Randomized Phase II Study Investigating Pazopanib Versus Weekly Paclitaxel in Relapsed or Progressive Urothelial Cancer


ABSTRACT

Purpose
Two previous single-arm trials have drawn conflicting conclusions regarding the activity of pazopanib in urothelial cancers after failure of platinum-based chemotherapy.

Patients and Methods
This randomized (1:1) open-label phase II trial compared the efficacy of pazopanib 800 mg orally with paclitaxel (80 mg/m² days 1, 8, and 15 every 28 days) in the second-line setting. The primary end point was overall survival (OS).

Results
Between August 2012 and October 2014, 131 patients, out of 140 planned, were randomly assigned. The study was terminated early on the recommendation of the independent data monitoring committee because of futility. Final analysis after the preplanned number of deaths (n = 110) occurred after a median follow-up of 18 months. One hundred fifteen deaths had occurred at the final data extract presented here. Median OS was 8.0 months for paclitaxel (80% CI, 6.9 to 9.7 months) and 4.7 months for pazopanib (80% CI, 4.2 to 6.4 months). The hazard ratio (HR) adjusted for baseline stratification factors was 1.28 (80% CI, 0.99 to 1.67; one-sided P = .89).

Median progression-free survival was 4.1 months for paclitaxel (80% CI, 3.0 to 5.6 months) and 3.1 months for pazopanib (80% CI, 2.7 to 4.6 months; HR, 1.09; 80% CI, 0.85 to 1.40; one-sided P = .67). Discontinuations for toxicity occurred in 7.8% and 23.1% for paclitaxel and pazopanib, respectively.

Conclusion
Pazopanib did not have greater efficacy than paclitaxel in the second-line treatment of urothelial cancers. There was a trend toward superior OS for paclitaxel.

INTRODUCTION

Patients with advanced/metastatic urothelial cancer (UC) are initially treated with platinum-based chemotherapy.¹,² This results in responses and subsequent clinical benefit. However, the vast majority of these patients relapse and die as a result of their disease. When relapse occurs after initial chemotherapy, further chemotherapy, such as paclitaxel, docetaxel, or vinflunine, is recommended.³,⁴ Vinflunine is licensed in Europe in this setting. However, other agents are more widely used globally.⁵,⁶ At the time this study started, no chemotherapy agents were approved in this setting in the United States.

Outcomes for these patients are particularly poor, with a median survival in the region of 8 months.³ To date, no regimen has a proven survival advantage over best supportive care in randomized trials.⁶ Results from randomized trials with immune therapies in this setting are awaited.

There is in vitro and clinical rationale for targeting vascular endothelial growth factor (VEGF) in UC.⁷,⁸ Pazopanib is a VEGF receptor tyrosine kinase inhibitor with a favorable toxicity profile.⁹ It is licensed in a number of malignancies, including renal cancer.¹⁰ Preliminary data from two single-arm phase II studies in platinum-refractory metastatic UC are contradictory.¹⁰,¹¹ Clinical benefit was as high as 80% in one study, whereas the other showed...
limited activity with no responses. To clarify this issue and plan for a randomized phase III study, the United Kingdom Bladder Cancer Clinical Studies Group tested pazopanib against weekly paclitaxel in a randomized phase II study. The control arm was chosen on the basis of previously published phase II data and a survey, before the study, which showed that paclitaxel was the most widely used drug in this setting in the UK.\textsuperscript{1,2}

### PATIENTS AND METHODS

#### Patients

Patients participating in this study were required to have: histologically confirmed transitional-cell carcinoma of the bladder, renal pelvis, ureter, or urethra that was locally advanced or metastatic (T4b and/or N1-3 and/or M1); progressive disease during or after one prior platinum-based chemotherapy regimen for advanced disease (patients may have had two platinum-containing regimens if one of these was administered as adjuvant/neoadjuvant treatment), with progression of disease determined radiologically by sites; measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; adequate organ function (bone marrow, liver, and renal function); signed and dated informed consent; and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with established cardiac or GI disease, uncontrolled hypertension, a recent history of bleeding, thrombotic events, or major surgery (within 6 weeks) were excluded from the study. Patients with untreated brain metastasis, significant prior malignancy, or prior exposure to taxane chemotherapy or VEGF-targeted therapy were also excluded.

#### Outcome Measures

Overall survival (OS) from date of randomization was the primary outcome measure. Secondary outcome measures included toxicity according to Common Terminology Criteria for Adverse Events v4.02, response rate (RR) by RECIST 1.1, progression-free survival (PFS), and clinical benefit rate (CBR; proportion of patients with complete response, partial response, or stable disease) 12 and 24 weeks after start of treatment.

Quality of life was assessed using the validated bladder cancer–specific tool, Functional Assessment of Cancer Therapy–Bladder (FACT-BL), which assesses physical, social/family, emotional, and functional well-being and additional concerns domains to give an overall score. It also combines the physical, functional, and cancer-specific subscales (those most likely to change in a chemotherapy clinical trial) to give a trial outcome index.

#### Randomization, Treatment, and Follow-Up

This was a two-arm, open-label randomized (1:1) phase II study (see supplementary data). A computerized algorithm, which used a minimization approach\textsuperscript{13} and incorporated a random component to avoid predictability, was used to randomly assign patients and ensure that the groups were well matched with respect to the following factors: response to previous treatment (time to progression: \( \leq 6 \) months \( v > 6 \) months), presence of visceral and/or bone metastasis, performance status, and investigational site. Patients in the control arm received paclitaxel 80 mg/m\(^2\) by intravenous infusion on days 1, 8, and 15 of a 28-day cycle, with a maximum duration of 24 weeks. Dose reductions (to 70 then 60 mg/m\(^2\)) and interruptions were permitted to manage toxicity. Patients in the investigational arm received pazopanib 800 mg orally once daily until progression. Dose reductions according to the manufacturer’s instruction and interruptions (up to 14 days) were permitted to manage toxicity. Patients were assessed every four weeks for the first 24 weeks and then six-weekly. Cross-section imaging to assess RR and PFS were performed 12-weekly until progression.

### Statistical Consideration and Oversight

The study was designed to detect a 50% improvement in median overall survival among patients receiving pazopanib compared with paclitaxel (improvement from 8 months to 12 months with 90% power, 20% one-sided level of statistical significance, or equivalently with 80% power at the 10% level of statistical significance). This required 110 events, which could be achieved with 140 patients (70 per arm). The study design was based around a phase II screening design, with the three-outcome design forming the basis of the decision-making process.\textsuperscript{14,15} A result favoring pazopanib that was significant at the one-sided 10% level would suggest that a subsequent phase III trial should be performed. A result in favor of pazopanib that was statistically significant at the one-sided 20% level, but not at the one-sided 10% level, would require other supportive data in terms of a statistically significant improvement in PFS, at the 10% level, to indicate a phase III study was warranted. A result not reaching statistical significance at the 20% level would suggest that no further investigation of pazopanib should be performed in this setting.

The primary analysis of the overall survival end point was conducted on an intention-to-treat basis. OS and PFS were compared between the study arms in the context of the hazard ratio (HR) from a Cox model incorporating study arm and the factors used in the minimization algorithm. A test for interaction was conducted to assess whether any observed effect of the study intervention depended on the other clinical factors used in the minimization algorithm. The final analysis was planned at the end of the minimum follow-up period once the required number of events (110 deaths) had been observed. A Kaplan-Meier curve was used to illustrate the relative OS in the two treatment arms. Toxicity was compared between the study arms using a Mann-Whitney test. Clinical benefit rate was compared using the odds ratio (OR) from a logistic regression model incorporating study arm and the factors used in the minimization algorithm. Quality-of-life data were calculated and interpreted using FACT-BL scoring and interpretation materials (http://www.facit.org/FACTOrg/Questionnaires) and assessed using area under the curve (AUC) techniques.\textsuperscript{16} Missing values were filled in using interpolation or last value carried forward, as appropriate. Missing baseline values were imputed with the earliest available value. The calculated AUC scores were standardized by the quality-of-life assessment duration, which was time to progression, death, or 97 weeks, whichever was shortest. These standardized AUC scores were adjusted by subtracting the cycle one/week one value. To adjust for multiple testing, the false discovery rate (FDR) was calculated using the p.adjust function (frd option) of the stats library in R.\textsuperscript{17}

The trial was open labeled, and an independent data monitoring committee monitored the adverse events (for toxicity) and efficacy (for futility). A trial steering committee convened on a regular basis. The trial had appropriate ethical and regulatory approval (ISRCTN73030316).

### RESULTS

Between August 2012 and October 2014, 131 patients were randomly assigned from 24 United Kingdom sites, 65 to receive paclitaxel and 66 to receive pazopanib. Recruitment was terminated prematurely (October 14, 2014) on recommendation of the independent data monitoring committee after an interim analysis of the first 60 deaths in the study showed that the trial was unlikely to achieve the objective of demonstrating superiority for pazopanib compared with paclitaxel. At this time, 131 of 140 planned patients had been enrolled.

Investigators were informed of this decision immediately, but patients were permitted to continue with their allocated study treatment if both the patient and the investigator believed it was in the patient’s best interests. Patient distribution in the trial is
illustrated in Figure 1 (CONSORT diagram). No patients stopped pazopanib because of futility of the trial. At the time of final data extraction (May 20, 2016), there were 115 OS events. The median follow-up of the patients was 18 months.

**Patient Characteristics**

Patient characteristics are listed in Table 1. Notably, only two patients had prior cystectomy; 24.4% had liver metastases, and 61% had impaired performance status.

### Efficacy

Median OS from randomization was 8.0 months (80% CI, 6.9 to 9.7 months) and 4.7 months (80% CI, 4.2 to 6.4 months) for paclitaxel and pazopanib, respectively (adjusted HR, 1.28; 80% CI, 0.99 to 1.67; one-sided \( P = .89 \); two-sided \( P = .23 \)). Median PFS was 4.1 months (80% CI, 3.0 to 5.6 months) and 3.1 months (80% CI, 2.7 to 4.6 months) for paclitaxel and pazopanib, respectively (adjusted HR, 1.09; 80% CI, 0.85 to 1.40; one-sided \( P = .67 \); two-sided \( P = .66 \)). Kaplan-Meier survival distributions are show in Figure 2 (Kaplan-Meier

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**Table 1. Distribution of Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Paclitaxel (n = 65)</th>
<th>Pazopanib (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>70 (63-77)</td>
<td>69 (61-75)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td><strong>Bladder primary</strong></td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td><strong>T4 disease at diagnosis</strong></td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td><strong>Liver metastases</strong></td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td><strong>Nodal metastases</strong></td>
<td>45</td>
<td>53</td>
</tr>
<tr>
<td><strong>Time since last platinum therapy to randomization, days</strong></td>
<td>146 (65-244)</td>
<td>161 (81-273)</td>
</tr>
<tr>
<td>( \leq 6 ) months from previous treatment to progression</td>
<td>75</td>
<td>73</td>
</tr>
<tr>
<td><strong>Time from initial diagnosis to randomization, days</strong></td>
<td>444 (325-661)</td>
<td>478 (300-781)</td>
</tr>
</tbody>
</table>

**NOTE.** Data presented as percentage or median (interquartile range). Abbreviation: ECOG, Eastern Cooperative Oncology Group.
curves for OS and PFS). OS and PFS by preplanned subgroups are illustrated in Figure 3. Nine (13.9%) of 65 and three (4.5%) of 66 patients had complete or partial response at 12 weeks in the paclitaxel and pazopanib arms, respectively. The CBR of 66 patients had complete or partial response at 12 weeks in the paclitaxel and pazopanib arms, respectively. The CBR of 66 patients had complete or partial response at 12 weeks in the paclitaxel and pazopanib arms, respectively.

**Quality of Life**

Seventeen patients were excluded from the FACT-BI AUC analyses, because of a lack of data (usually incomplete or absence of completed questionnaires [76%]). FACT-BI trial outcome index is significantly reduced in the pazopanib arm (baseline adjusted standardized AUC median, −2.7; interquartile range (IQR), −10.3 to 0.0) compared with paclitaxel (baseline adjusted standardized AUC median, 0.0; IQR, −4.9 to 2.0); two-sided $P = .0028$ (FDR adjusted $P = .0034$). Similarly, FACT-BI total score is also significantly reduced with pazopanib (baseline adjusted standardized AUC median, −3.8; IQR, −9.8 to 0.0) compared with paclitaxel (baseline adjusted standardized AUC median, 0.0; IQR, −5.2 to 0.8); two-sided $P = .0034$ (FDR adjusted $P = .0034$). The change from baseline in each quality of life measure is illustrated in Figure 4.

**Subsequent Therapies**

Twenty percent and 24% of patients received further chemotherapy, 15% and 18% received palliative radiotherapy, and 6% and 0% received an immune checkpoint inhibitor after completing study treatment in the paclitaxel and pazopanib arms, respectively. Of the four patients receiving immune checkpoint inhibitors, one received nivolumab and three received atezolizumab.
DISCUSSION

There is no globally accepted standard of care in second-line treatment of advanced UC after the failure of prior platinum-based chemotherapy. A variety of chemotherapy drugs have demonstrated modest activity in small proportions of patients, but none have demonstrated conclusive clinical benefits compared with best supportive care. It is possible that such benefits exist among a defined subgroup of patients, but there are no data to guide us in making such a selection. Vinflunine is licensed in Europe despite no survival benefit over best supportive care in the intention-to-treat population. The OS of these patients was 6.9 months, with a nonsignificant 22% reduction in the risk of death over best supportive care. Other agents, such as single-agent taxanes or chemotherapy doublets, have been investigated in single-arm trials without success. Meta-analysis suggests doublets are not superior to single-agent therapy. Median OS for patients in these

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Fig 3. Forest plot of (A) overall survival, and (B) progression-free survival by subgroup. Hazard ratios (HRs) were calculated using Cox model incorporating study arm and the factors used in the minimization algorithm. ECOG, Eastern Cooperative Oncology Group.
chemotherapy trials remains well below 10 months and is usually closer to 7 months.3

Recent early-phase single-arm trials of immune checkpoint inhibitors have clearly demonstrated efficacy for these drugs in a significant proportion of patients.19 Atezolizumab is an inhibitor of programmed death-ligand 1. Results from a large phase II study in a chemotherapy-refractory UC population showed significant activity, particularly in tumors that overexpress the programmed death-ligand 1 biomarker in the immune component of the tumor (RR, 27%; 95% CI, 19% to 37%).20 Overall survival for the entire cohort was 7.9 months (6.7, NE). Atezolizumab is licensed in both biomarker-positive and -negative patients in the United States in this setting. A recent randomized phase III trial showed that pembrolizumab, an inhibitor of programmed death-1, prolonged survival compared with chemotherapy agents, including taxanes, in platinum-refractory UC (HR, 0.73; 95% CI, 0.59 to 0.91; P = .002).21

The results presented here show pazopanib is not better than weekly paclitaxel. Indeed, the trial was stopped with nine patients still to recruit after a futility analysis indicated that the trial would not meet its primary objective of demonstrating superiority of pazopanib over paclitaxel. Final results showed a trend toward an OS benefit for paclitaxel, with an HR of 1.28 (80% CI, 0.99 to 1.67; one-sided P = .089; two-sided P = .23) in favor of paclitaxel. Other efficacy results for paclitaxel were in line with previous results for chemotherapy in the second-line setting (RR, 14%; and median PFS, 4.1 months), and the fractionated chemotherapy schedule used here was generally well tolerated. The reasons for the relative lack of efficacy for pazopanib remain unclear. Previous data with pazopanib in this setting were contradictory, highlighting shortcomings of single-arm single-institution trials in UC, where patient baseline characteristics have a significant effect on outcome. The data presented here support the study by Pil et al11 suggesting limited activity. Pazopanib was administered at standard doses and was relatively well tolerated. However, 23% of patients stopped therapy because of toxicity, compared with 8% of those on chemotherapy. Thus, lack of exposure to study drug may have partly contributed to the relatively poor outcomes for those receiving pazopanib. Pharmacokinetic studies were not performed in this study, but there is no reason to suggest the lack of efficacy was dose related (32% of patients required a dose reduction, which is in line with those seen with pazopanib in other settings).

VEGF-targeted therapy has been investigated previously in UC with mixed results. Single-arm trials are difficult to interpret, as described above. Three randomized trials are noteworthy. The first is a phase II trial with ramucirumab (an anti-VEGF receptor 2 antibody), which, when administered in combination with taxane-based chemotherapy, significantly delayed PFS compared with taxane and placebo.22 Although these positive results may be drug specific, it is also possible that combination strategies (chemotherapy/VEGF-targeted therapy) are preferable to the single-agent strategy used in our study, although other such combinations have proven difficult to deliver.23

The second study of note relates to maintenance sunitinib administered after first-line chemotherapy, compared with placebo. This trial was stopped early, and the numbers were small. However, median PFS was 2.9 versus 2.7 months for sunitinib and placebo, respectively. Also, patients whose disease progressed on placebo crossed over to receive sunitinib (n = 16). These patients did not benefit from therapy, with only one response, suggesting limited activity for single-agent VEGF therapy in line with those seen in our study.24 The third study investigated paclitaxel with or without vandetanib, which is a broad-spectrum tyrosine kinase inhibitor (TKI) with VEGF receptor inhibition. This study showed no improvement in outcome associated with the addition of the targeted therapy. Together, these studies fail to form a consensus on the role of VEGF-targeted therapy in UC.25

It is possible that there are molecularly defined subgroups of patients who do benefit from VEGF-targeted therapy, or, conversely, who may be specifically sensitive to taxanes. As part of this trial, we have a comprehensive archival tissue and blood collection.

Table 2. Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Paclitaxel (n = 64)</th>
<th>Pazopanib (n = 65)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>Any Grade (≥ 1)</td>
<td>Grade ≥ 3</td>
<td>Any Grade (≥ 1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>94</td>
<td>27</td>
<td>91</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>36</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Elevated alanine transaminase</td>
<td>38</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34</td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td>Alopecia</td>
<td>41</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>41</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Anorexia</td>
<td>16</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>2</td>
<td>49</td>
</tr>
<tr>
<td>Altered taste</td>
<td>7</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Fatigue</td>
<td>72</td>
<td>5</td>
<td>74</td>
</tr>
<tr>
<td>Mucositis</td>
<td>20</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>38</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>PPE</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

NOTE. Data presented as percentage. All percentages presented are based on the safety population (n = 129). Adverse events measured by Common Terminology Criteria for Adverse Events v4.02. The most common 14 events are given, which occurred in > 9% of patients.

*Two-sided P values from Mann-Whitney test (on the basis of ordered toxicity grades).
Analyses are ongoing to establish putative predictive markers to differentiate those patients who may benefit from one or other of these approaches.

High levels of grade 3 or 4 toxicity occurred in both arms. This was numerically higher in the pazopanib arm. Specific toxicity was in line with expected toxicity associated with the respective drugs. Higher levels of discontinuation of study drug occurred with pazopanib (23% vs 8%). Quality of life dropped from baseline in both arms, although more markedly with pazopanib. Overall, these results demonstrate the difficulty of giving systemic therapy in these patients and do not suggest pazopanib is easily tolerable in this setting.

No patients switched from pazopanib to paclitaxel when the study was stopped, despite the opportunity being offered to them. We speculate that this is a reflection of the perceived inactivity of chemotherapy in this setting.

### Change From Baseline in FACT-Bl Total Score

<table>
<thead>
<tr>
<th>Cycle 3/Week 9</th>
<th>Cycle 5/Week 25</th>
<th>EoT/Week 25</th>
<th>12-week follow-up</th>
<th>24-week follow-up</th>
<th>36-week follow-up</th>
<th>48-week follow-up</th>
<th>60-week follow-up</th>
<th>72-week follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - Paclitaxel 80 mg/m²</td>
<td>B - Pazopanib 800 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>28</td>
<td>21</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

### Change From Baseline in FACT-Bl TOI

<table>
<thead>
<tr>
<th>Cycle 3/Week 9</th>
<th>Cycle 5/Week 25</th>
<th>EoT/Week 25</th>
<th>12-week follow-up</th>
<th>24-week follow-up</th>
<th>36-week follow-up</th>
<th>48-week follow-up</th>
<th>60-week follow-up</th>
<th>72-week follow-up</th>
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<tbody>
<tr>
<td>A - Paclitaxel 80 mg/m²</td>
<td>B - Pazopanib 800 mg</td>
<td></td>
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<td>34</td>
<td>29</td>
<td>23</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Fig 4. Quality of life analysis of change from baseline in (A) Functional Assessment of Cancer Therapy–Bladder (FACT-Bl) total score, and (B) FACT-Bl trial outcome index (TOI) by arm, assessed using area under the curve techniques. Number of data points is included. EoT, end of treatment.
The study presented here conclusively showed that single-agent pazopanib should not be further pursued in unselected patients, resolving the controversy in this setting. Alternative approaches should not be excluded with this or other VEGF-targeted therapy. Also, a biomarker-based personalized approach should not be discounted, although VEGF-based biomarkers have been elusive.

Disclosures provided by the authors are available with this article at jco.org.

REFERENCES


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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase II Study Investigating Pazopanib Versus Weekly Paclitaxel in Relapsed or Progressive Urothelial Cancer

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Research Funding: Merck Sharp & Dohme
Travel, Accommodations, Expenses: Merck Sharp & Dohme

Satinder Jagdev
Honoria: Novartis
Travel, Accommodations, Expenses: Astellas Pharma

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