Background

The ligand for the receptor tyrosine kinase FMS-like tyrosine kinase 3 (FLT3) plays an important role in hematopoiesis. FLT3 signaling is required for the differentiation and expansion of dendritic cells. In the context of cancer immunity, the conventional dendritic cell subtype 1 (cDC1) are required for the generation of tumor-specific T cell responses in mouse preclinical models. In human tumors cDC1 are often underrepresented in the tumor microenvironment, supporting the hypothesis that therapeutically increasing their number via FLT3 pathway stimulation has the potential to promote T cell-mediated anti-tumor activity.

Methods

GS-3583 is a fusion protein composed of the extracellular domain of human FLT3 ligand (FLT3L) combined with a modified fragment crystallizable (Fc) region of human IgG4. GS-3583 was designed to induce cDC1 expansion and subsequently promote tumor-reactive T cell priming, activation and recruitment into the tumor microenvironment. The pharmacokinetics (PK) and pharmacodynamics (PD) of GS-3583 has been characterized in a 4-week repeat dose GLP study in cynomolgus monkeys at doses ranging from 0.3 to 10 mg/kg GS-3583 was given as an intravenous injection.

Results

Immunophenotyping analysis of peripheral blood cells from GS-3583 treated monkeys demonstrated a non-dose-dependent expansion of cDC1 and cDC2 populations. The peak expansion for cDC1 and cDC2 occurred at Day 8 to Day 15. At peak, there was a 160-fold relative increase in cDC1 and 150-fold increase in cDC2 at the highest dose tested. There were dose-dependent increases in the exposure (AUC and Cmax) of GS-3583. GS-3583 was well-tolerated with no mortality or adverse clinical signs.

Conclusions

The administration of GS-3583 leads to increases in cDC1 and cDC2 populations. It was well tolerated at the maximal dose tested with no adverse clinical signs. Further clinical development of GS-3583 is warranted.

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