Synergy of an anti-HER2 ADC TAK-522 (XMT-1522) in combination with anti-PD1 mAb in a syngeneic breast cancer model expressing human HER2

Tary Traore1, Mithun Khattar2, Jessica Roebe1, Kristin Horton1, Melissa Gallery1, Pamela Brauer1, Natasha Bodyak1, Marina Prototopopova1, Qingshu Zhang1, Timothy B. Lowinger1, Peter Weible1, Dennis Huszar1, Frank Weinberg1

1 Department of Immuno-Oncology Biology, Takeda Pharmaceuticals International Co., 40 Lansdowne street, Cambridge, Massachusetts, 02139, USA
2 Mersana Therapeutics, 840 Memorial Drive, Cambridge, Massachusetts, 02139, USA

Abstract

Antibody-drug conjugates (ADCs) are a highly potent class of drugs that specifically target cancer cells expressing a tumor associated antigen (TAA). The ADC TAK-522 (XMT-1522) consists of a novel human IgG1 anti-HER2 monoclonal antibody and a novel, auristatin-based cytotoxic payload ( Auristatin F - hydronitroanilide, AF-HPA). An average DAR of twelve AF-HPA molecules is achieved via a biodegradable polymer conjugation platform. We have characterized the ability of both the free payload AF-HPA and the ADC TAK-522 to induce immunogenic cell death (ICD) in vitro in multiple cell lines (MCF-7, BT-29, SKBR3), as measured by cell surface expression of the ICD marker calreticulin (CRT) using microscopy and flow cytometry. CRT was usually contained in the lumen of the endoplasmic reticulum, translocated to the cell surface within a few hours after treatment with AF-HPA or TAK-522. Furthermore, we developed a novel syngeneic breast cancer (4T1) model expressing human HER2 at a relatively low antigen density. Treatment in this poorly immunogenic tumor model with TAK-522 but not Kadcyla showed significant inhibition of tumor growth in vivo. Importantly, a combination of anti-PD1 mAb and TAK-522 therapy substantially enhanced the anti-tumor efficacy synergistically, resulting in complete responses in some mice. The frequency of complete responders was further increased when the two drugs were sequentially, rather than concurrently, administered such that TAK-522 administration was followed by anti-PD1 mAb therapy. These results suggest an immunological synergism involved in the immunogenicity of cellular death by TAK-522, which in turn may activate the adaptive immune system by releasing tumor specific antigens. TAK-522 is currently being tested in a phase II clinical trial in patients with advanced breast, lung and gastric cancer expressing HER2. Based on our data, TAK-522 represents a potential candidate for combination therapies with immune checkpoint modulators in patients with poorly immunogenic HER2 expressing tumors.

Immunological effects of TAK-522

TAK-522 induces Immunogenic Cell Death (ICD) hallmarks in vitro

DC maturation/ activation induced by Aur F HPA Payload

Generation of a mouse breast cancer model expressing human Her2

TAK-522 increases the tumor infiltration of CD8+ T cells

Tumor regression in tumors expressing both TAK-522 and anti-PD1 as compared to tumors expressing the 2 alone. Additionally, the combination of TAK-522 and anti-PD1 was able to induce a durable immune memory response, as evidenced by the persistence of long-term tumor-free mice.

In Vivo efficacy Studies

TAK-522 (XMT-1522)

Novel anti-HER2 Antibody:
• Mersana proprietary
• Fully human IgG1 identified after screening Adnab yeast display library
• Optimized for internalization
• Binds to a novel, distinct epitope from trastuzumab or pertuzumab
• Does not compete for binding

Novel Linker:
• Mersana Fleximer® polymer
• Allows for much higher drug loading (Average DAR = 19)
• Compatible with diverse payload classes

Proprietary payload:
• Dolastatin derivative with unique pharmacology

A

B

Summary and Model

TAK-522 induces immunogenic cell death (ICD) in vitro in multiple cell lines.

In a syngeneic breast cancer model expressing human HER2, TGI was observed with TAK-522 alone, which was enhanced in combination with anti-PD1 therapy, leading to complete responses in a few mice. Such activity was not observed with Kadcyla.

TAK-522 enhanced CD8+ T-cell infiltration and PD-1 expression on CD8+ T cells in the tumors.

The results are in support of a clinical trial with TAK-522/anti-PD1 combo in HER2 expressing cancers.