

Abstract # 2638

Hsp90 inhibitor STA-9090 induces HIF-1 α degradation in the hypoxic regions of solid tumors.

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BACKGROUND: Solid tumors typically exhibit regions of poor oxygen supply, or hypoxia, due to disorganized tumor microvasculature limiting the efficient circulation of blood. The hypoxia-inducible transcription factor HIF-1 α regulates an adaptive response to hypoxia that is characterized by increased glycolytic metabolism, angiogenesis and a propensity to metastasize. HIF-1 α expression has also been correlated with resistance to radiation and chemotherapy, as well as poor clinical prognosis. However, inhibiting HIF-1 α has proven to be challenging, not only because transcription factors are difficult to directly target, but also because its expression is confined to the most poorly vascularized regions of tumors, which therefore limits efficient distribution of therapeutic agents. An alternative approach to targeting HIF-1 α is by inhibiting heat shock protein 90 (Hsp90), a molecular chaperone that regulates the proper folding and stability of HIF-1 α . STA-9090 is a highly potent and less toxic, next-generation Hsp90 inhibitor that is structurally unrelated to first-generation agents such as 17-AAG and IPI-504. STA-9090 is currently being evaluated in multiple Phase 1/2 clinical trials in solid tumor and hematologic malignancies. We have examined the ability of STA-9090 to disrupt the hypoxic tumor response mediated by HIF-1 α in preclinical models.

RESULTS: In vitro in hypoxic NCI-H1975 lung cancer cells, STA-9090 was found to potently down-regulate the expression of HIF-1 α and other Hsp90 client proteins. STA-9090 also inhibited the expression of downstream HIF-1 α targets. In vivo in the NCI-H1975 xenograft model, a single MTD dose of STA-9090 reduced HIF-1 α expression by 6-fold at 24 hr after treatment, despite a 39% decrease in microvascular density and a 2.5-fold increase in tumor hypoxia relative to control tumors. Importantly, this effect on HIF-1 α was found to be uniform throughout tumors and independent of distance from microvasculature, indicating that STA-9090 was efficiently distributed to the hypoxic regions of tumors >150 μ M from the nearest blood vessels. Similarly, STA-9090 treatment decreased EGFR expression, inhibited cell proliferation and induced apoptosis in tumors independent of vascular distance.

CONCLUSIONS: Our results demonstrate that STA-9090 significantly inhibits HIF-1 α expression in the hypoxic regions of tumors. In contrast to many other chemotherapeutic agents, STA-9090 is also efficiently distributed into the poorly vascularized, hypoxic tumor tissue where HIF-1 α is expressed. Hsp90 inhibition using STA-9090 represents a promising approach to indirectly target HIF-1 α and disrupt the hypoxic tumor response.