**Product Description**

**Name:** ABT-737  
**CAS:** [852808-04-9]  
C$_{42}$H$_{45}$ClN$_6$O$_5$S$_2$  
MW: 813,45  
**Catalog #:** LSA861, 10 mg  
**Solubility:**  
DMSO ≥160mg/mL  
Water <1.2mg/mL  
Ethanol <1.2mg/mL  
**Storage:**  
−20°C (stable for 2 years)

For Research Use Only

**Introduction**

ABT-737 is a pan-Bcl-2 inhibitor that has a wide range of single-agent activity against acute lymphoblastic leukemia (ALL) cell lines and xenografts. Increased expression of the Bcl-2 family of proteins in cancers has been associated with chemotherapy resistance, inhibiting Bcl-2 or Bcl-XL overexpression could potentially induce apoptosis in cancer cells while having minimal effects on normal cells.

**References**

1. Rooswinkel RW, van de Kooij B, Verheij M, Borst J. Bcl-2 is a better ABT-737 target than Bcl-xL or Bcl-w and only Noxa overcomes resistance mediated by Mcl-1, Bfl-1, or Bcl-B. Cell Death Dis. 2012 Aug 9;3:e366.  
   **Abstract**
   The novel anticancer drug ABT-737 is a Bcl-2 Homology 3 (BH3)-mimetic that induces apoptosis by inhibiting pro-survival Bcl-2 proteins. ABT-737 binds with equal affinity to Bcl-2, Bcl-xL and Bcl-w in vitro and is expected to override apoptosis resistance mediated by these Bcl-2 proteins in equal measure. We have profiled ABT-737 specificity for all six pro-survival Bcl-2 proteins, in p53 wild-type or p53-mutant human T-leukemic cells. Bcl-B was untargeted, like Bfl-1 and Mcl-1, in accord with their low affinity for ABT-737 in vitro. However, Bcl-2 proved a better ABT-737 target than Bcl-xL and Bcl-w. This was reflected in differential apoptosis-sensitivity to ABT-737 alone, or combined with etoposide. ABT-737 was not equally effective in displacing BH3-only proteins or Bax from Bcl-2, as compared with Bcl-xL or Bcl-w, offering an explanation for the differential ABT-737 sensitivity of tumor cells overexpressing these proteins. Inducible expression demonstrated that BH3-only proteins, Noxa, but not Bim, Puma or truncated Bid could override ABT-737 resistance conferred by Bcl-B, Bfl-1 or Mcl-1. These data identify Bcl-B, Bfl-1 and Mcl-1, but also Bcl-xL and Bcl-w as potential mediators of ABT-737 resistance and indicate that target proteins can be differentially sensitive to BH3-mimetics, depending on the pro-apoptotic Bcl-2 proteins they are complexed with.

   **Abstract**
   Cells that exhibit an absolute dependence on the anti-apoptotic BCL-2 protein for survival are termed "primed for death" and are killed by the BCL-2 antagonist ABT-737. Many cancers exhibit a primed phenotype, including some that are resistant to conventional chemotherapy due to high BCL-2 expression. We show here that 1) stable BCL-2 overexpression alone can induce a primed for death state and 2) that an ABT-737-induced loss of functional cytochrome c from the electron transport chain causes a reduction in maximal respiration that is readily detectable by microplate-based respirometry. Stable BCL-2 overexpression sensitized non-tumorigenic MCF10A mammary epithelial cells to ABT-737-induced caspase-dependent apoptosis. Mitochondria within permeabilized BCL-2 overexpressing cells were selectively vulnerable to ABT-737-induced cytochrome c release compared to those from control-transfected cells, consistent with a primed state. ABT-737 treatment caused a dose-dependent impairment of maximal O(2) consumption in MCF10A BCL-2 overexpressing cells but not in control-transfected cells or in immortalized mouse embryonic fibroblasts lacking both BAX and BAK. This impairment was rescued by delivering exogenous cytochrome c to mitochondria via saponin-mediated plasma membrane permeabilization. An ABT-737-induced reduction in maximal O(2) consumption was also detectable in SP53, JeKo-1, and WEHI-231 B-cell lymphoma cell lines, with sensitivity correlating with BCL-2/MCL-1 ratio and with susceptibility (SP53 and JeKo-1) or resistance (WEHI-231) to ABT-737-induced apoptosis. Multiplexing respirometry assays to ELISA-based determination of cytochrome c redistribution confirmed that respiratory inhibition was associated with cytochrome c release. In summary, cell-based respiration assays were able to rapidly identify a primed for death state in cells with either artificially overexpressed or high endogenous BCL-2. Rapid detection of a primed for death state in individual cancers by "bioenergetics-based profiling" may eventually help identify the subset of patients with chemoresistant but primed tumors who can benefit from treatment that incorporates a BCL-2 antagonist.
ABSTRACT: BH3 mimetics such as ABT-737 and navitoclax bind to the BCL-2 family of proteins and induce apoptosis through the intrinsic apoptosis pathway. There is considerable variability in the sensitivity of different cells to these drugs. Understanding the molecular basis of this variability will help to determine which patients will benefit from these drugs. Furthermore, this understanding aids in the design of rational strategies to increase the sensitivity of cells which are otherwise resistant to BH3 mimetics. We discuss how the expression of BCL-2 family proteins regulates the sensitivity to ABT-737. One of these, MCL-1, has been widely described as contributing to resistance to ABT-737 which might suggest a poor response in patients with cancers that express levels of MCL-1. In some cases, resistance to ABT-737 conferred by MCL-1 is overcome by the expression of pro-apoptotic proteins that bind to apoptosis inhibitors such as MCL-1. However, the distribution of the pro-apoptotic proteins amongst the various apoptosis inhibitors also influences sensitivity to ABT-737. Furthermore, the expression of both pro- and anti-apoptotic proteins can change dynamically in response to exposure to ABT-737. Thus, there is significant complexity associated with predicting response to ABT-737. This provides a paradigm for the multiplicity of intricate factors that determine drug sensitivity which must be considered for the full implementation of personalized medicine.


Abstract
OBJECTIVE: This study investigated the potential synergistic effects of two inducers of apoptosis: the small molecule ABT-737 and arsenic trioxide (ATO). METHODS: Human gastric carcinoma cell lines SGC-7901 and MGC-803 were used to determine the effects of ABT-737 and ATO (alone or in combination) on cell proliferation and apoptosis in vitro. In vivo effects of these drugs were investigated in SGC-7901 solid tumours, grown in immunodecient mice...

5. Bardwell, Philip D.; Gu, Jijie; McCarthy, Donna; Wallace, Craig; Bryant, Shaughn; The Bcl-2 Family Antagonist ABT-737 Significantly Inhibits Multiple Animal Models of Autoimmunity. Journal of Immunology, 2009, 182(12), 7482-7489

Abstract
Inhibition of tumor angiogenesis through blockade of the vascular endothelial growth factor (VEGF) signaling pathway is a novel treatment modality in oncology. Preclinical findings suggest that long-term clinical outcomes may improve with blockade of additional proangiogenic receptor tyrosine kinases: platelet-derived growth factor receptors (PDGFR) and fibroblast growth factor receptors (FGFR). BIBF 1120 is an indolinone derivative potently blocking VEGF receptor (VEGFR), PDGFR and FGFR kinase activity in enzymatic assays (IC50, 20-100 nmol/L). BIBF 1120 inhibits mitogenactivated protein kinase and Akt signaling pathways in three cell types contributing to angiogenesis, endothelial cells, pericytes, and smooth muscle cells, resulting in inhibition of cell proliferation (EC50, 10-80 nmol/L) and apoptosis....