Platinum Priority – Editorial

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New Treatments for Men with Castration-resistant Prostate Cancer: Can We Move from Small Steps to Giant Leaps?

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In this month’s issue of *European Urology*, Sridhar et al. bring us up to date on the rapidly evolving landscape of approved and emerging treatments for men with castration-resistant prostate cancer (CRPC) [1]. After >6 yr with no approvals or positive trials since the demonstration of improved survival with docetaxel, we now have the novel androgen synthesis inhibitor abiraterone acetate, the second-generation anti-androgen enzalutamide, an immunomodulatory cellular therapy (sipuleucel-T, where available), a novel taxane in cabazitaxel, and two bone-targeting agents in radium 223 and denosumab.

This wealth of agents that have incrementally improved survival come with a price. We still do not know how best to use the agents, which patients benefit the most (or least), and whether society can (or should) afford the agents in the absence of curing the disease. We have made important steps for men with CRPC as of 2013, but the giant leap for mankind—notably, the ability to eradicate or prevent metastatic disease with systemic therapy—is still elusive. This editorial will lay out five principles for the next 5–10 yr (summarized in Table 1) that may help to guide drug development for men with advanced, potentially lethal prostate cancer (PCa).

1. **Optimize drug delivery and minimize unnecessary harms and costs to individuals and society by developing predictive biomarkers for these new systemic therapies**

Recent approvals in oncology are rich with companion predictive biomarkers that identify patients with tumors that are more likely to respond to a given systemic therapy, ranging from v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (*ERBB2*) in breast cancer to anaplastic lymphoma receptor tyrosine kinase (*ALK* fusion) in lung cancer. PCa is not one of those cancers whose drug approvals have had associated predictive biomarkers, although many potential measures are emerging [2]. All recent drug approvals for men with CRPC lacked companion diagnostic tests or predictive biomarkers that can subsequently help determine the optimal use and delivery of the agents outside the clinical eligibility criteria of the trial.

Future emphasis should be on creating real connections between biology and therapy to maximize benefit and minimize avoidable toxicity and costs. These connections are made possible through the emerging ability to molecularly barcode various PCa genotypes and understand their pathobiology. For example, as men are developing enzalutamide or abiraterone resistance, should the next line of hormonal therapy be driven by the presence of androgen receptor mutations and splice variants, or by mutations in androgen synthetic enzymes [3–5]? Do measures of bone turnover indicate a greater benefit from radium 223? Can we identify PCa-specific molecular aberrations in plasma rather than in circulating tumor cells (CTCs), given that most men with nonmetastatic disease do not have detectable CTCs using conventional assays?

2. **Prevent, not just delay, death from prostate cancer by studying the early use of effective systemic therapies prior to macrometastatic disease**

Currently approved drugs discussed by Sridhar et al. each improve median survival by 3–5 mo without resulting in cures. Adjuvant systemic therapy has emerged as routine practice in many aggressive solid tumors to improve cure
The planned acquisition and high throughput analysis by modeling and preventing such dissemination is imperative. PCS-resistant to systemic therapy eradication, emphasis on osteomimicry, and for bone and visceral sites to be highly susceptible to bone, possibly through the setting of a range of PCa-specific genomic lesions. Given the current limitations of preclinical models and human correlative studies to better understand the molecular underpinnings of how prostate cancer disseminates to bone and viscera, resists current therapies, and changes over time.

1. Optimize drug delivery and minimize unnecessary harms and costs to individuals and society by developing predictive biomarkers for these new systemic therapies.
2. Prevent, not just delay, death from prostate cancer by studying the early use of effective systemic therapies prior to macrometastatic disease.
3. Improve our preclinical models and human correlative studies to better understand the molecular underpinnings of how prostate cancer disseminates to bone and viscera, resists current therapies, and changes over time.
4. Develop screening strategies and biomarkers that identify men with aggressive, potentially lethal organ-confined prostate cancer but do not detect indolent nonlethal disease.
5. Ensure the real clinical value of new systemic therapies by developing transparent guidelines that account for society-level values.

Table 1 – Suggestions for five guiding principles for prostate cancer research and drug development

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| 2. | Prevent, not just delay, death from prostate cancer by studying the early use of effective systemic therapies prior to macrometastatic disease. |
| 3. | Improve our preclinical models and human correlative studies to better understand the molecular underpinnings of how prostate cancer disseminates to bone and viscera, resists current therapies, and changes over time. |
| 4. | Develop screening strategies and biomarkers that identify men with aggressive, potentially lethal organ-confined prostate cancer but do not detect indolent nonlethal disease. |
| 5. | Ensure the real clinical value of new systemic therapies by developing transparent guidelines that account for society-level values. |

PECa is essentially multiple diseases that share one initiating organ; some PECa could arguably be called benign lesions, while others disseminate quickly if left untreated. PSA screening offers only modest protection against lethal PECa while leaving unfiltered millions of men who may not need immediate diagnosis or biopsy and therapy. We should refine screening and preventive efforts for aggressive PECa while intentionally missing indolent disease. Active surveillance using biopsy- or urine/blood-based biomarker studies has the potential to spare many men from immediate therapy. Large consortiums for prospective data collection and clinical trials are ongoing and required to develop these strategies for regulatory approval, along with suitable shorter-term end points, such as the prevention or accurate detection of aggressive disease. The novel agents discussed by Sridhar et al. could play a role in these early-stage studies once a biomarker-defined population at risk is identified.

4. Develop screening strategies and biomarkers that identify men with aggressive, potentially lethal, organ-confined prostate cancer but do not detect indolent nonlethal disease

Each day in my clinic, my patients are faced with the rising costs of health care that affects their ability to receive the novel therapies described by Sridhar et al. [1]. This burden is felt worldwide; in many places, the use of many agents is simply not even thinkable. A framework must be developed to provide improved cost effectiveness without squashing research, innovation, and drug discovery, as well as to measure and assign value to both quality of life and quantity of life by experts. This framework should include transparent rules around specific benefits that society, compared with the individual, is willing to pay. In the United States, this framework is largely lacking currently, and the upward pressure to raise the costs of drugs is putting these agents out of reach for many men with CRPC and depleting resources that could be focused better on the first four objectives, as well as many other health care priorities.

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Stand Up to Cancer Dream Teams of a range of metastatic biopsies in the context of new hormonal and other systemic therapies will be essential to developing combination approaches similar to those used for chronic infectious diseases such as HIV infection or tuberculosis, which can be controlled or possibly eradicated with systemic treatment [6]. Modeling such drug synergy in preclinical models will permit the anticipation of resistance mechanisms.
References


