PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Predictive Biomarkers in Advanced Prostate Cancer

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H&O What is the difference between a prognostic biomarker and a predictive biomarker?

AA Prognostic biomarkers estimate the natural history of a disease, or in other words, the chance of a medically important event. The most important endpoint in cancer is survival, but prognostic biomarkers can also be used for intermediate, shorter-term endpoints, such as progression-free survival, the risk of relapse, or the risk of metastasis over time. Predictive biomarkers, by contrast, let us know how likely a specific treatment will help a particular patient. For example, will docetaxel, enzalutamide (Xtandi; Astellas, Pfizer), or abiraterone lead to prostate-specific antigen responses, tumor responses, or improved survival? In prostate cancer, predictive biomarkers help identify men with metastatic castration-resistant prostate cancer (mCRPC) who would benefit from therapies such as poly(ADP-ribose) polymerase (PARP) inhibitors, immunotherapy, and radioligand therapy. One of the research goals in prostate cancer is to develop more predictive biomarkers to optimize patient care by delivering effective therapies to patients who will benefit the most while avoiding the toxicities and costs associated with ineffective therapy.

H&O Could you discuss the predictive biomarkers that are being used to identify candidates for PARP inhibitors?

AA The US Food and Drug Administration (FDA) has approved 2 PARP inhibitors for use in mCRPC: olaparib (Lynparza, AstraZeneca) and rucaparib (Rubraca, Clovis Oncology). The olaparib approval was based on the improved overall survival seen in the phase 3 PROfound study, which included men with homologous recombination repair–deficient mCRPC,[1] whereas the rucaparib approval was based on the results of the phase 2 TRITON2 study, which involved men with *BRCA*-mutated mCRPC.[2] In order to be eligible for olaparib, patients need to have a germline or somatic mutation in *BRCA1, BRCA2, ATM,* or one of several other DNA repair genes based on an FDA-approved companion diagnostic test or a College of American Pathologists (CAP)- or Clinical Laboratory Improvement Amendments (CLIA)-approved academic or commercial platform that reliably measures these genetic alterations. For rucaparib eligibility, patients need to have a germline or somatic mutation in *BRCA1* or *BRCA2*. FDA-approved tests include BRACAnalysis CDx (Myriad Genetic Laboratories), FoundationOne CDx (Foundation Medicine), FoundationOne Liquid CDx (Foundation Medicine), or Guardant360 CDx (Guardant). Many academic research institutions have their own assays available that perform similarly to these commercial tests.

Research has shown that *BRCA2* and *BRCA1* mutations are much more predictive than *ATM* mutations of PARP inhibitor benefit. Mutations in *PALB2* and *RAD51* also have been shown to predict sensitivity to PARP inhibitors, whereas patients with mutations in *CHEK2* and *CDK12* do not seem to derive much benefit—not

every DNA homologous recombination repair gene mutation increases the response to PARP inhibitors. In addition, we continue to discover new gene mutations, such as those in *RNASEH2B*, that confer PARP inhibitor sensitivity but are not currently in our testing panels. Ongoing research is dedicated to finding new predictive biomarkers specific to PARP inhibition, either alone or combined with potent androgen receptor (AR) inhibitors, such as genomic scar assays, gene expression signatures, and alterations in individual genes.

AI is emerging as a highly sophisticated way for computers to identify new predictive biomarkers based on large amounts of data.

H&O Could you discuss the predictive biomarkers that are being used to identify candidates for immunotherapy?

AA Pembrolizumab (Keytruda, Merck) received a tissue-agnostic FDA indication in 2017 for patients with unresectable or metastatic solid tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This approval was based on an analysis by Le and colleagues of 5 trials.[3,4] This indication was extended in 2020 to patients with solid tumors and a high tumor mutational burden, defined as 10 or more mutations per megabase on a tumor assay using the FoundationOne CDX platform and companion diagnostic. Pembrolizumab works so well in patients with MSI-H disease because these patients also have a high tumor mutational burden, which means that the immune system is more likely to recognize these tumors as foreign. These tumors are highly inflamed, but the infiltrating T cells are often exhausted. The response rate to the programmed death 1 (PD-1) inhibitor pembrolizumab and similar agents is nearly 50% in patients with metastatic MSI-H prostate cancer, and these responses are often very durable. This is compared with a response rate of just 6% in patients with mCRPC that is not MSI-H. Recent phase 3 trials have demonstrated a lack of survival benefit for pembrolizumab in unselected men with mCRPC or metastatic hormone-sensitive prostate cancer (mHSPC), even when combined with enzalutamide, docetaxel, or olaparib. This suggests that predictive biomarkers beyond tumor mutational burden or MSI-H status are sorely needed, in addition to better immunotherapies. As an oncologist, some of the best experiences I have had are seeing patients with MSI-H mCRPC achieve complete and durable remission owing to PD-1 blockade, which is maintained even after stopping hormonal therapy. This is why we recommend doing next-generation sequencing tests on tumors or plasma DNA to identify actionable alterations that can improve the outcomes of patients dealing with cancer.

H&O Could you discuss the predictive biomarkers that are being used to identify candidates for radioligand therapy?

AA A predictive biomarker does not necessarily have to be a genetic test; it can also be a clinical feature of a patient that we pick up on imaging, such as prostate specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT). The phase 3 VISION trial found that the greater the uptake of PSMA on PET imaging, the greater the benefit of PSMA-targeted radioligand therapy with ^{177}Lu-PSMA-617, also known as lutetium Lu 177 vipivotide tetraxetan (Pluvicto, Novartis).[5] However, all patients that were PSMA PET–positive using VISION criteria benefited from this therapy over the standard of care, suggesting that the PSMA PET standardized uptake value can be helpful to estimate outcomes but is not completely predictive. Even patients with dim uptake of PSMA can benefit, whereas patients without PSMA uptake do not benefit. Based on the results of the VISION trial, the FDA approved the use of ^{177}Lu-PSMA-617 in 2022 for patients with mCRPC whose cancer is identified as PSMA-positive on PET imaging and lack PSMA-negative soft tissue metastatic lesions.

All the phase 3 trials that are looking at PSMA targeting in metastatic prostate cancer, including PSMAfore (NCT04689828), PSMAddition (NCT04720157), and SPLASH (NCT04647526), require the use of a companion diagnostic imaging test to detect tumor expression of PSMA to more appropriately treat those patients most likely to benefit. Patients with PSMA-negative mCRPC might benefit from alternative radioligand therapies, such as for neuroendocrine prostate cancer. This is an active area of research for both imaging and treatment.

H&O What is the role of androgen receptor splice variant 7 (AR-V7) as a biomarker?

AA The presence of AR-V7 in circulating tumor cells of men with mCRPC has been shown to be not only a negative prognostic factor, meaning it is associated with worse outcomes, but also a negative predictive factor for response to the potent AR inhibitors enzalutamide and abiraterone. The presence of AR-V7 creates a constitutively active AR that cannot be blocked by ligand binding–domain inhibitors of the AR. Such patients still benefit from taxane chemotherapy but have close to a 0% chance of benefiting from a second AR inhibitor. As a results, these patients should instead be offered chemotherapy, radioligand therapy, radium-223 (Xofigo, Bayer), or other more effective therapies, including clinical trials. The PROPHECY study is the largest prospective, blinded, multicenter trial to date, and showed that patients with mCRPC who test positive for AR-V7 on a validated liquid biopsy assay do not benefit from a second AR inhibitor, such as enzalutamide or abiraterone.[6] AR-V7 testing in men with advanced prostate cancer is now reimbursed by Medicare and can be considered for some men who face this treatment dilemma in the second-line mCRPC setting.

H&O Could you discuss your research on artificial intelligence (AI) biomarkers?

AA AI is emerging as a highly sophisticated way for computers to identify new predictive biomarkers based on large amounts of data, such as that from imaging or pathology. I am presenting data at the 2023 American Society of Clinical Oncology Annual Meeting on a novel multimodal digital pathology AI biomarker that has predictive accuracy for the value of long-term hormonal therapy in men with localized prostate cancer who are treated with radiation.[7] Because this interview will appear in print after the meeting, I can share the details of my presentation.

The study was designed to see whether an AI biomarker developed by Artera could determine whether certain men with high-risk, localized prostate cancer could receive short-term androgen deprivation therapy (ADT) instead of long-term ADT, which is the standard of care. We used AI to analyze data from thousands of patients across several RTOG trials, with external validation in the phase 3 RTOG 9202 trial (n=1192). The analysis found that approximately one-third of high-risk men tested negative using the AI biomarker. These patients had excellent long-term outcomes with short-term ADT, and demonstrated a low risk of distant metastases. There were no additional benefits from long-term ADT in these patients. This finding has the potential to reduce the risks and toxicities associated with ADT for patients without affecting their cancer control in the long term. Conversely, approximately 40% of intermediate-risk men by National Comprehensive Cancer Network criteria had a high-risk AI biomarker. This subgroup would benefit from long-term ADT—meaning treatment intensification. Therefore, this AI pathology predictive biomarker could be useful in guiding treatment decisions for many patients with localized prostate cancer.

H&O What other predictive biomarkers are being investigated in metastatic prostate cancer?

AA Multiple predictive biomarkers are currently being investigated in patients with metastatic prostate cancer. Imaging techniques, such as somatostatin imaging and neuroendocrine PET imaging, are being developed to guide new radioligand therapies. New genetic biomarkers, such as *PTEN* loss, are being investigated to predict the benefits of phosphoinositide 3-kinase (PI3K) inhibitors and AKT inhibitors. For example, the phase 3 CAPItello-281 trial is examining the addition of the AKT inhibitor capivasertib to abiraterone in patients with mHSPC and *PTEN* deficiency (NCT04493853).

Specific immune patterns in tumors or peripheral blood are also being developed as biomarkers to guide new immunotherapies in prostate cancer. The FDA provides some guidance on biomarker development, including a taxonomy for classifying and developing biomarkers called the Biomarkers, Endpoints, and Other Tools (BEST) glossary.[8] The goal is to help investigators and companies develop a parallel pathway for biomarker development, especially for companion molecular diagnostics and any biomarkers that are going to guide therapy for patients.

Patient characteristics can also be useful as biomarkers. At Duke, the biostatistician Susan Halabi has developed and recently validated a prognostic model that factors in performance status, disease site, lactate dehydrogenase level, opioid analgesic use, albumin level, hemoglobin level, prostate-specific antigen level, and alkaline phosphatase level to predict overall survival in mCRPC in the setting of docetaxel or potent AR inhibitor use.[9] We would like to build on this prognostic model by adding molecular features from plasma or tumor DNA or RNA testing to predict which treatments, such as AR inhibitors or combinations with other agents such as PARP inhibitors, which would be most effective.

H&O When should biomarker testing be conducted?

AA International guidelines currently recommend germline testing for all men with advanced prostate cancer, ranging from high-risk to metastatic disease. In addition, patients with low- and intermediate-risk disease who have a strong suggestive family history of prostate, breast,

ovarian, or other cancers associated with hereditary cancer syndromes (such as Lynch syndrome) should receive germline testing. Not only can this help patients determine whether they can benefit from PARP inhibition, it can also help us identify whether other members of their family need more-intensive screening and risk-reducing treatments.

Tumor testing can be done using either a tumor sample or a liquid biopsy technique. The preferred option is a tumor sample using the most recent biopsy, a fresh biopsy, or an archival sample. The optimal time for tumor testing in men with mCRPC is before the decision to use PARP inhibition or pembrolizumab, and thus it is reasonable to order testing in the mHSPC or early mCRPC setting.

H&O When should tissue biopsy vs liquid biopsy be used to inform treatment selection in men with metastatic prostate cancer?

AA Tissue biopsy is always the preferred first step. Most patients with prostate cancer have tissue collected at the time of diagnosis, whether that includes a prostate biopsy or a specimen from a radical prostatectomy. Some of these tissues have been in storage for a decade or longer, however, and may have degraded. Many prospective and retrospective studies have shown that in approximately one-third of cases, the tumor tissue is inadequate in quality or quantity to get an informative result. In these patients, we try to collect fresh metastatic tissue for next-generation sequencing. If getting metastatic tissue is too difficult, particularly if the patient has either bone-only metastases or very small lymph node metastases, liquid biopsy with plasma testing becomes an important option. Liquid biopsies have very good concordance with solid-tumor biopsies, but they do have limitations and occasionally pick up alterations that are not present in the cancer, such as AR mutations or somatic late-event alterations in *BRCA* or mismatch repair genes. Sometimes the blood sample does not have enough tumor DNA at the time of collection, which can lead to a failure to pick up on certain mutations and thus an uninformative result that may need to be repeated. Ordering this test at the time of progression rather than during treatment response is critical.

H&O What do you see happening in the future with predictive biomarkers?

AA The development of biomarkers to inform treatment in cancer will continue to progress rapidly, and is certainly going to become more complicated. Oncologists will need to be knowledgeable about a wide range of biomarkers, including AI algorithms, the microbiome, immune phenotyping, RNA sequencing, and complex RNA signatures, if these become reliable as predictive biomarkers in the future. The important concept here is to rely on biomarkers that have undergone rigorous analytic and clinical testing, ideally in randomized controlled prospective trials, and have been shown to reliably identify patients who are most likely benefit from specific therapies.

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