PROTOCOL SYNOPSIS

Protocol Title: An Open-Label, Multicenter Study of Subjects With Metastatic Castrate-Resistant Prostate Cancer Treated With Provenge and Boosted With a Single Infusion of Sipuleucel-T to Measure Immune Response

Protocol Number: P23-1

Clinical Phase: 3

Investigational Product, Dosage Form, Route, and Dose Regimen:

Provenge® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer (mCRPC; Provenge, 2017). The recommended course of therapy for Provenge is 3 complete doses, given at approximately 2-week intervals. In controlled clinical trials, the median dosing interval between infusions was 2 weeks (range 1 to 15 weeks); the maximum dosing interval has not been established.

Provenge elicits sustained immune responses (IFN-γ enzyme-linked immunosorbent spot assay [ELISPOT], proliferation, antibody titers, and antigen spread), and these immune responses have correlated with overall survival in patients with mCRPC (Sheikh, 2013; GuhaThakurta, 2015; Antonarakis, 2018). Previous results from the P10-1 study showed that immune responses to sipuleucel-T persisted and could be boosted, similar to a vaccine (Beer, 2013; Beer, 2017; Zhang, 2020).

Sipuleucel-T is an autologous cellular immunotherapy available as a suspension for intravenous infusion. Sipuleucel-T consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs) that have been activated during a defined culture period with a recombinant human protein, PAP-GM-CSF (also called PA2024). This protein comprises prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. Each dose of sipuleucel-T contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF (PA2024), suspended in 250 mL of Lactated Ringer's Injection, USP. The recombinant antigen is designed to target APCs and may help direct the immune response to PAP. Minimal residual levels of the intact PAP-GM-CSF are detectable in the final sipuleucel-T product.

The patient's PBMCs are obtained via a standard leukapheresis procedure approximately 3 days prior to the infusion date. Due to the autologous nature of sipuleucel-T, it is important that the patient and physician adhere to the personalized leukapheresis and infusion schedules.

The cellular composition of sipuleucel-T is dependent on the composition of cells obtained during the patient's leukapheresis. In addition to APCs, the final product contains T cells, B cells, natural killer (NK) cells, and other cells. The number and types of cells present in each sipuleucel-T dose will vary.

The potency of sipuleucel-T is in part determined by measuring the increased expression of the CD54 molecule, also known as ICAM-1, on the surface of APCs after culture with PAP-

Inclusion Criteria

For a subject to be eligible for participation in this study, *all* of the following criteria must be satisfied.

1. Potential subjects are men aged ≥18 years who are clinically indicated for treatment with Provenge (asymptomatic or minimally symptomatic metastatic castrate-resistant [hormone refractory] prostate cancer)
2. Have qualified for on-label Provenge infusion
3. Have received all 3 infusions of Provenge prior to randomization
4. Written informed consent provided prior to the initiation of study procedures
5. Estimated life expectancy ≥12 months

Exclusion Criteria

A subject will not be eligible for participation in this study if *any* of the following criteria apply.

1. Men who are <u>not</u> clinically indicated for treatment with Provenge (asymptomatic or minimally symptomatic metastatic castrate-resistant [hormone refractory] prostate cancer)
2. Need for systemic chronic immunosuppressive therapy (eg, antitumor necrosis factor alpha monoclonal antibodies, or glucocorticoids)
3. Uncontrolled, concurrent illness including, but not limited to the following: ongoing or active infection (bacterial, viral, or fungal), or psychiatric illness that would limit compliance with study requirements, as well as any condition that would preclude a subject from completing Provenge or sipuleucel-T treatment
4. On experimental or investigational therapy

Statistical Considerations