

#2677 Novel Hsp90 Inhibitor, Ganetespib (STA-9090), For Combination With Radiotherapy

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Abstract

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.

Ganetespib 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. Ganetespib has demonstrated encouraging activity in a Phase II trial in patients with stage IIIB and IV non-small cell lung cancer. Importantly, ganetespib 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 ganetespib *in vivo*. Monotherapy treatment with either ganetespib or 2 Gray (Gy) ionizing irradiation resulted in moderate reductions in human tumor growth rates in a mouse xenograft model. Combination of ganetespib 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, ganetespib offers a safe and effective strategy for improving the outcome of radiotherapy in human cancers.

Ganetespib Does Not Generate DNA Damage

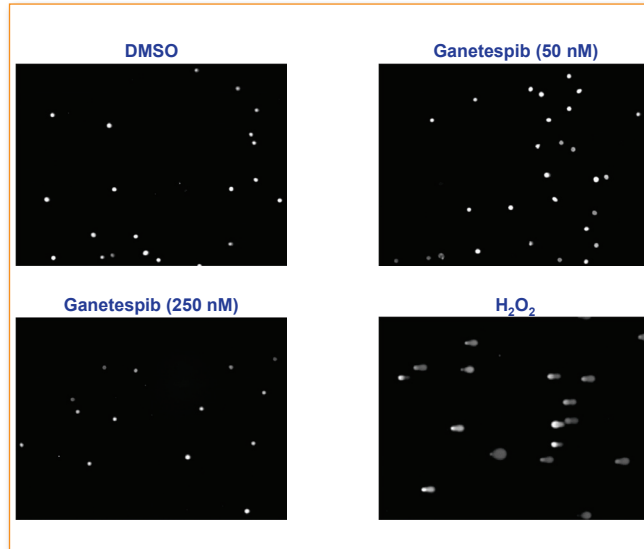


Figure 1. Inhibition of Hsp90 by ganetespib does not induce DNA damage. Set-2 AML cells were exposed to ganetespib at the indicated concentrations for 24 hr, or hydrogen peroxide (100 μM) for 15 min. DNA integrity was assessed by the comet assay.

Ganetespib Sensitizes Head and Neck Cancer Cells to Radiation

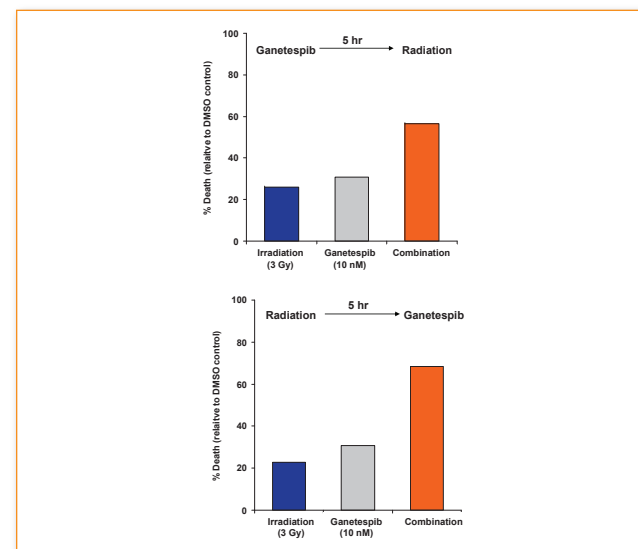


Figure 3. Ganetespib enhances the activity of radiation *in vitro*. Head and neck cancer cells (Detroit 562) were treated as shown with either radiation (3 Gy) or ganetespib (10 nM). Five hours later, cells were exposed to ganetespib or radiation. Cell viability was assessed 72 hr later.

Optimizing Dosing Schedule of Ganetespib and Radiation Results in Tumor Regression

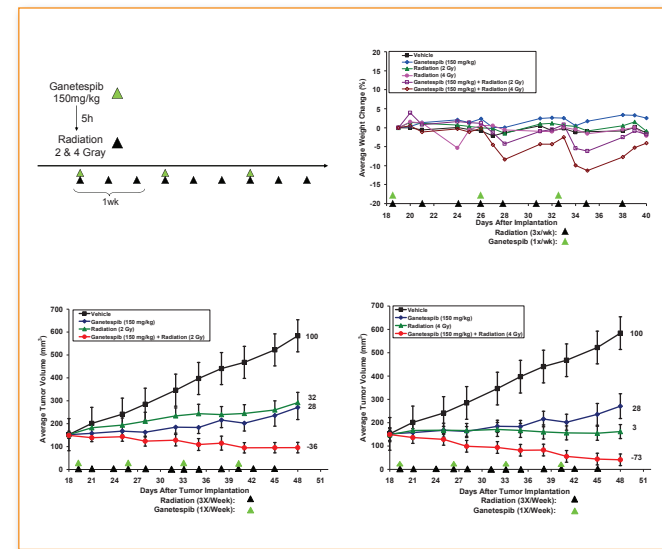
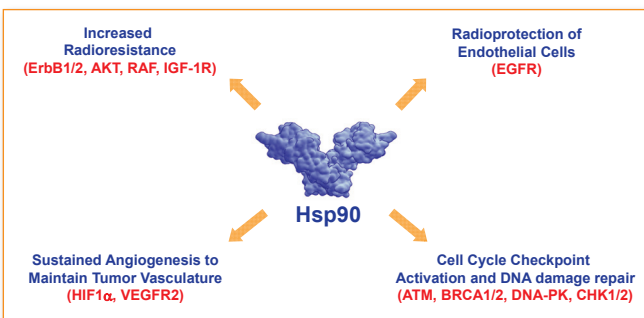


Figure 5. Ganetespib promotes schedule-dependent tumor regression when combined with radiation *in vivo*. Human cervical cancer xenografts (HeLa) were subject to 3x/week treatment with ganetespib (150 mg/kg), radiation (2, 4 Gy) or the combination of the two as described. Extending the time between ganetespib and radiation exposure significantly increased tumor regression.

Introduction

Hsp90 Client Proteins Involved in Hindering Radiotherapy



Use of Hsp90 inhibitors for radiosensitisation. Several key Hsp90 client proteins such as those involved in DNA damage repair (ATM/ATR, CHK1/2, DNA-PKc) and survival signaling (AKT, HER2, RAF-1) have been shown to be associated with protection against radiation-induced cell death. Numerous studies have demonstrated that inhibition of Hsp90 by small molecule inhibitors can thus sensitize tumor cells to radiation. Ganetespib represents a novel class of second generation Hsp90 inhibitors, with more than 10-fold greater activity than the ansamycin derivatives. Here, we sought to investigate the potential for ganetespib in sensitizing cancer cells to irradiation.

Modulation of DNA Repair and Cell Cycle Checkpoint Proteins by Ganetespib

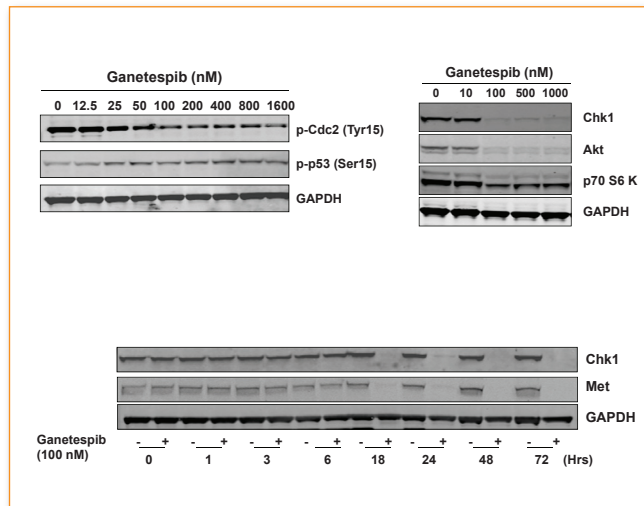


Figure 2. Ganetespib destabilizes proteins required for DNA repair and cell cycle checkpoints. HCT-116 colon cancer cells were treated with ganetespib for 24 hr (top panel) at indicated concentrations or over time (ganetespib, 100 nM).

In vivo Synergy Between Ganetespib and Radiation in Cervical Cancer Xenografts

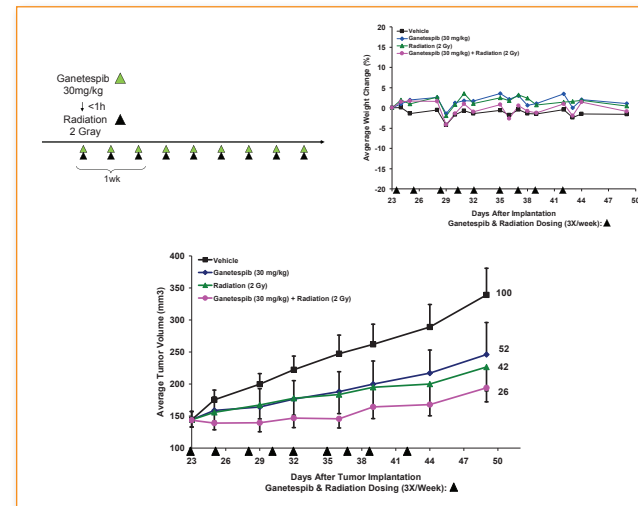


Figure 4. Ganetespib enhances the antitumor activity of radiation *in vivo*. Human cervical cancer xenografts (HeLa) were subject to 3x/week treatment with ganetespib, radiation or the combination of the two as described. No toxicity was observed in the monotherapy or combination exposures.

Conclusions

- Inhibition of Hsp90 by ganetespib potently destabilizes proteins required for both the DNA repair checkpoint as well as the cell cycle checkpoint but does not alter the integrity of DNA
- Combining the double-strand breaks caused by irradiation with the loss of DNA repair induced by ganetespib results in enhanced anticancer activity *in vitro* versus monotherapy
- Ganetespib radiosensitizes cervical cancer xenografts in a schedule-dependent fashion owing to the requirement for abrogation of Hsp90 client proteins prior to DNA damage
- Taken together, ganetespib offers a promising strategy for improving the outcome of radiotherapy in human cancers



For further information on Ganetespib: www.syntapharma.com