Exploring Therapeutic Combinations with anti-CTLA-4 Antibody

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Disclosures

- **Served on advisory board, BMS, received honorarium**
- **Served on advisory board, Dendreon, received honorarium**

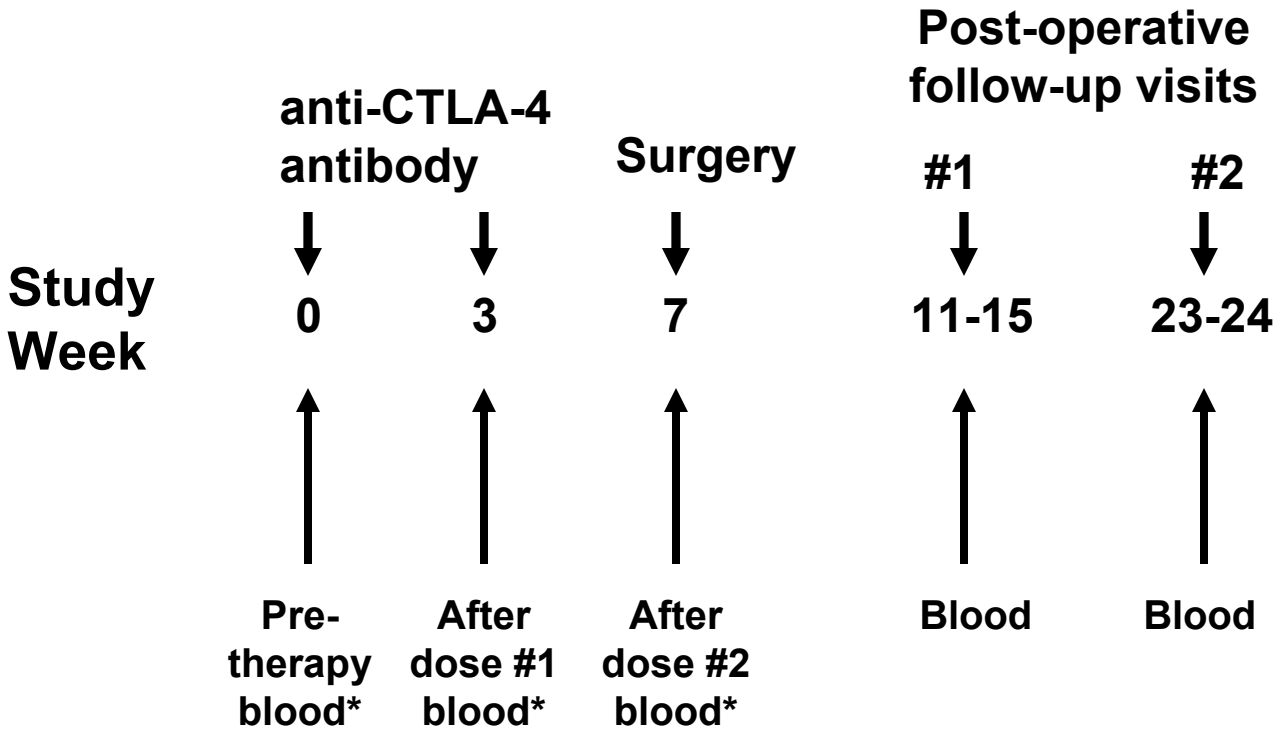
Improving on CTLA-4 blockade

- CTLA-4 blockade has a consistent anti-tumor response rate of ~10% and survival benefit of ~20-30%; Phase III trial with documented survival benefit

- Durable partial and complete regression of disease observed in a subset of patients

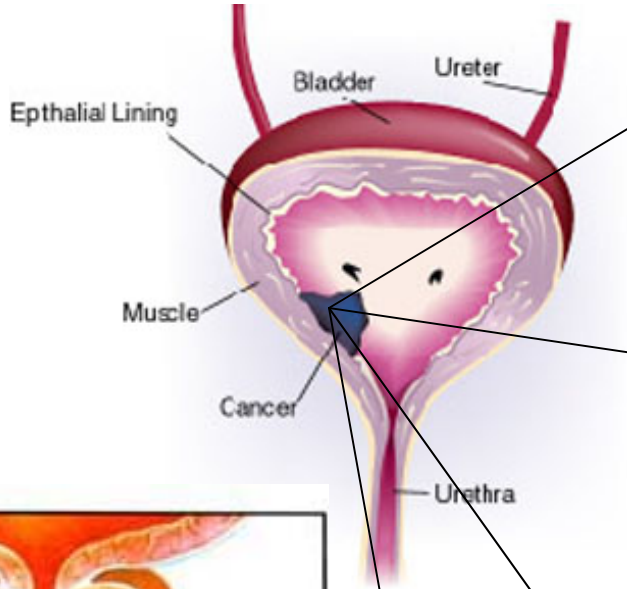
- How can we do better?
  - Identify immunologic markers that predict which patients will benefit and provide therapy to those patients
  - Explore combination therapies to increase the numbers of patients who will benefit

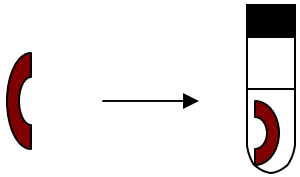
Part I
Identification of immunologic markers: Pre-surgical clinical trial with anti-CTLA-4 monotherapy



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

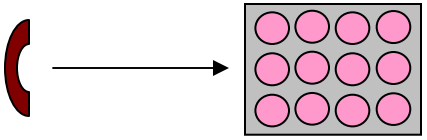
Tissue Analysis





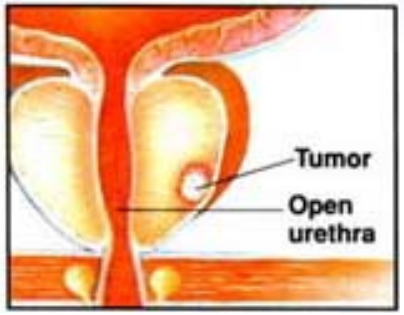
RNA later

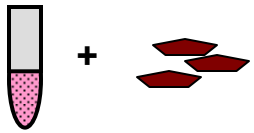
Core biopsy (~ 1 cm x 1mm x 1mm)

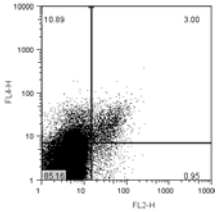


Core biopsy

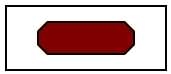
TIL expansion

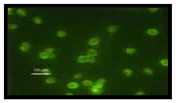






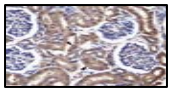
Fine needle aspiration and chunks





IF in frozen sections

Histology sections

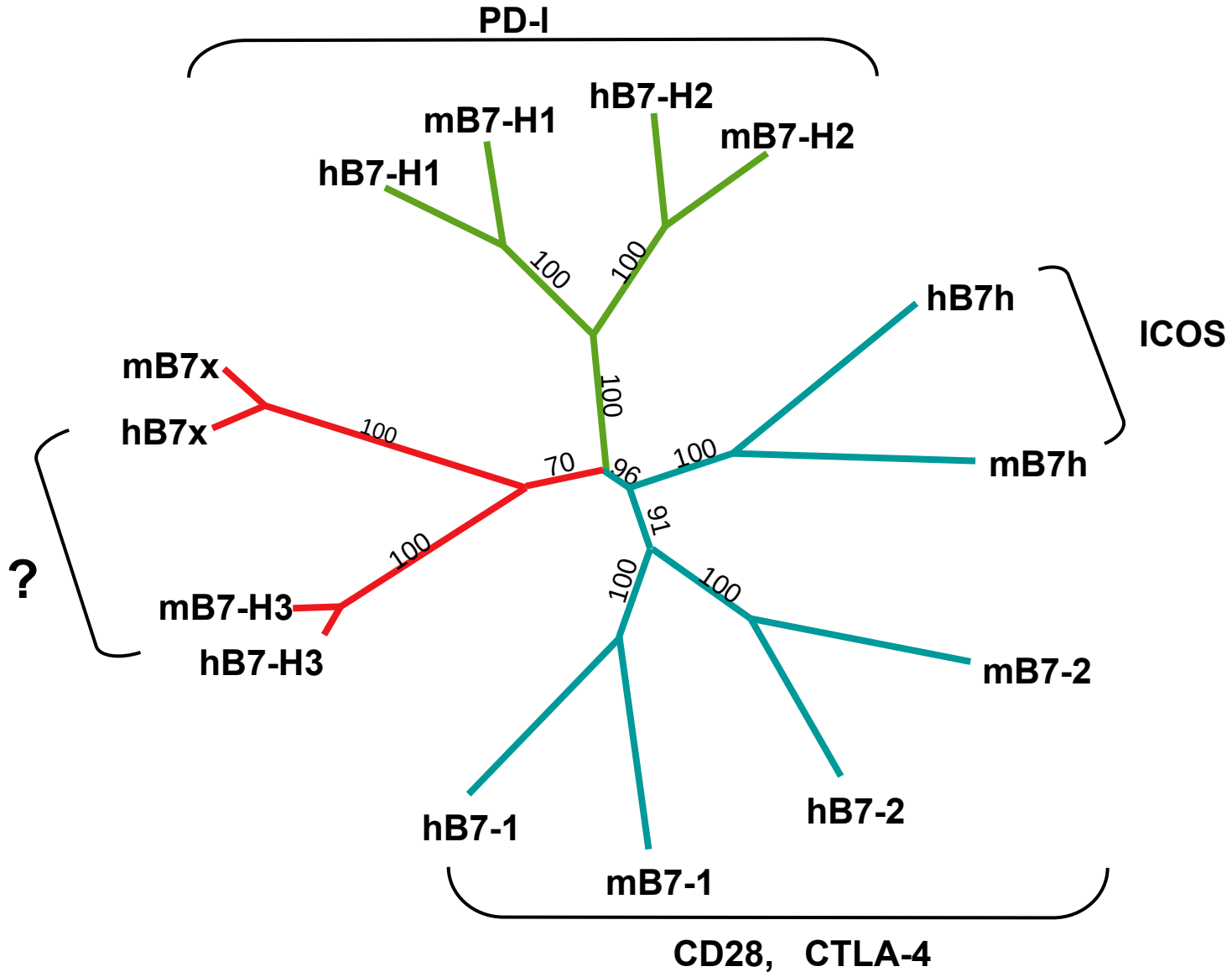


IHC in paraffin sections

Clinical Trial

- Patients who are surgical candidates (N=12)
  - 6 patients dosed at 3mg/kg/dose and 6 patients dosed at 10 mg/kg/dose
  - Organ-confined localized disease; did not require any therapy other than surgery as treatment
- Primary endpoint: safety
- Secondary endpoint: immunologic correlates

Choosing biomarkers for immune monitoring



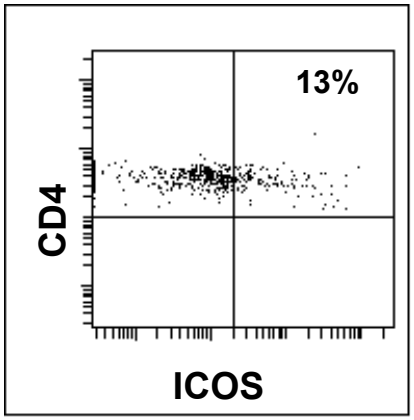
Immune Monitoring

- **Assessed T cell markers including: HLA-DR, CD69, CD45RA, CD45RO, PD-1, etc. and**

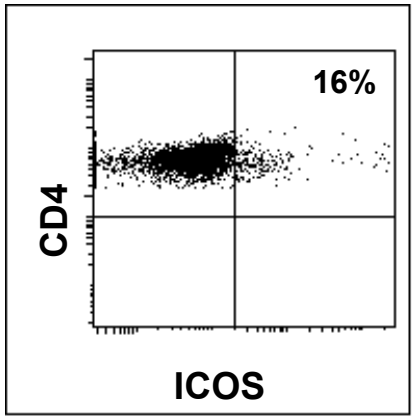
- **Inducible costimulator (ICOS)**
  - **-belongs to CD28 family**
  - **-expression increased on activated T cells**
  - **-plays a role in function of Th1, Th2, Th17, Tfh, Treg cells**
  - **-is not a marker of a particular T cell subset but plays a role in the function of a given T cell subset that has been activated**

Increased frequency of ICOS^{hi} T cells in tumors from anti-CTLA-4 treated patients

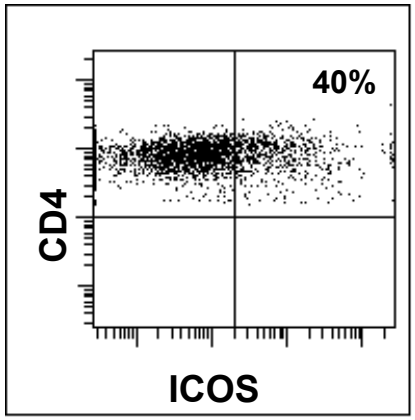
Non-malignant tissues: untreated



Tumor tissues: untreated

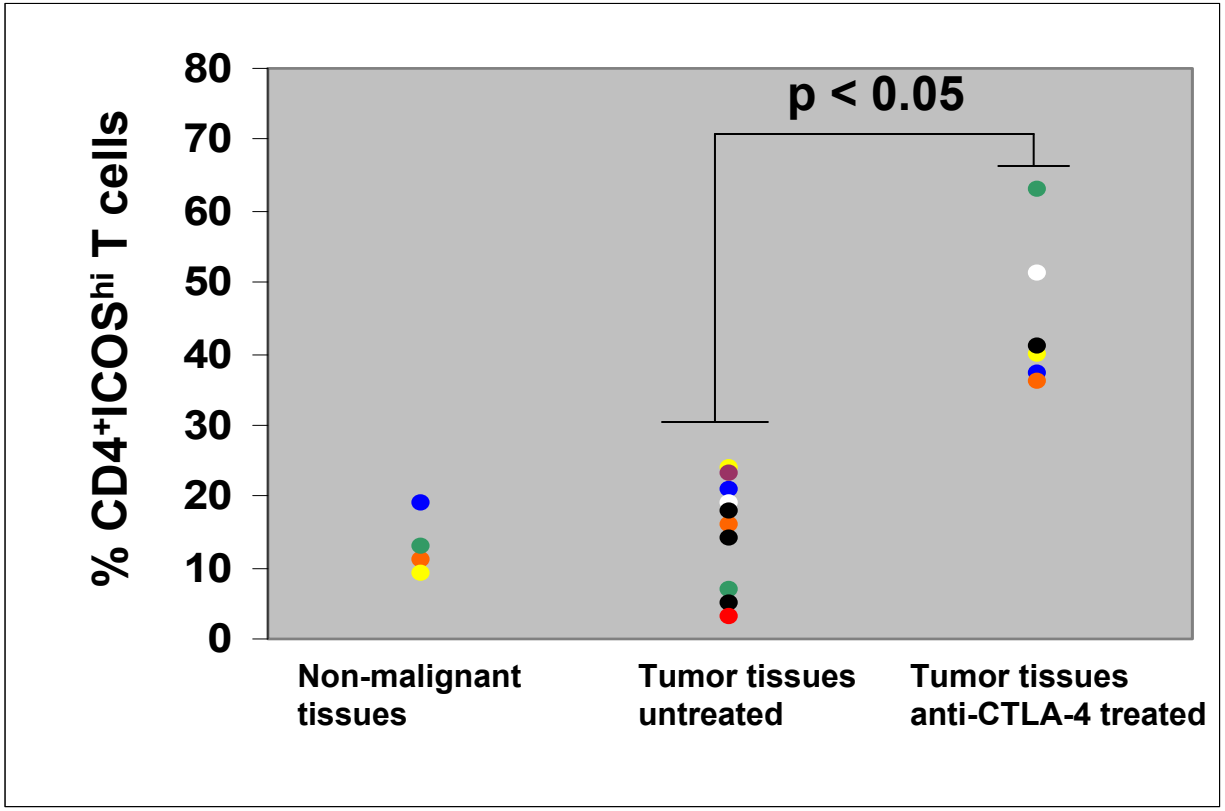


Tumor tissues: anti-CTLA-4 treated



Liakou et al., *Proc Natl Acad Sci*, 2008

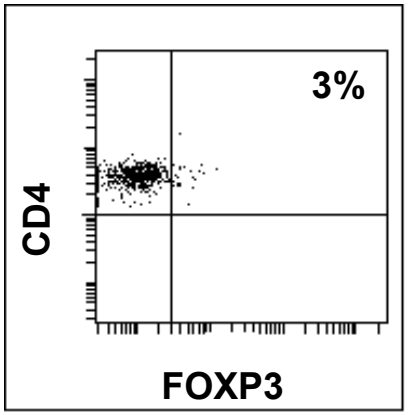
ICOS expression increases in tumor tissues of treated patients



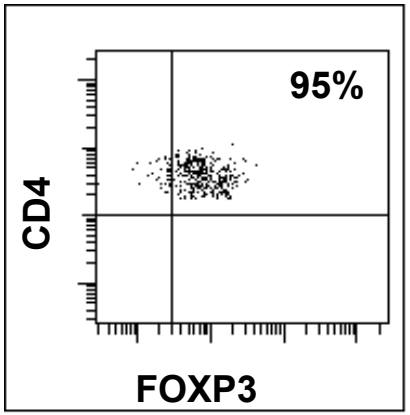
Liakou et al., *Proc Natl Acad Sci*, 2008

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

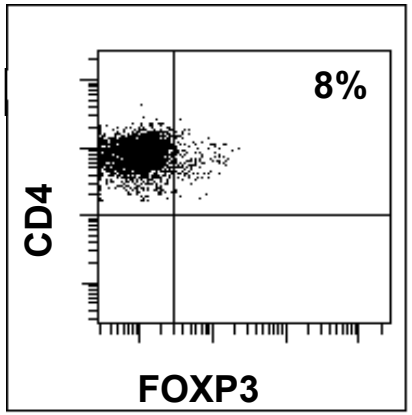
Non-malignant tissues: untreated



Tumor tissues: untreated

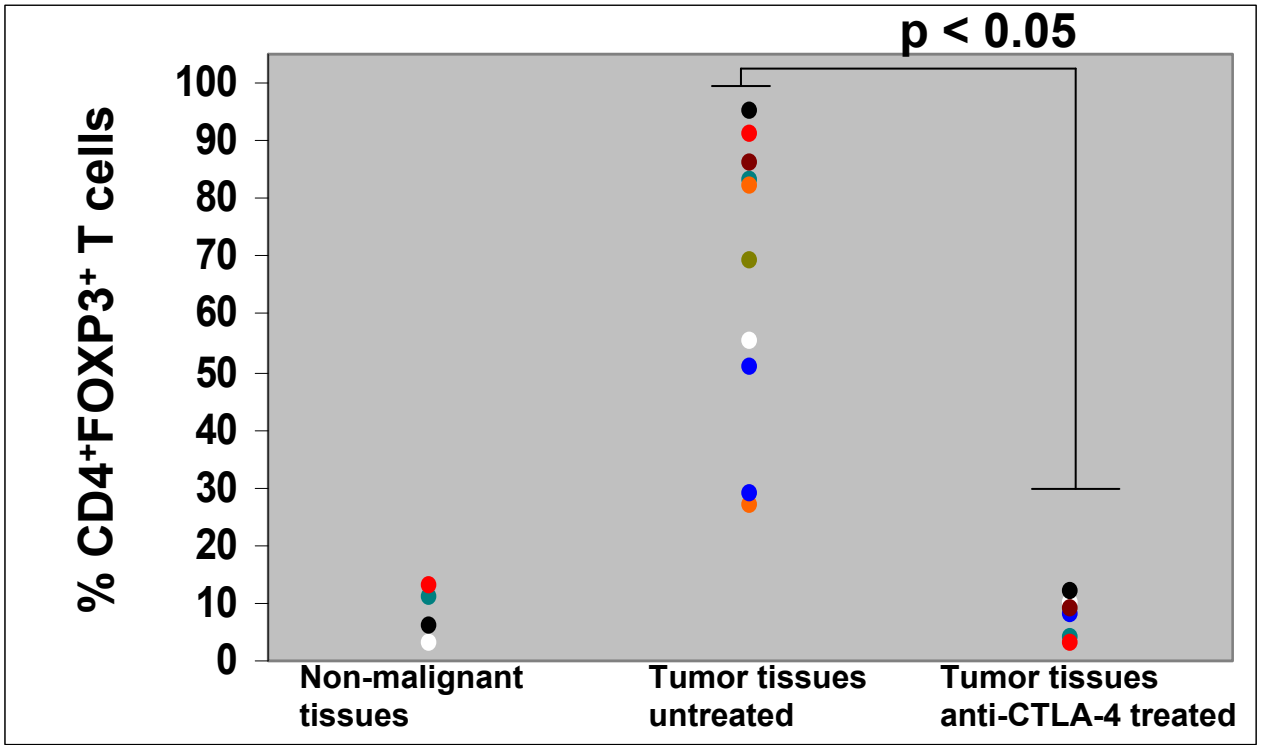


Tumor tissues: anti-CTLA-4 treated



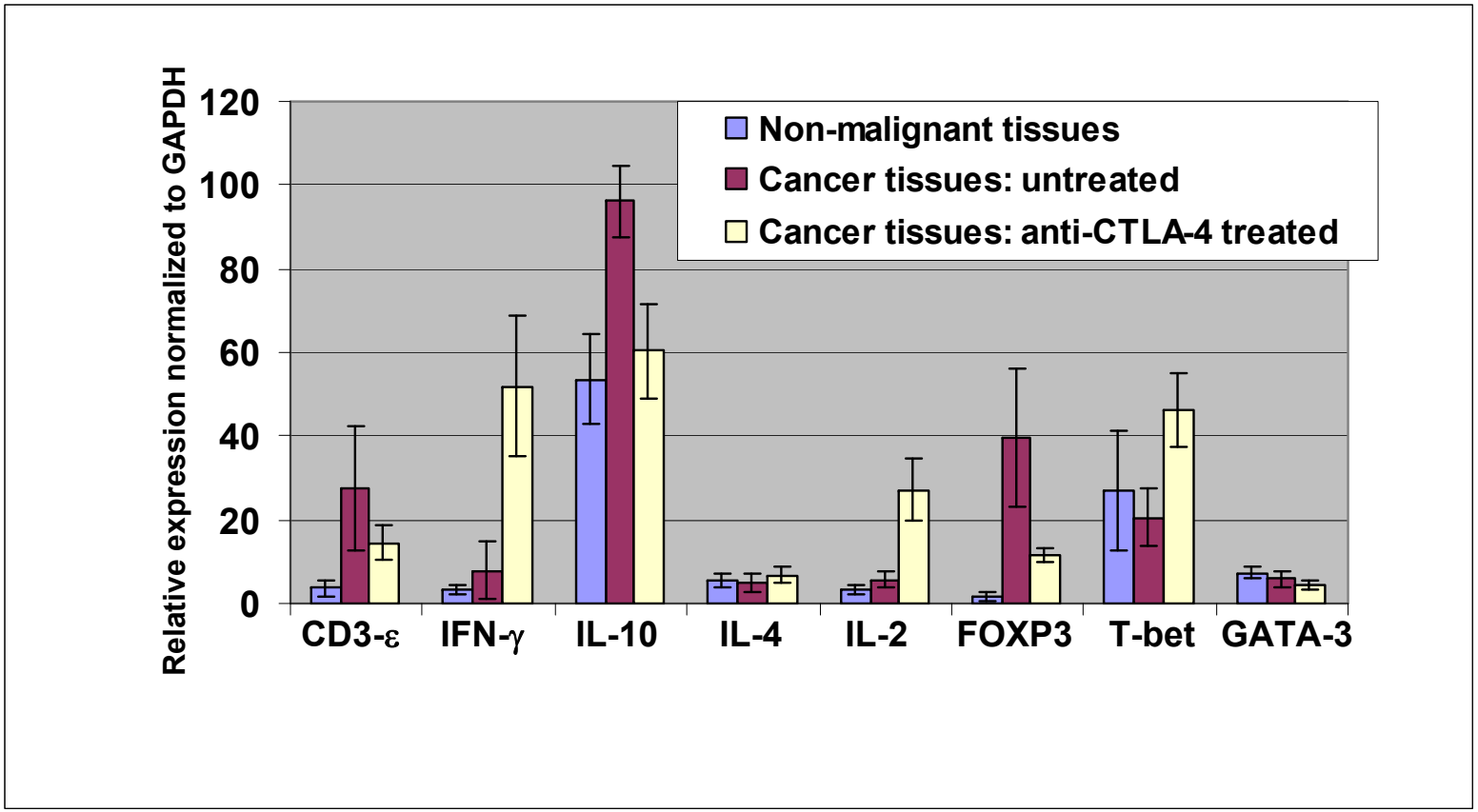
Liakou et al., *Proc Natl Acad Sci*, 2008

FOXP3 expression decreases in tumor tissues of treated patients



Liakou et al., *Proc Natl Acad Sci*, 2008

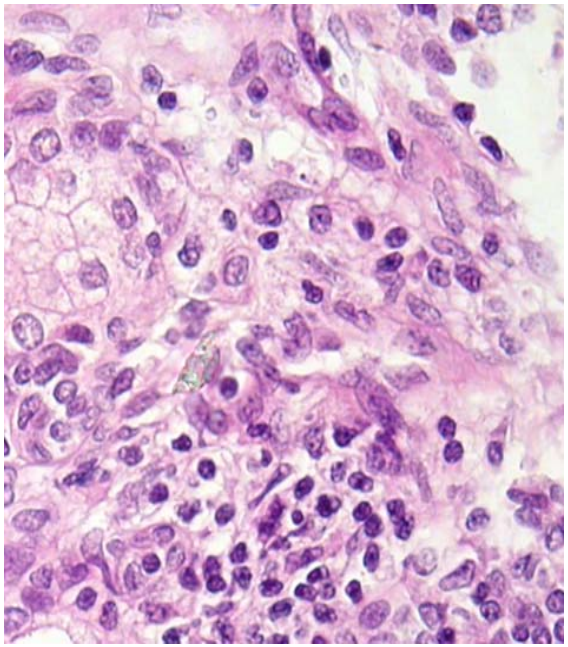
Increased IFN-γ and T-bet mRNA in treated tissues with concomitant decrease in FOXP3 mRNA levels



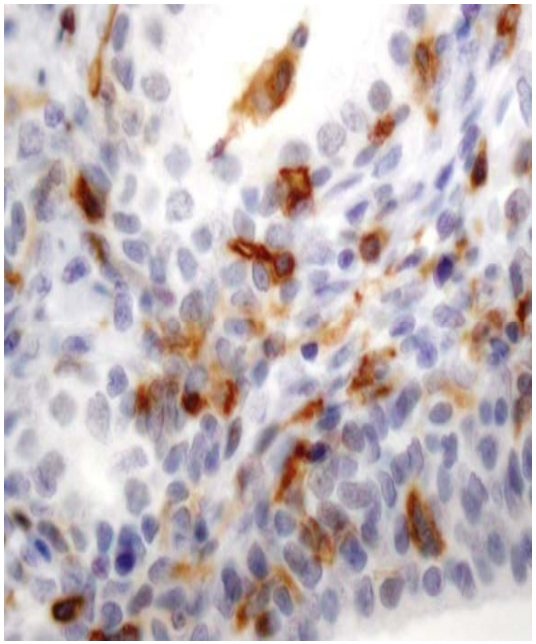
Liakou et al., *Proc Natl Acad Sci*, 2008

What is the function of ICOS^{hi} cells in tumors?: Expression of NY-ESO-1 antigen allowed for functional analyses of TILs

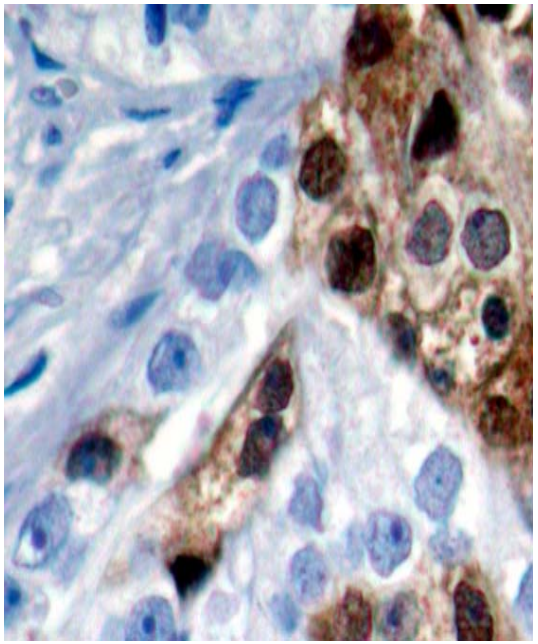
H & E



CD4 T cells

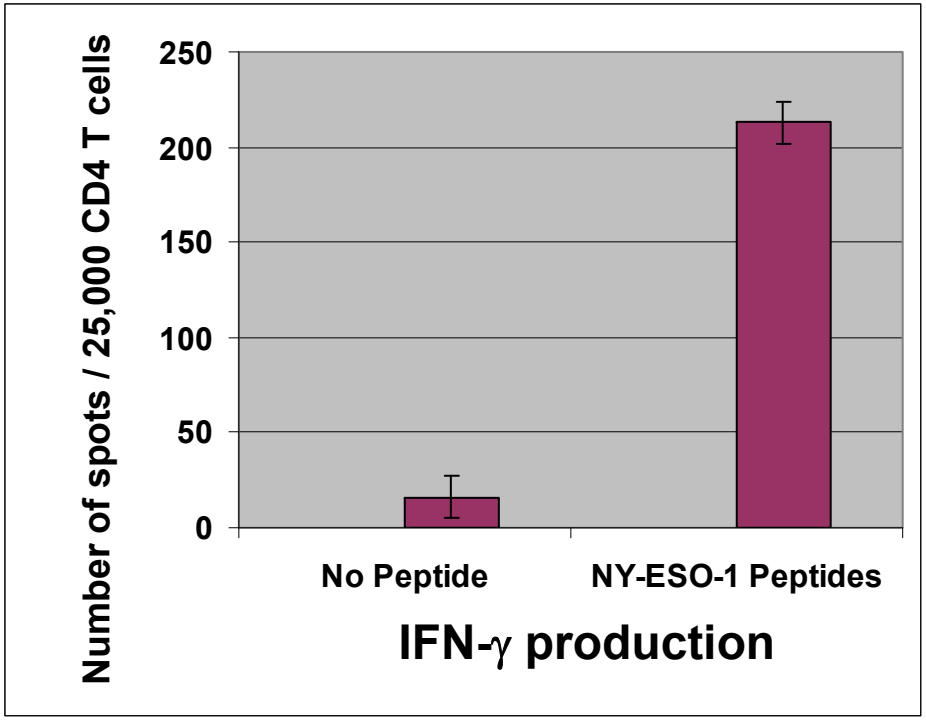


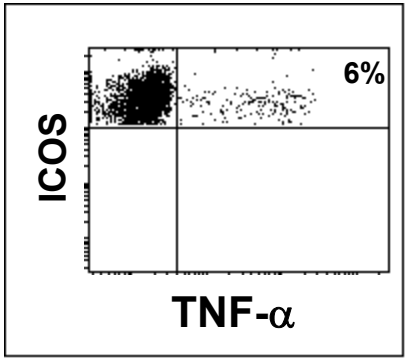
NY-ESO-1

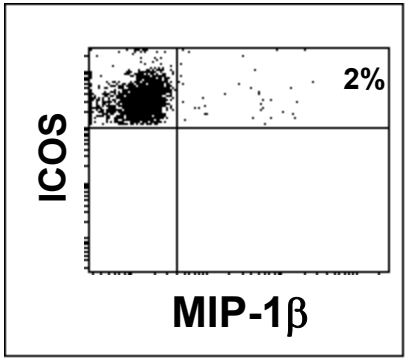


Chen et al., *Proc Natl Acad Sci*, 2009

Recognition of NY-ESO-1 by TILs





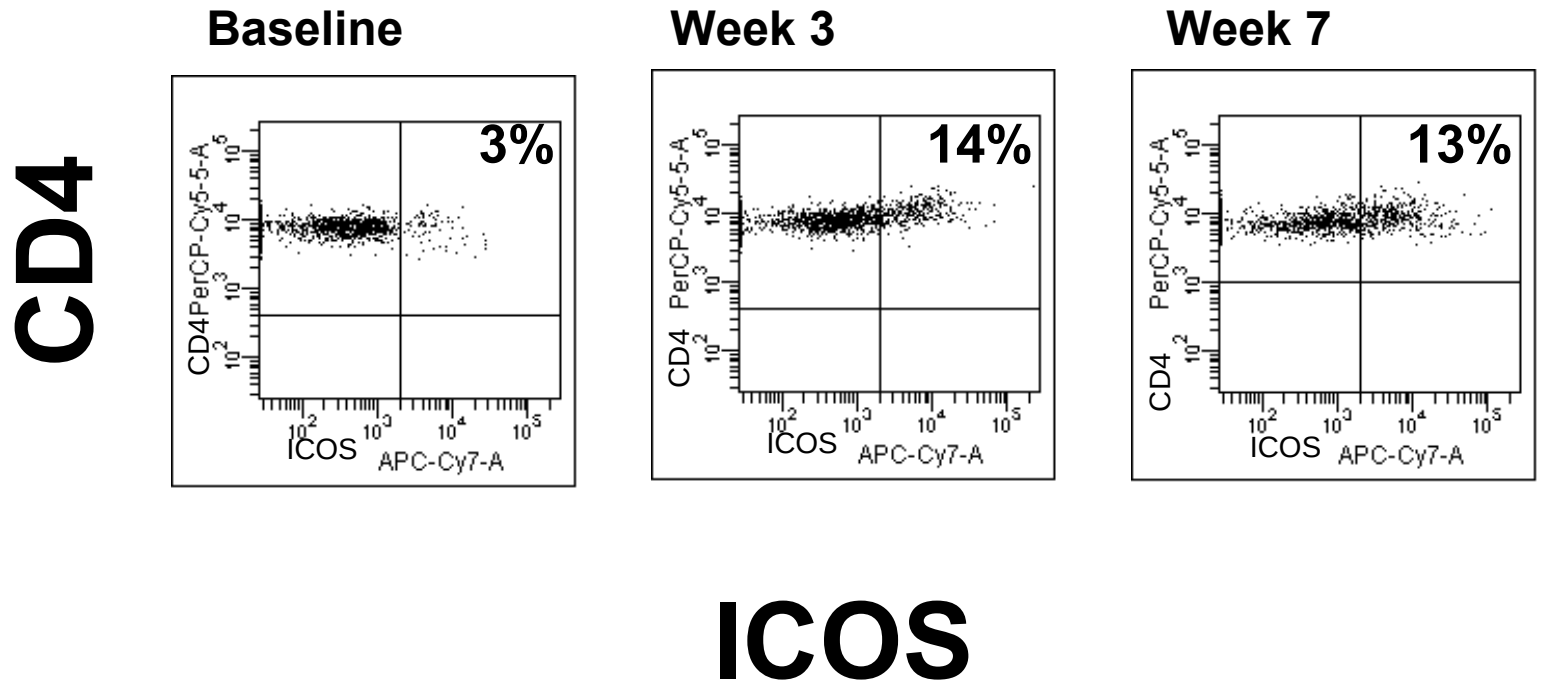


Chen et al., *Proc Natl Acad Sci*, 2009

What about immunologic events in the systemic circulation?

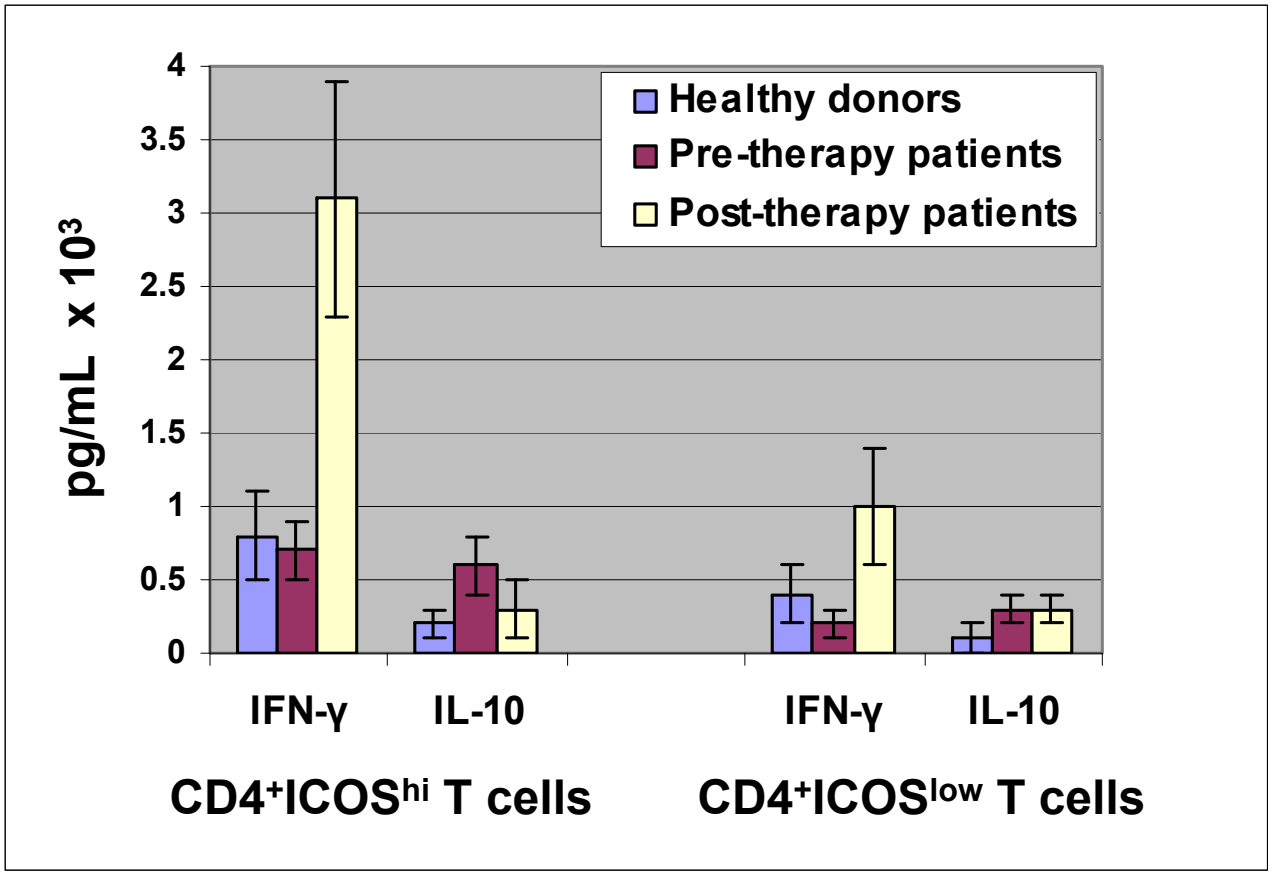
Do they correlate with observed changes in tumor tissues?

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



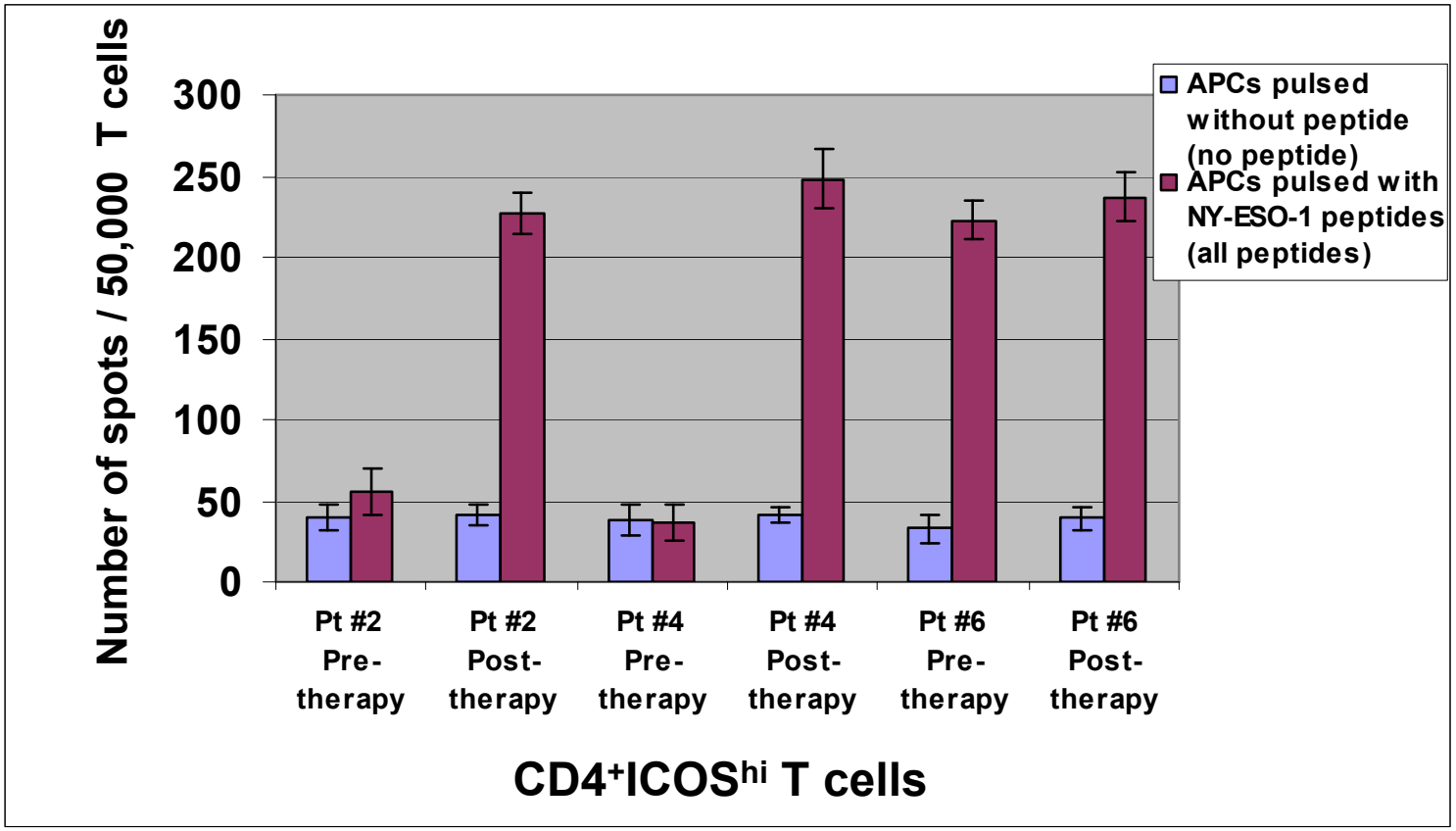
Liakou et al., *Proc Natl Acad Sci*, 2008

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



Liakou et al., *Proc Natl Acad Sci*, 2008

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



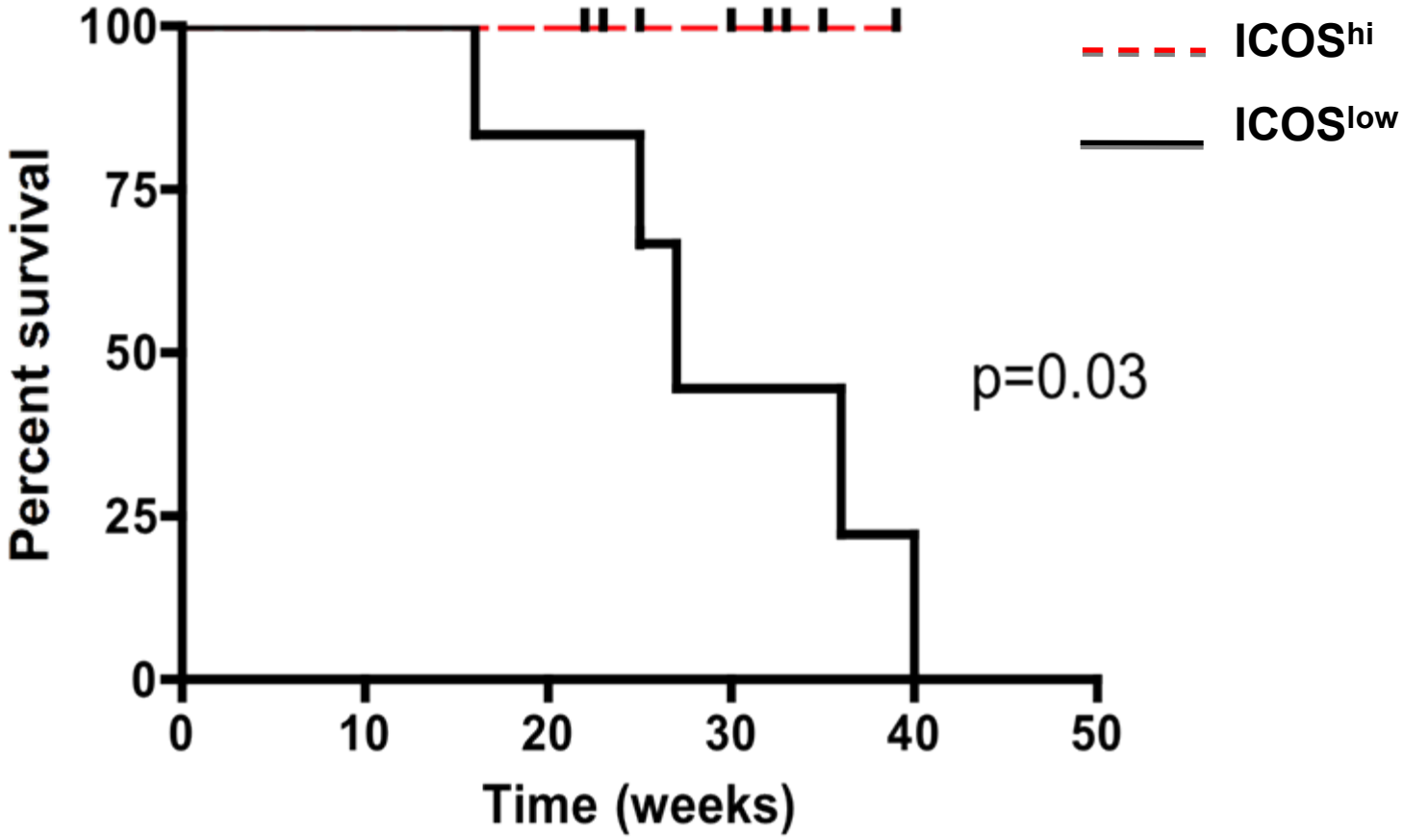
Are changes in ICOS expression associated with clinical benefit?

Pre-Operative CTLA-4 Blockade: Pathology and Cytology Data

Patient Number	Pre-Therapy Pathology (UC, HighGrade)	Post-Therapy Pathology	Pre-Therapy Cytology Fluorescence in situ hybridization (FISH)	Post-Therapy Cytology Fluorescence in situ hybridization (FISH)
1	T1N0M0	T0N0M0	Positive Cytology, Positive FISH	Negative Cytology, Negative FISH
2	T1N0M0	T4N0M0	Positive Cytology, Positive FISH	Positive Cytology, Positive FISH
3	T1N0M0	TisN0M0	Negative Cytology, Positive FISH	Negative Cytology, Negative FISH
4	T2N0M0	T3N1M0	Negative Cytology, Non-contributory FISH	Negative Cytology
5	T1N0M0	TaN0M0	Positive Cytology	Positive Cytology
6	T1N0M0	T0N0M0	Positive Cytology	Negative Cytology, Negative FISH
7	T1N0M0	TaN0M0	Positive Cytology	Positive Cytology
8	T2N0M0	T0N0M0	Negative Cytology, Negative FISH	Negative Cytology, Negative FISH
9	T1N0M0	TisN0M0	Positive Cytology	Positive Cytology
10	T2N0M0	T0N0M0	Positive Cytology	Negative Cytology, Negative FISH
11	T1N0M0	pTXN0M1	Positive Cytology	Positive Cytology
12	T2N0M0, UC & Micropapillary Disease	T2N1M0, UC, Sarcomatoid & Micropapillary Disease	Positive Cytology	Positive Cytology, Positive FISH

Carthon et al., *Clinical Cancer Research*, 2010

Metastatic Melanoma: Sustained elevation of $CD4^{+}ICOS^{hi}$ T cells correlates with survival



Carthon et al., *Clinical Cancer Research,* 2010

Part II
Combination Therapies

Why Combination Therapy?

- Each tumor has multiple (90?) mutations resulting in coding changes (Vogelstein et al. Science 2006)

- Many of these, depending on MHC type of host, will represent neoantigens

Neoepitopes generated by genomic instability inherent in cancer

- **Algorithms predict 9/tumor for HLA-0201**
- **6 MHC alleles/tumor, so assuming even distribution predicts 54 total neoepitopes/tumor**
- **Assuming algorithm is wrong 90% of time, would predict 5-6 neoepitopes/tumor**

Effective checkpoint blockade with anti-CTLA-4 therapy may turn 1 drug/therapy into 6-7, raising the possibility of combinatorial therapies to improve anti-tumor responses

Segal N and Allison JP

Rationale for Combination Therapy

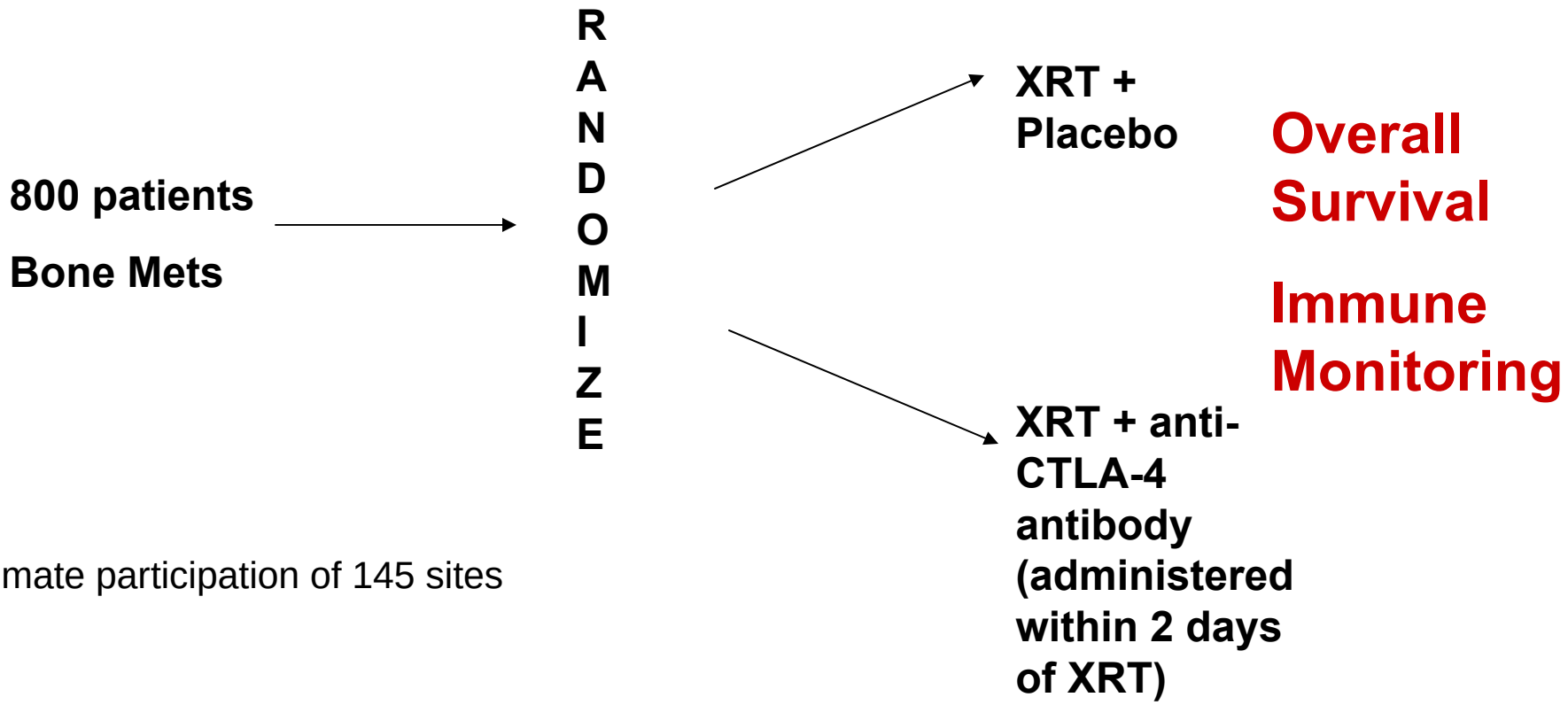
Agents that kill tumor cells (e.g. chemotherapy, radiation, hormone therapy, antibodies, “targeted” therapies) can be used to prime an immune response against multiple antigens

In combination with checkpoint blockade, can unleash the immune system to maximize T cell responses to multiple targets

Combination Studies with Ipilimumab

- Phase III study with Ipilimumab plus XRT in patients with metastatic prostate cancer
- Phase III study with Ipilimumab plus DTIC in patients with melanoma
- Phase II study with Ipilimumab plus Temozolamide in patients with metastatic melanoma
- Phase II study with Ipilimumab plus Taxol plus Paraplatin in patients with lung cancer
- Phase II study with Ipilimumab plus androgen blockade in patients with metastatic prostate cancer
- Pre-surgical Phase IIa study with Ipilimumab plus Lupron in patients with localized prostate cancer
- Phase I study with Ipilimumab plus MDX-1106 (anti-PD-1) in patients with melanoma
- Phase I/II study with Ipilimumab plus cryoablation in patients with breast cancer
- Planned study with Ipilimumab plus Sipuleucel-T in patients with prostate cancer
- Planned study with Ipilimumab plus BRAF inhibitor in patients with melanoma

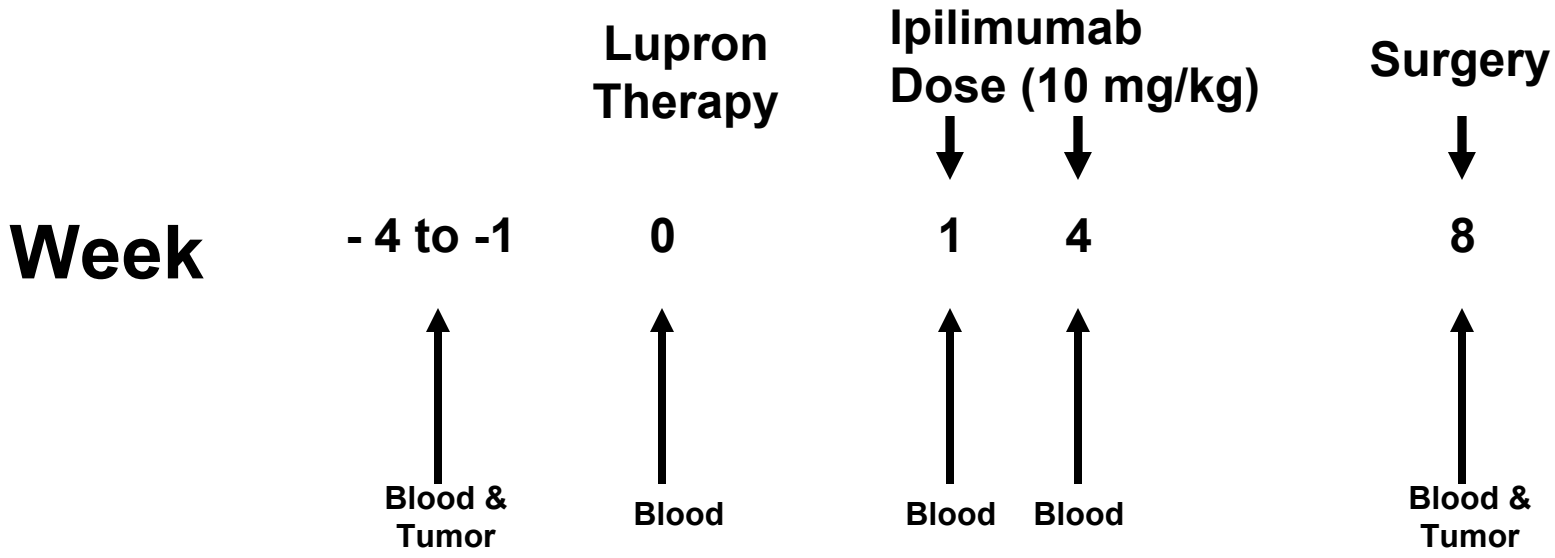
Phase III clinical trial with Ipilimumab + XRT vs. Placebo + XRT in CRPC



Estimate participation of 145 sites

No crossovers allowed

Pre-surgical trial: Lupron + Ipilimumab



Clinical Trial for Patients with Localized Prostate Cancer

Conclusions

- **CTLA-4 blockade increases ICOS expression on T cells in tumor tissues and peripheral blood**
- **ICOS^{hi} T cells from treated patients contain a population that are IFNγ-producing effector T cells and can recognize tumor antigen**
- **ICOS may serve as a biologic marker of disease response but, this has to be tested in a larger cohort of patients**
- **ICOS/ICOSL may serve as another immunotherapy target**
- **Pre-surgical clinical trials provide a feasible platform to study biologic effects on tumor tissues thus providing data that can be applied to the metastatic disease setting and improve our understanding of mechanisms**
- **Pre-clinical data supports the development of combination therapies with anti-CTLA-4 and any agent that is capable of killing tumor cells to prime a T cell response**

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- BMS Team
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