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REVIEW ARTICLE

Treatment of Patients With Metastatic Urothelial Cancer "Unfit" for Cisplatin-Based Chemotherapy

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ABSTRACT

Purpose
Cisplatin-based combination chemotherapy is considered standard first-line treatment for patients with metastatic urothelial carcinoma. However, a large proportion of patients with metastatic urothelial carcinoma are considered "unfit" for cisplatin. The purpose of this review is to define unfit patients and to identify treatment options for this subgroup of patients.

Patients and Methods
In this review, the criteria used to define unfit patients are explored and the results of prospective clinical trials evaluating chemotherapeutic regimens in unfit patients are summarized.

Results
Several phase II trials and a single, large phase III trial have explored chemotherapeutic regimens for the treatment of unfit patients with metastatic urothelial carcinoma. Heterogeneous eligibility criteria have been used to define unfit patients in these studies. A uniform definition of unfit is proposed on the basis of the results of a survey of genitourinary medical oncologists. According to this definition, unfit patients would meet at least one of the following criteria: Eastern Cooperative Oncology Group performance status of 2, creatinine clearance less than 60 mL/min, grade $\geq$ 2 hearing loss, grade $\geq$ 2 neuropathy, and/or New York Heart Association Class III heart failure.

Conclusion
Additional studies to optimize treatment for this important subset of patients are needed. A uniform definition of unfit patients will lead to more uniform clinical trials, enhanced ability to interpret the results of these trials, and a greater likelihood of developing a viable strategy for regulatory approval.

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INTRODUCTION

More than 386,000 patients worldwide are diagnosed with urothelial carcinoma (UC) each year, and more than 150,000 patients will die of the disease.[1] Cisplatin-based combination chemotherapy is considered standard first-line treatment for patients with metastatic UC on the basis of randomized clinical trials.[2-6] However, UC is largely a disease of the elderly[7] and, due to age-associated (and disease-associated) impairment in renal function and performance status (PS), approximately 30% to 50% of patients are ineligible for cisplatin.[8] As a result, a disconnect has emerged between the efficacy of treatment as demonstrated by randomized trials and the effectiveness of treatment when applied to the general population of patients with UC. Investigators, long appreciating this disconnect, have designed trials specifically for patients "unfit" for cisplatin-based chemotherapy.[9-14]

CISPLATIN VERSUS CARBOPLATIN IN UC

Although there have been no completed randomized phase III trials comparing cisplatin-based chemotherapy with carboplatin-based therapy in patients with advanced UC, multiple randomized phase II trials have reported superior activity with cisplatin-based regimens (Table 1).[15-17] A meta-analysis of randomized trials comparing cisplatin- versus carboplatin-based therapy in UC revealed that cisplatin-based chemotherapy was associated with a significant improvement in the likelihood of achieving a complete response (relative risk, 3.54; 95% CI, 1.48 to 8.49; $P = .004$) and overall response (relative risk, 1.33; 95% CI, 1.04 to 1.71; $P = .025$).[18] The National Comprehensive Cancer Network guidelines recommend gemcitabine plus cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) as first-line chemotherapy for patients with metastatic UC and state that, "carboplatin

Table 1. Randomized Trials Comparing Cisplatin- and Carboplatin-Based Combinations in Metastatic Urothelial Carcinoma

Reference	No. of Patients	Phase	Treatment Arm	OR (%)	*P*	CR (%)
Bellmunt et al[15]	47	II	MVAC	52	.3	13
			M-CAVI	39		0
Petrioli et al[17]	57	II	MVE-cisplatin	71	.04	25
			MVE-carboplatin	41		11
Dogliotti et al[16]	110	II	Gemcitabine + cisplatin	49	N/P	15
			Gemcitabine + carboplatin	40		2
Dreicer et al[3]	85*	III	MVAC	36	.6	13
			Paclitaxel + carboplatin	28		3

Abbreviations: CR, complete response; M-CAVI, methotrexate, carboplatin, vinblastine; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; MVE, methotrexate, vinblastine, epirubicin; N/P, not provided; OR, overall response.
*Trial closed early because of poor accrual.

should not be substituted for cisplatin in patients with normal renal function." Therefore, simply developing carboplatin-based regimens for all comers with metastatic UC, as has been the approach in other cancers (such as ovarian cancer and non–small-cell lung cancer), is not supported for the treatment of UC.

DEFINING UNFIT PATIENTS

Recognizing that a large proportion of patients with UC are unfit for cisplatin, in 1997 the European Organisation for Research and Treatment of Cancer (EORTC) conducted a survey of 40 genitourinary oncologists in an attempt to define "cisplatin ineligibility."[19] Of 37 respondents, 28 considered preserved renal function and WHO PS of 0 or 1 as prerequisites for cisplatin-based chemotherapy. Adequate renal function for cisplatin was considered to be either a measured or a calculated creatinine clearance of $\geq$ 60 mL/min.

Multiple clinical trials have subsequently been performed in the unfit population by using heterogeneous eligibility criteria (Table 2). Bellmunt et al[9,10,12] have completed several trials in patients with metastatic UC unfit for cisplatin-based chemotherapy as defined by either a creatinine clearance less than 60 mL/min or a WHO PS of 2. Other investigators[11,13,14,20-23] have used different eligibility criteria, including old age, a solitary kidney, poor functional status, comorbidities, or impaired renal function alone with intact PS. Although the majority of these criteria defining cisplatin ineligibility are rooted in common clinical practice, a discussion of the available data to support or refute inclusion of each parameter is warranted, particularly in an effort to establish a uniform definition.

Age

Although age (eg, $>$ 75 years old) has been included as a component of the definition of unfit in several trials in UC, there is little evidence to support routine exclusion of elderly patients from cisplatin-based therapy on the basis of age alone.[24] A report of 15 patients age 70 to 79 years with invasive bladder cancer treated with neoadjuvant cisplatin (80 to 100 mg/m^2) plus radical radiotherapy revealed that this regimen could be administered to septuagenarians without causing excessive morbidity.[25] Large randomized trials exploring cisplatin-based regimens in non–small-cell lung cancer have demonstrated similar efficacy and only slightly increased toxicity between elderly patients ($\geq$ 65 or 70 years old) and younger patients.[26-28] Although similar analyses are not currently available in patients with bladder cancer, age has not been shown to be a prognostic factor for survival in patients with advanced bladder cancer treated with cisplatin-based chemotherapy.[29-31]

Although advanced age alone may not be associated with an increased likelihood of developing severe toxicities with cisplatin-based chemotherapy, more thorough assessments of functional capacity in the elderly could potentially identify subsets of patients at particularly high risk.[32] Comprehensive geriatric assessments have been incorporated in a few trials in metastatic UC to date but have not been used in trials exploring cisplatin-based therapy.[20,33] Prospective evaluation of such tools to refine the definition of cisplatin ineligibility is warranted.

Renal Function

Renal function declines by approximately 1% per year beyond age 30 to 40 years such that renal function has declined by approximately 40% at the median age of diagnosis of advanced UC.[34] There is a high rate of renal impairment due to age, bladder cancer–related urinary tract obstruction, and smoking-related vascular disease in patients with advanced UC. For example, an analysis of patients undergoing radical cystectomy for bladder cancer revealed that 28% of all patients had a creatinine clearance of less than 60 mL/min, and more than 40% of patients age $\geq$ 70 years had a creatinine clearance of less than 60 mL/min.[8] Cisplatin is routinely avoided in patients with renal impairment because pre-existing renal impairment is a risk factor for cisplatin-induced nephrotoxicity.

The optimal method of measurement of renal function that balances cost, convenience, and accuracy has been the subject of debate. The International Society for Geriatric Oncology Task Force on Renal Safety in the Elderly recommends the use of the Cockroft-Gault equation (which includes age, body mass, creatinine, and sex) for calculating creatinine clearance in most elderly patients, although it suggests that the Modification of Diet in Renal Disease equation may be preferred in patients with chronic renal impairment.[35] The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (which incorporates creatinine, age, sex, and race) has recently been shown to perform better than the Modification of Diet in Renal Disease equation (which also incorporates creatinine, age, sex, and race) in estimating glomerular filtration rate in a data set of more than 8,000 patients and may be the preferred equation for clinical use; further evaluation in patients with malignancies is warranted.[36] The optimal threshold level of renal function that should preclude cisplatin

Table 2. Clinical Trials of First-Line Systemic Therapy in "Unfit" Patients With Metastatic Bladder Cancer

Reference or Trial Name	Regimen	Definition of Unfit	No. of Patients	ORR (%)	Median PFS (months)	Median OS (months)
Bamias et al[20]	Gemcitabine + carboplatin	At least one of the following: ECOG PS ≥ 2 Creatinine clearance of < 50 mL/min Comorbidities precluding cisplatin administration	34	34	4.4	9.8
Bellmunt et al[9]	Methotrexate + carboplatin + vinblastine	At least one of the following: WHO PS 2 Creatinine clearance of < 60 mL/min	23	48	N/R	N/R
Bellmunt et al[10]	Gemcitabine + carboplatin	At least one of the following: WHO PS 2 Creatinine clearance of < 60 mL/min	16	44	N/R	N/R
Bellmunt et al[11]	Sunitinib	Both of the following: ECOG PS ≥ 1 Creatinine clearance of > 30 mL/min and < 60 mL/min	16	8	5.9	N/R
Calabrò et al[59]	Gemcitabine + paclitaxel	All of the following: WHO PS 0-2 Creatinine clearance of ≥ 40 mL/min	54	37	5.8	13.2
Carles et al[21]	Gemcitabine + oxaliplatin	Creatinine clearance of > 30 mL/min	46	48	5	6.5
De Santis et al[12]	Gemcitabine + carboplatin	At least one of the following: WHO PS 2 Creatinine clearance of > 30 mL/min and < 60 mL/min	88	38	5.8	9.3
De Santis et al[12]	Methotrexate + carboplatin + vinblastine	At least one of the following: WHO PS 2 Creatinine clearance of > 30 mL/min and < 60 mL/min	87	20	4.2	8.1
Galsky et al[13]	Dose-dense doxorubicin + gemcitabine followed by paclitaxel + carboplatin	At least one of the following: Serum creatinine > 1.5 mg/dL Creatinine clearance of > 30 mL/min and < 60 mL/min Prior nephrectomy	25	56	N/A	15
Linardou et al[14]	Gemcitabine + carboplatin	At least one of the following: ECOG PS 3 Age older than 75 years Creatinine clearance of < 50 mL/min	56	36	4.8	7.2
Ricci et al[55]	Gemcitabine + epirubicin	At least one of the following: ECOG PS ≥ 2 Age ≥ 75 years Creatinine clearance of < 60 mL/min	38	40	4.8	8
Turkolmez et al[56]	Gemcitabine + vinorelbine	Creatinine clearance of < 50 mL/min	21	47.6	5	15
Small et al[22]	Methotrexate + vinblastine + mitoxantrone + carboplatin	All of the following: Karnofsky performance status ≥ 60% Creatinine clearance ≥ 30 mL/min Cardiac ejection fraction ≥ 40%	23	57	N/R	10
Vaughn et al[23]	Paclitaxel + carboplatin	Serum creatinine of 1.6-4.0 mg/dL	42	24	3	7.1
VINCENT	Vinflunine + gemcitabine versus placebo + gemcitabine	At least one of the following: New York Heart Association Class III-IV congestive heart failure Creatinine clearance of ≤ 60 mL/min	N/A	N/A	N/A	N/A

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N/A, not available; N/R, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; VINCENT, Vinflunine in Cisplatin-Ineligible Patients Trial.

is also unclear; however, a review of cisplatin-based chemotherapy trials listed on clinicaltrials.gov as of December 14, 2010, confirms the standard threshold of a creatinine clearance of ≥ 60 mL/min as the most commonly used inclusion criterion.

Solitary Kidney

The presence of a solitary kidney has been included in the definition of unfit in some clinical trials in advanced UC. This situation is most applicable to patients with UC of the ureter or renal pelvis who have previously undergone nephroureterectomy. The renal safety of cisplatin-based chemotherapy in 60 patients with metastatic urothelial cancer and a solitary kidney was recently evaluated in a prospective trial.[37] This study revealed a significant decline in estimated glomerular filtration rate after three cycles of treatment, although the decline in estimated glomerular filtration rate correlated with baseline renal insufficiency and led to clinically significant renal toxicity in only three patients, suggesting that cisplatin need not be uniformly excluded in this population. However, attention to adequate hydration is particularly important to minimize morbidity in this subset. Splitting the dose of cisplatin over 2 days is also often considered, acknowledging

that the impact of split-dose cisplatin on the efficacy of treatment has not been definitively defined.[38]

Functional Status and Comorbidities

Many clinical trials of patients with UC unfit for cisplatin have included patients with a poor functional status. Most commonly, patients with an Eastern Cooperative Oncology Group (ECOG) or WHO performance status of 2 have been included. The safety and efficacy of cisplatin- versus carboplatin-based therapy in patients with a poor performance status has not been evaluated prospectively in patients with UC. However, poor functional status has been associated with increased toxicity and decreased efficacy in patients with metastatic UC treated with cisplatin-based chemotherapy.[29,39]

The relationship between comorbidities, treatment-related toxicities, and efficacy of therapy is complex and has not been adequately explored in patients with advanced solid tumors.[40] Studies exploring the impact of increased comorbidities, as measured by a variety of indices, on clinical outcomes in patients treated with cisplatin who have other advanced solid tumors have generally revealed no clear relationship with adverse events.[41-47] Few trials have included comorbidity scores as inclusion criterion for enrollment in clinical trials.[48,49] At least one study in unfit patients with metastatic UC has included patients with congestive heart failure. The New York Heart Association Class III designation of heart failure indicates marked limitation of any activity; the patient is comfortable only at rest. Such patients are generally intolerant to the hydration schemes used with cisplatin, and other chemotherapeutic agents are typically substituted.

The use of cisplatin in patients with comorbidities that may be exacerbated because of cisplatin-related toxicities (eg, neurotoxicity and ototoxicity) is generally avoided in clinical practice. Risk factors for cisplatin-induced ototoxicity include renal impairment, older age, and pre-existing hearing loss.[50] With cisplatin use, hearing loss occurs mainly at high frequencies and at cisplatin dosages greater than 60 mg/m^2.[51] Common Terminology Criteria for Adverse Events (CTCAE) version 4[52] grade 2 auditory loss is defined as decibel losses of 25 dB at two contiguous frequencies. Given that cisplatin can frequently induce hearing loss of 19 to 20 dB, the use of cisplatin in patients with baseline grade 2 hearing loss is likely to induce additional damage potentially resulting in grade $\geq$ 3 hearing loss.

Cisplatin-induced peripheral neuropathy is increased in patients with pre-existing neuropathy.[53] The CTCAE version 4 defines grade 2 neuropathy as moderate symptoms limiting instrumental activities of daily living and grade 3 neuropathy as severe symptoms limiting self-care activities of daily living. The presence of baseline grade $\geq$ 2 peripheral neuropathy is generally an exclusion criterion in clinical trials that explore cisplatin-based regimens.

Working Group Definition

In an effort to develop a consensus definition of patients with metastatic UC unfit for cisplatin-based chemotherapy, we assembled a working group and conducted a survey of 120 international academic and community-based genitourinary oncologists. The survey questions and results are shown in Table 3. Responses were returned from 65 (54%) of 120 of those surveyed. The majority of respondents (62%) cited prior experience in the development and conduct of clinical trials for cisplatin-ineligible patients with metastatic UC. On the basis of the survey results and the available literature regarding the safety of cisplatin in various patient subsets, we generated a proposed definition of unfit patients with metastatic UC (Table 4) with the goal of establishing uniform eligibility criteria for clinical trials moving forward.[54]

Table 3. Results of "Unfit" Bladder Cancer Survey (n = 65)

Parameter	No. of Responses	%
How should renal function be measured?		
Measured creatinine clearance	12	19
Calculated creatinine clearance	31	48
Measured GFR	0	
Any of these methods	22	33
What threshold creatinine clearance should be used to define "cisplatin-ineligible" patients?		
< 60 mL/min	27	42
< 55 mL/min	4	6
< 50 mL/min	22	34
< 45 mL/min	12	19
What threshold age should be used to define "cisplatin-ineligible" patients?		
Age should not be used as a criterion	53	82
> 65 years	0	
> 70 years	3	5
> 75 years	3	5
> 80 years	5	8
Other	1	2
What threshold performance status should be used to define "cisplatin-ineligible" patients?		
Performance status should not be used as a criterion	9	14
ECOG PS $\geq$ 1	8	12
ECOG PS 2	21	32
ECOG PS $\geq$ 2	27	42
What comorbidities should be used to define "cisplatin-ineligible" patients?		
Comorbidities (other than renal impairment) should not be used as criteria	18	28
Heart failure	30	46
Hearing loss	27	42
Solitary kidney	14	22
Other	13	20
Have you previously been involved with clinical trials enrolling cisplatin-ineligible patients with metastatic bladder cancer?		
Yes	40	62
No	25	39
What is your preferred chemotherapy regimen for "cisplatin-ineligible" patients?		
Gemcitabine + carboplatin	48	74
Paclitaxel + carboplatin	5	8
Gemcitabine	2	3
Paclitaxel	1	2
Other	9	14

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; PS, performance status.

PHASE II TRIALS IN UNFIT PATIENTS

Multiple small phase II trials have explored a variety of treatment regimens in cisplatin-ineligible patients with metastatic UC (Table 2).

Table 4. Proposed Working Group Eligibility Criteria for Clinical Trials Enrolling Patients With Metastatic Urothelial Carcinoma "Unfit" for Cisplatin-Based Chemotherapy

Eligibility Criteria (at least one of the following)
WHO or ECOG PS of 2 or Karnofsky PS of 60%-70%
Creatinine clearance (calculated or measured) $<$ 60 mL/min
CTCAE v4 grade $\geq$ 2 audiometric hearing loss
CTCAE v4 grade $\geq$ 2 peripheral neuropathy
NYHA Class III heart failure

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status.

The most common regimen explored has been the doublet of gemcitabine plus carboplatin (GC), evaluated in at least three phase II trials.[10,14,20] Other small trials[13,21,23] have evaluated a variety of approaches, including integrating taxanes and oxaliplatin and administering treatment in a dose-dense sequential fashion. Regimens devoid of platinum agents have also been explored.[55,56] These small phase II trials have generally demonstrated that chemotherapy can be administered safely in the unfit population with an overall response rate of approximately 30% to 40% and a median progression-free survival of approximately 4 to 5 months.

A novel clinical trial paradigm recently assessed the activity of single-agent sunitinib as first-line treatment in patients with metastatic UC ineligible for cisplatin (on the basis of either a PS of $\geq$ 1 or creatinine clearance $>$ 30 mL/min and $<$ 60 mL/min).[11] In a preliminary analysis of 37 patients, sunitinib was associated with a clinical benefit rate (partial response + stable disease $>$ 3 months) of 62% and a median progression-free survival of 5.9 months, comparable with results achieved with historical controls treated with cytotoxic chemotherapy. Additional approaches exploring targeted therapies in an effort to delay and/or replace the need for cytotoxic chemotherapy in this population warrant further investigation.

PHASE III TRIALS IN UNFIT PATIENTS

EORTC 30986 is a randomized phase II/III trial of GC versus methotrexate and vinblastine plus carboplatin (M-CAVI) in unfit patients (WHO PS of 2 and/or creatinine clearance of 30 to 60 mL/min) with metastatic bladder cancer.[12] The phase II portion was designed to evaluate the response rate and the severe acute toxicity rate of both regimens. Severe acute toxicity was defined as the occurrence of any of the following events: grade 3 or 4 mucositis, grade 4 thrombocytopenia associated with bleeding, neutropenic fever, grade 3 or 4 renal toxicity, or death. The phase II portion reported a severe acute toxicity rate of 13.6% with GC and 23% with M-CAVI while the overall response rates were 42% for GC and 30% for M-CAVI, meeting criteria for expansion to phase III. Notably, there was a high rate of severe acute toxicities in patients with both impaired renal function and poor PS treated with either regimen.

The results of the phase III portion of EORTC 30986, the first phase III study completed in this patient population, were presented at the 46th Annual Meeting of the American Society of Clinical Oncology in 2010.[57] Both treatment arms enrolled 119 patients, and the criteria for cisplatin ineligibility were equally distributed among the arms (PS 2, 18%; renal impairment, 56%; both, 26%). There was no significant difference in the progression-free survival (GC, 5.8 months; M-CAVI, 4.2 months; hazard ratio, 1.04; 95% CI, 0.8 to 1.35; $P = .78$) or the overall survival (GC, 9.3 months; M-CAVI, 8.1 months; hazard ratio, 0.94; 95% CI, 0.72 to 1.22; $P = .64$) between the treatment arms. The GC arm was generally better tolerated, although it was associated with a higher incidence of grade 4 thrombocytopenia. The M-CAVI arm was associated with a higher incidence of neutropenic fever, grade 3 mucositis, and treatment-related deaths. This trial provides a benchmark for clinical outcomes in unfit patients.

The only other phase III trial to be initiated in unfit patients with metastatic bladder cancer was the Vinflunine in Cisplatin-Ineligible Patients Trial (VINCENT), an industry-sponsored trial of vinflunine plus gemcitabine versus placebo plus gemcitabine. Eligibility for the VINCENT trial was based on either renal impairment (creatinine clearance $\leq$ 60 mL/min) or New York Heart Association Class III to IV congestive heart failure. Patients were required to have an ECOG PS of 0 to 2. This trial was designed to accrue 450 patients; however, the trial was prematurely closed to accrual on the basis of a decision by the sponsor. An ongoing trial is evaluating the combination of vinflunine plus gemcitabine versus vinflunine plus carboplatin in patients unfit for cisplatin.

TREATMENT OF UNFIT PATIENTS: GENERAL CONSIDERATIONS

On the basis of the results of EORTC 30986, and consistent with conventional clinical practice (Table 3), gemcitabine plus carboplatin represents a reasonable first-line treatment regimen for patients with metastatic UC unfit for cisplatin. Clearly, the declaration of a creatinine clearance of less than 60 mL/min as an exclusion criterion for cisplatin-based chemotherapy is meant to establish uniformity with regard to eligibility criteria for clinical trials and should not replace clinical judgment when the use of cisplatin in patients with borderline renal function is being considered, particular in those patients with potentially curable disease (eg, clinical stage T4b disease, lymph node only metastases). A small prospective trial[58] has demonstrated the safety and feasibility of administration of gemcitabine plus split-dose cisplatin in patients with metastatic UC and a creatinine clearance $\geq$ 45 mL/min, although the impact of this cisplatin schedule on efficacy has not been extensively explored.[38] In the absence of a randomized trial, the relative risks and benefits of split-dose cisplatin-based chemotherapy versus carboplatin-based chemotherapy in patients with impaired renal function is unclear.

There are currently no randomized data to support the use of carboplatin-based regimens in patients with UC treated in the neoadjuvant or adjuvant settings, and observation may be most appropriate for such patients if cisplatin cannot be administered safely. This represents an area of need for active clinical investigation.

Given the high rate of severe acute toxicity (approximately 25%) in patients with both borderline PS and impaired renal function in EORTC 30986 treated with either GC or M-CAVI, the optimal treatment of this small subset of patients remains to be elucidated. Clinical trials exploring noncytotoxic regimens or single-agent cytotoxic therapy in this population could be considered, although significant barriers exist to enrolling this small subgroup of patients in independent trials. In the absence of a clinical trial, single-agent chemotherapy or best supportive care are also reasonable considerations.

In conclusion, a large proportion of patients with metastatic UC are unfit for cisplatin. Efforts of investigators to develop therapies for this subset of patients have recently culminated in the first completed phase III trial in this population, confirming the doublet of gemcitabine plus carboplatin as a reasonable first-line regimen. However, several challenges remain, including standardization of the definition of unfit patients (Table 4), which will lead to more uniform clinical trials, enhanced ability to interpret the results of these trials, and a greater likelihood of developing a viable strategy for regulatory approval. Optimally, novel agents with improved efficacy and tolerability may eliminate the need to evaluate patients with metastatic bladder cancer in separate cisplatin-eligible and cisplatin-ineligible cohorts in the future.

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