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ORIGINAL REPORT

Double-Blind, Randomized Trial of Docetaxel Plus Vandetanib Versus Docetaxel Plus Placebo in Platinum-Pretreated Metastatic Urothelial Cancer

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A B S T R A C T

Purpose

Vandetanib is an oral once-daily tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptor 2 and epidermal growth factor receptor. Vandetanib in combination with docetaxel was assessed in patients with advanced urothelial cancer (UC) who progressed on prior platinum-based chemotherapy.

Patients and Methods

The primary objective was to determine whether vandetanib 100 mg plus docetaxel 75 mg/m^2 intravenously every 21 days prolonged progression-free survival (PFS) versus placebo plus docetaxel. The study was designed to detect a 60% improvement in median PFS with 80% power and one-sided α at 5%. Patients receiving docetaxel plus placebo had the option to cross over to single-agent vandetanib at progression. Overall survival (OS), overall response rate (ORR), and safety were secondary objectives.

Results

In all, 142 patients were randomly assigned and received at least one dose of therapy. Median PFS was 2.56 months for the docetaxel plus vandetanib arm versus 1.58 months for the docetaxel plus placebo arm, and the hazard ratio for PFS was 1.02 (95% CI, 0.69 to 1.49; $P = .9$). ORR and OS were not different between both arms. Grade 3 or higher toxicities were more commonly seen in the docetaxel plus vandetanib arm and included rash/photosensitivity (11% *v* 0%) and diarrhea (7% *v* 0%). Among 37 patients who crossed over to single-agent vandetanib, ORR was 3% and OS was 5.2 months.

Conclusion

In this platinum-pretreated population of advanced UC, the addition of vandetanib to docetaxel did not result in a significant improvement in PFS, ORR, or OS. The toxicity of vandetanib plus docetaxel was greater than that for vendetanib plus placebo. Single-agent vandetanib activity was minimal.

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INTRODUCTION

Urothelial carcinoma (UC) is the fifth most common malignancy in the United States and accounts for more than 13,000 deaths yearly.[1] Few advances have been made in the treatment of advanced UC in the last decade. Standard of care in the United States consists of a platinum-based therapy (eg, gemcitabine plus cisplatin or methotrexate, cisplatin, doxorubicin and vinblastine).[2] Once patients progress through one of these regimens, there is no standard second line-therapy.[3] In the second-line setting, many agents, including docetaxel,[4] paclitaxel,[5,6] and pemetrexed,[7,8] demonstrate response rates between 10% and 20%, yet no drug has been proven to prolong overall survival (OS). Vinflunine, a novel synthetic vinca alkaloid, did not confer an OS advantage over placebo in an intent-to-treat population and is not approved in the United States.[9] Because of this lack of a standard second-line agent, practice patterns differ, although taxanes are the most commonly used agents.[10]

An appealing therapy strategy for the treatment of advanced UC is the addition of targeted agents to

chemotherapy.[11,12] Several targets in UC may be biologically relevant, including vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR).[12] VEGFR- and EGFR-directed therapy have proven clinically useful in multiple tumor types, usually in combination with chemotherapy. Preclinically, combination therapy with a taxane and DC101, a VEGFR antibody,[13] or cetuximab, an EGFR antibody,[14] caused significant regression of human UC growing in nude mice, with the combination being more active than either agent alone.

Vandetanib (AstraZeneca, Macclesfield, United Kingdom) is an oral once-daily selective tyrosine kinase inhibitor of key signaling pathways in cancer, including VEGFR-2 (median inhibition concentration [IC_{50}], 0.04 μmol/L) and EGFR (IC_{50}, 0.5 μmol/L). Early clinical trials showed that this agent alone or in combination with docetaxel has an acceptable adverse effect profile and produced tumor responses.[15] Randomized studies in non–small-cell lung cancer showed that the addition of vandetanib to docetaxel resulted in a significant prolongation of progression-free survival (PFS) compared with docetaxel alone. Vandetanib is currently approved by the US Food and Drug Administration (FDA) for the treatment of advanced medullary thyroid cancer.[16,17]

On the basis of the above data and the potential importance of VEGFR and EGFR in UC, a randomized phase II study of docetaxel with vandetanib or placebo was initiated. This trial is a multicenter study in patients with advanced UC who have experienced progression after a platinum-containing regimen. Our primary hypothesis was that the addition of vandetanib to docetaxel would result in a significant PFS advantage.

PATIENTS AND METHODS

Eligibility

Eligible patients required histologically or cytologically confirmed locally advanced or metastatic UC, progression of disease documented by the investigator after platinum-containing chemotherapy, age $\geq$ 18 years, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Prior docetaxel and prior VEGF-targeted therapies were not allowed. The study did not initially allow prior paclitaxel, but because of an initial slow accrual rate, the study was amended to allow it. Overall, up to three systemic therapies were allowed (given in the metastatic and/or within 2 years of adjuvant or neoadjuvant settings). Patients were required to have adequate hematologic, hepatic, and renal (calculated creatinine clearance $\geq$ 30 mL/min by the Cockcroft-Gault formula) function. Patients with uncontrolled arrhythmias, QTc $\geq$ 480 ms on screening ECG, serum calcium or magnesium below lower limits of normal, and serum potassium less than 4 mmol/L (despite supplementation) were excluded. Patients with brain metastasis could be included if they were treated more than 4 weeks before enrollment, were asymptomatic, and had a stable post-treatment brain magnetic resonance imaging scan. The trial was approved by all relevant institutional ethical committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.[18] Each patient provided written informed consent.

Study Design and Treatment Plan

This was a randomized, multicenter, double-blind, placebo-controlled, investigator-initiated phase II trial. Patients were randomly assigned 1:1 to vandetanib plus docetaxel or placebo plus docetaxel. Randomized treatment codes were generated by the Dana-Farber Cancer Institute's Quality Assurance Office for Clinical Trials (QACT) office. A computerized random number generator was used to produce permuted blocks of treatment codes.[19] The number of possible permutations depended on the block size and number of individual treatments and was undisclosed to investigators. A string of permuted blocks was generated for each stratification factor combination, and treatment assignments were consumed sequentially. Patients were stratified on the basis of measurable disease at presentation (v evaluable-only disease), ECOG PS of 0 and no visceral metastasis (v either ECOG PS of 1 or visceral metastasis or both), and number of prior systemic chemotherapy regimens (one $v >$ one regimen). Patients on both arms underwent 21-day dosing cycles with docetaxel 75 mg/m^2 via 1-hour infusion on day 1 and dexamethasone 8 mg at about 12, 3, and 1 hour before docetaxel. Vandetanib and matching placebo were given as 100-mg tablets orally once daily. Patients receiving placebo tablets were assigned to take them on the same schedule as the patients receiving vandetanib. Treatment was administered until documented progression, unacceptable toxicity, or patient refusal. Once eligibility for crossover treatment was documented, the blind was broken and, if the patient was on the placebo arm and met crossover eligibility, single-agent vandetanib was offered.

Clinical Assessment

Preregistration assessments included a detailed medical history, physical examination, and imaging for tumor assessment. Imaging studies were obtained every 6 weeks for the first two cycles and every 9 weeks thereafter. Investigators assessed efficacy by using Response Evaluation Criteria in Solid Tumors (RECIST 1.0).[20] The maximum percentage of tumor shrinkage on study was also recorded. Physical examination, ECOG PS, and vital signs were assessed on day 1 of each cycle. ECGs were obtained at baseline and on day 1 of cycles 1 to 5, and then every four cycles. A CBC and a biochemical assessment with electrolytes were obtained on day 1 of every cycle. Blood specimens and archival tumor tissue for correlative studies were collected at baseline.

Toxicity was assessed throughout the treatment period and before each administration according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Docetaxel and therapy were withheld for any CTCAE grade 3 or 4 toxicities (other than alopecia, anemia, and fatigue) until they resolved to grade $\leq$ 1. If the toxicity was felt to be related to study treatment, therapy was reduced one dose level. Docetaxel dose reductions were dose level -1 (60 mg/m^2) and dose level -2 (48 mg/m^2). For vandetanib and placebo, there was one dose reduction at 100 mg every other day. Patients completed a diary to report compliance with study drug and premedications.

Statistical Methods

The primary end point of the trial was PFS, which was defined as the time between random assignment and documented progression per RECIST criteria or death. Patients alive and without evidence of progression were censored on the date of last evaluation. The study was designed with 80% power to detect a 60% improvement in median PFS from 4.5 to 7.2 months: the docetaxel plus vandetanib and/or docetaxel plus placebo hazard ratio (HR) was 0.625 with the addition of vandetanib, given a one-sided overall significance level of 5% and 140 randomly assigned patients. This assumes exponential distribution of events, accrual of 1.75 patients per week (seven to eight patients per month) for 78 weeks, with 34 weeks of additional follow-up (112 weeks total) and full information on 118 PFS events. Group-sequential design methods were used with a truncated O'Brien-Fleming upper bound for early rejection of the null hypothesis of no treatment difference by using a log-rank test. One planned interim analysis occurred at 40% (49 of 118) PFS events. Secondary end points included overall response rate (ORR) by RECIST, disease control rate (DCR: ORR plus stable disease), OS, safety, and efficacy of single-agent vandetanib in the crossover portion of the study. OS was measured from date of random assignment until date of death.

Time to events distributions were estimated by the Kaplan-Meier method. The log-rank test was used to compare time-to-event distributions. Cox proportional hazards regression was used to estimate the treatment HR (docetaxel plus vandetanib and/or docetaxel plus placebo) in unadjusted and adjusted models. Multiple regression models were undertaken to estimate the effect of treatment on survival taking into account several prespecified clinical and/or laboratory prognostic factors: age, ECOG PS, visceral and liver metastases, hemoglobin (Hb), number of prior systemic therapies, prior cystectomy, prior paclitaxel, and the recently identified Bellmunt prognostic model.[21] Two-sided Fisher's exact test was used to compare toxicity and response rates by treatment arm. Patients who were randomly assigned but never received

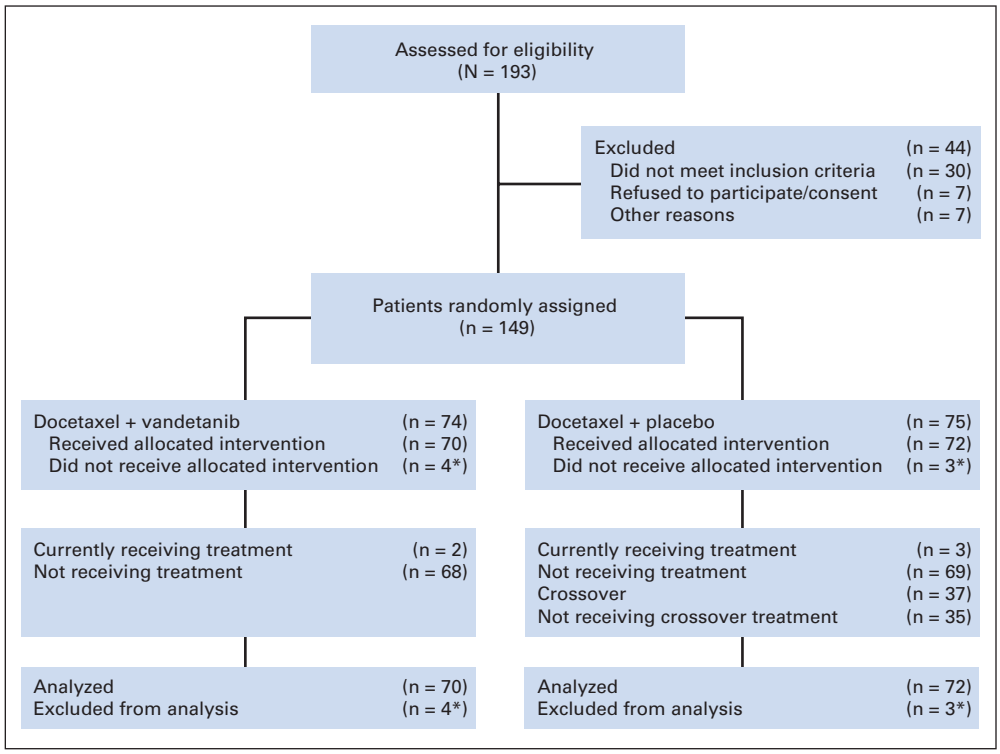

Fig 1. CONSORT diagram. (*) Reasons include new brain metastases; failure to meet eligibility requirements on day 1 because of electrolyte abnormalities; and consent withdrawal, failure to come to the appointment, or use of an alternative regimen on the first day of the protocol.

any treatment dose were allowed to be replaced. Analyses for safety and efficacy used results from patients who received at least one dose of therapy.

RESULTS

In all, 149 patients (docetaxel plus vandetanib, n = 74; docetaxel plus placebo, n = 75) were enrolled and randomly assigned between February 2007 and May 2010 at 16 active sites in the United States. In total, 142 patients received at least one dose of treatment. Completed diaries were returned at more than 90% of visits. Seven patients were randomly assigned but were not able to receive any study drug for various reasons. Figure 1 shows the study profile. Median follow-up for the patients still alive is 7.1 months.

Demographics

Baseline demographics were well balanced between both arms (Table 1). However, there was a greater proportion of patients with Hb less than 10g/dL on the docetaxel plus vandetanib arm ($P = .035$).

Primary End Point: PFS

Median PFS for the docetaxel plus vandetanib combination was 2.56 months versus 1.58 months for the docetaxel plus placebo combination (HR, 1.02; 95% CI, 0.69 to 1.49) with no statistical significance ($P = .939$; Fig 2). Similarly the 3-month PFS rate was not different: 36% in the docetaxel plus vandetanib arm versus 40% in the docetaxel plus placebo arm.

Secondary End Points and Subgroup Analysis

Median OS for the docetaxel plus vandetanib arm was 5.85 months versus 7.03 months for the docetaxel plus placebo combination (HR, 1.21; 95% CI, 0.81 to 1.79; $P = .347$; Fig 3). ORR and DCR were also similar between study arm versus control arm (ORR: 7% [eight of 72] *v* 11% [five of 70], respectively; $P = .56$; DCR: 51% [36 of 70] *v* 42% [30 of 72], respectively; $P = .31$). One patient achieved a complete response on the docetaxel plus vandetanib arm. Overall, 41% of patients experienced some form of tumor shrinkage on the docetaxel plus vandetanib arm (median, −10.8%) versus 37% on the docetaxel plus placebo arm (median, −16.3%).

Table 1. Patient Demographic Characteristics

Characteristic	Docetaxel Plus Vandetanib (n = 70) No.	%	Docetaxel Plus Placebo (n = 72) No.	%
Age ≥ 65 years	38	54.3	33	45.8
Male sex	48	68.6	49	68.1
ECOG PS 1	30	42.9	38	52.8
Visceral metastases	47	67.1	46	63.9
Liver metastases	23	32.9	27	37.5
PS 1 and/or visceral metastases	58	82.9	55	76.4
No. of prior systemic therapies				
> 1	34	48.6	28	38.9
> 2	12	17.1	10	13.9
Prior cystectomy	32	46.4	36	50
Prior radiation	17	24.3	15	20.8
Prior paclitaxel	13	18.6	8	11.1
Hemoglobin < 10g/dL*	15	21.4	6	8.5
Bellmunt risk score > 0[21]	46	65.7	49	69

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*$P < .05$.

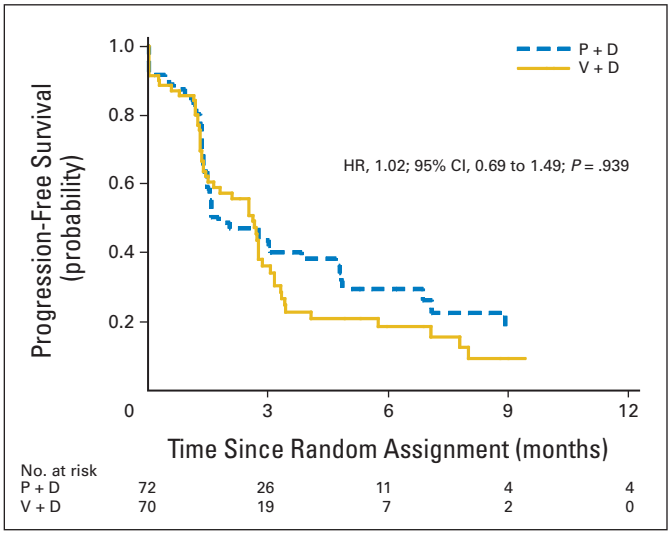

Fig 2. Progression-free survival (months). D, docetaxel; HR, hazard ratio; P, placebo; V, vandetanib.

Table 2. Most Common Treatment-Related Adverse Events and Hematologic Abnormalities

Adverse Event or Hematologic Abnormality	Docetaxel Plus Vandetanib (n = 70)				Docetaxel Plus Placebo (n = 72)			
	All Grades		Grades 3 to 4		All Grades		Grades 3 to 4	
	No.	%	No.	%	No.	%	No.	%
Hematologic	15	21	13	19	15	21	14	19
Anemia	4	6	3	4	2	3	1	1
Neutropenia	10	14	10	14	10	14	10	14
Nonhematologic*	40	57	35	50	26	36	18	25
Diarrhea*	11	16	5	7	0	0	0	0
Fatigue	15	21	6	9	10	14	4	6
Rash/photosensitivity*	9	13	8	11	2	3	0	0
Infections	5	7	3	4	5	7	4	6
Neuropathy	4	6	2	3	2	3	0	0
Electrolyte abnormalities	10	14	7	10	4	6	4	6

*$P < .05$ for both all-grade and high-grade toxicities.

Exploratory analyses were conducted in several subgroups to detect whether there is any preferential activity for the docetaxel plus vandetanib group over docetaxel plus placebo in terms of PFS or OS. No differences were found to favor the study group arm over the control arm for both PFS and OS. For example, patients with one and more than one prior systemic therapies had a PFS of 1.54 and 1.58 months on the docetaxel plus placebo arm versus 2.53 and 2.66 months on the docetaxel plus vandetanib arm, respectively. OS was similar in both arms (6.8 months) in patients with more than one prior systemic therapy; in those with one prior therapy, OS was 7.39 months in the docetaxel plus placebo arm versus 5.62 months in the docetaxel plus vandetanib arm (Appendix Figs A1 and A2, online only).

Study Drug Exposure and Tolerability

Approximately 74% of patients completed four cycles of treatment on each arm. The median treatment duration for patients on study was two cycles, and the mean was 3.9 cycles. As of the December 1, 2010, cutoff for the study analysis, five patients were still receiving treatment. Their median treatment duration was 14 cycles (range, 11 to 24 cycles). All-grade and high-grade toxicities were 66% and 60% in the docetaxel plus vandetanib arm and 44% and 36% in the docetaxel plus placebo arm, respectively ($P = .012$ for all-grade and $P = .007$ for high-grade toxicities). However, grade 4 toxicities were not different between both arms (14.3% for the docetaxel plus vandetanib arm and 11.1% for the docetaxel plus placebo arm). Nonhematologic adverse effects were more common in the vandetanib plus docetaxel arm, with the most frequent being diarrhea and rash/photosensitivity. Table 2 provides the most common treatment-related adverse events and hematologic toxicities for both arms. Only one patient's death was possibly related to the study drug in the vandetanib plus docetaxel arm (pulmonary infection).

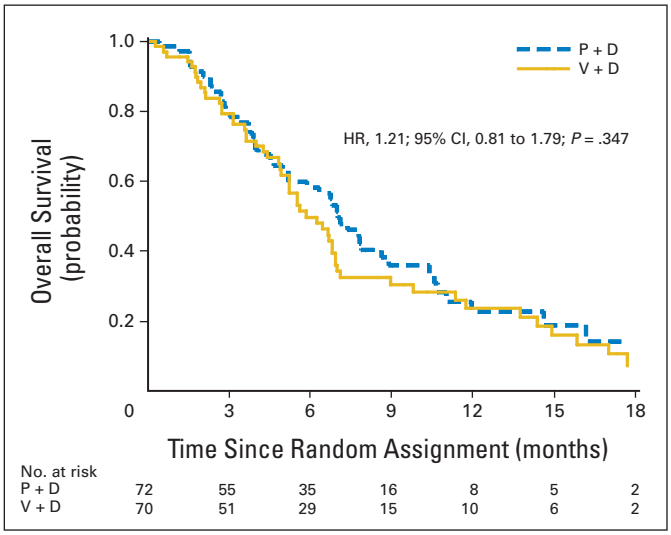

Fig 3. Overall survival (months). D, docetaxel; HR, hazard ratio; P, placebo; V, vandetanib.

Single-Agent Activity and Toxicity

Thirty-seven patients who progressed on the randomized portion of the trial were found to be on the docetaxel plus placebo arm on unblinding, and they met the eligibility criteria to cross over to vandetanib. Overall, one patient who crossed over had a partial response corresponding to an ORR of 2.8%. Stable disease was seen in five patients (13.5%). Median OS from starting vandetanib treatment was 5.2 months. Thirty percent of patients experienced all-grade toxicities, with 16% being grade 3. Fatigue (all-grade: five of 37 [13.5%]; high-grade: two of 37 [5.4%]) was the most common toxicity seen with single-agent vandetanib, followed by dyspnea (all-grade: three of 37 [8.1%]; high-grade: two of 37 [5.4%]).

Prognostic Factors

To identify prognostic factors associated with OS, we performed a multivariable analysis of prespecified clinical and laboratory factors.[21,22] In addition, we assessed the performance of the prognostic model published by Bellmunt et al[21] in patients for whom prior

Table 3. Results of the Multivariate Cox Proportional Hazard Model for Overall Survival

Variable	HR	95% CI	*P*
Male sex	0.93	0.61 to 1.41	.928
ECOG PS > 0	0.40	0.27 to 0.61	< .001
Visceral metastases	0.73	0.49 to 1.11	.150
> One prior systemic therapy	0.83	0.56 to 1.24	.363
No prior cystectomy	0.61	0.41 to 0.92	.017
Prior paclitaxel	0.92	0.52 to 1.62	.771
Hemoglobin < 10g/dL	0.46	0.27 to 0.78	.004
Liver metastases	0.54	0.36 to 0.82	.004
Bellmunt risk score > 0	0.30	0.18 to 0.48	< .001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PS, performance status.

platinum-based therapies failed. This model includes three adverse prognostic factors: Hb less than 10 g/dL, the presence of liver metastasis, and ECOG PS > 0.[21] Patients were dichotomized into two groups: one group with zero risk factors and one group with one or more risk factors, as detailed in Table 1. In our analysis, each of the three factors identified by Bellmunt et al[21] were significant prognostic factors strongly associated with the risk of death, with the lowest HR seen for the Bellmunt risk score model (HR, 0.30; 95% CI, 0.18 to 0.48; $P < .001$). In addition, prior cystectomy was also found to be associated with a better OS (Table 3).

DISCUSSION

This randomized multicenter study of docetaxel plus placebo versus docetaxel plus vandetanib showed that the addition of vandetanib (a dual inhibitor of VEGFR and EGFR) to docetaxel did not result in clinical benefit. PFS and OS in the whole cohort were relatively short. The vandetanib plus docetaxel arm had more patients with Hb less than 10 g/dL (13% difference), a known adverse factor, but this imbalance that favored the placebo group is unlikely to have biased the results, since the rest of the patients' characteristics were balanced between both arms. We also did not find any advantage (in term of PFS or OS) of adding vandetanib to docetaxel when we looked at several subgroups stratified by number of prior lines of systemic therapies, use of prior paclitaxel, and adverse prognostic factors. Furthermore, toxicities (both all-grade and high-grade) were greater, despite the fact that they were manageable with only one death possibly attributed to study drug.

Despite their minimal activity, taxanes are the most commonly used salvage agents in UC. A phase III study of vinflunine (a novel vinca-alkaloid)[9] in pretreated patients with UC showed an OS of 6.9 months versus 4.6 months in patients who received best supportive care ($P = .28$). The OS in the vinflunine study is quite similar to the OS in our study, suggesting that salvage chemotherapy has little effect on the natural history of this disease.

The median OS in our study was less than 7 months, inferior to what was reported (OS, 9 months) more than 10 years ago in a single-arm phase II study of docetaxel.[4] Although our study is more recent, our patient population was heavily pretreated: 43% of patients received two or more systemic therapies, and 15% had already received another taxane (paclitaxel). In the older study, only one prior therapy was allowed, and patients with prior exposure to paclitaxel were excluded. Therefore, one possible explanation for poor activity of docetaxel in our study is that the previously treated patients who were selected had disease that was too advanced to detect any activity.

Despite the encouraging preclinical data with agents targeting the EGF or the VEGF axis in bladder cancer, early trials of single-agent EGFR or VEGFR inhibitors have yielded poor results. Although gefitinib has shown activity against two bladder cell lines in vitro[23] and resulted in a decrease in DNA synthesis in bladder cancer cell lines,[24] phase II studies of single-agent gefitinib and lapatinib in platinum-refractory patients with UC did not show any meaningful activity.[25,26] Similarly, single-agent phase II trials of VEGFR inhibitors did not show convincing results. In one trial, sorafenib did not show any responses in 27 treated patients.[27] Conversely, sunitinib showed few responses in 77 patients who were pretreated with platinum, with minor responses or stable disease in 43% of patients.[28] Nevertheless, OS was 6 months, in line with several other trials of salvage chemotherapy.

Patients who crossed over to single-agent vandetanib also rarely responded to therapy, and their survival was only 5.2 months. The patients treated with single-agent vandetanib (n = 37) had to have progressed through at least one platinum-based therapy and then have experienced treatment failure with a taxane (docetaxel); thus, they were an even more refractory population.

The results of the multivariate Cox regression model confirmed the prognostic value of several factors on OS, specifically in our population of patients who had platinum-based pretreatment. We found that a prior cystectomy confers better OS, likely a reflection of the fact that such patients presented with organ-confined and less aggressive disease amenable to cystectomy. We also externally validated the Bellmunt model itself[21] as the strongest predictor of OS (HR, 0.3) in a platinum-refractory population. This model, derived from patients treated with vinflunine, is now more generalizable and applicable to patients treated with taxanes. It can be used for counseling patients and future stratification in clinical trials of novel agents.

Our study has several strengths: It is a randomized, placebo-controlled study that represents the second largest trial of salvage chemotherapy in bladder cancer and the largest trial with EGFR and VEGFR inhibitors. Nevertheless, it remains a phase II study, able to detect only large differences in clinical outcomes. Nonetheless, it is unlikely that vandetanib offers any benefit to a similar population of patients. Future trials with vandetanib based on preselected biomarkers or less heavily treated patients are potential areas of investigation.

In conclusion, the addition of vandetanib (a dual EGFR and VEGFR inhibitor) to docetaxel did not result in clinical benefit in a population of patients with advanced UC who were previously treated with platinum-based therapies. At this time, vandetanib cannot be recommended for future studies in the salvage setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest.

No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. 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.

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