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A SPECIAL MEETING REVIEW EDITION

Highlights in Advanced Prostate Cancer From the 2013 American Urological Association Annual Meeting and the 2013 American Society of Clinical Oncology Annual Meeting

Special Reporting on:

- A Randomized Phase 2 Trial of Sipuleucel-T With Concurrent or Sequential Abiraterone Acetate Plus Prednisone in Metastatic Castrate-Resistant Prostate Cancer (mCRPC)
- Clinical Outcomes in Patients With Castrate-Refractory Prostate Cancer (CRPC) Metastatic to Bone Randomized in the Factorial TRAPEZE Trial to Docetaxel (D) With Strontium-89 (Sr89), Zoledronic Acid (ZA), Neither, or Both (ISRCTN 12808747)
- Randomized Phase 2 Trial Evaluating the Optimal Sequencing of Sipuleucel-T and Androgen Deprivation Therapy (ADT) in Patients (PTS) With Biochemically Recurrent Prostate Cancer (BRPC): Immune Results
- Double-Blind Randomized Trial of Aflibercept Versus Placebo With Docetaxel and Prednisone for Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC)
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PLUS Meeting Abstract Summaries

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A Randomized Phase 2 Trial of Sipuleucel-T With Concurrent or Sequential Abiraterone Acetate Plus Prednisone in Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

The randomized, open-label phase II P11-3 (A Randomized, Open-label, Phase 2 Trial of Sipuleucel-T With Concurrent Versus Sequential Administration of Abiraterone Acetate Plus Prednisone in Men With Metastatic Castrate Resistant Prostate Cancer [mCRPC]) trial is the first study to assess the combination of sipuleucel-T and abiraterone acetate plus prednisone in metastatic castrate-resistant prostate cancer patients (mCRPC).[1] The autologous cellular immunotherapy sipuleucel-T is approved by the US Food and Drug Administration for the treatment of men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Abiraterone acetate, which suppresses both circulating and intratumoral androgen levels, is approved for co-administration with prednisone. Androgen suppression may be immunostimulatory—suggesting synergy between abiraterone acetate and sipuleucel-T—but it is unclear whether the immunosuppressive effects of abiraterone acetate plus prednisone could interfere with sipuleucel-T function. An interim analysis of this ongoing study was conducted to assess sipuleucel-T product characteristics, immune response, and safety.[2]

Sipuleucel-T was administered as 3 infusions, approximately 2 weeks apart. Abiraterone acetate (1,000 mg once daily) and prednisone (5 mg twice daily) were administered to patients who were randomized 1:1 to receive sipuleucel-T either concurrently (1 day after sipuleucel-T infusion) or sequentially (starting 10 weeks after the first sipuleucel-T infusion). Abiraterone acetate plus prednisone was given for 26 weeks or until disease progression, unacceptable toxicity, or both.

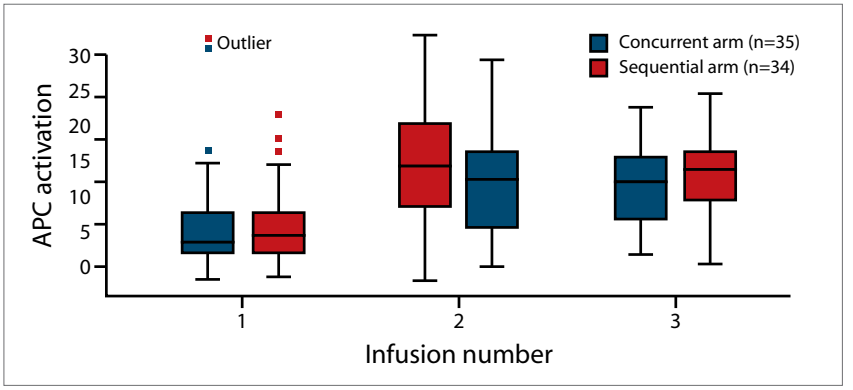

Figure 1. In an interim analysis of the phase II P11-3 trial, sipuleucel-T product parameters were similar between both arms of the study. APC=antigen-presenting cell; P11-3=A Randomized, Open-label, Phase 2 Trial of Sipuleucel-T With Concurrent Versus Sequential Administration of Abiraterone Acetate Plus Prednisone in Men With Metastatic Castrate Resistant Prostate Cancer (mCRPC). Adapted from Small EJ et al. A randomized phase II trial of sipuleucel-T with concurrent or sequential abiraterone acetate (AA) plus prednisone (P) in metastatic castrate-resistant prostate cancer (mCRPC) [ASCO abstract 5047]. *J Clin Oncol*. 2013;31(15S):319S.

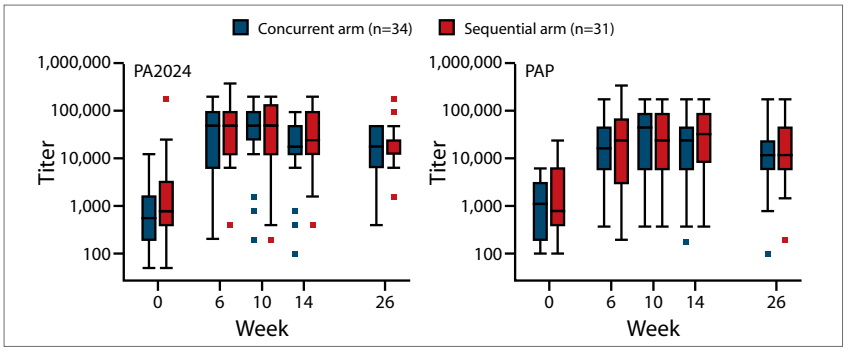

Figure 2. Antibody titers for anti-PAP and anti-PA2024 increased significantly at all time points after baseline (P<.001), but were not significantly different between the 2 treatment arms. Adapted from Small EJ et al. A randomized phase II trial of sipuleucel-T with concurrent or sequential abiraterone acetate (AA) plus prednisone (P) in metastatic castrate-resistant prostate cancer (mCRPC) [ASCO abstract 5047]. *J Clin Oncol*. 2013;31(15S):319S.

Cumulative antigen-presenting cell (APC) activation, defined as the increase in cell surface expression of CD54 from preculture to postculture, was the primary endpoint for this analysis. The secondary and tertiary endpoints included APC counts (large cells expressing CD54), cumulative total nucleated cell (TNC) counts,

immune response to prostatic acid phosphatase (PAP) and PA2024 (a recombinant protein consisting of PAP fused to granulocyte-macrophage colony-stimulating factor), and safety. Immune response was assessed by enzyme-linked immunosorbent assay (ELISA) for antibody response, ^{3}H-thymidine incorporation for T-cell proliferation, and IFNγ enzyme-linked immunosorbent spot (ELISPOT) assay for memory T-cell counts. These assays were conducted at baseline, before and after leukapheresis, and at 6, 10, 14, and 26 weeks.

The interim analysis included 69 randomized patients (35 in the concurrent arm and 34 in the sequential arm). Baseline characteristics were similar in the 2 treatment arms. Sixteen patients in the concurrent arm and 9 in the sequential arm completed 26 weeks of abiraterone acetate plus prednisone. For various reasons, 16 patients discontinued treatment. Reasons for leaving the study included adverse events (AEs) in 1 concurrent and 3 sequential patients, disease progression in 5 concurrent and 6 sequential patients, and investigator/sponsor decision in 1 concurrent patient. Three infusions of sipuleucel-T were administered to 66 of the 69 patients.

Sipuleucel-T product parameters were similar between both arms of the study (Figure 1). The median TNC count ($\times 10^9$) was 9.17 in the concurrent arm and 10.80 in the sequential arm (P=.30). The APC count ($\times 10^9$) was 1.94 and 1.53 (P=.22), respectively, and the APC activation was 37.48 and 41.11 (P=.22). APC activation also showed similar increases with the second and third sipuleucel-T infusions. Antibody titers for anti-PAP and anti-PA2024 increased significantly at all time points after baseline (P<.001) but were not significantly different between the 2 treatment arms (Figure 2). Cellular immune responses were also comparable between the sequential and concurrent treatment arms. In addition, both treatment regimens had similar safety profiles, with comparable overall AEs occurring in at least 15% of patients in both arms and similar incidences of AEs that occurred by 1 day following sipuleucel-T infusion.

Results of this interim analysis revealed that neither concurrent nor sequential administration of abiraterone acetate plus prednisone with sipuleucel-T affected product potency (APC activation, APC counts, or TNC counts). Immune responses were similar in both treatment arms and were indicative of a prime-boost response. In addition, the most frequent AEs were mild to moderate in severity and similar in both treatment arms.

References

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Clinical Outcomes in Patients With Castrate-Refractory Prostate Cancer (CRPC) Metastatic to Bone Randomized in the Factorial TRAPEZE Trial to Docetaxel (D) With Strontium-89 (Sr89), Zoledronic Acid (ZA), Neither, or Both (ISRCTN 12808747)

Bone metastases are a major cause of morbidity in CRPC. Taxane-based chemotherapy, such as docetaxel, improves overall survival (OS) and quality of life. Zoledronic acid reduces skeletal-related events (SREs). Strontium-89 was approved to control pain from metastases and to reduce the need for subsequent bone treatments. Zoledronic acid is often combined with docetaxel in practice, but there is limited evidence to suggest that this combination is effective and worth the substantial cost. Strontium-89 is generally used as a palliative therapy in patients unfit for chemotherapy. One trial combining strontium-89 with pretaxane chemotherapy showed a survival advantage.[1] Clinical data from the randomized factorial phase II TRAPEZE (A Randomised Phase III Trial of Docetaxel Plus Prednisolone vs Docetaxel With Prednisolone Plus Either Zoledronic Acid, Strontium-89, or Both Agents Combined) trial were presented.[2] This study was designed to assess the toxicity, tolerability, and effectiveness of docetaxel plus prednisolone, with or without zoledronic acid and/or strontium-89, in treating patients with prostate cancer metastatic to bone who have not responded to hormone therapy. Primary outcomes were clinical progression-free survival (PFS; pain progression, SREs, or death) and cost-effectiveness. Secondary outcomes were SRE-free interval, total SREs, and OS.

The study had 4 treatment arms. The control arm (arm A) was standard intravenous (IV) docetaxel at 75 mg/m^2 every 3 weeks combined with 10 mg prednisolone for up to 10 cycles. Arm B

ABSTRACT SUMMARY Safety and Changes in Laboratory Parameters Associated With Sipuleucel-T in Patients With Metastatic Castration-Resistant Prostate Cancer: Phase 2 ProACT Study

ProACT is an ongoing phase II trial evaluating whether the immune responses and rates of OS associated with sipuleucel-T differ according to the concentration of PA2024 used in the manufacture of this agent. A preliminary analysis of safety and changes in laboratory parameters was conducted in patients with asymptomatic or minimally symptomatic mCRPC (AUA Abstract 971). Patients received 3 infusions of sipuleucel-T separated by 2-week intervals. Data were gathered for 120 patients, who were evenly divided among 3 PA2024 concentrations: 2 µg/mL, 5 µg/mL, or 10 µg/mL. Adverse events did not differ according to the PA2024 concentration. The most common adverse events were fatigue, back pain, nausea, arthralgia, and chills. Four patients experienced treatment-related serious adverse events; fatigue (n=3) and dehydration (n=2) were the only events occurring in more than 1 patient. Some laboratory parameters differed according to PA2024 concentration. In the 5-µg/mL and 10-µg/mL arms, there was a significant increase in globulin protein levels from baseline to all 3 assessment time points (2, 4, and 6 months after the first infusion). In the 2-µg/mL arm, a significant increase was seen only at the 2-month assessment. Eosinophil counts significantly increased from baseline at the 2-month assessment in the 5-µg/mL and 10-µg/mL arms ($P<.05$). Immune responder frequencies (any immune response at any time point) did not significantly differ according to the PA2024 concentration.

ABSTRACT SUMMARY Outcomes in Patients With Liver or Lung Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated With the Androgen Receptor Inhibitor Enzalutamide: Results From the Phase III AFFIRM Trial

The phase III AFFIRM trial was a multinational, randomized, double-blind study in postdocetaxel mCRPC patients (*N Engl J Med*. 2012;367[13]:1187-1197). This study demonstrated that enzalutamide, which inhibits multiple steps in the androgen receptor signaling pathway, increased median OS by 4.8 months versus placebo (HR, 0.63; $P<.001$) in post-docetaxel mCRPC patients. The effect of enzalutamide on the outcome of patients with liver or lung metastases in the AFFIRM trial was assessed (ASCO Abstract 5065). Patients were randomized 2:1 to enzalutamide 160 mg/day or placebo, and stratified by baseline ECOG performance status and mean pain score. OS was the primary endpoint, and radiographic rPFS was a key secondary endpoint. Responses assessed included PSA, defined as a decline of greater than or equal to 50% compared with baseline, and soft tissue objective response per RECIST 1.1. Liver mCRPC was reported in 11.5% (92 of 800) of enzalutamide patients and in 8.5% (34 of 399) of placebo patients. Lung mCRPC was reported in 15.3% (122 of 800) of enzalutamide patients and 14.8% (59 of 399) of placebo patients. In the AFFIRM trial, the median OS for patients with liver and/or lung mCRPC was 13.4 months in the enzalutamide arm and 9.5 months in the placebo arm. Among patients with lung metastatic disease, the median objective response was 29.3% in the enzalutamide arm versus 4.9% in the placebo arm. Enzalutamide was also associated with a higher objective response in patients with liver metastatic disease (14.9% vs 3.3%). Patients with lung mCRPC had higher median OS (enzalutamide, 16.5 months; placebo, 10.4 months) than patients with liver mCRPC (enzalutamide, 9.0 months; placebo, 5.7 months).

was docetaxel plus prednisolone plus 4 mg of intravenous zoledronic acid with every cycle, adjusted for renal function. arm C was docetaxel for 6 cycles, followed by a single strontium-89 dose and, after a 28-day gap, further chemotherapy up to a total of 10 cycles, according to investigator preference. Arm D combined all 3 treatments. For the zoledronic acid arms, postchemotherapy zoledronic acid was administered at 4-week intervals until protocol-defined disease progression. The statistical design utilized a 2-by-2 methodology. The primary outcome analysis employed the log-rank test for the univariate analysis and the Cox model for the multivariate analysis. Patients were stratified by Eastern Cooperative Oncology Group (ECOG) score and treatment center. The study utilized 80% power and significance at 5%. Data analysis for the strontium-89 treatment effect compared arms A plus B with arms C plus D. The statistical plan was designed for 618 evaluable patients. Strontium-89 was administered after 6 cycles of chemotherapy, and it was estimated that approximately 750 patients would be needed to account for those with early progression. For the zoledronic acid comparison, arms A plus C were compared with arms B plus D. For this comparison, only 618 patients were required for statistical analysis because zoledronic acid was administered from the beginning.

The target enrollment for the study was met, and 757 patients were randomized to the 4 treatment arms. The randomization algorithm resulted in equal distribution of patient characteristics across the treatment arms. The median age was 68.7 years, and the median prostate-specific antigen (PSA) level was 144 ng/mL (range, 51–354 ng/mL). Most patients (52%) had an ECOG score of 1, 8% had an ECOG score of 2, and 40% had an ECOG score of 0. Scores were evenly distributed across the treatment arms. Fewer than half of the patients had undergone prior radiotherapy. At study entry, patients reported significant pain and significant

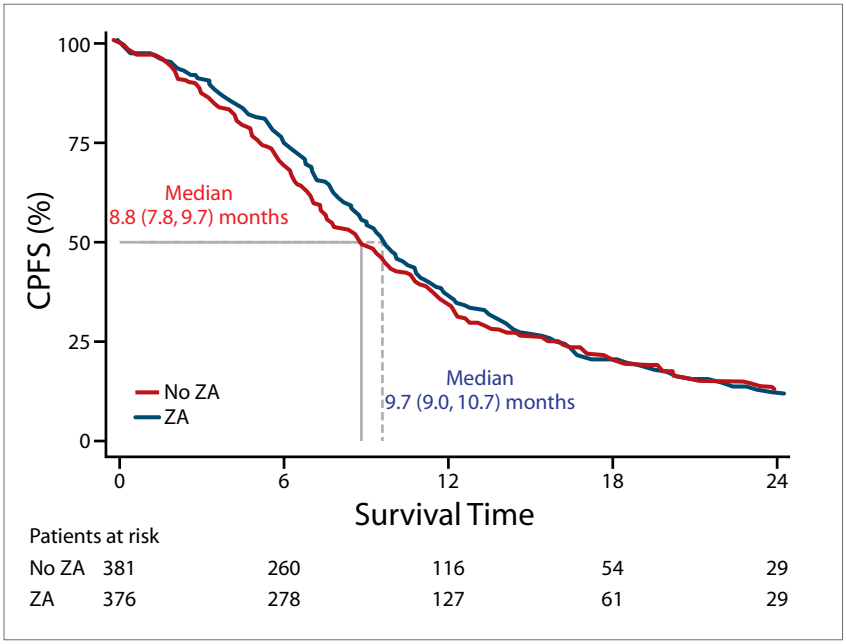

Figure 3. In the phase II TRAPEZE trial of docetaxel plus prednisolone, with or without zoledronic acid (ZA) and/or strontium-89, ZA was associated with a nonsignificant increase in the median time to clinical progression-free survival. TRAPEZE=A Randomised Phase III Trial of Docetaxel Plus Prednisolone vs Docetaxel With Prednisolone Plus Either Zoledronic Acid, Strontium-89, or Both Agents Combined. Adapted from James ND et al. Clinical outcomes in patients with castrate-refractory prostate cancer (CRPC) metastatic to bone randomized in the factorial TRAPEZE trial to docetaxel (D) with strontium-89 (Sr89), zoledronic acid (ZA), neither, or both (ISRCTN 12808747) [ASCO abstract LBA5000]. *J Clin Oncol*. 2013;31(15S):308S.

analgesic consumption, indicating the highly diseased state of the population.

The 2-by-2 trial design permits the outcomes to be presented separately. For the zoledronic acid comparison, there was a modest impact on the median time to clinical PFS, extending from 8.8 months to 9.7 months (Figure 3). Neither the univariate nor the multivariate analysis reached statistical significance. Cox regression analysis that was adjusted for all stratification variables showed that strontium-89 improved clinical PFS (hazard ratio [HR], 0.845; 95% CI, 0.72–0.99; *P*=.036) and confirmed no effect of zoledronic acid (*P*=.46). Zoledronic acid showed a significant effect on the SRE-free interval (HR, 0.76; 95% CI, 0.63–0.93; *P*=.008). For the strontium-89 comparison, there was a similar effect on the median PFS, from 8.8 months to 9.8 months. The univariate analysis again did not reach statistical significance, but the multivariate analysis had an HR of .85. Among patients who had received 6 or more cycles of chemotherapy, the HR increased to 0.8 (*P*=.02). Although this difference is statistically significant, its clinical significance is unclear. Regarding secondary outcomes, the SRE-free interval data for zoledronic acid showed that patients can continue to experience SREs postprogression. The median time to first SRE occurred postprogression and increased from 13.1 months to 18.1 months with zoledronic acid, a statistically significant difference in both univariate and multivariate analyses (HR of approximately 0.75). For strontium-89, given the effect on the primary outcome, there was less of an effect on the SRE-free interval. The median increased from 14.7 months to 16.4 months, which was not statistically significant (HRs of .91 and .87).

The types of SREs per patient were further analyzed. SREs were assessed at baseline, but there was no blinded radiologic assessment or protocol-mandated imaging. Any imaging to confirm SREs was performed to assess clinical symptoms. Among patients in the strontium-89 arm, the need for radiation to treat bone metastases was the most common SRE. In addition, a substantial number of patients developed very serious SREs, such as symptomatic pathologic fractures and spinal cord or nerve root compression resulting in neurologic deficit and cancer-related surgery to bone. Approximately half of the strontium-89–treated patients reported no SREs, and of those who reported SREs, most reported just 1. Patients treated with zoledronic acid experienced a reduction of approximately one-third in the total number of SREs, including a significant reduction of approximately 50% for more serious SREs (fracture, cord compression, and surgery to bone). The number of zoledronic acid–treated patients reporting no SREs increased, and those reporting 3 or more SREs showed a substantial reduction. Overall, zoledronic acid treatment resulted in fewer SREs per patient, an increase in the number of patients without SREs, and a reduction in serious SREs, such as fracture and cord compression. Neither zoledronic acid nor strontium-89 had an impact on the median survival of the patients (strontium-89, *P*=.74; zoledronic acid, *P*=.91). Median survival in this study was relatively short compared with the TAX 327 trial,[3] likely owing to the relatively poor prognosis of the patients at study entry rather than factors related to treatment.

In conclusion, strontium-89 after 6 cycles of docetaxel treatment significantly increased the bony clinical PFS as a primary outcome. Zoledronic acid did not improve clinical PFS or OS but significantly improved median SRE-free interval and decreased total SRE numbers, mostly via a postprogression effect. This finding suggests a role for zoledronic acid as a postchemotherapy maintenance therapy. There were no significant differences in toxicity between the different treatment arms. Further health-related, economic, and quality of life analyses are pending.

References

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Randomized Phase 2 Trial Evaluating the Optimal Sequencing of Sipuleucel-T and Androgen Deprivation Therapy (ADT) in Patients (PTS) With Biochemically Recurrent Prostate Cancer (BRPC): Immune Results

Localized prostate cancer recurs in 20–40% of patients after primary therapy, as indicated by a subsequent rise in PSA, a condition known as *biochemically recurrent prostate cancer* (BRPC). Patients with BRPC represent an ideal population for immunologic intervention because they have low disease burden and minimal immune tolerance. Androgen-deprivation therapy (ADT) is a common treatment for patients with BRPC because it has been shown to enhance antitumor immunity and augment other cancer immunotherapies. An optimized clinical regimen of sipuleucel-T and ADT may enhance the immune response and clinical effect. Interim data were presented from a phase II trial that is evaluating how to sequence the administration of sipuleucel-T and ADT in BRPC patients at high risk for metastases.[1]

The primary objective of this study is to determine whether ADT initiated before or after sipuleucel-T enhances the immune response, as measured by the enzyme linked immunosorbent assay (ELISA) of prostatic acid phosphatase (PAP) and PA2024 (recombinant PAP fused to granulocyte-macrophage colony-stimulating factor). Secondary endpoints of the study include safety, sipuleucel-T product parameters, humoral immune responses, cytokine responses, and clinical effect. The sipuleucel-T product parameters

Table 1. Adverse Events Occurring in >5% of Patients ≤1 Day After Sipuleucel-T Infusion in a Phase II Trial

Event	Arm 1 (Sipuleucel-T First) N (%)	Arm 2 (ADT First) N (%)
N	34	34
Any adverse events	17 (50.0)	15 (44.1)
Chills	8 (23.5)	4 (11.8)
Headache	7 (20.8)	3 (8.8)
Fatigue	5 (14.7)	3 (8.8)
Influenza-like illness	0 (0.0)	3 (8.8)
Pyrexia	3 (8.3)	0 (0.0)
Dizziness	2 (5.9)	0 (0.0)
Nausea	2 (5.9)	0 (0.0)
Paresthesia	2 (5.9)	0 (0.0)
Urinary retention	2 (5.9)	0 (0.0)

Data from Antonarakis ES et al. A randomized phase II study evaluating the optimal sequencing of sipuleucel-T and androgen deprivation therapy (ADT) in biochemically recurrent prostate cancer (BRPC): immune results [ASCO abstract 5016]. *J Clin Oncol.* 2013;31(15S):312S.

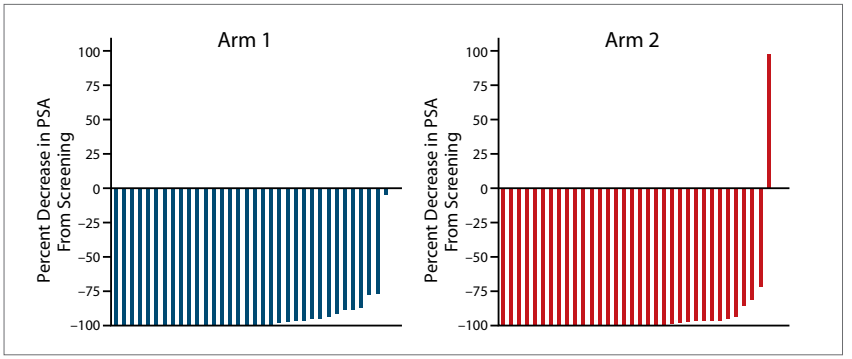

Figure 4. In a phase II trial evaluating the optimal sequencing of sipuleucel-T and ADT in patients with biochemically recurrent prostate cancer, 50.0% of patients in the sipuleucel-T–first group (Arm 1) and 55.9% of patients in the ADT-first group (Arm 2) had undetectable PSA levels in 1 or more follow-up visits. ADT=androgen-deprivation therapy; PSA=prostate-specific antigen. Adapted from Antonarakis ES et al. A randomized phase II study evaluating the optimal sequencing of sipuleucel-T and androgen deprivation therapy (ADT) in biochemically recurrent prostate cancer (BRPC): immune results [ASCO abstract 5016]. *J Clin Oncol.* 2013;31(15S):312S.

measured included total nucleated cell (TNC) count, antigen-presenting cell (APC) count (large cells expressing CD54), and APC activation (upregulation of CD54 expression). Immune assays included serum cytokines measured using multiplex assays, cellular responses by IFNγ enzyme-linked immunosorbent spot (ELISPOT) assay and ^{3}H-thymidine incorporation, and humoral responses by anti-PA2024 and anti-PAP IgG plus IgM titers via ELISA. Patients were randomized 1:1 to 2 treatments. In arm 1, sipuleucel-T was started first, and ADT followed 2 weeks after the final sipuleucel-T infusion. In arm 2, a 3-month ADT lead-in was followed by sipuleucel-T. All patients received 3 infusions of sipuleucel-T and 12 months of ADT (2 × 45 mg leuprolide depot injections at 6-month intervals). Over the course of 9 months, 68 patients were randomized for the trial (34 in each arm). Patient demographics were balanced across the arms for median age, Gleason score, European Cooperative Oncology Group (ECOG) score, median time from diagnosis to randomization, median serum PSA level, and PSA doubling time.

Changes in PSA levels from baseline showed that 50.0% of patients in the sipuleucel-T–first group and 55.9% of patients in the ADT-first group had undetectable PSA levels in 1 or more follow-up visits (Figure 4). In addition, 73.5% of sipuleucel-T–first patients and 82.3% of ADT-first patients reached PSA levels that were 5% or less of baseline levels. Only 1 patient did not achieve castrate levels of testosterone. Cellular immune response as measured by IFNγ ELISPOT suggested a trend towards more activity in the ADT-first arm, which corresponds with the serum cytokine data. At this interim analysis, however, the difference was not statistically significant (P=.086). Antigen-specific immune responses were seen after the first sipuleucel-T infusion and were enhanced by subsequent infusions. The 2 treatment regimens were not statistically different in the magnitude of response. Sipuleucel-T product parameters for APC counts and TNC counts were also similar between the treatment arms, and APC activation showed a statistically significant (P<.001) increase at infusions 2 and 3, but there was no statistically significant difference between the response in the 2 treatment arms. Patients in the ADT-first group had a statistically significant increase in Th1 (IFNγ and IL-2), Th2 (IL-4, IL-5, IL-10, and IL-13), and Th17 (IL17) serum cytokines compared with the sipuleucel-T–first group (P<.05 between groups). The safety assessment revealed similar frequency and type of AEs in the 2 arms.

In this interim analysis, the combination of sipuleucel-T and ADT was well-tolerated in BRPC patients. The immune response produced by sipuleucel-T was unchanged by ADT. Higher serum IFNγ and ELISPOT numbers in the ADT-first group suggest that ADT may enhance T-cell activity when it is administered before sipuleucel-T, perhaps owing to the castrate environment imposed by ADT. Thus, the anti-tumor response of sipuleucel-T may be increased by prior administration of ADT.

ABSTRACT SUMMARY Phase II Trial of Intravenous Carboplatin (C), Oral Everolimus (E), and Prednisone (P) in Docetaxel-Pretreated (DP) Metastatic Castrate-Resistant Prostate Cancer (mCRPC): A Prostate Cancer Clinical Trials Consortium Study

A phase II clinical trial explored the possible synergistic combination of carboplatin and everolimus with prednisone in men with pretreated mCRPC (ASCO Abstract 5041). The primary endpoint was time to progression (TTP). Secondary endpoints included OS and the correlation of TTP with phosphorylated mTOR, pAKT, p70S6, and circulating tumor cells (CTC). Treatment was administered in 21-day cycles, including intravenous carboplatin at a target area under the curve (AUC) of 5 mg/mL*min on day 1 in combination with oral everolimus (5 mg once daily) and prednisone (5 mg twice daily). Every 3 cycles, radiologic response was assessed. PSA was assessed every 21 days. The median age of the 26 enrolled patients was 69 years (range, 54–86 years). Patients received a median of 3 treatment cycles (range, 1–16 cycles), with 125 cycles total. PSA responses included 4 (15%) patients who had a greater than 30% decline and 1 patient who had a greater than 90% decline. The median TTP and OS were 2.5 months (90% CI, 1.8–4.3) and 12.5 months (90% CI, 6.7–16.1), respectively, with 8 of 19 patients achieving a stable response. Carboplatin given alone was associated with a median AUC of 5.9 mg/mL*min (range, 4.3–11.0 mg/mL*min). Everolimus in combination with carboplatin resulted in an AUC of 4.5 mg/mL*min (range, 4.1–7.1 mg/mL*min) without influencing the pharmacokinetics of carboplatin. Patients with TTP exceeding 18 weeks had a median CTC decrease of 63% (range, 11–100%). pAKT staining was absent in both of the 2 patients on therapy for more than 30 weeks, and increased expression was noted in all 8 patients on therapy for less than 9 weeks. Toxicities were predominantly grade 3 or 4. No treatment-related deaths occurred. Although the combination was tolerable, only modest clinical efficacy was achieved. Biomarker evaluations may help identify a target population for further study.

Reference

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Double-Blind Randomized Trial of Aflibercept Versus Placebo With Docetaxel and Prednisone for Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Since docetaxel/prednisone became the standard treatment for men with CRPC, many trials have attempted to improve outcome by adding a targeted agent to this regimen. The VENICE (Aflibercept in Combination With Docetaxel in Metastatic Androgen Independent Prostate Cancer) trial was a multicenter, randomized, double-blind study comparing the efficacy and safety of aflibercept in patients treated with docetaxel plus prednisone for mCRPC.[1,2] Aflibercept is a recombinant human fusion protein that binds A and B isoforms of VEGF and platelet-derived growth factors (PlGF1 and PlGF2), thereby inhibiting angiogenesis. It has a half-life of approximately 6 days. Patients with mCRPC stratified by ECOG performance status were randomized 1:1 to receive aflibercept (6 mg/kg) or placebo intravenously every 3 weeks, along with docetaxel (75 mg/m^2 intravenously every 3 weeks) and oral prednisone (5 mg twice daily). The primary endpoint was OS using intent-to-treat analysis. The intention was to treat patients for at least 12 weeks until progressive disease, withdrawal of consent, or unacceptable toxicity. The main secondary endpoints were PSA response, pain response, time to occurrence of SREs, PFS, safety, pharmacokinetics, and immunogenicity.

The required number of events or deaths was 873 to detect an HR of 0.8 with 90% power. The anticipated survival was 19 months, based on the TAX 327 trial with docetaxel and prednisone.[3] The expected accrual was 3 years. There were 2 planned interim analyses, 1 for futility and 1 for efficacy. The trial was reviewed by the Data Safety Monitoring Committee every 6 months. The patient population for this trial had biopsy-proven prostate cancer and metastatic disease. Patients had progressive disease while receiving hormonal or surgical castration, in accordance to criteria from the Prostate Cancer Clinical Trials Working Group 2. In addition, patients had low serum testosterone and had not received prior chemotherapy (except estramustine therapy that was completed at least 3 years before enrollment).

A total of 1,224 men were randomized into the trial. The demographics were similar to those described for other mCRPC trials; the median age was 68 years, and almost all (96%) of the patients had ECOG scores of 0 or 1. The trial was conducted in 31 countries at 187 sites. The median time from diagnosis was approximately 4 years, and Gleason scores were distributed evenly between the groups. ECOG scores of 2–4 were rare, but they were evenly distributed between intermediate and high-grade disease. Approximately 40% of patients had rising PSA alone, but others had symptomatic or tumor progression. All patients had received treatment with at least 1 hormonal therapy; 60% had received at least 3 different hormonal therapies. Approximately 25% of patients had received zoledronic acid, which could be continued during the trial.

The patients were randomized evenly to the aflibercept and placebo

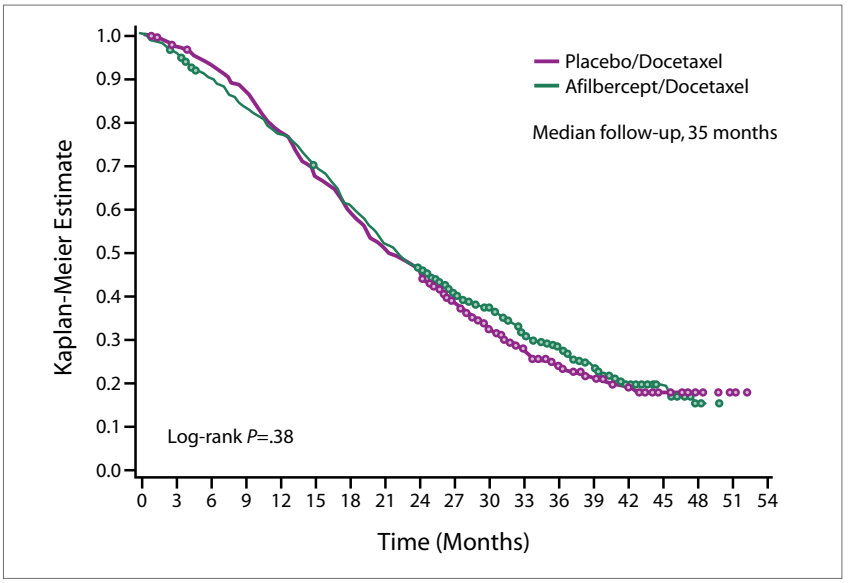

Figure 5. In the VENICE trial of aflibercept in combination with docetaxel in metastatic androgen-independent prostate cancer, the addition of aflibercept did not significantly improve overall survival. VENICE=Aflibercept in Combination With Docetaxel in Metastatic Androgen Independent Prostate Cancer. Adapted from Tannock I et al. Double-blind randomized trial of aflibercept versus placebo with docetaxel and prednisone for treatment of metastatic castration-resistant prostate cancer (mCRPC) [ASCO abstract 5002]. *J Clin Oncol*. 2013;31(15S):308S.

groups, and baseline characteristics were well balanced between arms. Participants received a median of 8 (aflibercept) and 9 (placebo) cycles of therapy. At final analysis, median follow-up was 35 months, and 873 patients had died. There was no significant difference in OS between the 2 treatment arms (Figure 5). The median survival was 22.1 months (95.6% CI, 20.3–24.1 months) in the aflibercept arm and 21.2 months (95.6% CI, 19.6–23.8 months) in the placebo arm (stratified HR, 0.94; 95.6% CI, 0.82–1.08; *P*=.38). The longer-than-expected survival (compared with the 19 months in the TAX 327 trial[3]) probably reflects the fact that patients were offered chemotherapy earlier in the course of their disease. There were no significant differences between the aflibercept and placebo arms among the secondary endpoints, including PSA response rate (68.6% and 63.5%), time to first SRE (median, 15.3 and 15.0 months), and PFS (median, 6.9 and 6.2 months). Patients in the aflibercept group were more likely to have tumor response and a better PSA response than patients in the placebo group, although these differences were not statistically significant. There were no detected differences in the other secondary outcomes, including time to first SRE and PFS. Quality of life analyses will be reported at a later date.

Treatment-emergent grade 3/4 AEs were more common in the aflibercept group (77% vs 49%) and included gastrointestinal disorders (30% vs 8.0%), hemorrhagic events (5.2% vs 1.7%), hypertension (13% vs 3.3%), fatigue (16% vs 7.7%), and infections (20% vs 10%). More patients in the aflibercept group than in the placebo group stopped treatment and received 3 or fewer treatment cycles because of these toxicities. Treatment-related fatal AEs occurred in 3.4% of the aflibercept patients, double that of the approximately 1.5% of the fatal AEs thought to be related to treatment in the docetaxel/placebo arm (which is slightly higher than in the TAX 327 trial).[3]

Aflibercept did not improve the survival of men with CRPC when used with docetaxel and prednisone. There were some subtle signs of biological activity, with trends toward increased PSA and tumor response rate, but there was also increased toxicity leading to shorter duration of treatment. VENICE represents yet another negative trial investigating the addition of a targeted agent to docetaxel and prednisone. Several other trials have failed to show an improvement in survival, and almost all have shown increased toxicity with the addition of a targeted agent. Additional studies continue, such as one that is adding the antisense oligonucleotide custirsen[4] and another that is adding OGXO11,[5] with results expected in approximately a year. In consideration of the many trials that have failed in this area, lessons must be learned from prior experience in order to set a higher bar for future trials.

ABSTRACT SUMMARY Optimal Timing for Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC): Sequencing and Identifying Parameters of Early Progression With Sipuleucel-T

An analysis of mCRPC patients from the phase III IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) trial examined whether any patient characteristics were associated with increased OS benefit and whether bone metastatic burden could identify men at risk of early progression (AUA Abstract 960). In the IMPACT trial, sipuleucel-T significantly improved OS as compared with placebo in men with mCRPC (HR, 0.78; 95% CI, 0.61–0.98; *P*=.03; median OS difference, 4.1 months). Subgroups in this trial were evaluated to assist in treatment decisions, such as the sequencing of regimens. The administration of sipuleucel-T early after mCRPC diagnosis is supported by some biomarkers. Analysis of IMPACT data across subgroups of baseline prognostic variables showed a consistent treatment effect with sipuleucel-T. A post hoc analysis dividing the patients into quartiles by baseline PSA levels confirmed that sipuleucel-T was effective across all subgroups, with the greatest benefit observed in the lowest PSA quartile group. The longest OS was associated with the lowest baseline metastatic burden and slowest tumor velocity. These data support the use of sipuleucel-T soon after diagnosis of metastatic disease, when patients have a lower disease burden and, most likely, a higher-functioning immune system. The decision process associated with the earlier addition of therapies in men with risk factors for early progression can also be aided by bone scan data.

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Effect of Corticosteroid (CS) Use at Baseline (CUB) on Overall Survival (OS) in Patients (pts) Receiving Abiraterone Acetate (AA): Results From a Randomized Study (COU-AA-301) in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Post-Docetaxel (D)

Corticosteroids have previously been used to mitigate mineralocorticoid-related effects and restore sensitivity to abiraterone acetate.[1] Abiraterone acetate is a CYP17 inhibitor that suppresses circulating androgen levels. Pivotal studies of abiraterone acetate utilized prednisone as an active comparator.[2,3] An analysis of the prognostic impact of baseline corticosteroid use upon entry into the Cougar 301 trial (COU-AA-301) was performed.[4] Cougar 301 is a phase III randomized study of prednisone with or without abiraterone acetate in men with mCRPC previously treated with docetaxel.[5] Corticosteroids have been used for many years in the treatment of men with advanced prostate cancer. They have modest therapeutic effects and clear palliative benefits in specific situations that offset the potential toxicities associated with drugs such as abiraterone acetate and docetaxel. (These toxicities include hyperglycemia, hypertension, and risk of infection.) More recently, through work by a number of different groups, it has been recognized that corticosteroids may also have the potential to drive progression of prostate cancer. Corticosteroid use at baseline was reported to adversely influence OS in the AFFIRM (A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients With Progressive Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) study.[6]

To understand the mechanism of corticosteroid-driven resistance to cancer, preclinical data have been generated in essentially androgen-null or androgen receptor (AR)-suppressed settings. In the clinical prostate cancer setting, the correlate is patients who are receiving the most effective AR signaling inhibitors: enzalutamide or abiraterone acetate. Corticosteroid-driven resistance to prostate cancer and AR signaling intercept one another on 2 levels. First, the AR can develop activating mutations in the ligand-binding domain of the receptor. When that occurs, the receptor becomes much more promiscuous, and instead of just binding testosterone and dihydrotestosterone, it will bind other ligands, such as progestins, estrogens, and corticosteroid, which can then activate the AR pathway. Second, the glucocorticoid receptor (GR), which has a ligand binding domain that is very similar to AR, has also been shown in a number of preclinical and in vitro settings to transcribe a genetic program that is essentially a duplicate of the AR. Many of the AR-specific transcription programs that were thought to be truly dependent on AR are in fact duplicated by GR activation. These potential mechanisms of resistance become relevant in the COU-AA-301 trial, in which the use of corticosteroids seemed to be driving cancer progression in some patients.[5]

ABSTRACT SUMMARY Impact of Prior Docetaxel on Sipuleucel-T Product Parameters in PROCEED Patients

In the IMPACT trial, immunosuppression concerns led to the exclusion of patients who had received docetaxel 3 months or less before enrollment (*N Engl J Med*. 2010;363[5]:411-422). The ongoing PROCEED (Provenge Registry for Observation, Collection, and Evaluation of Experience Data) phase IV trial of mCRPC patients treated with commercial sipuleucel-T does not restrict use of prior docetaxel. An assessment of the PROCEED trial focused on parameters including TNC count, APC count (CD54+ large cells), and APC activation (upregulation of CD54). Results were presented for 1,260 patients who had completed their sipuleucel-T treatment (ASCO Abstract 5034). Among the 10.6% of patients who had received prior docetaxel, 1.6% had received it 90 days or less before sipuleucel-T treatment, and 9.0% had received it between 91 days and 113 days before sipuleucel-T treatment. In the IMPACT trial, 53 (15.5%) patients had received docetaxel more than 90 days before sipuleucel-T treatment. Overall, PROCEED patients appear to have lower median PSA levels than IMPACT patients, but patients who had received docetaxel appeared to have higher PSA levels. When further broken down into subgroups by baseline ECOG status or Gleason score, all groups showed APC activation, and APC and TNC were comparable. This initial analysis showed that patients who received previous treatment with docetaxel had comparable product parameters to those patients who had not received prior docetaxel.

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The most compelling data for the benefit of corticosteroids come from phase II and phase III studies. Recent phase III randomized studies were conducted in the predocetaxel and postdocetaxel setting of abiraterone acetate plus prednisone versus prednisone alone. With prednisone alone, there were modest but definable PSA and tumor responses depending on the state of the disease. The AFFIRM phase III randomized trial evaluated enzalutamide (MDV3100) versus placebo in men with mCRPC previously treated with chemotherapy. In this study, use of corticosteroids at study entry and throughout the treatment cycles was permitted but not required.[6] In a post hoc analysis, approximately one-third of patients entering the study were on corticosteroids and had worse prognostic features.[7] In the multivariate analysis, after adjustment for other factors, corticosteroid use at baseline was not associated with survival.

To further characterize the relationship between corticosteroids and cancer progression, an analysis was conducted on a similar clinical study, Cougar 301.[4] This randomized phase III study utilized prednisone with or without abiraterone acetate in men with mCRPC previously treated with docetaxel. This positive study led to the FDA approval of abiraterone acetate. A post hoc analysis explored the impact on these patients of entering the study while already on steroids. Because the patients who entered the study subsequently went on to prednisone use, the purpose of this analysis was to explore the impact of corticosteroid use at study entry. At study entry, approximately one-third of the patients were on corticosteroids (usually prednisone or prednisolone). The groups already on steroids were found to be statistically more likely to have a higher proportion of poor prognostic features, with the exception of liver metastases. OS was 4 months shorter for patients with baseline corticosteroid use, in both the abiraterone acetate and placebo arms (Figure 6). Patients treated with abiraterone acetate had a survival advantage over those who were not. Secondary endpoints, including PSA progression and radiographic PFS, were also examined. Again, abiraterone acetate provided some advantage with regard to PFS, but patients on corticosteroids at study entry had a PFS interval that was approximately 3 months shorter, whether receiving abiraterone acetate or prednisone.

ABSTRACT SUMMARY Pain Analyses From the Phase 3 Randomized ALSYMPCA Study With Ra-223 Dichloride (Ra-223) in Castration-Resistant Prostate Cancer (CRPC) Patients With Bone Metastases

The ALSYMPCA trial (NCT00699751) examined the efficacy and safety of radium-223 in CRPC patients with bone metastases receiving best standard of care. A post hoc analysis of pain parameters and pain-related quality of life was conducted on patients who received radium-223 (n=614) or placebo (n=307; ASCO Abstract 5038). Delays in timing to use of external beam radiation therapy (EBRT) for bone pain were analyzed using a Cox proportional hazards model adjusted for prior docetaxel use, baseline alkaline phosphatase levels, and current bisphosphonate use. Pain was reduced in the radium-223 patients as compared with placebo at week 16 (*P*=.001). The radium-223 patients experienced significant pain reduction relative to baseline at weeks 16 (*P*=.001) and 24 (*P*=.077). Radium-223 significantly prolonged median time to EBRT, with a 33% reduction in EBRT needed for bone pain (HR, 0.67). It was also associated with a decreased need for opioid use (38% reduction). In addition, despite longer survival time, fewer radium-223 patients (50%) than placebo patients (62%) reported bone pain as an AE. Radium-223 patients had a 36% reduced probability of having bone pain as an AE compared with placebo patients (relative risk, 0.64; 95% CI, 0.54–0.76; *P*<.0001). Radium-223 was associated with a highly favorable safety and tolerability profile, including a low incidence of myelosuppression.

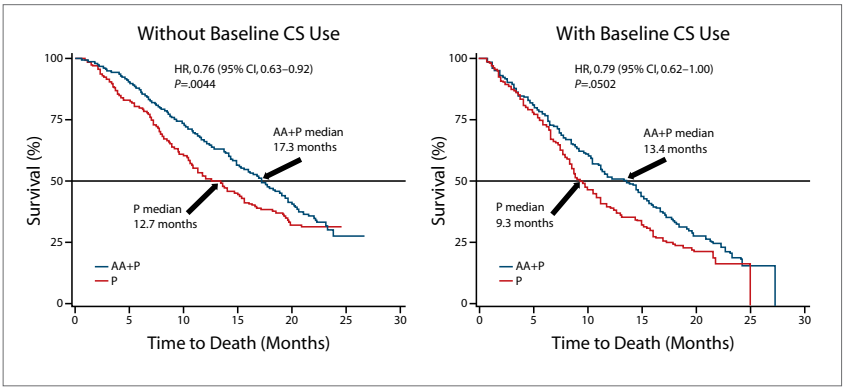

Figure 6. In an analysis of the COU-AA-301 study, which examined the effect of corticosteroid (CS) use at baseline on overall survival in patients receiving abiraterone acetate (AA), overall survival was 4 months shorter for patients with baseline corticosteroid use, in both the AA and placebo (P) arms. Adapted from Montgomery RB et al. Effect of corticosteroid (CS) use at baseline (CUB) on overall survival (OS) in patients (pts) receiving abiraterone acetate (AA): results from a randomized study (COU-AA 301) in metastatic castration-resistant prostate cancer (mCRPC) post-docetaxel (D) [ASCO abstract 5014]. *J Clin Oncol.* 2013;31(15S):311S.

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To model the independent effect of corticosteroid use on prognostic outcome, each of the study prognostic features that were known to have an impact on survival were run through univariate analysis along with corticosteroid use. The model was then optimized by running those statistically significant factors through a multivariate stepwise selection process in which those that had the greatest impact on survival were given priority. Baseline use of corticosteroids had an impact on OS, with an HR of approximately 1.5 for patients who had received them.

The prior AFFIRM analysis and the current analysis have some clear similarities, as they were performed in very similar patient populations in a postdocetaxel setting, in which approximately one-third of the patients were receiving corticosteroids at baseline. Those patients who were on corticosteroids at baseline had worse prognostic features in both studies. The difference between the 2 analyses was that in this Cougar 301 post hoc analysis, all patients went on to corticosteroid use, whereas in the AFFIRM study, patients did not receive protocol-mandated prednisone. In addition, multivariate analysis showed that the majority of the prognostic information was contained in the other prognostic features mentioned above. Clinical dataset analyses are powerful tools but have very significant limitations. There were no data concerning why the corticosteroids were administered and for how long they were used. Clinical analysis for translational biology requires defining subsets and phenotypes of patients in whom corticosteroids are driving progression. In analyzing the Cougar 301 study population, it was concluded that corticosteroid use at baseline was a poor prognostic feature. Additional studies will be required to determine the role of corticosteroids in driving prostate cancer progression.

ABSTRACT SUMMARY Efficacy and Safety of Ra-223 Dichloride (Ra-223) in Castration-Resistant Prostate Cancer (CRPC) Patients With Bone Metastases Who Did or Did Not Receive Prior Docetaxel (D) in the Phase III ALSYMPCA Trial

In the ALSYMPCA (A Phase III Study of Alpharadin [Radium-223] in Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases) trial, radium-223 significantly improved median OS by 3.6 months versus placebo in CRPC patients with bone metastases receiving best standard of care (HR, 0.695; 95% CI, 0.581–0.832; *P*=.00007). Radium-223 had a highly favorable safety profile. A predefined subgroup analysis evaluated whether prior treatment with docetaxel affected the efficacy and safety of radium-223 (ASCO Abstract 5068). Patients in this analysis had progressive, symptomatic CRPC with at least 2 bone metastases, without known visceral metastases. They were receiving best standard of care. Patients were randomized 2:1 to receive radium-223 (6 injections; 50 kBq/kg IV) or placebo. Patients were stratified by prior docetaxel use, baseline alkaline phosphatase level, and current bisphosphonate use. The analysis included 395 of 921 (43%) randomized patients who had not received docetaxel (radium-223, n=262; placebo, n=133) and 526 of 921 (57%) patients who had received prior docetaxel (radium-223, n=352; placebo, n=174). The median age was 74 years for patients who had not received docetaxel and 69 years for prior docetaxel patients. In patients who had not received docetaxel, the median OS was 16.1 months with radium-223 versus 11.5 months with placebo (HR, 0.745; 95% CI, 0.562–0.987; *P*=.039). In patients with prior docetaxel use, the median OS was 14.4 months versus 11.3 months in the radium-223 and placebo groups, respectively (HR, 0.710; 95% CI, 0.565–0.891; *P*=.003). Overall, there was a low incidence of myelosuppression. Incidences of neutropenia and thrombocytopenia were higher in patients with prior docetaxel use versus patients who had not received docetaxel. Radium-223 significantly prolonged OS and had a highly favorable safety profile in CRPC patients with bone metastases, regardless of whether they had or had not received prior docetaxel. The prior docetaxel patients had a slightly increased rate of grade 3/4 bone marrow suppression with radium-223.

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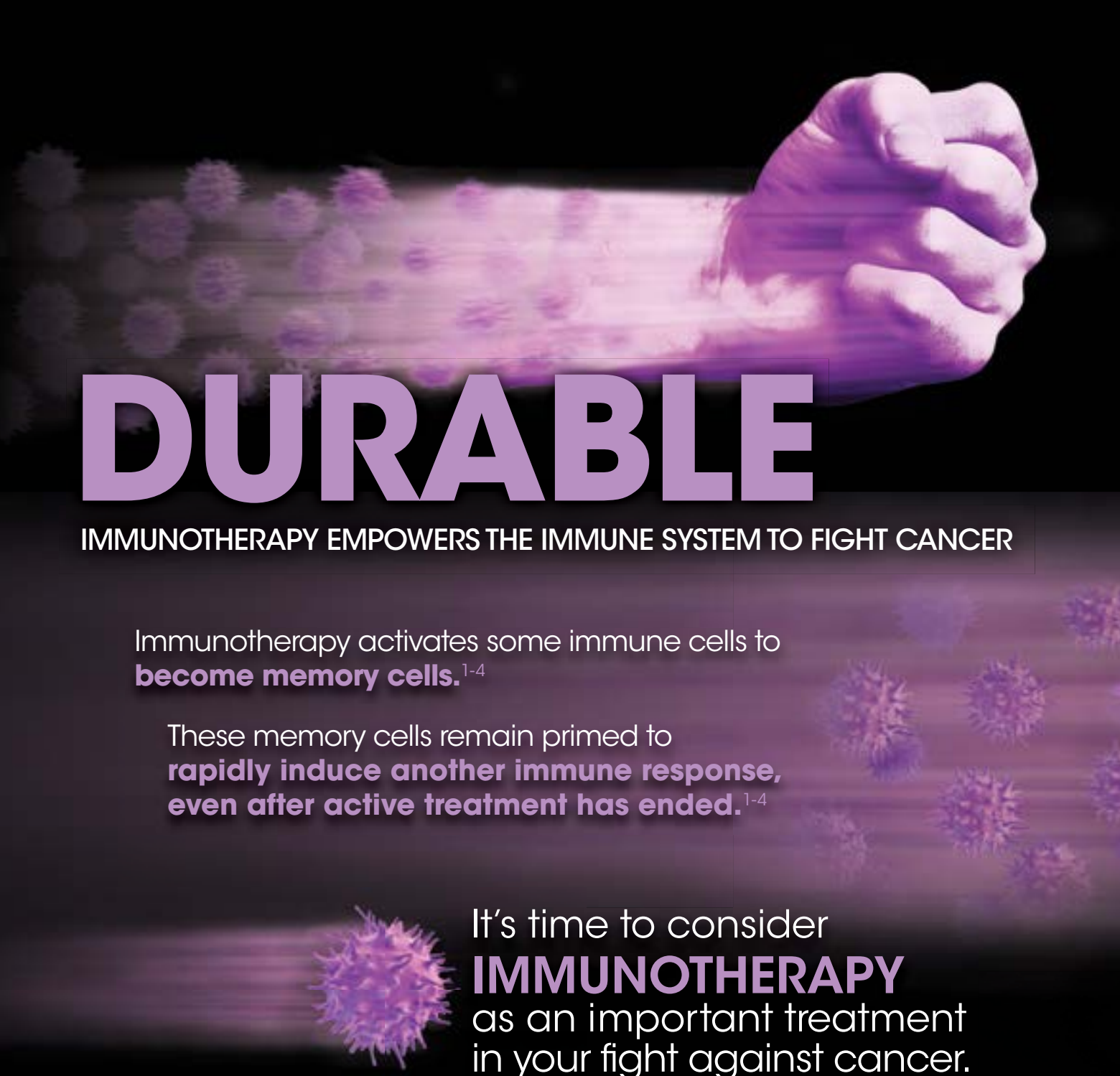

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Commentary

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Presentations at the 2013 meetings of the American Urological Association and the American Society of Clinical Oncology offered important new data in the treatment of men with advanced prostate cancer. Analyses focused on the optimal use of therapies such as sipuleucel-T, radium-223, strontium-89, zoledronic acid, abiraterone acetate, and enzalutamide.

Sipuleucel-T

A randomized study presented by Small and colleagues was conducted to evaluate the optimal sequencing of sipuleucel-T and abiraterone acetate with prednisone in men with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (mCRPC).[1] Patients were randomized to either sipuleucel-T with concurrent abiraterone acetate plus prednisone for 26 weeks, beginning after the first of 3 infusions of sipuleucel-T (Arm 1) or sipuleucel-T with sequential abiraterone acetate plus prednisone for 26 weeks, beginning 10 weeks after the completion of sipuleucel-T (Arm 2). Among the 63 randomized patients, 60 completed sipuleucel-T treatment, with no differences between mean cumulative antigen-presenting cell (APC) activation or count. Furthermore, no statistical difference was seen between antigen-specific humoral or cellular responses between the arms. The authors concluded that these findings suggest that sipuleucel-T can be administered before or during treatment with abiraterone acetate plus prednisone without negative effects on product potency. This study demonstrates an important first step in the understanding of how best to sequence various treatments for men with mCRPC. Because both sipuleucel-T and abiraterone acetate plus prednisone are indicated for men with asymptomatic or minimally symptomatic mCRPC, most clinicians will decide to initiate treatment with one or the other. However, the clinical benefit of sipuleucel-T is long-term overall survival, whereas abiraterone acetate plus prednisone in this setting is known to affect PSA response and progression-free survival (PFS). Therefore, immediate sequential or even concomitant treatment with these agents would be rational. The current study demonstrates no apparent impact of low-dose prednisone on immune activation following sipuleucel-T. These results should give clinicians more confidence in rapidly transitioning patients to abiraterone acetate plus prednisone following completion of sipuleucel-T therapy.

Roughly one-third of men diagnosed with localized prostate cancer will relapse with biochemical recurrence. Although outcomes will vary, many of these patients will eventually be treated with androgen-deprivation therapy (ADT). Although this approach is effective at controlling disease progression, the majority of these patients will progress to a metastatic castration-resistant state, at which time sipuleucel-T will be indicated. The STAND (Sequencing of Sipuleucel-T and ADT in Men With Non-metastatic Prostate Cancer) trial was a phase II study designed to evaluate the optimal dosing of sipuleucel-T and ADT in men with biochemical recurrence.[2] Patients were randomized to either sipuleucel-T followed by ADT (arm 1) or 3 months of ADT lead-in, followed by sipuleucel-T (arm 2). Results of immune-based monitoring revealed higher cytokine levels and a trend toward a higher enzyme-linked immunosorbent spot (ELISPOT) response to the fusion protein PA2024 in arm 2 compared with arm 1. The authors concluded that sipuleucel-T immune response is augmented by ADT, an observation that is consistent with preclinical studies.

These findings give support to the rationale for studying sipuleucel-T in earlier disease settings, such as biochemical relapsed prostate cancer, and for examining the optimal sequencing of treatment. Currently, sipuleucel-T is indicated in asymptomatic to minimally symptomatic men with mCRPC, the majority of whom have progressive disease with rising PSA and/or new radiographic progression. However, since the approval of sipuleucel-T in 2010, 2 other secondary hormonal therapies have been approved for treatment of metastatic CRPC, abiraterone acetate and enzalutamide, which clearly augment the effects of ADT alone in this setting. Based on the above findings, one might begin to hypothesize that using secondary hormonal manipulations such as abiraterone acetate or enzalutamide as a lead-in might also enhance the immune response to sipuleucel-T.

ABSTRACT SUMMARY Correlation Between Baseline Variables and Survival in the Radium-223 Dichloride Phase 3 ALSYMPCA Trial With Attention to Total ALP Changes

Prognostic markers for survival in the phase III ALSYMPCA trial included baseline factors such as age, performance status, and levels of albumin, hemoglobin, lactate dehydrogenase, PSA, and alkaline phosphatase. Serum bone-specific alkaline phosphatase is a prognostic marker for OS in CRPC, and the correlation of total alkaline phosphatase with serum bone-specific alkaline phosphatase in patients with high disease volume may be predictive of patient outcome. An analysis of the ALSYMPCA trial examined the prognostic value of total alkaline phosphatase and other variables in predicting OS in patients who received radium-223 or placebo (ASCO Abstract 5080). Intent-to-treat (ITT) patients with total alkaline phosphatase measurements at baseline and week 12 were included in the analysis (radium-223, n=497; placebo, n=211). Total alkaline phosphatase levels at 12 weeks versus baseline showed that 87% of radium-223–treated patients had a decrease compared with 23% of placebo patients. Analysis of total alkaline phosphatase changes from baseline to week 12 showed that radium-223 patients had a 32% decrease in total alkaline phosphatase compared with a 37% increase in total alkaline phosphatase ($P<.001$) for placebo patients. The radium-223 patients who had decreased total alkaline phosphatase at week 12 also had a significantly longer median OS versus radium-223 patients with no confirmed total alkaline phosphatase decline (median OS,17.8 vs 10.4 months; HR, 0.45; 95% CI, 0.34–0.61; $P<.0001$). A lower risk of death was associated with a decline in total alkaline phosphatase, and higher baseline levels of total alkaline phosphatase were significantly associated with an increased risk of death in mCRPC patients enrolled in the placebo ($P<.001$) and ITT ($P<.001$) populations.

PROCEED (Provenge Registry for Observation, Collection, and Evaluation of Experience Data) is an ongoing phase IV prospective registry of patients with mCRPC who have received sipuleucel-T within 6 months of enrollment.[3] Prior docetaxel treatment is not an exclusion criteria, so patients with prior exposure to the chemotherapy were evaluated for total nucleated cell count (TNC) and for APC activation and count. Results demonstrate similar TNC and APC counts in patients who were docetaxel-naïve, whereas APC activation was slightly lower in the patients treated with prior docetaxel but still well within product parameters. Within the prior docetaxel treatment group, patients treated with sipuleucel-T within 90 days of docetaxel had lower median APC activation, higher Gleason scores, and higher Eastern Cooperative Oncology Group (ECOG) performance status.

Our clinical experience with sipuleucel-T has grown enormously since its commercial approval in 2010, yet little is known outside of randomized controlled trials. The PROCEED registry is a valuable resource to further explore the baseline characteristics of patients with mCRPC who are treated with sipuleucel-T and their association with the product parameters. Interestingly, prior docetaxel chemotherapy does not appear to have a lasting detrimental effect on the sipuleucel-T product parameters, although short-term (<3 months) use appears to be associated with some effect. Current treatment algorithms suggest that most patients receive sipuleucel-T prior to treatment with docetaxel, but there are circumstances in which this order might be reversed (eg, adjuvant use of docetaxel, use of docetaxel for a prior cancer, or a previously symptomatic patient who responds well to docetaxel and is no longer symptomatic). These results should further justify the on-label use of sipuleucel-T under these circumstances and in other settings of prior docetaxel exposure.

The question of how to sequence immunotherapy in relation to other therapies (abiraterone, enzalutamide, docetaxel) is a major clinical issue faced by patients and providers during the treatment of men with mCRPC. The IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) trial of sipuleucel-T versus sham pheresis enrolled primarily a predocetaxel mCRPC population, and prior docetaxel use did not preclude a survival benefit in this trial, provided there was a suitable wash-out period (ie, 3 months) for these highly selected men.[4] The current analysis examined data from the IMPACT trial to determine whether the relative improvement in survival was different across disease subgroups stratified by prostate-specific antigen (PSA) quartiles, with the hypothesis that immunotherapy may be more effective when disease burden is low, as one might expect, particularly given the relatively slow onset for survival curve separation with sipuleucel-T of 6–8 months.[5] In this prespecified analysis of the IMPACT trial, the hazard ratio [HR] for death progressively improved as the PSA level decreased. The HR was 0.84 in men with a PSA exceeding 134 ng/mL, 0.81 in men with a PSA from 50–134 ng/mL, 0.74 in men with a PSA from 22–50 ng/mL, and 0.51 in men with a PSA less than 22.1 ng/mL. In these 4 subgroups, there were improvements in absolute survival with sipuleucel-T of 2.8, 5.4, 7.1, and 13.1, respectively. Although no statistical interaction testing was performed, and the size of these subgroups was small (n=128 each), the

ABSTRACT SUMMARY Open-Label, Multicenter Study of Sipuleucel-T in Men With Metastatic Castrate-Resistant Prostate Cancer (mCRPC) Previously Treated With Sipuleucel-T: Evaluation of Antigen Presenting Cell (APC) Activation and ELISPOT Data

P10-1 is an uncontrolled, open-label, phase II multicenter study of sipuleucel-T in men previously treated with sipuleucel-T as part of the PROTECT (Provenge Treatment and Early Cancer Treatment) trial. A preliminary analysis of P10-1 evaluated APC activation and immune responses in patients re-treated with sipuleucel-T after progression to mCRPC (ASCO Abstract 5053). Men who received at least 1 infusion of sipuleucel-T in PROTECT and progressed to mCRPC were re-treated with 3 infusions of sipuleucel-T, 2 weeks apart. Seven men were enrolled and received at least 1 infusion (as of October 2012). APC activation was assessed by CD54 upregulation. T-cell responses to prostatic acid phosphatase (PAP) and PA2024 (PAP-GM-CSF) antigens were assessed by interferon gamma (IFN-γ) ELISPOT assay. The median time between the third PROTECT infusion and the first P10-1 infusion was 9.2 years (range, 7.8–10.0). APC activation was greater at the first P10-1 treatment versus the third infusion in PROTECT. In general, the increased APC activation at the first re-treatment was maintained at the second and third infusions in PROTECT. The median CD54 upregulation for infusions 1, 2, and 3 was 6.2, 14.7, and 13.2 for PROTECT, and 19.8, 20.5, and 22.5 for P10-1, respectively. PA2024 and PAP ELISPOT responses were present prior to re-treatment, indicating long-term immunologic memory. The IFN-γ ELISPOT responses were boosted after the first infusion of sipuleucel-T re-treatment, consistent with an immune memory response. Re-treatment with sipuleucel-T appears to be well tolerated, with 45 of 51 (88.2%) of adverse events being mild to moderate in severity. The P10-1 trial shows the feasibility of sipuleucel-T re-treatment in mCRPC patients and the presence of immunologic memory several years after initial treatment.

trend in these data is compelling. The findings support the current clinical practice of offering sipuleucel-T to men with asymptomatic mCRPC or minimally symptomatic, nonvisceral mCRPC and a low disease burden (such as those with a relatively low PSA), as opposed to withholding sipuleucel-T until after treatment with docetaxel or until the PSA is very high and the disease burden and symptoms are great. In more advanced and symptomatic men or in those with a high burden of disease, the overall risk/benefit and cost-effectiveness of sipuleucel-T are smaller, particularly given that sipuleucel-T does not provide any short-term benefits in terms of disease response. Further prospective controlled trials will need to establish the role of prostate cancer immunotherapy in men with nonmetastatic prostate cancer or hormone-sensitive metastatic prostate cancer.

As mentioned, the IMPACT trial enrolled patients with asymptomatic and minimally symptomatic mCRPC. By contrast, PROTECT (Provenge Treatment and Early Cancer Treatment) was a phase IIIB study in men with hormone-sensitive, nonmetastatic prostate cancer (N=159).[6] This abstract reported on the subset of men in PROTECT who received re-treatment with sipuleucel-T upon development of mCRPC (P10-1).[7] Seven men were enrolled on P10-1, all of whom received at least 1 infusion of sipuleucel-T. Interestingly, the median time between the third PROTECT infusion and first P10-1 infusion was 9.2 years (range, 7.8–10.0 years). CD54 upregulation—a marker of APC activation—was greater at the first P10-1 treatment compared with the last PROTECT treatment. PA2024, the recombinant fusion protein of prostatic acid phosphatase (PAP) and GM-CSF, as well as PAP ELISPOT responses, were also present prior to re-treatment. These findings appear to indicate a long-term immunologic memory effect. For example, such ELISPOT responses are not usually present prior to the first sipuleucel-T treatment. This very small study provides interesting preliminary data on the length of immune responses with sipuleucel-T in men treated at the time of biochemical relapse. The clinical significance of these data is uncertain in the on-label population (men with mCRPC). Proponents of sipuleucel-T have argued that its mechanism of action results in a long-term survival advantage over sham infusion because of a long-lasting immune response, without changes in more short-term parameters, such as PSA or radiographic tumor progression. This study will not silence opponents of sipuleucel-T, but it does suggest that a long-lasting change in immune parameters could be related to this agent's purported mechanism of action.

Strontium-89 Versus Zoledronic Acid

The TRAPEZE (A Randomised Phase III Trial of Docetaxel Plus Prednisolone vs Docetaxel With Prednisolone Plus Either Zoledronic Acid, Strontium-89, or Both Agents Combined) study is a multifactorial randomized trial from the United Kingdom of strontium-89 or zoledronic acid in men with bone mCRPC.[8] The case for strontium-89 is based on the clinical efficacy and palliation seen by other groups when used as consolidation therapy after initial chemotherapy in smaller randomized studies, but to date, strontium-89 has not been shown to improve survival in a well-powered trial. Zoledronic acid is

already well known to prolong the time to skeletal events such as pathologic fracture or spinal cord compression or radiation, but the impact on survival is less clear from prior work. A 4-arm trial presented by James and colleagues utilized docetaxel chemotherapy in all arms at standard every-3-week dosing, but evaluated zoledronic acid at 4 mg every 3 weeks for 10 cycles in 2 arms and strontium-89 for 1 dose at 150 mBq during day 28 of cycle 6 of treatment in 2 arms. The primary analysis compared each of these 2 arms with the 2 arms that did not receive these therapies. The primary outcome was bone PFS, including skeletal events, death, and bone pain progression. Overall survival was a key secondary outcome. In this trial of more than 750 randomized men, zoledronic acid delayed PFS by 0.9 months (HR, 0.94; *P*=NS), and strontium-89 delayed PFS by 1.0 months (HR, 0.84; *P*=.11), a difference considered nonsignificant by conventional standards both statistically and clinically. However, skeletal-related events were delayed by a median of 5 months with zoledronic acid (mostly clinical symptomatic fractures, spinal cord compression events, and need for radiation therapy to bone), whereas no such delay was observed with strontium-89 (1.7 months). No survival benefit was seen with either drug. These studies validate the current practice of giving zoledronic acid (or denosumab) to men with bone metastatic CRPC to delay skeletal events and provide little rationale for continued interest in or evaluation of strontium-89, particularly given the improved toxicity profile and efficacy associated with radium-223.

The VENICE Trial

The rationale for anti–vascular endothelial growth factor (VEGF) therapy in men with metastatic CRPC was based on the findings of elevated VEGF levels in these men—which were associated with poor prognosis—and the increasing prevalence of angiogenesis and microvessel density as the disease progresses. In addition, early phase II trial results suggest improved response rates and survival with docetaxel combinations. ZIV-aflibercept (VEGF Trap) is a recombinant human fusion decoy receptor against VEGF A and B isoforms and placental growth factor and has shown improvements in survival in patients with metastatic colorectal cancer. It was largely unstudied in men with prostate cancer prior to the phase III trial, and the basis for its development was largely based on several preclinical studies and the general anti-VEGF excitement of the past decade that is now diminishing. The negative results of the Cancer and Leukemia Group B (CALGB) 90401[9] trial of docetaxel with or without bevacizumab last year anticipated the current negative VENICE trial results, in which 1,224 men were randomized to docetaxel with or without VEGF Trap every 3 weeks.[10] The results of the trial were quite negative. The addition of VEGF Trap actually led to a higher risk of treatment-related severe adverse events (hemorrhage, infection, gastrointestinal symptoms, hypertension), and more men in the VEGF-Trap arm died without disease progression, likely from toxicity. No improvement in survival or PFS was noted, although both groups of men with mCRPC lived longer than men in the original TAX 327 study,[11] likely indicating either improved prognosis of the selected men or improvements in systemic therapies. Thus, the use of VEGF targeted therapies in men with mCRPC in an unselected population cannot be recommended because the harms outweigh any possible benefits. Future directions should focus on identifying subgroups or biomarkers that derive the greatest benefit from an anti-angiogenic strategy.

Corticosteroids in mCRPC

There is much controversy over the role of corticosteroids in the management of men with mCRPC. Corticosteroids clearly have a palliative benefit in these men, as shown in older controlled trials, and thus formed the backbone of our modern chemotherapeutic regimens of mitoxantrone, then docetaxel, and most recently cabazitaxel. With abiraterone, prednisone reduces the feedback upregulation of mineralocorticoids induced by the inhibition of adrenal steroid synthesis, thus improving not only the safety of abiraterone but also its efficacy, by limiting androgenic activity of these upregulated androgen precursors. However, glucocorticoids have multiple risks, including metabolic syndrome, infection, mood disturbances, and diabetes, and emerging effective agents, such as enzalutamide, are active without requiring steroid use. In addition, there are suggestions that one mechanism of castration-resistant progression includes promiscuous activation of the glucocorticoid receptor to active androgen receptor genes, in which one could envisage corticosteroids driving cancer progression in some men. In this context, Montgomery and coworkers evaluated the Cougar 301 postdocetaxel randomized phase III trial for whether prior corticosteroid use might drive cancer progression and subsequent resistance to abiraterone acetate with prednisone.[12] This analysis was likely motivated by the AFFIRM (A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients With Progressive Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) subanalysis of whether baseline corticosteroid use promoted resistance to enzalutamide.[12] In the AFFIRM study, 30% of men took baseline steroids at entry, typically because of symptoms or other poor-risk prognostic factors, and these men had a poor survival outcome.[13] In this trial, enzalutamide was beneficial in all men, regardless of baseline corticosteroid use, and thus corticosteroid use did not necessarily promote

enzalutamide resistance, although the absolute benefits of enzalutamide were less in men on corticosteroids, suggesting that in some men, there could be some induced resistance. In the 301 trial, 33% of men were taking corticosteroids at baseline (22% abiraterone, 12% placebo), and again, men who were on corticosteroids at entry had multiple poor prognosis risk factors such as worse performance status and pain, more prior therapy, and lower levels of androgens at baseline. Overall survival was similarly improved with abiraterone acetate independent of prior corticosteroid use (HR, 0.76 without prior use and 0.79 with), although men on prior corticosteroids had a shorter survival by about 4 months. Baseline steroid use was not an independent factor in predicting outcome in multivariate analysis in Cougar 301.

Thus, in both of these studies, baseline corticosteroid use was adversely prognostic, likely because the reason that corticosteroids were given was because of symptomatic disease, but each of these novel hormonal therapies conferred benefit regardless of baseline use. One *cannot* conclude that corticosteroids are harmful in men with mCRPC, nor can one say that corticosteroids promote CRPC progression and resistance to these agents without additional prospective trials that examine this question directly and in which corticosteroid use is randomized and not selected owing to patient symptoms.

The AFFIRM study demonstrated a 4.8-month longer median overall survival for patients treated with enzalutamide compared with placebo in patients with mCRPC and prior docetaxel exposure.[13] Among patients in the AFFIRM trial treated with enzalutamide, 11.5% had liver metastases, and 15.3% had lung metastases, whereas among placebo patients, 8.5% had liver metastases and 14.8% had lung metastases. The median overall survival for enzalutamide-treated patients with liver metastases was 9.0 months versus 16.4 months for enzalutamide-treated patients with lung metastases.[14] For placebo patients, those with liver metastases had a median survival of 5.7 months versus 10.4 months for those with lung metastases. Objective responses and prostate-specific antigen responses were also higher for enzalutamide patients with liver and or lung metastases versus placebo. The authors concluded that sites of visceral metastases (lung vs liver) have different outcomes and should be subcategorized in clinical trials separately. Enzalutamide improves the outcomes of both patient subgroups compared with placebo.

Enzalutamide is a potent and clinically beneficial androgen receptor antagonist that inhibits both the ligand binding and nuclear translocation of the androgen receptor, resulting in significant improvements in survival and disease progression for patients with metastatic prostate cancer who have progressed on primary androgen deprivation. Importantly, the benefits were seen across a spectrum of baseline patient characteristics, including the presence of visceral metastases. As in other phase III trials, it appears that patients with liver metastases, which generally occur in approximately 10% of mCRPC study populations, have a worse prognosis. Interestingly, lung metastases do not appear to carry such a poor prognosis. They occur more frequently (roughly 15% of the population) and have a median overall survival nearly double that of liver metastases (5.7 vs 10.4 months) in the placebo population. Furthermore, enzalutamide resulted in a median survival of 16.4 months for lung metastases patients (which is only 2 months less than the median survival for the entire enzalutamide population of 18.4 months), suggesting a similar dependency of the androgen receptor. In contrast, the median survival for patients with liver metastases on enzalutamide is 9.0 months, with a median time to radiographic progression of just 2.9 months, suggesting much less dependency on the androgen receptor to drive this disease. Nonetheless, there is a clear separation in outcome of a subset of patients with liver metastases treated with enzalutamide versus placebo, suggesting that not all patients with liver metastases are resistant to this strategy. In summary, this study sheds new light on the differences of visceral metastases in mCRPC patients and identifies an unmet need population (those with mCRPC and liver metastases) for future drug development.

Analyses of Phase III Data in Radium-223

Three abstracts reported on secondary endpoints and post-hoc analyses of the phase III trial of radium-223 dichloride (Ra-223) versus placebo. This first-in-class alpha-emitter was approved on May 15, 2013 for patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease based on the favorable results of the ALSYMPCA (A Phase III Study of Alpharadin [Radium-223] in Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases) trial.[15] Notably, overall survival was improved (14.9 vs 11.3 months, HR 0.70; 95% confidence interval [CI], 0.58–0.83; $P<.001$), and time to first symptomatic skeletal-related event was delayed (15.6 vs 9.8 months, HR 0.66; 95% CI, 0.52–0.83; $P<.001$). Whereas prior trials in mCRPC studied populations of predocetaxel- or postdocetaxel-treated men, in ALSYMPCA, 57% of men had received prior docetaxel and 43% had not. The ALSYMPCA population included 55% in each arm with moderate/severe pain and opioid use based on the World Health Organization ladder for cancer pain. Side effects of Ra-223 included minor gastrointestinal toxicity, as well as mild neutropenia and thrombocytopenia that were rarely severe.

In men with mCRPC, pain is a strong independent prognostic factor for death, and it is included in contemporary nomograms for survival. Previous

trials of survival-prolonging therapies in mCRPC (eg, TAX 327, with docetaxel/prednisone[11] and COU-AA-301, with abiraterone acetate/prednisone[16]) have demonstrated favorable pain responses but have used differing pain scales and variable incorporation of the composite analgesic score. The post-hoc analysis of pain in ALSYMPCA by Nilsson and colleagues demonstrated improvements in the following endpoints with Ra-223 versus placebo: time to external beam radiation, time to opioid use, quality of life pain score, and pain at 16 and 24 weeks from baseline.[17] Although β-emitters (eg, strontium-89 and samarium-153) may have provided pain palliation, they never were definitively shown to improve survival. Thus, Ra-223 stands apart from β-emitters and compares favorably with contemporary survival-prolonging therapies in mCRPC.

Vogelzang and coworkers reported on a predefined subgroup analysis of patients who did or did not receive prior docetaxel, which is of interest because use of β-emitters has been plagued by hematologic toxicity, and docetaxel treatment is known to result in hypoproliferative bone marrow.[18] The ALSYMPCA trial included a slight majority of docetaxel-pretreated men. Overall survival was numerically longer in the no prior docetaxel group, both compared with placebo and with the prior docetaxel group. With no prior docetaxel, median survival was 16.1 versus 11.5 months (HR, 0.75, 95% CI, 0.56–0.99; *P*=.039), whereas in the prior docetaxel group, it was 14.4 vs 11.3 months (HR, 0.71, 95% CI, 0.57–0.89; *P*=.003). As mentioned above, there was a low incidence of myelosuppression overall. However, the overall and grade 3/4 incidences of neutropenia and thrombocytopenia were higher in the prior docetaxel group. Still, the incidence of grade 3/4 neutropenia and thrombocytopenia were 3% and 9%, respectively, in the docetaxel-pretreated group. Of note, 58% of patients on the Ra-223 arm received all 6 planned injections, whereas re-treatment with β-emitters was not common. These rates of hematologic toxicity again set Ra-223 apart from β-emitters and also compare favorably with survival-prolonging cytotoxic chemotherapies in mCRPC.

Baseline alkaline phosphatase (ALP), a biomarker of osteoblast activity, is a known baseline prognostic factor in mCRPC; furthermore, improvements in ALP have been associated with improvements in survival after the initiation of hormonal therapy and docetaxel chemotherapy. The mechanism of action of Ra-223 is predicated on its ability to mimic calcium and target areas of osteoblastic activity. Thus, the ALSYMPCA trial stratified patients on the basis of total ALP (<220 U/L vs ≥220 U/L). The abstract by Sartor and associates sought to explore the prognostic value of total ALP, as well as total ALP dynamics.[19] Higher total ALP was associated with an increased risk of death and, at 12 weeks, patients on the Ra-223 arm demonstrated increased decline in total ALP and total ALP percentage change compared with baseline. In the Ra-223 arm, 34% had normalization of total ALP compared with 1% in the placebo arm. Thus, despite the fact that total ALP is a poor prognostic marker, elevations in osteoblast activity (total ALP) may be linked to greater uptake and pharmacodynamic effects of Ra-223 in bone, and may be predictive of the benefits of this drug for improved survival. More work is needed to correlate total ALP dynamics with survival and, more importantly, to understand the precise mechanisms of these findings and translate them to clinical use. Such efforts are already under way.

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Notes