Background Metastatic castration-resistant prostate cancer (mCRPC) is a lethal, heterogeneous disease that has been largely resistant to immunotherapy. The lack of efficacy is due, in part, to the immunosuppressive tumor microenvironment and new therapeutic strategies for mCRPC must stimulate an antitumor response in the immunologically ‘cold’ tumors. Combination therapies that target both the tumor stroma and cancer cells could overcome the limitations of current immunotherapies and are demonstrated to be effective in multiple cancer models.1,2 NK cells are being explored as cell therapies and targeting NK cells to solid tumors can be improved by engineering the effector cells to express CD64, a high-affinity Fc receptor for human IgG. CD64 can capture soluble antibodies with 30–100x higher affinity than CD16A and mediates cell killing when antibody is bound.3 This docking platform allows for switchable targeting elements to redirect NK cells to multiple tumor antigens and facilitates the development of combination cell therapies.

Methods NK-92MI CD64 cell therapy was evaluated in combination with antibodies targeting the prostate tumor antigen-tumor-associated calcium signal transducer 2 (TROP2) and the cancer-associated fibroblast (CAF) marker fibroblast activation protein alpha (FAP). Antibodies were bound to CD64 and effector cells (1:1 aTROP2 and aFAP mAb) were co-cultured with prostate cancer and CAF target cells (1:1 DU145 and hPrCSC-44 cells). Killing effect was measured using the DELFIA Cell Cytotoxicity assay and IFN-γ production was assessed by flow cytometry. Tumor-bearing NSG mice (DU145 and hPrCSC-44 cells; 100–200 mm³; N=4/group) received adoptive transfer of NK-92MI CD64 cells alone (ANOVA P=0.012; figure 1) and six-fold higher than NK-92MI CD64 cells alone (ANOVA P=0.0018; figure 1). The killing effect was lost when the antibodies were switched to an isotype control, indicating that the targeting mechanism is antigen dependent. Robust antitumor activity was demonstrated in vivo and the combination therapy significantly reduced tumor growth by 78% compared to the saline control (ANOVA P=0.004; figure 2).

Conclusions Our study suggests that NK-92MI CD64 cell therapy with antibodies targeting the tumor stroma and malignant cells is effective in a prostate cancer model. Validation of this combination therapy presents a new approach for treating mCRPC and could improve antitumor response.

Ethics Approval The study was approved by the University of Minnesota Institutional Animal Care and Use Committee (IACUC) approval number 1708A-35052.

REFERENCES

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