



## Bladder Cancer

# Gemcitabine plus Cisplatin versus Gemcitabine plus Carboplatin as First-Line Chemotherapy in Advanced Transitional Cell Carcinoma of the Urothelium: Results of a Randomized Phase 2 Trial

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### Abstract

**Objectives:** This phase 2 randomized study compared the toxicity and assessed the efficacy of gemcitabine–cisplatin (GP) and gemcitabine–carboplatin (GC) in patients with advanced transitional cell carcinoma of the urothelium (TCC), with the main objective to demonstrate a reduction in toxicity of at least 25% in the GC arm.

**Methods:** A total of 110 chemo-naïve patients (55 per arm) with locally advanced or metastatic TCC received gemcitabine 1250 mg/m<sup>2</sup> on days 1 and 8 plus cisplatin 70 mg/m<sup>2</sup> on day 2 (GP) every 3 wk or gemcitabine 1250 mg/m<sup>2</sup> on days 1 and 8 plus carboplatin AUC 5 on day 2 (GC) every 3 wk for a maximum of six cycles.

**Results:** No differences between arms were noted in the overall toxicity profiles and any parameter of toxicity. The most frequent grade 3–4 hematologic toxicity was neutropenia in 34.6% of patients for GP and 45.4% for GC. The most frequent grade 3–4 nonhematologic toxicity was nausea and vomiting (GP: 9.1%; GC: 3.6%). Grade 1–2 nephrotoxicity occurred in 14 GP-treated patients (26.0%) and 9 GC-treated patients (16.3%). Per an intent-to-treat analysis, overall response, evaluated on 80 patients, was 49.1% for GP (CR: 14.5%; PR: 34.5%) and 40.0% for GC (CR: 1.8%; PR: 38.2%). Median time to progression was 8.3 mo for GP and 7.7 mo for GC. Median survival was 12.8 mo and 9.8 mo for GP and GC, respectively.

**Conclusions:** GC has a comparably acceptable toxicity profile compared with that of GP and seems active in patients with TCC.

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## 1. Introduction

Advanced transitional cell carcinoma (TCC) of the urothelium remains an incurable disease, with a median survival time of only 12 to 14 mo [1]. In the past, combination chemotherapy regimens such as methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) or cisplatin, methotrexate, and vinblastine (CMV) were considered the standard treatment for TCC [2,3]. These regimens, in particular M-VAC, were associated with a high toxicity profile, and treatment-related deaths as high as 3–4% [4–7].

Gemcitabine, a nucleoside analogue, has demonstrated activity against a range of solid tumors [8–11]. In particular, in metastatic urothelial cancer, single-agent gemcitabine has yielded response rates ranging from 23% to 29%, with complete response (CR) rates ranging from 4% to 13%, in both previously treated and untreated patients [12].

The favorable activity and toxicity profile of single-agent gemcitabine and its synergism with cisplatin in preclinical models led to the development of this combination in treating advanced TCC [13]. Four phase 2 trials have evaluated the combination of gemcitabine and cisplatin (GP) as first- or second-line treatment in TCC patients. Response rates ranged from 41% to 57%, and median survival times from 12.5 to 14.3 mo. Toxicity was generally acceptable [14–17]. Following these encouraging results, von der Maase et al [18] reported the results of a multinational phase 3 trial, the largest trial conducted in bladder cancer to date, comparing M-VAC with GP [18]. The results were similar in terms of response rate, time to progression, and survival; however, GP had a significantly better safety profile than M-VAC. On the basis of these data, the GP combination has increasingly become a standard treatment in patients with advanced TCC.

The encouraging activity and tolerability of GP made it logical to study gemcitabine in combination with other platinum agents, such as carboplatin, in the treatment of TCC [19,20]. Carboplatin shares a common mechanism of action with cisplatin, but has different pharmacokinetic and dose-limiting toxicities [21]. The dose-limiting toxicity of carboplatin is myelosuppression, especially thrombocytopenia. Unlike cisplatin, however, standard doses of carboplatin (up to 400 mg/m<sup>2</sup>) do not cause nephrotoxicity, neurotoxicity, or ototoxicity. In addition, patients with TCC are often elderly, with frequent concomitant diseases, in particular, clinical or subclinical renal function impairment. Thus, the substitution of cisplatin with carboplatin may be a promising alternative for these patients.

On the basis of these considerations, we conducted an open-label, multicenter, randomized phase 2 trial whose primary objective was to compare the toxicity of GP and GC in patients with locally advanced and metastatic TCC. Secondary objectives included assessments of objective response rate, time to progressive disease (TtPD), and median survival time.

## 2. Methods

### 2.1. Patients

#### 2.1.1. Inclusion criteria

Chemonaive patients  $\geq 18$  yr of age with measurable or evaluable disease were included in the study if they met all of the following criteria: histologic diagnosis of locally advanced (stage III T3b–T4a or stage IV T4b) or metastatic (N2, N3, M1) TCC of the urothelium not suitable for cystectomy, Zubrod performance status (PS) of 0–2, estimated life expectancy  $\geq 12$  weeks, adequate renal function (creatinine clearance  $\geq 60$  ml/min). Prior radiotherapy was allowed as long as the irradiated area was not the only source of measurable disease, and treatment was completed  $\geq 12$  weeks before enrollment.

All patients gave written informed consent before study entry. The study was approved by the local ethical review board(s) and was conducted according to ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection of the individual.

### 2.2. Study design and statistical analysis

In this phase 2, multicenter, randomized study, patients were randomized to receive GP or GC. The original sample size goal was to randomize 138 patients (69 patients per treatment arm). Assuming a World Health Organization (WHO) grade 3 and 4 toxicity incidence of 56% in the GP arm (ie, 56% of the patient on the GP arm with at least one grade 3–4 event), we aimed to demonstrate a reduction in toxicity of at least 25% in the GC arm. This sample size of 69 patients per treatment arm ensured an 80% power to detect such a reduction at the two-sided significance level of 5%.

The trial was stopped after 110 evaluable patients (55 patients per arm) were enrolled and took up 3 mo of the study because of the difficulty of patient enrollment. This sample size ensured a 75% power to detect a difference between arms of 25%. The sample size was also adequate to show clinically significant differences between treatment arms in toxicities known to adversely affect the tolerability of the two platinum-based regimens: grade 3–4 neurotoxicity, ototoxicity, nephrotoxicity, nausea/vomiting, anemia requiring transfusion, thrombocytopenia resulting in hemorrhage, hematuria, and neutropenic sepsis or febrile neutropenia. The study was not designed with sufficient power to detect differences between arms in objective tumor response rate or survival, since it was hypothesized that the response rates for both treatment arms would be similar.

Characteristics of treatment group patients at baseline were compared with the use of Pearson chi-square tests (for categorical data) and Student *t* tests (for continuous data). Toxicity incidences were compared with the use of Pearson chi-square tests. Estimates of TtPD and OS were calculated with the use of the Kaplan-Meier method [22]. Medians for time to progressive disease and OS were derived from these estimates. The proportion of patients surviving at 1 yr was also reported. All confidence intervals (CIs) were constructed at the 95% level. A *p* value below .05 indicated statistical significance.

### 2.3. Treatment plan

Patients were randomized to receive gemcitabine 1250 mg/m<sup>2</sup> on days 1 and 8 plus cisplatin 70 mg/m<sup>2</sup> on day 2 every 3 weeks, or gemcitabine 1250 mg/m<sup>2</sup> on days 1 and 8 plus carboplatin AUC 5 on day 2 every 3 wk, for a maximum of six cycles. A cycle was defined as 2 consecutive weeks of treatment followed by 1 wk of rest. Gemcitabine (Gemzar; Eli Lilly and Company, Indianapolis, IN, USA) was administered as a continuous infusion over 30–60 min, with a 30-min infusion considered ideal. Cisplatin (Platinol, Bristol-Myers Squibb, Princeton, NJ, USA) was administered according to guidelines at each site to ensure that adequate hydration was given, with urine output monitored and serum electrolytes and renal parameters followed appropriately. Carboplatin (Paraplatin, Bristol-Myers Squibb, Princeton, NJ, USA) was administered as a 30–60 min intravenous infusion. The calculation of carboplatin dosage was based on glomerular filtration rate according to the Calvert formula [23]. Patients were discontinued from the study if the disease progressed or intolerable toxicity developed, or if the investigator thought it was in the patient's best interest to discontinue.

Dose adjustments of both gemcitabine and cisplatin or gemcitabine alone within a cycle were based on weekly absolute granulocyte counts (AGC) ( $\times 10^9/l$ ), platelet counts ( $\times 10^9/l$ ), and clinical assessment of nonhematologic toxicities. For an AGC  $\leq 0.99$  or platelets  $\leq 74$  or evidence of bleeding, gemcitabine was omitted. No new cycle of GP or GC was started unless the AGC was  $\geq 1.5$  and platelets  $\geq 100$ . The platinum dose was reduced by 50% for grade 2 neurotoxicity, omitted for grade 3, and stopped for grade 4. For renal toxicity, the platinum dose was given over 2 d for creatinine clearance 50–59 (ml/min) and omitted for creatinine clearance  $< 50$ . Patients received full-dose gemcitabine except for WHO grade  $\geq 3$  creatinine, in which case the gemcitabine dose was omitted.

For other grade 3 nonhematologic toxicities (except nausea, vomiting, and alopecia), gemcitabine and platinum doses were reduced by 50% or omitted per the investigator; for grade 4 toxicities, doses were reduced by 50% or stopped (unless the patient was responding to therapy). Doses held because of toxicity or missed were not given at a later time.

### 2.4. Baseline and treatment assessments

No more than 1 wk before enrollment, the disease status of each patient was assessed with medical history and physical examination, including measurements of height and weight, pulse rate, systolic and diastolic blood pressure, body

temperature, preexisting conditions, and concomitant therapies; evaluation of Zubrod PS; and tumor measurement of palpable lesions. No more than 3 wk before enrollment, each patient had at least one chest x-ray and was assessed by computer tomography scan or magnetic resonance imaging. Full blood count and prothrombin; blood chemistries (bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, serum creatinine, proteinuria, hematuria); magnesium; calculated creatinine clearance using the Cockcroft and Gault formula [24] and measured creatinine clearance; electrocardiogram; and vital signs were assessed no more than 2 wk before enrollment. Prior surgery, radiotherapy, or other treatment for this cancer was assessed at this time as well.

Before every other cycle, efficacy was examined in each patient by radiologic imaging studies that demonstrated disease. Disease status was assessed 4 wk after the last dose of the study drug, and patients were followed until death or loss to follow-up. The same assessment method used to determine the disease status at baseline was used consistently for the efficacy evaluation throughout the study. Responses were assessed using WHO criteria and were confirmed within 4 wk.

All patients who received at least one dose of study drug were included in the safety analysis. Safety was assessed according to WHO criteria. Patients who received at least one dose and had at least one tumor assessment were evaluable for tumor response. All patients who received at least one dose of study drug and had at least one observation were analyzed for progression-free survival and overall survival (OS).

Time to progressive disease was calculated from the time of initial therapy until progression or death due to any cause. Survival was measured from administration of the first dose until the last clinic visit or death due to any cause. The duration of a partial response (PR) was measured from the time of the initial administration of the first dose of chemotherapy until the time of documented progressive disease. The duration of a complete response (CR) was measured from the time the CR was documented until the date of the first observation of progressive disease.

## 3. Results

### 3.1. Patient characteristics

From August 2000 to December 2002, 114 patients were entered into the study in 17 centers (15 in Italy and 2 in Turkey). Four patients did not receive any study drug; reasons were inadequate renal function (measured creatinine clearance  $\leq 60$  ml/min) for two patients and two patient refusals. The remaining 110 patients (55 GP-arm, 55 GC-arm) were evaluable for the safety analyses.

Baseline clinical characteristics were generally well balanced across treatment arms (Table 1). The median age was 67 in both arms. Fifty-two patients (94.5%) in the GP-arm and 47 patients (85.4%) in the

**Table 1 – Patient characteristics**

	GP (N = 55)	GC (N = 55)
Median age, yr (range)	67 (32–80)	67 (36–76)
Gender, n (%)		
Male	47 (85.5)	48 (87.3)
Female	8 (14.5)	7 (12.7)
Zubrod PS, n (%)		
0	29 (52.7)	23 (41.8)
1	23 (41.8)	24 (43.6)
2	3 (5.5)	8 (14.5)
Status of disease, n (%)		
Grade 3 (T3b–T4a)	5 (9.1)	5 (9.1)
Grade 4 (T4b)	50 (90.9)	50 (90.9)
Sites of metastasis, n (%)		
Lung	24 (43.6)	12 (21.8)
Liver	10 (18.2)	10 (18.2)
Bone	10 (18.2)	9 (16.4)
Bladder	10 (18.2)	15 (27.3)
Lymph nodes	18 (32.7)	21 (38.2)
Others	19 (34.5)	28 (50.9)
No. of metastatic sites, n (%)		
1	23 (41.8)	23 (41.8)
≥2	32 (58.2)	31 (56.4)

GC-arm had PS 0–1. The majority of patients in both arms had metastatic disease, with two or more sites in 32 patients (58.2%) in the GP-arm and 31 patients (56.4%) in the GC-arm. Three patients (5.5%) in the GP arm and 8 patients (14.5%) in the GC arm presented with a Zubrod PS of 2. None of the differences between treatments in baseline characteristics was statistically significant.

### 3.2. Dose administration

Patients in the GP-arm received a total of 263 cycles and a median of 4 cycles (range: 1–6) compared with a total of 255 cycles and a median of 4 cycles (range: 1–6) for patients in the GC-arm. The relative dose intensity for gemcitabine was 94.0% for GP and 94.7% for GC. The relative dose intensity for cisplatin was 91.3%, while that for carboplatin was not calculated because of the unavailability of dose adjustment data.

### 3.3. Toxicity

Overall toxicity observed during the study did not show any significant difference between treatment groups. The same was true for toxicities grade  $\geq 3$  (60.0% for GP vs. 69.1% for GC) and incidences of individual toxicities. Grade 3–4 neutropenia was the most frequent toxicity reported in both GP- and GC-treated patients, occurring in 34.6% and 45.4% of patients, respectively (Table 2). Respective percentages for grade 3–4 thrombocytopenia were 45.4% and 38.2%. Grade 3–4 nonhematologic toxicities included nausea and vomiting in five patients (9.1%) in the GP-arm and two patients (3.6%) in the GC-arm, infection in one patient in the GP-arm, and mucositis in one patient in the GC-arm (Table 3). Grade 1–2 nephrotoxicity occurred in 26.0% of GP-treated patients and 16.3% of GC-treated patients. Grade 2 ototoxicity occurred in one patient treated with GP. Supportive therapies included growth factor (granulocyte colony-stimulating factor) (12.7% GP, 18.2% GC) and erythropoietin (7.3% for both groups). Eight GP-treated patients (14.5%) and 17 GC-treated patients (30.9%) required red blood cell transfusion, and two GP-treated patients (3.6%) and three GC-treated patients (4.5%) required platelet transfusion. None of these treatment-group differences reached statistical significance.

In both groups, 30 patients completed treatment, while 25 patients discontinued the study early. Adverse events were the primary reason for discontinuation in both treatment groups and occurred in 12.7% of patients in each group. Fourteen deaths (7 GP, 7 GC) were reported: Thirteen were not considered drug related in either arm, whereas one patient, in the GP group, died during the follow-up because of acute renal failure possibly related to cisplatin (no toxicity data were available for this patient because a blood sample was not collected).

### 3.4. Efficacy

Overall response was evaluated in 80 patients (41 GP, 39 GC; Table 4). In 30 patients (14 GP, 16 GC) tumor

**Table 2 – WHO grade 3–4 hematologic toxicity**

Toxicity	GP (N = 55)		GC (N = 55)	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Leukopenia	8 (14.5)	1 (1.8)	10 (18.2)	6 (10.9)
Neutropenia	15 (27.3)	4 (7.3)	12 (21.8)	13 (23.6)
Thrombocytopenia	8 (14.5)	9 (16.4)	11 (20.0)	10 (18.2)
Anemia	10 (18.2)	1 (1.8)	13 (23.6)	1 (1.8)

WHO = World Health Organization.

**Table 3 – WHO nonhematologic toxicity**

Toxicity	GP (N = 55)		GC (N = 55)	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Infection	5 (9.1)	1 (1.8)	8 (14.6)	0
Nausea and vomiting	36 (65.5)	5 (9.1)	34 (61.8)	2 (3.6)
Mucositis	2 (3.6)	0	6 (10.9)	1 (1.8)
Diarrhea	8 (14.6)	0	11 (20.0)	0
Neurotoxicity	4 (7.3)	0	4 (7.3)	0
Nephrotoxicity	14 (26.0)	0	9 (16.3)	0

WHO = World Health Organization.

response could not be assessed; 4 GP- and 3 GC-treated patients discontinued prior to completing one cycle, and 10 GP- and 13 GC-treated patients were nonevaluable because of unaddressable, non-medical reasons. Complete response was observed in 8 patients treated with GP and in 1 patient treated with GC. Partial response was observed in 19 patients in the GP-arm and 21 patients in the GC-arm. Overall response rates were 65.9% (95%CI, 49.4–79.9) for GP and 56.4% (95%CI, 39.6–72.2) for GC. No differences between arms were observed in terms of response grouped by locally advanced versus metastatic disease, location or number of metastatic sites, or PS.

Overall, 110 patients were evaluable for TtPD and OS. The median time to follow-up was 7.2 mo for GP and 6.9 mo for GC. Median TtPD was 8.3 mo (range: 7.5–9.1 mo) in the GP-group and 7.7 mo (range: 5.1–10.3 mo) in the GC-group. Median survival was 12.8 mo in the GP-arm and 9.8 mo in the GC-arm. Kaplan-Meier curves for TtPD and OS are shown in Figs. 1 and 2, respectively. At 12 mo, survival rates were 63.6% for GP and 37.3% for GC.

#### 4. Discussion

In this phase 2, randomized study of GP versus GC in patients with locally advanced or metastatic TCC of

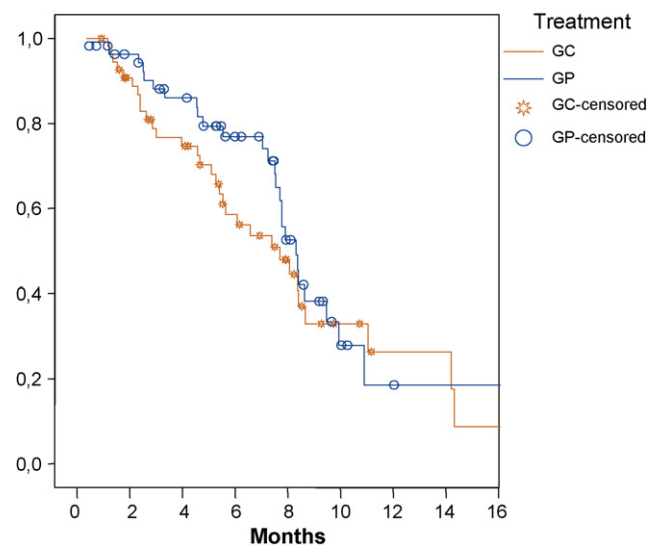
the urothelium, we chose a 21-d regimen to eliminate the need for administering a gemcitabine dose on day 15, which often needs to be adjusted or omitted because of hematologic toxicity when administered on a 4-wk schedule [18]. Moreover, the feasibility of a 21-d schedule has previously been validated in patients with non-small cell lung cancer [25,26]. We did not detect any significant differences between arms in terms of overall toxicity (including grade  $\geq 3$  toxicity) or any parameter of toxicity. In addition, we observed not clinically significant difference in overall response rates of 65.9% and 56.4%, median survival times of 12.8 mo and 9.8 mo, and TtPDs of 8.3 and 7.7 in the GP and GC arms, respectively. These data are consistent with efficacy reported with the van der Maase schedule [18].

In the first phase 2 study of GC, reported at the 1998 National Cancer Institute Meeting in Amsterdam, 22 patients with locally advanced or metastatic bladder cancer received carboplatin

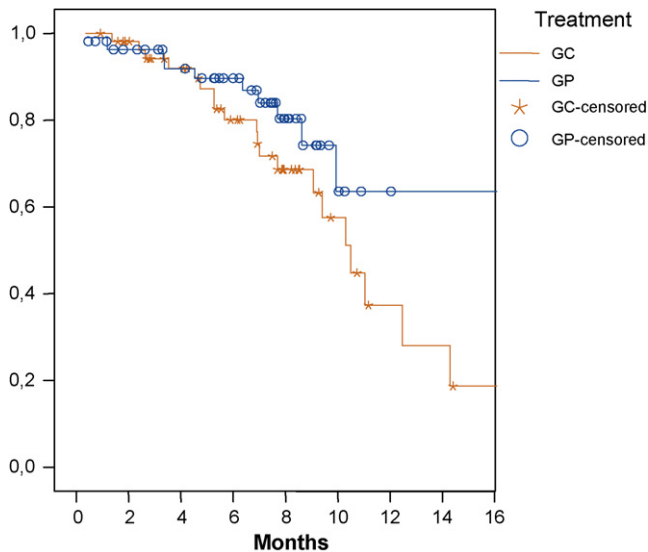
**Table 4 – Overall tumor response\***

	Evaluable patients only (%)	
	GP (N = 41)	GC (N = 39)
ORR, n (%)	27 (65.9)	22 (56.4)
CR, n (%)	8 (19.5)	1 (2.6)
PR, n (%)	19 (46.3)	21 (53.8)
SD, n (%)	12 (29.3)	14 (35.9)
PD, n (%)	2 (4.9)	3 (7.7)

\* The tumor response rate was calculated as follows: tumor response rate = number of responders/responders + not responders. ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.



**Fig. 1 – Time to progressive disease for the gemcitabine-carboplatin (GC) arm and the gemcitabine-cisplatin (GP) arm.**



**Fig. 2 – Overall survival for the gemcitabine–carboplatin (GC) arm and the gemcitabine–cisplatin (GP) arm.**

300 mg/m<sup>2</sup> on day 1 and gemcitabine 1000 mg/m<sup>2</sup> on days 1 and 8 every 3 weeks for 6 cycles [19]. Five CRs and 10 PRs were observed. Myelosuppression was the major toxicity, with grade 3–4 neutropenia or thrombocytopenia occurring in 60% of patients.

Four additional phase 2 trials were conducted to evaluate the activity and toxicity of the GC combination in locally advanced or metastatic TCC. Carles et al [27] enrolled 17 patients with advanced TCC and compromised renal function (creatinine clearance: 20–55 ml/min) [27]. Patients received gemcitabine 1000 mg/m<sup>2</sup> on days 1 and 8 of a 21-d schedule plus carboplatin AUC 5 on day 1. Fifty-six percent of patients obtained an objective response, with a median survival time of 10 mo. Grade 3–4 hematologic toxicities included anemia in three patients, neutropenia in four patients, and thrombocytopenia in three patients. Two trials [28,29] used the same schedule and doses as those of the Carles trial and demonstrated response rates in the range of 45–68% with the GC combination. The major toxicities were myelosuppression, with grade 3–4 neutropenia and thrombocytopenia in 60–68% of patients, respectively. Nogue-Aliguer et al [30] reported results of a phase 2 trial in which patients were given gemcitabine 1000 mg/m<sup>2</sup> on days 1 and 8 and carboplatin AUC 5 on day 1 every 21 d. They reported an overall response rate of 56.1%, a progression-free survival time of 7.2 mo, and a median survival time of 10.1 mo in 41 patients with advanced TCC [30]. Hematologic toxicities included grade 3–4 neutropenia in 63%, grade 3–4 thrombocytopenia in 32%, and grade 3–4 anemia in 54% of patients.

Our data compare favorably with the results of previous phase 2 GC trials [19,20,28–30] with grade 3–4 neutropenia reported in 45.4%, grade 3–4 anemia occurring in 25.4%, and grade 3–4 thrombocytopenia in 38.2% of patients. Our response rate of 56.4% for GC is also consistent with that found in previous studies of GC.

Because the trial was not designed with sufficient power to detect significant differences between arms in terms of efficacy, these data are descriptive in nature and as such must be interpreted with caution. Despite this limitation, however, it is worth noting that there were no significant differences found between arms in baseline disease characteristics that could have contributed to the differences observed in the efficacy results.

## 5. Conclusion

GC has a comparably acceptable toxicity profile compared with that of GP and is active in the treatment of locally advanced or metastatic TCC of the urothelium when administered on a 21-d schedule. The GC combination might be considered an alternative to GP in selected patients, especially when they present with moderate renal failure.

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