Small-Molecule BCL2 BH4 Antagonist BDA-366 for Multiple Myeloma therapy

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Multiple myeloma (MM) is a heterogeneous plasma cell malignancy. Despite improvements in MM treatment, the disease remains incurable. B-cell lymphoma-2 (Bcl2) protein has two functional anti-apoptotic domains – the BH2-BH1-BH3 hydrophobic pocket and the BH4 domain – which play essential roles in promoting the survival and drug resistance of myeloma cells. BH3 mimetics have been developed to disrupt the binding between BCL2 and its pro-apoptotic Bcl2 family partners for the treatment of MM, but their therapeutic efficacy is limited. We recently identified a small molecule Bcl2 BH4 domain antagonist, BDA-366, which induces a conformational change in BCL2 that converts it from an anti-apoptotic into a pro-apoptotic molecule, and has potent anti-cancer activity. In this study, we demonstrate that BDA-366 induces robust apoptosis in MM cell lines and in primary MM cells from patients by inducing Bcl2 conformational change. Delivery of BDA-366 substantially suppressed the growth of human MM xenografts in NOD-scid/IL2Rγ^{null} mice, without significant cytotoxic effects on normal hematopoietic cells or body weight. Thus, BDA-366 functions as a novel BH4-based Bcl2 inhibitor and offers an entirely new tool for MM targeted therapy.