

Interdisciplinary Critique of Sipuleucel-T as Immunotherapy in Castration-Resistant Prostate Cancer

Marie L. Huber, Laura Haynes, Chris Parker, Peter Iversen

Manuscript received July 11, 2011; revised November 7, 2011; accepted November 16, 2011.

Correspondence to: Marie L. Huber, MPhil, PO Box 925, New York, NY 10009 (e-mail: marie.huber@cantab.net).

Sipuleucel-T was approved by the US Food and Drug Administration on April 29, 2010, as an immunotherapy for late-stage prostate cancer. To manufacture sipuleucel-T, mononuclear cells harvested from the patient are incubated with a recombinant prostatic acid phosphatase (PAP) antigen and reinfused. The manufacturer proposes that antigen-presenting cells exogenously activated by PAP induce endogenous T-cells to attack PAP-bearing prostate cancer cells. However, the lack of demonstrable tumor responses has prompted calls for scrutiny of the design of the trials in which sipuleucel-T demonstrated a 4-month survival benefit. Previously unpublished data from the sipuleucel-T trials show worse overall survival in older vs younger patients in the placebo groups, which have not been shown previously to be prognostic for survival in castration-resistant prostate cancer patients receiving chemotherapy. Because two-thirds of the cells harvested from placebo patients, but not from the sipuleucel-T arm, were frozen and not reinfused, a detrimental effect of this large repeated cell loss provides a potential alternative explanation for the survival "benefit." Patient safety depends on adequately addressing this alternative explanation for the trial results.

J Natl Cancer Inst 2012;104:273–279

Sipuleucel-T, an autologous cellular immunotherapy, was approved in April 2010 by the US Food and Drug Administration (FDA) for the treatment of patients with castration-resistant prostate cancer. In July 2010, Kantoff et al. (1) reported the results of the phase III trial (IMPACT), which was central to the FDA's approval, and also underpins the pending application for approval with the European Medicines Agency. Both the accompanying editorial (2) and the FDA reviewers noted the lack of supportive evidence for the mechanism proposed by sipuleucel-T's manufacturer (Figure 1 and Table 1). The absence of such supportive data has raised the concern that the 4.1-month survival benefit could be the result of a flaw in the trial design or from the chance imbalance of unmeasured prognostic variables.

We have reconsidered these trial results in light of unpublished data obtained from internal FDA documents that became available only after the approval of sipuleucel-T. We believe that analysis of the data in their totality challenges the published interpretation of the trial results and suggests a different conclusion about the efficacy, and potentially safety, of sipuleucel-T. Because these data have not been debated publicly, we hope that this commentary will stimulate consideration of their implications.

New Observations From Previously Unpublished Data

Observation 1: Two Unexpected Interactions Between Patient Age and Survival

The most striking observation from the new data was an unexpected 11-month difference in median survival between placebo patients younger than age 65 years and patients older than age 65 years

(28.2 vs 17.2 months, respectively) (Table 2). Age is not normally prognostic for survival in castration-resistant prostate cancer patients receiving chemotherapy (7–9), as illustrated by the 17.6-month median survival for the 504 patients younger than 68 years vs the 18.1-month survival for the 502 patients aged 69 years or older in the pivotal TAX 327 trial (10). Although post hoc subgroup analyses should be interpreted with caution, it is still noteworthy that the age dependence of overall survival (OS) in the placebo arm (two-sided $P < .001$) is stronger than the treatment effect itself (Table 2).

Also, it could be observed for the first time in the unpublished data from the FDA that among the IMPACT patients younger than 65 years, sipuleucel-T treatment appeared to have no effect on survival (hazard ratio of death = 1.41, 95% confidence interval = 0.87 to 2.29), in contrast with patients 65 years or older (hazard ratio of death = 0.58, 95% confidence interval = 0.43 to 0.76) (11). This observation suggests that the overall results were driven entirely by the differential survival in older patients. This is counterintuitive given that standard vaccination strategies (12,13), and immunotherapies in particular (14,15), are consistently less effective in the elderly and therefore raises further questions concerning the immune enhancement mechanism proposed for sipuleucel-T. In addition, it appears remarkable that the younger patients for whom the intervention did not appear to be effective lived longer (median = 29.0 months) than the older patients for whom the intervention did appear to be effective (median = 23.4 months).

These observations from the unpublished data from the sipuleucel-T studies generated the hypothesis that the placebo intervention might have had a clinically significant age-related impact on OS and should be further investigated to assess whether

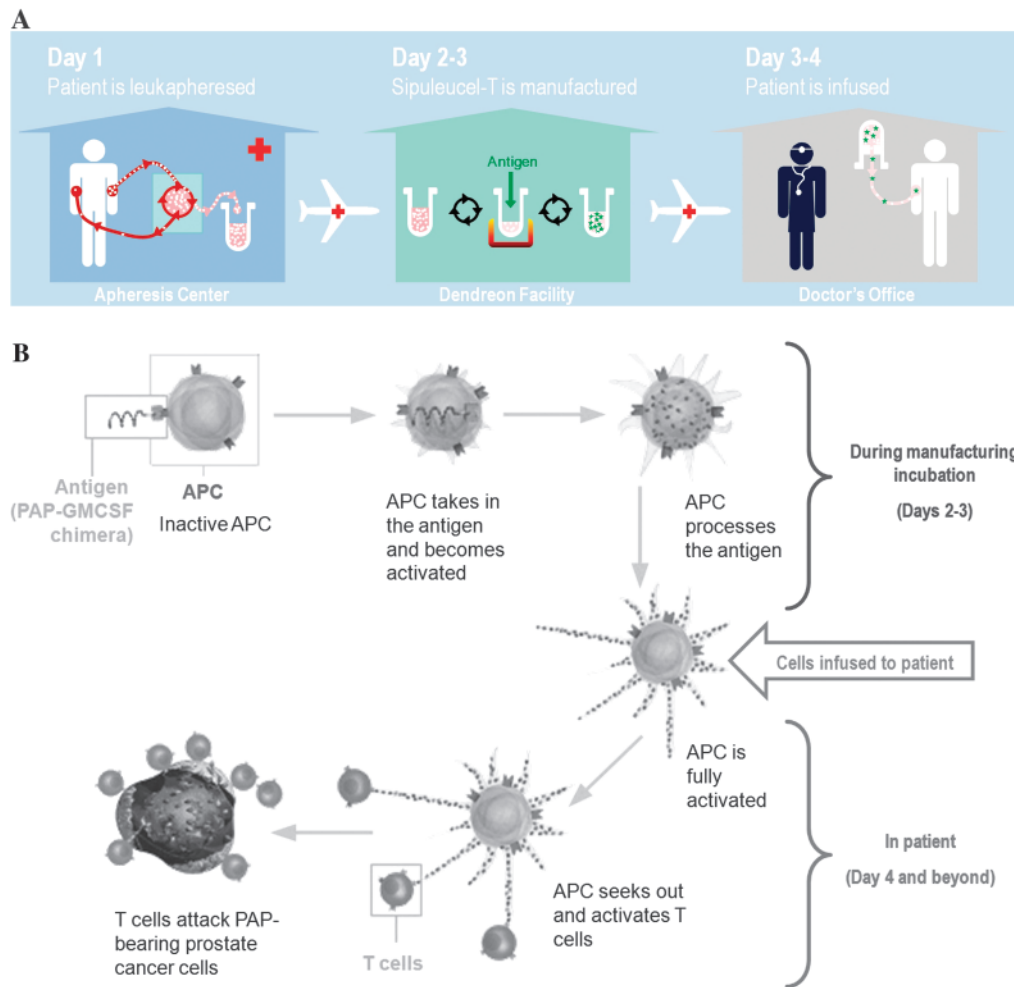


Figure 1. The manufacturing process and proposed mechanism for sipuleucel-T (3). **A)** The manufacturing process for sipuleucel-T is depicted. Mononuclear cells are harvested from the patient and shipped to the manufacturing facility (approximately 46% T cells, 7% B cells, 13% natural killer cells, and 25% monocytes) (4) on day 1. On days 2–3, cells are put through two buoyant density centrifugation steps before incubation for 36–48 hours with a chimeric antigen (PA2024), consisting of granulocyte-macrophage colony-stimulating factor (GM-CSF) to activate antigen presentation, which is linked to the prostatic acid phosphatase

(PAP) tumor-associated antigen. Cells are given a final wash on days 3–4 before shipment back to the clinic for reinfusion into the patient. This process is repeated every 2 weeks for a complete course of three cycles. **B)** The proposed mechanism for sipuleucel-T antitumor activity is given. The manufacturer proposes that during incubation on days 2–3, antigen-presenting cells (APCs) process and present the synthetic antigen PA2024 on their surface, thereby becoming activated. Upon reinfusion, these cells are hypothesized to activate endogenous T-cells, thereby stimulating them to attack PAP-bearing prostate cancer cells.

it might have unintentionally introduced this active non-placebo effect. In the sipuleucel-T arm, the 5.6-month longer survival of the younger group, although less statistically significant, is also unexpected and should be tested against alternative interpretations of the trial results.

Observation 2: Older Patients in the Placebo Group Appear to Have Shorter OS Than Might Be Expected From Other Studies

To test the hypothesis that the placebo intervention had an age-dependent effect on OS, we sought placebo groups from other trials with which their survival might be compared. In the original publication of the IMPACT trial results, Kantoff et al. (1) state, “The 21.7-month median survival of patients in the placebo group compares favorably with that in control groups in other randomized trials involving similar patient populations (range, 15.5 to 21.7 months) (9,16–21), indicating that the treatment effect cannot

be attributed to a poor outcome in the placebo group.” However, the control groups in the seven cited trials were not appropriate comparators for the IMPACT placebo group (Table 3). The initial IMPACT enrollment criteria selected asymptomatic patients with an Eastern Cooperative Oncology Group performance status of 0 or 1, Gleason score of 7 or lower, and no visceral metastases. Each of these restrictions is associated with improved OS in multivariable predictive models developed by both Halabi et al. (7) and Armstrong et al. (8). After 40% of patients had already been enrolled, the Gleason restriction was removed and minimally symptomatic patients were accepted. The placebo groups cited by Kantoff et al. (1) did not share these restrictions and might therefore have been anticipated to have a shorter survival than that of the IMPACT placebo group. An illustration of how the multiple enrollment restrictions in IMPACT selected for a favorable prognosis is seen in the 21.2-month Halabi-predicted survival of its placebo group vs 16 months for the placebo group in the cited

Table 1. Areas of concern regarding support for observed survival benefit of sipuleucel-T for castration-resistant prostate cancer*

Concern	Public expressions of concern	Source
Improvement in overall survival came without evidence of a measurable antitumor effect	“Study group assignment had no significant effect on the time to tumor progression.”	(2)
	“1 of 341 patients in the sipuleucel-T group had a partial tumor response, and 3% had a reduction of at least 50% in PSA . . . Thus, the improvement in survival came without evidence of a measurable antitumor effect.”	(2)
	“It is hard to understand how the natural history of a cancer can be affected without some apparent measurable change in the tumor, either evidence of tumor shrinkage or at least disease stabilization reflected in a delay in tumor progression.”	(2)
Observations predicted by the proposed mechanism of sipuleucel-T have not been made. The absence of alternative mechanisms leaves the 4.1-month survival benefit without mechanistic underpinning	“It is not clear that Dendreon has put a high priority on measuring the immune response in patients in their trials. Considering that there appears to be very little tumor- and antigen-specific immune response in the vaccinated patient, one would think that this would be a high priority.”	(5)
T-cell proliferative responses to the chimeric antigen (PA2024) did not translate to responses to physiologic, human PAP	“The fact that they are able to get a response to PA2024 but consistently not to PAP tumor antigen is troubling.”	(5)
	“It was asked if they had any evidence of a specific response to human PAP. They stated that, no, they do not yet have any evidence.”	
T-cell proliferative response to the chimeric antigen (PA2024) or human PAP did not correlate with improved survival	“No survival difference could be detected between patients in the sipuleucel-T group who had T-cell proliferation responses to PA2024 or prostatic acid phosphatase at week 6 and those who did not.”	(1)

* PAP = prostatic acid phosphatase; PSA = prostate-specific antigen.

GVAX trial (18). In fact, this predicted 5.2-month survival advantage was not realized because the placebo groups from both of these two trials lived for a median of 21.7 months.

To find a placebo group with similar baseline characteristics to those of the IMPACT placebo group, we searched both published literature and abstracts. We did not find any other castration-resistant prostate cancer trials with similarly restrictive enrollment criteria. However, we identified two subanalyses of larger trials that might provide more appropriate populations to which the IMPACT placebo group may be compared. 1) In the aforementioned GVAX trial, Higano et al. (18) reported a subanalysis of the 264 men with the best baseline prognosis. For men with a Halabi-predicted survival greater than 18 months at enrollment, median survival was 29.7 months on GVAX and 27.1 months in the placebo group. Because approximately 86% of patients in the IMPACT placebo group had an Halabi-predicted survival greater than 16 months (23), the 28.2-month median survival of pooled placebo patients younger than 65 is in the range that might be anticipated for the entire IMPACT placebo group. 2) Berthold et al. (24) conducted a retrospective sub-analysis of the 110 minimally symptomatic patients from the TAX 327 study; a group similar to, though still not as highly

selected for good prognosis, the IMPACT population. Men with minimal symptoms had prolonged survival (median = 25.6 months) compared with symptomatic patients (median = 17.1 months, $P = .009$). Furthermore, the median survival for minimally symptomatic patients in the group given docetaxel every 3 weeks (the chemotherapy regimen received by most of the IMPACT placebo patients) was 28.4 months. This comparison too suggests that the 28.2-month median survival of the patients younger than 65 years in the sipuleucel-T trials is in the range of what should have been expected for all patients, regardless of age.

These comparisons with OS in other CPRC trials support the hypothesis that the “placebo” intervention might have had a clinically significant adverse impact on OS in older patients. This observation too calls for scrutiny of the placebo intervention, to assess whether it might unintentionally have introduced this effect.

Observation 3: Potential Harm From the IMPACT Study Interventions

To better understand the potential for harm from the study interventions, we sought data regarding the cellular manipulation in IMPACT. Kantoff et al. (1) reported no specific cell-level data, which might be appropriate for a trial investigating the collection and manipulation of immune cells. Comparison of the cell counts performed on 526 lots of patient cells received from apheresis centers during an earlier phase III study (9901) (4,25) to the baseline circulating white blood cell measurements (11) shows that the “standard leukapheresis processing 1.5–2.0 times the patient’s estimated blood volume” removed more than 90% (median) of the patients’ circulating mononuclear cells. Cells in each lot were counted twice between steps in the manufacture of sipuleucel-T and underwent a final count before shipment for reinfusion into patients. Such data extracted from highly redacted FDA documents revealed that more

Table 2. Subgroup analysis by age of overall survival of patients in the phase III trials of sipuleucel-T for castration-resistant prostate cancer (6)*

Patient age, y	Sipuleucel-T		Placebo	
	No. of patients	Median survival (95% CI), mo	No. of patients	Median survival (95% CI), mo
<65	106	29.0 (22.8 to 34.2)	66	28.2 (23.4 to 32.5)
≥65	382	23.4 (22.0 to 27.1)	183	17.3 (13.5 to 21.4)

* CI = confidence interval.

Table 3. Comparison of the IMPACT placebo group with placebo groups cited by Kantoff et al. (1)*

Study	No of patients	Median OS for placebo, mo	Reasons why cited placebo group would be expected to have shorter OS compared with the IMPACT placebo group	Study funding source(s)
Zoledronic acid (16)	208	15.5	The study did not restrict enrollment to minimal or absent symptomatology. Among patients, 73% had baseline pain vs 47% in IMPACT. The study conducted before TAX 327 demonstrated a 2.9-month survival benefit for docetaxel, leading to its approval by the FDA in the year 2004	Novartis Pharmaceuticals Corporation (now Novartis International AG)
Docetaxel (TAX 327) (10,17)	335	19.2	The study did not restrict enrollment to minimal or absent symptomatology, and 45% of patients had clinically significant baseline pain vs 0% in IMPACT. Baseline visceral metastases was present in 22% of patients vs 0% in IMPACT. Clinically significantly worse baseline performance status and Gleason scores than IMPACT patients	Aventis (now Sanofi S.A.)
Atrasentan (19)	401	20.3	The study excluded patients requiring opiate analgesia but, unlike IMPACT, did not enroll 40% of patients under explicit exclusion of all pain and with favorable Gleason scores. No eligibility restrictions on patients with visceral metastases were given. Enrolled from June 2001 to September 2002, before TAX 327 demonstrated a 2.9-month survival benefit for docetaxel, leading to its approval by the FDA. The study was conducted at 180 sites in 21 countries, with variable local supportive care practices, which could induce bias in either direction	Abbott Laboratories
ZD4054 phase II (20)	107	17.3	The study excluded patients requiring opiate analgesia, but unlike IMPACT, did not impose eligibility restrictions on ECOG status, visceral metastases, pain, and Gleason score. The study was conducted at 65 centers (of which only 12 were in North America) across four continents where placebo patients were given "best supportive care according to local practice," which could induce bias in either direction	Astrazeneca PLC
Mitoxantrone (21)				
Mitoxantrone plus prednisone arm	56	23	Kantoff et al. (1) chose the arm receiving the low-dose prednisone (median OS = 19 months) for comparison, yet the mitoxantrone plus low-dose prednisone (median OS = 23 months) would represent a more appropriate comparator for the IMPACT placebo group in which 50.3% of patients received docetaxel and 8% received other chemotherapy. The IMPACT placebo group excluded patients with visceral metastases [6% of mitoxantrone group in the study by Berry et al. (21)] and enrolled 75.4% of patients with favorable Gleason scores. Patients were enrolled from March 1997 to Jan 1999, and the results were reported in the year 2001, before docetaxel was granted FDA approval	Immunex Corporation (now Amgen Inc)
Prednisone alone arm	63	19		
PROSTVAC phase II (9)	40	16.6	Post-treatment chemotherapy usage was neither prescribed nor monitored. Results reported for the 40 placebo patients are problematic for the many reasons outlined by Small and Fong (22)	BN Immunotherapeutics (now Bavarian Nordic)
GVAX (18)	~310†	21.7	Exclusion of opiate pain medication was the only enrollment criterion used to select for a favorable prognosis	Cell Genesys (now BioSante Pharmaceuticals Inc)

* FDA = US Food and Drug Administration; OS = overall survival.

† There is an approximate number of participants given for this trial because full results have not been published. The study completed accrual of 626 patients in the year 2007, randomized 1:1 between study arms, and all patients completed the initial 6-month treatment period.

than 65% (median) of the cells harvested from patients were lost at the manufacturing facility during the two centrifugation steps performed on incoming cell lots and during the final cell wash (4). A more complete description of the sipuleucel-T intervention would therefore include the extraction of more than 90% of circu-

lating mononuclear cells followed by the return of less than 35% of these cells 2 days later after incubation with chimeric antigen. This intervention is repeated three times at 2-week intervals.

Of particular note, the interventions administered to the placebo group differed from those in the sipuleucel-T group in three

important respects. 1) After the two centrifugations that begin the manufacturing process, two-thirds of the cells in each placebo lot were removed and frozen for possible later use, leaving only one-third of the cells for further processing and reinfusion into placebo patients. Thus, given the greater than 65% (median) of cells lost in processing and the further two-thirds removed for freezing, less than 12% of the original pheresed cell load was left for reinfusion into the placebo patients. 2) Also, cells processed into sipuleucel-T were incubated with the granulocyte-macrophage colony-stimulating factor/prostatic acid phosphatase (GM-CSF/PAP) chimeric protein, whereas cells processed into placebo were stored in medium containing no GM-CSF. GM-CSF is a cytokine that functions as a white blood cell growth factor, and furthermore, may have antitumor activity as a single agent in prostate cancer (26). 3) Whereas cells being processed into sipuleucel-T were incubated at 37°C for 36–44 hours, placebo cells were stored at 2°C–8°C. In our experience, storage of isolated mononuclear cells at 2°C–8°C for 36–44 hours can result in the death of most, if not all, of those cells. Neither the article by Kantoff et al. (1) nor the FDA review documents for sipuleucel-T specify a determination of the viability of placebo cells before reinfusion into the patient. Thus, at best, at each of the three interventions, placebo patients received less than 12% of their harvested cells back; and at worst, they received an infusion with an equivalent number of dead cells. These three differences between the placebo and experimental interventions were assumed to be benign and have no impact on OS in this population. However, this assumption remains to be proven, and the term “placebo” is inappropriate. The IMPACT placebo constituted a biologically significantly different intervention that could have had distinct clinical properties and was therefore an inappropriate control for sipuleucel-T.

Synthesis and Discussion of Observations

The observations above suggest a simple, albeit unproven, alternative explanation of the IMPACT trial outcome. According to this alternative explanation, the enrollment criteria selected for a patient population with a favorable prognosis of approximately 28–29 months and the placebo intervention, involving a repeated depletion of circulating mononuclear cells, exerted an age-dependent adverse impact on OS. There are several possible explanations for this. Most simply, patients younger than 65 years may have been able to replace the lost cells (and clear the dead cells) with few or no negative consequences, as reflected in their 28.2-month survival (6). However, patients older than 65 years may have been harmed by the cell loss (or the infusion of dead cells), as reflected in their 17.3-month survival, which is 11 months shorter than might have been predicted without the placebo intervention. It is noteworthy that the sipuleucel-T intervention, involving a similar, though smaller, repeated depletion of circulating lymphocytes, may have resulted in a similar, but less severe, age-dependent impact on survival. Although the patients younger than age 65 lived 29 months, the survival time expected of the entire group, the cells lost during sipuleucel-T manufacture may have contributed to the 5.6-month shorter survival of patients older than 65 years. Such an explanation would not involve a therapeutic benefit related to the chimeric antigen.

The field of immunosenescence provides support for this alternative explanation. The age-dependent deterioration of

Box 1. Select aged-related impairments of the immune system

Decreased thymic production of naive T cells (27,28)

Collapse in diversity of both naive and memory T cell subcompartments (13,29,30)

Decreased T-cell responsiveness resulting from both decreased expression of CD28 and proliferative exhaustion (14,31,32)

Increased numbers of circulating natural killer cells with reduced responsiveness and cytotoxicity per cell (33)

Impaired differentiation of CD34-positive cells into mature dendritic cells (34)

Decreased frequency of myeloid peripheral blood dendritic cells (35)

Disruptions in T-cell/B-cell interactions (36)

Alterations in immune cell trafficking as a consequence of widespread changes in cytokine and chemokine signaling (37–39)

multiple components of the immune system are widely accepted and believed to contribute to the increased incidence of cancer in the elderly (Box 1) (40,41). Each of these affected elements is believed to be involved in the recognition and suppression of developing malignancies (42–45), and therefore a depletion of cellular elements by apheresis with inadequate replacement could exacerbate some or all of these age-related immunodeficiencies.

Because T cells are proposed to be enacting the purported treatment effect of sipuleucel-T, it is of particular note that the age-related decline in both naive and memory T-cell diversity is not linear, but that age 65–70 years is associated with a precipitous contraction (29,46). This collapse in both number and diversity of circulating naive T-cells is believed to underlie the poor response to vaccination in elderly humans and primates (13,14,47) and by similar mechanisms leads to a reduced ability to respond to new tumor antigens (14,15). Thus, there is a solid scientific and mechanistic basis for belief that the intervention-related depletion could have a greater detrimental effect on the anticancer immune competence of older individuals, with 65 years representing an important threshold age. Homeostatic proliferation and migration of peripheral T-cells might maintain the absolute numbers in the circulation (48); yet the resultant population would differ from the unperturbed population in important functional ways (49).

Overall, we believe that a detrimental effect of the placebo intervention is at least as plausible as a beneficial effect of sipuleucel-T as an explanation of the survival difference observed in the IMPACT trial. We would be interested in other possible explanations for the 11-month survival difference between placebo patients older and younger than age 65, as well as explanations for why the patients in whom sipuleucel-T is apparently efficacious (aged >65 years) live clinically and statistically significantly shorter lives than the patients in whom it has no apparent efficacy (aged <65 years). The safety of prostate cancer patients as well as the

judicious development of beneficial immunotherapies depends on addressing the concerns raised and considering all possible interpretations of the IMPACT trial results.

References

- Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *New Engl J Med.* 2010;363(5):411–422.
- Longo D. New therapies for castration-resistant prostate cancer. *New Engl J Med.* 2010;363(5):479–481.
- March 2007 CTGT Advisory Committee Meeting FDA CMC Presentation, Slides 4 & 11. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4291S1_2.ppt. Accessed December 3, 2011.
- March 2007 CTGT Advisory Committee Meeting CMC Briefing Document. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1_04a.pdf. Accessed December 3, 2011.
- Wonnacott K, Moos M, Husain S, Finn T. CMC Review, BLA 125197, Sipuleucel-T. <http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214565.pdf>. Accessed December 3, 2011.
- Zhen B, Gupta G. FDA Statistical Review and Evaluation Sipuleucel-T. <http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214543.pdf>. Accessed December 3, 2011. Completed April 30, 2010.
- Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol.* 2003;21(7):1232–1237.
- Armstrong AJ, Garrett-Mayer ES, Yang YC, de Wit R, Tannock IF, Eisenberger M. A contemporary prognostic nomogram for men with hormone refractory metastatic prostate cancer: a TAX327 study analysis. *Clin Cancer Res.* 2007;13(21):6396–6403.
- Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2010;28(7):1099–1105.
- Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *New Engl J Med.* 2004;351(15):1502–1512.
- Fan C, George B, Bross P. FDA Clinical Review Sipuleucel-T. <http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214540.pdf>. Accessed December 3, 2011. Completed April 28, 2010.
- Burns EA, Lum LG, L’Hommedieu G, Goodwin JS. Specific humoral immunity in the elderly: in vivo and in vitro response to vaccination. *J Gerontol.* 1993;48(6):B231–B236.
- Grubeck-Loebenstien B. Fading immune protection in old age: vaccination in the elderly. *J Comp Pathol.* 2010;142(suppl 1):s116–s119.
- Gravekamp C. The importance of the age factor in cancer vaccination at older age. *Cancer Immunol Immunother.* 2009;58(12):1969–1977.
- Pawelec G, Lustgarten J, Ruby C, Gravekamp C. Impact of aging on cancer immunity and immunotherapy. *Cancer Immunol Immunother.* 2009;58(12):1907–1908.
- Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone refractory metastatic prostate carcinoma. *J Natl Cancer Inst.* 2002;94(19):1458–1468.
- Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol.* 2008;26(2):242–245.
- Higano C, Saad F, Somer B, et al. A phase 3 trial of GVAX immunotherapy for prostate cancer versus docetaxel plus prednisone in asymptomatic, castration-resistant prostate cancer (CRPC). Presented at the 2009 Genitourinary Cancers Symposium; February 26–28, 2009; Orlando, FL. Abstract LBA150. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=64&abstractID=20543. Accessed December 3, 2011.
- Carducci MA, Saad F, Abrahamsson PA, et al. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer.* 2007;110(9):1959–1966.
- James ND, Caty A, Payne H, et al. Final safety and efficacy analysis of the specific endothelin A receptor antagonist zibotentan (ZD4054) in patients with metastatic castration-resistant prostate cancer and bone metastases who were pain-free or mildly symptomatic for pain: a double-blind, placebo-controlled, randomized phase II trial. *BJU Int.* 2010;106(7):966–973.
- Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase 3 study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. *J Urol.* 2002;168(6):2439–2443.
- Small EJ, Fong L. Developing immunotherapy as legitimate therapy for patients with prostate cancer. *J Clin Oncol.* 2010;28(7):1085–1087.
- Kantoff PW. Updated results of the IMPACT trial of sipuleucel-T for metastatic, castration-resistant prostate cancer. Presentation at the ASCO Genitourinary Cancers Symposium; March 5–7, 2010; San Francisco, CA.
- Berthold DR, Pond GR, Roessner M, et al. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate specific antigen, pain, and quality of life response and survival in the TAX-327 Study. *Clin Cancer Res.* 2008;14(9):2763–2767.
- Registry entry for first Phase III sipuleucel-T trial D9901 (n=127). <http://clinicaltrials.gov/ct2/show/NCT00005947>. Accessed December 3, 2011.
- Small EJ, Reese DM, Um B, et al. Therapy of advanced prostate cancer with granulocyte macrophage colony-stimulating factor. *Clin Cancer Res.* 1999;5(7):1738–1744.
- Aspinall R, Del Giudice G, Effros R, Grubeck-Loebenstien B, Sambhara S. Challenges for vaccination in the elderly. *Immun Ageing.* 2007;4(1):9.
- Hakim FT, Gress RE. Immunosenescence: deficits in adaptive immunity in the elderly. *Tissue Antigens.* 2007;70(3):179–189.
- Goronzy JJ, Weyand CM. T cell development and receptor diversity during aging. *Curr Opin Immunol.* 2005;17(5):468–475.
- Goronzy JJ, Lee WW, Weyand CM. Aging and T-cell diversity. *Exp Gerontol.* 2007;42(5):400–406.
- Schindowski K, Fröhlich L, Maurer K, Müller WE, Eckert A. Age-related impairment of human T lymphocytes’ activation: specific differences between CD4(+) and CD8(+) subsets. *Mech Ageing Dev.* 2002;123(4):375–390.
- Song L, Kim Y, Chopra R, et al. Age-related effects in T cell activation and proliferation. *Exp Gerontol.* 1993;28(4–5):313–321.
- Borrego F, Alonso MC, Galiani MD. NK phenotypic markers and IL2 response in NK cells from elderly people. *Exp Gerontol.* 1999;34(2):253–265.
- Kiertseher S, Luo J, Dubinett SM, Roth MD. Tumors promote altered maturation and early apoptosis of monocyte-derived dendritic cells. *J Immunol.* 2000;164(3):1269–1276.
- Della Bella S, Bierti L, Presicce P, et al. Peripheral blood dendritic cells and monocyte are differently regulated in elderly. *Clin Immunol.* 2007;122(2):220–228.
- Lazuardi L, Jenewein B, Wolf AM, Pfister G, Tzankov A, Grubeck-Loebenstien B. Age-related loss of naïve T cells and dysregulation of T cell/B cell interactions in human lymph nodes. *Immunology.* 2005;114(1):37–43.
- Mo R, Chen J, Han Y. T cell chemokine receptor expression in aging. *J Immunol.* 2003;170(2):895–904.
- Rose-John S, Scheller J, Elson G, Jones SA. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. *J Leukoc Biol.* 2006;80(2):227–236.
- Blankenstein T. The role of tumor stroma in the interaction between tumor and immune system. *Curr Opin Immunol.* 2005;17(2):180–186.
- Taub D, Longo D. Insights into thymic aging and regeneration. *Immunol Rev.* 2005;205(1):72–93.
- Fulop T, Kotb R, Fortin CF, Pawelec G, de Angelis F, Larbi A. Potential role of immunosenescence in cancer development. *Ann NY Acad Sci.* 2010;1197(1):158–165.

42. Malaguarnera L, Ferlito L, Di Mauro S, Imbesi RM, Scalia G, Malaguarnera M. Immunosenescence and cancer: a review. *Arch Gerontol Geriatr.* 2001;32(2):77–93.
43. Dominguez AL, Lustgarten J. Implications of aging and self-tolerance on the generation of immune and antitumor immune responses. *Cancer Res.* 2008;68(13):5423–5431.
44. Zhang HG, Grizzle WE. Aging, immunity, and tumor susceptibility. *Immunol Allergy Clin North Am.* 2003;23(1):83–102.
45. Cambier J. Immunosenescence: a problem of lymphopoiesis, homeostasis, microenvironment, and signaling. *Immunol Rev.* 2005;205(1):5–6.
46. Naylor K, Li G, Vallejo AN, et al. The influence of age on T cell generation and TCR diversity. *J Immunol.* 2005;174(11):7446–7452.
47. Cicin-Sain L, Smyk-Pearson S, Currier N, et al. Loss of naive T cells and repertoire constriction predict poor response to vaccination in old primates. *J Immunol.* 2010;184(12):6739–6745.
48. Mackall CL, Hakim FT, Gress RE. Restoration of T-cell homeostasis after T-cell depletion. *Semin Immunol.* 1997;9(6):339–346.
49. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the

treatment of patients with refractory metastatic melanoma. *J Clin Oncol.* 2005;23(10):2346–2357.

Notes

No author has received financial support for the submitted work. Dr P. Iversen has had advisory and/or lecturing relationships with Dendreon, Bavarian Nordic, AstraZeneca, Ferring, Amgen, Astellas, Janssen, and Sanofi-Aventis. Dr C. Parker has had advisory and/or lecturing relationships with Dendreon, Takeda, Janssen, Bayer, and Amgen, who might have had an interest in the submitted work in the previous 3 years. The spouses, partners, or children of the authors have no financial relationships that may be relevant to the submitted work. No author has nonfinancial interests that may be relevant to the submitted work.

Affiliations of authors: Trudeau Institute, Saranac Lake, NY (LH); Academic Urology Unit, The Royal Marsden NHS Foundation Trust, UK (CP); Department of Urology, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark (PI).