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**Combination of MCL-1 Selective Inhibitor A-1210477 and BH3-mimetic ABT-263 exhibit synergistic anti-proliferative effect on cervical cancer cell lines**

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**ABSTRACT**

Anti-apoptotic proteins are expressed in many tumours and hence have become attractive targets for cancer therapy. The interest to target them increased with development of BH3-mimetics, which specifically target these proteins. BH3 mimetic ABT-263 is a small molecule inhibitor of anti-apoptotic proteins BCL-2, BCL-XL and BCL-w while A-1210477 is the selective inhibitor of MCL-1. Pre-clinical studies have reported that ABT-263 demonstrated impressive single agent activity in hematological tumors and small cell lung carcinoma (SCLC) but not in most solid tumors. Studies have shown that the sensitivity to ABT-263 rely on the expression MCL-1. Thus, the down regulation or neutralization of MCL-1 is predicted to sensitize cells to ABT-263. The aim of the study is to investigate the sensitivity of the cervical cancer cell lines to combination of ABT-263 and A-1210477. The cervical cancer cell lines, SiHa, C33A, HeLa and CaSki were treated with ABT-263 and A-1210477, either alone or in combination. All the cell lines were treated with increasing concentrations of ABT-263 or A-1210477 (0-32µM) or combination of ABT-263 and A-1210477 at 1:1 drug concentration ratios. Cell proliferation was assessed using the Sybr Green I assay. The combination of MCL-1 selective inhibitor A-1210477 (AbbVie) and ABT-263 (Navitoclax, AbbVie) exhibited synergistic effects on cervical cancer cell lines SiHa, C33A, CaSki and HeLa. Furthermore, drug potentiation studies revealed that A-1210477 potentiated SiHa and CaSki to ABT-263 by 5- and 11-fold respectively. The potentiation in the opposite direction showed that ABT-263 was able to potentiate SiHa and CaSki to A-1210477 by 8-fold. Together these findings show that combination of ABT-263 and A-1210477 could be a potential treatment strategy for cervical cancer. Future studies, which involve testing this combination in 3D spheroids and xenograft models, are necessary to fully unleash the prospect of this combination to combat cervical cancer.