## Cost-Effectiveness of Pazopanib Versus Sunitinib for Renal Cancer in the United States

We write to comment on a recently published study by Delea et al. in the January 2015 issue of *JMCP* that evaluated the cost-effectiveness (CE) of sunitinib (SU) versus pazopanib (PAZ) as first-line treatment for metastatic renal cell carcinoma (mRCC) from a U.S. third-party payer perspective.[1] This analysis was based on COMPARZ and PISCES, clinical trials that compared SU and PAZ[2,3] and led the authors to conclude that PAZ is cost-effective (in fact, dominant, according to the base-case results) compared with SU. Such assessment of economic value is clearly important for deciding between therapies to ensure fair access; therefore, we welcome a comparative evaluation of SU and PAZ. However, we believe that some of the key assumptions and inputs used in the model by Delea et al. render their results and conclusions invalid.

Best practice requires that results from a health economic model should reflect the most likely outcomes based on sound methodology and robust evidence for its inputs, as recommended by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR).[4] Here, we focus on 2 key areas (utilities and survival modeling) where, in our view, the analysis by Delea et al. falls short of this standard, and a third area (treatment costs) where the basis for the data derived is unclear.

### Utilities

The CE analysis by Delea et al. sourced utility values (as measured by the EuroQol 5-dimensions [EQ-5D] questionnaire) from the PISCES study, a blinded study that mandated switching between SU and PAZ before disease progression. The aim was to assess patient preferences with regard to tolerability and safety under the explicit assumption of equal efficacy.[3] However, for the reasons stated below, the PISCES study could not, by design, provide a valid measure of utility—a crucial input for the type of CE analysis conducted by Delea et al.

First, PICSES did not provide EQ-5D data from patients while on active treatment with PAZ or SU before the switch to the subsequent agent. Instead, EQ-5D was assessed at baseline (i.e., before any treatment), at the end of the 2-week washout period before the switch (week 12), and after the switch at the end of treatment (week 22). In the case of SU, the PISCES study design took into account the drug's intermittent 4/2 dosing schedule (i.e., 4 weeks on treatment followed by 2 weeks off) by correctly conducting the postwashout assessment at the end of 2 complete 6-week treatment cycles. As a result, the mean EQ-5D estimate for SU-first patients at washout was 0.8103, a 0.0478 *improvement* from their mean predose EQ-5D of 0.7625 for SU.[5] For the corresponding PAZ-first group, the mean EQ-5D utility score at the end of washout, 0.7595, was much lower than for SU and perhaps unchanged from the mean predose level of 0.7664. However, since there is no 2-week pause in the treatment regimen for PAZ, it is unclear what these data mean.

Faced with this paucity of data, Delea et al. imputed a weighted average of the mean EQ-5D estimates—but only for SU—before the switch to PAZ from 1 arm (0.8103) and after the switch from PAZ from the other arm (0.6325), thereby yielding an EQ-5D estimate of 0.6918, which is significantly *lower* than the mean baseline value of 0.7625. For PAZ, only the EQ-5D estimate *after* the switch from SU was used (0.7487). However, it is clearly not meaningful to use the data after the switch or to intermix utility values before and after a mandated switch. In the real world, where disease progression or tolerability issues motivate a switch in treatment,[6] utility values may fully reflect the trade-offs that patients and physicians make, but that is not the case here.

Of note, unequal disease progression rates in PAZ and SU observed in PISCES before the switch (20% vs. 11%, respectively) and a high degree of overall dropouts (~37%)[5] led to noncomparable patient populations before and after the switch, resulting in potential bias and difficulty in interpreting the EQ-5D data.

It is also notable that the EQ-5D data were not included in the peer-reviewed primary PISCES publication.[3] Indeed, interpretation of the EQ-5D results (which trend in the opposite direction to patient preference data in PISCES) has previously been considered "highly problematic" by GlaxoSmithKline, the trial's sponsor.[5]

Importantly, too, the imputed EQ-5D data in the Delea et al. study are not consistent with more robust published data. In Cella et al. (2008), EQ-5D scores for SU as measured in the pivotal phase III trial of SU in mRCC with a much longer treatment period (11 cycles or 66 weeks), a larger patient population, and no switch prior to progression were stable throughout treatment and equivalent to scores at baseline (~0.76).[7] We therefore believe that not making use of the results in Cella et al. is a major limitation of the Delea et al. analysis, since it contradicts ISPOR recommendations to identify and incorporate all relevant evidence.[4,7] Furthermore, the difference in EQ-5D results between the "on" and "off" treatment periods for SU is rendered unrealistically high in the data imputed by Delea et al., compared with the measured data reported from the same SU trial (0.1778 vs. 0.03, respectively).[7,8] The fact that the 0.1778 difference in health utility is as great as that between pre- and postprogression in many different cancers makes this an implausible input.[9-12]

Finally, the large imputed difference in EQ-5D for SU in the Delea et al. analysis is not consistent with evidence from the COMPARZ trial,[2] which found there was unlikely to be a clinically meaningful difference in quality of life, as measured by the Functional Assessment of Cancer Therapy–Kidney Symptom Index–19 item (FKSI-19) questionnaire. This is despite the fact that no assessment using FSKI-19 was included during the break in the SU dosing schedule (a potential source

of bias against the drug[8,13]). Therefore, to impute large clinically meaningful differences in EQ-5D, despite the weight of evidence from Cella et al. and COMPARZ, is not justifiable.[2,7]

In summary, data from PISCES used to derive EQ-5D utility, one of the key inputs driving the results of the analyses, were not suitable for use in the CE model by Delea et al.

## Survival Modeling

We also have doubts about the model inputs and assumptions used in estimating survival in Delea et al.'s analysis. This was, for instance, based on a 37.5-month time horizon, rather than using a lifetime perspective—the standard requirement in health economics analysis to guarantee that the model is "long enough to capture relevant differences in outcomes across strategies."[4] Because of the short time horizon, it excluded the overall survival (OS) benefit for SU that occurs after the follow-up, as seen in Figure 1B in Delea et al.'s article—a treatment effect that would otherwise reduce or possibly eliminate the life-year gain (LYG) for PAZ in Table 2. Indeed, sensitivity analysis (Figure 3) suggests that a shorter time horizon benefits PAZ.

The Kaplan-Meier curves for OS are dependent on post-progression treatment patterns that are very complex. For instance, the COMPARZ study report (Table 17, page 69)[14] shows that, beyond a median per-protocol treatment duration of approximately 8 months, more than half of the patients were treated with a variety of other anticancer agents, with clear differences between the arms. For example, 27% of the PAZ group received SU and 14% of the SU group received SU as follow-up therapy while, in contrast, only 3% of PAZ patients and 8% of SU patients received PAZ as follow-up therapy.[14] OS reflects the efficacy of the different treatment arms, including first-line and subsequent lines of therapies. Therefore, any attribution of OS to the original treatment groups is highly problematic, unless the subsequent lines of treatment are similar between the treatment arms, which is not the case in the COMPARZ study. Consequently, it may not be valid to attribute any computed LYG advantage to PAZ, as is done in Delea et al.

Furthermore, Delea et al. chose to use investigator-assessed progression-free survival (PFS) from COMPARZ, arguing that this may better reflect real-world practice, which is a reasonable assumption in general. But, in this case, investigator-assessed PFS favored PAZ, whereas the primary endpoint, PFS as assessed by the independent review committee (IRC), actually favored SU. Apart from the selective use of data, this raises the possibility of bias, since COMPARZ was an open-label study in which only the IRC assessments were blinded.

In summary, the selective model inputs for survival modeling in Delea et al.'s analysis may have also led to invalid CE results for PAZ and SU.

## Treatment Costs

Costs associated with SU and PAZ in the model analyses, based on the health care resource utilization (HCRU) data from COMPARZ, appear questionable, since they are inconsistent with data in a companion article by Hansen et al. (2015),[15] the source cited by Delea et al. for corresponding detailed cost analysis and results. In Hansen et al. (Figure 2A), the derived total average medical and ambulatory costs for PAZ- and SU-related treatment were $2,151 versus $3,153, respectively, over a duration of approximately 10.6 months; however, in Delea et al. (Table 2), the same costs over a slightly longer time period (~13 months by the estimated progression-free life-years in Table 2), were around 4 times higher ($9,147 vs. $12,381, respectively). While such a difference between the drugs in this item may appear small compared with the overall costs, it is still important to consider. Where treatments have similar derived efficacy in a CE analysis (as suggested by available data for SU and PAZ), the incremental cost-effectiveness ratio becomes very sensitive to cost differences, so otherwise unimportant cost differences may drive results.

Finally, it is worth noting that COMPARZ was a noninferiority study, and CE analyses do not distinguish evidence from such studies from that provided by superiority trials. A potentially small cost difference in favor of PAZ, as suggested by Delea et al., must therefore be viewed in the context of possibly lower efficacy for PAZ, particularly given that noninferiority criteria in COMPARZ were only met for the intent-to-treat analysis but not for the per-protocol analysis (rather than for both analyses, as required to confirm a drug's noninferiority).[16-18]

In conclusion, to argue that PAZ is dominant or cost-effective compared with SU on the basis of data used by Delea et al. is not justified. Available clinical trial evidence (including studies run by the drug's sponsor) appears to be overlooked in their study. Also, the EQ-5D and survival analysis estimates that drive the QALY estimates lack credibility and validity. Making essential corrections for the base-case analysis would result in a change in the main results. CE models, which in many countries may impact patient access to cancer treatments, need to be based on more reliable data than those used by Delea et al.

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## DISCLOSURES

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## The Authors Respond

We thank Benedict et al. for their comments regarding our study entitled "Cost-Effectiveness of Pazopanib Versus Sunitinib for Renal Cancer in the United States."[1] In their comments, they identify 3 main areas of criticism: (1) the utility values estimated for sunitinib that was based on the PISCES trial[2]; (2) the model time frame and approach for survival modeling; and (3) health care resource use cost estimates derived from COMPARZ.[2] We discuss each of these areas below.

### Utility Values Estimated for Sunitinib Based on the PISCES Trial

Regarding the utilities, we agree with Benedict et al. that the timing of assessments and the nonrandomized nature of the comparison conducted in PISCES potentially bias our estimate of the difference in utility values for pazopanib versus sunitinib. This was noted as a key limitation of the analysis in our original article.[1] We also agree that the quality of life (QoL) data from the phase III study of sunitinib represents a potentially more robust source for the estimated utility value for sunitinib.[3] However, because this trial did not include pazopanib as a comparator, the use of data from this source in our model would have required a "naïve" indirect comparison, which would also be subject to potential bias. Although the difference in the on-treatment versus off-treatment utility values for sunitinib estimated from PISCES differ from those reported by Bushmakin et al. (2012),[4] we believe that the more relevant comparison is the average utility value during progression-free survival (PFS) for pazopanib versus sunitinib used in our model. In our base-case analysis, we assumed a mean utility value during PFS of 0.7487 for pazopanib and 0.6918 for sunitinib, representing a difference in mean utility of 0.0569. We believe that this estimated difference is not unreasonable, given the clinically significant improvements in QoL demonstrated for pazopanib versus sunitinib in COMPARZ and PISCES,[5] as well as the statistically significant patient preferences for pazopanib versus sunitinib demonstrated in PISCES.[6] The

minimally important difference (MID) in EuroQol 5-dimensions (EQ-5D) questionnaire utility scores in cancer patients has been estimated to range from 0.06 to 0.12.[7] The MID has been defined as the smallest change in a measure that is perceived by patients as beneficial or that would result in a change in treatment.[8] The fact that patients and physicians in PISCES preferred pazopanib to sunitinib suggests that the estimated difference in EQ-5D-based utility values for patients receiving pazopanib versus sunitinib should be at least as great as the MID.

Nevertheless, we must acknowledge that the precise magnitude of expected benefit of pazopanib versus sunitinib on QoL measured in terms of utility values is uncertain and debatable. Accordingly, we have conducted an updated analysis assuming mean (standard error) utility values during the preprogression state of 0.7487 (0.0273) for pazopanib and 0.7287 (0.0273) for sunitinib (i.e., a difference of 0.02). These values reflect an assumption of equal utility values for pazopanib on-treatment and sunitinib off-treatment, and a 0.03 decrement in utility for sunitinib on-treatment versus off-treatment. The latter estimate is consistent with results of the sunitinib phase III trial as described by Bushmakin et al.[4] Under these assumptions, pazopanib remains dominant versus sunitinib in the base case ($6,828 savings, 0.049 quality-adjusted life-years [QALYs] gained, and $11,684 net monetary benefit [NMB] at threshold value of $100,000 per QALY). In probabilistic sensitivity analyses, the probability that pazopanib is dominant is estimated to be 58%, and the probability that pazopanib is cost-effective is 87%, given a threshold value for cost-effectiveness of $100,000 per QALY gained. Even under the conservative assumption that the utility during PFS is *the same* with sunitinib as with pazopanib—that is, assuming *no benefit* for pazopanib versus sunitinib in QoL during PFS—the probability that pazopanib is cost-effective at a threshold value of $100,000 per QALY is 82%.

## Model Time Frame and Approach for Survival Modeling

Benedict et al. also suggest that the time frame employed in the analysis (37.5 months) was too short to capture important differences in relevant outcome across treatments. Using a time frame of 37.5 months is equivalent to assuming that costs and QALYs beyond that time frame are equal across treatments—a reasonable assumption in this case given the similarity of PFS and overall survival (OS) for pazopanib and sunitinib observed in COMPARZ. While results are *more* favorable for sunitinib when a 10-year time horizon is employed, this is true only if survival is modeled using the Kaplan Meier curves out to 37.5 months and the Weibull distributions thereafter. Results, measured in terms of net NMB, are slightly more favorable for pazopanib with the 10-year time horizon if Weibull distributions are used for the entire time horizon. Given that the Weibull distributions fit the empirical data well, we believe the latter approach is preferred, since it is less influenced by the relatively high degree of uncertainty that may occur in the Kaplan Meier survival distributions around the end of follow-up. Nevertheless, regardless of the approach employed, results based on a 10-year time horizon are not materially different from those in our base case. Using a 10-year time horizon—with survival during the trial period based on Kaplan Meier distributions, basing the remainder of the projection on Weibull distributions, and conservatively assuming the same utility during PFS with sunitinib as with pazopanib—pazopanib is not projected to be dominant, but the incremental cost-effectiveness ratio of sunitinib versus pazopanib is $512,517 per QALY gained (NMB of pazopanib vs. sunitinib = $8,479 at a threshold of $100,000 per QALY). In probabilistic sensitivity analyses, the probability that pazopanib is cost-effective at a threshold value of $100,000 per QALY is 69%.

It should be noted that since we conducted our study, the final analyses of OS from COMPARZ have been reported.[9] These analyses were based on a data cutoff of September 30, 2013, with a maximum follow-up for OS of just over 5 years and at a point when 60% and 61% of patients randomly assigned to pazopanib and sunitinib, respectively, had died. In these analyses, OS was similar in the 2 groups (hazard ratio = 0.92 for pazopanib vs. sunitinib; 95% confidence interval = 0.79-1.06; $P = 0.24$). These data suggest that our assumption that there are no differences in outcomes beyond the time frame of the initial analysis did not bias the analysis in favor of pazopanib.

Another point correctly noted by Benedict et al. were differences between treatment arms in COMPARZ in the utilization of poststudy anticancer therapies (PSACT) and that the use of these therapies may have impacted postprogression survival and hence OS. While we agree that it may not be appropriate to attribute differences in life expectancy between arms to exposure to pazopanib versus sunitinib per se, we do not agree that it is inappropriate to attribute such differences to randomization to first-line treatment with pazopanib versus sunitinib. Patients who receive first-line treatment with pazopanib and sunitinib may receive a variety of second and subsequent lines of treatment in real-world clinical practice, and the choice of these treatments may be affected by the first-line therapy received. Therefore, we believe that use of the unadjusted OS data from COMPARZ was appropriate for our economic evaluation. Rather than attempting to adjust OS for differences in PSACT, which would be difficult given the extent of use of PSACT in COMPARZ, we included the costs of such therapy in our analysis. With this approach, estimates of costs and outcomes are internally consistent. Although patients in the sunitinib arm of COMPARZ were less likely to receive pazopanib or sunitinib as PSACT than those in the pazopanib arm, patients in the sunitinib arm were more likely to receive

other relatively costly treatments, such as sorafenib and temsirolimus. Consequently, the expected costs of PSACT were estimated to be *greater* for patients randomized to sunitinib than pazopanib. We conservatively did not include these costs in our base-case analysis.

Benedict at al. also criticized the use of investigator-assessed rather than independent review committee (IRC)-assessed PFS in our model. Although it has been hypothesized that investigator-assessed PFS may be subject to bias due to lack of blinding, analyses of hazard ratios for PFS from controlled trials find no evidence of such bias.[10] Also, a comparison of investigator- and IRC-assessed PFS in COMPARZ found no evidence of such bias because the proportion of subjects in the pazopanib arm was higher versus the sunitinib arm for progression later by investigator than by IRC (40% vs. 35%, respectively) and progression earlier by investigator than by IRC (10% vs. 7%).[11] While IRC-assessed PFS was the primary endpoint in COMPARZ, our study was a post hoc evaluation that did not involve hypothesis testing, so the primacy of this endpoint over the other should not influence the selection of which measure of PFS should be used in our model. Although the use of investigator- rather than IRC-assessed PFS did modestly favor pazopanib in the base case, this effect was not material (NMB at threshold value of $100,000 per QALY equal to $15,767 based on IRC-assessed PFS vs. $15,857 in our base case).

We take issue with Benedict et al.'s statement that "a potentially small cost difference in favor of PAZ, as suggested by Delea et al., must therefore be viewed in the context of possibly lower efficacy for PAZ, particularly given that noninferiority criteria in COMPARZ were only met for the intent-to-treat analysis but not the per-protocol analysis (rather than for both analyses, as required to confirm a drug's noninferiority)." First, we believe that Benedict et al.'s suggestion that there is a "small cost difference" between pazopanib and sunitinib is potentially misleading. Perhaps the most influential parameter of our model, and one that Benedict et al. have not criticized—and so presumably is not in dispute—is the estimated medication costs of pazopanib versus first-line sunitinib. Based on our projections, expected first-line medication costs for patients receiving first-line treatment with sunitinib are over $6,000 greater than for patients receiving first-line treatment with pazopanib. We would argue that this difference in cost is highly economically significant. Second, regarding the conclusions of the COMPARZ trial with respect to the demonstration of noninferiority, these issues have been discussed in detail elsewhere.[12] It is worth mentioning, however, that the European Medicines Agency (EMA) had previously issued pazopanib with a conditional license subject to results from COMPARZ demonstrating noninferiority of pazopanib versus sunitinib using the investigator-assessed PFS analysis in the intent-to-treat population (i.e., noninferiority margin ≤ 1.22). EMA granted full license to pazopanib once COMPARZ demonstrated that the agreed noninferiority margin had been met.[13] In any case, as Benedict et al. have pointed out, these issues are not relevant to post hoc economic evaluations, which do not entail hypothesis testing and therefore do not distinguish between superiority and noninferiority trials. Finally, regarding reporting cost savings in the context of possibly lower efficacy, we have presented estimates of differences in costs and outcomes in the context of deterministic and probabilistic sensitivity analyses that reflect the likelihood of lower (or greater) efficacy with pazopanib.

## Health Care Resource Use Cost Estimates Derived from COMPARZ

As correctly indicated by Benedict et al., estimates of monthly health care costs derived from medical resource use data in COMPARZ reported in our study are different from those reported by Hansen et al. (2015).[2] It is not surprising that the Hansen et al. estimates are different from our study because the estimation of unit costs for the 2 studies were conducted independently and used different data sources for the unit cost estimates. Specifically, the Hansen et al. study used unit cost estimates derived from a health insurance claims database; our study used estimates from a variety of published sources. Unit costs used in both studies are reported in their respective online appendices. The most important difference in the unit cost estimates between the 2 studies is the estimated cost per day in the hospital general ward. Whereas the study by Hansen et al. used an estimate of $76.74 per day,[2] we used an estimate of $2,406 per day. Our estimate is based on the mean per diem cost of hospitalizations with a primary diagnosis of malignant neoplasm of kidney except renal pelvis and with a nonsurgical principal procedure, as retrieved from the Healthcare Costs and Utilization Project (HCUP) National Inpatient Sample database.[14] We believe that the estimate used in our study is reasonable, as we did not assign any facility or professional services costs to medical/surgical procedures performed during hospitalizations. Accordingly, the unit costs for hospital days should reflect the costs of *all* services associated with those days in hospital, not just the room and board costs. In any case, while the precise magnitude of the difference in health care costs between pazopanib and sunitinib differ in the 2 studies, the directionality of the findings is consistent and suggests that these costs are likely to be greater with sunitinib than with pazopanib.

Finally, it should be noted that, contrary to what was implied by Benedict et al., our study concluded that pazopanib is *cost-effective,* not that it was *dominant*. While pazopanib was dominant in the base-case and one-way sensitivity analyses, the probabilistic sensitivity analyses showed that pazopanib, while cost-effective in 94% of simulations at a threshold of $100,000 per QALY, was dominant in only 69% of simula-

tions. Given the acknowledged limitations of the utilities data, we agree that a conclusion that pazopanib is dominant is not warranted.

In conclusion, as is often the case when comparing 2 similar treatments, there is uncertainty as to whether pazopanib or sunitinib is more effective. The data from COMPARZ suggest similar PFS and OS but improved tolerability and QoL with pazopanib versus sunitinib.[5] Although the precise magnitude of the expected benefits of pazopanib, measured in QALYs, is uncertain and debatable, what is not in dispute is that expected medication costs are greater for patients receiving sunitinib than pazopanib in the United States. The higher expected acquisition cost of sunitinib—approximately $6,000 more per course of therapy based on list prices—is economically significant. This higher acquisition cost, combined with the demonstrated lower heath care resource utilization with pazopanib versus sunitinib observed in COMPARZ, make it likely that pazopanib is cost saving when compared with sunitinib. Under such circumstances, pazopanib can be considered to be cost-effective unless there is substantial likelihood that sunitinib provides longer survival and/or improved QoL. The evidence, however imperfect, suggests the opposite is more likely than not to be true. Based on these factors, we stand by our original conclusion that pazopanib is a cost-effective option for first-line treatment of patients with metastatic renal cell carcinoma in the United States.

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## DISCLOSURES

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