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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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CELLULAR, TISSUE AND GENE THERAPIES ADVISORY COMMITTEE

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OPEN SESSION

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THURSDAY,
MARCH 29, 2007

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The meeting convened at 8:00 a.m. at the Hilton Washington D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, James J. Mulé, Ph.D., Chair, presiding.

PRESENT:

JAMES J. MULÉ, Ph.D., Chair
RICHARD B. ALEXANDER, M.D., Temporary Voting Member
MATTHEW J. ALLEN, Vet., M.B., Ph.D. Member
MICHÉLE P. CALOS, Ph.D., Member
JEFFREY S. CHAMBERLAIN, Ph.D., Member
RICHARD J. CHAPPELL, Ph.D., Member
GLENN DRANOFF, M.D., Temporary Non-voting Member
STEVEN M. DUBINETT, M.D., Temporary Voting Member

PRESENT:

STANTON L. GERSON, M.D., Member
(Topic II only)
FARSHID GUILAK, Ph.D., Member
KURT C. GUNTER, M.D., Industry
Representative
MAHA HUSSAIN, M.D., FACP, Temporary Voting
Member
LARRY W. KWAK, M.D., Ph.D., Member
FRANCESCO MARINCOLA, M.D., Temporary Voting
Member
ROBERT J. SAMUELS, Patient Representative
HOWARD I. SCHER, M.D., Temporary Voting
Member
DORIS A. TAYLOR, Ph.D., Member
SHARON F. TERRY, M.S., Consumer
Representative
WILLIAM W. TOMFORD, M.D., Member
WALTER J. URBA, M.D., Ph.D.Member
(Topic II only)
SAVIO LAU-CHING WOO, Ph.D., Member

FDA PARTICIPANTS:

GAIL DAPOLITO, Executive Secretary
STEVEN R. BAUER, Ph.D., Chief, Cellular and
Tissue Therapy Branch
KATHRYN M. CARBONE, M.D.
KE LIU, M.D., Ph.D., Division of Clinical
Evaluation, Pharmacology and
Toxicology
RAJ K. PURI, M.D., Ph.D., Director, DCGT,
and Chief, Tumor Vaccines and
Biotechnology Branch
CELIA WITTEN, M.D., Ph.D., Director, Office
of Cellular, Tissue and Gene Therapies
KEITH WONNACOTT, Ph.D., Chief, Cell Therapy
Branch
BO-GUANG ZHEN, Ph.D., Division of
Biostatistics

A-G-E-N-D-A

TOPIC I: Sipuleucel-T, Dendreon Corporation (BLA-STN 125197)

FDA PRESENTATION

OPEN PUBLIC HEARING

P-R-O-C-E-E-D-I-N-G-S

8:01 a.m.

DR. MULÉ: I'd like to welcome you to the March 29 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee for the FDA. We have a very full schedule today and so what I'd like to do is, as much as possible to keep us on time, I would ask again the speakers to be cognizant of the fact of the schedule and my job of course is to try to keep things moving along. So again I'd like to welcome you. I'd like to welcome the new members of the committee as well as the other members of our advisory committee for this meeting. So we'll get started by having Gail read the conflict.

MS. DAPOLITO: Good morning and welcome. I'm Gail Dapolito, the Executive Secretary for the Cellular, Tissue and Gene Therapies Advisory Committee. Before I read the conflict of interest statement I would like to request that you please silence cell

phones and pagers, and also I would like to request that any media inquiries be directed to Karen Riley or Heidi Rebello from the FDA Office of Public Affairs. And if Karen or Heidi could stand up. They're waving. They're over to my left. Thank you. Now I will read for the public record the conflict of interest statement. One more matter for press inquiries. Dr. Celia Witten will be the sole spokesperson for the FDA. Thank you.

The Food and Drug Administration convenes today's meeting of the Cellular, Tissue and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all participants of the committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations. The following

information on the status of this advisory committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18 USC Subsection 208 and 21 USC Subsection 355(n)(4) is being provided to participants in today's meeting and to the public.

FDA has determined that members of this advisory committee are in compliance with federal ethics and conflict of interest laws, including but not limited to 18 USC 208 and 21 USC 355(n)(4). Under 18 USC 208, applicable to all government agencies, and 21 USC 355, applicable to certain FDA committees, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest, Section 208, and where participation is necessary to afford

essential expertise, Section 355. Members and participants of the committee who are special government employees at today's meeting, including special government employees appointed as temporary voting members, were screened for potential conflicts of interest of their own as well as those imputed to them, including those of their employer, spouse, or minor child related to the following: Topic I, the discussion of Provenge sponsored by Dendreon; Topic II, an overview of research programs in the Division of Cellular and Gene Therapy's Center for Biologics Evaluation and Research; Topic III, draft guidance for industry, minimally manipulated, unrelated allogeneic placental umbilical cord blood intended for hematopoietic reconstitution in patients with hematological malignancies; and Topic IV, a discussion of scientific issues regarding minimally manipulated unrelated

allogeneic peripheral blood stem cells. These interests may include investments, consulting, expert witness testimony, contracts, grants, credits, teaching, speaking, writing, patents and royalties and primary employment.

For today's agenda regarding Topic I the committee will discuss and make recommendations on Provenge sponsored by Dendreon in accordance with 18 USC 208(b)(3). Waivers were granted to Drs. Maha Hussain, Howard Scher and Savio Woo. Dr. Glenn Dranoff was granted a limited waiver to permit his participation in the discussions. Dr. Dranoff will not vote on this topic.

For the discussion of Topic III, draft guidance to industry, Drs. James Mulé, Mary Horowitz and Mary Lachlan each received a waiver under 18 USC Section 208(b)(3). Drs. Stanton Gerson and Walter Urba recused themselves from participation in Topic I.

They may participate fully in Topics II, III and IV. A copy of the written waivers may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

With regard to FDA's guest speaker Dr. Pablo Rubinstein - that will be on March 30 - the agency has determined that the information provided by him is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments made by him. Dr. Pablo Rubinstein is employed by the National Cord Blood Program at the New York Blood Center. Dr. Kurt Gunter is serving as the industry representative acting on behalf of all related industry and is employed by Hospira Incorporated. Industry representatives are not special government employees and do not vote.

This conflict of interest

statement will be available for review at the registration table. We would like to remind participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with the sponsor, its product and, if known, its direct competitors in any firms that could be affected by the committee discussions. Thank you.

DR. MULÉ: Thank you, Gail. We'll continue by introducing the members of the committee, both the standing members as well as the ad hoc members. To my left is Dr. Woo. If you can kindly give your affiliation and your expertise.

DR. WOO: My name is Savio Woo. I am Professor and Chairman at the Mount Sinai School of Medicine, New York City and my expertise is in the area of gene therapy.

DR. MARINCOLA: I'm Franco Marincola. I'm Chief of the Immunogenetic Section and the Clinical Center at National Institutes of Health and my main interest is in immune responses to viral disease and cancer.

DR. SCHER: Howard Scher. I'm the Chief of the Geneto-Urinary Oncology Service at Memorial Sloane Kettering in New York with expertise in prostate cancer clinical trials.

DR. TOMFORD: William Tomford, Professor of Orthopedic Surgery, Harvard Medical School. I have an interest in bone and cartilage transplantation.

DR. GUILAK: Farshid Guilak, Duke University Medical Center. I work in tissue engineering and stem cell therapies for

osteoarthritis.

DR. GUNTER: My name's Kurt Gunter. I'm the industry representative on the panel.

DR. DRANOFF: I'm Glenn Dranoff from Dana Farber Cancer Institute and I work in cancer immunology.

DR. ZHEN: My name is Bo Zhen. I'm a statistical reviewer, CBER, FDA.

DR. LIU: Ke Liu, clinical reviewer in the Office of Cellular, Tissue and Gene Therapies, CBER.

DR. WONNACOTT: I'm Keith Wonnacott. I'm a product reviewer on the Provenge file.

DR. WITTEN: Dr. Celia Witten, Office Director of the Office of Cellular, Tissue and Gene Therapies, CBER, FDA.

DR. ALEXANDER: My name is Rich Alexander. I'm Professor of Urology at the University of Maryland. My interest is prostate cancer and cancer immunotherapy.

DR. CHAMBERLAIN: I'm Jeff Chamberlain, a Professor at the University of Washington. I work in areas of gene and stem cell therapies for the muscular dystrophies.

DR. KWAK: Larry Kwak, Chairman of the Department of Lymphoma and Myeloma at MD Anderson Cancer Center. My area of interest is tumor immunology.

DR. CALOS: Michele Calos. I'm a Professor at Stanford University and my interest is gene therapy.

DR. DUBINETT: Steve Dubinett. I'm from UCLA. I direct the UCLA Lung Cancer Research Program in the Division of Pulmonary and Critical Care Medicine. Our research interests focus on lung cancer, immunology and inflammation.

DR. ALLEN: Matthew Allen. I'm Associate Professor, Orthopedic Surgery at State University of New York in Syracuse. I'm a veterinarian with an interest in pre-

clinical orthopedic animal models and also animal models of cancer.

DR. CHAPPELL: Rich Chappell, the Department of Biostatistics and Medical Informatics at University of Wisconsin where I'm a Professor. And my area of interest is statistical methods and design of clinical trials.

DR. HUSSAIN: Maha Hussain, University of Michigan. I'm a Professor of Medicine and Urology there and I am a GU medical oncologist.

MR. SAMUELS: My name is Bob Samuels. I am the patient advocate. I am a 13-year survivor of prostate cancer, a 7-year survivor of throat cancer. I was a founding chairman of the National Prostate Cancer Coalition and also the Florida Prostate Cancer Network.

MS. TERRY: Sharon Terry, President and CEO of Genetic Alliance which is a coalition of 600 disease advocacy

groups and also Chair of the Genetic Alliance Biobank. My expertise is in advocacy, general genetics research and biobanking.

DR. TAYLOR: Doris Taylor, Director of the Center for Cardiovascular Repair, University of Minnesota. My interest is in cell therapy for cardiovascular disease.

MS. DAPOLITO: Gail Dapolito, Executive Secretary for the committee. And I'd also like to introduce the Committee Management Specialist, Rosanna Harvey. Thank you.

DR. MULÉ: Jim Mulé, Executive Vice President for Applied Research, H. Lee Moffitt Comprehensive Cancer Center. My expertise is in tumor immunology and immunotherapy.

So we're ahead of time and if Dendreon is ready we can proceed with the presentations. We're about 20 minutes ahead

of schedule. So the first speaker is an introduction from Elizabeth Smith.

MS. SMITH: We're ready, but our projector is not ready. Okay. Mr. Chairman, members of the committee, ladies and gentlemen, good morning. My name is Elizabeth Smith. I'm the Vice President of Regulatory Affairs at Dendreon Corporation and on behalf of Dendreon we are honored to be here today to work with this committee to further advance the field of cancer immunotherapies and turn theoretical concepts into real treatment options that have the potential to improve the lives of patients suffering from prostate cancer.

Provenge or sipuleucel-T is one of many cell- and immune-based therapies that have been under development over the last decade, but this is the first in this new class of therapy to come before this committee in consideration for licensure. Sipuleucel-T is an autologous active

cellular immunotherapy that is designed to activate the patient's immune system against his prostate cancer. This is a patient-specific product consisting of autologous antigen-presenting cells that are loaded ex vivo with a recombinant fusion protein consisting of human prosthetic acid phosphatase, or PAP, fused to human granulocyte macrophage colony stimulating factor, or GMCSF. Specifically, in a simple and well-defined process peripheral blood mononuclear cells are obtained from each patient via apheresis. These cells are shipped to a Dendreon manufacturing facility for preparation of the sipuleucel-T final product. Using validated aseptic GMP processes, the cells are isolated and they are cultured with the recombinant fusion protein ex vivo. After culture, the cells are harvested, washed, formulated, sampled for QC testing and then shipped to the physician's office for infusion to the

patient. This process is repeated three times at 2-week intervals. The whole course of treatment involves three donations of blood followed by three infusions of product. This basic process was used throughout the clinical development program for sipuleucel-T which has been conducted solely in the prostate cancer setting.

After filing our IND in 1996, our initial Phase I and II studies were conducted in men with both asymptomatic and symptomatic hormone-refractory, also known as androgen-independent prostate cancer. The results of these studies demonstrated that infusions of sipuleucel-T up to the maximum dose achieved in the manufacturing process were well tolerated. Signals of delay in disease progression and the generation of immune responses following treatment led us to the design of our Phase III program in men with asymptomatic metastatic AIPC shown here in yellow.

Studies 9901 and 9902A which we will refer to today as Studies 1 and 2 respectively, were multi-center, randomized, double blind, placebo-controlled trials. The survival results from these studies will be the focus of our efficacy presentation today. The third study, 9902B, which we will refer to as Study 3, is currently enrolling men with asymptomatic and minimally symptomatic androgen-independent prostate cancer. This study was initiated and designed before the availability of the survival results from Studies 1 and 2. Lastly, Study P11 is being conducted in men with androgen-dependent prostate cancer, and all of these studies contribute to the safety database for sipuleucel-T.

The Phase III regulatory history provides important context for the results that will be presented today. In 1999 and early 2000, Studies 1 and 2 were initiated at multiple centers across the United

States. The original intent of the Phase III program was to evaluate the ability of sipuleucel-T to delay the time-to-disease-progression in men with AIPC, which was the primary endpoint of the study, compared to a placebo control. Additionally, while both FDA and Dendreon recognize that neither study was prospectively powered to detect a difference in overall survival, we included a plan to follow all patients for survival for 36 months or until death after randomization.

In 2002, Dendreon analyzed the results for Study 1, time to progression. The primary endpoint was not met. The p-value approached but did not achieve statistical significance, suggesting a lack of power, particularly in light of the observed delayed treatment effect of this immunotherapy. The magnitude of the treatment effect, however, was consistent with patient benefit. The results from

Study 1 signaled that Study 2 was unlikely to meet its primary endpoint of progression. Thus Dendreon stopped enrollment in Study 2 prematurely. The survival results from Study 1 were not sufficiently mature to conduct an analysis in 2002, so all patients in Studies 1 and 2 continued to be followed for survival per protocol.

In 2003, under a special protocol assessment, Study 3 was initiated. Study 3 was initiated to continue our clinical investigation of sipuleucel-T, now in men with both asymptomatic and minimally symptomatic androgen-independent prostate cancer complimented by our increased understanding of sipuleucel-T efficacy gained from Study 1. Initially the primary endpoint for Study 3 was time to objective disease progression. It has since been changed to overall survival. The final survival results from Study 3 will be available in 2010.

In 2004, after every subject was followed until death or 36 months, per protocol, the final survival results in the intent-to-treat population demonstrated a clinically meaningful improvement in overall survival compared to placebo. The results from Study 2 showed a trend in the same direction. These results were then discussed with FDA and fast-track designation was granted on the basis of the demonstrated potential of sipuleucel-T to prolong survival while avoiding the toxicities associated with current therapies.

Dendreon filed its biologics license application in 2006 and it is currently under priority review. The proposed basis for Dendreon's biologics license application has been demonstrated in multi-center, randomized, double blind, placebo-controlled trials. The primary evidence of efficacy is provided from Study

1. Time to progression was the primary endpoint. The magnitude of the treatment effect for progression in Study 1 was consistent with patient benefit. More important, however, are the results for overall survival. This is the most clinically relevant and objective measure of efficacy in clinical trials in oncology. The overall survival results in the intent-to-treat population were clinically meaningful and statistically persuasive. There was internal consistency within the study. The primary and secondary endpoints all in the same direction and a positive treatment effect across all patient subsets. The survival results have also held up to the challenge of multiple sensitivity analyses.

Supportive evidence of efficacy is provided from Study 2 which has shown a trend in the same direction for improvement in survival. The results of exploratory

analyses which integrate the data from Studies 1 and 2 confirm patient benefit and also demonstrate that there is a strong correlation between product potency, a measure of cell activation and overall survival. The totality of the evidence from these studies demonstrate that the results from Study 1 are unlikely to be due to chance. And finally, sipuleucel-T appears to be well-tolerated, providing an appealing benefit-to-risk profile, particularly in light of the limitations of current treatment options. Taken together, these data establish the safety and efficacy of sipuleucel-T and support our proposed indication in the patient population that we studied, namely men with asymptomatic metastatic androgen-independent prostate cancer.

In the last 20 years, only four drugs have been approved for the treatment of advanced prostate cancer, and only one of

these, a cytotoxic agent, has shown a modest improvement in overall survival. The expected survival in these patients is approximately 14 to 22 months. Today's proceedings are a significant step toward changing the landscape of prostate cancer treatment. We will present data today to facilitate the committee's review and understanding of sipuleucel-T and demonstrate how, if approved, sipuleucel-T will meet an important unmet medical need to prolong survival in this ultimately fatal disease.

Our first speaker today is Dr. Mark Frohlich, Vice President of Clinical Affairs at Dendreon who will describe the clinical development, efficacy and safety of sipuleucel-T.

DR. MULÉ: Thank you, Ms. Smith.

DR. FROHLICH: Thank you, Liz. Good morning. I'm Mark Frohlich, Vice President of Clinical Affairs at Dendreon

and a medical oncologist. I've been focused on the development of cancer immunotherapies for about the past eight years. My interest in the field was stimulated in part from my experience as a faculty member at University of California-San Francisco in the 1990s where I treated some of the first patients with sipuleucel-T on the Phase I/II clinical trials being conducted there by Dr. Eric Small.

The primary evidence for clinical efficacy for sipuleucel-T is the results from two Phase III multi-center, randomized, double blind, placebo-controlled trials that were identical in original design. These trials enrolled men with asymptomatic metastatic androgen-independent prostate cancer. They were randomized 2 to 1 to treatment with sipuleucel-T or placebo. Placebo was designed to serve as an inactive cellular control. It was identical in appearance to sipuleucel-T in order to

preserve the integrity of the study blind. All patients underwent leukapheresis followed by treatment. This was scheduled to occur on three occasions separated approximately two weeks apart. At the time of disease progression patients could be treated at the physician's discretion. Those patients on the placebo arm had the option of being treated on a salvage protocol in which they received a version of sipuleucel-T manufactured from cells cryopreserved at the time of placebo generation. This design allowed men to participate in the salvage protocol without having to undergo three additional leukapheresis procedures.

The primary endpoint of the trials was time-to-disease-progression. Time-to-disease-progression was specified as an intent-to-treat analysis, namely including all patients as randomized. The Kaplan-Meier method was used to estimate

survival distributions. The method of analysis was log rank with two-sided p-values and the hazard ratios were calculated from a Cox regression model. The protocol also specified that an efficacy analysis for overall survival would be performed after 36 months of follow-up in all patients. It was stated that the Kaplan-Meier method would be used to estimate survival rates at three, six, nine and twelve months and every six months thereafter, and that the Cox regression model would be used to adjust for baseline prognostic factors. The primary method of analysis was log rank, the same method used for the primary endpoint of time-to-disease-progression. The major eligibility criteria were metastatic prostate cancer, no visceral metastases, tumor progression despite androgen deprivation therapy, no cancer-related pain, no systemic steroids or prior immunotherapy and ECOG performance status of zero or 1.

The primary evidence of clinical efficacy in this application is the results from Study 1. The baseline characteristics of Study 1 were well balanced between the treatment arms in terms of age, weight, performance status, ethnicity, laboratory values such as PSA, alkaline phosphatase and LDH. Less than 10 percent of patients on each arm received chemotherapy prior to enrollment. Additional baseline disease parameters were relatively well-balanced in terms of the percentage of patients who had moderately or well-differentiated tumors as assessed by Gleason score. There were a higher percentage or a number of patients - percentage of patients with bone and soft tissue disease in the placebo arm, but a higher percentage of patients on the treatment arm who had greater than 10 bony metastases. None of these between-arm differences had p-values less than 0.05.

We further investigated the

balance between the treatment arms using an independently validated model. The model published by Dr. Halabi and colleagues from the CLBG Cooperative Cancer Group is based on more than a thousand patients from six advanced prostate cancer trials. The final model includes seven baseline prognostic factors. We determined an estimated or predicted survival for each patient on the study and the medians of these predicted survivals was very comparable between the two treatment arms at 20.1 and 19.9 months.

The primary endpoint of the trial was time-to-disease-progression. Time-to-disease-progression was defined as either radiographic progression, clinical progression events such as development of pathologic fracture or cord compression, or the development of cancer-related pain. PSA increases were not included in the definition of disease progression. The median time-to-disease-progression was

estimated to be 16 weeks in the placebo arm based on the assumption that patients with asymptomatic disease would progress more slowly than those with symptomatic disease. The time-to-disease-progression in the treatment arm was estimated to be 31 weeks for an overall hazard ratio of 1.925.

Demonstrating an effect on the time-to-disease-progression endpoint proved challenging because the patients progressed much more rapidly than anticipated. The Kaplan-Meier curves for the intent-to-treat analysis separated 10 weeks and then remained separated throughout the duration of follow-up. The initial p-value reported was 0.085. After unblinding, we found eight errors, four of them clerical in nature and four of them where the algorithm specified in the statistical analysis plan was initially not followed. After correction, the p-value was 0.052 with minimal effect on the hazard ratio. The median time-to-

disease progression was 11.7 weeks in the treatment arm and 10 weeks in the placebo arm. The rate of progression in the asymptomatic patients was much more rapid than the 16 weeks estimated for the placebo arm. The zoledronic acid and atracentin studies have subsequently confirmed that these asymptomatic patients in fact progress at rates that are comparable to those with symptomatic disease.

Given the delayed separation of the Kaplan-Meier curves, the treatment effect is best estimated by the hazard ratio of 1.45. This indicates a 45 percent increase in the risk of disease progression in the placebo arm relative to the treatment arm. Stated another way, there's a 31 percent reduction in the risk of disease progression in the treatment arm relative to placebo as calculated by 1 minus the reciprocal of the hazard ratio. The secondary endpoints of Study 1 demonstrated

trends in favor of sipuleucel-T. These included time to clinical progression, time to treatment failure and time to disease-related pain. There were no objective responses based on radiographic assessments.

In a subset of patients enrolled in the trial we measured immune responses to the immunizing antigen. T-cell proliferation was measured at Weeks Zero, 8 and 16. There was a significant immune response in those patients treated with sipuleucel-T as shown in yellow, but not in those who received placebo, as shown in grey. While responses to the immunizing PAP GMCSF antigen have proven a robust and reliable means of assessing the immune response to sipuleucel-T, it has proven challenging to demonstrate immune responses specific for prostatic acid phosphatase.

Overall survival is the primary basis of clinical efficacy. Survival was not the primary endpoint, but it was a

planned efficacy analysis. Overall survival is the least biased, least variable and most clinically meaningful assessment of an oncology product. Survival is also the reference endpoint for the putative surrogate endpoint of time-to-disease-progression. The results of Study 1 showed a clinically meaningful improvement in overall survival. The Kaplan-Meier curves separate after approximately 10 months and then continue to separate throughout the follow-up, the 36-month duration of follow-up. The p-value by log rank was 0.01. The hazard ratio 1.71, indicating a 71 percent increase in the risk of disease progression in the placebo arm relative to treatment which translates to a 41 percent reduction in the risk of death in the treatment arm relative to placebo. No patients were lost to follow-up so there was no early censoring prior to the 36-month time point.

The survival results by quartile

reflect the increasing separation of the Kaplan-Meier curves over time. The median survival in the treatment arm was 25.9 months compared to 21.4 in the placebo arm, a 4 and a half month median survival benefit which increases to more than five months at the 25th percentile. The same trend towards an increasing survival advantage over time is reflected by the percentage of patients alive at 12, 24 and 36 months, such that at 36 months there were 34 percent of patients alive in the treatment arm compared to 11 percent on the placebo arm. Measured by the overall hazard ratio, the median survival benefit and the percentage of patients alive at 36 months, sipuleucel-T conferred a large survival benefit which increased over time. This survival benefit was observed despite the crossover design of the study.

Because overall survival was not the primary endpoint we wanted to ensure that these survival results were real and

not a random result or chance finding. Accordingly, we performed multiple sensitivity analyses in order to test the robustness of these survival results. Specifically, we assessed the consistency of the treatment effect in study cell populations, performed adjustments for baseline prognostic factors, assessed chemotherapy use and timing following investigational therapy and determined prostate cancer-specific survival. To assess for treatment effect consistency in study subpopulations we examined 21 known or potential prognostic factors, many of them well-described in the literature. We categorized each of these variables into two or more subpopulations. So for continuous variables for example this was achieved by partitioning the population into those with values above versus below the median value. As examples, force plots are shown for those eight baseline prognostic factors that

independently were predictive for overall survival in this patient population. This includes factors such as age, laboratory parameters such as PSA, alkaline phosphatase, LDH, localization of disease and the number of bony metastases. The plot shows the magnitude of the treatment effect in each of these partitioned subpopulations. All subpopulations demonstrated a positive treatment effect in terms of the hazard ratio greater than 1. And as you'll find in Appendix 5 of your briefing document, this was true of more than 40 subpopulations based on these 21 baseline prognostic factors. This demonstrates that every subpopulation was contributing to the treatment effect and that it is not being driven by a particular subgroup of patients.

Next we sought to adjust the treatment effect for baseline prognostic factors. To adjust for multiple baseline prognostic factors we started with those

eight factors that, individually, were predictive for overall survival in this patient population. Because some of these prognostic factors were correlated we used backwards, stepwise selection to determine the factors that contributed significantly to the fit of the final model. The final model included the five factors, LDH, PSA, number of bone metastases, weight and localization of disease. After adjusting for these factors in the multiple regression model, the treatment effect remained consistent with a hazard ratio of 2.16. This demonstrates that the survival results cannot be explained by imbalances in potential baseline prognostic factors.

We next sought to understand whether chemotherapy use following investigational therapy could have affected the survival results now that we know that docetaxel confers a modest survival benefit in this patient population. However, we

were unable to find any evidence of a difference in chemotherapy use or docetaxel use. There was also no evidence of a delay in time to initiation of docetaxel therapy in the placebo arm. The treatment effect also remained strong in the subpopulation of patients who went on to receive docetaxel, both those who received it early and those who received it later, and the treatment effect remained strong after adjusting for docetaxel use in a time-dependent covariant model. We were therefore unable to find any evidence to suggest that post-progression treatment with chemotherapy affects the interpretation of the survival results.

Finally, we examined the influence of non-prostate cancer deaths. For this analysis the 17 deaths not attributed to prostate cancer were treated as competing events. The yellow and grey circles represent patients who died from causes other than known or probable prostate

cancer. The blue circles at 36 months represent patients who were still alive at the conclusion of the study. Compared to the overall survival analysis, the treatment effect remains strong with a hazard ratio of 2.04, a 51 percent reduction in the risk of prostate cancer death.

To summarize, the Study 1 overall survival result treatment effect remained consistent in multiple study subpopulations and after performing adjustments for baseline prognostic factors, for docetaxel use and in determining prostate cancer-specific survival. After considering the totality of the evidence, the survival benefit appears to be, not only clinically significant, but also statistically persuasive. The p-value 0.01, the hazard ratio 1.71 indicating a 41 percent reduction in the risk of death in the treatment arm. The median survival benefit is 4.5 months and the percentage of patients alive at 36

months, 34 percent compared to 11 percent. There was no early censoring prior to the 36-month time point.

Enrollment in Study 2 was discontinued early and there were therefore fewer events than in Study 1. The baseline prognostic factors were generally balanced between the treatment arms, but some imbalances were noted for PSA, LDH and the number of bony metastases. As shown in the briefing document, the primary endpoint of time-to-disease-progression was not met. The survival data show a trend in the same direction as Study 1. The Kaplan-Meier curves demonstrate an increasing separation over time resulting in a hazard ratio of 1.27. This hazard ratio is less than the 1.71 observed in Study 1, but does represent a 21 percent reduction in the risk of death in the treatment arm. The p-value was 0.331. The median survival benefit was 3.3 months. As in Study 1 there was complete

follow-up in these patients through 36 months with the exception of two patients who were censored at 26 and 27 months.

To test the observed survival result we performed the same sensitivity analyses that we did for Study 1. The hazard ratio remained consistent after adjustment for baseline prognostic factors, adjustment for docetaxel use and in determining prostate cancer-specific survival. The change in hazard ratio following adjustment for prognostic factors likely in part reflects the baseline prognostic factor imbalances noted previously.

An additional estimate for the treatment effect in this patient population can be obtained by integrating the data from Studies 1 and 2. The rationale for integrating these two studies is based on the identical trial design, the identical eligibility criteria and the consistent

treatment effect direction. There are 225 patients in this analysis which was stratified by study. The p-value was 0.011, the hazard ratio 1.50, indicating a 33 percent reduction in the risk of death in the treatment arm. The median survival was 4.3 months.

The survival results from Study 1, Study 2 and the integrated analysis of Studies 1 and 2 demonstrate the clinical efficacy of sipuleucel-T. Studies 1 and 2 were randomized, multi-center, double blind, placebo-controlled trials. The hazard ratio in Study 1 was 1.71, in Study 2 it was 1.27 and it was 1.5 in the integrated analysis. The median survival benefit was 4.5 months, 3.3 months and 4.3 months, and there was consistently a higher percentage of patients alive in the treatment arm at 36 months compared to placebo. The data demonstrate that this survival benefit is real and unlikely to be a false positive, or in

statistical terms, the result of a Type 1 error. This is based on the nature of the endpoint, survival being the least variable, the least susceptible to bias and the most clinically meaningful endpoint. Also based on the magnitude of the treatment effect, the hazard ratio of 1.71, a 41 percent reduction in the risk of death in the treatment arm and the low nominal p-value of 0.01. We were unable to find any alternative explanation for the survival benefit as demonstrated in multiple sensitivity analyses, including demonstration of consistency of the treatment effect in study subpopulations, adjustment for baseline prognostic factors, adjustment for chemotherapy use and in the determination of prostate cancer-specific survival. Additional support is also provided by the time-to-disease-progression and secondary endpoints of Study 1 and the overall survival results of Study 2 and the

integrated analysis of Studies 1 and 2. As Dr. Provost will explain, there's also a correlation between product potency and overall survival.

The safety of sipuleucel-T has been demonstrated in hundreds of patients who collectively have received over a thousand infusions of sipuleucel-T. Dendreon's safety experience to date with autologous cellular infusions for prostate cancer involves the product sipuleucel-T, placebo and the version of sipuleucel-T used in the salvage or crossover protocols. The safety database to date for all cellular products includes more than 2,000 infusions in 669 patients and specifically for sipuleucel-T including estimates for patients - for blinded patients in ongoing studies a total of more than 1,300 infusions in 478 patients. The most common adverse events were infusion-related, transient and did not result in treatment discontinuation.

Seven adverse events were observed where the between-arm differences had p-values of less than 0.05. These included chills, pyrexia, headache, asthenia, dyspnea, vomiting and tremor. The tremor appears to be more the shaking associated with chills as opposed to a neurologic event. These seven adverse event terms were considered to be adverse drug reactions likely related to sipuleucel-T and based on a review of the entire safety database, two additional terms, nausea and fatigue, were added to this list of adverse drug reactions. The majority of these events occurred within a day of infusion and typically resolved within one to two days following treatment. Most of the events were mild to moderate in severity with very few Grade 3 or 4 events. The most common of these were chills, dyspnea and pyrexia.

We investigated the relationship

between adverse drug reactions and the total nucleated cell dose, the number of CD54 cells and CD54 up-regulation ratio. As an example, the adverse drug reaction to sipuleucel-T are shown for those patients with total nucleated cell counts below versus above the median. There was no evidence to suggest an increase in either Grade 1 or 2 events as shown in the first and third columns, or Grade 3 or 4 events as shown in the second and fourth columns for those patients with doses below versus above the median. We found similar results for the total number of CD54 cells and CD54 up-regulation ratio.

The percentage of patients who experienced any serious adverse event was comparable between the treatment arms at 23.8 percent and 22.4 percent. A higher percentage of serious adverse events were noted in the treatment arm for the serious adverse events of chills, dyspnea, pyrexia

and cerebral vascular events. Adverse events rarely led to discontinuation of treatment in total. Only four patients, or less than 3 percent of the sipuleucel-T safety population were unable to receive all three infusions due to treatment-related adverse events.

In order to thoroughly evaluate the possible safety signal for cerebral vascular events we performed additional analyses which included data from two ongoing randomized studies. Conservatively, all types of cerebral vascular events including ischemic, hemorrhagic, transient ischemic attacks or bleeding from dural metastases were included in the definition. The incidence of cerebral vascular events of any etiology was 3.9 percent in the treatment arm and 2.6 percent in the placebo arm, a 1.3 percent absolute difference. The odds ratio was 1.52 with a broad confidence interval overlapping 1. The p-value was

0.5. When the analysis was restricted to studies with only androgen-independent prostate cancer the odds ratio was higher at 2.92, but a trend in the opposite direction was noted for the androgen-dependent study. Given the small number of events involved, the figures for all studies may provide the best estimate of the incidences.

Of the 231 patients included in the placebo arm, it's important to note that 100 of these patients subsequently went on to be treated on the salvage protocol. None of these patients were reported to have experienced a cerebral vascular event. Consistent with the general occurrence of cerebral vascular events in this - in the overall population, there were more ischemic than hemorrhagic events. The incidence of ischemic events was 2.4 percent compared to 2.2 percent and for hemorrhagic events 0.6 compared to 0.4 percent. The majority of all CVAs reported were not fatal. The

incidence was 1.5 percent in the treatment arm and 0.9 percent in placebo for an odds ratio of 1.77. The p-value was 0.72.

Additional analyses performed have demonstrated a variable time-to-onset in these events. The median time-to-onset was somewhat sooner in patients treated with sipuleucel-T relative to placebo, but there was a broad range in both treatment arms ranging from a few days to more than two years. There was no evidence of an increased risk of non-neurologic vascular events and no correlation with cell dose or CD54 up-regulation. We performed an analysis of more than 9,000 patients in a SEER-Medicare database of patients with Stage IV prostate cancer and found a comparable event rate to that in the sipuleucel-T treated patients.

In summary, we've observed a 1.3 percent increased incidence in sipuleucel-T compared to placebo for cerebral vascular

events. There are large p-values and wide confidence intervals associated with the small number of events. Based on these findings we can find no conclusive evidence demonstrating an association between sipuleucel-T and cerebral vascular events. However, because we cannot definitively rule out an association, we are working with the agency to develop a pharmacovigilance plan to better characterize the nature of these events. A thorough surveillance of events of special interest was also performed. There was no evidence of an increased incidence of autoimmune events, no evidence of an increased incidence of secondary malignancies and no deaths were attributed to the product in the safety population of 669 patients as reported by study investigators.

In summary, the known adverse drug reactions to sipuleucel-T demonstrate a favorable safety profile. The most frequent

events associated with the product include chills and fever. These were generally mild to moderate in severity with the majority resolving within 24 hours and less than 3 percent of patients were unable to receive all three infusions due to treatment-related adverse events.

I'd now like to introduce Dr. Nicole Provost, Dendreon's Vice President for Product Development, who will discuss sipuleucel-T's development history and key product attributes.

DR. MULÉ: Thank you, Dr. Frohlich.

DR. PROVOST: Thanks, Mark. Good morning. I'm Nicole Provost, Vice President of Product Development and I've been working in the expanding field of cellular immunotherapy product development for over 15 years. Prior to joining the Dendreon team I helped develop products for hematopoietic stem cell transplantations in

cancer patients.

Sipuleucel-T reflects years of work on cancer immunotherapies. As a novel therapeutic, sipuleucel-T has required novel approaches to product development, assessment and trial design. Earlier Liz Smith introduced you to sipuleucel-T. My presentation will briefly describe the development history of sipuleucel-T, some key product attributes and the ways in which those product parameters may relate to clinical outcome.

From the start, Dendreon's rationale has been to activate the immune system against cancerous tissues by using well-characterized recombinant antigens and the patient's own immune cells. The pioneering work of Ron Levy, Ed Engleman and their coworkers at Stanford University provided a model for isolating antigen presenting cells, APCs, loading those cells with a target antigen and using those cells

to treat lymphoma. Dendreon's approach to prostate cancer treatment was to target prostatic acid phosphatase, or PAP, a protein relatively specific to prostate tissue and highly expressed in more than 90 percent of prostate tumors. The guiding principle was that if self-tolerance to PAP could be overcome, an immune response against prostate cancer cells could also be induced. Granulocyte macrophage colony stimulating factor, or GMCSF, was known to enhance immune responses.

Dendreon scientists combined these concepts and demonstrated the ability to break immune tolerance to healthy prostate tissue using a rat pre-clinical model. In those pre-clinical studies when rats were treated with rat PAP alone or with an irrelevant antigen fused to rat GMCSF, their prostate histology was normal as seen in the upper photo panel. However, when rat APCs were pulsed with a recombinant fusion

protein consisting of rat PAP fused to rat GMCSF the treatment induced autoimmune prostatitis. As shown in the lower photo panel, this inflammatory response is characterized by immune cell infiltrates into the prostate tissue. The immune response was tissue-specific. No other organ, system or tissue was affected by the cellular treatment with antigen-pulsed APCs. This pre-clinical framework, ex vivo culture of APCs with a recombinant fusion protein, formed the basis for the human cell product.

The manufacturing process is shown here in schematic form. The starting material is peripheral blood mononuclear cells obtained via apheresis. During product manufacturing the cells are isolated by buoyant density separations, then incubated with a recombinant fusion protein comprised of human PAP fused to human GMCSF. After incubation the cells are washed, re-suspended, packaged and shipped for final

infusion. Before being released for infusion, every product is tested to ensure conformance with quality standards. Key manufacturing product parameters include potency, total nucleated cell or TNC counts, identity, viability, sterility and other safety tests. Potency tests include up-regulation of the co-stimulatory molecule CD54 on the APC surface, an enumeration of CD54 positive APCs. When we explored the relationship between these key product parameters and survival we saw some striking results.

In order to better illustrate these results I'll first briefly describe the CD54 up-regulation potency assay. I described the potency assay to this committee in February of last year. Here are the essential features of the assay. When APCs are incubated with a recombinant antigen, their expression of the co-stimulatory molecule, CD54, increases, as

indicated by the red spikes in the cartoon above. We used fluorescently labeled antibodies specific for CD54 to quantitate the expression of CD54 on the APC surface. For each lot of sipuleucel-T or salvage product, cells are assayed before and after their ex vivo culture with the recombinant antigen. For each lot of the placebo product, cells are similarly assayed before and after their ex vivo culture in the absence of the recombinant antigen. The mean fluorescence intensity of each sample, illustrated in the box below, is used to calculate the average number of CD54 molecules on the APC surface. The ratio of post-culture CD54 expression to pre-culture CD54 expression is defined as CD54 up-regulation, as reflected in the shift to the right on the graph, indicating more CD54 molecules on the APC surface. Sipuleucel-T and salvage products demonstrate a several-fold increase in the CD54 expression, while

placebo products do not greatly increase their CD54 expression. When we analyze only manufacturing product release data -- no clinical or immune response information -- we find that in general the level of up-regulation increases after the Week Zero infusion of sipuleucel-T.

Here, the CD54 up-regulation final manufacturing product release values for over 350 sipuleucel-T product lots are shown as box and whisker plots. The horizontal lines indicate the median values. The boxes describe the inter-quartile range represented by the 25^{th} to 75^{th} percentiles where the bulk of the experimental data reside. The vertical lines and bars denote the upper and lower boundaries of one and a half times the inter-quartile range. The median CD54 up-regulation product release value goes up at the Week 2 infusion and stays up at the Week 4 infusion. The fact that the median CD54 up-regulation, a

product release measure of cell activation, goes up after the first infusion suggests that the immune system may be responding to treatment with sipuleucel-T.

We were eager to examine the relationship between CD54 up-regulation and survival once the Phase III clinical data became available. When we looked, we found a positive correlation between CD54 up-regulation and survival. Cumulative values for CD54 up-regulation and TNC were calculated by adding up the manufacturing lot release values over the course of three infusions for all products in Studies 1 and 2. Cumulative values for CD54 up-regulation and total nucleated cell counts were then each analyzed as a continuous variable in a correlation analysis with patient survival. There was a positive correlation between greater cumulative CD54 up-regulation and survival with a p-value of 0.009. For TNC, the p-value for the positive correlation was

0.018. These analyses suggest that increasing CD54 up-regulation and total nucleated cell number correlate with prolonged survival. A Kaplan-Meier plot demonstrates this relationship graphically.

This is the Kaplan-Meier plot of survival for the integrated Studies 1 and 2. Cumulative CD54 up-regulation was calculated as I just described. The patients treated with sipuleucel-T were stratified into four groups according to their cumulative CD54 up-regulation values. The pink line describes the patients with the highest quartile of cumulative CD54 up-regulation. The blue line represents the high middle quartile, the green line the low middle quartile and the orange line represents the lowest quartile of cumulative CD54 values. The overall result is clear. More CD54 up-regulation and hence more cell activation correlated with prolonged survival. We also examined the cumulative TNC values in a

Kaplan-Meier analysis of survival and found a similar result. Higher TNC numbers generally correlated with prolonged survival.

Now, one potential explanation for these findings is that patients with higher cumulative CD54 up-regulation values, or higher cumulative TNC values, were just healthier or had better prognoses and therefore had better survival outcomes. To explore this possibility we applied the Cox regression model Mark described earlier to adjust for the five factors that were prognostic for survival. As a reminder, these prognostic factors were LDH, PSA, number of bony metastases, weight and localization of disease. The right-hand column shows the p-values for the correlations after adjusting for these five prognostic variables. The correlation remains strong for CD54 up-regulation with a p-value of 0.022. The p-value for TNC

increased to 0.138 after adjustment, suggesting that TNC is more influenced by patient prognostic factors. The positive correlation between cumulative CD54 up-regulation and survival is strong, and the relationship persists after adjusting for baseline prognostic factors.

While we don't know the exact mechanism of action for sipuleucel-T, these results strongly suggest that sipuleucel-T engages the immune system and that the product potency correlates with clinical outcome. The correlation between CD54 up-regulation and overall survival suggests that CD54 up-regulation is a biologically meaningful product parameter to measure. CD54 up-regulation appears to be relatively independent of patient prognostic factors. Even cells from patients with poor prognostic factors were activated by the sipuleucel-T manufacturing process. Finally, the correlation between CD54 up-

regulation and survival provides additional support for the conclusion that sipuleucel-T prolongs survival in men with asymptomatic metastatic androgen-independent prostate cancer. Next, Dr. Christopher Logothetis will present an overview of disease management and treatment options in androgen-independent prostate cancer.

DR. MULÉ: Thank you, Dr. Provost.

DR. LOGOTHETIS: My name is Christopher Logothetis. I am a medical oncologist at the MD Anderson Cancer Center with a 30-year interest in GU tumors and particularly prostate cancer. I'm going to try to provide context to you on the results that were presented. So what I will discuss is challenges to clinical trial design in prostate cancer patients and the current clinical practice in prostate cancer as it's rolled out in our clinics.

There are several limitations

that are specific to prostate cancer in the conduct of clinical trials. These include in the areas of response, progression, and the use of survival. Responses are difficult to assess because a bone scan is a non-specific, sensitive and indirect measure of the disease. PSA remains controversial in patients with advanced disease because it's not tightly correlated with prognosis or survival. As a consequence, progression is difficult to measure. Results are inconsistent, the bone scan issues again remain as a vexing problem and they fail to correlate closely with survival, an important feature that has been confounding the conduct of trials. This appreciation is relatively new and as a consequence, survival has become the most meaningful measure of efficacy of drugs that are reliably presented.

Now there are also specific trial design challenges to the use of a therapy

such as sipuleucel-T which has a delayed effect. Because of the recently appreciated in the two clinical trials presented early observed progression of patients with prostate cancer, an agent which has a delayed effect will be greatly influenced by this. Thus, distant endpoints such as survival are more reliable measures for this therapy rather than progression which is a very imprecise clinical measure.

Now the challenge of prostate cancer as it confronts us in North America today. There are a total of 132,600 patients with androgen-independent prostate cancer today, 96,000 of these approximately have metastatic disease and they're almost evenly split with those patients who have asymptomatic metastatic androgen-independent prostate cancer as opposed to those with metastatic symptomatic androgen-independent prostate cancer.

The treatment options in

relationship to the disease state are outlined here, and as I'll note there's a tremendous amount of empiricism that is applied into their application in the clinic today. For patients with localized disease whose survival can be expected to be greater than 15 years the option of surveillance for patients who have low-risk disease is one that is often offered, and among those patients in whom cross the threshold to virulence in their disease, either surgery or radiation therapy is recommended. For those patients who, despite an initial attempt at control of their disease have a later rise in PSA concentration, termed here as serological recurrence, there's even a subset that observation is recommended because of the delayed rise or the rate of rise being so slow which would not indicate an immediate threat. For the patients who have immediate progression of their disease and that rise is considered to be

threatening, hormonal therapy at present remains the standard. The options for patients with truly advanced disease with lethal potential are limited. For patients with serological relapse whose survival is estimated to be less than five years surveillance is recommended for some subsets, motivated different here by the fact that futility for our therapy is often an issue and the use of these agents delayed in order to avoid side effects, and second line hormonal therapies are often given with empirical use and often change the course of PSA concentrations, but have no established long-term efficacy.

For patients with visible metastatic disease, the survival will range in the asymptomatic patients from 14 to 22 months depending on the study, and in here again because of feeling that the agents may not have possessed sufficient toxicity -- sufficient efficacy and the toxicity profile

doesn't favor routine use, observation is used and second-line hormonal therapy. And in a subset of patients in whom symptoms are considered to be imminent, chemotherapy will be used. For patients with metastatic disease, the choices are often between cytotoxic chemotherapy, the only agent that has an impact on survival, or palliative care in order to manage the anticipated symptoms.

The improved agents are enumerated here. Only one, docetaxel, impacts the survival of patients with metastatic disease. The remaining agents possess significant but modest effect directed principally at altering the course of the symptoms that patients possess. The impact on survival of docetaxel in the trial comparing docetaxel to mitoxantrone is unquestioned, but unfortunately relatively modest. Seen here you can see in the two categories of patients in question, those

both with asymptomatic and symptomatic disease, there is a modest difference in the palliative effect and the prolongation of survival observed with these agents, leading to the common practice in the clinic of delaying the initiation of cytotoxic therapy till symptoms are either imminent or present in patients with prostate cancer. This perhaps accounts for this surprising finding, and that is that in androgen-independent patients with prostate cancer nationally there's relatively little penetrance of the widespread use of cytotoxic therapy. Only 8 percent of patients at any point in time receive cytotoxic therapy, and for the patients who have metastatic symptomatic disease it's almost 20 percent, for the asymptomatic patients it's 4 percent.

So what role would sipuleucel-T be considered for in patients with metastatic prostate cancer? And I believe

it fits into the subset of patients in whom there are minimal symptoms, minimal to no symptoms and in whom hopefully a prolongation of good survival will result in an improved both quality-of-life and length of survival. The limited efficacy of agents in these places, the absence of therapeutic alternatives for patients that are imminently threatened is one that would be a great advance for the patients with prostate cancer. Thank you. And our next speaker.

DR. MULÉ: Thank you, Dr. Logothetis.

MS. SMITH: Thank you, Dr. Logothetis. The results presented today from Dendreon's multi-center, randomized, double blind, placebo-controlled trials demonstrate that treatment with sipuleucel-T outweighs both the known and potential risks. The risks associated with sipuleucel-T have been well-characterized. Nearly 500 men have received well over 1,350

infusions of product in both controlled and uncontrolled trials. Of the known risks that are treatment-related, the most frequent are chills, fatigue, asthenia, fever, headache, nausea, vomiting, dyspnea and tremor. These are modest in severity, they are most commonly associated with the infusion and they are well-managed through the adequate pre-medication with acetaminophen and diphenhydramine. This represents an excellent tolerability profile in this cancer patient population.

Potential risks include those associated with venous access, including the need in some patients to place in-dwelling catheters. The frequency of complications due to catheters was low in all clinical trials. Other process-related risks include the possibility that a patient must undergo an additional leukapheresis in the event that either his leukapheresis product or his final product fails to meet the release

specifications, or fails to be delivered within the expiration period. This requirement was infrequent in clinical trials and exposed the patient to minimal additional risks.

Our clinical trial experience to date in controlled trials suggests a possible increased risk of cerebral vascular events. This incidence appears consistent with that seen in men of advanced age with cancer and other risk factors, and while it cannot yet be determined if there's an association between sipuleucel-T treatment and cerebral vascular events, Dendreon will propose increased surveillance in a pharmacovigilance program to better characterize this possible safety signal. In the context of advanced prostate cancer, these risks are very well balanced against the demonstrated benefits of sipuleucel-T treatment, the most important of which is a prolongation in overall survival. This is

achieved in a relatively short duration of a well-tolerated treatment.

There was a high rate of compliance in clinical trials. Over 90 percent of all subjects received all three infusions and only 3 percent of subjects discontinued due to a treatment-related adverse event. This should translate into high acceptance and high compliance in clinical practice. Finally, treatment with sipuleucel-T does not appear to preclude the use of later treatment with other therapies.

In a patient population where the estimated median survival is 14 to 22 months, sipuleucel-T, if approved, would provide a well-tolerated treatment option to prolong survival in men with asymptomatic metastatic androgen-independent prostate cancer. Today represents a significant milestone in the development of cellular immunotherapies. This reflects the collective dedication of patients,

physicians and researchers working to improve the lives of patients suffering from prostate cancer. We thank you very much for your attention today. We have the following experts here available for questions. Unfortunately Dr. Eric Small could not join us today due to compliments of United Airlines. Dr. Tia Higano is here who's also an investigator in our study from the University of Washington. Another investigator, Dr. Paul Schellhammer, a urologist at the Virginia Prostate Cancer Center and Eastern Virginia Medical School. In addition, we have Dr. Christopher Logothetis to provide an immunologist perspective, Dr. Hy Levitsky from Johns Hopkins University and finally our external statistician Dr. Brent Blumenstein will address questions relating to the difficulties in interpreting clinical trials when the primary endpoint has not been met.

DR. MULÉ: On behalf of the

committee I'd like to thank the Dendreon presenters. And the next phase is to have a question/answer period, and I'll open this up to the committee for any questions for the speakers.

MR. SAMUELS: Yes. One of the concerns that I had when I looked at it was the lack of broad participation by diverse communities. As we understand the incidence of the disease, African-American men as you know have a 60 percent higher incidence rate and die at twice the rate of white males, and I'm curious why there was not broader participation by African-Americans in this study. Or in Study 1 and 2, actually.

MS. SMITH: We share your concern with the lack of high participation of African-Americans in our trials. We made several attempts to include investigators and study sites who would have a high enrollment rate of African-Americans. We found that our enrollment rate is consistent

with that of other trials in advanced prostate cancer. We are developing a pharmacovigilance plan to better improve our enrollment of African-American men in our ongoing studies. We intend to work with specialized organizations like the National Medical Association and the Prostate Health Education Network to help us improve our enrollment in this population.

MR. SAMUELS: Do you think the fact that I saw where two centers enrolled probably 25 percent of your patients. I was curious about where are these centers located and perhaps there may be a broader inclusion of centers that affect that market.

MS. SMITH: We have several centers that are in inner cities. We spoke with Howard University, for example, and we were unable to get them on board as a clinical site. There are sites in - several sites in New Jersey, there are several sites

in large cities on the West Coast as well.

MR. SAMUELS: My other question had to do with costs to the patient. Understanding that this audience of advanced prostate cancer includes many elderly males on fixed incomes, and again I'm wondering if the company plans for any patient assistance programs that will take into consideration the cost factor.

MS. SMITH: We believe that sipuleucel-T should be made available to all patients regardless of their ability to pay or regardless of their insurance coverage. We will work to develop a program for indigent care coverage. We plan to assist in every appropriate way to make sipuleucel-T available to all patients regardless of their insurance coverage.

DR. MULÉ: Maha?

DR. HUSSAIN: If it's okay I have three hopefully not too long questions. The first one, you showed us the CD54 quartile

levels. What were the number of patients in these quartiles? So the ones that went from 75 percent and higher lived the longest, but were there 10 patients, 50 patients in that category? If you don't mind showing us that. And if you are able to put that out, perhaps I can ask another question while somebody else is pulling out this one.

MS. SMITH: I'm going to ask Dr. Leon Yu, our Dendreon biostatistician to discuss the number of patients in each one of those quartiles. We basically took the 147 subjects that were randomized to treatment and broke them up into equal quartiles. So I can't do the math quickly in my head here, but if you just divided it by four, each one is the same number of patients.

DR. HUSSAIN: No, but I thought the quartiles represented actually the level of the CD54, not the number of patients. And so that was if - the group of patients

that had a CD54-positive above 75 percent were the upper quartile lived longer, but what number of patients were in those quartiles?

MS. SMITH: I'm sorry, I misunderstood your question. Dr. Provost can expound.

DR. PROVOST: They were divided. The patients were divided equally into four quartiles by their CD54 up-regulation values.

DR. HUSSAIN: So this is not the level of the CD54.

DR. PROVOST: No. It's the patients that had the highest CD54 levels, the patients that had the next highest CD54 levels.

DR. HUSSAIN: This is 25 percent of the total, 25 percent of the total -

DR. PROVOST: Of the total patients.

DR. HUSSAIN: Of patients, not

levels.

DR. PROVOST: Pardon me? The ratio or the? Absolute number of CD54 or patients? We're looking at the cumulative CD54 up-regulation ratio.

DR. SCHER: Right, so it's not the absolute number.

DR. PROVOST: Not the absolute number of cells, correct. It's the CD54 up-regulation product release value added for each - for three of the doses.

DR. MULÉ: If you would overlap the placebo curve on that graph where would it lie?

DR. PROVOST: The placebo patients had CD54 up-regulation values that were lower than the lowest quartile. I'll have to preface. I think I can bring up the slide that has the placebo patients compared. Yes. If we look at the intent-to-treat placebo population, many of them went on to receive salvage which confounds

the issue. So what I can show you that's more clear in terms of CD54 is those patients that had only placebo treatment for comparison with the CD54 up-regulation, and I'll have to also add the disclaimer that this particular analysis has not been formally reviewed by the FDA.

DR. WITTEN: You can ask that, but we'd like to point out that it hasn't been reviewed by us and so I think that, you know, this is something the FDA hasn't commented on, but I will just mention this just to clarify this. It says placebo nerve salvage product. So in other words that gray curve does not include all the placebo patients in the trial.

DR. PROVOST: Right. Right. These are only patients that did not go on to receive the salvage product. So it's not as randomized. Roughly 25 percent of the placebo patients.

DR. HUSSAIN: Okay, so my second

question has to do with Study 3. If I'm not mistaken in the documents we received there was mention about that early on there was an issue about the Gleason score correlation with outcome, and consequently a Study 3 was designed to look at the Gleason 7, or less than 7 I believe. Can you comment about the actual eligibility criteria for Study 3, the sample size of Study 3 and I understand that you were - that that trial is now powered for survival? And when do you expect the results to be available?

MS. SMITH: Currently Study 3 is designed to enroll men with asymptomatic metastatic AIPC regardless of their Gleason score. The study is powered for the primary endpoint of survival. It has 90 percent power for an alpha of 0.05. We're targeting about 500 men in this trial.

DR. HUSSAIN: And where is that now? When do you expect the survival results to be available?

MS. SMITH: The survival results from Study 3 will be available in 2010. It's an event-driven analysis and based on the current enrollment rate it will be about 2010 before those results are available.

DR. HUSSAIN: And my final question, and I apologize if it sounds antagonistic, but I can't help but ask it because you've argued so eloquently, both you and your consultant presenters, that survival is the gold standard, it is what we should be using, what we should be looking at. If that is the case, why would you choose, if you really believe that, to do two trials, I believe 1 or 2, and then the other trial, and yet you chose to go with time-to-progression when in fact in prostate cancer the last 70 years of research in this disease tells you time-to-progression is very difficult to obtain. So my question is if you really believe survival is the gold standard, why did you choose to design two

trials that have a problematic endpoint?

MS. SMITH: Eight years ago when Studies 1 and 2 were designed, progression was an endpoint that was appropriate for this patient population and was felt that would provide important information for these men, particularly who are asymptomatic. Our Phase I and II studies suggested that sipuleucel-T treatment did have an impact on progression and we took that information to use as the hypothesis for the design of our Phase III trials. We did not have any information at that time on whether sipuleucel-T impacted survival, but we knew that survival was a very important endpoint, it was a very important clinical efficacy measure, so we did include a plan to collect that information and analyze survival after all patients were followed. We just had the most information on progression at that time.

DR. MULÉ: Dr. Scher.

DR. SCHER: Personally I have no experience with this agent, so I'd just like to ask the clinicians who have used it, we all understand the difficulties assessing time-to-progression and how it does not associate with survival as we are currently measuring it. So the question is at some point if in fact there is a survival benefit that's real, you have to alter the natural history. So were there other parameters that would - I mean what happened to these patients? They were asymptomatic when they started and then they didn't progress at the same rate using the endpoints that you reported. Did they have you know timing to additional treatment, was that different? I mean, how did this work. Did they all of a sudden become symptomatic and then unfortunately succumb to disease, or were there other ways that you as a treating clinician can say this changed the course for those patients?

MS. SMITH: I'd like to invite Dr. Paul Schellhammer who participated in most of Dendreon's clinical trials of sipuleucel-T.

DR. SCHELLHAMMER: I participated in the Phase III clinical trials, all of them. Therefore I have experience with approximately 50 patients. And in answer to your question there were certainly patients who I observed who from a clinical standpoint had a reversal of fortune with regard to their current status, or their status as they entered the trial. Since it was a blinded trial there was difficulties associated with regard to who was obtaining the therapy, but I will comment on the fact that the well-tolerated therapy as it was delivered with absence of adverse events made the attraction to enrollment very high and in my opinion the benefit as well high. Can I answer anything more specifically, Howard?

DR. SCHER: I'm just - I still don't get a sense of how this drug is prolonging survival. Are the patients not developing pain later on? I mean, was therapy immediately changed? I know you looked at docetaxel use in particular and chemotherapy use, but a number of these patients are still hormonally sensitive. So is there a possibility they got for example ketoconazole which may have changed the course? So unfortunately while you do show an intent-to-treat analysis, you still have a relatively small population at the end of the day, and shifts in a few patients can dramatically change the analysis. So I'm just trying to get a sense as a clinician, if I sit with a patient who is asymptomatic, who is progressing biochemically, who has bone metastasis and is destined to develop symptoms let's say in six months based on randomized trials in this group, what do I tell him? You won't develop pain?

DR. SCHELLHAMMER: As I sit with them I think I'm very comfortable with regard to my experience with regard to the adverse event profile and the statistical issue of survival benefit that I know - am aware of because of the trial analysis to convey to them information that is positive and that is optimistic. But in answer to your detailed question about other than an anecdotal memory of individual patients I must look at the statistical overview as my endpoint for advising the patient.

MS. SMITH: And Dr. Scher, perhaps we can also provide some more information on the intermediate endpoints that were examined in both studies. We had secondary endpoints. In addition to time-to-progression, the primary endpoint, we had time-to-clinical-progression, time-to-treatment-failure and time-to-pain. Dr. Frohlich?

DR. FROHLICH: For those

secondary endpoints, as Ms. Smith noted, showed trends in the same direction as shown here. So time-to-disease-progression, time-to-objective progression as measured only by radiographic means. Time-to-clinical-progression, time-to-treatment-failure as well as time-to-disease-related-pain all showed trends in the same direction. It's also important to note I think part of the challenge with not seeing a stronger association between the two has to do with the variability of the endpoint and in fact how we define disease progression at the present time. If we're seeing an effect in overall survival, presumably we're slowing the progression of the disease subsequent to that disease progression endpoint as we currently define it. And as I'm sure you're aware, there's a lot of interest in divining new ways of defining progression which kind of integrate progression that happens over a longer period of time because this event is

happening so quickly as we currently define it at the present time.

DR. MULÉ: We have a number of questions coming up from the committees so we have a list and I'm not ignoring you. What I'm doing is with Gail we're going through the names. So we have Drs. Taylor, Allen, Dranoff, Marincola and Dr. Kwak. Okay, we'll just add to the list. So, Doris?

DR. TAYLOR: I have a couple of questions with regard to the CD54 up-regulation again. And was there a difference in the up-regulation of CD54 in the fresh versus frozen sample, and what percentage of patients were treated with the frozen sample, that is the salvage patients? And if you analyze the data with regard to adverse events in those patients was there any difference?

MS. SMITH: Dr. Provost? And then I'll invite Dr. Bob Sims to discuss

adverse event profile of the salvage product.

DR. PROVOST: Roughly three-quarters of those patients that were randomized to the placebo arm went on to get the salvage treatment. That salvage product was made from frozen cells that were frozen at the time of their initial apheresis. But otherwise the manufacturing process was the same and the product release parameters were the same as the active product.

When we look at the CD54 up-regulation values for the salvage patients, if we look in the Week Zero, 2 and 4, on the left is what I showed you in my talk. On the right is those up-regulation values for the salvage products. The median up-regulations were the same between those two groups. The slight differences, you don't see the same bump up in the Week 2 and Week 4 infusions.

DR. TAYLOR: And these are

measurements made on the product prior to infusion? These are -

DR. PROVOST: These are - correct. These are manufacturing product release values.

DR. TAYLOR: Okay. And what about adverse events? Was there any difference in the --

DR. WITTEN: Can I just make a comment as FDA, please? Yes. I just want to comment that first of all we haven't done an assessment of comparability of the frozen and the fresh product. It's the fresh product that's being proposed for marketing so the advisory committee should keep that in mind, that in our minds we want you to focus on data related to the fresh product. And also, I think that what the sponsor's going to present is if it's information that hasn't been reviewed by FDA they'll let you know. But the comparisons that we're focusing on are from the randomized trial.

DR. TAYLOR: The question really speaks to whether the cardiovascular accident incidence, cerebral vascular accident incidence is increased based on this population.

DR. SIMS: As Dr. Frohlich mentioned in his presentation, there were 100 patients that received salvage product, and none of those patients experienced a cerebral vascular event following salvage therapy. With regards to your earlier question on adverse events following salvage, this slide summarizes the adverse events. You can see in the column second from the right the 81 subjects treated with placebo followed by salvage have an intermediate incidence of chills, fatigue, fever, pyrexia, headache, nausea. The percentages are intermediate between the sipuleucel-T-treated patients and the placebo-only patients.

DR. MULÉ: Dr. Allen.

DR. ALLEN: I have a couple of questions regarding potency of the product. It seems from the data, and correct me if I'm wrong, but it seems that essentially the amount of CD54 up-regulation is fairly predictive of patient response and actually that the patient demographic is less important apparently. Is that correct?

MS. SMITH: It appears to be independent of the known prognostic factors.

DR. ALLEN: Okay. So based on that then essentially you have a product that, lot to lot, depending on how much patient up-regulation there is, patient-specific up-regulation in your product, that would probably be as good as anything for the clinician to know. The difficulty I see is it appears you have no a priori way of defining that. So in other words your best prognostic data is a correlation between cumulative CD54 over the course of three collections and clinical outcome. So what

are you doing in terms of looking at ways to prospectively determine how good your lot is, how potent it is? Is there anything you can do to increase CD54 at the start of collection, for example, to boost that? Because it seems based on your data you have two clinical studies. One study shows a significant effect. The other study doesn't reach statistical significance although there's a trend. And if you look at the progression data and the survival data, it seems that there's a big difference in basically the progression of disease in those two placebo groups. One potential interpretation would be that you really have a product that is more effective in a slowly advancing disease state and so my suggestion would be that we should focus on ways to essentially get the patient's CD54 activity up and running quicker so we can catch this progressive disease. Do you have any comments?

MS. SMITH: May I have Dr. Provost comment?

DR. PROVOST: CD54 up-regulation is a manufacturing potency release criterion. The data that I showed you for the Kaplan-Meier curves came from adding up the potency measurements from those three infusions for each patient. While CD54 up-regulation correlates with prolonged survival, it's not the only prognostic factor. There were other prognostic factors that influenced survival. So one might be reluctant to rely solely on CD54 up-regulation to try and predict certainly from one dose or one infusion to the next using this kind of value, this manufacturing kind of value to predict survival. I will say, having said that, that we're looking at ways to increase the activation in CD54 up-regulation on cells and that is in active development right now.

DR. ALLEN: Just to follow up on

that. So at this point though there is no - essentially you have a product that has a total nucleated cell count and you have a measure of in that batch what the response is to the antigen, but you have - do you have a cutoff value that you - you know, you'll only release at X or Y? And is that cutoff value based in anything like the predictive values from the correlations?

DR. PROVOST: The cutoff value is based on manufacturing experience. We do have a minimum specification. We don't have a maximum specification.

DR. ALLEN: Okay. And what is the trend in survival for that minimum specification? So in other words, if the lot goes out with that minimum specification, where does it fall on the -

DR. PROVOST: We don't - we don't specify manufacturing criteria based on survival data. We - these are manufacturing criteria so that we know that the cells were

incubated with antigen, that they did respond to antigen. The other tests that I listed in addition to the potency tests indicate that the manufacturing was performed correctly and that the product is safe for infusion.

DR. TAYLOR: That actually - my second question was related to dose and right now my understanding is your dosing is simply based on the ability - or based on what you are able to obtain from the patient. And is there a minimum dose that you're giving, or is there a threshold below which you haven't seen an effect?

DR. PROVOST: We have specifications for the number of cells, total nucleated cells, and that specification is for the incoming apheresis package, the cells that come in, so that we know we have enough to manufacture and get a reasonable infusion out at the end. We also have specifications for the number of APCs

and then all the safety tests, identity, potency, et cetera. So we have experience with a wide variety of cell numbers for these products, and as I indicated before we've examined that cell dose, the TNC cell dose. It's not particularly correlated with - or strongly correlated with survival. It's not as strongly correlated as CD54 up-regulation.

DR. TAYLOR: But there's not a minimum CD54 dose requirement?

DR. PROVOST: There is a minimum CD54 APC dose requirement and a minimum CD54 up-regulation requirement for the product to be released.

DR. MULÉ: Glenn?

DR. DRANOFF: One of the most striking immunologic findings that you include in your report is the relative frequency of responses against your fusion protein, but not against the native PAP protein. So I'm curious how you have

approached this issue, whether in fact you know that the reactivity is devoted toward the novel sequence that's involved in your fusion, but not the PAP, and whether that has any implications for the relative contribution of the PAP part of the product to the efficacy.

DR. PROVOST: We have examined the specificity of the immune reaction. The data that you're referring to I think are shown in the briefing document. I'll bring that up. This shows that we get a robust T-cell proliferation immune response when we sample blood, whole blood from the patients at Week Zero, at baseline, and then at Week 8 and at 16 as Mark described. But we don't see strong responses to seminal PAP or GMCSF. We find a lot of responses to that junction region because - it's not surprising because this is two molecules fused together. Their confirmation may be slightly different and their immunogenicity

may be slightly different. We do see responses against PAP and we have found T-cells in patients that are directed against PAP epitopes. So their frequency is rather low. We don't know whether this is due to the timing or the compartment, whether we're looking at peripheral blood may be the wrong place to go. Maybe we should be looking at metastases or tumor sites, or whether the assays are just not tuned up. We're working on that actively right now.

DR. DRANOFF: And do you know whether those immune responses correlate with the degree of CD54 up-regulation in any way?

DR. PROVOST: They do not correlate with CD54 up-regulation. Yes. If you have more kind of general questions regarding immune response I might defer to Dr. Levitsky.

DR. LEVITSKY: Thanks. Yes, it is an unfortunate wide experience in the

field to have difficulty in correlating measured immune responses to relevant antigens and in clinical outcome. I've thought a bit about the problem that specifically is before us and the unique fusion protein that is used as the immunogen here clearly has neoepitopes at the fusion junction. And I think of it as somewhat analogous to the large experience with either mutated antigens or orthologous genes where in fact you can raise a very strong response against the ortholog and a relatively modest response against the natural self-antigen, yet that response to the self-antigen in animal models is frequently enough to induce autoimmunity reminiscent of the very nice work that Allen Houten's group has done in pigmented mice. So I think it's still conceivable that PAP-specific responses have in fact been generated. It may be difficult to detect in the blood and as you all know many groups

around the world, notably the group in Brussels, has gone to great pains to literally sequence T-cell receptor sequences and find changes that do correlate, but are far below the level of frequency that could possibly be detected in these kinds of assays, so.

DR. MULÉ: Franco.

DR. MARINCOLA: One of the questions that was raised about the immune monitoring and the relevance of the immunologic assays. But I still think it would be nice to have some kind of evidence that the immunologic assays are relevant to the disease process. And the recombinant antigen per se I don't think is really useful. But I understand that the reason - hybridoma that you have been using to test the recognition of the antigen presentation, and what is that recognizing? Is that recognizing something that is specific to the recombinant antigen, or just to maybe

the prostate antigen?

MS. SMITH: Are you referring to the T-cell hybridomas we've used to correlate with our potency assay?

DR. MARINCOLA: Yes, that have been discussed in the briefing.

MS. SMITH: Yes. Dr. Provost?

DR. MARINCOLA: The R I think 1. The RB1.

MS. SMITH: I'm sorry, I couldn't hear you.

DR. MARINCOLA: The R beta 1 I think specific associated.

DR. PROVOST: Right. We used T-cell hybridomas that are specific for PAP peptides, PAP protein peptides in order to assess the uptake, processing and presentation of those PAP peptides by APCs in this product. It's an in vitro immunological assay. It's not an immune response assay. But what we have done is to show that - these are development data that

show that the cells in the product take up, process and present PAP peptides to PAP-specific T-cell hybridomas. Other fusion proteins which we have which are fused to GMCSF and in a relevant antigen do not stimulate those antigens and stimulate those T-cell hybridomas as well. We've also shown that those cells which present antigen are contained in the CD54 cell population.

DR. MARINCOLA: So what about then starting patients they are expressed the R beta 1 ANC, if they're recognized specifically after vaccination? Would that be a reasonable model to look at whether the vaccine is really making a difference in the immune response to the PAP antigen?

DR. PROVOST: We have used patient cells to assess their responses in the T-cell hybridoma assay. However, getting those patients to donate blood for the immune monitoring protocol is another thing and that is actually one of the

challenges of a multi-center trial is just getting enough samples together so that you can get all the immune monitoring done.

DR. MARINCOLA: I have another question about the survival analysis which seems to be the core of the application is the overall survival. And I have to say that if you look at the first - second study doesn't really show much difference at all, but the most concerning thing is when you combine the two. It seems to me that doesn't make it any better. In fact, even the results of the first get dampened somehow. And one of the reasons maybe is that in the first study I thought there was a pretty strong, although probably not significant, bias in the Gleason score. If you look at the individuals that were less - six or less, or like 26 - 27 - 26.8 percent versus 15.6 percent. And I wonder if somebody can comment on this. Maybe I'm wrong, but.

MS. SMITH: I'll ask Dr. Mark Frohlich to comment on the consistency between Studies 1 and 2 and the impact of Gleason score on the studies.

DR. FROHLICH: A lower hazard ratio was observed in Study 2, 1.27, but I'll note the magnitude of that hazard ratio is in fact - demonstrates a 21 percent reduction in risk of death and kind of is on the order of how clinical trials are being designed. CALGB is designing a docetaxel plus or minus bevacizumab trial with a target hazard ratio of 1.25. So still clinically relevant. The p-value is larger because of the smaller number of events.

Another potential reason for the smaller hazard ratio observed in Study 2 relative to Study 1 may have to do with the degree of imbalance between the two arms in terms of PSA, LDH and the number of bony metastases as shown here. And when one adjusts for those using a Cox multiple

regression model, one finds that the treatment effect in Study 2 is in fact as shown in the blue here. So the unadjusted are shown in yellow, the adjusted shown in blue. You can see that the treatment effect becomes more consistent with that in Study 1. Even unadjusted there's consistency of the treatment effects as shown here. They're in the same direction and the confidence intervals overlap. And it's important to note that there are fewer events in Study 2, so there's actually 30 percent more death events in Study 1 than Study 2 so it provides - Study 2 provides a less precise estimate than does Study 1.

In terms of the Gleason score, there were slight imbalances. We performed univariate adjustments for Gleason score. You'll find in your appendix both for Study 1 and also done for Study 2 in which the treatment effect remained consistently strong after adjusting for Gleason score.

We found in both of our studies that Gleason score was not an important predictive factor for overall survival in those patient populations.

DR. MULÉ: Larry?

DR. KWAK: So I have - my questions focus on product characterization. You showed us up-regulation of CD54 for example on antigen-presenting cells, but what were the characteristics of these cells that were being analyzed, and how much heterogeneity is there within patient products and between patients? For example, is - have you done any experiment, could GMCSF alone be responsible for the CD54 up-regulation, or perhaps impurities in the recombinant protein that they're exposed to?

MS. SMITH: Dr. Provost?

DR. PROVOST: We've characterized hundreds of sipuleucel-T products, and we can say without a doubt there's a large variability in the number and composition of

the cells. That being said, the manufacturing process and the final results actually accommodate a large variability in the incoming material. Most of the variability that we find is due to the incoming apheresis material. It comes from the patients.

If I could have the slide that looks at cell compositions for the products. It gives you a survey of the different cell types throughout the product. We've measured both in the products and in a model system from healthy donors, measured antigen-presenting cells are 54-positive, APCs, T-cells, monocytes, B-cells. That's shown here throughout the manufacturing process. It just illustrates the point that the relative ratios remained fairly constant throughout the manufacturing process and that we have a fairly wide distribution of those cell types in the product.

Regarding the CD54 assay, we use

a flow cytometric method to measure CD54. We gate on the monocyte or APC fraction - sorry, I just pulled that down when I meant to pull it up. Can you bring that back up? Thank you. I'll advance that now. This illustrates the method basically that we gate on large CD54-positive cells. We relate the mean fluorescence intensity which is shown in the bottom left - sorry, bottom right. Get my left and right mixed up. The green peak illustrates the mean fluorescence intensity. That mean fluorescence intensity is related back to a standard curve derived from beads which have a known number of PE molecules on each one and we use that to calibrate how many 54 molecules there are on the surface.

Within that population we've looked at other - we've done dual staining analyses to assess whether we're looking at antigen-presenting cells primarily or other cells and that's illustrated here. The

predominant portion of that fraction that we gate on is monocyte-derived CD14-positive cells. Very few of them have CD3 or other lineage markers on them.

And the role of GM is to activate APCs. That's what it's doing in the fusion protein. We can activate cells with GM alone, but we cannot get PAP-specific presentation to PAP-specific T-cells with GM alone. In addition, in the characterization studies we've done on the product GM alone does not elicit the same sort of cytokine responses and other phenotypic responses we get on the cells in the product.

This shows that - here we go. On the left we have responses, CD54 up-regulation ratios. This is from development data. I think I presented this last year at the committee meeting. PA2024 is the immunizing antigen. BA7072 is an irrelevant antigen fused to GMCSF. We get similar up-regulation with those two molecules. Allo-

MLR responses which respond specifically to CD54 up-regulation or APC activation are roughly equivalent, but antigen presentation to PAP-specific T-cells require the use of the PA2024 immunizing antigen.

DR. TAYLOR: A question about your previous slide. You said that 82 percent - approximately are CD54-positive monocytes. In the FITC data - uptake data you showed us it didn't look like the majority of uptake was into monocytes. Can you - I was confused about how that correlates with this.

DR. PROVOST: Let me show you that again. That is a scatter plot, not a FITC label.

DR. TAYLOR: But in the briefing document you showed a CD54 uptake - showed uptake of the GMCSF PAP FITC molecule into CD14-positive cells and it didn't seem that that was - that the majority of CD14 cells took this up and yet here you're saying 82

percent of the CD54-positive cells were CD14-positive. And I'm trying to understand the difference in those. And maybe I just - maybe it's a different denominator.

DR. PROVOST: I'm trying to recall from the briefing document.

DR. TAYLOR: I think that looks like what - yes.

DR. PROVOST: Let me display this. This is I believe from the briefing document. What this shows is that the antigen is taken up by CD54-positive cells and also CD40-positive and HLADR-positive cells basically shows that there are other markers, co-stimulatory molecules on the cells that take up the antigen. In addition, we have some data that I believe is in the BLA showing that PA2024 - FITC-labeled PA2024 is taken up by CD54-positive cells, CD14-positive cells. Very little of those cells stain for CD3. CD19-positive B-cells and CD56-positive NK cells have low

uptake.

DR. MULÉ: For the sake of time we have a list of committee members who are still waiting for their questions. And what I would ask you to do is we have two more sessions in the agenda for questions and answers. So I would ask you to keep that in mind if those questions are more related to the topics later in the day. With that said, Rich, you're up next.

DR. ALEXANDER: I want to ask if you assessed whether at the end the patients were able to discern if they thought they were on the active drug or not compared to placebo. And the reason I want to ask this is because sort of a follow-up to Howard Scher's question is that people before they enter a clinical trial have to be told what the side effects of the drug are, and I'm expecting you probably had to explain to them they were likely to get fever and chills. And so if people with a 50 percent

chance of that in the group getting the treatment and a much lower percent in the placebo, and we're asking what happens to these people and you know, why do men who are facing a lethal disease and want to live longer actually live longer. That's a - I'm not trying to be a Zen master here or something, or a philosophical question, but people who are thinking that they're on an active agent that will help them live longer and they want that to happen, perhaps there's some way that that can happen. So I wonder if - and it would reassure me if they were unable to predict whether they got the drug or not at the end of the trial is a typical thing that we've done in most of the studies that I've been involved with.

MS. SMITH: Dr. Frohlich?

DR. FROHLICH: First, it's important to note that while there is a characteristic adverse drug reaction profile for the product overall, for example the

most common being chills as you noted at 50 percent, that means that half the patients don't have that. So for the individual patient it's not entirely clear and many - a significant percentage of the placebo patients had some of those adverse drug reactions. We actually performed a survey of the patients on the trial in a subset of patients which essentially showed that a third of the patients thought they were on placebo, a third thought they were on treatment and a third said they didn't know which is actually worse than you would expect if you were anticipating a 2 to 1 randomization. So there didn't appear to be any knowledge of the patients as to which treatment arm they were on.

In terms of influencing subsequent therapy, the only data we have, the only agent which has been shown to prolong survival in this patient population is the agent docetaxel, and that we've

looked very closely at as I outlined in my core presentation, unable to find any evidence to suggest an increased use in the placebo arm, a delayed time to use in the placebo arm - I'm sorry, increased use in the treatment arm, or delayed time to use in placebo arm. And we've also performed adjustments for time-to-chemotherapy use and the treatment effects still remain strong.

DR. MULÉ: Bob.

MR. SAMUELS: Yes. My question actually relates to the same question and that is that patient-related outcomes are becoming more of an integral part of clinical trials, and I was curious as to whether or not you guys had a formal process for patient-reported outcomes included in this, and if not, do you plan on doing it in future studies.

DR. FROHLICH: We have not included formal quality-of-life assessments in Studies 1 and 2. Quality-of-life is

somewhat of a challenging endpoint to interpret the results of, but we are interested in doing that potentially in future studies.

MR. SAMUELS: Again, I guess I'm - maybe I'm not clear. Patient-reported outcomes are people who are on studies reporting how they are doing, how they are feeling, are being more and more put into the clinical trial design process.

DR. FROHLICH: I'm sorry. To clarify, that's what I meant by quality-of-life assessment. So asking the patient specifically how they're doing, what their impression is, there are instruments that have been designed to assess that, but there are challenges in interpreting those results because of the variability and subjectivity associated with them. But it is an important thing to assess, I agree with you, and that's something we're interested in doing in the future to get a better

understanding of the experience for patients as they go through the process.

DR. MULÉ: For the sake of time we have five more individuals with questions, so I'm going to cut off this session for questions after the fifth member of the committee has an opportunity to ask their question. So next is Dr. Chamberlain.

DR. CHAMBERLAIN: Okay. Well, I had some questions about again the immune response elicited against your product. Most of those were already answered, but I wanted to follow up two quick areas. One, I guess you implied that the - you appeared to be getting a T-cell response against the novel fusion portion of your antigen, but have you followed that up at all to, for example, by screening peptide libraries around that fusion region to - and in particular, can you tell whether there are any epitopes being recognized that are on the PAP side of the fusion junction?

MS. SMITH: Dr. Provost?

DR. PROVOST: We have looked a little bit at the specificity, and we do see reactivities against the PAP portion of the molecule. We are investigating other assays, overlapping peptides, et cetera, so we can better characterize those immune responses.

DR. CHAMBERLAIN: Okay, and then a slight follow-up. You may have already answered this, but do you have any data in vivo with stimulating cells only with the GMCSF?

DR. PROVOST: Do we have data in vivo? No, that wasn't the objective of the trial. We had plenty of pre-clinical information that told us that the GM alone wasn't going to be the active agent in terms of eliciting the prostatitis. And so we had that fusion protein and had both ends of the molecule there for different reasons.

DR. SCHER: I just have a

statistical question. Essentially the one trial that is definitive even in a post hoc analysis is essentially - evaluates 82 patients. And the question is how comfortable can you feel extrapolating this if you used Dr. Logothetis's estimates to 55,000 men who would represent asymptomatic castration-resistant or androgen-independent disease. There's a lot of sub-analysis here, but I guess the concern is you know again, one or two patients shift and all of a sudden you lose the significance. And many of the analyses, while they do show a relative increase in the hazard ratio, they still touch unity. So again, how confident can you feel in these kinds of extrapolations?

MS. SMITH: I'd like to ask Dr. Brent Blumenstein to comment on the statistical implications.

DR. BLUMENSTEIN: Well, I think that first of all that the size of the trial

is small, but I think the confidence that you should have in the result would be reflected in the confidence intervals. And one of the computations that we did was to show that the lower confidence interval from this trial for example is higher than the low confidence interval from the docetaxel trial. And so I think that you have - you can take this trial with, even though small, that you can take the results with a great deal of confidence. Did I answer your question?

DR. SCHER: A little bit. But in point of fact, the populations in TAX 327 are npt comparable to this population. Those are - there's a large percentage of those patients who had symptomatic cancer-related pain. So I'm not sure that comparison is -

DR. BLUMENSTEIN: Well, I wasn't really comparing the two trials in the sense of that these agents would be used in the

same trial, but I'm talking about the size of the clinical benefit that you can observe from this trial. I mean, I understand the dilemma facing the panel because I've served on these panels before, and as usual, you're having to base your decision on less than perfect data. I think it's important, maybe I can review some of the reasons that I feel that there's compelling evidence of efficacy from Study 1, even though it's not a perfect trial.

I think the formal evidence of efficacy is based on survival which is a definite gold standard in oncology. But as you probably have recognized, there was less than complete specification of survival in the - the survival analysis in the protocol and the SAP. But it's also important to note that in all other respects Study 1 and Study 2 can be characterized as well-controlled and well-conducted clinical trials.

I think that the dilemma that is induced by Study 1 is really relatively minor compared to some of the other dilemmas that have been induced by other oncology studies. For example, you're not being asked to make your decision based on a post hoc identification of a subset of patients, and you're not being asked to base your decision on non-standard statistical methods, and you're not being asked to make your decision based on a variation of a primary endpoint. You're also not being asked to base your decision on the secondary endpoint designed to measure some other aspect of the patient's outcome. Finally, you're not being asked to base your decision on a significant time-to-progression finding in the absence of a survival finding.

So the main issue is that this Study 1 did not meet the TTP statistical goal, and had Study 1 met that goal there would be no issue considering the fact that

there's a significant survival. So let's talk about that for a minute. And there's one possible explanation of why Study 1 didn't meet the survival goal, the statistical goal, and that is based on this delayed effect which you can see, and especially in the right plot there on the graph, that there's a late-emerging separation of the Kaplan-Meier curves. Now this has been observed in other immunotherapies in the last few years. Now, when there exists an identifiable explanation for the lack of statistical significance such as a delayed effect like this, then I think you're compelled to take the clinically meaningful estimate of the hazard ratio of 1.45 from the time-to-progression Kaplan-Meier plot that you see there and that also represents a 31 percent decrease in the hazard of progression, and use that in assessing the overall outcome from this trial when you combine the TTP

results and the survival results. It's also important to think about whether time-to-progression is a putative surrogate for survival, and I think most would agree that under ideal circumstances if time-to-progression is measured well that it is a - that there's a good reason to think of it as a putative surrogate for survival. And what this - the reason that this is important is that in the - under the paradigm of surrogacy, you have the requirement that both endpoints meet statistical significance and that doesn't induce the need to share alpha between two endpoints where you could make a choice between those two endpoints. And if you take the evidence from Study 1's time-to-progression hazard ratio of 1.45 and accept that as an indication of clinical significance from Study 1, then I think it's easy to feel comfortable. And in fact, I mean this is the thought process that leads me to have a high degree of confidence that

these study - the results from Study 1 are real and that there's no inflation of the probability of making a false positive conclusion here.

DR. MULÉ: Richard.

DR. CHAPPELL: I'd like to ask another question about the cumulative CD54 up-regulation clinical results in Slide 60. There's a very dramatic predictive effect of the up-regulation with survival and some of it must be due to the fact that healthier patients have higher up-regulations because if you would overlay the placebo curve it would be at about the green, it would lie pretty much on top of the green curve and placebos have zero percent up-regulation. So if it were only the drug, it would be below all of them. But still, as you demonstrated by your regression analyses, there is some hint that this is a kind of dose response effect. So either way, patients with good up-regulation seem to do

better and my question to you is is there any way to screen patients based on some preliminary information on up-regulation, or do you have any baseline variables, pre-treatment variables that would predict this up-regulation so that you might be able to apply this treatment to the patients who might benefit most?

DR. PROVOST: First, just let me say that CD54 up-regulation is not a prognostic variable. When we're looking at these data they're post-manufacturing and cannot be determined until after the -

DR. CHAPPELL: Well, my question - can you create a prognostic variable as a substitute for -

DR. PROVOST: These are manufacturing data. We can actually - we're investigating now how - what other influences the manufacturing milieu might have on CD54 up-regulation. And we see some slight variations that suggest that the

cellular composition might have an influence, in particular granulocytes may have some influence just in competition for CD54 immunizing antigen for the PAP immunizing antigen. That being said, this is more of a kind of a global issue in terms of overall immune responses and I think I'd like to defer to perhaps Dr. Levitsky who could comment a little more broadly on this type of a readout.

DR. LEVITSKY: Thanks. I'd like to give an immunologist's perspective on the observation that the cumulative CD54 up-regulation has a correlation with survival. So first, just a small piece of biology. CD54, also known as ICAM-1, is one of a series of co-stimulatory or adhesion molecules found on antigen-presenting cells that increases when the antigen-presenting cell is activated. And that activation can occur through a number of ways, toll-like receptors and notably CD40. Now, the reason

I'm going into the biology here is because it's at first counter-intuitive that pulling cells out of a patient in Cycle 2 or 3 would give you any different type of antigen-presenting cell than you got from Cycle 1. So how do you explain the cumulative increase in the second and third cycle? And I think the best explanation is not that the antigen-presenting cells are changing, but rather that the T-cells are changing that are in the bag. The reason I'm going through this with you is I would posit that what they're actually measuring, even though it's on the antigen-presenting cells is really reflecting the nature of the T-cell priming that's taking place over time. So by that criteria, if that hypothesis proves to be correct it in and of itself can't be a prognostic variable. And in fact, the company may not even have control over that in terms of it being something that they could control in the manufacturing process.

It is perhaps more indicative of a patient-specific parameter.

DR. CHAPPELL: So is there any way to get something like that, or a surrogate for it in advance to know which patients would benefit most?

DR. LEVITSKY: So now you're in the realm of who's immunologically responsive and who isn't, and the field hasn't gotten to that point yet.

DR. MULÉ: Maha? You're okay. Kurt?

DR. GUNTER: I have two very quick questions related to the CVA issue. Perhaps I could ask both questions. I'm guessing you could answer them at the same time. The first question relates to any pre-clinical work which I didn't see a lot of description of that in the briefing package, but were there any safety signals related to neurotoxicity or CVA-like events in any pre-clinical animal studies? That's

question one. Question two is looking at the CVA events in the hormone-independent versus hormone-dependent population, I was struck by the fact that there was about 5 percent incidence in the placebo arm versus about 1 percent in the treatment arm in the hormone-dependent and almost the opposite results in the hormone-independent. So can you think of any biological or clinical mechanism or rationale for those apparent discordant results in the two groups?

MS. SMITH: Dr. Frohlich? And I'll comment on your first question. We did not have any information from our pre-clinical studies nor our Phase I and II studies to suggest that there was a possible increased incidence of CVA in these patients. This was not observed until we accumulated the safety database from the Phase III trials.

DR. FROHLICH: And specifically in terms of the rat models that Dr. Provost

showed which demonstrated autoimmune prostatitis, sections of other organ systems were performed and there was no evidence of cerebritis or lymphocytic infiltrate in the brain. In terms of the difference between androgen-independent prostate cancer and androgen-dependent prostate cancer, there are trends in the opposite direction and I think the challenge here is given the small number of events you know in total out of this roughly 700 patients, you know 18 events in treatment and 6 in the placebo, keeping in mind the 2 to 1 randomization, so you're talking about a small number of events here. And I think the key point that we want to make is given the large confidence intervals which overlap one here, it's hard to know whether this is a real difference between androgen-independent and androgen-dependent. And for that reason perhaps the numbers for all studies best reflects this. I mean I think there's no

reason that we would expect that sipuleucel-T would be protective in the androgen-dependent prostate cancer setting.

DR. MULÉ: Okay. At this juncture what we'll do is take a 10-minute break and plan to be back at 10:30.

(Whereupon, the foregoing matter went off the record at 10:19 a.m. and went back on the record at 10:33 a.m.)

DR. MULÉ: Okay, we'll begin with the FDA presentation, and the first speaker is Dr. Wonnacott.

DR. WONNACOTT: Good morning. My name is Keith Wonnacott, and I'll lead off the presentations providing the FDA perspective on sipuleucel-T. I'm co-chair of the review committee, and I will represent the product review team. Dr. Ke Liu is the other co-chair of the committee, and he will represent the clinical review team and present the findings - the FDA perspective on the findings from the

clinical trials. And Dr. Bo Zhen is our statistical reviewer, and will talk about the statistical findings. Although you will not hear from the other members of the review team, I would like to acknowledge them, and emphasize that the review of this BLA is a large, multi-disciplinary effort.

So I'm going to start with my presentation by providing an overview of the manufacturing process, and there are a few points I'd like to make about the process. The first is that the patient cells are collected by leukapheresis. This means that the patient is hooked up to an apheresis device that collects the white blood cells, or leukocytes, from the patient's blood, and this procedure can take up to several hours. And I mention this step because, as we've heard, the apheresis starting material is the greatest source of variability in the product. The next point I wanted to point out is that the patient cells are cultured

with PA2024 antigen, that is composed of GMCSF, which is an immune stimulant and the prostatic acid phosphatase, which serves as the tumor antigen. And this is the critical step for creating an active product. And finally, this whole process takes three to four days, and the entire process is repeated for each of the three infusions that a patient will receive during the course of therapy.

The placebo product is made in generally the same way as sipuleucel-T, with the exception that no PA2024 antigen is added, and the cells are refrigerated rather than cultured. In addition, a portion of the cells are cryopreserved at the end of day zero processing for potential crossover therapy. And the patients who later cross over to receive active therapy will have their cryopreserved cells thawed and reintroduced back into the manufacturing process to be cultured with the antigen, and

later administered to the patients.

So this slide outlines in slightly more detail the impact of the manufacturing process on the patient cells. The apheresis starting material, when it arrives at the manufacturing facility, contains a variety of blood cells. The first steps in the manufacturing process are the buoyant density centrifugation steps, designated BDS77 and 65. And these steps enrich for the mononuclear cells, including monocytes, B-cells, T-cells and NK cells. These cells are then put into culture with the PA2024 antigen, and according to the proposed mechanism of action, the monocytes will take up the antigen and become activated antigen-presenting cells. And we've heard about this. So the manufacturing process is designed to enrich for mononuclear leukocytes, and activate antigen-presenting cells, but it is not designed to control cell number, nor is it

designed to control the relative percentages of the different cell types. And so we hope that the - I hope that the data I present in the next few slides will illustrate each of these points, and provide a framework for a meaningful discussion this afternoon about the implications for product quality and consistency.

So this slide is intended to show that the manufacturing process does not control the number of cells in sipuleucel-T. The figure shows data from Dendreon's clinical manufacturing experience, and I would like to point out - make three observations about the data. First, as Nicole said, Dendreon has established a minimum number of total nucleated cells required for the apheresis starting material, but there is no maximum number, and the range in total nucleated cell number is quite large. Second, the manufacturing process does significantly reduce the number

of total nucleated cells in the product, from apheresis starting material to the final product. And finally, in the final product there is no upper or lower limit for total nucleated cell number, and the range is still quite broad. In fact, there have been differences of greater than a hundredfold in the number of cells that a patient receives.

So this slide is intended to show that the manufacturing process doesn't control the relative percentages of cell types in sipuleucel-T. And you've seen a version of this figure already. It depicts the change in relative percentage of the predominant cell types in the product during manufacturing. The predominant cell types include monocytes which express CD14 and as you heard also are the major cell type expressing CD54, B-cells, which express CD19, T-cells which express CD3, and NK cells which express CD56. The relative

percentages were measured at several steps in the manufacturing process, in the apheresis starting material, after the BDS77 separation, after the BDS65 separation, and in the final product. And what you can see for each of the cell types is that the change in the relative percentage of the cell type is small due to manufacturing compared to the relative variability inherent in the patient themselves. And of note, the potent cells, the CD54 cells, can range from above 50 percent to less than 5 percent of the total number of cells present. So as I said earlier, the process is designed to activate antigen-presenting cells, and this is consistent with the proposed mechanism of action.

So I wanted to present the proposed mechanism of action. And as I mentioned, the antigen-presenting cells take up the antigen, become activated, and process and present the antigen on the cell

surface, all of this occurring during the manufacturing process. The cells are then given back to the patient where the APCs are thought to be able to stimulate antigen-specific T-cells that can go back and attack the cancer cells. So based on this mechanism of action, there could be a potential delay in the effect of the therapy as the immune response develops in the patient. The therapy is thus unlike other cytotoxic cancer agents that directly kill cancer cells. But I will say that, while this is the proposed mechanism of action, we don't know if it is the correct mechanism of action, or alternatively, if it is the only mechanism of action.

So in the next few slides I'll summarize the types of in vitro data to support the proposed activation and antigen presentation activity of sipuleucel-T. First I would like to talk about which cells in sipuleucel-T are responsible for antigen

uptake, and based on all the good questions, you've seen a little bit of this data already. So these data show the ability of the cell types present in sipuleucel-T to take up fluorescently labeled PA2024 antigen. The Y-axis is - represents a cell type-specific marker, and the X-axis represents antigen uptake. So the cells that are specific for the marker and take up antigen will be found in the upper right-hand quadrant of the histograms. This data shows that monocytes efficiently take up the antigen, while T-cells, B-cells and NK cells only weakly or don't take up antigen. These cells - or I mean, this data show that monocytes, which are CD14-positive, are the predominant cell type in sipuleucel-T that express CD54 as it is measured, or as the cells are gated by Dendreon, although we know that other cell types present in the product do express CD54.

Dendreon also provided data to

demonstrate that the antigen-presenting cells show increased expression of co-stimulatory molecules. And so these histograms show the up-regulation of various cell surface markers before and after culture. These molecules are generally recognized as co-stimulatory molecules, and are used to measure cellular activation. The expression of each of these markers is increased during culture with PA2024 antigen. And the expression of these - Dendreon has provided data to show that, as was asked, the GMCSF portion of the fusion protein is responsible for this antigen-presenting cell activation, and the expression of these markers does not increase in the placebo product, supporting the idea that the manufacturing process is able to activate the antigen-presenting cells. But as was also mentioned, it's important that there be a response to the PAP, which is the tumor antigen, and so the

last set of slides will show that the sponsor - what the sponsor did to correlate - or Dendreon did to correlate CD54 expression with antigen presentation.

And so this slide shows IL-2 production by a PAP-specific T-cell clone that Dendreon generated. This T-cell clone secretes IL-2 when it is able to recognize antigen PAP that is processed and presented on the cell surface. The data show that CD54-positive cells are able to present antigen, the PAP antigen on its cell surface, that can be recognized by these T-cell clones, while CD54-negative cells do not present antigen that can be recognized by these T-cell clones. So the ability of CD54-positive cells to process and present antigen is consistent with the idea that they are the active antigen-presenting cells.

So based on these data, Dendreon has established the potency assay described

that is designed to detect activated antigen-presenting cells. Potency is measured as a minimum number of CD54-positive cells that must be present in the product. CD54 is used as a marker of antigen-presenting cells, and it's an indirect indication, based on the data that we've seen, that cells can process and present antigen. Potency is also measured by the up-regulation of CD54, which is a ratio of the CD54 expression before and after culture with PA2024, and up-regulation of CD54 indicates, or is a direct measure of cellular activation.

While the potency assay tells us some valuable information about product quality, there are limitations. One limitation is that the impact of the manufacturing process on cell types other than the antigen-presenting cells, and the role of those cells is unknown. This is a concern since CD54 cells typically represent

only about 20 percent of the final product, and as we saw, can be even less than 5 percent of the total cell population. The role and impact of manufacturing on B-cells, T-cells and NK cells is also unknown. Another limitation of the potency assay is that the ability of sipuleucel-T to induce an immune response against the patient's prostate cancer is unknown, and we've heard a little bit, and Dr. Liu will discuss a little bit more the immune response data in his clinical presentation.

So these points summarize what we hope will form the foundation of a meaningful discussion this afternoon. First, the number of cells present in sipuleucel-T is quite variable. Second, the relative percentages of the different cell types in sipuleucel-T is highly variable. Third, sipuleucel-T contains activated antigen-presenting cells that can process and present tumor antigen, but the function

of these cells when they are returned to the patient is not fully understood. And finally, the contribution of other cells to product activity is not known. And so we're asking the advice of the committee on the potential impact of these observations on the quality and consistency of sipuleucel-T. And that concludes my remarks. Our next speaker will be Dr. Ke Liu.

DR. LIU: Good morning. My name is Ke Liu. I am the clinical reviewer for this BLA. And I'm going to present FDA clinical review and the findings efficacy and safety as outlined here.

Before I start, I'd like to make sure that all of us are on the same page in terms of terminology for my presentation. Study names Study 1 as sponsor referred to, D9901, and Study 2 meaning D9902A. So you see 1 is 1, 2 is 2. Study agents: sipuleucel-T you go to APC8015, and placebo meaning APC placebo, APC8015F meaning frozen

and thawed peripheral blood mononuclear cells as source material, and then prepared similarly as sipuleucel-T.

Proposed indication for this BLA is for the treatment of men with asymptomatic metastatic androgen-independent prostate cancer, or AIPC. The efficacy - the basis for the efficacy claim is based on overall survival difference observed in two Phase III studies, D9901 and D9902A. In D9901, a 4.5-month overall survival difference was seen, and in D9902A, a 3.3-month overall survival was seen, but not statistically significant.

These two Phase III studies were similarly designed, randomized, double-blinded, placebo-controlled trials in men with asymptomatic metastatic AIPC. The primary endpoint for each study was time-to-disease-progression. D9901 enrolled 127 subjects, 82 in sipuleucel-T arm, 45 in placebo. D9902A planned 120 subject, but

terminated early, as I will discuss later, contained 65 subjects in sipuleucel-T arm, 33 in placebo. Study periods are shown here. The key eligibility criteria, treatment schema and treatment regimen has been presented by the sponsor in detail. I will not discuss this further here.

Now I turn to study design. The primary endpoint for each study was time-to-disease-progression as defined by time from randomization to the first observation of disease progression, and assessed by three criteria. First, radiologic progression by scans. Bone scans at the baseline, and every eight weeks, CT or an MRI at baseline, and only if the results were positive, repeat every eight weeks. It should be noted that, by this study design, the soft tissue disease progression in bone-only subject may have been missed because of a lack of regular scans for soft tissue. The second criterion for the disease progression

was new onset of cancer-related pain correlated with X-ray findings. The third one was occurrence of the clinical events such as pathologic fracture, cord or nerve root compression, or other clinically significant disease-specific events. The second endpoint is shown on this slide. I am not going to read them.

Statistical assumptions are as follows. Based on sponsor's past Phase II experience and review of literature, the median time-to-progression was assumed for placebo arm to be 16 weeks. For the sipuleucel-T arm, predicted to be 31 weeks. The trial was designed with 2 to 1 randomization of sipuleucel-T to placebo, 80 percent power and 5 percent of two-sided alpha error.

Now I turn to efficacy results, starting with D9901 first, followed by D9902A. This slide shows D9901 patients' demographic and baseline characteristics.

There's no significant imbalance between two arms for median age, ethnicity, or ECOG performance status. However, about 90 percent of subjects are Caucasian men, with 10 percent of subjects being other ethnic populations. Because of this under-representation of other ethnic populations, it is not known whether the study results can be generalized to the general population, because the biology and prognosis of the prostate cancer in other ethnic populations may be different from those of Caucasian men.

This slide shows distribution of disease status between the two arms in Study D9901 subjects. There are some imbalances noted in Gleason score, disease location, and number of bone metastases per subject. For example, sipuleucel-T arm had more subjects who had lower Gleason score, and more subjects with bone-only disease, and has more subjects with more than 10 bone

metastases per subject than placebo. On the other hand, placebo arm had more subjects who had higher a Gleason score, and more subjects with disease lesions in both bone and soft tissue. These imbalances could have led to the biases to the study results. However, sensitivity analysis indicated that these imbalances did not have impact on overall survival results.

Now the results for D9901. Primary endpoint, time-to-disease-progression, or TTP. One hundred twenty-seven subjects randomized, 114 had disease progression events. No deaths prior to progression events. Progression was documented by imaging in 97 subjects, by clinical events in 10 subjects, and by new onset of disease-related pain correlated with imaging in seven subjects. Shown here is the Kaplan-Meier curves for primary endpoint TTP. Top curve sipuleucel-T, bottom curve APC placebo. Although the

curve appears to be separating around Week 10, there was no overall statistical significance between the two curves. The p-value was 0.085. Median TTP in sipuleucel-T arm was 11.1 week, placebo, 9.1 week. As you recall, the sponsor presented p-value of 0.052. That was a change from 0.085 after initial analysis. This change from 0.085 to 0.052 was based upon unblended audit of clinical data, and revisions in the progression dates, primarily driven by the change of progression dates, or censoring from two subjects in a study with a small sample size.

In addition, difficulties in the interpretation of TTP results are shown in these slides. First, overestimation of time-to-progression. The sipuleucel-T arm presumed TTP was 31 weeks. Actually observed was only 11.1. That's about one-third of the prediction, illustrating the overestimation of the TTP in sipuleucel-T

based on non-randomized Phase II study. Second, median progression occurred before the scheduled second assessment for progression around Week 16. Third, lack of soft tissue scans in some bone-only subjects could have missed the detection of the soft tissue progression in the subject according to the study design. Lastly, some progression dates in some subjects were not interpretable because of the protocol violations. Thus, FDA considers the p-value of 0.05 by log rank test to be the primary results from the primary analysis specified in the protocol, and the p-value of 0.052 to be derived from an exploratory analysis. To conclude on TTP, D9901 failed to show a sipuleucel-T treatment effects on the primary endpoint in delaying time-to-progression. There was no difference observed between the two arms for any of the following second endpoints as listed here.

Now, D9901 overall survival

results. Shown here are the Kaplan-Meier survival curves for D9901 subjects. Top one is sipuleucel-T, bottom one is placebo. There was a separation of the curve occurring around Month 10, and this separation remains throughout the study period. There was an overall statistical significance between these two curves, p-value equal to 0.10. Median survival time for sipuleucel-T arm was 25.9 months, for placebo 21.4 months, 4.5-month difference. Looking at survival rate, at Month 36 where the data was cut off, 34 percent of sipuleucel-T subjects were still alive, and 11 percent of placebo subjects were still alive, 23 percent difference, also reached statistical significance. Dr. Bo-Guang Zhen will discuss to you about how to interpret those p-values in his presentation.

There are several factors that might have potentially compounded overall survival results observed in D9901. First

was a crossover. This crossover could have actually negated the overall survival results observed in D9901. The other one is chemotherapy use. The higher percentage and earlier, longer, or higher dosage of chemotherapy in sipuleucel-T subjects could have led to increased overall survival difference observed in D9901. Now looking at crossover, 75.6 percent of placebo subjects was crossover to receive this APC8015F, a different product other than the sipuleucel-T. Looking at chemotherapy use, shown here is a percentage of the subjects who received chemotherapy after disease progression. Actually, the higher percentage of placebo subjects received chemotherapy, either taxane or any chemotherapy. Analysis of the time from randomization to first chemotherapy use also performed, which did not suggest an early initiation of chemotherapy in sipuleucel-T subjects. However, the dose and cycles of

chemotherapy were not collected during study period. Thus, although unlikely, the potential chemotherapy confounding effects on overall survival cannot be ruled out.

To summarize for D9901 efficacy results, 127 subjects randomized 2 to 1, to sipuleucel-T, to placebo, a small sample size. No difference was observed between two arms in the pre-specified endpoint. Overall survival analysis, however, revealed a 4.5 months difference in the median survival in sipuleucel-T arm.

As Dr. Provost and Dr. Wonnacott described earlier, CD54 up-regulation was used in the potency measurement. Shown here is the correlation of the CD54 up-regulation and survival in Study D9901 subjects using the mean. The top curve is the curve for sipuleucel-T subjects whose CD54 up-regulation above the mean, the middle curve is the subjects, sipuleucel-T subjects with CD54 up-regulation below the mean, and the

third curve is placebo subject. It appears that a higher CD54 up-regulation had better survival. However, the results are difficult to interpret because of the following. It's not known whether this up-regulation of CD54 results represents intrinsic property of the individual patients. Meaning, if patients are going to do better would have a higher CD54 up-regulation, or it's due to the intrinsic property of the individual products after manufacturing process. Should be noted that the placebo cells did not undergo the similar manufacturing process as sipuleucel-T, or this up-regulation is due to other factors.

Another analysis, as Dr. Wonnacott alluded to earlier, was the T-cell stimulation immune response monitoring. Shown here are the T-cell stimulation assay in a limited number of sipuleucel-T and placebo subjects analyzed at Week 8 and Week

16, normalized to Week Zero, using antigens of PA2024 or human seminal PAP. End results are compared between the two arms. It appears that the sipuleucel-T subjects had a higher T-cell stimulation index. Again, the results are difficult to interpret because the proliferation assay used was not the direct measure for T-cell response, and assays performed were only in a small subset of patients. More difficult to interpret, as we had a little bit of discussion, was the fact there's no immune response were found to the human PAP.

Now I turn to D9902A efficacy results. A little history about D9902. It was similarly designed as D9901, planned to enroll 120 subjects, and primary endpoint was time-to-disease-progression. It was terminated early because of D9901 overall negative efficacy results. At the time of termination, 98 subjects already enrolled. The study was renamed the D9902A. Because

of this early termination, this study contained insufficient sample size, not powered to see a difference in TTP or overall survival.

This slide shows D9902A subject patient demographic and baseline characteristics. There's no significant imbalances between median age - between two arms for median age, ethnicity, or ECOG performance status. However, again noted is 90 percent of the study subjects being Caucasian men with under-representation of other ethnic populations. This slide shows the distribution of disease status in D9902A subjects between the two arms. The same patterns of imbalances were noted here in Gleason score, disease location, and number of bony metastases per subject as noted in the Study D9901.

Now the results for D9902A. Primary endpoint time-to-disease-progression. Shown here are two curves of

sipuleucel-T and placebo Kaplan-Meier curves basically overlaps each other. No statistical significance. P-value is 0.719. The median time-to-progression was 10.9 weeks in sipuleucel-T arm, and 9.9 weeks in placebo arm, which was consistent with what's seen in Study D9901. Survival for D9902A. Shown here is the Kaplan-Meier survival curves. Top curve is sipuleucel-T, bottom curve is placebo. There was no overall statistical significance between these two curves. P-value equal to 0.331. Median survival time for sipuleucel-T, 19 months, and placebo, 15.7 months, 3.3 months difference. It should be noted that the survival time in this study was shorter than the counterparts in the D9901, which suggests that the patient populations in these two studies may not be exactly the same. To summarize for D9902A efficacy results, 98 subjects randomized 2 to 1 to sipuleucel-T to placebo. Similar trial

design and execution as D9901. Stopped early, insufficient sample size to detect a difference in TTP or overall survival.

Now I turn to safety evaluation. The mean analysis were derived from D9901 and D9902A database, which included 146 subjects who received sipuleucel-T, and 76 subjects who received placebo. In addition, the sponsor submitted an updated information on cerebral vascular accident events, or CVA events, included CVA events from other Phase III trials, D9902B and P-11. The complete safety database update was suddenly last week to include a total of 461 subjects in sipuleucel-T, and 231 subjects who received a placebo. Looking at infusion exposure, vast majority of subjects received scheduled three infusions, about 90 percent in each arm. This slide shows death events in these two studies. Most subjects died from disease progression, and it appeared that fewer sipuleucel-T subjects died from

prostate cancer, 65 percent versus 78 percent. No deaths were reported within 30 days after last infusion. Noted here was the deaths related to CVA increase in the sipuleucel-T arm, 4.6 percent versus 1.5 percent.

This slide shows serious adverse events other than death in these two studies. Noted again was the increased CVA events among other events in sipuleucel-T arm was 2.0 compared to none in placebo. This slide shows common adverse events that occurred in more than 10 percent sipuleucel-T subjects in these two studies. Adverse events listed here occurred more often in sipuleucel-T arms compared to placebo, including chills, pyrexia, headache, and others as listed in this table.

Now, I'll turn to the CVA events. As you saw previously, it appears that more CVA events were observed in sipuleucel-T subjects than in the placebo. The sponsor

subsequently updated CVA safety information, which included D9902B, 198 subjects in sipuleucel-T, and 96 subjects in placebo. D9902B is another Phase III study with similar patient population as D9901 and D9902A. Ongoing, study is still blinded. Also updated information for CVA included 116 subjects of sipuleucel-T, and 59 placebo. In another Phase III study, P-11, which closed to enrollment with a different patient population which was androgen-dependent prostate cancer, gave rise to a total of subject number for the CVA summary of 461 for sipuleucel-T, and 231 for placebo.

For all subjects from these four randomized trials, the rate of CVA was 3.9 percent in sipuleucel-T compared to 0.6 percent in placebo, odds ratio 1.52. The deaths attributed to CVA was 1.5 percent in sipuleucel-T compared to 0.9 percent, odds ratio of 1.76. In the proposed indication

for intended population, androgen-independent prostate cancer, the CVA rate was 4.9 percent in sipuleucel-T compared to 1.7 percent in placebo. The deaths attributed to CVA in sipuleucel-T arm was 2.0 percent compared to 1.2 percent, the odds ratio 1.76. In P-11, the different patient population, ADPC, the CVA rate increase went to the other direction, higher in the placebo arm. Percentage was 5.1 percent compared to 0.9 percent in sipuleucel-T. And no deaths were attributable to CVA in P-11. So overall in these four Phase III trials, a higher percentage of CVA event was observed in subjects who received sipuleucel-T, 1.3 percent more than the placebo.

To conclude on safety, almost all sipuleucel-T subjects developed adverse events, not different from placebo. Most AEs were Grade I or II, and resolved within 48 hours. Twenty-four percent sipuleucel-T

subjects developed serious adverse events not different from 23 percent of placebo-treated subjects. Although the difference did not reach statistical significance, the increased CVA events observed in sipuleucel-T subjects is a potential safety signal.

To conclude on efficacy, neither studies of D9901 and D9902A met pre-specified efficacy endpoint. However, survival analysis revealed a 4.5-month overall survival difference, statistically significant in D9901, and a 3.3-month overall survival difference in D9902A, which was not statistically significant. This slide shows the advantage of using overall survival in cancer clinical trials as contained in the FDA draft guidance document entitled Clinical Trial Endpoints for the Approval of Cancer Drugs in Biologics. Overall survival is the most reliable cancer endpoint, usually the preferred endpoint, and studies can be conducted to adequately

assess it. An improvement in survival is a clinical benefit. The endpoint is precise and easy to measure, document by the date of death. Bias is not a factor in endpoint measurement. Demonstration of a statistical significant improvement in overall survival has supported new drug approvals.

Now, let's look at overall survival difference in D9901. This 4.5-month median survival difference is clinically meaningful, but it has the following limitations, as Dr. Bo-Guang Zhen will discuss in detail in his presentation. First, post hoc analysis. All survival analysis were done post hoc, because survival was not the pre-specified endpoint, the primary method for survival analysis, and its comparison was not pre-specified. Second, it's one study with a small sample size, so the difference could be due to chance alone. Therefore, uncertainties exist regarding the persuasiveness of the

survival results in the support of sipuleucel-T BLA efficacy claim, and that's the reason why we're all here to discuss these issues today, and FDA would like to seek advice from the advisory committee. Now I turn the podium to Dr. Bo-Guang Zhen, who is going to discuss the overall survival difference from statistical perspective.

DR. MULÉ: Thanks, Dr. Liu.

DR. ZHEN: Good morning. My name's Bo Zhen. I'm a statistical reviewer for FDA. I'm going to present statistical review and findings. First, I will give a quick review on efficacy results, and then bring up the issues in survival analysis, and the limitations of using post hoc analysis results. Then I will describe the challenges we are facing for this BLA from statistical standpoint.

Here is the quick review. Data from two Phase III studies were submitted to support license application. I call them

Study 1 and Study 2. Both studies failed to meet the primary endpoint, and also failed to demonstrate statistical significance for other pre-specified endpoints. The key efficacy evidence was based on the difference in overall survival between the two arms. So the focus of this talk will be on survival.

Here is the review for survival analysis. The sample size is relatively small for Study 1 and Study 2. And the differences in median survival between the two arms is 4.5 months for Study 1, and 3.3 months for Study 2. However, there are higher levels of variation. As you can see there, the confidence interval for median survival between the two arms, they are overlapped. And the lower bounds of the confidence interval for hazard ratio is 1.13, which is quite close to 1. One means there's no difference between the two groups. And also the survival experience

between the two studies are quite different. The placebo patients, the median survival in Study 1 is 21.4 months, compared to the treated patients, the median survival in treated patients in Study 2. This difference could be due to the difference in baseline characteristics between the two studies, and also could be due to the variation, because the sample size is relatively smaller for both studies.

This slide shows some of the sensitivity analysis for Study 1. P equals 0.01 from log rank test. And this p-value reduced to 0.002 using the Cox regression model after adjusting for a set of covariates. However, there are so many ways to use Cox regression model. You can select different sets of covariates. You can also pick different scale for a covariate. For example, in the way you use the original scale and use the log scale for PSA and the power points for bone metastases. As you

can see there, different models. Using different models can come up with different hazard ratios and p-values. This one you get a p-value, it's 0.002, which could be in one of the best case scenario. And this one, you've got p-value of 0.078, which is not statistically significant. That could be in one of the worst case scenario. And this one is 0.048. The other critical issues in using Cox model is excluding patients from the model because of missing covariate data. For this model, 10 patients were excluded. And the next slide will show you how bias can be introduced by excluding patients from the model.

This slide shows that sipuleucel-T treated patients who were excluded from the model had a median survival of 19.4 compared to the rest of the treated patients in the model. And in contrast, placebo-treated patients excluded from the model had median survival is 22.1 months compared to

the rest of the placebo-treated patients. This is how bias could make the p-value look smaller, and also make the treatment effect looks much better than what it should be.

Here is the summary for Study 1. Exclusion of patients due to missing covariate data could lead to biased estimate. This bias could be in either direction, which means you could increase the treatment effect, or decrease the method of the treatment effect. Although p-values for treatment effect were greater than 0.05 in a few sensitivity analyses, the majority of the sensitivity analyses result in a p-value of less than 0.05. So the sensitivity analyses supported the statistically significant findings for overall survival for Study 1. However, I used quotation marks here. Means the so-called statistical significance have the p-value less than 0.05 without adjustment for multiple comparisons. I will have more discussions for these

later.

And for Study 2, p equals 0.331 based on log rank test. Also excluding patients in Cox model could also lead to biased estimate. Hypothesis test for treatment effect in Cox model resulted in a p-value range from 0.023 to 0.642. However, in most analyses, p is greater than 0.05, so the sensitivity analysis did not support the statistically significant findings for Study 2. I also used quotation marks here. This graph summarizes the efficacy survival results. Some of you would like to look at the scale on the log scale. But I used the informatic scale just in order to be consistent with the other presentations.

So the sensitivity analysis support the statistically significant findings for Study 1, but not for Study 2. So it seems the difference in Study 1 is real. However, is this difference statistically significant? In other words,

is this difference due to the treatment effect, or by chance alone. There are some issues here for these kinds of analysis. Here's the issues in survival analysis. Overall survival as an endpoint was not defined in either study protocol. A statistical analysis method for the primary comparisons in overall survival was not pre-specified. Because of these two reasons, so the alpha level, which means the probability of making a false positive claim for treatment effect was not allocated to the primary test for overall survival. We call this as post hoc analysis. And the post hoc analysis make it difficult to interpret the hypothesis test result.

To know the limitations of post hoc analysis, first of all we should know what is a well pre-specified analysis. For this type of analysis it is very essential to, number one, define endpoint clearly, describe statistical analysis methods, and,

if it's more than one method, state which one would be used for primary comparison, and set the alpha level, which in general is 0.05 level. These are also called statistical significance level sometimes. And allocate the alpha level to each test if multiplicity adjustment is needed. Then one is able to say the difference is statistically significant or not based on the p-value from the primary comparisons. Otherwise, it is difficult to interpret the p-values.

And this slide has nothing to do with the submission, but it's very important for statistical concepts. I use hypothetical cases just to show the interpretation of p-value in studies with pre-specified analysis. Just hopefully, through these hypothetical cases, you understand how difficult to interpret the p-value from post hoc analysis. Three different designs are presented here. Trial

1, there's only one primary endpoint here, but three primary comparisons, two for interim, and one for final. In order to control the alpha level, that's the probability of making a false positive claim for treatment effect. At the 0.05 level, we need to split this level into several parts. This is one of the ways to split the level. If this is the p-value you obtained from the hypothesis test, they are now statistically significant, although you can see this one is 0.01, because it is greater than the corresponding values. And Trial B and C have two primary endpoints, one primary comparisons for each endpoint, and this is the way how they split the alpha level. If this is the p-value you get from the hypothesis test, this trial is also not statistically significant. So therefore, if you want to control the probability of making a false positive claim for treatment effect under this level, 0.05 level. So all

these trials should be considered failure.

So from the previous slide we show that obtaining a p-value of 0.01 or less than 0.05 may not always be considered statistically significant in the well pre-specified analysis. When a study fails to meet its primary endpoints, there's no alpha left for other endpoints analysis. So literally, means from pure statistical point of view, the difference in other endpoints should not be considered statistically significant. Therefore, it is very difficult to interpret the hypothesis test result for overall survival in Study 1.

Because in post hoc analysis, one could keep conducting hypothesis tests for treatment effect on different endpoints and - or on the same endpoint using different analyses methods. Just as I show you the Cox regression model for Study 1, different methods, you would come up with different p-values and hazard ratio. Then one - it's

very easy to obtain a so-called statistically significant result, even when there's no treatment effect. So if overall survival is one of the many unspecified endpoints, under testing it is very possible that a p-value of 0.01 was observed just by chance. However, survival is not one of the many, many endpoints that can be randomly selected for testing. Survival is a preferred endpoint for cancer trial. As Dendreon and Dr. Liu just mentioned, this endpoint is reliable, clinically meaningful. This is why we are here seeking advice from the advisory committee meeting.

But here's the changes in survival analysis. Since the analysis was based on post hoc analysis. So it's difficult to interpret the p-value. Here's 0.01 for Study 1. Even someone can make a judgment, this 0.01 is statistically significant. But that statistical significance only demonstrate in Study 1,

though there's a trend for Study 2. And the lower bound of 95 percent confidence interval for hazard ratio is 1.13, quite close to 1, so these results also may not be that robust. That's the end of my talk. Thank you.

DR. MULÉ: Thanks, Dr. Zhen. Okay, we'll open the floor up for questions from the committee. And again, I just want you to be cognizant that the questions may come up this afternoon again. So why don't we proceed and see what we have.

DR. HUSSAIN: This is a question not so much on the presentations, but to the FDA based on the documents you provided us. When I looked at the timelines and the discussions and the summaries of these discussions and agreements between the FDA and the sponsor, one is left with the impression that the FDA did agree to a progression - sort of time-to-progression endpoint for a possible registration trial.

Is that accurate?

And if that's the case, in another committee that I'm part of, ODAC, it was clearly made by several FDA representatives that in the - the progression-free survival will be only accepted in lieu of survival if somehow it was proven in that disease entity as being predictive. And there are some members sitting in the back; they can confirm if I'm misquoting. And that it's my understanding since in prostate cancer progression-free survival or time-to-progression have never been proven to be predictive of survival, that generally this would not be accepted for the purpose of registration. Can you clarify that for us, please?

DR. WITTEN: I can't comment on what we would or wouldn't accept in general, and I do want to point out a couple of things, and one is some of these trials are developed as the discussions take place, and

then there are subsequent, you know, scientific information and discussions that, you know, that might inform the development. But if we have an ongoing trial, we, you know, we may have developed that trial prior to those discussions. We do participate in the endpoint development program with ODAC. We have representatives there, and so we're - you know, we do keep in mind what those, you know, what those discussions are.

DR. HUSSAIN: Yes, I can't help but feel that there is an inconsistency in the FDA position on what would be or would not be accepted for a registration purpose. So here we heard that survival is an endpoint that is accepted. That's not an issue. That's not a problem. In my two years on ODAC, I am left with the impression that, in a disease where there's never been surrogacy demonstrated, a progression-free survival will not be accepted, or time-to-progression is not accepted. So my question

goes back to 1999 and thereafter, the conversations. Why would, say, the CBER I guess accept it, but not CDER accepts it. That's my request for clarification.

DR. WITTEN: Well, maybe I didn't explain it clearly, but we do collaborate with the Center for Drugs in these discussions about endpoints. But when there are studies, they may be developed prior to discussions, and so you have to look at the study development based on where the science is, where the field is, and, you know, the FDA also, when they design trials, they have to do it based on what the information is at that time. So there may be subsequent discussions that would affect studies, you know, future studies in that area, but you don't go back, you know, I don't think anywhere in FDA that you then go back in general and look at all the studies you have ongoing and ask sponsors to redesign those trials. So I think that's, you know, that's

true here. That's true in other indications. That's true elsewhere. And, you know, I think in this case, you know, what we really are focusing on now is, is survival, which I think is not disputable as something that, you know, should be looked at in one of these trials, or would be desirable to look at in one of these trials.

DR. MULÉ: Howard?

DR. SCHER: So I guess there's no argument that overall survival is a definitive endpoint, and that's what we're all seeking to achieve with our treatments. And the question I guess we're being faced with is, how do we estimate what the probability of this being an incorrect or false positive conclusion is. And I was wondering if the statisticians might comment on that to some degree.

DR. ZHEN: Well, my comment is I don't have any way to estimate the probability of making false positive claim

for the treatment effect, which means the Type 1 error rate. We don't know with this study. I don't see any methods to estimate. There's the use of the alpha level for the primary endpoint. That's it.

DR. MULÉ: Kurt?

DR. GUNTER: Thank you very much. I'm not a biostatistician, but I understand that survival, overall survival is a gold standard endpoint. I wonder if the - you could comment on the use of the log rank test. I see that used a lot in survival analysis. Is that a standard way - would that be considered a gold standard test for estimating survival?

DR. ZHEN: I'm not sure I can think log rank test is a gold standard way for survival. I can see many studies that use log rank test. But also there are some studies also use Cox regression models too, and there's also pros and cons between these two methods. But for these type of data

sets I would prefer - for the post hoc analysis, I would prefer to look at the values from log rank test, because if you use models, you could end up with excluding some of the patients due to the missing information for covariate data sets. That could introduce a lot of bias there.

DR. MULÉ: Maha?

DR. HUSSAIN: This is a question perhaps for Dr. Chappell and Dr. Zhen, but Dr. Zhen first. If - so the sponsor presented how changes in a couple of patients brought the p-value down to 0.052, and I understand the FDA position about not accepting that. And supposing there was a third patient, and that p-value came down smack into 0.045. Does that mean if a survival - in that setting, if the survival was not a primary or secondary endpoint, and their primary endpoint hit the p-value that was unequivocally positive, would we still be here? Do you understand what I'm trying

to say here?

DR. WITTEN: Can I answer that?

DR. HUSSAIN: Please.

DR. WITTEN: Because I'm not sure it's a statistical question versus, you know, just a general FDA question. And I'll just say it's a little bit hard to answer hypothetical questions like that. You know, we're given the application based on survival. We think there's no question that this application shows that the study failed in terms of time-to-progression. And so what we would do if the study had shown something else, I don't think we really can answer that. I think we, you know, we really want to focus on what did the study results as demonstrated in this study mean.

DR. HUSSAIN: I still think it's statistical, but I'm going to accept your answer. Because you went through the whole trouble of explaining why is it if your p-value was not significant for your primary

endpoint, why the rest of it doesn't flow, but I will accept that.

I guess my question is this. It's my understanding from colleagues within the Southwest Oncology Group, biostatistical colleagues, that in - there had been at least literature or exercises in terms of simulations driven by different sample sizes and estimates of error rates based on the sample size. Can anyone from the biostatistical group here comment about that by any chance? Because it goes to the heart of the sample size in this case. That a trial with a lower sample size, you have a higher chance of potential error as opposed to a 700-patient trial.

DR. ZHEN: I can just have like a general comments. That's true, if you have a very small sample size, the variation is large, and there's always raise the issues that when you see something different, it's difference due to treatment effect or due to

just by chance alone. There's always issues there, unless you have like a large sample size to stabilize everything. That's one issue is sample size, small sample size. But the other things also important is the alpha level. When you use up all the alpha level, and then there's no alpha level left, you apparently just compare to zero. So it becomes difficult to interpret that kind of results, too.

DR. CHAPPELL: I agree with Dr. Zhen, and would rephrase that there's various issues. One, bias has been mentioned, but if one avoids dropping missing data and the randomization will eliminate the bias, so I'm not so worried about that. Another is the test used, but log rank, if not the gold standard, is the most common. And the third, as Dr. Zhen eloquently put it, is the division of the alpha, which an informal way of describing that is worrying about fishing, a fishing

expedition after the analysis has been done. We're not so worried about what will be done if you specify the protocol, but picking what has been done afterwards, and statisticians have no way of adjusting for all the multiple possibilities of what might have happened.

DR. MULÉ: Doris?

DR. TAYLOR: I'm trying to - excuse me. Trying to speak. I'm trying to understand what the likelihood is of underestimating or incorrectly estimating the relationship between active treatment and cerebral vascular accidents. And then you didn't mention anything about the temporal relationship trend between active treatment and those accidents. Is there anything that we can understand from those data that is statistically meaningful?

DR. LIU: You were asking about the onset of CVAs after the product administration in each of the two arms.

Actually, I think the sponsor may have the better answer for that. They did - yes.

DR. TAYLOR: I guess the statistical part of my question is, the data we saw earlier this morning, we were told there was no good evidence for a statistical relationship between an increased risk for cerebral vascular accidents and the active treatment. And I guess I'm asking for your interpretation of that. Do you concur with that assessment?

DR. BRAUN: I'd just like to address - my name's Miles Braun with the Division of Epidemiology at CBER. And one needs to realize that, as we were discussing, there is one primary outcome that was specified in the study, and Dr. Zhen spoke very well about the statistical aspects of that. Once one enters into the multiplicity of adverse events which are almost infinite that can occur, the concept of asking to assess the statistics I think

is very challenging, and a lot of the certainty that's associated with specifying primary endpoints falls away. And so to some extent, I think one is left with a clinical kind of assessment, and a lot of judgment needs to be used. And I think time-to-onset is certainly one that we use in biological plausibility, but I think it becomes, except in exceptional circumstances, not necessarily a statistical issue. Thank you.

DR. MULÉ: Bill?

DR. TOMFORD: Thank you. I've heard it said twice that if a difference was noted at 10 or 11 months, that we wouldn't be here. So I'll turn that around and ask, at 36 months, was this trial continued at the request of the FDA? How does the FDA deal with a situation where when the trial is continued on a difference or possible difference is noted at 36 months, is that built into, obviously not a predetermined

point, but built into all trials? Or how did that happen?

DR. WITTEN: I'm not sure I understand your question, but can I answer - rephrase it and answer it? So, the trial was designed as to follow the subjects for 36 months or until death. And I think that, you know, the majority of the patients had, except for 30 percent, as you say, in the treatment arm and 10 percent in the control arm had reached the mortality endpoint at that time. There was some additional information that I think was provided the sponsor, but not on a formally planned way on later death events. So the 36-months follow-up for mortality, I think, is what we can you know rely on in terms of having information that's comparative between the two arms. Does that answer your question?

DR. TOMFORD: Yes, thank you.

DR. WITTEN: Okay.

DR. MULÉ: Franco?

DR. MARINCOLA: Maybe it's a naive question, but I'm somewhat bothered by the - some of the p-values that have been presented. The first study showed a significance of 0.01. The second study was not significant, although there was a trend to improve survival, but the rationalization is because it was under-powered. But then when you put the two studies together you would expect in that case, and naive it may be since I'm not a statistician, that the p-value would get better, but in fact it's worse, 0.011 using the same method. Can somebody explain to me what the implication is that and the reason for it? Why wouldn't it get better if it was just a matter of numbers?

DR. ZHEN: One explanation is, when you look at the median survival, the survival experience is quite different between the two studies. Okay, you can see the placebo, the median survival for the

placebo is 31. It's better than the treated patients in Study 2. That's one reason when you combine together they did not add anything. And the 0.01 and 0.011 I would think pretty much the same.

DR. MARINCOLA: So what's the implication for interpretation of the overall experience? What is the interpretation?

DR. ZHEN: Well, there's two ways to explain that. One would be just a baseline characteristic difference. There are some baseline characteristic difference or some unknown prognostic factors, they are different, if there is a treatment effect there. The other explanation is because sample size relatively small. That could be due to the variations, which is also make us think - whether that difference is because the variations or is the treatment effect.

DR. MULÉ: Matthew?

DR. CHAPPELL: Sample sizes of

that size, that small magnitude I would say it's less surprising than expected.

DR. ALLEN: I have a question that's about statistical design. This is purely for informational purposes for myself and educational purposes, but if one was to design a study now so I understand that when one designs a study and looks at power of the study, the variables there are important things. Basically the natural progression of this disease, the fact that it's fairly variable. In 1998-1999 the assumption was made the disease would have a median survival of X, and now it's actually Y in this study group. If one was now going to ask a potential sponsor of a new agent to design a study that would demonstrate as a primary endpoint survival, how many patients would need to be treated in order to demonstrate statistical significance to the happiness and satisfaction of the FDA, and how long would it take to enroll such a

study?

DR. ZHEN: Well, this also depends on what is the delta. What is the treatment effect you believe, okay? If you believe the -

DR. ALLEN: Let me just - let me put it this way. What about demonstrating that something, any new agent is better than docetaxel?

DR. ZHEN: Okay.

DR. ALLEN: 2.4 months. Something that's better than 2.4 months to give patients who need this therapy some improvement in length of life.

(Applause)

DR. ZHEN: And if you say 2.4 months -- I don't think I have a calculator here, but it could require like at least more than 500 patients is my rough estimate.

DR. ALLEN: I guess that was my concept. Okay, thank you.

DR. DRANOFF: I may have missed

this, but the Phase III study that's ongoing now, what are the primary endpoints and the statistical analysis for that?

DR. LIU: You are asking FDA or sponsor?

DR. DRANOFF: Either one. It just seems appropriate at this time to know.

DR. WITTEN: I think we would defer to the sponsor to provide any information on that study that the advisory committee was interested in.

DR. MULÉ: We're speaking about the 9902B, is that correct?

DR. FROHLICH: The primary endpoint of Study 3 is overall survival. Secondary endpoint is time-to-disease-progression. It has 80 percent power to detect a hazard ratio of 1.45.

DR. DRANOFF: How large is the trial?

MS. DAPOLITO: Please use your microphone.

DR. FROHLICH: It's an event-driven analysis for 360 death events. We anticipate roughly 500 patients to achieve that. The primary method of analysis was - is presently a Cox regression model.

DR. SCHER: Just a question to the agency statistician, Dr. Zhen. You mentioned having a pre-specified survival analysis plan. So if the sponsor has to design a trial with a TTP endpoint and then does not meet that endpoint, it seems - was there some agreement on the 36-month as an endpoint, or is there still an opportunity to pre-specify a survival analysis plan? Or is it all done on completion of the trial? I mean, is there any opportunity to sort of I won't say salvage, but salvage the study as you look for longer follow-up and see if, in fact, you do impact on survival.

DR. ZHEN: I think from pure statistical point of view there's no chance to justify this. However, I think that

because overall survival is such an important endpoint it does - one can just use your judgment. It's difficult to quantify the level of the false claim positive treatment effect. It's very difficult.

DR. MULÉ: Okay, I think for the sake of time we'll move ahead to the open public forum. And each speaker will be allowed three and a half minutes. You can use any of the microphones in the room, including the podium, particularly if you have papers and a need to read. So I'll begin by reading the following from the FDA, which is the open public hearing announcement for particular matters meeting, for example product-specific.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing

session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, or if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you did not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. So the first speaker is Jim Kiefert.

DR. KIEFERT: Mr. Chairman, committee members and active participants, I really value the opportunity to be here. My name is Jim Kiefert. I'm a 17-year and a half survivor of prostate cancer and I'm here to make the point that we need more options for treatment for men with prostate cancer.

I was diagnosed in 1989 with a PSA of 39. I was 50 years old. I did my surgery, I did my radiation, and when it failed my doctor looked at me and said, `You better get your life in order because you might have one to three years.' That was 17 and a half years ago. Right now, we need options.

I spent most of my career as an educator. I have a doctorate in education. I was a school administrator, university professor and now I've turned my energies to working with Us TOO, International. Us TOO, International is the largest prostate cancer

education and support organization in the world. We're made up of thousands of volunteers, 325 chapters throughout the United States and many throughout other countries. We're a non-profit organization. Our commitment is to have - to communicate timely and reliable information enabling informed choices regarding detection and treatment of prostate cancer. We need more options for the men with advanced prostate cancer. I manage a support group in Olympia, Washington. I have a number of men who have advanced prostate cancer, and they are pleading for something other than the one drug that's been approved in the last 30 years that will extend survival, and that's chemotherapy.

Us TOO meets with people with prostate cancer through our chapter meetings. We have a website that gets approximately 325,000 hits a month. Men trying to get information about prostate

cancer diagnosis and treatment. We're getting more and more people attending our meetings. We send out 20,000 hot sheets every month to all of our chapters. We're trying to get men informed so they can make informed decisions about their treatments. We also encourage men to be involved in clinical trials, which is not an easy task, as most of you know.

I talk to men on a daily basis about prostate cancer. They call me, scared to death, when they're diagnosed and then they call me really scared to death when they become androgen-independent. That is the scariest time of any man's life when he has prostate cancer because the only option available to them is to go through a chemotherapy regime. We found out in a survey of our members that only 52 percent of the men with advanced prostate cancer would even consider chemotherapy. Sixty-four percent of them said the adverse effect

on their quality-of-life was too great for them to consider that kind of a treatment. I have a handout for you that'll be coming around with some statements from the men who were in our survey. They said, "I'm concerned about the limited options that I have." "I would like some long-term, not just short-term treatments." "I want to enjoy life for a little while." They see their end of life getting very close to them. "I don't believe that any of the options will improve the quality of my life," and many of them say things like, I would just as soon take pain pills and die of my disease than to take a treatment that has such adverse effects on them.

I had the privilege of meeting some of the men that were in the Provenge study. They came to our support group. And when they started telling us about the minimal side effects of their treatment, the guys in my group stood up and applauded.

They said we finally have something that is a treatment that's not such an assault on our masculinity. Prostate cancer is a family disease. It affects my wife, my children, my grandchildren and it seems to last a while for some of us, fortunately.

My urge to you is that we need options. I've said it twice. There's a group called A Voice for Cancer. We are trying to get our word out that we need options. Men are begging for anything else that they can do to save their life and have some quality-of-life. Thank you very much for your consideration.

(Applause)

DR. MULÉ: Thank you, Dr. Kiefert. Dr. Penson?

DR. PENSON: Ladies and gentlemen, members of the panel, good afternoon. I am Dr. David Penson. I am an Associate Professor of Urology and Preventative Medicine at the Keck School of

Medicine, University of Southern California, in Los Angeles, California. As per FDA policy, I'd like to make a few disclosures. I am a site investigator for Dendreon's 9902B study. That means my institution receives research support, but it also means I have firsthand experience with this agent. I do have a consulting agreement with Dendreon. However, neither I nor any member of my family has any financial position, stock or otherwise, with the company. Those statements aside, I come to you today as an independent clinician scientist. I am not receiving any support from Dendreon. They have not paid for my lodging, they are not providing me with an honorarium, and importantly, I have not discussed my testimony with anyone from the company, any employees. As they say, I've come to you on my own dime.

I do not come to you today as a clinician who treats prostate cancer

patients. I am, but you already have those people on your committee. Rather, I come to you today as a health services researcher with a Master's in Public Health and a research expertise in quality-of-life in prostate cancer. I am well-published in this area and I am the principal investigator of an NCI-funded study examining long-term quality-of-life outcomes in prostate cancer.

With that stated, I want to start by saying that I firmly believe that Provenge is effective and will extend life in androgen-independent prostate cancer, based on the clinical trial data showed today. However, that is not my decision to make, it is yours and ultimately the FDA's. What my goal is today is to provide you with additional information to help in your deliberations. I want to make two points to you today. The first is that I believe that there is a quality-of-life advantage to

Provenge over existing therapies, and the second is, I want to remind you that your decision today has public health ramifications beyond what you may think. Let me address each of those points individually.

First, to quality-of-life. As was already stated, there is a single FDA-approved agent which has been shown to extend life in androgen-independent prostate cancer. There is no doubt that docetaxel is effective and is a valuable tool in treating these patients, but it has been said time and time again today, the median survival advantage is roughly two to three months. As the last speaker alluded to, this is a difficult drug for patients. The administration is prolonged, and there are many side effects that come with it. These toxicities are significant and often will require inpatient hospitalization, and this clearly affects quality-of-life. With this

in mind we have to ask the question is the modest survival benefit that we get with docetaxel negated by the potential negative quality-of-life effect of prolonged administration and potential toxicity? I am afraid that the answer to this question is yes.

Now unfortunately, quality-of-life was not studied in the Provenge trials. However, as you've seen this morning, the toxicity profile is clearly quite benign. This drug allows patients to live their lives while they are on the drug. It does not seem to affect quality-of-life in my opinion. So let me repeat again. It is my expert opinion that Provenge offers a considerable quality-of-life advantage over the existing treatment docetaxel with an equivalent or possibly better survival advantage, and I implore the panel to consider this in you deliberations.

My second point concerns the

public health ramifications. I don't need to tell you that prostate cancer is a considerable public health burden in this country. Hundreds of thousands of men are diagnosed with this disease every year and tens of thousands of men die of it. As you know, any delay in approval, assuming this drug is effective, will likely shorten the lives of tens of thousands of men with androgen-independent prostate cancer. The advocates will drive that point home shortly.

But I want to make a point to you. There is an additional ramification here. Delayed approval of this drug will send the wrong message to the research community. If you turn this drug down, it will likely set back the innovative field of active cellular immunotherapy in cancer many, many years. So this will not only affect prostate cancer patients, but it may have an effect on the larger population of

oncology patients in general. So I do hope that the panel will consider both of these points in your deliberations. I am very confident that you will make the right choice. Thank you very much for your attention.

DR. MULÉ: Thank you, Dr. Penson.

(Applause)

DR. MULÉ: Thomas Farrington?

MR. FARRINGTON: Good afternoon panel members and thank you for the opportunity to present before you today. My name is Thomas Farrington. I am a 7-year prostate cancer survivor who has witnessed the deaths of my father and both grandfathers from this sinister prostate cancer disease. I have seen the devastation of this disease up close and personal for much of my life, and believe me, it is not a pretty picture. I have written two books and founded the Prostate Health Education Network in efforts to address the African-

American prostate cancer disparity. PHEN is on a continuing quest to identify treatments and other strategies to help eliminate these disparities.

I would also like to point out that with me today is Mr. Lou Delvidio who is the District Director in Congressman Albert Wynn's office here. He represents this district in the U.S. House of Representatives. I am pleased - Congressman Wynn also is a cosponsor of legislation that has now been filed in the U.S. Congress to designate prostate cancer among African-American men as an epidemic. He is one of 100 cosponsors of this legislation.

As African-Americans, we are in the midst of a prostate cancer epidemic within all of our communities, and we need help now. With a death rate 140 percent higher than for other men coupled with a comparable level of suffering and quality-of-life loss, our need for new and

innovative treatments is desperate and unparalleled relative to any other type of cancer in terms of the death rate disparity.

PHEN has studied active cellular immunotherapy. After closely studying these results, our position is that Provenge should be approved because of the treatment advantage it provides when compared to chemotherapy treatments which are now the only choices for men with late-stage prostate cancer. We understand, appreciate, and respect the challenges before this committee. However, I cannot stress strong enough the immediate need for relief from this disease, a disease that during its later stages is relentless -- and taken away our quality-of-life and then our lives. All prostate cancer survivors live in fear of cancer recurrence. We also live with hope that should our cancer reoccur our lives and the quality of our lives can be saved. This is our reality, what I refer to as battling

the killer within.

Relative to current treatments available for hormone-refractory metastatic disease, data shows that treatment with Provenge allowed patients to maintain a much higher quality-of-life. If Provenge did not exhibit a survival benefit at all, the quality-of-life benefit alone would represent a tremendous help and improvement for survivors. However, Provenge clinical trials show a statistically significant survival benefit, which represents increased hope. We ask that the committee understand, appreciate and respect the real-life needs of prostate cancer survivors and approve Provenge to make it immediately available to help reduce the suffering currently experienced by men with hormone-refractory metastatic disease. Would it be a right or moral decision to deny any prostate cancer patient faced with the possible end of his life the relief that Provenge has proven to

provide now? What is the benefit in waiting?

During this deliberation, we also ask that the committee strongly consider the urgent needs of the segment of the U.S. population that is suffering from prostate cancer at epidemic levels. If the entire U.S. prostate cancer population was experiencing a death rate 2.4 times the current level, would there not be an all-out urgency to quickly bring to market treatments that could help reduce suffering and extend life? This is the critical condition within black communities today, and it is real. We are due the same valuation on our lives and urgency of action. Most every African-American family today is facing prostate cancer at some level, and the fear and suffering is palpable. We ask that the committee both understand and accept that another important reason for approval of Provenge immediately

is because it is needed to help fight the ravages of an epidemic-level condition in a segment of our nation's population. Again, I ask would it be a right or moral decision to deny addressing an epidemic-level condition with Provenge, a treatment that has proven to be safe with the ability to help reduce suffering now? What is the benefit in waiting?

The prostate cancer survivor community is excited that active cellular immunotherapy could eventually provide a broader range of treatment options to help us fight this disease and maintain our quality-of-life. We are prayerful that the dawn of this new era will be launched with the immediate approval of Provenge. I appreciate the committee's consideration of my comments and thank you for allowing me to raise a voice on this issue.

(Applause)

DR. MULÉ: Thank you, Mr.

Farrington. Eduardo Garcia?

MR. GIACOMO: My name is George Giacomo. This is my cousin Eddie, and this is our grandfather Eduardo Garcia.

About six years our grandfather was diagnosed with prostate cancer. It was a difficult time for me and my family because he was the patriarch of our family. We had always known him to be very energetic and fun. In fact, at 60 he started his own business. He enjoyed taking us camping and to the movies, and for his age he was extremely active. Shortly after the cancer spread to his bones, however, he became listless. He no longer had the energy or the will to do things he regularly did. He was often tired and wasn't able to play with his dogs or take his regular walks. His illness was keeping him from doing the things he loved.

Doctors offered him few treatment options, including radiation and chemo.

They warned him about the side effect profile and the little benefit they may - he may receive from treatment for his advanced diseases. My grandfather refused because, as he put it, he preferred to die with dignity. Then his doctor mentioned a study that was being done for an experimental treatment. We urged him to try it and he figured he had nothing to lose. Just a few months after beginning the clinical study for Provenge, his bone scans showed that the cancer had stopped growing. After a while, he started to get some of his energy back. Even his mood improved. He was able to play with his dogs again, which you have to understand is a very important part of his life. He was able to travel and see his friends. He was back to doing the things that he loved to do regularly before the cancer. As you can imagine, it was a relief for all of us.

Before my grandfather took part

in Dendreon's study, we had been preparing ourselves for the end. This new drug offered us some hope. We're grateful for it because Provenge extended his life. Since taking Provenge he's had the opportunity to see two grandchildren get married and the birth of his first great-grandchild. He's taken multiple trips to Mexico and toured around Europe. He's even making plans to open another business. As far as his family is concerned, we're extremely grateful for Provenge because it's given us more time with him. It's allowed him to live a full life and one with dignity. On behalf of myself and my family, I'd like to thank the doctors and scientists who created Provenge, and we'd like to ask this panel to recommend to the FDA to approve Provenge so that other families can have more time with their loved ones, as we've had with our grandfather.

MR. GARCIA: Good morning. My name is Eduardo Garcia, and I would like to

have a few words why Provenge is important to me. Since my grandmother passed, I have been the only one that's lived with my grandfather. I live with him, same house, same roof, and through these eight years that Provenge has given him, it's given me an opportunity to spend very memorable times with my grandfather, such as 16, buying the new car, he was there. Eighteen is the legal drinking age in Mexico, he was there.

(Laughter)

MR. GARCIA: And finally, just recently, 21 which is now legal here. You see, my grandfather is not just an old man you go see on Sundays. He is like a third parent to me, and if it were not for Provenge he would not be here with me. So I would just like to thank the people who created the drug and this panel for recommending the approval of this drug so that other families can experience some of the memorable moments that I experienced

with my grandpa.

MR. GARCIA: I am not a doctor. I cannot tell you all the things I've been hearing all morning. I mean to me it was like a foreign language.

(Laughter)

MR. GARCIA: My name is Eduardo Garcia. I'm 83 years old and I've been a survivor of the bone cancer for seven years. Now, the way I see things here, the way I hear things here is that everything has been studied, you know, what's going to happen. The main thing is, suppose you don't approve this drug and there's thousands of patients who are going to have to look for something different, different options, which is not the chemo because I know chemo would really - I mean, the quality-of-life is very important, especially for an old man like me. So it's really up to you people to think about it, not us, but the ones who are coming, the ones who are going to need

something to do besides the others. Thank you very much.

(Applause)

DR. MULÉ: Thank you, gentlemen. Steven Fleischmann.

MR. FLEISCHMANN: Good morning, ladies and gentlemen. My name is Steve Fleischmann, and my wife Patty and I are honored to be here today, and we're from Seattle, Washington.

In July of 2003 I was 47 years old, and I went in for my routine physical. And although my PSA level was very low, my doctor thought that he had felt something odd on my prostate, so he encouraged me to go in for a biopsy. So of course, to be safe, I went in soon after and had a biopsy done. And I can tell you that I will never forget what happened the next week when I received a call from my doctor. While holding my breath, he said what I never thought I would hear. "Steve, you have

prostate cancer. And not only do you have prostate cancer, but you have a very aggressive prostate cancer." and at 47 years old I had a Gleason 7. I was scared to death. I went into shock. I could not believe that I had cancer, but it quickly became my reality.

After searching my options, I chose to have a radical prostatectomy on September 9, 2003. And after that I had a new sense of purpose in life. I wanted to make this difference and this experience less frightening for other men diagnosed with prostate cancer, and number two, I wanted to raise money to advance research to eventually cure this disease.

So I have made it my life's mission, aside from taking care of my family and my health, to be an advocate for the men throughout the United States who are diagnosed with prostate cancer. I created the first prostate cancer fundraiser in the

United States where I did a fundraising breakfast, which I call Survivor Celebration, in Seattle, Washington, and where every table captain is a prostate cancer survivor. In just two years I have raised $4 million for prostate cancer research, and I am proud to say that at my last breakfast where I had 1,200 attendees that Lance Armstrong was my keynote speaker.

In addition, I receive two to three phone calls a week from men from all over the United States who contact me who have just been diagnosed with prostate cancer, and I help them to deal with the initial shock. They are scared and confused and don't know what to do. And I help them establish a game plan for dealing with their options. So I know firsthand how badly prostate cancer patients need help. They want and deserve treatments that will help them live longer but won't compromise the quality of their life, like chemotherapy.

And that's why I'm here today, to tell you they need a treatment like Provenge. We need it now, not in several years from now. We need it today.

Just a few weeks ago, I was told that my cancer has now come back. Being told that I had had cancer in 2003 was the biggest shock of my life, but I got over it. I just dealt with it. Hearing that my cancer is back is ten times more frightening, and it feels ten times more devastating for me and my family. So as a man who has time working against him, how young I am, advancing care for prostate cancer patients is of vital importance. The timely approval of Provenge just has to happen.

You all have the opportunity to make history today. Provenge would not only be the first cancer immunotherapy ever approved by the FDA, but its approval would be the only thing that will help drive

future research to find a cure for prostate cancer. As someone who has made a living in the financial and investing business, I know how it works. A positive decision today will accelerate the research, investment and support of immunotherapy prostate cancers and other cancers. By you recommending the approval of this first generation of Provenge, you are creating a launching pad for a dramatic increase in the enthusiasm and investment for cancer research, which we all know will ultimately put us much closer to the second and the third and the fourth generation of this kind of product.

I have an 8-year-old daughter and a 5-year-old son. I want to be around to see my kids grow up. I want to see them go to college, get married, and I want to see them have their children. I don't want to die. I want to stay alive.

Now that I have cancer again, I know how it feels to be vulnerable every

single day, and I am concerned about my future now more than ever. This kind of drug, Provenge, is all I can think of right now to give me hope, and as someone who coaches new patients each week I can tell you that the idea of Provenge will give them hope and the will to survive if they get their cancer back. What is the harm of approving a drug that has been shown to let men live longer? I don't care whether it helped 100 or 100,000 men to live longer, it does, and that's what counts, and it is incredibly safe.

I know that you are all a panel of esteemed medical experts who are charged with looking at the data that has been presented to you in making a decision. I only ask that you also consider the fact that you have the power to alter the way cancer is treated by approving Provenge. You can give the 230,000 who will be diagnosed with prostate cancer this year

alone the opportunity to live longer, better lives. You can give me the opportunity to live and with time working against me I can't afford to wait any longer. On behalf of my wife and my two children I thank you for the opportunity to speak here today and for listening to me. Thank you.

(Applause)

DR. MULÉ: Thank you, Mr. Fleischmann. Jack Kriney?

MR. KRINEY: Thank you. Good morning. Ladies and gentlemen, my name is John Kriney, and I'm a patient advocate with Raise a Voice speaking in support of Provenge. I have no relationship to the sponsor and I must say I'm humbled to be in the company of the advocates that I've seen and heard here today.

I was diagnosed with prostate cancer in November of 2005 with a Gleason score of 8, four plus four. I underwent a robotic-assisted laporoscopic radical

prostatectomy on December 20, 2005, but the procedure failed and I began initial hormone therapy in January, 2006. After some difficulties with my initial urologist I was ultimately successful in drawing together a team comprised of a new urologist, medical oncologist and radiation oncologist, all specialists in prostate cancer treatment. I quickly began receiving increased dosages of additional hormone therapies, and a second expert opinion was ordered on my surgical pathology which upgraded my Gleason score to 9, four plus five.

I began 45 IMRT radiation treatments in August, 2006, which then ended in October, 2006. During the time I was undergoing radiation therapy, I had three severe drug reactions and was diagnosed with Grover's Disease after suffering six iterations of full body rashes and boils as well as stress onset bipolar 2 mental disorder. A good portion of the radiation

1 therapy was into the rectum and caused a
2 fair amount of transitory side effects,
3 which passed within months. However, my
4 hormone therapy side effects of
5 irritability, lack of focus, lack of
6 concentration, depression, inability to
7 multitask and physical effects like breast
8 growth with tenderness and fatigue continued
9 to plague me. I do not suffer the normal
10 side effects of lack of sexual drive, since
11 my prostatectomy was non-nerve sparing. In
12 August, 2007, my oncologist and I have
13 decided that I will go on intermittent
14 hormone therapy in order to ameliorate these
15 effects as well as the other long-term
16 systemic side effects associated with
17 hormone therapy.
18 Drugs like Provenge, when you
19 deem them safe and effective, are important
20 in our arsenal of tools that we must have to
21 fight prostate cancer with every today. I
22 am not here to tell you how safe or

effective I think Provenge is. I would not presume to do so. That is your job, and you know it and do it well. What I do know as an advanced prostate cancer patient is that I need drugs and treatments that do not leave me with unnecessary side effects, especially side effects that interact with other drugs and make my life miserable. As a patient, I want longevity if you can give it to me, but as importantly I want quality-of-life along with that longevity. I am not hormone-refractory yet, but I do have metastatic disease, and I know I am playing a waiting and delaying game, a nightmare that I live with every day.

I want to raise a voice today so that when the time comes with drugs like Provenge I will have it available for me while I still have a chance to use it, while I still have an immune system, while I still have something left to fight with. I am here today to try to help others who are

advancing with disease before me and who may not have or get the opportunity to wait another six or nine months for a drug like Provenge to get to market. I hope that you will look at the people and not just look at the numbers or the design of a study. I am here asking today for you to help me and others like me. You can help with the stress of my disease by making Provenge available to the market so that we patients with our doctors can make the informed choice to determine if a safe and effective drug that you have investigated may help prolong our lives and our quality-of-life for us when we need it. Some of us don't have the time to wait for trials and more trials. We depend on you, all of you sitting here, to lead us to the innovative life-saving drug, vaccine, or therapy that will save our lives and not protect us from that same vaccine or therapy while we stand in line dying, waiting for it. As

importantly, when you approve this drug and mode of treatment that others offer - I'm sorry. When you approve this drug and mode of treatment that offers little or no side effects, you will dramatically improve the quality-of-life for a great number of advanced prostate cancer patients. When it is available, we can use it as indicated or off-label and improve our survivability and quality-of-life. Relief from hormone therapy, chemotherapy and the roller coaster of wondering what will work and when are the benefits we will have if we have access to a vaccine that helps our immune system do as it was designed to do in the first place.

FDA Commissioner of Food and Drugs Dr. Andrew C. Von Eschenbach is quoted as saying, "From new life-saving drugs and vaccines to innovative devices, the lives of millions of people have been improved by the dedicated efforts of FDA employees. It is a strong foundation upon which to build in the

21st century." If you deem Provenge to be safe and effective at all, your action will be the very first innovative step on the path of a longer and better life for the advanced prostate cancer patient and survivor in this 21st century. Thank you very much for your care, understanding and patience in listening to us, the surviving prostate cancer patient.

DR. MULÉ: Thank you, Mr. Kriney.

(Applause)

DR. MULÉ: Is Thomas Powell here? Thomas Powell? Okay. Michael Bernstein.

MR. BERNSTEIN: Good afternoon. Thank you for allowing me the opportunity to address the committee. I don't have any financial interest in the sponsor here. I'm a partner in a large Washington-based law firm, and we do represent various pharmaceutical companies, but not the sponsor.

I'm here today not in my

professional capacity but because my father has advanced prostate cancer and he's recently found out that it's androgen-independent and his PSA is going up. He's asymptomatic at this point, so I understand and he understands from his doctors at the Cleveland Clinic that he's in the population group for which Provenge would be ideally targeted. He said that his medical oncologist and his urologist are watching very carefully the Provenge approval process because of the stage of his disease and because this is the time when it would be likely to have the biggest effect for him.

My father is a religious Jew and he goes to synagogue every day, every morning, praying that he'll have the opportunity to see my son become Bar Mitzvah in three years and two months from now. This is his remaining goal in life, really his only substantial remaining goal in life. Of course, it's not clear that he'll make it

even with Provenge. Who knows? But it does seem clear to me that his chances are much more - are substantially enhanced with Provenge than without Provenge. And we have the hope that with this treatment, combined with other treatments which he's willing to deal with even though they have very substantial side effects in order to achieve his goal, that he may make it to see Josh's Bar Mitzvah.

Now I know that if you look at this from the perspective of a statistician, I'm sure you could come up with reasons to defer approval if you wanted to. You could talk about what the primary endpoint was and what it should have been and statistical analysis and Cox regression and other regressions and so forth. And I'm sure you could come up with a reason to defer it. But if you look at this from the perspective of my father and those like him, it seems clear that the better course is to approve

the treatment now. If you ask the question during your deliberations, "Is Mr. Bernstein in Florida more likely to live to see his grandson's Bar Mitzvah with Provenge approved or without it approved," I think the answer is very clear. And I submit to you that under the present circumstances that's the right question to ask. You have a terminal disease. You have no other treatments that are particularly effective, and the couple of treatments that there are at this stage, or maybe the one treatment is very, very unpleasant. And you have a new, apparently safe treatment with very modest side effects that gives guys like my dad a chance to make it a few more years, which is all he's asking for. You should look at this from the patients' perspective. You should put the patients' interest first. I heard reference to the gold standard here. I can tell you, I can assure you that from my dad's perspective survival is absolutely

the gold standard. So on behalf of my father, who can't be here today I ask you to recommend prompt approval of Provenge so that we can have the best possible chance for him to attend Josh's Bar Mitzvah. Thank you.

(Applause)

DR. MULÉ: Thank you, Mr. Bernstein. Joel Nowak?

MR. NOWAK: Good afternoon. I'd like to first say that I nor any of my family members to the best of my knowledge have any financial interest in the sponsor. My name is Joel T. Nowak, and I'm here today both as a consumer and also as a representative of the advocacy groups Raise a Voice and MaleCare, for which I serve as the Program Director for Advanced Prostate Cancer.

I am 56 years old, I live in Brooklyn, and I am a 3-time cancer survivor. I have been diagnosed with thyroid cancer,

kidney cancer and prostate cancer, advanced prostate cancer. The cancer that scares me the most, probably based on my condition, is the prostate cancer. Fortunately, both the thyroid and the kidney cancer are currently under control, but the prostate cancer is not. My initial diagnosis was in August of 2001 and I had a laparoscopic prostatectomy. In December of 2005 I was diagnosed with recurrent advanced prostate cancer. This is not a curable disease. That's the key. It is not curable, at least not yet.

According to the National Cancer Institute, the expected mortality rate for advanced prostate cancer is over 50 percent within 36 months of diagnosis. If you take the statistical next step, since I've already exhausted 16 of those months, which means I may have only but 20 months left to be on this Earth. What are my treatment choices? Unfortunately they're fairly non-existent with other than one exception.

Those of us who suffer with advanced prostate cancer have already gone through the mill of barbaric treatments. We've had our prostates removed or radiated, often leaving us with varying degrees of incontinence and impotence, and then 30 percent of us suffer a recurrence. This signals the beginning of our clock's final countdown on this Earth. We try to buy a little more time. We try salvage radiation or surgery. We start a hormone blockade that leaves us as physical and chemical eunuchs. We lose the little sexual ability that we may have managed to cobble together and trade it for hot flashes, loss of muscle mass, loss of bone density, peripheral neuropathy, mood swings, and a host of other ailments. Despite the suffering that we endure, our cancer continues to march on. Now our only option to survive a little longer as it exists today is chemotherapy, where we have to introduce into our bodies

chemicals that will hopefully kill the cancer, but will also kill us.

Provenge will not cure my disease, that's clear, but it does offer an opportunity to extend my life. Even a 4.5-month life extension, which probably doesn't sound like a lot to those of you who are blessedly healthy, but to me this is a 20 percent increase of my life expectancy. I still will not live long enough to see my son successful in the theater, or my younger son fulfill his dream of going to law school, or more importantly to ever meet any of my grandchildren. But I will have some additional time to hold my wife and laugh with my children, and therefore, I wish to urge this committee to recommend that the FDA approve the pending application. I appreciate this opportunity to have addressed you and thank you so much.

(Applause)

DR. MULÉ: Thank you, Mr. Nowak.

James Waldenfels?

MR. WALDENFELS: I am Jim Waldenfels, a board member of the Virginia Prostate Cancer Coalition, but speaking on my own behalf. I have no financial conflicts of interest or sponsor ties. Thank you for incorporating a public comment period into your review process. This is why I have a very personal interest in Provenge.

My first PSA test result, when I was age 56, was 113 and within days of biopsy indicated an aggressive Gleason 7 cancer with all cores positive, most 100 percent. Within a month, respected urologists from Johns Hopkins and the City of Hope had both given me a prognosis of five years, three good years and two declining years. That was December and January of 1999 and 2000. Today, seven years later, I am fit and vigorous as I enter the fourth off-therapy - fourth month

off therapy under my second off-therapy cycle of intermittent triple blockade, achieved without surgery or radiation. At the end of both off-therapy cycles I achieved a PSA low point of less than 0.01. During the first off-therapy period, virtually all my side effects disappeared, and I expect the same for this period. However, despite my highly successful treatment, my cancer is still likely to become resistant to hormone blockade at some point. My case illustrates that prostate cancer is developing so rapidly that the - technology, the knowledge about it is developing so rapidly that even good doctors cannot keep up with all developments, and key new knowledge emerges in the middle of clinical trials.

Before retiring, I served as a Navy contract specialist and contracting officer for the research and development test and evaluation of weapons systems. DoD

faced a similar problem to that facing the prognostic factor prostate cancer community. The nature of the threats and technologies was changing so rapidly in the `90s that our standard procurement and development methods were not keeping up, and we were risking obsolescence at first delivery of equipment. In order to meet needs, we had to radically change our way of doing business, and we did. Similarly here, cancer technology and particularly the knowledge of the effect of prostate cancer immune responses to drugs is changing more rapidly than can be accommodate in trial designs. That puts a high premium on judgment in capitalizing on trial results.

The 55,000 patients now hormone-refractory and asymptomatic and those of us waiting in the wings are counting on this committee to give us Provenge as a badly-needed option. Its effectiveness has been proven. Remember those patients who beat

the heck out of the median like Mr. Garcia. We haven't heard much about that in this meeting, but remember that. We can look forward to even better targeting of this drug. It has an excellent side effect profile. Please help us.

(Applause)

DR. MULÉ: Thank you, Mr. Waldenfels. Ed Grove?

MR. GROVE: Good afternoon. My name is Ed Grove. I have no financial connection with the sponsor, and I would also like to thank Raise a Voice because if I hadn't heard from them I wouldn't be here, and I think it's just very, very important for me to be here along with the rest of you.

My name is Ed Grove and I'm a prostate cancer survivor for 14 years. I've been chairman of the INOVA Fairfax Virginia prostate cancer support group for 10 years, and we have about 60 members in our email

list. We are very active and have a monthly meeting with a very rich group of speakers. I am also on the board of the Virginia Prostate Cancer Coalition along with Jim Waldenfels.

In my situation I currently have a slow-growing recurrent prostate cancer. It is asymptomatic, but probably not metastatic, and certainly not now hormone-refractory. However, I strongly believe Provenge could help me and my situation, and have tried to get on existing Provenge trials to no avail because they are only for men with very advanced disease. Those of us with recurrent disease must be warriors actively fighting this disease, rather than passive warriors, and this is the reason why I am sort of looking out towards Provenge right now, because I have the sense, and again this is just an intuitive sense, that for people with - and it may be in the data too, but for people with less advanced

disease, Provenge might even work better, and it might even work better earlier. So again I'm, you know, I really firmly believe that those of us with recurrent disease must be warriors actively fighting it rather than passive survivors, and I am so glad to see so many active warriors here today. So and another way I look at this is I believe that prostate cancer warriors, we all need as many arrows as we can get for our quivers, and Provenge really could be one of them, particularly since it could strengthen our immune system with minimal side effects.

Indeed, I have a unique journey here. My immune system has played quite a critical role in my journey with prostate cancer. Diagnosed with early-stage disease in `92 and after having had what I call plain vanilla external beam radiation in early `93 I was doing fine with a nadir PSA of 0.06. However, I also had thyroid cancer in 1966 and it was in remission, but in 1997

it came back again after 30 years. And so what happened to me is when I had this recurrent thyroid cancer in 1997 I had to go off my thyroid medication. This substantially reduced my metabolism. Then I was zapped by a significant dose of radioactive iodine, which further compromised my immune system. The good news is that my thyroid cancer was driven into remission and has not returned. However, during and following this treatment my PSA rose, at one point tripling at only nine months. Fortunately, as my immune system recovered from the thyroid cancer treatment, the PSA rise slowed.

During the eight years from 1998 to 2006, I was able to slow further the rise of my PSA, and this is because I found three non-invasive arrows for my quiver. The first was the active form of Vitamin D called calcitriol. A small study by Dr. Thomas Stamey at Stanford showed that

calcitriol markedly decreased the PSA doubling time of radiation in surgery patients with recurrent disease. Calcitriol did a good job for me of slowing my PSA for two years.

I then began to use the alpha 5 reductase inhibitors, first proscar and later avodart. The second arrow worked for an additional four years. However, after this time my PSA had reached the mid-teens, but then I saw a West Coast study on leukine by Dr. Eric Small which substantially increased the PSA doubling time of most men with recurrent prostate cancer in this trial. The immunotherapy leukine which I was able to be able to use kept my PSA stable for two more years before it reached 18. However, because of reaching this level and it looked like the leukine was having to work hard just to keep it there, last fall I went on triple hormonal therapy, adding casodex and lupron to the avodart I was

taking. It is working well, and I hope to stop it after a year.

However, when I go off hormonal therapy and knowing that Provenge, like leukine, also strengthens the immune system, I would hope Provenge would at least be available then for men with advanced disease. This is especially true, since clinical trials of Provenge have shown significant additional survival for men with very advanced disease. Once Provenge becomes available, I believe there's a further possibility that men with less advanced disease and good immune systems like myself could conceivably benefit markedly from it. I would really like to see Provenge be the fourth arrow in my quiver. I appreciate the time this committee has taken for careful consideration of Provenge and I fervently hope that you approve its use now.

DR. MULÉ: Thank you, Mr. Grove.

(Applause)

DR. MULÉ: Alvin Chin?

MR. CHIN: Good afternoon. I have no conflicts of interest to declare. I am here as the coordinator for the speaker's bureau of the Virginia Prostate Cancer Coalition, member of the planning group of the Fairfax INOVA prostate cancer support group and as a member of the Prostate Pointers listserv.

I was diagnosed about three years ago, shortly after retiring from government service. I got my diagnosis shortly after retiring and I thought maybe I should have gone to the beach and gotten skin cancer instead. But that was not my fate and I'm here today spending time with you, your valuable time and I thank you for that.

At my support group I meet some of those men who are metastatic, are hormone-resistant and are with or without symptoms. They become different people when

they hear that they have moved to the next stage, a stage that takes them closer to their final hour. They are bewildered, they are often aimless and they are scared. That has been repeated. You've heard that before.

Noone wants to die a hopeless and painful death, and worst of all noone gladly accepts chemotherapy, the ultimate treatment now that you have run your course with the limited treatments available to men with hormone-resistant prostate cancer.

Typically you have suffered through surgery and/or radiation or cryoablation, and if the primary treatments fail you then have to face the fatigue, the mental exhaustion of hormonal therapy. Finally, with hormone resistance you are left with just chemotherapy where they burn the rest of your insides futilely, trying to kill the cancer cells. The side effects are so bad that men refuse to accept the

treatment because they choose to have an improved quality-of-life in their final years.

But lo, on the horizon comes a vaccine which has few side effects, Provenge, because it is autologous and uses dendritic cells from one's own body to spark the body's own immune system. Hope is restored. Little or no side effects, and yet one is able to prolong life. I've spoken to many men and they want this. They want another option besides the pain of chemotherapy. They want something that will work and allow them to keep the quality-of-life, especially if it is to be the last years of their life. It is important to them that they live it well. They and their families demand it. It is also important that they attempt to extend their lives. Provenge offers them this, and for the many men that have prostate cancer I ask that you recommend to the FDA that they approve this

revolutionary and historical prostate cancer treatment.

At this point in my notes I would have - it says I would have introduced Andy. And I saw Andy, he's a member of my prostate cancer support group. I saw him last night, and I would have asked him to hold up his hands and picture this. He had Band-aids on each one of his fingertips. I don't know about you, but years ago I lost a thumbnail because I hit it with a hammer, and it was painful for months until another nail grew back. In his case all 10 of his fingernails fell off because of the Taxotere treatment that he's on. So it must be very painful for him, and he would have brought it home, but he had to leave early because he was feeling exhausted.

Anyway, I understand that Taxotere was approved as a primary chemotherapy when it extended life over placebo by only a couple of months.

Provenge extends life more than twice as long without the pain. The loss of hair, fingernails, vitality, your dignity is something you don't lose with Provenge. Men will gladly trade the side effects of the present hormonal and chemotherapy side effects for the few and transient side effects associated with Provenge and gain more life in the process. The public perception is that Provenge is safe and effective and should be approved.

By recommending approval you will give up to 50,000 waiting men, maybe more, new hope and new life with an alternative treatment that works. You will be making substantial history today by approving this new alternative treatment, and I thank you from all those men that you will help today. Thank you.

(Applause)

DR. MULÉ: Thank you, Mr. Chin. Richard Gillespie?

MR. GILLESPIE: My name is Dick Gillespie. I'm chairman of the Virginia Prostate Cancer Coalition. I also run a very successful Us TOO group.

My cancer is low-grade, but within my group there are a number of senior individuals, basically, whose hormone therapy is no longer working. They're sort of bereft of hope, and they're scared to death of chemotherapy. And to bring a little more - something more personal in this thing, one of the members of my prostate cancer support group, my neighbor, was one of the most conscientious individuals in learning new procedures and following them. All of a sudden he got to the point, hormone therapy really was not working anymore, and it - we had a speaker from the National Cancer Institute come over and talk about vaccines. After that, he went up and talked to them and the individuals felt very strongly he should get

into the clinical trial program, probably on Provenge. His health wasn't quite up to it, however, and before he was able to start, the PSA really spiked. He was put on Taxotere. Taxotere, the side effects drove his white blood cells and his red blood cells down to nothing. He went into the hospital for a whole series of blood transfusions. From there on in, his demise was painful and quick. Here again, as I review my own relationship with my neighbor over there, if he had Provenge this all might have been prevented. Thank you.

(Applause)

DR. MULÉ: Thank you, Mr. Gillespie. The final speaker is Jan Manarite.

MS. MANARITE: I'd like to ask you all to close your eyes for a moment because I want to paint you a picture. PSA 7,096.0. Prostate cancer to the bone, including hips, pelvis, spine and skull.

Bone metastasis to the entire spinal cord, including the thoracic 7, 8 and 9, which included complete marrow involvement and spinal cord compression. This patient had to be totally sedated for MRI and bone scan because of undiagnosed pain. He did not know his PSA was over 7,000 because he had never had one. He was 58. This patient named Dominic awoke from sedation for his imaging. He looked at his wife and said, "Baby, did they cut me because I'm so cold?" "No, honey," I said, "they didn't cut you. You're okay." Dominic was paralyzed from the waist down and his entire left side. This man is my husband.

My name is Jan Manarite. I am the Florida educational facilitator for the Prostate Cancer Research Institute. I am here on behalf of a grassroots initiative for advanced prostate cancer patients called Raise a Voice. Today, I am one voice.

We went to a leading cancer

institution for a second opinion. By the way, my husband did recover and four days later, after bilateral laminectomy he walked out of that hospital. I want you to know that. I am told that that doesn't always happen. So we went to a leading cancer institution in Florida, about two hours north of Fort Myers, very close to St. Petersburg for a second expert opinion. They wrote my husband off and offered no treatment options. The one doctor we saw was a urologist who specialized in geriatric medicine. My husband was only 58. He said, "I would not give a bisphosphonate to my brother." He said something about efficacy, which I didn't fully understand at the time and an endpoint which was never proven at his institution. It made no sense to me even though I was not a physician and I knew little about prostate cancer at the time, so we fought for a bisphosphonate. We fought for Aredia because Omeda was not yet

approved. We fought the doctor, we fought the insurance company. My poor husband was just trying to fight his cancer. We won.

Dominic went seven years without a fracture, pathologic or because of osteoporosis, induced by hormone therapy which gave him no testosterone for seven years. That is because of the bisphosphonate that we fought for. The bisphosphonate is what he needed. A miracle is what we fought for and what we received.

I forgave that institution because God had bigger plans for this family. That was March of 2000. Today Dominic's PSA is about 2.7. Our son is 16. He's preparing for varsity football in his senior year in high school. He was nine when my husband was diagnosed in fourth grade. We purchased new memories because we fought. I forgave that institution because it is not the nature of science to be perfect. It is the nature of science to

provide for humanity with excellent probabilities. One famous scientist said, "It runs as follows. The state is made for man, not man for the state. The same may be said of science." Science is made to serve humanity, not humanity to serve science. This scientist went on to say, "These are old sayings, coined by men for whom human personality has the highest human value. I should shrink from repeating them were it not that they were forever threatening to fall into oblivion." That was Albert Einstein. It was 1931.

Dr. Mulé, you know more about immunology than most of us in this room will ever hope to forget or pronounce. We are thankful for that and we are thankful to all of you because all of you here do something that we cannot. I forgave that institution. Dr. Mulé, I'm going to ask you to forgive me because I'm about to quote you. You have a commentary that was published with Jeffrey

S. Weber in the Journal of Clinical Investigation, March, 2001. It was entitled, "How Much Help Does a Vaccine-Induced T-Cell Response Need?" The commentary was about breast cancer immunotherapy, including HER-2/neu. At the conclusion, trial design was discussed, including this statement. "A secondary endpoint would be to correlate immune response with survival, the ultimate challenge to the cancer vaccine field." If that be the case, then hasn't Provenge met the ultimate challenge?

Today there are things we know and there are things that we do not know. Here's what I do not know. Can Provenge be single-handedly responsible for reducing the prostate cancer death rate of 27,000 per year, 520 a week? Since I got here 24 hours ago, 74 more men have died and their families are mourning right now. I don't know if that's possible, but I wonder. Will

you make history today by approving the first therapeutic immunotherapy for cancer? I don't know, but I wonder. Will other cancers eventually benefit from Provenge being approved, melanoma, breast cancer, lymphoma? I don't know, but I wonder.

It is not the nature of science to be perfect. No studies are perfect. None yield 100 percent results. It is the nature of science to be sound, to give us excellent probabilities with honest representation and to serve humanity. Today you bring us the science. We bring you humanity. Thank you.

(Applause)

DR. MULÉ: Thank you, Mrs. Manarite. On behalf of the committee, I'd like to thank all the speakers for sharing your personal experiences and stories with us. At this juncture, we'll break for lunch and we'll plan to reconvene at 1:45.

(Whereupon, the foregoing matter

went off the record at 1:03 p.m. and went back on the record at 1:52 p.m.)

DR. MULÉ: Okay, this part of the agenda will deal with specific questions that were comprised by the FDA for the committee and for discussion by the committee. To expedite the process individuals were selected from the committee to start off each question for discussion. Once we go through that then we'll have the vote. With respect to the vote, when I ask a committee member for his or her vote, I will also ask for a brief reason for the vote. And again, there will be two separate votes which will cover Questions 7 and 8 which are the voting questions.

So we'll begin with Advisory Committee Question Number 1 which is listed here and we have Dr. Dubinett to lead us off on that discussion.

DR. DUBINETT: So the first question relates to how the variability in

each product dose in respect to the total number and range in cell ratios can be expected to affect product quality, safety, or effectiveness. And just -- you know -- to briefly summarize, to go back as summarized in the final slide as presented by Dr. Wonnacott earlier, the product has cell numbers that vary, the relative percentage of those cells vary and the contribution of other cells to the product activity is not known. And so I think that, in terms of how we view the product, we're actually dealing with something that does not draw any real analogy perhaps to cytotoxics or other types of therapies. And so I think what is before us is making some assessment of a product that, by necessity, is variable by virtue not necessarily of the manufacturing process from the data that we've seen, but in fact is variable by - as a function of the individual patient's leukapheresis product is what I've

understood from what we've seen.

And so I think we could begin the discussion just to ask - have a discussion of how these variables might affect quality, safety and effectiveness. And I can just begin the discussion by suggesting and going back to something I think that was said earlier, and that is that although we're looking at CD54, that this I think as Dr. Levitsky mentioned and I think built a cogent hypothesis to suggest, that, in fact, the phenotype of the antigen-presenting cell may well be dictated by T-cell elements in the environment, either in vivo or in the product. So I think one of the questions that we could ask is what other cellular elements and phenotypes might be there in addition to those that we've seen. For example, are the CD3 cells containing a population of T-regulatory cells that are not appreciated. So we can have some discussion of that from committee members.

DR. MULÉ: Any comments about the other cell types within the product and how those other cells may influence positively or negatively the APCs within the product?

DR. TAYLOR: I'd like to ask if there's been any double-staining of CD54 and the other markers, CD14, CD3. I didn't see any of those data. And if so, if we could get a sense of what percentage of the population is doubly positive that might actually narrow down the efficacious cells.

DR. MULÉ: Is there someone from Dendreon who would like to take that?

MS. SMITH: Nicole Provost.

DR. PROVOST: We don't routinely double-stain for manufacturing data. It's a - adds double the work. But we have done development studies to look at the CD54 population, both from the large cell forward scatter graph that I showed you and the total CD54 population. We're having trouble getting data projected. Yes, we're shifting

between systems here.

DR. MULÉ: Maybe you could just summarize without the slide.

DR. PROVOST: Okay. The vast majority of CD54-positive cells are monocyte-derived. However, you do see a shift in the total CD54 population, not the large cells. The large cells are what we use for lot release and it is that number, the large cell APC fraction of 54-positive cells that we use as the lot release value for determining acceptance or rejection of the product. And it's that APC number that is correlated with the Kaplan-Meier survival.

I can refer you to Figure 36 in the briefing document, in our briefing document, if you want to read along. When we looked just at CD54-positive cells in total - at Week Zero we have a higher fraction of those cells being monocyte or CD14. And the relative percentage as a

function of the weeks of infusion, Weeks Zero, 2 and 4 goes up over time. We see slight variations, although probably not really significant in the B-cells and the NK-cells and their percentage of the CD54 population. So we do have reason to believe that the T-cells may be getting activated during the course of the treatment. We don't have antigen-specific information in terms of what those T-cells are directed against because of the difficulties with HLA typing and actually assaying each patient lot.

DR. DUBINETT: So do you know anything about the population of CD3 cells in terms of the percentage that may be T-regulatory or CD4-, CD25-positive?

DR. PROVOST: We've done phenotyping, but we haven't done systematic studies for the patient populations. Those are difficult studies to do just in terms of getting samples from manufacturing lots. We

can tell you they're there. We haven't seen large changes in those populations, but I couldn't definitively give you information on the T-regs.

DR. MULÉ: Dr. Levitsky made a very good point, and he's rarely wrong, about the role, potential role of T-cells in further activating or up-regulating CD54 on monocytes, particularly in the second leukapheresis product. You know, the question always is is there any evidence that the T-cells within the second product are reactive to antigen, and also are the B-cells within the second product producing antibodies say to PAP. Because it gets back to the issue do you really want to remove cells that may be beneficial and complicate the process if there's really no need to do that, first of all if there's no negative influence and secondly, if there is indeed some evidence, even if it's laboratory-based data that there's a hint that the T-cells or

B-cells within the second and third products may have activity.

DR. PROVOST: Regarding antibody concentrations, the only solid data we have are from the immune monitoring patients where we assayed for antibody concentrations as well as T-cell stimulations. And we did find antibody responses against the PA2024 again, not that many against seminal PAP, kind of middling values against the GMCSF portion of the molecule, and virtually none in the placebo group that were studied.

Regarding the notion of separating or otherwise segregating the cell population, the rationale was that this is - these are blood-borne cells, they come in with a large variety of cells. We are targeting the APC fraction, but we're not precluding the interaction of all the other cell types that are there. We didn't see any dose relationships for those other cell types with regard to survival. And that's

not necessarily surprising because you wouldn't expect this to be a titrate-able sort of activity as you would a drug which binds to a receptor on a particular set of cells.

DR. DUBINETT: I think that you had mentioned earlier that there was a granulocyte relationship you thought with the CD54 expression?

DR. PROVOST: Yes, I mentioned that we have some weak correlations right now. We haven't got enough to actually stand on it yet. That's why I'm not showing it to you. One of the issues is that our process actually reduces granulocytes. I think that was pointed out well in the FDA briefing document. And when you get down to those low levels, they're actually hard to measure, actually hard to quantitate. So getting a reliable number is difficult. What we've done are some add-back studies to show that we can affect that.

DR. MULÉ: Franco.

DR. MARINCOLA: A clarification, maybe I missed it, but in the material you provided I saw that a lot of CD54 up-regulation is due to T-cell activation. It's not only just the monocytes component, but also T-cell and NK-cell seems to up-regulate. In the data that you showed about the relationship with CD54 expression and survival, are - what are you looking on? Are you looking only at large cells, or the whole population? Because that might explain why you might have a better --

DR. PROVOST: Right. The data that I showed you regarding the survival correlation was only for the APC population.

DR. MARINCOLA: So is that specific?

DR. PROVOST: That's specific for the APC population. That's the release assay for manufacturing.

DR. MULÉ: So when you did the

analysis of the quartile of increases in CD54 up-regulation with survival, was there any link with contaminants like NK, presence of T-cells, or no?

DR. PROVOST: We phenotyped all of those cell populations as part of the lot release criteria. We didn't see any other linkage.

DR. MULÉ: Kurt?

DR. GUNTER: It would seem to me that since this is an autologous product, you know, the product should be given some latitude in terms of specs because every product is unique for every patient. We could easily sit here and decide we're going to define arbitrary thresholds below or above which you can't give the product, but that would probably result in a lot of patients not being able to get product. I mean I could see if this was an allogeneic product where we should work really hard to define some reasonable specs for the

product, but I just don't think it's going to be reasonable, except if we find some data that would indicate that there's a safety issue. Then I think we should make some pretty strict cutoffs about cell numbers, et cetera.

DR. MULÉ: Other comments? Matthew.

DR. ALLEN: I'd preface this; I'm not an immunologist, so this may be a bit naive, but can I just - point of clarity. When you stimulate with the antigen, you're doing what with essentially the product, the whole product, so it's antigen-presenting cells plus whatever else is in there. So I guess my question is, and this is just approaching it from a sort of simplistic point of view, is if you have a product that contains antigen-presenting cells and other cells, and if you have the ability with flow to determine. do they have phenotype, can you not do cell sorting and select out. So

for example, could I not do an - if I wanted to know whether or not activation of T-cells in some way was an issue, could I not do an experiment where, admittedly with frozen products, I took the original product and then the product from the second pheresis and then split up the antigen-presenting cells and the T-cells and fed them back and did a flip-flop experiment. Because the premise would be if T-cells are important, then I'm going to get more CD54 up-regulation with my antigen-presenting cells from batch one using batch two's T-cells. Is that not a logical thing that could be done, and has anything like that been done?

DR. PROVOST: Well, you might be able to do that in syngeneic mice. I'm not even sure you could, but in the patient population batch two, Week 2 depends on Week 1 or Week Zero having been infused. So since this is a fresh product, all the uptake of antigen is in the presence of all

the other cell types, all of those cell types go back into the patient. Those sorts of experiments, while they would be very interesting to do turn out to be logistically very difficult.

DR. MULÉ: Maha, do you have a question?

DR. HUSSAIN: In the concept of therapeutics we try to give what we think an effective dose, and then you understand that not every patient is going to respond to what you've given them, and if they don't respond then you know you have done the best you can, you've given the effective dose and it did not work for that cancer. How do you, in the setting of this, ensure that every single patient of those 55,000 patients out there who may get this drug are in fact getting a quality-assured treatment, understanding that we heard from the FDA speakers that there's the issue of leukapheresis and there's a variety of

parameters that impact that, not the least of which availability of leukapheresis machines, and then of course who's running them and how long did it take before it got to you, and all of these details. And judging by the fact that, if I understood the quartiles again correctly, that only certain patients who are above a certain level are the ones who benefitted, that even adds another glitch in this whole process, you know. And when you have a second study that's negative then it adds a third glitch in the process. So what do you do to assure that a single patient anywhere in the United States who's going to get this is getting what you have given them in the study and have been given a fair trial?

DR. PROVOST: The apheresis process is actually a standard medical procedure used for donating white blood cells and fractionating platelets, et cetera. Standard processing parameters are

used. We qualify the apheresis centers to make sure they're following protocols. We have a program that's being planned at the moment to register those centers and these apheresis centers will need to be registered with the FDA as tissue establishments. We have - I think I mentioned that we have a normal donor program that we use for development as well as assay validation and process validation. And what we see is that we do occasionally have repeat donors that come in and those, even if they're going to the same site, same person, same apheresis center you do see slight variations, but not great. And even that being said, early clinical studies set out to establish some sort of dose and to look for a response. The early studies were not survival studies. They were looking for immune responses or some indication of disease progression.

And those early studies, one, looked for the lowest dose as a fraction of

an apheresis that could elicit an immune response against the immunizing antigen. That turned out to be very low, around one-tenth of an apheresis. On the flip side, the early studies looked for limiting dose toxicities, how high could you go, how many cells could you infuse before you started to see adverse events. And we bumped up against the maximum number of cells that we could apherese and didn't see them. And that's how we established one apheresis, one and a half to two blood volumes in duration. And that coupled with the CD54 data which suggests that it's that APC fraction that takes up, processes, and presents the antigen led us to then focus on the APC fraction for dose and allow the rest of those cells to be there since they didn't have a positive or negative effect that we could measure.

DR. MULÉ: Larry?

DR. KWAK: On the topic of

product characterization we haven't heard very much either from the sponsor or the FDA about the recombinant antigen. Just wondering if you know, quality control, purity: is this considered a reagent and therefore not relevant to the discussion, or?

DR. WONNACOTT: I can say that we find it to be very relevant to the product and we - I think where we're at is that we just don't feel like we need the recommendations of the committee on the antigen. We're comfortable with the information that was provided in the BLA.

DR. MULÉ: Savio.

DR. WOO: My question is just for some clarification in my own mind. I mean, today I've heard the presentation on the CD34 correlates and is being used as a potency issue that's for the product in terms of the trial. And then we learned that the immune response was really seen

with the hybrid protein, but not to the PAP antigen. And then we were told that the CD54 up-regulation is really not correlated with the reactivity to even the hybrid protein. As we hear more and more about the CD34 things, and then we heard the sponsor indicates that the CD54 is really a manufacturing thing and is not prognostic and that it's not the only predictor. So I was wondering you know is CD54 being used for the potency claim still being maintained by the sponsor, or is it being withdrawn because I'm confused.

DR. PROVOST: CD54 up-regulation is used as a product release -- manufacturing product release parameter. We presented the data looking at CD54 up-regulation and correlating that with survival basically as a reality check, to see is this survival benefit that we measured attributable or correlating with anything. Is it a fluke? We don't use CD54

up-regulation in any way as a prognostic factor. We basically use it as a biological correlate for activity inasmuch as we activate cells in the process. We have a minimum spec for that.

DR. WOO: If that were the case then because the entire concept of this product is really to stimulate the patient's immune response to go reject the cancer. And yet CD54 up-regulation being used in this correlative sense is not correlated with the reactivity to even the hybrid protein. So how can we be assured that this treatment was actually leading to a T-cell mediated, or immune-mediated rejection of tumors? Or is this something that has happened?

DR. PROVOST: Let me back up a minute and state again that the immune response against the PA2024 immunizing antigen, the magnitude of that immune response as measured in our assays by a T-

cell proliferation assay doesn't correlate with CD54 up-regulation. Now that's a small subset of the patients that were measured in the total trial and that T-cell stimulation assay was not meant to be correlative to any other immunological parameter. It was basically to see whether the patients responded to the immunizing antigen, and the data we showed said that yes, they did. It was a clear difference between those that were immunized and those that weren't, but we're not putting any credence behind the magnitude of the immune response from that assay.

DR. WOO: Could I ask then what evidence is there to suggest that the treatment actually leads to any anti-tumor immune response in the patients? Any evidence at all.

DR. PROVOST: We are not trying to imply that we're seeing tumor shrinkage. We didn't see objective responses. We

believe it is probably -

DR. WOO: That's not my question. I'm sorry. My question is: is there any evidence that the treatment leads to an anti-tumor immune response in patients.

DR. PROVOST: None other than the survival effect and the differences in prostate cancer survival.

DR. WOO: Okay, thank you.

DR. MULÉ: Savio, my -- in my view this is more condemnation of the field as it is not necessarily a condemnation of what we're asked to review today because in reality if you scan the literature and you look at all the clinical trials that have been done in Phase I/Phase II and you look at all the intricate monitoring of patients that have been done with specific peptides, with T-cell clones, with LE spots, very quantitative, coded, blinded samples I think it's fair to say there's absolutely no correlation between the robustness, the

specificity of whatever monitoring is being done and clinical response. That's the reality. That's the reality.

DR. DUBINETT: I was going to say something similar, but also in the same vein. I would be very surprised, in fact, if a single antigen-presenting cell marker predicted a response and I would be very surprised if it were CD54. So I think I wouldn't be distracted by the fact that in fact it may be a manufacturing tool, but as a single marker I think it would be rather extraordinary to find a single factor that predicted that response. It's likely to be multiple and would require clearly much more work to be done to define that.

DR. MARINCOLA: Can I make a just brief comment too? I think that in your help I think that the most compelling reason to use CD54 as the data show that seems to be the best marker to delineate those cells that actually present in the antigen, where

100 percent of the cells. So it's the potency I think it's the closest that I can imagine it showing that they're delivering the number of cells they're delivering and the quality is appropriate. So definitely the immune response will tell a different story and I agree with how everything else has been said, but I think it's pretty compelling. CD54 seems to be very, very good marker for what it's supposed to do.

DR. MULÉ: The CD54 discussion, when I look at the questions they're more related to 2 so we can continue this discussion and maybe combine Questions 1 and 2, and Glenn, if you want to continue the discussion related to 54 with Question 2 that'd be good.

DR. DRANOFF: Sure. I think Question 2 is also intimately linked to Question 3.

(Laughter)

DR. DRANOFF: So essentially this

relates to what is the mechanism of action of this immunotherapeutic approach. And I think there are several important parameters to point out. We should talk a little bit about the prostatic acid phosphatase as an antigen, whether in fact that is the major antigen that an immune response is elicited against, whether there are involvement of other potential prostate cancer antigens. We need to talk about what are the specific immune effector mechanisms that are likely to be active here. Then we need to think about whether the antigen-presenting cells in this product function directly to stimulate T-cell or B-cell responses to the prostatic acid phosphatase, or whether they might work indirectly in vivo. And I think it's fair to say that all of these issues are essentially at the heart of much current work in cancer immunology. We could spend days at meetings talking about these, so I don't think we're going to come to a final

resolution, but at least for the folks who don't think about the cancer immunology issues all the time it's important to represent what some of these considerations are.

So first the antigen, prostatic acid phosphatase. As far as the literature indicates, it's a protein whose expression really is limited to prostate or prostatic carcinoma. The literature doesn't indicate that it involves any mutations, so it's fair to classify this protein as a normal differentiation antigen, and it's fair to point out that many people in the field believe that targeting differentiation antigens can be therapeutic and there are a large number of clinical trials exploring that. On the other hand, the protein is also secreted. We saw how that was used as one of the patient characteristics and these characteristics of having a large amount of the protein in the patient actually make it

much more difficult to generate an immune response and might account in part for why the investigators have had difficulty detecting these responses. Now, in the literature it is clear, however, that there are antibodies that can be developed to the protein. There are CD4 T-cells, or helper T-cells, and then there also are CD8 cytotoxic T-cells. And while the exact importance of each of those cell types and antibodies to an anti-tumor effect is still a matter of investigation, I think the field would agree that if you could develop responses to any one of them or more of them that would be a useful thing.

So we've heard mostly thus far that the monocyte population in the product is likely to be the most important antigen-presenting cell. I think the data is compelling that the large proportion of the exogenous protein is taken up by the CD14 probably monocyte population. But there's

another cell population that's much rarer, the dendritic cells, which are several orders of magnitude more potent as antigen-presenting cells than monocytes, and we really haven't characterized their role yet. But it's likely that the provision of GMCSF has been enhancing the activity of both the monocytes and the dendritic cells.

Now, the antigen is given to the antigen-presenting cells essentially as a soluble protein and it's quite clear that that mode of presentation is efficient for stimulating CD4 responses and indirectly antibody responses, but it's not a very efficient way to generate cytotoxic T-cell responses. And indeed we haven't heard any discussion about measuring CD8 responses which many would think might be of great importance. So it's unlikely in my view that this approach is going to be a good way for generating CD8 responses in the direct mode of presentation. Now, in terms of

measuring whether the antigen-presenting cells are properly activated, we've heard from many people already that ICAM is almost certainly a part of that process, and there's good evidence that if you block ICAM function or if you make animals with deletions in this gene that their antigen-presenting cells don't work as well. And it certainly is an easy thing to measure, and I think the data presented have indicated quite convincingly that ICAM up-regulation is an indicator of the response of their PBMCs to the PAP GMCSF protein.

So, from this data can we really conclude that the intended mode of improving antigen presentation actually has occurred in vivo? And, although there really are not very convincing evidence for PAP-specific responses in my view, I think there is compelling evidence for reactivity to the fusion protein. And it's likely that that reactivity is because it's easier to

generate immune responses to novel sequences the patient hasn't been living with, and I think that that frequency of developing T-cell and antibody responses to the fusion protein really does support the idea that there is improved antigen presentation going on as a function of this therapy. Now, is that actually the direct way that this might work in vivo? And there I think it's fair to say that's less clear. It is probably very useful, though, to be infusing into patients activated antigen-presenting cells. Rather a large number are being infused and in my judgment these cells are likely to traffic throughout the patient and indeed may even be attracted to areas where there is some ongoing inflammation, perhaps due to a tumor deposit. And I think it's plausible, though clearly more study would be required, that it's actually the trafficking of these cells to sites of tumors or maybe even draining lymph nodes in

the patient which might provide a secondary activation of antigen-presenting cells in the patient which could lead to presentation of many more antigens than PAP, probably those that could be more important for tumor rejection. So I'm just trying to outline some of the complexity of this pathway.

There are many unknowns, but there is clear evidence in my view, that this manipulation is activating antigen-presenting cells and I find compelling, actually, the scenario that Hy Levitsky had raised that the activation of the PBMCs that's apparent in the second and third products is an indirect, but probably important indicator that the immune system in the patient has been activated. They provided in the appendix evidence that cytokines are being produced. So from the first principle that you're going to try to improve antigen presentation; does this product have the capacity to do that? I

think the answer is clearly yes. The specificity of that, however, is unclear.

DR. MULÉ: Dr. Provost, so talking about CD54 up-regulation, the numbers are small, but if you combine Studies 1 and 2 there were 20 patients that never received the third infusion, and I think the numbers were about five or so that only received one infusion. Have you done any analysis, number one, of whether or not the number of infusions are important or any correlation with cerebrovascular effects, number one. And number two, I know there was no correlation with cell number and cerebrovascular effects, but I don't know if an analysis - certainly I failed to see it in the documents, of whether infusion number had an impact on that, number one, and number two, when you look at the survival curves of the quartiles, where do those patients sit in that analysis?

DR. PROVOST: Sorry, I'll go to

the microphone so I can clarify. Where did - when we look at the quartiles, where did - which patients? You mean those that only got one or two?

DR. MULÉ: Look at number of infusions where patients only received one infusion of Provenge versus two, where do they lie?

DR. PROVOST: I don't have the data before me, but I could make a guess. Since the data that I showed you were cumulative CD54 values, they were more likely to lie on the lower end, but I preface that by saying we have not done that analysis.

DR. MULÉ: It's an interesting component because if you look at the third - an analysis of phenotype of the third infusion versus the second infusion, there's really not a lot of difference.

DR. PROVOST: Right.

DR. MULÉ: So it begs the

question, do you really need the third infusion. You know, that's an issue, but the numbers are small obviously.

DR. PROVOST: Right.

DR. MULÉ: But I think it's an analysis that would be worthwhile. And getting back to the serious adverse events, did you look at that, whether those patients, with infusion number?

MS. SMITH: I'm going to ask Mark Frohlich, Vice President of Development.

DR. FROHLICH: In terms of the CVA patients, all of those patients received three infusions so there didn't appear to be a correlation with the number of infusions.

DR. MULÉ: Other comments? Doris.

DR. TAYLOR: Following up on that though, you said the salvage patients did not show any cerebral vascular incidents. Did they also receive three infusions?

DR. FROHLICH: They were all

scheduled to receive three infusions. I can't speak to the number broken down. The patients who get the salvage treatment do receive a somewhat lower dose than the standard sipuleucel-T.

DR. MULÉ: Let's move on to Question 3 which again was spilling into the next question with these discussions. But, Franco, if you could maybe talk a little bit more about the immune monitoring component.

DR. MARINCOLA: Well, a lot has been said already, so I will summarize briefly. And I have to say that the - from the quantitative aspect the effect of the product has been very striking, so obviously it is doing something. But the question is what it's doing as was being pointed out just now. And you know, of course you can go into esoteric discussion about the junction or region of the recombinant protein being particularly immunogenic because it's seen as foreign or maybe, I

mean it could be other issues like contaminant products, contaminants in the product. There may be - would serve as immunogens both in in vitro and in vivo. So I don't know, it's interesting, but of course lacks a lot of specificity. So I don't know whether the immunological data that have been provided are informative at all to answer the question of whether this product reaches the desired biological endpoint - I mean, effects. And of course it would be nice to know what the contribution of CD8 cells versus CD4, cytotoxic T-cells. It would be nice to prove antigen specificities using the R1 patients who epitopes are known, or use epitope libraries somebody suggested, or use - and also use tests, maybe a little bit more specific than proliferation assays like - which are obviously biased CD4 responses or CD8 responses, like LE spot and other arrays.

So having said that, however, I have to agree with what Hy and - so many times Hy Levitsky and maybe Jim just said, that truly, does it really matter because the evidence in the literature is that looking at the systemic responses to vaccines there's not a relationship whatsoever with the clinical outcome. Maybe because we are looking at the wrong place, we should look at the tumor side. So there is so much immunology that we don't know yet, and maybe it's just a nice, very important intellectual exercise, academic to discuss what happens, but maybe not relevant whatsoever to the product. So I think discussing the immunology of this product I think should be encouraged because obviously if you could find -- the sponsor could find eventually some kind of relationship between some immune responses and clinical outcome then one day it could be a good surrogate marker instead of having to wait for years

to see what the outcome would be, and to predict, maybe, the effect of the treatment. But for the moment I don't think really the data provide as well as the knowledge of immunology should bear in the decision-making about whether the product should be approved or not. I think it's just an interesting discussion, and I think we can talk about that if we have to, but that's my impression. So whoever wants to say something.

DR. MULÉ: Other comments?

DR. DUBINETT: I would only add that some measure of assessment of what we've done to T-regulatory activities and suppression would add to this. And I think this is in part echoed in what Glenn Dranoff has recently written about. But we really have of course embarked on therapies, a number of which we now know are very good inducers of suppression. And this would be an opportunity to find out where this

particular therapy sits in that spectrum of activity.

DR. MARINCOLA: From the academic standpoint there are lots of interesting questions to look at, but practically speaking I think - I guess the most important thing is whether we believe the survival data or not.

DR. DUBINETT: I agree. Absolutely.

DR. MULÉ: Other comments? Okay, let's move on to Question 4. What I'd like to do is go through the questions and then at the end, I'll ask FDA specifically whether we've covered what you need and then we can go back if necessary. Howard?

DR. SCHER: So with respect to the cardiovascular accidents or CVAs as a potential safety issue, I think this analysis really reflects some of the issues that have come up in terms of small numbers of patients and extrapolating results from

particular prostate cancer cohorts, in this case patients enrolled on different trials with different eligibility criteria. So if you look across the population, the absolute difference in the cardiovascular events of 1.3 percent certainly is not different. But then if you look within the androgen-independent population, for whom the indication is requested, you do see a difference that although it does not reach a 0.05 p-value, absolute numbers of 5 percent versus 1.7 percent, 4.9, do raise some concerns. And the hazard ratio again of 2.9 again raises concern, but looking at the numbers of patients this could be anywhere from protective, 0.84, all the way up to risk factor - a hazard ratio of 10. So I believe these sponsors correctly point this out and do plan to include monitoring for these effects or these events in future studies. I do think it remains an issue.

In the briefing documents

provided there was some mention of risk profiles of strokes and I would suggest that more could be done prospectively to better define the population in terms of their cardiovascular histories, concurrent medications and other comorbidities, and again I would urge that be included prospectively in future studies. So I think it's still an open question.

DR. MULÉ: Other comments? Okay. Number 5, Maha.

DR. HUSSAIN: So the essence of the question is the survival data that's presented. The intent is to discuss the persuasiveness of the efficacy evidence reported in the BLA application and in the table. And as I read this, it is clear that there is a survival difference, so we're not disagreeing on that. The question is does one believe that the survival difference is related to a therapy effect. Am I interpreting that correct? Okay.

So I'm going to speak not as a statistician, but rather as a clinician who has been taking care of prostate cancer patients for 17 years, or 18 years by now. I'm getting old. And as a clinical trialist who has written numerous institutional and cooperative group clinical trials. And so I put that up front so that I can explain the rationale, or give you sort of -- in essence, a feel for the rationale or the position where I'm coming from. So the first thing I want to point out, that no one disagrees that survival ought to be the key factor. However, it's the spirit of how that survival has been looked at, not an after-effect, not an afterthought, it's intended in the first place to be looked at. And at ODAC, the FDA had convened a committee of clinical trialists and prostate cancer experts last year to look at endpoints in prostate cancer specifically, and I think the unanimous decision was that

the primary endpoints for purposes of approving a drug, at least among the people sitting on the table who were not FDA members, but clinicians, that had to be a specified up front survival. Unfortunately that's not the case and the only conclusion I have is that the trials were designed not to look at survival, because probably they didn't think they were going to see a survival difference and the sample size and everything else in my opinion is very small, to me almost equal to a randomized Phase II trial. So that's one point.

The second point is that there was a lot of discussion back and forth about side effects, quality-of-life and docetaxel and such. And I want to point out that this is not a comparison between this drug and docetaxel because that's not what the study on the table is. What's on the table is a comparison between a vaccine and a placebo. In a population of patients that are much

more healthy relatively speaking by comparison to the Taxotere trials who were a lot sicker patients, and consequently the burden of benefit is totally different and cannot really be compared, that you see four months here, two months there, that for them this is better, I would try to stress these are totally different populations.

Now, the context in looking at this is that when I sit down on Monday to talk to patients, I have to feel maybe not 100 percent, but 90 percent confident that everything that was presented today is related to the treatment, and that this is the best drug for Mr. Smith, who I'm going to see Monday morning if it's available on the market, and that I have to feel confident in advising him about that. And I guess the answer is I'm not sure. And the reason I want to say I am not persuaded - if that's the conclusion, but I'm going to go through the list if that's okay - is the

following. We start with a study design that, in effect, is a total of less than 150 patients, 80 patients went on treatment, so the study is incredibly under-powered. Why that is important, let me give contrast by several Phase III trials that are - have been conducted and are ongoing, and the smallest of these trials are 700 patients in prostate cancer that have been conducted and completed in a timely manner. So it's not an impossible task, number one.

The problem is that when we look at the confidence interval, and I'm not speaking as a statistician. When I look at a result, I want to say that this is not in the eye of the beholder, that you can go to the bank and this is real. This is not something that two people would disagree on. So I would point out that two randomized Phase III trials with the drug docetaxel were conducted. It's incredible how the survival of the arms, the mitoxantrone, the

Taxotere, despite different sets of eligibility, different sites, different everything, were very consistent in that you could tell a patient that I expect your median survival with mitoxantrone will be about 16 months and it's about 18 months with Taxotere. And that's true for both of these trials independent of each other.

The problem here is that's not the case. So you have the same company conducting two trials, and the first trial gave a median survival on the average of about 25 months and a hazard ratio that would have been claimed to be in favor of the treatment. And yet there is a comparable eligibility second trial that failed to demonstrate the effect, but to me what's scary is the fact that the best arm in the second trial with a median survival of 19 months is worse than the mitoxantrone arm from the asymptomatic cohort in TAX 327 trial where their median survival was 19.8

months. Now that was in Dr. Logothetis's slide, so I'm not making this up. It's presented. And that to me is concerning. Why that is concerning is that, even though you're starting with patients who you are assuming are asymptomatic and therefore comparable, something in there is not jiving. Immediately you're getting a drop in the median survival of about six months, again suggesting there are subtle things that are not clearly reflected within the trial.

Now, the first trial, so Number 1, had really some imbalance between the arms. Now, the imbalance cannot be brushed off because if you're talking about a 1,000-patient trial and you have maybe 5 percent change differences is one thing, but when you're talking about a 80-patient and a 40 in the control arm, little differences in the potential prognostic variables can impact interpretation of results. And I

would say that it could be just by chance that the second trial was not matching the first trial and has nothing to do with biology. Again, it's small sample sizes.

One area we have not touched on here and I'm not an expert in immunology, but it's my understanding that the hormonal environment impacts the immunologic response. I don't know if anybody cares to comment on that later. And there was really nothing presented here as to the prior duration of hormone therapy, and as we all know, those of us who deal with prostate cancer, people who have a longer natural history -- respond longer to hormones -- tend to do better in general as opposed to the ones who have a very violent course. And that has not been accounted for in there. Can I keep going? Thank you.

The issue with the p-value and its significance is to me very concerning, and again I'm not a statistician, but as the

statistical reviewer from the FDA presented that a p-value of 0.01 does not always correspond to statistical significance. And we saw a bunch of p-values being flashed both from the sponsor and the FDA. It's really the context. So a 0.01 in the setting of a survival being the primary endpoint is one thing, as opposed to a 0.01 in the context of a post hoc analysis is something else. And I think that that ought to be kept in mind.

There is another, to me, concerning observation and that is none of the disease-related manifestation was impacted. So as a clinician it's hard to conceive if the disease is progressing at the same rate, what else is keeping people alive. And that really is very concerning. In most of the prostate cancer trials, and I cannot think of any solid tumor, understanding it's not vaccines, but chemotherapy or other biologics that we talk

about, generally the disease manifestation and disease-related, I guess, manifestation of disease go together with the survival. So when you see a survival advantage you see a time-to-progression advantage, you see a pain response benefit, you see all of that. And that was true in the Taxotere trials, at least if we talk about prostate cancer. That has not occurred here and that to me says something. It's maybe the vaccine didn't really work and maybe that's why there was no - anything picked up in terms of immune stimulation and everything that we're talking about. Maybe something else was the reason why these patients lived longer.

There are two more things that I want to mention and that is the reason we do clinical trials and we use statistics it is because we want to put a standard for care that is - that if it's my father, I am happy with him doing that. I don't want something

that two people look at and say, well, really oh yes, absolutely this works, or it really doesn't work. And in this case I think that a combination of two trials that went to different ends, a very limited observation on 80 patients, I feel very uncomfortable recommending it to the patients out there. There is an ongoing definitive trial which I have asked about three times how far is that trial, so how many patients have been accrued of the 500? Four hundred? Okay. So 400 of 500 have been accrued which means within 100 patients we would have those results in the next two to three years reported. If you couple that with a potentially open or expanded access program, which is not an impossible thing. And an expanded access program, I don't know if - I'm sure you're all familiar with it, but other companies when there is a promising drug, and you could always make it available within certain guidelines to the

patients while you're waiting for your definitive trial. So I don't see that rushing to say this is great now is of utmost urgency because certainly the company could choose to have open access programs.

And I think the reason that's important is collecting more safety data is going to be extremely important. I would only cite out the issue of growth factors such as the erythropoietin that has been used for a very long time and we all thought it was safe and recently there was this whole thing about it is harmful. And so to say that we have safety data from three, four years on a thousand patients, to be honest with you I'm not so sure that I'm comfortable in the context of a small, limited trial that this is actually adequate safety data. And to say CVA is about three times the rate, even though it's not statistically significant, if you open it up to the 20,000 - 30,000 patients out there,

only you know you have no idea what could happen. So I think collecting this kind of information in a controlled manner becomes important, and I think that's all. Thank you.

DR. MULÉ: Thanks, Maha. Comments? Howard?

DR. SCHER: I would just like to reiterate that I don't think there's any debate here about the need for more options and more effective treatments for what's clearly a lethal disease. But I would also say that as a physician and a researcher echoing Maha's comments that part of the failure and the lack of availability of drugs is not the fault of the FDA, it's really our fault in terms of how we design trials and conduct them. So the 01 and 02 studies were very well-designed for a primary endpoint of time-to-progression. They were well-conducted, prospective, double-blind, randomized. It's really as

good as it gets. Unfortunately it didn't meet the primary endpoint and then three years later a survival analysis is reported, it is observed and there's no question that this is the gold standard by which we live.

So again the question boils down to is this really a drug effect or is it simply related to the patient populations. So as we look back on what was presented we didn't really see any evidence of a direct anti-tumor effect, granted that was not part of the trial, and we all recognize there are problems. The primary endpoint was not met, but if you look at the - where the patients failed, it was again with bone scans which is similar to another agent that was presented to the agency a few years ago. We did see an imbalance in the distribution of soft tissue disease, but we didn't see reports of serial imaging actually to monitor that disease to see that there was a change in the tempo of the illness. And

again, I would agree there has to be some point where this is affecting the natural history and we just haven't seen that.

We weren't provided any information on quality-of-life such as pain relief or delaying to the development of pain and the time to the development of - to the need for chemotherapy which is arguably an indication that the physicians treating them felt that the disease had taken a turn for the worse, also appeared to be similar. And while we are all looking for replacements for hormones and recognize the adverse effects associated with them, there's no data presented here that this is in fact a potential replacement for hormone. It just wasn't the question.

So actually what we're shown is a post hoc analysis with a small number of patients, and if we were looking at that result as a Phase II study, and prospectively asking the question to

demonstrate that treatment effect we need approximately 500 - 700 patients. And at some point during the day I would like to see the details of the Phase III design, you know, again with the idea to make sure that it is sufficiently powered and, you know, again it may be an opportunity to add more patients if there's any question.

So you know, if you ask me the question does this drug prolong life, I just don't know at this point in time. So I start thinking, you know wearing my physician's hat, obviously I feel extremely frustrated when there are no options to offer patients. So if I start thinking, am I denying a potentially useful agent to men who clearly need it, the answer is unfortunately I don't know. So I say well, what if we think that this really should be available, start thinking about the number of agents that are currently under development. There's now issues of

prioritization. We still have the issue of toxicity. There was a higher frequency of strokes, and again if you amplify across the global population this does create potentially very serious problems. So in the same vein where I want to offer effective therapies, I don't want to offer those that are ineffective and potentially toxic. So I think all of these considerations have to be factored in and I would reinforce that there are ways to make drugs available in appropriately controlled contexts so that patients are not denied it if they so choose to have it - or want to pursue it.

DR. MULÉ: Other comments? Richard.

DR. CHAPPELL: I also don't doubt the need for this, need for further effective and less toxic therapies, and I've carefully read the comments and listened to those who have benefitted from Provenge. We

obviously can't hear from those who - the treatment has failed, and there are many of those, unfortunately. The statisticians focus on p-value, which is the probability of erroneously accepting the drug as improving survival, and Dr. Zhen correctly said that you can't - it's impossible to compute a p-value, which hasn't stopped me from trying just to illustrate some of the problems in my own mind, and perhaps yours. So when would we possibly accept or recommend approving this drug? Now I can only speculate, but I presume that if in both trials the primary endpoint were a significant probability less than 0.05, that would probably work. Or even if one were significant, which is a chance of 1 in 20 if it weren't, and the other wasn't too bad, and so that's two chances in that case. Or if neither were significant and the survival in the first trial were significant, we're debating approving, recommending approval,

or if neither were significant for the primary endpoint and survival in the second, but not the first were significant. And that's too many - well, that's a lot of combinations. I'm still not sure it's too many. But it's a lot of ways in which one can make a mistake. And so I'm worried about it. I've seen other clinical trials in which I've seen p-values of last one 0.004. I won't give you the details, but the hypothesis was so ridiculous that nobody would have accepted it. It was just one of those a posteriori hypotheses which turned out by coincidence to be significant.

And I echo Dr. Scher's emphasis on the next trial. One always wished one could change the past. The second best time to plant a tree is today, if you quote Confucius, rather than 20 years ago. And so I am concerned with the possibility of correcting deficiencies in the design of this next trial, that the endpoint be what

we would call hard, that is be survival, be for something very simple, like the log rank test, rather than a model so we don't have a debate in a few years over which model do we choose, one is significant, one is not significant. Some have missing covariates. Do we include those or not? And also whether the outcome, whether we really want something like the log rank test, because we realize that at first there is no advantage. It takes awhile - if it works, it takes awhile to work. Do we want to a priori specify a test that down-weights any early differences in survival curves and emphasizes later differences which one expects. So I hope to, regardless of the outcome today, to emphasize the future, and make sure that any future results are not subject to such debate as we've had.

DR. MULÉ: Would someone from Dendreon wish to comment on 9902B? Because that has come up a number of times by

several members of the advisory committee.

DR. FROHLICH: D9902B is a randomized, multi-center, double-blind, placebo-controlled trial that's very similar in design to Studies 1 and 2 that have been described today. The eligibility criteria are men with asymptomatic or minimally symptomatic metastatic androgen-independent prostate cancer. It's a similar 2 to 1 randomization. The primary endpoint is overall survival. The secondary endpoint is time-to-disease-progression. It's an event-driven analysis for 360 death events. It's powered at 90 percent for a hazard ratio of 1.45.

DR. MULÉ: Howard, does that help you in your?

DR. SCHER: What would come up, is there a rationale or need to increase that sample size? Because 1.45 is significant. I mean, it's been a big bar in this disease. So assuming that the

analysis, there's been no analyses to date.

DR. FROHLICH: So the integrated analysis of Studies 1 and 2 showed a hazard ratio of 1.5, so 1.45 was deemed to be a reasonable estimate given the data we have to date.

DR. MULÉ: Maha?

DR. HUSSAIN: I think it's a good size for looking for that much difference. The only question, Dr. Frohlich, I had and that is the symptoms you refer to is not any symptoms, it's pain I assume.

DR. FROHLICH: For the eligibility criteria?

DR. HUSSAIN: Yes.

DR. FROHLICH: Minimally symptomatic disease, right.

DR. HUSSAIN: But what is minimally? Is that -

DR. FROHLICH: Not requiring any narcotic analgesics, and on a visual analog scale a score of 3 or less.

DR. HUSSAIN: And are you somehow doing any kind of stratification to account for potential prognostic variables?

DR. FROHLICH: We are stratifying for Gleason score bisphosphonate use and study center.

DR. HUSSAIN: Thank you.

DR. FROHLICH: I'm sorry, number of bony metastases as well.

DR. MULÉ: Richard?

DR. CHAPPELL: Dr. Mulé, is it within our purview today - should we be discussing this third trial in making recommendations? Or just the evidence from -

DR. MULÉ: No, it's really to provide additional information to several of the committee members who have been trying to get a better sense of where this is going.

DR. CHAPPELL: Okay.

MS. SMITH: Mr. Chairman, is it

possible that we comment on some of the statistical comments that were made?

DR. MULÉ: Yes, sure, go ahead.

MS. SMITH: I invite Dr. Brent Blumenstein to comment on some of the statistical issues raised.

DR. BLUMENSTEIN: The issue of how to interpret the p-value from the survival trial is of course central to the deliberations here. And I agree that it is difficult to know what significance level to compare the 0.01 to. In other words, what kind of adjustment for the actions, the post hoc nature of the survival and so forth should be taken into account. However, I think that one of the things that hasn't been mentioned so far in this is the special status that survival has with respect to time-to-progression. That is, there is a putative surrogacy relationship between these two endpoints, and if you accept the fact that there is that possibility, or even

believe that there is that. I know that it's not been proven, it's not validated, that's a very difficult thing to do for those of you who've been watching that process of trying to validate surrogate endpoints. While it isn't validated, one has to take into account that there's the possibility that the outcomes of time-to-progression and survival are correlated in some manner. And when one thinks about making p-value adjustments, one can take into account the correlation between two endpoints in deciding what should be used as the significance level at which to judge an outcome, a p-value. And if one assumed that these two endpoints were perfectly correlated, then when you start to make that adjustment, you would find out that you didn't need to make the adjustment because of the correlation.

But that's only one way to look at it because actually I prefer not to look

at TTP, the time-to-progression, and survival as two endpoints that one is going to choose between within this trial. Rather, I like to think of these endpoints as having this surrogacy relationship. I mean, I'm trying to - what I'm trying to do is communicate to you why I feel that the data from this Study 1 does provide evidence of efficacy. So I prefer to think of these endpoints as having that surrogacy relationship, and thereby not wanting to make the kind of adjustment one would make if these two endpoints measured two distinct features of the patient, perhaps related, but two features of the patient. So if I go down the surrogacy route, then I'm in the position of thinking of the outcome as being something where both endpoints need to be met for you to have an overall significance of the study. Under those conditions, when you have perfectly correlated endpoints as I mentioned before you get to the same p-

value, that is - I mean the same significance level to be used. That would be 0.05. And so you can get to the 0.05 significance level both ways by making different assumptions about whether you're looking at a surrogacy relationship, or whether you're looking at two endpoints that might have a high correlation.

But I think that the bottom line of all of this is that we have to stop and say, well, we really can't know that because you can only make assumptions, and then maybe you could do some computations and so forth and try to get at a significance level to be used. I think even if you were to do that you wouldn't find that there would be a severe penalty on the significance level because of the correlation, whether you assume it's one or something less than that. But I think that there are other things that have to be taken into consideration, and I spoke about this briefly this morning. And

one of them is the fact that, and Richard Chappell mentioned this as well, is that we have this issue of a delayed effect. And what that says to me is that the results of - for TTP in Study 1 can be viewed as having been spoiled by the failure to take into account a delayed effect, that is the amount of time it takes these immunotherapies to behave. Now, if we assume that the trial was just under-powered, and we got a insignificant p-value for TTP, that would be the end of the story. But if you have a valid explanation, something that is not only present in Study 1 but is present in other immunotherapies and there's a biologic theory behind it, then you're compelled to not just look at that p-value for TTP, but also to look at the estimate of the hazard ratio, and to see whether that has some kind of a clinical meaning for you. And the hazard ratio for Study 1 TTP is 1.45. That's a large hazard ratio. And so you're

therefore compelled to take that into account when you compare the even larger hazard ratio of 1.71.

Now, the small trial issue is another difficulty that's been discussed here and I think the biggest - the most important thing to take into account when you look at the survival result, and in light of the small trial, that is you have a - you're sitting there with a significant p-value, or at least putatively significant p-value, depending on what kind of reference significance level you wish to use. You're sitting there looking at this 0.01 and you're saying, well, is this 0.01 significant or not, or what does it mean in the context of this small trial. What you have to do there is take a look at the confidence interval, and when you do you find out that the confidence interval, the lower bound of that confidence interval is 1.13. Now, Bo Zhen this morning, the

statistician from the FDA says that that's small. Well, I don't think it is myself. I think representing a 13 percent higher hazard rate in the control arm is important and in fact would, as a lower bound of a confidence interval, does translate to an implication of clinical benefit.

And finally, Maha Hussain said that the - indicated that she thought that the rest of the data from Study 1 didn't really speak to the whole study being significant. I think I see it a different way. To me, all of the secondary endpoints go in the right direction. TTP as I've mentioned before goes in the right direction. There may be a good explanation for why it's not statistically significant based on the presence of this delayed effect that wasn't taken into account at the time the study was planned because nobody understood that at that time. But the other thing that's important is that we showed

some forest plots where various subsets of the patients were compared with respect to the important prognostic factors. And I think that, again, to get a sense of whether the study has this internal consistency that's so important in the interpretation of a small trial is that you have to remember that those forest plots, and let's see if you can bring up the one that shows all the factors for Study 1. That would be the most useful one. But if you look at those, then you can see that almost all of the factors looked at, almost all of the subgroups - we're still looking for the one that - almost the preponderance of them are, in fact all of them, I think, are on the right side of the vertical line indicating no effect, and many of them of course from Study 1 have confidence intervals that don't cross that line. This is the one. And so I think that this is an indication that the expected outcomes with respect to the

factors that would control - that indicate consistency, that these factors are all pretty much in the right direction with respect to establishing the internal consistency of this trial.

So here I am a statistician, and I know the rules. In fact I sit on committees and I often invoke those rules, but this time I'm sitting on the other side of the podium, or not at that table, and I'm going to argue as a mostly naysayer, but I'm going to argue that in this case, I would be presented with this dilemma of looking at all of this evidence together, and I think that, you know my feeling would be, yes, this 1.71 hazard ratio with the lower confidence interval that is 1.13 and all of these other consistency things, and the fact that the TTP isn't statistically significant, but there may be a good biologic reason to see why it isn't and so forth. All of this to me would say, yes,

this is a treatment that men probably should have access to. And then in the end of the game, if the other trial isn't significant, nobody will buy it.

DR. MULÉ: Kurt?

DR. GUNTER: Thank you very much. So, I wanted to just think about what we're doing here. We're not reviewing a grant, we're not reviewing a manuscript, we're trying to figure out whether needy patients who don't have anything available can benefit from this. Personally, I think the data are persuasive. Now, I know it's not a perfect study. I think we've covered the nature of the post hoc problem pretty substantially thanks to all the statisticians. I will remind everyone that it was an endpoint that the FDA states is the best in current FDA guidance. The statistical analysis was log rank, did not exclude anyone, as I understand it, and is probably the most common way to analyze

survival in current methodology.

Now, let's talk about the safety. Oh, and I should point out that the FDA has stated that the secondary - excuse me, the sensitivity analyses all support the significant result on survival. That's in the FDA's own words. Now, safety. I think clearly the product is safe except for the issue of CVA. I think that bears very close watching. I think it may be a red herring. I'm impressed or concerned that, in one study we see a significant effect or much more CVA effects on the placebo arm than the treatment arm. I'm sure the company would be willing to watch that carefully in post-marketing.

So I think that this committee should take a courageous step. I think that actually listening to the patients today, not only was I impressed with their stories, but I was impressed with their intelligence. I think patients and physicians could look

at some of these data in labeling and make their own decisions about whether they want to take a chance on this.

(Applause)

DR. GUNTER: So in summary, I think that we do have persuasive evidence of efficacy on balance given all the limitations in the data, and I urge the committee to think about it very carefully before they vote.

DR. MULÉ: Doris, you had a question?

DR. TAYLOR: Yes. I think there's no question that we need a treatment, and but that we need a safe treatment that's available to everyone. And I guess the question that continues to be present in my mind is, does the benefit outweigh the risk, and what will be done to continue to assess this risk going forward. We've heard that there may potentially - that there will be a vigilance plan put in

place, but I haven't heard anything with regard to that. And we just heard mention of biology and growth factors and cells and looking at models that might be relevant, but more and more cell therapy data are emerging that suggest that there can be a relationship between cells and cardiovascular events, or even cerebrovascular events and/or some of the growth factors, and I think that might bear monitoring going forward to include safety.

The other thing I haven't heard other than a very brief mention early on was inclusion of the African-American community and of other individuals that were under-represented in the original study. So we can't really comment on safety or efficacy in those groups, and those are groups which also very much need access to a therapeutic agent. And so I really -

DR. MULÉ: Doris, we have - that's related to Question 6. We'll get to

that specifically and spend some time with that, okay? So Michelle?

DR. CALOS: Yes. I just wonder if we could discuss, it seems to me that this treatment, it's - all the data we've seen is consistent with it being efficacious, but perhaps not compelling at this point. So could we could just discuss a little what are the consequences of approving something in this situation and then going forward and finding out that it's not actually effective. What are the consequences of that mainly for the patient population, but also for science and for the company and for the FDA?

DR. MULÉ: Comments about that? Franco?

DR. MARINCOLA: Or the other way around. What if it is not approved and it turns out that it is effective and delayed for years? So either way.

DR. MULÉ: Maha.

DR. HUSSAIN: So I want to - I think the point that was brought is a very important point, but I want to remind the members of the committee first of all there is a 400 of a 500-patient accrued on the definitive trial. I don't think anybody around this table suggested that this is a definitive trial. I think that we all agree on. And so the definitive trial is being done and is being completed. I would hope that if the - whichever way the FDA decides, pointing out that our role is not to approve the drug or disapprove it. That's the FDA decision. But if the decision is made to approve, that there would be guarantees that that trial will be continued, because this will have an implication on the other definitive trial.

And finally, access to patients can be provided until the results are available. I can't imagine why this could not be done. Other companies have done that

waiting for the definitive trials. And finally, I think somehow we heard repeatedly there's really nothing out there for patients. I will tell you that we have patients in our practice that we are all caring for with hormone-refractory disease over a 2-, 3-, 4-year period, so it is desperate, yes. There aren't anything out there, but having nothing out there is no justification to get something that is suboptimal to patients.

DR. MULÉ: Savio.

DR. WOO: I'd like to address a couple of points. I think we're all very sympathetic to the patients with this disease, and we've heard from the advocacy groups very impressive presentations. Certainly if there is something that in our judgment is effective, we will love not any less than you to make it available to the patients. So the question before us is really is treatment availability versus

effectiveness. Do we really believe that this product works? If it works, that's great, but if it doesn't work, are we then recommending to tens and hundreds of thousands of patients a treatment, a very -- albeit maybe not as healthy as some of these others, but still a potentially toxic event that could occur, and the morbidity and so on. Are we recommending to hundreds of thousands of patients a treatment that's absolutely worthless? And there are plenty of examples of those in the New York Times stories about other conditions in the recent years. So that's something that to me I think is very important that some treatment that comes forward must -- that are we satisfied that it is most likely to be effective.

The other concern that I have is that we talk about survival advantage as a post hoc analysis and so on between Studies 1 and 2. Could it be real effectiveness, or

could it be some other factors? Well, as I look at the two arms of the trials in both Studies 1 and 2, there are differences in terms of the enrolled subjects. The Gleason scores are different, soft tissue metastases are different. So because of the small sample size, can we really rely upon those post hoc survival advantage data as definitive proof for effectiveness? I'm not so sure that I can be convinced. So I'm also thinking that, gee, you know, since we have a definitive trial that is ongoing that is close to completion, perhaps it would be more prudent to look at those results to be assured that it is effective before we recommend them to the patients.

DR. MULÉ: Bob?

MR. SAMUELS: Yes. You know, it's been very difficult for me to sit here and try to be totally objective because I am a 13-year survivor of prostate cancer. And when I got diagnosed in 1994 and I got

opened up and there was a cancer cell on one of my lymph nodes, I was told that I probably had five years left on this earth. However, I decided to become aggressive and take charge of this disease that was in my body. And I sit here now 13 years later feeling that I'm still doing hormonal therapy, and at some point it's going to fail. I know that. And so when it does fail, I've got to look around and say, okay, what do I do next. And I look upon this as an opportunity for me to make a choice, and I think that's all the patients want. An opportunity to make a choice.

(Applause)

MR. SAMUELS: That's what this is about. Because as they look down the road, they don't have a very bright future. And if we can buy them a couple of minutes, a couple of months, or a couple of years, then it's our obligation to do that. So it is not something that I - and I understand and

appreciate the hard work of this committee. I mean I admire you, and I don't envy you the decision that you have to make, but at the end of the day it's not about statistics, it's about people's lives. And indeed, we have an obligation to give patients like us a choice to say, we'll take the risk. We understand it's a risk, but it's a risk that I think most of us are willing to take. But you have to give us that opportunity.

(Applause)

DR. MULÉ: Franco.

DR. MARINCOLA: Yes, I'd like to make another comment which is a little broader. Historically, we're in a very special moment of tumor immunology. This is a very rapidly evolving field, and in some ways this product was designed years ago, and so it's, you know it's just showing now some - it is providing one of the best outcomes so far in immunotherapy, yet

probably is not perfect because it's delivered as a single agent, and there is so much more that can be done to understand the biology of this and make it better. And I think it's true that maybe the information has been provided, but the study is not conclusive, but definitely it is intriguing enough to believe that it's worth pursuing it, and definitely - let's put it another way. If I had prostate cancer, I'd like to try this before chemotherapy, no matter - maybe not as a scientist, but as somebody who has prostate cancer.

I think that maybe we are a little bit too harsh, and most importantly we are missing the point that we are opening a new field, and I think the experience, even if we make the mistake, I think that maybe this product was not that effective as it may be. Still, there is so much to learn by start seeing patients being treated with this and see what else can be added, and

applying even the new modern understanding of like the effect of T-regulatory cells and so forth, adding so much that I think we should not - we should not underestimate the importance of this decision. I don't think it's just about deriving what the drug does, but it's more opening a field, and the investigation on that field and the clinical grounds test of being kind of an esoteric academic exercise.

DR. MULÉ: Bob?

MR. SAMUELS: Yes. I would like to just do an informal survey. How many men on this panel have ever had a PSA test? Here we are over 25 years later trying to evaluate the effectiveness of a PSA test, all right? We still have not come to conclusive evidence that it has real value, but I daresay that the majority of men who are over age 40 or 50 are getting PSA tests. But there's no conclusive evidence. However, prostate cancer has declined, but

we still can't say that the two are related. So we're still discussing something 25 years later that most of us feel have had an impact on diagnosing prostate cancer in this country. So there's no conclusive evidence. So I mean we're sort of where we are today. Somebody had to take a chance, and that's all we're asking this committee to do.

(Applause)

DR. MULÉ: Steve?

DR. DUBINETT: I would like to go back to Dr. Zhen and ask you to perhaps clarify something for us on your second to last slide, I think it is. You make these three bullet points about the post hoc analysis, and -- but finally come in your last sentence on that slide to say however, overall survival is a preferred endpoint for a cancer trial. And I'm wondering if you could just elaborate for us a little bit to say, did you mean to have the word "primary" before "endpoint" in that last bullet point?

I'd like to sort of have you kind of just really weigh in on this a little bit in terms of what you meant by that slide.

DR. ZHEN: No. Overall survival is not - was not the primary endpoint for the two studies. Basically what I'm trying to say here is, if overall survival is just like many, many other endpoints that's like random research. In that case, you can always get one endpoint which with the p-value less than 0.05. It's just by chance. Here I make cases that overall survival is just not manner of endpoint that can be randomly selected. It is a very important endpoint. It is unfortunately the two studies was not designed to use overall survival as the primary endpoint and power the studies with overall survival.

DR. MULÉ: Okay. Before we move on to Question 6, let me remind the committee that, again, we're not here to approve or disapprove the product. We're

here obviously to advise the FDA on decisions relative to the product. And within that context, I think it's important to reflect on a comment that Maha had made, which is there are options in our advice. In other words, it's not necessarily a no or a yes. It could reflect a going forward with this larger definitive trial, but in essence advising the FDA that maybe there are options to include a go-ahead with the proviso that that definitive trial is completed and reviewed. So again, I think it's important that we keep in context what our role here is, and it's not necessarily a black and white sort of recommendation that we make. We're here to advise. So with that said, let's move on to Question 6 and, Larry, if you can take us through that.

DR. KWAK: Okay, so the question was actually raised by one of our - one of my fellow panelists earlier this morning, and it's been pointed out already that it's

a serious, but -- serious limitation, but it's unfortunately a limitation that's common to many clinical trials in the United States. And I guess before -- I mean, clearly the issue is whether there are genetic or biologic differences that would limit us from generalizing the results of this study to other populations with this disease. Before I open it up for panel discussion, I would just say it's a difficult question, and hopefully this is going to be addressed in the third study that's in progress.

DR. MULÉ: Other comments? Jeff?

DR. CHAMBERLAIN: Well, I mean I guess I'd sort of like to follow up the comment that you made, Jim, and I think that that applies to this question, as well. That, you know, if we were to advise that this treatment move forward and be made available to more people, I would hope that we would also include a stipulation there

that there absolutely must be additional data gathered on additional ethnic minorities, because the data we have I think absolutely does not generally apply to other ethnic minorities, yet we absolutely need to have that information available.

DR. MULÉ: Doris, you were next, then Maha.

DR. TAYLOR: Of the 400 patients that have enrolled in the trial to date, what's the breakdown with regard to ethnicity?

DR. FROHLICH: Mark Frohlich. It's similar to Study 1 and 2. We have roughly 5 percent African-Americans.

DR. TAYLOR: Given that, what - I heard you say this morning that you were going to do everything you could to ensure that this was made available to everyone possible. If you are unable to reach those patients in the clinical studies, what evidence do we have that you'll be able to

reach those groups in the community?

DR. FROHLICH: I think it's a problem that pervades all of clinical trials, enrolling minority subjects. Once commercial, there are less barriers to patients enrolling. There's a lot of, you know, requirement for extensive follow-up and testing as part of a clinical trial, which is not required once in clinical practice. So it would be our goal to try to specifically target minority patients through providing information to them, advertising specifically to those patients to try to enroll them. It's part of our planned pharmacovigilance program to specifically target minorities. We have a plan to enroll roughly 3,000 patients in a pharmacovigilance plan, and target roughly 10 percent of those for African-Americans specifically.

DR. MULÉ: Maha?

DR. HUSSAIN: This is a question

to the immunologist in the group. Is there any data that says ethnic subgroups respond differently to immune stimulation from, say, any setting? And what is that?

DR. MARINCOLA: For example, African-Americans do not respond as well to interferon alpha therapy that have chronic hepatitis C, and there is a group at Stanford that recently proposed some kind of a theory, but they don't have - the signaling is different in response to interferon alpha, although the reason, the polymorphism is not known. But definitely they simply have a lower response to interferon alpha, even in in vitro testing to the point you can predict who is going to respond or not by doing in vitro testing. So definitely there's plenty of evidence. And there are other cases, but this is one of the most striking.

MR. SAMUELS: Yes, I just want to comment on that, which I guess I started

this morning. And that is that, you know, I've been a survivor now for 13 years. Prior to that I was a banker in New York for 31 years, and I used to hear many of the companies that I dealt with talk about the difficulty they would have in trying to find African-Americans to be part of their senior management on their board. And I kept saying, well perhaps you're looking in the wrong places, and you're not talking to the right people. And I've got to say the same thing here, because if we're talking about a disease that 30,000 men a year in African-American communities get diagnosed with, that's a significant number of men being diagnosed every year with this disease. And we can't find more than nine to participate in a clinical trial? Then I say you're looking in the wrong places and you're talking to the wrong people, because it can be done. And I said it and you look at the boards today, and boards are much more

integrated, but they made a concentrated effort to do it, and that's what you've got to do.

DR. MULÉ: Howard?

DR. SCHER: This is a question to Mark. On the one hand, we hear about the drug available to more people, you don't need the intensive monitoring, and then the next sentence is a 3,000-patient pharmacovigilance. So can you explain the difference, and maybe give a little more detail of what the pharmaco -- let's call it the safety monitoring, pharmacovigilance entails.

DR. FROHLICH: The pharmacovigilance plan would be roughly 3,000 patients. There would be select centers that would enroll patients with consent to be followed. It would require essentially a collection of basic demographic historic information on those patients. They would be followed every six

months for events of special interest, including cerebral vascular events, infusion-related events, autoimmune events. They would be followed for a minimum of three years for overall survival.

DR. MULÉ: Maha?

MS. SMITH: It might also be useful to add, in this context, we have a very unique access to information for patients who receive sipuleucel-T. Because of the autologous nature, we know everybody who gets it. We have the ability to consent everybody, to track everyone, to keep in contact with their physician. So in contrast to what maybe has been observed in other pharmacovigilance studies where sponsors have not done as good a job in completing those studies. We have a very good handle on that information.

DR. HUSSAIN: And Dr. Frohlich, just a question, and I don't mean to put you on the spot, I'm sure there are other

considerations, but could an expanded access program be made available to patients pending the definitive trial results?

DR. FROHLICH: I'd like to ask Liz Smith to take that question.

(Laughter)

MS. SMITH: Again, with this autologous product, it is not quite as simple to open up expanded access programs as we would like. I mean, we are very committed to making this product available to as many people as possible, and in fact we've been quite transparent, I think, about our commitment to 9902B. It's a large, highly-powered study. We started this awhile ago. We are following it very closely. We are enrolling very aggressively. Expanded access in this point, when you open up to whoever is - whoever wants it, that also takes out manufacturing capacity, and it actually takes it away from our clinical trial that

we're trying to finish. So it's sort of a Catch-22. We know that if we were to open it up to an expanded access program, we would probably have a very high demand. That would not help us get our clinical trial enrolled.

We also have a strong commitment to making sure that, when this product is approved, it is widely available, but as a biotech company who doesn't have a product approved right now, it's sort of a chicken and egg thing. When we have approval, we will have launched up our capacity, we will be able to serve the whole market. It's different when you're in a pre-approval phase.

DR. MULÉ: All right. Let me stop here and ask Dr. Witten and her colleagues if we've covered at least these six questions to your satisfaction. If you have other needs, if you can let us know? And then we'll move on to the voting

questions.

DR. WITTEN: Thank you, no; you've answered the questions.

DR. MULÉ: Okay. So now we'll move on to the voting questions. There are two. I'll read the first one. We'll see if there is additional discussion. These two questions really reflect what we, in my opinion what I think we've already covered in the first six questions. So I'll just ask for comments, and then we can go forward with the voting.

So the first voting question is, does the submitted data establish that sipuleucel-T is reasonably safe for the intended population. Other comments? Additional comments? Okay. And the second voting question is, does the submitted data establish the efficacy of sipuleucel-T in the intended population. Okay. All right. So I think we're ready to move ahead. So let's go with the first voting question.

Again, I'll read it. Does the submitted data establish that sipuleucel-T is reasonably safe for the intended population? We'll start with Dr. Alexander.

DR. ALEXANDER: Yes, I believe that the data that are submitted has established that the drug is reasonably, reasonably safe for the population. And with the small numbers of patients, the stroke issue remains very significant to me, but the plans that I hear around it from the companies with regard to the intensive follow-up of a certain number of these patients I think is reasonable. But yes, I think it's reasonably safe, and that those data are persuasive about reasonable safety-ness.

DR. MULÉ: Dr. Chamberlain?

DR. CHAMBERLAIN: Yes, so I also agree that the data at this point makes it look like the product is reasonably safe. I also have concerns about the cerebrovascular

incidents, and I would urge that data continue to be gathered in that area. But I think with what we know, it's safe enough to go forward with.

DR. MULÉ: Dr. Kwak?

DR. KWAK: Yes, I think unequivocally that it - the available data suggests, as one might expect for an ultimate targeted therapy, that it's reasonably safe.

DR. MULÉ: Dr. Calos?

DR. CALOS: Yes, I believe that it's established that it's reasonably safe, especially relative to the alternatives, and with continued vigilance, I think that's fine.

DR. MULÉ: Dr. Dubinett?

DR. DUBINETT: I agree with the appearance of its reasonable safety, and also concur with what's been said about the appropriate plans of the sponsor.

DR. MULÉ: Dr. Allen?

DR. ALLEN: I concur with that. I believe it's to be safe, and I think that appropriate monitoring can be followed appropriately.

DR. MULÉ: Dr. Chappell?

DR. CHAPPELL: Certainly seems to be safe in the context of disease commonly treated with radiation and cytotoxic chemotherapy.

DR. MULÉ: Dr. Hussain?

DR. HUSSAIN: Yes.

DR. MULÉ: Mr. Samuels?

MR. SAMUELS: I believe it to be reasonably safe, and suggest we move forward with vigilance, of course.

DR. MULÉ: Ms. Terry?

MS. TERRY: I agree with that, and I'd also add that I think many times we measure these kinds of things, we measure them up against what is safe in a healthy population, and we have to be mindful that once you cross the line through diagnosis,

what is safe and what is not is measured in a different way. And I agree that, if we're vigilant, this is safe.

DR. MULÉ: Dr. Taylor?

DR. TAYLOR: Yes, I would agree this is safe in a Caucasian population, and that vigilance needs to be put forward in all populations.

DR. MULÉ: Dr. Woo?

DR. WOO: I agree with all the other committee members that this appears to be relatively safe for the patient population.

DR. MULÉ: Dr. Marincola?

DR. MARINCOLA: Same. I think it's safe, and I agree with all the comments so far.

DR. MULÉ: Dr. Tomford.

DR. TOMFORD: Yes, I agree that it appears to be reasonably safe in the population.

DR. MULÉ: Dr. Guilak.

DR. GUILAK: I agree that it appears to be safe in this population.

DR. MULÉ: Okay. And Dr. Gunter, you're the industry rep. You have no voting, but you're free to comment.

DR. GUNTER: Well, I think I've already commented. I believe the product is safe. I think the sponsor has done a good job showing us that. I think labeling should reflect the potential for CVAs, and obviously post-marketing pharmacovigilance is going to be very important.

DR. MULÉ: And I agree with the committee members as well, with additional vigilance and also taking into account the need for this question to be better answered in African-American population, other minorities.

MS. DAPOLITO: Okay, for the record the vote was 17 yes, zero no, zero abstain for Question 1.

DR. MULÉ: Okay, we'll move on to

Question 2. Again I'll read it. Does the submitted data establish the efficacy of sipuleucel-T in the intended population? Dr. Alexander.

DR. ALEXANDER: I don't know how I got the short straw to go first here, but -

(Laughter)

DR. ALEXANDER: But my - I took a lot of notes here, and I'm going to read. Some of the words that I heard that made an impact on me, that this Study 1 provides evidence of efficacy, and there is no question that Study 1 provides evidence of efficacy. I think that there's no question that survival is the most important outcome that is important in the treatment of cancer, and followed -- and arguably by quality-of-life. And there's no question in my mind that four months of an increased median survival in the population of men with metastatic androgen-independent

prostate cancer is a very important improvement in survival.

The question that I grapple with is, is the evidence that's here so far, does it establish the therapy. Is the therapy established that, with full confidence, I can look my patient in the eye and say that this is established to be an efficacious therapy for your disease. And I've lived my life by the evidence in medicine, and there are many, many -- there are many ways to manage patients and deal with them, and there are many things and many competing reasons that we seek to do the things that we do with patients, but for me the most important, and the thing that we have the luxury of being asked to do is to say, does the data establish that this therapy has efficacy. I think it's a very strong suggestion, but it is not in my mind definitive and establish that the therapy is extending survival because of -- that the

therapy itself is the reason that we see the differences that's been seen in the data so far. So I -- my vote is not to say no, but it's to say that there's clear evidence that there's some efficacy to the therapy, and I think that a trial with some 400 patients already randomized that's ongoing clearly is going to be the trial that will establish whether this therapy establishes its efficacy for patients.

I am -- I take care of patients and I sit opposite, when I hear your stories I am very compelled by what you say, and I sit opposite you on a daily basis in the office and I feel -- I see it, it's the thing I've led my life trying to do is to make new immunotherapies for prostate cancer. And I want this, wanted this, so wanted to see that I was going to come here and be totally convinced that the data were compelling to establish the efficacy of this, the first treatment, but I haven't

seen it yet. It's close, but I haven't -- I'm still waiting for me to cast a vote to say that everyone in this room should go home and tell their next of kin that this is an established therapy for this disease. I don't think it's there yet. So I would say that the trial that's ongoing and actively enrolling must continue, and I would encourage the company to redouble their efforts to get that finished, and that it sounds like they're well on their way to recruitment. So that's - so my vote is, I don't know what you would call that. It's a -

DR. MULÉ: For the purpose of enumerating the votes.

(Laughter)

DR. MULÉ: And I understand you're the first on the list here.

DR. ALEXANDER: The answer to the question has the submitted data established that this is an efficacious therapy, my

answer is no, not yet. But very close. And with the proviso that if they need to continue the big Phase III study.

DR. MULÉ: Dr. Chamberlain.

DR. CHAMBERLAIN: Well, so I guess at this point I'm not entirely sure how to answer this question. It's not a yes or no question in my opinion the way it's phrased. I mean, it's really very absolutely phrased, and I guess I tend to lean towards agreeing with what Richard was saying that I think the data is strongly suggestive that it's an efficacious treatment. I would like very much to see this made available to many more patients as quickly as possible, with the provision that the ongoing Phase III trial be completed, and also with the provision that significantly more ethnic minorities are enrolled in trials. With the safety data and with what we've seen, I see no reason not to make this drug available, but I don't

think it's 100 percent proven that it's efficacious.

DR. MULÉ: Dr. Witten, with respect to this question --

(Laughter)

DR. MULÉ: Is it -- from your standpoint and the FDA's standpoint, are you looking for definitive answers to this question? Is it necessary to rephrase this question?

DR. WITTEN: Well, it sounds like everyone on the advisory committee would like to rephrase the question, but, you know, we do need to look at this in terms of getting advice for what our next step, you know, your recommendations as our next step. But having said that, it might be useful to, you know, instead of -- it might be useful to actually go around the room, find out everybody's opinions and then vote, because it sounds like everybody's sort of struggling, so. But we do need a vote and,

you know, but if people in the discussion want to state a different question that they'd like to answer, and then at the end vote on the question that we want an answer to, I'm sure that would be useful to us, as well.

DR. MULÉ: Okay. So I guess what we'll do is, yes, we'll just move around and then we can re-vote, I guess. Okay. So Dr. Kwak?

DR. KWAK: Well, as a clinician who treats cancer patients, I am certainly aware of the exceptional need for additional therapies. But I think what's been posed to us by the FDA is a fairly specific question, and for this I have to put my scientist hat on, and give them a yes or no answer against the statement that the submitted data established the efficacy of the product. My reasons for doing that I think have been stated by many around the table. Concerns about small sample size, the post hoc nature

of the overall survival analysis, and in addition to those, for me, the lack of demonstrated immune responses against the target antigen. So but you know, I would agree with Dr. Alexander that it's really a question, the key word is really, does the data establish the efficacy, and if forced to give an answer to that question, I think for me the answer is no.

DR. MULÉ: Okay. Dr. Calos?

DR. WITTEN: Excuse me, Dr. Mulé? Yes. Maybe we should try to rephrase it as -- I mean, the question is really asking for you, you know, on the advisory committee, do you believe that this product works, that it's efficacious. I mean that's really what we're asking. So if it's somehow some of the words are not clear, that's what's intended. We want to know whether you believe, as individuals, that this works, that they've shown that it works.

DR. CHAPPELL: There's a degree

of belief, and "establish" implies much more certainty than a guess. And so if you were to ask us, you need please, to specify, at least to me, what you mean.

DR. ALEXANDER: Like is it a reasonable doubt, a shadow of a doubt?

(Laughter)

DR. WITTEN: Yes. The regulatory definition is "provide substantial evidence." So that's our standard. Is there substantial evidence that it works. Is there substantial evidence of efficacy, if that helps. So is there substantial evidence.

DR. MULÉ: Okay. So just to clarify what you're asking, is there substantial evidence that the product is efficacious.

DR. WITTEN: Yes.

DR. MULÉ: Okay. Okay. So for the sake of time, I'd like to finish this voting. So Richard, can you just take this

question now and give us a vote and we'll go around the table, okay?

DR. ALEXANDER: Yes. I mean the issue is -- yes, there is substantial evidence. I mean, the 150-some patients, they're substantial evidence.

(Applause)

DR. ALEXANDER: Is the evidence enough to be conclusive to the standard that we need for approving something? That's up to the FDA to decide. And from my standpoint, as designing clinical trials where I am trying to say that it uses definitive evidence that something is conclusive based on a secondary, or not even a secondary endpoint is, you know, is statistically not a valid thing. And that's what -- if we're going to design the study to answer a question, we have to design the best study possible, and that study is ongoing. So that's where I would say, you know, is there substantial evidence that the

drug has efficacy? Yes. I would say this qualifies as substantial evidence, but is not enough for me that if I was in the seat of saying yea or nay that I would say yea. I would say nay.

DR. MULÉ: Okay. Dr. Chamberlain?

DR. CHAMBERLAIN: I vote yes, there is substantial evidence.

DR. MULÉ: Dr. Kwak?

DR. KWAK: Yes, substantial evidence.

DR. MULÉ: Dr. Calos?

DR. CALOS: Yes, I think there's substantial evidence. I don't think that it's been conclusively established, but there's substantial evidence, and certainly it's very exciting, and certainly something that one would want to see continued, and hopefully patients would have access to. But scientifically it falls short of being established.

DR. MULÉ: Dr. Dubinett?

DR. DUBINETT: Yes, I think that there is substantial evidence for this. You know, and I also say in sort of coming to some middle ground is that, you know, I think that there is precedent if we look to what happened with gefitnib in lung cancer is that things went forward with gefitnib, it was found to not be demonstrated in a Phase III trial, but another EGFR inhibitor was. So I think both the patients and the community benefitted from that approach. So I think that there is more than one way to actually approach this, but I would come down on saying that there's substantial evidence.

DR. MULÉ: Dr. Allen?

DR. ALLEN: I believe there's substantial evidence. I think what's compelling to me is, although there are doubts about these primary outcome measures, for me the point is that this is a new

therapy. We may not -- as scientists, it is important for us to understand what we don't know, and one thing we don't know is what this thing is doing really. It may be changing the biology of the disease in a way that chemo drugs just aren't. So for me the fact that you've got evidence of, in my opinion, substantial evidence of survival advantage means that it should be opened up, given the dire landscape of other drugs out there, it should be opened up and followed very, very carefully, but nevertheless I believe it should be approved.

DR. MULÉ: Dr. Chappell?

DR. CHAPPELL: No. Regretfully and very sympathetically, I don't believe that the data establish efficacy. I dearly hope that the next trial does, but -- and I realize the need for hope, but I don't want to give that hope on a false premise.

DR. MULÉ: Dr. Hussain?

DR. HUSSAIN: So to me

"substantial" and "establish" are the same, and no to either. So no to both.

DR. MULÉ: Mr. Samuels?

MR. SAMUELS: Yes.

DR. MULÉ: Ms. Terry?

MS. TERRY: So I'm a layperson and don't have the scientific knowledge to answer this question scientifically, but I'm here as the consumer representative, and so I'm going to answer it from the consumer point of view. And one of the things I'm going to harken back to for myself is remembering going with my brother, who had a glioblastoma multiforme, to his physician who said, "There's substantial evidence that this stereotactic radiosurgery will keep you alive for 10 years," and he died nine months later. I think new fields need this kind of foray, and new fields are hard to foray into if we wait till everything is perfect. And so therefore I'm going to vote that there is substantial evidence.

DR. MULÉ: Dr. Taylor?

DR. TAYLOR: I agree with everything I've heard. I think the real question, in my mind is, is there a risk-benefit ratio here that's appropriate go forward. We've all voted that we believe that this is safe, and I think we really don't yet know whether or not there's compelling data that it's efficacious, but I think there is substantial evidence, so I have to vote yes, and let patients make that decision.

DR. MULÉ: Dr. Woo?

DR. WOO: In this day and age of evidence-based medicine, essentially we're presented results of two studies, and we were asked to make a judgment on those. The first one appears to be effective, the second one does not. So in my opinion there is some evidence to suggest that this treatment may be doing something. Does it rise to the level of substantial evidence

that it is effective? I don't think so, not even near.

DR. MULÉ: Dr. Marincola?

DR. MARINCOLA: Well, I think that, based on the facts and on the information that we have so far, I think there is substantial evidence, and I think that not only about this particular treatment, but in general in the field, and I do believe that this is just the beginning of an era where there is going to be so much more that can be done to improve these kind of therapies. If you look at the evolution of these therapies, it's just the beginning, and I do think that there is evidence, and there is a lot of evidence besides this particular study that immunological intervention can be very useful, and I think this is not counter-intuitive as a result, and so I think it's something that is promising, and I would offer it to the people.

DR. MULÉ: Dr. Scher?

DR. SCHER: I think we are really poised at the beginning of what will be hopefully an outstanding era of immunotherapy. I think there is sufficient evidence demonstrated which justifies the definitive study, and obviously there are investors in that who concurred, but I think it does not meet the -- as the question was phrased, to establish the efficacy. I think this is still an open question.

DR. MULÉ: So I take it you're saying yes with these provisos?

DR. SCHER: We have two questions. I would say yes to one, no to the second. The first question as posed, as established, I say no.

DR. MULÉ: No, it's substantial evidence.

DR. SCHER: I will say no.

DR. MULÉ: No. Dr. Tomford?

DR. TOMFORD: Well, I was

prepared to say no to the submitted data establish the efficacy, but I believe there is substantial evidence that the treatment works in some form. And so what I'm concerned about is, if it goes forward from here, and substantial resources are put into this treatment, I'm not convinced that it will be something that's really worthwhile. Immunotherapy I support, but I'm not -- there are too many questions about this. However, for the substantial evidence question, yes, I believe there is substantial evidence for the treatment.

DR. MULÉ: Dr. Guilak?

DR. GUILAK: I think it's not unusual in science to have these borderline p-values, or studies that aren't completely definitive. I wish we could all have voted maybe on this, but I don't think we can. And so I think it does boil down to, as Dr. Taylor said, a risk-reward issue, and a way to promote this type of research in the

field, and so I have to say yes, substantial evidence.

DR. MULÉ: Comments from Dr. Gunter?

DR. GUNTER: I appreciate the chance to comment, and I think I already stuck my neck out on this one. I do think it both meets the measure of substantial evidence, and I also believe that it's pretty definitive. I think that, in this day and age, in the treatment of patients, you know, like Dr. Alexander said, you don't have to look them in the eye and say, this is good for you. You need to be able to look them in the eye and discuss their treatment options, and present them in a way that they can understand. And I think that these data, even though they're complex, can be presented by oncologists to patients in a way that they can understand and make reasonable choices. So I definitely support that this is an effective therapy.

DR. MULÉ: When I look at the field in general, immunotherapy field, and given the question as it's restated substantial evidence, I vote yes, with the proviso, however, that the definitive Study 3 is completed, and there's a commitment for doing so. And wrapped into that is the concern raised by Mr. Samuels with respect to recruitment of minority population.

MS. DAPOLITO: Okay, for the public record, the question was, is there substantial evidence the product is efficacious. The vote was 13 yes, 4 no, zero abstain.

(Applause)

DR. MULÉ: Okay. So I'd like to thank the members of the committee, and I'd like to thank our presenters today for providing us with the information. We're going to take a short break, 10-minute break, reconvene for the next portion of the agenda.

(Whereupon, the foregoing matter went off the record at 4:05 p.m. and went back on the record at 4:33 p.m.)

DR. MULÉ: So we're going to have an overview of the research programs. Okay, so we'll start with Dr. Puri, Chief of Tumor Vaccines and Biotechnology Branch.

DR. PURI: So thank you, Mr. Chairman, thank you, committee members, for having a long day and still here to listen to our presentation. In this session you will hear two presentations, one by me. I summarize the research activities, predominantly a summary of Tumor Vaccines and Biotechnology Branch that I am the branch chief, acting branch chief of, and also Dr. Steve Bauer who is a branch chief of Cell Tissue Therapy Branch is going to summarize the research summary of the site visit presentations that were made by that branch. In addition, too, we tried to consolidate our presentations that our

associate director of research would have made. To spare you one additional presentation I have merged it with my presentation. I'll talk to you a little bit about the mission and organizational structure of the Office of Cell Tissue and Gene Therapy and the Division of Cellular and Gene Therapy. In addition I'll speak to you a little bit about regulatory scope and approach to research.

The Office of Cell Tissue and Gene Therapy has three divisions, and those divisions are listed in the lower boxes in addition to a regulatory management staff. This office is directed by Dr. Celia Witten and additional - the rest of her staff and management staff is listed in this slide. The Division of Cellular and Gene Therapy has five branches. Two branches, Gene Therapies branch and Cell Therapy branch is comprised of regulatory scientists. Their full-time job is to not only evaluate the

regulatory submission that includes multiple submission mechanisms and I'll show you one of the slides, but they're also involved in many policy and guidance document development. Two branches that were evaluated at the site visit last year by the subcommittee of this committee includes Tumor Vaccines and Biotechnology Branch and Cellular and Tissue Therapy Branch.

The products that our staff evaluates are a multitude of products we have, including cell therapy. That could be cell therapy for Alzheimer's Disease, Parkinson's Disease, diabetes and what have you. We have gene therapy, ex vivo or in vivo gene therapy, cancer vaccines, you heard the presentation this all day, immunotherapy, tissue-engineered products, xenotransplantation products and combination products where the cells and device or drugs can be combined, and the devices used with the cells and tissues in addition to that.

We have greater than 1,100 INDs, IDEs, investigational device exemptions, master files and several thousand amendments per year in addition to consult review that our staff provides. We have one licensed product and a growing number of products are released to the Phase III clinical trial. We evaluate devices and a lot of our staff has spent a good chunk of our time in providing advice to investigators in a pre-IND setting as well as pre-pre-IND setting. Our staff is involved in organizing and presentations at the advisory committee such as here today. They're involved in inspections with our colleagues in compliance and enforcement actions.

We participate and partner with the various programs such as National Toxicology Program. Our staff is engaged in testing the safety of the retroviral vectors, with the NIH, CDC, NCI/FDA Interagency Oncology Task Force and a stem

cell task force and other task forces with the - and in this case MATES is a Multi-Agency Tissue Engineering Group. We participate with the international bodies such as ICH and WHO, and our staff performs and does a lot of outreach presentations at various national and international conferences, academic institutions and patient and consumer advocacy groups. We provide a liaison to various professional societies and our staff publishes articles based on simplifying the guidance documents in a publication forum which is available for peer-reviewed, for publishing in peer-reviewed and non-peer reviewed journals.

The roles of the research-reviewer is that you are - you evaluated - the subcommittee evaluated last year and the full committee is looking - we are being presented a summary is the product application review of policy and guidance document development, and the various

outreach activities, regulatory mentoring, advisory committee preparations and various enforcement actions and international activities. In addition to that research-reviewers perform research, they do training of the postdoctoral fellows and mentoring. They do administrative activities, some of the like branch chief duties. They participate in various center-wide or inter-center or outside committees. They are involved in writing grant applications wherever we are allowed to write grants and participate in various scientific communities similar to that any principal investigator at NIH or an academic institution would do.

So our staff pursues research, Critical Path research to address some of the technological challenges and to stay ahead of the curve, but yet we cannot have expertise in every product area. And we are cognizant of the fact that we have to stay

abreast with the latest technologies. The research strategy in the Division of Cell and Gene Therapy involves to perform a Critical Path research to fill the gaps, deal with the scientific challenges and figure out quickly what is important. As type of product that we evaluate, the regulatory paradigm has not been established or is still being established. Therefore, we have to be proactive in figuring out what is important in the cutting edge area of research that we evaluate.

As the sponsors evaluate single products and the results are often proprietary, our scientists perform studies relevant to the entire product class and we make the result public rapidly, thus accessible to all the sponsors to advance the entire field. We have a variety of different project areas that our staff is engaged in in research, including virology. We have expertise on various different

biovectors and viruses, immunology. We have cell biology, cancer biology and biotechnology involving genomics, flow cytometry and proteomics technologies.

In the next section of my talk I'll talk about - present the summary of the research presentations that were made by two PIs in Tumor Vaccines and Biotechnology Branch, myself who studied the cancer biology and also chair and run the CBER - participate in CBER's genomics program, and Dr. Michail Alterman who was recruited last year, or less than a year go in April to replace a proteomics PI who had departed FDA to fill that position and set up a proteomics program for the Center for Biologics.

So the research in my lab is focused on targeting cancer and identifying the new cancer antigens and develop various different animal models that I'll show you in a few next slides. But I'd like to

introduce to you some of the key public health issues and some of the scientific and regulatory challenges that we try to address in my research program. As you heard and as you know, cancer is one of the most difficult public health problems and the statistics that American Cancer Society provided for 2005 alone, more than 1.3 million Americans are diagnosed with this cancer and about half of them die from this dreadful disease. One of the scientific challenges for identifying new treatment for cancer is to understanding the biology of cancer and identifying the appropriate target that one can deliver to the tumor site to cause a tumor regression. And some of the products that you actually heard today, a cancer vaccine in addition to a variety of different cancer vaccines include tumor antigens, peptide antigens, dendritic cells, T lymphocytes, T lymphocyte designed to express certain T-cell receptors and what

have you. A lot of different types of cancer vaccines are being tested and one of the regulatory challenges that this type of product deal with the appropriate test to identify a biomarker for the purity, the identity, and potency of these products. In addition to they have to have the appropriate animal model, how to test the safety of these products and also how to determine the starting dose in the Phase I clinical trial. And of course lastly, but not the least important, is identifying a biomarker for the disease monitoring as well as in the response to substantiate the clinical outcome.

So the research program in my lab that we summarized in last site visit presentation in the fall of 2006 had three specific aims and we continue to study on those three aims, and one is to characterize the tumor-associated cell surface proteins which are antigen receptors and to establish

identity of tumor vaccines and identify new targets for cancer therapy. The second specific aim in my research program and to deal with the regulatory challenge is to establish animal models of human cancer to assess the safety and the efficacy of tumor-targeted agents and gene therapy products. And third aim includes the characterization of tumor vaccines and use stem cells by genomics technology to identify biomarkers for purity, identity and potency, and research involving stem cell identify cancer stem cell, perhaps providing additional target for cancer therapy.

So in the next couple of slides I'll only show you the summary of the presentation that we made. I am not going to go in detail, present you every slide we presented to tell you that we have discovered two antigens, two targets in the name of IL-4 receptors and IL-13 receptors, and these, both of them, are Th2-derived

cytokines. They are produced by Th2 cells. For some reason nature had provided so many of these receptors on the cancer cells. We still do not understand why these receptors are present on the cancer cells. However, we have taken the advantage of the knowledge of the expression of these antigens on the tumor in targeting these tumors with a targeted agent. And in that regard, in collaboration with - at the National Cancer Institute we created a fusion protein to demonstrate the proof of principal studies that this target can be useful target for the targeting of cancer. And we have looked at variety of human tumors as shown in this slide. The tumors listed in yellow were studied in the review period of four years prior to my last site visit. For the IL-13 receptor which is a cousin of Interleukin-4 that we have studied in these two tumors in last review period and we have find that IL-13 receptors are also highly over-expressed

on the tumor cells.

We have studied various different pathways, why these receptors are present. We look at the mutation of this receptor on cancer which we have found none. We have done a single transduction studies to identify if the signaling is different from the tumor cells to the normal cells, and we have found there are major differences between the two and actually some of the summary is provided in the briefing document.

The other specific aim that we have addressed and I'm going to summarize here today is that developing the animal models of human cancer to assess the safety, toxicity, and effectiveness of the cancer targeted agent. And again we use - we were fortunate that we identified two targets and we developed the two targeted agents. We used them as a model to test in the appropriate animal models that we have

established to test the safety and effectiveness of these approaches. And the tumor listed here in ovarian cancer shown here are the immune histochemistry of two different types of ovarian cancer, serous adenocarcinoma and clear cell carcinoma seem to express high level of one of the chains of IL-13 receptor called IL-13 receptor alpha 2 chain while the normal ovary or isotype control does not seem to express these receptors. And we have developed an animal model where we created a simulated Stage III/Stage IV ovarian cancer model by ototopically implanting ovarian tumor on the ovary and then in looking at the metastasis of the tumor as well as the therapy, the effect of IL-13 toxin and we have published, this paper just came out recently in *Cancer*.

Now, I'll shift to Dr. Michail Alterman's presentation, and, Dr. Alterman, if you can identify yourself by raising your hand. He is in the audience and if you have

any questions he will be very - more than happy to answer any questions. And also if I do not represent his slides very well, please feel free to correct me.

Dr. Alterman is addressing the - and developing analytical proteomics for the characterization of the biological products and trying to identify the biomarkers for different types of products. The specific aim for his projects are now recently ongoing, realizing that he has only spent about less than a year at our place and he has now established his lab and began to pursue some of these projects. He took one of them to develop the mass spectroscopy-based analytical tools for testing of biological product quality and identity. In addition to identify a proteomics-based cellular molecular signature to be tested as a predictor of therapeutic success. In that regard he is focused on two independent projects, one of them is characterization of

cell substrate used to produce gene therapy products or preventive and therapeutic vaccines that you heard. Proteomic characterization of different cell lines with the emphasis on the stem cell lines. In addition to his prior work before he came to CBER, focused on cytochrome P450 isozyme expression in tumors and he wanted to explore that further to identify whether this P450 isozyme expression serves as a potential biomarker for cancer.

The expected outcome and deliverables for his research include development of a simple genetic sample pre-fabrication technique enabling the reliable analysis of a representative part of the cell proteome. Proteomic profiling of the cell substrate, in this case he chose two cell substrates which are commonly also used to create flu vaccine and other cell substrates are used to produce gene therapy vectors. Identification of unique protein

signature or a biomarker for human embryonic stem cells in CD34 cells, hematopoietic stem cells and an analysis of quantitative and qualitative changes during the differentiation of ES cells into CD34 cells, and that had been already demonstrated in the literature that you can convert these cells to these cells which is a very useful outcome. The discovery of new cytochrome P450 isozyme in tumor may lead to development of new biomarkers and perhaps new anti-cancer drugs and therapy.

So overall, the branch's outcome, regulatory outcome of our research involves - leads to identification of new antigens for cancer vaccine characterization and target for cancer therapy. We are developing the animal models for a variety of human cancer to test the safety and efficacy of targeted agents. We are promoting the development of novel technologies such as genomics and proteomics

for product characterization. For example, biomarker for purity, identity and potency and safety. And of course this technology can provide a unique opportunity to identify molecular markers with the in vivo outcomes in animals and also hopefully in the clinic. So I'd like to stop here and, Chair, if you have any questions I will be happy to answer and Dr. Alterman is also available to answer any questions. Thank you.

DR. MULÉ: Thanks, Dr. Puri. Before we open it up for questions I just want to acknowledge we have new individuals, well not new individuals, but individuals from the FDA who have joined us for this session. If you'll kindly introduce yourself, I'll start with Dr. Bauer.

DR. BAUER: Hi, I'm Steve Bauer. I'm Chief of the Cell Tissue Gene Therapy Branch in Division of Cell and Gene Therapies.

DR. EPSTEIN: Suzanne Epstein,

Associate Director for Research of the Office of Cellular Tissue and Gene Therapies.

DR. CARBONE: Kathy Carbone, Associate Director of Research for CBER.

DR. MULÉ: Thank you. So I'll open up the floor for questions for Dr. Puri. Raj, I have one. So I'm going to lower my voice when I say embryonic stem cells, but can you give me a sense of where you're going with the project? More specifics.

DR. PURI: So we are interested in identifying cancer stem cells and the approach in the literature, you might have seen that people have used a one analyte, for example CD133 or CD24 being expressed in a variety of different tumors such as brain tumors and - or in the head and neck tumors. CD24 being as a cancer stem cell in head and neck tumors. And because cancer stem cells provide a unique opportunity to identify

them as a potential target and for the renewing the cancer that it provides - opens an entirely new field that I suspect that will be used as for a potential target for therapy. That most of the approaches have been used in the literature were based on their prior knowledge of one analyte or one expression of one cell type people have gone after in identifying cancer stem cells. We have a unique approach which has not been tested before and the unique approach being that we want to express and profile human embryonic stem cells, the totipotent, multipotent embryonic stem cell forms all different types of tissues and identify - and we have actually identified a signature of 92 genes. It's called stem nests. And those genes are uniquely expressed in human embryonic stem cells but not any of the adult tissues. Now we want to take advantage of that knowledge and try to express and profile the human tumor, cell

lines first and then the tumor tissue obtained from the Cooperative Human Tissue Network under the FDA risk-approved protocols and isolate the tumor from the tissue section in the expression profile to see if we can identify that signature or some of the genes, the cluster of genes which are present on the tumor that may provide us some insight rather than one analyte at a time, identify multi analyte and maybe we can pull out those cancer stem cells and to show that they are indeed cancer stem cells. So that's a very early stage of this project, but it provides a unique opportunity to identify new stem cells in cancer itself.

DR. MULÉ: Questions from the committee?

DR. TAYLOR: Why CD34-positive cells?

DR. PURI: So that's a different project. So that's Dr. Alterman's project.

So there's literature suggests that now that folks are very impressively can convert human embryonic stem cells with the cocultivation - with the different cell type and convert embryonic stem cell to CD34-positive cell. So CD34 being hematopoietic stem cell has many different applications. And that because it's already established in the literature, for Dr. Alterman's project it will be useful to identify the CD34 cells that you differentiated from ES cells, even though the expressing CD34 marker have similar gene expression profile. Are these cells are different? A simple question: are these cells different? So I think that's the initial thinking on this, and also in addition to that expression profiling, embryonic stem cells and CD34 cells that as this technology advance further when the application is submitted to the FDA we will be interested in knowing that you do not have any contaminating embryonic stem cells

in the differentiated product. Because embryonic stem cells by definition call teratomas. They call all three germ layers, ectoderm, endoderm, and mesoderm, and we will be interested in showing - asking a question are these cells completely free of stem cells, embryonic stem cells. So I think that's some of the work we are trying to do in-house to come up with some sort of an assay to assess the perhaps help a sponsor, advise them to perhaps consider those tests to come up with the - the safety of those products before administration.

DR. TAYLOR: So then CD34 is just a population that you chose because it's being used clinically?

DR. PURI: And also been shown in the literature that ES cells can differentiate to CD34 cells, right.

DR. TAYLOR: Okay. And so really it's just an example of a cell type to allow you to look at differentiated cells versus

undifferentiated human embryonic stem cells so that you can rule out the potential for teratoma formation down the road.

DR. PURI: Absolutely. Yes. That's one of the applications, right. Right.

DR. TAYLOR: Okay. I guess - I understand that. I guess I would - the broader question about why CD34-positive cells are a huge number of cells that embryonic stem cells can obviously give rise to that have been proposed for clinical studies. CD34 cells are only one and probably not even the most relevant because you can get those from so many other places easily. And so I just wondered if you're using it as a prototype or if you're really interested in the CD34-positive cell itself.

DR. PURI: We are just using it as a prototype for our studies. The feasibility that you can detect the embryonic stem cells.

DR. MULÉ: Other questions? Okay, great. Thanks. Before we go to Dr. Bauer's presentation, an announcement. So there's a reservation at an Italian restaurant for dinner at 7:30. If you are interested the plan is to meet in the lobby at about 7:15. Do you need, Gail, do you need a head count? You're okay? We're okay? All right.

Okay, Dr. Bauer.

DR. BAUER: Well, good evening everyone. My name is Steve Bauer as I said a minute ago and as you just heard, and I'm going to be talking to you about the research programs that were site visited on November 3 of last year for the Cellular and Tissue Therapies Branch. I'll introduce the people that are here with us in case we have questions that come up later on. Deborah Hursh is back here. Deb, would you raise your hand or stand up? And Dr. Malcolm Moos is in the back. I think Dr. Marti intended

to be here but since we're so far ahead of schedule hasn't arrived yet. Brent McCright is not here with us today, and then John Terrig Thomas is also back here. He is part of Dr. Moos's lab.

So this group handles primarily nowadays a variety of stem cell and other cellular therapy products, but many of us have been here for many years and have a wide variety of expertise in other areas as well, gene therapy and device regulation and protein chemistry and so on. So it's a group that has many years of experience and is bringing that all to bear on some of the challenges nowadays with cell therapies. So as I think you can appreciate from today and from general knowledge of this area, for a lot of cell therapies that are currently being tried and anticipated clinical benefit is highly variable, it's often hard to demonstrate and just a few problems are some - for instance in many cases most cells

actually die pretty quickly after administration. One of the things we're worried about is products could be "misdifferentiating," not doing the intended function once they're given to a patient. And often we're manufacturing cells ex vivo because there's an inadequate supply of the native cells, so we need to expand them.

But really for us the challenges from these kinds of problems, we really have a relatively poor understanding of how cells interact with their microenvironment. And from our perspective we see often that really what is currently done to characterize cell therapy products really is inadequate in terms of being able to really predict robustly what cells are going to do once they're administered to patients and how they will function and how to predict whether cells will survive and you know, if we could increase their survival. So these are just a few of the challenges, but some

of the ones that I wanted to highlight.

I think this group that has been brought together as the Cell and Tissue Therapies Branch, we use complementary approaches. We use frogs, flies, mouse and man, all of the above, to study some of these questions, and some of the basic approaches that we look at are to take interactions between genes, proteins, cells and tissues and use what we can find out about those interactions to study processes of normal development and tumorigenicity. And for instance, knowledge and manipulation of things like growth factor pathways we think will help us understand cell therapies better, be able to better predict their efficacy. And then how we understand tumorigenicity we think will help us improve our safety profile for cell therapies because tumorigenicity is an issue in that field.

So I'm going to now just touch a

few highlights from each one of the research programs and at least Deb and Malcolm and John are here - Terrig are here to correct me if I misspeak representing them. I don't think Dr. Marti or McCright are here, and I'll try to field questions if there are any on their segments. So what I've illustrated on this slide is a system that I've used where you can grow mesenchymally derived stromal cells that support precursor-B cells upon them. And we discovered - and this is an illustration. These cells are self-replicating with - in the presence of IL-7 and the stromal cells, and we discovered on the surface of the stromal cell there's a molecule called dlk. And normally under these circumstances if you remove IL-7, cells begin to differentiate and die, and they can become immunoglobulin-positive B-cells in this culture system. So what we discovered in efforts to try to figure out what kind of signals the stroma were passing

to the pre-B cells, if you down-regulated the dlk on the stromal cells, this normal process of differentiation or cell death ceased and these cells instead just kind of perked along and maintained their status as pre-B cells. And there were no changes in any of the markers that we look at normally to characterize pre-B cells. So this is analogous to what a cell therapy characterization protocol would be. You take the cell surface markers that you know about and you look at them. So we did that with flow cytometry, with gene expression markers. Really no changes, but the take-home lesson here is that abnormal stromal cells resulted in abnormal B-lineage cells I should have said here, cells that look normal by all the criteria you normally would apply, but actually are abnormal.

We've gone on to look at this in vivo as well with a dlk mouse, a knockout mouse. That does alter B-cell development

and function. And we use that to study the microenvironment in the host and how that can affect both cells that you take out of such a host and cells that you might put in. And I won't go into that.

Also, in my lab we've been using the same system whereby we can - from normal or frankly neoplastic or pre-neoplastic pre-B cells establish clonally related colonies of those and then have a large - of cells by which we can study mechanisms of transformation. And we're pursuing that in hopes of identifying biomarkers of transformation that could be useful in looking at cell therapies, and a microarray is one approach that we're doing that. We can also take genes that have been identified as candidates and put them back into these cells and study, you know, as a validation approach for biomarker discovery.

So the impact for cell therapy of this kind of research is - I think this is

something that we haven't thought about a lot in cell therapy in the past, that the stroma itself, the feeder layers that are used to propagate cells can alter a product in a way that might not be revealed in lot release tests as they currently are done. And that efficacy of a cell therapy product could be affected by the microenvironment during cell product manufacturing, and perhaps the microenvironment in the patient as well. In fact, we know that cells can induce changes in the patient microenvironment as well as vice versa. And I've just described our efforts in this improved tumorigenicity assessments.

So now I'll turn to Dr. McCright. He is pursuing mouse models of organogenesis in looking at this from the perspective of cellular- and tissue-engineered therapies. The approach is to genetically modify mice and study the functions of proteins that are thought to be required or shown to be

required for mammalian organ development in vivo. And this is just an illustration. So Brent brought with him this technology and can create multiple animal models. He's been using that to create models that allow us to inactivate or over-express Notch2 in a tissue-specific manner. And you can isolate stem cells from a mouse, for instance, with a GFP knock-in so you know that they're Notch2 expressing, and also to study an anti-oncogene, B56gamma. So that's basically the model and just some highlights. He's been looking at the role of Notch2 in heart development and shown that Notch2 expression in heart-specific inactivation allows you to say that there's a cell-autonomous requirement for Notch2 during mouse heart development. So this is an example of putting a marker under the expression of Notch2. And you can, with beta-gal for instance show that Notch2 is expressed in a lot of the tissues and sites

within heart development.

What's illustrated over here is that he's been able to use cell-specific knockout by using the Cre recombinase system and having flox Notch2 alleles and then using tissue in cell-specific Cre over-expression or expression to specifically knock out different cells and shown defects in the heart that are mapped to Notch2 expression. So hearts from newborn mice which have this Notch2 heart-specific inactivation die perinatally and you can see the histological evidence of malformation.

So what are the importance of this kind of research? You can use this sort of approach to identify and analyze molecules that we think are required for mammalian organogenesis. We've shown that Notch2 could potentially be a biomarker for evaluating developmental cells that you might isolate that you think are useful for cardiac repair. And I didn't really talk

about this, but he also has shown by doing domain switches at Notch1 or 2 activation can have similar effects on cell products, and that exogenous notch activation and functional requirements for Notch2 can be studied in most tissues.

So now I'll move on to describe briefly some of the things that Dr. Deborah Hursh are doing. She's developing a genetic model of growth factor action to develop - aimed at developing markers of safety and efficacy of cell-based products. This is her depiction of Drosophila as a test tube with wings and she's using this - it's a powerful system in order to be able to study such things as cell communication and intact tissues using the tools that have been developed over the years to Drosophila genetics. You can alter gene expression very specifically within certain microenvironments. You can conduct high throughput screens that are useful to

identify critical control points for cell development differentiation, and it's a very nice way to start looking at markers, biomarkers that can be predictive of pathway activity, pathways that affect cell development. You can also do such things as analyzing cell stress and viability. I mentioned earlier that that's one of the problems in cell therapies, that cells seem to die pretty quickly after administration, so it would be good to understand that process and perhaps figure out if there are markers predictive of survival.

So one of the things you can do very elegantly in Drosophila is do genetic interaction screens and as I said a minute ago put genes in specific functional pathways so you're really using the model organism to identify critical control points. This approach avoids some of the bias of other approaches and abundance in immunogenicity, other modifications of some

of the other models. But another thing you can do is look at many, many, many flies so you can do a sufficiently powerful screen. I think I've said this several times, but knowledge of the control points that really affect cell state and fate we think is very critical for understanding cell therapies better. And in her lab, Deb's group has identified more than 20 genes that interact with the BMP pathway which is a pretty profound growth signaling pathway.

And as an illustration in this next slide comparing wild-type fly and one, it's a BMP mutant. If BMP is lacking this induces the Jun kinase pathway, and the loss of this BMP factor causes some of these cells to be - lose their ability to compete with their normal neighbors. And here you can see caspase activity so these cells are undergoing apoptosis. And this is we think a very elegant system to explore some of the problems in cell and tissue engineering, and

particularly having biomarkers that will improve our ability to predict the survival of transplanted cells in their new location. And as a more general approach, to look at gene and cell interactions in tissue development.

I'll now turn to Dr. Moos's presentation, and he's primarily been looking at protein-protein interactions that are important in joint development. And what you see here is joint formation in developing xenopus limbs. And the arrows point to areas where there needs to be or there is co-expression in the same place and at the same time of what are shown in red, proprotein convertases and GDF5 which need to colocalize in order to give you a well-formed joint. This is an illustration of that same point where you can see where the colocalization maps.

In another similar series of experiments, Dr. Moos's group with Terrig

Thomas's participation have identified a novel BMP antagonist that copurifies and colocalizes, again, with GDF5. And it's the same idea here, that you need to have spatial, temporal co-expression, colocalization in order to successfully make a joint. The articulate - specifically articular surface in those joints. So this illustrates the importance of feedback and crosstalk in cell and tissue specification, that colocalization of several signals is necessary to instruct formation of cartilage and again, looking at a more global picture, a system in a way to study developmental signals that could be important as we move towards better characterization of cell and tissue engineering products.

And Dr. Marti has had a career-long interest in chronic lymphocytic leukemia and studies that both in a mouse model and in man, and in his work has been interested in the molecular lesion in

chronic lymphocytic leukemia. And in his work he's characterized precursor states for CLL, specifically one called monoclonal B-cell lymphocytosis and studied familial chronic lymphocytic leukemia. And more recently has been - published work in *Blood* about an NZB mouse model of CLL and the remarkable finding from that is there's a shared micro-RNA lesion that both mouse and - in the mouse model of CLL and which occurs in human CLL with high frequency.

He's also been involved in setting up consortia to better understand a biomarker of CLL which correlates with a bad prognosis in looking at ZAP70 characterization by flow cytometry. And that leads to the next point. He's had a long-term interest and involvement in developing better methods for quantitative flow cytometry. And I think you saw today how important that can be in cell therapy characterization, and he's spent a lot of

time and effort with the community and in collaboration with NIST and colleagues at CDC and NIH developing standards for flow cytometry, both in terms of fluorescence reference materials, documents that tell you how to do this. And they've been useful and continue to be useful in how we characterize cell therapy products.

This is just a diagram showing the locus that's affected in both the NZB CLL model and mouse - and human CLL, a locus called Mir16. So his work is very important in the concept of earlier detection of disease and looking at molecular lesions that are associated with the onset of the transformed state in leukemogenesis, potentially targets for intervention. But his work in flow cytometry in particular is very important in product characterization and that's important for flow cytometry, both in process and as lot release for cellular and gene therapy products. Another

area I won't say much about, but more and more we're getting into the area where flow-sorted cells will be used clinically. So his expertise and advice in quantitative flow cytometry has been key in interactions and facilitating those product developments.

So what I hope I've given you a very quick overview is that in the Cell and Tissue Therapies Branch we're addressing many of these cell therapy challenges through complementary approaches, looking at cell-cell interactions, genetic interaction screens, protein-protein interactions, models of organogenesis and tumorigenesis in mouse and man. So the current state of the art is sort of looking at a jet from the outside where you can see it's a jet, you know it's underway. We look at, you know, some of the surface markers of the jet, but what we really would like to do in order to facilitate development of cell therapy is understand what's really going on inside the

cockpit, and that's analogous to what's going on inside the cell. And that'll tell us a lot about where cells are going, where they're headed and so on. So we're looking at both ways, specific biomarkers that are associated with certain directions cells take, but also generalized approaches for getting a better understanding what those instructions are within the cell and then determine cell fate and cell specification and we hope will lead to improved cell therapies. And with that I'll take your questions.

DR. MULÉ: Thanks, Dr. Bauer. Questions?

DR. BAUER: Everybody's tired.

DR. MULÉ: Okay, I think we're set. Thank you.

DR. BAUER: Thank you.

DR. MULÉ: Before we go ahead, we have two members of the committee who have joined us for this evening, and that's Dr.

Gerson and Dr. Urba. Okay, so we have closed session now.

(Whereupon, the foregoing matter went off the record at 5:22 p.m.)