Prostate cancer

Unmet needs & challenges in clinical trials

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Introduction

Prostate cancer is a typical example of a cancer indication where clinical researchers have to overcome several challenges to be successful. This white paper presents an analysis of the challenges involved in clinical development of potential drugs for prostate cancer, including medical, operational and scientific perspectives.
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Executive summary

Other than skin cancer, prostate cancer is the most common cancer in American men. The American Cancer Society estimates that in 2013, about 238,590 new cases of prostate cancer will be diagnosed, and around 29,720 men will die of prostate cancer; some one in six men will be diagnosed with prostate cancer during his lifetime. Due to its widespread incidence and unmet medical need, prostate cancer is the target of a significant proportion of clinical research and ranks fifth in terms of number of Development Programs in phase I to phase III, after breast cancer, leukemia, colorectal cancer and lymphoma.

Prostate cancer faces almost all the main challenges typically found in oncology clinical development, including:

1. **Operational**: The prostate cancer patient pathway has always been a critical component of clinical trials for this patient population, involving urologists, medical oncologists, as well as primary care physicians. Mapping this pathway at various sites becomes crucial for the recruitment and retention of patients in prostate cancer studies.

2. **Medical**: For both non-metastatic castration resistant prostate cancer (a constantly growing patient population, in need of innovative effective drugs) and metastatic castration resistant prostate cancer there is a high unmet clinical need for novel therapies aimed at new molecular targets.

3. **Scientific**: As we enter the era of personalized medicine, it is essential to identify predictive biomarkers for currently approved therapies and for those in development. Recently, many therapeutic agents for prostate cancer have been approved that target the androgen receptor and/or the prostate tumor microenvironment. Each of these therapies has modestly increased patient survival. A better understanding of when in the course of prostate cancer progression specific therapies should be applied, and of what biomarkers indicate when resistance arises, would almost certainly improve outcomes achieved by these therapies.

4. **Study population definition**: The Castration Resistant Prostate Cancer (CRPC) population can be divided in four main subsets of patients: those without evidence of metastatic involvement (M0); those with metastatic (M1) asymptomatic or mildly symptomatic disease that can postpone chemotherapy; symptomatic M1 patients eligible to receive the standard chemotherapy; and M1 patients post-chemotherapy.

5. **Imaging Methodology**: In the setting of CRPC, approved drugs, including cytotoxic agents, have been shown to provide a benefit in terms of disease control that translates into prolonged overall survival (OS). The disease control includes tumor shrinkage and disease stabilization, and requires a careful and unbiased assessment to accurately evaluate the non-progressing pool of patients. In addition, the study population has to be defined as non-metastatic or metastatic. Therefore, there is the need for standardized, high resolution imaging techniques and for centralized recording of outcomes to ensure maximum quality.

Understanding these key challenges is the first step to successfully manage prostate cancer trials.

This white paper is a detailed analysis of all these aspects, offering suggestions on how to manage trials effectively in this indication.
Section 1 – Prostate cancer: An overview

Other than skin cancer, prostate cancer is the most common cancer in American men. The American Cancer Society estimates that in 2013, about 238,590 new cases of prostate cancer will be diagnosed, and around 29,720 men will die of prostate cancer; some one in six men will be diagnosed with prostate cancer during his lifetime. Prostate cancer occurs mainly in older men. About six cases in 10 are diagnosed in men aged 65 or older, and it is rare before age 40. The average age at the time of diagnosis is about 67.

Prostate cancer is the second leading cause of cancer death in American men, behind only lung cancer. About 1 man in 36 will die of prostate cancer.

In the minority of patients whose cancers are aggressive or advanced, therapeutic options include prostatectomy, radiation therapy and, more commonly, androgen-deprivation therapy.

Prostate cancer deaths are typically the result of metastatic castration-resistant prostate cancer (mCRPC), and historically the median survival for men with mCRPC has been less than two years, despite the recent availability of novel treatments for mCRPC that have proven to improve survival. mCRPC remains an incurable disease.

The exact mechanism of transition from castration-sensitive prostate cancer to castration-resistant disease is not fully understood. Despite castrate levels of androgens, the androgen receptor (AR) remains active and continues to drive prostate cancer progression. This understanding has led to the development of novel agents aimed at further decreasing androgen production or blocking AR function. However, there are also many other biologic pathways that function independently of androgen signaling, resulting in CRPC. With a greater understanding of the tumor biology, there is hope for continued development of innovative treatment options that will improve survival for men with mCRPC.

The treatment of mCRPC has dramatically changed over the past decade. Prior to 2004, once patients had failed primary androgen deprivation, treatments were administered solely for palliation. Docetaxel was the first chemotherapy agent that improved survival for these patients. Since the approval of docetaxel, five additional agents that show a survival benefit have been approved by the US Food and Drug Administration (FDA) on the basis of randomized clinical trials. These include enzalutamide and abiraterone, two agents designed specifically to affect the androgen axis; sipuleucel-T, which stimulates the immune system; cabazitaxel, a chemotherapeutic agent; and alpharadin (or radium Ra 223 dichloride), an alpha particle-emitting radioactive therapeutic agent. These agents have been tested in multiple “disease states” of CRPC to determine whether or when patients might benefit from each treatment. Other potential treatments for mCRPC have been shown to improve outcomes, but have not yet been approved by regulatory authorities. Despite recent advances, the prognosis for patients with CRPC with disseminated metastatic spread remains poor, with a significant impact on patients’ quality of life resulting predominantly from skeletal metastases. Non-metastatic CRPC patients represent a constantly growing population in need of innovative and effective drugs to slow disease progression, and improve patient prognosis and quality of life by delaying metastatic spread and the need for highly toxic chemotherapeutic agents. It is expected that over the next few years, more novel drugs will be developed and approved for this indication, once again shifting the treatment landscape of prostate cancer.
Epidemiology

Worldwide, prostate cancer is the second most frequently diagnosed cancer of men (899,000 new cases, 13.6% of the total) and the fifth most common cancer overall. Incidence rates for prostate cancer (Figure 1) vary by more than 25-fold worldwide; the highest rates are in Australia/New Zealand (104.2 per 100,000), Western and Northern Europe, Northern America, largely because the practice of prostate specific antigen (PSA) testing and subsequent biopsy has become widespread in those regions. Nearly three-quarters of the registered cases occur in developed countries and incidence rates are relatively high in certain developing regions such as the Caribbean, South America and sub-Saharan Africa. The lowest age-standardized incidence rate is estimated in South-Central Asia (4.1 per 100,000). In the United States, the estimated incidence is of 241,740 new cases diagnosed and approximately 28,170 men expected to die of the disease in 2012.

Figure 1 Estimated prostate cancer incidence worldwide in 2008

Because PSA testing has a much greater effect on diagnosed incidence than on mortality, there is less variation in mortality rates worldwide (10-fold) than is observed for incidence (25-fold), and the number of deaths from prostate cancer is almost the same in developed and developing regions. Mortality rates (Table 1 and Figure 2) are generally high in predominantly black populations (Caribbean, 26.3 per 100,000 and sub-Saharan Africa, ASRs 18-19 per 100,000), very low in Asia (ASR 2.5 per 100,000 in Eastern Asia for example) and intermediate in Europe and Oceania.
### Table 1 Prostate cancer incidence and mortality worldwide in 2008 – summary

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<th>Estimated numbers (thousands)</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
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<tr>
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<td>WHO Western Pacific region (WPRO)</td>
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<td>33</td>
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<td>United States of America</td>
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<tr>
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<tr>
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<td>10</td>
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<tr>
<td>European Union (EU-27)</td>
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<td>71</td>
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</table>

### Figure 2 Estimated prostate cancer mortality worldwide in 2008

In the minority of patients whose cancers are aggressive or advanced, therapeutic options include prostatectomy, radiation therapy and, more commonly, androgen-deprivation therapy.
Diagnosis

Most prostate cancers are first found during screening with a prostate-specific antigen (PSA) blood test and/or a digital rectal exam (DRE).

Early prostate cancers usually do not cause symptoms, but more advanced cancers are sometimes first found because of symptoms they cause. Whether cancer is suspected based on screening tests or symptoms, the actual diagnosis can only be made with a prostate biopsy.

The prostate-specific antigen (PSA) blood test is used mainly to try to find prostate cancer early in men without symptoms. But it is also one of the first tests done in men who have symptoms that might be caused by prostate cancer.

In men just diagnosed with prostate cancer, the PSA test can be used together with physical exam results and tumor grade from the biopsy, to help decide if other tests (such as CT scans or bone scans) are needed.

The PSA test is a part of staging: very high levels indicate the likelihood that prostate cancer has spread beyond the prostate. PSA tests are also an important part of monitoring prostate cancer during and after treatment.

Transrectal ultrasound (TRUS) is often used to look at the prostate when a man has a high PSA level or has an abnormal DRE. It is also used during a prostate biopsy to guide the needles into the right area of the prostate. TRUS can be used to measure the size of the prostate gland, which can help determine the PSA density and may also affect which treatment options a man has. TRUS is also used as a guide during some forms of treatment such as brachytherapy (internal radiation therapy) or cryosurgery.

A core needle biopsy is the main method used to diagnose prostate cancer. This is usually done by a urologist, using transrectal ultrasound to guide the biopsy.

Pathologists grade prostate cancers according to the Gleason system. This system assigns a Gleason grade, using numbers from 1 to 5 based on how much the cells in the cancerous tissue look like normal prostate tissue:

- Cancers with a Gleason score of 6 or less are often called well-differentiated or low-grade.
- Cancers with a Gleason score of 7 may be called moderately differentiated or intermediate-grade.
- Cancers with Gleason scores of 8 to 10 may be called poorly differentiated or high-grade.

The higher the Gleason score, the more likely it is that prostate cancer will grow and spread quickly.

Other information in a biopsy report will include:

- The number of biopsy core samples that contain cancer (for example, “7 out of 12”).
- The percentage of cancer in each of the cores.
- Whether the cancer is on one side (left or right) of the prostate or both sides (bilateral).

Other terminology used in prostate cancer diagnosis includes:

- **Prostatic intraepithelial neoplasia (PIN):** This is confined to the prostate gland and is often divided into low-grade and high grade. Many men begin to develop low-grade PIN at an early age but do not necessarily develop prostate cancer.

- **Atypical small acinar proliferation (ASAP):** This is sometimes just called atypia. In ASAP, the cells look as if they might be cancerous when viewed under the microscope, but there are too few of them to be sure. If ASAP is found, there’s a high chance that cancer is also present in the prostate, which is why many doctors recommend getting a repeat biopsy within a few months.
• **Proliferative inflammatory atrophy (PIA):** In PIA, the prostate cells look smaller than normal, and there are signs of inflammation in the area. PIA is not cancer, but researchers believe that PIA may sometimes lead to high-grade PIN or to prostate cancer directly.

The imaging tests used most often to look for prostate cancer spread include:

• **Bone scan:** If prostate cancer spreads to distant sites, it often goes to the bones first. To make an accurate diagnosis, other imaging tests such as plain x-rays, CT or MRI scans, or even a bone biopsy might be needed.

• **Computed tomography (CT):** This is used to evaluate the primary tumor, lymph node involvement and distant metastases.

• **Magnetic resonance imaging (MRI):** MRI scans can be helpful in looking at prostate cancer. They can produce a very clear picture of the prostate and show whether the cancer has spread outside the prostate into the seminal vesicles or other nearby structures.

• **ProstaScint scan:** Like the bone scan, the ProstaScint scan uses an injection of low-level radioactive material to find cancer that has spread beyond the prostate.

• **Lymph node biopsy:** This can determine whether the cancer has spread from the prostate to nearby lymph nodes.

• **Laparoscopic biopsy:** A laparoscopic biopsy is uncommon and is performed through small incisions in the abdomen to introduce the laparoscope, a long, slender tube with a small video camera on the end. The surgeon can take tumor tissue samples and remove lymph nodes for pathological evaluation. The recovery from this procedure usually takes one or two days, leaving small residual scars.

• **Fine needle aspiration (FNA) of lymph nodes.**

European and American Cancer Society guidelines for the early detection of prostate cancer include annual screening by digital rectal examination (DRE) and serum prostate specific antigen (PSA) levels for men aged 50 years or older who have a 10-year life expectancy.

The measurement of PSA level has revolutionized the diagnosis of prostate cancer. This marker is used for early diagnosis and monitoring for disease recurrence. PSA is the most commonly used biochemical marker for prostate cancer and currently the only widely accepted screening tool for this cancer (apart from DRE); it is prostate specific but not prostate cancer specific. Any process that disrupts the normal architecture of the prostate allows diffusion of PSA into the stroma and microvasculature. The level of PSA is a continuous parameter: the higher the value, the more likely is the existence of this tumor. Although this molecule has an important role in the diagnosis and management of prostate cancer, it has limited usefulness in the routine clinical setting.

Despite its limitations, PSA remains the only generally accepted biomarker for this cancer. To improve on traditional serum PSA, other tests based in PSA are being developed. Although PSA has been used broadly for a substantial amount of time, Prostate Cancer Gene 3 (PCA3), a prostate but not cancer-specific marker, has been recommended as a molecular marker. PCA3 is a messenger RNA (mRNA) that is found specifically in cancer tissue, which can be detected in urine after DRE. Several studies claim a better area under curve (AUC) for diagnosis than PSA, as well as an improved prognostic value. Further research into this topic suggests that a panel of markers will work better than a single one in the diagnosis and prognosis of prostate cancer.

**Castration resistant prostate cancer**

Various terms have been used to describe prostate cancer that relapses after initial hormonal ablation therapy, including hormone-refractory, androgen-independent and hormone-independent cancers. In recent years, the term castration resistant prostate cancer (CRPC) has become more frequently used than hormone refractory or androgen-independent prostate cancer. This is based predominantly on recent findings suggesting that advancing prostate cancer is not uniformly refractory to further hormonal
manipulation and that androgens and disease progression are frequently dependent on androgen receptor interactions. Castration-resistant prostate cancer, which is still hormone sensitive, has been clearly characterized, with new drugs targeting the AR, such as MDV3100 (enzalutamide), or androgen synthesis, via CYP 17 inhibition, such as abiraterone acetate or TAK700.

**Biology and genetics**

According to European Association of Urology (EAU) guidelines, CRPC can be defined as follows:

- Castrate serum levels of testosterone < 50 ng/dL or < 1.7 nmol/L.
- Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA 2 ng/mL.
- Anti-androgen withdrawal for at least 4 weeks for flutamide and for at least six weeks for bicalutamide.*
- PSA progression, despite consecutive standard hormonal manipulations.
- Progression of osseous or soft tissue lesions.†

* Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done to fulfill the criteria for CRPC if patients have been treated with anti-androgens in the context of maximum androgen blockade or step-up therapy following PSA progression after failure of LHRH treatment.

† Progression or appearance of two or more bone lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumors) with nodes > 2 cm in diameter.

CRPC is an advanced form of prostate cancer characterized by disease progression following surgical or pharmaceutical (androgen deprivation) castration. The process by which prostate cancer cells become castration resistant is unclear, but it has been proposed that androgen ablation provides a selective advantage to androgen-independent cells, which grow and eventually repopulate the tumor. Compared with castration-sensitive prostate cancer, the prognosis for patients with CRPC is poor and survival is reduced.

An alteration in normal androgen signaling is thought to be central to the pathogenesis of CRPC. It is mediated through two main, overlapping, mechanisms, which are androgen-receptor (AR)-independent and AR-dependent.

AR-independent mechanisms may be associated with the deregulation of apoptosis through the deregulation of oncogenes. High levels of bcl-2 expression are seen with greater frequency as prostate cancer progresses. The regulation of microtubule integrity may be a mechanism through which bcl-2 induces its antiapoptotic effect. Indeed, most drugs that are active in CRPC work by inhibiting microtubule formation. The tumor suppressor gene p53 is more frequently mutated in CRPC. Overexpression of bcl-2 and p53 in prostatectomy specimens has been shown to predict an aggressive clinical course. Clinical trials are underway to target the bcl-2 pathway, and the MDM2 (mouse double minute 2) oncogene and the PTEN (phosphatase and tensin homolog) suppressor gene may also be involved.

AR-dependent mechanisms comprise the main pathway for disease progression. Ligand-independent androgen receptor (AR) activation has been suspected, such as the tyrosine-kinase-activated pathway [insulin-like growth factor-1, keratinocyte growth factor, and epidermal growth factor (EGF)]. EGF is a potent mitogen of prostate stromal and epithelial cells. It is produced in high levels locally and acts as a paracrine stimulator. In AR-independent tumors, autocrine stimulation may become more important, which could allow unregulated growth. Androgen receptor amplification and overexpression are observed in one-third of CRPC tissues and may lead to AR hypersensitivity. Androgen receptor mutations may lead to a functional change in receptor function. At the same time, there is an intracellular increase in androgens from in-situ conversion. This increase may be secondary to an increase in the enzymes involved in intracellular androgen synthesis. Androgen receptor mutations are found in only a subpopulation of tumor cells, therefore they are unlikely to be responsible for the entire spectrum of the AR-independent state.

The AR mutations might be related to the selective pressure of anti-androgens. The recent discovery of gene fusion between the androgen driven TMPRSS2 and the EGR-ETS oncogene family raises the question...
of oncogene regulation through androgen regulation pathways. In gene fusion, an androgen-responsive element from an androgen-regulated gene becomes associated with genes that are usually not androgen-regulated, so that they too become subject to androgen regulation. Currently, their implication in CRPC is hypothetical. Even in castrated patients, metastatic tissues have repeatedly shown high levels of androgens, suggesting a high level of intracrine synthesis. It is possible that a high intraprostatic cholesterol level can activate specific androgen.

To better describe the biological changes occurring in the different phases of evolution of prostate cancer a new molecular classification of prostate cancer progression based on three phases has been proposed, as follows:

- An endocrine-driven phase which is dependent on the presence (and biologic levels) of dihydrotestosterone (DHT) and driven by the conversion of testosterone to DHT by 5α-reductase enzymes.
- A micro-environment-dependent phase which encompasses the transition from endocrine-driven to paracrine-driven prostate cancer, and which indicates the onset of potentially lethal disease.
- A tumor cell autonomous phase, which can be characterized clinically by the presence of a large tumor mass in the prostate itself, or in the lymph nodes, and visceral metastases without a commensurate rise in the patient’s PSA level (with predominantly lytic bone metastases if bone metastases are present).

CRPC is usually a debilitating disease, often affecting the elderly male as shown in Table 2. However, a significant proportion of patients are fit for active anti-cancer medical treatment, as shown in Table 3. A multidisciplinary approach is often required with input from medical oncologists, radiation oncologists, urologists, nurses, psychologists and social workers.

### Table 2 Castration resistant prostate cancer demographics (IPSOS data)

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<th>Patient age groups</th>
<th>France Total %</th>
<th>Germany Total %</th>
<th>Italy Total %</th>
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*Source: IPSOS Healthcare-Global Oncology Monitor; Assessed on March 2013*
Table 3 Castration resistant prostate cancer eastern cooperative oncology group (ECOG; IPSOS data)

<table>
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<tr>
<th>Performance - ECOG</th>
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<td>1%</td>
<td>-</td>
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Source: IPSOS Healthcare-Global Oncology Monitor; Assessed on March 2013

Men with metastatic castration-resistant prostate cancer (mCRPC) have a poor prognosis with a median survival of 1–2 years, and until recently, treatment options that improved survival in this setting were limited to docetaxel-based regimens. The responses to docetaxel and prednisone are generally short-lived, with a modest survival benefit.

Recent major advances have resulted in the regulatory approval of sipuleucel-T and cabazitaxel in 2010, of abiraterone acetate (AA) in 2011, of enzalutamide in 2012 and of alpharadin in 2013 for mCRPC patients.

Despite these additions to the therapeutic arsenal for this patient population, mCRPC remains incurable and the demand for novel therapies will continue with the pursuit of new druggable targets.

In the meantime, several highly promising candidates/regimens have failed in late stages of development; challenges remain for clinical scientists to improve upon existing treatment paradigms and develop more effective strategies for mCRPC. It is vital to optimize target selection, design meaningful outcome measures, and advance biomarker development with implementation in future clinical trials.

Standard of care and guidelines

Treatment options have, until very recently, been limited mainly to symptomatic relief of bone metastases, which are more common in CRPC than in castration-sensitive disease.

Defining epidemiological parameters of disease is an essential component of understanding how, when and where the disease develops; knowledge of the natural history of the disease and the likely outcomes of disease enable effective targeting and development of treatments.

To give a clear picture of the burden of CRPC, one must take into account the prevalence of the disease, relative timing of onset in relation to prostate cancer diagnosis, characteristics of the patients including demographics and comorbidity, onset of metastatic disease, and likely survival. There is, however, a paucity of epidemiological evidence specifically characterizing CRPC outside of controlled trial settings in which patients may not represent the general population and normal disease progression.

This may result in suboptimal disease management; for example, identifying patients with CRPC who are at risk of developing metastases is currently hindered by poor understanding of the epidemiology of CRPC. Identifying individuals with CRPC may seem straightforward to treating physicians, who are responsible for managing this progression of the disease after castration treatment.

Characterization of the disease in epidemiological terms – for example incidence, prevalence and survival – is, however, less clear. This may be attributed at least in part to the difficulty in defining, and hence studying, the patient population.
The varying terminology – CRPC, HRPC (hormone refractory), AIPC (androgen independent), ERPC (endocrine resistant) – reflect subtle differences in definition that may hinder comparison of research.

Physicians may also use different methods in diagnosis: PSA testing, development of metastases or other factors may determine whether a patient is defined as CRPC.

CRPC is a heterogeneous disease, and despite the availability of such practical guides to diagnose CRPC, in practice, these factors may vary.

Furthermore, treatment pathways and clinical practice, in particular, the stage in the disease at which androgen-deprivation therapy is initiated, vary markedly between geographical locations and even individual clinics.

National Comprehensive Cancer Network Guidelines are available for prostate cancer (NCCN Guidelines Version 4.2013), providing treatment diagnostic and treatment guidelines for prostate cancer, including treatment guidelines for the advanced prostate cancer negative or positive for metastases. American Urological Association (AUA) Guideline on Castration-Resistant Prostate Cancer was also published in 2013.

Guidelines on Prostate Cancer are also available from the European Association of Urology. These state that for the patient with progressive disease after ADT, there are many therapeutic options. They include antiandrogen withdrawal, addition of anti-androgens, anti-androgen replacement, estrogenic compounds, adrenolytic agents, and novel approaches.

Anti-androgen withdrawal syndrome is a critical discovery in understanding the biology of androgen independence, interpreting clinical trials, and treating patients. Approximately one-third of patients respond to anti-androgen withdrawal, as indicated by a >50% PSA decrease, for a median duration of approximately four months. Androgen withdrawal must be systematically considered as a first-line modality in relapsing patients, even if its efficacy is limited.

Other treatment modalities include:

- **Classical hormonal treatment alternatives** after CRPC occurrence.
- Switching to an alternative anti-androgen therapy.
- **Anti-androgen withdrawal** accompanied by simultaneous ketoconazole.
- **Oestrogens.**
- **Novel hormonal drugs** targeting the endocrine pathways like abiraterone acetate and MDV 3100.
- **Non-hormonal therapy.**
- **Docetaxel** is currently the standard of care. The patients considered for docetaxel represent a heterogeneous population. A risk group definition has been recently presented, based on the TAX 327 study cohort. The predictive factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine before docetaxel. Patients were categorized into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), leading to three different lengths of median OS: 25.7, 18.7 and 12.8 months, respectively. In addition, two independent studies have suggested that improved survival can be predicted by C-reactive protein (CRP) levels < 8 mg/L (HR, 2.96). Age by itself is not a contraindication to docetaxel.
- **Other classical regimen**: Mitoxantrone combined with corticosteroids.
- **Other chemotherapy regimen**: estramustine combined with other drugs that target microtubule action, combination with vinblastine is the most frequently studied. A recent meta-analysis concluded that addition of estramustine to chemotherapy increased the time to PSA progression and OS. However, there was a significant increased risk (up to 7%) of thromboembolic events requiring systematic prevention with Coumadin. Combination of estramustine, etoposide and cisplatin (or carboplatin) has significant
activity against poorly differentiated CRPC. Combination of estramustine, etoposide and paclitaxel has high response rates. Preliminary results from phase II with alternative chemotherapy regimens have been reported, but the lack of large phase III trials and unknown long-term efficacy are major problems associated with all these studies. Therefore none of the above drugs are considered as clear valid options in CRPC.

- **Specific bone-targeted therapies**: Bone is a primary target for prostatic metastatic cells, which forms a rationale for bone-protective drugs that prevent cancer cells from colonising and developing in bone. Besides zoledronic acid and denosumab, the only bone-specific drug that is associated with a survival benefit is alpharadin, a radium 223 $\alpha$-emitter.

- **Vaccine**: In 2010, a phase III trial of Sipuleucel T showed a survival benefit in 512 CRPC patients. This was the first time that a prostate cancer vaccine had shown a benefit, and led to FDA approval and a submission to the European Medicines Agency. Sipuleucel T is an active cellular immunotherapy agent consisting of autologous peripheral blood mononuclear cells, activated in vitro by a recombinant fusion protein comprising prostatic acid phosphatase fused to granulocyte–macrophage colony-stimulating factor, which is an immune-cell activator.

Provided it is available, Sipuleucel T should probably be used early in the course of the disease. Until abiraterone acetate became available clinically, the discussion focused solely on when to start docetaxel therapy, after all the secondary classical hormonal manipulation had been undertaken.

The only indication for chemotherapy in CRPC non-metastatic patients is inside clinical trials.

All patients who receive docetaxel-based chemotherapy for CRPC will progress, and thus, there have been many clinical trials investigating the role of salvage chemotherapy. Two treatment possibilities are now available: new hormonal treatment or new chemotherapy regimens. The results suggest that the most appropriate approaches are cabazitaxel, intermittent docetaxel chemotherapy, and potentially, molecular-targeted therapy.

Platinum-based chemotherapeutic regimes have been investigated in patients with CRPC. Although the platinum complex, satraplatin, has shown activity against CRPC and some promise in clinical trials, the FDA rejected it for CRPC in 2008.

Many new drugs, such as gefitinib, bevacizumab (phase III trial CALB 90401 ongoing), oblimersen (phase II trial EORTC 30021), and also a vaccine, G-Vax (108), have been tested in phase II/III trials without any positive impact on the primary end-point. The G-Vax trial was stopped prematurely because of a significantly higher mortality in the treatment arm as compared to the docetaxel control arm.

Cabazitaxel is a taxane derivative with some significant differences compared to docetaxel. Positive results have been published from a large prospective, randomized, phase III trial (TROPIC trial) comparing cabazitaxel + prednisone vs. mitoxantrone + prednisone in 755 patients with CRPC, who had progressed after or during docetaxel-based chemotherapy. An OS benefit (15.1 vs. 12.7 months, $P < 0.0001$) was observed in the cabazitaxel arm.

Enzalutamide (formerly known as MDV3100) is a novel anti-androgen that blocks AR transfer to the nucleus, in contrast to currently available drugs with which AR is able to transfer to the nucleus. Enzalutamide is used as a once-daily oral treatment. The planned preliminary analysis of the AFFIRM study of enzalutamide or placebo showed an expected OS HR benefit of 0.76 in favor of enzalutamide. In October 2013, Medivation and Astellas announced that the Phase 3 PREVAIL Trial of enzalutamide met both co-primary endpoints of overall survival and radiographic progression-free survival in chemotherapy-naïve patients with advanced prostate cancer, with a 30% reduction in the risk of death, hazard ratio=0.70 ($P < 0.0001$) and 81% reduction in the risk of radiographic progression or death, hazard ratio=0.19 ($P < 0.0001$). These results are unprecedented in this setting and are expected to change the standard of care.
Abiraterone acetate is a CYP17 inhibitor. It is used once daily combined with prednisone twice daily (10 mg/day). Positive preliminary results of the large phase III COU-AA-301 trial were reported with a planned HR of 0.8 of the OS as primary end-point in favor of abiraterone.

However, the choice between third-line hormonal treatment (using enzalutamide or abiraterone) or second-line chemotherapy (cabazitaxel) remains unclear, with no clear decision-making findings published. They are urgently awaited because nothing is known regarding the optimal sequencing of drugs. The cost of each drug will be a major challenge to public health.

EUA recommendations on salvage treatment after docetaxel are as follows:

- Cabazitaxel is a valid option for management of progressive CRPC following docetaxel therapy.
- Abiraterone and enzalutamide are both valid options for management of progressive CRPC following docetaxel therapy.
- No definitive strategy regarding treatment choice (which drug/which drug family first) can be devised.

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective. Common complications due to bone metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. Osteoporosis may also cause fractures and should be prevented. Cementation is an effective treatment for painful fracture, clearly improving both pain and QoL. However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases. Impending spinal cord compression is an emergency. It must be recognized early and patients should be educated to recognize the warning signs.

Bisphosphonates have been used to inhibit osteoclast-mediated bone resorption and osteoclast precursors in CRPC. Currently, bisphosphonates can be offered to patients with CRPC bone metastases to prevent skeletal complications, even if the best dosing interval is unclear.

RANK ligand inhibitors include denosumab, a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κB ligand), a key mediator of osteoclast formation, function, and survival. Denosumab is FDA and EMA approved for preventing SREs in patients with bone metastases from solid tumors. Alpharadin (Xofigo, radium Ra 223 dichloride), an alpha particle-emitting radioactive therapeutic agent, was recently approved by FDA as indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

**Appropriate outcome measures**

Choosing the most suitable primary endpoints for prostate cancer trials has been challenging historically. Although OS is the gold standard for demonstrating clinical benefit due to its objectivity, it requires larger patient numbers and longer follow-up. Survival analysis may also be confounded by crossover or subsequent therapies administered after a study drug is discontinued.

Valid intermediate surrogate endpoints have been the center of debate for the past few years. Analyses of PSA response rates, objective response rates and progression-free survival (PFS) have all been proposed as means to accelerate the drug development process.

Most phase II trials have used PSA decline of more than 50 percent as the primary endpoint, based on its high predictive value of survival from a multivariate analysis and the prostate cancer clinical trials working group’s (PCWG1) recommendation. Some trials also incorporate 3-month 30% PSA decline since it was found to be the optimal biochemical surrogate from a retrospective analysis of the phase III SWOG 9916 trial.

However, the limitations of PSA and PSA-based surrogates in predicting survival have been increasingly recognized. In TAX 327, despite a statistical significant improvement in the rates of PSA response in patients taking docetaxel weekly compared to mitoxantrone (48% vs. 32%, p < 0.001, respectively), there was no difference in OS between the two groups.
The significance of solely using PSA progression without evidence of radiographic or symptomatic progression became questionable. Several trials involving TKIs have observed rising PSAs after treatment. The discordance between the PSA increase and radiographic improvement may be due to the effect of noncytotoxic agents modulating PSA secretion independent of its activity on tumor suppression. Without other well-defined indicators for disease progression, PSA progression is no longer considered representative of treatment failure.

Response rates have also been assessed in patients with measurable diseases on CT scans. However, the clinical picture of mCRPC is dominated by bone metastases in 90-95% of the patients, as reported in Table 4.

### Table 4 Distinct sites metastasized in castration resistant prostate cancer (IPSOS Data)

<table>
<thead>
<tr>
<th>Distant sites metastasized (frequency)</th>
<th>France</th>
<th>Germany</th>
<th>Italy</th>
<th>Spain</th>
<th>UK</th>
<th>Japan</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Bone</td>
<td>96%</td>
<td>86%</td>
<td>80%</td>
<td>90%</td>
<td>92%</td>
<td>78%</td>
<td>88%</td>
</tr>
<tr>
<td>Brain &amp; nervous system</td>
<td>-</td>
<td>*</td>
<td>*</td>
<td>1%</td>
<td>2%</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Liver (hepatobiliary)</td>
<td>8%</td>
<td>18%</td>
<td>9%</td>
<td>7%</td>
<td>4%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Lung</td>
<td>6%</td>
<td>18%</td>
<td>11%</td>
<td>8%</td>
<td>7%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>37%</td>
<td>52%</td>
<td>45%</td>
<td>37%</td>
<td>37%</td>
<td>29%</td>
<td>19%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>2%</td>
<td>11%</td>
<td>*</td>
<td>1%</td>
<td>*</td>
<td>*</td>
<td>-</td>
</tr>
<tr>
<td>Other sites</td>
<td>3%</td>
<td>5%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


Radionuclide bone scans are routinely used to assess these bony lesions but the criteria for response categorization are not well defined and reported in clinical trials. Other imaging modalities (MRI and PET) to assess bone metastasis are still under investigation. Moreover, as cytostatic biologic agents are increasingly being evaluated in clinical trials, the expectation of tumor shrinkage by these agents seems unrealistic. In a small number of patients, usually less than half of the study accrual, with soft tissue or visceral metastases that are evaluable, the response rate defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria is far from being acceptable for cytostatic agents.

Newer anticancer agents with targeted mechanisms of action have demonstrated an inherent limitation and unsuitability of anatomic tumor evaluation that assesses only lesion size. In addition, the effect of these new drugs changes the paradigm according to which tumor response or response rate is measured. Complete and partial responses cannot be the end points in all clinical trials; in some cases, disease control or progression-free survival may be the more relevant endpoint.

The standard evaluation of solid tumors is not associated with response to therapy in patients with CRPC. RECIST considers bone metastasis a non-target lesion. As prostate cancer frequently metastasizes to bone, RECIST is not the best tool to evaluate the tumor response to therapies in patients with prostate cancer. Biomarkers such as PSA, clusterin, novel imaging methods, and circulating tumor cell (CTC) analysis have therefore gained momentum.

Immunotherapeutic agents are increasingly being evaluated in prostate cancer. These produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. Resulting
clinical response patterns extend beyond those of cytotoxic agents and can manifest after an initial increase in tumor burden or the appearance of new lesions (progressive disease). RECIST or WHO criteria, designed to detect early effects of cytotoxic agents, may not provide a complete assessment of immunotherapeutic agents. Novel criteria for the evaluation of antitumor responses with immunotherapeutic agents are required.

Thus, an alternative endpoint may be needed for this group of targeted agents. Whether PFS is a justifiable intermediate surrogate endpoint in prostate cancer is still an open question. PFS is defined as the time from study entry or randomization of a patient until objective tumor progression or death. The use of PFS in trials has several advantages that include a smaller sample size and shorter duration of follow-up. PFS is also not affected by crossover or subsequent treatments. Various definitions for PFS, including PSA, radiographic changes, new metastatic lesions, and disease-related symptoms, have been used in clinical practice. However, data has shown that current measures of PFS for men with CRPC are not strong surrogates for OS.

On the other hand the increasing availability of post-progression treatments will further confound the OS as primary end-point for CRPC clinical trials and thus will require finding a reliable surrogate to OS. The current guideline only requires either “no new lesions” or “new lesions” being documented for bone disease assessment and may have overlooked subtle changes in bone which carries meaningful survival value. The ability to accurately determine disease status in prostate cancer, i.e. PFS, is likely compromised given the lack of reproducible and effective modalities to delineate changes of bone metastases.

Imaging

Like in most cancers, imaging in prostate cancer plays an important role for the diagnosis, initial staging and pre-treatment evaluation, treatment monitoring, evaluation of recurrence and of regional and distant extent of disease. Many imaging techniques are routinely used and recent advances in imaging technology and dedicated tracers are becoming increasingly available, thus allowing for significant improvements in tumor detection and staging.

Evaluation of local/locoregional disease

Diagnosis of prostate cancer relies primarily on the evaluation of rising levels of serum PSA and a digital rectal examination. The role of imaging at this stage is tumor localization that will guide biopsy for initial diagnosis and staging. Trans-rectal ultrasonography (US) and magnetic resonance imaging (MRI) are the techniques of choice for the anatomical localization of tumors. Anatomical MRI combined with functional MRI that include dynamic contrast-enhanced MRI (DCE), diffusion weighted (DWI) and MR spectroscopy (MRS) also known as multi-parametric MRI increases specificity of detection. DCE-MRI explores the hypervascular nature of tumors due to higher expression of VEGF and FGF, DWI-MRI explores the restriction of motion of water within tumors because of their high cellularity and MRS provides specific spectral analyses of several metabolites within the tumor such as choline and creatine that are typically increased and citrate that is typically decreased; the choline+creatine/citrate ratio is typically used as a marker for MRS detection. Multi-parametric MRI is routinely available on MRI scanners at 1.5 Tesla. Both ultrasonography and MRI serve as modalities to locate the primary or dominant tumor and to guide biopsy. Ultrasonography serves also for seed placement to guide brachytherapy and MRI is used to evaluate local and regional extent of disease.

Functional imaging such as positron emission tomography (PET), typically combined with computed tomography (CT) for increased spatial resolution, is an established technology that uses glucose and other metabolite-specific molecular probes, thus increasing specificity in detection. $^{18}$F- fluorodeoxyglucose (FDG) is the most commonly used PET tracer in oncology. Increased FDG within cancer cells reflects the increased expression of surface glucose transporters and intracellular kinases involved in glycolysis such as hexokinase. Unlike other cancers, the evaluation of prostate cancer with FDG PET suffers from low sensitivity and specificity and FDG PET is therefore not routinely used. Fluorine ($^{18}$F) or carbon ($^{11}$C) labeled choline is the most commonly used tracer in prostate cancer due to the highly specific increased intracellular accumulation of choline. Other PET tracers using either $^{18}$F or $^{11}$C to target acetate that is highly incorporated into the increased lipid synthesis within tumor cells and $^{11}$C to target the amino-acid methionine that represents an indirect measurement of increased protein synthesis in the cell. The major advantage of using $^{18}$F compared to $^{11}$C is its longer half-life of 5 hours vs. 20 minutes, which does not require an on-site cyclotron.
Evaluation of bone disease

In case of PSA recurrence after radical treatment or when the tumor becomes resistant to castration (CRPC), detection of bone metastases is relevant for the initiation of systemic therapy. Extension to bone involves mainly the axial skeleton (spine, pelvis) and may manifest as osteoblastic lesions on conventional radiography and CT.

Staging metastatic bone disease typically requires radionuclide studies using technetium-99m-labeled diphosphonates (typically, methylene diphosphonate or 99mTc-MDP; Figure 3). Bone scanning is a technique with an excellent sensitivity in prostate cancer patients; however, it suffers from a low specificity as many benign conditions such as trauma or inflammation appear equally as foci of increased activity.

**Figure 3** 99mTc bone scan showing foci of activity in the spine (long arrow) and ribs of a CRPC patient. A CT scan confirms the osteoblastic (osteo-condensation) nature of a vertebral lesion (arrow)

PET scanning using 18F–fluoride is an alternative to bone scans. The tracer follows the same pattern of uptake in the bone as 99mTc-MDP on bone scans; the main advantage is that PET can be combined with CT for cross-sectional localization.

Bone MRI has also been suggested as an alternative to bone scans because of its higher sensitivity and specificity. Modern approaches that include whole-body MRI (WB-MRI) have been shown to be superior to bone scans. The appearance of bone lesions on MRI is well characterized as metastatic lesions replace normal bone marrow.

Anatomic criteria focus predominantly on the physical measurement of solid tumors. Disease that is not easily measurable with a ruler or calipers, such as most bone metastases, is designated as unmeasurable. Cancer patients with no measurable disease (e.g. individuals with bone-only metastases following the resection of a primary tumor) are often ineligible for clinical trials, which may be the only available source of therapy. Therefore, the absence of measurable tumors can significantly affect patient disease management.

To address this gap, in addition to anatomic (RECIST 1.1) response criteria, both bone response criteria (MD Anderson [MDA]), and metabolic cancer response criteria (Positron Emission Tomography Response Criteria in Solid Tumors [PERCIST]) were developed, with a focus on the developing role of bone metastases and the interpretation of the treatment response of bone metastases seen on imaging studies.

The main differences between the RECIST, MDA and PERCIST are shown in Table 5.
Table 5 Comparison of RECIST, MDA and PERCIST

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RECIST</th>
<th>MDA criteria</th>
<th>PERCIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic response criteria for soft tissue metastases</td>
<td>Anatomic response criteria for bone metastases</td>
<td>Functional response criteria reflecting tumor metabolism</td>
<td></td>
</tr>
<tr>
<td>Advantages</td>
<td>Common use allows direct comparison of the results of different studies</td>
<td>Allows the response of the majority of bone metastases to be factored into therapeutic response</td>
<td>Allows response determination regardless of the location of the metastasis</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Limited to “measurable” soft tissue metastases or unequivocal progression of unmeasurable disease</td>
<td>Limited to bone metastases</td>
<td>Limited to FDG avid metastases</td>
</tr>
</tbody>
</table>

Evaluation of visceral disease
Visceral disease can be evaluated by CT or MRI, metastases to lymph nodes in the pelvis and retroperitoneal nodal stations or to viscera. The imaging patterns are similar to those seen in other “solid” tumors.

Longitudinal quantification of extent of disease and imaging endpoints
Quantification of bone disease in CRPC patients faces the challenges of the limitation of the imaging techniques. Serial longitudinal evaluations and quantification of bone scans to evaluate response to therapy carry several limitations: increase in uptake or the appearance of new hot spots from one bone scan to the next does not necessarily indicate progression of disease and may represent actually bone healing that has been described as the “flare” phenomenon which is typically observed within three months of treatment initiation. With these caveats, quantification using bone scans can be limited to lesion count or to semi-quantitative approaches evaluating the extent of bone activity to the entire skeleton by expressing the tumor burden in bone as a percent of the total skeletal mass. Such methods include the Soloway index or the bone scan index (BSI). These indexes have been shown to be correlated somewhat with PSA and with survival.

Visceral disease can be evaluated using standard solid tumor response criteria such as the response evaluation criteria in solid tumors (RECIST): nodal lesions above 2cm and visceral metastatic lesions are measured in their longest diameters and the tumor burden is measured serially to define visceral response and progression.

The PCWG-2 criteria provide a guideline for using imaging in clinical trials for CRPC patients. Such patients are to have baseline and serial evaluations with bone scintigraphy and CT or MRI scans of the body as well as monitoring of skeletal-related events (SRE) where imaging can be used. While prevention of bone progression, prevention of bone metastasis and SRE represent direct clinical benefits that reduce bone morbidity, stability or response of visceral disease using RECIST have not shown to correlate with clinical outcomes. Similarly, progression of visceral disease, and particularly of nodal lesions, may not represent true progression.
Median Technologies, a central imaging review service provider, provides technology and service solutions that enable lesion detection, quantification and tracking for longitudinal assessment of prostate cancer patients (Figure 4). Imaging processing software allows semi-automated comparison of tumor burden in bone, lymph nodes and viscera for a standardized endpoint evaluation of patients in clinical trials.

This allows for automated lesion detection, quantification and longitudinal tracking in support of visceral and nodal disease.

Section 2 – Drugs currently in development

Several new treatment options have recently become available for patients with mCRPC. Many trials were designed to combine docetaxel with multiple agents with distinct mechanisms of action including TKIs, anti-angiogenic drugs, bone-targeted agents, BCL-2 inhibitors, chemotherapies, immunologic agents, and Vitamin D analogs. Strategies combining docetaxel with single (sunitinib, bevacizumab, lenalidomide) or dual antiangiogenic agents (bevacizumab and thalidomide) are also in development.

Combinations of cytotoxic and hormonal agents are being evaluated to see if there is a possible synergistic antitumor activity: hormonal therapy combined with docetaxel was tested in a phase I trial using ketoconazole and docetaxel, with active tumor response observed in 62% of patients with PSA response, and 28% with partial response in measurable disease.

Docetaxel-based combinations also include the following:

- Docetaxel plus calcitriol (Vitamin D).
- Docetaxel plus oblimersen (an antisense oligodeoxynucleotide that blocks BCL-2, an apoptotic regulator).
- Docetaxel plus OGX-011 (an antisense inhibitor of clusterin).
- Docetaxel, estramustine, and bevacizumab.
- Docetaxel and prednisone with or without aflibercept, another agent that targets VEGF (clinicaltrials.gov NCT00519285).
New cytotoxic agents include epothilones (ixabepilone, patupilone, sagopilone), a newer class of cancer drugs that act similarly to taxanes, interfering with tubulin within cancer cells. Eribulin mesylate, a fully synthetic macrocyclic ketone analogue, is a potent inhibitor of microtubule dynamics.

Several multicenter phase III trials combining first-line conventional hormonal agents with docetaxel are currently ongoing to address the question regarding early versus late initiation of chemotherapy in metastatic, hormonal-sensitive patients (ClinicalTrials.gov NCT00268476, NCT00104715).

Abiraterone acetate has been shown to be able to continuously inhibit adrenal androgen synthesis even at the time of disease progression, as evident by continued suppressed level of serum androgen in several phase I/II studies of abiraterone acetate. Studies evaluating a combination therapy that integrates uninterrupted androgen deprivation by a novel, potent agent like abiraterone acetate and cytotoxic agents with a proven survival benefit such as docetaxel or cabazitaxel, are currently underway in phase I testing (ClinicalTrials.gov NCT01400555, NCT01511536).

Immunotherapy and vaccine-based immune therapies include GVAX, a cellular vaccine composed of two prostate cell lines, PC-3 and LNCaP, modified to secrete granulocyte-macrophage colony stimulating factor, and sipuleucel-T used to stimulate a T-cell mediated immune response within treated patients with CRPC.

Novel targets include endothelin-receptor antagonists (atrasentan), BCL-2 inhibitors (AT-101), Src kinase inhibitors (dasatinib), VEGF receptor inhibitors (sunitinib, a multi-targeted tyrosine kinase inhibitor with known selectivity for VEGF receptors).

Other therapeutics targeting angiogenesis and related pathways include cabozantinib and tasquinimod. Cabozantinib (XL-184) is a VEGF receptor 2 and MET inhibitor that potentially targets both angiogenesis and tumor invasion. Tasquinimod is a synthetic compound that upregulates thrombospondin-1, which inhibits neovascularization by interfering with VEGF signalling and angiogenesis, suppressing nitric oxide-dependent pathways, and also down-regulates several oncogenes.

Anti-prostate-specific membrane antigen (PSMA)-based therapy (The mAb J591) is a well-established and highly restricted prostate epithelial cell membrane antigen. Its expression is highly upregulated in prostate cancer and studies indicate that PSMA is expressed by virtually all prostate cancers.

Two phase I radioimmunotherapy trials were performed using Yttrium-90 or Lutetium-177 (177 Lu) linked to J591 in patients with metastatic CRPC.

Bone targeted radionuclide therapy included the evaluation of strontium-89, rhenium-186 etidronate, radium-223.

Clinical trials currently ongoing in the non-metastatic setting include, but are not limited to, the following compounds:

- **ARN-509** (androgen receptor antagonist) from Aragon Pharmaceuticals recently purchased by J&J.
- **MDV3100** (androgen receptor antagonist) from Medivation.
- **Zytiga** (abiraterone, inhibitor of CYP17) from J&J.
- **TAK-700** (androgen synthesis inhibitor) from Takeda.
- **ODM-1** (androgen receptor antagonist) from Orion currently in phase I/II.
- **Galeteron** (TOK-001, Tokai Pharma) is a CYP17 inhibitor + AR antagonist + AR degrader in one compound currently in phase I/II development.
VT-464 (Viamet) is a selective CYP17 inhibitor currently in Phase I/II development.

For patients positive for the TMPRSS2-ERG fusion gene, Veliparib (AbbVie), a PARP inhibitor.

Olaparib (PARP inhibitor) is also under current early development in CRPC.

SMIP004, which acts on the androgen receptor, making it a promising molecule for treatment of CRPC.

SMIP004 has only been tested in laboratory studies and animal (mouse) studies to date but it is expected to enter clinical development very soon.

Given the heterogeneity of the disease at the molecular level, it remains a challenge to identify suitable druggable target(s). Subsequent molecular studies are warranted to justify and/or validate the targeted therapy under investigation.

Failures from several recent phase III trials based on expedited approaches in advancing a drug from phase I/II to III suggest incorporating biomarker strategies from the early phase of development. Existing intermediate surrogate biomarkers and easily accessible surrogates, such as CTC, can be analyzed and validated prospectively in large phase III trials and can be vital to the understanding of the benefits of particular agents and treatment combinations.

Clinical trials challenges and opportunities: operational aspects

Prostate cancer landscape assessment

Countries and sites assessed

Due to the increasing interest in the prostate cancer studies, and in order to proactively assess key operational issues, a survey was conducted to support the Castration Resistant Prostate Cancer Landscape Assessment in the second quarter of 2013. A total of 127 investigator responses were received from 40 countries globally as shown in Table 6 and Figure 5.

The primary objective of this assessment was to establish an internal global database on disease standard of care, patient pathway, medical practice and considerations for therapy choice, end-point preference, competitive landscape, recruitment and retention, thus providing a baseline for future development and review as the landscape evolves over time.

In order to meet those objectives, this assessment included four components:

1. Mining of various data sources
2. Outreach to feasibility experts with country level questions
3. Outreach to investigators with site level questions
4. Medical inputs and review, and strategic site intelligence inputs.
Table 6 List of assessed countries

<table>
<thead>
<tr>
<th>Asia Pacific</th>
<th>Central/Eastern Europe</th>
<th>Latin America</th>
<th>North America</th>
<th>Africa/Middle East</th>
<th>Western Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Belarus</td>
<td>Argentina</td>
<td>USA</td>
<td>Egypt</td>
<td>Denmark</td>
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<td>Hong Kong</td>
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<td>Brazil</td>
<td>Israel</td>
<td>Finland</td>
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<td>Bulgaria</td>
<td>Chile</td>
<td>Jordan</td>
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<td>Croatia</td>
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<td>UK</td>
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<td>Sri Lanka</td>
<td>Georgia</td>
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<td></td>
<td>Lithuania</td>
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<td>Poland</td>
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<td>Russia</td>
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<td></td>
<td>Ukraine</td>
<td></td>
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</tbody>
</table>

Figure 5 Map of assessed countries

Investigators were targeted for this exercise based on the following criteria:

- Oncologists or urologists who had recent experience (including self-reported experience) in prostate cancer studies.
- An existing relationship, e.g., partner/prime site status.

The majority of responding investigators practice in institutions – hospitals or cancer centers (68%), and some of them are in academia (13%) or private clinics (13%); the distribution of site settings are shown in Figure 6.
The specialists who participated in this feasibility study were largely oncologists (75%, 95 out of 127), and one quarter were urologists (32 out of 127). This is consistent with our initial understanding that both oncologists and urologists are relevant stakeholders for CRPC.

**Medical practice: End-point preference**

The end-point preference were assessed for an ideal therapy for CRPC patients (both metastatic and non-metastatic), with 71% (90 out of 126 responders) of physicians ranking efficacy as the first choice, followed by tolerability (16%, 20 out of 126 responders) of physicians ranking efficacy as the first choice, followed by tolerability (16%, 20 out of 126 responders). The most popular rankings for the five endpoint considerations are shown in Figure 7.

**Medical practice: Referral method preference**

The preferred referral method for physicians and target countries was assessed (Figure 8). Among investigators who responded, only 26% indicated that their sites have adequate patient numbers and do not need referrals, and majority (75%; 91 of 121 responders) would like to have referrals from other specialists.
or from primary care physicians (21%; 26 of 121 responders), patient advocacy groups (7%; 9 of 121 responders) and call centers (5%; 6 of 121 responders). The other specialists that were included in the survey included oncologists, urologists, surgeons, internists, pathologists, orthopedists and radiation therapists.

Figure 8 Referral methods (N = 121)

Patient pathway
The prostate cancer patient pathway has always been a critical component of clinical trials for this patient population, involving similar numbers of urologists and medical oncologists, as well as few primary care physicians (see Figure 9). As treatment paradigms shift with the introduction of new drug agents, mapping this pathway at various sites becomes even more important for the recruitment and retention of patients.

Figure 9 Patient pathways versus the disease stage

Adapted from Higano CS. In: Figg WD et al. Drug Management of Prostate Cancer. 2010:321
The typical patient pathway for CRPC is through referrals from urologists to oncologists, and primary care physicians and radiotherapists may also serve as referral channels in some sites.

The typical patient pathway for non-metastatic (M0) CRPC patients and for new metastatic (M1) mCRPC patients and for metastatic (M1) mCRPC patients who failed androgen-deprivation therapy was generally the same in each country contacted.

In Latin America, Europe and North America, patients are usually diagnosed within urology clinics/departments, and redirected to the specialized oncologist if needed. Oncologists treat CRPC patients most frequently in most of those countries, and they work in collaboration with urologists in order to provide access to the patients.

If prostate cancer patients are qualified for hormone treatment, they will be mainly treated by urologists but not be seen by oncologists. Patients post hormone failure, or resistant to castration or with other disease progression will be transferred from urologists to oncologists. Patients who have had the PSA test, bone scan, prostate biopsy or other investigations starting the metastatic stage of disease are often directed to oncology specialists.

In some Asian countries, such as China and Malaysia, it has been noted that urologists may keep seeing CRPC patients and discuss treatment decisions with other specialists (e.g., oncologists, pathologists, and radiologists).

Almost all the sites contacted had established referral networks that included both oncologists and urologists, and did not anticipate any difficulties with referrals. Therefore, to enroll CRPC patients into clinical trials both urology and oncology departments must be contacted.

A key factor is that the pathway is highly site specific, and therefore when initiating a clinical trial it is extremely important to know where patients are seen and treated on a site-by-site basis.

**Biomarker development and personalized medicine**

Improvements in understanding of the biologic and molecular drivers of prostate cancer growth and progression in the past few years have resulted in investigations of numerous novel targeted therapies, including androgen receptor (AR) targeting agents, tyrosine kinase inhibitors (TKIs), antiangiogenic agents, endothelin receptor antagonists, anti-apoptotic protein inhibitors and proteasome inhibitors. Several of these drugs have either received FDA approval or moved to the frontline of late stage development based on improvement of intermediate surrogate endpoints such as PSA levels or circulating tumor cell (CTC) counts in small phase I/II trials. While the biology of AR synthesis and regulation is well studied, no predictive markers have been adopted to guide development or use of drugs targeted this central pathway in early stage prostate cancer and CRPR.

The development of diagnostic or predictive biomarkers in prostate cancer has focused in the past on serum factors based on the importance of PSA and related biomarkers, prostatic acid phosphatase (PAP) and other proteins. These markers have contributed to the diagnosis of prostate cancer as well as drug studies as surrogate endpoints. However, their clinical utility has been limited by suboptimal technical performance and the difficulty of dealing with the complexity and large dynamic range of factors in human circulation. Recent improvements have been made through the use of combined indices taking advantage of multiple factors. In addition, nucleic acid-based tests that may be performed on fluid samples have been developed such as the prostate antigen 3 (PCA3) test for the diagnosis of prostate cancer. This test has been shown to have improved performance compared to a PSA test. CTC enumeration may also be used and can be performed on the FDA-approved Veridex platform.

Research into the genomic alterations present in prostate cancer and CRPC have revealed new drug targets as well as biomarkers to support clinical research. ERG fusion in a large percentage of prostate cancer patients generated a great deal of interest given the role of the TMPRSS gene in AR biology.
Additional ETS rearrangements continue to be identified adding to the number of prognostic markers available to distinguish aggressive from indolent disease\(^1\). The majority of these alterations are related to AR signaling. Therefore, the translocations are of interest in helping to identify patients most likely to respond to drugs targeting the AR pathway or AR synthesis or metabolism.

The PTEN, PIK3CA and AKT1 genes and pathway are also often altered in prostate cancer and may be linked to CRPR and response to AR-targeted therapies\(^1\). Therefore, there has been drug development targeted this pathway, often with mTOR inhibitors such as the rapamycin analogs. However, these studies have generally not been successful, possibly because of the complexity of this pathway and related, linked pathways and the biology of PTEN. Genomic alterations in AR itself, including mutations and amplification, promise to be more direct predictive markers for drug targeting this pathway including newer drugs such as MDV3100 that target a wider range of AR activities.

Genomic research has also identified alterations in novel genes and potential biomarkers, including the BRAF, KRAS, RB1, c-MYC and aurora kinase genes\(^1\). These findings open up new opportunities for drugs currently in clinical development or use. Some of these alterations have also been linked to AR regulation and may support existing clinical development in prostate cancer with AR targeted therapies. Interestingly, PARP inhibitors are in development in prostate cancer based upon the evidence linking ETS rearrangements, PTEN loss and sensitivity to DNA damage and repair.

Despite these promising findings and opportunities for molecular targeting of patient subgroups, there has been relatively little use of patient selection or personalized medicine in prostate cancer clinical studies. However, the clinical adoption of next-gen sequencing techniques as well as the use of alternative and more feasible sample types including CTCs\(^1\) and circulating DNA/RNA\(^1\) should facilitate uptake of genomic predictive biomarkers in prostate cancer.

---

**Section 3 – Quintiles’ experience**

Quintiles’ experience with the challenges in prostate cancer trials and the solutions to ensure successful implementation are summarized in Table 7. These observations are particularly relevant to non-metastatic or newly metastatic patients as these are the situations where it is most challenging to enroll clinical trial participants.
<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>The prostate cancer patient pathway has always been a critical component of clinical trials for this patient population, involving different specialties: urologists, medical oncologists, and primary care physicians</td>
<td>The importance of mapping the patient pathway at various sites is the crucial success factor for the recruitment and retention of patients with CRPC, particularly in the case of non-metastatic patients who are at high risk of developing metastasis or patients with new metastasis who have failed hormonal therapy. Quintiles has an understanding of the patient pathway in all major countries, allowing us to target the correct sites in a timely and efficient way. Depending on the study design and targeted patients, a mix of oncologist (50%), urologist (45%) and other principal investigators (PIs) (5%) is the expected mix for sites.</td>
</tr>
<tr>
<td>Depending on the sites involved in the study, different approaches may be used to find the patients to be included. The main methods listed by the sites are:</td>
<td>An individualized recruitment plan for each site is prepared upfront and sites are supported in implementation. This site plan is based on how the site routinely identifies prostate cancer patients so that adequate and targeted support can be provided. Key goals are to:</td>
</tr>
</tbody>
</table>
Quintiles is committed to supporting development of personalized or precision medicine approaches to prostate cancer treatment. The Quintiles Central Laboratory and clinical staff have the resources to support the use of potential surrogate endpoints for prostate cancer, and the Quintiles EA genomic laboratory is a leader in establishing best practices for genomic testing in clinical research. These early discoveries require technical and clinical validation as well as incorporation prostate cancer clinical trials. Quintiles planning and design staff consider opportunities for targeting of molecularly defined patient subgroups as well as the impact of these options on trial feasibility and cost.

The strategies and viewpoint expressed in the included references by Quintiles authors – as well as Quintiles’s acquisitions of EA, TMD and other investments in personalized medicine, including I-SPY and Oxford Cancer Biomarkers – demonstrate the company’s commitment to personalized or precision medicine.

**Site availability**

Quintiles has an extensive database of investigators with prostate cancer experience, including a total of 1,849 sites across 61 countries. Having access to this large network of sites allows Quintiles to efficiently run prostate cancer trials in all the regions of the globe. Quintiles can implement the most efficient strategy specifically tailored for each protocol or program based on customer needs and preferred marketing and regulatory tactics.

At Quintiles, our site relationships are a top priority. We have constructed a worldwide network of elite Partner and Prime sites, which typically recruit at a rate above that of non-partner sites. As shown in Table 8 and Figure 10, we have a total of 1849 sites in our network of prostate cancer sites, of which 336 are classified as Prime or Partner sites. We use these, as well as established templates, to offer time savings during the start-up process.

Quintiles’ knowledge of patient-referral patterns on a global basis enables quick identification of key investigators and maximization of referrals.

**Table 8 Quintiles total prostate cancer sites per region**

<table>
<thead>
<tr>
<th>Region</th>
<th>Non-Partner</th>
<th>Partner</th>
<th>Prime</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
<td>113</td>
<td>19</td>
<td>5</td>
<td>137</td>
</tr>
<tr>
<td>Europe/Middle East/ Africa (EMA)</td>
<td>593</td>
<td>136</td>
<td>12</td>
<td>741</td>
</tr>
<tr>
<td>Japan</td>
<td>12</td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Latin America</td>
<td>158</td>
<td>29</td>
<td></td>
<td>187</td>
</tr>
<tr>
<td>USA/Canada</td>
<td>637</td>
<td>55</td>
<td>80</td>
<td>772</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>1513</strong></td>
<td><strong>239</strong></td>
<td><strong>97</strong></td>
<td><strong>1849</strong></td>
</tr>
</tbody>
</table>
Metrics
Quintiles has conducted more than 23 prostate cancer studies since 2002. Countries that have been involved in these prostate cancer trials up to June 2013 are listed in Table 9.

Table 9 Quintiles prostate cancer trials, 2002-13

<table>
<thead>
<tr>
<th>Africa</th>
<th>Asia Pacific</th>
<th>Central/Eastern Europe</th>
<th>Latin America</th>
<th>Middle East</th>
<th>North America</th>
<th>Southeast Asia</th>
<th>Western Europe</th>
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</thead>
<tbody>
<tr>
<td>South Africa</td>
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<td>Canada</td>
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<td>Serbia</td>
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</tbody>
</table>

Source: Quintiles Investigator Performance Database (May 2013)
Quintiles has experience conducting prostate cancer clinical trials across every trial phase, with a particular focus on phase II and III studies as shown in Table 10.

### Table 10 Quintiles’ study experience by phase, 2002-13

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of studies</th>
<th>Average enrollment rate (per site per month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>3</td>
<td>0.45</td>
</tr>
<tr>
<td>Phase II</td>
<td>6</td>
<td>0.19</td>
</tr>
<tr>
<td>Phase III</td>
<td>12</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Source: Quintiles Investigator Performance Database, accessed May 2013

The average enrollment rate globally across all such studies within the Quintiles Investigator Performance database since 2002 (17 studies with enrollment data) is 0.24 patients/site/month. This rate is included as a general indicator for planning purposes. Enrollment performance by study and country is highly variable based on protocol design and the indication landscape at the time of study startup, and therefore this rate needs to be confirmed through a feasibility exercise for each protocol based on design, the regions/countries involved and the level of the investigator’s interest.

### Competitive landscape

The presence of competing trials can affect the availability of both patients and sites for clinical trial participation. An examination of the trial landscape was conducted using www.biopharmclinical.com, which includes data retrieved from www.clinicaltrials.gov and other public sources globally. A search on 26 August 2013 found over 2,400 trials globally with 781 open trials that are or will be enrolling prostate cancer patients. Of these 781 studies, 485 studies include sites in the U.S. and Canada, 369 in the EU and Middle East countries, and 29 in Latin America.

Table 11 presents a global picture of the clinical landscape to give insight into the breakdown by trial phase and the number of patients being sought by phase.

For each new protocol being started, it is extremely important to conduct a specific assessment of the competitive landscape, taking into account the patient population being targeted. However, it is also important to have a full knowledge of the competitive environment at a given site, so that the site can ensure that it has enough staff and resources to manage all clinical and administrative tasks.

### Table 11 Average enrollment by phase: Global landscape

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of studies</th>
<th>Average number of patients by phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>76</td>
<td>37</td>
</tr>
<tr>
<td>Phase I/II</td>
<td>54</td>
<td>64</td>
</tr>
<tr>
<td>Phase II</td>
<td>212</td>
<td>85</td>
</tr>
<tr>
<td>Phase II/III</td>
<td>10</td>
<td>618</td>
</tr>
<tr>
<td>Phase III</td>
<td>83</td>
<td>651</td>
</tr>
<tr>
<td>Phase IV</td>
<td>13</td>
<td>147</td>
</tr>
<tr>
<td>Unknown</td>
<td>333</td>
<td>1,485</td>
</tr>
</tbody>
</table>

Source: www.biopharmclinical.com 26th August 2013
As shown in Figure 11, the number of studies in the prostate cancer landscape has been increasing over the past 10 years, with a peak in 2009 when 215 studies were started, compared with only 61 studies initiated in 2002. Although the number of new start-ups has subsequently decreased, it remains high, with 304 studies initiated since 2012.

Figure 11 Prostate cancer studies by year

Source: www.biopharmclinical.com, 26 August 2013

Choosing the right countries

Selecting the right countries and sites is critical to the success of a prostate cancer program. Careful country/site identification represents the major mechanism by which patient recruitment can be facilitated. Initial country/site recommendations for a given trial should be based on a data-driven process which includes a country algorithm and site tiering (as shown in the preceding Biomarker Development & Personalized Medicine section), based on weighted variables tailored to the success of the specific studies. Using a variety of data sources, Quintiles has developed a preliminary country ranking algorithm for prostate cancer studies that includes the characteristics and key success factors summarized in Table 12.

Table 12 Country ranking algorithm data points and weighting

<table>
<thead>
<tr>
<th>Data points</th>
<th>Source</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintiles historical start-up timeline</td>
<td>Quintiles regulatory database</td>
<td>15</td>
</tr>
<tr>
<td>Prevalence of prostate cancer</td>
<td>GLOBOCAN 2008</td>
<td>15</td>
</tr>
<tr>
<td>Impact of competing trials</td>
<td><a href="http://www.biopharmclinical.com">www.biopharmclinical.com</a></td>
<td>15</td>
</tr>
<tr>
<td>Number of completed prostate cancer trials</td>
<td><a href="http://www.biopharmclinical.com">www.biopharmclinical.com</a></td>
<td>10</td>
</tr>
<tr>
<td>Number of Quintiles prostate cancer studies conducted</td>
<td>Quintiles investigator database</td>
<td>10</td>
</tr>
<tr>
<td>Number of experienced investigators</td>
<td>Quintiles investigator database</td>
<td>15</td>
</tr>
<tr>
<td>Enrollment rates for similar studies</td>
<td>Quintiles investigator database</td>
<td>20</td>
</tr>
<tr>
<td>Screen failure rate for similar studies</td>
<td>Quintiles investigator database</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 13 indicates the result of this country ranking methodology in CRPC as of September 2013. This ranking is updated on an ongoing basis, depending on available data. Also, the ranking is tailored to the needs of each specific study, taking into account the key challenges and success factors. The resulting tiering is specific and tailored to the needs of each protocol.

### Table 13 Country tiering: prostate cancer

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>Spain</td>
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<td>Latvia</td>
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<td>Egypt</td>
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<td></td>
<td>Turkey</td>
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</tbody>
</table>

### Recruitment and retention strategies

In conclusion, Quintiles recommends consideration of the following recruitment strategies are considered for prostate cancer trials:

1. **Maximize site-based recruitment** by helping sites to pre-identify patients from within their practice, keep the study top of mind with the site staff, and providing materials that investigators can use in explaining the study to patients and their families. Pre-ID website is a tool that is used by sites to quickly and easily pre-identify potential patients from their own patient population. This provides the study teams with early insights into the recruitment potential of individual sites, and enables scheduling of screening visit immediately after the Site Initiation Visit.

2. **Support referrals from urologists** by providing materials to investigators for use in outreach to their referral networks (referral brochures, letter and email templates, and presentation materials). The focus will be to capture patients at the point of referral to an oncologist for further treatment of their prostate cancer.

3. **Prepare for contingency outreach** by building a study website in order to quickly launch a direct-to-patient campaign if needed to meet enrollment goals.

4. **Drive retention and prevent loss-to-follow up** by consenting patients and caregivers to third-party contact and maintaining communication with patients. During the enrollment process, patients consent to receive study communications and be contacted in the event of withdrawal or loss to follow-up. They are asked to provide an email address, cell phone number (for SMS text messages), and cell/landline phone number (for personal calls) for themselves and a designated friend or family member.
Quintiles is able to adapt the strategy to each trial and to each of the involved countries, selecting only those tactics and tools that are applicable to a given trial and approvable by local EC/Regulatory Authorities, as well as culturally acceptable to sites and patients. Quintiles’ CRAs further adapt the country strategy to each site through development of a Site Recruitment and Retention Action Plan. Table 14 summarizes possible tactics to drive recruitment and retention in prostate cancer trials.

### Table 14 Patient recruitment tactics in prostate cancer trials

<table>
<thead>
<tr>
<th>Tactic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study branding</td>
</tr>
<tr>
<td>Integrated study portal with modules for patient pre-ID plus SMS/text messaging (visit reminders)</td>
</tr>
<tr>
<td>Investigator/site tools</td>
</tr>
<tr>
<td>Referral materials</td>
</tr>
<tr>
<td>Patient materials</td>
</tr>
<tr>
<td>Recruitment website needs</td>
</tr>
<tr>
<td>Digital outreach media</td>
</tr>
</tbody>
</table>

### Conclusion

To summarize, prostate cancer is a key area of interest in oncology. Due to the current unmet need, an expansion of the clinical development plans for new drugs in this indication is predicted.

Quintiles has a deep understanding of the challenges involved in prostate cancer trials and has the expertise and the methodological solutions to support customers in this indication. Through our feasibility and site intelligence team we can identify the best countries where a trial can be run, and through our network of prime/partner sites and other specialized sites in this indication, we can involve the best sites based on each trial profile and strategy.

Our patient recruitment team (which is integrated with the Quintiles team managing the project through the assignment of patient recruitment manager) is well-versed in oncology studies and has considerable experience developing and implementing recruitment programs designed to support and motivate the investigators and site staff and facilitate conversations with patients.

Our team of medics within the Oncology Therapeutic Area can support the sponsor team to make sure the final study design is feasible and in line with desired objectives. In addition, Quintiles’ Translational Medicine team within Center for Integrated Drug Development can provide recommendations and support for the clinical, laboratory and biomarker strategies for drug development as well as the development of innovative tools for targeted drugs and companion diagnostics.

Median Technology, Quintiles’ partner for imaging, has available solutions to support the imaging component of the clinical trials in prostate cancer.

Quintiles is the ideal partner for clinical development of new drugs for prostate cancer.

### Acknowledgment

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References


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Giovanni Piazzi has 20 years’ clinical trials experience, including 13 years in the Quintiles Oncology Therapeutic Area focusing exclusively on the execution and project management of large global oncology trials. Mr. Piazzi’s experience as Clinical Project Manager encompasses a wide variety of different cancer types and project phases. In his current role as Therapeutic Strategy Lead, Mr. Piazzi combines strategic and operational expertise to help customers with delivery strategies for projects and programs. Prior to joining Quintiles, he worked at Synthelabo and SmithKline Beecham.

Ettore Mari, MD
Medical Director, Oncology Therapeutic Area, Quintiles
Dr. Ettore Mari has 23 years of extensive experience in oncology clinical trials, targeted therapy, chemotherapy, hormone therapy, and non-interventional studies. Dr. Mari’s experience encompasses all phases of clinical development and a wide variety of frequently-occurring and rare cancers including castration-resistant prostate cancer, NSCLC, breast cancer, colorectal cancer, thyroid cancer, myeloproliferative neoplasms, head and neck cancer, glioblastoma, pancreatic cancer, hepatocellular carcinoma, biliary tract carcinoma, AML, ovarian cancer and testicular cancer. Prior to joining Quintiles, Dr. Ettore held medical positions in oncology clinical development at AstraZeneca, Gentium, and at “Mario Negri Sud” Consortium for Pharmacological Research. He has published 28 full papers and 25 abstracts.

Daoying Hu, Ph.D.
MBA Feasibility Manager, Integrated Site Services, Quintiles
Daoying Hu has over 10 years of experience in the life science and pharmaceutical industry. She obtained her Ph.D. in Biomedical Science at Baylor College of Medicine, and continued in preclinical research at Novartis pharmaceuticals. Dr. Hu later took on project management and business development roles at a life science technology start-up company, where she developed and commercialized biomedical products, and established strategic alliances with academic and industrial partners. Dr. Hu completed her MBA at Duke University in 2012 and joined Quintiles as Feasibility Manager. Her current role is to perform, manage and coordinate global feasibility activities.
About the authors

**Katarzyna Kurek, M.Sc.**
Director, Strategic Site Intelligence, Oncology Lead, Quintiles
Katarzyna Kurek has over 15 years of experience in clinical research at Quintiles. During this time, she has held various positions on projects and in country management. Since October 2010, Ms. Kurek has been Strategy Site Intelligence Director, Oncology Lead, with responsibility for country and site strategy for projects, pipeline analysis, landscape assessment for oncology indications and site development.

**Brad Smith, Ph.D.**
Vice President, Translational Medicine, Quintiles
In his role at Quintiles, Dr. Brad Smith supports laboratory, clinical and diagnostic strategies for drug development as well as the development of innovative tools for targeted drugs and companion diagnostics. Previously, Dr. Smith led Corporate Development at Cell Signaling Technology, an innovative biotechnology company. In this position, Dr. Smith focused on new diagnostic and clinical partnerships and markets. His previous positions at Cell Signaling Technology included management of research and clinical technology development departments and laboratories. Prior to Cell Signaling Technology, Dr. Smith directed product development and production at Santa Cruz Biotechnology, helping to build that company into one of the largest suppliers of research tools for basic research. Dr. Smith's scientific background includes research positions at Stanford University and the University of California, San Francisco, focused on cellular signaling mechanisms of disease. Dr. Smith holds a Doctoral degree from Stanford University and Master's and Bachelor's degrees from University of California, Santa Cruz.

**Souhil Zaim, MD**
Chief Medical Officer, Median Technologies
Dr. Souhil Zaim is a board-certified radiologist with over 20 years of experience in imaging for clinical trials. Dr. Zaim trained and practiced as a clinical radiologist at the University Hospital in Paris VI, France, and spent four years at the University of California, San Francisco as an Assistant Professor of Radiology. Prior to joining Median, he spent 12 years at Synarc Inc., a central core lab exclusively dedicated to clinical trials. Dr. Zaim has authored more than 30 publications in imaging in oncology and arthritis, most of which have data from clinical trials or observational epidemiological studies.