We thank Necchi and colleagues for their interest in our article (1). Their comments serve to highlight key challenges that we face in evaluating new treatments in advanced urothelial cancer.

Necchi and colleagues presented the results of their phase II study of the angiogenesis inhibitor pazopanib in treatment-refractory urothelial cancer at the 2012 American Society of Oncology annual meeting (2). Their abstract was eloquently discussed by Dr. Feldman from the Memorial Sloan Kettering Cancer Center New York, NY (3). Despite strong preclinical support for the activity of angiogenesis inhibitors in urothelial cancer, clinically they have only had modest but inconsistent activity and cannot be considered standard of care for this disease. Further research is needed to determine whether the angiogenesis inhibitors may have a therapeutic role if used earlier in the course of the disease, whether they should be used in combination with other targeted therapies or chemotherapies, and whether there is a subset of patients who are most likely to derive benefit from these agents.

Necchi and colleagues have attempted to address the latter point and should be commended for the biomarker component of their study. They showed that higher levels of IL-8 were associated with progressive disease and worse outcomes. Similar results have also been reported by Bellmunt and colleagues in a first-line study of another angiogenesis inhibitor, sunitinib, in advanced urothelial cancer. More recently, a retrospective analysis of phases II and III trials of pazopanib in metastatic renal cell cancer also showed that higher concentrations of IL-8 were associated with a shorter progression free survival (4, 5). We agree that a better understanding of both prognostic and predictive biomarkers is important and may help us to select the patients who are most likely to benefit from this class of agents. Biomarkers may also help us to identify and overcome de novo or acquired resistance mechanisms used by cancers against targeted therapies. Ultimately, well-designed clinical trials will be critical to move this field forward. Ideally, trials should have clinically meaningful endpoints, with quality of life parameters, and should attempt to incorporate correlative studies and functional imaging wherever feasible and possible.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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