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TRITAC-XR IS AN EXTENDED-RELEASE T CELL ENGAGER PLATFORM DESIGNED TO MINIMIZE CYTOKINE RELEASE SYNDROME BY REDUCING CMAX IN SYSTEMIC CIRCULATION

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Background CD3-targeted T cell engagers are potent anti-tumor therapies, but their development often requires management of cytokine release syndrome (CRS). Subcutaneous dosing is a promising strategy to reduce CRS, but its application is limited by its increased immunogenicity risks. Subcutaneous dosing is hypothesized to mitigate CRS by reducing the maximum drug concentration (C_{max}) and preserve efficacy by maintaining the same minimum drug concentration (C_{min}) as intravenous dosing. A T cell engager designed to be dosed intravenously but engineered to mimic the PK properties of subcutaneous dosing could alleviate CRS without increasing immunogenicity.

Methods TriTAC-XR molecules are engineered T cell engager prodrugs that become slowly activated in systemic circulation. This extended-release mechanism results in a slow build-up of circulating active drug, similar to subcutaneous dosing, and extends drug exposure to enable longer dosing intervals. The prodrug was engineered by adding a peptide mask and protease-cleavable linker to the N-terminus of a TriTAC, a constitutively active and half-life extended T cell engager. The mask binds to the anti-CD3 ϵ domain and prevents T cell binding. Upon cleavage by systemic proteases, active T cell engager is released. Binding was assessed using ELISA on recombinant CD3 ϵ protein and using flow cytometry on primary T cells. T cell engager function was assessed using T cell-dependent cellular cytotoxicity (TDCC) assays with resting human T cells. Safety and efficacy were modeled in non-human primates.

Results TriTAC-XR had markedly reduced binding to recombinant CD3 ϵ protein and to primary T cells as well as reduced potency in functional TDCC assays compared to its unmasked active drug. In cynomolgus monkeys, TriTAC-XR had significantly attenuated cytokine production while maintaining comparable pharmacodynamic effects as a non-masked active drug. The ratio of C_{max} to C_{min} for the active TriTAC-XR was significantly smaller than a non-masked control.

Conclusions TriTAC-XR is activated in a time released manner by systemic proteases to minimize differences between the C_{max} and C_{min} of systemic active drug. This mechanism is different from other protease-activated T cell engager prodrugs that are only activated by tumor-associated proteases. Compared to canonical T cell engagers, TriTAC-XR is expected to improve safety by reducing CRS and to provide convenience by extending dosing intervals.

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