

Manipulation of the Tumor Microenvironment by CTLA-4 Blockade

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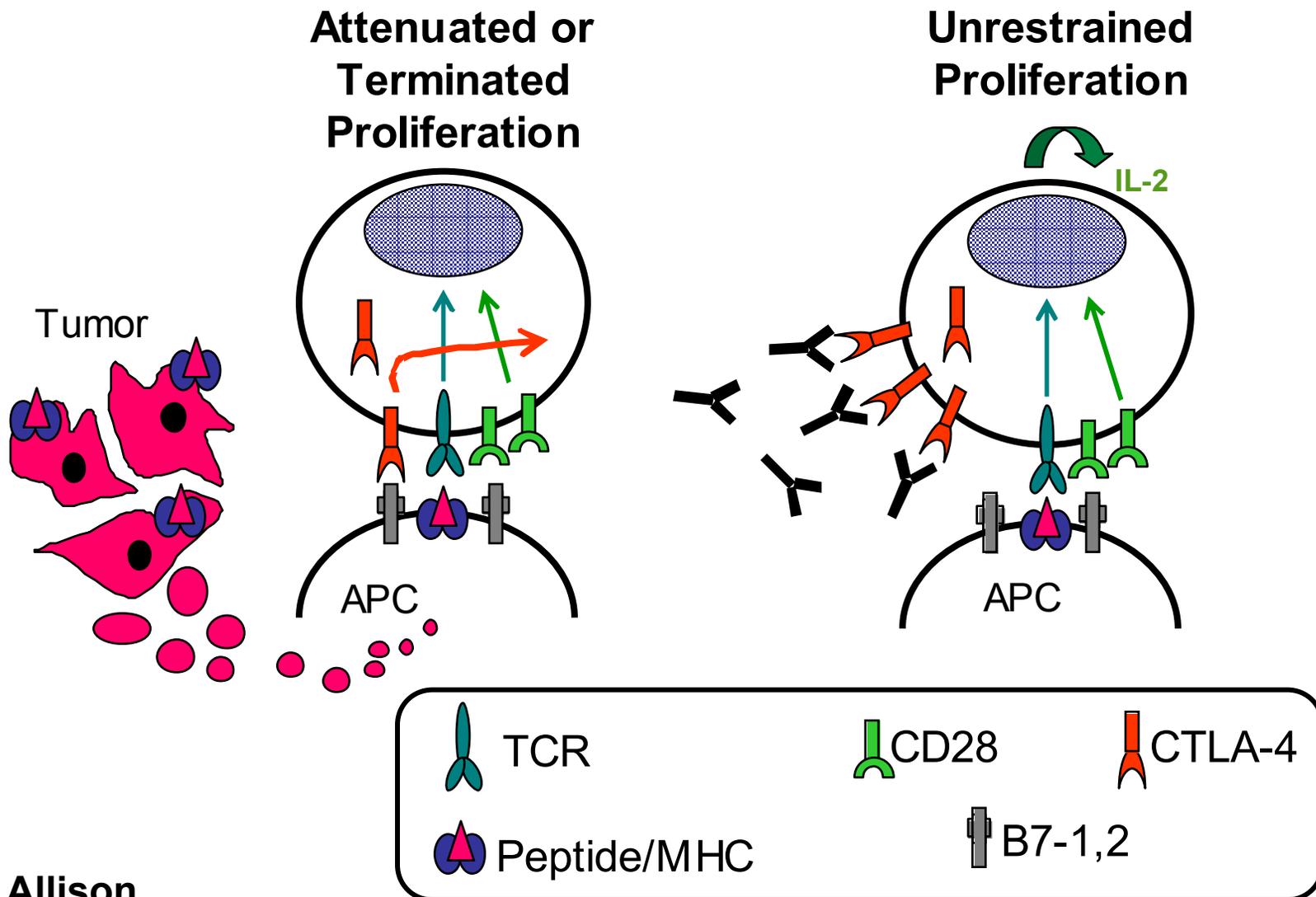
M. D. Anderson Cancer Center

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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

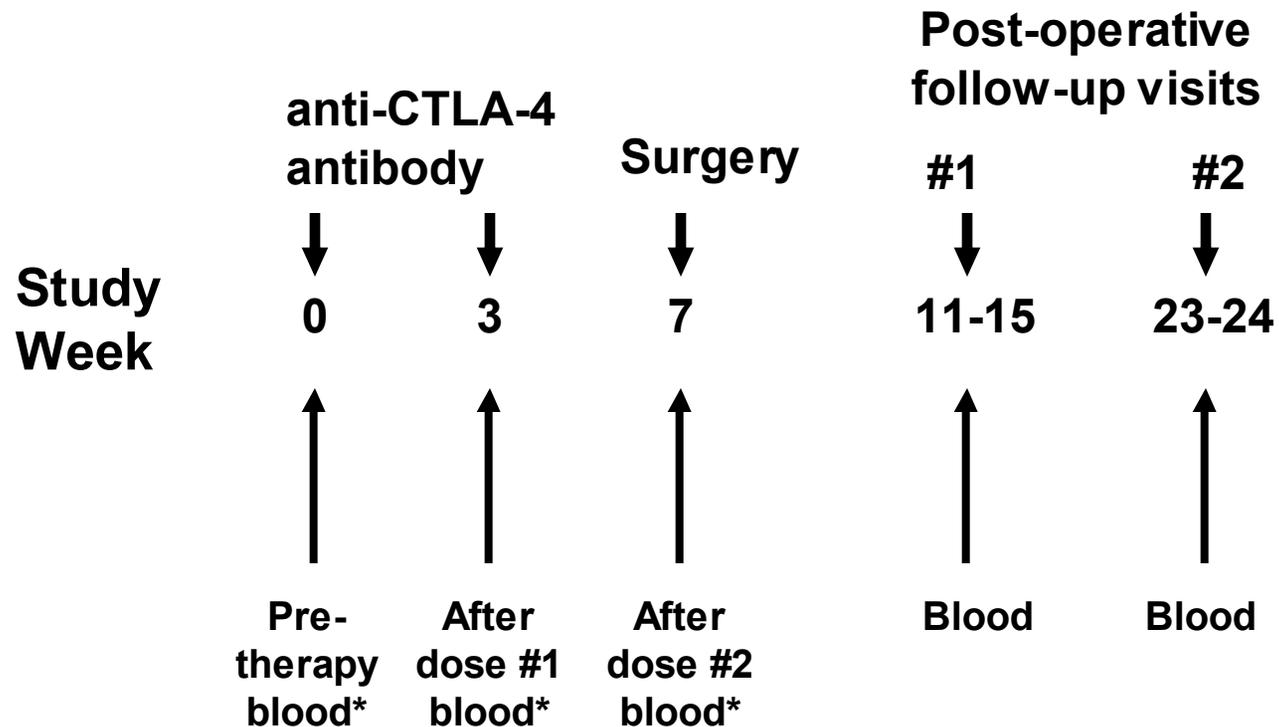
Critical Questions for Further Clinical Development of anti-CTLA-4

- 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

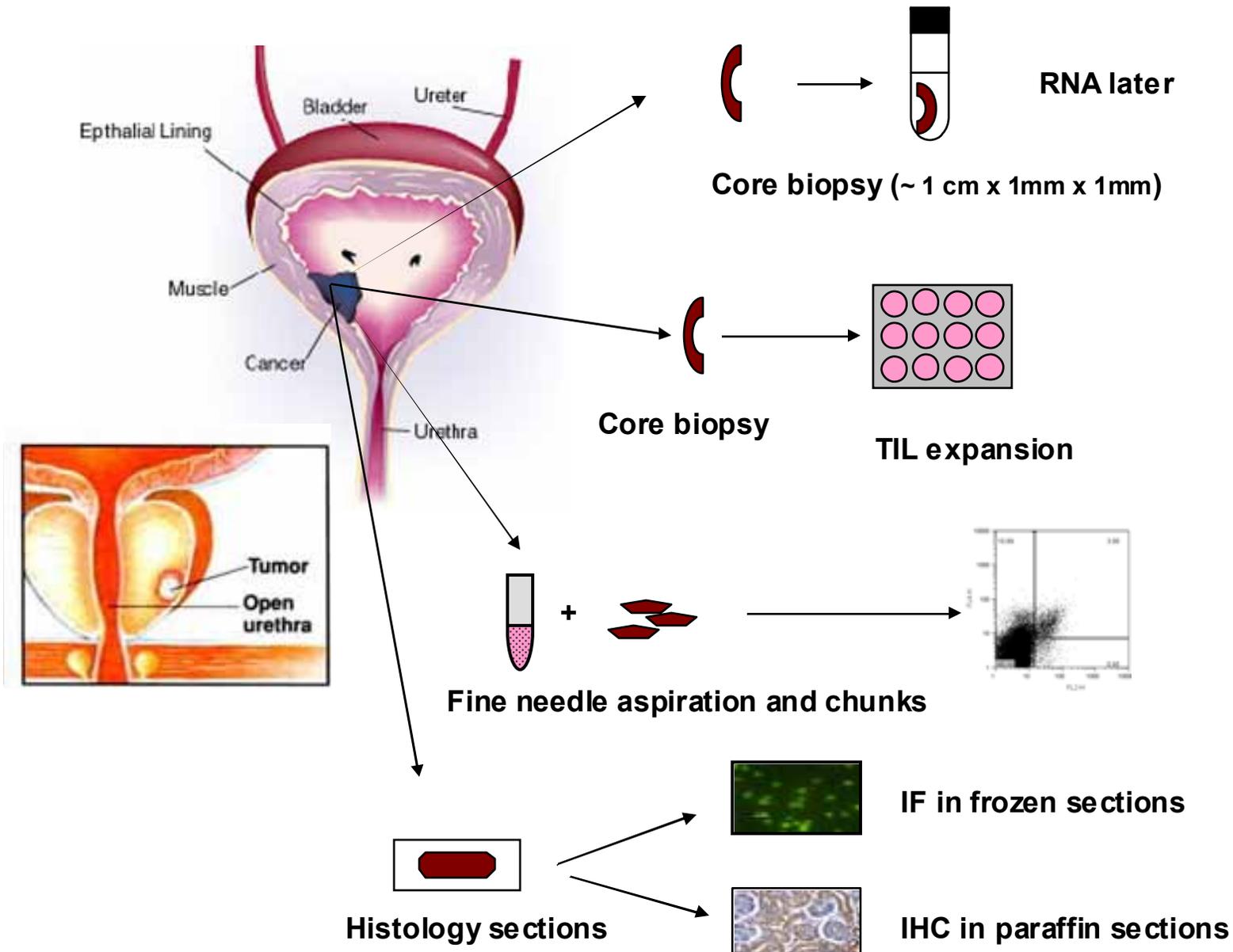
- **Cannot rely on solely monitoring of peripheral blood**
- **Need to identify immunological events that occur in tumor tissues after therapy**
- **Need to correlate changes in tumor tissues with those that occur in systemic circulation**
- **Identified markers can then be used for future immune monitoring**

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



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

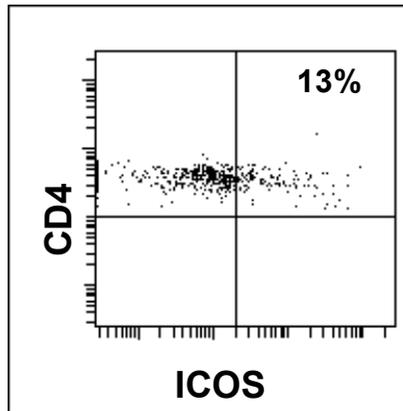
Tissue Analysis



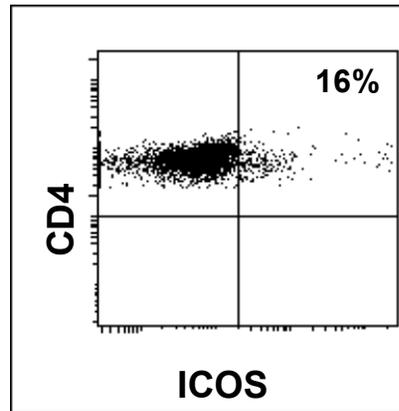
BLADDER

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

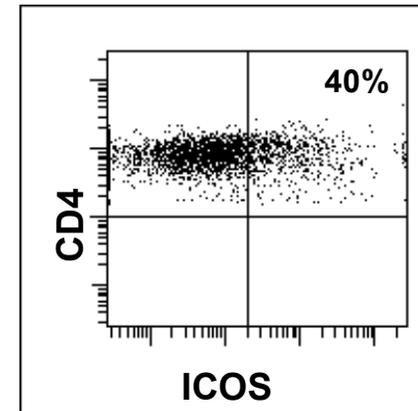
**Non-malignant tissues:
untreated**



**Tumor tissues:
untreated**



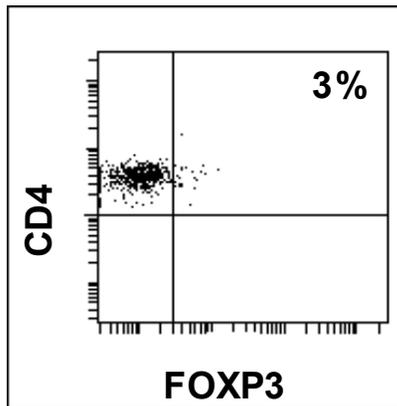
**Tumor tissues:
anti-CTLA-4 treated**



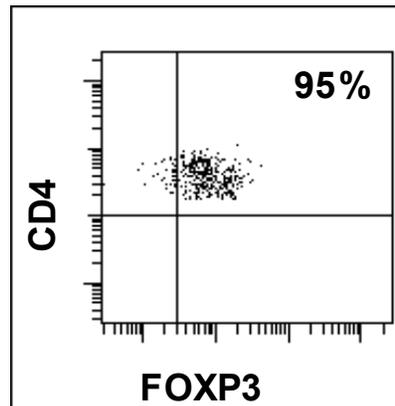
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FOXP3 expression is lower in tumor tissues from anti-CTLA-4 treated patients

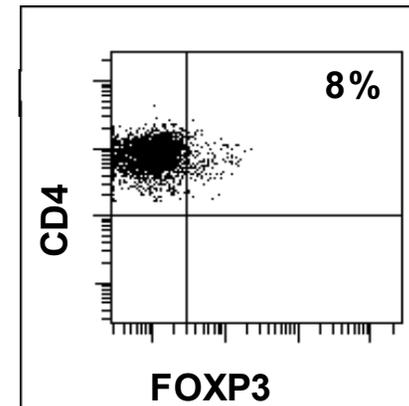
**Non-malignant tissues:
untreated**



**Tumor tissues:
untreated**



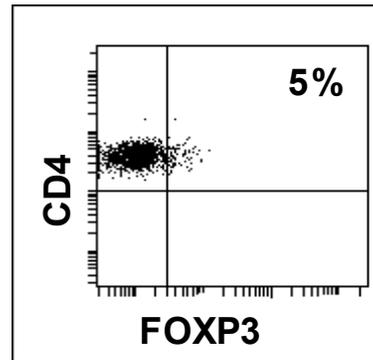
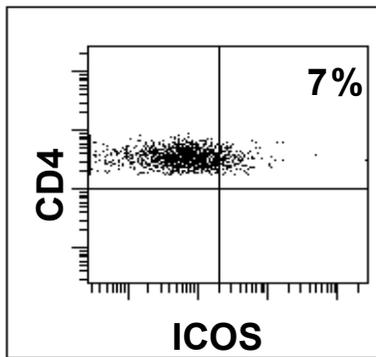
**Tumor tissues:
anti-CTLA-4 treated**



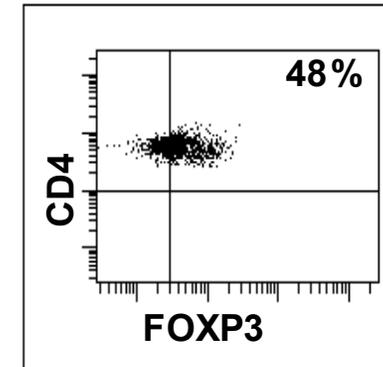
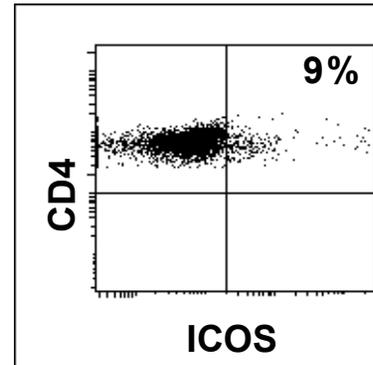
PROSTATE

ICOS and FOXP3 expression

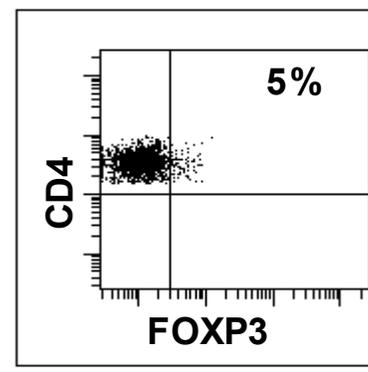
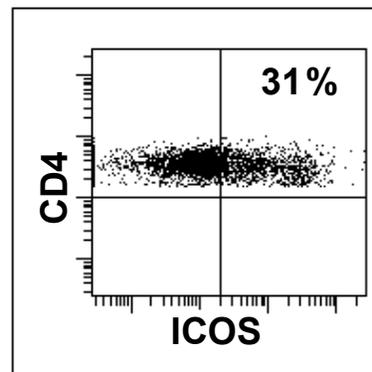
Untreated:
Non-malignant prostate



Untreated:
Prostate cancer



Anti-CTLA-4 treated:
Prostate cancer



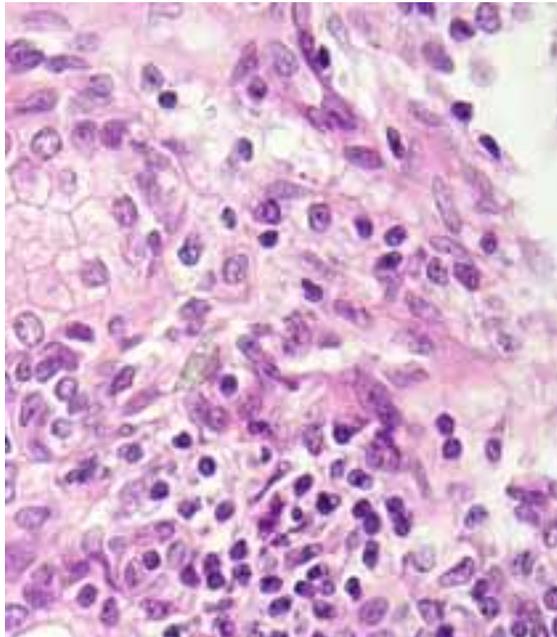
ICOS: Marker of Treg or Teff? Important for Th2 or Th1 immune responses?

- Diverse function of ICOS
 - Marker of follicular helper T cells and plays a role in T:B cell interactions
 - ICOS^{-/-} 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- γ production and containment of viral infection (Humphreys et al., 2006)
 - ICOS^{hi}, ICOS^{med}, and ICOS^{low} 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

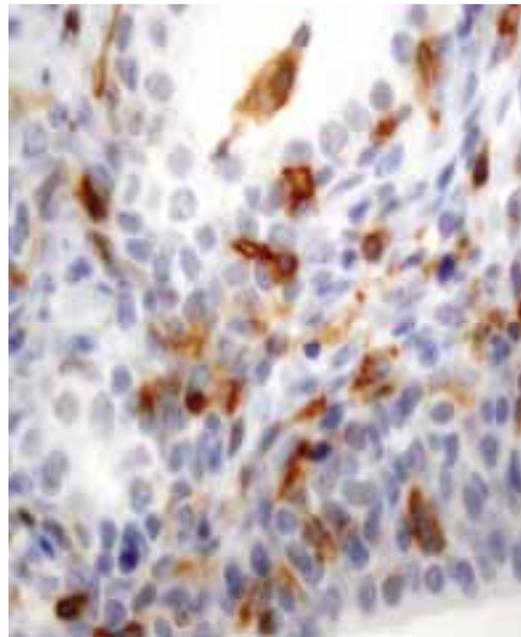
Are ICOS-expressing T cells effector cells in the setting of anti-CTLA-4 therapy?

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

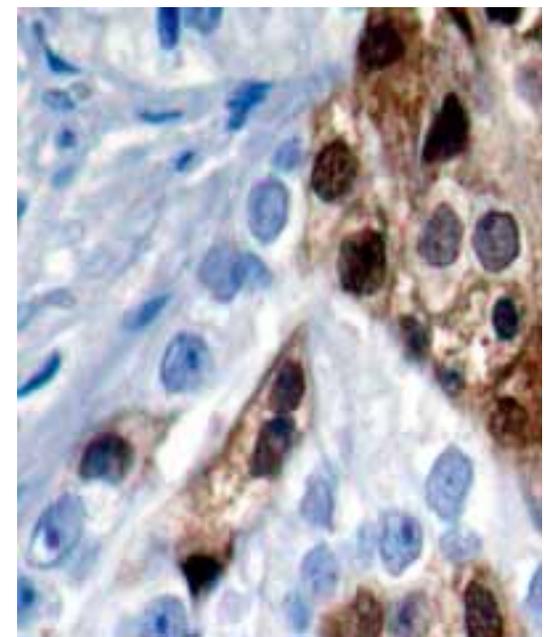
H & E



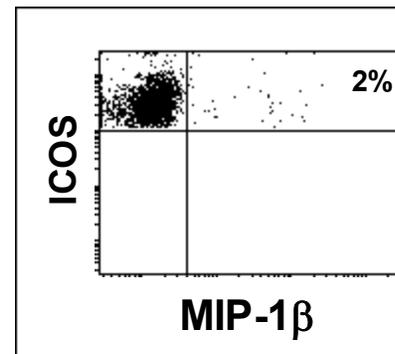
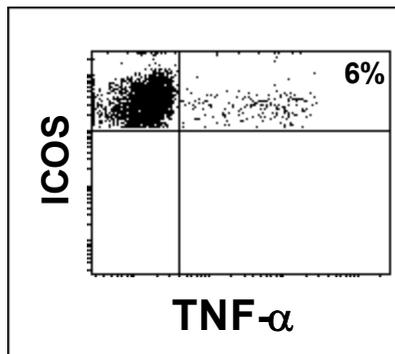
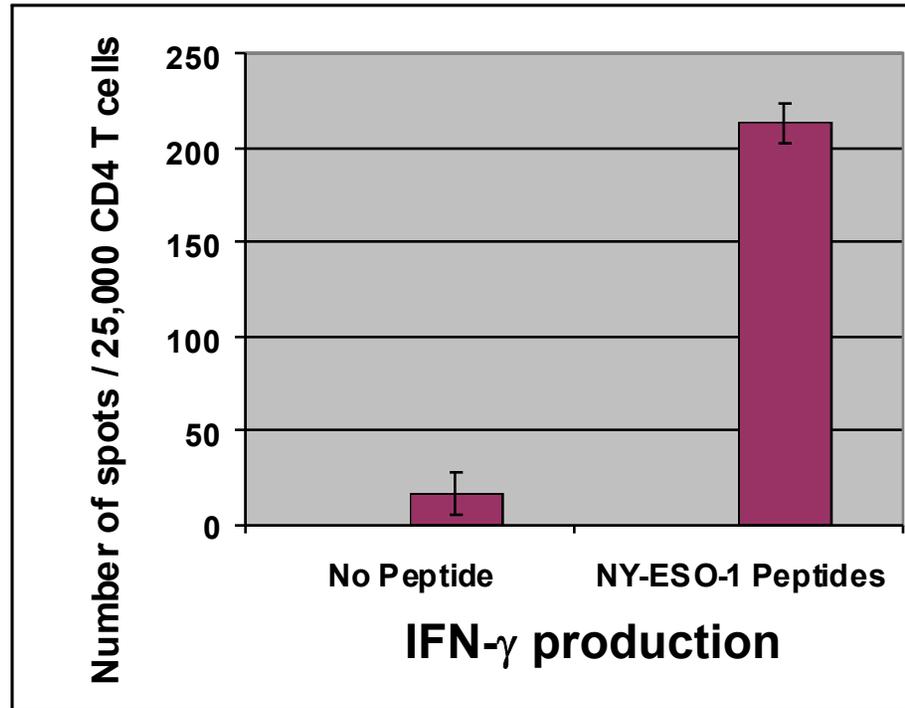
CD4 T cells



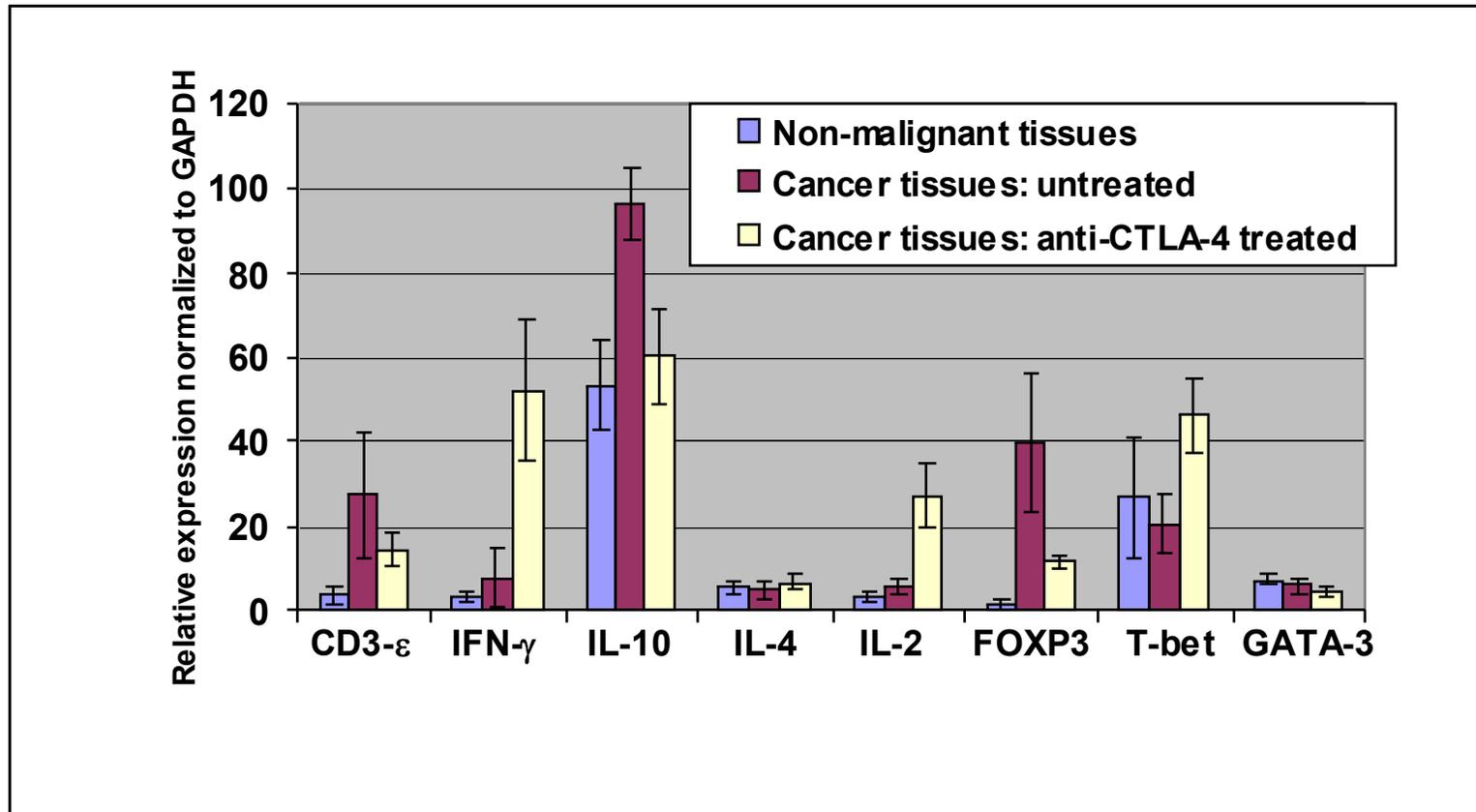
NY-ESO-1



Recognition of NY-ESO-1 by TILs



Increased IFN- γ and T-bet mRNA in treated tissues with concomitant decrease in FOXP3 mRNA levels

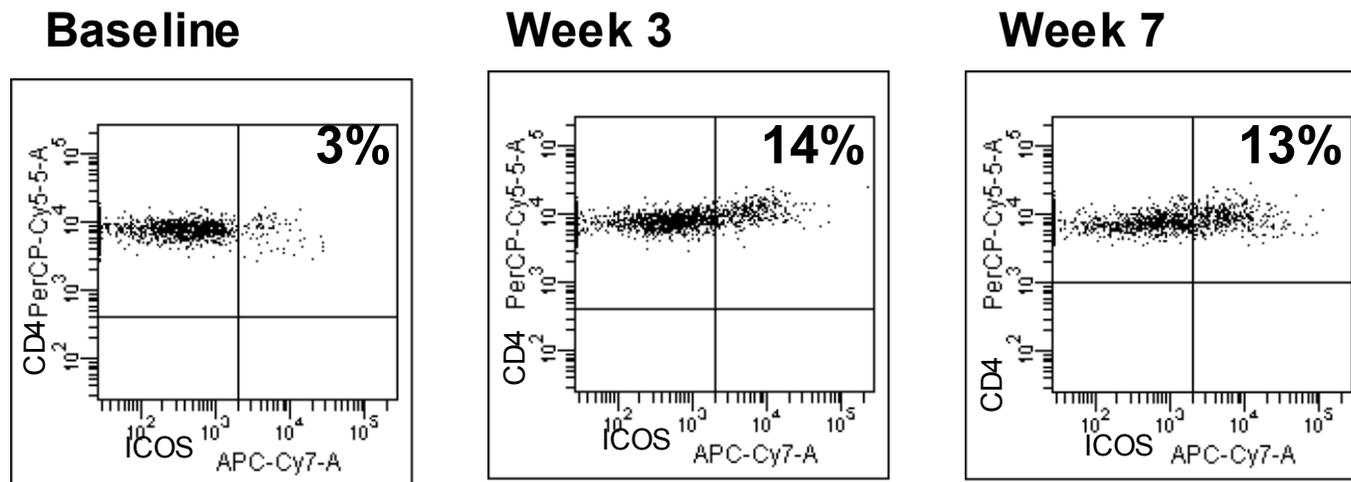


What about immunologic events in the systemic circulation?

Do they correlate with observed changes in tumor tissues?

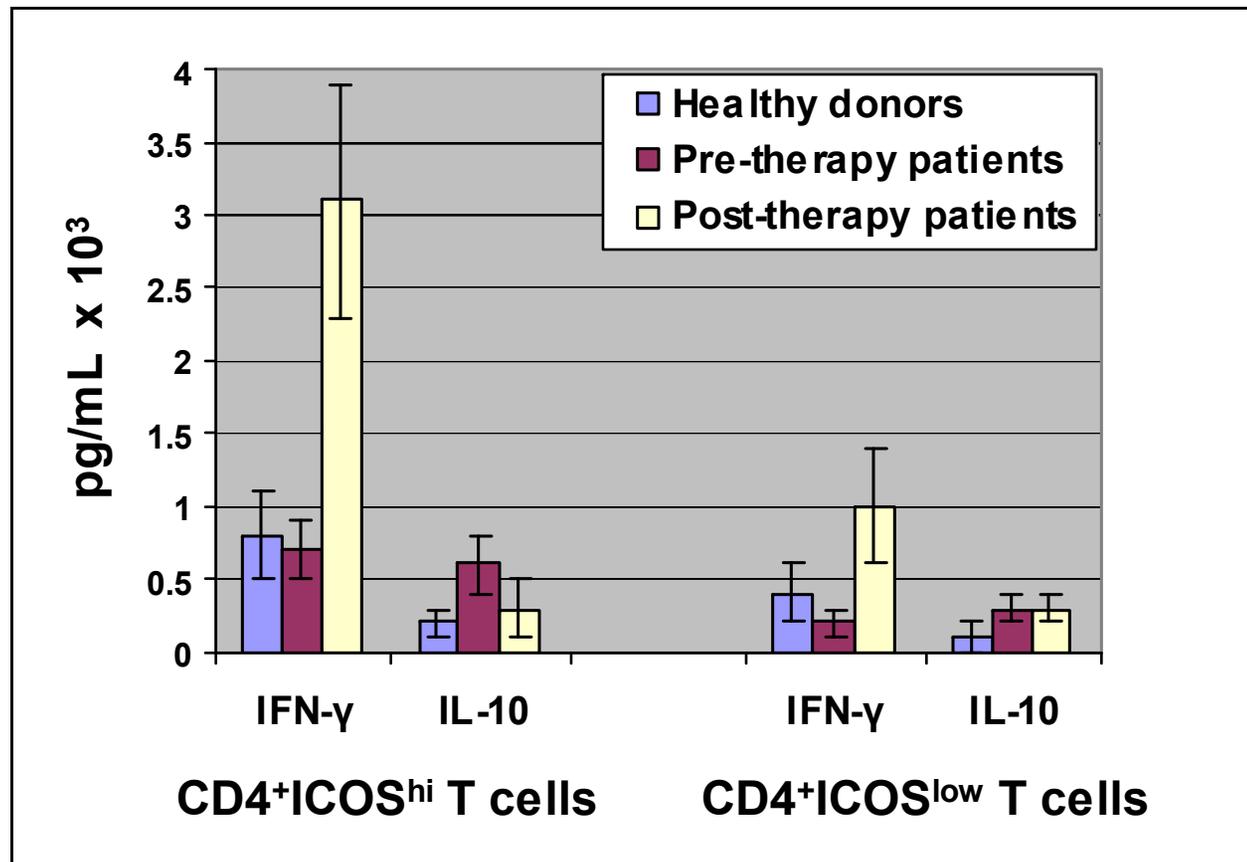
ICOS expression significantly increases on CD4 T cells in peripheral blood after treatment with anti-CTLA-4 antibody

CD4

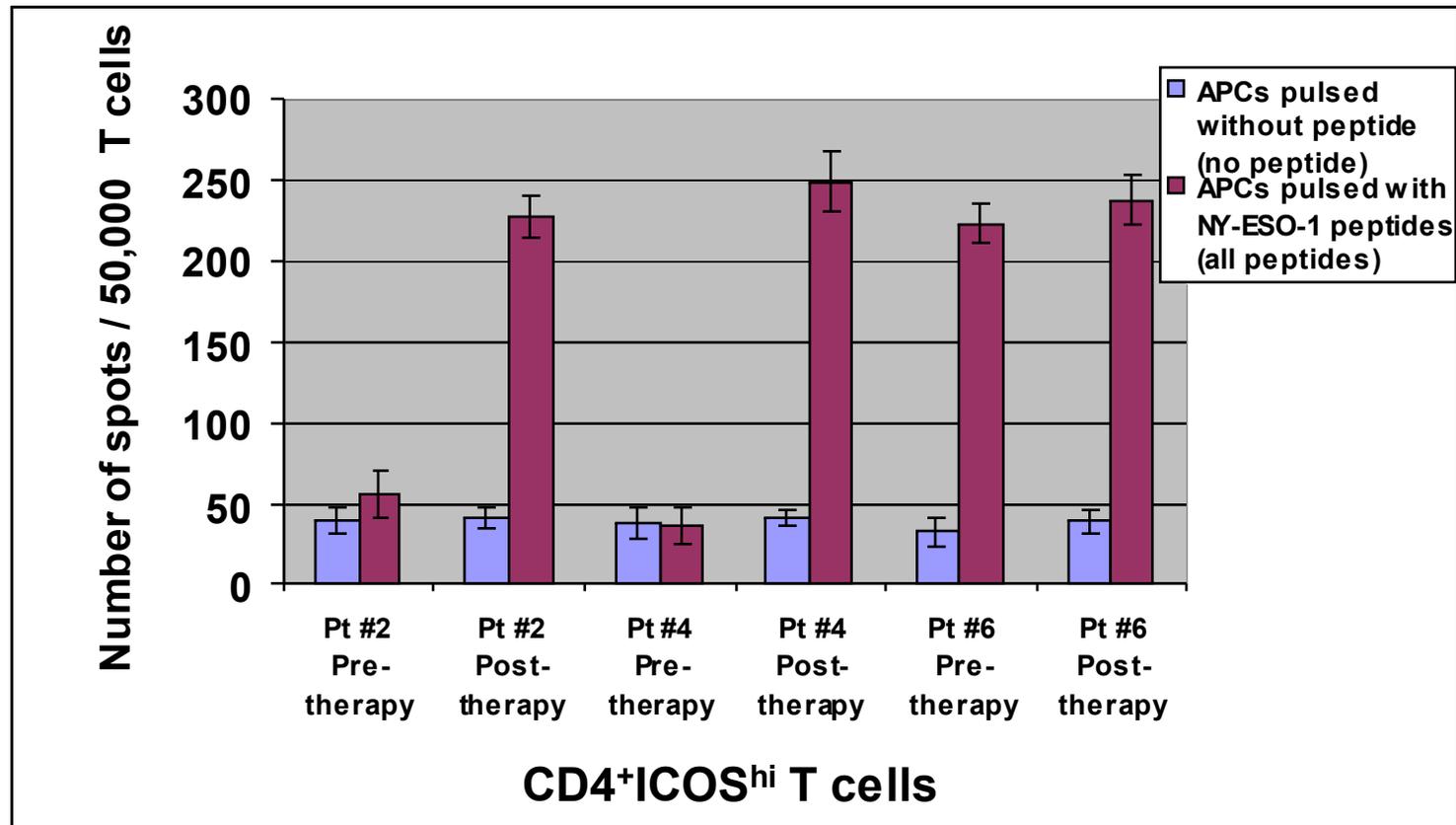
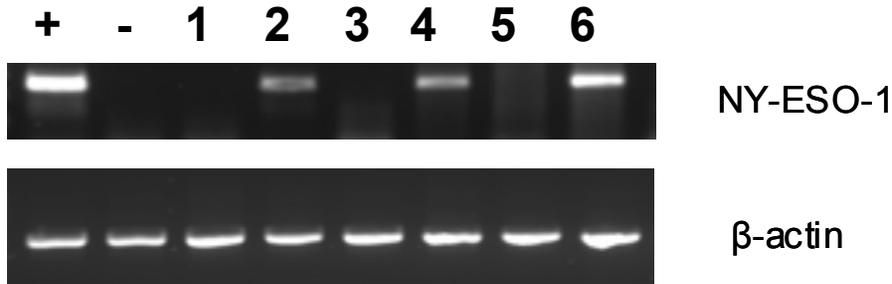


ICOS

ICOS^{hi} T cells in peripheral blood from anti-CTLA-4 treated patients produce IFN- γ



ICOS^{hi} T cells from peripheral blood recognize NY-ESO-1 tumor antigen



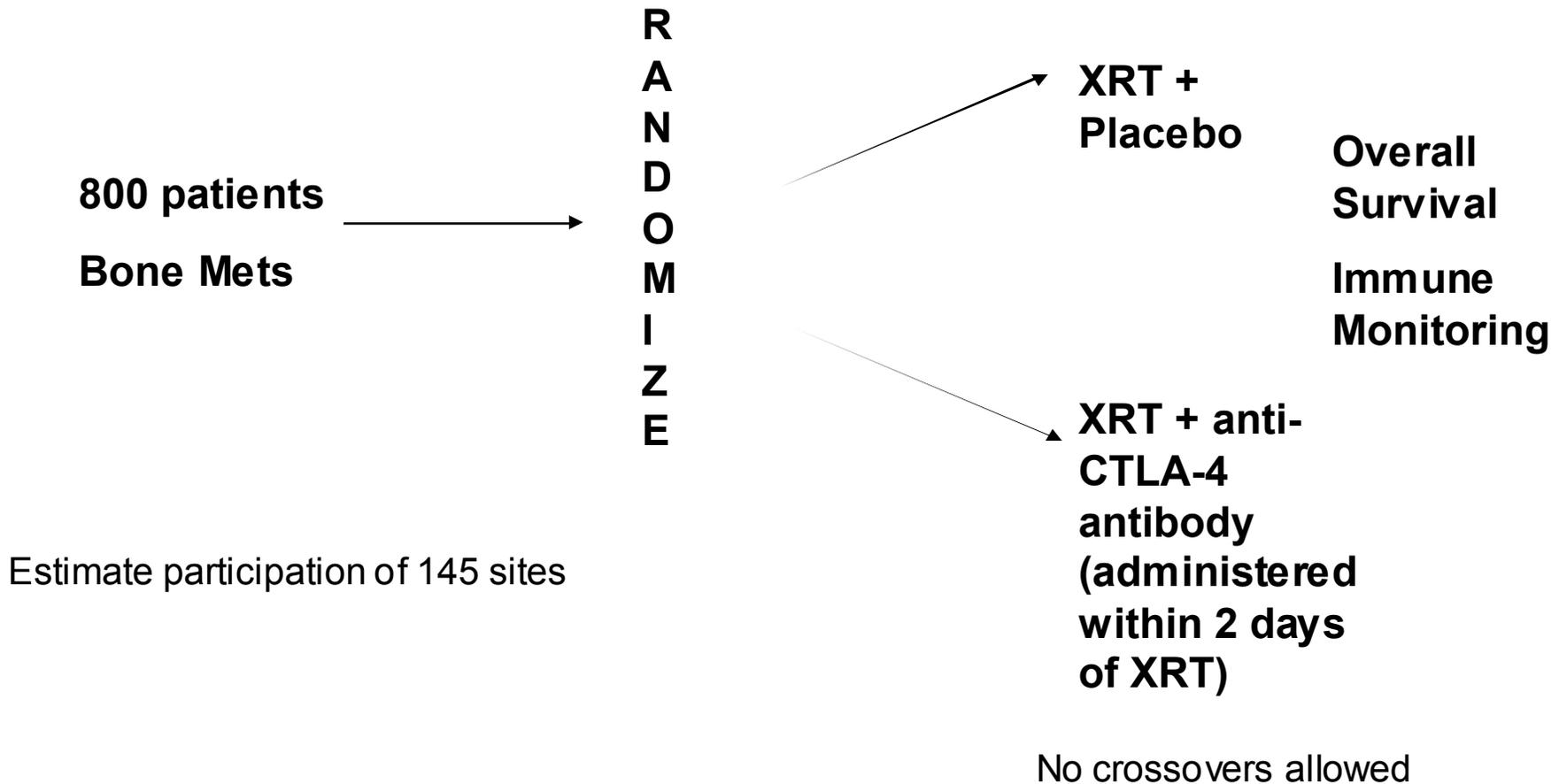
Next Steps

- **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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 - Tihui Fu
 - Qiuming He
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 - Jim Allison, Jedd Wolchok, Jianda Yuan (LCCI, MSKCC)
- **BMS Team**
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