A novel HSP90 inhibitor-drug conjugate to SN38 is highly effective in small cell lung cancer

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Abstract

©2016 AACR.Purpose: Small cell lung cancer (SCLC) is a highly aggressive disease representing 12% to 13% of total lung cancers, with median survival of <2 years. No targeted therapies have proven effective in SCLC. Although most patients respond initially to cytotoxic chemotherapies, resistance rapidly emerges, response to second-line agents is limited, and dose-limiting toxicities (DLT) are a major issue. This study performs preclinical evaluation of a new compound, STA-8666, in SCLC. Experimental Design: To avoid DLT for useful cytotoxic agents, the recently developed drug STA-8666 combines a chemical moiety targeting active HSP90 (concentrated in tumors) fused via cleavable linker to SN38, the active metabolite of irinotecan. We compare potency and mechanism of action of STA-8666 and irinotecan in vitro and in vivo. Results: In two SCLC xenograft and patient-derived xenograft models, STA-8666 was tolerated without side effects up to 150 mg/kg. At this dose, STA-8666 controlled or eliminated established tumors whether used in a first-line setting or in tumors that had progressed following treatment on standard first- and second-line agents for SCLC. At 50 mg/kg, STA-8666 strongly enhanced the action of carboplatin. Pharmacokinetic profiling confirmed durable STA-8666 exposure in tumors compared with irinotecan. STA-8666 induced a more rapid, robust, and stable induction of cell-cycle arrest, expression of signaling proteins associated with DNA damage and cell-cycle checkpoints, and apoptosis in vitro and in vivo, in comparison with irinotecan. Conclusions: Together, these results strongly support clinical development of STA-8666 for use in the first- or second-line setting for SCLC.