Bladder cancer is the fifth most common cancer diagnosed in the United States. Prognosis for this disease is dependent on both tumor stage and grade. Radical cystectomy has been the standard treatment for muscle-invasive local disease; however, combined-modality approaches with the use of chemotherapy are gaining momentum with data suggesting survival improvement. Patients with metastatic disease have poor long-term survival rates despite systemic multiagent chemotherapy. A variety of agents, including newer cytotoxic drugs and biologically targeted agents, are under investigation to determine the most effective regimen. The special needs of specific patient populations, such as the elderly, those with a suboptimal performance status, and patients with medical comorbidities have gained more attention. Progress in the treatment of this disease is dependent on supporting ongoing and future clinical trials.

Invasive Disease Surgery
The current standard approach for treatment of muscle-invasive bladder cancer involves radical cystectomy and bilateral pelvic lymphadenectomy. Long-term survival in this setting has been evaluated in multiple surgical series (Table 1).[2-4] The 5-year survival rate is 68% for patients with pathologically organ-confined bladder cancer (pT2), compared with about 25% to 30% for those with extravesicular extension.[3] Analysis of subsets of patients with muscle-invasive disease has determined that both extravesicular disease and node-positive disease are predictive of decreased survival.[4] The poor outcomes seen with surgical resection alone have provided the rationale for investigating a multimodality approach to the management of invasive bladder cancer patients. Learning from the positive outcomes with the utilization of adjuvant or neoadjuvant chemotherapy for a variety of other solid tumors, such trials evaluating perioperative chemotherapy for invasive bladder cancer have been conducted.
Neoadjuvant Chemotherapy
The goal of neoadjuvant chemotherapy is to improve survival via the "eradication" of micrometastatic disease. There are several potential advantages to the neoadjuvant approach, including the facilitation of bladdersparing strategies. In addition, because patients have the bladder in place, oncologists are able to monitor for response during treatment, which has prognostic value.[5] Patients may also be better able to tolerate chemotherapy before surgery when their performance status is higher, whereas they may not be good candidates for chemotherapy following a major surgical procedure. One of the disadvantages of this approach is that patients with chemoresistant disease may progress while receiving neoadjuvant treatment and, therefore, risk progressing to a nonoperable stage due to the delay in providing definitive local therapy. Several randomized clinical trials have been performed to evaluate the use of neoadjuvant platinum-based regimens (Table 2).[6-15] Most of these trials failed to demonstrate a survival advantage, but many of the studies have shortcomings. They included small numbers of patients and are underpowered to detect a difference in survival. Some trials evaluated single-agent chemotherapy, which is known to be less efficacious than combination regimens. Other trials allowed patients to receive either radiation or cystectomy for local therapy, and these two modalities have not been directly compared. Poor local control may impact overall outcomes and affect the results of these studies. Three of these trials, however, strongly suggest an advantage for neoadjuvant chemotherapy.

- **International Collaboration**- A multi-institutional trial randomized 976 patients to either local therapy alone or three cycles of CMV (cisplatin, methotrexate, vinblastine) followed by local therapy.[6] Local therapy consisted of either cystectomy or radiation therapy at the treating physician's discretion, and a portion of patients received both radiation and surgical resection. Eligible patients had T2-4a, N0 or NX, M0 disease, and T3 patients comprised 58% of the study population. Eighty percent of patients in the chemotherapy arm were able to receive all three cycles of neoadjuvant chemotherapy. Study results showed a 3-year absolute survival difference of 5.5% \( (P = .075) \).[6] The survival rate was 55.5% in the chemotherapy arm vs 50% in the local therapy-only arm. A trend toward improved overall survival with neoadjuvant chemotherapy was demonstrated, although these differences did not reach statistical significance. In a follow-up published in abstract form only, after 7.4 years, a 6% statistically significant improvement in overall survival was observed in patients treated with neoadjuvant chemotherapy \( (P = .048) \).[16]

- **INT-0080**- In 2003, Grossman et al reported the results of a Southwest Oncology Group (SWOG)-intergroup randomized neoadjuvant trial, which also suggested a trend toward a survival advantage with combination therapy.[9] In this study, 307 patients with invasive bladder cancer were randomized to either radical cystectomy alone or to three cycles of
MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) followed by radical cystectomy. The study included patients who had T2-4a disease without evidence of lymph node involvement or distant metastasis, and 60% of patients had more advanced disease (either T3 or T4a). By intent-to-treat analysis, the median survival in the surgery arm was 46 months and in the combination therapy arm was 77 months, but this trend failed to reach statistical significance when evaluated by a two-sided stratified log-rank test ($P = .06$). Similar results were found for 5-year overall survival rates. Of note, the study was initially designed to be analyzed using a one-sided stratified log-rank test. At the time of cystectomy, a significant difference in residual disease was noted between the two groups. While only 15% of the cystectomy group were without residual disease, 38% of the combination-therapy group were disease free at cystectomy ($P < .001$), and 85% of patients with pT0 disease at the time of surgery were alive at 5 years. In patients who received neoadjuvant MVAC, the toxicity profile was acceptable with no associated toxic deaths reported, and compared to the surgery-alone arm they did not experience an increase in postoperative complications. This study demonstrated the feasibility of neoadjuvant MVAC in patients with muscle-invasive muscle bladder cancer. A strong trend toward a survival advantage was identified, as well as a reduction in risk of death and an increased disease-free rate at cystectomy.

**Nordic Trials**- Trials-A more recent publication by Sherif et al presented the combined results of two Nordic trials that evaluated neoadjuvant platinum-containing regimens prior to cystectomy.[12] A total of 620 patients with grade 3 T1 disease or T2-4a, NX disease were included, and 51% of enrolled patients had T3 or T4a disease. The first trial included 311 patients and evaluated cisplatin plus doxorubicin vs no chemotherapy, followed by radiation therapy and then surgery.[10] In this right, the second trial included 309 patients and compared cisplatin plus methotrexate followed by surgery to surgery alone.[13] Overall survival at 5 years in the neoadjuvant chemotherapy group was 56% and in the surgery-alone group was 48% ($P = .049$). Although this report is a combination of two trials that differ both in the chemotherapeutic agents used and in the use of radiation therapy, the results support the use of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer.

**Meta-analysis**- A meta-analysis of data for 2,688 individual patients with T2-4a transitional cell carcinoma from 10 trials demonstrated a non-statistically significant 9% reduction in the relative risk of death for patients treated with neoadjuvant chemotherapy, equivalent to an absolute survival increase of 3% at 5 years.[7] While no benefit for neoadjuvant chemotherapy was observed in patients treated with cisplatin alone, patients treated with platinum-based combination chemotherapy regimens had a statistically significant 13% reduction in relative risk of death, equivalent to an absolute survival benefit of 5% at 5 years. Five-year overall survival increased from 45% to 50%, an effect that was seen regardless of the local treatment modality. In summary, although no single trial has conclusively demonstrated the benefit of neoadjuvant chemotherapy, the preponderance of the evidence from multiple randomized trials indicate that neoadjuvant combination chemotherapy should be offered to all patients with muscle-invasive bladder cancer.

**Adjuvant Chemotherapy**
Adjuvant chemotherapy has also been evaluated in an attempt to improve outcome in patients with muscle-invasive bladder cancer. By treating patients postoperatively, definitive local treatment is provided up front without delay. Because the surgery is performed first, complete pathologic staging information can be obtained for making treatment decisions, allowing better patient selection. Some of the limitations of the adjuvant approach include delay in initiating systemic therapy directed toward micrometastatic disease, an inability to assess response to chemotherapy postcystectomy, and difficulties in the delivery of chemotherapy in the adjuvant setting due to surgical complications and decreased patient tolerance.
Randomized Trials—Two randomized trials suggested a benefit for adjuvant therapy for bladder cancer. Skinner et al randomized 91 high-risk patients to cystectomy alone or to cystectomy and adjuvant CISCA (cisplatin, cyclophosphamide, doxorubicin [Adriamycin]).[17] No significant difference in 5-year overall survival was identified, but patients in the chemotherapy arm had a prolonged disease-free survival of 51% vs 34% for cystectomy alone at 5 years ($P = .011$). Although this difference in disease-free survival reached statistical significance, the disease-free survival curves crossed after 7 years. Investigators have suggested that this pattern reflects the fact that the chemotherapy regimen was ineffective for curing disease and merely delayed progression. The subgroup of patients with only one positive lymph node had an improved disease-free survival and overall survival with adjuvant chemotherapy, but no survival benefit was found if two or more lymph nodes were involved.[17] Numerous aspects of this study have been criticized, including its retrospective use of subgroup analyses, small sample size, and questionable statistical methodology. Another small trial was reported by Stockle et al, who randomized patients with pT3-pT4a disease postcystectomy to either observation, three cycles of MVAC, or three cycles of MVEC (methotrexate, vinblastine, epirubicin [Ellence], cisplatin).[18] After 3.5 years, the study was halted because an interim analysis of 49 patients demonstrated a large difference in disease-free survival at 3 years. In an intention-to-treat analysis, the 3.5-year disease-free survival rate was 63% with adjuvant therapy and only 13% with cystectomy alone. A
significant benefit was noted for patients with lymph node-positive disease who received adjuvant chemotherapy. Only 27% of patients who received chemotherapy had evidence of disease progression, as compared to 92% of those treated with surgery alone. In 2000, Sylvester et al published a review of four previously conducted adjuvant chemotherapy trials, including the two described above. The authors determined that these trials contained significant flaws in methodology and are therefore insufficient to justify the routine use of adjuvant chemotherapy.[19] Although the studies performed have included small numbers of patients and are underpowered to demonstrate a survival benefit, current data demonstrate that adjuvant chemotherapy delays recurrence of disease. Current guidelines from the National Comprehensive Cancer Network (NCCN) therefore recommend the use of adjuvant chemotherapy to radiation in patients at high risk for relapse.[20]

Combined-Modality Therapy
Not all patients are candidates for radical cystectomy, either because of significant comorbidities or due to unresectable disease. Other patients refuse surgery for fear of compromising quality of life. As an alternative, these patients may be treated with definitive radiotherapy, but radiation alone has poor curative potential, as data indicate that up to 70% of these patients may experience a local recurrence and 5-year survival rates are generally suboptimal.[21] The addition of chemotherapy to radiation has been shown to improve local control but not overall survival.[8] Typically, a trimodality approach is used in which a maximum transurethral resection (TUR) is performed followed by bladder irradiation concurrent with radiosensitizing chemotherapy. In addition, either neoadjuvant or adjuvant chemotherapy is sometimes given. Periodic cystoscopies are performed to monitor for disease, and if recurrence is noted, patients undergo salvage radical cystectomy. To date, there has not been a randomized trial to address the issue of bladder preservation adequately.

- **Clinical Trials** - Rodel et al evaluated 415 patients with high-risk T1 and T2-4 disease treated with transurethral resection of bladder tumor (TURBT) followed by radiation or radiochemotherapy.[22] The patients underwent restaging TUR 6 weeks after completion of adjuvant therapy, and 72% achieved a complete response. Combination radiation and chemotherapy resulted in higher rates of complete response and survival than radiotherapy alone. Overall survival for all patients was 51% and 31% at 5 and 10 years, respectively. Patients with muscle-invasive tumors had 5- and 10-year overall survival rates of 45% and 29%, respectively. Of surviving patients, 80% maintained their bladders. Patients who did not achieve a complete response following initial therapy underwent radical cystectomy. The major limitation of this series is that patients were not prospectively randomized, hence limiting the conclusions regarding outcome. Shipley et al performed a similar study of 190 patients with muscleinvasive T2-4a disease.[23] Following TURBT and radiochemotherapy, only 35% of patients required radical cystectomy, either because of inability to achieve complete response or because of disease recurrence. The 5- and 10-year overall survival rates were 54% and 36%, respectively, similar to results reported for radical cystectomy. Sternberg et al investigated an alternative approach. A total of 104 patients with T2-4, N0, M0 bladder cancer were treated with three cycles of neoadjuvant MVAC.[24] Patients then underwent treatment with TURBT, partial cystectomy, or radical cystectomy based on response to chemotherapy. Of the 52 patients who underwent TURBT, 44% maintained an intact bladder and 60% were alive at a median follow-up of 56 months. The subset of patients who underwent radical cystectomy after chemotherapy had a survival rate of 38% at a median follow-up of 45 months. In both cohorts, patients had higher survival rates if they were staged as T0 following chemotherapy.

- **Limitations of Bladder Preservation** - Despite encouraging outcomes, there are concerns regarding bladder preservation approaches. Critics of bladder preservation fear that with an intact bladder, metachronous bladder cancers remain and are a source for recurrent and possibly fatal disease. In the series by Shipley et al, 13% of patients experienced recurrent invasive disease necessitating cystectomy.[23] but similar outcomes were observed whether cystectomy was performed for incomplete initial response or for recurrence, suggesting that even with recurrent disease, bladder preservation protocols can achieve similar outcomes to primary cystectomy. The use of neoadjuvant chemotherapy is associated with a lack of up-front pathologic staging and a significant rate of understaging of patients by clinical measures. As many as 30% of clinically T0 tumors following chemotherapy have been found to have residual disease at cystectomy.[25]
Conclusions - Until definitive data are available, it is reasonable to conclude that bladder preservation may be a suitable alternative to radical cystectomy for a select group of patients who achieve complete response to initial therapy. No randomized trials comparing radical cystectomy to a bladder-sparing approach have been conducted. While prospective studies are needed to address the important question regarding the efficacy of organ preservation relative to cystectomy-based therapy, it is important to establish several key metrics to judge the success and suitability of the preservation approaches. Possible measures include not only survival and rates of adequate local control, but also primary disease relapse rates, rates of functioning bladder, development of new bladder primaries, systemic disease control, and feasibility in the general bladder cancer population.

Patients must be carefully selected for bladder-preservation protocols. Ideal candidates have minimal or no carcinoma in situ, have small-volume unifocal disease, have no poor risk features such as hydronephrosis, have undergone maximum TUR,[22,23] and are motivated to participate in regular follow-up.

Metastatic Disease Systemic Chemotherapy
Metastatic bladder cancer is a fatal disease, for which numerous chemotherapeutic regimens have been studied (Tables 3-5).[26-55] In randomized trials, MVAC resulted in superior survival rates as compared to either single-agent cisplatin[26] or CISCA.[27] Thus, MVAC was established as the gold standard against which other regimens are compared (Table 3). The experience with chemotherapy in general and MVAC in particular has been instructive as to the chemosensitivity of urothelial carcinoma, the importance of multiagent chemotherapy, the toxicities and treatment-related deaths associated with cisplatin-based therapy, the effects of clinical prognostic factors on outcome, and the inability of dose escalation with growth factor support in enhancing survival. (Attempts to
improve the efficacy of MVAC by dose escalation with growth factor support failed to result in survival improvement.[28]) In addition, although complete response rates are relatively high, cures are rare in advanced bladder cancer.

### Tailoring Drug Therapy

- **The characteristics of bladder cancer patients require special consideration when designing new treatment regimens.** Given a peak age at presentation between 60 and 70 years, many bladder cancer patients are elderly.[56] With age comes an increased incidence of comorbidities; on average, elderly patients have three different diseases.[57-59] While age alone does not necessarily dictate choice of therapy, a number of comorbid conditions would preclude patients from receiving MVAC or cisplatin-based therapy, even if they had an excellent performance status. GC, which has an efficacy similar to MVAC but is better tolerated, is considered by many to be a reasonable alternative for the elderly. However, cases of nephrotic syndrome and interstitial pneumonitis have been noted in elderly patients treated with gemcitabine.[36] For the elderly and those with comorbidities, effective alternatives to cisplatin-containing regimens are needed. Data are

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Response Rate</th>
<th>Overall Survival</th>
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<tr>
<td>Kaufman[33]</td>
<td>GC</td>
<td>46</td>
<td>41%</td>
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<td>Moore[34]</td>
<td>GC</td>
<td>31</td>
<td>57%</td>
<td>13.2 mo</td>
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<td>Hussain[35]</td>
<td>GC</td>
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<td>65%</td>
<td>16.0 mo</td>
</tr>
<tr>
<td>Liado[36]</td>
<td>GCb</td>
<td>16</td>
<td>44%</td>
<td>NR</td>
</tr>
<tr>
<td>Carles[37]</td>
<td>GCb</td>
<td>17</td>
<td>53%</td>
<td>10.0 mo</td>
</tr>
<tr>
<td>Shannon[39]</td>
<td>GCb</td>
<td>17</td>
<td>59%</td>
<td>10.5 mo</td>
</tr>
<tr>
<td>Nogue-Aliguer[38]</td>
<td>GCb</td>
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<td>56%</td>
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</tr>
<tr>
<td>Dreicer[46]</td>
<td>CT</td>
<td>52</td>
<td>50%</td>
<td>10.6 mo</td>
</tr>
<tr>
<td>Burch[47]</td>
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<td>34</td>
<td>70%</td>
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<tr>
<td>Vaughn[40]</td>
<td>CbT</td>
<td>37</td>
<td>24%</td>
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<tr>
<td>Dreicer[30]</td>
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<td>41</td>
<td>28%</td>
<td>13.8 mo</td>
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<tr>
<td>Redman[48]</td>
<td>CbT</td>
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<td>52%</td>
<td>9.5 mo</td>
</tr>
<tr>
<td>Small[42]</td>
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<td>Sternberg[43]</td>
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<td>60%</td>
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<td>Parameswaran[44]</td>
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<td>Dimopoulos[50]</td>
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<td>52%</td>
<td>8.0 mo</td>
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</tbody>
</table>

C = cisplatin; Cb = carboplatin; G = gemcitabine; T = paclitaxel (Taxol); D = docetaxel; NR = not recorded.
available on carboplatin-based and non-platinum-based therapies. Carboplatin is an attractive alternative in these populations, as it is not nephrotoxic, does not require hydration and is not generally emetogenic, making its administration more convenient. This drug, however, is thought to be less effective than cisplatin in bladder cancer. No phase III randomized studies have been reported that directly compare equal combinations of carboplatin against cisplatin in patients with urothelial carcinoma, and many of the phase II trials are flawed by study design limitations. However, preliminary results from a randomized phase II trial of gemcitabine plus either cisplatin or carboplatin in chemotherapy-naïve patients suggested that the use of cisplatin may result in higher response rates and overall survival.[60] Considering the priorities in drug development for this disease, it is unlikely that a definitive answer will be investigated. In selecting therapies, physicians should consider the performance status, presence of comorbidities, organ dysfunction, and objectives of therapy.

- **Doublets and Triplets** The availability of multiple active agents against urothelial cancer led to studies of a variety of doublets, including gemcitabine and carboplatin, which produced response rates of 44% to 59% and an overall survival of about 10 months, as well as paclitaxel and carboplatin, which produced response rates of 21% to 52% and an overall survival of roughly 9 months (Table 4).[33-50]. These regimens are also feasible and active in patients with renal impairment.[37,40] Both regimens have significant hematologic toxicity, and neurologic toxicity was noted with the paclitaxel doublet. Doublets without a platinum have also been evaluated.[41,43-45] For paclitaxel and gemcitabine, response rates are 50% to 60% with a median overall survival of approximately 14 months. These results appear comparable to those seen with MVAC and GC, although the regimens have not been compared directly. Toxicity with this doublet was primarily hematologic. In an attempt to build on the gemcitabine- or paclitaxel-containing doublets, several combinations of three active chemotherapy agents have been studied in phase II trials (Table 5).[51-55] In general, these phase II trials demonstrated a trend toward relatively higher overall and complete response rates and overall survival as compared with data from doublet chemotherapy regimens. In addition, there is evidence of significant activity of these triplet regimens in patients with visceral involvement—a subgroup of patients who usually respond poorly to treatment.[52] These promising results provided the rationale for a recently completed phase III trial comparing the combination of paclitaxel, gemcitabine, and cisplatin to GC (European Organization for Research and Treatment of Cancer [EORTC] 30987/SWOG).

**Clinically Relevant Prognostic Factors**
As with locally advanced disease, significant prognostic factors have also been identified for patients with metastatic disease who have been predominantly treated with cisplatin-based regimens. Bajorin et al performed a retrospective trial of 203 patients treated with MVAC.[61] The independent prognostic factors most predictive of poor survival included presence of lung, bone, or liver metastases and Karnofsky score < 80%. In patients with neither risk factor, 5-year survival was 33%, but in patients with both visceral metastases and poor performance status, 5-year survival was 0%. The investigators therefore recommended that phase III trials stratify patients according to the number of risk factors, to avoid imbalance in treatment arms. Similar results were seen in patients treated with the combination of paclitaxel, gemcitabine, and cisplatin.[62]
Molecular Predictive/Prognostic Markers for Localized and Metastatic Disease

In various stages of bladder cancer, molecular markers are being evaluated as potential novel prognostic factors in order to better classify patients' risk of progression to invasive disease or systemic recurrence, and some are being evaluated as therapeutic targets (Table 6).[63-67] Other reviews have dealt with this subject in more detail.[63,68] Briefly, multiple genes have been evaluated,[64-67] but the most extensive data pertain to mutations of the tumor suppressor p53, which are associated with genomic instability and formation of carcinoma. Accumulation of p53 within tumor nuclei, when detected by immunohistochemical staining, has been associated with an increased risk of recurrence from bladder cancer in some studies[69] but not others.[64,70] In a multivariate analysis stratified for tumor grade, pathologic stage, and nodal status, alteration in p53 was found to be an independent prognostic factor associated with increased recurrence and reduced survival.[69] Other studies of p53 accumulation in both locally advanced and node-positive disease, however, have not demonstrated a correlation with disease-free survival.[64,70] Based on these observations, an ongoing National Cancer Institute (NCI)-sponsored trial is randomizing patients with invasive bladder cancer and mutations in p53 to adjuvant chemotherapy vs observation following radical cystectomy. The epidermal growth factor (EGF) receptor and HER2/neu are tyrosine kinases involved in cell proliferation, cell survival, angiogenesis, and metastasis.[63,71] The EGF receptor is overexpressed in high-grade invasive transitional cell carcinomas and is associated with more aggressive clinical behavior.[63] Another member of the EGF receptor family, HER2/neu, has also been studied in urothelial tumors. In patients with metastatic bladder cancer, Jimenez et al demonstrated HER2/neu overexpression in 22 (37%) of 60 primary tumors, 20 (63%) of 32 regional...
lymph node metastases, and 6 (86%) of 7 distant metastases.[72] Absence of overexpression of HER2/neu in the primary tumor failed to predict absence of HER2/neu overexpression in distant metastases. The increased expression in distant sites suggests that overexpression is an acquired feature during the metastatic process. Agents targeting the EGF receptor and HER2/neu have been developed, making these targets potentially of therapeutic value as well as prognostic significance. Preclinical studies in a murine model have suggested that the anti-EGF receptor antibody cetuximab (Erbitux) has activity in bladder cancer.[73] Based on prior results showing enhancement of antitumor activity of chemotherapy with the addition of trastuzumab (Herceptin) in patients with metastatic breast cancer overexpressing HER2/neu, studies are under way in advanced bladder cancer to evaluate both single-agent trastuzumab and the addition of trastuzumab to chemotherapy. The Cancer and Leukemia Group B (CALGB) is currently evaluating single-agent trastuzumab, and we have recently completed accrual to an NCI-sponsored trial designed to prospectively evaluate the frequency of HER2/neu overexpression and the feasibility of the combination of trastuzumab with paclitaxel, carboplatin, and gemcitabine.[74]

Other targeted therapies that are under investigation include the epothilone B analogs and the antifolate pemetrexed (Alimta). The epothilones comprise a new class of nontaxane tubulin-polymerizing agents that result in mitotic arrest at the G2/M transition. In both in vitro and in vivo tumor models of numerous solid tumors, epothilone B analogs have been shown to have a high level of antitumor activity, even in paclitaxel-resistant tumors.[75,76] The epothilone B analog ixabepilone is currently being evaluated in an Eastern Cooperative Oncology Group (ECOG) phase II trial (E3800) of previously treated patients with advanced transitional cell urothelial cancer. The antifolate agent pemetrexed has multiple enzyme targets involved in both purine and pyrimidine biosynthesis. It has previously been studied in other tumor types, both as a single agent and in combination with other chemotherapy agents, and it is now being evaluated in advanced urothelial cancer. A phase II trial of pemetrexed was conducted in 31 chemotherapy-naive patients with advanced bladder cancer, 61% of whom had visceral metastases.[77] The response rate was 32%, and median survival was 9.4 months. Toxicity was greater in pemetrexed-treated patients with bladder cancer compared to other primary tumors, which was thought to be due to a higher prevalence of renal insufficiency in these patients, resulting in delayed clearance of pemetrexed and higher rates of neutropenia.[77] The other primary toxicity was hematologic, and therefore, subsequent studies have included folate and vitamin B12 supplementation along with pemetrexed. Pemetrexed is currently being evaluated in combination with gemcitabine in patients with advanced bladder cancer in a phase II study (ECOG-E4802). Conclusions Despite progress in the management of urothelial cancer, there remain several challenges that are driving research efforts. Transforming high response rates into cures, improving multiagent chemotherapy and multimodality treatment, investigating new agents, and defining second-line salvage therapy are some of the current research objectives. Improvement in understanding the biology of urothelial cancers has begun to define molecular markers that are not only prognostic but are also clinically relevant targets for existing or yet to be developed drugs. Progress in systemic therapy is the key to better outcome for newly diagnosed highrisk patients. Finally, particular attention to the toxicity of treatment is needed, as many bladder cancer patients are elderly or have comorbidities. Overall progress is only possible if all involved in the care of this disease support clinical trials.

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