

Rollins, James (CMS/OCSQ)

From: Dolina, Elaine L. (CMS/OCSQ)
Sent: Thursday, July 29, 2010 7:51 AM
To: Jacques, Louis B. (CMS/OCSQ); Rollins, James (CMS/OCSQ); PASERCHIA, LORI A. (CMS/OCSQ); Fitterman, Leslye (CMS/OCSQ)
Subject: RE: NCA Tracking Sheet for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer (CAG-00422N)

I went ahead and entered the comment.

https://www.cms.gov/mcd/publiccomment_popup.asp?comment_id=21547

We can worry about the attachments later. They might be difficult to make 508 compliant.

-----Original Message-----

From: Jacques, Louis B. (CMS/OCSQ)
Sent: Wednesday, July 28, 2010 11:23 PM
To: Rollins, James (CMS/OCSQ); PASERCHIA, LORI A. (CMS/OCSQ); Fitterman, Leslye (CMS/OCSQ); Dolina, Elaine L. (CMS/OCSQ)
Subject: FW: NCA Tracking Sheet for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer (CAG-00422N)

-----Original Message-----

From: Larson, Tricia [mailto:tlarson@Dendreon.com]
Sent: Wed 7/28/2010 10:25 PM
To: Jacques, Louis B. (CMS/OCSQ)
Cc: Bishop, Hans; Frohlich, Mark; Lockett, Chris
Subject: NCA Tracking Sheet for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer (CAG-00422N)

July 28, 2010

Louis Jacques, MD

Director, Coverage and Analysis Group

Centers for Medicare & Medicaid Services

Mail Stop S3-02-01

7500 Security Blvd.

Baltimore, MD 21244

Re: NCA Tracking Sheet for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer (CAG-00422N)

Dear Dr. Jacques:

On behalf of Dendreon Corporation (Dendreon), I am submitting the following comments on the opening of a national coverage analysis (NCA) for autologous cellular immunotherapy treatment of metastatic prostate cancer.[1] Dendreon is the manufacturer of PROVENGE® (sipuleucel-T), an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. PROVENGE is the first in a new class of biological products designed to induce a tumor-specific immune response. The Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA) approved PROVENGE on April 29, 2010 under a biologic license application (BLA, license number 1749). Bringing PROVENGE to market has been a 15-year journey that has involved more than a thousand courageous patients, 15 clinical trials, and nearly one billion dollars of funding of research and development.

Dendreon appreciates the numerous opportunities we have had to meet with the Centers for Medicare and Medicaid Services (CMS) to discuss PROVENGE both pre- and post- FDA approval. We believe that the agency should be very familiar with PROVENGE's clinical benefits and manufacturing process as a result of these meetings and all of the additional information we have provided in other various forms. Specifically, in just the past few months, Dendreon applied for a Healthcare Common Procedure Coding System (HCPCS) code and for pass-through biological status under the hospital outpatient prospective payment system (OPPS). Each application requires substantial clinical and product information that further demonstrates the appropriateness and reasonableness of immediate Medicare coverage. As we describe in further detail below, we are now enhancing the breadth and depth of evidence of PROVENGE's effectiveness in the Medicare population by including a recently published study in the New England Journal of Medicine. Based upon the overwhelming clinical evidence showing a significant improvement in overall survival in this patient population, the "gold standard" of all endpoints in oncology clinical trials, we ask CMS to reconsider whether a NCA is necessary. We make this request based on the fact that CMS's initiation of this process was highly unusual. Since the current NCA process was implemented after the Medicare Modernization Act of 2003 (MMA), this is the first time CMS has internally initiated a NCA for an approved use of an innovative new cancer biological. The evidence we have submitted demonstrates that consistent with other drugs and biologicals CMS currently covers, PROVENGE clearly is reasonable and necessary for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer. Dendreon believes that upon further review, CMS should conclude that the NCA can be closed at this time, without the need for further evaluation, a technology assessment (TA), or a Medicare Evidence Development and Coverage Advisory Committee (MedCAC) meeting.

Under CMS's Guidance for the Public, Industry and CMS Staff: Factors CMS Considers in Opening a National Coverage Determination, CMS identifies several circumstances in which CMS could internally initiate a NCA for a new technology. Although we do not know the precise reason CMS opened this NCA, we think the agency may have initiated it based on a belief that "significant uncertainty exists concerning the health benefits, patient selection, or appropriate facility and staffing requirements for the new technology." [2] As stated above, we believe that any uncertainty about the health benefits, patient selection, and appropriate provision of PROVENGE can be addressed without further analysis by CMS. FDA's review of PROVENGE was comprehensive and rigorous. The agency reviewed data from 4 randomized trials involving over 900 patients. The pivotal registration study was conducted under a Special Protocol Assessment agreement with the FDA and demonstrated a statistically significant survival benefit. Similar results were seen in a previous smaller randomized trial.

In addition to the data relied upon by the FDA, the attached article, published in the New England Journal of Medicine on July 29, 2010, presents the results of the double-blind, placebo-controlled phase III trial for PROVENGE, as well as summarizes the findings from 2 earlier phase III trials. The article concludes that the "use of sipuleucel-T prolonged overall survival among men with metastatic castration-resistant prostate cancer." [3]

As described in the New England Journal of Medicine article, sipuleucel-T has shown evidence of efficacy in reducing the risk of death among men with metastatic castration-resistant prostate cancer. In the randomized double-blind, placebo-controlled, multicenter phase III "IMPACT" trial, we randomly assigned 512 patients with median age of 71, in a 2:1 ratio to receive either sipuleucel-T (341 patients) or placebo (171 patients) administered intravenously every 2 weeks, for a total of 3 infusions.

The primary endpoint of this study was overall survival, the most meaningful clinical outcome for patients, analyzed by means of a stratified Cox regression model adjusted for baseline levels of serum prostate-specific antigen (PSA) and lactate dehydrogenase. In the sipuleucel-T group, there was a relative reduction of 22% in the risk of death as compared with the placebo group (hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.61 to 0.98; $P = 0.03$). There was a 4.1-month improvement in median survival (25.8 months in the sipuleucel-T group vs. 21.7 months in the placebo group). The 36-month survival probability was 31.7% in the sipuleucel-T group versus 23.0% in the placebo group. The treatment effect was also observed with the use of an unadjusted Cox model and a log-rank test (HR, 0.77; 95% CI, 0.61 to 0.97; $P = 0.02$) and after adjustment for use of docetaxel after the study therapy (HR, 0.78; 95% CI, 0.62 to 0.98; $P = 0.03$).

Importantly, the results of the IMPACT trial confirmed the results of the earlier D9901 study, published in the attached article in the Journal of Clinical Oncology. [4] Specifically, in this study there was a relative reduction of 41% in the risk of death in the sipuleucel-T group compared with the placebo group (HR, 0.586; 95% CI, 0.388 to 0.884; $P=0.010$). There was a 4.5 month improvement in median survival (25.9 months in the sipuleucel-T group vs. 21.4 months in the placebo group). In this study, 34% of the men were alive at the 3 year follow-up compared to 11% in the placebo group. An integrated survival analysis completed with these results together with the results from the D9902A [5] trial and IMPACT demonstrated a p-value of <0.001 , suggesting a less than 1 in 1000 chance that the results would have been observed by chance alone.

Additionally, PROVENGE has a favorable side effect profile. The most common adverse events (AEs), reported in patients in the sipuleucel-T group at a rate $\approx 15\%$, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. The majority of AEs in trials were grades 1 or 2. The most common ($\approx 2\%$) Grade 3-5 adverse events reported in the sipuleucel-T group were back pain and chills. The percentage of patients in each arm experiencing serious AEs (SAEs) was comparable, including the percentage with cerebral vascular accidents (CVAs), of which none were attributed to sipuleucel-T. Safety concerns raised earlier by the FDA about the incidence of CVAs are addressed by a Risk Management Plan submitted as part of the amendment to the BLA and a post-marketing registry study.

In conclusion, multiple randomized trials have shown that PROVENGE prolonged survival among men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. This strong clinical evidence led to FDA approval and should serve as the foundation for coverage by CMS. There is a current unmet need for the treatment of men with metastatic castrate resistant prostate cancer who have yet become symptomatic enough to receive traditional chemotherapy manipulation. PROVENGE provides a new, innovative, safe, and proven opportunity for such patients to extend their lives with minimal daily interruptions.

The evidence provided to CMS and contained in the New England Journal of Medicine article, demonstrates that PROVENGE is reasonable and necessary for patients with asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer and that the NCA is not warranted. More important, it creates an unnecessary additional hurdle for patients to navigate as they seek treatment for this deadly disease. Now that CMS has adequately gathered "comments and additional information or evidence of studies" about the policy under consideration,[6] the agency need not invest additional time and resources into evaluating coverage of PROVENGE. This is particularly true as the primary endpoint of the IMPACT trial was overall survival, and the median age of patients enrolled was 71 years, with 75% of the patients being 65 years of age or older and eligible for Medicare. The subgroup analysis of patients 65 years of age or older in the integrated dataset for the 3 randomized trials in metastatic castrate resistant prostate cancer demonstrated consistency of the PROVENGE treatment effect. The median survival was 23.4 months in the PROVENGE group and 17.1 months in the placebo group. PROVENGE clearly shows effectiveness in the Medicare population and improves health outcomes in patients with prostate cancer. Accordingly, we request that CMS close this NCA and instead allow its local contractors to cover PROVENGE, applying the same coverage criteria as they apply to any other new cancer drug or biological. We believe that CMS should rely on its local contractors and physicians, through its local processes to determine appropriate use. CMS should not stand in the way of the adoption of new technologies and perhaps a new standard of care; rather, it should partner with its local contractors and physicians to educate Medicare beneficiaries on the clinical benefits and appropriate use of PROVENGE.

To the extent that CMS initiated this NCA based on concerns about "health inequalities" and "local variation" and a desire to ensure that this "substantial clinical advance . . . diffuses more rapidly to all patients for whom it is indicated,"[7] this uniformity and diffusion already is occurring. Although we expressed concerns during our most recent meeting with you about the variations in coverage of PROVENGE between contractors, these variations have subsided. Currently most Medicare contractors have published guidelines or verbally indicated they are/will cover PROVENGE as a biological product for its on-label indication, and Medicare beneficiaries across the country have access to PROVENGE in their battle against metastatic castrate resistant prostate cancer. Again, this reinforces why the NCA is not necessary at this time.

We believe that if CMS does decide to move forward with this NCA, it should conclude the process quickly, without a TA or a MedCAC meeting. We believe that a TA is not needed because none of the conditions listed in the guidance document regarding factors CMS considers in commissioning a TA exist. In particular, there are no "significant differences in opinion among experts," as shown by the fact that soon after PROVENGE was approved by the FDA, the National Comprehensive Cancer Network (NCCN) listed PROVENGE in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines^T) for Prostate Cancer (version 2.2010) and

NCCN Drugs & Biologics Compendium (NCCN CompendiumT) as a category 1 treatment recommendation for patients with castration-recurrent prostate cancer.[8] A category 1 recommendation means that "the recommendation is based on high level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus." [9] NCCN is a not-for-profit alliance of 21 of the world's leading cancer centers. Its experts are world renowned, and its Prostate Cancer Panel includes 28 members from the best cancer hospitals across the country. NCCN's rapid inclusion of PROVENGE in its Guidelines and Compendium with a category 1 recommendation shows the high level of consensus that exists regarding PROVENGE's clinical data as well as PROVENGE's role in the treatment regimen for prostate cancer.

Furthermore, although the description of the TA on the Agency for Healthcare Research and Quality (AHRQ) website recently was changed from "The Efficacy and Safety of Sipuleucel T" to "The Outcomes of Sipuleucel T," [10] we continue to be concerned that the scope of the assessment duplicates the review already conducted by the FDA. For the same reasons, we believe that a meeting of the MedCAC is not needed to assess the data on PROVENGE, all of which already has been reviewed by CMS.

If CMS proceeds with the NCA, we believe the agency should issue a proposed decision as soon as possible covering PROVENGE under the same standards as apply to any other drug or biological used in an anticancer chemotherapeutic regimen. Under the Social Security Act (SSA), any FDA-approved use of a drug or biological in an anticancer chemotherapeutic drug regimen is a "medically accepted indication" that is included in the definition of "drugs and biologicals" that may be covered by Medicare.[11] The use of PROVENGE for asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer is approved by the FDA and thus is a "medically accepted indication" used in an anticancer chemotherapeutic drug regimen that should be covered by Medicare. In addition, other uses of FDA-approved drugs used in anticancer chemotherapeutic drug regimens are "medically accepted indications" if the use is supported by authoritative compendia recognized by the Secretary of Health and Human Services.[12] The NCCN Drugs and Biologics Compendium is one of these compendia,[13] and it supports use of PROVENGE for "asymptomatic or minimally symptomatic patients with performance status 0-1 and a life expectancy of greater than 6 months and no visceral disease." [14] By virtue of this listing in the NCCN Compendium, PROVENGE would satisfy the criteria for coverage even if it had not been approved for asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer; therefore, it undoubtedly should be covered for its FDA-approved use.

Thank you for your thoughtful consideration of our comments. We remind you that the patients we serve have late-stage cancer and few, if any, appealing treatment options available to them, with only chemotherapy as an FDA-approved alternative. Not only is PROVENGE clearly reasonable and necessary for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer, but it provides an unambiguous survival benefit and real hope for patients battling their disease. At Dendreon, so many of us have been affected by cancer, which is why we have dedicated our lives to transforming the way cancer is treated. The patients PROVENGE treats are our fathers, our husbands, our brothers and sons, our teachers and physicians, our veterans and our friends. We urge you not to deny them access to PROVENGE and recognize that survival is more than just surviving: it allows cancer patients the freedom to live. We appreciate the opportunity to submit these comments and would be pleased to meet with the agency again to address any questions you may have.

Sincerely,

Hans Bishop, Chief Operating Officer of Dendreon

Mark Frohlich, Chief Medical Officer of Dendreon

[1] NCA Tracking Sheet for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer (CAG-00422N), June 30, 2010, <http://www.cms.gov/mcd/viewtrackingsheet.asp?id=247>.

2 Guidance for the Public, Industry and CMS Staff: Factors CMS Considers in Opening a National Coverage Determination, April 11, 2006, http://www.cms.gov/mcd/ncpc_view_document.asp?id=6.

3 Kantoff PW, Higano CS, et al. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. *N Engl J Med* 2010;363:411-22.

4 Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol* 2006; 24:3089-94.

5 Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer* 2009;115:3670-9.

6 68 Fed. Reg. 55634, 55639; see also Guidance Document on Factors CMS Considers in Opening a National Coverage Determination, April 11, 2006,