Background

Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) can mediate durable responses in advanced solid tumors.\(^1\)\(^2\) Effectiveness is driven by tumor-antigen recognition and maintenance of the diversity of T-cell receptors (TCR) found in the source tumor. As with all ACT, T-cell quality also impacts treatment efficacy, with more stemlike qualities associated with improved outcomes.\(^3\)\(^4\) Current rapid-expansion protocols reduce TIL stemness and TCR diversity through progressive differentiation during \textit{ex vivo} expansion. Therefore, strategies that enrich for stemness and preserve polyclonality, while maintaining a high production success rate, are needed. LYL845 is an autologous TIL product produced with our proprietary Epi-RTM epigenetic reprogramming protocol, which was developed to preserve polyclonality and tumor-reactive clones and enhance stem-like qualities and anti-tumor function of manufactured TIL products.

Methods

TIL products were produced from 3 different tumor types (melanoma, lung and colorectal cancer) treated with/without checkpoint inhibitors [CPI] using the Epi-R technology and standard protocol. Characteristics of the resulting products (LYL845 and control, respectively) were compared using a matrix of assays and methods, including flow cytometry, bulk RNA sequencing (RNA-seq), and TCR beta sequencing.

Results

Epi-R technology resulted in 100% success rate of TIL expansion across all three tumor types; versus 70% with the control process. LYL845 was enriched for CD8+ T cells without compromising polyclonality compared to control TIL. LYL845 was also enriched for stem-like CD4+ and CD8+ T cells with reduced terminal differentiation and exhaustion, as demonstrated by flow data and transcriptomic profiling. In addition, LYL845 exhibited better metabolic fitness as evidenced by low glycolysis and hypoxia gene signatures. Metabolic fitness and enrichment of stemness indicate that LYL845 has attributes that correlated with positive clinical outcome in previous ACT trials. Furthermore, polyclonality was preserved in LYL845 as measured by Simpson clonality index using bulk TCR sequencing data. Finally, LYL845 maintained these favorable characteristics regardless of prior patient CPI use. These key product attributes were further translated to LYL845 large-scale products.

Conclusions

Results from research- and large-scale productions demonstrate that the Epi-R technology enables successful TIL expansion from both immunologically hot and cold tumors, while maintaining a greater proportion of stem-like T cells that demonstrate better metabolic fitness with preserved polyclonality (i.e., maintenance of tumor-reactive TCR diversity) across all 3 tumor types investigated. These findings support the clinical development of LYL845 in an upcoming first-in-human Phase 1 clinical trial.

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REFERENCES


Ethics Approval

Research was performed with tissues obtained from patients through a procurement protocol approved by WCG IRB, tracking number 20210857.