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Review Article

PARP inhibitor maintenance in first-line ovarian cancer therapy: emerging standards and strategies to overcome resistance

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Abstract: Maintenance therapy has become a central component of first-line treatment for advanced epithelial ovarian cancer, and poly(ADP-ribose) polymerase (PARP) inhibitors now occupy a pivotal position in this setting. Their greatest benefit is observed in tumors with BRCA1/2 mutations or broader homologous recombination deficiency (HRD), where synthetic lethality can be therapeutically exploited. However, clinical use of PARP inhibitors in the frontline setting has also raised new questions regarding optimal biomarker selection, treatment duration, combination strategies, long-term safety, and management of disease that recurs after PARP exposure. In this review, we summarize the evidence supporting first-line PARP inhibitor maintenance across biomarker-defined subgroups, with particular emphasis on BRCA-mutated and HRD-positive disease. We then examine emerging strategies designed to extend benefit or overcome resistance, including combinations with anti-angiogenic agents, immune checkpoint inhibitors, and next-generation DNA damage response (DDR) inhibitors. Mechanisms of resistance are discussed in a translational framework that includes restoration of homologous recombination, replication-fork protection, altered PARP1 trapping, and adaptive rewiring of the DDR network. Finally, we outline practical clinical approaches to post-PARP management and highlight future priorities, including dynamic biomarkers, rational sequencing, and more individualized maintenance strategies. Taken together, current evidence supports a biomarker-driven use of frontline PARP maintenance while underscoring the need for resistance-aware treatment planning and more precise integration of combination approaches.

Keywords: PARP inhibitors, first-line maintenance, ovarian cancer, homologous recombination deficiency (HRD), drug resistance

Introduction

Epithelial ovarian cancer remains the deadliest gynecologic malignancy worldwide, largely because most patients are diagnosed with advanced-stage disease and, despite high initial response rates to platinum-based chemotherapy, the majority ultimately experience relapse [1]. Over the past decade, the therapeutic paradigm has shifted from an exclusive emphasis on cytoreductive surgery and cytotoxic chemotherapy toward biologically informed strategies designed to prolong remission and improve long-term disease control. In this context, maintenance therapy has emerged as a rational therapeutic approach aimed at suppressing residual microscopic disease, delaying recurrence, and extending the duration of response after frontline treatment.

One of the key change agents has been the clinical advancement of poly(ADP-ribose) polymerase (PARP) inhibitors [2, 3]. Through inhibition of PARP, the amassing of single-strand breaks in DNA and replication-linked genomic damage ensues, which cannot be accurately replicated in tumors with faulty homologous recombination repair (HRR), especially tumors that have BRCA1/2 mutations [4-6]. This artificial lethal interaction offers the biologic rationale of the pronounced effect of PARP inhibitors in ovarian cancer. Notably, the clinical advantage of PARP blockage is not limited to those with germline or somatic BRCA muta-

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tions, but also to a larger group with homologous recombination deficiency (HRD) [7], and in select contexts, can be seen to appear in a subgroup of homologous recombination-capable tumors as well. First-line, randomized controlled trials have continued to show significant gains in progression-free survival with maintenance using PARP inhibitors, making them a standard in the modern frontline setting and hastening the integration of biomarker-based treatment regimens [8-11].

With the introduction of maintenance using PARP inhibitors in the everyday clinical setting, the field has left the proof-of-concept behind and started the refinement of the therapy. Among the major issues today is how to become more efficient about patient selection using more sophisticated genomic and functional biomarkers; how to determine the appropriate timing to use PARP inhibitors and anti-angiogenic agents or immunotherapeutic modalities; and how to balance long-term disease control with accumulating toxicity, quality-of-life factors, and the practicality of long-term oral therapy. The available trial data also is not straightforward to interpret due to variations in study designs, biomarkers assays, control-arm plans, crossover, and changing standards of care. The greatest clinical and biological limitation has been resistance as the most important. Despite the long-term benefit derived by many patients, a significant number of patients can progress during or following maintenance with PARP inhibitors, and outcomes may be dismal especially when cross-resistance to platinum and other DNA-damaging agents develop. Regulation against resistance occurs through a multifactorial mechanism and encompasses restoration of stalled homologous recombination forks, stabilization of stalled replication forks, decreased PARP trapping, rewiring of DNA damage response signaling, changes in drug availability, and adaptive modifications in the tumor microenvironment. The biology of recurrent ovarian cancer is being redefined with respect to the earlier use of PARP inhibitors during the disease course, and with significant consequences to the sensitivity of subsequent treatment and the design of mechanism-based therapeutic strategies.

This review is a summary of the changing role of PARP inhibitor maintenance in the initial treatment of ovarian cancer and is a critical evaluation of the translational and clinical evidence used to inform patient selection, duration of treatment and combination therapies. We cover existing concepts of PARP inhibitor resistance, and connect them to translatable therapeutic prospects, such as combining DNA damage response pathways, including ATR, WEE1, and CHK1, replication stress regulation, epigenetic reprogramming, as well as the combination of anti-angiogenic and immune-based therapies. We hope to offer a framework of clinical relevance and proactivity in optimizing the value of PARP inhibitor maintenance, and responding to the resistance mechanisms that are increasingly becoming a hallmark of the next generation of frontline ovarian cancer treatment with the connection of evidence at the trial level to the emerging molecular understanding.

Biological rationale for first-line PARP maintenance

Clinical incorporation of PARP inhibitors into first-line therapy of ovarian cancer is based on a biologically plausible hypothesis: tumors with impaired homologous recombination (HR) rely disproportionately on repair of DNA damage by PARP, and are susceptible to pharmacologic PARP inhibition. This weakness is especially pertinent in high grade ovarian cancer, where breakages in DNA damage reaction pathways are widespread and may frequently emerge at an initial period of tumor development. In the first-line environment, it is not just the extension of platinum sensitivity to maintenance with PARP inhibitors, but an effort to manipulate residual genomic instability at the time when tumor burden is minimal, clonal complexity is relatively limited, and therapeutic pressure can still translate initial vulnerability to sustained disease control [12-14]. On this basis, the case of frontline PARP maintenance lies in four concepts that are interrelated: synthetic lethality of disease with HR deficiency, pharmacologic differences between the PARP inhibitors, the predictive but less than perfect nature of BRCA and HRD biomarkers and the biological benefits of introducing a PARP inhibitor earlier versus later in the disease course (**Table 1**).

Synthetic lethality and homologous recombination deficiency

Synthetic lethality is the key biological assumption of the action of PARP inhibitors. PARP1 and

Table 1. Biomarker-defined subgroups and current standards for first-line PARP inhibitor maintenance in advanced ovarian cancer

Biomarker-defined subgroup	Molecular definition & preferred testing	Recommended PARP-based maintenance after response to first-line platinum	Pivotal front-line trials/ evidence (maintenance setting)	Regulatory/guideline positioning (conceptual)	Clinical priority of PARP maintenance	Key decision modifiers, competing options, and resistance/sequencing considerations
BRCA-mutated (germline or somatic) high-grade serous/ high-grade endometrioid	Pathogenic or likely pathogenic BRCA1/2 variant detected by germline (blood/ saliva) and/or somatic (tumor tissue or ctDNA) testing; next-generation sequencing (NGS) panels preferred to capture co-mutations and broader HRR context.	Olaparib monotherapy for up to 2 yrs (or until progression/ unacceptable toxicity) is the reference standard; other approved PARP inhibitors may be considered per regional label and individual tolerance.	SOLO-1 (olaparib vs placebo) establishing profound and durable PFS benefit in newly diagnosed advanced BRCA-mutated patients responding to platinum; supportive data from all-comer/BRCA-stratified studies (e.g., PRIMA, PAOLA-1 subgroup analyses).	Widely considered standard-of-care first-line maintenance where available; reflected as a high-strength recommendation in contemporary guidelines. Regulatory labels in most regions explicitly endorse first-line maintenance in BRCA-mutated disease.	Highest priority group for PARP maintenance; PARP is the default strategy barring contraindications.	PARP maintenance is favored over bevacizumab alone in the absence of strong anti-VEGF indications. Counseling emphasizes high probability of prolonged first remission and delayed need for second-line chemotherapy. At the same time, clinicians must anticipate that progression on frontline PARP may diminish subsequent platinum sensitivity and constrain later PARP rechallenge strategies, making early resistance profiling and thoughtful sequencing (e.g., consideration of non-cross-resistant combinations or clinical trials at first relapse) particularly important.
HRD-positive, BRCA-wild-type	BRCA-wild-type tumors with genomic instability meeting HRD assay cut-off (e.g., genomic instability score above validated threshold, LOH-based or composite HRD scores); NGS-based assays increasingly preferred to align with trial-defined HRD algorithms.	Two principal strategies: (1) Olaparib + bevacizumab maintenance for patients treated with bevacizumab-containing platinum-taxane induction (PAOLA-1 pathway); (2) PARP inhibitor monotherapy (e.g., niraparib, olaparib depending on label) when bevacizumab was not used upfront or is contraindicated.	PAOLA-1 (olaparib + bevacizumab vs bevacizumab alone) demonstrating substantial PFS benefit confined to HRD-positive tumors; PRIMA and other trials showing meaningful but more variable PFS benefit with PARP monotherapy in HRD-positive/ BRCA-wild-type disease.	In most guidelines, HRD-positive/BRCA-wild-type disease carries a strong recommendation for PARP-based maintenance. Where bevacizumab was given upfront, combination olaparib + bevacizumab is often the preferred, evidence-aligned regimen; where bevacizumab was not used, PARP monotherapy is endorsed.	High priority group, second only to BRCA-mutated disease in terms of expected magnitude of benefit.	Decision-making weighs incremental benefit of combination therapy against increased toxicity, cost, and logistics. Anti-VEGF toxicities (hypertension, proteinuria, thromboembolism) and patient comorbidities may steer choices toward monotherapy. In HRD-positive tumors, strong DNA-damage selective pressure with prolonged PARP ± bevacizumab should prompt early planning for resistance mechanisms (e.g., BRCA reversion, restoration of HR proficiency, drug efflux), including potential integration of novel combinations (e.g., PARP + ATR/CHK1/PI3K inhibition) in subsequent lines and strategic timing of reintroduction of platinum.

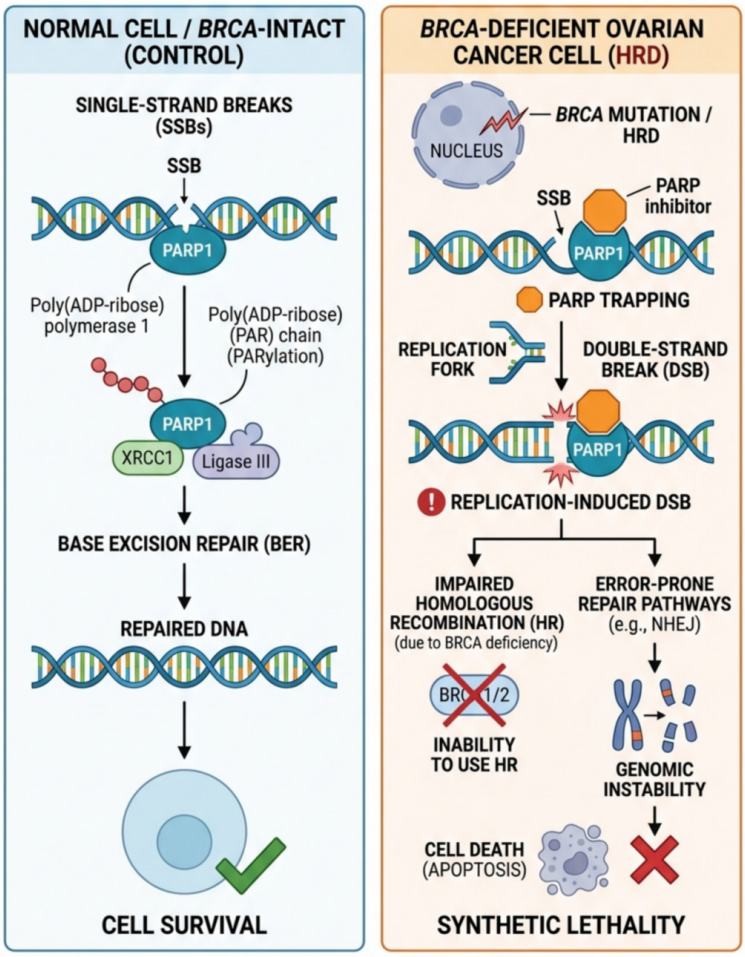

Figure 1. Mechanism of PARP inhibitor (PARPi) therapy in ovarian cancer. In BRCA-intact cells (left), PARP1 detects single-strand breaks (SSBs) and promotes poly(ADP-ribose) (PAR) chain formation, thereby recruiting base excision repair machinery, including XRCC1 and DNA ligase III, to restore DNA integrity and maintain cell survival. In contrast, in BRCA-deficient or homologous recombination-deficient (HRD) ovarian cancer cells (right), pharmacologic PARP inhibition not only suppresses PARylation but also traps PARP1 on damaged DNA, leading to replication fork stalling and the conversion of unrepaired SSBs into replication-associated double-strand breaks (DSBs). Because BRCA1/2-dependent homologous recombination is impaired, these lesions cannot be accurately repaired and are instead processed through error-prone pathways such as non-homologous end joining (NHEJ), resulting in genomic instability, mitotic catastrophe, and ultimately tumor cell death. This synthetic lethal interaction provides the mechanistic foundation for PARP inhibitor maintenance therapy in first-line ovarian cancer.

PARP2 are essential factors in the single-strand DNA break repair, base excision repair, and replication fork surveillance [15]. Unrepaired lesions in single strands pile up and are transformed into a break of two strands during replication when the PARP activity is inhibited. These lesions are precisely repaired in normal cells by a high-fidelity process called homologous recombination that is regulated by BRCA1, BRCA2, RAD51, PALB2, and other DNA damage response factors. In contrast, in tumors that lack HR (HRD), the repair pathway is dysfunctional, and repair of lesions requires the use of error-prone backup pathways, like non-homologous end joining or microhomology-mediated repair [16, 17]. The outcome is disastrous genomic damage, mitotic failure and cell death.

This model is particularly applicable in epithelial ovarian cancer especially in high-grade serous ovarian carcinoma that is particularly enriched with genomic instability and often with changes in genes related to the HR. The best molecular context to understand PARP sensitivity is germline or somatic BRCA1/2 mutations, although HRD is not limited to BRCA but is a more general functional condition of an impaired ability to repair the double-strand break. Notably, the biological connection between platinum sensitivity and sensitivity to PARP inhibitors is based on such a common reliance on faulty homologous recombination. Platinum agents cause crosslinks of DNA and damage to both strands that preferentially kill cells that have lost HR; PARP inhibitors take advantage of this repair defect via a mechanistically distinct yet biologically convergent pathway [18]. This overlap is useful in clarifying why the concept of platinum responsiveness has in the past historically benefited a PARP, but also highlights why PARP inhibitors cannot be construed as simply a continuation therapy, but instead as a directed exploitation of a particular DNA repair defect (**Figure 1**).

PARP trapping versus catalytic inhibition

The biological action of PARP inhibitors cannot be simplified to mere enzyme blocking, despite

there being often a tendency to talk about them as a group. Besides suppressing the catalytic activity of PARP and preventing the formation of poly(ADP-ribose) chains, these agents also have the potential to trap PARP proteins to damaged DNA, thus forming highly toxic protein-DNA complexes that block the advancement of replication forks and increases the replication stress. This has been known as PARP trapping, and is now considered to be one of the significant determinants of antitumor potency. The relative trapping potency of PARP inhibitors varies, and relative to other pharmacologic differences, these pharmacologic differences can cause variations in efficacy and toxicity profiles, although cross-trial comparisons are inherently limited. Mechanistically, more potent PARP trapping can augment the cytotoxicity of HR-deficient tumor cells by amplifying effects of replication-related DNA damage, but it can also cause hematologic toxicity by impacting rapidly growing normal tissues [19-22].

This distinction is important in terms of conceptualization when it comes to first-line maintenance. Maintenance therapy is used during the long periods of the patient who has already reacted to the platinum-based chemotherapy, and can still survive months or years. Within this context, the biological endpoint is not acute tumor debulking but durable remnants disease suppression. Therefore, the efficacy of frontline PARP therapy is not only whether a given drug can cause lethal damage to vulnerable clones, but also whether this pressure can be sustained to delay growth without causing cumulative toxicity which is prohibitive. The clinical logic of maintenance intersects itself directly with the biology of PARP trapping.

Biomarker and treatment-timing considerations for first-line PARP maintenance

BRCA mutation, HRD, and the limits of current biomarkers

BRCA1 and BRCA2 mutations are the most powerful predictors of the benefit of PARP inhibitors, both biologically and clinically. Their applications are simple BRCA proteins play a central role in homologous recombination, and BRCA loss produces a condition of extreme dependency on HR that predisposes tumor cells to PARP inhibition [23-25]. BRCA-non-complicated tumors also have significant shares of genomic alterations typical of HRD, such as loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions. These findings were used to design assays of HRD that are aimed at identifying a broader population that could be responding positively to the PARP-based approaches. However, HRD as a biomarker is not a perfect one at the moment. The vast majority of available assays are sensitive to some form of genomic scar, i.e., the historical impact of a failed homologous recombination, as opposed to an immediate functional value of the current DNA repair capacity [26]. Even with partial reinstatement of HR proficiency, such as via BRCA reversion mutations or compensatory rewiring of DNA damage response pathways, a tumor can still have a genomic scar [27, 28]. Conversely, some tumors without a high HRD score may still harbor context-dependent vulnerabilities to PARP inhibition that are not adequately captured by current tests. In addition, HRD-positive, BRCA-wild-type tumors likely represent a biologically heterogeneous group rather than a single therapeutic entity, which may help explain why their magnitude of benefit is generally less consistent than that observed in BRCA-mutated disease.

For frontline decision-making, BRCA mutation and HRD status remain indispensable, but they should not be interpreted as absolute or biologically static categories. Rather, they function as probability-enriching tools that improve selection for PARP benefit while leaving important uncertainty at the individual-patient level. This limitation becomes even more consequential once PARP inhibitors are used early in the disease course, because baseline biomarkers may progressively lose explanatory power after treatment-induced clonal selection. Thus, the current biomarker framework is sufficient to guide present-day practice, but it is unlikely to remain adequate for resistance-aware precision therapy.

Why first-line exposure matters biologically more than late-line exposure

The biological rationale for using PARP inhibitors in the first-line setting is stronger than a simple “earlier is better” argument. Ovarian cancer responded to platinum chemotherapy

with newly diagnosed disease presents a unique treatment window with minimal residual disease and clones responding to therapy already enriched by therapy and resistant subclones may not dominate the tumor ecosystem yet. By initiating PARP inhibition at this point, the cells can maintain a long-term selective pressure between the residual HR-deficient cells and normal cells, protecting them before recurring relapse-treatment regimens initiate the development of clonal diversification, an adaptation to the microenvironment, and a more widespread resistance to DNA-damaging therapy [29].

Recurring tumors are also likely to have increased intratumoral heterogeneity, increased replication stress tolerance, and increased rewiring of repair programs, and prior exposure to platinum, which has resulted in cumulative selection pressure [30, 31]. These features have the capacity to dampen PARP sensitivity even in case the original tumor had a defect in the HR. Conversely, frontline maintenance might choose to exploit a less evolutionarily sophisticated disease condition, possibly extending first remission and postponing the development of a resistant population. This theory can be used to elucidate why first-line maintenance has proven to be the most sustaining advantage of PARP inhibitors, especially in BRCA-mutated cancer.

Frontline therapy can prefer the emergence of clones with repaired homologous recombination, replication fork protection, or altered PARP1 binding, or other escape mechanisms by subjecting a clone to PARP-selective pressure at the start of systemic management. That is, it is the biological benefits of first-line PARP maintenance that make it specifically effective, namely, that it is the time of maximum vulnerability that is targeted, yet it is also the early pressure that can redefine the biology of relapse [32-34]. This is the duality of the new era of PARP: it provides the highest chance of achieving long-term control, but it also makes resistance the late-line complication a characteristic of future disease treatment.

Taken together, these biology considerations underlie the reason why maintenance with PARP inhibitors has emerged as a major trend in the initial treatment of ovarian cancer. The therapeutic rationale is most compelling when there is a lack of HR, as best exemplified by BRCA-mutated tumours, but the generalisability of PARP inhibition to a broader range of DNA repair vulnerabilities. Simultaneously, various pharmacological characteristics of drugs, the imperfectness of the existing biomarkers, and the evolutionary implications of early exposure to drugs all influence both the potential and the constraints of this method. These concerns furnish the biological basis of modern-day frontline maintenance approaches and form the new clinical dilemma of the optimal means of preventing, interpreting and overcoming PARP inhibitor resistance.

The challenge of resistance: mechanisms

Maintenance with PARP inhibitors has been demonstrated to be more effective in the first-line, and has inevitably introduced the resistance as a characteristic of the maintenance effort to contain the disease in the long term. Clinically, resistance can occur along a continuum with the onset in the early stages of progression of the maintenance or soon after its initiation, to late relapse after many years of therapy-free disease control, with patterns that become more influential on therapy choices in the future [44]. With PARP-inhibitors having the opportunity to gain successful use in an earlier place within the treatment algorithm, a substantial number of patients are now having their first occurrence of a relapse within a PARP-exposed, frequently platinum-pretreated setting, and rapidly growing evidence indicates that the pathology of post-PARP relapse is significantly different than that of PARP-naive disease. Two related questions have been associated with this change: how do tumors circumvent PARP induced synthetic lethality, and how this resistance affects cross-sensitivity to platinum, follow-up PARP re-challenge, and rational combination plans?

On the molecular level, PARP inhibition resistance is heterogeneous but recalled conceptually according to restoration or circumvention of homologous recombination (HR) deficiency, protection of replication forks at stalling, and damping of effective PARP trapping [45]. Genetic restoration of HR by reversion mutation in BRCA1/2 or other genes that involve HR is one of the most defined. Secondary frameshift-correcting events, intragenic deletions or

splice changes, which restore an open reading frame and, at minimum part, BRCA activity, have also been reported in multiple translational studies in high-grade serous ovarian cancer to re-establish error-free HR and abrogated synthetic lethality [46, 47]. Such reversions have been found in tumor tissue, ascites, and soluble tumor DNA of patients relapsing on PARP inhibitors and often correlate with acquired resistance to both PARP inhibitors and platinum which highlights the common reliance of these classes of agents on HR deficiency. Mechanistically, this class of resistance is particularly important because PARP inhibitor sensitivity in BRCA1/2-deficient tumors depends not simply on the presence of genomic scars, but on persistent inability to complete high-fidelity RAD51-dependent DNA repair at collapsed replication forks. Once even partial HR function is restored, the cell can reroute double-strand break repair away from error-prone pathways, reduce unrepaired fork-associated lesions, and thereby escape the synthetic lethal interaction on which PARP inhibition depends. This also explains why BRCA reversions often confer cross-resistance to platinum: both drug classes exploit the same core defect in homologous recombination, albeit through different proximal forms of DNA damage.

Other than traditional reversions, epigenetic reprogramming can as well re-establish HR capacity. As an illustration, a typical pathway of HRD in high-grade serous ovarian cancer is BRCA1 promoter hypermethylation [48]; demethylation due to therapeutic pressure can restore BRCA1 expression and re-establish HR, which is resistant to PARP inhibition without altering the original genomic architecture. Similar effects have been reported of other HR-related genes like RAD51C/D. Concurrently, proteomic changes in proteins regulating DNA end resection and RAD51 loading (e.g., loss of 53BP1, REV7 or shieldin complex components) can tip the balance between non-homologous end-joining and HR, reinstalling the BRCAness that originally predisposed tumors to PARP inhibition. This is important clinically because it is now clear that HRD is not fixed; when tumors are subjected to the selective pressure of long term maintenance therapy they can dynamically re-arrange their repair potential, in many cases in a manner that itself contributes to platinum resistance. Biologically, these alterations all lead to the same ultimate destination, namely, the regaining of the DNA end resection competence and more effective RAD51 filament assembly. Thus, resistance can emerge even without canonical BRCA reversion if tumor cells regain enough HR functionality to survive replication-associated DNA damage. This is an important conceptual point for clinical interpretation, because a tumor may remain “HRD-positive” by historical genomic scar assays while no longer being functionally HR-deficient at the time of relapse.

It has been demonstrated in preclinical models that the initial effect of BRCA-deficient cells to exposure of PARP inhibitor or platinum is extensive fork degradation by nucleases including MRE11 and DNA2 [49, 50]; but subsequent changes, including loss of PTIP or CHD4, or expression of FANCD2 can stabilize stalled forks, which in turn enables the cells to survive replication stress despite ongoing HR defects. Here, the tumors are genomically HRD using traditional assays but functionally resistant to PARP trapping indicating a critical weakness of a static HRD score to predict post-exposure sensitivity. Clinically, this could perhaps be why not all patients with progressive signs of HRD (such as large genomic-instability scores) undergo early progression on PARP maintenance and fail respond to PARP re-challenge post-relapse. The given fork protection phenotype is worth highlighting since it is a mechanistically different path to resistance: tumor cells do not repair lethal fork collapse, but instead they do not allow it to take place. Within this environment, nucleolytic degradation is regulated, replication stress is buffered and the cells can survive PARP inhibition while maintaining numerous genomic hallmarks of previous HR deficiency. Consequently, fork stability can represent a functional resistance stratum that cannot be detected by most base biomarker assessment strategies and might be particularly appropriate in tumours that otherwise seem molecularly HRD, but demonstrate relative benefit through the unexpected maintenance by PARP.

Third category of resistance involves alterations that maintain the activity of PARP trapping or drug target engagement. They are mutations in PARP1 itself that disrupt binding to

DNA and leave the enzyme active, alterations in drug efflux transporters that lower intracellular levels of PARP inhibitors, and deregulation of other DDR pathways (e.g., loss of SLFN11) that blunt replication catastrophe [51]. Interestingly, recent cases of PARP1 mutations in long-term PARP treatment patients raise questions that in some cases, resistance can be closely tied to the binding mode of the particular agent, as well as the possibility of switching to other PARP1-selective agents or to next-generation agents. Mechanistically, this group particularly applies to the influence of the cytotoxic effect of PARP inhibitors since catalytic inhibition of PARylation is not the only mechanism that leads to toxic PARP-DNA complexes and amplification of replication-associated lesions. Hence, any other change that promotes PARP1 trapping, decreases effective intracellular drug exposure, or catastrophe of downstream replication can significantly decrease drug efficacy in spite of the continued presence of HR deficiency. This framework could be used to understand why certain resistant tumors do not exhibit apparent restoration of HR, but still become clinically unresponsive to further treatment with PARP (**Figure 2**).

These biological processes are converted into intricate clinical patterns of resistance. Retrospective series and real world cohorts indicate that patients that relapse on or soon after the practice of maintaining PARP inhibitors commonly have diminished reactions to subsequent platinum-based chemotherapy especially when resistance is caused by HR restoration through BRCA reversion [52-55]. Conversely, patients whose duration of PARP-free increase and show no trace of restoration of HR might not have all cases of PARP-resistant disease being equal and the same, implying that not all the cases of PARP-resistant disease are platinum-refractory. This heterogeneity would also become more and more applicable when oncologists seek to understand progression-free survival on PARP maintenance in the context of post-progression options and overall survival: even deep and prolonged first remission would still be beneficial despite future cross-resistance, but in the context of biomarker-negative or marginal-benefit, the risk of undermining the efficacy of platinum in the future would be worrisome. A more mechanistic reading of these clinical patterns suggests that the timing of relapse may itself be biologically informative: early progression during maintenance is more consistent with strong functional resistance mechanisms already selected under treatment pressure, whereas later relapse after a prolonged treatment-free interval may reflect partial resistance, subclonal evolution, or re-emergence of disease that remains exploitable by DNA-damaging therapy. For this reason, post-PARP relapse should not be treated as a biologically uniform clinical entity, and future studies should better integrate relapse timing, molecular resistance mechanism, and subsequent treatment sensitivity into the interpretation of survival endpoints.

The issue is further augmented by the existing shortcomings of the indicators of acquired resistance. Routine clinical tools, including germline/somatic BRCA testing and normal levels of HRD, provide the vulnerability of pre-treatment, although they do not indicate dynamic evolutionary changes to therapy. Even when it is a BRCA reversal and other resistance-related changes at progression are detected by next-generation sequencing and circulating tumor DNA profiling, they are not broadly implemented yet, and their application in real-time decisions (i.e., whether to continue platinum rechallenge, switch to non-cross-resistant DDR combinations, or prioritize antibody-drug conjugates) remains under investigation. Furthermore, periodic HRD measurements informed by genomic scars are unable to differentiate between tumors in which HR function or forks are rescued, and an excess to be benefitted through ongoing or repeated PARP-inhibition is overestimated. The key limitation is that most currently available biomarkers are historical rather than functional: they record that a tumor once evolved under HR deficiency, but they do not determine whether that vulnerability is still operative under current treatment selection. This distinction is central in the post-maintenance setting, where resistant clones may preserve genomic scar signatures while having already restored repair competence or replication fork stability. Accordingly, there is a growing need for dynamic biomarkers that can capture real-time HR proficiency, fork protection status, and target engagement at relapse.

New therapeutic perspective PARP resistance developed during the first-line maintenance

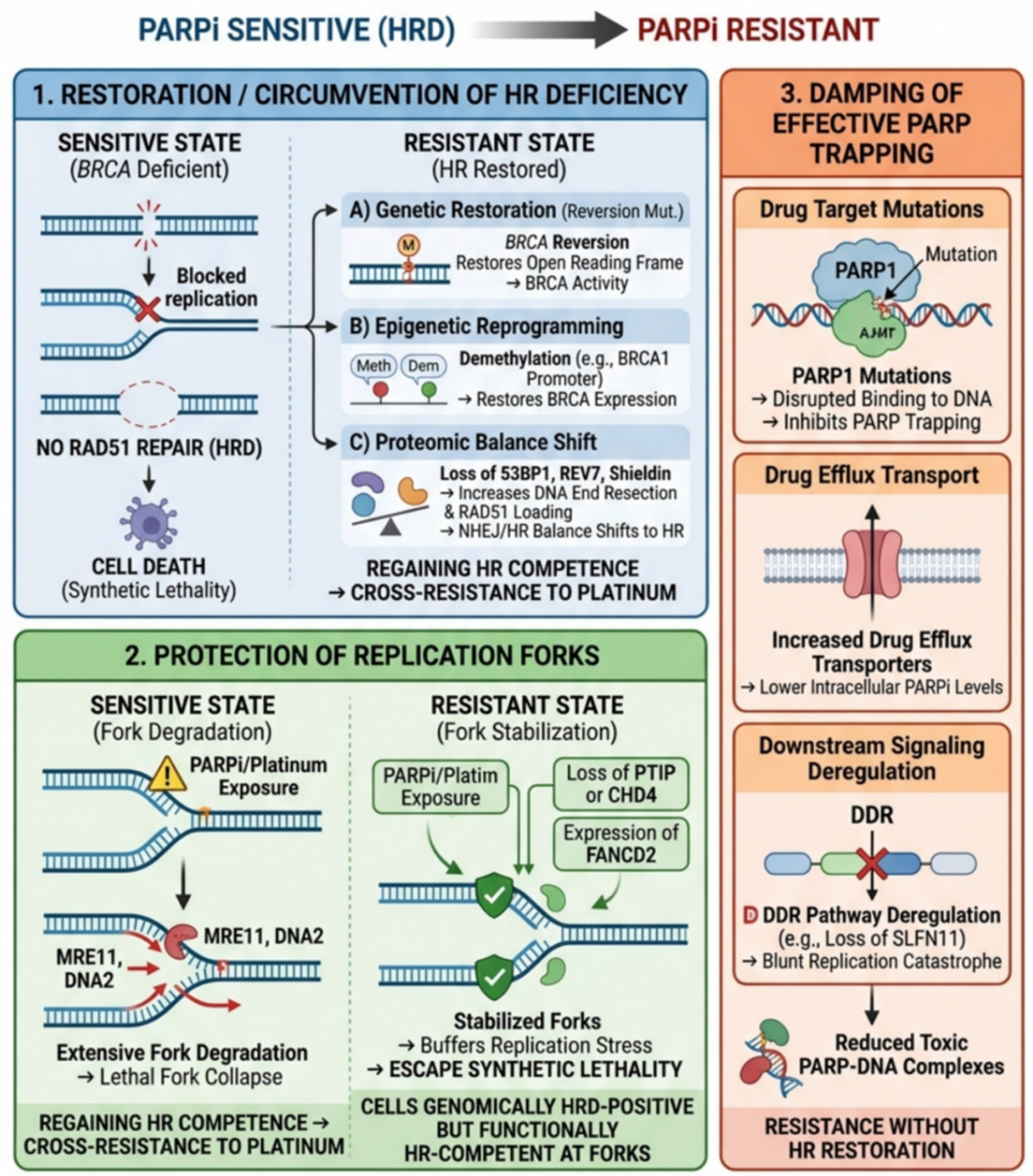

Figure 2. Major mechanisms of acquired resistance to PARP inhibitors in ovarian cancer. This schematic illustrates the transition from a PARP inhibitor (PARPi)-sensitive, homologous recombination-deficient (HRD) state to a PARPi-resistant state under therapeutic selective pressure. Three broad, partially overlapping resistance mechanisms are highlighted. First, resistance may arise through restoration or circumvention of HR deficiency, including BRCA1/2 reversion mutations, epigenetic re-expression of HR-related genes (for example, BRCA1 promoter demethylation), and proteomic alterations that favor DNA end resection and RAD51 loading, thereby re-establishing HR competence and frequently conferring cross-resistance to platinum. Second, resistant cells may preserve viability through replication fork protection, in which suppression of nuclease-mediated fork degradation and compensatory factors such as loss of PTIP or CHD4, or increased FANCD2 activity, stabilize stalled forks and buffer replication stress despite persistent genomic scar features. Third, resistance may develop through attenuation of effective PARP trapping, including PARP1 alterations that impair PARP-DNA complex formation, increased drug efflux that lowers intracellular PARPi exposure, and downstream DNA damage response rewiring that blunts replication catastrophe. Collectively, these adaptive mechanisms explain why post-PARPi relapse is biologically heterogeneous and why resistance may reduce the efficacy of subsequent platinum-based or PARPi-based therapies.

stage requires reexamination of the sequencing and salvage strategies. The classical out-of-cycle-ideas platinum-non-platinum chemotherapy-build-up-and-inter-change and target-agent-or-bevacizumab-sequence are currently under stress-testing in groups whose cancer has already evolved resistance to acute levels of DNA damage and DNA repair inhibition. Initial and small scale trials of combining PARP and ATR, WEE1, or CHK1 inhibitors in PARP-pretreated patients, have proven that certain resistance mechanisms can still be exploited and synthetic lethality can be re-induced in some specific and limited molecular environments. Simultaneously, the danger of overlapping myelosuppression as well as the possibility to further select to highly repair-competent and therapy-refractory clones reflect the issue of cautious patient selection and mechanistically guided trial designs. Mechanistically, these combinations are attractive because they target adaptive dependencies created by PARP resistance itself: ATR and CHK1 blockade can exacerbate replication stress in fork-protected tumors, whereas WEE1 inhibition can force damaged cells through mitotic entry before repair is complete. In other words, the resistant state may create new liabilities, but those liabilities are unlikely to be universal and should ideally be matched to the dominant resistance mechanism in each tumor.

Finally, significant long-term safety and survivorship implications of resistance. Increased incidence of therapy-related myelodysplastic syndrome and acute myeloid leukemia have been associated with prolonged exposure to PARP and especially in patients who are heavily pretreated. Although the absolute risk of the frontline maintenance scenario may be less, the finding that PARP-resistant tumors frequently contain other genomic rearrangements in DDR and chromosomal stability pathways makes the possibility of cumulative genotoxic stress in normal hematopoietic progenitors a concern. The trade-off between seeking as much duration of benefit as possible and the risks of indefinite DDR blockade is thus a primary clinical dilemma, particularly in younger patients with BRCA mutations and a possible long life expectancy. Combined, PARP inhibitor resistance cannot be considered a dichotomous event but a dynamic systems-level response to DNA repair rewiring, replication fork remodelling, target engagement restructuring and treatment-mediated clonal selection. This framing of resistance is more explanatory of the highly heterogeneous nature post-maintenance of the frontline and offers a more robust biological justification to biomarker-informed next-generation sequencing and next-generation combination approaches.

In aggregate, the maintenance of PARP-resistance is not an event, but a multifactorial process of evolution, the definition of the antitumor effect and therapeutic potential in the course of the disease. The interaction between HR restoration, replication fork protection, attenuated trapping of the PARP, and cross-resistance to platinum would be of significance in designing rational trials, in the development of next-generation DDR agents, and in designing algorithms driven by biomarkers that do not prejudice subsequent decisions. It is these that drive new approaches to preclude, postpone or take advantage of resistance; such as combination fronts and adaptive dosing, dynamic biomarker surveillance, that the next section of this review shall examine.

Clinical strategies for managing PARPi resistance

The clinical management of ovarian cancer recurring after first-line PARP inhibitor (PARPi) maintenance should not be reduced to the simple question of whether a patient remains “platinum sensitive”. Once PARPi exposure has been moved into the frontline setting, relapse occurs in a biologically altered disease state, and the central task is to determine what kind of PARPi resistance has emerged, how likely it is to confer cross-resistance to platinum, and whether the tumor remains vulnerable to DNA damage response (DDR)-directed therapy at all. In practice, this means that the first step is not treatment selection, but resistance phenotyping: progression during PARPi, progression shortly after PARPi discontinuation, and relapse after a prolonged treatment-free interval almost certainly represent distinct clinical-biological scenarios. Early progression on maintenance is more consistent with strong, treatment-selected resistance - such as homologous recombination (HR) restoration or effective replication-fork protection - whereas later relapse after a durable first remission may still reflect partial

dependency on DDR vulnerabilities and may preserve therapeutic opportunities not seen in primary refractory disease. Thus, the management of PARPi resistance should be framed as a problem of post-PARPi disease biology, not merely post-maintenance sequencing (**Table 2**).

Historical BRCA or HRD status remains informative, but it is no longer sufficient once the tumor has evolved under sustained PARPi selection pressure. A tumor that was clearly HR-deficient at diagnosis may no longer be functionally HR-deficient at relapse, and in this setting the predictive value of static genomic scar assays is limited. Whenever feasible, repeat molecular assessment - particularly plasma-based sequencing for BRCA reversion and other restoration-associated events - should be incorporated into clinical decision-making. Although such testing is not yet universally standardized in routine practice, its clinical logic is increasingly compelling: it may help identify patients in whom further platinum or PARPi-based strategies are unlikely to succeed, while sparing ineffective re-exposure and redirecting patients earlier toward non-cross-resistant therapies or clinical trials. In other words, management after frontline PARPi should increasingly rely on dynamic biomarkers of residual vulnerability, not only on archival markers of initial sensitivity.

The initial pragmatic choice that many patients can still face is whether platinum rechallenge is still warranted. However, platinum sensitivity remains an issue which should not be viewed in strictly chronological terms. PARPi and platinum share overlapping addictions to HR deficiency, and the possibility of cross-resistance to platinum in case of acquired PARPi resistance is among the clinical implications with the greatest potential impact. Correspondingly, a platinum-sensitive post-PARPi window would not necessarily mean that platinum continues to act as effectively as before in PARPi-naive relapse. However, platinum-based combinations are still suitable in the selected patients and in particular, patients with a long treatment-free interval, no evidence of overt HR restoration and a disease course that indicates incomplete rather than absolute resistance. Platinum doublets which are in most cases supplemented by bevacizumab when medically suitable, can still result in effective disease control in such patients. In comparison, patients who respond to PARPi or relapse shortly after withdrawal should be approached with more caution since calendar-based platinum sensitivity may be an overstated measure of what the actual probability in the context of acquired repair restoration is. This is why the use of post-PARPi platinum needs to be more and more viewed through the prism of biology, rather than through the traditional platinum-free interval.

PARPi rechallenge occupies a narrow but clinically real niche. The OReO/ENGOT-ov38 trial demonstrated that maintenance olaparib rechallenge in patients with platinum-sensitive relapsed ovarian cancer previously treated with a PARPi produced a statistically significant, but clearly modest, progression-free survival benefit over placebo in both BRCA-mutated and non-BRCA cohorts. These data are important less because they establish PARPi retreatment as a new default strategy, and more because they define the conditions under which rechallenge may still be rational. The trial supports a highly selective approach: PARPi rechallenge may be considered in patients who derived substantial prior benefit from PARPi, retained platinum sensitivity, and experienced a sufficiently long PARPi-free interval to make persistent target dependence plausible. It should not, however, be interpreted as evidence that PARPi reuse is broadly effective after frontline failure. In patients with early resistance, rapid relapse, or molecular evidence of HR restoration, PARPi rechallenge is biologically difficult to justify and is unlikely to represent the best use of subsequent treatment time. Thus, the real lesson from OReO is not that “PARPi can be used again”, but that a minority of carefully selected patients may still derive value from PARPi retreatment, whereas most will require a mechanistically distinct strategy.

As cross-resistance is a key issue, non-cross-resistant treatments are gaining more importance following PARPi exposure. Strategies involving Bevacizumab are also pertinent, especially in patients with symptomatic evolution, ascites or vascular manifestations of the disease, due to the independent nature of its activity regardless of the preserved HR deficiency. More to the point, antibody-drug conju-

Table 2. Clinical trials with PARP inhibitors

Agent	Trial (NCT)	Phase	Status/purpose	Clinical setting	Key efficacy results	Relevance to first-line maintenance and resistance
Olaparib	Study 42 (NCT01078662)	II	Historical published proof-of-concept trial	Late-line treatment	ORR 31%; median PFS 7.0 mo; median OS 16.6 mo	Established proof-of-concept for PARP inhibitor monotherapy in BRCA-altered ovarian cancer
Olaparib	Study 19 (NCT00753545)	II	Historical published maintenance trial	Platinum-sensitive recurrent maintenance	Median PFS 8.4 vs 4.8 mo overall; BRCA-mutated subgroup 11.2 vs 4.3 mo	First randomized maintenance signal after platinum response; framed the paradigm later moved into first line
Olaparib	SOLO-2/ENGOT-Ov21 (NCT01874353)	III	Published benchmark recurrent-maintenance trial	Platinum-sensitive recurrent maintenance	Median PFS 19.1 vs 5.5 mo; HR 0.30	Confirmed major benefit in BRCA-mutated disease
Olaparib	SOLO-1 (NCT01844986)	III	Published landmark first-line registration-defining trial	First-line maintenance	Risk of progression/death reduced by 70%; HR 0.30; durable long-term benefit	Established first-line olaparib as a standard in BRCA-mutated disease
Olaparib + bevacizumab	PAOLA-1/ENGOT-ov25 (NCT02477644)	III	Published landmark first-line combination trial	First-line maintenance	ITT median PFS 22.1 vs 16.6 mo; HR 0.59; greatest benefit in HRD-positive tumors	Established the bevacizumab + olaparib option in first-line maintenance, especially for HRD-positive disease
Rucaparib	Study 10 (NCT01482715) + integrated analysis with ARIEL2	I/II	Historical published treatment-development trial	Late-line treatment	Integrated ORR 53.8%; median duration of response 9.2 mo	Supported rucaparib activity as treatment in BRCA-associated ovarian cancer
Rucaparib	ARIEL2 (NCT01891344)	II	Published biomarker-development trial	Recurrent treatment/ biomarker development	Median PFS 12.8 mo in BRCA-mutated, 5.7 mo in LOH-high, 5.2 mo in LOH-low tumors	Helped operationalize genomic scarring/ HRD concepts
Rucaparib	ARIEL3 (NCT01968213)	III	Published registration-defining recurrent-maintenance trial	Platinum-sensitive recurrent maintenance	Median PFS 16.6 vs 5.4 mo in BRCA-mutated; 13.6 vs 5.4 mo in HRD; 10.8 vs 5.4 mo in ITT	Important comparator when discussing whether earlier PARPi exposure may alter later platinum/PARPi sensitivity
Rucaparib	ATHENA-MONO/GOG-3020/ ENGOT-ov45 (NCT03522246)	III	Published first-line trial with long-term follow-up report	First-line maintenance	ITT median PFS 20.2 vs 9.2 mo; HR 0.52; benefit also seen in HRD-defined subgroups	Extends the first-line maintenance concept beyond olaparib- and niraparib-based pathways
Rucaparib	ARIEL4 (NCT02855944)	III	Published comparative treatment trial	Recurrent treatment	Met primary endpoint for investigator-assessed PFS vs chemotherapy; later reports raised concern that PFS gain did not translate into OS benefit	Central to resistance discussion because it complicates interpretation of sequencing benefit
Niraparib	NOVA/ENGOT-OV16 (NCT01847274)	III	Published pivotal recurrent-maintenance trial	Platinum-sensitive recurrent maintenance	Median PFS 21.0 vs 5.5 mo in gBRCA cohort; 12.9 vs 3.8 mo in HRD-positive non-gBRCA cohort	Showed niraparib benefit was not confined to BRCA-mutated disease
Niraparib	QUADRA (NCT02354586)	II	Published late-line salvage trial	Late-line treatment	Clinically meaningful activity, especially in HRD-positive/PARPi-naive platinum-sensitive subsets	Relevant for post-multiple-line activity and biomarker-based salvage use
Niraparib	PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016)	III	Published landmark first-line trial	First-line maintenance	HRD-positive population: median PFS 21.9 vs 10.4 mo, HR 0.43; ITT: 13.8 vs 8.2 mo, HR 0.62	Established first-line niraparib as a broad maintenance option, with greatest benefit in HRD-positive disease

Note: This table summarizes landmark completed and published trials, together with selected follow-up reports, and is not intended as a list of currently ongoing or recruiting studies. For approved PARP inhibitors, the included trials are presented to clarify their role as proof-of-concept studies, registration-defining trials, first-line maintenance-establishing studies, or clinically relevant post-approval evidence for resistance and treatment sequencing.

gates have opened a new therapeutic niche in disease that has received PARPi therapy. Mirvetuximab soravtansine demonstrated a statistically significant and clinically meaningful increase in progression-free survival, overall survival, and objective response rate versus chemotherapy in the phase III MIRASOL trial in FRa-positive platinum-resistant ovarian cancer, which has completely avoided reliance on HR. Particularly in PARPi-resistant disease, where the biologic argument of repeating the point of attack on DNA repair may be poor, this is true. Consequently, planning post-PARPi treatment ought to include early testing of other actionable features, like FRa expression but not delay biologically distinct options until later, more refractory stages. The escalating importance of these agents highlights a key conceptual change, namely that once a tumor has become resistant to PARPi, it might no longer be necessary to seek a more effective PARPi strategy to achieve success, but rather to transition to a different group of mechanisms that will not involve the same damaged-repair phenotype that the tumor has now learned how to avoid.

It is possible that tumors which resist PARPi due to replication-fork stabilization or rewiring of DDR become further reliant on stress tolerance via ATR-, CHK1-, or WEE1-mediated mechanisms. This gives the mechanistic basis to the combination of PARPi with next generation DDR inhibitors, specifically ATR inhibitors. CAPRI and similar trials of olaparib plus ceralasertib have demonstrated that such a combination may induce significant activity in either PARPi-resistant or PARPi-exposed high-grade serous ovarian cancer as an indication of the possibility of resistance to one DDR-directed agent creating sensitivity to another. Yet, these data are to be regarded as evidence-of-principle rather than it is a practice-changing standard. Phase III data to support the notion that ATRPARPi or WEE1PARPi plans can be systematically advised following initial PARPi failure, and overlapping myelosuppression is a functional constraint. In turn, these combinations can be regarded as trial-prioritized strategies, especially in patients whose relapse pattern or molecular profile indicates the fact that replication stress persists, but does not lead to the restoration of HR functionality. That is, these regimens are not most rationally deployed to do empirical salvage in any patient, but rather biomarker-guided treatment of resistant tumors, which continue to be biologically reliant on the DDR buffering pathways.

One of the best methods of dealing with resistance is to avoid breeding it in the first place. This is a strong case to pursue a restrained, biomarker-guided frontline use of PARPi, focusing treatment at the location with the most favorable treatment index, i.e. BRCA-mutated and HRD-positive disease, and not to extend the treatment to other groups with a low expected benefit. It also facilitates careful attention to dose individualization, and management of toxicity, since long-term exposure interspersed with repeated dose adjustments can result in a heterogeneous selective pressure without providing the optimal biological inhibition. Similarly, frontline combination strategies can be construed in part by a resistance-management perspective. The ability of regimens like olaparib together with bevacizumab to already demonstrate deeper and longer initial remission in selected molecular subgroups, specifically the ones HRD-positive, and new triplet strategies aim to delay or remodel the development of resistance clones. However, intensification is not inherently good; it must be based on biological or clinical benefit of the additional elements, and not merely be a waste of future possibilities at an earlier stage of the disease process.

Taken together, the best clinical approach to the issue of PARPi resistance can be thought of as a resistance-aware algorithm on a layered basis. Even patients who have a long history of prior benefit, maintained platinum-sensitivity and no signs of HR restoration can remain eligible to platinum-based therapy, and in some cases, PARPi rechallenge. Early progression, short PARPi-free period, or even repair restoration patients should be redirected to non-cross-resistant treatments, such as bevacizumab-based, FR a-directed antibody-drug conjugate, and biomarker-directed DDR combination trials. In every situation, repeat molecular testing must be used more frequently to inform treatment choices wherever possible and practical. The broader implication is that PARPi resistance should no longer be managed as a late-line complication of maintenance therapy; it should be addressed as a central organizing problem of modern ovarian cancer care. In this

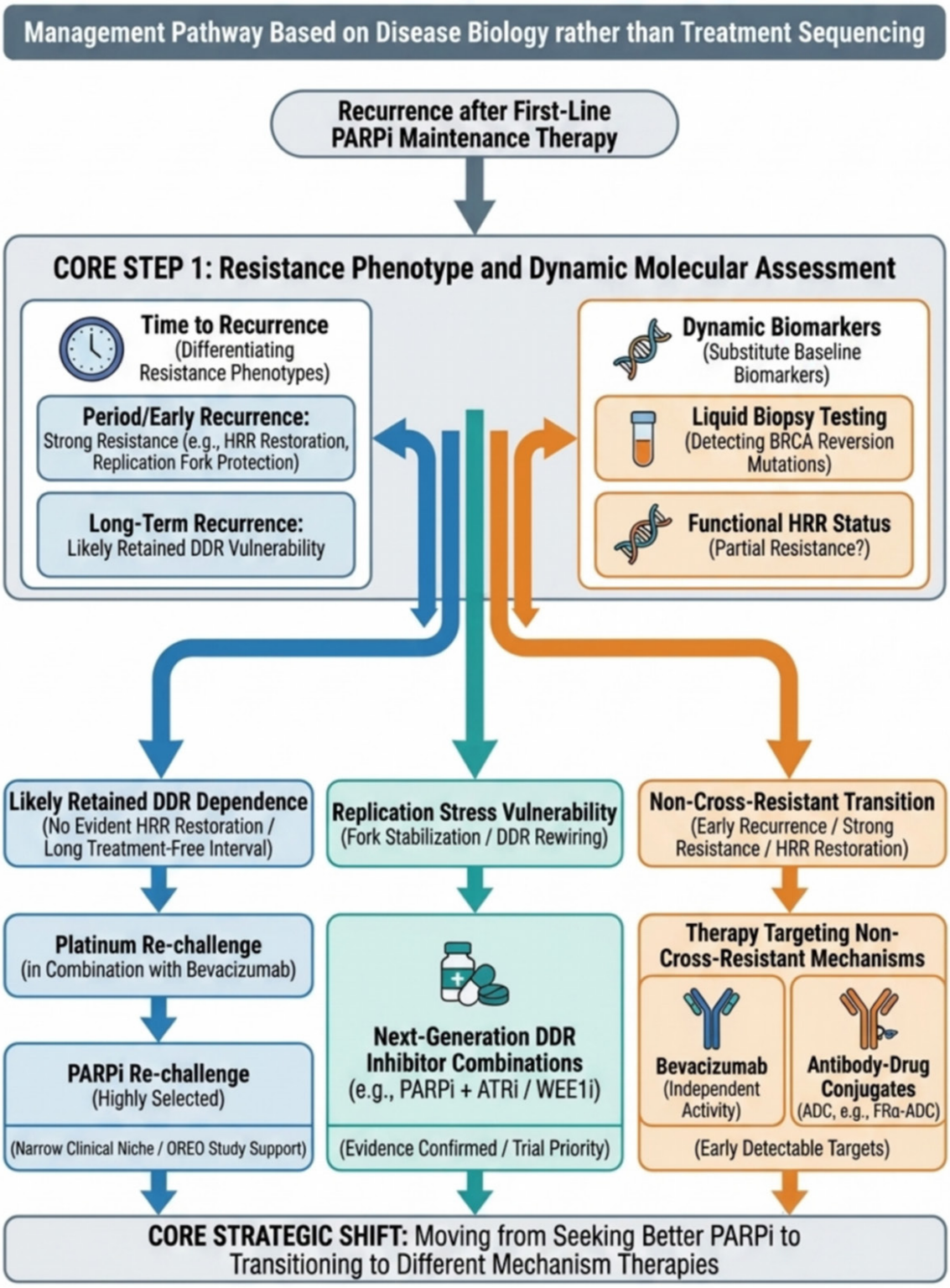

Figure 3. Strategic mechanistic diagram for the clinical management of ovarian cancer post first-line PARP inhibitor resistance. This schematic illustrates a resistance-aware, biology-driven framework for managing ovarian cancer recurrence after first-line PARP inhibitor (PARPi) maintenance. The initial step is resistance phenotyping, integrating time to recurrence with dynamic molecular reassessment, including liquid biopsy-based detection of BRCA reversion mutations and functional evaluation of homologous recombination repair (HRR) status. On this basis, three broad post-PARPi clinical-biological states are proposed. First, tumors with a long treatment-free interval and no

clear evidence of homologous recombination (HR) restoration may retain dependence on DNA damage response (DDR) vulnerabilities and remain candidates for platinum rechallenge, commonly with bevacizumab when appropriate, and in highly selected cases for PARPi rechallenge. Second, tumors characterized by replication-fork stabilization or broader DDR rewiring may remain susceptible to next-generation DDR-targeted strategies, including ATR- or WEE1-directed combinations, which are currently best prioritized in biomarker-enriched clinical trials. Third, tumors with early recurrence, strong functional resistance, or molecular evidence of HR restoration are more appropriately redirected toward non-cross-resistant therapies, including bevacizumab-based approaches and antibody-drug conjugates such as folate receptor alpha (FRa)-targeted agents. Overall, this pathway emphasizes a strategic shift from empirical retreatment with PARPi toward mechanism-matched therapy selection, with the goal of preserving subsequent treatment options and aligning intervention with the resistant biology present at relapse.

setting, the clinical objective is not merely to control the next relapse, but to preserve the architecture of subsequent options by matching each intervention to the resistant biology that is actually present (**Figure 3**).

Emerging strategies to overcome PARP inhibitor resistance

The therapeutic value of PARP inhibitor maintenance in newly diagnosed ovarian cancer has in essence changed the field of treatment provision in the disease, yet it has introduced resistance at the heart of disease treatment. Recurrent setting is not an exception anymore but an ever-growing clinical situation following previous exposure to PARP. This change has significant implications: no longer is it whether PARP inhibitors can take advantage of homologous recombination deficiency, but whether there are remaining weaknesses when the tumor biology has been selected by selective pressure. New approaches to circumvent resistance to PARP inhibitors are thus not only meant to allow the reinstatement of previous drug sensitivity, but also to discover and target the adaptive states that occur following exposure to first line PARP. They can be broadly categorized into four strategies that include retargeting the DNA damage response, disrupting compensatory replication fork protection, rational combination strategies to expand therapeutic vulnerability and biomarker-directed re-stratification of resistant disease.

Resistance is biologically heterogeneous and unlikely to be reversed by a single strategy

The clinical efficacy of PARP inhibitor maintenance in first-line ovarian cancer has established a novel clinical fact: recurrent disease has become more common following initial exposure to PARP and resistance is now a clinical phenomenon and not a rare phenomenon at the end-of-line. The process of resistance overcoming should not be perceived in this context as a one-pharmacologic activity. Post-PARP relapse is not a single biologic condition, and is a continuum of escape phenotypes that incorporate restored homologous recombination, replication fork protection, altered drug transport, decreased PARP trapping, and extended rewiring of the DNA damage response [35-37]. An effective resistance-driven model should thus go beyond the concept of merely-adding-another-agent to PARP inhibition. The more relevant question is which residual dependency remains once PARP-sensitive clones have been depleted.

From a translational perspective, four resistance-oriented strategies are now emerging. The first is to reduce pharmacologic escape by favoring PARP inhibitors less exposed to efflux-mediated resistance. The second is to convert PARP resistance into a new form of synthetic lethality through ATR- or WEE1-directed DDR targeting. The third is to reconsider not only whether PARP inhibitors should be combined with immunotherapy, but also when such combinations are biologically appropriate [38]. The fourth is to recognize that some post-PARPi tumors may be better treated not by trying to restore PARP sensitivity, but by shifting to non-cross-resistant targeted agents, including antibody-drug conjugates (ADCs) [39, 40]. Together, these approaches reflect a broader change in the field: resistance is increasingly being managed as an adaptive systems problem rather than as failure of a single drug class.

Avoiding pharmacologic escape: efflux-aware selection of PARP inhibitors

One underappreciated aspect of PARP inhibitor resistance is that it is not purely genomic. In some tumors, loss of drug sensitivity may be amplified by altered intracellular drug disposi-

tion, including upregulation of ATP-binding cassette transporters such as P-glycoprotein (P-gp, encoded by ABCB1/MDR1). This is important as the class of PARP inhibitors is pharmacologically diverse. Even the previous body of literature on ovarian cancer highlighted the fact that the inhibition of PARP by different drugs varies not only in catalytic potential but also in the ability to trap PARP with talazoparib having the best trapping capacity and veliparib the worst but olaparib, rucaparib and niraparib occupy intermediate and non-identical positions [41]. These pharmacologic variations cannot be considered the academic details in a resistance-conscious treatment paradigm. After ovarian cancer has been subjected to the extended maintenance of PARP, a selective pressure is probably exerted on the homologous recombination, transport and drug-delivery systems. This poses a clinically important hypothesis: in tumors with bowel serosal disease, extreme prior therapy or molecular evidence suggestive of overexpression of MDR1, the choice of a PARP inhibitor with a lower propensity to efflux might be more rational than assuming a class effect. This approach, though not yet backed by concrete comparative clinical evidence, represents a valuable concept in the post-PARPi world: resistance does not necessarily get diminished by increasing the dose, but by the selection of agents that have lower intracellular exposures that are more readily counteracted.

The next-generation PARPi sequencing, therefore, is unlikely to be harmonised around BRCA or HRD status. A more developed model would then add the use of pharmacologic susceptibility as another aspect of patient selection particularly when efflux-related biomarkers of resistance can be clinically accessible. This will not salvage patients with full-blown biologic escape, but it can be useful to postpone or reduce one of the ways of resistance development.

Synthetic lethality 2.0: redirecting resistant tumors into ATR- and WEE1-dependent states

The best approach to resistances to PARP inhibitors is the most convincing, which is to admit the fact that classical PARP-based synthetic lethality might be no longer intact and intentionally induce a second synthetic lethal condition. The reason why resistant tumors tend to survive is not that genomic instability is no longer present, but that they have learnt to compensate it. With this environment, the therapeutic objective changes away from the exploitation of baseline homologous recombination deficiency to other newly-important stress-response pathways that sustain resistant cells.

The most evident one is ATR. Being a master regulator of replication stress signaling and fork stabilization, ATR is of particular importance after tumor cells are compelled to endure long-term S-phase damage when subjected to PARP pressure. This rationale was already pre-empted in the previous landscape of ovarian cancer trials by trials using ATR inhibitor-PARP inhibitor combinations (like CAPRI), which explicitly placed ATR blockage in combination with olaparib in recurrent high-grade serous ovarian cancer [42]. The theoretical power of this strategy is that, it does not try to restore the tumor to a pre-resistance level. Rather, it takes advantage of the fact that post-PARPi cells can often be reliant on ATR-mediated soft-landing of replication stress, fork protection and incomplete recovery of homologous recombination.

The same thing should be considered with regard to WEE1 inhibition, but with a different focus. When ATR targeting is the major cause of disrupting replication stress surveillance, WEE1 targeting erases the cell-cycle checkpoint in which damaged cells can evade mitotic catastrophe. This could be especially the case with HR-competent or HR-recovered tumors that are no longer classically PARP sensitive yet have significant replication stress loads. There, WEE1 inhibition can serve as an induction of an artificial lethality-like condition in HR-proficient disease, and not as a supplement to PARP inhibition. This is the reason why ATR and WEE1 strategies can not be combined as generic DDR combinations. They lie in the same conceptual leap: by redefining PARPi resistance as a new dependency [43] state. Practically, it will imply that the most logical future research will not merely enquire whether ceralasertib or adavosertib enhances progression-free survival when incorporated with a PARP inhibitor.

Immunotherapy is a problem of timing, not just combination

One reason PARP inhibitor-immunotherapy combinations have produced mixed enthusi-

asm is that the field often asks the wrong question. The issue is not whether PARP inhibition can be combined with PD-1 or PD-L1 blockade. It can. The more difficult and more important question is when such a combination is biologically meaningful. The earlier ovarian cancer trial landscape already made clear how strongly the field moved in this direction, with frontline or recurrent strategies incorporating durvalumab, pembrolizumab, nivolumab and triplet platforms involving PARP inhibition, antiangiogenic therapy and immunotherapy, including studies later connected conceptually to ATHENA, FIRST and other platform trials. Yet the disappointing or difficult-to-interpret results from modern first-line immune-containing studies suggest that resistance is not simply solved by appending checkpoint blockade to PARP maintenance.

A more coherent interpretation is that PARP inhibitors exert two opposing immunologic effects. On one hand, they can increase DNA damage, cytosolic DNA accumulation, interferon signaling and immune visibility. On the other hand, prolonged PARP exposure may select for tumors that remain biologically "cold", suppress antigenic translation of genomic instability, or progress through mechanisms only weakly influenced by T-cell reinvigoration. In this framework, failure of frontline PARPi plus anti-PD-1/PD-L1 combinations should not be read as evidence that immune biology is irrelevant. Rather, it suggests that the window of immune susceptibility may not coincide with the window of maximal PARP dependence.

This has major implications for resistance management. Immunotherapy can be more rational where they are to intercept discrete transitional states e.g. in tumors with signs of PARPi-induced inflammatory signalling prior to outgrowth of HR-restored, immune-evasive clones. In comparison, combinatorial introduction of the checkpoint blockade to post-PARPi progression determined by prior biologic selection can just dilute signal through a resistant population that has lost immunological priming.

Beyond PARP rescue: ADCs as a non-cross-resistant post-PARPi strategy

One of the key limitations of the existing discourse on resistance is that it tends to believe that success is required to entail a restoration of PARP inhibitor sensitivity. The frontline PARP maintenance may no longer be treated by DNA repair biology at all with some of the tumors developing resistance after it. Alternatively, a more effective approach can be to move at once to agents that have little mechanical overlap, and have low cross-resistance. Herein ADCs are gaining prominence. Folate receptor alpha (FR 2)-targeted therapy has already provided a proof of principle of clinical relevance in ovarian cancer, demonstrating that a post-PARPi tumor can be targeted with a lineage-associated surface antigen, but not by homologous recombination status. This is important in the context of resistance since ADCs have what PARP-directed combinations frequently lack: the ability to break out of the PARP-platinum-DDR loop altogether. That can mean a lot more to patients whose tumors have already become platinum and PARP pressure vulnerable, than a second time effort to recreate historical vulnerability.

The most powerful recent example is mirvetuximab soravtansine that offers a rational ADC handoff approach in properly chosen FRa positive disease. Hypothetically, other upcoming ADC paradigms like HER2-low can also take effect in the event that development of biomarkers in ovarian cancer is expanded. The main argument is not that the ADCs in itself reverse the resistance of PARPi. They do not. Their importance lies in providing an effective non-cross-resistant therapeutic axis for tumors in which DDR-directed salvage has become biologically implausible or clinically exhausted. This reframing is useful because it widens the definition of resistance management. In a top-tier clinical strategy paper, overcoming resistance should include not only resensitization, but also intelligent therapeutic succession. For some post-PARPi patients, the best resistance strategy may be not another PARP combination, but an orderly transition to ADC-based targeted therapy.

Future directions and conclusions

Introduction of PARP inhibitors into the first-line maintenance has changed advanced ovarian cancer into a disease with uniformly relapsing disease to a disease with deep and long-lasting remissions that are now able to be obtained by a significant number of patients.

However, the result has at once revealed the weaknesses of our paradigm: dependence on stagnant genomic biomarkers, insufficient knowledge of evolutionary mechanisms in response to chronic DDR pressure and the growing complexity of salvage CR of PARP-exposed relapse. The following wave of development will not focus on the further number of PARP inhibitors, but rather their application in a new way - more biological in nature, more time-dependent, and more combined into complex, multi-modal approaches that predict resistance instead of only responding to it.

One of the future priorities is the elucidation of the biomarker structures to the level of binary BRCA/HRD. Genomic scar assays of the first generation would only retain historic homologous recombination deficiency and is oblivious of dynamic restoration of HR or fork protection, which occurs in response to therapy. Passively More advanced methods of diagnosing HRD, such as functional HRD assays, dynamic RAD51 foci quantification and transcriptomic and proteomic replication stress signatures, and serial circulating tumor DNA profiling to detect reversion will be required to inform not only initial eligibility but also the choice of duration of maintenance, PARP rechallenge, or determine combinations of DDRs. Integrating these types of assays both prospectively into first-line trials and post-progression trials will be of paramount importance to the advancement of leaving broad categories of biomarkers (so-called buckets) and instead enable a far more personalized, adaptive, treatment paradigm.

Next-generation agents and rational combinations based specifically on mechanisms of resistance will make parallel advancement. PARP1-selective inhibitors have the potential to maintain or increase trapping and reduce non-target hematologic toxicity, which could allow more intensive and prolonged maintenance and more aspirational DDR doublets with ATR, WEE1, or CHK1 inhibitors. The most interesting future regimens are probably those in vertically integrated around the DNA damage response axis-pairs of PARP inhibitors in combination with replication stress and cell cycle control modulators- or horizontally integrated with anti-angiogenic and immune regimens in approaches that make use of the interactions between hypoxia, genomic instability, and tumorimmune interactions. Of crucial importance to this effort will be those trial designs not just additive in nature (PARP + X) but rather mechanistically based, biomarker-enriched and adequately powered to help immigrants understand which patients are really in need of intensified triplets compared to those well-service by simpler doublets or monotherapy.

On a systems level systems are becoming increasingly aware that the sequencing of treatment and its length is themselves manipulable drivers of evolution and resistance. Instead of defaulting to as long as tolerated, the future research should test stringently finite and response-adapted maintenance, such as de-escalation approach based on minimum residual disease indicators or clearance of ctDNA and escalation or switch approach based on molecular indicators of resistance. Efficient testing of these concepts is provided by adaptive platform trials in which assignments can be dynamically changed depending on the changing biomarkers and not a single steady-state snapshot. Simultaneously, long term pharmacovigilance and real-world data will become essential in determining the accumulating risks of long term DDR inhibition, particularly therapy-related myeloid neoplasms and also in determining which groups of patients risks may exceed marginal benefits.

The use of patient-centered outcomes in the measure of maintaining strategies is also vital. With front-line treatment spans of years, the lived experience of the persistent oral therapy treatment with systemic exhaustion, Hb-based surveillance, economical intoxicating, and psychological load of never achieving an end must be balanced against the scale and permanence of progression delay. Future trials must emphasize quality of life measurement that is longitudinal, quality, and should place more focus on the use of patient-reported outcomes as the major decision-making outcomes and examining one aimed at supportive-care interventions as a strategy to maintain function and well-being over longer intervals of maintenance treatment. The values and preferences of the patient will be more and more influential in differentiating competing strategies in an age of many available reasonable options to most of the biomarker subgroups.

In conclusion, maintenance with PARP inhibitor in ovarian cancer during the first line is at an inflection point. The existing standards that are pegged on BRCA and HRD status have produced unmatched gains in progression-free survival and, in BRCA-mutated and HRD-positive tumors, new overall survival gains. Concurrently they have demonstrated the instability of fixed biomarker models and the unavoidable resistance in the event of the use of powerful, pathway-defining targeted therapies in an extensive manner and early in the disease. The future will belong to the approaches that do not consider PARP inhibitors as discrete isomorphic structures but components of an extended DDR and immune-oncology ecosystem, which will be implemented in a cautious fashion anticipating its timing, combinations, and evolutionary consequences. The vision will be achieved with unified advances in the areas of translational science, trial methodology, and clinical practice: powerful, impressive biomarkers; combination and sequencing approaches based on mechanisms; cautious use of DDR agents to leave future options; and the active involvement of patients in the complicated balance of risks and benefits during the disease. Should this be successful the conquest of the coming decade will not only render PARP the use of maintenance a standard component of first line ovarian cancer treatment, but also make it a precision focused, resistance sensitive treatment that can be employed to prolong remission and extend survival and redefine the natural history of this once fatal disease altogether.

Disclosure of conflict of interest

None.

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