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Systemic Therapy for the Treatment of Hormone-Sensitive Metastatic Prostate Cancer: from Intermittent Androgen Deprivation Therapy to Chemotherapy

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Abstract Treatment of advanced prostate cancer has changed considerably in recent years, but the vast majority of advances have been made in patients with metastatic castration-resistant disease. There have been relatively fewer advances in the earlier, hormonally responsive stage of metastatic disease. Since the empiric establishment of androgen deprivation therapy as first-line therapy for metastatic prostate cancer decades ago, there have been multiple studies looking at variations of suppressing testosterone, but the overall paradigm has not been strongly challenged until more recently. In particular, the dramatic results reported by the CHAARTED trial not only bring chemotherapy to an arena historically dominated solely by hormonal therapy but also stimulate renewed efforts into improving upon our management of metastatic hormone-sensitive prostate cancer.

Keywords Hormone-sensitive · Metastatic · Prostate cancer · Androgen deprivation therapy · Intermittent · Combined androgen blockade

Introduction

In 1941, Charles Huggins and Clarence Hodges published their seminal work establishing the relationship between growth of prostate adenocarcinoma and androgenic hormones [1, 2]. By suppressing testosterone production, either pharmacologically or surgically, improvements in acid and alkaline phosphatases were observed [1], and dramatic clinical benefits were observed in men with advanced, metastatic prostate cancer [2]. These findings quickly paved the way for androgen deprivation therapy to be empirically accepted as first-line treatment for prostate cancer patients with metastatic disease. Since then, despite years of collective clinical experience and multiple large multicenter clinical trials, many questions about the optimal management of hormone-sensitive metastatic prostate cancer remained unanswered. For instance, was there an optimal manner by which to suppress testosterone? Was combined androgen deprivation therapy better than monotherapy? Did intermittent androgen deprivation therapy (ADT) have a role in extending survival and improving quality of life? Could the addition of other therapies at the time of diagnosis of metastatic disease improve survival? Recent randomized trials have brought some intriguing new data to consider (Fig. 1).

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Primary Androgen Deprivation Therapy

ADT remains the mainstay of treatment for metastatic hormone-sensitive prostate cancer. Castrate levels of testosterone can be effectively achieved by either bilateral orchiectomy or gonadotropin releasing hormone (GnRH) agonists or antagonists. Both approaches are recommended by consensus guidelines issued by the American Society of Clinical Oncology (ASCO) and the European Association of Urology (EAU) [3, 4].

While ADT demonstrates antitumor activity, it is not curative. Decreases in serum prostate-specific antigen (PSA) levels are observed in >90 % of patients following initiation

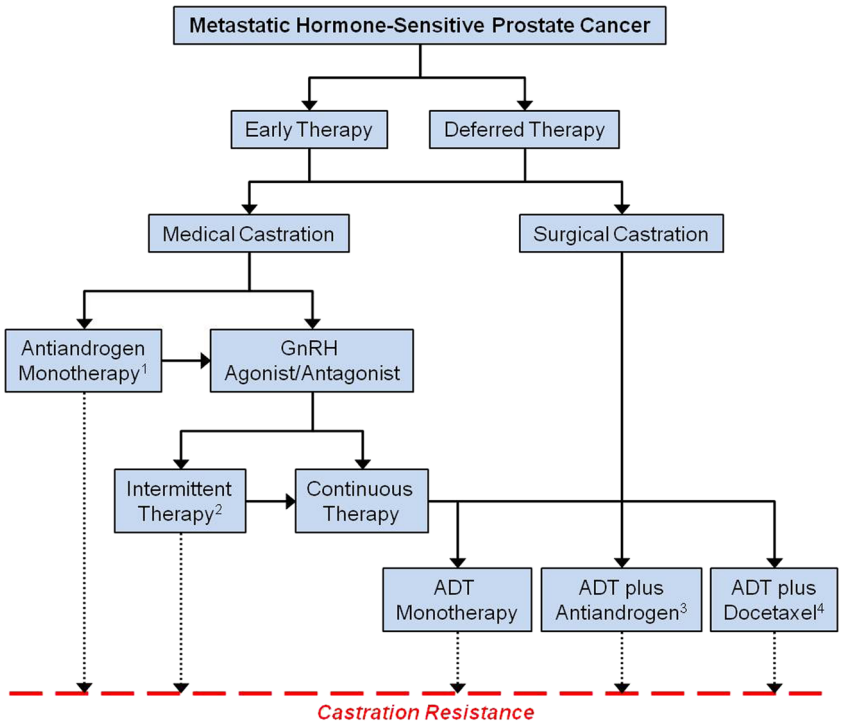

Fig. 1 Treatment options for metastatic hormone-sensitive prostate cancer. *1* Consideration in select low-risk patients, serum testosterone remains normal to high. *2* Consideration in select patients, may be associated with limited QOL benefits. *3* Small benefit for 5-year cancer-specific survival, but higher rates of adverse events. *4* Convincing data in high volume disease, but data not yet mature for low volume disease

of ADT, with objective tumor responses seen in 80–90 %. This response is often associated with improvements in quality of life (QOL) by reducing bone pain, decreasing skeletal-related events (SRE), and improving symptoms of urinary obstruction. Time to the development of resistance to primary ADT is variable, but the median duration is approximately 18 to 24 months. Response to primary ADT varies from person to person and is influenced by factors such as Gleason score, sites of metastases, and overall volume of disease. The depth of PSA nadir following initiation of ADT has been shown to be a strong predictor of survival. In a large intergroup study in which all patients received 7 months of induction ADT, a nadir PSA ≤0.2 ng/mL was associated with the best survival outcomes, followed by attaining PSA levels between 0.2 and ≤4.0 ng/mL, and lastly PSA nadirs >4.0 ng/mL (75 vs. 44 vs. 13 months, $p<0.0001$) [5]. These results suggest that persistent PSA levels are a powerful indicator of the presence of residual castration-resistant cancer cells.

Medical Castration The initial Nobel Prize-winning work pioneered by Huggins and Hodges used diethylstilbestrol (DES) as the castrating agent. DES was further studied by the Veterans Administration Cooperative Urological Research Group (VACURG) in a series of clinical trials that showed that DES plus orchiectomy provided no benefit over DES alone, that early initiation of DES had no survival benefit over delayed DES, and that DES had significant cardiovascular toxicities at higher doses [6, 7]. DES thus became the first widely accepted medical regimen for pharmacologic castration.

GnRH was later isolated in 1971 [8]. Modifications to the peptide at the sixth amino acid position yielded potent GnRH analogues that have a paradoxical effect on pituitary cells. Tonic stimulation by the synthetic GnRH analogues causes an initial surge in hormone production, but subsequent down-regulation of the GnRH receptors which leads to inhibition of LH and FSH production, ultimately resulting in the suppression of androgen production.

Leuprolide, one of the first GnRH analogues introduced, was compared to DES in a randomized clinical trial of men with metastatic prostate cancer, where it was found to be therapeutically equivalent to DES [9]. Other than having a higher rate of hot flashes, leuprolide had fewer cardiovascular side effects, less gynecomastia, and less nausea and vomiting compared to DES [9]. Leuprolide quickly replaced DES as the preferred agent.

Other GnRH agonists (analogues) have since been introduced (i.e., goserelin, triptorelin, buserelin, histrelin) and are the current standards of care for ADT. In the present context, DES is no longer considered a first-line treatment option and is not commercially available in North America (although it is available through compounding pharmacies) [3]. Each GnRH agonist varies in its frequency and route of administration, but their efficacy is generally accepted to be similar. For instance, in a randomized trial triptorelin versus leuprolide, triptorelin reduced testosterone concentrations at a slightly slower rate, but there was no evidence that this difference caused any deleterious effects [7].

Adverse effects of GnRH agonists include hot flashes, decreased bone density, decreased libido and sexual function, gynecomastia, cardiovascular events, and increased insulin resistance. In addition, due to the initial surge in androgen production, prostate cancer-related pain and obstructive urinary symptoms can be exacerbated in the short term [10]. Antiandrogens were found in a placebo-controlled trial to be an effective solution, significantly decreasing these transient effects [11]. However, in a large retrospective study of 1566 men with metastatic prostate cancer, the use of antiandrogen prior to initiating a GnRH agonist to ameliorate the testosterone flare was not associated with any significant differences in fractures, spinal cord compression, or bladder outlet obstruction [12]. The rates of spinal cord compression or fractures were <1 % in the first 30 days after starting GnRH agonist regardless of antiandrogen use [12].

The general practice has evolved to avoid initiating men with severe urinary obstruction or painful bony metastases on a GnRH agonist alone without first using an antiandrogen to mitigate the transient testosterone flare. Antiandrogen therapy is usually started 1–2 weeks prior to a GnRH agonist for patients at high risk for a clinical flare and continued for at least 2–4 weeks.

Surgical Castration Although less frequently utilized as the primary modality for ADT, bilateral orchiectomy offers the advantage of being able to rapidly decrease testosterone to castrate levels and also to be a permanent, single intervention. In emergent situations, such as impending fracture or spinal cord compression where an immediate decrease in serum testosterone is required, bilateral orchiectomy may be an effective option that can be considered. Orchiectomy may also present a more practical and less costly alternative in cases where clinical follow-up and medical compliance are difficult.

Medical vs. Surgical Castration The decision to pursue medical or surgical castration usually comes down to personal preference, although cost and availability are factors to consider as well. Bilateral orchiectomy is a permanent procedure and can potentially come with a high psychological cost. GnRH agonists are generally reversible upon cessation, although depending on age and duration on treatment, testosterone levels may not fully return to their pretreatment baselines.

Both approaches are clinically effective, although the depth of testosterone suppression achieved by GnRH agonists may not be equal to that induced by orchiectomy, as a small but clinically significant number of men fail to maintain castrate levels of testosterone on GnRH agonists [13, 14]. A meta-analysis of 10 trials comparing GnRH agonists with orchiectomy found no statistically significant difference in overall survival [15]. Equivalence was also seen in progression-related outcomes and time to treatment failure [15]. Thus, either surgical or medical castration is an appropriate option to consider for primary ADT in the setting of metastatic, hormone-sensitive prostate cancer.

Defining "Castrate" Levels of Testosterone

The ideal serum testosterone level after ADT remains a controversial issue. The definition of castrate levels of testosterone was set at <50 ng/dL based on measurements found in post-orchiectomy patients using older-generation laboratory technology. Modern chemiluminescent technology, however, reports the median post-orchiectomy testosterone levels to be 15 ng/dL [16]. This difference has led some to suggest that "castrate" levels should be redefined to be <20 ng/dL, although no clinical trials have definitely correlated this lower level with any additional therapeutic or survival advantage.

In the absence of definitive data, the National Comprehensive Cancer Network (NCCN) has retained the <50 ng/dL standard for castrate levels of testosterone. Monitoring a patient's testosterone response while on a GnRH agonist can be clinically helpful, especially if the expected clinical or biochemical response is not observed [17]. Additional hormonal manipulations can be considered for patients who do not achieve adequate suppression of testosterone following either medical or surgical castration, although the clinical benefits of this approach have not yet been proven.

Antiandrogen Monotherapy

Nonsteroidal antiandrogens competitively inhibit the binding of testosterone and dihydrotestosterone (DHT) to the androgen receptor but do not block the hypothalamic-pituitary axis or the subsequent production of testosterone. As a result, serum testosterone levels in patients treated with antiandrogens alone are often normal or higher than normal. Antiandrogen monotherapy was explored in early clinical trials with the goal of minimizing unfavorable side effects associated with castrate levels of testosterone, while still controlling cancer.

Compared to GnRH agonist therapy, sexual function and libido are indeed better preserved with antiandrogen monotherapy, with up to one third of patients maintaining sexual function over the course of therapy, even at higher doses (bicalutamide 150 mg daily) [18]. Antiandrogen monotherapy is also associated with better maintenance of bone marrow density and less fat accumulation [19, 20], but gynecomastia and breast tenderness occur in up to 80 % of patients [21]. This is an expected toxicity since the supraphysiologic levels of testosterone are converted to estrogen, which causes these side effects in male breast tissue. Tamoxifen and prophylactic breast irradiation have been shown to reduce the incidence of gynecomastia and breast pain. While tamoxifen is more

effective than radiotherapy [22], its other potential effects on the hypothalamic-pituitary axis prevent it from being our first recommended strategy.

Multiple studies have compared antiandrogen monotherapy with bilateral orchiectomy, DES, or GnRH agonists. Survival data are mixed, with some studies showing that antiandrogen monotherapy is not as effective as [23–25] or confers similar survival benefits as medical or surgical castration [26, 27]. There have been no trials directly comparing different antiandrogen agents head to head. In one meta-analysis, antiandrogen monotherapy trended towards a shorter OS as compared to castration, but this difference did not reach statistical significance [15].

Nonsteroidal antiandrogens are still often used in combination with GnRH agonists as part of primary combined androgen blockade, or added as a secondary hormonal agent when castration resistance develops. Antiandrogen monotherapy remains an option for lower risk metastatic disease patients that wish to prioritize preservation of sexual function [3], but that decision should be preceded by a conversation detailing risks and benefits.

Combined Androgen Blockade

Combined androgen blockade (CAB) employs the concurrent use of a GnRH agonist and an antiandrogen to maximize androgen ablation. In two of the largest randomized studies evaluating the combined approach, leuprolide plus flutamide demonstrated an improved median overall survival (OS) (35.6 vs. 28.3 months, $p=0.035$) and progression-free survival (PFS) (16.5 vs. 13.9 months, $p=0.039$) over leuprolide alone [28], whereas orchiectomy plus flutamide had no significant OS benefit ($p=0.14$) over orchiectomy alone [29]. The difference in results across the two trials is unclear, as they had similar eligibility requirements, but noncompliance with daily leuprolide injections may have resulted in suboptimal androgen suppression [29]. Evaluation of serum testosterone was not performed to confirm castrate levels as part of the leuprolide trial.

Several meta-analyses have explored CAB, each demonstrating a small 5-year survival benefit with the addition of an antiandrogen to medical or surgical castration [30–32]. The Prostate Cancer Trialists' Collaborative Group meta-analysis reports an absolute 5-year survival advantage to CAB of 2–3 % [31]. Similarly, the meta-analysis performed by Samson et al. found an overall survival benefit at 5 years (hazard ratio (HR) 0.871, 95 % confidence interval (CI) 0.805–0.942), although they did not find the same benefit at the 2-year time point (HR 0.970, 95 % CI 0.866–1.087) [32]. Lastly, a Cochrane review demonstrated an improved 5-year cancer-specific survival with CAB but noted that CAB was associated with more frequent adverse events, leading to higher rates of therapy withdrawal (10 vs. 4 %) [30].

Practice guidelines do not make any specific recommendations about CAB but consider it an option that can be considered [3]. The limited advantage of CAB over monotherapy needs to be weighed against the increased risk of adverse effects, higher cost, and possible decrease in QOL.

GnRH Antagonists

Gonadotropin releasing hormone antagonists bind the GnRH receptors in the pituitary, but do not stimulate the release of LH and FSH, bypassing the initial testosterone flare seen with GnRH agonists. In a phase III trial, degarelix demonstrated noninferiority to leuprolide at maintaining testosterone suppression (≤50 ng/dL) over a 1-year treatment period [33]. Following the standard 240 mg loading dose, both degarelix cohorts (80 and 160 mg monthly) achieved a rapid suppression of testosterone, with 96.1 and 95.5 % reaching ≤50 ng/dL within 3 days of initiation of treatment, respectively, as compared to 0 % in the leuprolide group. The median PSA levels 14 and 28 days were significantly lower in the degarelix groups as well ($p<0.001$). Hormonal side effect profiles were similar, but degarelix had notably higher rates of injection site reactions (40 vs. <1 %, $p<0.001$). A secondary analysis showed that cardiovascular complications were similar for both leuprolide and degarelix [34].

In an extension study, patients originally assigned to degarelix were continued on maintenance degarelix, and those originally assigned to leuprolide were crossed over to receive degarelix. Over a 5-year period, treatment with degarelix following leuprolide was well-tolerated and provided sustained testosterone suppression throughout [35•].

A common recent practice when initiating patients on ADT has been to start with a GnRH antagonist in order to avoid the testosterone flare and acquire rapid control over serum testosterone, then subsequently transition to a GnRH agonist which can be administered on a less frequent schedule. Monthly maintenance injections, as well as the injection site reactions, may make GnRH antagonists less appealing to some patients.

Newer Androgen Receptor-Targeted Therapies

Enzalutamide, a potent second-generation androgen receptor antagonist, has shown significant OS and PFS benefits in the metastatic castration-resistant disease setting [36, 37]. Its utility in the hormone-sensitive patients remains an area of active investigation.

A phase II, single-arm study of enzalutamide, as an alternative to primary ADT, was carried out to assess its potential as first-line therapy in metastatic hormone-sensitive disease. PSA declines with enzalutamide monotherapy were similar to historical controls with GnRH agonists, with 92.5 % of patients achieving a ≥80 % decline in serum PSA by 25 weeks [38•]. As expected of an antiandrogen given as monotherapy, levels of FSH, LH, testosterone, and SHBG were all substantially elevated. Though generally well-tolerated, common side effects over the 25 weeks observational period included gynecomastia (36 %), nipple pain (34 %), fatigue (19 %), and hot flashes (18 %) [38•]. These figures appear lower than those historically reported for bicalutamide monotherapy. Extended follow-up of these trial patients is still ongoing; survival data is not yet available.

With only limited clinical evidence available at this time, the use of enzalutamide for treatment of hormone-sensitive prostate cancer remains investigational. There is no data yet to suggest that enzalutamide in conjunction with primary ADT is more efficacious, but this is the subject of ongoing studies.

Intermittent vs. Continuous ADT

Intermittent androgen deprivation (IADT) has been explored as an alternative to standard continuous ADT (CADT) in hormone-sensitive metastatic prostate cancer. The general rationale for this approach has been multifold: minimize ADT-associated adverse effects, potentially improve time to castration resistance and thus survival, and decrease cost of therapy. A small early study randomized 68 men with castration-sensitive advanced or relapsing prostate cancer to receive either intermittent or continuous CAB. With a mean follow-up of 30.8 months, the 3-year progression to androgen independence was significantly lower in the intermittent arm than the continuous arm (7.0 vs. 38.9 %, p=0.0052) [39]. Since then, several studies have been designed to compare IADT and CADT, each with varying aims and results (Table 1).

The SEUG trial randomized 626 patients with locally advanced or metastatic disease to either IADT or CADT and found no significant OS benefit for CADT when compared to IADT (HR 0.99, p=0.84) [40]. Adverse effects were slightly more pronounced in the continuous arm, but this did not translate to a QOL benefit in the IADT arm [40]. The FinnProstate VII trial studied a similar population of 554 men with locally advanced or metastatic disease and also found no difference in OS (45.2 vs. 45.7 months, p=0.17) [41•]. However, the authors commented that aggressive disease with inadequate PSA responses to ADT should not be candidates for intermittent therapy. In both trials, nonsignificant trends favoring CADT for prostate cancer-specific survival were observed.

The TAP22 trial evaluated IADT vs. CADT in 173 men with metastatic disease who had good responses (PSA <4 ng/

Table 1 Key intermittent vs. continuous ADT trials

Trial	Study population	ADT regimen	Median follow-up	Endpoints and results (IADT vs. CADT)
De Leval et al., 2002 [39]	Advanced or relapsing prostate cancer	GnRHa+antiandrogen	30.8 months	• 3-year progression rate 7.0 vs. 38.9 % (p=0.0052)
SEUG 9401 Calais et al., 2009 [40]	Locally advance or metastatic prostate cancer	GnRHa+cyproterone acetate	51 months	• TTP: HR 0.81 in favor of CADT (95 % CI 0.63–1.05, p=0.11) • OS: HR 0.99 (95 % CI 0.80–1.23, p=0.84) • QOL: no significant differences
FinnProstate VII Salonen et al., 2012 [41•]	Locally advance or metastatic prostate cancer	GnRHa only	65.0 months	• TTP 34.5 vs. 30.2 months (HR 1.08, p=0.43) • PCa-specific survival 45.2 vs. 44.3 months (HR 1.17, p=0.29) • OS 45.2 vs. 45.7 months (HR 1.15, p=0.17)
TAP22 Mottet et al., 2012 [42•]	Metastatic prostate cancer	Leuprolide+flutamide	3.7 years	• OS 42.2 vs. 52.0 months (p=0.75) • PFS 20.7 vs. 15.1 months (p=0.74) • QOL: No significant differences
TULP Langenhuijsen et al., 2013 [43••]	Metastatic prostate cancer	Busereline+nilutamide	31 months	• 2-year risk of progression with PSA nadir ≤0.2 ng/ml, 53 vs. 31 % (p=0.03)
SWOG 9346 Hussain et al., 2013 [44••]	Metastatic prostate cancer	Goserelin+bicalutamide	9.8 years	• OS 5.1 vs. 5.8 years (HR 1.10) • QOL: IADT with better erectile function and mental health at 3 months, but not afterwards

TTP time to progression, *PCa* prostate cancer, *OS* overall survival, *QOL* quality of life, *PSA* prostate-specific antigen, *IADT* intermittent androgen deprivation therapy, *CADT* continuous androgen deprivation therapy, *GnRHa* gonadotropin releasing hormone analogue

mL) to a 6-month induction course of ADT. The median OS favored CADT (42.2 vs. 52.0 months, $p=0.75$), whereas the median PFS favored IADT (20.7 vs. 15.1 months, $p=0.74$), but neither was statistically significant [42•]. The TULP study randomized 193 men with serum PSA levels measuring <4 ng/mL after 6 months of ADT to receive IADT or CADT and found that IADT was associated with a significantly higher 2-year risk of progression in patients with PSA nadir ≤0.2 ng/mL as compared to CADT (53 vs. 31 %, $p=0.03$) [43••], which is particularly salient, as PSA nadir has been previously shown to be a strong independent predictor of survival in metastatic prostate cancer [5]. Neither the TAP22 nor the TULP study found any clinically significant differences between the two treatment approaches for health-related QOL.

The strongest data comes from the large noninferiority trial by the Southwestern Oncology Group (SWOG). Of the 1749 patients randomized, 1535 were available for analysis at a median follow-up of 9.8 years. The median survival in the CADT arm was longer than that of the IADT arm (5.8 vs. 5.1 years, HR 1.10, 90 % CI 0.99–1.23), but the trial was considered "statistically inconclusive" [44••]. Noninferiority of IADT could not be established based on the trial's statistical design as the upper 90 % confidence interval extended beyond the inferiority threshold of 1.20. Post hoc subset analyses showed that the overall treatment effect was consistent across all subgroup of patients, with the exception of patients with extensive metastatic disease, where IADT met criteria for noninferiority [44••]. IADT improved erectile function and mental health at 3 months post-randomization, but this advantage did not hold at later time points.

A meta-analysis of eight prospective randomized trials in mixed disease states found slight increases in all-cause and prostate cancer-specific mortality (2 and 4 %, respectively) associated with IADT but were not significantly significant [45••]. In the subgroup of patients with confirmed metastatic disease, there was again no significant difference in OS between the two ADT approaches [45••]. Similarly, a critical review of seven prospective randomized trials concluded that IADT produces oncologic results similar to CADT in the metastatic disease setting, but with QOL benefits that are modest at best [46•].

Continuous ADT remains the standard of care for patients with metastatic disease based on primary data from the SWOG study. However, intermittent ADT should no longer be considered an investigational approach and can be a consideration in select patients [4]. The general practice for IADT is to treat patients with ADT for either a preset period of time or until maximal biochemical remission is realized, at which time treatment is withheld and the patient closely monitored until there is evidence of appreciable disease recurrence. Practices vary, but PSA threshold for restarting ADT is typically set in the 10–20 ng/mL range.

Early vs. Deferred ADT

For patients with symptomatic metastases, ADT should be started as soon as possible for palliation of symptoms and prevention of complications such as pathologic fracture or spinal cord compression.

Optimal timing for initiation of ADT in asymptomatic patients remains a point of contention. Early ADT is associated with treatment-related adverse effects that can significantly impact the QOL in an otherwise asymptomatic patient. In contrast, by not providing active treatment, deferred ADT runs the risk of allowing potentially irreversible disease complications, such as fracture or spinal cord compression. This has been the topic of randomized trials, but due to heterogeneities

Table 2 Key immediate vs. deferred ADT trials

Trial	Study population	ADT regimen	Criteria to initiate deferred ADT
ECOG Messing et al., 1999 [47]	Lymph node-positive prostate cancer following radical prostatectomy	Orchiectomy or goserelin	Non-PSA progression
MRC PR03 Kirk et al., 2004 [48]	Locally advanced and asymptomatic metastatic prostate cancer	Orchiectomy or GnRH analogue	Once an indication occurred
SAKK 08/88 Studer et al., 2004 [49]	Asymptomatic patients not undergoing curative local treatment	Orchiectomy	Symptomatic progression
EORTC 30846 Schroder et al., 2004 [50]	Lymph node-positive prostate cancer without radical prostatectomy	Orchiectomy or buserelin	Radiographic or symptomatic progression
EPCP McLeod et al., 2005 [51]	Localized and locally advanced prostate cancer	Bicalutamide	At progression, per physician discretion
EORTC 30891 Studer et al., 2006 [52]	Localized, locally advanced, and node-positive prostate cancer	Orchiectomy or buserelin	Symptomatic progression

in trial designs and cohorts enrolled (Table 2), general conclusions have been difficult. A meta-analysis of four trials, totaling 3065 patients, found that early ADT was associated with a decrease in prostate cancer-related deaths (relative risk (RR) 0.84, 95 % CI 0.77–0.92, p=0.0001), but no OS improvement (RR 0.98, 95 % CI, 0.95–1.01, p=0.18) [3]. Prognostic factors for disease progression such as age, Gleason score, PSA doubling time, and PSA response to ADT were not factored into any of these trials, so subcategories of patients at higher risk for prostate cancer-specific or overall mortality were not able to be identified.

Practice guidelines currently do not make a strong recommendation for early ADT in metastatic hormone-sensitive prostate cancer [3]. While clinical practice varies, we like many clinicians generally favor early initiation of ADT to prevent morbidity from potential complications, especially in patients who have disease with high-risk features or who are rapidly progressing. Patients that choose to defer ADT until a time when symptoms develop require regular follow-ups for close monitoring, including a minimum of quarterly PSA tests and annual imaging. PSA doubling time calculation and careful symptom assessment at regular intervals are critical for determining the need for intervention.

Chemohormonal Therapy for Hormone-Sensitive Metastatic Prostate Cancer

Androgen deprivation therapy, whether monotherapy or combined androgen blockade, intermittent or continuous, immediate or deferred, has long been the primary standard of care for management of metastatic castration-sensitive disease. This concept has been recently challenged with a clinical trial which reports a statistically significant clinical benefit with the addition of docetaxel chemotherapy to ADT in this earlier metastatic setting.

The CHAARTED trial randomized 790 men with previously untreated metastatic hormone-sensitive prostate cancer to receive either ADT plus docetaxel (75 mg/m^2, every 3 weeks, 6 cycles) vs. ADT alone, with OS being the primary endpoint of the study. Preliminary findings were reported at the ASCO plenary session in June 2014.

With a median follow-up interval of 29 months, the addition of 6 cycles of docetaxel within 120 days of initiation of ADT significantly improved OS as compared to ADT alone (57.6 vs. 44.0 months, HR 0.61, 95 % CI 0.47–0.80, p= 0.0003) [53••]. In subgroup analyses, patients with high-volume metastatic disease (65 %), as defined by the presence of visceral metastasis or ≥4 bone metastases (with at least one being extra-axial), had an even more dramatic OS improvement of 17 months with ADT plus docetaxel (49.2 vs. 32.2 months, HR 0.60, 95 % CI 0.45–0.81, p=0.0006) [53••]. The median OS was not yet reached for low-volume disease at time of interim analysis, but the hazard ratio for survival also favored the chemotherapy arm. All other subgroups also favored early chemohormonal therapy.

Secondary endpoints of PSA <0.2 ng/mL at 6 months (27.5 vs. 14.0 %, p<0.0001), PSA <0.2 ng/mL at 12 months (22.7 vs. 11.7 %, p<0.0001), median time to CRPC (20.7 vs. 14.7 months, HR 0.56, 95 % CI 0.44–0.70, p<0.0001), and median time to clinical progression (32.7 vs. 19.8 months, HR 0.49, 95 % CI 0.37–0.65, p<0.0001) all strongly favored the combination therapy arm as well [53••].

In contrast, a smaller study from Europe—GETUG 15—randomized 385 men with metastatic hormone-sensitive prostate cancer to ADT plus docetaxel (75 mg/m^2, every 3 weeks, up to 9 cycles) vs. ADT alone. With a median follow-up period of 50 months, OS was not different between the ADT plus docetaxel patients as compared to patients receiving ADT alone (58.9 vs. 54.2 months, HR 1.01, 95 % CI 0.75–1.36, p= 0.955) [54•]. However, significant improvements were seen in biochemical PFS (22.9 vs. 12.9, HR 0.72, 95 % CI 0.57–0.91, p=0.005) and clinical PFS (23.5 vs. 15.4 months, HR 0.75, 95 % CI 0.59–0.94, p=0.015) [54•].

Differences in the prognosis of the two cohorts enrolled likely explain the difference in OS benefit between the CHAARTED and GETUG 15 studies. CHAARTED was initially designed to only enroll patients with high-volume disease, but later allowed low-volume patients to participate in order to meet accrual goals. This accounts for the large disparity between the percentages of high-risk/volume patients enrolled in each trial, 65 % in CHAARTED vs. 22 % in GETUG-AFU, which is further reflected in the OS differences in their ADT alone control arms, 44.0 and 54.2 months, respectively.

At the time of this review, the final publication of the CHAARTED trial is not yet in print. In addition, an ongoing trial in Europe STAMPEDE, will also address the issue of efficacy of chemohormonal therapy in hormone-sensitive metastatic prostate cancer. Nonetheless, data for high-volume patients treated in CHAARTED is very convincing and will likely change practice at least for this subgroup of patients. There is currently insufficient evidence to strongly recommend early chemohormonal therapy for low-volume patients; longer follow-up and further investigation will yield more data to help answer that question. One caveat is that both chemohormonal trials were conducted at a time where availability of newer therapeutic agents such as enzalutamide and abiraterone was not yet prevalent, and so the value of aggressive early therapy will need to be reevaluated in this modern context. The full impact of the CHAARTED study will be shown with time, but by extending the OS benefit of docetaxel from 2–3 months in the castration-resistant setting [55] to 13.6 months by giving it upfront in the hormone-sensitive setting sets the stage for evaluating other advanced therapies in earlier stages of disease.

Bone-Targeting Agents

A key adverse effect of ADT is the loss of bone mineral density. The incidence of fracture increases with prolonged ADT exposure [56, 57], with risk of skeletal fracture occurring in up to 19.4 % of men following 5 years of ADT [58]. In addition to regular weight-bearing exercises and smoking cessation, calcium and vitamin D should be supplemented if dietary sources are not sufficient to reach a total daily intake of 1000–1200 mg of calcium and 800–1000 IU of vitamin D. Periodic bone densitometry testing is valuable for monitoring of osteoporosis. Various bisphosphonates (zoledronic acid, alendronate, risedronate, pamidronate) [59–63] and the RANKL inhibitor, denosumab [64, 65], have shown the ability to increase bone mineral density while on ADT.

While zoledronic acid and denosumab are effective at palliating bone pain and decreasing the frequency of SREs in castration-resistant metastatic prostate cancer [66, 67•], the same has not been demonstrated in hormone-sensitive metastatic disease. In a randomized trial, the use of zoledronic acid in hormone-sensitive metastatic prostate cancer was not associated with a definite clinical benefit; time to first SRE (31.9 vs. 29.8 months, p=0.39) and overall survival (HR 0.88, p=0.29) were not significantly different compared to placebo [68••]. No trial has evaluated the use of denosumab in metastatic hormone-sensitive disease; however, this agent is FDA-approved for the prevention of SREs in solid tumors with bone metastases, without specific identification of tumor type or hormone-sensitivity.

Clinical practice for the use of bone-targeting agents varies widely for metastatic hormone-sensitive disease. Some choose to introduce a bone-targeting agent at osteoporotic dosing only if there is evidence of osteopenia or osteoporosis on bone densitometry, while some clinicians start denosumab at full treatment dosing for prevention of SREs as allowed by its labeled indication, despite lack of data to recommend its use. Still others compromise and give denosumab at a less frequent or limited schedule to decrease its potential adverse effects, knowing that while no data exists, administering an agent with activity against osteoporosis and bone metastases progression may provide clinical benefit.

Conclusions

Androgen deprivation therapy remains the mainstay of treatment in metastatic hormone-sensitive prostate cancer. Over the years, efforts have been made to improve upon the original regimen by modifying timing and schedule or adding adjunctive agents, but the optimal management of this disease state is still unknown. Realistically, it is unlikely that a diverse heterogeneous disease such as prostate cancer will have one unified optimal plan of management. A recent breakthrough finding that early chemohormonal therapy is associated with a significant survival benefit in metastatic hormone-sensitive disease highlights the fact that more can be done for such patients. In the future, better identifying subgroups of patients that will benefit from specific treatment approaches are needed. Also, we will need to understand whether chemotherapy used in the hormone-sensitive setting will retain efficacy once castration-resistance develops and whether there is a role for other newer therapies currently reserved for metastatic castration-resistant disease such as abiraterone and enzalutamide.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Bobby C. Liaw and Dr. Jeffrey Shevach each declare no potential conflicts of interest.

Dr. William K. Oh serves on the advisory board for Sanofi.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Huggins C, Hodges CV. The effects of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res. 1941;1(4):293–7.
2. Huggins C, Stevens RE, Hodgkins CV. The effects of castration on advanced carcinoma of the prostate. Arch Surg. 1941;43(2):209–23.
3. Loblaw DA, Virgo KS, Nam R, Somerfield MR, Ben-Josef E, Mendelson DS et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol. 2007;25(12):1596–605.
4. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65(2):467–79.
5. Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol. 2006;24(24):3984–90.
6. Treatment and survival of patients with cancer of the prostate. The Veterans Administration Co-operative Urological Research Group. Surg Gynecol Obstet. 1967;124(5):1011–7.
7. Heyns CF, Simonin MP, Grosgurin P, Schall R, Porchet HC, South African Triptorelin Study Group. Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. BJU Int. 2003;92(3):226–31.
8. Schally AV, Arimura A, Baba Y, Nair RM, Matsuo H, Redding TW et al. Isolation and properties of the FSH and LH-releasing hormone. Biochem Biophys Res Commun. 1971;43(2):393–9.
9. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. The Leuprolide Study Group. N Engl J Med. 1984;311(20):1281–6.

10. Waxman J, Man A, Hendry WF, Whitfield HN, Besser GM, Tiptaft RC et al. Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. Br Med J (Clin Res Ed). 1985;291(6506):1387–8.
11. Kuhn JM, Billebaud T, Navratil H, Moulonguet A, Fiet J, Grise P et al. Prevention of the transient adverse effects of a gonadotropin-releasing hormone analogue (buserelin) in metastatic prostatic carcinoma by administration of an antiandrogen (nilutamide). N Engl J Med. 1989;321(7):413–8.
12. Oh WK, Landrum MB, Lamont EB, McNeil BJ, Keating NL. Does oral antiandrogen use before leuteinizing hormone-releasing hormone therapy in patients with metastatic prostate cancer prevent clinical consequences of a testosterone flare? Urology. 2010;75(3):642–7.
13. Yri OE, Bjoro T, Fossa SD. Failure to achieve castration levels in patients using leuprolide acetate in locally advanced prostate cancer. Eur Urol. 2006;49(1):54–8. *discussion 58*.
14. Morote J, Esquena S, Abascal JM, Trilla E, Cecchini L, Raventos CX et al. Failure to maintain a suppressed level of serum testosterone during long-acting depot luteinizing hormone-releasing hormone agonist therapy in patients with advanced prostate cancer. Urol Int. 2006;77(2):135–8.
15. Seidenfeld J, Samson DJ, Hasselblad V, Aronson N, Albertsen PC, Bennett CL et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med. 2000;132(7):566–77.
16. Oefelein MG, Feng A, Scolieri MJ, Ricchiutti D, Resnick MI. Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. Urology. 2000;56(6):1021–4.
17. Oefelein MG, Cornum R. Failure to achieve castrate levels of testosterone during luteinizing hormone releasing hormone agonist therapy: the case for monitoring serum testosterone and a treatment decision algorithm. J Urol. 2000;164(3 Pt 1):726–9.
18. Iversen P. Bicalutamide monotherapy for early stage prostate cancer: an update. J Urol. 2003;170(6 Pt 2):S48–52. *discussion S52-4*.
19. Smith MR, Goode M, Zietman AL, McGovern FJ, Lee H, Finkelstein JS. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol. 2004;22(13):2546–53.
20. Sieber PR, Keiller DL, Kahnoski RJ, Gallo J, McFadden S. Bicalutamide 150 mg maintains bone mineral density during monotherapy for localized or locally advanced prostate cancer. J Urol. 2004;171(6 Pt 1):2272–6. *quiz 2435*.
21. Wirth MP, Hakenberg OW, Froehner M. Antiandrogens in the treatment of prostate cancer. Eur Urol. 2007;51(2):306–13. *discussion 314*.
22. Perdona S, Autorino R, De Placido S, D'Armiento M, Gallo A, Damiano R. Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. Lancet Oncol. 2005;6(5):295–300.
23. Chang A, Yeap B, Davis T, Blum R, Hahn R, Khanna O et al. Double-blind, randomized study of primary hormonal treatment of stage D2 prostate carcinoma: flutamide versus diethylstilbestrol. J Clin Oncol. 1996;14(8):2250–7.
24. Iversen P, Tveter K, Varenhorst E. Randomised study of Casodex 50 mg monotherapy vs orchidectomy in the treatment of metastatic prostate cancer. The Scandinavian Casodex Cooperative Group. Scand J Urol Nephrol. 1996;30(2):93–8.
25. Chodak G, Sharifi R, Kasimis B, Block NL, Macramalla E, Kennealey GT. Single-agent therapy with bicalutamide: a comparison with medical or surgical castration in the treatment of advanced prostate carcinoma. Urology. 1995;46(6):849–55.
26. Kaisary AV, Tyrrell CJ, Beacock C, Lunglmayr G, Debruyne F. A randomised comparison of monotherapy with Casodex 50 mg daily and castration in the treatment of metastatic prostate carcinoma. Casodex Study Group. Eur Urol. 1995;28(3):215–22.
27. Iversen P, Tyrrell CJ, Kaisary AV, Anderson JB, Baert L, Tammela T et al. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. Urology. 1998;51(3):389–96.
28. Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med. 1989;321(7):419–24.
29. Eisenberger MA, Blumenstein BA, Crawford ED, Miller G, McLeod DG, Loehrer PJ et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med. 1998;339(15):1036–42.
30. Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T. Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev. 2000;2, CD001526.
31. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet. 2000;355(9214):1491–8.
32. Samson DJ, Seidenfeld J, Schmitt B, Hasselblad V, Albertsen PC, Bennett CL. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer. 2002;95(2):361–76.
33. Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int. 2008;102(11):1531–8.
34. Smith MR, Klotz L, Persson BE, Olesen TK, Wilde AA. Cardiovascular safety of degarelix: results from a 12-month, comparative, randomized, open label, parallel group phase III trial in patients with prostate cancer. J Urol. 2010;184(6):2313–9.
35.• Crawford ED, Shore ND, Moul JW, Tombal B, Schroder FH, Miller K et al. Long-term tolerability and efficacy of degarelix: 5-year results from a phase III extension trial with a 1-arm crossover from leuprolide to degarelix. Urology. 2014;83(5):1122–8. *Extension study of original prospective, randomized phase III degarelix vs. leuprolide study demonstrating long term efficacy of degarelix, even after crossover from leuprolide.*
36. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014.
37. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187–97.
38.• Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol. 2014;15(6):592–600. *Phase II trial demonstrating activity of enzalutamide as first line therapy of metastatic castrate sensitive prostate cancer.*
39. de Leval J, Boca P, Yousef E, Nicolas H, Jeukenne M, Seidel L et al. Intermittent versus continuous total androgen blockade in the treatment of patients with advanced hormone-naive prostate cancer: results of a prospective randomized multicenter trial. Clin Prostate Cancer. 2002;1(3):163–71.
40. Calais da Silva FE, Bono AV, Whelan P, Brausi M, Marques Queimadelos A, Martin JA et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. Eur Urol. 2009;55(6):1269–77.
41.• Salonen AJ, Taari K, Ala-Opas M, Viitanen J, Lundstedt S, Tammela TL et al. The FinnProstate Study VII: intermittent versus continuous androgen deprivation in patients with advanced prostate cancer. J Urol. 2012;187(6):2074–81. *Phase III trial comparing IADT and CADT in locally advanced and metastatic prostate cancer, suggests that IADT is feasible and safe in patients with advanced prostate cancer.*

42.• Mottet N, Van Damme J, Loulidi S, Russel C, Leitenberger A, Wolff JM et al. Intermittent hormonal therapy in the treatment of metastatic prostate cancer: a randomized trial. BJU Int. 2012;110(9):1262–9. *Phase III trial comparing IADT and CADT in metastatic prostate cancer, suggests that IADT is a treatment option in metastatic setting.*

43.•• Langenhuijsen JF, Badhauser D, Schaaf B, Kiemeney LA, Witjes JA, Mulders PF. Continuous vs. intermittent androgen deprivation therapy for metastatic prostate cancer. Urol Oncol. 2013;31(5):549–56. *Phase III trial comparing IADT and CADT in metastatic prostate cancer, IADT with higher rates of progression in patients who attain low serum PSA nadir with ADT.*

44.•• Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med. 2013;368(14):1314–25. *Key phase III non-inferiority trial comparing IADT and CADT in metastatic prostate cancer, statistically inconclusive study leading to CADT remaining the standard of care*.

45.•• Tsai HT, Penson DF, Makambi KH, Lynch JH, Van Den Eeden SK, Potosky AL. Efficacy of intermittent androgen deprivation therapy vs conventional continuous androgen deprivation therapy for advanced prostate cancer: a meta-analysis. Urology. 2013;82(2):327–33. *Meta-analysis of 8 trials comparing IADT and CADT.*

46.• Sciarra A, Abrahamsson PA, Brausi M, Galsky M, Mottet N, Sartor O et al. Intermittent androgen-deprivation therapy in prostate cancer: a critical review focused on phase 3 trials. Eur Urol. 2013;64(5):722–30. *Critical review of 7 trials comparing IADT and CADT.*

47. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med. 1999;341(24):1781–8.

48. Kirk D. Timing and choice of androgen ablation. Prostate Cancer Prostatic Dis. 2004;7(3):217–22.

49. Studer UE, Hauri D, Hanselmann S, Chollet D, Leisinger HJ, Gasser T et al. Immediate versus deferred hormonal treatment for patients with prostate cancer who are not suitable for curative local treatment: results of the randomized trial SAKK 08/88. J Clin Oncol. 2004;22(20):4109–18.

50. Schroder FH, Kurth KH, Fossa SD, Hoekstra W, Karthaus PP, Debois M et al. Early versus delayed endocrine treatment of pN1–3 M0 prostate cancer without local treatment of the primary tumor: results of European Organisation for the Research and Treatment of Cancer 30846–a phase III study. J Urol. 2004;172(3):923–7.

51. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP, Casodex Early Prostate Cancer Trialists Group. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int. 2006;97(2):247–54.

52. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol. 2006;24(12):1868–76.

53.•• Sweeney C, Chen Y, Carducci MA, Liu G, Jarrard DF, Eisenberger MA et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial. J Clin Oncol. 2014;32(suppl 5; abstr LBA2). Preliminary findings of CHAA RTED trial demonstrating significant OS benefit with early chemohormonal therapy in hormone sensitive metastatic prostate cancer.

54.• Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(2):149–58. *Prospective, randomized phase III trial of early chemohormonal therapy in metastatic castrate sensitive prostate cancer which did not show OS benefit. Contrasting study to CHAARTED.*

55. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol. 2008;26(2):242–5.

56. Smith MR, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol. 2005;23(31):7897–903.

57. Krupski TL, Smith MR, Lee WC, Pashos CL, Brandman J, Wang Q et al. Natural history of bone complications in men with prostate carcinoma initiating androgen deprivation therapy. Cancer. 2004;101(3):541–9.

58. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005;352(2):154–64.

59. Choo R, Lukka H, Cheung P, Corbett T, Briones-Urbina R, Vieth R et al. Randomized, double-blinded, placebo-controlled, trial of risedronate for the prevention of bone mineral density loss in nonmetastatic prostate cancer patients receiving radiation therapy plus androgen deprivation therapy. Int J Radiat Oncol Biol Phys. 2013;85(5):1239–45.

60. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. Ann Intern Med. 2007;146(6):416–24.

61. Klotz LH, McNeill IY, Kebabdjian M, Zhang L, Chin JL, Canadian Urology Research Consortium. A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: the Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) study. Eur Urol. 2013;63(5):927–35.

62. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol. 2003;169(6):2008–12.

63. Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med. 2001;345(13):948–55.

64. Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med. 2009;361(8):745–55.

65. Smith MR, Saad F, Egerdie B, Szwedowski M, Tammela TL, Ke C et al. Effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer. J Urol. 2009;182(6):2670–5.

66. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004;96(11):879–82.

67.• Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813–22. *Phase III trial demonstrating improved prevention of skeletal related events with denosumab as compared to zoledronic acid in metastatic castrate resistant prostate cancer.*

68.•• Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stadler W et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). J Clin Oncol. 2014;32(11):1143–50. *Phase III trial demonstrating that zoledronic acid is not associated with lower risk of skeletal related events in metastatic castration sensitive prostate cancer.*