Background Tumor-specific immune cells possessing effector functions to infiltrate and eradicate tumors circulate in peripheral blood and can infiltrate tumors but are impaired in their effector functions due to immune checkpoint control by Cbl-b (Casitas B-lineage lymphoma-b). Further, tumor antigen (TA) expression and recognition is limited in time and magnitude due to frequent alterations in the TA repertoire and low abundance of TA-specific immune cells within a patient’s peripheral blood mononuclear cells (PBMCs). Here, we present a clinical trial of an autologous cell therapy APN401 that blocks Cbl-b in patient PBMCs using a rapid manufacturing process with the goal of enhancing immune effector functions and cytotoxicity against tumor cells. For this, we have developed the closed cell processing Enhancement Platform for immune Cells (EPiC). This platform enables manufacturing of high numbers of PBMCs with transiently silenced Cbl-b in a short processing time for the drug product (DP) APN401. In a first clinical phase 1b multiple dose study, APN401 showed clinical safety and tolerability in patients with advanced solid tumors (NCT02166255).

Methods The APN401 DP is manufactured by the 3-step EPiC process comprising (I) purification of PBMCs from leukapheresis products, (II) electroporation of PBMCs to incorporate Cbl-b siRNA and (III) final PBMC formulation for re-infusion. The final DP is specified for release according to GMP standards specific for ATMPs. The entire process requires less than 6 hours and is approved by the national competent authorities for a same-day out patient therapy in a phase 1b trial. This clinical trial is designed as an open-label, multi-center, dose escalation and expansion study and is performed in two parts. In Part A the maximum tolerated dose (MTD) will be determined, evaluating three dose levels of APN401. Key eligibility criteria include patients with advanced solid tumors for whom standard therapies have failed. Part B is an expansion study at the MTD with 15 patients for each of three specific tumor types – lung cancer, colorectal cancer and squamous cell carcinoma of the head and neck.

Results The ongoing phase 1b Part A study demonstrates the feasibility of APN401 autologous cell therapy through releasing 14 manufacturing batches (mean manufacturing dose: 5.3 x 10⁸ PBMCs) of Cbl-b silenced patient PBMCs. Safety and tolerability have been shown for the first dosing cohort (infused cell number: 5.0 x 10⁶ PBMCs/kg). Dose escalation is ongoing, and patients are being enrolled in the second dosing cohort (1.5 x10⁷ PBMCs/kg).

Ethics Approval The study is approved by Medical University of Vienna institution’s independent Ethics Board, approval number 1778/2020.