Reviewer’s report

Title: WEE1 inhibition sensitizes Osteosarcoma to Radiotherapy

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Reviewer: Claudia Blattmann

Reviewer’s report:

The manuscript is well written, well though out and appears to contribute worthy observations. However, the manuscript could use some improvements.

Major revisions

1. The authors talk about “radioresistance” of osteosarcoma through out the whole manuscript which is not correct. Today, we know that it is possible to achieve local control and to improve outcome in selected patients using high dose irradiation as local treatment as reported by several authors [Machak GN 2003; Hundsdoerfer P 2009; Schwarz R 2010]. Of course, higher irradiation doses are needed which might be accompanied with a higher incidence of side-effects and which is still an argument against radiotherapy in OS. But new irradiation strategies for example proton or heavy ion irradiation offer new possibilities to increase local dosage by reducing side-effects on normal tissue. The authors should discuss that more detailed and talk about “relative radioresistance”.

2. Abstract: WEE1 is expressed in most of the OS samples investigated by the authors. It is unlikely that all osteosarcoma express WEE1.

3. Background: The statement “As monotherapy, irradiation has never been effective…” is not completely correct and also applies to surgery. The treatment “gold standard” of OS consists of multimodal strategies, including chemotherapy and local treatment (either surgery and/or radiotherapy).

4. Methods: Why did the authors use the doses of 4 Gy irradiation and 0.5 µM PD0166285? Do these doses correspond to the LD50 of all investigated cell lines?

5. Methods: Did the authors examine also apoptosis where PD0166285 is supposed to sensitize cancer cells to apoptosis through the described pathomechanism?

6. Discussion: The authors should discuss more critically the difficulties of “targeted therapies”. Especially in vivo studies are necessary to prove the potential therapeutic effect of PD0166285.

Minor revisions

1. Title page: The address of T. Würdinger is not complete.

2. Background: Do not talk about “categories of patients” # “additional treatment …, especially for these patients.
3. Methods: Please spell the Title “Dr” not “dr”.
4. Please use the correct terms for the cell cycle distribution in the whole manuscript including figures: G0/1, S, G2/M,
5. Figures: Fig. 2A: Log y-scale might be more instructive.

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.