

Title: A randomized, double-blind, placebo-controlled, multi-center, phase III trial of sipuleucel-T in men with metastatic, androgen independent prostatic adenocarcinoma (AIPC)

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Background: Sipuleucel-T (APC8015, Provenge[®]) is an autologous cell product consisting of antigen presenting cells (APCs) loaded with prostate antigen PA2024, a recombinant fusion protein composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). Previous studies demonstrated that sipuleucel-T can result in specific immune responses, is well tolerated, and demonstrated evidence of a survival advantage for sipuleucel-T treated patients. Reported here are final overall survival (OS) data from a larger randomized Phase III trial.

Methods: 512 patients with asymptomatic or minimally symptomatic, metastatic AIPC were randomized (2:1) to receive sipuleucel-T (N=341) or placebo (N=171) intravenously every 2 weeks x 3. Patients randomized to placebo who had documented disease progression were eligible to receive salvage therapy with a version of sipuleucel-T prepared from cells cryopreserved at the time of placebo generation. The primary endpoint was OS and the secondary endpoint was time to objective disease progression (TTP). All analyses were performed on the intent to treat population. The primary analysis p-value was derived from a stratified Cox regression model adjusted for prostate specific antigen (PSA) and lactate dehydrogenase (LDH). To achieve statistical significance, the p-value at the final analysis was required to be < 0.043.

Results: Patient demographics and baseline characteristics were well-balanced between treatment arms. Patients on the sipuleucel-T treatment arm experienced a 22.5% reduction in the risk of death (HR=0.775; 95% CI: 0.614, 0.979; p=0.032). The median survival in the sipuleucel-T arm was 25.8 months vs 21.7 on the placebo arm, a 4.1 month difference. At 36 months from randomization, the estimated survival probability was 31.7% for the sipuleucel-T arm vs 23.0% for placebo arm. The treatment effect was consistent across multiple patient subsets. The treatment effect remained consistent using the log rank test and an unadjusted Cox model (HR=0.766, p=0.023), and after adjustment for docetaxel use following investigational therapy (HR=0.763; p=0.036). Prostate cancer specific survival also favored the sipuleucel-T arm (HR=0.772; p=0.036). There was no significant delay in the time to objective disease progression (HR=0.951 [95% CI: 0.77, 1.17]; P=0.628). The adverse events seen more commonly in sipuleucel-T treated patients included chills (54.1%), pyrexia (29.3%), and headache (16.0%). Only 1.2% of patients did not receive all 3 infusions due to treatment related adverse events.

Conclusions: Sipuleucel-T is the first active cellular immunotherapy to demonstrate a statistically significant and clinically meaningful improvement in overall survival for cancer, and demonstrates a favorable benefit to risk profile. It has the potential to create a new paradigm for the treatment of advanced prostate cancer