Use of Immunotherapy in Advanced Ovarian Cancer: A Systematic Review

Uso de Imunoterapia no Câncer de Ovário Avançado: Revisão Sistemática
Uso de la Inmunoterapia en el Cáncer de Ovario Avanzado: Revisión Sistemática

RESUMO
Introdução: O câncer de ovário avançado é uma das neoplasias ginecológicas mais letais, com altas taxas de recidiva e resistência aos tratamentos convencionais baseados em cirurgia e quimioterapia com platina. **Metodologia:** A revisão foi conduzida segundo as recomendações do protocolo PRISMA, incluindo artigos publicados entre 2016 e 2024 nas bases PubMed, Scopus, Web of Science e ScienceDirect. Foram selecionados estudos que abordaram o uso de imunoterapia — isolada ou combinada — em pacientes com câncer de ovário avançado ou recorrente. **Resultados:** A monoterapia com inibidores de checkpoint imune demonstrou taxas de resposta modestas, atribuídas à baixa carga mutacional e ao microambiente imunossupressor. Em contrapartida, as estratégias combinatórias — envolvendo ICIs com antiangiogênicos, inibidores de PARP, vacinas e agonistas de STING/TLR — mostraram resultados superiores em subgrupos de pacientes selecionadas por biomarcadores e perfil imunológico. As vacinas terapêuticas e as terapias celulares, incluindo TILs e CAR-T, apresentaram potencial promissor, especialmente em cenários de doença mínima residual. O desenvolvimento de imunofenótipos tumorais tem se mostrado uma ferramenta relevante para a individualização do tratamento. **Conclusão:** A imunoterapia no câncer de ovário avançado encontra-se em processo de consolidação científica, com resultados encorajadores em abordagens combinadas e guiadas por biomarcadores. Embora ainda não tenha alcançado impacto expressivo em sobrevida global, o avanço das terapias personalizadas e a compreensão do microambiente tumoral representam marcos decisivos rumo a uma nova era na oncologia ginecológica.
DESCRITORES: Câncer de ovário avançado; Imunoterapia; Inibidores de checkpoint imune; Biomarcadores; Terapias combinadas; Medicina personalizada.

ABSTRACT
Introduction: Advanced ovarian cancer is one of the most lethal gynecologic malignancies, characterized by high recurrence rates and resistance to conventional treatments based on surgery and platinum-based chemotherapy. **Methodology:** The review was conducted according to the PRISMA protocol, including articles published between 2016 and 2024 in the PubMed, Scopus, Web of Science, and ScienceDirect databases. Studies addressing the use of immunotherapy — alone or in combination — in patients with advanced or recurrent ovarian cancer were selected. **Results:** Monotherapy with immune checkpoint inhibitors showed modest response rates, attributed to low mutational burden and an immunosuppressive tumor microenvironment. In contrast, combinatory strategies — involving ICIs with antiangiogenic agents, PARP inhibitors, vaccines, and STING/TLR agonists — showed superior results in subgroups of patients selected by biomarkers and immune profiles. Therapeutic vaccines and cellular therapies, including TILs and CAR-T cells, demonstrated promising potential, especially in minimal residual disease settings. The development of tumor immunophenotypes has proven to be a relevant tool for individualized treatment. **Conclusion:** Immunotherapy in advanced ovarian cancer is undergoing scientific consolidation, with encouraging results in combination and biomarker-guided approaches. Although it has not yet achieved a significant impact on overall survival, advances in personalized therapies and the understanding of the tumor microenvironment represent decisive milestones toward a new era in gynecologic oncology.
DESCRIPTORS: Advanced ovarian cancer; Immunotherapy; Immune checkpoint inhibitors; Biomarkers; Combination therapy; Personalized medicine.

RESUMEN
Introducción: El cáncer de ovario avanzado es una de las neoplasias ginecológicas más letales, con altas tasas de recidiva y resistencia a los tratamientos convencionales basados en cirugía y quimioterapia con platino. **Metodología:** La revisión se llevó a cabo según las recomendaciones del protocolo PRISMA, incluyendo artículos publicados entre 2016 y 2024 en las bases de datos PubMed, Scopus, Web of Science y ScienceDirect. Se seleccionaron estudios que abordaban el uso de la inmunoterapia, sola o combinada, en pacientes con cáncer de ovario avanzado o recurrente. **Resultados:** La monoterapia con inhibidores de puntos de control inmunitario mostró tasas de respuesta modestas, atribuidas a la baja carga mutacional y al microambiente inmunosupresor. Por el contrario, las estrategias combinadas —que incluyen ICIs con antiangiogénicos, inhibidores de PARP, vacunas y agonistas de STING/TLR— mostraron resultados superiores en subgrupos de pacientes seleccionados por biomarcadores y perfil inmunológico. Las vacunas terapéuticas y las terapias celulares, incluidas las TIL y las CAR-T, han mostrado un potencial prometedor, especialmente en escenarios de enfermedad residual mínima. El desarrollo de inmunofenotipos tumorales ha demostrado ser una herramienta relevante para la individualización del tratamiento. **Conclusión:** La inmunoterapia en el cáncer de ovario avanzado se encuentra en proceso de consolidación científica, con resultados alentadores en enfoques combinados y guiados por biomarcadores. Aunque aún no ha logrado un impacto significativo en la supervivencia global, el avance de las terapias personalizadas y la comprensión del microambiente tumoral representan hitos decisivos hacia una nueva era en la oncología ginecológica.
DESCRIPTORES: Cáncer de ovario avanzado; Inmunoterapia; Inhibidores de puntos de control inmunitario; Biomarcadores; Terapias combinadas; Medicina personalizada.

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INTRODUCTION

Ovarian cancer is one of the most lethal gynecological malignancies and represents a major global public health challenge. Most patients are diagnosed at advanced stages, when the disease has already spread beyond the pelvis and is present in the peritoneum. Despite advances in cytoreductive surgery and platinum-based chemotherapy, approximately 70% of patients experience recurrence within a few years, highlighting the urgent need for new therapeutic approaches [2,12]. In recent decades, a better understanding of tumor biology and the immune microenvironment of ovarian cancer has sparked interest in the use of immunotherapy as an alternative or complement to conventional treatment.

Immunotherapy, defined as a set of therapeutic strategies aimed at stimulating or restoring the antitumor immune response, has revolutionized the treatment of several solid tumors, such as melanoma and lung cancer[3,4]. However, in ovarian cancer, its effectiveness is still limited and inconsistent, reflecting the "immunologically cold" nature of this tumor, characterized by low mutational burden, variable PD-L1 expression, and intense presence of immunosuppressive cells in the tumor microenvironment [7,12,14]. The interaction between the immune system and ovarian tumor cells is complex, involving immune evasion mechanisms, downregulation of costimulatory molecules, and secretion of inhibitory cytokines. These factors hinder the effective activation of cytotoxic T lymphocytes and reduce the impact of isolated immunostimulatory therapies.

Given this scenario, current research seeks combinatorial strategies that enhance the immune response, reverse tumor immunosuppression, and improve clinical outcomes for patients. The main approaches include the use of immune checkpoint inhibitors, therapeutic vaccines, cell therapies (such as tumor-infiltrating lymphocytes and CAR-T cells), oncolytic viruses, and pattern recognition receptor agonists, in addition to combination with antiangiogenic agents and PARP inhibitors [3,4,9,14,16]. Recent trials have explored the integration of predictive biomarkers, such as BRCA mutations, homologous recombination deficiency (HRD), and specific immune signatures, with the aim of developing a personalized approach guided by tumor immunophenotype [9]. Thus, immunotherapy emerges as a promising and constantly evolving frontier in the management of advanced ovarian cancer.

MATERIALS AND METHODS

This systematic review was conducted with the aim of synthesizing the latest scientific evidence on the use of immunotherapy in the treatment of advanced ovarian cancer. The design followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), covering studies published between 2016 and 2024, a period in which immunotherapy established itself as a relevant investigational therapeutic strategy for gynecological tumors [1–16]. We included systematic review articles, original studies, clinical trials, and bibliometric analyses that addressed the use of immunotherapeutic agents, alone or in combination, in patients with advanced or recurrent ovarian cancer.

The literature search was conducted in recognized electronic databases, such as PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect, using combinations of controlled descriptors and free terms: “ovarian cancer,” “advanced ovarian carcinoma,” “immunotherapy,” “checkpoint inhibitors,” “cancer vaccines,” “cell therapy,” and “oncolytic virus.” Studies identified through reference lists and articles cited in the selected publications were also considered. There was no language restriction, provided that the full text was available. Preclinical studies without direct translational relevance, isolated case reports, and narrative reviews without structured methodology were excluded [2,4,12].

The selection of articles took place

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in two stages. In the first stage, titles and abstracts were analyzed, excluding duplicate studies or those unrelated to the topic. In the second stage, the full texts of potentially eligible articles were evaluated for inclusion criteria. Data extraction included the following variables: type of immunotherapy, study phase and design, population evaluated, efficacy and safety outcomes, biomarkers studied, and main conclusions. The information was grouped into thematic categories—checkpoint inhibitors, vaccines, cell therapies, oncolytic viruses, immunostimulatory agonists, and therapeutic combinations—for comparative qualitative analysis [3,4,7,14,15].

The methodological quality of the included studies was assessed descriptively, considering criteria of internal validity, sample representativeness, clarity of outcomes, and potential publication bias. Given the heterogeneity of the designs and the absence of comparable quantitative data, no statistical meta-analysis was performed. Thus, the results are presented through a narrative synthesis, emphasizing trends, advances, limitations, and future perspectives of the use of immunotherapy in advanced ovarian cancer [5,8,9,13,14,16].

RESULTS

Immunological overview of advanced ovarian cancer (AOC)

Advanced ovarian cancer is recognized as a tumor of intermediate immunogenicity, presenting characteristics of a predominantly immunosuppressive tumor microenvironment. The presence of infiltrating T lymphocytes (TILs) is associated with a better prognosis, especially when there is a predominance of cytotoxic $CD8^+$ cells and a favorable balance between effector cells and regulatory T cells (Tregs). However, the density and functionality of these lymphocytes vary widely between histological subtypes and between patients [3,7,12,14].

The tumor microenvironment (TME) of ACS is marked by inconsistent PD-L1 expression, secretion of immunosuppressive cytokines (such as IL-10 and TGF-β), infiltration of myeloid-derived suppressor cells (MDSCs), and activation of M2 macrophages, which inhibit T cell effector activity. Low tumor mutational burden (TMB) and scarcity of neoantigens hinder immune recognition of the tumor, contributing to poor responses to monotherapy immunotherapy [3,7,12,14].

Given this scenario, recent studies emphasize the importance of detailed immune characterization of the tumor and ascites, including transcriptomic and proteomic profiles. This approach may allow the identification of distinct "immunophenotypes" — inflammatory, excluded, and desertified — capable of guiding individualized therapeutic decisions [9]. This personalization represents a new frontier in the treatment of ASC, allowing the selection of patients who are more responsive to specific immunotherapy strategies.

Immune checkpoint inhibitors (ICIs)

The isolated use of immune checkpoint inhibitors, such as nivolumab, pembrolizumab, and atezolizumab, has shown modest clinical responses in SSC. Objective response rates range from 8% to 15% in unselected populations, with a median duration of less than 6 months [2,12,15]. Although a minority of patients show a lasting response, the absence of robust predictive biomarkers limits the broad clinical applicability of these agents.

Resistance to monotherapy appears to result from multiple mechanisms: low tumor immunogenicity, immune exclusion (absence of T lymphocytes in the tumor parenchyma), T cell exhaustion mediated by high expression of TIM-3, LAG-3, and TIGIT, and activation of immune escape pathways within the microenvironment [3,7,14]. Thus, the current focus has shifted to the development of rational therapeutic combinations that can overcome these biological barriers.

VEGF plays a dual role in the TUMOR MICROENVIRONMENT: in addition to promoting angiogenesis, it contributes to the recruitment of Tregs and MDSCs, increasing immunosuppression. The combination of antiangiogenic agents (such as bevacizumab) with ICIs aims to normalize the vascular environment and improve T-cell penetration. Phase II and III clinical trials have shown increased response rates and greater disease control, especially in patients with a basal inflammatory microenvironment [3,4,10,14].

In tumors with BRCA1/2 mutations or homologous recombination deficiency (HRD), PARP inhibitors (e.g., olaparib, niraparib) increase cytosolic DNA accumulation, activating the cGAS-STING pathway and amplifying the innate immune response. The combination of PARP with ICIs has shown superior responses in HRD-positive patients, with promising biological synergism [3,10,11,14,16]. However, studies also indicate significant heterogeneity, and cumulative hematologic toxicity requires dose adjustment and careful selection.

Immunogenic cell death induced by chemotherapy (such as paclitaxel and carboplatin) or radiotherapy increases the release of tumor antigens and calreticulin exposure, favoring the activation of dendritic cells. Despite this, overlapping toxicities and the absence of consistent benefits in phase III studies limit the routine use of this combination [4,10,14]. The benefit may be more evident in patients with intermediate tumor burden and good functional status.

The combination of anti-PD-1/PD-L1 with anti-CTLA-4 (such as ip-

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ilimumab) can reverse multiple mechanisms of immune exhaustion and increase memory T cell activation. Early trials show a higher response rate (20–30%), but with a high incidence of grade ≥3 toxicity, mainly colitis and autoimmune hepatitis [3,15]. Ongoing studies seek to optimize doses and schedules to balance efficacy and safety.

Vaccine protection

Therapeutic vaccines aim to stimulate the adaptive antitumor immune response. Different platforms are being explored, including synthetic peptides, dendritic cell (DC) vaccines, and personalized neoantigen-based vaccines. Antigens such as NY-ESO-1, WT1, p53, and MUC16 are frequently used due to their overexpression in ASCS [1,4,6].

Although clinical trials have shown robust immunogenicity, with expansion of specific T cells and increased circulating IFN-γ, objective clinical responses are still limited. The greatest benefit appears to occur in patients with minimal residual disease or in adjuvant use after complete cytoreduction, suggesting that a less immunosuppressive tumor environment is critical for the success of the strategy [1,4]. Combinations with ICIs, STING/TLR agonists, and antiangiogenic agents are under investigation to enhance these effects [6].

Cell therapies

TIL therapy involves the ex vivo expansion of lymphocytes obtained from the tumor and their reinfusion after lymphodepletion. Pilot studies have shown durable responses in selected patients, but infiltrate variability, processing time, and cost are significant practical limitations. Support with IL-2 and concomitant use of ICIs have the potential to improve efficacy[3,4,7].

CAR-T and CAR-NK cell-based therapies represent an emerging frontier. Targets such as MUC16 (CA-125), mesothelin, FRα, and B7-H3 are being explored in phase I/II trials. Cell "armament" strategies (insertion of cytokine genes, TGF-β resistance receptors) and intraperitoneal administration seek to circumvent the hostile microenvironment of ACS [3,6,7,11,16]. Despite encouraging initial results, toxicity control and response durability remain central challenges.

Oncolytic viruses and pattern-recognition agonists

Oncolytic viruses, such as adenovirus, HSV, and vaccinia, act by directly destroying tumor cells and inducing secondary immunogenicity. Clinical trials have shown increased lymphocyte infiltration and PD-L1 expression after treatment, justifying their combined use with ICIs [4,11,14].

At the same time, TLR and STING agonists activate innate immunity and promote the release of inflammatory cytokines (type I IFN), converting "immunologically cold" tumors into "hot" ones. The combination with ICIs or vaccines has shown to be particularly promising, although robust phase III evidence for COA is still lacking.

Biomarkers and patient selection

The identification of effective biomarkers is essential for optimizing immunotherapy response. Isolated PD-L1 expression is insufficient, as many PD-L1-negative tumors also respond partially to treatment [3,9,14,15]. Composite profiles, which integrate mutational burden, inflammatory signatures (IFN-γ, CXCL9/10), BRCA/HRD status, and intratumoral $CD8^+$ lymphocyte density, have greater predictive value.

The studies analyzed propose the creation of tumor "immunophenotypes" based on the immune landscape of the tumor and ascites, capable of guiding therapeutic choices. This "immunophenotype-guided" approach is emerging as a paradigm of precision immunotherapy [9]. Bibliometric analyses confirm this shift in focus—from isolated ICIs to personalized and multimodal therapies [5,13].

Toxicity and management

Immune-mediated adverse events (irAEs), such as dermatitis, colitis, hepatitis, and endocrinopathies, are the most common toxicities of ICIs and should be promptly recognized and managed with corticosteroids or immunosuppressants [10,11,14,15]. Combinations with PARP or antiangiogenic agents add risks of myelosuppression, hypertension, and proteinuria.

The implementation of early surveillance protocols, multidisciplinary education, and risk stratification is essential, especially in patients who have already received multiple lines of treatment. Proper management of toxicity is considered crucial for maintaining adherence and continuity of immunotherapy.

Clinical scenarios and lines of treatment

The response to immunotherapy varies according to the platinum resistance profile. Platinum-resistant tumors tend to exhibit a more immunosuppressive microenvironment, with high Treg content and low effector lymphocyte infiltration. In these patients, monotherapy is not very effective, and current efforts are focused on regional and intraperitoneal combinations [2,3,14,16].

The combination of PARP ± ICIs as maintenance in HRD-positive tumors is one of the most studied approaches. Evidence suggests prolonged progression-free interval and potential biological synergism, although the impact on overall survival is still under investigation [3,10,14].

Subtypes such as clear cell and endometrioid carcinoma have greater genomic instability and inflammato-

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ry signatures, including mutations in ARID1A and activation of the PI3K/AKT pathway, which may make them more susceptible to immunotherapy [3,9,14]. This molecular differentiation reinforces the need for tailored therapeutic approaches.

DISCUSSION

The results of this study show that, although immunotherapy represents a relevant conceptual advance in the treatment of advanced ovarian cancer (AOC), its clinical efficacy still faces substantial limitations when used alone. Understanding the tumor microenvironment, molecular biology, and mechanisms of immune evasion is essential for the development of more effective strategies. AOC is characterized by a predominantly immunosuppressive microenvironment, marked by the infiltration of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and inconsistent PD-L1 expression, which contributes to primary resistance to immune checkpoint inhibitors (ICIs) [3,7,12,14]. This heterogeneity explains the modest response observed with monotherapy, with response rates below 15% in unselected populations [2,12,15].

Comparison between different immunotherapy modalities reveals that the future of AOC treatment depends on the rational combination of therapies, aiming to reverse immune exclusion and restore T cell activity. The combined use of ICIs and antiangiogenic agents, such as bevacizumab, has stood out for normalizing the vascular environment and increasing lymphocytic infiltration, showing higher response rates in inflammatory subgroups [3,4,10,14]. Similarly, combinations of ICIs with PARP inhibitors, especially in tumors with homologous recombination deficiency (HRD) or BRCA1/2 mutations, demonstrate biological synergism, enhancing tumor immunogenicity through activation of the cGAS-STING pathway [3,10,11,14,16]. However, interindividual heterogeneity and increased hematological toxicity limit the routine use of these strategies outside clinical trials.

Another relevant point is the transition from empirical approaches to biomarker-guided therapies. The simple expression of PD-L1 has not been shown to be sufficient to predict response, which has led to the development of composite profiles integrating mutational burden, inflammatory gene signatures, and DNA repair status [3,9,14,15]. This trend reflects a paradigm shift toward "personalized immunotherapy," in which tumor and ascites immunophenotypes guide therapeutic choices. Recently proposed "immunophenotype-guided" approaches offer a promising basis for stratifying patients, allowing the selection of those most likely to respond to combination immunotherapy [9].

In addition to ICIs, other immunotherapeutic modalities are emerging with promising results. Therapeutic vaccines, based on both classic tumor antigens (NY-ESO-1, WT1, p53) and personalized neoantigens, have shown strong immunogenic capacity, although clinical responses are modest in advanced disease [1,4,6]. The most favorable scenario for their use appears to be maintenance after cytoreductive surgery, when the tumor burden is minimal and immunosuppression is less intense. In this context, the combination with ICIs and STING/TLR agonists may increase the amplitude and durability of the immune response [4,6,14].

Cell therapies, especially those based on tumor-infiltrating lymphocytes (TILs) and CAR-T cells, are another important area of development. Initial trials with TILs have demonstrated lasting responses in specific subgroups, but cost and technical complexity limit their broad clinical applicability [3,4,7]. In the case of CAR-T and CAR-NK, challenges include antigenic heterogeneity and the risk of on-target/off-tumor toxicity, which has led to the development of new-generation CARs with intraperitoneal vectors and safety control mechanisms [6,11,16]. These therapies represent a promising horizon, especially in combination with ICIs, which can increase the persistence and expansion of modified cells.

Oncolytic viruses and molecular pattern agonists (TLR and STING) also stand out as immunological adjuvants capable of converting "cold" tumors into "hot" ones. These strategies stimulate the release of inflammatory cytokines, increase antigen presentation, and promote T-cell infiltration, creating a more favorable environment for the success of ICIs [4,11,14]. However, phase III evidence is still needed to confirm the clinical impact of these approaches in COA.

In terms of safety, immunotherapy has a characteristic toxicity profile, marked by immune-mediated adverse events (irAEs), such as dermatitis, colitis, and endocrinopathies [10,11,14,15]. When identified early, these events are usually reversible with the use of corticosteroids and immunosuppressants. However, therapeutic combinations, especially with antiangiogenic agents and PARP inhibitors, may amplify the risk of myelosuppression and hypertension, reinforcing the importance of multidisciplinary management and follow-up protocols.

From a clinical standpoint, immunotherapy outcomes vary depending on the therapeutic context. Patients with platinum-sensitive recurrence may have a better immune response, while those with platinum-resistant disease exhibit a more immunosuppressive microenvironment, which limits the efficacy of monotherapy [2,3,14,16]. The use of immunotherapy in maintenance therapy, especially in

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HRD-positive patients, emerges as a rational strategy to prolong progression-free interval and enhance the effect of PARP inhibitors [3,10,14]. In addition, specific histological subtypes, such as clear cell and endometrioid carcinoma, show greater response potential due to mutations such as ARID1A and the activation of inflammatory pathways [3,9,14].

Despite advances, significant challenges remain. The absence of universally validated biomarkers, the scarcity of positive phase III studies, and methodological heterogeneity between trials limit the translation of results into clinical practice [7,10,12,15]. Many studies have small samples, heterogeneous inclusion criteria, and surrogate endpoints, which makes direct comparison between interventions difficult. Nevertheless, there has been a clear conceptual evolution: from initial attempts with isolated ICIs to integrated and multimodal platforms, focusing on the combination of immunotherapy, targeted agents, and chemotherapy [8,9,14].

In summary, immunotherapy in advanced ovarian cancer is at a stage of scientific maturation and clinical consolidation. Although current results do not yet translate into consistent overall survival benefits, there is strong evidence that the path of combination therapy and personalization based on immunophenotypes could transform the treatment paradigm in the coming years. The development of adaptive clinical trials, the use of omics tools, and the integration of composite biomarkers represent fundamental steps toward precision immunological medicine. Thus, the advancement of immunotherapy in ASCLC depends not only on the discovery of new agents, but above all on a deep understanding of the interactions between the tumor, the immune system, and the tumor microenvironment—the true axis of modern oncology [3,4,8–11,14–16].

CONCLUSION

Immunotherapy represents one of the most promising frontiers in the treatment of advanced ovarian cancer, offering new possibilities for a disease historically marked by high rates of recurrence and therapeutic resistance. Although results are still limited in monotherapy, available evidence shows that combination strategies—integrating immune checkpoint inhibitors, antiangiogenic agents, PARP inhibitors, vaccines, and cell therapies—have the potential to transform the therapeutic landscape, especially when guided by specific biomarkers and tumor immunophenotypes.

Advances in the field depend on the consolidation of a truly personalized approach capable of recognizing the biological and immunological heterogeneity of ovarian cancer. Future clinical trials should prioritize the accurate stratification of patients, the development of composite biomarkers, and the rational use of therapeutic combinations, seeking to maximize efficacy and minimize toxicity. The integration of immunology, genomics, and clinical oncology is essential to translate immunotherapeutic potential into concrete gains in survival and quality of life.

In summary, immunotherapy in advanced ovarian cancer is at a transition point between hope and consolidation. The current challenge is not only to expand the therapeutic arsenal, but to deeply understand the biology of the disease and adapt interventions to each patient's immune profile. The evolution of this field points to a new era of precision oncology, in which the immune response will not only be modulated but strategically guided to achieve lasting and transformative results.

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