Background TIL therapy, a personalized cell therapy comprising T cells that have been expanded ex vivo, is a promising treatment approach for advanced solid tumors. Retention of tumor-specific T-cell clonotypes and maintenance of stemness, characteristics associated with improved clinical efficacy, are compromised during conventional manufacturing. New approaches are needed to optimize ex vivo TIL expansion processes to preserve relevant T-cell clones and stemness.

LYL845 is an investigational autologous TIL therapy produced with Lyell’s epigenetic reprogramming (Epi-R™) protocol, which generates populations of tumor-reactive T cells with stem-like qualities and a more favorable phenotype (including CD8 skewing) associated with improved clinical outcomes relative to control TIL expanded with conventional processes. Preclinical data demonstrate these findings in both immunologically hot (melanoma, non-small cell lung cancer [NSCLC]) and cold (colorectal cancer [CRC]) tumors, supporting clinical development in these tumor types.

LYL845-101 is a Phase 1, first-in-human, multicenter, single-arm, open-label, dose-escalation and -expansion trial (NCT05573035) designed to evaluate the safety and anti-tumor activity of LYL845 in patients (pts) with advanced solid tumors.

Methods The trial is enrolling adult pts with locally advanced or metastatic melanoma, NSCLC, or CRC that has progressed after ≥1 line of therapy, including an immune checkpoint inhibitor (melanoma, NSCLC) or chemotherapy (CRC). Pts must have ECOG status 0-1; life expectancy ≥3 months; and measurable disease, including a target lesion evaluable per RECIST and an additional resectable lesion for TIL manufacturing. Bridging therapy is allowed during LYL845 manufacturing.

Part A (dose escalation) will evaluate 2 planned dose level ranges of LYL845 using the modified toxicity probability interval-2 (mTPI-2), with a 28-day dose-limiting toxicity (DLT) period. Part B (dose-expansion) will treat 15-30 pts in each disease cohort at the recommended phase 2 dose range (RP2DR), determined in Part A.

After TIL tumor tissue collection surgery and successful LYL845 manufacturing, pts receive fludarabine and cyclophosphamide followed 2-3 days later by a single infusion of LYL845. After LYL845 infusion, high-dose intravenous interleukin-2 is administered every 8 hours for up to 6 doses as tolerated. Primary objectives include evaluation of safety, tolerability, and determination of the RP2DR. The secondary objective is evaluation of anti-tumor activity. Exploratory objectives include measurement of tumor mutational burden, clonal diversity of the TIL drug product, T cell clonal expansion and persistence in the periphery and the presence of TIL drug product derived T cell clones in the tumor post-infusion. The trial is open and currently enrolling.