Poly (ADP-Ribose) Polymerase Inhibitors in Patients With Urothelial Cancer

Teresa Gamba,[1,*] Jessica Paparo,[1,*] Olimpia Panepinto,[1,*] Rossana Dionisio,[2] Massimo Di Maio,[1] Francesca Vignani[2]

ABSTRACT

Poly ADP-ribose polymerase inhibitors (PARPis) have clinical activity in several cancers. The rationale of their therapeutic use in urothelial cancer (UC) resides in the high homologous-recombination repair (HRR) deficiency (HRD) prevalence and potential cross-sensitivity with platinum-based chemotherapy (PBCT). This review aims to summarize and analyze trials exploring the activity of PARPis in UC, focusing on patients who may benefit from those agents, the best clinical setting for the treatment and the benefit of the association with immune-checkpoint inhibitors (ICIs). We included all the available trials analyzing the activity of PARPis in UC in neoadjuvant, adjuvant, first or subsequent lines, and maintenance setting. We included PARPis in monotherapy and in association with other agents. The results in the maintenance setting are intriguing: ATLANTIS trial showed signals of improved progression-free survival in patients with known HRR aberrations, although the Meet-URO12 trial, with its negative results, suggested the failure of clinical selection based on platinum sensitivity only. Single-agent PARPis in pretreated patients showed discouraging results in an unselected population of chemo-refractory patients. Concerning the association of PARPis with ICIs, several trials are exploring their role in platinum-naïve setting; the results in the advanced setting were globally negative. Prior selection of HRD status is essential to identify patients who might benefit from PARPis. The ideal clinical settings seem to be the maintenance treatment and the combination with ICIs in platinum-naïve patients. Definitive results of ongoing and further trials will delineate the position for PARPis, if any, in UC therapy.

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Introduction

Epidemiology, Staging, and Treatment

In the Western world, urothelial bladder cancer (BC) is the fourth most common malignancy in men and the eighth in women; upper tract urothelial carcinoma (UTUC) has a lower incidence, representing less than 1% of all cancer types, with a greater homogeneity in the prevalence among genders.[1]

Radical cystectomy with pelvic lymphadenectomy is currently the standard treatment for clinically localized, muscle-infiltrating bladder cancer (MIBC). However, the risk of relapse is high, especially in ≥pT2 disease and/or nodal involvement: the 5-year relapse-free survival after radical cystectomy is 68% with an overall survival that does not exceed 50%.[2] Several neoadjuvant and adjuvant strategies have therefore been investigated, with the aim of improving clinical outcomes in this setting. Similarly, these strategies have been explored for UTUC, a poor prognosis cancer with a 5-year OS of around 50% for pT2/pT3 cancer and less than 10% for pT4 stage.[2,3]

Platinum-based chemotherapy (PBCT) is the gold standard (neo)adjuvant treatment for resected UC and first-line treatment of metastatic/unresectable UC.[4-6] In patients with advanced disease, objective response occurs in 40% to 50% of patients, and disease control in 75% to 80%. Despite this activity, unfortunately, the prognosis is still poor: most patients experience disease progression within approximately 9 months, with a median OS of 14 months with cisplatin-based regimens[7,8] and 9 months with carboplatin-based regimens.[9] In this context, several studies are exploring the activity of novel molecular target therapies and immune checkpoint inhibitors (ICIs). In patients obtaining objective response or stable disease with PBCT, maintenance therapy with the anti-Programmed Death-Ligand1 (PD-L1) checkpoint inhibitor avelumab plus best supportive care (BSC) has shown a significant benefit in terms of OS compared to BSC alone.[10] ICIs have demonstrated efficacy also in second line after disease progression with PBCT and in first line for patients ineligible for cisplatin-based therapy which tumor has a CPS ≥10. Furthermore, enfortumab vedotin, an anti-nectin-

[1]Department of Oncology, University of Turin, AO Ordine Mauriziano Hospital, Turin, Italy
[2]Division of Medical Oncology, AO Ordine Mauriziano Hospital, Turin, Italy

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Address for correspondence: Massimo Di Maio, MD, Department of Oncology, University of Turin, AO Ordine Mauriziano Hospital, Via Magellano 1, Turin, 10128, Italy
E-mail contact: massimo.dimaio@unito.it

* T.G., J.P., and O.P. contributed equally to this work as first authors.

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4 antibody-drug conjugate[11] and erdafitinib[12] obtained accelerated approval from the U.S. Food and Drug Administration (FDA) in a third line setting and in the molecularly selected subgroup of patients with fibroblast growth factor receptor (FGFR2/3) alterations, respectively.

In this context, in the last few years, the activity of PARP inhibitors has been tested in several clinical trials.

DNA-Damage Repair, PARP Inhibitors and Synthetic Lethality

The poly (ADP-ribose) polymerase (PARP) enzymes PARP1 and PARP2 belong to a class of proteins involved in DNA damage response (DDR) that bind and repair single-strand DNA breaks.[13,14]

PARP-inhibitors (PARPis) are a class of drugs that represent a successful example of precision medicine. Indeed, in several tumors one of the main DDR pathways, the homologous recombination repair (HRR) pathway, is no longer functional, due to mutations in one of its main regulatory genes (eg, *BRCA1* or *BRCA2* genes). In these cases, the high DNA damage burden originating from the genetic instability of the tumor cannot be repaired neither by PARP enzyme, if inhibited by the drug, nor by the alternative pathway of HRR, whose functionality in these types of tumor is intrinsically compromised. This therapeutic strategy exploits the concept of synthetic lethality: the simultaneous mutation (or inhibition) of a pair of genes or biochemical pathways, unlike the mutation (or inhibition) of only one of the 2, causes cell death.[15-16]

PARP Inhibitors in Cancer Treatment

Firstly, several clinical trials demonstrated the efficacy of the PARPi olaparib in breast and ovarian cancer patients with germline *BRCA1/2* mutations. The phase III OlympiA study (NCT02000622)[17] and the phase III EMBRACA study (NCT01945775)[18] demonstrated that respectively olaparib and talazoparib significantly prolong progression-free survival (PFS) in patients with locally advanced or metastatic breast cancer and a *BRCA1/2* germline mutation, compared to standard therapy. According to these results, olaparib and talazoparib were approved in that setting. The phase III study SOLO1 (NCT01844986)[19] demonstrated a long-term advantage in PFS (70% reduction in the risk of disease progression) for olaparib vs. placebo in first line maintenance treatment in patients with advanced *BRCA*-mutated ovarian cancer who have responded to PBCT. Based on this result, olaparib is approved in this clinical context. In the same setting, phase III trials produced positive results with other PARPis, also in patients without HRR deficiency.[20,21]

Among the trials conducted in prostate cancer, the phase II TOPARP-B study (NCT01682772) enrolled patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with chemotherapy and new-generation hormone therapy (ARTAs).[22] Patients carrying one or more DNA repair-related gene mutations were treated with olaparib and a response was observed (defined as radiological response or ≥50% decrease in PSA or decrease in number of circulating tumor cells to <5 / 7.5 mL). The PROFOUND trial showed the superiority of olaparib vs. ARTAs in terms of PFS (median PFS 7.4 vs. 3.6 months, Hazard Ratio [HR] 0.34, $P < .001$) and objective response rate [ORR] (33% vs. 2%), with a prolongation in overall survival [OS] (median OS 18.5 vs. 15.1 months, HR 0.64; $P = .02$) in patients with metastatic CRPC with HRR genes aberrations who had experienced disease progression while receiving enzalutamide or abiraterone.[23] In patients eligible for first line treatment with abiraterone plus prednisone for metastatic CRPC, the addition of niraparib to hormonal treatment demonstrated a significant PFS prolongation in the HRR+ cohort of the MAGNITUDE trial,[24] while in the PROpel trial the addition of olaparib to hormonal treatment demonstrated a significant PFS benefit irrespective of HRR status.[25] According to these results, olaparib was approved as monotherapy in *BRCA 1-2* mutated mCRPC patients after ARTAs therapy or in association with abiraterone plus prednisone/prednisolone in newly detected mCRPC patients who had not received prior first line therapy, irrespective of HRR status.

In metastatic pancreatic cancer, the POLO phase III trial showed an improvement in PFS with olaparib compared to placebo in patients with a germline *BRCA1/2* mutation who had not progressed during first line PBCT.[26] Based on this trial, olaparib was approved in this clinical setting, although it is not reimbursed in some countries, including Italy.

HRR Deficiency in Urothelial Cancer

Platinum chemotherapy, used as the standard (neo)adjuvant and first line treatment for UC, has highly mutagenic properties that creates DNA strands alterations, determining cytotoxic effects that interfere with DNA replication. An intrastrand alteration is usually repaired by nucleotide excision repair pathway (NER). A somatic mutation on the NER gene (*ERCC2*) confers platinum sensitivity.[27] Complete response is frequently observed in patients with MIBC treated with neoadjuvant PBCT and an *ERCC2* mutation. Deficiencies in HRR pathways, that repairs double-strands mutations, increase the response to platinum treatments.[28] In addition, the onset of HRR deficiency (HRD), particularly *BRCA 1/2* alterations, could define other therapeutic strategies. Three scoring systems were used to quantify the degree of HRD: HRD-LOH, the large state transitions (LST) and the number of telomeric imbalances (TAI). They are now adapted to NGS and the sum of these scores is now known as HRD score.[29-31] HRDetect is a composite mutational signature that combines features of the HRD score with HRD-induced point mutation and short indel profiles. In breast cancer, the threshold used to detect HRD is >0,7.[32] The prevalence of HRD in UC and other cancer types is largely unknown. Multiple studies are trying to identify the incidence of mutations or mutational signatures that could lead to significant opportunities in terms of treatment targets.

In a clinical setting, Teo et al. studied the association between any DDR gene alterations and ORR, OS, and PFS in patients with diagnosis of locally advanced or metastatic UC.[33] In this study, 100 patients with unresectable or metastatic disease, candidates for a first line treatment with PBCT underwent pretreatment next-generation sequencing thanks to the Integrated Molecular Profiling of Actionable Cancer Target (MSK-IMPACT). All loss of function were considered deleterious. Forty-seven of these patients harbored DDR gene alterations and 120 alterations were identi-

Table 1 Completed Clinical Trials With PARP Inhibitors in Urothelial Cancer

Identifier	Year of Publication	Phase	Setting	Drug	DRD Status	Primary Endpoint
ATLAS (NCT03397394)[39]	2021	II	Previously treated (≥ 1 PBCT/ICI line) advanced/unresectable or metastatic UC	Rucaparib monotherapy	Unselected for DRD status	ORR in ITT and HRD+ subpopulation
Meet-URO12 (NCT03945084)[42]	Presented at ASCO 2022 Genitourinary cancers symposium, published in 2023	II	Maintenance treatment in locally advanced/ metastatic UC without progression after first-line PBCT	Niraparib monotherapy	Unselected for DRD status	PFS
ATLANTIS (ISRCTN25859465)[43]	Presented at ASCO 2022 Genitourinary cancers symposium	II	Maintenance treatment in locally advanced/ metastatic UC without progression after first-line PBCT	Rucaparib monotherapy	DRD +	PFS
BISCAY (NCT02546661)[44]	Presented at ESMO 2019, published in 2021	Ib	Chemo-refractory population with advanced/unresectable or metastatic UC	Olaparib + Durvalumab	HRD +	Safety, efficacy, pharmacokinetics, antitumor activity and relevant biomarkers
BAYOU (NCT03459846)[45]	Presented at ASCO 2022 Genitourinary cancers symposium, published in 2023	II	First-line therapy in platinum-ineligible patients with locally advanced/ metastatic UC	Olaparib + Durvalumab	Unselected for DRD status	PFS
JAVELIN PARP Medley (NCT03330405)[46]	Published in 2023	Ib-II	Platinum-naïve or platinum-pretreated (but not refractory) patients with locally advanced/metastatic UC	Talazoparib + Avelumab	Unselected for DRD status	ORR
NEODURVARIB (NCT03534492)[49,50]	Completed, presented at ASCO 2020 Genitourinary cancers symposium	II	Neoadjuvant therapy in resectable UC	Olaparib + Durvalumab	Unselected for DRD status	Impact of neoadjuvant treatment with durvalumab plus olaparib on the molecular profile of resectable UC (pathological complete response rate)

Abbreviations: DRD = DNA-damage response deficiency; HRD = homologous recombination repair deficiency; ICI = immune-checkpoint inhibitor; ITT = intention-to-treat; mUC = metastatic urothelial cancer; MIBC = muscle-invasive bladder cancer; ORR = objective response rate; PFS = progression-free survival; PBCT = platinum-based chemotherapy.

fied. Most of them were missense (83%). The DDR alterations found were nucleotide excision repair (NER, 15%), mismatch repair (9%), homologous recombination (11%), Fanconi anemia (16%), and DNA damage response checkpoint (23%). A higher number of mutations showed a trend toward better PFS and OS if compared with patients with wild type DDR genes. Increasing number of total alterations had a trend toward better response rate.

Börcsök et al. investigated the presence of HRD in bladder cancer cell-lines.[34] In this study, 533 whole-genome sequenced (WGS) and whole-exome sequenced (WES) pretreatment samples of urothelial carcinomas were analyzed from 3 cohorts: The Cancer Genome Atlas (TCGA), Dana-Farber Cancer Institute/Memorial Sloan Kettering Cancer Center (DFCI/MSKCC) and the Philadelphia cohorts. A *BRCA1/2* mutation was considered capable to confer HRD if it determined loss of heterozygosity (LOH) or if it had biallelic mutation. In all 3 cohorts, only a minority of cases harbored loss of function in *BRCA1/2* genes. Other mechanisms determined suppression of homologous recombination function, such as *RBBP8* promoter methylation, which is associated with higher HRD and HRDetect scores in the TCGA WES cohort. It was also associated with decreased *RBBP8* mRNA levels in wildtype *BRCA1/2* cases, and a significant negative correlation was observed between *RBBP8* methylation and *RBBP8* mRNA expression levels. This could represent an epigenetic mechanism for HRD in bladder cancer that could occur in the absence of observed mutations in HR genes.

Heeke et al. searched pathogenic mutations in homologous recombination DNA damage repair (HR-DDR) genes (*ARID1A, ATM, ATXR, BA1, BARD1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, WRN*) across multiple tumors.[35] Namely, 52,426 tumors underwent extended NGS sequencing. In the NGS600 cohort, bladder cancer (n = 283) had a 23.9% frequency of mutations in HR-DDR genes. The NGS600 cohort showed *BRCA1* and *BRCA2* mutations in bladder cancer in 2.99% and 4.48% respectively.

Targeting DDR gene alterations could be a promising therapeutic strategy for the treatment of advanced urothelial cancer.[36]

The aim of this review is to summarize the results of all the trials (both completed and ongoing) with PARPis in UC and to take stock of the future implication of these findings.

Methods

Search was first performed in December 2022 and updated in May 2023. We included all available trials analyzing the activity of PARP-is in UC in neoadjuvant, adjuvant, first or subsequent lines, and maintenance setting. We included PARP-is both in monotherapy and in association with other agents. We conducted our research on MEDLINE (PubMed) using as keywords "PARP inhibitor" or "rucaparib" or "niraparib" or "olaparib" or "talazoparib" or "veliparib" and "urothelial cancer". We also performed a research on the ClinicalTrials.Gov platform. We also included results presented during recent years at American Society of Clinical Oncology (ASCO) meeting, European Society for Medical Oncology (ESMO) congress and ASCO Genitourinary Cancers Symposium for studies still unpublished *in extenso*. An extra search was performed to check reviews indexed in the Cochrane Database of Systematic Reviews (CDSR); we found 2 previous reviews reporting results from PARP-is trials in both prostate and bladder cancer.[37,38] Publications were screened according to the PRISMA method.

All the studies are summarized in descriptive tables that report: trial name/NCT identifier, year of publication, type and phase of the study, type of therapy (type of PARPi, monotherapy vs. combination), primary endpoint, clinical setting, and molecular selection (if applicable).

Results

In recent years, the promising evidence of PARPis in ovarian, breast and prostate cancers showing DDR alterations and the findings about the role of HRD in bladder cancer prompted several trials conducted in patients with urothelial cancers (Table 1 and Table 2).

Monotherapy with a PARP-Inhibitor

Advanced Disease (Second or Further Line)

The phase II ATLAS study[39] showed very poor activity of rucaparib in 95 patients with unresectable locally advanced or metastatic UC previously treated with PBCT and/or ICI, without any confirmed objective response, neither in the intention-to-treat population nor in the subgroup of HRD patients. Although among the patients assessed for genomic LOH around 40% had HRD-positive tumors, this study presented a lack of *a priori* selection of specific genomic characteristics; additionally, it included a heavily pretreated population, since a large part of the patients (45.5%) had received 2 or more lines of chemotherapy before the enrollment.

As of May 2023, two ongoing studies are exploring the activity of olaparib in patients with advanced or metastatic UC progressed to at least 1 line of PBCT and/or ICI and confirmed DDR alterations. The phase II trial NCT03375307[40] is recruiting patients selected by DNA repair defects tested with FoundationOneCDx. Phase II trial NCT03448718[41] included patients harboring DNA HRR gene alterations; the accrual is now closed. Both trials have ORR as primary endpoint, and we are currently waiting for the results.

Advanced Disease (Maintenance After First Line)

All above-mentioned trials, however, enrolled patients in a very advanced setting, after the failure of multiple lines of therapy.

Table 2 Ongoing Clinical Trials With PARP Inhibitors in Urothelial Cancer

Identifier	Year of Publication	Phase	Setting	Drug	DRD Status	Primary Endpoint
MORPHEUS-UC (NCT03869190)[47]	Active, recruiting	II	Second line after PBCT in mUS	Niraparib + Atezolizumab	Unselected for DRD status	ORR (mUC cohort)
TALASUR (NCT04678362)[48]	Active, recruiting	II	Maintenance treatment in locally advanced / metastatic UC without progression after first line PBCT	Talazoparib + Avelumab	Unselected for DRD status	PFS
NCT03375307[40]	Active, not recruiting	II	Previously treated (≥ 1 PBCT/ICI line) advanced/unresectable or metastatic UC	Olaparib monotherapy	DRD +	ORR
NCT03448718[41]	Active, not recruiting	II	Previously treated (≥ 1 PBCT/ICI line) advanced/unresectable or metastatic UC	Olaparib monotherapy	DRD +	ORR

Abbreviations: DRD = DNA-damage response deficiency; HRD = homologous recombination repair deficiency; ICI = immune-checkpoint inhibitor; ITT = intention-to-treat; MIBC = muscle-invasive bladder cancer; mUC = metastatic urothelial cancer; ORR = objective response rate; PFS = progression-free survival; PBCT = platinum-based chemotherapy.

Conversely, during recent years, 2 trials have been conducted to evaluate PARPis activity as maintenance therapy in patients with advanced disease who had obtained complete response (CR), partial response (PR) or stable disease (SD) after first-line PBCT.[42,43] This setting allowed a clinical selection of platinum-sensitive and less pretreated patients, which means a potentially more responsive population.

In the phase II Meet-URO12 trial, 58 patients without progression after PBCT were randomized, in a 2:1 ratio, to receive maintenance niraparib plus best supportive care (BSC) vs. BSC alone.[42] No molecular selection was required for the enrolment; the analysis of molecular characteristics (including HRR alterations) by FoundationOneCDx was an exploratory endpoint. The accrual of the study was prematurely closed because of the availability of avelumab in Italian clinical practice as maintenance treatment after PBCT. In fact, avelumab had showed a significant benefit in OS vs. BSC, making further accrual in the Meet-URO12 trial unethical. The Meet-URO12 study did not meet its primary endpoint: PFS was not significantly different between the 2 arms (median PFS was 2.1 months in the experimental arm with niraparib vs. 2.4 months in the control arm, HR 0.92, $P = .81$).

Differently from the Meet-URO12 trial, the phase II umbrella trial ATLANTIS[43] performed previous molecular selection by FoundationOneCDx: 40 patients with advanced urothelial cancer without disease progression after PBCT, with DDR alterations (≥10% genomic LOH and/or somatic alteration in defined DNA repair deficiency-associated genes and/or germline *BRCA1/2* alteration), were randomized to receive rucaparib or placebo as maintenance treatment. Although not reaching a statistically significant difference, rucaparib was associated with a numerically better PFS (median PFS was 35.3 vs. 15.1 weeks; HR: 0.53, $P = .07$). The cohort of patients enrolled in this study was characterized by a more selected population compared to the Meet-URO12 trial in terms of CR and overall response rate, with a major proportion of patients who had received cisplatin, so the overall profile could be slightly more favorable for the experimental treatment (Table 3). However, besides the above reported clinical characteristics, the more meaningful difference of the ATLANTIS trial compared to the Meet-URO12 trial was the presence of a genomic screening to assess eligibility, suggesting the potential importance of molecular selection.

Combination of PARP-Inhibitor + Immune Checkpoint Inhibitor

The presence of DNA repair gene aberrations is associated with an increase in tumor mutation load and infiltration of lymphocytes in the tumor environment,[51,52] that could also lead to an activation of the stimulator of interferon genes (*STING*) pathway, which improves immune response and PDL1 expression on cancer cells.[53,54] So, in bladder cancer harboring known and unknown deleterious HRR gene mutations, monotherapy with PD1/PDL1 inhibitors showed higher response rates.[55] Consequently, it could be hypothesized that the combination of PARP inhibitors with PD1/PDL1 inhibitors in urothelial cancer can improve antitumor activity and clinical outcomes.[56] Based on these considerations, and encouraged by the promising results of PD-L1 inhibitors activity in UC, several combination strategies of PARPis with ICIs have been proposed.

Advanced Disease

The phase Ib, multidrug, biomarker-directed trial BISCAY[44] evaluated the safety profile and the antitumoral activity of several novel agents as monotherapy or as combination in a biomarker-selected chemotherapy-refractory advanced UC populations: overall, 54 patients presented HRR aberrations. Notably, the association of durvalumab and olaparib produced a 9.1% ORR in 22 unselected patients, whilst in 14 patients with *BRCA1/2*, *ATM* and HRR gene alterations (with around 50% patients showing TMB high >10 or positive PD-L1 expression) the ORR was 35.7%. This ORR was similar to the response rate observed in 29 patients treated with durvalumab monotherapy (27.6%), although the study was not designed to formally compare different treatments. Moreover, no dynamic changes in circulating tumor DNA levels during the combination therapy were observed. The investigators concluded that this combination strategy should be tested out in a platinum-naïve population.

In the phase II double-blind randomized BAYOU trial, 154 untreated and platinum ineligible metastatic UC patients received durvalumab + olaparib vs. durvalumab + placebo without molecular selection by HRR status.[45] No significant difference was observed between the arms in terms of PFS in ITT (primary endpoint) and OS. Nevertheless, a statistically significant improvement in PFS was observed for the combination therapy in the subset of patients with HRR mutations (5.6 vs. 1.8 months, HR 0.18, $P < .001$).

Within the phase Ib and II basket nonrandomized JAVELIN PARP Medley trial, including patients with advanced solid tumors, 40 UC patients not amenable to treatment with curative intent were treated with the combination of talazoparib and avelumab.[46] In that cohort, ORR was 15.0% (95% CI, 5.7%-29.8%) and response rate was similar in patients with vs. without prior platinum therapy (4 patients [14.3%] vs. 2 patients [16.7%]). One patient with a BRCA-altered, PD-L1–negative tumor obtained a complete response, still ongoing at the data cutoff.

As part of combination strategies with immunotherapy, a cohort of patients through the umbrella trial MORPHEUS—UC (NCT03869190) received the combination of atezolizumab + niraparib as second line treatment after progression to PBCT in mUC.[47] Primary endpoint for the mUC cohort was ORR with the combination, and we are currently waiting for the definitive results. Finally, we wait for the result of phase II TALASUR trial which is assessing the activity of the combination of avelumab with talazoparib among patients with advanced UC in maintenance therapy after PBCT.[48]

Early Disease

Olaparib in combination with durvalumab was tested in the neoadjuvant setting prior to cystectomy in patients with T2-T4a urothelial bladder cancer ineligible to PBCT through the phase II trial NEODURVARIB.[49] The primary endpoint was the impact of the combination on the molecular profile of MIBC; efficacy and safety were secondary endpoints. Noteworthy is the lack of prior

Table 3 Main Characteristics of the Meet-URO12 and ATLANTIS Randomized Phase II Trials With PARP Inhibitors as Maintenance Treatment After First-Line Platinum-Based Chemotherapy for Patients With Advanced/Metastatic Urothelial Cancer

	MEET-URO12[42]	ATLANTIS[43]
Phase	II	II
Setting	Maintenance treatment in patients without progression after I line PBCT for advanced/metastatic UC	Maintenance treatment in patients without progression after I line PBCT for advanced/metastatic UC
DRD Selection	*No prior selection was required* HRR alterations collected as an exploratory endpoint (somatic alteration in DRD-associated genes *BRCA1/2 ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, PPP2R2A*) but not required for inclusion.	*Selection of positive DRD biomarker patients*One or more of the following: • ≥10% genomic LOH • somatic alteration in defined DRD-associated genes (*BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*) • germline *BRCA1/2* alteration
Drug	Niraparib 300 mg per os once daily (or 200 mg in weight <77 kg or PLTs<150,000/μL)	Rucaparib 600 mg per os BID
Control arm	Best supportive care	Placebo
Previous PBCT (%)	Cisplatin (52%) Carboplatin (48%)	Cisplatin (62.5%) Carboplatin (37.5%)
Response to PBCT (%)	CR (5%) PR (50%) SD (45%)	CR (30%) PR (60%) SD (10%)
Primary endpoint	PFS	PFS
Results	Median PFS 2.1 vs. 2.4 mo, HR 0.92, 95% CI, 0.49-1.75, *P* = .81	Median PFS 35.3 vs. 15.1 wk, HR 0.53, 80% CI, 0.30-0.92, *P* = .07

Abbreviations: BID = *bis in die;* CR = complete response; DRD = DNA-damage response deficiency; HR = hazard ratio; HRR = homologous recombination repair; LOH = loss of heterozygosity; PBCT = platinum-based chemotherapy; PR = partial response; PFS = progression-free survival; SD = stable disease; UC = urothelial cancer.

molecular selection of patients based on HRR aberrations. Preliminary data published in abstract form at ASCO 2020 Genitourinary Cancers Symposium point out the potential efficacy of the strategy, showing a very high rate of pathological CR after the NAT (pCR rate 50%) along with an adequate safety profile.[49] These impressive results suggest the opportunity of further trials. Furthermore, at 2022 ASCO Genitourinary Cancers Symposium were presented the results of molecular characterization of MIBC treated with durvalumab plus olaparib: although genetic alterations remained overall unchanged, in resistant tumors an enrichment of EMT signatures and a switch towards basal/squamous phenotypes were observed, suggesting that modifications in gene expression are a potential mechanism of resistance to the combination.[50]

Discussion

The use of PARPis is not part of current clinical practice for patients with UC; all the drugs of this class are not yet approved by regulatory agencies for any of the indications explored in this review. However, some preliminary evidence of activity has been reported in recent years: the most important questions are which patients might benefit from PARPis, which is the most proper clinical setting for the treatment and if the association with other drugs (including ICIs) can achieve a more concrete benefit.

PARPis have been explored in UC as a maintenance therapy after a PBCT following the unprecedented and practice-changing results obtained in patients with ovarian cancer with olaparib as a maintenance treatment in BRCA-mutated patients and with niraparib even in an unselected platinum-sensitive population. Meet-URO12 trial aimed to explore the role of niraparib in this setting, resulting however in negative findings.[42] The small sample size due to the exploratory design of the trial, further limited by the early closure of the accrual due to the approval of avelumab in the same setting, may have partially impacted the results. However, even acknowledging these limitations, the planning of further phase III trial with single-agent treatment does not appear to be justified, at least in the same molecularly unselected population. As a matter of fact, the biology and the platinum sensitivity of UC, as well as the prognosis of the disease, are different from those of ovarian cancer: a clinical selection in UC is not enough to identify the responders to PARPis. Meet-URO12 trial did not select according to HRD status, and out of the 58 randomized patients, only 6 patients reported DDR mutations of known pathogenic significance, definitely too few to draw meaningful conclusions in this molecularly selected subgroup.

Preliminary results of the ATLANTIS trial showed that an adequate molecular selection could be a promising strategy in the maintenance setting.[43] An improvement in PFS, although not statistically significant, was observed with rucaparib in patients with known DDR aberrations. These findings suggest that the benefit of PARPis in selected HRD+ patients could be further explored in further phase III trials.

The role of PARP-is monotherapy for the advanced pretreated UC seems to be unsupported. The results of a large cohort of unselected patients in the ATLAS trial are discouraging and do not lead to further studies on an indiscriminate population of chemorefractory patients.[39] However, similarly to other clinical backgrounds, a proper molecular selection will be probably relevant to find out a subpopulation who would benefit from PARPis. In this regard, the final results of NCT03375307[40] and NCT03448718[41] trials of olaparib will be meaningful.

The future role of PARPi and ICIs combination is currently uncertain. The phase Ib BISCAY trial showed modest improvement of clinical activity compared to immunotherapy alone, and HRR biomarker appeared unsupportive in selecting patients previously treated with at least 1 line of PBC, probably also due to the high tumor mutational burden of this type of population.[44] Platinum-naïve patients are likely the ideal population for the combination strategy, and the 2 phase II trials investigating the potential benefit in this setting have shown interesting results. Once again, the findings of these studies suggest that a molecular selection is required. In the BAYOU trial, no significant PFS and OS benefit was observed in ITT unselected population, but a benefit could be observed in HRR mutated subpopulation, so further trials in platinum-ineligible patients with proper molecular selection are needed.[45] NEODURVARIB trial showed excellent results in terms of pathological response in a neoadjuvant setting.[49] An overall pCR rate of 50% was detected, which is even more impressive if compared to overall rate reported in literature, with around 25% of pCR with MVAC or cisplatin-gemcitabine chemotherapy: these data encourage the design of new studies assessing the superiority of the strategy in terms of activity and safety.

The safety profile of PARPis in UC trials was consistent with the toxicities reported in other cancer types, both as monotherapy and as combination therapy. Asthenia/fatigue, nausea and hyporexia of any grade were the most common AEs with consistently high prevalence. Anemia (45%-50%), thrombocytopenia (25%), neutropenia (20%), AST/ALT increased, diarrhea of any grade were also common with a variable degree of toxicity according to the molecule. Severe AES were quite uncommon.[39,42,43,49]

The emerging importance of a proper molecular selection by DRD status leads to the need of novel and reliable biomarkers; a future challenge will be to identify a standardized test to detect tumors with HRD, regardless of the mechanisms involved. Mutational analysis of known HRR genes could be combined with mutational signature approaches to identify candidates for PARPi in UC.[34,57]

Conclusion

Despite the lack of solid evidence and the need for further randomized trials, the studies so far conducted allowed the comprehension of some key issues. It is increasingly evident that a prior selection by DRD status is essential to identify patients who are most likely to benefit from PARP-is therapy. Moreover, the ideal clinical setting seems to be the maintenance treatment after PBCT rather than a second or third line for highly pretreated patients, but we should wait for the results of ongoing trials. There seems to be a potential benefit in platinum-naïve patients, especially as part of the neoadjuvant treatment before cystectomy for bladder cancer, for the combination of PARPis with ICIs. Based on these considerations, we believe that there is still room for conducting clinical trials for PARP-I in UC in the above described settings.

In the next future, the definitive results of ongoing trials, as well as the potential conduction of randomized phase III studies, will be helpful to delineate the best indications for PARPis in the treatment algorithm of patients with urothelial cancer.

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