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# The Emerging Role of Personalized Medicine in Immunotherapy for Ovarian Cancer

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**Abstract**:
The ability of immunotherapy to treat ovarian cancer is currently limited, however evaluating sensitive/resistant target treatment subpopulations based on stratification by tumor biomarkers may enhance this ability. These indicators include the number of tumor mutations, PD-L1, tumor-infiltrating lymphocytes, a lack of homologous recombination, and intratumoral heterogeneity of neoantigens. The use of these indicators to choose the best candidates for ovarian cancer treatment is one of the future directions. In addition to reviewing innovative treatments and study designs including tumor biomarkers that improve the chances of immunotherapy success in ovarian cancer, this paper also analyzes the function of immunotherapy in ovarian cancer.

## INTRODUCTION

Ovarian cancer is the tenth most prevalent cancer among female patients and the fifth largest cause of cancer-related mortality in women in the United States, where 22,240 individuals are diagnosed with it each year (1). Currently, debulking surgery combined with platinum-taxane maintenance chemotherapy is the first-line standard of treatment (2, 3). After receiving front-line treatment, 60–70% of patients with optimum debulking (1 cm residual disease) and 80–85% of patients with inadequate debulking (>1 cm residual disease) may experience a cancer recurrence, bringing the five-year survival rate down to roughly 45%. Front-line maintenance treatment advancements have attempted to increase this time frame (4, 5, 6). More efficient maintenance treatment is required since it has been demonstrated to effectively prolong progression-free survival (PFS) with bevacizumab or PARP inhibitors, but not overall survival (OS) (7). Currently, the majority of clinical studies concentrate on targeted strategies, including more recent initiatives to add immune therapies to the landscape of ovarian cancer treatment (7).

Through a variety of methods, including immunostimulatory cytokines, tumor antigen vaccines, and monoclonal antibodies that target inhibitory ligands generated by tumor cells, immunotherapy improves the antitumor immune response. The latter strategy focuses mostly on immunological checkpoint inhibition (ICI). Immune checkpoints such as programmed death receptor-1 and its ligand (PD-1:PD-L1) and cytotoxic T-lymphocyte associated protein 4 and its ligand (CTLA-4:B7/CD80) are used to identify pathogens from self-cells (8). A T-lymphocyte searches for epitopes that are compatible with its T-cell receptor (TCR) affinity when it comes into contact with a peripheral cell to identify whether it is a pathogen or a self-cell. T-cells recognize the epitope as a self-cell when immunological checkpoints like PD-L1 are present (9). When immunological checkpoints are absent, the T-cell recognizes the target as pathogenic, which triggers the killing response. Immune checkpoints are upregulated by cancer cells, which reduces the local immune response and enables immune evasion. By binding CTLA-4, PD-1, or PD-L1, ICIs prevent the immune checkpoint interaction between the tumor and T-cell, thereby restoring T-cell cytotoxicity (10). The importance of immunotherapy in ovarian cancer is discussed in this paper, along with innovative treatments and research designs including tumor biomarkers that improve the chances of immunotherapy effectiveness in ovarian cancer.

### *Molecular profiling*

Even though ICIs can result in long-lasting responses in certain patients, there is still a small percentage of patients who do not react, such as those whose tumors express PD-L1. Therefore, molecular profiling that indicates immunogenic phenotypes is increasingly used to determine the indication for immunotherapy, and new knowledge is exploding in this area. PD-1, PD-L1, and tumor mutational burden (TMB) are

immunophenotype indicators (11, 12). Other indicators include homologous repair deficient and proficient (HRD, HRP) phenotypes and elements governing the tumor microenvironment (TME), such as the characteristics of lymphocytes that infiltrate the tumor (TILs). These elements together provide a picture of the immunogenicity of the cancer cell itself, the immune system's capacity to reach the tumor, and the capacity of immune cells to carry out lethal operations (13, 14).

*TMB*

The amount of nonsynonymous mutations found in a tumor sample is known as the tumor mutational load, which also indicates the degree of genomic instability and the possibility that neoepitopes would emerge on the cell surface (15). Neoepitopes are cancer-specific proteins that are expressed on the cell surface and therefore accessible to the immune system. Different research teams have established different TMB criteria; generally speaking, TMB is split into high and low categories, with TMB high being defined as >10 mutations/Megabase of DNA. A TMB-high phenotype denotes a high level of mutant proteins that may be expressed as neoepitopes on the cell surface (16).

It has been shown in both preclinical and clinical efficacy trials showing the TMB-high phenotype predicts response to treatment with ICIs in solid tumors. A monoclonal antibody that targets PD-1, pembrolizumab, was recently authorized for treatment in any TMB-high (10) tumor, regardless of histology (17, 18, 19).

Consideration of other markers that may increase a patient's likelihood of responding to immunotherapy (e.g., combined TMB-high and PD-L1-high) or predict resistance to immunotherapy despite the TMB-high phenotype (e.g., combined TMB-high and high neoantigen intratumoral heterogeneity) generally improves TMB's predictive ability (ITH). According to estimates, 45% of ovarian cancers express PD-1/PD-L1 highly, which is defined as more than 10% of tumor cells in a tissue sample expressing PD-L1 on their surface (20, 21, 22). ICIs were created to stop this checkpoint-mediated immunosuppression, which is immunoinhibitory when PD-1/PD-L1 expression is high. Independent of TMB status, elevated PD-1/PD-L1 expression predicts responsiveness to ICIs. However, the two markers work better together to predict response than they do alone. Single biomarkers have been utilized as treatment indications up until now, but taking into account mixed biomarkers may increase the accuracy of choosing individuals who are most likely to respond to immunotherapy, particularly in cases of ovarian cancer (23, 24).

*HRD*

Homologous repair deficit (HRD) is a biomarker that predicts how cancers will react to platinum chemotherapy and poly-(ADP ribose) polymerase (PARP) inhibitors. It defines malignancies with inadequate reaction to DNA damage. 41–50% of epithelial ovarian cancers are thought to be HRD, and more than one in four people with ovarian cancer have germline mutations in HRD genes (25, 26). 25.7% of people with ovarian cancer have somatic or germline mutations in their BRCA genes. BRCA mutant cells are called HRD cells. HRD is linked to cancer genes that run in families, such as germline BRCA mutations in breast and ovarian cancer and mismatch repair (MMR) in Lynch syndrome. Surprisingly, a family history of cancer is linked to a higher objective response rate (ORR), disease control rate (DCR), the median time to treatment failure (MTTF), and median overall survival (OS) after ICIs are given. This makes us wonder if HRD may be the link between ICIs and this response in familial cancers. Some genes, like RAD51, BARD1, and TP53, that are part of the homologous recombination pathway, also show that DNA can't be fixed. This is called a "gene signature." Pembrolizumab, which is a PD-L1 inhibitor, works well on tumors with MMR (26, 27, 28). So, pembrolizumab was approved as the first treatment for colorectal tumors that lack MMR. But tumors with BRCA1/2 mutations haven't responded to avelumab or other immunotherapies. In this group, immune checkpoint inhibitors have been less successful than expected. HRD causes more tumors to grow, more mutations to happen in the tumors, and then more tumor neoantigens to be expressed. Compared to HRP tumors, HRD tumors have more immunophenotype markers like TMB-high, more CD3+ and CD8+ TILs, and higher levels of PD-1/PD-L1 (29, 30). Even though HRD is common in ovarian cancer, TMB is lower than would be expected. In a study of breast cancer samples, it was found that HRD tumors had more PD-L1 expression, which was linked to the activation of the STING pathway. The same study found that CXCL10 and CCL5 expression was 3.5 to 11.9 times higher than in HRP tumors and that CXCL10 and CCL5 expression, not neoantigen expression, was linked to the increased recruitment of peripheral blood mononuclear cells (PBMCs) (31). Dunphy et al. went into more detail about the non-canonical, antigen-independent recruitment of NK cells, M1-macrophages, T- and B-cells to the ovarian TME via CXCL10 and CCL5. The same group saw that the ATM-TRAF6-mediated "alternate STING pathway" made IL-6 and TGF-beta and brought in regulatory T-cells (Tregs) and protumor M2-macrophages. This ATM-TRAF6 also helps to raise the level of PD-L1 even more, which helps to explain why the immune system doesn't react much to ovarian cancer. So, immunomodulation in HRD tumors is controlled by the STING pathway and the alternative-

STING pathway. Depending on the molecular profile of the tumor, the immune response can be either boosted or slowed down (32, 33).

*Tumor-infiltrating lymphocytes*

Quantification of tumor-infiltrating lymphocytes (TIL), which measures immune cell infiltration of the tumor microenvironment (TME) and predicts a good response to immunotherapy, is another biomarker that may predict response. T-cells, NK cells, and, more recently, B cells' roles in the TME have been brought to people's attention. Different findings about how TILs affect survival and prognosis have made it harder to analyze (14, 34). For example, a study of the TME in melanoma found that the aggressiveness and stage of the tumor were linked to the number of TILs. In the same study, high levels of CD69+, which is a sign of activated lymphocytes, were linked to survival, showing that the number and quality of TILs are important for predicting prognosis. When it comes to ovarian cancer, the presence of TILs is linked to a longer PFS and OS. TILs in ovarian cancer are a good sign, especially when CD8+ T-cells are present, no matter what stage the tumor is in (35, 36, 37). Westergaard et al. found that the TIL profile of ovarian tumors is similar to that of melanoma, but there are more CD4+ T-cells than CD8+ T-cells in ovarian tumors. Most of these T-cells had the phenotype CD45RO+CCR7-CD62L, which is typical of effector memory T-cells (38).

***Clinical trials of immune therapy for ovarian cancer***

Even though ovarian cancer has a lot of HRD tumors with suspected high TMB, more CD8+ TILs, and high expression of tumor antigens that can trigger anti-tumor responses on their own, the first immunotherapy attempts were mostly not very successful (6, 39, 40). In the JAVELIN Ovarian 100 trial, avelumab, a PD-L1 inhibitor, was used as maintenance therapy for stage III/IV epithelial ovarian cancer that hadn't been treated before. Arms included chemotherapy followed by avelumab, avelumab plus chemotherapy followed by avelumab, and chemotherapy followed by watching as a control. The study was stopped before it was finished because the limits of futility had been set and there was no improvement in PFS compared to the control group (11.1 months, 11.0 months, and 10.2 months, respectively across arms) (40). Similarly, IMagyn050/GOG3015/ENGOT-OV39 compared atezolizumab, a PD-L1 inhibitor, to placebo plus paclitaxel, carboplatin, and bevacizumab in patients with advanced epithelial ovarian cancer. Researchers found no significant difference in median PFS between the PD-L1 positive group and the placebo group (18.5 months vs. 19.5 months, HR = 0.92) or between the PD-L1 positive group and the placebo group (19.5 months vs. 18.5 months) (20.8 months vs. 18.4 months, HR 0.80). Both of these studies came up with negative results, which suggests that using checkpoint inhibitors in ovarian cancer may need more biomarker efficacy analysis to find a potentially sensitive population (41).

In the KEYNOTE-158 trial, patients with solid tumors like ovarian, endometrial, and gastric cancer that had been treated with standard chemotherapy and were found to have cytologically confirmed high microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR) were given pembrolizumab as a single treatment. The patients were thought to have a high number of tumor mutations because at least one of the four mismatch repair proteins, MLH1, MSH2, MSH6, and PMS2, was missing from their tumors. Also, high microsatellite instability was found in two of the five allelic loci shifts of BAT25, BAT26, Di 5S346, Di 2S123, or Di 17S250. Pembrolizumab was given every three weeks at a dose of 200 mg for two years or until the disease got worse. Five of the 15 people with ovarian cancer who had been resistant to treatment in the past had an objective response, and three of them had a full response. Since the study is still going on, more results are still to come. A total of 223 people took part in the study. 23 of them (9.9%) reported a full response, and 57 of them (24.5%) reported a partial response. It was said that the ORR was 34.3% (95% CI, 28.3–40.8). The good results of this study are one reason why the FDA approved pembrolizumab for use in metastatic MSI-H/dMMR solid tumors, like ovarian cancer, in May 2017. The results of the study as a whole, which include other kinds of tumors, are also important (42).

In the KEYNOTE- 100 trial, pembrolizumab was also tested on people with ovarian cancer that came back. In this trial, the first 100 people who signed up were used to figure out the cut-off score for PD-L1 (CPS). From this group of patients, CPS scores between 1 and 10 were used to figure out how well the treatment worked. Patients with recurrent ovarian cancer were split into two groups. Cohort A was made up of people who had one to three previous lines of therapy and had gone 2 to 12 months without platinum. Patients in Cohort B had four to six lines of therapy before and went three months without platinum. In both groups, a higher CPS score was linked to a better response, and responses were seen 6 months later. But antitumor activity was said to be small (43).

The MIMOSA study was a phase III, double-blind, placebo-controlled, multicenter trial that looked at the effects of abagovomab maintenance therapy on ovarian cancer patients in their first clinical remission. Abagovomab is a murine monoclonal antibody that goes after the CA-125 antigen that is found in tumors. Patients in the study had stage III or stage IV ovarian cancer and were in complete clinical remission after surgery and chemotherapy with platinum and taxanes.

Abagovomab or a placebo was given once every two weeks for the first six weeks, and then once every four weeks until the disease came back, or for up to 21 months after the last patient was randomly assigned. Out of the 888 patients who were studied, 81.5% had the serous papillary subtype, 85.9% were in stage III, and 80.9% had a cancer antigen 125 35 U/mL after the third cycle. The study treatment was used for a mean of 449.7 days. When the tumor size was broken down into two groups (1 cm and >1 cm), there was no improvement in RFS (HR = 1.099; 95% CI = 0.919–1.315; p = 0.301). In the same way, no benefit was shown in OS (1.150, 95% CI, 0.872–1.518; p = 0.322). At two years, 80% of people in both groups were still alive. The SE was 1.71 in the abagovomab group and 2.43 in the placebo group. At the last visit, the median level of anti–anti-idiotypic antibody was 493,000.0 ng/mL, which shows that a strong immune response was achieved. The trial found that maintenance therapy with abagovomab in the first remission does not extend RFS or OS. The treatment was safe, and there was a measurable immune response. The study was eventually stopped because the main goal wasn't reached (RFS) (44).

***Clinical trials in progress***

Even though immunotherapies aren't effective in treating ovarian cancer in previous trials, researchers are still looking for biomarkers that can predict how subgroups of ovarian cancer patients will respond to immunotherapies. There are also studies going on that combine immune therapies with other treatments. Many trials are going on right now to study the effects of different immunotherapies on ovarian cancer. Here, we'll look at some ongoing trials that use biomarkers to sort patients by how well they respond to treatment, which is listed in Table 1.

These ongoing phase I, II, and III trials have shown that immunotherapy, which is often used in combination with other treatments, makes ovarian cancer patients respond better. It is important to do more research on biomarkers and how they relate to increased and decreased response. Immunotherapy has a lot of potential as a treatment for ovarian cancer, and some patients do seem to respond to it. However, more research needs to be done before we can fully understand its potential.

***The current state of personalized immunotherapy***

For immunotherapy to be successful, the TME must activate an anti-tumor T-cell response. To do this, a variety of strategies, including dendric cells, autologous tumor vaccines, and other combination treatments, are now being researched.

*Dendritic cells*

Pulsing autologous dendritic cells (DCs) with a tumor peptide is one method. The kidneys, testis Sertoli cells, and ovarian granulosa cells all ordinarily express the chosen peptide, Wilms' tumor protein 1 (WT1) (45, 46). However, a study of 100 patients revealed that 78% of EOC tissues expressed WT1, and WT1 was linked to tumors with higher grades and staging (p = 0.006 and p = 0.002, respectively). The Wilms tumor protein 1 (WT1), which is associated with a poor prognosis in ovarian cancer with a 5-year survival rate of 47%, was studied in phase I/II clinical research. In individuals with ovarian, breast, and gastric cancer who presented with a WT1 mutation, vaccination with autologous DCs produced a substantial CD8+ T-cell activation against WT1 ($p < 0.05$) (47, 48). After therapy, seven out of ten patients (70%) had stable disease, with three of the seven patients having reported tumor-shrinking on a CT scan. Two out of ten (20%) patients had indicated limited response. The therapy was deemed to be safe and well tolerated since all adverse events were grade 1 or 2 (46). This research illustrates the necessity for customized vaccines that aim to target certain mutations in patient subgroups to achieve better results.

*Autologous vaccines*

Autologous vaccines may potentially be essential for the evolving function of immunotherapy in the treatment of cancer. Autologous vaccines are one such combination that may simultaneously reduce tumor evasion and increase immune responses to target tumor cells. In one pilot research, six late-stage, chemotherapy-resistant ovarian cancer patients received combination treatment (49). Surgery, ex vivo expanded autologous TILs, IL-2, and nivolumab, an anti-PD-1 antibody, were administered after ipilimumab, an anti-CTLA4 antibody. The median progressive-free survival was found to be 86 days, with a range of 84 to 342 days in the study's outcomes of one patient with partial response and five with stable illness after 12 months. These findings were contrasted with earlier findings obtained without the use of ipilimumab, which showed that ipilimumab enhanced the success rate of ex vivo expanded autologous TILs by causing an uptick in CD8+ T-cell activity (50, 51).

Overall, the research emphasizes the positive outcomes of ICIs and autologous vaccination combination treatment. The natural next step is to use ICIs in conjunction with Vigil, an additional autologous vaccination that trains T-cells to the pertinent clonal tumor neoantigens and enhances peripheral circulating CD3+/CD8+ T-cells. In a phase I study, women with relapsed ovarian cancer were given the combination of Vigil and atezolizumab. The time of administration was discovered by the investigators to be crucial for both safety and effectiveness. Predating atezolizumab

**Table 1.** Some clinical trials using biomarkers.

| Trial Name | References | Short Description | Experiment Arms/Cohorts | Biomarker Stratification |
|---|---|---|---|---|
| **KEYNOTE-158** | [43] | People with advanced solid tumors took part in a Phase II, two-arm, open-label study of pembrolizumab and predictive biomarkers. | Arm 1: Pembrolizumab 200 mg<br>Arm 2: Participants failed at least<br>one line of therapy and have TMB<br>high. | TMB high |
| **CT03428802** | ClinicalTrials.gov | Phase II, single-arm, open-label trial studying the use of pembrolizumab in people with metastatic, recurrent, or locally advanced solid tumors and genetic mutations. | Arm 1: Pembrolizumab and lab<br>biomarker analysis | Response rate will be divided into groups based on the type of mutatio (POLE and POLD1 vs. BRCA1/2). PD-L1 expression, the presence of PD-1/PDL-1 polymorphisms, and th presence of immunoregulatory gene mutations will be used to divide patients into groups with different clinical outcomes (via deep sequencing) |
| **DUO-O** | ClinicalTrials.gov | Phase III, randomized, double-blind, placebo-controlled, multicenter trial looking at the use of durvalumab with chemotherapy and bevacizumab, followed by maintenance durvalumab, bevacizumab, and olaparib in advanced ovarian cancer. | Arm 1: Platinum-based chemotherapy with bevacizumab and durvalumab placebos, followed by maintenance bevacizumab, durvalumab placebo, and olaparib placebo<br>Arm 2: Platinum-based chemotherapy with bevacizumab<br>and durvalumab followed by maintenance bevacizumab, durvalumab, and olaparib placebo<br>Arm 3: Platinum-based chemotherapy with bevacizumab<br>and durvalumab followed by maintenance bevacizumab, durvalumab, and Olaparib<br>tBRCAm Cohort: Platinum-based<br>chemotherapy with bevacizumab<br>and durvalumab followed by maintenance bevacizumab, durvalumab, and olaparib (bevacizumab is optional) | Somatic BRCA mutation status |
| **V3-OVA** | ClinicalTrials.gov | A single-arm, open-label Phase II trial is being done to study the use of the V3-OVA vaccine in ovarian cancer. | Arm 1: V3-OVA vaccine (containing ovarian cancer antigens | The effect on the level of tumor markers in the blood will be measure as a secondary outcome (including CA-125) |
| **AdORN** | ClinicalTrials.gov | A Phase I/II, single-arm, open-label trial is being done to study the use of atezolizumab with neoadjuvant chemotherapy in patients with newly diagnosed advanced-stage epithelial ovarian cancer before and after cytoreductive surgery. | Arm 1: Atezolizumab, carboplatin, and paclitaxel (and<br>optional bevacizumab) | PFS will be divided into groups base on how much PD-L1, tumor-infiltrating lymphocytes, immune checkpoint receptors, cytokines, and gene expression profiles are expressed.<br>Each of these subsets will be divide into even smaller groups based on th BRCA mutation status and the tumo mutation profile. |
| **OLAPem** | ClinicalTrials.gov | A single-arm, open-label Phase II trial is being done to study the use of olaparib alone and olaparib and pembrolizumab together to treat ovarian cancer. | Arm 1, Cohort 1: Olaparib before<br>surgery<br>Arm 1, Cohort 2: Olaparib and<br>pembrolizumab before surgery | Biomarkers (germline mutations), changes in tumor-infiltrating lymphocytes, and the number of mutations in the tumor will be used t determine the therapeutic effect. |

with Vigil improved effectiveness and lowered atezolizumab-related side effects associated with therapy. OS was not achieved in the first treatment arm of Vigil and was 10.8 months in the first arm of atezolizumab (HR 0.33). It was also shown in this study that Vigil may have a greater therapeutic benefit in BRCA wild-type patients (NR in Vigil first vs. 5.2 in atezolizumab first HR 0.16, p = 0.027). Continued research is necessary, according to the limited cohort of patient's clinical outcomes and safety profiles (51).

*Combined treatment approaches*

Research studies examining the effects of autologous DC vaccination combined with ICIs and chemotherapy should also be taken into account. One included three therapy groups in a phase I investigation of women with recurrent ovarian cancer. The autologous DC vaccination that had been pulsed with tumor cells was administered as monotherapy to the first group. The autologous DC vaccine was also administered in combination with bevacizumab to the second group. The findings showed that following immunization, CD4+, and CD8+ T-cell numbers considerably increased. Two of the 25 patients who received treatment were indicated to have shown a partial response, while 13 patients reported stable illness for a median of 14 months after immunization (52). The data were further examined based on vaccination response, which was identified by T-cell identification of tumor cells. The 2-year survival rate among the 11 out of 25 people who reacted to the vaccination was 100%; whereas, the 2-year survival rate among the non-responders was 25%. This research is essential in demonstrating how the proper patients with the best probability of responding to the medication might be crucial in improving results. Determining the elements that influence therapy response is thus quite helpful and should be investigated going forward. The study's emphasis on the advantages of cyclophosphamide, bevacizumab, and the autologous DC vaccination in combination is another crucial point. Eight out of ten patients were found to have responded to the vaccination in the group receiving cyclophosphamide in combination, compared to three out of 12 in the group receiving just the vaccine. A rise in TGF-β was seen after vaccination and again after cyclophosphamide injection, related to the responsiveness of the vaccine, according to further serum studies (52). It is necessary to do further study to show the full impacts of autologous vaccinations, which might have additional advantages when combined with already fully studied and effective medicines to give customized medicine.

These trials show promising outcomes for cancer vaccination. Additionally, a promising next step to make tumors sensitive to the neoantigen repertoire is the combination of immunotherapy and vaccination (53). This approach has to be developed further, as does the understanding of the biomarkers that predict response. A major part of how the body reacts to immunotherapies may be played by autophagy. Elevated MHC-II levels are linked to a better prognosis and overall survival in ovarian cancer (53).

One way for cells to produce more neoantigens for MHC-II presentation is via autophagy. One mechanism for the complicated control of autophagy includes BRCA1/2 (54). Compared to BRCA1/2 wild-type cells, autophagy is increased in BRCA1/2 mutant cells. Autophagy inducers in combination with immunological treatments, such as checkpoint inhibitors and autologous tumor vaccines, may thus be a sensible strategy in BRCA wild-type malignancies (55). However, autophagy inhibitors may also be employed to make tumors more sensitive to chemotherapy or to improve their response. In reaction to stress, particularly chemotherapy, autophagy is increased. Autophagy inhibitors may reduce cell viability by collaborating with chemotherapy, according to preclinical investigations. Context may affect whether autophagy inducers or inhibitors are used (56).

## CONCLUSIONS

Early research suggested that ovarian cancer may be immunogenic as a result of several causes, including homologous repair inadequacy brought on by widespread BRCA mutation. However, compared to the majority of other immunogenic tumor forms, such NSCLC and melanoma, ovarian cancer immunotherapies have had less effectiveness. To increase the effectiveness of immunotherapy application to ovarian cancer, many strategies are being modified. These include choosing individuals based on immune profile, such as MSI-H/dMMR, HRD, and combining ICI with other therapies. Further study is required to properly describe immunological features common to ovarian cancer, identify optimum response indicators, and improve the patient selection for treatment. To reliably predict response, more than one biomarker could be required due to the complicated immunological landscape of ovarian cancer. It is vital to do deeper investigation of effectiveness and risk since combinatorial therapies seem to be an optimistic alternative for optimizing therapeutic benefit.

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