available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 170–176 of this issue

Synergistic Interactions: Targeted Radiopharmaceuticals and Homologous Recombination Repair Alterations in Prostate Cancer

Oliver Sartor *

Cancer Center, Tulane Medical School, New Orleans, LA, USA

Why is a small retrospective study with radium-223 [1] important enough to warrant publication in this *European Urology* issue? To better understand the context, one needs to understand the actionable mutations in prostate cancer. In 2016, a seminal study [2] investigating the molecular genetics of prostate cancer in depth revealed a surprise. In addition to the widely known and appreciated importance of androgen receptors in advanced prostate cancer, there was also a remarkably frequent occurrence of DNA repair defects present in metastatic castrate-resistant prostate cancer (CRPC). Mutations in the DNA repair pathway were especially common: more than 20% of cases harbored pathogenic alterations in well-described homologous recombination genes, including *BRCA2*, *BRCA1*, *ATM*, and *CDK12*. Interestingly, nearly half of the *BRCA2*, *BRCA1*, and *ATM* gene alterations were in the germline, another surprising finding with important repercussions for patients and their families.

The finding that homologous recombination defects (HRDs) are common in advanced prostate cancer has therapeutic implications on several fronts. This includes potential sensitivity to PARP inhibitors, susceptibility to DNA-damaging agents such as platinum and various forms of radiation, and perhaps even enhanced responsiveness to immunotherapy.

It is now clear that prostate cancer patients harboring mutant *BRCA* in their tumors can respond to treatment with PARP inhibitors [3,4], and multiple PARP inhibitors are now in advanced clinical trials. Patients with *BRCA* mutations can also be successfully treated with platinum-containing regimens [5,6] and these agents are also in advanced clinical trials in prostate cancer. Responsiveness to immunotherapies for patients with mismatch repair-deficient tumors (*MSH2*, *MSH6*, *MLH1*) is well described, but the possibility that HRD tumors also have enhanced responsiveness to immunotherapy is a recent and intriguing finding [7].

Radiation comes in various forms. External beam radiation, brachytherapy, electrons, β particles, and α particles all exert their anticancer activity via DNA damage, and cancers with DNA repair defects should be particularly susceptible to radiation.

Radium-223 is an α-emitting radiopharmaceutical associated with prolongation of survival in men with bone metastatic CRPC [8], and α particles exert their action by damaging DNA in tumor cells and the cellular microenvironment adjacent to their region of deposition. Although α particles have a very short path length in tissue, their energy is high.

In the study by Velho et al. [1], the efficacy of radium-223 is examined in bone metastatic CRPC with and without a HRD. Their manuscript builds on a case report in which a patient with biallelic *BRCA2* mutations had an exceptional response to radium-223 [9]. In the Hopkins study, men with HRD had a higher percentage alkaline phosphatase (ALP) decline, a longer time to ALP progression, and a trend toward longer survival. These are important findings. ALP declines have been linked to radium-223 clinical activity [10]. Limitations of the study by Velho et al. include its retrospective nature and the small number of patients enrolled. More definitive data on this topic should be considered. Similar studies are warranted with other targeted isotopic therapies, including lutetium-177 and actinium-225.

Given conceptual synergy between the DNA-damaging agents and agents that inhibit DNA repair, it makes sense that such agents would be combined in clinical trials. These trials should necessarily start at lower doses, given that synergistic effects could lead to additional toxicity. These

DOI of original article: https://doi.org/10.1016/j.eururo.2018.09.040.
* Cancer Center, Tulane Medical School, 1430 Tulane Avenue, New Orleans, LA 70112, USA. Tel. +1 504 3557970.
E-mail address: osartor@tulane.edu.

https://doi.org/10.1016/j.eururo.2018.11.041
0302-2838/© 2018 European Association of Urology. Published by Elsevier B.V. All rights reserved.

trials could take various forms, such as PSMA-targeted lutetium-177 or actinium-225 and a PARP inhibitor, or radium-223 and a PARP inhibitor. Other forms of DNA repair inhibition such as ATR inhibitors combined with various forms of radiation should also be explored.

Targeted radiopharmaceuticals will be ideal for these potentially synergistic interactions with DNA repair inhibitors, given their relatively low toxicities. External beam therapies typically use doses that are close to normal tissue tolerance, and thus the therapeutic index is probably lower. Taken together, clinical trials with radiopharmaceuticals (especially those with low-energy β or α particles) combined with DNA repair inhibitors such as ATR or PARP inhibitors should be a priority given their potential to be highly active with minimal toxicity. More prospective clinical trials are necessary to test this concept and the sooner they are completed, the better.

Conflicts of interest: The author is a consultant for Bayer, Endocyte, AAA, Fusion, Noria, Merck KGaA, AstraZeneca, Janssen, and Pfizer, and an investigator for Bayer, Endocyte, AAA, Invitae, Merck, and BMS.

References

[1] Velho PI, Qazi F, Hassan MA, et al. Efficacy of radium-223 in bone-metastatic castrate resistant prostate cancer with and without homologous repair gene defects. Eur Urol 2019;76:170–6.

[2] Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215–28.

[3] Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–708.

[4] Abida W, Bryce AH, Vogelzang NJ, et al. Preliminary results from TRITON2: a phase 2 study of rucaparib in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. Annals Oncol 2018;29(Suppl 8), vii271-302.

[5] Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 2016;69:992–5.

[6] Pomerantz MM, Spisák S, Jia L, et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer 2017;123:3532–9.

[7] Boudadi K, Suzman DL, Anagnostou V, et al. Ipilimumab plus nivolumab and DNA-repair defects in AR-V7-expressing metastatic prostate cancer. Oncotarget 2018;9:2856–71.

[8] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–23.

[9] Steinberger AE, Cotogno P, Ledet EM, et al. Exceptional duration of radium-223 in prostate cancer with a BRCA2 mutation. Clin Genitourin Cancer 2017;15:e69–71.

[10] Sartor O, Coleman RE, Nilsson S, et al. An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223. Ann Oncol 2017;28:1090–7.