MT-4019: a de-immunized engineered toxin body targeting CD38 for multiple myeloma


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Abstract 2659

Background

ETBs were administered for two cycles at 0.05 mg/kg/dose IV with a two week break between cycles (days 1, 3, 5, 8, 10, 12; 29, 31, 33).

In NHPs, there is greater serum exposure to MT3724 compared to MT4019 binding signal to TLR4.

Binding of the catalytic SLTA subunit to CD38 mediates the powerful direct cytotoxicity of the Shiga toxin A subunit (SLTA).

Increased neutrophil and monocyte counts were observed with MT3724.

No adverse body weight effects or clinical observations were directly attributable to the test articles.

Catalytic inactivation of the SLTA subunit (inactive ETB) abolishes cytotoxicity.

MT3724 is a 1st generation ETB with wild type furin activity for the B-cell marker CD20 with monotherapy activity and safety in newly treated DLBCL patients with low rates of neutralizing antibodies.

ETBs induce their own internalization, route to endosomal compartments containing cell surface CD38, and are associated with Desaturumam intensity.

Increased IgG ADA responses were observed with MT3724 compared to MT4019.

Compared to MT3724, MT4019 has improved potency of 2nd generation ETBs under development targeting HER2, PD-L1, and other oncology targets.

MT4019 is a CD38 scFv2 immunization targeted to CD38 generating ETBs.

MT4019 has concentrated (single day) binding to ETBs and SLTA subunits.

In vitro binding assay: ETBs were incubated with cells for 48 hours.

In vivo binding assay: ETBs were diluted in PBS and administered at 1 mg/kg/dose by IP to mice (n=5 or 6/group) for one cycle.

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Serum exposure, target cell depletion and IgG ADA response in non-human primates.

In NHPs, there is greater serum exposure to MT3724 than MT4019.

MT4019 is 1st generation ETB scaffold displaying lower innate and adaptive immune responses.

Stronger direct cytotoxicity of the Shiga toxin A subunit (SLTA) shows much lower ADA response compared to 1st generation ETBs.

Methods

ETBs were incubated with cells for 48 hours.

In vivo cell marker CD20 with monotherapy targeting CD38.

MT3724 compared to MT4019 has reduced IgG ADA response in NHPs throughout the study.

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Conclusions

The next generation ETB scaffold displays lower innate and adaptive immune responses in vitro and in animal models.

MT4019 has picomolar efficacy against CD38+ cells in vitro including cell lines that do not respond to Daratumumab; it will enter human clinical studies in 2018.

MT4019 has reduced IgG ADA responses in non-human primates.

ETBs were administered for two cycles at 0.05 mg/kg/dose IV with a two week break between cycles (days 1, 3, 5, 8, 10, 12; 29, 31, 33).