Why Chemotherapy Should be Given Early for Men with Metastatic Prostate Cancer
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OVERVIEW

Metastatic hormone-sensitive prostate cancer (mHSPC) is an incurable disease, and despite a high response rate to androgen-deprivation therapy (ADT), outcomes have not significantly changed for many decades. Earlier attempts at multitargeted strategies with the addition of cytotoxic chemotherapy to ADT did not affect survival. As more effective therapies are emerging, including cytotoxic therapy for patients with metastatic castrate-resistant prostate cancer (mCRPC), there is increasing interest for testing these drugs earlier in the disease course. The premise is that agents with clinical benefit in advanced mCRPC may have a better effect if used preemptively before the development of significant resistance and to attack earlier de novo androgen resistant/independent clones. The recent results of the phase III clinical trial E3805 investigating ADT with or without docetaxel in mHSPC provide compelling support for this strategy. Docetaxel combined with ADT significantly improved overall survival from 44 to 57.6 months ($p = 0.0003$), particularly in patients with high-volume disease (from 32.2 to 49.2 months; $p = 0.0006$). Longer follow-up is needed to assess the effect on patients with low disease burden. Further studies are needed to further maximize the antitumor effect in patients with mHSPC and to investigate the effects of advancing therapy to this disease setting on the efficacy of respective agents in the castration-resistant setting.

Despite stage migration, a significant number of patients with prostate cancer develop metastasis despite curative intent primary therapy or are diagnosed with de novo metastatic disease. Until recently, the initial management of patients with newly diagnosed mHSPC has not radically changed. Since 1941 when Huggins and Hodges demonstrated the androgen dependency of prostate cancer, the mainstay of therapy has been surgical or medical castration. Clinical research has mostly focused on investigating and optimizing different strategies to deliver, potentially enhance the ADT effect, and reduce its side effects such as combining androgen receptor (AR) blockade with primary gonadal suppression, peripheral blockade only, or using intermittent versus continuous ADT. ADT with a luteinizing-hormone-releasing hormone (LHRH) agonist with or without an antiandrogen, and more recently LHRH antagonist, has almost completely replaced surgical castration as first-line treatment. Irrespective of ADT modality or schedule, patients with mHSPC treated with ADT have a median overall survival (OS) around 49 months.1 Despite the very high initial response rates to ADT, the duration of response is limited and most patients will eventually progress to castration resistance, the deadly phenotype of the disease.

The last decade has witnessed substantial scientific progress and developments that have impacted management of metastatic castration-resistant prostate cancer (mCRPC). This began with the key discoveries indicating that emergence of resistance to ADT is in part an adaptive process via AR-dependent and AR-independent mechanisms.2-4 Microtubule targeting chemotherapy, docetaxel and cabazitaxel, have demonstrated activity in advanced prostate cancer, supporting the concept that castration-resistant cells are inhibited by chemotherapy.5-7 The effect of targeting the AR signaling in patients with advanced prostate cancer is now well established with the survival benefits demonstrated by abiraterone and enzalutamide in men with castration resistance disease irrespective of prior chemotherapy.8-11 Drugs targeting other pathways such as sipuleucel-T (dendritic cell-based vaccine) and radium-223 (alpha-emitter and calcium mimetic) have also shown improved survival benefits in patients with mCRPC.12-13 Despite the recent success of novel therapies, the overall effects on survival are still modest. Furthermore, the quality/quantity of responses observed in patients being treated with AR-signaling agents decrease in the context of prior treatment with another AR-signaling agent in mCRPC.14 Although docetaxel was the first agent approved for mCRPC, the rapid proliferation of newer non chemotherapy particularly oral AR targeted therapy has shifted the dynamics to delay chemotherapy. Population based studies have shown that only about a third of patients with mCRPC...
are receiving docetaxel.\textsuperscript{15} Although speculative, one explanation may be the poor performance status of patients in the context of disease progression after receiving several lines of therapy. Anecdotal experience and recent report by Azad et al\textsuperscript{14} on a retrospective study investigating the efficacy of enzalutamide following abiraterone in docetaxel-naïve and docetaxel-exposed patients indicated that the antitumor activity of enzalutamide following abiraterone is limited. The median duration of enzalutamide treatment was 4.1 months. Importantly, the efficacy of enzalutamide was comparable in docetaxel-naïve and docetaxel-exposed patients in terms of PSA response rates (26% vs 22%; \(p = 0.8\)), median time to radiologic/clinical progression (6.6 vs. 4.6 months; \(p = 0.6\)), and median OS (8.6 vs. 10.6 months; \(p = 0.2\)). These findings are important given the increasing evidence suggesting benefits with earlier use of docetaxel in advanced prostate cancer.

**CHEMOTHERAPY IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER: SCIENTIFIC RATIONALE**

Elucidating the mechanisms of prostate cancer progression to castration resistance has captivated the interest of researchers over several decades. Molecular adaptation of cancer cells to an androgen-deprived environment, including AR-driven pathways, activation of survival pathways bypassing AR, and clonal selection of androgen-insensitive clones, appear to be some of the major mechanisms of resistance. Molecular adaptation involves the activation of the AR through different mechanisms including AR-gene amplification, AR-overexpression or mutation, extragonadal production of androgens, ligand-independent activation by growth factors, or alteration in survival pathways bypassing AR.\textsuperscript{2-4} In clonal selection, androgen ablation creates a host environment in which the androgen-insensitive tumor cells have a selective growth advantage over the androgen-dependent cells. The continuous proliferative growth of these androgen-independent tumor cells leads to the relapse phenomenon.\textsuperscript{16} Isaacs and Coffey conducted the initial studies to show that progression from an androgen-sensitive to androgen-insensitive state is dependent on the initial heterogeneity of the tumor with preexisting clones of both androgen-dependent and androgen-independent cells.\textsuperscript{16} Following castration, adult male rats bearing the androgen-sensitive Dunning R-3327-H tumor showed an initial response with decreased growth rate. However, after 60 days, androgen ablation causes selection and growth advantage of androgen-independent cells. In this model, the continuous exponential growth of the androgen-insensitive tumor cells eventually kills the host animals.\textsuperscript{16}

The heterogeneity with regard to androgen sensitivity and the selection of resistant cells supports the need for a multi-targeted treatment approach early in the course of the disease to maximize the antitumor effect and prevent development of resistance. The use of early chemotherapy may address the phenotypically heterogeneous subpopulation of tumor cells and eliminate androgen-independent clones, allowing for a potentially improved therapeutic effect.

Traditionally, chemotherapy including docetaxel is offered to patients with mCRPC, often when symptomatic and with large disease burden. In fact, several of the recently designed trials had “delay time to chemotherapy” as a metric for “clinical success.” However, delaying chemotherapy to this point may very well limit the efficacy of chemotherapy possibly because of a larger proportion of resistant cells, including chemotherapy-resistant cells within the bigger population of castration-resistant cells. The early use of cytotoxic chemotherapy may improve outcomes by attacking clones resistant to ADT before they expand or acquire more resistance or simply killing more cancer cells when they are more vulnerable.

Preclinical data by Tang et al\textsuperscript{17} evaluated different sequences of docetaxel and androgen ablation in severe combined immunodeficient mice inoculated with the LNCaP prostate cell line. Tumor volume was at least 50% smaller in all docetaxel groups compared with castration alone. The smallest tumors at week 4 and the greatest growth delay were found in mice treated with docetaxel for 2 weeks, followed by castration. Apoptosis assays also indicated a greater degree of apoptosis in the docetaxel followed by castration group. As in other studies, the bax-to-bcl-2 ratio decreased following cas-
tration. However, the bax-to-bcl-2 ratio remained increased following docetaxel, indicating increased apoptosis.17

Numerous AR-independent intracellular oncogenic pathways including MAPK, RB1, and PI3K/AKT/mTOR are dysregulated through a variety of mechanisms in advanced prostate cancer. Downstream effects of genetic alterations in these pathways promote survival, proliferation, cell-cycle progression, and conversely regulate AR signaling through feedback mechanisms.18-23 Chemotherapy may attack cells with AR-independent signaling pathways driving mechanisms of castration resistance. Considering the biologic observations and the experience in prostate cancer and other cancers, it is logical to hypothesize that earlier use of effective systemic therapies could result in a more significant impact in hormone-sensitive disease.

**TABLE 1. Early Clinical Trials of Androgen Deprivation Therapy with or without Chemotherapy in Hormone-Naive Metastatic Prostate Cancer**

<table>
<thead>
<tr>
<th>First Author and Accrual</th>
<th>No. of Patients</th>
<th>Treatment Arms</th>
<th>Median PFS (Months)</th>
<th>Median OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy14, 1976-1980</td>
<td>246</td>
<td>A: DES/orch</td>
<td>Not reported</td>
<td>23 mo in all arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: DES + CTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: CTX + estramustine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murphy15, 1980-1983</td>
<td>319</td>
<td>A: DES/orch</td>
<td>15 mo in all arms</td>
<td>33 mo in all arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: CTX + 5FU + DES</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: Estramustine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: DES/orch + CTX + Dox</td>
<td>B: 18</td>
<td>B: 22.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.8)</td>
<td>(p = 0.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: Flut/orch + epirubicin</td>
<td>B: 22</td>
<td>B: 30</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(p = &lt;0.02)</td>
<td>(p = 0.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: Orch + estramustine</td>
<td>B: 24</td>
<td>B: 27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.3)</td>
<td>(NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: Orch + mitomycin C</td>
<td>B: 26</td>
<td>B: 31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.64)</td>
<td>(NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: Orch + mitomycin C</td>
<td>B: 12</td>
<td>B: 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.67)</td>
<td>(p = 0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: DES or orch + UFT</td>
<td>B: 72</td>
<td>B: &gt;96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.06)</td>
<td>(p = 0.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: LHRH + estramustine</td>
<td>B: 25.4</td>
<td>B: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.03)</td>
<td>(NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: LHRH/orch + ketoc + dox + vinb + estramustine (KAVE regimen)</td>
<td>B: 35</td>
<td>B: 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.39)</td>
<td>(p = 0.41)</td>
</tr>
</tbody>
</table>

Abbreviations: orch, bilateral orchietomy; DES, diethylstilbestrol; dox, doxorubicin; NS, not significant; LHRH, super agonist of luteinizing hormone-releasing hormone; CTX, cyclophosphamide; FU, fluorouracil; UFT, uracil plus tegafur (an oral fluoropyrimidine); FLT, flutamide; ketoc, ketoconazole; vinb, vinblastine.

Adapted from Millikan et al.23

**CLINICAL TRIALS OF CHEMOTHERAPY IN MHSPC**

The initial trials investigating the combination of chemotherapy with ADT in mHSPC did not show overall survival advantage. Since the 1970s, more than 10 randomized studies were conducted investigating different chemotherapy drugs in combination with ADT. Regimens included a variety of cytotoxic drugs such as cyclophosphamide, estramustine, doxorubicin, fluorouracil, mitomycin, and vinblastine, but failed to demonstrate a significant survival benefit when combined with ADT in metastatic prostate cancer24-33 (Table 1). However, there were some hints with regard to potential benefits of chemotherapy in specific subgroups of patients. Murphy et al conducted a randomized trial comparing diethylstilbestrol (DES) or orchietomy, DES plus cyclophosph-
amide, or estramustine plus cyclophosphamide in patients with newly diagnosed metastatic prostate cancer. There was no overall survival difference between the three groups (92, 91, and 94 weeks, respectively); however, subgroup analysis within groups having pain versus those not having pain showed a survival benefit for the cyclophosphamide and estramustine arm in patients presenting with pain at study entry.24 Osborne et al compared endocrine therapy alone (DES or orchiectomy) to a chemo-endocrine approach (DES plus cyclophosphamide/doxorubicin hydrochloride) in a randomized trial lead by SWOG.26 Although there was a higher response rate in the chemo-endocrine group (63%) compared with endocrine alone (48%), this effect did not translate to a significant difference in overall survival. Epirubicin has also been studied in this setting. A prospective randomized trial conducted by Pummer et al investigated the addition of weekly epirubicin to androgen blockade (orchiectomy and flutamide) for 18 weeks.27 At a median follow-up of 81 months, the chemo-hormonal arm showed a significant benefit in progression-free survival (PFS; 18 months) compared with the hormonal arm (12 months, p < 0.02). However, there were no OS differences between the groups. In patients with more than five sites of bone metastasis, PFS was 9 and 14 months (p = 0.005) and OS, 17 and 27 months (p = 0.06), respectively. Estramustine has also been tested in addition to hormone therapy in patients with newly diagnosed metastatic prostate cancer without evidence of survival advantage. In subgroup analysis, estramustine prolonged time to progression when added to orchiectomy in patients with bone metastasis.28

More recently, Millikan et al conducted a phase III clinical trial investigating the addition of ketoconazole, doxorubicin, vinblastine, and estramustine (KAVE regimen) to androgen ablation therapy.33 The primary endpoint of time to castrate-resistant progression was 24 months for the androgen ablation arm, and 35 months for the chemo-hormone therapy (p = 0.39). Median overall survival was not different between the groups (5.4 and 6.1 years, respectively). Similar to other trials, time to progression was significantly delayed in the high-volume group but not in those with less advanced disease. In patients with high-volume disease (three or more bone lesions or visceral involvement) the median time to progression was 11.2 months in the control group and 20.5 months in the KAVE arm (p = 0.08). Nearly all patients (in either arm) did receive cytotoxic therapy for castrate-resistant disease, usually including a taxane.33

Most of these trials had substantial limitations in design, sample size, and most importantly, used chemotherapy drugs without significant clinical activity in advanced prostate cancer. Specifically, none of the trials included cytotoxic chemotherapy that prolonged survival in the castration-resistant setting.

**DOCETAXEL: FIRST AGENT TO IMPROVE SURVIVAL IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER**

Docetaxel, a taxane chemotherapeutic drug, induces polymerization of microtubules and phosphorylation of the bcl-2 protein.34 Docetaxel was approved in castration-resistant prostate cancer after two randomized landmark studies, TAX 327 and SWOG-9916, independently demonstrated improvements in overall survival in men with mCRPC.5,6 Docetaxel triumphed over the longstanding paradigm that prostate cancer cells were resistant to cytotoxic agents. The TAX 327 study reported an improved overall survival of the group treated with docetaxel every 3 weeks (18.9 months) compared to the group treated with mitoxantrone (16.5 months). The hazard ratio for death of docetaxel compared with mitoxantrone was 0.83 (95% CI, 0.70 to 0.99; p = 0.04). Quality of life was also significantly improved in the group treated with docetaxel.5 Petrylak et al reported a similar improvement in survival for docetaxel plus estramustine in comparison with mitoxantrone plus prednisone in the SWOG-9916 study.6 The median overall survival was 17.5 months in those treated with docetaxel-based therapy versus 15.6 months in patients in the mitoxantrone group (p < 0.001). Docetaxel became the standard of care for men with CRPC in 2004.

The role of chemotherapy in prostate cancer management was further supported by the approval of a third chemotherapy agent, cabazitaxel, which is also an inhibitor of microtubule depolymerization based on improving survival in a phase III trial in patients with CRPC previously treated with docetaxel as compared to mitoxantrone (15.1 vs. 12.7 months; 95% CI, 0.61 to 0.84).7 The risk of death was significantly lower in those patients treated with cabazitaxel versus patients treated with mitoxantrone (HR 0.70; p < 0.0001). Cabazitaxel received U.S. Food and Drug Administration (FDA)-approval in 2010 for men with CRPC that had progressed on docetaxel.

**RANDOMIZED CLINICAL TRIALS OF EARLY DOCETAXEL PLUS ADT**

The use of docetaxel in the mHSPC setting was driven by its established activity in two phase III randomized clinical trials demonstrating a survival advantage as compared with an active control of mitoxantrone. The underlying premise is that an agent with clinical benefit in mCRPC might prolong the lives of men with mHSPC if used before the disease becomes resistant to ADT and to attack the de novo androgen resistant/independent clones much earlier. There are also emerging data that docetaxel may act as a hormonal agent, interfering with androgen receptor (AR) nuclear translocation on microtubules.35

Two phase III clinical trials were designed to evaluate the role of docetaxel in mHSPC (Table 2). GETUG-AFU 15 was a randomized, open-label, phase III trial that enrolled 385 patients with newly diagnosed mHSPC.36 In this study, patients were randomly assigned to receive ADT alone (orchiectomy or LHRH agonists) or in combination with docetaxel (75 mg/m² on day 1 of a 3-week cycle; nine planned cycles). The median number of docetaxel cycles was eight. With median follow-up of 50 months, there was a trend in favor of do-
TABLE 2. Randomized Clinical Trials of ADT with or without Docetaxel in Hormone-Naive Metastatic Prostate Cancer

![Table 2](https://ascopubs.org/doi/10.3816/EDBOOK-2015-07-1882)

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cetaxel; however, the primary endpoint of overall survival was not significantly different between the groups at 58.9 months for patients that received docetaxel plus ADT versus 54.2 months for those who were treated with ADT alone (HR 1.01; 95% CI, 0.75 to 1.36; p = 0.955). On the contrary, the addition of docetaxel to ADT did significantly improve the biochemical PFS (secondary endpoint), which was 22.9 months for the combined treatment group and 12.9 months for those treated with ADT alone (HR 0.72; 95% CI, 0.57 to 0.91; p = 0.005). Seventy-two serious adverse events were reported in the group given ADT plus docetaxel: more frequently neutropenia (21%), febrile neutropenia (3%), abnormal liver function tests (2%), and neutropenia with infection (1%). Four treatment-related deaths occurred in the ADT plus docetaxel group. An updated report with longer follow-up of the GETUG-AFU 15 trial was presented at the 2015 Genitourinary Cancers Symposium. With a median follow-up of 82.9 months, the median OS was 60.9 months and 46.5 months in the ADT plus docetaxel and ADT alone arms, respectively (HR 0.9, 95% CI, 0.7 to 1.2; p = 0.44). In patients with high-volume disease, median OS rates were 39 months in ADT plus docetaxel arm and 35.1 months in the ADT alone arm (HR 0.8; 95% CI, 0.6 to 1.2; p = 0.35).

The GETUG-AFU 15 trial did not show statistically significant survival benefit to adding docetaxel to ADT for mHSPC. However, the overall survival trend and the HR in the high-volume patients favors the docetaxel arm. The trial had a relatively small sample size, included a substantial percentage of patients with good prognostic factors at baseline: 49% of the patients in the ADT plus docetaxel group and 50% of the patients treated with ADT alone. Another concern about this trial is the unusually high toxicity reported, with more than 10% incidence of grade 3 neutropenia and four deaths in the group given ADT plus docetaxel; 21% of men who received docetaxel plus ADT discontinued treatment because of toxicity. Results may have also been affected by cross-over treatments since 62% of patients given ADT alone received docetaxel at progression, compared with 28% of patients given ADT plus docetaxel who were re-treated with docetaxel. Interestingly, the Kaplan-Meier curves for overall survival seem to separate after 36 months of follow-up. However, only 199 patients are at risk at 36 months, and 124 at 48 months.

Data Presented at the 2014 ASCO Annual Meeting Plenary Session

The results of the E3805 (Chemo-Hormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer [CHAARTED]) trial recently reported by Sweeney et al. provide practice-changing evidence. CHAARTED is a U.S. intergroup phase III trial in which 790 men with hormone-naive mHSPC received either ADT alone or ADT with 75 mg/m² of docetaxel every 3 weeks for a maximum of six cycles. At enrollment, patients were stratified by extent of metastatic disease as high-volume or low-volume; high volume was defined as visceral metastasis and/or four or more bone metastases with at least one beyond axial skeleton (pelvis and vertebral column). The primary endpoint was OS, and secondary endpoints included time to biochemical, radiographic, or symptomatic progressive disease (PD) and time to radiographic or symptomatic PD. The trial was first designed to include high-volume patients as they have poor prognosis. Eligibility was subsequently expanded to allow all patients with mHSPC.

The addition of docetaxel to ADT significantly improved overall survival; a median of 57.6 months in the ADT plus docetaxel arm and 44.0 months in the ADT arm (HR 0.61; 95% CI, 0.47 to 0.80; p = 0.0003). The survival improvement was seen specifically in men with high-volume disease; median OS was 49.2 months with docetaxel plus ADT compared with 32.2 months with ADT, a difference of 17 months (HR 0.60; 95% CI, 0.45 to 0.81; p = 0.0006). In men with low-volume disease, median OS had not been reached at the time of the presentation. The secondary endpoints demonstrated higher PSA responses (< 0.2 ng/mL) at 6 and 12 months in the docetaxel plus ADT group (27.5% and 22.7%, respectively) compared to the ADT alone group (14% and 11.7%, respectively), longer median time to castration resistance (20.7 months vs. 14.7 months) and longer median time to clinical progression in favor or the combination arm; 32.7 months, compared to 19.8 months (p < 0.0001).

With regard to toxicity, 6% of men receiving docetaxel plus ADT experienced febrile neutropenia, 1% experienced sig-
ificant effects on sensory nerves, and 1% on motor nerves, and 1 of the 397 patients who received early docetaxel died as a result of treatment. The cause of death was prostate cancer in 84 patients in the ADT plus docetaxel arm (83.2%) and 112 patients in the ADT-alone arm (83.6%).

In summary, this study shows that starting docetaxel along with hormone therapy in men with newly diagnosed hormone-sensitive prostate cancer improved OS by more than 13.6 months in comparison with standard hormone therapy alone. The bulk of the benefit appears to be in patients with high-volume disease. This striking survival benefit supports the use of upfront docetaxel in hormone-sensitive prostate cancer, especially in patients with high-volume disease.

Before CHAARTED, docetaxel was reserved for patients relapsing after initial ADT. In that setting, docetaxel produced only 2 to 3 months prolongation of survival. More recently, abiraterone, enzalutamide, and radium-223 also produce 3- to 5-month prolongations of median survival when they are given as successive single agents. The magnitude of survival improvement with docetaxel plus ADT upfront is unprecedented. The most likely explanation is biologic; therapy works best when it is multitargeted, administered in a lesser disease volume as a preemptive strike before adaptive resistance. Other potential factors include better drug tolerance and less toxicity in less sick patients.

CONCLUSION

The heterogeneity of prostate cancer and the diverse mechanisms of resistance support a multitargeted approach to maximize the antitumor impact. The totality of the current data would favor not delaying the use of docetaxel chemotherapy; pending the final peer-review publication of the CHAARTED trial, results strongly suggest that survival benefits of docetaxel are significantly higher when given in combination with ADT early in the course of mHSPC and that the combination has a more profound return on investment as compared with sequential therapy. The unprecedented survival benefits of this chemo-hormonal approach appear to be related to the better antitumor effect as reflected by higher rates of undetectable PSA levels and longer median time to castration resistance and clinical progression. Overall, patients tolerated therapy very well. Therefore, patients with newly diagnosed mHSPC who are deemed chemotherapy eligible, especially those with high-volume disease, should be counseled regarding this data and offered combination therapy.

Disclosures of Potential Conflicts of Interest


References


16. Isaacs JT, Coffey DS. Adaptation versus selection as the mechanism responsible for the relapse of prostate cancer to androgen ablation therapy as studied in the Dunning R-3327-H adenocarcinoma. *Cancer Res*. 1981;41:5070-5075.


