and OS compared to the normal CG cohort, but better outcomes compared to those with HRCA. The recently presented Phase III MIDAS study evaluated an MRD-driven consolidation and maintenance approach following induction of all NDMM patients with quadruplet therapy of isatuximab, carfilzomib, lenalidomide and dexamethasone.[40] Post induction and consolidation, NDMM patients with t(11;14) demonstrated lower minimal residual disease (MRD) negativity rates compared to those who were non-t(11;14), at 40% vs 59% and 63% vs 78% respectively. Results from the Mayo clinic support early ASCT in t(11;14) patients; patients with t(11;14) had shorter estimated OS compared to the no-translocation group (74.4m vs 103.6m (p=0.003), with early ASCT demonstrated to improve OS in all cohorts.[5] In the t(11;14) cohort, median OS with early ASCT was 88.4m versus 58.1m with delayed ASCT (p=0.002).

Overall, cumulative evidence strongly suggest that t(11;14) confers poorer prognosis compared to other standard-risk subgroups. It is also vital to consider coexisting cytogenetic lesions when evaluating the prognostic power of t(11;14), particularly the presence of del(17p) and 1q+. This can help predict response to therapy both at diagnosis as well as at relapse. Concurrent del(17p) and/or 1q+ portends poorer outcomes in all MM patients, but also appears to reduce sensitivity to treatment with BCL2-inhibition in t(11;14) patients. In a retrospective study of 232 relapsed and/or refractory multiple myeloma (RRMM) patients treated at Mayo Clinic with venetoclax-based regimens, 37/190 (19.5%) and 64/190 (33.7%) of t(11;14) patients had concurrent del(17p) and 1q+ respectively. The t(11;14) patients with either of these CG abnormalities had lower overall response rates (ORR) (57% vs 71%, p=0.04) and significantly shorter median PFS (7.7m vs 15.1m; p=0.013) when compared to those with no abnormalities.[41] Findings of these studies bring to the forefront the importance of utilizing highly effective treatments in the treatment of t(11;14) patients early in the

disease course, prior to the development of secondary CG lesions that confer an even poorer prognosis. The question of the most optimal BCL2i-combination regimen in this subpopulation of patients with t(11;14) and concurrent high-risk CG remains unanswered.

TARGETED THERAPY IN THE TREATMENT OF t(11;14) MULTIPLE MYELOMA

Currently, translocation t(11;14) is the only targetable lesion in MM. Given this, as well as the fact that these patients have worse outcomes compared to standard-risk MM, the use of BCL2i as a preferred therapeutic strategy in this cohort of patients is of particular interest. To date, no BCL2i have received regulatory approval for the treatment of MM. Despite the fact that BCL2i are not yet licensed, the current international recommendation for t(11;14) patients with relapsed disease is to use a BCL2i-based regimen, where accessible.[42, 43]

Venetoclax

BCL2i was first investigated for use in MM in a Phase I study in which RRMM patients were treated with venetoclax monotherapy at doses up to 1200mg daily.[10] Overall response rate (ORR) was 21% (14/66) in all patients, with a higher ORR of 40% (12/30) demonstrated in the subset with t(11;14). The t(11;14) subgroup were heavily pre-treated with median prior lines of therapy (LOT) of five (range 1-10); 77% of patients were lenalidomide-refractory, and 67% were double-class refractory.

A subsequent phase I/II study by Kaufman et al[11] investigated the combination of venetoclax and dexamethasone in RRMM patients specifically with t(11;14). The phase II portion of this study included 31 patients who had five (range 2-12) median prior LOT with majority of patients being IMiD, PI and/or daratumumab-refractory. Doublet therapy demonstrated encouraging ORR of 48%, with 36% of patients achieving ≥VGPR. Median time to progression was 10.8 months. Exploratory studies also confirmed that higher BCL2 levels were seen in patients who achieved a partial response (PR) or better, consistent with our known understanding of the mechanism of action of BCL2i in t(11;14) MM. The positive results of this study also support in vitro findings by Matulis et al[44] regarding the synergistic effect of venetoclax and dexamethasone. In MM cell lines, dexamethasone shifts BIM binding towards BCL2, resulting in increased sensitivity to venetoclax and hence increased cell death.

Clinical studies on venetoclax-combination treatments

A number of studies have since explored the use of venetoclax and dexamethasone in combination with other standard-of-care (SOC) drugs, including bortezomib, daratumumab and carfilzomib, with clinical evidence of synergism.[12-16, 34] These studies are summarized in Table 2.

The phase III BELLINI study investigated the addition of venetoclax to bortezomib and dexamethasone in RRMM patients who had had one to three prior LOT.[12, 13, 34, 45] This study included both non-t(11;14) (n=256) and t(11;14) patients (n=35), and demonstrated significant improvement in PFS across all patients with venetoclax versus placebo plus bortezomib and dexamethasone (median PFS 23.4 months vs 11.4 months; HR 0.58). The positive effect of venetoclax on patient outcomes was particularly evident in the subgroup of patients with t(11;14) and/or high BCL2 expression.[46] Interestingly, of the patients who were t(11;14)-positive, 45.7% (16/35) were non-BCL2-high. A total of 98 patients were BCL2-high, of which majority (80.6%; 79/98) were non-t(11;14). In the t(11;14) cohort, median PFS was 36.8 months in the venetoclax arm versus 9.3 months in the placebo arm (HR 0.17). Similarly, BCL2-high patients had significantly longer PFS with the addition of venetoclax (30.1 months vs 9.9 months; HR 0.36). In the recently published final survival results, at a median follow up of 45.6 months, OS in the t(11;14) subgroup was not reached in either treatment group.[45] Conversely, OS was in favour of the placebo group in the subgroup with non-t(11;14) and low BCL2 expression (median OS 46.1m with venetoclax vs not reached with placebo; HR 1.38). Another critical finding of the BELLINI study was that of increased rates of ≥Grade 3 infections in the venetoclax group, with increased proportion of infection-related deaths. In the subgroup with t(11;14) and/or high BCL2 expression, this was in keeping with longer duration of venetoclax exposure, and rates were within expected range for the relapsed/refractory MM setting. However, in the non-t(11;14) and low BCL2 expression subgroup, higher infection rates were seen despite shorter time on venetoclax compared to placebo; this was likely secondary to suboptimal disease control in these patients, in combination with venetoclax-induced immunosuppression. The BELLINI study concluded an overall favourable benefit-risk profile of venetoclax in patients with t(11;14) and/or high BCL2 expression.[45] These results have been crucial in informing the landscape of future studies on BCL2i and the importance of a biomarker-driven approach in patient selection. It also emphasizes the importance of adequate anti-microbial prophylaxis when using BCL2i-based regimens to reduce the risk of serious infections.

A recently published update of a Phase I/II study comparing venetoclax versus bortezomib in combination with daratumumab and dexamethasone (VenDd vs DVd) in 80 patients with t(11;14) and one or more prior LOT, again demonstrated a significantly higher ORR (96.4% vs 65.4%) with the

use of venetoclax.[17] Responses were also significantly deeper in the VenDd arm with MRD-negativity rates of 38% versus 8% with DVd. This finding was consistent across all key subgroups including high-risk cytogenetics and lenalidomide refractory status. This translated to longer PFS in the venetoclax cohort with a 33-month PFS rate of 73.4% in the VenDd cohort, versus 38.8% with DVd.

The CANOVA study, designed to be a Phase III registration level study, compared venetoclax and dexamethasone versus pomalidomide and dexamethasone (VenDex vs PomDex) in 263 patients with t(11;14)-positive RRMM who had had two or more prior LOT. In the first read out of this study, VenDex was associated with a higher ORR of 63% versus 35% with PomDex ($p<0.001$).[47] However, while PFS was longer in the VenDex arm (9.9 months vs 5.8 months), this did not reach statistical significance and this study did not meet its primary endpoint. This was likely due to informative censoring.[48] On reviewing the data, investigators found that 21 patients in the PomDex arm, versus four patients in the VenDex arm, discontinued treatment for reasons other than disease progression or adverse events; these patients were censored in the primary PFS analysis. In the post hoc PFS analysis where censored patients were included and in which the start of a new anti-myeloma therapy was accounted for as an event, investigators demonstrated a significantly longer PFS of 9.4 months versus 4.0 months for VenDex versus PomDex (HR 0.651; $p=0.003$). The findings of the CANOVA study emphasizes the importance of ensuring a study is sufficiently powered to account for informed censorship.

Second generation BCL2-inhibitors

Despite these preliminary results of the CANOVA study, current cumulative evidence, including that of real-world data,[49, 50] remains in strong support of the use of BCL2i in the treatment of t(11;14) MM patients. Second generation BCL2i drugs are now being explored.

Early data on sonrotoclax, a second generation BH3-mimetic that bind and inhibits BCL2 with a potency more than 10-times that of venetoclax, has shown promising efficacy in the relapsed/refractory setting.[31] At a recommended phase II dose (RP2D) of 640mg daily and in combination with dexamethasone, sonrotoclax has been found to be safe and tolerable and able to induce deep responses with ORR of 80.6% and ≥VGPR rate of 55.6% in heavily pre-treated patients (median prior LOT 3 (1-12)).[32, 51] This study is ongoing, with sonrotoclax currently being investigated in combination with other SOC drugs including daratumumab and carfilzomib. ABBV-453 (surzetoclax) is another highly potent second generation BCL2i that has demonstrated high affinity and selectivity for BCL2 over BCL-XL and MCL1 with superior activity in xenograft models compared

to other BCL2i drugs,[52] and is currently being investigated in combination with dexamethasone, daratumumab and lenalidomide. Table 3 summaries ongoing clinical trials of venetoclax and second generation BCL2i.

Safety profile of BCL2-inhibitors

BCL2i are also tolerable with an acceptable safety profile. The most common Grade 3 or 4 hematological adverse events (AE) observed are neutropenia and thrombocytopenia. Careful study design and risk management should be considered when combining BCL2i with drugs that have overlapping hematological toxicities. A Phase II study investigating venetoclax with pomalidomide and dexamethasone was terminated early due to all patients experiencing a ≥Grade 3 adverse event, most commonly neutropenia (75%; 6/8 patients).[53] However, only three out of eight patients in this study had t(11;14). This study again highlights the importance of a biomarker driven approach. There is currently an active study investigating a novel combination of venetoclax with iberdomide (cereblon E3 ligase modulator) and dexamethasone, specifically in t(11;14) patients with one to two prior LOT (ACTRN12622001158752).

Common non-haematological AE include infections and gastrointestinal symptoms, particularly diarrhoea.[54] As highlighted in the BELLINI study, infections remain one of the most serious non-haematological AEs with the use of BCL2i.[45] In a recently published real-world retrospective analysis of t(11;14) RRMM patients from nine French centres treated with venetoclax-based therapies (n=46), there was a 24% incidence of ≥grade 3 infections.[50] Of the eighteen patients who died, two were due to infections. Majority of patients were reported to be on Pneumocystis jirovecii pneumonia (PJP) and herpes simplex virus (HSV) prophylaxis (95% and 96% respectively), while only 11% received immunoglobulin replacement therapy. Encouragingly, early data from studies on sonrotoclax 640mg and dexamethasone have shown lower rates of severe infections; rates of G3/4 neutropenia and G3/4 infections were only 14% and 11% respectively.[32, 51]

MECHANISMS OF RESISTANCE TO BCL2-INHIBITORS

Our understanding of the mechanisms of resistance to BCL2i in MM remains limited, and much of our current knowledge is that gained from work done in AML and lymphoid malignancies.[55-57] Acquired resistance has been reported to occur secondary to overexpression of non-BCL2 anti-

apoptotic proteins (MCL1 and BCL-XL),[58-61] acquired mutations in BCL2,[62-64] and alterations in mitochondrial metabolism[65] (see Figure 1D).

The upregulation of MCL1 is a key mechanism of resistance identified. In the presence of BCL2i, increased MCL1 sequesters BH3-only proteins that have been released from BCL2, thus preserving mitochondrial metabolism and cell survival. In AML and lymphoid cell lines, concurrent treatment with MCL1-inhibition resulted in restoration of venetoclax sensitivity.[58-61] In myeloma, upregulation of non-BCL2 anti-apoptotic proteins has been linked to copy number amplification of 1q21 and changes in the bone marrow microenvironment.[66-69] Human myeloma cell lines with co-expression of BCL2 and BCL-XL have been shown to be resistant to venetoclax, but sensitive to a BCL-XL-selective inhibitor. In xenograft models, co-expression of BCL2 and MCL1 also resulted in venetoclax resistance; this was circumvented by co-treatment with bortezomib, as the latter upregulates the pro-apoptotic factor NOXA, which functions to neutralise MCL1.[36]

BCL2 BH3-binding groove mutations, such as Gly101Val and Asp104Tyr, reduce the affinity of BCL2i and is also a recognised mechanism of resistance.[62-64] In CLL cells, Gly101Val has been demonstrated to reduce the affinity of venetoclax to BCL2 by approximately 180-fold, thus preventing the displacement of BIM/BAX from BCL2.[62]

The pathogenesis of acquired resistance to BCL2i is complex and diverse. It is also likely that there are independent mechanisms at play in individual malignant subclones.[55] This is particularly pertinent in MM given that this is an intrinsically heterogeneous disease with multiple subclones seen. More work is required to understand BCL2i resistance in MM, to allow for mechanistically rational combination treatments and/or development of new drugs that can overcome resistance.

FUTURE OF BCL2-INHIBITOR THERAPY IN t(11;14) MULTIPLE MYELOMA

As we work towards regulatory approval of BCL2i, there are many ongoing key questions to be addressed by future clinical studies. This include incorporation of BCL2i into induction therapy for NDMM t(11;14) patients, examination of the role of BCL2i in the era of T-cell engager therapies, establishment of a standardized and accessible method of BCL2-protein quantification, and further investigation of mechanisms of resistance of BCL2i in MM.

All patients should be screened for t(11;14) at diagnosis, to enable early access to BCL2i-based combination treatment, before the disease becomes more resistant via the acquisition of high-risk secondary mutations at relapse, such as del(17p) and 1q+.[41] Indeed, recent meta-analysis by Xu et al[54] demonstrated higher response rates to venetoclax in patients who were less heavily pre-treated. Considering this, and the fact that t(11;14) is associated with suboptimal responses to IMiD- and PI-based induction therapies (as outlined in Table 1), BCL2i-combination treatments warrants investigation in the newly diagnosed setting. These studies should also include patients with primary plasma cell leukemia, where t(11;14) occurs in nearly 50% of cases and prognosis remains dismal.[23-25] Patients with t(11;14) may benefit from a different treatment approach, including incorporating a BCL2i at the outset. This strategy is rational, as t(11;14) is present in all subclones, and early intervention with a BCL2i could effectively target the entire myeloma clone population. Currently, a Phase I study testing the safety and efficacy of combination venetoclax with lenalidomide-dexamethasone, daratumumab-dexamethasone, and daratumumab-lenalidomide-dexamethasone in NDMM transplant ineligible patients with t(11;14) exists (NCT06042725), but not in transplant eligible patients. The incorporation of a BCL2i into the induction phase, as well its role in maintenance post-ASCT with or without lenalidomide, would be an area of interest for future studies.

Perhaps the most exciting key area for exploration is the role and sequencing of BCL2i therapy in the era of T-cell engager therapies (e.g. bispecific or trispecific antibodies, CAR-T cell therapy). The significant impact the latter has had on patient survival raises the all-important question of whether t(11;14) patients should preferentially access venetoclax-based treatments or T-cell engagers. While this would largely be dependent on access in many countries, sequencing remains a salient consideration. Evidence on the outcomes of t(11;14) patients with T-cell engager therapies is sparse, and certainly future studies should report specifically on this when analyzing the impact of CG/FISH on treatment efficacy and patient survival. Certainly, the prospect of combining BCL2i and a T-cell engager therapy is an attractive one, not just as targeted therapy in t(11;14) MM, but also due to its potential synergism. Venetoclax has been shown in pre-clinical studies to have immunomodulatory effects; in a study of CLL patient samples, flow cytometry analysis demonstrated less T-helper and T-cytotoxic T-cell exhaustion following venetoclax treatment.[70] This positive impact of BCL2i on T-cell fitness can be harnessed to boost the efficacy of T-cell engagers, and raises interesting opportunities in terms of treatment sequencing. Potential regimens including utilizing BCL2i as bridging therapy pre-CAR-T, or maintenance therapy post CAR-T cell therapy. BCL2i could also be used to limit exposure to bispecific/trispecific antibodies, and therefore minimize long term side effects. For

example, one could consider fixed treatment duration of a bispecific/trispecific antibody followed by maintenance treatment with a BCL2i, or even an alternating BCL2i/T-cell engager therapy regimen to minimize T-cell exhaustion over time and reduce the risk of resistance. A clear area of unmet need is also in patients with concurrent t(11;14) and del(17p) and/or 1q+. Currently literature remains sparse in terms of the best BCL2i-based treatment combination in this high-risk population. In this cohort, the concept of combining BCL2i and T-cell engager therapy is an attractive one.

Certainly, for this BCL2i/T-cell engager combination to be feasible, it is also vital to consider the overlapping and cumulative infection risk of these two agents. Studies should be designed with this in mind. Indeed, stringent anti-infective prophylactic strategies is crucial in any BCL2i regimen and should be initiated from the start. This includes shingles prophylaxis (e.g. valaciclovir) for all patients, and Pneumocystis jirovecii pneumonia prophylaxis (e.g. trimethoprim/sulfamethoxazole) especially in heavily pre-treated patients. Adequate use of filgrastim for neutropenia treatment and/or prophylaxis as well as early immunoglobulin replacement therapy for hypogammaglobulinemia is also strongly encouraged. Future studies should also consider incorporating response-adapted therapy. An MRD-adapted strategy where patients with sustained MRD-negativity could cease therapy would certainly be beneficial to minimize toxicities, particularly the infection risk that comes with prolonged BCL2i exposure as reported in the BELLINI study.[45]

While t(11;14) remains the main current biomarker for response to BCL2i therapy, this is arguably an oversimplified method of patient selection. High BCL2/BCL-XL and BCL2/MCL1 ratios are certainly not exclusive to the t(11;14) cohort.[37] There is a need for more data on the efficacy of BCL2i in non-t(11;14) patients who are BCL2-high, who may indeed be missing out on an effective treatment option. This must start firstly with standardisation of BCL2-protein quantification techniques, including the determination of the optimal "cut-off" that defines BCL2-high expression in relation to sensitivity to BCL2i treatment. Considering the variability of BCL2-protein expression even within the t(11;14) cohort,[37] this may also help stratify t(11;14) patients who are BCL2-low in whom BCL2i may not in fact be the optimal option, with preference for alternative treatment regimens instead.

Ongoing work is also required to better understand the diverse mechanisms of BCL2i resistance in myeloma cell lines. It is vital that rational BCL2i-based treatment regimens take into consideration potential mechanisms of drug resistance (Figure 1D), and should include combination therapies, such as MCL1- and BCL-XL inhibitors, in order to empirically circumvent pathways that can promote escape from targeted BCL2-inhibition.

In order to further our understanding of how best to place BCL2i drugs in the current treatment landscape and also to pave the way for regulatory approval, future clinical trials of BCL2i in t(11;14) MM should be carefully designed to ensure that they are sufficiently powered, with a clinically relevant control arm, vigilant consideration of overlapping toxicities when used in combination with other anti-myeloma drugs, and with clinically meaningful correlative studies incorporated at the outset. Given the 20% incidence of t(11;14) MM, large co-operative multicentre studies are preferred to facilitate robust and timely patient recruitment in a rapidly moving field.

CONCLUSION

Translocation t(11;14) is a key biomarker for predicting response to BCL2i in MM, and its identification is becoming increasingly important in the advent of BCL2-targeted therapies. As a primary cytogenetic lesion, t(11;14) not only predicts sensitivity to BCL2 inhibition but also correlates with suboptimal responses to IMiD/PI-based induction therapy. This defines a population with an unmet clinical need, one that may benefit from the incorporation of BCL2i early in the treatment course, rather than reserving them for the relapsed/refractory setting. Further investigation is required to study the utility of BCL2i in upfront treatment of NDMM patients, examine BCL2i combinations that can overcome additional HRCA that are present at either diagnosis or relapse, and explore the role and placement of BCL2i in the era of T-cell engager therapies. While BCL2i are yet to receive regulatory approval, it remains the treatment of choice in t(11;14) MM.

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TABLE 1: Summary of key studies on t(11;14) in newly diagnosed multiple myeloma

STUDIES	COHORTS	n	RESULTS				STUDY DETAILS	MAIN FINDINGS
Sasaki K et al 2013[4]			**3-yr PFS**	**mPFS**	**3-yr OS**		• Retrospective study • 67% patients received IMiD-based or PI-based induction	• Post ASCT, patients with t(11;14) had worse outcomes compared to normal CG, but better than HRCA.
	Normal CG	869	47%	33m	83%			
	t(11;14)	27	27%	23m	63%			
	HRCA[†]	97	13%	9.7m	34%			
			p<0.00001	p<0.00001	p<0.00001			
Lakshman A et al 2018[5]			**mPFS**	**mTTNT**	**mOS**	**mOS excluding del(17p)**	• Retrospective study • Induction regimen: - IMiD+PI: 14.9% - PI-based: 32.6% - IMiD-based: 45.5%	• t(11;14) had worse outcomes than the no translocation group, but better outcomes than high-risk translocations. • Del(17p) and ISS stage III predicted worse OS in t(11;14). • With del(17p), OS similar between the t(11;14) and no translocation group.
	t(11;14)	65	23m	20.8m	74.4m	81.7m		
	Non-(11;14) translocations	132	19m	18.2m	49.8m	58.2m		
	No translocations	598	28.3m	27m	103.6m	108.3m		
			p<0.01	p=0.01	p<0.01	p<0.01		
Kaufman et al 2018[8]			**Post-VRd induction ≥VGPR rate**	**mPFS**			• Retrospective study • All patients received IMiD+PI with VRd	• t(11;14) had poorer outcomes than standard risk
	t(11;14)	122	49.5%	51m				
	Standard risk (i.e. no del(17p), t(4;14), t(14;16) or complex karyotype)	527	76.3%	75m				
			p<0.001	p<0.001				
Bal et al 2021[6]			**mPFS**					• t(11;14) had poorer outcomes
	Del(17p)	544						

	HRCA††	415	(Worse PFS compared to t(11;14))			• Retrospective study • Induction regimen: - IMiD+PI: 43.6% - PI-based: 28.8% - IMiD-based: 17.4%	compared to the non-t(11;14) group, but better than HRCA • No PFS/OS difference between t(11;14) and non-t(11;14) with IMiD+PI induction • t(11;14) + del(17p) had worse OS than del(17p) alone (34m vs 47m, p<0.01)
	Chr(1) abnormality	1124					
	t(11;14) with no high-risk lesions	589	36.1m				
	Non-t(11;14)	2909	40.1m				
			p=0.03				
Gasparetto et al 2022[28]			**mPFS**	**mOS**		• Multi-centre prospective cohort study • Induction regimen: - IMiD+PI: 34.7% - PI-based: 40% - IMiD-based: 12.8%	• t(11;14) was a neutral prognostic factor regardless of induction type
	t(11;14)	378	34.8m	74m			
	Non-t(11;14)	1196	35.7m	77.3m			
			p=0.77	p=0.94			
Lim et al 2023[7]			**mPFS1**	**mPFS2**	**mOS**	• Retrospective study • Induction regimen: - IMiD+PI: 0% - PI-based: 81% - IMiD-based: 14%	• No PFS1 difference, but PFS2 shorter in t(11;14) versus hyperdiploid.
	t(11;14)	74	22.1m	8.2m	64.2m		
	Hyperdiploid without translocations	111	27.9m	19.8m	100.9m		
	High-risk IgH translocations	159	26.7m	10.0m	59.0m		
			p=0.503	p=0.002	p=0.055		

ASCT: Autologous stem cell transplant; CG: Cytogenetics; HRCA: High-risk chromosomal abnormalities; IMiD: Immunomodulatory drug; ISS: International staging system; m: Median; NDMM: Newly diagnosed multiple myeloma; OS: Overall survival; PFS: Progression free survival; PI: Proteasome inhibitor; VRd: Bortezomib, lenalidomide and dexamethasone; TTNT: Time to next treatment; VGPR: Very good partial response

† del(13q), hypodiploidy, t(4;14), t(14;16), t(14;20), or del(17p); †† t(4;14), t(14;16) or t(14;20)

TABLE 2: Summary of published studies on BCL2-inhibitor based regimens in RRMM patients

Study	Regimen	Number of patients	Efficacy results in t(11;14) patients[†]	Safety results across all patients
Kaufman et al 2021[11] Phase I/II	Ven 800mg + Dex	All with t(11;14) • Phase I = 20 • Phase II = 31	• Phase I: ORR 60% • Phase II: ORR 48%	• Neutropenia: 18% (≥G3: 10%) • Thrombocytopenia: 18% (≥G3: 10%) • Diarrhea: 35% • Nausea: 28% • RTI: 30% • Sepsis: 8%
Kumar et al 2021 (BELLINI)[12, 13, 34, 45] Phase III	Ven 800mg + Vd vs Vd	n = 291 • t(11;14) = 35 • Non-t(11;14) = 256 Biomarker subsets: • BCL2 high = 98 • t(11;14) and/or BCL2 high = 114	Median follow up 45.6m • mPFS: 36.8m vs 9.3m (HR 0.17; p=0.00041) • mOS: NR (NE-NE) vs NR (43.6m-NE) (HR 0.77; p=0.47) • In BCL2-high subset: mPFS 30.1m vs 9.9m (HR 0.36; p=0.00014)	AE for VenVd • ≥G3 Neutropenia: 31% vs 8% • ≥G3 Thrombocytopenia: 26% vs 40% • ≥G3 Infections: 42% vs 29% • Pneumonia: 31% vs 21% • Fatigue: 33% vs 32% • Diarrhea: 60% vs 50% • Constipation: 36% vs 31%
Bahlis et al 2021[16] Phase I	Part 1: Ven (400mg or 800mg) + Dd Part 2: VenDVd	Part 1: n=24; all with t(11;14) Part 2: n=24 • t(11;14) = 6 • Non-t(11;14) = 18	Part 1: • ORR 95.8% • ≥VGPR 95.8% • 24m PFS: 90.8% Part 2: • ORR: 91.7% • ≥VGPR 79.1% • 24m PFS: Not reported for t(11;14) patients (66.7% for all patients)	AE for VenDVd • Neutropenia: 17% (≥G3 4%) • Thrombocytopenia: 21% (≥G3 17%) • Fatigue: 25% • Diarrhea: 54% • Nausea 50% • URTI: 21% • Pneumonia: 4%
Costa et al	Ven (400mg or 800mg)	n = 49	• ORR: 92%	• Neutropenia: 22% (≥G3 12%)

2021[15] Phase II	+ Kd	• t(11;14) = 13 • Non-t(11;14) = 36	• ≥VGPR: 85% • Median duration of response: Not reached (at a median follow up of 27m)	• Thrombocytopenia: 31% (≥G3 8%) • Diarrhea: 65% (≥G3 10%) • Nausea: 47% (≥G3 4%) • URTI: 39% (≥G3 0%) • Sinusitis: 20% (≥G3 0%) • Pneumonia: 18% (≥G3 12%) • Influenza: 16% (≥G3 6%)
Gasparetto et al 2021[53] Phase II	Ven 400mg + PomDex	n = 8 • t(11;14) = 3 • Non-t(11;14) = 5	Study terminated early due to concerns regarding adverse events. Decision to pursue biomarker driven strategy. All patients had a ≥G3 adverse event, mainly neutropenia.	• G3/4 neutropenia: 75%
Bahlis et al 2023[17] Phase I/II	Ven (400mg or 800mg) + Dd vs DVd	All t(11;14) • Ven(400mg)Dd = 26 Ven(800mg)Dd = 29 • DVd = 26	• ORR: 96% vs 65% • ≥VGPR: 93% vs 39% • 33-month PFS: 73.4% vs 38.8% • MRD-negative rates: 38% vs 8% (consistent across subgroups including lenalidomide refractory status and high-risk CG)	AE for VenDd[71] • ≥G3 neutropenia: 12.7% • ≥G3 thrombocytopenia: 3.6% • ≥G3 infections: 34.5% • ≥G3 diarrhea: 7.8%
Mateos et al 2023[47] *(CANOVA)* Phase III	Ven 800mg + Dex vs PomDex	All t(11;14) • VenDex = 133 • PomDex = 130	• ORR: 62% vs 35% (p<0.001) • mPFS: 9.9m vs 5.8m (p=0.237) • Post-hoc analysis including censored patients – mPFS: 9.4m vs 4.0m (HR 0.651; p=0.003)	AE for VenDex: • ≥G3 neutropenia: 19% • ≥G3 thrombocytopenia: 13% • ≥G3 anemia: 13% • ≥G3 infections: 22% (all grade 61%) • ≥G3 diarrhea: 4%
Dhakal et al 2024[32, 51]	Sonrotoclax 640mg + Dex	All t(11;14)	• ORR: 80.6%	• ≥G3 Neutropenia: 14%

Phase Ib/II		• n=24	• ≥VGPR: 55.6%	• ≥G3 Thrombocytopenia: 11.% • Infection: 72% (≥G3: 11%) • Fatigue: 30.6% • Diarrhea: 38.9% • Nausea: 19.4% • Constipation: 16.7%

†Note that some studies included all-comers (i.e. both t(11;14) and non-t(11;14) patients). The efficacy data presented in this table is only that reported in the cohort of patients with t(11;14).

AE: Adverse event; D: Daratumumab; Dex/d: Dexamethasone; ≥G3: Grade 3, 4 or 5 AE as per CTCAE; HR: Hazard ratio; K: Carfilzomib; MRD: Minimal residual disease; NE: not estimable; ORR: Overall response rate; OS: Overall survival; PFS: Progression free survival; Pom: Pomalidomide; RRMM: Relapsed and/or refractory multiple myeloma; URTI: Upper respiratory tract infection; V: Bortezomib; Ven: Venetoclax; VGPR: Very good partial response.

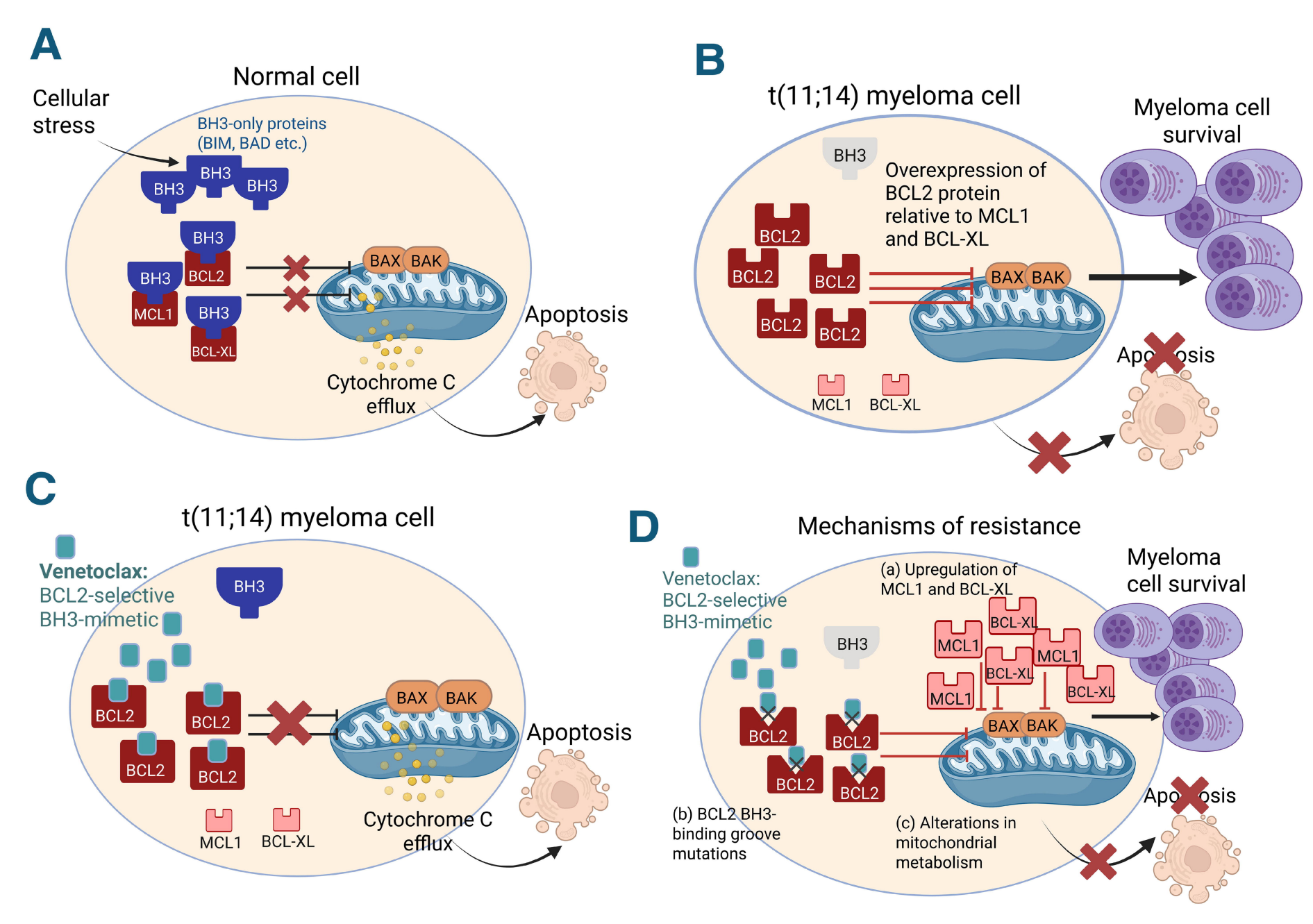
TABLE 3: Current ongoing recruiting clinical trials with BCL2-inhibitor based regimens

BCL2-inhibitor	Phase of study	Patient population	Regimens	Clinical Trials ID
Venetoclax	Phase Ib/II Phase I	t(11;14) RRMM t(11;14) NDMM (TIE)	Venetoclax + Iberdomide + Dexamethasone Venetoclax + Daratumumab + Dexamethasone Venetoclax + Lenalidomide + Dexamethasone Venetoclax + Daratumumab + Lenalidomide + Dexamethasone	ACTRN12622001158752 NCT06042725
		t(11;14) RRMM	Venetoclax + Lenalidomide + Dexamethasone Venetoclax + Daratumumab + Lenalidomide + Dexamethasone	
	Phase II	t(11;14) RRMM	Venetoclax + Selinexor + Dexamethasone	NCT05530421
	Phase I	t(11;14) RRMM	Venetoclax + Tocilizumab	NCT05391750
	Phase II	t(11;14) RRMM	Venetoclax + Isatuximab + Dexamethasone	NCT06115135
	Phase I/II	t(11;14) RRMM	Venetoclax + Belantamab mafadotin +/- Dexamethasone	NCT05853965
Sonrotoclax	Phase Ib/II	t(11;14) RRMM	Sonrotoclax monotherapy Sonrotoclax + Dexamethasone Sonrotoclax + Carfilzomib + Dexamethasone Sonrotoclax + Daratumumab + Dexamethasone Sonrotoclax + Pomalidomide + Dexamethasone	NCT04973605
Surzetoclax (ABBV-453)	Phase I	RRMM with t(11;14) and/or BCL2 high	Surzetoclax monotherapy Surzetoclax + Dexamethasone Surzetoclax + Daratumumab + Dexamethasone Surzetoclax + Daratumumab + Lenalidomide + Dexamethasone	NCT05308654
	Phase I/II	RRMM with t(11;14) and/or BCL2 high	Surzetoclax monotherapy Surzetoclax + Daratumumab + Dexamethasone	NCT06953960
Lisaftoclax (APG-2575)	Phase Ib/II	RRMM with or without t(11;14)	Lisaftoclax monotherapy Lisaftoclax + Lenalidomide + Dexamethasone	NCT04674514
	Phase Ib/II	RRMM with or without t(11;14)	Lisaftoclax + Pomalidomide + Dexamethasone Lisaftoclax + Daratumumab + Lenalidomide + Dexamethasone	NCT04942067

NDMM: Newly diagnosed multiple myeloma; RRMM: Relapsed and/or refractory multiple myeloma; TIE: Transplant ineligible

FIGURE 1: BCL2 protein family driven regulation of cellular survival and apoptosis: Dysregulation in t(11;14) myeloma cells, mechanism of action of BH3-mimetics and potential mechanisms of resistance.

(A) Regulation of the intrinsic apoptotic pathway by the BCL2 family of proteins in normal cells: In response to physiological stressors, expression of BH3-only proteins is increased. These proteins bind and inhibit pro-survival BCL2-proteins, thus allowing for BAX/BAK-driven apoptosis. **(B)** The presence of t(11;14) in myeloma cells confers an increase dependence on BCL2, with high levels of expression compared to the other anti-apoptotic proteins, BCL-XL and MCL1. This dysregulated balance of pro-survival and pro-apoptotic proteins drives ongoing MM cell survival. **(C)** Venetoclax is a first-in-class oral BCL2-selective BH3-mimetic that binds tightly to pro-survival BCL2-proteins and inhibits their ability to bind to BAX/BAK, thus allowing for cellular apoptosis. **(D)** Acquired resistance has been reported to occur secondary to (a) upregulation of non-BCL2 anti-apoptotic proteins (MCL1 and BCL-XL), (b) acquired BCL2 BH3-binding groove mutations, and (c) alterations in mitochondrial metabolism.
Figure 1A: Created in BioRender. Sim, S. (2025) https://BioRender.com/4ihz60d
Figure 1B: Created in BioRender. Sim, S. (2025) https://BioRender.com/wdj4eop
Figure 1C: Created in BioRender. Sim, S. (2025) https://BioRender.com/vze45a5
Figure 1D: Created in BioRender. Sim, S. (2025) https://BioRender.com/inasltz


A
Normal cell
Cellular stress
BH3-only proteins (BIM, BAD etc.)
BH3
BH3
BH3
BH3
BH3
BCL2
MCL1
BH3
BCL-XL
BAX
BAK
Cytochrome C efflux
Apoptosis
B
t(11;14) myeloma cell
BH3
Overexpression of BCL2 protein relative to MCL1 and BCL-XL
BCL2
BCL2
BCL2
BCL2
BCL2
BAX
BAK
MCL1
BCL-XL
Myeloma cell survival
C
t(11;14) myeloma cell
Venetoclax:
BCL2-selective
BH3-mimetic
BH3
BCL2
BCL2
BCL2
BCL2
BAX
BAK
MCL1
BCL-XL
Cytochrome C efflux
Apoptosis
D
Mechanisms of resistance
Venetoclax:
BCL2-selective
BH3-mimetic
(a) Upregulation of MCL1 and BCL-XL
BH3
MCL1
BCL-XL
MCL1
BCL-XL
MCL1
BCL-XL
BCL2
BCL2
BCL2
BCL2
BAX
BAK
Myeloma cell survival
(b) BCL2 BH3-binding groove mutations
(c) Alterations in mitochondrial metabolism