Platinum Priority

Reply form Authors re: Bertrand Tombal. Continuous Improvement Versus Innovation: The Case for Sipuleucel-T. Eur Urol 2012;61:648–9

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We agree with Tombal [1] and others [2] that sipuleucel-T, an autologous antigen-presenting cell (APC)–based and antigen-targeted immunotherapeutic, represents a paradigm-altering innovation for men with metastatic castration-resistant prostate cancer (CRPC). The extension of survival with sipuleucel-T (25.8 mo compared with 21.7 mo; hazard ratio [HR]: 0.78; $p = 0.03$) validates the immune system as a target in CRPC, which joins melanoma and renal cell carcinoma as an immune-responsive malignancy. Moreover, the success of sipuleucel-T in therapy for metastatic CRPC has provided the impetus to investigate this therapy in earlier settings of prostate cancer and to develop immunotherapy, in general, for CRPC as well as for other malignancies not traditionally considered responsive to immunotherapy. The approval of sipuleucel-T almost did not occur after the initial randomized phase 3 trials (D9901 and D9902A) demonstrated an extension in only the secondary end point (survival) and not in the primary end point (time to progression) [3]. These data led to the rejection by regulatory authorities of an earlier application for approval in 2007, before formal approval in 2010 based on the subsequent pivotal Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial.

Conversely, skepticism regarding the value of sipuleucel-T persists. The uncertainty regarding its mechanism of activity, the lack of early benefits (responses and progression-free survival), and concerns regarding its costs have fueled this skepticism. It is noteworthy that the survival benefit seen in the earlier but smaller phase 3 studies was recapitulated in the pivotal IMPACT trial and therefore is unlikely to be an aberration attributable to unknown imbalances [3,4]. Regarding the mechanism of activity, the limited immune response data from IMPACT that have been presented in abstract form support the activation of APCs and an association of an antigen-targeted immune response and potency of the product with better survival [5]. Additionally, supportive evidence for a delayed benefit in clinical symptoms (time to disease-related pain) was recently presented [6]. Intriguingly, a separation in the time to disease-related pain curves was seen at approximately 6 mo, with 39.3% of sipuleucel-T patients compared with 18.9% of controls pain-free at 12 mo. Finally, concerns regarding costs remain despite the decision on June 30, 2011, by the US Centers for Medicare and Medicaid Services that declared sipuleucel-T to be "reasonable and necessary." The formal incorporation of cost-efficacy analyses in prospective randomized trials is warranted for all novel agents in the future, especially given the current economic climate. Cost efficacy analyses are decidedly a difficult undertaking, but society must seriously engage in this debate.

Tombal [1] mentioned the finding that the small subset of patients in the study who are <65 yr (median age in the study was 72 yr) do not benefit from therapy [7]. However, this finding was a component of unplanned subanalyses that is hypothesis generating and warrants further study but that does not provide practice-altering data. Indeed, when examining age as below median compared with above median, both groups displayed an HR in favor of sipuleucel-T. Notably, all of the other subgroup analyses demonstrated better outcomes for the sipuleucel-T group, especially the critical subanalysis that controlled for subsequent docetaxel. Additionally, patients who crossed over from placebo to the frozen product appeared to benefit (median survival: 20.0 mo compared with 9.8 mo; HR: 0.52; $p = 0.0001$).

Regarding the exceptionally poor median survival in the placebo group of IMPACT that did not receive delayed docetaxel (13.6 mo, $n = 85$), this group probably represents patients with biologically aggressive disease, patients who refused therapy, or patients who were poor candidates for systemic therapy because of declining performance status or comorbidities. Provocatively, despite patient-selection caveats, the group that received sipuleucel-T and subsequently received docetaxel exhibited the best median survival (28.5 mo, $n = 195$). A detrimental impact of leukapheresis that was overcome by sipuleucel-T in the treatment group (and the placebo group that later received the frozen product) but not in the placebo group that never received further therapy seems implausible, since leukapheresis has not been demonstrated to have a negative impact on clinical outcomes in any other malignancy or in healthy donors [8]. It is noteworthy that even in the overall population enrolled in IMPACT, the median time to clinical progression was only approximately 14.5 wk in both arms of the trial. Thus, even relatively asymptomatic patients appear to progress rapidly, and biomarkers are necessary to separate the patients with indolent tumors (who may warrant close observation as a strategy) from the patients with biologically aggressive tumors who warrant immediate therapy.

On the heels of sipuleucel-T, another immunotherapeutic agent with a distinctly different mechanism of activity has been approved by regulatory authorities for another advanced malignancy. Ipilimumab, a T-lymphocyte checkpoint (cytotoxic T-lymphocyte antigen-4)–inhibiting monoclonal antibody, demonstrated improved outcomes

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in the context of advanced melanoma [9]. Unlike sipuleucel-T, which requires a leukapheresis before each of the three intravenous doses to prepare the customized product, ipilimumab does not entail customized, patient-specific manufacture and is currently undergoing phase 3 evaluation for use in patients with CRPC. On the downside, ipilimumab induces a nonspecific upregulation of systemic T-lymphocyte activity, which is associated with potentially life-threatening complications (hypophysitis, enterocolitis, and hepatitis). Pox virus–based antigen-targeted immunotherapy also does not require customized preparation, and promising phase 2 data have led to a phase 3 trial [10]. Additionally, novel immunotherapeutic agents—for example, PD-1 inhibitors, designer antigen-targeted T-lymphocytes, and APC-based products—are undergoing vigorous evaluation. Thus, sipuleucel-T may simply be the first among new and more potent immunotherapeutic agents in therapy for CRPC.

As the development of novel biologic agents proceeds, the intent to discover biomarkers predictive of efficacy for currently approved and future therapies (eg, *HER2* amplification to use trastuzumab for breast cancer and wild-type *K-ras* to use cetuximab or panitumumab for colon cancer) is of paramount importance and should be considered mandatory. Administration of agents to patients most likely to benefit will yield more cost-effective therapy. Moreover, optimal combinations and sequencing of new agents remain to be determined.

Conflicts of interest: Guru Sonpavde receives research support to his institution from Bellicum Pharmaceuticals and is on the speakers' bureau or advisory board for Dendreon, Centocor Biotech, Amgen, Novartis, and Sanofi-Aventis. Giuseppe Di Lorenzo receives research support and is on the advisory board for Dendreon. Celestia S. Higano receives research support to her institution from Dendreon, Medivation, and Cougar Biotech and is on the advisory board for Dendreon, Medivation, and Amgen. Philip W. Kantoff is a consultant to Dendreon, Bellicum Pharmaceuticals, and BN-IT. Neal D. Shore receives research support from, and is the advisory board of, Dendreon.

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