

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Daniel J. George, MD

The Role of Genomics in Patients With Advanced Prostate Cancer



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H&O What are the main technologic advances that have spurred on the current interest in genomics?

MH The current interest in genomics was a downstream effect of the publication of the human genome in 2001 as part of the Human Genome Project. There have been tremendous changes since then—the cost of sequencing has gone down, and the turnaround time has dramatically decreased compared with 2001 and even compared with 2 years ago. We can also analyze data much more effectively now, thanks to computer programs and shared bioinformatics analysis. A major reason the process has become less expensive, faster, and more informative is that academic institutions and private research laboratories have been working in parallel and also collaborating with each other.

H&O What are the potential applications of genomics in patients with cancer?

MH We are still working our way toward understanding what is relevant for a specific disease and for a specific person. This is a very complicated process, and as they say, “the devil is in the details.”

Examples of relevant applications include the discovery of alterations in genes—such as human epidermal growth factor 2 (*HER2*) in breast cancer, anaplastic lymphoma kinase (*ALK*) in lung cancer, and DNA repair defects in ovarian and breast cancer—that have led to targeted treatments. Using agents that target a specific mutation means increasing the potential for benefit among patients who have the genetic alteration, and sparing patients without the mutation from receiving a

costly drug that will produce toxicity but no benefit.

Looking at differences in the patient’s genome before and after therapy also gives us the ability to better understand the enemy, so to speak, and to plan ahead. If we understand the ways in which the cancer is becoming smarter, we can think about upfront combination treatments that might prevent the cancer from escaping the control. In most cases, targeted therapies are not curative in cancer, and patients have to stay on treatment continuously. Can we get to the point of curing cancer, the way we are now able to cure hepatitis C? Having a better understanding of the genomics of the cancer—both the susceptibility and the resistance mechanisms—could help us get there.

H&O Is there any role for genomics in the treatment of advanced prostate cancer?

MH In terms of the day-in and day-out validated results, I would have to say not really. Advances in prostate cancer have lagged behind those for other solid tumors, although I’m thrilled to say we are catching up. One of the biggest areas in which we are beginning to catch up is in targeting patients for clinical trials who have tumors that carry DNA repair defects, specifically *BRCA1*, *BRCA2*, *ATM*, and other noncanonical-type defects.

I am currently finishing up a phase 2 study that moved the whole principle of treatment personalization beyond castration-resistant disease to upfront therapy of metastatic hormone-sensitive disease (NCT02059213). We recruited 60 men with metastatic hormone-sensitive disease who prospectively underwent a biopsy of the bone, lymph node, or metastatic site. Patients whose tumors had an intact retinoblastoma tumor suppressor gene (*RB*) were

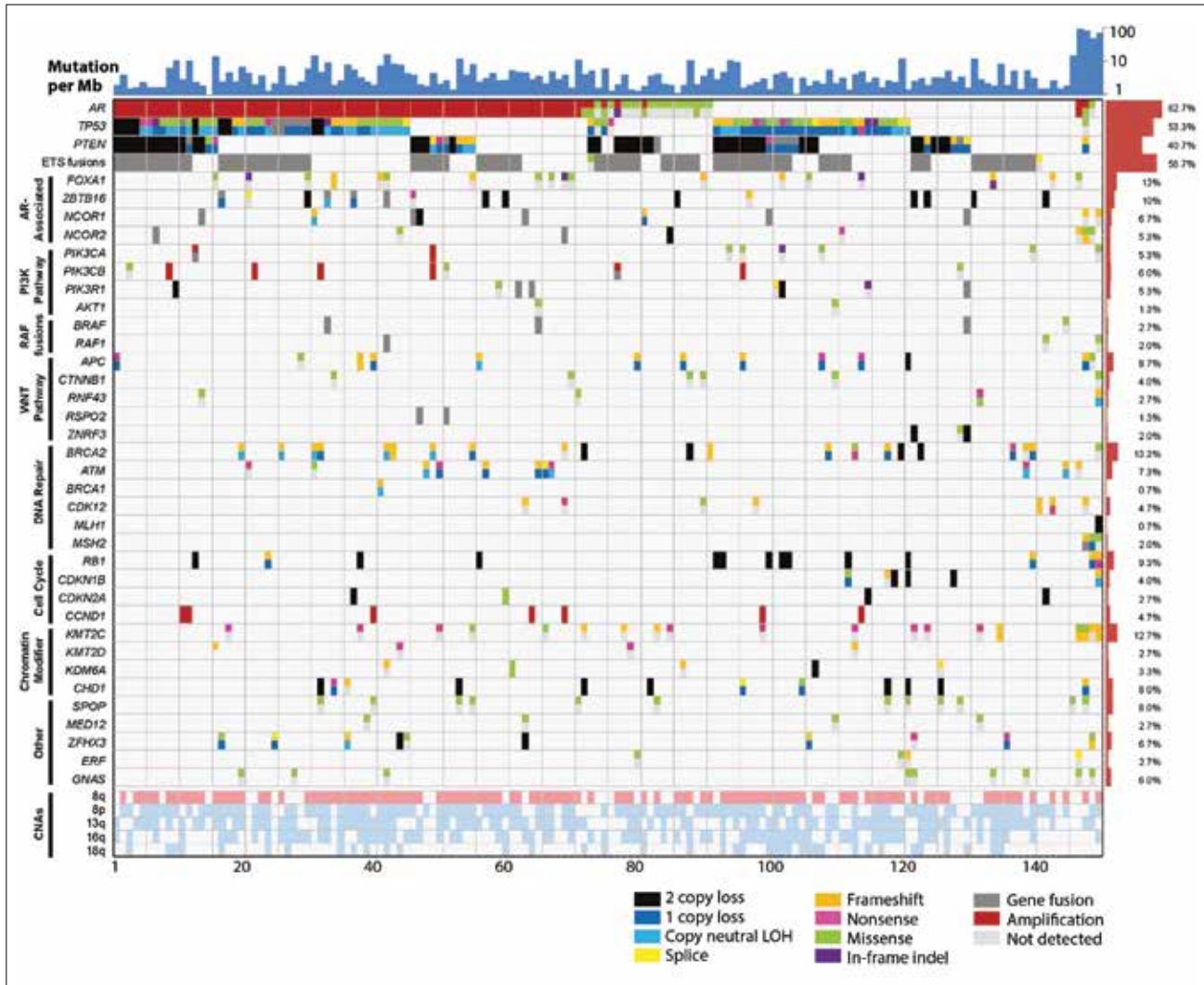


Figure. Integrative landscape analysis of somatic and germline aberrations in metastatic castrate-resistant prostate cancer (CRPC) obtained through DNA and RNA sequencing of clinically obtained biopsies. Columns represent individual affected individuals, and rows represent specific genes grouped in pathways. Mutations per megabase are shown in the upper histogram, and incidence of aberrations in the cohort is in the right histogram. Copy number variations common to metastatic CRPC are shown in the lower matrix, with pink representing gain and light blue representing loss. Color legend of the aberrations represented including amplification, 2 copy loss, 1 copy loss, copy neutral loss of heterozygosity, splice site mutation, frameshift mutation, nonsense mutation, missense mutation, in-frame indel, and gene fusion. Cases with more aberration in a gene are represented by split colors. AR, androgen receptor; CNA, circulating nucleic acid; CRPC, castration-resistant prostate cancer; LOH, loss of heterozygosity; Mb, megabase; PI3K, phosphoinositide 3-kinase.

Source: Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell*. 2015;161(5):1215-1228. Republished with permission.

randomly assigned 2:1 to receive the cyclin-dependent kinase 4/6 (CDK4/6)-targeted agent palbociclib (Ibrance, Pfizer) plus hormonal therapy vs hormonal therapy alone. This strategy has been shown to benefit patients with breast cancer who have RB-intact tumors, and we hope to establish proof of principle for use in prostate cancer. The primary endpoint of our study is the rate of prostate-specific antigen decline after 7 months of treatment. We

are currently analyzing the data, and anticipate submitting it to the 2018 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium.

An international phase 3 trial called PROfound (Study of Olaparib Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer; NCT02987543) is currently looking at second-line treatment of preselected patients with tumors

that have DNA repair defects. This is an AstraZeneca-sponsored study, and I am one of the coordinating investigators. For this study, we are enrolling patients who have either archival tissue or a tumor that has somatic or germline DNA repair defects. Patients are randomly assigned to either standard treatment with abiraterone acetate (Zytiga, Janssen Biotech) or enzalutamide (Xtandi, Astellas/Medivation), or olaparib (Lynparza, AstraZeneca).

In addition, our group at Northwestern Medicine is recruiting participants for a study of olaparib vs abiraterone vs a combination of the 2 agents for frontline treatment of metastatic castration-resistant disease in patients whose tumors have DNA repair defects (NCT03012321).

These types of trials are important to show that it is feasible to do real-time biomarker preselected studies in prostate cancer. Part of the concern is getting the tissue from the metastatic lesions. Prostate cancer goes to bone, and bone biopsy is difficult. We demonstrated in the NCI 9012 trial (Abiraterone Acetate and Prednisone With or Without Veliparib in Treating Patients With Metastatic Castration-Resistant Prostate Cancer) that bone biopsy can be done; I gave an updated presentation at the 2017 annual meeting of ASCO. These are all examples showing that it is feasible to do complex, smarter trials in prostate cancer.

H&O Could you talk about the study your group published in *Cell* in 2015?

MH This study is one that clearly highlights the complexity of prostate cancer. It was a large, multi-institutional study of 150 men with metastatic castration-resistant prostate cancer that detected clinically actionable molecular alterations in approximately 90% of cases (Figure). Genomic alterations were found in *PIK3CA/B*, *RSPO*, *RAF*, *APC*, β -catenin, and *ZBTB16*. It is critical to understand the implications of this study because it highlights many characteristics of cancer. One of these characteristics is that cancer is not static. End-stage cancer can be very complicated and have various genetic alterations that complicate treatment. Instead of using a one-size-fits-all approach, we should consider the best way for us to outsmart the cancer.

A 2015 study by Gundem and colleagues that appeared in *Nature* in 2015 also is very instructive. In this study, the researchers obtained postmortem tissue from several patients with end-stage prostate cancer. When the researchers analyzed tissue from different areas of metastasis within the same patient, they found that tissue from a lymph node and a bone—or even from 2 different bones—showed different molecular profiles. Even within the same patient, the biology is complicated. We need

to think outside of the box, and come up with a way to outsmart the cancer.

H&O How do you see genomics being used in the future for patients with advanced prostate cancer?

MH Of course, we are not there yet. In fact, a survey from the Medscape Physician Oncology Report on Genomics Testing found that most oncologists believe that genomic testing has the potential to be a major advance, but have reservations about promoting it at this point. But as we do our homework and learn more from our successes and failures, the field will evolve. We definitely will be doing smarter clinical trials that will incorporate genomics and will better inform therapeutic decision-making. We have seen in other diseases in which patients are preselected for a particular genomic alteration that not everybody who has those alterations responds to treatment and those who respond do not always respond for a long period; this highlights the complexity of cancer and its adaptive capacity. Therapy development moving forward must focus on the totality of disease biology, including comprehensive molecular understanding of disease states, thorough validation of candidate targets/pathways/biomarkers of response and resistance, and multitargeted approaches aimed at cytotoxic impact.

Disclosure

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Suggested Readings

A phase II study of androgen deprivation therapy with or without palbociclib in RB-positive metastatic prostate cancer. <https://clinicaltrials.gov/ct2/show/NCT02059213>. Identifier: NCT02059213. Updated: May 2, 2017. Accessed: August 28, 2017.

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