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Case Report

Personalized treatment with PARP inhibitors in advanced urothelial carcinoma: a case report and literature review

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***Abstract*:** Bladder cancer (BC) poses a significant health challenge, particularly in metastatic cases, where the prognosis is unfavorable and therapeutic options are limited. Poly ADP-ribose polymerase (PARP) inhibitors have gained approval for use in various cancer types, but their application in BC remains controversial, despite the notable prevalence of DNA damage response alterations in advanced or metastatic urothelial carcinomas. In this report, we describe a 66-year-old heavy-smoking female diagnosed with muscle-invasive BC. She underwent multiple rounds of chemotherapy and radiation, yet her disease remained poorly controlled, leading to metastasis in the left obturator internus muscle. Comprehensive genomic profiling through FoundationOne® Liquid CDx, examining a 324-gene panel using circulating tumor DNA from blood samples, revealed a pathogenic *ATM* gene alteration (p.Q654fs*10, c.1960delC), suggesting potential eligibility for PARP inhibitor therapy. Remarkably, the patient achieved a complete response to talazoparib, prompting an optimal investigation into BC candidates for this promising therapy.

Plain language summary

A new hope for advanced bladder cancer treatment: a case study on the success of PARP inhibitors

Bladder cancer is a significant health problem, particularly when it spreads to other parts of the body. The outcome for these advanced cases is often poor and treatment options are limited. One type of treatment, called PARP inhibitors, has shown success in treating other types of cancer, but its use in bladder cancer is still under investigation. This article presents the case of a 66-year-old heavy-smoker woman who was diagnosed with an aggressive form of bladder cancer. Despite several rounds of chemotherapy and radiation, her cancer was not well-controlled and spread to a hip muscle. A detailed genetic analysis revealed specific alterations that suggested she might benefit from treatment with a PARP inhibitor. This type of treatment works by blocking a protein that cancer cells need to repair their DNA, causing the cancer cells to die. The patient was treated with a PARP inhibitor called talazoparib and her cancer completely disappeared with this treatment. This positive response highlights the potential of PARP inhibitors as a promising treatment for bladder cancer, especially in patients who don't respond to conventional treatments and whose cancer has specific genetic changes. Our study also provides an overview of clinical trials evaluating PARP inhibitors in bladder cancer and summaries reported bladder cancer cases in the literature showing a good response to PARP inhibitors, along with their respective genetic alterations. In conclusion, this case study contributes to the growing understanding of personalized medicine, where treatment is tailored to

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the specific genetic mutations of each patient's cancer. It emphasizes the importance of identifying bladder cancer patients who could benefit most from PARP inhibitor therapy, offering a potential lifeline for those who haven't responded to initial treatment.

Keywords: bladder cancer, case report, genetic testing, homologous recombination deficiency, PARP inhibitor, talazoparib

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Introduction

Bladder cancer (BC) is a significant global health concern, ranking among the top 10 most prevalent cancers worldwide.[1] Most BC cases are classified as urothelial carcinomas (UC), with the primary risk factor being tobacco smoking.

The management of BC depends on the extent and aggressiveness of the disease. Metastatic BC carries a dismal prognosis, with a 5-year relative survival rate of less than 10%.[2] Despite ongoing research efforts, treatment options remain limited. The standard treatment for locally advanced or metastatic UC is platinum-based chemotherapy.[3] However, about one-third of patients are ineligible for this treatment due to comorbidities, and only half respond to treatment.[4] In 2016–2017, immune checkpoint inhibitors were approved as second-line treatments for patients refractory to or ineligible for platinum-based therapy,[5] and in 2021, the antibody–drug conjugate enfortumab vedotin was introduced.[6] Yet, response rates vary widely due to patient characteristics and the presence of different genomic subtypes with distinct oncogenic mechanisms.[7] These challenges emphasize the need for further investigation into more personalized treatment strategies for metastatic BC. Recent advancements in BC treatment have underscored the importance of targeted therapies directed against specific biomarkers like fibroblast growth factor receptor 3 (FGFR3)[8] or human epidermal growth factor receptor 2 (HER2).[9]

The role of DNA damage response (DDR) genes in BC is increasingly recognized, with about 34% of BC cases harboring DDR mutations.[4] This includes notable genes such as *BRCA1* and *BRCA2*, which are found in approximately 6% and 12% of BC cases, respectively, according to the *MSK/TCGA 2020* cohort (Supplemental Figure S1),[10] and play a crucial role in the homologous recombination repair (HRR) mechanisms. Among other significant DDR genes is *ATM*, found in 12% of BC cases. These mutations can lead to the accumulation of double-strand breaks (DSB) and heighten the susceptibility of tumors to poly ADP-ribose polymerase (PARP) inhibitors through a phenomenon known as synthetic lethality.[11]

While the use of PARP inhibitors has been validated for ovarian, breast, pancreatic, and recently prostate cancers,[12] their application in BC is not yet approved. This highlights a potential avenue for therapeutic intervention given the significant role of DDR in BC.

Case presentation

In this context, we present a case of a 66-year-old woman with a history of heavy smoking who presented with dysuria, hematuria, and lower abdominal pain in February 2019. She was diagnosed with high-grade UC manifesting as muscle-invasive bladder cancer following transurethral resection of the bladder tumor (TURBT). A whole-body positron emission tomography and computed tomography (PET–CT) scan confirmed the primary malignancy, with a maximum bladder wall thickening of 1.6 cm ($SUV_{max} = 8.5$) and no evidence of regional adenopathy or distant metastases.

The patient received four cycles of neoadjuvant chemotherapy with cisplatin and gemcitabine, from March to May 2019, with stable disease. In July 2019, a second TURBT revealed a high-grade T1 tumor, leading to a complete cystectomy, continent diversion, neobladder construction, and radical pelvic lymphadenectomy in August 2019. The cystectomy specimen was negative for residual invasive carcinoma, but a microscopic focus of carcinoma *in situ* was noted near the urethral margin of resection. Overall, the patient's postoperative course was

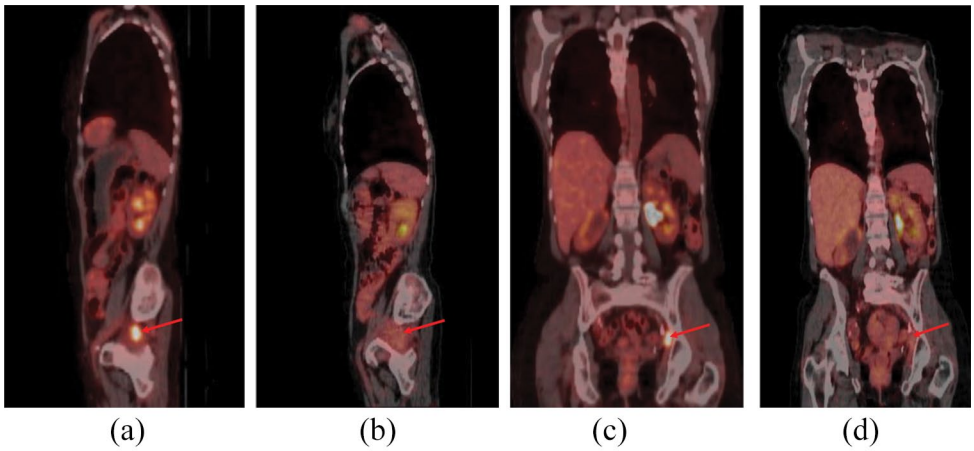

Figure 1. Comparative PET-CT scans before (20 May 2021) and after (9 March 2022) PARP inhibitor therapy initiation, demonstrating complete response to treatment. (a) Before treatment sagittal section (SUV_{max} = 6.3); (b) during treatment sagittal section (no suspicious uptake); (c) before treatment coronal section (SUV_{max} = 6.3); (d) and during treatment coronal section (no suspicious uptake).

favorable, except for left-sided perineal pain, managed with nerve and plexus blocks.

In November 2019, a CT scan of the abdomen and pelvis showed no recurrence. However, a PET-CT scan in September 2020 revealed a mass in the left posterior pelvis, measuring 6.5 × 4.7 cm with an SUV_{max} of 15.3, invading pelvic wall muscles, and suggestive of regional tumor recurrence. In response to the recurrence, the patient underwent five sessions of cisplatin chemotherapy with concurrent radiotherapy (22 fractions of 2 Grays each), for symptomatic relief and local disease control. Subsequent CT imaging in November 2020 demonstrated a partial response with a substantial decrease in the size of the pelvic mass to 2.4 × 1.7 cm.

Biomarker testing was performed on the second TURBT in November 2020. Programmed cell death ligand 1 (*PD-L1*) expression was negative, with a combined positive score of 5. The HER2/neu protein analysis, using the Ventana 4B5 assay with a multimer detection system, indicated a non-overexpression status, with a score of +0/3. Furthermore, the DNA mismatch repair proteins, including MLH1, MSH2, MSH6, and PMS2, were retained in the cells with normal DNA repair functioning. Due to elevated creatinine levels, the patient was not eligible for cisplatin-based therapy and, therefore, received six cycles of gemcitabine as adjuvant chemotherapy monotherapy from December 2020 to April 2021. The PET-CT scan of February 2021 showed interval resolution of the previously described mass.

However, in May 2021, 1 month after completing chemotherapy, the patient presented a new lesion in the left obturator internus muscle of 2.5 × 1.5 cm with an SUV_{max} of 6.3, consistent with disease relapse [Figure 1(a) and (c)]. This finding was further confirmed by magnetic resonance imaging of the pelvis, leading to the administration of five sessions of stereotactic body radiotherapy.

In June 2021, FoundationOne® Liquid CDx testing of a 324-gene panel through blood-based comprehensive genome sequencing, analyzing circulating tumor DNA, identified a pathogenic biallelic mutation in the *ATM* gene (p.Q654fs*10, c.1960delC, with a variant allele frequency of 0.28%, likely somatic) suggesting potential eligibility for targeted therapy, and mutations in the *BRCA2* (p.K3326*, c.9976A>T, rs11571833), and *CHEK2* (p.R145Q, c.434G>A) genes, classified as variants of unknown significance (VUS) (Supplemental Table S1). The tumor was microsatellite stable, with a low blood tumor mutational burden of 1 mutation per megabase. Following the genetic analysis results, the patient started on talazoparib, a PARP inhibitor, initially at a daily dose of 1 mg, beginning in August 2021, followed by a reduced daily dose of 0.5 mg from September 2021 to April 2022 due to fatigue and dizziness. Subsequent PET-CT scans conducted

in November 2021 and March 2022 revealed a complete response to treatment with no suspicious uptake [Figure 1(b) and (d)].

Unfortunately, the PARP inhibitor therapy was discontinued in April 2022 due to medication unavailability. Eight months later, in December 2022, a PET-CT scan revealed a recurrent lesion in the left posterolateral pelvic wall measuring 4.3×3.6 cm, with an SUV_{max} of 8.5, prompting the patient to resume PARP inhibitor treatment, receiving either talazoparib 1 mg every other day or olaparib 150 mg twice a day, based on drug availability.

In an attempt to investigate the cause of an enlarging pelvic mass, a trial of dexamethasone 8 mg three times daily for 4 days was initiated to assess for potential radiation myositis. However, minimal improvement in symptoms suggested an alternative etiology.

A follow-up PET-CT scan performed in February 2023 demonstrated a further increase in tumor size to 5×4.6 cm. Given the disease progression, a CT needle biopsy was recommended for additional evaluation, but could not be performed due to the patient's lethargy and syncope.

Regrettably, despite supportive care, the patient's condition continued to deteriorate, and she succumbed to the disease in March 2023.

Discussion

This case report complies with the CARE guidelines[13] (Supplemental Material 1). A comprehensive, but not systematic, literature search was performed through PubMed/PMC and Medline, with some additional articles selected based on their clinical relevance, to capture the reported cases, ongoing clinical trials, and most important aspects of the topic.

The current case provides valuable insights into the potential of PARP inhibitors for BC patients who progress on prior treatments. The patient achieved a disease-free survival period of 1 year and 4 months, with disease recurrence coinciding with medication cessation due to drug unavailability.

Several clinical trials have explored PARP inhibitors in advanced or metastatic UC, as part of combination therapies with standard treatments like cisplatin[14] or anti-PD-L1 immunotherapy,[4] a standalone treatment for patients who experienced progression on prior treatments, or maintenance therapy for patients without progression. A summary of published and ongoing phase I or II trials is provided in Supplemental Table S2. These trials are categorized based on the different FDA-approved PARP inhibitors, encompassing olaparib, rucaparib, niraparib, and talazoparib.[12] Some studies suggest talazoparib may exhibit superiority over olaparib against BC cells.[14]

The majority of these studies reported either stable disease or a partial response to treatment. For instance, the BISCAY trial combined durvalumab with either FGFR inhibitor (AZD4547), olaparib, or vistusertib (TORC1/2 inhibitor), and none of the combination arms achieved a meaningful complete response.[15] The NICARAGUA trial, involving 19 patients with UC and kidney cancer, showed that niraparib plus cabozantinib resulted in a partial response in only three patients and the rest had stable disease.[16] Similar results were observed in the SEASTAR study.[17] Our study stands out by reporting a complete response to talazoparib, sustained throughout the treatment course and for 8 months after treatment suspension in a patient with an *ATM* alteration.

PARP inhibitors exhibit enhanced effectiveness when specific DDR genes are concomitantly mutated. These genes include *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, and *RAD1*, among others.[18] Some studies have highlighted favorable responses to PARP inhibitors in BC patients harboring these specific mutations, with a particular focus on *BRCA1* and *BRCA2* mutations (Table 1). In a phase I study, a patient with BC, who had a *BRCA2* germline mutation and a VUS of *ATM* gene, achieved a partial response to talazoparib and carboplatin after undergoing three prior lines of platinum therapy.[19] Also, a phase II trial included a BC patient with *PALB2* mutation who exhibited a positive response to talazoparib.[20] However, none of these studies reported a complete response of BC to PARP inhibitors. Our study is the first to report a BC case with a pathogenic *ATM* mutation (p.Q654fs*10, c.1960delC) who achieved a complete response to talazoparib after chemotherapy failure, sustained longer than other studies.

To avoid apoptosis, cells respond to threats to their genetic material by activating the DDR system to repair DNA DSBs. The two major DSB

Table 1. Summary of studies documenting good response to PARP inhibitor monotherapies in patients with recurrent advanced or metastatic bladder cancer.

Study	Previous treatment(s)	DDR gene mutation	Other genetic findings	PARP inhibitor received	Response to treatment
Necchi *et al.*, 2018[21]	Anti-PD-L1, MVAC (6 cycles), vinflunine (4 cycles) with palliative RT	*BRCA2* loss (homozygous); *BRCA2* germline mutation (p.I267V)	MSS; TMB 7 mutations per megabase	Olaparib 400 mg PO b.i.d.	Partial response for more than[a] 5 months
Sweis *et al.*, 2018[22]	Gemcitabine-cisplatin (4 cycles)	*BRCA1* (p.N1018fs*8) with VAF 62%; *CHEK2* (p.T367fs*15)	MSS; TMB 4 mutations per megabase	Olaparib	Partial response for 1 year, then progressed
Sweis *et al.*, 2018[22]	Gemcitabine–cisplatin (6 cycles), alternating ifosfamide/doxorubicin and etoposide/cisplatin, RT (55 Gy) with capecitabine, pembrolizumab	*BRCA2* (c.7436-294_7567del)	MSS; TMB 4 mutations per megabase	Olaparib 400 mg PO b.i.d., then reduced to 300 mg (due to thrombocytopenia)	Partial response for more than[a] 6 months
Piha-Paul *et al.*, 2018[20]	Taken but not reported	*PALB2* (mutation not specified)	No additional genetic finding	Talazoparib 1 mg PO q.d.	Partial response
Yang *et al.*, 2020[23]	Gemcitabine–cisplatin (4 cycles)	*BRCA2* germline mutation (p.L557*, c.1670T > A); BRCA1 somatic mutation	TMB decreased from 6.11 to 0.76 mutations per megabase after PARP inhibitor	Olaparib 300 mg PO b.i.d.	Partial response for more than[a] 4 months
Current study	Gemcitabine–cisplatin (4 cycles), cisplatin with RT (44 Gy), gemcitabine (6 cycles)	*ATM* deletion (p.Q654fs*10, c.1960delC) with VAF 0.28%; *BRCA2* (p.K3326*, c.9976A>T)	MSS; TMB 1 mutation per megabase	Talazoparib 1 mg PO q.d., then reduced to 0.5 mg (due to fatigue and dizziness)	Complete response for 1 year and 4 months (8 months after treatment interruption)

[a]The term 'more than' indicates that the patient was still showing a positive response to the treatment at the time of reporting the case.
ATM, ataxia-telangiectasia mutated; b.i.d. (bis in die), twice a day; *BRCA1*, breast cancer gene 1; *BRCA2*, breast cancer gene 2; *CHEK2*, checkpoint kinase 2; DDR, DNA damage response; MSS, microsatellite stable; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; *PALB2*, partner and localizer of *BRCA2*; PARP, poly ADP-ribose polymerase; PD-L1, programmed cell death ligand 1; PO (per os), orally; q.d. (quaque die), once a day; RT, radiotherapy; TMB, tumor mutational burden; VAF, variant allele frequency.

repair pathways are HRR and nonhomologous end joining (NHEJ).[24,25] The ATM protein is at the core of this signaling network and participates in many HRR-mediated cellular processes.[24] *ATM* mutations are observed in about 12% of BC cases (Supplemental Figure S1) and have been described as an independent prognostic factor associated with chemotherapy resistance and poor overall survival (hazard ratio: 2.25–2.82) in advanced UC.[24,26] This could be due to backup mechanisms like the upregulation of ATR signaling, which prevents the replication of damaged DNA, or the activation of alternative pathways like NHEJ *via* DNA-dependent protein kinases catalytic subunit (DNA-PKcs).[24,25] Therefore, *ATM*-deficient cancer cells seem to be particularly susceptible to ATR inhibitors and DNA-PKcs inhibitors.

Despite promising results with PARP inhibitors, many patients fail to maintain a good response. A phase II trial investigating olaparib monotherapy in metastatic UC patients with DDR gene alterations was discontinued as none of the 19 participants achieved a partial response.[27] Two other ongoing studies (NCT03448718 and NCT03375307) are evaluating olaparib monotherapy, but the results are yet to be determined. Some patients initially respond to PARP inhibitors but later become resistant, by increasing drug efflux or restoring functional HRR.[25] The combination of PARP inhibitors and ATR inhibitors has demonstrated synergistic effects against ATM-deficient prostate cancer cells *in vitro*[28] and promising outcomes in ovarian cancer patients.[25] DNA-PKcs inhibitors could offer another therapeutic option in tumors with *ATM* loss, as *ATM*-defective cells strongly depend on

DNA-PKcs for DNA repair.[24] However, the efficacy of these treatments in BC needs to be further validated in clinical trials.

In addition to the *ATM* alteration, the patient in our case had other mutations in DDR genes, such as *BRCA2* (p.K3326*, c.9976A>T, rs11571833) and *CHEK2* (p.R145Q, c.434G>A), which may enhance the tumor's susceptibility to PARP inhibition. Although these mutations were initially described as VUS, the *BRCA2* (p.K3326*) mutation holds particular relevance, as it has been associated with various cancer types, including breast cancer,[29] small-cell lung cancer, and squamous cell carcinoma of the skin.[30] Another study revealed an increased predisposition to urinary tract cancers among patients with the *BRCA2* (p.K3326*) mutation.[31]

The patient did not receive immunotherapy given its reduced efficacy in microsatellite-stable tumors with low tumor mutational burden and negative *PD-L1* expression, although the dynamism of *PD-L1* expression hampers its use as a reliable biomarker.[7,22]

Conclusion

In conclusion, this study reports a compelling case of advanced BC harboring DDR mutations conferring an excellent response to talazoparib after cisplatin-based chemotherapy failure. In addition, it offers a comprehensive overview of trials investigating PARP inhibitors in BC. The variation in molecular profiles and treatment responses underscores the need for a patient-tailored approach and emphasizes the importance of understanding the specific profiles of BC patients who could benefit most from PARP inhibitor therapy after progression on initial treatments.

Declarations

Ethics approval and consent to participate

The present study complies with the internationally accepted ethical standards. According to local regulations, this study did not require Institutional Review Board approval or consent to participate.

Consent for publication

Written informed consent for publication was obtained by the authors from the patient's next of kin (son).

Author contributions

Noura Abbas: Conceptualization; Data curation; Visualization; Writing – original draft; Writing – review & editing.

Laudy Chehade: Conceptualization; Data curation; Visualization; Writing – review & editing.

Ali Shamseddine: Conceptualization; Data curation; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data supporting the findings of this study are available upon request from the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

References

1. Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209–249.
2. SEER*Explorer. An interactive website for SEER cancer statistics [Internet], Surveillance Research Program, National Cancer Institute, 2023. https://seer.cancer.gov/statistics-network/explorer/ (accessed 8 October 2023).

3. Witjes JA, Bruins HM, Cathomas R, *et al*. European association of urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. *Eur Urol* 2021; 79: 82–104.
4. Criscuolo D, Morra F, Giannella R, *et al*. New combinatorial strategies to improve the PARP inhibitors efficacy in the urothelial bladder cancer treatment. *J Exp Clin Cancer Res* 2019; 38: 91.
5. Lopez-Beltran A, Cimadamore A, Blanca A, *et al*. Immune checkpoint inhibitors for the treatment of bladder cancer. *Cancers* (*Basel*) 2021; 13: 131.
6. Powles T, Rosenberg JE, Sonpavde GP, *et al*. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med* 2021; 384: 1125–1135.
7. Parent P, Marcq G, Adeleke S, *et al*. Predictive biomarkers for immune checkpoint inhibitor response in urothelial cancer. *Ther Adv Med Oncol* 2023; 15: 17588359231192402.
8. Siefker-Radtke AO, Necchi A, Park SH, *et al*. Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study. *Lancet Oncol* 2022; 23: 248–258.
9. Patelli G, Zeppellini A, Spina F, *et al*. The evolving panorama of HER2-targeted treatments in metastatic urothelial cancer: a systematic review and future perspectives. *Cancer Treat Rev* 2022; 104: 102351.
10. Robertson AG, Kim J, Al-Ahmadie H, *et al*. Comprehensive molecular characterization of muscle-invasive bladder cancer. *Cell* 2017; 171: 540–556.e25.
11. Lord CJ and Ashworth A. PARP inhibitors: synthetic lethality in the clinic. *Science* 2017; 355: 1152–1158.
12. Hunia J, Gawalski K, Szredzka A, *et al*. The potential of PARP inhibitors in targeted cancer therapy and immunotherapy. *Front Mol Biosci* 2022; 9: 1073797.
13. Gagnier JJ, Kienle G, Altman DG, *et al*.; CARE Group*. The CARE guidelines: consensus-based clinical case reporting guideline development. *Glob Adv Health Med* 2013; 2: 38–43.
14. Bhattacharjee S, Sullivan MJ, Wynn RR, *et al*. PARP inhibitors chemopotentiate and synergize with cisplatin to inhibit bladder cancer cell survival and tumor growth. *BMC Cancer* 2022; 22: 312.
15. Powles T, Carroll D, Chowdhury S, *et al*. An adaptive, biomarker-directed platform study of durvalumab in combination with targeted therapies in advanced urothelial cancer. *Nat Med* 2021; 27: 793–801.
16. Castellano DE, Duran I, Mellado B, *et al*. Phase I–II study to evaluate safety and efficacy of niraparib plus cabozantinib in patients with advanced urothelial/kidney cancer (NICARAGUA trial): preliminary data of phase I study. *J Clin Oncol* 2022; 40(6_Suppl): 490–490.
17. Yap TA, Hamilton E, Bauer T, *et al*. Phase Ib SEASTAR study: combining rucaparib and sacituzumab govitecan in patients with cancer with or without mutations in homologous recombination repair genes. *JCO Precis Oncol* 2022; 6: e2100456.
18. Crabb SJ, Hussain S, Soulis E, *et al*. A randomized, double-blind, biomarker-selected, phase II clinical trial of maintenance poly ADP-ribose polymerase inhibition with rucaparib following chemotherapy for metastatic urothelial carcinoma. *J Clin Oncol* 2023; 41: 54–64.
19. 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: 6400–6410.
20. Piha-Paul SA, Xiong WW, Moss T, *et al*. Abstract A096: phase II study of the PARP inhibitor talazoparib in advanced cancer patients with somatic alterations in BRCA1/2, mutations/deletions in PTEN or PTEN loss, aberrations in other BRCA pathway genes, and germline mutations in BRCA1/2 (not breast or ovarian cancer). *Mol Cancer Ther* 2018; 17(1_Suppl): A096.
21. Necchi A, Raggi D, Giannatempo P, *et al*. Exceptional response to olaparib in BRCA2-altered urothelial carcinoma after PD-L1 inhibitor and chemotherapy failure. *Eur J Cancer* 2018; 96: 128–130.
22. Sweis RF, Heiss B, Segal J, *et al*. Clinical activity of olaparib in urothelial bladder cancer with DNA damage response gene mutations. *JCO Precis Oncol* 2018; 2: 1–7.
23. Yang H, Liu Z, Wang Y, *et al*. Olaparib is effective for recurrent urothelial carcinoma with BRCA2 pathogenic germline mutation: first report on olaparib response in recurrent UC. *Ther Adv Med Oncol* 2020; 12: 1758835920970845.
24. Riabinska A, Daheim M, Herter-Sprie GS, *et al*. Therapeutic targeting of a robust non-oncogene addiction to PRKDC in ATM-defective tumors. *Sci Transl Med* 2013; 5: 189ra78.
25. Bhamidipati D, Haro-Silerio JI, Yap TA, *et al*. PARP inhibitors: enhancing efficacy through

rational combinations. *Br J Cancer* 2023; 129: 904–916.

26. Yin M, Grivas P, Wang QE, *et al.* Prognostic value of DNA damage response genomic alterations in relapsed/advanced urothelial cancer. *Oncologist* 2020; 25: 680–688.
27. Doroshow DB, O'Donnell PH, Hoffman-Censits JH, *et al.* Phase II trial of olaparib in patients with metastatic urothelial cancer harboring DNA damage response gene alterations. *JCO Precis Oncol* 2023; 7: e2300095.
28. Neeb A, Herranz N, Arce-Gallego S, *et al.* Advanced prostate cancer with ATM loss: PARP and ATR inhibitors. *Eur Urol* 2021; 79: 200–211.
29. Thompson ER, Gorringe KL, Rowley SM, *et al.* Reevaluation of the BRCA2 truncating allele c.9976A > T (p.Lys3326Ter) in a familial breast cancer context. *Sci Rep* 2015; 5: 14800.
30. Rafnar T, Sigurjonsdottir GR, Stacey SN, *et al.* Association of BRCA2 K3326* with small cell lung cancer and squamous cell cancer of the skin. *J Natl Cancer Inst* 2018; 110: 967–974.
31. Ge Y, Wang Y, Shao W, *et al.* Rare variants in BRCA2 and CHEK2 are associated with the risk of urinary tract cancers. *Sci Rep* 2016; 6: 33542.