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APN401, A NOVEL EPIC-BASED ANTI-CANCER CELL THERAPY, CASE REPORT: CBL-B SILENCED, AUTOLOGOUS PBMCS INDUCED STABLE DISEASE IN AN APPENDIX CARCINOMA PATIENT

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Background While the immune system of cancer patients is generally capable of generating tumor-specific effector cells, their function is impaired due to immune checkpoint control. We and others have shown that the E3 ubiquitin ligase Cbl-b (Casitas B-lineage lymphoma-b) functions as a master checkpoint and plays a central role in suppressing both adaptive and innate anti-tumor responses. Thus, by blocking Cbl-b function, immune effector functions against tumor cells may be restored. We have developed a novel way to transiently silence Cbl-b in a patient's peripheral blood mononuclear cells (PBMCs), named APN401, an autologous cell therapy. The use of an innovative closed cell processing Enhancement Platform for immune Cells (EPiC) enables manufacturing of high numbers of modified PBMCs for APN401 in a short processing time and allows for same-day out patient therapy.

Methods In our ongoing phase 1b trial, a 59-year-old white male patient with appendix carcinoma was treated with APN401, a drug product composed of a suspension of his own viable PBMCs. Those PBMCs were transfected *ex vivo* with a small interfering ribonucleic acid (siRNA) in order to reduce Cbl-b expression by using the innovative EPiC manufacturing 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 entire manufacturing 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. The trial is evaluating clinical outcome, safety, activity, and potency of the drug product; in addition, specific biomarkers are being analyzed.

Results This case report is part of an open-label, multi-center, dose escalation and expansion clinical trial evaluating three dose levels of APN401 using a 3+3 design in advanced solid tumor patients. The first cohort of the phase 1b study demonstrated feasibility, safety and tolerability for the lowest dose level (infused cell number: 5.0×10^6 PBMCs/kg). The patient with appendix carcinoma presented stable disease after APN401 treatment. Subsequent biomarker analyses revealed increased IL-2 levels indicating potency and an elevated CD8/CD4 ratio suggesting potential cytotoxic efficacy. In stimulation assays with HLA-1 restricted viral or tumor antigens, increased IFN γ levels were detected as surrogate markers for improved immunity and tumor reactivity.

Conclusions Our findings highlight that APN401, an autologous cell therapy based on selective Cbl-b silencing, may be a safe, potent, and effective immunotherapy for solid tumors.

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

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