

Impact of DNA-PK Inhibition on 177-LuPSMA Response in PSMA-low Prostate Cancer Models

Alice Bernard-Tessier¹, Martin Bakht², Andria Rakotomalala², Rebecca Kim², Min Kim², Jacob Egelberg², Varadha Balaji Venkadakrishnan², Ramyar Molania², Anthony Belanger², Louise Clarke², Prafulla Gokhale², Fay Nicolson², Himisha Beltran²

¹Gustave Roussy, Villejuif, France

²Dana-Farber Cancer Institute, Boston, MA, USA

Background: 177Lu-PSMA-617 represents a standard-of-care treatment for metastatic castration-resistant prostate cancer (mCRPC) with PSMA-avid lesions. However, only 51% of patients achieve PSA response with median duration of 11.6 months, indicating an unmet need for strategies to deepen response. Major determinants of response include PSMA expression and intrinsic radiosensitivity. DNA-PK plays a critical role in DNA damage repair and AR pathway regulation in prostate cancer. We hypothesized that DNA-PK inhibition could enhance 177Lu-PSMA efficacy, particularly in PSMA-low models.

Methods: We evaluated peposertib (M3814), a DNA-PK inhibitor, combined with 177Lu-DOTA or external beam radiation (EBRT) across multiple prostate cancer models (LNCaP, C4-2, 22Rv1, 22Rv1-LMD - a PSMA-low cell line derived from a liver metastasis of a 22Rv1 mouse xenograft, and DU145). In vitro studies assessed cell viability via CellTiter-Glo, DNA damage (γ H2AX), PSMA expression (Western blot), and pDNA-PK autophosphorylation. In vivo studies used 22Rv1 and 22Rv1-LMD xenografts and WCM12 PDX model. IHC and imaging (68Ga-PSMA PET/CT) assessed PSMA expression and tumor response.

Results: DNA-PK inhibition potentiated both γ and β -particle ionizing radiation toxicity in vitro, with radiosensitization mediated through increased unresolved DNA double-strand breaks (DSBs) marked by sustained γ H2AX. Peposertib inhibited DNA-PK Ser2056 autophosphorylation in a dose- and time-dependent manner. The combination of peposertib and 177Lu-DOTA significantly increased cytotoxicity across mCRPC models. Interestingly, peposertib modulated PSMA expression in 22Rv1-LMD, a PSMA-low model. This observation was confirmed in vivo with increased 68Ga-PSMA in 22Rv1-LMD xenografts treated with peposertib. Ultimately, the peposertib and 177Lu-PSMA combination reduced tumor volume in mice compared to 177Lu-PSMA alone.

Conclusions: DNA-PK inhibition radiosensitizes prostate cancer cells to 177Lu-therapy through enhanced DSBs and PSMA modulation, showing particular promise in PSMA-low models typically resistant to radioligand therapy. These findings suggest DNA-PK inhibitors warrant clinical evaluation as adjuncts to 177Lu-PSMA therapy.

Funding Acknowledgements: A.B.-T. was supported by the Prostate Cancer Foundation (PCF) Young Investigator Award.

Conflicts of Interest: H.B. has served as a consultant for Harpoon, Merck, Janssen, AstraZeneca, Pfizer, Amgen, Astellas, Sanofi Genzyme, Novartis, Bayer, and Daiichi Sankyo and has received institutional research funding from Janssen, Bristol Myers Squibb, Circle Pharma, Daiichi Sankyo, Novartis, and Abbvie. A.B.-T. has received research grants from Servier and has served as a consultant for Novartis, Janssen, MSD, Astellas, and Bayer. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.