Novel Strategies to Test Biological Hypotheses in Early Drug Development for Advanced Prostate Cancer

Roberta Ferraldeschi, Gerhardt Attard, and Johann S. de Bono

BACKGROUND: Major advances in our understanding of the underlying biology of prostate cancer have helped to herald a new era in the treatment of castration-resistant prostate cancer (CRPC), with 5 new agents having shown a survival advantage in the last 3 years and an impressive number of promising novel agents now entering the clinic.

CONTENT: We discuss the challenges facing drug development for CRPC and strategies to meet these challenges, with a focus not only on the development of predictive and intermediate endpoint biomarkers, but also on novel hypothesis-testing, biomarker-driven clinical trial designs.

SUMMARY: With several promising agents now entering the clinic, there is increasing pressure to rethink drug development for CRPC to ensure that novel agents are appropriately evaluated and that patients and resources are appropriately allocated. We envision that biomarker-driven, reiterative clinical trials will have a major impact on CRPC treatment through the testing of robust scientific hypotheses with rationally designed drugs and drug combinations administered to selected patients.

Prostate cancer is the most common malignancy in males and a leading cause of cancer mortality in men in Western countries (1). Androgen depletion by medical or surgical castration has been the mainstay of treatment for advanced prostate cancer and remains beyond a doubt the most effective therapeutic option. Androgen deprivation can result in prolonged periods of clinical and biochemical control, but the disease eventually progresses in most men despite ongoing castrate levels of testosterone. Before 2010, castration-resistant prostate cancer (CRPC)2 patients had few treatment options, with the most effective standard chemotherapeutic regimens producing a 2-month improvement in median survival (2, 3). Second-line hormonal manipulations included antiandrogen withdrawal, use of a second-line antiandrogen, inhibition of adrenal steroidogenesis with agents such as ketoconazole, and the use of alternative hormones such as estrogens—all of which showed only modest and transient antitumor activity (4). In 2010, the autologous cellular immunotherapy sipuleucel-T (Provenge; Dendreon) (5) and the novel taxane cabazitaxel (Jevtana; Sanofi-Aventis) (6) were shown to prolong survival significantly and were subsequently approved by the US Food and Drug Administration (FDA). This trend continued in 2011 and 2012, when 3 therapies, the CYP17 inhibitor abiraterone acetate (Zytiga; Janssen Biotech) (7), the bone-targeting agent223Ra dichloride (Alpharadin; Algeta/Bayer Pharma) (8), and the next-generation antiandrogen enzalutamide (Xtandi; Medivation/Astellas) (9), were shown in phase III clinical trials to confer a survival benefit (Table 1).

A decade of scientific discoveries has improved our understanding of the molecular biology underlying prostate cancer progression and has driven the development of these successful new agents. It is probable that most patients with CRPC will now live substantially longer than 5 years ago; however, the effects of 3 or 4 novel agents on the survival prospects of individual patients are unlikely to be cumulative. Indeed, some patients do not respond to therapy, and drug resistance arises in most patients. Currently, no biomarkers are available to ensure the benefit is maximal for an individual patient, to guide selection for specific therapies, or to optimize the sequence of treatments.

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Table 1. Phase III studies showing an improvement in survival for patients with progressive metastatic CRPC.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>Patients, n</th>
<th>Population</th>
<th>Median OS, a months</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT</td>
<td>Sipuleucel-T</td>
<td>Placebo</td>
<td>512</td>
<td>Chemotherapy-naive CRPC</td>
<td>25.8 vs 21.7</td>
<td>Sipuleucel-T approved for chemotherapy-naive patients with asymptomatic or mildly symptomatic CRPC</td>
<td>Kantoff et al. (5)</td>
</tr>
<tr>
<td>TAX 327</td>
<td>Prednisone + docetaxel 75 mg/m² q 3 weeks; prednisone + docetaxel 30 mg/m² q week</td>
<td>Prednisone + mitoxantrone</td>
<td>1006</td>
<td>Chemotherapy-naive CRPC</td>
<td>18.9 vs 17.4 vs 16.5</td>
<td>Docetaxel approved as first-line chemotherapy for CRPC</td>
<td>Tannock et al. (2)</td>
</tr>
<tr>
<td>SWOG 9916</td>
<td>Docetaxel + estramustine</td>
<td>Mitoxantrone + prednisone</td>
<td>770</td>
<td>Chemotherapy-naive CRPC</td>
<td>17.5 vs 15.6</td>
<td>Docetaxel and estramustine not widely used because docetaxel and prednisone considered standard</td>
<td>Petrylak et al. (3)</td>
</tr>
<tr>
<td>TROPIC</td>
<td>Prednisone + cabazitaxel</td>
<td>Prednisone + mitoxantrone</td>
<td>755</td>
<td>Docetaxel-treated CRPC</td>
<td>15.1 vs 12.7</td>
<td>Cabazitaxel approved as second-line chemotherapy for patients previously treated with a docetaxel-containing regimen</td>
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<tr>
<td>COU-AA-301</td>
<td>Prednisone + abiraterone acetate</td>
<td>Prednisolone + placebo</td>
<td>1195</td>
<td>Docetaxel-treated CRPC</td>
<td>15.8 vs 11.2</td>
<td>Abiraterone approved in postdocetaxel setting</td>
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<td>AFFIRM</td>
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<td>18.4 vs 13.6</td>
<td>Interim analysis</td>
<td>Scher et al. (8)</td>
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<tr>
<td>ALSYMPCA</td>
<td>Alpharadin (²²³Ra)</td>
<td>Placebo</td>
<td>922</td>
<td>Docetaxel-treated CRPC</td>
<td>14 vs 11.2</td>
<td>Final analysis</td>
<td>Parker et al. (9)</td>
</tr>
</tbody>
</table>

*a OS, overall survival.*
Several potential new therapeutic targets have been identified, and large portfolios of rationally designed compounds that affect these targets are now competing in the same drug development space. With more agents entering the development phase, however, pressure is increasing to rethink the standard drug development process to ensure that these agents are given the best chance to succeed and that patients acquire maximal benefit with minimal risk. Moreover, the escalating costs of healthcare, the fiscal restrictions of healthcare providers, and the current economic climate are placing substantial pressures on the monetary resources available for new drug development.

Novel agents will continue to be evaluated most easily in the late-stage postchemotherapy setting because of the lack of intermediate endpoint biomarkers. With several lines of standard hormonal and chemotherapy treatment now available, however, late-stage patients may have a more “drug-resistant” phenotype, more extensive disease, and a poorer performance status. New approaches to the design of clinical trials, careful evaluation of regulatory approval strategies (e.g., single vs combinatorial approaches), and the setting(s) in which the drug(s) will be tested (e.g., after abiraterone or after abiraterone and enzalutamide) are required for treating CRPC so that the momentum provided by successful therapeutic trials can be maintained. Careful consideration must now be given to: (a) patient selection for specific molecularly targeted therapies, (b) robust evaluations of strategies for optimizing treatment sequences, and (c) drug combinations for overcoming drug resistance.

This review discusses novel strategies and challenges in early drug development for advanced prostate cancer, with a focus on the development and implementation of predictive and intermediate endpoint biomarkers (Table 2).

From Biology to Hypothesis-Testing, Biomarker-Driven, Early Phase Clinical Trials

CODEVELOPMENT OF THERAPEUTIC AND PARTNER BIOMARKERS

The landscape of oncology therapeutics has shifted in the last decade from cytotoxic compounds to molecularly targeted agents that aim to deliver improved efficacy in molecularly defined susceptible cancers. The use of companion diagnostics in oncology is making the promise of patient stratification and the delivery of precision medicine more of a reality. In 2011 alone, the FDA approved 3 oncology agents indicated for biomarker-identified patient subpopulations: bren-tuximab vedotin (Adcetris; Seattle Genetics) for CD30-expressing Hodgkin lymphoma, crizotinib (Xalkori; Pfizer) for anaplastic lymphoma kinase (ALK)-positive metastatic non–small cell lung cancer, and vemurafenib (Zelboraf; Genentech) for metastatic melanoma with the BRAF (serine/threonine-protein kinase B-raf) V600E mutation (10).

Clinical trials for molecularly targeted therapies are more likely to prove effective when a strong biological hypothesis is evaluated in patients selected on the basis of the presence of a specific molecular aberration. Successful examples of a biomarker-enriched strategy include the use of ERBB2 (receptor tyrosine-protein kinase erbB-2) for predicting the response to trastuzumab in breast cancer (11) and c-kit mutations (mast/stem cell growth factor receptor Kit) for predicting the response to imatinib in gastrointestinal stromal tumors (12). An unselected “all comers” approach has been successful for endocrine therapy, because the fact that most, although not all, prostate cancers are hormone driven, but the evaluation of novel agents targeting a specific molecular aberration has a high likelihood of late-stage attrition if patient selection is not
used (13). In addition, this approach has not only a high risk of discarding a drug that is potentially effective in a subset of patients but also a risk of exposing nonsensitive patients to costly and potentially toxic therapies. Several recent failures have highlighted the need for early phase studies to better predict phase III outcomes in CRPC and for improvements in the drug development process (14). We envision that future early phase clinical trials for prostate cancer will focus on the development of predictive tissue and circulating biomarkers in parallel with new molecularly targeted agents. That would improve the selection of patients most likely to benefit from therapy (Table 2).

The codevelopment of a predictive biomarker and a targeted drug requires robust biological hypotheses and preclinical data that support the use of the biomarker in therapeutic decision-making and analytically validated assays that can detect the biomarker in clinical samples. Furthermore, the proportion of patients who are likely to benefit from treatment and the magnitude of that benefit should be sufficient to warrant the use of the biomarker. Our conviction is that early trials of new agents should involve the use, wherever possible, of predictive and/or enrichment biomarkers for patient selection, together with pharmacodynamic biomarkers that test for target modulation and biological activity according to what we have termed the “pharmacologic audit trail” (15) (Fig. 1). Moreover, identification, validation, and clinical qualification of intermediate endpoint biomarkers, including explorations of yet unestablished but potentially superior imaging modalities (including multiparametric magnetic resonance imaging and positron-emitting tomography studies with various positron-emitting radionuclides such as fluorinated choline and fluorinated dihydrotestosterone), will also be crucial to minimize the time on treatment that does not impart benefit to the patient. Integrating the preclinical and clinical aspects of drug development is key to achieving this goal (Fig. 2).

The level of collaboration resources, infrastructure, and cohesive efforts required for developing and integrating biomarkers in early clinical trials must not be underestimated. Biomarkers must undergo a rigorous process of optimization and analytical validation before they can be implemented. Prospective collections of tumor tissue samples should be embedded in trial protocols whenever possible to allow proof-of-concept analyses and the development of additional biological hypotheses that could be tested with a iterative hypothesis-testing approach to therapy. Major investments in resources and infrastructure that facilitate biomarker analyses should also be made (16). Paradoxically, the codevelopment of biomarkers and therapeutic agents may slow down the drug development process because of the extensive (and costly) development processes required not only for the therapeutic agent but also for companion diagnostics and biomarkers. The ability of imatinib to generate revenues of >$4 billion per year in less common molecularly selected disease subtypes encourages the pursuit of more precisely stratified population strategies.

**Adaptive Trial Designs for Molecular Stratification in the Absence of a Validated Predictive Biomarker**

Often (and usually for prostate cancer), biomarkers that identify molecular subtypes with a predicted sensitivity for a targeted agent are not immediately available. Identifying possibly enrichment or putative predictive biomarkers early on and then continuously integrating acquired biomarker data into the ongoing trials are increasingly being recognized as necessary and as the most ethical means for minimizing harm and maximizing patient benefit.

Adaptive designs use data gathered as the trial progresses for changing some aspect of the trial and/or its statistical analysis procedures midstream without undermining the integrity of the trial (17). Adaptive trials have increasingly been adopted over the last decade, a trend that has been encouraged by the FDA and the European Medicines Agency (18–19) and fueled by the need to reduce late-stage attrition rates and the costs of
novel anticancer therapeutics. Recent examples of clinical studies that have used an adaptive strategy include the BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial for non–small cell lung cancer (20) and the I-SPY 2 Trial (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2) for locally advanced breast cancer (21). Our TO-PARP (Trial of Olaparib in Patients with Advanced Castration-Resistant Prostate Cancer), one of the first adaptive, biomarker-driven trials for CRPC, has recently started recruitment (NCT01682772).

The rationale for examining the antitumor activity of olaparib, a potent poly(ADP-ribose) polymerase 1 (PARP1) inhibitor for prostate cancer, had its origins in an increasing appreciation of the multiple targetable...
roles that PARP1 plays in this disease, including mediating DNA repair and regulating the activity of key factors such as ERG (ETS related gene) (22). It is increasingly evident that a subgroup of prostate cancers manifest underlying defects in DNA repair (23). Such defects not only may lead to the accumulation of genetic rearrangements and mutations but also may confer a vulnerability unique to a synthetic lethality approach (24). The TO-PARP design incorporates multiple prespecified design adaptations, the broad aims of which are to: (a) identify a sensitive subgroup of sporadic CRPC patients who would benefit significantly from PARP inhibition, and (b) accelerate the development of olaparib for this target population. This study is divided into 3 distinct parts (Fig. 3). The initial 2 parts of the study are nonrandomized and involve a predictive biomarker identification phase (test set cohort) and a subsequent prospective validation phase (validation set cohort). Built-in adaptations include: (a) early-stopping rules for trial futility or significant efficacy, (b) interim analyses, (c) use of putative intermediate biomarkers of response [e.g., enumeration of circulating tumor cells (CTCs)], and (d) seamless transition to a randomized trial. Putative candidate biomarkers to be explored in the first part of the study include the presence of rearrangements of ETS genes based on preclinical evidence that tumors with rearranged ETS have increased sensitivity to PARP1 inhibition (22); and the status of homologous recombination DNA repair genes that can associate with a synthetic lethal vulnerability to PARP1 inhibition (24).

Importantly, an adaptive trial design may provide a framework for the codevelopment of drugs and companion diagnostics in the early clinical setting, with identification of relevant biomarkers and subsequent clinical qualification. We envision an adaptive design to be particularly relevant in studies of novel agents that target complex pathways that can be disrupted at multiple levels. An example is the PI3K/AKT pathways, which probably will require assessing different pathway components with a combination of biomarkers to identify sensitive patient populations. Adaptive designs offer flexibility, increase efficiencies in resource utilization (fewer study participants, shorter durations, reductions in costs and times to market), increase the likelihood of later success, and provide a better understanding of treatment effects (by identifying sensitive populations).

**SELECTION OF TRIAL ENDPOINTS**

The standard criteria for measuring a radiologic response [Response Evaluation Criteria in Solid Tumors (RECIST)] are frequently not applicable for patients with advanced prostate cancer, because metastases are often predominantly in bone. This has led to the use of changes in prostate-specific antigen (PSA) concentrations as the primary endpoint in phase II trials. Although PSA is a useful biomarker of androgen receptor (AR) signaling, PSA-decrease algorithms do not provide robust intermediate endpoints for overall survival benefit in CRPC. In 2008, a committee of investigators defined new consensus criteria for planning and conducting trials for advanced prostate cancer in an effort to maximize the ability of phase II trials to select promising therapies for moving toward definitive testing. The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) has recommended an increased emphasis on time-to-event endpoints (such as failure to progress or time to progression) and a reduced reliance on solely PSA changes in phase II clinical trials (25). Until better intermediate endpoints are developed, treatment should continue for at least 12 weeks to ensure that drug exposure is adequate before a switch in treatment is considered. Furthermore, the working group recommends that bone scans should be reported as “new lesions” or “no new lesions” and that at least 2 new bone lesions should be present to qualify disease progression. Increasingly, composite endpoints that collectively assess different components of response are being used as primary endpoints in phase II studies. These endpoints include RECIST-defined radiologic responses for patients with measurable disease, decreases in PSA of \( \geq 50\% \) or \( \geq 30\% \), evidence of new bone lesions, and changes in CTC counts in late-stage patients (26–28).

**ADDRESSING BOTH PHASE I AND PHASE II TRIAL QUESTIONS IN A SINGLE STUDY PROTOCOL**

To allow better selection of a potentially effective dose, phase I trials increasingly are testing biological hypotheses besides evaluating safety and toxicity. This approach includes assessing multiple biomarkers to determine target engagement and biological effect (pharmacodynamic biomarker), defining a biologically active dose, and identifying the patient population most appropriate for a given therapy (predictive biomarkers) (Fig. 2). The use of “seamless” designs, in which a phase I protocol defines an expansion to phase II a priori, were used in early clinical trials of abiraterone and enzalutamide (26, 27). Such designs offer the prospect of optimizing and expediting drug development. Moreover, because targeted agents are typically better tolerated than cytotoxics, dose escalation to the maximally tolerated dose may not be feasible. Phase I trials with simultaneous cohort expansion at \( \geq 1 \) dose level provide more comprehensive information on safety, pharmacodynamic effect, and antitumor activity at multiple dose levels within a relatively short time. This strategy is considered
useful for optimizing the selection of dose and dosing schedule (27).

**Evaluating Combinatorial Drug Therapy**

Drug resistance to conventional cytotoxic agents and to novel molecularly targeted agents continues to pose a challenge in the clinical management of cancer patients. The improvements in our understanding of redundant and compensatory signaling networks in cancer and in our awareness of substantial intrapatient molecular heterogeneity support a role for rational combinatorial targeted therapeutic approaches (29). Examples of rational approaches to combination therapy for CRPC that have been supported by preclinical

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**Fig. 3. TO-PARP trial: adaptive study design.**

The TO-PARP trial is an adaptive biomarker-driven, multicenter phase II study that is divided into 3 parts (A, B, and C). Part A is designed to evaluate the activity of olaparib in unselected patients with advanced CRPC and to allow the development of putative predictive biomarkers of response to olaparib [including next-generation sequencing of DNA-repair genes such as breast cancer 1, early onset (BRCA1) and breast cancer 2, early onset (BRCA2)]. The first stage will recruit 30 patients. If ≥3 responses are observed, the study will be terminated. If ≥4 but <15 patients meet the primary endpoint in the first stage of part A, patient accrual will continue to 45 patients. If the response rate achieved at the end of part A is ≥50%, further evaluation in a randomized trial of an unselected group of patients will then be pursued (part C). If the response rate is <50% but significant antitumor activity is reported (9–22 responding patients of 45), part B will be conducted in 45 more patients selected for the presence of the putative predictive biomarkers of olaparib sensitivity identified in part A. Part B will prospectively qualify these putative predictive biomarkers. If a response rate >50% is identified in this selected population, a randomized trial will be pursued in that molecularly selected patient population (part C). pts, patients.
Ongoing Challenges in Drug Development for Advanced Prostate Cancer

BIOLOGICAL HETEROGENEITY OF PROSTATE CANCER

In the last decade, next-generation sequencing and “omics” technologies have dramatically changed our appreciation of the genetic, epigenetic, and phenotypic complexity of prostate cancer (23, 33, 34). Recurrent genetic aberrations, most commonly caused by chromosomal rearrangements and copy number gains and losses [such as fusions in the v-ets erythroblastosis virus E26 oncogene homolog 1 (avian) (ETS)3 gene family and phosphatase and tensin homolog (PTEN) loss] have been identified in many patients (33, 34). In addition, the mutational landscape of CRPC has increasingly been elucidated as evidence has accumulated for recurrent mutations that have potential as candidates for new drug development (23). Our increasing understanding of this genetic heterogeneity helps explain the observed clinical diversity and provides a basis for molecular stratification of this disease, which until now has been treated as a single entity (34). In addition to interpatient heterogeneity, substantial intratumor heterogeneity in CRPC may also contribute to the molecular complexity of this disease, the variable responses to treatment, and drug resistance (35).

INTERMEDIATE ENDPOINTS

Overall survival remains the primary endpoint for advanced prostate cancer and for the regulatory approval of novel agents. Consequently, phase III clinical trials have traditionally involved large patient cohorts and an extended follow-up period. There is an urgent need to identify and clinically qualify intermediate endpoints for survival that could be used to guide early drug development and shorten the duration of pivotal phase III trials. That would accelerate both regulatory approval and widespread delivery of novel and effective therapeutics. In addition, several novel agents have recently been approved, and numerous others are in the late stages of development. Therefore, demonstrating a survival benefit in early-stage CRPC is going to become increasingly more difficult because of possible crossover to other effective treatments for patients treated in a study’s control arm.

CTC enumeration is of prognostic value in prostate cancer and other cancers, and several studies are evaluating changes in the CTC count as intermediate endpoints for survival. CTC enumeration before and after initiating treatment has been associated with overall survival in the randomized phase III trial of abiraterone; however, proving surrogacy for decreases in CTC counts remains a major challenge (36). Other potential intermediate endpoints that have been suggested include radiologic progression-free survival, time to chemotherapy, and time to development of metastases; however, none of these variables...
have been clinically qualified as bona fide surrogates of overall survival.

ACQUIRING CRPC TISSUE

We hypothesize that molecular characterization of both metastatic CRPC tissue and primary archival tissue is critically important, but the acquisition of CRPC tissue presents a challenge, owing to the predominance of bone metastases and the difficulties of extracting tumor nucleic acids from such metastases. Furthermore, analyses of intratumor heterogeneity would require access to adequate samples from different regions of tumors and from both primary and multiple metastatic sites.

Strategies to assess CTCs and other circulating biomarkers, such as tumor DNA/RNA in plasma or exosomes, have been pursued for real-time disease characterization without the need for repeated invasive biopsies. Studies to date have used single-assay analysis on CTCs using fluorescence in situ hybridization for gene amplifications and fusions [e.g., rearrangements in ERG, v-ets erythroblastosis virus E26 oncogene homolog (avian)], and immunofluorescence for biomarker expression (37). Next-generation cell-capture devices and single-cell genomics technologies are bringing us closer to genomic profiling of these tumors via less invasive means (38).

CROSS-RESISTANCE

The significant survival advantage demonstrated for abiraterone and enzalutamide therapy in patients with metastatic CRPC has provided the clinical evidence that targeting AR signaling is a rational and effective approach for CRPC. The hypothesis that continued activation of the AR and/or other steroid receptor–signaling pathways leads to drug resistance in a substantial proportion of CRPC patients who experience disease progression while on abiraterone and/or enzalutamide therapy remains to be proved. A proportion of the patients who experience disease progression while on abiraterone and enzalutamide with a rise in PSA are likely to benefit from additional hormonal manipulations with novel AR-targeting therapeutics (multiple novel agents are currently in clinical development). It is probable, however, that the response rate will decrease with each treatment. Novel approaches such as direct inhibition of the AR amino-terminal domain (39) or the use of AR-degrading agents (40) therefore may be required to achieve the next substantial improvement in outcome for CRPC patients.

TREATMENT BEYOND PROGRESSION

A critical challenge is when to discontinue or change treatments. We hypothesize that patients may continue to derive benefit from continuous maximal inhibition of AR with agents such as abiraterone or enzalutamide, despite a rising PSA. Urgently required are studies that evaluate the additional benefit of continuing treatment after rise in PSA and commencing subsequent therapies. Addressing this question in the absence of endpoints based on time-to-event may not be feasible, however.

Conclusions

The past several decades have witnessed an improved understanding of the underlying biology of CRPC and better ways for developing appropriate drugs for use in the clinic. The challenge now is to maintain this pace of progress. We hypothesize that biomarker-driven iterative clinical trials will have a major impact on CRPC treatment by testing robust scientific hypotheses through the use of rationally designed drugs and drug combinations. Facilitating a rational approach by increasing the use of biomarkers at all stages of preclinical and clinical drug development will accelerate the progression of promising drugs from phase I studies to phase III studies, maximize the benefit for patients, decrease late drug development attrition, and reduce the overall costs of drug development.

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