CREATING AN IMMUNE-FAVORABLE TUMOR MICROENVIRONMENT BY A NOVEL ANTI-CD39/TGF β -TRAP BISPECIFIC ANTIBODY

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Background Adenosine and TGF β are two key immune suppressors in tumor microenvironment ("TME") that cause broad immune suppression resulting in resistance to current CPI immunotherapies. Cancers frequently express transforming growth factor- β (TGF β), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs), inhibiting CD8+ activation and infiltration into TME, and promoting epithelial-mesenchymal transition (EMT). We observed that TGF β induces the expression of CD39, a critical enzyme that regulates adenosine generation. CD39 is highly expressed in Tregs within TME, it drives the production of adenosine, an immunoinhibitory molecule that partly mediates Treg inhibitory function. To inhibit CD39-Adenosine and TGF β simultaneously to create an immune favorable tumor microenvironment, we designed a bi-specific antibody targeting both CD39 and TGF β (ES014), which aims to inhibit the generation of adenosine and iTreg in TME. The immuno-stimulating effect of ES014 was demonstrated in a PD-1-unresponsive mouse model where tumor growth was significantly inhibited after the treatment of the bi-specific antibody.

Methods The bifunctional antibody-ligand trap ES014 was created by fusing the TGF β receptor II ectodomain to an antibody targeting CD39. ES014 molecule could simultaneously inhibit CD39 enzymatic function to prevent extracellular ATP from degradation and neutralize autocrine/paracrine TGF β in the target cell microenvironment. The immunological function of ES014 was studied in an in vitro Elpiscience proprietary ImmunoShine platform which includes T cell activation and apoptosis assay, iTreg differentiation and suppression assay, NK cell activation assay and DC maturation activity. The in vivo efficacy of ES014 was investigated in a human PBMC engrafted cancer model.

Results We demonstrated that ES014 bispecific antibody can inhibit CD39 enzymatic activity and neutralizes TGF β -induced effect, resulting in greater T cell activation and suppression of Treg differentiation. Interestingly, we found ES014 molecule demonstrated a unique mechanism by significantly protecting effector T cell from anti-Fas induced apoptosis or activation induced cell death (AICD) that is not observed in monotherapy or combo treatment. The ES014 molecule is more effective in inhibiting tumor growth as compared with anti-CD39 antibody or TGF β -trap in a human PBMC engrafted in vivo model.

Conclusions We find that by simultaneously targeting CD39 and TGF β by a novel bi-specific molecule ES014, a more immune-favorable TME and synergistic anti-tumor effects can be achieved. Our pre-clinical data demonstrate that ES014 counteracts TGF β -mediated inhibitory effect and adenosine induced immune tolerance and has a unique ability to protect T cell from apoptosis. ES014 demonstrated strong efficacy in in vivo tumor growth inhibition.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.792>