00001

CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Evidence Development & Coverage Advisory Committee

November 17, 2010

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

00002

Panelists

Chairperson
Clifford Goodman, Ph.D.

Vice-Chair
Saty Satya-Murti, M.D., F.A.A.N.

Voting Members
Helen Darling, M.A.
Roger Dmochowski, M.D.
Dale Fuller, M.D.
Karl Matuszewski, M.S., Pharm.D.
David M. Mintzer, M.D.
Pearl Moore, R.N., M.N., F.A.A.N.
Louis Potters, M.D., F.A.C.R.
Kevin Schulman, M.D., M.B.A.
Robert L. Steinbrook, M.D.

CMS Liaison
James Rollins, M.D.

Industry Representative
G. Gregory Raab, Ph.D.

00003

Guest Panel Members
Ravi A. Madan, M.D.
Mitchell Howard Sokoloff, M.D., F.A.C.S.

Invited Guest Speaker
James L. Gulley, M.D., Ph.D., F.A.C.P.

Executive Secretary
Maria Ellis

00004

TABLE OF CONTENTS

00005

TABLE OF CONTENTS (Continued)

00006

TABLE OF CONTENTS (Continued)

00007

PANEL PROCEEDINGS

(The meeting was called to order at 8:14 a.m., Wednesday, November 17, 2010.)

MS. ELLIS: Good morning and welcome, committee

chairperson, vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, MedCAC. The committee is here today to discuss the evidence, hear presentations and public comment, and make recommendations concerning the currently available evidence regarding the clinical benefits and harms from on-label and off-label use of autologous cellular immunotherapy treatment of metastatic prostate cancer. The following announcement addresses conflict of interest issues associated with this meeting and will be made part of the record: The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations disclose if you or any member of your immediate family owns stock or has another formal financial interest in any company, including Internet or E-commerce organizations

00008

that develops, manufactures, distributes and/or markets any autologous cellular immunotherapy treatment for metastatic prostate cancer. This includes direct financial investments, consulting fees, and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker, and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the mike and state your name.

For the record, voting members present today for today's meeting are: Dr. Saty Satya-Murti, Mrs. Helen Darling, Dr. Roger Dmochowski, Dr. Dale Fuller, Dr. Karl Matuszewski, Dr. David Mintzer, Mrs. Pearl Moore, Dr. Louis Potters, Dr. Kevin Schulman, Dr. Robert Steinbrook. A quorum is present and no one has been recused because of conflicts of interest.

The entire panel, including nonvoting members,

00009

will participate in the voting. The voting scores will be available on our website following the meeting. Two averages will be calculated, one for voting members and one for the entire panel. I ask that all panel members please speak directly into the mikes, and you may have to move the mikes since we may have to share.

There is a TV network broadcasting and recording today's MedCAC meeting. This is in addition to the CMS Webinar and transcriptionist. By your attendance, you are giving consent to the use and distribution of your name, likeness and voice during the meeting. You are also giving consent to use and distribution of any personally identifiable information that you or others may disclose about you during today's meeting. Please do not disclose personal health information.

If you require a taxicab, there is a signup sheet at the desk outside of the auditorium, please submit your name during the lunch break. Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending today's MedCAC meeting are only permitted in the following areas of CMS single site, the main lobby, the auditorium, the lower level lobby, and the cafeteria. Any persons found in any other area other than those mentioned will be asked

00010

to leave the conference and will not be allowed back on CMS property again.

And now, I would like to turn the meeting over to Dr. James Rollins.

DR. ROLLINS: Good morning. My name is Jim Rollins, and I am the director of the Division of Items and Devices in the Coverage and Analysis Group here at CMS.

MedCAC serves three purposes for CMS, to give input from experts in the field on a topic, and that information helps us strategize our efforts related to future activities on that topic. Number two, help disseminate information to the general public. And a more immediate use of MedCAC along with the external technology assessment is to help us craft the national coverage determination.

I would like to thank the members of the MedCAC, especially the chairman as well as the vice chair for participating in today's discussion.

DR. GOODMAN: Thank you very much, Dr. Rollins. Cliff Goodman here. We have just this day until 4:30 as it turns out, according to FLACO regs, for a topic that has considerable potential impact on the wellbeing of a large number of beneficiaries. With that in mind, we expect that all our guest speakers, those providing

00011

scheduled public comments and any who provide open public comments a little bit later in the day, as well as my fellow MedCAC members, will be on point and concise today. On point and concise today.

As Maria said, please do speak into the microphone. If you don't do that, then our court reporter won't hear you and you won't be entered into the record, and if you've got something important to say, it needs to

be in the record.
We've got time today for various scheduled public presentations, there will be eight scheduled public presenters, each of which has been allocated a maximum of five minutes by CMS. Given the tight agenda, please do follow Ms. Ellis's instructions about speaking into the mike and being on time and so forth. Later on towards the middle of the day we're going to hear from a certain number of open public comments, there's a signup sheet outside for those, each of which will be allocated I believe no more than one minute.
And so we kindly, though firmly, suggest that each scheduled speaker think now about focusing your comments on the questions before this panel. I know that there are a lot of fascinating issues that surround this particular topic today, but this panel has been charged with looking at a set of evidence questions that deal with

00012

the benefits and harms, and validity of evidence with regard to this particular topic. So the best thing you can do to put your point across is to stay on point and try to address those questions. That will help this committee do its job today.
Please do watch for the traffic light system. Please don't be insulted if I start waving two fingers at you, or my index finger, indicating how much time you've got left, and I hope you won't mind if I ask you kindly to close your comments so we can move to the next person. We want to get to all of the very important information today.
With that we'll move to identifying ourselves and any disclosures or conflicts that we've got. Again, I'm Cliff Goodman. I'm the senior vice president of the Lewin Group, which is a healthcare policy consulting firm. The Lewin Group is one of multiple subsidiaries of an outfit called Ingenix. Ingenix is a healthcare data information and analysis firm. Ingenix in turn is one of multiple subsidiaries of United Health Group. On behalf of the Lewin Group I work on projects for a range of government agencies and the private sector in the United States and abroad, including pharma, biotech, medical device firms large and small.
I have no interests to declare pertaining to

00013

today's topic, and will now turn to Dr. Satya-Murti.
DR. SATYA-MURTI: Saty Satya-Murti. I am a neurologist and a health policy consultant. I do have the following to report. In February 2010, before the announcement of MedCAC or FDA approval, I was consulted once by a maker of autologous cellular immunotherapy treatment. Since then I have not consulted on the topic, and I've informed CMS of this activity. I have no other conflicts of interest.
DR. GOODMAN: Thank you. Helen?

MS. DARLING: I'm Helen Darling, I'm president of the National Business Group on Health, which is a nonprofit membership group of mostly very large employers, over 300. I have no conflicts regarding this subject.
DR. DMOCHOWSKI: I'm Roger Dmochowski, I'm a urologist, a reconstructive urologist at Vanderbilt University Medical Center in Nashville, Tennessee. I have no conflicts relative to this subject matter.
DR. FULLER: I'm Dale Fuller, I'm a radiation oncologist (mostly retired) from Dallas, Texas. My affiliation prior to retirement was with an organization called Texas Oncology. One of the colleagues in that organization is an investigator in a Phase III trial for this product, but he's an individual that I've met twice and have had no contact with.

00014

DR. MATUSZEWSKI: My name is Karl Matuszewski, I'm a pharmacist by training. I am currently a vice president and editor-in-chief at a company called Gold Standard, and I'm in charge of clinical content in a drug information database, and I have no conflicts of interest to report.
DR. MINTZER: My name is David Mintzer, I'm a medical oncologist and hematologist at the Pennsylvania Hospital in Philadelphia. I have no conflicts of interest.
MS. MOORE: I'm Pearl Moore. I was an oncology clinical nurse specialist, specifically neuro-oncology, and I am the retired CEO of the Oncology Nursing Society, and I have no conflicts of interest to disclose.
DR. POTTERS: I am Louis Potters, I chair radiation medicine for North Shore LIJH Health Systems, and have no conflicts.
DR. SCHULMAN: I'm Kevin Schulman, an internist from Duke University. I'm one of the associate directors of the Duke Clinical Research Institute. I also head the health center management program at the Fuqua School of Business at Duke. Duke University is considering doing clinical trials on this technology but I've recused myself from participating in those activities.
DR. STEINBROOK: Robert Steinbrook, internist at

00015

Dartmouth Medical School. No conflicts of interest to declare.
DR. RAAB: I'm Greg Raab, I'm a health policy consultant, I have no conflicts.
DR. MADAN: I'm Ravi Madan, from the National Cancer Institute, a medical oncologist, and I have no conflicts of interest to disclose.
DR. SOKOLOFF: I'm Mitchell Sokoloff, surgical urologic oncologist at the University of Arizona and chief of the section. I have no conflicts.
DR. GOODMAN: Good, thank you all. We will now move to the CMS presentation of the voting questions by

Dr. Lori Paserchia, here at CMS. Dr. Paserchia.
DR. PASERCHIA: Good morning and welcome. Can you hear me all right?
The FDA label states Provenge, also known as sipuleucel-T or APC8015, is an autologous cellular immunotherapy product consisting of peripheral blood mononuclear cells obtained from patients by leukapheresis and activated in vitro with a recombinant fusion protein which consists of prostatic acid phosphatase fused with GM-CSF. Provenge is approved for the treatment of asymptomatic or minimally metastatic castrate-resistant, also known as hormone refractory prostate cancer.
The MedCAC voting questions: For all voting

00016

questions, the health outcomes of interest are overall survival, control of disease-related symptoms, avoidance or minimization of the burdens to patients associated with anticancer therapy. For all voting questions the comparator is the management that the patient would otherwise have received. A scale identifying the level of confidence with one being the lowest or no confidence and five representing a high level of confidence will be used for the voting questions.
Question number one: How confident are you that there is adequate evidence to determine whether or not the use of autologous cellular immunotherapy treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer significantly improves overall survival, control of disease-related symptoms, avoidance or minimization of the burdens associated with anticancer therapy, while maintaining overall survival and control of disease-related symptoms?
Of note, questions two through six should be addressed only for those outcomes under question one where the panel is confident that there is at least intermediate confidence, with a mean vote of 2.5, that there is adequate evidence to make the determination of improvement.
Question number two: How confident are you that

00017

there is adequate evidence to conclude that autologous cellular immunotherapy treatment significantly improves overall survival in patients with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer?
Question number three: How confident are you that there is adequate evidence to conclude that autologous cellular immunotherapy treatment significantly improves control of disease-related symptoms in patients with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer?
Question number four: How confident are you that there is adequate evidence to conclude that autologous cellular immunotherapy treatment significantly

improves the avoidance of the treatment burdens, for example access, delivery or side effects, associated with anticancer therapy in patients with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer?
Question number five: How confident are you that these conclusions are generalizable to unlabeled use in patients whose prostate cancer has not metastasized, patients who have metastatic castrate-resistant disease and symptoms more severe than minimally symptomatic, patients who have metastatic prostate cancer but who have

00018

not failed hormonal therapy?
Question number six: How confident are you that these conclusions are generalizable to community-based settings, patients belonging to demographic groups that may have been underrepresented in the enrolled clinical trial population?
Discussion questions, this one is numbered seven: Do you believe that there is adequate evidence to identify patients who are more likely or less likely to respond favorably to autologous cellular immunotherapy treatment based on pretreatment evaluation of any of the following factors: Site or sites, or number of metastases as detected by imaging studies. Gleason score. Alkaline phosphate. Hemoglobin. Serum LDH. Serum PSA. Pain associated with metastatic castrate-resistant prostate cancer. Or other.
Discussion question labeled number eight: What significant evidence gaps exist regarding the health outcomes attributable to autologous cellular immunotherapy treatment for the FDA labeled indication for off-label uses?
Discussion question number nine: What clinical study designs would adequately address any evidence gaps?
Thank you.
DR. GOODMAN: Thank you very much, Dr.

00019

Paserchia. I know a lot of people here today have not been at a MedCAC meeting before. The nature of the questions, actually the basic order and the general content of these questions is very similar to those that we've seen before. We typically first look at whether there is enough evidence upon which to draw any findings, so we tend to look at sort of the adequacy of the evidence, and then if there is adequate evidence upon which to make some sort of observation or judgment about its strength, then we'll move on to look at the evidence itself insofar as what does it say. That's a typical thing that we do at the MedCAC.
And then we often look at to what extent is the available evidence generalizable to the broad community, to what extent is the evidence applicable to the Medicare beneficiary population in general.

And then we typically close with one or more questions regarding any evidence gaps and how we might fill them. So this is pretty much our basic approach to looking at these issues, these are the questions that we're going to deal with today.

We're going to move now to Dr. James Gulley, who is the director of the Clinical Trials Group, Laboratory of Tumor, Immunology and Biology, and a principal investigator of the medical oncology branch at the Center

00020

for Cancer Research at NCI, the National Cancer Institute. We'll get real kind of physiological and molecular and biological here first, and then we'll move more into the evidence, but here's a little bit of the hard science for you, everyone.

And Dr. Gulley, thank you for being here today.

DR. GULLEY: Thank you very much, Dr. Goodman. My goal today is to give you a brief overview of metastatic prostate cancer. We're going to first talk about some definitions of castrate-resistant prostate cancer, talk a little bit about the metastatic disease and what that means, and talk about some issues around symptoms and severity of symptoms. Then we're going to talk about available treatment options that are currently FDA-approved.

It's important to put this in the context of the disease continuum for our discussions today as seen in prostate cancer. The vast majority of patients diagnosed with prostate cancer will be asymptomatic at the beginning, but eventually many of these patients will develop symptomatic disease later on in the disease course. The majority of patients also have nonmetastatic disease at diagnosis but eventually may progress to metastatic disease. And the vast majority of patients diagnosed with prostate cancer have disease that is

00021

sensitive to the removal of testosterone, castrate-sensitive disease, but eventually after removing testosterone, patients may progress to castration-resistant disease.

It is also important to note that early on in the disease there may be many competing causes of mortality for patients diagnosed with prostate cancer. However, by the time somebody has metastatic castration-resistant prostate cancer, the vast majority of those patients will die from their prostate cancer.

So let's go through a brief overview of treatment options for patients. Patients that are initially diagnosed usually in the United States have localized disease. These patients may be treated with radiation therapy or surgery. Some of these patients are cured of their disease, in fact most of these patients are cured with localized therapy. However, a subset of patients will eventually develop rising PSA, approximately

a third of the patients. These patients often will be treated with initial treatments of testosterone-lowering therapy which will, as we mentioned before, cause a decrease in their PSA in the vast majority of patients. Eventually, however, many of these patients will have rising PSA despite low levels of testosterone, and may be treated with second line hormonal therapy agents,

00022

which we're going to talk about in a little bit. Eventually, however, patients will develop metastatic disease and may develop symptoms, and may be offered drugs such as docetaxel, which we'll talk more about later. Cabazitaxel was recently FDA approved this year for patients who had progressive disease following docetaxel-based regimens. There is another drug, abiraterone that, recent data from a Phase III clinical trial was presented at the European Society of Medical Oncology meetings suggesting an improved overall survival in this post-docetaxel setting. However, this drug has not yet been FDA-approved.

What I'd really like to focus the panel on here is the patient population seen in the IMPACT trial, that is patients with castration-resistant metastatic prostate cancer that is either asymptomatic or minimally symptomatic. And so we're going to spend a little bit of time talking about the definitions of each of these. First, the definition of castration-resistant prostate cancer, I think is a very simple definition. It's a disease that has progressed despite castrate levels of testosterone, so first let's talk about castrate levels of testosterone and what that means. Historically, patients that have a testosterone level of less than 50, those patients are considered to have castrate range of

00023

testosterone. Now in the clinical practice, if somebody is on a GnRH agonist or antagonist and remains on continuous therapy with that, or if somebody has had a bilateral orchiectomy, which is surgical removal of the testes, we don't generally get testosterone levels in those patients. However, when we do, the vast majority of those patients will have testosterone levels in the 50s. So let's talk about progression. Progression is generally defined as either rising PSA, new or enlarging lesions seen on imaging, or clinical progression consistent with prostate cancer. This is generally outlined in the article that I have put forward here, which was the PSA Working Group II criteria. This is generally viewed as the eligibility criteria for all patients showing progressive disease with castration-resistant prostate cancer for trials done in the U.S., and abroad actually.

Let's talk a little bit about metastatic prostate cancer. Prostate cancer tends to spread to bone and lymph nodes. However, metastatic lesions have been

found in virtually all organs, including the brain, liver and lungs. Most patients will have metastatic lesions detectable on imaging prior to developing symptoms from their cancer and we'll touch on that a little bit later also.

00024

So, I just want to share with you what this might look like. This is an example of one of my patients who has a bone scan here. As you can see here, it looks a little bit like a skeleton and the areas of uptake of the technetium shown here in white, are areas consistent with osteoblastic lesions from the prostate cancer. You can see lesions in the skull, the backbone here, the ribs, and the pelvis. These lesions are generally not measurable lesions, they're just what we call evaluable lesions, either they're present or absent.

This is an example of one of my patients who has a lesion, a lymph node lesion that you can see on a CAT scan. Just for purposes of orientation, the dark area here is the lungs, you can see the heart, here's the backbone, and you can see this gray area here is a lymph node which shrunk down following treatment for a decreasing PSA. These lesions are measurable. So, this is just an example of the distribution of the lesions.

You see most patients with metastatic prostate cancer have bone metastases, about 90 percent of patients, whereas the minority of patients have measurable lesions.

So let's talk a little bit about symptoms now.

Generally there is a stepwise progression in prostate cancer, where initially you will have rising PSAs, and then you may see progression on imaging, and then you may

00025

see symptoms from the disease. There may be a variable time period between each of these different steps that could be months to years.

So, the most typical manifestation of symptomatic disease is bone pain that is progressive with either rising PSA or progression on imaging. Sometimes this bone pain requires narcotics or change in therapy such as radiation or chemotherapy. Prostate cancer-related pain can really be divided into the minimal symptoms or asymptomatic patients. Minimum symptoms are ones that require no treatment or treatment with nonsteroidal anti-inflammatory drugs, acetaminophen, or the rare use of a narcotic, whereas patients that have more moderate or severe symptoms, they may require more intensive pain management such as continuous narcotics with or without nonsteroidal anti-inflammatories or acetaminophen, radiation therapy, or systemic anticancer treatment directed at improving the pain. Systemic anticancer treatment can be given to patients regardless of their symptomatic status, however.

I think this is an important point also. From a clinician's perspective, disease symptoms from prostate

cancer can usually be readily distinguished from symptoms from other conditions. As a physician we look at things like how long the symptoms have been going on, a

00026

correlation in the change of symptoms with either rising PSA or radiographic progression, and also the site of the pain, especially in combination with the imaging findings. So let me just give you a couple of brief examples. A patient who has rising PSA, has new onset of rib pain without any known trauma to that area, and has a bone scan lighting up at that area, that bone pain is likely from prostate cancer. However, with somebody that has chronic knee pain, has rising PSA, no evidence of osteoblastic lesions on the lower extremity, no history of osteoarthritis, that knee pain is unlikely to be from the prostate cancer and is more likely to be from his osteoarthritis.

So now let's change gears and talk about treatment of metastatic prostate cancer. Back in 1941, Charles Huggins showed that in patients with advanced prostate cancer, the treatment, sorry, the symptoms and tumor markers could actually be improved by decreasing testosterone, either by using estrogen which deprives them of testosterone levels, or by doing surgical castration. Interestingly, he also showed that by adding back in testosterone, the symptoms and the tumor markers could get worse. And in fact in 1966, he won the Nobel Prize in medicine for this finding.

So basically patients with metastatic disease,

00027

the initial treatment options is testosterone lowering therapy. This can be given with either GnRH agonists such as leuprolide or goserelin, which are shots, a GnRH antagonist which has recently been updated as FDA-approved, and this is degarelix, also another shot, and orchiectomy or surgical removal of the testicles. There are multiple side effects from antigen deprivation therapy, and I'm just going to highlight a couple of them because of time today. Decreased libido, erectile dysfunction, thinning of the bone, increased risk of diabetes, some cognitive dysfunctions, and these are all reviewed in the review articles I've outlined there.

I should also mention that there are FDA-approved antigen receptor antagonists. What happens is these compounds can go in and bind to the androgen receptor and decrease the activity of the androgen receptor androgen on prostate cancer growth. There are different dosing schedules, potency and different side effect profiles, but for purposes of today one thing that's important to note is the androgen receptor antagonist withdrawal finding or antiandrogen withdrawal. Over time these can actually turn from blocking the growth of cancer into potentially driving the growth of the cancer. It's only seen in a minority of patients, but

what happens is if you stop the antiandrogen, or the
00028
androgen receptor antagonist, you can actually see a reversal of PSA. Usually this is relatively short lived, I think one can see that within four to six weeks of stopping the androgen receptor antagonist.
For sake of completeness, I'll just mention some other hormonal therapy agents. Ketoconazole, which blocks the formation of adrenal androgens, it is not FDA approved for this. Abiraterone and MDV-3100 are experimental agents both in late Phase III testing. But I think it's important to note that patients may respond to multiple sequential hormonal therapy manipulations; however, none of this has been shown to improve overall survival in patients with metastatic disease.
Let's talk now about chemotherapy. The studies done prior to 2004 were largely disappointing and didn't show survival benefits to chemotherapy. There's also difficulty, as I mentioned before, in evaluating response to symptoms and only a minority of patients had measurable disease. There were quality of life measurements that were used to improve one drug, mitoxantrone, and this was improved following two Phase III clinical trials, moderately powered. It showed that there was improved quality of life when compared to glucocorticoid alone. So based on this, the FDA-approved mitoxantrone and glucocorticoid for palliation of painful lesions in 1996.
00029
In the late 1990s there was several Phase II studies showing activity of docetaxel in patients with metastatic castration-resistant prostate cancer. And based on that, there were two Phase III clinical trials that went on with docetaxel, and I'm just going to, because of time, I'm going to talk about one of them today, and that's the TAX327 study. In this trial patients with castration-resistant prostate cancer, metastatic, were randomized to receive docetaxel every three weeks versus docetaxel weekly, versus mitoxantrone and Prednisone.
The primary outcome in this trial was overall survival and as you can see, the patients who received docetaxel every three weeks have an improvement in survival compared with mitoxantrone and Prednisone. This was statistically significant and you have the hazard ratios here. And I should just mention briefly that there was a crossover allowed for patients that received mitoxantrone, they could cross over to get the docetaxel, and about 20 percent of patients did so.
Here is a list of the side effects seen with docetaxel therapy, and you can see that the majority of these were low grade, but there were a substantial proportion of patients that received some toxicity from this. Grade three and four toxicities were seen in at
00030

least five percent of the patients in four different categories, anemia, neutropenia, fatigue, and infection. Based on this study the FDA approved docetaxel for patients with metastatic castration-resistant prostate cancer in 2004. Docetaxel is typically given until disease progression or until side effects dictate discontinuation. In the Phase III study this was given for a median of 9.5 cycles or 29 weeks, out of a total planned ten cycles.

Next up I'm just going to talk about cabazitaxel, which is a newly approved agent. This is another chemotherapy agent that is active in the laboratory in docetaxel-resistant cell lines. 755 men with metastatic castration-resistant prostate cancer were enrolled on this Phase III study and randomized to receive cabazitaxel versus mitoxantrone, and both arms received Prednisone. The primary endpoint of this study was overall survival. As you can see here, patients that received cabazitaxel had an improvement in overall survival compared with mitoxantrone and Prednisone, and this was statistically significant, as you can see here. This mean improvement was similar to, was 2.4 months, which also was the case with the docetaxel. The side effects seen with cabazitaxel were generally more in number and frequency than with

00031

docetaxel, and you can see here that in seven categories there were grade three or four adverse events seen in greater than five percent, or at least five percent of the patients.

So, the FDA approved cabazitaxel for patients who had metastatic castration-resistant prostate cancer and had previously received a docetaxel-containing regimen, in June of this year. And typically cabazitaxel is given until disease progression or until side effects, again, dictate discontinuation of treatment. Patients received a mean of six cycles or 18 weeks of cabazitaxel, out of a total planned up to ten cycles.

Next I'm just going to mention briefly sipuleucel-T. This is the clinical trial design. Patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer were randomized to receive sipuleucel-T versus placebo, and the primary endpoint was overall survival. This is the Kaplan-Meier curve for the overall survival, and you can see there was a four-month median improvement in overall survival that was statistically significant, and you can see the hazard ratio here. The side effects from sipuleucel-T are shown here and this is, most of these side effects were transient, and you can see here that the number of

00032

patients was generally in the one percent range number, affected by each of these individual therapies. There

were no grade three or four side effects seen in greater than five percent of patients.

So based on this study and the previous study, the FDA approved sipuleucel-T for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. This product, unlike the previous products that I mentioned, is infused three times over a one-month period of time.

I just want to mention briefly bone-targeted therapy. Bisphosphonates are used for patients with metastatic castration-resistant prostate cancer. Zoledronate, or zoledronic acid, is approved for the prevention of skeletal-related events in patients with castration-resistant prostate cancer and bone disease. Radionuclides are also used, such as Strontium and Samarium, and they're approved for the palliation of painful osteoblastic lesions. None of these bone targeted therapies have been shown to impact overall survival.

So, these are the three therapies that are currently FDA-approved and have been shown to impact overall survival. You see that the hazard ratios in the clinical trials are all between .7 and .78. The median improvement in survival seen in these studies, again, is

00033

between 2.4 months and 4.1 months. I think one of the big differences that we see is the percent of patients having side effects, and this is, one way of looking at it is the need to stop treatment because of side effects. And you see that about 1.5 of the patients in the sipuleucel-T trial had to stop treatment because of side effects, versus approximately 15 percent, or approximately a tenfold higher role with the chemotherapy drugs.

So, how do we use sipuleucel-T in our treatment? I think there's a working paradigm for where sipuleucel-T should fall into the treatment of patients with metastatic castration-resistant prostate cancer. Basically patients with no symptoms or minimal symptoms have several different options. They can receive sipuleucel-T, they can receive second-line hormonal therapy, or they can receive chemotherapy, whereas patients with more than just minimal symptoms may benefit most from receiving chemotherapy.

How about treatment after sipuleucel-T? Again, I think you could go to second-line hormonal therapy, chemotherapy, or patients may not need initial treatment at the time they discontinue the sipuleucel-T and could be monitored clinically for progression, and at that time potentially treated with chemotherapy or second-line hormonal therapy.

00034

Thank you for your attention and if the panel has any questions, I have been instructed to ask that, or if there's time, I could answer any of the questions at this time.

DR. GOODMAN: Thank you very much, Dr. Gulley. We have a couple of minutes, so if there's a question or two that can't really wait, we can take that now. Otherwise, we will hold off until the discussion time, where I know Dr. Gulley will be available. Is that okay, panel? Dr. Schulman has a question.

DR. SCHULMAN: In looking at outcomes of patients with prostate cancer, how do you consider the impact of therapy on both survival and quality of life? Because obviously these patients, this is a very debilitating disease with significant complications that continue to progress. We saw a lot of evidence of survival. How much evidence, or how do you consider progression of disease across kind of the totality of the burden on the patient?

DR. GULLEY: I think it's very important when you're treating patients who have symptoms to see what effect the treatment has on the patient. I think for the majority of patients that have minimal symptoms, symptom control is not a big issue. For patients that have more severe symptoms, that typically becomes the driving force

00035

for looking at treatment options, so I think that that is a very important component of deciding which therapy a patient might be best suited for.

For patients with minimal symptoms, I think that immunotherapies, or patients with no symptoms, I think immunotherapies are very reasonable options, whereas I think in patients with more than minimal symptoms, I think that becomes more a case where I would be in favor of treating it more aggressively with chemotherapy if they are castration-resistant.

DR. GOODMAN: Does that help, Dr. Schulman? Okay. Any other pressing questions at this time? Seeing none, thank you very much, Dr. Gulley. Dr. Gulley, we trust you will be available for the balance of the day, and chances are this afternoon we will probably ask you to take a seat up here in the front when the panel will have various questions for you and others. Thank you.

Dr. David Mark will now speak. Dr. Mark is going to give the TA presentation, that's the technology assessment, it looks like this in text form, and a lot of you saw that this was posted on line not long ago. Dr. Mark is a senior scientist with the Blue Cross and Blue Shield Association Technology Evaluation Center.

I should take a moment just to explain to folks that aren't familiar with the process that it's often the

00036

case that when CMS is looking at a national coverage analysis, that it will request a technology assessment via the Agency for Health Research and Quality, AHRQ, one of its sister agencies in HHS. AHRQ has 13 evidence-based practice centers that are available to AHRQ under contract to conduct technology assessments, sometimes they call

them systematic reviews or evidence reports, and Blue Cross Blue Shield TEC is one of those EPCs. And they've got a pretty nicely worked out process insofar as being given a set of evidence questions, doing systematic literature reviews, and addressing these evidence questions in a comprehensive systematic way. So this is, again, a typical step here in the process, and we're very glad to have Dr. Mark with us here today. Dr. Mark, sir.

DR. MARK: Thank you. Here are the disclosures. I have no personal disclosures regarding this topic, but here are the other disclosures. This report does not represent the opinion of the Agency for Health Research and Quality, nor an official position for the U.S. Department of Health and Human Services, and we did this under contract from CMS. These are my colleagues on this project. Dr. Gulley did a great presentation on hormone refractory prostate cancer, which has several names. He called it

00037

castrate-resistant, hormonal refractory is the same thing. I will skip this slide. He described one of the studies, pivotal studies on docetaxel. I will mention the other one that occurred approximately the same time, just to give you an eyeball of what the survival benefit in these trials was. So the one listed on top with about a 2.4 month difference in survival, and the other study published about the same time with a similar but not quite the same protocols, had a 1.9 month difference in median survival. Mitoxantrone, which he mentioned, has been shown to have palliative benefits for hormone-refractory prostate cancer as compared to docetaxel, which improved overall survival. One thing to keep in mind in comparing the docetaxel trials compared to the clinical trials with sipuleucel-T was that the indications for entry into the trial were a little bit different, a higher proportion of the patients in the docetaxel trial had baseline pain, whereas the sipuleucel-T clinical trials were restricted to asymptomatic and minimally symptomatic patients. Because of the toxicity of docetaxel in actual clinical practice, there's often a common practice pattern to delay treatment until symptoms occur, or there is this tradeoff that the physicians try to do of improving overall quality of life by delaying treatment until there

00038

is a significant symptomatic burden to overcome. The NCCN guidelines do not address the timing of docetaxel chemotherapy so there's possibly a broader range of, again, different times in the progress of prostate cancer that the treatment could be given. Just to review briefly the, what sipuleucel-T is, is a biologic therapy derived from the patient's own white cells. Again, the cells are cultured in this fusion

protein and then they're reinfused into the patient in a very short interval of time, three doses are given two weeks apart for a total of four weeks. The product has large variability in cell composition, both between patients and between individual doses of the drug, and this is something that basically cannot be controlled by the manufacturer, it's dependent on the quantity of cells that are achieved in the leukapheresis product, though currently there are minimum standards for cell number that are dictated in the manufacturing standards, and if the biologic product does meet these standards the patient undergoes a repeat leukapheresis procedure.
So in the early studies of sipuleucel-T, which will be part of the review, the immunologic effects of the drug were studied, and in various types of tests it was shown that the patient's immunologic system did tend to respond according to various tests, in response to

00039

exposure to sipuleucel-T. So there are these T-cell proliferation tests in which you see the T-cells proliferate or multiply in response to exposure to the fusion protein, the prostatic acid phosphatase, and to GM-CSF. They found that these tests did show that the patients in a very sensitive and specific manner did proliferate in response to these antigens but not in response to other antigens.
Certain proportions of patients developed antibodies to the fusion protein PAP and GM-CSF after treatment with sipuleucel-T. And then a phenomenon called CD54 upregulation, which is a measurement on a specific type of white cell in the body, that showed that the patients, there's a particular molecule called CD54, and that the expression of this molecule increased after treatment with sipuleucel-T. These are not clinical outcomes, they are merely immunologic tests done on patients or the cells of patients in response to exposure to sipuleucel-T.
FDA approved sipuleucel-T in April of this year, and just to briefly mention some of the labeling instructions that might be of interest, so the FDA approved it for asymptomatic or minimally symptomatic disease, and in the section in the labeling instructions called contraindications, there were none. There were a

00040

few warnings listed on the label, but they related to the incidence of possible infusion reactions in patients, and then warnings to healthcare professionals that the product may contain infectious agents, possibly from the patients themselves, and that the concomitant use of chemotherapy and immunosuppressive agents have not been studied.
In the NCCN practice guidelines it was given a category one recommended treatment, which is the highest level of recommendation for a cancer treatment. And of note, they mentioned that the treatment is indicated for

patients with good physical performance, life expectancy greater than six months, no visceral disease, which would be abdominal disease or lung disease, and low or minimal symptoms. And they mentioned that markers that benefit response cannot be currently ascertained.

So when we do an evidence review, we do this formal process of combing the literature for possible articles. This was a little bit of an excessive activity in this case because there's a quite defined literature looking at this particular treatment, but we did our usual process. Of note for this TA, there's a lot of material available from the FDA, which is in addition to the published papers, a lot of additional analyses, insights into the data, there were specific statistical reviews done by the FDA statisticians, and this was all considered

00041

for our use. So this was different from our normal technology assessments, having these materials, and it also caused some problematic issues that I will go into.

Then we looked at selected conference abstracts to see if any of the existing studies had been updated or provided further results. We kind of had to make a selective decision as to whether to include these or not, because oftentimes there's not complete information available on these abstracts.

So what we do when we do a technology assessment is we design patient populations, so we look specifically at the FDA-labeled indication, and then the papers themselves will often give kind of an implied indication, they will describe the types of patients. Now rather than calling these off-label, they're probably more properly called pre-label, because these tended to be early studies, and it's probably not fair to call these off-label studies because they're really done before formal studies of efficacy were done.

In clinical trials, the comparator treatment is explicit, it's what the placebo group undergoes, you have to kind of discount the placebo, but in this case the placebo group is worth looking at in particular. And in case series studies, there's often an implied comparator, which in this case tended to be no active treatment at the

00042

time the sipuleucel-T was being given.

We were interested in looking at outcomes of overall survival to see if there were any measures of quality of life ascertainable from the studies. Cancer progression is a common endpoint used for cancer clinical trials. And then we specifically looked at the adverse effects of treatment. In general, we did not consider PSA-based outcome measures as health outcomes, nor did we look at the studies of immunologic function. A few studies only used as their principal measure a PSA-based measure of outcome, and we will note this.

So basically we tried to formulate in our head

the kind of study that we're going to look at. We realized there was a pretty limited set of studies on this topic, so we took all comers basically, case series and randomized control trials for, in which this therapy had been used, and this was both for the FDA-approved indication and for the other indications.

Adverse effects is kind of a difficult topic to study because adverse effects are often rare, or at least severe effects are rare, so in order to do that you'd probably like to have the largest data had to do available, and one of the FDA clinical reviews has a pooled analysis of safety data from four randomized clinical trials of sipuleucel-T, and this is presented

00043

with some possible warts and some possibly, you know, not so complete editing, but it probably provides the best overall mostly uniform analysis of the adverse effects of sipuleucel-T, so rather than looking at the individual papers, we looked at these pooled safety data from one of the FDA clinical reviews.

We did an assessment of study quality. In terms of synthesizing the analysis, we did not incorporate a formal quantitative data synthesis, which is called a meta-analysis, where you do statistical summing up of the trials. We did not do that, we thought that the presentation of the individual clinical trials would be sufficient. And we, there's a grade system of rating totality of the evidence, it's still in evolution in materials of the exact criteria, but this seems to be the way that the field is going in terms of trying to provide overall assessment of evidence. And so we had, you can see the criteria, and you can disagree with how we rate it, but at least you can see what the different factors that go into the decision for a particular grade.

So, we divided our report into evidence questions, did this without knowledge of the MedCAC questions, and we just look at the data and say okay, what is a way of parsing this data into answerable units.

Our key question one had to do with the

00044

FDA-labeled indication and the clinical outcomes as they exist in the literature. Key question 1.A concerned issues about subgroup analysis, so are there baseline factors that predict better or worse outcomes from sipuleucel-T treatment. This happened to correspond to a MedCAC question. And then there's some analyses regarding intermediate aspects of the treatment, such as the aspects of measuring the cell number or immune response characteristics of the patients and whether those have a relationship with the outcome of treatment.

Question two and 2.A mirror question one and 1.A for the off-label indications.

And then we asked a separate question about adverse events potentially attributable to the use of

sipuleucel-T, and we say potentially attributable because the issue of directly saying that sipuleucel-T is responsible for a particular adverse event is not a simple question.

So, these are the results of our search. Now, 47 citations will include everything that includes sipuleucel-T in the title, so there's just a lot of data here which is not original research data or review articles. And then because of the additional data from the FDA, the number of articles does not correspond exactly to the number of studies, studies are reported in

00045

multiple publications, so ultimately I will try to describe the findings in terms of separate independent data sets rather than papers.

So, regarding our key question one, which is the clinical outcomes for the FDA-approved indication, there are three sets of findings and they're reported in various venues. I decided to call them by their research names, IMPACT, D9901 and D9902A, and there are multiple sources of results for each study. And what we have here is kind of a unique insight into, you know, the performance and analysis of studies, kind of more than you want sometimes, and what you see here is that analyzing a study is not exactly always a straightforward manner. We did find that there are slight discordance from various sources, there's possibly some errors, FDA does not proofread everything they do, there are mislabeled tables. The data can be analyzed at various times, so you can have different data cutoffs, and different analysis done before or after data correction of errors. So when possible, we tried to abstract the data from the published peer reviewed source, and although there might be slight differences in numbers between analyses, I'm not sure that any of these are critically important or, if they are, I will try to recall and mention those.

And then because of FDA statistical review and

00046

various presentations by various groups, you end up with multiple versions of filtered analyses, and these never appear in published journal articles, and so we were left with the problem of how much of these multiple versions of similar analyses to present to you. Some of it is overkill, some of it is redundant, some may have some particular flaws that make them questionable in terms of the merit of the study. Probably the most numerous alternative analyses were done were the survival analyses of the studies where they adjust for this, adjust for that, they look at a subset of deaths.

I think our overall conclusion was that they neither strengthen nor weaken the case for the efficacy of the drug, and so we relegated these analyses to an appendix in our report, but you can kind of see some of the back and forth between the FDA and the sponsor

regarding these alternative analyses. But the thing to keep in mind is that this is all churning through the same data again and again, so if there is some biases in one analysis, one particular analysis is not going to get rid of that bias, you're repeating the same analysis over and over again, and so you should not look at the same report repeated many times as additional evidence. Probably the best way to look at this data is to look at three sets of independently gathered data and gain an impression from

00047

that.

Finally, these studies were not performed in a fully independent manner. The design and the decision to do various things in the study was often based on what happened in the prior studies.

So, Dr. Gulley outlined the design of the IMPACT, D9901 and D9902A studies. They were blinded randomized design. The placebo group is interesting in these studies. The patients were subjected to a leukapheresis, their cells were untreated, and one third of their cells were given back to them at zero, two and four weeks. The placebo group's remaining cells were cryopreserved with the option of receiving what I call frozen salvage product, I'll just call it that for the rest of the talk, after disease progression. And then after that, both groups were treated at the discretion of their physician after disease progression.

Disease progression was based on a particular combination of imaging with correlation with clinical events. The trials had slightly different disease progression algorithms, but they're quite complicated, they take two or three pages of a protocol document to describe the combination of factors of bone scans, measurable disease, unmeasurable disease, correlation with clinical events, but the important thing is that it was

00048

attempted to be done in an objective fashion between the two groups. And so if a decision rule is applied in the same fashion to both groups, we can assume or try to assume that it was a fair process between the two groups.

Now the reason the studies were blinded with the placebo control was that the original endpoint for all the trials was a disease progression endpoint, and because of the difficulty in assessing disease progression, they decided to have blinded placebo controlled trials in order to avoid bias on the part of investigators in terms of interpreting the images, or patients in terms of interpreting their symptoms as being relatable to their disease, and in an attempt to be as objective as possible about developing a disease progression endpoint.

Crossover trials in general are potentially problematic in terms of, you know, contaminating one group with a treatment that was given to the other groups, so I will point out that the frozen salvage product was given

to the placebo group and a significant number of patients, and I will show you what those proportions were. Now, the frozen salvage product is potentially different from the actual product, it's based on cryopreserved cells, it's a proportion of the patient's leukapheresis product, and when we think about the repeated leukapheresis procedures that a patient

00049

underwent, all the placebo patients undergo leukapheresis without having been exposed to real sipuleucel-T, whereas in the intervention group the second and third leukapheresis procedures occur after a real sipuleucel-T infusion, so the frozen salvage product cannot be considered identical to the sipuleucel-T product. And then because the studies were originally designed for a disease progression endpoint and there was less control and protocol in the study after that point, we want to look at differences in treatment after disease progression as another course of potential bias.

So just to review the types of patients that entered the trials, this is a descriptive summary of the entry criteria and inclusion characteristics of the IMPACT trial, which was the largest randomized clinical trial, so what's notable here is because of different entry criteria related to this trial versus the other two earlier trials, 75 percent of patients had a Gleason score equal to or less than seven, less than seven is the less aggressive form of prostate cancer, and so this proportion is different from the other two studies. An ECOG score of zero indicates pretty much a fully functioning patient, that's 82 percent, or over 80 percent in each trial, and the entry criteria was an ECOG score of just zero or one. So these are patients really that are, you know, going

00050

around their business, pretty much fully functioning, and they only have mild symptoms related to their disease. Other notable inclusion and exclusion characteristics, with the patients with visceral metastases, which are associated with much worse prognoses, were excluded from the study, as were patients with pathologic fractures, spinal cord compression. There's a rather complex algorithm regarding prior therapies and prior chemotherapy, you probably wouldn't think of it as they are reasonably distant from prior therapies, prior chemotherapies or other treatments. So it's kind of a complicated algorithm in actual practice, but they're just a ways away from prior therapies.

So, this is the bottom line of the three studies, IMPACT, D9901 and D9902A. IMPACT was the largest study, 341 in the sipuleucel-T to 171 in the placebo group. Now the studies are not always followed until death for every patient, but you want to have a substantial number of outcome events to have reliable and

statistically significant results. And the median outcome for the sipuleucel-T group was 25.8 months versus a median survival of 21.7 months, which is published in the New England Journal and probably everybody knows these numbers.

00051

The hazard ratio represents the relative risk of the treatment and it takes the survival curves and kind of summarizes statistically at any point in time, what's the relative risk of death in sipuleucel-T compared to placebo? And as you know, survival curves are kind of messy things, they fluctuate up and down, but overall the hazard ratio is .78 in favor of sipuleucel-T with a statistically significant P value.

The early studies, D9901 and 9902 are shown also. Their sample size was significantly smaller. D9901, a median survival of 25.9 months versus 21.4 months, a hazard ratio of .59. Because this had a more extreme hazard ratio with smaller numbers, they were able to show statistical significance.

D9902A was a smaller study and apparently terminated because D9901 did not meet its endpoints for disease progression, so we can see that's a smaller study. The median survival was 19 months versus 15.7 months. The hazard ratio was a point estimate, which is kind of what the analysis spits out at you in terms of the best estimate of effect, is .79, which is in a similar ballpark as the other studies, but because of the smaller numbers is not statistically significant.

Another way of expressing the same results is to say at 36 months, what is the probability of survival at

00052

36 months, and we call it a probability rather than an actual survival. When these numbers are generated, not everybody has reached follow-up at 36 months, and so patients are censored and the analysis is adjusted to account for that censoring, and if you assume that the patients who have not been followed up all the way out to 36 months, if you imagine that they have the identical experience as everybody else in the study, you know, what will their projected probability of survival be. And so for the IMPACT trial it was 31.7 percent versus 23 percent, for D9901 34 percent versus 10.7 percent, and for D9902, 31.6 versus 21.2. And because of the smaller numbers of the smaller studies, these are probabilities and there is some error factor that's not accounted for in the presentation of these numbers, these are just the point estimates.

So these studies were originally designed for a disease progression endpoint. Let me back up and say that before IMPACT was fully analyzed, the protocol was amended for a survival endpoint, although when instigated it was designed for a disease progression endpoint but during the performance of the trial the outcome was changed to a

survival endpoint, so it wasn't that the survival analysis was post hoc. So the disease progression outcome was based on

00053

an algorithm of imaging plus or minus some clinical correlation with the imaging tests, and there were slight differences between IMPACT and D9901 and 2 regarding the exact definition of a disease progression endpoint. But for IMPACT it was 14.6 weeks versus 14.4 weeks, you can see that's very close, the hazard ratio was close to one, indicating no benefit, not statistically significant. D9901, 11.7 versus 10, a potentially beneficial hazard ratio that turned out not quite to meet statistical significance, and 9902, 10.9 versus 9.9 with a hazard ratio close to one, and not statistically significant. The studies that did not include a formal quality of life assessment or clinical measure of outcome, the best we could find was a time to pain progression, which was only measured up to a certain point in the clinical trial, and then after that point in the clinical trial the patients were censored, they were no longer followed up. So unfortunately, not all patients were followed to a pain progression endpoint and this reflects an estimation of effect, assuming that patients who were censored had the same pain outcome as patients who had been followed completely so it's not, you know, a full thorough time to pain progression analysis. But what was shown and is available only for a pooled analysis of 9901 and 9902A is this result, a pain progression of 33.9

00054

versus 32.7 weeks, which is not statistically significant. Time to clinical progression was kind of a variation of the disease progression endpoint that updated some progression endpoints to a clinical symptom, so it's just a slight variation of the disease progression endpoint, and that was not statistically significant in the D9901 study. So we wanted to look at an issue that all the journal articles and the FDA was particularly interested in, was the percentage of receipt and median time to receipt of post-progression treatment. So if we looked across all three studies in terms of the number of patients that received frozen salvage product, in each study it was 63.7, 75.6 and 66.7 percent of patients. So the majority of patients in the control groups received frozen salvage product, and they received it at the intervals you can see on the table. The 4.6 month estimate is guesstimated or pooled between the two studies, 9901 and 2A, because we could not find that number separately between the two trials and it just reported as a pooled number that was reported in a pooled analysis. In terms of the percent of patients each receiving docetaxel chemotherapy, in the IMPACT trial 57

percent received sipuleucel-T and 50 percent in the
00055
placebo group. And then the median time to receipt of docetaxel was 7.2 months in the sipuleucel-T and 9.6 months in the placebo group. These numbers are different than what you see reported in the New England Journal and that's due to the difference between looking at the actual time chemotherapy was received and a Kaplan-Meier estimate of when chemotherapy is received where, again, you're estimating a probability of receiving chemotherapy and taking into account death and loss to follow-up, so the 7.2 and 9.6 represent the actual time that they received the docetaxel chemotherapy.
We couldn't dig out the numbers for 9901 and 9902A. And then there were some numbers presented in various documents about other treatments received, docetaxel plus some other type of secondary treatment after disease progression, and those numbers are reported in the second to last column, 81.8 percent with sipuleucel-T versus 73 percent in the placebo group for the IMPACT trial, and then the other numbers that you see.
For D9902A, those are estimated numbers based on subtracting numbers from a pooled analysis and subtracting numbers from D9901 to estimate those, so I can't be sure of the accuracy of those numbers, there's possibly some missing values that can't be taken into account.
What we've done in order to try to account for
00056
docetaxel treatment after disease progression were two types of statistical analysis, and one is to censor patients at the time of docetaxel initiation, so you consider that patient lost to follow-up at the time that they're given docetaxel, and you presume that the experience of the remaining patients who are not given docetaxel represent the true experience of survival between the two drugs, because docetaxel is potentially a confounding factor. So when this analysis was done in the IMPACT trial the hazard ratio was .649, indicating a treatment benefit, with a significant P value.
Another method to use is called time-dependent covariate for docetaxel use, and what you're doing in that is you're kind of doing a statistical adjustment at the time of docetaxel use, so the patients are being followed up and they're kind of given a different treatment assignment at the time they're given docetaxel, and you're imagining that their survival curve is kind of bumped up or bumped down, and then you let the data determine how much it's bumped up or bumped down, so you assign a different statistical value to them at that point. You assume that there's a finite single treatment benefit for docetaxel, you assume that it's the same no matter when or who is given docetaxel, but the patient remains in the study after docetaxel use. This analysis showed a
00057

treatment hazard ratio of .777, meeting standards of statistical significance in the IMPACT trial. In the various published documents, or not published documents, there's an analysis called adjustment for time to docetaxel chemotherapy. It's not quite clear, I assumed it was time-dependent covariate use, but I'm just quoting from the documents, because it possibly could be some sort of analysis. So for D9901 this produced a point estimate of .649, not quite meeting statistical significance, and in D9902, a point estimate in favor of sipuleucel-T that's not statistically significant. Just to make a comment about these alternative analyses, is that although they mark the onset of docetaxel chemotherapy, they do not account for differences in the quality or performance of that treatment regimen, so anything about the characteristics of that treatment is not really measurable, it's just a yes-no indicator for whether docetaxel was given. The validity of a time-dependent analysis or a censoring analysis requires some assumptions, all statistical analyses require assumptions, but the usual stringent assumption is that the time of this censoring or the time of the change in exposure from no docetaxel to docetaxel provide no information about the probability of survival, that is that it's a random time. And given that docetaxel

00058

is given in response to either symptoms or a treatment failure or patient choice, that is an unlikely assumption in this study, but it's kind of difficult, then, to know what the eventual bias on the study is, because this is occurring in both arms of the trial, and so you kind of have to ask the open question, is there a differential bias in this time of onset of a potentially confounding treatment, and that is a difficult question. There are statistical techniques that have been developed to handle this kind of situation. The problem itself is called time-dependent confounding. So docetaxel is a confounding factor in that it can potentially affect the outcome of the patient, but it's given in response to the occurrence of a confounding event, which is treatment failure or progression of disease. The technique is called marginal structural models and they largely have been applied to HIV disease in trying to determine the effects of treatment after patients have worsening condition of their HIV, and to determine the effects of subsequent treatments on patients. I'm not an expert in this technique and I'm not, it's uncertain to me whether this could be applied to this data and whether additional types of observational variables were required to be collected in order to apply this particular type of analysis.

00059

So, this is the criteria for a grade assessment of the overall evidence for a therapy. We look at the

study design and if the study design is a randomized clinical trial, then it's usually considered the highest level of evidence. There is a potential bias, as I've briefly mentioned, the potential confounding effects of frozen salvage product in post-progression treatments, and the fact that there are limits to the use of statistical adjustment approaches.

Survival is a direct, easily measured outcome. In this study the disease progression outcome showed no difference. I understand that disease progression is a difficult outcome to measure in metastatic prostate cancer. Survival is a direct outcome. And because of these potential confounding effects and the relatively small overall sample size, the precision of our estimate of benefit is perhaps not precise because of unknown direction and magnitude of confounding variables. So we call this moderate, but again, I think this is an evolving issue for what is your ultimate evaluation to be given these criteria.

So, beyond the overall treatment effects shown in the clinical trials, what are some of the issues in our question 1.A? Subgroup effects. The issue of subgroup effects is given certain characteristics of patients that

00060

we know beforehand, older, younger, more severe disease, less severe disease, Gleason grade, are there potentially some identical sizable effects that show greater or lesser benefit of the treatment. And the issue in any trial regardless of the field is that whenever you split groups into smaller groups, each group now has a smaller sample size, and so your statistical ability to detect subgroup effects is immediately problematic. So it's very difficult to detect subgroup effects because you have smaller groups in each side. And depending on the balance or the size of the subgroups, it's even harder. If you're dividing your study into two subgroups and one of the subgroups is really small, your subgroup analysis is limited by the size of the smaller group.

Then there are potentially an infinite number of subgroup analyses that you could do, and the more times you look at the data, the more times you roll the dice, there's a higher chance that what you see could in fact not be a real one, so I call that low specificity. There might be false positive subgroup effects because you've looked at the data many many times. In an ideal clinical trial you have a limited number of subgroup analyses that are preplanned and declared beforehand, and there's some good evidence basis, perhaps a biologic basis for looking at these particular subgroup effects. Or if they're of

00061

particular interest, you design your study around looking at that subgroup and you make sure that your study has a sufficient sample size to look at that specific subgroup effect. In these studies we're looking largely at

post hoc subgroup analyses in relatively small studies. The way to look at these subgroup effects is rather difficult. What we want to see is, the hazard ratios are flipped from my prior presentation, a higher number indicates benefit of sipuleucel-T, and a potential subgroup effect that is made problematic by small sample size would be, let's look at as an example, PSA above the median, the point that's submitted here is close to one, and below the median it's close to two. Well, if this effect was apparent in a larger study and you had planned for it ahead of time and thought there was a biologic coherent reason to look at this subgroup effect, you might say that this just is real, because the distance is actually quite large, this is potentially consistent with no benefit of sipuleucel-T and this is consistent with a large benefit. These lines indicate the confidence interval and they overlap, so it's unlikely that this would be statistically significant.

So it's kind of like while the point estimate is high, the sample sizes are unfortunately not large enough to determine the significance of this. In addition, I'm

00062

doing it many many times, so the answer basically is I don't know, and so you would look at these and each of these which is in a pair of subgroups, you could say is potentially a subgroup effect, but then at least in this pooled 9901 and 9902, you kind of have to say I don't know, we have to do another study.

These are a set of subgroup analyses done on the IMPACT study, so again, you kind of see the same thing here. In any pair of subgroups where the sample was divided into those above the median or below the median, that there's some that could be potentially, you know, worthy of looking at further, but given this one study, you don't know.

The one that kind of pokes out at you here is the age breakdown below 65 and above 65. Now the confidence interval is larger for less than 65 because that's a smaller subgroup, the median age of these patients is not 65, it's about 72. But what we see here is striking and would likely be statistically significant in the usual kind of interaction analysis, where the point estimate here is 1.5. Now in this set of analyses, less than one favors sipuleucel-T, so the point estimate is in the direction of harm with sipuleucel-T. This is counterbalanced with that finding by being more extreme in the direction of benefit with sipuleucel-T in the greater

00063

than 65, and the confidence intervals do not overlap at all, so these look like they would be statistically significant, so is it a fluke or is it real? And it kind of stands out just from all the others.

So anyway, any of these subgroup analyses where the little point on the dot, you know, if one looks closer

to one and the other is more extreme away from the one, it's a potential subgroup analysis which is unfortunately not powered to detect the difference in treatment effect of the therapy.

So the FDA clinical review decided to pool the analyses using the age 65 cutoff, because in any one study statistical fluke or noise could cause an extreme result, so the results were pooled by this age 65 cutoff for all three studies. And so the survival for younger than 65 was 29 versus 28 months, in younger than 65 the hazard ratio was .919. In 65 years old it was 23.4 versus 17.3, a more extreme hazard ratio to basically counterbalance the one that's closer to one.

So is this or is this not a real subgroup effect, and again, we have to point to uncertainty, so .919 is certainly consistent with a small benefit or no benefit. They are in the same direction and the finding is less extreme than in the IMPACT study itself.

There have been various analyses of cell product

00064

parameters, measures of immune response and patient outcome, and our view of this was that they may not contribute to the evidence that really supports the efficacy of the drug, they may point to issues of predicting response in the patient, but if these measures correlated with survival but there was no survival benefit due to the drug, they would be potentially of interest but may not provide useful additional information regarding the effectiveness of the treatment. Now, many analyses have been done to correlate these with survival but they may not in fact correlate with treatment benefit because they may just be prognosticators of patients who do well, but they may perhaps have been predictors of patients who would have done better without the sipuleucel-T treatment.

And some of these measures are possibly measurable in the control patients, but in fact only measurable in the abstract, or impossible to measure in the control groups.

So for example, if you're measuring CD54 upregulation ratio and you were imagining that you could measure it in the control group, you really can't, because the CD54 upregulation ratio changes in response to sipuleucel-T treatments and the control treatment had no, or had an imaginary CD54 upregulation ratio to measure.

So in the abstract, I mean in reality some of these measures could not be measured in the control group, but

00065

these things could be correlated with perhaps unmeasured characteristics of patients that predict that they would do well either in the presence of sipuleucel-T or in the absence of treatment.

DR. GOODMAN: Dr. Mark, you've got about eight minutes left.

DR. MARK: Okay. Then why don't we skip this because I've kind of said it is probably not of critical

9 importance.
10 DR. GOODMAN: Don't skip the good stuff, but do
11 your best in eight minutes.
12 DR. MARK: So in general, there were kind of
13 variable conflict correlations with various measures of
14 the product, which were CD54 upregulation ratio, total
15 nucleated cell count and CD54 cell count. So patients
16 that got more stuff than their sipuleucel-T tended to have
17 overall longer survival, but these are analyses only done
18 in the intervention groups, not done in the control
19 groups.
20 Okay. Let's look at the off-label, or better
21 termed pre-label indications for sipuleucel-T, and these
22 were only Phase I and Phase II trials. The treatment
23 differed in many ways from the current treatment as
24 offered in the previously mentioned clinical trials, and
25 the goal was not really efficacy, the goal was measurement
00066
1 of biologic effects. So it's not fair to apply an
2 efficacy standard to these studies, but they did publish
3 outcome data.
4 So if we look at metastatic hormone refractory
5 prostate cancer but unspecified with respect to symptoms,
6 but my summary is that these patients were probably very
7 similar to patients in the randomized clinical trials if
8 we look at the descriptive characteristics. These were
9 all case series, there's basically a single arm trial, no
10 comparative arm, median time to clinical progression, and
11 the number can't be compared to the clinical trials
12 because the follow-up protocols were different, probably
13 less stringent, probably less complex decision rules for
14 determining clinical progression. So without a comparison
15 group, these do not provide information.
16 A portion of one study looked at nonmetastatic
17 hormone refractory prostate cancer. Dr. Gulley said these
18 patients just do not have imageable metastases so you're
19 kind of actually agnostic about their actual metastatic
20 state. Again, a single case series, and you can see,
21 without positive imaging their median time to progression
22 is longer, but again, a single case series study.
23 There was some case series studies on
24 nonmetastatic hormone sensitive prostate cancer. These
25 patients can still be treated with androgen deprivation
00067
1 therapy and in these studies the outcome was PSA failure.
2 You don't want to look at patients kind of prolonged with
3 a clinical endpoint because they can be successfully
4 treated with androgen deprivation therapy, and you can see
5 that this type of patient has a very long time to disease
6 progression, almost one year. Again, this is case series
7 data without a comparison group.
8 We do have conference abstract results of a
9 randomized clinical trial for nonmetastatic hormone
10 sensitive prostate cancer, a trial which was called

PROTECT, and the only results that I was able to obtain is in an abstract in 2007. Patients with a primary therapy of radical prostatectomy, they underwent hormonal therapy and then they were randomized to sipuleucel-T or placebo in the same manner as the randomized clinical trials. The principal outcome here for this study was a PSA failure, PSA greater or equal to three, and then some secondary endpoints. In the results that we have available or that I was able to find, the median time to biochemical failure was 18 months versus 15.4 months, not statistically significant. In terms of subsequent time to distant metastases, a hazard ratio of .73 in favor of sipuleucel-T, not enough endpoints to be statistically significant, and then a secondary analysis of PSA doubling time, which is a measure of how quickly your PSA

00068

increases, showed statistical significance.

So for these pre-label or off-label uses of sipuleucel-T, we have either case series studies or randomized clinical trials which at this point in time does not have statistically significant findings.

So for our key question two, it's rather easy. There's basically no data to ascertain issues about subgroup analyses or characteristics of the product and outcomes.

So our last question was to look at the adverse effects attributable to the use of sipuleucel-T, so this is a difficult issue. Severe adverse effects tend to be rare because they have been rooted out by prior studies, so if an early study shows that a treatment is really awful, we never get to this stage, so you're always at a statistical power question. These patients over time become sicker and things happen to patients with a bad disease. The placebo was a leukapheresis procedure with an infusion, and that can cause some rather acute adverse effects, so for some of the analysis we have to take the perspective that in fact the placebo patients are undergoing a procedure that at least can cause some known acute adverse short-term effects.

We were unable to find much information about frozen salvage product and any adverse effects associated

00069

with that, so that's just kind of a big gap in the data that I was able to look at in terms of acute effects or whether any of the adverse effect analyses that I'm going to present to you account for frozen salvage product.

And then there are all the post-progression treatments. My belief is these do not tend to cause a problem because in fact patients know they're getting chemotherapy, and late in the trial after disease progression, adverse effects were only reported if they were thought to be related to sipuleucel-T, and it seems unlikely that any kind of adverse effect could have been related to sipuleucel-T given everything else that was

going on in the patients. So my belief is that the adverse effects for sipuleucel-T reflect a pretty rigorous reporting of adverse effects through the period of infusions and then up to the time of objective disease progression.
DR. GOODMAN: Dr. Mark, why don't you just take another minute or two and then we'll close?
DR. MARK: Okay. Deaths really showed nothing remarkable, they were very rare in terms of occurring proximate to treatment. Nonfatal adverse events is a set of adverse events that are of sufficient severity and are measured throughout the trial, and they were in fact overall equal between the two arms of the study.

00070

These are the kinds of events that kind of play into the overall calculation of that incidence, and you can see it's just a long list of things that probably have not been fully edited, and this is taken directly from the FDA report, and you can see some things are listed twice with slightly different numbers, so this has not been fully edited. But in terms of, they were counted one per patient up to that total incidence number you saw before. Cerebrovascular events were of particular interest because of the early trials showing a potential increase in cerebrovascular events in the 9901 and 9902 settings, but when you pool all three studies plus the PROTECT trial together, the cerebrovascular incidence is slightly higher in the sipuleucel-T group, again, it's a 1.1 percent difference, again that is inconclusive, it's just a higher point estimate than the sipuleucel-T group. Infections occurred overall equal between the two groups but when you recall that the placebo group received leukapheresis and infusion with the potential for infection, you kind of parse that data slightly differently, you look at infection rates within one week of the infusion. Catheter-related infections and catheters would not have been put in the placebo group except for needing sipuleucel-T placebo. We see that there's this finite incidence of catheter-related

00071

infections, so there's probably some unknown proportion of these total number of infections that is due to the leukapheresis and infusion procedure, and it's kind of an artifact of being in this particular clinical trial in the placebo group.
Lastly, and this is useful, is that various events, types of acute events, some of which are not severe, are consistent with an infusion reaction. So the FDA kind of summed up all the events that are consistent with an infusion reaction and summed them up and looked at the difference between the two groups. And we can see that even in the presence of what the placebo group underwent, that there's a much higher incidence of infusion events in the sipuleucel-T group, chills, fevers,

soreness, kind of just feeling bad for a little while after the infusion, and a very small number of these were severe.
So grade three is something that's kind of alarming, requires treatment, and makes the patient definitely sick. This occurred in 21 patients in the sipuleucel-T and no patients in the placebo group. Hospitalization, which would be not quite as severe a patient reaction, had seven patients in sipuleucel-T versus zero in the placebo group.
DR. GOODMAN: You want to wrap up now, Dr. Mark.

00072

DR. MARK: Okay. So adverse events, I believe it causes some unknown proportion of the events of infection, so without the placebo group there are more infections than there would be. It definitely causes infusion reactions at an incidence beyond the placebo group. And regarding other types of adverse events including CVE, there's no conclusive evidence.
So, let me not talk about this, but hopefully I've outlined the issues of the clinical trials for your interest, and clinical trials are a difficult business, it's hard to do them perfectly, and there's room for potential improvement in the design now that survival seems to be a point of interest for clinical trials, and that clinical trials should be designed for other indications with respect to the survival endpoint. Thank you.
DR. GOODMAN: Thank you very much, Dr. Mark. We don't have time for questions now, but Dr. Mark, be assured that we will ask you and other subsequent presenters to sit up front during the afternoon when we will have, I'm sure, inquiries for you and others.
We're going to take a 15-minute break now, not 16, 15, so do look at your watches or whatever your time piece happens to be, add 15 minutes to it, and Ms. Ellis is going to tee up our first scheduled presenter. Ms.

00073

Ellis, did you have a comment?
MS. ELLIS: Yes, real quick. Some individuals did not register this morning when you came in, you went straight through security, so basically you do not have a visitor's pass. You need to go out front to the lobby to the table and register and receive your visitor's pass. You cannot access the building without your visitor's pass, so you will not be able to go to the cafeteria, the restrooms and things of that nature without your badge, so please go to the desk and register and receive your visitor's sticker, and make sure it is visible.
DR. GOODMAN: 15 minutes.
(Recess.)
DR. GOODMAN: We're going to move to our scheduled public comments. These are people that arranged ahead of time with CMS to speak. I see that we have nine,

not eight but nine such scheduled public speakers. Each speaker is limited to five minutes, that's the bad news, and we will have to enforce it. The good news is that, depending on who you are, we're going to ask all of the speakers to come front and center for our discussion period, so we can and hope to hear from our speakers beyond the five minutes, so I hope that's an encouragement to our speakers to stick to their five, and we'll remind you.

00074

Our first scheduled speaker is Paul Schellhammer. He's a professor of urology at Eastern Virginia Medical School and he is noted here as representing the American Urological Association. Dr. Schellhammer.

DR. SCHELLHAMMER: Thank you. With regard to my disclosures, I have been an investigator on Provenge trials and I serve on the advisory board and speakers bureau of Dendreon. As noted, I practice in Norfolk, Virginia, I'm a urologic oncologist with a specific interest in men with prostate cancer, specifically advanced disease, and I also am spokesman for the American Urologic Association, which represents approximately 90 percent of practicing urologists in the U.S., and I was privileged to serve as the president of the AUA in the year 2007.

From a personal standpoint, I was diagnosed with prostate cancer in the year 2000. I currently have nonmetastatic castrate-resistant prostate cancer, it has no metastases, and therefore I am not a candidate for Provenge. I make this statement now to emphasize that everything I say subsequently deals with on-label use of autologous cellular immunotherapy, sipuleucel-T, Provenge for men with advanced prostate cancer, metastatic castrate-resistant, as approved by the FDA based on

00075

clinical trial data.

In 1999 our department began enrolling patients in the initial trials and over the decade have accrued approximately 75 patients to the various trials, so I am familiar with the product. As you heard from Dr. Gulley, patients with localized prostate cancer who receive definitive local therapy will progress on frequent enough occasion to metastatic castrate-resistant disease, and their option is chemotherapy, Taxotere currently, which confers a 2.4-month survival benefit, but that's at the price of toxicity as you saw, with up to 30 percent of patients experiencing neutropenia, neuropathy or significant fatigue, which can be significant enough so that 10 to 15 percent of those patients will withdraw from therapy.

Add to this the fact that Taxotere is given with Prednisone, a steroid, and this compounds some of the side effects, including difficulty with management of diabetes,

impairment of bone health and immune suppression. So it's not surprising that a number of men, in fact up to 50 percent may never come to chemotherapy because of these quality of life issues.

So we now have two randomized trials, controlled randomized trials demonstrating a survival benefit for Provenge or autologous cellular immunotherapy. And the

00076

pivotal trial, IMPACT, as you saw, confers a 4.1-month survival benefit, it's delivered over four to six weeks, and the toxicity is really quite minimal. It's quite remarkable that only three patients, or approximately one percent, withdrew from therapy because of adverse events.

So we have the following scenario. With Provenge a 4.1 month survival benefit with four to six weeks of therapy with relatively minimal toxicity, compared to docetaxel with a 2.4 month survival benefit with treatment delivered over six months, so a benefit to burden ratio certainly far in favor of sipuleucel-T immunotherapy. And add to this the toxicity which sometimes requires hospitalization, and then benefit to burden ratio is further amplified. So I think we can say that Provenge is quite unique in the treatment of advanced prostate cancer in that the survival benefit is not consumed to a large part with the therapy and with management of side effects from the treatment.

So to address briefly the primary question of the MedCAC, is there evidence of efficacy, survival, and minimization of toxicity, I would say the impact data certainly emphasized that this can be answered with a strong affirmative. And so the FDA approved the product and the NCCN, as you heard, placed it as a primary recommendation for patients with this disease state.

00077

DR. GOODMAN: Dr. Schellhammer, one minute, please.

DR. SCHELLHAMMER: I will also say that in my 35 years of experience, medical oncologists and urologists are certainly very capable of identifying patients with this disease state who would be eligible for therapy. So in conclusion, as a urologic oncologist, a spokesman for the AUA, a prostate cancer patient and a physician dedicated to delivery of the best possible therapy for patients with metastatic castrate-resistant disease, I urge the Center for Medicare and Medicaid Services to recognize the evidence of safety and effectiveness accepted by the FDA establishing Provenge as reasonable and necessary. It is a breakthrough immunotherapy strategy that fulfills an unmet need and I hope, we hope that CMS will recognize that promise and approve Medicare coverage for labeled indications through a prompt national coverage determination, and thank you for your attention.

DR. GOODMAN: Thank you very much, Dr. Schellhammer, thank you for those concise comments. Next

is Brad Loncar, from Lenexa, Kansas. And Mr. Loncar, please identify yourself. Mr. Loncar does have slides.
MR. LONCAR: Thank you very much. My name is Brad Loncar, I'm from Lenexa, Kansas, and I don't represent any specific company or organization, I'm just
00078
here as a citizen, and I would like to thank the panel for allowing me the opportunity to speak this morning. To quickly go over all of my disclosures, first of all, in 2006 my grandfather, Michael Loncar, passed away from late stage prostate cancer, so I personally experienced how this disease affects the lives of men and their families. I'm also an investor in the maker of Provenge, a proud investor I might add, because I believe in the innovative work that they're doing with this disease and I want to support that. However, I have never had any direct relationship with that company or any company, and I'm 100 percent here on my own today.
I wanted to be here to speak with you because I'm deeply concerned with the way this Agency has handled the proposed coverage assessment and I think it has ill served the public in the process, especially as it relates to the on-label usage of the already approved drug. In short, I'll argue that the FDA has already largely spoken on many of these issues, and for a second government agency to openly second-guess that is at best not constructive.
And to illustrate what I'm talking about, I'd like to specifically focus on two questions from today's agenda, questions eight and nine. These questions essentially ask what significant evidence gaps exist with
00079
this treatment and what new study designs could be used to resolve any such gaps.
Well, I think it's very important to first look at what the FDA said on those issues. Back in April when the FDA approved Provenge, it published a report which explained to the public how it went about its review and how it came to its conclusions. I have a copy of that report right here and anyone can download if from the FDA's website. The title of the report is The Summary Basis For Regulatory Action, and it was published by Dr. Thomas Finn, chair of the FDA's review committee. On page 14 of that report the FDA very clearly brings up the issue of the strength of the data and the need for additional studies by saying the following, and I quote: Because D9902B provides substantial evidence of improved survival, a second study would be neither ethical nor feasible in the United States.
Now that's a very clear statement and with all due respect, the FDA didn't qualify their feelings on a scale of one to five. No. They were much clearer than that, as I believe a regulatory body should be when speaking with the public. So given that clarity, I think

one has to wonder if today's meeting is indeed about something other than the science, namely the cost, because remember, when the FDA does their review they don't look

00080

at cost, no, their review is based solely on the scientific merits of the drug. And based on that study of the scientific merits, they came to the crystal clear conclusions that, one, there was substantial evidence of improved survival, and two, because of that substantial evidence, a second study would be neither ethical nor feasible.

So I think it's very concerning that this Agency today seems willing to consider something that very recently the FDA has already said is unethical. I think that raises a lot of questions, two of which at the top of my list are, how many men will have their lives prolonged because of potential confusion or delays caused by the CMS, and how much future innovation will be stifled by a government that regulates with two voices? When it comes to informing the public about the safety and efficacy of drugs, the United States Government needs to speak with one clear and concise voice, and that voice is the FDA.

So to conclude, I am very concerned that this Agency, seemingly for financial reasons, seems willing to consider something that another government agency, the FDA, has already publicly said would be neither ethical nor feasible because substantial evidence of efficacy already exists. Therefore, I do not believe that CMS should be considering questions eight or nine or any

00081

questions as they relate to on-label usage, because the FDA has already clearly spoken on those matters. Thank you very much.

DR. GOODMAN: Thank you very much, Mr. Loncar, we appreciate your points, we hope you will stay for the remainder of the day to share in our examination of the evidence. I would also just remind our panel that as we look at our questions, none of them deals with financial matters, cost or the like. But thank you indeed, Mr. Loncar, and I hope we will see you through the rest of the day.

Next up is Dr. James Kiefert, who's the board chairman emeritus of Us TOO International. Welcome, Dr. Kiefert.

DR. KIEFERT: Thank you. I need to make a brief correction to the announcement. I have a doctor's degree in education, not in medicine.

DR. GOODMAN: That's quite all right, sir, to be preferred in some instances.

DR. KIEFERT: This is a little bit of my background and my journey with prostate cancer, but in the interest of time I would like to go right to my conclusion so that in case I get going too long, we don't forget this part.

First of all, I was a part of the FDA team that
00082
reviewed Provenge, I was a patient representative brought in from the beginning to review stacks of data dealing with all of the studies that came in. I have to admit I felt a little bit uneasy when I looked on the website for this meeting and there was a reference to a memo from the FDA that said that the patient representative, Jim Kiefert, questioned about stroke as an adverse effect. Well, I did my job as a patient representative, I went through all the data, and in our discussions I said have we looked at this data thoroughly. And of course statistically it was not significant, and yet this was brought up as one of the factors in background information for this study. Stroke is not a concern statistically. When I was on the team we used the word compelling data from the studies. We know that the FDA has both the authority and the responsibility to review the data carefully. We know that during this litigious society the FDA has become very careful and conservative in analyzing data to assure safety and efficacy. The data was so compelling that, as you noted, and our previous speakers noted, the labeling does not have a lot of warnings.
I might -- I have no financial interest in Provenge or the Dendreon Corporation, but I do have another kind of personal interest. After we completed our
00083
study -- I do have metastatic castrate-resistant prostate cancer, and I was able to qualify for a clinical study of Provenge, it was a dosing study. And having read all the data about it I felt very comfortable about going through the procedure. And they always warned me that when I go in for my leukapheresis, and my wife came with me, because you may need to have someone drive you home. Well, I had absolutely no side effects, I drove the 60 miles from Seattle to Olympia, I felt so good I took my wife out to lunch every time. The men in my support group, and I have been a support group leader now for 17 years, I have some who have been through the trials, I don't have any men who have said that they had any adverse events other than being a little nervous and upset and going through the procedure, nothing lasted more than 24 hours. So we do have a safe and effective treatment.
Us TOO International is the largest prostate cancer education and support organization in the world, and we did a survey of our members about four years ago and asked the question, if you got to the stage of your disease where you were going to take chemotherapy, would you do it, and less than half indicated that they would take chemotherapy. And the reason, because of the adverse effects. I have witnessed the men going through chemotherapy treatment who lose their hair, lose their
00084

taste, lose their fingernails and toenails, become hospitalized, and if you stay on chemotherapy long enough, your quality of life is adversely affected, and I can say with Provenge there were no side effects that were adverse at all.

In summary, I would like to say that this kind of discussion has caused members of my support group to be so concerned about whether they're going to have the opportunity to participate in the treatment of a drug that has been approved by the FDA for safety and efficacy. When one of the men in my group who is 67 years old heard that we're going to have this meeting, I see tears running down the side of his face. He said I can't, I can't go through this not having an opportunity to extend my life by four months. So what does four months mean? When Steve in my group died at age 42, I can tell you his three kids that were still in school and his daughter who had just gone on to college would have given anything to have four months with their father.

In conclusion, I would like to say that this is a new biologic that revolutionizes the way we treat men with prostate cancer. It's no longer one drug fits all, it's customized and effective, and I look forward to making this opportunity to all the men who meet the qualifications for sipuleucel-T. Thank you.

00085

DR. GOODMAN: Thank you very much, Dr. Kiefert, and we very much appreciate your personal view and your sharing your experience. We very much appreciate you being here today.

Next is Dr. Daniel Petrylak, who is a professor of medicine at the Columbia University Medical Center. Welcome, Dr. Petrylak.

DR. PETRYLAK: Good morning. My name is Dr. Daniel Petrylak, I'm a professor of medicine and co-director of the Herbert Irving Comprehensive Cancer Center prostate program. I was an investigator on the IMPACT trial and have received research support and consulted for Dendreon previously, but I am here today on my own accord.

Today I will discuss the treatment of asymptomatic or minimally symptomatic men with castration-resistant prostate cancer. I was the principal investigator on one of the trials that got docetaxel approved for castrate-resistant disease and have served as a principal investigator on four other national prostate cancer trials.

In the United States in 2010, more than 200,000 men will be diagnosed with prostate cancer. Eventually 30,000 will develop metastatic disease and die from metastases. Approximately 20,000 of these patients were

00086

asymptomatic. The problem with clinical trials for metastatic castration-resistant prostate cancer is

multiple agents tested in Phase III have failed to show a survival benefit in the past decade. These clinical trial failures have been observed despite the fact that there have been improvements in objective responses, improvements in symptoms and declines in PSA with these agents. Of all these multi-clinical trials, only mitoxantrone is approved by the FDA for palliation of symptomatic castration-resistant disease.

Prior to 2004, chemotherapy was infrequently administered to asymptomatic patients. With the approval of docetaxel, in addition to the supportive care, second-line hormone therapy and docetaxel treatment were options for patients who were asymptomatic. Docetaxel was approved on the basis of two randomized clinical trials, one performed by Dr. Tannock and the second performed by myself. The FDA approval of docetaxel, the first agent to demonstrate a survival improvement in this population, was a milestone event for prostate cancer patients. Docetaxel demonstrated approximately a two-to-three-month improvement in median survival and a 20 to 24 percent reduction in the risk of death. The median survival for three-week docetaxel was approximately 19 months. However, this survival benefit comes at the cost

00087

of significant toxicity. Docetaxel toxicity includes neutropenia, diarrhea, infections, sensory neuropathy as well. Hospitalizations may be required for cytopenias and infections, and deaths occur in approximately two to three percent of the patients. These side effects are particularly relevant for the asymptomatic patient who does not have bone pain for their prostate cancer, and explains the reluctance of some oncologists to administer chemotherapy to these patients.

Only 50 percent of all eligible patients are treated with docetaxel. With the approval of sipuleucel-T this year, there are now three options for the initial treatment of castration-resistant prostate cancer, sipuleucel-T for those patients who are asymptomatic or minimally symptomatic, docetaxel, and second-line hormone therapy.

The approval of sipuleucel-T was based primarily on the IMPACT trial which demonstrated survival benefit relative to placebo, consistent with two previous randomized studies. Comparatively speaking, side effects are relatively modest, the most common being chills, pyrexia, headache, influenza-like symptoms and myalgia. Thus, for an asymptomatic or minimally symptomatic patient, docetaxel and sipuleucel-T are options which prolong overall survival. However, the toxicity posed to

00088

these patients favors sipuleucel-T.

An important clinical question is how the benefit of sipuleucel-T is affected by prior and subsequent docetaxel treatment. I presented this analysis

at ASCO in June of this year addressing this question. The analysis demonstrated that it was a key treatment effect in both those who had prior docetaxel and those who did not, as well as those who had subsequent docetaxel and those who did not. There was no evidence of a treatment by subsequent docetaxel to yield interaction. Moreover, in patients who were initially symptomatic and received docetaxel treatment to become asymptomatic, sipuleucel-T may be a treatment consideration provided that the symptoms resolve to the asymptomatic or minimally symptomatic state.

Based on FDA approval and the survival benefit seen with sipuleucel-T, as well as the safety and toxicity profile, the NCCN has listed sipuleucel-T as one of the three treatments for initial management of castration-resistant prostate cancer with a category one recommendation, which means the highest level of evidence. Treatment selection is based on a balance between survival benefit and toxicity. Whereas both docetaxel and sipuleucel-T prolong overall survival, the substantial toxicity associated with docetaxel favors the use of

00089

sipuleucel-T in asymptomatic or minimally symptomatic patients. Expected management has been on the toxicity but no survival benefits.

In conclusion, there is a high level of evidence favoring sipuleucel-T as frontline therapy for men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. Thank you for your attention.

DR. GOODMAN: Thank you very much, Dr. Petrylak. We especially appreciate your providing information that is pursuant to some of our questions, and appreciate that, I believe you were one of the first authors in an important publication that's relevant to today's proceedings. Thank you, sir.

Next up is Dr. Saurabh Aggarwal, who's a healthcare consultant based in Bethesda, Maryland. Dr. Aggarwal.

DR. AGGARWAL: Good morning. I am Saurabh Aggarwal. I will be presenting my comments for on-label and off-label use of targeted cancer therapies this morning. For disclosure, I have no conflict of interest with Dendreon or Provenge, I'm here at my own expense, and these are my personal views.

Before I state my comment, I want to briefly throw out an overview of my background in cancer

00090

therapies. First, during the last ten years I worked on several cancer drugs as a researcher, as a consultant, and as an industry analyst. In my current role I advise drug and device companies on market and exit strategies, currently at PAREXEL and previously at IMS. Previously I was at Sanford Bernstein, where I worked on a number of

projects on evaluating evidence for emerging cancer therapies. I independently also have written strategy perspectives on cancer drugs for two national magazines, and I conducted cancer research at Johns Hopkins, where I coauthored two cancer drugs that are currently in early stages of clinical testing.

First, I want to mention that during the last 20 years we have seen several new drugs for targeted cancer therapies which have reached the market, and based on listing of studies of clinical trials, currently approximately 40 percent of all ongoing studies are related to cancer, implying there are a few hundred novel cancer drugs which are in the pipeline. This is good news for patients but I think it poses some future challenges for payers such as CMS.

This is related to my first comment, which is that clinical issues we are discussing today are likely to be similar for these emerging cancer drugs, and I would request CMS to develop a process so that we can evaluate

00091

these drugs.

So, let's step back and ask a question, why there is such a high interest in cancer drugs, and there are several reasons. First, as we all know, cancer is still one of the leading causes of death in the U.S. Second is the ability to price drugs at a range of up to $100,000. Third is the advancement in medical science which has enabled this flurry of new technology and novel mechanism of action drugs, and I think this panel has been provided with good examples of these new therapies. Fourth, there's a regulatory pathway which allows you surrogate endpoints such as PFS, which has made it relatively easier to seek regulatory approval for cancer drugs. And last, I think the most important reason is that payers are reimbursing for on-label and off-label use of these drugs, which is largely due to the Social Security Section 1861.

To focus on Provenge, I want to provide my comments from various perspectives. First, as a technology, I think Provenge is a breakthrough therapy. What we've already seen, I think, is the tip of the iceberg. I think we have yet to see the full potential of this therapy. Second, from an efficacy standpoint, I think there is some confusion about efficacy, I think this is an area where CMS can help doctors and patients

00092

understand the efficacy of these therapies. Third, from a private payer's perspective I'm hearing that they are worried about this drug, that the expectations are very high, and I think CMS needs to bridge this gap between Provenge efficacy and expectations of doctors, patients and payers. Lastly, I will close by saying that we might not have answers to all questions today, but I think it is critical that CMS puts a process in place so we can

collect more data and have answers to these questions in the near term, and hopefully we can see the full potential of this technology. Thank you.

DR. GOODMAN: Thank you very much, Dr. Aggarwal, we appreciate those various viewpoints, and we hope that you will stay for the remainder of the day.

Next up is Dr. Mark Scholz, who is the medical director of Prostate Oncology Specialists, Inc., in Marina Del Rey, California. Welcome, Dr. Scholz.

DR. SCHOLZ: Thank you. Marina Del Rey is in Los Angeles, it's a medical oncology practice specializing only in prostate cancer. My partner Dr. Lam and I actively manage about 1,500 men with prostate cancer, which is a little unusual for medical oncologists, who are typically more weighted towards breast, colon and lung cancer, so we have a lot of experience with this illness. The points that I wanted to make are that of a

00093

community oncologist who sees a lot of prostate cancer and has to deal with this on a day-to-day basis. I don't have any connections with Dendreon, I paid my own way out here, and I just am quite encouraged to have a new tool in my tool chest to treat these men that we have to face on a daily basis. So I'm just here to try to encourage that this, access to this treatment be maintained. So, I didn't participate in any of the Provenge trials, and so I've gotten into treating patients since the approval of this, and we've treated somewhere I think close to 30 patients now with this drug and have found that it is as advertised, very simple to administer and has very little toxicity.

On deciding what to do with these patients, we're always faced with major quality of life issues. The men that have advanced prostate cancer are elderly, they have been deprived of their testosterone, they're often quite frail, and they're not tolerant of toxic treatments, and they are certainly not very interested in things that could ruin their lives in the waning years of their lives. The average survival, as you can see, is on the order of a year or two. People want to have good quality during those last couple of years of their lives.

So the other options, hormone therapy and chemotherapy, as Dr. Petrylak pointed out, are more toxic

00094

than Provenge, so we have an effective treatment that can be administered to relatively frail patients without any major concerns of ruining their quality of life with our good intentions. And this is filling a gap in the prostate cancer area where men don't have preexisting bone pain and symptoms. Certainly we can justify toxic treatments in men that have a lot of symptoms from their disease, but many men with prostate cancer don't, so it's very nice to have an agent that we can administer that is not likely to make them feel worse.

In our experience administering this, we found it to be a very seamless approach. One of the attractive things is this is not a treatment that goes on and on and on and on, it's given on three separate infusions over a six-week period and the treatment is done. That means less visits to the doctor. I don't know about the rest of you, but most of us don't think that quality of life is spending time in a doctor's office, so this is another advantage for quality of life for this agent compared to the other options that we have.

I think another option to consider, another advantage to consider is that as a medical oncologist, I'm in the minority. Most of these patients are being treated by urologists who are actually surgeons. This fortunately is a simple treatment that urologists can easily manage,

00095

whereas chemotherapy requires referral to a medical oncologist, it's very very rare for surgeons to be comfortable administering Taxotere. So there's easy access because the doctors that are going to be managing these patients, the surgeons, the urologists don't have to worry about managing toxic side effects of chemotherapy.

I've already mentioned that the selection of patients is relatively simple, this has been discussed many times, we don't need to review that. The actual administration I've reviewed with you, is also quite simple.

So to summarize, then, this is a new agent that is clearly beneficial for patients. This four-month number that keeps getting thrown around as if that's the magic outcome for every patient is ridiculous. Every patient that gets this medicine going into it does not know if they personally will benefit. However, we know based on these excellent trials that certain people do benefit. Everyone who has this prostate cancer situation wants a chance at a benefit. Some men are not going to get benefit from it. Fortunately, they will not suffer excessive side effects.

Other men are going to get a greater benefit than four months; remember, four months is just the average outcome. Some men are going to get far greater

00096

benefit than four months. We don't know who that will be, we wish we could predict it in advance, and that certainly would be a wonderful area of research for the future, to figure out who's going to benefit, and administer this medicine only to those individuals. At this time we don't know that, but since the treatment is nontoxic, we can safely administer it to a group of men and expect that a certain number of them are going to get a major benefit.

Thank you very much.

DR. GOODMAN: Thank you very much, Dr. Scholz, and we do appreciate your perspective from community practice. Thank you, sir.

Next is Thair Phillips, who is the president of Retire Safe. Welcome, Mr. Phillips.

MR. PHILLIPS: Thank you very much, good morning. My name is Thair Phillips, I'm the president and CEO of Retire Safe, which is an advocacy organization, a nonprofit advocacy organization representing approximately 400,000 seniors across the nation. We have received no money or benefit from anyone who has a commercial interest in this issue.

Today you have, or will hear from many cancer centered associations, doctors, pharmaceutical groups, and cancer patient groups. They speak mostly for those who now have prostate cancer and will be immediately affected

00097

by your decision concerning Provenge. I'm here today to represent those older Americans who haven't yet been directly affected by the disease but who will nonetheless be affected by your decision. I can tell you that these older Americans care very deeply about the suffering and choices of those individuals who have prostate cancer and about the role of government and the role that government plays in those decisions and choices. This decision will establish a precedent that will affect the very foundation of innovation and establish a template for government's roles in the way health care is administered.

I will speak very plainly and directly today. It is how the Retire Safe supporters have spoken to me, and I can do no less as I speak today. In the spirit of directness, I will disclose how our organization is funded. We receive 92 percent of our funding in small donations from individuals all over this nation. We sell no insurance or have any other commercial interests. We get no grants from the government. We are focused only on what is best for our supporters and we get that knowledge from listening to them. We do that through surveys, direct mail, e-mail, and talking directly to seniors at expos and seminars.

I had the opportunity last week to spend a day in Pennsylvania talking with and listening to seniors.

00098

They looked me in the eye and told me what made them nervous. It is evident to me that unless seniors or a loved one gets prostate cancer, most seniors do not understand all of the clinical details about why Provenge works, why it costs so much, why an insurance company or Medicare would or would not approve coverage.

Historically seniors have relied on their doctors to know these details. Many of them are beginning to realize that the way things are going, maybe they can't rely completely on their doctor, not that their doctor is unreliable, but because the government is seeking to limit the doctors' choices. The limiting of choices was and remains an important issue in the healthcare reform debate, and this government intrusion makes them nervous.

Seniors have trusted the FDA to ensure the safety of medicine but now they see government bureaucrats seeking to overrule these decisions. If the MedCAC truly believes that the FDA approved a drug that has a questionable benefit, why is the FDA not part of these discussions today? This overstep of regulatory oversight makes seniors very nervous.
They see inconsistencies in the government's response to different medicines, such as the hands off and proper reaction to breast cancer medicines, compared to the immediate and aggressive response to FDA-approved

00099

Provenge. They have believed over the years that their government is fair and unbiased, but they see the difference in the media coverage in the focus afforded to breast cancer and then they see the inconsistent response and they get nervous. They don't hear people asking the proper questions or whether this treatment benefits the Medicare community, they only inquire about how much it costs. This makes them nervous. The bigger effect of what these changes predict concerning the path of health care in America is what makes them nervous.
When a pharmaceutical industry who spends billions of dollars seeking cures to diseases loses faith that an FDA approval means a drug can be manufactured, distributed, prescribed and sold, then we have severely crippled the very mechanism that has made America the world's leader in the development of lifesaving medicines.
It will cripple innovation in cancer research if new FDA-approved treatment against cancer must now go through a second round of efficacy and safety reviews from CMS even for their use on label. It will dim the hope of those who pray for a cure for the disease that affects their loved ones.
I am convinced that the final decision on this issue will have a big and lasting impact on innovation.
The clinical effectiveness of Provenge treatment is not in

00100

dispute. Whether the MedCAC admits it or not, the real core of this discussion is price, and price is the very thing that should not be a point of discussion. If the government is willing to break its own rule and precedent in reviewing Provenge because of its cost, we have started down the road to rationed health care. I see no other word to use in this case but rationing.
DR. GOODMAN: Mr. Phillips, just less than a minute please, sir.
MR. PHILLIPS: Thank you. Government intervention in healthcare decisions worries older Americans. They have told me that over and over. This important decision concerning Provenge impacts not only prostate patients but every American, especially older Americans, and MedCAC should carefully consider the far reaching implications of this landmark and precedent

setting decision. Thank you for your time.
DR. GOODMAN: Thank you very much, Mr. Phillips. We do appreciate your being a liaison to large groups of patients in the field. And I just remind the panel once again, and perhaps Mr. Phillips as well, that none of our questions concerns costs or other financial matters, and we hope that a good examination of the evidence today will not limit anyone's choices, but perhaps provide evidence-based information that will support those choices

00101

for doctors, patients and families.
Next up is Dr. Mark Frohlich, who's the chief medical officer of Dendreon. Welcome, Dr. Frohlich.
DR. FROHLICH: Thank you. I'm Mark Frohlich, chief medical officer at Dendreon, a medical oncologist. I continue to see patients at the University of Washington where I have a faculty appointment.
Today I'm going to focus on each of the questions. Questions 1.A and 2 concern the adequacy of evidence to determine whether treatment with sipuleucel-T improves overall survival. The FDA approval of sipuleucel-T is based on the highest level of evidence. The largest trial, IMPACT, was a multicenter double blind randomized placebo controlled trial with a primary endpoint of overall survival. The trial included an option for crossover in the control arm. Giving them the salvage product had the same relief specifications as sipuleucel-T. One would anticipate that the survival benefit may have been greater in the absence of that crossover. Treatment compliance and follow-up for survival were very high.
The trial demonstrated a statistically significant improvement in overall survival, which is supported by the results of another Phase III trial, D9901. These trials were the basis of the FDA label for

00102

sipuleucel-T and are consistent in terms of the median survival benefit, 4.5 and 4.1 months, and the percentage of patients alive at three years in both studies.
Questions 1.B and 3 concern whether treatment significantly improves disease-related symptoms. The trial only measured asymptomatic or minimally symptomatic disease, so assessment of the control of disease-related symptoms or palliation of disease-related symptoms could not be assessed. The primary endpoint of overall survival is the best measure of patient benefit; it reflects the control of the natural history of the disease. In the IMPACT trial adverse events that may be associated with advancing prostate cancer, such as anorexia, flank pain, hydronephrosis, were seen more commonly in the control arm, suggesting that sipuleucel-T may have reduced these events.
Of particular relevance is a recent analysis showing a strong trend towards a delay in the time to

development of disease-related pain with a more than doubling of the pain-free rate at one year, and I think Dr. Kantoff will speak more of this.
Questions 1.C and 4, concerning adequacy of evidence regarding avoidance or minimization of the burdens associated with anticancer therapy. Treatment with sipuleucel-T avoided the burdens associated with

00103

chemotherapy alternatives. In the focal trial for sipuleucel-T, approximately half the patients did not go on to subsequently receive docetaxel-based chemotherapy. The relative burdens of chemotherapy to sipuleucel-T can be assessed by comparison of their well characterized adverse event profiles. The most common adverse events associated with sipuleucel-T are chills, fatigue, back pain and nausea. Docetaxel and cabazitaxel are associated with significant rates of hematologic toxicities as well as events such as infections, diarrhea and nail changes. The comparison of grade three or four events observed in five percent or more of subjects reveals none for sipuleucel-T. Docetaxel and cabazitaxel have significant rates of grade three or four toxicities, which may require the use of growth factor injections and lead to infections.
Question 5 concerns the generalizability of the conclusions to unlabeled uses. There are no sure efficacy data supporting off-label uses of sipuleucel-T.
Question 6.A concerns the generalizability of the conclusions to a community-based setting. More than half the patients were enrolled in community practices. There was a positive treatment effect in the subgroup of patients with a hazard ratio of 0.667 and a comparable adverse event profile.

00104

Question 6.B concerns the generalizability of the conclusions to demographic groups that may have been underrepresented. In terms of the Medicare population, more than three-quarters of the patients were age 65 and greater, and there was a positive treatment effect in these patients with a hazard ratio of 0.62, and for the FDA label a median survival difference of 6.1 months. Their adverse event profile was comparable with the overall population.
5.8 percent of enrolled patients were African-Americans. Because of the small sample size, no definitive conclusions can be drawn. However, the observed treatment effect appears large with a hazard ratio of 0.288 and the upper bound of the 95 percent comfortable is well below one. The adverse event profile was not higher in African-Americans.
Finally, Question 7 concerns the ability to identify patients who are more or less likely to benefit from treatment. Subgroups based on these baseline prognostic factors indicates a positive treatment effect

in all of these subgroups. In summary, sipuleucel-T significantly improves overall survival, the gold standard endpoint in oncology. The IMPACT trial with its randomized multicenter double blind placebo controlled design provides the highest level

00105

of clinical evidence, which is why sipuleucel-T has been designated a category one recommendation by the NCCN guidelines. Sipuleucel-T is not associated with burdens observed with alternative cancer therapies. And the results are generalizable to the community setting and to underrepresented populations, including African-Americans. Sipuleucel-T provides an important new treatment for men with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. Thank you.

DR. GOODMAN: Thank you very much, Dr. Frohlich, and we particularly appreciate your addressing the questions specifically and within the five minutes, that's very much appreciated, and we hope to speak to you a little bit later as we will with our other presenters. Our last scheduled presenter is Dr. Philip Kantoff. He's a professor of medicine at Harvard Medical School, also director of the genitourinary oncology unit, chief clinical research officer and chief of the division of solid tumor oncology at Dana-Farber, which is a cancer institute near Boston. Welcome, Dr. Kantoff.

DR. KANTOFF: It's actually in Boston. Good morning. I'm Phil Kantoff, principal investigator of the IMPACT study. Please refer to my handout to follow my slides; I know the panel has the handout, not everything does. By way of disclosure, I'm

00106

not a paid consultant to Dendreon. I have been in the field of prostate cancer for approximately 24 years and have been involved or led many of the major studies involved in this disease area. Slide two. I'll highlight some of the key results from the IMPACT trial published in the New England Journal on July 29, 2010. Slide three. The IMPACT study, as you've heard, is a double blind randomized multicenter placebo controlled trial of 512 patients with metastatic castration-resistant prostate cancer. Patients are randomized in a two-to-one fashion to receive either sipuleucel-T or placebo. Placebo is used as a control as opposed to chemotherapy with the intent of creating a clinical niche for the development of treatments which prolong survival while causing few treatment-related side effects. Patients were followed until progression and at time of progression patients were unblinded and placebo-treated patients were allowed to cross over to treatment. The primary endpoint in this study was overall survival. Slide four and five. In the interest of time I

will not cover, as you've heard before, the products' mechanism of action or logistics of administration. Slide six. Baseline characteristics were evenly

00107

balanced between the two arms. Note that the average age of the patients was above 70, that a subgroup of patients in both arms received docetaxel prior to protocol entry, and that over one half of the patients treated in the study were from the community study. Slide seven. Survival analysis, as you've heard, demonstrated statistically significant improvement in overall survival. The hazard ratio was 0.775 with a P value of 0.032. The median survival difference was 4.1 months. At three years, 31.7 percent of patients in the sipuleucel-T arm versus 23 percent of patients in the placebo arm were still alive. This represented a 38 percent relative improvement in survival. Slide eight. Prostate cancer-specific survival was improved with sipuleucel-T to the same degree as was overall survival, consistent with the fact that you heard before, that most patients with metastatic castration-resistant prostate cancer die of their disease. Slide nine. The overall survival benefit remained robust in the final data analysis as well, performed after additional events had been collected. Slide 10. The survival benefit was consistent across multiple patient subpopulations, as you've heard several times. Slide 11. Findings were robust where the

00108

primary analysis was adjusted for predetermined covariates, it remained robust in the unadjusted analysis and then an analysis which was adjusted for docetaxel use and timing, and finally, if only prostate cancer-specific survival was considered. Slide 12. The study did not show a difference in a secondary endpoint, which was objective disease progression. Why might this be the case? This is a common phenomenon in trials in this disease state. Other prostate cancer trials have shown a disconnect between progression and overall survival. Progression is a difficult endpoint to capture reliably in castration-resistant prostate cancer because of the predominance of bony disease and the reliance on bone scans. And finally, the time for the biological effect of sipuleucel-T may also exceed the time to first progression. Slide 13. In contrast to objective disease progression, differences in time for the development of disease-related pain were observed. This analysis was performed recently in response to MedCAC's questions regarding control of disease-related symptoms. Data on this endpoint are available for the first 203 patients in the IMPACT trial. The data analysis did not achieve

statistical significance, but revealed a delay in the time
00109
for disease-related pain such that at the 12-month time frame, the percentage of patients free of pain in the sipuleucel-T arm was 32 percent, compared to 14 percent in the control arm.
DR. GOODMAN: About one minute, Dr. Kantoff.
DR. KANTOFF: Thank you.
Slide 14. A similar result was observed in the prior Phase III trial, D9901. These data, which will be submitted in an upcoming meeting, are also present at the end of your handout.
Slide 15. As you heard, adverse events that were commonly seen more commonly in the sipuleucel-T arm were those of chills, pyrexia, headache and flu-like illness, and the majority of these were transient.
Slide 16. There were no significant differences in serious adverse events between the treatment arms.
Slide 17. In conclusion, sipuleucel-T demonstrates a clear statistically significant and clinically meaningful survival advantage for patients with castration-resistant prostate cancer. In my mind, this trial confirms the overall survival findings of the two prior randomized studies. I feel this trial is definitive proof that sipuleucel-T works and provides clinically important benefit to patients. The treatment represents the largest median survival increment of any therapeutic
00110
in the treatment of castration-resistant prostate cancer to date, delivered with modest side effects and of short duration. Sipuleucel-T represents a needed advance for patients with lethal prostate cancer.
Thank you very much for your time.
DR. GOODMAN: Thank you very much, Dr. Kantoff, and thank you for your concise explanation of some of these differences, and the viewpoints on the outcomes and so forth, very much appreciated.
That concludes our time slot for the scheduled public comments, and now as always we move to the open public comments. These are people that signed up today on this sign-up sheet, and by my count, Ms. Ellis, there are 13 such speakers, right? Thank you very much.
And I apologize ahead of time for my inability to read certain handwriting, maybe some of you are doctors, perhaps not. In any case, just before we get started, one of the folks on the list, I believe it's a Mr. Drake, has not yet handed in his disclosure form to Ms. Ellis, so I just want to give you a heads up on that so you can take care of that in time for us to hear from you at your point along the way.
So these speakers, we can only give you one minute, and I hope you will be as concise as possible.
Please understand that we are just confined as far as the
00111

amount of time for today, so please do get to the point, tell us something that we really need to know, and especially if it addresses the questions, that would be most welcome.

And the first is Scott, I believe Scott Williams, from the Men's Health Network. I hope I read that correctly. And then just a heads up, it will be Dan George and Kristin Davis, and Theresa Morgan after that. So it will be Mr. Williams, Mr. George, Ms. Davis, Ms. M-O-R something, from Women Against Prostate Cancer. Mr. Williams, sir, please.

MR. WILLIAMS: Thank you for your time and I will speak as fast as I can.

DR. GOODMAN: Not fast, just good, give us the good stuff.

MR. WILLIAMS: Thank you. I'm speaking today on behalf of Men's Health Network, a national organization whose mission is to reach men and their families where they live, work, play and pray. I'm before this committee to formally request that CMS implement a national coverage policy for Provenge that promotes equal and appropriate access for Medicare beneficiaries for this truly innovative therapy. Provenge offers hope for men and their families to significantly extend and improve the quality of life for those who are

00112

suffering from advanced prostate cancer. Given the extensive review of the clinical trial data by FDA as well as the demonstrated survival advantage conveyed by the product, it should be clear to all involved that we should be discussing how to improve access to this therapy instead of considering limiting access. There's an immense need for innovative treatment options like this one in hopes of improving the plight of men with advanced prostate cancer. We want patients empowered to have conversations with their healthcare provider to determine if they're an appropriate candidate for Provenge.

To conclude, members of the Prostate Cancer Roundtable, a group of 12 independent not-for-profit organizations and three other partners, have offered an important statement which is available on the table outside for all interested parties. Thank you.

DR. GOODMAN: Thank you very much, Mr. Williams, and thank you for the reference to the materials outside. Thank you.

Dan George is next, from Duke University.

DR. GEORGE: Yes, thank you. I'm Dan George, from Duke University, I'm a medical oncologist there, and I was an investigator and a consultant for Dendreon in the past, but I'm here at my own expense.

00113

I would like to address just one issue that was in the technology report and that was also brought up by

Dr. Mark, and that was really the question about the effect of the salvage frozen product on overall survival and outcomes. We've done a little analysis looking at all three randomized trials of the placebo group focusing on from the time of progression to outcome, and we saw no deleterious effect to the patients who were treated with the salvage product. In fact we actually saw the contrary, patients who received the salvage product had a superior outcome to those who had no treatment after placebo.
When we looked at an unadjusted analysis, this had a hazard ratio of .52. When we adjusted for prognostic factors and prior docetaxel treatment, we saw a hazard ratio of .55. We've submitted this for presentation at the ASCO GU oncology symposium early next year. And I'll just remind the committee that actually within this report, on page 12 and 13, it actually states that it was actually a positive benefit associated with the salvage product that would actually decrease the overall improvement in survival that we see with sipuleucel-T, and I think that's what we see in this case.
Thank you very much.
DR. GOODMAN: Thank you, sir. I do note that

00114

the findings that you reported on have not been published, but were submitted in abstract form. Thank you very much.
Next is Ms. Kristin Davis, also from Duke University.
MS. DAVIS: My name is Kristin Davis, I'm a physician's assistant in GU oncology at Duke University. I've consulted for Dendreon in the past but I'm here today to speak on behalf of our many patients with metastatic castrate-resistant prostate cancer. I've had the privilege of working closely with these men on Provenge therapy. I can tell you that they're eager and very grateful to have the opportunity to receive Provenge. These men know their cancer is not curable, but they hope to have as much time as possible with their loved ones. Many of these men have residual side effects from prior therapies. When discussing Provenge, they're very relieved to learn that the side effects of Provenge are short lived and also generally infusion-related. This is exactly what we've seen at Duke. Our patients are able to go about their usual routine and activities. For these cancer patients, Provenge offers the hope of extending their life without adding additional debilitating symptoms. There is not another treatment option available with these two valuable benefits. Thank you.
DR. GOODMAN: Thank you very much, Dr. Davis.

00115

We appreciate that important input.
Next is Theresa --
MS. MORROW: Morrow.
DR. GOODMAN: Morrow, M-O-R-R-O-W?

MS. MORROW: Correct.
DR. GOODMAN: I need to visit the eye doctors.
Thank you, Ms. Morrow, and you're from the Women Against Prostate Cancer Association?
MS. MORROW: I am speaking on behalf of Women Against Prostate Cancer. We are an advocacy nonprofit organization. We provide support and resources to the women who are affected by prostate cancer in their loved ones.
We were very excited in April to hear about the approval of Provenge as an additional tool that patients and physicians can use to improve survival in men's prostate cancer. And as you know, over 32,000 families will lose their loved ones to prostate cancer this year alone, and with its proven clinical effectiveness, we believe that Provenge should be an available option to all men who are facing advanced prostate cancer. It will provide the opportunity for more men to walk their daughters down the aisle, meet their grandchildren, and enjoy their golden years of retirement. So on behalf of the wives, partners, mothers, daughters, friends and loved

00116

ones of prostate cancer patients, we urge you to make this innovative treatment an option for men with advanced prostate cancer.
DR. GOODMAN: Thank you very much, Ms. Morrow. We appreciate you representing Women Against Prostate Cancer here today.
Next are, Katherine Meade will be next and just, she will be followed, so you can get ready, Fred Gersch, Dr. Tom Berger, Thomas Barrington, it will be in that order. Welcome, Ms. Meade. You're from Virginia Prostate Cancer Coalition, I believe?
MS. MEADE: Yes, I am, and thank you very much for the opportunity to represent the patients in Virginia, and nationally actually. I'm a widow and I am unschooled in, I am not a doctor, I don't have anything like that, but through going through the experience with prostate cancer, I have been self-taught, I read, I take advantage of everything that I can.
Listening to the presentations today, there are two issues that I have. Number one, I think that -- I've been told that it's three years after a drug is approved by FDA before we have any real world experience as to what the impact of that drug is going to be in the general population. It's too soon for us to have that, and I think it makes it difficult for this panel to evaluate the

00117

drug on a complete basis and a real word basis, and I feel sorry for you all trying to do that right now.
DR. GOODMAN: We get paid such a great amount to do this. The Agency is very generous with its panelists.
(Laughter.)
MS. MEADE: Yeah. The other thing is, we have

one of our board members whose doctors recommended that he go on Provenge, and he started in June talking to the physician who was supplying the Provenge, and he has still not been put on the waiting list. And the reason has been that there is a lot of confusion in the patient and in the physician-clinician community about what's going to happen at today's meeting. He got a note yesterday that said they would not tell him exactly what's going to happen and whether Medicare would pay for it until after this meeting was being held. And I'm not even sure, since you're not talking about payment, whether or not that will clarify the issue, and we really do need to have that issue clarified. They did ask him for a $20,000 deposit, so you know that this is a major confusing issue. Thank you very much.

DR. GOODMAN: Thank you, Ms. Meade. We hope he didn't hand over his credit card just yet.

We're very glad that you brought up, by the way, the matter of how well things work in practice, you have

00118

clinicians here, but effectiveness as opposed to efficacy in ideal conditions, effectiveness in real world conditions is of great importance, and we appreciate you bringing that up.

And you are indeed correct, that payment is not our matter today. We're looking at the evidence as presented in those questions. This panel, this committee is not a policy-making committee, we don't make decisions, we look at the evidence and we try to relay our recommendations and findings regarding the evidence to the Agency, so I don't imagine there will be a payment decision made at 4:30 today when we complete our work, but we do very much appreciate your input.

Next up is Fred Gersch, also from Us TOO.

Mr. Gersch, welcome.

MR. GERSCH: Thank you. I am Fred Gersch, a 74-year-old advanced metastatic prostate cancer warrior. I hope you will allow me access to a treatment option that will help me have more quality time with my family, my sons and our community.

I was diagnosed at the age of 52, in 1989. In 1989 there were very few treatment options. I chose surgery. The cancer returned and I had external beam radiation, followed by a series of other treatments, Lupron, Proscar, Casodex. These treatments have enabled

00119

me to keep the cancer at bay, each time selecting the treatment arrows from my quiver.

Since September of '09 after two ER visits, I have had Taxotere, along with medications for nausea, chemo rage, depression, fatigue, neuropathy, headaches, chemo taste, and anemia. My annual CMS charges and other expenses approach $120,000. I am not in remission. Men with prostate cancer are willing to fight this deadly

enemy. Please give us more arrows for our quiver. Thank you for listening to me.
DR. GOODMAN: Thank you very much, Mr. Gersch. We appreciate your representation of yourself as an individual patient who has fortunately been with us since 1989, even though diagnosed at that time, and we appreciate you representing Us TOO as well.
Next is Dr. Tom Berger from, is it UVA, sir?
DR. BERGER: VVA, Vietnam Veterans of America. I'm executive director of the veterans health council for the Vietnam Veterans of America, the only congressionally chartered organization solely composed of Vietnam era veterans. Thank you for allowing me to address this issue today.
In November 1966 then VA Secretary Jesse Brown issued a final directive recognizing prostate cancer as a service-connected presumptive disease associated with

00120

exposure to Agent Orange, because the IOM contracted research clearly showed these following two things amongst others: One, vets exposed to Agent Orange are at least twice as likely to develop prostate cancer as nonexposed. And number two, most importantly for today's hearing, Agent Orange-exposed men were nearly four times more likely to present with metastatic prostate cancer than nonexposed.
Agent Orange-exposed veterans with metastatic prostate cancer deserve appropriate access to this new and innovative therapy because it provides yet another evidence-based treatment option for them. Vietnam veterans in particular have painfully learned that the government cannot always be trusted to make the best decision as it relates to their health care, but all veterans deserve the best health care possible. Thank you.
DR. GOODMAN: Thank you very much, Dr. Berger, and thank you for your service, and thanks to those who you represent through the Vietnam Veterans Association. We're very appreciative of your presence and of your comments, sir, thank you.
Next up is Thomas Farrington. He will be followed, it appears, by Mr. Drake, Chuck Drake, and Roland Hill, and Kimberly Pae. I'm sorry if I'm not doing

00121

these names well, but in any case, welcome, Mr. Farrington.
MR. FARRINGTON: Thank you, and thank you for this opportunity. I'm the president and founder of the Prostate Health Education Network. There are two distinct worlds of prostate cancer, one for blacks and one for other men. In black America men are dying of this disease at a rate two-and-a-half times higher than other men. I'm a ten-year survivor and my world desperately needs prompt attention and new solutions.

In 2005, PHEN hosted the first ever African-American Prostate Cancer Disparity Summit, focusing on new developments to eliminate the disparity. Presentations on the potential of new immunotherapy treatments were included in each of our six annual summits.

Today we're hearing about the FDA approval of Provenge, and the data you saw today showed that the survival benefit for black men is at least three times greater than that for other men, the type of therapy that my world needs. I plead on behalf of all men for CMS to seize this unprecedented window of opportunity. Provenge offers a much needed treatment and addresses one of the largest health disparities in our country. Not to do so would constitute negligence, and this class of new

00122

treatment will be available only to those who can afford to pay for it out of pocket. This would be viewed as inhumane in my world. Thank you.

DR. GOODMAN: Thank you very much, Mr. Farrington, and we thank you especially for your attention to the matter of priority populations as you noted, and I think that some of the analyses about which you've heard today and which we'll hear later address subgroup analyses and ways to try to get at special population groups, and the group that you brought up today is of particular note in this disease area. And I would also mention that various federal agencies, CMS, FDA, NIH, the Agency for Healthcare Research and Quality have all been clear about the need to address with greater support, with better evidence for priority populations. Thank you for your comments, sir.

Next is Mr. Chuck Drake, and it says unaffiliated, sir.

DR. DRAKE: My name is Dr. Charles Drake, or Chuck is fine. I am an immunologist, I have a Ph.D. in immunology, and I'm also a medical oncologist, I take care of prostate cancer patients and I do basic research on immunotherapy for prostate cancer. I work at Johns Hopkins, I came here at my own expense, it was only a few miles along the beltway, but in the past I have consulted

00123

for multiple immunotherapy corporations, including Pfizer, Medarex, DMS, and the corporation at hand.

I'm here, and per your earlier instructions I would like to address one single specific point, and that is the conclusion in the draft review of the study that says that there is evidence that this agent works only in the context of a substantial amount of subsequent chemotherapy intervention, and then it goes on further to suggest that clinical trials need to be performed to address that issue. I disagree with two things. First of all, I disagree with the word only there, because the correct randomized trial has not been

conducted. And then you might think okay, that's a great idea, let's do some clinical trials, let's do some more clinical trials, we haven't done enough clinical trials. Unfortunately, those trials actually have three major problems. The first problem is that's not standard actually. When we take care of patients on a clinical trial, we treat them on the trial, and when they progress, we go forward and treat them with what's best for them, either standard therapy or additional therapy, or sometimes even just observing actually. So that's not what usually happens. Patients are treated with one treatment on a trial and then we do what we think is best for them.

00124

DR. GOODMAN: You may want to make your final point, sir.

DR. DRAKE: Okay. Two more quick ones. The second thing is that trial is not practical on this point, and the reason it's not practical is because now there are multiple therapies for prostate cancer. Abiraterone will soon be approved, this is an approved agent, and there's additional chemotherapies, so such clinical trials are not practicable. On the other hand, there is a way to answer that question, and this will also answer the question of relative efficacy in African-American versus Caucasian, and that's pretty simple. That's the registration component that FDA has already forced on these agents, by conducting a large registry of patients treated with these agents, there will be sufficient patients to do large subgroup analysis and figure out the questions that have been posed. Thank you.

DR. GOODMAN: Thank you for your comments, sir. Next is Rollins Hill, I believe, followed by Kimberly Pae, Laurel Todd, and Neal Shore.

MR. HILL: I'm Roland Hill, I'm a U.S. Army chaplain retired. I was exposed to Agent Orange in Vietnam. In 1993 I was diagnosed with prostate cancer which had spread already to the lymph nodes. I received a

00125

variety of treatments through Medical College of Virginia, through the military and that type of thing, and then finally I was allowed to come up and become part of the CPDR, the Center for Prostate Cancer Research at Walter Reed, and I received outstanding treatment from these people, and Dr. Gulley, Dr. Dahut, a whole bunch of very brilliant experts, I have received outstanding treatment. I was enrolled in the Provenge treatment in 1995, it took three-and-a-half years, I was on that Provenge before I was unblinded, and I still receive the benefit from that. One person that I do want to say thank you to, and you'll hear from her, is Kimberly Pae, my prostate cancer treatment specialist. She will not leave any rock unturned to provide me with the best treatment I can have.

I know I'm going to be in trouble for saying this, but I would not trade her in for a thousand urologists. Thank you.

DR. GOODMAN: I can't imagine a single urologist who would beg to differ with you.

(Laughter.)

Mr. Hill, thank you for your service, sir, and I can see that you must have been a superb chaplain. You must have offered great comfort.

Next is Kimberly Pae, as aforementioned.

MS. PAE: Hi. Good morning, good afternoon, I'm

00126

not quite sure what it is right now. I appreciate the opportunity to speak to all of you. My training is, I am a nurse and then a nurse practitioner, I have a master's of science. I graduated ten years ago and all that time I've worked at Walter Reed in the Center For Prostate Disease Research. I am here to represent only myself, I don't represent the military or Walter Reed in any way, and I am acting as a patient advocate as quite often nurses do.

I want to point out that I do have some disclosures. I do own a small number of publicly owned, publicly traded stocks, and I did work, as Chaplain Hill reported earlier, in the Provenge trial. So prior to the trial, I had worked with prostate cancer patients, castrate-resistant patients, and also since then with these patients, and I will get to the point.

I saw great improvement, prolonged survival and low toxicity for these patients. And so what I would like to do just as a patient advocate is urge you to support sipuleucel-T for the FDA-approved on-label use, because it provides an important treatment advantage for men with castrate-resistant prostate cancer.

DR. GOODMAN: Thank you very much, Ms. Pae. We appreciate your comments, and obviously you've had an impact on Mr. Hill as well, so you've done quite well for

00127

him as well as us today. Thank you.

Next up is Laurel Todd, from BIO, is the next on the list I've got. Ms. Todd.

MS. TODD: Thank you. My name is Laurel Todd, I'm with the Biotechnology Industry Organization, and I appreciate the opportunity to make a statement today to raise several concerns of BIO and our members, of which Dendreon is one. I'd also note that my dad has prostate cancer.

The biotechnology industry is involved in the research and development of cancer therapies that play a critical role in prolonging life and reducing the burden of disease for cancer patients worldwide. We are concerned that CMS opening a national coverage analysis on an FDA-approved therapy so soon after approval could establish a precedent that would reduce Medicare patient

access to a wide range of novel drugs and biologics. These processes could curtail labeled and appropriate uses of an FDA-approved therapy, particularly before the medical community has the opportunity to develop experience with the labeled therapy. There should be no question that an FDA-approved therapy should be covered by Medicare for patients and conditions indicated on its label. The FDA is the logical responsible federal agency to consider any label

00128

modifications. BIO urges this MedCAC panel and CMS to ensure that their decisions do not harm access to needed care, and encourage the continued development of new therapies while following sound principles of evidence-based medicine in formulating coverage policies. Thanks.

DR. GOODMAN: Thank you very much, Ms. Todd. I just do note that there are instances in which FDA has approved a product for market and in which case Medicare and oftentimes other payers don't necessarily cover it. There have even been instances where a product has not yet been approved by the FDA that is covered by Medicare and other third-party payers. So we don't always line up, and typically for very good reasons, and we'll get into that as we examine the evidence later today. Thank you for those comments, though.

Neal Shore is next, from CURC. Mr. Shore.

DR. SHORE: Yes, thank you. Neal Shore, I'm a community urologist, I'm the director of Carolina Urologic Research Center in Myrtle Beach, South Carolina. We're a 12-person urology group. I was involved in trials and I've been a consultant for Dendreon and the Provenge program, but I'm here at my own expense. I think I would like to just address the issue of the community urologist and the applicability, the

00129

generalizability of Provenge to our patients. I've treated and had now over a hundred infusions, and it's very simple to stay on label with the protocol of the Phase III, the IMPACT, which you heard in great detail today, and the FDA guidance and the FDA-approved label mirrors that. We've had absolutely no difficulty in treating those patients and in finding the appropriate use for those patients, and I would urge this panel to not find precedent to not follow FDA guidance, and thank you very much.

DR. GOODMAN: Thank you very much, Mr. Shore, or was that Dr. Shore?

DR. SHORE: Yes, sir.

DR. GOODMAN: I apologize.

Ms. Ellis, are those our 13 speakers that signed up?

MS. ELLIS: Yes, sir.

DR. GOODMAN: Okay, great. Thank you all very

much for volunteering to speak today and for signing up on the sheet this morning. Again, we apologize for only being able to allow a minute or so for each of you, but you will see that we want to use the balance of our day as efficiently as we can.
What we'll do now is move to the session on questions to presenters, and if they wouldn't mind, I
00130
would like to ask our earlier presenters to come to the front of the room, I get a little pushy about this, because I'm thinking about efficiency, let's see, if Dr. Mark, could you come up where we can see you and if you could sit in that chair kind of close to the mike. Just based on previous experience, it tends to be the case that the folks that did the technology assessment get asked a lot of questions. And our other speakers as well from this morning who spoke for five minutes each. Of course Dr. Gulley is already up there, I saw him go up. So, everyone's got a seat there. Is that all of them, Ms. Ellis?
MS. ELLIS: I believe so.
DR. GOODMAN: So, let's do this, panel. This session is our initial questions to presenters and we will do this leading up to lunch, but we will still bring them back after lunch as needed for further questions, and obviously we didn't have an opportunity to ask them thus far. And so we'll open it up if you have a question for the presenters, and what I will ask you to do is if you have a particular presenter in mind you would like to answer a question, that would be very helpful. Please also do keep in mind that what we're trying to move toward at the end of the day is to be able to answer our questions, and so inquiries that are in pursuit of those
00131
questions are probably most relevant. And also as panelists, if you could be concise in your questions, as have been nearly all of our speakers.
So with that, let's open it to questions for our panelists. And let me get my list, is that Dr. Sokoloff?
DR. SOKOLOFF: Yes, I have two questions. The first is geared towards Dr. Frohlich and Dr. Mark. Dr. Mark in his presentation gave a lot of data on post-exposure predictors of immunologic response. I was wondering, first, if there were any pretreatment predictors of response, and two, how important is that, to monitor for cellular immunotherapies. So I'd like you two to address that, and should I ask my second question while we're at it?
DR. GOODMAN: Let's take the first one first, and would you like Dr. Frohlich to come to the mike, or Dr. Mark, or both?
DR. SOKOLOFF: Let's start with Dr. Mark, and then Dr. Frohlich.
DR. MARK: Well, my understanding is, by

pretreatment --
DR. SOKOLOFF: Is there anything that one can find out about a patient prior to treating them that might give an idea of how well they respond to immune-based therapies.

00132

DR. MARK: I think that was presented in terms of what I called the subgroup analyses, which was that long list of analyses with the diagram showing the point estimate, and in each of these analyses it's the same group divided by high versus low FLDH, high versus low PSA, and what you can see in most clinical trials, things kind of vary between the groups, and it's a difficult matter in the presence of many predictors to look at, plus the diminished sample size within each one, to make definitive statements about what kind of pretreatment factors are associated with greater or lesser benefit. So what I pointed out is when you see a difference between the two, you know, most researchers, in the absence of a predefined sense of what they're looking for, view those as signals of potential pretreatment effects. In the ideal clinical world trial you limit yourself to fewer than a half dozen pretreatment effects, you design the clinical trial appropriately and power the study to look at those subgroup effects. And then you also can have kind of a hypothesis in your idea of which direction, is it unlikely or likely given the, you know, the biology of it.
DR. SOKOLOFF: I was actually interested specifically in the immunologic factors. In the old days of vaccines there was a lot of concern about HLA subtype

00133

matching, things like that for patients who underwent immune-based therapies. I was wondering if in your view, or perhaps Dr. Frohlich can add anything to that particular question.
DR. MARK: What I see is that list of subgroup analyses and, you know, in terms of baseline factors, things about immunologic function were not on those lists, and the immunologic issues related to, were related to factors about the treatment.
DR. GOODMAN: Thank you. Dr. Frohlich.
DR. FROHLICH: I just want to echo that, so certainly all the subgroup analyses we saw, saw consistent treatment effect of all those subgroups, along with the burden of disease, which could be related to immunocompetency. Specifically with your question on HLA, we haven't looked at that.
DR. GOODMAN: Further questions? Pardon me. Dr. Sokoloff, did you have a follow-up?
DR. SOKOLOFF: I had just one other question, and this is for Dr. George. In the back of the handout we got with Dr. Kantoff's, there is a quick abstract on the

breakdown of those patients who got the salvage frozen, and I wish he could just explain a little bit further because that's a subject I'm very interested in, and I

00134

just have to see the abstract.

DR. KANTOFF: Sure.

DR. SOKOLOFF: So if you could just clarify in a minute or two just what you found.

DR. KANTOFF: Absolutely. So what we did is, we looked at all the patients that were treated on the placebo arm of all three randomized trials, we pooled that analysis. We looked at the time from disease progression and in those patients, I think as Dr. Mark pointed out, between 60 to 75 percent of the patients got the frozen salvage product. And we looked at from the time of progression to death, that survival, and what we saw was actually a significant improvement in survival associated with treatment with that salvage product, we did get that. And that was with an unadjusted analysis, just looking at all comers.

We then looked at prognostic factors, LPH, PSA, et cetera, and we were able to show that that statistical analysis held up. We then looked, as was pointed out, that many of these patients get docetaxel treatment post-salvage product or post-progression, and we looked at that analysis by that stratification, and also found that essentially that analysis held up.

So it would suggest that, if anything, there's an improved survival associated with that salvage product,

00135

not that there's some further delay or some other detrimental effect. And that improved survival would, if anything, decrease the actual impact that the sipuleucel-T arm would have versus placebo in terms of overall survival. So, I think one of the concerns that was raised by Dr. Mark in the TEC report was that, you know, there was a modest overall view of the survival benefit partly because of these confounding factors, and at least by our analysis, these confounding subsequent therapies don't seem to be having a negative effect at all.

DR. GOODMAN: Thank you very much. And Dr. Sokoloff, I just remind you that this was not yet published, submitted as an abstract, not yet accepted for a meeting. Dr. Satya-Murti.

DR. SATYA-MURTI: This is first for Dr. Mark, and then Dr. Frohlich. On your slide 23 and 24, you don't have to pull it back up, you talked about the time at which docetaxel was given, which was at least two months earlier on the intervention arm, compared to the placebo arm; they received it much earlier, in other words. Was that indicative of a difference, or because it was left to the oncologist's choice, there was some personal preference to pick those patients for whom in their opinion they might have survived and lived longer? So

what, why was there that much difference, two months?
00136
We're talking about four months median survival and if they received it two months earlier, did the disease progress faster with them, or was that just because it was unstructured?
DR. GOODMAN: Dr. Mark.
DR. MARK: Well, you know, the patients were left to their own treatment after disease progression, so I really can't know the actual reasons. Apparently, and I think the people who are in the know can answer this, there is, the frozen Provenge takes one month to administer, and my assumption is that they do not want to give concomitant to chemotherapy with the frozen salvage product, you know, shortly afterwards in order to overcome those effects. But again, that time course may or may not correspond, so again, you're right, there was earlier and more frequent chemotherapy, and the time course between progression and that chemotherapy is somewhat long, so I have no real explanation for that.
DR. GOODMAN: Thank you, Dr. Mark. Dr. Frohlich.
DR. FROHLICH: I'd just like to clarify the delay in chemotherapy that you're speaking to. What was noted in the technology assessment was the time to chemotherapy, and most patients actually got chemotherapy. I think as Dr. Mark noted, in our New England Journal
00137
paper, we did a modeled approach where you take into account all patients. So it's just like looking at time to progression, only in those patients who progressed, when you're comparing between two arms is not an appropriate way to do that. So we're really looking at all the patients, including censoring is a more appropriate way to do that, and when we did that it was less than two months, and when you look at all three studies actually less than one month, so it's really not a substantive difference.
Part of that might be due to salvage, as Dr. Mark noted. And I will point out, we did another analysis to look at time to initiation of salvage or first docetaxel use, looked at the relative difference between the arms, and there's actually a six-month delay in the sipuleucel-T arm in terms of initiating therapy, as opposed to roughly equal in that analysis. And you know, obviously there's no perfect way to adjust for this, but we did multiple ways of looking at this, the FDA looked at this very rigorously, and when you do a centering analysis, when you do a covariate analysis, the survival results are very robust.
DR. GOODMAN: Thank you. Dr. Steinbrook is next.
DR. STEINBROOK: I was hoping to have some
00138

discussion of the issue of the placebo group in the IMPACT trial, and I guess my question is for Dr. Gulley, Dr. Frohlich and possibly Dr. Kantoff. There's been some discussion in the medical literature about the choice of a control group and if I could summarize, on the one hand are the people who might say that the control group should have been more biologically narrowed from what was chosen. There's another point which was made in the New England Journal of Medicine editorial, and the letters which were published recently about that editorial, an article which said that a control group should have involved the GM-CSF incubation of the cells and not simply with the product, and that that would have been a better way to tease out the effect of the product or of the Provenge.

And another comment which I believe was in the response to the editorial had to do with, I'm doing this from memory, I don't have it in front of me, whether it was feasible. In other words, if you went in this direction then you would need to have three arms, not two arms, and feasibility is a different issue than what might be best from a scientific standpoint.

DR. FROHLICH: So to clarify, Dr. Longren's editorial suggested that perhaps inclusion of a control in which there were antigen presenting cells pulsed with GM

00139

alone, to clarify what the role of GM was, specifically what the path was in that fusion protein. And the point we made in our response to that editorial was that first of all, there wasn't a strong biologic rationale for that. The first cell studies were based on some rat studies with the conduction of autoimmune prostatitis, where we saw robust induction of a lipocytic infiltration in the prostate when you pulse antigen presenting cells with the fusion protein but not with GM alone.

And I think the response that we had in the editorial further was from a clinical basis in terms of what's important to patients, while yes, scientifically that might be the question of interest, the bottom line is does this product prolong overall survival compared to not? So I think if you had done the trial with GM alone, I think it's likely based on the preclinical data it would have looked exactly the say as placebo. If you had shown no difference, you know, it's conceivable that if GM was effective, you would have discarded a therapy along the way, and I don't think that would have been in the patient's interest. So if you had to pick between the two arms, the arms that were chosen would have been the appropriate ones.

DR. GOODMAN: Thank you. Dr. Steinbrook, is that satisfactory for now?

00140

DR. STEINBROOK: That's fine. I was wondering if Dr. Gulley had any comments on this.

DR. GULLEY: I would just, I think what Mark said is exactly right, I would pick exactly the same two arms that were used.
DR. STEINBROOK: Thank you.
DR. GOODMAN: Dr. Matuszewski is next.
DR. MATUSZEWSKI: I have a couple questions for Dr. Mark. You said your biomedical literature review was of English only studies, so I assume that Provenge is not approved in the EU and there is no clinical data available from other countries.
DR. MARK: Correct.
DR. MATUSZEWSKI: That was an easy answer. And the second question, your overall conclusion in the tech assessment was that the evidence was moderate. Would that rating be something that you would consider as fulfilling the second TEC criteria as conclusive available to judge the technology?
DR. MARK: His mention of the criteria is something that my reports on behalf of, my usual work with Blue Cross Blue Shield Association tech assessments, meets criteria. You know, I didn't think about that, but it probably would need a positive ranking overall.
DR. GOODMAN: Let's clarify that, because it's

00141

just kind of gibberish to a lots of folks. Your evidence-paced practice center, Blue Cross Blue Shield Association TEC Center, has on its own a set of, is it five or six criteria, is it five criteria --
DR. MARK: Five.
DR. GOODMAN: -- that the association uses for its own examination of evidence on various questions. Those criteria aren't necessarily shared by all others, and Dr. Matuszewski asked Dr. Mark in his capacity as also serving the Blue Cross Blue Shield Association TEC Center, whether or not the judgment of the strength of evidence, in this case moderate, would or would not meet the appropriate criterion among the set of five that you use, correct?
DR. MARK: And I do not make the -- I solely do not make the decision on those criteria. We present our reports to a panel in draft form, they're revised, they reflect the input and the judgment of many people beyond myself.
DR. GOODMAN: Thank you, Dr. Mark. Dr. Matuszewski, a follow-up?
DR. MATUSZEWSKI: I was trying to be brief without doing the one-minute preamble, but in your opinion, your personal opinion, a moderate rating would have probably in your opinion met that?

00142

DR. MARK: Right, but it relied on --
DR. MATUSZEWSKI: The medical advisory panel?
DR. MARK: Correct.
DR. MATUSZEWSKI: I have a question for

Dr. Frohlich, and that involves the dosing, the duration, and I don't know if you have data on file, so the three doses of the therapy is what was found to be appropriate, and would a fourth dose have been compressing the dosing, or a follow-up course after three months would have no clinical advantages?

DR. FROHLICH: The dosing schedule is based on early Phase I-II trials where we looked at the mean response as a function of doses, and we found that the maximum response happened after three doses, greater than after two doses. We were interested at that time in looking at disease progression, which happened relatively rapidly in this patient population, and so that's why the choice of looking at them over a one-month time frame was chosen. We had also done studies looking at four weeks apart, and the response appeared to be comparable to two weeks apart.

DR. MATUSZEWSKI: But given that the disease progression didn't pan out, is there some opening to look at overall survival and some additional dosing strategies?

DR. FROHLICH: That's something we're beginning

00143

to look at, boosting in patients, we looked at that in earlier stage disease, but there's no evidence at this time to demonstrate that.

DR. GOODMAN: Thank you. Dr. Fuller is next.

DR. FULLER: A couple things. Chaplain Hill struck a nerve for me when he left me with the impression that when he was treated, and Dr. Gulley is probably the appropriate respondent to this, that the actual number of treatments he got with Provenge were significantly more than three. And I could have been mistaken, but am I right or wrong, and if so, and Dr. Frohlich talked to this just a minute ago, how did you get where you are now? In the old days did it go longer?

DR. GULLEY: Let me clarify. I did not treat him with Provenge. I work at Walter Reed Army Medical Center in addition to the National Cancer Institute. I do not believe he got more than three treatments.

DR. FULLER: Okay, that takes care of that. Then any of the physicians who were participating in trials who have had significant numbers of patients, I'm wondering if the pattern of failure in the people who went on to develop further metastatic disease and eventually died is any different in the group that was treated with Provenge versus the group who was treated in a more or less conventional matter with other

00144

chemotherapies.

DR. KANTOFF: I think simply not. You know, the patterns of failure look very similar. The patterns of follow-up were a little bit different than regular practice. They were watched very closely on the clinical trial, as many clinical trials are conducted, so bone

scans were performed very frequently, monthly, CAT scans were performed every two months during the time between treatment and progression, so that we captured progression earlier. But the patterns of care that follow were fairly typical of what we've seen, patterns of treatment also were fairly typical.

In this study, about half the patients ultimately went on to receive docetaxel, and then if you look at surveys of the proportion of patients that go on to get docetaxel in the community, it's about 50 percent. So the treatment that patients received and the patterns of failure look to be very similar to what's seen.

DR. GOODMAN: Good, thank you. Dr. Dmochowski.

DR. DMOCHOWSKI: This is a question for Dr. Frohlich. Dr. Frohlich, it's been mentioned I think a couple times during the tech assessment at least, this issue about establishing minimal criteria for the treatment dose. In other words, there seems to be some variability in each of the lots based somewhat on, I

00145

guess, idiosyncratic issues with each patient, and potentially the reaction each patient's cells have with the stimulating. So could you address how the minimal criteria were set, was that only on animal data per se, and have you looked at the subsequent results in light of lot variability to determine, are there other factors that you can now prospectively look at certain individual patients based upon unique aspects of their particular stimulated cells to determine what the response might be.

DR. FROHLICH: So, we worked very closely with the FDA to determine the release criteria for sipuleucel-T. And specifically, the FDA requires a potency assay, which is a measure to demonstrate consistency for the product. And the criteria that Dendreon uses are ones that are based on the absence of antigen-presenting cells as defined by large CD54 molecules, as well as the ability of those antigen-presenting cells to be activated following incubation with the recombinant fusion protein, so we have a particular ratio of CD54 upregulation that is required for product release.

And those criteria are set basically based on our clinical experience with making product with patients, so it's basically looking at the standard distribution and picking, you know, a bar at which you will reject patients

00146

that are kind of below, you know, two standard deviations versus not. We have subsequently -- and those criteria are defined before the clinical trials are actually randomized, Phase III trials with clinical endpoints are determined.

But we went back then and looked at some of those potency criteria to see whether or not in fact it did correlate with clinical outcome, and we were actually

quite encouraged that, I think it was noted in the technology assessment that a number of those parameters, certainly if you look at the integrated data for all three studies, both the total number of cells, the absent number of antigen-presenting cells, and the degree of antigen-presenting cell activation all appeared to correlate with overall survival, and that correlation appeared to persist when we adjusted for baseline prognostic factors as well.

DR. GOODMAN: Thank you. Dr. Kantoff, do you have a point, sir?

DR. KANTOFF: This is on the third control arm with GM-CSF, which I think was an interesting question, and was brought out in the New England Journal, two issues. One is there were early studies done by Eric Small and others using much higher doses of GM-CSF in men with castration-resistant prostate cancer, and the

00147

activity of GM-CSF alone is really quite modest. Secondly, there was a large, actually two large vaccine trials using GM-CSF, in fact it was called G-VACS, and in both of those trials there was no survival advantage associated with GM-CSF in those vaccines. So we strongly don't feel that the effect of the sipuleucel-T is related to GM-CSF alone.

DR. GOODMAN: Okay, thank you. Dr. Steinbrook, did that answer your question?

DR. STEINBROOK: Only to clarify, when you said vaccine, did you mean prostate cancer vaccine? I just don't understand what you meant by vaccine there, that's all.

DR. KANTOFF: I don't understand your question.

DR. STEINBROOK: Well, with the context where you said two large vaccine trials --

DR. KANTOFF: Two large G-VACS trials. G-VACS was a GM-CSF loaded immunotherapy that was used for patients with castration-resistant prostate cancer.

DR. STEINBROOK: Thank you for the clarification.

DR. GOODMAN: Thank you. Let's -- Dr. Mintzer, a brief question, yes, sir?

DR. MINTZER: On the point of randomization in the IMPACT trial, the overall survival improvement was

00148

about four months, but to me it's striking that for the patients who received salvage product it's a 12-month, a doubling of the survival, and I realize that wasn't a randomization. I was interested in maybe Dr. Petrylak, maybe Dr. Kantoff's comments about how that compares to other clinical trials. I think that's particularly striking, clearly the initial effect seems striking, and the question is how much attention do we pay to the salvage product considerations?

DR. MARK: I would say that in terms of trying

to compare things that occur at a certain point in time, at some baseline time, if the patient and -- sorry about being geeky about statistics here -- but if patients are grouped by events that occur subsequent to time zero, the survival of those patients is 100 percent up to the point, and so as time progresses and you group patients by things that occur afterwards, such as chemotherapy or frozen therapy, those patients switch groups over time with patients who have had 100 percent survival. So a very raw analysis of looking post hoc at everybody who got one treatment at a later time versus the patients who didn't get that treatment at a later time will naturally cause the survival curves to deviate. If you had two groups of patients that were dying at a similar rate over time and you started passing out red

00149

T-shirts at regular intervals also over time, and at the end of the study you would find, and that getting a red T-shirt was conditional on being alive, you would find that having a red T-shirt would show remarkably better survival, only because getting that treatment after is conditional upon being alive.

DR. GOODMAN: We got that point. Dr. Petrylak, did you want Dr. Petrylak next?

DR. MINTZER: I was just interested in the magnitude of that effect.

DR. MARK: It could be quite considerable depending on how that subsequent treatment is doled out.

DR. GOODMAN: Dr. Mark said it could be quite considerable. If you're going to answer a question, you've got to make it to a mike; otherwise, it's going to be lost. Dr. Petrylak.

DR. PETRYLAK: Thank you. Would you repeat your question one more time?

DR. MINTZER: Looking at the patients who had salvage product and had initially been in the placebo arm, the magnitude of their survival compared to the placebo patients who did not get product was quite considerable, far greater than the four-month overall survival. I was just interested in your interpretation of that with the limited, any statistical impact we can perhaps give to

00150

that, because it seems substantial.

DR. PETRYLAK: It certainly is, but we saw this from Dr. George's data as well, and it certainly seems that there is some effect from that. It's also difficult to figure out exactly what the effects are in this particular control are. The control arm of the study approaches that what we see with docetaxel in some of the contemporary studies, it's about 23-month overall survival. So again, you know, from this particular standpoint, those that did not receive the frozen product, lower survival than what we saw in George's abstract, but that is certainly an important effect.

DR. GOODMAN: Thank you very much. Dr. Mark, or others, just a closing question before lunch. I want to make sure that we understand the order of the clinical trials here. I know that IMPACT is the one that is usually shown first in the tables and so forth, but tell me if I'm not getting this. The first in that sequence was D9901, and tumor progression was the primary endpoint. The second trial was then started, which was called D9902A, which also had tumor progression as its primary endpoint. However, D9902A was terminated, given some data from 9901 that found no, was finding no impact on tumor progression, but in a subsequent analysis started to show an impact on the survival, so 9902A was terminated, which

00151

is one reason why it's a small trial.
Then IMPACT was originally D9902B, correct? I see heads nodding.
So 9902B, which we call IMPACT, came after 9902A, and in that one based on the information about lack of tumor progression impact, but an apparent impact on survival, was set up as a trial to look at overall survival; is that correct? Okay.
So of the three trials, then, the only one that was prospectively designed to look at overall survival was the third, i.e., 9902B, otherwise known as IMPACT. The others were not designed with that as a prospective primary endpoint overall survival, they were designed to look for tumor progression, which neither of them detected. I see Dr. Mark's head is nodding and people's heads are nodding. Okay. That's very helpful.
Dr. Steinbrook, before lunch?
DR. STEINBROOK: Could I ask a clarification on that point? I interpreted, and I would appreciate being corrected if I didn't interpret this correctly, but as I interpreted the publication of the IMPACT trial in the New England Journal of Medicine, the IMPACT trial started with survival, but when the data were still blinded, a decision was made to turn it to survival as the primary endpoint with a protocol modification; is that correct? Because

00152

then it would have started prospectively from day one as being disease progression, it would have switched while the patients were still blinded with a protocol amendment approved by the FDA.
DR. GOODMAN: That's an excellent point. I recall some mention being made in the documentation that it was before the trial was unblinded that that decision was made.
DR. FROHLICH: Correct. That was before the trial was unblinded. In 2005 the protocol was amended based on the learnings from the first two trials, 01 and 02A showing a dramatic survival difference, so overall survival was elevated to the primary endpoint, again, before unblinding the trial, done under a special protocol

assessment with the FDA.
DR. GOODMAN: And that was IMPACT, i.e., 9902B.
DR. FROHLICH: Correct.
DR. GOODMAN: That's a very helpful clarification, Dr. Steinbrook. The trial, 9902B had indeed, as you point out, begun, was enrolling patients, and it wasn't until after that but before its unblinding that the decision was made to change the primary endpoint of interest from tumor progression to overall survival. Thank you for that clarification.
What we need to do -- Dr. Satya-Murti, quickly

00153

before lunch?
DR. SATYA-MURTI: Yes.
DR. GOODMAN: Okay, yes, sir.
DR. SATYA-MURTI: Dr. Mark talked about the sample size leading to interpretation and further data analysis. We've heard your point of view. But I'm wondering if some of these primary investigators and Dendreon folks have any comment on that. The TA clearly says in a sum-up paragraph that the sample size is not adequate for some of the other analysis.
DR. GOODMAN: We would appreciate a very concise answer to that question at this point, and we can revisit it after lunch. Dr. Frohlich.
DR. FROHLICH: I believe that the point that Dr. Mark was making, that for some of these subgroup analyses to try to look for, you know, statistically significant differences between those above versus below the median, for example, the trial's not powered for that, and that's true for most trials in oncology. The point of the subgroup analysis is really just looking for consistency of the treatment effect by looking at the point estimate, not looking for statistical significance.
DR. GOODMAN: Thank you. These are not large trials, and some subgroup analyses are not planned prospectively, knowing, because the study designers are

00154

aware that it's going to be a small trial, it's going to be hard to find statistically significant findings in subgroup analyses when the trials are that small.
Okay. What we're going to do now is break for lunch. We will reconvene one hour from now, we will ask our presenters to refind their seats, and we will see you in one hour. Thank you very much.
(Lunch recess.)
DR. GOODMAN: We're going to reconvene now, and thanks everybody for coming back so promptly after lunch. And we're going to have a discussion, continue our discussion that involves our MedCAC members asking questions of our presenters, and it can also be questions among ourselves as well, and then at some point we'll decide to kind of pursue the set of questions.
I see Dr. Madan, and then Dr. Schulman. Dr.

Madan, please begin, sir.
DR. MADAN: Thank you. I think a lot of our morning conversation centers around a thing that was mentioned by Dr. Kantoff earlier. As is characteristic with some emerging new therapeutic agents, the biological effect that is seen with this agent may be something that develops beyond conventional time of progression, and I think for that reason we're focusing a lot on subsequent chemotherapy and time to subsequent chemotherapy. And I

00155

know Dr. Gulley, who was one of our presenters this morning, has done some research in this area and has presented some data at a recent national meeting for the American Society of Clinical Oncology, so I was hoping that maybe he can provide some background on this apparent discrepancy between progression but yet delayed effect on the survival benefit.
DR. GOODMAN: Dr. Gulley, would you care to respond to that, to the specific question about the distinction between progression and survival?
DR. GULLEY: Yes. So, I think it's important when we're thinking of immunotherapies to understand that they're a little bit different than the conventional therapies in several key areas. First of all, with immunotherapies, we're not directly targeting the tumor, but rather we're directly targeting the immune system. In the immune responses engendered following the therapeutic maneuver with vaccines, it can take a little while to take effect and because of this, you may not see over the short term any evidence of benefit clinically.
But eventually, the second thing that is different between the conventional therapy and immunologic therapy is you can generate a memory response, and that eventually can supply downward negative pressure on the growth rate of the tumor. So that early on you might not

00156

see much of a difference, but over a long period of time with this memory response that can be around for months to years, you might see a continued downward negative pressure on the growth rate of the tumor that gets translated into improved survival and still not have improved time to progression.
Now a lot of this is based on data that we've done at the NCI with clinical trials; none of it is definitive at this point, though.
DR. GOODMAN: Dr. Madan, does that help?
DR. MADAN: Yes, thank you.
DR. GOODMAN: Okay. Dr. Schulman.
DR. SCHULMAN: I have two questions for Dr. Kantoff. We talked a lot today about suggesting this therapy would be a substitute for chemotherapy, but in the New England Journal article it says 80 percent of patients in the sipuleucel group received anticancer therapy, only 70-some odd percent in the control group, and from the

Small report, about 50 percent of those were docetaxel. What were the other chemotherapeutic agents that people received to get it up to 80 percent?
DR. KANTOFF: I don't know if there's an impression that this should be a substitute for chemotherapy, that's not our intention. We really have no control after giving the vaccine in the clinical trials,

00157

or in practice, how people practice with subsequent treatments. Having said that, about 50 percent of the patients, as I mentioned before, in practice, will receive docetaxel. In the study we saw that about 50 percent of the patients got docetaxel. The remaining 30 percent that you described got a variety of different other chemotherapies, mitoxantrone being probably the dominant chemotherapy that was used in that setting.
DR. GOODMAN: So at least, summarize this once again at sort of a high level. Of all the patients in the three trials that got this new immunotherapy, what percentage of them went on to receive docetaxel or another chemotherapy?
DR. KANTOFF: I can speak to the IMPACT trial which was initiated in 2004. The earlier trials were initiated in 1999, so there would be different drugs available at different times, so I can speak for the IMPACT trial. In the IMPACT trial 80 percent of patients went on to other chemotherapy. 50 percent of patients went on to receive subsequent chemotherapy, subsequent docetaxel chemotherapy specifically, which is the only chemotherapy to date that has been documented in that setting to prolong survival, other than the new chemotherapy which is cabazitaxel.
I can only surmise, maybe Dr. Frohlich can speak

00158

to the earlier studies in terms of chemotherapies used, but those studies were initiated at a time when docetaxel was not an approved agent, 9901 and 9902.
DR. GOODMAN: Dr. Schulman, follow-up, or did that address your question?
DR. SCHULMAN: No, the question was more the proportion of patients who had chemotherapy, and in terms of patient burden, 80 percent still require additional therapy. That was the question.
DR. FROHLICH: If I can just clarify that, 80 percent is systemic therapy of any nature, so it would have included other chemotherapy agents as well as other investigation or other therapies that occurred, so it was all types of systemic therapy.
And in D9901 and 2A the percentage that got docetaxel was lower, it was roughly in the 35 percent range.
DR. GOODMAN: So it would not be appropriate to say that sipuleucel-T is a substitute for chemotherapy, or obviates the need for chemotherapy. In D9902A 38.6

21 percent went on to receive chemo, in 9901 35.9 went on to
22 receive chemo, and in IMPACT 57.2 percent went on to
23 receive chemo, docetaxel at the very least, and then the
24 other figure given was that 80 percent overall received
25 subsequent therapy. Dr. Schulman, is that getting at it
00159
1 for you?
2 DR. SCHULMAN: Yes. And then actually a
3 question for Dr. Scholz, who came all this way. We're
4 going to be asked to vote on the evidence not of
5 statistical significance but of clinical significance.
6 Could you just kind of answer how you describe the
7 benefits for your patients, because the data in the New
8 England Journal article suggests that time to progression
9 is equivalent, the subsequent chemotherapy in both arms is
10 significant and equivalent, and the five-year survival of
11 both arms suggests that this is still a progressive and
12 fatal disease, so how do you describe the clinical
13 significance of this to your patients?
14 DR. SCHOLZ: To answer that question, I think
15 it's partly been addressed by the unusual nature of this
16 medicine, which seems to have a mild prolonged effect
17 rather than a toxic sudden impact on the cancer. And
18 since this is only FDA-approved in the last four or five
19 months, with the 30 patients or so that we've treated, I
20 would say it's far too early to judge the clinical impact.
21 So at this point we're advising patients that careful
22 prospective randomized trials have shown better survival
23 with the treatment and very minimal toxicity. So while
24 patients have been going on it, I cannot honestly tell you
25 that we've seen dramatic immediate clinical benefit that I
00160
1 can quantify.
2 DR. SCHULMAN: Thank you.
3 DR. GOODMAN: You said a mild prolonged effect,
4 and it's too early to make a determination of its what,
5 ultimate effectiveness?
6 DR. SCHOLZ: The way we normally measure a
7 clinical effect with prostate cancer patients is either a
8 reduction in pain, a reduction in PSA or an improvement on
9 scans, those are the short-term methodologies we use to
10 try to measure the effectiveness of treatments. It's
11 particularly important for most treatments which are
12 continued indefinitely as long as they're still effective,
13 and often have a lot of toxicity, so we look at those
14 issues very closely.
15 With this new product, it's only given over a
16 six-week period and it stops, and we don't have to make
17 start-stop decisions. And so the clinical impact of the
18 medicine hasn't been as important a priority for us in the
19 determination of its use, so we have been using it based
20 on the clinical trials showing better survival in those
21 receiving the medicine. And then we have been
22 implementing further treatment as indicated, just as was

done in the trials, depending on whether or not there is a progression of the disease over the ensuing months. We do try to delay treatment for a certain period of months to
00161
allow the treatment to take hold, and there may be a possibility that chemotherapy immediately after the infusion can reduce the impact of the immune effect, which we don't want to do, there would be a conflict.
DR. GOODMAN: Thank you very much. Dr. Kantoff has a comment.
DR. KANTOFF: Yeah. I should mention that the opposite is not necessarily true, and that is reductions in PSA in patients, reductions in pain, reductions in time to progression do not necessarily and frequently do not correlate with the overall survival advantage in many studies that have been done.
DR. GOODMAN: Right. The first two trials looked for intermediate outcomes as opposed to the longer-term outcome of survival, and it wasn't until the third trial was already rolling that it was decided to move over and look at survival as opposed to tumor progression as we discussed earlier. Okay. Yes, Doctor?
DR. SCHELLHAMMER: Just with regard to this ongoing disconnect discussion between progression endpoints and survival, in my discussion with patients I frankly tell them that many of the progression endpoints that we've used are somewhat subjective, they're imaging studies that can be interpreted variously, and that the fact that there's a survival benefit to me speaks strongly
00162
to the fact that progression is being halted or modified or slowed, and the true inevitable easily defined endpoint that's most important to them is how long they're going to live. So whether their x-ray is a little worse or stable is such a subjective factor, and the time intervals with which it's obtained is variable, so all of those factors are relatively weak in face of the survival endpoint.
DR. GOODMAN: Okay. It's interesting that if they're relatively weak, that they were the ones chosen for the first couple of trials as the primary endpoints. Dr. Petrylak.
DR. PETRYLAK: I'd actually like to comment on that.
DR. GOODMAN: Please do.
DR. PETRYLAK: It's important to point out that the clinical trial methodology for prostate cancer has evolved significantly over the last 20 years. In 1993 we had a survival of about 10 to 12 months with castration-resistant disease. 1996, two studies approved mitoxantrone, one had a palliative endpoint, the other failed the survival endpoint. The FDA approved it based upon palliative needs, we didn't have any better drugs at that particular point. May 12, 1999, I went to the FDA, we had our preliminary data with docetaxel. They agreed

to do two survival studies because they felt that the
00163
endpoints, at least clinically, were not as strong as with pain. They also felt that now we're starting to see at least some improvement in survival with the particular endpoint that we had in Phase II.
So that's why we've had a shift. In 1999 progression was acceptable, at least at the time that the methodology developed, was an acceptable endpoint to use for those particular trials. Now the FDA is saying and mandating survival. We saw the same thing with satraplatin. Satraplatin had a progression-free survival endpoint as its primary endpoint. It failed the survival endpoint, it did have a positive progression-free survival but it failed survival eventually.
So when we're looking at the evolution of the Provenge studies, in the first two trials we looked at progression-free survival because we really didn't have a better way of getting a handle on the activity of the drug. Survival was co-primary endpoints in those particular, or a co -- they were following the patients for survival, it wasn't necessarily a primary endpoint, but they were being followed for survival in these particular trials. So if you're looking at these studies from the standpoint, especially in the third trial, that they changed their primary endpoint to overall survival, these patients were still being followed in the proper
00164
fashion, and so these are not statistical issues from those particular trials, those are actual, I think true and valid endpoints.
Now when you look back to the TAX 327 study or the SWOG 9916 study, TAX 327 was the primary endpoint, or the primary study, the primary approval study, SWOG 9916 was supplemental. The treatment that was given in SWOG 9916, my study, was Taxotere plus estramustine at a lower dose, showing a similar survival benefit. So you really have one registration trial with a survival endpoint. Progression-free survival wasn't really looked at in the TAX 327 study, but was seen in our trial.
And the other issue about progression-free survival, we've seen the opposite situation happen. We've seen in a very very recent trial where Avastin was combined with docetaxel, that there was an improvement in progression-free survival. So, you know, this is I think a very very problematic endpoint to use in this situation, but nonetheless, that's why the FDA accepted the change to the primary endpoint.
DR. GOODMAN: It is now accepting it. Thank you very much for that clarification. Dr. Steinbrook, into the mike.
DR. STEINBROOK: I had a question about the IMPACT study. If I understand correctly, the study close
00165

date was the end of April 2009. Are the patients sometimes continued to be followed for survival beyond that time, and I understand we don't have it now, but if so, will that information become public.
DR. KANTOFF: The data was locked, Margo, what date was that? It was a month or two later, I showed a slide, or in my handout more data. We don't have any more survival data beyond that time.
DR. STEINBROOK: Thank you.
DR. GOODMAN: Further questions at this point? I'm going to push our own pro, Dr. Matuszewski, on a question here, since I know he has a pharmacy background. Dr. Matuszewski, when you hear about the treatment regimens here and what you might otherwise call dosage, it sounds as though there's not a small amount of variation in the regimens and in the cell counts and so forth. Does that make you think or look for, or seek greater standardization, or are you at ease with the variation that was cited in the tech assessment and some of the literature?
DR. MATUSZEWSKI: The oncology area is probably 70 to 80 percent off-label use, and in terms of oncologists trying to find the right dose, the right combination of product, that's an ever-evolving effort. I am fairly comfortable with the somewhat varying cell

00166

counts that have been expressed in the Provenge therapy, that again, the ultimate survival benefit is what was shown in the study. My concern for all these secondary therapies, whether docetaxel was given before or after is really not of major concern, because again, we're looking at a therapy that is not meant to cure, that is not necessarily meant to control, but is primarily intended in this cancer stage to improve survival, and in this case improve survival without the additional adverse reactions that are noted in some of the other standard chemotherapy agents. So combination use, multiple products at different points in time, adjuvant therapy, that's just a fact of oncology.
DR. GOODMAN: And henceforth as this potentially diffuses into use, would you want to see more data about dosages and regimens and cell counts, or do you think that that might start to become more standard, or would you not seek that as someone who cares about evidence?
DR. MATUSZEWSKI: Oh, I think you will see a lot of it. I think you will see -- again, it depends on the control mechanisms that are put in place, and my suspicion is there will be substantial mechanisms in place, but we're not talking about coverage. I think what you're going to see, as you saw on some of these treatment protocols, it's placed in an armamentarium, and hopefully

00167

you will see at some point further studies about quality of life, specifically related to quality of life on this

agent and other agents accumulated. You'll also be able to see at some point some comparative effectiveness research done on that, there's a lot of funding in that arena, so that may not necessarily be funded by the company, but may be funded by other independent entities, that will put more clarity around the issue of the value of this therapy.

But as was mentioned before, this is really another option in a state that the other options were there, and they all have their pluses and minuses, whether it be a two-month additional survival at the expense of some additional adverse reaction to deal with.

DR. GOODMAN: Thank you, Dr. Matuszewski, that's very helpful. Ms. Moore, into the microphone, please.

MS. MOORE: It's wonderful with the mild side effect profile but I'm wondering if in the survival data, did anybody report, because nurses are often the first to see some untoward side effects of subsequent chemotherapy, things that haven't been reported before, and what I'm worried about is if that will be something we want to look at and get more data on in the future, and you're seeing patients masking and so on.

DR. GOODMAN: Dr. Kantoff.

00168

DR. KANTOFF: You're right. I think in a study of this sort with the number of patients, you don't capture everything that goes on subsequently, so the company has very nicely, Dendreon has nicely set up a registry to capture in the community setting and the academic setting the side effects that might occur beyond what we realized in the IMPACT study.

DR. GOODMAN: Thank you. Ms. Darling, or, pardon me, sir, did you have a comment on this question? This is Brad Loncar.

MR. LONCAR: Thank you very much. I just wanted to add kind of a real world comment to the previous question. In the clinical trials a high percentage of the men went on to take a chemotherapy after this treatment, but one thing I would like to say is, I think in the broader world there are many men for whom chemotherapy is not a very appealing treatment option. My grandfather was that way, we really had to push him to get his treatments. So I think one of the great things about this drug is its low side effect profile and I think it would open up, you know, it would open up another option for a whole new subgroup of men who aren't very interested in chemotherapy. I think people who participate in clinical trials are more prone to take different therapies, so I think that's one reason why so many men in the clinical

00169

trials went on to take chemotherapy, but I think if you looked at it in the real world and out there, you know, in the country, you would find that it would be a much smaller percentage of people in the real world, I think

there would be a much larger group of people for who this would open a whole new door to them.
DR. GOODMAN: Thank you, Mr. Loncar. So of the patients that go on to survive, nevertheless the majority appear to, a large percentage appear to require chemotherapy, so this intervention itself is not a substitute for chemotherapy, and it sounds as though much data need to be collected, even to fulfill the point that you proposed insofar as perhaps in practice the use of chemotherapy might be lower. We don't know that yet, and it might be a good idea to collect those data. Thank you for your point. Ms. Darling.
MS. DARLING: Actually, it was on that point as well. I was wanting a little more detail about what patients will be in the registry, included in the registry, and what information will be collected. And will we know, say two years from now, a lot of answers to questions that we don't have now, if we just continue to do what we're doing.
DR. GOODMAN: Thank you, Ms. Darling. Dr. Frohlich.

00170

DR. FROHLICH: So, the registry is 1,500 patients that will be enrolled who are receiving commercial sipuleucel-T. Those patients would be followed for a minimum of three years for overall survival to further assess the risk of cerebrovascular events as well as for serious side effects, so they will be collected over time. Subsequent therapies will be collected as part of that registry as well.
DR. GOODMAN: Is the 1,500 a ceiling amount, a targeted amount?
DR. FROHLICH: A minimum of 1,500.
DR. GOODMAN: A minimum of 1,500, and this is what was requested by the FDA?
DR. FROHLICH: That's correct.
DR. GOODMAN: Thank you. So that should provide some data, Ms. Darling, as to some things we don't know yet at the time of approval by the FDA, so we do need to collect more data. Further questions on this or other issues, up and down the line here. Yes, Dr. Schulman?
DR. SCHULMAN: Just, we have been looking at the survival first, and can you just clarify what the best estimate is of the proportion of patients that are alive at the end of 36 months on therapy?
DR. KANTOFF: On the IMPACT trial it was 36 percent on the sipuleucel-T arm versus 24 percent on the

00171

control arm. On the earlier trial, 9901, at 36 months it was 33 percent versus 11 percent.
DR. STEINBROOK: Could you clarify for the IMPACT trial, at three years, was that an estimated number or are those actuals?
DR. KANTOFF: Estimated.

DR. STEINBROOK: So those are estimated, and the number taken from the report which gets you to the four-month survival number, those are actual numbers from the Kaplan-Meier, et cetera, or were they both done in the same way? I'm just trying to, is the three-year number and also the earlier number, the median, whatever gets you to the four-month difference, are they both done in the same way?

DR. FROHLICH: This is the standard way we analyze oncology trials, so it's a Kaplan-Meier method that takes into account all patients, so essentially those that don't have survival information at the time are also still alive at the time, so it's basically, the median is reading a classic Kaplan-Meier curve and then down, and the 36-month survival is taking a line and then drawing it up and then over.

DR. KANTOFF: And I would say that the confidence at the median is a lot greater than the confidence at the three-year mark.

00172

DR. SCHULMAN: Thank you.

DR. GOODMAN: Yes, Dr. Satya-Murti.

DR. SATYA-MURTI: So the indication for chemo, particularly docetaxel, is more general, not as specific as sipuleucel-T. So in the future, I foresee a certain percentage of otherwise chemo-bound patients who would now be receiving Provenge for a while, and then perhaps a proportion of those would go on to chemotherapy. Is that how you visualize that happening? Dr. Gulley might be able to answer it, since he showed us a slide, I think your third or fourth slide.

DR. GULLEY: Yes. You know, I think that often patients self-select whether, you know, there's a discussion between the doctor and the patient where the patient will ask, what are the treatment options for me? A lot of times patients when offered chemotherapy if they don't have symptoms or if they're not having rapidly progressive disease, will often look at getting other therapy such as second line hormonal therapy or immunotherapy.

So I don't think it's quite as -- I think that more patients later on with more symptoms tend to get the chemotherapy. It is always an option for other patients, though, earlier on. There may be some patients who would be potential candidates for chemotherapy who might choose

00173

to get immunotherapy first.

DR. SATYA-MURTI: Can you project a percentage of that?

DR. GULLEY: I didn't bring my crystal ball today, I'm sorry. It's difficult for me to say exactly, but I think a minority, it would be a small minority of patients that would otherwise get chemotherapy that would --

DR. SATYA-MURTI: Would migrate to Provenge.
DR. GULLEY: That would migrate to Provenge, yes.
DR. GOODMAN: So Dr. Satya-Murti, what response do you infer from this exchange with regard to your question?
DR. SATYA-MURTI: Well, that is good to know, because they would have further events, so that's the positive side. But I'm also wondering if it would postpone eventual chemotherapy, a so-called layering effect which we see in medicines. An ultimate therapy is finally given to someone, but before they reach the therapy, like total knee replacement, they might go through a stage of physical supplementation or other modes of therapy.
So what we're looking at is an eventual destination therapy so far that would fail, or not fail,

00174

but en route to that destination therapy, a proportion now would have a slightly longer life before they reach that, with fewer symptoms and side effects. That seems to be the projection, that's what I derived out of that answer.
DR. GOODMAN: Thank you. Dr. Gulley.
DR. GULLEY: I would just like to add that potentially with the immunotherapies, remember, it's not just impacting on the median time but potentially for months down the road too, so even during the subsequent therapy, that immunotherapy could potentially still be impacting the patient's outcomes.
DR. GOODMAN: Thank you. This is Dr. Frohlich again.
DR. FROHLICH: I just wanted to clarify that what we're talking about here is not unique to prostate cancer, this is the state of oncology in general. If you look at breast cancer, et cetera, when patients fail an initial therapy, there's always a possibility of them going on to some other therapy. And I think what we do have for the Provenge trials is that roughly half the patients did go on to get docetaxel but half did not, so half of those patients were getting the survival benefit without subsequently going on to other chemotherapies.
DR. GOODMAN: Dr. Satya-Murti.
DR. SATYA-MURTI: There is an exception, though.

00175

The other trials you suggested were all chemotherapy straight, or radiation and then chemo. Here is a newer modality that is introduced instead of going from one chemo to another chemo.
DR. GOODMAN: Thank you. Dr. Frohlich, do you have an answer to that point?
DR. FROHLICH: Yes. I think there are certain chemotherapy trials where we have another lab with other small molecules, time inhibitors where patients are in the same boat, where patients get one of those and then they

may subsequently go on to get those or subsequent chemotherapy, so I think it really is a general phenomenon in oncology.
DR. GOODMAN: A general phenomenon in oncology, still most of these people do need some form of chemotherapy at some point to survive. Was it Dr. Mintzer next?
DR. MINTZER: I just want to comment and amplify my point that, you know, as a practicing medical oncologist, I've heard repeatedly that patients are going to get Provenge instead of chemotherapy and that's really not the model at all. If you look at the paradigm of non-small cell lung cancer and non-Hodgkin's lymphoma, as new available agents come out they don't eliminate other drugs, they just apply them in sequence hoping to convert

00176

them to more chronic disease, which is the model we're seeing. But to say this is a desirable product to avoid chemotherapy, at least the way I see it is not correct, and in fact the data doesn't bear that out, and in these studies just as many patients got chemotherapy. So it's got to be in addition to, not instead of, so I wouldn't look at that from my viewpoint as a benefit of this drug. It's saying the patient will probably get chemotherapy, so I would think, we're not curing anyone with this.
DR. GOODMAN: Thank you, Dr. Mintzer. Dr. Satya-Murti, on this same point?
DR. SATYA-MURTI: The same point, and very brief. It's not unique to oncology. That is the case, very often in pain management too, there are multiple modalities, invasive, noninvasive, surgery, and then an ultimate last resort therapy, so very often they happen to be incremental or subsequent.
DR. GOODMAN: Thank you. Dr. Fuller is next, sir.
DR. FULLER: I'm wondering if the professionals in the cancer of the prostate world ever find it troubling, as I do, that 65 is some sort of a breaking point here. As far as I know with cancer of the prostate, you've got a rather heterogeneous disease which behaves differently as you grow older and presents differently as

00177

you grow older, and about the only thing I can see that happens when you turn 65 is you get eligible for Medicare, and I was wondering if that bothers any of you as it bothered me when I read the studies initially.
DR. GOODMAN: Any comment on that?
DR. SCHELLHAMMER: Well, the emphasis on chronological age, I think is overdone. So it's true that 65 is the break-point for Medicare and that's a big positive for many 65-year-old men with regard to their coverage. But with regard to interacting with the patients, the issue is their comorbidities and the state of the disease, and the aggressive posture as we can

currently determine it. So age is just one of the factors, and sometimes it's not the most important one.

DR. GOODMAN: So Dr. Fuller, then, at this point in the life cycle of this technology, it's not yet to the point where it's fine tuned enough to differentiate enough with regard to having subgroup data that would allow the differential application to this not one disease, but many kinds of prostate cancer, correct?

DR. FULLER: I don't think the study to date is capable of identifying the differences that might or might not exist. I'm hoping that the registry may be a little more precise in that as you get another 1,500-plus patients and can pay a little more attention to it.

00178

DR. GOODMAN: Thank you. So that is also pursuant to the point made earlier about the need to keep collecting data. We don't know everything we need to know about this at the time it was approved by the FDA, it's a good thing a registry's in place and we have some other data collection mechanisms.

Other points to other presenters before we get into our questions specifically?

Dr. Mark, I just wanted to follow up on something you said earlier, this is a different train of thought, but it pertains to the literature review that you did. We here on this panel see many systematic literature reviews and you made a few comments about the need to go further afield to find the literature, more so than you might otherwise, you had to look in various places and so forth, and it also sounded as though it took you a while to kind of sort through the distinct patient populations because there was some overlap. Would you say it was just kind of a difficult body of literature to describe and characterize compared to other bodies of literature that you have examined?

DR. MARK: Well, no. This was unique because actually, the actual number of data sets was relatively small, but publicly available information from other sources, particularly FDA clinical review, FDA statistical

00179

review, really offers, kind of relative to other types of reviews we do, unparalleled insight into a clinical trial and the way a clinical trial is analyzed, and it's not as straightforward as a journal article, particularly highly edited, brief, compact, almost barebones presentation that the New England Journal and JAMA and Lancet allow you to do. And what it does, it actually raises issues about analyses that are presented in various venues, because the FDA statistician can apply these analyses.

So to provide an example of that, in at least one of the peer reviewed papers they present a multivariable adjusted analysis of survival, I think this is D9901, which showed a hazard ratio showing greater benefit than the unadjusted survival rate. While we might

have taken that on face value, the FDA did an analysis of that and showed that in fact that analysis was based on some missing values in the analysis. And apparently the missing values favored sipuleucel-T, the missing values deleted patients, short surviving patients on placebo treatment.
And therefore, what I had described in my report, the multiple variations of analysis, it was our challenge as to how to kind of organize that and make some decisions as to what was useful, what was superfluous, and I think we tried to do our best job in terms of editing

00180

what could have been a presentation of 50 hazard ratios based on the same three steps. The challenge was actually in too much information and the judgment in presenting what was reasonable and fair.
DR. GOODMAN: So you basically had three RCTs, but you had too much information of other types to sort through?
DR. MARK: If I had abstracted every hazard ratio, there might have been 50 to 70 of them.
DR. GOODMAN: Thanks. I just observe that insofar as the body of evidence, it seemed to me pretty difficult for you to get a handle on this overall body of evidence, you had to sort through and find the distinct patient groups, you had to go to the FDA documents and so forth, so it would seem that people who are trying to get a handle on the relative benefits and harms of this technology might have at least as difficult a time as you did sorting through this, and you actually get paid to do this.
DR. MARK: Well, only because the information was there. So for another technology, we abstract studies from clinical reviews and we're oblivious to what is probably the reality of these clinical trials in terms of the interactive nature of data analyses and presentation.
So it was only because it was available that we had to

00181

make a different set of kind of judgments.
DR. GOODMAN: Thank you, Dr. Mark, that's helpful.
DR. FROHLICH: I'd just like to comment that I think it speaks to the rigorousness of the review. There was an extensive review process with the FDA, a lot of requested analyses to try to address some of these questions. I mean, that's why we have the volume of analyses that were performed there. But I think for the lay public, there's three publications in peer reviewed journals that speak very concisely to the overall survival benefit of these three trials.
DR. GOODMAN: Thank you. Yes, Doctor?
DR. SCHELLHAMMER: Just briefly, I come away with the conclusion not that there was more obscurity but there was more accuracy, because the data was in its raw

form and it was available. So the spin I get otherwise is that there's some confusion, I think that it's just the reverse, so can you clarify that for me? Your question seemed to indicate that there was obscurity, and I hear from Dr. Mark that it's actually the raw available data that were available to him that made his life maybe more difficult, but more accurate in his assessments.
DR. GOODMAN: Thank you. We very much appreciate the great effort that Dr. Mark had to go

00182

through to pull this together, which he did, and he pulled together some data that were available that might not be otherwise available in other instances. It's a good thing that that group did it, because now we can find it all in one place in a nice report, having not done that before, had it not been done before, it maybe would have been difficult to find that other valuable data.
Dr. Schulman.
DR. SCHULMAN: Dr. Kantoff, kind of related to that. Did you have your own statisticians and do your own analysis of the trial data, did you have access to their trial database.
DR. KANTOFF: There were Dendreon-based statisticians as well as independently contracted statisticians involved in the analysis. I didn't have my own statisticians look at the data, but they were contracted outside statisticians as well as inhouse Dendreon statisticians.
DR. SCHULMAN: Contracted to the steering committee or contracted to Dendreon?
DR. KANTOFF: I was not involved in the -- there was a separate body of the steering committee who got presented the data. Who's on that committee was blinded to us. But they would see, the DSND would see the data that came out.

00183

DR. SCHULMAN: So when you wrote the journal article, it was the Dendreon statisticians you were working with?
DR. KANTOFF: Correct.
DR. GOODMAN: Ms. Darling, and then Dr. Satya-Murti. Ms. Darling.
MS. DARLING: I know the sample size is too small but I'm wondering, since we have everybody lined up and available to possibly answer this, do we have any reason to think that because the burden of disease may be greater, that African-American men might benefit more, or is it we just can't possibly know that from this treatment, or what would make us think about that?
DR. GOODMAN: Dr. Kantoff.
DR. KANTOFF: You know, it gets back to the points that were made, multiple points with regard to retrospective subset analysis, and it's very hard to come to any definitive conclusions with regard to either the

potential benefits or risks, or subgroups of patients that may benefit more or less, from subgroups from a relatively small study, where some of the subpopulations are small enough themselves.

But having said that, I'm heartened by the fact that there isn't any evidence that African-Americans did not benefit from the therapy. The magnitude of the

00184

benefit, I think, is up in the air at this point.

DR. GOODMAN: Thank you, Ms. Darling. Further questions at this point? Dr. Satya-Murti, yes.

DR. SATYA-MURTI: This is for any one of you. In the TA you concluded there is a concern that survival difference between the two arms may be attributable to the posttreatment docetaxel. You have heard other presenters and other dissenters to that concern. Are you, do any of you still hold the concern or have we melted away the concern from listening to presenters this morning?

DR. GOODMAN: Any comments on that? Dr. Petrylak.

DR. PETRYLAK: Well, I will refer you back to the presentation where we showed the data that presented at ASCO this year, that the effect of sipuleucel-T was independent of the docetaxel effect, both pre and post sipuleucel-T.

I would also like to point out that the data that was captured on docetaxel is, didn't specify the type of docetaxel administered. The weekly regimen does not show survival benefit, yet there still is a significant amount of docetaxel administered out in the community weekly. So even though we may look at chemotherapy, and even though we see a positive, we don't see the interaction from this particular trial, and it would be

00185

very very difficult to quantify what the exact effect is here.

DR. KANTOFF: I would add that it's very difficult at clinical trials, as I think many of us realize, to mandate exactly when a particular agent is given, how it's given, et cetera. So all the analyses that were done were done in a less than perfect fashion. Having said that, the analyses that were done that corrected for the amount of docetaxel used and the times of the docetaxel use met many of our satisfaction with regard to eliminating those differences which were very minute to begin with, as being a significant factor with regard to the benefits of sipuleucel-T.

DR. GOODMAN: Thank you, Doctor. Dr. Frohlich.

DR. FROHLICH: I just want to add to that, if you look at the FDA website, they have documentation of their internal review process, and they invited external statisticians in to address this issue. Ralph D'Agostino, who frequently presides on ODAC, was one of those. And again, the conclusion after looking at all those analyses

and suggesting any additional ones was that there was no alternative explanation for the survival benefit, so the chemotherapy did not appear to be a cause for the observed survival benefit.
DR. GOODMAN: Thank you, Dr. Frohlich.

00186

Dr. Mark, do you have a comment on that matter?
DR. MARK: Yes. Only that in my report, my wording was that, again, all these effects stated about the alternative analysis were true, but that I was willing to state that the effect of docetaxel appears in the milieu of the proportion of docetaxel that was given. I also looked extensively at the FDA alternative analyses and there are some issues about simulating various hypothetical situations about the patient selection to get docetaxel or not, and essentially I found it very hard to follow, and that particularly if patients appeared to be analyzed as they were in terms of what treatment was ultimately received, that looking at those types of survival curves was not in and of itself evidence of effectiveness either in the absence or presence of chemotherapy. In other words, the data did not allow a clear conclusion that you could say sipuleucel is effective if you decide ultimately you don't want chemotherapy, or if you do, that the effect could be -- if it was effective, that it could be, you know, partitioned possibly in different ways to equal or unequal benefits, that you could not make a conclusion as to whether the benefit was greater or lesser depending on whether you got chemotherapy or not.
DR. GOODMAN: So Dr. Mark, are you still saying,

00187

then, that it is difficult to distinguish between the impact on outcomes of sipuleucel versus the chemotherapy, you still can't quite separate those?
DR. MARK: No. I would say that if it is effective, I would be hesitant to tell a patient that if up front you do not want to ever have chemotherapy that you're going to achieve the same benefit overall. I can't tell you what the degree of benefit you will get, compared to the average benefit shown overall in the clinical trial.
DR. GOODMAN: So that's consistent with what the report said?
DR. MARK: Yes, that if there is a benefit, it is effective in the context of a trial in which patients received chemotherapy as they did in the arms of the trial.
DR. GOODMAN: Thanks for that clarification.
Dr. Frohlich.
DR. FROHLICH: Just to clarify for the panel, to make sure that you're not confused on this issue.
DR. GOODMAN: We're not confused, we're trying to get to the bottom of it.

DR. FROHLICH: This is a common phenomenon in oncology, that we can't control subsequent therapy, and that's why we do randomized trials, because patients are

00188

equally outgraded based on baseline characteristics to both arms, and then they should be roughly balanced about what types and when subsequent therapies are instituted, and that's what we found in the data, roughly the same percentage of patients got docetaxel, timing roughly comparable.

And yes, none of these analyses to adjust for that are perfect because the only way to definitively answer that is to randomize patients to subsequent therapies, which is not ethical, not feasible, not possible to do. But to the best of our ability, looking at this very extensively and exhaustively, both with our internal statisticians, external consultant statisticians, and as was mentioned, FDA statisticians, the conclusion that there's no alternative explanation, the chemotherapy does not appear to be an alternative explanation for the observed survival benefit.

DR. GOODMAN: Thank you, Dr. Frohlich. Dr. Satya-Murti.

DR. SATYA-MURTI: That's a very good back and forth. I think this is going to be a crucial aspect, of listening to you both in answering the question. I'm sympathetic to your point, and that is as a clinician, I know oncologists do think and act that way. I'm just wondering if we should provide an exception for oncology

00189

as a clinical discipline as opposed to other areas where we do expect this kind of removal of confounders and interpretation of data.

DR. GOODMAN: Do any presenters care to respond to that, or should we just leave that as it is? Okay. Thank you for your point, Dr. Satya-Murti, and thank you very much for that interchange. That was very helpful in clarifying this matter.

Dr. Madan.

DR. MADAN: I think it's also important at this point to interject that the trial that was done with IMPACT was the cleanest possible trial that can be done in metastatic prostate cancer moving forward. In June cabazitaxel was approved for metastatic prostate cancer that is castrate-resistant, and in just the last few weeks abiraterone demonstrated an overall survival benefit that I'm sure the FDA will be evaluating in the coming months. So what we're looking at is a landscape now where previously you only had docetaxel as one possible accepted therapy, you now potentially in six more months have three, docetaxel, cabazitaxel and abiraterone, and the ideal sequence of those treatments is not yet determined. So future studies would be complicated not only by what treatment they got, but how many of those

treatments they got and in what sequence they received
00190
them. So I think this is a great thing for patients with prostate cancer, it makes the clinical trials a little difficult, but I think in the context of this discussion, it's important to consider that situation.
DR. GOODMAN: Thank you very much, Dr. Madan. It is indeed a moving target here, and innovation continues to proceed and alternatives appear and go by the wayside at the same time, so it's an important consideration, and finding a clinical trial is sometimes a victim of time, because things move in real time while you're trying to plan and conduct a trial. Point well made, thank you for that.
Dr. Fuller, yes, sir.
DR. FULLER: I have been sitting here enjoying your conversation, and this thought just came to mind a few minutes ago. You know, we're dealing with increments of time which are sometimes relatively small, and one of those increments of time is when you decide that you've got to go on to the follow-up treatment, and it appears to me that sometimes that decision is made on the basis of imaging, and in the absence of clinical symptoms, sometimes it's just imaging. What you and I both know is it takes a while for an image to turn positive, and it varies somewhat with the behavior of the individual cancers.
00191
But I'm wondering if you have any sort of agreement on how often you ought to take a look. Sometimes, I remember a wonderful woman at M.D. Anderson who used to run the medical breast service, and she said I'd rather not know in a patient who had no symptoms. So since we're dealing with such small increments in time, I'm just wondering if there is any sort of agreement among you about how frequently you should look in otherwise asymptomatic patients.
DR. GOODMAN: It looks like Dr. Kantoff has a response.
DR. KANTOFF: I can venture to say if you asked all the quote-unquote experts on the panel, they will come up with a different answer for you with regard to their practice patterns, with regard to how frequently they do ultra scans and CAT scans for patients who are asymptomatic with rising PSA, but you can hear other people's opinions, but I'm in the camp of getting fewer rather than more.
DR. FULLER: I'm with you.
DR. SCHELLHAMMER: I'm in that camp as well, and one of the triggers might be if you're going to change a therapy and you're going to progress to something new, you might get a baseline so you have some assessment of that for you and the patient, although sometimes it's not
00192

overly clinically meaningful.
DR. PETRYLAK: I think we have two different ways of looking at this from the clinical trial standpoint and also from the clinical practice standpoint. From the Prostate Cancer Working Group it was recommended that we look at imaging every 12 weeks at most points in the trials. Practically, when we're taking care of patients, it's very different. I use symptoms a lot to determine when I'm going to image somebody, particularly if I'm going to treat them with agents that may be palliative given time. So there isn't really a standard answer, and I agree with Phil, you will be getting different answers from different providers.
DR. FULLER: It just struck me in this particular example, you're going to make a change in therapy based on an image, and I thought your answers would be as they were, but that influences the rate at which you will go on to subsequent therapy.
DR. GOODMAN: Thank you, Dr. Fuller. Unless anyone has any questions, we would like to proceed to addressing in particular our questions for the day. Any questions before we do that? Okay. Right now Maria Ellis is handing out a better formatted score sheet for us, and the formatted score sheet that she's handing out along with these little

00193

gizmos, has a place for the panelist to sign before they leave today, a place at the bottom, but in either case the voting questions are the same.
So let's just get familiar with this first voting question, and you will recall that the questions come in sequence so far as looking at the adequacy of the evidence, not yet what it says, the adequacy of the evidence, and then having looked at the adequacy of the evidence in a given instance, then we look to see what the evidence says. So the questions are worded almost the same but not quite, and we will make that a clear distinction.
The first question, which I will read out now, we've had quite a bit of discussion on it, is, how confident are you that there is adequate evidence to determine whether or not the use of autologous cellular immunotherapy treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer clinically significantly improves three things?
So again, this is about the adequacy of the evidence, it talks about the therapy itself as a treatment, the patient population are asymptomatic or minimally symptomatic, patients with metastatic castrate-resistant prostate cancer. So it's the adequacy of evidence of the therapy for that particular patient,

00194

and then it asks about three main aspects, one is overall survival, which is A; the second, B, is controls or

maintains disease-related symptoms; and C is the avoidance or minimization of the burdens associated with anticancer therapy.

Now, just a note here with C. That's kind of a long question that's been posed to us, avoidance or minimization of burdens associated with anticancer therapy while maintaining overall survival and control of disease-related symptoms. As I understand, we're basically trying to set those aside; the question is really about avoidance or minimization of the burdens associated with anticancer therapy. And as noted in your original MedCAC question sheet, it talks about the burdens to the patients and the healthcare system associated with that therapy. And as always, the comparator is the management that the patient would have otherwise received.

So I understand, I see most panelists nodding their heads, I understand it's a bit wordy, but we'll do our best to kind of move through these.

So on this matter of how confident are you that there's adequate evidence to determine whether or not this treatment of these particular patients clinically significantly improves overall survival, symptoms, or the burden, any comments about adequacy of the evidence

00195

regarding overall survival at this point that you would like to discuss? I think what we'll do is have a full discussion of number 1.A through 1.C, and then proceed to vote on it. Any comments about what you would like, questions about what you would like to know regarding the adequacy of evidence for this therapy for that set of patients on the matter of overall survival? It's one of the main outcomes we've been talking about earlier this morning. Dr. Schulman.

DR. SCHULMAN: This may be a technical question for Medicare, but kind of across therapeutic areas, we're asked now for clinical significance, and do they think the clinical significance is related to basically three-year survival, five-year survival, or median survival irrespective of duration of survival?

DR. GOODMAN: It isn't specific here, it simply says overall survival, and the phrase clinically significant relates to those clinical aspects A, B and C. I don't know that it is specified -- it is not specified. If you have a preference, if you think it ought to be one or the other, or you just want to keep it in general and allow for other comments to qualify that, that's fine. Do you have a preference, Dr. Schulman?

DR. SCHULMAN: I guess this is more for CMS, and how they, is that up to us to decide what clinically

00196

significant impact is amongst the panel?

DR. GOODMAN: Yeah. I think the distinction there is we will often see statistical significance and that may prevail, but that isn't necessarily everything

that CMS wants to know, it wants to also know about clinical significance.
Yes, Dr. Potters.
DR. POTTERS: Right before the break, Dr. Mark, I couldn't understand the statement that you made regarding the decision that you had in the TA on moderate, and how that came about, because it appeared, at least my interpretation was that precision really represented the weakest link in the analysis, which was based on the number of patients that were in the studies. So it wasn't clear to me how the TA came up with the vote for moderate and whether that reflected your opinion, and there was a comment made right before the break.
DR. GOODMAN: And this is Dr. Mark, who presented the technology assessment, and the finding in your assessment that the evidence overall is moderate as opposed to strong. Dr. Mark.
DR. MARK: Yes. I would suggest that a better way to evaluate that page is the summary statements of each criteria, and the grade system as developed by comparative effectiveness researchers is an evolution, and

00197

I would say at this point there's no solid criteria that I could give you regarding what would bump it up into one category or another, but just based on our group's experience in evaluating different technologies and different types of studies, sizes of studies, different areas, so I would say that the standard would probably be different depending on the level of research being conducted in that area.
DR. GOODMAN: Dr. Mark, as I recall, you were pretty specific on the criteria or the dimensions or the aspects that caused you to conclude that this was moderate as opposed to something stronger, I recall three or four things. Do you happen to know them off the top of your head at this point, what were those things that made you decide it was moderate?
DR. MARK: Well, I think the greater comments were mostly in the area of the precision of the results.
DR. GOODMAN: Precision of the results?
DR. MARK: You know, precision of the results is how confident are we of that .775 hazard ratio, and is it off by a considerable degree too high or too low. And there were, you know, potentially three factors that could affect that precision of the estimate up or down, and that would be the sample size, and potential confounding factors of the post-progression treatments, and unknown

00198

effects of frozen salvage product.
DR. GOODMAN: Dr. Satya-Murti.
DR. SATYA-MURTI: As for the overall survival question, please correct me if I'm wrong, but there is a Halopi score or something like that I read in the literature, this is collective natural history data that

shows how long someone will survive, but we are not talking about that. We are talking about overall survival using the comparator of any other treatment that will be given, that's in the preface of the MedCAC question. So the overall survival, I interpreted that meaning how long would they have survived had they received the currently practiced ongoing treatments, and not the historic natural history curve.

DR. MARK: The comparator in the IMPACT and other trials was placebo, which is the equivalent of doing nothing at that time, expectant management. So I think your task would be either compare it, sipuleucel-T compared to nothing at the time, or to follow the patients throughout the trajectory of their care, and make your judgments based on everything that was received to the survival endpoint.

DR. GOODMAN: Thank you. A couple clarifications. Thank you, Dr. Mark. First of all, I apologize to everyone here.

00199

This slide projector above us was at least deafening to me, and so it was kind of hard for you, I know it was hard for some of our other folks to listen to that too. It's a little bit quieter now, but in order to make it quieter we had to turn off this slide projector, which now makes it hard for you to read any questions in front of you and behind us. However, the quiet slide projector is now on, and it projects to the back of the room. So I hope now that you get to crane your necks instead of having us crane our necks, and so we can all communicate a little more clearly, I direct you to the back of the room if you want to see the questions, they're the same as you saw. And Dr. Schulman, just for clarification, Ms. Ellis handed out the appropriate set of questions, which in number one simply says significantly improves, not clinically significantly improves, so that word is no longer in the question, and this is the appropriate set, this is the one she just handed out. Otherwise it's the same as is shown in the back of the room, so I'll read it one more time.

How confident are you that there is adequate evidence to determine whether or not the use of autologous cellular immunotherapy treatment of asymptomatic or minimally symptomatic castrate-resistant prostate cancer significantly improves those three items?

00200

And I see that Mr. Loncar has a comment. Yes, sir.

MR. LONCAR: Thank you. In regards to this point, I just want to remind everyone that four months ago in their summary basis for regulatory action the FDA publicly said that they believed there was substantial evidence of improved survival.

DR. GOODMAN: Thank you very much for that

point, Mr. Loncar, I believe you made it earlier, and we did hear it clearly the first time. I do appreciate your interest in it, and I would point out that our job today is to answer this question, and perhaps shed even more light than was available subsequent to the FDA approval, it might be interesting. Dr. Steinbrook, yes?
DR. STEINBROOK: Is it okay to move to B?
DR. GOODMAN: Let's talk about A, B and C, and then we will grade them together.
DR. STEINBROOK: With regard to B, control of disease-related symptoms, this is really just a question for the members of the panel. I'm struggling with what I've actually heard which was directly on point to that, and I see two abstracts which were handed out today of studies which were done, I guess after the MedCAC questions were posed. Is that it, is there something I'm missing which is directly relevant to that point that

00201

we've heard?
DR. GOODMAN: The question stands, and sometimes questions, there's not a lot of evidence for a particular question. And you have, like other panelists, received all the information ahead of time, and some was handed out, and that's what we've got.
DR. STEINBROOK: So I'm not missing something that I've forgotten about?
DR. GOODMAN: I believe not.
DR. STEINBROOK: Thank you.
DR. GOODMAN: Great. Anything else on the matter of overall survival, or control of disease-related symptoms, or the avoidance or minimization of the burdens associated with the therapies, whatever those might be? Okay. We can actually start voting, Ms. Ellis, if that's okay with you. Ms. Ellis, did you want to remind us about the voting mechanism and this high tech gizmo that we've got here?
MS. ELLIS: Yes. Panel members, if you would just make sure that you select your number, you push down on the key pad hard to make sure that your vote goes through. Please state your vote for the record of the court reporter, and those individuals on the Webinar. And at the end of the voting I will collect your MedCAC pre-score sheets so that we can make sure all the votes

00202

are accurate for web posting, and that's it.
DR. GOODMAN: Okay. We're going to start voting in a moment. Pursuant to Dr. Steinbrook's question, is there anything else we absolutely need to hear -- I see Dr. Frohlich rising right away, thank you, sir. Is there anything else that we need to hear that's germane to this question that will be of interest to the panel now that we otherwise would not have heard? Dr. Frohlich.
DR. FROHLICH: Just to summarize the points that I made in my remarks, there is strong evidence for a trend

for the delay in time, disease-related pain, both in the IMPACT study as well as the former D9901 --
DR. GOODMAN: Dr. Frohlich, I'm sorry. Is this new information or a repeat of what we've heard?
DR. FROHLICH: I just heard him mention two things, and then there was another thing, which was I showed you on my slides the adverse events that were seen more commonly in the control arm, things like anorexia, flank pain, hydronephrosis, suggesting a decrease in those events from sipuleucel-T. And then overall survival, I would argue, is the best measure of patient benefit, and reflects a control of the natural history of the disease.
DR. GOODMAN: Thank you, Dr. Frohlich. Anything else that we have not heard that we need to hear at this point? Yes, Dr. Matuszewski?

00203

DR. MATUSZEWSKI: Cliff, I just want to ask one question of Dr. Frohlich. How scaleable, I mean, can you make this therapy available to patients? There's been some discussion in the press about production problems and availability. Is that an issue at all to think about?
DR. FROHLICH: The short answer is no. Once we had the positive data, we invested heavily in building out our New Jersey facility as well as two additional facilities. They should be on line in the middle of next year, so we anticipate we should be able to meet demand at that point.
DR. MATUSZEWSKI: Okay, thanks.
DR. GOODMAN: Dr. Matuszewski, interesting, I'm not sure it's quite germane to the question, but it's probably interesting.
Dr. Gulley, you look as though you want to say something.
DR. GULLEY: Just real briefly, I haven't heard this being mentioned, but what Dr. Mark was mentioning about the patients that had crossover. I don't think that, you know, I don't think there's any biologic rationale for patients to actually do worse with the crossover treatment, in fact, the opposite appeared to be true from what Dr. George said.
DR. GOODMAN: Thank you for that comment, Dr.

00204

Gulley.
All right then. On this matter of the rating, do recall that it's on a one to five scale, one being a low confidence, three being intermediate confidence, and five being high confidence, so it's that scale of one to five, one is low, five is high.
And I'm sorry to sound so repetitive here, but again, this first question for A, B and C is about the adequacy of the evidence, it's not what the evidence says, it's kind of how good is the evidence. And you did hear today from Dr. Mark about how evidence was graded in certain ways and so forth, so it's that aspect, not what

it actually says.
So, on the matter of question one with regard to overall survival, how confident are you that there's adequate evidence to determine whether or not the use of autologous cellular immunotherapy treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer significantly improves overall survival? Would you please enter your rating, ranking from one to five?
And Ms. Ellis, are we going to have folks announce their answers?
MS. ELLIS: Yes, please.
DR. GOODMAN: And we could just start anyplace

00205

in the table that we desire.
MS. ELLIS: If you don't mind, if you could start with Dr. Saty Satya-Murti.
DR. GOODMAN: Is it necessary we go in that order?
MS. ELLIS: No, as long as you state your name as you vote for the record.
DR. GOODMAN: Okay. Well, let's start with Dr. Satya-Murti this time, and we'll probably mix it up so we don't have any bias introduced by earlier votes.
MS. DARLING: Do we vote first and then say it, or say it as we vote.
DR. GOODMAN: As long as you enter it electronically at some point, that's independent of what you say. Of course, we depend on you to make sure those are the same. Okay. Dr. Satya-Murti, one through five?
DR. SATYA-MURTI: Satya-Murti. Three on 1.A.
DR. GOODMAN: Yes, this is 1.A. Ms. Darling.
MS. DARLING: Helen Darling, three, 1.A.
DR. DMOCHOWSKI: Roger Dmochowski, three, 1.A.
DR. FULLER: Dale Fuller. I had a three when I came to town, but I'm going to put a four.
DR. MATUSZEWSKI: Karl Matuszewski, five.
DR. MINTZER: Mintzer, four.
MS. MOORE: Moore, four.

00206

DR. POTTERS: Potters, four.
DR. SCHULMAN: Schulman, four.
DR. STEINBROOK: Steinbrook, three.
DR. RAAB: Raab, five.
DR. MADAN: Madan, five.
DR. SOKOLOFF: Sokoloff, five.
DR. GOODMAN: Okay, thank you all very much. Everyone has pushed the button, correct?
MS. ELLIS: We're waiting for one person. There we go.
DR. GOODMAN: Thank you very much. We're going to move now to B --
MS. ELLIS: We have two voting scores, one with just voting members, and then two with the overall

committee. We do have three nonvoting members on the panel. What will happen at the end of the meeting, both scores will be posted to our coverage website, okay?
DR. GOODMAN: This is only showing the voting members.
SPEAKER: Who are the nonvoting members?
MS. ELLIS: The nonvoting members are the last three gentlemen at the end of the row. If you have your MedCAC roster, the industry rep and the two guest panel members, they are nonvoting panel members, they are nonvoting members.

00207

DR. GOODMAN: So what we're posting now are only the voting members, those are shown as correct. The full roster of folks on the panel, as mentioned before, they will be posted later?
MS. ELLIS: Correct. At the end of the meeting, all scores will be posted to our coverage website once they have been approved and cleared. Okay?
DR. GOODMAN: Thank you very much. All right. Let's move to B now, it's the same question about confidence in the adequacy of the evidence, this time it's for control of disease-related symptoms, one is low confidence, three is intermediate, five is high, one, two, three, four or five. We're going to start this time with Dr. Mintzer and move to his right and circle back. Dr. Mintzer.
DR. MINTZER: Mintzer, one.
MS. MOORE: Moore, two.
DR. POTTERS: Potters, two.
DR. SCHULMAN: Schulman, two.
DR. STEINBROOK: Steinbrook, one.
DR. RAAB: Raab, three.
DR. MADAN: Madan, three.
DR. SOKOLOFF: Sokoloff, two.
DR. GOODMAN: Dr. Satya-Murti.
DR. SATYA-MURTI: Satya-Murti, two.

00208

MS. DARLING: Helen Darling, three.
DR. DMOCHOWSKI: Dmochowski, two.
DR. FULLER: Fuller, two.
DR. MATUSZEWSKI: Matuszewski, three.
DR. GOODMAN: Okay. Those are the votes that you wanted us to gather, everyone on board?
MS. ELLIS: Yes, everyone has voted.
DR. GOODMAN: Those numbers are displayed on the back wall again, and those numbers look like the ones I was tracking at the same time, so I think we're in good shape now, okay?
MS. ELLIS: Yes.
DR. GOODMAN: Thank you, Ms. Ellis. Now we're going to move to adequacy of evidence regarding letter C, and this pertains to the avoidance or minimization of the burdens associated with anticancer therapy while

maintaining the overall survival and control of disease-related symptoms. So this has to do with the avoidance or minimization of burdens associated with anticancer therapy, and those burdens were addressed a little bit at the beginning of the day, okay?
So at this point, is everyone ready to vote?
All right, let's start with Dr. Sokoloff this time, and then we'll turn to this end of the table. Dr. Sokoloff.
DR. SOKOLOFF: Sokoloff, five.

00209

DR. MADAN: Madan, five.
DR. RAAB: Raab, five.
DR. STEINBROOK: Steinbrook, four.
DR. SCHULMAN: Schulman, three.
DR. POTTERS: Potters, three.
MS. MOORE: Moore, five.
DR. MINTZER: Mintzer, five.
DR. MATUSZEWSKI: Matuszewski, four.
DR. FULLER: Fuller, four.
DR. DMOCHOWSKI: Dmochowski, three.
MS. DARLING: Helen Darling, four.
DR. SATYA-MURTI: Satya-Murti, four.
DR. GOODMAN: Is that everyone, Ms. Ellis?
MS. ELLIS: That's everyone.
DR. GOODMAN: Once again, just to be repetitive, this reflects the votes of the voting members, not everyone at the table, but the nonvoting members' votes are still recorded, and will all be posted. That's 1.A, B and C.
Now, panel, we can move to question two. I do want to take, and I know that our court reporter would very much like a ten-minute break. Would now be a good time to take a ten-minute break? Let's do a ten-minute break now and we will reconvene in ten minutes. We've got our steps down with regard to voting, so we'll take ten

00210

minutes and then take up question two. Thank you.
(Recess.)
DR. GOODMAN: We're going to reconvene now, and we are going to move to question two, and put it up on the back wall. Okay.
Question two now has to do not with the adequacy of the evidence but what you're going to conclude about it. I expect that we will see it up on the back wall in a minute here. Question two concerns, how confident are you that there is adequate evidence to conclude that autologous cellular immunotherapy treatment significantly improves the overall survival in patients who are symptomatic or minimally symptomatic with metastatic castrate-resistant prostate cancer, that's question two.
And do keep in mind that not all of A, B and C from question one are going to go forward. Remember, when we answered question one for overall survival, that's 3.7, so that's greater than 2.5, so we will answer that. B, which

had to do with control of the disease-related symptoms, only rated two, so we won't vote for that. But C, which has to do with avoidance or a minimization of the burdens associated with the therapy rated 3.9 among our voting members. And so therefore, we will answer question two but not question three, correct, Ms. Ellis, and we will answer question four. So we answer question two and not

00211

question three.
Well, with respect to question two and the adequacy, whether or not the evidence can be used to conclude that this has an impact on overall survival, any further discussion on that, questions or discussion from the panel? Again, not about how good the evidence is but what the evidence says here in this point. I don't see any questions. No questions? Okay.
So we're going to answer question two now. We're continuously learning the system, by the way, and so with regard to the voting, let's think about another way to reduce bias. When we voted earlier, people could still change their vote after perhaps having heard what somebody said. So let's do this, panel, if you wouldn't mind. When we ask you to vote, do enter your vote, push that button, make sure it registers, and then when Ms. Ellis tells us that all ten people who are voting members have voted, we'll ask you to put your gizmo down, and then we'll vote with the verbals on this, and we still need the verbals for the people that are coming in via Webinar and need other access to that information.
So once again, and I'm being repetitive on purpose here, this question has to do with overall survival with the indication listed there, asymptomatic or minimally symptomatic metastatic castrate-resistant

00212

prostate cancer. So how confident are you that there's adequate evidence to conclude that the therapy significantly improves overall survival in this group of patients? Overall survival, where one is low confidence, five is high confidence, please enter your number, and when we see ten, we will ask you to verbalize.
If you will put your little machines down, and this time we'll start with Dr. Matuszewski and move to his right, and circle back. Dr. Matuszewski.
DR. MATUSZEWSKI: Matuszewski, four.
DR. MINTZER: Mintzer, four.
MS. MOORE: Moore, four.
DR. POTTERS: Potters, four.
DR. SCHULMAN: Schulman, four.
DR. STEINBROOK: Steinbrook, three.
DR. RAAB: Raab, five.
DR. MADAN: Madan, five.
DR. SOKOLOFF: Sokoloff, five.
DR. GOODMAN: Dr. Satya-Murti.
DR. SATYA-MURTI: Dr. Goodman, that's a nice

experiment. I don't think we have bias, but Satya-Murti, three.
MS. DARLING: Helen Darling, four.
DR. DMOCHOWSKI: Dmochowski, three.
DR. FULLER: Fuller voted one, but he wouldn't

00213

mind changing his vote on account of I misinterpreted the question.
DR. GOODMAN: Well, Dr. Fuller, since we know that you're an upstanding and honest man, we'll let you re-enter it as appropriate.
DR. FULLER: I'm going to give it a three.
DR. GOODMAN: Is your vote three, Dr. Fuller?
DR. FULLER: Yes.
DR. GOODMAN: But we have a record of what the totals are, so we won't expect any change. Dr. Fuller, the fact that you have to revote means that we have to kind of start all over again, but that's quite all right. So please put in the numbers that you had earlier, and let's get back up to ten.
MS. ELLIS: We have ten.
DR. GOODMAN: That's ten. And of course our nonvoting members, yes, we have ten, okay. That's question two. Thank you, panel, for getting our steps down. Very good.
We will dispense with question three because its score in question one was only a two rather than the 2.5 or greater. So, question four has to do with the impact on avoidance of the treatment burdens, avoidance of the treatment burdens, so this addresses, how confident are you that there is adequate evidence to conclude that

00214

autologous cellular immunotherapy treatment significantly improves the avoidance of the treatment burdens, and there you see that they are identified as access, delivery or side effects associated with this therapy in the patients who are asymptomatic or minimally symptomatic who have metastatic castrate-resistant prostate cancer. So if you would please -- yes, Ms. Darling?
MS. DARLING: I just want to clarify one point. The assumption, then, is we're comparing it to the alternative treatment or no treatment at that time, so the fact that a significant portion of people down the road go on to not avoiding other treatment is irrelevant, it is, the comparison is to exactly what would have been happening otherwise at the time?
DR. GOODMAN: Well, I'm not sure if that's exactly true, because you will get a treatment at some point, and it may allow you to avoid some of these burdens later on, but it is in comparison to what you would have had, yes, that part is correct. Dr. Steinbrook.
DR. STEINBROOK: Just to follow up on that, I interpreted the question differently, which was looking over the course of treatment as a continuum, as opposed to

simply a point A yes or no. Is there guidance on the proper interpretation of the question?
DR. GOODMAN: Well, what you're going to avoid
00215
is over time. Dr. Jacques, do you have a comment on that?
DR. JACQUES: Hi. I'm Dr. Louis Jacques, the director of the Coverage and Analysis Group. I think the way to interpret this question is simply a patient is going to be managed according to some strategy, and that strategy at some point is going to bifurcate into they will get Provenge or they will follow up some other strategy, and that other strategy may be immediate treatment with something else, that strategy may be watchful waiting until they become appropriate candidates for some other treatment. So in the context of that bifurcation, do you believe that the evidence is adequate to conclude that the Provenge arm of that strategy will in its totality essentially save the patient from experiencing certain adverse effects or other burdens.
DR. GOODMAN: Thanks, Dr. Jacques. Is that consistent with your understanding, Ms. Darling?
MS. DARLING: Yes.
DR. GOODMAN: And Dr. Steinbrook, okay? Any further discussion on question four, anything else that we need to have clarified, any other questions that you have for our presenters that will help inform your response to this? Okay.
Are we missing any important evidence, something that has not been said about the evidence pertaining to
00216
this question that this panel needs to hear before we proceed? Yes, Dr. Potters.
DR. POTTERS: You know, I guess that addresses the abstract that was handed out, and the delayed increase in pain relative to the published results that chemotherapy was given at 7.2 months in the IMPACT study. And I was wondering if there's an answer to the paradox of perhaps disease-related pain versus the toxicity and complications of the treatment that may shed some light on that.
DR. GOODMAN: Why don't you restate your question, Dr. Potters.
DR. POTTERS: Okay. The paradox at least the way that I see it is that you have two things happening simultaneously. You have this abstract that shows that there's a decrease in disease-related pain in the Provenge arm, and yet in the Provenge arm you have an earlier initiation of chemotherapy and then all of the discussion that we had about the complications and toxicity associated with the chemotherapy, so that in one sense you may have complications from toxicity in the range of 18 to 20 percent or higher, versus a decrease in bone pain as a result of prostate cancer.
DR. GOODMAN: This is Dr. Kantoff.

DR. KANTOFF: I hope I can answer your question
00217
correctly. First of all, the quality of life pain data is imperfect in that it's not a complete data set, we did not collect data on pain on every patient in the study. We collected data from the IMPACT study in the first 203 patients until the time of progression and then ceased collecting it afterwards. And as you may remember, and it's in the handouts, there is a splaying of the pain curves after a period of about six months, and a pretty dramatic difference at 12 months. So there's an indication, I would say signal that there is some clinical benefit associated with the administration of the immunotherapy.

The issue with the chemotherapy and the fact that the sipuleucel-T arm got chemotherapy earlier than the patients who received the placebo, I think that's the other end of the question, I think is confounded by the fact that many of the patients who received the placebo went on to receive the crossover which was, delayed things by at least a month, and probably in some cases many months, so it would push back chemotherapy in that arm considerably and mask the time to the administration of chemotherapy, and the benefit of potentially lengthening that in the immunotherapy arm considerably. We don't know that for sure, it's going to be another one of these retrospective post hoc analyses, but that is a reason for
00218
why we don't see a difference between the two arms with regard to the administration of chemotherapy.

DR. POTTERS: I think the better way to say it is what the overall quality of life is, so one may be a tradeoff on less disease-related pain versus, you know, a therapeutic intervention that represents a burden to the patient.

DR. KANTOFF: Right. With regard to the burden of chemotherapy, it's very hard to make a definitive statement with regard to the difference in the two arms, but we have early returns from the 203 patients with regard to the time of the onset of the pain, we have some adverse event data that Dr. Frohlich presented with regard to a couple statistically significant differences between arms in favor of the sipuleucel-T arm, including less anorexia, less fatigue associated with the sipuleucel-T arm.

So we have some signals that there are some symptomatic benefits associated with it, but once again, we didn't collect quality of life data in a systematic fashion in that study, so it's hard to balance that, sort of balance the effect of subsequent therapies with the potential quality of life benefits of the chemotherapy.

DR. GOODMAN: Thank you, Dr. Kantoff. Dr. Frohlich.
00219

DR. FROHLICH: I just want to follow up on the point that Dr. Kantoff made in terms of the delay in chemotherapy, so again, an artifact of the salvage in the control arm potentially leading to a delay, a greater delay in docetaxel in the control arm relative to the treatment arm. I mentioned before, we did an analysis where we looked at time to initiation of docetaxel or salvage, whichever came first, and in that analysis in fact, there was a six-month delay to initiation of therapy in the sipuleucel-T arm relative to the control arm. I think another way to look at this question is clearly, you know, that the label indication for docetaxel overlaps the label indication for sipuleucel-T. So clearly there are some patients, prior to approval of sipuleucel-T, there were patients who had gotten chemotherapy in this situation that are now getting sipuleucel-T, and I think Dr. Petrylak really laid out very clearly the adverse events associated with that choice, to get chemotherapy at that time versus getting sipuleucel-T, and I think clearly there that there's a major difference in the adverse events that those two patients are going to experience at that time.
DR. GOODMAN: Thank you, Dr. Frohlich. Any other questions to help us with regard to our current question four on this matter of avoidance of treatment

00220

burdens? Are we missing anything else, anything that's directly germane to this question that this panel needs to hear before it proceeds to its vote? It looks like not at this point.
So for question four, on a scale of one to five where one is low confidence and five is high confidence, how confident are you that there's adequate evidence to conclude that autologous cellular immunotherapy treatment significantly improves the avoidance of the treatment burdens, for example, access and severe side effects associated with anticancer therapy in this same group of patients, i.e., the ones who are either asymptomatic or minimally symptomatic and who have metastatic castrate-resistant prostate cancer? Low confidence, one, high confidence, five.
And have we got all ten votes yet?
MS. ELLIS: Yes.
DR. GOODMAN: That's great, thank you. And we'll start with Dr. Dmochowski and move to his left.
DR. DMOCHOWSKI: Dmochowski, three.
MS. DARLING: Darling, four.
DR. SATYA-MURTI: Satya-Murti, four.
DR. GOODMAN: Dr. Sokoloff.
DR. SOKOLOFF: Sokoloff, four.
DR. MADAN: Madan, four.

00221

DR. RAAB: Raab, four.
DR. STEINBROOK: Steinbrook, two.

DR. SCHULMAN: Schulman, two.
MS. MOORE: Moore, three.
DR. POTTERS: Potters, three.
DR. MINTZER: Mintzer, three.
DR. MATUSZEWSKI: Matuszewski, four.
DR. FULLER: Fuller is not a liar this time, on the high side, five.
DR. GOODMAN: Thank you, Dr. Fuller, and is that everyone? It looks like it is now 3.1. So that deals with our three areas that were first enumerated under question one with regard to survival; for disease-related symptoms, which we did not address because of the lower score on one; and the avoidance or minimization of the burdens. So we have now completed questions one, two, haven't addressed three, or did not address three because of low vote, and question four, so we can now proceed to question five.
Now, we're moving from that original set of indications which are often referred to as the FDA-labeled indications to the unlabeled indications, and the question before us now is, how confident are you that these conclusions, that is the conclusions that you reached in your earlier questions, how confident are you that these

00222

conclusions are generalizable to unlabeled use in those three categories, unlabeled use? And the first category, A is patients whose prostate cancer has not metastasized; B is patients who have metastatic castrate-resistant disease and symptoms more severe, more severe than minimally symptomatic; and C, patients who have metastatic prostate cancer but who have not failed hormonal therapy. Okay. So those are the three main unlabeled indications there. Dr. Satya-Murti.
DR. SATYA-MURTI: So, is this based on only the evidence we've heard so far today, not on biologic possibility or expertise, because there are lots of experts here in this field?
DR. GOODMAN: Do consider all the evidence that's been presented and you've heard about today. I would not ask or require you to forget everything else you might know about biology, physiology, molecular biology or whatever else you might have in mind, in your case neurology. So I would not necessarily set aside your separate knowledge of those, but we're most concerned about the evidence that has been presented to us here today. Is that okay, Dr. Satya-Murti?
DR. SATYA-MURTI: Yes.
DR. GOODMAN: Any questions from the panel, do we have anything else you need to hear about in order to

00223

help you answer this question about these three unlabeled uses, any questions for our presenters? I don't see any. Let's look at A first. Is there anything about A, which is patients whose prostate cancer has not

metastasized, is there anything else that this committee has not heard heretofore that it needs to hear about this question? I don't see it. Okay. Let's proceed to vote then, with regard to 5.A. This is, how confident are you that these conclusions are generalizable to unlabeled use in, A, patients whose prostate cancer has not metastasized? It looks like we got ten quick votes there. Thank you, all ten, Ms. Ellis?
MS. ELLIS: Yes.
DR. GOODMAN: Very good. Let's start with Dr. Raab and move to his right, and please read off your votes.
DR. RAAB: Raab, two.
DR. MADAN: Madan, two.
DR. SOKOLOFF: Sokoloff, one.
DR. SATYA-MURTI: Satya-Murti, one.
MS. DARLING: Darling, one.
DR. DMOCHOWSKI: Dmochowski, one.
DR. FULLER: Fuller, one.
DR. MATUSZEWSKI: Matuszewski, one.
DR. MINTZER: Mintzer, one.

00224

MS. MOORE: Moore, two.
DR. POTTERS: Potters, one.
DR. SCHULMAN: Schulman, one.
DR. STEINBROOK: Steinbrook, one.
DR. GOODMAN: Great, thank you all very much, and these were all reported. Thank you.
Let's proceed, then, to 5.B. 5.B concerns the unlabeled use in patients with metastatic castrate-resistant disease and symptoms more severe, more severe than minimally symptomatic. So one is low confidence, five is high confidence. How confident are you that the conclusions discussed earlier in the earlier questions are generalizable to this population under B, those that have symptoms more severe than minimally symptomatic?
Has anyone not voted that they know of? All right, Ms. Ellis, I think we're missing -- oh, there it goes. So, if you'd put down your little gadgets, the mean vote here is 1.5. Dr. Satya-Murti, we'll start with you and move to your right.
DR. SATYA-MURTI: Satya-Murti, one.
MS. DARLING: Darling, one.
DR. DMOCHOWSKI: Dmochowski, one.
DR. FULLER: Fuller, one.
DR. MATUSZEWSKI: Matuszewski, two.

00225

DR. MINTZER: Mintzer, two.
MS. MOORE: Moore, two.
DR. POTTERS: Potters, two.
DR. SCHULMAN: Schulman, one.
DR. STEINBROOK: Steinbrook, one.
DR. RAAB: Raab, one.

DR. MADAN: Madan, one.
DR. SOKOLOFF: Sokoloff, one.
DR. GOODMAN: Thank you all very much. Okay. Let's proceed to question 5.C. Once again, this pertains to the unlabeled use, in this case under C. It's for patients who have metastatic prostate cancer but who have not failed, have not failed hormonal therapy. Patients who have metastatic prostate cancer but who have not failed hormonal therapy. Please rate it on a one to five scale, one is low confidence, five is high confidence. Oh, pardon me. I failed to ask the question, excuse me, my error, any questions on the part of our panel, and I do apologize for not saying that, any questions that our panel has for our presenters on this? And is there anything we should have heard that we haven't heard from our presenters? Okay. Do proceed then. I see a mean of 1.2 for that one. Let's start with Dr. Schulman and move to his right.
DR. SCHULMAN: Schulman, one.

00226

DR. STEINBROOK: Steinbrook, one.
DR. RAAB: Raab, two.
DR. MADAN: Madan, two.
DR. SOKOLOFF: Sokoloff, one.
DR. SATYA-MURTI: Satya-Murti, one.
MS. DARLING: Darling, one.
DR. DMOCHOWSKI: Dmochowski, one.
DR. FULLER: Fuller, one.
DR. MATUSZEWSKI: Matuszewski, two.
DR. MINTZER: Mintzer, one.
MS. MOORE: Moore, two.
DR. POTTERS: Potters, one.
DR. GOODMAN: Thank you very much. Let's proceed now to question six, and as I mentioned earlier today, this is yet another question that we generally ask at the MedCAC meetings, and that has to do with the generalizability to community settings and to certain demographic groups. So question six asks, how confident are you that these conclusions, that is, the conclusions reached heretofore, are generalizable to, A, community-based settings, and B, patients belonging to demographic groups that may have been underrepresented in the enrolled clinical trial populations. And just again, the point about community-based settings, and this is true for so many kinds of

00227

interventions, not just this one, not just things in oncology, but across many disease areas, we often see that things work to a certain level in RCTs, randomized control trials, where they've very carefully managed studies, and things don't really play out in the real world in community settings that way. And in some instances our expectation that something will play out in community settings is it will be the same that happens in the

clinical trials, and sometimes they don't play out that way.
And so the purpose of this question is for the folks here at CMS to get the panel's insight with regard to how, the extent to which we've heard about the evidence thus far is applicable to broader community settings because, after all, nearly all Medicare is delivered in community settings. So, any points with regard to 6.A, the community-based settings, any questions? Yes, Dr. Sokoloff.
DR. SOKOLOFF: I just wanted to clarify. One of the earlier presentations said that over 50 percent of IMPACT was from the community; is that right?
DR. KANTOFF: That is correct, it was a quick presentation, but over 50 percent of patients were treated in community-based settings.
DR. GOODMAN: Dr. Kantoff, when you say

00228

community-based settings, can you describe to us how you know a community-based setting is or isn't, and it just might help us.
DR. KANTOFF: Many of the centers that administered the protocol were smaller urology practices, some medical oncology practices, but not academic settings.
DR. GOODMAN: That's very helpful, thank you. Dr. Sokoloff, did that help?
DR. SOKOLOFF: Yes, thank you.
DR. GOODMAN: Any other questions with regard to community-based settings? Dr. Mintzer.
DR. MINTZER: I have a question. What I wanted to know, does this mean that the results of the therapy delivered in the community-based setting would be similar, or that patients will be able to access the therapy if they're in the middle of Alaska or something?
DR. GOODMAN: I believe it's the former, Dr. Mintzer, and what you want to do is sort of based on the answers that we've given to this point, does that apply to the community-based settings. Dr. Satya-Murti.
DR. SATYA-MURTI: I would think it's both actually. I'm wondering if Cancer Centers of America has changed. I am putting them in the community rather than the academic, the nationwide centers. Even if it weren't,

00229

I'm assuming it's both.
DR. GOODMAN: Dr. Frohlich, would you like to comment?
DR. FROHLICH: If I could summarize an answer to both, first in terms of the results, as I presented on my slide, 55 percent on the three studies, patients were treated in community-based settings and the hazard ratio was comparable to the overall treatment effect as well as the adverse effect profile.
In terms of access, as I noted, we're rapidly

increasing our capacity, anticipate having a network that will reach throughout the entire country so that all patients will have access to it regardless of what their geography is.

DR. GOODMAN: Thank you, Dr. Frohlich. Other points here? I see none. Does anyone else have anything else to comment that's germane to this question about generalizability to community settings, anything else this panel needs to hear before it proceeds to vote, other evidence? I see none.

Dr. Satya-Murti, do you want to talk about B before we vote on A? Let's discuss that, and then we'll vote on A and B.

DR. MATUSZEWSKI: Cliff, I have a quick question.

00230

DR. GOODMAN: Sure. Dr. Matuszewski.

DR. MATUSZEWSKI: I'd like to just add in the IMPACT study and all the other studies, were they recording the time of when they administered the Provenge, so that, again, I think it has an 18-hour window from when it's prepared, and would that expectation be then that in more broad use that sort of diligence of applying it would have occurred.

DR. FROHLICH: That's included in the FDA label, that product will not be expired, or should not be infused after product expiry. So it's clearly labeled on the product, what time the expiry is, and it can't be infused after that time.

DR. MATUSZEWSKI: As a pharmacist I can tell you that sometimes when something is expired by an hour, if it's an antibiotic, you just slap another label on it and give it another three hours. So, is that related to some precipitous decline in efficacy?

DR. FROHLICH: I mean, we have data actually extending beyond 18 hours, but our current FDA label is for 18 hours based on stability studies. We actually have stability studies going beyond that to 24 hours, so no, there's no precipitous decline after 18 hours.

DR. GOODMAN: Thank you. The panel was pretty quick on the draw, faster than I was in calling for the

00231

question, so everyone has voted, I don't see any need to revote at this point, so all ten of ten have voted, correct, Ms. Ellis?

MS. ELLIS: Yes.

DR. GOODMAN: Let's start with Dr. Potters and move to his left in declaring the votes.

DR. POTTERS: Potters, five.

MS. MOORE: Moore, five.

DR. MINTZER: Mintzer, four.

DR. MATUSZEWSKI: Matuszewski, four.

DR. FULLER: Fuller is three.

DR. DMOCHOWSKI: Dmochowski, three.

MS. DARLING: Darling, four.
DR. SATYA-MURTI: Satya-Murti, five.
DR. SOKOLOFF: Sokoloff, five.
DR. MADAN: Madan, five.
DR. RAAB: Raab, five.
DR. STEINBROOK: Steinbrook, four.
DR. SCHULMAN: Schulman, four.
DR. GOODMAN: Okay. Thank you very much, all ten votes are in and all declared. Thank you. Let's proceed to 6.B, and 6.B addresses the generalizability to patients belonging to demographic groups. Let's not vote just yet. Let's make sure we have a chance for discussion as needed. Patients belonging to

00232

demographic groups that may have been underrepresented in the involved clinical trial populations, how confident are you that the results are generalizable to that group? Dr. Madan.
DR. MADAN: I think it would be helpful for the panel if perhaps Dr. Petrylak and Dr. Kantoff commented as to how minorities, underrepresented groups in this trial compared to other Phase III trials.
DR. GOODMAN: I would invite as well Dr. Mark, if he has comments on these questions as well, because I know he looked at patient populations. Let's start with Dr. Kantoff.
DR. KANTOFF: I think the straightforward answer is that it is comparable to other studies in this case, about six percent of patients were a minority, so it's not atypical, it's fairly representative of this phase in these kinds of clinical trials.
DR. GOODMAN: What percentage was that?
DR. KANTOFF: Six percent, 6.0 percent.
DR. GOODMAN: Thank you.
DR. SCHELLHAMMER: And if I remember correctly, this trial was very similar to the SWOG study and the percentage of minority populations was probably better than TAX 327.
DR. GOODMAN: And you referred to the SWOG study

00233

before, that's Southwest Oncology?
DR. SCHELLHAMMER: That's the 9916 trial that was the supplemental trial for Taxotere approval.
DR. GOODMAN: Thank you. Dr. Mark.
DR. MARK: I would say that the studies themselves give you no information given the small size of the minority groups, and that any such decision or judgment that you might make would be based on understanding of the differences in biology, if there are any, between the studied populations and the underrepresented. So the studies themselves do not provide that confidence, but it would be based on the basic science understanding of the disease in different populations.

DR. GOODMAN: So the studies did report to some greater or lesser extent when there were certain demographic groups, but in terms of --
DR. MARK: But in terms of analyzing for a measurable difference in response or patient treatment benefit, unfortunately the size of the studies are too small to make a meaningful decision about whether they are the same or different, and you would make, to me, you would make such a decision based on your understanding of prostate cancer in these different populations, information outside the studies.

00234

DR. GOODMAN: Thank you, Dr. Mark. We're going to try to stick with the evidence we've got to a great extent. Dr. Satya-Murti had a comment first.
DR. SATYA-MURTI: This is interesting. Demographic is a bit of a flexible term. I know what you mean and there is no substitute for the record right now, but African-American responses were much better. Still the numbers were low, and there was hardly any Asian representation. And then again, what was the Hispanic representation? And this is all becoming a melange pretty soon, and may be a moot question in 50 years to come, but those two groups are just not represented here at all.
So the question comes up as Dr. Madan asked about recruiting for these patients. I think the cancer incidence might be higher, but they just weren't coming forward to whatever methods of recruitment you were using.
DR. FROHLICH: Yeah. It's been a challenge in all advanced cancer trials and prostate cancer trials, and I think the experience that we had was comparable to what was seen in other recent prostate cancer trials. We certainly are making efforts to try to increase that, particularly in our registry outreach through some of the African-American support groups to try to improve our knowledge base.
That said, there was still the data that I

00235

presented on the subgroup of African-Americans. As you noted, the treatment effect appeared quite large, small sample size, but what I would clarify is that the upper bound of that 95 percent capturable was still way below one, so, you know, the possibility that those patients are not benefitting from treatment is well less than five percent.
DR. GOODMAN: And how many patients were there?
DR. FROHLICH: It was 5.8 percent of the total, so I think it was roughly 43 patients.
DR. GOODMAN: Thank you.
DR. FROHLICH: And in terms of the other question about other minority populations, the total was 10 or 11 percent, so the difference between six percent and 11 percent was other Hispanic, Asian populations. And if you look at the overall population, same thing, in a

subgroup analysis the treatment effect appears to be consistent with the overall treatment effect.
DR. GOODMAN: Other questions on this matter of 6.B? Dr. Madan.
DR. MADAN: (Inaudible, off microphone.)
DR. GOODMAN: And Dr. Madan, it may be your mike or your voice, but can you speak directly into the microphone, and repeat that question?
DR. MADAN: Sure. So just to follow up to the

00236

point that was made about different biologic responses in different minority subgroups, I'd like to ask Dr. Gulley if he's aware of any reason or any known evidence that the biological response would vary in the underrepresented populations.
DR. GULLEY: Well, we have done a lot of immunologic assays in our clinical trials of immunotherapy, and we have not seen a large variation based on the ethnicity or any other demographic features.
DR. GOODMAN: Thank you, Dr. Gulley. It is interesting to note that at a time when many of us care a lot about personalized medicine that in some instances there's not a lot to go on with regard to subgroup analyses and trying to make medicine more personalized or more individualized, and that's one good reason for asking this question at this point. Any other comments that the group has? Okay. Dr. Satya-Murti.
DR. SATYA-MURTI: Not only that, but you know, other drugs have a particularly different effect on Asians, so there are known differences, ethnic and other differences, so your point is well taken, but it's another area that's underexplored as a whole.
DR. GOODMAN: Great, thank you very much. Other comments or questions? Is there any other evidence that you haven't put forth that this committee needs to know at

00237

this point for this question? Okay. Seeing none, let's vote on question 6.B, how confident are you that these conclusions are generalizable to patients belonging to demographic groups that may have been underrepresented in the enrolled clinical trial populations? One is low confidence, five is high confidence.
It looks to me like all ten votes are in. Ms. Ellis, I see a 2.9 as the mean, correct?
MS. ELLIS: Yes.
DR. GOODMAN: And Ms. Darling, let's start with you and move to your right.
MS. DARLING: Darling, two.
DR. DMOCHOWSKI: Dmochowski, three.
DR. FULLER: Fuller, four.
DR. MATUSZEWSKI: Matuszewski, three, and I think we can definitely say that it is not appropriate for females.
DR. GOODMAN: We can always depend on Dr.

Matuszewski for those timely comments.
DR. MINTZER: Mintzer, three.
MS. MOORE: Moore, three.
DR. POTTERS: Potters, four.
DR. SCHULMAN: Schulman, three.
DR. STEINBROOK: Steinbrook, three.
DR. RAAB: Raab, four.

00238

DR. MADAN: Madan, four.
DR. SOKOLOFF: Sokoloff, four.
DR. SATYA-MURTI: Satya-Murti, one.
DR. GOODMAN: All right then. So Ms. Ellis, I believe that puts us through the voting questions; is that correct?
MS. ELLIS: Yes.
DR. GOODMAN: Okay. What instruction do you have for us that may involve signing our little pieces of paper here, anything else?
MS. ELLIS: No. I'm going to come around and collect everyone's pre-score sheet and their recorder, and then you can go on to the discussion questions.
DR. GOODMAN: We still have three discussion questions. As Ms. Ellis is going to pick up your score sheets, do make sure that you sign your score sheet at the bottom, panel, there's a place where it says name, your signature will go there.
Now, we have three very important discussion questions here, they're not voting questions, they're discussion questions. Why these are very important is that as CMS pursues any national coverage analysis, it of course needs the input you've just given on your votes, but it may also need in some instances your views on evidence gaps and how they might be filled. This of

00239

course is of interest not just to CMS but to certainly other stakeholders here in the United States, and abroad frankly.
And we've heard quite a lot today about what type of studies, how many of what type of studies, various endpoints, primary and secondary endpoints, strengths and weaknesses, alternative study designs, what populations have been covered and so forth, and it would appear that this is not, the book is not full, shall we say, on the body of evidence pertaining to this intervention.
So with that, I want to move to discussion question number seven. And it has to do with identifying patients who are more likely or less likely to respond favorably. And this has to do with letters A through H, it has to do with certain factors that may be prognostic or otherwise determinative of how patients fare here.
I'll just read the question for the record. Do you believe that there is adequate evidence to identify patients who are more likely or less likely to respond favorably to autologous cellular immunotherapy treatment

based on pretreatment evaluation of any of the following factors?
And panel, you will recognize many if not all of those factors that were noted in some of the presentations today with regard to things that may be predictive or
00240
prognostic for response, and you will see A through H listed. Sites or number of metastases as detected through imaging. Gleason score. Alkaline phosphatase reading. Hemoglobin. Serum LDH. Serum PSA, prostate-specific antigen. Pain associated with metastatic castrate-resistant prostate cancer, that first group of whom you spoke. And other.
So who would like to begin the discussion with regard to the adequacy of the evidence for the pretreatment valuation of these factors? I'll probably pick on someone if no one puts their hand up. Dr. Matuszewski.
DR. MATUSZEWSKI: Let me kick it off, that I do not believe there is adequate evidence to identify patients more or less likely to respond, and part of that is drug use knowledge as you use the agent, so some of this will come to fruition looking at registry data as you enter 1,500 or ultimately 2,500. Some of it may come in a couple years from doing retrospective database reviews of other payers claims databases in terms of survival. There may be factors that aren't listed there that may have an impact such as smoking, such as nutritional status, for all we know socioeconomic status.
So these are all, you know, great questions, they allow you to narrow down who the therapy's going to
00241
work for or not, but rarely is this known except for maybe five or ten years after a substantial experience with the drug, and then again, very proactive looks at very rich data sources that have all this information embedded in them. So with the advent of electronic medical records and the digitalization of health care, this sort of exercise may be able to be done sooner rather than later, to really fine tune this therapy.
DR. GOODMAN: Thank you, Dr. Matuszewski, points well made. Yes, Dr. Sokoloff.
DR. SOKOLOFF: Without being redundant, and I agree completely. The other thing, too, that I would imagine Dendreon and other investigators will do is start looking at molecular markers and whether it's a PCA3, or whatever genes to help better stratify who's going to benefit the most from it, and that is what the registry should be for, and hopefully will be used for.
DR. GOODMAN: Great, thank you. Dr. Schulman.
DR. SCHULMAN: I guess I want to take a different view, that since we have no biomarkers that this therapy works, the only thing you would be able to measure is survival, and in a world that's increasingly

confounded, so I think you will have no ability to direct the therapy going forward, because we have no idea what the response is. 80 percent of these people went on to

00242

further therapy in seven months, so I'm not sure what you would pick to try to predict on. And on the other hand, you have a randomized trial that began on survival with many type of similar patterns here, so I don't think that's possible.

DR. GOODMAN: That's a very important point, Dr. Schulman, and I would ask you, in part because your mike isn't that close, could you restate in a more brief fashion, if you would, the point you made with regard to the ability of the data collection mechanisms through study designs to pick up this evidence?

By the way, Dr. Frohlich, I will be glad to hear from you in a moment, but we're still talking to the panel, so please, I'll ask you to stand up when we're ready. Thank you very much.

Dr. Schulman.

DR. SCHULMAN: Yeah, sorry about the microphone. The issue is we have no marker of response. We didn't have, we eliminated disease progression and we eliminated biomarkers, at least that's what Dr. Mark told us, so I don't feel good about assessing who responded to this therapy. The other disease progression endpoints that we talked about, there's no difference, so in trying to predict who's going to respond to this, I can't tell response except in terms of overall survival, and a

00243

registry won't be able to help me assess that. And on top of that, we've heard that a variety of new products are coming to the marketplace, and so the treatment pattern of people will never again be identifiable, and so I would say that there's probably no potential to do this.

DR. GOODMAN: So, Dr. Schulman is wondering whether a registry design will be sufficient to detect any relationship between these pretreatment factors or risk factors with regard to their impact on outcome, it would be hard to kind of detect that in a rigorous way is what you're saying. Okay. Thank you. It was Dr. Madan, and then Dr. Mintzer. Dr. Madan.

DR. MADAN: I think it's important to note that the biomarker, the search for biomarkers for the origin of response are ongoing. As of this time it's not clear what such a biomarker is, but as an ongoing process it will be reasonable to feel that that would be investigated rigorously with greater use of this agent, as well as was discussed earlier, other genetic polymorphisms. So the absence of such markers now does not preclude the possibility of determining that with greater use of this agent.

DR. GOODMAN: Point well made, thanks, Dr.

Madan. Dr. Mintzer, I believe, sir.

00244

DR. MINTZER: Just to amplify on that, you might be able to use the databases to develop prognostic markers for outcomes, but unless these predictive markers come to fruition, I don't see how we are going to be able to answer that in the future at all.

DR. GOODMAN: You do not see how we will be able to answer that, okay. Yes, Dr. Fuller, and then Dr. Steinbrook. Dr. Fuller.

DR. FULLER: When I started going through this stack of stuff here a week or so ago I was really sad that everybody seemed to punt on the issue of quality of life, well, we can't look at that, we don't know how to express it. I'm not in a position of wanting to tell you how to do your business, but when we do the registry, you could easily develop an automated system where the patient would be called and asked questions that they could respond to on their key pad on the phone, and you could make the questions anything you wanted, but I believe there probably is a way of slicing and dicing their life after you do your thing so you can figure out whether you really made a difference in the quality of life short of just making them live longer. Just a suggestion.

DR. GOODMAN: Thank you for that point, quality of life. Further discussion on these factors? Dr. Steinbrook, yes.

00245

DR. STEINBROOK: Just to follow up, and I suspect this is going to be a question for Dr. Frohlich. My understanding is that the registry, again, correct me if I'm wrong, comes from the FDA's concern about cerebrovascular adverse events and getting a better handle on that. From the standpoint of this question and our discussion, it would seem to be a missed opportunity to not make the registry as rigorous as possible, with some other information which could be collected without putting another burden on it or making it too expensive. But is the registry set up to answer some of these things that we're getting at, because I think it would be good if it could try to.

DR. GOODMAN: Great, thank you. Dr. Frohlich, and thank you for your patience, Dr. Frohlich.

DR. FROHLICH: In terms of biomarkers, we do plan to do some ancillary protocols associated with the registry to try to address some of these issues. I will say although the data is preliminary, we do have data published in the New England Journal. We noted, for example, that there is a correlation between immune response, (inaudible) antigen, and a correlation of that with overall survival. We also see transient cellular response, which was well presented in some of this data at the ICTC meetings.

00246

So we are very encouraged that we're seeing correlations between new parameters of overall survival, as well as the product brand which we've discussed before, total number of cells, degree of antigen cell activation, absolute number of antigen-presenting cells, and correlation with overall survival. So in terms of drug development, these are things that we plan on using to guide our development of making the therapy even better and applying this technology to other disease states.

DR. GOODMAN: Thank you, Dr. Frohlich. Dr. Satya-Murti.

DR. SATYA-MURTI: That confused me. You said cellular response is not an indicator. I thought earlier this number of CD54, the absolute count was a prognosticator.

DR. FROHLICH: I said a number of these different cellular parameters, so antigen-presenting cell activation, absence of antigen-presenting cells, and total number of cells do correlate with overall survival, and a number of those even after adjustment for baseline prognostic factors. And those are things that one can study in a single arm trial, so we clearly have seen a difference between immune responses in those who get the product and those who don't get the product, so now what we've started to do at the next level is does the

00247

magnitude of the immune response correlate with overall survival, you don't necessarily need a control arm for that, so that is something that you can study in single arm trials like registries.

DR. GOODMAN: Thank you. Dr. Madan, on this point?

DR. MADAN: Yes. I think it's also important to point out that this is a relevant question throughout the field of oncology and the chemotherapy targeted molecular inhibitors, and perhaps one of the best examples is a drug, tamoxifen, used in breast cancer, where only recently have we, in the past decade or so, have realized that there is a subset of the population who doesn't respond as well to that drug, so this is an ongoing question throughout medical oncology.

DR. GOODMAN: Dr. Petrylak, yes, sir.

DR. PETRYLAK: I think it's an important point to add that we have yet to identify a prognostic marker for docetaxel therapy or for second line hormone therapy, so we still don't have any of these treatments molecularly characterized as to what the markers of progression are, or response.

DR. GOODMAN: So it sounds like there's some work needed to be done at this point.

DR. PETRYLAK: All across the board.

00248

DR. GOODMAN: All across the board, thank you. Okay. Any other comments about this discussion

question? It sounds as though there probably is not adequate evidence to identify patients based on these factors and a lot of work needs to be done. It sounds as though the registry that was requested by the Food and Drug Administration which will have up to 1,500 patients will provide at least partial answers to these. But to Dr. Schulman's point, the study design that's inherent in the registry may not reveal some of the factors that we would like to find. Any other comments at this point on question seven? Good, thank you. And I hope that our answer to that discussion question will be helpful to CMS and others.

Let's proceed to question eight, and I know that we've already addressed this somewhat, including our immediately previous conversation as well as earlier in the day. And this regards, and let's make sure that question eight is up on the board, please, in the back of the room. I'll proceed to read it, and I assume that very soon it will appear. Question eight asks, what significant evidence gaps exist regarding the health outcomes attributable to autologous cellular immunotherapy treatment for two aspects, one, the FDA-labeled indication, and second, for off-label use.

00249

So this is about any evidence gaps that we might perceive at this point regarding health outcomes, and we've talked about those, attributable to this therapy for those two conditions, FDA-labeled and off label, what are the main evidence gaps? Panel, anything you want to start out identifying? Dr. Raab, I'll pick on you.

DR. RAAB: Well, we still don't know long-term follow-up. We had a data cutoff point in the trial, so we don't know eventual survival, we don't know other treatments that have been offered, and so that's kind of a blind spot.

DR. GOODMAN: Okay, long-term effects, thank you. Dr. Steinbrook.

DR. STEINBROOK: I guess this would be considered a problem we're having, because there are now several treatments which weren't FDA-approved if we go back several years, and another one it sounds like is on the horizon, but it seems to me that there's a great need to figure out the best way to coordinate this immunotherapy with chemotherapy. There may be certain patients who for personal reasons and choices don't want chemotherapy, we've heard about that, but certainly I would think that as a physician or a patient where the thought was chemotherapy, but what's the best time and how do I coordinate it if there's a big evidence gap, and are

00250

there ways to standardize the delivery of chemotherapy on a trial basis which could help to address that.

DR. GOODMAN: That's very helpful. Other points? I would indicate that for the off-label uses it's

almost all a gap. There's, based on what we heard today and based on the ratings of the panel, there's just not very much to go on with regard to off-label uses. And of course a lot of that is understandable given the history of development here and the purposes of those studies, but there's just an extraordinary evidence gap, just about all gap when it comes to the off-label uses.

Dr. Schulman, I do want to ask you, though, because you made the point about the registries. Are you thinking that there should be other study designs to supplement a registry, or do you think we're going to have to kind of get what we can out of a registry, or are there other ways to gather this evidence?

DR. SCHULMAN: I think that there, actually I think we have pretty good evidence of mortality, we've observed almost the entire mortality of the cohort that was treated, so that obviously we have a much better estimate than say in cardiology or a lot of other therapeutic areas. Over 70 percent of the patients had unfortunately passed away by the time the database was closed, so we do know a lot about that.

00251

We also seem to know a lot about at least the requirements for additional therapy and morbidity of this disease that contributes to the deaths of these people. We don't have that statistically, we just have windows into that, and I think that's really going to be critical. Patients are going to have to make very complicated treatments, for any prostate cancer patients make very complicated treatments, there's a variety of different alternatives out there and not good comparative data. But these patients in particular are going to have to decide how they want to sequence available therapies. And it's not an issue that we're going to talk about today, but there's a huge burden on the individual patient, and how many of these things can they afford to do, because there's a fairly significant cost sharing on the patient side. So are they going to do one, two or three of these advanced therapies and be able to afford that? So I think anything that would help them understand how to sequence, how much of a benefit is this therapy, this strategy starting with this compared to a strategy of watchful waiting and delaying for something else, I think is going to be fairly useful.

DR. GOODMAN: Thank you, Dr. Schulman. Ms. Darling is next.

MS. DARLING: This may not be the right place to

00252

raise it, but we just quickly were talking about evidence of off-label use and the larger question is should we have off-label use, and if so, under what circumstances, before you even worry about whether you need evidence for it, it seems to me.

DR. GOODMAN: Thank you, Ms. Darling, a point

well made. Dr. Matuszewski, did I see your hand up?
DR. MATUSZEWSKI: Yes. I think there is a real opportunity probably, to look at patients who have survived, continue to survive and do well on the therapy, and what is different about them, is it just an acute response, and maybe being a prognostic factor,there is some modification you can make to the patient before administering the therapy or during this therapy. So again, the long-term survivors who continue to do very well post those three doses, they are an interesting subgroup to continue further studies on.
DR. GOODMAN: Point well made. Thank you, Dr. Matuszewski. Dr. Satya-Murti.
DR. SATYA-MURTI: What is a minimal clinically important prolongation in survival, is it five years as in traditional cancers, solid tumors, acceptable? Is any survival better, one month? It's a question applicable across the board to all advanced cancers, but that is an evidence gap not just for this particular metastatic

00253

prostate cancer but for any oncologic issue, particularly when you sit on many of these panels which discuss nononcologic devices and treatments, you start to wonder, what would that be. It may not be the purview of a panel like this to discuss, it's more societal, but that question keeps coming up.
DR. GOODMAN: A point well made, that question's unanswered at this point.
I would add with regard to evidence gaps that there's a great big evidence gap now between the number of people that have been involved in clinical trials to date, which I believe numbers in the high hundreds, and the, what, 220,000 new cases every year in the United States and the 32,000 deaths that occur due to this. So we've got data, and largely not in entirely rigorous studies for hundreds of people, and we've got 220,000 new patients who are diagnosed with this thing, so we need a lot more data to address this extraordinary need in the Medicare beneficiary population and we're way behind the curve on collecting data, whether it's in RCTs or registries or anything else.
I recall the point, I believe made by Dr. Fuller, reminding us that prostate cancer is not a single disease, it manifests in many different ways, and at least thus far with the data that I think we've seen,

00254

we don't know very much at all about how this therapy, how patients with different forms of prostate cancer would fare with this therapy, we just don't have the data, so we have a long way to go. But there are a lot of people that are victims of this condition from whom we might learn about how well this works in real practice and see what the true benefits are.
Dr. Schulman.

DR. SCHULMAN: I would say one other piece of data that we got all day was that it was very easy to identify patients who actually met label criteria, it was told to us several times. But it's not clear to me that we have a checklist that CMS could use to say a person's on label or not and meet those criteria, and to make sure, given the gap between the labeled and non-label applications, that there's not any creep out there in terms of diagnosing patients, or inappropriately treating patients with this therapy.
DR. GOODMAN: So the implication then is what, Dr. Schulman?
DR. SCHULMAN: Some tool to make sure that the patients who are getting the therapy are getting it on label.
DR. GOODMAN: Thank you for that point. Dr. Madan.

00255

DR. MADAN: Just going back to the point of how long a survival is significant or important. I think philosophically that's beyond this panel, but I think in terms of clinically relevant in metastatic castrate-resistant prostate cancer, we do have several trials that do tell us how agents have improved survival in other approaches, and I think we've seen today data presented on how that's roughly two-and-a-half to three-and-a-half months with different modalities, but I think that's some of the context that we can use to assess the survival data presented with this agent.
DR. GOODMAN: That is a very good point, thank you, and it will be helpful for future data collection. Dr. Raab, were you about to comment?
DR. RAAB: It was nice to hear about the FDA-required registry here, and then there will be another product and maybe it will require a registry, and then another one with another one, and I'm wondering about the interrelationship with the various registries.
DR. GOODMAN: That's a good question. I'm aware that under our CER funding, comparative effectiveness research funding, there's going to be a registry of registries, as I recall, so someone's going to be tasked with tracking these multiple registries. I don't know if they're going to involve the FDA ones, though.

00256

DR. RAAB: Well, where I'm going is here in this context of product-specific registries, and I'm wondering if we need a disease-specific registry.
DR. GOODMAN: Ah, point well made. Sometimes people get into a registry because they've got a condition, and sometimes because they get a particular intervention. Good point.
Other points or questions with regard to this matter of the significant evidence gaps from the panel? Any of our presenters have anything to say about important

evidence gaps that might need to be filled here, anything that we haven't heard thus far today that will be helpful for addressing this question?
DR. RAAB: Well, it was raised with the previous question -- sorry to jump back in.
DR. GOODMAN: That's all right. Dr. Raab.
DR. RAAB: The issue was raised earlier about quality of life in this area, and I really think that what we're really talking about from the testimony we've heard has been the impact of treatment that works on individual lives, and we don't have a metric yet in this area, and I think that would be a major contribution.
DR. GOODMAN: Yes, it was. And speaking of this, Ms. Moore, do you want to add to your earlier comment about understanding quality of life better, or do

00257

you think we've got it covered. You raised that earlier.
MS. MOORE: Yeah, I did in relation to long-term effects that may be coming up and I think the registry, from your comment, that will probably capture that. But the quality of life beyond side effects is an area that I think we have to address, and as was said previously, we could develop questions that would capture that real simply, and it's important.
DR. GOODMAN: Thank you, Ms. Moore. Yes, Dr. Potters.
DR. POTTERS: One of the limiting factors is we're taking a disease with 220 or greater thousand men and just dealing with the 20,000 that are dying, so we're also dealing with a disease that has declared itself in one way, shape or form, and is a potentially killing disease. And so there may be, I mean, there's a huge gap in terms of our ability to predict patients who present with very high risk disease de novo, up front, who have a very high likelihood of developing metastatic disease with the burden of disease, which is initially considerably less where the impact potentially could be more positive, where an outcome such as disease progression or other types of biomarkers may actually pick up significance.
DR. GOODMAN: Thank you, Dr. Potters. Any other comments or questions on discussion question number eight?

00258

This has to do with your observations about adequacy of evidence and filling evidence gaps with regard to health outcomes for this therapy? No further comments do I see. So, let's move to question nine. Interestingly enough, I believe we have already discussed this in part, but let's just make sure we've got it covered. Question nine concerns what clinical study designs would adequately address any evidence gaps. I know that we've discussed registries a bit and different sorts of them, there has been some discussion, and I may return to Dr. Schulman with regard to the extent to which we can do further sorts of clinical trials, but any other comments about the

clinical trials that would help us get at these evidence gaps that were identified earlier? Dr. Schulman, I will pick on you one more time, sir.

DR. SCHULMAN: Obviously Medicare will have the ability to track every patient who's on therapy going forward, there's something called a chronic condition warehouse where they can do that. They won't have information on disease stage, so they would have to merge that with some clinical information in order to make some inferences about whether or not the Medicare population is actually getting the benefit that we would hope they would get from this therapy, whether we're seeing survival of, you know, the median survivals that we're talking about in

00259

the Medicare population from the initiation of the therapy on. So I think that you would have to couple claims data with some clinical data at the time when a patient got therapy for Medicare to be able to track, to see over time.

They did this with erythropoietin when erythropoietin first came out, and found there were significant problems with erythropoietin in the Medicare population, and that was in terms of dosing. But obviously there would be, it would not be that hard to do, and there would be a huge advantage to putting that in place. It could couple with or complement the FDA group as well in an attempt to figure that out.

DR. GOODMAN: That's very specific and helpful information, directly pursuant to the question, and very helpful. Dr. Madan.

DR. MADAN: I think, based on the gaps that we all acknowledge, I think that there will be investigations ongoing looking at earlier disease states, not the metastatic castrate-resistant, but maybe the pre-metastatic or pre-castrate-resistant population, and I think the other area of investigation will be combination therapies, and I'm sure there's a lot of those trials that are already either ongoing or in the final stages of planning as we speak.

00260

DR. GOODMAN: Dr. Madan, since you put it on the table, maybe you can help us out a little bit. As Dr. Schulman and several other panelists have noted, including yourself, the array of treatment options is getting larger all the time. The epidemiology may be changing. A lot of us baby boomers are at risk. My x-ray vision tells me there are quite a few prostates here at this table, and we might care about that. So from a standpoint of understanding that we've got this moving target problem that's changing rapidly, how do you design studies or other data correction mechanisms to provide valid findings for patients, doctors, families and payers under these circumstances?

DR. MADAN: That's certainly a question that

we're all wrestling with. I think that again, in metastatic disease, combination studies with some of these agents that are coming on line or already available will potentially yield clinical outcome information such as, it will be good to capture progression. Survival may be more elusive but I think it's something to capture. As more biomarkers become available, they will be added on, in terms of assessing responses. And in addition to combination therapies, sequence of therapies will also be something that can be evaluated. It's impossible to mandate therapies forever after a patient is off the

00261

study, but it may be possible to do a trial that looks at the sequence of two in particular, perhaps the two that are most likely to be employed in a given patient's disease course.

DR. GOODMAN: Great, that's helpful.

Dr. Potters.

DR. POTTERS: The largest gap in prostate cancer is accrual in general, and given the fact that there are so many options and the sense of entitlement for so many different opportunities to be treated that, you know, the biggest issue has always been accrual. I mean, we have been trying to design and have been able to design trials, you know, for years in this disease. You just don't get enough accrual.

DR. GOODMAN: Thank you. I'm going to pose a question to Dr. Madan and Dr. Schulman for starters, and I'll also ask our presenters if they see any merit to this. To the extent that treatments are changing, comparators are changing and populations are changing, is there an opportunity here for adaptive clinical trial designs where we might have a more potentially efficient way to accrue randomized patients to groups along the way? At that point we could be locked into certain trial designs. Might that be a useful approach at least in some instances here given that set of circumstances? So,

00262

Dr. Madan.

DR. MADAN: I'll answer that question. Getting back to the accrual of trials, it is difficult to accrue patients to trials. However, as this year has demonstrated, or the last two years, we've had significant results in multiple Phase III trials. So it can always be better, but I think the patients are very willing, and maybe a little more community outreach and things like that will help facilitate accrual in these studies.

In terms of adaptive clinical trial design, I think that's especially true in these immunotherapeutics as they are, again, coming on line and there's more of them. There have been efforts to develop more adaptive assessments of responses in patients who are treated with immune-based therapies, and I think some of those new approaches need to be vetted in upcoming trials, and

that's one way I think we can maybe have a better assessment of the responses that we're seeing in some of these newer agents and the combinations.

DR. GOODMAN: Thank you. Other comments on that issue? Dr. Schulman.

DR. SCHULMAN: There are very large efficacy and effectiveness issues and I think there are differences in what we might want to look at. So I think in the Medicare population, does this work in people over age 80? You

00263

know, these people were in the trial, but the cutoff we looked at was age 65 because of the population, so how do we understand that when obviously the median age of prostate cancer in Medicare patients is very high. But there also will be natural experiments. I mean, there will be different physician practices around the country that are going to have different practice patterns, and so that's not adaptive design. If in fact we did collect some clinical data at baseline for people getting these advanced cancer therapies, we could use the natural experience that we see in Medicare, the regional variation that exists, to try to help us tease out some of these questions in real time in a way that's generalizable to this population.

DR. GOODMAN: That's a very good observation. Would any of our presenters care to comment on this question about clinical study designs that might address the evidence gaps, do any of our presenters have anything to add to that? No, not at this point. Okay. Any final comments about question nine then, before we move on? Okay. We've got a couple things, important things to do before we close today, and we've got a few more minutes to do this. I'm going to give a little warning, I'm going to start with you, Dr. Madan, and I'll give you a little

00264

break here on time. I want to ask every panelist here to tell CMS and/or any other stakeholder in a sentence, not a paragraph, in a sentence what you think the single most important action at this point would be to strengthen evidence and/or improve the basis, strengthen evidence and/or improve the basis for decision-making here at CMS. After all, there is a national coverage analysis on the table. It's our job to help provide insight information to that. We don't make the policy, we don't make the decision, but we provide some insights or suggestions to that effect. So in a few minutes we're going to ask Dr. Madan to start, and I'm going to move to our left. And while we're thinking about this, a couple minor ground rules on this one. Don't say ditto to something someone said before, we want something different from each person. Now while we're thinking about that, in the meantime I want to ask our presenters, is there anything

with regard to the matter on the table today that we did not hear that we should have heard, something about evidence, study design, populations? Is there something that should have been said that would be relevant to the work of this MedCAC and/or the Agency on this matter today? Any presenters? I don't see any further comments. Is there anyone in the room who has something to

00265

say that's relevant to this MedCAC and these questions that we faced today? We've got to hear something. Yes, and please do keep this short because we are close on time here, and if you would approach the microphone and say who you are and your affiliation, and in a concise way tell us what we needed to hear.

DR. CLAUSEN: My name is Bart Clausen, I'm an M.D., a physician, I'm an immunologist. For 20 years I have been publishing on vaccine trial designs and clinical safety. I also, besides that, researched trials for Wall Street trial design, work for some other research partners. I have spent a lot of time reviewing this data. The biggest question I have is that you have a trial design from the most recent Phase III trial, the IMPACT trial, and the issue is, did you show that you've improved survival or did you reduce survival in your control group because you removed white blood cells and discarded most of them? We know that removing white blood cells will decrease your survival rate. Look at AIDS, for example.

Now, specific white cells are there, so in a situation where you had no impact on disease progression, the opposite thing was that removing the white blood cells actually decreased survival in your control group.

DR. GOODMAN: Doctor, we got your point, thank

00266

you very much. Yes, Dr. Gulley.

DR. GULLEY: I would just like to respond to that one comment.

DR. GOODMAN: Please keep it brief.

DR. GULLEY: I will. The number of white blood cells that were, the proportion of white blood cells that are removed in terms of the total body white blood cell count is around two percent, so it is not a clinically meaningful amount.

DR. GOODMAN: Thank you, Dr. Gulley. I should mention to the prior commenter, before you leave, if you would meet with Ms. Ellis, we need to ask for disclosures from everyone, and I appreciate your comment and I should have mentioned it earlier. Anything else that we missed? Yes, Dr. Petrylak.

DR. PETRYLAK: I would just like to follow up to that. The control group of this study, the Provenge study, was exactly the same in survival as the Taxotere group in the GVAC study, so I don't think that this significantly impacted on the overall survival, lack of

white cells.
DR. GOODMAN: Good, thank you for that response.
Dr. Frohlich.
DR. FROHLICH: Just my view on your question about what CMS could do here. I think if you look back at
00267
oncology development, huge advances have been made by drugs that have been approved and made available to smart clinicians, who then do investigational studies to better refine how those agents can be used. And so I think in this situation we've got a lot of interest in investigation about how to use sipuleucel-T and combine it with other agents, how to sequence it with other agents, but in order for that to happen, it needs to be made available and reimbursed.
DR. GOODMAN: We appreciate your comment, thank you. Other comments here? I think we've heard everybody. Now, let's move to our closing one-sentence insights, and Dr. Madan is prepared to get us off on a great start. Sir, one sentence if you would.
DR. MADAN: Sure. I think it's imperative for CMS, when they evaluate a drug such as this, they rigorously establish a clinical context, and certainly I think that the context of oncology and patients with cancer is very unique when dealing with medical treatments, and I think that's very important in this evaluation and other evaluations moving forward.
DR. GOODMAN: Thank you, Dr. Madan. Dr. Raab.
DR. RAAB: The last numbers I saw were that very few Medicare beneficiaries participate in cancer clinical trials, and I think Medicare could look at its current
00268
coverage for clinical trials policy and streamline it, and create better incentives to have those people participate.
DR. GOODMAN: Thank you, Dr. Raab. Dr. Steinbrook.
DR. STEINBROOK: I agree with that comment, and I would just make the general point that whatever Medicare decides to do, that it should include a data collection component so that something can be learned from the patients who do take this treatment.
DR. GOODMAN: The data collection component is part of the care given to its beneficiaries.
DR. STEINBROOK: Given the constraints within which Medicare operates and what it can and it can't do, that there's a tremendous opportunity here to gain information appropriately from the patients who receive this therapy, and that that should be designed at the same time that Medicare figures out what it's going to do in terms of coverage.
DR. GOODMAN: Excellent, thank you, Dr. Steinbrook. Dr. Schulman.
DR. SCHULMAN: I can't say ditto, huh?
DR. GOODMAN: You can say ditto, and then

something else.
DR. SCHULMAN: Okay. One of the things that's very clear is this company has made a tremendous effort to
00269
get this product approved and get it to market, there's a huge need for this in the population, and yet we're still stuck with a lot of questions where there aren't satisfactory answers, so I think the idea that at one point in time we know the future is not clear. We need, you know, ideally after this whatever, hopefully Medicare and Dendreon can have a partnership to kind of collaborate on the future development and making sure for everybody that the appropriate people are getting this therapy and that they're benefitting from it in the real world.
DR. GOODMAN: Thank you, Dr. Schulman, real world, thank you. Dr. Potters.
DR. POTTERS: So, I'm just going to take a little broader approach in the context that nothing today really that we talked about was about finances despite all the lead-up to this meeting. I think that the limitations of this process in general is the selection of the criteria and the limitation of running this group only six times a year, which creates an illusion to the public that we're limiting things that CMS are looking at for the purposes of payment, and so it creates a public bias that I think is one that is sort of self-evident based on the newspaper articles that came out before today. I do, however, think that the transparency of the discussion today, despite the fact that we beat up basically one
00270
series of clinical trials for six hours, was a good discussion, and I think that we were able to provide insight into the directions that we need to go, but it's not completely clear whether the mechanism that CMS is going in, whether this is really the best mechanism for the determination of payment.
DR. GOODMAN: Thank you, Dr. Potters. With several semicolons, I guess that qualified as a sentence, but very good observations and we very much appreciate that.
I would just want to clarify, I hope we weren't beating up this set of clinical trials, but we certainly scrutinized them. How about that?
DR. POTTERS: That's fine.
DR. GOODMAN: Thank you, sir. Ms. Moore.
MS. MOORE: I guess I want to thank CMS for the material we got far enough in advance to really do my homework, and for the new members, the roles and responsibilities you sent me, but you didn't tell me how daunting this would be, so for new panel members I would say a little bit about that too.
DR. GOODMAN: Thank you, Ms. Moore. Given your line of work working directly with cancer patients, I would think you can handle just about anything. Thank

you, Ms. Moore. This is Dr. Mintzer.
00271
DR. MINTZER: I would agree that unless we somehow control finance this is all going to become irrelevant soon, supporting advances in technology.
DR. GOODMAN: Thank you, Dr. Mintzer. Dr. Matuszewski.
DR. MATUSZEWSKI: I have two sentences. The first suggestion to CMS is to maybe provide bagels to the MedCAC panel first thing in the morning, and have an endless pot of coffee right behind us on the table, that would be wonderful, and cut down on the time you spend in line downstairs.
The other comment would be that I think maybe some presentation of the other alternative therapies in the pipeline might be warranted, some of that was in the tech assessment, so PROSPECT has some incredible survival numbers that are being floated about, and I'm not sure if this is Phase II or Phase III data, or what their trial designs are. But if any of that is available and could be presented, to see how those companies are going about clinical trials, and they may be in the EU right now, and I'm sure the FDA has some of them too. I mean abiraterone, I've heard it mentioned, but again, how far along are those trials, and so how does this therapy sort of fit in with what might be a very expansive armamentarium in the next year or two.
00272
DR. GOODMAN: Great, thanks, Dr. Matuszewski. Dr. Fuller.
DR. FULLER: Well, normally when I sit here and I don't look like a very excited guy, but what I have heard today is very exciting, because the idea that we're going to create a therapy for patients which is specifically addressing the issues that are going on inside of them is something, and I think we will look back and this will seem like the dark ages a decade from now and we'll laugh at it, we did that, but this is a great beginning, and I hope that the climate will never be such that we stifle the initiative of the people that you work for, Dr. Frohlich, that got this job off the ground.
DR. GOODMAN: Thanks, Dr. Fuller. Dr. Dmochowski.
DR. DMOCHOWSKI: I think since technology is clearly not going to stop for this or any other field, I would propose a proactive prospective collaboration between various federal entities that are stakeholders in this process, i.e., CMS, i.e., FDA, along with entities that are developing products under the guidance of the medical expertise, whatever field that is, to really anticipate these problems so they can actually be answered before the event, in other words, at the time of approval all the concerns regarding coverage or regarding
00273

generalizability may be answered. That may be too large of a task for a simple registration trial, but in a way to sort of create the field of affairs, so that people know what the tick boxes are as they move forward with new technology.

DR. GOODMAN: That's a great point, Dr. Dmochowski. If you will just forgive me for a moment, you may know that in September of this year in the Federal Register was a discussion of a potential parallel review process involving FDA and CMS, and comments were due and I understand they received quite a few comments. This effort to try to somehow better align evidence requirements and expectations for regulatory and payment purposes is something that's apparent not just in the U.S., but as it turns out globally, and I think this is important for how innovative companies are trying to understand the evidence environment with the various payers and decision-makers that can affect the adoption and diffusion of technology based on their evidence requirements, to the extent that FDA and CMS might talk a little bit more, which may be an example of the kind of effort to which you refer. Thank you, sir.

Ms. Darling.

MS. DARLING: So, I think CMS would benefit by promoting participation in research registries, even the

00274

use of observational data, and to the extent that information, even though it's quite different, can be available to frame the discussion, to have some understanding of, for example, the epidemiology of something. So, second would be to know more about the subgroups, even basic numbers that, Medicare and Medicaid serve, so you would know something more about the populations, you would know something about disease burden, you would know more about the context and how important some of these considerations would be to how many people under what circumstances, how urgent is it, so more that gives you a sense of the context in which we are looking at these things.

DR. GOODMAN: Great point, thank you. Thanks, Ms. Darling. Dr. Satya-Murti.

DR. SATYA-MURTI: That if coverage is going to occur as a result of this, make it mandatory to provide a two or three-year follow-up on archival data or repurpose data using tissue and the white cells for continued coverage. It is a modification of registry, but make it very specific that these are the data expected.

DR. GOODMAN: Great, thank you, Dr. Satya-Murti. Before I turn it back to Dr. Rollins, part of the chair's job is to make some summary comments, and I think I'm allowed more than a couple semicolons, though

00275

I'll try to be brief about this insofar as the summary observations.

We know, and this is true not just of the therapy that was discussed today, we know that it's very common across many types of regimens that even when something is approved by the Food and Drug Administration using their rigorous approaches, we still don't know enough of what we're going to need to know. And here the "we" refers to patients, it refers to families, doctors and other clinicians, payers and other decision-makers. When something comes out of the FDA it is essential information but oftentimes not enough to support many of these decisions in practice.

You may have noted, as is apparent in some of the respective missions of the FDA and CMS, the law pertaining to FDA talks about demonstrating safety and effectiveness, safety and effectiveness. Looking carefully at the term effectiveness, we see that in using current terminology, efficacy was probably meant there, to the extent that efficacy refers typically to evidence gathered under well controlled, oftentimes ideal settings, and sometimes what's collected for the purposes of FDA decision-making may not be effectiveness data, which is more often community-based data. I have to say, we were very fortunate to hear in some detail about the extent to

00276

which the data collected thus far is community-based, and that was very very helpful information. It's still not everything we need to know, as I think was detailed here so far today.

Medicare, on the other hand, its law tells it that it can't pay for something unless it's reasonable and necessary. So where the FDA talks about safety and effectiveness, meaning efficacy in our terms, Medicare is about reasonableness and necessity, reasonable and necessary. Those aren't the same thing, and so these two agencies have their respective missions that aren't exactly the same. And what we're seeing now in this current environment of trying to innovate in areas that could potentially benefit a lot of patients, having to innovate in this environment requires trying to satisfy those different sorts of evidence requirements.

That's not an easy thing to do. Just because it's not an easy thing to do doesn't mean we're going to lower our requirements for solid evidence, because that's what patients, doctors, families and others certainly do need.

It was notable today that, and we're very grateful to the evidence-based practice center, Blue Cross Blue Shield TEC, that it did take quite a bit of effort for them to pull together all the relevant evidence, in

00277

part for the good reason that there was some good evidence but it was hard to find. And it occurred to me that had they not done that, it would be hard for others to pull together that diffuse body of evidence, you couldn't find

it in any one place. So if they had a tough time finding it in any one place, you can imagine it would be hard for other decision-makers and other people that needed that kind of information to find it as well? So we're grateful that they did it, but it does point up the challenge of pulling it all together to support decision-making.

I want to iterate the importance of the gap between the 220,000 people that are affected by this disease every year, the incident rolls, and the 32,000 that die from it each year, the gap between those big numbers and the small numbers thus far for the people who have been enrolled in rigorous clinical trials. There's a great opportunity there to get more evidence of the real world effects, real world benefits and harms because of the size of this population. Clearly this is a condition that merits this rigorous evidence to support those very important decisions.

Another matter that we cannot avoid here has to do with what comprises this therapeutic regimen, what's the dose, what are the cell counts? This is not the same as taking a pill, getting a pill at the pharmacy where you

00278

know how many milligrams it's got. So there's a lot of variation there and a lot of room there to learn about what regimens worked. There's a lot of variation and this is something we've got to deal with, and the registries are going to help, and the data collection is going to help.

So just in closing, we have some pretty good evidence here, it was rated as moderate, not the most strong but moderate. So the evidence here, derived primarily from FDA trials, is pretty solid, rated as moderate, but it is not an expansive, broad or deep body of evidence. So the base of evidence upon which this therapy rests certainly is of moderate strength, but it's not really wide and it's not really deep. So much work is needed to collect evidence to make it broader and deeper, to help serve these 220,000 people that get this disease every year, and to try to avert some of these 32,000 deaths. This is a very important juncture to make those realizations and to go out and get this evidence on an ongoing basis. Medicare beneficiaries deserve that attention, they deserve better data for this kind of decision-making.

With that I want to thank very much, very much on behalf of the MedCAC and CMS, I want to thank all eight of, excuse me, all nine of our scheduled presenters who

00279

did a superb job under some bright lights and some very probing questions. We're very very grateful for your presence here, and nearly all of you stuck here through the entire day. I don't think we were beating up the studies, but we were scrutinizing them very carefully, and we appreciate your candor and your openness.

I want to also thank everyone who remains in the room now. Many of you got here at seven o'clock or earlier, you stayed here now until nearly 4:20, and we very much appreciate your attention, your perseverance and your openness to this sort of information, and know that this is part of what CMS intends. This is an open public process and the discussions we had here today are certainly to help CMS, but they also provide a host of pretty helpful signals to innovators, patients, families and doctors and others about the kinds of evidence that is sought when it comes time to help make decisions about providing greater access to proven therapies, so thank you all very very much.

And I want to thank the panel, of course, for your perseverance and insightfulness, and I will now turn it back over to Dr. Rollins.

MS. ELLIS: Excuse me. Before everyone leaves, there has been a pair of glasses found. If these are your glasses, please see me so you can retrieve them. Also,

00280

please remember to discard your trash in the trash cans located outside of the room.

DR. ROLLINS: In closing, CMS would like to thank the members of the MedCAC committee, the participants, as well as the presenters for today's discussion. Have a safe trip home. Thank you.

(Whereupon, the meeting concluded at 4:20 p.m.)