New and Promising Strategies in the Management of Bladder Cancer

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OVERVIEW

Bladder cancer is a complex and aggressive disease for which treatment strategies have had limited success. Improvements in detection, treatment, and outcomes in bladder cancer will require the integration of multiple new approaches, including genomic profiling, immunotherapeutics, and large randomized clinical trials. New and promising strategies are being tested in all disease states, including nonmuscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and metastatic urothelial carcinoma (UC). Efforts are underway to develop better noninvasive urine biomarkers for use in primary or secondary detection of NMIBC, exploiting our genomic knowledge of mutations in genes such as RAS, FGFR3, PIK3CA, and TP53 and methylation pathways alone or in combination. Recent data from a large, randomized phase III trial of adjuvant cisplatin-based chemotherapy add to our knowledge of the value of perioperative chemotherapy in patients with MIBC. Finally, bladder cancer is one of a growing list of tumor types that respond to immune checkpoint inhibition, opening the potential for new therapeutic strategies for treatment of this complex and aggressive disease.

Cancer is a genetic disease. A cancer cell inherits or acquires mutations that enable it to grow efficiently, replicate indefinitely, support angiogenesis, avoid apoptosis, and in some cases, metastasize. Molecular profiles obtained by host and tumor DNA sequencing, single nucleotide polymorphism, RNA, and protein microarrays, and methylation screens are helping to pinpoint which mutations drive the cancerous phenotype and which are merely passengers on the malignant journey. Notwithstanding the role of individual genes, aggregate molecular profiles provide patient- and tumor-specific information that details the biologic complexity of a particular cancer and can be exploited for its clinical implications, therapeutic insights, and diagnostic benefit.

DETECTION AND MONITORING OF BLADDER CANCER IN THE GENOMIC ERA

Although the treatment for UC has improved over the last several decades, diagnostic techniques have progressed more slowly. Cystoscopy is still considered the best method for diagnosing UC, but it is invasive, uncomfortable, and can only detect approximately 90% of lesions. In addition, when a tumor is discovered and must be biopsied and/or removed, a second procedure is required, transurethral resection of the bladder tumor (TURBT), which requires general anesthesia. Last, the cost of cystoscopy, especially when used to monitor recurrence, is the major reason why per-patient expenses for UC are among the highest for all cancers. The major problem associated with NMIBC is that after initial TURBT, 50% to 70% of patients develop multiple recurrences; 10% to 20% of these will progress to MIBC. This risk of recurrence and progression calls for life-long surveillance. The current standard procedure is to perform cystoscopy and evaluate urine cytology every 3 to 4 months in the first 2 years, twice per year in years 3 to 4, and yearly thereafter. The burden of this follow-up on the patient, as well as the direct and indirect costs for the patient and society in terms of lost wages, have led to extensive efforts to develop noninvasive urine biomarkers for UC. However, to date, none have demonstrated sufficient specificity and sensitivity to monitor the general population or replace cystoscopy and cytology in monitoring for recurrence. Urine cytology is particularly insensitive for detecting low-grade tumors. However, advances in genomics have clearly demonstrated that DNA alterations offer great promise for detecting primary or secondary bladder cancer.

NMIBC and MIBC are genetically different. NMIBC is characterized by a high frequency of mutations in the FGFR3 oncogene, leading to constitutive activation of the RAS/MAPK pathway. In MIBC, mutations in the TP53 gene prevail. In general, mutations in FGFR3 and TP53 are mutually exclusive, suggesting that NMIBC and MIBC develop along different oncogenetic pathways. However, these mutations often occur simultaneously in stage pT1 tumors that invade the connective tissue layer underlying the urothelium. Re-
cently, somatic mutations in the PIK3CA oncogene, which encodes the catalytic subunit p110α of class-IA PI3 kinase, were described in 13% to 27% of bladder tumors.11 These mutations often coincided with FGFR3 mutations. Mutations in the RAS oncogenes (HRAS, KRAS, and NRAS) have also been found in 13% of bladder tumors and in all stages and grades; they are mutually exclusive with FGFR3 mutations. Given these findings, analyzing urine sediment for genic mutations may be a promising strategy for noninvasive detection of bladder cancer.

**FGFR3**

FGFR3 mutations occur in around 50% of both lower and upper urinary tract tumors, clustering in three distinct hotspots in exons 7, 10, and 15.12 The most common mutations in exon 7 and 10 favor ligand-independent dimerization, transactivation, and signaling.13-17 Mutations in exon 15 are rare and induce a conformational change in the kinase domain, resulting in ligand-independent receptor activation and signaling, as well as FGFR3 cellular localization, with aberrant endoplasmic reticulum signaling.18 FGFR3 mutations are thought to occur early during urothelial transformation, as they are reported in over 80% of preneoplastic lesions,13,14 pointing to an overall “benign” effect of FGFR3 mutation in the bladder.17,19 FGFR3-mutant tumors are more chromosomally stable than their wild-type counterparts. A mutually exclusive relationship between FGFR3 mutation and over-representation of 8q was observed in NMIBC.20 A recent study found that around 80% of NMIBC and 54% of MIBC have dysregulated FGFR3 with discordant mutation and protein expression patterns, suggesting a key role for FGFR3 in both NMIBC and MIBC, either through mutation, overexpression, or both.21 These discrepancies may reflect differential downstream signaling of wild-type and mutant receptors or the different molecular pathways instigating the development of these tumors. The mechanisms driving FGFR3 overexpression in UC are largely unknown, although a recent study demonstrated the regulation of FGFR3 expression in urothelial cells by two microRNAs (miR-99a/100) that are often downregulated in UC, particularly in low-grade and low-stage tumors.22

FGFR3 mutations were among the first to be used as urine biomarkers of recurrent disease, especially low-grade disease, which is challenging to detect by urine cytology. van Rhijn et al23 reported that combined microsatellite and FGFR3 mutation analysis could detect UC in voided urine. FGFR3 mutations were found in 44% of urothelial tumors (59 tumors), but were absent in 15 G3 tumors. The sensitivity of microsatellites to detect cancer in voided urine was lower for tumors harboring FGFR3 mutations (15 out of 21 tumors; 71%) than for FGFR3 wild-type UC (29 out of 32 tumors; 91%). By including the FGFR3 mutation, the sensitivity of molecular cytology increased from 71% to 89% and was superior to the sensitivity of morphologic cytology (25%) for every clinical subdivision. These findings highlighted the potential of molecular biology as an adjunct to cystoscopy and cytology in informing follow-up care.

**HRAS**
The HRAS gene, which codes for p21 Ras (or Ras), a small GTPase, was the first identified human oncogene. It was found in the T24/EJ urothelial cell line.24-26 In the normal urothelium, normal Ras protein diminishes with differentiation, with highest expression in the basal (progenitor) cells.27 The role of Ras in UC is supported by its ability to transform Simian vacuolating virus 40 (SV40)-immortalized human urothelial cells into invasive transitional-cell carcinomas.28,29 In addition, in elegant transgenic studies, Ras overexpression has been shown to lead to NMIBC.30 Ras interacts with Raf, a serine/threonine kinase, which is activated in tumor cells containing enhanced growth signaling pathways in both NMIBC, MIBC, and metastatic disease with subsequent activation of MAPK.31,32

**P53**
The p53 tumor suppressor encoded by the **TP53** gene located on chromosome 17p13.13 inhibits phase-specific cell cycle progression (G1-S) through transcriptional activation of p21<sup>WAF1/CIP1</sup>.34 Most UCs exhibit loss of a single 17p allele. Additional mutations in the remaining allele can inactivate TP53, leading to increased nuclear accumulation of the mutant protein, which has a longer half-life than its wild-type counterpart.35 TP53 deletion was correlated with grade and stage of UC.36-41 Invasive carcinoma can also progress from recurrent papillary carcinoma by acquiring additional alterations in TP53, RB1, PTEN, EGFRs, CCND1, MDM2, or EZF.42 In addition, oncogenic HRas has been shown to promote the malignant potency of UC cells that have acquired
deficiencies of TP53, RB1, and PTEN. Mutations in the TP53 gene that result in a truncated protein (or no protein), homozygous deletion of both alleles of the gene, or gene silencing by methylation of the promoters of both alleles cannot be detected by nuclear accumulation of p53 protein, thus limiting the sensitivity of immunohistochemistry (IHC) for p53 alterations. Notwithstanding this caveat, overexpression of nuclear p53 protein by IHC has been used as a surrogate marker for detection of mutant p53 in clinical specimens. The expression of p53 has been associated with increased risk of progression of NMIBC or mortality in patients with MIBC, independent of tumor grade, stage, and lymph node status. Interestingly, in a recently reported randomized, prospective trial, this was not borne out in patients treated with cystectomy. In this and other studies, discordance in the identification of p53 as an independent prognostic marker for UC progression, recurrence, mortality, and response to therapy may be a result of patients' genetic and epigenetic status, cohort selection, and technical and statistical variations.

**COMBINING GENOMIC ASSAYS**

To develop more sensitive and specific assays, recent studies have simultaneously evaluated RAS, FGFR3, and PIK3CA in UC. A study of 257 patients with primary bladder tumors found that 64% (164 out of 257) of tumors contained an FGFR3 mutation, 11% (28) samples were mutant for one of the RAS genes, and 24% (61) harbored a PIK3CA mutation. Of the 257 primary tumors, 26% overexpressed p53, which is indicative of missense mutations, as noted above. When RAS, FGFR3, and PIK3CA mutations were calculated with TP53 mutations, only 27 tumors (11%) were wild-type for all examined genes. In 54 patients who developed one or more recurrences, tissue was available from 184 recurrent tumors, including multifocal recurrences. Using the SNaPshot-based mutation assay, investigators examined these tumors for FGFR3, PIK3CA, and RAS mutations. The frequency of p53 overexpression was low (6 out of 54) in the primary tumors of this group of patients, consisting mainly of NMIBC tumors. In patients with a wild-type primary tumor, recurrences were mostly wild-type (49 out of 54), whereas five harbored an FGFR3 mutation. One recurrent tumor contained two different PIK3CA mutations. In recurrences, PIK3CA mutations in addition to an FGFR3 mutation were associated with higher-grade tumors compared with recurrences harboring an FGFR3 mutation alone. Importantly, there was 100% consistency in the type of mutation for RAS and PIK3CA among different tumors in the same patient.

Investigators also developed a methylation assay for specific detection of recurrent NMIBC in voided urine. Microsatellite analysis was also used to detect loss of heterozygosity in voided urine samples. Mutation analysis of FGFR3, PIK3CA, HRAS, KRAS, and NRAS was recently combined with methylation-specific assays to determine whether this combination outperformed either examination alone. Results were compared with those of urine cytology in a large, retrospective, longitudinal cohort that was part of the European FP7 UROMOL project. A total of 716 voided urine samples from 136 patients with NMIBC (Ta/T1, G1/2) were collected at TURBT. Patients with a history of carcinoma in situ were excluded from the analysis. Urine was collected at regular follow-up visits immediately before cystoscopy. During follow-up, 552 histologically proven recurrences were detected, including mainly stage Ta (92%), G1/2 (82%), and solitary tumors (67%). Sensitivity for detecting a recurrent tumor varied between 66% and 68% for the molecular tests after patient stratification based on tumor DNA analysis. A combination of markers increased sensitivity, but decreased the number of patients eligible for a certain test combination. Combining urine cytology with FGFR3 analysis without stratifying for FGFR3 status of the incident tumor increased sensitivity from 56% to 76%.

This study highlights the challenge of molecular examination of urine using genomics, and the importance of including all available information (i.e., cytology). However, there is no doubt that next-generation exome sequencing of paired tumor and peripheral blood samples will uncover many more potential biomarkers that could be added to these panels to improve their performance. Such examination was first performed in 2011 in a small set of patients. Initial findings from this cohort were examined in light of findings from an additional 88 patients with bladder cancer and by the The Cancer Genome Atlas (TCGA) consortium. From these contributions, several previously defined mutations were observed (in TP53, RB1, and HRAS), but novel mutations were also noted, the most common of which was in UTX, which was identified in 21% of tested individuals. Of note, most of the identified new mutations were related to chromatin remodeling, suggesting a potential new area for bladder cancer research. Mutations in chromatin remodeling genes are commonly found in several other cancer types, suggesting their fundamental contribution to carcinogenesis. Adding to this complexity is a recent study of 537 patients with locally advanced or metastatic UC of the bladder, 74 patients with non-bladder, and 55 patients with nonurothelial bladder cancers profiled using mutation analysis, in situ hybridization, and IHC assays. Compared with nonbladder UC, bladder UC exhibited more frequent expression of abnormal protein (and increased amplification) in HER2, androgen receptor, serum protein acidic and rich in cysteine (SPARC), and topoisomerase 1. These findings suggest that bladder UC has higher levels of actionable biomarkers that may have clinical implications for treatment and diagnostic options.

**NEOADJUVANT AND ADJUVANT CHEMOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER**

Approximately 25% of patients with bladder cancer present with a tumor invading the muscle layer of the bladder wall (T2 to T4). MIBC is associated with a high rate of recurrence and poor overall prognosis, despite aggressive local and systemic therapies. Radical cystectomy is the standard treatment for MIBC, but even with substantial improvements in surgical techniques, mortality remains high because of a high
TABLE 1. Summary of Phase III Perioperative Cisplatin-Based Chemotherapy Clinic Trials in Patients with Muscle-Invasive Bladder Cancer

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Stadler (p53)</th>
<th>Cognetti</th>
<th>Paz-Ares</th>
<th>Sternberg</th>
<th>Grossman</th>
<th>MRC/EORTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>T1 and T2 negative LN</td>
<td>T2G3, T3 to T4, N0-2</td>
<td>T3 to T4, N0 to N2</td>
<td>T3 to T4 and/or N1 to N3</td>
<td>T2 to T4aN0</td>
<td>T2 to T4aN0</td>
</tr>
<tr>
<td>Design</td>
<td>α error 5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Power</td>
<td>90%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Recurrence</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td>0.5 to 0.3 at 3 years (20%)</td>
<td>50% to &gt; 60% at 2 years (10%)</td>
<td>50% to &gt; 65% at 2 years (15%)</td>
<td>35% to &gt; 42% at 5 years (7%)</td>
<td>35% to &gt; 42% median OS (50%)</td>
<td>50% to &gt; 60% at 2 years (10%)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.52</td>
<td>0.75</td>
<td>0.77</td>
<td>0.826</td>
<td>0.78</td>
<td>1.08</td>
</tr>
<tr>
<td>Planned Sample Size</td>
<td>190</td>
<td>610</td>
<td>340</td>
<td>660 (originally 1,344)</td>
<td>298</td>
<td>915</td>
</tr>
</tbody>
</table>

Results

| Patients randomized | 114 (499 tested and 272 + p53) | 192 | 142 | 284 | 307 | 916 |
| Years to Accrue    | 9 | 6 | 7 | 6 | 11 | 6 |
| 5-Year Recurrence (Observation vs. Chemotherapy) | TTR, 0.20; p = 0.62; HR, 0.78 | DFS, 42.3% vs. 37.2%; p = 0.70; HR, 1.08; all, 40% | 3 years 44% vs. 73%; p < 0.0001; HR, 0.36; all, 54% | PFS, 31.8% vs. 47.6%; p = < 0.0001; HR, 0.54 | 5-year DFS, 32% vs. 39%; 10-year DFS, 20% vs. 27% p = 0.008; HR, 0.82 |
| 5-Year OS (Observation vs. Chemotherapy) | 85% (both arms) | 53.7% vs. 43.4%; p = 0.24; HR, 1.29; all, 48.5% | 31% vs. 60%; p < 0.0009; HR, 0.44; all, 49% | 47.7% vs. 53.6%; p = 0.13; HR, 0.78; all, 38.6% | 43% vs. 57%; p = 0.06 | 5-year OS, 43% vs. 49%; 10-year OS, 30% vs. 36%; p = 0.03; HR, 0.84 |
| Median Follow-up   | 5.4 years | 35 months | 30 months | 7 years | 8.7 years | 8 years |

Abbreviations: CMV, cisplatin/methotrexate/vinblastine; dd, dose-dense; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; GC, gemcitabine/cisplatin; HR, hazard ratio; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; OS, overall survival; PFS, progression-free survival; PGC, paclitaxel/gemcitabine/cisplatin; TTR, time to progression.

The disease process to eradicate micrometastases.69

Invasive tumors (stage T2 to T4a) to nonmuscle-invasive tumors (stage T2).67,72-74 In the randomized Southwest Oncology group 8710 trial, neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy demonstrated a 77-month median survival compared with a 46-month median survival with cystectomy alone. In the randomized Southwest Oncology group 8710 trial, neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy demonstrated a 77-month median survival compared with a 46-month median survival with cystectomy alone. In the randomized Southwest Oncology group 8710 trial, neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy demonstrated a 77-month median survival compared with a 46-month median survival with cystectomy alone.

Table 1: Summary of Phase III Perioperative Cisplatin-Based Chemotherapy Clinic Trials in Patients with Muscle-Invasive Bladder Cancer

- **Chemotherapy**
  - Stadler (p53): Adjuvant MVAC × 3
  - Cognetti: Adjuvant GC × 4
  - Paz-Ares: Adjuvant PGC × 4
  - Sternberg: Adjuvant ddMVAC/GC/MVAC × 4
  - Grossman: Neoadjuvant MVAC
  - MRC/EORTC: Neoadjuvant CMV

- **Patients**
  - Stadler: T1 and T2 negative LN
  - Cognetti: T2G3, T3 to T4, N0-2
  - Paz-Ares: T3 to T4, N0 to N2
  - Sternberg: T3 to T4 and/or N1 to N3
  - Grossman: T2 to T4aN0
  - MRC/EORTC: T2 to T4aN0

- **Design**
  - α error: 5%
  - Power: 90%
  - Endpoint: Recurrence OS OS OS OS OS OS
  - Years to Accrue: 9 6 7 6 11 6
  - 5-Year Recurrence (Observation vs. Chemotherapy): TTR, 0.20; p = 0.62; HR, 0.78
  - 5-Year OS (Observation vs. Chemotherapy): 85% (both arms)

- **Results**
  - Planned Sample Size: 190
  - Median Follow-up: 5.4 years

- **Abbreviations**
  - CMV: cisplatin/methotrexate/vinblastine
  - dd: dose-dense
  - DFS: disease-free survival
  - EORTC: European Organisation for Research and Treatment of Cancer
  - GC: gemcitabine/cisplatin
  - HR: hazard ratio
  - MVAC: methotrexate/vinblastine/doxorubicin/cisplatin
  - OS: overall survival
  - PFS: progression-free survival
  - PGC: paclitaxel/gemcitabine/cisplatin
  - TTR: time to progression

Data for adjuvant chemotherapy67,75-77 are less compelling than for neoadjuvant chemotherapy. However, some patients benefit from adjuvant chemotherapy, including those who received up-front radical cystectomy and have extensive tumor invasion of the bladder wall or lymph node involvement. For these patients, adjuvant chemotherapy may be considered, even if the patient is not at high risk for recurrence.
was limited in power to show a significant improvement in overall survival with adjuvant chemotherapy, it is possible that some subgroups of patients might benefit from adjuvant chemotherapy. Cisplatin-based neoadjuvant chemotherapy remains the standard of care in MIBC. Table 1 summarizes neoadjuvant and adjuvant clinic trials in MIBC.

**IMMUNE CHECKPOINT INHIBITION IN SOLID TUMORS**

Immune checkpoint inhibition for cancer treatment is an area of growing research. Immune checkpoint pathways regulate T-cell activation to escape antitumor immunity. Immune checkpoint molecules involved in this mechanism include CTLA-4, programmed cell death 1 (PD-1) and its ligands PD-L1 and PD-L2, T-cell immunoglobulin mucin-3, and lymphocyte activation gene-3. Ipilimumab, a monoclonal antibody targeting CTLA-4, a potent immune checkpoint molecule expressed on T cells, demonstrated a survival benefit in a phase III study of patients with metastatic melanoma. PD-1 is an immune inhibitory receptor expressed on several immune-cell subsets, particularly cytotoxic T cells. Recent studies have demonstrated that upregulation of PD-L1 is an important mechanism of immune escape in NMIBC. Overexpression of PD-L1 in UC correlates with high-grade disease and worse clinical outcome. Anti-PD-1 and anti-PD-L1 have an improved toxicity profile compared with historic data from anti-CTLA-4 clinical trials. In September 2014, the U.S. Food and Drug Administration (FDA) granted accelerated approval of pembrolizumab for the treatment of unresectable or metastatic melanoma, and in December 2014 granted accelerated approval to nivolumab for unresectable or metastatic melanoma refractory to standard therapy.

**TREATMENT OF METASTATIC BLADDER CANCER**

The treatment options for metastatic UC are very limited; however, progress has been made in treating metastatic transitional carcinoma of the urothelial tract with combination chemotherapy. The median survival of 15 to 18 months with either MVAC or gemcitabine/cisplatin is substantially better than the 6 to 9 months with single-agent chemotherapy. In fact, 5% of patients have a complete, sometimes durable, remission.

**CLINICAL STUDIES OF PD-1/PD-L1 INHIBITORS IN UROTHELIAL CARCINOMA**

Two clinical trials of checkpoint inhibitors have reported preliminary efficacy in advanced/refractory metastatic UC. Remarkable efficacy and safety was seen in a phase I expansion cohort of 67 patients with heavily pretreated metastatic bladder cancer. Patients received 15 mg/kg of MPDL3280A, a human monoclonal antibody to PD-L1 containing an engineered Fc-domain, later revised to a flat dose of 1,200 mg intravenously every 3 weeks. Response rates were reported by PD-L1 positivity status, defined as 5% or higher of tumor-infiltrating immune cells staining for PD-L1 by IHC. In this study, 27% of tumors were IHC 2- or 3-positive, as defined by expression of PD-L1 on tumor-infiltrating immune cells. The overall response rate for all patients by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was 26%, and was even more remarkable (43%) among patients with PD-L1+ tumor-infiltrating cells. Even among patients whose tumor infiltrating immune cells were PD-L1“, the response rate was 11% as measured by RECIST v1.1. The median time to first response was 42 days (range, 38 to 85 days). Based on these results, MPDL3280A received breakthrough designation by the FDA in June 2014.

A phase 1 trial of pembrolizumab/MK-3475, a PD-1 inhibitor, studied 33 patients with advanced UC expressing PD-L1 in at least 1% of tumor cells by IHC. Patients received 10 mg/kg of pembrolizumab every 2 weeks. A response was seen in 7 out of 29 (24%) evaluable patients, and 64% of patients experienced a decrease in target lesions. With a median follow-up of 11 months, six patients have ongoing responses (median duration 16 to 40 weeks; median not reached).

Multiple PD-1/PDL-1 agents are currently being tested alone or in combination in advanced/refractory UC. Many more trials are in development in earlier disease states, testing agents such as MPDL3280A (NCT02302807) in the first-line setting in cisplatin-ineligible patients with metastatic bladder cancer, nivolumab in the maintenance setting after first-line cisplatin-based chemotherapy, and pembrolizumab in patients with NMIBC (NCT02324582).

**ACKNOWLEDGMENT**

The authors thank Bonnie L. Casey for editorial assistance in the preparation of this manuscript.


76. Paz-Ares L, Solsona E, Esteban E, et al. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: results of the Spanish
Oncology Genitourinary Group (SOGUG) 99/01 study. *J Clin Oncol.* 2010;28 (suppl; abstr LBA4518).


