



Advances in the Management of GU Cancers:
Highlights from the 2010 Genitourinary Cancers Symposium

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Target Audience

The target audience for this program includes medical, surgical, and radiation oncologists, as well as allied oncology healthcare professionals who treat genitourinary cancers.

Learning Objectives

Upon completion of this educational activity, participants should be better able to:

- Describe the design and results of studies on treatment of genitourinary cancers presented at the 2010 Genitourinary Cancers Symposium
- Interpret study results in light of current standard of care of genitourinary cancers
- Outline recent information on risk factors for, prevention of, and management of serious treatment-related side effects in genitourinary cancers
- Incorporate individual patient parameters and toxicity considerations in selection of treatment for genitourinary cancers

Statement of Need

Advances in genitourinary cancers have resulted from decades of well-designed clinical trials and new insights into the biology as well as shifts in epidemiology, increasing development of and access to new agents, and rapid advances in diagnostic and therapeutic technologies. The management of genitourinary cancers in recent years has involved increasingly complex, combined-modality treatment approaches. Advances in treatment strategies have affected all the approaches used in genitourinary cancers: radiation therapy, chemotherapy, targeted agents, and surgery and supports a best practices model of multidisciplinary team involvement. Numerous ongoing trials are assessing the benefits of these and other novel agents, and as such, it is imperative that physicians and allied healthcare professionals (including nurses, nutritionists, and pharmacists) treating patients with genitourinary cancers be informed of the results of these trials to facilitate optimal management of genitourinary cancers. This newsletter will highlight areas of new knowledge from the 2010 Genitourinary Cancers Symposium, a meeting specially designed for the education and presentation of new data in genitourinary cancers.

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INTRODUCTION

Exciting presentations of new results, important updates of seminal trials, and expert perspectives were featured at the 2010 Genitourinary Cancers Symposium held in San Francisco, California in March. The co-sponsors for the meeting were the Society of Surgical Urology, the American Society of Clinical Oncology, and the American Society for Radiation Oncology. This newsletter highlights reports of interest for clinicians caring for patients with genitourinary (GU) cancers. Complete abstracts are available at <http://www.asco.org/ASCOv2/Meetings/Abstracts>.

PROSTATE CANCER (PC)

Sartor AO, Oudard S, Ozguroglu M, et al. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational phase III trial (TROPIC). Abstract 9.

After initial treatment with androgen-depleting therapy, patients with metastatic PC develop a clone of malignant cells whose growth is independent of such treatment, in other words, castration-resistant. Guidelines suggest that every 3-week docetaxel and prednisone is the standard first-line treatment in such patients due to survival benefit in 2 studies, but the options are few when progression on docetaxel occurs. One choice is mitoxantrone, an agent that was approved by the FDA as first-line chemotherapy in 1996 based on improvement symptom measures. Cabazitaxel (CBZ) is a semi-synthetic taxane designed to overcome taxane resistance. The final analysis of the TROPIC trial with CBZ were reported at the GU Cancers Symposium. Conducted in 26 countries at 146 sites, this study randomized 755 patients with mCRPC who progressed during or after treatment with a docetaxel-based regimen to CBZ 25 mg/m² every 3 weeks or mitoxantrone 12 mg/m² every 3 weeks. Patients in both groups received daily prednisone. The 2 arms were well matched in important characteristics, including the total amount of prior docetaxel (median

576.5 mg and 529.2 mg, respectively). The primary endpoint of overall survival (OS) was significantly superior in the CBZ-treated patients. A higher rate of febrile neutropenia and gastrointestinal toxicity were observed in the CBZ arm. Results are shown in **Table 1**.

Table 1. Outcomes of cabazitaxel in castration-resistant prostate cancer

Parameter	Cabazitaxel + Prednisone	Mitoxantrone + Prednisone
Overall survival	Median 15.1 mo	Median 12.7 mo
HR (95% CI)	0.70 (0.59-0.83)	
Progression-free survival	Median 2.8 mo	Median 1.4 mo
HR (95% CI)	0.74 (0.64-0.86)	
Grade 3/4 febrile neutropenia (%)	7.5	1.3
Grade 3/4 diarrhea (%)	6.2	0.3
Grade 3/4 asthenia (%)	4.6	2.4
Grade 3/4 nausea (%)	1.9	0.3
Grade 3/4 vomiting (%)	1.9	0
Grade 3/4 hematuria (%)	1.9	0.5
Grade 3/4 abdominal pain (%)	1.9	0

Kantoff P, Higano CS, Berger ER, et al. Updated survival results of the IMPACT trial of sipuleucel-T for metastatic castration-resistant prostate cancer (mCRPC). Abstract 8.

Sipuleucel-T is an investigational biologic agent for PC produced with a unique technology. Patients undergo leukapheresis on day 1 of each of 3 cycles, 2 weeks apart. One days 2-3, the antigen-processing cells (APCs) are combined with a recombinant prostatic acid phosphatase (PAP) fusion protein in a central laboratory, thereby activating the APCs into the product designated as sipuleucel-T. These activated APCs are reinfused on day 4. The IMPACT trial enrolled patients on a 2:1 basis to sipuleucel-T (n = 341) or placebo (n = 171). A retrospective analysis found of groups had similar demographic and clinical characteristics, including the predicted survival based on the Halabi model. The



OS results were initially presented at the American Urological Association meeting when the median follow-up was 34.1 months. Those presented at the GU Cancers Symposium represent 36.5-month median follow-up and are shown in **Table 2**.

Table 2. Results of IMPACT trial in metastatic castration-resistant PC

Parameter	Sipuleucel-T	Placebo
Overall survival	Median 25.8 mo	Median 21.7 mo
HR (95% CI)	0.759 (0.606-0.951)	
Time to ODP	Median 14.6 wk	Median 14.4 wk
HR (95% CI)	0.951 (0.77-1.17)	
Chills (%)	54.1	12.5
Pyrexia (%)	29.3	13.7
Headache (%)	16.0	4.8
Myalgia (%)	9.8	4.8
Hypertension (%)	7.4	3.0
Hyperhidrosis (%)	5.3	0.6
Groin pain (%)	5.0	2.4

ODP = objective disease progression by independent radiologic review

While OS was improved, progression-free survival (PFS) is not significantly different between the 2 arms. Examples were presented of other treatment trials in PC where OS was improved and OPD was not (poxviral-based PSA-targeted immunotherapy [Kantoff P, et al. 2010] and endothelin-A antagonist ZD4054 [James ND, 2009]). Possible explanations were offered, including that bony disease is difficult to measure reliably and that the anti-tumor effect of immunotherapy may be delayed and prolonged. Overall, post-study therapy was received by 81.8% and 86.4% of sipuleucel-T and placebo patients, respectively. Another investigational biologic therapy consisting of autologous mononuclear cells enriched with a different PAP fusion protein (APC8015) was used in 63.7% of those in the placebo arm. Docetaxel was administered to 57.2% of sipuleucel-T patients and 50.3% of placebo patients.

The 2 phase III studies presented at the GU Cancers Symposium evaluating sipuleucel-T and cabazitaxel have important implications for the treatment of men with endocrine resistant prostate cancer, as well as clinical trial design, pending their approval by the FDA. Sipuleucel-T represents a paradigm shift for the treatment of these patients, as for the first time immunotherapy has been shown to improve survival in prostate cancer. Since the anticipated label for this process is in the pre-docetaxel setting, and correlative studies have demonstrated prolonged activation of the immune system by sipuleucel-T, future clinical trials of chemotherapy or other hormonal agents will have to take into account previous administration of sipuleucel-T as an inclusion criterion or pretreatment stratification factor. Second-line trials will also have to incorporate cabazitaxel in the control arm. Important questions need to be answered as to whether further chemotherapy provides similar or superior survival benefits to the newer hormonal agents now currently under investigation.

McGowan D, Hunt D, Jones C, et al. Effect of short-term endocrine therapy prior to and during radiation therapy on overall survival in patients with T1b-T2b adenocarcinoma of the prostate and PSA equal to or less than 20: initial results of RTOG 94-08. Abstract 6.

This multi-center trial with over 9 years of follow-up was presented. Patients with a PSA ≤ 20 and newly diagnosed T1b-T2b PC were randomized to radiation therapy (RT) alone or RT plus 4 months of total androgen suppression (H + RT), starting 2 months prior to RT. The RT regimen was the standard approach in 1994 with a total dose of 66.6 Gy. Total androgen suppression was achieved with flutamide 250 mg tid plus either monthly goserelin or monthly leuprolide. Seventy-six percent of the 1979 patients were white, the proportion of T1 and T2 were evenly divided and 61% had a Gleason score of 2-6. The findings included:

- Overall survival at 10 years (primary endpoint)
 - 62% with H + RT
 - 57% with RT
 - HR 1.17 (95% CI 1.01-1.35)
 - $P = 0.03$
 - Subgroup analysis for low-, intermediate-, and high-risk groups and for white and African-American race showed benefit of H + RT for all
- Disease-specific survival
 - 96% with H + RT
 - 93% with RT
 - HR 1.84 (95% CI 1.25-2.70)
 - $P < 0.01$
- Non-PC death rate similar in each arm
- Acute and late radiation toxicity similar
- Hormonal toxicity
 - Grade 3-4 hepatotoxicity < 5%
 - Grade 1-2 cardiovascular 1%

In summary, this trial showed that the addition of 4 months of androgen suppression significantly improved OS over RT given in the pre-intensity modulated radiation therapy (IMRT) era. Whether these results would persist when anti-androgen therapy is combined with IMRT or other modalities are unknown.

Shah SK, Ryan CJ, Molina A, Kheoh TS, Haqq CM, Small EJ. Bone scan flare in patients (pts) receiving abiraterone acetate (AA) for metastatic androgen deprivation resistant prostate cancer (mADRPC): analysis of data from a phase II study of the Department of Defense Prostate Cancer Clinical Trials Program. Abstract 4.

Bone flare occurs in up to 75% of patients with PC. It is typically defined as the appearance of progressive disease on bone scintigraphy scan concurrently with PSA decline of $\geq 50\%$ and is considered to be a consequence of rapid bone repair (increased osteoblastic activity) around a responding lesion. Bone flare can complicate assessment of treatment effects, trigger additional diagnostic testing, and potentially lead to premature discontinuation of therapy; therefore, awareness of the phenomenon is important. AA is an oral inhibitor of 17 alpha-monooxygenase

(17 alpha hydroxylase/C_{17,20}-Lyase complex), a member of the cytochrome p450 family that catalyzes intermediates in testosterone synthesis. This phase II study, originally reported at the ASCO Annual Meeting in 2009, evaluated 33 chemotherapy-naïve men with mADRPC who were treated with AA plus prednisone. The previous report documented high rates of PSA response. At the GU Cancers Symposium, an analysis to determine the incidence of bone flare was reported. Bone scan interpretations by the local radiologist were compared with PSA changes from baseline to month 4 and month 7 in 27 patients. Of these, 24 experienced a PSA decline $\geq 50\%$ at month 4 and 17 of 24 had bone scans with the official report of disease progression. A majority of these patients (10 of 17) had subsequent improvement in bone scan at cycle 7. The overall incidence of bone flare in PSA responders was 43%.

Crook JM, Gomez-Iturriaga A, Wallace K, et al. Comparison of health-related quality of life 5 years after SPIRIT (Surgical Prostatectomy [RP] versus Interstitial Radiation [BT] Intervention Trial ACOSOG Z0070). Abstract 11.

The SPIRIT trial was conducted from 2002 to 2004. Initially patients were to be randomized to RP or BT. Later the study was amended to allow patients to choose RP, BT, or to be randomized to one of the treatments. Investigators subsequently implemented an extensive multi-disciplinary education session to improve recruitment. Despite these changes, the study closed prematurely due to poor accrual. Patients who enrolled in the trial after the education session and who received their treatment at the University Health Network (N = 190) were eligible for this study of health-related quality of life (HRQOL) and 168 completed questionnaires. Of the 168 men, 18% had chosen randomization. Overall, 60% had BT and 40% had RP. The questionnaires were completed at a median time of 5.2 years after enrollment. There was no difference in the bowel domain, hormonal domain, or SF-12 physical component score. However, men treated with BT scored better in the urinary domain (91.85 vs 88.15, $P = 0.02$), sexual domain (52.34 vs 39.72, $P = 0.002$), and satisfaction score (93.56 vs 77.24, $P < 0.0001$).



Sylvester JE, Grimm PD, Wong J, et al. Fifteen-year biochemical relapse-free survival and overall survival following ¹²⁵I prostate brachytherapy in clinically localized prostate cancer: Seattle experience. Abstract 14.

Clinical experience with ¹²⁵I brachytherapy (BT) administered at a single institution from 1988 to 1992 was reported at the GU Cancers Symposium. The study cohort consisted of 173 patients of 215 patients treated during that time with BT monotherapy. The average age at the time of treatment was 70 years. The minimum follow-up in this group was 3.6 years and the median was 11.7 years. The 15-year biochemical relapse-free survival (BRFS) was 80.4% and OS was 37.1%.

The 2 trials above still leave many questions unanswered regarding the optimal treatment for localized prostate cancer. The initial ambitious goals of the randomized SPIRIT trial were tempered when the study was amended to allow patients to choose their own treatment. The question regarding the comparative efficacy of radical prostatectomy and brachytherapy thus will not be settled for years to come.

Nguyen PL, Lipsitz SR, Choueiri TK, et al. Time trends in the utilization of higher-cost treatment for prostate cancer: 2002-2007. Abstract 18.

Investigators from Boston analyzed the SEER (Surveillance, Epidemiology, and End Results) – Medicare linked database to compare the treatment patterns for non-metastatic PC in 2002 and in 2005. Common Procedural Terminology (CPT) codes were used to distinguish IMRT from standard conformal beam radiation, and minimally invasive radical prostatectomy (MIRP) from open RP. The utilization of RT and surgery overall were similar throughout in the interval; however, IMRT utilization as a percentage of all RT increased substantially (28.7% of patients vs 81.7%, $P < 0.001$), as did the use of MIRP as a percentage of all surgery (9.5% vs 28.7%, $P < 0.001$). Patients living in areas with higher educational levels, higher income, and in the Northeast or West regions were more likely to receive the newer IMRT or MIRP procedures.

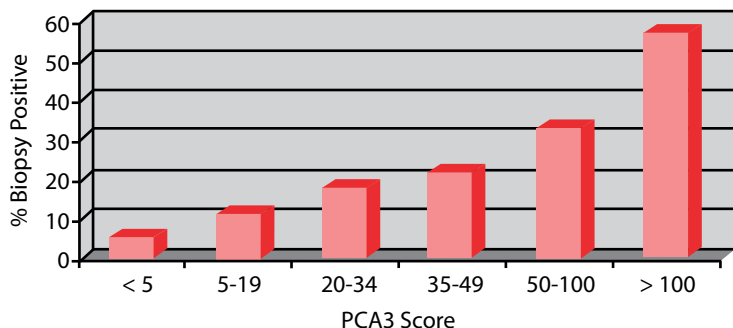
Given the difficulties in performing randomized trials in patients with localized prostate cancer, it would seem the comparative effectiveness research would be an alternative method to compare these treatments. Retrospective data was published in the October 14, 2009 issue of *JAMA* evaluating using the SEER database comparing toxicity seen with radical retropubic prostatectomy versus robotic surgery. Surprisingly, there was a higher rate of long-term incontinence and impotence in patients treated robotically. Similar studies are needed evaluating newer forms of radiation therapy, as well as proton beam therapy.

Groskopf J, Aubin SM, Reid J, et al. Validation of the PCA3 molecular urine test for predicting repeat prostate biopsy outcome in the placebo arm of the dutasteride REDUCE trial. Abstract 5.

Messenger RNA (mRNA) for the Prostate Cancer Gene 3 (PCA3) has been found to be overexpressed in 95% of all prostate cancers at a level 60-100 fold higher than normal or benign hypertrophied prostate tissue. A test using transcription-mediated amplification can detect the mRNA for PCA3 in urine is marketed in Europe and is performed by some CLIA-certified laboratories in the US as a lab-developed test, although it is not FDA approved. The results are expressed as a score of mRNA of PCA3/mRNA of PSA. Small studies have evaluated for ability of urine PCA3 to predict the result of prostate biopsy with promising results. At the GU Cancers Symposium investigators reported results of a study that analyzed PCA3 levels in banked frozen urine specimens from 1072 patients who were in the placebo arm of the REDUCE trial that evaluated the effect of dutasteride on patients with high serum PSA levels (2.5-10 ng/mL) and negative biopsy. These urine PCA3 results taken at year 2 and year 4 were compared to the biopsy results from the same timepoints. PC was detected by biopsy in 18% of patients and the PCA3 score correlated with biopsy outcome (**Figure 1**, $P < 0.0001$) and to a Gleason score < 7 or ≥ 7 ($P = 0.0017$) to a higher degree than did serum total PSA or free PSA. Using a PCA3 cutoff of 35, the test showed 48.4% sensitivity and 78.6% specificity for a diagnosis

of PC. Urine PCA3 levels at 2 years also predicted the biopsy result (55 cancers in 567 patients) at 4 years with a sensitivity of 36.4% and specificity of 79.1%.

Figure 1. PCA3 and biopsy result



Further comparative studies clearly are needed to determine whether PCA3 can be used to reduce the number of biopsies for patients with suspected prostate cancer.

RENAL CELL CARCINOMA (RCC)

Rini BI, Cohen DP, Lu D, et al. Hypertension (HTN) as a biomarker of efficacy in patients (pts) with metastatic renal cell carcinoma treated with sunitinib. Abstract 312.

Pooled data from 3 prospective clinical trials of sunitinib for treatment of metastatic renal cell carcinoma (mRCC) was evaluated to determine if hypertension (HTN), a well recognized adverse reaction of vascular endothelial growth factor (VEGF) inhibitors, is associated with superior survival outcomes. Sunitinib was administered in the standard regimen of 50 mg daily for 4 weeks followed by a 2-week break. Development of systolic HTN (defined as maximum systolic blood pressure [SBP] ≥ 140 mm Hg) or of diastolic HTN (defined as diastolic blood pressure [DBP] ≥ 90 mm Hg) were significantly associated with all efficacy parameters as shown in **Table 3** ($P < 0.0001$ in all cases). Relative dose intensity did not correlate with occurrence of HTN and administration of anti-HTN therapy did not influence oncologic outcomes. Patients with sunitinib-related HTN had more renal

adverse events (5% vs 3%, $P = 0.169$), but there was no difference in cerebrovascular, ocular, or cardiac events. This analysis adds to other data supporting that treatment-induced HTN may be a biomarker of clinical outcome to VEGF-inhibiting agents.

Table 3. Association of sunitinib-associated hypertension and outcome in mRCC

	Max SBP ≥ 140 mm Hg (n = 441)	Max SBP < 140 mm Hg (n = 93)
OR (%)	54.6	9.7
PFS (months)	12.5	2.5
OS (months)	30.5	7.8
	Max DBP ≥ 90 mm Hg (n = 362)	Max DBP < 90 mm Hg (n = 172)
OR (%)	57.2	25.0
PFS (months)	13.4	5.3
OS (months)	32.1	15.0

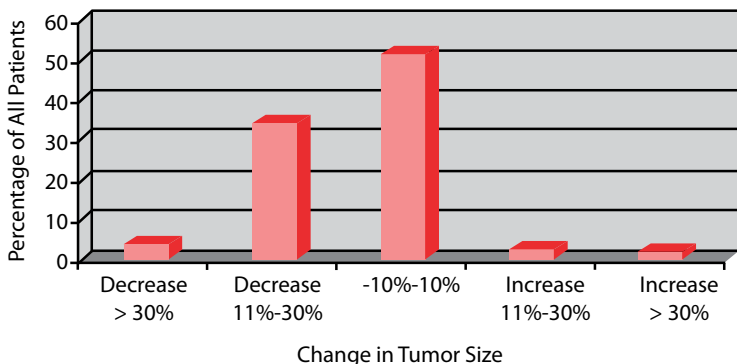
Abel EJ, Tannir NM, Culp SH, Matin SF, Jonasch E, Wood CG. Does targeted therapy result in reliable and meaningful primary tumor downstaging in patients with metastatic renal cell carcinoma? Abstract 318.

Targeted therapy (TT) in mRCC has typically been evaluated in patients with prior nephrectomy to remove the primary tumor. There is little information on the efficacy of TT to shrink tumors within the kidney, but the ability to downstage these lesions could have surgical implications. Therefore, investigators at a single center retrospectively identified 151 patients who had received pre-operative TT for mRCC and where the primary tumor was still in place. The most frequent type of TT administered was sunitinib (61 cases); others were (in descending order) bevacizumab, bevacizumab + erlotinib, sorafenib, temsirolimus, bevacizumab + gemcitabine, erlotinib, and bevacizumab + sunitinib. Graphical representation of the maximum response of the primary tumor is shown in **Figure 2**. Only 5 (3.3%) of patients achieved



a partial response by RECIST criteria. Meaningful downstaging of primary renal tumors is unlikely with currently available TT.

Figure 2. Maximum primary tumor response to targeted therapy for RCC



Rini BI, Hutson TE, Elson P, et al. Clinical activity of sunitinib rechallenge in metastatic renal cell carcinoma. Abstract 319.

Numerous agents are available for the treatment of mRCC, but none produce long-term remissions. Therefore, additional effective options would be helpful for clinicians caring for mRCC patients. Investigators identified a small group of patients (N = 23) from a multi-center database who had initially been treated with sunitinib until disease progression and were rechallenged with the drug some time later, after other therapy had been given. Most (87%) had favorable or intermediate risk by Memorial Sloan-Kettering Cancer Center criteria. A partial response with initial therapy was observed in 65% and the median PFS was 13.7 months. Thereafter, various treatments were used (sorafenib, sorafenib + bevacizumab, an mTOR inhibitor, or inhibitors of both VEGF and mTOR). Sunitinib rechallenge occurred at a median of 6.7 months after initial progression. Five (22%) achieved a partial response and the median PFS was 7.2 months. Therefore, sunitinib rechallenge can be considered for multi-relapsed mRCC, especially if the interval since initial therapy is greater than 6 months.

Weight J, Larson B, Lieser G, et al. Pathological upstaging and survival in patients with pT2/ T3 renal tumors treated with either partial nephrectomy (PN) or radical nephrectomy (RN). Abstract 313.

Thompson RH, Lane BR, Lohse CM, et al. Every minute counts when you clamp the renal hilum during partial nephrectomy. Abstract 315.

Two presentations focused on technical aspects of RCC surgery. The first was based on recommendations that patients with all cT1 renal masses receive a partial nephrectomy (PN). A single institution kidney cancer registry was queried to determine if a PN results in poorer outcomes than radical nephrectomy (RN) if the tumor is upstaged to pT2 or pT3. Of 1981 consecutive RCC patients with cT1 tumors and resection, 10.7% were upstaged on final pathology. At a median follow-up time of 36 months, multivariate analysis demonstrated that pathologic stage and Fuhrman grade predicted cancer-specific survival, whereas nephrectomy type and tumor size did not. A different clinical database with 362 patients with RCC, a solitary kidney, and PN was queried to determine whether renal hilum clamping time during PN was associated with adverse outcomes. Postoperative acute renal failure (ARF) occurred in 19% and new onset stage IV chronic kidney disease (CKD) occurred in 17%. Each additional minute of warm ischemia time was statistically significantly associated with ARF and new onset CKD ($P < 0.001$). When evaluating warm ischemia time in 5-minute increments, a cutpoint of 25 minutes provided the best distinction between the presence or absence of ARF and CKD. These analyses provide useful information for the surgical management of RCC with PN.

BLADDER CANCER

Messing EM, Ely B, Scosyrev E, et al. Do mixed histologic features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancers? Abstract 274.



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The Southwest Oncology Group trial S8710 evaluated the effect of 3 cycles of neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) when added to radical cystectomy compared to cystectomy alone. When initially reported in 2001, the 5-year survival rate was statistically significantly better with MVAC plus surgery compared to surgery alone (57% vs 42%, respectively). At the GU Cancers Symposium, a secondary analysis of histologic features was presented. Tumors were classified as either pure urothelial carcinoma (UC, $n = 236$) or mixed ($n = 59$). Cox regression models determined that OS benefit from MVAC was greater among patients with mixed tumors (HR 0.46, $P = 0.02$) than in those with pure UC (HR 0.90, $P = 0.48$). There was marginal evidence of a statistical interaction ($P = 0.09$). In summary, the use of MVAC prior to cystectomy should be considered for patients with squamous or glandular differentiation in locally advanced bladder UC.

CONCLUSION

This annual multi-disciplinary meeting continues to provide a forum for the dissemination of new research results and multi-disciplinary discussions across the entire spectrum of genitourinary cancers. For RCC, important surgical abstracts highlight that preserving the functioning kidney is critical and not associated with worse cancer outcomes. VEGF therapy continues to dominate the treatment of metastatic RCC, with recent data highlighting efforts to optimize treatment application. In patients with castration-resistant prostate cancer, 2 new treatments, sipuleucel-T and cabazitaxel, demonstrate promising activity in the pre-docetaxel and post-docetaxel treated patients, respectively.