Humanized mouse model: A preclinical platform feasible for a bispecific T cell-engaging antibody (BiTE)

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INTRODUCTION

The selection of appropriate preclinical models based on similarity to human biology and disease genotype and phenotype carries considerable potential to ensure higher predictability of preclinical trials. The design and interpretation of first-in-man trials remains a major challenge in the development of novel anti-cancer agents. Key study design elements such as schedule, escalation strategy, targeted patient population, etc. rely heavily on preclinical (usually in vivo) data. It is especially difficult to model for preclinical assessment of cancer immunotherapy, the most actively developing area in oncology.

Bispecific T-cell engager molecules (BiTEs) constitute a class of bispecific single-chain antibodies for the polyclonal activation and redirection of cytotoxic T cells against pathogenic target cells. Here we proposed preclinical studies in NPI (NOD. Prkdc^{cs} Il2rg^{tm1}) mice engrafted with human CD34 positive hematopoietic stem cells (HSCs) from cord blood, which indicate the importance of the desired balance between potency, PK, and safety for optimizing the performance of a T cell–recruiting bispecific antibody.

RESULTS

Fig. 1 Mechanism of BiTEs:

BiTES are engineered from the binding domains of two different antibodies. One end binds to CD3 found on T cells and the other end binds to a tumor-specific protein epitope presented on the surface of the tumor. When both of its binding domains are engaged, the BiTE creates a cytolytic synapse, leading to T cell-mediated killing of the target tumor cell. (Adapted from Frankel, S. et.al. 2013. Cur Opin Chem Bio 17(3). Science Direct.)

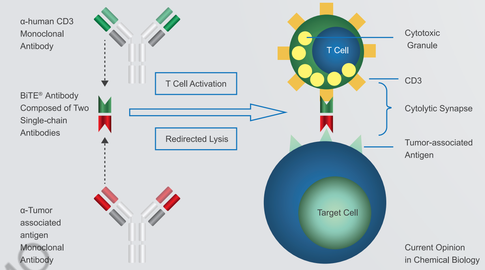
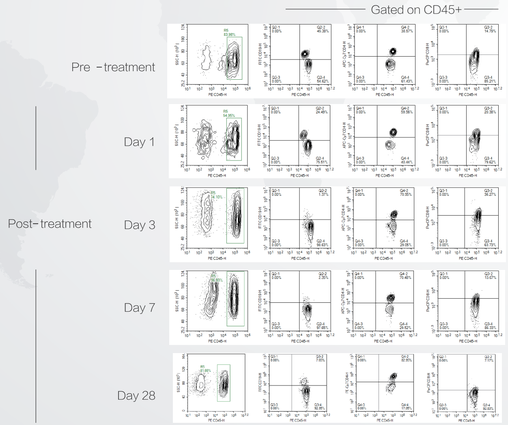


Fig. 2 B cell depletion in Hu-CD34 NPI mice:

NPI (NOD. Prkdc^{cs} Il2rg^{tm1}) mice were preconditioned and engrafted with human CD34 positive hematopoietic stem cells from cord blood.(A) Study design; (B) FACS analysis of T cell and B cell populations in peripheral blood after Rituximab treatment (single dose, i.v.); (C) FACS analysis of T cell and B cell populations in peripheral blood after Blinatumumab treatment (single dose, i.v.)

(A)



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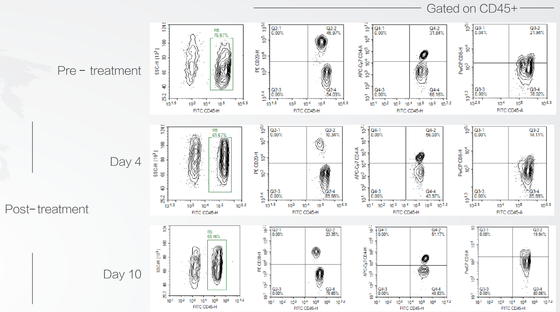


(C)

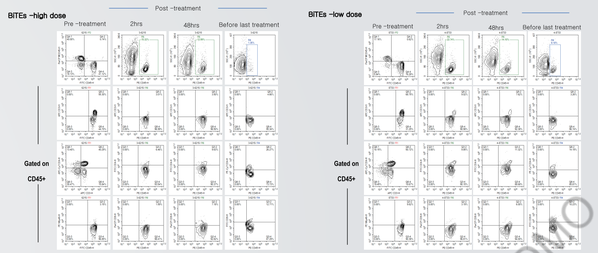
Fig. 3 In vivo efficacy and toxicity:

Tumor cell line was implanted subcutaneously into HuNPI mice. (A) Study design; (B) HLA matching results (C) FACS analysis of T cell and B cell populations in peripheral blood after BiTes treatment (Q2d, i.v.); (D) % tumor inhibition: Mean % Inhibition = (mean(C)-mean(T))/mean(C) * 100%, T-test group, C-control group.(E) Body weight change

(A)

Sample Name	HLA typing		
	A	B	DR
HuNPI	A*02	B*37	DRB1*10
	A*24	B*48	DRB1*15
Tumor cell line	A*23	B*37	DRB1*07
	A*23	B*37	DRB1*07

(B)



(C)

(D)

(E)

CONCLUSIONS

HuNPI mice can be used to evaluate efficacy and safety of BiTEs in vivo. These preclinical studies in HuNPI mouse models indicate the importance of selecting a CD3 affinity resulting in the desired balance between potency, PK, and safety for optimizing the performance of a T cell–recruiting bispecific antibody.

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