Combination of the KSP Inhibitor ARRY-520 with Bortezomib Causes Sustained Tumor Regressions and Significantly Increased Time to Regrowth in Bortezomib Sensitive and Resistant Models of Multiple Myeloma

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Abstract

The allosteric kinesin spindle protein (KSP) inhibitor ARRY-520 has potent antitumor activity as a single agent in xenograft models of multiple myeloma, with complete response rates as high as 100%. It has shown promising signs of activity in a phase 1 trial in patients with advanced / refractory multiple myeloma, and a phase 2 study in this patient population is in progress. We report here on the striking activity of ARRY-520 in combination with bortezomib in multiple myeloma xenograft models. We investigated the activity of the combination of ARRY-520 with bortezomib in several xenograft models of multiple myeloma that are sensitive (Kas-6, ANBL-6, and H929) and resistant (RPMI8226, JJN3, an ANBL-6 line made resistant to bortezomib by in vitro treatment, and an RPMI8226 line that acquired a PI3K activating mutation) to bortezomib. The combination of ARRY-520 with bortezomib showed additive or superadditive activity, compared to either drug alone, in 6 of the 8 models tested. Complete responses and cures were observed in several models. The Kas-6 model was particularly sensitive, with a 100% cure rate (complete response through day 100). Since previous work from our lab (Mol. Cancer Ther. 9(7), 2046, 2010) implicates mcl-1 status as a predictor of response to ARRY-520 in multiple myeloma cell lines, we evaluated the effect of the ARRY-520 + bortezomib combination on mcl-1 and other markers of apoptosis. Treatment with the combination resulted in elevation of the cleaved / full length PARP ratio (up to 7X), compared to tumors treated with the single agents, along with a decline in mcl-1 levels that coincided with elevation of the level of a 28kd fragment of mcl-1 (up to 15X). This shortened form of mcl-1 has been
reported to be pro-apoptotic. Thus, the cleavage of mcl-1 to a proapoptotic form, leading to a decrease in survival signaling and an increase in apoptotic signaling, may play a role in the activity of the ARRY-520 + bortezomib combination. The observation that the combination remained highly active even in models that were poorly responsive to single agent bortezomib suggests that the mechanisms underlying resistance to bortezomib may be distinct from those that contribute to activity of the combination. These results support ARRY-520 + bortezomib as a rational combination for clinical evaluation, including patients with bortezomib-refractory disease. A phase 1 trial to evaluate the combination of ARRY-520 + bortezomib is in progress.