Background A critical checkpoint in the tumor microenvironment (TME) of solid tumors is the CD47-SIRPα axis that acts as a ‘don’t eat me’ signal and prevents macrophages from phagocytosing CD47-expressing tumors. Several agents aiming to block this checkpoint have entered early clinical trials in recent years, including anti-CD47 and anti-SIRPα monoclonal antibodies. Combining these checkpoint inhibitors with adaptively transferred immune cells targeting tumors could potentially increase clinical efficacy. Recently, autologous macrophages have gained increasing attention for cancer treatment due to their potential to infiltrate into the immunosuppressive tumor microenvironment (TME) and their unique immunomodulatory characteristics. While early clinical results are encouraging, producing autologous macrophage cell products for clinical and commercial application is challenging due to limited patient material, intricate genetic manipulations, and manufacturing complexity. Induced pluripotent stem cell (iPSC)-derived macrophages (iMACs) offer the opportunity to overcome many of these challenges and allow the production of allogenic cell products with consistent high quality. Additionally, the use of iPSCs as starting material enables the facilitated introduction of genetic modifications to further optimize the iMACs cell product and limit the need for combination therapies. A promising modification is the knock-out (KO) of SIRPα in iMACs to generate a potent cell therapy product resistant to phagocytosis inhibition by CD47-expressing tumor cells.

Methods We introduced a KO of the SIRPα gene into a fully characterized GMP iPSC line and differentiated these gene edited iPSC to iMACs with Evotec’s 3D differentiation protocol. SIRPα KO iMACs were loaded with tumor-targeting monoclonal antibodies before co-culture with CD47-expressing tumor cells and evaluated for their antibody-dependent cellular phagocytosis (ADCP) capacity in comparison to antibody-loaded wildtype (WT) iMACs.

Results SIRPα KO iMACs showed cell morphology and marker expression typical for fully differentiated macrophages. When exposed to CD47-positive tumor cells, SIRPα KO iMACs loaded with tumor-targeting monoclonal antibodies exhibited increased phagocytic potency and killing capacity compared to WT iMACs loaded with the same antibody. Additionally, in the presence of tumor-targeting antibody, SIRPα KO iMACs showed a boosted phagocytosis that was comparable to WT iMACs treated with a therapeutic anti-CD47 blocking antibody.

Conclusions Using Evotec’s 3D iMAC differentiation process we were able to manufacture highly pure, genetically modified iMACs that lack SIRPα expression rendering them resistant to CD47-dependent inhibition of phagocytosis. This novel allogenic off-the-shelf iMAC cell product removes the need for a treatment combination with anti-CD47 or anti-SIRPα checkpoint inhibitors and will serve as the basis to develop innovative treatments for solid tumors.