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Dissecting Structural Determinants of PARP Trapping Potency Among Clinically Approved PARP Inhibitors in Ovarian Cancer

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ABSTRACT

Poly(ADP-ribose) polymerase (PARP) inhibitors have become an important treatment option for ovarian cancer, particularly in tumors with BRCA1/2 mutations or homologous recombination deficiency (HRD). Although clinically approved PARP inhibitors target the same general catalytic region of PARP, they differ substantially in their ability to trap PARP proteins on DNA. This literature review examines how structural differences among olaparib, rucaparib, niraparib, and talazoparib influence PARP-trapping potency and how these differences relate to clinical activity in ovarian cancer. The literature indicates that variations in molecular structure, rigidity, binding interactions, and effects on PARP conformation contribute to differences in trapping activity. Talazoparib demonstrates particularly strong PARP-trapping potency, while niraparib, olaparib, and rucaparib exhibit lower levels of trapping. However, structural features and trapping potency alone do not fully predict clinical effectiveness. Tumor biology, BRCA and HRD status, drug exposure, pharmacokinetics, treatment setting, toxicity, and resistance mechanisms also influence treatment outcomes. Emerging PARP1-selective inhibitors, such as saruparib, further demonstrate a shift toward optimizing selectivity and therapeutic window rather than simply increasing trapping potency. Overall, the evidence suggests that PARP trapping results from the combined effects of inhibitor structure, PARP binding, protein conformation, and DNA interactions. Understanding these relationships may support the development of more selective and personalized PARP inhibitor therapies that maximize antitumor activity while minimizing toxicity.

Keywords: *PARP inhibitors; PARP trapping; ovarian cancer; homologous recombination deficiency; BRCA1/2; DNA damage repair; structure-activity relationships; synthetic lethality*

1. INTRODUCTION

Ovarian cancer is a serious disease that remains difficult to treat because it is often diagnosed at an advanced stage. Many patients initially respond well to chemotherapy, but the cancer can return and become harder to treat over time. This makes long-term disease control a major challenge in ovarian cancer treatment. These challenges have increased interest in identifying molecular weaknesses the ovarian cancer cells to target them more precisely. One important molecular feature of many ovarian cancers is homologous recombination deficiency (HRD), which affects the cell's ability to repair damaged DNA. In particular, mutations in the BRCA1 and BRCA2 genes can interfere with homologous

recombination repair, a pathway that normally repairs double-stranded breaks in DNA (Arcieri et al., 2024). Because cancer cells with these mutations already have problems repairing DNA, they can be more vulnerable to treatments that target other DNA repair mechanisms. This has led researchers to investigate DNA repair proteins as potential targets for more precise cancer treatments.

One of the most important developments from this research has been the use of poly(ADP-ribose) polymerase, or PARP, inhibitors. PARP proteins help detect DNA damage and coordinate DNA repair processes, including the response to single-strand breaks. By blocking PARP activity, PARP inhibitors make it more difficult for cancer cells to respond to and repair DNA damage. This is especially important in tumors that already have defects in homologous recombination repair, such as tumors with BRCA1 or BRCA2 mutations. The combination of these two weaknesses can cause cancer cells to die, a concept known as synthetic lethality. This has made PARP inhibitors an important example of precision oncology, where treatment is selected based on the genetic characteristics of a patient's tumor. Several PARP inhibitors have been developed, including olaparib, rucaparib, niraparib, and talazoparib, although their approved uses differ depending on the type of cancer and the patient's specific disease characteristics. Despite targeting the same general pathway, these inhibitors can also differ in their biological effects.

Although PARP inhibitors were originally understood mainly as drugs that block the catalytic activity of PARP, research has shown that their effects are more complicated. In addition to preventing PARP from carrying out its normal enzymatic function, some PARP inhibitors can stabilize PARP proteins on damaged DNA. This process is known as PARP trapping, and it can interfere with DNA replication and create additional replication stress that can contribute to cancer cell death. Importantly, not all PARP inhibitors trap PARP with the same strength. For example, talazoparib has been shown to have much stronger PARP-trapping activity than olaparib, rucaparib, or niraparib, despite their ability to inhibit PARP catalytic activity. Research suggests that these differences may partly be related to inhibitor-specific interactions with PARP and their effects on the conformation and stability of PARP-DNA complexes (Zandarashvili et al., 2020). Therefore, understanding the structural differences between PARP inhibitors may help explain why some drugs are stronger PARP trappers than others. This leads to the central question of this paper: How do structural differences among clinically approved PARP inhibitors influence PARP-trapping potency in ovarian cancer?

2. METHODS

This review used a narrative literature review approach to examine the relationship between the structural characteristics of PARP inhibitors and their PARP-trapping activity, with particular emphasis on ovarian cancer. Literature identification followed an iterative, topic-based process in which initial reading of general articles and reviews established major themes, while subsequent searches were used to investigate specific structural, biochemical, pharmacological, and clinical questions.

PubMed was used to identify relevant publications, supplemented by searches for general review articles and the consultation of references cited in relevant papers. Literature identification and source selection

occurred on multiple occasions between June 2026 and September 2026. Search topics included PARP structure and function, catalytic inhibition, PARP trapping, inhibitor-protein interactions, structure-activity relationships, homologous recombination deficiency (HRD), BRCA1/2 mutations, and the clinical application of PARP inhibitors in ovarian cancer. Relevant search terms included "PARP inhibitor," "PARP trapping," "PARP1 structure," "helical domain," "structure-activity relationship," "olaparib," "rucaparib," "niraparib," "talazoparib," and "ovarian cancer."

Publications were selected according to their relevance to the review's central research question. Primary research articles were emphasized when discussing experimentally measured trapping activity, structural interactions, and molecular mechanisms. Review articles and clinical studies were used to provide broader biological and therapeutic context. Evidence from structural biology, biochemical and cellular experiments, pharmacological studies, and clinical trials was considered according to the content each study addressed.

The evidence was synthesized narratively, with findings organized by biological mechanisms, structural characteristics, and clinical relevance. In interpreting the literature, emphasis was placed on distinguishing direct experimental observations from proposed mechanistic explanations. Structural features such as molecular rigidity, inhibitor-protein interactions, and potential effects on PARP conformation were considered in relation to the available experimental evidence. Clinical efficacy was considered separately from preclinical trapping potency because trapping activity alone does not establish comparative clinical benefit.

This review did not employ a formal systematic screening procedure or a standardized risk-of-bias assessment. Accordingly, the findings are presented as a critical narrative synthesis of relevant literature.

3. BIOLOGY OF PARP AND MECHANISMS OF ACTION OF PARP INHIBITORS

3.1 DNA Damage Repair Pathways

DNA damage occurs continuously in cells and can result from normal cellular processes, environmental exposures, or carcinogenic agents. To prevent the accumulation of potentially harmful mutations, cells rely on several DNA repair pathways that recognize and repair different forms of damage. One important pathway is base excision repair (BER), which corrects small, non-helix-distorting lesions in individual DNA bases and contributes to the repair of many single-strand breaks. Another major pathway is homologous recombination (HR), which repairs DNA double-strand breaks and other lesions that arise during DNA replication by using a homologous DNA sequence as a template (Kulkarni et al., 2025; Langelier et al., 2018). Proteins such as BRCA1 and BRCA2 are essential components of this pathway, and mutations that impair their function can reduce the cell's ability to accurately repair double-strand DNA breaks (Arcieri et al., 2024; Kulkarni et al., 2025). When one DNA repair pathway is compromised, cells may become increasingly dependent on alternative repair mechanisms to maintain genome stability.

This dependence is particularly relevant in cancer, where many cancer cells experience DNA damage and replication stress (Kulkarni et al., 2025).

This dependence on alternative repair pathways is especially relevant to ovarian cancer because defects in homologous recombination are common in high-grade serous ovarian carcinomas, the predominant histologic subtype of epithelial ovarian cancer. Germline or somatic BRCA1/2 alterations account for an important subset of these tumors, while additional tumors exhibit HRD through alterations in other components of the pathway. Estimates suggest that approximately 41–50% of epithelial ovarian cancers exhibit HRD (Arcieri et al., 2024), although the exact prevalence varies according to the population studied and the method used to define HRD. These defects can leave ovarian cancer cells particularly dependent on alternative DNA damage repair processes and mechanisms that help cells in tolerating replication stress (Arcieri et al., 2024; Kulkarni et al., 2025).

PARP1 is important within this context because it acts as an early sensor of DNA damage, particularly single-strand breaks and abnormal DNA structures. Following DNA damage, PARP1 initiates a response through poly(ADP-ribose) (PAR) signaling, which helps in recruiting and regulating proteins involved in the DNA damage response. Through these functions, PARP1 contributes to the maintenance of DNA integrity and the cellular response to replication-associated damage, representing an important part of the network of repair pathways that maintain genomic stability (Langelier et al., 2018; Murai et al., 2014).

3.2 PARP Structure and Function

Poly(ADP-ribose) polymerase 1 (PARP1) is a multidomain protein that plays an important role in detecting DNA damage and coordinating the cellular response to damaged DNA. Its N-terminal DNA-binding region contains three zinc-finger domains, Zn1, Zn2, and Zn3. Zn1 and Zn2 recognize DNA structures associated with strand breaks. Importantly, Zn3 contributes to the interdomain interactions required for PARP1 activation. Although the three domains have different roles, they work together in PARP1 to connect DNA damage recognition with catalytic activation. This coordination allows DNA binding to initiate the conformational changes required for downstream enzymatic activation (Langelier et al., 2018; Zandarashvili et al., 2020).

The central region of PARP1 functions primarily as a regulatory and automodification domain, providing sites where PARP1 can attach ADP-ribose chains to itself and interact with other proteins involved in the DNA damage response. This region is followed by the WGR domain, which is named for its conserved tryptophan-glycine-arginine residues and plays an important role in DNA binding and the transmission of DNA-damage signals to the catalytic domain. In contrast, the C-terminal catalytic region is responsible for producing ADP-ribose polymers. This catalytic region contains a helical domain (HD) and an ADP-ribosyltransferase (ART) domain. The HD contributes to the regulation of catalytic activity, while the ART domain contains the binding site for NAD^+ and performs the enzymatic transfer of ADP-ribose. Thus, the N-terminal region primarily detects DNA damage, while the WGR and regulatory regions help transmit these signals to the C-terminal catalytic region, which converts DNA damage recognition into a

biochemical signal that coordinates DNA repair. Communication between these domains allows DNA binding to promote the conformational changes required for catalytic activation (Langelier et al., 2018).

When PARP1 detects a DNA break, interactions between its DNA-binding domains and the damaged DNA trigger conformational changes that relieve autoinhibition of the catalytic region. The ART domain can then bind NAD^+ and catalyze the addition of ADP-ribose to PARP1 and nearby proteins. This process, known as PARylation, creates a transient signaling platform that helps recruit and organize DNA repair factors. PARylation of PARP1 itself also promotes its dissociation from DNA, allowing the repair machinery to access the damaged site (Murai et al., 2012; Zandarashvili et al., 2020). Therefore, PARP1 normally functions through a coordinated cycle of DNA binding, catalytic activation, PARylation, and release.

3.3 Mechanisms of Action of PARP Inhibitors

PARP inhibitors exert their anticancer effects through two closely related mechanisms relevant to their DNA damage response activity: catalytic inhibition of PARP enzymatic activity and retention of PARP on damaged DNA, commonly referred to as PARP trapping. These mechanisms increase replication-associated DNA damage and are particularly detrimental to cancer cells with defective homologous recombination. Importantly, PARP inhibitors differ substantially in their ability to trap PARP despite sharing the ability to inhibit its catalytic activity, contributing to differences in their biological and pharmacological properties. Understanding these mechanisms is important for explaining why the structure of a PARP inhibitor can influence how strongly it traps PARP on DNA.

3.3.1 Catalytic Inhibition

The first major mechanism of PARP inhibitors is catalytic inhibition. Normally, PARP1 uses NAD^+ as a substrate to add ADP-ribose molecules to itself and other proteins near a site of DNA damage. This process, known as PARylation, helps organize the DNA damage response and promotes the eventual release of PARP1 from damaged DNA. PARP inhibitors interfere with this process by occupying the NAD^+-binding region within the ART catalytic domain. Because the inhibitors bind within the catalytic pocket used by NAD^+, they competitively prevent NAD^+ from accessing the active site and thereby inhibit PARylation (Murai et al., 2012; Murai et al., 2014). This suppresses PARP1 automodification and the PARylation of other proteins involved in the DNA damage repair process (Murai et al., 2014).

The NAD^+-binding region of the ART domain contains conserved residues that normally recognize the nicotinamide portion of NAD^+ and interact with the PARP inhibitors (Rudolph et al., 2022). However, the inhibitors are not simply interchangeable substitutes for NAD^+. Their distinct chemical structures allow them to establish different interactions within and around the catalytic pocket, which can influence both their binding affinity and their effects on the conformation of PARP1. Consequently, inhibitors with broadly similar catalytic inhibitory activity can produce substantially different biological effects (Langelier et al., 2018; Rudolph et al., 2022).

Catalytic inhibition alone does not fully explain the differences among PARP inhibitors. Experimental studies have demonstrated that compounds with comparable abilities to inhibit PARP enzymatic activity can differ markedly in their ability to retain PARP on DNA. This distinction is particularly important in ovarian cancer and other PARPi-sensitive cancer types because the cytotoxic consequences of PARP inhibition depend not only on the loss of PARylation but also on the persistence of PARP-DNA complexes that interfere with DNA replication.

3.3.2 PARP Trapping

PARP trapping occurs when a PARP inhibitor promotes the persistence of PARP1 or PARP2 at sites of DNA damage rather than allowing the protein to dissociate after recognizing the lesion. When a PARP inhibitor occupies the catalytic site and prevents PARylation, this release mechanism is disrupted, allowing PARP to remain associated with DNA (Murai et al., 2012; Murai et al., 2014). In addition to this effect of catalytic inhibition, inhibitor-specific interactions with the PARP1 catalytic region and surrounding structural elements can influence the stability of the PARP-DNA complex. Therefore, PARP trapping appears to result from a combination of loss of PARylation dependent release and inhibitor specific effects on the PARP-DNA complex (Zandarashvili et al., 2020).

The biological consequences of PARP trapping can be substantial. A trapped PARP-DNA complex can physically obstruct replication machinery and interfere with the progression of replication forks (Hopkins et al., 2015; Murai et al., 2012). When a replication fork encounters a persistent DNA-bound PARP complex, the resulting replication stress can contribute to fork stalling, and the generation of more severe DNA lesions. These effects are particularly damaging to cells with homologous recombination defects because their ability to repair replication-associated DNA damage is already compromised (Murai et al., 2014).

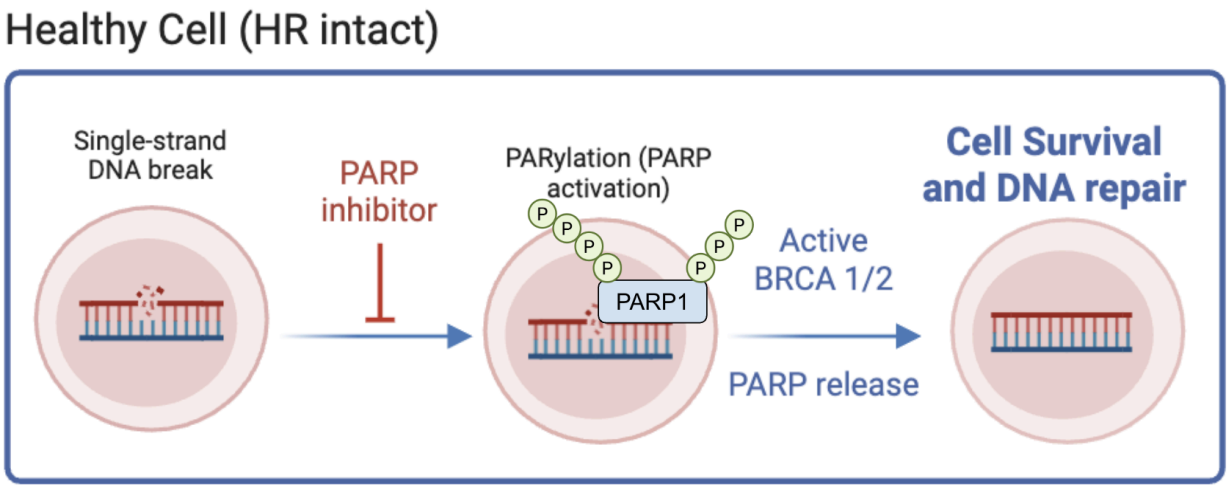
Importantly, PARP-trapping ability varies considerably among inhibitors. Preclinical studies have generally ranked talazoparib as a particularly strong PARP trapper, followed by niraparib, with olaparib and rucaparib displaying substantially weaker trapping activity in certain assays examined (Hopkins et al., 2015; Murai et al., 2012). Talazoparib has been reported to trap PARP approximately 100-fold more efficiently than olaparib or rucaparib in some experimental systems (Rudolph et al., 2022); however, the relative ranking of the inhibitors is not necessarily identical across experimental systems. Differences in trapping activity may contribute to differences in the cellular effects and cytotoxicity of individual PARP inhibitors, although cellular response is influenced by multiple factors beyond trapping potency alone. Therefore, reported trapping rankings should be interpreted as experimental comparisons instead of as universal properties of each drug.

3.3.3 Synthetic Lethality

Another important concept underlying PARP inhibitor therapy is synthetic lethality, in which disruption of either of two cellular pathways individually can be tolerated, whereas simultaneous disruption of both pathways results in cell death (Murai et al., 2014; Xie et al., 2022). This principle is particularly relevant

to ovarian cancers with defects in homologous recombination, including tumors harboring BRCA1 or BRCA2 mutations.

BRCA1- or BRCA2-deficient cancer cells have impaired capacity to repair replication-associated DNA damage through homologous recombination (Arcieri et al., 2024; Kulkarni et al., 2025). Although these cells can survive because other repair pathways remain functional, inhibition of PARP places additional stress on the mechanisms responsible for maintaining DNA integrity. PARP inhibition suppresses PARylation and disrupts PARP-dependent DNA damage responses while also increasing the persistence of PARP-DNA complexes. During DNA replication, these lesions and trapped complexes can interfere with replication-fork progression and generate DNA damage that requires homologous recombination for accurate repair, as illustrated in Figure 1.



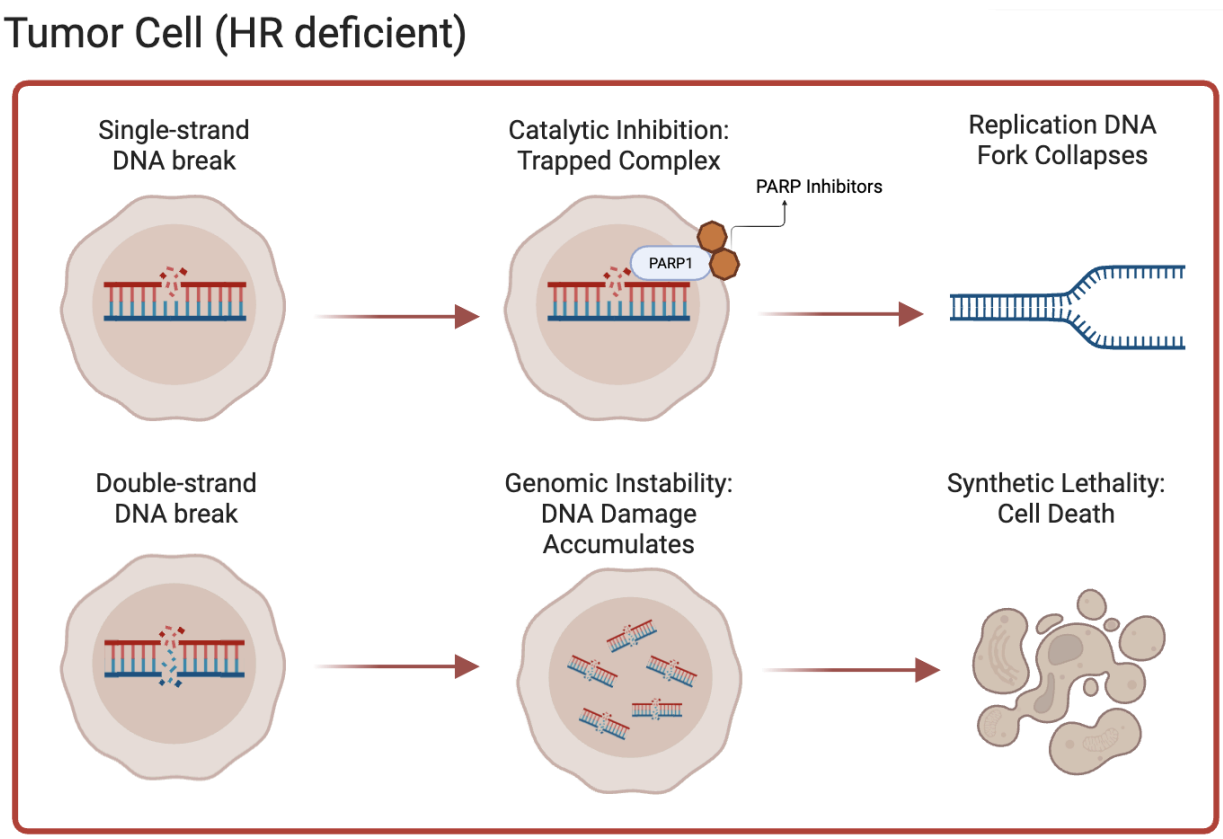


Figure 1: Mechanism of PARP inhibitor-induced synthetic lethality in homologous recombination-deficient tumor cells. In healthy cells/HR proficient cells, PARP inhibition can lead to the accumulation of DNA damage, including replication associated with double-stranded breaks (DSBs), which can be repaired through BRCA1/2-mediated homologous recombination. In contrast, HR-deficient tumors fail to repair these lesions, causing DNA damage accumulation, genomic instability, and synthetic lethality, potentially leading to cell death. The extent of these effects depends on the cellular context and the biological properties of the tumor (Murai et al., 2014; Kulkarni et al., 2025).

In BRCA1/2-deficient ovarian cancer cells, the combination of impaired homologous recombination and PARP inhibition can therefore exceed the cell's capacity to maintain genome stability, resulting in cell-cycle arrest and ultimately cell death. This provides the biological basis for the selective sensitivity of many BRCA-mutated ovarian cancers to PARP inhibitors. However, PARP inhibitor sensitivity is not restricted exclusively to BRCA1/2-mutated tumors. Other alterations affecting homologous recombination can produce an HRD phenotype and may also increase sensitivity to PARP inhibition, although the degree of response can vary depending on the underlying molecular defect.

PARP trapping may further enhance this synthetic-lethal effect by introducing a physical barrier to DNA replication in addition to the loss of PARylation-dependent repair signaling. Therefore, the antitumor activity of PARP inhibitors can arise from the combined effects of impaired PARP catalytic function,

persistence of PARP-DNA complexes, increased replication stress, and the reduced capacity of HR-deficient ovarian cancer cells to repair the resulting damage (Kulkarni et al., 2025).

3.4 Clinical Development and Diversity of Approved PARP Inhibitors

The clinical development of PARP inhibitors was based on the observation that tumors with homologous recombination defects, particularly those harboring BRCA1 or BRCA2 alterations, could be selectively targeted by disrupting PARP-dependent DNA repair. Olaparib became the first PARP inhibitor to receive regulatory approval, initially for patients with BRCA-mutated ovarian cancer, establishing PARP inhibition as a clinically relevant strategy for exploiting DNA repair deficiencies (Moore et al., 2018). Rucaparib and niraparib were subsequently developed and evaluated extensively in ovarian cancer, particularly as maintenance therapies following response to platinum-based chemotherapy (Coleman et al., 2017; González-Martín et al., 2023). These agents have since become important components of the therapeutic landscape for ovarian cancer, although their specific regulatory indications and treatment settings have changed over time.

The four PARP inhibitors examined in this review are olaparib, rucaparib, niraparib, and talazoparib. Olaparib has played a particularly important role in ovarian cancer because of its initial development in BRCA-mutated disease and its subsequent evaluation as maintenance therapy. Rucaparib and niraparib were also developed extensively for ovarian cancer and have contributed to the expansion of PARP inhibitor therapy beyond patients with BRCA mutations. In contrast, talazoparib was developed primarily in breast cancer and does not have an FDA approval for ovarian cancer (Robson et al., 2019). Its lack of an ovarian cancer approval should not be interpreted as evidence that talazoparib is biologically ineffective against ovarian cancer; rather, regulatory approval depends on the clinical evidence submitted for a particular indication, including the design and results of disease-specific clinical trials. Talazoparib's clinical development and pivotal evidence were focused on breast cancer, whereas olaparib, rucaparib, and niraparib underwent substantial clinical development in ovarian cancer. Consequently, the strong preclinical PARP-trapping activity of talazoparib does not by itself establish clinical efficacy or justify an ovarian cancer indication.

Although olaparib, rucaparib, niraparib, and talazoparib target the catalytic region of PARP1 and PARP2, their molecular structures and pharmacological properties differ. Structural studies have identified both conserved interactions within the NAD^+-binding pocket and inhibitor-specific contacts that may influence binding geometry and protein conformation (Rudolph et al., 2022). These differences provide a basis for investigating the relationship between inhibitor structure and trapping activity, but they do not establish a direct or universal relationship between molecular architecture and trapping potency.

4. STRUCTURAL BASIS OF PARP TRAPPING

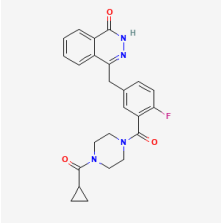
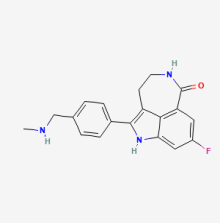
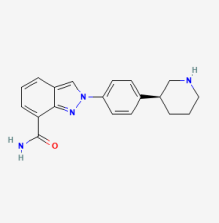
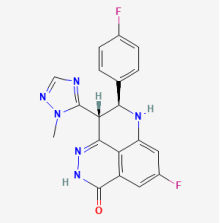
4.1 Molecular Architecture of Clinically Approved PARP Inhibitors

Although the four clinically approved PARP inhibitors have different overall structures, they share an important feature: they are designed to interact with the catalytic pocket of PARP in a way that resembles the nicotinamide portion of the natural NAD^+ substrate (Kirby & Cohen., 2019; Rudolph et al., 2022). This allows them to compete with NAD^+ and block the enzyme's catalytic activity.

The differences become more noticeable when the entire molecules are compared. Some inhibitors are relatively flexible, while others contain more rigid ring systems (Rudolph et al., 2022). The size, shape, flexibility, and electrical properties of these molecules can affect how they fit into the PARP binding pocket and how they influence the surrounding protein. These effects are important because PARP is not a completely rigid structure. When PARP binds to DNA or an inhibitor, parts of the protein can change their position. Therefore, an inhibitor's structure can influence not only its direct interactions with the catalytic site but may also affect the conformational and allosteric communication between the different regions of PARP (Langelier et al., 2018; Zandarashvili et al., 2020). This provides one possible explanation for why two inhibitors that both strongly block PARP's catalytic activity can have very different PARP-trapping abilities.

Olaparib, rucaparib, niraparib, and talazoparib have different chemical structures, even though they target the same general region of PARP. In particular, their structures contain groups that can form hydrogen bonds with amino acids in the catalytic pocket, helping the inhibitors remain bound to PARP. Each inhibitor contains a heterocyclic ring system that allows it to interact with the NAD^+-binding portion of the catalytic domain (Rudolph et al., 2022). Beyond this shared feature, however, the molecules differ in their ring systems, side chains, flexibility, and overall shape, as seen in Table 1. These differences determine how each inhibitor fits within the PARP binding site.

Table 1: Structural and pharmacological differences among selected clinically approved PARP inhibitors. Data compiled from Xie et al. (2022); Kirby & Cohen., (2019); Murai et al. (2012); Hopkins et al. (2015); Rudolph et al. (2022); Zandarashvili et al. (2020). Structural features are descriptive characteristics of the compounds and should not be interpreted as independent determinants of PARP-trapping potency. Reported trapping profiles summarize findings from selected experimental comparisons and do not represent a universal ranking across all assay conditions, drug concentrations, or PARP isoforms.

	Olaparib	Rucaparib	Niraparib	Talazoparib
2D Structure (taken from PubChem on September 16, 2026)				
Core Scaffold	Phthalazinone	Tricyclic indole-fused lactam	2H-indazole-7-carboxamide	Fused pyridazinone
Key Structural Features	Piperazine linker + fluorophenyl group	Indole-derived fused ring + fluorophenyl group	Piperidine/phenyl side chain	Rigid fused tricyclic ring system
Reported PARP Trapping Profile	Lower than talazoparib in commonly cited comparisons	Lower than talazoparib in commonly cited comparisons	Relatively strong in several experimental comparisons	Particularly strong in several experimental comparisons

Olaparib contains a phthalazinone-based core and a piperazine-containing side chain (Rudolph et al., 2022). Its structure contains several rotatable bonds, giving it greater flexibility than talazoparib. Rucaparib has a more compact, fused-ring structure, while niraparib contains a fully saturated piperidine ring with a less rigid overall arrangement. Talazoparib is structurally distinct because it contains a highly rigid, fused tricyclic system that restricts the number of conformations the molecule can adopt.

These differences in molecular architecture are important because a drug does not interact with a protein simply as a flat chemical structure. Its three-dimensional shape determines which parts of the molecule can approach particular amino acid residues and how closely it can fit within the binding site. A flexible inhibitor can adjust its conformation after entering the pocket, whereas a more rigid inhibitor is more restricted in the shapes it can adopt. Similarly, differences in the size and position of chemical groups can allow individual inhibitors to occupy slightly different portions of the catalytic region.

4.2 Structural Differences Among Clinically Approved PARP Inhibitors

The different chemical structures of PARP inhibitors influence how each drug is positioned within the PARP binding site. Although the inhibitors occupy overlapping regions of the catalytic pocket, they do

not make exactly the same contacts with PARP. Differences in hydrogen bonding, hydrophobic interactions, and the extent and regions of the binding pocket contacted by each molecule can affect the binding geometry and stability of the resulting PARP-inhibitor complex (Murai et al., 2012).

Olaparib forms hydrogen-bonding interactions within the catalytic region and fits into the NAD^+-binding pocket through its phthalazinone-containing core. Its side chain extends into an adjacent portion of the binding site, allowing additional interactions with surrounding residues (Rudolph et al., 2022). Because the molecule is relatively flexible, different parts of the inhibitor may adopt different conformations within the pocket. Its binding arrangement therefore depends on both the conserved interactions made by the core structure and the positioning of its flexible groups (Rudolph et al., 2022).

Rucaparib uses a different binding arrangement because of its more compact tricyclic scaffold. Its ring system occupies the catalytic pocket while allowing interactions with residues surrounding the NAD^+-binding region (Rudolph et al., 2022). These interactions are not identical to those made by olaparib, even though both inhibitors target the same general site. The differences illustrate how changing the chemical framework of an inhibitor can alter the specific contacts formed with PARP without changing the overall target (Rudolph et al., 2022).

Niraparib also occupies the catalytic pocket but has a different orientation and interaction pattern from olaparib and rucaparib. Structural studies have identified interactions between niraparib and residues in the region surrounding the catalytic site, including interactions involving the helical domain (Rudolph et al., 2022). The helical domain is positioned next to the catalytic domain and can influence the shape and movement of PARP1 (Langelier et al., 2018). Consequently, interactions between an inhibitor and this surrounding region may affect the overall conformation of the protein rather than simply anchoring the drug within the active site.

Talazoparib has a highly conformationally constrained binding arrangement among the four inhibitors. Its rigid tricyclic structure allows it to occupy the catalytic pocket with relatively little conformational flexibility. Structural studies have shown that talazoparib extends into both the nicotinamide and N-ribose regions of the binding site and forms multiple interactions with residues within the catalytic domain (Rudolph et al., 2022). Its compact structure also allows it to make close contacts within the binding pocket. These characteristics help explain its exceptionally strong association with PARP1 (Rudolph et al., 2022).

The differences among these binding modes are important because they demonstrate that inhibitors occupying the same general pocket can affect PARP in different ways (Rudolph et al., 2022). The relevant structural question is therefore not simply whether an inhibitor binds to PARP, but which residues and regions of PARP it contacts and how those contacts influence the resulting protein structure. This provides the basis for considering whether differences in binding mode can explain the different trapping potencies observed experimentally while recognizing that current structural evidence does not fully explain why these inhibitors differ in trapping potency (Hopkins et al., 2015; Murai et al., 2012; Rudolph et al., 2022).

4.3 Structure-Activity Relationships Governing PARP Trapping

The structural differences among PARP inhibitors provide possible explanations for their different trapping abilities, but they do not provide a simple one-to-one relationship. As discussed in Section 2, the clinically approved inhibitors differ substantially in trapping potency even though all inhibit PARP catalytic activity (Hopkins et al., 2015; Murai et al., 2012). The structural comparison therefore raises an important question about which properties of an inhibitor are actually associated with stronger PARP trapping.

One factor that may influence PARP-trapping potency is the strength and stability of the inhibitor–PARP interaction. An inhibitor that forms extensive interactions within the catalytic pocket may produce a more stable inhibitor-bound state and remain associated with PARP for a longer period of time. Both binding affinity and the rate at which an inhibitor dissociates from PARP may influence the duration of this interaction, particularly when PARP is already associated with DNA (Hopkins et al., 2015; Zandarashvili et al., 2020). However, binding affinity alone does not fully predict trapping potency, as inhibitors with strong binding to the catalytic domain can still differ in their ability to promote prolonged PARP retention on DNA. Therefore, the stability and duration of the inhibitor–PARP interaction may be important factors contributing to differences in PARP-trapping activity (Langelier et al., 2018).

The physical properties of the inhibitor may also contribute. Molecular rigidity, for example, can affect how efficiently a compound fits within a binding pocket. Talazoparib provides an important example, as its strong trapping activity is consistent with the idea that the stability and geometry of the inhibitor–PARP complex can influence trapping (Hopkins et al., 2015; Murai et al., 2012). However, rigidity should not be considered an independent rule for predicting trapping because the other inhibitors demonstrate that trapping depends on several properties acting together.

Another possible factor is the effect of inhibitor binding on regions of PARP outside the immediate catalytic site. In particular, interactions near the helical domain may alter the position or movement of this region. Because the helical domain is connected structurally to the catalytic domain and participates in allosteric communication between the catalytic and DNA-binding regions of PARP1, changes in its conformation could influence the behavior of DNA-bound PARP (Langelier et al., 2018; Zandarashvili et al., 2020). Some structural studies have suggested that different inhibitors can stabilize different conformational states of PARP1, which could affect the tendency of the protein to remain associated with DNA.

However, these structural effects do not completely explain the measured differences in trapping potency among the inhibitors. For example, differences in proposed allosteric effects do not consistently reproduce the experimental ranking of trapping potency. The trapping phenotype likely results from the combined effects of catalytic inhibition, inhibitor binding, protein conformation, allosteric communication, and the kinetics of PARP association with and release from DNA. However, the relative contribution of each of these factors remains incompletely understood, which helps explain why trapping potency cannot yet be reliably predicted from molecular structure alone (Zandarashvili et al., 2020).

4.3.1 Determinants of PARP Trapping Potency

The available structural and biochemical evidence suggests that several properties contribute to PARP-trapping potency. These include the ability of an inhibitor to effectively inhibit PARP catalysis, the nature and stability of inhibitor–PARP interactions, and the effect of inhibitor binding on PARP conformation, as shown in Table 2 (Hopkins et al., 2015; Murai et al., 2012). Together, these factors alter the stability and duration of PARP-DNA complexes and influence the extent of trapping. Therefore, structure–activity relationships are useful for understanding PARP trapping, but they should be interpreted in the context of the complete PARP–inhibitor–DNA system, as stronger trapping appears to depend on the overall properties of this complex rather than on one specific structural feature or chemical group (Murai et al., 2012).

Table 2: Evidence linking structural properties of PARP inhibitors to PARP-trapping activity. Data compiled from Murai et al. (2012); Hopkins et al. (2015); Rudolph et al. (2022); Zandarashvili et al. (2020). Structural features are descriptive characteristics of the compounds and should not be interpreted as independent determinants of PARP-trapping potency. Reported trapping profiles summarize findings from selected experimental comparisons and do not represent a universal ranking across all assay conditions, drug concentrations, or PARP isoforms.

Structural Feature or Proposed Determinant	Relevant Evidence	Interpretation	Strength and application of evidence
Conserved interactions in the NAD^+ binding pocket	Crystal structure demonstrates shared hydrogen-bonding and aromatic interactions between inhibitors and catalytic-site residues (Rudolph et al., 2022).	Establishes a common structural basis for catalytic inhibition, but does not explain trapping differences on its own.	Strong for active binding site but limited for explaining differences in trapping
Molecular rigidity	Talazoparib's fused-ring structure is conformationally constrained (Rudolph et al., 2022).	Rigidity may favor a particular binding geometry but it can't be definitively established as a universal predictor of trapping.	Strong for a description of structure but has inadequate evidence denoting independent causation
Inhibitor-dependent helical-domain effects	Hydrogen/deuterium exchange, structural analysis, and mutagenesis	Supports a mechanistic link between specific protein interactions, allosteric	Strong within the tested experimental system but cannot be generalized to apply to

	demonstrate that inhibitor-dependent effects on PARP1 allostery can influence DNA retention (Zandarashvili et al., 2020).	communication, and DNA retention.	every inhibitor at this time
Inhibitor-specific DNA-retention effects	Biochemical assays show that inhibitors can differ in their effects in PARP1-DNA association and dissociation (Zandarashvili et al., 2020).	Directly supports the conclusion that catalytic inhibition alone does not fully describe DNA retention	Strong for the tested biochemical conditions

5. CLINICAL AND PHARMACOLOGICAL CONSIDERATIONS OF PARP INHIBITORS IN OVARIAN CANCER

5.1 Clinical Evidence in Ovarian Cancer

PARP inhibitors have demonstrated substantial clinical benefit in ovarian cancer, particularly in patients with BRCA1/2 mutations or HRD. The phase III SOLO-1 trial established olaparib as an effective frontline maintenance treatment in patients with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation. Patients receiving olaparib had a significantly longer progression-free survival (PFS) than those receiving placebo, with a 70% reduction in risk of disease progression or death (Moore et al., 2018). These findings provided early evidence that PARP inhibition could produce substantial and durable clinical benefit when used in tumors with impaired homologous recombination repair (Moore et al., 2018).

The PAOLA-1 trial subsequently evaluated olaparib in combination with bevacizumab as a maintenance treatment in patients with advanced ovarian cancer who had responded to platinum-based chemotherapy. The addition of olaparib to bevacizumab significantly improved PFS in the HRD-positive subgroup, with substantial benefit observed in patients whose tumors had both HRD and a BRCA1/2 mutation (Ray-Coquard et al., 2023). However, patients without evidence of HRD did not obtain the same degree of benefit, highlighting the importance of tumor DNA-repair status in determining response to PARP inhibition (Ray-Coquard et al., 2023).

The PRIMA trial investigated niraparib as a therapy in patients with newly diagnosed advanced ovarian cancer who were at high risk of disease progression. Niraparib significantly improved PFS compared with

placebo in the overall population, with a larger magnitude of benefit in patients with HRD-positive tumors. Within the HRD-positive population, strong benefit was observed in patients with BRCA-mutated tumors, while benefit was also seen in HRD-positive tumors without BRCA mutations. A more modest benefit was also observed in the homologous recombination-proficient population. This suggested that niraparib could provide clinical benefit beyond tumors with BRCA mutations alone, while still demonstrating a stronger effect in tumors with defects in homologous recombination repair (González-Martín et al., 2023).

The ARIEL3 trial provided further evidence for the use of PARP inhibitors as maintenance therapy by evaluating rucaparib in patients with recurrent ovarian cancer who had responded to platinum-based chemotherapy. Rucaparib significantly improved PFS compared with placebo in the overall population, with the largest benefit observed in patients with BRCA-mutated tumors, followed by patients with other forms of HRD (Coleman et al., 2017). The trial therefore supported the use of molecular characteristics, particularly BRCA mutation and HRD status, as important predictors of response to PARP inhibition in recurrent disease (Coleman et al., 2017).

Taken together, SOLO-1, PAOLA-1, PRIMA, and ARIEL3 demonstrate that PARP inhibitors can substantially prolong PFS across different treatment settings, including first-line and recurrent ovarian cancer. However, the magnitude of clinical benefit varies according to BRCA1/2 mutation status, HRD status, previous treatment, and the specific PARP inhibitor and treatment strategy used. These differences indicate that clinical efficacy cannot be explained by PARP inhibition alone and that the pharmacological properties of individual PARP inhibitors must also be considered.

5.2 Clinical Relevance of PARP Trapping in Ovarian Cancer

The clinical activity of PARP inhibitors is influenced by their ability to inhibit PARP catalytic activity and to trap PARP1 on DNA at sites of damage. However, the extent of PARP trapping differs between individual inhibitors and does not necessarily correspond directly to their clinical efficacy. Talazoparib has been shown to have particularly strong PARP-trapping activity, whereas olaparib, niraparib, and rucaparib generally demonstrate lower trapping potency in comparison (Murai et al., 2012; Hopkins et al., 2015). These differences are partly related to the molecular structures of the individual drugs and their interactions with PARP1.

Despite these differences in trapping potency, clinical outcomes cannot be predicted from PARP trapping alone. The concentration of drug that reaches the tumor, pharmacokinetic properties, duration of drug exposure, dosing, PARP1/PARP2 selectivity, and the biological characteristics of the tumor can all influence treatment response (Bruin et al., 2022). In addition, BRCA1/2 mutation and HRD status affect the ability of tumor cells to repair DNA damage, while acquired resistance mechanisms can reduce sensitivity to PARP inhibition even when PARP is effectively trapped (Kulkarni et al., 2025).

This distinction is particularly important when comparing PARP inhibitors with different trapping profiles. A drug with greater trapping potency may produce more extensive DNA damage under

experimental conditions, but its clinical effectiveness depends on the intersection of trapping potency, drug exposure, tumor biology, and treatment characteristics. Therefore, PARP trapping should be considered an important pharmacological property of PARP inhibitors, rather than an independent predictor of clinical efficacy (Bruin et al., 2022; Hopkins et al., 2015).

5.2.1 Potential Toxicity Associated with Increased PARP Trapping

Although stronger PARP trapping can increase cancer-cell death, it can also increase toxicity in normal tissues. PARP inhibitors affect normal cells as well as cancer cells, particularly cells that frequently divide, such as bone marrow cells, leading patients to risk experiencing side effects such as anemia, thrombocytopenia, and neutropenia (Bruin et al., 2022; Hopkins et al., 2015). The goal is to find a balance between enough PARP trapping to damage cancer cells and acceptable toxicity to healthy tissues. This is an important consideration when developing and comparing PARP inhibitors for ovarian cancer (Hopkins et al., 2015).

This creates an important therapeutic consideration when developing and selecting PARP inhibitors. Increasing PARP trapping may enhance the ability of a drug to induce lethal DNA damage, particularly in tumors with impaired homologous recombination repair, but increased effects on normal tissues may also narrow the therapeutic window by increasing toxicity to healthy tissues. Consequently, the clinical value of a PARP inhibitor depends not simply on achieving the highest possible trapping activity, but on achieving sufficient antitumor activity at a dose that can be administered safely and maintained over an appropriate treatment duration. This balance between antitumor potency and tolerability is therefore an important factor when comparing PARP inhibitors with different trapping profiles (Hopkins et al., 2015).

6. CURRENT AND EMERGING STRATEGIES

PARP inhibitors are currently used mainly as maintenance therapy in ovarian cancer, particularly in patients whose tumors have BRCA mutations or HRD. Combination therapy has also become clinically important, with olaparib plus the anti-angiogenic agent bevacizumab established as a leading maintenance option for selected patients with HRD-positive advanced ovarian cancer (Ray-Coquard et al., 2023). These findings established the combination as an important treatment option for HRD-positive advanced ovarian cancer.

Researchers continue to investigate PARP inhibitors in combination with other treatments, including anti-angiogenic drugs, chemotherapy, and immune checkpoint inhibitors. These combinations are designed to increase cancer-cell stress by simultaneously interfering with DNA repair and other pathways involved in tumor survival. However, combining PARP inhibitors with chemotherapy can be challenging because both treatments can produce overlapping toxicities, particularly hematologic toxicities such as anemia, neutropenia, and thrombocytopenia (Bhamidipati et al., 2023). Early clinical studies of PARP inhibitors–chemotherapy combinations were therefore limited by myelosuppression, which can require dose reductions or treatment discontinuation. More recent studies have focused on identifying appropriate dosing schedules and biomarkers that may allow these combinations to provide benefits while reducing

toxicity (Bhamidipati et al., 2023). Targeting additional DNA damage response pathways, such as ATR and WEE1 inhibition to increase replication stress and POLQ inhibition to disrupt an alternative DNA repair pathway, is also being investigated as a strategy to overcome PARP inhibitor resistance and enhance tumor-cell killing (Kulkarni et al., 2025).

Another important area of research is the development of more selective PARP1 inhibitors. Rather than simply developing inhibitors with increasingly strong PARP-trapping activity, researchers are investigating whether selective inhibition of PARP1 can maintain anticancer effects while reducing unwanted effects associated with inhibition of other PARP family members. Saruparib (AZD5305) is an example of this next-generation approach. Unlike earlier PARP inhibitors, which generally inhibit both PARP1 and PARP2, saruparib was specifically designed to be highly selective for PARP1. Preclinical studies found that AZD5305 has more than 500-fold selectivity for PARP1 over PARP2 and can selectively trap PARP1 without detectable PARP2 trapping at comparable concentrations (Illuzzi et al., 2022). This distinction is important because PARP2 inhibition has been proposed as a contributor to hematologic toxicity, particularly through effects on hematopoietic cells (Illuzzi et al., 2022; Hopkins et al., 2015). By selectively targeting PARP1, saruparib may therefore provide an opportunity to preserve antitumor activity while potentially widening the therapeutic window and making PARP inhibitors more suitable for combination treatment (Illuzzi et al., 2022). Saruparib remains under clinical development, including phase III studies, so its potential advantages over currently approved PARP inhibitors still require confirmation in clinical trials.

Overcoming resistance is another major goal in the development of PARP inhibitor therapy. Although PARP inhibitors can be highly effective in tumors with BRCA mutations or other defects in homologous recombination repair, some tumors eventually develop resistance. One mechanism involves the restoration of homologous recombination repair, including secondary or “reversion” mutations in BRCA1 or BRCA2 that restore partial protein function. Other resistance mechanisms can alter PARP1 itself, DNA replication, or cellular responses to DNA damage (Kulkarni et al., 2025). Understanding these mechanisms may allow researchers to identify patients who are likely to develop resistance and develop combination treatments that prevent or overcome it.

7. FUTURE DIRECTIONS OF PARP INHIBITORS

Future PARP inhibitor development will benefit from a clearer understanding of how molecular structure, catalytic inhibition, protein conformation, and DNA-binding dynamics contribute to trapping. Structural studies can identify inhibitor-protein contacts, while biochemical and cellular experiments are needed to establish whether these interactions cause changes in trapping activity (Rudolph et al., 2022; Zandarashvili et al., 2020). Comparative studies using standardized assays and matched experimental conditions would help distinguish the contributions of binding affinity, conformational constraint, and allosteric effects. Such studies are particularly important because trapping rankings derived from different experimental systems may not be directly comparable.

Another direction is the development of inhibitors that balance antitumor activity with selectivity and tolerability. Future treatment selection may also benefit from integrating BRCA and HRD status with pharmacological factors and resistance mechanisms (Bruin et al., 2022; Illuzzi et al., 2022). Overall, the objective is not necessarily to maximize trapping potency, but to understand while structural and biological features produce the most favorable therapeutic effects in a given context.

8. CONCLUSION

PARP inhibitors have become an important component of cancer treatment by exploiting weaknesses in DNA repair pathways, particularly in tumors with BRCA mutations or HRD. Although olaparib, rucaparib, niraparib, and talazoparib target the catalytic region of PARP1 and PARP2, their distinct molecular structures produce differences in binding interactions and pharmacological behavior. Structural studies have identified conserved interactions within the catalytic pocket as well as inhibitor specific contacts that may influence PARP binding and conformation (Rudolph et al., 2022).

The available evidence supports a multifaceted relationship between inhibitor structure and PARP-trapping potency. Talazoparib exhibits particularly strong trapping activity in several preclinical systems, and its rigid scaffold and extensive catalytic-pocket interactions provide plausible structural explanations for its behavior (Hopkins et al., 2015; Rudolph et al., 2022). However molecular rigidity alone does not establish trapping potency, and the relative contributions of catalytic inhibition, protein conformation, allosteric regulation, and DNA-binding dynamics remain incompletely resolved (Zandarashvili et al., 2020). Furthermore, trapping measurements depend on experimental conditions and cannot be translated directly into a universal ranking of clinical effectiveness.

Future research should combine structural analysis with biochemical and cellular experiments performed under comparable conditions to establish which molecular interactions causally influence trapping. The development of PARP1-selective inhibitors also illustrates the importance of optimizing selectivity and tolerability alongside antitumor activity (Bruin et al., 2022; Illuzzi et al., 2022). Ultimately, a clearer understanding of the relationship between inhibitor structure, PARP trapping, and cellular response may support the development of PARP inhibitors with favorable therapeutic profiles.

LIST OF ABBREVIATIONS

ART – ADP-ribosyltransferase
BER – Base excision repair
BRCA1/2 – Breast cancer gene 1/2
DSB – Double-strand break
HR – Homologous recombination
HRD – Homologous recombination deficiency
NAD^+ – Nicotinamide adenine dinucleotide
PARP – Poly(ADP-ribose) polymerase
PARP1/2 – Poly(ADP-ribose) polymerase 1/2

PARPi – Poly(ADP-ribose) inhibitor
PFS – Progression-free survival
WGR – Tryptophan-glycine-arginine

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COMPETING INTERESTS

The author declares no conflict of interest. All the images were created using Biorender (https://www.biorender.com), and Google Gemini was only used to help understand and synthesize complex concepts from publicly available research papers.

REFERENCES

Arcieri, M., Tius, V., Andreetta, C., Restaino, S., Biasioli, A., Poletto, E., Damante, G., Ercoli, A., Driul, L., Fagotti, A., Lorusso, D., Scambia, G., & Vizzielli, G. (2024). How BRCA and homologous recombination deficiency change therapeutic strategies in ovarian cancer: a review of literature. *Frontiers in oncology*, *14*, 1335196. https://doi.org/10.3389/fonc.2024.1335196

Bhamidipati, D., Haro-Silerio, J. I., Yap, T. A., & Ngoi, N. (2023). PARP inhibitors: enhancing efficacy through rational combinations. *British journal of cancer*, *129*(6), 904–916. https://doi.org/10.1038/s41416-023-02326-7

Bruin, M. A. C., Sonke, G. S., Beijnen, J. H., & Huitema, A. D. R. (2022). Pharmacokinetics and Pharmacodynamics of PARP Inhibitors in Oncology. *Clinical pharmacokinetics*, *61*(12), 1649–1675. https://doi.org/10.1007/s40262-022-01167-6

Coleman, R. L., Oza, A. M., Lorusso, D., Aghajanian, C., Oaknin, A., Dean, A., Colombo, N., Weberpals, J. I., Clamp, A., Scambia, G., Leary, A., Holloway, R. W., Gancedo, M. A., Fong, P. C., Goh, J. C., O'Malley, D. M., Armstrong, D. K., Garcia-Donas, J., Swisher, E. M., Floquet, A., … ARIEL3 investigators (2017). Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet (London, England)*, *390*(10106), 1949–1961. https://doi.org/10.1016/S0140-6736(17)32440-6

Dottino, J. A., Esselen, K. M., Costa, R., Argetsinger, S., Shahzad, M., Ross-Degnan, D., & Wagner, A.

K. (2024). Financial Toxicity of Withdrawn Poly (Adenosine Diphosphate Ribose) Polymerase Inhibitor Indications for Ovarian Cancer. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, *27*(9), 1175–1178. https://doi.org/10.1016/j.jval.2024.05.022

González-Martín, A., Pothuri, B., Vergote, I., Graybill, W., Lorusso, D., McCormick, C. C., Freyer, G., Backes, F., Heitz, F., Redondo, A., Moore, R. G., Vulsteke, C., O'Cearbhaill, R. E., Malinowska, I. A., Shtessel, L., Compton, N., Mirza, M. R., & Monk, B. J. (2023). Progression-free survival and safety at 3.5years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. *European journal of cancer (Oxford, England : 1990)*, *189*, 112908. https://doi.org/10.1016/j.ejca.2023.04.024

Hopkins, T. A., Shi, Y., Rodriguez, L. E., Solomon, L. R., Donawho, C. K., DiGiammarino, E. L., Panchal, S. C., Wilsbacher, J. L., Gao, W., Olson, A. M., Stolarik, D. F., Osterling, D. J., Johnson, E. F., & Maag, D. (2015). Mechanistic Dissection of PARP1 Trapping and the Impact on In Vivo Tolerability and Efficacy of PARP Inhibitors. *Molecular cancer research : MCR*, *13*(11), 1465–1477. https://doi.org/10.1158/1541-7786.MCR-15-0191-T

Illuzzi, G., Staniszewska, A. D., Gill, S. J., Pike, A., McWilliams, L., Critchlow, S. E., Cronin, A., Fawell, S., Hawthorne, G., Jamal, K., Johannes, J., Leonard, E., Macdonald, R., Maglennon, G., Nikkilä, J., O'Connor, M. J., Smith, A., Southgate, H., Wilson, J., Yates, J., … Leo, E. (2022). Preclinical Characterization of AZD5305, A Next-Generation, Highly Selective PARP1 Inhibitor and Trapper. *Clinical cancer research : an official journal of the American Association for Cancer Research*, *28*(21), 4724–4736. https://doi.org/10.1158/1078-0432.CCR-22-0301

Kirby, I. T., & Cohen, M. S. (2019). Small-Molecule Inhibitors of PARPs: From Tools for Investigating ADP-Ribosylation to Therapeutics. *Current topics in microbiology and immunology*, *420*, 211–231. https://doi.org/10.1007/82_2018_137

Kulkarni, S., Seneviratne, N., Tosun, Ç., & Madhusudan, S. (2025). PARP inhibitors in ovarian cancer: Mechanisms of resistance and implications to therapy. *DNA repair*, *149*, 103830. https://doi.org/10.1016/j.dnarep.2025.103830

Langelier, M. F., Eisemann, T., Riccio, A. A., & Pascal, J. M. (2018). PARP family enzymes: regulation and catalysis of the poly(ADP-ribose) posttranslational modification. *Current opinion in structural biology*, *53*, 187–198. https://doi.org/10.1016/j.sbi.2018.11.002

Liang, M. I., Chen, L., Hershman, D. L., Hillyer, G. C., Huh, W. K., Guyton, A., & Wright, J. D. (2021). Total and out-of-pocket costs for PARP inhibitors among insured ovarian cancer patients. *Gynecologic oncology*, *160*(3), 793–799. https://doi.org/10.1016/j.ygyno.2020.12.015

Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., Lisyanskaya, A.,

Floquet, A., Leary, A., Sonke, G. S., Gourley, C., Banerjee, S., Oza, A., González-Martín, A., Aghajanian, C., Bradley, W., Mathews, C., Liu, J., Lowe, E. S., Bloomfield, R., … DiSilvestro, P. (2018). Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *The New England journal of medicine*, *379*(26), 2495–2505. https://doi.org/10.1056/NEJMoa1810858

Murai, J., Huang, S. Y., Das, B. B., Renaud, A., Zhang, Y., Doroshow, J. H., Ji, J., Takeda, S., & Pommier, Y. (2012). Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer research*, *72*(21), 5588–5599. https://doi.org/10.1158/0008-5472.CAN-12-2753

Murai, J., Zhang, Y., Morris, J., Ji, J., Takeda, S., Doroshow, J. H., & Pommier, Y. (2014). Rationale for poly(ADP-ribose) polymerase (PARP) inhibitors in combination therapy with camptothecins or temozolomide based on PARP trapping versus catalytic inhibition. *The Journal of pharmacology and experimental therapeutics*, *349*(3), 408–416. https://doi.org/10.1124/jpet.113.210146

Ray-Coquard, I., Leary, A., Pignata, S., Cropet, C., González-Martín, A., Marth, C., Nagao, S., Vergote, I., Colombo, N., Mäenpää, J., Selle, F., Sehouli, J., Lorusso, D., Guerra Alia, E. M., Bogner, G., Yoshida, H., Lefeuvre-Plesse, C., Buderath, P., Mosconi, A. M., Lortholary, A., … PAOLA-1/ENGOT-ov25 investigators (2023). Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Annals of oncology : official journal of the European Society for Medical Oncology*, *34*(8), 681–692. https://doi.org/10.1016/j.annonc.2023.05.005

Robson, M. E., Tung, N., Conte, P., Im, S. A., Senkus, E., Xu, B., Masuda, N., Delaloge, S., Li, W., Armstrong, A., Wu, W., Goessl, C., Runswick, S., & Domchek, S. M. (2019). OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Annals of oncology : official journal of the European Society for Medical Oncology*, *30*(4), 558–566. https://doi.org/10.1093/annonc/mdz012

Rudolph, J., Jung, K., & Luger, K. (2022). Inhibitors of PARP: Number crunching and structure gazing. *Proceedings of the National Academy of Sciences of the United States of America*, *119*(11), e2121979119. https://doi.org/10.1073/pnas.2121979119

Xie, T., Dickson, K. A., Yee, C., Ma, Y., Ford, C. E., Bowden, N. A., & Marsh, D. J. (2022). Targeting Homologous Recombination Deficiency in Ovarian Cancer with PARP Inhibitors: Synthetic Lethal Strategies That Impact Overall Survival. *Cancers*, *14*(19), 4621. https://doi.org/10.3390/cancers14194621

Zandarashvili, L., Langelier, M. F., Velagapudi, U. K., Hancock, M. A., Steffen, J. D., Billur, R., Hannan, Z. M., Wicks, A. J., Krastev, D. B., Pettitt, S. J., Lord, C. J., Talele, T. T., Pascal, J. M., & Black, B. E. (2020). Structural basis for allosteric PARP-1 retention on DNA breaks. *Science (New York, N.Y.)*, *368*(6486), eaax6367. https://doi.org/10.1126/science.aax636