

# **Manipulation of the Tumor Microenvironment by CTLA-4 Blockade**

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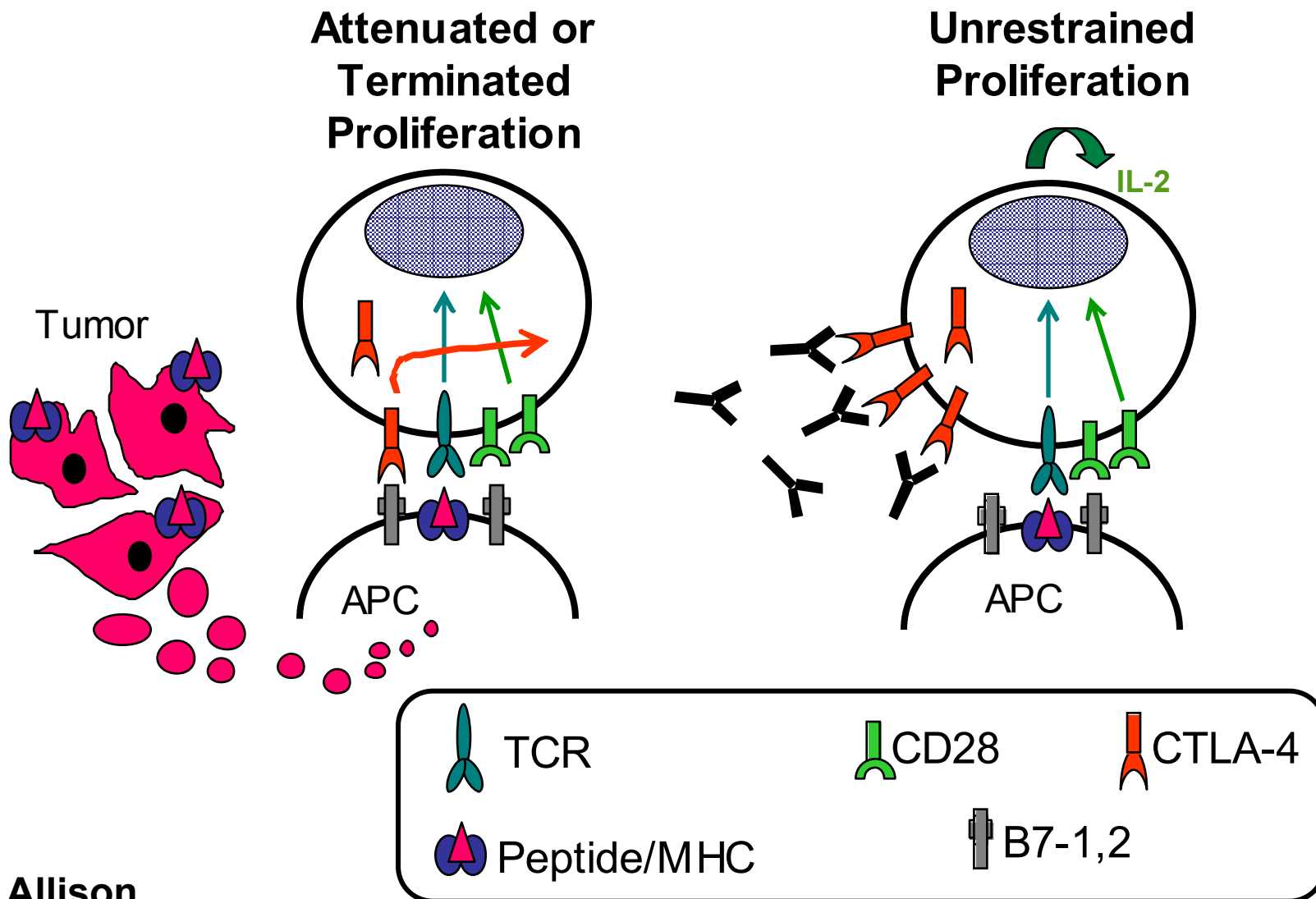
**M. D. Anderson Cancer Center**

**GU Medical Oncology & Immunology**

**iSBTc Annual Meeting**

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# CTLA-4 blockade enhances tumor-specific immune responses



- CTLA-4 blockade has a consistent anti-tumor response rate of ~10%
- Partial and complete regression of disease observed
- All studies to date (> 4000 patients) conducted in metastatic disease setting (limited access to tumor tissues)
- Identification of biomarker to predict disease outcome or select appropriate patients for therapy is necessary

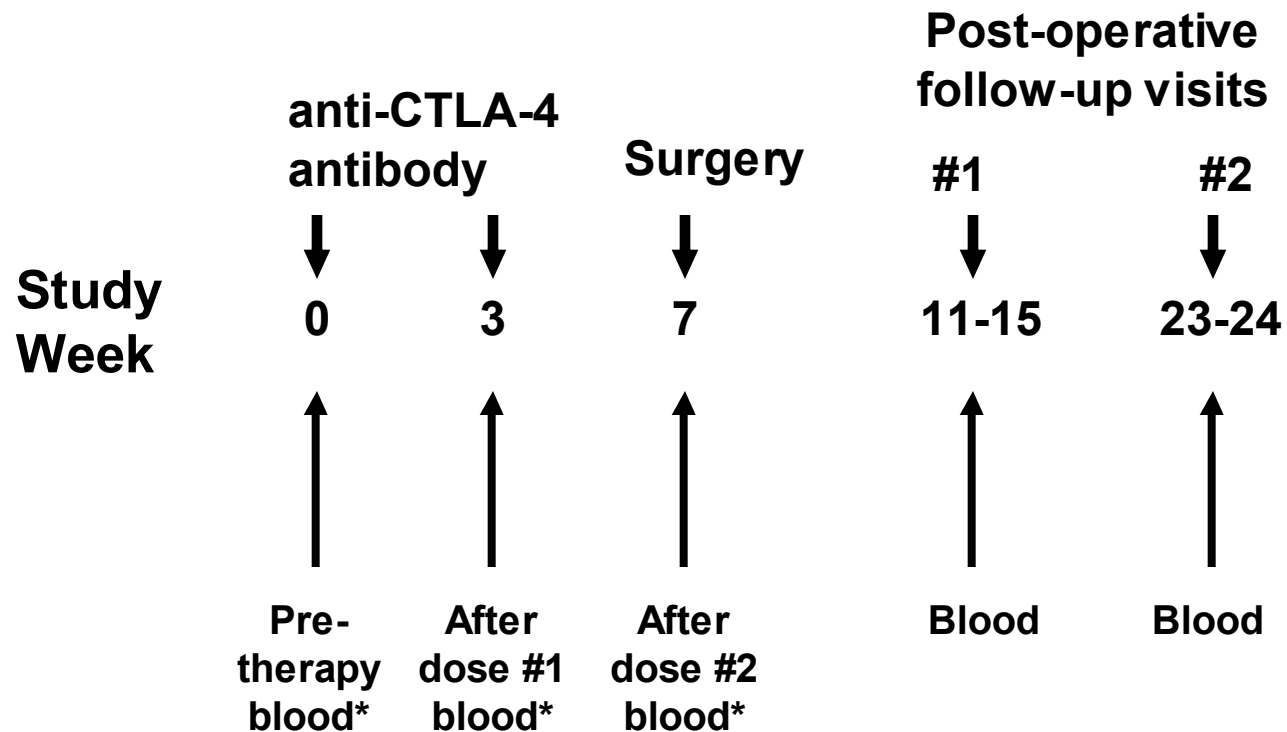
# **Critical Questions for Further Clinical Development of anti-CTLA-4**

- **What are the cellular and molecular mechanisms involved in the anti-tumor effect?**
- **What distinguishes responders from non-responders?**
- **What are the best conventional therapies or vaccines to be used combinatorially?**

# **Immune Monitoring**

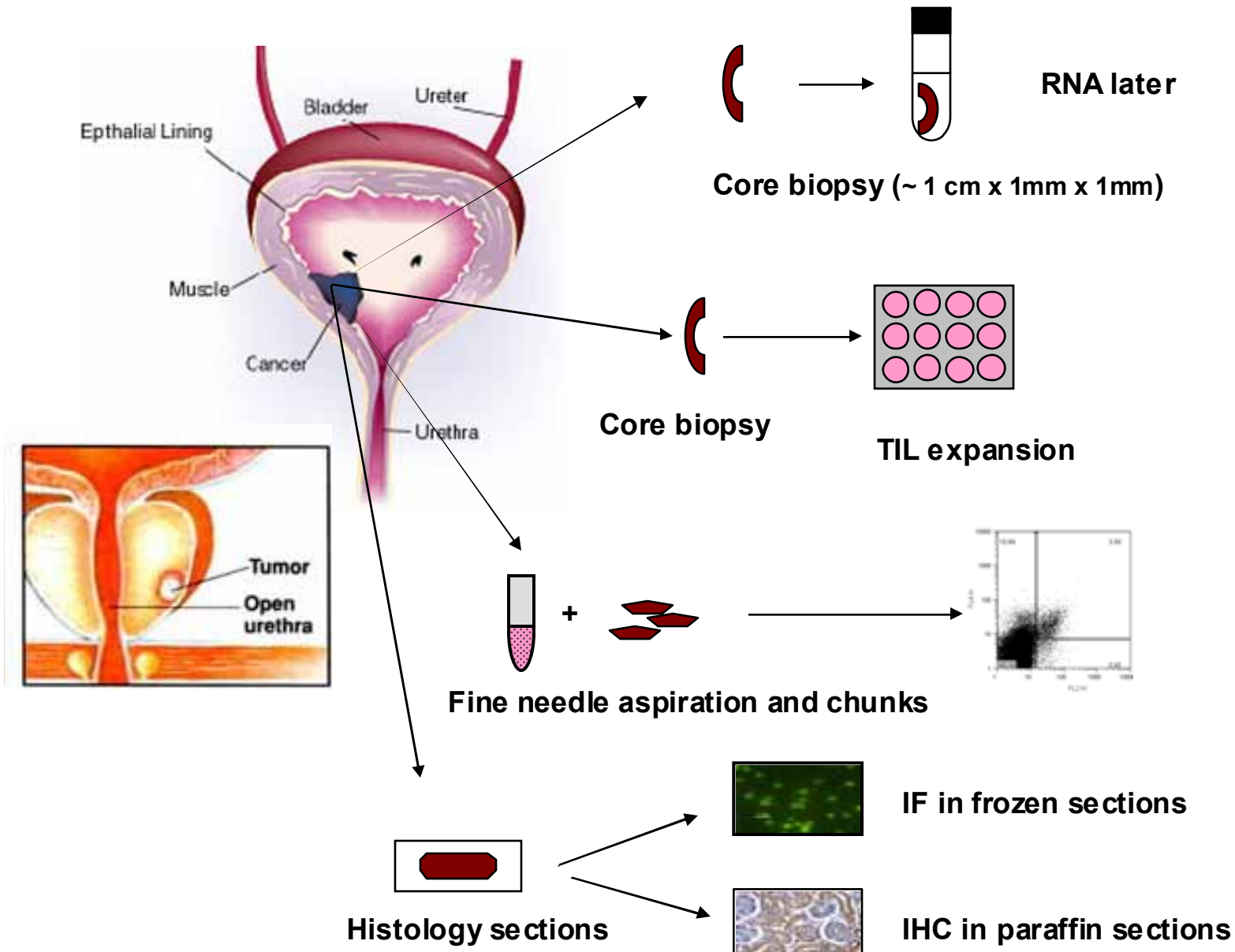
- **Cannot rely on solely monitoring of peripheral blood**
- **Need to identify immunological events that occur in tumor tissues after therapy**
- **Need to correlate changes in tumor tissues with those that occur in systemic circulation**
- **Identified markers can then be used for future immune monitoring**

# Pre-surgical clinical trial : Analysis of blood and tumor tissues



\*Blood drawn prior to antibody dose administered and prior to surgery

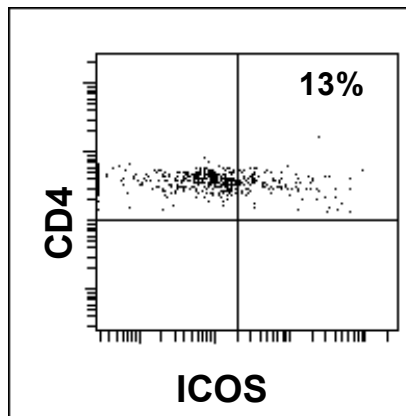
# Tissue Analysis



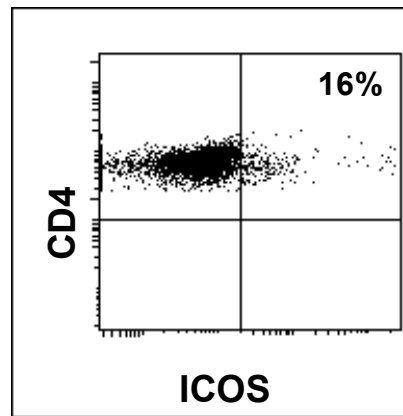
# BLADDER

## ICOS expression is higher in tumor tissues from anti-CTLA-4 treated patients

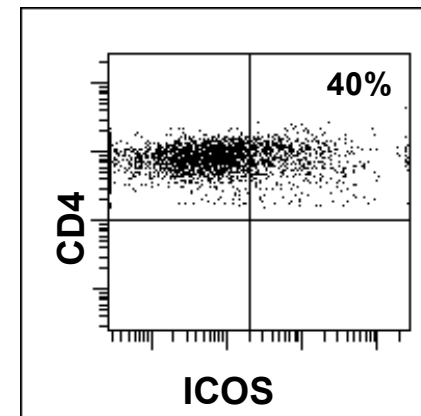
Non-malignant tissues:  
untreated



Tumor tissues:  
untreated



Tumor tissues:  
anti-CTLA-4 treated

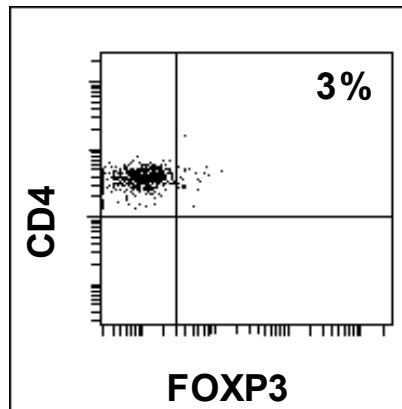




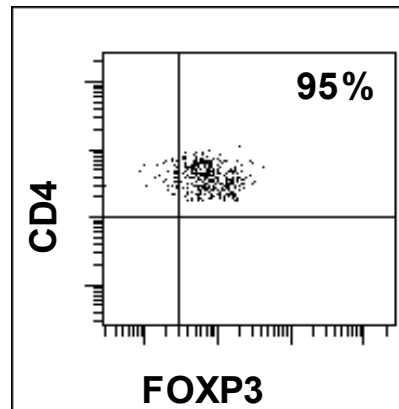
# BLADDER

## FOXP3 expression is lower in tumor tissues from anti-CTLA-4 treated patients

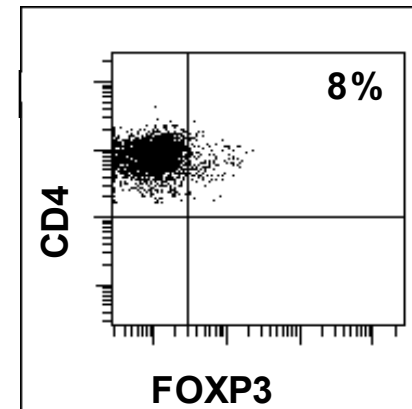
Non-malignant tissues:  
untreated



Tumor tissues:  
untreated



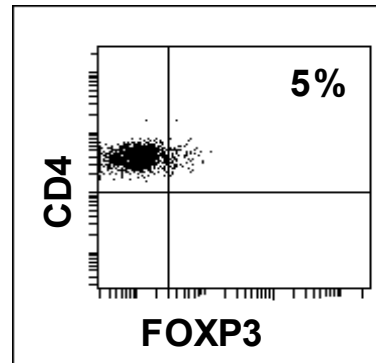
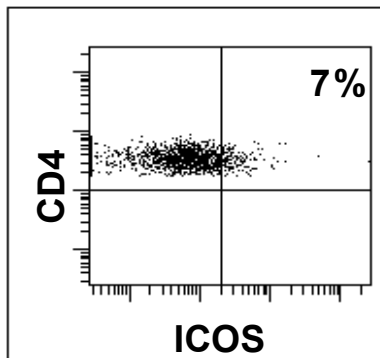
Tumor tissues:  
anti-CTLA-4 treated



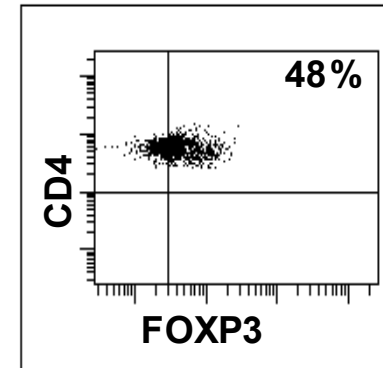
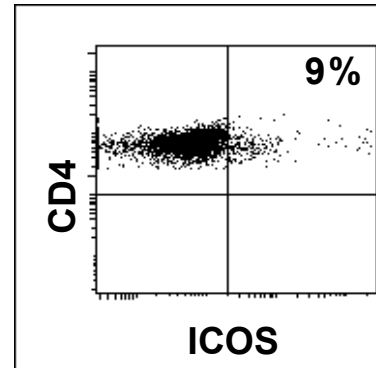
# PROSTATE

## ICOS and FOXP3 expression

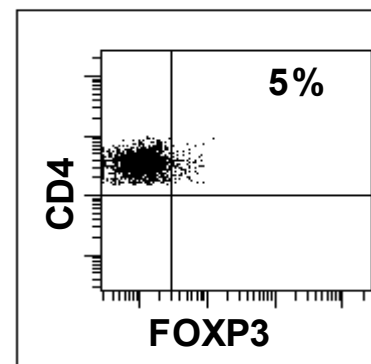
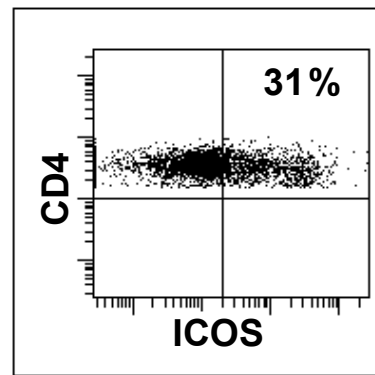
Untreated:  
Non-malignant prostate



Untreated:  
Prostate cancer



Anti-CTLA-4 treated:  
Prostate cancer



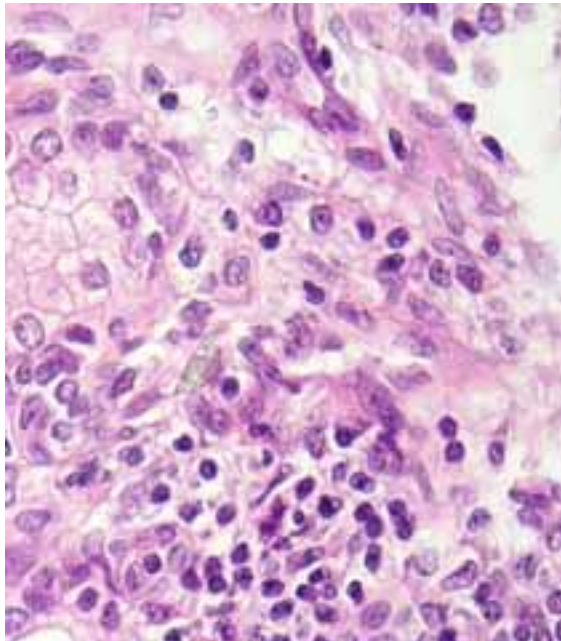
# ICOS: Marker of Treg or Teff? Important for Th2 or Th1 immune responses?

- Diverse function of ICOS
  - Marker of follicular helper T cells and plays a role in T:B cell interactions
  - ICOS<sup>-/-</sup> mice have decreased IL-10 production and defect in antibody class switching (Dong et al., 2001)
  - IL-10 producing Tregs are induced by pDCs expressing ICOS-ligand (Ito et al., 2007)
  - ICOS co-stimulation is necessary for IFN- $\gamma$  production and containment of viral infection (Humphreys et al., 2006)
  - ICOS<sup>hi</sup>, ICOS<sup>med</sup>, and ICOS<sup>low</sup> cells have different cytokine profiles (Lohning et al., 2003)
  - ICOS may promote survival of activated T cells, including Tregs and Teff (Burmeister et al., 2008)
- Impact of ICOS expression on T cell function appears to be dependent on T cell subset and possibly interaction with ICOS-ligand on APCs

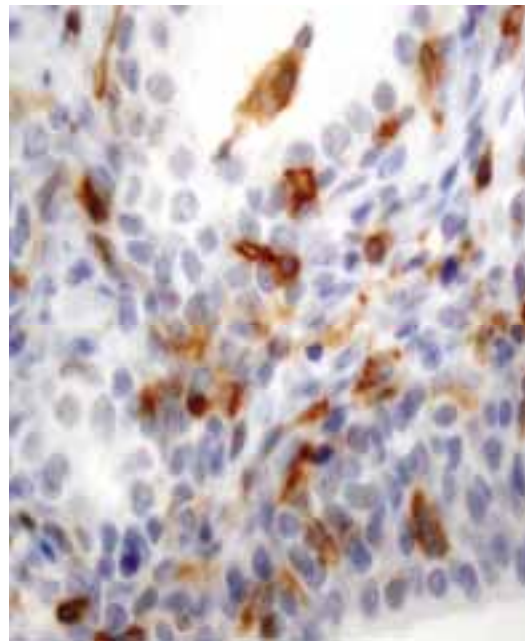
**Are ICOS-expressing T cells effector cells in the setting of anti-CTLA-4 therapy?**

# Expression of NY-ESO-1 tumor antigen allowed for functional analyses of TILs

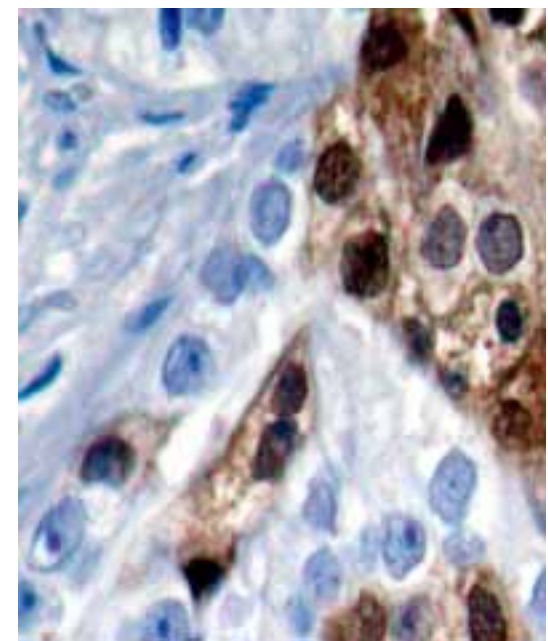
H & E



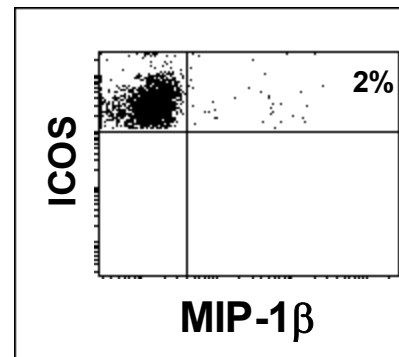
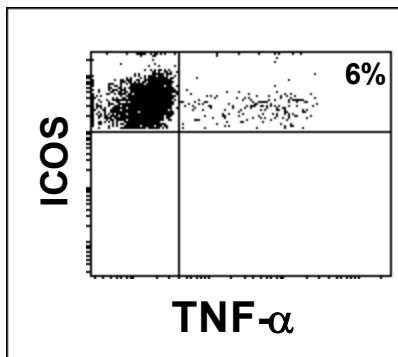
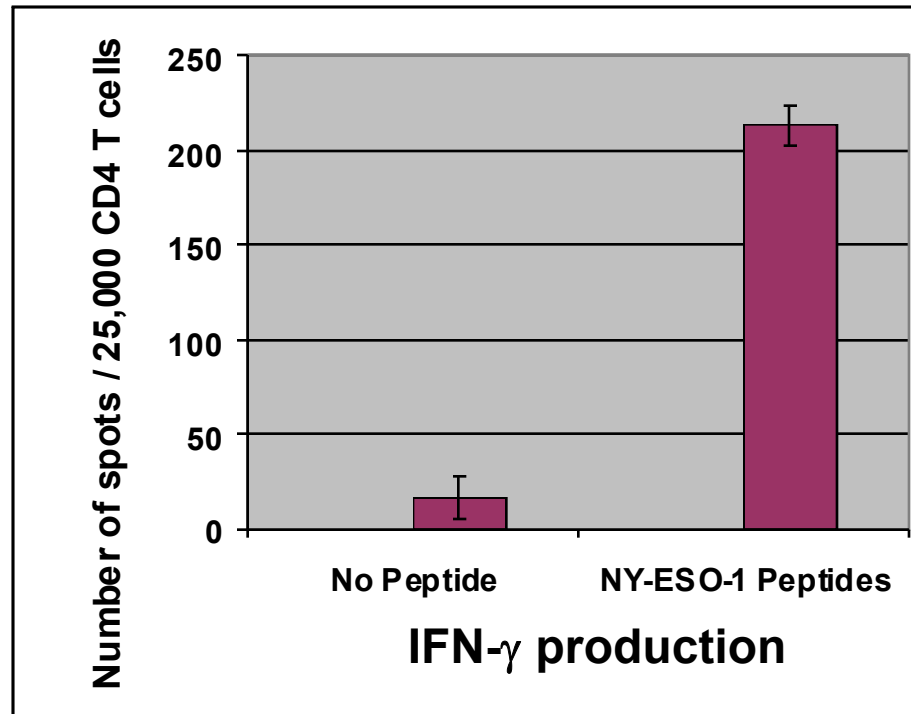
CD4 T cells



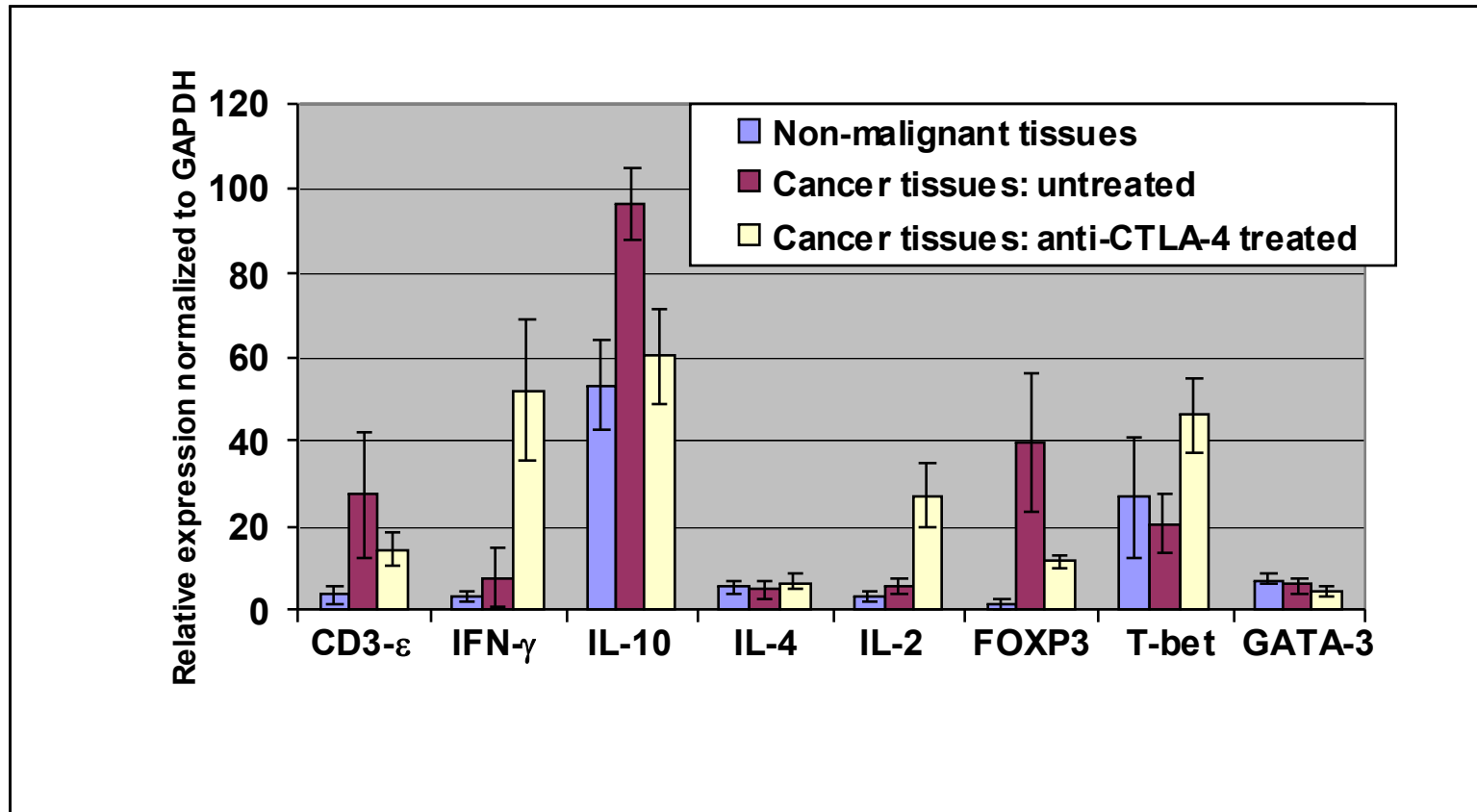
NY-ESO-1



# Recognition of NY-ESO-1 by TILs



# Increased IFN- $\gamma$ and T-bet mRNA in treated tissues with concomitant decrease in FOXP3 mRNA levels



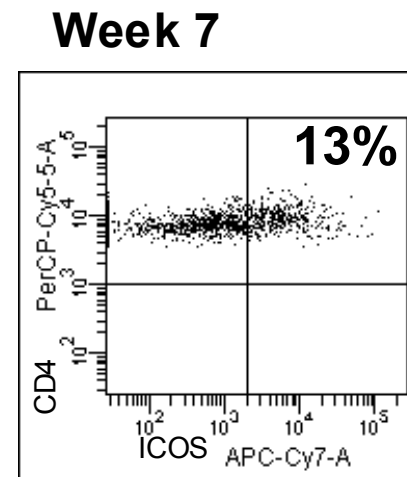
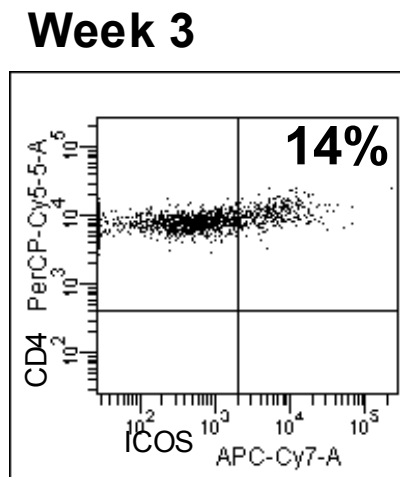
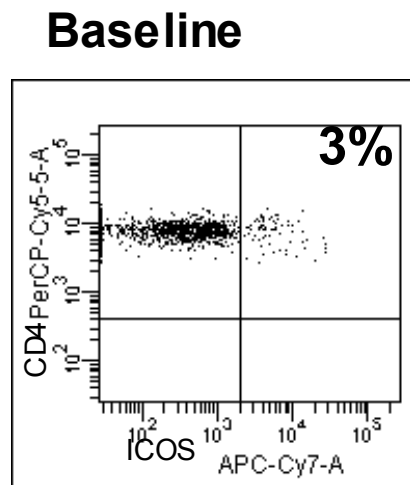
**What about immunologic events in the systemic circulation?**

**Do they correlate with observed changes in tumor tissues?**



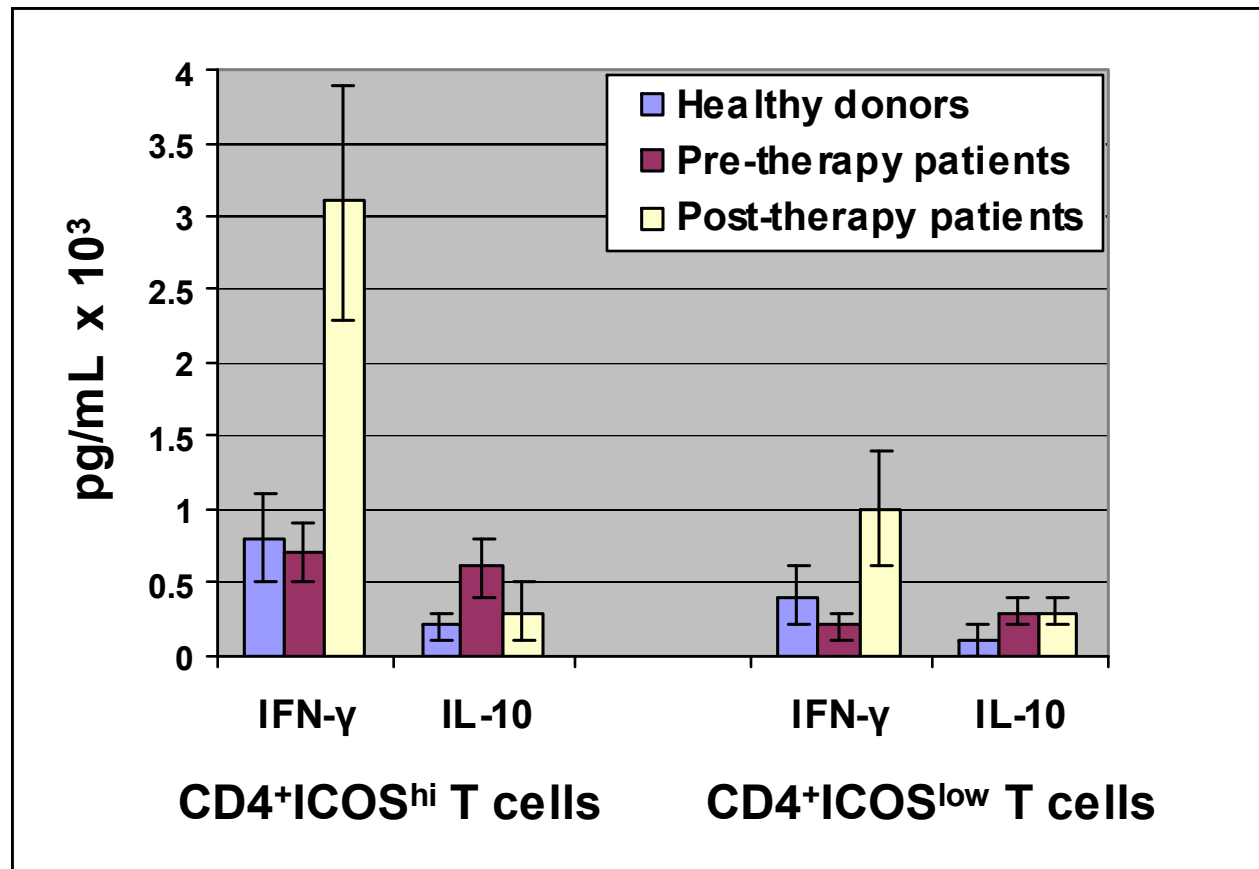
# ICOS expression significantly increases on CD4 T cells in peripheral blood after treatment with anti-CTLA-4 antibody

CD4

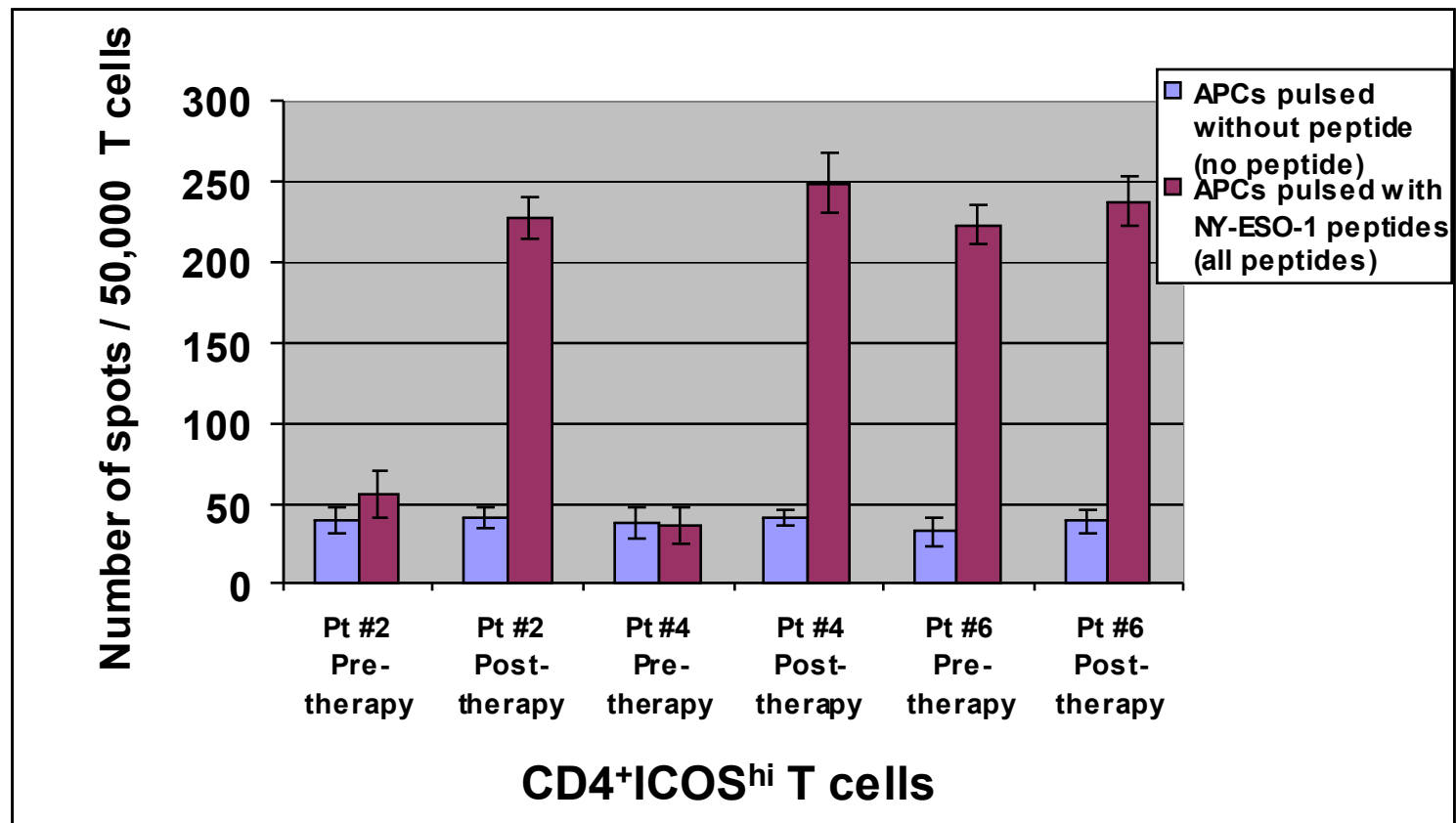
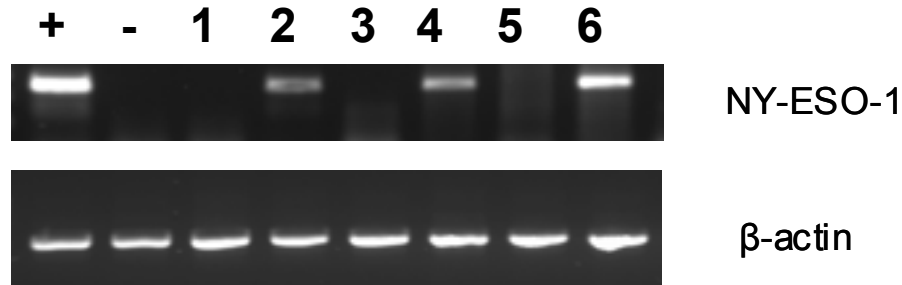


ICOS

# ICOS<sup>hi</sup> T cells in peripheral blood from anti-CTLA-4 treated patients produce IFN- $\gamma$



# ICOS<sup>hi</sup> T cells from peripheral blood recognize NY-ESO-1 tumor antigen



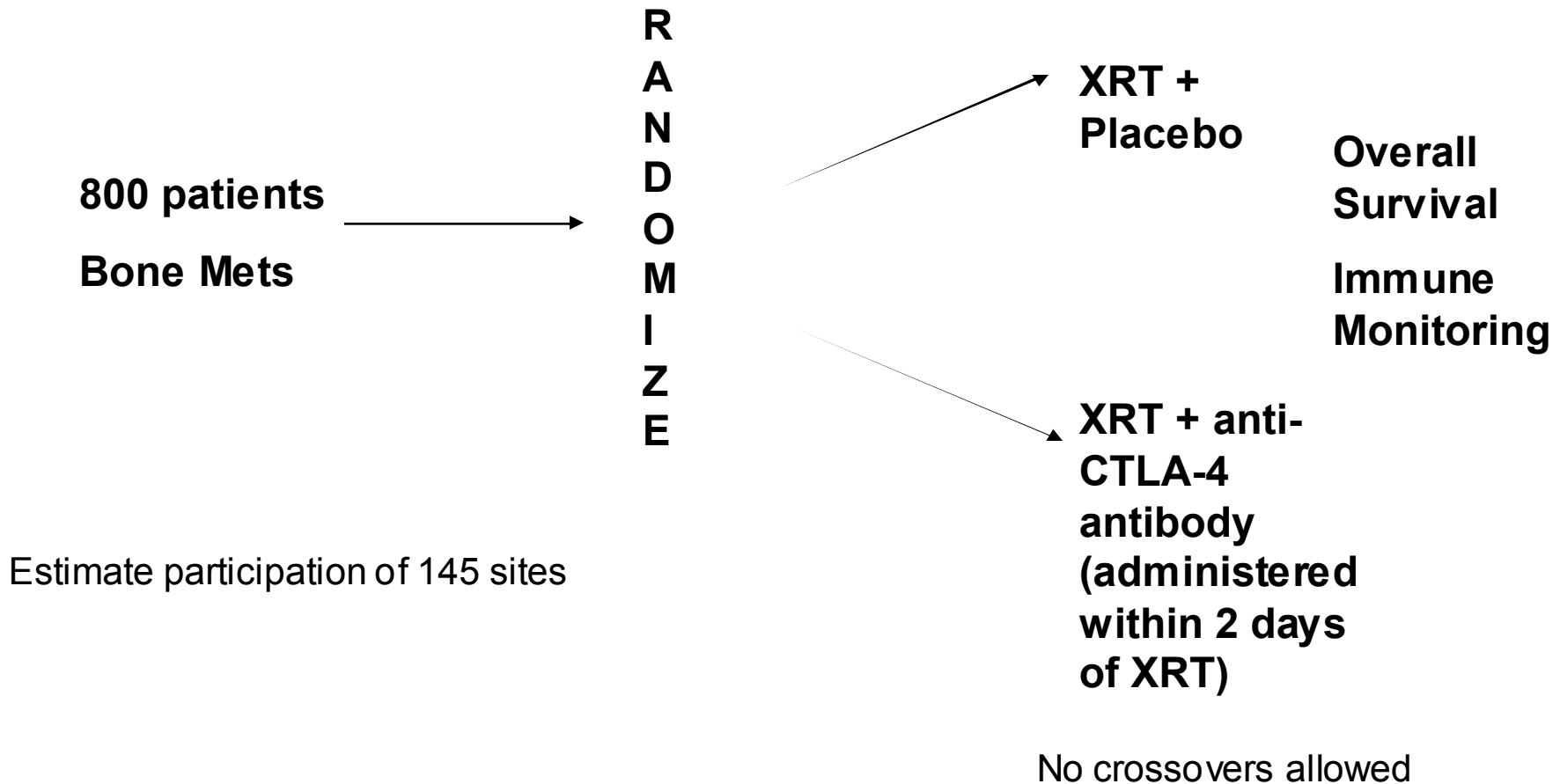
# Next Steps

- **Larger cohorts of patients to correlate ICOS-expression and clinical outcomes**

Phase III clinical trial in prostate cancer patients

- **Combination Strategies: clinical trials with anti-CTLA-4 therapy plus other agents that prime T cell responses**
- **Murine Studies: 1) determine the role of ICOS-expressing T cells in anti-tumor responses and; 2) identify rational combinations for future clinical trials**

# Phase III clinical trial with Ipilimumab + XRT vs. Placebo + XRT in CRPC



- **Sharma Lab Team**
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  - Jingjing Sun
  - Tihui Fu
  - Qiuming He
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- **BMS Team**
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