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HIGHLIGHTS | Volume 11, Issue 1 June 2014

Highlights from the 24th International Prostate Cancer Update

February 19-22, 2014 | Vail, Colorado

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patient: MARK SMITH

PSA	6.2
Gleason Score	6
Oncotype DX GPS	8

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The Oncotype DX® Genomic Prostate Score (GPS) improves risk stratification to help guide initial treatment decisions. The test is for newly diagnosed men with very low, low, and low-intermediate (low volume 3+4) risk prostate cancer.

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OVERVIEW

Patterns of care in prostate cancer (PCa) have changed tremendously in the past 20 years, altering the way patients with this tumor present and how they are evaluated before and after diagnosis. With the use of new and combined treatments, the frequency and variety of complications have differed from those previously reported. Advances have been made in PCa imaging, biopsy methodology, in understanding causative factors and disease, in treatment-related quality of life, and in predicting the behavior of individual tumors using risk strata. Despite these advances, no consensus has emerged regarding the optimal treatment for the most common patient with PCa.

A number of educational gaps between recent research in PCa and its integration into professional practice at the international, national, and community levels that were presented and discussed at the 24th annual International Prostate Cancer Update (IPCU 24), held February 19-22, 2014 in Vail, Colorado. The IPCU 24 educational planning committee identified:

- Current best practices in prevention and screening of prostate cancer
- Promising therapies, issues, and economic concerns in the treatment of prostate cancer
- Role of newly available therapies in 2014
- Emerging treatment options for advanced and castration-resistant PCa

There is a need for oncologists, urologists, and nurses to understand the rationale behind targeted therapy for the treatment of advanced PCa, and how trial entry could improve the efficacy of drugs and decrease the toxicity.

This activity seeks to educate urologists and other healthcare professionals about the latest advances in the prevention, screening, and treatment of PCa, and is a highlights of selected presentation topics presented in February 2014 in Vail, Colorado.

LEARNING OBJECTIVES

This educational initiative aims to reach urologists, oncologists, urologic oncologists, and nurses. Upon completion of this activity, participants will be able to:

- Evaluate the growing use of biomarkers in prostate cancer detection
- Integrating available hormonal, cytotoxic and immunotherapeutic agents for advanced and castration-resistant prostate cancer
- Define recent developments in prostate cancer treatment that can impact patient quality-of-life outcomes
- Assess the options for personalizing treatment and sequencing new therapies in individual patients

TARGET AUDIENCE

This activity has been developed and is intended for urologists, medical oncologists, radiation oncologists, and other healthcare professionals involved in the treatment of prostate cancer.

ACKNOWLEDGMENT OF SUPPORT

This activity has been supported by funding from Bayer HealthCare Pharmaceuticals and Genomic Health.

FROM THE EDITOR

In February 2014, nearly 250 medical professionals gathered in Colorado to learn about and discuss the latest research and treatment options in prostate cancer. The 24th annual International Prostate Cancer Update (IPCU 24) conference offered attendees an opportunity to hear about important things that happened in prostate cancer in 2013, and that are likely going to happen in the future.

This issue of *Grand Rounds in Urology (GRU)* is devoted to coverage of the highlights of two very important sessions of the conference for which I was privileged to serve as Program Director: Biomarkers and treatment options for hormone resistant prostate cancer, a term that I like better than castrate resistant prostate cancer.

This annual conference is all about prostate cancer, and most everyone receiving this publication is familiar with the facts that prostate cancer is the most common cancer in men, and the second leading cause of death. We also are familiar with some of the challenges that occur with the healthcare costs of the treatment, repeat biopsies, and all of these other issues that present a challenge in diagnosing and treating this disease. Nearly 18 months ago urologists were presented with a challenge about screening and early detection of prostate cancer. The US Services Preventive Task Force (USSPTF) gave current standards a D rating, and just this past year the American Urological Association came out with early detection guidelines. One of the points I believe that is overlooked is that the main focus about prostate cancer is it is a race against time in tumor biology.

The other issue is about asking, "Who is ordering the PSA test?" It is not just urologists, who are more or less in the minority. Most of the tests are ordered by family practice and internal medicine. This is a fox hunt, and instead of stirring up controversy, I think we ought to "go with the flow," and really move forward and try to solve these issues one by one to deal with the challenges.

For the biomarkers, this is really an exciting time. We have had several that received FDA approval in the past year, and there are other trials ongoing. In my opinion, these markers really fall under three categories: when to biopsy, when to re-biopsy, and when to treat or when not to treat. The first section in this issue of *GRU* covers three presentations from an educational session entirely devoted to biomarkers, as presented by leading experts Alan W. Partin, M. Scott Lucia, and Peter F.A. Mulders.

The second section of this publication is devoted to coverage of presentations about the new agents in prostate cancer. Urologists don't like the term "castrate-resistant," the patients don't like it either. Now we use pre- and post-chemotherapy, or castrate-resistant. Perhaps there is a better term, like "hormone-resistant prostate cancer," and under that terminology umbrella we might be able to discuss a variety of other treatment options.

In the last three or four years there have been seven new agents approved to treat hormone-resistant prostate cancer. The most recent addition, in May 2013, was with the approval of Radium-223. The response to this new treatment option has been extremely positive so far because it is a new type of drug that we now have in our armamentarium to treat advanced prostate cancer. Daniel P. Petrylak, Neal D. Shore, and Leonard G. Gomella discuss several of the current treatment options in this issue.

Please enjoy reading this issue of *Grand Rounds in Urology*, and we hope you plan on attending the **25th anniversary International Prostate Cancer Update (IPCU 25) meeting in Vail, being held January 21-24, 2015.** Please let us know if you have any comments, suggestions concerns.

Sincerely,

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The Oncotype DX® Prostate Cancer Assay development and validation data published in

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NEW PUBLICATION: A 17-Gene Assay to Predict Prostate Cancer Aggressiveness in the Context of Gleason Grade Heterogeneity, Tumor Multifocality, and Biopsy Undersampling.

Eric A. Klein, Matthew R. Cooperberg, Peter R. Carroll, et al.

This publication summarizes the development and validation of the biopsy based Oncotype DX Genomic Prostate Score (GPS) in men with very low, low and low-intermediate risk prostate cancer.

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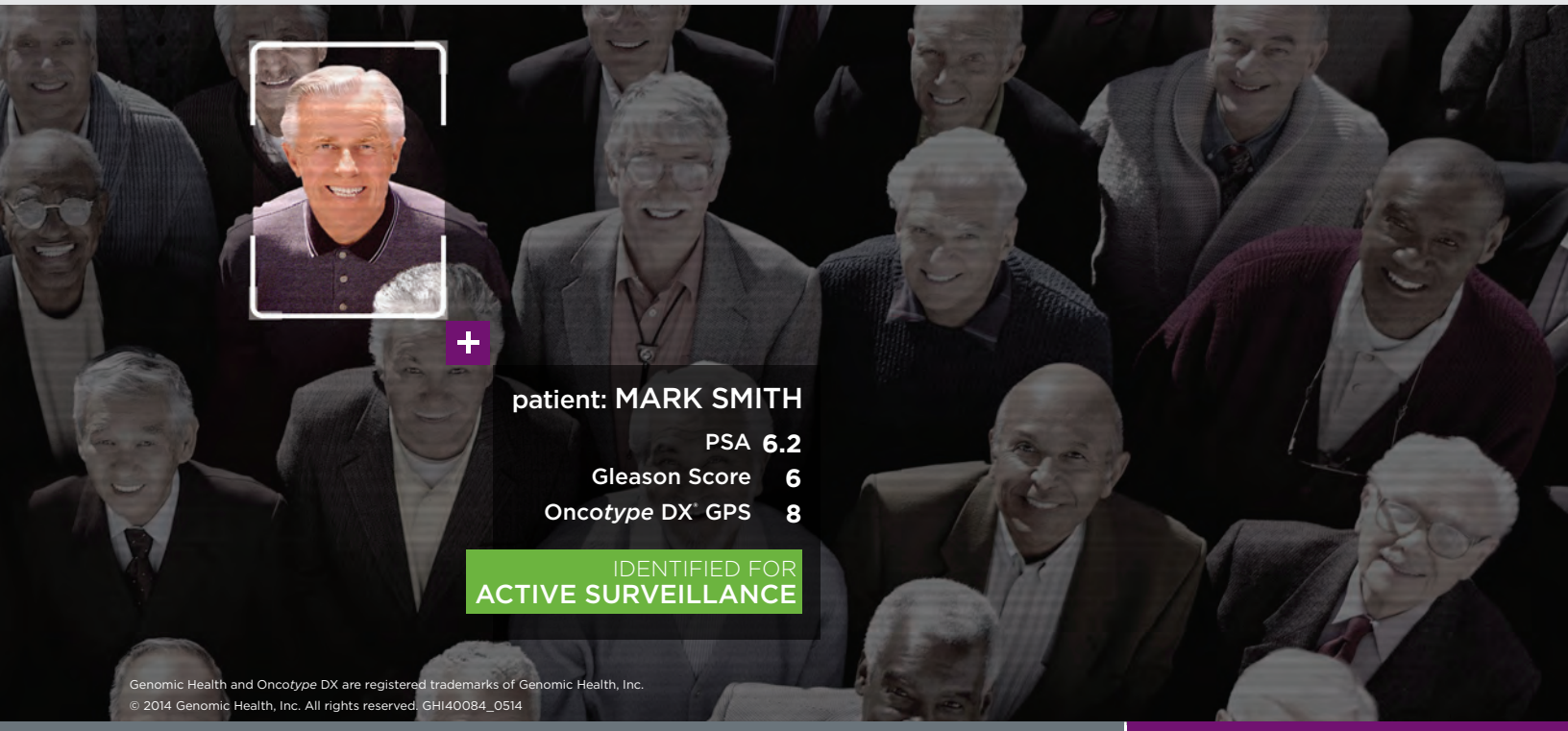

Genomic Health®

oncotype DX® Prostate Cancer Assay

Highlights from the 24th International Prostate Cancer Update

Part I: Prostate Cancer Biomarkers

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INTRODUCTION

Prostate specific antigen (PSA) has revolutionized the diagnosis and management of prostate cancer. As a biomarker, however, PSA is limited in its ability to discriminate clinically indolent from more aggressive cancers. Widespread PSA screening has lead to unnecessary prostate biopsies and to the identification and treatment of some indolent tumors. Several new and emerging biomarkers are playing important roles in the biopsy-decision pathway. In addition, researchers are focusing on the use of biomarkers to inform and support treatment decisions, such as the decision to treat or pursue active surveillance in early-stage cancer; choice of therapy for localized cancer; choice and timing of endocrine therapy for advanced cancer; and choice of therapy for castration-resistant prostate cancer (CRPC).

Prostate Cancer Biomarkers: Early Detection

Alan W. Partin, MD, PhD

PROSTATE HEALTH INDEX (PHI)

The Prostate Health Index (PHI) is compiles several PSA measures, including [-2] pro-PSA (p2PSA), free PSA (fPSA), and total PSA (tPSA), into a single score. Specifically, PHI is calculated as p2PSA/fPSA multiplied by the square-root of tPSA. In a study of men with no history of prostate cancer, normal DRE, and PSA 2-10 ng/mL, PHI demonstrated high specificity for prostate cancer -jat biopsy, with individual risk increasing from 11% to 52% with increasing PHI [1]. The PHI score discriminated higher-grade disease (Gleason 4 or greater + 3) from lower-grade disease or negative biopsy, suggesting a role in preventing unnecessary biopsy [1].

Investigators have developed a PHI-based nomogram to help clinicians determine the need for a prostate biopsy in patients with suspected prostate cancer [2]. The nomogram combines and PHI, patient age, prostate volume, DRE, and biopsy history, and strongly strongly predicts the presence of prostate cancer at biopsy (AUC, 0.80) [2]. Computer modeling showed that using the PHI-based nomogram would result in 21 fewer patients per 100 undergoing unnecessary prostate biopsy [2]. Investigators recently reported additional findings in support of the PHI-based nomogram from a validation cohort of 833 patients, including 365 (41.3%) who were diagnosed with prostate cancer [3]. PHI was the most informative predictor of prostate cancer (AUC, 0.68), outperforming tPSA (0.51) and %fPSA (0.64). The predictive accuracy of the PHI-based nomogram was 75.2% (95% CI, 71.4%-78.1%) [3].

PROSTATE CANCER ANTIGEN 3 (PCA3)

The PCA3 gene is a highly prostate-specific gene that expresses a non-coding RNA. PCA3 is overexpressed by 60- to 100-fold in prostate cancer cells. Unlike PSA, PCA3 does not increase with prostate volume. The PCA3 score reflects the ratio of the PCA3 mRNA to PSA mRNA captured in post-DRE urine [4]. The quantitative PCA3 score also significantly correlates with the probability of a positive biopsy result [4]. In 2012, the PCA3 assay gained FDA approval as the first molecular test to help determine the need for repeat prostate biopsies in men aged 50 years or older who have had a previous negative biopsy.

In 2014, Wei and colleagues described the use of a PCA3 assay to supplement PSA-based prostate cancer screening (Table 1) [5]. In the initial biopsy setting, a PCA3 score >60 showed a high positive predictive value (PPV) for prostate cancer (0.80). In the repeat biopsy setting, a PCA3 score <20 carried a high negative predictive value (NPV) for prostate cancer (0.88). These findings support the use of PCA3 to enhance clinical decision-making regarding the need for biopsy.

Table 1. PCA3 Urinary Assay: Performance on Initial and Repeat Prostate Biopsy [5]

Performance	Initial Biopsy (PCA3 Score >60)	Repeat Biopsy (PCA3 Score <20)
Sensitivity	42%	76%
Specificity	90%	51%
PPV	80%	31%
NPV	64%	88%

NPV = negative predictive value; PPV = positive predictive value.

TMPRSS2:ERG GENE FUSION

Rearrangement of the ETS-related gene (ERG) is an early event in the development of prostate cancer. The most common ERG rearrangement involves TMPRSS2, an androgen-regulated transcription factor located approximately 3 Mb from ERG on chromosome 21. Through aberrations such as insertion or deletion, TMPRSS2 can fuse with ERG, a member of the ETS oncogene family. The TMPRSS2:ERG gene fusion leads to overexpression of ERG [6].

In 2013, Day and colleagues described the combined use of PCA3 and TMPRSS2:ERG for predicting the outcome of prostate biopsy [7]. Based on results from both assays, patients were categorized into biomarker risk groups ranging from low risk (group 1) to high risk (group 5). As PCA3 and TMPRSS2:ERG test scores increased, the risk of a positive biopsy, a significant cancer, and a Gleason score >6 also increased (Figure 1). Combining PCA3 and TMPRSS2:ERG assay results provided greater accuracy than either test alone and outperformed PSA as a predictive marker. These findings suggest a role for combined PCA3 and TMPRSS2:ERG testing to predict prostate biopsy results as well as the presence of indolent and significant cancer.

4KSCORE

The 4Kscore™ prostate cancer test is a multimarker assay that incorporates 4 kallikrein markers: tPSA, fPSA, intact PSA, and human kallikrein 2 (hK2). In several studies, incorporating the all of the components of the 4-marker test significantly improves the performance of standard clinical prediction models [8-10]. In a study of 740 men undergoing initial prostate biopsy, the addition of fPSA, intact PSA, and hK2 improved the AUC from 0.68 to 0.83 when compared with modeling based on age and PSA alone [8]. In this cohort, using a 20% risk of prostate cancer as the threshold for biopsy, incorporating the 4-biomarker panel would have reduced the number of biopsies by 424 (57%), missed only 31 of 152 low-grade cancers, and missed 3 of 40 high-grade cancers.

Another study cohort included 2,914 previously unscreened men undergoing biopsy due to elevated PSA (≥ 3 ng/mL) [9]. The addition of fPSA, intact PSA, and hK2 improved the AUC from 0.64 to 0.76 compared with age and tPSA alone (P < .001). Overall, 807 prostate cancers (28%) were detected in this study group. Using the 4-panel marker would have decreased the number of biopsies by 513 at the cost of missing 54 of 177 low-grade cancers and 12 of 100 high-grade cancers.

Most recently, the 4Kscore was examined in the population-based Malmö Diet and Cancer study cohort of 11,063 Swedish men aged 45 to 73 years [10]. Compared with tPSA and age alone, the full 4-kallikrein panel enhanced the predictive accuracy for clinically diagnosed prostate cancer from 0.65 to 0.74 (P <.001). Computer modeling estimated that men with a PSA level of ≥ 3 ng/mL were unlikely to develop incurable prostate cancer if they were categorized as low-risk by the panel of 4 kallikrein markers. Of 421 men who were classified as low risk, only 2 would be diagnosed with advanced prostate cancer within 5 years.

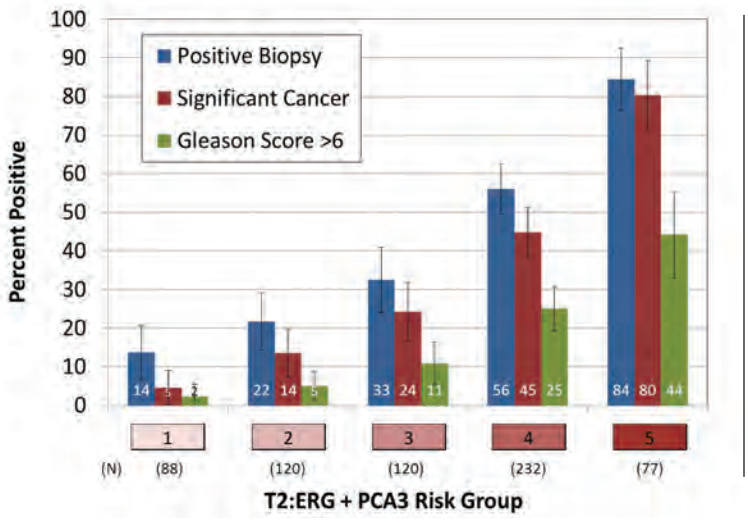

Figure 1. PCA3 + T2:ERG risk groups stratify prostate cancer risk prior to initial biopsy [7].

SINGLE NUCLEOTIDE POLYMORPHISMS

Single-nucleotide polymorphisms (SNPs) are inherited chromosomal alterations that have been evaluated to improve current risk-prediction models in prostate cancer. SNPs occur when a single nucleotide (A, T, C, G) is substituted for another nucleotide in coding or non-coding regions of the genome. The substitution can alter gene expression, alter protein function, or have no apparent effect at all. Because some SNPs can be detected with simple blood tests or cheek swabs, they are often used in forensic investigations.

In 2006, Amundadottir and colleagues were the first to identify a region on chromosome 8q24 that was possibly linked to prostate cancer [11]. Since that initial discovery, several SNPs have been linked to prostate cancer [12]. In a Swedish population study, the presence of any 5 SNPs at three chromosomal regions (8q24, 17q12, and 17q24.3), plus a family history of prostate cancer, has been estimated to account for 46% of the prostate cancer cases [12].

Investigators have examined the use of SNP testing to predict prostate biopsy results [13]. In the Stockholm-1 study (N = 5241), a total of 35 validated SNPs were analyzed and converted into a polygenic risk score [13]. Compared with a clinical model based on age, fPSA, tPSA, and family history, including of the polygenic risk score would have avoided 480 biopsies (22.7%), at a cost of missing a prostate cancer diagnosis in 3% of patients characterized as having

aggressive disease. However, the polygenic model was not able to discriminate between aggressive and non-aggressive disease.

In 2008, deCODE Genetics developed an assay to examine 2 SNPs: rs5945572 on Xp11.22 and rs721048 on 2p15. Both variants are significantly associated with prostate cancer, although the 2p15 variant shows a stronger association with more aggressive disease [14]. After acquiring deCODE Genetics in 2012, Amgen is continuing the development of a prostate cancer assay based on this technology.

In 2012, Kader and colleagues described the combined use of 33 SNPs to enhance the prediction of prostate cancer risk compared with traditional clinical markers [15]. Adding the genetic score to the standard clinical model improved the AUC from 0.62 to 0.66 (P <.001) and reclassified prostate cancer risk in 33% of men (P =.002).

To date, more than 50 SNPs have been found that significantly correlate with prostate cancer risk. Commercial assays for SNP analysis have been developed, and my soon be widely available following FDA approval.

EXOSOME ANALYSIS

Another area of biomarker development involves the examination of exosomes, the specialized extracellular vesicles that transfer mRNA, microRNA (miRNA), non-coding RNA, and proteins between normal and tumor cells. Exosomes modulate intracellular signaling, the tumor microenvironment, and gene expression in distant cells. Exosome RNA serves as a snapshot of events in the tumor and surrounding microenvironment in real-time.

The majority of the transcriptome can be detected in the exosome, thereby enabling global RNA profiling. Due to the protective nature of the exosomes, the RNA profiles are stable and reproducible. This enables the detection of cancer "fingerprints," defined by specific patterns of mRNA, miRNA, and non-coding RNA levels, as well as the detection of cancer-specific mutations (e.g., KRAS, BRAF, EGFR, IDH1, and PI3K). By examining multiple samples taken over time, exosome analysis is an effective tool for tracking dynamic tumor changes longitudinally. This increases the chance of finding a rare mutation.

EXO106 Assay

EXO106 is an investigational assay that analyzes RNA in urine exosomes from random (i.e., non-DRE) samples. To date, the EXO106 clinical development program has enrolled more than 3,000 patients. Preliminary data suggest that EXO106 testing can predict the likelihood of positive versus negative biopsy findings (AUC, 0.75) and differentiate pathologic Gleason ≤ 7 versus Gleason ≥ 8 cancers (AUC, 0.73) [16].

DNA METHYLATION

DNA methylation is a frequent epigenetic mechanism for controlling gene expression. Although the enzyme-induced modification occurs without altering the specific DNA sequence, the genes may fail to express their functional proteins when the promotor regions of genes become methylated. DNA methylation is a widespread phenomenon in cancer and may be among the earliest changes in oncogenesis.

Testing for DNA methylation relies on the premise that the risk of cancer is increased when candidate genes show evidence of DNA methylation. DNA methylation is highly stable relative to mRNA and many types of proteins, making it an attractive target for biomarker testing. Moreover, sensitive detection methods enable the detection of 1 cancer cell among 10,000 normal cells. Methylation-specific polymerase chain reaction (PCR) runs on any PCR machine, allowing for automatable, reproducible, and reliable results.

The False-Negative Prostate Biopsy Dilemma

DNA methylation testing may address the current limitations of prostate biopsy [17,18]. First, prostate biopsy is associated with a high false-negative rate of approximately 25%. Second, the standard biopsy procedure involves 12 cores, which introduces the possibility of a substantial sampling error. Overall, a biopsy procedure samples less than 1% of the entire gland. The biopsy needle may miss the tumor focus entirely, while pathologists can only interpret what is on the slide. The fear of occult cancer leads to a high rate of repeat biopsies.

The ideal biomarker to support the biopsy-decision pathway would allow clinicians to rule out the need for unnecessary repeat biopsies in men who are free from prostate cancer, while supporting the decision for repeat biopsy in men who have a high risk of occult cancer. This level of discrimination would require a negative predictive value (NPV) of ≥ 90%, which is higher than that of standard histopathologic evaluation (~75%). The goal is improved stratification of patients, leading to more informed repeat biopsy decisions and a reduction in unnecessary repeat biopsies.

ConfirmMDx for Prostate Cancer

The ConfirmMDx(TM) epigenetic assay for prostate cancer uses quantitative methylation-specific PCR testing to determine the methylation status of GSTP1, APC and RASSF1 in the "halo" of tissue that surrounds a known lesion.

Two recent trials examined the performance of DNA methylation analysis as a tool for predicting repeat biopsy outcome (Table 2) [19,20]. The MATLOC (Methylation Analysis To Locate Occult Cancer) study examined the performance of the epigenetic assay in detecting occult prostate cancer in patients with negative prostate biopsies [19]. The study examined archived needle biopsy core tissue samples collected from 498 patients with histopathologically negative prostate biopsies who underwent repeat biopsy within 30 months. The NPV was 90%. In a multivariate analysis, the epigenetic assay was a significant and independent predictor of repeat biopsy outcomes (OR, 3.17; 95% CI, 1.81-5.53).

In 2014, the DOCUMENT (Detection Of Cancer Using Methylated Events in Negative Tissue) trial validated the performance of the epigenetic test as an independent predictor of prostate cancer risk [20]. The study examined biopsy core tissue samples from 350 patients who underwent a repeat biopsy within 24 months. The assay resulted in a NPV of 88%. In a multivariate analysis, the epigenetic test was the strongest independent predictor of outcome on repeat biopsy (OR, 2.69; 95% CI, 1.60-4.51). Adding the epigenetic assay to other know risk factors may guide clinical decision making and help reduce the rate of unnecessary repeat biopsies.

Table 2. DNA Methylation Analysis: Prostate Cancer Detection on Repeat Prostate Biopsy

Performance	DOCUMENT Trial [19]	MATLOC Trial [20]
Sensitivity	60%	68%
Specificity	64%	64%
NPV	88%	90%

NPV = negative predictive value; PPV = positive predictive value.

Gene Expression Assays for Prognostic Value in Prostate Cancer

M. Scott Lucia, MD

Gene expression is defined as the conversion of information from a gene into mRNA (transcription) and then to protein (translation) by protein coding genes or to non-coding RNAs (transcription) for non-protein coding genes. Gene expression profiling is the measurement of RNA expression of multiple genes simultaneously to create a global picture of cellular function.

Oncogenesis is a multistep process. Different genomic signatures expressed via RNA at various points during oncogenesis can predict the potential for progression and metastasis.

PREDICTING RECURRENCE AFTER PROSTATECTOMY

Predicting the likelihood of recurrence after prostatectomy requires the genetic analysis of tumor tissue harvested during the procedure. Commercial assays are currently available to predict the recurrence of prostate cancer, including the cell-cycle progression (CCP) score (Prolaris®, Myriad Genetics) and the Prostate Cancer Genomic Classifier (Decipher®, GenomeDx). Several additional prognostic models are currently under evaluation.

In 2011, Cuzik and colleagues described the prognostic value of an RNA-expression signature derived from CCP genes in patients managed with prostatectomy (n = 366) or transurethral resection of the prostate (TURP) (n = 337) [21]. The assay calculated the CCP score by measuring the expression of 31 CCP genes in relation to 15 housekeeping reference genes using quantitative RT-PCR. In the prostatectomy cohort, each unit increase in the CCP score was associated with an 89% increase in the risk of biochemical failure over 10 years (HR, 1.89; 95 CI, 1.54-2.31). In the TURP cohort, each unit increase in the CCP score was associated with a nearly 3-fold increase in the risk of death from prostate cancer over 10 years (HR, 2.92; 95% CI, 2.38-3.57). For all patients, combining the CCP score with other standard clinical and pathologic findings enhanced the prognostic utility of traditional risk models.

The Decipher(R) assay (GenomeDX Biosciences, Inc.) incorporates a probability model to predict the development of metastases within 5 years of radical prostatectomy (RP) in patients with high-risk prostate cancer. The assay measures the expression levels of 22 RNA biomarkers using formalin-fixed, paraffin-embedded tissue harvested from the index lesion (i.e., tumor with seminal vesicle involvement [SVI], extraprostatic extension [EPE], or highest Gleason grade) during RP. The biomarker panel was derived from a genome-wide search of cancers in more than 500 patients from the Mayo Clinic Tumor Registry. The RNA biomarkers represent multiple oncogenic pathways, including those involved with cycle-cycle progression; cell adhesion, motility, and migration; and immune-system modulation.

In 2013, Erho and colleagues described the development and validation of the prostate cancer genomic classifier (GC) using the 22-marker panel [22]. The analysis included genomic expression profiles from 545 patient samples and a median follow-up of 16.9 years. The GC achieved an AUC of 0.75, outperforming standard clinical markers including Gleason score, PSA, surgical margin status, SVI, EPE, and nodal status. Patients with higher GC scores (> 0.5) had significantly worse prostate cancer-specific mortality (PCSM) after metastases (P = .003) and overall survival after metastases (P = .03) than patients with lower GC scores (≤ 0.5). Thus, genomic expression in the primary tumor can be used to predict development of metastasis, PCSM, and OS in patients treated with RP.

The 22-marker genomic classifier has also been validated for the prediction of metastasis following RP [23]. The GC score was evaluated in a cohort of patients with high-risk markers, including preoperative PSA ≥ 20 ng/mL, Gleason 8 or greater, pT3b, or a Mayo Clinic nomogram score of 10 or greater. After a median follow-up of 6.7 years, the GC score AUC for predicting 5-year metastasis was 0.79, higher than any other predictive model based on clinical parameters only. The 5-year cumulative incidence of metastasis in the low-, intermediate, and high-risk groups based on GC score was 2.4%, 6.0%, and 22.5%, respectively (P < .001).

Most recently, Ross and colleagues described the use of the GC score for predicting metastatic disease progression in clinically high-risk patients with biochemical recurrence (BCR) after prostatectomy [24]. In the GC low-score and high-score groups, 8% and 40% of patients developed metastasis after BCR, respectively (P < .001). The AUC for predicting metastasis after BCR was 0.82. In a multivariate model, the risk for metastasis increased by 49% for each 0.1-point increase in GC score (HR, 1.49; P < .001) (Figure 2). Compared with standard clinicopathologic variables, the GC score was a better predictor of metastasis, suggesting its potential use as a tool to identify patients who require earlier initiation of treatment at the time of BCR.

PREDICTING PROGRESSION DURING ACTIVE SURVEILLANCE

Predicting the risk of disease progression during active surveillance requires the genetic analysis of tumor tissue harvested during biopsy. Two examples of validated assays for this indication include the cell cycle progression (CCP) score (Prolaris®, Myriad Genetics) and the Prostate Genomic Score (GPS) RT-PCR expression assay (OncotypeDX®, Genomic Health).

In 2012, Cuzik and colleagues described the prognostic value of the CCP score for predicting prostate cancer death in a conservatively managed needle biopsy cohort [25]. The CCP score was calculated from the expression levels of 31 genes with total RNA extracted from paraffin-embedded tumor specimens. In a multivariate analysis, each 1-unit increase in

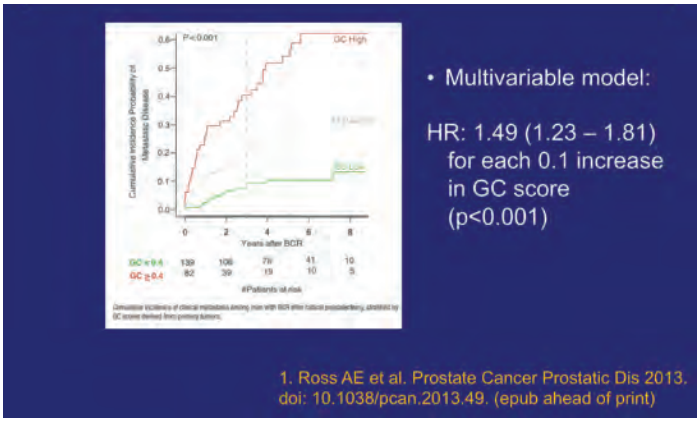

Figure 2.
A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy [24].

the CCP score increased the hazard ratio for prostate cancer death by 2.02 (95% CI, 1.62-2.53; $P < .001$). Compared with standard clinical markers such as Gleason score and PSA, the CCP score was the strongest independent predictor of prostate cancer death.

The GPS assay measures the expression of 17 genes (Table 3). This includes 5 reference genes and 12 genes covering 4 distinct biological pathways (androgen signaling, stromal response, cellular organization and proliferation) that are strongly predictive of metastasis and death when measured in RP specimens. The GPS assay calculates a 100-unit score based on gene expression levels. Higher scores associate with more aggressive cancers, while lower scores with less aggressive, more favorable pathology. In 2013, researchers presented data from the GPS validation study showing that GPS provides significant additional risk discrimination beyond what could be achieved with the National Comprehensive Cancer Network (NCCN) criteria [26].

Another emerging prognostic tool involves a 3-gene panel that distinguishes indolent and aggressive subgroups of low-Gleason-score prostate tumors [27]. Based on the expression levels of the 3 component genes (FGFR1, PMP22, and CDKN1A), the panel also correctly identified Gleason 6 patients who failed surveillance over a 10-year follow-up period.

Table 3. Components of the Genomic Prostate Score [26]

Genes Associated with Worse Outcomes	Genes Associated with Better Outcomes	Reference Genes
Stromal response genes • BGN • COL1A1 • SFRP4 Proliferation genes • TPX2	Androgen signaling genes • FAM13C • KLK2 • AZGP1 • SRD5A2 Cellular organization genes • FLNC • GSN • TPM2 • GSTM2	• ARF1 • ATP5E • CLTC • GPS1 • PGK1

Table 4. PCA3 and mMRI Performance as Predictors of Prostate Biopsy Outcomes [32]

Performance	PCA3 Score >35 Alone	PCA3 Score >35 Plus mMRI
Sensitivity	68%	79%
Specificity	75%	73%
PPV	53%	61%
NPV	84%	87%
Accuracy	73%	75%
AUC	0.825	0.857

AUC = area under the curve; mMRI = multiparametric magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value.

MRI and Biomarkers: Targeting Treatment Decisions in Prostate Cancer

Peter F. A. Mulders, MD, PhD

Magnetic resonance imaging (MRI) is a valuable tool for visualizing several aspects of prostate cancer. In particular, MRI provides excellent functional soft-tissue contrast for standard anatomic imaging and tumor localization. Multiparametric MRI (mMRI) is an imaging technique that consists of anatomic images, dynamic contrast-enhanced MRI, diffusion weighted imaging, and proton MR spectroscopic imaging. In current clinical practice, mMRI is increasingly being used to detect and localize clinically significant prostate cancer [28, 29]. However, costs and other limitations keep the routine use of mMRI and MR-guided biopsy out of reach in most practice settings. An inexpensive and more practical test to identify patients who require mMRI and subsequent MR-guided biopsy would be a valuable addition to clinical practice.

The PCA3 assay is a promising tool for identifying which patients require MRI. A recent retrospective analysis correlated PCA3 score results with biopsy findings and MRI outcome in 591 patients with elevated PSA levels [30]. The PCA3 score was highly predictive for biopsy outcome ($P < .001$), although there was no apparent relationship between PCA3 score and Gleason score at the time of biopsy ($P = .194$). The PCA3 score was significantly higher in patients with a suspicious region for prostate cancer on MRI than in patients with no suspicious region (median PCA3 score, 52 vs. 21; $P < .001$). These findings suggest that PCA3 may play a role in selecting appropriate candidates for mMRI. Importantly, however, the study authors note that a negative PCA3 score should not be a contraindication for mMRI in patients with a high clinical suspicion of prostate cancer.

In 2013, Busetto and colleagues reported findings from a prospective study of patients with negative findings on transrectal ultrasound (TRUS)-guided biopsy and persistent high PSA levels (N = 163) [31]. All patients underwent PCA3 testing and mMRI followed by a repeat TRUS-guided biopsy. The repeat biopsy identified 68 patients with prostate cancer (41.7%). The sensitivity and specificity for predicting biopsy results were 68% and 49%, respectively, for the PCA3 test, and 74% and 90%, respectively, for the mMRI. The base clinical prediction model, which included age, PSA, and DRE, resulted in an AUC of 0.551. The best predictive model added both PCA3 and mMRI to the clinical parameters, resulting in an AUC of 0.808. Moreover, the use of the full prediction model significantly improved the cost/benefit ratio by avoiding unnecessary TRUS-guided biopsies.

In a prospective randomized trial, Sciarra and colleagues examined the role of PCA3 testing and mMRI to improve the diagnostic accuracy of a repeat biopsy in patients with elevated PSA levels and prior negative prostate biopsies (N = 168) [32]. After undergoing PCA3 testing, patients were randomly assigned to receive a repeat TRUS-guided biopsy (group A) or mMRI followed by a repeat TRUS-guided biopsy (group B). The use of mMRI for indicating sites suitable for repeat biopsy significantly improved the sensitivity of the PCA3 test (score > 35) as a predictor of biopsy outcomes (Table 4). The AUC for PCA3 improved from 0.825 in group A to 0.857 in group B ($P < .001$).

Circulating and Disseminated Tumor Cells: Prognostic Value for Prostate Cancer

M. Scott Lucia, MD

Circulating tumor cells (CTCs) are rare cancer cells that are released into the bloodstream, where they can disperse and settle in secondary organs as disseminated tumor cells (DTCs). The presence of CTCs predicts worse prognosis, as tumor cell circulation and dissemination are key processes in cancer metastasis. Given their potential prognostic value, there is considerable interest in CTCs and DTCs as potential biomarkers to enhance diagnosis, treatment selection, and drug development for a range of cancer types.

CIRCULATING TUMOR CELLS

Three major approaches have been developed to isolate CTCs from whole blood, each with its advantages and limitations [33]. First, immunoaffinity-based techniques target specific cell-surface markers to selectively enrich CTCs or deplete leukocytes. Second, the physical properties of CTCs can be exploited to separate CTCs from blood cells based on differences in density, size/deformability, and electrical properties. Third, the direct analysis of CTCs is possible via high throughput assaying of all cells in blood following erythrocyte lysis. Following isolation, the CTCs can be analyzed by techniques such as immunophenotyping, mutational analysis, genome analysis, and genetic and molecular expression profiling.

Potential advantages of CTC analysis include the ease of blood collection, the value of serial collection and analysis, and the ability to perform molecular and genetic analyses from tumor-derived cells. In addition, the process of CTC analysis can be automated and avoids sampling problems associated with primary tumor heterogeneity. The limitations of CTC analysis include the need to enrich the sample to compensate for rare CTCs. Selective enrichment may lead to a skewed sample. In addition, CTCs may be contaminated by blood cells. The costs associated with CTC analysis may be prohibitive in some settings.

The CellSearch® CTC Test (Veridex, Raritan, NJ) is a simple blood test approved for use in patients with metastatic prostate, colorectal, and breast carcinomas [34]. The assay uses ferrofluid nanoparticles coated with anti-epithelial cell adhesion antibodies to magnetically separate CTCs from most other cells in the blood, and then identifies CTCs using anti-cytokeratin antibodies and manual verification [34].

The CTC analysis is currently approved by the FDA as a baseline prognostic marker for mCRPC and as a tool for monitoring treatment efficacy. Investigational applications include the use of CTCs as a surrogate endpoint in clinical trials. Studies are also examining the role of CTCs as a predictive marker to predict response to ADT in hormone-sensitive prostate cancer and response to chemotherapy or targeted molecular therapy in other prostate cancer settings.

In a landmark study in 2008, de Bono and colleagues showed that baseline CTC counts significantly correlated with OS in patients with CRCP [35]. Among patients with a low CTC count (<5 CTCs per 7.5 mL), the median OS was 21.7 months, compared with 11.5 months among patients with higher CTC counts (≥5 per 7.5 mL) ($P < .0001$). The probability of survival significantly improved among patients whose CTC counts converted from unfavorable to favorable as a result of treatment (HR, 2.2; $P < .0001$). Furthermore, CTC counts correlated more strongly with survival outcomes than PSA modeling at all time points ($P = .0218$). Thus, CTC was the most accurate independent predictor of survival in patients with CRPC. On the basis of these findings, the FDA approved the CTC assay for the evaluation of CRPC prognosis.

Over the past several years, additional research has shed light on the optimal use of CTC assays in the management of CRPC. In 2009, Scher and colleagues validated the use of CTC count as a prognostic factor for OS in patients receiving first-line chemotherapy for progressive mCRPC [36]. In the prospective study, changes in CTC number at post-treatment weeks 4, 8, and 12 strongly correlated with mortality risk ($P \leq .0001$). By comparison, changes in PSA were only weakly associated or not associated with mortality at these time points. Thus, CTC count, evaluated as a continuous variable, was an effective tool for monitoring treatment efficacy and patient prognosis in the first-line setting.

Several studies have evaluated CTCs as a predictive biomarker in patients with hormone-sensitive prostate cancer [37,38]. In a study of 33 patients who were initiating treatment with ADT, the baseline CTC count significantly predicted time to CRPC [37]. The median time to CRPC was 8.3 months for patients with high baseline CTC counts (≥ 3 cells per 7.5 mL), whereas the median time to CRPC was not reached for patients with low CTC counts (< 3 cells per 7.5 mL) (HR, 7.78; $P < 0.001$). These findings support the use of CTC counts to predict the duration and magnitude of response to ADT in patients with hormone-sensitive prostate cancer [37].

Another study examined AR signaling in CTCs as a marker of hormonally responsive prostate cancer [38]. Researchers used microfluidic capture of CTCs and single-cell immunofluorescence to measure AR signaling before and after hormonal therapy. Treatment-naïve patients showed predominantly "AR-on" CTC patterns, compared with heterogeneous CTC populations ("AR-on," "AR-off," and "AR-mixed") in patients with CRPC. Patients who started first-line ADT showed a dramatic switch from "AR-on" to "AR-off" CTCs, reflecting acquired treatment resistance, while secondary hormonal therapy produced variable AR responses. Overall, the presence of "AR-mixed" CTCs and "AR-on" CTCs despite abiraterone treatment predicted worse outcomes. These findings demonstrate the potential use of CTCs to evaluate AR signaling and identify appropriate therapy for prostate cancer.

DISSEMINATED TUMOR CELLS

In 2013, Lilleby and colleagues showed that the detection of pretreatment bone marrow-derived DTCs (pre-DTCs), as an early prognostic variable, improves upon current models used to predict recurrence and survival in patients with nonmetastatic prostate cancer [39]. However, DTCs are more challenging than CTCs to obtain, and may have practical applications only in very narrow circumstances.

SUMMARY

The development of new biomarkers in prostate cancer may improve patient management by guiding the selection of appropriate treatment and imaging modalities, improving the diagnostic accuracy of repeat prostate biopsies, and reducing overtreatment. When added to standard clinical, histological, and pathological markers, novel molecular and genetic signatures can add independent information as to prognosis for patients undergoing local therapy and expectant management. Novel sources for prostate cancer biomarkers, including exosomes, CTCs, and DTCs, may also provide important information regarding tumor severity, the likelihood of response to treatment, and the potential for progression and metastasis. Although biomarkers are increasingly used in prostate cancer research and clinical practice, the technical, financial, and biological limitations of biomarkers must be considered in patient-management decisions.

Highlights from the 24th International Prostate Cancer Update

Part II: Treatment Advances in Castration-Resistant Prostate Cancer

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The Latest on Chemotherapeutic Approaches

Daniel P. Petrylak, MD

Despite considerable research efforts and several phase III trials, to date no agent has significantly improved overall survival (OS) in combination with standard docetaxel/prednisone therapy (Table 1). Among the most recent negative trials were those evaluating lenalidomide and atrasentan and potential add-on therapies.

In the phase III trial of add-on lenalidomide, 533 chemotherapy-naïve patients with progressive metastatic CRPC were randomly assigned to docetaxel/prednisone plus either lenalidomide 25 mg (days 1-14) or placebo every 21 days until disease progression [40]. There was no improvement in overall survival with lenalidomide over the standard docetaxel/prednisone regimen. The median OS was 77 weeks in the lenalidomide arm, and not reached in the placebo arm (HR, 1.53; P = .0017). Dose reductions were twice as common with lenalidomide compared with placebo (14.9% versus 7.9%), primarily due to an increase in adverse events with lenalidomide.

The Southwest Oncology Group (SWOG) S0421 trial compared docetaxel with or without atrasentan in patients with advanced CRPC [41]. This study showed no improvement in OS with the addition of atrasentan to standard docetaxel therapy. The median overall survival was 18 months in both study arms.

Given multiple negative trials of add-on therapy, there has been increased interest in identifying specific subgroups of patients who are more likely to respond to treatment. Baseline bone markers such as serum bone alkaline phosphatase (BAP) and urinary N-terminal telopeptide (NTX) have previously been shown to correlate with therapeutic response [42,43].

Serum markers of bone metabolism may also predict response to atrasentan in patients with CRPC [44]. In a subgroup analysis of the S0421 trial, patients with the highest quartile of baseline bone metabolism biomarker (BMB) levels had a poor prognosis (HR, 4.3; P < .001), but showed a significant survival benefit from atrasentan (HR, 0.34; P = .002) [44]. By comparison, patients in the lowest quartile of BMB levels showed no improvement in OS with atrasentan treatment. These findings suggest a potential role for BMB in selecting candidates for atrasentan therapy.

Table 1. Phase III Trials of Docetaxel-Based Combination Chemotherapy

Docetaxel/Prednisone vs Docetaxel combined with:	Status	Results
DN-101	Terminated early	Negative
GVAX	Terminated early	Negative
Bevacizumab	Completed	Negative
VEGF-Trap	Completed	Negative
ZD4054	Completed	Negative
Dasatinib	Completed	Negative
Lenalidomide	Completed	Negative
Atrasentan	Completed	Negative
Custersin (OGX-011)	On-going	Pending

PROMISING COMBINATION THERAPIES

Custirsen (OGX-011)

Clusterin is an anti-apoptotic protein that is overexpressed in a variety of cancers. In prostate cancer, clusterin overexpression correlates with higher Gleason grade disease [45]. Clusterin overexpression confers resistance to hormone therapy, chemotherapy, and radiation therapy both in vitro and in vivo, whereas inhibiting clusterin expression increases sensitivity to these treatment modalities [46-48].

Custirsen (OGX-011) is an antisense oligonucleotide that is complementary to the clusterin mRNA translation initiation site and strongly inhibits clusterin expression. Preclinical data demonstrate dose-dependent effects with custirsen, including inhibition of clusterin mRNA and increased apoptosis [49]. In a phase II trial, 81 patients with mCRCP were randomly assigned to docetaxel/prednisone with or without custirsen 640 mg IV weekly [50]. In a multivariate analysis, treatment assignment to custirsen was associated with improved OS (HR, 0.50; $P = .012$).

The development of custirsen has continued in the phase III setting. The phase III SYNERGY study will examine first-line docetaxel/prednisone with or without custirsen 640 mg IV weekly in patients with mCRPC. The primary endpoint is OS. Secondary endpoints will include PFS, PSA, patient-reported outcomes, serum custirsen levels, and safety.

Cabazitaxel

Cabazitaxel, a potent microtubule inhibitor, was discovered after screening more than 450 docetaxel derivatives to identify activity on tubulin polymerization. In pre-clinical studies, cabazitaxel demonstrated the same potency as docetaxel against sensitive tumor models, and greater potency than docetaxel in models of tumors resistant to chemotherapeutic agents, including docetaxel.

The phase III TROPIC trial compared cabazitaxel and mitoxantrone in patients with mCRPC who progressed during and after prior treatment with a docetaxel-based regimen (N = 755) [51]. The median OS was 15.1 months in the cabazitaxel arm and 12.7 months in the mitoxantrone arm (HR, 0.70; $P < .0001$). The safety analysis showed an increased risk in grade 3 or higher adverse events with cabazitaxel compared with placebo (57.4% vs. 39.4%), including anemia (10.5% vs. 4.9%) and febrile neutropenia (7.5% vs. 1.3%). Based on findings from TROPIC, cabazitaxel gained FDA approval for the treatment of CRPC following docetaxel-based therapy. Given the risk of neutropenia, the prophylactic use of growth factors is recommended during treatment with cabazitaxel, particularly for patients who are elderly and are not high risk for neutropenia.

Several phase III trials are evaluating cabazitaxel with modified dosing schedules or in combination with other agents. The phase III AFFINITY trial (OGX-011-12) will evaluate cabazitaxel/prednisone alone and in combination with custirsen for second-line therapy in mCRPC (Figure 1) (NCT01578655). The PROSELICA trial will compare cabazitaxel 20 mg/m2 versus cabazitaxel 25 mg/m2 in combination with prednisone in patients with mCRPC previously treated with docetaxel (NCT01308580). The FIRSTANA trial will evaluate cabazitaxel at 2 dose levels (20 mg/m2 and 25 mg/m2) in combination with prednisone versus docetaxel 75 mg/m2 plus prednisone in patients with chemotherapy-naïve mCRPC (NCT01308567).

TAXANES AS ANTIANDROGENS

Another emerging area of research focuses on the role of taxanes as potential antiandrogens. The administration of anti-tubulin agents has been shown to prevent the translocation of the AR across the nucleus and impair AR activity in prostate cancer [52]. In addition, a retrospective analysis found diminished docetaxel activity in 35 patients with mCRPC who were previously treated with abiraterone [53]. Only 26% of patients achieved a PSA decline of ≥ 50%, compared with other docetaxel trials that show PSA decline rates of 45% to 54%. Moreover, the median OS was only 12.5 months with post-abiraterone docetaxel, compared with 18.9 months observed in other docetaxel trials such as TAX-327 [54].

These findings highlight the potential importance of the sequence of therapy and the need for more research on optimal sequencing of chemotherapy and anti-androgen agents.

Update on Vaccine and Immunotherapy

Neal D. Shore, MD

Several therapies that prolong survival have recently been approved for mCRPC, yet therapies that provide durable disease control are still needed [55]. The rationale for immunotherapy in prostate cancer is compelling. Clonal populations of inflammatory cells often infiltrate prostate cancer tissues, suggesting that prostate cancer cells are the targets of

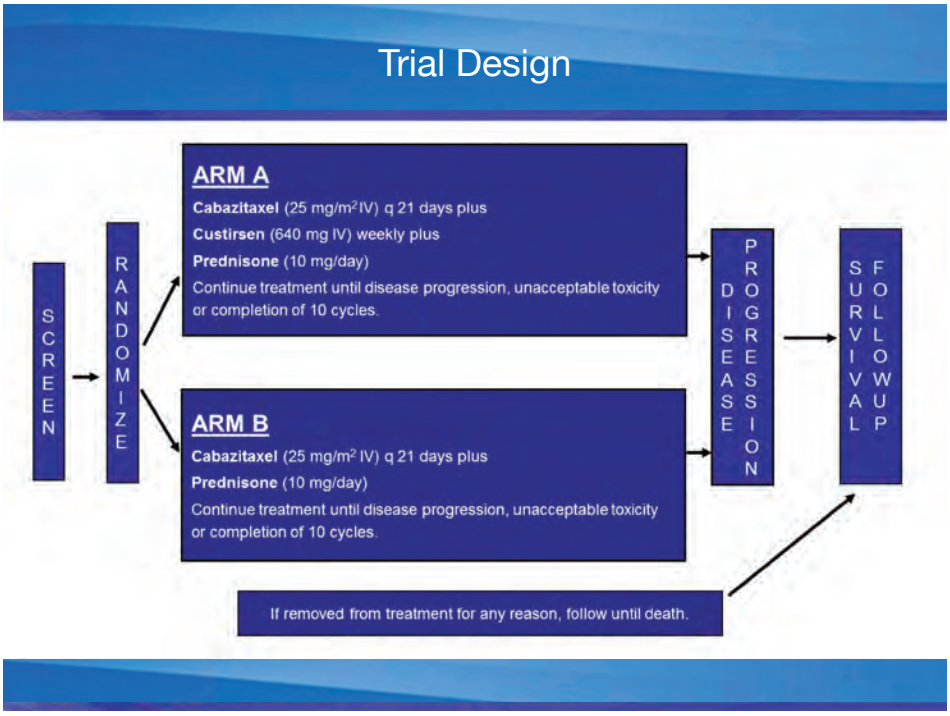

Figure 1. Phase III AFFINITY trial of Cabazitaxel/Predisone With or Without Custirsen in Second-Line CRPC

an innate antitumor immune response [56]. While prostate cancer cells exploit multiple mechanisms to evade an immune response, immunotherapy may boost and expand the innate anticancer immune response [56].

SIPULEUCEL-T

Sipuleucel-T is an autologous cellular immunotherapy for patients with asymptomatic or minimally symptomatic mCRPC. Sipuleucel-T gained FDA approval on the basis of the phase III Immunotherapy Prostate Adenocarcinoma Treatment (IMPACT) trial [57]. In patients with asymptomatic or minimally symptomatic mCRPC (N = 512), sipuleucel-T prolonged significantly prolonged OS by 4.1 months compared with placebo (25.8 months versus 21.7 months, respectively; HR, 0.759; $P = .017$).

Several additional analyses from the IMPACT trial have provided further insight on the mechanism of action of sipuleucel-T. Sheikh and colleagues found evidence of immune-system activation following sipuleucel-T treatment, as measured by the upregulation of CD54, a marker of APC activation [58]. Sipuleucel-T also induced proliferative responses to prostatic acid phosphatase (PAP) and to PA2024, the PAP-granulocyte-macrophage colony-stimulating factor (GM-CSF) recombinant fusion antigen, and generated persistent antigen-specific humoral responses against PAP and the PAP-GM-CSF fusion antigen.

Sipuleucel-T has also been evaluated in the neoadjuvant setting [59]. In an open-label phase II trial, 42 patients with localized prostate cancer received 3 infusions of sipuleucel-T prior to radical prostatectomy (RP). Compared with pre-treatment biopsy samples, tumor tissue harvested during RP showed significant increases (≥3 fold) in CD3+ and CD4+ T cell populations at the rim between the benign and malignant glands ($P < .0001$ for each comparison). These findings suggest that treatment with sipuleucel-T may modulate lymphocyte infiltration at the prostate tumor site.

Another recent analysis of the IMPACT trial showed a trend toward greater survival with sipuleucel-T in patients with lower baseline PSA levels [60]. The estimated improvement in median OS with sipuleucel-T ranged from 13.0 months in the lowest baseline PSA quartile (HR, 0.50; 95% CI, 0.31-0.85) to 2.8 months in the highest quartile (HR, 0.84; 95% CI, 0.55-1.29). This is in contrast to agents with different mechanisms of action, such as docetaxel, cabazitaxel, and abiraterone, where lower baseline PSA levels do not predict improved response (Figure 2). These findings suggest a role for immunotherapy as an early treatment strategy in sequencing algorithms for mCRPC.

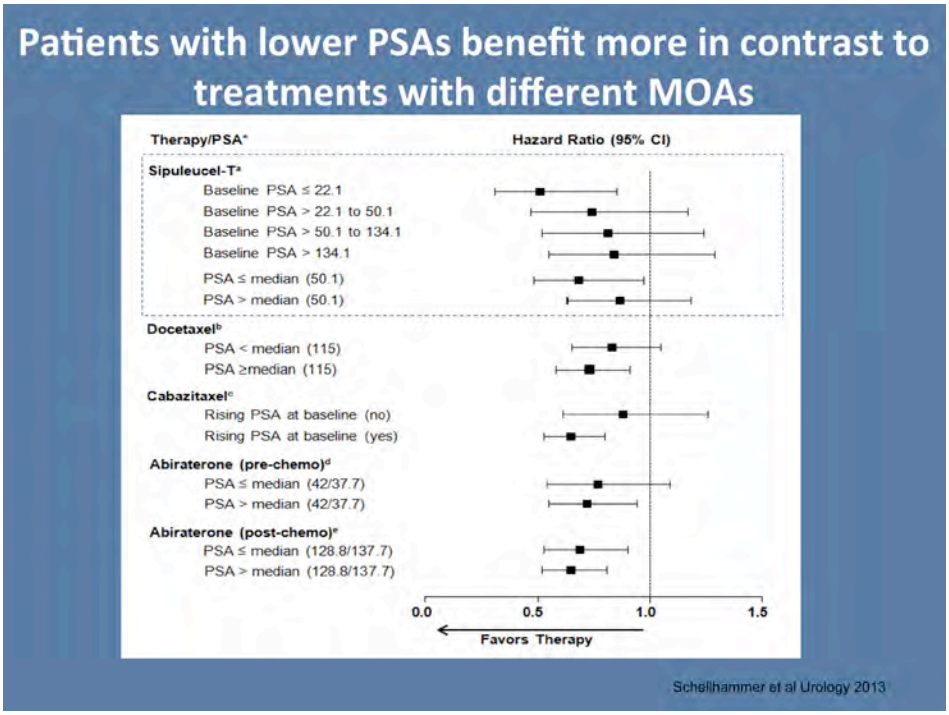

Figure 2. Correlation between baseline PSA levels and therapeutic benefit with sipuleucel-T compared with agents with different mechanisms of action [60].

Antigen Cascade

Antigen cascade describes the phenomenon of tumor antigen spreading that facilitates an immune response beyond the target antigen. Although a therapeutic vaccine targets a single tumor antigen, tumor cell death may lead to the release of secondary, non-targeted tumor antigens that prime a subsequent immune response [61].

At the 2014 ASCO Genitourinary Cancers Symposium, Drake and colleagues presented evidence of humoral antigen spreading following sipuleucel-T treatment in the IMPACT trial [62]. Approximately 3 to 4 months following treatment, serum samples showed IgG responses against a range of secondary antigens, including K-RAS and hK2, in the sipuleucel-T group, but not in the control group. Moreover, in the sipuleucel-T group, the median OS was longer in patients who developed an immune response to 2 or more secondary antigens compared with those who did not show a secondary antigen response (HR ≤ 0.4; $P \leq .01$). These findings provide further insight into the mechanism of action of sipuleucel-T in prostate cancer and highlight the role of post-treatment biomarkers as potential markers of clinical outcome.

PROSTVAC VF-TRICOM

PROSTVAC-VF-TRICOM is a therapeutic vaccine developed using vaccinia and fowlpox as vectors for the delivery of vaccines carrying PSA. The PSA gene in the vaccine is slightly modulated at the HLA-A2 locus, resulting in increased HLA-A2 binding and immunogenicity. Co-stimulatory molecules are included in the vaccinia and fowlpox vectors, including lymphocyte function-associated antigen (LFA-3; CD58), intercellular adhesion molecule (ICAM-1; CD54), and costimulatory molecule for the T-cell receptor (B7.1; CD80). Thus, the PROSTVAC-VF-TRICOM vaccine carries PSA plus 3 co-stimulatory molecules.

In 2010, Kantoff and colleagues presented findings from a phase II study of PROSTVAC-VF-TRICOM in patients with asymptomatic or minimally symptomatic metastatic CRPC (N = 125) [63]. There were no differences between PROSTVAC plus GM-CSF or placebo in progression-free survival, the primary endpoint. However, median OS was significantly better

in therapeutic vaccine arm compared with placebo (25.1 months versus 16.6 months, respectively; HR, 0.56; $P = .006$).

The clinical development of the PROSTVAC-VF-TRICOM vaccine is moving forward in the phase III PROSPECT trial (Figure 3). Approximately 1,200 patients with non- or minimally symptomatic metastatic CRPC will be randomly assigned to 1 of 3 treatment groups: PROSTVAC-VF-TRICOM with GM-CSF, PROSTVAC-VF-TRICOM without GM-CSF, and a placebo vector and placebo adjuvant. Crossover is not permitted, but patients can receive any type of treatment at the time of progression. The primary endpoint is OS.

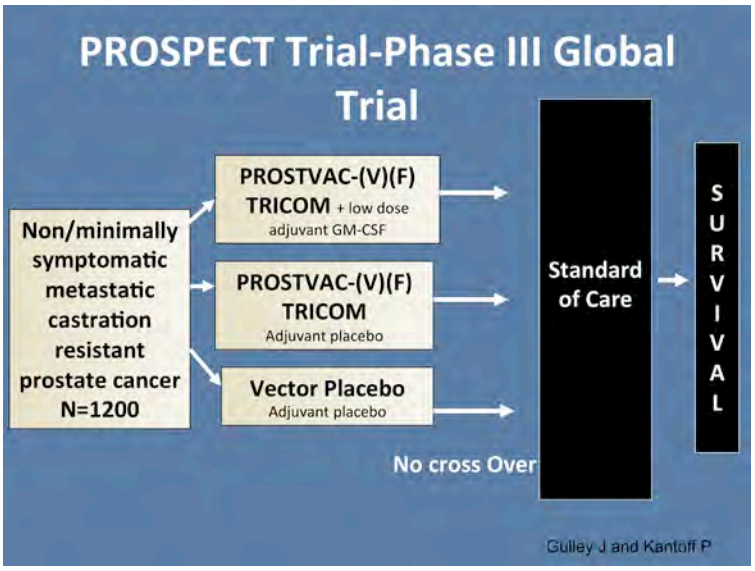

Figure 3. Study design of the phase III PROSPECT trial: PROSTVAC-VF-TRICOM in mCRPC.

IPILIMUMAB

Ipilimumab blocks the immune checkpoint molecule, cytotoxic T-lymphocyte antigen-4 (CTLA-4). Currently approved in patients with previously treated metastatic melanoma, ipilimumab is under investigation for the treatment of multiple tumor types, including prostate cancer.

The phase III CA184-043 evaluated ipilimumab versus placebo patients with mCRPC who previously received docetaxel but experienced disease progression within 6 months of treatment (N = 799) [64]. All patients had at least 1 site of symptomatic bone metastasis. Following a single dose of bone-directed radiation therapy (8 Gy), patients were randomly assigned to treatment with ipilimumab 10 mg/kg (n = 399) or placebo (n = 400). Treatment was given on weeks 1, 4, 7, and 10, and then every 12 weeks until disease progression or intolerable toxicity. The primary endpoint was OS.

At the 2013 European Cancer Congress, investigators presented the main findings of the CA184-043 trial [64]. In the intent-to-treat (ITT) analysis, the median OS was 11.2 months in the ipilimumab group and 10.0 months in the placebo group, just missing the cutoff for statistical significance (HR = 0.85; $P = 0.053$). The AE profile was consistent with previous observations reported for ipilimumab. The most common immune-related severe AEs were diarrhea and colitis.

Although the CA184-043 study failed to meet the primary endpoint of improved OS, several subgroup analyses identified patients with an increased likelihood of achieving a survival benefit with ipilimumab [64]. The presence of visceral metastases at baseline was found to negatively influence response to ipilimumab treatment ($P = 0.0056$). Patients with no visceral metastases had a longer median OS, regardless of treatment, compared with patients who had visceral metastases (Figure 4). This finding suggests that the different immunological microenvironments of visceral and bone metastases may contribute to differences in response to immunotherapy.

Several additional factors also correlated with OS, including logarithmic increases in alkaline phosphatase (ALP) (HR = 1.40; $P < 0.0001$) and hemoglobin (Hb) ≥ 11 g/dL (HR = 0.54; $P < 0.0001$) [64]. Patients with all 3 favorable prognostic features—low ALP, Hb ≥ 11 g/d, and no visceral metastases—derived the greatest benefit from ipilimumab treatment. In this subgroup, ipilimumab significantly improved median OS by 6.9 months compared with placebo (22.7 months versus 15.8 months, respectively; HR = 0.62) (Figure 5). These findings may help in the selection of patients who are the best candidates for ipilimumab therapy.

Findings from the CA184-043 trial support the further evaluation of ipilimumab in mCRPC patients with favorable prognostic features. The ongoing phase III CA184-095 trial will evaluate ipilimumab in chemotherapy-naïve mCRPC without visceral metastases.

FUTURE DIRECTIONS IN IMMUNOTHERAPY

Several studies have provided a strong rationale for initiating immunotherapy in patients with a low tumor burden, before the tumor-generated immunosuppressive environment has an opportunity to decrease the efficacy of immunotherapy [65-68]. The cumulative experience with sipuleucel-T to date provides sufficient proof of concept that immunotherapy is beneficial in prostate cancer. In the next fewer years, the potential for further advances may be realized with additional immunotherapy approaches, including PROSTVAC VF-Tricom, ipilimumab, and combination therapies.

New Oral Androgen Receptor Pathway Agents are Changing the Way Prostate Cancer is Treated

Leonard G. Gomella, MD

PROSTATE CANCER AND THE ANDROGEN RECEPTOR

The natural history of prostate cancer occurs over stages defined by tumor size, morphology, and organ confinement. Treatment for localized, early stage prostate cancer typically involves either surgery or radiation, followed by antiandrogen treatment for patients with hormone-sensitive disease. This therapeutic strategy results in decreased PSA levels followed by tumor regression [69]. However, prostate cancer cells develop the ability to survive and proliferate with low levels of circulating androgens. Despite castrate levels of serum testosterone (<50 ng/dL), all patients who progress following local therapy will develop mCRPC, which is marked by an increase in PSA levels, the presence of radiographic progression, and/or clinical symptoms [70].

Recent translational research has provided the foundation for new theories for

CRPC. Prostate cancer responds to castration by synthesizing androgens from weaker androgens and/or cholesterol [71]. Indeed, several studies have shown high levels of AR expression in CRPC tumors [72-74].

The androgen receptor (AR) may respond to castration with molecular and biochemical alterations that cause hypersensitivity to low levels of androgens [75]. Documented mechanisms include increased AR expression, AR gene mutations, and increased expression of AR transcriptional co-activators [75-77]. Prostate cancer can remain sensitive to androgens, even in the setting of low or castrate levels of testosterone.

ANDROGEN PATHWAY AGENTS

Prostate cancer progression appears to rely on continued AR signaling and the overexpression of key enzymes involved in androgen synthesis. Many treatments that purportedly target the AR, however, such as antiandrogens, ketoconazole, or glucocorticoids, result in only modest therapeutic benefits and no detrimental survival impairment. New agents were needed to suppress AR-related prostate cancer progression.

The next-generation, orally available, AR pathway agents include abiraterone acetate and enzalutamide (MDV3100), which were initially approved for prostate cancer in 2011 and 2012, respectively (Table 2). Several additional AR-targeted agents are in active development, including TAK700 (orteronel), TOK001 (galeterone), and ARN 509.

Abiraterone Acetate

Abiraterone is an irreversible, high-affinity inhibitor of the CYP17 enzyme complex that is required for androgen biosynthesis in testicular, adrenal, and prostatic tumor tissue [78]. In the phase III COU-AA-301 trial, patients with mCRPC who received prior docetaxel were randomly assigned to abiraterone plus prednisone or placebo plus prednisone [79]. Abiraterone significantly improved median OS compared with placebo (14.8 month versus 10.9 months, respectively; HR, 0.646; $P < .0001$), which led to the approval of abiraterone for post-docetaxel mCRPC. Although it is generally well tolerated, abiraterone is associated with mineralocorticoid excess-related adverse events such as fluid retention and hypokalemia. Concomitant steroid use (e.g., prednisone 5 mg BID) mitigates many of these symptoms, although patients should be monitored for liver abnormalities, hypertension, and hypokalemia.

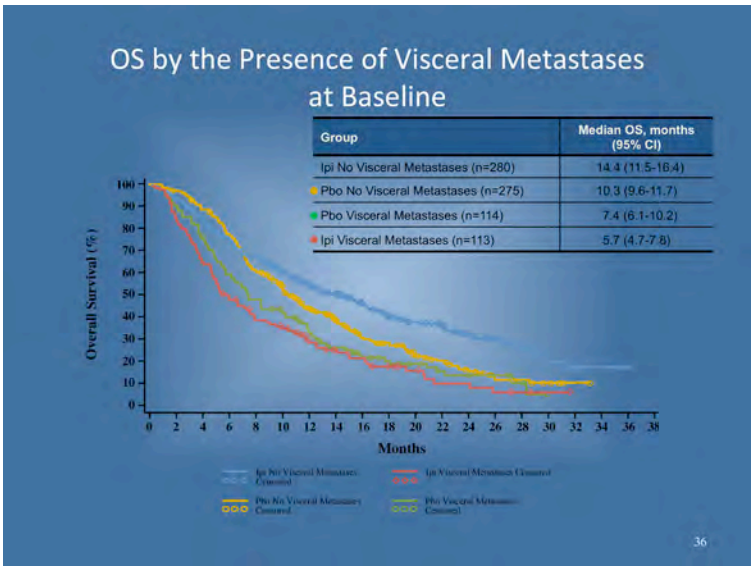

Figure 4. CA184-043: Overall survival by the presence of visceral metastases at baseline [64].

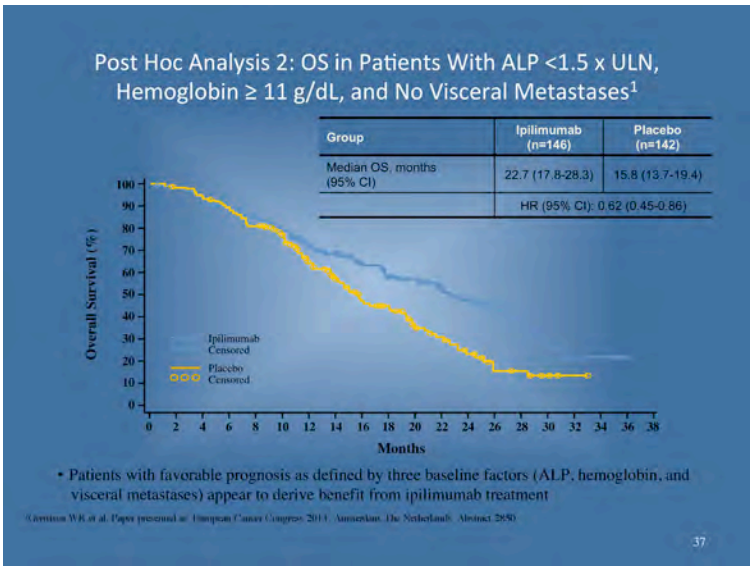

Figure 5. CA184-043: Overall survival in patients with favorable prognostic features (ALP <1.5 x ULN, hemoglobin ≥ 11 g/dL, and no visceral metastases [64].

Table 2. Comparison of Abiraterone Acetate and Enzalutamide

	Abiraterone Acetate	Enzalutamide
Mechanism of action	CYP17 inhibition	Antiandrogen
Efficacy after docetaxel	OS, PFS	OS, PFS
Efficacy before docetaxel	PFS, OS (NS)	PFS, OS
Major potential adverse effects	Hypertension Hypokalemia LFT abnormalities	Seizures Hypertension ALT elevation
Requires prednisone	Yes	No
Cost	$$$$	$$$$

ALT = alanine transferase; LFT = liver function test; NS = not significant; OS = overall survival; PFS = progression-free survival.

The phase III COU-AA-302 study evaluated abiraterone in patients with asymptomatic or mildly symptomatic metastatic CRPC prior to docetaxel chemotherapy [80]. The trial was terminated early due to a clear progression free survival benefit with abiraterone. In the final analysis, abiraterone significantly improved the primary endpoint of radiographic

progression-free survival (rPFS). The median rPFS had not been reached in the abiraterone arm, compared with 8.3 months in the placebo arm (HR, 0.43; $P < .0001$). The median OS was also statistically significantly better in the abiraterone arm (not reached) compared with the placebo arm (27.2 months; HR, 0.75; $P = .0097$), although it failed to meet the O'Brien Flemming boundary, most likely due to early termination. Based on these findings, abiraterone is now approved in the pre-docetaxel mCRPC setting.

Enzalutamide

Enzalutamide (MDV3100) is an anti-androgen with high affinity and selectivity for the AR [81,82]. The first phase III trial of MDV3100 was the AFFIRM study in patients with progressive mCRPC who had failed prior treatment with docetaxel [Scher 2012]. Patients were randomly assigned to daily oral MDV3100 or placebo. Treatment with MDV3100 significantly prolonged median OS by 4.8 months compared with placebo (18.4 months versus 13.6 months, respectively; HR, 0.631; $P < .0001$) [Scher 2012].

The phase III PREVAIL study compared enzalutamide and placebo in patients with asymptomatic or mildly symptomatic mCRPC who had progressed on ADT (N = 1717) [84]. The co-primary endpoints were rPFS and OS. In 2013, the PREVAIL trial was terminated early after a planned interim analysis found statistically significant benefits in the enzalutamide arm. The study was unblinded and patients initially assigned to placebo were offered treatment with enzalutamide. Investigators published final results from the PREVAIL study in the *New England Journal of Medicine* on June 1, 2014 [84].

Enzalutamide significantly improved rPFS by 81% compared with placebo (Figure 6). At 12 months, the risk of rPFS was 65% in the enzalutamide group, compared with 14% with placebo (HR = 0.19; $P < .001$). In addition, enzalutamide reduced the risk of death by 29% (HR = 0.71; $P < .0001$). At the data cut-off date, 72% of patients in the enzalutamide group were alive, compared with 63% of patients in the placebo group.

Enzalutamide demonstrated a favorable tolerability profile [84]. The adverse events of any grade that occurred more frequently with enzalutamide included fatigue (35.6%), back pain (27.0%), constipation (22.2%), arthralgia (20.3%), cardiac adverse events (20.3%), hypertension (13.4%), and increased liver enzymes (0.9%). Seizures were extremely rare and occurred at the same rate in the enzalutamide and placebo groups.

FUTURE DIRECTIONS IN ANDROGEN PATHWAY INHIBITION

Abiraterone acetate and enzalutamide have expanded the treatment options for patients with mCRPC (Table 3). Findings from PRE-

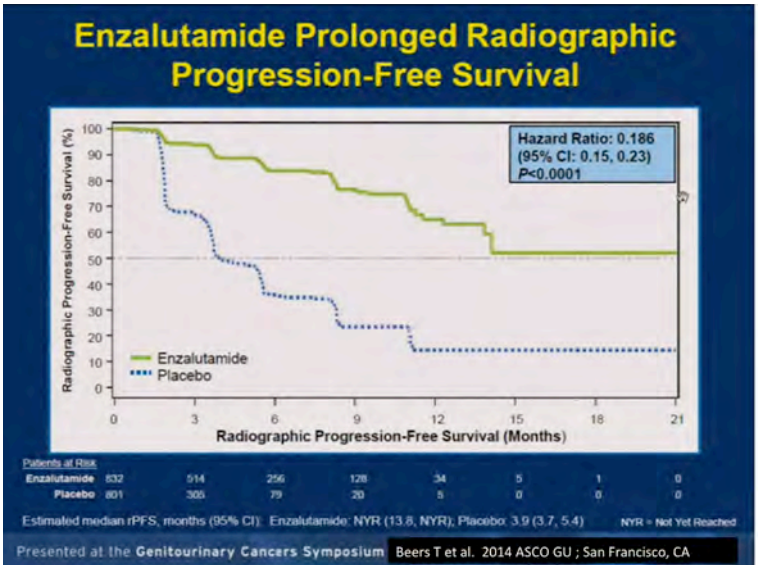

Figure 6. PREVAIL: Enzalutamide prolonged radiographic progression-free survival compared with placebo in pre-docetaxel mCRPC [84].

Table 3. Agents with Survival Benefits in mCRPC [80,84,86,87]

Agent	Trial	Comparator	Primary Endpoint	FDA Approval
Chemotherapy-naïve				
Abiraterone acetate + prednisone	COU-AA-302	Placebo + prednisone	OS benefit 5.2 months*	Dec 2012
Sipuleucel-T	IMPACT	Placebo	OS benefit 4.1 months	Apr 2010
Radium-223	ALSYMPCA	Placebo	OS benefit 3.6 months	May 2013
Enzalutamide	PREVAIL	Placebo	OS benefit 2.2 months	N/A
Post-chemotherapy				
Abiraterone acetate + prednisone	COU-AA-301	Placebo + prednisone	OS benefit 4.6 months	Apr 2011
Enzalutamide	AFFIRM	Placebo	OS benefit 4.8 months	Aug 2012
Cabazitaxel + prednisone	TROPIC	Mitoxantrone + prednisone	OS benefit 2.4 months	June 2010
Docetaxel + prednisone	TAX327	Mitoxantrone + prednisone	OS benefit 2.4 months	May 2004

*P=0.0151. Did not meet the prespecified value for statistical significance.
N/A = not applicable; OS = overall survival.

VAIL may lead to an expanded indication for enzalutamide that includes patients with chemotherapy-naïve mCRPC. Also in the pre-docetaxel setting, the ongoing phase II STRIVE trial will compare enzalutamide and bicalutamide in patients CRPC who have failed primary ADT (NCT01664923) [82].

Another promising strategy involves the use of enzalutamide plus abiraterone acetate to circumvent the compensatory mechanisms observed with either agent alone. A phase II study will examine the safety of the enzalutamide/abiraterone acetate combination in patients with bone-metastatic CRPC [85]. The randomized phase III ALLIANCE (A031201) study will compare enzalutamide alone versus enzalutamide plus abiraterone acetate and prednisone in approximately 1,400 patients with mCRPC who have not received docetaxel. The primary endpoint is OS.

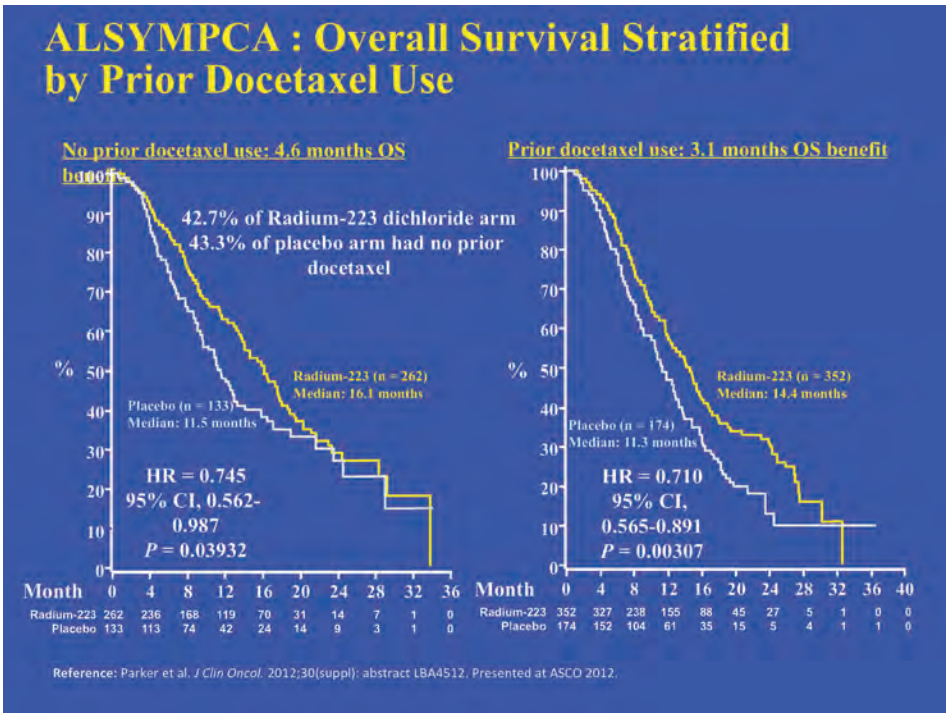

Figure 7. ALSYMPCA: Overall survival stratified by prior docetaxel use [91].

Bone Targeted Therapies and Radiopharmaceuticals

Daniel P. Petrylak, MD

Several bone-targeted agents are used to manage skeletal symptoms in patients with prostate cancer. In a landmark study of bone health, Saad and colleagues showed that zoledronic acid prolonged the time to first skeletal-related event (SRE) compared with placebo (P = .001) [88]. In a head-to-head trial with zoledronic acid, denosumab provided even stronger protection against SKE in patients with CRPC [89].

Recent attention has focused on the use of radiopharmaceuticals to improve disease-related outcomes, including survival, in patients with prostate cancer.

RADIUM-223

Radium-223 is an alpha particle-emitting radiopharmaceutical approved for the treatment of mCRPC in patients with symptomatic bone disease and no known visceral metastases. The National Comprehensive Cancer Network (NCCN) currently recommends treatment with radium-223 in both the pre- and post-docetaxel settings [55]. Radium-223 was approved in 2013 on the basis of findings from the phase III Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial [90,91].

The ALSYMPCA trial compared radium-223 versus placebo in 921 men with mCRPC, 2 or more bone metastases, and no known visceral metastases [90,91]. Patients received a total of 6 injections of radium-223 (n = 614) or placebo (n = 307) at 4-week intervals in addition to best standard of care. Radium-223 significantly improved the primary endpoint of OS by 3.6 months compared with placebo [91]. The median OS was 14.9 months in the radium-233 arm, and 11.3 months in the placebo arm (HR, 0.695; P = .00007).

Treatment with radium-223 was beneficial regardless of prior exposure to docetaxel (Figure 7) [91]. Among patients who received prior docetaxel, radium-223 extended survival by 3.1 months compared with placebo (14.4 months vs. 11.3 months, respectively; P = .00307). For those with no prior docetaxel treatment, the relative survival benefit with radium-223 was 4.6 months compared with placebo (16.1 months vs. 11.5 months, respectively; P = .03932). Radium-223 also showed a consistent survival benefit across other patient subgroups defined by total ALP, current use of bisphosphonates, and baseline ECOG status. The only factor that lost statistical significance for overall survival was ECOG performance status ≥2, although the trend remained in favor of radium-223.

Bone health was significantly improved with radium-223 treatment [91]. The median time to first SRE was 12.2 months in the radium-223 group and 6.7 months in the placebo group (HR, 0.64; P < .0001). In addition, radium-223 showed a consistent benefit in reducing the time to external-beam radiotherapy (HR, 0.67; P = .00117), spinal cord compression (HR, 0.61; P = .025); and pathologic bone fracture (HR, 0.62; P = .09). There was also a non-significant trend toward reduced need for surgical intervention with radium-223 compared with placebo (HR, 0.71; P = .479).

Radium-223 is generally well tolerated, with a similar rate of adverse events between the radium-223 and placebo groups (Table 4).

At the 2014 ASCO Genitourinary Cancer Symposium, investigators presented findings from a long-term safety analysis of the ALSYMPCA trial [92]. The risk of myelosuppression was rare during the follow-up period, which was a median of 10.4 months in the radium-223 group and 7.6 months for the placebo group. Grade 3/4 hematologic AEs in the radium-223 group included anemia, aplastic anemia, leukopenia, and neutropenia (≤1% for all events). The only grade 3/4 nonhematologic treatment-related AE during the follow-up period was a pathologic fracture in a patient taking radium-223. Two treatment-related deaths attributed to multiorgan failure and pneumonia in the radium-223 group.

Overall, the long-term follow-up found no additional safety concerns approximately 1.5 years after the patient's final injection with radium-223. These long-term results support the evaluation of radium-223 in combination with other agents in the treatment of patients with mCRPC and bone metastases.

Chemotherapy Post-Radium-223

One of the important considerations regarding radium-223 treatment is whether chemotherapy can be administered safely post-radium-223. Another post-hoc subgroup analysis from the ALSYMPCA trial has helped to alleviate this concern [93].

After participating in ALSYMPCA, 90 patients in the radium-223 group (15%) and 54 patients in the placebo group (18%) received chemotherapy [93]. The most common chemotherapeutic agents administered after study drug treatment were docetaxel (n = 105), mitoxantrone (n = 23), and cyclophosphamide (n = 19). Most baseline characteristics were similar in both treatment groups. In the radium-223 arm, 71% of patients had received all 6 injections of study drug, compared with 50% of those in the placebo group. The prevalence of prior docetaxel use was 68% in the radium-223 arm and 59% in the placebo arm.

Following treatment with cytotoxic chemotherapy, the median platelet counts and median hemoglobin counts were very similar in the radium-223 and placebo groups. The post-chemotherapy neutrophil counts also showed a similar pattern, although the baseline neutrophil count was somewhat lower in the radium-223 arm. Overall, these findings suggest that cytotoxic chemotherapy can be administered after radium-223 without an increased risk in hematologic adverse events.

Radium-223-Based Combination Therapies

With the range of benefits demonstrated in the ALSYMPCA trial, radium-223 is an attractive backbone for combination therapy [91]. A phase I trial examined the combination of radium-223 and docetaxel given in 3 treatment schedules [94]:

- Cohort 1: Radium-223 25 kbq/kg q 6 weeks x 2 + docetaxel 75 mg/m2 (n = 7)
- Cohort 2: Radium-223 25 kbq/kg q 6 weeks x 2 + docetaxel 60 mg/m2 (n = 3)
- Cohort 3: Radium-223 50 kbq/kg q 6 weeks x 2 + docetaxel 60 mg/m2 (n = 7)

No patients discontinued treatment or delayed radium-223 treatment due to protocol-defined adverse events. No grade 3/4 anemia or thrombocytopenia was reported, although 10 patients had grade 3/4 neutropenia. Four cases of febrile neutropenia were reported: 3 patients in cohort 1, and 1 patient in cohort 3. Based on these findings, the radium-223/docetaxel combination will be examined in a randomized phase II trial. The dosing schedule selected for the phase II trial is radium-223 50 kbq/kg every 6 weeks for 5 cycles in combination with docetaxel 60 mg/m2.

SUMMARY

Docetaxel/prednisone remains the standard of care for first-line chemotherapy for metastatic CRPC. Further manipulation of docetaxel-based chemotherapy is unlikely to provide therapeutic improvements. However, markers for drug response are being evaluated to identify subgroups of patients who are more likely to benefit from novel combinations. Indeed, combining agents with different mechanisms of action is standard practice in oncology, with most treatment regimens for patients with advanced cancer including multiple chemotherapeutic agents or a combination of radiation therapy and chemotherapy. Immunotherapy offers a different mechanistic approach than traditional treatments, suggesting the potential for synergy with other modalities.

Abiraterone acetate and enzalutamide, two new oral inhibitors of the AR-signaling pathway, have shown survival benefits in the pre- and post-docetaxel settings. Radium-223 also extends survival in patients with mCRPC and bone metastases regardless of prior docetaxel exposure. Of the new therapies, many are very well tolerated and may therefore be applied to a wide variety of patients. An understanding of the clinical approval and patient eligibility criteria for the various studies is critical to the appropriate use of these agents. The diverse mechanisms of action of the new therapies will allow for significant patient selection and clinician input on treatment choice, although the optimal sequencing of these therapies will take years to establish with additional clinical trials.

Table 4. ALSYMPCA: Radium-223 Safety [91]

Adverse Events, n (%)	All Grades		Grades 3 or 4	
	Radium-223 dichloride (n = 600)	Placebo (n = 301)	Radium-223 dichloride (n = 600)	Placebo (n = 301)
Hematologic				
Anemia	187 (31.2)	92 (31)	77 (13)	40(13)
Neutropenia	30 (5)	3 (1)	13 (2)	2 (1)
Thrombocytopenia	69 (11.5)	17 (5.6)	39 (6.5)	6 (2)
Non-hematologic				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhea	151 (25)	45 (15)	9 (1.5)	5 (1.7)
Nausea	213 (35.5)	104 (35)	10 (2)	5 (2)
Vomiting	111 (18.5)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

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XOFIGO® IS INDICATED

for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.[1]

Not an actual patient. Models used for illustrative purposes only.

Important Safety Information[1]

- **Contraindications:** Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman
- **Bone Marrow Suppression:** In the randomized trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression. In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) was similar for patients treated with Xofigo and placebo. Myelosuppression—notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia—has been reported in patients treated with Xofigo.

  Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure
- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be $\geq 1 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care
- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established.

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Prolong life.
Treat bone metastases.

The first agent to extend overall survival by exerting an antitumor effect on bone metastases in CRPC[1,2]

- **Exploratory updated analysis[a]: 3.6-month increase in median overall survival** vs placebo (HR=0.695; 95% confidence interval [CI]: 0.581-0.832)[1]
  - —14.9 months for Xofigo (95% CI: 13.9-16.1) vs 11.3 months for placebo (95% CI: 10.4-12.8)[1]
- **Prespecified interim analysis: 2.8-month increase in median overall survival** vs placebo, *P*=0.00185 (HR=0.695; 95% CI: 0.552-0.875)[1]
  - —14.0 months for Xofigo (95% CI: 12.1-15.8) vs 11.2 months for placebo (95% CI: 9.0-13.2)[1]
- Overall survival benefit supported by delay in time to first symptomatic skeletal event (SSE), favoring Xofigo.[b] The majority of events consisted of external beam radiation therapy to bone metastases[1]
- 1-minute intravenous injection every 4 weeks for 6 injections[1]

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[a]An exploratory updated overall survival analysis was performed before patient crossover, incorporating an additional 214 events, resulting in findings consistent with the interim analysis.

[b]SSEs defined as external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.

Outside of a clinical trial, concomitant use of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued

- **Administration and Radiation Protection:** Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations
- **Adverse Reactions:** The most common adverse reactions (≥10%) in the Xofigo arm vs the placebo arm, respectively, were nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%). Grade 3 and 4 adverse events were reported in 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in the Xofigo arm (≥10%) vs the placebo arm, respectively, were anemia (93% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%), and neutropenia (18% vs 5%)

References: 1. Xofigo® (radium Ra 223 dichloride) injection [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; May 2013. **2.** Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.

Please see following pages for brief summary of full Prescribing Information.

Xofigo®
radium Ra 223 dichloride
INJECTION

Xofigo (radium Ra 223 dichloride) Injection, for intravenous use

Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xofigo™ is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

2 DOSAGE AND ADMINISTRATION

2.3 Instructions for Use/Handling

General warning

Xofigo (an alpha particle-emitting pharmaceutical) should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal Xofigo are subject to the regulations and/or appropriate licenses of the competent official organization.

Xofigo should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Radiation protection

The administration of Xofigo is associated with potential risks to other persons (e.g., medical staff, caregivers and patient's household members) from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

For drug handling

Follow the normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns when handling blood and bodily fluids to avoid contamination. In case of contact with skin or eyes, the affected area should be flushed immediately with water. In the event of spillage of Xofigo, the local radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. A complexing agent such as 0.01 M ethylene-diamine-tetraacetic acid (EDTA) solution is recommended to remove contamination.

For patient care

Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. When handling bodily fluids, simply wearing gloves and hand washing will protect caregivers. Clothing soiled with Xofigo or patient fecal matter or urine should be washed promptly and separately from other clothing.

Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is expected to be low, because the typical treatment activity will be below 8,000 kBq (216 microcurie). In keeping with the **A**s **L**ow **A**s **R**easonably **A**chievable (ALARA) principle for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

The gamma radiation associated with the decay of radium-223 and its daughters allows for the radioactivity measurement of Xofigo and the detection of contamination with standard instruments.

4 CONTRAINDICATIONS

Xofigo is contraindicated in pregnancy.

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Xofigo is not indicated for use in women. Xofigo is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

In the randomized trial, 2% of patients on the Xofigo arm experienced bone marrow failure or ongoing pancytopenia compared to no patients treated with placebo. There were two deaths due to bone marrow failure and for 7 of 13 patients treated with Xofigo, bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients on the Xofigo arm and 2% on the placebo arm permanently discontinued therapy due to bone marrow suppression.

In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) were similar for patients treated with Xofigo and placebo. Myelosuppression; notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia; has been reported in patients treated with Xofigo. In the randomized trial, complete blood counts (CBCs) were obtained every 4 weeks prior to each dose and the nadir CBCs and times of recovery were not well characterized. In a separate single-dose phase 1 study of Xofigo, neutrophil and platelet count nadirs occurred 2 to 3 weeks after Xofigo administration at doses that were up to 1 to 5 times the recommended dose, and most patients recovered approximately 6 to 8 weeks after administration *[see Adverse Reactions (6)]*.

Hematologic evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration of Xofigo, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L and hemoglobin ≥ 10 g/dL. Before subsequent administrations of Xofigo, the ANC should be $\geq 1 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L. If there is no recovery to these values within 6 to 8 weeks after the last administration of Xofigo, despite receiving supportive care, further treatment with Xofigo should be discontinued. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

The safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use with chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer with bone metastases, 600 patients received intravenous injections of 50 kBq/kg (1.35 microcurie/kg) of Xofigo and best standard of care and 301 patients received placebo and best standard of care once every 4 weeks for up to 6 injections. Prior to randomization, 58% and 57% of patients had received docetaxel in the Xofigo and placebo arms, respectively. The median duration of treatment was 20 weeks (6 cycles) for Xofigo and 18 weeks (5 cycles) for placebo.

The most common adverse reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema (Table 3). Grade 3 and 4 adverse events were reported among 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in Xofigo-treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (Table 4).

Treatment discontinuations due to adverse events occurred in 17% of patients who received Xofigo and 21% of patients who received placebo. The most common hematologic laboratory abnormalities leading to discontinuation for Xofigo were anemia (2%) and thrombocytopenia (2%).

Table 3 shows adverse reactions occurring in ≥ 2% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 3: Adverse Reactions in the Randomized Trial

System/Organ Class Preferred Term	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and lymphatic system disorders				
Pancytopenia	2	1	0	0
Gastrointestinal disorders				
Nausea	36	2	35	2
Diarrhea	25	2	15	2
Vomiting	19	2	14	2
General disorders and administration site conditions				
Peripheral edema	13	2	10	1
Renal and urinary disorders				
Renal failure and impairment	3	1	1	1

Laboratory Abnormalities

Table 4 shows hematologic laboratory abnormalities occurring in ≥ 10% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 4: Hematologic Laboratory Abnormalities

Hematologic Laboratory Abnormalities	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Anemia	93	6	88	6
Lymphocytopenia	72	20	53	7
Leukopenia	35	3	10	<1
Thrombocytopenia	31	3	22	<1
Neutropenia	18	2	5	<1

Laboratory values were obtained at baseline and prior to each 4-week cycle.

As an adverse reaction, grade 3-4 thrombocytopenia was reported in 6% of patients on Xofigo and in 2% of patients on placebo. Among patients who received Xofigo, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel naïve patients and in 3% of patients who have received prior docetaxel.

Fluid Status

Dehydration occurred in 3% of patients on Xofigo and 1% of patients on placebo. Xofigo increases adverse reactions such as diarrhea, nausea, and vomiting which may result in dehydration. Monitor patients' oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia.

Injection Site Reactions

Erythema, pain, and edema at the injection site were reported in 1% of patients on Xofigo.

Secondary Malignant Neoplasms

Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Due to its mechanism of action and neoplastic changes, including osteosarcomas, in rats following administration of radium-223 dichloride, Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms *[see Nonclinical Toxicology (13.1)]*. However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs. 2%; respectively), but the expected latency period for the development of secondary malignancies exceeds the duration of follow up for patients on the trial.

Subsequent Treatment with Cytotoxic Chemotherapy

In the randomized clinical trial, 16% patients in the Xofigo group and 18% patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy.

7 DRUG INTERACTIONS

No formal clinical drug interaction studies have been performed.

Subgroup analyses indicated that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of Xofigo in the randomized clinical trial.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category X *[see Contraindications (4)]*

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of Xofigo in pregnancy and Xofigo is not indicated for use in women, maternal use of a radioactive therapeutic agent could affect development of a fetus. Xofigo is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with Xofigo.

8.3 Nursing Mothers

Xofigo is not indicated for use in women. It is not known whether radium-223 dichloride is excreted in human milk. Because many drugs are excreted in human milk, and because of potential for serious adverse reactions in nursing infants from Xofigo, a decision should be made whether to discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Xofigo in pediatric patients have not been established.

In single- and repeat-dose toxicity studies in rats, findings in the bones (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganization of the physis/growth line) and teeth (missing, irregular growth, fibro-osseous lesions in bone socket) correlated with a reduction of osteogenesis that occurred at clinically relevant doses beginning in the range of 20 – 80 kBq (0.541 - 2.16 microcurie) per kg body weight.

8.5 Geriatric Use

Of the 600 patients treated with Xofigo in the randomized trial, 75% were 65 years of age and over and while 33% were 75 years of age and over. No dosage adjustment is considered necessary in elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

No dedicated hepatic impairment trial for Xofigo has been conducted. Since radium-223 is neither metabolized by the liver nor eliminated via the bile, hepatic impairment is unlikely to affect the pharmacokinetics of radium-223 dichloride *[see Clinical Pharmacology (12.3)]*. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with mild hepatic impairment. No dose adjustments can be recommended for patients with moderate or severe hepatic impairment due to lack of clinical data.

8.7 Patients with Renal Impairment

No dedicated renal impairment trial for Xofigo has been conducted. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with existing mild (creatinine clearance [CrCl] 60 to 89 mL/min) or moderate (CrCl 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CrCl less than 30 mL/min) due to limited data available (n = 2) *[see Clinical Pharmacology (12.3)]*.

8.8 Males of Reproductive Potential

Contraception

Because of potential effects on spermatogenesis associated with radiation, advise men who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective contraceptive method during and for 6 months after completing treatment with Xofigo.

Infertility

There are no data on the effects of Xofigo on human fertility. There is a potential risk that radiation by Xofigo could impair human fertility *[see Nonclinical Toxicology (13.1)]*.

10 OVERDOSAGE

There have been no reports of inadvertent overdosing of Xofigo during clinical studies.

There is no specific antidote. In the event of an inadvertent overdose of Xofigo, utilize general supportive measures, including monitoring for potential hematological and gastrointestinal toxicity, and consider using medical countermeasures such as aluminum hydroxide, barium sulfate, calcium carbonate, calcium gluconate, calcium phosphate, or sodium alginate.[1]

Single Xofigo doses up to 250 kBq (6.76 microcurie) per kg body weight were evaluated in a phase 1 clinical trial and no dose-limiting toxicities were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic potential of radium-223 dichloride. However, in repeat-dose toxicity studies in rats, osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses 7 to 12 months after the start of treatment. The presence of other neoplastic changes, including lymphoma and mammary gland carcinoma, was also reported in 12- to 15-month repeat-dose toxicity studies in rats.

Genetic toxicology studies have not been conducted with radium-223 dichloride. However, the mechanism of action of radium-223 dichloride involves induction of double-strand DNA breaks, which is a known effect of radiation.

Animal studies have not been conducted to evaluate the effects of radium-223 dichloride on male or female fertility or reproductive function. Xofigo may impair fertility and reproductive function in humans based on its mechanism of action.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To be compliant with blood cell count monitoring appointments while receiving Xofigo. Explain the importance of routine blood cell counts. Instruct patients to report signs of bleeding or infections.
- To stay well hydrated and to monitor oral intake, fluid status, and urine output while being treated with Xofigo. Instruct patients to report signs of dehydration, hypovolemia, urinary retention, or renal failure / insufficiency.
- There are no restrictions regarding contact with other people after receiving Xofigo. Follow good hygiene practices while receiving Xofigo and for at least 1 week after the last injection in order to minimize radiation exposure from bodily fluids to household members and caregivers. Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing. Caregivers should use universal precautions for patient care such as gloves and barrier gowns when handling bodily fluids to avoid contamination. When handling bodily fluids, wearing gloves and hand washing will protect caregivers.
- Who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective method of birth control during treatment and for 6 months following completion of Xofigo treatment.

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