Evasion of cell death is recognized as one of the key hallmarks of cancer. Members of the Inhibitor of Apoptosis (IAP) gene family are key oncogenes found in many solid and blood cancers. Consequently, targeting the IAPs is a promising therapeutic approach against cancer. A class of drugs called SMAC mimetics have been developed to antagonize the function of the IAPs. I will highlight our recent research into understanding the mechanism of SMAC mimetic efficacy and of the potential of this class of IAP antagonists to potentiate immune-based therapies for the treatment of cancer.