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Pharmacokinetics of TNX-1700 in Non-Human Primates and Human FcRn/Serum Albumin Transgenic Mice



Abstract 7940

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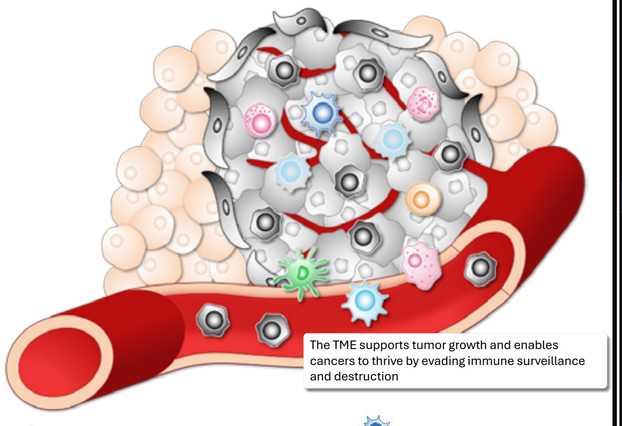
Abstract

Introduction: TNX-1700 is a novel recombinant fusion molecule of human Trefoil Factor-2 (TFF2) protein and human serum albumin (HSA) that is being investigated as a potential therapeutic for gastric cancer. In syngeneic mouse models of gastric and colorectal cancer, TNX-1700 functions as a CXCR4 partial agonist that activates antitumor immunity in the tumor microenvironment by modulating myeloid cell trafficking to reduce tumor-induced granulopoiesis and accumulation of immunosuppressive neutrophils[1]. TNX-1700 is engineered to extend plasma half-life, enhance systemic exposure, and improve cancer immunotherapy. The HSA domain in TNX-1700 provides a long circulatory half-life (>14 days) and multiple ligand-binding sites. Approved albumin-linked drugs include detemir (Levemir®), liraglutide (Victoza®), and albiglutide (Eperzan®/Tanzeum®) for diabetes, and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) for cancer therapy. TNX-1700 represents a next-generation application of the albumin platform in immuno-oncology.

Methods: The pharmacokinetics (PK) of TNX-1700 were evaluated in non-human primates (NHP; cynomolgus macaques) and double-transgenic mice expressing human neonatal Fc receptor (FcRn) and human serum albumin (HSA). Animals received a single dose of 1 mg/kg or 3 mg/kg TNX-1700, administered intravenously (IV) to NHPs or intraperitoneally (IP) to FcRn/HSA mice. For comparison, untagged human TFF2 (molar equivalent to TNX-1700) was also administered into FcRn/HSA mice. Serial blood samples were collected over 0-35 days and analyzed using the Boster PicoKine™ Human TFF2 ELISA kit. Pharmacokinetic parameters were determined by non-compartmental analysis.

Introduction

Tumors Create a Toxic, Immunosuppressive Microenvironment (TME)



- Tumors are surrounded by endothelial and stroma cells, and invading immune cells, both innate and adaptive[2,3]
- Complex regulatory network supports tumor growth, enabling cancers to thrive by evading immune surveillance and destruction[3,4]
- The TME sabotages tumor-killing cytotoxic CD8 T cells[2]
- Myeloid-derived suppressor cells (MDSCs) interfere with anticancer immunity[3,4]

Study Design for a Pharmacokinetic Study in Humanized Mice and Non-Human Primates

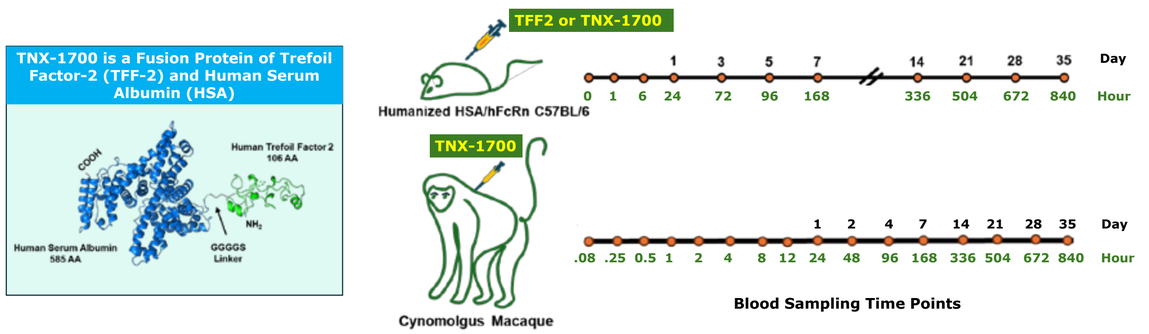


Figure 1: Study design adopted for single dose pharmacokinetics (PK) of TNX-1700 in double-transgenic mice expressing human neonatal Fc receptor (FcRn) and human serum albumin (HSA), and non-human primates (NHP; cynomolgus macaques). TNX-1700 was administered intraperitoneally (IP) to FcRn/HSA mice. For comparison, untagged human TFF2 (molar equivalent to TNX-1700) was also administered into FcRn/HSA mice. TNX-1700 was administered intravenously (IV) to NHPs.

Results

Pharmacokinetic Profile of TFF2 and TNX-1700 in Humanized FcRn/HSA C57BL/6 Mice

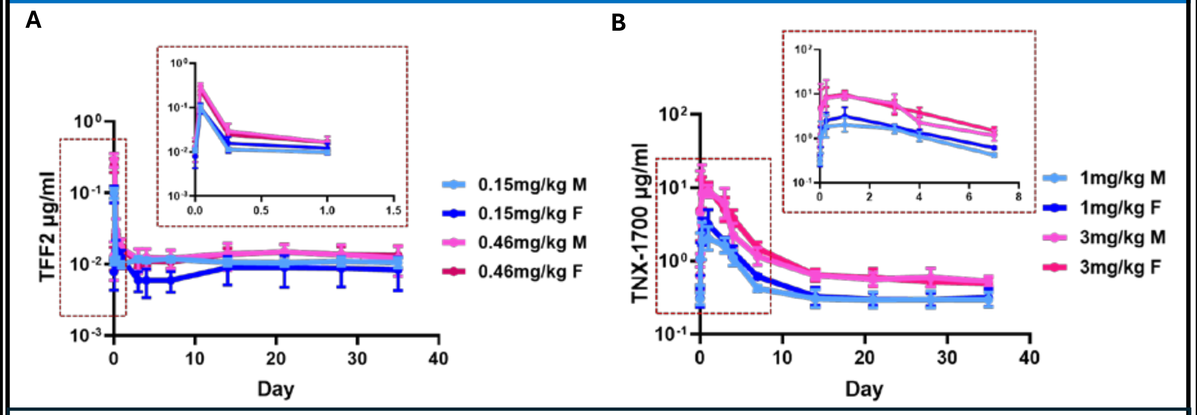


Figure 2: PK profile of TFF2 and TNX-1700 in humanized mice. A. TFF2 dosed via IP at 0.15 or 0.46 mg/kg. B. TNX-1700 dosed via IP at 1 or 3 mg/kg.

Pharmacokinetic Profile of TNX-1700 in Cynomolgus Macaques

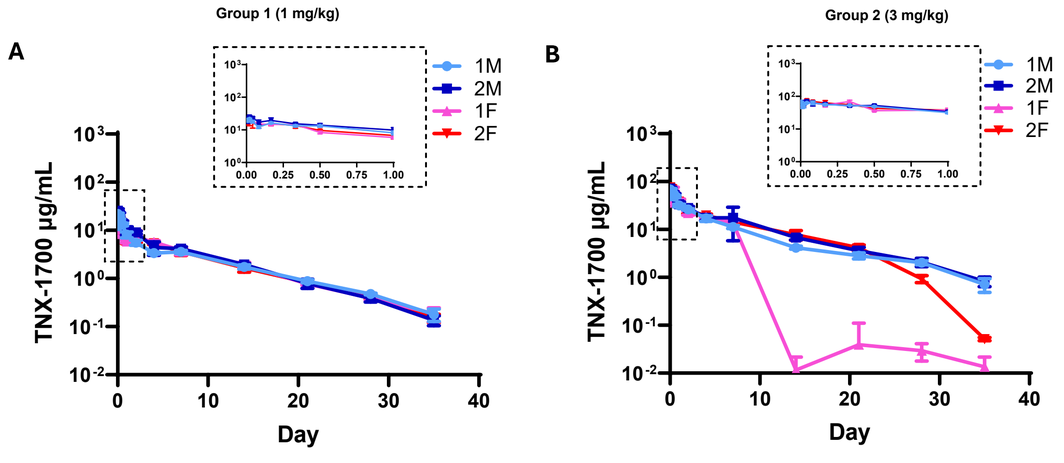


Figure 3: PK profile of TNX-1700 in NHPs. A. Group 1 was dosed via IV at 1 mg/kg TNX-1700. B. Group 2 was dosed via IV at 3 mg/kg TNX-1700.

Antibody Response in NHPs

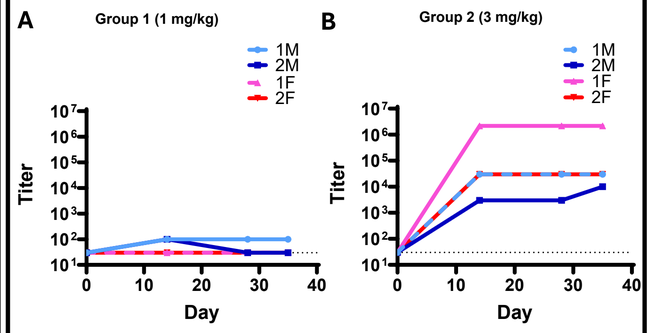


Figure 4: Anti-TNX-1700 IgG ELISA responses. A. Group 1 represents the anti-TNX-1700 profile in NHPs dosed with 1 mg/kg of TNX-1700. B. Group 2 represents the anti-TNX-1700 profile in NHPs dosed with 3 mg/kg of TNX-1700.

Pharmacokinetics of TFF2 and TNX-1700 in Human FcRn/HSA Mice and Non-human Primates

Human FcRn/HSA Mice, Single Dose, IP

TFF2	0.15 mg/kg	0.46 mg/kg
C_{max}	0.10 µg/mL	0.27 µg/mL
AUC_{0-t}	8.2 h*µg/mL	12.0 h*µg/mL

TNX-1700	1.0 mg/kg	3.0 mg/kg
C_{max}	3.0 µg/mL	10.3 µg/mL
AUC_{0-t}	1642 h*µg/mL	2318 h*µg/mL

NHP, Single Dose, IV

TNX-1700	1.0 mg/kg	3.0 mg/kg
C_{max}	21.3 mg/mL	71.4 mg/mL
AUC_{0-t}	1868 h*mg/mL	6484 h*mg/mL
$T_{1/2}$	7.1 Days	7.0 Days

All animals survived without clinical signs or >10% body-weight loss. Comparable PK profiles were observed across species and doses. In cynomolgus macaques, mean terminal half-life (t½) was 7.1 days (%CV = 9.65), clearance (CL) 13.3 mL/day (%CV = 14.3), and volume of distribution (Vz) 135.2 mL (%CV = 18.3). Allometric scaling predicted in humans a t½ of 14.2 days (%CV = 12.9), CL = 105.2 mL/day (%CV = 26.4), and Vz = 2,158 mL (%CV = 34.0). Results from the humanized murine studies provided evidence that untagged human TFF2 is rapidly cleared and that fusion with HSA significantly increased the PK profile similar to that observed in NHPs and to levels supportive for clinical candidates.

Conclusions

TNX-1700 exhibited dose-independent, linear pharmacokinetics with low inter-animal variability, and exposure was consistent across doses and species. Although its half-life is shorter and clearance higher than IgG-based biologics, TNX-1700 substantially extends the half-life of TFF2 and achieves durable systemic exposure, supporting its potential as a therapeutic candidate for gastric cancer.

References

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