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European Association of Urology

## Letter to the Editor

**Re: Catherine H. Marshall, Alexandra O. Sokolova, Andrea L. McNatty, et al. Differential Response to Olaparib Treatment Among Men with Metastatic Castration-resistant Prostate Cancer Harboring *BRCA1* or *BRCA2* Versus *ATM* Mutations. Eur Urol 2019;76:452–8**

Exploiting the molecular heterogeneity of prostate cancer has the potential to unlock precise, personalized treatment for men afflicted with the disease. In metastatic castration-resistant prostate cancer (mCRPC), PARP inhibitors are approved for use in patients with mutations in homologous recombination (HR) DNA-repair genes, specifically *BRCA1* and *BRCA2* [1]. However, it is unclear if mCRPC patients with *ATM* mutations would benefit from PARP inhibitor therapy owing to the nonessential role of ATM in HR-driven repair [2]. We read with great interest the recent study by Marshall et al. [1] retrospectively comparing the response to olaparib between mCRPC patients with *BRCA1/2* and *ATM* mutations. The authors reported that patients harboring *ATM* mutations exhibited an "inferior response" to olaparib. Although the authors conclude that patients with *ATM*-mutated mCRPC do not benefit from olaparib therapy when compared to BRCA1/2-mutated mCRPC, methodological aspects of the study lend uncertainty to those conclusions.

Marshall et al. examined 17 mCRPC patients with *BRCA1/2* mutations and six patients with *ATM* mutations. While there were no statistically significant differences observed in the baseline demographics between the two groups, our interpretation of the study suggests a potentially significant clinical difference. The patients with an *ATM* mutation had a notably higher median baseline prostate-specific antigen (PSA) of 278 ng/ml (interquartile range [IQR] 95.2–365), whereas those with a *BRCA1/2* mutation had median PSA of only 22 ng/ml (IQR 5.4–53.9). Since the authors chose to define treatment response for the two populations as the "proportion of patients achieving a $\geq$50% decline in PSA", this fundamental difference in baseline PSA levels cannot be overlooked.

Although this large difference in baseline PSA levels might have influenced the authors' conclusions, it is important to acknowledge that the selection criteria for PARP inhibitor therapy in mCRPC cases with *ATM* mutations remain to be determined. In fact, distinct selection methods used in *ATM* status assessment could be one of the reasons why different conclusions were reached in similar studies [3,4]. Various factors require consideration, including the specific mutation(s) in *ATM*, the proportion of mutations in *ATM* gene copies, expression levels of the ATM protein, changes in epigenetic modifications, and potentially impactful co-mutations. Whole-exome sequencing, transcriptome detection methods, immunohistochemical assays, and the Ventana ATM (Y170) assay [5] could be used to distinguish and stratify patients with precise *ATM* mutations in future studies.

Overall, despite the differential response to olaparib observed between mCRPC patients with ATM and BRCA1/2 mutations in this study, there is insufficient evidence to close the door on the use of PARP inhibitors in cases of mCRPC with *ATM* mutations.

***Conflicts of interest:*** RSB is a scientific co-founder, consultant, and equity stakeholder in Cybrexa Therapeutics. Cybrexa is developing tumor-targeted DNA repair inhibitors for the treatment of solid tumors. The major focus of the company is on the development of chemo/radiosensitizers for HRD proficient tumors, and thus there is no perceived COI related to this publication.

## References

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Jiayu Liang[a,b]
Jason M. Beckta[a]
Ranjit S. Bindra[a,*]

[a]*Therapeutic Radiology, Yale University School of Medicine, New Haven, CT, USA*
[b]*Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China*

*Corresponding author. Therapeutic Radiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520, USA.
Tel. +1 203 5840924.
E-mail address: ranjit.bindra@yale.edu (R.S. Bindra).

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