Product: PROVENGE

Proper Name: Sipuleucel-T

Indication: PROVENGE is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

Description: PROVENGE consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs), that have been activated during a defined culture period with a recombinant human protein, PAP-GM-CSF, consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator**.**

BLA: STN BL 125197

Regulatory Milestone:

Date	Milestone Description
22 DEC 1996	IND Original submission, BB-IND 6933, in effect.
03 NOV 1998	End of Phase 2 Meeting to discuss a prospective Phase 3 trial including product issues, clinical target population, study endpoints, assessment of treatment benefit, and appropriate controls.
04 MAR 1999	Follow-Up to End of Phase 2 Teleconference to discuss a prospective Phase 3 trial and a Phase 2 open-label salvage trial
03 SEP 1999	Follow-Up to End of Phase 2 Teleconference on Phase 3 Protocols D9901 and D9902, discussing study design and statistical analysis plan
20 JUL 2001	Sipuleucel-T Clinical Development Plan and new Phase 3 study P-11
26 JUL 2002	D9901 Final Statistical Analysis Plan (SAP) submitted to FDA

Oct 2002	D9901 Primary Analysis
22 NOV 2002	Type A Meeting to discuss results of D9901 and proposed changes to D9902
30 MAY 2003	Special Protocol Assessment agreement received for Protocol D9902B
30 JUL 2003	Sipuleucel-T received Fast Track designation for the treatment of asymptomatic patients with metastatic, Gleason Sum ≤ 7 AIPC
October 2004	D9901 Survival Analysis Performed
24 NOV 2004	D9902A Final Statistical Analysis Plan submitted to FDA
28 JUL 2005	Type C Meeting (CMC Licensing Strategy)
11 OCT 2005	Amendment 7 for Protocol D9902B submitted
25 NOV 2005	SPA agreement for Amendment 7
21 Aug 2006	Clinical section of BLA submitted electronically
29 March 2007	Meeting of CTGT advisory committee to discuss BLA 125197
8 May 2007	CR letter issued by FDA
9 Jan 2008	SPA amendment submitted
29 Apr 2008	Type C pre-BLA clinical issues
29 Jan 2009	Revised statistical analysis plan submitted to IND 6933 Amd # 279
14 April 2009	Revised IDMC charter submitted to IND 6933 Amd # 282

PDUFA Goal Date: May 1, 2010

FDA Approval Date: April 29, 2010

EU approval: September 06, 2013 (withdrawn)

Package Insert: Package Insert - Provenge

Summary Basis for Regulatory Approval: April 29, 2010 Summary Basis for Regulatory Action - Provenge

European Public Assessment Report: June 27, 2013 Assessment report - Provenge

Manufacturing Platform:

PARAMETER	DATA	REFERENCE
Manufacturer	Dendreon Corporation	
Transgene	Autologous peripheral blood mononuclear cells (PBMCs)	1
Indication	PROVENGE is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.	1
Virus and Serotype	Baculovirus expression vector	2
Cell Substrate	Sf21 cell line	3
Manufacturing platform	Provenge is manufactured from a patient's own peripheral blood cells obtained via apheresis (APH). The APH is considered a cellular starting material. The manufacturing process involves several concentration and separation steps using proprietary separation solutions and devices to reduce certain cell types. The resulting population is then incubated with the fusion protein PA2024 under specified conditions (temperature and time), to activate the antigen presenting cells. Following incubation with the antigen, the cells are aseptically harvested, washed, suspended in lactated ringers, and packed for delivery to the infusion center.	3
Dose in vial/final container	50 million autologous CD54+ cells activated with PAPGM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP	1

Dose / patient	3 doses at approximately 2-week intervals.	1

1. Package insert: Package Insert - Provenge
2. EPAR full: Provenge
3. EPAR quality: June 27, 2013 Assessment report - Provenge
4. FDA SBAR: April 29, 2010 Summary Basis for Regulatory Action - Provenge

Advisory Committee:

The original BLA for sipuleucel-T for treatment of prostate cancer was submitted in 2006. That application was based on results from Studies D9901 and D9902A. On March 29, 2007, FDA held an advisory committee meeting (Cellular, Tissue and Gene Therapies Advisory Committee, supplemented by members of the Oncology Drugs Advisory Committee and several prostate cancer specialists) to seek advice on the persuasiveness of the sipuleucel-T efficacy and safety results. In addition, several questions regarding product potency, variability, and mechanism of action were discussed.

The committee generally agreed that the data supported the proposed mechanism of action, that CD54 up-regulation was a good indicator of antigen presenting cell activation, and that the therapy has the potential to improve antigen presentation to tumor-specific T cells. Regarding the immune monitoring data, the Committee stated that more information was needed in order to 1) determine the function of antigen presenting cells in the product in stimulating T and B cell responses, 2) determine the role of PAP antigen in eliciting an immune response, and 3) evaluate host T cell activation and suppression in product function, and how that will or will not correlate with survival.

After discussions regarding the significance of the CVEs reported in the submitted studies, the committee voted unanimously (17-0) that safety had been established. The Committee recommended that post marketing pharmacovigilance studies be performed to monitor the incidence of CVEs, with attention to the African American population and other minorities.

After additional discussion, the Committee voted 13 yes and 4 n o to the question of whether there was substantial evidence that the product was effective. Despite the majority of yes votes, the majority of Committee members expressed uncertainty regarding treatment effect (increased survival) of sipuleucel-T in the intended patient population. In addition, there was a consensus that the ongoing D9902B trial must be completed; that, to confirm the survival advantage seen in D9901, the integrity of D9902B must not be compromised, and that the under-representation of the African American population should be addressed.

After complete review of the original BLA submission, the FDA determined that the efficacy result in the original application was not statistically persuasive. Therefore, the FDA issued a complete response letter requiring submission of the results of Study D9902B before licensure.

Clinical Trials:

NCT	TRIAL PHASE	SUBJECTS ENROLLED	TITLE	COUNTRIES
NCT00005947	3	127	Vaccine Therapy in Treating Patients with Metastatic Prostate Cancer That Has Not Responded to Hormone Therapy	United States
NCT00065442	3	512	Provenge® (Sipuleucel-T) Active Cellular Immunotherapy Treatment of Metastatic	United States, Canada

			Prostate Cancer After Failing Hormone Therapy	
NCT00779402	3	176	PROvenge Treatment and Early Cancer Treatment	United States
NCT00849290	2	113	Immunotherapy for Men With Objective Disease Progression On Protocol D9902 Part B (NCT00065442)	United States, Canada
NCT01133704	3	98	Immunotherapy with APC8015 (Sipuleucel-T, Provenge) for Asymptomatic, Metastatic, Hormone-Refractory Prostate Cancer	

EudraCT Numbers:

- 2011-001192-39

Publications:

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- Kantoff, P. W., Higano, C. S., Shore, N. D., Berger, E. R., Small, E. J., Penson, D. F., Redfern, C. H., Ferrari, A. C., Dreicer, R., Sims, R. B., Xu, Y., Frohlich, M. W., Schellhammer, P. F., & IMPACT Study Investigators (2010). Sipuleucel-T immunotherapy for castration-resistant prostate cancer. The New England journal of medicine, 363(5), 411–422. https://doi.org/10.1056/NEJMoa1001294
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