Pharmacokinetic Evaluation and Tolerability Assessment of ES414 (anti-PSMA x anti-CD3 ADAPTIR\textsuperscript{TM} Molecule) in Humanized Mice and Non-Human Primates

Catherine J. McMahan, Gabriela Hernandez-Hoyos, Jeanette Bannink, Robert Bader, Padma Ravikumar, Toddly Sewell, Ken Bannink, Rebecca Gottschalk, Hang Fang, Starlia Johnson, Megan Aguilar, John Kumer, Paul A. Algate, David Bienvenue, Jane Gross, and John W. Blankenship

Abstract

Tocilizumab, a recombinant monoclonal antibody (rMAB) receives a highly coveted medical need. We have developed a bispecific ADAPTIR\textsuperscript{TM} (multi-specific protein therapeutic) molecule, ES414, that targets prostate-specific membrane antigen (PSMA) and CD3, an antigen expressed on mature T cells. ADAPTIR molecules are antibody-like therapeutics containing an engineered Fc region and an anti-antigen scFv antibody fragment. ADAPTIRs are under development for a variety of indications with potential for indicating a wide range of pharmacodynamic results. ADAPTIRs can be developed against target antigens where other antibodies are not efficacious, due to poor binding, poor pharmacodynamics, or off-target effects, or where it is desired to increase the range of therapeutic responses.

The ADAPTIR ES414 was evaluated in two sets of biodistribution studies in humanized NSG mice, which included a single site of injection. In the first set of studies, ES414 was administered at 0.1 mg/kg and 1 mg/kg, using an implantable osmotic pump. Tolerability was assessed by pre-dose, 24 and 168 hours after the single dose (no toxicological signal in the data collected).

Materials and Methods

Results

ADAPTIR Therapeutics

ADAPTIR molecules are designed to be highly tolerant of the biodistribution testing in non-human primates (NHPs) and cynomolgus monkeys to include the terminal phase of elimination (in the cynomolgus monkey). The ADAPTIR molecule ES414 was dosed at 0.01 mg/kg and 0.1 mg/kg, using a single-dose, intravenous injection. Tolerability was assessed by pre-dose, 24 and 168 hours after the single dose (no toxicological signal in the data collected). The PK and single-dose tolerability of ES414 were assessed in male cynomolgus monkeys. 4 dose groups were assigned to the three dose levels: 0.01 mg/kg, 0.1 mg/kg, and 1 mg/kg. Tolerability was assessed following single intravenous injection in BALB/c mice (not shown) and cynomolgus monkeys. Cross-reactivity of ES414 to cynomolgus antigens was first assessed by measuring binding to relevant cynomolgus antigens (OKT3, FN18).

ES414 is Cross-Reactive on Human and NHP Cells

Figure 4. ES414 is Cross-Reactive on Human and NHP Cells

Results

ES414 was cross-reactive on human and NHP cells. The antibody-like therapeutic ES414 precisely binds human and NHP PSMA. The anti-CD3 binding domain is a humanized scFv adapted from a system that could lead to CD3 clustering and non-specific T cell activation.

ES414 and a limited dose-dependent effect on cytokine release and T cell redistribution. This cytokine release for ES414 that was less than that produced by the comparator scFv-scFv format or anti-PSMA-x-OKT3.

Conclusion

Figure 5. ES414 Tolerability in NHP

Conclusions

Figure 9. ES414 Serum Concentrations in NHP

EMERGENT BIOSOLUTIONS

Emergent Product Development Seattle LLC, Seattle, WA, USA

References

Figure 10. Comparing Cytokine Release: ES414 to FN-18\textsuperscript{*}