A SPECIAL MEETING REVIEW EDITION

Highlights in Advanced Prostate Cancer From the 2013 American Society of Clinical Oncology Genitourinary Cancers Symposium

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Special Reporting on:

- A Randomized, Phase II, Open-Label Study of Sipuleucel-T With Concurrent or Sequential Abiraterone Acetate in Metastatic Castrate-Resistant Prostate Cancer

- High-Risk Prostate Cancer Treated With Pelvic Radiotherapy and 36 Versus 18 Months of Androgen Blockade: Results of a Phase III Randomized Study

- Updated Interim Analysis of COU-AA-302, a Randomized Phase III Study of Abiraterone Acetate in Patients With Metastatic Castration-Resistant Prostate Cancer Without Prior Chemotherapy

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- Aflibercept Versus Placebo in Combination With Docetaxel/Prednisone for First-Line Treatment of Men With Metastatic Castration-Resistant Prostate Cancer: Results From the Multinational Phase III Trial (VENICE)

- Overall Survival and Safety of Dasatinib/Docetaxel Versus Docetaxel in Patients With Metastatic Castration-Resistant Prostate Cancer: Results From the Randomized Phase III READY Trial

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PLUS Meeting Abstract Summaries

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A Randomized, Phase II, Open-Label Study of Sipuleucel-T With Concurrent or Sequential Abiraterone Acetate in Metastatic Castrate-Resistant Prostate Cancer

Sipuleucel-T is an autologous cellular immunotherapy that stimulates an immune response against prostate cancer. It was approved by the US Food and Drug Administration (FDA) in 2010 for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). The phase III IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial found that sipuleucel-T improved overall survival (OS) compared with placebo.[1]

Abiraterone acetate is an inhibitor of CYP17 that is FDA-approved for mCRPC, and it suppresses circulating androgen levels, which is immunostimulatory. These facts suggested that the combination of sipuleucel-T and abiraterone acetate may be synergistic.[2] However, abiraterone acetate is usually administered with prednisone, which has immunosuppressive effects. This pairing could theoretically impair or blunt the immunologic response to sipuleucel-T.

Dr. Eric Small presented an interim analysis of an ongoing, randomized, open-label, phase II study that is the first to examine the combination of sipuleucel-T and abiraterone acetate plus prednisone in patients with mCRPC.[3] The patients were ages 18 or older and had asymptomatic or minimally symptomatic mCRPC. Their cancer was histologically documented with radiological evidence of bone or lymph node metastasis. Their serum prostate-specific antigen (PSA) level was 2 ng/mL or greater, and their Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 1 or less. Patients were excluded if they had known lung, liver, or brain metastases; malignant pleural effusions; malignant ascites;

medical contraindications to receiving prednisone; or if they had been treated with sipuleucel-T, abiraterone acetate, chemotherapy, a vaccine, or immunotherapy prior to registration.

Of the 64 patients randomized, 63 completed the 3 infusions of sipuleucel-T at approximately 2-week intervals that occurred either concurrently (n=31) or sequentially (n=32) with abiraterone acetate 1,000 mg once daily and prednisone twice daily. Abiraterone acetate plus prednisone

were administered for 26 weeks or until disease progression, unacceptable toxicity, or death. The 26 weeks of abiraterone acetate plus prednisone were completed by 4 patients in the concurrent arm and none in the sequential arm. Treatment with abiraterone acetate plus prednisone was discontinued early because of an adverse event (AE) in 1 patient in the concurrent arm and because of disease progression in 2 patients in the concurrent arm and 1 in the sequential arm.

Randomized Phase II Trial Evaluating the Optimal Sequencing of Sipuleucel-T and Androgen-Deprivation Therapy in Patients With Biochemically Recurrent Prostate Cancer: Immune Results

Preliminary evidence suggests that administration of androgen-deprivation therapy (ADT) before sipuleucel-T may lead to an improved anti-tumor immune response (Abstract 34). This interim data from a phase II trial evaluating the sequencing of sipuleucel-T and ADT examined immune parameters in patients with biochemically-recurrent prostate cancer who were at high risk for metastases. The prime-boost pattern of immune activation from sipuleucel-T was similar, independent of the timing of the ADT. The enrolled patients received either sipuleucel-T followed by ADT (n=34) or ADT followed by sipuleucel-T (n=34). Patients who received ADT first had increased serum interferon-γ compared to those who received sipuleucel-T first ($P<.05$ between treatment groups). This result was consistent with the increase in ELISPOT response at week 2 after infusion, which suggested more effector T-cell activity when ADT was administered first. Notably, the ELISPOT results did not reach statistical significance at this interim analysis ($P=.0866$). The findings suggested that T-cell activity may be enhanced by ADT when ADT is administered prior to sipuleucel-T. Both arms generated antigen-specific responses after the first infusions that were enhanced by subsequent infusions, and no significant differences occurred in the magnitude of the responses between the treatment arms. No differences occurred in ex vivo product parameters between the arms, but the patients who received ADT before sipuleucel-T had increased in vivo cytokines and cellular responses. This suggested that a different immunologic response to treatment may result from the castrate environment imposed by ADT. The combination of sipuleucel-T and ADT appeared to be well-tolerated in these patients, and AEs were similar in both arms. The frequency of grade 3 AEs was similar in both arms, affecting 2 patients who received sipuleucel-T first and 4 patients who received ADT first.
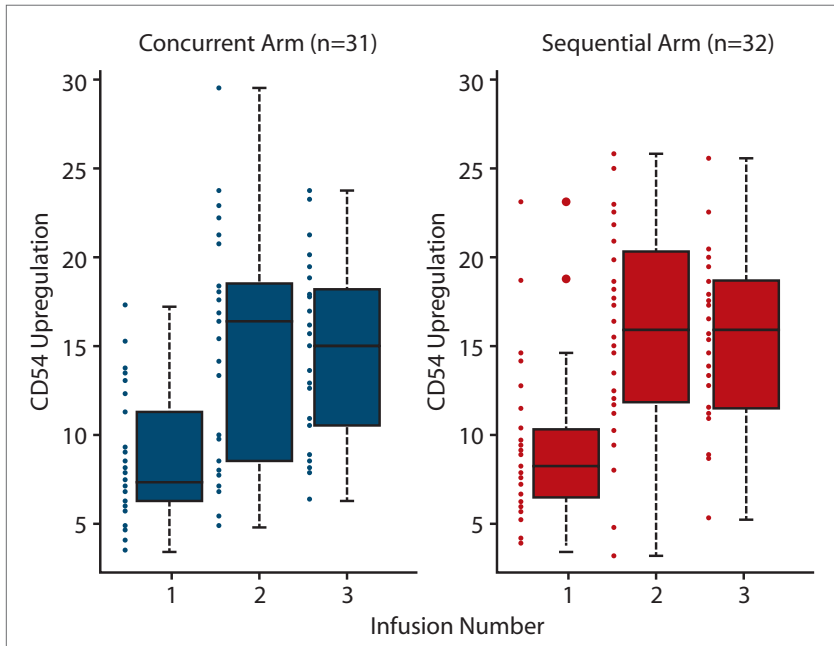
Figure 1. Upregulation of CD54 in mCRPC patients who received infusions of sipuleucel-T at approximately 2-week intervals that occurred either concurrently (A) or sequentially (B) with abiraterone acetate and prednisone.

mCRPC=metastatic castrate-resistant prostate cancer. Adapted from Small E et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL. Abstract 114.
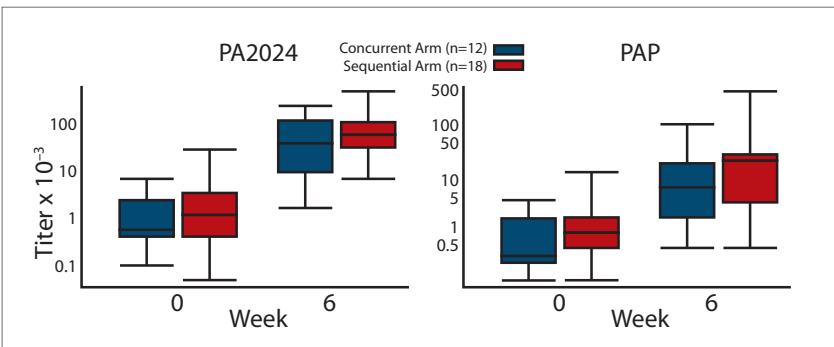

Figure 2. PA2024 (A) and PAP (B) as measured by ELISA in mCRPC patients who received infusions of sipuleucel-T at approximately 2-week intervals that occurred either concurrently or sequentially with abiraterone acetate and prednisone.

ELISA=enzyme-linked immunosorbent assay; mCRPC=metastatic castrate-resistant prostate cancer. Adapted from Small E et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL. Abstract 114.

The sipuleucel-T was produced from fresh leukapheresis that was performed at weeks 0 (baseline), 2, and 4. Before the sipuleucel-T was released for infusion, measurements were taken of total nucleated cell (TNC) count, antigen-presenting cell (APC) count, and APC activation—which was defined as large cells expressing CD54. Immune response was measured at weeks 0 (baseline), 2, 4, and 6 as antibody response based on serum PA2024-specific and prostatic acid phosphatase (PAP)-specific IgG-IgM levels, PA2024-specific and PAP-specific T-cell proliferation, and PA2024-specific and PAP-specific memory T-cell counts. Humoral and cellular immune responses to sipuleucel-T were measured by antibody response through an enzyme-linked immunosorbent assay (ELISA), T-cell proliferation through ^{3}H-thymidine

incorporation, and memory T-cell counts through an interferon-γ enzyme-linked immunosorbent spot (ELISPOT) assay.

The primary endpoint was the cumulative APC activation in sipuleucel-T product, which is the sum of values across 3 infusions. The secondary and tertiary endpoints were cumulative APC counts in sipuleucel-T product, cumulative TNC in sipuleucel-T product, peripheral immune response to PA2024 and PAP, and safety profile. Exploratory endpoints were change in PSA levels and OS.

The sipuleucel-T product potency and the prime boost effect were similar with concurrent or sequential abiraterone acetate plus prednisone. Activation of APC was substantially greater at the second and third infusions than at baseline. This finding was indicative of the prime boost effect,[4] and it occurred in both the concurrent and sequential arms, which were not significantly different in their responses.

In the concurrent arm, the cumulative APC activation, expressed as a ratio of the average number of CD54 molecules on cells post-culture versus pre-culture with PA2024, was 36.4 (range, 5.9–65.6), cumulative APC count was 1.8×10^9 (range, 0.2×10^9–5.0×10^9; Figure 1), and cumulative TNC count was 8.3×10^9 (range, 0.5×10^9–24.2×10^9). In the sequential arm, cumulative APC activation was 40.7 (range, 15.1–62.5), cumulative APC count was 1.5×10^9 (range, 0.5×10^9–4.0×10^9), and cumulative TNC count was 10.3×10^9 (range, 3.3×10^9–24.4×10^9).

The concurrent and sequential arms had comparable humoral and cellular immune responses to sipuleucel-T. Significant differences occurred between baseline and week 6 for PA2024 ($P<.001$) and PAP ($P<.001$) as measured by ELISA (Figure 2), but no difference was found between concurrent and sequential administration of abiraterone acetate ($P=.300$ for PA2024 and $P=.338$ for PAP). T-cell proliferation differed between weeks

0 and 6 for PA2024 (*P*<.001) but not for PAP (*P*=.940). Memory T-cell counts, as measured by interferon-γ ELISPOT, differed between weeks 0 and 6 for both PA2024 (*P*<.001) and PAP (*P*<.001).

The 2 treatment arms had similar rates of AEs. A total of 8 patients experienced grade 3 AEs. In the concurrent treatment arm, 3 patients experienced grade 3 pathological fracture, pulmonary embolism, and transient ischemic attack. In the sequential treatment arm, 5 patients experienced grade 3 cystitis, hearing impairment, hypertensive crisis, obstructive uropathy, sepsis, syncope (vasovagal), and systemic inflammatory response syndrome. The 3 adverse events

considered possibly related to treatment were pulmonary embolism, systemic inflammatory response syndrome, and syncope, each of which occurred in 1 patient. These events resolved. Other adverse events that occurred in 10% or more of patients were muscle spasms, chills, oral paresthesia, back pain, nausea, extremity pain, fatigue, headache, paresthesia, and pyrexia.

In conclusion, both sipuleucel-T product potency and the prime boost effect were similar with either concurrent or sequential abiraterone acetate plus prednisone. Both treatment arms had similar humoral and cellular immune responses. Both treatment arms were reasonably well-tolerated,

and both treatment arms had similar incidences of the most frequent AEs.

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High-Risk Prostate Cancer Treated With Pelvic Radiotherapy and 36 Versus 18 Months of Androgen Blockade: Results of a Phase III Randomized Study

In high-risk prostate cancer, the optimal duration of androgen blockade is unknown. In 1997, improved OS was reported when long-term androgen blockade was added to radiotherapy.[1] However, this androgen blockade is the source of many side effects, particularly the castration syndrome, which greatly diminishes quality of life for most patients. Dr. Abdenour Nabid and colleagues thought to challenge the 1997 study by cutting the duration of the androgen blockade in half, bringing it from 36 months to 18 months. Recruitment started in 2000 and involved 10 centers in Quebec, Canada. Dr. Nabid presented the results of this phase III, multicenter, prospective, randomized trial.[2]

Patients in this study had high-risk prostate cancer, which was defined as stage T3/T4, PSA higher than 20 ng/mL, or Gleason score higher than 7. They were younger than 80, had normal liver function, and had no regional disease. The
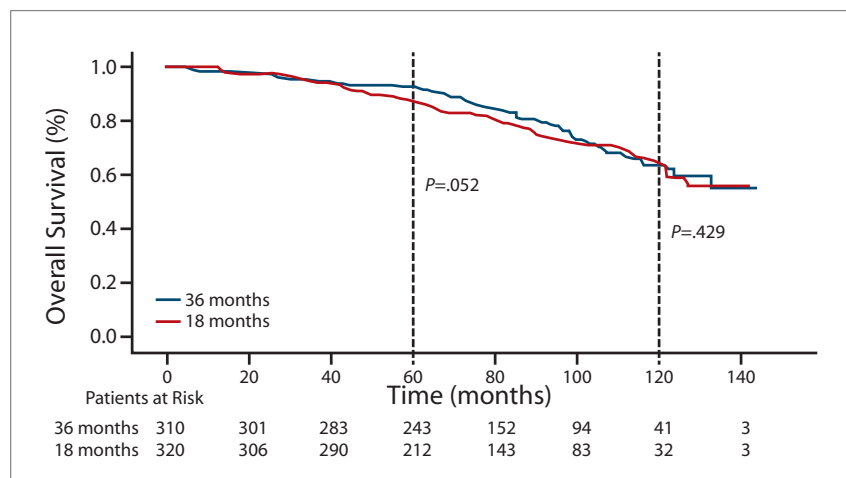
Figure 3. Overall survival among high-risk prostate cancer patients treated with pelvic radiotherapy who received androgen blockage for 36 months or 18 months.

Adapted from Nabid A et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL. Abstract 3.

patients had a computed tomography scan or magnetic resonance image scan, a negative bone scan, no previous malignancy, and a signed consent form. Patients were excluded if they had preexisting medical conditions

that precluded the use of androgen blockade or radiotherapy.

The primary endpoints were OS, disease-specific survival, and quality of life. The secondary endpoints were disease-free survival, biochemical

failure, and site of tumor relapse. The statistical analysis used Chi square, Kaplan-Meier survival rate curves with log-rank test, and univariate and multivariate Cox regression.

From October 2000 to January 2008, patients were randomized to the 36-month group (n=310) or the 18-month group (n=320). The androgen blockade consisted of bicalutamide 50 mg per day for 1 month, and goserelin 10.8 mg every 3 months for 36 months versus 18 months. The androgen blockade was given neoadjuvantly, concomitantly, and adjuvantly to radiotherapy. Radiotherapy started 4 months after the beginning of the androgen blockade. The median follow-up of the study was 77 months.

The patient characteristics were similar between both treatment groups, with very similar median age (71 years), interquartile age ranges, PSA, and Gleason scores. The 2 groups were comparable in clinical stage. No statistical difference existed between the groups.

The risk factors selected were T3/T4, PSA over 20 ng/mL, and Gleason score higher than 7. The numbers were comparable between the 2 treatment groups. The Gleason score was split into 2 groups, with Gleason scores of 8 and below versus 9 and above, and the 2 treatment groups were comparable. In this study, 24% of the patients were T3/T4, 44% had PSA over 20 ng/mL, and nearly 60%

had a Gleason score over 7, with 20% having Gleason scores of 9 or 10.

Biochemical failure was defined as nadir PSA plus 2 ng/mL, and 100 biochemical failures occurred (22%). All of these patients received the second course of androgen blockade. The 18-month treatment group had more biochemical failures (80 patients vs 60 patients in the 36-month group), and more second courses of androgen blockade occurred in the 18-month group, but these differences were not statistically significant.

Pelvic node failures occurred in 1% of the patients, and the proportion was the same in both treatment groups. The proportion of bone metastasis was the same for both treatment groups (8.1% with 36-month treatment vs 7.8% with 18-month treatment). Prolonging the duration of androgen blockade for these patients did not prevent more bone or node metastasis.

A total of 147 deaths occurred, and the proportions were the same in both treatment groups (22.9% for 36-month treatment vs 23.8% for 18-month treatment). More second cancers occurred in the 18-month treatment group (28 patients in the 18-month treatment group vs 18 patients in the 36-month treatment group), but the increase was not statistically significant. Less than 5% of the patients had a second cancer caused by prostate cancer, with no difference between the 2 treatment groups. The cause of death was unknown for 4 patients, and from a statistical perspective, their deaths were considered death from prostate cancer. Cardiovascular deaths comprised 4.4% of deaths and did not differ between the treatment groups.

The rates of OS were 92.1% for the 36-month treatment arm versus 86.8% for the 18-month treatment arm at 5 years (*P*=.052) and 63.6% versus 63.2% at 10 years (*P*=.429; Figure 3). The disease-specific survival was identical between the 2 treatment groups (97% vs 96% at 5 years and 87.2% for

Exploratory Analysis of the Visceral Disease Patient Subset in COU-AA-301, a Phase III Study of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer

This post hoc exploratory analysis from the COU-AA-301 trial found that the clinical benefit of abiraterone acetate and prednisone on OS and other clinical outcomes was maintained in those with visceral disease, indicating that it is a therapeutically active treatment option for these patients (Abstract 14). This phase III, multinational, randomized, double-blind, placebo-controlled trial compared abiraterone acetate and prednisone (n=797) with placebo and prednisone (n=398) in previously treated men with mCRPC who were progressing after docetaxel treatment. Among the enrolled patients, visceral disease occurred in 253 patients in the abiraterone acetate arm and 99 in the placebo arm. Visceral metastatic disease was associated with a poorer prognosis, as the median OS was 12.9 months for those with visceral disease treated with abiraterone acetate versus 17.1 months for patients in the same treatment arm without visceral disease. Likewise, patients in the placebo arm had an OS of 8.3 months with visceral disease versus 12.3 months without visceral disease (hazard ratio, 0.79; 95% CI, 0.6–1.05; *P*=.102). However, the absolute benefit favoring abiraterone acetate over placebo was similar in patients with or without visceral disease. Both for patients with and without visceral disease, abiraterone acetate provided clinical benefit. These benefits were evident for patients with visceral disease in regards to rPFS (median 5.6 months vs 2.8 months; *P*=.0002), PSA response rate (28% vs 7%; *P*<.0001), and objective response rate (11% vs 0%; *P*=.0058). Median OS was markedly shorter in patients with liver metastases only (6.7 months) compared with lung metastases only (12.0 months), although those treated with abiraterone acetate had longer OS in both groups (7.3 months with liver metastases only and 13.9 months with lung metastases only) compared with those treated with placebo (4.0 months with liver metastases only and 7.9 months with lung metastases only). The safety and tolerability of abiraterone acetate in patients with visceral disease were similar to those in patients without visceral disease.

both groups at 10 years). Multivariate analysis for OS found that only age was statistically significant, meaning that older patients died more rapidly. Treatment group, PSA higher than 20, Gleason score higher than 20, T3/T4, and biochemical failure did not contribute to significant differences in outcome.

This study was compared with the 2009 study by the European Organisation for Research and Treatment of Cancer (EORTC) Radiation Oncology Group, which found that 36 months of androgen blockade was superior to 6 months.[3] That study had 970 patients, and it had a similar follow-up time of 630 patients. The EORTC study had 5-year OS of 81% in the 6-month treatment group and 84.8% in the 36-month group, whereas this study had 5-year OS of 86.8% in the 18-month treatment group and 92.1% in the 36-month group. In conclusion, androgen blockade duration can be safely reduced from 36 months to 18 months in localized high-risk prostate cancer. The hypothesis is that androgen blockade delivered during 18 months could represent a threshold effect. No further gain and no benefit occurred afterward. For the patients, the duration of side effects and treatment cost can be significantly reduced. The primary endpoints of the study also include quality of life data, which is undergoing analysis.

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Updated Interim Analysis of COU-AA-302, a Randomized Phase III Study of Abiraterone Acetate in Patients With Metastatic Castration-Resistant Prostate Cancer Without Prior Chemotherapy

Data from an updated analysis of the COU-AA-302 trial has resulted in the expanded approval of abiraterone acetate for mCRPC patients without prior chemotherapy and has changed the way the disease is treated.[1] Although prostate cancer can be an indolent disease for many, the subset of patients who progress to mCRPC are at higher risk of death from prostate cancer than from other causes. Treatments are needed for these patients, not only to improve OS, but also to impart a more inclusive clinical benefit as measured by a delay in symptomatic disease progression while quality of life is maintained.

The use of abiraterone builds on an increased understanding of the continued relevance of the androgen signaling pathway in CRPC. Abiraterone impairs androgen synthesis by selectively inhibiting the CYP17 enzyme complex, and it is now approved for
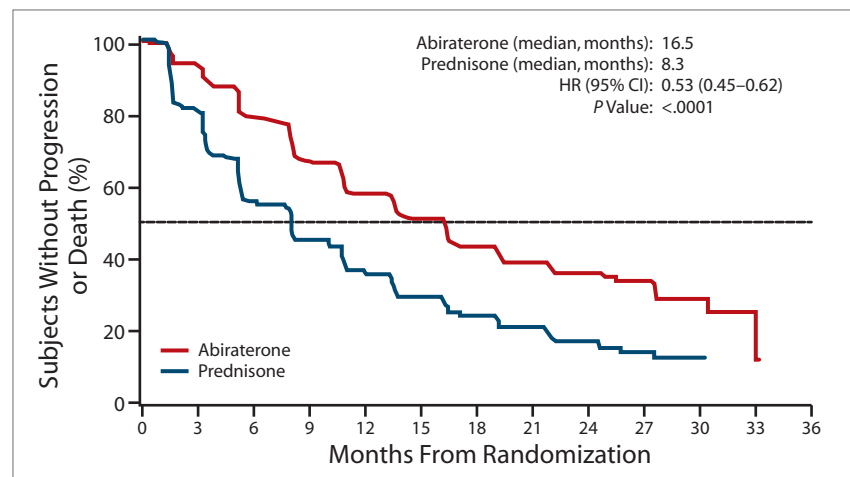
Figure 4. In an updated interim analysis of the COU-AA-302 trial, the rPFS for abiraterone acetate was 16.5 months versus 8.3 months for the prednisone control.

rPFS=radiographic progression-free survival. Adapted from Rathkopf D et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL. Abstract 5.

the treatment of mCRPC across the spectrum of disease states.

This presentation focused on the updated analysis of COU-AA-302 for the prechemotherapy population.[2] The study has co–primary endpoints. In addition to the more traditional phase III endpoint of OS, the study design

included radiographic progression-free survival (rPFS) as a distinct measure of clinical benefit and also as an interim measure of success in a patient population that was likely to live at least 2–4 years. Additional secondary and exploratory endpoints include measures of clinical benefit and health-related quality of life as reported by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and the Brief Pain Inventory (short form).

The study protocol called for 3 planned interim analyses for OS and 1 planned interim analysis for rPFS by central review. These analyses were to be performed on an event-driven basis. This presentation of the data is from interim analysis 3, which was performed at 56% of events at the clinical cutoff date of May 2012. The actual alpha value required for OS to reach significance at 56% of events

was 0.0035. A final analysis is planned after the occurrence of 773 events.

The treatment arms were evenly matched with regard to common clinical variables. At a median follow-up of 27.1 months, therapy had been discontinued by 77% of patients treated with abiraterone and 89% of patients treated with the prednisone control. The majority of the patients who went off-study did so because of disease progression.

An important feature of this study was the focus on clinical benefit in addition to tumor response. As such, patients were allowed to remain on-study past radiographic progression until a time point of unequivocal clinical progression. For the purposes of this protocol, unequivocal clinical progression was defined as 1 or more of the following: pain requiring opiates, chemotherapy, palliative radiation therapy, decline in ECOG PS, or surgical intervention.

Another critical component of this study was standardization of the rPFS endpoint. The definition of rPFS was adapted from the Prostate Cancer Clinical Trials Working Group 2 criteria[3] and required that the appearance of 2 or more bone lesions be confirmed on subsequent imaging so that patients would not be taken off the study prematurely for bone flare. A key feature of implementing this endpoint was the adaptation and use of the bone scan form, which allowed the investigator to graphically demonstrate the location of specific lesions and assess changes in these lesions over time. Given the logistical and methodological challenges of including individual investigators at more than 150 sites around the world, extensive investigator training and real-time site monitoring occurred. This rigorous standardization and training for rPFS resulted in a high level of consistency between the central and investigator reviews. At the first planned interim analysis in 2010, general agreement was reached as to the occurrence and timing of radiographic progression in both treatment arms.

The updated Kaplan-Meier curve for the co–primary endpoint of rPFS as assessed by investigator review found that abiraterone doubled the time to radiographic progression relative to the prednisone control. The rPFS for abiraterone was 16.5 months versus 8.3 months for the prednisone control (HR=0.53; *P*<.0001; Figure 4). There was a treatment benefit across a wide spectrum of patient subgroups, and all hazard ratios favored the abiraterone arm over the prednisone control.

The co–primary endpoint of OS had a median survival for the abiraterone arm of 35.3 months versus 30.1 months for the prednisone control (HR=0.79; *P*=.0151). Since the actual alpha value for significance of OS at 56% of events was 0.0035, OS favored the abiraterone arm but did not cross the boundary for significance. Similar to the Forrest plot for rPFS, the OS benefit for abiraterone was uniform across subgroups.

Sipuleucel-T Delayed Time to First Use of Opioid Analgesics in Patients With Asymptomatic or Minimally Symptomatic Metastatic Castration-Resistant Prostate Cancer in the IMPACT Trial

Sipuleucel-T significantly delayed the time to first opioid use in patients with asymptomatic or minimally symptomatic mCRPC who were enrolled in the IMPACT trial (Abstract 74). Patients with mCRPC who were enrolled in the phase III IMPACT trial received either sipuleucel-T (n=341) or placebo (n=171). Time to first use of opioid analgesics was analyzed by a Kaplan-Meier curve, which found that curve separation began approximately 6 months after treatment with either sipuleucel-T or placebo was initiated. The median time to first opioid use was 11.9 months for patients in the sipuleucel-T arm versus 8.3 months for those in the placebo arm (HR=0.727; 95% CI, 0.536–0.987; P=.041). Enrolled patients had a median time to disease-related pain of 4.3 months in the sipuleucel-T arm, which occurred prior to the median of 11.9 months when their opioid use began. The delay in time to first opioid use denotes the delayed treatment effect associated with sipuleucel-T, which presumably occurs after the median time to progression but before the median time to first opioid use is reached. Among those patients with progressive disease, a requirement for opioid use developed for 34.5% of patients in the sipuleucel-T arm and 39.0% in the placebo arm. At 12 months, 48.7% of the patients in the sipuleucel-T arm and 39.7% of those in the placebo arm were opioid-free. The median follow-up for opioid use was 5.2 months. A shorter time to first opioid use was associated with several prognostic factors that are indicative of the presence of more advanced disease, including higher PSA levels, an increased number of bone metastases, and worse ECOG PS. For unknown reasons, primary radiotherapy was predictive of a shorter time to first use of opioids. Overall, the data suggest that sipuleucel-T clinically impacts patients with asymptomatic or minimally symptomatic mCRPC in addition to its effect on OS.

Subsequent therapy was common for patients who came off study. The most common post-trial anti-cancer agent was docetaxel in both treatment arms. Of the patients who discontinued treatment, subsequent abiraterone was received by 9% of the patients in the abiraterone arm and 16% of the patients in the prednisone control arm.

Both the secondary endpoints of clinical benefit and the exploratory endpoints related to patient-reported outcomes demonstrated statistically significant benefits favoring abiraterone over the prednisone control. Abiraterone doubled the maximum decline in PSA relative to the prednisone control arm. Notably, the observation that 29% of the patients in the prednisone control arm had a decline in PSA that was greater than or equal to 50% suggests that prednisone is an active control therapy.

The most common AE for both treatment arms was fatigue. Expected toxicities of mineralocorticoid excess, such as fluid retention, hypokalemia, and hypertension, were common but low grade. Potential toxicities of glucocorticoid use, such as hyperglycemia and weight gain, were relatively infrequent. The abiraterone arm had a higher incidence of all-grade cardiac and liver function test abnormalities than the prednisone control arm, but the difference did not reach statistical significance. Importantly, no new safety signals emerged with a longer duration of treatment with abiraterone or prednisone beyond 2 years.

In summary, treatment with abiraterone plus prednisone reduced the risk of disease progression by 47%, decreased the risk of death by 21%, significantly delayed the time to opiate and chemotherapy use, improved quality of life measures, and remained safe and well-tolerated with longer exposure.

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Impact of On-Study Corticosteroid Use on Efficacy and Safety in the Phase III AFFIRM Study of Enzalutamide, an Androgen Receptor Inhibitor

This presentation discussed the impact of on-study corticosteroid use on efficacy and safety in the phase III AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-Based Chemotherapy) study of enzalutamide.[1] Enzalutamide (MDV3100) is a novel and rationally designed oral androgen-receptor inhibitor that targets multiple steps in the androgen-receptor signaling pathway. In addition to greater binding affinity relative to other approved anti-androgens, enzalutamide inhibits nuclear translocation of the receptor as well as androgen receptor–mediated DNA binding.[2,3]

In the phase III AFFIRM trial of enzalutamide versus placebo, baseline corticosteroid use was associated with an inferior OS independent of study

Table 1. Impact of Baseline Corticosteroid Use in the Phase III AFFIRM Study of Enzalutamide

Variable	Parameter Coefficient	Estimated *P* Value	HR for Death (95% CI)
Treatment (enzalutamide vs placebo)	-0.54±0.090	<.0001	0.58 (0.49–0.70)
Median pain score (<4 vs ≥4)	-0.26±0.098	.0091	0.78 (0.64–0.94)
Progression at study entry (PSA only vs radiographic)	-0.35±0.094	.0002	0.70 (0.59–0.85)
Visceral disease at screening (no vs yes)	-0.42±0.097	<.0001	0.66 (0.54–0.80)
Baseline hemoglobin result	-0.03±0.003	<.0001	0.97 (0.97–0.98)
Baseline LDH result	0.002±0.000	<.0001	1.002 (1.001–1.002)
Baseline corticosteroid use (no vs yes)	-0.62±0.091	<.0001	0.54 (0.45–0.64)

AFFIRM=Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-Based Chemotherapy; CI=confidence interval; HR=hazard ratio; LDH=lactate dehydrogenase; PSA=prostate-specific antigen.

Adapted from Scher H et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL: Abstract 6.

treatment.[4] This presentation is the result of a univariate analysis. Patients who did not receive glucocorticoids had a 7.5-month longer median survival and a 53% reduction in the risk of death.

Corticosteroids have a range of applications in managing prostate cancer. A rise of PSA signifies the transition to a castration-resistant state, which is lethal for most patients. Patients are often classified based on prior chemotherapy exposure. But in both the pre–first-line and post-docetaxel settings, corticosteroids have been used for their anti-tumor effects, for palliation of symptoms, and to reduce the toxicity or AEs associated with approved therapies. Corticosteroids have also been used as an active control in phase III registration trials based on their anti-tumor effects and their role in palliation in both prechemotherapy and postchemotherapy settings.

However, a body of evidence is now emerging suggesting that corticosteroids may stimulate prostate cancer growth.[5] Several mechanisms have been proposed, including activation of promiscuous androgen receptors, stimulation of human *SGK* gene expression, promotion of IL-6 expression, and direct activation of glucocorticoid signalling.

The phase III AFFIRM registration trial was conducted in CRPC patients who had received treatment with chemotherapy. Corticosteroids were permitted at study entry but were not an entry requirement. Enzalutamide prolonged survival by a median of 4.8 months in the AFFIRM study, which translated to a 37% reduction in the risk of death.[4] The median survival was 18.4 months with enzalutamide versus 13.6 months with placebo.

Scher and colleagues hypothesized that corticosteroid use may have adversely affected survival in the AFFIRM study. This unplanned ad hoc analysis explored the relationship between corticosteroid use and survival. If a potential association were found, the analysis would then aim to clarify whether patients would still benefit from enzalutamide. Corticosteroid use in AFFIRM varied widely. Some patients had not received any before the study and did not receive any during the study. Some patients came on-study with baseline corticosteroid use, and some had corticosteroids added at entry. Overall, 30% of the patients were on corticosteroids at the time they started the study. All patients had previously received corticosteroids during docetaxel therapy.

Focusing first on baseline use at study entry, the following statistical methods were applied: hazard ratios for death were calculated after adjustment for prognostic factors, treatment group, and baseline corticosteroid use. Prespecified factors were entered into a Cox proportional hazard model. As shown earlier in this trial, corticosteroid use at baseline was associated with inferior overall survival independent of study treatment.[6]

A number of prognostic factors were prespecified to develop a multivariate model around the question. They included components of the primary analysis, such as enzalutamide treatment arm versus placebo; use of baseline oral corticosteroids; stratification factors at entry; and prognostic factors that have been reported in the literature or included in nomograms, including type of progression at entry: PSA versus radiographic, baseline parameters, presence or absence of visceral disease, and number of prior chemotherapy regimens. Age and region of treatment were also considered.

The multivariate analysis suggested that baseline corticosteroid use was an independent predictor of overall survival. The multivariate model included lactate dehydrogenase (LDH), hemoglobin, visceral disease, progression at entry, and mean pain score (Table 1). Notably, in the multivariate model, corticosteroid

ARN-509 in Men With High-Risk Nonmetastatic Castration-Resistant Prostate Cancer

In men with high-risk non-metastatic CRPC, this phase II portion of a multicenter phase I/II study found that the anti-androgen ARN-509 has promising preliminary activity and is safe and well tolerated (Abstract 7). The novel, second-generation anti-androgen ARN-509 binds directly to the ligand-binding domain of the androgen receptor. ARN-509 inhibits nuclear translocation of the androgen receptor and DNA binding to androgen response elements. In contrast to bicalutamide, ARN-509 has shown no significant agonist properties. Upon study entry, the 47 enrolled patients had high-risk non-metastatic CRPC and were a median age of 71 years. A high proportion had an ECOG PS of 0 (77%) and a Gleason score of 8–10 (32%). The median PSA at study entry was 10.7 ng/mL. The patients had all received treatment with a luteinizing hormone-releasing hormone agonist (LHRH) at the time of study entry, either with or without a first-generation anti-androgen. Prior anti-androgen therapy was received by 83% of the enrolled patients. The patients were all high-risk for metastases, as defined by a PSA value above 8 ng/mL and/or a PSA doubling time of less than 10 months. A decline in PSA greater than 50% occurred in 91% of patients at 12 and 24 weeks. At 12 months, the estimated PFS rate was 88.7%. The time to PSA progression had not yet been reached. The median treatment duration was 8.1 months. This patient population tolerated ARN-509 well; no treatment-related serious AEs and no seizures occurred. The most common AEs were fatigue (30%), diarrhea (28%), nausea (17%), rash (13%), and abdominal pain (11%). The vast majority of these events were grade 1 or 2. The incidence of grade 3 events was 6.4%. Two patients discontinued the study due to AEs, and 2 patients discontinued for objective or clinical progression. Dose reductions were required for 3 patients. Of the 47 enrolled patients, 41 are still receiving treatment.

use remained a significant adverse feature, whereas the treatment effect with enzalutamide remained.

Baseline use of corticosteroids was associated with an inferior OS. The result was independent of study treatment after adjusting for prognostic and other factors. Nevertheless, enzalutamide improved OS regardless of the baseline use of corticosteroids. The only statistically significant biochemical parameter that was associated with corticosteroid use was LDH.

Next, the relation of baseline use of corticosteroids as well as on-study use of corticosteroids in relation to survival were considered. These patients had corticosteroids added at some point during the study. Approximately 47% had been receiving corticosteroids for 6 months, and 59% for 3 months. The frequency and type of corticosteroids were very similar between those who used corticosteroids at baseline and those who added them on. Prednisone and dexamethasone were the most common agents; approximately 40% of the patients received them.

Compared with patients who did not receive corticosteroids, patients who did receive corticosteroids were sicker and had more advanced disease. This observation was indicated by the higher frequency of pain at entry, a higher median PSA level, a higher frequency of visceral liver disease at study entry, and a higher frequency of 20 or more bone metastases among patients who received corticosteroids.

Patients who received corticosteroids had worse survival times and progressed more rapidly when measures of OS, rPFS, and time to PSA progression were considered. The median survival time was 11.5 months for those who received corticosteroids at baseline or on-study versus not yet reached in those who did not receive corticosteroids. Survival times with enzalutamide were superior to placebo in both the groups that received no corticosteroids (not yet reached vs 18.8 months) and those treated with corticosteroids (12.8 months vs 9.6 months), with a significant difference

between patients with no on-study corticosteroids at baseline versus patients with on-study corticosteroids. Notably, patients who received enzalutamide and corticosteroids had an inferior OS.

Times for rPFS had a similar result. Patients who received corticosteroids had a shorter time to radiographic progression versus patients who did not receive corticosteroids. The effect of enzalutamide was again preserved among comparable enzalutamide-treated patients (rPFS was 5.6 months with corticosteroids vs 11.1 months with no corticosteroids). A similar relationship occurred for time to PSA progression, with a shorter time to PSA progression in patients who were receiving corticosteroids (5.6 months for enzalutamide and 3.1 months for placebo) versus a longer time in those who were not receiving corticosteroids (8.6 months and 2.9 months).

The use of corticosteroids was associated with more patient-reported grade 3/4 AEs relative to the no-corticosteroid group. Anemia and fatigue were more frequent in those who did not receive corticosteroids. The group that used corticosteroids had no significant difference in infection rate, frequency of sepsis, hyperglycemia, or diabetes mellitus.
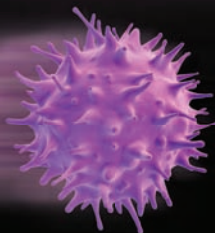
In conclusion, although AFFIRM was not designed to assess corticosteroid use on efficacy, patients who received corticosteroids had reduced survival in this post hoc analysis. Enzalutamide was superior to placebo with respect to OS, rPFS, and time to PSA progression after accounting for known prognostic factors and other variables. Patients taking corticosteroids had higher rates of grade 3/4 AEs. These inferior outcomes in patients receiving corticosteroids may be related to the biologic properties of the tumor, such as promiscuous androgen receptors,

Cabazitaxel for Metastatic Castration-Resistant Prostate Cancer: Final Quality-of-Life Results With Safety Data From the United Kingdom Early Access Programme (NCT01254279)

A trend toward improved quality of life in mCRPC patients who received cabazitaxel was demonstrated in this final report of quality of life and safety data from the international phase IIIB/IV study of cabazitaxel (Abstract 91). Cabazitaxel is a next-generation taxane that has been developed to overcome resistance to older taxanes, and it provides a much-needed second-line chemotherapy option for these patients. This study enrolled 112 patients at 12 centers in the United Kingdom, and these patients received cabazitaxel every 3 weeks and prednisone daily. Their quality of life was assessed at baseline, at alternate cycles, and at 30 days posttreatment. The overall mean quality of life was stable. The EQ-5D-3L index and visual analog scale (VAS) indicated a trend toward improved quality of life with increasing cycles of cabazitaxel. This trend suggested that patients who met objective response criteria also gained quality of life benefit. This was further assessed through paired "within patient" analyses, which also supported this trend. Pain is a major symptom in mCRPC, mainly because of bone metastases, which affected 92% of the enrolled patients. At each assessment time point, the proportion of patients who reported no pain according to the EQ-5D increased relative to baseline. For the 28 patients who received 10 cycles of cabazitaxel, 96% had stable pain (27/28), and 39.3% (11/29) reported improved pain. The patients received a median of 6 cycles, with 34 patients (30%) receiving 10 or more cycles. The most frequent grade 3/4 AEs were fatigue (13%), diarrhea (5%), and neutropenia (10%). Prophylactic GM-CSF was received by 80% (89/112) of the patients at cycle 1. Treatment was stopped prematurely due to non-progressive AEs in 32% (11/112) of the patients. Fatigue was the most frequent AE leading to discontinuation, accounting for 7% (8/112) of the patients.

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other mechanisms, or other unknown confounders. Importantly, these findings require prospective validation.

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Aflibercept Versus Placebo in Combination With Docetaxel/Prednisone for First-Line Treatment of Men With Metastatic Castration-Resistant Prostate Cancer: Results From the Multinational Phase III Trial (VENICE)

The VENICE (VEGF Trap Administered With Docetaxel in Metastatic Androgen-Independent Prostate Cancer) trial was designed after the TAX 327 study showed the superiority of docetaxel and prednisone compared to mitoxantrone and prednisone for mCRPC.[1] VENICE is one of several studies that have tried to add targeted therapy—in this case, the anti-vascular agent aflibercept—to the docetaxel/prednisone regimen, with the aim of improving survival.[2]

Aflibercept was constructed with components of the VEGF receptors 1 and 2 to create a potent anti-angiogenic agent that binds to VEGF-A, VEGF-B, and PlGF. Preclinical data supported its use in prostate cancer models, including the DU145 prostate cancer model in mice.[3] Aflibercept alone was able to delay the appearance of tumors. In other preclinical models, aflibercept combined with docetaxel delayed growth of xenografts.[4]

The patients in VENICE had metastatic, progressive disease that persisted after hormonal or surgical castration. The study treatment was intended to be first-line chemotherapy, although prior treatment with estramustine was allowed. The primary endpoint was OS. Second-

P10-1 Open-Label, Multicenter Study of Sipuleucel-T in Metastatic Castrate-Resistant Prostate Cancer Patients Previously Treated With Sipuleucel-T: Evaluation of Antigen-Presenting Cell Activation

When patients who had previously been treated with sipuleucel-T were re-treated with sipuleucel-T after they progressed to asymptomatic or minimally symptomatic mCRPC, the data were consistent with the existence of a memory immune response to immunizing antigen several years after the initial treatment (Abstract 147). The phase III PROTECT (Prostate Testing for Cancer and Treatment) trial investigated sipuleucel-T in patients with rising PSA levels after radical prostatectomy following 3–4 months of androgen suppression (Beer TM et al. *Clin Cancer Res.* 2011;17:4558-4567). The open-label, uncontrolled, phase II, multicenter P10-1 study evaluated the immune responses generated by sipuleucel-T in patients with mCRPC who had previously been treated in the PROTECT trial. P10-1 enrolled 7 patients, who were a median age of 70 years as of September 2012. The median interval between their last infusion in the PROTECT trial and their first infusion in P10-1 was 8.6 years. The patients had a higher APC activation with the first sipuleucel-T treatment in P10-1 than with their initial infusion in PROTECT, which indicated the presence of under-lying immunological memory. Immunological memory was further indicated by antigen-specific cellular responses that were detected prior to re-treatment in P10-1. Antigen-specific interferon-γ patterns by ELISPOT were also consistent with the presence of an immune memory response. Both PA2024 and PAP interferon-γ ELISPOT responses were boosted after the first infusion of sipuleucel-T, which is a classic vaccine immunological memory response. The ELISPOT for PA2024 correlated with PAP ELISPOT responses. The re-treatment with sipuleucel-T was well tolerated. Most AEs (88%) were mild to moderate in severity. Grade 3 or higher AEs were experienced by 2 patients. One had a cerebrovascular accident and myocardial infarction, and the other experienced cystitis radiation, hematuria, and pneumonia. Most AEs (43%) were related to the infusion, such as arthralgia, chills, fatigue, headache, and pyrexia. These events occurred within 1 day of infusion and were mild to moderate.
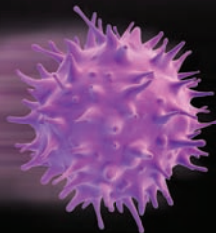
ADAPTABLE

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ary endpoints included PSA response, tumor response, pain response, quality of life response, and various progression endpoints, such as time to occurrence of skeletal-related events and an overall PFS that was a composite endpoint. The study design included 2 defined interim analyses: the first one for futility and the second one for early efficacy. The trial was reviewed at 6-month intervals by its data monitoring committee, which suggested that the study continue without modification after each review. The patient demographics were fairly typical. The median age was 68, which is very similar to other trials of this type, including the TAX 327 study.[1] The majority of the patients were ECOG PS 0 and 1.

At the time of study closure, 612 patients were randomized to each arm. Data on PSA response were obtained for slightly fewer than the total number of patients enrolled. A very small number of protocol violations led to assignment to the opposite study arm; in particular, 6 patients received aflibercept when they had been assigned to placebo. The safety analysis was based on the treatment that was received. The primary analysis was intent-to-treat.

The time from diagnosis to randomization was about 4 years. Most of the patients had received 3 or more hormonal therapies. A number of patients had received prior corticosteroids and prior primary treatment with radiotherapy and surgery. A difference did exist in the duration and amount of treatment received between the 2 arms that may be relevant to the results. The patients who were randomized to aflibercept had a median of 1 fewer cycle (n=8) than those randomized to placebo (n=9), and had a median duration of treatment that was about 5 weeks shorter. In general, more patients in the aflibercept arm received a smaller number of cycles.

No difference occurred in the primary endpoint of OS, as the survival curves for both arms were essentially superimposable (HR=0.94; log-rank P=.38; Figure 5). The median follow-up was 3 years, following study protocol.
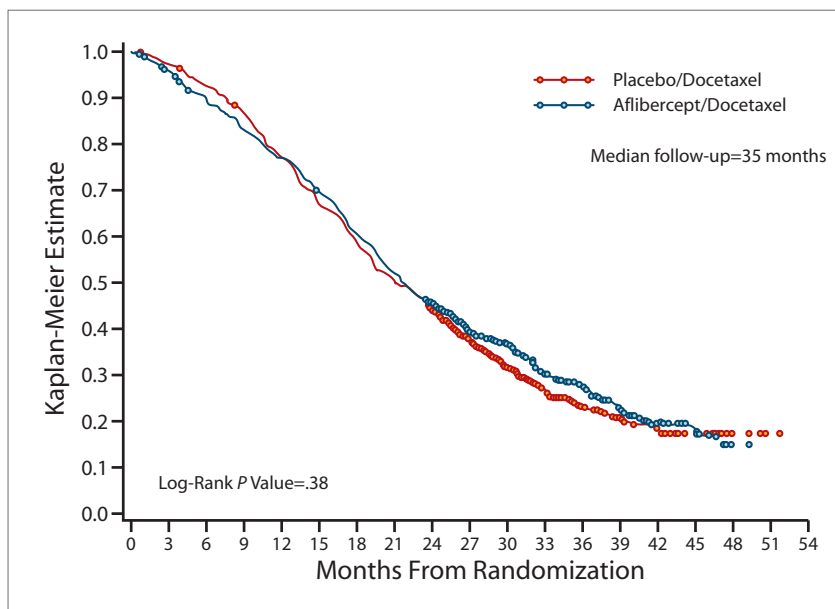
Figure 5. In the phase III VENICE trial, the addition of aflibercept to a regimen of docetaxel and prednisone did not improve overall survival.

VENICE=VEGF Trap Administered With Docetaxel in Metastatic Androgen-Independent Prostate Cancer. Adapted from Tannock I et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL. Abstract 13.

Median OS was 22.1 months in the aflibercept arm and 21.2 months in the placebo arm, which was slightly longer than was projected based on data from TAX 327. The time-to-event endpoints of PFS and time to skeletal-related events were essentially identical between the 2 arms of the study (P=.31 for both).

The rate of PSA response was slightly higher in the aflibercept arm (68.6% vs 63.5% with placebo), and tumor response was also slightly greater in the aflibercept arm. By design, these measures were not formally tested for significance because the primary endpoint lacked significance. Clearly, any significance would have been borderline. Quality of life data will be presented at the 2013 American Society of Clinical Oncology (ASCO) meeting.

There were more AEs in the aflibercept arm than the placebo arm, and discontinuation was more common in this arm. Delays in treatment due to toxicity and dose adjustments were more common in the aflibercept arm. The aflibercept arm had more GI toxicity, hemorrhagic toxicity, vascular events, fatigue, and infection. A higher rate of fatal AEs

occurred in the aflibercept arm. The placebo control arm had a toxic death rate of 3.3% with docetaxel and placebo, which is higher than other trials that have been reported using the same control arm.

In conclusion, aflibercept did not improve survival of men with mCRPC when used with docetaxel and prednisone. Although aflibercept showed some signs of biological activity, they were minimal. Aflibercept increased toxicity, which led to shortened treatment durations. The outcome of this trial stresses the need for evidence of substantial increased activity in earlier trials before the design of large and expensive phase III trials. VENICE is another negative trial in which a targeted agent was added to docetaxel and prednisone. As yet, no added agent has increased the therapeutic benefits of docetaxel and prednisone for men with mCRPC.

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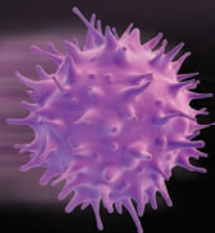
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Overall Survival and Safety of Dasatinib/Docetaxel Versus Docetaxel in Patients With Metastatic Castration-Resistant Prostate Cancer: Results From the Randomized Phase III READY Trial

The phase III READY (Randomized Study Comparing Docetaxel Plus Placebo in Castration-Resistant Prostate Cancer) trial studied OS in the addition of dasatinib to docetaxel in patients with mCRPC.[1] Bone metastasis dominates the clinical phenotype of the disease.[2] Current treatment options are palliative and provide only modest survival improvement. New treatments are needed.

The Src family kinases are central to prostate cancer progression in bone. The Src family kinases mediate crosstalk between prostate cancer cells and osteoclasts.[3] Dasatinib inhibits tyrosine kinases, including Src family kinases.[4] Also, dasatinib has anti-tumor activity, inhibits osteoclast function, and has synergistic activity with docetaxel.[5,6] Initial clinical experience in a small, multicenter phase I/II trial that added dasatinib to docetaxel revealed that the combination was well tolerated.[7] The combination was associated with anti-tumor activity, decline in PSA, and promising partial tumor responses. The combination also had an effect on bone and urinary N-telopeptides and on bone outgoing phosphatase. Those bone turnover markers were reduced even in the presence of bisphosphonates.

This trial was designed to randomize 1,522 patients with mCRPC with progressive disease. Patients were stratified based on known prognostic factors that included PS, baseline bisphosphonate use, and urinary N-telopeptide, which is a novel bone turnover marker. Patients

were stratified based on urinary N-telopeptide levels less than 60 nmol/mmol creatinine or 60 nmol/mmol creatinine and higher. They were randomized 1:1 to receive docetaxel and prednisone with either double-blind dasatinib or placebo.

The primary objective was OS. The study aimed to determine superiority of

dasatinib over placebo with a 2-sided alpha of 0.05. Critical secondary endpoints included overall response rate, time to first skeletal-related event, reduction of urinary N-telopeptides, and PFS. Safety and tolerability were also studied.

Randomization was successful, and the 2 arms had virtually identical

Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (*MCLnet*)

In a randomized international study of 455 patients (aged <65 years) with untreated MCL, an alternating course of 3 × CHOP and 3 × dexamethasone, cytarabine, and cisplatin (DHAP) plus rituximab followed by high-dose cytarabine (10 Gray total body irradiation, 4×1.5 g/m^{2} cytarabine, 140 mg/m^{2} melphalan) and SCT (experimental arm) significantly improved response rates, time to treatment failure, and overall survival compared to the control arm (6 courses of R-CHOP followed by myeloablative radiochemotherapy and ASCT; Abstract 151). The overall response was 95% in the experimental arm and 90% in the control arm (*P*=.19). The experimental arm had a significantly higher complete response rate (36% vs 25%, respectively; *P*=.012). The number of transplants was similar in both arms (80% vs 83%), with similar overall response rates (98% vs 97%) and complete remission rates (61% vs 62%) following transplantation. Patients in the experimental arm had a longer time to treatment failure (88 months) than patients in the control arm (46 months; *P*=.0382; HR, 0.68). This was primarily due to a lower number of relapses after response (experimental arm, n=44 vs control arm, n=88). Following ASCT, the complete remission rate was not significantly different between the 2 treatment arms, but remission duration was longer in the experimental arm (84 months vs 49 months, respectively; *P*=.0001). In addition, overall survival was significantly longer in the experimental arm (not reached vs 82 months; *P*=.045). Increased rates of grade 3/4 hematologic toxicity, renal toxicity, and grade 1/2 nausea and vomiting occurred in the experimental arm.

distributions of ECOG status, urinary N-telopeptide values, and bisphosphonate use. The age distribution was similar between the 2 groups. Additionally, the 2 groups showed no meaningful differences in the distribution of disease characteristics, including measurable disease, type of progression, and type of metastasis.

Dasatinib did not improve OS compared to docetaxel alone (Figure 6). The Kaplan-Meier curves were virtually identical. Median OS was 21.2 months in the docetaxel arm and 21.5 months in the dasatinib arm (HR=0.99; log-rank P=.90). Subgroup analysis indicated no advantage of dasatinib over the entire population for any of the subgroups analyzed.

No meaningful changes occurred between the 2 arms regarding response rate, urinary N-telopeptides, PFS, or pain reduction. However, time to first skeletal-related events was 31.1 months in the placebo arm, whereas it has not yet been reached in the dasatinib arm. Since dasatinib targets bone and osteoclasts, this result was further investigated. There was a modest decrease in time to first skeletal-related event in the dasatinib arm, which is now being investigated.

Patients came off trial for similar reasons in both groups. The groups had similar rates of disease progression and maximum clinical benefit. However, the AEs related to treatment were 9% in the placebo arm and 18% in the dasatinib arm. Treatment exposure of patients to placebo or dasatinib was similar in the amount and number of cycles. Patients received a median of 8–9 cycles of docetaxel.

Salvage treatments have evolved over the 3 years of this trial. Therefore, Araujo and colleagues wanted to see if the type of salvage treatment used would change the primary endpoint. The researchers analyzed use of salvage treatments, in particular abiraterone and cabazitaxel. Both of these agents were approved during the course of this trial, and their use was nearly evenly distributed between the 2 treatment groups.
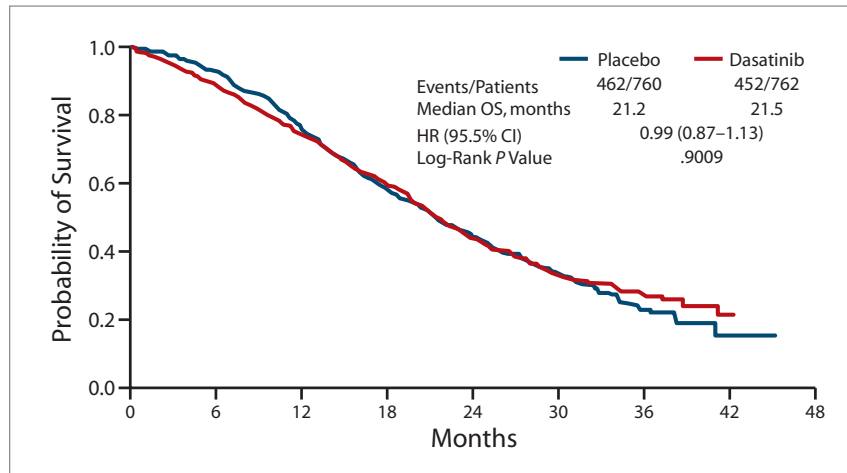
Figure 6. In the phase III READY trial, the addition of dasatinib to docetaxel did not improve overall survival.

READY=Randomized Study Comparing Docetaxel Plus Placebo in Castration-Resistant Prostate Cancer. Adapted from Araujo J et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL. Abstract LBA8.

Among patients in the placebo group, 6% died within 30 days of the last dose. In the dasatinib group, 10% died within 30 days of the last dose. Approximately 30% of patients overall experienced serious AEs. Dasatinib has a well-known safety profile. Special AEs of interest that could be altered by dasatinib were examined, and no new safety signals were identified for pleural effusion, hypocalcemia, hypomagnesemia, anemia, neutropenia, thrombocytopenia, or gastrointestinal bleeding. No unanticipated events were noted.

In conclusion, dasatinib added to docetaxel did not improve OS in this study population. Although no differences in secondary endpoints were observed, a modest delay in skeletal-related events was seen in the dasatinib arm. Excess toxicity, docetaxel dose intensity, baseline factors, or differences in salvage therapies do not account for these results. No unexpected safety findings occurred.

Importantly, understanding how to optimally combine promising targeted agents in chemotherapy will be required to make further advances. In the last 18 months to 2 years, multiple trials have indicated that persistent androgen receptor signaling is very important to this disease. Androgen signaling might

be acting as a resistance mechanism and may account for the poor performance of targeted therapies in mCRPC. Studies of this theory are ongoing. The dual compartment with osteoclast in bone will have to be further investigated since dasatinib had a potential effect on skeletal-related events.

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Immune Response With Sipuleucel-T in Patients With Metastatic Castration-Resistant Prostate Cancer: Phase II ProACT Study

The phase II ProACT (Prostate Advanced Cancer Treatment) trial is an ongoing, randomized, single-blind study designed to evaluate immune response and OS in patients with mCRPC treated with sipuleucel-T manufactured using 3 different concentrations of PA2024: 2 μg/mL, 5 μg/mL, and 10 μg/mL. Previous sipuleucel-T clinical trials used 10 μg/mL, which is the FDA-approved concentration.

Sipuleucel-T, an autologous cellular immunotherapy, is FDA-approved to treat asymptomatic or minimally symptomatic mCRPC. It is prepared by culturing isolated peripheral blood mononuclear cells (PBMCs) with 10 μg/mL PA2024. PA2024 is a recombinant protein with PAP that is fused to granulocyte-macrophage colony-stimulating factor (GM-CSF). When sipuleucel-T is produced with 10 μg/mL PA2024, immune response is stimulated and OS is prolonged.[1,2] The phase III IMPACT study revealed that sipuleucel-T reduced the risk of death by 22.5% (HR=0.78; P=.032) and increased median OS by 4.1 months compared to the control.[1]

This study examined the immune response in patients with mCRPC who were treated with sipuleucel-T that was manufactured using the FDA-approved concentration of 10 μg/mL PA2024.[3] The enrolled patients had asymptomatic or minimally symptomatic mCRPC. Patients were excluded if they had been treated with more than 2 prior chemotherapy regimens, chemotherapy within 3 months, external beam radiation or surgery within 28 days, or systemic steroid therapy within 28 days. They were also excluded if they had previously participated in a study involving sipuleucel-T, had prior treatment with any investigational vaccine for prostate cancer within 2 years, or required systemic immunosuppressive therapy.

The eligible patients were randomized to receive sipuleucel-T that was manufactured with 2 μg/mL (n=40), 5 μg/mL (n=40), or 10 μg/mL (n=40) PA2024. This analysis focused on those patients who received 3 infusions of sipuleucel-T at intervals of approximately 2 weeks, which were prepared by culturing PBMCs with 10 μg/mL PA2024. The patients were followed for the first 6 months for immune monitoring and safety, and thereafter at 6-month intervals for survival and long-term safety.

Detailed patient demographic information was provided for the cohort receiving the 10-μg/mL dose of sipuleucel-T. Among these patients, the median age was 71 years. ECOG PS was 0 in 28 patients (70%) and 1 or higher in 12 patients (30%). Gleason scores were 7 or below for 18 patients (45%), 8 or above for 21 patients (53%), and missing for 1 patient. The median time from diagnosis to randomization was 8.4 years, and 11 of the patients (28%) had received prior chemotherapy. All 40 of the patients received 1 or more study infusions. The median baseline PSA level was 20 ng/mL (range, 6–1,299 ng/mL).

Real-World Experience With Sipuleucel-T in Patients ≥80 Years Old With Metastatic Castration-Resistant Prostate Cancer: Data From PROCEED

Among patients ages 80 years and older, immune activation was similar to that seen in younger patients in these preliminary results from the ongoing, multicenter, phase IV registry trial PROCEED (A Registry of Sipuleucel-T in Men With Advanced Prostate Cancer), which includes patients receiving sipuleucel-T (Abstract 131). PROCEED has no age limit for enrollment. Its primary objective is to further quantify the risk of cerebrovascular events, which were reported with a low frequency following sipuleucel-T treatment in a pooled analysis (3.5% of patients treated with sipuleucel-T vs 2.6% of patients who received placebo). The secondary objective of PROCEED is to evaluate OS in patients treated with sipuleucel-T. The registry is collecting product manufacturing parameters, including cell counts and APC activation, and also demographic data. As of data cutoff, PROCEED had enrolled 560 patients, including 110 who were ages 80 or older (19.6%). The patients younger than 80 were a median age of 70.0, and those ages 80 and older were a median age of 83.0 (range, 80.0–93.0). The older cohort had lower rates of patients with an ECOG PS of 0 (59.1% for those ≥80 years vs 72.9% for those <80 years), a Gleason score of 8 or higher (47.3% vs 59.1%), and 10 or more bone metastases (14.5% vs 20.1%). Median PSA was higher in the older patients (34.4 ng/mL for those ≥80 years vs 16.0 ng/mL for those <80 years). Previous treatment with radical prostatectomy or radiation was less common in the older patients (mean 21.8%) than the younger patients (mean 28.4%). Counts of APC and TNC were relatively consistent across time in both groups. Both groups had a similar trend in APC activation that was consistent with immunologic prime-boosting. APC activation was measured by CD54 upregulation.

Table 2. Fold Increase in Antibody Titers Versus Baseline (IgG + IgM)

Time Point	n	Anti-PA2024	Anti-PAP	Anti–GM-CSF
Month 0 (baseline)	40	N/A	N/A	N/A
Month 2	34	128*	32	16
Month 4	26	64*	16	8
Month 6	19	32*	4	8

*P<.001 vs anti–GM-CSF.

GM-CSF=granulocyte-macrophage colony-stimulating factor; IgG=immunoglobulin G; IgM=immunoglobulin M; N/A=not applicable.

Adapted from Gardner T et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL: Abstract 148.
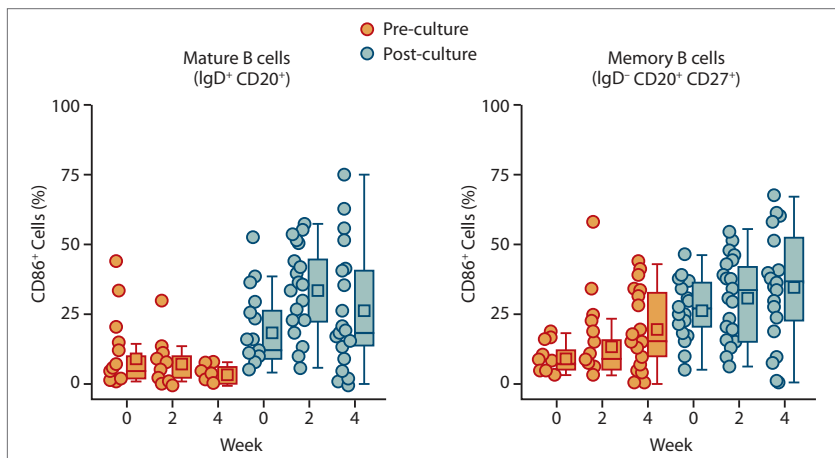
Figure 7. Activation of mature and memory B cells during the manufacture of sipuleucel-T, as assessed in the phase II ProACT trial.

ProACT=Prostate Advanced Cancer Treatment. Adapted from Gardner T et al. Paper presented at: ASCO Genitourinary Cancers Symposium; February 14-16, 2013; Orlando, FL. Abstract 148.

During the manufacture of sipuleucel-T, both mature and memory B cells were activated (Figure 7). Flow cytometry measured B-cell activation during sipuleucel-T manufacture, and found that only after culture of each successive treatment did the percentage of B cells with a mature phenotype (IgD+, CD20+, CD27+) increase. Also, activated memory B cells (IgD-, CD20+, CD27+) increased after culture of each successive treatment, and in the preculture cells, they increased at the third treatment. In vivo memory B cells were markedly increased at the third treatment.

Peripheral immune response patterns were analyzed by ELISA using titers of IgG only, IgM only, and combined IgG and IgM against tetanus, PA2024, PAP, and GM-CSF. At month 2, median anti-PA2024 titers were 128-fold higher than at baseline, and anti-PAP titers were 32-fold higher than at baseline (Table 2). The anti-PA2024 response was mostly IgM, but an increase in anti-PA2024 IgG was also observed, which indicated seroconversion to a memory B-cell response. Serum anti-PA2024 and anti-PAP titers (IgG and IgM) were increased markedly at months 2, 4, and 6 relative to baseline.

The anti-tetanus antibody titers were almost entirely IgG and did not change between sampling timepoints, which indicated that the patients were immunocompetent and that non-specific bystander activation did not occur. At all timepoints, the increases in post-treatment anti-PA2024 titers of IgG and IgM combined were significantly higher than those for GM-CSF (P<.001). Although anti–GM-CSF antibodies developed, the absolute neutrophil count (ANC) remained within normal limits for all patients, and no episodes of neutropenia were noted. The titers of anti-PA2024 (IgG and IgM) correlated with anti-PAP (IgG and IgM) titers (r=0.840). Antigen-specific humoral responses were mounted by an overall majority of the patients. The frequencies of antibody response (IgG and IgM titers combined >12,800) were 79% against PA2024 and 47% against PAP at any time post-treatment. The antibody response against PA2024 was greater than that against PAP.

In conclusion, the data indicated that sipuleucel-T induced activated memory B cells. This finding was evident after each culture in vivo after the first 2 treatments. Robust, long-lasting anti-PA2024 and anti-PAP responses were generated by sipuleucel-T, and these responses evolved into an IgG phenotype. Future analyses will compare data for the 3 dosing cohorts, including T-cell immune response data.

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Commentary

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Presentations at the 2013 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium offered new data and analysis in the management of men with advanced prostate cancer. Clinical trials examined treatments such as androgen deprivation, abiraterone acetate, ARN-509, docetaxel in combination with other agents, and sipuleucel-T.

Dr. Abdenour Nabid presented an interesting and provocative study comparing 2 durations of androgen deprivation therapy (ADT)—36 months and 18 months—in men with node-negative, high-risk prostate cancer.[1] High risk was defined as clinical stage T3/T4, prostate-specific antigen (PSA) higher than 20, or Gleason score higher than 7. This study addresses the question of whether these patients require a full 3 years of androgen blockade. Prior studies had demonstrated that 36 months of hormonal therapy was superior to 6 months.[2]

All patients received whole pelvic radiation therapy with 70 Gy to the prostate. Patients were randomized to 36 months of ADT (n=310) or 18 months of ADT (n=320), and characteristics were reasonably balanced. The study did not follow a noninferiority design, and the number of patients was relatively small. At the median follow-up of 77 months, there was no significant difference in overall survival. The authors concluded that the study demonstrated that it is possible to safely reduce androgen deprivation in this setting from 36 months to 18 months without compromising outcomes. This conclusion is reasonable, although not absolute. As Dr. Anthony D'Amico mentioned in the abstract discussion session, a noninferiority design would have been preferable.[3] However, this study is potentially practice-changing. Based on the degree of follow-up and the similar outcomes of the 2 treatment arms, I am willing to change my practice to use only 18 months of ADT for a considerable number of patients in this setting. I may continue to use a longer form of androgen deprivation for patients who are at the very highest risk.

Dr. Dana Rathkopf presented an updated interim analysis of the COU-AA-302 trial, which examined abiraterone acetate plus prednisone versus placebo plus prednisone in patients with either mildly symptomatic or asymptomatic metastatic castration-resistant prostate cancer (CRPC) and, importantly, who had not received prior chemotherapy.[4] Results of this pivotal trial were initially presented at ASCO in 2012[5] and subsequently published in the *New England Journal of Medicine*.[6] In December 2012, the US Food and Drug Administration (FDA) approved abiraterone acetate in combination with prednisone for the treatment of patients with metastatic CRPC.[7] Dr. Rathkopf presented a new analysis of data from the prechemotherapy population. The median overall survival rates are now available for both arms; they were 35.3 months in the abiraterone acetate arm and 30.1 months in the prednisone arm (hazard ratio [HR], 0.79; 95% confidence interval (CI), 0.66–0.96; *P*=.0151). Although survival was clearly prolonged in the abiraterone acetate arm, this difference did not meet the prespecified study endpoint. The alpha value for significance of OS at 56% of events was 0.0035. This updated analysis shows a slight decrease in the HR for overall survival—from 0.75 in the prior analysis to the updated level of 0.79—as predicted by Dr. Susan Halabi in her discussion at the 2012 ASCO Meeting.[8] This trend in overall survival, with a HR of 0.79, can be cautiously categorized as clinically significant. The radiographic progression-free survival was approximately doubled in the abiraterone acetate arm, with a HR of 0.53. Time to PSA progression was 11.1 months in the abiraterone acetate arm and 5.6 months in the placebo arm (HR, 0.5). Time to deterioration of Eastern Cooperative Oncology Group performance status slightly improved with abiraterone acetate, although the difference was not significant (12.3 months in the abiraterone acetate arm vs 10.9 months in the placebo arm). In addition, there is evidence that time to opioid use and time to chemotherapy use were improved in the abiraterone arm. Overall, these findings are sufficient to confirm clinical benefit. I believe that the FDA was correct to approve the abiraterone/prednisone combination in this setting, as this regimen provides clinical benefit. Most clinicians I know are now using abiraterone in the prechemotherapy setting in patients with metastatic CRPC.

A subset analysis was also presented for the COU-AA-301 trial,[9] which examined the activity of abiraterone acetate and prednisone versus placebo and prednisone in patients who had previously received docetaxel.[10] This subset analysis focused on patients with visceral disease, defined as the presence of liver or lung metastases in addition to whatever other metastases might be present. Previous studies have demonstrated that patients with visceral disease do worse than those patients without visceral disease.[11] In the COU-AA-301 trial, patients with visceral disease did worse, as anticipated.

In the exploratory analysis of COU-AA-301, it was interesting to see that the patients treated with abiraterone seemed to have a strong—although nonsignificant—trend in overall survival benefit as compared to patients treated with prednisone alone. These patients also experienced a radiographic progression-free survival benefit and improvement in the PSA response rate and objective response

rate. Among patients with visceral disease, the median overall survival of the prednisone arm was 8.3 months versus 12.9 months in the abiraterone arm (HR, 0.79; 95% CI, 0.6–1.05; *P*=.102). (These survival data are based on an underpowered subset analysis.) This study was an exploratory analysis, and the strong trend shown in the subset suggests that there is most likely a clinical benefit to the use of abiraterone in patients with visceral disease. This message is potentially important as some may have thought that hormonal therapy is not particularly active in men with visceral disease.

Dr. Matthew Smith presented results for a study of ARN-509, a novel antiandrogen developed by Dr. Charles Sawyers and colleagues.[12,13] ARN-509 is conceptually similar to enzalutamide, but it may have less permeability across the blood-brain barrier. The hope is that it does not alter the seizure threshold. Whether or not such an agent exists will need to be proven in a clinical trial and not assumed based on preclinical data.

ARN-509 had clear evidence of activity at a dose of 240 mg in nonmetastatic CRPC.[12] The 12-week PSA response was 91%. Time to PSA progression was not reached, but the follow-up was short. Until there is longer follow-up, the duration will not be known. Adverse events included fatigue in 30% of patients and diarrhea in 28%. The authors noted that no seizures were observed. This trial suggests that ARN-509 appears to be active. Further studies are required to determine its clinical utility and the possibility of seizures.

Dr. John Araujo presented results from the randomized, phase III READY (Randomized Study Comparing Docetaxel Plus Dasatinib to Docetaxel Plus Placebo in Castration-Resistant Prostate Cancer) study.[14] In this trial, dasatinib plus docetaxel was compared to placebo plus docetaxel. There had been considerable preclinical evidence to suggest that inhibition of Src family kinases might be important

for patients with metastatic CRPC.[15] Dasatinib inhibits various tyrosine kinases, including Src kinase, and thus there was a strong preclinical rationale to this trial.[16] However, as with all trials to date that have tried to improve upon docetaxel by adding another agent, it was not a positive trial. The rates of median progression-free survival and overall survival—the primary endpoint in the study—did not significantly differ according to the treatment regimen. Although the preclinical rationale was reasonable, this trial was not positive, and it illustrates the importance of randomized clinical studies.

The VENICE (VEGF Trap Administered With Docetaxel in Metastatic Androgen-Independent Prostate Cancer) trial was another one that examined the use of docetaxel in combination with another agent.[17] Aflibercept is a recombinant human protein that combines VEGF-A, VEGF-B, and placental growth factor. Aflibercept has been shown to prolong survival in other settings, such as metastatic colon cancer.[18] In this study of prostate cancer patients with metastatic, progressive disease that persisted after hormonal or surgical castration, however, aflibercept did not prolong survival. The median overall survival was essentially the same in the docetaxel plus aflibercept arm and the single-agent docetaxel arm. This study is another one that underlines the importance of docetaxel and reiterates that no combination has shown improvement over the single agent. Docetaxel remains the standard frontline chemotherapy for these patients.

A large number of trials have failed to show an improvement when docetaxel is combined with another agent, which indicates that docetaxel is an active chemotherapy. There are 2 trials under way that might provide interesting data: one on docetaxel versus cabazitaxel in frontline chemotherapy,[19] and one examining the combination of docetaxel and

custersin as compared to docetaxel.[20] Whether either of these trials will be positive is unclear, but the randomized clinical trial data are eagerly awaited.

Dr. Eric Small presented a retrospective analysis of the IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial, which examined sipuleucel-T in metastatic but asymptomatic or minimally asymptomatic men.[21] Patients were randomized to sipuleucel-T or placebo; patients who progressed on placebo were able to received sipuleucel-T later as a frozen product.[22] The IMPACT trial has been much discussed, as it demonstrated improvement in overall survival but no differences in progression-free survival or various PSA endpoints. The interpretation of this finding is that there has been no prior intermediate endpoint between sipuleucel-T administration and death that might be indicative of patient benefit. This retrospective analysis of a subset of patients in the IMPACT trial examined the novel endpoint of time to first use of opioid analgesics, and showed improvement in the sipuleucel-T arm. This finding is potentially important because it might indicate that something beyond radiographic progression, but before the endpoint of overall survival, was significant in patients receiving sipuleucel-T. The authors note that the very high censoring rate might have led to some unstable estimates, and so this data analysis must be considered nondefinitive. These data are interesting, however, and indicate a possibility of a clinically relevant endpoint prior to survival in patients treated with sipuleucel-T.

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The safety evaluation of PROVENGE is based on 601 prostate cancer patients in the PROVENGE group who underwent at least 1 leukapheresis procedure in four randomized, controlled clinical trials. The control was non-activated autologous peripheral blood mononuclear cells.

The most common adverse events, reported in patients in the PROVENGE group at a rate ≥15%, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the PROVENGE group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the PROVENGE group compared with 3.6% of patients in the control group.

Serious adverse events were reported in 24.0% of patients in the PROVENGE group and 25.1% of patients in the control group. Serious adverse events in the PROVENGE group included acute infusion reactions *(see Warnings and Precautions)*, cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

PROVENGE was discontinued in 1.5% of patients in Study 1 (PROVENGE group n=341; Control group n=171) due to adverse events. Some patients who required central venous catheters for treatment with PROVENGE developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of PROVENGE requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤1 day following a leukapheresis procedure in ≥5% of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in ≥5% of patients in the PROVENGE group of randomized, controlled trials of men with prostate cancer. The population included 485 patients with metastatic castrate resistant prostate cancer and 116 patients with non-metastatic androgen dependent prostate cancer who were scheduled to receive 3 infusions of PROVENGE at approximately 2-week intervals. The population was age 40 to 91 years (median 70 years), and 90.6% of patients were Caucasian.

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	**591 (98.3)**	**186 (30.9)**	**291 (96.0)**	**97 (32.0)**
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Fever	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Joint ache	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Muscle ache	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza-like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

*Control was non-activated autologous peripheral blood mononuclear cells.

Cerebrovascular Events. In controlled clinical trials, cerebrovascular events, including hemorrhagic and ischemic strokes, were reported in 3.5% of patients in the PROVENGE group compared with 2.6% of patients in the control group.

(See Adverse Reactions [6] of full Prescribing Information.)

To report SUSPECTED ADVERSE REACTIONS, contact Dendreon Corporation at 1-877-336-3736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**Dendreon Corporation
Seattle, Washington 98101**

REFERENCES: 1. PROVENGE [package insert]. Dendreon Corporation; June 2011. **2.** Kantoff PW, Higano CS, Shore ND, et al; for the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.

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