Study title	**A Phase II, Randomized, Trial of Niraparib Versus Best Supportive Care as Maintenance Treatment In Patients With Locally Advanced Or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion Of First-line Platinum-containing Chemotherapy**
Sponsor (non-profit):	Dipartimento di Oncologia, Università degli Studi di Torino
Supported by:	TESARO, Inc.
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Coordinating Center	A.O. Ordine Mauriziano, S.C.D.U. Oncologia Medica, Torino
Study design	Two-arm, prospective, randomized (2:1 ratio), multi-centre, phase II study.
Population	Patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy
Study drug	Niraparib (provided by TESARO)
Background and Rationale	Niraparib is an oral, small molecule inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1 and PARP-2 (1). PARP-1/2 are nuclear proteins that detect DNA damage and promote the base excision repair. Inhibition of PARPs is an effective strategy for treating cancers, in particular PARPs inhibitors induce syntetic lethality in presence of specific aberrations in BRCA1 and BRCA2 genes which impair the homologous recombination (HR). (2) Niraparib is now approved for maintenance therapy post response to platinum-based chemotherapy in recurrent ovarian cancer on the basis of NOVA trial results. (3) With this trial, our aim is to test the efficacy of Niraparib in patients with advanced urothelial cancer, on the basis of a strong biological rationale. The presence of HR defects is a potential mechanism also implicated in the sensitivity to platinum chemotherapy (4), for this reason the potential cross-sensitivity and cross-resistance between platinum drugs and PARP inhibitors are also areas of interest and clinical relevance. (5) Platinum analogues, in particular cisplatin, are active

	agents against urothelial cancer (UC) and constitute the backbone of perioperative and first-line chemotherapy used in this disease. The enhanced platinum sensitivity of UC tumors is thought to be related to an underlying defect in HR–mediated DNA repair (6). Plimack et al. demonstrated that sensitivity to neoadjuvant platinum-based chemotherapy in UC is significantly associated with mutations in genes involved in HR repair.(7) The only published data regarding PARP inhibitors in UC have been obtained in preclinical cell culture and xenograft models: Jian et al demonstrated in this setting that a reduced capacity for HR repair is associated with increased sensitivity to PARP inhibitor and that the combination of PARP inhibitor and cisplatin causes a significant increase in DNA damage versus the use of cisplatin alone (8). On these bases, the prevalence of somatic mutations in homologous recombination (HR) genes, as well as their association with platinum sensitivity represent a good rationale to consider PARP as a target for the treatment of UC in selected patients.
Sample Size	77 patients. Patients will be randomized in a 2:1 ratio to Niraparib plus Best Supportive Care (BSC) or BSC
Objective	To compare maintenance treatment with Niraparib plus BSC vs. BSC alone, to determine if maintenance treatment with Niraparib has an effect on progression-free survival in patients with locally advanced or metastatic urothelial cancer that obtained disease control (objective response or stable disease) with first-line platinum-based chemotherapy.
Study endpoints	Primary endpoint: ❖ Progression-free survival (PFS). Secondary endpoints: ❖ Objective response rate. ❖ Duration of response. ❖ Overall survival. ❖ Rate of progression-free survival at 6 months. ❖ Safety and tolerability. ❖ Patient reported outcomes. ❖ BRCA mutation test, HRD diagnostic test (exploratory endpoint).

Schema and Intervention	• Patients assigned to experimental arm will receive Niraparib 300 mg* daily plus best supportive care (BSC), in 28-day cycles, until disease progression or unacceptable toxicity or death. **Starting dose of niraparib will be 200 mg daily if baseline body weight <77 kg or baseline platelets <150,000 µL. Escalation to 300 mg daily will be permitted if no treatment interruption or discontinuation will be required during the first 2 cycles of therapy* • Patients assigned to control arm will receive BSC alone, until disease progression or death.
Inclusion Criteria	❖ Histologically / citologically confirmed, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium (transitional cell carcinoma either pure or mixed histology). ❖ Measurable disease (per RECIST v1.1) prior to the start of first-line chemotherapy. ❖ Prior first-line chemotherapy must have consisted of at least 4 cycles and no more than 6 cycles of platinum containing regimen (cisplatin or carboplatin). ❖ No evidence of progressive disease following completion of first-line chemotherapy (i.e., ongoing CR, PR, or SD per RECIST v1.1 guidelines). ❖ Patients must be enrolled within 28 days of scans demonstrating stable disease/partial-complete response and no more than 42 days after receiving the last standard chemotherapy dose. ❖ Blood sample avaibility to determine germline BRCA mutation status. ❖ Archived tumor tissue sample availability to determine homologous recombination deficiency (HRD) status. ❖ ECOG performance status 0-1. ❖ Adequate bone marrow, kidney and liver function.
Exclusion Criteria	❖ Known hypersensitivity to the components of Niraparib. ❖ Known active hepatic disease. ❖ Prior treatment with a known PARP inhibitor agent ❖ Persisting toxicity related to prior therapy (Grade >1 NCI CTCAE v4.0); however, alopecia, sensory neuropathy (Grade 2 or less), or other (Grade 2 or less)

	adverse events not constituting a safety risk based on the investigator's judgement are acceptable. ❖ History of or known spinal cord compression, or carcinomatous meningitis, or evidence of symptomatic brain or leptomeningeal disease on screening CT or MRI scan. However treated, stable and asymptomatic brain metastases are allowed. ❖ Diagnosis of any other malignancy within 2 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the breast or of the cervix, low grade prostate cancer on surveillance without any plans for treatment intervention, or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms.
Statistical Analysis	A total of 65 PFS events (disease progression or death) are needed to provide 80% power to detect an Hazard Ratio of 0.57 (1.75), corresponding to a median increase in progression-free survival from 4 to 7 months, with one-tailed alpha 0.1.
References	1. Jones P, Wilcoxen K, Rowley M, et al. Niraparib: a poly(ADPribose) polymerase (PARP) inhibitor for the treatment of tumors with defective homologous recombination. J Med Chem. 2015;58(8):3302–14. 2. Walsh CS Two decades beyond BRCA1/2: Homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy. Gynecol Oncol. 2015 May;137(2):343-50. 3. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164. 4. Mullane SA, Werner L, Guancial EA, et al. Expression levels of DNA damage repair proteins are associated with overall survival in platinum-treated advanced urothelial carcinoma. Clin Genitourin Cancer. 2016;14:352-359. 5. Rimar KJ, Tran PT, Matulewicz RS et al. The Emerging Role of Homologous Recombination Repair and PARP Inhibitors in Genitourinary Malignancies. Cancer. 2017 Jun 1;123(11):1912-1924. 6. Mouw KW. DNA Repair Pathway Alterations in Bladder Cancer. Cancers (Basel). 2017 Mar 27;9(4). 7. Plimack ER, Dunbrack RL, Brennan TA, et al. Defects in DNA repair genes predict response to neoadjuvant cisplatin-based chemotherapy in muscle-invasive bladder cancer. Eur Urol. 2015;68:959-967. 8. Jian W, Xu HG, Chen J, et al. Activity of CEP-9722, a poly (ADP-ribose) polymerase inhibitor, in urothelial carcinoma correlates inversely with homologous recombination repair response to DNA damage. Anticancer Drugs. 2014;25:878-886.