Cell-based immunotherapies in gynecologic cancers

Susan M. Lang and Oliver Dorigo

Purpose of review
This review provides an update on recent developments in cell-based immunotherapy in gynecologic cancers.

Recent findings
Chimeric antigen receptor (CAR) technology has made significant progress allowing now for not only expressing CARs on T-cells, but also on other immune effector cells, such as natural killer cells and macrophages. Cell-based vaccines have started to show promising results in clinical trials.

Summary
Cell-based immunotherapies in gynecologic cancers continue to evolve with promising clinical efficacy in select patients.

Keywords
immune cell-targeted therapy, immune cells, ovarian cancer, tumor microenvironment

INTRODUCTION

Cell therapies have broadened the landscape of therapeutic options in the treatment of cancer, including gynecologic malignancy. Therapies using cells from both the innate and adaptive immune system have been investigated in clinical trials, including tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), natural killer (NK) cells, and T-cells [1]. Although prior work has focused largely on T-cells in both solid tumors and hematologic malignancy [2], more recent work has expanded the scope of immune-based therapies to include immune effector cells other than T-cells [1]. Herein, we provide an update on cell therapies specifically directed toward gynecologic malignancies.

TUMOR-INFILTRATING LYMPHOCYTES

Tumor-infiltrating lymphocytes (TILs) are T-cells that infiltrate tumor tissue and are involved in the antitumor response. TILs have been shown to be a prognostic biomarker in patients with ovarian cancer [3]. A systematic review by Hao *et al.* which compared pooled hazard ratios (HRs) from TIL-positive and TIL-negative patients with high grade serous ovarian cancer, demonstrated a positive correlation with TIL presence and both progression-free survival (PFS) and overall survival (OS) [4]. In this study, pooled HRs revealed that both intra-epithelial and intra-stromal CD8+ TILs were positively correlated with OS [4].

TILs can be used for adoptive cell therapy (ACT) where they are extracted from the tumor, expanded ex vivo, intravenously infused and act at the site of the tumor via recognition of tumor-specific antigens [5,6]. Such therapy has been used previously in both ovarian and cervical cancer [6–9]. In cervical cancer, one phase II trial reported a 28% clinical response rate [10]. A 44% objective response rate and a 89% disease control rate was achieved with TIL treatment in recurrent, metastatic or persistent cervical cancer at a median follow-up of 3.5 months in a separate trial [11].

In contrast, while TIL therapy in ovarian cancer is feasible, clinical efficacy is still lacking with one small study demonstrating initial responses or stable disease but ultimately disease progression [12]. The activity of TILs in the tumor microenvironment of ovarian cancer may be decreased by antigen-presenting cells or tumor cells via immune checkpoints, such as cytotoxic T-lymphocyte-associated-protein-4 (CTLA-4) [13,14]. In a recent study, the expansion

Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Stanford School of Medicine, Stanford Cancer Institute, Stanford, California, USA

Correspondence to Oliver Dorigo, MD, PhD, Division of Gynecologic Oncology, Stanford Women's Cancer Center, Stanford Cancer Institute, Department of Obstetrics and Gynecology, 300 Pasteur Drive, HG332, Stanford, CA 94305-5317, USA. Tel: +650 736 2227; e-mail: odorigo@stanford.edu

Curr Opin Obstet Gynecol 2022, 34:10–14
DOI:10.1097/GCO.0000000000000760

KEY POINTS

- Cell-based immunotherapy has evolved to include all major effector cells of the immune system.
- Novel engineering approaches in CAR therapy with bi-specific CAR molecules may improve efficacy of CAR therapy in solid tumors.
- Cell-based vaccines are a promising area of clinical research and may become an effective therapeutic option.

of TILs from ovarian cancer tissue was enhanced by CTLA-4 blockade resulting in potent antitumor CD8+ TILs, compared to standard TILs in autologous cell lines [14].

At present, a prospective, multicenter, single-arm, open label study using TILs is enrolling patients with recurrent, metastatic or persistent cervical carcinoma (NCT 03108495). Another phase II trial is investigating the role of cell therapy with TILs in the treatment of locally advanced, metastatic or recurrent solid cancers and is including malignancies that are mismatch repair deficient or microsatellite unstable, including gynecologic cancers (NCT 03935893).

T-CELL RECEPTOR TARGETING

T-cell receptors (TCRs) allow T-cells to recognize specific tumor-associated antigens on the surface of tumor cells. The generation of TCR modified T-cells (TCR-T) involves the expression of tumor-specific TCR genes in naïve T-cells [15–17]. TCR-T-cell therapy is major histocompatibility complex (MHC) restricted and the specific tumor antigen must be present to generate antitumor responses [16]. Although other therapies, such as chimeric antigen receptor (CAR) T-cell therapy rely solely on recognition of cell surface proteins, TCR-T-cells are able to recognize intracellular antigen fragments presented by the MHC providing them a distinct advantage in personalized cell-based therapy [15–17].

Several ongoing clinical trials are currently investigating the clinical efficacy of TCR-T-cell therapy in gynecologic cancers targeting antigens like Melanoma-associated antigen 4 (MAGE-A4) and New York esophageal squamous cell carcinoma 1 (NY-ESO-1) expressed in ovarian cancers [15].

TCR-T-cell immunotherapy has also been investigated for E7 positive cervical dysplasia. In a Phase 1 study, Hinrichs *et al.* investigated the safety and efficacy of TCR-T-cells directed against the HPV associated E7 protein for the treatment of patients with high grade cervical dysplasia (NCT 04411134); however, this study was terminated early due to similar study's lack of perceived clinical activity. Similarly, Norberg *et al.* sought to determine the clinical efficacy of E7 TCR-T-cell treatment of stage IIB-IVA, HPV-16 positive cervical cancers (NCT 04476251). This study was likewise suspended in early 2021 citing multiple logistical challenges. There remain several actively recruiting clinical trials for the treatment of HPV-associated cervical cancer all of which are in early development. HPV-16 positive metastatic cancers are being treated with E7 TCR-T-cells along with aldesleukin, a recombinant analog of IL-2, to determine safety and clinical efficacy (NCT 02858310). Another ongoing phase Ia/Ib, open-label, first in human study of gene-edited autologous Neo-TCR-T-cells administered with or without anti programmed-cell death (PD)-1 treatment is ongoing in patients with solid tumors, including ovarian cancer (NCT03970382). NeoTCR are proprietary cells (PACT Pharma) that use autologous T-cells to express tumor-specific neoepitope TCRs [18]. The NeoTCR-T-cells exhibit T-memory stem cell and T central memory phenotypes which allow for their rapid transformation into highly active tumor-targeting cells [18]. In an ongoing study, patients will be treated with either NeoTCR in a single dose; NeoTCR in a single dose plus nivolumab 480 mg IV every 4 weeks for up to 6 doses; or NeoTCR in a single dose plus IL-2 500,00 IU/m^2 twice daily for 7 days.

CHIMERIC ANTIGEN RECEPTOR T-CELLS

CAR T-cells were among the first approved cell therapies and have demonstrated the greatest clinical efficacy in hematologic malignancies. CAR T-cells are genetically engineered T-cells that bind tumor-associated antigens by MHC complex-independent mechanisms, subsequently eliciting an antitumor response [19]. Though effective in hematologic malignancies, solid tumors have shown to be less responsive to the treatment with CAR T-cells [19,20]. Preclinical data in ovarian cancer models have shown promising efficacy but thus far clinical efficacy and durable responses in ovarian cancer patients are still lacking [21–23].

Some of the challenges using CAR T-cell therapy are the variable immune landscape and the presence of antigen escape, which provides mechanism of resistance in both solid tumors and hematologic malignancies [24,25]. Attempts are currently under way to improve the efficacy of CAR-T-cell therapy through multiple-antigen targeting. Prior work demonstrated efficacy of a bispecific (tandem) CARs targeting both HER2 and IL13Rα2 in a glioblastoma model showed superior PFS compared to monotherapy [26]. This

dual-expression was recently explored in models of ovarian cancer. Li *et al*. paired the glycoprotein mucin 16 (MUC16) with PD-1 to create a tandem-specific CAR-T target which yielded survival benefits over both singly specific CAR-T therapy and control when assessing OS (antiMUC16-PD1 CAR-T 80.6+10.3 days; PD1 CAR-T 45.1 ± 6.34 days; antiMUC16 23.0 ± 1.55 days; control 19.8 ± 2.14 days) [27]. Additionally, generation of dual CAR-T-cell targeting tumor-associated glycoprotein (TAG)-72, a glycoprotein overexpressed in adenocarcinomas, and CD47, a cell surface protein expressed on ovarian cancer cells, demonstrated that use of a novel dual-expressing CAR-T-cell therapy was effectively able to eliminate cancer cells that expressed low levels of TAG-72 *in vitro* [28]. An engineered synthetic Notch (synNotch) CAR that recognizes alkaline phosphatase placental-like 2 (ALPPL2), a tumor-specific antigen present on solid tumors including ovarian cancer in combination with HER2, mesothelin or melanoma cell adhesion molecule has been created and these demonstrated more potent activity than conventional CAR-T-cells *in vitro* [29▪▪]. Together these preclinical data suggest potential clinical efficacy for dual-antigen targeting CAR-T therapy in clinical practice for gynecologic cancers.

A Phase I clinical trial of lentiviral-transduced CAR-T-cells recognizing mesothelin (CART-meso) in advanced solid tumors, including ovarian cancers, was shown to be well tolerated but only produced minimal antitumor activity [30]. An early phase I clinical trial in China is presently determining the feasibility and safety of anti-Mesothelin CAR-T-cells in patients with mesothelin positive ovarian cancer (NCT03799913). Other novel CAR-T therapies are targeting other antigens including MOv19 (NCT03585764); B7-H3 antigen (NCT04670068); and the dual expression of MUC16 and membrane-bound IL15 (PRGN-3005) UltraCAR-T (NCT03907527). It is noteworthy that using UltraCAR-T-cells circumvents the need for *in vitro* proliferation, and therefore have a much shorter processing time of one day compared to weeks [15]. This therapy could therefore not only be effective but also more practical because of shorter processing times.

NATURAL KILLER CELLS

NK cells are a member of the innate system whose role is to recognize and induce cell death in a variety of cells, including cancer cells [31,32]. NK cells appear to have a dynamic interaction with the tumor microenvironment. These cells have a distinct advantage for cell therapy since they do not induce graft versus host disease and therefore can be generated from unrelated donors (i.e., allogeneic NK cells) [33–35].

Preclinical studies have demonstrated NK cell-mediated cytotoxicity on ovarian cancer cells [36–38]. Recent clinical data have suggested that NK cells may be a prognostic indicator in patients with recurrent ovarian cancer, with data suggesting that low blood levels of NK cells correlate with poorer prognosis [39,40].

Improvement in the functionality of NK cell therapy continues to be at the forefront of NK cell research. The modification of NK cells with CAR has been successful in preclinical murine models [41,42]. Specifically, mesothelin-specific CAR-NK cell administration in an *in vivo* model of ovarian cancer demonstrated effective regression of tumor cells and prolonged survival in tumor-bearing mice [43].

Newer combination therapies are also being investigated. Oncolytic viruses can infect and selectively replicate within malignant cells, allowing for direct cytotoxicity and direct triggering of the innate and adaptive immune system [44,45]. NK-cell-based immunotherapy has been combined with oncolytic viruses [44,46,47▪]. Promising preclinical results were reported when assessing the effects of combining reovirus or vesicular stomatitis virus (VSV) with NK cell immunotherapy, specifically using NKT-cells which share both NK and T cell-like properties, in ID8 murine model of ovarian cancer which decreased metastatic burden and increased survival [47▪]. An actively recruiting Phase I/II clinical trial is investigating treatment with a double-deleted vaccinia virus and cytokine induced killer cells, a sub-population of NK cells, in patients with advanced solid tumors including ovarian cancer (NCT04282044).

NK cells have been combined with cytotoxic therapies in preclinical models and might be effective even in platinum-resistant ovarian cancers. One preclinical study of cisplatin alongside NK92MI, a human NK cell line, on cisplatin-resistant A2780 ovarian cancer cells (A2780cis) demonstrated an increased sensitivity to NK92MI after pretreatment with cisplatin [48▪].

One recently closed clinical study assessed the combination of cryotherapy for percutaneous ablation of all identifiable tumor using an argon-helium cryosurgical system with NK immunotherapy given IV (NCT02849353). Another phase I open-label clinical trial, which closed earlier in 2021, assessed intraperitoneal (IP) delivery of adaptive NK cells (FATE-NK100) with IP IL-2 in women with recurrent ovarian cancer (NCT03213964). The INTRO trial study is evaluating the safety and feasibility of IP infusion of ex vivo-cultured allogeneic NK cells in recurrent ovarian carcinoma (NCT03539406).

MACROPHAGES

Macrophages are important effector cells of the innate immune system and play an important role in modulating antitumor immune responses [49–51]. In various solid tumors, including ovarian cancer, macrophages can mediate metastasis [52,53]. Macrophages have become an area of increased interest in cell-based immunotherapy because unlike lymphocyte cells, monocytes and macrophages actively penetrate solid tumors and the surrounding tissue potentially making them more efficacious as therapy [54].

CAR strategies have been used to both target immune-suppressive macrophages through CAR-T-cells as well as create CAR expressing macrophages (CAR-M cells). A preclinical model has shown that a subpopulation of TAMs express folate receptor β (FRβ) [55]. More recent preclinical data suggest FRβ positive TAMs exist in the ovarian TME and display an M2-like pro-inflammatory profile [56▪]. Further, CAR-T-cell mediated selective targeting of FRβ positive TAMs slowed tumor progression and prolonged survival in murine models of ovarian cancer [56▪].

CAR-M targeting HER2 in a preclinical model showed improved tumor clearance when compared with control or M1 polarized macrophages alone in a xenograft (SKOV3 $HER2^{+}$) ovarian cancer [57]. Additionally, CAR-M cells maintained their antitumor activity in the presence of M2 macrophages while being able to cross-present tumor antigens [57]. Given these advantages, it is conceivable that CAR-M therapy might overcome some of the key limitations encountered with CAR-T therapy. Currently, a phase I, open label clinical trial is recruiting patients with HER2-overexpressing solid tumors as the first in-human study of adenoviral transduced autologous macrophages which have been engineered to contain an anti-HER2 CAR (NCT04660929).

DENDRITIC CELLS

Dendritic cells are effective antigen-presenting cells within the innate immune system and can activate antitumor immunity when loaded with tumor-specific antigens [58–60]. DCs have been used to create dendritic cell vaccines for the treatment of various malignancies [60,61]. Clinical trials have demonstrated promising efficacy in patients with epithelial ovarian cancer using dendritic cell therapies [62–64].

Recently, a case of treatment in chemotherapy-refractory ovarian cancer has been reported using intra-nodally injected, neoantigen peptide-pulsed DCs [58]. In this case, CA-125 values decreased from ~4500 U/mL to just over 1300 U/mL over the course of 4 vaccinations, and evaluation of the patient's ascites demonstrated an increase in immune cells and a decrease in tumor cells [58]. In a separate trial, dendritic cell-based immunotherapy combined with chemotherapy in recurrent platinum sensitive ovarian cancer, demonstrated no differences in PFS between the study groups. The median OS in the DC vaccine group compared to the control group was prolonged (35.5 mo vs 22.1 mo) though the data are not yet mature [65▪].

CONCLUSION

Cell-based immunotherapy continues to make progress as a potential treatment option for gynecologic malignancy. Key improvements have been made across all immune effector cells in attempts to increase specificity of treatment, identify better antigen targets, improve tumor infiltration and create novel cancer vaccines. It remains to be seen if newer therapies can overcome challenges in antigen escape and resistance. Early phase I/II trials across the immune landscape will continue to provide information regarding the potential for cell-based immunotherapy in these solid tumors.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

S.M.L.: None, O.D.: Advisory/Consulting: Merck, PACT, IMV, Tesaro/GSK, Genentech, EIsai Research Grants: AstraZeneca, IMV, Millenium, Pharmamar, Genentech, Bioeclipse.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Baci D, Bosi A, Gallazzi M, *et al.* The Ovarian Cancer Tumor Immune Microenvironment (TIME) as target for therapy: a focus on innate immunity cells as therapeutic effectors. Int J Mol Sci 2020; 21:3125.
2. Weber EW, Maus MV, Mackall CL. The emerging landscape of immune cell therapies. Cell 2020; 181:46–62.
3. Zhang L, Conejo-Garcia JR, Katsaros D, *et al.* Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003; 348:203–213.
4. Hao J, Yu H, Zhang T, *et al.* Prognostic impact of tumor-infiltrating lymphocytes in high grade serous ovarian cancer: a systematic review and meta-analysis. Ther Adv Med Oncol 2020; 12:. 1758835920967241.
5. Santoiemma PP, Powell DJ Jr. Tumor infiltrating lymphocytes in ovarian cancer. Cancer Biol Ther 2015; 16:807–820.
6. Morotti M, Albukhari A, Alsaadi A, *et al.* Promises and challenges of adoptive T-cell therapies for solid tumours. Br J Cancer 2021; 124:1759–1776.
7. Fujita K, Ikarashi H, Takakuwa K, *et al.* Prolonged disease-free period in patients with advanced epithelial ovarian cancer after adoptive transfer of tumor-infiltrating lymphocytes. Clin Cancer Res 1995; 1:501–507.
8. Aoki Y, Takakuwa K, Kodama S, *et al.* Use of adoptive transfer of tumor-infiltrating lymphocytes alone or in combination with cisplatin-containing

chemotherapy in patients with epithelial ovarian cancer. Cancer Res 1991 1934; 51:9.
9. Jazaeri AA, Zsiros E, Amaria RN, *et al.* Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma. J Clin Oncol 2019; 37(no. 15_suppl):2538–12538.
10. Stevanovic S, Helman SR, Wunderlich JR, *et al.* A Phase II study of tumor-infiltrating lymphocyte therapy for human papillomavirus-associated epithelial cancers. Clin Cancer Res 2019; 25:1486–1493.
11. Jazaeri AA, Zsiros E, Amaria RN, *et al.* Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma,. J Clin Oncol 2019; 37(15_suppl):2538–12538.
12. Pedersen M, Westergaard MCW, Milne K, *et al.* Adoptive cell therapy with tumor-infiltrating lymphocytes in patients with metastatic ovarian cancer: a pilot study. Oncoimmunology 2018; 7:e1502905.
13. Li X, Shao C, Shi Y, *et al.* Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. J Hematol Oncol 2018; 11:31.
14. Friese C, Harbst K, Borch TH, *et al.* CTA-4 blockade boosts the expansion of tumor-reactive CD8(+) tumor-infiltrating lymphocytes in ovarian cancer. Sci Rep 2020; 10:3914.
15. Xu Y, Jiang J, Wang Y, *et al.* Engineered T cell therapy for gynecologic malignancies: challenges and opportunities. Front Immunol 2021; 12:725330.
16. Zhao L, Cao YJ. Engineered T cell therapy for cancer in the clinic. Front Immunol 2019; 10:2250.
17. Wu JWY, Dand S, Doig L, *et al.* T-cell receptor therapy in the treatment of ovarian cancer: a mini review. Front Immunol 2021; 12:672502.
18. Sennino B, Conroy A, Purandare B et al. NeoTCR-P1, a novel neoepitope-specific adoptive cell therapy, consists of T cells with 'younger' phenotypes that rapidly proliferate and kill target cells upon recognition of cognate antigen. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019; 2019 Mar 29-Apr 3; Atlanta, GA. Philadelphia (PA): AACR; Cancer Res 2019;79(13 Suppl):Abstract nr 1433.
19. Scarfo I, Maus MV. Current approaches to increase CAR T cell potency in solid tumors: targeting the tumor microenvironment. J Immunother Cancer 2017; 5:28.
20. Marofi F, Motavalli R, Safonov VA, *et al.* CAR T cells in solid tumors: challenges and opportunities. Stem Cell Res Ther 2021; 12:81.
21. Fu J, Shang Y, Qian Z, *et al.* Chimeric Antigen receptor-T (CAR-T) cells targeting Epithelial cell adhesion molecule (EpCAM) can inhibit tumor growth in ovarian cancer mouse model. J Vet Med Sci 2021; 83:241–247.
22. Schoutrop E, El-Serafi I, Poiret T, *et al.* Mesothelin-specific CAR T cells target ovarian cancer. Cancer Res 2021; 81:3022–3035.
23. Rodriguez-Garcia A, Sharma P, Poussin M, *et al.* CAR T cells targeting MISIIR for the treatment of ovarian cancer and other gynecologic malignancies. Mol Ther 2020; 28:548–560.
24. Majzner RG, Mackall CL. Tumor antigen escape from CAR T-cell therapy. Cancer Discov 2018; 8:1219–1226.
25. Brown CE, Mackall CL. CAR T cell therapy: inroads to response and resistance. Nat Rev Immunol 2019; 19:73–74.
26. Hegde M, Mukherjee M, Grada Z, *et al.* Tandem CAR T cells targeting HER2 and IL13Ralpha2 mitigate tumor antigen escape. J Clin Investig 2016; 126:3036–3052.
27. Li T, Wang J. Therapeutic effect of dual CAR-T targeting PDL1 and MUC16 antigens on ovarian cancer cells in mice. BMC Cancer 2020; 20:678.
28. Shu R, Evtimov VJ, Hammett MV, *et al.* Engineered CAR-T cells targeting TAG-72 and CD47 in ovarian cancer. Mol Ther Oncolytics 2021; 20:325–341.
29. ■■ Hyrenius-Wittsten A, Su Y, Park M, *et al.* SynNotch CAR circuits enhance solid tumor recognition and promote persistent antitumor activity in mouse models. Sci Transl Med 2021; 13:eabd8836.
This study highlights the use of dual-expressing CAR-T-cells in a preclinical model of ovarian cancer and their advantages in overcoming CAR-T resistance in solid tumors. This observation could have important treatment implications if replicated in clinical trials.
30. Haas AR, Tanyi JL, O'Hara MH, *et al.* Phase I study of lentiviral-transduced chimeric antigen receptor-modified T cells recognizing mesothelin in advanced solid cancers. Mol Ther 2019; 27:1919–1929.
31. Wu SY, Fu T, Jiang YZ, *et al.* Natural killer cells in cancer biology and therapy. Mol Cancer 2020; 19:120.
32. Crinier A, Narni-Mancinelli E, Ugolini S, *et al.* SnapShot: natural killer cells. Cell 2020; 180:1280–1280. e1.
33. Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. Nat Rev Cancer 2016; 16:7–19.
34. Guillerey C, Huntington ND, Smyth MJ. Targeting natural killer cells in cancer immunotherapy. Nat Immunol 2016; 17:1025–1036.
35. Martin-Antonio B, Sune G, Perez-Amill L, *et al.* Natural killer cells: angels and devils for immunotherapy. Int J Mol Sci 2017; 18:1868.
36. Felices M, Chu S, Kodal B, *et al.* IL-15 super-agonist (ALT-803) enhances natural killer (NK) cell function against ovarian cancer. Gynecol Oncol 2017; 145:453–461.
37. Uppendahl LD, Dahl CM, Miller JS, *et al.* Natural killer cell-based immunotherapy in gynecologic malignancy: a review. Front Immunol 2017; 8:1825.
38. Hoogstad-van Evert JS, Bekkers R, Ottevanger N, *et al.* Harnessing natural killer cells for the treatment of ovarian cancer. Gynecol Oncol 2020; 157:810–816.
39. Henriksen JR, Nederby L, Donskov F, *et al.* Blood natural killer cells during treatment in recurrent ovarian cancer. Acta Oncol 2020; 59:1365–1373.
40. Nersesian S, Glazebrook H, Toulany J, *et al.* Naturally killing the silent killer: NK cell-based immunotherapy for ovarian cancer. Front Immunol 2019; 10:1782.
41. Ao X, Yang Y, Li W, *et al.* AntialphaFR CAR-engineered NK-92 cells display potent cytotoxicity against alphaFR-positive ovarian cancer. J Immunother 2019; 42:284–296.
42. Li Y, Hermanson DL, Moriarity BS, *et al.* Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance antitumor activity. Cell Stem Cell 2018; 23:181–192. e5.
43. Cao B, Liu M, Wang L, *et al.* Use of chimeric antigen receptor NK-92 cells to target mesothelin in ovarian cancer. Biochem Biophys Res Commun 2020; 524:96–102.
44. Leung EYL, Ennis DP, Kennedy PR, *et al.* NK cells augment oncolytic adenovirus cytotoxicity in ovarian cancer. Mol Ther Oncolytics 2020; 16:289–301.
45. Lemos de Matos A, Franco LS, McFadden G. Oncolytic viruses the immune system: the dynamic duo. Mol Ther Methods Clin Dev 2020; 17:349–358.
46. Lichty BD, Breitbach CJ, Stojdl DF, *et al.* Going viral with cancer immunotherapy. Nat Rev Cancer 2014; 14:559–567.
47. ■ Gebremeskel S, Nelson A, Walker B, *et al.* Natural killer T cell immunotherapy combined with oncolytic vesicular stomatitis virus or reovirus treatments differentially increases survival in mouse models of ovarian and breast cancer metastasis. J Immunother Cancer 2021; 9:e002096.
This study highlights the use of oncolytic virus along with cell therapy to decrease tumor burden.
48. ■ Choi SH, Jung D, Kim KY, *et al.* Combined use of cisplatin plus natural killer cells overcomes immunoresistance of cisplatin resistant ovarian cancer. Biochem Biophys Res Commun 2021; 563:40–46.
This study demonstrates a potential use of cell-based treatment to overcome difficulties in treating platinum-resistant disease.
49. Krishnan V, Schaar B, Tallapragada S, *et al.* Tumor associated macrophages in gynecologic cancers. Gynecol Oncol 2018; 149:205–213.
50. Lee S, Kivimae S, Dolor A, *et al.* Macrophage-based cell therapies: the long and winding road. J Control Release 2016; 240:527–540.
51. Lim WA, June CH. The principles of engineering immune cells to treat cancer. Cell 2017; 168:724–740.
52. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer 2004; 4:71–78.
53. Etzerodt A, Moulin M, Doktor TK, *et al.* Tissue-resident macrophages in omentum promote metastatic spread of ovarian cancer. J Exp Med 2020; 217:e20191869.
54. Anderson NR, Minutolo NG, Gill S, *et al.* Macrophage-based approaches for cancer immunotherapy. Cancer Res 2021; 81:1201–1208.
55. Penn CA, Yang K, Zong H, *et al.* Therapeutic impact of nanoparticle therapy targeting tumor-associated macrophages. Mol Cancer Ther 2018; 17:96–106.
56. ■ Rodriguez-Garcia A, Lynn RC, Poussin M, *et al.* CAR-T cell-mediated depletion of immunosuppressive tumor-associated macrophages promotes endogenous antitumor immunity and augments adoptive immunotherapy. Nat Commun 2021; 12:877.
This study demonstrates how manipulation of the tumor microenvironment as an adjunct to treatment with immunotherapy may be beneficial.
57. Klichinsky M, Ruella M, Shestova O, *et al.* Human chimeric antigen receptor macrophages for cancer immunotherapy. Nat Biotechnol 2020; 38:947–953.
58. Morisaki T, Hikichi T, Onishi H, *et al.* Intranodal administration of neoantigen peptide-loaded dendritic cell vaccine elicits epitope-specific T cell responses and clinical effects in a patient with chemorefractory ovarian cancer with malignant ascites. Immunol Invest 2021; 50:562–579.
59. Zhang X, He T, Li Y, *et al.* Dendritic cell vaccines in ovarian cancer. Front Immunol 2020; 11:613773.
60. Guo Q, Yang Q, Li J, *et al.* Advanced clinical trials of dendritic cell vaccines in ovarian cancer. J Investig Med 2020; 68:1223–1227.
61. Garg AD, Coulie PG, Van den Eynde BJ, *et al.* Integrating next-generation dendritic cell vaccines into the current cancer immunotherapy landscape. Trends Immunol 2017; 38:577–593.
62. Chiang CL, Kandalaft LE, Tanyi J, *et al.* A dendritic cell vaccine pulsed with autologous hypochlorous acid-oxidized ovarian cancer lysate primes effective broad antitumor immunity: from bench to bedside. Clin Cancer Res 2013; 19:4801–4815.
63. Kandalaft LE, Powell DJ Jr, Chiang CL, *et al.* Autologous lysate-pulsed dendritic cell vaccination followed by adoptive transfer of vaccine-primed ex vivo co-stimulated T cells in recurrent ovarian cancer. Oncoimmunology 2013; 2:e22664.
64. Tanyi JL, Bobisse S, Ophir E, *et al.* Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. Sci Transl Med 2018; 10:eaao5931.
65. ■ Cibula D, Rob L, Mallmann P, *et al.* Dendritic cell-based immunotherapy (DCVAC/OvCa) combined with second-line chemotherapy in platinum-sensitive ovarian cancer (SOV02): a randomized, open-label, phase 2 trial. Gynecol Oncol 2021; 162:652–660.
This clinical trial represents the potential importance of cell-based vaccines in gynecologic cancers.