

# The Rationale for Optimal Combination Therapy With Sipuleucel-T for Patients With Castration-resistant Prostate Cancer

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Immunotherapy encourages the recipient's own immune response to destroy cancer cells, and current evidence suggests that immunotherapies may be most beneficial in early metastatic castration-resistant prostate cancer (mCRPC). Sipuleucel-T is the first therapeutic cancer vaccine to be approved by both the US Food and Drug Administration and European Medicines Agency for the treatment of asymptomatic or minimally symptomatic mCRPC. Combining immunotherapy with other treatments may have potent anticancer effects; cytoreductive therapies can release tumor antigens and promote a proinflammatory environment that could augment immunotherapies. However, some cytoreductive agents or coadministered drugs may be immunosuppressive. Understanding these interactions between different mCRPC treatment modalities may offer further potential to improve patient outcomes.

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## KEY WORDS

Combination therapy • Prostate cancer • Sipuleucel-T

Immunotherapy has emerged as a powerful tool against prostate cancer, in addition to surgery, radiotherapy, hormone therapy, and chemotherapy. For 30 years, investigators tried to rebalance the compromised immune system in patients with urologic cancers using a number of different agents.<sup>1,2</sup> In April 2010, the autologous cellular immunotherapy sipuleucel-T became the first therapeutic

cancer vaccine to be approved by the US Food and Drug Administration (FDA).<sup>3</sup> This therapy targets the prostatic acid phosphatase (PAP) and has been indicated for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC), based on results from three randomized, controlled, phase 3 studies.<sup>3-6</sup> Recently, sipuleucel-T was also approved

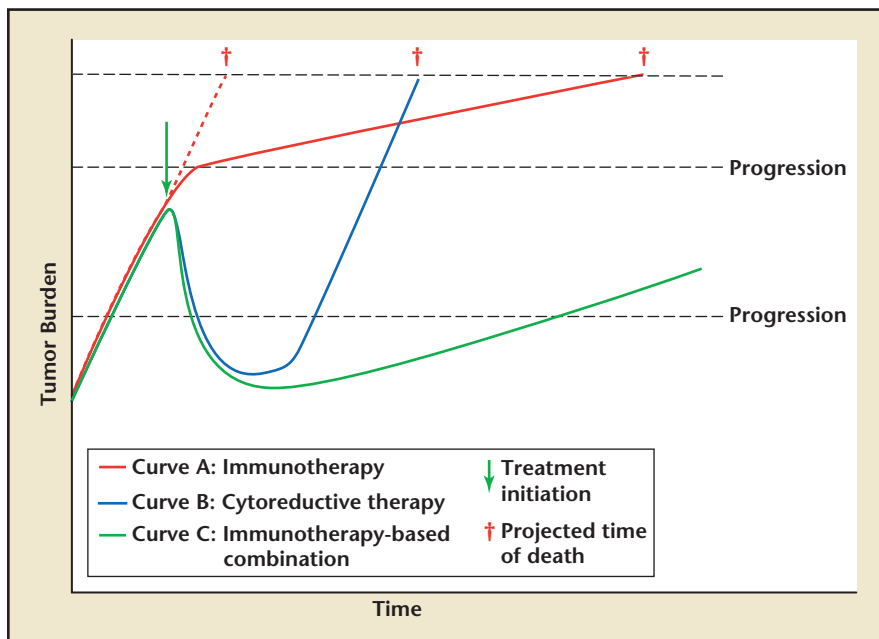


Figure 1. Theoretical growth-moderating effect of (A) immunotherapy or (B) cytoreductive therapy as monotherapies, or (C) in combination. Adapted from Madan RA et al<sup>10</sup> and Schlom J.<sup>11</sup>

by the European Medicines Agency (EMA) for the treatment of asymptomatic or minimally symptomatic mCRPC in men in whom chemotherapy is not yet clinically indicated.<sup>7</sup>

Although this immunotherapy has been shown to extend overall survival (OS),<sup>5</sup> sequencing or combining immunotherapy with other treatments for mCRPC has the potential to further improve outcomes.<sup>8,9</sup> However, before immunotherapy-based combination regimens can be integrated into clinical practice, it is critical to have a better understanding of the interactions between these different modalities.

## Evidence Acquisition

This article focuses primarily on sipuleucel-T, which is the only currently available immunotherapy for mCRPC. Manuscripts and conference abstracts that reported key sipuleucel-T clinical trials and subanalyses were identified. Other information on sipuleucel-T available through the FDA and EMA

was searched. Additional publications relevant to immunotherapies in general and other specific immunotherapies were identified, and relevant Web sites such as clinicaltrials.gov were also searched.

## Evidence Synthesis

This article presents clinical data on combining immunotherapies, particularly sipuleucel-T, with other treatments for prostate cancer. In the absence of clinical data, theoretical or other relevant information is included.

### Immunotherapy

By definition, cancer immunotherapies enhance anticancer immune responses, helping the body to control cancerous cells. This mechanism of action is clearly distinct from that of traditional therapies such as radio- or chemotherapy. Indeed, a kinetic model of tumor growth rate has been proposed for patients receiving immunotherapy versus cytoreductive therapy (Figure 1).<sup>10,11</sup> In this model, immunotherapies slow tumor growth

rate over time without producing the marked short-term tumor shrinkage that is the hallmark of cytoreductive therapy. This may explain the improved OS observed after immunotherapy, without an increase in time to progression in advanced prostate cancer.

Data for sipuleucel-T support this model. Sipuleucel-T is an autologous cellular immunotherapy, produced by culturing the patient's purified peripheral blood mononuclear cells with a recombinant fusion protein of PAP coupled to granulocyte-macrophage colony-stimulating factor (GM-CSF).<sup>3</sup> These cells are then reinfused into the patient, where the product is designed to generate a prostate cell-specific immune response.<sup>3</sup> Consistent with the kinetics of the immunotherapy model described above, the pivotal phase 3 sipuleucel-T study, Immunotherapy Prostate Adenocarcinoma Therapy (IMPACT), did not show a significant effect on time to disease progression, but rather demonstrated a statistically significant improvement in the primary endpoint of OS.<sup>5</sup> There was a 22% relative reduction in the risk of death with sipuleucel-T versus the placebo group, which represents a survival increase of 4.1 months for the sipuleucel-T group (25.8 vs 21.7 months).<sup>5</sup> The 36-month survival probabilities were 31.7% and 23.0% in the sipuleucel-T and placebo groups, respectively.<sup>5</sup> These data are supported by an integrated analysis of two earlier phase 3 trials, D9901 and D9902A, which also demonstrated a survival benefit for patients treated with sipuleucel-T versus placebo.<sup>4</sup> The survival benefit following sipuleucel-T treatment is associated with the development of immune responses,<sup>12</sup> confirming the immunomodulatory effects of therapy. In addition, the concept that immunotherapy slows tumor

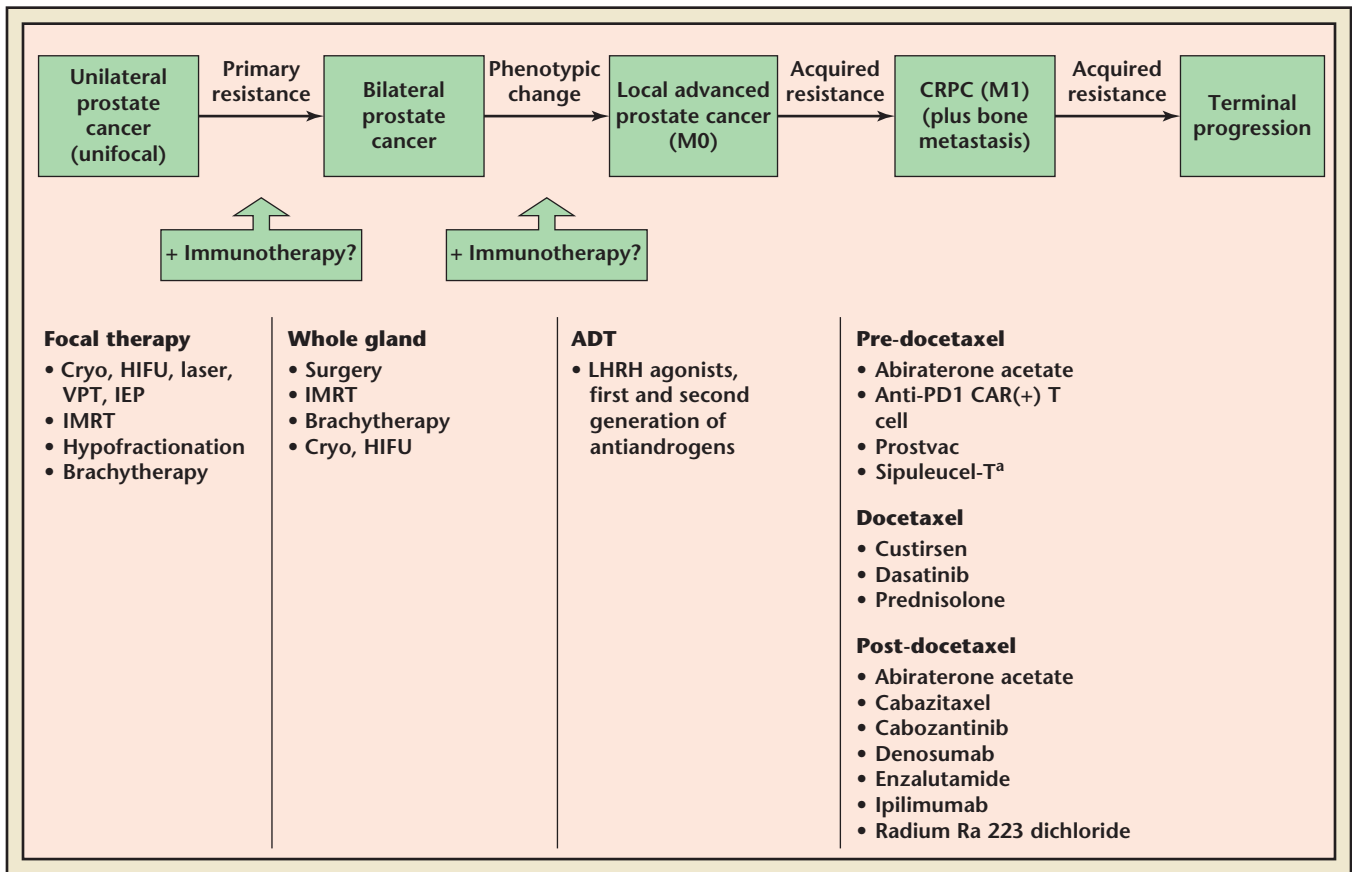


Figure 2. The position of sipuleucel-T treatment and other modalities in the natural course of prostate cancer. <sup>a</sup>Approved indication. ADT, androgen deprivation therapy; CAR, chimeric antigen receptor; Cryo, cryoablation; CRPC, castrate-resistant prostate cancer; HIFU, high-intensity focused ultrasound; IEP, irreversible electro-poration; IMRT, intensity-modulated radiation therapy; LHRH, luteinizing hormone-releasing hormone; M0, nonmetastatic; M1, metastatic; PD, programmed death; VPT, vascular photodynamic therapy.

growth is supported by the lengthening of prostate-specific antigen (PSA) doubling time with sipuleucel-T versus control that was noted in patients with androgen-dependent prostate cancer.<sup>13</sup> Sipuleucel-T was generally well tolerated in the phase 3 trials, and most patients received all three of the scheduled infusions.<sup>4,5</sup> Although traditional short-term markers of success, such as a reduction in PSA levels, are not associated with the OS benefit of sipuleucel-T treatment, the development of antigen-specific immune responses during therapy are associated with OS.<sup>12</sup> Some of these immunologic effects, such as a transient increase in circulating eosinophil levels, may prove to be useful future markers of treatment success.<sup>14</sup>

Patients with a relatively low mCRPC disease burden appear

to benefit most from immunotherapy with sipuleucel-T; those with the lowest PSA baseline levels had the greatest OS benefit compared with control treatment.<sup>5,15</sup> A 49% reduction in the risk of death (hazard ratio [HR] 0.51; 95% confidence interval [CI], 0.31-0.85) and a median OS difference of 13.0 months was achieved by patients in the lowest baseline PSA quartile (< 22.1 ng/mL), compared with a 16% reduction in the risk of death (HR 0.84; 95% CI, 0.55-1.29) and a 2.8 month median OS difference for patients in the highest PSA quartile (> 134 ng/mL).<sup>15</sup>

Indeed, patients treated early in mCRPC may be less immunocompromised, have more time for the immune system to respond, and have an increased opportunity for prolonged OS improvement.<sup>11,15</sup> These findings suggest that, in

terms of the current prostate cancer treatment paradigm (Figure 2), immunotherapy may be best placed early in the mCRPC treatment course.

Another interesting aspect of immunotherapy that may help to explain its long-term benefits is antigen spread, which is also called *epitope spreading* or *determinant spreading*. This is a process in which the immune response, which initially targets defined antigenic peptides, begins to target additional antigens that are distinct from the initial target(s) and may be derived from completely different proteins.<sup>16</sup> This process is facilitated by cellular toxicity or apoptosis; dead cells are taken up by activated antigen-presenting cells (APCs) that can then stimulate immune responses against different molecular targets from

within the same tissues as the original target.<sup>16</sup> Preliminary studies on immunotherapy suggest that there is a high frequency of antigen spreading in clinical responders, whereas nonresponders may not display reactivity to antigens other than those used for the original treatment.<sup>16</sup> This phenomenon has been noted during sipuleucel-T treatment, which initially targets the immune response against PAP. Patients treated with sipuleucel-T consistently mounted elevated IgG antibody responses against a range of cancer antigens, whereas patients in the control arm did not.<sup>17</sup> These responses were associated with improved OS.<sup>17</sup>

*Several planned or ongoing clinical studies are currently investigating cytoreductive therapies in combination with sipuleucel-T.*

Although this article focuses on sipuleucel-T, as it is the only currently available immunotherapy for prostate cancer, other immunotherapies currently in development for the treatment of prostate cancer include PSA-TRICOM (recombinant viral therapy encoding PSA and the costimulatory molecules cluster of differentiation 80, intercellular adhesion molecule-1, and lymphocyte function-associated antigen-3),<sup>18,19</sup> ipilimumab (monoclonal antibody that blocks the immunoregulatory molecule cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]),<sup>19,20</sup> GVAX (GM-CSF-transduced allogeneic prostate cancer cells),<sup>21,22</sup> and modified T-cell therapy (anti-prostate-specific membrane antigen chimeric antigen receptor T cells).<sup>23</sup>

## Potential Combination Therapies for Patients With mCRPC

In addition to immunotherapy, recent advances in the treatment of mCRPC have also introduced novel, cytoreductive,

nonchemotherapeutic targeted treatments (Figure 3).<sup>24</sup>

Cytoreductive therapy for mCRPC encompasses a broad spectrum of approaches, including systemic chemotherapy, radiation therapy, and secondary hormone therapies (eg, novel antiandrogens such as abiraterone acetate and enzalutamide). Cytoreductive therapies provide a transient decrease in tumor size, whereas immunotherapies slow the tumor growth rate and have a long-term effect (Figure 1). Therefore, theoretically, combining immunotherapy and cytoreductive therapy could produce both an immediate and long-lasting effect on tumor burden (curve C in Figure 1). This

concept supports the use of combination therapy early in the mCRPC treatment paradigm, in order to maximize the long-term benefits. In addition, this combination has the potential to be synergistic; cytoreductive therapy initiates the release of large amounts of tumor antigens, which may facilitate the development of immune responses. However, some cytoreductive therapies may have immunosuppressive effects, so the timing of concurrent or sequential use of cytoreductive treatments with immunotherapies requires careful consideration and investigation. Several planned or ongoing clinical studies are currently investigating cytoreductive therapies in combination with sipuleucel-T (Table 1).

### *Immunotherapy Plus Chemotherapy or Radiotherapy*

The combination of immunotherapy and radiotherapy may also hold promise for patients with mCRPC. In addition to reducing tumor burden, radiotherapy can

be immunostimulatory under certain circumstances.<sup>25</sup> For example, a rare phenomenon is the abscopal effect in which radiotherapy leads to regression of tumors distant from the site to which it is administered, and is believed to occur through stimulation of antitumor immune responses. In fact, there is evidence that radiation-induced tumor cell death and related changes in antigen expression and inflammatory signals can affect lymphocyte and dendritic cell activation.<sup>26,27</sup> It is therefore logical that the immunostimulatory effects of radiotherapy could be augmented by immunotherapy.

Two ongoing, phase 2 studies are evaluating sipuleucel-T and radiotherapy for patients with mCRPC, one in combination with external beam radiation therapy (EBRT) to a single site of metastasis, and one with stereotactic ablative body radiation to multiple metastatic sites (Table 1). The use of ipilimumab after low-dose, palliative radiation therapy is also being investigated in mCRPC (NCT00861614). Combinations that may be of additional future interest could include the administration of radium Ra 223 dichloride concurrently with, or prior to, sipuleucel-T treatment. Radium Ra 223 dichloride is an alpha particle-emitting radioactive therapeutic agent that was recently approved by the FDA and is indicated for the treatment of patients with mCRPC, symptomatic bone metastases, and no known visceral metastatic disease.<sup>28</sup> Approval was based on a large, phase 3 study that showed improved OS with radium Ra 223 dichloride versus placebo.<sup>29</sup>

Although cytotoxic chemotherapy and the concomitant use of corticosteroids can be immunosuppressive, the immunostimulatory effects of radiotherapy may also be seen with chemotherapy.<sup>30</sup> Indeed,

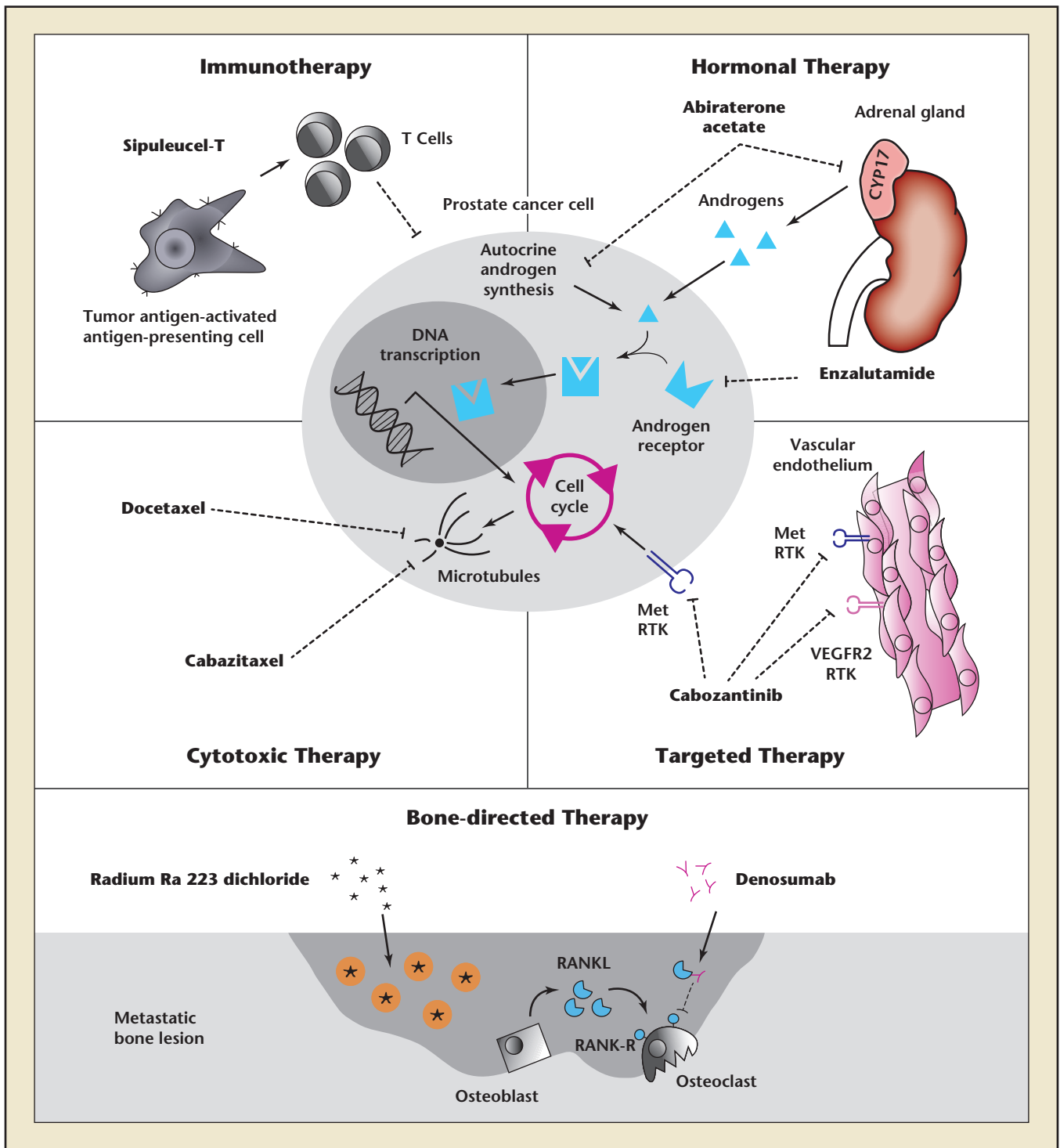


Figure 3. Potential modalities to be used as a combinatorial approach for castration-resistant prostate cancer. Reproduced with permission from Galsky MD et al.<sup>24</sup> CYP17 indicates a cytochrome p450 complex involved in adrenal steroidal synthesis; Met RTK, Met receptor tyrosine kinase; VEGFR2, vascular endothelial growth factor receptor 2; RANKL, receptor activator of nuclear factor  $\kappa$ -B ligand; RANK, receptor activator of nuclear factor  $\kappa$ -B.

there is evidence that combining cytotoxic chemotherapy with immunotherapy can be beneficial under certain circumstances. For example, in a murine model of prostate cancer, low-dose cyclophosphamide given prior to GVAX greatly

enhanced immune responses, resulting in tumor regression.<sup>31</sup> The dosage and timing of cyclophosphamide were critical in this study, with additive effects observed only when cyclophosphamide was given 1 day before immunotherapy and

only with doses that did not result in T-cell depletion. Similarly, in preclinical models, chemotherapy converted the tumor into a site permissive for the activation of an adaptive immune response.<sup>32</sup> In addition, regulatory T cells may be



**TABLE 1****Ongoing and Completed Phase 2 Clinical Studies of Sipuleucel-T in Combination With Other Modalities for mCRPC<sup>a</sup>**

ClinicalTrials.gov Identifier	Combination Therapy	Planned or Estimated Enrollment (N)	Primary Endpoint	Study Status
<b>Sipuleucel-T Combined With Nonimmunotherapies for mCRPC</b>				
NCT01818986	Sipuleucel-T and stereotactic ablative body radiation	41	To evaluate an improvement in time to progression compared with historical data for sipuleucel-T alone	Recruiting
NCT01807065	Sipuleucel-T with or without radiotherapy	50	Proportion of patients able or willing to receive all three injections of sipuleucel-T	Recruiting
NCT01981122 (P12-2)	Concurrent vs sequential treatment with sipuleucel-T and enzalutamide	100	To evaluate T cell responses (proliferation) over the course of therapy	Recruiting
NCT01487863 (P11-3)	Concurrent vs sequential treatment with sipuleucel-T and abiraterone acetate	60	To evaluate cumulative CD54 upregulation over the course of sipuleucel-T therapy	Ongoing
NCT00027599	Sipuleucel-T plus bevacizumab	25	To determine efficacy in terms of decline in PSA value and effect on PSA doubling time	Completed
<b>Sipuleucel-T Combined With Other Immunotherapies for mCRPC</b>				
NCT01706458	Sipuleucel-T with or without pTVG-HP DNA booster vaccine	30	To measure immune responses	Recruiting
NCT01560923	Sipuleucel-T with indoximod or placebo	50	To assess the augmentation of immune response with indoximod or placebo	Recruiting
NCT01420965	Sipuleucel-T with or without CT-011 and cyclophosphamide	57	To test the effectiveness of combined treatment	Recruiting
NCT01804465	Sipuleucel-T with immediate vs delayed ipilimumab	66	To assess safety and antibody responses	Ongoing

<sup>a</sup>Based on studies listed on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) on March 18, 2014.

CD, cluster of differentiation; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

more sensitive to low-dose cyclophosphamide treatment than other cells,<sup>33</sup> offering further insights into how this treatment could boost antitumor immune responses. Patients with high-risk, localized prostate cancer undergoing radical prostatectomy are currently being recruited for a neoadjuvant study evaluating the combination

of GVAX, cyclophosphamide, and androgen ablation (NCT01696877). The study is expected to be completed in October 2015. Importantly, the sequential use of chemotherapy 6 or fewer months prior to sipuleucel-T treatment did not appear to have a deleterious effect on APCs in the phase 4 A Registry of Sipuleucel-T Therapy in Men

with Advanced Prostate Cancer (PROCEED) study, and sipuleucel-T could be generated with similar product parameters as in patients who had not received previous docetaxel treatment.<sup>34</sup> In addition, docetaxel after sipuleucel-T treatment was associated with a significantly higher median OS compared with docetaxel after placebo in the

phase 3 D9901 and D9902A studies ( $P = .023$ ).<sup>35</sup>

### ***Immunotherapy Plus Novel Antiandrogens***

Several planned or ongoing clinical studies are investigating novel antiandrogens in combination with sipuleucel-T. The ongoing, randomized, phase 2 P11-3 study is investigating abiraterone acetate and prednisone given concurrently with sipuleucel-T or approximately 6 weeks afterward in asymptomatic or minimally symptomatic mCRPC (Table 1).<sup>36</sup> In preliminary findings, despite the known immunosuppressive action of prednisone, no significant differences were reported in immunologic parameters such as APC activation, total nucleated cell and APC count, or antigen-specific humoral and cellular immune responses between sequential or concurrent administration.<sup>36</sup> In addition, the ongoing, randomized, phase 2 P12-2 trial is exploring concurrent or sequential administration of sipuleucel-T and the androgen receptor inhibitor enzalutamide (Table 1). Two ongoing phase 2 studies are also evaluating enzalutamide plus PSA-TRICOM versus enzalutamide alone in patients with chemotherapy-naïve mCRPC or nonmetastatic prostate cancer (NCT01867333 and NCT01875250, respectively).

### ***Combining Multiple Immunotherapies***

The immunotherapy repertoire is broadening, and early clinical studies have suggested that combining immunotherapies with a different but complementary mode of action may enhance immune responses.<sup>8</sup> For example, in a phase 1 study in mCRPC, combined treatment with PSA-TRICOM and ipilimumab did not exacerbate the known immune-related adverse events associated with ipilimumab

use, and many patients experienced a PSA decline from baseline.<sup>19</sup> Similarly, the combination of ipilimumab and GVAX resulted in substantial PSA declines for some mCRPC patients.<sup>37</sup> Preclinical data have also suggested that combining agents that block CTLA-4 and programmed death-1 may boost tumor-specific immune responses.<sup>38</sup> An overview of ongoing phase 2 clinical studies investigating sipuleucel-T combined with other immunotherapies for the treatment of mCRPC is shown in Table 1.

### **Future Development: Concepts for Combining Immunotherapies and Other Treatment Modalities in Earlier-Stage Prostate Cancer**

#### ***Immunotherapy Plus Androgen Deprivation Therapy***

Combining androgen deprivation therapy (ADT) and immuno-

PSA and without any evidence of systemic progression.<sup>41</sup> The phase 2 Sequencing of Sipuleucel-T and ADT in Men with Nonmetastatic Prostate Cancer (STAND) trial (NCT01431391) is evaluating sipuleucel-T either 2 weeks before or 3 months after the start of ADT in 68 men with biochemically recurrent prostate cancer at high risk for metastasis.<sup>42</sup> Preliminary data suggest that tumor-specific immune responses are augmented when sipuleucel-T is administered after ADT.<sup>42</sup> Similarly, an ongoing, open-label, crossover, phase 1 study is investigating type 1 dendritic cell-based immunotherapy in combination with androgen ablation for patients with nonmetastatic, hormone-sensitive prostate cancer (NCT00970203). These novel type-1 polarized dendritic cells are mature cells with an increased ability to stimulate T helper 1 type immune responses, which are pro-inflammatory and may mediate tumor elimination.<sup>2</sup>

*Evidence suggests that combining an immunotherapy with thermo- or cryoablation may improve survival in patients with early-stage disease.*

therapy is an attractive therapeutic option, due to the acceptable toxicity profile of both agents, as well as the potential immunological action of ADT. ADT encourages T-cell trafficking to the prostate and decreases immune tolerance to self-antigens that are overexpressed on prostate cancer cells.<sup>39</sup> ADT has also been shown to induce the thymus to produce naive T cells, which could then be activated by immunotherapy.<sup>40</sup> With regard to timing, the most appropriate opportunity to use this combination may be at early biochemical recurrence after primary definitive therapy, when up to 40% of men present with slowly rising

#### ***Immunotherapy Plus Thermoablation or Cryoablation***

Cytoreductive therapies can result in necrotic cell death and release large amounts of tumor antigen, which can facilitate the development of an antitumor immune response. In a similar way, thermoablation has been shown to induce necrotic cell death in preclinical studies<sup>43</sup> and cryoablation may also have immunostimulatory effects.<sup>44,45</sup> Evidence suggests that combining an immunotherapy with thermo- or cryoablation may improve survival in patients with early-stage disease.<sup>45</sup> There is some preclinical evidence that

high-intensity focused ultrasound tumor ablation may also be immunostimulatory,<sup>46</sup> potentially through similar mechanisms.

### *Immunotherapy Plus External Beam Radiation Therapy*

In a small study of clinically localized prostate cancer, 36 patients were treated with EBRT plus a poxviral vector-based immunotherapy, and 7 patients were treated with EBRT alone.<sup>47</sup> There were no significant differences between the treatment groups with or without immunotherapy in terms of OS and prostate cancer-specific survival. However, this was a very small study, and long-term immune responses were not generated, suggesting that the overall treatment regimen may not have been optimal.

### *Combined Immunotherapies*

Although studies of combined immunotherapies for patients with early-stage prostate cancer are not ongoing, this is a potential combination strategy.

## Conclusions

The treatment paradigm for mCRPC is evolving rapidly.

Combining sipuleucel-T or future immunotherapies for mCRPC with other agents may offer substantial clinical benefits to patients. Combining a cytoreductive treatment with immunotherapy has the potential to rapidly diminish tumor burden and then slow cancer growth in the long term, extending OS. Furthermore, cytoreductive therapies can release tumor antigens and may promote a proinflammatory environment in and around the cancer lesion that could augment the action of immunotherapies. Preliminary evidence suggests that it may be possible to combine immunotherapy with radiotherapy, chemotherapy, or novel antiandrogens for mCRPC, but further clinical data are needed, as some of the cytoreductive agents, or coadministered drugs, can have immunosuppressive effects. Investigating the optimal timing and dosages will be essential to effectively combine or sequence these different therapeutic approaches. The use of immunotherapies with treatment modalities used in even earlier stages of prostate cancer is also under investigation. ■

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## MAIN POINTS

- The treatment paradigm for metastatic castration-resistant prostate cancer (mCRPC) is evolving rapidly. The first US Food and Drug Administration–approved vaccine for the treatment of asymptomatic or minimally symptomatic mCRPC, sipuleucel-T, or future immunotherapies, combined with other agents may offer substantial clinical benefit to patients.
- Based on their success in decreasing tumor size, cytoreductive therapies can release tumor antigens and may promote a proinflammatory environment in and around the cancer lesion that could augment the action of immunotherapies.
- The combination of immunotherapy with radiotherapy, chemotherapy, or novel antiandrogens for mCRPC holds promise, but further clinical data are needed, as some of the cytoreductive agents, or coadministered drugs, can have immunosuppressive effects.
- Further studies on the interactions between different mCRPC treatment modalities, and investigation of the optimal timing and dosages are necessary to determine the most effective combinations and/or sequences of these approaches.



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