REVIEW

Optimal timing of sipuleucel-T treatment in metastatic castration-resistant prostate cancer

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Introduction: *Numerous treatments are approved for metastatic castration-resistant prostate cancer (mCRPC), including sipuleucel-T, an FDA-approved immunotherapy.*
Materials and methods: *In this paper we review recent data providing insights into the mechanism of action of sipuleucel-T which suggests sipuleucel-T may be most effective when administered to mCRPC patients with a low burden of disease. Published and presented data from the sipuleucel-T clinical trials NeoACT (NCT00715104), IMPACT (NCT00065442), ProACT (NCT00715078), PROTECT (NCT00779402), OpenACT (NCT00901342), STAMP (NCT01487863) and STAND (NCT01431391), individually or across trials, were included in this review.*
Results: *Overall, a growing body of evidence supports the concept that sipuleucel-T, like some other immunotherapies, has long term effects that result in an overall survival benefit. mCRPC patients with a low tumor burden may derive a greater therapeutic benefit, since the immune response may be more robust when the disease is less advanced and immunosuppressive effects from the tumor or traditional therapies may be less marked. In addition, treatment with sipuleucel-T in early mCRPC does not preclude subsequent treatment with other approved mCRPC therapies.*
Conclusions: *Collectively, clinical data to date suggest the optimal timing for sipuleucel-T treatment may be early in the mCRPC treatment paradigm.*

Key Words: prostatic neoplasms, sipuleucel-T

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Introduction

Numerous treatments are approved for patients with metastatic castration-resistant prostate cancer (mCRPC). One such treatment is sipuleucel-T, an autologous cellular immunotherapy, which is approved by the US Food and Drug Administration (FDA), for the treatment of men with asymptomatic or minimally symptomatic mCRPC.[1] This approval was supported by data from the randomized, controlled, phase III IMPACT study. With a 34.1 month median follow up, sipuleucel-T demonstrated a 22% reduction in the risk of death (hazard ratio [HR] 0.78; 95% confidence interval [CI] 0.61-0.98; p = 0.03).[2] Overall, sipuleucel-T was well tolerated and < 1% of patients were unable to receive all three infusions due to

infusion-related adverse events (AEs).[2] Evidence-based prostate cancer treatment guidelines in the United States recommend a wide range of treatments for mCRPC, and sipuleucel-T is one of the treatments recommended for patients with asymptomatic or minimally symptomatic mCRPC, and a good performance status.[3,4]

Sipuleucel-T is designed to stimulate an immune response against prostatic acid phosphatase (PAP),[5] as this enzyme is expressed in both normal and malignant prostate cells, and at very low levels elsewhere in the body.[6,7] Clinical trials, such as IMPACT, have demonstrated that sipuleucel-T effectively stimulates immune responses in mCRPC.[2,8,9] Table 1 outlines the characteristics of key sipuleucel-T clinical trials.

In this article, we summarize recent clinical and immunological data from sipuleucel-T clinical trials that suggest a greater therapeutic benefit may be achieved with sipuleucel-T therapy earlier in mCRPC, when patients have a relatively low tumor burden. We review the mechanism of action of sipuleucel-T and the rationale for sequencing this therapy earlier in the course of mCRPC.

Sipuleucel-T treatment overview and key clinical trials

To manufacture sipuleucel-T, the patient's peripheral blood mononuclear cells (PBMCs) are isolated by

TABLE 1. **Key sipuleucel-T clinical trials**

Trial name	Clinicaltrials.gov identifier	N	Patient population	Description	Reference
NeoACT	NCT00715104	42	Localized prostate cancer	Open-label, phase II study investigating sipuleucel-T as neoadjuvant treatment	10
IMPACT	NCT00065442	512	Asymptomatic or minimally symptomatic mCRPC	Pivotal placebo-controlled, phase III study	2
ProACT	NCT00715078	120	Asymptomatic or minimally symptomatic mCRPC	Randomized, single-blind, phase II study to evaluate sipuleucel-T manufactured using different PA2024 concentrations	11
PROTECT	NCT00779402	176	Detectable PSA levels following radical prostatectomy having received 3-4 months of ADT	Phase II, randomized, double-blind, controlled trial investing sipuleucel-T in the androgen-dependent setting	12
STAND	NCT01431391	64	Non-metastatic prostate cancer and a rising serum PSA after primary therapy	Randomized, open-label, phase II trial examining the sequencing of sipuleucel-T and ADT	13,14
OpenACT	NCT00901342	104	mCRPC including patients with symptomatic disease	Open-label, single-arm, phase II study to further evaluate safety and immune responses; provided access to sipuleucel-T prior to FDA approval	15
STAMP	NCT01487863	29	mCRPC	Randomized, open-label phase II trial investigating sipuleucel-T with concurrent versus sequential administration of abiraterone acetate plus prednisone	16

ADT = androgen-deprivation therapy; FDA = Food and Drug Administration; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen

leukapheresis, purified, and co-cultured with PA2024 (a recombinant protein comprising PAP fused to granulocyte-macrophage colony-stimulating factor [GM-CSF]) for approximately 40 hours. The product is then washed and tested for total nucleated cell count, cluster of differentiation (CD) 54+ cell count, and CD54 upregulation. Product meeting the release specifications is delivered to the clinic, generally 2-3 days after the leukapheresis, for infusion over approximately 1 hour, Figure 1. In a full course of therapy, this process is repeated for a total of three infusions of sipuleucel-T, administered approximately every 2 weeks. Thus, a full course of therapy is received over about 1 month. Antigen-presenting cell (APC) activation, an indicator of the sipuleucel-T product potency, is evaluated in each sipuleucel-T

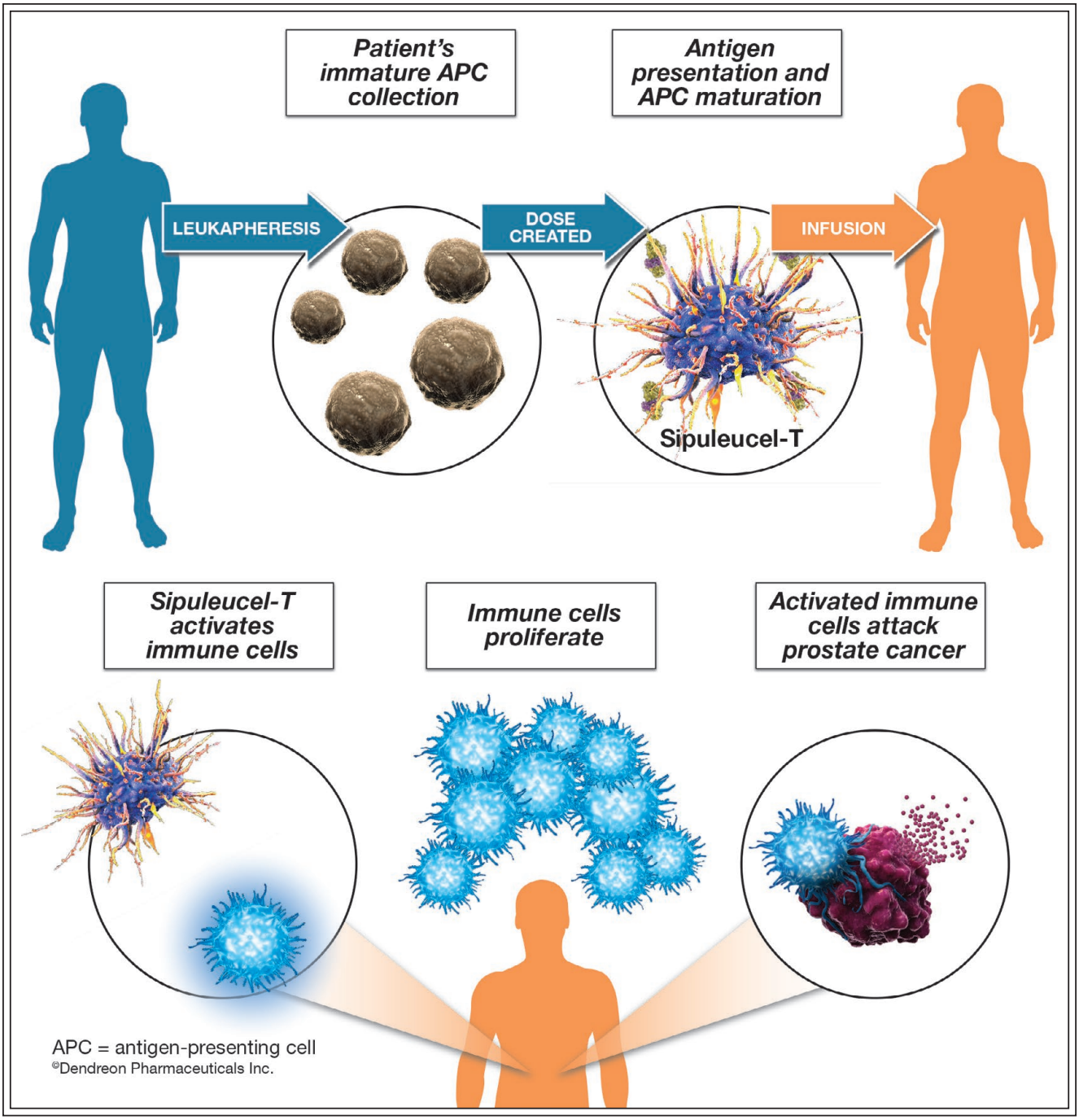

Figure 1. Presumed mechanism of action for sipuleucel-T.

product; APC activation is defined as the ratio of $CD54^+$ molecules post-/pre-incubation with PA2024.[17]

Evidence supporting the presumed mechanism of action of sipuleucel-T

In a pooled analysis of data from three phase III trials of sipuleucel-T in mCRPC, the magnitude of in vitro APC activation during sipuleucel-T manufacture and the development of PA2024- and PAP-specific immune responses correlated with OS.[9] Peripheral immune responses in patients with prostate cancer persisted well beyond the treatment period, as demonstrated by the immune responses noted at week 12 in NeoACT,[10] week 26 in IMPACT,[9] PROTECT,[12] and STAMP,[16] and at 2 years in STAND.[14] In addition, NeoACT (a trial of neoadjuvant sipuleucel-T followed by radical prostatectomy) demonstrated that sipuleucel-T induces immunological effects at the level of the prostate cancer tissue.[10] In this study, a ≥ 3-fold increase in mean tumor-infiltrating lymphocytes per square micrometer, including total T cells (CD3+), T-helper cells (CD3+ CD4+) and cytotoxic T cells (CD3+ CD8+), was detected at the tumor interface by immunohistochemistry compared with pre-prostatectomy biopsy tissue, tumor tissue, and benign tissue (all $p < 0.0001$).[10]

Prolonged but "delayed" action of sipuleucel-T

It has been suggested that the benefits of immunotherapy require time to manifest, compared with faster-acting cytotoxic therapies.[18] Madan et al, proposed a theoretical model to compare the potential impact of cytotoxic therapy and immunotherapy on tumor growth, Figure 2.[18] Cytotoxic agents exert their greatest effect on the neoplasm soon after the initiation of therapy. In contrast, the antitumor immune responses stimulated by immunotherapeutics may take several months to fully develop. However, the beneficial effects of immunotherapy may potentially be more advantageous due to their longer-lasting impact, specifically inducing a memory response, compared with cytotoxic therapeutics, which are direct acting and, therefore, are effective during their administration.[18] In support of this hypothesis, sipuleucel-T therapy usually does not have a positive effect on proximal endpoints such as objective disease response,[8] but does show a statistically significant improvement in median OS.[2,19] This improvement in OS may be due to a dampening of the rate of disease progression. There is evidence from several clinical trials that sipuleucel-T-induced peripheral immune responses are sustained for prolonged periods after the approximately 1 month course, as previously described.[9,10,12,14,16]

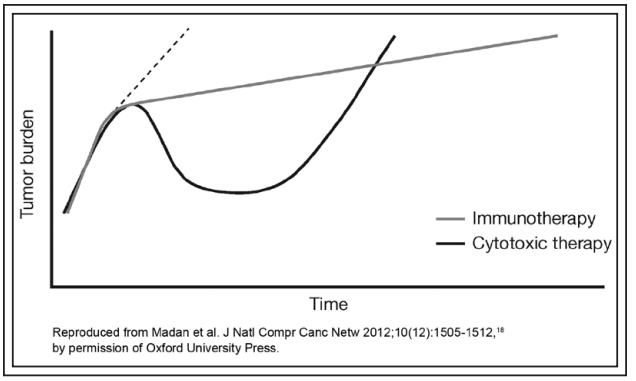

Figure 2. Immunotherapies can alter disease velocity.

Although immune responses resulting from immunotherapy do not appear to be sufficient to reduce the size of the tumor when they are initiated within 3 months of treatment, they do subsequently reduce tumor growth rate.[18,20] In the PROTECT study, patients with androgen-dependent prostate cancer and serologic progression were randomized to receive either sipuleucel-T or control, the prostate-specific antigen doubling time (PSADT) was 48% longer with sipuleucel-T following testosterone recovery, versus control ($p = 0.038$).[12]

The delayed effect of immunotherapy predicted by the Madan model may be further demonstrated by the apparent effects of sipuleucel-T on endpoints that occur later in the natural progression of the disease.[2,19,20] In IMPACT, the median time to objective disease progression was 3.7 months and 3.6 months with an HR of 0.95 (95% CI 0.77-1.17; $p = 0.63$) in the sipuleucel-T and control arms, respectively.[2] In a pooled analysis of IMPACT, D9901, and D9902A, the median time to disease-related pain (an endpoint that occurs generally later in the natural progression of the disease) after objective disease progression was 5.6 months and 5.3 months for the sipuleucel-T and control arms, respectively (HR 0.804; 95% CI 0.602-1.076; $p = 0.142$).[21] When a clinical event later in the natural history of the disease is considered, time to first opioid analgesic was 12.6 months for the sipuleucel-T arm and 9.7 months for the control arm (HR 0.754; 95% CI 0.571-0.995; $p = 0.046$). In this pooled analysis, the Kaplan-Meier curves were seen to diverge after approximately 6 months from time to disease-related pain and time to first opioid analgesic,[21] consistent with the delayed effect of immunotherapy.

Furthermore, a phenomenon called "antigen spread" described by Kudo-Saito et al[22] occurs when a tumor cell, killed by a specific immune targeted therapy, releases other tumor-associated antigens. These tumor-

associated antigens then induce additional immune responses to those antigens that were not part of the initial immune target. In the IMPACT and ProACT studies, immune responses to multiple prostate tumor antigens were detected after sipuleucel-T treatment, suggesting that sipuleucel-T induces antigen spread in mCRPC patients.[23] In STAND, sipuleucel-T mediated antigen spread was maintained through 2 years in patients with biochemically-recurrent prostate cancer (BRPC).[14]

Greater immunological potential in patients with lower versus higher tumor burden

Patients with advanced disease and high tumor burden are likely to be immunocompromised.[24] These patients may be further immunocompromised by other mCRPC treatments such as concomitant high-dose corticosteroids and prior exposure to cytotoxic therapies.[25]

A pooled analysis of 509 patients with localized prostate cancer (NeoACT; n = 41), asymptomatic or minimally symptomatic mCRPC (IMPACT and ProACT; n = 370), and symptomatic mCRPC (OpenACT; n = 98) compared the immunosuppressive effects of prior systemic therapy on sipuleucel-T across different disease states.[26] NeoACT patients were younger with less advanced disease (localized prostate cancer), whereas mCRPC patients had more advanced disease and had more commonly undergone prior chemotherapy.[26] In all disease settings, there was a similar trend in APC upregulation at weeks 2 and 4, relative to week 0, consistent with an immunological prime-boost effect, Figure 3.[26] However, the magnitude of increase was greater in the neoadjuvant setting, compared with more advanced disease ($p < 0.001$). Similarly, within the mCRPC population, the magnitude of APC activation was greater in patients with asymptomatic or minimally symptomatic mCRPC (IMPACT and ProACT) versus patients with symptomatic mCRPC (OpenACT). An immunological prime-boost effect with sipuleucel-T was also seen in BRPC patients in STAND.[13]

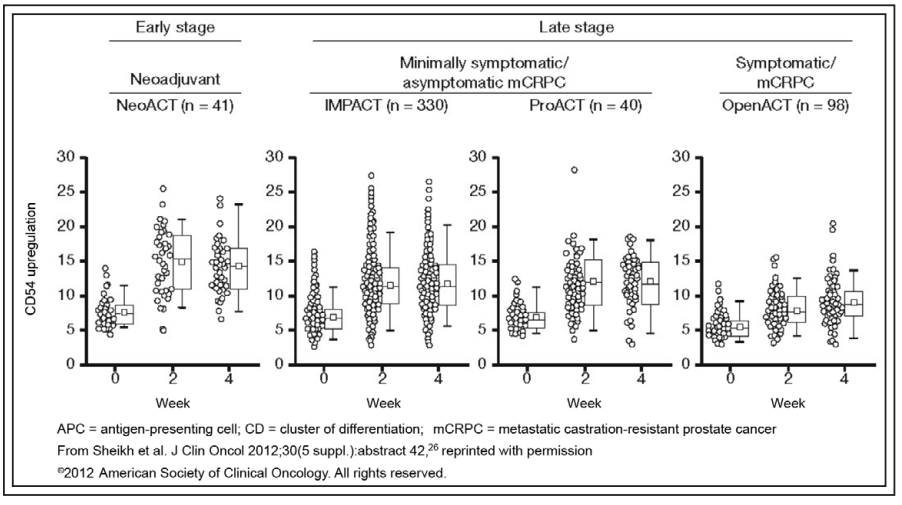

Figure 3. APC activation (CD54 upregulation) is greatest in patients with less advanced disease.[26]

Potential benefits of sipuleucel-T in patients with a lower disease burden

Sipuleucel-T demonstrates a long term but "delayed" benefit, i.e. OS in mCRPC. A recent paper reported that OS improvement with sipuleucel-T in mCRPC may be more robust than previous estimates.[27] Control patients from the three phase III trials with sipuleucel-T had the option of receiving APC8015F (an autologous immunotherapy produced from cells collected during control manufacture and cryopreserved) after disease progression. Median OS was 20.0 (APC8015F, n = 155) versus 9.8 months (control, n = 61) (HR 0.53; 95% CI 0.38-0.74; $p < 0.001$); although more favorable baseline characteristics were seen in the APC8015F group.[27]

Patients with a lower tumor burden and/or less aggressive disease kinetics, who are unlikely to require cytoreductive therapy to reduce tumor burden in the short term, may potentially be suitable for sipuleucel-T treatment as the slow tumor growth pattern may mean that there could be more time for immunological responses to develop. It is now recognized that tumors use immunosuppressive mechanisms to promote tumorigenesis and progression, and evade immune destruction.[28] A high tumor burden is often associated with greater immunosuppression via regulatory T cells, myeloid-derived suppressor cells, and transforming growth factor receptor-β. In patients with a lower disease burden, these factors are found at very low levels[29] and the immune system appears to be more "responsive" than those with a greater disease burden.[30,31] Given the likelihood that the immune response to sipuleucel-T takes several months after administration, patients with a lower tumor burden who have more indolent disease and less prior therapy are probably the best candidates for treatment with sipuleucel-T.

The results of several subgroup analyses of IMPACT data generate the hypothesis that treating patients

TABLE 2. **Overall survival by PSA quartile**[32]

Baseline PSA, ng/mL	**≤ 22.1 (n = 128)**	**> 22.1 to 50.1 (n = 128)**	**> 50.1 to 134.1 (n = 128)**	**> 134.1 (n = 128)**
Median OS, months				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference, months	13.0	7.1	5.4	2.8
HR (95% CI)	0.51 (0.31-0.85)	0.74 (0.47-1.17)	0.81 (0.52-1.24)	0.84 (0.55-1.29)

CI = confidence interval; HR = hazard ratio; OS = overall survival; PSA = prostate-specific antigen. Patients in the lowest PSA quartile had the greatest benefit with sipuleucel-T.
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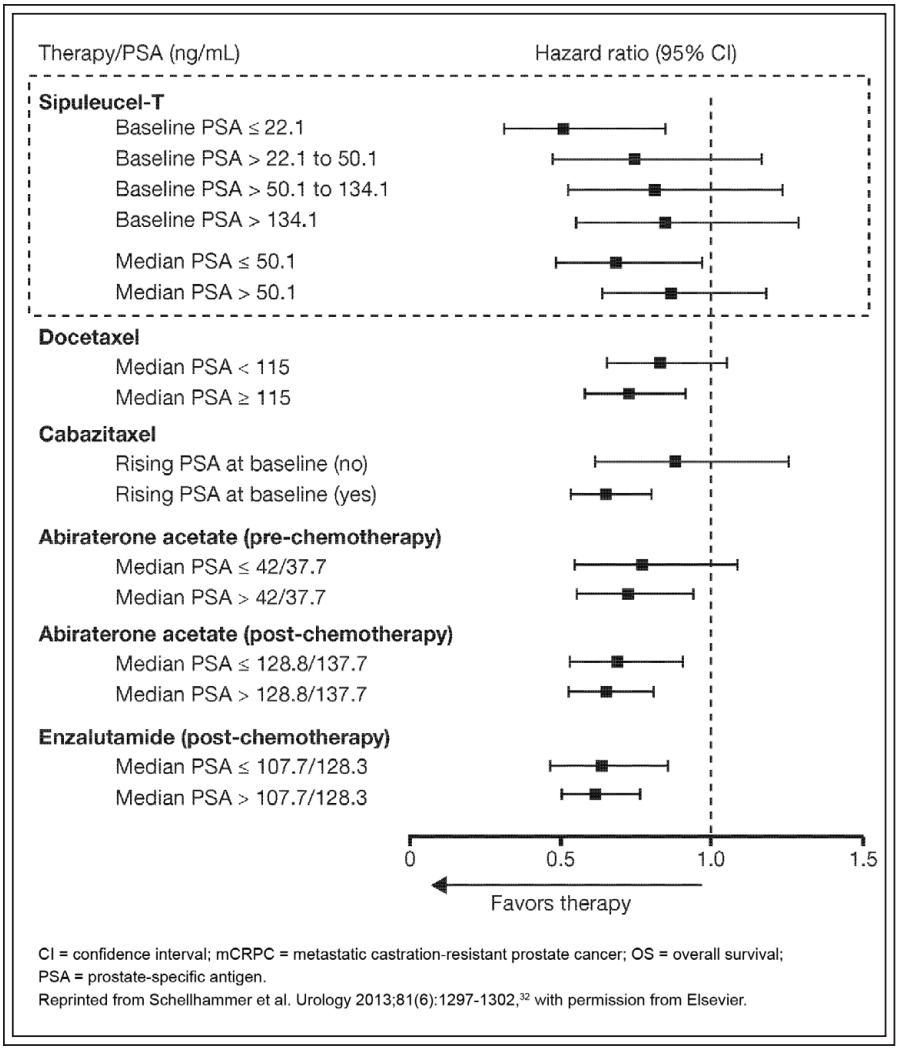
earlier in the course of mCRPC is beneficial. A prespecified subgroup analysis of baseline PSA values showed a greater treatment effect with sipuleucel-T in patients with baseline PSA below versus above the median (HR 0.685 versus 0.865, respectively).[2,32] In a retrospective, post hoc analysis, patients in the sipuleucel-T arm in the lowest PSA quartile had a greater benefit in OS than those in the highest PSA quartile, Table 2.[32] The effect of baseline PSA on outcome differs from findings with other active agents in mCRPC, Figure 4,[32] but is consistent with the model proposed by Madan and colleagues in which immunotherapy may result in an increased magnitude of benefit for patients with lower disease burden.[18]



CI = confidence interval; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PSA = prostate-specific antigen.
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Figure 4. Summary of OS in mCRPC trials by baseline PSA.[32]

Data on bone metastases in IMPACT also support this hypothesis.[33] Spiuleucel-T-treated patients with the lowest baseline metastatic burden and slowest tumor growth rates had the longest OS and prostate cancer-specific survival (PCSS), Table 3.[33] Primary factors associated with longest OS and PCSS included: baseline bone scan with < 7 lesions; increase of ≤ 2 in the number of lesions at week 10 versus baseline; and increase of ≤ 5 in the number of lesions at week 18 versus baseline.[33] In a blinded radiographic assessment, 13 of 14 (93%) and 6 of 9 (67%) patients with PCSS were correctly predicted to have the longest

TABLE 3. **Bone scans predict survival**

Bone scans reviewed for patients treated with sipuleucel-T	Actual median OS, months	Halabi-predicted OS months	Predicted by radiologist, n	Correctly predicted by radiologist, n (%)
OS (n = 26)				
Long OS (n = 16)	54.2	27.1	17	13 (76)
Short OS (n = 10)	10.8	17.9	9	6 (67)
PCSS (n = 23)				
Long OS (n = 16)	54.2	27.1	14	13 (93)
Short OS (n = 7)	10.8	15.8	9	6 (67)

OS = overall survival; PCSS = prostate cancer-specific survival.
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or shortest OS, respectively (significantly different from a 50% rate of uninformed correct prediction; $p < 0.01$, Fisher's exact test). Collectively, these data suggest that less aggressive disease kinetics may allow more time for a positive treatment effect with sipuleucel-T.

Subsequent therapy after administration of sipuleucel-T

It is important to consider the decision-making process regarding the timing and choice of therapy for the individual patient after completion of sipuleucel-T. Compared with other therapies for mCRPC, sipuleucel-T is administered over a short time period and is generally very well tolerated,[2,10,12,14,16] so patients are unlikely to experience side effects requiring a long recovery period prior to starting another therapy. Some patients with indolent disease may not require immediate additional therapy, whereas those with more rapid tumor growth may benefit from additional therapy soon after completion of sipuleucel-T infusions.

Options for therapy after sipuleucel-T (outside of a clinical trial) include hormonal agents such as abiraterone acetate/prednisone or enzalutamide, docetaxel chemotherapy, or radium-223 radioisotope therapy. Both abiraterone acetate/prednisone and enzalutamide[34] are FDA-approved for use prior to docetaxel administration. The advantage of enzalutamide is that it does not require the use of low-dose prednisone which could alter the immune response to sipuleucel-T. However, data from STAMP study (abiraterone acetate and prednisone started simultaneously with sipuleucel-T or just after sipuleucel-T) demonstrate that low-dose prednisone does not adversely impact the product parameters defined by in vitro APC activation.[16] The effect of low-dose prednisone on long term in vivo immunity or efficacy of sipuleucel in the STAMP trial is unknown. A similar trial of concurrent or sequential enzalutamide and sipuleucel-T is in progress (STRIDE). A subgroup analysis of patients in the IMPACT trial indicated that sipuleucel-T had a survival benefit in patients whether or not they received docetaxel.[2]

Based on a subgroup analysis from the ALSYMPCA trial,[35] addition of radium-223 after sipuleucel-T may be a good choice if there are > 6 bone metastases (those with < 6 bone metastases did not derive the same magnitude of benefit). In addition, since radium-223 is a bone-directed therapy, it should only be used as a single agent when there are no visceral or significant nodal metastases. Combination trials (radium-223 plus enzalutamide or abiraterone acetate) are in progress and may offer yet further treatment options after sipuleucel-T.

Conclusion

Sipuleucel-T was the first immune therapy approved for prostate cancer, and has been shown to improve OS compared with placebo. Optimal sequencing of the newer agents discussed above may improve OS as well as potentially providing earlier anti-tumor effects. Understanding how these additional therapies affect the immune response will be important in evaluating how best to sequence these agents with immunotherapy.

Disclosures

EDC has acted as a consultant and advisor to Dendreon. DPP, CSH, ASK, NDS and AF have received research support from Dendreon, and have served on advisory boards for Dendreon. ASK and AF are principal investigators on Dendreon-sponsored clinical trials. PWK has served on advisory boards for Dendreon. EJS has no disclosures. □

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