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ORIGINAL REPORT

# Phase II Trial of Cetuximab With or Without Paclitaxel in Patients With Advanced Urothelial Tract Carcinoma

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## ABSTRACT

### Purpose
The benefit of salvage chemotherapy is modest in metastatic urothelial cancer. We conducted a randomized, noncomparative phase II study to measure the efficacy of cetuximab with or without paclitaxel in patients with previously treated urothelial cancer.

### Patients and Methods
Patients with metastatic urothelial cancer who received one line of chemotherapy in the perioperative or metastatic setting were randomly assigned to 4-week cycles of cetuximab 250 mg/m$^2$ with or without paclitaxel 80 mg/m$^2$ per week. We used early progression as an indicator of futility. Either arm would close if seven of the initial 15 patients in that arm progressed at the first disease evaluation at 8 weeks.

### Results
We enrolled 39 evaluable patients. The single-agent cetuximab arm closed after nine of the first 11 patients progressed by 8 weeks. The combination arm completed the full accrual of 28 patients, of whom 22 patients (78.5%) had visceral disease. Twelve of 28 patients had progression-free survival greater than 16 weeks. The overall response rate was 25% (95% CI, 11% to 45%; three complete responses and four partial responses). The median progression-free survival was 16.4 weeks (95% CI, 12 to 25.1 weeks), and the median overall survival was 42 weeks (95% CI, 30.4 to 78 weeks). Treatment-related grade 3 and 4 adverse events that occurred in at least two patients were rash (six cases), fatigue (five cases), and low magnesium (three cases).

### Conclusion
Although it had limited activity as a single agent, cetuximab appears to augment the antitumor activity of paclitaxel in previously treated urothelial cancers. The cetuximab and paclitaxel combination merits additional study to establish its role in the treatment of urothelial cancers.

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## INTRODUCTION

Urothelial carcinoma of the bladder is the most common cancer of the urinary tract, with 73,510 new cases expected in 2012 in the United States.[1] Approximately 30% of these patients have muscle invasive disease. Despite aggressive surgical resection and perioperative chemotherapy, relapses in patients with muscle invasive disease are common and result in approximately 14,000 deaths annually. Only one third of patients will have a pathologic complete response (CR) at surgery after neoadjuvant chemotherapy. The median survival for patients with residual disease despite neoadjuvant chemotherapy is less than 4 years.[2]

The median survival for patients with metastatic urothelial cancer is approximately 15 months.[3] This poor overall survival is largely due to the lack of effective salvage regimens. With the exception of gemcitabine, which is frequently used in first-line therapy in combination with cisplatin, treatments after the failure of platinum-based chemotherapy have shown limited benefit, with a median progression-free survival (PFS) of less than 3 months (Table 1).[4]

Novel approaches are needed for patients with platinum refractory urothelial carcinoma. One plausible target is the epidermal growth factor receptor (EGFR). Strong expression of EGFR is found in 50% of bladder cancers. Invasive tumors (pT2-4) and high-grade tumors are more likely to overexpress EGFR compared with superficial tumors and low-grade tumors.[5-8] In addition, increased expression of EGFR is associated with tumor progression and shorter disease-free survival.[5,9,10]

Cetuximab (Erbitux; Bristol-Myers Squibb, Princeton, NJ) is a monoclonal antibody against EGFR that has been approved for the treatment of

**Table 1.** Studies in Advanced Urothelial Cancer

| Agent | Dose | Setting | Eligible if Patient Received Perioperative Therapy Only? | % Receiving Perioperative Therapy | RR (%) | 95% CI (%) | TTP or PFS (months) | OS (months) |
|---|---|---|---|---|---|---|---|---|
| Gemcitabine[18]; n = 35 | 1,200 mg/m$^2$ per day on days 1, 8, and 15 of a 28-day cycle | Previous cisplatin-based chemotherapy | Yes | 17 | 22.5 | 8.0 to 37.0 | TTP, 3.8 | 5 |
| Gemcitabine[19]; n = 30 | 1,250 mg/m$^2$ per day on days 1 and 8 of a 21-day cycle | Previous cisplatin-based chemotherapy | Yes | 95 | 11 | Not reported | TTP, 4.8 | Not reported |
| Paclitaxel[20]; n = 45 | 80 mg/m$^2$ per day on days 1, 8, and 15 of a 28-day cycle | Progressive measurable disease after previous line of chemotherapy for advanced disease | Yes | 71 | 9 | 2.0 to 21.0 | PFS, 3.0 | 6.9 |
| Docetaxel[21]; n = 30 | 100 mg/m$^2$ per day every 3 weeks | Progression after one previous cisplatin-containing regimen | Yes | 43 | 13.3 | 3.8 to 30.7 | Not reported | 9 |
| Pemetrexed[4]; n = 47 | 500 mg/m$^2$ per day every 3 weeks | Progression after chemotherapy for advanced or metastatic disease | Yes, within 12 months | 38 | 27.7 | 15.6 to 42.6 | TTP, 2.9 | 9.6 |
| Sunitinib[22]; n = 45 | 50 mg per day for 4 weeks on and 2 weeks off | Up to four previous cytoxic regimens; 58% received three or four regimens | Yes | 40 | 0.7 | 1.0 to 18.0 | PFS, 2.4 | 7.1 |
| Sunitinib[22]; n = 32 | 37.5 mg per day | Up to four previous cytoxic regimens; 37% received three or four regimens | Yes | 37 | 0 | 0 to 16.0 | PFS, 2.3 | 6 |
| Paclitaxel[23]; n = 31 | 80 mg/m$^2$ weekly | Progression after one previous therapy for advanced disease | No | | 10 | 0 to 20.0 | TTP, 2.2 | 7.2 |
| Vinflunine[24]; n = 253, randomly assigned against best supportive care | 320 or 180 mg/m$^2$ on the basis of previous RT and PS | After first-line platinum-containing chemotherapy for locally advanced or metastatic disease | No | | 8.6 | 5.0 to 13.7 | PFS, 3.0 | 6.9 |

Abbreviations: OS, overall survival; PFS, progression-free survival; PS, performance status; RR, response rate; RT, radiotherapy; TTP, time to progression.

patients with head and neck and colorectal cancers.[11-13] Activity has also been demonstrated in advanced non–small-cell lung cancer.[14] Preclincal activity has been shown in orthotopic bladder tumor models treated with cetuximab.[15] In addition, the combination of cetuximab and paclitaxel in the same in vivo tumor model resulted in additive or better tumor reduction and inhibition of angiogenesis compared with the effects of each agent alone.[16]

To determine the efficacy of EGFR inhibition in urothelial cancers, we conducted a randomized, open-label, noncomparative phase II study to measure the efficacy of cetuximab with and without paclitaxel in patients with chemotherapy refractory metastatic urothelial cancer who have progressed after one previous treatment. Because of the short time to progression seen with other salvage regimens (including single-agent paclitaxel), we used a design in which early progression was used to assess futility.[17]

## PATIENTS AND METHODS

### *Patient Selection*

Patients were enrolled who were older than age 18 years, had a histologically confirmed diagnosis of urothelial cancer, and radiographic evidence of metastases. Mixed histologies were allowed provided they included a component of urothelial cancer. Patients must have had progressive disease after therapy for advanced disease or progressive disease after perioperative (neoadjuvant or adjuvant) therapy. There was no restriction on the time from previous therapy. Patients must have had at least one measurable lesion by RECIST, an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate hematologic, renal (creatine clearance $>$ 30), and hepatic function. Patients who received previous taxanes were excluded. The study was approved by institutional review boards at each protocol site; all patients provided written informed consent. This investigator-initiated study was sponsored by the Office of Extramural Research at Fox Chase Cancer Center (FCCC).

### *Treatment*

Patients were randomly assigned by using permutated blocks designed for each site to receive either single-agent cetuximab weekly (arm A) or cetuximab in combination with paclitaxel weekly (arm B). Each cycle was four weeks.

All patients received cetuximab 400 mg/m$^2$ intravenously (IV) as a loading dose followed by weekly doses of 250 mg/m$^2$ IV. Patients in arm B also received paclitaxel 80 mg/m$^2$ IV weekly. Patients received standard premedications for both cetuximab and paclitaxel, including corticosteroids, diphenhydramine, and ranitidine. Patients could receive up to two dose reductions for toxicity; patients in the combination arm could undergo two dose reductions for each drug. There were no breaks between

  

cycles. Treatment was continued until disease progression, unacceptable toxicity, or death.

### Patient Evaluation

The baseline evaluation included a complete history, examination including height, weight, and assessment of Eastern Cooperative Oncology Group performance status. Imaging included baseline chest, abdominal, and pelvic computed tomography scans and/or magnetic resonance imaging.

Patients were seen by physicians at the beginning of each 4-week cycle. They were also assessed for toxicity before each weekly treatment by the protocol staff. Complete blood counts and chemistry studies, including magnesium, potassium, and calcium levels, were monitored weekly. For cycle three and beyond, the frequency of complete blood counts and serum chemistry tests could be decreased to every 2 weeks if there was no hematologic toxicity above grade 1, and the magnesium, calcium, and potassium levels were within normal limits, with or without supplementation. Adverse events were graded by using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

### Analysis of Progression-Free Survival and Response

Patients were evaluated by using imaging every 8 weeks. Patients who were taken off study before progression were followed for progression. When follow-up scans were available, they were assessed for disease progression.

RECIST criteria were used to evaluate for the response to therapy. All responses were required to be confirmed by a subsequent scan $\geq$ 4 weeks later. Investigator assessments were used to determine PFS and responses. At the FCCC, all clinical trial participants with partial responses and CRs were reviewed by an independent response verification committee. In addition, we were able to obtain images from four of the five patients from outside centers who met our primary end point (progression free at 16 weeks) for review by a single FCCC radiologist (M.B.).

### Study Design and End Points

This study was a noncomparative phase II study; each arm was evaluated independently. We previously reported our study design, which used early progression to assess for futility.[17] This schema is shown in Appendix Figure A1 (online only). The primary end point was PFS. On the basis of the activity of other salvage therapies (Table 1), we considered an arm not worthy of pursuit if the median PFS was $\leq$ 8 weeks. However, either arm was considered to be worthy of additional investigation if 45% of the patients were progression free at 16 weeks. This approximates the median time to progression of 4 months reported for single-agent gemcitabine, which is among the most active agents but is now frequently used in the front-line setting.

Our composite null hypothesis was that the median PFS would be 8 weeks (ie, the chance that the 8-week PFS would be 50%), and $\leq$ 20% of patients would have a PFS greater than 16 weeks. The early stopping rules were based on a 20% increase in 8-week PFS to 70%. To meet the study end point, either arm would need a 16-week PFS of 45% (an increase of 25% over the null).

Under these assumptions, early stopping rules stated that either arm would close unless at least eight of the first 15 patients in that arm were progression free at 8 weeks. The probabilities of stopping early if the agent was effective or ineffective were 5% and 50%, respectively. If one arm closed as a result of futility, the other arm could remain open if it did not meet criteria for early stopping.

The target accrual was 28 patients per arm. Either arm was considered positive if at least nine of 28 patients were progression free at 16 weeks. Each arm had 90.4% power with 7.1% type I error to detect an improvement in 16-week PFS from 20% to 45%.

## RESULTS

We enrolled a total of 39 evaluable patients, with 11 patients in the single-agent cetuximab arm and 28 patients in the cetuximab and paclitaxel arm. Patient characteristics are shown in Table 2. Two nonevaluable patients were replaced. One patient was found ineligible as a result of the lack of metastatic disease. Another patient had a grade 4 hypersensitivity reaction to paclitaxel during his first cycle of therapy.

### Single-Agent Cetuximab

The single-agent cetuximab arm was closed for futility after nine of the first 11 patients were found to have progressed by their first disease evaluation at 8 weeks. The median PFS was 7.6 weeks (95% CI, 6.0 weeks to NR [not reached]). There were no objective responses. The median overall survival was 17.0 weeks (95% CI, 14.3 weeks to NR). The PFS and overall survival curves are shown

**Table 2.** Patient Demographics and Clinical Characteristics

| Demographic or Characteristic | Arm A: Single-Agent Cetuximab | Arm B: Cetuximab and Paclitaxel |
|---|---|---|
| No. of patients | 11 | 28 |
| Sex, No. of patients | | |
| M | 9 | 21 |
| F | 2 | 7 |
| Age, years | | |
| Median | 70 | 69 |
| Range | 49-83 | 46-82 |
| Race, No. of patients | | |
| White | 9 | 23 |
| African descent | 2 | 5 |
| Asian | | 1 |
| Performance status, No. of patients | | |
| 0-1 | 11 | 25 |
| 2 | | 3 |
| Primary site, No. of patients | | |
| Bladder | 9 | 26 |
| Renal pelvis | 2 | 2 |
| Previous chemotherapy, No. of patients | | |
| Gemcitabine and platinum | 11 | 26 |
| MVAC | | 2 |
| Setting of previous chemotherapy, No. of patients | | |
| Neoadjuvant therapy | 0 | 7 |
| Adjuvant therapy | 7 | 6 |
| Metastatic disease | 4 | 15 |
| Time for last chemotherapy dose to protocol registration, days | | |
| Neoadjuvant therapy | | 364 |
| Range | | 79-653 |
| Adjuvant therapy | 160 | 182 |
| Range | 23-425 | 39-388 |
| Metastatic disease | 91 | 59 |
| Range | 34-147 | 22-140 |
| Sites of disease, No. of patients | | |
| Lung | 9 | 14 |
| Liver | 4 | 5 |
| Adrenal gland | 0 | 4 |
| Lymph node | 10 | 20 |
| Soft tissue | 3 | 7 |
| Bladder | 1 | 2 |
| Bone | 0 | 6 |
| Visceral metastases, No. of patients | 10 | 17 |

Abbreviation: MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.

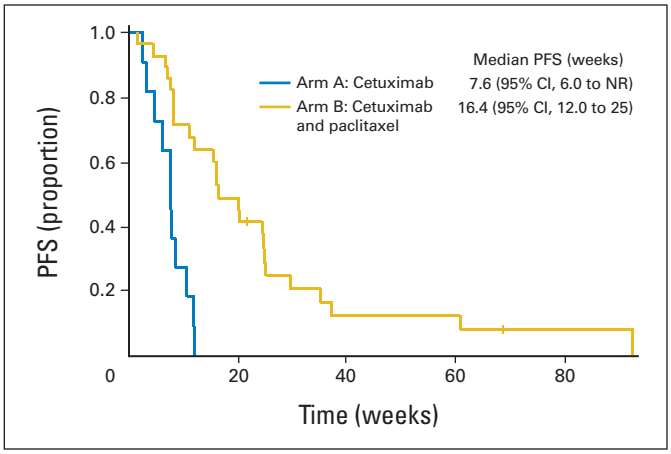


**Fig 1.** Kaplan-Meier curves for progression-free survival (PFS). NR, not reached.

in Figures 1 and 2. The median number of cycles received was two cycles. All 11 patients given single-agent cetuximab were taken off study for disease progression.

The 11 patients received a total of 22 cycles of single-agent cetuximab. There were no dose reductions. Two patients each had 1 week held as a result of a grade 3 rash. The treatment of another patient was held 1 week as a result of a grade 2 hypersensitivity reaction. The only treatment-related adverse effects were grade 3 rash (two patients) and grade 3 pruritus (one patient). There were no treatment-related deaths. Grade 3 to 5 treatment-related toxicities are summarized in Table 3.

### *Cetuximab and Paclitaxel Combination*

*Efficacy.* The combination arm proceeded to full accrual (28 patients). Of the full cohort, 12 patients were found to be progression free at 16 weeks, which met the primary end point. The median PFS was 16.4 weeks (95% CI, 12.0 to 25.1 weeks). The median overall survival was 42 weeks (95% CI, 30.4 to 78.0 weeks). PFS and overall survival curves are shown in Figures 1 and 2.

In addition, seven patients had confirmed responses (three CRs and four partial responses), which resulted in an overall response rate of 25% (95% CI, 11% to 45%). A waterfall plot that shows the maximum tumor shrinkage in the combination arm is shown in Figure 3. Two patients maintained responses after discontinuing therapy; these patients remained off any therapy for 25.1 and 26 weeks before ultimately progressing. Another patient continued in CR 51+ weeks after discontinuing therapy.

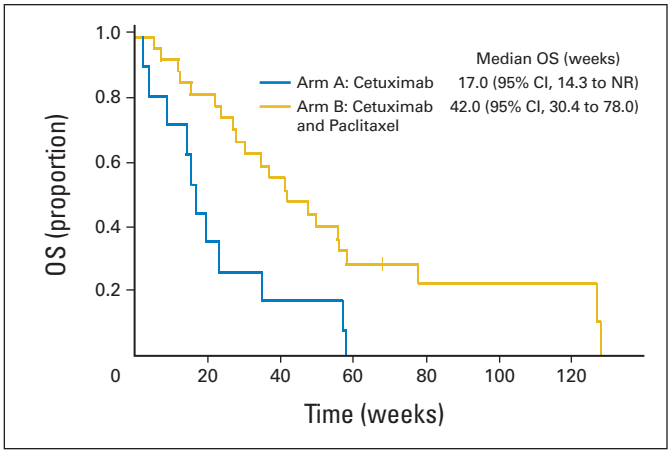


**Fig 2.** Kaplan-Meier curves for overall survival (OS).

Seventeen patients had visceral metastases to the lung, liver, bone, and/or adrenal glands. In this subgroup, the median PFS was 16.1 weeks (95% CI, 8.3 to 29.6 weeks). The median overall survival was 30.4 weeks (95% CI, 23.9 weeks to NR). Fifteen patients received previous chemotherapy in the metastatic setting; the remainder of patients received treatment in a perioperative setting. The median PFS in this group of patients who received chemotherapy for metastatic disease was 12 weeks (95% CI, 7.6 weeks to NR), with a median overall survival of 27 weeks (95% CI, 15.6 weeks to NR).

*Reasons for discontinuation.* Nineteen patients were taken off study for disease progression, four patients were taken off study for toxicity, two patients were taken off study because of patient decision, and three patients were taken off study as a result of physician discretion.

*Safety and tolerability.* The 28 patients who were enrolled in arm B received at total of 132 cycles of cetuximab and paclitaxel. Eleven patients had dose reductions of paclitaxel to 70 mg/m$^2$. Five of these patients underwent a second dose reduction to 60 mg/m$^2$. One patient had an additional dose reduction of paclitaxel to 50 mg/m$^2$ for neutropenia. The patient received one dose at this level and then stopped protocol therapy when his scans after cycle 4 demonstrated a CR. Five patients underwent dose reductions of cetuximab to 200 mg/m$^2$ (one patient for rash, one patient for rash and fatigue, two patients for hypomagnesemia, and one patient for infected paronychia). An additional patient underwent two dose reductions to 150 mg/m$^2$ for a grade 3 rash.

The most common treatment-related grade 3 and 4 adverse events were rash (six patients) and hypomagnesemia (three patients). Pruritus, pain, and fatigue occurred in two patients each. Paresthesia, hypokalemia, dehydration, anemia, leukopenia, neutropenia, vomiting, infection (without neutropenia), and hypersensitivity reaction occurred in one patient each. Grade 3 to 5 treatment-related toxicities are summarized in Table 3.

## DISCUSSION

Although we found single-agent cetuximab to be inactive in advanced urothelial cancer, the results of the combination arm suggested that EGFR inhibition with cetuximab may augment the antitumor activity of paclitaxel. This arm of the study met its primary end point and showed a median PFS of 16.4 weeks, which demonstrated that the combination of cetuximab and paclitaxel prolonged PFS compared with historical controls of single-agent paclitaxel. In addition, we noted a response rate of 25%. This multicenter study demonstrated that the combination of cetuximab and paclitaxel can be safely administered in the community setting. The most frequent toxicities of rash, fatigue, and hypomagnesemia were expected from both agents and were manageable.

We used a phase II design in this study that recognizes rapid progression as an early time point as a marker of futility.[17] In this noncomparative, randomized design, either arm would close unless at least eight of the first 15 patients are progression free at their first

  

**Table 3.** Grade 3-5 Adverse Events

| Adverse Event | Arm A: Grades 3 and 4 | | | | Arm B: Grades 3-5 | | | |
|---|---|---|---|---|---|---|---|---|
| | Any | | Treatment Related | | Any | | Treatment Related | |
| | No. | % | No. | % | No. | % | No. | % |
| Nonlaboratory | | | | | | | | |
| Rash | 2 | 18.2 | 2 | 18.2 | 6 | 21.4 | 6 | 21.4 |
| Fatigue | 1 | 9.1 | | | 5 | 17.9 | 2 | 7.1 |
| Infection without neutropenia | 0 | 0.0 | | | 3 | 10.7 | 1 | 3.6 |
| Hypertension | 3 | 27.3 | | | 3 | 10.7 | | |
| Vomiting | 0 | 0.0 | | | 3 | 10.7 | | |
| Pain | 1 | 9.1 | | | 3 | 10.7 | 2 | 7.1 |
| DVT | 0 | 0.0 | | | 2 | 7.1 | | |
| Diarrhea | 2 | 18.2 | | | 2 | 7.1 | | |
| Paresthesia | 0 | 0.0 | | | 2 | 7.1 | 1 | 3.6 |
| Nausea | 0 | 0.0 | | | 2 | 7.1 | | |
| HSR | 0 | 0.0 | | | 1 | 3.6 | | |
| Dizziness | 0 | 0.0 | | | 1 | 3.6 | | |
| Fever | 0 | 0.0 | | | 1 | 3.6 | | |
| Pruritus | 1 | 9.1 | 1 | 9.1 | 1 | 3.6 | 2 | 7.1 |
| Headache | 0 | 0.0 | | | 1 | 3.6 | | |
| Myalgias | 0 | 0.0 | | | 1 | 3.6 | | |
| Dyspena-SOB | 2 | 18.2 | | | 1 | 3.6 | | |
| Dehydration | 0 | 0.0 | | | 1 | 3.6 | 1 | 3.6 |
| Liver failure | 0 | 0.0 | | | 1 | 3.6 | | |
| Laboratory | | | | | | | | |
| Anemia | 1 | 9.1 | | | 4 | 14.3 | 1 | 3.6 |
| Hypomagnesemia | 0 | 0.0 | | | 3 | 10.7 | 3 | 10.7 |
| Neutropenia | 0 | 0.0 | | | 2 | 7.1 | 1 | 3.6 |
| Leukopenia | 0 | 0.0 | | | 1 | 3.6 | 1 | 3.6 |
| Elevated ALP | 1 | 9.1 | | | 1 | 3.6 | | |
| Hypokalemia | 0 | 0.0 | | | 1 | 3.6 | 1 | 3.6 |
| Hyperkalemia | 0 | 0.0 | | | 1 | 3.6 | | |
| Hypoalbuminemia | 0 | 0.0 | | | 1 | 3.6 | | |
| Hyperbilirubinemia | 0 | 0.0 | | | 1 | 3.6 | | |
| Hypocalcemia | 0 | 0.0 | | | 1 | 3.6 | | |
| Hypercalcemia | 0 | 0.0 | | | 1 | 3.6 | | |

Abbreviations: ALP, alkaline phosphatase; DVT, deep venous thrombosis; HSR, hypersensitivity reaction; SOB, shortness of breath.

disease evaluation at 8 weeks. An arm that enrolls fully (28 patients) is considered promising if at least nine patients are progression-free at 16 weeks. This design, in which each patient is evaluated for progression at both an early and final time point, has several advantages over the traditional Simon phase II design, which evaluates efficacy at only one time point. As soon as we ensure that eight of the first 15 patients are progression free at 8 weeks, we may recruit the second cohort of patients. This method can be more efficient than the traditional Simon design, which requires patient evaluation at one time point, typically later than with our design (eg, 16 weeks in this study if we had used the traditional Simon design). The probability of early stopping in error was only 5%, and we were able to demonstrate with adequate power (90.4%) and type 1 error (7.1%) that we met our primary end point for the combination arm.

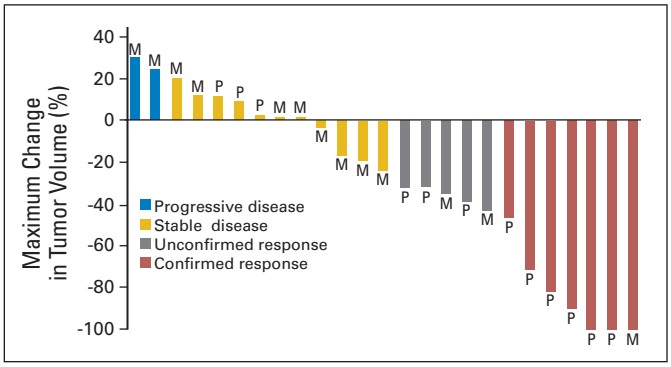


**Fig 3.** Waterfall plot of maximum changes in tumor volume for patients treated with paclitaxel and cetuximab. Three patients were not evaluable for response. M, patients who received chemotherapy for metastatic disease; P, patients who received perioperative chemotherapy.

Another reason for choosing PFS rather than the objective response rate as our primary end point pertains to the observation that some molecularly targeted agents such as cetuximab may cause disease stabilization rather than tumor shrinkage. By using the 4-month median time to progression observed with gemcitabine in platinum-refractory metastatic urothelial cancer as a historical reference,[18,19] we considered either arm worthy of additional investigation if it produced a median PFS of approximately the same time period. Paclitaxel is used in the second-line setting with a median PFS of slightly greater than 2 months.[20,23] Therefore, we believed that cetuximab with or without paclitaxel would not be worthy of additional investigation if the median PFS was no better than 8 weeks.

Our results should be viewed within the context of the study limitations. One potential limitation of this and several other uncontrolled phase II studies in urothelial cancer is the inclusion of patients with metastatic disease whose only previous chemotherapy was in the perioperative setting together with patients who progressed after the first line of chemotherapy in the metastatic setting (Table 1). Our study was not powered to compare these subgroups. Therefore, our results are hypothesis generating and require confirmation in a larger randomized study with prospective stratification according to the previous treatment setting.

Other studies of salvage chemotherapy have shown a modest benefit. An earlier study of single-agent paclitaxel demonstrated a response rate of 10% with a time to progression of 2.2 months.[23] A contemporary study of the same treatment suggested a similarly modest response rate (9%) and time to progression of 3 months.[20] Both studies included patients who received only perioperative chemotherapy as a previous treatment. A phase II study of pemetrexed in a mixed population of patients who received previous therapy in both the perioperative and advanced-disease setting demonstrated a response rate of 27.7% and a median time to progression of 2.9 months.[24] In a phase II study of two dosing schedules of sunitinib (50 mg 6 weeks on and 2 weeks off and 37.5 mg per day), the median PFS was 2.4 and 2.3 months, respectively.[22] In a randomized controlled trial of patients with cisplatin-refractory urothelial cancer, patients treated with vinflunine had a median PFS of 3 months compared with 1.5 months with best supportive care.[24]

The results presented in this study support the preclinical findings of a potential positive interaction between cetuximab and paclitaxel.[16] Although the mechanism of this interaction is not clear, one hypothesis is that the induction of apoptosis by paclitaxel followed by the inhibition of proliferation by cetuximab yields at least additive antitumor effects in a sequence-dependent manner.[25,26] This hypothesis should be explored further in a randomized trial of paclitaxel with or without cetuximab. Our results were consistent with findings in other disease sites such as colorectal cancer, in which studies suggested that cetuximab is synergistic with irinotecan. In a large phase III study of patients with advanced colorectal cancer, the combination of cetuximab and irinotecan resulted in an improved PFS (median, 4.0 *v* 2.6 months) and response rate (16.4% *v* 4.2%) compared with single-agent irinotecan.[27]

In conclusion, although cetuximab is inactive as a single agent in advanced urothelial cancer, it may augment the antitumor activity of paclitaxel when given in combination. The combination of paclitaxel and cetuximab should be compared with single-agent paclitaxel in a randomized controlled trial to establish the role of EGFR inhibition by monoclonal antibodies in advanced urothelial cancers.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(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.*
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**Data analysis and interpretation:** Yu-Ning Wong, Samuel Litwin, Elizabeth R. Plimack, Marion Brody, Gary Hudes
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

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