A ROUNDTABLE DISCUSSION

CANCER IMMUNOTHERAPY

A joint publication produced by:

CANCER RESEARCH INSTITUTE
Advancing Immunology. Conquering Cancer.

MD BECKER PARTNERS LLC
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THE CANCER RESEARCH INSTITUTE AND MD BECKER PARTNERS HAVE UNITED KEY OPINION LEADERS, ANALYSTS, AND INDUSTRY EXECUTIVES TO ENGAGE IN DISCUSSIONS, EXCHANGE INFORMATION, AND HIGHLIGHT OPPORTUNITIES IN THE FIELD OF CANCER IMMUNOTHERAPY.
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Has the approval of Provenge® (sipuleucel-T) in prostate cancer and Yervoy™ (ipilimumab) in melanoma impacted the field of active immunotherapy as evidenced during the ASCO meeting? In particular, is there greater acceptance of improved overall survival despite the absence of anti-tumor effect?

TOPIC #2 23
What new data, with emphasis on Phase II programs or later, were presented around the time of the ASCO meeting in major disease areas, such as melanoma, prostate cancer, breast cancer, bladder cancer, colorectal cancer, and glioma?

Melanoma 23
TOPIC #3

With more than 50 clinical programs in development, it is expected that more than one form of immunotherapy may be approved in certain disease settings. In addition to immunotherapies, newer small molecule and other biologic therapies are also competing in these settings. How are immunotherapies differentiated within some of these crowded disease segments and how will they be sequenced with traditional or newer small molecule/biologic agents?

TOPIC #4

With the recent approval of the first active immunotherapy for cancer and the subsequent approval of Yervoy, what are some of the more promising combination therapy approaches presented at ASCO?

TOPIC #5

With regard to active immunotherapy, what was the most promising clinical data presented at ASCO?

TOPIC #6

To date, biotechnology companies have successfully commercialized autologous therapies without the benefit of a stronger or more established commercial partner (e.g., Dendreon with Provenge, Genzyme with Carticel®). Despite the fact that twice as many non-autologous active immunotherapies have failed in clinical trials, larger pharmaceutical companies appear to prefer non-autologous approaches. What new information was presented at ASCO that supports one or the other approach (autologous versus non-autologous)?
TOPIC #7

A dozen active immunotherapy programs have failed in Phase 3 trials. What has been learned from these failures and how has this knowledge been incorporated into current clinical trials as evidenced at ASCO? In particular, proper patient identification, stage of disease, tumor burden, etc.

TOPIC #8

Biomarkers to identify likely responders to cancer immunotherapy, to provide predictive signals to a patient’s likely clinical outcome following immunotherapy, and to help guide the development of appropriate surrogate endpoints are increasingly important to development of this new class of therapies. What news about such biomarkers came out recently?

APPENDIX A: 40 Cancer Immunotherapies in 60 Clinical Trials

LEGAL DISCLAIMER
ABOUT THE REPORT

The American Society of Clinical Oncology® (ASCO®) recently hosted its annual meeting in Chicago, Illinois. Staff from both the Cancer Research Institute and MD Becker Partners LLC attended the meeting to follow the latest developments in cancer immunotherapy. With so many interesting presentations and discussions during the ASCO meeting, we convened an expert roundtable consisting of key opinion leaders, Wall Street analysts, industry executives, and others to share their impressions of various topics of interest from this year’s meeting, especially those relevant to the field of cancer immunotherapy. In particular, we sought to address the following topics:

• Has the approval of Provenge® (sipuleucel-T) in prostate cancer and Yervoy™ (ipilimumab) in melanoma impacted the field of active immunotherapy as evidenced during the ASCO meeting? In particular, is there greater acceptance of improved overall survival despite the absence of anti-tumor effect?

• What new data were presented at ASCO in major disease areas, such as melanoma, prostate cancer, breast cancer, bladder cancer, colorectal cancer, and glioma?

• With more than 50 clinical programs in development, it is expected that more than one form of immunotherapy may be approved in certain disease settings. In addition to immunotherapies, newer small molecule and other biologic therapies are also competing in these settings. How are immunotherapies differentiated within some of these crowded disease segments and how will they be sequenced with traditional or newer small molecule/biologic agents?

• With the recent approval of the first active immunotherapy for cancer and the subsequent approval of Yervoy, what are some of the more promising combination therapy approaches presented at ASCO?

• With regard to active immunotherapy, what was the most promising clinical data presented at ASCO?

• To date, biotechnology companies have successfully commercialized autologous therapies without the benefit of a stronger or more established commercial partner (e.g., Dendreon with Provenge, Genzyme with Carticel®). Despite the fact that twice as many non-autologous active immunotherapies have failed in clinical trials, larger pharmaceutical companies appear to prefer non-autologous approaches. What new information was presented at ASCO that supports one or the other approach (autologous versus non-autologous)?

• A dozen active immunotherapy programs have failed in Phase III trials. What has been learned from these failures and how has this knowledge been incorporated into current clinical trials as evidenced at ASCO? In particular, proper patient identification, stage of disease, tumor burden, etc.

• Biomarkers to identify likely responders to cancer immunotherapy, to provide predictive signals to a patient’s likely clinical outcome following immunotherapy, and to help guide the development of appropriate surrogate endpoints are increasingly important to development of this new class of therapies. What news about such biomarkers came out recently?

* This publication is not sponsored or endorsed by the American Society of Clinical Oncology® (ASCO).
ABOUT THE ORGANIZERS

The Cancer Research Institute (CRI), established in 1953, is the world’s only nonprofit organization dedicated exclusively to transforming cancer patient care by advancing scientific efforts leading to new and effective immune system-based strategies to treat, control, and prevent cancer. Guided by a world-renowned Scientific Advisory Council that includes four Nobel laureates and thirty-one members of the National Academy of Sciences, CRI has invested more than $200 million in support of laboratory and clinical research conducted by immunologists and tumor immunologists at leading medical centers and universities around the world, and has contributed to many of the key scientific advances that demonstrate the potential for immunotherapy to change the face of cancer treatment. Through its International Cancer Immunotherapy Symposium Series, Cancer Immunotherapy Consortium Annual Colloquia Series, CRI/LICR Cancer Vaccine Collaborative global clinical trials network, and Cancer Vaccine Acceleration Fund venture philanthropy program, CRI convenes, coordinates, and funds collaborations and outcome-driven dialogue among academics, industry scientists and decision makers, regulatory representatives, and health research associations focused on discovery, development, and refinement of new cancer immunotherapies. For more information, visit www.cancerresearch.org.

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MD Becker Partners is a boutique management and strategy consulting firm focusing on both public and private companies in the life sciences industry. The firm also works with venture capitalists, institutional investors, and others that provide capital to these companies. As a strategic advisor and partner, MD Becker Partners provides a full range of services to help its clients increase visibility, unlock stakeholder value, and access resources to grow their business. To accomplish this, the firm integrates relations, strategy, and operational capabilities and apply them to carefully conceived and expertly enacted tactics. In early April 2010, MD Becker Partners published a 150-page industry report titled "Cancer Vaccine Therapies: Failures and Future Opportunities," which included an overview of the cancer immunotherapy market, interviews with several key opinion leaders, profiles of nearly 40 companies, and a discussion of the scientific, clinical, and commercial considerations for major industry participants. For more information, visit the firm’s website www.mdbpartners.com and online newsletter at www.lifesciencedigest.com.
ROUNDTABLE EXPERT BIOGRAPHIES
(in alphabetical order by last name)

Sanjiv S. Agarwala, M.D.
Professor of Medicine
Temple University School of Medicine
Chief, Oncology & Hematology
St. Luke’s Cancer Center

Dr. Agarwala is Chief of Medical Oncology and Director of the Melanoma and Immunology Program at St. Luke’s Cancer Center, Bethlehem, PA, and Professor of Medicine at Temple University School of Medicine, Philadelphia, PA. He is nationally and internationally recognized as an expert in the treatment of melanoma, immunotherapy and kidney cancers and is a pioneer in development of new drugs for treating these diseases. He is on the core committee for melanoma at the Eastern Cooperative Oncology Group and is the study chair for E 1697, the largest adjuvant trial in melanoma conducted to date. He is the founder and Chair Person for the International Symposium in Melanoma and Other Cutaneous Malignancies held annually in New York City since 2004. He has special interest and expertise in immunotherapy for cancer. He serves and has served as Principal Investigator for several clinical trials involving immunotherapy and targeted therapy for melanoma and other malignancies. He has over 75 publications and book chapters written on melanoma and other research areas. He is board certified in Oncology, Hematology and Internal Medicine and is an active member of several professional and scientific societies including the American Association for Cancer Research, the American Society of Clinical Oncology and the European Society of Medical Oncology. He has served on the editorial board for the Journal of Clinical Oncology and is currently is section editor for melanoma on for the American Journal of Hematology/Oncology and HemOnc Today.

Reni Benjamin, Ph.D.
Managing Director, Senior Analyst, Biotechnology
Rodman & Renshaw, LLC

Dr. Reni Benjamin is Managing Director and Senior Biotechnology Analyst at Rodman & Renshaw, LLC. His expertise and company coverage consists of small-cap companies in the oncology and stem cell sectors. Dr. Benjamin has previously been ranked among the top analysts for recommendation performance and earnings accuracy by StarMine and has been cited in a variety of sources including The Wall Street Journal, Business Week, Financial Times, Dow Jones Newswire, and Smart Money. He has also made appearances on Bloomberg television/radio and CNBC. Prior to joining Rodman & Renshaw, Dr. Benjamin was an associate analyst in Needham and company’s biotechnology equity research department. Prior to that, he earned his doctorate in Biochemistry by discovering and characterizing a novel gene implicated in germ cell development. His expertise includes biochemistry, functional genomics, gene therapy and molecular biology. Dr. Benjamin has presented at various regional and international conferences and published in peer-reviewed journals. Dr. Benjamin received his Ph.D. from the University of Alabama at Birmingham and his Bachelors of Science degree in Biology from Allegheny College.
David Berd, M.D.
National Director of Immunotherapy and Medical Oncologist
Cancer Treatment Centers of America
Eastern Regional Medical Center

Dr. Berd is a medical oncologist and tumor immunologist. Previously, he was Professor of Medicine at Thomas Jefferson University, where he had taught and did clinical and laboratory research. Subsequently, he served as the Chief Medical Officer for AVAX Technologies, Inc. Dr. Berd joined CTCA in 2009. Over the course of his career, Dr. Berd has published 83 original papers in numerous medical journals alongside dozens of editorials, reviews and abstracts. He has also attended numerous conferences, seminars, and over 100 lectures by invitation. He is the inventor of an autologous, hapten-modified human cancer vaccine, for which he has been awarded 8 patents. This AC Vaccine is currently under development by AVAX Technologies Inc. As National Director for Immunotherapy at CTCA, Dr. Berd is investigating the application of the AC Vaccine to ovarian cancer. Dr. Berd is a member of the American Association for Cancer Research, the American Society for Clinical Oncology, and the American Association of Immunologists. He also serves on review committees for various government and private advisory groups.

Liz Bromley, Ph.D.
Associate Director, Scientific Affairs
Light Sciences Oncology, Inc

Liz Bromley, Ph.D., is associate director of scientific affairs at Light Sciences Oncology, a biotechnology company focusing on the development of light-activated talaporfin sodium for the treatment of solid tumors and other malignancies. Previously, she served as clinical science manager at Abbott Laboratories. Dr. Bromley earned an A.B. in biology from the University of Chicago and an M.S. in biology from the Massachusetts Institute of Technology, and holds a Ph.D. in genetics from Harvard University.

Thomas Davis, M.D.
Senior Vice President and Chief Medical Officer
Celldex Therapeutics, Inc.

Dr. Davis joined Celldex in 2006 as Vice President of Clinical Development and Chief Medical Officer and was appointed to Senior Vice President in March 2008. He was formerly Chief Medical Officer at GenVec and Senior Director of Clinical Science at Medarex. He has supervised clinical efforts in adult hematologic malignancies and marrow transplantation and therapeutic antibodies and vaccines at the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) and worked with Dr. Ron Levy on the development of rituximab and idiotype vaccines at Stanford University. Dr. Davis received his B.A. in Biophysics from Johns Hopkins, M.S. in Physiology and M.D. from Georgetown University, and Oncology training at Stanford University.
Mark W. Frohlich, M.D.
Executive Vice President of Research and Development and Chief Medical Officer
Dendreon Corporation

Dr. Frohlich is executive vice president of research and development and chief medical officer at Dendreon, a biotechnology company with expertise in antigen identification, engineering, and cell processing that is focused on targeting cancer and transforming lives through the discovery, development, and commercialization of novel therapeutics that may significantly improve cancer treatment options for patients. Dr. Frohlich previously served as the company’s vice president of clinical affairs and prior to that as its senior medical director. Before joining Dendreon, Dr. Frohlich was vice president and medical director at Xcyte Therapies, a biotechnology company. Prior to that was an assistant professor in the Division of Hematology/Oncology at the University of California, San Francisco, where he specialized in urologic oncology and was active in laboratory, translational and clinical research. Dr. Frohlich did his post doctoral training in oncology at the University of California, San Francisco. He received his B.S. from Yale University in electrical engineering and economics and his M.D. from Harvard Medical School.

James L. Gulley, M.D., Ph.D., F.A.C.P.
Director, Clinical Trials Group &
Deputy Chief, Laboratory of Tumor Immunology and Biology
Senior Investigator, Medical Oncology Branch
Center for Cancer Research, National Cancer Institute/National Institutes of Health

Dr. Gulley is a board-certified medical oncologist that leads a programmatic effort in translating promising preclinical immunotherapy efforts into the clinic at the NCI. He received his medical training at Loma Linda University in its medical scientist training program where he obtained a Ph.D. with his work in tumor immunology as well as an M.D. He went to Emory University for a residency in internal medicine and then to NCI for a fellowship in medical oncology. Following his fellowship, he was retained as senior staff within NCI. Since 1999 he has authored and run a variety of immunotherapy clinical trials at the NCI, serving as Principal Investigator or an Associate Investigator on approximately 50 trials. Dr. Gulley has authored over 130 manuscripts or book chapters, edited 3 textbooks, and has given over 150 invited lectures. He has served on numerous review committees and government advisory groups and is an internationally recognized expert in the field of tumor immunotherapy.

Dirk Jäger, M.D.
Director of the Medical Oncology Department
National Center for Tumor Diseases
University of Heidelberg

Dirk Jäger, M.D., is director of the Medical Oncology Department, National Center for Tumor Diseases, University Hospital Heidelberg. Dr. Jäger’s research focuses on analyzing the interactions between the immune system and cancer, with the goal of identifying and testing novel tumor-associated antigens and their potential as targets for cancer immunotherapy. Dr. Jäger received his M.D. in 1991 and carried out postdoctoral training at Weill Medical College of Cornell University, where he held the Rose Marie Finnell Memorial Fellowship for Breast Cancer Research from the Cancer Research Institute. Dr. Jäger has been affiliated with the Ludwig Institute for Cancer Research since 2006. He is also a member of the CRI/LICR Cancer Vaccine Collaborative, a global network of clinical trial sites with immune monitoring expertise focused on therapeutic cancer vaccines.
John M. Kirkwood, M.D.
Professor and Vice Chairman for Clinical Research, Department of Medicine
University of Pittsburgh School of Medicine
Director, Melanoma Center
University of Pittsburgh Cancer Institute

John M. Kirkwood, M.D., received his medical degree in 1973 from Yale University and completed postgraduate work at Yale-New Haven Hospital and Harvard University. He joined the University of Pittsburgh Cancer Institute in 1986 as director of the Melanoma Center and as professor and chief of the Division of Medical Oncology at the University of Pittsburgh School of Medicine, where he was named vice chairman for clinical research in 1996. Dr. Kirkwood’s research has focused on melanoma, a cancer that kills more than 7,000 people in the United States each year. Under Dr. Kirkwood’s direction, the Melanoma Center has developed new and effective treatment approaches for this disease. He has received international acclaim for leading a multi-center study developed on the basis of his pioneering work with biological treatments for melanoma that has provided the first adjuvant therapy for treating patients with high-risk melanoma, a type likely to recur despite surgery. Dr. Kirkwood is currently leading a number of clinical trials of promising cancer vaccines. Dr. Kirkwood also conducts basic research on the molecular and biological changes normal moles undergo as they transform into melanoma. These studies are aimed at providing earlier detection methods and means to prevent this cancer.

Larry W. Kwak, M.D., Ph.D.
Professor, Chairman and Justin Distinguished Endowed Chair in Leukemia Research, Department of Lymphoma/Myloma, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center, Houston, TX

Dr. Larry W. Kwak received his M.D. and Ph.D. in tumor cell biology from Northwestern University Medical School. After completing clinical training in internal medicine and medical oncology at Stanford University, he was recruited to the Biological Response Modifiers Program of the National Cancer Institute in 1992. In 1996, he was appointed head of the vaccine biology section at the National Institutes of Health (NIH), then was recruited to M. D. Anderson Cancer Center in 2004, where is he currently the Chairman of the department of lymphoma and myeloma. He has served on the editorial board of the scientific journal Blood and on the scientific advisory board of the Multiple Myeloma Research Foundation. Recognized for his 20-year commitment to the science of cancer vaccines, specifically a personalized therapy for follicular lymphoma, Dr. Kwak was named to the 2010 TIME 100. His translational scientific and clinical interests span tumor immunology, cancer vaccines, adoptive T-cell immunotherapy, and clinical management of lymphomas and myelomas. He has pioneered use of patient-specific vaccines as treatment against human lymphomas and has served as principal investigator of a multi-center Phase III randomized clinical trial of lymphoma vaccination. He is frequently invited to speak at national and international scientific meetings. He has published in journals such as Science, Nature Medicine, New England Journal of Medicine and The Lancet.
Reiner Laus, M.D.
Chief Executive Officer, BN ImmunoTherapeutics
President, Cancer Vaccines, Bavarian Nordic

Dr. Laus is founding CEO of BN ImmunoTherapeutics and President, Cancer Vaccines, Bavarian-Nordic. BN ImmunoTherapeutics was formed in 2005, is a wholly-owned subsidiary of Bavarian-Nordic and focuses on the development of recombinant poxviral vaccines for the immunotherapy of cancer. Recently, the company published highly statistically significant positive survival data from a randomized, placebo-controlled study of its lead product, the prostate cancer vaccine PROSTVAC. Prior to this, Dr. Laus held the position of Vice President of Research and Development at Dendreon Corporation, where he worked for 11 years since Dendreon’s inception in 1993. During his tenure at Dendreon, Dr. Laus invented PROVENGE, the first cancer vaccine to get approved by the FDA, and was instrumental in its development. He is also author of key patents relating to this product. Previously, Dr. Laus held academic appointments at the University of Kiel, Germany and at Stanford University, California. Dr. Laus received his M.D. from the University of Kiel.

Mark Monane, M.D., M.S.
Managing Director, Equity Research
Needham and Company, LLC

Dr. Mark Monane joined Needham & Company in 2000. He currently serves as Needham’s Senior Analyst in biotechnology and biopharmaceuticals covering small and mid-cap stocks in the therapeutics areas of cardiovascular medicine, oncology, CNS/metabolic diseases, and infectious/inflammatory disorders. Dr. Monane’s research on medication use and geriatrics has resulted in more than 50 original articles and review publications in journals such as Archives of Internal Medicine, Journal of the American Medical Association, Journal of the American Geriatrics Society, Hypertension and Clinical Pharmacology and Therapeutics. He served as an Assistant Professor of Medicine at Harvard Medical School until he joined Merck-Medco Managed Care as Senior Director of Geriatrics in 1996. He is also an Adjunct Associate Clinical Professor at Rutgers School of Pharmacy in New Jersey. Mark is board certified in internal medicine, geriatric medicine, clinical pharmacology, utilization review/quality assurance, and healthcare management. He holds an AB degree from Columbia University, an MD from New York University School of Medicine, an MS degree from Harvard School of Public Health, and an MBA from Columbia Business School. He completed postdoctoral training in primary care internal medicine at Montefiore Hospital, geriatric medicine at Harvard Medical School, and geriatric clinical pharmacology at Harvard Medical School.

Michael Novod
Senior Analyst, Healthcare
Nordea Bank

Michael Novod is Senior Analyst, Healthcare at Nordea Markets in Denmark, the largest commercial and investment bank in Scandinavia. Before joining Nordea Markets in 2011, Michael was Senior Analyst and Sector Head for Healthcare coverage at Handelsbanken Capital Markets. At Nordea Michael as the day-to-day responsibility for equity coverage of the Danish pharmaceutical and biotech universe with major focus on especially diabetes and cancer companies and relevant international peer companies. Michael Novod has been covering the sector since 2002 and has consistently been top ranked across all pan-Nordic broker surveys.
Joseph Pantginis, Ph.D.
Senior Biotechnology Analyst
ROTH Capital Partners

Joseph Pantginis, Ph.D. joined Roth Capital Partners in 2009. Prior to joining Roth Dr. Pantginis was a senior biotech analyst at Merriman Curhan Ford. Dr. Pantginis was also a senior biotechnology analyst at Canaccord Adams, focusing on the oncology, inflammation and infectious disease spaces. Prior to Canaccord Adams he was a biotech analyst at several firms, including JH Anauer & Co., First Albany Corporation, Commerce Capital Markets and Ladenburg Thalmann & Co., Inc. Prior to his tenure on Wall Street, Dr. Pantginis served as an associate manager/scientist of Regeneron Pharmaceuticals’ Retrovirus Core Facility. Dr. Pantginis received an M.B.A. in Finance from Pace University; a Ph.D. in Molecular Genetics and an M.S. from Albert Einstein College of Medicine; and a B.S. from Fordham University.

Andrew T. Parsa, M.D., Ph.D.
Associate Professor in Residence of Neurological Surgery
Principal Investigator, Brain Tumor Research Center
Reza and Georgianna Khatib Endowed Chair in Skull Base Tumor Surgery
University of California, San Francisco (UCSF)

Dr. Andrew Parsa is a neurosurgeon who specializes in brain and spinal cord tumors in adults. He’s experienced in the surgical treatment of skull base tumors, acoustic neuromas and intra-operative mapping of brain function to optimize tumor resection and is an active member of the Gamma Knife radiosurgery program. Dr. Parsa’s research interests include the development of a brain tumor vaccine. He won the 2003 Young Clinician Investigator Award from the American Association of Neurological Surgeons. Dr. Parsa earned a medical degree at the Brooklyn College of Medicine at the State University of New York and completed a residency in neurosurgery at Columbia Presbyterian Medical Center in New York.

Col. George E. Peoples, M.D., F.A.C.S.
Director, Cancer Vaccine Development Program
Deputy Director, United States Military Cancer Institute
Professor (adjunct), Surgical Oncology, MD Anderson Cancer Center
Professor, Surgery, Uniformed Services University
Chief, Surgical Oncology
Brooke Army Medical Center

Dr. Peoples graduated from West Point in 1984 and from Johns Hopkins School of Medicine in 1988. After a surgical internship at Walter Reed Army Medical Center (WRAMC), he completed his surgical training at the Brigham and Women’s Hospital in Boston, MA in 1996. During that time, Dr. Peoples also completed a research fellowship at the Laboratory of Biologic Cancer Therapy at Harvard Medical School. He then completed a surgical oncology fellowship at MD Anderson Cancer Center (MDACC) in Houston, TX in 1998. He served as the Chief, Surgical Oncology at WRAMC until 2006 when he assumed the same position at Brooke Army Medical Center in San Antonio, TX. Currently, Dr. Peoples continues in this clinical role as well as serves as the Director of the Cancer Vaccine Development Program, Deputy Director of the United States Military Cancer Institute, Professor of Surgery at the Uniformed Services University of the Health Sciences, and Adjunct Professor of Surgical Oncology at MDACC. He is the PI on numerous multi-center clinical trials of cancer vaccines being conducted nationally and internationally. He has written extensively on the immune response to cancer.
Jianda Yuan, M.D., Ph.D.
Assistant Laboratory Member, Director, Immune Monitoring Core, Ludwig Center for Cancer Immunotherapy, Memorial Sloan-Kettering Cancer Center

Jianda Yuan, M.D., Ph.D., is an assistant lab member and director of the immune monitoring facility (IMF) at the Ludwig Center for Cancer Immunotherapy, Memorial Sloan-Kettering Cancer Center. As director of the IMF, Dr. Yuan has supervised the immune monitoring of more than forty clinical trials for patients with melanoma, prostate cancer, renal cell cancer, lymphoma, chronic myelogenous leukemia, and hepatocellularcarcinoma, and has established optimal immunologic assessments and assays for the evaluation immune responses to cancer treatment. Under his leadership, the IMF has become a leader in the immunological monitoring field and has helped identify several novel biomarkers for anti-CTLA-4 antibody therapy including ICOS, ALC, and cytokine polyfunctionality. A member of the steering committee of the CRI Cancer Immunotherapy Consortium, Dr. Yuan received his M.D. and Ph.D. degrees from Shanghai Medical University in China and carried out postdoctoral training at Columbia University and Memorial Sloan-Kettering Cancer Center.
EXECUTIVE SUMMARY

Since the early 1990s, cancer immunotherapy has provided hope to patients, physicians, and investors as a new treatment modality with limited side effects and superior efficacy. Cancer immunotherapy broadly includes passive immunization, active immunization, and immunostimulation.

Passive immunotherapy is the transfer of an exogenous therapeutic agent to a patient where the therapy has a direct pharmacological action on the desired target. The best examples of passive immunotherapy are monoclonal antibodies (mAbs), which were hailed as “magic bullets” when they were developed in the 1970s.

However, clinical results with mAbs were largely disappointing for the first 10 years of development. In fact, it wasn’t until November 1997 that the first mAb for cancer therapy, Rituxan® (rituximab), was approved by the U.S. Food and Drug Administration (FDA). Developed by IDEC Pharmaceuticals, Rituxan is a chimeric monoclonal antibody against the protein CD20 that is currently approved for the treatment of chronic lymphocytic leukemia (CLL), non-Hodgkin’s Lymphoma (NHL), and rheumatoid arthritis (RA).

After reporting its first year of profitability in 1998, shares of IDEC Pharmaceuticals traded at an all-time high of $140 with a market capitalization above $3.3 billion. Worldwide net sales of Rituxan reached $1.5 billion in 2002 and the following summer IDEC Pharmaceuticals acquired Biogen, Inc. in a stock transaction valued at approximately $6.65 billion to create Biogen Idec, Inc. (BIIB).

While the success of Rituxan spurred the development of other anti-CD20 mAbs, it wasn’t until October 2009 that Arzerra® (ofatumumab) was approved by the FDA for the treatment of CLL. Ofatumumab, which was developed by Genmab A/S (GNMSF.PK) and GlaxoSmithKline plc (GSK), is a human mAb that targets an epitope different from Rituxan and other anti-CD20 mAbs.

Today, passive immunotherapies represent one of the most successful therapeutic classes and there are currently eleven mAbs approved for cancer therapy. Three blockbuster products sold by the Roche Group (RHHBY) – Avastin® (bevacizumab), Rituxan, and Herceptin® (trastuzumab) – collectively represented nearly $17 billion in revenue for 2009. As useful as many of these mAbs have become in cancer therapy, they often have the greatest impact when used in combination with other therapeutic modalities, particularly cytotoxic agents.

Similar to passive immunotherapy with mAbs, the early development of active immunotherapies proved to be an enormous challenge. In fact, nearly a dozen product candidates failed in Phase III trials. Unlike passive immunotherapy, active immunotherapies contain a specific antigen or set of antigens that are designed to activate the patient’s own immune system to seek out and destroy cells that carry the same antigen. They have no direct therapeutic action, but rather rely on the patient’s immune system to recognize and destroy the intended target.

Growing evidence indicates that the field of active immunotherapy for the treatment of cancer is undergoing a renaissance. On April 29, 2010, the FDA approved the very first active immunotherapy for the treatment of cancer – Dendreon Corporation’s (DNDN) Provenge®
(sipuleucel-T) for metastatic castrate-resistant prostate cancer (CRPC). This event reignited enthusiasm for the field of active immunotherapy and shares of Dendreon, which traded below $5 in March 2009, subsequently reached an all-time high above $57 and a market capitalization of approximately $7.8 billion.

More recently, the FDA approved Yervoy™ (ipilimumab) by Bristol-Myers Squibb (BMY) for the treatment of patients with unresectable or metastatic melanoma on March 25, 2011. With the news, ipilimumab became the eleventh mAb approved for the treatment of cancer since 1997 (see Figure 1 below).

**Figure 1.**

![FDA Approved mAbs for Cancer Therapy](image)

Beyond the approvals of both Provenge and Yervoy, there are a number of additional catalysts that could ignite further interest in the field of cancer immunotherapy.

First, 40 unique active cancer immunotherapies are currently being tested in 60 clinical trials (see Appendix A), including nearly a dozen that are in pivotal Phase III development (see Table 1). For example, GlaxoSmithKline plc (GSK) is conducting the largest ever Phase III clinical trial in lung cancer treatment with its investigational MAGE-A3 ASCI immunotherapy.
Table 1: Late-stage active immunotherapies in development

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Disease</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen (AMGN)</td>
<td>OncoVEX(GM-CSF)</td>
<td>Melanoma and head &amp; neck cancer</td>
<td>Phase III underway</td>
</tr>
<tr>
<td>Argos Therapeutics (private)</td>
<td>AGS-003</td>
<td>Renal cell carcinoma</td>
<td>Phase III planned 2011</td>
</tr>
<tr>
<td>AVAX Technologies (AVXT.PK)</td>
<td>MVAX</td>
<td>Melanoma</td>
<td>SPA granted, Phase III</td>
</tr>
<tr>
<td>Bavarian Nordic (BAVA.CO)</td>
<td>Prostvac®</td>
<td>Prostate cancer</td>
<td>SPA granted, Phase III</td>
</tr>
<tr>
<td>Biovest International (OTCQB: BVTI)</td>
<td>BiovaxID®</td>
<td>Follicular lymphoma</td>
<td>Phase III completed</td>
</tr>
<tr>
<td>Celldex Therapeutics (CLDX)</td>
<td>rindopepimut/CDX-110</td>
<td>Glioblastoma</td>
<td>Phase III planned H2 2011</td>
</tr>
<tr>
<td>GlaxoSmithKline (GSK)</td>
<td>MAGE-A3 ASCI</td>
<td>NSCLC and melanoma</td>
<td>Phase III trials underway</td>
</tr>
<tr>
<td>Novax (private)</td>
<td>Lucanix™/belagenpumatucele-L</td>
<td>NSCLC</td>
<td>Phase III trial underway</td>
</tr>
<tr>
<td>Oncothyreon (ONTY)/Merck KGaa</td>
<td>Stimuvax®/BLP25 liposome vaccine</td>
<td>NSCLC</td>
<td>Phase III underway</td>
</tr>
<tr>
<td>Transgene (TNG.PA)/Novartis (NVS)</td>
<td>TG4010/MVA-MUC1-IL2</td>
<td>NSCLC</td>
<td>Phase IIb/III planned 2011</td>
</tr>
<tr>
<td>Vical (VICL)/AnGes</td>
<td>Allovector-7®</td>
<td>Melanoma</td>
<td>Phase III underway</td>
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Second, positive results from at least three randomized studies have recently been published in peer-reviewed journals. The first study published in the March 1, 2010, edition of the the Journal of Clinical Oncology was a Phase II randomized controlled trial of Bavarian Nordic’s (BAVA) poxviral-based, PSA-targeted immunotherapy (Prostvac®) in metastatic castration-resistant prostate cancer. Patients receiving Prostvac had an 8.5-month improvement in median overall survival versus control. These provocative data resulted in a pivotal Phase III trial that is planned to begin in the second half of 2011.

The next study published in the May 31, 2011, online edition of the Journal of Clinical Oncology demonstrated that vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival by 14 months in follicular lymphoma. For 117 patients who received Biovest International, Inc.’s (BVTI) autologous, active immunotherapy called BiovaxID® (n = 76) or control (n = 41), median disease-free survival after randomization was 44.2 months for the vaccine arm versus 30.6 months for control arm (P=0.047) at median follow-up of 56.6 months. Results were even more robust for patients with a specific biological marker in an unplanned subgroup analysis.

A third study published in the June 2, 2011, edition of the New England Journal of Medicine, demonstrated that patients with metastatic melanoma receiving high-dose interleukin-2 (IL-2) plus a gp100 peptide vaccine had a significant improvement in centrally verified overall clinical
response (16% vs. 6%; P=0.03), as well as longer progression-free survival (2.2 months versus 1.6 months; P=0.008). There was a trend toward longer overall survival in the gp100 vaccine arm (17.8 months versus 11.1 months; P=0.06) although the results were not statistically significant.

In addition, cancer immunotherapy was a prominent topic during the recent American Society of Clinical Oncology® (ASCO) annual meeting. With so many interesting presentations and discussions during the meeting, however, the Cancer Research Institute and MD Becker Partners organized a cancer immunotherapy roundtable following the event to provide additional focus on the field of cancer immunotherapy.

We united key opinion leaders, analysts, and industry executives to exchange data, knowledge, and experience, facilitated by discussion and debate. In total, 17 experts participated in discussions about the current status and the future outlook for cancer immunotherapy. The roundtable started with general questions and topics about cancer immunotherapy posed by the organizers, followed by a comprehensive discussion among the various participants. This report does not cover all of the cancer immunotherapy presentations from ASCO 2011, but aims to highlight selected points of interest.

Sincerely,

Jill O’Donnell-Tormey, Ph.D.
Executive Director
Cancer Research Institute

Michael D. Becker
Founder, Senior Partner
MD Becker Partners LLC
TOPIC #1

Has the approval of Provenge® (sipuleucel-T) in prostate cancer and Yervoy™ (ipilimumab) in melanoma impacted the field of active immunotherapy as evidenced during the ASCO meeting? In particular, is there greater acceptance of improved overall survival despite the absence of anti-tumor effect?

James L. Gulley: Yes, there does appear to be greater approval and acceptance of immunotherapy now that significant improvement in overall survival despite the lack of improvement in time to progression has been seen in multiple studies. This suggests a possible class effect for therapeutic vaccines.

Jianda Yuan: I agree, there was a big impact from two approvals in the field of active immunotherapy. Immunotherapy-related sections, presentations, and posters received a lot of attention at this year’s ASCO meeting.

Liz Bromley: I really expected to hear more excitement about immunotherapies. Last year the ipilimumab plenary talk generated so much buzz, and then of course the drug was approved. Provenge had already been approved before ASCO 2010 and was certainly much discussed as well. I thought this might be the year of the immunotherapy, but I did not sense that at ASCO 2011. I thought there were far fewer talks in this area than I would have expected, for one. I did hear speakers on non-immune-related topics refer to new immunotherapies a couple of times as recently-added options in the treatment toolkit, but not as often or with as much enthusiasm as I was expecting. It was certainly nothing like two or three years ago when every single speaker seemed under some kind of contract requiring them to use the term “the era of personalized medicine” when glowing about targeted therapies. I think the proof is in the pudding now, and perhaps we won’t see any more waves of excitement surrounding these therapies until one of them starts to show an effect (and make a profit) in the real world.

John M. Kirkwood: The role of Provenge given the discordance of immune response and other endpoints with the survival benefit has yet to be defined. The approval of ipilimumab will bring this into therapy of advanced melanoma, although the lack of evidence relating to the mechanism of action remains a major gap in our rational development of this agent in combination with vaccines, other immunotherapies, and molecularly targeted therapies.

Joseph Pantginis: Based on our observations and discussions, we believe that ASCO 2008 was the transformative year for immunotherapy where physicians finally first “agreed and accepted” that immune response could correlate with survival. At the time of the positive IMPACT Provenge study and ever since, there is still a base of skeptics regarding the overall mechanism of action leading to overall survival, while not necessarily showing an anti-tumor effect (though others are). We are still in the early stages in explaining the reason for these observations, including the theory that tumor size does not change due to infiltrating lymphocytes. We believe the field/investment community is much more accepting of overall survival benefits seen irrespective of mechanism.

George E. Peoples: Yes, absolutely. Much more interest this year in active specific immunotherapy than in any previous year by far. The world of small molecules is a bit confined right now due to the limitation of targetable pathways. There have already been some notable
failures with tyrosine kinase inhibitors. The world of monoclonal antibodies is also somewhat limited and now everyone is trying to make better antibodies against already targeted antigens.

In contrast, the world of active specific immunotherapies is just opening. Due to the recent successes of Provenge and Yervoy, there will be considerable movement into this new arena. These two approved agents are very different: one antigen specific vaccine-type agent and the other a very non-specific release of the endogenous immune response. The latter begs for combination as witnessed by over 250 abstracts presented at ASCO using Yervoy. The former opens up the world of antigen-specific, disease-specific vaccines.

Still the vaccine world is a bit divided between therapeutic vaccines (metastatic setting) and preventive vaccines (adjuvant setting). The recent successes of Provenge and now a peptide vaccine against gp100 that demonstrated a benefit in combination with high-dose IL-2, an immune activating agent, in the metastatic melanoma setting has invigorated the therapeutic vaccine advocates. However, many of the more advanced products have elected the adjuvant setting to include MAGE-A3, E75 and AE37.

Reni Benjamin: We think the sentiment for immunotherapy has been improving for the last several years. Even though Provenge was approved last year, I would say that the sentiment was mixed at ASCO 2011. Those of us who believe in the power of immunotherapy felt that it was a wonderful conference, while the skeptics were clearly calling into question everything they could - from the manufacturing feasibility of autologous vaccines to the survival benefit to the mechanism of action.

On more than one occasion we heard that perhaps Provenge’s data was a fluke. But with the approval of ipilimumab in melanoma, I think that pretty much puts a nail in the coffin for those who thought that immunotherapy wasn’t here to stay.

Dirk Jäger: Ipilimumab has definitely changed the treatment in melanoma. I don’t think we can say the same for Provenge in prostate cancer.

Mark Monane: The ASCO 2011 meeting provided a broad review of the current and emerging potential drug targets and future therapeutics. In addition to the increasing importance of targeted therapies with novel mechanism of action and use in combination regimens, we noted the added attention on passive and active immunotherapies.

Michael Novod: We have seen a clear turn in focus and sentiment for cancer immunotherapy in recent years and at this year’s ASCO in Chicago. At ASCO 2009, just after Dendreon had reported positive IMPACT data, the clear message from the conference was that cancer immunotherapy was still considered to be some form of voodoo with no scientific backing. This perception had changed by the 2010 ASCO as the FDA had just approved Provenge, but there was still strong skepticism. At this year’s ASCO, we saw that there was a major focus on immunotherapy in cancer and the perception seems to have changed dramatically, for the better. Immunotherapy is suddenly perceived by most to be a valuable tool to treat certain types of cancer, and in addition to Provenge for prostate cancer, Yervoy (ipilimumab) from Bristol-Myers Squibb (BMS) has been made available for melanoma. It is clear that not everybody is convinced of cancer immunotherapy, but based on multiple conversations we had with doctors and key opinion leaders during the five-day conference and all of the symposia and educational sessions we attended, we argue that 80%-90% of the community is convinced – mainly based on the
consistency of the data presented with Provenge and Prostvac in prostate cancer, as well as the
ground-breaking data for ipilimumab in melanoma – a disease for which there has been no
strong medical breakthroughs for the last few decades. Hence, we have seen a positive shift in
perception in favor of cancer immunotherapy and we believe this trend will continue with more
data being generated and more patients being treated.

**Larry W. Kwak:** The approvals of Provenge and ipilimumab, combined with the publication of
positive results from several randomized trials, has the potential to usher in a new age of cancer
vaccines. In this regard, a few days before the ASCO 2011 meeting we published positive Phase
III trial results with a follicular lymphoma vaccine uniquely tailored for each patient. The vaccine
extended disease-free survival by 14 months, with signs of an even better response for patients
with a specific biological marker. The results were significant because most cancer drugs are
approved on the basis of extending survival only a few months.

I believe a whole flood of agents will soon begin to show positive results.

**Reiner Laus:** What you see is a gradually increased acceptance of immunotherapy as a valid
approach in oncology. Two years ago, there was a lot of initial doubt about the Phase III data
with Provenge. There were a lot of questions about the lack of improvement in progression free
survival and PSA levels, yet the patients lived longer. Some experts quipped that “this must be
magic.”

By ASCO 2010, the data with ipilimumab was first being reported and you started to see a
gradual change. There was acceptance for improvement in overall survival despite the lack of
improvement in time to progression and that this was a unique feature that really only applied
to cancer immunotherapies as a class. I think this was a big step.

At ASCO 2011, there was no big Phase III data that further validated this unique aspect of cancer
immunotherapy, but I think that the majority of experts are now getting around to this notion of
having an effective therapy with no short-term end point that signals benefit to the patient.

A couple of years ago, I thought that there would be a flip-of-the-switch analogous to what
happened with monoclonal antibodies after rituximab was approved. Nobody believes in
immunotherapy, then you have positive Phase III data and suddenly everybody believes in it -
similar to the reaction following approval of the first monoclonal antibody for cancer therapy.
And it really hasn’t been like that with cancer vaccines, it’s more of a gradual process. Each year,
there is another little piece of encouraging data that convinces more people that cancer
immunotherapy is indeed a valid addition to the wide array of oncology treatments. But it will
take more approved products and more successes in the field for everybody to be convinced
about it.

**Andrew T. Parsa:** This unique pattern of response seen with active immunotherapies, which is
primarily cytostatic versus cytotoxic in nature, has been reported extensively in the literature
and the evidence of this has been growing over the past 5+ years. However, I believe the recent
approvals of sipuleucel-T and ipilimumab finally provide the needed validation and acceptance
for this biological mechanism.

**Thomas Davis:** People are more open-minded about immunotherapy, unlike two or three years
ago. The success of Provenge has certainly helped cancer vaccines and I think everyone
acknowledges that as a vaccine it works, although there’s still some baseline skepticism out
there. Ipilimumab made a significantly bigger splash in melanoma, but in reality the overall survival benefit from both products is about the same. I think people are just more comfortable with a nonspecific immunotherapy like ipilimumab.

At the plenary session, where they presented the ipilimumab data from upfront therapy, the description was that this is the “year of melanoma” because it seems like melanoma is where we’re seeing the biggest benefits and there’s definitely a buzz around ipilimumab. Diseases seem to take turns having advances made. It was breast cancer probably two decades back. More recently colon, and perhaps even lung, have seen some significant benefits, and now it’s melanoma’s turn. Hopefully it will be glioblastoma’s turn in the not too distant future.

Historically, access to immunotherapy agents has been a challenge in this field, as they’ve been fairly tightly controlled. With Provenge now a commercially available vaccine and some of the TLR agonists becoming more available, there certainly are greater opportunities now to test combinations and push the field forward.

The biggest challenge is still funding and I think there needs to be some external access to funding to help a lot of investigators drive the field forward. While companies can do a certain amount of development with immunotherapies, ultimately you do need either the pockets of Big Pharma or NIH/NCI funding to drive much of that.

Sanjiv S. Agarwala: As a melanoma specialist, obviously I focused on the melanoma sessions at ASCO. Having ipilimumab featured at the two most recent ASCO annual meetings in a disease like melanoma, which has never had a positive trial, and now having two randomized positive Phase III studies for survival is a huge boost to the field as a whole. So yes, I think in general immunotherapy is now looking like it might be a viable treatment option for cancer in general and melanoma in particular.

David Berd: For Provenge, there weren’t very many presentations. Most of the experimental work was long completed, published and presented in previous meetings, so this was not a big Provenge meeting. If you talk to people one-on-one, there is a fair amount of skepticism about Provenge among the medical people, although I don’t think the urologist have the same skepticism. In general, it depends on who you talk to. The clinical immunologists like ipilimumab but not Provenge, because ipilimumab does a lot of things and it has toxicity that reflects its immunologic effects. They are of interest to everybody and are things you can measure, although none of them have really been very well qualified to the anti-tumor effect.

Mark W. Frohlich: The approval of sipuleucel-T and ipilimumab has indeed validated that the immune system can identify and attack cancer. At this meeting, we heard past skeptics of immunotherapy acknowledge the definitive survival benefit conferred by sipuleucel-T. While there is interest in better understanding the lack of a measurable effect on disease progression or tumor response, we no longer hear people voicing skepticism of the overall survival results as a result of these observations. A rationale for the disconnect between proximal measures of disease response/progression and overall survival has been provided by recent work at the National Cancer Institute where analysis of several prostate cancer trials suggests that therapeutic immunization has a favorable influence on the balance between tumor regression and growth (Stein, Clinical Cancer Research, 2011) This model is supported by the effect of sipuleucel-T in prolonging PSA doubling time in a randomized trial in men with androgen dependent prostate cancer (Beer, Clinical Cancer Research 2011).
TOPIC #2

What new data, with emphasis on Phase II programs or later, were presented around the time of the ASCO meeting in major disease areas, such as melanoma, prostate cancer, breast cancer, bladder cancer, colorectal cancer, and glioma?

Melanoma

Note: Since Yervoy (ipilimumab) is discussed extensively throughout this document, it will not be included in this section.

Pegylated Interferon Alfa-2b (PEG-IFN)

Sanjiv S. Agarwala: There were presentations both this year and last year at ASCO with PEG-IFN and the agent was also recently approved by the FDA for high-risk melanoma, so now we have yet another approval for an immunotherapy agent in melanoma and this time in the adjuvant setting. This is very interesting and now provides an option for patients instead of just standard interferon.

Expanding upon that theme, I had an abstract (abstract #8505) that was presented at ASCO demonstrating that one month of therapy with high-dose interferon alfa-2b was not efficacious. We learned from that trial and from the PEG-IFN trial that if we use interferon in the adjuvant setting for melanoma it needs to be given for an extended duration of time - at least a year.

Allovecin-7

Sanjiv S. Agarwala: The Allovecin-7 data presented at ASCO was interesting, although we don’t have the Phase III results yet. It looks like there are some durable responses and maybe even a survival advantage that might come out of this. Obviously, I would have to say that we need to await the results of the Phase III study before we know for sure, which could come by the end of this year or early next year.

PV-10

Sanjiv S. Agarwala: At the HemOnc Today Conference in New York City on June 25, 2011, Professor Merrick Ross, M.D. of the MD Anderson Cancer Center reviewed some data on PV-10, which is an agent that causes necrosis and has a bystander effect in non-injected lesions. This is similar to treatment with OncoVEX(GM-CSF) and Allovecin-7, where you inject the tumor directly.

With PV-10, the tumor shrinks and also, in about 25 percent or 30 percent of cases, non-injected tumors shrink as well. We have no idea how that is happening, although it’s likely the immune system due to the necrosis effect, which recruits immune cells. As those immune cells get primed due to the antigens released, they travel elsewhere and the other tumors shrink.

gp100

Sanjiv S. Agarwala: Around the time of the ASCO meeting, results were published in the New England Journal of Medicine demonstrating a benefit with gp100 in combination with IL-2, which is interesting in view of the fact that there wasn’t a benefit when gp100 was combined with ipilimumab. This raises a very important question - why did gp100 seem to work with IL-2
and not with ipilimumab? At the HemOnc Today Conference in New York City we discussed this exact question and whether or not it has something to do with the way the IL-2 works and the way ipilimumab works. There was a great analogy provided at the meeting describing ipilimumab as taking the brakes off the immune system, whereas IL-2 is pushing the gas pedal on the immune system. But if the car isn’t moving, pushing the brake isn’t going to do anything. First, you have to step on the gas and make the car move, which might help explain the disparity between ipilimumab and IL-2 in combination with gp100.

Prostate Cancer

Provenge (sipuleucel-T)

**Mark W. Frohlich:** The prostate cancer treatment landscape has never been more exciting. For patients with metastatic prostate cancer, physicians have several new agents in their armamentarium, and these medications provide patients with clinically meaningfully survival benefits. There was a great deal of discussion during ASCO about how to sequence these agents. Given that immunotherapy is likely most effective when given early, that immune responses can be sustained, potentially interact beneficially with subsequent therapies and alter the net tumor growth kinetics, we are seeing increasing consensus that immunotherapy should be used soon after the diagnosis of metastatic castrate resistant prostate cancer, and prior to agents which are potentially immunosuppressive and have increased toxicities. New data on pain palliation with abiraterone, and separately, with cabozantinib, are encouraging for symptomatic patients.

**Mark Monane:** Provenge was the subject of at least nine abstracts presented at ASCO 2011, some of which I will briefly review.

First, analyses of time to disease-related pain (TDRP) data from three randomized Phase III trials of Provenge (D9901, D9902A, and IMPACT) in asymptomatic patients with metastatic castrate-resistant prostate cancer (CRPC) were presented (abstract #4661). Analyses were based on all asymptomatic patients randomized in the trials, including all randomized patients on D9901 (n=127) and D9902A (n=98), and on IMPACT patients randomized prior to the protocol amendment to include minimal symptomatic patients (n=203). Unadjusted Cox regression model showed hazard ratios (HR) of 0.68 for D9901, 1.39 for D9902A, 0.80 for IMPACT. Integrated results showed a HR of 0.84 (P=0.24). Separation in the Kaplan-Meier curves was seen at approximately 6 months. Median TDRP was 5.6 for the treatment group vs. 5.3 months for the placebo group. At 12 months, 39.3% of sipuleucel-T versus 18.9% of control patients were estimated to be pain-free. While the TDRP did not show statistical significance, we believe the data showed an encouraging trend towards a delay in TDRP. We note the trend towards a delay to TDRP beginning 6 months after randomization may be consistent with the delayed anti-tumor effect of immunotherapy. These analyses provide support for the potential Provenge benefit on a clinically relevant endpoint, which is seen more proximal to therapy (which may be seen in months) versus the benefit in overall survival (which may be seen in years).

Data were also presented from a Phase III study of Provenge in men with PSA progression after radical prostatectomy (abstract #4648). Following 3-4 months of androgen deprivation therapy (ADT), men were randomized 2:1 to either sipuleucel-T or control. 176 patients were randomized to sipuleucel-T (n=117) or control (n=59). As expected with ADT, in the 3 months prior to sipuleucel-T, quality of life (QoL) measures declined and were comparable in both arms.
Following initiation of study treatment, no significant differences in QoL were observed between treatment groups. These results demonstrated that, unlike other traditional chemotherapies, sipuleucel-T treatment does not affect patients QoL in this patient population.

Dendreon presented an analysis of results from patients in the control group from three randomized trials of Provenge in patients with CRPC (abstract #4534). After disease progression, subjects in the control arms were allowed to cross over to receive 3 infusions of APC8015F, an autologous immunotherapy made from cells cryopreserved at the time of control generation. 165/249 (66.3%) of the control group received APC8015F. 145 subjects (87.9%) received all 3 infusions. APC8015F-treated subjects had improved post-progression survival relative to untreated controls (HR = 0.52, P = 0.0001), with median survival times of 20.0 and 9.8 months, respectively. After adjusting for prognostic factors, including lactate dehydrogenase, alkaline phosphatase, ECOG status, age, number of bone metastases, and hemoglobin, as well as post-randomization salvage treatment and docetaxel use, results showed a positive docetaxel effect (HR = 0.86, P = 0.40), and a positive APCF8015F treatment effect (HR = 0.78, P = 0.17). These post-hoc analyses indicate that post-progression treatment with APC8015F may have extended survival of control subjects, potentially reducing the magnitude of survival difference observed between sipuleucel-T treatment arm and control arm in the randomized CRPC trials.

A pooled analysis of African American men in the three Phase III trials of Provenge in CRPC was published online (abstract #E15148). Of the 737 men enrolled in the trial, 43 patients were African American. Sipuleucel-T treatment showed similar effect on overall survival (OS) in the African American subgroup (HR=0.288, P = 0.003), with a median OS of 45.3 months in the sipuleucel-T arm vs. 14.6 months in the control arm. Adverse events for the African American subgroup were comparable to the overall study population. We note the limitation of the small sample size, yet the analysis suggest that African American patients benefit from treatment with sipuleucel-T, with no difference in adverse events profile as compared to the overall population.

With regard to trials in progress, a poster describing a proposed Phase III global trial to evaluate the efficacy of sipuleucel-T in patients with metastatic androgen dependent (hormone sensitive) prostate cancer the (mADPC) was presented (abstract #TPS188). The global, randomized, open-label, multi-center trial will enroll ~1684 patients. Patients will receive ADT to achieve castration-level testosterone and then will be randomized 1:1 to receive sipuleucel-T or continue on ADT alone. The primary endpoint is overall survival. Secondary endpoints include safety, quality of life, time to castration resistance, and chemotherapy-free survival. From a subset of the study subpopulation (n=600), pharmacodynamic measures will be evaluated including serum and blood samples for cellular and humoral immune response analyses as well as circulating tumor cells (CTC). We believe the trial has the potential to expand the Provenge label indication to an earlier stage disease, which may substantially expand the market potential.

In addition, a poster described a planned Phase II trial evaluating the effect of Provenge before or after ADT on markers of immune response in non-metastatic prostate cancer patients with a rising PSA after primary therapy (abstract #TPS189). The primary study objective is to determine which treatment sequence leads to a superior augmentation of immune markers. Secondary objectives include safety and the maintenance of immune markers over time. 60 subjects will be randomized 1:1 to receive sipuleucel-T followed by ADT (given 2 weeks after the third immunotherapy infusion), or ADT followed by sipuleucel-T (given 3 months after ADT initiation).
In both arms, ADT treatment will continue through Month 18. As more treatment options become available, we believe this trial is an important next step to understand the potential combination treatment effect as well as sequencing of different treatments.

**PROSTVAC**

**Michael Novod:** We saw interesting data released by Dr. James Gulley at a prostate cancer symposium and also presented by Dr. Christopher Heery at one of the poster sessions. Dr. Heery’s trial involved intra-prostatic injection of Prostvac in order to review the safety and efficacy of that administration route. 21 patients were vaccinated and four of eight evaluable patients had immune response by ELISPOT. In terms of immune response, CD3+ cells increased from 12.3 → 21.3/high power field (hpf) (p=0.0079). CD4+ cells increased from 1.3 →13.1/hpf (p=0.0002) and CD8+ cells rose from 6.4 →14/hpf (p=0.0002). Hence, there was some substantial immune response to the vaccine, supporting the mechanism of action and findings by Dr. Gulley as well. Interestingly, data from Dr. Gulley also highlighted the unique properties of the TRICOM construct of Prostvac where the vaccine is attached to three co-stimulatory molecules. The immune response or t-cell activation is very limited from the vaccine alone as well as when only one of each of the co-stimulatory molecules is attached to the vaccine. However, when all three are combined in the TRICOM construct, there is a several fold increase in t-cell activation, or the immune response.

**Breast Cancer**

**NeuVax (E75)**

**Joseph Pantginis:** RXi Pharmaceuticals Corporation presented 36-month follow-up data from the NeuVax study in adjuvant setting breast cancer patients. After 36-months post treatment no recurrences had yet taken place (albeit small group of patients) in what we are describing at the “Phase III targeted group.”

NeuVax is a cancer immunotherapy product using the E75 peptide from the HER2/neu protein administered in conjunction with GM-CSF. E75 is a highly conserved nine amino acid peptide (K-I-F-G-S-L-A-F-L) derived from the extracellular domain (ECD) of HER2/neu and is restricted to MHC Class I: HLA-A2 and HLA-A3. HER2/neu is a member of the epidermal growth factor receptor family of transmembrane tyrosine kinases. It has been shown that HER2/neu is over-expressed in several different tumor types, which can lead to a 100-200 fold increase in concentration of the HER2/neu protein in tumor versus normal tissue.

In the new dawn of cancer immunotherapy, NeuVax is expected to enter a Phase III study for breast cancer, under SPA, in 1H12 following trial preparations and final manufacturing validation. In Phase I/II studies, NeuVax demonstrated what we believe to be positive and significant impacts to disease free survival (DFS).

In the June 2, 2011 issue of the *New England Journal of Medicine*, positive randomized Phase III data were published using the gp100 peptide vaccine in melanoma patients. This 8 amino acid vaccine was compared against IL-2 in late stage melanoma patients. The primary endpoint of overall clinical response was met (16% on vaccine arm versus 6% on IL-2 arm; p=0.03). Additionally there was a statistically significant impact to the secondary endpoint of progression free survival (PFS) and a solid trend in overall survival (OS). With multiple technology
approaches in cancer immunotherapy in development, we believe that this gp100 outcome helps to validate the small peptide vaccine approach.

**AE37 and GP2**

*George E. Peoples:* While not presented, but published, we showed the use of circulating tumor cells (CTC) as a meaningful marker of vaccine response. CTC have received a large amount of attention in the chemo world. Veridex’s CellSearch is an FDA-approved assay for chemo response in the metastatic breast cancer setting. The reduction in CTC after chemo has been correlated with PFS and OS. We have extended the use of this clinically validated assay to our vaccine trials of AE37 and GP2. The vaccines produced a reduction in CTC compared to the randomized controlled group. Furthermore, there appeared to be a clinical benefit associated with the reduced CTC.

**Bladder Cancer**

**DN24-02**

*Mark Monane:* A poster describing a planned Phase II randomized, open-label trial evaluating DN24-02, Dendreon’s second cellular immunotherapy product targeting HER2/Neu, given as adjuvant therapy in patients with surgically resected urothelial at high risk of recurrence (abstract #TPS187). Up to 180 subjects will be randomized 1:1 to receive DN24-02 as adjuvant therapy approximately every 2 weeks, given as IV infusions 3 times, or standard of care. The primary endpoint is OS. Secondary endpoints include disease-free survival, safety, and immune responses to DN24-02.

**Glioma**

*Prophage Series G-200 (HSPPC-96)*

*Andrew T. Parsa:* As a neurosurgeon who treats patients with glioma, I am pleased to see the emergence of new immune-based agents undergoing clinical trials in this disease setting. At ASCO this year, I presented results from a multi-center Phase II trial of an autologous cancer vaccine, HSPPC-96, tested in patients with resectable recurrent glioblastoma. The overall survival results from this study were encouraging and were supported by demonstration of robust immune responses that were seen both in the periphery and at the local tumor site. Based on the evidence generated from this Phase II trial, I am pleased that this important potential treatment option will now advance into a late phase trial for regulatory approval.

**Colorectal**

*PANVAC*

*Reiner Laus:* The PANVAC Phase II data in colorectal cancer from investigators at Duke University was very dramatic. While not a randomized or placebo controlled study, data from a prospectively registered, comparable, contemporary control group of patients who had undergone metastasectomy for colorectal cancer at Duke were also available with apparently no bias as to one group or the other. The arms of the study and contemporary controls were well balanced.

The study investigated whether administration of an antigen-presenting cell vaccine based on dendritic cells after metastasectomy would reduce the risk of recurrence and increase survival.
Patients with no evidence of disease after resection of colorectal cancer metastases and completion of their physician-determined peri-operative chemotherapy were randomized to four immunizations with dendritic cells modified with the PANVAC-VF poxvectors encoding CEA, MUC1, CD54, CD58, and CD80 with or without GM-CSF at the injection site.

The two year recurrence-free survival was similar in all groups. However, at a median follow-up of 40 months, the combined survival rate in the PANVAC groups exceeded that of the unvaccinated control patients. Those data confirmed in a Phase III study comparing patients vaccinated after resection with the vaccine and observation would be rather dramatic.

One has to be careful to declare victory in this setting because the study as has certain flaws that make it vulnerable to skepticism. The main one being it wasn't randomized controlled, but rather it was a case controlled study. But seeing this enormous effect size strongly suggests that there is something there. In addition, this is the same effect that we have demonstrated with poxvectors encoding PSA for the treatment of prostate cancer.
TOPIC #3

With more than 50 clinical programs in development, it is expected that more than one form of immunotherapy may be approved in certain disease settings. In addition to immunotherapies, newer small molecule and other biologic therapies are also competing in these settings. How are immunotherapies differentiated within some of these crowded disease segments and how will they be sequenced with traditional or newer small molecule/biologic agents?

Jianda Yuan: The results of two Phase III Yervoy clinical trials (last year phase III trial (3 mg/kg) as reported by Dr. Stephen Hodi and this year’s Phase III trial reported by Dr. Jedd Wolchok) showed the durable clinical response. Sustained clinical response is the major evidence of immunotherapy, which is different from traditional or newer small molecule/biologic agents.

Liz Bromley: I think immunotherapies can play a very important role in these indications and occupy a unique niche as something that can provide lasting benefit even after treatment ceases. However, cost and, in some cases, the labor-intensive nature of therapies like autologous cell transfers are limiting factors. Ideally, immunotherapies would be used as first line treatments because they are best suited for this—they may take a while to show effect and so they are not best suited for those with debilitating symptoms who need a rapid decrease in tumor load. But as first line therapy they also can take full advantage of remaining immune function and hopefully have a lasting protective effect.

I think eventually the order of treatments will depend on disease severity as stated above. Targeted therapies (and other, SOC treatments) will be used for patients with advanced disease and high tumor burdens. Immune therapies may not be used second line at all if practitioners have little faith in remaining immune function after chemotherapy and disease progression have crippled it. But if precedent can successfully be set for using immune therapies first line, that is the best place for them. If not too toxic, they could also establish a foothold in the adjuvant setting.

James L. Gulley: In prostate cancer, the number of new and emerging drugs to treat metastatic CRPC is increasing greatly. The timing of treatment with an immunotherapy in this setting seems to be settling out. It is most likely that the best place to offer immunotherapy will be early on in the disease state. This is based both on biology (better chance for T-cells to be active at the site of a smaller tumor) and clinical considerations (patients wish to use drugs known to have less side effects when they are asymptomatic, whereas symptomatic patients may be better treated with something that is more likely to cause a reduction in symptoms).

Joseph Pantginis: As the disease segments become more crowded we believe that immunotherapy finds itself in a unique position. This unique differentiation is its ability to be potentially combined synergistically with other treatment modalities.

George E. Peoples: There is good data to support the combination of chemotherapy and passive immunotherapy especially in breast cancer, but more importantly, there is additional real and theoretical data to support chemotherapy and active specific immunotherapy. There is reason to believe that the two modalities may be synergistic especially if used sequentially.
The other combination that will be seen with increasing frequency is combination immunotherapy. We presented a poster of sequential passive followed by active immunotherapy. This combination may be especially useful in the adjuvant setting.

As mentioned above the combination of non-specific and specific immunotherapy is likely to be pursued in the metastatic setting.

**Reni Benjamin:** The fact that vaccines have a unique safety profile may be a key differentiator. With regard to how immunotherapies differentiate themselves, the way I look at it is that it’s no different than a chemotherapeutic or tyrosine-kinase inhibitor. Physicians have figured out how to implement different novel therapies in the past — cancer vaccines are no different.

For example, Provenge really secured itself as the agent of choice in asymptomatic, or minimally symptomatic, metastatic hormone resistant prostate cancer especially for patients who were not necessarily keen on receiving Taxotere. Based on its benign side effect profile, Provenge came into an area where the standard of care was watching and waiting and showed a statistically significant survival benefit. I don’t believe this could have happened if the product’s side effect profile resembled that of Taxotere. So I think immunotherapy is uniquely positioned to be used in key areas - either asymptomatic, minimally symptomatic areas or more importantly adjuvant areas where the patient has achieved some type of response (complete, partial, or stable disease), and afterwards, the typical standard of care is to wait for progression. Maybe the thing to do in this instance is add a cancer vaccine that has the ability to up-regulate the immune system and destroy the minimal residual disease, which often is associated with recurrence.

One of the other key findings that came out of this year’s ASCO is the use of therapeutics in a chronic manner. For example, the GIST study looking at imatinib as an adjuvant therapy and what would happen if you treated these patients continuously even though they initially responded. They continued treating the patients chronically and saw a significant benefit in survival. Now, you can’t do this with every drug that’s out there because obviously it depends on the toxicity profile. However, for the right drug or for the right immunotherapy, this could very well become a standard. We’re just at the beginning of how to essentially convert cancer into more of a chronic disease and as more these products are approved, I think the marketplace will become very efficient at figuring out the appropriate cycling, sequencing, or setting to use these products.

**Dirk Jäger:** In glioma, small molecules do not lead to long term remissions, this was only shown for immunotherapies. I would expect that combination of immunotherapy with small molecules/chemotherapy as an initial treatment might be effective.

**Michael Novod:** Sequencing was a clear buzz-word at ASCO regarding prostate cancer, as many more agents have become available in the treatment cascade. Importantly, most of these agents do not compete directly, but instead key opinion leaders stated that it will be a matter of sequencing, i.e. to continuously move the patient from therapy to therapy. That also means that biomarkers to monitor efficacy will be very important and that there will be plenty of room for many different therapies in the prostate cancer space.

**Larry W. Kwak:** We do not have a curative therapy for low grade lymphomas, so while rituximab is a great drug - it doesn’t cure anybody. Even in combination with chemotherapy it probably
does not cure people with low grade lymphoma. There is currently a need for curative therapy or at least a therapy that prolongs remissions beyond that seen with rituximab, so adding a cancer vaccine in the maintenance setting makes sense. That could very easily be the place for BiovaxID - making it a maintenance therapy after rituximab and chemotherapy get a patient into remission. The reason I think it’s a winner for a maintenance therapy, even above the other drugs that have been tried in this setting such as lenalidomide, is the superior safety profile that the other agents do not have. That’s particularly important for maintenance therapy as opposed to induction or consolidation therapy.

**Andrew T. Parsa:** Immunotherapies are differentiated based on mechanism of action. Most broadly they can be divided into therapeutic vaccines, which activate antigen-specific T cell responses, and immune modulators which regulate various immune pathways irrespective of the specific cancer antigen target. Provenge is an example of the former, while Yervoy is an example of the latter. Vaccines themselves can be differentiated based on their composition. Provenge targets only one tumor antigen while other vaccines in development are polyvalent. Several immune modulators act on different T cell signaling pathways although the unifying concept is to maintain and even heighten the anti-tumor T cell response.

There is every reason to believe that cancer vaccines and immune modulators have potential for synergistic outcomes when used in combination and this is an area that is expected to receive more attention in the clinical setting. Immunotherapy may also be integrated into treatment regimens which include traditional or newer small molecule/biologic agents - although careful attention needs to be paid to immune toxicities associated with some of these agents which will govern how the agents are sequenced with immune therapy in clinical practice. In general, the concept of combining an anti-cancer agent which, e.g., interrupts tumor cell signaling or inhibits angiogenesis with a vaccine or immune modulator is attractive because it represents an even more multi-faceted attack on cancer.

**Thomas Davis:** The data with the BRAF inhibitors, which was addressed by Kim Margolin in her summary session, made for a very interesting future approach to melanoma. If a patient has a mutation and can receive the small molecule inhibitor upfront, they’re quite likely to have significant tumor shrinkage. Then use ipilimumab as a second line, perhaps even overlapping, to have a much more dramatic impact on melanoma overall when you add those agents together.

**Sanjiv S. Agarwala:** For melanoma, I think what is going to happen is that all of the patients that are going to get immunotherapy, at least initially, are going to be BRAF negative patients. Because if you are BRAF positive, you are going to go on BRAF targeted therapy and you are only going to get immunotherapy if you’re BRAF negative or you fail a BRAF inhibitor and you progress. Alternatively, if you are BRAF positive and you fit the immunotherapy paradigm which is slow growing disease, low volume, etc. then you could wait and hold the BRAF drug until later. The only way to answer these questions is through clinical trials. Ultimately, I think there will be room for everybody and we’ll finally have treatment algorithms in melanoma, which we never had. We’ll be able to approach the disease logically and if the patient has local or regional disease that is not progressing rapidly, and the patient’s not symptomatic, maybe I can spare the patient some of the systemic therapy toxicities by giving them something like Allovecin-7, especially if the are BRAF negative. If a patient has metastatic disease and local regional disease, perhaps there is the benefit of the local regional treatment with something like Allovecin-7, OncoVEX(GM-CSF), or PV-10, which gives me a local effect and a systemic effect and combine it
with a systemic drug, such as a BRAF inhibitor in a BRAF positive patient or ipilimumab in a BRAF negative patient.

All of these will have to be done and companies need to very quickly do at least small studies that would look for safety signals. We will want to know if the combinations are safe, because as these therapies are approved people will want to put them together. But they won’t do it unless you show them that it’s safe to do so because you can be surprised sometimes when you put two agents together.

**David Berd:** I have a feeling that targeted small molecules and immunotherapy may not be a good mix. People are looking for more targets and new mechanisms of resistance, or looking for ways to overcome resistance, which will clearly require combinations of multiple targeted small molecules. Unfortunately, the people in those fields may not be terribly interested in immunology. People who really think that immunotherapy is worth something are going to be tremendously challenged by this. In other words, whenever you have something new, it is going to be a challenge to keep people interested in other areas, such as immunotherapy.

The question is how far can small molecules go right now with the science that we have? They can certainly go to the point of being tested in adjuvant trials. But everyone becomes resistant to them and in general they are not creative treatment, as they don’t produce long term remissions. I think the small molecule field is going to be developed on its own pretty much without the help of any immunologist.

**Mark W. Frohlich:** Sipuleucel-T is differentiated from traditional anti-cancer agents by fact that it provides a clinically meaningful survival benefit and a short duration of therapy, with adverse events being generally low grade and transient. These features, along with the potential for a long-lived immune response that may favorably alter the long term tumor growth kinetics provide support for the use of sipuleucel-T and similar active immunotherapies early in the treatment paradigm, and prior to traditional and/or small molecule agents.
TOPIC #4

With the recent approval of the first active immunotherapy for cancer and the subsequent approval of Yervoy, what are some of the more promising combination therapy approaches presented at ASCO?

Jianda Yuan: At this ASCO meeting, Dr. Stephen Hodi presented a Phase I trial of ipilimumab plus bevacizumab in patients with unresectable stage III or stage IV melanoma. (Abstract # 8511). 14 of 21 patients experienced clinical benefit, including 8 patients with partial response and 6 patients with stable disease. The clinical response is promising. There are no synergistic toxicities. All toxicities resolved. Since the VEGF inhibitor had been widely investigated in other types of cancers, i.e. renal cancer, this study leads to Yervoy in combination with VEGF inhibitor in other types of cancer too.

Also, the combination of chemotherapy and immunotherapy is a possible therapeutic approach, because the impact of chemo on the immune system has been recognized recently. Preliminary clinical trial data show that chemotherapy plus vaccination enhanced clinical response. However we need to learn more about the immune modulation of chemo in order to optimize this combination.

At the CRI Cancer Immunotherapy Consortium annual colloquium held in March this year, which focused on schedule and dosing for combination therapy, presenters showed data from clinical studies of combination approaches, including paclitaxel and IMP321 (LAG-31g), an antigen-presenting cell activator, in metastatic breast cancer patients; tyrosine kinase inhibitors and vaccines in chronic myelogenous leukemia patients; BRAF-inhibitors plus immunotherapy in melanoma; and combinations of radiation therapy with immunotherapy. Together, these presentations along with those given at ASCO provide the rationale for combination of various therapeutic approaches with immunotherapy.

Getting investigational therapeutic agents into the hands of academic scientists to test in combination with other agents has been a challenge. The Cancer Vaccine Acceleration Fund of the Cancer Research Institute has developed a new model of academic-industry partnership that is helping to bring promising investigational drugs into clinical trials in combination with therapeutic cancer vaccines. These combinations are being testing in the CRI/LICR Cancer Vaccine Collaborative, for which my laboratory serves as a central immune monitoring facility. Therefore we are able to drill deep into the effect these combinations have on the immune response to cancer and on patient health.

Liz Bromley: I liked the idea presented by Dr. Margolin in the plenary discussion section of melanoma drugs-- i.e. choosing treatments according to disease stage, as I mentioned in the previous question (faster-acting but temporary benefit from targeted drugs for advanced, symptomatic disease; immune therapy when there’s time to let it take effect and enough immune function to be worthwhile).

Immune therapy combined with chemo doesn’t appeal since the chemo destroys immune function and there is little hope of any synergistic effect.
Immune therapy with local therapy makes a whole lot of sense, as local ablation could enhance antigen presentation. In that case I would do the ablation first, or possibly start the immune therapy at the same time as ablation. Of course I should disclose that this is the area my company specializes in—we are developing a novel local therapy that appears to induce some anti-tumor immunity as well, and we are testing it in combination with other immunotherapies. The barriers to this idea in the market are frustrating and arise from the lack of overlap in thinking between interventionalists and medical oncologists. But it is an idea that needs far more attention and research.

Combining immune therapies is something I can’t comment on since there are so few available and they are so different that each combo would need to be carefully tested first.

**James L. Gulley:** I think that we will see combinations of all of the above, but now for the very first time, there is the ability to do immune therapy plus immune therapy combinations with an approved active agent in at least one of the drugs. This will spur more combination studies. I would like to point out that the Cancer Immunotherapy Trials Network led by Mac Cheever is also attempting to provide a platform for greatly improved access for combinations of experimental agents.

**Joseph Pantginis:** The most common combination initially will be various chemotherapy combinations and sequencing of the therapies will be important in order to take into account the immunosuppressive effects of chemo. Time must be allowed for the immune system to “rebound.” Chemotherapy could potentiate an immunotherapy approach by providing the immune system with more free “antigen” to recognize as cells are destroyed. Regarding targeted therapies, we are still in very early days in assessing the combination potential of various approaches.

In our belief, there are several exciting potential combinations. First, vaccine combinations with Yervoy, though careful monitoring of immune side effects would be critical. Yervoy would take the “brakes” off the T-reg cells allowing the potentiation of the vaccine. Second, vaccine combinations with anti-angiogenesis approaches – data exists supporting the role of this combination based, in part, on the ability of VEGF to inhibit dendritic cell function. Third, the potential combination effects of Provence and abiraterone. While the focus is currently on the competitive environment and reimbursement landscape, it is possible that the use of both drugs could be complementary because prostate cancer would be attacked from two distinct directions.

**Michael Novod:** At a company-sponsored event held during ASCO, investigators highlighted data generated by the NCI with Prostvac combined with Yervoy (ipilimumab), the radioactive isotope samarium-153 (mainly used to relieve pain in mCRPC) or with the anti-androgen Flutamide. Data on Prostvac in combination with other agents shows the same compelling data, which again is a very important factor in our conviction on the drug’s prospects and potential success in phase III clinical trials starting in September 2011. Looking at the overall survival in the study in which Prostvac is combined with the anti-CTLA4 agent ipilimumab, survival is increased by 15.9 months in combination versus 9.1 months on Prostvac alone. The Prostvac survival increase is in line with other data published, which is a strong sign and the combination survival increase looks very promising.
Andrew T. Parsa: The approval of Yervoy offers a great opportunity for exploring combination studies with cancer vaccines, in particular. Although the Phase III trial showed no additive benefit of combining Yervoy with the cancer vaccine gp100, this should not dissuade further efforts of studying Yervoy with other cancer vaccine constructs. I believe autologous vaccines that include many unique, tumor-specific antigens have the greatest potential for showing improved efficacy as these types of vaccines provide the most robust targeting.

I also found the presentation combining bevacizumab and ipilimumab in melanoma very interesting. It appears that the combination revealed activated vessel endothelium with extensive T cell trafficking not seen with ipilimumab alone and 14 of 21 patients experienced clinical benefit. This is of personal interest as bevacizumab is approved for use in recurrent glioma yet the benefit is modest at best. I think this experience of bevacizumab and ipilimumab suggest similar synergy might be realized if combining a cancer vaccine with bevacizumab.

David Berd: At the plenary session, there was the combination of ipilimumab with dacarbazine, which was compared to dacarbazine alone. However, it was made pretty clear by the presenter that nobody is going to combine dacarbazine with Yervoy in the real world. It was done for the purpose of the study just to have a clean control that everybody would acknowledge as standard of care and it is never going to happen again.

Mark W. Frohlich: There was a new emphasis at this year’s meeting on combining agents earlier in development, which has led to novel partnerships in clinical development programs (e.g., Merck and AstraZeneca presented Phase I data on the MEK inhibitor MK-2206 and the AKT inhibitor selumetinib). Combining immunomodulatory agents with each other has great potential and we anticipate seeing more of this at subsequent ASCO meetings.
With regard to active immunotherapy, what was the most promising clinical data presented at ASCO?

**Jianda Yuan**: The most promising clinical data presented at 2011 ASCO is “the Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma” presented by Dr. Jedd Wolchok at the plenary session. IPI (10 mg/kg) + DTIC significantly improved OS in 1st line metastatic melanoma vs DTIC alone; durable survival and objective responses were noted in some patients after follow-up for up to 4 yrs. Type of AEs was consistent with prior IPI studies: however, frequencies of some AEs differed with a higher transaminitis and lower diarrhea/colitis/GI perforation rates than expected.

**Liz Bromley**: The ipilimumab data were certainly nice to see. I didn’t feel there were enough sessions on immunotherapies in general, especially outside of melanoma, so I spent most of my time on other topics. There were no big immune breakthroughs at this year’s ASCO in my opinion.

**John M. Kirkwood**: The plenary data upon ipilimumab was important, demonstrating that despite trebled dose regimen given with dacarbazine for first line therapy of melanoma, there is no increment in benefit over the lower dose regimen approved in March of 2011 by the US FDA. On the other hand, the toxicity of this regimen was less than had been feared, but the role of dacarbazine in this combination is at issue. While the rationale for using dacarbazine in combination with ipilimumab to achieve regulatory approval was practical, the scientific basis for this combination was never clear, and the use of dacarbazine in combination with ipilimumab for the future is hard to justify. In the absence of compelling evidence for superior anti-tumor activity of the higher dosage of ipilimumab the lower dosage approved by US FDA will likely remain the choice of clinicians.

In the adjuvant therapy of melanoma, we saw several trials building upon the established high-dose interferon (IFN) regimen that has demonstrated significant improvement of both survival and reductions of the rate of relapse that has been durable to >10 years in multiple US cooperative group trials. The Italian Melanoma Intergroup trial testing repetitive IV induction with IFN was presented by Chiaran-Sileni, demonstrating no significant difference between repetitive induction and standard high-dose IFN for one year. The US intergroup tested one month of IV induction IFN against observation, showing that this abbreviated regimen is not effective, arguing that the one year regimen remains the standard of care for high-risk melanomas including deep primary melanomas, and both microscopic and macroscopic (IIla and IIlb) nodal disease that is resectable. This year, we also saw more mature data from the EORTC trial 18891 demonstrating that the peg-IFN regimen approved by the US FDA in March 2011 on the basis of earlier suggestions of an 18% reduction in relapse (p=.01) without any significant impact upon either distant disease-free or overall survival, has lost some of its margin of benefit upon relapse-free survival. At maturity of 7.6 years, approximately when the e1684 trial had shown its significant impact upon both overall and relapse free survival, this trial now shows 13% reduction in relapse rate, (hr .87 with p=.05 ). This also continues to support
the durable results of the e1684 one year high-dose IFN regimen approved by the US FDA in 1996, which has achieved worldwide regulatory approval, and to date has never been surpassed in its benefit upon relapse free or overall survival. Finally, it was announced that the US intergroup trial of high-dose ipilimumab for one year vs. high-dose IFN-alfa was activated on May 25, 2011, and is beginning to accrue subjects, while the EORTC trial testing the high-dose ipilimumab regimen vs. placebo is close to completion, although no data are expected from either of these trials for several years.

**James L. Gulley:** The ipilimumab data and the preliminary data from the phase II PANVAC trial.

**George E Peoples:** The gp100 vaccine trial published in NEJM and the AE37 data in breast cancer published at ASCO.

**Reni Benjamin:** Other than the Yervoy data, it's tough to single out anything else that was randomized and controlled and demonstrated a clear-cut benefit in survival. There are plenty single arm studies that were presented at the conference, but again, you’re analyzing that data in a vacuum. It’s encouraging and they need to move on to Phase II and III studies. The key takeaway from this year’s ASCO, in our opinion, is that ipilimumab pretty much solidified immunotherapy as a new weapon in the oncologist’s arsenal to fight cancer.

Beyond ASCO, something that is probably out of the limelight and not followed as well but should be in the minds of investors is the TLR space. For example, both Idera and Celldex are involved in developing TLR agonists as potential adjuvants in the cancer vaccine space as well as adjuvants in combination chemotherapy. This isn’t a new class of immunotherapy in view of the amount of work that’s being done on it, but I believe it’s a class of compounds that investors should be aware of given the new hope that we have in immunotherapy, as it is one of those areas that could launch immunotherapy to the next level.

**Dirk Jäger:** The Phase III ipilimumab trial.

**Mark Monane:** Dendreon presented additional analyses from Provenge trials in patients with metastatic CRPC, suggesting that Provenge treatment may delay the time to disease-related pain (HR=0.84), a clinical relevant endpoint, and Provenge treatment does not affect the patient’s quality of life, a distinct feature of immunotherapy versus traditional therapy. In addition, multiple planned trials were described, including the Phase 3 ACTION trial of Provenge in an earlier stage of disease (metastatic, androgen-dependent prostate cancer), a Phase 2 trial to explore the effect of treatment sequencing of Provenge with ADT, and a RCT Phase 2 to evaluate DN24-02, a cellular therapy targeting HER2/Neu, in urothelial cancer. We believe the data presentations suggest additional clinical benefits of Provenge beyond its demonstrated overall survival benefit. The Phase 3 ACTION trial may expand the Provenge label to earlier stage disease in the long-term as well as provide EU physicians with experience with Provenge before the anticipated market launch there. We expect the effect of treatment sequencing of Provenge with other therapies to gain increasing interest as more treatment options become available in this indication.

**Michael Novod:** Beyond specific clinical data, another interesting trend at ASCO is that immunologists are starting to participate heavily in cancer immunotherapy discussions. We also note that some of the world’s leading immunologists are taking the lead in terms of presenting and providing immunotherapy crash courses, including Dr. Charles Drake from Johns Hopkins
Sidney Kimmel Comprehensive Cancer Center, who delivered a very clear lecture on immunotherapy at one of the biggest cancer immunotherapy symposiums at ASCO.

Involvement of the immunologists is important as they are able to try to identify and explain the mechanism of immunotherapy and thus also generate better acceptance of the “delayed efficacy.” This is what has been shown in the Provenge, Prostvac, and other studies where the true effect of the drug is not seen until after 11-12 months. Traditional oncology and oncologists mainly look at markers for efficacy such as PSA decline or tumor shrinkage in prostate cancer, and immunotherapy does not have an effect on these parameters. Since oncologists are generally the lead persons in many Big Pharma cancer business development divisions, and immunologists are some layers below, it is also important that immunologists are having an increasing say in the changing landscape for cancer treatment. This also allows immunologists to move up the ladder in the business development hierarchy, which could increase deal making in the immunotherapy space in the future. At the very least, an increasing understanding of the science, especially by oncologists, with the help of immunologists will be beneficial for the space.

Reiner Laus: I think it is fair to say that the only thing that's really seen as a significant advance in the Phase III setting is ipilimumab. In the past, there have been too many interesting approaches and promising data in early studies that didn’t hold up in later studies. So I think people are looking for more definitive studies rather than interesting pilot studies.

But there are a significant number of cancer vaccine programs in late-stage development and while not all of them will be successful, some of them will. As somebody who believes that the field has a great future, I think we’re going to continue to see immunotherapy successes. It may be a bold statement, but I truly believe that cancer immunotherapies will replace conventional therapies. It’s just that the time scale is clearly slower than one would have wished.

It may take 10 or more years before we have a large number of immunotherapies that are standard of care, but if you look at the class properties such as the side effect profile, I think there is no doubt that the main pressure points will be conventional therapies. If a patient has prostate cancer and is offered choices such as hormonal therapy, which is just a gentle word for chemical castration, or chemotherapy that makes you vomit, lose your hair, and increase your risk for infection, would you chose those options over a cancer vaccine? I think from a patient perspective there is no doubt that the immunotherapy drug class has great advantages.

Andrew T. Parsa: The confirmatory data coming from the first line study of ipilimumab is extremely exciting and the potential now to take advantage of ipilimumab’s mechanism of action in combining with other agents is also highly promising. I also think the progress reported with autologous cancer vaccines is an important highlight, as it seems a number of the set backs and gaps in knowledge experienced a number of years ago are being overcome. I have seen this personally as an investigator studying autologous HSPPC-96 where lessons from past clinical trials in other indications are being used to optimize patient selection and study designs in glioblastoma. I think this is being done across the cancer vaccine field in general, which is why I expect more success stories similar to Provenge over the next 3 to 5 years.

Thomas Davis: There certainly was a litany of other clinical data presented in gliomas and glioblastomas, some very interesting data with vaccines in recurrent setting. Andrew Parsa’s
data with HSPPC-96 is interesting in the recurrent disease setting where they appear to see a benefit, but it’s all fairly early data.

David Berd: The melanoma area was dominated by the biology of BRAF and now several drugs or small molecules that inhibit cells with BRAF point mutations. That’s what really overwhelmed all of the other melanoma presentations and was by far the greatest interest. There was the plenary session regarding Yervoy, but the majority of attention was focused on the BRAF story. As a result, ASCO was not really an immunotherapy meeting for melanoma.

I didn’t get a chance to see the HSPPC-96 data at ASCO, but I was told that they had some glioma data that was interesting.

Mark W. Frohlich: If one considers ipilimumab to be an “active” immunotherapy, the most promising news presented at this ASCO was the 2.1 months OS benefit of ipilimumab plus dacarbazine compared with dacarbazine alone in treatment-naïve patients with unresectable stage IIIc/IV metastatic melanoma.

There were several presentations of data from the Phase III sipuleucel-T trials which provided additional insights into its risk/benefit profile. First, the potential effect of patients on the control arms crossing-over to active cellular immunotherapy in the Phase III trials was explored (Gomella et al). Using statistical models that adjusted for differences in prognostic factors near the time of disease progression, a strong treatment effect for the salvage product was observed, suggesting that cross-over may have prolonged the survival of patients on the control arm. While definitive conclusions cannot be made in the absence of a randomized comparision, this analysis raises the possibility that the true benefit of sipuleucel-T may be greater than that observed in the trials. A second presentation provided evidence for a potential effect on a clinically relevant endpoint proximal to overall survival. Specifically, the analyses demonstrated a trend towards a delay in time to disease related pain, originally a co-primary endpoint in the pivotal IMPACT study and a secondary endpoint in the other two Phase III studies in metastatic castrate resistant prostate cancer (Small et al). The delayed onset of the pain endpoint relative to the progression endpoint may contribute to the differential effects on these endpoints. A third presentation (Beer et al) demonstrated that quality of life was maintained relative to controls in patients receiving sipuleucel-T in a randomized trial in men with non-metastatic androgen dependent prostate cancer. (These patients did not have metastatic disease and therefore did not have disease related symptoms, except for the toxicities of androgen deprivation therapy.)
To date, biotechnology companies have successfully commercialized autologous therapies without the benefit of a stronger or more established commercial partner (e.g., Dendreon with Provenge, Genzyme with Carticel®). Despite the fact that twice as many non-autologous active immunotherapies have failed in clinical trials, larger pharmaceutical companies appear to prefer non-autologous approaches. What new information was presented at ASCO that supports one or the other approach (autologous versus non-autologous)?

Jianda Yuan: Dr. Shapira-Frommer presented her talk entitled “Adoptive transfer of short-term cultured tumor-infiltrating lymphocytes (young TIL) in metastatic melanoma patient”. (Abstract #8510). Her study showed that the Young TIL could be an alternative approach to improve the autologous therapy. Dr. Paul Robbins also discussed their study of adoptive immunotherapy of synovial-cell sarcoma targeting cancer / Testis antigens as it was published in Journal of Clinical Oncology, in March of this year. Both supported autologous therapies.

With regard to peptide vaccines, long peptides might be a better approach, as it induces multiple CD4 and CD8 T cell response or other immune responses. Dr. Cornelis Melief’s group showed vaccination with a synthetic long-peptide vaccine against the HPV-16 oncoproteins E6 and E7 included clinical response in women with HPV-16-positive, grade 3 vulvar intraepithelial neoplasia. (N Engl J Med. 2009 Nov 5;361(19):1838-47.) Their study suggested that long peptide vaccination was effective in this disease setting. However the selection of antigens, peptides, length of peptide, and adjuvant could influence the immunologic and clinical responses. Future clinical trials need to address these questions.

Liz Bromley: I can see why larger drug companies might not want to get into cell transfer therapies—it requires expansion into new areas of expertise for them. They just want to license and market drugs, not worry about manufacture of autologous vaccines that require cell culture facilities, etc. I think it’s had less to do with the likelihood of success and more about needing a higher activation energy to get into the field. Without any autologous therapies approved or successfully marketed, there has been more trepidation within Big Pharma. If Provenge starts making money, they will come around. Big Pharma doesn’t innovate. It’s too risky. But if the seeds of profit are sowed by someone else, you can bet they’ll climb aboard the autologous therapy train.

John M. Kirkwood: Most of these have not used current optimal adjuvant agents such as TLR agonists, nor have they used the most current approaches to polarization of the DC/APC system. The recent publication of the significant enhancement of established immunotherapy with IL-2 and gp100 has yet to be squared with the negative impact of gp100 in combination with ipilimumab, and the lack of evaluation of immune responses to gp100 in each of these combinations is a deficiency of the trial designs.

James L. Gulley: Some data presented at ASCO on Prostvac (intraprostatic vaccine) suggesting a novel strategy of directly injecting tumor cells with a vector that contains foreign antigens and multiple co-stimulatory molecules. This was found to be safe and feasible with a substantial increase in both CD4 and CD8 infiltrate within the prostate post-vaccine. Two other abstracts reviewed data from a multi-center randomized study of PANVAC in patients with metastatic CRC.
who had been surgically rendered NED. In this study, there was good immune responses but the startling data was the dramatic improvement in OS compared with a contemporary control group.

**Joseph Pantginis:** Just prior to ASCO, positive data with the peptide vaccine gp100 was published in the *New England Journal of Medicine*, which also lent support to the simplistic peptide approach versus an autologous approach. Overall, however, we believe the jury is still out with regard to which approach will ultimately win and will be based on a case by case basis based on many of the parameters listed in Question 5 (tumor stage, disease burden etc). From a Big Pharma standpoint, we believe the sheer logistics of an autologous process, disease specificity and high costs deem the technology prohibitive to an industry used to small molecule “pill” approaches. This goes against though the mainstream push for “personalized” medicines. We believe Big Pharma would be most interested in products, i.e. off the shelf, that could be applicable to more than one tumor type such as NeuVax, Stimuvax, and also potentially the whole cell approaches, which are not patient specific, such as GVAX.

**George E. Peoples:** Autologous cell therapies present a huge FDA challenge that many Big Pharmas are not ready to assume. In fact, cell therapies in general are challenging. Given the choice between non-cell-based approaches to cell-based strategies, I think the Big Pharmas will choose non-cell-based every time despite Provenge’s success.

**Reni Benjamin:** I didn’t see anything of this year’s ASCO that necessarily highlighted one way or the other and I wouldn’t be bold enough to make the call as to which one will eventually succeed. The only way to legitimately answer the autologous versus non-autologous debate is with Phase III clinical data. The bottom line is that Provenge is an autologous product that succeeded in Phase III. We have yet to see an allogeneic product that is cell-based or viral-based show positive Phase III data yet.

From a monetary point of view and from a health care cost point of view, obviously allogeneic would be a lot better. It would be cheaper to manufacture and therefore should lead to lower prices for the therapy.

I think what’s holding back the majority of the Big Pharma companies based on talking with people in the business development arena is the manufacturing and production of autologous products. This is not something that Big Pharma is used to. However, if Dendreon is able to meet their end-year numbers and is able to scale up efficiently and make this model work, I just don’t see how Big Pharma can ignore this type of revenue stream with the patent cliff staring at them in the face.

**Michael Novod:** So far, the launch of Provenge has been promising and demand for the vaccine is solid across most parts of the USA. The drug is being reimbursed by the majority of the regional 15 Medicare divisions (14 in total) and big HMOs such as Aetna and Blue Cross also provide full reimbursement according to the label of the drug. Furthermore, the initial decision by Medicare (CMS) has been positive with regards to reimbursement. The final Medicare reimbursement decision will be announced by June 30, 2011, and we expect it to be positive, identical with the draft decision. Most sites in the USA administering Provenge have long waiting lists (to our knowledge based on quarterly conference calls, up to 3,000 patients in total), but Dendreon does not have sufficient capacity to cover this yet. This means that Dendreon has not done much on the marketing side to generate demand; it is largely market-
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driven. For 2010, Provenge generated revenue of USD $48 million and for 2011, as much as USD $350-400 million has been issued as guidance. With this traction in sales, 2012 revenue from Provenge is likely to reach USD $1 billion-plus just two and a half years after launch, which we find impressive. According to the KOLs we talked to at ASCO, patients really like the drug, given the benign side-effect profile, but education is needed to inform the patients what to expect (no PSA declines and no tumor shrinkage, but increase in overall survival).

**Reiner Laus:** I think the lack of large pharmaceutical company support for autologous approaches clearly complicates the development of some cancer immunotherapies. If you have to run a Phase III program and need money for it, or you want to commercialize a product, Big Pharma could be an asset by adding those development dollars. Also, there is the fact that Big Pharma partnerships frequently have been seen as validation of certain technologies. Right now, Big Pharma validation for autologous approaches is missing. However, I still believe that the key doubt is really more around the mode of action for immunotherapy rather than the autologous aspect. If you look at the history with rituximab, it worked just like the other drugs that oncologists were used to seeing. There were decreases in the tumor burden that could be measured. So I think it really comes back to questions around mode of action and not having the same short-term effect that conventional therapies have.

Another drawback with autologous products was evidenced at this year’s ASCO meeting. As you can see with ipilimumab, once a product is on the market and you can buy it off the shelf, or you can distribute a large number of doses to investigators, there is an enormous wave of secondary development. While Provenge has been commercially available before ipilimumab, there were only a dozen or so abstracts related to Provenge at ASCO 2011 compared to 290 for ipilimumab. The big disparity between secondary ipilimumab studies and secondary Provenge studies is simply due to the lack of access for the autologous product in view of constraints in meeting commercial demand.

But right now, the only approved active immunotherapy product is Provenge and it is very important because it’s a proof-of-concept for the field. In terms of cost structure, a lot has been made of the $93,000 price tag, but ipilimumab isn’t any cheaper. So I think there is nothing terribly wrong with having an autologous product. I just think there are additional hurdles for autologous products. They are more difficult to make, more difficult to scale, more difficult to distribute, and very expensive to make. So there are a lot of class drawbacks, but if they are effective, they can be quite useful and there is a market for such programs.

**Andrew T. Parsa:** In looking at the landscape of different cancer vaccines in development, many of them presenting data at ASCO, it is evident that a strong scientific rationale continues to compel companies to develop autologous cancer vaccine approaches. It is the strong biological rationale that scientifically persuaded me to study an autologous vaccine in the setting of glioma. That said, it is important to highlight that autologous cancer vaccines come in many different formats and not all of them carry the same level of complexity. I have been the lead investigator on a trial of HSPPC-96 in glioblastoma which is an autologous vaccine, but this is a protein preparation for intra dermal injection, not a cellular therapy for infusion. The protein is extracted from the tumor tissue that is removed as part of standard surgical procedure so it does not require any procedures that are out of routine practice. From my perspective it is not much different than an off-the-shelf product.

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Thomas Davis: It’s pretty clear that autologous approaches are the best current technology based on the Provenge data and what we’ve learned about an individual’s immune system - that they are quite unique and you can’t just take an off-the-shelf vaccine, at least not the ones people have used, and expect it to function in a lot of different people.

However, at ASCO there was increasing data and a general trend that you can impact individuals using off-the-shelf products. There’s an increasing trend towards intratumoral injections and also vaccine technologies that target the tumor using viral vectors where you can effectively create an autologous therapy using a non-patient specific immune approach. I think there will be a trend in that direction because autologous therapies are quite labor-intensive. Big Pharma is likely sitting on the sidelines waiting for this next wave of individually targeted vaccines to prove themselves effective.

Sanjiv S. Agarwala: I am biased towards non-autologous approaches for a couple of reasons. The approaches in melanoma that have been most successful have been non-autologous. They have been general, broad immune stimulation, or they have been allogeneic-type approaches.

The other reason I don’t like autologous approaches is that they are just too cumbersome. In the case of melanoma, they are also difficult, unreliable, and invasive. If the product is tumor-derived, you have to subject the patient to a surgical procedure and not everybody wants to go through that or is a candidate for that.

David Berd: As far as Big Pharma is concerned, not much has changed and they are going for technologies that they feel comfortable with. Ipilimumab is basically a drug that fits in perfectly with what Big Pharma has been doing for a long time, so it’s not a big deal for Bristol to pick up ipilimumab. Targeted agents like the BRAF inhibitors are also traditional drugs. I don’t think Big Pharma has changed and will suddenly take a risk on some of these technically difficult, autologous approaches.

Mark W. Frohlich: Data presented at ASCO provided support for both approaches as evidenced by the success of both Provenge and Yervoy. The benefit of autologous approaches to immunotherapy is the ability to truly personalize each patient’s treatment, with the possibility of a more targeted approach with less toxicity. Activating and loading antigen presenting cells ex vivo also has the advantage of removing the cells from the potentially immunosuppressive host environment.
A dozen active immunotherapy programs have failed in Phase 3 trials. What has been learned from these failures and how has this knowledge been incorporated into current clinical trials as evidenced at ASCO? In particular, proper patient identification, stage of disease, tumor burden, etc.

Jianda Yuan: For four Phase III melanoma clinical trials, the major problem is the selection of antigen in the study, neither antigen selected nor the right immunogenic antigen. Whole tumor cells or tumor cell lysates might push the immune system to the wrong direction.

Liz Bromley: One thing that has definitely been learned is that immune therapies need to be evaluated using different criteria and a different timeline. The so-called “Immune-related response criteria” developed by the CRI’s Cancer Immunotherapy Consortium. This was mentioned in Jedd Wolchok’s plenary talk about ipilimumab. Immunotherapies require a longer time to see effect (12 weeks or more) and they may even appear to cause disease progression (including with “new” lesions) before the effect is seen. I noted that the ipilimumab trial did not include any tumor assessment until week 12. This was very smart/sly, because 12 weeks is when an immune effect might be noted but hopefully after the time period when the tumor might appear to show progression (from lymphocyte infiltration or whatever other reasons there may be). Also, it is clear that, in the case of ipilimumab, the immune-related side effects in responders are being handled much better than in earlier trials. They did not see any GI perforations or treatment-related deaths this time around, which is a very good thing to see.

John M. Kirkwood: The failures may relate more to the deficiencies in immunization strategy, and the lack of careful attention to the assessment of the induced immune responses.

James L. Gulley: Data from the PANVAC study mentioned above suggests that picking an earlier patient population with less disease (NED) may show efficacy whereas a later population (second-line gemcitabine failures in pancreatic cancer) shows no activity of this same vaccine.

Joseph Pantginis: Since cancer immunotherapy has so many multiple confounding factors, we believe that previous failures have gone far in helping to define future studies and to understand the intricacies of the various mechanisms of actions at play.

For example, the concept of immune stimulation versus suppression. This is an important broad reaching area of clinical research that needs to be conducted and revolves around monitoring the immune system. The immune system is highly complex with both positive and negative regulators and a patient’s immune “status” could affect their ability to mount an effective response to a vaccine approach.

In addition, the need for biomarkers. As the conduct of clinical trials matures across not only oncology but many indications, one of the key areas of development is the identification of predictive biomarkers. This is the ability to identify patients who would be more likely to respond to therapy prior to receiving it based on a specific profile of the patient. Data would also most likely be accumulated that links these biomarkers and correlates their presence with clinical outcomes.
Not just for immunotherapy, but in the field of oncology as a whole, the cry for randomized Phase II studies also continues to grow in volume. Currently, a large percentage of companies conduct single arm Phase II studies and then, if “positive” design large Phase III’s based on these data without potentially having a sense as to how the therapy would stack up to an active comparator until it’s too late.

Employing adequate clinical endpoints is another lesson from previous failures. After years of cancer immunotherapy physicians pleading their case, the concept of using overall survival has finally sunk in with doctors, investors and the FDA alike. In short, endpoints that have been considered the staple of monitoring a drug’s efficacy, such as RECIST criteria, just do not apply to cancer immunotherapy approaches.

Finally, with regard to patient selection we’ve learned that one of the attractive clinical applications of cancer immunotherapy is its use in earlier stage cancer patients. The overall rationale is that a patient’s immune system is “healthier” and response to a vaccine could potentially provide longer term tumor control through immune surveillance. Unfortunately at this point, for development stage biotechs, moving to earlier stage patients is not necessarily a viable option since the cost of running such studies would be prohibitive based on the great length of time required to conduct such a study.

**George E. Peoples:** I think that the general lessons are first, use vaccines for what they are intended - to prevent disease and not to treat established, end stage metastatic disease. Second, the proper endpoint for a therapeutic vaccine has to be overall survival not tumor response or even progression-free survival. Third, melanoma, especially, metastatic melanoma, is a different disease that does not behave immunologically like any other type of cancer. Finally, that future trials should be run in more indolent diseases.

**Reni Benjamin:** I am with the camp that until we start to publish failed studies and talk about failed studies instead of burying them and only highlighting the success stories, we are doomed to repeat the past. We continue to test hypotheses that have, in my opinion, already been answered.

Pressure from investors can be a factor in why a company pursues trials in late-stage disease to obtain a result earlier and with less capital. But if a company really wants to do the right study in earlier stage patients, they should work very hard to find the investors who are willing to take that long term bet or find a partner who’s going to put money into the product to take the long term bet. Unfortunately, investors in general tend to have shorter timelines with regard to seeking a return on their investment. But you have cooperative groups and Big Pharma partners that run multi-year studies. I think that at some point you have to work hard in getting the product approved as opposed to trying to spend less money or answering a question quickly.

Another history lesson that is often ignored is the use of single arm Phase II studies. In Phase II trials, the only reason that you would want to run a single arm study in this day and age is because you are capital constrained and you need to have more data in order to potentially secure additional investment from investors or get a Big Pharma partner involved. The question of running a 50 patient single arm study versus a 100 patient randomized study comes down to cost. The company knows the randomized trial will cost twice as much and perhaps doesn’t have the cash to do it or investors who are willing to fund the trial. But a corporate partner will
want to know how the drug compares to a control – in addition, the data helps you design a better Phase III trial.

Dirk Jäger: Surprisingly, patients entering immunotherapy trials are selected based on a histomorphological diagnosis, no immunological parameters were assessed. I believe we need to better characterize patients (assess preexisting immunity, local milieu, etc.) to be more effective in a better selected patient population.

Larry W. Kwak: There were tons of failures in the field of monoclonal antibodies, but now that nearly a dozen have been approved for cancer therapy people tend to forget about the early history. This is likely the same with cancer vaccines - there were failures in the beginning, but now that you have several approved products people are going to forget about them pretty quickly.

In the case of three cancer vaccines for lymphoma, key differences in terms of induction therapy, eligibility of the patients and method of idioype production may account for the disparate results in Phase III trials that have been completed to date. First, only patients who achieved complete remission were randomized in the BiovaxID clinical trial whereas MyVax trial included patients in partial response and the Mitumprotimub-t trial included patients in partial and stable disease. Moreover, the choice of a doxorubicin-containing chemotherapy regimen likely resulted in a higher proportion of patients achieving complete remission in the BiovaxID trial. Results from these trials suggest that a minimal residual disease state may be required for the vaccine induced immune responses to be effective. Second, BiovaxID was prepared by heterohybridoma method whereas MyVax and Mitumprotimub-t are recombinant proteins suggesting that the immunogenicity of the idioype vaccines may be different between the different formulations. Finally, it is possible that B-cell depletion, resulting from the use of rituximab in the Mitumprotimub-t trial, may have had a deleterious effect on subsequent vaccine efficacy. Taken together, we speculate that minimal residual disease status, as exemplified by complete clinical remission, appears to be necessary for the clinical anti-tumor effect of idioype vaccines, as demonstrated by the success of BiovaxID in a pivotal Phase III trial.

In the case of cancer vaccines trials for other tumor types that have failed, those were either study design flaws, such as putting cancer vaccines in the setting of advanced tumors where they are not likely to be active, or the products are undefined (crude extracts) of cell lines such as an early melanoma vaccine for example that failed. So there is a lot of very plausible scientific reasons why these other trials failed. And I think those were the answers.

Reiner Laus: If you look at why many immunotherapies have failed, one of my favorite explanations is that many studies were just not very well designed. They were done on a low budget by smaller biotech companies that had little time and money, but needed a Phase III program to attract investors and I think this damaged the field. There were a lot of studies that went into Phase III without a valid hypothesis and then failed. It is very important to have a solid Phase III hypothesis that is based on a randomized placebo controlled study with the same end point and in the same population.

This why I think we are in a good situation with Prostvac because the company is basing its pivotal Phase III trial on the success of a randomized, placebo controlled Phase II study. In addition, our randomized Phase II was about as big as the early Provenge Phase III study.
**Andrew T. Parsa:** There has been a long and steep learning curve with active immunotherapy development, but now all of that experience and general knowledge that has flooded the field with respect to cancer immunology is translating into the advancement of important new treatments. A good illustration of this is the GSK MAGE-A3 trials in NSCLC and melanoma. With respect to patient selection they are including only those patients who over express MAGE-A3, so they are using a molecular classifier to select patients. Additionally, the vaccine is being used in the adjuvant setting where patients have been rendered disease free by surgery, which makes for a better prognosis patient population and likely a population that could be more responsive.

**Thomas Davis:** There’s definitely a greater emphasis on randomized studies as early as possible, but you almost invariably need to start out with some single-arm data just to see what happens. A relevant example is found in a recent cell based therapy whose single arm Phase I data are frequently presented. This study did specifically enroll very favorable patients who had not progressed in the 6 to 12 months between diagnosis and vaccination. While the planned randomized Phase II study is a critical next step, the Phase I data from the heterogeneous and highly favorable population provides little relevant data for design of the randomized trial. We’ll have to see what the happens, but there is a key lesson that the design of even the earliest stage trials must provide useful information for the design of later stage randomized studies.

In general, people have learned that you need to come up with the most reliable data you can. We, of course, only have single arm data right now. But with a fairly detailed analysis of what to expect from the historical controls, we’re pretty confident of the general range that we would see as we head into Phase III and can make the design appropriate.

There is also a lot of discussion regarding the fact that immunotherapies may take six months to demonstrate an effect and that some of the past failures are due to testing these therapies in patients with rapidly progressing disease, but I personally feel we’re selling immunotherapy short. There are many examples where you can get dramatic and very rapid effects with an appropriate immunotherapy. No one has been able to reliably reproduce that with much of our technologies, which I think attests more to the fact that our technologies aren’t aggressive enough at this point. Instead of sitting back and only looking for very subtle effects, we should be choosing to make more aggressive immunotherapies, either through combinations or specific products that may have a more potent effect. At Celldex, we’re very focused on pursuing those combinations and hope to be able to present data within the next several years looking at combinations of different products that should synergize together. The information that we have today suggests that the effects are somewhat modest with immunotherapies and that waiting a lot of time in clinical trials may unearth an effect that you wouldn’t see over shorter time periods. But there’s every reason to think that the old RECIST (Response Evaluation Criteria In Solid Tumors) criteria is still relevant with immunotherapy; you’re just going to need to have a more potent treatment in order to achieve that.

**Sanjiv S. Agarwala:** That’s a great question and I don’t know that we have learned things enough to be able to understand why some trials are positive and some are negative. In melanoma, many of the trials had good biology behind them and if you look at the laboratory preclinical work, it all looked very promising. So I think that’s a bit of an unknown at this point in time.

What seems to be happening now is that the non-specific immunotherapies that hit the immune system in a broader way like IL-2, interferon, ipilimumab, and perhaps Allovecitn-7 in
the future, tend to be a little bit more successful. All the other ones that have failed, like the ganglioside vaccine, tend to be vaccines that have like focused on a few antigens, so maybe that’s the reason, but we don’t really know for sure.

**Mark W. Frohlich:** Recent experience has taught us that overall survival is currently the best endpoint for immunotherapies. In addition, we have learned that immunotherapies can be successful in patients with advanced disease, but the patient population should have an anticipated survival that is long enough to benefit from the potentially delayed onset of action of immunotherapy. It also appears that within a particular patient population, selecting for those patients with more indolent disease may be advantageous. The Phase 3 Prostvac trial appears to be taking these lessons into consideration, with eligibility criteria that exclude patients with rapidly progressive disease or high tumor burdens. The planned label expansion trial of Provenge in men with metastatic androgen dependent disease will explore whether there will be a greater treatment effect in a patient population with a longer natural history (median survival approximately 5 years compared to approximately 2 years for men with metastatic castrate resistant prostate cancer). The primary endpoints for both these trials are overall survival.
Biomarkers to identify likely responders to cancer immunotherapy, to provide predictive signals to a patient’s likely clinical outcome following immunotherapy, and to help guide the development of appropriate surrogate endpoints are increasingly important to development of this new class of therapies. What news about such biomarkers came out recently?

Jianda Yuan: Dr. Jeffery Weber presented their recent study of predictive markers of ipilimumab on melanoma patients’ T cells (abstract # 2503). They suggested that some transcript factor such as eomesodermin (EOMES) on CD8 T cells might correlate with clinical response. Immune related adverse events (irAEs) are the most common side effect associated with ipilimumab. Grade III/IV irAE occur in approximately 10-15% of treated patients and colitis is the most common irAE within this group. Dr. Maggie Callahan gave an oral presentation entitled “Evaluation of serum IL-17 levels during ipilimumab therapy: correlation with colitis (abstract: 2505).” Her data suggest that fluctuations in serum IL-17 are significantly correlated with the development and resolution of colitis in ipilimumab-treated patients.

Liz Bromley: I went to a few biomarker talks and was disappointed. There just doesn’t seem to be much progress on this. I think it is helpful to expand our definition of biomarkers to include not just genes or proteins that are expressed under certain conditions (i.e. disease and progression), but also pathological markers and other indicators. It’s tough, though. I don’t think we can pin our hopes on a panel of specific biomarkers being discovered for each indication that will magically illuminate the path of treatment. There’s just too much luck and detective work involved in finding each one and no shotgun approach to finding enough of them.

John M. Kirkwood: Multiple original presentations as well as educational sessions focused upon the importance of biomarkers of response to the tailoring of immunotherapy to the most responsive subpopulations. The neoadjuvant studies of ipilimumab presented in poster discussion reveal that MDSC as well as T-REG populations may need to be analyzed in relation to this new agent.

James L. Gulley: We are still looking for the best biomarker. I’m not sure if it will be vaccine specific or if there will be one marker that can be used for multiple types of therapies. One possible biomarker suggested in a poster discussion session is tumor growth rates which may eventually slow down following treatment with immunotherapy. This can be found at: http://tumorgrowthanalyses.com

Joseph Pantginis: The biomarker field is also still in its infancy and there is currently no clear road especially based on the wide variety of antigens and approaches. One major point that we took away from a leading physician on the NeuVax study was using the simplistic approach of the tried and true DTH test, which is a very important tell for immunity and signs that the vaccine has “taken hold”.

Michael Novod: To be able to monitor the efficacy of immunotherapy in the absence of PSA declines and tumor shrinkage, there is a dire need for biomarkers to evaluate progression. Currently, it is difficult for doctors to monitor efficacy with immunotherapies and to know when to sequence patients to the next therapy, as there are no valid signals of improvement.
At ASCO, in late breaking abstracts and at scientific sessions we attended, data was presented demonstrating the potential of circulating tumor cells (CTC) as a biomarker for metastatic prostate cancer progression, which could be very useful not only in clinical trials but also in real life practice. If validated, CTCs could be a new clinical endpoint and a potential surrogate for overall survival.

Results at ASCO of a randomized study “Evaluation of circulating tumour cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration resistant prostate cancer (mCRPC)” indicated that pre-treatment, CTCs and lactate dehydrogenase (LDH), both alone and in combination, were prognostic biomarkers, while baseline prostate-specific antigen (PSA) was not. Following the start of treatment, CTC counts were measured at four, eight and 12 weeks. The data suggests that changes in CTC counts can predict overall survival during treatment. Data also indicated LDH was strongly associated with survival. As there is no impact on PSA from immunotherapy such as Provenge and Prostvac in CRPC, circulating tumor cells could be very important in future treatment and the sequencing of prostate cancer therapy.

**Larry W. Kwak:** I think you have potentially two biomarkers that emerge from the BiovaxID trial that was published in the *Journal of Clinical Oncology* during the week of ASCO. The first is selection for minimal residual disease, as exemplified by complete clinical remission, which appears to be necessary for the clinical anti-tumor effect of idiotype vaccines. The second biomarker, which needs to be confirmed in subsequent studies, is the IgM isotype. In addition to strengthening the clinical evidence for the efficacy of BiovaxID, the IgM data likely explain why prior lymphoma vaccine clinical trials, such as those by Favrille, Inc. and Genitope Corporation failed, as those vaccines universally employed IgG isotype. These results expand the industry’s knowledge in the field of cancer vaccines by demonstrating that cancer vaccine isotype profoundly impacts vaccination outcomes.

**Reiner Laus:** If you look at what GlaxoSmithKline is doing with their lung cancer vaccine, they are taking a large-scale genomic approach looking at molecular markers for successful immunizations. If their study is positive and there is a significant improvement in overall survival, they might be able to correlate various gene expression patterns and determine who will benefit from the therapy. Some of that early data looked attractive, but we'll see whether or not it holds up in the Phase III studies.

Right now, there are no other large Phase III trials that have concluded successfully, so for the time being there is a gap where we can't tell whether or not the patient has benefitted. I think we'll learn much more about that over the next year.

**Andrew T. Parsa:** The biomarker discovery and characterization process is one of tremendous complexity where a lot of markers and data are being generated yet we are still trying to figure out what it all means. With some of the small molecules/targeted agents, there has been some reasonable success with identifying and validating biomarker targets which classify patients such as KRAS and BRAF. Finding such definitive predictive markers for assessing active immunotherapies is much more difficult.

There were a number of abstracts reporting on the involvement of PTEN and how loss of PTEN function may predict sensitivity to drugs targeting the PI3K/mTOR pathway. Alternatively, the loss of PTEN may also lead to an immunoresistant phenotype that could dampen or hinder an
active immunotherapy approach. There is still much to be learned regarding the relevance of this marker as potentially predictive and hopefully future ASCO meetings will provided further knowledge.

**Thomas Davis:** There’s an increasing understanding of the different cell types within an immune response, and increasing emphasis on looking at tumor tissue to determine the immunoreactivity of that individual tumor. Based on infiltrating lymphocytes, T regulatory cells, etc., I think more and more we’re getting a picture of what they could mean for the individual patient, and that may be a good way to select for those who would be amenable to immunotherapy. As always, it’s not a simple answer. There are some situations where greater immune infiltration into a tumor can portend a worse prognosis as well as a better prognosis, so we still have a ways to go to clearly understand it.

I think we’re still at a fairly early stage in biomarkers for immunotherapy and immune response assays have not necessarily progressed a great deal in recent years. We still don’t really know what many of the immune targets are for drugs like ipilimumab. So, there’s plenty of opportunity for further improvement there.

**Sanjiv S. Agarwala:** I looking at biomarkers in two distinct settings. The first is a biomarker or some kind of indicator that the treatment is actually working, which is a post-treatment biomarker. You are looking at clinical benefit in terms of like response or shrinkage or PSA declines in prostate cancer.

The second, and what we’re lacking in melanoma specifically and with Provenge in prostate cancer as well is a pretreatment biomarker. Instead of giving ipilimumab at a cost of $120,000 to every melanoma patient and only getting a clinical benefit in 10 percent of patients, what we need to know is who are the 90 percent of people that should not receive the treatment, which would reduce healthcare expenses. And that doesn't exist right now.

So I consider the most valuable biomarker a predictive biomarker for benefit, whether it’s response, survival, etc. Because none of these treatments are cheap or non-toxic and I want to spare my patients the toxicity and the expense.

**David Berd:** With regard to biomarker development, it’s actually going in a funny direction - choosing people who would respond to therapy by molecular profiling of tumors, which is not traditionally what people mean by biomarkers. For example, in the case of BRAF where people need to have tumors with the mutation in order for a drug to work and if they don’t there is zero effectiveness.

Circulating tumor cells are making their tenth comeback since 1970 because a couple of companies have a new message and they are pushing it really hard. The newer tests are more sophisticated where you need high level of cell separation plus cytometry. It’s getting a lot of attention, but I don’t know if it’s going to make it to prime time, as the results to me look very similar to the results from 1970 by doing it the old way.

**Mark W. Frohlich:** While greater acceptance of an overall survival benefit independent of a measurable anti-tumor effect was expressed in this meeting, so was the increasing difficulty of reaching the gold standard endpoint of overall survival. As more agents are approved for each disease, crossover to multiple subsequent therapies will become standard, making it more difficult to demonstrate an effect on overall survival. In prostate cancer this is particularly
challenging because disease progression and PSA have not proven to be reliable surrogates for overall survival. Establishing new surrogate markers will be important to reduce drug development timelines. At this meeting, changes in circulating tumor cells (CTCs) in a large prostate cancer trial were shown to correlate with overall survival outcome. While these are encouraging data, it is likely that for immunotherapies we will not see the same acute reductions in CTCs that are evident with cytoreductive treatments like chemotherapy or hormonal therapy. Different methods of evaluating CTCs, e.g. changes in the rate of increase over time, or the time to reaching a particular CTC threshold may be required for active immunotherapies.

Other predictive markers of response that were presented at ASCO include genomic signatures (e.g., PTEN loss), circulating levels of cytokines and alkaline phosphatase normalization. Also, PSA recurrence-free survival was shown to be reduced in patients with higher numbers of FOXP3-positive T-regulatory cells. All of these observations may be functionally relevant but will require further validation.
# Appendix A: 40 Cancer Immunotherapies in 60 Clinical Trials

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<th>Company</th>
<th>Product(s)</th>
<th>Partner</th>
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<th>ClinicalTrials.gov Identifier</th>
<th>Disease(s)</th>
<th>Autologous (Y/N)</th>
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<td>Yes</td>
<td>DC</td>
<td>Patient’s DCs are transfected with their own tumor RNA and then reintroduced</td>
</tr>
<tr>
<td>Avax (AVXT.PK)</td>
<td>MVAX LUNGVAX OVAX</td>
<td>Ph I/II</td>
<td>Ph I/II</td>
<td>NCT00477906* NCT00298289* NCT00660101</td>
<td>Melanoma NSCLC Ovarian</td>
<td>Yes</td>
<td>Cellular</td>
<td>Whole tumor cells are isolated and the antigens are chemically modified by haptenization prior to reintroduction</td>
</tr>
<tr>
<td>Bavarian Nordic A/S (OMX: BAVA)</td>
<td>PROSTVAC PROSTVAC MVA-BN PRO MVA-BN HER2</td>
<td>NCI</td>
<td></td>
<td>NCT01322490 NCT00450463 NCT00629057 NCT01152398</td>
<td>Prostate Prostate Prostate Breast</td>
<td>No</td>
<td>Gene Transfer</td>
<td>PROSTVAC uses two different poxviruses that each encode PSA plus three co-stimulatory molecules</td>
</tr>
<tr>
<td>BioSante (BPAX)</td>
<td>GVAX</td>
<td>Ph II</td>
<td>Ph II</td>
<td>NCT00727441 NCT00426205</td>
<td>Pancreatic AML</td>
<td>No</td>
<td>Cellular</td>
<td>Whole tumor cell lines are isolated and engineered to secrete GM-CSF</td>
</tr>
<tr>
<td>BioVest International (OTCGB: BVTI)</td>
<td>BiovaxID</td>
<td>Ph III</td>
<td></td>
<td>NCT00091676</td>
<td>NHL</td>
<td>Yes</td>
<td>Peptide</td>
<td>Purified peptides from each patient are coupled with GM-CSF and KLH</td>
</tr>
<tr>
<td>Cel-Sci (CVM)</td>
<td>Multikine</td>
<td>Teva</td>
<td>Ph III</td>
<td>NCT01265849</td>
<td>Head and Neck</td>
<td>No</td>
<td>Peptide</td>
<td>Mixture of interleukins, interferons, chemokines, and colony-stimulating factors that simulate the body’s immune response</td>
</tr>
<tr>
<td>CellDex Therap (CLDX)</td>
<td>CDX-110</td>
<td>Ph II</td>
<td>Ph I/II</td>
<td>NCT00458601 NCT00626015</td>
<td>Glioblastoma</td>
<td>No</td>
<td>Peptide</td>
<td>Peptide targeting EGFRVIII with KLH</td>
</tr>
<tr>
<td>Dendreon Corp. (DNDN)</td>
<td>DN24-02</td>
<td>Ph II</td>
<td></td>
<td>NCT01353222</td>
<td>Bladder</td>
<td>Yes</td>
<td>DC</td>
<td>DCs co-cultured with a recombinant fusion protein of HER2/neu and GM-CSF</td>
</tr>
<tr>
<td>Generex Biotech (GNBT)</td>
<td>AE37</td>
<td>Ph II</td>
<td></td>
<td>NCT00524277</td>
<td>Breast</td>
<td>No</td>
<td>Peptide</td>
<td>Peptide targeting li-Key/HER2/ neu</td>
</tr>
<tr>
<td>Geron Corp. (GERN)</td>
<td>GRNVAC1</td>
<td>Ph II</td>
<td></td>
<td>NCT00510133</td>
<td>AML</td>
<td>Yes</td>
<td>DC</td>
<td>DCs pulsed with RNA for hTERT and LAMP</td>
</tr>
<tr>
<td>GliaxoSmithKline plc (GSK)</td>
<td>MAGE-A3 ASCI</td>
<td>Ph III</td>
<td>Ph III</td>
<td>NCT00480025 NCT00796445 NCT00706238 NCT00886480 NCT00942162</td>
<td>Lung Melanoma Melanoma Melanoma</td>
<td>No</td>
<td>Peptide</td>
<td>A recombinant fusion protein derived from the melanoma antigen MAGE-3</td>
</tr>
<tr>
<td>Idera Pharma (IDRA)</td>
<td>IMO-2055</td>
<td>Merck KGaA</td>
<td>Ph I</td>
<td>NCT00719199</td>
<td>Colorectal</td>
<td>No</td>
<td>Other</td>
<td>Toll-like Receptor 9 (TLR9) agonist</td>
</tr>
<tr>
<td>Company</td>
<td>Product(s)</td>
<td>Partner</td>
<td>Stage</td>
<td>ClinicalTrials.gov Identifier</td>
<td>Disease(s)</td>
<td>Autologous (Y/N)</td>
<td>Strategy</td>
<td>Description</td>
</tr>
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<tr>
<td>Immatics Biotech (private)</td>
<td>IMA901</td>
<td>Ph III</td>
<td>NCT01265901</td>
<td>Renal</td>
<td>No Peptide</td>
<td>Peptides with multiple antigens from Class I/II TUMAPs</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>IMA910</td>
<td>Ph I/II</td>
<td>NCT00785122</td>
<td>Colorectal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Immunocellular Therap (IMUC.OB)</td>
<td>ICT-107</td>
<td>Ph II</td>
<td>NCT01280552</td>
<td>Glioblastoma</td>
<td>Yes DC</td>
<td>DCs with IM2, Her-2/neu, gp-100, MAGE-1, TRP-2 and IL13Ra2 antigens.</td>
<td></td>
<td></td>
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<tr>
<td>ImmuneP S.A.</td>
<td>IMP321</td>
<td>Ph I/II</td>
<td>NCT01308294</td>
<td>Melanoma</td>
<td>No Peptide</td>
<td>Soluble form of LAG-3 that binds, with high affinity, to MHC class II molecules expressed by dendritic cells and monocytes causing a robust T cell response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inovio Biomedical (INO)</td>
<td>VGX™-3100</td>
<td>Ph I</td>
<td>NCT00685412</td>
<td>Cervical</td>
<td>No Gene Transfer</td>
<td>DNA based vaccines based on commonly expressed antigens and delivered through electroporation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>V934</td>
<td>Ph I</td>
<td>NCT00753415</td>
<td>Multiple</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>V930</td>
<td>Ph I</td>
<td>NCT00647114</td>
<td>Multiple</td>
<td></td>
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<tr>
<td>Juvaris (private)</td>
<td>JVRS-100</td>
<td>Ph I</td>
<td>NCT00860522</td>
<td>Leukemia</td>
<td>No Adjuvant</td>
<td>Induction of innate immunity via stimulation of both toll-like receptors and cytokine interferon induction pathways</td>
<td></td>
<td></td>
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<tr>
<td>MannKind Corp. (MNK)</td>
<td>MKC1106-PP</td>
<td>Ph II</td>
<td>NCT01026051</td>
<td>Melanoma</td>
<td>No Gene Transfer</td>
<td>Peptide with a DNA vector delivering two synthetic peptides (PRAME and PSMA)</td>
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<tr>
<td>Northwest Biotherapeutics Inc. (NWBO,OB)</td>
<td>DCVax</td>
<td>Ph II</td>
<td>NCT0045968</td>
<td>Glioblastoma</td>
<td>Yes DC</td>
<td>DCs extracted from the patient and loaded with tumor lysate/antigens</td>
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<tr>
<td></td>
<td></td>
<td>Ph III</td>
<td>NCT0043212*</td>
<td>Prostate</td>
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<tr>
<td></td>
<td></td>
<td>Ph I</td>
<td>NCT00683241</td>
<td>Ovarian</td>
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<tr>
<td>NovaRx Corp. (private)</td>
<td>Lucanix</td>
<td>Ph III</td>
<td>NCT00676507</td>
<td>Lung</td>
<td>No Cellular</td>
<td>NSCLC cell line with siRNA against TGF-B</td>
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<tr>
<td>Oncothyreon Inc. (ONTY)</td>
<td>Stimuvax</td>
<td>Ph II</td>
<td>NCT01094548</td>
<td>Myeloma</td>
<td>No Peptide</td>
<td>Incorporates a 25-amino acid sequence of the cancer-associated marker MUC-1 in a liposomal formulation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Merck Serono</td>
<td>Ph III</td>
<td>NCT00925548</td>
<td>Breast</td>
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<tr>
<td></td>
<td></td>
<td>Ph I</td>
<td>NCT00409188</td>
<td>Lung</td>
<td></td>
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<tr>
<td>Oxford BioMedica (OXBL)</td>
<td>TroVax</td>
<td>Ph II</td>
<td>NCT01194960</td>
<td>Prostate</td>
<td>No Gene Transfer</td>
<td>ST4-specific therapeutic vaccine delivered via vaccinia virus Ankara</td>
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<tr>
<td>Prima Biomed (PRR.AX)</td>
<td>CVax</td>
<td>Ph II</td>
<td>NCT01068509</td>
<td>Ovarian</td>
<td>Yes DC</td>
<td>DCs primed with MUC-1 and mannan adjuvant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progenics Pharmaceuticals (PGNX)</td>
<td>rsPSMA</td>
<td>Ph I</td>
<td>NCT00705835</td>
<td>Prostate</td>
<td>No Other</td>
<td>Recombinant soluble PSMA protein vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provectus Pharmaceuticals Inc. (PVCT.OB)</td>
<td>PV-10 (rose bengal)</td>
<td>Ph II</td>
<td>NCT00521053</td>
<td>Melanoma</td>
<td>No Other</td>
<td>Intralesional PV-10 is selectively toxic to cancer cells with bystander response in untreated lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantum Immunologics (private)</td>
<td>OFA</td>
<td>Ph I</td>
<td>NCT00715832</td>
<td>Breast</td>
<td>Yes DC</td>
<td>DCs with oncofetal antigen/immature laminin receptor protein (OFA/LRP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph I/II</td>
<td>NCT00879489</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Transgene S.A. (TNG.NX)</td>
<td>TG4010</td>
<td>Novartis</td>
<td>NCT01383148</td>
<td>Lung</td>
<td>No Gene Transfer</td>
<td>Recombinant vaccinia virus expressing MUC-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TVAX Biomedical (private)</td>
<td>TVI-Brain-1</td>
<td>Ph II</td>
<td>NCT01290692</td>
<td>Glioblastoma</td>
<td>Yes Cellular</td>
<td>Radiated tumor cells with GM-CSF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VaxOnco Inc. (private)</td>
<td>Onyvax-P</td>
<td>Ph II</td>
<td>NCT00514072**</td>
<td>Prostate</td>
<td>No Cellular</td>
<td>Combination of inactivated cell lines that are representative of different stages of the disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vical Inc. (VICL)</td>
<td>Allovecin-7</td>
<td>Ph III</td>
<td>NCT00395070</td>
<td>Melanoma</td>
<td>No Gene Transfer</td>
<td>Plasmid/lipid complex containing the DNA sequences encoding HLA-B7 and B2 microglobulin, and directly injected into tumor lesion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Study terminated according to ClinicalTrials.gov ** Status not verified in more than two years
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For ROTH Capital Partners:

ROTH provides research coverage and makes a market for BVTI, RXII, DNDN, CLDX.

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