Acta Biomed 2023; Vol. 94, Supplement 1: e2023017 DOI: 10.23750/abm.v94iS1.14114

Case report

Enfortumab Vedotin in metastatic bladder cancer: a case report of durable clinical efficacy in a pretreated patient

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Abstract. Metastatic urothelial bladder cancer is associated with high mortality rates. The advent of immunocheckpoint inhibitors (ICIs), with the approval of pembrolizumab in second line treatment, has changed the treatment landscape and improved clinical outcomes of patients. Until recently, subsequent lines of therapy have been limited to single-agents chemotherapy, poor efficacy and relevant toxicities. Recent studies in pretreated urothelial bladder cancer have led to the approval in clinical practice of enfortumab vedotin, demonstrating better clinical efficacy compared with the standard of care. Herein we report a case of a 57-year-old male patient with metastatic bladder cancer, who had unsatisfactory responses to first-line chemotherapy and subsequent second-line immunotherapy. Based on robust data of efficacy and safety from clinical trials, we treated the patient with enfortumab vedotin as third-line therapy. An initial adverse event, probably not strictly related to the drug, led to temporarily discontinuation of enfortumab vedotin and subsequent administration with a dose reduction. Despite this, the drug induced a first partial response on most of the metastatic sites and a complete response on lung and pelvic metastases was subsequently observed. Of note, responses were durable, with good tolerability and improvement in cancer-associated symptoms, such as pain. (www.actabiomedica.it)

Key words: metastatic bladder cancer, enfortumab vedotin, ADCs, immunotherapy, response to oncological treatment

Introduction

Advanced urothelial carcinoma of bladder is an incurable and aggressive disease. According to GLOBOCAN estimates, in Europe approximately 150.000 new cases of urothelial bladder cancer are diagnosed and more than 50.000 people die every year for this malignancy. Approximately 10-15% of patients present with locally advanced or metastatic disease at diagnosis (1).

For these patients, platinum-based chemotherapy represents the first-line standard of care, followed by immune checkpoint inhibitors (ICIs) targeting programmed death 1/programmed death-ligand 1 (PD-1/PD-L1) (2-3). Subsequent treatment options are limited and include chemotherapy (vinflunine, docetaxel, paclitaxel) which is associated with modest clinical benefit and significant toxicities. The major advance in this setting concerns the use of new drug such as erdafitinib, a tyrosine kinase inhibitor (TKI) targeting FGFR2-3 (4), and enfortumab vedotin. Enfortumab vedotin is an antibody–drug conjugate (ADC) targeting Nectin-4, a cell-adhesion protein overexpressed in urothelial cancer. The antibody is conjugated to the microtubule-disrupting agent, monomethyl auristatin E (MMAE), through a protease-cleavable linker and binds Nectin-4 expressing

cells, leading to internalization and release of MMAE. This link disrupts microtubule networks and induces cell-cycle arrest and apoptosis. The safety and efficacy of this drug in patients with locally advanced or metastatic urothelial carcinoma previously treated with a platinum agent and a PD-1/PD-L1 inhibitor were investigated by a phase II study, EV-201, demonstrating an objective response rate (ORR) of 44% (5). Based on these results, FDA granted accelerated approval in this setting in December 2019 (6). The results obtained were consolidated by the phase III study, EV-301. Overall. 608 patients with locally advanced or metastatic urothelial carcinoma who received a prior PD-1 or PD-L1 inhibitor and platinum-based chemotherapy were randomized (1:1) to receive either enfortumab vedotin 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle or investigator's choice of single-agent chemotherapy (docetaxel, paclitaxel or vinflunine). Enfortumab vedotin demonstrated a significant higher benefit compared to standard chemotherapy in terms of median overall survival (OS; primary endpoint 12.88 vs 8.97 months, HR 0.70), median progression free survival (PFS; secondary endpoint 5,55 vs 3,71 months, HR 0.62) and ORR (40.6 vs 17.9%) with an acceptable safety profile compared to chemotherapy (7). These data underline the important role of enfortumab vedotin in the management of pretreated urothelial carcinoma. However, more data from clinical trials and from real-world studies are needed to define the optimal sequence of all the currently available drugs, also considering toxicities and quality of life of patients with urothelial cancer. Herein, we describe a case of a male patient with advanced urothelial carcinoma whose disease relapsed following platinum-based chemotherapy and a PD-1 inhibitor treatment and was then treated with enfortumab vedotin, the patients showed an initial partial response and, at subsequent radiological evaluations, a disappearance of lung and pelvic metastases. Most important, responses were durable and a significant improvement in cancer-related symptoms, including pain, was obtained.

Case report

A 57-year-old male patient, in April 2020 performed a urine test for persistent dysuria, with evidence of microscopic hematuria. An ultrasound imaging of abdomen was performed as first-level diagnostic exam and showed a lesion infiltrating the left side of the bladder wall, confirmed at the subsequent computed tomography (CT) with contrast of chest, abdomen-pelvis, as the only suspected finding. The histologic exam of this lesion obtained by transurethral resection revealed high-grade, non-papillary urothelial carcinoma, muscle-invasive, with angioinvasion and necrosis features. Contextually to the above diagnosis, the patient started to complain with moderate pain to the lumbar column with irradiation to lower limbs and a bone scan and the 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT revealed hypermetabolic activity of bone lesions in the left acetabulum and ischium-pubic segment. Hence, the patient underwent to curative Intensity-modulated radiation therapy (IMRT), for a total of 19,5 Gy during three days. In May 2020, according to international guidelines, standard first-line chemotherapy with cisplatin and gemcitabine was started. In June 2020, he also started treatment with denosumab at standard dose. After completing three cycles of chemotherapy, restaging with FDG PET/CT in July 2020 showed a partial response on bone lesions, therefore treatment was continued with additional three cycles until September 2020. Restaging with FDG PET/CT in December 2020 revealed an increased hypermetabolic activity of known bone metastases, and a whole-body MRI with contrast confirmed disease progression in bone.

In March 2021 he started a second-line treatment with the anti-PD-1 agent pembrolizumab. The whole-body MRI with contrast of July 2021, after six cycles of pembrolizumab, showed bone progression disease, appearance of multiple bilateral pulmonary metastases with maximum diameter of 9 millimeters and a pathologic pelvic tissue with maximum diameter of 22 millimeters. According to irRECIST guidelines, he received other two cycles, for a total of eight cycles, and revaluated after 12 weeks, in August 2021. The FDG PET/CT revealed reduction in the FDG uptake on all known bone lesions, conversely it was reported the appearance of new bone metastases with hypermetabolic activity in ischium-pubic bone bilaterally, in right acetabulum and in right femur trochanter, as well as an increase in the metabolic activity of pulmonary lesions and of the pelvic lesion.

In consideration of the progression of the disease and the robust data supporting the use of enfortumab vedotin in this setting of advanced urothelial cancer, in September 2021 he started third-line metastatic treatment with this ADC at a dose of 1,25 mg/kg with schedule 1, 8, 15, every 28 days. While on treatment, after completing the first cycle, he was admitted to the hospital for abdominal pain, nausea and diarrhea of grade 3 (as per NCI-CTCAE v5.0), poorly responding to loperamide therapy. In the suspect of an adverse event correlated with enfortumab vedotin, the drug was temporarily discontinued. Hematic exams revealed leukocytosis of grade 1 and elevation of inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), instead transaminases, cholestasis indices and bilirubin were within the normal range. The fecal pathogen panel and research of toxin of Clostridium difficile in stool sample were negative. A pan-coloscopy was then performed and revealed extensive mucosal hyperemia, multiple erosions and ulcerations by the ileum to the sigmoid-rectum colon. Histological evaluation of the multiple biopsies reported an ulcerative-erosive ileo-pancolitis, with marked active cryptitis and luminal necrosis (Fig. 1).

This histological feature was compatible with an iatrogenic colitis, more typically associated with the use of immune checkpoint inhibitors. Hence, based on endoscopic and histologic findings of pancolitis, he started steroid therapy with oral prednisolone 1 mg/kg/day until complete resolution of diarrhea. In December 2021, after almost two months of discontinuation and supported by multidisciplinary discussion of the case between oncologists and gastroenterologists, the patient restarted treatment with enfortumab vedotin with a dose reduction to 1 mg/kg according to the drug indications, with good tolerance. In January 2022 after completing the second cycle, restaging with whole-body MRI with contrast showed complete response on some bone lesions and of all lung metastases and a partial response of the pelvic pathological tissue on left side of the bladder wall and of the other bone lesions. The patient also referred significant reduction of pain associated to the bone disease. Restaging with FDG-PET/TC in March 2022, following other two additional cycles of enfortumab vedotin, showed further reduction of hypermetabolic activity on all known bone lesions (Fig. 2), except for the lesions localized on right femur, iliac wing and second sacral vertebra. He

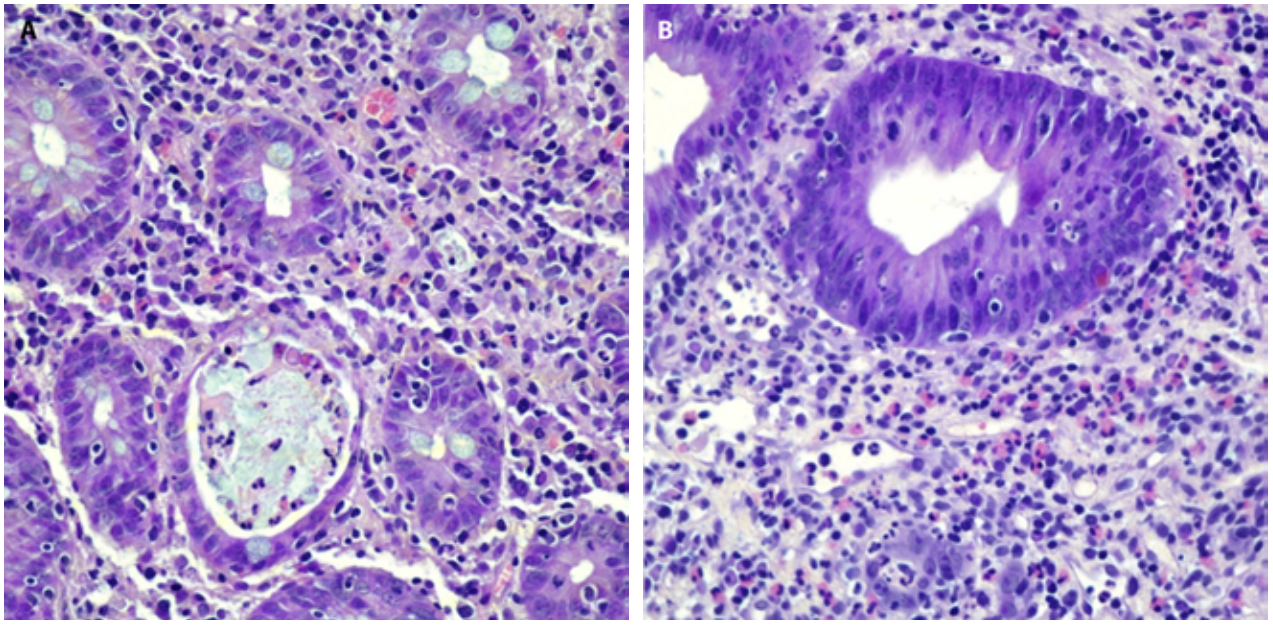

Figure 1. Microscopic images of colic biopsy. A) Numerous eosinophils infiltrate the lamina propria and crypt epithelium, forming micro-abscesses (H&E, 20x); B) At higher magnification intestinal mucosa with increased numbers of eosinophils in the lamina propria, as well as an apoptotic micro-abscess and cryptitis (H&E, 40x). H&E: hematoxylin and eosin stain.

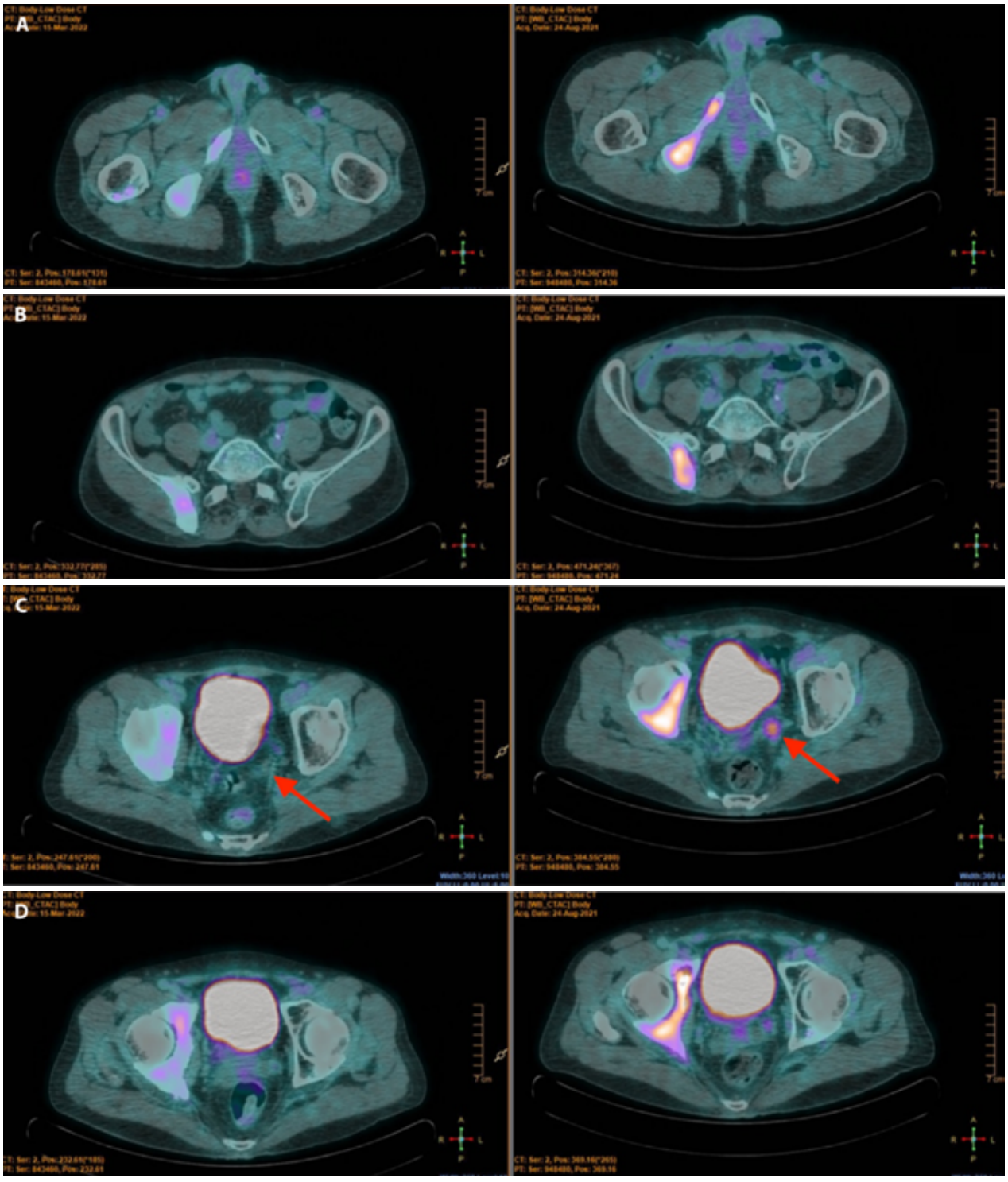

Figure 2. Comparative 18-F-FDG-PET/CT images of metastatic lesions before enfortumab vedotin start (on the left) and after six months of treatment (on the right). In August 2021, hypermetabolic activity was reported in right ischium pubic segment (A), in right iliac bone (B), in right acetabulum (C-D) and in the known pelvic pathological tissue on the left of the bladder (C). In March 2022, no metabolic activity of pelvic pathological tissue (C) and a notable reduction of 18-FDG uptake in bone lesions (on the right A-B-C-D) have been reported.

underwent to palliative radiotherapy on right trochanteric symptomatic metastasis.

After other two cycles with good tolerance, in July 2022 a new whole-body MRI with contrast showed a disappearance of the pelvic pathological tissue on left side of the bladder wall and a complete response of the second lumbar vertebra and further partial response of all bone lesions. The patient therefore continued to receive the treatment, demonstrating significant clinical benefit. The last evaluation with FDG-PET/TC has been performed in November 2022, after other four complete cycles without new toxicities, and detection of metabolic stable disease.

Discussion

Treatment with enfortumab vedotin showed in this pretreated patient a significant clinical and radiological response, with an initial partial response on all the pathologic sites and, after 8 months of treatment, a complete response on pulmonary lesions, some bone lesions and on pelvic tissue. This is the best response reached until the last restaging performed, but the progression free survival reported is about 14 months, well above the median PFS reported in EV-301 trial (5,5 months).

Tolerability of this drug was very good, although the treatment was early temporarily discontinued after the first cycle for the documented pancolitis, both endoscopic and histologically, with a strong suspect of the pathologist of iatrogenic ileitis. Despite being diarrhea a potential adverse event of enfortumab vedotin, in literature there are no reported cases of pancolitis induced by the drug; in fact, this type of colitis does not seem to be an adverse event typically related to ADCs. For example, in the EV-301 trial, which led to the approval of enfortumab vedotin in this setting, no case was reported (6). This condition is probably adducible to a delayed immunorelated adverse event of the previous treatment with pembrolizumab, occurred two months after the last administration, but also after enfortumab vedotin start. This temporal onset of the adverse event, that was then associated with significant clinical response, could also underline a higher benefit of ADC after ICI therapy, and a potential synergistic effect of these two different classes of agents that, although in different ways, potentiate the host's anti-tumor immune response. In the meanwhile, Phase 2 data (EV-103/ KEYNOTE-869) for enfortumab vedotin in combination with pembrolizumab as first-line treatment for metastatic disease have led to a Food and Drug Administration Breakthrough Therapy designation (8) based on high response rates and response duration (9).

Sequencing strategies need to be better investigated, by analysing a large cohort of patients in well-designed trials. Also, the identification of potential predictive biomarkers, such as cellular infiltrates and lymphocyte subpopulation in tumor-microenvironment, that has been proved to play a role in response to immunotherapy, remains crucial to select the optimal therapeutic strategy in front-line and in subsequent lines of therapy. In this patient, Pembrolizumab did not give the expected result. In Keynote-045, objective response rate was superior in pembrolizumab over chemotherapy in patients whose tumors expressed PD-L1 CPS 10, but it was also similar to that in the overall ITT population and our patient had a CPS<10 [3]. Across new therapeutic options, erdafitinib has been also mentioned, but the choice fell on enfortumab vedotin because in this case FGFR2 amplification or FGFR3 mutation have not been found and because data supporting the enfortumab vedotin efficacy are very strong in overall response rate (40.6 vs 17.9%) and in complete response, achieved in 4.9% (n=14/288) of patients in the experimental arm of EV-301 trial. Moreover, safety profile showed comparable events of grade ≥3 severity in enfortumab vedotin and chemotherapy arm (51.4% and 49.8%, respectively), with specific occurrence of skin reactions, peripheral neuropathy, and hyperglycemia toxicities in experimental arm, but these events were commonly mild-to-moderate in severity (7).

In conclusion, in our experience of clinical practise enfortumab vedotin demonstrated to be the most effective and better tolerated therapeutic option in pretreated advanced bladder cancer.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Informed Consent statement: the authors obtained informed consent from the patient to publish his medical images and medical information.

Authors Contribution: Conception and design: Maria Ilenia Passalacqua, Andrea Squeri, Mariacarmela Santarpia. Provision of study material or patients: Mariacarmela Santarpia, Antonio Ieni. Collection and assembly of data: Maria Ilenia Passalacqua, Andrea Squeri, Calogero Sciumè. Data analysis and interpretation: Maria Ilenia Passalacqua, Andrea Squeri, Mariacarmela Santarpia. Manuscript writing: All authors. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors.

References

1. Antoni S, Ferlay J, Soerjomataram I, et al. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol. 2017 Jan; 71(1):96-108.
2. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020; 383:1218–30.
3. Fradet Y, Bellmunt J, Vaughn DJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. Ann Oncol. 2019; 30:970–6.
4. 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(2):248-258.
5. Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol. 2019; 37:2592–600.
6. Chang E, Weinstock C, Zhang L, et al. FDA Approval Summary: Enfortumab Vedotin for Locally Advanced or Metastatic Urothelial Carcinoma. Clin Cancer Res. 2021; 27(4):922-927.
7. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021; 384: 1125-1135.
8. Astellas and Seattle Genetics receive FDA Breakthrough Therapy designation for PADCEV™ (enfortumab vedotin-ejfv) in combination with pembrolizumab in first-line advanced bladder cancer. (Accessed December 18, 2020, at https://www.astellas.com/system/files/news/2020-02/20200220_en_1.pdf.)
9. Rosenberg JE, Flaig TW, Friedlander TW, et al. Study EV-103: Preliminary durability results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma. American Society of Clinical Oncology - Genitourinary Cancers Symposium; 214, 2020. Virtual Location, Abstract 441.

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Received: 24 December 2022
Accepted: 30 January 2023
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