

Phase I Trial of a Monoclonal Antibody to OX-40 in Patients with Advanced Cancer

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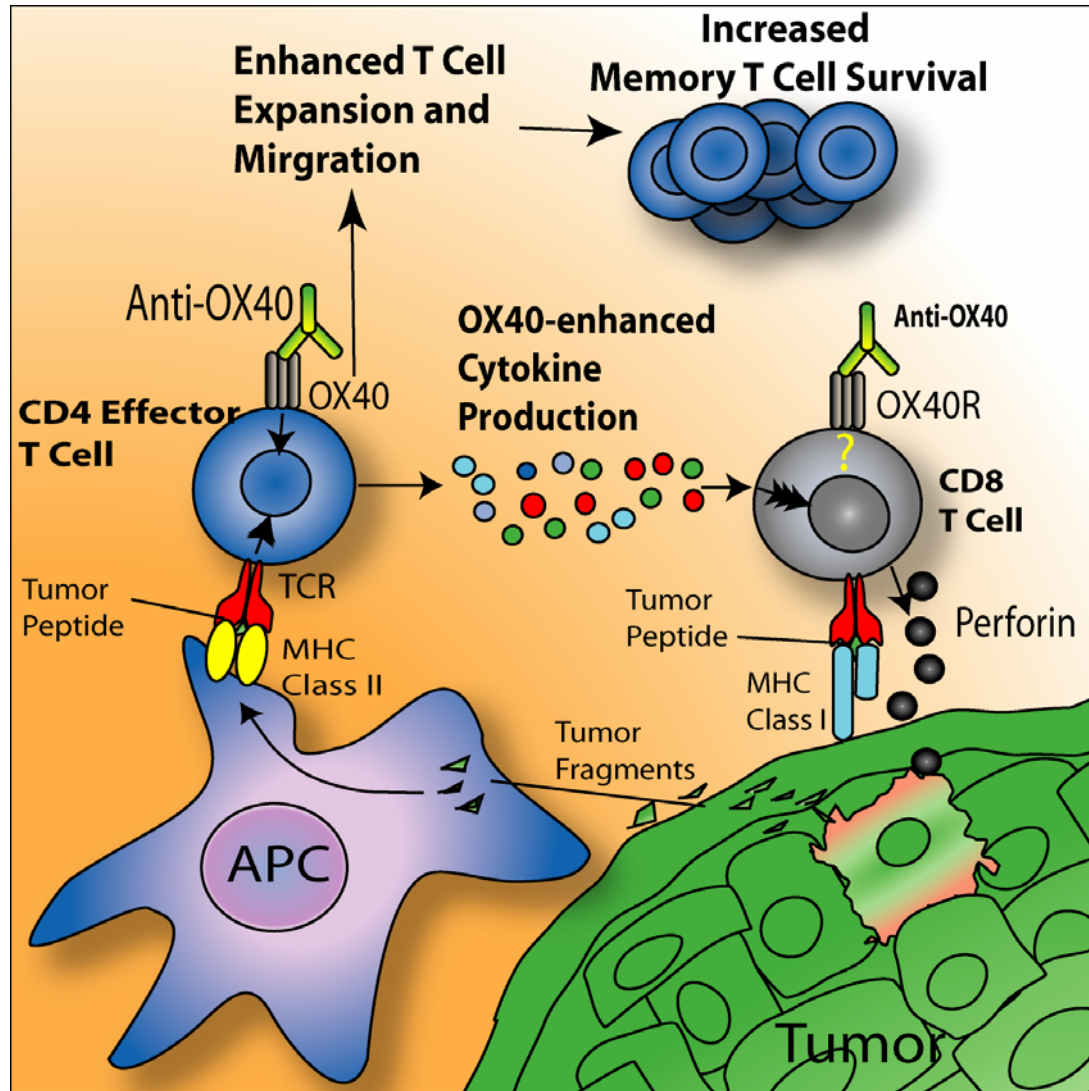
Supporters of the RWFCRC
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Selected OX40 Biology

- OX40 is a T cell activation protein expressed after TCR engagement primarily on CD4+ and CD8+ T cells.
- OX40 expression is transient, peaking 24-48 hr after TCR engagement and downregulated 72-96 hr later.
- OX40 engagement results in proliferation and enhanced survival of CD4 T cells and mediates anti-tumor effects against breast, sarcoma, melanoma and colon cancers in murine models.
- T cells expressing OX40 found in many human cancers (breast, colon, melanoma, prostate, bladder, lung, head and neck).

OX40 Pathway in Tumor Immunity



Anti-OX40 Antibody

- IgG1 kappa murine monoclonal antibody (150 kd) that recognizes the human OX40 receptor (CD134)
- Well-tolerated in non-human primates at doses up to 10/mg/kg (IV on days 1, 3 and 5)
 - Increased LN and spleen size in some animals
 - Serum levels of anti-OX40 increased in a dose-related fashion.
 - Monkey anti-mouse antibodies observed in all animals

Clinical Trial Objectives

- **Determine the maximal tolerated dose of anti-OX40 in patients with advanced malignancy.**
- **Determine if antigen-specific T cell and antibody responses to KLH, tetanus and CMV are enhanced via anti-OX40.**
- **Measure pharmacokinetics of anti-OX40**
- **Determine the most biologically active dose of anti-OX40 to induce antigen-specific responses**
- **Monitor for tumor regression.**

Patient Eligibility

- Metastatic carcinoma not curable with standard treatment
- ECOG 0-2
- WBC > 2000, HGB >8, platelets >100,000
- AST, ALT, alk phos < 2.5x ULN
- Negative for HIV, hepatitis
- No autoimmune disease (except hypothyroidism or vitiligo)

Exclusion Criteria

- Not yet recovered from prior treatment toxicities
- Active brain mets (treated mets OK) or primary brain cancer
- Requirement for steroids
- Previous mouse monoclonal abs
- Allergies to shellfish or tetanus
- Splenomegaly

Dose Levels

- 0.1 mg/kg, 0.4 mg/kg, 2 mg/kg
- Consecutive enrollment to cohorts
- 10 patients per cohort (random assignment to arms A and B)

Treatment Plan

- Arm A
 - Anti-OX40 on days 1, 3 and 5
 - KLH on day 1
 - Tetanus on day 29
- Arm B
 - Anti-OX40 on days 1, 3 and 5
 - Tetanus on day 1
 - KLH on day 29

Planned Immunologic Monitoring

- Antibody responses to KLH and tetanus
- T cell responses to KLH, tetanus, CMV
- Cytometry on peripheral blood
- HAMA

Exploratory Monitoring

- Serum cytokine analysis (complicated by HAMA)
- Tumor-specific immune responses
- Proliferation of naïve and memory CD4+ and CD8+ T cells

Patient Characteristics

Diagnosis	Age	Surgery	Radiation	Chemo
Melanoma	54	WLE and SLN	no	IFN, IL-2 CTLA-4
NSCLCA	55	RUL-ectomy	Gamma knife (brain XRT)	Carboplatin, paclitaxel, pemetrexed, gemcitabine, gefitinib, erlotinib, Xyotac
Ovarian CA	63	Debulking, TAH, BSO	no	Paclitaxel, carboplatin, liposomal adriamycin, gemcitabine

Toxicities

- Constitutional symptoms: 2 pts (grade I)
- Hypercoagulable state and infection:
1 patient*

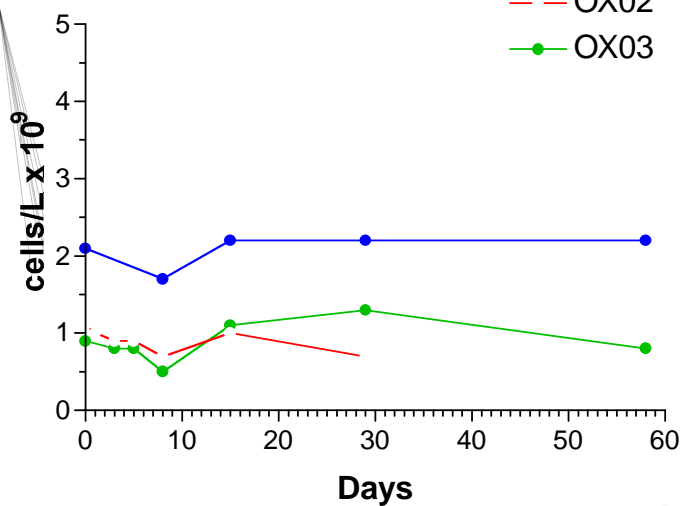
*Multiple thromboembolic strokes, deep venous thrombosis, elevated PT/PTT/INR, elevated rheumatoid factor, pneumonia, Rapidly progressive cancer

WBC Subsets Following anti-OX40

(OX1, OX2, OX3)

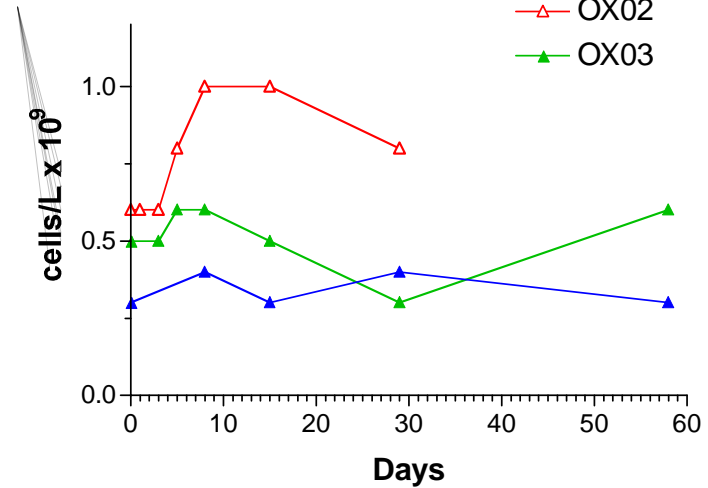
lymphocyte counts

OX01
OX02
OX03



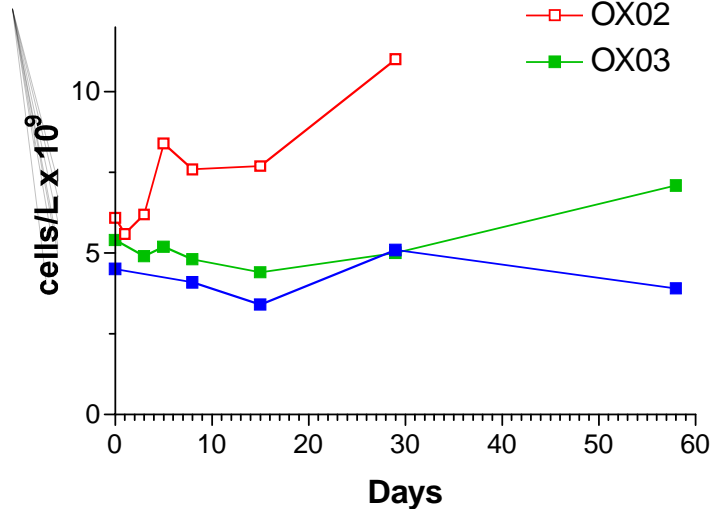
monocyte counts

OX01
OX02
OX03



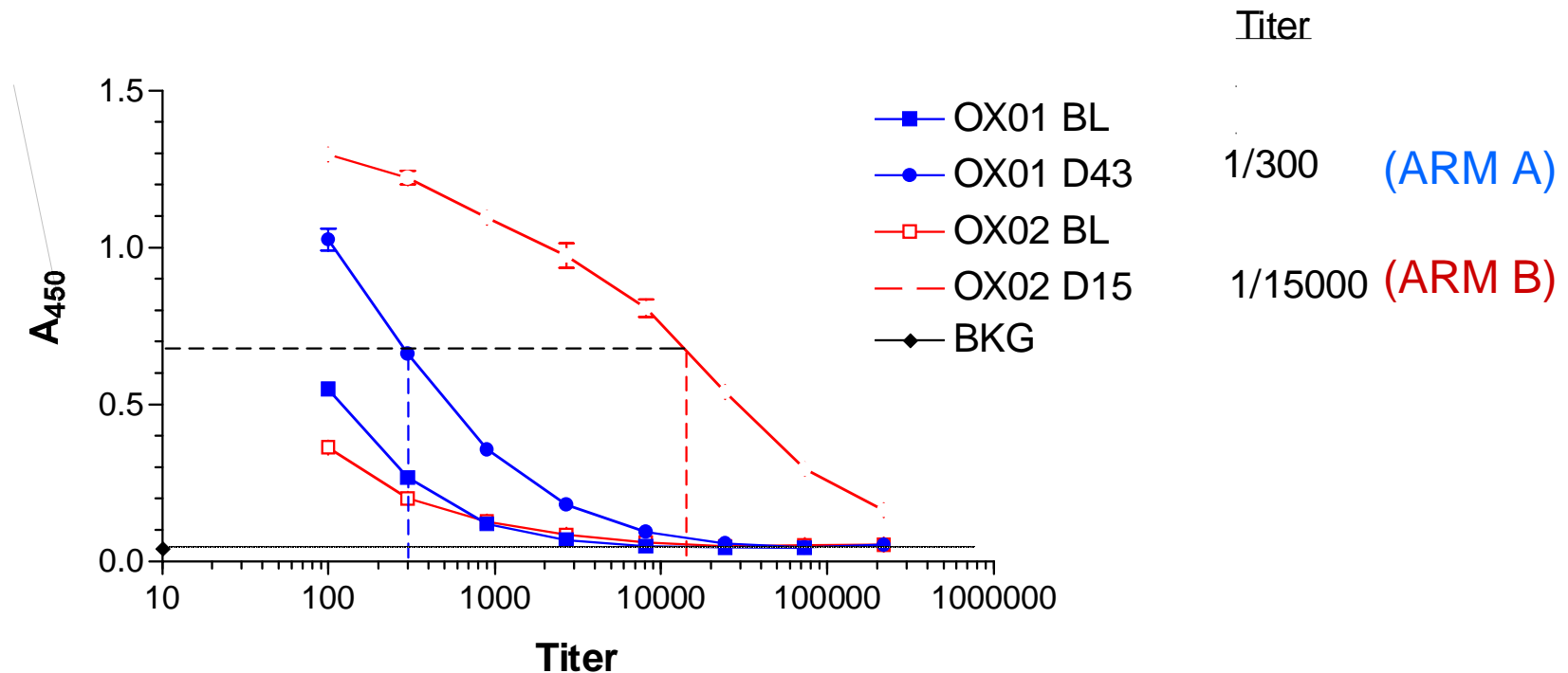
neutrophil counts

OX01
OX02
OX03



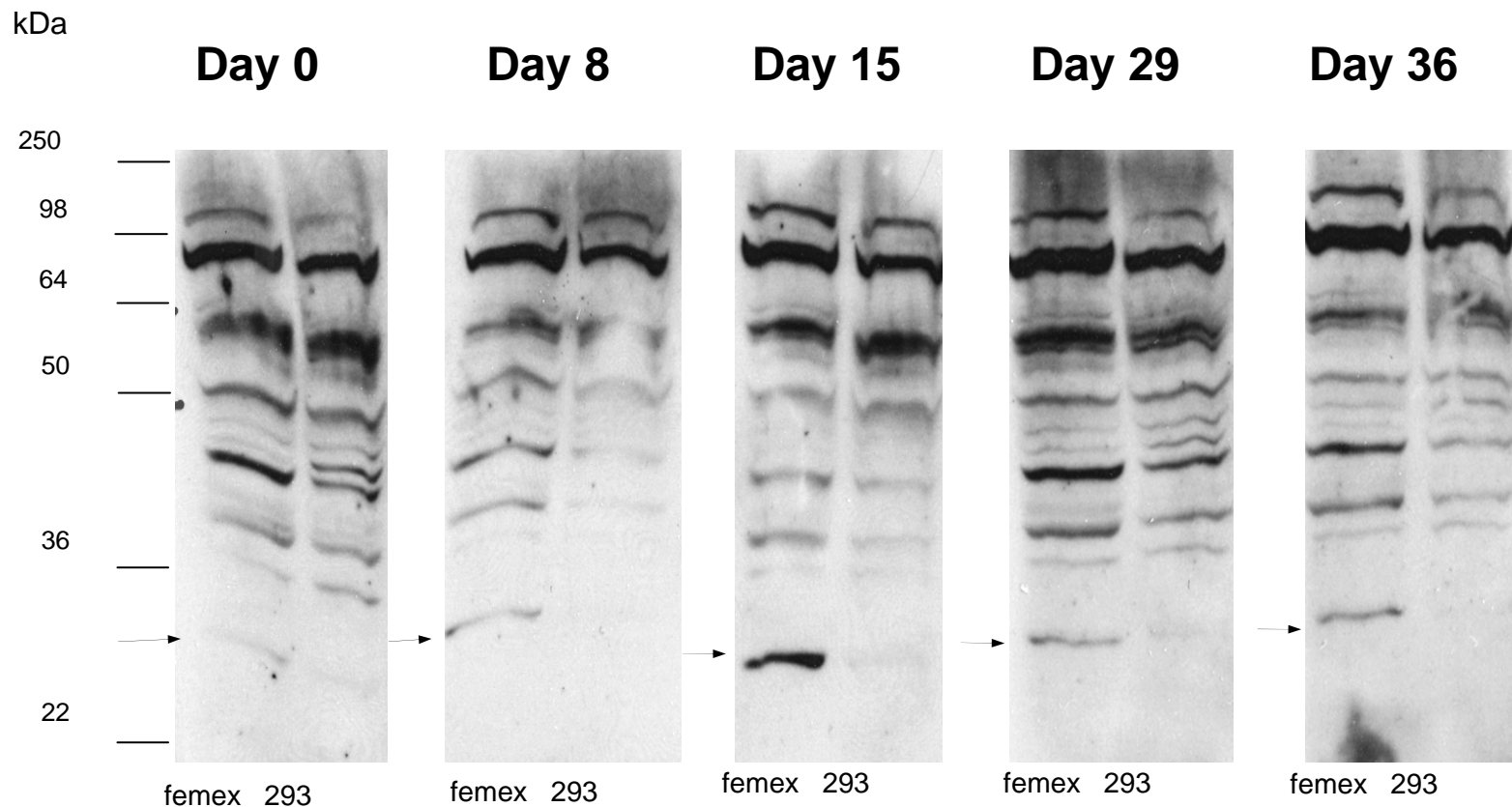
Tetanus-Specific ELISA

OX01 vs OX02

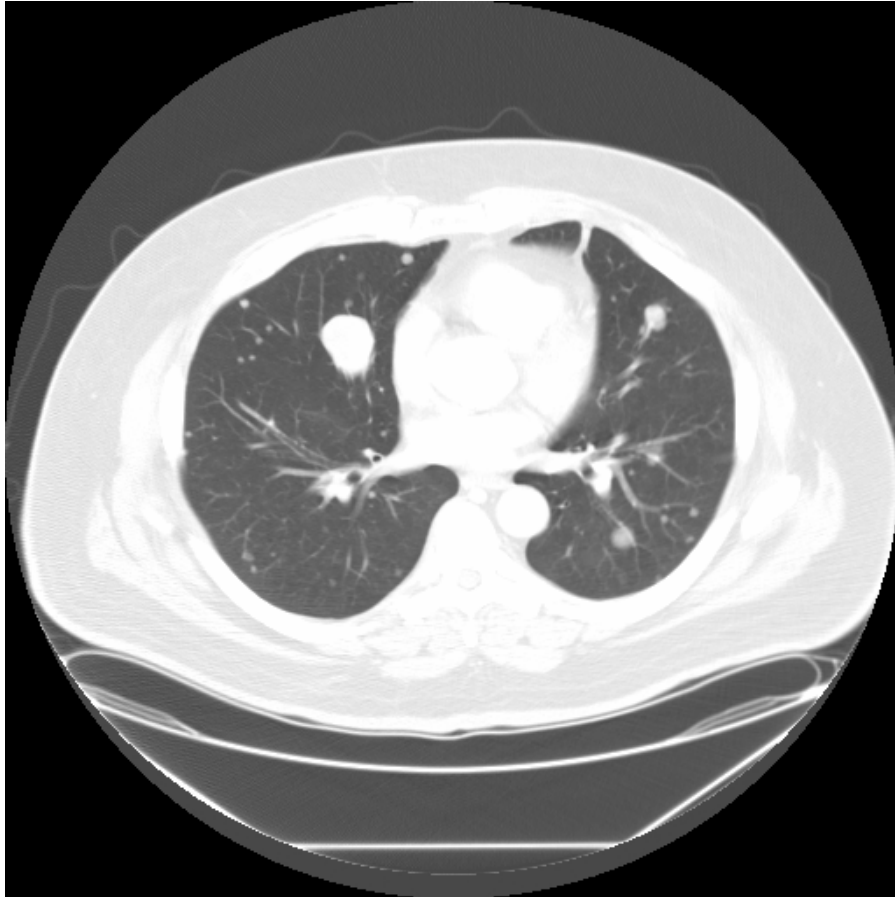


Patient Serum Western Blot (OX1)

Melanoma (femex) and Kidney (293) lysates



“IR” in Melanoma Patient



March 2006



July 2006

Examination of T Cell Subsets By Expression of:

- CD95 (fas)
 - Naïve vs memory
- CD28
 - Central vs effector memory
- Ki-67
 - Proliferation

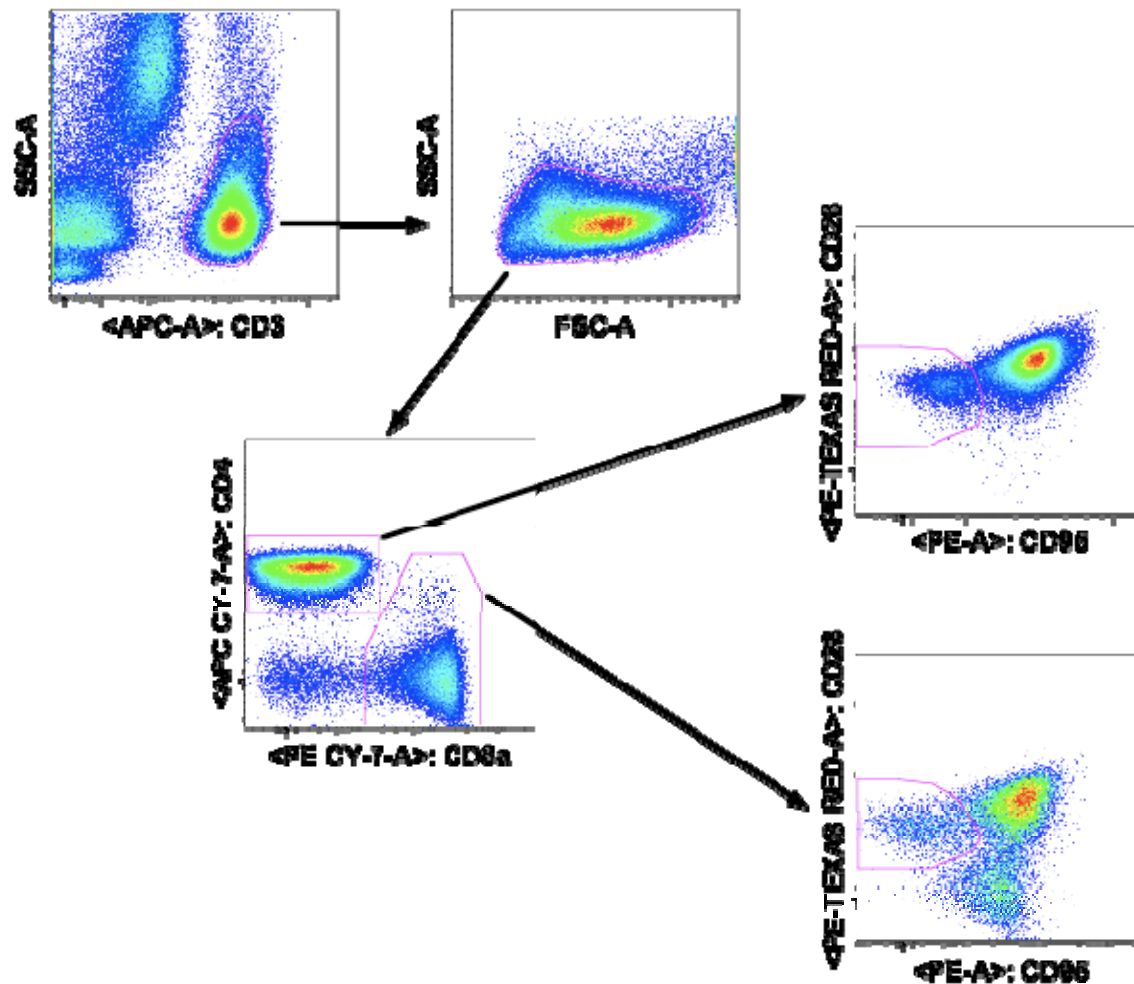
Strategy adapted from Louis Picker (SIV monkey studies)

J of Immunol, 2002, 168:29.

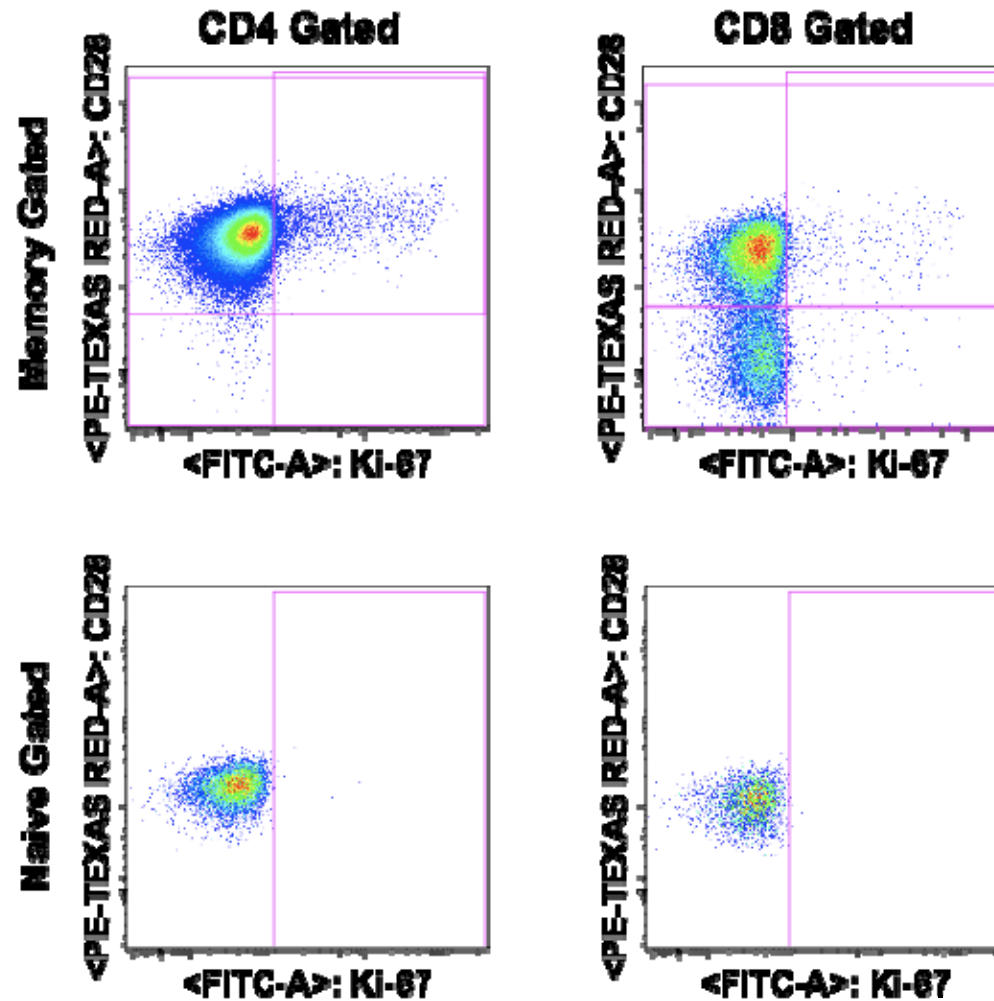
J of Exp Med, 2004, 200:1299.

J of Clin Invest, 2006, 116:1514

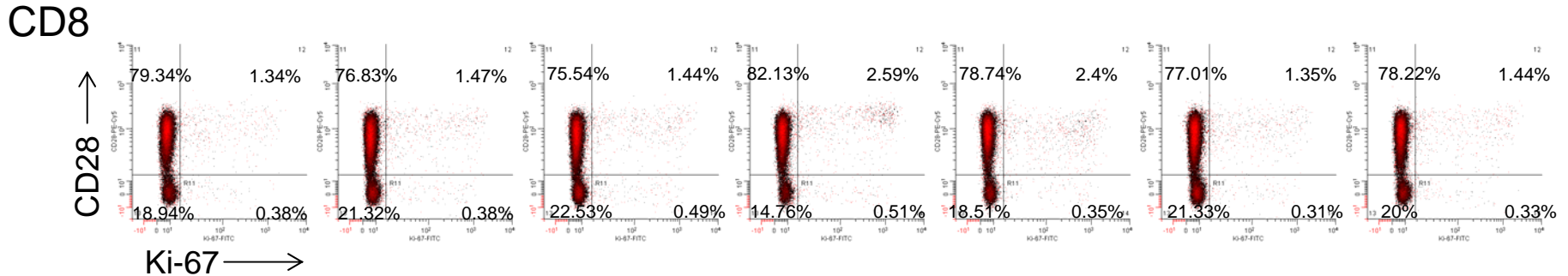
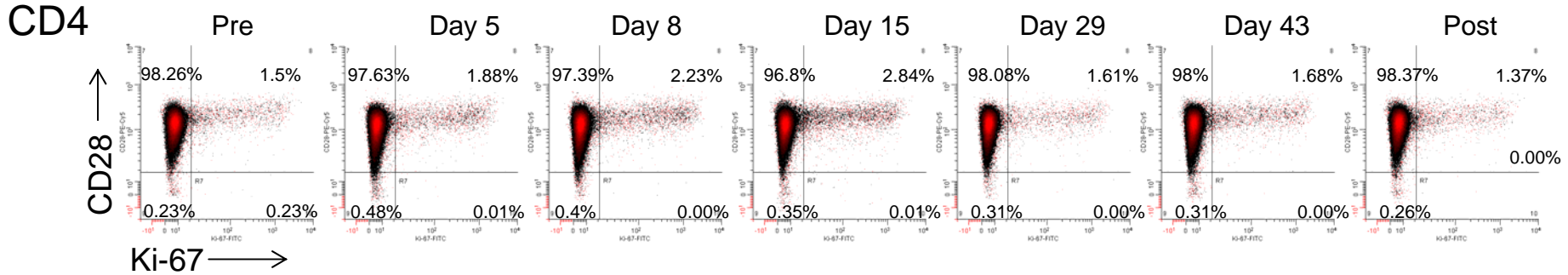
Gating Strategy for OX-40 Clinical Trial: Part I



Gating Strategy: Part II

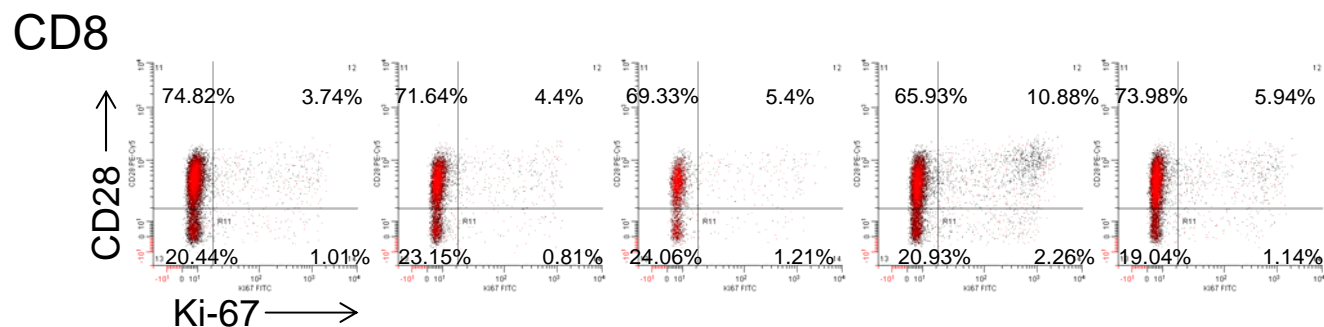
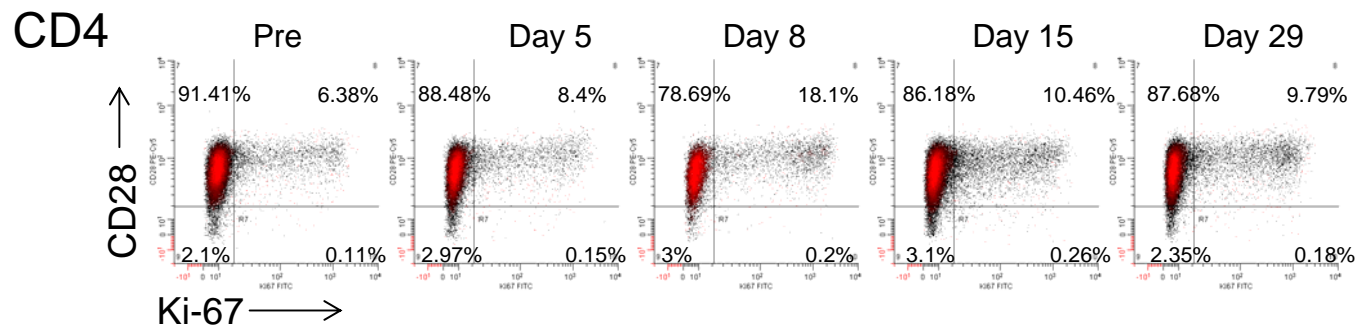


OX01 (Gated on CD95⁺)



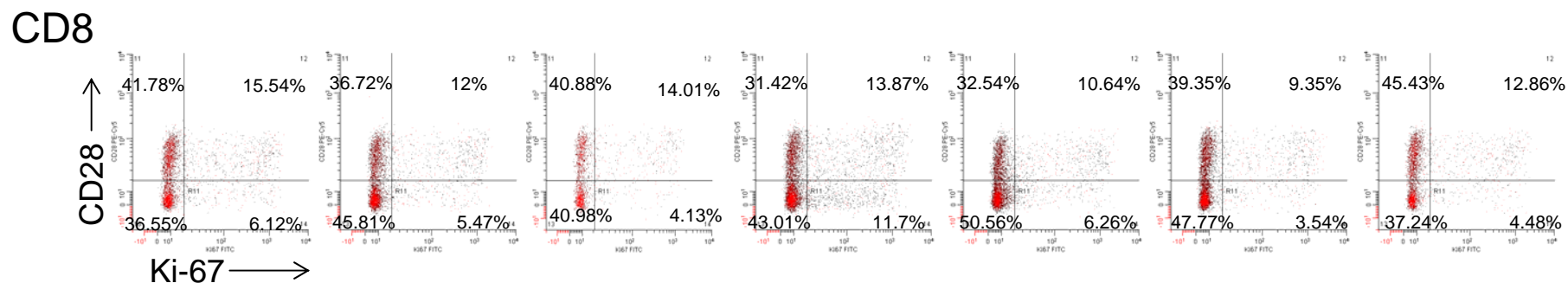
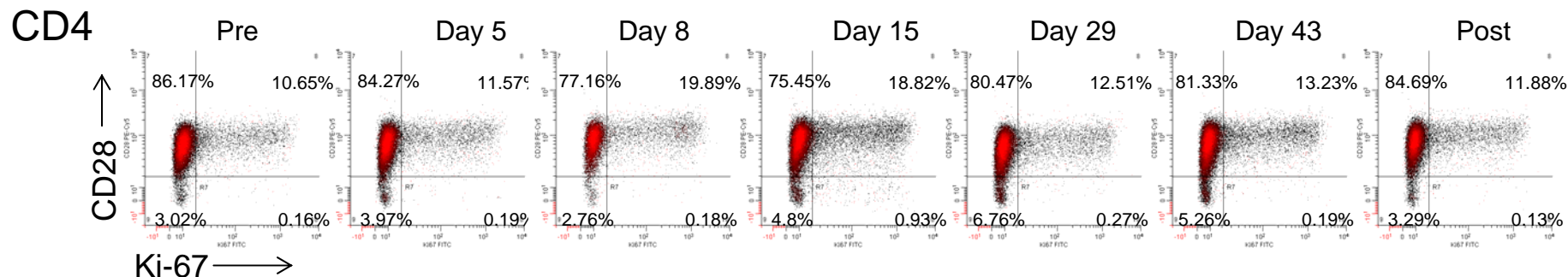
OX02

(Gated on CD95⁺)

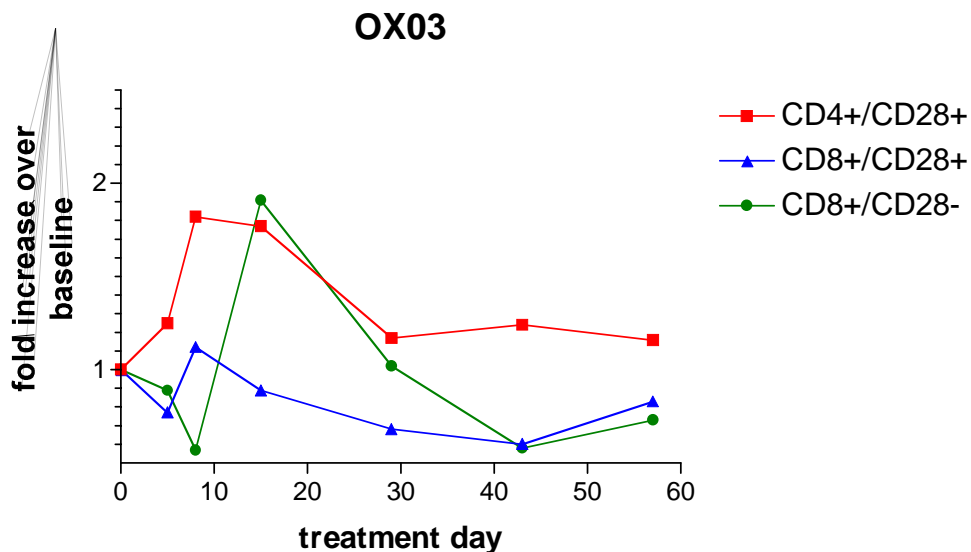
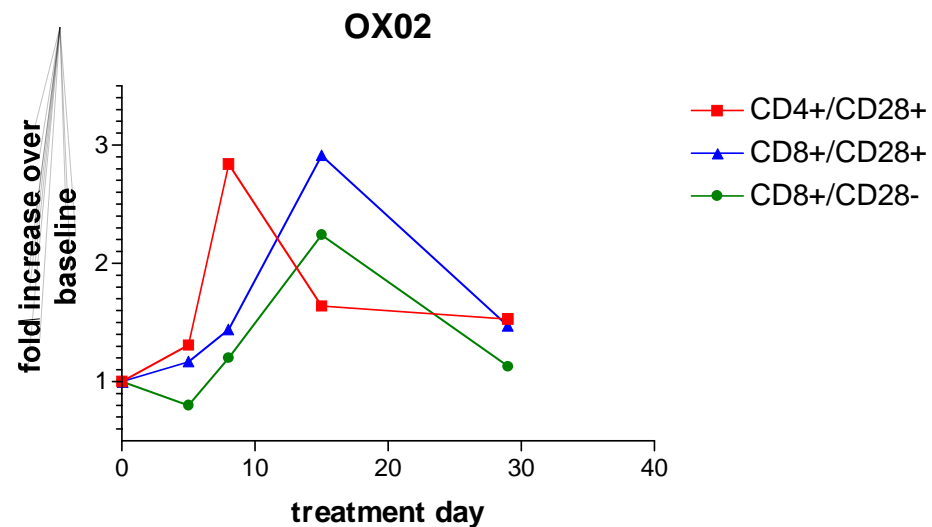
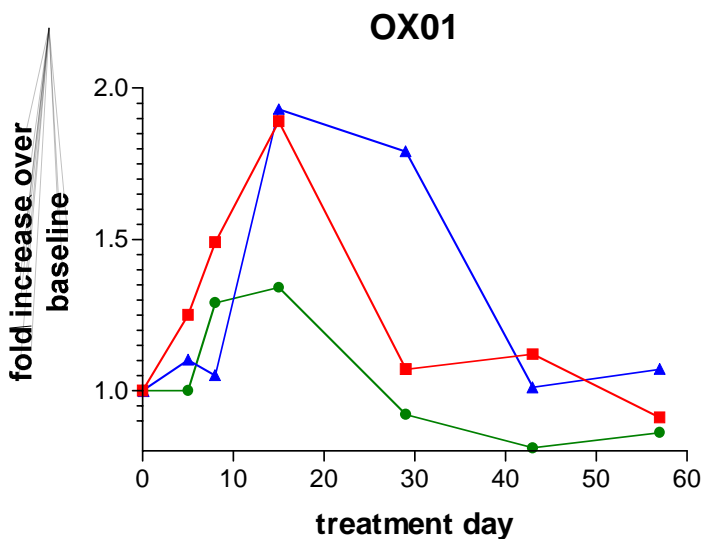


OX03

(Gated on CD95⁺)



Fold Increase of Ki-67+ **CD4+CD28+**, **CD8+CD28+** and **CD8+CD28-**



Preliminary Conclusions

- More patients needed
- Immune events occurring
 - Antibody responses to tumor and reporter antigens
 - Increased proliferation of T cell subsets
- Dose-limiting toxicity not yet found