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A Novel Nonpeptide Drug Conjugate (NDC) for the Treatment of Somatostatin Receptor 2-Expressing Tumors

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BACKGROUND

Somatostatin receptor 2 (SST2) is an established target for the treatment of neuroendocrine tumors (NETs) and a potentially useful one for many other solid tumors including breast cancer, melanoma, thyroid cancer, and meningioma. Here, we provide the first report of CRN09682, a non-radioactive, nonpeptide drug-conjugate (NDC) optimized for the delivery of a cytotoxic MMAE payload to SST2-expressing tumors.

METHODS

CRN09682 was developed by linking a small molecule, nonpeptide SST2 agonist with the cytotoxic drug monomethyl auristatin E (MMAE) via a spacer and a cleavable linker. SST2 activation was assessed by monitoring cAMP production in SST2-expressing CHO cells using a cAMP HTRF assay. CRN09682-SST2 complex internalization and endosomal localization were evaluated using the PathHunter β-arrestin recruitment assay and the PathHunter ENDO-EA pharmacotrafficking assay, respectively. The SST2 expressing small cell lung cancer (SCLC) cell lines NCI-H524, NCI-H69 and the SST2 receptor null cells H460 were treated with CRN09682 to characterize the anti-proliferative effects in vitro. The plasma stability of CRN09682 was investigated in vitro and in vivo. Intratumoral concentrations of CRN09682 and MMAE were determined in NCI-H524 xenografts (CDX). Anti-tumor activity of CRN09682 was characterized in NCI-H524 and NCI-H69 CDX models.

RESULTS

CRN09682 activated SST2 G-protein signaling and induced internalization with low nanomolar potency. In vitro, the anti-proliferative effect of CRN09682 was comparable to MMAE alone. Co-incubation with an SST2 antagonist blocked the anti-proliferative response and CRN09682 had no effect in H460 cells. CRN09682 was stable in mouse, dog, and human plasma. In vivo, CRN09682 displayed a half-life of 7.4 h in mouse, 1.1 h in rats and 7.1 h in dogs. MMAE plasma concentrations remained below 1% of total injected NDC. Biodistribution studies in NCI-H524 CDX model demonstrated high tumor uptake for CRN09682 and rapid MMAE release within the tumors. MMAE accumulated and remained in the tumor for up to 10 days. CRN09682 demonstrated dose-dependent anti-tumor activity in CDX models without significant weight loss, whereas the analog with no SST2 agonist activity did not inhibit tumor growth.

CONCLUSIONS

These data demonstrate the potent anti-tumor activity of CRN09682, a first-in-class NDC targeting SST2 expressing solid tumors. CRN09682 could provide a novel alternative for the treatment of NETs and other SST2-expressing tumors. CRN09682 is expected to enter a Phase I clinical trial in 2025.

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