Platinum Opinion

Precision Oncology for Metastatic Prostate Cancer: Translation into Practice

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Precision oncology has been defined as “a healthcare approach with the primary aim of identifying which interventions are likely to be of most benefit to which patients based upon the features of the individual and their disease” [1].

The prostate cancer (PCa) community has been complaining about much slower development of precision medicine than for other malignancies. For breast, lung, colorectal, and other cancers, upfront genomic testing has already become part of standard management [2].

The recent publication of results from PROfound, a randomised, open-label, phase 3 trial evaluating the poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitor olaparib in men with metastatic castration-resistant prostate cancer (mCRPC), provides level 1 evidence for a precision oncology approach for the treatment of advanced PCa [3]. This trial showed that in patients with at least one alteration in BRCA1, BRCA2, or ATM genes, imaging-based progression-free survival was significantly longer with olaparib than with the androgen receptor–targeted agents (ARla) abiraterone or enzalutamide. These encouraging data are supported by results from phase 2 trials using olaparib [4–6] or other PARP inhibitors such as rucaparib and niraparib [7]. Approval of olaparib and access to this new treatment option were eagerly awaited by patients and their families and physicians [8].

Very recently, rucaparib became the first PARP inhibitor to receive approval from the US Food and Drug Administration (FDA) for pretreated mCRPC patients with a deleterious BRCA mutation [9] on the basis of response data in a single-arm phase 2 trial (TRITON2) [5]. This was closely followed by FDA approval of olaparib [8].

While the principles of precision medicine have been readily embraced by all stakeholders, multiple conceptual and structural challenges hinder its broad implementation in clinical practice.

PROfound, so far, provides the highest level of evidence for the use of a PARP inhibitor in PCa. It is an undoubtedly positive trial, but it also clearly shows the complexity of precision oncology for PCa and the challenges of translating genomics into treatment for mCRPC.

1. Testing, timing, and tissue

The Cancer Genome Atlas project showed that deleterious DNA-repair aberrations affected 20–25% of primary tumour PCa samples [10]. In clinical trials such as PROfound and simply in our clinical practice, most disappointingly, the percentage of patients qualifying for PARP inhibitor therapy is much lower [10]. How does this happen?

In contrast to other cancers, PCa often progresses to metastases many years after first diagnosis, surgery, or biopsy. Old archival tissue might no longer be available or may not fulfill the quality criteria for sequencing. Obtaining fresh biopsies from bone metastases is often a challenge and...
the decalcification procedure causes damage to the DNA needed for sequencing.

In PROfound, only tissue from the primary tumour or metastases was used for genomic testing and there was no liquid biopsy. The authors report a 30% sample failure rate, and of those successfully sequenced and harbouring a qualifying genomic alteration, only approximately 50% started the trial medication. The absolute numbers highlight the full challenge: 4425 patients were enrolled, 2792 had successful sequencing and biomarker status reported, 778 had one or more of 15 prespecified genes, 168 did not qualify for treatment or had progressed and started another cancer treatment, and only 8.7% (387 patients) of the population enrolled could be randomised and treated.

These numbers support our experience in daily practice that for patients with advanced mCRPC it often takes far too long to obtain external primary tumour biopsies, select and prepare representative tissue, send the samples away for sequencing, receive the report, counsel the patient, and start treatment. Some patients experience progression and need an immediate anticancer therapy, while others might deteriorate in terms of performance status or become anaemic and might no longer qualify for a PARP inhibitor or any other treatment.

In essence, we have to identify upfront patients who might derive a benefit from PARP inhibitors (and/or other precision oncology approaches) [11].

Strategies for improving and translating genomic testing for a broader population of PCa patients in clinical practice might include:

- **Reduce delays**
  - Start genomic testing early on, at the first diagnosis of metastases.
  - Reduce the tissue failure rate; close cooperation with a dedicated pathologist is required to be sure that the best tissue samples from all tumour regions of interest are selected and prepared accordingly.
  - Establish a standard operating procedure with the pathology laboratory with agreed timelines.
- **Increase the probability of finding genomic alterations**
  - Explore implementation of liquid biopsy; circulating tumour DNA (ctDNA) was not used in PROfound but has been used in other trials [4,6]. ctDNA sensitivity increases with tumour volume and thus its use in later-stage PCa should be preferred. Blood-based genomic testing is promising and already approved for other cancers [12]. However, for PCa challenges such as surprisingly low congruence of commercially available tests gives rise to uncertainties, and more testing and data are needed [13].
  - Consider including germline sequencing, at least for patients with a positive family history [14].

2. **Should we test only for BRCA alterations?**

The FDA approved the PARP inhibitor olaparib for patients with deleterious or a suspected deleterious germline or somatic homologous recombination repair gene mutation in mCRPC who have progressed following prior ARTA treatment [8].

Rucaparib was approved only for men with mCRPC and a deleterious BRCA mutation (germline and/or somatic) who have been treated with an ARTA and taxane-based chemotherapy [9].

Efficacy results for the other genes were reported in the TRITON2 ad hoc analysis of patients and provide compelling evidence that response to PARP inhibitors is limited in men with mCRPC harbouring an ATM, CDK12, or CHEK2 alteration [15]. For PALB2, the data confirm previous reports [16] and allow more optimism for non-BRCA alterations. PALB2 mutations, whether germline or somatic, might predict response to PARP inhibition as well as to platinum-based chemotherapy. Therefore, there is a claim that a more comprehensive genomic characterisation of PCa patients undergoing PARP inhibitor therapy will be necessary to define the entire spectrum of predictive biomarkers.

Only a small proportion of mutations identified so far have functional data suggesting that they could serve as therapeutic targets. More comprehensive testing requires expert interpretation (molecular tumour board). There is already a call for common reporting of results from comprehensive genomic profiling, distinguishing between known pathogenic and more likely benign alterations. In addition, variants of unknown significance should be reported as they might provide information for research and findings of potential clinical significance for a later point in time on the patient’s journey.

3. **Incorporation of PARP inhibitors in the sequence of treatments for mCRPC**

PROfound provides limited information regarding the best use of olaparib in the sequence of available treatments. All patients were pretreated with a novel hormonal agent (abiraterone or enzalutamide), many patients had prior docetaxel, and a minority had both taxanes (docetaxel and cabazitaxel). Moreover, 25% of patients did not receive any taxanes before starting olaparib [3].

PROfound and the ongoing TRITON3 trial [17] used abiraterone or enzalutamide in sequence for the control arm. While oral treatment admittedly is convenient as the control arm, there is increasing evidence that there is cross-resistance between the ARTAs [18]. In the randomised phase 3 CARD trial, overall survival was significantly prolonged by cabazitaxel compared to the second ARTA in patients progressing after docetaxel and within 12 mo of the first ARTA (abiraterone or enzalutamide) [19]. Furthermore, 20% of PROfound patients had both abiraterone and enzalutamide before entering the trial and thus received retreatment in the control arm. In view of the control arm in PROfound, the best position for a PARP inhibitor in the sequence of agents for patients with mCRPC harbouring a deleterious mutation in a DNA repair gene remains blurred [3].

There is no doubt that precision medicine has started for PCa. However, many questions remain and its translation
into daily practice in PCa clinics requires more work, more trials, and multidisciplinary efforts.

Appendix A. Members of the EAU-ENAM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel who contributed to group authorship of this letter

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Conflicts of interest: Maria De Santis is a company consultant for Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc, Ferring, GSK, IPSEN, Incyte, Janssen, Celag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SOTIO and Cancer Research UK; participates in various trials as a member of the EORTC GU group; has received research grants from Pierre Fabre Oncologie; and has received travel grants from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Ferring, GSK, IPSEN, Incyte, Janssen, Celag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthony, Takeda, and Teva/OncoGenex. Nicolas Mottet is a company consultant for Janssen, GE, BMS, Sanofi, and Astellas; has received speaker honoraria from Astellas, Pierre Fabre, Steba, Janssen, and Ferring; and has received fellowships and travel grants from Astellas, Ipsen, Sanofi, Janssen, and Roche. Philip Cornford is a company consultant for Astellas, Ipsen, and Ferring; has received company speaker honoraria from Astellas, Janssen, Ipsen, and Pfizer; has participated in trials run by Ferring; and has received fellowships and travel grants from Astellas and Janssen. Silke Gillesen is a company consultant for AAA International, Astellas Pharma, Bayer, Bristol-Myers Squibb, Clovis, CureVac, Ferring, Innocrin Pharmaceuticals, Janssen Cilag, MaxiVAX SA, Orion, Roche, Sanofi Aventis Group, Nectar, and ProteoMedix; has received speaker honoraria from Janssen and Novartis; and participates in multiple trials for different companies. Erik Briers has received grant and research support from IPSEN, the European Association of Urology, and Bayer; is an ex officio board member for Europa UOMO; is an ethics committee and advisory group member for REQUITE; is a patient advisory board member for PAGMI; and is a member of SCA and EMA PCWP. Stefano Fant is a company consultant for Bayer and ANMI; has received speaker honoraria from Bayer, Genzyme, ANMI, and GE Healthcare; and participates in trials by Amgen, Bayer, BMS, Genzyme, Janssen, Merck, and Novartis. Jeremy Grummet has received speaker honoraria from Mundipharma, a travel grant from Astellas, and a research grant from Cancer Australia. He is the owner of MRI PRO Pty Ltd., an online training platform. Ann M. Henry is a company consultant for Nucletron-Elektro; participates in trials by Cancer Research UK and the National Institute of Health Research (UK); has received travel grants from the Medical Research Council, the National Institute of Health Research (UK), and Cancer Research UK; and has received research grants from Cancer Research UK and the Sir John Fisher Foundation. Thomas B. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GSK, Astellas, and IPSEN. Malcolm D. Mason is a company consultant for Ellipses Pharma and Oncethers. Derya Tilki has received speaker honoraria from Astellas and a travel grant from Janssen. Henk G. van der Poel is a company consultant for Intuitive Surgical; has participated in trials for Astellas and Steba Biotech; and has received grant and research support from Astellas. Thomas Wiegel is an advisory board member for IPSEN; receives company speaker honoraria from IPSEN and Hexal; is a member of the Janssen Steering Committee; and has participated in the ATLAS/AIUO trial. Roderick C.N. van den Bergh, Olivier Rouvière, Theodorus van der Kwast,
Guillaume Ploussard, and Ivo G. Schoots have nothing to disclose.

References