TriTAC-XR is an extended-release T cell engager platform that improves safety by minimizing risk of cytokine release syndrome

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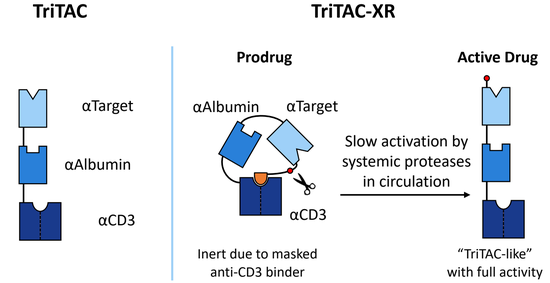
Introduction

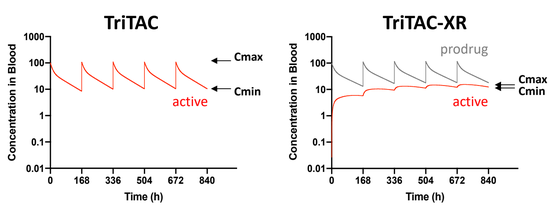
- T cell engagers are potent anti-tumor drugs, but they frequently induce cytokine release syndrome (CRS) in patients
- Existing approaches to manage CRS, while effective, can be suboptimal:
  - Corticosteroids: blunted T cell response and reduced efficacy
  - Step-up dosing: inconvenient, needed after every treatment interruption
  - Continuous I.V. dosing: inconvenient, increased infection risks
  - Subcutaneous dosing: increased immunogenicity risks
- TriTAC-XR molecules are T cell engager prodrugs that become slowly activated in circulation by systemic proteases
- This extended-release mechanism enables slow build-up of active drug and minimizes induction of cytokines while maintaining efficacy

TriTAC-XR Concept



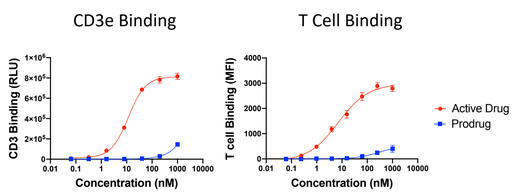
Hypothesis: PK impacts the therapeutic index of T cell engagers

- Cmax drives CRS tox
- Cmin maintained above a threshold level is needed for efficacy
- Slow build-up of active drug and a reduced Cmax/Cmin ratio in circulation will reduce CRS and expand therapeutic index



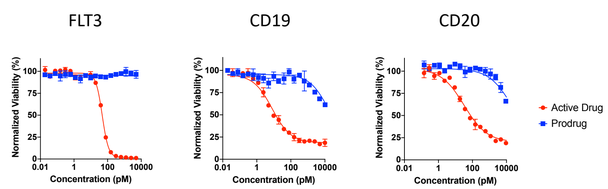
Differential Biological Activity in Vitro

Active drug has >1000x more CD3 binding than prodrug



Binding was assessed by ELISA with recombinant human CD3e protein (left) and by flow cytometry with purified human T cells (right). Bound TriTAC-XR protein was detected using an anti-idiotype antibody against TriTAC-XR.

Active drug has >100x more functional activity than prodrug

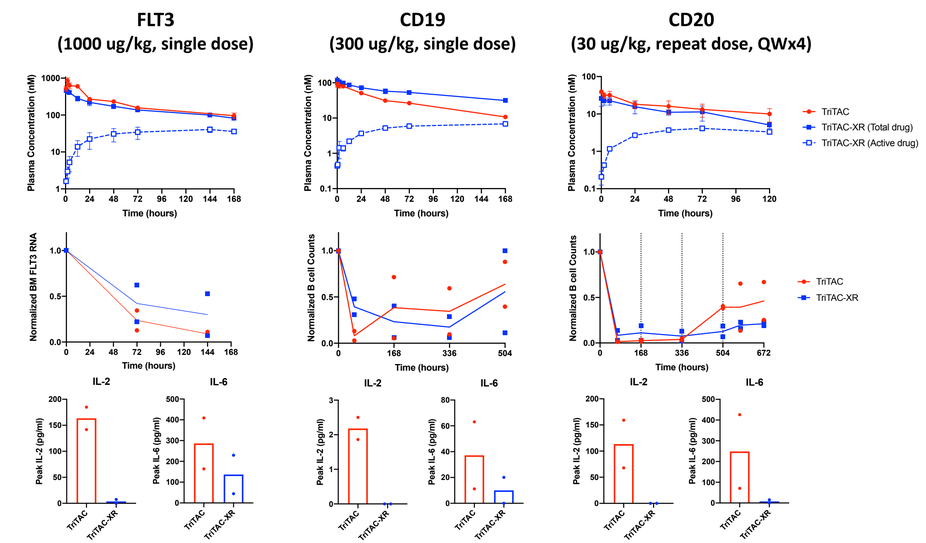


Functional activity was assessed by T cell-directed killing assay where co-cultures of resting human T cells and target cells (MOLM13 for FLT3, Raji for CD19, Daudi for CD20) were treated with TriTAC-XRs at 10:1 effector:target cell ratio. Tumor cell viability was measured after 48-72 hour incubation.

Expansion of Therapeutic Index in Non-Human Primates

Slow build-up of active drug reduces cytokine release while maintaining comparable levels of target cell depletion

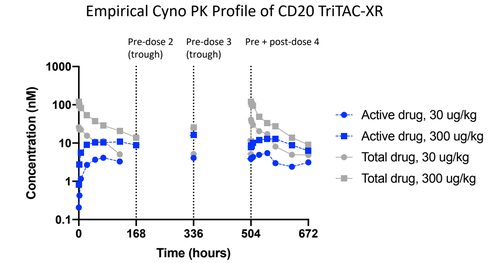
- Cyno cross-reactive TriTAC and TriTAC-XR molecules targeting FLT3, CD19, and CD20 were dosed at the indicated concentrations in cyno monkeys by intravenous infusion
- PK, target cell depletion, and cytokine release were measured from the same animals to assess therapeutic index expansion



PK was assessed with two separate ligand binding assays using specific anti-idiotype antibodies: one specific for TriTAC and TriTAC-XR (active drug) and one specific for both active and prodrug forms of TriTAC-XR (total drug). FLT3 target cell depletion was assessed by qPCR of bone marrow samples collected from cyno monkeys at the indicated time points. B cell depletion was assessed by flow cytometry for CD3- / CD20+ cell population from peripheral blood in cyno monkey at the indicated time points. Peak cytokine release was measured by cyno cross-reactive ligand binding assays.

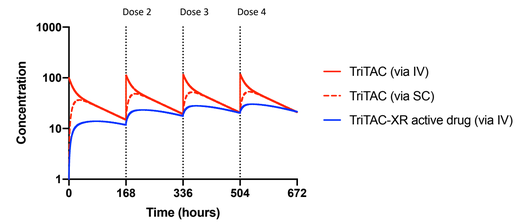
Improved PK in Repeat Dose Setting

TriTAC-XR results in near-constant exposure of active drug even with intravenous dosing



- TriTAC-XR active drug concentration is relatively constant due to continual conversion of prodrug to active drug
- Empirical PK profile confirms the predicted PK model

TriTAC-XR via intravenous dosing is predicted to have superior PK profile than TriTAC via subcutaneous dosing



Benefits of TriTAC-XR compared to subcutaneous dosing:

- More gradual dose ramp-up
- Reduced risks for immunogenicity and injection site reactions

Summary

- PK of TriTAC-XR confirms the slow build-up of active drug with reduced Cmax/Cmin ratio in systemic circulation
- This enhanced PK profile of TriTAC-XR translates to improved therapeutic index, observed across multiple targets in cyno monkeys
- TriTAC-XR and its underlying extended-release mechanism represents a new approach to managing CRS, either alone or in combination with other existing CRS-mitigation approaches
- The expected safety improvements would enable T cell engagers targeting immune cells to broaden its adoption from oncology to autoimmune and other non-oncology diseases

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