Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cancer Treatment and Research Communications 24 (2020) 100190

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.elsevier.com/locate/ctarc

The rapidly evolving treatment landscape of advanced prostate, bladder, and renal cell carcinomas

For the medical field and society as a whole, 2020 will be remembered as the year of the COVID-19 coronavirus pandemic, yet for genitourinary medical oncologists, 2020 also brings encouraging therapeutic advances for our patients with advanced prostate, bladder, and renal cell carcinomas (RCC). Prior to 2020, the last time a novel treatment was approved for patients with metastatic castration-resistant prostate cancer (mCRPC) was 2014. In 2020, two PARP inhibitors, olaparib and rucaparib, were approved by the US Food and Drug Administration (FDA) for the treatment of mCRPC. Over the past few years, multiple novel therapeutic classes were added for patients with platinum-refractory metastatic urothelial carcinoma (mUC); however, a first-line treatment had not improved overall survival (OS) compared to platinum-based chemotherapy until the JAVELIN Bladder 100 trial was presented at the American Society of Clinical Oncology (ASCO) Virtual Scientific Meeting in 2020. Herein, we will briefly review these studies as an introduction to the more in-depth articles available in this special issue of *Cancer Treatments and Research Communications*.

Germline mutations in genes associated with DNA homologous recombination repair (HRR) are present in approximately 10% of men with mCRPC, and another 20% of men have somatic mutations in these same genes [1,2]. The most commonly altered HRR genes are *BRCA2, ATM*, and *BRCA1*. Deficiency in HRR makes cancers susceptible to poly (adenosine diphosphate-ribose) (PARP) inhibitors, such as olaparib and rucaparib, as was previously observed in breast, ovarian, and pancreatic cancers. Olaparib was evaluated in a phase III clinical trial, PROfound, that randomized 387 men with mCRPC and HRR alterations to olaparib or physician's choice of abiraterone or enzalutamide after progression on novel hormonal therapy (NHT) [3]. There were two cohorts of patients depending upon the type of HRR alteration present. Cohort A was men with at least one alteration in *BRCA1, BRCA2*, or *ATM*; whereas, cohort B was men with an alteration in any of the 12 other pre-specified HRR genes. In cohort A, olaparib significantly improved radiographic progression-free survival (rPFS) (7.4 vs. 3.6 months, HR 0.34, 95% CI 0.25–0.47) and OS (18.5 vs 15.1 months, HR 0.64, 95% CI 0.43–0.97) compared to the control arm. Efficacy outcomes were not independently assessed for cohort B. In a composite of cohorts A and B, olaparib significantly improved median rPFS compared to control, yet to a lesser degree than observed in cohort A. Based upon these promising results, the US FDA approved olaparib for men with mCRPC and any HRR alteration after progression on NHT. Although, enrollment of patients who had previously progressed on both abiraterone and enzalutamide was a limitation of the PROfound trial.

There are other PARP inhibitors being evaluated for the treatment of mCRPC, including niraparib, rucaparib, talazoparib, and veliparib. In 2020, rucaparib received FDA approval for men with *BRCA1/2* mutated mCRPC based upon an updated analysis of the ongoing, single arm, phase II trial, TRITON2 [4]. TRITON2 is evaluating the efficacy of rucaparib in patients with mCRPC and a deleterious alteration in HRR genes after progression on at least one NHT and taxane-based chemotherapy. Rucaparib produced an objective response rate (ORR) of 43.9% in 98 patients with a *BRCA* alteration. Rucaparib's efficacy was less impressive in patients with non-*BRCA* alterations. PARP inhibitors continue to be evaluated as monotherapy in ongoing, late phase clinical trials, and they are being evaluated in combination with NHTs, immune checkpoint inhibitors, and radium-223 [5].

Recent advances for the treatment of mUC after progression on platinum-based chemotherapy have limited impact because many patients become too frail to receive further treatment upon progression. The treatment paradigm for first-line treatment of patients with mUC has not improved in the last several decades. Accordingly, this is a patient population with a huge unmet need. JAVELIN Bladder 100 was a phase III clinical trial that randomized 700 patients to switch maintenance avelumab or best supportive care (BSC) within 10 weeks of achieving an objective response or stable disease with platinum-based chemotherapy [6]. Maintenance avelumab significantly improved median OS (21.4 vs. 14.3 months, HR 0.69, 95% CI 0.56–0.86) compared to BSC, a magnitude of OS benefit hitherto not seen in this patient population with prior immune checkpoint inhibitor studies. The JAVELIN Bladder 100 trial was limited by the combination of no crossover with international accrual where post-platinum treatment can vary substantially. A similar phase II clinical trial evaluated maintenance pembrolizumab and found that it significantly improved median PFS, but did not significantly improve OS (22 vs. 18.7 months, HR 0.91, 95% CI 0.52–1.59) [7].

In sum, clinical studies reported this year have rapidly influenced routine clinical practice by introducing PARP inhibitors for men with mCRPC and HRR deficiency and maintenance avelumab for patients with mUC who respond to platinum-based chemotherapy. These and other advances in the treatment of advanced prostate, bladder, and renal cell carcinomas are discussed in further detail in this special issue of *Cancer Treatments and Research Communications*.

Declaration of Competing Interest

Andrew W. Hahn has no conflicts to disclose. Neeraj Agarwal reports **consultancy** to: Astellas, Astra Zeneca, Bayer, Bristol Myers Squibb, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Janssen, Merck, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics. Neeraj Agarwal also reports

https://doi.org/10.1016/j.ctarc.2020.100190

research funding to my institution from the following: AstraZeneca, Bavarian Nordic , Bayer, Bristol-Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Glaxo Smith Kline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon.

References

[1] C.C. Pritchard, J. Mateo, M.F. Walsh, et al., Inherited DNA-repair gene mutations in men with metastatic prostate cancer, N. Engl. J. Med. 375 (2016) 443–453.

[2] D. Robinson, E.M. Van Allen, Y.M. Wu, et al., Integrative clinical genomics of advanced prostate cancer, Cell 162 (2015) 454.

[3] J. de Bono, J. Mateo, K. Fizazi, et al., Olaparib for metastatic castration-resistant prostate cancer, N. Engl. J. Med. 382 (2020) 2091–2102.

[4] W. Abida, D. Campbell, A. Patnaik, et al., Preliminary results from the TRITON2 study of rucaparib in patients with DNA damage repair-deficient metastatic castration-resistant prostate cancer: updated analysis, Ann. Oncol. (2019) 30.

[5] J.J. Adashek, R.K. Jain, J Zhang, Clinical development of PARP inhibitors in treating metastatic castration-resistant prostate cancer, Cells (2019) 8.

[6] T. Powles, S.H. Park, E. Voog, et al., Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 phase III interim analysis, J. Clin. Oncol. (2020) 38 LBA1-LBA.

[7] M.D. Galsky, A. Mortazavi, M.I. Milowsky, et al., Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer, J. Clin. Oncol. 38 (2020) 1797–1806.

Andrew W. Hahn[a], Neeraj Agarwal[b,*]

[a] *Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

[b] *Division of Oncology, Department of Internal Medicine, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA*

E-mail address: neeraj.agarwal@hci.utah.edu (N. Agarwal).

* Corresponding author.