PBMC HUMANIZED MOUSE MODEL WITH CLINICAL RELEVANCE IN ASSESSING THE SAFETY PROFILE OF 4–1BB AGONISTS UTOMILUMAB AND URELUMAB

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Background Immunotherapy is an important tool that can be used to stimulate a patient's own immune system against cancer. 4-1BB agonists were designed to target costimulatory molecules on a patient’s immune cells to activate anti-tumor activity. Two 4-1BB agonists were recently investigated in clinical trials. Urelumab demonstrated clinical efficacy but also induced severe liver toxicity while utomilumab was well tolerated. Preclinical toxicity evaluations were unable to predict the clinical safety profile of urelumab.

Methods We developed a PBMC humanized mouse model to better meet the needs of preclinical toxicity evaluations. This model can be used to test a variety of therapeutics that target human immune cells, including both monoclonal and bispecific antibodies, and induce acute or systemic cytokine release responses which can manifest within hours or days later resulting in tissue damage and lethality of the mice. For this study PBMC humanized mice were dosed with 10 or 1 mg/kg of urelumab or utomilumab. Mice were evaluated on a daily basis for bodyweight loss and clinical evaluation scores. Toxicity was also evaluated by liver histology and terminal serum clinical chemistry.

Results Mice dosed with 10 mg/kg of urelumab experienced body weight loss, met the clinical criteria for early euthanasia, and showed marked liver necrosis compared to utomilumab treated animals and PBS controls. Serum levels of AST, ALT and GLDH were also significantly higher in urelumab treated mice. Cytokine analysis of terminal serum revealed similarities with those found to be increased in urelumab clinical trials, including elevated IFNγ, IP-10, MIG, and MIP-1α and MIP-1β. Toxicity of urelumab could be reduced by lowering the dose to 1 mg/kg, while utomilumab was safe at both 10 mg/kg and 1 mg/kg doses.

Conclusions The data generated in PBMC humanized mice were similar to findings from the clinical trials of utomilumab and urelumab and suggest that our model could identify the clinically relevant toxicity profile induced by 4-1BB agonists. The use of PBMC humanized mouse models for preclinical safety assessments could become an important part of novel immunotherapeutic development for both patient safety and reducing drug development costs.

REFERENCE

Ethics Approval The Jackson Laboratory Institutional Animal Care and Use Committee and institutional review board approved all protocols used.