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REVIEW ARTICLE OPEN ACCESS

PARP Inhibitors in Genitourinary Cancer: A New Paradigm Beyond Prostate Cancer

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ABSTRACT

Alterations in the homologous recombination repair genes, such as *BRCA1* and *BRCA2*, are prevalent in various cancers, presenting a unique opportunity to develop synthetic lethal strategies that target homologous recombination deficiency (HRD). Poly ADP-ribose polymerase inhibitors (PARPis) have been developed to induce synthetic lethality in tumors with HRD by inhibiting the repair of single-strand DNA breaks. Beyond the initial approach to target cancers associated with HRD, the utility of PARPis has expanded to combination therapy with immune checkpoint inhibitors, anti-angiogenic drugs, or anti-androgen drugs based on the molecular biological rationale. In the field of genitourinary (GU) cancer, PARPis, such as olaparib, rucaparib, and talazoparib, are approved by the Food and Drug Administration in metastatic prostate cancer patients with *BRCA1/2* mutations, sometimes in combination with other agents (e.g., olaparib plus abiraterone acetate, or talazoparib plus enzalutamide). More recently, pivotal clinical trials have broadened the potential of PARPis to the other GU cancers, including urothelial carcinoma and renal cell carcinoma. In this review, we examine the biomarkers for the response to PARPis beyond mutations in *BRCA1/2* and discuss the current state and future perspectives of PARPis in GU cancers.

1 | Introduction

Poly(ADP-ribose) polymerases (PARPs) are enzymes involved in poly ADP-ribosylation (PARylation), a post-translational modification critical for repairing DNA single-strand breaks (SSBs). Among the 17 PARP family members, PARP1 and PARP2 are the primary mediators of DNA repair and genomic stability, especially in response to SSBs [1–3]. Inhibition of these enzymes leads to SSB accumulation and replication-associated

double-strand breaks (DSBs), ultimately triggering cancer cell death—a concept that led to the development of PARP inhibitors (PARPis) [4–6].

The clinical relevance of PARPis grew dramatically following the discovery of synthetic lethality in *BRCA1/2*-mutated tumors, which lack homologous recombination (HR)-mediated DSB repair [7, 8]. *BRCA1* and *BRCA2* genes are central to the HR repair (HRR) pathway, and their inactivation results in

Abbreviations: ACC, adrenocortical carcinoma; BER, base excision repair; BSC, best supportive care; CAR-T cell, chimeric antigen receptor T-cell; CI, confidence interval; DCR, disease control rate; DDR, dna damage repair; DSBs, double-strand breaks; FAP, familial adenomatous polyposis; GCT, germ cell tumor; GU, genitourinary; HR, homologous recombination; HRD, homologous recombination deficiency; HRR, homologous recombination repair; ICI, immune checkpoint inhibitor; KIRC, kidney renal clear cell carcinoma; KPRC, kidney papillary renal cell carcinoma; LOH, loss of heterozygosity; MIBC, muscle-invasive bladder cancer; NHEJ, non-homologous end joining; ORR, objective response rate; OS, overall survival; PARP, poly ADP-ribose polymerase; PARPi, PARP inhibitor; PBC, platinum-based chemotherapy; PC, prostate cancer; PCC, pheochromocytoma; PFS, progression-free survival; PGL, paraganglioma; RCC, renal cell carcinoma; SD, stable disease; SSBs, single-strand breaks; TCGA, the cancer genome atlas; TGCT, testicular germ cell tumor; UC, urothelial carcinoma; UTUC, upper tract urothelial carcinoma; WES, whole-exome sequencing.

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genomic instability and increased cancer susceptibility [9–11]. While synthetic lethality was initially attributed to the accumulation of DSBs caused by unrepaired SSBs, alternative mechanisms such as PARP trapping, replication fork collapse, and single-strand gap accumulation have also been proposed [12–18].

BRCA1/2 mutations are found in approximately 10%–18% of patients with advanced prostate cancer (PC) [19, 20]. The U.S. Food and Drug Administration has approved olaparib, rucaparib, and talazoparib for *BRCA1/2*-mutant metastatic PC [19–22], and more recently, PARPi-based combination therapies (e.g., with androgen receptor signaling inhibitors) have been approved [23–26]. Compared to the *BRCA1/2* mutant population in PC patients, *BRCA1/2* mutation rates in other genitourinary (GU) cancers are generally low, which might delay the application of PARPi in patients with these cancers [27, 28]. However, with advances in understanding HR and expanded genome sequencing efforts, mutations in HR-related genes beyond *BRCA1/2* are now being identified in GU cancers, opening new avenues for PARPi-based strategies [29, 30].

In light of these advancements, this article provides the potential biomarkers of PARPi beyond mutations in *BRCA1* and *BRCA2* and discusses the current state and future perspectives of PARPi in GU cancers.

2 | Biomarkers of PARP Inhibitors Beyond *BRCA1/2*

Although *BRCA1/2* mutations remain the most established predictors of PARPi sensitivity, accumulating evidence indicates that tumors with homologous recombination deficiency (HRD) can also respond to PARPi even in the absence of *BRCA1/2* alterations [31, 32]. HRD denotes an impaired ability to repair DNA double strand breaks via the HRR pathway. Clinically, HRD is often inferred from genomic “scar” assays—most notably the HRD score—which combines three chromosomal instability metrics: loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions [33, 34]. Higher HRD scores generally correlate with improved responses to PARPi and platinum based chemotherapy regardless of *BRCA1/2* status [35]. Commercial assays such as Myriad myChoice CDx incorporate the HRD score and help guide PARPi therapy across several cancer types [36, 37].

In parallel, the concept of “BRCaness” was introduced to describe tumors that phenotypically resemble *BRCA*-mutant cancers despite lacking *BRCA1/2* mutations [19, 20]. These tumors often harbor alterations in other HRR-related genes such as *ATM*, *CHEK2*, *PALB2*, *RAD51*, and *FANCA*, and may exhibit comparable therapeutic efficacy to *BRCA*-mutated cancers. For example, favorable responses to PARPi have been reported in *PALB2*-mutated breast and pancreatic cancers, as well as *ATM*-mutated PCs [21, 22, 24]. These findings imply the possible and broader use of PARPi for patients with BRCaness, depending on the findings by means of cancer gene panel testing.

Beyond genes commonly included in cancer gene panels, certain genes play a critical role at the transcription levels in determining

sensitivity to PARPi. For instance, *Schlafen 11 (SLFN11)*, a putative DNA/RNA helicase, has emerged as a significant determinant of PARPi sensitivity [38, 39]. In previous research, high *SLFN11* expression enhanced PARPi cytotoxicity by preventing stalled replication fork recovery, which was closely associated with improved outcomes following olaparib treatment [38, 40]. Notably, over 50% of clear cell renal cell carcinomas (RCCs) exhibit high *SLFN11* expression [41, 42], suggesting that *SLFN11* may serve as a predictive biomarker in GU cancers even in the absence of *BRCA1/2* mutations.

Taken together, these markers support a paradigm in which PARPi may benefit selected patients based on molecular features beyond *BRCA1/2* mutation status and expand the therapeutic application of PARPi in GU cancers.

3 | PARP Inhibitors as Antitumor Immune Activators

Improvement of the antitumor immune microenvironment by PARPi has been reported in multiple studies [43]. For instance, talazoparib, a PARPi in PC treatment, promotes the accumulation of cytoplasmic DNA and the activation of the STING pathway in vitro [44]. Huang et al. also demonstrated that talazoparib promotes STING activation in murine ovarian cancer models, leading to increased infiltration of antitumor immune cells and enhanced functionality of CD8⁺ T and NK cells [45]. In addition, PARPi (olaparib and talazoparib) are associated with the upregulation of PD-L1 expression on cancer cells in vitro and in vivo [46]. Given that GU cancers are often treated with immune checkpoint inhibitors (ICIs), these findings provide a strong rationale for combining PARPi with ICIs in GU cancers, regardless of *BRCA* mutation.

4 | PARP Inhibition in Urothelial Carcinoma

Urothelial carcinoma (UC) has a complex genomic landscape that includes deficiencies in DNA damage repair (DDR) genes at both the germline and somatic levels. The DDR gene mutations were relatively common across all UC subtypes, with the most frequently mutated genes being *ATM* (4.3%), *ERCC2* (4.1%), *PRKDC* (2.4%), and *ATR* (2.2%), particularly in muscle-invasive bladder cancer (MIBC) [47–50]. These alterations generally increase tumor mutational burden and may contribute to the sensitivity to DNA-damaging agents such as PARPi [51, 52]. Although PARPi have not yet been approved for UC, their efficacy has been investigated in multiple clinical trials as monotherapy, in combination with immune checkpoint inhibitors, and as maintenance or neoadjuvant therapy (Table 1). Key trials are summarized in Table 1.

4.1 | PARPi Monotherapy in UC

4.1.1 | ATLAS Trial

The ATLAS trial (NCT03397394) was a phase II, single-arm study evaluating rucaparib monotherapy in 97 patients with locally advanced or metastatic UC who had previously received

TABLE 1 | Clinical trials on poly ADP-ribose polymerase inhibitors for urothelial carcinoma.

Trial name	Year of enrollment	Phase	Study design	Patient population	HRD status	Treatment	Enrollment number	Control	Primary endpoint	Results
BISCAY [53]	2016–2019	Ib	Open-label	Advanced/metastatic UC who had progressed on previous PBC treatment	Yes/No	Durvalumab + Olaparib	<i>n</i> = 35	Durvalumab	The safety of treatment	RR was 35.7% mutations with HRD and 9.1% without HRD
BAYOU [54]	2016–2019	II	Randomized, double-blind	Untreated, platinum-ineligible metastatic UC patients	Yes/No	Durvalumab + Olaparib	<i>n</i> = 76	Durvalumab + placebo	PFS	4.2 months (95% CI, 3.6–5.6) vs. 3.5 months (95% CI, 1.9–5.1)
ATLAS [55]	2018–2019	II	Open-label	Locally advanced/unresectable or metastatic UC patients post-PBC and/or ICI treatment	Yes/No	Rucaparib	<i>n</i> = 97	None	ORR	0% (95% CI, 0–3.8)
ATLANTIS [56, 57]	2017–2021	II	Randomized, umbrella-design screening trial	Metastatic or locally advanced UC patients with response or stable disease post 1st-line chemotherapy	Yes	Rucaparib	<i>n</i> = 19	Placebo	PFS	35.3 weeks (80% CI, 11.7–35.6) vs. 15.1 weeks (80% CI, 11.9–22.6)
JAVELIN PARP Medley [58]	2017–2019	II	Open-label, basket-type	Patients with advanced solid tumors (including UC)	Yes/No	Talazoparib + Avelumab	<i>n</i> = 40	None	ORR	15.0% (95% CI, 5.7–29.8)
Meet-URO12 [59, 60]	2019–2021	II	Randomized, open-label	Advanced UC patients post-platinum-based chemotherapy without disease progression	Yes/No	Niraparib + best supportive care (BSC)	<i>n</i> = 39	BSC alone	PFS	2.1 months (95% CI, 0.9–3.2) vs. 2.4 months (95% CI, 1.6–3.2)
NEODURVARIB [61, 62]	2018–2019	II	Open-label	MIBC patients scheduled for radical cystectomy	Yes/No	Durvalumab + Olaparib	<i>n</i> = 29	None	Impact of neoadjuvant treatment in the molecular profile of MIBC	Genetic alterations remained unchanged

Abbreviations: BSC, best supportive care; CI, confidence interval; HRD, homologous recombination deficiency; ICI, immune checkpoint inhibitor; MIBC, muscle-invasive bladder cancer; ORR, objective response rate; PBC, platinum-based chemotherapy; PFS, progression-free survival; UC, urothelial carcinoma.

platinum-based chemotherapy (PBC) and/or ICIs [55]. Overall, 44/97 (45.4%) patients had received two prior therapies for advanced disease; 93/97 (95.9%) patients had received prior PBC, 71/97 (73.2%) patients had received prior ICIs, and 67/97 (69.1%) had received both a PBC and an ICI (separately or combined). Among the 97 enrolled patients, 20 (20.6%) were HRD-positive, 30 (30.9%) were HRD-negative, and 47 (48.5%) had an unknown HRD status. No confirmed objective responses were observed in either the overall cohort or the HRD-positive subgroup (0%; 95% CI, 0%–3.8%). Although 20.6% of patients were HRD-positive, none achieved an objective response. Median progression-free survival was 1.8 months, and efficacy showed no correlation with HRD status. These findings indicate that PARPi monotherapy offers limited benefit in unselected or HRD-positive urothelial carcinoma, possibly owing to insufficient biomarker specificity or the advanced disease stage.

4.2 | PARPis in Combination With ICIs

4.2.1 | BISCAY Trial

The BISCAY trial (NCT02546661) is a phase Ib study investigating the safety and improvement of clinical activity of durvalumab, a PD-L1 inhibitor, in combination with various targeted therapies [53]. The trial included two non-randomized cohorts combining olaparib with durvalumab immunotherapy, selected based on six biomarkers for second-line or later treatment of metastatic UC. One cohort included an HRR-selected group ($n=14$) comprising patients with mutations in HRR genes, such as *ATM* and *BRCA1/2*, while the other was an HRR-unselected group ($n=21$). In the HRR-selected cohort, the objective response rate (ORR) was 35.7%, compared with 9.1% in the HRR-unselected group receiving the same combination. Nonetheless, the regimen did not meet the predefined efficacy threshold for further development, and survival outcomes were comparable between the two arms. These results highlight the need for robust biomarker strategies and larger randomized studies to clarify the value of PARPi-ICI combinations.

4.2.2 | BAYOU Trial

The BAYOU trial (NCT03459846) is a phase II, double-blind, randomized trial designed to evaluate the efficacy and safety of durvalumab combined with olaparib in untreated, platinum-ineligible patients with metastatic UC [54]. The trial enrolled 154 patients with UC who were not selected based on their HRR status. Of these, 78 patients were assigned to the durvalumab plus olaparib group and 76 to the durvalumab plus placebo group. HRR mutations were found in 17 patients (21.8%) in the durvalumab plus olaparib group and 14 patients (18.4%) in the durvalumab plus placebo group. In the durvalumab plus olaparib group, the median PFS was 4.2 months (95% CI, 3.6–5.6), compared to 3.5 months (95% CI, 1.9–5.1) in the durvalumab plus placebo group (hazard ratio, 0.94; 95% CI, 0.64–1.39; stratified log-rank $p=0.789$). The study failed to meet its primary endpoint because the durvalumab-olaparib arm showed no PFS benefit in the overall population. In patients with HRR mutations, however, combination therapy significantly prolonged PFS (5.6 vs. 1.8 months; $p<0.001$). These data suggest

that PARPi-ICI synergy may be confined to biomarker-selected populations.

4.2.3 | JAVELIN PARP Medley

The JAVELIN PARP Medley trial (NCT03330405) is a non-randomized, basket-type phase Ib and phase II trial involving patients with advanced solid tumors, including UC [58]. This trial is assessing the safety and clinical efficacy of combination therapy involving talazoparib and the anti-PD-L1 antibody, avelumab. For the enrollment of UC cases, HRR biomarker selection was not applied, and out of the 211 total patients enrolled, 40 were UC cases. Among them, 18 patients (45%) were DDR-positive. The ORR was comparable between patients who had and had not received prior platinum-based therapy (14.3% vs. 16.7%). The median duration of response was not reached (range, 3.9 to ≥ 14.7 months). Although durable responses occurred in a minority of patients, the absence of stratification limits the interpretability and clinical relevance of these findings.

4.3 | PARPis As Maintenance Therapy

4.3.1 | ATLANTIS Trial

The ATLANTIS trial (ISRCTN25859465) is a multi-center, randomized phase II umbrella design screening trial exploring novel targeted therapies in biomarker-defined subgroups [56, 57]. Eligible patients are those with metastatic or locally advanced UC who achieved objective response or SD after 4–8 cycles of first-line chemotherapy. Multiple novel agents are being used in parallel, and patients are entered into ATLANTIS subgroup trials according to their tumor biomarker profiles. Each comparison control arm is matched with a placebo, and, where possible, comparisons are double-blind. Of the 248 patients who underwent pre-screening for biomarkers, 74 (29.8%) were DDR biomarker-positive. Among these, 40 patients were randomly assigned to the rucaparib comparison arm (rucaparib: 20 patients, placebo: 20 patients). The median PFS was 35.3 weeks with rucaparib (80% CI, 11.7–35.6) versus 15.1 weeks with the placebo (80% CI, 11.9–22.6), with an adjusted hazard ratio of 0.53 (80% CI, 0.30–0.92; one-sided $p=0.07$). Median OS was not reached in the rucaparib arm, whereas it was 72.3 weeks in the placebo arm (adjusted hazard ratio 1.22; 80% CI 0.62–2.38; $p=0.35$). Although exploratory, these results suggest a potential role for PARP inhibitors as maintenance therapy, particularly for patients with DDR alterations who respond to first-line chemotherapy.

4.3.2 | Meet-URO12 Trial

The Meet-URO 12 trial (NCT03945084) was a multi-center, randomized, open-label phase II trial that investigated the efficacy of niraparib as maintenance therapy for patients with advanced UC [60]. The study included 58 patients with advanced UC who had completed PBC and had no disease progression. The patients were randomized to receive either niraparib plus best supportive care (BSC) ($n=39$) or BSC alone ($n=19$). No significant PFS benefit was observed (2.1 vs. 2.4 months; hazard ratio, 0.92;

95% CI, 0.49–1.75; $p=0.81$), and the trial was halted early, partly due to the availability of avelumab maintenance, which demonstrated a clear survival benefit in this setting [59].

4.4 | Neoadjuvant Applications

4.4.1 | NEODURVARIB Trial

The NEODURVARIB trial (NCT03534492) was a phase II clinical trial designed to evaluate the impact of neoadjuvant combination therapy with durvalumab and olaparib on the molecular profile of MIBC [61, 62]. A total of 29 patients with cT2–T4a MIBC, scheduled for radical cystectomy, were enrolled. Imaging-based evaluations following neoadjuvant therapy showed a partial response rate of 24.1% and stable disease in 51.7% of the cases, progressive disease in 10.3% of the cases, and non-evaluable in 13.8% of the cases. Of the 26 cystectomies performed, the pathological complete response rate was 50%. Although no clear genomic predictors of response were identified, these early findings are promising and suggest that PARPi–ICI combinations may be feasible in the neoadjuvant setting, especially in patients ineligible for cisplatin-based chemotherapy.

4.5 | Clinical Implications and Future Perspectives

Taken together, these trials indicate that the efficacy of PARP inhibitors in UC depends strongly on patient selection. PARPi monotherapy offers limited benefit, whereas PARPi–ICI combinations or use in maintenance or neoadjuvant settings appear more promising, particularly for patients with DDR or HRR alterations. Future studies should adopt biomarker-enriched designs, evaluate earlier lines of therapy, and explore combination strategies that enhance PARPi sensitivity and overcome resistance.

5 | PARP Inhibition in Renal Cell Carcinoma

Although BRCA1/2 mutations are rare in RCC, recent genomic profiling has shown that a subset of patients harbor HRR or DDR gene alterations [63]. These molecular features provide a rationale for evaluating PARPis in RCC. Although no PARPi is currently approved for this indication, several early-phase trials are assessing their efficacy as monotherapy, in combination with ICIs, or even in HRR wild-type cases (Table 2). Key examples are summarized in Table 2.

5.1 | Monotherapy Potential of PARPis in RCC

5.1.1 | ORCHID Trial

The ORCHID trial (NCT03786796) is a phase II, single-arm study evaluating olaparib monotherapy in patients with metastatic RCC and mutations in DDR genes (e.g., *BAP1*, *ATM*, *PALB2*, *BRCA1/2*) [64]. The trial targets patients with metastatic RCC who have previously undergone treatment with angiogenesis inhibitors or ICIs, with a planned enrollment of up to 20 participants. The trial is expected to be completed

in 2025, and interim results from 11 patients, whose genetic abnormalities were identified in *BAP1* (61.5%), *ATM* (15.4%), *PALB2* (15.4%), *BRCA1* (7.7%), and *BRCA2* (7.7%), showed a disease control rate of 18% and tumor shrinkage in 27%, although the ORR was low (9%). These findings suggest limited but detectable activity of olaparib in molecularly selected RCC patients.

5.1.2 | WIRE Trial (Monotherapy Arms)

The WIRE trial (NCT03741426) is a phase II, multi-arm, multi-center, non-randomized, proof-of-mechanism study using a Bayesian adaptive design to evaluate monotherapy or combination therapy of investigational drugs during the “window-of-opportunity” period of at least 2 weeks prior to nephrectomy or partial nephrectomy [65]. Participants would undergo multiparametric MRI before and after treatment, and angiogenic and non-angiogenic tissues would be collected at surgery. One of the five initial arms includes olaparib monotherapy in patients with surgically resectable ccRCC. While clinical efficacy endpoints such as PFS or OS are not the primary focus of this trial, the primary endpoint for the olaparib monotherapy arm is a $>30\%$ reduction in tumor vascular permeability, measured by K^{trans} on dynamic contrast-enhanced MRI (DCE-MRI).

This trial is expected to elucidate whether PARP inhibition alone can induce biologically meaningful effects in ccRCC, a disease not classically associated with HRD but potentially effective due to replication stress induced by *VHL* loss or *SETD2* mutations, both common in ccRCC.

5.2 | Combination Therapy With ICIs

5.2.1 | WIRE Trial (Combination Arms)

The WIRE trial also investigates the immunomodulatory potential of PARP inhibitors through two additional arms: durvalumab monotherapy and durvalumab combined with olaparib. The primary endpoint in these arms is a $\geq 30\%$ increase in CD8⁺ T cell infiltration, measured by immunohistochemistry comparing pre-treatment biopsy and nephrectomy tissue. Importantly, preclinical data suggest that PARP inhibition may upregulate PD-L1 expression and activate the STING pathway, potentially enhancing antitumor immune responses. By comparing monotherapy and combination arms, the WIRE trial will determine whether olaparib enhances the immunogenicity of RCC tumors and whether PARPi–ICI synergy exists in this tumor type, which has shown moderate sensitivity to immune checkpoint blockade in metastatic settings. Translational endpoints will assess changes in cytokine profiles, immune cell subsets, and potential predictive biomarkers of response or resistance.

5.2.2 | IMAGENE Trial

The IMAGENE trial (JRCT2051210120), a multi-center, phase II study, is currently being conducted to investigate niraparib

TABLE 2 | Clinical trials on poly ADP-ribose polymerase inhibitors for renal cell carcinoma.

Trial name	Year of enrollment	Phase	Study design	Patient population	Treatment	HRD status	Enrollment number	Control	Primary endpoint	Results
ORCHID [64]	2019—	II	Non-randomized, open-label	Patients with mRCC having BAP1 or other DNA repair gene mutations	Olaparib	Yes	11 (still recruiting up to 20 participants)	None	DCR	DCR was 22%
WIRE [65]	2020—	II	Non-randomized, proof-of-mechanism	Patients after nephrectomy	Cediranib, Olaparib, Durvalumab (monotherapy or combination)	Yes/No	76 (recruiting)	None	Changes in capillary permeability and changes to intra-tumoral CD8+ T-cell infiltration	Not reported yet
NICARAGUA [66]	2019–2014	II	Non-randomized, open-label	Patients with RCC (including UC)	Niraparib, Cabozantinib	Yes/No	5 RCC and 14 UC	None	PFS	Not reported yet. 14 (74%) patients had SD
IMAGENE [67]	2022–2023	II	Non-randomized, proof-of-concept	Patients with HRR gene mutations resistant to ICIs	Niraparib, PD-1 inhibitor	Yes	Not reported yet	None	ORR	Not reported yet

Abbreviations: DCR, disease control rate; HRD, homologous recombination deficiency; HRR, homologous recombination repair; ICi, immune checkpoint inhibitor; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; RCC, renal cell carcinoma; SD, stable disease; UC, urothelial carcinoma.

plus anti-PD-1 antibody in patients with HRR-mutant solid tumors after previous ICI treatment [67]. Patients with a variety of metastatic cancers, including UC and RCC, have been enrolled in this trial. This trial aims to confirm which patients would benefit from the targeted combination therapy for patients with HRR gene-mutated tumors even after the failure of ICIs.

5.3 | Application Beyond Classical HRR Mutations

5.3.1 | Non-BRCA/Non-HRR Mutations

Several studies indicate that DDR gene mutations beyond *BRCA1/2*, such as *ATM*, *CHEK2*, and *CDK12*, occur in RCC and may predict response to PARPi [68, 69]. A case report documented niraparib efficacy in a patient with metastatic clear cell RCC harboring *CDK12* and *RAD51C* mutations, further expanding the potential biomarker landscape [70].

5.3.2 | *DDX11* As a Novel Biomarker

In vitro studies have reported that a deficiency in *DDX11*, a DEAD/DEAH box helicase involved in sister chromatid cohesion, significantly increases sensitivity to olaparib, suggesting that *DDX11* may determine PARPi sensitivity in RCC [71]. While clinical evidence is still limited, these findings raise the possibility of PARPi beyond canonical HRR contexts.

5.4 | PARPi in Combination With Other Targeted Therapies

5.4.1 | NICARAGUA Trial

The NICARAGUA trial (NCT03425201), a phase II trial, aimed to evaluate the efficacy of niraparib and cabozantinib, a tyrosine kinase inhibitor targeting c-MET and TAM kinases, in patients with advanced UC or RCC [66]. Among 19 patients (predominantly urothelial), combination therapy, including niraparib and cabozantinib, resulted in partial remission in only three patients (16%) (all of them with mUC disease), while the remaining 14 cases (74%) showed SD. This suggests that the benefit of this combination therapy in RCC may be modest and highlights the need for biomarker-guided patient selection.

5.5 | Clinical Implications and Future Perspectives

Although current data remain preliminary, the presence of DDR gene alterations, early signs of PARPi activity, and immunomodulatory effects provide a rationale for continued investigation of PARPi in RCC. Future research should aim to deepen our understanding of predictive biomarkers by incorporating both HRR and non-HRR DDR gene alterations into trial designs. It will also be important to explore the potential role of PARP inhibitors in patients who have developed resistance to ICI or who are ICI-naïve. In addition, integrating functional assays and

molecular imaging—such as those used in the WIRE trial—may help refine patient selection strategies. Collectively, these approaches will be essential for optimizing the clinical use of PARPi in RCC and advancing toward more personalized therapeutic paradigms.

6 | PARP Inhibition in Testicular Germ Cell Tumors

Testicular germ cell tumors (TGCTs) are highly curable with cisplatin-based chemotherapy; however, a small subset of patients develops refractory or relapsed disease, for which effective therapeutic options remain limited [72]. Recent molecular studies have identified features of HRD and epigenetic silencing of DNA repair genes in TGCTs, providing a biological rationale for evaluating PARP inhibitors (PARPi) in this context. Although clinical evidence is still limited, preclinical studies and early-phase trials suggest the potential utility of PARPi, particularly in biomarker-defined populations and in combination with other agents (Table 3).

6.1 | PARP Inhibitor Monotherapy in TGCTs

6.1.1 | Biological Rationale and Preclinical Data

Immunohistochemical studies have shown that PARP is overexpressed in TGCTs compared to normal testicular tissue, suggesting that PARP activation may be an early event in tumorigenesis [76]. Additionally, functional studies in embryonal carcinoma cell lines have demonstrated that HR repair is compromised, contributing to increased sensitivity to olaparib [77]. In TGCT models, loss of the *CCDC6* gene—a regulator of DNA damage response—also impairs homologous recombination and enhances PARPi sensitivity [78].

Genomic analyses, however, show that somatic mutation rates in TGCTs are relatively low, with few recurrent mutations in HRR-related genes [79]. However, only a mutation in the *XRCC2* gene, a member of the *RecA/Rad51*-related protein family, was identified at a rate of approximately 2.4%. Importantly, epigenetic alterations such as promoter hypermethylation of *BRCA1* and *RAD51C* have been consistently reported, suggesting that transcriptional silencing of HR genes may represent a mechanism of HRD in TGCTs [80, 81].

6.1.2 | IGG-02 Trial

The IGG-02 trial (NCT02533765) is a phase II, open-label, single-arm study evaluating olaparib monotherapy in patients with refractory or relapsed metastatic GCTs following cisplatin-based chemotherapy [73]. Among 18 heavily pretreated patients (most with ≥ 3 prior lines of therapy), no objective responses were observed. SD was achieved in five patients (27.8%), with a 12-week PFS rate of 27.8%. One patient with a *BRCA1* germline mutation had SD for 4 months. The study suggests that PARPi monotherapy may have limited activity in unselected, heavily pretreated TGCT patients, though further evaluation in biomarker-enriched or less heavily treated populations is warranted.

TABLE 3 | Clinical trials on poly ADP-ribose polymerase inhibitors for rare cancers.

Trial name	Cancer type	Year of enrollment	Phase	Study design	Patient population	Treatment	HRD status	Enrollment number	Control	Primary endpoint	Results
IGG-02 [73]	GCTs	2015–2019	II	Open-label	Patients with relapsed or refractory metastatic GCTs	Olaparib	Yes/No	18	None	OS	The 12-month OS was 27.8% (95% CI: 10.1–48.9)
GCT-SK-004 [74]	GCTs	2016–2020	II	Non-randomized, open-label	Patients with relapsed or refractory GCTs	Veliparib + Gemcitabine + Carboplatin	Yes/No	15	None	12-month PFS	12-month PFS was achieved in 1 (6.7%) patient
NCT04394858 [75]	PCC/ PGL	2021—	II	Randomized, open-label	Patients with APP with radiographic evidence of disease progression	Olaparib + Temozolomide	Yes/No	76 (recruiting)	Temozolomide	PFS	Not reported yet

Abbreviations: GCTs, germ cell tumors; HRD, homologous recombination deficiency; OS, overall survival; PCC, pheochromocytoma; PFS, progression-free survival; PGL, paraganglioma.

6.2 | Combination Therapy With PARPis in TGCTs

6.2.1 | GCT-SK-004 Trial

The GCT-SK-004 trial (NCT02860819) evaluated a combination of veliparib, gemcitabine, and carboplatin in 15 patients with relapsed or refractory extragonadal GCTs [74]. Partial responses were observed in four patients (26.7%), and SD in five patients (33.3%), although the primary endpoint of 12-month PFS was achieved in only 1 patient (6.7%). The regimen was well tolerated but did not demonstrate substantial benefit. The study hypothesized that PARP inhibition might potentiate DNA damage induced by cytotoxic agents, particularly in the context of *PTEN* inactivation or defects in nucleotide excision repair, but clinical efficacy remains unproven.

6.3 | Clinical Implications and Future Perspectives

Current clinical evidence for PARP inhibitors in TGCTs is limited and inconclusive, particularly in unselected, heavily pretreated populations. Preclinical data suggest that HRD exists in a subset of TGCTs, driven more by epigenetic silencing than genetic mutations. Therefore, future trials should emphasize biomarker-driven patient selection, potentially integrating methylation profiling or functional HRD assays. In addition, combination therapies, particularly with DNA-damaging agents or ICIs, may enhance efficacy in otherwise resistant cases. Further investigation in earlier treatment settings or less heavily pretreated cohorts will be essential to determine whether PARPis can play a therapeutic role in TGCT management.

7 | Emerging and Exploratory Applications of PARP Inhibitors

Recent preclinical and early genomic evidence suggests that PARPis may have potential applications in rare genitourinary and endocrine tumors, including adrenocortical carcinoma (ACC) and pheochromocytoma/paraganglioma (PCC/PGL).

In ACC, germline HRR gene mutations are uncommon; however, somatic alterations and epigenetic dysregulation of DNA repair pathways, including *BRCA1/2* and *CHEK2*, have been identified in small cohorts [82–85]. These findings suggest that a molecularly defined subset of ACC may harbor PARPi-sensitive phenotypes, although no clinical trials have yet been conducted to confirm this hypothesis. On the other hand, in PCC/PGL, particularly in tumors with “Cluster 1 mutations” (e.g., *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *FH*, and *VHL*), results in the activation of the DNA repair system mediated by PARP, which contributes to chemotherapy resistance (specifically to temozolomide) [86, 87]. Therefore, combination therapy of the standard drug temozolomide with olaparib presents a promising approach for treating metastatic tumors with “Cluster 1 mutations.” [88] Preclinical studies utilizing an allograft mouse model have shown that combining olaparib with temozolomide can sensitize PCC/PGL models and suppress metastasis in *SDHB*-deficient tumors [89]. A phase II clinical trial (NCT04394858) is currently evaluating this combination in metastatic cases, and its results are awaited [75].

Overall, while these exploratory findings are scientifically compelling, the clinical applicability of PARPis in ACC and PCC/PGL remains unproven, and further research is warranted to define biomarkers of response and identify patient populations most likely to benefit from PARP-targeted strategies.

8 | Conclusion

PARPis are primarily effective in patients with cancer harboring GU cancers with *BRCA1/2* mutations. However, recent evidence prompts us to reconsider using PARPis with or without the other types of therapy depending on biomarkers beyond *BRCA1/2* mutations. Further research will be needed to explore the exact mechanism for potential biomarkers to apply PARPis into the routine clinical practice in GU cancers.

Author Contributions

Yohei Okuda: conceptualization, writing – original draft, data curation, methodology, software, investigation, validation, formal analysis, visualization. **Taigo Kato:** conceptualization, writing – review and editing, supervision, data curation, writing – original draft, funding acquisition. **Yu Ishizuya:** supervision, writing – review and editing. **Takuji Hayashi:** writing – review and editing. **Yoshiyuki Yamamoto:** writing – review and editing, supervision. **Koji Hatano:** writing – review and editing, supervision. **Atsunari Kawashima:** writing – review and editing, supervision. **Junko Murai:** writing – review and editing, supervision, writing – original draft, funding acquisition. **Norio Nonomura:** writing – review and editing, project administration, supervision, resources.

Conflicts of Interest

Taigo Kato received lecture fees from Takeda Pharmaceutical Company Limited and Pfizer Global Supply Japan Inc. Junko Murai received lecture fees from Takeda Pharmaceutical Company Limited, Pfizer Global Supply Japan Inc., and AstraZeneca plc. The other authors declare that they have no conflicts of interest or financial ties related to this study. Norio Nonomura is an Editorial Board member of *International Journal of Urology* and a co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

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