REVIEW ARTICLE

Metastatic Prostate Cancer

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CARE FOR MEN WITH PROSTATE CANCER IS A MAJOR GLOBAL HEALTH CARE challenge, compounded by an aging population and increasing frequency of diagnosis. The priorities today are similar to those in the recent past: minimizing overtreatment of indolent disease and improving outcomes for patients with aggressive disease. Herein we focus on recent accomplishments and future challenges in the management of metastatic disease, which continues to be associated with a high rate of death despite multiple new-drug approvals in recent years. Metastatic prostate cancer can be broadly divided into two groups: disease that has not been treated with androgen deprivation and disease that is resistant to such therapy. Treating metastatic prostate cancer is becomingly increasingly complex. We review studies that are changing the standard of care, and we offer a conceptual perspective for addressing ongoing challenges and opportunities.

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METASTATIC DISEASE NOT PREVIOUSLY TREATED WITH ANDROGEN DEPRIVATION

In 1941, Charles Huggins and a colleague showed that metastatic prostate cancer responds to endocrine manipulation,[1] and this advance led to a Nobel Prize in Physiology or Medicine for Huggins in 1966. The endocrine responsiveness of prostate cancer continues to influence care today, with androgen-deprivation therapy remaining the standard of care for patients presenting with metastatic disease. Dr. Andrew Schally (who won the Nobel Prize in Physiology or Medicine in 1977) and colleagues elucidated the hypothalamic control of pituitary function.[2] The characterization of gonadotropin-releasing hormone analogues paved the way for medical therapy as an alternative to surgical therapy, and this approach is now the most commonly used method of androgen-deprivation therapy in developed countries. Surgical castration remains an effective, inexpensive alternative with some advantages.[3]

For men with an initial diagnosis of metastatic prostate cancer, continuous androgen-deprivation therapy represented the standard of care from 1941 until 2015, when two trials (Androgen Ablation Therapy with or without Chemotherapy in Treating Patients with Metastatic Prostate Cancer [CHAARTED], ClinicalTrials.gov number, NCT00309985; and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy [STAMPEDE], NCT00268476) showed that androgen-deprivation therapy combined with six courses of docetaxel improved survival[4,5] (Table 1). Docetaxel is a taxane that binds tubulin and stabilizes microtubules, thereby inhibiting mitosis and androgen-receptor signaling by disrupting nuclear transport of the receptor.[17] A meta-analysis of all available data from randomized trials comparing docetaxel with the standard of care showed an overall survival benefit with docetaxel (hazard ratio for death, 0.77; 95% confidence interval [CI], 0.68 to 0.87; P<0.001).[18]

Table 1. Practice-Changing Trials of Treatments for Metastatic Prostate Cancer That Improve Survival.*

Trial and Registration No.	Treatment		Median Overall Survival (months)		Hazard Ratio for Death (95% CI)	Year of Initial Report†
	Study Treatment	Control	Study Treatment	Control		
No previous ADT						
CHAARTED, NCT00309985	Docetaxel plus ADT	ADT	57.6	44.0	0.61 (0.47–0.80)	2015[4]
STAMPEDE, NCT00268476	Docetaxel plus ADT	ADT	60	45	0.76 (0.62–0.92)	2015[5]
LATITUDE, NCT01715285	Abiraterone and prednisone, plus ADT	ADT	Not reached	34.7	0.62 (0.51–0.76)	2017[6]
STAMPEDE, NCT00268476	Abiraterone and prednisolone, plus ADT	ADT	Not reached	48	0.61 (0.49–0.75)	2017[7]
Recurrent disease after ADT without chemotherapy						
TAX 327‡	Docetaxel and prednisone	Mitoxantrone and prednisone	18.9	16.5	0.76 (0.62–0.94)	2004[8]
SWOG 9916, NCT00004001	Docetaxel and estramustine	Mitoxantrone and prednisone	17.5	15.6	0.80 (0.67–0.97)	2004[9]
COU-302, NCT00887198 (minimal or no symptoms)	Abiraterone and prednisone	Prednisone	Not reached	27.2	0.75 (0.61–0.93)	2013[10]
PREVAIL, NCT01212991 (minimal or no symptoms)	Enzalutamide	Placebo	32.4	30.2	0.71 (0.60–0.84)	2014[11]
Recurrent disease after ADT and docetaxel						
TROPIC, NCT00417079	Cabazitaxel and prednisone	Mitoxantrone and prednisone	15.1	12.7	0.70 (0.59–0.83)	2010[12]
COU-301, NCT00638690	Abiraterone and prednisone	Prednisone	14.8	10.9	0.65 (0.54–0.77)	2011[13]
AFFIRM, NCT00974311	Enzalutamide	Placebo	18.4	13.6	0.63 (0.53–0.75)	2012[14]
Recurrent disease after ADT, docetaxel status unspecified						
IMPACT, NCT00065442 (minimal symptoms)	Sipuleucel-T	Placebo	25.8	21.7	0.77 (0.61–0.98)	2010[15]
ALSYMPCA, NCT00699751 (symptomatic)	Standard of care plus radium-223	Standard of care	14.9	11.3	0.70 (0.58–0.83)	2013[16]

* ADT denotes androgen-deprivation therapy, and CI confidence interval.
† The date of the initial report may not be the same as the date of the cited publication.
‡ There is no trial registration number for TAX 327.

The CHAARTED study analyzed treatment with docetaxel in a subset of patients who had low-volume disease and a subset with high-volume disease (high-volume disease was defined as disease involving any visceral metastases or at least four bone lesions [with at least one lesion beyond the vertebral bodies and pelvis]).[4] Whereas a considerable benefit was noted for patients with high-volume disease (hazard ratio for death, 0.61; 95% CI, 0.45 to 0.81; P<0.001; median overall survival, 49.2 vs. 32.2 months), patients with low-volume disease had fewer events, with survival data not reaching statistical significance (hazard ratio for death, 0.60; 95% CI, 0.32 to 1.13; P=0.11); longer follow-up data are awaited. The distinction between high- and low-volume metastatic disease is incompletely explored beyond the CHAARTED study. Thus, in assessing data from other trials, distinctions between these subsets are unclear. Toxic effects of docetaxel included grade 3 or 4 febrile neutropenia (in 8 to 12% of patients), neuropathies, alopecia, diarrhea, and fatigue.

The combination of androgen-deprivation therapy and abiraterone with prednisone represents a new standard of care for metastatic disease that is based on data from the CHAARTED and STAMPEDE trials. Abiraterone inhibits androgenic steroid synthesis, targeting cytochrome P450 17A1 (CYP17A1) and blocking 17 alpha-hydroxylase and 17,20 lyase.[19] Recent studies indicate that a common abiraterone metabolite is also an androgen-receptor antagonist, though its clinical significance has not yet been proved.[20] Abiraterone decreases androgens beyond the castrate state by inhibiting adrenal (and possibly intratumoral) steroid synthesis but increases steroid precursors upstream of CYP17, if given without glucocorticoids.[21] Upstream accumulation of steroid precursors can result in hypokalemia and hypertension, as in hereditary CYP17 deficiency.[22] Abiraterone alone has antitumor activity and has been safely administered without glucocorticoids, in combination with the mineralocorticoid receptor antagonist eplerenone, but full clinical activity is unproven.[23] Administration of glucocorticoids in addition to abiraterone decreases upstream mineralocorticoids, as well as related adverse events, and may enhance anticancer activity.[24]

The STAMPEDE trial and the LATITUDE trial (NCT01715285) evaluated androgen-deprivation therapy with or without abiraterone and a glucocorticoid (Table 1). The STAMPEDE trial randomly assigned a total of 1917 patients to a study treatment, 1002 (52%) of whom had received an initial diagnosis of metastatic disease.[7] For patients with metastatic disease, no landmark survival data were reported, but the reduction in the risk of death was substantial for those in the group that received abiraterone and prednisolone (hazard ratio, 0.61; 95% CI, 0.49 to 0.75; P<0.001). For the STAMPEDE group as a whole, including both patients with metastatic disease and those with nonmetastatic disease, the 3-year survival rate was 76% for those who received androgen-deprivation therapy alone, as compared with 83% for those treated with abiraterone and prednisolone in addition to androgen deprivation (hazard ratio with combination treatment, 0.63; 95% CI, 0.52 to 0.76; P<0.001).[7] There was heterogeneity in the outcome according to age, with no survival benefit observed for combined treatment in men with metastatic or nonmetastatic disease who were more than 70 years old.

The LATITUDE trial randomly assigned 1199 men with metastatic prostate cancer to receive androgen-deprivation therapy with or without abiraterone and prednisone.[6] Survival was clearly improved in the abiraterone group (hazard ratio for death, 0.62; 95% CI, 0.51 to 0.76; P<0.001). The 3-year survival rate was 66% for combination therapy, as compared with 49% for androgen deprivation alone. Primary toxic effects included hypertension, hypokalemia, and increased risk of elevated hepatic-enzyme levels.

Overall, these data provide the basis for adding androgen-deprivation therapy combined with abiraterone and a glucocorticoid to the standard of care for patients with metastatic disease at diagnosis; however, neither trial prospectively planned crossover to abiraterone for patients with castration-resistant disease. Thus, the question regarding earlier versus later treatment remains unanswered. Earlier treatment raises concerns about the increased risk of chronic toxic effects of glucocorticoids and androgen-deprivation therapy — specifically, weight gain and myopathy with prednisone, and osteoporosis and metabolic and cardiovascular side effects with protracted, more intensive androgen deprivation.

Though the effectiveness of abiraterone and that of docetaxel in prolonging survival appear

to be equivalent,[25] clear distinctions are noted in the duration of therapy used in previous trials for patients with an initial diagnosis of metastatic disease. The docetaxel regimen is completed after 18 weeks (one infusion given every 3 weeks, for a total of six infusions), whereas the abiraterone–prednisone regimen is given until disease progression, which may result in prolonged drug exposure. The duration and cost of treatment may influence clinical decision making. Comparisons of docetaxel and abiraterone according to the duration of therapy have been incompletely explored.

Data from studies determining whether contemporaneous administration of androgen-deprivation therapy, docetaxel, and abiraterone–prednisone is superior to serial administration of these agents are awaited. Selection of patients for treatment on the basis of molecular biomarkers has been notably absent in studies of hormone treatment for patients with an initial diagnosis of metastatic disease.

As more therapies are proved to be effective for metastatic disease, the question of their effectiveness in patients with nonmetastatic but high-risk disease will arise. Such questions can be answered only by means of direct clinical trials.

DETECTION OF METASTATIC DISEASE AND IMPROVED IMAGING

The definition of metastatic disease depends on the type of imaging used. Older definitions were typically based on the use of radionuclide bone scanning and computed tomography (CT), but approaches to imaging are currently in a state of flux, with newer, more sensitive imaging methods detecting evidence of disease spread, even though conventional imaging shows no signs of metastasis. The implications of using more sensitive imaging techniques, and their relationship to therapy, are not yet fully understood.

Improved imaging, including positron-emission tomography (PET) with prostate-specific membrane antigen (PSMA) or with choline or fluciclovine and whole-body magnetic resonance imaging (MRI), is enabling earlier and better identification of metastases.[26,27] PSMA PET shows the expression of PSMA on the cell surface in prostate cancer. More accurate imaging may change the diagnosis from nonmetastatic to metastatic disease. However, pathological con-

firmation of positive imaging studies is incomplete. Earlier detection of metastases may affect treatment selection for both local and metastatic disease. Trials evaluating treatment of oligometastatic disease with stereotactic body irradiation are under way. The usefulness of new imaging techniques in patients with prostate cancer will remain uncertain until a clinical benefit has been shown in trials that directly assess these techniques.

TREATMENT OF THE PRIMARY SITE IN MEN WITH METASTATIC DISEASE

Because of better treatments for metastatic disease, men are living longer with local disease that may provide a sanctuary from systemic therapy and may result in an increased risk of local complications and a need for urologic interventions. Grade A evidence is needed to guide local treatment in men with metastatic disease. Trials addressing this issue are under way.

PATHOPHYSIOLOGICAL AND GENETIC FEATURES OF CASTRATION-RESISTANT PROSTATE CANCER

DEFECTS IN ANDROGEN-RECEPTOR SIGNALING

Androgen-receptor signaling is altered in castration-resistant prostate cancer, with increased intratumoral steroidogenesis, altered steroid-transporter expression, increased androgen-receptor expression frequently due to gene copy-number gains, androgen-receptor gene mutations imparting ligand promiscuity and activated by glucocorticoids or androgen-receptor antagonist therapeutics, and androgen-receptor gene rearrangements resulting in preferential expression of constitutively active receptor splice variants.[28-30] These androgen-receptor splice variants, the most common of which is AR-V7, can also be generated in the absence of gene rearrangements and can delete the androgen-receptor ligand-binding regulatory domain.[31] Constitutive receptor-mediated transcriptional activation can occur despite the absence of ligand.[32] Strategies targeting these splice variants are now being prioritized.

SOMATIC GENOMIC ALTERATIONS

Genomic aberrations in metastatic, castration-resistant prostate cancer may be similar to or distinct from genomic alterations in primary

prostate tumors that have not been treated with androgen deprivation[33,34] (Table 2). The most common alterations in patients with metastatic disease involve the androgen receptor (in >60% of patients), but p53 mutations or deletions are also common and can be concurrent with RB1 loss, together leading to lineage plasticity from luminal to basal phenotypes.[35] The loss of tumor suppressor PTEN, as well as other aberrations activating AKT signaling, and ETS rearrangements (e.g., TMPRSS2–ERG) commonly occur together.[34] SPOP mutations, which are found in 10% of metastatic, castration-resistant prostate cancers, activate both androgen-receptor and AKT signaling.[36] Deleterious DNA-repair aberrations in genes, including BRCA2, ATM, BRCA1, PALB2, and RAD51D, occur in 20 to 25% of patients.[34] Defective mismatch repair has also been reported,[34,37] and this may be missed by targeted exome or exon sequencing.[37]

The use of advanced genomic analysis is now feasible to a greater extent than ever before. Whether its use improves treatment decisions is not yet clear.

GERMLINE MUTATIONS

Deleterious germline DNA-repair defects (Table 3) are present in at least 12% of patients with metastatic, castration-resistant prostate cancer; the most common defects are alterations in BRCA2, CHEK2, and ATM.[38] Germline DNA-repair mutations have implications not only for the patient's treatment and prognosis but also for the care of family members.[39,40] BRCA1/2 mutations are highly penetrant for female family members, increasing the risk of breast or ovarian cancer. For male family members, penetrance is lower, but prostate cancer, breast cancer, and pancreatic cancer all occur at increased rates among those with BRCA mutations. Estimates of the incidence of prostate cancer by the age of 80 years range from 19 to 61% for BRCA2 mutations (depending on the risk scores for each mutation) and from 7 to 26% for BRCA1 mutations.[8]

Germline mutations in mismatch-repair genes (MLH1, MSH2, MSH6, and PMS2) are clearly described in the Lynch syndrome and are also clearly described in a small percentage of men with advanced prostate cancer (0.6%), but convincing evidence that these mutations contribute to an increased incidence of advanced disease is sparse. No increased mutational frequency in

Table 2. Selected Gene Aberrations in Patients with Metastatic Prostate Cancer.*

Gene	% of Patients with Aberrant Gene	Pathway	Common Aberrations†
AR gene	62.7	Androgen signaling	Amplification, splice variants, mutation
TP53	53.3	Cell cycle or tumor suppressor	Mutation, copy loss
PTEN	40.7	PI3K–AKT regulator	Copy loss, mutation
ETS	56.7	Transcriptional regulator	Gene fusions
BRCA2	13.3	DNA repair	Copy loss, mutation
KMT2C	12.7	Chromatin modifier	Mutation
FOXA1	12.0	AR-associated	Mutation
ZBTB16	10.0	AR-associated	Copy loss
RB1	9.3	Cell cycle	Copy loss
APC	8.7	Wnt pathway	Copy loss, mutation
CHD1	8.0	Chromatin modifier	Copy loss, mutation
SPOP	8.0	Androgen signaling	Mutation
ATM	7.3	DNA repair	Copy loss, mutation

* Data are from Robinson et al.[34] AR denotes androgen receptor.
† Aberrations are listed in descending order of predominance (e.g., for TP53, mutation is the predominant gene alteration, and for PTEN, copy loss is predominant).

Table 3. Selected Common Germline DNA-Repair Mutations in Patients with Metastatic Prostate Cancer.*

Gene	% of Patients with Mutation	Relative Risk of Metastases†
BRCA2	5.35	18.6
CHEK2	1.87	3.1
ATM	1.59	6.3
BRCA1	0.87	3.9
GEN1	0.46	5.8
RAD51D	0.43	5.7
PALB2	0.43	3.5

* Data are from Pritchard et al.[37]
† Relative risks are for the comparison with men who do not have known prostate cancer.

mismatch-repair genes has been detected among men with metastatic disease as compared with controls (men without prostate cancer).[38]

TREATMENT OF CASTRATION-RESISTANT PROSTATE CANCER

The first agent that was shown to prolong survival among men with metastatic, castration-resis-

tant prostate cancer was docetaxel. Two phase 3 trials showed a significant overall survival benefit in 2004.[9,15] One trial (TAX 327), which compared two schedules of docetaxel and prednisone with mitoxantrone and prednisone (control), showed improved overall survival for patients treated with 75 mg of docetaxel per square meter of body-surface area every 3 weeks (hazard ratio for death, 0.76; 95% CI, 0.62 to 0.94; P=0.009); the median survival was 18.9 months for this group and 16.5 months for the control group.[9] The second phase 3 trial (Southwest Oncology Group [SWOG] Intergroup protocol 99-16 [NCT00004001]), which compared docetaxel and estramustine, administered in 3-week cycles, with mitoxantrone and prednisone, also showed superior overall survival with docetaxel.[15] Given the toxic effects of estramustine, docetaxel at a dose of 75 mg per square meter with oral prednisone at a dose of 5 mg twice a day became the de facto standard frontline chemotherapy regimen. Docetaxel has a variety of toxic effects, including bone marrow suppression, dysgeusia, alopecia, nail changes, and allergic reactions.

Clinical progress in treating metastatic, castration-resistant prostate cancer during the past 7 years has been remarkable. Pivotal trials resulting in an overall survival benefit have led to regulatory approval for two hormonal therapies, an additional taxane, a bone-targeted and alpha-emitting radionuclide, and an immunotherapy.

In 2010, an autologous cellular immunotherapeutic agent (sipuleucel-T) was shown to provide an overall survival benefit in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) study (NCT00065442), a pivotal phase 3 trial comparing sipuleucel-T (administered every 2 weeks for a total of three doses) with an unstimulated cellular product in 512 patients with metastatic, castration-resistant prostate cancer who had minimal or no symptoms.[13] For sipuleucel-T, autologous peripheral-blood mononuclear cells (including antigen-presenting cells) were activated ex vivo with the use of a combination of cytokines and a recombinant fusion protein consisting of prostatic acid phosphatase and granulocyte–macrophage colony-stimulating factor. The median overall survival was 25.8 months for patients receiving sipuleucel-T and 21.7 months for controls (hazard ratio for death in the sipuleucel-T group, 0.78; 95% CI, 0.61 to 0.98; P=0.03). Adverse events included pyrexia, chills, fatigue, nausea, and headache.

Two new hormonal agents, abiraterone and enzalutamide, have had the largest effect on castration-resistant prostate cancer. The activity of 1000 mg of abiraterone and prednisone at a dose of 5 mg twice a day, as compared with placebo plus prednisone, was initially proved in a study involving patients with metastatic, castration-resistant prostate cancer who had been treated with docetaxel.[10] An overall survival advantage with abiraterone and prednisone as compared with placebo and prednisone was noted (hazard ratio for death, 0.65; 95% CI, 0.54 to 0.77; P<0.001), with elevated liver-function values as mineralocorticoid-associated side effects (hypertension, hypokalemia, and edema). The median overall survival was 14.8 months for the group treated with abiraterone and prednisone versus 10.9 months for the control group.

The combination of abiraterone and prednisone was subsequently compared with placebo and prednisone in the COU-AA-302 trial (NCT00887198) for the treatment of men with metastatic, castration-resistant disease, minimal or no symptoms and no previous chemotherapy.[41] Survival with no radiographic evidence of disease progression and overall survival were used as the coprimary end points. The initial analysis showed that the abiraterone–prednisone group had significantly improved progression-free survival (hazard ratio for radiographic evidence of progression, 0.53; 95% CI, 0.45 to 0.62; P<0.001), with a trend toward improved overall survival.[41] The final planned analysis showed a benefit of abiraterone and prednisone with respect to overall survival, with a median overall survival of 34.7 months, versus 30.3 months with placebo and prednisone (hazard ratio for death, 0.81; 95% CI, 0.70 to 0.93; P=0.003).[42] Mineralocorticoid-associated adverse events were noted, as well as occasional liver-function abnormalities and hyperglycemia.

Enzalutamide is a potent and new androgen-receptor antagonist.[14] The initial phase 3 trial (AFFIRM [A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100], NCT00974311) evaluated enzalutamide for metastatic, castration-resistant prostate cancer previously treated with docetaxel. Treatment with oral

enzalutamide at a dose of 160 mg per day was associated with improved overall survival, as compared with placebo (hazard ratio for death, 0.63; 95% CI, 0.53 to 0.75; P<0.001; median survival, 18.4 months with enzalutamide vs. 13.6 months with placebo).[43] Toxic effects included fatigue and hot flashes; seizures were reported in a small proportion of patients (<1%).

Enzalutamide at a dose of 160 mg per day also improved both radiographic progression-free survival and overall survival in men with asymptomatic or mildly symptomatic disease who had not previously received chemotherapy (PREVAIL, NCT01212991).[11] The hazard ratio for death with enzalutamide as compared with placebo was 0.71 (95% CI, 0.60 to 0.84; P<0.001). On the basis of the initial analysis, the median overall survival was 32.4 months with enzalutamide and 30.2 months with placebo.[43] The final analysis showed median estimates of 35.3 and 31.3 months, respectively (hazard ratio for death with enzalutamide, 0.77; 95% CI, 0.67 to 0.88; P< 0.001).[12] Adverse events in this trial did not include seizures but did include fatigue, falls, and nonpathologic fractures.

Cabazitaxel is a taxane specifically designed for antitumor activity in docetaxel-resistant models.[44] The pivotal phase 3 trial (TROPIC, NCT00417079) evaluated cabazitaxel in patients with disease progression after treatment with docetaxel. Cabazitaxel at a dose of 25 mg per square meter was administered intravenously every 3 weeks. The end point was overall survival, with a median of 12.7 months in the control group and 15.1 months in the cabazitaxel group (hazard ratio for death with cabazitaxel, 0.70; 95% CI, 0.59 to 0.83; P<0.001). Febrile neutropenia and diarrhea were significantly more frequent in the cabazitaxel group than in the control group. In a subsequent phase 3 trial with a noninferiority design (PROSELICA, NCT01308580), a dose of 20 mg of cabazitaxel per square meter was noninferior to a dose of 25 mg per square meter with respect to overall survival, with the lower dose capturing at least 50% of the survival benefit of the higher dose with decreased toxicity, making a dose of 20 mg per square meter an alternative standard of care.[45]

Radium-223 is an alpha-particle–emitting radionuclide that binds preferentially to the hydroxyapatite in osteoblastic bone metastases.[16] A phase 3 trial (Alpharadin in Symptomatic Prostate Cancer Patients [ALSYMPCA], NCT00699751) showed that radium-223 combined with the "best standard of care" resulted in improved overall survival, as compared with the best standard of care alone, for men who had symptomatic bone metastases without visceral metastasis and without nodal metastases larger than 3 cm in the short-axis diameter.[46] The best standard of care included older hormonal therapies (e.g., antiandrogens, glucocorticoids, and estrogens), bisphosphonates, and external-beam radiation therapy but excluded chemotherapies. Overall survival was prolonged in the radium-223 group (median, 14.9 months, vs. 11.3 months in the control group; hazard ratio for death, 0.70; 95% CI, 0.58 to 0.83; P<0.001). Patients who had not previously received chemotherapy and those previously treated with docetaxel both had improved overall survival with radium-223 as compared with placebo. Adverse events with radium-223 included diarrhea and a small number of cases of thrombocytopenia.

Bone-targeted agents such as zoledronic acid and denosumab are approved by the Food and Drug Administration (FDA) for use in patients with castration-resistant prostate cancer and bone metastases in order to prevent skeletal adverse events such as pathologic fractures, spinal cord compression, and the effects of radiation and surgery on bone. However, the use of these agents is somewhat controversial because a clinical benefit has not been clearly shown in patients receiving concomitant newer anticancer agents such as abiraterone and enzalutamide.

METASTASIS-FREE SURVIVAL

Multiple ongoing trials are evaluating antiandrogens as compared with placebo in men with nonmetastatic, castration-resistant prostate cancer, with metastasis-free survival as an end point. The definition of nonmetastatic prostate cancer, however, depends on the sensitivity of the imaging technique used and is likely to change with improved PET and MRI technologies. It is not yet clear whether prolongation of the time to radiographic evidence of metastases is clinically useful or provides an overall survival benefit in this patient population.

COMPARISONS, COMBINATIONS, AND SEQUENCING

Multiple trials have shown improvement in overall survival with the use of various agents, but only one large trial to date has compared two life-prolonging therapies. That trial (FIRSTANA, NCT01308567) failed to show that cabazitaxel was superior to docetaxel in men with metastatic, castration-resistant prostate cancer who had not received previous chemotherapy.[47] Overall, grade A data support the use of sipuleucel-T, enzalutamide, abiraterone–prednisone, docetaxel, and radium-223 in selected populations of men with metastatic, castration-resistant prostate cancer who have not received previous chemotherapy. Grade A evidence also supports the use of enzalutamide, abiraterone–prednisone, cabazitaxel, and radium-223 in selected patients after treatment with docetaxel. Grade A data are lacking for combinations of these therapies or for sequential use, apart from the use of radium-223 after docetaxel, leaving clinicians with imperfect guidance on treatment selection for individual patients.

Despite limitations, some consistent observations have arisen. First, cross-resistance occurs between the new androgen-receptor–targeting agents. The rate of response to abiraterone therapy after treatment with enzalutamide is less than 10%, whereas the response rate for enzalutamide after abiraterone is 15 to 30%.[48-50] The benefit from taxanes appears to be diminished after treatment with abiraterone or enzalutamide, as compared with the benefit in patients who have not received such treatment, although taxanes remain active.[51] No large, prospective, randomized trials of treatment with taxanes in men previously treated with abiraterone or enzalutamide have been completed. Thus, guidance in making treatment decisions for such patients is limited.

Combination therapy is being explored clinically on several fronts (Table 4). Both enzalutamide and apalutamide with or without abiraterone are being evaluated in large, prospective trials. A trial involving patients with disease progression during treatment with enzalutamide with or without abiraterone failed to meet the primary end point.[52] Abiraterone with or without radium-223 and enzalutamide with or without radium-223 are both being evaluated but without overall survival as the primary end point.

NEUROENDOCRINE AND SMALL-CELL VARIANTS OF PROSTATE CANCER

Prostate cancer is typically adenocarcinoma, although small-cell and neuroendocrine variants are described in a minority of cases. The small-cell variant is typically CD56-positive with RB1 deletion, and the usual treatment for this variant, like that for any other small-cell tumor, is usually a platinum-based regimen. The neuroendocrine variants are now a focus of considerable research, although from a pathological perspective, there is no consensus on definitions of these variants. Some evidence indicates that neuroendocrine tumors are more likely to arise after extreme androgen deprivation, such as that induced by exposure to abiraterone or enzalutamide. Trials evaluating treatments for neuroendocrine tumors (variously defined) are under way but without practice-changing results to date.

PROGNOSTIC AND PREDICTIVE BIOMARKERS

A variety of prognostic schemata have been proposed, including many nomograms. Performance status; extent of disease; pain status; location of disease (e.g., bone or liver); levels of hemoglobin, serum alkaline phosphatase, lactate dehydrogenase, albumin, aspartate aminotransferase, circulating tumor cells, and plasma cell-free DNA; neutrophil-to-lymphocyte ratio; and kinetics of disease progression contribute to the prognosis.[53-55]

Predictive biomarkers are being explored. Androgen-receptor aberrations have been linked to resistance in various patient populations. AR-V7–encoding RNA expression in circulating tumor cells is associated with a poor prognosis and resistance to abiraterone and enzalutamide but not to taxanes.[56,57] AR-V7 protein in tumor cells is also correlated with resistance to abiraterone and enzalutamide but not to taxanes.[58] Studies using circulating cell-free DNA assays have shown that androgen-receptor amplifica-

Table 4. Selected Potentially Practice-Changing Trials in Progress.*

Trial	Treatment Regimen	Comments	Trial Registration No.
Metastatic disease, no previous ADT			
STAMPEDE, group H	Standard of care with or without prostate irradiation	Enrollment complete	NCT00268476
STAMPEDE, group J	Standard of care with or without enzalutamide, abiraterone, and prednisolone	Enrollment complete	NCT00268476
ENZAMET	ADT plus antiandrogen vs. ADT plus enzalutamide	Enrollment complete	NCT02446405
STAMPEDE, group K	Standard of care with or without metformin	Enrollment ongoing	NCT00268476
STAMPEDE, group L	Standard of care with or without transdermal estrogen	Enrollment ongoing	NCT00268476
PEACE-1	ADT with or without docetaxel, with or without prostate irradiation, with or without abiraterone and prednisone	Enrollment ongoing	NCT01957436
ARASENS	ADT plus docetaxel with or without darolutamide	Enrollment ongoing	NCT02799602
SWOG 1216	ADT plus bicalutamide vs. ADT plus orteronel	Enrollment ongoing	NCT01809691
Metastatic CRPC			
VIABLE	Docetaxel with or without DCVAC	Enrollment ongoing	NCT02111577
Alliance A031201	Enzalutamide with or without abiraterone and prednisone	Enrollment complete	NCT01949337
IPATential150	Abiraterone and prednisone, with or without ipatasertib	Enrollment ongoing: biomarker-stratified PTEN loss	NCT03072238
IMbassador250	Enzalutamide with or without atezolizumab	Enrollment ongoing (after abiraterone or enzalutamide)	NCT03016312
CRPC with bone metastasis			
PEACE-3	Enzalutamide with or without radium-223	Enrollment ongoing	NCT02194842
ERA 223†	Abiraterone with or without radium-223	Enrollment complete	NCT02043678
Metastatic CRPC with DNA-repair mutation, PARP-inhibitor studies			
TRITON3	Physician's choice vs. rucaparib	No prior treatments for CRPC required	NCT02975934
PROfound	Enzalutamide or abiraterone vs. olaparib	Administered after abiraterone or enzalutamide	NCT02987543
Galahad	Niraparib (phase 2)	Administered after abiraterone or enzalutamide and after docetaxel	NCT02854436
Nonmetastatic CRPC			
SPARTAN‡	Placebo vs. apalutamide	Enrollment complete	NCT01946204
ARAMIS	Placebo vs. darolutamide	Enrollment ongoing	NCT02200614
PROSPER‡	Placebo vs. enzalutamide	Enrollment ongoing	NCT02003924

* According to the STAMPEDE trial results in 2015, the standard of care is androgen-deprivation therapy plus optional docetaxel if the clinician recommends it. CRPC denotes castration-resistant prostate cancer.
† The ERA 223 trial was unblinded in December 2017 after a recommendation from an independent data monitoring committee regarding safety concerns focused on bone fractures and survival.
‡ Data from the SPARTAN and PROSPER trials will be presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium in February 2018.

tion and certain mutations (positions 702 and 878) are also associated with resistance to abiraterone and enzalutamide.[29,59,60] The clinical usefulness of these assays has yet to be ascertained in large, prospective studies, and the assay results may not be assessable in all patients.

Deleterious somatic and germline aberrations in DNA-repair genes are common in men with metastatic, castration-resistant prostate cancer.[34] Homologous recombination repair defects, the most common of which is BRCA2, may confer sensitivity to poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors and platinum-based therapy.[61,62] Multiple trials of PARP inhibitors in this patient population are ongoing.

Mismatch repair in tumor cells is deficient in 5 to 12% of men with metastatic, castration-resistant prostate cancer.[34,37,38] Pembrolizumab, an antibody that targets programmed death 1 (PD-1), is now approved by the FDA for cancers with defective mismatch repair.[63] Further studies are needed to elucidate the relationship between this disease state and immunotherapy. Preliminary data indicate that not all men with tumors that are deficient in mismatch repair have a response to immunotherapy, although impressive responses have been reported in some cases. Response rates in the range of 10 to 20% have been reported for molecularly unselected men treated with PD-1 inhibition.[64,65]

Loss of PTEN expression, which is common in metastatic, castration-resistant prostate cancer (observed in >40% of cases), activates AKT signaling.[34,66,67] Targeting the AKT kinase may have therapeutic value in men with PTEN loss.[68] Studies of inhibitors of this pathway are ongoing.

PSMA is expressed in most tumors, although intrapatient heterogeneity of expression has been reported.[69] PSMA ligands or anti-PSMA antibodies can be conjugated to radionuclides (either alpha- or beta-particle emitters) or cytotoxic agents, and multiple PSMA strategies are currently undergoing evaluation.[70-73]

RESPONSE AND SURROGATE BIOMARKERS

The validation and clinical qualification of improved response and surrogate biomarkers are a high priority in research on prostate cancer. Biomarkers, including circulating tumor-cell counts and cell-free DNA, have shown promise.[74] Radiographic evidence of progression-free survival, with the use of CT scans and bone scans, has been evaluated as a response biomarker,[75] but surrogacy for an overall survival benefit has not been shown. Clinical deterioration may be more important than radiographic progression,[76] but full acceptance of this end point has not been verified.

UNMET NEEDS, CHALLENGES, AND OPPORTUNITIES

Advanced prostate cancer is a disease that reliably progresses and is fatal. Today, the new hormonal agents are typically used for the treatment of prostate cancer before chemotherapy, but large, prospective trials involving patients with disease progression while receiving treatment with abiraterone or enzalutamide have failed to yield clear evidence that these new hormonal agents provide a clinical benefit. Optimal sequencing of the various agents is currently unknown. Furthermore, despite a rationale for combination therapy (which is typically used for most cancers), no large, randomized trials testing combination therapy for advanced prostate cancer have been reported to date.

Though newer studies indicate that a variety of potentially actionable genetic alterations can be detected in prostate cancer, no therapy targeting these alterations has yet been shown to have a clinical benefit. Novel forms of immunotherapy, especially PD-1 inhibitors, are active in a variety of cancers, especially those with high mutational frequencies. Prostate cancer has a lower mutational burden, and the use of PD-1 inhibitors for prostate cancer remains experimental (though the activity of these agents may be higher in tumors with defective mismatch repair than in tumors with other genetic alterations). Thus, advanced genetics and immunology, two major drivers of progress in oncology, are not routinely incorporated into the care of patients with prostate cancer.

Although we celebrate the life-prolonging effects of the new hormonal therapies, the diagnosis of metastatic prostate cancer currently leads to lifelong androgen-deprivation therapy. Despite progress on multiple research fronts, we have imperfect tools to identify patients who need

therapy in the first place, and once the disease spreads beyond the control of local therapies, we do not know how best to sequence or combine the expanding number of active therapies.

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