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# Co-inhibition of MPS-1 with BCL-2 family inhibitors enhances lung cancer cell killing in 2D and 3D culture systems

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## Abstract

**Background:** Lung cancer is the leading cause of cancer death worldwide, posing a significant public health challenge [1]. Currently available therapies, when administered as monotherapy, have limited efficacy, high toxicity, and can lead to increased tumor resistance. Overexpression of MPS-1, a protein kinase involved in mitosis, has been observed in various types of tumors. Its inhibition is associated with aberrant chromosome segregation, leading to cell death. Also, overexpression of anti-apoptotic proteins from the BCL-2 family has been reported in different cancer types, and inhibiting them can enhance cancer cell killing [2,3]. **Objective:** To assess the antitumor potential of combining an MPS-1 inhibitor with a BCL-2 family inhibitor, in both 2D and 3D lung cancer cells (A549). **Methods:** MPS-1 mRNA and protein levels were assessed by qRT-PCR and Western blot, respectively. In 2D cultures, the compounds cytotoxic activity was evaluated by MTT assay. The effects of the combination (antagonistic/additive/synergistic effects) were determined using the Combenefit software. The cell death was evaluated by TUNEL method and by flow cytometry (annexin V/propidium iodide). To assess the antiproliferative activity, the colony formation assay was performed. In 3D cultures, spheroid viability and apoptosis were determined by CellTiter-Glo assay and annexin V/ propidium iodide labeling, respectively. **Results:** Our results demonstrated that MPS-1 mRNA and protein levels were increased in A549 cells. Co-treatment of 2D cultures with the MPS-1 inhibitor and the BCL-2 family inhibitor resulted in various synergistic points. The combination with the lowest pharmacological concentrations inhibited cancer cell proliferation, and induced cell death by apoptosis. The results were confirmed in a 3D spheroid model. **Conclusions:** Cancer cell killing activity of the MPS-1 inhibitor is enhanced when combined with the BCL-2 family inhibitor, both in 2D and 3D cultures.

**Keywords:** MPS-1 inhibitor; BCL-2 family inhibitor; antimitotics; antitumoral activity; combination therapy

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