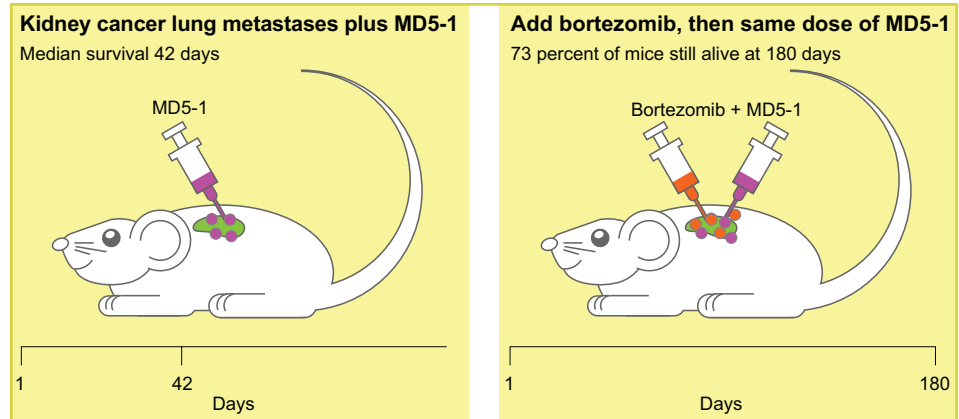


Combined Therapy Conquers Resistant Tumors: Bortezomib and TRAIL

The principal strategy in the battle against cancer is simple: kill as many tumor cells as possible while sparing healthy cells. Unfortunately, traditional treatments, such as chemotherapy and radiation, have substantial side effects, and many cancers develop resistance to therapy.

Emerging molecular-targeted therapies attempt to achieve more specific destruction of tumor cells with minimal collateral damage. Some targeted molecules are proteins called TRAIL death receptors that signal for cell suicide by a process called apoptosis. Previous studies showed that binding of the TRAIL death receptors with their ligand TRAIL or agonist antibodies activates the apoptotic cell death pathway and can shrink certain tumors in mice with minimal damage to healthy cells. However, some types of cancer are still resistant to TRAIL receptor-targeted therapy.

Thomas J. Sayers, Ph.D., a Senior Investigator in CCR's Laboratory of Experimental Immunology in the Cancer and Inflammation Program, and Anil Shanker, Ph.D., a Post-Doctoral Fellow in the same lab, led a team to explore the potential of combining two targeted therapies to combat resistance to TRAIL receptor-mediated cell death. They



In mice, the combination of bortezomib, a proteasome inhibitor, and MD5-1, an agonist antibody to activate the TRAIL receptor, was superior to either agent alone in reducing the number of lung metastases of kidney origin. Mice receiving the combination treatment survived four times longer than did mice with the same tumor burden treated with either drug alone.

treated mice with lung metastases of kidney or breast cancer with a combination of bortezomib, a drug used for treating multiple myeloma that triggers cancer cell death by interfering with protein degradation, and MD5-1, an agonist antibody that can activate a TRAIL death receptor. As reported in the May 7, 2008, issue of the *Journal of the National Cancer Institute*, Sayers' team found that the combination of bortezomib and MD5-1 was superior to either drug alone in reducing the number of lung metastases of kidney and breast cancer cells. Mice bearing lung metastases of kidney cancer survived up to four times longer after the combination treatment than those treated with either drug alone. Furthermore, the combination treatment

did not cause any apparent toxic side effects. The success of the combination regimen does not appear to be dependent on the immune system, an important observation because patients often have weakened immunity during cancer treatment.

This study demonstrates that bortezomib can overcome resistance to TRAIL receptor antibodies and to TRAIL in some types of cancer. Importantly, Sayers and colleagues identified one molecular basis of bortezomib's ability to enhance the effect of TRAIL receptor antibodies. They found that bortezomib treatment amplifies the activity of caspase-8, a critical enzyme in the cell death pathway triggered by TRAIL. Identification of specific

molecular changes that are necessary for bortezomib-induced sensitization of tumor cells to TRAIL might help scientists determine a molecular profile for selecting patients who are most likely to benefit from this combination therapy.

Reference

Shanker A, Brooks AD, Tristan CA, Wine JW, Elliott PJ, Yagita H, Takeda K, Smyth MJ, Murphy WJ, Sayers TJ. Treating metastatic solid tumors with bortezomib and a tumor necrosis factor–related apoptosis-inducing ligand receptor agonist antibody. *J Natl Cancer Inst* 100: 649–62, 2008.