



## Tailoring Treatment in Metastatic Prostate Cancer: Optimizing Outcomes With What Is Available Now

Howard I. Scher

Department of Medicine, Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, New York, USA



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### TREATING ADVANCED PROSTATE CANCER: SUCCESSFUL AGENTS TARGET DIVERSE DISEASE BIOLOGY

An evaluation of the treatments available in 2013 for men with metastatic prostate cancer that has progressed with castrate levels of testosterone shows that there are six agents that have been proven to prolong life. Of particular interest as we determine how to utilize these agents to maximize patient benefit is to recognize that these six agents target diverse aspects of the malignant process that contribute to prostate cancer growth and spread. Docetaxel and cabazitaxel are cytotoxic agents that interfere with the mechanics of cell division and replication [1-5]; the alpha emitter Alpharadin (Radium-223 chloride) targets the bone micro-environment [6]; sipuleucel-T is the first therapeutic cancer vaccine approved by the United States Food and Drug Administration (FDA) [7]; while abiraterone acetate [8] and enzalutamide [9] are hormonal agents that target two oncogenic drivers of growth: increased androgen biosynthesis and overexpression of the androgen receptor [10].

Our understanding of the biology of advanced prostate cancer has not only led us to reclassify metastatic hormone refractory prostate cancer (mHRPC) as metastatic castrate-resistant prostate cancer (mCRPC), it has also opened up a therapeutic avenue for that subset of mCRPC patients whose tumors remain dependent on the androgen receptor (AR) and AR signalling. These patients, previously categorized as hormone refractory—implying that they would no longer respond to a “hormonal” treatment—can now receive a safe and life-prolonging hormone treatment. There is a recognition that there are different clinical subtypes based on the pattern of spread, which are also underpinned by diverse disease biology. Different drugs are needed for different subtypes, while our increased understanding is also providing insights into the development of combinations that are likely to be more beneficial than either drug alone.

### CLINICAL RESEARCH TO CLINICAL REALITY: ADJUST THE MINDSET!

The successful demonstration of a survival benefit in recent large-scale phase III clinical trials has enabled effective therapies to move from the research arena into clinical practice. Key questions now are which agents are most likely to benefit which patients and in what sequence? Here, it is important to learn from our experience with docetaxel, where its success as a front-line monotherapy prompted an ever-increasing number of combination approaches, none of which demonstrated increased efficacy, with some even resulting in poorer overall survival [10].

A second lesson is that in spite of the promise of genomic signatures (none of which have been definitively proven to predict for response in an individual), it is essential that we consider clinical information—the routine “biomarkers” that are readily available at no additional cost that we use in daily practice. An example is performance status, a “human biomarker” that may not have the same aura as a genetic signature, but which we use intuitively when considering a therapy that may offer the chance for a superior outcome at the risk of greater toxicity [11]. Ultimately, treatment is guided by prioritizing the unmet needs of the individual patient. All patients want a treatment that can prolong life, but for a patient experiencing severe pain, a therapy that can provide immediate relief of the pain takes the highest priority. In this setting, mitoxantrone plus prednisone and docetaxel can be utilized, or alpharadin if the pain is confined to bone.

### GETTING IT RIGHT: RIGHT PATIENT, RIGHT TREATMENT, RIGHT TIME

With the expansion in treatment options for the management of mCRPC, clinicians face an emerging challenge in deciding which therapeutic approach will work for which subgroup of patients. The sequencing of treatment combinations represents a crucial facet

of our new therapeutic algorithm. Docetaxel still represents a critical component of this algorithm, but the increasing use of AR and AR-signaling targeted approaches will undoubtedly lead to a later use with cytotoxic therapies.

Sequencing approaches will also be guided by the influence of the first therapy given on the biology of the relapsing disease. A number of studies have indicated that this may have particular relevance in patients receiving therapies involving both abiraterone acetate and enzalutamide [12, 13]. The recent observation that abiraterone acetate activates glucocorticoid receptor signaling, leading to resistance to enzalutamide (V. Arora and C.L. Sawyer, unpublished data), is also relevant to the sequencing approach employed when using these two hormone/hormone receptor targeting agents.

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### THE WAY FORWARD: HARNESSING THE THERAPEUTIC ARSENAL

We are now in the unique position of having many options with proven benefit, the result of well-designed definitive tri-

als of agents directed against different aspects of the malignant process that contribute to prostate cancer growth. The progress of the last few years is unprecedented. How we harness this therapeutic arsenal will influence our ability to further improve the quality and prolong the duration of life of prostate cancer patients.

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### REFERENCES

1. Carducci MA. NCCN: New chemotherapeutic approaches to hormone refractory prostate cancer.; NCCN Prostate Cancer practice Guidelines Panel. *Cancer Control* 2001; 8(6 Suppl 2):62-65.
2. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-1512.
3. Pienta KJ, Smith DC. Advances in prostate cancer chemotherapy: a new era begins. *CA Cancer J Clin* 2005; 55:300-318.
4. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147-1154.
5. Dorff TB, Quinn DI. Cabazitaxel in prostate cancer: stretching a string. *Lancet* 2010; 376:1119-1120.
6. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213-223.
7. Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411-22.
8. Schweizer MT, Antonarakis ES. Abiraterone acetate: a hat trick of clinical benefits. *Lancet Oncol* 2012;13:1173-1174.
9. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187-1197.
10. Antonarakis ES, Eisenberger MA. Phase III trials with docetaxel-based combinations for metastatic castration-resistant prostate cancer: time to learn from past experiences. *J Clin Oncol* 2013;31:1709-1712.
11. Templeton AJ, Vera-Badillo FE, Wang L et al. Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials. *Ann Oncol* 2013;24:2972-2977.
12. Lortol Y, Bianchini D, Ileana E et al. Antitumor activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann Oncol* 2013 24: 1807-12.
13. Noonan KL, North S, Bitting RL et al. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol* 2013;24:1802-1807.