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Sipuleucel-T: Prototype for Development of Anti-tumor Vaccines

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Abstract Prostate cancer immunotherapy officially debuted with the recent FDA approval of Sipuleucel-T. The novel trend of cancer immunotherapy relies on the identification of particular tumor-associated antigens, like prostatic acid phosphatase (PAP). Sipuleucel-T consists of autologous dendritic cells activated in vitro with recombinant fusion protein PA2024, PAP-linked to granulocyte-macrophage colony-stimulating factor. Sipuleucel-T represents a prototype for the development of cancer vaccines. Preclinical and clinical data as well as landmark studies for the existing narrow chemotherapy alternatives and early immunotherapy trials will be discussed. The pivotal trial demonstrated a 4.1-month difference of median survival, but with no effect on time to progression in asymptomatic or minimally symptomatic metastatic castrate-resistant patients. Several immunologic effects were observed in the treated population, including antibody and T cell–specific activity to P2024 and PAP. With all new therapies the extent of clinical and objective benefits versus encountered limitations should be evaluated. This review highlights the events and decisions in the process of the development of Sipuleucel-T. We discuss how this successful immunotherapy outcome challenges us to use it as a starting point for variations to or try to amplify practical anticancer progress within the antitumor vaccine paradigm.

Keywords Dendritic cell vaccine · Vaccines · Immunotherapy · Prostate cancer · PAP-GM-CSF fusion protein

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Introduction

Defining the Scope of a Cancer Immunotherapy Development Project

The appeal of immunological anticancer treatment is diverse. For the patient, it may represent a holistic expiation of the disease state or just therapy with a chance for nontoxic life extension. The clinician may view the interplay of understanding both the mechanism of the treatment and the disease features defining susceptibility. For the scientist, conceptual validation in clinical application represents the challenge of the complexity of human anticancer immunology. Industry faces infrastructure development coupled to a highly valued, critical unmet need.

The US FDA approval of sipuleucel-T (Provenge; Dendreon Corporation, Seattle, WA) at the end of April 2010 marked an unprecedented milestone in development of a personalized immunologic product for anticancer therapy. The triumph puts it ahead of many nuanced, appealing concepts—often tied to astonishing effectiveness in murine models or proof-of-concept early-phase clinical trials. It is the first such immunotherapy for which there is realization of a marketed product. The positive trial of CTLA-4 blockade (ipilimumab) with vaccine therapy in therapy of melanoma promises a further expansion of the immune anticancer paradigm [1••], and the manufacturer (BMS) has opened an ipilimumab therapy pivotal trial in prostate cancer [2].

From Concept to Practice

Data for the pivotal trial of sipuleucel-T are described in the most recent summary publication [3••] and in less-final subsets in a series of presentations at national and

international oncology and urology meetings, and publications [4, 5•, 6]. While the pivotal trial meets the benchmark of prolonged overall survival, and several secondary immune-response evaluations, the acceptance and understanding are not universal. The absence of an observed effect on disease time-to-progression, objective response on PSA, and objective response of measurable disease are three features for which some see some basis for discussion. A separate issue is the magnitude of the survival increment and the pricing model.

Figure 1 illustrates some of the decision points that were addressed on the road to sipuleucel-T implementation. The mechanistic relevance and the definition of the population for treatment of these many decision points are not always obvious. We discuss here the choices within the conceptualization behind the treatment as presented in the pivotal trial publication [3••] and on the product label, practical issues and choices in the implementation of the clinical trial, and a review of the trial results—emphasizing the immunologic features that could lend to refinement of treatments and contrasting with some other recent prostate cancer pivotal trials.

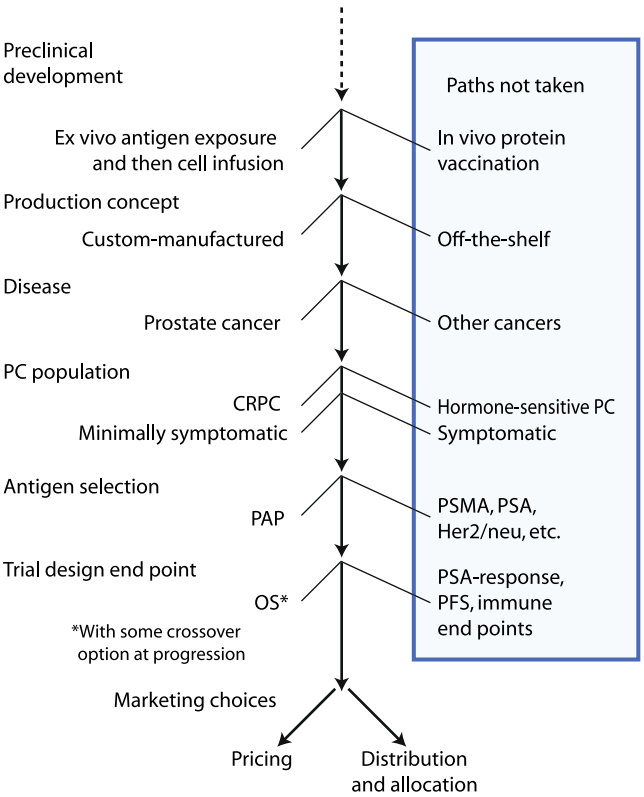

Fig. 1 Diagram depicting a series of development decisions in the implementation of sipuleucel-T for the current indication, starting from preclinical development and ending with marketing. CRPC, castration-resistant prostate cancer; OS, overall survival; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen

Choices of Conceptualization

Defining a Target Clinical Population

The identification of the niche for an anticancer therapeutics project is an early decision point. Murine xenograft systems seem almost histology-independent, with similar responses generated toward tumor types that are divergent, from a clinical perspective. Both the clinician and translational researcher are faced with the thorny decision of identifying which, of many, unmet medical needs can be the best fit for development of a new approach that has strong theoretical underpinning.

With the goal of impacting on survival, a target population could be potentially either too healthy or too ill. For the practical purpose of explicitly demonstrating an observable difference of survival, a group early in the disease course, while more appealing for theoretical immune competence, or at least having a higher frequency of adequate capacity for response, is potentially not informative. The latency to a visible end point, that is deaths, may be long and there also may be a frequency of non–cancer-related deaths so high as to overwhelm the therapeutic drug effect. Besides this, the time course of trial in this group would be simply chronologically longer, with corresponding increased expense and delay to marketability.

In contrast, the further along the disease course that the trial population would be defined, advantages that the trial time course is faster, the contribution of non–cancer-related events is lower, and the unmet clinical need is clearly more urgent are present. However, a theoretically ongoing degradation of the capacity for anticancer response looms, particularly for active immunotherapy. Further, the question of relative impact on patients at an earlier point of the disease course comes into focus very quickly if the trial is positive, but with a relative gap in the data.

Prostate cancer has features that are suitable for vaccine development: the rate of disease progression may be slow enough to allow for a month-long immune intervention, and then some latency until it is evident; the organ is biologically "dispensable," providing a theoretical safety margin. There are a variety of response end points—PSA response, time to PSA progression, time to radiologic progression, time to symptomatic progression, or overall survival. The data of the pivotal sipuleucel-T trial are in terms of overall survival, discussed again below.

Immunologic Implications of Population Disease Parameters

Immune deficit states do not have a causal association with prostate cancer, but the capacity of the immune system to attack the cancer could vary along the disease course.

Looking first at the immune side, and of general relevance to immunotherapy, the overall balance of activating versus tolerizing antigen-presenting cells is an accessible immunologic metric of host competence that may merit exploration [7•, 8]. Of particular relevance to the potential development of a single protein-specific strategy such as sipuleucel-T, antigen-specific regulatory T cells (CD4+ CD25+) could, at least theoretically, represent a patient-specific assay that could be tested for relevance to prostatic-acid phosphatase (PAP) immunogenicity.

Considering the effect of tumor on the immune system side, theoretical susceptibility of the tumor to immune-mediated attack is difficult to quantify. Any visible or clinically relevant tumor may be presumed to have modified the capacity of the immune system to attack it. Some intratumoral features with possible relevance to impaired immune attack could include class I HLA downregulation (corresponding to decreasing susceptibility to CD8 CTL lysis) [9–11], PD-1 ligand expression [12, 13], or Fas-ligand expression (inducing apoptosis of infiltrating lymphocytes) [14]. A more indirect effect may be a consequence of local expression of cytokines including vascular endothelial growth factor (VEGF), interleukin 10 (IL-10), tumor growth factor beta (TGF-β) that induce a tolerogenic phenotype in APC; granulocyte colony-stimulating factor (G-CSF) that induces invasion of myeloid cells that are functionally tolerizing APC. Other intratumoral escape mechanisms [7•, 8, 15] include indoleamine 2,3-dioxygenase [16] and nitric oxide synthetase [17, 18]. The difficulties of quantitative assessment of these anti-immune mechanisms are not only for an individual, but also for a group of patients, including in prostate cancer, for which metastases may be diffuse and comorbidities diverse.

One may envision therapy in the future directed specifically at modifying the immune-impact of the tumor, as a preparatory step for modulation of the host context for introduction of an anticancer vaccine. The sipuleucel-T processing uses an ex vivo loading of antigen-presenting cells and lymphocyte exposure. This affords a physical (albeit temporary) separation from the direct influence of tumor cytokines during the antigen presentation step. Further, the culture process itself may be a specific context for which tolerizing APC are suppressed.

Choosing a Target Antigen

Cancers bear many epitopes of potential interest for anticancer vaccination. Some can be defined as cancer associated and others as prostate tissue associated. Of at least theoretical importance, a distinction can be made between self-antigens, for which self-tolerance in the relevant antigen-specific CTL population must be broken, versus cancer neoantigens, for which a response could be potentially generated without the interference of a pre-existing regulatory T-cell population. For prostate cancer, those antigens can include PAP, prostate-specific antigen (PSA), and prostate-specific membrane antigen (PSMA), also expressed on endothelial cells, including tumor-associated endothelial cells, among others. These have features of near universal presence in prostate cancer cells. For commercial development, another consideration will also be intellectual property acquisition. Many other rejection antigens are under study [9]. Another issue that could be considered is the relative importance of a specific target protein to the malignant phenotype.

Description of Sipuleucel-T

An Ex Vivo Stimulation

At the point of infusion, sipuleucel-T is a cellular product. As an anticancer treatment, it is more of a process. As detailed in the pivotal trial publication [3••] and others [4, 5•, 19], the patient first has an apheresis; this is transported to a central facility, then the product is prepared there from the collected cells, by co-culturing APC for 36–44 h in media containing PA2024, which is synthetic protein antigen with a PAP and a granulocyte-monocyte colony-stimulating factor (GM-CSF) moiety. After manufacture and quality control testing, there is the transport of the infusable autologous cells back to a local center. The cellular product contains antigen-presenting cells (at least 50 million CD54+ cells) [19]. Further, it contains 60%–70% lymphocytes and other mononuclear cells, which may contribute or constitute the clinical activity. The process consists of three apheresis and infusions, generally at 2-week intervals. Thus, later apheresis product could contain cells that were primed at early processing and infusion. This may be of significance versus serial application of cells from a single apheresis, because it allows for a boost-and-prime paradigm, with direct analogy to classical ("antigen directly into the patient") vaccination as in clinical application for infectious disease prevention.

Many details of measurement of patient immunophenotypic characteristics that are now available (albeit not of specific validated relevance to anticancer therapy) were not incorporated explicitly into the definitions used for inclusion criteria of the pivotal trial population. This is not surprising considering that the technology and understanding of these have advanced in the decade since the trials were started. However, some quantitative tests of leukocytes are a part of standardized product characterization. As presented by Stewart et al. in abstract form [20•], quantification of CD54+ dendritic cells in the apheresis product and in the ready-to-ship sipuleucel-T product does define an identifiable difference

of clinical outcome, with a statistically significant difference in the overall survival of the portion of the sipuleucel-T–treated population with CD54+ cells above versus below the median. Of course, this type of retrospective nonrandomized analysis cannot define if the phenomenon represents an achievable modification of the product preparation, versus a non-causative marker of prostate cancer disease features.

For the purpose of the D9902B (and D9902A and D9901) trial, the treatment population was selected on a clinical basis only without prerequisites of immunologic assessment, except requirements to be not on concurrent corticosteroids and for CD4+ cell count at least 400/mm^3. The choice of "asymptomatic or minimally symptomatic" from prostate cancer clearly has implication for defining a part of the prostate cancer population with a likely better level of immune competency than a general "metastatic, castrate-refractory" population. Either way, the further quantitative assessment of patient immunologic characteristics—as defined distinctly from tumor-growth characteristics—may be an inroad to an immunologically based refinement of the optimal setting for sipuleucel-T application.

Pharmacodynamic End Points: Beyond the Overall Survival Data

Evidence of immune pharmacodynamic effect is described in several dimensions [3••]. While none of these assays, in isolation, represents something that should supersede (mathematically or clinically) the primary end point, these are important for understanding the product and the treatment population. Antibody responses (titer greater than 400) against the PA2024 antigen were in a much higher proportion of the treatment group than placebo (66.2% vs 2.9%), and a similar pattern for anti-PAP response (28.5% vs 1.4%). Cellular immunity for T cells versus PA2024 was 73.0% vs 12.1%, and again a similar pattern for response to PAP was 27.3% vs 8.0% (no *P* values presented). While an antibody titer of >400 against PA2024 or PAP was a marker for longer survival ($P<0.001$ for PA2024 and a trend, $P=0.08$ for PAP), the test on T-cell proliferation at week 6 did not define a difference.

These differences of survival within "immunologic response" subsets, contrast versus clinically defined subsets (age, performance status: 0 vs 1), prior therapies or the pathologic (Gleason score), radiologic (number of visible bone metastases, pain score), and protein blood tests (PSA, LDH, alkaline phosphatase, PAP), for which no subset was significantly more likely to benefit. The authors state "no conclusions could be made about the clinical significance of the observed immune responses" correctly; indeed, this was not the primary purpose of the study. Certainly, the database of the pivotal trial presents some hypotheses for exploration if same immunologic phenomenon that causes the increased antibody titer is tightly associated with a survival impact. The association may be in either directions: the capacity to have an increased titer could mark the subset of patients for whom the cancer has not passed a certain point; or it could mark a therapeutic mechanism which could be amplified.

Contrasts Versus Prostate Cancer New Agents

In the prostate cancer field, drawing from the experiences of hormone suppression and conventional cytotoxic therapy with docetaxel or mitoxantrone [21–23] with prednisone, a usual clinical practice is to follow PSA testing, to gauge disease response. This assessment is generally not in isolation from other monitoring, spanning radiologic changes—including bone scan (which may "flare" in favorable response); symptomatic response and progression-free and overall survival. In some cases PSA movement may be the only accessible metric of disease change. For many therapies, PSA response to treatment was identifiable at least as a marker of more slow disease course than in no PSA response subsets. Serial PSA evaluation has particular relevance as "signal" in prostate cancer developmental therapeutics, as an early sign of drug utility [24].

On the other hand, the FDA and others remain cognizant of the potential disconnect between PSA and more clinically crucial outcomes such as increments of progression-free and overall survival. Three recently reported (negative) pivotal trial experiences underscore the potential disconnection between PSA response and a survival impact. These examples include a conventional cytotoxic drug (satraplatin), anti-angiogenic drug (bevacizumab) studied in combination with a microtubule drug (docetaxel), and a biological modifier (calcitriol) in combination with docetaxel.

Sternberg et al. [25•] published a phase 3 clinical trial where 950 patients (51% with disease progression after prior docetaxel therapy) were randomized between prednisone plus satraplatin versus prednisone plus placebo. The investigational treatment arm was significantly favored at early end points for: PSA response 25.4% and 12.4% ($P<0.001$); tumor regression 8.0% vs 0.7% ($P=0.002$); and median time to progression 66.1 vs 22.3 weeks in intent-to-treat (ITT) population. Overall survival was not better, with superimposable survival curves showing a median OS for the stratified ITT analysis of 61.3 vs 61.4 weeks for placebo (HR=0.98; 95% CI=0.84–1.15; $P=0.80$) [25•].

The same pattern was seen in a similarly sized ($n=1,050$) pivotal trial of docetaxel, prednisone plus bevacizumab versus docetaxel and prednisone in chemotherapy-naïve castrate-refractory prostate cancer patients. End points that were favored in the combination arm included PSA response

(69.5% vs 57.9%, P=0.0002), and objective response (53.2% vs 42.1% P=.0113); again, overall survival was not significantly improved (22.6 vs 21.5 median OS, P=0.181; HR=0.91; CI=0.78–1.05) [26].

A third developmental drug with a somewhat different type of disconnection between PSA and OS impact was calcitriol (DN-101). A randomized phase 2 trial [27] with a primary end point of PSA response did not show a difference, but a surprisingly large, favorable increment of median survival was estimated with the adjusted hazard ratio (24.5 vs 16.4 months). The subsequent pivotal trial was closed early after a shorter survival was observed on the experimental arm with a medial OS of 16.8 (95% CI=15.8–19.3) vs 19.9 months (95% CI=18.6–22.7). Data from this phase 3 trial comparing docetaxel plus calcitriol vs docetaxel plus prednisone were presented at ASCO 2010 [28]. This pivotal trial was closed early for a finding of excess cardiac events on the combination arm. Mature long-term follow-up is not yet reported; that could confirm the result.

A common feature of these examples was the PSA change pattern, which was better than the eventual OS finding. In the last, an initial observation in the randomized phase 2 study of improved OS despite unmet PFS increment was not borne out in the phase 3 trial. In Table 1, there is a comparison between the populations and OS of recent relevant immunotherapy trials.

In the sipuleucel-T trial the dissonance between median OS and PSA response (as well as the other secondary end points, including PFS and time to symptomatic progression) is in the opposite direction. This pattern is, on the face of it, not as teleological. As per data from phase 2 trials, the maximum T-cell reactivity takes 8–10 weeks to achieve [29], and thus longer for a change of the target tumor to be even potentially discerned. Evaluating for time to progression (TTP) before or near this window imperatively one must acknowledge that relevant onset of immune antitumor response may lag. The lack of immediate evident response may engender discussion about whether the OS data are “logical” or “credible.”

Contrasts Versus Anticancer Immunotherapies

In another large contemporary pivotal prostate cancer immunotherapy experience, two trials were initiated using GVAX. The GVAX product consisted of an off-the-shelf allogeneic cellular material, a mixture of two modified prostate cancer cell lines. The PC-3 and LnCAP cell lines were modified to secrete GM-CSF. As observed by Small et

Table 1 Similarities and differences of other recent prostate cancer and immunotherapy trials

	Trial population	Significant advantage		Components			
		PFS	OS	Biologic product	Other part of investigational arm	Comparator class	Approval outcome
Sipuleucel-T [3••]	CRPC, asymptomatic or minimally symptomatic	x	√	Auto leukocytes	–	Placebo	FDA approved
GVAX vs Doc+P (VITAL-1) [30]	CRPC, minimally symptomatic Chemo naive	x	x	Allo cell line	–	Chemo	Withdrawn
GVAX + doc vs P + Doc (VITAL-2) [31]	CRPC, symptomatic	x	x	Allo cell line	Chemo	Chemo + steroid	Withdrawn
Satraplatin vs placebo [25•]	CRPC, post-docetaxel	√	x	–	Chemo	Placebo	Withdrawn
Cabazitaxel vs mitoxantrone [33•]	CRPC, post-doc	√	√	–	Chemo	Chemo	FDA approved
Doc+P ±bevacizumab [26]	CRPC	√	x	Anti-VEGF antibody	Chemo	Chemo	None
Doc-P ±calcitriol [27, 28]	CRPC	√	x	Vitamin	Chemo	Chemo	None
Oncophage [35]	RCC, adjuvant	x[a]	–	Auto tumor	None	None	Russian approval
Reniale [36]	RCC, adjuvant	√	x[b]	Auto tumor	None	None	None
Ipilumimab vs GP100 vaccine vs both [1••]	Stage IV melanoma, HLA-A2 only	√	√	GP100 vaccine	Anti-CTLA-4 antibody	GP100 vaccine	At FDA (anticipated late 2010)

[a] Oncophage: “no renal vein invasion” subset: √

[b] Reniale: OS trend favorable, but not significant

Allo, allogeneic; Auto, autologous; Chemo, conventional cytotoxic chemotherapy; CRPC, castration-resistant prostate cancer; doc, docetaxel; GP100, HLA-A2 restricted peptides derived from GP100 protein; P, prednisone

al. [29], dendritic cells pulsed with PAP alone (not with GM-CSF added) elicited significantly weaker immune responses, emphasizing GM-CSF as a key factor for activating antigen presentation. The allogeneic GVAX cell lines would serve as a source of antigens such as PSA, PSMA, and (in common with sipuleucel-T) PAP; other prostate-specific and cancer-related antigens would also be presented. Both trials were in CRPC patients (as for sipuleucel-T), but both had an active therapy, docetaxel, in the control arm (in contrast to the unmodified autologous cells used as the control group for sipuleucel-T). The VITAL-1 trial (NCT00089856) compared GVAX versus docetaxel plus prednisone, but with inclusion of only asymptomatic men (similar to sipuleucel-T) with no prior chemotherapy. It was stopped (after having met its accrual of 626) but for having less than 30% chance of meeting the overall survival end point [30].

The VITAL-2 trial (NCT00133224) [31] was in patients with CRPC and with symptoms, with a comparison planned for GVAX + docetaxel vs prednisone + docetaxel. The halt of that trial was due to a data safety monitoring committee finding of 67 versus 47 deaths, favoring the standard-therapy arm, at a point when there were 408 patients accrued. This contrasts, obviously, with the generally excellent safety experience reported in the completed sipuleucel-T trials. (An ongoing post-marketing surveillance study to assess adverse event frequency, particularly stroke risk, was mandated in the FDA approval of sipuleucel-T.)

Another ex vivo antigen loading product, DCvax, used a PSMA peptide as the immunogen. It was not tested in a pivotal trial, although one was registered (NCT00043212) [32]. It did not use a tandem-apheresis algorithm, as does sipuleucel-T.

Conclusions

Prototypes are exciting. At their best, they are a window to the future of technology. Even so, it is usual to accept some intrinsic limitations. The limitations of sipuleucel-T are significant: an obvious immediate anticancer impact is lacking. While this has no mathematical bearing on the conclusion of a carefully conducted, placebo-controlled study, a detectable pharmacodynamic effect—rising titer of antibodies with specificity to PA2024 sipuleucel-T—was seen; it will remain to be seen if that can be used as a surrogate for a (realistic) patient-perceived need for feedback that the procedure has "done something," or as leverage point for amplifying therapeutic effect.

Another limitation is on the absolute extent of benefit. While the 4.1-month difference of median survival certainly compares favorably with the increment seen in the pivotal trials of the two approved taxane drugs (docetaxel [21, 23] and cabazitaxel [33•]), it is a clinically short duration that does not change the overall tone of the medical care of CRPC. A substantial segment of advanced prostate cancer patients are motivated to eschew conventional cytotoxic chemotherapy because of the side effect potential. The recently reported positive trial of abiraterone presented by de Bono at ESMO Congress (October 8–12, 2010) described a similar increment (14.8 vs 10.9 months).

A further limitation, which is hardly unusual in a pivotal trial, is that the population treated was a narrow slice of the potentially eligible patients. Earlier, non-CRPC patients are interested. There would seem no immunological basis to consider that their responses would be especially worse than the trial population, and could be better. African American subjects (in a disease known to have a greater than twofold relative incidence) were represented only in single digits (6.7%). Geographic distribution of patients was basically limited to North America—logistics of European, Asian, and other product manufacture remain to be approached.

The favorable side effect profile augments the enthusiasm. The excitement is tempered stiffly by the price and production capacity issues. This is a difficult problem to address in developmental therapeutics, as discussed above. The compromise of using narrow inclusion criteria to obtain relative uniformity of disease features—tumor burden, time to progression—inevitably leaves at least those at an earlier point in the disease process wondering. If the benefit is the same, or even theoretically greater, through an earlier application of the therapy is still unanswered. This simply has not had time to occur yet. The concept of waiting to "ripen" until the disease progresses to the point of meeting the sipuleucel-T pivotal trial entrance criteria is unsettling.

Marketing of the product remains a potentially incomplete process. A wholesale price point of $31,000 per infusion ($93,000 for a course of three infusions) has been the source of debate. Two separate potential barriers can be identified—treating patients within the specific criteria as were used in the trial but also extension of treatment to other settings.

From the technological side, the production process of sipuleucel-T (that is to say, the product preparation, independent of the clinical issues of disease selection, outcome selection, empiric clinical trial experience) is modular in terms of the addition of antigen. Working within the paradigm, other antigens, including Her2/neu [34•] and kidney cancer antigens, are in development. Subtleties of clinical development of these antigens on the sipuleucel-T platform will need to be separately and empirically addressed.

We may remain hopeful, as with any successful prototype, that it is a beginning and not a fixed, marketed drug. Technology of immune quantitative assessment and immune modulation are advancing significantly. This will make today's sipuleucel-T just a starting point for a future

with more clinical impact for prostate cancer patients, better and more economically appealing production processes, and more applications outside of the prostate cancer diagnosis. Lessons from this successful product development include a demonstration (as also observed in the ipilimumab clinical trial in melanoma) of a disconnection between immediate disease response and eventual positive outcome.

The demonstrated goal of efficient production of personalized ex vivo antigen exposure may be exploited in other new immune stimulation concepts, unrelated to GM-CSF fusion antigens. The most interesting practical question for anticancer immunotherapy development is whether ex vivo stimulation is a requirement, as used in Dendreon's platform used for sipuleucel-T.

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