Reviewer’s report

Title: Phase I trial of bortezomib in combination with celecoxib in patients with advanced solid tumors

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Reviewer: LUIS CAMACHO

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General

TITLE: Phase I trial of bortezomib in combination with celecoxib in patients with advanced solid tumors

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1. DESCRIPTION:
This is a Standard 3+3 designed Phase I trial evaluating the safety and toxicities of a combination of bortezomib and cvelecoxib. Below please find my critique and recommendations.

2. CRITIQUE AND SUGGESTIONS:
• The abstract reads poorly. The objective of the study is repeated in the background of the abstract.
• The methods and results fail to describe how many patients were enrolled, their diagnoses, the number of courses, and the most common toxicities observed.
• The study requires substantial editing. (i.e. page 7 line 8: “if two patients experience….;
• Criteria to continue therapy: “patients with stable or responding disease were allowed to continue on therapy at the discretion of the treating physician…”.
  Please explain why would the physician not let stable or responding patients receive further therapy if deriving clinical benefit…
• Treatment assessments (Page 8 Line 3). The full assessment during study must be listed. The paragraph is brief and does not mention baseline evaluations or the frequency and type of studies ordered. Additionally, the authors do not report on the frequency of clinical assessments, or the toxicity criteria followed (NCI CTC v 2.0 vs. 3.0)
• Table 2 lacks number of cycles administered to the study participants.
• Results: The last line in the first paragraph is written in an unconventional manner.
• Table 2 may be better presented if the number of previous therapies is clustered in 0-3, 3-6, and >6.
• Table 3. Cohort 6. There is a typographic error under 3-4 toxicities.
• Under table 3. (with the use of a symbol like an asterisk, please state type of grade 3-4 infection observed in cohort 2.
• Table 3. Please modify pruritis to “pruritus”.
• Tumor Response: first line: correct term should be RECIST guidelines instead of RECIST criteria.
• Discussion. Second paragraph states that “the purpose of this study was to define the MTD of the combination of these agents at the proposed schedule”. However, the investigators also state that no dose limiting toxicities of overlapping toxicity was encountered. In absence of limiting toxicities, biological endpoints, and objective antitumor responses, it seems very difficult to arrive to such conclusion. Please elaborate.

3. SUMMARY AND RECOMMENDATION.

The manuscript requires extensive editing. The combination regimen is novel. There are no biological correlates. There is no preclinical data to support the synergistic effects of this combination. The investigators of this study seem more optimistic than the results reported herein. While no objective responses were observed during the trial conduct and no dose limiting toxicities were reported by the patients, the investigators are planning a Phase II study with this regimen. My concern is whether or not there is synergistic activity with this regimen and whether or not there is a biological effect other than the inhibition of NFkB by the means already established during the development of bortezomib alone. The maximum tolerated dose of 1.3 mg/m2 is the same dose proposed by Aghajanian et al when administered in combination with Carboplatin (AUC 5) every 21 days. Diarrhea, rash, neuropathy, and constipation (with colonic wall thickening on computed tomography) were dose-limiting toxicities, occurring in the two patients treated at the 1.5 mg/m2/dose level. However, that was not the case in this trial.

I recommend approval of the manuscript once satisfactory response to the comments above is received.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests