Reviewer's report

Title: Axitinib and crizotinib combination therapy inhibits bone loss in a mouse model of castration resistant prostate cancer

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Reviewer: Colin Rae

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This study demonstrates an important advance in the potential use of a drug combination to reduce the debilitating effect of disrupted bone remodeling, bone weakness and associated pain in prostate cancer, for which there is currently no effective treatment. This is hoped to lead to improvements in the quality of life and survival of patients with advanced disease. The combination of drugs targeting different pathways simultaneously is likely to be an effective strategy and this study demonstrates the role of both pathways in intact and castrated mice. Well-established methodology is utilized which demonstrate the effectiveness of the drugs and, importantly, demonstrates the alterations in tumor growth and bone remodeling associated with castration.

Discretionary Revisions:
1. Due to the stated importance of angiogenesis in disease progression and metastasis, the study may be enhanced by a demonstration of the effect of the drugs (alone and in combination) on blood vessel formation or endothelial cells proliferation.
2. A comparison of the drug combination used in this study with cabozantinib would have been useful, although may be beyond the scope of this manuscript.
3. Although the growth of tumors in castrated mice was slower than in intact mice, tumor sizes were still suitable for the experiments (and were similar according to BLI measurement in Fig 3). However, PSA levels were “below level of detection” in castrated mice, suggesting that PSA levels do not correlate to tumor size and are not a suitable marker. The usefulness of PSA or alternative markers could be discussed.
4. It is stated repeatedly that the combination treatment is effective. However, in both intact (Fig 3A) and castrated (Fig 3C) mice, administration of the drug combination had no greater effect than axitinib alone. This should be addressed in the Discussion.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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.