Background Ovarian and endometrial cancers are commonly occurring cancers in women with very limited treatment options for relapse and metastasis. While immune checkpoint inhibitors have generated unprecedented responses in certain other cancer types, results from early attempts in ovarian and endometrial cancers have been suboptimal. To develop a CAR-T therapy against these cancers, multi-omics data mining identified ALPP (alkaline phosphatase, placental), a cell surface protein with expression restricted to female reproductive tissues, as a potential target.

Methods To validate its tumor-specific expression, immunohistochemical arrays were performed to assess cell surface display of ALPP in normal and cancerous tissues. An anti-ALPP CAR (TC-A101) was developed and validated for its targeting specificity against multiple ALP homologs, as well as its killing efficacy in vitro. The pre-clinical efficacy of TC-A101 was validated in an animal model of ovarian cancer peritoneal metastasis. The CAR structure was further optimized through alternative hinge and transmembrane domains for lower tonic signaling and better stability of CAR expression.

Results Preclinical models demonstrate that TC-A101 T cells specifically recognize and kill ALPP-expressing tumor targets, and their administration significantly reduces tumor burdens and extends the survival of mice bearing metastatic SiHa tumors and ascites. CAR structure optimization, particularly incorporating a CD28 hinge domain (TC-A103), further potentiates CAR-T cells with stabilized CAR surface expression, lowered tonic signaling, and augmented antitumor efficacy.

Conclusions The preclinical findings reported here indicate that ALPP could be a good target and anti-ALPP CAR-T cell immunotherapy is potentially safe and efficacious against female reproductive cancers expressing ALPP.

Ethics Approval All in vivo experiments in this study were conducted according to guidelines under a protocol approved by Mispro Biotech Services Institutional Animal Care and Use Committee.