Reviewer's report

Title: ENMD-1198, a novel tubulin-binding agent with anti-HIF-1alpha activity, reduces growth and vascularization of hepatocellular carcinoma (HCC) in vivo

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Reviewer: Jong-Wan Park

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2-methoxyestradiol has been known to inhibit tumor adaptation to hypoxia by suppressing HIF-1 and VEGF expression. Likewise, the authors found that ENMD-1198, an analog of 2-methoxyestradiol, inhibited HIF-1 and VEGF expression. Moreover, ENMD-1198 inhibited MEK/ERK, PI-3K, FAK, and STAT3 pathways. They also demonstrated that ENMD-1198 inhibited cell migration and invasion in vitro. In aspect of drug development, all data are required for preclinical evaluation of ENMD-1198. However, in a scientific aspect, this manuscript should be somehow revised before publication.

Comment 1) Title. Authors did not show the relationship between most data (Fig. 1, Fig. 2, Fig. 3, and Fig. 6) and HIF-1 inhibition. If these data are independent of HIF-1 inhibition, the title should be changed because the present title strongly focuses on HIF-1 inhibition. If authors want to keep the present title, they should do more experiments using HIF-1 expression and knock-down methods.

Comment 2) Data quality. Fig. 4A Western blot and Fig. 6A&B Immunohistochemistry results should be replaced with higher quality ones.

Comment 3) In Fig. 6, authors should measure HIF-1alpha levels by immunohistochemistry in order to examine whether reduced vascularization in ENMD-1198-treated tumors is related with HIF-1 inhibition activity of ENMD-1198.

Comment 4) Fig. 4B. Normoxic values should be present in this figure, and the experimental number should be also mentioned in its legend.

Comment 5) Authors mentioned there were no differences in body weights of mice between control and drug treatment group, but they did not show the data. Since the body weight change is important in drug evaluation, they should present the changes in body weights as a figure or in text.

What next?: Accept after minor essential revisions

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