Combination of MT-3724 with sirolimus reduces anti-drug antibody response and prolongs drug exposure

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Background

Molecular Templates is developing engineered toxin bodies (ETBs), potent recombinant immunotoxins that combine the specificity of an antibody fragment with the cytotoxicity of the Shiga-like toxin A subunit. ETBs can induce their own internalization, route through the cell in a predictable manner, enzymatically and irreversibly destroy ribosomes to shutdown protein synthesis and induce apoptosis of tumor cells. This mechanism is distinct from that of other therapeutics, making ETBs an attractive treatment for patients who have become resistant to chemotherapy and other treatment modalities.

MT-3724 is a Molecular Templates’ first-generation ETB targeting CD20, a surface receptor that is highly expressed on malignant B cells in hematological malignancies. Pre-clinical and clinical studies have shown promising results for non-Hodgkin’s lymphoma cell lines and patients; however anti-drug antibodies are formed in experimental animals and patients after repeat dosing. Sirolimus (rapamycin) is a macrolide compound approved to prevent organ rejection and treatment of LAM, and has been used in taliezer protocols with replacement enzymes. In preclinical studies, we have co-administered sirolimus in combination with MT-3724 in rodents as well as in a non-human primate model in order to reduce the anti-drug antibody response to MT-3724. These studies demonstrated that the combination of sirolimus with MT-3724 decreased anti-drug antibody response, prolonged serum exposure of MT-3724, and improved B-cell depletion as compared to MT-3724 alone.

The combination of sirolimus with MT-3724 is an attractive and feasible regimen which could be further explored in clinical studies.

Methods

Engineered toxin bodies are a mechanism of action that is unique to oncology

MT-3724 entails protein translation by irreversibly and enzymatically inactivating ribosomes, leading to cellular death by apoptosis and autophagy. MT-3724 specifically targets and potently kills CD20 expressing tumor cells, and demonstrates minimal cytotoxicity on cells that lack CD20 surface expression.

Developments of anti-drug antibodies in primates & patients

Antibody responses to MT-3724 likely develop more rapidly in non-human primates than in humans due to delayed ADA responses observed in NHL Subjects

MT-3724 reduces anti-drug antibody response in mice

Optimal dosing of MT-3724 and sirolimus reduces MT-3724 IgG antibody response in mice

Optimal combination of MT-3724 and sirolimus reduces MT-3724 IgG antibody response in mice

• Optimal reduction of ADA response after Cycle 1 and 2 when sirolimus loading and maintenance dose provided during
• No additional reduction of ADA response when sirolimus also provided during Cycle 3 (Table 4).

Sirolimus treatment without loading dose reduces ADA response after first MT-3724 Cycle, but not Cycle 2 (Fig. 3, Table 4). Sirolimus administration during first three MT-3724 doses provided minimal reduction in ADA response (Fig. 3, Day 10 MT-3724 ADAs). In Figure 4, ADA responses in non-human primates measured by MSD bridging assay.

Conclusions

In primates, sirolimus reduced ADA levels enabling longer serum exposure and prolonged PD response of MT-3724

The combination of sirolimus with MT-3724 is an attractive and feasible regimen which could be further explored in clinical studies.

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