VOLUME 30 · NUMBER 2 · JANUARY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy: EORTC Study 30986

Maria De Santis, Joaquim Bellmunt, Graham Mead, J. Martijn Kerst, Michael Leahy, Pablo Maroto, Thierry Gil, Sandrine Marreaud, Gedske Daugaard, Iwona Skoneczna, Sandra Collette, Julie Lorent, Ronald de Wit, and Richard Sylvester

Author affiliations appear at the end of this article.

Submitted June 3, 2011; accepted October 20, 2011; published online ahead of print at www.jco.org on December 12, 2011.

Supported by Grants No. 2U10 CA11488-28 through 5U10 CA011488-40 from the National Cancer Institute (Bethesda, MD), by the European Organisation for Research and Treatment of Cancer Charitable Trust and by Eli Lilly (study code B9E-MC-S018).

Presented in part at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, June 4-8, 2010 (preliminary results of phase III); presented at the ASCO Genitourinary Cancers Symposium, San Francisco, CA, February 14-16, 2008, and at the 44th Annual Meeting of ASCO, Chicago, IL, May 30-June 3, 2008 (results of phase II).

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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Corresponding author: Maria De Santis, MD, Kaiser Franz Josef Hospital and ACR-ITR Vienna/CEADDP and LBI-ACR Vienna-CTO, Kundratstraße 3,Vienna, Austria 1100; e-mail: maria.desantis@wienkav.at.

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0732-183X/12/3002-191/$20.00

DOI: 10.1200/JCO.2011.37.3571

ABSTRACT

Purpose
This is the first randomized phase II/III trial comparing two carboplatin-based chemotherapy regimens in patients with urothelial cancer who are ineligible ("unfit") for cisplatin chemotherapy.

Patients and Methods
The primary objective of the phase III part of this study was to compare the overall survival (OS) of chemotherapy-naive patients with measurable disease and an impaired renal function (glomerular filtration rate < 60 but > 30 mL/min) and/or performance score of 2 who were randomly assigned to receive either gemcitabine/carboplatin (GC) or methotrexate/carboplatin/vinblastine (M-CAVI). To detect an increase of 50% in median survival with GC compared with M-CAVI (13.5 *v* 9 months) based on a two-sided log-rank test at error rates $\alpha = .05$ and $\beta = .20$, 225 patients were required. Secondary end points were overall response rate (ORR), progression-free survival (PFS), toxicity, and quality of life.

Results
In all, 238 patients were randomly assigned by 29 institutions over a period of 7 years. The median follow-up was 4.5 years. Best ORRs were 41.2% (36.1% confirmed response) for patients receiving GC versus 30.3% (21.0% confirmed response) for patients receiving M-CAVI ($P = .08$). Median OS was 9.3 months in the GC arm and 8.1 months in the M-CAVI arm ($P = .64$). There was no difference in PFS ($P = .78$) between the two arms. Severe acute toxicity (death, grade 4 thrombocytopenia with bleeding, grade 3 or 4 renal toxicity, neutropenic fever, or mucositis) was observed in 9.3% of patients receiving GC and 21.2% of patients receiving M-CAVI.

Conclusion
There were no significant differences in efficacy between the two treatment groups. The incidence of severe acute toxicities was higher for those receiving M-CAVI.

J Clin Oncol 30:191-199. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Cisplatin-containing combination chemotherapy has been the standard of care in the treatment of advanced or metastatic urothelial cancer (UC) since the late 1980s. However, more than 50% of patients are ineligible ("unfit") for cisplatin because of poor performance status (PS), impaired renal function, or comorbidity that forbids high-volume hydration.[1-4] So far, no standard chemotherapy has been established for this patient group.[5]

To the best of our knowledge, the first randomized phase II/III trial in this setting has now been conducted by the European Organisation for Research and Treatment of Cancer-Genitourinary Tract Cancer (EORTC GU) group. Patients with UC were categorized as ineligible ("unfit") for cisplatin-containing chemotherapy[6,7] because they had a PS of 2 and/or impaired renal function (glomerular filtration rate [GFR] < 60 mL/min). Two carboplatin-based chemotherapy regimens—gemcitabine/carboplatin (GC) and methotrexate/carboplatin/vinblastine (M-CAVI)—were compared. Carboplatin is a less nephrotoxic platinum analog than cisplatin. M-CAVI is a well-tolerated and widely used palliative combination chemotherapy regimen.[7-12]

Several new agents and combinations have been explored to reduce toxicity and improve efficacy in the treatment of UC. Among them is gemcitabine, a pyrimidine antimetabolite.[13-17] Gemcitabine is well tolerated and can be safely used in patients with impaired renal function (GFR ≥ 30 mL/min).[18] Trial history and background of this study were presented earlier together with the analysis of the phase II results.[19]

This phase II/III study was initiated to evaluate the efficacy and toxicity of the two treatment arms. The phase II part included 178 patients. Both treatment combinations were shown to be active and safe in this group of unfit patients, and it was decided to proceed to phase III, the results of which are reported here.

PATIENTS AND METHODS

Patients

Detailed inclusion and exclusion criteria were published elsewhere.[19] In short, patients with histologically proven UC of the urinary tract (including renal pelvis, ureter, and urinary bladder), unresected lymph nodes (N+), distant metastases (M1, stage IV), or unresectable primary bladder cancer (T3-4) with measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST)[20] were included. No previous cytotoxic or biologic systemic treatment was allowed. All patients had to be ineligible (unfit) for cisplatin-based chemotherapy, defined by a WHO PS of 2 and/or impaired renal function (GFR > 30 but < 60 mL/min). GFR could be assessed by direct measurement (EDTA or creatinine clearance) if available or by calculation from serum or plasma creatinine.[21]

The protocol was approved by the ethics review boards of the participating institutions. Before random assignment, written informed consent was obtained from all patients in accordance with the Declaration of Helsinki, applicable guidelines for good clinical practice, or laws and regulations of the countries where the study was conducted, whichever represented the greater protection of the individual.

Treatment Schedule

Patients who were given M-CAVI received methotrexate 30 mg/m^2 intravenously (IV) on days 1, 15, and 22. It was omitted in patients presenting with pleural effusions or ascites until complete resolution. Carboplatin was dosed in milligrams (4.5 × [GFR + 25]) and given over 1 hour IV on day 1 in

Table 1. Patient and Disease Characteristics

Characteristic	GC (n = 119)		M-CAVI (n = 119)		Total (N = 238)	
	No.	%	No.	%	No.	%
Age, years						
Median	70		72		71	
Range	36-87		34-86		34-87	
Sex						
Male	90	75.6	96	80.7	186	78.2
Female	29	24.4	23	19.3	52	21.8
Associated chronic disease						
No	59	49.6	64	53.8	123	51.7
Yes	60	50.4	55	46.2	115	48.3
WHO PS						
0	20	16.8	19	16.0	39	16.4
1	46	38.7	46	38.7	92	38.7
2	53	44.5	54	45.4	107	45.0
GFR, mL/min						
Median	50.0		48.0		49.0	
Range	30.8-128.0		30.0-126.0		30.0-128.0	
Reason unfit for cisplatin therapy						
WHO PS 2	21	17.6	21	17.6	42	17.6
GFR 30-60 mL/min	66	55.5	65	54.6	131	55.0
Both	32	26.9	33	27.7	65	27.3
Site of primary tumor						
Bladder	90	75.6	87	73.1	177	74.4
Renal pelvis	12	10.1	17	14.3	29	12.2
Ureter	12	10.1	11	9.2	23	9.7
Urethra	3	2.5	2	1.7	5	2.1
Other	2	1.7	2	1.7	4	1.7
Liver metastases						
No	99	83.2	90	75.6	189	79.4
Yes	20	16.8	29	24.4	49	20.6
Visceral metastases						
No	64	53.8	53	44.5	117	49.2
Yes	55	46.2	66	55.5	121	50.8
Bajorin risk group						
0	45	37.8	36	30.3	81	34.0
1	40	33.6	46	38.7	86	36.1
2	34	28.6	37	31.1	71	29.8

Abbreviations: GC, gemcitabine/carboplatin; GFR, glomerular filtration rate; M-CAVI, methotrexate/carboplatin/vinblastine; PS, performance status.

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both treatment arms, once every 4 weeks. Vinblastine 3 mg/m^2 IV was given on days 1, 15, and 22. Patients allocated to the GC arm received gemcitabine 1,000 mg/m^2 over 30 minutes IV on days 1 and 8, followed by carboplatin on day 1, every 3 weeks. Treatment was continued until disease progression or intolerable toxicity. In case of complete response, two more cycles were to be given. Granulocyte colony-stimulating factor was allowed and documented but was reserved for those patients in whom the recommended dose modifications were insufficient. Detailed protocol requirements for dose adjustments and dose delays as well as information about amendments were detailed in a previous article in the *Journal of Clinical Oncology*.[19]

Treatment Evaluation

The main objective of this phase III study was to compare overall survival (OS) in the two treatment groups. Adverse effects and quality of life (QoL) were secondary end points. Furthermore, response rates and progression-free survival (PFS) were also assessed. The main end points were also analyzed taking into account the stratification factors (WHO PS, renal function, and institution) and, in a post hoc analysis, the Bajorin risk groups.[22] Severe acute toxicity (SAT) was defined by death resulting from toxicity, grade 4 thrombocytopenia with bleeding, grade 3 to 4 renal toxicity, neutropenic fever, or grade 3 to 4 mucositis. All patients were evaluated by the study coordinators who took into account eligibility, response to treatment, and the date of first progression and/or death.

Statistical Considerations

The median duration of survival on the M-CAVI arm was assumed to be 9 months. To detect an increase of 50% in median survival on the GC arm to 13.5 months, based on a two-sided log-rank test at error rates $\alpha = .05$ and $\beta = .20$, a total of 192 deaths were required. Assuming that 85% of the patients would be followed to death, a total of 225 patients were required. With an expected entry rate of 45 patients per year, the required number of patients would be entered in 5 years.

Patients were centrally randomly assigned at the EORTC Headquarters to receive either GC or M-CAVI by using the minimization technique, with stratification for WHO PS, renal function (GFR), and institution. No formal interim efficacy analyses were planned.

OS in the two treatment groups was compared by using all randomly assigned patients on the basis of an intent-to-treat analysis; a sensitivity analysis was also performed in all patients according to WHO PS and GFR. In a post hoc attempt to evaluate outcome measures in this unfit patient population by using the Bajorin risk groups on the basis of PS and visceral metastases, PS 0 and 1 were transformed into Karnofsky performance status $\geq$ 80% and PS 2 into Karnofsky performance status less than 80%. When adding presence or absence of visceral metastases, patients were regrouped into three prognostic groups depending on their number of adverse prognostic factors (Bajorin risk groups 0, 1, or 2).[19,22]

RESULTS

A total of 238 patients were recruited by 29 centers (12 countries) between March 2001 and March 2008; 119 patients were randomly assigned to each treatment group (GC or M-CAVI). Two ineligible patients on M-CAVI had no lesions. The median follow-up was 4.5 years, and the maximum follow-up was 7.8 years.

Patient characteristics were generally well balanced between the arms, as were the stratification factors. There was only a slight imbalance in the distribution of liver and visceral metastases ($P = .15$; Table 1). Of the randomly assigned patients, 236 of 238 started the protocol treatment (one patient refusal, one patient died before the first cycle of treatment; Fig 1). The majority of patients received four cycles of chemotherapy. Fifty-one patients (21.4%) stopped the treatment due to toxicity, 25 (21.0%) in the GC arm and 26 (21.8%) in the M-CAVI arm. Dose reductions were required in 78.8% (72.9% in the GC arm and 84.7% in the M-CAVI arm) and delays were required in 65.7%

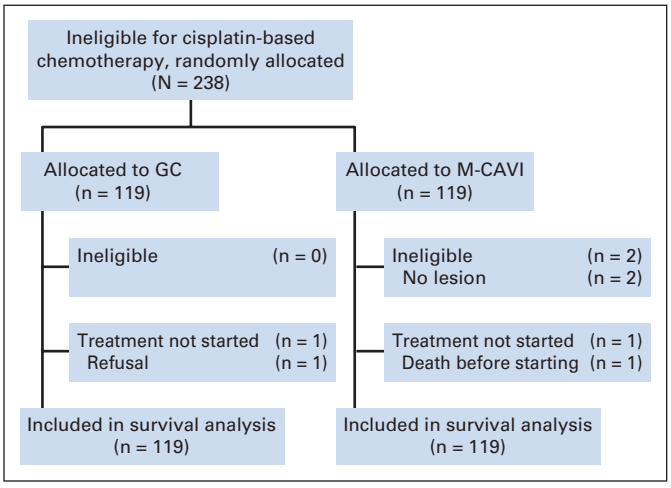

Fig 1. CONSORT diagram. GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine.

(71.2% in the GC arm and 60.2% in the M-CAVI arm) of patients. Detailed information about patient characteristics, number of cycles, dose reductions, and dose delays is given in Tables 1 and 2.

Toxicity

SAT was observed in 9.3% of patients in the GC arm (including two deaths resulting from toxicity) and 21.2% in the M-CAVI arm (including four deaths resulting from toxicity). The most common grade 3 to 4 toxicities were leucopenia (44.9%, 46.6%), neutropenia (52.5%, 63.5%), febrile neutropenia (4.2%, 14.4%), thrombocytopenia (48.3%, 19.4%), and infection (11.8%, 12.7%) in the GC and M-CAVI arms, respectively. There were more SATs in patients with impaired renal function, and there were also more SATs in the M-CAVI arm, both overall and also in subgroups, according to the reason for being unfit for cisplatin therapy and Bajorin risk groups. Details can be found in Tables 2 and 3.

Efficacy

The main reason for stopping treatment was treatment failure (recurrence, progression, or death resulting from malignant disease) in 73 patients (25.2% in the GC arm and 36.1% in the M-CAVI arm; Table 4).

Of the patients receiving GC, 41.2% had a complete or partial response (including six unconfirmed responses). Of the patients receiving M-CAVI, 30.3% had a complete or partial response (including 11 unconfirmed responses). The difference between the two treatment arms was not statistically significant ($P = .08$). However, considering only confirmed responses, this difference became significant ($P = .01$) favoring GC. Patients in Bajorin risk group 2 had a lower response rate (Table 3).

OS and PFS

Death was reported in 218 patients (110 in the GC arm and 108 in the M-CAVI arm). The main cause of death was progression of malignant disease (72%).

The intent-to-treat analysis of the primary end point showed a median OS of 9.3 months in the GC arm and 8.1 months in the M-CAVI arm, with a hazard ratio of 0.94 (95% CI, 0.72 to 1.22;

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Table 2. Amount of Treatment Received and Toxicity

Amount of Treatment Received	GC (n = 118) No.	GC (n = 118) %	M-CAVI (n = 118) No.	M-CAVI (n = 118) %	Total (N = 236) No.	Total (N = 236) %
No. of cycles of therapy						
1	12	10.2	23	19.5	35	14.7
2	17	14.4	23	19.5	40	16.8
3	10	8.5	11	9.3	21	8.8
4	18	15.3	18	15.3	36	15.1
5	10	8.5	11	9.3	21	8.8
6	38	32.2	22	18.6	60	25.4
> 6	13	11.0	10	8.5	23	9.7
Median	4.0		5.0		4.0	
Range	1.0-23.0		1.0-10.0		1.0-23.0	
Duration of treatment, weeks						
Median	13.9		15.0		14.3	
Range	1.0-36.1		0.1-98.0		0.1-98.0	
Dose reduction (any reason)						
No	32	27.1	18	15.3	50	21.2
Yes	86	72.9	100	84.7	186	78.8
Treatment delay (any reason)						
No	34	28.8	47	39.8	81	34.3
Yes	84	71.2	71	60.2	155	65.7
Severe acute toxicity*						
No	107	90.7	93	78.8	200	84.7
Yes	11	9.3	25	21.2	36	15.3
Leucopenia grade†						
0-2	65	55.1	63	53.4	128	54.2
3	40	33.9	34	28.8	74	31.4
4	13	11.0	21	17.8	34	14.4
Neutropenia grade†						
0-2	54	45.8	38	32.2	92	39.0
3	38	32.2	30	25.4	68	28.8
4	24	20.3	45	38.1	69	29.2
Missing	2	1.7	5	4.2	7	3.0
Thrombocytopenia grade†						
0-2	61	51.7	95	80.5	156	66.1
3	47	39.8	22	18.6	69	29.2
4	10	8.5	1	0.8	11	4.7
Febrile neutropenia grade†						
0-2	112	94.9	99	83.9	211	89.4
3	2	1.7	14	11.9	16	6.8
4	3	2.5	3	2.5	6	2.5
Missing	1	0.8	2	1.7	3	1.3
Infection grade†						
0-2	103	87.3	101	85.6	204	86.4
3	13	11.0	15	12.7	28	11.9
4	1	0.8	0	0.0	1	0.4
Missing	1	0.8	2	1.7	3	1.3

Abbreviations: GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine.
*Severe acute toxicity, death as a result of toxicity, renal toxicity (grade 3 to 4), febrile neutropenia (grade 3 to 4), hemorrhage/bleeding with thrombocytopenia (grade 4), or mucositis (grade 3 to 4).
†Common Toxicity Criteria v2.0.

$P = .64$; Fig 2). Median PFS was 5.8 months in the GC arm and 4.2 months in the M-CAVI arm in the intent-to-treat analysis, with a hazard ratio of 1.04 (95% CI, 0.80 to 1.35). We also evaluated the differences in OS according to the number of reasons for being unfit (PS 2, GFR < 60 mL/min, or both) and the Bajorin risk groups. Patients with only one reason for being unfit for cisplatin had a better OS than patients with both reasons (GFR < 60 mL/min and WHO PS 2; Fig 3). The post hoc analysis of OS by the Bajorin risk groups showed that, as the number of Bajorin risk factors increased, OS decreased significantly (Fig 3).

QoL Analysis

QoL was assessed at baseline, after every two cycles, and at the time of stopping treatment by using the EORTC Quality of Life Questionnaire C30 (QLQ-C30) Version 3.0 to which four trial-specific questions were added. The available data revealed no differences

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Table 3. Impact of Reason Ineligible (unfit) for Cisplatin and Bajorin Risk Groups by Treatment Group (severe acute toxicity, response rate, survival)

	GC						M-CAVI					
	WHO PS ≥ 2 (n = 21)		GFR (< 60 mL/min) (n = 66)		Both (n = 32)		WHO PS ≥ 2 (n = 21)		GFR (< 60 mL/min) (n = 65)		Both (n = 33)	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Severe acute toxicity												
No	20	95.2	60	90.9	28	87.5	19	90.5	51	78.5	24	72.7
Yes	1	4.8	6	9.1	4	12.5	2	9.5	14	21.5	9	27.3
Best overall response												
Complete response	0	0.0	4	6.1	0	0.0	0	0.0	4	6.2	0	0.0
Confirmed	0		3		0		0		3		0	
Unconfirmed	0		1		0		0		1		0	
Partial response	10	47.6	27	40.9	8	25.0	4	19.0	19	29.2	9	27.3
Confirmed	9		26		5		3		14		5	
Unconfirmed	1		1		3		1		5		4	
Stable disease	6	28.6	24	36.4	9	28.1	7	33.3	23	35.4	11	33.3
Progression	3	14.3	8	12.1	7	21.9	7	33.3	9	13.8	1	3.0
Early death	1	4.8	2	3.0	1	3.1	0	0.0	4	6.1	6	18.1
Not assessable	1	4.8	1	1.5	7	21.9	3	14.3	6	9.2	6	18.2
Survival status												
Alive	0	0.0	6	9.1	3	9.4	3	14.3	5	7.7	3	9.1
Dead	21	100.0	60	90.9	29	90.6	18	85.7	60	92.3	30	90.9
Bajorin Risk Group	0 (n = 45)		1 (n = 40)		2 (n = 34)		0 (n = 36)		1 (n = 46)		2 (n = 37)	
Severe acute toxicity*												
No	42	93.3	35	87.5	31	91.2	29	80.6	37	80.4	28	75.7
Yes	3	6.7	5	12.5	3	8.8	7	19.4	9	19.6	9	24.3
Best overall response												
Complete response	3	6.7	1	2.5	0	0.0	4	11.1	0	0.0	0	0.0
Confirmed	3		0		0		3		0		0	
Unconfirmed	0		1		0		1		0		0	
Partial response	17	37.8	19	47.5	9	26.5	14	38.9	12	26.1	6	16.2
Confirmed	16		18		6		10		9		3	
Unconfirmed	1		1		3		4		3		3	
Stable disease	18	40.0	11	27.5	10	29.4	10	27.8	19	41.3	12	32.4
Progression	4	8.9	6	15.0	8	23.5	3	8.3	8	17.4	6	16.2
Early death	2	4.4	0	0.0	2	5.9	1	2.8	4	8.7	5	13.5
Not assessable	1	2.2	3	7.5	5	14.7	4	11.1	3	6.5	8	21.6
Survival status												
Alive	5	11.1	4	10.0	0	0.0	4	11.1	5	10.9	2	5.4
Dead	40	88.9	36	90.0	34	100.0	32	88.9	41	89.1	35	94.6

Abbreviations: GC, gemcitabine/carboplatin; GFR, glomerular filtration rate ; M-CAVI, methotrexate/carboplatin/vinblastine ; PS, performance status.
*Severe acute toxicity, death resulting from toxicity, renal toxicity (grade 3 to 4), febrile neutropenia (grade 3 to 4), hemorrhage/bleeding with thrombocytopenia (grade 4), or mucositis (grade 3 to 4).

($P = .47$) between the two treatment arms for changes in the primary scale global health status/QoL from baseline to the end of cycle 2. However, because of low compliance (90% at baseline and less than 50% afterward), the results remain inconclusive.

DISCUSSION

We have conducted, to the best of our knowledge, the first randomized phase II/III trial comparing two carboplatin-based combination chemotherapies in patients with advanced UC who were ineligible for cisplatin therapy. This study was designed to establish a treatment standard in patients unfit for therapy with cisplatin. Valuable information in a clear-cut group of cisplatin-ineligible patients was collected and analyzed and, for the first time, well-grounded reference figures for PFS and OS in this patient population have been generated.

The hypothesized increase in OS from 9 months with the older M-CAVI regimen to 13.5 months with GC was not reached. The primary end point of the study, OS, showed no statistically significant difference between the two treatment arms. Median survival was 8.1 months in the M-CAVI arm and 9.3 months in the GC arm. On the basis of the number of patients included in the study, it is not possible to determine whether GC therapy might provide a survival benefit in any of the patient subgroups. PFS was also short, with no statistically significant difference between treatments.

Although the most effective treatment for patients ineligible for cisplatin remains to be defined, the results of this randomized phase

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Table 4. End of Treatment, Response Rate, and Disease Status

Variable	GC (n = 119)		M-CAVI (n = 119)		Total (N = 238)	
	No.	%	No.	%	No.	%
Reason for treatment discontinuation						
Progression/relapse/death resulting from PD	30	25.2	43	36.1	73	30.7
Toxicity	25	21.0	26	21.8	51	21.4
Patient's refusal	14	11.8	10	8.4	24	10.1
End of protocol treatment	5	4.2	3	2.5	8	3.4
Intercurrent death	7	5.9	4	3.4	11	4.6
Major protocol violation	0	0.0	3	2.5	3	1.3
Other*	38	31.9	29	24.4	67	28.2
Missing	0	0.0	1	0.8	1	0.4
Best overall response						
Complete response	4	3.4	4	3.4	8	3.4
Confirmed	3		3		6	
Unconfirmed	1		1		2	
Partial response	45	37.8	32	26.9	77	32.4
Confirmed	40		22		62	
Unconfirmed	5		10		15	
Stable disease	39	32.8	41	34.5	80	33.6
Progression	18	15.1	17	14.3	35	14.7
Early death	4	3.4	10	8.4	14	5.9
Not assessable	9	7.6	15	12.6	24	10.1
Progression-free survival status						
Alive without progression	4	3.4	6	5.0	10	4.2
Progression	84	70.6	79	66.4	163	68.5
Death resulting from progression	11	9.2	10	8.4	21	8.8
Death resulting from other cause	20	16.8	24	20.2	44	18.5
Survival status						
Alive	9	7.6	11	9.2	20	8.4
Dead	110	92.4	108	90.8	218	91.6
Progression	82		75		157	
Toxicity	3		4		7	
Chronic disease	2		3		5	
Other†	12		16		28	
Missing	11		10		21	

Abbreviations: GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine; PD, progressive disease.
*Most common reasons: stable disease after more than six chemotherapy cycles, no further clinical benefit at discretion of local investigator, general deterioration.
†Most common reasons: cardiac events, pulmonary embolism, clinical deterioration.

II/III study are still a major step forward. This study with GC and M-CAVI, the two most studied regimens in this setting, has shown that M-CAVI is more toxic than GC and, in particular, more toxic in patients with impaired renal function. SAT occurred more often in patients with both factors for being unfit for cisplatin and being in Bajorin risk group 2 and even more often when patients were treated with M-CAVI. Because there were more SATs in the M-CAVI arm, these results make GC the preferred treatment and reference regimen for patients ineligible for cisplatin therapy. This is in line with the experience for patients who are eligible for cisplatin therapy in whom GC was found to be less toxic than methotrexate/vinblastine/doxorubicin/cisplatin (MVAC).[23]

However, in view of the results of several single-arm phase II studies,[15,24] it remains uncertain to what extent carboplatin adds to the effect of gemcitabine monotherapy. Only a randomized phase III study will be able to answer this question.

Platinum-free chemotherapy has, so far, not been particularly promising in the first-line setting of patients with UC. In a recent study by Calabro et al,[25] the combination of gemcitabine/paclitaxel in the first-line setting for advanced disease in patients with mostly PS 0 to 1, a median GFR of 62 mL/min, and a 15% rate of liver metastases showed a response rate of 37% and a median survival of 13.5 months. These results are rather disappointing in the context of a single-arm phase II trial. The non-nephrotoxic combination chemotherapy oxaliplatin/gemcitabine,[26,27] has been studied in fit as well as in unfit patients. In both settings, this combination was well tolerated but only modestly effective, and it needs to be compared with platinum-based standard chemotherapy in randomized controlled trials.

The definition of being unfit for cisplatin has been a matter of controversy. In our study, the definition for being ineligible for cisplatin included the factors PS 2 and/or impaired renal function (GFR $>$ 30 but $<$ 60 mL/min). Patients with comorbidities such as congestive heart failure, cerebrovascular disease, or severe hearing impairment are usually precluded from treatment with cisplatin. There is consensus that the use of cisplatin is contraindicated in patients with impaired renal function. However, there is still dissent about the absolute figures—whether cisplatin is safe in patients with a GFR as low as 50 mL/min or even less if given in split dose and which method to use for

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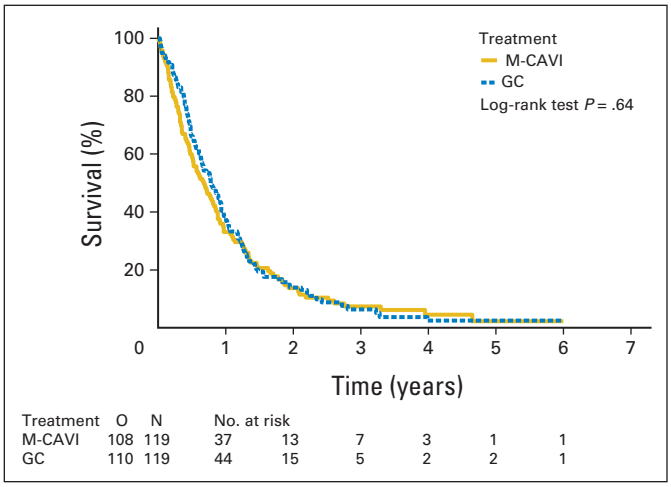

Fig 2. Duration of survival by treatment group. GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine; O, observed number of deaths.

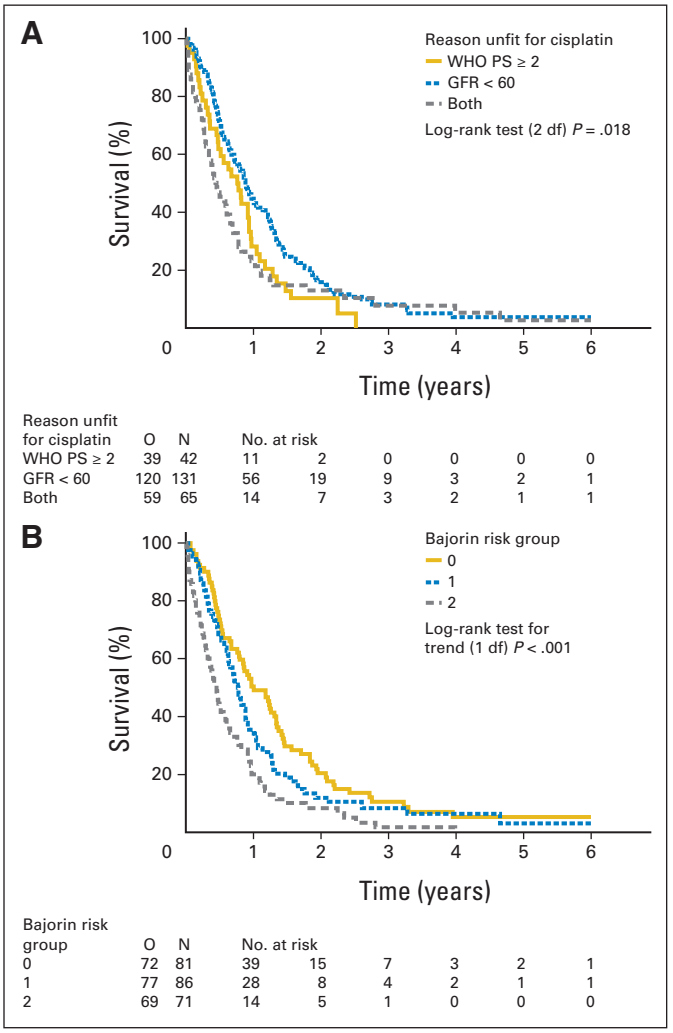

Fig 3. (A) Impact of stratification factors and (B) Bajorin risk groups on survival. GFR, glomerular filtration rate (mL/min); O, observed number of deaths; PS, performance status.

determining the creatinine clearance. According to the manufacturer, drugs like cisplatin that are primarily excreted through the kidney, need to be reduced in dose when the estimated GFR falls below 60 mL/min.[28]

In the International Society of Geriatric Oncology (SIOG) recommendations for dose adjustment in elderly patients with cancer who have renal insufficiency,[29] cisplatin is not recommended if the estimated GFR is less than 60 mL/min. In view of this, including a GFR of less than 60 mL/min in the definition for patients being unfit for cisplatin seems to be appropriate. Recent publications indicate that in patients older than age 70 years, calculated creatinine clearance tends to underestimate the GFR. Creatinine clearance measurement by 24-hour urine collection seems to be more appropriate.[30]

The true reason for the short duration of OS and PFS in our study compared with that in patients treated with cisplatin-based chemotherapy remains a matter of speculation. It might be due to patient selection (unfit) or the use of carboplatin instead of cisplatin. The question of whether carboplatin is as effective as cisplatin combination chemotherapy in patients eligible for cisplatin has, so far, not been answered sufficiently,[8,31-33] but there is the general belief, supported by limited data, that it probably is not. Patients treated with cisplatin-based chemotherapy in randomized trials had a nearly 50% longer median survival than those in our trial. Moreover, patients receiving cisplatin have a small but realistic chance of long-term survival.[34,35] At a median follow-up of 4.5 years, nine patients receiving GC and 11 patients receiving M-CAVI were still alive. These few long-term survivors (8.4%) were observed among patients with only one reason for being unfit for cisplatin and in those with 0 or 1 Bajorin risk factors.

The post hoc analysis of OS by Bajorin risk groups showed that as the number of Bajorin risk factors increased, OS significantly decreased. Our data thus suggest that the Bajorin risk groups are also valid in this population of patients ineligible for cisplatin therapy. Fit patients with no Bajorin risk factors have been found to have a median OS of 33.0 months when treated with MVAC.[22] In this subgroup in our trial, the median survival was only 12.0 months for both carboplatin-based regimens. The small number of patients in each risk group ruled out a definitive treatment comparison within these subgroups.

Concerning the reason for being unfit for cisplatin, the difference between the three OS curves was statistically significant, with patients who had only one reason for being unfit appearing to have a better OS than patients who had both reasons (GFR $<$ 60 and WHO PS 2).

The questions of whether renal dysfunction is an adverse prognostic factor by itself and whether the inability to administer cisplatin has an adverse impact on the outcome have not been explored systematically thus far and are, indeed, matters of debate.[36] The subgroup of patients with no Bajorin risk factors had the longest OS, suggesting that renal insufficiency probably has the least adverse impact on outcome compared with a lowered PS and/or the presence of visceral metastases. Conversely, patients with two Bajorin risk factors had the lowest response rate.

Because these are post hoc findings, they are only hypothesis generating, and further investigation in prospective study cohorts is still needed and should be addressed in future trials. A formal prognostic factor analysis of these current data will be the subject of a future report.

In the phase III part of this trial, several of the phase II findings were confirmed. Patients with two reasons for being ineligible for

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cisplatin therapy and patients in Bajorin risk group 2 derived little, if any, benefit from combination chemotherapy with a low response, a high rate of SATs, and low OS (Table 4). This new knowledge about ineligible patients and the respective subgroups should guide future trial design. Ineligible patients should no longer be studied as a uniform group.

The median age in this study was 10 years older compared with that in cisplatin-based chemotherapy trials. As previously discussed,[19] comprehensive geriatric assessment tools have been recommended by several societies and might be integrated into study designs to better select elderly patients with bladder cancer (those older than age 70 years) for trials and different schedules of treatment.[37-39]

In conclusion, this is the first randomized phase II/III trial in patients ineligible for cisplatin therapy. There were no significant differences between the GC and M-CAVI arms in OS or for the secondary end points of response and PFS. Both regimens were active. However, SAT was higher in patients treated with M-CAVI, which makes GC the preferred and reference treatment in patients ineligible for cisplatin. Further studies should be designed to find more effective treatment options in this patient population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Joaquim Bellmunt, Eli Lilly (C); Ronald de Wit, Eli Lilly (C) **Stock Ownership:** None **Honoraria:** Maria De Santis, Eli Lilly; Joaquim Bellmunt, Eli Lilly; Iwona Skoneczna, Eli Lilly; Ronald de Wit, Eli Lilly **Research Funding:** Iwona Skoneczna, Eli Lilly **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Maria De Santis, Joaquim Bellmunt, Ronald de Wit, Richard Sylvester
Administrative support: Richard Sylvester
Provision of study materials or patients: Maria De Santis, Joaquim Bellmunt, Graham Mead, J. Martijn Kerst, Michael Leahy, Pablo Maroto, Thierry Gil, Gedske Daugaard, Iwona Skoneczna, Ronald de Wit
Collection and assembly of data: Maria De Santis, Sandrine Marreaud, Sandra Collette, Richard Sylvester
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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Affiliations

Maria De Santis, Kaiser Franz Josef Hospital and Applied Cancer Research-Institution for Translational Research Vienna/Central European Anticancer Drug Development Platform and Ludwig Boltzmann Institute for Applied Cancer Research Vienna-Cluster Translational Oncology, Vienna, Austria; Joaquim Bellmunt, Hospital Vall d'Hebrón and Hospital del Mar-L'Institut Municipal d'Investigació Mèdica; Pablo Maroto, University Hospital of San Pablo, Barcelona, Spain; Graham Mead, Southampton General Hospital, Southampton; Michael Leahy, St James's University Hospital, Leeds, United Kingdom; J. Martijn Kerst, Netherlands Cancer Institute, Amsterdam; Ronald de Wit, Erasmus University Medical Center, Rotterdam, the Netherlands; Thierry Gil, Institut Jules Bordet; Sandrine Marreaud, Sandra Collette, Julie Lorent, and Richard Sylvester, European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; Gedske Daugaard, Rigshospitalet, Copenhagen, Denmark; Iwona Skoneczna, Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw, Poland.

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