Provenge Shows Survival Benefit in Prostate Cancer

BY SUSAIR KIRK

CHICAGO — Autologous active cellular immunotherapy with sipuleucel-T, the controver- sial investigative agent with the brand name Provenge, extended survival by a median of 4.1 months in men with metastatic androgen-independent prostate cancer, according to the 7-year follow-up data from the IMPACT study.

The much-anticipated results of the phase III, multicenter, randomized, double-blind, placebo-controlled trial were presented in a late-breaking science session at the annual meeting of the American Urological Association.

“The data show that sipuleucel-T is the first active immunotherapy to demonstrate an improvement in overall survival for advanced prostate cancer,” said conversigator Dr. David F. Penson of the University of Southern California in Los Angeles.

“Provenge appears to have a highly favorable benefit-to-risk profile [and] a short duration of therapy, and perhaps most im- portantly, will not only change the way we manage prostate cancer, but also has the potential to create an entirely novel ther- apeutic paradigm across the field of oncology,” he said.

Median survival reached 25.8 months in the treatment group and 21.7 months with placebo. The 3- year survival rate was 31.7% with treatment and 23% with placebo, a relative increase of 38% (P = .032). The hazard ratio was 0.775, indicating a 22.5% reduction in the risk of death in the sipuleucel-T treatment arm.

The experimental vaccine from Dendreon Corp. still had not met the primary end point when interim results from the IMPACT trial were reported for Prostate Adenocarcinoma Treat- ment (PRO) trial were made public in fall 2008. An earlier Food and Drug Administration decision not to approve Provenge, pending more data, had triggered demonstrations by patient ad- vocates of the therapy.

The IMPACT trial included 512 patients with minimally symptomatic or asymptomatic advanced androgen-independent prostate adenocarcinoma with metastasis to lymph nodes or bone, who had a life ex- pectancy of at least 3 months and a serum prostate-specific antigen (PSA) level greater than 5 ng/mL. They were random- ized at a 2:1 ratio to receive the experimental vaccine or a placebo. In all, 99% of patients com- pleted treatment.

The active cellular immunother- apy is designed to stimulate and optimize production of the patient’s T cells and to enlist these cells in the destruction of specific tumor cell types.

At the time of disease pro- gression, patients in both arms of the study were able to re- ceive treatment at the physi- cian’s discretion. Patients were randomized to PSA scanning once every 4 years or to no regular scanning. The screening proto- col varied by country: PSA cutoffs trigger- ing more frequent testing ranged from 2.5 to 7 ng/mL.

Researchers found 5,990 prostate can- cers in the screening group vs. 4,307 in the control group. But the increased diag- noses carried a price. Of the men who underwent biopsy for an elevated PSA, 76% had a false- positive result. The positive pre- dictive value of a prostate biopsy was also low— just 24% on average.

In a preselected core group of men aged 65-69 years, there were significant- ly more prostate cancer deaths in the control group (326 vs. 214; odds ratio 0.80). In the intent-to-screen analysis, which included all subjects, the absolute difference between the screening and control groups was 0.71 deaths/1,000 men, yielding 1,410 screenings and 48 cancers to prevent 1 prostate cancer death.

Criticism of PLCO Study

The PLCO study garnered criticism at the meeting from specialists who said the research was seriously flawed and that public confusion regarding the finding of no mortality reduction with screening could prevent men from seeking a test that could predict their future risk of prostate cancer and ultimately re- duce mortality.

During the press briefing, Dr. William J. Catalona, medical director of the Urologi- cal Research Foundation and director of the clinical prostate cancer program at the Robert H. Lurie Comprehensive Cancer Center at Northwestern Memo- rial Hospital, Chicago, described PLCO as “just a snapshot taken halfway around the track” that has been incorrectly pro- moted as the “Holy Grail.”

“This is a trivial matter, because giving the wrong message out to the public could dis- suade men from undergoing po- tentially life-sav- ing testing and potentially life- saving treat- ment,” said Dr. Catalona, who moderated the press briefing, which was also attended by Dr. Crawford and Dr. Schroder. Dr. Catalona, who developed the PSA test, disclosed that he has grants from two PSA assay companies and from deCODE Genetics of Reykjavik, Iceland.

“Death from prostate cancer in 7 years is meaningless” because the average in- terval between prostate cancer recur- rence after radical prostate surgery is 7 years, Dr. Catalona added.

The mortality curves for the screening and control arms of the study began to diverge at about 7-8 years and continued to do so over time.

PLCO’s use of the PSA cutoff of 4 ng/mL for biopsy and the fact that few- er than half of subjects in the screening arm actually underwent a biopsy also point to serious problems, he said.

“How could anybody expect a trial like this to show that screening saves lives when the people who are screened don’t get a biopsy? If the PLCO people had set out to design a study that would dis- credit PSA testing, it would be difficult to do a better job. And if they wanted to simulate what would happen if every man in the United States got tested for PSA but few followed up with a biopsy or treatment, we could have guessed the answer.”

Reductions in death rates with PSA screening are appearing in World Health Organization databases in westernized countries where PSA testing is wide- spread, Dr. Catalona said. “These studies are not a message in the wilderness. They unequivocally demonstrate that PSA testing, if done right, can save lives.”

Dr. Carroll said in an interview that contamination in the PLCO study dilut- ed its ability to show a difference be- tween the two study groups.

Approximately 40% of men in the study changed their PSA levels in the previous year. “That cuts out cancer that may have been detected during the trial,” he said. Further, at least 53% of men in the control group actually re- ceived PSA screening. “We think that number may actually be much higher, because virtually all of the cancers de- tected [in this group] were stage 1 and 2, which are virtually always detected by PSA and DRE.”

To recommend a biopsy, the study used a single PSA cut point rather than PSA in conjunction with family history, ethnicity, and other factors that may play a role in prostate cancer risk. “Based on the PLCO trial, you cannot say that ear- ly detection does not reduce mortality. The European trial showed that it did,” he said.

Michael G. Sullivan contributed to this report.