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Novel Hsp90 inhibitor, STA-9090, for combination with radiotherapy.

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Introduction: Radiation is accepted as an important standard therapy for locally unresectable cancers, and as such is given to approximately 60% of cancer patients. However, radio-resistance and repair of sublethal radiation damage can limit its efficacy. Recent studies have shown that Heat Shock Protein 90 (Hsp90), a molecular chaperone that mediates maturation and activation of client proteins, plays a critical role in establishing resistance to radiation therapy. Inhibiting Hsp90 has been reported to sensitize tumors to radiation, resulting in tumor growth suppression and augmenting therapeutic cell death induction. Unfortunately, many of the Hsp90 inhibitors currently in clinical trials exhibit hepatotoxicity as well as ocular toxicity, hindering their clinical use. Taken together, development of clinically acceptable Hsp90 inhibitors for combination with radiation could serve as an important strategy for improving radiotherapy success.

STA-9090 is a second generation Hsp90 inhibitor that has shown potent preclinical activity and is currently in twelve Phase II trials across a broad range of indications. STA-9090 has demonstrated encouraging activity in a Phase II trial in patients with stage IIIB and IV non-small cell lung cancer. Importantly, STA-9090 has displayed a favorable safety profile with substantially lower incidence of hepatic or ocular toxicity than that reported for other Hsp90 inhibitors.

Results: We evaluated the radiosensitizing potential of STA-9090 *in vivo*. Monotherapy treatment with either STA-9090 or 2 Gray (Gy) ionizing irradiation resulted in moderate reductions in human tumor growth rates in a mouse xenograft model. Combination of STA-9090 with 2 Gy irradiation resulted in substantial tumor regression. Increasing the dose of radiation in the combination arm to 4 Gy further enhanced tumor regression, resulting in a 50% reduction in tumor volume. In summary, STA-9090 offers a safe and effective strategy for improving the outcome of radiotherapy in human cancers.