Background Immune checkpoint inhibitors (ICls), has revolutionized the treatment landscape or malignancies. However, many patients present with or develop resistance to them. Tumors with little anti-tumor immune cell infiltration or lack of pre-existing antitumor immune responses are defined as immunologically “cold” tumor. Patients with these tumors have a poor prognosis following PD-L1 blocking therapy. On the other hand, malignancies that initially respond well to ICls may develop acquired drug resistance, in part as a result of a condition known as T cell exhaustion. ATG-101 is a tetravalent PD-L1×4-1BB bispecific antibody (BsAb), which activates 4-1BB signaling upon PD-L1 crosslinking. In this study, we evaluated the potential of ATG-101 in treating ICI-resistant or refractory diseases using mouse syngeneic tumor models.

Methods To assess the efficacy of ATG-101 on exhausted T cells, human T cells were isolated, and the cell exhaustion was induced through consistent strong activation with anti-CD3/CD28 beads for up to 6 days. The in vivo efficacy of ATG-101 was tested in 4-1BB humanized mouse bearing syngeneic B16F10 (Melanoma), EL4 (Lymphoma) or Pan02 (Pancreatic) tumors, all of which have been suggested to be ICI-resistant. To evaluate ATG-101 efficacy in tumors progressing after anti-PD(L)1 treatment, mice bearing MC38 colorectal tumors were treated with anti-PD-L1 initially to achieve tumor growth inhibition, and half of the mice switched to ATG-101 upon disease progression. TIL was analyzed using flow cytometry or multiplex IHC.

Results In the presence of PD-L1 positive cells, ATG-101 enhanced the IL2 and INF-γ production by the terminally exhausted T cells and progenitor exhausted T cells. In Pan02 murine pancreatic model, Atezolizumab (anti-PD-L1) did not show anti-tumor efficacy at 7.5mg/kg. While ATG-101 at molar-equivalent 10 mg/kg was well tolerated and significantly inhibited tumor growth, with a TGI value of 78.48% (figure 1). ATG-101 also demonstrated significant tumor growth inhibition in EL4 and B16F10 model compared with control. Furthermore, ATG-101 induced growth inhibition or regression in MC38 tumors that had progressed on Atezolizumab, revealing a significant survival advantage over Atezolizumab or the control group. TIL analysis suggested that ATG-101 increases the infiltration, proliferation and activation of CD8+ T cells, the infiltration of natural killer T cells and the CD8+/Treg ratio in TILs (figure 2).

Conclusions ATG-101 activates exhausted T cells upon PD-L1 crosslinking and exhibits effectiveness against ICI-resistant diseases, a significant unmet medical need. A phase I, multicenter, dose-escalating clinical trial evaluating ATG-101 in patients with solid tumors and hematologic malignancies is ongoing.

REFERENCES

Abstract 1150 Figure 1 ATG-101 demonstrates in vivo efficacy in Pan02 model.

Average tumor growth curves (top panel) and individual tumor growth spaghetti plots (bottom) of Pan02.

Abstract 1150 Figure 2 ATG-101 increased the anti-tumor immunity in the TME

Representative images of multiplex immunohistochemistry (IHC) staining of samples collected from mouse bearing MC38 tumors that had progressed on Atezolizumab. Mouse were treated with PBS, 10mpk atezolizumab only or mice initially treated with 10mpk atezolizumab and switched to 13mpk ATG-101 upon disease progression (Atezo to ATG-101). The tumor slices were stained for CD4 (helper T cell, red), CD8 (effector T cell, purple), Foxp3 (Treg, green), and PD-L1 (cancer cells, dark orange). Nucleus were labelled with DAPI (blue). Areas highlighted in the merged images are enlarged. Scale bars are 50 µm.