Avoiding Pitfalls and Encouraging Success with Immuno-Oncology Clinical Trials

CLINIPACE WORLDWIDE

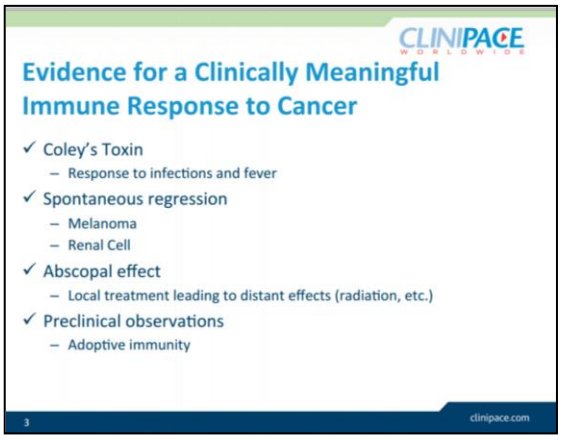
SLIDE 1: Introduction
Speaker: Barb Geiger

Hi everyone and welcome to today's presentation, **Avoiding Pitfalls and Encouraging Success with Immuno-Oncology Clinical Trials**

- Who is Clinipace Worldwide?
  - Clinipace is a digital CRO
  - We pioneered an innovative, technology-amplified CRO service delivery model
  - We serve venture-backed, mid-tier and strategic pharmaceutical, biotechnology and medical device firms
  - Our service is powered by proprietary TEMPO eClinical technology platform and team of experts with extensive knowledge across many therapeutic areas
  - Global headquarters in RTP, additional offices around US and across the globe (EU, Asia, Latin America)
- So what are we going to be talking about today?
  - Clinical and preclinical observations of an immune response to cancer suggest the potential of immune therapies for effective cancer treatment (i.e., immuno-oncology).
  - However, demonstrating the prophylactic or therapeutic effectiveness of immuno-oncology remains challenging.
  - There has been varying success with antigen and non-antigen-specific therapies; however, even when they are successful, side effects can be prohibitive.
  - Perhaps the most promising advancement is the understanding and use of checkpoint inhibitors. These therapies have led to new approaches to vaccines with demonstrated success in the treatment of cancer.
  - Regardless of the underlying mechanism, clinical trials for immuno-oncology must consider the most appropriate study design, including the sample and endpoints, as well as logistic concerns regarding tissue handling and testing.
  - **Experts will be sharing:**
    - History of cancer vaccines
    - Current immuno-oncology development efforts
    - Overview of why immuno-oncology trials typically fail
    - Suggested considerations to make immuno-oncology trials successful
    - FDA guidance for vaccine and immunotherapy trials

SLIDE 2: Introductions

SLIDE 3: Evidence for a Clinically Meaningful Immune Response to Cancer
Speaker: Lee Schacter

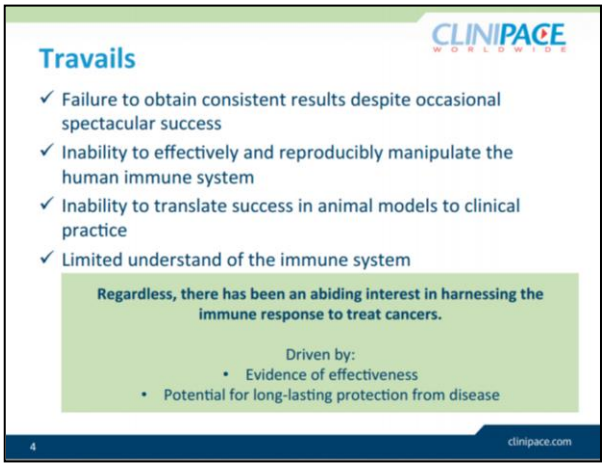


A full review of cancer immunotherapy would require many hundreds of hours. In the time available, I hope you will get an overview and perspective of the field.

Evidence for an immune response to cancer goes back over 100 years, but it is only in the last 10 to 20 years that major progress has been made. Historical evidence includes:

- Coley's toxin
  - Found that local and remote injections of streptococci, and Serratia marcescens as an enhancer, resulted in a response and tumor destruction
  - Used for 45 years, with varying response based on cancer type and patient's response to the infection
  - Indicated that can manipulate the immune system balance to recognize and kill the tumor
- Spontaneous regression
  - Observed that some cancers, such as melanoma and renal cell cancer, spontaneously regress
  - Thought that immune system successfully overcomes the tumor without exogenous help
  - However, a preceding febrile infection has been suggested as a primer for the immune response
- Abscopal effect – can occur with radiation therapy
  - Regression at distant tumor sites following local radiation to a different tumor
  - Indicates systemic immune response
- Preclinical observations
  - Tumor transplantation
    - Cancers could be transmitted by infectious agents, and immunization against these agents was possible
    - In mice, a transplanted tumor graft could stimulat the immune system
    - Inconsistent results, but helped us understand that cancer-specific antigens exist
  - Thoracic duct cells
    - When intravenously administered in mice, provided protection against tumor cells that were later administered
    - Immunological activation of the cells before transfer is likely

SLIDE 4: Travails
Speaker: Lee Schacter

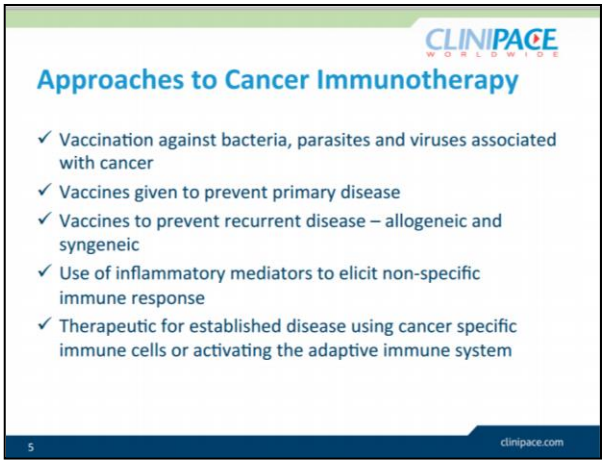


- Failure to obtain consistent results despite occasional spectacular success
- Inability to effectively and reproducibly manipulate the human immune system
- Inability to translate success in animal models to clinical practice
- Limited understand of the immune system
- No true cancer antigens
- Cancer cells too close to normal cells to be recognized by immune system

Regardless there has been an abiding interest in harnessing the immune response to treat cancers. Driven by:

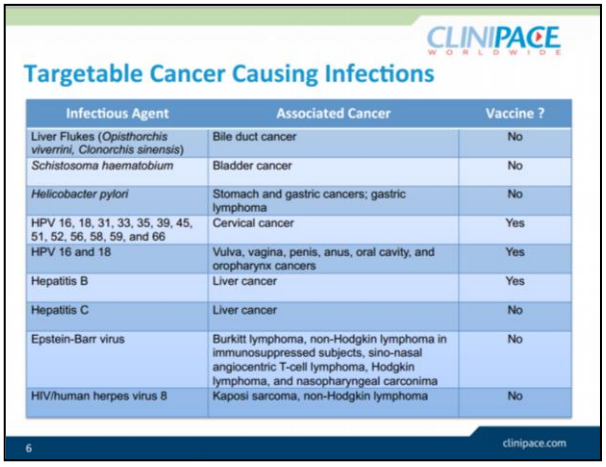
- Evidence of effectiveness
- Potential for long lasting protection from disease

SLIDE 5: Approaches to Cancer Immunotherapy
Speaker: Lee Schacter



- Vaccination against bacteria, parasites and viruses that are associated with cancer
- Vaccines given to prevent primary disease
- Vaccines to prevent recurrent disease – allogeneic and syngeneic
- Use of inflammatory mediators to elicit a non-specific immune response
- Therapeutic for established disease using cancer specific immune cells or activating the adaptive immune system

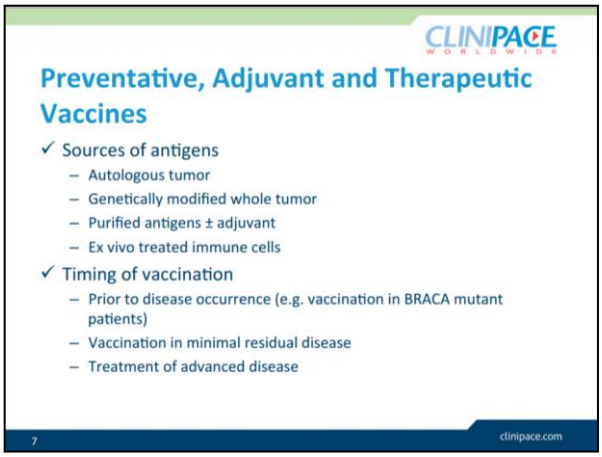
SLIDE 6: Targetable Cancer Causing Infections
Speaker: Lee Schacter



- Cancers linked to infections: ~18% of global cancer burden
- The table provides the primary viral causes of cancer.
- Vaccines are currently only available for HPV and Hepatitis B
- The former are considered successful for prevention of infection and a recent publication in the New England Journal of

Medicine (volume 372: 711-723 2015) shows a 97% risk reduction in high grade neoplasm related to the strains of HPV targeted by a 9 valent vaccine. Hepatitis B vaccine has been in use since 1981, originally for viral hepatitis, but is expected to decrease Hepatitis B-associated hepatocellular carcinoma

SLIDE 7: Preventative, Adjuvant and Therapeutic Vaccines
Speaker: Lee Schacter



- Failure to obtain consistent results despite occasional spectacular success
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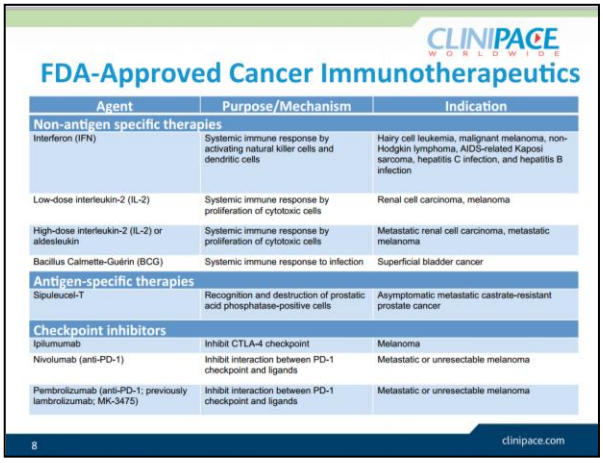
- Limited understand of the immune system
- Regardless there has been an abiding interest in harnessing the immune response to treat cancers
- Driven by:
  - Evidence of effectiveness
  - Potential for long lasting protection from disease
    - Vaccine trials was only 3.8%

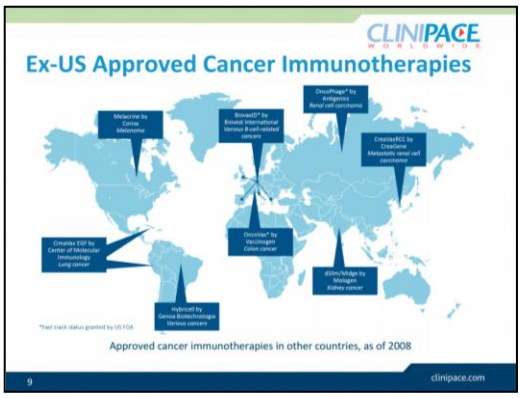
SLIDE 8: FDA-Approved Cancer Immunotherapeutics
Speaker: Lee Schacter



Range from inflammatory cytokines – antigen non-specific to Sipuleucel-T to check point inhibitors:

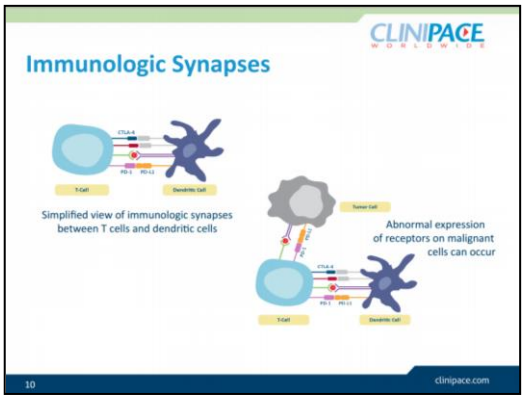
- First cell-based cancer immunotherapy approved by the FDA in 2010
- Asymptomatic metastatic castrate-resistant prostate cancer
- Patient's cells are externally activated by a fusion protein of recombinant GM-CSF and recombinant prostatic acid phosphatase, which is an antigen expressed by prostate cancer cells
- Administered intravenously in 3 doses, activated cells can then recognize and kill PAP-positive prostate cancer cells
- Increases median survival by 4 months and reduces death
- However, cell culture processing required for each patient, which limits number of treatments available
- The parent company, Dendreon has since filed bankruptcy (November 2014)

SLIDE 9: Approved Cancer Immunotherapies (Ex-US)
Speaker: Lee Schacter



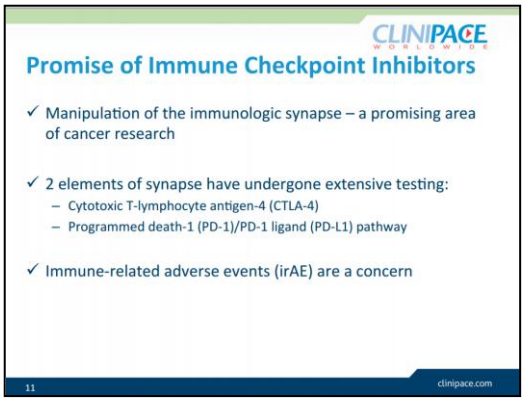
- Potpourri of antigen and other immunotherapies that failed to meet US standards of patient benefit

SLIDE 10: Immunologic Synapses
Speaker: Lee Schacter



- Most promising area of cancer research
- Immune checkpoints prevent excessive activity by T cells under normal conditions
- In cancer, these checkpoint pathways can be modified to inhibit the innate adaptive immunity
- New checkpoint inhibitor agents target signaling between the antigen-presenting cells and T effector cells
  - Change from tolerance of the tumor to targeting of the tumor

SLIDE 11: Promise of Immune Checkpoint Inhibitors
Speaker: Lee Schacter

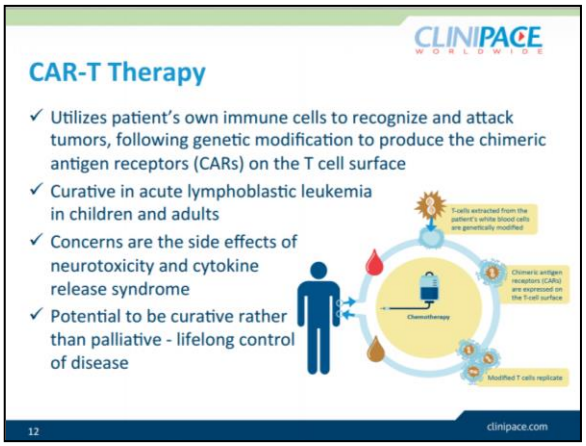


- 2 elements of the synapse have undergone extensive clinical testing
  - Cytotoxic T-lymphocyte antigen-4 (CTLA-4)
    - Competes with other molecules that share ligands on the antigen-presenting cell, regulating cytotoxic activity
    - In cancer, this is abnormally expressed, allowing malignant cells to go unnoticed by T cells
    - Example: ipilimumab
      - Approved by FDA in 2011
      - Advanced melanoma
      - Reduced relative risk of recurrence by 25% compared with placebo, but ~1/2 had to stop therapy early because of adverse events
      - Being investigated for non-small cell lung cancer in combination with chemotherapy
  - Programmed death-1 (PD-1)/PD-1 ligand (PD-L1) pathway
    - PD-1 is surface receptor on activated T cells, B cells, and natural killer cells, and PD-L1 is its ligand
    - Together, induce T cell tolerance

- In cancer, abnormal expression of PD-L1 can occur on malignant cells, which inhibits recognition
- Drugs can block either PD-1 protein on surface of T cells or PD-L1 protein on surface of cancer cells to increase recognition
- Example PD-1: pembrolizumab
  - Approved by FDA September 4, 2014
  - Unresectable or metastatic melanoma and disease progression after treatment with ipilimumab
  - 24% of patients experienced tumor regression
- Example PD-L1: MPDL3280A
  - Received breakthrough therapy designation by FDA for non-small cell lung cancer with disease progression during or after platinum-based therapy
  - Had received this designation for metastatic bladder cancer in 2014

- Immune-related adverse events (irAE) are a concern
  - Autoimmunity to any organ or organ system with anti-CTLA-4
  - 64.2% of 1498 patients in phase I-III trials experienced an irAE of any grade
  - Associated with dose, antitumor response, survival
  - Corticosteroids might manage this

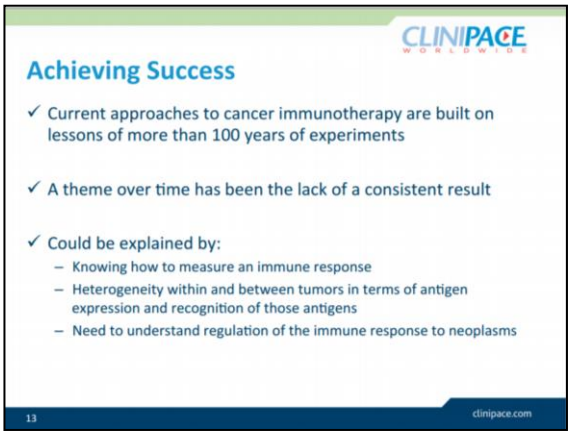
SLIDE 12: CAR-T Therapy
Speaker: Lee Schacter



- **CAR-T therapy**
  - Another emerging therapy
  - Utilizes patient's own genetically modified immune cells to recognize and attack tumors
    - Modified to produce chimeric antigen receptors (CARs) on the T cell surface
    - Promising for acute lymphoblastic leukemia in children and adults
      - 88% of adult patients experienced remission after CAR-T infusion
      - CTL019 – breakthrough therapy status in July 2014
        - Refractory leukemia
        - 92% complete remission rate in pediatrics
    - Side effects of neurotoxicity and cytokine release syndrome (cytokine storm)
      - Large T cell activation
      - Dangerously high fevers and drops in blood pressure
      - FDA might not approve CAR-T therapy that does not include a safety feature for this
        - Because potentially associated with inflammation, drugs to treat inflammatory conditions might help with toxicity

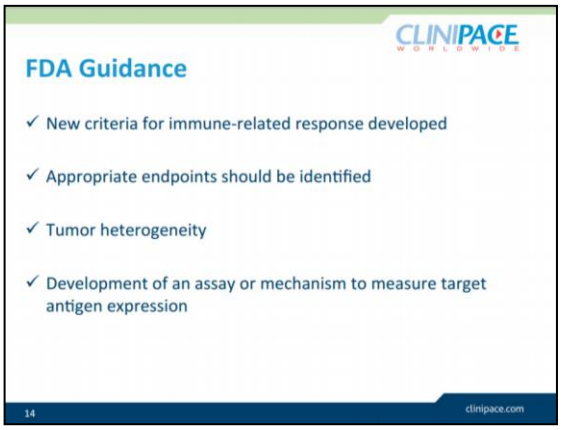
- Potential to be curative rather than palliative, unlike surgery, chemotherapy, or radiation, and might provide lifelong control of disease

SLIDE 13: Achieving Success
Speaker: Ofelia Nievas



- Given the seemingly poor success rate for immuno-oncology agents in the past, it is understandable to have a pessimistic view of the future of these therapies
- For example, a review published in 2004 indicated that the overall response rate to cancer immunotherapies was only 3.3%; however, 96% of the patients had melanoma
- Supporters of the potential applications of immunotherapies in cancer have taken advantage of the long history of research and the data provided by both failed and successful trials to identify the factors that might improve their success in the future
- One common theme throughout the literature is the lack of a consistent result, which could be explained by the following:
  - Definitions of response to treatment
  - Heterogeneity within and between cancers, tumors, and mutations
  - Availability of infrastructure to understand, identify, and monitor targets
  - Sampling and handling process
- Key to success appears to be overcoming cancers ability to block the immune response. To date this has been achieved by immune check point inhibitors or CAR-T

SLIDE 14: FDA Guidance
Speaker: Ofelia Nievas

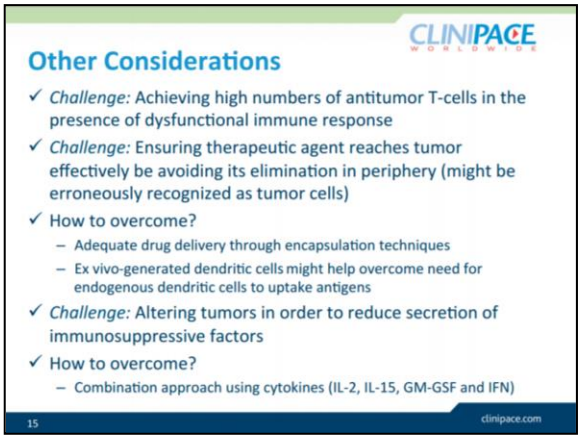


- Increasing recognition that considerations for development of a cancer immunotherapy are different than those for a more traditional biological product or cytotoxic drug for the treatment of cancer
- As a result, the FDA developed specific guidance for vaccine and immunotherapy trials (antigen-specific therapeutic only)
- In this guidance document, clinical considerations of particular interest are highlighted:
  - First, therapies are traditionally first tested in patients with advanced cancers who have failed multiple treatment regimens with potential detriment to the immune system

    - In addition to minimizing the potential responsiveness to the cancer vaccine, the vaccine may be more effective with low disease burden in the first place
    - Furthermore, the time to develop an anti-tumor immune response to a cancer immunotherapy is typically 2-3 months, compared with shorter times for traditional cytotoxic therapy
    - The kinetics of tumor growth rates differ, and this can present as shrinkage in all baseline lesions, stable disease followed by a slow decline in tumor burden, increase in tumor burden followed by response, or presence of new lesions
    - A delayed response is also often observed, and inflammation and tumor enlargement (pseudoprogression) from cytotoxic T lymphocytes and immune cells can be difficult to differentiate from tumor progression
- Because of this, criteria traditionally used to estimate the response to typical cytotoxic agents (e.g., Response Evaluation Criteria in Solid Tumors [RECIST] or World Health Organization [WHO] criteria) might underestimate the response with immunologic agents and result in treatment cessation in patients that might respond given enough time
    - Therefore, new criteria for immune-related response have been developed
    - However, these criteria have not been fully validated, and modified RECIST and modified WHO are also being evaluated in clinical trials
    - Regardless, an appropriate length of time is necessary to observe an effect
- Similarly, appropriate endpoints should be identified
    - Therapeutic immunotherapies do not directly the tumor, but instead target the immune system
    - As mentioned, adequate time is required for the immune system to develop, and booster treatments might also be required
    - Instead of immediate and significant reduction in tumor burden, the resulting effects might be related to slower tumor growth rate
    - Therefore, overall survival (OS) might be a better endpoint than the traditional endpoints of response or progression-free survival
        - For example, in the trials of Sipuleucel-T, the primary objective of time to disease progression was not different between the intervention and control groups
        - However, the risk of death was lower, overall survival time was higher with Sipuleucel-T, and time to first opioid analgesic was longer, which indicated a delayed treatment effect that was likely from active immunotherapy
- Tumor heterogeneity is the next important consideration in the FDA guidance document
    - The inherent heterogeneity of tumors (among patients, among different tumors from the same patient, and among different regions of the same tumor) affects the ability to respond to vaccines, resulting in difficulties in interpreting trial results and the risk of not achieving trial objectives
    - Specifically, the tumor/mutation type should be considered because only small number of mutations are of biological relevance and therapeutic benefit
    - Predicted immunoreactivity and high levels of tumor infiltrating lymphocytes (TILs) can provide some insight; the presence of a high number of TILs might identify tumors that are more immunogenic, with a failed endogenous immune response that has already occurred, and less likely to respond to immunotherapy

    - In these cases, the use of a vaccination might not be appropriate, while first line immunotherapy involving checkpoint inhibition might be more appropriate
- Identification of subtypes or groups that respond to a treatment in an ongoing trial is often used to continue the trial in only those specific groups, with greater success
    - For example, in a trial of anti-PDL1 as first line therapy for NSCLC, delayed disease progression without serious adverse effects was observed more in patients with PD-L1 positive tumor cells (response rate of 67%) than patients with PD-L1-negative tumors or unknown status (no response)
    - Another example trial with belagenpumatucel-L, an allogeneic genetically modified NSCLC tumor cell therapy, did not find significantly increased median survival
    - However, those that received the therapy within 12 weeks of chemotherapy did have a significant improvement, and the study is continuing with this subgroup
- The FDA also recommends the development of an assay or mechanism to measure the target antigen expression to help with patient selection and to monitor response
    - Because a clinically effective anti-tumor response is often a multi-component process, multiple assays may be required
    - Personalized therapies based on immune type and mutation profile would help to counteract tissue heterogeneity, but markers are needed to identify patients that will respond
    - The most common biomarker is the immune response to the tumor-associated antigen following vaccination, compared with before the vaccination
    - However, a T cell's cytokine production is not always associated with its lytic ability, and no study has identified a surrogate for clinical response
        - For example, in the clinical trials of sipuleucel-T, responses to PAP were present in only approximately 30% of the patients, despite demonstrated benefits in survival
        - However, markers that have been shown to correlate with clinical outcome include antigen-specific T-cell response based on IFN-gamma enzyme-linked ImmunoSpot (ELISPOT) assays, cytokine expression levels, reduction in regulatory T-cells, and eosinophil count

SLIDE 15: Other Considerations
Speaker: Ofelia Nievas

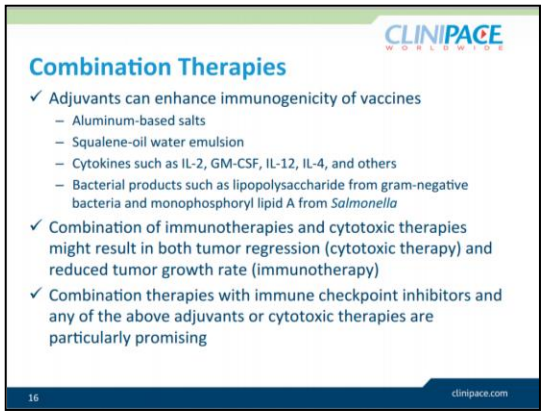


- An effective therapeutic cancer vaccine must induce a high number of antigen-specific T-cells against an established tumor that can then migrate to the tumor to perform their effector functions
    - The first challenge is achieving high numbers of antitumor T-cells in the presence of an ongoing, dysfunctional immune response
    - Second, the therapy might be recognized as tumor cells in the periphery and eliminated; if

the therapeutic agent does reach the tumor, it has to overcome the immune evasion techniques used by the tumor to support tumor growth and metastatic spread

- To overcome these difficulties:
  - Adequate drug delivery through encapsulation techniques might be useful
  - In addition, ex vivo-generated dendritic cells might help to overcome the need for endogenous dendritic cells, which are often dysfunctioning because of tumor-related suppressive factors, to uptake the antigens; these ex vivo dendritic cells can mature in the absence of tumor-related immunosuppression, allowing more control of this process
- The next challenge to overcome is the lack of the proinflammatory signals required to promote effective tumor responses because they are replaced by tumor-induced immunosuppressive/anti-inflammatory signals that predominate in cancer patients
- The immunosuppressive tumor microenvironment must also be overcome in order to kill the tumor cells; this microenvironment consists of regulatory T cells, suppressor cells, and natural killer cells, which can then release soluble immunosuppressive factors such as TGF-beta, IL-10, and VEGF
  - A combination approach that alters the tumor to reduce the secreted immunosuppressive factors using cytokines such as IL-2, IL-15, IL-7, GM-CSF, and IFN in addition to the immunotherapy could be useful

SLIDE 16: Combination Therapies
Speaker: Ofelia Nievas



- Some cancer immunotherapies might not suffice on their own to adequately induce or augment the immune response
- The use of adjuvants can enhance the immunogenicity of vaccines by activating antigen-presenting cells to stimulate T cells more efficiently, activating natural killer cells or other cells of the innate system to produce cytokines, or promoting the survival of antigen-specific T cells
  - These can include aluminum-based salts
  - A squalene-oil water emulsion
  - Cytokines such as IL-2, GM-CSF, IL-12, IL-4, and others
  - And bacterial products such as lipopolysaccharide from gram-negative bacteria and monophosphoryl lipid A from *Salmonella*
- The combination of immunotherapies and cytotoxic therapies might result in both tumor regression (cytotoxic therapy) and reduced tumor growth rate (immunotherapy)
- Chemotherapy, radiation, and small-molecule targeted therapeutics can alter the tumor cell phenotype
- In addition, immunotherapy-mediated killing of T cells by chemotherapeutic agents might occur as a result immune-related tumor cell death and enriched ratios of effector and regulator cells

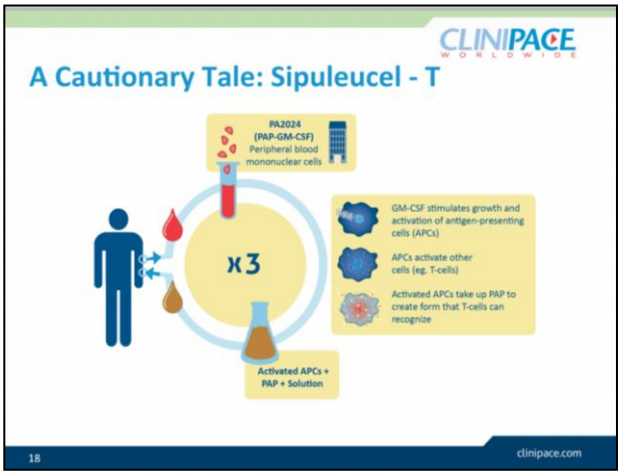
- It has been suggested that combination therapies with immune checkpoint inhibitors and any of the above adjuvants or cytotoxic therapies are particularly promising
- However, combination therapies require the assessment of each component, which can prolong the development

SLIDE 17: Trial Logistics
Speaker: Ofelia Nievas

- Certain aspects of the trial logistics for cancer immunotherapies can differ from or require greater attention than other clinical trials
- The combination of experience and enabling technology is key to successful implementation of these trials
- Clinipace Worldwide has experience with immuno-oncology clinical trials for ovarian cancer (phase 3), Ewing's sarcoma (phase 2), colon cancer (phase 3), metastatic colorectal cancer (phases 1 and 2), acute myeloid leukemia (phase 2), glioblastoma multiform (phase 2), renal cell carcinoma (phase 3), and non-small cell lung cancer (phase 3) in the US, Asia, South America, and Europe, and some of the learnings from these trials are provided here.
- Best practices:
  - First, investigators must have access to the specific types of patients needed, and a considerable number of inclusion and exclusion criteria typically have to be fulfilled owing to the specific set of patient characteristics
    - Common eligibility criteria include specific disease state, age, gender, prior therapies, lab results, activity levels, and current and previous medications
    - More stringent eligibility criteria make it harder to enroll appropriate numbers of participants, especially in a population where many patients have undergone intense treatments and may be reluctant to undergo a clinical trial
    - When tissue staging is critical to the study design, eligibility criteria must specify that patients either have previous tissue samples or be willing to undergo a biopsy prior to enrollment
  - Cooperation from many departments of the hospital is also required (e.g., pathology, surgical, oncology), which can be a large challenge
    - Access to a well-qualified pathologist may be important, and access to a radiology department is essential for timely and consistent tumor size evaluations
    - Interaction with ancillary units such as a cryolab and the shipping department might be required for storage and transport
  - Distribution of the samples and therapies can also be particularly challenging
    - Specialized containers might be required
    - Airline access and scheduling options are critical if tissue samples for autologous vaccines need to be processed within 48 hours after collection

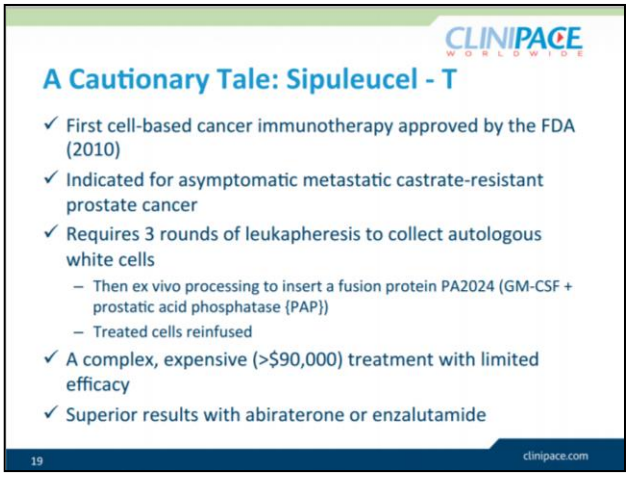
  - This might restrict the countries that can be involved in a global study given international flight schedules and custom requirements
  - If the products are shipped prior to final release by quality control, Action Plans for Positive Sterility might need to be developed
- Specialized methods for product receipt, storage, and thaw are needed that do not deviate from site standard procedures; if they do deviate, enough time is required to negotiate study-specific procedures with the applicable site departments
  - Furthermore, a specific clean room might be required to handle the therapies and/or adjuvants (e.g., BCG) at the sites
  - In some cases, this can mitigated with changes in packaging or the thaw procedure
- Cold chain management during transport and storage is important and requires particular consideration
  - Continuous temperature devices can be required for shipment, and the site has to check the devices immediately after arrival and store all of the therapies in certified refrigerators or liquid nitrogen freezers, which also require special cartridges
  - Each refrigerator is typically certified by the sponsor following the review of a temperature log over a 1-week period, including one weekend, which must be completed prior to shipment and maintained on a monthly basis
  - Every temperature deviation must be recorded
  - Therefore, the requirements for continuous monitoring, certificate of validation, and documentation by the sites for the refrigerators are considerable
  - If the sites are not able to comply with these requirements, a sponsor-provided device should be considered; however, this still requires a certain level of maintenance
- Careful tracking of all samples and therapies from the patient to off-site handling facilities back to the patient is required
  - Often, this process occurs within a short period of time (~72 hours)
  - A central database is instrumental in monitoring this process
    - TEMPO™, which is a proprietary, cloud-based e-clinical software platform developed by Clinipace Worldwide, not only provides the general collection and storage of all study-related data but also includes specialized modules for these types of situations
    - Moreover, the central platform enables appropriate management and reporting of the large volumes of data, including medications and irAEs, that are part of these trials
- None of these issues are insurmountable, but significant time must be spent in the trial planning stages to make sure that these considerations are included in the study protocol and subsequent discussions with the sites
  - During this process, it is useful to have the insight of an experienced contract research organization, such as Clinipace Worldwide, who can help to mitigate the risks that are inherent to this type of study and address any issues that occur as the study is implemented

SLIDES 18 and 19: Case Study: A Cautionary Tale: Sipuleucel - T
Speaker: Lee Schacter



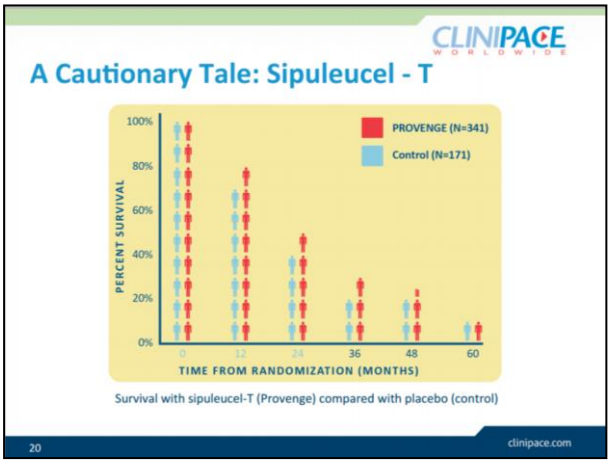
The commercial failure of Dendreon (sipuleucel-T/Provenge)

- Sipuleucel-T (Provenge) is an autologous cellular immune therapy that involves harvesting of the patient's peripheral white cells by leukophoresis at an approved cell collection center and incubation with a recombinant construct of PAP and GM-CSF at a central processing facility, which is then reinfused into the patient
- The complex administration process, over multiple visits and multiple treatment cycles, in practice means that not all patients can actually be treated
- In addition, sipuleucel-T is indicated only for asymptomatic or minimally symptomatic patients with castrate-resistant (hormone-refractory) prostate cancer (FDA package insert), and the benefits are limited
- In addition to being difficult to administer and of limited benefit, the estimated cost of sipuleucel-T is $93,000 USD per treatment course, and a single estimated economic analysis resulted in a 96.5% certainty that it is not cost-effective
- Finally, since the initial approval of sipuleucel-T in 2010, abiraterone (CYP17 inihibitor approved in 2011 in combination with prednisone) and enzalutamide (androgen-receptor inhibitor approved in 2012) have become available



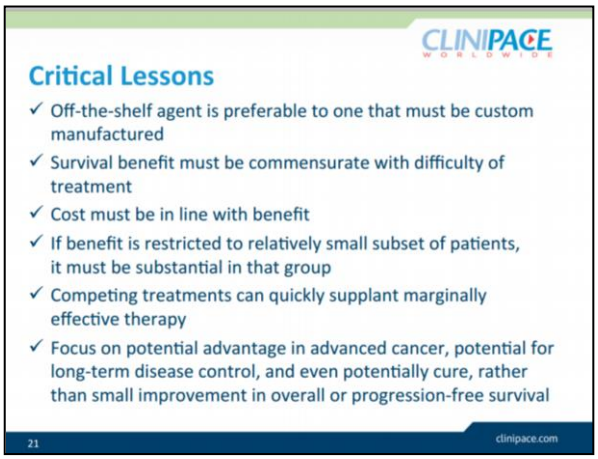
- Both are oral, off-the-shelf drugs administered once daily, approved for men with metastatic hormone-refractory prostate cancer regardless of symptom status, and associated with a median survival of 35.3 months for men without prior cytotoxic treatment (abiraterone), 18.4 months in those with prior docetaxel treatment (enzalutamide), and 32.4 months, with an 81% reduced risk of radiographic progression, in chemotherapy-naïve patients (enzalutamide). In contrast comparable patients (those with no prior docetaxel) treated with sipuleucel-T had a median survival of 25.9 months

SLIDE 20: Case Study: A Cautionary Tale: Sipuleucel - T
Speaker: Lee Schacter



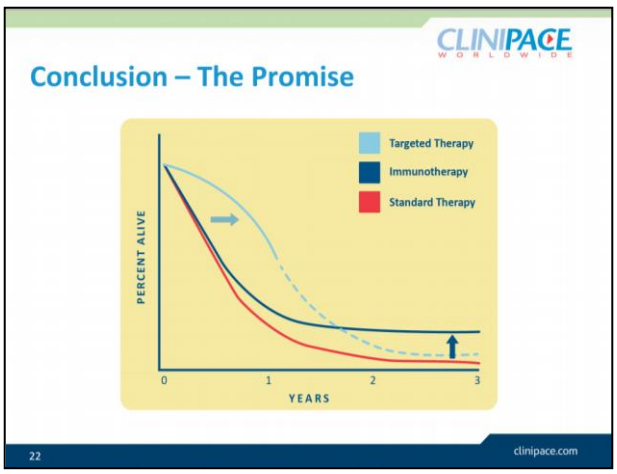
- Only a 4.1–4.5-month improvement in overall survival was observed in two randomized controlled trials compared with a placebo (FIGURE)
- Furthermore, it does not decrease tumor size or prolong time to progression; therefore, it should not be used in patients with rapidly progressing metastatic castrate-resistant prostate cancer
- However, research continues with sipuleucel-T, and a recent focus is its use in combination therapy with chemotherapy, radiation, checkpoint inhibitors or as an adjuvant to surgery

SLIDE 21: Critical Lessons
Speaker: Lee Schacter



- An off-the-shelf agent is preferable to one that must be custom manufactured.
- Survival benefit must be commensurate with difficulty of treatment.
- Cost must be in line with the benefit.
- If the benefit is restricted to a relatively small subset of patients, it must be substantial in that group.
- New competing treatments, either immune, hormonal, or targeted, can quickly supplant a marginally effective therapy.
- It is important to focus on the potential advantage of immunotherapy in advanced cancer, the potential for long-term disease control, and even potentially cure, rather than a small improvement in overall or progression-free survival.

SLIDE 22: Conclusion
Speaker: Lee Schacter



- After over 120 years of basic and clinical research, immunotherapy has become a true part of the anti-cancer armamentarium in the last decade
- The dissection of immune regulation and response has made effective therapy possible

- Although therapeutic vaccines remain to be proven, the new insights into and the ability to affect the immune synapse may open the door to effective vaccines, whether personalized or off the shelf
- Furthermore, our definitions of success might need to change and different criteria efficacy criteria used
- Immunotherapy, especially vaccines, has the potential of greatly reduced toxicity and, most importantly, durable disease control