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REVIEW

Advances in PARP Inhibition in Improving Outcomes of Breast Cancer, Ovarian Cancer, and Other Solid Tumors: Journey of Discovery, Development, and Clinical Updates of Talazoparib

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Abstract: Poly(ADP-ribose) polymerase (PARP) inhibition has emerged as a prominent approach in cancer treatment, leading to the development of several poly(ADP-ribose) polymerase inhibitors (PARPi), which have demonstrated substantial progress in clinical trials and efficacy in the management of ovarian cancer (OC), breast cancer (BC), and solid tumors (STs). These PARPi are approved for several cancers, including BC and OC. Among PARPi, Talazoparib (Talzenna®) is a potent therapy for patients with locally advanced or metastatic BC (*mBC*) with germline *BRCA* mutations (*gBRCAm*) and *HER2*-negative status, demonstrating the highest potency (IC_{50} = 0.57 nM), which is 4–10 times lower than that of other PARP inhibitors; olaparib (2.0 nM), rucaparib (1.9 nM), and veliparib (4.7 nM), indicating superior efficacy. This review describes the role of *BRCA1/2* in BC and OC, highlighting key discovery milestones and providing an overview of available PARP inhibitors (PARPi) at various stages of development. Additionally, it details the discovery and development of talazoparib, one of the key PARPis, its current clinical status, and therapeutic implications. The latest advancements in talazoparib research, including all related clinical trials (Phase 1–3) for the treatment of BC, OC, and other solid tumors (STs), are also summarized. A comprehensive analysis of all clinical trials involving talazoparib, whether as monotherapy or in combination with other drugs, elucidates its potential to improve clinical outcomes, address drug resistance, and explore synergistic combinations with other PARPi or novel agents, thereby providing insights into the clinical utility of talazoparib.

Keywords: clinical trials, breast cancer, ovarian cancer, third-generation inhibitor, synthetic strategies

Introduction

Cancer continues to represent a significant global health challenge, contributing to millions of new diagnoses and fatalities annually. Recent global estimates reveal that nearly 20 million new cancer cases and approximately 9.7 million deaths were recorded worldwide in 2022, underscoring the increasing burden of malignancies in both developed and developing regions.[1–3] Among these, solid tumors (STs) account for the majority of global cancer cases, with lung, breast, colorectal, and prostate cancers being the most frequently diagnosed malignancies. BC and OC collectively

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contribute significantly to the global burden of solid tumors, which account for over 90% of all newly diagnosed cancer cases worldwide. According to the GLOBOCAN 2022 global estimates, female breast cancer remains the most prevalent malignancy among women, with an estimated 2.30 million new cases in 2022 and an age-standardized incidence rate (ASR) of approximately 46.8 per 100,000 population.[1,4] This reflects substantial regional disparities, with higher ASRs in developed regions such as Northern America and Europe compared to lower rates in parts of Asia and Africa. In the same year, OC accounted for approximately 324,603 new cases globally, with an ASR of 6.7 per 100,000, ranking among the top ten cancers in women by incidence. STs overall—including breast, lung, colorectal, prostate, and stomach cancers—constituted the vast majority of cancer incidence, with approximately 19.98 million new cases worldwide. The combined age-standardized rates for all cancers (excluding non-melanoma skin cancer) were approximately 186.5 per 100,000 across both sexes, underscoring the dominant contribution of solid malignancies to global cancer incidence and highlighting the need for continued emphasis on solid tumor epidemiology in research and healthcare planning.[4–6]

The prevalence of cancer has risen dramatically in countries with low and middle incomes, and this pattern is anticipated to persist, as economic growth leads to lifestyle changes that elevate women's risk of disease in these nations. Furthermore, low- and middle-income nations lack financial resources to provide extensive technology-driven healthcare to their citizens. In wealthy countries, the anticipated cost of medical treatment has escalated rapidly.[7] The mortality rate is consistently declining, particularly among younger female patients, owing to advancements in treatment and earlier detection methods.[8]

The prognosis of patients with BC varies significantly based on factors such as the stage at diagnosis, molecular subtype, and other clinical and pathological features. Among these factors, the stage at which the cancer is detected is the most robust predictor of survival. The 5-year relative survival rate demonstrates a marked contrast across different stages: it exceeds 99% for cancer diagnosed at a localized stage, decreases to 87% for regional stage disease, and declines further to 32% for cases which cancer has metastasized to reserved parts of the body. Over the past two decades, BC survival rates have improved remarkably.[9] The lifetime risk of BC or OC is greatly amplified if a woman inherits a mutation in *BRCA1* or *BRCA2* genes. A positive family history of BC is a significant risk factor for the development of this type of cancer. After an individual's age, family history is considered the most established factor contributing to an increased risk.[10] According to current scientific understanding, hereditary cancer susceptibility syndromes resulting from high-penetrance gene mutations are account for almost 5% of all BC cases. A substantial proportion of hereditary BC, approximately 50%, is linked with the germline mutations in the *BRCA1/2* genes.[11,12]

A literature search was conducted to gather publications related to the subject matter. Major scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, and the Food and Drug Administration website, were utilized to ensure comprehensive coverage of the available literature. The search employed various combinations of predefined keywords and Boolean operators pertinent to the research topic. Only peer-reviewed articles published in reputable journals were considered. Additionally, the reference lists of selected articles were manually screened to identify further relevant studies. The retrieved literature was critically evaluated and curated to provide an up-to-date and comprehensive synthesis of current developments in the field. The data searches were restricted to peer-reviewed articles published in English. Recent studies were prioritized to incorporate the most up-to-date findings, while earlier publications were also included when pertinent to the conceptual framework of the field, thereby providing a comprehensive dataset focused on talazoparib.

This review describes the role of *BRCA1/2* in BC and OC, highlighting key discovery milestones and providing an overview of available PARP inhibitors (PARPi) at various stages of development. Additionally, it details the discovery and development of talazoparib, one of the key PARPis, its current clinical status, and its therapeutic implications. We summarize the latest advancements in talazoparib research, including all related clinical trials (Phase 1–3) for the treatment of BC, OC, and STs, are summarized. A comprehensive analysis of all clinical trials involving talazoparib, whether as monotherapy or in combination with other drugs, elucidates its potential to improve clinical outcomes, address drug resistance, and explore synergistic combinations with other PARPi or novel agents, thereby providing insights into the clinical utility of talazoparib.

Discovery and Structure of BRCA1/2

BRCA1/2 genes were identified in the 1990s. *BRCA1* was initially associated with BC in 1990 through linkage analysis of a large group of families with early onset of BC and was found to be localized to chromosome 17q21.[13] *BRCA1* was subsequently cloned in 1994, with truncating mutations found in its coding sequence in families with multiple BC cases.[14] The quest for additional genes potentially involved in hereditary BC susceptibility resulted in the discovery of *BRCA2* in 1995, which is located on chromosome 13q12.3. Researchers have discovered *BRCA2* through the application of linkage analysis and positional cloning techniques to multigenerational familial BC pedigrees.[15,16] Simultaneously, various families exhibiting high rates of male BC have been found to carry *BRCA2* mutations.[17] Multiple studies have shown that individuals with *BRCA1/2* mutations not only have BC and OC but also face enhanced risks of malignancies in the fallopian tubes, colon, prostate, skin (melanoma), and pancreas.[18–24] *BRCA1/2* genes possess intricate genomic structures and are essential for DNA repair mechanisms; they create complexes that assist in repairing double-strand breaks (DSBs) and trigger homologous recombination (HR).[25,26] Cells lacking functional *BRCA1* and *BRCA2* show increased vulnerability to DSB-inducing agents such as mitomycin C and cisplatin.[27–29] Additionally, ionizing radiation causes these breaks, which are repaired using error-prone methods, such as non-homologous end-joining.[30,31] Individuals with *BRCA1*/2 gene mutations have a high lifetime risk of developing BC ranging from 60% to 85%. These mutations also increase the lifetime risk of OC, with *BRCA1* carriers having a 26% to 54% risk and *BRCA2* mutation carriers having a 10% to 23% risk. *BRCA1*/2 gene mutations are responsible for approximately 45% of families with multiple BC cases and up to 90% of families with both BC and OC.[32–35] Importantly, hereditary BC associated with *BRCA1* or *BRCA2* mutations exhibits both unique clinical and pathological features.[36–38]

Poly (ADP-Ribose) Polymerases and BRCA1/2

Poly (ADP-ribose) polymerases (PARPs) constitute a family of enzymes capable of facilitating the transfer of ADP-ribose to target proteins through a process known as poly ADP-ribosylation (pADPr). This family is comprised of at least 17 members (with only 10 putative), each encoded by distinct genes and sharing homology in a conserved catalytic domain. While PARP1 and PARP2 are predominantly associated with DNA repair functions, investigations have demonstrated that these and other PARP isoforms are crucial for numerous cellular processes, including regulation of cell proliferation and programmed cell death. Researchers have identified numerous cellular substrates of PARP, with the majority comprising proteins localized in the nucleus that are involved in nucleic acid metabolism, DNA synthesis and repair, and modification of chromatin structure. Upon the occurrence of DNA strand breaks, PARP undergoes self-modification and functions as one of the primary acceptors of poly-ADP ribose in biological systems and *in* vivo models. PARP1 is considered a first-in-class and the most thoroughly investigated key member of the PARP family and is closely related to PARP2. The latter shares 69% similarity in its catalytic domain with PARP1 and was found because of the persistence of PARP potential in cells lacking PARP1. As mentioned above, the most prevalent form of PARP-1 is crucial in repairing DNA single-strand breaks via the base excision repair Pathway.[39] PARP1 also modifies *BRCA1* with pADPr, influencing DSB repair during HR[40] and hindering non-homologous end-joining (NHEJ) repair by preventing Ku protein attachment to DNA ends.[41,42] Moreover, PARP1 is essential for other microhomology-mediated end-joining repair pathways.[43,44] It is noteworthy that both PARP2 and PARP3 also aid in DNA repair; PARP2 works alongside PARP1 in pADPr synthesis, whereas PARP3 suppresses error-prone NHEJ.[45–47]

The inhibition of PARP enzymes results in the accumulation of single-strand breaks in the DNA. This accumulation subsequently leads to the formation of DSBs at sites of DNA replication. In normal cells, these DSBs are primarily repaired by the error-free HR pathway, which relies on the *BRCA1* and *BRCA2* tumor suppressor proteins. In the absence of *BRCA1* or *BRCA2*, this damage remains unrepaired, causing cell cycle arrest and death, despite the alternative NHEJ pathway for DSB repair. Some authors have elucidated the significance of PARP in DNA repair mechanisms and the fundamental actions of PARP inhibitors.[48]

The Discovery Journey of PARP1/2 Inhibitors

The discovery and development of several key PARPi as anti-tumor agents have demonstrated their efficacy and effectiveness in both in vitro and in vivo models. It has been shown that under the concept of synthetic lethality, PARPi can be employed as a monotherapy agent; however, their use in combination with chemotherapy or radiotherapy to induce a synergistic effect is another therapeutic arena.

The translation of this biological concept, termed synthetic lethality, into a clinically oriented practice has been objectified by PARPs. It is an imperial illustration of translational medicine. The basic mechanistic pathway of PARP inhibition is shown in Figure 1, and the milestones in the discovery of clinically relevant PARPi developed from the nicotinamide pharmacophore are shown in Figure 2.

Poly (ADP-ribose) polymerase inhibitors (PARPi) are synthetic molecules that disrupt the capacity of cells to repair their DNA. Mutations in the *BRCA1/2* genes are responsible for 5–10% of all BC cases. Studies have demonstrated that cancers associated with BRCA1/2 mutations exhibit increased susceptibility to PARPi. PARP1/2 inhibitors have emerged as an inspiring class of anti-cancer agents, and many PARP1/2 inhibitors have been reported. Several small molecules targeting PARP have been synthesized and developed as DNA-damaging chemotherapeutic agents or chemosensitizers in conjugation with ionizing radiation (especially for *BRCA1/2* mutant BC or OC).[45,49] To date, many PARPi have been identified, most of which are nicotinamide analogs.[50–53] Most PARPi are in Phase II and III (late phase) clinical therapeutic trials, including rucaparib (AG-014699),[54,55] olaparib (AZD-2281),[56] veliparib (ABT-888),[57–59] niraparib (MK-4827, Zejula®)[60,61] and talazoparib (BMN 673).[62] Among nicotinamide analogs, talazoparib (BMN 673) is a novel, orally bioavailable, dual-mechanism PARPi that effectively traps PARP in DNA.

Most PARP1 inhibitors developed to date are nicotinamide mimetics (NAMs). This structural mimic of nicotinamide allows PARP1 inhibitors to support favorable binding to the enzyme. Figures 3 and 4 show the first and 2nd-generation PARPi, which were based on the i)-nicotinamide core, ii)-benzamide motif, and iii)-substituted benzamides, such as 3-aminobenzamide (3-AB). Nicotinamide, a weak PARP inhibitor, was discovered in 1971, wherein 5′-methyl nicotinamide and nicotinamide were investigated as inhibitors of poly ADP-ribose polymerase and nicotinamide adenine dinucleotide (NAD) nucleosidase.[63] Since 1980, discovery efforts have made the nicotinamide core a key motif in first-generation PARPi, and 3-AB was developed as the first widely investigated agent.[64] Currently, there are at least nine PARPi in clinical development (Table 1).

Specificity is considered an essential element in reducing off-target effects and toxicities associated with PARPi.[78] The 2nd-generation PARPi, such as NU1025 and PD128763, demonstrated more potency (>50-fold more potent) than 3-AB competitors. Numerous 3rd-generation PARPi with 3-AB are under development and have shown higher potency and superior specificity for PARP. The majority of 3rd-generation PARPi comprised benzamide-type or purine-type scaffolds (Figures 5 and 6). These included talazoparib (BMN 673; BioMarin/LEAD/Medivation), veliparib (ABT-888; AbbVie), niraparib (MK-4827; Tesaro/Merck), rucaparib (AG-014699; Clovis/Pfizer), and olaparib (AZD-2281; AstraZeneca/Kudos). These PARPi are available in the market at the commercial level or in late-phases (phases 2 and 3) clinical trials. However, some recently reported new PARPi have been used in pre-clinical or early stage clinical evaluations.

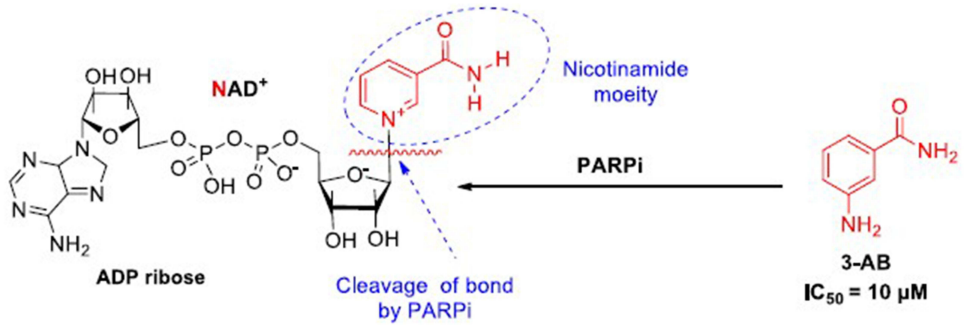

Figure 1 The basic mechanistic pathway of PARP inhibitors.

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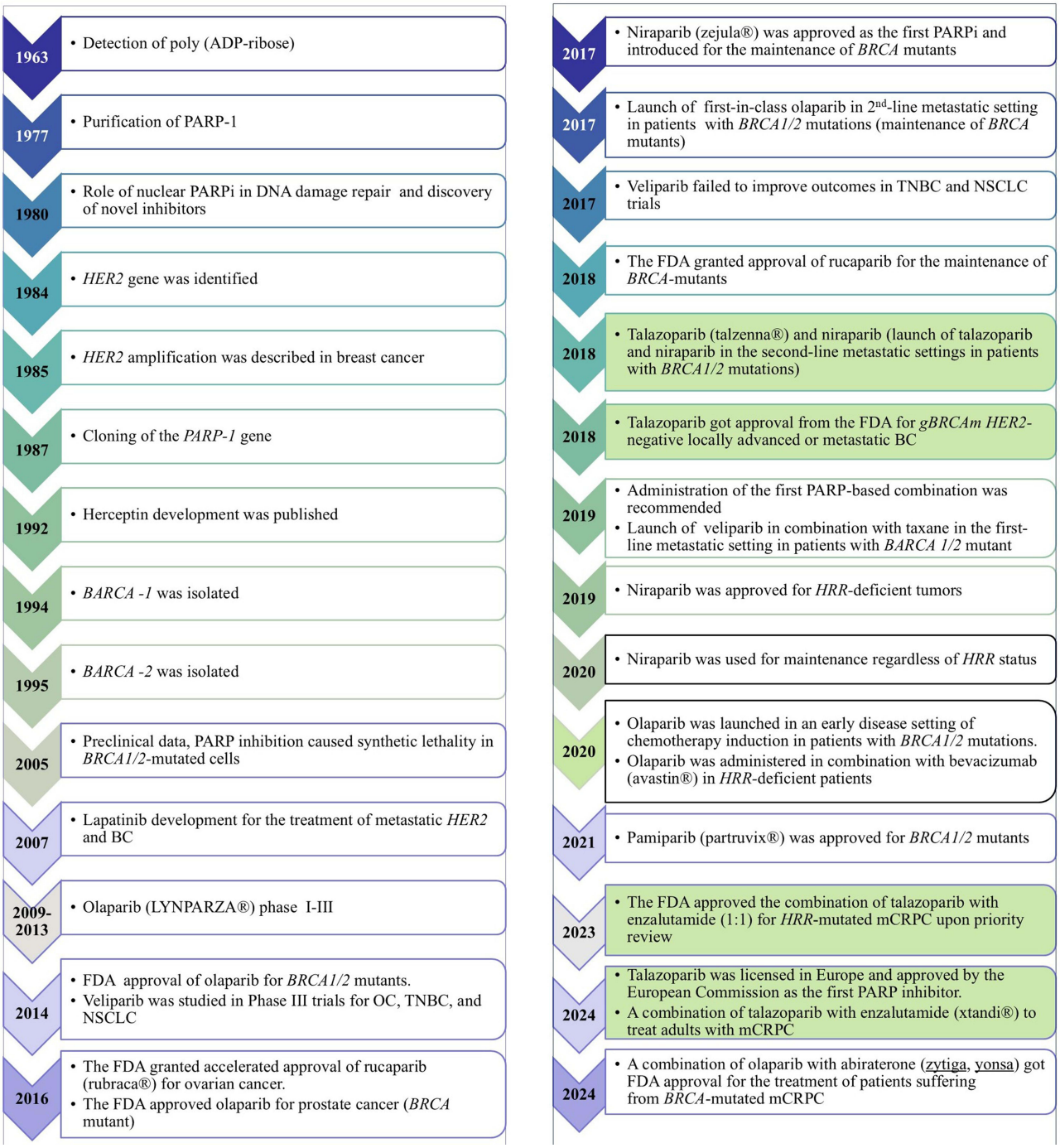

Figure 2 The discovery milestone of PARPi containing a nicotinamide pharmacophore for the treatment of BC, OC, and STs.

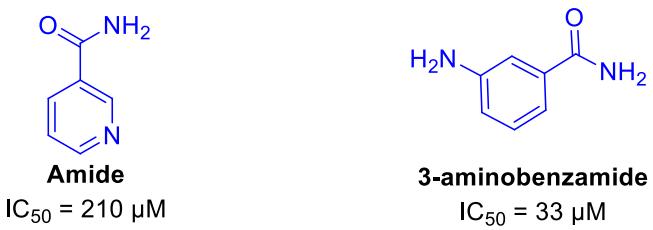

Figure 3 Core structure of first-generation PARP inhibitors.

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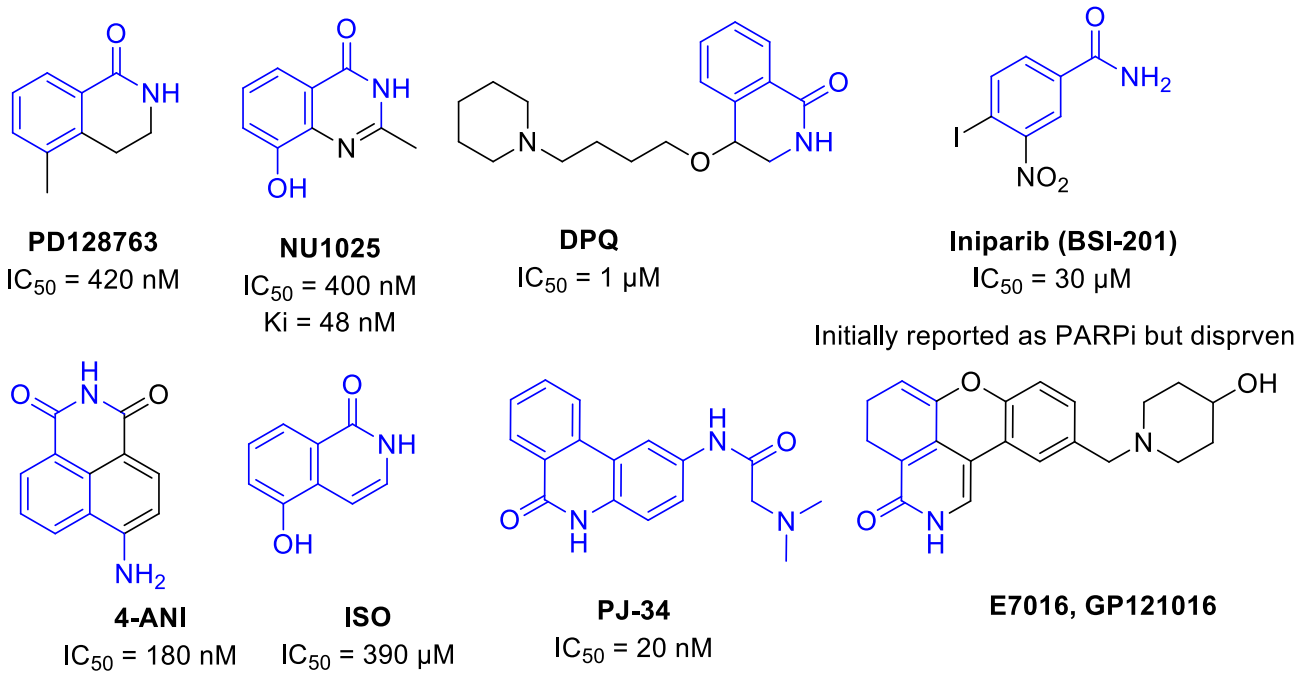
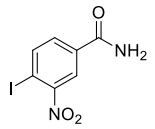
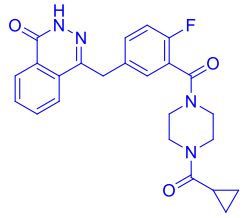
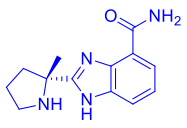


Figure 4 Structural characteristics of selected second-generation PARP inhibitors.

Talazoparib, a highly effective PARP1/2 inhibitor approved for treating germline *BRCA*-mutated, *HER2*-negative advanced BC, is consistently highlighted in both preclinical and clinical studies for its remarkable ability to trap PARP. This mechanism involves the inhibitor stabilizing PARP-DNA complexes at DNA single-strand break sites, transforming

Table 1 A Summary of the Key PARPi Currently Undergoing Clinical Trials

Name/Structure	Phase, Company, Therapy Type, Indication at Present/Tumor Type
 Iniparib (BSI 201) BiPar/Sanofi	Bipar Sciences developed this molecule. Research conducted by BiPar/Sanofi indicates that Iniparib lacks the typical characteristics of PARP inhibitors. In addition to BC, NSCLC is another relevant condition and is administered intravenously. The combination of Iniparib with carboplatin and gemcitabine demonstrated significant efficacy in treating mTNBC. A randomized phase II trial (NCT01045304) in 2011 evaluated the efficacy of carboplatin and gemcitabine, with or without Iniparib, in TNBC patients who had received up to two prior chemotherapy regimens for metastatic disease. Information on BRCA status was not provided.[65] In Phase III (NCT00938652), Iniparib exhibited improved progression-free survival (5.1 months) and overall survival (11.8 months).[66]
 Olaparib (AZD2281) AstraZeneca	AstraZeneca developed this compound, which is currently progressing in Phase II (single agent) and Phase III (combination) clinical trials. Olaparib, an orally administered PARP inhibitor, exhibits superior efficacy compared to conventional treatments in *HER*-negative mBC and *gBRCAm* BC patients. Investigations have explored its potential in various conditions, including BC, OC, colorectal, fallopian tube, breast, lung, prostate, pancreatic, gastric, and advanced tumors. The drug is utilized as both monotherapy and in combination regimens, demonstrating promising results in treating TNBC patients. When combined with radiotherapy, olaparib was well-tolerated in TNBC cases[67] and may function as an effective radiosensitizer for this subtype of BC.[68]
 Veliparib (ABTT888) Abbott	This molecule was developed by Abbott and currently undergoing Phase II clinical trials (monotherapy or combination). It is an orally available agent. Other targets are melanoma, fallopian tube, peritoneal, BC, OC, peritoneal, lung, colorectal, cervical, prostate, glioblastoma pancreatic, and advanced tumors. In Phase III (combination therapy), BC, lung cancer, and glioblastoma are among other targets.

(*Continued*)

Table 1 (Continued).

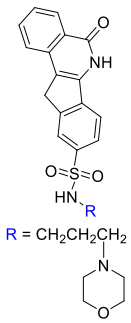
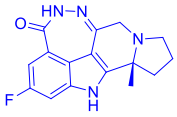
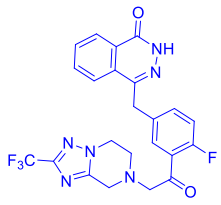
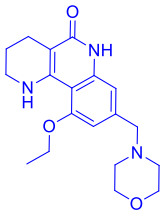
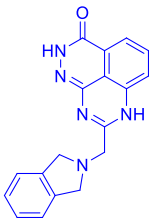
Name/Structure	Phase, Company, Therapy Type, Indication at Present/Tumor Type
 INO-1001 Inotek/Genentech	This is an early-stage PARPi named INO-1001, which was developed by Inotek/Genentech but discontinued after the outcome of Phase I clinical trials.[69] This compound exhibited potent PARP1/2 binding and demonstrated notable selectivity of PARP1 over PARP2. INO-1001 showed almost 30-fold more selectivity (PARP1/PARP2; 7.9 vs 217.2 nM). The selectivity profile of INO-1001 was comparable to that of niraparib, potentially owing to the structural similarities, although direct comparisons of their PARP binding mechanisms are not available. Significantly, the DLT observed with this small molecule was hematological in nature. These toxicities were retrospectively attributed to the PARP2 inhibition. The rationale for halting clinical development remains unclear because no serious AEs were reported in the Phase I trials. The pharmacokinetic data displayed by INO-1001 were encouraging. However, concerns regarding potential hepatotoxicity might have influenced this decision.[70,71]
 Primapraib (BGB-290) BeiGene	This molecule is currently progressing in Phase II clinical trials (NCT03427814). BeiGene, a company based in Beijing, China, has developed pamiparib (BGB-290) and is currently progressing multiple phase II/III clinical trials. This substance, characterized as a fused pentacyclic dihydrodiazepinoindolone derivative, demonstrates significant efficacy against both PARP-1 and PARP-2 enzymes, with IC_{50} values of 1.3 and 0.9 nM, respectively. Furthermore, pamiparib exhibits substantial selectivity when compared to TNKS1 and TNKS-2, with IC_{50} values of 230 and 140 nM, respectively.[72]
 Fluzopraib (SHR-3162) Jiangsu HengRui Medicine	Jiangsu HengRui Medicine Co., Ltd, China, is currently developing Fluzoparib. The compound is progressing in Phase II clinical trials (NCT05732129, not currently recruiting). Furthermore, a Phase I trial (NCT03509636) is in progress for patients with *BRCA1*/2-mutant OC. In a Phase I study, Fluzoparib, a PARP inhibitor, exhibited promising anti-tumor effects in advanced OC cases. This agent, also known as SHR3162 or HS10160, is an oral and highly potent PARP inhibitor that demonstrates anti-tumor properties, with a PARP1 IC_{50} of 1.46±0.72 nM.[73,74]
 Amelpraib (JPI-289) Jeil Pharmaceuticals	This molecule was developed by Jeil Pharmaceuticals, Korea. It is presently enduring Phase II clinical Trials (CT03062397). JPI-289, or Amelparib (free base), is a highly potent, orally available, and water-soluble PARP-1 inhibitor. This compound demonstrates nanomolar-range inhibition of PARP-1 (IC_{50}=18.5 nM) and cellular PAR formation (IC_{50}=10.6 nM). Amelparib shows promise as a neuroprotective agent and may have applications in acute ischemic stroke research. The substance exhibits promising potential as a neuroprotective agent in acute ischemic stroke; however, it has not demonstrated efficacy for acute kidney injury resulting from ischemia and has shown a negative impact on healing.[75]
 Stenoparib (E7449, 2X-121, MGI25036)	Allarity Therapeutics, a US-based company, is currently advancing this compound through Phase II clinical trials (NCT03562832). Stenoparib (E7449, 2X-121, MGI25036) is characterized as an orally administered, brain-penetrating small molecule that functions as a dual inhibitor of PARP1/2. This compound also demonstrates inhibitory effects on PARP5a/5b and possesses a unique dual-inhibitory mechanism targeting both PARP 1/2 and Tankyrase 1/2 (TNKS1/2), the latter being a crucial regulator of canonical Wnt/β-catenin signaling. The agent exhibits promising PARP inhibition (PARP1; C_{50}=1.0 nM, and PARP2; IC_{50}=1.2 nM). Additionally, the molecule shows efficacy in P-glycoprotein-expressing cells, indicating its potential to overcome certain forms of PARP inhibitor resistance.

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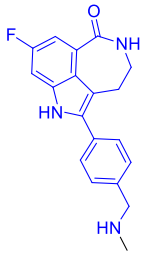
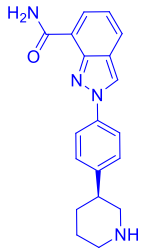
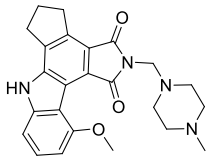
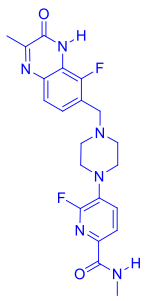
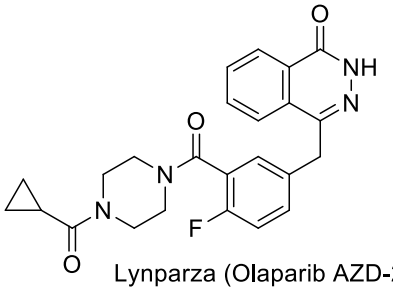
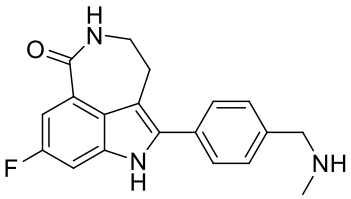
Table 1 (Continued).

Name/Structure	Phase, Company, Therapy Type, Indication at Present/Tumor Type
 Rucaparib (Rubraca, AG014699, PF01367338)	This molecule was developed by Pharmaand GmbH, Germany. At present, Phase III clinical trials are in evolution for rucaparib. In a cell-free assay, rucaparib phosphate demonstrates inhibition of PARP1 (*Ki*=1.4 nM) and exhibits binding affinity to a further 8 additional PARP domains (NCT04539327). It is the first PARP inhibitor utilized in clinical trials in combination with TMZ. This compound is under development for the therapy of OC associated with HR DNA repair deficiency (HRD) and is presently continuing in Phase 1/2 clinical trials (NCT01482715). Furthermore, investigators have assessed the safety as well as efficacy of rucaparib in individuals with relapsed OC harboring *BRCA* mutations.[76]
 Nirapraib (MK-4827) Merck	This molecule was developed by Merck. Niraparib, a PARP inhibitor, has received FDA consent to treat platinum-sensitive ovarian serous carcinoma. Phase III clinical trials have established its safety profile. This compound demonstrates selectivity for PARP inhibition (PARP1, IC_{50}=3.8 nM and PARP2, IC_{50} = 2.1 nM) and demonstrates significant efficacy in cancer cells with *BRCA1* and *BRCA2* mutations. It exhibits greater than 330-fold selectivity against V-PARP, PARP3 and Tank1. Through the formation of PARP–DNA complexes, niraparib induces DNA damage, apoptosis, and cell death. At present, several clinical trials are investigating niraparib's therapeutic potential for serous endometrial carcinoma (NCT05289648, Early Phase 1, Not yet recruiting). Monotherapy and a combination of niraparib and GSK4524101 for STs has also been evaluated (NCT06077877).
 CEP-9722, proagent of CEP-8983, (Teva)	CEP-9722, which functions as the proagent for CEP-8983, is a potent and orally administered inhibitor that specifically targets PARP-1 and PARP-2, with IC_{50} values of 20 nM and 6 nM, respectively. This compound exhibits anticancer properties and is at this time undergoing evaluation in Phase 1/2 Clinical trials (NCT01311713) under the supervision of Teva Branded Pharmaceutical Products R&D, Inc. The primary objective of these studies is to regulate the maximum tolerated dose that can be safely administered on a daily basis to patients with advanced or metastatic STs, as well as to measure the tolerability and safety of this established dose.
 AZD9574	AZD9574 is a newly developed brain-penetrant compound with a distinct structural framework. It acts as a PARP inhibitor and demonstrates exceptional PARP1 selectivity (>8000-fold selectivity for PARP1 over PARP2), trapping ability, and enhanced CNS penetration within a single molecule. This compound exhibits PARP1 IC_{50} in the range between 0.3–2 nM. Experimental data from animal studies supports its advancement as a promising next-generation therapeutic candidate for addressing metastatic diseases and primary brain tumors. Thus, for patients with HRD^{+} BC that has metastasized to the brain, AZD9574 represents a potentially efficacious therapeutic intervention.[77]

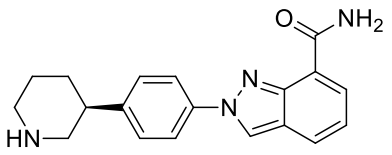
them into deadly DSBs in cells deficient in homologous recombination. When compared to other clinically approved PARP inhibitors like olaparib, rucaparib, niraparib, and veliparib, talazoparib demonstrates significantly greater trapping potency. Quantitative studies indicate that its stabilization of PARP-DNA complexes can be approximately 100 times more potent than that of olaparib and rucaparib, and considerably higher than niraparib or veliparib, placing talazoparib at the forefront of PARP trapping efficiency within its class. This enhanced trapping is linked to its strong cytotoxic effects at nanomolar concentrations in *BRCA*-deficient models and supports its powerful anti-tumor activity at relatively low clinical doses (1 mg once daily), unlike the higher doses required for other PARP inhibitors. Mechanistically, this superior trapping is attributed to talazoparib's unique structural characteristics that promote a strong PARP1/2-DNA



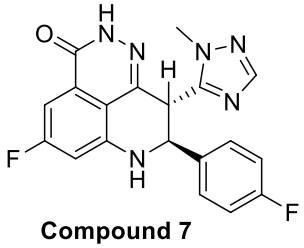
Lynparza (Olaparib AZD-2281 / KU-0059436)
PARP1 IC_{50} = 5 nM
PARP2 IC_{50} = 1 nM
(Astrazeneca)



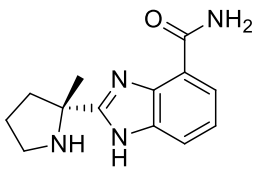
Rucaparib/Rubraca (AG-014699/PF-01367338)
IC_{50} = 1 nM
(Clovis oncology/ Pharmaand GmbH)



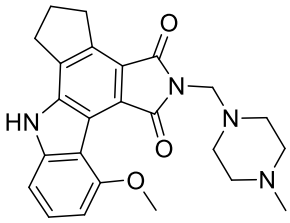
Niraparib, MK-4827, Tesaro (Zejula),
PARP1, IC_{50} = 3.8 nM
PARP2, IC_{50} = 2.1 nM
(Merck)



Compound 7
Talazoparib (BMN 673)/(Talzenna)
PARPi EC_{50} = 5.48 nM
EIA IC_{50} = 2.14 nM
PARP1 *Ki* = 1.2 nM
PARP2 *Ki* = 0.87 nM
(Lead Therapeutics/BioMarin/Medivation)

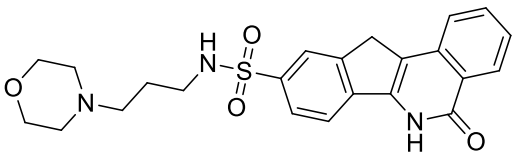


Veliparib (ABT888)
PARP1 *Ki* = 5.2 nM
PARP2 *Ki* = 2.9 nM
(Abbvie/Abbott)

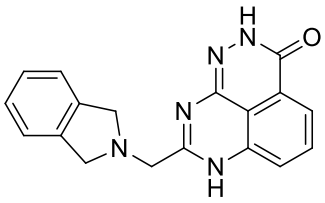


CEP-9722, proagent of CEP-8983
PARP1, IC_{50} = 20 nM
PARP2, IC_{50} = 6 nM
(Teva)

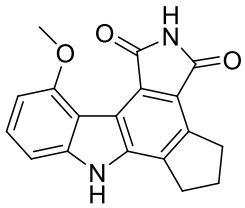
Figure 5 Chemical structures of selected third-generation PARP inhibitors.



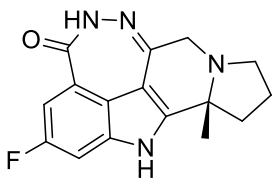
NO-1001
IC_{50} = 105 nM



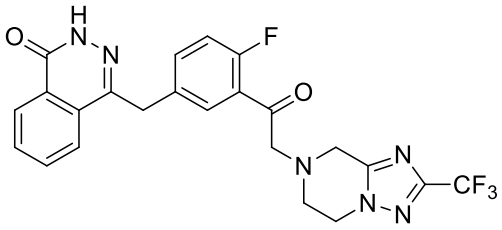
2x-121
IC_{50} = 1 nM



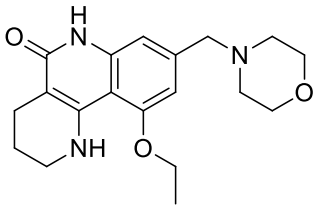
CEP-8983
IC_{50} = 20 nM



Pamiparib (BGB-290)
IC_{50} = 0.83 nM



Fluzoparib (SHR-3162)
IC_{50} = 1.5 nM



Amelparib (JPI-289)
PARP-1 IC_{50} = 18.5 nM
Cellular PAR formation
(IC_{50}=10.7 nM)

Figure 6 Chemical structures of selected clinical-stage third-generation PARP inhibitors.

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interaction and extended retention on DNA, thereby increasing replication stress and synthetic lethality in HR-deficient tumors. These differences in PARP trapping potency are now widely acknowledged as a crucial differentiator in the pharmacodynamic profiles of PARP inhibitors and a vital factor in optimizing therapeutic strategies in oncology. Thus, talazoparib has emerged as one of the most promising PARP inhibitors in advanced-level clinical trials. It is significant to note that talazoparib was granted FDA approval for BC patients with inherited *BRCA1/2* mutations in 2018 (US) and 2019 (Europe), following the promising outcomes of the *EMBRACA* randomized, phase III clinical trial;[79] however, it has not yet been approved for OC treatment. The FDA granted approval in June 2023 for the use of talazoparib in combination with enzalutamide for the management of adult patients with metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (*HRR*) mutations. Clinical trial data indicate that this combination therapy can reduce the risk of disease progression or death up to 55% in patients with HRR gene-mutated mCRPC. Furthermore, OC has long been recognized as the most lethal malignancy affecting the female reproductive system. It has been shown that over 15% of OC patients exhibit a defective *BRCA*-mediated *HRR* pathway, which can be targeted therapeutically using PARPi such as talazoparib. The expansion of talazoparib's clinical approval beyond BC has been hampered by its extremely strong systemic side effects, which are comparable to those of chemotherapeutics.

Recent clinical and regulatory advancements have underscored the increasing significance of talazoparib as a next-generation PARP inhibitor in precision oncology. Beyond its established role in germline *BRCA*-mutated BC, talazoparib has been incorporated into prostate cancer treatment following regulatory approvals endorsing its combination with the androgen-receptor signaling inhibitor enzalutamide for *HRR* gene–mutated metastatic castration-resistant prostate cancer (mCRPC).[80] Evidence from the phase III TALAPRO-2 study demonstrated that the dual targeting of DNA-damage repair and androgen-receptor signaling provides clinically meaningful and durable benefits compared to androgen-receptor inhibition alone, ultimately leading to regulatory endorsement by the US FDA and subsequent clinical adoption.[81,82] Nonetheless, the FDA has opted not to expand the labeling for the combination of talazoparib and enzalutamide to include patients with mCRPC who possess non–homologous recombination repair (*HRR*) gene mutations.[83] Updated analyses reported through 2025–2026 further substantiate the robustness of this strategy, confirming sustained disease control and survival advantages, particularly in tumors harboring *HRR* alterations such as BRCA1/2. These developments highlight talazoparib's potent PARP-trapping capability and its capacity to enhance synthetic lethality when paired with complementary targeted therapies. Ongoing clinical programs are investigating talazoparib across disease settings, additional STs, and combination regimens involving immunotherapies and other DNA-damage response inhibitors. Such efforts aim to overcome resistance mechanisms, refine biomarker-guided patient selection, and expand the therapeutic scope of PARP inhibition, positioning talazoparib as an increasingly integral component of future precision-oncology strategies.

In the subsequent sections, we present and comprehensively summarize the most significant findings from discovery to phases 1, 2, and 3 of clinical trials assessing the efficacy of talazoparib as a PARPi for the treatment of STs, BC, and OC. The most recent data related to clinical trials of talazoparib in BC, OC, and STs are summarized in Clinical Trial Data of Talazoparib (Phase III).

Discovery and Development Strategy of Talazoparib

Talazoparib has been discovered and developed as a highly selective, novel, and effective PARP1/2 inhibitor. It was identified by lead optimization during the discovery and expansion of a novel series of tetrahydropyridophthlazinones as PARP 1/2 inhibitors. The IUPAC name of talazoparib (BMN 673) is (8S, 9R)-5-fluoro-8-(4-fluorophenyl)-9-(1methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,de] phthalazin-3-one).[84] Talazoparib was first synthesized by Lead Therapeutics and was developed by BioMarin in 2010. which, in 2015 it was transferred to Medivation.[85] A comprehensive study by Wang et al on various substituted tetrahydropyridophthlazinone derivatives identified talazoparib as the most efficacious anti-cancer agent. The discovery and development of talazoparib were first reported by Wang et al in 2016.[84] During this discovery, after synthesizing several compounds bearing heteroaryl moieties at positions 8 and 9 of tetrahydropyridophthalazinone, a series of compounds bearing 9-azoles was exploited. The enzymatic PARP1 inhibition activity of all prepared analogs was compared with that of rucaparib (AG-014699), which was used as a standard in the evaluation.[61] These compounds were then established in three supplementary functional assessments, in addition to the

PARP1 inhibition assay, including a Capan-1 cytotoxicity assay to demonstrate the single-agent anti-tumor activity in *BRCA*2-mutation, a cellular PARylation assay to evaluate their proficiency in intracellular PARP1/2 inhibitory activity, and a Temozolomide (TMZ) sensitization assay to determine their cell-killing ability. In this series, Compound (**1**), having 9-(thiazol-2-yl) moiety, exhibited an enzymatic activity IC_{50} = 7.35 nM that was slightly decreased compared to the rucaparib (IC_{50} = 1.98 nM). Compound (**2**), bearing a 9-(1-methyl-pyrazol-5-yl) group, showed an inhibitory activity comparable to that of the PARP enzyme with rucaparib. The PARP1 inhibition potency of compound (**2**) with an IC_{50} of 1.84 nM and single-agent activity in Capan-1 cells (EC_{50} = 0.956 μM) was observed. Compound (**3**) demonstrated effective PARP1 inhibitory activity with an IC_{50} of 2.6 nM but the single-agent activity in the Capan-1 assay was much lower (EC_{50} = 172 μM). Compound (**4**) in which the (4-methyl-1,2,4-triazol-3-yl) group was present at position 9 showed EC_{50} = 0.17 μM, showed metabolic stability (rLM $t_{1/2}$ = 6.9 h). Although there was an elusive structural difference between compounds (**3**) and (**4**), their single-agent activity differences were considerable (25-fold difference). Compound (**5**) was obtained by replacing the 5-fluoro in (**3**) with hydrogen, which showed the same enzymatic activity (IC_{50} = 2.7 nM) which was identical to analog (**3**). Likewise, the introduction of 4-fluorophenyl at position 8 into (**3**), led to the synthesis of compound (**6**). In the resulting analog (**6**), single-agent cytotoxicity was further diminished to a single-digit nanomolar range approximately 19-fold higher than (**3**) but exhibited enhanced cellular activities, such as chemosensitization (GI_{50} = 44 μM), PARylation (EC_{50} = 6.94 nM), and single-agent cytotoxicity (EC_{50} = 0.071 μM). Because of the excellent biological potential measured for (**5**) and (**6**), further synthetic extension was executed for the synthesis of a compound in which the *tetra*-hydropyridophthalazinone core was switched with 5-fluoro, 8-(4-fluorophenyl), and 9-(1methyl-1,2,4-triazol-5-yl) moieties. This substitution led to the development of (8S,9R) and talazoparib (BMN 673) (**7**) as shown in Scheme 1. Compound (**7**) was identified as the most potent compound in that series. Through SFC separation, enantiomers were successfully isolated, resulting in significant enhancements in both the separation efficiency and scalability. The active enantiomer of compound (**7**) had an absolute configuration which was determined by X-ray crystallography of its tosylate salt crystal. This analysis showed that the active enantiomer of (**7**) has an (8S,9R) configuration. Interestingly, another enantiomer of (**7**) was found to be inactive in the (8R,9S) configuration. The unique binding of the enantiomer possessing a trans-(8S,9R)-configuration involving fluoroaryl and 1,2,4-triazole groups establishes specific non-covalent π- and hydrogen-bonding interactions with key PARP1 amino acid residues. It has been demonstrated that such interactions are essential for inhibiting PARP-mediated PARylation, enhancing metabolic stability, and augmenting cytotoxic effects.[86]

Compound (**7**) possesses cellular PARylation (EC_{50} = 5.48 nM) and enzymatic inhibitory activity (IC_{50} = 2.14 nM). It also exhibited metabolic stability (rLM $t_{1/2}$ = 359 min), but more prominently, it attained remarkable cytotoxicity either as a single agent in Capan-1 cells (EC_{50} = 0.008 μM) or in combination with other reagents, including TMZ, in a chemosensitization assay (GI_{50} = 19 μM). Talazoparib showed excellent efficacy in inhibiting the enzymatic activity of PARP1 (*Ki* = 1.2 nM) and PARP2 (*Ki* = 0.87 nM). It displayed remarkable anticancer potency in *BRCA*1-mutation MX-1 BC xenograft models, eg EC_{50} of talazoparib (**7**) in *BRCA*1-deficient MX-1 cells and *BRCA*2-deficient Capan-1 cells were >2000 times lower than those of veliparib and >50X less than the EC_{50} of olaparib.[61,84] Talazoparib exhibited promising in vitro safety profiles and displayed exceptionally effective in vitro anticancer activity, especially in *BRCA1/2*-deficient cells (EC_{50} (Capan-1) = 5 nM; EC_{50} (MX1) = 0.3 nM), as well as excellent pharmacokinetic properties.[87] The high potency of Talazoparib as a PARP inhibitor has been reported by Murai et al who described a mechanistic rationalization for the excellent anticancer activity of talazoparib (**7**) compared to other PARPi[88] Talazoparib also exhibits good oral bioavailability and excellent liver microsome stability. These properties have enabled talazoparib (**7**) to show a significant anticancer effect at much lower doses in *xenograft* models following oral dosing, making it a favorable anticancer agent.[61] Pommier et al reported that talazoparib exhibits significantly higher cytotoxicity as a single agent or in combination with other alkylating agents, and its potency in trapping PARP-DNA complexes is 100-fold greater than that of other PARPi. Talazoparib (**7**) can strongly trap PARP enzymes and possesses unique antitumor-killing activity.[88,89] The superb potency and pharmacokinetic characteristics of talazoparib (**7**) after oral administration were translated into in vivo anti-tumor efficacy as a single agent in *BRCA1* deficient MX-1 BC *xenograft* model and several other *xenograft* tumor models.[61] A summary of in vitro activities of the five enantiomer pairs after chiral resolution is shown in Table 2.

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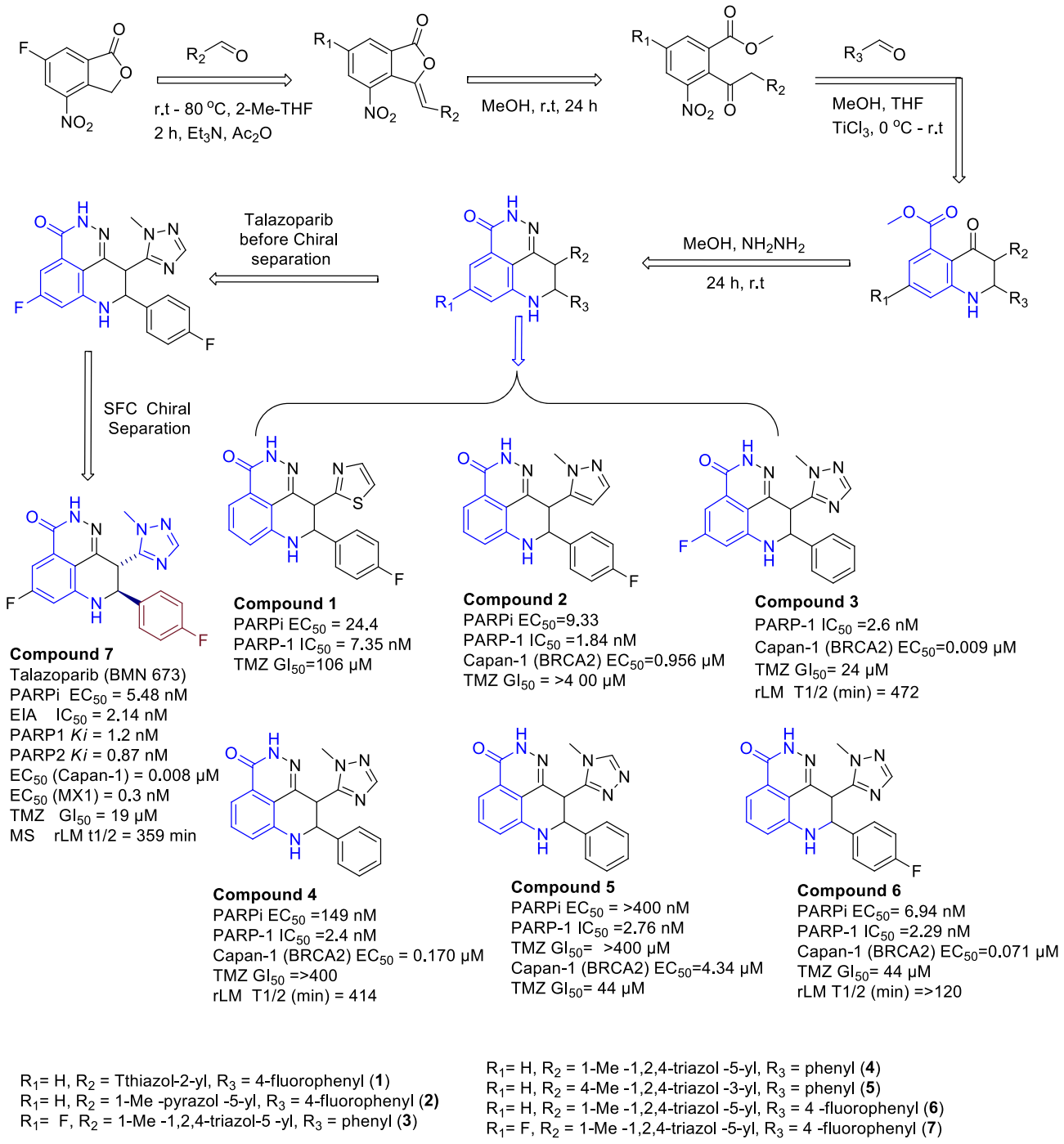


Scheme 1 The strategic development of talazoparib (**7**) from 4-nitroisobenzofuranone through different intermediates and compound (**1**) having 9-(thiazol-2-yl) moiety.

Gram Scale Synthesis of Talazoparib

Guangzhou Well-Health Bio-Pharmaceutical Co., Ltd. reported the gram-scale synthesis of talazoparib in 99.5% (Scheme 2).[90] This offers several benefits: it involves fewer reaction steps, is easy to implement, does not require metal catalysts or low temperatures, and is well suited for industrial-scale production (WO2017215166A1). Given the importance of PARPi and talazopriab, Li et al reported a light-activated talazoparib prodrug that exhibited good stability and was rapidly deprotected after UV irradiation.[91]

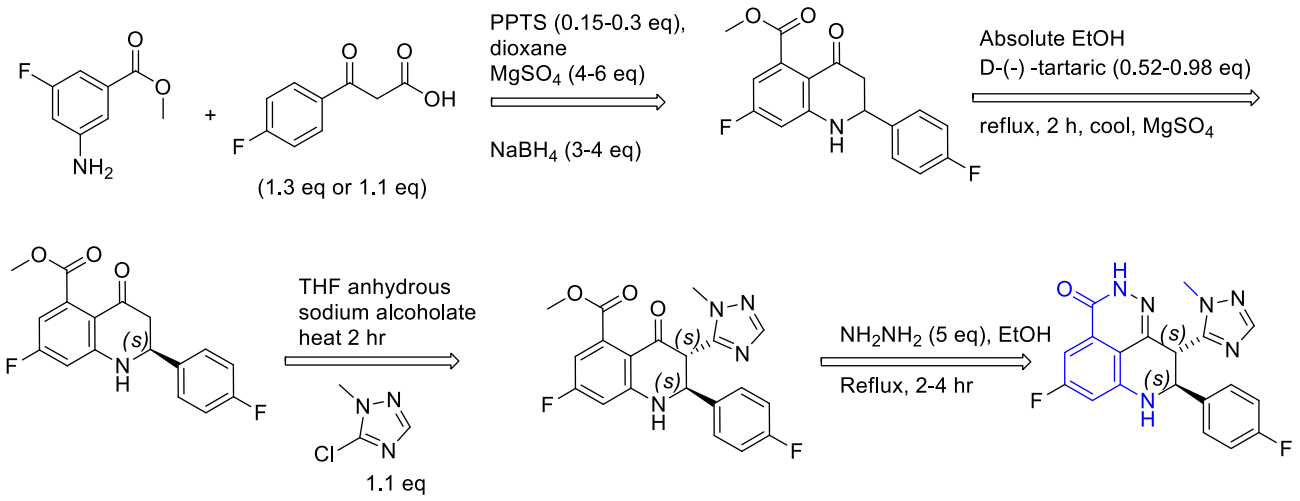
Table 2 Comparison of the in vitro Potential and Metabolic Stability of 8, 9-Substituted *Tetra*-Hydropyridophthalazinone Compounds Obtained During the Development of Talazoparib

Comp	Cellular PARP Inhibition EC_{50} (nM)	PARP-1 Enzyme IC_{50} (nM)	Capan-1 (*BRCA2*- Deficient) EC_{50} (μM)	TMZ Chemo- Sensitization GI_{50} (nM)	rLM $T_{1/2}$ (Min)
Rucaparib	4.69	1.98	0.61	144	Not given
1	24.4	7.35		106	ND
2	9.33	1.84	0.956	>400	ND
3	24	2.6	0.009	24	472
4	149	2.4	0.170	>400	414
5	>400	2.76	4.34	44	ND
6	6.94	2.29	0.071	44	>120
7	5.48	2.14	0.008	19	359

Notes: *F = Fluoro, Rucaparib= Standard drug.
Abbreviation: ND, Not determined.

Clinical Therapeutics of Talazoparib

Metastatic BC (*mBC*) is the main cause of cancer-related death in many populations. Although there has been much work in clinical development in recent years, therapies that mainly target *mBC* remain inadequate and fail to decrease the death rate in late-stage BC. A coherent combination of therapeutic agents targeting micro-environmental components and intrinsic tumor properties provides an encouraging strategy to improve these therapies with less toxicity and higher specificity. Until 2013, patients diagnosed with metastatic and/or locally advanced BC had a 5-year survival rate of approximately 26% at the time of analysis,[92] revealing a need for both understanding of the metastatic process and the development of new therapies. This discrepancy in decreasing mortality between early- and late-stage *mBC* is a standard problem with BC administration. A total of 25 oncology drugs approved by the FDA can be categorized into three groups: cytotoxic chemotherapy, endocrine therapy, and targeted therapies for treating BC. The majority of these FDA-approved drugs are classified as cytotoxic chemotherapies (44%), targeted therapies (16%), and endocrine therapies (24%). Regarding *HER-2* targeting therapies, only four drugs (16%) targeted microenvironment-specific molecules and intrinsic tumors. The limited availability of targeted therapies has been exacerbated by numerous significant issues in mBC treatment of *m*BC. Among these issues, the most important is the variation in response rates to systematic chemotherapy; results indicate that only 50% of metastatic cancers respond, in contrast to 90% of primary tumors. A lower RR in *m*BC is associated with an increased likelihood of acquired resistance to therapeutics.[93,94] In 2013, combinatorial therapies were developed to target both the associated stromal components and drivers of metastasis. Targeted drug transport to tumor cells, illustrated by the antibody-drug conjugate (ADC) discovered by Sassoon et al and



Scheme 2 Gram scale synthesis of talazoparib.

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Sievers et al, has emerged as a new and encouraging approach for treating *m*BC.[95,96] The management of ADC leads to high intra-carcinomal drug concentrations, even though the non-target tissues are mainly protected from chemotherapeutic disclosures.[97]

Clinical trials involving the use of platinum compounds, in addition to other drugs, in metastatic settings have demonstrated conflicting results. Platinum-based compounds have demonstrated efficacy in the treatment of metastatic diseases and have emerged as the primary therapeutic option for *BRCA*-positive individuals. A phase 1 trial of talazoparib (NCT01286987) showed the single-agent anti-tumor activity with an ORR of 33% in *BRCA*-mutated BC.[92] Phase 2 was a 2-cohort trial with an optimal Simon strategy involving two stages that evaluated the activity of talazoparib in *BRCA 1/2* BC (wild-type). In this study, participants were selected from one of two parallel cohorts. Patients with advanced TNBC with an underlying HRD assay were included in the first cohort (n=29), whereas the second cohort (n=29) included patients with advanced *HER2*-negative BC with a germline or somatic deleterious mutation in a non-*BRCA 1/2* HR gene pathway. During this treatment, qualified patients received talazoparib orally (4 weeks, 1.0 mg/day) until disease progression (NCT02401347).[98] An ongoing international phase III trial (EMBRACA) of talazoparib in *BRCA*-mutation with metastatic and/or locally advanced BC has been launched. Tables 3–5 summarize various clinical trials of talazoparib for BC, OC, and STs, respectively.

Clinical Trial Data of Talazoparib (Phase I)

Talazoparib (also identified as MDV 3800 and BMN 673) is an orally bioavailable PARP1/2 inhibitor that exhibits a dual mechanism.[61,87,89,142] It has remarkable anticancer activity in *BRCA*-mutated patients with BC and OC.[143] Talazoparib has both PARP-trapping activity and catalytic PARP-inhibition; however, its PARP-trapping effect is 100-fold higher than that of earlier generation PARP inhibitors.[144] The initial clinical results reported in 2013 and updated in 2017 by De Bono et al demonstrated that talazoparib is a single-agent PARPi,[145] revealing that its potency is much more to trap PARP-DNA complexes than that of earlier PARPi.[87] Phase I dose escalation experiments determined the maximum tolerated dose (MTD) of talazoparib to be 1000 mg once per day. Talazoparib shows promising clinical activity. During the Phase 1 trial, 17 patients were recruited, 11 of whom had germaline *BRCA* (*gBRCA*)-associated primary peritoneal cancer (PPC) or OC and had a neutral response to talazoparib.[146] In this dose-escalation trial, patients with OC were treated with talazoparib and TMZ. This study established the maximum tolerated dose (MTD) utilizing the standard dose of PARPi, in addition to a reduced dose of the sensitizing chemotherapeutic agent.[144] A synergistic effect was detected when talazoparib was combined with TMZ or platinum drugs in a xenograft model. The PARPi dose was kept greater from the start at a prescribed amount with verified single-agent activity, whereas the TMZ dose was started at a lower dose and increased carefully until the MTD level was achieved. When assessed in chicken DT40 cell lines, *PALB2* mutation predicted a unique in vivo response to talazoparib.[145] Further experiments proved that the nanomolar cytotoxicity of talazoparib was higher than that of the early generation, which was assumed to be associated with the trapping of PARP-DNA complexes in knockout mouse models.[88] The favorable preclinical results of talazoparib have enabled further investigation in several clinical trials, either alone or in combination with other agents, as reported in many clinical trials, including NCT02317874, NCT02116777, NCT02049593, and NCT02358200. It has completed a phase I clinical trial and is currently recruiting patients in phase II (ABRAZO) and III (EMBRACA) clinical trials to treat locally advanced and mBC with g*BRCA*1/2 deleterious mutations. ABRAZO is a phase 2 study of BC patients initially treated with g*BRCA* mutations[147] while EMBRACA (NCT01945775) is an ongoing phase III trial (completed and not recruiting) assessing the effectiveness and safety of talazoparib in metastatic or locally advanced BC patients with *BRCA* mutations.[148]

Clinical Trial Data of Talazoparib (Phase II)

The 2017 ASCO Annual Meeting (2017) by Nicholas et al of the Royal Marsden Hospital (RMH) and Institute of Cancer Research (ICR) in London revealed that talazoparib as a single agent has promising efficacy in patients with metastatic BC with *gBRCA1/2* mutations in a phase II trial.[149] ABRAZO (NCT02034916) was a phase II, 2-stage, 2-cohort, study of talazoparib at an optimal dose of 1 mg/day. Cohort 1 was platinum-based therapy, whereas Cohort 2 was based on ≥ 3 platinum-free cytotoxic-based treatments in patients with mBC and/or locally advanced BC, and g*BRCA1/2* mutations.

Table 3 An Overview of the Clinical Trials of Talazoparib for BC Treatment

Patients (Phase)	Description	Population	Outcome	Trial, Status	Study Ref
N=28 (I)	***Two-parts study*: 1**)-Dose escalation part (N=18) and, **2**)-Expansion part (N=17). (1 mg/day; 0.75 mg/day oral administration, each cycle comprised of 28 days. A moderate renal impairment was observed.	A total of 19 Japanese individuals having metastatic or locally advanced *gBRCA1/2m* BC were recruited and included in the study.[99]	Stable disease was recorded in 36.8% of patients, while the ORR attained 57.9%. The OS rate at 12 months was 84.7%, and the PFS exhibited a median of 7.2 months (95%).	Open-label study, Multicenter (Phase I) study (NCT03343054). It is active but not recruiting at this time.	[99]
N=84 (II)	Two phases, a 2-cohort study using 1mg of Talazoparib in *gBRCA*m carriers. ***Cohort A:*** PR or CR to a previous regimen that contained platinum ***Cohort B:*** Had more than two previous CTH regimens but no prior platinum treatment.	**1**)-TNBC 59% (*Cohort A*) and 17% (*Cohort B*), **2**)-Locally advanced or mBC, **3**)-*gBRCA*m	**1**)-ORR was 21% (*Cohort A*) and 37% in (*Cohort B*, **2**)-CBR (CR, PR or SD for > 24 wks), **3**)-PFS: (*Cohort A*: 4 months, *Cohort B*: 5.6 months), **4**)-OS: (*Cohort A*: 11.8 months, *Cohort B*: 16.5 months), **5**)- Safety and adverse events, **6**)-Pharmacodynamics **7**)- Standard of life, **8**)-All grades of adverse events (AE) include fatigue (45%), nausea (42%) and anemia (52%), were observed.	NCT02034916 Primary analysis completed	[100]
N=20 (II)	***Arm 1***: 6 cycles of talazopraib followed by the doctor's recommended course of care therapy, ***Arm 2***: Four to six cycles of talazopraib tracked by surgery. Talazoparib (single agent) x one tablet for each day for 6 months. Insignificant toxicity found without chemotherapy yielded a substantial RCB-0 rate.	**1**)- *HER2*-negative BC with tumour more than 1.0 cm, **2**)-Neoadjuvant setting, **3**)- *gBRCAm* BC (N=16 (*gBRCA*1, N=4 *gBRCA*2 positive)	**1**)-Adverse events and safety, **2**)-Clinical outcomes in the neoadjuvant setting, **3**)-Predictive biomarkers	(NCT03499353, and NCT02282345) This study is active and recruiting	[101]
N=29 (II)	1 mg daily of talazoparib was administered: ***Cohort A***: TNBC with HRD determined based on Myriad HRD Assay. ***Cohort B***: *HER2*-negative BC or solid tumor with a deleterious inherited or cancer-related somatic alteration in any of these genes: *PTEN, ATR, MRE11, RAD51D, RAD51C, RAD50, BRIP1, BARD1, NBNM ATM, CHEK2, PALB2*, or genes in the Fanconi anemia complementation	**1**)-*BRCA1/2* wild-type advanced TNBC and HRD, **2**)-*HER2*-negative BC or other solid cancers with a mutation in a gene involved in the HR pathway	**1**)-ORR, **2**)-CBR, **3**)-PFS, **4**)-AEs	(NCT02401347) Recruiting	[102]
N=431 (III)	Out of 412 patients (N=286, talazoparib), took ≥1 dose of talazoparib, and (N = 126, physician's opted chemotherapy.	Among patients treated with talazoparib, 52.4% (150 individuals) experienced adverse events that necessitated a dose reduction.	Superior efficacy, favourable PROs, and lower HRU rate, and grade 3–4 AEs were observed.	EMBRACA Phase III study (NCT01945775), Completed	[103]
N=5000 (II)	I-SPY2 study, Standard therapy: Weekly doses of Paclitaxel 80 mg/m^2, succeeded either Cyclophosphamide or Doxorubicin (standard of therapy). ***Experimental arm***: Talazoparib plus Irinotecan and others terminated.	Eligibility criteria include: **1)-**Operable BC in stages II–III with a maximum dimension of at least 2.5 cm, **2)-**Tumors of any ER/PgR and HER-2 status, **3)-**pre-surgical treatment contexts	**1**)-Probability of enhanced pCR through the incorporation of experimental agents into standard neoadjuvant therapies **2**) Biomarkers for predicting and evaluating pCR **3**) PFS, **4**) OS, **5**) AEs, **6**) MRI volume measurement.	NCT01042379 Recruiting	[104]

(*Continued*)

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Table 3 (Continued).

Patients (Phase)	Description	Population	Outcome	Trial, Status	Study Ref
N =10 (II)	A daily administration of 1 mg talazoparib in combination with 800 mg Avelumab was administered intravenously at biweekly intervals within a 28-day treatment cycle.	The study involved two patient groups. The first group, ***Cohort 1***: Included 10 individuals diagnosed with ccRCC exhibiting VHL alterations. These patients had all previously undergone ICB treatment. ***Cohort 2***: comprised 8 patients with diverse renal cell carcinoma subtypes: four had FH-deficient RCC, one presented with SDH-deficient RCC, and three were diagnosed with RMC.	Talazoparib inhibited the normal function of poly ADP-ribose polymerase enzymes, thereby impeding the self-repair and proliferation of cancer cells. PFS was 3.5 and 1.2 months in *Cohorts 1* and *2*, respectively. The most common AEs, such as anemia, nausea, and headache, were 28%, 22%, and 22% respectively.	Single-center, investigator-initiated Phase II trial. A combined form of these agents was demonstrated to be safe; however, it was found to be ineffective in specific types of renal carcinoma.	[105]
N =61 (II)	Patients with TNBC who have an early-stage germline BRCA1/2 mutation were given talazoparib 1 mg once a day for 24 weeks.	Among the 61 study participants, 48 completed at least 80% of their talazoparib treatment, underwent surgical procedures and were evaluated for pCR. The pCR rate was determined to be 45.8% in the treated group and 49.2% in the ITT population. Furthermore, the rate of RCB 0/I was determined to be 45.8% in the evaluable group and 50.8% in the ITT population.	Although the predetermined pCR threshold was not attained but single-agent neoadjuvant talazoparib demonstrated efficacy. Most common TRAEs such as anemia, neutropenia, and headache were 39.3%, 9.8%, and 22%, respectively. No deaths occurred.	Phase II, single-arm, open-label study (NCT03499353) Terminated	[106]
N=36 (I/II)	Biweekly doses of 800 mg of Avelumab were administered in combination with either Binimetinib (45 mg or 30 mg twice per day) or talazoparib (0.75 mg daily) plus Binimetinib (45 mg or 30 mg twice daily).	**1**)-Avelumab in combination with Binimetinib 45 mg was administered to a group of 22 patients. **2**)-In the subset of DLT-evaluable individuals, 5 out of 11 individuals (45.5%) experienced DLT at the 45-mg dosage. **3**)-Additionally, a separate cohort of 13 patients received a combination of Talazoparib and Binimetinib 45 mg.[107]	The combination of talazoparib or Avelumab with Binimetinib led to DLT rates that were higher than anticipated.	Phase Ib/2, open-label, multicenter, safety, clinical activity, PK and PD study (Terminated)	[107]
N=431 (III)	The study participants were divided into two groups (Arms) with a 2:1 ratio. Arm 1, consisting of 287 individuals, received a daily dose of 1 mg talazoparib. Arm 2, comprising 127 participants, underwent standard therapy as determined by the physician, which included options such as Capecitabine, Eribulin, Gemcitabine, or Vinorelbine.	Advanced BC with *gBRCA1*/2-mutated cohort, **1**)-inactive regionally developed, metastatic BC, **2**)- ≤ 3 previous CTH-inclusive regimens, **3**)-*gBRCA*m.	**1**)-PFS (8.6 months), **2**)-ORR (62.6%), **3**)-OS, **4**)- AEs (anemia 55%), **5**)-pharmacodynamics, **6**)-Response interval, **7**)-Well-being of life. Talazoparib therapy showed significant benefits with good outcomes.	Randomized, open-label, Phase II trial (NCT01945775) Active but not recruiting	[79]
N =21 (II)	A study was conducted to test talazoparib Beyond *BRCA* mutation. Previously pretreated advanced HER2-negative BC (n =13), and STs (n = 7) patients having other than g*BRCA1*/2 mutations were included.	HER2-negative BC (n = 13), and STs (n = 7) patients with other than g*BRCA1*/2 mutations.	The results indicate that the sensitivity of *gPALB2* to PARP inhibition. The ORR (31%) and *gPALB2*-associated mutational signatures showed a link to tumor response.	Open-label Phase II Trial Completed	[108]

N =33 (III)	*EGFR2–negative gBRCA1/2*-mutated advanced BC patients were randomized 2:1. The patients were enrolled from Asian regions (Korea and Taiwan).	The patient received either chemotherapy (the doctor's choice) or 1 mg of talazoparib daily.	PFS (9 months for talazoparib-treated patients and 7.1 months for the physician's choice chemotherapy. ORR (62.5% for talazoparib treated patients, 25.0% for the physician's choice chemotherapy). OS (talazoparib: 20.7 months and for physician's choice chemotherapy was 21.2 months). Grade 3/4 AEs.	EMBRACA trial. Talazoparib was found to be optimal in Asian patients. Small groups of patients were the main limitation. (Active)	[109]
N=431 (III)	This study demonstrates the conclusive OS results obtained for talazoparib compared with chemotherapy. Patients were allocated 2:1 to either arm 1 or arm 2 ***Arm 1***: 1mg of talazoparib on daily basis (N=287, talazoparib), OR ***Arm 2***: Doctor's discretion of chemotherapy (N=126, standard therapy).	Advanced BC with *gBRCA1/2*-mutated cohort, **1)**-inactive regionally developed, metastatic BC, **2**)- ≤ 3 prior CTH-inclusive regimens, **3**)- *gBRCA*m.	OS (talazoparib vs chemotherapy; 19.3 months vs 19.5 months). AEs were reported in 69.6% of patients receiving talazoparib and 64.3% of those undergoing chemotherapy. Mortality occurred in 75.3% of the talazoparib group and 75.0% of the chemotherapy group.	Randomized Phase III trial (NCT01945775) Active but not recruiting	[110]
N=367 (II/III)	This investigation examined the association between talazoparib exposure and the most prevalent severe (grade ≥ 3) hematopoietic AEs.	**1**)-A total of N=286 patients were treated in the EMBRACA trial of talazoparib arm. **2**)-N=83 patients were from the Trial of ABRAZO.	The study elaborates that modifying the dosing of talazoparib can effectively manage AEs.	Phase II (ABRAZO) and Phase III (EMBRACA) Trials.	[111]
N=285 (III)	This research examines the influence of talazoparib exposure, along with other baseline variables, on the PFR rate. 1mg of talazoparib on daily basis.: daily (as used in previous Trials).	Advanced BC and *gBRCA1/2* Mutated patients were recruited. A total of N=285 patients were treated with talazoparib.	The suggested starting dose is 1 mg on a daily basis, which is the highest tolerable dose.	Phase III EMBRACA Trials	[112]
N=84 (II)	This investigation examined the outcomes reported in patients with advanced BC who received talazoparib. The subjects had previously undergone Platinum-based treatment. Talazoparib was administered at a daily dosage of 1 mg	Patients were administered talazoparib at a daily dosage of 1 mg. PROs were evaluated at baseline (first day) and subsequently at 6-week intervals during the initial 24-week period. Thereafter, assessments were conducted every 12 weeks until disease progression was observed.	The research revealed notable improvements in breast and arm symptoms, along with an improved future perspective of patients observed in patients across both cohorts.	ABRAZO was a Phase 2 study with two cohorts and two stages. (NCT02034916) (Terminated)	[113]
N=431 (III)	Study participants were allocated in a 2:1 ratio to one of two treatment groups. The first group (Arm 1) received a daily dose of 1 mg talazoparib, while the second group (Arm 2) was administered one of four medications selected by the physician: Capecitabine, Eribulin, Gemcitabine, or Vinorelbine.	Out of 431 study participants, 287 were enrolled in the talazoparib group, while 144 received standard treatment. The inclusion criteria were: **1**) Metastatic or inoperable locally advanced BC, **2**) No more than 3 previous chemotherapy-containing regimens, **3**) Germline *BRCA* mutation.	**1**)-PFS, **2**)-ORR was 62.6%, **3**)-hematologic AEs occurred in 55% of patients while non-hematologic AEs occurred in 32% of patients, **4**)- OS, **5**)- Pharmacodynamics, **6**)- Response interval, **7**)- Quality of life	(NCT01945775) Active, not recruiting	[79]

(*Continued*)

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Table 3 (Continued).

Patients (Phase)	Description	Population	Outcome	Trial, Status	Study Ref
N=84 (II)	Two-stages, two-cohort investigation of talazoparib 1 mg Group A: Partial or complete response to previous platinum-based treatment, Group B: More than 2 prior chemotherapy regimens, without previous platinum exposure	This trial enrolled participants with either (**1**) metastatic or locally advanced BC, or (**2**) germline *BRCA* mutation (*gBRCAm*).	**1**)-Confirmed ORR was 23% (*BRCA1*), 33% (*BRCA2*), 26% (TN BC), and 29% (hormone receptor-positive), **2**)- CBR (CR, PR or SD for > 24 wk), **3**)- PFS: (Cohort A: 4 mo, Cohort B: 5.6 mo), **4**)- OS: (Cohort A: 11.8 mo, Cohort B: 16.5 mo), **5**)-The most frequent AEs included anemia (52%), fatigue (45%), and nausea (42%), **6**)- Pharmacodynamics **7**)- Quality of life	(NCT02034916) Primary analysis completed	[100]
N=122 (II)	***Arm 1***: Six cycles of talazoparib treatment, followed by physician-selected standard care therapy. ***Arm 2***: Four to six cycles of talazoparib treatment, followed by surgical intervention.	**1**)-HER2-negative BC with a tumor larger than 1.0 cm; **2**)-Neoadjuvant environments; and **3**)-*gBRCAm* BC	**1**)-AEs and safety, **2**)-Clinical response in the neoadjuvant setting, **3**)-Predictive biomarkers, **4**)-RCB-0 (pathologic complete response) rate was 53% and RCB-0/I was 63%, **5**)-Eight patients (40%) experienced grade 3 anemia.	Non-randomized, open-label, multicenter study (NCT03499353) Active, recruiting	[101]
N=40 (II)	Daily administration of 1 mg talazoparib was allocated to two groups: Group A: TNBC patients exhibiting HRD, as determined by the Myriad HRD Assay. Group B: Patients with HER2-negative BC or other STs carrying a deleterious inherited or cancer-specific mutation in any of these genes: *PTEN, ATR, MRE11, RAD51C, RAD51D, RAD50, BRIP1, BARD1, NBN, ATM, CHEK2, PALB2*, or genes from the Fanconi anemia complementation group.	**1**)-TNBC with wild-type *BRCA1/2* and HRD, **2**)-Metastatic BC (HER2-negative) or other advanced STs with mutations in *HER* pathway genes.	**1**)-ORR, **2**)- CBR, **3**)-PFS, **4**)-AEs	(NCT02401347) Recruiting	[114]
N=1920 (II)	The standard treatment protocol was adopted: weekly administration of Paclitaxel at 80 mg/m2, followed by either Doxorubicin or Cyclophosphamide (the current standard of care). Alternative therapeutic approach: a combination of Irinotecan and Talazoparib	**1**)- Operable BC in stages II–III with a maximum dimension of at least 2.5 cm **2**)- Tumors of any ER/PgR and HER-2 status **3**)- Preoperative treatment or n setting	**1**)-Likelihood of enhanced pCR through the addition of experimental treatments to conventional neoadjuvant therapies, **2**)-Biomarkers that predict and indicate prognosis for pCR, **3**)- PFS, **4**)-OS, **5**)-AEs **6)**- MRI volume	I-SPY TRIAL (NCT01042379) Recruiting	[115]

Note: † Terminated (closed by the Cancer Therapy Evaluation Program).

Abbreviations: RCB, Residual cancer burden; CR, Complete response; BRCA, Breast cancer genes; VHL, Von Hippel-Lindau; CTH, Chemotherapy; ccRCC, Clear cell renal cell carcinoma; FH, Fumarate hydratase; RCC, Renal cell carcinoma; SDH, Succinate dehydrogenase; RMC, Renal medullary carcinoma; TNBC, Triple-negative breast cancer; TRAEs, Treatment-related adverse events; PK, Pharmacokinetic; PD, Pharmacodynamics; DLT, Dose-limiting toxicity; EGFR2, Epidermal growth factor receptor 2; gBRCA1/2m, Germline BRCA1/2 mutation; PFS, Progression-free survival; OS, Overall survival; PROs, Patient-reported outcomes; PARPi, Poly(ADP-ribose) polymerase inhibition; HRD, Homologous recombination deficiency; EOC, Epithelial ovarian cancer; LOH, Loss of heterozygosis; PARP, Poly(ADP-ribose) polymerase; ORR, Objective response rate; SD, Stable disease; PR, Partial response; pCR, Pathological complete response; IRB, immune checkpoint blockade; ITT, intent-to-treat; RCB, Rate of residual cancer burden; AEs, Adverse events; ATM, Ataxia-telangiectasia mutated gene; BC, Breast cancer; CRPC, Castration-resistant prostate cancer; BC, Breast cancer; CBR, Clinical benefit rate; ER/PgR, Estrogen and progesterone receptor; EOC, Epithelial ovarian cancer; HER2, Human epidermal growth factor receptor 2; HR, Homologous recombination; HRD, Homologous recombination deficiency; LOH, Loss of heterozygosis; MRI, Magnetic resonance imaging; EWS, Ewing sarcoma; FEP, Full eligible population; NSCLC, Non-small-cell lung cancer; OS, Overall survival; PAP, Primary analysis population; PFS, Progression-free survival; PO, Per OS (oral); SC, Subcutaneous; RP2D, Recommended phase II dose; SCLC, Small cell lung cancer; TEAEs, Treatment-emergent adverse events; TMZ, Temozolomide; wk, Weeks; MTD, Maximum tolerated dose; mo, Months; PR, Partial response; Pt, Platinum; QoL, Quality of life; ICI, Immune checkpoint inhibitor.

Table 4 An Overview of Talazoparib Clinical Studies for OC Treatment

Patients (Phase)	Description	Population	Outcome	Trial, Status	Ref Study
N=113 (I)	This trial was conducted in two phases: **1)-**In the initial stage (part 1), 39 participants received talazoparib in varying doses, ranging from 0.025 to 1.1 mg daily, across nine different levels. **2)-** Subsequently, an additional 71 subjects were administered talazoparib at a fixed dose of 1.0 mg per day in the second phase (part 2) of the study.	Among the 113 cases of platinum-treated EOC, primary peritoneal cancer, or fallopian tube cancer, 34 were categorized as STs. Of these 34 EOC cases, 25 demonstrated *gBRCAm*.	The ORR reached 41.7%. For patients with *gBRCAm*, the ORR was 55% in those sensitive to platinum, while it dropped to 20% in platinum-resistant cases. PFS extended to 36.4 months. Side effects related to treatment included fatigue, affecting 37% (26/71) of patients, and anemia, observed in 35% (25/71) of patients. Severe adverse events (grade 3 to 4) comprised anemia in 24% (17/71) of patients and thrombocytopenia in 18% (13/71) of patients.	(NCT01286987) Completed	[116]
N=24 (I)	Daily administration of talazoparib at doses of 0.75 and 1 mg, in combination with weekly Carboplatin administration. A single treatment cycle comprised 21 days.	1)-Among the enrolled patients, 2 out of 24 exhibited EOC with STs. 2)-Prior platinum CTH was administered to 58% (14/24) of the patients. 3)-The genetic analysis revealed gBRCAm in 29% (7/24) and *sBRCAm* in 12.5% (3/24) of cases.	The study reported the following outcomes: 1)-Overall response rate was 14%, 2)-Disease control rate (DCR) reached 52%, 3)-Half of the patients required dose reductions, 4)- Three-quarters of participants (75%) experienced dose interruptions, 5)- Pharmacokinetic analysis was conducted.	Completed	[117]
N=30 (II)	Enrolled participants in this study received a daily dose of 1 mg talazoparib.	The study participants consisted of individuals with 1) epithelial OC, primary peritoneal cancer, or fallopian tube cancer, and 2) those in neoadjuvant settings.	Initial concentration and impact of talazoparib on DNA copy number, loss of heterozygosity, and genetic mutations, as well as RNA and protein expression levels in *HER* deficiency-associated pathways prior to and following treatment.	(NCT02316834) Ongoing	[118]
N/A (II)	***Arm 1***: Enrolled participants in this study received a daily dose of 1 mg Talazoparib. ***Arm 2***: Talazoparib	This study encompassed patients diagnosed with recurrent epithelial OC, as well as those with primary peritoneal or fallopian tube malignancies.	ORR	(NCT02836028) Withdrawn	[119]
N=3 (II)	Enrolled participants in this study received a daily dose of 1 mg talazoparib.	**1**)-Recurrent and/or metastatic OC of epithelial origin, **2**)-Progression of disease during monotherapy with a PARP inhibitor, **3**) BRCA mutation in the germline.	**1)**-OR (complete response + complete response), **2**) Safety, **3**) Response duration, **4**) Progression-free survival	Pilot Study of BMN 673 (talazoparib) (NCT02326844) †	[120]

Note: † Terminated (closed by the Cancer Therapy Evaluation Program).

Abbreviations: RCB, Residual cancer burden; CR, Complete response; BRCA, Breast cancer genes; VHL, Von Hippel-Lindau; CTH, Chemotherapy; ccRCC, Clear cell renal cell carcinoma; FH, Fumarate hydratase; RCC, Renal cell carcinoma; SDH, Succinate dehydrogenase; RMC, Renal medullary carcinoma; TNBC, Triple-negative breast cancer; TRAEs, Treatment-related adverse events; PK, Pharmacokinetic; PD, Pharmacodynamics; DLT, Dose-limiting toxicity; EGFR2, Epidermal growth factor receptor 2; gBRCA1/2m, Germline BRCA1/2 mutation; PFS, Progression-free survival; OS, Overall survival; PROs, Patient-reported outcomes; PARPi, Poly(ADP-ribose) polymerase inhibition; HRD, Homologous recombination deficiency; EOC, Epithelial ovarian cancer; LOH, Loss of heterozygosis; PARP, Poly(ADP-ribose) polymerase; ORR, Objective response rate; SD, Stable disease; PR, Partial response; pCR, Pathological complete response; IRB, immune checkpoint blockade; ITT, intent-to-treat; RCB, Rate of residual cancer burden; AEs, Adverse events; ATM, Ataxia-telangiectasia mutated gene; BC, Breast cancer; CRPC, Castration-resistant prostate cancer; BC, Breast cancer; CBR, Clinical benefit rate; ER/PgR, Estrogen and progesterone receptor; EOC, Epithelial ovarian cancer; HER2, Human epidermal growth factor receptor 2; HR, Homologous recombination; HRD, Homologous recombination deficiency; LOH, Loss of heterozygosis; MRI, Magnetic resonance imaging; EWS, Ewing sarcoma; FEP, Full eligible population; NSCLC, Non-small-cell lung cancer; OS, Overall survival; PAP, Primary analysis population; PFS, Progression-free survival; PO, Per OS (oral); SC, Subcutaneous; RP2D, Recommended phase II dose; SCLC, Small cell lung cancer; TEAEs, Treatment-emergent adverse events; TMZ, Temozolomide; wk, Weeks; MTD, Maximum tolerated dose; mo, Months; PR, Partial response; Pt, Platinum; QoL, Quality of life; ICI, Immune checkpoint inhibitor.

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Table 5 A Summary of Clinical Trials of Talazoparib as a Single Agent in STs

Patients (Phase)	Description	Population	Outcome	Trial, Status	Study
N=150 (II)	1 mg of talazoparib administered daily	**1**)-Individuals with STs, **2**)-Patients with somatic of g*BRCAm*, **3**)- Study subjects with genomic mutations in other *BRCA* pathway genes (*ATM, PALB2*, Fanconi Anemia genes, *ARIDIA, MER11, RAD50, NBS1, ATR)*	**1**)-CBR (CR, PR or SD > 24 w), **2**)-PFS, **3**)-OS, **4**)-Baseline predictive molecular markers, **5**)-Pharmacodynamics	(NCT02286687) Recruiting	[121]
N=24 (I/II)	1 mg of talazoparib administered daily	**1**)- Individuals were Pt-sensitive or nave EOC, **2**)- Patients showed recurrent primary peritoneal, BC, prostate, pancreas, gastric, or other STs and followed at least one conventional treatment, **3**)- Somatic or g*BRCAm*	**1**)-Pharmacodynamics, **2**)-ORR	(NCT01989546) Recruiting	[122]
No enrollment	Daily dose-escalation study for talazoparib	The study encompasses: 1) Individuals with advanced or metastatic STs (including CRPC, pancreatic cancer, mesothelioma, gastric cancer, NSCLC, SCLC, EOC, and TNBC), 2) Subjects presenting with varying degrees of hepatic and renal impairment	**1**)-Patient safety and stability, **2**)-Recommended Phase 2 Dose, **3**)-Acceptability, **4**)-Indicators of treatment efficacy and resistance, **5**)-Objective Response Rate. **6**)-Drug pharmacokinetics, **7**)-Progression-Free Survival, **8**)-Pharmacodynamic effects of the drug.	(NCT02567396) Withdrawn	[123]
N=10 (I)	Arm 1: Daily oral administration of 1 mg talazoparib, Arm 2: Daily subcutaneous injection of 1 mg talazoparib was administered orally at a dose of 1 mg per day in cycles of 28 days	The investigation encompasses advanced STs that have previously undergone 1–3 cycles of platinum-based chemotherapy.	**1**)-Adverse events, **2**)-Clinical benefit rate (complete response + partial response + stable disease for more than 24 weeks).	(NCT03426254) Active, not Recruiting	[124]
N=9 (I/II)	The research employs oral administration of Talazoparib at a dosage of 1 mg daily, with treatment cycles lasting 28 days.	1)-Patients with progressive STs who underwent 1–3 prior platinum-based chemotherapy regimens. 2)-Individuals diagnosed with advanced solid malignancies carrying confirmed or potential pathogenic mutations in *BRCA1* or *BRCA2* genes.	**1**)-The overall response rate attained 55%. **2**)-Primary pharmacodynamic (PD) endpoint, 67% of patients were evaluable. **3**)-A statistically significant reduction in PARylation was observed in 83% of patients.	(NCT01989546) Completed	[125]
N=15 (I)	Daily oral administration of 1 mg Talazoparib	The study investigated the pharmacological profile, tolerability, and anti-tumor activity of talazoparib as monotherapy in Chinese patients with advanced STs.	1) TEAEs was 86.7%, 2) ORR was 6.7%, 3) 36.4% of patients had a stable illness, and 4) pharmacokinetics	Open-label (phase 1) study, completed (NCT04635631)	[126]
N=200 (II)	Administration of 800 mg of Avelumab biweekly in conjunction with a daily dose of 1 mg Talazoparib.	Two separate parallel cohorts were established for patients with advanced STs exhibiting *BRCA1/2* or ATM alterations. The *BRCA1/2* cohort demonstrated a response rate of 26.4% (42 patients), which included 9 complete responses (5.7%). In contrast, the ATM cohort showed a response rate of 4.9% (2 patients).	The *BRCA1/2* cohort exhibited an ORR of 26.4%, whereas the ATM cohort demonstrated an ORR of 4.9%, corresponding to two patients.	A non-randomized, open-label, multicenter Phase 2b study with a tumor-agnostic approach, which was discontinued (NCT03565991)	[127]
N=223 (I/II)	Two-phase study: The investigation included Phase 1b with 12 participants and Phase 2 with 211 subjects. Both phases involved administering Avelumab and Talazoparib. In Phase 2, the dosage was set at 800 mg of Avelumab biweekly and 1 mg of Talazoparib daily.	The study enrolled individuals with advanced STs. In total, 223 subjects, with an average (SD) age of 63 years, received treatment.	ORR exhibited variation among patient cohorts, with 18.2% observed in those presenting with NBC and 34.8% in individuals diagnosed with hormone receptor-positive disease.	Nonrandomized controlled trial, Terminated (NCT03330405)	[128]

Recruited Patients (Phase)	**Description**	**Population**	**Outcome**	**Trial, Status**	**Study**
N=43 (I)	The combination therapy comprises talazoparib administered in conjunction with Carboplatin AUC5-6 and Paclitaxel at a dosage of 80 mg/m2 on days 1, 8, and 15 within 21-day treatment cycles.	The study included individuals with advanced STs. It is a dual-cohort investigation. Participants were recruited utilizing a 3 + 3 design and allocated into two cohorts. One cohort received Talazoparib for a week (plan A), while the other received it for three days (plan B).	**1**)-Dose adjustments were observed in 87% and 100% of patients, respectively. **2**)-TRAEs resulted in treatment discontinuation for 13% of patients in Schedule A and 10% in Schedule B. **3**)-The primary toxicity observed was myelosuppression, which included grade 3/4 TRAEs.	Completed (NCT02317874)	[129]
N=34 (I)	For a period of 22 days, patients received oral doses of talazoparib at 0.5 mg daily.	This investigation enrolled subjects with advanced STs who exhibited either normal renal function or varying degrees of renal impairment.	**1**)-This trial validates existing dosage guidelines for individuals with mild to moderate renal dysfunction. **2**)-Additionally, the TEAE profile showed no significant variations across patient groups.	Phase I, open-label, non-randomized study, completed (NCT02997163)	[130]
N=28 (I)	Talazoparib was administered orally once daily at a dose of 0.75 or 1 mg.	This investigation enrolled Japanese participants with advanced local or metastatic STs, irrespective of mutations in DNA damage repair genes.	TEAEs were anemia, stomatitis, maculopapular rash, decreased platelet count, decreased neutrophil count, and elevated alanine aminotransferase.	Phase I trial, open-label, non-randomized, continuous, not recruiting (NCT03343054)	[131]
Patients (Phase)	Description	Population	Outcome	Trial, Status	Study
N=40 (I/II)	Talazoparib was administered orally at a dose of 400–600 µg/m2 (with a daily maximum of 800–1000 µg) on the first day, followed by oral TMZ at 20–55 mg/m2/day from days 2 through 6. The regimen was repeated every 28 days.	The study enrolled participants ranging from 4 to 25 years of age, comprising both pediatric and adult subjects with STs that were either recurrent or refractory to treatment.	*In Phase 1*: Prolonged SD was observed in 2 out of 5 EWS participants and 4 out of 25 non-EWS participants. *In Phase 2*: In the subsequent phase 2, none of the 10 EWS subjects experienced an OR, while two encountered prolonged SD.	Completed (NCT02116777)	[132]
N=6 (I)	An oral solution of Talazoparib at a 1-mg dosage in combination with ^{14}C-labeled Talazoparib at 100 µCi	Individuals who had an advanced solid tumor confirmed by histopathology and were at least eighteen years old were included in the study.	Talazoparib demonstrated minimal metabolic activity. A primary route of elimination for unmetabolized Talazoparib was renal excretion.	Phase I study, first in humans. Finalized (NCT01286987)	[133]
N=40 (I)	Administered Talazoparib at a daily dose ranging from 500 mcg to 1 mg prior to escalating the dosage of Temozolomide/Irinotecan	Patients with advanced cancers who did not exhibit *BRCA* mutations were stratified into two cohorts for treatment. One group received a combination of Talazoparib and Temozolomide, while the other was administered Talazoparib in conjunction with Irinotecan.	The combination of Talazoparib with low doses of Temozolomide or Irinotecan demonstrated acceptable tolerability	Preclinical and clinical trials. Phase I dose-escalation study (accomplished)	[134]
N=47 (II)	The Talazoparib was administered at a dosage of 1 mg per day without interruption in 21-day cycles.	1) FEP had tumors with deleterious mutation and had not previously been treated with a PARP inhibitor. 2) PAP represents a subgroup of FEP characterized by mutations in the *ATM, ATR, BRCA1, BRCA2, or PALB2* gene.	**1**)-PAP had an ORR of 4% and an OS of 95%; **2**)-FEP had an ORR of 11%, which represented the DCR.	Completed	[135]

(*Continued*)

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Table 5 (Continued).

Patients (Phase)	Description	Population	Outcome	Trial, Status	Study
N=33 (I)	Two Cohort Study: Patients in Cohort 1 (N = 25) and Cohort 2 (N = 8) were allocated daily doses of Talazoparib (0.1–2.0 mg).	**1**)-The MTD was exceeded at 2.0 mg/day in cohort 1 and at 0.9 mg/day in cohort 2. **2**)-Grade ≥3 adverse events were predominantly hematologic.	**1**)-In patients with hematological malignancies, Talazoparib exhibited favorable tolerability, with an MTD comparable to that observed in STs. **2**)-Furthermore, the drug demonstrates preliminary evidence of efficacy against leukemia.	Completed (NCT01399840)	[136]
N = 41 (I)	Cohorts of 3–6 subjects.-Talazoparib was administered orally, and Irinotecan was administered intravenously. **2**)-Talazoparib administered orally, Temozolomide administered orally, and Irinotecan administered intravenously Both arms utilize a 3 + 3 design	The investigation encompassed pediatric patients with recurrent or refractory STs.	**1**)-The research demonstrated that combining Talazoparib with Irinotecan and Temozolomide was found to be safe for use in pediatric patients. **2**)-The study identified the following adverse effects: 1) neutropenia, 2) thrombocytopenia, 3) febrile neutropenia, and 4) diarrhea	Study completed	[137]
N=24 (I)	Daily administration of talazoparib at doses of 0.75 and 1 mg, in combination with weekly carboplatin administration. A single treatment cycle comprised of 21 days.	1)-Among the enrolled patients, 2 out of 24 exhibited EOC with STs. 2)-Prior platinum CTH was administered to 58% (14/24) of the patients. 3)-The genetic analysis revealed gBRCAm in 29% (7/24) and *sBRCAm* in 12.5% (3/24) of cases.	The study reported the following outcomes: 1)-Overall response rate was 14%, 2)-DCR reached 52%, 3)-Half of the patients required dose reductions, 4)- Three-quarters of participants (75%) experienced dose interruptions, 5)- Pharmacokinetic analysis was conducted.	Completed	[117]
N=223	All patients were administered a combination of avelumab and talazoparib.	1)-NSCLC patients, 2)- TNBC patients, 3)- mCRPC patients, 4)_*BRCA1/2*-altered OC patients, 5)- HR^{+} -BC patients,	The combination of avelumab and talazoparib showed similar results to those observed with either PARPi or ICI monotherapy.	Phase 1b and 2 basket nonrandomized controlled trial (NCT03330405).	[128,138]
N=28	Patients had advanced STs, and 20 cancer types were enrolled and administered with talazopraib.	Advanced solid tumors	Talazoparib showed effectiveness against tumors in individuals with advanced solid tumors and BRCA1/2 mutations.	Phase II basket trial, NCT02693535, (completed in 2028)	[139]
N=34	1 mg/day and 0.75 mg/day	Patients with advanced STs who had normal kidney function or varying levels of kidney impairment.	As renal impairment worsens, exposure to talazoparib increases, suggesting that patients with severe renal impairment should consider starting with a reduced dose of 0.5 mg/day.	PHASE I OPEN-LABEL (NCT02997163, completed)	[130]
N=128	Oral talazoparib (1 mg daily; or 0.75 mg daily for patients with moderate renal impairment) until the disease advances	Male patients with progressive, metastatic, castration-resistant prostate cancer of adenocarcinoma histology were enrolled.	In men with advanced metastatic castration-resistant prostate cancer who had undergone extensive prior treatments, talazoparib demonstrated sustained antitumor effects, particularly in those with DDR-HRR gene mutations.	Open-label, phase 2 trial (TALAPRO-1), NCT03148795, completed	[140]
N=36	Talazoparib (1 mg once daily). Arm A [itraconazole], n = 19; Arm B [rifampicin], n = 17)	Patients with advanced solid tumors were enrolled.	The study focused on patients with advanced solid tumors to examine the effects of P-gp inhibition and induction on the pharmacokinetics of talazoparib.	Open-label, 2-arm, drug-drug interaction Phase I study (NCT03077607).	[141]

Note: [†] Terminated (closed by the Cancer Therapy Evaluation Program).

Abbreviations: RCB, Residual cancer burden; CR, Complete response; BRCA, Breast cancer genes; VHL, Von Hippel-Lindau; CTH, Chemotherapy; ccRCC, Clear cell renal cell carcinoma; FH, Fumarate hydratase; RCC, Renal cell carcinoma; SDH, Succinate dehydrogenase; RMC, Renal medullary carcinoma; TNBC, Triple-negative breast cancer; TRAEs, Treatment-related adverse events; PK, Pharmacokinetic; PD, Pharmacodynamics; DLT, Dose-limiting toxicity; EGFR2, Epidermal growth factor receptor 2; gBRCA1/2m, Germline BRCA1/2 mutation; PFS, Progression-free survival; OS, Overall survival; PROs, Patient-reported outcomes; PARPi, Poly(ADP-ribose) polymerase inhibition; HRD, Homologous recombination deficiency; EOC, Epithelial ovarian cancer; LOH, Loss of heterozygosis; PARP, Poly(ADP-ribose) polymerase; ORR, Objective response rate; SD, Stable disease; PR, Partial response; pCR, Pathological complete response; IRB, immune checkpoint blockade; ITT, intent-to-treat; RCB, Rate of residual cancer burden; AEs, Adverse events; ATM, Ataxia-telangiectasia mutated gene; BC, Breast cancer; CRPC, Castration-resistant prostate cancer; BC, Breast cancer; CBR, Clinical benefit rate; ER/PgR, Estrogen and progesterone receptor; EOC, Epithelial ovarian cancer; HER2, Human epidermal growth factor receptor 2; HR, Homologous recombination; HRD, Homologous recombination deficiency; LOH, Loss of heterozygosis; MRI, Magnetic resonance imaging; EWS, Ewing sarcoma; FEP, Full eligible population; NSCLC, Non-small-cell lung cancer; OS, Overall survival; PAP, Primary analysis population; PFS, Progression-free survival; PO, Per OS (oral); SC, Subcutaneous; RP2D, Recommended phase II dose; SCLC, Small cell lung cancer; TEAEs, Treatment-emergent adverse events; TMZ, Temozolomide; wk, Weeks; MTD, Maximum tolerated dose; mo, Months; PR, Partial response; Pt, Platinum; QoL, Quality of life; ICI, Immune checkpoint inhibitor.

This study is not enlisting patients, but is an ongoing trial. The data for this phase 2 clinical trial (NCT02034916) were first posted in January 2014 and then updated in November 2017. The main objective of this phase 2 trial was to demonstrate the potency and safety profile of a single agent, talazoparib (BMN 673), in patients with metastatic or locally advanced BC with a deleterious g*BRCA*1/2 mutation.[150] The patients had an ECOG PS ≤ 1 and assessable disease according to the RECIST v1.1. In this study, almost five responses for each cohort were required in ≤ 35 patients for the development of stage 2 in ≤ 35 patients.[149] There were two endpoints in the ABRAZO trial for talazoparib. The primary endpoint was the objective response rate (ORR), while the secondary endpoints included the duration of response (DOR) and clinical benefit rate for ≥ 24 weeks (CBR24), overall survival (OS), and progression-free survival (PFS). The detail of the investigation studied, as provided by Pfizer, revealed that in primary and secondary endpoints (CBR 24 and DOR), the complete response (CR) for the disappearance of all non-target lesions and non-nodal targets, with non-target and target lymph node deterioration of less than 10 mm in the short axis. Partial response (PR) was found to as ≥30% decline in the sum of diameters of target lesions compared to the sum at baseline. An independent radiology facility (IRF) conducted response evaluation.[150] The results showed that from May 2014 to Feb 2016, 84 patients were registered in a 2-cohort (C1, N = 49; C2, N = 35) 2-stage study, and nine patients continued treatment until September 1, 2016 (the data cutoff time). Both cohorts progressed to stage 2 before enrollment. The patients had a median age of 50 (range, 31–75) years; 41%/59% of patients had an HR^+/TNBC incidence in C1 and 83%/17% in C2, while 58% of the patients had an ECOG PS of 0. The ORR by IRF for *BRCA1/2* was 24%/34% and 29%/26% for HR^+/TNBC, respectively. The most common AEs were observed in patients (20%) with neutropenia (27%), thrombocytopenia (33%), diarrhea (33%), nausea (42%), fatigue (45%), and anemia (52%). AEs (grade ≥ 3) revealed that participants only had neutropenia (15%), thrombocytopenia (19%), and anemia (35%), whereas the non-hematological adverse events (grade ≥ 3) did not come about. Adverse events (AEs) related to talazoparib had led to the discontinuation of drug in 4% of patients, ie only 3 patients, while 4 patients died from AEs unrelated to talazoparib. From phase II trial data, it was concluded that talazoparib was well tolerated in *mBC* patients with a g*BRCA1/2* mutation, demonstrating favorable anticancer activity in cohorts 1 and 2.[150] The phase II trial data for talazoparib, along with the recommended clinical response rate (RECIST) by tumor type, and the suggested dose level for phase 2 (1.0 mg/day) in patients treated with talazoparib have been reported. After the Phase 2 study, a Phase 3 EMBRACA trial (NCT01945775) of talazoparib vs. the physician's choice of treatment in g*BRCA1/2*-mutated metastatic BC was assessed, as discussed in the following section.

Clinical Trial Data of Talazoparib (Phase III)

Talazoparib was generally well tolerated and has shown encouraging single-agent anti-cancer efficacy in several solid tumor types in Phase I/II clinical trials.[151] This international Phase III trial, EMBRACA (NCT01945775), compares the safety and efficacy of talazoparib versus the physician's choice in patients with advanced BC. Data related to the EMBRACA trial of talazoparib were first posted in September 2013 and updated in September 2017.[152] This trial was conducted to compare the safety profile and efficiency of talazoparib with the protocol-specific physician's choice (Eribulin, Capecitabine, Vinorelbine or Gemcitabine) in patients with metastatic and/or locally advanced BC. The primary aim of this trial was PFS to identify OS, ORR, and safety as the secondary objectives. The exploratory objective was to evaluate health-related quality of life (HRQ) evaluations DOR. In this trial, the subject eligibility was to involve ≥ 18 years of individuals, cytologically/histologically established metastatic and/or locally advanced BC with g*BRCA1/2* mutations, less than or equal to two earlier chemotherapy-inclusive treatments (no frontier on preceding hormonal treatments or targeted anti-tumor treatments, eg mechanistic target of VEGF or monoclonal antibodies against CTL4 or tyrosine kinase inhibitors, CDK4/6 inhibitors, rapamycin (mTOR), or immune-oncology agents),[151,152] previous therapies with an anthracycline and/or taxane, and ECOG performance status less than or equal to 1. Phase III subjects (n = 429) will be randomized (2:1) to receive either the physician's choice therapy or single-agent talazoparib oral capsules (1.0 mg/d, 3 weeks). This clinical trial is currently enrolling participants from Asia, the US, Europe, South America, and Israel.[151]

The percentage of baseline peripheral blood mononuclear cell (PBMC) activity of PARP was defined as the mean of the early dose PARP activity evaluations during the multiple daily dosing valuation phase, ie, early dose evaluations on days 15, 22, and 35 of cycle one. The mean percentage of baseline PBMC PARP activity with talazoparib (multiple dose

levels) has also been documented. It has been indicated that the overall PBMC activity of PARP decreases with the estimated dose limit of talazoparib. Concentration-response and dose-response associations between PMBC, PARP and Talazoparib activities, and the maximum enzyme inhibitory effect model.[116] A summary of various clinical trials of talazoparib for BC, OC, and STs is given in Tables 3–5, respectively.

Talazoparib in Solid Tumors as a Combination Therapy

As previously outlined, talazoparib, a selective PARP inhibitor, has shown increased therapeutic efficacy when used in conjunction with other agents in patients with advanced STs, particularly those harboring BRCA1/2 mutations or other deficiencies in DNA damage response (DDR). A summary of clinical and translational development of talazoparib combination regimens in STs is shown in Table 6. Preclinical studies indicate synergistic effects with immune checkpoint inhibitors, chemotherapy, and targeted therapies, with the aim of overcoming resistance and enhancing outcomes in tumor types such as breast, ovarian, prostate, and NSCLC. Clinical trials have predominantly focused on phase I/II studies to determine safety, dosing, and preliminary efficacy, with ongoing research into biomarker-driven patient selection.

In the JAVELIN PARP Medley trial, the combination of talazoparib (1 mg daily) and avelumab (800 mg biweekly) was assessed using a basket design across multiple solid tumor cohorts. ORRs were significant in *BRCA*-altered subgroups, including 63.6% in platinum-sensitive, *BRCA1/2*-altered OC (median duration of response [DOR] not reached; range 5.6 to ≥18.4 months), 34.8% in hormone receptor-positive, DDR-positive BC (median DOR 15.7 months), and 18.2% TNBC (median DOR 11.1 months). Limited activity was observed in *non-BRCA* DDR-positive tumors, highlighting the importance of *BRCA* status for response. The regimen was well-tolerated, with common grade 3/4 adverse events including anemia (33.6%), thrombocytopenia (21.5%), and neutropenia (13.9%), leading to dose reductions in 34.5% of patients, primarily due to hematologic toxicities.[128]

The JAVELIN BRCA/ATM trial further evaluated talazoparib plus avelumab in a tumor-agnostic approach for *BRCA1/2*- or ATM-altered advanced STs. In the *BRCA1/2* cohort (n=159), the confirmed ORR was 26.4% (including 5.7% complete responses), with higher rates (30.3%) in *BRCA*-associated tumor types such as ovarian, breast, prostate, and pancreatic cancers (median DOR 10.9 months; median PFS 3.7 months). Responses were numerically greater in tumors with high mutational burden (≥10 mut/Mb; ORR 62.5%). However, the ATM cohort exhibited low activity (ORR 4.9%), leading to early discontinuation. Safety was consistent, with grade ≥3 treatment-related adverse events in 49.0% of patients, predominantly anemia (34.0%), thrombocytopenia (15.0%), and neutropenia (11.0%), and no treatment-related deaths. These findings suggest that the combination's efficacy is largely driven by *BRCA1/2* alterations rather than a broad tumor-agnostic benefit.[127]

The combination with chemotherapy, such as talazoparib plus carboplatin and paclitaxel, has been investigated in a phase I trial (NCI9782) for advanced STs. The recommended phase II dose was talazoparib 250 mcg daily (for 3–7 days per cycle), carboplatin AUC 6, and paclitaxel 80 mg/m², with an ORR of 39.5% (including 3 complete responses) among 38 evaluable patients, particularly in those with DDR alterations like *BRCA1/2* or *PALB2*. The clinical benefit rate was 84.2%, with maintenance talazoparib feasible (median 8 cycles in monotherapy). Myelosuppression was prominent, with grade 3/4 neutropenia in 95% and anemia in 52%, necessitating dose modifications in nearly all patients and supportive care.[129]

Emerging therapeutic combinations include talazoparib in conjunction with the BET inhibitor ZEN-3694, as investigated in the ongoing phase II ComBET trial (NCT05327010). This trial targets molecularly selected advanced STs characterized by mutations in *BRCA1/2*, other DNA damage repair (DDR) genes, or KRAS. The primary objective was to assess the ORR according to RECIST v1.1 criteria, while secondary endpoints encompass safety, clinical benefit rate, PFS, and biomarker analyses. Eligibility criteria necessitate the presence of biopsiable lesions and specific genetic profiles, with exclusion of individuals with prior exposure to BET inhibitors. Although preliminary results are yet to be reported, the trial underscores the transition towards precision oncology in the context of talazoparib combinations.[155]

Chatterjee et al investigated the cellular toxicity of PARP inhibitors, specifically talazoparib and/or olaparib, in oral cancer cells, focusing on the underlying mechanisms, using in vitro, *in silico*, and i*n vivo* preclinical model systems. In oral cancer cell lines, including the H-357 line, the combination of talazoparib and olaparib, following pretreatment with

Table 6 Clinical and Translational Development of Talazoparib Combination Regimens in Solid Tumors

Combination Strategy	Tumor Types Studied	Study Phase	Biological Rationale	Key Findings	Reference
Talazoparib + Avelumab (PD-L1 inhibitor)	*BRCA1*/2- or ATM-altered solid tumors; TNBC; NSCLC; ovarian; mCRPC (NCT03330405)	Phase 1b/2 (JAVELIN PARP Medley)	PARP inhibition increases DNA damage and neoantigen signaling, enhancing immune response	Manageable safety; durable responses in DDR-positive cohorts; activity comparable to PARP monotherapy in some subgroups	[128]
Talazoparib + Avelumab (DDR-selected population)	*BRCA1*/2- or ATM-altered advanced STs. (NCT03565991)	Phase 2b (JAVELIN BRCA/ATM)	Synthetic lethality + immune modulation in DDR-deficient tumors	Clinical activity observed in *BRCA*-altered tumors; limited activity in ATM-altered cohorts	[127]
Talazoparib + Temozolomide	Refractory/recurrent pediatric STs (Ewing sarcoma, others) (NCT02116777)	Phase 1/2	Alkylator-induced DNA damage combined with PARP inhibition	Feasible regimen; hematologic toxicity dose-limiting; modest response rates	[132]
Talazoparib + enzalutamide (androgen receptor inhibitor)	Neuroendocrine prostate cancer (NEPC)	Preclinical	Indicated role of glucocorticoid receptor signaling in ENZ-induced and PARP inhibitor-suppressed NEPC.	Tumor inhibition in vitro and in vivo	[153]
Talazoparib + Radiation therapy	Multiple solid tumor models	Preclinical/early translational	PARP inhibition impairs DNA repair following radiation	Enhanced radiosensitization and DNA damage accumulation	[154]

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a DNA-damaging agent (curcumin), resulted in increased apoptosis, elevated levels of the DNA damage marker γH2AX, and greater PARP-trapping compared to either drug alone.[156] In a separate study, talazoparib combined with quinacrine, a topoisomerase inhibitor, targeted oral mucosa cancer stem cells (OM-CSCs) by modulating the histone acetyltransferases GCN5 and P300. This led to inhibition of chromatin remodeling, increased genomic instability (indicated by γH2AX accumulation), and enhanced apoptosis (up to 43.8% apoptotic cells). This combination demonstrated synergy in patient-derived xenografts, suggesting its potential to eliminate therapy-resistant stem cell populations in oral squamous cell carcinoma (OSCC).[157]

Most data on oral cancer are in the preclinical phase (cell lines and xenografts) rather than in large clinical trials. Although talazoparib is a well-established single-agent treatment for certain *BRCA/HRR*-mutated cancers, its use as a combination therapy in oral cancers remains under investigation. Preclinical data suggest promising synergy when combined with DNA-damaging agents (curcumin, radiation) or other PARP inhibitors, particularly in contexts where DNA damage is induced and the repair capacity is compromised. Although there exists a mechanistic rationale for using talazoparib as a combination therapy in oral cancer (eg, PARP inhibition + radiation or DNA damage in HNSCC),[158] specific clinical trials in this area are limited or not publicly available. Considering the biomarker-driven approach, talazoparib shows promise for tumors with underlying DNA repair defects. While BRCA mutations are rare in OSCC, other alterations in the HRD pathway (eg, in genes such as *ATM, ATR,* and *FANCA*) are present in some patients, making them potential candidates for this therapy.

Conclusions

Cancer remains a formidable global health challenge, with BC and OC contributing significantly to the burden of STs, particularly in individuals harboring germline BRCA1/2 mutations. *BRCA1/2* genes play a critical role in DNA double-strand break repair via homologous recombination, and their mutations confer heightened susceptibility to BC and OC, with lifetime risks ranging from 60–85% for BC and 10–54% for OC, depending on the specific gene affected. The discovery of *BRCA1* in 1994 and *BRCA2* in 1995 marked pivotal milestones in understanding hereditary cancer predisposition, revealing associations with additional malignancies such as prostate, pancreatic, and colorectal cancers. Poly(ADP-ribose) polymerases, particularly PARP1/2, are essential enzymes in single-strand DNA break repair through base excision repair pathways. Inhibition of PARP leads to the accumulation of unrepaired DNA damage, which, in *BRCA1/2*-deficient cells, exploits synthetic lethality by overwhelming alternative repair mechanisms like non-homologous end-joining, resulting in cell death. This principle has driven the development of PARPi as targeted therapies, evolving from early nicotinamide analogs like 3-aminobenzamide in the 1980s to advanced agents.

The discovery journey of PARPi, highlights key FDA approved drugs such as iniparib, olaparib, veliparib, niraparib, rucaparib, and talazoparib, many of which are nicotinamide mimetics that competitively bind PARP's catalytic domain. Talazoparib stands out for its superior potency (IC_{50} = 0.57 nM), demonstrating approximately 100-fold greater potency than other PARPi, and its dual mechanism of PARP inhibition and DNA trapping. Its development progressed from preclinical models demonstrating efficacy in *BRCA*-mutated tumors to clinical trials evaluating monotherapy and combinations. Clinical updates on talazoparib underscore its therapeutic implications across BC, OC, and other STs. Phase 1–3 trials, including EMBRACA (Phase 3) and ABRAZO (Phase 2), have shown improved progression-free survival and overall survival in patients with *gBRCA*-mutated, HER2-negative advanced BC compared to standard chemotherapy, with manageable safety profiles. Clinical trials like TALAPRO-2 (Phase 3) have explored talazoparib in combination with agents such as enzalutamide, temozolomide, or avelumab, revealing potential to overcome resistance and enhance outcomes in homologous recombination-deficient tumors. Ongoing studies in neoadjuvant settings and other solid malignancies further affirm the versatility of talazoparib.

Overall, the advancements in PARP inhibition, exemplified by talazoparib, represent a transformative approach in therapy offering improved clinical outcomes for patients with *BRCA1/2*-mutated cancers by leveraging synthetic lethality, addressing drug resistance through synergistic combinations, and expanding therapeutic options beyond traditional chemotherapy. These developments highlight the potential to mitigate the global cancer burden, particularly in high-risk populations, through continued integration into clinical practice. All clinically approved PARP inhibitors, including talazoparib, have partial BBB penetration. Therefore, the search for new PARPi continues, and AZD9574 is emerging as

a promising candidate. This selective inhibitor has been developed to address challenges related to the BBB, efflux transporters, and subtype selectivity. Drug resistance has become a significant barrier in talazoparib's clinical application. Future investigations focusing on resistance mechanisms, disease settings, and rational combination regimens with immunotherapy or DNA-damage response inhibitors are likely to broaden talazoparib's clinical impact in precision oncology. Future clinical research should prioritize solutions to overcome BBB penetration issues and PARPi drug resistance.

Data Sharing Statement

Data supporting the findings of this study are included in this article.

Author Contributions

All authors made significant contributions to the reported work, including conception, study design, execution, data acquisition, formal analysis, resource provision, and interpretation. They participated in drafting, revising, or critically reviewing the manuscript and provided final approval of the version to be published. The corresponding author supervised and played a key role in project administration. All authors concur with the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *Ca a Cancer J Clin*. 2024;74(1):12–49. doi:10.3322/caac.21820
3. Kim J, Harper A, McCormack V, et al. Global patterns and trends in breast cancer incidence and mortality across 185 countries. *Nat Med*. 2025;31(4):1154–1162. doi:10.1038/s41591-025-03502-3
4. Gu H, Wang R, Beeraka NM, et al. Global burden and trends of breast cancer: GLOBOCAN 2022 estimates of incidence and mortality in 185 countries. *Chinese Med J*. 2026;139(3):404–414. doi:10.1097/CM9.0000000000003921
5. Arnold M, Morgan E, Rumgay H, et al. Current and future burden of breast cancer: global statistics for 2020 and 2040. *Breast*. 2022;66:15–23. doi:10.1016/j.breast.2022.08.010
6. Cai Y, Dai F, Ye Y, Qian J. The global burden of breast cancer among women of reproductive age: a comprehensive analysis. *Sci Rep*. 2025;15 (1):9347. doi:10.1038/s41598-025-93883-9
7. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol*. 2011;12(10):933–980. doi:10.1016/S1470-2045(11)70141-3
8. Star J, Jemal A, Sung H, et al. Breast cancer statistics 2024. *Ca a Cancer J Clin*. 2024;74(6):477–495. doi:10.3322/caac.21863
9. Giaquinto AN, Sung H, Newman LA, et al. Breast cancer statistics 2024. *CA Cancer J Clin*. 2024;74(6):477–495. doi:10.3322/caac.21863
10. Claus EB, Schildkraut J, Iversen ES, Berry D, Parmigiani G. Effect of BRCA1 and BRCA2 on the association between breast cancer risk and family history. *J Natl Cancer Inst*. 1998;90(23):1824–1829. doi:10.1093/jnci/90.23.1824
11. Peto J, Collins N, Barfoot R, et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. *J Natl Cancer Inst*. 1999;91(11):943–949. doi:10.1093/jnci/91.11.943
12. Kuchenbaecker KB, Hopper JL, Barnes DR, et al.; B. and the, B.C. Consortium. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317(23):2402–2416. doi:10.1001/jama.2017.7112
13. Hall JM, Lee MK, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science*. 1990;250(4988):1684–1689. doi:10.1126/science.2270482
14. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science*. 1994;266(5182):66–71. doi:10.1126/science.7545954
15. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. *Nature*. 1995;378(6559):789–792. doi:10.1038/378789a0
16. Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science*. 1994;265(5181):2088–2090. doi:10.1126/science.8091231

17. Stratton MR, Ford D, Neuhasen S, et al. Familial male breast cancer is not linked to the BRCA1 locus on chromosome 17q. *Nat Genet*. 1994;7(1):103–107. doi:10.1038/ng0594-103
18. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst*. 2003;95(3):214–221. doi:10.1093/jnci/95.3.214
19. Iscovich J, Abdulrazik M, Cour C, Fischbein A, Pe'er J, Goldgar DE. Prevalence of the BRCA2 6174 del T mutation in Israeli uveal melanoma patients. *Int J Cancer*. 2002;98(1):42–44. doi:10.1002/ijc.10155
20. Kirchhoff T, Kauff ND, Mitra N, et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. *Clin Cancer Res*. 2004;10(9):2918–2921. doi:10.1158/1078-0432.CCR-03-0604
21. Narod SA, Feunteun J, Lynch HT, et al. Familial breast-ovarian cancer locus on chromosome 17q12-q23. *Lancet*. 1991;338(8759):82–83. doi:10.1016/0140-6736(91)90076-2
22. Niell BL, Rennert G, Bonner JD, Almog R, Tomsho LP, Gruber SB. BRCA1 and BRCA2 founder mutations and the risk of colorectal cancer. *J Natl Cancer Inst*. 2004;96(1):15–21. doi:10.1093/jnci/djh008
23. Ozcelik H, Schmocker B, Di Nicola N, et al. Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. *Nat Genet*. 1997;16(1):17–18. doi:10.1038/ng0597-17
24. Zweemer RP, van Diest PJ, Verheijen RH, et al. Molecular evidence linking primary cancer of the fallopian tube to BRCA1 germline mutations. *Gynecologic Oncol*. 2000;76(1):45–50. doi:10.1006/gyno.1999.5623
25. Galanty Y, Belotserkovskaya R, Coates J, Polo S, Miller KM, Jackson SP. Mammalian SUMOE3-ligases PIAS1 and PIAS4 promote responses to DNA double-strand breaks. *Nature*. 2009;462(7275):935–939. doi:10.1038/nature08657
26. Morris JR, Boutell C, Keppler M, et al. The SUMO modification pathway is involved in the BRCA1 response to genotoxic stress. *Nature*. 2009;462(7275):886–890. doi:10.1038/nature08593
27. Moynahan ME, Cui TY, Jasin M. Homology-directed dna repair, mitomycin-c resistance, and chromosome stability is restored with correction of a Brca1 mutation. *Cancer Res*. 2001;61(12):4842–4850.
28. Patel KJ, Yu VP, Lee H, et al. Involvement of Brca2 in DNA repair. *Mol Cell*. 1998;1(3):347–357. doi:10.1016/S1097-2765(00)80035-0
29. Tassone P, Tagliaferri P, Perricelli A, et al. BRCA1 expression modulates chemosensitivity of BRCA1-defective HCC1937 human breast cancer cells. *Br J Cancer*. 2003;88(8):1285–1291. doi:10.1038/sj.bjc.6600859
30. Yuan SS, Lee SY, Chen G, Song M, Tomlinson GE, Lee EY. BRCA2 is required for ionizing radiation-induced assembly of Rad51 complex in vivo. *Cancer Res*. 1999;59(15):3547–3551.
31. Zhong Q, Chen CF, Li S, et al. Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response. *Science*. 1999;285(5428):747–750. doi:10.1126/science.285.5428.747
32. Schwartz GF, Hughes KS, Lynch HT, et al. Proceedings of the international consensus conference on breast cancer risk, genetics, & risk management, April, 2007. *The Breast Journal*. 2009;15(1):4–16. doi:10.1111/j.1524-4741.2008.00665.x
33. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *J Natl Cancer Inst*. 2002;94(18):1365–1372. doi:10.1093/jnci/94.18.1365
34. Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The breast cancer linkage consortium. *Am J Hum Genet*. 1993;52(4):678–701.
35. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003;302(5645):643–646. doi:10.1126/science.1088759
36. Honrado E, Osorio A, Palacios J, Benitez J. Pathology and gene expression of hereditary breast tumors associated with BRCA1, BRCA2 and CHEK2 gene mutations. *Oncogene*. 2006;25(43):5837–5845. doi:10.1038/sj.onc.1209875
37. Foulkes WD, Stefansson IM, Chappuis PO, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. *J Natl Cancer Inst*. 2003;95(19):1482–1485. doi:10.1093/jnci/djg050
38. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. *J Clin Oncol*. 2004;22(4):735–742. doi:10.1200/JCO.2004.05.055
39. Sousa FG, Matuo R, Soares DG, et al. PARPs and the DNA damage response. *Carcinogenesis*. 2012;33(8):1433–1440. doi:10.1093/carcin/bgs132
40. Hu Y, Petit SA, Ficarro SB, et al. PARP1-driven poly-ADP-ribosylation regulates BRCA1 function in homologous recombination-mediated DNA repair. *Cancer Discov*. 2014;4(12):1430–1447. doi:10.1158/2159-8290.CD-13-0891
41. Wang M, Wu W, Wu W, et al. PARP-1 and Ku compete for repair of DNA double strand breaks by distinct NHEJ pathways. *Nucleic Acids Res*. 2006;34(21):6170–6182. doi:10.1093/nar/gkl840
42. Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development. *J Clin Oncol*. 2015;33(12):1397–1406. doi:10.1200/JCO.2014.58.8848
43. Robert I, Dantzer F, Reina-San-Martin B. Parp1 facilitates alternative NHEJ, whereas Parp2 suppresses IgH/c-myc translocations during immunoglobulin class switch recombination. *J Exp Med*. 2009;206(5):1047–1056. doi:10.1084/jem.20082468
44. Soni A, Siemann M, Grabos M, Murmann T, Pantelias GE, Iliakis G. Requirement for Parp-1 and DNA ligases 1 or 3 but not of Xrcc1 in chromosomal translocation formation by backup end joining. *Nucleic Acids Res*. 2014;42(10):6380–6392. doi:10.1093/nar/gku298
45. Ame JC, Rolli V, Schreiber V, et al. PARP-2, A novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase. *J Biol Chem*. 1999;274(25):17860–17868. doi:10.1074/jbc.274.25.17860
46. Schreiber V, Ame JC, Dolle P, et al. Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1. *J Biol Chem*. 2002;277(25):23028–23036. doi:10.1074/jbc.M202390200
47. Rulten SL, Fisher AE, Robert I, et al. PARP-3 and APLF function together to accelerate nonhomologous end-joining. *Mol Cell*. 2011;41(1):33–45. doi:10.1016/j.molcel.2010.12.006
48. Konecny GE, Kristeleit RS. PARP inhibitors for BRCA1/2-mutated and sporadic ovarian cancer: current practice and future directions. *Br J Cancer*. 2016;115(10):1157–1173. doi:10.1038/bjc.2016.311
49. Kummar S, Chen A, Parchment RE, et al. Advances in using PARP inhibitors to treat cancer. *BMC Med*. 2012;10(1):25. doi:10.1186/1741-7015-10-25

50. Curtin NJ, Szabo C. Therapeutic applications of PARP inhibitors: anticancer therapy and beyond. *Mol Aspect Med*. 2013;34(6):1217–1256. doi:10.1016/j.mam.2013.01.006
51. Ekblad T, Camaioni E, Schuler H, Macchiarulo A. PARP inhibitors: polypharmacology versus selective inhibition. *FEBS J*. 2013;280(15):3563–3575. doi:10.1111/febs.12298
52. Lupo B, Trusolino L. Inhibition of poly(ADP-ribosyl)ation in cancer: old and new paradigms revisited. *Biochim Biophys Acta*. 2014;1846 (1):201–215. doi:10.1016/j.bbcan.2014.07.004
53. Thomas HD, Calabrese CR, Batey MA, et al. Preclinical selection of a novel poly(ADP-ribose) polymerase inhibitor for clinical trial. *Mol Cancer Ther*. 2007;6(3):945–956. doi:10.1158/1535-7163.MCT-06-0552
54. Canan Koch SS, Thoresen LH, Tikhe JG, et al. Novel tricyclic poly(ADP-ribose) polymerase-1 inhibitors with potent anticancer chemopotentiating activity: design, synthesis, and X-ray cocrystal structure. *J Med Chem*. 2002;45(23):4961–4974. doi:10.1021/jm020259n
55. Menear KA, Adcock C, Boulter R, et al. 4-[3-(4-cyclopropanecarbonylpiperazine-1-carbonyl)-4-fluorobenzyl]-2H-phthalazin- 1-one: a novel bioavailable inhibitor of poly(ADP-ribose) polymerase-1. *J Med Chem*. 2008;51(20):6581–6591. doi:10.1021/jm8001263
56. Donawho CK, Luo Y, Luo Y, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. *Clin Cancer Res*. 2007;13(9):2728–2737. doi:10.1158/1078-0432.CCR-06-3039
57. Penning TD, Zhu GD, Gandhi VB, et al. Discovery and SAR of 2-(1-propylpiperidin-4-yl)-1H-benzimidazole-4-carboxamide: a potent inhibitor of poly(ADP-ribose) polymerase (PARP) for the treatment of cancer. *Bioorg Med Chem*. 2008;16(14):6965–6975. doi:10.1016/j.bmc.2008.05.044
58. Penning TD, Zhu GD, Gandhi VB, et al. Discovery of the Poly(ADP-ribose) polymerase (PARP) inhibitor 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (ABT-888) for the treatment of cancer. *J Med Chem*. 2009;52(2):514–523. doi:10.1021/jm801171j
59. Jones P, Altamura S, Boueres J, et al. Discovery of 2-{4-[(3S)-Piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (MK-4827): a novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in BRCA-1 and −2 mutant tumors. *J Med Chem*. 2009;52(22):7170–7185. doi:10.1021/jm901188v
60. Jones P, Wilcoxen K, Rowley M, Toniatti C. Niraparib: a Poly(ADP-ribose) Polymerase (PARP) inhibitor for the treatment of tumors with defective homologous recombination. *J Med Chem*. 2015;58(8):3302–3314. doi:10.1021/jm5018237
61. Shen Y, Rehman FL, Feng Y, et al. BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. *Clin Cancer Res*. 2013;19(18):5003–5015. doi:10.1158/1078-0432.CCR-13-1391
62. Livraghi L, Garber JE. PARP inhibitors in the management of breast cancer: current data and future prospects. *BMC Med*. 2015;13(1):188. doi:10.1186/s12916-015-0425-1
63. Clark JB, Ferris GM, Pinder S. Inhibition of nuclear NAD nucleosidase and poly ADP-ribose polymerase activity from rat liver by nicotinamide and 5′-methyl nicotinamide. *Biochimica Et Biophysica Acta*. 1971;238(1):82–85. doi:10.1016/0005-2787(71)90012-8
64. Durkacz BW, Omidiji O, Gray DA, Shall S. ADP-ribose)n participates in DNA excision repair. *Nature*. 1980;283(5747):593. doi:10.1038/283593a0
65. Diéras V, Bonnefoi H, Alba E, et al. Iniparib administered weekly or twice-weekly in combination with gemcitabine/carboplatin in patients with metastatic triple-negative breast cancer: a phase II randomized open-label study with pharmacokinetics. *Breast Cancer Res Treat*. 2019;177 (2):383–393. doi:10.1007/s10549-019-05305-w
66. O'Shaughnessy J, Schwartzberg L, Danso MA, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. *J Clin Oncol*. 2014;32(34):3840–3847. doi:10.1200/JCO.2014.55.2984
67. Loap P, Loirat D, Berger F, et al. Combination of olaparib and radiation therapy for triple negative breast cancer: preliminary results of the RADIOPARP phase 1 trial. *Int J Radiation Oncol*Biol*Phys*. 2021;109(2):436–440. doi:10.1016/j.ijrobp.2020.09.032
68. Kawanishi M, Fujita M, Karasawa K. Combining carbon-ion irradiation and PARP inhibitor, olaparib efficiently kills BRCA1-mutated triple-negative breast cancer cells. *Breast Cancer*. 2022;16:11782234221080553. doi:10.1177/11782234221080553
69. Bedikian AY, Papadopoulos NE, Kim KB, et al. A phase IB trial of intravenous INO-1001 plus oral temozolomide in subjects with unresectable stage-III or IV melanoma. *Cancer Invest*. 2009;27(7):756–763. doi:10.1080/07357900802709159
70. Morrow DA, Brickman CM, Murphy SA, et al. A randomized, placebo-controlled trial to evaluate the tolerability, safety, pharmacokinetics, and pharmacodynamics of a potent inhibitor of poly(ADP-ribose) polymerase (INO-1001) in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of the TIMI 37 trial. *J Thrombosis Thrombolysis*. 2009;27(4):359–364. doi:10.1007/s11239-008-0230-1
71. Bai Y-R, Yang W-G, Jia R, et al. The recent advance and prospect of poly(ADP-ribose) polymerase inhibitors for the treatment of cancer. *Med Res Rev*. 2025;45(1):214–273.
72. Wang H, Ren B, Liu Y, et al. Discovery of Pamiparib (BGB-290), a potent and selective Poly (ADP-ribose) Polymerase (PARP) inhibitor in clinical development. *J Med Chem*. 2020;63(24):15541–15563. doi:10.1021/acs.jmedchem.0c01346
73. Han Y, Chen MK, Wang HL, et al. Synergism of PARP inhibitor fluzoparib (HS10160) and MET inhibitor HS10241 in breast and ovarian cancer cells. *Am J Cancer Res*. 2019;9(3):608–618.
74. Li N, Bu H, Liu J, et al. An open-label, multicenter, single-arm, phase II study of fluzoparib in patients with germline BRCA1/2 mutation and platinum-sensitive recurrent ovarian cancer. *Clin Cancer Res*. 2021;27(9):2452–2458. doi:10.1158/1078-0432.CCR-20-3546
75. Jeon J, Lee K, Jang HR, et al. Effects of poly (ADP-ribose) polymerase inhibitor treatment on the repair process of ischemic acute kidney injury. *Sci Rep*. 2024;14(1):159. doi:10.1038/s41598-023-50630-2
76. Kristeleit RS, Drew Y, Oza AM, et al. Efficacy and safety of rucaparib treatment in patients with BRCA-mutated, relapsed ovarian cancer: final results from Study 10. *Br J Cancer*. 2023;128(2):255–265. doi:10.1038/s41416-022-02022-y
77. Jamal K, Staniszewska A, Gordon J, et al. Abstract 2609: AZD9574 is a novel, brain penetrant PARP-1 selective inhibitor with activity in an orthotopic, intracranial xenograft model with aberrant DNA repair. *Cancer Res*. 2022;82(12_Supplement):2609. doi:10.1158/1538-7445.AM2022-2609
78. Rouleau M, Patel A, Hendzel MJ, Kaufmann SH, Poirier GG. PARP inhibition: PARP1 and beyond. *Nat Rev Cancer*. 2010;10(4):293–301. doi:10.1038/nrc2812
79. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379 (8):753–763. doi:10.1056/NEJMoa1802905

80. Heiss BL, Chang E, Gao X, et al. US food and drug administration approval summary: talazoparib in combination with enzalutamide for treatment of patients with homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2024;42 (15):1851–1860. doi:10.1200/JCO.23.02182
81. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial. *Lancet*. 2025;406(10502):447–460. doi:10.1016/S0140-6736(25)00684-1
82. Fizazi K, Azad AA, Matsubara N, et al. Talazoparib plus enzalutamide in men with HRR-deficient metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial. *Lancet*. 2025;406(10502):461–474. doi:10.1016/S0140-6736(25)00683-X
83. Pfizer provides update on U.S. regulatory review of Talzenna in combination with Xtandi for broader use in metastatic castration-resistant prostate cancer. *News release*. Pfizer; 2025. Available from: https://www.pfizer.com/news/announcements/pfizer-provides-update-us-regulatory-review-talzenna-combination-xtandi-broader. Accessed Feb 22, 2026.
84. Wang B, Chu D, Feng Y, Shen Y, Aoyagi-Scharber M, Post LE. Discovery and Characterization of (8S,9R)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,2-de]phthalazin-3-one (BMN 673, Talazoparib), a novel, highly potent, and orally efficacious Poly(ADP-ribose) Polymerase-1/2 inhibitor, as an anticancer agent. *J Med Chem*. 2016;59(1):335–357. doi:10.1021/acs.jmedchem.5b01498
85. Yuan Z, Chen J, Li W, et al. PARP inhibitors as antitumor agents: a patent update (2013-2015). *Expert Opin Ther Patents*. 2017;27(3):363–382. doi:10.1080/13543776.2017.1259413
86. Sheikhi N, Bahraminejad M, Saeedi M, Mirfazli SS. A review: FDA-approved fluorine-containing small molecules from 2015 to 2022. *Eur J Med Chem*. 2023;260:115758. doi:10.1016/j.ejmech.2023.115758
87. Wainberg ZA, Rafii S, Ramanathan RK, et al. Safety and antitumor activity of the PARP inhibitor BMN673 in a phase 1 trial recruiting metastatic small-cell lung cancer (SCLC) and germline BRCA-mutation carrier cancer patients. *J Clin Oncol*. 2014;32(15_suppl):7522. doi:10.1200/jco.2014.32.15_suppl.7522
88. Murai J, Huang SY, Renaud A, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. *Mol Cancer Ther*. 2014;13(2):433–443. doi:10.1158/1535-7163.MCT-13-0803
89. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res*. 2012;72(21):5588–5599. doi:10.1158/0008-5472.CAN-12-2753
90. Yong X, Yohi PW, Xu M, Cruise D, Huang L. Synthesis of PARP inhibitor Talazoparib. 2017. (WO2017215166A1).
91. Li J, Xiao D, Liu L, et al. Design, synthesis, and in vitro evaluation of the photoactivatable prodrug of the PARP inhibitor talazoparib. *Molecules*. 2020;25(2):407.
92. Li Z, Kang Y. Emerging therapeutic targets in metastatic progression: a focus on breast cancer. *Pharmacol Ther*. 2016;161:79–96.
93. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. *Adv Exp Med Biol*. 2007;608:1–22.
94. Coley HM. Mechanisms and strategies to overcome chemotherapy resistance in metastatic breast cancer. *Cancer Treat Rev*. 2008;34(4):378–390. doi:10.1016/j.ctrv.2008.01.007
95. Sassoon I, Blanc V. Antibody-drug conjugate (ADC) clinical pipeline: a review. *Methods Mol Biol*. 2013;1045:1–27.
96. Sievers EL, Senter PD. Antibody-drug conjugates in cancer therapy. *Ann Rev Med*. 2013;64(1):15–29. doi:10.1146/annurev-med-050311-201823
97. Alley SC, Okeley NM, Senter PD. Antibody-drug conjugates: targeted drug delivery for cancer. *Curr Opin Chem Biol*. 2010;14(4):529–537. doi:10.1016/j.cbpa.2010.06.170
98. Andrei AZ, Hall A, Smith AL, et al. Increased in vitro and in vivo sensitivity of BRCA2-associated pancreatic cancer to the poly(ADP-ribose) polymerase-1/2 inhibitor BMN 673. *Cancer Lett*. 2015;364(1):8–16. doi:10.1016/j.canlet.2015.04.003
99. Kotani H, Masuda N, Yamashita T, et al. Efficacy and safety of talazoparib in Japanese patients with germline BRCA-mutated locally advanced or metastatic breast cancer: results of the phase 1 dose-expansion study. *Breast Cancer*. 2022;29(6):1088–1098. doi:10.1007/s12282-022-01390-w
100. Turner NC, Telli ML, Rugo HS, et al. A phase II study of talazoparib after platinum or cytotoxic nonplatinum regimens in patients with advanced breast cancer and germline BRCA1/2 mutations (ABRAZO). *Clin Cancer Res*. 2019;25(9):2717–2724. doi:10.1158/1078-0432.CCR-18-1891
101. Litton JK, Scoggins ME, Hess KR, et al. Neoadjuvant talazoparib for patients with operable breast cancer with a germline BRCA pathogenic variant. *J Clin Oncol*. 2020;38(5):388.
102. Phase II talazoparib in BRCA1 +BRCA2 wild-type & triple-neg/HER2-negative breast cancer/solid tumors. Available from: https://clinicaltrials.gov/ct2/show/NCT02401347. Accessed May 31, 2024.
103. Hurvitz SA, Gonçalves A, Rugo HS, et al. Talazoparib in patients with a germline BRCA-mutated advanced breast cancer: detailed safety analyses from the phase III EMBRACA trial. *Oncologist*. 2020;25(3):e439–e450. doi:10.1634/theoncologist.2019-0493
104. I-SPY TRIAL: neoadjuvant and personalized adaptive novel agents to treat breast cancer. Available from: https://clinicaltrials.gov/ct2/show/NCT01042379. Accessed May 31, 2024.
105. Kotecha RR, Doshi SD, Knezevic A, et al. A phase 2 trial of talazoparib and avelumab in genomically defined metastatic kidney cancer. *European Urol Oncol*;7(4):804–811.
106. Litton JK, Beck JT, Jones JM, et al. Neoadjuvant talazoparib in patients with germline BRCA1/2 mutation-positive, early-stage triple-negative breast cancer: results of a phase II study. *Oncologist*. 2023;28(10):845–855. doi:10.1093/oncolo/oyad139
107. Ahnert JR, Tan DSW, Garrido-Laguna I, et al. Avelumab or talazoparib in combination with binimetinib in metastatic pancreatic ductal adenocarcinoma: dose-finding results from phase Ib of the JAVELIN PARP MEKi trial☆. *ESMO Open*. 2023;8(4):101584.
108. Gruber JJ, Afghahi A, Timms K, et al. A phase II study of talazoparib monotherapy in patients with wild-type BRCA1 and BRCA2 with a mutation in other homologous recombination genes. *Nat Cancer*. 2022;3(10):1181–1191. doi:10.1038/s43018-022-00439-1
109. Lee K-H, Sohn J, Goodwin A, et al. Talazoparib versus chemotherapy in patients with HER2-negative advanced breast cancer and a germline BRCA1/2 mutation enrolled in Asian countries: exploratory subgroup analysis of the phase III EMBRACA trial. *Cancer Res Treat*. 2021;53 (4):1084–1095. doi:10.4143/crt.2020.1381

110. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. *Ann Oncol*. 2020;31(11):1526–1535. doi:10.1016/j.annonc.2020.08.2098
111. Elmeliegy M, Yu Y, Litton JK, et al. Exposure-safety analyses of talazoparib in patients with advanced breast cancer and germline BRCA1/2 mutations in the EMBRACA and ABRAZO trials. *J Clin Pharmacol*. 2020;60(10):1334–1343. doi:10.1002/jcph.1626
112. Yu Y, Elmeliegy M, Litton JK, et al. Talazoparib exposure-efficacy analysis in patients with advanced breast cancer and germline BRCA1/2 mutations in the EMBRACA trial. *J Clin Pharmacol*. 2020;60(10):1324–1333. doi:10.1002/jcph.1623
113. Hurvitz SA, Quek RGW, Turner NC, et al. Quality of life with talazoparib after platinum or multiple cytotoxic non-platinum regimens in patients with advanced breast cancer and germline BRCA1/2 mutations: patient-reported outcomes from the ABRAZO phase 2 trial. *Eur J Cancer*. 2018;104:160–168. doi:10.1016/j.ejca.2018.09.003
114. Phase II talazoparib in BRCA1 +BRCA2 wild-type & triple-neg/HER2-negative breast cancer/solid tumors. Available from: https://clinicaltrials.gov/ct2/show/NCT02401347. Accessed August 02, 2024.
115. I-SPY 2 TRIAL: neoadjuvant and personalized adaptive novel agents to treat breast cancer (I-SPY 2). Available from: https://clinicaltrials.gov/ct2/show/NCT01042379. Accessed August 02, 2024.
116. de Bono J, Ramanathan RK, Mina L, et al. Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers. *Cancer Discov*. 2017;7(6):620–629. doi:10.1158/2159-8290.CD-16-1250
117. Dhawan MS, Bartelink IH, Aggarwal RR, et al. Differential toxicity in patients with and without DNA repair mutations: phase I study of carboplatin and talazoparib in advanced solid tumors. *Clin Cancer Res*. 2017;23(21):6400–6410. doi:10.1158/1078-0432.CCR-17-0703
118. Talazoparib in determining genetic effects on disease response in patients with advanced ovarian, fallopian tube, or primary peritoneal cancer (POSITION). Available from: https://clinicaltrials.gov/ct2/show/NCT02316834. Accessed August 02, 2024.
119. A phase 2, multiple-cohort, open-label, international study of talazoparib monotherapy and talazoparib plus temozolomide in women with relapsed ovarian, fallopian tube, and peritoneal cancer. I. Myriad Genetic Laboratories, I. Medivation; 2016.
120. A phase 2 pilot study of BMN 673 (Talazoparib), an oral PARP inhibitor, in patients with deleterious BRCA1/2 mutation-associated ovarian cancer who have had prior PARP inhibitor treatment. 2014.
121. Phase II study of the PARP inhibitor talazoparib in advanced cancer patients with somatic alterations in BRCA1/2, mutations/deletions in other BRCA pathway genes and germline mutation in BRCA1/2 (Not breast or ovarian cancer). I. National Cancer; 2014.
122. Pilot trial of BMN 673, an oral PARP inhibitor, in patients with advanced solid tumors and deleterious BRCA mutations. 2013.
123. A phase I study of single agent talazoparib (BMN 673) in advanced cancer patients with hepatic and renal dysfunction. 2015.
124. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. *Cancer Discovery*. 2015;5(11):1137–1154. doi:10.1158/2159-8290.CD-15-0714
125. Mittra A, Coyne GHOS, Zlott J, et al. Pharmacodynamic effects of the PARP inhibitor talazoparib (MDV3800, BMN 673) in patients with BRCA-mutated advanced solid tumors. *Cancer Chemother Pharmacol*. 2024;93(3):177–189. doi:10.1007/s00280-023-04600-0
126. Luo Y, Cheng Y, Wu C, et al. Pharmacokinetics, safety, and antitumor activity of talazoparib monotherapy in Chinese patients with advanced solid tumors. *Invest New Drugs*. 2023;41(3):503–511. doi:10.1007/s10637-023-01351-w
127. Schram AM, Colombo N, Arrowsmith E, et al. Avelumab plus talazoparib in patients with BRCA1/2- or ATM-altered advanced solid tumors: results from JAVELIN BRCA/ATM, an open-label, multicenter, phase 2b, tumor-agnostic trial. *JAMA Oncol*. 2023;9(1):29–39.
128. Yap TA, Bardia A, Dvorkin M, et al. Avelumab plus talazoparib in patients with advanced solid tumors: the JAVELIN PARP medley nonrandomized controlled trial. *JAMA Oncol*. 2023;9(1):40–50. doi:10.1001/jamaoncol.2022.5228
129. Leal TA, Sharifi MN, Chan N, et al. A phase I study of talazoparib (BMN 673) combined with carboplatin and paclitaxel in patients with advanced solid tumors (NCI9782). *Cancer Med*. 2022;11(21):3969–3981. doi:10.1002/cam4.4724
130. Durairaj C, Chakrabarti J, Ferrario C, et al. The effect of renal impairment on the pharmacokinetics and safety of talazoparib in patients with advanced solid tumors. *Clin Pharmacokinet*. 2021;60(7):921–930. doi:10.1007/s40262-020-00983-y
131. Naito Y, Kuboki Y, Ikeda M, et al. Safety, pharmacokinetics, and preliminary efficacy of the PARP inhibitor talazoparib in Japanese patients with advanced solid tumors: phase 1 study. *Invest New Drugs*. 2021;39(6):1568–1576. doi:10.1007/s10637-021-01120-7
132. Schafer ES, Rau RE, Berg SL, et al. Phase 1/2 trial of talazoparib in combination with temozolomide in children and adolescents with refractory/recurrent solid tumors including Ewing sarcoma: a children's oncology group phase 1 consortium study (ADVL1411). *Pediatr Blood Cancer*. 2020;67(2):e28073. doi:10.1002/pbc.28073
133. Yu Y, Chung CH, Plotka A, et al. A phase 1 mass balance study of 14C-labeled talazoparib in patients with advanced solid tumors. *J Clin Pharmacol*. 2019;59(9):1195–1203. doi:10.1002/jcph.1415
134. Wainberg ZA, Singh AS, Konecny GE, et al. Preclinical and clinical trial results using talazoparib and low-dose chemotherapy. *Clin Cancer Res*. 2023;29(1):40–49. doi:10.1158/1078-0432.CCR-22-1553
135. Owonikoko TK, Redman MW, Byers LA, et al. Phase 2 study of talazoparib in patients with homologous recombination repair–deficient squamous cell lung cancer: lung-MAP substudy S1400G. *Clin Lung Cancer*. 2021;22(3):187–194.e1. doi:10.1016/j.cllc.2021.01.001
136. Phase 1, two-arm, open-label study of once daily, oral Bmn 673 in patients with advanced hematological malignancies. I. Medivation; 2011.
137. Federico SM, Pappo AS, Sahr N, et al. A phase I trial of talazoparib and irinotecan with and without temozolomide in children and young adults with recurrent or refractory solid malignancies. *Eur J Cancer*. 2020;137:204–213. doi:10.1016/j.ejca.2020.06.014
138. A phase 1B/2 study to evaluate safety and anti tumor activity of avelumab in combination with the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor talazoparib in patients with locally advanced or metastatic solid tumors. 2017.
139. Srkalovic G, Rothe M, Mangat PK, et al. Talazoparib in patients with solid tumors with BRCA1/2 mutation: results from the targeted agent and profiling utilization registry study. *JCO Precis Oncol*. 2024;8(8):e2400026. doi:10.1200/PO.24.00026
140. TALAPRO-1: a phase 2, open-label, response rate study of talazoparib in men with dna repair defects and metastatic castration-resistant prostate cancer who previously received taxane-based chemotherapy and progressed on at least 1 novel hormonal agent (Enzalutamide and/or abiraterone acetate/prednisone). I. Medivation; 2017.
141. Elmeliegy M, Láng I, Smolyarchuk EA, et al. Evaluation of the effect of P-glycoprotein inhibition and induction on talazoparib disposition in patients with advanced solid tumours. *Br J Clin Pharmacol*. 2020;86(4):771–778. doi:10.1111/bcp.14178
142. Hopkins TA, Shi Y, Rodriguez LE, et al. Mechanistic dissection of PARP1 trapping and the impact on in vivo tolerability and efficacy of PARP inhibitors. *Mol Cancer Res*. 2015;13(11):1465–1477. doi:10.1158/1541-7786.MCR-15-0191-T

143. De Bono JS, Mina LA, Gonzalez M, et al. Ramanathan First-in-human trial of novel oral PARP inhibitor BMN 673 in patients with solid tumors. *J Clin Oncol*. 2013;31(15_suppl):2580. doi:10.1200/jco.2013.31.15_suppl.2580
144. Wainberg ZA, Hecht JR, Konecny GE, et al. Abstract CT011: safety and efficacy results from a phase I dose-escalation trial of the PARP inhibitor talazoparib in combination with either temozolomide or irinotecan in patients with advanced malignancies. *Cancer Res*. 2016;76(14 Supplement):CT011. doi:10.1158/1538-7445.AM2016-CT011
145. Smith MA, Hampton OA, Reynolds CP, et al. Initial testing (stage 1) of the PARP inhibitor BMN 673 by the pediatric preclinical testing program: PALB2 mutation predicts exceptional in vivo response to BMN 673. *Pediatr Blood Cancer*. 2015;62(1):91–98. doi:10.1002/pbc.25201
146. De Bono JS, Mina LA, Gonzalez M, et al. First-in-human trial of novel oral PARP inhibitor BMN 673 in patients with solid tumors. *J Clin Oncol*. 2013;31(15_suppl):2580.
147. Turner NC, Balmaña J, Fasching PA, et al. A phase 2 study (2-stage, 2-cohort) of the oral PARP inhibitor talazoparib (BMN 673) in patients with germline BRCA mutation and locally advanced and/or metastatic breast cancer (ABRAZO). *J Clin Oncol*. 2015;33(15_suppl):TPS1108–TPS1108. doi:10.1200/jco.2015.33.15_suppl.tps1108
148. Litton JK, Blum JL, Im Y-H, et al. A phase 3, open-label, randomized, parallel, 2-arm international study of the oral PARP inhibitor talazoparib (BMN 673) in BRCA mutation subjects with locally advanced and/or metastatic breast cancer (EMBRACA). *J Clin Oncol*. 2015;33(15_suppl): TPS1107–TPS1107. doi:10.1200/jco.2015.33.15_suppl.tps1107
149. Turner NC, Telli ML, Rugo HS, et al. Final results of a phase 2 study of talazoparib (TALA) following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline BRCA1/2 mutations (ABRAZO). *J Clin Oncol*. 2017;35(15_suppl):1007. doi:10.1200/JCO.2017.35.15_suppl.1007
150. A phase 2, 2-stage, 2-cohort study of talazoparib (BMN 673) administered to germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer. I. Myriad Genetic Laboratories, I. Medivation; 2014.
151. Litton JK, Blum JL, Im YH, et al. Abstract OT1-03-16: EMBRACA: a phase 3, open-label, randomized, parallel, 2-arm international study of the oral PARP inhibitor talazoparib (BMN 673) versus physician's choice in BRCA mutation subjects with locally advanced and/or metastatic breast cancer. *Cancer Res*. 2016;76(4 Supplement):OT1–03–16. doi:10.1158/1538-7445.SABCS15-OT1-03-16
152. A phase 3, open-label, randomized parallel, 2-arm, multi-center study of talazoparib(BMN 673) versus physician's choice in germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer, who have received prior chemotherapy regimens for metastatic disease. I. Medivation; 2013.
153. Liu B, Li L, Yang G, et al. PARP inhibition suppresses GR-MYCN-CDK5-RB1-E2F1 signaling and neuroendocrine differentiation in castration-resistant prostate cancer. *Clin Cancer Res*. 2019;25(22):6839–6851. doi:10.1158/1078-0432.CCR-19-0317
154. Lesueur P, Chevalier F, Austry JB, et al. Poly-(ADP-ribose)-polymerase inhibitors as radiosensitizers: a systematic review of pre-clinical and clinical human studies. *Oncotarget*. 2017;8(40):69105–69124. doi:10.18632/oncotarget.19079
155. Phase 2 trial of the Combination of the BET inhibitor, ZEN003694 (ZEN-3694), and the PARP inhibitor talazoparib, in patients with molecularly-selected solid tumors (ComBET). 2022.
156. Chatterjee S, Dhal AK, Paul S, et al. Combination of talazoparib and olaparib enhanced the curcumin-mediated apoptosis in oral cancer cells by PARP-1 trapping. *J Cancer Res Clin Oncol*. 2022;148(12):3521–3535. doi:10.1007/s00432-022-04269-7
157. Das C, Dash SR, Sinha S, et al. Talazoparib enhances the quinacrine-mediated apoptosis in patient-derived oral mucosa CSCs by inhibiting BER pathway through the modulation of GCN5 and P300. *Med Oncol*. 2023;40(12):351. doi:10.1007/s12032-023-02222-3
158. Mentzel J, Hildebrand LS, Kuhlmann L, Fietkau R, Distel LV. Effective radiosensitization of HNSCC cell lines by DNA-PKcs inhibitor AZD7648 and PARP inhibitors talazoparib and niraparib. *Int J Mol Sci*. 2024;25(11):5629. doi:10.3390/ijms25115629