Discovery of a Nonpeptide Drug Conjugate (NDC) for the Treatment of Neuroendocrine Tumors (NETs) and Other SST2 Expressing Cancers

Jian Zhao, Emmanuel Sturchler, Bing Yang, Melissa A. Fowler, Mi Chen, Ryan Middleton, Szu-Wei Lee, Teacel Hines, Yang Tang, Connie Zhao, Deepak Dalvie, Hassan Hussein, Elaine Hsieh, Jeff Schkeryantz, Stacy Markison, R. Scott Struthers, Stephen F. Betz
Crinetics Pharmaceuticals, San Diego, CA.

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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 the cytotoxic MMAE payload to SST2-expressing tumors.

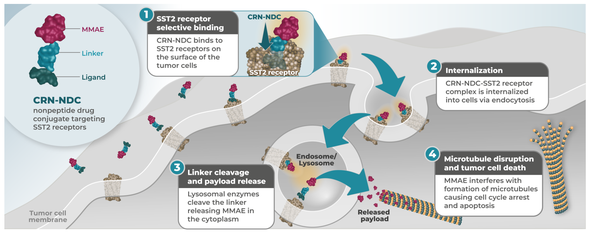


Figure 1. CRN09682 concept and mechanism of action

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 Homogeneous Time Resolved Fluorescence assay. CRN09682-SST2 complex internalization and endosomal localization were evaluated using the PathHunter β-arrestin recruitment assay and the PathHunter internalization assay, respectively.

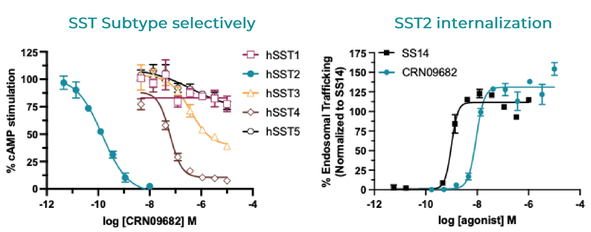
CRN09682 effects on the viability of the SST2 expressing small cell lung cancer (SCLC) cell lines NCI-H524, NCI-H69 and the SST2 receptor null cells NCI-H460 were assessed using CellTiter-Glo luminescent cell viability assay.

Concentrations of CRN09682 and MMAE following a single intravenous injection were determined in plasma from mice and dogs, as well as tumor tissues from athymic nude mice bearing NCI-H524 tumors using validated liquid chromatography–tandem mass spectrometry plasma.

To assess in vivo anti-tumor activity, CRN09682 and an analog conjugate with no agonist activity were administrated using a variety of doses and schedules to NCI-H524 and NCI-H69 CDX models. Tumor volumes and body weight were measured using standard methods. Percentage of tumor growth inhibition (TGI %) and percentage change in body weight from vehicle (BW %) were calculated.

RESULTS

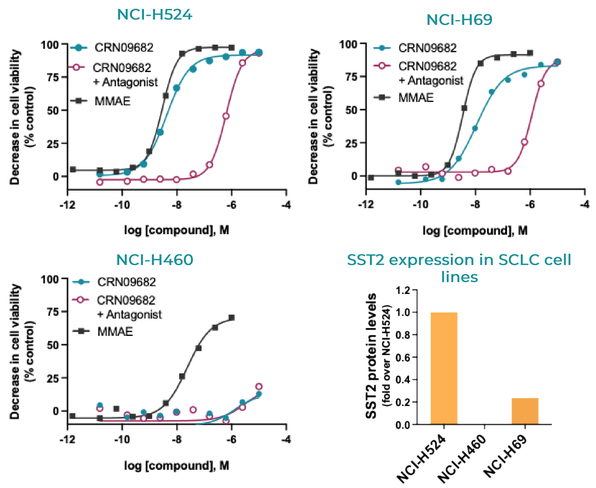
CRN09682 Selectively Activates and Induces Internalization of SST2



SST activation	SST1	SST2	SST3	SST4	SST5
EC_{50} (nM)	>1000	0.14	380	61	>1000
SST2 internalization		SS14		CRN09682	
EC_{50} (nM)		1.0		9.2	

Figure 2. In vitro pharmacology of CRN09682
- CRN09682 is a potent full agonist at human SST2 in cAMP and internalization assays
- CRN09682 displayed more than 400-fold selectivity over other SST-subtypes in cAMP assays
- CRN09682 displays desirable pharmacology and trafficking properties for the delivery of MMAE into cells expressing SST2

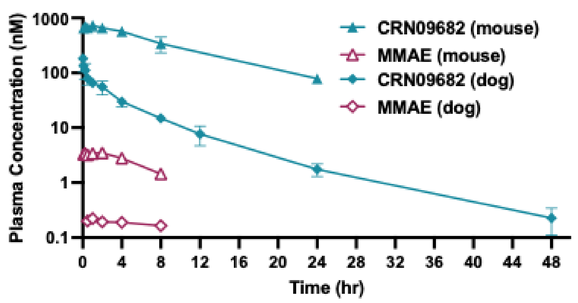
CRN09682 Decreases Cell Viability in an SST2-Dependent Manner in SCLC cell Lines



Cell viability	EC_{50} (nM) NCI-H524	EC_{50} (nM) NCI-H69	EC_{50} (nM) NCI-H460
MMAE	3.0	3.5	27
CRN09682	4.3	11	N/A
CRN09682 + Antagonist	630	1200	N/A

Figure 3. In vitro effect of CRN09682 on cell viability.
- SST2 is expressed in NCI-H524 and NCI-H69 cell lines but not NCI-H460 cells
- CRN09682 decreases cell viability on SCLC cells expressing SST2 with efficacy and potency comparable to MMAE alone
- CRN09682 potency in SST2-expressing cell lines is reduced by co-treatment with 10 μM SST2 antagonist (CYN154806; pIC_{50} = 8.58. Neuropharmacology. 2000 Jun 8;39(8):1443-50)

CRN09682 Demonstrates Moderate Half-life and Low Plasma MMAE Exposure in Mouse and Dog



CD-1 Mouse (1.0 mg/kg)	C_{max}	$t_{1/2}$	T_{max}	$AUC_{0\text{-last}}$
CRN09682	NA	7.4 h	NA	7788 nM*h
MMAE	3.6 nM	NA	0.44 h	21 nM*h

Beagle Dog (0.1 mg/kg)	C_{max}	$t_{1/2}$	T_{max}	$AUC_{0\text{-last}}$
CRN09682	NA	7.1 h	NA	433 nM*h
MMAE	0.23 nM	NA	1.3 h	1.42 nM*h

Figure 4. IV PK parameters for CRN09682 and MMAE in CD-1 mouse and Beagle dog
- CRN09682 has a short plasma half-life in preclinical species
- Plasma levels of unconjugated MMAE are low in both species (<0.5% of parent)

CRN09682 Exhibits Rapid Tumor Uptake and Cleavage with a Prolonged MMAE Tumor Half-life

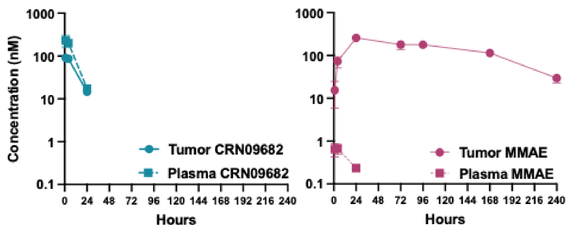


Figure 5. Tumor PK of IV CRN09682 0.3 mg/kg in NCI-H524 CDX mice.
- CRN09682 rapidly cleaved in the tumor and below LLQ after 24h
- Tumor MMAE uptake peaked at 24 h with a terminal $t_{1/2}$=65-75 h
- Plasma MMAE rapidly cleared and below LLQ after 24h

CRN09682 Inhibits Tumor Growth in NCI-H524 CDX Mice in a Dose- and SST2-dependent Manner

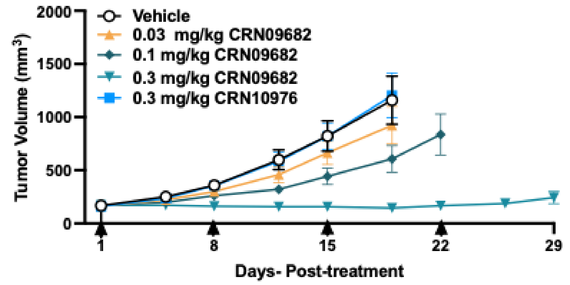


Figure 6 . Assessment of Tumor Growth Inhibition (TGI) of QWx4 IV dosing of CRN09682 in NCI-H524 SCLC xenograft model
- CRN09682 displayed dose-dependent anti-tumor activity (MED=0.3 mg/kg)
- CRN10976 (NDC with no SST2 activity) had no effect on TGI
- No significant body weight change at all doses tested

CRN09682 Induces Tumor Regression in NCI-H524 CDX Mice Bearing Large Tumors

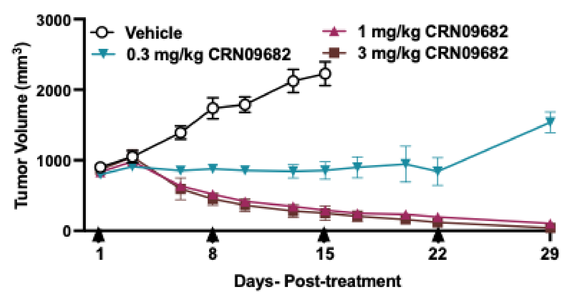


Figure 7. Assessment of Tumor Growth Inhibition (TGI) of QWx4 IV dosing of CRN09682 in NCI-H524 SCLC xenograft model bearing large tumors (>700 mm^3).
- CRN09682 displays dose-dependent anti-tumor activity (MED=0.3 mg/kg)
- CRN09682 at 1 and 3 mg/kg induced tumor regression
- No significant body weight change at all doses tested

Tumor Regression by CRN09682 Exhibits Dose and Dose-Frequency Dependence

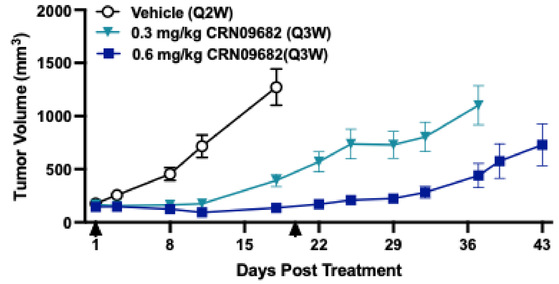


Figure 8. Effects of IV CRN09682 dosed every 3 weeks on tumor growth in NCI-H524 SCLC CDX mice.
- Anti-tumor activity can be obtained with less frequent dosing by increasing the CRN09682 dose
- No significant body weight change at all doses tested

CRN09682 Inhibits Tumor Growth in Xenograft Model of NCI-H69 with Lower SST2 Expression

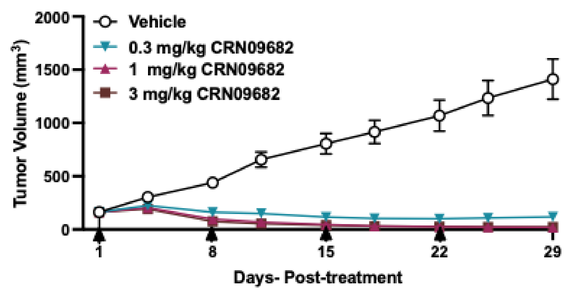


Figure 9 . Assessment of anti-tumor activity of IV QWx4 dosing of CRN09682 in NCI-H69 SCLC xenograft model.
- CRN09682 displayed anti-tumor activity and induced tumor regression
- No significant body weight change in all doses tested

CONCLUSIONS

- CRN09682 is selectively internalized by SST2 positive tumor cells and induces cytotoxicity
- CRN09682 gives rise to rapid and prolonged delivery of MMAE into tumors with minimum systemic exposure to free MMAE
- CRN09682 displays antitumor activity in CDX models of SCLC with different SST2 expression levels
- CRN09682 could provide a novel and differentiated approach for the treatment of NETs and other SST2-expressing tumors

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