Clinical Cancer Research 2016 vol.22 N20, pages 5120-5129

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

Gaponova A., Nikonova A., Deneka A., Kopp M., Kudinov A., Skobeleva N., Khazak V., Ogawa L., Cai K., Duncan K., Duncan J., Egleston B., Proia D., Boumber Y., Golemis E.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

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.

http://dx.doi.org/10.1158/1078-0432.CCR-15-3068