Background Letetresgene autoleucel (lete-cel; GSK3377794) is a first-generation (1st gen) NY-ESO-1-specific T-cell receptor (TCR) therapy with demonstrated clinical activity in solid tumors.1-2 Next-generation T-cell therapies are in development with the goal of further improving response rates and durability. Gen-R is an ex vivo genetic reprogramming technology in which T cells are engineered to overexpress c-Jun, a member of the activator protein 1 (AP-1) family of transcription factors. Dysregulation of AP-1 family members is implicated in chimeric antigen receptor (CAR) T-cell exhaustion, and previous studies demonstrate that overexpressing c-Jun can delay functional exhaustion, thereby improving anti-tumor efficacy and CAR T-cell persistence in pre-clinical solid tumor models.3

LYL331 (GSK4349560) is a next-generation NY-ESO-1-specific TCR therapy that incorporates Gen-R technology. Here we show pre-clinical data for LYL331 evaluating the impact of c-Jun overexpression on primary and long-term durable T-cell functions in vitro.

Methods Donor T cells were transduced with a lentiviral vector encoding EF1α, NY-ESO-1 (1st gen NY-ESO-1 TCR control) or EF1α-c-JunWT_NY-ESO-1 (LYL331) and characterized for primary functional activities (cytotoxicity, cytokine secretion, and proliferation) and NY-ESO-1 antigen sensitivity. In addition, we used an in vitro serial re-stimulation assay as a model for measuring features of T-cell exhaustion and evaluating long-term durable functions.

Results LYL331 displayed stable and high expression of c-Jun and showed multiple enhancements to primary T-cell functions in vitro compared to the control, including superior cytotoxic activity, as well as increased cytokine secretion (IFNγ and IL-2), proliferative capacity, and sensitivity towards the NY-ESO-1 peptide. Enhanced proliferation was observed in both CD4+ and CD8+ T-cell populations, indicating that overexpressing c-Jun can improve T-cell functions in CD4+ T cells transduced with an HLA class I restricted NY-ESO-1 TCR. In addition, while the control displayed characteristics of exhaustion (i.e., loss of cytotoxic activity and cytokine secretion and increased expression of multiple exhaustion markers) in the serial re-stimulation assay, LYL331 maintained the ability to kill and secrete cytokines and displayed reduced expression of exhaustion markers TIGIT, PD-1, and CD39.

Conclusions In addition to supporting the hypothesis that genetic reprogramming with Gen-R technology can delay the onset of exhaustion and improve the long-term durable functions of LYL331, these data show that c-Jun overexpression can provide immediate benefits to the NY-ESO-1-specific TCR therapy during primary stimulation in vitro. Based on these promising pre-clinical data, LYL331 may have the potential to improve clinical responses in patients with solid tumor malignancies.

REFERENCES

Ethics Approval Experiments presented in this abstract relied on human donor material that was obtained from commercial vendors. These vendors use their own IRB-approved protocol and consent process.