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Beyond immunotherapy—treatment advances in cell-based therapy for ovarian cancer and associated challenges

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Despite unprecedented activity and indications to treat many tumors, benefit from immune checkpoint inhibitors (ICIs) remains elusive for women with ovarian cancer. Trials of single agent pembrolizumab and avelumab in recurrent ovarian cancer yielded response rates of less than 10% and a comparison of nivolumab to standard single agent chemotherapy demonstrated worse progression-free survival (PFS) in the immunotherapy group (1–5). Positive data from phase II trials combining immunotherapy with standard of care therapies led to several phase III trials. In the front-line setting, JAVELIN Ovarian 100 compared chemotherapy followed by avelumab maintenance to chemotherapy and avelumab followed by avelumab maintenance to chemotherapy only, demonstrating no PFS improvement in the immunotherapy arms over standard chemotherapy (6). Similarly, the IMAgyn50 trial compared atezolizumab or placebo combined with paclitaxel, carboplatin, and bevacizumab in the neoadjuvant setting and demonstrated no improvement in PFS with the addition of atezolizumab (7). In the recurrent setting, the phase III JAVELIN Ovarian 200 trial randomized participants to avelumab alone, pegylated liposomal doxorubicin (PLD) alone,

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or avelumab and PLD with no improvement of either overall survival (OS) or PFS in either immunotherapy arm over chemotherapy alone (8). Similarly, in ATLANTE/ENGOT-ov29 atezolizumab or placebo was added to bevacizumab and a platinum doublet, with no improvement in PFS (9) (Table 1). Taken together, ICIs appear ineffective as single agents, in combination, in the front-line and recurrent settings.

Immunotherapy resistance in ovarian cancer is primarily mediated by a “cold” or immunosuppressive tumor microenvironment characterized by low infiltration of $CD4^+$ and $CD8^+$ T-cells as well as the presence of immunosuppressive macrophages, fibroblasts, and increased expression of regulatory T-cells, which secrete immunosuppressive cytokines (10,11). Cold tumors are also less likely to exhibit clinically useful biomarkers including tumor mutation burden (TMB), programmed cell death ligand 1 (PD-L1) expression, and microsatellite instability/mismatch repair deficiency (MSI/MMR). A recent meta-analysis including 42 clinical trials assessing immunotherapy in ovarian cancer patients demonstrated that approximately half of ovarian cancers had a combined positive score (CPS) of ≥1%, while less than 10% had a CPS score ≥10%. Moreover, PD-L1 positivity did not predict OS or PFS, suggesting PD-L1 is not a useful biomarker in ovarian cancer (12). In contrast, high TMB, MSI-high (MSI-H), and MMR deficiency are rare in ovarian cancer, but do predict response to ICIs. The median TMB in ovarian cancer is 3.6 mutations per megabase and approximately 10% have a TMB ≥10 (13,14). ICI’s appear effective with similar response rates across cancer types in this population, and pembrolizumab has a disease agnostic indication for TMB ≥10 (15,16). Likewise, less than 5% of ovarian cancers are MSI-H or MMR deficient, but ICIs appear effective regardless of tumor type and pembrolizumab has a disease agnostic indication for MSI-H (16). Clearly, new strategies are needed for the majority of ovarian cancers.

Based on the early recognition of the importance of $CD3^+$ tumor infiltrating lymphocytes (TILs) in ovarian cancer clinical outcomes, cell-based therapies (CTs), which are manufactured for individual patients using their own immune effector cells, have garnered significant interest in ovarian cancer (17) (Table 2).

Green and colleagues recently tested a novel CT strategy of combining intraperitoneal monocytes and interferon (IFN) (18). Based on data demonstrating that IFN-activated monocytes are synergistic in a xenograft mouse model of ovarian cancer, and the combination differentiates monocytes into anticancer M1 macrophages, the investigators performed a phase I dose escalation study (18,25). Eighteen participants underwent an apheresis procedure to obtain monocytes on day 0, and on day 1 of every 28-day cycle received pegylated IFNα−2b and IFNγ−1b with or without autologous monocytes by intraperitoneal administration. Three patients were excluded for catheter related problems or difficulty tolerating apheresis. According to CTCAE 4.0 criteria, there was one dose limiting toxicity (DLT), a grade 3 anemia in dose level 2. The recommended phase 2 dose (RP2D) was the highest dose tested, 250 mcg IFN-α, 50 mcg IFN-γ, and 750×10^6 monocytes. Of the 9 heavily pre-treated patients with RECIST measurable disease, there were 2 patients with a partial response (PR), 4 with stable disease (SD), and 3 with progressive disease. Long term responders (LTRs), defined as completing more than 5 cycles of therapy, had significantly lower immunosuppressive cells [natural killer (NK) cells],

T-regs at baseline, and myeloid-derived suppressor cells (MDSCs) at baseline compared to the other patients and most had a marked increase in MDSCs at the time of progression. Exploratory biomarker studies suggested the antitumor effect of IFN-activated monocytes relies on tumor-necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) (18).

Strengths of this approach include proof of concept of anticancer activity and tolerability. This study enrolled heavily pre-treated patients with a median of 5 prior lines of therapy and as a dose escalation study, only a small number of patients were treated at the recommended phase 2 dose. Nevertheless, 2 of 9 patients achieved a PR and 3 of 18 patients were LTRs. In addition, of 18 patients included in the safety analysis, only one DLT occurred in dose level 2, a grade 3 anemia. The major weakness of the study is feasibility, with several patients experiencing catheter problems or unable to tolerate apheresis (18). Also of concern, few patients responded and the LTRs were less immunosuppressed at baseline, suggesting that the regimen, like ICIs, is more effective in the small number of women with immunologically active ovarian cancer rather than truly activating “cold” tumors.

Other strategies for the development of ovarian cancer CTs include TILs, T-cell receptor (TCR) engineered T-cells, dendritic cells (DCs), NK cells, and CAR-T cell therapy. TILs are manufactured by isolating autologous $CD4^+$ and $CD8^+$ lymphocytes from the patient’s tumor tissue, which are expanded in the laboratory, further activated with cytokines, and re-infused to the patient. TILs are given alone or in combination with additional cytokines and sometimes chemotherapy or immunotherapy. Lymphodepleting chemotherapy with or without whole body irradiation is also often used. The majority of development and success in TIL therapy has been in melanoma, and one product, lifileucel, is currently under review by the Food and Drug Administration (FDA) (26). In addition, a number of small clinical trials in ovarian cancer have been conducted in both the maintenance and recurrent settings. Most recently, 6 patients with recurrent, platinum resistant high-grade serous ovarian cancer underwent surgical removal of their ovarian cancer after being pre-treated with ipilimumab to enhance TIL harvest (19). Expansion of TILs was successful in all patients, although one patient discontinued due to rapidly progressive disease. After infusion of TILs patients received low dose IL-2 and nivolumab. By 12 weeks, 4 of 6 patients had progressed, however one patient had prolonged SD of greater than one year. Two patients discontinued study treatment due to toxicity. As observed with ICIs and IFN-activated monocytes, a small fraction of ovarian cancers appears to benefit from TILs. However, TILs have substantial toxicity, even with reduced dose IL-2, resulting in 2/6 subjects discontinuing study therapy and require a surgical procedure to isolate TILs. Further efforts are needed to improve activity of TIL cells outside of melanoma include selection of antigen specific TILs as well as combinations with immunotherapy.

Afamitresgone autoleucel (afemi-cel) is an autologous T-cell therapy targeting melanoma-associated antigen A4 (MAGE-A4) which is expressed in multiple solid tumors, including ovarian cancer. Afemi-cel is produced by obtaining T-cells via apheresis which are subsequently transduced to express a high affinity TCR targeted against a MAGE-A4230−239 peptide, GVYDGREHTV, presented by HLA-A*02. Afemi-cel was studied in a phase I trial in patients with relapsed/refractory metastatic solid tumors with measurable disease and tumors expressing MAGE-A4 and HLA-A*02. Doses were based

on total transduced cells and were escalated in three groups ranging from 0.8×10^9 to 10×10^9 transduced cells along with lymphodepleting chemotherapy prior to afemi-cel administration. The highest dose was selected for the dose expansion phase. All DLTs occurred in the expansion group and included cytopenia (4), aplastic anemia (1), and cerebrovascular accident (1). The modified intention to treat population (mITT) included 38 patients, of which 9 had ovarian cancer, who received afemi-cel therapy and all patients in this group had grade 3 adverse effects, most commonly lymphocytopenia, neutropenia and thrombocytopenia, with 9/38 (24%) with prolonged neutropenia lasting more than 4 weeks. There were also two deaths on study that were possibly related to treatment. Cytokine release syndrome (CRS) was a frequent occurrence in responders, affecting 21 patients (55%). The objective response rate (ORR) was 24% (9/38) and all were PR. Synovial sarcoma appeared have the most benefit, with 44% (7/16) patients responding. All responders had tumor MAGE-A4 H-scores of >200. Five of six patients with ovarian cancer in the mITT group had SD, but no responses were observed, likely due to lower MAGE-A4 scores which ranged from 15–220 among ovarian cancer participants. Overall, the phase I study demonstrated afemi-cel is a promising therapy for patients high MAGE-A4 scores and a phase II SPEARHEAD-1 trial is planned in synovial sarcoma (20). However, the therapy is limited by substantial toxicity and little activity in ovarian cancer.

CAR-T cells produce clinically meaningful results in hematopoietic cancers, with six approved products, however, success has been limited in solid tumors. CAR-T cells are manufactured by obtaining T-cells from an apheresis procedure and engineered to express a CAR that recognizes specific tumor antigens. CAR-Ts also typically include co-stimulatory molecules to enhance T-cell activation. When the CAR-T binds to the antigen on a cancer cell, T-cell activation and expansion occurs resulting in cancer cell death. One challenge in development of CAR-T cells is that ovarian tumors often lack tumor-specific antigens. As a result, tumor-associated antigens (TAAs) that are expressed in normal tissue and tumor tissue are under evaluation for CAR-T cell development including erb-b2 receptor tyrosine kinase (ERBB2, HER2), epithelial cell adhesion molecule (Ep-CAM), folate receptor alpha (FOLR1, FRα), mesothelin (MSLN), and CA125/MUC16. CAR-T cells against ovarian cancer TAAs have demonstrated potential as treatment for ovarian cancer in mouse models (21,27,28). A phase 1 dose escalation has also been reported. In this trial 18 heavily pre-treated women with high grade serous ovarian cancer who expressed MUC16 received escalating doses of MUC16 targeted CAR-T cells. Doses were escalated between 3×10^5–1×10^7 cells and were given without lymphodepletion in the dose escalation phase. Half of the CAR-T dose was given intravenously (IV), followed by the remainder of the dose administered intraperitoneally 1–2 days later if the IV dose was tolerated. A dose expansion phase at the highest dose also included lymphodepleting chemotherapy. There were no DLTs in the dose escalation phase, however, 2/3 patients in the dose expansion phase with lymphodepletion experienced a DLT and all patients experienced CRS. Best response was SD, however some patients demonstrated prolonged persistence of CAR-T cells (22). Another phase I study is actively recruiting recurrent ovarian cancer patients with a confirmation of tumor FRα expression (21). Further work is needed to improve CAR-T effectiveness against solid tumors and minimize toxicity when there are few targetable tumor specific antigens.

Beyond T-cells, DCs and NK cells are being evaluated as potential CTs. DCs are antigen presenting cells that activate T-cells. DC-based vaccines (DCVAC) require isolation of monocytes via an apheresis procedure, which are differentiated to immature DCs and primed by exposure to TAAs sourced from ovarian cancer immortalized cells (OV-90). An open-label phase II trial studying DCVAC in women with newly diagnosed ovarian cancer who have completed cytoreductive surgery is ongoing. Patients are randomized to three groups to receive either DCVAC concomitantly or sequentially with carboplatin plus paclitaxel or chemotherapy alone. The interim safety analysis included 130 patients, with patients receiving a median number of 10 DCVAC doses. DCVAC related adverse events (AEs) occurred in 4 of 87 patients who received DCVAC and one patient discontinued DCVAC treatment due to AEs. There were possibly two treatment related deaths in the sequential DCVAC group. An interim analysis performed at 42.2% data maturity suggested a median PFS benefit of DCVAC when used sequentially to chemotherapy with estimate of PFS at 2 years 47% [95% confidence interval (CI): 28–64%] in the concomitant DCVAC group, 75% (95% CI: 55–87%) in the sequential DCVAC group, and 46% (95% CI: 27–63%) in the chemotherapy alone group (23). On further analysis, clinical benefit of DCVAC was found to be more pronounced in patients with lower-than median TMB and scant $CD8^+$ T-cell infiltration (29). This appears promising as patients with a low TMB likely harbor immunologically cold tumors that are unlikely to respond to ICIs.

NK-cells are lymphocytes that can induce apoptosis through Fas and TRAIL in cells expressing stress-induced ligands or decreased class I major histocompatibility complexes and produce cytokines critical to the innate immune response (30). Prior studies show low-dose IL-2 administration activates NK-cells in cancer patients and demonstrated anticancer activity of haplo-identical NK-cell infusion and low dose IL-2 with 5 of 19 acute myeloid leukemia (AML) patients achieving a complete remission (31). Based on these promising results, a phase II study of allogenic NK-cells from haplo-identical donors infused in combination with subcutaneous IL-2 following lymphodepleting chemotherapy or immune suppressing total body irradiation in recurrent ovarian and breast cancer patients was performed (24). At 4–6 weeks following treatment 4 of 20 patients had a PR (4 ovarian), 12 with SD (8 ovarian), and 3 with progression (1 ovarian). The median time to progression was 2 months (range, 1–6 months). Unfortunately, none of the patients had successful *in vivo* NK-cell expansion or persistence of donor-derived NK cells as seen in AML patients. Moreover, most patients had increased immunosuppressive regulatory T-cells 14 days after treatment, which likely limited treatment effect. Additionally, there is potential for toxicity with unanticipated severe AEs including decreased cardiac ejection fraction, passenger lymphocyte syndrome, and death. The death was attributed to tumor lysis syndrome in an ovarian cancer patient (24). Though NK CT produced clinically meaningful results in AML, more work needs to be done in solid tumors to augment NK cell persistence and expansion.

Few advancements in ovarian cancer treatment have been made since GOG 111 determined a platinum-doublet which improved PFS and OS in 1996 (32). Increased understanding of the tumor microenvironment provides opportunity for innovative treatments, and several CTs are actively under development for the treatment of ovarian cancer. TILs, engineered TCRs, CAR-Ts, DCVACs, and NK CTs have been evaluated in small trials in ovarian cancer and generally have limited activity, substantial toxicity, and complex manufacturing

and administration schedules, which are challenges to overcome. Additional challenges to successful implementation of CTs in ovarian cancer include, low accumulation of anticancer immune cells due to an immunosuppressive microenvironment, persistence of the immunomodulating effects, and minimization of T-cell exhaustion (33,34). The recent trial evaluating intraperitoneal administration of IFN-activated monocytes showed promising activity in a heavily pre-treated population with little toxicity (18). In addition, while still requiring an apheresis procedure, monocytes are activated in the patient with IFN administration rather than engineered in the lab, suggesting a simplified manufacturing process compared to other CTs. Further studies are needed to assess the efficacy, safety, duration of effect, and appropriate patient population to derive clinically meaningful benefit from autologous infusion of IFN-activated monocytes, however this approach appears promising for further clinical development.

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References

1. Hamanishi J, Takeshima N, Katsumata N, et al. Nivolumab Versus Gemcitabine or Pegylated Liposomal Doxorubicin for Patients With Platinum-Resistant Ovarian Cancer: Open-Label, Randomized Trial in Japan (NINJA). J Clin Oncol 2021;39:3671–81. [PubMed: 34473544]
2. Lee EK, Xiong N, Cheng SC, et al. Combined pembrolizumab and pegylated liposomal doxorubicin in platinum resistant ovarian cancer: A phase 2 clinical trial. Gynecol Oncol 2020;159:72–8. [PubMed: 32771276]
3. Matulonis UA, Shapira-Frommer R, Santin AD, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol 2019;30:1080–7. [PubMed: 31046082]
4. Varga A, Piha-Paul S, Ott PA, et al. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of KEYNOTE-028. Gynecol Oncol 2019;152:243–50. [PubMed: 30522700]
5. Disis ML, Taylor MH, Kelly K, et al. Efficacy and Safety of Avelumab for Patients With Recurrent or Refractory Ovarian Cancer: Phase 1b Results From the JAVELIN Solid Tumor Trial. JAMA Oncol 2019;5:393–401. [PubMed: 30676622]
6. Monk BJ, Colombo N, Oza AM, et al. Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): an open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:1275–89. [PubMed: 34363762]
7. Moore KN, Bookman M, Sehouli J, et al. Atezolizumab, Bevacizumab, and Chemotherapy for Newly Diagnosed Stage III or IV Ovarian Cancer: Placebo-Controlled Randomized Phase III Trial (IMagyn050/GOG 3015/ENGOT-OV39). J Clin Oncol 2021;39:1842–55. [PubMed: 33891472]
8. Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. Lancet Oncol 2021;22:1034–46. [PubMed: 34143970]
9. Kurtz JE, Pujade-Lauraine E, Oaknin A, et al. Atezolizumab Combined With Bevacizumab and Platinum-Based Therapy for Platinum-Sensitive Ovarian Cancer: Placebo-Controlled Randomized Phase III ATALANTE/ENGOT-ov29 Trial. J Clin Oncol 2023;41:4768–78. [PubMed: 37643382]

10. Zhang Y, Cui Q, Xu M, et al. Current Advances in PD-1/PD-L1 Blockade in Recurrent Epithelial Ovarian Cancer. Front Immunol 2022;13:901772.
11. Schweer D, McAtee A, Neupane K, et al. Tumor-Associated Macrophages and Ovarian Cancer: Implications for Therapy. Cancers (Basel) 2022;14:2220. [PubMed: 35565348]
12. Fu H, Fu Z, Mao M, et al. Prevalence and prognostic role of PD-L1 in patients with gynecological cancers: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2023;189:104084.
13. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017;9:34. [PubMed: 28420421]
14. Contos G, Baca Y, Xiu J, et al. Assessment of immune biomarkers and establishing a triple negative phenotype in gynecologic cancers. Gynecol Oncol 2021;163:312–9. [PubMed: 34563366]
15. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353–65. [PubMed: 32919526]
16. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2020;38:1–10. [PubMed: 31682550]
17. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003;348:203–13. [PubMed: 12529460]
18. Green DS, Ning F, Duemler A, et al. Intraperitoneal Monocytes plus IFNs as a Novel Cellular Immunotherapy for Ovarian Cancer: Mechanistic Characterization and Results from a Phase I Clinical Trial. Clin Cancer Res 2023;29:349–63. [PubMed: 36099324]
19. Kverneland AH, Pedersen M, Westergaard MCW, et al. Adoptive cell therapy in combination with checkpoint inhibitors in ovarian cancer. Oncotarget 2020;11:2092–105. [PubMed: 32547707]
20. Hong DS, Van Tine BA, Biswas S, et al. Autologous T cell therapy for MAGE-A4(+) solid cancers in HLA-A*02(+) patients: a phase 1 trial. Nat Med 2023;29:104–14. [PubMed: 36624315]
21. ClinicalTrials.gov. MOv19-BBz CAR T Cells in aFR Expressing Recurrent High Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. ClinicalTrials.gov ID NCT03585764.
22. O'Cearbhaill RE, Park JH, Halton EF, et al. A phase I clinical trial of autologous chimeric antigen receptor (CAR) T cells genetically engineered to secrete IL-12 and to target the MUC16ecto antigen in patients with MUC16ecto+ recurrent high-grade serous ovarian cancer (HGSOC). Gynecol Oncol 2020;159:42.
23. Rob L, Cibula D, Knapp P, et al. Safety and efficacy of dendritic cell-based immunotherapy DCVAC/OvCa added to first-line chemotherapy (carboplatin plus paclitaxel) for epithelial ovarian cancer: a phase 2, open-label, multicenter, randomized trial. J Immunother Cancer 2022;10:e003190.
24. Geller MA, Cooley S, Judson PL, et al. A phase II study of allogeneic natural killer cell therapy to treat patients with recurrent ovarian and breast cancer. Cytotherapy 2011;13:98–107. [PubMed: 20849361]
25. Nakashima H, Miyake K, Clark CR, et al. Potent antitumor effects of combination therapy with IFNs and monocytes in mouse models of established human ovarian and melanoma tumors. Cancer Immunol Immunother 2012;61:1081–92. [PubMed: 22159517]
26. Monberg TJ, Borch TH, Svane IM, et al. TIL Therapy: Facts and Hopes. Clin Cancer Res 2023;29:3275–83. [PubMed: 37058256]
27. Ranoa DRE, Sharma P, Schane CP, et al. Single CAR-T cell treatment controls disseminated ovarian cancer in a syngeneic mouse model. J Immunother Cancer 2023;11:e006509.
28. Koneru M, O'Cearbhaill R, Pendharkar S, et al. A phase I clinical trial of adoptive T cell therapy using IL-12 secreting MUC-16(ecto) directed chimeric antigen receptors for recurrent ovarian cancer. J Transl Med 2015;13:102. [PubMed: 25890361]
29. Fucikova J, Hensler M, Kasikova L, et al. An Autologous Dendritic Cell Vaccine Promotes Anticancer Immunity in Patients with Ovarian Cancer with Low Mutational Burden and Cold Tumors. Clin Cancer Res 2022;28:3053–65. [PubMed: 35536547]
30. 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. [PubMed: 31456796]

31. Miller JS, Soignier Y, Panoskaltsis-Mortari A, et al. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. Blood 2005;105:3051–7. [PubMed: 15632206]

32. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1–6. [PubMed: 7494563]

33. Zhang XW, Wu YS, Xu TM, et al. CAR-T Cells in the Treatment of Ovarian Cancer: A Promising Cell Therapy. Biomolecules 2023;13:465. [PubMed: 36979400]

34. Mun SS, Meyerberg J, Peraro L, et al. Dual targeting ovarian cancer by Muc16 CAR T cells secreting a bispecific T cell engager antibody for an intracellular tumor antigen WT1. Cancer Immunol Immunother 2023;72:3773–86. [PubMed: 37635172]

Table 1

Completed phase 3 clinical trials of checkpoint therapy in ovarian cancer

Reference	Population (n)	Intervention	Biomarker	Outcomes
NCT02718417, JAVELIN Ovarian 100 (6), May 19, 2016–Jan 23, 2018	Newly diagnosed, untreated stage III–IV epithelial ovarian cancer (n=998)	Avelumab 10 mg/kg every 3 weeks in the chemotherapy phase and 10 mg/kg every 2 weeks in the maintenance phase	PD-L1 >1%	Chemotherapy followed by avelumab: median PFS 11.1 months (95% CI: 7.0–15.3); median OS 12.6 months (95% CI: 9.1–16.0)
		Paclitaxel either 80 mg/m^2 once weekly or 175 mg/m^2 once every 3 weeks and carboplatin AUC of 5 or 6 every 3 weeks		Chemotherapy plus avelumab followed by avelumab: median PFS 11.0 months (95% CI: 7.4–14.5); median OS 12.6 months (95% CI: 9.5–16.1)
NCT03038100, IMagyn050/GOG 3015/ENGOT-OV39 (7), Mar 8, 2017–Mar 26, 2019	Newly diagnosed, untreated stage III or IV ovarian cancer who had undergone primary cytoreductive surgery with gross residual disease or planned to receive neoadjuvant chemotherapy (n=1,301)	Atezolizumab 1,200 mg or placebo on D1, paclitaxel 175 mg/m^2 on D1, carboplatin AUC 6 on D1 during cycles 1–6, and bevacizumab 15 mg/kg on D1 during cycles 2–22	PD-L1 positive high (≥5%), PD-L1 tumor cell-positive (≥1%)	Atezolizumab: median PFS 19.5 months (95% CI: 18.1–20.8)
				Placebo: median PFS 18.4 months (95% CI: 17.2–19.8)
NCT02580058, JAVELIN Ovarian 200 (8), Jan 5, 2016–May 16, 2017	Recurrent platinum resistant or refractory ovarian cancer (n=566)	Avelumab 10 mg/kg every 2 weeks or avelumab + PLD 40 mg/m^2 every 4 weeks, or pegylated liposomal doxorubicin	Unselected	Avelumab: median PFS 1.9 months (95% CI: 1.8–1.9); median OS 11.8 months (95% CI: 8.9–14.1)
				Avelumab + PLD: median PFS 3.7 months (95% CI: 3.3–5.1); median OS 15.7 months (95% CI: 12.7–18.7)
				PLD: median PFS 3.5 months (95% CI: 2.1–4.0)
NCT02891824, ATALANTE/ENGOT-ov29 (9), Sep 28, 2016–Oct 4, 2019	Recurrent epithelial cancer with one to two previous chemotherapy lines, and a platinum free interval of >6 months (n=614)	Chemotherapy doublet and bevacizumab plus atezolizumab 1,200 mg every 3 weeks or placebo	Unselected	Atezolizumab: median PFS 13.6 months (95% CI: 12.2–14.2); median OS 35.5 months (95% CI: 8.9–14.1)
				Placebo: median PFS 11.1 months (95% CI: 11–13.5)

PD-L1, programmed cell death ligand 1; PFS, progression-free survival; CI, confidence interval; OS, overall survival; AUC, area under the curve; PLD, pegylated liposomal doxorubicin.

Table 2

Clinical trials of novel cell-based therapies in ovarian cancer

Reference	Population (n)	Intervention	Outcomes
Phase I intraperitoneal monocytes with interferons (18)	Platinum-resistant epithelial ovarian cancer patients (n=18)	Apheresis procedure followed by monocyte enrichment, on day 1 of each 28-day cycle intraperitoneal infusion of IFNα (25 or 250 mg) and IFNγ (5 or 50 mg), with or without autologous monocytes (75 or 750×10^6 cells)	RP2D of 250 mcg IFNα, 50 mcg IFNγ, and 750×10^6 monocytes; 2 PR, 4 SD of 9 patients with RECIST measurable disease
NCT03287674, adoptive cell therapy in combination with checkpoint inhibitors in ovarian cancer (19)	Recurrent, platinum-resistant epithelial ovarian cancer (n=6)	Ipilimumab (3 mg/kg) 2 weeks prior to surgery to obtain TILs and infusion of expanded TILs, low-dose IL-2 (2 MIE s. c. daily for 2 weeks), and nivolumab (3 mg/kg; q2w ×4), lymphodepletion chemotherapy cyclophosphamide (60 mg/kg × 2 days) followed by fludarabine phosphate (25 mg/m^2 × 5 days)	1 PR and 5 SD early after T-cell infusion, 1 long-lasting SD for almost a year
NCT02636855, phase I Autologous T-cell therapy for MAGE-A4$^+$ solid cancers (20)	38 patients with solid cancer, positive for at least one HLA-A*02 inclusion allele, MAGE-A4 RNA or protein expression in one or more tumor samples, with RECIST measurable disease, ovarian cancer patients (n=9, 23.7%)	Three afami-cel dose ranges in total transduced cell numbers: 0.8×10^9 to 0.12×10^9 cells (Group 1), 0.5×10^9 to 1.2×10^9 cells (Group 2), 1.2×10^9 to 6.0×10^9 cells (Group 3) and 1.2×10^9 to 10×10^9 cells (expansion group) Lymphodepletion chemotherapy with cyclophosphamide (600 mg/m^2/day) and fludarabine (30 mg/m^2/day)	ORR 24% (9 PR), disease control rate 74% (9 PR and 19 SD), including 5 ovarian cancer patients, median PFS 12.3 weeks (95% CI: 10.9–19.1)
NCT03585764, phase I MOv19-BBz CAR T Cells in aFR Expressing Recurrent ovarian cancer (21)	Persistent or recurrent stage II to IV ovarian cancer with measurable disease, can be platinum-sensitive or platinum-resistant, at least 2 prior lines, ≥70% of tumor cells with ≥2+ aFR staining	Intraperitoneal administration of lentiviral transduced MOv19-BBz CAR T cells in 4 cohorts with or without cyclophosphamide + fludarabine	Ongoing
Phase I trial of autologous CAR-T cells genetically engineered to target MUC16 and secrete IL-12 (22)	Recurrent MUC16^{ecto+} heavily pre-treated ovarian cancer patients (n=18)	4H11–28z/fIL-12/EFGRt+ CAR T cells were genetically modified to target MUC16^{ecto} antigen and to secrete IL-12, 50% dose given IV and if tolerated 50% intraperitoneal dose given 1–2 days later, four dose levels ranging from 3×10^5 to highest treated dose of 1×10^7 CAR-T cells/kg	No DLTs in the CAR-T only dose escalation phase; 2/3 of patients in cohort that received lymphodepletion chemotherapy experienced macrophage activation-like syndrome; cytokine release syndrome observed at all doses; best response SD
NCT02107937, phase II DCVAC/OvCa added to first-line chemotherapy (23)	Newly diagnosed stage III epithelial ovarian cancer patients who underwent cytoreductive surgery up to 3 weeks prior and were scheduled for first-line platinum-based chemotherapy (n=99)	DCVAC arm patients underwent leukapheresis with a dose consisting of approximately 10^7 autologous DCs in 5 mL Group A: DCVAC/OvCa given 2 weeks after second cycle with subsequent doses given 4 days before next chemotherapy cycle and every 6 weeks after completion of chemotherapy Group B: DCVAC/OvCa given 2 weeks after completion of chemotherapy every 3 weeks for the first 5 doses and then every 6 weeks until all doses used Carboplatin (AUC 5–7) and paclitaxel (175 mg/m^2 IV) every 3 weeks	Group A median PFS 20.3 (95% CI: 15.7 to NA); Group B median PFS NA (95% CI: 24.6 to NA); Group C chemo only median PFS 21.4 (95% CI: 12.6 to NA)
Phase II study of allogeneic NK cell therapy (24)	Recurrent breast (n=6) and ovarian (n=14) cancer patients, 7 median prior lines in OC patients	• Lymphodepleting chemotherapy given prior to the NK cell infusion cyclophosphamide (60 mg/kg × 2 days) and fludarabine (25 mg/m^2 × 5 days)	Grade 3 AE 11/20 patients. 10 unanticipated severe adverse events including decreased cardiac ejection

Reference	Population (n)	Intervention	Outcomes
		• Haplo-identical related donors underwent lymphapheresis for 3–5 h on the day prior to cell infusion • NK cells administered IV subcutaneous, median infused NK cell dose of 2.15×10^7 NK cells/kg (range, 8.33×10^6–3.94×10^7) • injections of IL-2 (10 MU) given three times weekly for a total of six doses • Seven patients received 200 cGy total body irradiation	fraction (n=1), passenger lymphocyte syndrome (n=2), and death (n=1)

IFN, interferon; RP2D, recommended phase 2 dose; PR, partial response; SD, stable disease; TILs, tumor infiltrating lymphocyte; MIE, million international equivalent; ORR, objective response rate; PFS, progression-free survival; CI, confidence interval; aFR, folate receptor alpha protein; DLT, dose limiting toxicity; DC, dendritic cell; NA, not available; AUC, area under the curve; OC, ovarian cancer; NK, natural killer; AE, adverse event.