313 EDIT-202, A MULTIPLEXED ASCAS12A EDITED IPSC DIFFERENTIATED INK, DISPLAYS A MATURE PHENOTYPE, HIGH KIR EXPRESSION, AND ADCC TOWARDS MULTIPLE SOLID TUMOR LINES

Alex Allen*, Kaitlyn Izzo, Mrunali Jagdale, Scott Mordecai, Jared Getgano, Laura Blaha, Abhijit Dandapat, Mark Shearman, Kai-Hsin Chang. *Editas Medicine, Cambridge, MA, USA*

Background Chimeric antigen receptor (CAR)-T cells have demonstrated that cell therapy can achieve durable remissions in hematologic malignancies. CAR-T cell therapies have limited efficacy in solid tumors, however, and are often associated with severe toxicity, highlighting the need for safer, more efficacious cell therapies. Natural killer (NK) cells with high-affinity CD16 represent an attractive alternative therapy option to CAR-T cells due to their natural cytotoxic ability and low toxicity.

Methods Using our proprietary engineered AsCas12a, we generated a multiplexed edited iPSC clone(s) that includes four edits: high affinity, cleavable, CD16 KI (knock-in), membrane-bound IL-15 (mbIL-15) KI, TGFBRII KO, and a CISH KO. The two gene knock-ins were enabled with our proprietary **Se**L**e**ction by **E**ssential **E**xon **K**nock-in (SLEEK™) technology which enables high levels of KI, while expressing the cargo transgene consistently over time. Subsequently, we differentiated the iPSC clone(s) into iNK cells, termed EDIT-202, using a feeder-free differentiation process. We have previously demonstrated that this unique combination of edits in EDIT-202 results in an enhanced ability to overcome TGF-β-mediated immunosuppression, persist long-term without exogenous cytokine support, and control ovarian tumors in vitro and in vivo via natural and antibody-dependent cellular cytotoxicity.

Results The phenotype of EDIT-202 and its effector function against multiple solid tumor cell lines were further characterized. EDIT-202 expressed high levels of CD16 and KIR, which are commonly used markers for maturation. In addition, EDIT-202 expressed high levels of perforin, granzyme b, and T-bet, a critical transcription factor that helps control maturation in NK cells. Higher expression of KIR correlated to potent NK cell killing with an R^2 of 0.78 in a 3D tumor spheroid killing assay. Tumor cells from head and neck squamous cell carcinoma (HNSCC), gastric cancer, and non-small cell lung cancer (NSCLC) were screened against cryopreserved EDIT-202 cells. When combined with cetuximab (anti-EGFR antibody) against HNSCC and NSCLC, or with trastuzumab (anti-HER-2 antibody) against gastric cancer cells, EDIT-202 showed an approximately 10-fold increase in IFN-γ secretion compared with an EDIT-202 alone control. Moreover, there were significant increases in ADCC at multiple effectors to target ratios (E:T) when EDIT-202 cells were screened against the aforementioned solid tumor types.

Conclusions In conclusion, iPSC derived NK cells (iNK) have the unique advantage of being an off-the-shelf, and fully characterizable cell therapy amenable to multiplexed gene editing to enhance anti-tumor activity. EDIT-202 demonstrates a mature phenotype which translates to a highly potent and persistent iNK cell for potential treatment of multiple solid tumor types.

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