Reviewer's report

Title: WEE1 inhibition sensitizes Osteosarcoma to Radiotherapy

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Reviewer: Hiroshi Hirai

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Manuscript by J. PosthumaDeBoer et al includes 2 interesting findings. First they showed WEE1 is overexpressed in osteosarcoma patient tumor samples by IHC and gene expression. Second, they demonstrated Wee1 inhibition by a small molecule inhibitor, PD0166285, abrogates G2 checkpoint and sensitizes OS cells to irradiation-induced cell death in vitro. They concluded that WEE1 inhibition may be a promising strategy to enhance the radiotherapy effects in OS patients.

WEE1 overexpression in OS is important. This makes sense to test WEE1 inhibitor in clinic as an enhancer of radiotherapy in OS patients. However, I think the second part is too preliminary for publication.

Major compulsory revisions

1) Radiosensitization of human tumor cell lines by PD0166285 is already reported by others (Wang Y et al, Cancer Res. 61, 8211-8217, 2001, Li J et al, Radiat Res, 157, 322-330, 2002). It seemed to me that data by authors are somewhat redundant. Authors should discuss clearly what new findings were added by their results.

2) Tumor cell selectivity is important as a target for therapeutic strategy of cancer patients. It is important to demonstrate that WEE1 inhibition does not affect on, or does not radiosensitize normal cells. Such results may greatly improve the manuscript and will support the conclusion by authors. Regarding G2 checkpoint abrogator, p53 context selectivity is one idea to distinguish tumor vs normal cells. Indeed, previous reports showed p53 deficient cell selective enhancement by PD0166285. Do the results in this manuscript support the idea? If not, how authors distinguish tumor cells from normal cells? In vivo results may also be very helpful to support the conclusion by authors.

Discretionary revision

1) Figure 2A. Authors should explain why they tested at 0.5 uM of PD0116285. Is there any correlation between WEE1 inhibition in cells vs radiosensitization?

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.