US Regulatory Considerations for Therapeutic Cancer Vaccines

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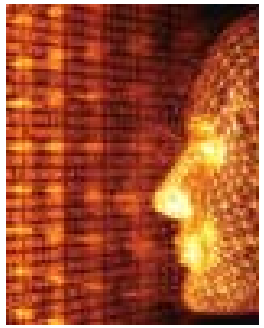
Immune Therapies: The Future Is Now
Tuesday, April 3, 2012, 8:15 a.m. – 10:15 a.m.
Presentations:
Targeted blockade of immune checkpoints in cancer therapy
Suzanne L. Topalian, Johns Hopkins, Baltimore, MD
CAR T cells for leukemia and more?
Carl H. June, University of Pennsylvania, Philadelphia, PA
Current status of recombinant pox-viral vaccines
James L. Gulley, National Cancer Institute, Bethesda, MD
The rational combination of BRAF inhibition with immunotherapy for the treatment of metastatic melanoma
Patrick Hwu, UT MD Anderson Cancer Center, Houston, TX

Outline



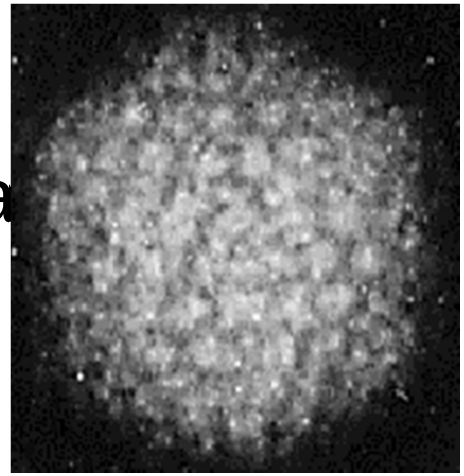
- FDA regulation of Oncologic products
- CBER, Office of Cellular, Tissue, and Gene Therapies
  - Regulated products
- Regulatory considerations for cancer vaccines and immunotherapy product development
- Regulatory considerations for personalized Medicine
  - Autologous cancer vaccines
  - Companion diagnostics

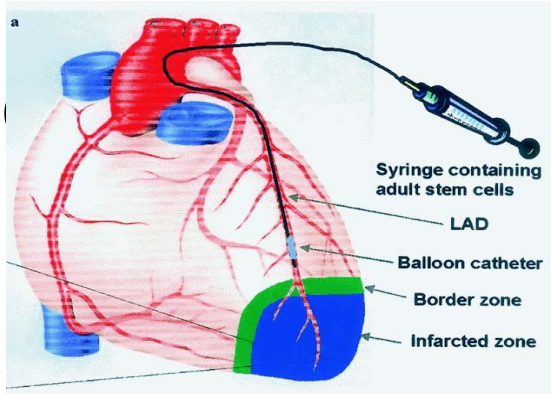
FDA Regulation of Oncology Products

- Office of Hematology and Oncology Drug Products, CDER
  - Drugs (small molecules)
  - Biologics, including
    - Monoclonal Antibodies
    - Therapeutic Proteins
    - Cytokines
- Office of Cellular, Tissue and Gene Therapy, CBER
  - Cell therapies
  - Gene Therapies
  - Oncolytic viruses
  - Therapeutic vaccines and immunotherapies

Office of Cellular, Tissue and Gene Therapies (OCTGT) Products

- Cellular Therapies
- Cancer Vaccines and Immunothera
- Gene Therapies
- Xenotransplantation Products
- Tissues and Tissue-Based Produ
- Combination Products
- Devices Used for Cells and Tissues



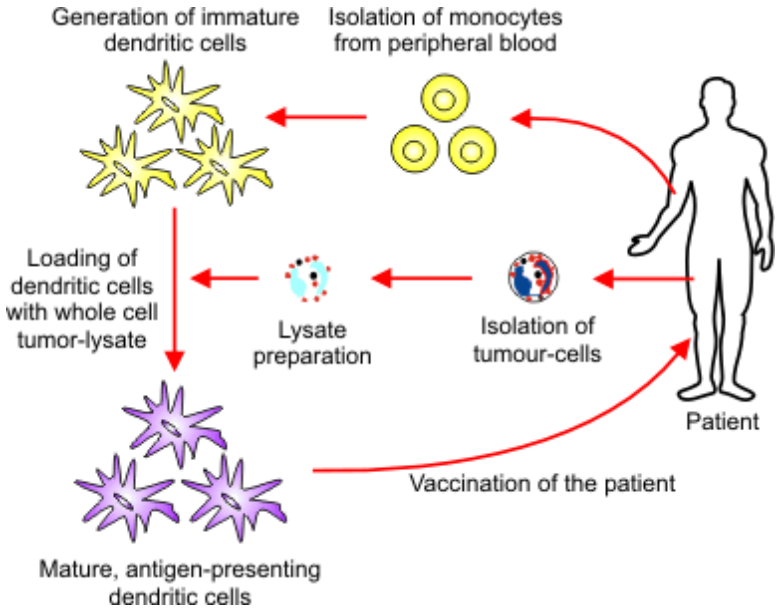


Challenges in the development of Cellular Cancer Vaccines

- Cell based cancer vaccines and immunotherapy products are not like a drug with a defined chemical formula – need to
- Determine identity of complex cell product mixtures
- Determine activity (potency) of cellular products
  - Consider surrogates of potency e.g., cell surface expression of protein, secreted product(s), which are correlated with biological activity
- Determine effects of storage conditions and transportation on stability of cellular products
- Confirm safety (sterility) of cellular products

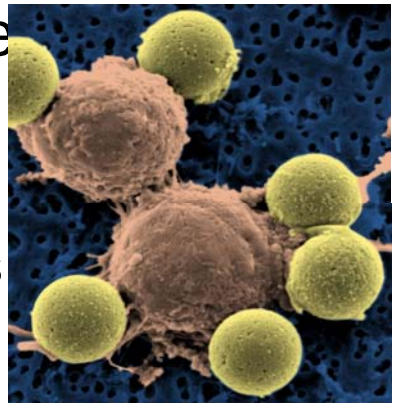
Cancer Vaccines in combination with other Biological Agents

- Dendritic cells pulsed with tumor antigens, peptides, purified or recombinant proteins, cell lysates, nucleic acids or transduced with gene transfer vectors
- Cells cultured and expanded in growth factors or cytokines and administered as such or mixed with growth factors
- Adjuvants (BCG, KLH, CPG, GM-CSF anti-CTLA-4 or montanide etc) may be used to enhance immune response – implications for clinical trial design



Special issues with Autologous Cancer Vaccines:

- Manufacturing process issues - may impact interpretation of clinical trial results
- Choice of antigen used e.g., peptide, mRNA or others
- Characterization of final product
  - Safety: sterility, mycoplasma, endotoxin, viability
  - Potency – biological activity, antigen presentation, surrogate marker
  - Identity e.g., antigen load, phenotype of ce
    - include many markers
  - Stability at storage temp or after freeze
    - thaw or shipping (include viability, markers and function)



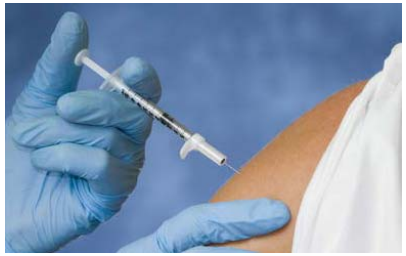
Phase 1 Clinical Considerations

- Understand MOA
- Demonstrate proof of principle (P1/2)
- Establish safety profile
- May or may not determine MTD
- Vaccine adjuvant: demonstrate enhanced immune response or other data supporting safe use
- Co-development of vaccine and assay for target antigen – consider if an assay may be required for subject eligibility (may require input from CDRH*)

*Center for Devices and Radiological Health

Endpoints for Early Phase Cancer Vaccine Trials

- Standard safety endpoints
  - May never reach MTD (but that's ok!)
  - Please define DLT in your protocol
- Vaccine-specific toxicities
  - including autoimmunity
  - Possible off-target antigen targets



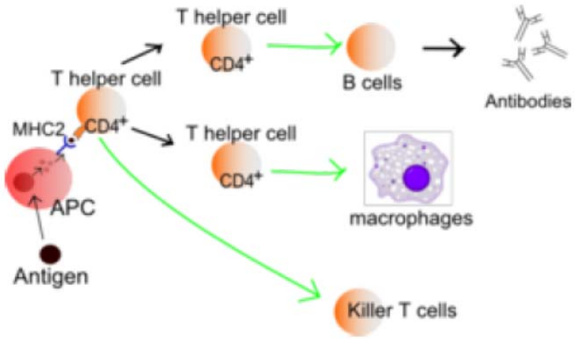
- Clinical activity is a secondary objective

Phase 2 Clinical Considerations

- Further define/optimize dose/schedule
- Define population
- Continue collection of safety data
- Define endpoints
- Explore continuation of vaccine after initial progression
- Estimate effect size
- *Single arm studies offer very limited information, as PFS, TTP, DFS are un-interpretable in this setting and historical controls are subject to bias*

Role of Exploratory Endpoints in Early Phase Studies

- Biomarker response (PSA, CA-125, etc)
  - May be suggestive of activity
  - Supportive of proof of concept
  - May help optimize regimen
- Immune response
  - To assess immunocompetency
  - Help understand MOA
  - To optimize dose and schedule
  - Evaluate adjuvants



- Move product forward if proof of principle demonstrated

Before Phase 3

- Have estimate of effect size
  - Interpretation of time to event is problematic in single-arm studies – may lead to over-optimistic interpretation of effect size
- Consider randomized P2 trial(s)
  - More realistic effect size
  - Useful data to plan for P3
- Develop Potency assay

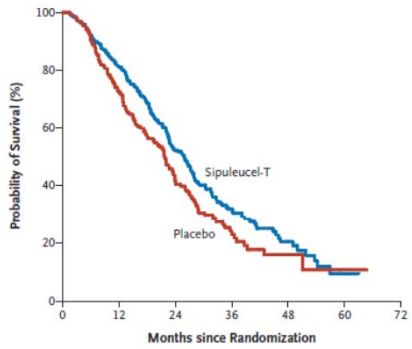
Phase 3 Clinical Considerations

- Determine appropriate P3 study population
- Biomarker clinical validation
- Statistical issues
  - Consider interim analysis for futility and resizing
  - Avoid early stopping for efficacy
  - Consider delayed effects
  - Adaptive designs

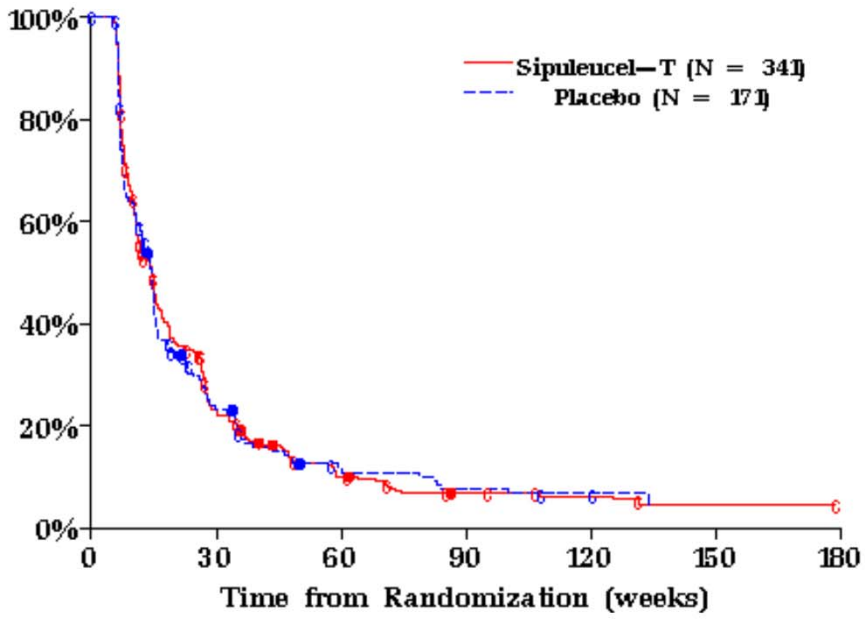
- Consider continued vaccination despite progression *if*
  - Subject continues to meet eligibility criteria
  - No DLT
  - No clinical deterioration
  - No curative salvage therapy exists
  - No imminent serious complication (CNS mets)
  - Prior clinical evidence suggests delayed effect

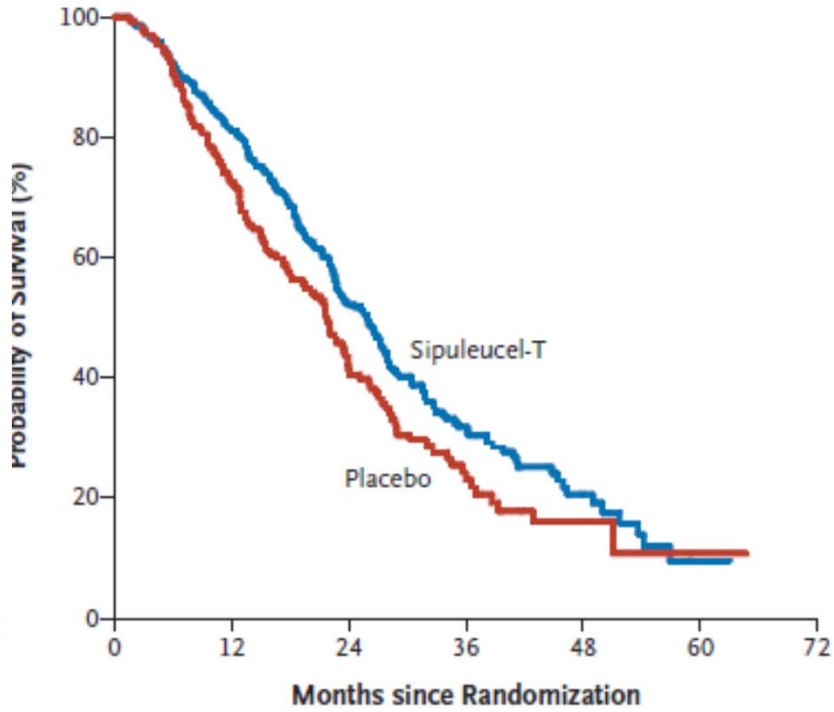
Phase 3 Endpoints

- Progression Free Survival (PFS) preferred over Time to Progression (TTP) – death is an event!
  - Acceptability of PFS is indication – specific
  - Requires careful analysis plan and study conduct to ensure symmetrical ascertainment
- Disease Free Survival (DFS) - adjuvant (postop) setting
- Patient Reported Outcomes (PROs) may provide supportive information or potentially support approval
- Overall Survival (OS) is still the gold standard
  - May be best endpoint for cancer vaccine studies
  - Crossover could potentially confound OS results
  - Subsequent therapy reflects real world practice



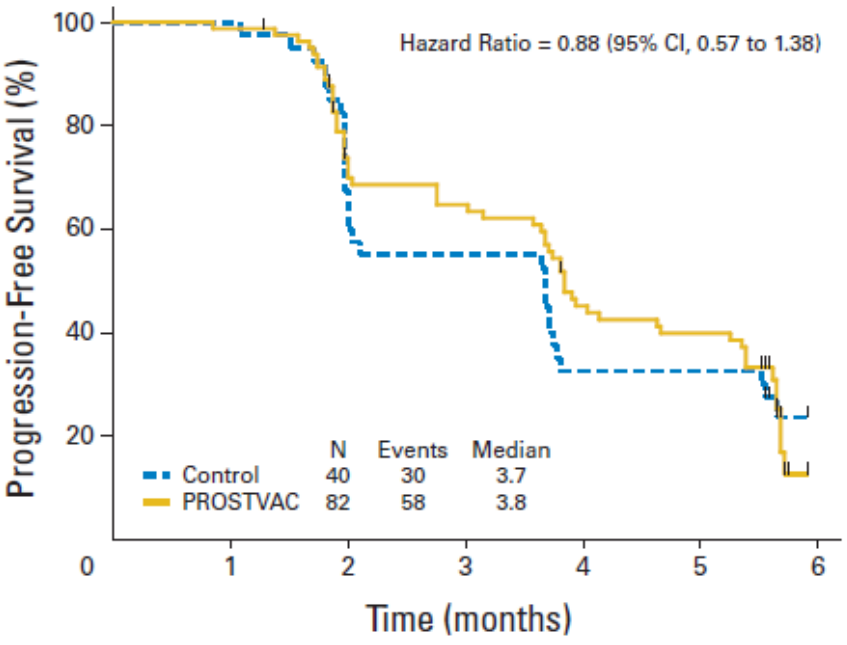
Progression Free vs. Overall Survival in a cancer immunotherapy – 1

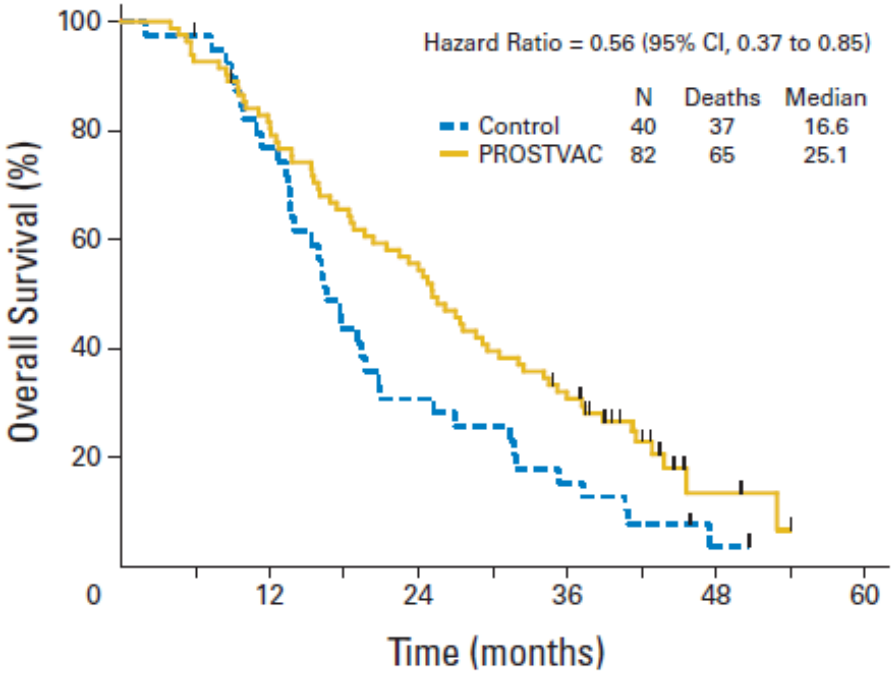




P Kantoff, NEJM, 2010

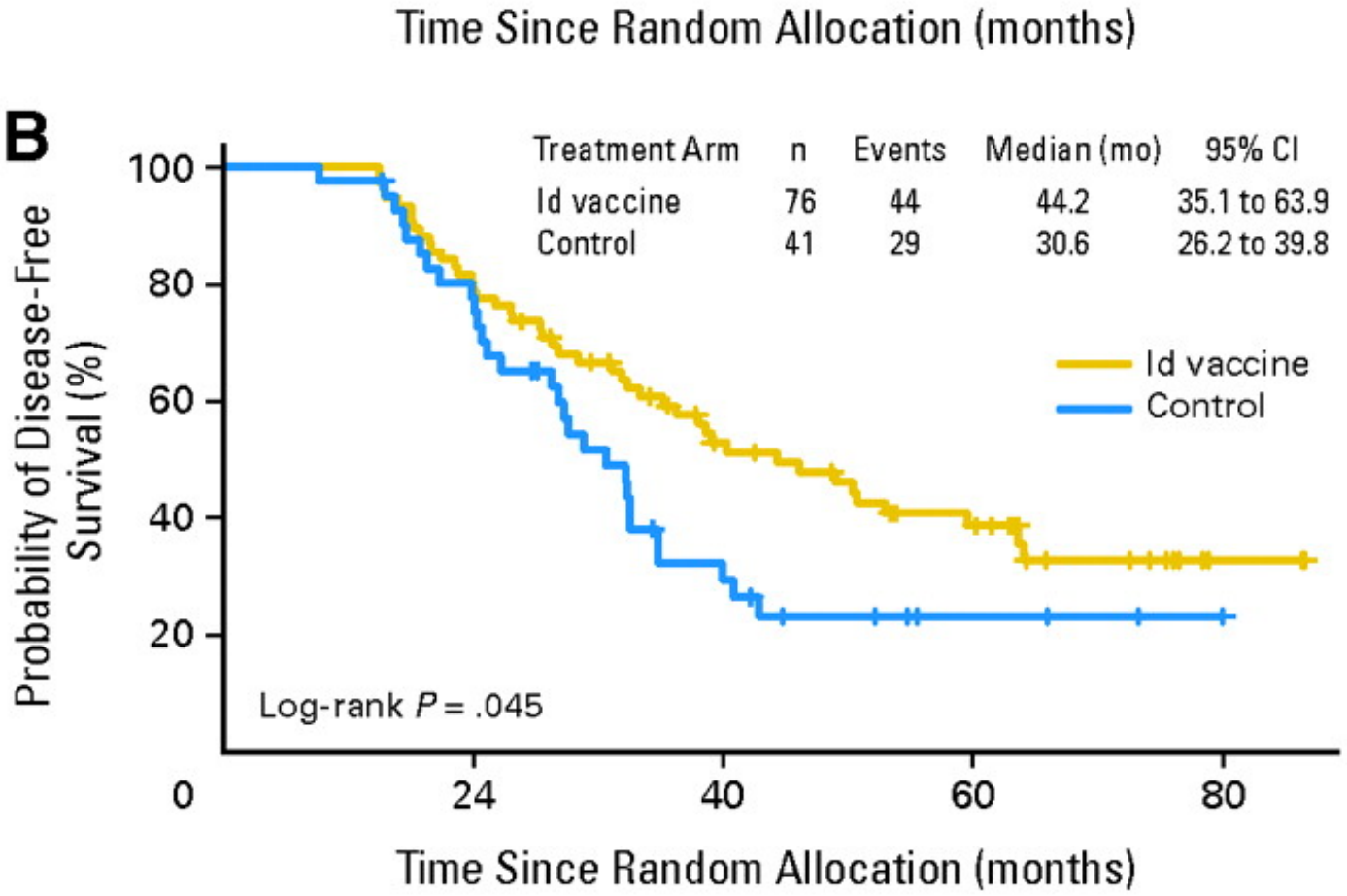
Progression Free vs. Overall Survival in a cancer immunotherapy – 2





P. Kantoff, JCO, 2010

Disease-free survival (DFS) according to treatment group for patients who received blinded vaccinations (n = 117).

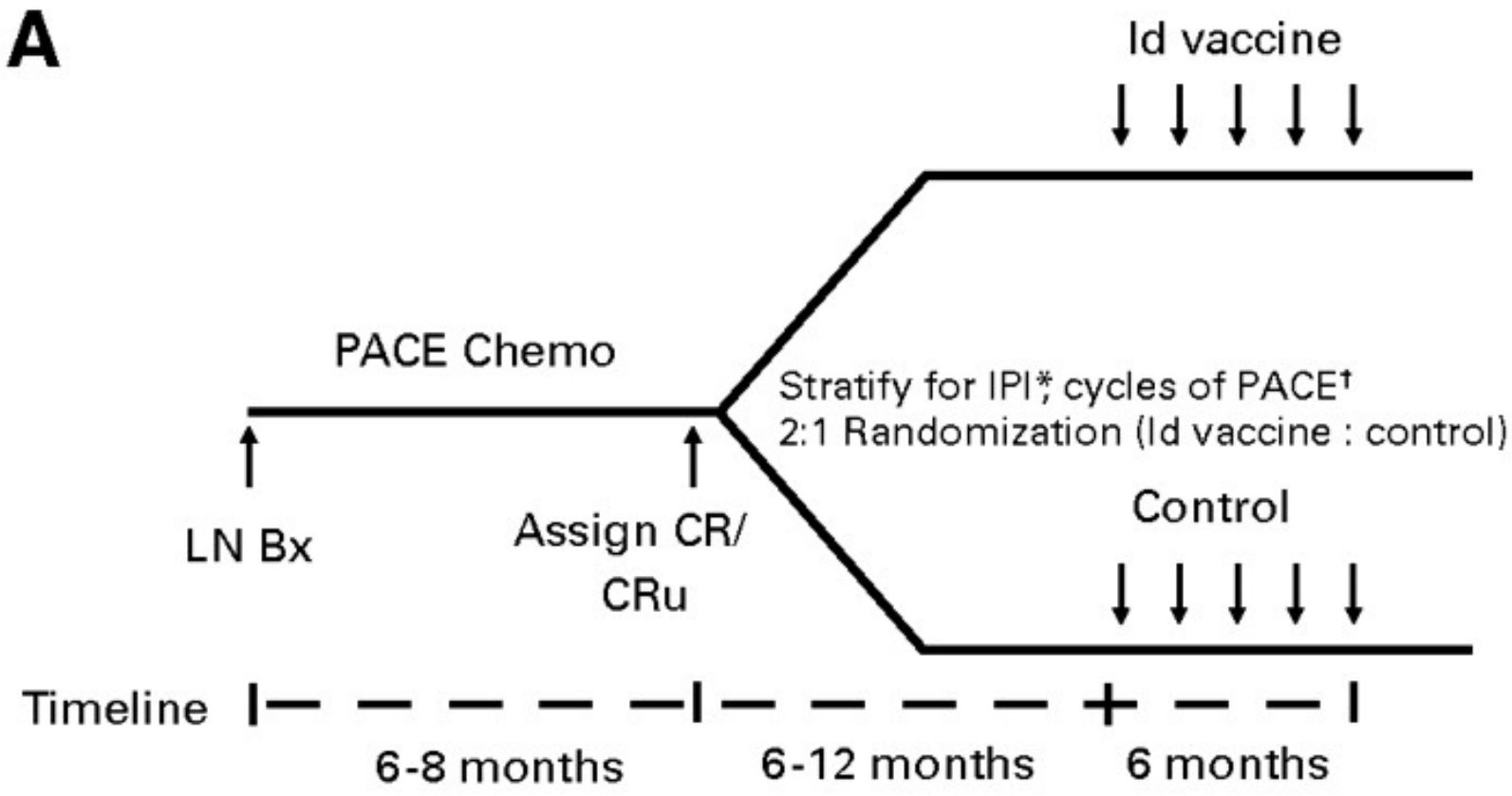


Schuster S J et al. JCO 2011;29:2787-2794

Lessons Learned in Phase 3

- Choice of primary endpoint – overall survival may be most appropriate
  - PFS is appealing but has not been successful thus far
- Choice of control – placebo vs. open label
  - Issues with leukapheresis for DC vaccines
  - Issues with endpoint (PFS vs. OS)
- Choice of combinatorial therapy need to reflect current practice standards
- Special issues with autologous vaccines

Case Study: Autologous Idiotype Vaccine for Follicular Lymphoma



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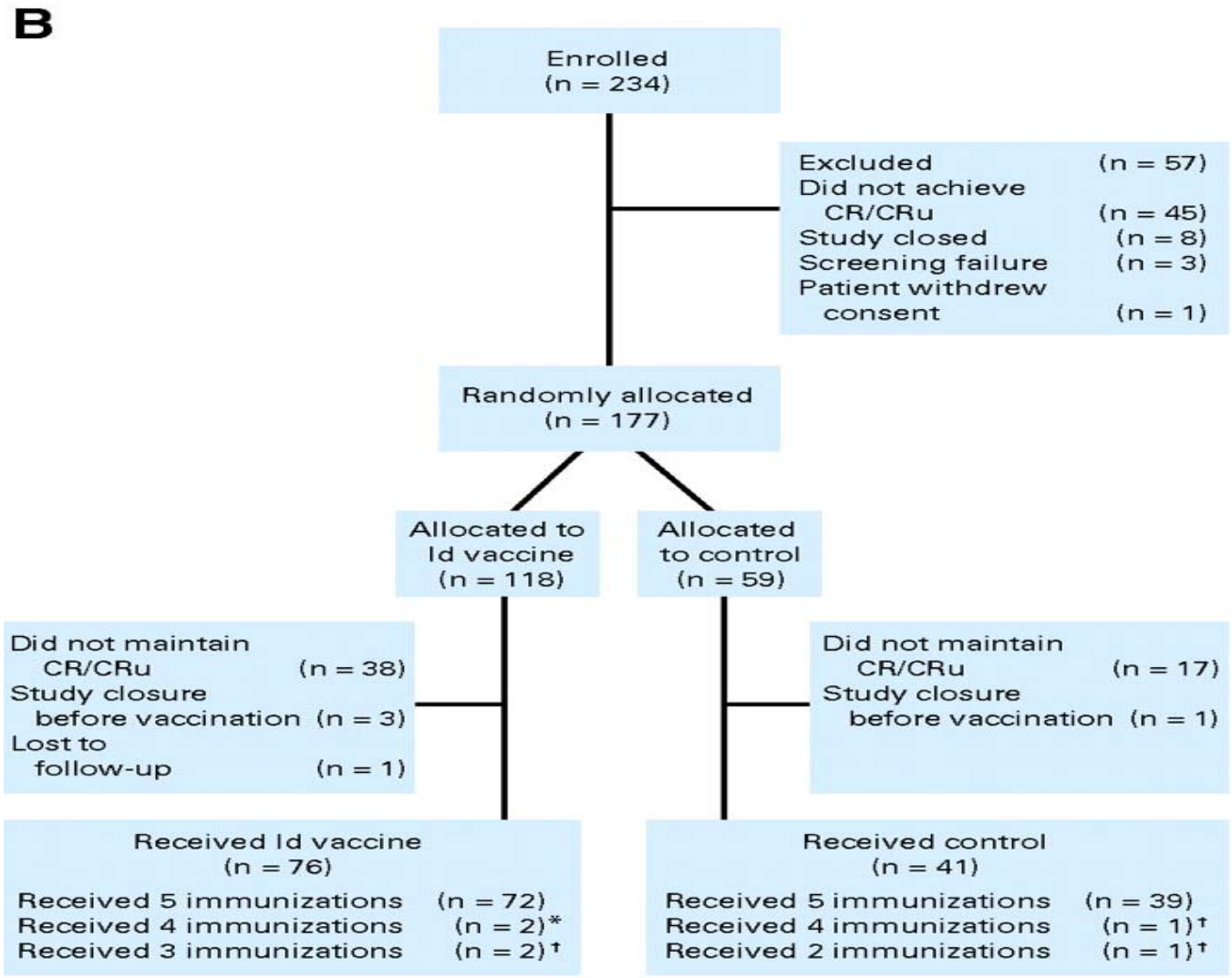
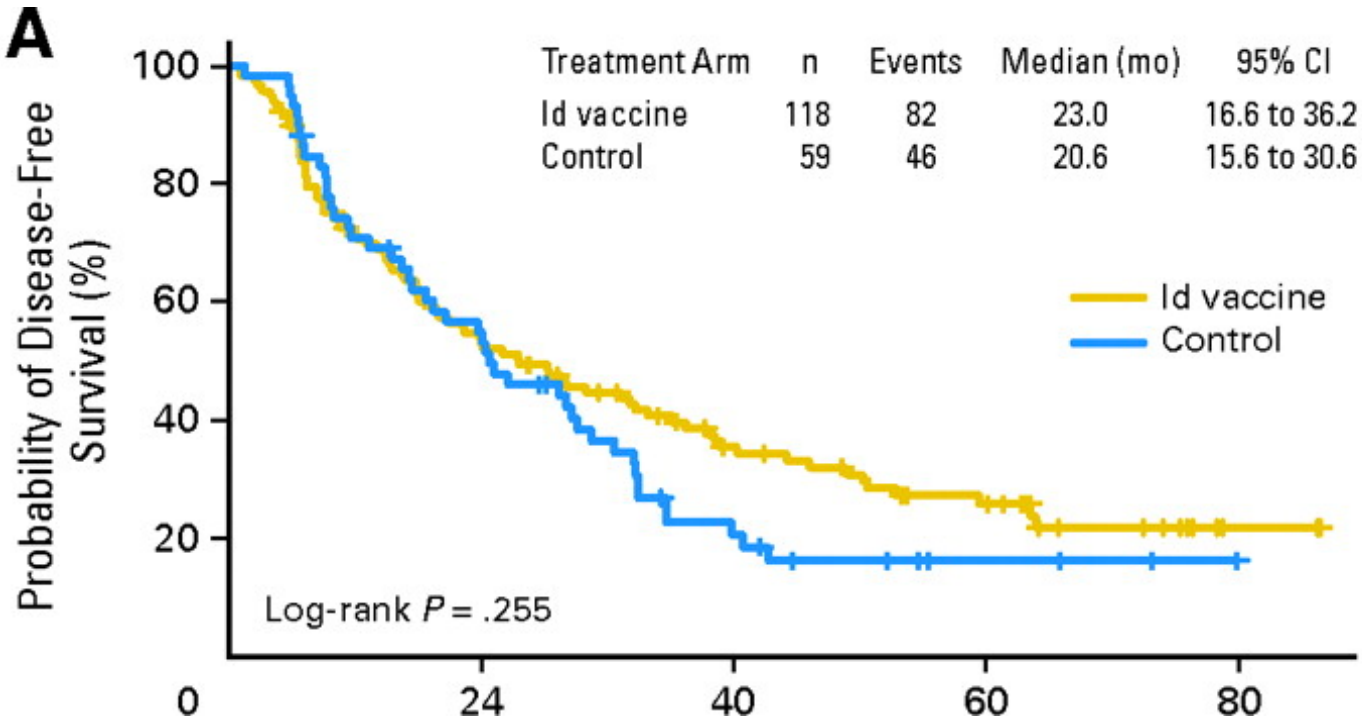


Disease-free survival (DFS) and overall survival (OS) according to treatment group for all randomly assigned patients (n = 177)



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Challenges of personalized autologous vaccines

- Manufacturing issues
  - Time to manufacture – patients may become ineligible over time
  - Manufacturing success rate
- Clinical trial design and analysis issues
  - Regulatory requirement of primary intent to treat analysis
  - Consider randomizing patients following successful manufacture of product

Lessons Learned in Phase 3 Summary

- Progression Free Survival may not be the optimal endpoint for cancer vaccines
  - Consider primary endpoint of Overall Survival
- Intent to treat is the primary analysis population, post hoc analyses will not support licensure
- Single arm Phase 2 trial results compared to historical controls can be misleading
- Consider randomized P2 trial(s) with concurrent comparator to provide estimate of clinical benefit (useful when determining size of P3 trial)

Guidance for Industry

Clinical Considerations for Therapeutic Cancer Vaccines

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
October 2011

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

EOP2/PP3 Meeting with FDA

- Discuss/justify dose and regimen
- Present safety data
- Present clinical activity data
- Target population
- Proposed control arm
- Statistical plan
- Consider Special Protocol Assessment
  - Agreement regarding study design
  - Statistical Analysis Plan (essential!)

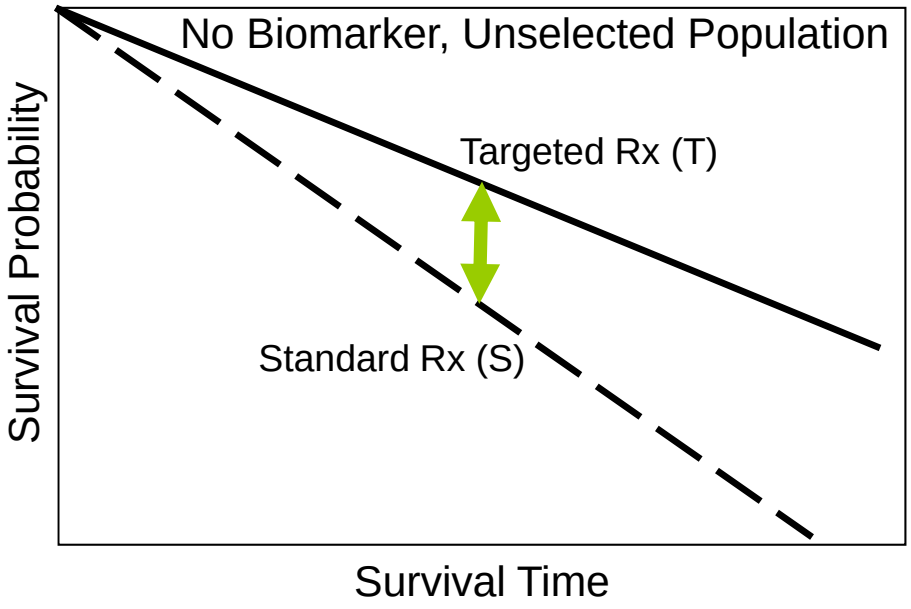
Personalized Medicine 2: Companion Diagnostics

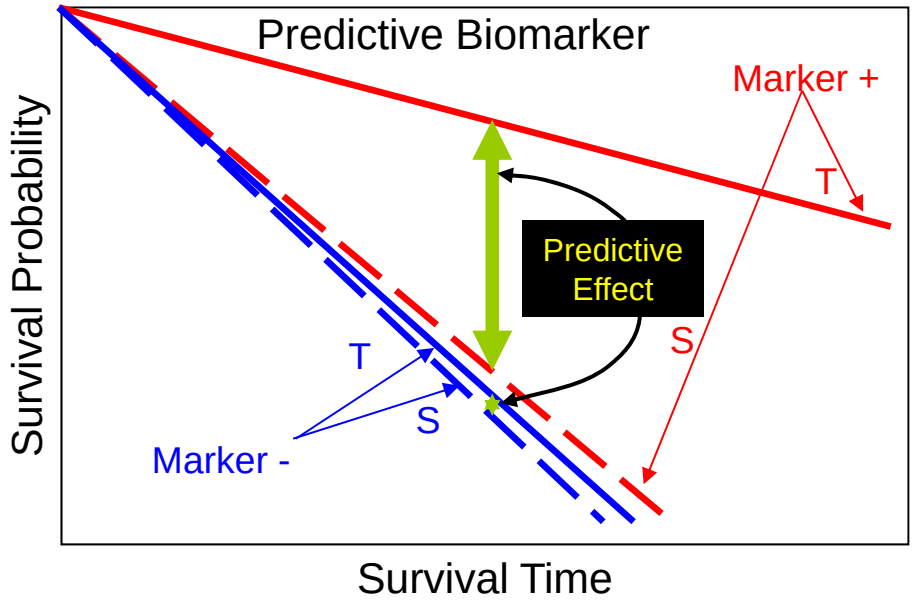
- In vitro diagnostic tests (IVDs) have long been used to guide therapeutic strategies (hormone receptors in breast cancer)
- More recently, IVDs may be the *critical* factor in therapeutic selection
- Need to ensure that the test selects the “right” patients for treatment with the drug (i.e., “personalized medicine”).
- Does the targeted drug design translate to a targeted clinical effect?
- US regulatory approach is different than in EU

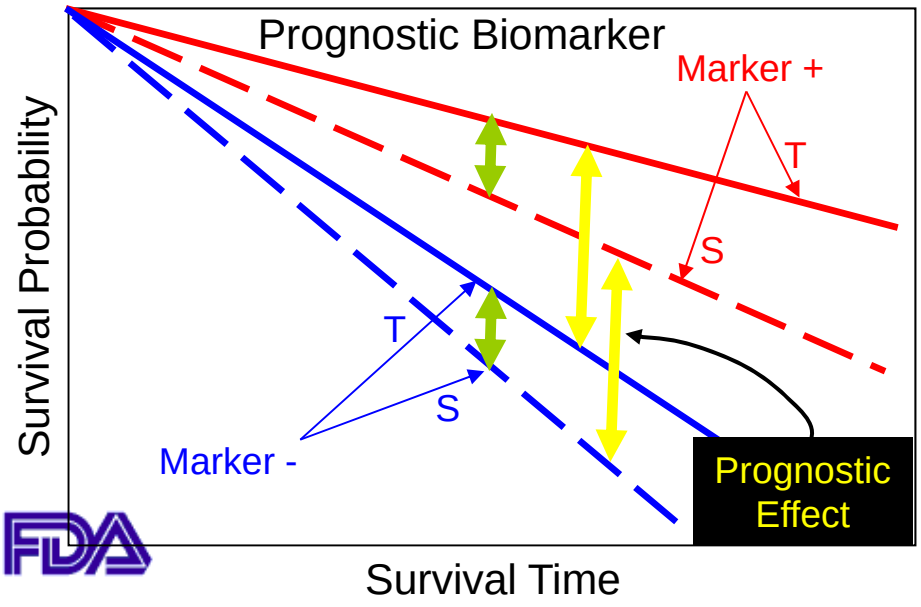
Companion Diagnostics: Biomarker Assay Validation

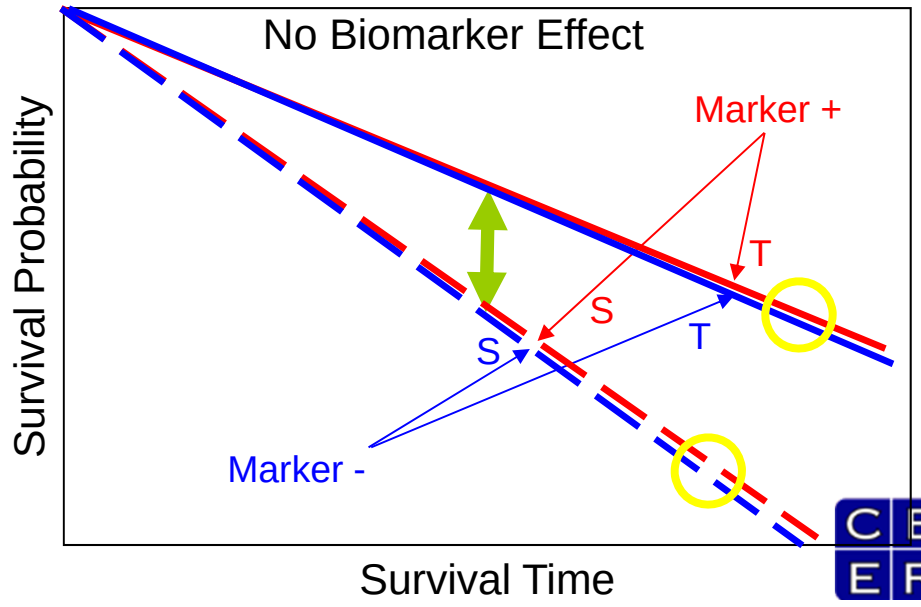
- Analytical Validation
- Accuracy
  - Measurements represent the intended analyte
  - Measurements are not biased
- Reproducibility
  - Under “constant” conditions
  - Across systematically “varied” conditions
- Clinical Validation
  - Demonstrated safety and effectiveness for the intended use

Predictive vs. Prognostic Biomarkers









Companion Diagnostic Summary

- Biomarker-targeted drug development presents opportunities for “personalized medicine”, complicated by trade-offs in Dx/Rx trial design
- Well controlled development and evaluation of predictive biomarker and diagnostic device are essential to understanding its value in guiding use of the therapeutic product.
- FDA CDRH regulates the companion assays in the US as part of the license application

Role of Center For Devices and Radiological Health (CDRH)

- CDRH input is essential - generally starts with a pre IDE meeting request
- When the trial is conducted under an IND, the device issues might be dealt with through the IND file (rather than a separate IDE filing).
- Separate IDE approval by FDA may facilitate more prompt communication and review of submitted information.

Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: July 14, 2011

http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm

FDA-EMA Interactions

- **Protocol Advice**
- **informal ad-hoc** FDA-EMA scientific advice exchange, without specific request from sponsor
- Increased dialogue between Agencies and sponsor from early stages of development
- Optimise and facilitate global development plans

- **PARALLEL FDA-EMA SCIENTIFIC ADVICE**
  - Voluntary, at request of sponsor
  - Questions on product development put to both FDA and EMA
  - Discussions between FDA-EMA, and joint discussion with sponsor
  - Each Agency will issue separate responses to sponsor‘s questions in line with usual procedures

FDA Clinical Guidances

- Adaptive Design Clinical Trials for Drugs and Biologics at *www.**fda**.gov/downloads/Drugs/**Guidance**ComplianceRegulatoryInformation/**Guidance**s/ucm201790.pdf*

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics at *www.fda.gov/downlands/Drugs/**Guidance**ComplianceRegulatoryInformation/**Guidance**s/ucm071590.pdf*

- Clinical Trial Endpoints for the Approval of NSCLC Drugs and Biologics at *www.fda.gov/downloads/Drugs/**Guidance**ComplianceRegulatoryInformation/**Guidance**s/UCM259421.pdf*

- Clinical Considerations for Therapeutic Cancer Vaccines at *www.fda.gov/downlands/biologicsbloodvaccines/guidancecompliancereguratoryinformation/guidances/vaccines/ucm278673.pdf*

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- OCTGT Regulatory Questions
  Dr. Patrick Riggins (Branch Chief RPM)
  patrick.riggins@fda.hhs.gov 301-827-5366
- OCTGT Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- Follow us on Twitter
  https://www.twitter.com/fdacber

Additional Regulatory Resources for Biologics

General CBER Issues

http://www.fda.gov/BiologicsBloodVaccines/default.htm

Office of Communication, Outreach and Development (OCOD)

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Thank you