Reviewer's report

Title: Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy: an open-label phase 1b study

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Reviewer: Ronald Bukowski

Reviewer's report:

The authors report the results of an open-label, multicenter phase 1b study enrolled Chinese patients with mRCC who were intolerant to, or progressed on, previous VEGFr-TKI therapy. Patients were treated with everolimus 10 mg daily until objective tumor progression unacceptable toxicity, death, or study discontinuation for any other reason. 64 patients were included in the study. Expected known class-effect toxicities related to everolimus included anemia (64%), hypertriglyceridemia (55%), mouth ulceration (53%), hyperglycemia (52%), hypercholesterolemia (50%), and pulmonary events (31%). The most common grade 3/4 adverse events included anemia (20%), hyperglycemia (13%), increased gamma-glutamyltransferase (11%), hyponatremia (8%), dyspnea (8%), hypertriglyceridemia (6%), and lymphopenia (6%). Median PFS was 6.9 months (95%CI, 3.7-12.5 months) and the overall response rate (ORR) was 5% (95% CI: 1-13%). The majority of patients (61%) had stable disease as their best overall tumor response. The authors conclude the safety and efficacy of everolimus in a population of Chinese RCC patients is similar to those reported in the RECORD-1 trial. Everolimus was generally well tolerated and provides clinical benefit to Chinese patients with VEGF-refractory mRCC. The study appeared to be well conducted, and the manuscript nicely summarizes the findings. The authors may wish to consider the followings issues.

1) Can the authors provide information of the frequency of TKI intolerance versus patients with PD? If the frequency of intolerant patients was high, e.g., >10% was there a difference in the efficacy outcomes between these populations?

2) In the abstract, the authors note: “Safety and efficacy results were comparable to those of the RECORD-1 trial.” In the results section this issue is discussed, & it is noted “Non-infectious pneumonitis events were reported in 20 patients (31%)…” In the discussion section, the authors state: “Although the percentage of pulmonary events was higher than in the overall RECORD-1 population (14%) [10]…” They should reconcile these statements, and discuss whether the sample size or population treated was the likely cause?

3) Were the radiographic studies which determined response and pulmonary events independently reviewed?

4) The pharmacokinetic analyses of everolimus are of interest, can the authors
provide the methods utilized to determine everolimus plasma concentrations or provide a reference for the method?

5) The analysis cutoff data was 11/30/11, the OS data are now likely more mature, can a final OS analysis be provided?

6) Can tables 2 & 3 provide information of the overall frequency of AEs as well as break them down into Grades 1/2 and 3/4?

7) Figure legends are lacking & should be included.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

Honoraria for speaking: Novartis, Pfizer, Genentech, GSK
Consulting: Pfizer, GSK, Novartis, Argos
Stock - none
Employment - none
Other - none