Monoclonal antibodies in the treatment of ovarian cancer

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Abstract. Ovarian cancer is a major threat to women's health, ranking fifth among cancer-related deaths globally. WHO data shows 321,731 new cases of ovarian cancer in 2022. Most patients are diagnosed late. Standard therapies of surgery plus platinum/taxane chemotherapy have poor survival. Chemoresistance leads to recurrence within 18 months in many patients, along with severe toxicities. PARP inhibitors have limitations such as variable efficacy and gaps in non-HRD populations. Monoclonal antibodies have played a pivotal role in cancer therapy for over 50 years and gained prominence with the 1997 approval of rituximab. They offer targeted immunotherapy, classified by origin from murine to fully human and mechanisms like ADCC and CDC. Types include naked mAbs, ADCs, bispecific antibodies, and ICIs. This review covers mAbs targeting VEGF like bevacizumab, FRα like mirvetuximab soravtansine, PD-1/PD-L1/CTLA-4 like nivolumab, MUC16/CA125 like oregovomab, and mesothelin like anetumab ravtansine. It addresses challenges such as resistance and inconsistent biomarkers and future directions, including novel combinations, multi-omics biomarkers, and next-gen mAbs for personalized care.

Keywords: Ovarian cancer, Monoclonal antibodies, Targeted therapy, Immune checkpoint inhibitors, Antibody-drug conjugates.

1. Introduction

As reported by the World Health Organization, the number of incident cases of ovarian cancer stands at 321,731 in 2022, with an age-standardized rate (world) of 6.7, a crude rate of 8.3, and a cumulative risk of 0.73. Among women, ovarian cancer is the fifth most frequent cause of cancer-related death. Approximately half of cases occur in those aged ≥65 years, and its high mortality is largely due to late-stage diagnosis in most patients [1]. The standard therapeutic approach for ovarian cancer involves surgical intervention followed by platinum/taxane-based chemotherapy. However, this regimen is associated with low survival outcomes, and chemoresistance frequently leads to disease recurrence within 18 months in a substantial proportion of patients. Additionally, toxic adverse effects are common, including thrombocytopenia, neutropenia, neurotoxicity, and gastrointestinal disturbances [2]. While PARP inhibitors serve as a therapeutic option, they are limited by variable patient benefit, cross-resistance with platinum agents, biased survival data, and insufficient evidence in non-homologous repair deficiency (non-HRD) populations. Immunotherapy, a widely researched innovative strategy, may soon surpass systematic chemotherapy for ovarian cancer. It harnesses the immune system to recognize cancer antigens: active approaches (e.g., vaccines, CAR-T cells) stimulate or engineer immune responses, while passive ones (e.g., checkpoint inhibitors, cytokines) enhance activity. Immunomodulatory therapies block checkpoint suppression or target immunosuppressive cells in the tumor microenvironment, activating tumor-specific T cells to eliminate cancer cells [3]. Monoclonal antibodies (mAbs) have a long history in cancer therapy, dating back over 50 years with early serologic insights, and gained prominence with the 1997 approval of Rituximab, a standard-of-care for B-cell non-Hodgkin's lymphoma. Monoclonal antibodies can be categorized based on their origin (murine, chimeric, humanized, or fully human), mechanism of action (neutralizing, opsonophagocytic, ADCC-mediated, or CDC-mediated), and application fields (therapeutic, diagnostic, or prophylactic) [4]. Their mechanisms primarily involve innate immune effector processes: activating Fc receptors on innate immune cells, triggering complement activity, and occasionally blocking oncogenic signalling. Efficacy depends on mAb isotype, binding site, avidity, target antigen properties, and tumor microenvironment regulation. These elements underpin mAbs' role as a major pharmaceutical therapeutic in cancer [5].

2. Classes of Monoclonal Antibodies and Mechanisms of Action

Monoclonal antibodies are key biopharmaceuticals for diseases like cancer and asthma. They are target-specific immunoglobulins or their fragments from a single cell clone. Structurally, they have two light and two heavy chains, which are held together by disulfide bonds, with constant and variable domains. Three complementary determining regions in each variable domain ensure binding specificity. Their quaternary structure has two antigen-binding fragments and one crystallizable fragment (Fig 1).

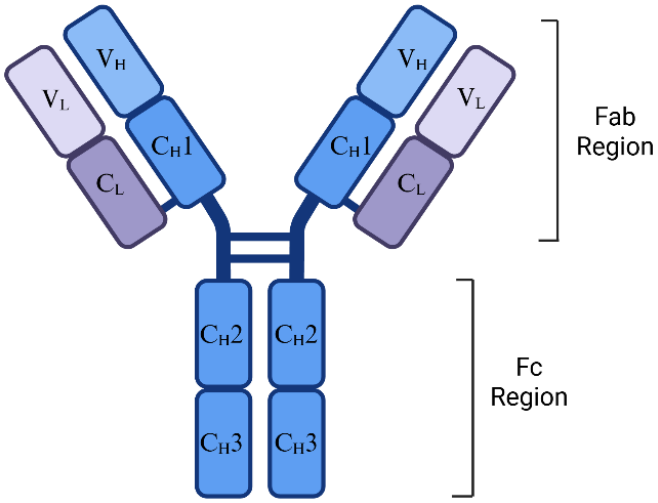

Figure 1. The structure of the antibody

Monoclonal antibodies play a crucial role in modern medicine, with diverse classes and distinct mechanisms of action. Naked monoclonal antibodies not only directly bind to antigens on target cells, but this binding can also trigger immune-mediated killing—a process in which the body's immune system, such as natural killer cells, macrophages, or complement proteins, recognizes the antibody-bound cells and eliminates them. Building on this mechanism, antibody–drug conjugates (ADCs) are engineered to selectively deliver cytotoxic drugs to cancer cells: here, the antibody part targets cancer-specific antigens, and once internalized, the attached drug is released inside the cell, ultimately leading to cell death [6]. Bispecific antibodies have the unique ability to target two different antigens simultaneously. They can bridge tumor cells and immune cells, enhancing the immune response against tumors [7]. Immune checkpoint inhibitors focus on the PD-1/PD-L1 and CTLA-4 pathways. CTLA-4 inhibitors block CTLA-4-B7 interactions in lymphoid tissues during early T-cell priming, preventing CD28 co-stimulation inhibition, enhancing T-cell proliferation, and reducing regulatory T-cell suppression. PD-1/PD-L1 inhibitors (e.g., nivolumab) disrupt PD-1-PD-L1/PD-L2 binding in peripheral tissues during the effector phase, restoring exhausted T cells by abrogating inhibitory signals, promoting cytokine production and overall survival. Both reinstate antitumor immunity [8]. Monoclonal antibodies in radioimmunoconjugates bind specifically to tumor antigens. They use chelators to stably deliver radionuclides. These complexes enter cells through receptor-mediated endocytosis. Inside, α/β emitters cause DNA double-strand breaks via direct ionization and reactive oxygen species (ROS). Bystander effects enhance this process, selectively killing cancer cells with little off-target damage [9].

3. Key Therapeutic Targets in Ovarian Cancer

3.1. VEGF Pathway

Bevacizumab, a monoclonal antibody, which targets vascular endothelial growth factor (VEGF), exerts its anti-tumor effect in ovarian cancer primarily by inhibiting angiogenesis, thereby suppressing tumor growth and metastasis. Newly published studies demonstrate that it also enhances the responsiveness of homologous recombination-proficient tumors to PARP inhibitors, which is

realized by suppressing CRY1 expression via the PI3K/AKT pathway [10]. Landmark trials validated its clinical role. ICON7 enrolled high-risk early/advanced ovarian cancer patients, using bevacizumab 7.5 mg/kg alongside carboplatin/paclitaxel, which was then followed by maintenance therapy (controls: chemotherapy alone). It showed a median PFS of 22.4 vs 24.1 months (bevacizumab vs control) but significant overall survival (OS) benefit in the high-risk subgroup (36.6 vs 28.8 months) [11]. Currently, bevacizumab is approved for use in the first-line treatment of high-risk advanced ovarian cancer in combination with chemotherapy followed by maintenance therapy, per NCCN guidelines. It is also used for platinum-sensitive and resistant disease. The PAOLA-1 trial further supports its synergy with olaparib for HRD-positive patients, extending PFS to 37.2 months in this subgroup. Real-world data confirms its benefit is most pronounced in patients with high-risk features. Bevacizumab resistance in ovarian cancer happens when GM-CSF causes MDSCs to gather, weakening anti-tumor immunity. At the same time, VEGF-C/D levels rise, activating pathways for blood vessel growth. ESM1 overexpression also helps resistance by boosting blood vessel growth. Combination methods include olaparib. In PAOLA-1, HRD patients had 37.2 months of PFS with the combo vs. 17.7 months with bevacizumab alone. Sorafenib, an inhibitor with a range of different kinases, works little in patients who had bevacizumab before but helps a bit in those who haven't [12].

3.2. Folate Receptor Alpha (FRα)

Farletuzumab and mirvetuximab soravtansine (MIRV) are monoclonal antibodies targeting folate receptor α (FRα), upregulated in 80%-100% of epithelial ovarian cancer (EOC). Farletuzumab, a humanized IgG1, exerts anti-tumor effects through antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), autophagy induction, and inhibition of FRα-Lyn kinase interaction. Its Phase III trial (n=1100) achieve the primary progression-free survival (PFS) endpoint in patients with platinum-sensitive relapsed EOC but showed a 51% reduced progression risk in patients with CA-125 ≤3×ULN [13]. MIRV, an FRα-targeting ADC with maytansinoid DM4, received UK MHRA approval in 2025 for FRα-positive platinum-resistant EOC. The Phase II SORAYA trial (n=106) showed 32.4% ORR with a 6.9-month median duration of response in FRα-high disease. A pooled analysis revealed 9% of patients achieved an extended treatment benefit (PFS >12 months) with 77.5% ORR and a 22.1-month median response duration [14]. Biomarker-driven patient selection for MIRV primarily relies on FRα expression. Eligibility is determined utilizing the Ventana FOLR1 (FOLR1-2.1) CDx test, defining high FRα as ≥75% tumor cells with 2+/3+ cell staining of the membrane. Candidates consist of individuals diagnosed with platinum-resistant epithelial ovarian/fallopian tube/peritoneal cancer and who received 1–3 courses of previous therapies. This stratification correlates with improved responses, with 32%-44% ORR in FRα-high populations, supporting FRα as a validated predictive biomarker [15].

3.3. Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) primarily include monoclonal antibodies. They target Programmed Cell Death Protein 1 (PD-1)/Programmed Death-Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4)—molecules expressed on tumor or immune cells. Representative anti-PD-L1 ICIs are atezolizumab and durvalumab; anti-PD-1 ICIs include nivolumab and pembrolizumab. Binding to these targets, ICIs abrogate immune suppression and unleash anti-tumor immunity. However, in ovarian cancer (OC), ICIs have shown modest efficacy. Some phase III trials were terminated early due to futility. Combining ICIs with agents like PARP inhibitors (PARPis) or anti-angiogenic drugs emerges as a promising strategy to enhance immunotherapeutic efficacy [16]. Monotherapy with anti-PD-1 agents shows modest efficacy. Pembrolizumab's phase II KEYNOTE-100 (ORR 8.0%, mPFS 2.1 months) supports this. Anti-PD-L1 agents have scarce data; phase III IMagyn050 saw no PFS gain with atezolizumab plus standard therapy. Combination strategies significantly enhance ICI efficacy versus monotherapy. For ICI-chemotherapy combinations, pembrolizumab + PLD achieved 19% ORR. Nivolumab + bevacizumab reported 28.9% ORR, and durvalumab + PLD yielded 15% ORR. ICI-PARP combinations show promise, especially in BRCA-

mutant patients. The TOPACIO trial (pembrolizumab + niraparib) reported 25% ORR, with 45% ORR in BRCA-mutant cases [17]. ICI response rates vary by strategy and subgroup. Anti-PD-1 monotherapy has an ORR of 8.0–12.2%. ICI-chemotherapy combinations reach 19–47.5% ORR, and ICI-PARP combinations reach 25–77.4% ORR. Combinations also outperform monotherapy in response durability. Biomarker data remain inconsistent. PD-L1 expression correlated with better outcomes in KEYNOTE-100 but not in NRG-GY003. It even showed an inverse correlation in NCT02873962 [18].

3.4. MUC16/CA125

Oregovomab is a monoclonal antibody of murine origin specifically targeting the cancer antigen (CA)-125. It exerts immunomodulatory effects by enhancing antigen uptake and cross-presentation to T cells, thereby activating both humoral and cellular immune responses. Clinical investigations of oregovomab have focused on ovarian cancer, with multiple phase II trials conducted in newly diagnosed or recurrent settings. In recurrent disease, 20 patients treated with oregovomab (with/without standard chemotherapy) had a median progression-free interval (mPFI) of 11 weeks and median overall survival (OS) of 70.4 weeks; patients with CA125/autologous tumor-specific T-cell responses showed significantly improved survival [19]. Immune modulation mediates vaccine-like effects via coordinated cellular and molecular mechanisms. Agents like MAT vaccines enhance antigen uptake by dendritic cells, activating inflammasomes and inducing IL-1β/IL-10 secretion to promote T-cell proliferation and tolerance. Hyaluronan adjuvants facilitate lymph node translocation, boosting humoral responses. Immunomodulators costimulate T cells through CD28-NF-κB signaling, enhancing cytokine release and adaptive immunity. Such effects induce long-term immune memory, bridging immunoregulation and protective responses in infectious disease and cancer immunotherapy [20].

3.5. Mesothelin

Mesothelin (MSLN), a tumor-differentiation antigen identified over two decades ago by Pastan and Willingham from the National Cancer Institute, belongs to the family of glycophosphatidylinositol (GPI)-anchored cell-surface glycoproteins. The normal expression of it is confined exclusively to mesothelial cells located in the pleura, peritoneum, and pericardium, while it is highly upregulated in multiple solid tumors (e.g., malignant mesothelioma, pancreatic, ovarian, and lung adenocarcinoma), making it a compelling therapeutic target. Unlike most tumor antigens, MSLN exhibits expression exclusively in dispensable tissues, which serves to reduce the risks of nonspecific toxicity to a minimum. Preclinical and early clinical data confirm antibodies targeting MSLN show selective localization to MSLN-positive tumors, validating antibody-based therapies and vaccines [21]. Amatuximab, previously designated as MORAb-009, is a chimeric IgG1/κ antibody targeting MSLN. In vitro experiments have shown that it can block MSLN-mediated cell adhesion and induce antibody-dependent cellular cytotoxicity (ADCC). While its monotherapy activity against MSLN-expressing xenografts is moderate, efficacy improves markedly with chemotherapy. A phase I trial reported dose-limiting toxicities (DLTs) of transaminitis and serum sickness, with a maximum tolerated dose (MTD) of 200 mg/m² [22]. Anetumab ravtansine falls into the category of antibody-drug conjugates (ADCs), which is made up of a human anti-MSLN antibody, a disulfide linker and DM4 (a tubulin inhibitor of the maytansinoid type). Preclinically, it selectively kills MSLN-expressing cells via internalization and linker degradation, releasing cell-permeable DM4 with bystander effects, and exerts an inhibitory effect on tumor growth across pancreatic, ovarian, and mesothelioma model systems. [23].

4. Conclusion

Monoclonal antibodies (mAbs) are pivotal in ovarian cancer treatment, addressing traditional therapy limitations via targeted mechanisms across types like naked mAbs (bevacizumab), ADCs

(mirvetuximab soravtansine, MIRV), and ICIs. They improve outcomes in advanced/recurrent disease and enable biomarker-driven stratification. Current successes include bevacizumab's prolonged PFS in high-risk cases and MIRV's approval for FRα-high platinum-resistant disease; ICI combinations enhance efficacy. However, challenges still exist, such as resistance, poor ICI monotherapy response, inconsistent biomarkers, and limited patient eligibility. Future directions may focus on novel combinations to overcome resistance, multi-omics biomarkers, next-generation mAbs, early-stage application, and mAb-mediated long-term immunomodulation. Overall, mAbs transform care, with further advancements promising personalized improvements in survival.

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