c-Met is a Potential Therapeutic Target for Antibody Drug Conjugates in Breast Cancer

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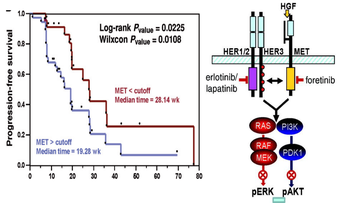
Abstract

c-Met, a transmembrane receptor tyrosine kinase, plays a key role in malignant transformation of epithelial cells by activating signal transduction pathways essential for cellular proliferation, survival, migration and invasion. c-Met overexpression, with or without gene amplification, has been reported in primary breast cancers and correlated with poor prognosis. c-Met signaling inhibition, such as tyrosine kinase inhibitors (TKIs), are usually not sufficient for sustained treatment efficacy. We believe that antibody drug conjugates (ADCs) offer the promise and potential of delivering potent anti tumor activity with the advantage of reduced side effects. We generated antibody drug conjugates containing a proprietary human anti-c-Met antibody (STI-0602) with either a tubulin inhibitor or DNA damaging agent, such as doxorubicin analogs. STI-0602, a fully human antibody (IgG1) selected from phage library was conjugated with the cytotoxin via site-specific bioconjugation. The conjugates retained binding affinity and showed potent cell killing in a variety of c-Met-positive cell lines. Progress will be reported in terms of *in vivo* efficacy in c-Met-positive human breast tumor xenograft in preclinical models.

Introduction

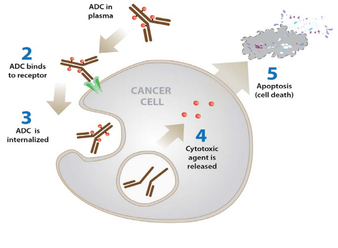
c-Met (MET), the proto-oncogene transmembrane tyrosine kinase receptor, is involved in cell proliferation, survival, motility, and invasion in normal and tumor cells[1]. MET is more widely expressed and associated with poor prognosis in breast, lung, liver, kidney and brain cancers. Hepatocyte growth factor (HGF) is the only known ligand of the MET receptor. The MET/HGF promotes cancer cell migration and invasion, and is also implicated in mediating resistance to current anticancer therapies, including radiation. Overexpression of MET is associated with poor prognosis in HER2-positive breast cancer patients as evidenced by shorter PFS following HER1/HER2-targeted lapatinib treatment[2] (see right panel). Dual EGFR/MET inhibition has shown to be synergistic in EGFR-directed therapy resistance triple negative breast cancer[3]. Hence, combination therapy with inhibitors of MET & HER signaling has been proposed for a subset of metastatic breast cancer patients with MET-amplified/overexpressed tumors.

High Expression of c-Met is Correlated with Adverse Survival Outcomes



Mol Cancer Ther. 2011. **10:**518-530

Antibody Drug Conjugates (ADCs)—Targeted Delivery of Potent Toxins



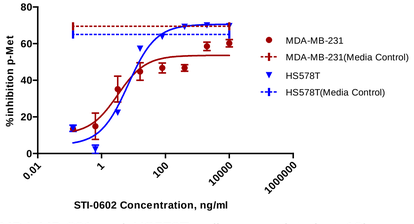
ADC Key Components

1. Target-specific internalizing antibody
2. Potent cytotoxic drugs
3. Linker and conjugation chemistries

Generation of Anti-c-Met Antibodies

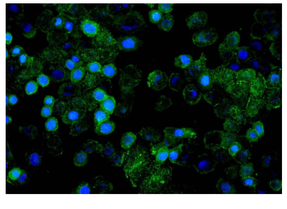
Sorrento's Anti-c-Met Antibodies are Fully Human IgG1 Identified from Proprietary G-MAB ® library

Anti-c-Met Antibody Inhibits Phosphorylation in Triple Negative Breast Cancer Cell Lines



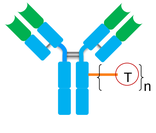
MDA-MB-231 and HS578T cells were plated at 10k cells/well overnight. Cells were treated with STI-0602 in serum-free media for 4 hours, then stimulated with HGF for 15 minutes.

Anti-c-Met Antibody is Internalized in a Triple Negative Breast Cancer Cell Line



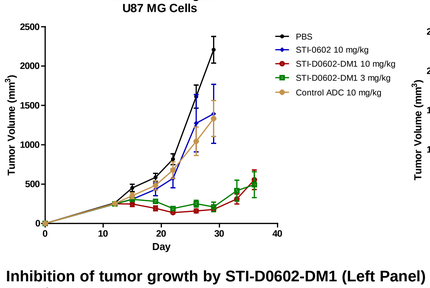
MDA-MB-468 cells were plated overnight and incubated with 1 ug/ml anti-c-Met antibody STI-0602 for 180 min at 37ºC. Internalization of the antibody was visualized with anti-Alexa Fluor 488 staining.

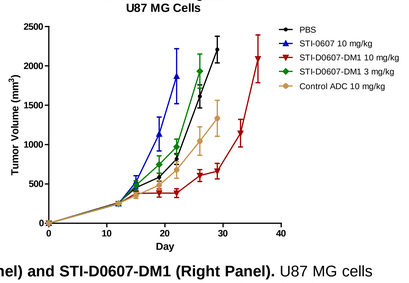
Generation of Anti-c-Met Antibody Drug Conjugates



- **mAb:** Anti-c-Met IgG1 STI-0602 and STI-0607 with distinct binding epitopes
- **Linker:** Cleavable or non-cleavable
- **Payload:** Tubulin inhibitors or DNA damaging agents

Anti-c-Met-ADCs STI-D0602 and STI-D0607 Displayed Different *in vivo* Efficacies

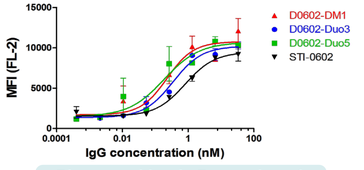




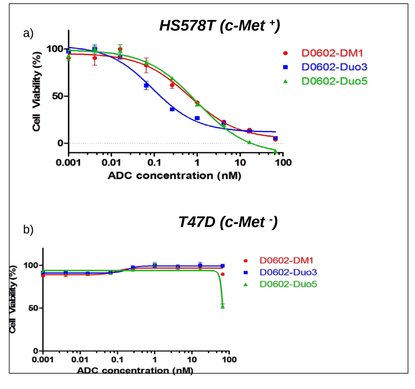
Inhibition of tumor growth by STI-D0602-DM1 (Left Panel) and STI-D0607-DM1 (Right Panel). U87 MG cells ($5x10^6$) were injected S.C. into female nu/nu mice, 10 mice/group. Animals were dosed by IP injection twice per week, 5 times total. Tumors were measured twice weekly.

Characterization of Anti-c-Met Antibody Drug Conjugates

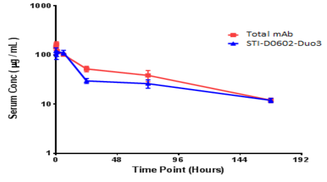
Anti-c-Met ADCs Retained Binding Affinity to c-Met⁺ TNBC Cells



Anti-c-Met ADCs Specifically Inhibit c-Met⁺ TNBC Cell Proliferation



Pharmacokinetic Properties of Anti-c-Met ADC in Mice



Binding of anti-c-Met ADCs to HS578T cells (Top Panel). and *in vivo* half-life of the ADC (Bottom Panel). Mice were given a single IV dose at 10 mg/kg. Mean concentrations of total antibody and ADC in serum were determined by ELISA.

Inhibition of cell proliferation in HS578T (Panel a) and T47D (Panel b). Cells were plated at 4000 per well and treated with the conjugates. After incubation for 4 days, proliferation was measured using the Cell Titer Glo assay.

Summary and Conclusions

- **Sorrento has developed fully human IgG1s against c-Met with distinct binding epitopes.**
- **The anti-c-Met antibodies inhibited signaling by stimulating c-Met internalization in the absence of receptor activation.**
- **Anti-c-Met ADCs retained binding affinity and demonstrated potent cell killing in a variety of TNBC cell lines.**
- **STI-D0602-DM1 conjugate showed potent *in vivo* efficacy without significant toxicity.**
- **High expression of c-Met in breast cancer patients has been shown to correlate with adverse survival outcomes and is a promising target for antibody drug conjugates.**
- **By owning all required components for ADC development, Sorrento can create ADCs free of royalties or milestone fees, representing a distinct and unique advantage in the field for internal ADC R&D.**

References

1. Martin TA and Jiang WG. Hepatocyte growth factor and its receptor complex signalling as targets in cancer therapy. *Anticancer Agents Med Chem.* 2010. **10:**2-6.
2. Liu, L. et al. Synergistic effects of foretinib with HER-targeted agents in Met and Her1 or Her2-coactivated tumor cells. *Mol Cancer Ther.* 2011. **10:**518-530.
3. Sohn et al. cMET activation and EGFR-directed therapy resistance in triple-negative breast cancer. *J Cancer.* 2014. **15:**745-53.