Reviewer’s report

Title: Spatial morphological and molecular differences within solid tumors contribute to the failure of vascular disruptive agent treatments.

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Reviewer: Martin Zweifel

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The authors investigate molecular and morphological differences between tumour centre and periphery before and after application of the vascular disrupting agent (VDA) OXi4503 in a liver metastasis mouse model. They find localised differences in terms of hypoxia, expression of angiogenic factors, and immune cell accumulation, concluding that the observed differences may account for the known differential resistance to VDA treatment.

The paper reads very well, and the quality of the experiments and especially the immunohistochemistry is remarkably good. Not all of the findings are entirely new, but the authors put them into a broader context, linking EMT, angiogenesis, and immune cell accumulation. The somewhat counterintuitive finding of VEGF expression in the less hypoxic tumour periphery fits well to earlier (Shaked & Kerbel) and recently (Nathan & Judson) published data showing a benefit for adding antiangiogenics to VDA treatment in order to prevent sustained growth of the tumour rim. The notion of tumour microenvironment involvement is of high importance and may make the paper a landmark publication for better understanding how VDAs do work and why they may fail.

While there is always space for rephrasings mainly in order to satisfy the reviewers’ own points of view, I don’t see a need for changes in order to further improve the quality of the paper and therefore am happy to recommend it for publication in its present form.

Level of interest: An article of outstanding merit and interest 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:

The reviewer declares not to have any conflicts of interest.