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

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Abstract

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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, mobility, and invasion in normal and tumor cells. 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, and is shown to be synergistic in EGFR-directed therapy resistance in triple-negative breast cancer patients as evidenced by shorter PFS following HER1/HER2-targeted lapatinib treatment (see right panel). Dual EGFR/MET inhibition has been proposed for a subset of metastatic breast cancer patients with MET-amplified/overexpressed tumors.

Generation of Anti-c-Met Antibodies

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

Conclusions

• Sorrento has developed fully human IgG1 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-0602-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 Anti-c-Met ADCs free of royalties or milestone fees, representing a distinct and unique advantage in the field for internal ADC R&D.

References