In Reply

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We thank Drs. Basso, Cassano, Schinzari, and Barone for raising some interesting points regarding the evaluation of clinical benefit provided by agents in the treatment of advanced renal cell cancer. Temsirolimus was approved based on an improvement in overall survival (OS). OS is clinically meaningful, not subject to bias, and easily assessed.

Results of the independent review of progression-free survival (PFS) and response rate (RR) were supportive of the improvement in OS. The PFS time for patients who received temsirolimus was 5.5 months, versus 3.1 months for the patients who received interferon (IFN)- α (hazard ratio [HR], 0.66; 95% confidence interval, 0.53–0.81; $p = .0001$, unadjusted for multiple comparisons). The RR was also numerically higher in the temsirolimus arm (8.6%, versus 4.8% in the IFN- α arm; HR, 0.12). A similar pattern was observed on investigator assessment. These findings demonstrate the internal consistency of the efficacy results for temsirolimus versus IFN- α and argue against concerns raised by Dr. Basso et al. that the longer OS time resulted from a detrimental effect of IFN- α on survival. It should be noted that IFN- α was the standard of care in advanced renal cell cancer patients at the time this study was initiated and

was considered an adequate comparator for temsirolimus for this indication.

With regard to the lack of discussion of the differences between independently reviewed PFS times and investigators' assessment of PFS, we provide the following responses. The disadvantages of using PFS as a regulatory endpoint have been discussed previously at many Oncology Drug Advisory Committee meetings and in several previous publications. A discussion on these was not the objective of our article. First, the independently reviewed PFS analysis was the preferred secondary endpoint because of the unblinded nature of the trial. Second, discordance is commonly observed in PFS results according to independent versus investigators' assessments. Several explanations for this phenomenon in addition to investigator bias are possible, including investigators and blinded reviewers choosing different target lesions, incomplete submission of scans to independent reviewers, and investigators' clinical determinations of progression prior to or without radiographically documented progression. These issues further underscore the importance of using OS as the primary regulatory endpoint for oncologic agents whenever possible.

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