

# BCL-2 Inhibition in the Treatment of Multiple Myeloma



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## Introduction

Multiple myeloma is the second most common haematological malignancy – though multiple effective therapeutic options exist for disease control – cure of myeloma still remains the exception. Our present therapeutic approach is founded on apoptosis induction in tumor cells by various different stimuli, most commonly by DNA damage, oxidative or endoplasmic reticular (proteomic) stress. Effective treatment of relapsed and/or refractory disease rarely provides long term disease control mainly due to development of resistance to pharmacological induction of apoptosis pathways.

As members of the B-cell lymphoma 2 (BCL-2) family of mitochondrial proteins are crucial regulators of common apoptotic pathways, inhibition of anti-apoptotic members of this protein family has gained acceptance in the clinical practice [1]. This is especially true in the treatment of chronic lymphocytic leukemia (CLL), hallmarked by the approval of the BCL-2 inhibitor venetoclax as a particularly effective salvage therapy for this disease [2]. Proteins of the BCL-2 family are commonly categorized as pro- or anti-apoptotic members, the latter being BCL-2, BCL-XL, MCL-1 and BCL-W [3]. The cell death mediator proteins BAK and BAX facilitate apoptosis by induction of mitochondrial depolarization, cytochrome c leakage and finally caspase-dependent cell death. The crucial function of anti-apoptotic BCL-2 family members is the inhibition of BAK/BAX activity through direct protein-protein interactions.

While CLL cells may effectively evade apoptosis by pronounced reliance on BCL-2 activity, in other malignancies distinct BCL-2 family members may have a greater influence. As prior preclinical studies indicated that in plasma cells as well as in multiple myeloma MCL-1 may be the major anti-apoptotic BCL-2 analogue [4], clinical testing of the BCL-2 specific venetoclax (ABT-199) in this disease started with a moderate level of enthusiasm. In the Phase I clinical study M13-367, venetoclax monotherapy was given to relapsed/refractory multiple myeloma patients with measurable disease (with a median of 5 prior lines of therapy). 1200 mg of

venetoclax was determined as a tolerated, safe (and effective) dose [5,6]. During the trial, the preclinical hypothesis [7] was confirmed that myeloma patients with translocation t(11;14) (IgH/CyclinD1) responded more favorably to this therapy.

Therefore, this specific cohort was expanded to include 30 patients, a feasible approach as approximately 20% of all myeloma patients harbor this translocation. With respect to the entire study population (66 patients), the objective response rate was 21%, however, nearly all of the responding patients came from the t(11;14) subgroup. In this subgroup, the response rate amounted to 40% that included 14% complete remissions. Looking in the reverse, only 2 of those patients without translocation t(11;14) in the entire trial population of 66 individuals had any meaningful response to venetoclax. This observation coincides with the preclinical experimental finding that in case of translocation t(11;14) in multiple myeloma, the ratio of BCL-2 to MCL-1 expression is shifted towards higher BCL-2 levels [7,8].

It was also observed that venetoclax-sensitive cells exhibited not only higher BCL-2 expression but venetoclax-resistant cells have higher BCL-XL and MCL-1 expression. If you consider venetoclax a targeted therapy for multiple myeloma with translocation t(11;14) and make a naive comparison with other available therapeutic options for a heavily pretreated relapsed-refractory patient population, judicious use of venetoclax may emerge as a particularly effective salvage option for these patients. 40% overall response rate (ORR) for venetoclax monotherapy compares favorably to 31% ORR for pomalidomide/dexamethason (from trial MM-003) [9], 29% ORR for daratumumab (from trial SIRIUS) [10] and 24% ORR for carfilzomib (from trial PX-171-003) [11]. The particular effectiveness of venetoclax in this genetic subpopulation is underlined by the 27% >VGPR (very good partial remission) rate, quite unprecedented in this severely pretreated population, and importantly independent of refractory status to prior therapies. Since this high efficacy of venetoclax is specifically limited to patients with translocation t(11;14), and even here the response

is not uniform, BCL-2 protein profiling may be the best option for selecting the right patients for this targeted therapy.

In selected myeloma patients with translocation t(11;14) and high BCL-2: BCL-XL ratio the overall response rate may amount to 88% with CR rate of 44%, that is really exceptional in multiple myeloma therapy. As an added bonus, duration of response in this subgroup of high BCL-2: BCL-XL ratio had a median of 12 months. Validity of these early trial observations was further supported by individual case reports of myeloma and plasma cell leukemia patients in dire clinical situation responding exceptionally well to venetoclax administration [12,13]. Combination of BCL-2 inhibition with other therapeutic modalities may be an option to widen the range of applicability of this approach. Preliminary experimental results indicated that the proteasome inhibitor bortezomib, a highly effective myeloma drug may exert some of its activity by stabilizing the MCL-1 neutralizing protein NOXA [14].

As MCL-1 expression may be a potential resistance mechanism to venetoclax activity, bortezomib may prove to be a good combination partner to venetoclax. It was also shown that dexamethason sensitizes myeloma cell lines and primary myeloma cells to venetoclax activity, therefore clinical study M12-901 was initiated to test this triple combination (bortezomib-venetoclax-dexamethason) in relapsed/refractory myeloma patients [15]. Here, the objective response level reached 67% and was not restricted at all to t(11;14) patients, proving the validity of the approach. Moreover, for those patients not refractory to proteasome inhibitors and immunomodulatory agents, the response rate for the triple combination reached an impressive 92%. Overall response rates were similar across different cytogenetic profiles; most notably it was 47% in those patients [15] who had deletion 17p, a particularly high-risk subgroup with severely compromised apoptosis process. The importance of high BCL-2 expression predicting better and more prolonged clinical response was also underlined in this study. Higher baseline BCL-2 levels were detected in patients that achieved a PR or better versus those who did not. Importantly, higher BCL-2 levels were seen in the patient subgroup that had only 1-3 prior lines of therapy compared to those with more than 4 lines of therapy. Median time to progression (11.6 months vs 5.7 months) was longer in patients with high versus low BCL-2 expression. These very promising early phase data prompted the initiation of the M14-031 (Bellini) clinical trial that aims for registration of the bortezomib-venetoclax-dexamethason triple combination as salvage therapy for relapsed/refractory multiple myeloma with 1-3 prior lines of therapy.

Based on these impressive early clinical data, it is conceivable that BCL-2 inhibition by venetoclax has just provided us the entry point of individualized targeted therapy for a certain important subset of multiple myeloma patients. As newer and newer apoptosis inducers, including MCL-1 inhibitors are entering the

clinic, hopefully many of our patients may soon enjoy the benefit of personalized myeloma treatment approaches.

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