

Advances in Phase III Clinical Trials and Future Challenges of Targeted Therapy in Advanced Ovarian Cancer

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Abstract: Advanced ovarian cancer (OC) is characterized by an insidious onset, a high recurrence rate, and complex mechanisms of drug resistance, and has long been associated with poor prognosis, representing one of the leading causes of cancer-related death among women worldwide. In recent years, rapid advances in molecular biology and translational medicine have markedly transformed the therapeutic landscape of advanced ovarian cancer. Targeted therapies, including bevacizumab-based anti-angiogenic therapy, PARP inhibitors, and antibody–drug conjugates, act on key oncogenic pathways involved in tumor angiogenesis, DNA damage repair, and tumor-specific antigens, and have significantly prolonged PFS, with OS benefits observed in selected patient populations. This review systematically summarizes the major mechanisms underlying targeted therapy in advanced ovarian cancer and highlights the key evidence and clinical value of these three major classes of targeted agents in phase III clinical trials. By integrating mechanistic insights with phase III clinical evidence, this review further proposes that future research should focus on the evolution of therapeutic resistance, long-term safety management, standardized biomarker testing, and the optimization of combination and sequential treatment strategies. With the continued refinement of predictive biomarkers, improvement of multi-target combination approaches, and development of novel targeted agents, further gains in survival and quality of life are anticipated for patients with advanced ovarian cancer.

Keywords: advanced ovarian cancer, targeted therapy, phase iii clinical trials

Introduction

Ovarian cancer ranks as the eighth most commonly diagnosed cancer and the fifth leading cause of cancer-related death among women worldwide.¹ According to the latest analysis from the Global Burden of Disease (GBD) 2021 study, although the age-standardized mortality rate (ASMR) and age-standardized disability-adjusted life-year rate (ASDR) of ovarian cancer have shown an overall decline between 1990 and 2021, its prevalence and projected disease burden continue to rise.² Furthermore, both global incidence and prevalence are expected to increase further by 2050, indicating that advanced ovarian cancer will remain a major public health challenge in the coming decades.^{1,2} Meanwhile, platinum-based combination chemotherapy in conjunction with cytoreductive surgery remains the standard first-line treatment for advanced ovarian cancer. However, tumor heterogeneity, the development of chemotherapy resistance, and treatment-related toxicities contribute to persistently high recurrence rates, with the 5-year overall survival rate remaining at approximately 30%.³ In recent years, rapid advances in molecular biology have progressively elucidated the pathogenic mechanisms and regulatory networks of the tumor microenvironment in ovarian cancer. Leveraging their high specificity and more manageable toxicity profiles, targeted therapies have propelled the treatment of advanced ovarian cancer into an era of precision and individualized medicine.⁴ Since the approval of bevacizumab as the first anti-angiogenic agent for the treatment of advanced ovarian cancer, the field of targeted therapy has evolved into a multi-target, multi-mechanistic therapeutic framework centered on anti-angiogenic agents, poly (ADP-ribose) polymerase (PARP) inhibitors, and antibody–drug conjugates (ADCs).⁵ These targeted agents exert their therapeutic effects by acting on critical oncogenic

pathways, including tumor angiogenesis, DNA damage repair, and specific antigens of tumor cell.⁶ They have significantly prolonged progression free survival (PFS) in patients with advanced ovarian cancer, and some agents have additionally demonstrated overall survival (OS) benefits, thereby reshaping the continuum of care in ovarian cancer management.⁶

With the conduct of numerous phase III clinical trials and the maturation of long-term follow-up data, key clinical issues have increasingly focused on patient stratification for targeted therapies, optimization of treatment regimens, elucidation of resistance mechanisms, and the exploration of combination strategies. This review comprehensively addresses targeted therapy for advanced ovarian cancer, outlining the mechanisms underlying anti-angiogenic therapy with bevacizumab, PARP inhibitors, and ADCs. It further summarizes the progress of phase III clinical trials evaluating these agents and other emerging strategies, with in-depth discussion of patient population expansion, regimen optimization, combination approaches, core principles of clinical application, and future research directions. The aim of this review is to provide evidence-based guidance for optimizing targeted treatment strategies in advanced ovarian cancer, to facilitate the implementation of individualized therapy in clinical practice, and ultimately to improve patient outcomes while promoting the transition of ovarian cancer toward a more manageable chronic disease model.

Literature Search Strategy

To identify relevant studies for this review, we systematically searched PubMed, Web of Science, Embase, and ClinicalTrials.gov from database inception to January 2026. The search strategy combined Medical Subject Headings (MeSH) terms and keywords related to “advanced ovarian cancer,” “targeted therapy,” “phase III clinical trials,” “bevacizumab,” “PARP inhibitors,” “olaparib,” “niraparib,” “rucaparib,” and “antibody–drug conjugates,” using Boolean operators. Eligible publications included phase III clinical trials, key clinical studies closely related to the development of phase III evidence, and high-quality review articles relevant to the topic. Additional studies were identified through manual screening of the reference lists of retrieved articles and relevant reviews. Only studies published in English were included. The final selection of the literature was based on its relevance to the scope of this review, methodological quality, and clinical significance.

Bevacizumab

Mechanisms of Action and Toxicity of Bevacizumab

Angiogenesis plays a pivotal role in the progression of ovarian cancer. Beyond sustaining tumor growth, it actively remodels the tumor microenvironment (TME). The vascular endothelial growth factor (VEGF)-VEGF receptor (VEGFR) signaling pathway constitutes the central regulatory axis of this process.⁷ VEGF-A, the most biologically active member of the VEGF family, selectively activates VEGFR-1 and VEGFR-2, thereby promoting endothelial cell proliferation, migration, and survival through downstream signaling cascades, ultimately inducing neovascularization.^{8–10}

Bevacizumab is a recombinant humanized monoclonal antibody targeting VEGF-A. By specifically binding to VEGF-A, it prevents its interaction with VEGFRs, thereby inhibiting VEGF-mediated signaling. This blockade results in endothelial cell cycle arrest and apoptosis, effectively suppressing tumor angiogenesis.^{11,12} In addition, bevacizumab reduces circulating VEGF levels, promoting regression and collapse of structurally abnormal tumor vasculature, decreasing microvessel density, and limiting tumor perfusion.¹³ Furthermore, interference with the VEGF/Notch signaling axis disrupts vascular sprouting, further inhibiting neovascular formation and vascular network expansion, thereby exerting antitumor effects.^{14,15} However, while bevacizumab selectively inhibits VEGF-A-mediated tumor angiogenesis, it also disrupts physiological vascular endothelial homeostasis, leading to a spectrum of treatment-related adverse events. The principal mechanisms include suppression of VEGF-mediated nitric oxide (NO) production and microvascular maintenance, resulting in increased peripheral vascular resistance and hypertension;^{16,17} inhibition of podocyte-derived VEGF expression, compromising the integrity of the glomerular filtration barrier and causing proteinuria;¹⁸ induction of endothelial dysfunction and apoptosis with reduced NO and prostacyclin levels, exposure of procoagulant factors, and an increased risk of thrombosis;¹⁹ impairment of endothelial repair and fibrinolytic function, predisposing to bleeding events;²⁰ inhibition of angiogenesis required for tissue repair, leading to delayed wound healing;²¹ and in rare cases,



suppression of gastrointestinal vascularization causing local ischemic necrosis and potentially ischemic gastrointestinal perforation.²² Although the incidence of these adverse events varies, some carry life-threatening risks, necessitating vigilant monitoring and careful management in clinical practice.

Mechanisms of Resistance to Bevacizumab

As a cornerstone of anti-angiogenic therapy, the long-term efficacy of bevacizumab is limited by multilayered and interconnected resistance mechanisms. These involve dynamic interactions among tumor cells, the vascular system, and the tumor immune microenvironment (TME), with substantial crosstalk between resistance pathways. Following VEGF pathway inhibition, tumors may activate alternative pro-angiogenic signaling pathways, such as fibroblast growth factor (FGF)/FGF receptor (FGFR) and angiopoietin-2 (Ang-2)/Tie2 signaling. In cooperation with tumor-associated macrophages, cancer-associated fibroblasts, and regulatory T cells, these pathways establish a positive feedback loop that promotes angiogenesis and immune suppression.²³ Concurrently, tumor cells may adopt compensatory mechanisms, including vessel co-option, lymphangiogenesis, and hypoxia-driven upregulation of VEGF-C mediated by hypoxia-inducible factor-1 α (HIF-1 α), thereby facilitating invasion and metastasis.²⁴ Hypoxia further contributes to resistance by activating the prostaglandin E2 (PGE2)-CXCL12/CXCR4 axis, which recruits immunosuppressive cells and inhibits effector T-cell function, creating a synergistic hypoxia-immune suppression resistance network.²⁵ In addition, STAT3-mediated polarization of M2 macrophages and sustained FGF2 secretion amplify bypass angiogenic signaling, driving adaptive remodeling of the immune microenvironment.²⁶ Finally, anti-VEGF therapy-induced epigenetic alterations may disrupt vascular homeostasis and accelerate the development of resistant phenotypes. For example, downregulation of miR-143-3p leads to excessive secretion of plasminogen activator inhibitor-1 (PAI-1), impairing vascular integrity and promoting resistance progression.²⁷

Phase III Clinical Trials of Bevacizumab

As the first targeted agent approved for advanced ovarian cancer, bevacizumab has established the core evidence base for anti-angiogenic therapy in this disease. Its clinical development has driven the transition from conventional chemotherapy to a “chemotherapy plus targeted therapy” paradigm and has provided critical guidance for precision stratification and regimen optimization. The phase III clinical trial landscape of bevacizumab spans first-line treatment to recurrent settings and extends from dual combinations to multi-agent strategies, as shown in [Table 1](#), offering important implications for clinical practice and future research directions.

First-Line Treatment in Newly Diagnosed Advanced Ovarian Cancer

In the frontline setting, the GOG-0218 and ICON7 trials established the standard role of bevacizumab and highlighted the importance of risk stratification in predicting therapeutic benefit.²⁸ GOG-0218 employed a fixed 15-month regimen and demonstrated that the addition of bevacizumab to carboplatin-paclitaxel significantly prolonged median PFS. Although no significant OS benefit was observed in the overall population, both PFS and OS improvements were noted in high-risk subgroups, such as patients with ascites or stage IV disease, without compromising quality of life.^{28,29} ICON7, using a lower dose of bevacizumab (7.5 mg/kg every 3 weeks) and a shorter duration of 12 months, further confirmed significant benefit in patients at high risk of progression (stage III with residual disease > 1 cm or stage IV). In these subgroups, both PFS and OS were improved.^{30,31} Collectively, these studies demonstrated that the efficacy of bevacizumab is not uniform across all patients with advanced disease; rather, those at high risk derive the most pronounced benefit. This evidence supported a shift from a “one-size-fits-all” approach to risk-adapted treatment strategies in advanced ovarian cancer.

Optimization of Treatment Duration

The optimal duration of bevacizumab therapy has been a key clinical question. The ROSiA and BOOST studies together form a comprehensive evidence trajectory from exploration to validation.^{32,33} The single-arm phase IIIB ROSiA study suggested that extending bevacizumab maintenance to 24 months was feasible and tolerable. Although the incidence of hypertension and proteinuria was slightly increased, treatment discontinuation rates were low, and median PFS reached

Table 1 Progress of Phase III Clinical Research of Bevacizumab in OC

Clinical Trial	Patient Population	Experimental Arm	Control Arm	Result (mo) INV vs STD	HR	P
GOG-0218 3-arm trial	EOC, FTC, or PPC; FIGO stage III–IV.	1.Bev+CP→Bev MT 2.Bev+CP→Pbo	Pbo+CP→Pbo	PFS:14.1 vs 10.3 (1 vs ctr) OS:43.4 vs 40.8 vs 41.1	0.717 NA	< 0.001 <0.050
ICON7 2-arm trial	HGSOC or endometrioid OC, FTC, or PPC	Bev (7.5mg/kg)+CP→Bev MT	CP standard chemotherapy	PFS:19.0 vs 17.3 Restricted average survival time: total:45.5 vs 44.6 High-risk subgroup: 39.3 vs 34.5	0.810 NA	0.004 0.850
ROSiA Single-arm	Non-progressive OC, FIGO stage IIB–IV or staged I–IIA (G3)	Bev 15/7.5mg/kg+CP→Bev MT until PD or 24 mo	/	PFS:25.5 OS:NA	NA NA	NA NA
BOOST 2-arm trial	AEOC/FTC/PPC, FIGO stage IIB–IV	CP+Bev (30 mo)	CP+Bev (15mo)	PFS:26.0 vs 24.2 OS:60.0 vs 54.4	0.990 1.040	>0.050 0.680
OCEANS 2-arm trial	PSROC/FTC/PPC	CG+Bev→Bev until PD or unacceptable	CG+Pbo→Pbo until PD	PFS:12.4 vs 8.4 OS:33.6 vs 32.9	0.484 0.950	<0.001 0.650
GOG-0213 2-arm trial	PSROC/FTC/PPC	CP+Bev→Bev until PD or unacceptable	CP standard chemotherapy	PFS:13.8 vs 10.4 OS:42.2 vs 37.3	0.628 0.823	< 0.001 0.045
AURELIA 2-arm trial	PRROC/FTC/PPC	ddPTX/PLD/TPT+ Bev until PD or unacceptable	ddPTX/PLD/TPT until PD or unacceptable	PFS: 6.7 vs 3.4 OS:16.6 vs 13.3	0.480 0.850	< 0.001 0.174
MITO16b 2-arm trial	PSROC (FIGO stage IIB–IV)	CBP+PTX/PLD/ GEM+Bev	CBP+PTX/PLD/GEM	PFS:11.8 vs 8.8 OS:26.7 vs 27.1	0.510 0.990	< 0.001 0.980
AGO-OVAR 2.21 2-arm trial	PSROC	CBP+PLD+Bev	CG+Bev	PFS:13.3 vs 11.6 OS:31.9 vs 27.8	0.810 0.810	0.012 0.032
PAOLA-1 2-arm trial	Newly diagnosed AEOC	Bev MT+ OLA	Bev MT + Pbo	PFS:22.1 vs 16.6 OS:Total:56.5 vs 51.6 HRD(+):75.2 vs 57.3	0.590 0.920 0.620	< 0.001 0.412 NA
AGO-OVAR 2.29 2-arm trial	OC with 1st/2nd relapse ≤ 6 mo after platinum, or 3rd relapse	Bev+ddPTX/PLD+Atezo(q2w) until PD or unacceptable	Bev+ddPTX/PLD+Pbo until PD or unacceptable	PFS:6.4 vs 6.7 OS:14.2 vs 13.0	0.870 0.830	0.120 0.060
ICON8B 3-arm trial	EOC/PPC/FTC	1.CBP+ddPTX 2.ddCBP+ddPTX+ Bev→Bev MT	0.CBP+PTX +Bev→Bev MT	PFS:22.2 vs 16.7(2.vs3) OS:49.8 vs 39.6 (2.vs3)	0.750 0.790	0.002 0.010

Abbreviations: Mo, Months; INV, Investigational arm; STD, Standard arm; Ctr, Control arm; FTC, Fallopian Tube Cancer; PPC, Primary Peritoneal Cancer; HGSOC, High-grade Serous Ovarian Cancer; PRROC, Platinum-resistant Recurrent Ovarian Cancer; PSROC, Platinum-Sensitive Recurrent Ovarian Cancer; CBP, Carboplatin; PTX, Paclitaxel; PLD, Pegylated Liposomal Doxorubicin; GEM, Gemcitabine; TPT, Topotecan; ddPTX, Dose-dense Paclitaxel, ddCBP, Dose-dense; CBP, CP, Carboplatin+Paclitaxel; CG, Carboplatin+Gemcitabine; OLA, Olaparib; Atezo, Atezolizumab; Pbo, Placebo; MT, Maintenance Treatment; TFI, Treatment Free Interval; →, Indicates a shift in treatment strategies; NA, Not Available.

25.5 months, providing preliminary support for a “treat-until-progression” strategy in high-risk patients.³² However, BOOST, the first global head-to-head phase III trial comparing treatment durations, addressed the lack of controlled evidence from ROSiA.³³ This study demonstrated no significant differences in PFS or OS between 15 and 30 months regimens. Prolonged therapy was associated with significantly higher rates of grade ≥ 3 hypertension, proteinuria, and treatment discontinuation. These findings established 15 months as the standard first-line duration, refuting the hypothesis that longer treatment confers superior outcomes. Importantly, this conclusion avoided overtreatment and excessive toxicity while informing health economic considerations. The 15-month regimen has since been incorporated into prescribing information and clinical guidelines.^{33,34}

Recurrent Ovarian Cancer

In recurrent ovarian cancer, the benefit of bevacizumab varies according to platinum sensitivity, and interactions with specific chemotherapy partners may influence outcomes.^{35–37} For platinum-sensitive recurrence, the OCEANS trial demonstrated that bevacizumab combined with carboplatin-gemcitabine significantly prolonged PFS and improved objective response rate (ORR), although OS differences were not statistically significant. These results nonetheless led to FDA and EMA approval of bevacizumab for platinum-sensitive recurrent ovarian cancer, including maintenance therapy.³⁵ In GOG-0213, bevacizumab combined with carboplatin-paclitaxel significantly improved PFS (13.8 vs. 10.4 months), and sensitivity analyses suggested a significant OS benefit.³⁶ The differing survival outcomes between OCEANS and GOG-0213 raise the possibility that the choice of chemotherapy backbone may modulate bevacizumab efficacy, although the underlying mechanisms remain to be clarified. Together, these trials established bevacizumab as a cornerstone in platinum-sensitive recurrence.



For platinum-resistant recurrence, the AURELIA trial demonstrated that bevacizumab combined with non-platinum chemotherapy (weekly paclitaxel, topotecan, or pegylated liposomal doxorubicin) significantly prolonged PFS and doubled ORR compared with chemotherapy alone (30.9% vs. 12.6%).³⁷ Although OS was not significantly improved, prolongation of PFS and symptom control represent meaningful clinical endpoints in this poor-prognosis population.³⁷ The MITO16b study further supported treatment beyond progression, demonstrating that continuation of bevacizumab in platinum-sensitive patients previously exposed to first-line bevacizumab improved PFS, thereby supporting a continuum-of-care strategy.³⁸ Additionally, AGO-OVAR 2.21 was the first trial to demonstrate an OS difference among platinum doublets combined with bevacizumab, showing that carboplatin plus pegylated liposomal doxorubicin was superior to carboplatin plus gemcitabine, thus informing optimal chemotherapy partner selection in recurrent disease.³⁹

Combination Strategies

Exploration of combination strategies has further expanded the therapeutic scope of bevacizumab. Synergy with PARP inhibitors has emerged as a major advance in precision treatment, whereas combinations with immune checkpoint inhibitors have yielded less encouraging results.^{40,41} The PAOLA-1 trial evaluated bevacizumab plus olaparib as first-line maintenance therapy and demonstrated a substantial PFS benefit in patients with homologous recombination deficiency (HRD), particularly those with *BRCA* mutations. In *HRD*-positive patients, median PFS reached 46.8 months, with clinically meaningful OS improvement. This strategy expanded benefit beyond *BRCA*-mutated (*BRCAm*) patients to a broader *HRD*-positive population.^{40,42} These findings have promoted routine *HRD* testing and established anti-angiogenic therapy combined with PARP inhibition as a preferred option in high-risk newly diagnosed patients. The regimen is currently listed as a Category 1 recommendation in NCCN guidelines for *HRD*-positive disease.³⁴

In contrast, immune combination strategies have not met expectations. The IMagyn050 trial added atezolizumab to bevacizumab plus chemotherapy in the first-line setting but failed to demonstrate a significant PFS improvement in the overall population.⁴¹ Similarly, AGO-OVAR 2.29, conducted in platinum-resistant recurrence, did not show PFS or OS benefit with the addition of atezolizumab to bevacizumab plus non-platinum chemotherapy, although duration of response was modestly prolonged.⁴³ These findings challenge the presumed synergy between anti-angiogenic therapy and immune checkpoint blockade, suggesting that the ovarian cancer immune microenvironment is highly complex and that VEGF inhibition alone may be insufficient to reverse immune suppression. Future strategies may require combinations with ADCs or novel immunomodulatory agents, alongside more precise biomarker-driven patient selection.⁴³

Regimen Optimization: ICON8B

The ICON8B study introduced an additional avenue for first-line regimen optimization. It demonstrated that a dose-dense weekly paclitaxel plus weekly carboplatin regimen combined with bevacizumab significantly improved both PFS (by 5.5 months) and OS (by 10.2 months) in high-risk stage III–IV patients, while reducing the incidence of grade ≥ 3 neuropathy compared with the standard 3-week regimen.⁴⁴ These findings challenged the conventional chemotherapy standard and established dose-dense therapy combined with bevacizumab as a preferred option in high-risk newly diagnosed patients, further expanding therapeutic choices and contributing to updates in international clinical guidelines.³⁴

PARP Inhibitors

Mechanisms of Action and Toxicity of PARP Inhibitors

Poly (ADP-ribose) polymerase (PARP) is a member of the poly (ADP-ribose) polymerase family and plays a critical role in DNA damage repair, transcriptional regulation, and innate immunity.^{45,46} Upon genotoxic stress-induced single-stranded DNA (ssDNA) breaks, PARP1 consumes nicotinamide adenine dinucleotide (NAD^+), catalyzing poly(ADP-ribosylation) (PARylation), which recruits the base excision repair (BER) complex to repair SSBs and prevent their progression to lethal DSBs.^{47,48} PARP inhibitors (PARPi) competitively bind to the catalytic domain of PARP, preventing NAD^+ binding and inhibiting PARylation.⁴⁷ In addition, PARPi trap PARP–DNA complexes on chromatin, leading to replication fork collapse and subsequent impairment of DNA repair mechanisms.⁴⁹ In tumors harboring homologous recombination deficiency, cells are unable to effectively repair DSBs and therefore become highly dependent on PARP-

mediated repair pathways. PARP inhibition in this context results in accumulation of unrepaired DNA damage and ultimately induces cell death—a mechanism known as synthetic lethality.^{50–53} Accordingly, PARP inhibitors selectively target tumor cells with homologous recombination repair (HRR) defects, such as *BRCA1/2* mutations, leading to persistent DSBs and cancer cell death. Clinical studies have demonstrated that PARPi substantially improve outcomes in ovarian cancer with DNA repair defects and also confer benefit in selected patients without *BRCA* mutations.^{54,55}

However, long-term PARPi therapy is associated with dose- and agent-specific toxicities. These include hematologic toxicities such as thrombocytopenia, anemia, and neutropenia; gastrointestinal adverse events including nausea and vomiting; fatigue; hypertension (particularly notable with niraparib); reversible hepatic transaminase elevation (more common with rucaparib); and rare but serious myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).^{56–58} These toxicities are closely related to impaired DNA repair, endothelial dysfunction, and metabolic dysregulation. Therefore, clinical use of PARPi requires a balance between precise patient selection, long-term safety monitoring, and individualized management.

Mechanisms of Resistance to PARP Inhibitors

On the other hand, PARP inhibitors can develop primary or acquired resistance through multiple overlapping molecular mechanisms. These mechanisms closely resemble those observed with platinum-based chemotherapy and can be broadly categorized as follows. First, tumor cells may acquire *BRCA1/2* reversion mutations that correct prior frameshift or nonsense mutations, restoring open reading frames and partially functional proteins, thereby reestablishing HR repair capacity.^{59,60} Secondary mutations in *RAD51C/D* and restoration of DNA end resection mediated by TP53BP1 inactivation can both reactivate *RAD51*-dependent HR repair, thereby attenuating the lethal effect of PARP inhibitors.⁶¹ Second, by inhibiting the degradation of stalled replication forks by nucleases such as *MRE11*, or by regulating fork protection factors including *DYNLL1* and *RADX*, tumor cells can maintain replication fork integrity, thereby reducing replication-associated DNA damage and PARP inhibitors mediated cytotoxicity.⁶² Third, alterations in drug transport and signaling pathways contribute to resistance.^{63–65} Finally, epigenetic dysregulation constitutes a multilayered and potentially reversible resistance mechanism.⁶⁶ DNA methylation, histone modifications, and chromatin remodeling can modulate the expression of genes involved in HR repair, replication fork stability, and survival pathways. For example, promoter demethylation or increased histone acetylation of HR genes (eg, *BRCA1*) may restore gene expression and counteract PARPi-induced DNA damage.^{67,68} Given their reversibility, epigenetic alterations represent promising therapeutic targets for overcoming PARPi resistance.

Phase III Clinical Trials of PARP Inhibitors

PARP inhibitors have become a cornerstone of precision therapy in ovarian cancer. Their evidence base spans first-line and recurrent maintenance therapy, later-line treatment, and combination regimens. With continued updates from pivotal phase III trials, the eligible population has expanded from *BRCA*-mutated tumors to *HRD*-positive and broader subgroups, while also revealing challenges related to long-term toxicity, acquired resistance, and dynamic indication adjustments. Below, we summarize key phase III trials of PARPi in ovarian cancer, highlighting their evolution from monotherapy to combination strategies and their profound impact on clinical practice.

Olaparib

Olaparib, an oral inhibitor targeting PARP-1, PARP-2, and PARP-3, was the first PARPi approved for metastatic ovarian cancer.^{69,70} The development trajectory of its phase III clinical trials is summarized below, as shown in Table 2. The Phase II Study 19 trial marked the beginning of precision therapy in ovarian cancer, demonstrating for the first time that PARPi maintenance therapy significantly delayed disease progression. Subgroup analysis in *BRCA*-mutated patients established the conceptual and clinical foundation of synthetic lethality and molecular stratification.⁷¹ Subsequently, SOLO2, a pivotal phase III trial, demonstrated a clinically meaningful OS improvement trend in patients with *BRCA*m platinum-sensitive recurrent ovarian cancer, establishing olaparib as standard maintenance therapy in this setting.^{72,73} Based on these data, the U.S. FDA granted multiple approvals, including accelerated approval in 2014 for germline

Table 2 Progress of Phase III Clinical Research of Olapali in OC

Clinical Trial	Patient Population	Experimental Arm	Control Arm	Result (mo) INV vs STD	HR	P
Study19 2-arm trial	PSROC (regardless of BRCA status)	OLA 400mg bid MT until PD	Pbo bid MT until PD	BRCaM:PFS:11.2 vs 4.3 OS:34.9 vs 31.9	0.18 0.73	< 0.001 0.190
SOLO2 2-arm trial	PSROC with gBRCA mutation	OLA 300mg bid MT until PD	Pbo bid MT until PD	PFS:19.1 vs 5.5 OS:51.7 vs 38.8	0.30 0.74	< 0.001 0.054
SOLO1 2-arm trial	HGSOC/endometrioid OC with gBRCA mutation after first-line chemotherapy	OLA 300mg bid MT until PD or for up to 2 years	Pbo bid MTuntil PD or for up to 2 years	PFS:56.0 vs 13.8 OS:INR vs 75.2	0.33 0.55	< 0.001 < 0.001
SOLO-3 2-arm trial	PSROC with BRCA1/2 mutation after ≥2 prior platinum-based regimens	OLA 300mg bid MTuntil PD	PLD/PTX/GEM/TPT MT until PD	PFS:13.4 vs 9.2 OS:34.9 vs 32.9	0.62 1.07	0.013 0.710
PAOLA-1 2-arm trial	Newly diagnosed AEOC	Bev MT + OLA	Bev MT + Pbo	PFS:22.1 vs 16.6 OS:Total:56.5 vs 51.6 HRD(+):75.2 vs 57.3	0.59 0.92 0.62	< 0.001 0.412 NA
OReO 2-arm trial	PSROC with prior 1 line of PARPi (benefit ≥18 mo for BRCaM; ≥12 mo for non-BRCaM)	OLA 300mg bid MT	Pbo po bid MT	PFS: BRCaM:4.3 vs 2.8 Non-BRCaM:5.3 vs 2.8	0.57 0.43	0.022 0.002
L-MOCA Single-arm	PSROC after ≥ 2 prior platinum-based lines with CR/PR to the most recent platinum; PARPi-naïve	OLA 300mg bid MT until PD	/	HRD(+):17.9 BRCaM:20.1 non-BRCaM:15.8 HRD(-):9.2	NA	NA
NRG-GY004 3-arm trial	PSROC,PARPi-naïve / prior anti-angiogenic therapy in the recurrent setting	1.OLA 300mg bid MT until PD 2.OLA 200mg bid+CED MT until PD	3.CP/CG/CBP+PLD	PFS:1 vs 2 vs 3: 8.2 vs 10.4 vs 10.3 OS:1 vs 2 vs 3: 29.2 vs 30.5 vs 31.3	NA NA	NA NA
NRG-GY005 3-arm trial	PSROC or PRROC/ high-grade endometrioid OC, PPC, or FTC	1:OLA 300mg bid MTuntil PD or unacceptable 2:OLA 200mg bid+CED MT until PD or unacceptable	3.ddPTX/PLD/TPT	PFS:1 vs 3: 4.0 vs 3.4 2 vs 3: 5.2 s 3.4 OS:1 vs 3: 10.5 vs 13.6 2 vs 3: 12.8 vs 13.6	0.97 0.79 1.06 1.03	NA NA NA NA
ICON9 2-arm trial	PSROC	OLA 300mg bid+ CED 20mg qd	OLA 300mg bid	PFS: 13.9 vs 11.0 OS: 37.2 vs 37.8	0.84 0.92	0.24 0.81
KEYLYNK-01 3-arm trial	BRCA1/2 wild-type,FIGO stage III–IV high-grade serous/Endometrioid EOC, FTC, or PPC	1.Pembro+CP→Pembro+ OLA MT until PD 2.Pembro+CP→Pembro+ Pbo MT until PD	3.Pembro+Pbo→ Pbo MT until PD	NA	NA	NA
DUO-O 3-arm trial	Newly diagnosed AEOC, non-tBRCaM	1.CP+Bev+D→Bev+Durva +OLA MT until PD 2.CP+Bev+D→Bev+Durva +Pbo MT until PD	3.CP+Bev+Pbo→ Bev+Pbo MT until PD	PFS:ITT: 1vs3: 24.2 vs 19.3 2vs3: 20.6 vs 19.3 HRD(+): 1vs3: 37.3 vs 23.0	0.63 0.87 0.49	<0.001 0.13 <0.001

Abbreviations: HGSOC, High-Grade Serous Ovarian Cancer; CED, Cediranib; Pembro:Pembrolizumab; Durva, Durvalumab; →:Indicates a shift in treatment strategies. NA, Not Available.

BRCA-mutated (g*BRCAm*) advanced ovarian cancer after ≥ 3 prior lines of chemotherapy, and full approval in 2017 for maintenance therapy in platinum-sensitive recurrent ovarian cancer responding to platinum-based chemotherapy.^{4,74}

SOLO1, the landmark first-line maintenance trial, established olaparib as a standard of care in newly diagnosed stage III–IV *BRCAm* high-grade serous or endometrioid ovarian cancer. Long-term follow-up demonstrated durable survival benefit, forming the basis for FDA, EMA, NCCN, ESMO, and CSCO recommendations.^{75–77} Moreover, SOLO1 provided the methodological and conceptual foundation for subsequent studies, including PAOLA-1 (*HRD*-expanded population) and PRIMA (non-*BRCA* population).

The SOLO-3 trial enrolled patients with germline *BRCA*-mutated platinum-sensitive recurrent ovarian cancer who had received ≥ 2 prior lines of platinum-based chemotherapy and randomized them in a 2:1 ratio to receive olaparib or physician's choice of non-platinum chemotherapy (eg, paclitaxel or topotecan). No significant OS advantage was observed. Exploratory analyses suggested that increasing numbers of prior treatment lines may attenuate benefit and that *BRCA* reversion mutations were associated with reduced efficacy.^{78,79} Notably, among patients in the olaparib arm with baseline *BRCA* reversion mutations, no objective responses were observed, indicating that restoration of *BRCA* function after multiple lines of therapy may confer resistance to PARP inhibition.^{79,80} Based on these unfavorable OS signals, AstraZeneca voluntarily withdrew the treatment indication for olaparib in third-line or later g*BRCAm* recurrent ovarian cancer in August 2022. Since then, the clinical application of olaparib in ovarian cancer has shifted toward earlier treatment settings, such as first-line and platinum-sensitive recurrent maintenance, aligning with the principles of precision medicine and early intervention.

OReO was the first global phase IIIb study specifically designed to evaluate PARP inhibitor rechallenge as maintenance therapy in ovarian cancer.⁸¹ The results demonstrated that in platinum-sensitive recurrent patients previously treated with PARPi, significant PFS prolongation was observed regardless of whether prior PARPi discontinuation was due to disease progression, irrespective of *BRCA/HRD* status, provided that patients achieved CR or PR to their most recent platinum-based chemotherapy. Patients with no evidence of disease after surgery and normal CA-125 levels also derived benefit.⁸¹ Clinically, these findings provide a new therapeutic option for this population and expand the scope of PARPi use beyond first exposure, supporting their integration into continuum-based ovarian cancer management according to individual response and tolerability.⁸¹ Together, SOLO-3 and OReO refined the evidence framework for olaparib from complementary perspectives. SOLO-3 clarified the limitations of late-line treatment and reinforced the importance of earlier maintenance strategies, whereas OReO challenged the traditional notion that PARPi can only be used once, supporting their role as a core component of long-term disease management.^{79,81} Collectively, these studies have advanced PARPi therapy in ovarian cancer toward a model of precision stratification and continuum-based care, enabling more optimized individualized treatment strategies.

The L-MOCA trial was the first phase III study to systematically evaluate olaparib maintenance therapy in Asian patients with PSROC, enrolling patients regardless of *BRCA* status. The study demonstrated PFS benefit in the overall population and across multiple subgroups, with a safety profile consistent with prior studies, thereby providing important evidence supporting long-term survival benefit of PARP inhibitor maintenance therapy in Asian patients with platinum-sensitive recurrent ovarian cancer.⁸²

Olaparib has been demonstrated to significantly prolong PFS in both PSROC and in the first-line maintenance setting. Meanwhile, preclinical studies have suggested that PARP inhibitors and anti-angiogenic agents may exert synergistic effects via a dual mechanism of synthetic lethality and hypoxia-induced DNA damage, providing a biological rationale for combination strategies.⁸³ Against this background, several randomized clinical trials have systematically evaluated the clinical value of olaparib combined with the VEGFR inhibitor cediranib across different treatment settings, including NRG-GY004/005 and ICON9. The results indicated that the combination regimen did not consistently outperform standard strategies in multiple scenarios and was associated with increased toxicity, suggesting that its benefit may be limited to specific molecular subtypes (eg, selected *BRCAm* populations) and that more precise biomarker-driven patient selection is required.^{84–86}

In recent years, the KEYLYNK-001 study has emerged as a focus of investigation in advanced ovarian cancer. The trial demonstrated that, in patients with *BRCA* wild-type advanced ovarian cancer, maintenance therapy with a PD-1 inhibitor combined with a PARP inhibitor following chemotherapy significantly prolonged PFS.⁸⁷ Ongoing data

maturation is expected to further clarify whether immunotherapy and PARP inhibition exert synergistic antitumor effects through a dual mechanism of repair inhibition and immune activation, potentially establishing the PD-1 inhibitor plus PARP inhibitor combination as a standard treatment option in advanced ovarian cancer.^{87,88} DUO-O, a landmark phase III trial, systematically evaluated the first-line triplet regimen of a PARP inhibitor, an immune checkpoint inhibitor, and an anti-angiogenic agent. The study demonstrated that the triplet combination significantly improved PFS in patients with advanced ovarian cancer regardless of *HRD* status, without new safety signals and with manageable tolerability. Notably, the benefit was particularly pronounced in the *HRD*-negative population.⁸⁹ These findings confirm that the triplet strategy of PARP inhibition, immune checkpoint blockade, and anti-angiogenic therapy can significantly extend PFS in the frontline setting and offers a novel therapeutic option for *HRD*-negative patients.⁸⁹

Niraparib

Niraparib is a highly selective PARP-1/2 inhibitor.⁹⁰ Since its initial approval in 2017, niraparib has been evaluated in a series of landmark clinical trials in ovarian cancer, progressively expanding its clinical indications and providing significant survival benefits for patients, as shown in Table 3.^{56,91}

The NOVA trial, a pivotal phase III study in the recurrent maintenance setting, demonstrated that niraparib significantly prolonged PFS regardless of *BRCA* mutation status. Its clinical activity in the non-*BRCA*-mutated population established niraparib as a standard option for maintenance therapy in recurrent ovarian cancer.⁵⁶ Based on the NOVA results, the U.S. FDA approved niraparib on March 27, 2017, for maintenance treatment of patients with recurrent ovarian cancer who achieved complete or partial response after platinum-based chemotherapy.^{56,91} NORA, the first randomized phase III trial conducted in China to evaluate PARP inhibitor maintenance therapy in an unselected population, used blinded independent central review (BICR)-assessed PFS in the intention-to-treat (ITT) population as its primary endpoint.⁹² The results demonstrated significant PFS improvement with niraparib regardless of germline *BRCA* mutation status.⁹² Notably, 94% of patients in NORA received an individualized starting dose (ISD) based on baseline body weight and platelet count. This study is considered the first phase III randomized trial to systematically

Table 3 Progress of Phase III Clinical Research of Niraparib in OC

Clinical Trial	Patient Population	Experimental Arm	Control Arm	Result (mo) INV vs STD	HR	P
NOVA 2-arm trial	PSROC with CR/PR after the most recent platinum-based chemotherapy	Nir:300mg qd MT	Pbo qd MT	PFS:BRCAm:21.0 vs 5.5 non-BRCAm:9.3 vs 3.9 OS:BRCAm:40.9 vs 38.1 non-BRCAm:31 vs 34.8	0.27 0.45 0.85 1.06	<0.001 <0.001 NA NA
NORA 2-arm trial	PSROC/FTC/PPC after ≥ 2 prior platinum-based regimens.	Weight ≥77kg and PLT≥150×10 ⁹ : Nir:300mg qd Weight <77kg and PLT<150×10 ⁹ : Nir:200mg qd	Pbo qd	PFS:18.3 vs 5.4 BRCAm: not reach vs 5.5 non-BRCAm:11.1 vs 3.9	0.32 0.22 0.40	<0.001 <0.001 <0.001
PRIMA 2-arm trial	FIGO stage III–IV HGSOc/ endometrioid OC, FTC, or PPC	Nir:300mg qd	Pbo qd	PFS:Total:13.8 vs 8.2 HRD(+):21.9 vs 10.4	0.62 0.43	<0.001 <0.001
PRIME 2-arm trial	AEOC/FTC/PPC with CR/PR after first-line platinum-based chemotherapy	Weight ≥77kg and PLT≥150×10 ⁹ :300mg qd Weight <77kg and PLT<150×10 ⁹ :200mg qd	Pbo qd	PFS:Total:24.8 vs 8.1 HRD(+):NR vs 11.0 BRCAm:NR vs 10.8 non-BRCAm:19.3 vs 8.3	0.45 0.48 0.40 0.48	<0.001 NA NA NA
AGO-OVAR 28 2-arm trial	Newly diagnosed HGSOc/PPC/FTC	CP+Bev→Nir+Bev	CP→Nir	NA	NA	NA
FIRST 3-arm trial	Newly diagnosed FIGO stage III–IV AEOC/FTC/PPC	1.CP+Dosta→Dosta+Nir 2.CP+Dosta→Dosta	3.CP+Pbo→ Pbo MT	PFS:1 vs 3: 20.6 vs 19.2 OS: 1 vs 3: 44.4 vs 45.4	0.85 1.01	0.035 0.906
ANITA 2-arm trial	Newly diagnosed FIGO stage III–IV AEOC/FTC/PPC	ATZ+CBP+PTX/GEM/PLD→ ATZ+Nir	Pbo+CBP+PTX/GEM/ PLD→Pbo+Nir	PFS:11.2vs10.1	0.89	0.280
NitCHE 2-arm trial	Recurrent EOC not eligible for platinum retreatment	Nir+Dosta MT until PD or unacceptable	PTX/GEM/PLD/TPT±Bev	NA	NA	NA

Abbreviations: Nir, Niraparib; Dosta, Dostarlimab; TFlp, Treatment-Free Interval since last Platinum; ATZ, Atezolizumab; →.Indicates a shift in treatment strategies; NA, Not Available.

establish and validate an individualized dosing strategy for a PARP inhibitor, providing important evidence for optimizing clinical safety management.⁹²

The PRIMA trial moved niraparib into the first-line maintenance setting for newly diagnosed advanced ovarian cancer patients at high risk of recurrence, demonstrating significant PFS benefit and supporting its use in a broader population.⁹³ Based on PRIMA, niraparib became the first PARP inhibitor approved for first-line maintenance therapy irrespective of biomarker status in newly diagnosed advanced ovarian cancer.⁹³ The PRIME study, a phase III trial conducted in a Chinese population, further validated the efficacy and safety of the ISD strategy in first-line maintenance therapy.⁹⁴ The study showed significant PFS improvement regardless of residual disease status after surgery or *BRCA*/*HRD* status, with favorable tolerability and risk–benefit balance under the ISD regimen.⁹⁴ PRIME reinforced the clinical relevance of biomarker-independent benefit and confirmed the feasibility of individualized dosing in frontline treatment.^{94,95}

The AGO-OVAR 28 study is an ongoing international phase III trial comparing niraparib monotherapy versus niraparib combined with bevacizumab as maintenance therapy following platinum-based chemotherapy in newly diagnosed advanced ovarian cancer. The primary endpoint is PFS, and results are expected in 2028, potentially clarifying the role of combination maintenance in the first-line setting.⁹⁶ The FIRST trial, the first global phase III study to demonstrate frontline benefit of a PD-1 inhibitor combined with a PARP inhibitor, showed in subgroup analyses that patients with *HRD*-positive tumors or high PD-L1 expression derived greater benefit, providing a basis for biomarker-driven patient selection in clinical practice.⁹⁷ Although the absolute PFS improvement of 1.4 months has sparked debate regarding its clinical relevance, these findings have been incorporated into the 2025 NCCN guidelines, which recommend this regimen as a first-line treatment option for patients with advanced ovarian cancer who are *HRD*-positive or have high PD-L1 expression.⁹⁷ OS data remain immature, and confirmation of long-term survival benefit requires further follow-up.⁹⁷

The ANITA trial was the first global phase III study in platinum-sensitive recurrent ovarian cancer to demonstrate that a PD-L1 inhibitor–based combination was superior to conventional platinum-based chemotherapy followed by PARP inhibitor maintenance.⁹³ Subgroup analyses showed benefit across the overall population, irrespective of *HRD* or PD-L1 status, with more pronounced efficacy observed in patients with *HRD*-positive tumors, PD-L1–positive expression (tumor cells $\geq 1\%$), and those who had received only one prior line of chemotherapy. The safety profile of the combination was consistent with the known toxicities of the individual agents, and no new safety signals were identified. Based on these findings, the 2024 NCCN guidelines list atezolizumab plus platinum-based chemotherapy followed by niraparib maintenance as one of the preferred treatment options for platinum-sensitive recurrent ovarian cancer. OS data remain immature (approximately 30% maturity), and further investigation is required to clarify long-term survival benefit and to identify more precise predictive biomarkers, such as tumor mutational burden (TMB) and immune cell infiltration. The NItCHE trial evaluates niraparib plus dostarlimab versus physician’s choice of single-agent chemotherapy in patients with recurrent ovarian cancer who are unsuitable for platinum-based treatment.⁹⁸ The primary endpoint results have not yet been reported. If positive, this strategy may provide a novel non-platinum therapeutic option for heavily pretreated patients.⁹⁸

Rucaparib

Rucaparib is a PARP-1/2/3 inhibitor whose phase III clinical evidence spans first-line maintenance, later-line comparative treatment, and recurrent maintenance settings. Available data suggest that patients across different biomarker-defined subgroups may derive benefit, although resistance mechanisms and optimal sequencing strategies remain key challenges, as shown in Table 4.^{99,100}

The ARIEL3 trial was the pivotal phase III study evaluating rucaparib as maintenance therapy in recurrent ovarian cancer. The results demonstrated that rucaparib significantly prolonged PFS regardless of biomarker status.⁹⁹ Based on these findings, the European Medicines Agency (EMA) approved rucaparib in 2019 for maintenance treatment of platinum-sensitive recurrent ovarian cancer, establishing it as an important therapeutic option in this setting.⁹⁹ Subsequently, the ARIEL4 trial was the first head-to-head phase III study comparing a PARP inhibitor with chemotherapy in patients with *BRCA*1/2-mutated recurrent ovarian cancer. The results confirmed that rucaparib significantly improved PFS compared with chemotherapy; however, no OS benefit was observed.^{101,102} Collectively, these two studies suggested that high crossover rates and the presence of *BRCA* reversion mutations limited the benefit derived from

**Table 4** Progress of Phase III Clinical Research of Other PARP Inhibitors in OC

Clinical Trial	Patient Population	Experimental Arm	Control Arm	Result (mo) INV vs STD	HR	P
ARIEL3 2-arm trial	PSR-HGSOC/EOC, PPC, or FTC	Ruca 600mg bid	Pbo bid	PFS1:10.8 vs 5.4 PFS2:20.6 vs 16.3 OS:36.0 vs 43.2	0.36 0.70 0.995	<0.001 NA NA
ARIEL4 2-arm trial	HGSOC or G2/3 endometrioid EOC, PPC, or FTC with <i>BRCA1/2</i> mutation	Ruca 600mg po bid	PRROC/partially PSROC: ddPTX; fully PSROC: platinum-based chemotherapy	PFS:7.4 vs 5.7 OS:19.4 vs 25.4	0.67 1.30	0.002 0.047
ATHENA-MONO 2-arm trial	Newly diagnosed HGSOC; prior cytoreductive surgery	Ruca 600mg po bid	Pbo bid	PFS: ITT:20.2vs9.2 HRD(+):28.7vs11.3	0.52 0.47	<0.001 <0.001
ATHENA-COMBO 2-arm trial	FIGO stage III–IV HGSOC, FTC, or PPC;	Ruca 600mg bid+Nivo MT until PD or unacceptable	Pbo+Nivo	NA	NA	NA
FZOCUS-1 3-arm trial	Newly diagnosed advanced OC, FTC, or PPC	1.FZPL 100mg bid+APA 300mg qd 2.FZPL 150mg bid	3.Pbo bid	PFS: 1 vs 3: 26.9 vs 11.1 2 vs 3: 29.9 vs 11.1	0.57 0.58	<0.001 <0.001
FZOCUS-2 2-arm trial	PSROC;≥2 prior platinum-based regimens	FZPL 150mg bid MTuntil PD or unacceptable	Pbo bid	PFS:12.9 vs 5.5	0.25	<0.001
VELIA 3-arm trial	Newly diagnosed FIGO stage III–IV HGSOC, FTC, or PPC, or high-grade endometrioid OC	1.CP+VER→VER 2.CP+VER→Pbo	CP+Pbo→Pbo	PFS: ITT: 23.5 vs 17.3 HRD(+):31.9 vs 20.5 BRCAm: 34.7vs 22.0	0.68 0.57 0.44	<0.001 <0.001 <0.001

Abbreviations: PSR-HGSOC, Platinum-Sensitive Recurrent HGSOC; Ruca, Rucaparib; PFS1, Time from Randomization to 1st PD or Death; PFS2, Time from Randomization to 2nd PD or Death; Nivo, Nivolumab; FZPL, Fuzuloparib; APA:Apatinib; VER, Veliparib; →:Indicates a shift in treatment strategies; NA, Not Available.

rucaparib, highlighting the substantial impact of acquired resistance mechanisms on the efficacy of PARP inhibitors.^{58,102,103} Overall, findings from the ARIEL program indicate that rucaparib exhibits clear antitumor activity in *BRCA*-mutated, *HRD*-positive, and even *HRD*-negative ovarian cancer populations. Nevertheless, in the later-line treatment of recurrent *BRCA*-mutated ovarian cancer, rucaparib appears less effective than chemotherapy and may adversely affect OS; therefore, chemotherapy or alternative combination strategies should be preferentially considered in this context.^{58,99,101,102}

ATHENA-MONO was a randomized phase III trial evaluating rucaparib as maintenance therapy in patients with stage II–IV advanced ovarian cancer who achieved response to first-line platinum-based chemotherapy. The study demonstrated a significant improvement in PFS with rucaparib regardless of *HRD* or *BRCA* status.¹⁰⁴ This was the first phase III trial to confirm a significant frontline maintenance PFS benefit with rucaparib across the overall advanced ovarian cancer population, leading to EMA approval for first-line maintenance treatment in all patients with advanced disease and expansion of the FDA indication to an unselected population.^{104,105} These findings further challenged the traditional view that PARP inhibitors are restricted to *HRD*-positive patients and laid the foundation for biomarker-inclusive precision therapy in advanced ovarian cancer.¹⁰⁴ The ongoing ATHENA-COMBO study is designed to explore the potential synergy between immunotherapy and PARP inhibition in the frontline maintenance setting, with the aim of further optimizing first-line treatment strategies. Results are anticipated in 2026.¹⁰⁵

Fluzoparib

Fluzoparib is a novel PARP inhibitor independently developed in China. Through the FZOCUS series of phase III clinical trials, a comprehensive evidence framework has been established covering both first-line maintenance and platinum-sensitive recurrent maintenance therapy in ovarian cancer, providing a precision treatment option better aligned with clinical needs for patients in China and globally, as shown in Table 4.^{106,107} FZOCUS-1 was a three-arm phase III trial conducted in patients with newly diagnosed ovarian cancer. Preliminary results presented at the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting demonstrated that fluzoparib was significantly superior to placebo, reducing the risk of disease progression or death by 51%. Subgroup analyses further confirmed benefit across the overall population. Among patients with *BRCA* mutations, median PFS was not reached (NR) in the fluzoparib group versus 14.9 months in the placebo group (HR = 0.40). In *BRCA* wild-type patients, median PFS was 25.5 months versus 8.4 months,

respectively (HR = 0.53).¹⁰⁶ Based on data derived from a Chinese population, this study established a “China-based strategy” for first-line maintenance therapy in ovarian cancer and provides important reference evidence for global clinical practice.¹⁰⁶

FZOCUS-2 was a randomized, double-blind, placebo-controlled phase III trial, with PFS assessed by blinded independent central review (BICR) in both the ITT population and the germline *BRCA*-mutated subgroup as the primary endpoint.¹⁰⁷ At a median follow-up of 8.5 months, fluzoparib was significantly superior to placebo, reducing the risk of disease progression or death by 75%. Subgroup analyses demonstrated that the PFS benefit was independent of *gBRCA* mutation status. OS data remain immature, and follow-up is ongoing.¹⁰⁷ This study established fluzoparib as a standard maintenance therapy option for platinum-sensitive recurrent ovarian cancer. Collectively, the FZOCUS program comprehensively covers the key treatment phases of first-line and platinum-sensitive recurrent maintenance therapy, confirming that fluzoparib significantly prolongs PFS across the overall population with a favorable safety profile. As a PARP inhibitor independently developed in China, its clinical data are closely aligned with the characteristics of Chinese patients, thereby promoting the localization of precision medicine in ovarian cancer.¹⁰⁷ With longer follow-up and continued exploration of combination strategies, fluzoparib is expected to further expand its role in ovarian cancer management and provide additional survival benefits for patients.

Veliparib

The phase III VELIA trial was designed to evaluate the efficacy and safety of veliparib combined with first-line platinum-based chemotherapy followed by veliparib maintenance, as well as veliparib combined with chemotherapy without subsequent maintenance, compared with chemotherapy alone in patients with newly diagnosed advanced high-grade serous ovarian cancer, as shown in Table 4.¹⁰⁸ The veliparib-throughout group demonstrated a significant prolongation of PFS. In subgroup analyses, median PFS was 34.7 versus 22.0 months in patients with *BRCA* mutations (HR = 0.44) and 31.9 versus 20.5 months in the *HRD*(+) population (HR = 0.57).¹⁰⁸ The most common grade ≥ 3 adverse events included anemia, thrombocytopenia, and gastrointestinal toxicity, particularly during the combination chemotherapy phase.¹⁰⁸ Notably, veliparib administered only during the induction phase without maintenance did not result in significant clinical benefit. The VELIA trial established the clinical relevance of veliparib in the first-line treatment of advanced ovarian cancer and confirmed the significant benefit of integrating PARP inhibition with chemotherapy followed by maintenance therapy.¹⁰⁸ Although veliparib has not yet received FDA approval for ovarian cancer, the study provides important reference evidence for clinical practice and lays the foundation for subsequent combination treatment strategies.

Antibody–Drug Conjugates(ADCs)

Structure and Mechanisms of Action of ADCs

Antibody–drug conjugates (ADCs) typically consist of three components: a monoclonal antibody (mAb) that specifically recognizes and binds to a tumor-associated antigen on the surface of cancer cells; a stable yet cleavable linker; and a cytotoxic payload, which represents the active drug moiety.^{109,110} The mechanism of action involves several key steps. First, the antibody component recognizes and binds to a specific antigen expressed on the cancer cell surface. The entire conjugate is then internalized via endocytosis. Within the cell, the linker is cleaved through enzymatic degradation or intracellular environmental changes. The released cytotoxic payload exerts its effect by damaging DNA or disrupting microtubule function, thereby inducing cancer cell death.^{111,112} Given tumor heterogeneity, not all cancer cells uniformly express the target antigen. Certain payloads possess membrane-permeable properties that allow diffusion into neighboring cells independent of antigen expression. Additionally, after apoptosis of target cells, cytotoxic metabolites and lysosomal enzymes may be released into the tumor microenvironment, affecting adjacent antigen-negative cells—a phenomenon known as the “bystander effect”.¹¹³

Although ADCs are designed for targeted delivery, they may still induce toxicities similar to conventional chemotherapy. This is partly because only a fraction of administered ADC reaches the intended target, and premature linker cleavage may release payload into systemic circulation, exposing normal tissues.¹¹⁴ ADC-related toxicities are generally categorized as on-target toxicity, which occurs when ADC binds to the intended antigen expressed on normal tissues, and

off-target toxicity, which arises from nonspecific binding, passive diffusion, or nonselective internalization by healthy cells.^{115,116} Consequently, ADCs may be associated with characteristic adverse events, including hemorrhage, stomatitis, ocular toxicity, and interstitial lung disease. Toxicity may originate from any individual ADC component and may involve immune activation in non-target tissues, premature linker degradation, or nonspecific cellular uptake.¹¹⁵

Mechanisms of Resistance to ADCs

Resistance to ADCs may arise through multiple mechanisms: I.Alterations in target antigen expression: Downregulation, loss, or mutation of the target antigen can impair ADC binding and recognition. Mutations in the target gene may alter antigen structure or function, reducing binding affinity.^{117,118} II.Abnormal internalization and trafficking: Dysregulation or dysfunction of endocytic proteins may impair ADC internalization. Enhanced lysosomal stability or altered lysosomal microenvironment may prevent effective payload release, leading to resistance.^{117,119} III.Drug metabolism and efflux: Overexpression of drug efflux transporters can reduce intracellular concentrations of ADC payloads, thereby diminishing cytotoxic efficacy.¹¹⁷ IV.Aberrant activation of signaling pathways: Activation of survival pathways such as PI3K/Akt/mTOR promotes tumor cell proliferation and survival, conferring resistance to ADC-induced cytotoxicity. Similarly, dysregulation of JAK/STAT signaling, including STAT3 activation, may contribute to resistance by modulating cell cycle progression and apoptosis.¹²⁰

Phase III Clinical Studies of ADCs

In recent years, ADCs have advanced rapidly in advanced ovarian cancer, particularly demonstrating meaningful breakthroughs in the PROC population, which represents a major therapeutic challenge.¹²¹ Folate receptor alpha (FR α)-targeted ADCs are currently among the most clinically mature ADC strategies and are expanding into broader patient populations and multiple treatment settings.¹²² In addition, novel targets such as CDH6 are entering pivotal stages of clinical development, as shown in Table 5.¹²³ FR α is a transmembrane glycoprotein that binds folate and its derivatives with high affinity and regulates cell proliferation and tissue growth through folate-mediated metabolic pathways. High FR α expression is observed in approximately 80% of primary and recurrent epithelial ovarian cancers, whereas its

Table 5 Progress of Phase III Clinical Research of ADCs in OC

Clinical Trial	Patient Population	Experimental Arm	Control Arm	Result (mo) INV vs STD	HR	P
FORWARD I 2-arm trial	FR α -positive patients with 1–3 prior lines of therapy	MIRV 6mg/kg ivgtt q3w	ddPTX /PLD/TPT	PFS: ITT: 4.1 vs 4.4 High FR α :4.8 vs 3.3	0.98 0.69	0.897 0.049
MIRASOL 2-arm trial	PSROC/FTCe/PPC; 1–3 prior systemic regimens; ADC-naïve	MIRV 6mg/kg ivgtt q3w	ddPTX /PLD/TPT	PFS: 5.62 vs 3.98 OS: 16.46 vs 12.75	0.65 0.67	<0.001 0.005
GLORIOSA 2-arm trial	PSROC/FTC/PPC; no PD after second-line platinum + Bev; ADC-naïve	MIRV 6mg/kg +Bev 15mg/kg	Bev 15mg/kg	NA	NA	NA
REFRaME-OI 2-arm trial	PRROC/FTC/PPC; 1–3 prior systemic regimens including bevacizumab	Luvelta 5.2 mg/kg (cycles 1–2).4.3 mg/kg (cycles 3) q3w	Luvelta4.3mg/kg (all cycles) q3w	NA	NA	NA
RAINFOL 2-arm trial	PRROC/FTC/PPC	Rina-S 120 mg/m ² q3w	PLD/TPT/GEM/ ddPTX	NA	NA	NA
MORAb-003 3-arm trial	PSROC/FTC/PPC	1.CP+FAR 2.5 mg/kg 2.CP+FAR 1.25 mg/kg	CP+Pbo	PFS:1 vs 3: 9.7 vs 9.0 PFS:2 vs 3: 9.5 vs 9.0	0.86 0.99	>0.050 >0.050
REJOICE-Ovarian OI 2-arm trial	PRROC or endometrioid OC, PPC, or FTC	R-DXd 5.6 mg/kg	PLD/TPT/GEM/ ddPTX	NA	NA	NA
ROSELLA 2-arm trial	PRROC or endometrioid OC, PPC, or FTC; prior Bev therapy	REL 150mg po +nab-PTX ivgtt	Nab-PTX ivgtt	PFS: 6.54 vs 5.52 OS:15.97 vs 11.5	0.70 0.69	0.008 0.012
SCORES 2-arm trial	PRROC, FTC, or PPC	PLD/TPT/ddPTX +SUV 5mg/kg	PLD/TPT/ddPTX	PFS: 5.5 vs 2.7 OS: 15.3 vs 14.0	0.46 0.77	<0.001 0.030
Olvi-Vec 2-arm trial	Platinum-refractory or platinum-resistant EOC, FTC, or PPC	GL-ONCI intraperitoneal infusion $\times$ 2 + platinum-based chemotherapy $\pm$ Bev	Platinum-based chemotherapy $\pm$ Bev	NA	NA	NA

Abbreviations: MIRV, Mirvetuximab Soravtansine; Luvelta, Luveltamab; Tazevibulin; Rina-S, Rinatubart Sesutecan; FAR, Farletuzumab; R-DXd, Raludotatug Deruxtecan; REL, Relacorilant; nab-PTX, nanoparticle albumin-bound paclitaxel; SUV, Suvemcitug; GL-ONCI, olvimulogene nanivacirepvec; $\rightarrow$: Indicates a shift in treatment strategies; NA: Not Available.

expression in normal tissues is limited.^{124,125} Therefore, FR α is considered an ideal biomarker and therapeutic target in EOC.

Mirvetuximab soravtansine (MIRV) is the first approved FR α -targeted ADC. It consists of an anti-FR α monoclonal antibody, a cleavable linker, and the microtubule inhibitor DM4 as its cytotoxic payload. Upon binding to FR α , MIRV is internalized and releases active metabolites within lysosomes, inducing cell cycle arrest and apoptosis. The released metabolites may diffuse into neighboring cells, generating a bystander effect that enhances overall antitumor activity.¹²⁶

Key phase III clinical studies include FORWARD I, which compared MIRV with investigator's choice chemotherapy in FR α -positive PROC patients (1–3 prior lines). Although no significant difference in PFS was observed in the overall population, MIRV demonstrated higher ORR, prolonged PFS, and lower rates of grade ≥ 3 adverse events and treatment discontinuation in the FR α -high subgroup, indicating that efficacy is highly dependent on FR α expression levels.^{127,128} MIRASOL, conducted in FR α -high PROC patients (≤ 3 prior lines), demonstrated that MIRV significantly improved key clinical endpoints compared with chemotherapy and was associated with lower rates of grade ≥ 3 adverse events and treatment discontinuation.¹²⁸ This study provided stronger evidence supporting MIRV as a standard treatment option in FR α -high PROC.¹²⁸ GLORIOSA, an ongoing study evaluating MIRV plus bevacizumab versus bevacizumab monotherapy as maintenance therapy in platinum-sensitive recurrent ovarian cancer; primary endpoint results are expected in 2027.¹²⁹

Luveltamab tazevibulin (STRO-002) has been optimized in terms of antibody affinity, linker stability, and microtubule inhibitor payload to enhance intratumoral drug release and reduce efflux-related resistance.¹³⁰ The ongoing phase II/III REFRaME-O1 study is assessing its efficacy and safety across varying levels of FR α expression, with early data demonstrating signals of ORR and DCR and manageable toxicity.¹³¹ Rinatabart sesutecan (Rina-S) is an FR α -targeted ADC conjugated with the topoisomerase I inhibitor exatecan and is applicable across different FR α expression levels. The phase III RAINFOL trial is evaluating the efficacy and safety of Rina-S versus investigator's choice standard chemotherapy in patients with platinum-resistant ovarian cancer, with primary endpoint completion anticipated in 2027.¹³² Arletuzumab (MORAb-003) was the first FR α -targeted monoclonal antibody to enter phase III clinical trials. Although its phase III combination chemotherapy study did not meet the primary endpoint, it provided critical validation of FR α as a therapeutic target and informed patient selection strategies, thereby laying the biological and pharmacological foundation for subsequent FR α -targeted ADC development.¹³³

Cadherin-6 (CDH6) is a cell adhesion protein overexpressed in most epithelial ovarian cancers and associated with poor prognosis. Raludotatug deruxtecan (R-DXd, DS-6000a) is a CDH6-targeted ADC that selectively binds CDH6-overexpressing cells, leading to intracellular release of a topoisomerase I inhibitor and induction of apoptosis.¹²³ The ongoing phase II/III REJOICE-Ovarian01 trial is evaluating R-DXd versus investigator's choice chemotherapy in patients with platinum-resistant high-grade ovarian, peritoneal, or fallopian tube cancer. In the phase III portion, R-DXd is being compared directly with standard chemotherapy, with ORR and PFS as primary endpoints.^{123,134}

Other Targeted Agents and Related Phase III Clinical Trials

Beyond ADCs, several additional therapeutic strategies have emerged in phase III clinical trials for advanced ovarian cancer, warranting attention, as shown in Table 5. The ROSELLA trial, evaluating the glucocorticoid receptor modulator relacorilant in combination with nab-paclitaxel, demonstrated improvements in both OS and PFS compared with nab-paclitaxel alone. These findings suggest that targeting the tumor microenvironment and endocrine stress axis may represent a novel chemosensitization strategy in ovarian cancer.¹³⁵ The Chinese phase III SCORES trial, investigating suvemcitug (a novel anti-angiogenic agent), reported significant improvements in both PFS and OS in an unselected platinum-resistant population, indicating that anti-angiogenic therapy remains a viable and potentially expandable treatment avenue in this challenging setting.¹³⁶ The oncolytic virus Olvi-Vec is being evaluated in a phase III trial assessing intraperitoneal administration of Olvi-Vec followed by platinum-based doublet chemotherapy plus bevacizumab versus chemotherapy plus bevacizumab alone in patients with platinum-resistant or platinum-refractory ovarian cancer. The primary endpoints include PFS and OS. Early signals suggest potential improvements in ORR and PFS; however, mature data are awaited to confirm these findings.^{137,138}

Future Challenges

The treatment of advanced ovarian cancer has evolved from surgery combined with chemotherapy alone to anti-angiogenic therapy, and further developed into a precision therapy paradigm centered on bevacizumab, PARP inhibitors, and ADCs, characterized by multi-mechanism, multi-target synergy, which has significantly improved patient survival outcomes, as shown in Figure 1.

Although the clinical value of bevacizumab in ovarian cancer has been fully confirmed, its application still needs to follow three core principles: I. precise patient stratification based on disease stage, residual disease status, and HRD status to identify those most likely to benefit; II. adherence to the standard 15-month treatment duration, with optimization of chemotherapy backbone and dose density according to patient risk characteristics; III. In the recurrent setting, rational selection of combination regimens and cross-line strategies according to platinum sensitivity and prior treatment history to achieve continuum-based management. In clinical practice, the unique toxicity profile of bevacizumab must be carefully considered. Comprehensive baseline risk assessment prior to treatment and close monitoring during therapy are essential to balance efficacy and safety. Given that bevacizumab resistance arises from coordinated activation of multiple pathways, in-depth elucidation of molecular and microenvironmental resistance mechanisms will provide a theoretical basis for optimizing combination strategies. Future efforts should focus on identifying and validating biomarkers capable of precisely defining high-risk and responsive populations, optimizing individualized combination strategies, and exploring novel agents targeting alternative angiogenic pathways, immune-suppressive microenvironments, and hypoxia-driven malignant phenotypes to overcome resistance and maximize survival benefit.

PARP inhibitors have demonstrated significant clinical value in the treatment of ovarian cancer. While PARPi have demonstrated substantial clinical benefit in ovarian cancer, long-term use is inevitably associated with systemic toxicities, and tumors may develop primary or acquired resistance through diverse molecular and cellular mechanisms. Overcoming resistance requires a deeper understanding of these biological processes to guide the development of more precise therapeutic strategies and improve long-term survival outcomes. These resistance mechanisms not only elucidate the biological basis of diminished PARPi efficacy but also provide a foundation for resistance prediction, biomarker development, and rational combination strategies.

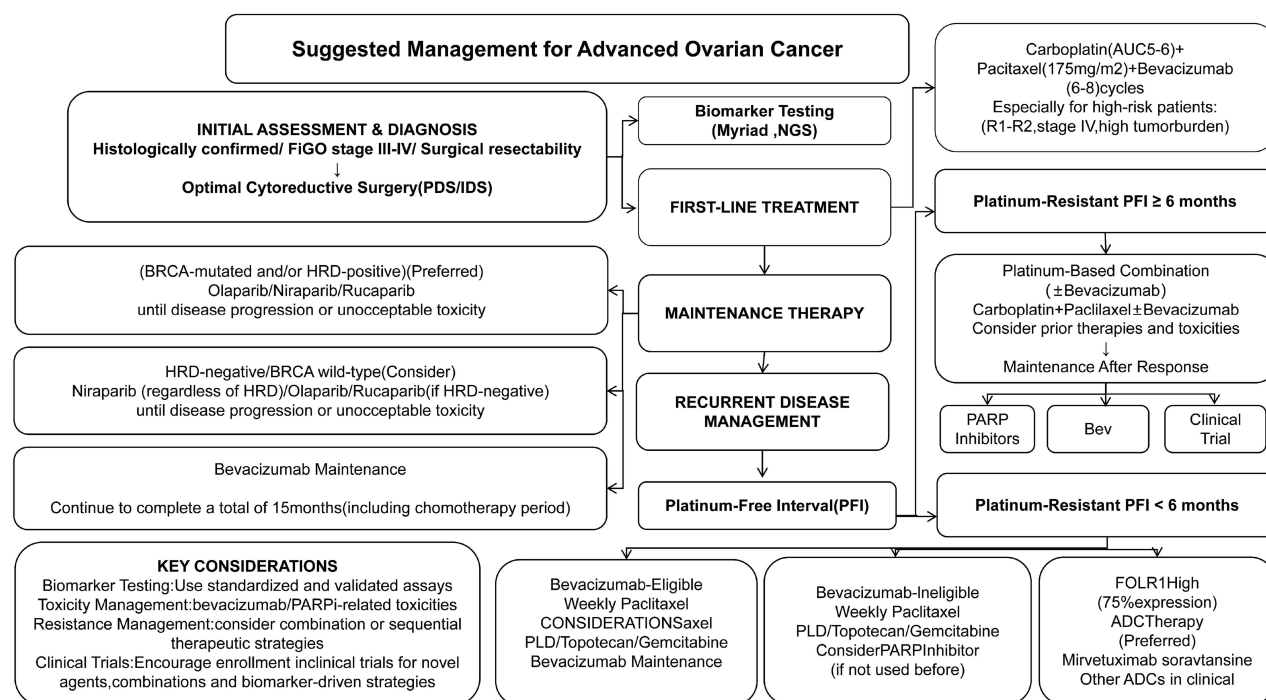


Figure 1 Suggested Management for Advanced Ovarian Cancer.

Overall, phase III evidence has shifted ovarian cancer management from a chemotherapy-dominant model to a maintenance-centered continuum-of-care paradigm. However, dynamic adjustment of late-line indications, as well as complex findings from rechallenge and combination trials, underscore the need for future research focused on more precise predictive biomarkers, resistance stratification, optimization of sequential and combination strategies, and long-term validation of overall survival and quality-of-life outcomes. PARP inhibitors have fundamentally reshaped the therapeutic landscape, expanding from biomarker-selected populations to broader patient groups. Nevertheless, long-term toxicity management, acquired resistance (eg, *BRCA* reversion mutations), and dynamic refinement of indications remain central challenges. Comprehensive dissection of PARPi resistance networks and biomarker-driven patient stratification will be critical to maximizing clinical benefit.

ADCs are reshaping the treatment landscape of advanced ovarian cancer, particularly in patients with high FR α expression and platinum-resistant disease. In the future, a deeper understanding of the molecular mechanisms underlying ADC-related toxicities and resistance will be critical for optimizing antigen selection, linker and payload design, rational combination therapy strategies, and improving patient stratification approaches.

The treatment of ovarian cancer has shifted from the traditional chemotherapy-based model to a continuum-of-care strategy centered on maintenance therapy. Bevacizumab, PARP inhibitors, and antibody-drug conjugates each have distinct clinical application principles and challenges. Future progress will depend on standardized diagnostic testing approaches, such as Myriad, NGS, and other tests, as well as the identification of predictive biomarkers, more refined resistance stratification strategies, and the development of individualized sequential and combination treatment approaches.

Conclusion

Targeted therapy for advanced ovarian cancer has achieved transformative progress, driven by advances in molecular biology and pivotal phase III clinical trials. The gradual establishment of a precision treatment framework centered on anti-angiogenic agents, PARP inhibitors, and antibody-drug conjugates has significantly improved PFS in this patient population, with selected subgroups also deriving OS benefit. Biomarker-driven strategies, particularly those based on *BRCA1/2* mutations and homologous recombination deficiency status, have shifted the therapeutic paradigm from a chemotherapy-dominant approach to one characterized by precision stratification and continuum-based management. Nevertheless, significant challenges remain, including the complexity of resistance mechanisms, long-term toxicity management, standardization of biomarker testing, and optimization of sequential and combination treatment strategies. Addressing these issues will be critical to further enhancing therapeutic efficacy. Future research should focus on elucidating the biological basis of resistance, refining biomarker-guided patient stratification, and optimizing rational combination strategies to enable dynamic and individualized treatment decision-making. With continued scientific innovation and deeper mechanistic insights, ovarian cancer may increasingly be transformed into a chronically manageable disease, offering patients prolonged survival and improved quality of life.

Disclosure

The authors declare no conflicts of interest in this work.

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