Results AKT inhibition resulted in the generation of a more consistent expansion and phenotype of the final T-cell product. This was observed using two SPEAR T-cell constructs, ADP-A2M4 and ADP-A2M4CD8. Ex vivo SPEAR T-cell expansion in the presence of an AKT inhibitor generated CD8+ T-cells that maintained a less differentiated phenotype (based on CCR7+CD45RA+ and CD62L+ expression). AKT inhibition was associated with enhanced antigen-specific responses of SPEAR T-cells in vitro, including effector cytokine production, target-cell killing, ability to proliferate in response to prolonged antigen-stimulation and maintenance of cytotoxic activity following antigen re-stimulation.

Conclusions We plan to introduce AKT inhibition into the GMP manufacturing process, and evaluate the efficacy of the resulting products in ongoing clinical studies.

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Abstracts

INHIBITION OF AKT SIGNALING DURING EXPANSION OF TCR-ENGINEERED T-CELLS FROM PATIENT LEUKOCYTE MATERIAL GENERATES SPEAR T-CELLS WITH ENHANCED FUNCTIONAL POTENTIAL IN VITRO

Katerina Mardilovich, Lilli Wang, Rachel Kenneil, Gareth Betts, Natalie Bath, Will Spinner, Vanessa De Mello, Seint Lwin, Joseph Sanderson, Jonathan Silk, Alex Tipping, Andrew Gerry, Phil Bassett, Karen Miller, Mark Dudley, Emily Schmidt. Adaptimmune, Abingdon, UK

Background T-cells attributes for adoptive cell therapy of patients with advanced cancer can be optimized during ex vivo expansion culture. Autologous TCR-engineered T-cells targeting the MAGE-A4 antigen with Specific Peptide Enhanced Affinity Receptors (SPEAR T-cells) have shown promise in the clinic. The highly variable leukocyte material obtained from individual patients during apheresis can present a manufacturing challenge for autologous T-cell therapies. The degree of ex vivo expansion and the functional attributes of the expanded T-cell product impact therapeutic efficacy and can be suboptimal for some patient apheresis material. Both TCR and cytokine growth factor signals used for ex vivo T-cell expansion promote robust activation of AKT (Protein Kinase B) signaling, which drives T-cell activation, proliferation, and terminal differentiation. It is hypothesized that inhibition of AKT signaling during T-cell expansion may uncouple proliferation and terminal differentiation, leading to the generation of less differentiated T-cells that may have functional benefit in vivo.

Methods We evaluated use of an AKT inhibitor during SPEAR T-cell manufacturing using leukocytes from healthy donors and patients with advanced solid cancers.

REFERENCES


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REFERENCES


DECITABINE GENE MODULATION SENSITIZES HUMAN NON–SCLER Cell LUNG CANCER (NSCLC) TO NY-ESO-1 TCR IMMUNOTHERAPY (LETETRESGENE AUTOLEUCEL; GSK3377794) IN VIVO

Dmitry Pankov*, Ioanna Eleftheriadou, Anna Domogala, Sara Brett, Lea Patac, Magdalena Kijewska, Gary Thripp, Jack Euesden, Jan Klapwijk, Katrina Soor, Mfis Damm, Mark D Hill, Mirrila Geougliou, Arman Shalabi, Cedric Britten. GlaxSmitKline, Collegeville, PA, USA

Background NY-ESO-1–specific T cells (letetresgene autoleucel [lete-cel] GSK3377794) are autologous CD4+ and CD8+ T cells transduced to express a high-affinity T-cell receptor (TCR) capable of recognizing NY-ESO-1 and LAGE-1a antigens in complex with human leukocyte antigen (HLA)-A*02. NY-ESO-1 (CTAG1B) and LAGE-1a (CTAG2) are tumor-associated antigens (TAA) that share the SLLMWITQC peptide bound to human leukocyte antigen HLA-A*02 and are expressed in various cancers. Emerging evidence suggests that TCR-engineered T cells targeting NY-ESO-1 hold promise for patients with solid tumors. Approximately 75% of synovial sarcomas can over-express NY-ESO-1 vs 12% of NSCLC, however, NSCLC expression of NY-ESO-1/LAGE1-a may have