Asian Journal of Andrology (2012) 14, 421–422

www.nature.com/aja

OPINION

Experimental therapeutics in prostate cancer: where are we now and where do we need to go

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Asian Journal of Andrology (2012) **14,** 421–422; doi:10.1038/aja.2012.36; published online 23 April 2012

The explosion of new therapeutics in metastatic castrate-resistant prostate cancer (mCRPC) is unprecedented, but much more work needs to be done before we are satisfied. Six phase III trials with an overall survival impact have now been reported (**Table 1**).[1–6] Four of these trials were exclusively or predominantly in the mCRPC post-docetaxel space (MDV3100, abiraterone, ^{223}radium and cabazitaxel). The ^{223}radium trial also uniquely offered therapy to patients who were unsuitable for or refused docetaxel. The sipuleucel-T trial focused on mCRPC patients who were asymptomatic or minimally symptomatic; most of these patients were chemotherapy naive.

So what is good about the current state of affairs? Patients with mCRPC will soon have access to drugs that target four distinct biological pathways: two new agents that target the androgen axis (abiraterone and MDV3100), the antigen presenting cell (sipuleucel-T), two microtubular targeted agents (docetaxel and cabazitaxel) and a novel bone targeted alpha-emitting radiopharmaceutical (^{223}radium). As a whole, these drugs are relatively well tolerated and will offer patients with mCRPC new options in the years ahead.

What is problematic with this picture? Several issues come to mind: a regulatory process that prioritizes overall survival (OS) end points preferentially targets terminally ill patients who have no chance for cure. For the various post-docetaxel treatment trials, median survivals in the *best* treatment arms were 14.8–18.4 months. Patients with earlier stage disease are clamoring for new agents, but most of the pivotal trials are in late-stage disease and reimbursement guidelines are typically similar to clinical trial inclusion criteria.

The sponsor for the Cougar 302 trial, a test of abiraterone in the pre-docetaxel mCRPC space, has recently reported[7] that the Independent Data Monitoring Committee terminated the trial as a consequence of efficacy. At the same time, it was apparent that OS was not statistically significantly approved in this trial. How the regulatory agencies will approach this trial is not clear given that only improvements in OS and skeletal-related events have been accepted as primary end points in pivotal trials over the past decade.

To date, other than OS and skeletal-related events, there are no clear biomarkers that (from a consensus perspective) predict patient benefit. There is nothing in the way of genetic/molecular biomarkers to serve as prognostic biomarkers that can drive physicians to select one treatment over another. This lack of ability to select the 'right drug for the right patient' is a major shortcoming in the field at this time.

There is an increasingly murky picture going forward as to how to move new agents from experimental to approvable status. What inclusion/exclusion should we use? Should we be exploring new subsets like the very late stage post-docetaxel, post-abiraterone space? What is the proper control group? Newer trials should probably not be incorporating placebo or prednisone or mitoxantrone control groups. How do we control for post-protocol therapies?

Thus far, there are many questions and no answers surrounding optimal sequences and combinations of therapy. These questions need to be answered sooner rather than later. At the same time, we are scientifically moving forward and conceptually addressing new and important questions, the new drugs are truly expensive and beyond some system's capacity to pay (abiraterone copays challenge usage in United States and abiraterone has not been approved in the United Kingdom, primarily for cost-related reasons).

What solutions might be suggested? Many people currently state that the answer is simple, better targeted therapy driven by personalized tumor genetic analysis. Though this is now the 'party line', the vast majority of interesting new and complex genetic alterations[8,9] are 'undruggable' with current approaches. Drugging the 'undruggable' target remains a huge challenge, but it is noted that alpha-particle radiation will kill cells with a wide variety of genetic alterations *via* highly lethal double strand breaks[10] and increasingly alpha-emitting radionuclides are capable of being targeted precisely to specific antigens.[11]

We are desperately in need to something relevant to measure besides OS, especially in immunological trials. Is it possible that functional imaging can fill this gap? New positron emitting imaging agents[12,13] that can assess either functional pathways and/or various tumor-associated antigens, and interesting MRI techniques using hyperpolarized C13 might provide interesting concepts to further explore.[14]

Prognostic and predictive biomarkers are easy to discuss and hard to credential. But the work needs to be done. This will require diligent work with patient cohorts that have careful clinical annotation combined with high-quality assays derived from biological samples that are consistently collected and properly stored.

Strong biology and science are necessary but not sufficient for success. Underlying all of these concepts must be a rational and appropriate level for drug pricing. Pharmaceutical and biotechnology companies face years of effort and uncertainty in an attempt to improve patient's lives and make a reasonable return for their investors. At the same time, governments and other health-care

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Table 1 Pivotal phase III trials reported in metastatic castrate-resistant prostate cancer that have a survival benefit

Trial name	*Treatment/control*	*Hazard ratio (95% CI)*	*Median survival (months)*
TAX 327 Tannock *et al.*[1]	Docetaxel/prednisone *vs.* Mitoxantrone/prednisone	0.76 (0.62–0.94)	18.9 *vs.* 16.5
IMPACT Kantoff *et al.*[2]	Sipuleucel-T *vs.* Non-activated cells	0.78 (0.61–0.97)	25.8 *vs.* 21.7
TROPIC de Bono *et al.*[3]	Cabazitaxel/prednisone *vs.* Mitoxantrone/prednisone	0.70 (0.59–0.83)	15.1 *vs.* 12.7
COU-AA-301 de Bono *et al.*[4]	Abiraterone/prednisone *vs.* Placebo/prednisone	0.65 (0.54–0.77)	14.8 *vs.* 10.9
ALSYMPCA Parker *et al.*[5]	Radium-223/supportive care *vs.* Placebo/supportive care	0.70 (0.55–0.87)	14.9 *vs.* 11.3
AFFIRM Scher *et al.*[6]	MDV3100 *vs.* Placebo	0.63 (0.53–0.75)	18.4 *vs.* 13.6

funding agencies are facing tighter and tighter budget restrictions. Should the pricing of new oncological therapies decline too much, investor's will flee to areas with better returns on invested capital. Should the price for new therapies be too high, health-care expenditures will increasingly be allocated to low cost treatments that are cost-effective but not innovative. Trying to strike the proper balance in this area, inherently filled with dynamic tension, is key for setting the stage for future success in prostate drug development.

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