Circulating regulatory T-cell function and overall survival in metastatic castration-resistant prostate cancer (mCRPC) patients treated with poxviral-based vaccine

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BACKGROUND

Increased levels of regulatory T cells (Tregs) have been reported in both the **tumor microenvironment** and in the **peripheral blood** of patients with several types of malignancies…

A low number of tumor-infiltrating FOXP3-positive cells during primary systemic chemotherapy correlates with favorable anti-tumor response in patients with **breast cancer**.
Aruga T, et al. Oncol Rep. 2009 Aug;22(2):273-8.

The prevalence of FOXP3+ regulatory T-cells in peripheral blood of patients with **NSCLC**.
Li L, et al. Cancer Biother Radiopharm. 2009 Jun;24(3):357-67.

Incidence and prognostic impact of FoxP3+ regulatory T cells in human **gliomas**.
Heimberger AB, et al. Clin Cancer Res. 2008 Aug 15;14(16):5166-72.

Intratumoural FOXP3-positive regulatory T cells are associated with adverse prognosis in radically resected **gastric cancer**.
Perrone G, et al. Eur J Cancer. 2008 Sep;44(13):1875-82. Epub 2008 Jul 9.

Prognostic impact of tumor infiltrating FOXP3 positive regulatory T cells in diffuse large **B-cell lymphoma** at diagnosis.
Lee NR, et al. Leuk Lymphoma. 2008 Feb;49(2):247-56.

Correlation of NK T-like CD3+CD56+ cells and CD4+CD25+(hi) regulatory T cells with VEGF and TNFalpha in ascites from **advanced ovarian cancer**: Association with platinum resistance and prognosis in patients receiving first-line, platinum-based chemotherapy.
Bamias A, et al. Gynecol Oncol. 2008 Feb;108(2):421-7. Epub 2007 Nov 26.

Tumor-infiltrating Foxp3-CD4+CD25+ T cells predict poor survival in **renal cell carcinoma**.
Siddiqui SA, et al. Clin Cancer Res. 2007 Apr 1;13(7):2075-81.

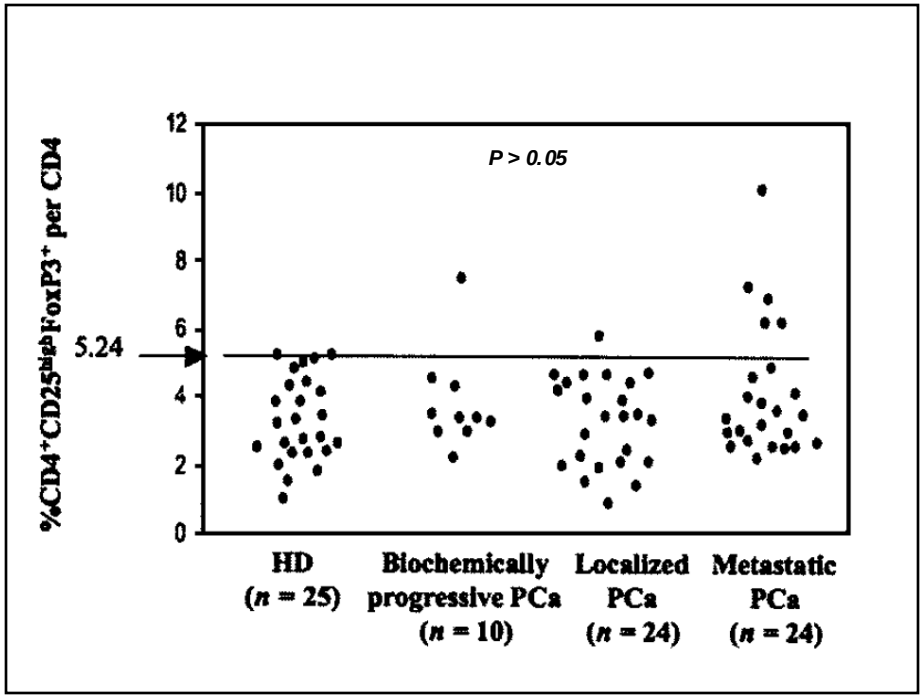
Increased frequency of regulatory T cells in peripheral blood and tumour infiltrating lymphocytes in **colorectal cancer patients**.
Ling KL,et al. Cancer Immun. 2007 Mar 28;7:7

…AND are generally related to poor clinical outcome

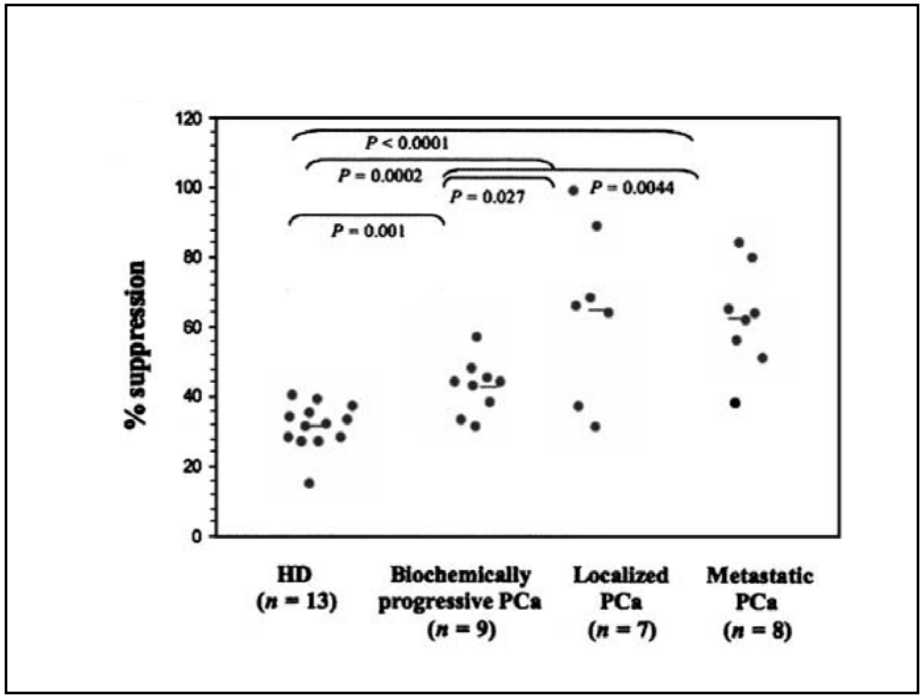
Enhanced functionality of CD4+CD25(high)FoxP3+ regulatory T cells in the peripheral blood of patients with prostate cancer.

Yokokawa J, Cereda V, Remondo C, Gulley JL, Arlen PM, Schlom J, Tsang KY.
Clin Cancer Res. 2008 Feb 15;14(4):1032-40.

Frequency of $CD4^+CD25^{high}FoxP3^+$ Tregs



Function of $CD4^+CD25^{high}FoxP3^+$ Tregs



DO TREGS PLAY A CENTRAL ROLE IN ANTI-TUMOR IMMUNITY?

Peripheral Tregs and overall survival in metastatic castration-resistant prostate cancer (mCRPC) patients treated with a poxviral-based vaccine (PSA-TRICOM)

TRICOM
TRIad of COstimulatory Molecules

A vaccine formulation consisting of recombinant vaccinia (rV) or fowlpox (rF) virus, encoding:

Costimulatory Molecule	Ligand on T cell
B7-1 (CD80)	CD28/CTLA-4
ICAM-1 (CD54)	LFA-1
LFA-3 (CD58)	CD2

TRICOM = B7-1/ICAM-1/LFA-3

PSA/TRICOM = PSA/B7-1/ICAM-1/LFA-3 (PROSTVAC)

All vaccines contain: rV- as a prime vaccine
avipox (fowlpox, rF-) as multiple booster vaccines

Randomized Multicenter Placebo-controlled Vaccine Therapy Trial in Castrate-resistant Metastatic Prostate Cancer Patients

Patients (n = 125)

- Metastatic prostate cancer (CT or bone scan +)
- Gleason score ≤ 7; no visceral disease
- Chemotherapy naïve

Vaccine: rV, rF-PSA-TRICOM (PROSTVAC) + GM-CSF

Control arm: empty vector

Randomization: 2:1 (double blind)

P.I.: P. Kantoff, Dana-Farber Cancer Center

Analyses: W. Godfrey, BNIT
B. Blumenstein, statistician

Randomized Multicenter Placebo-controlled Vaccine Therapy Trial in Castrate-resistant Metastatic Prostate Cancer Patients

Observations:

A. Time to Progression: no difference in arms

B. Median survival at 4 years

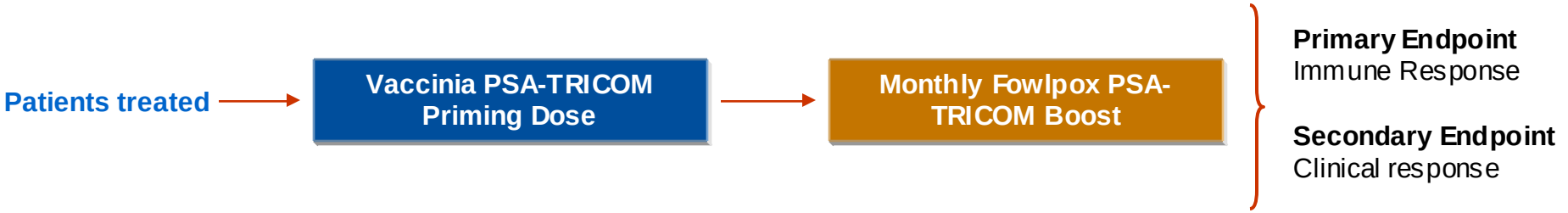
Placebo: 16.6 months

Vaccine: 25.1 months (p=0.006)

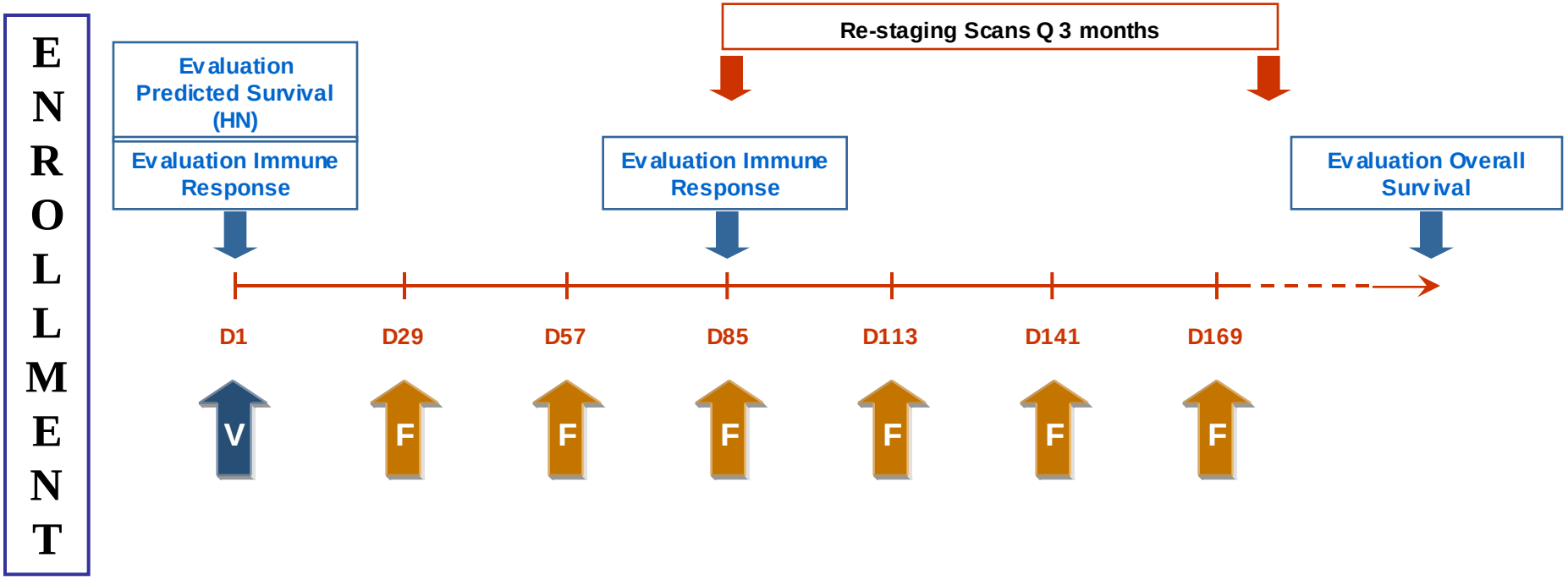
C. 40% reduction in death rate in vaccine arm

Phase III Trial Planned

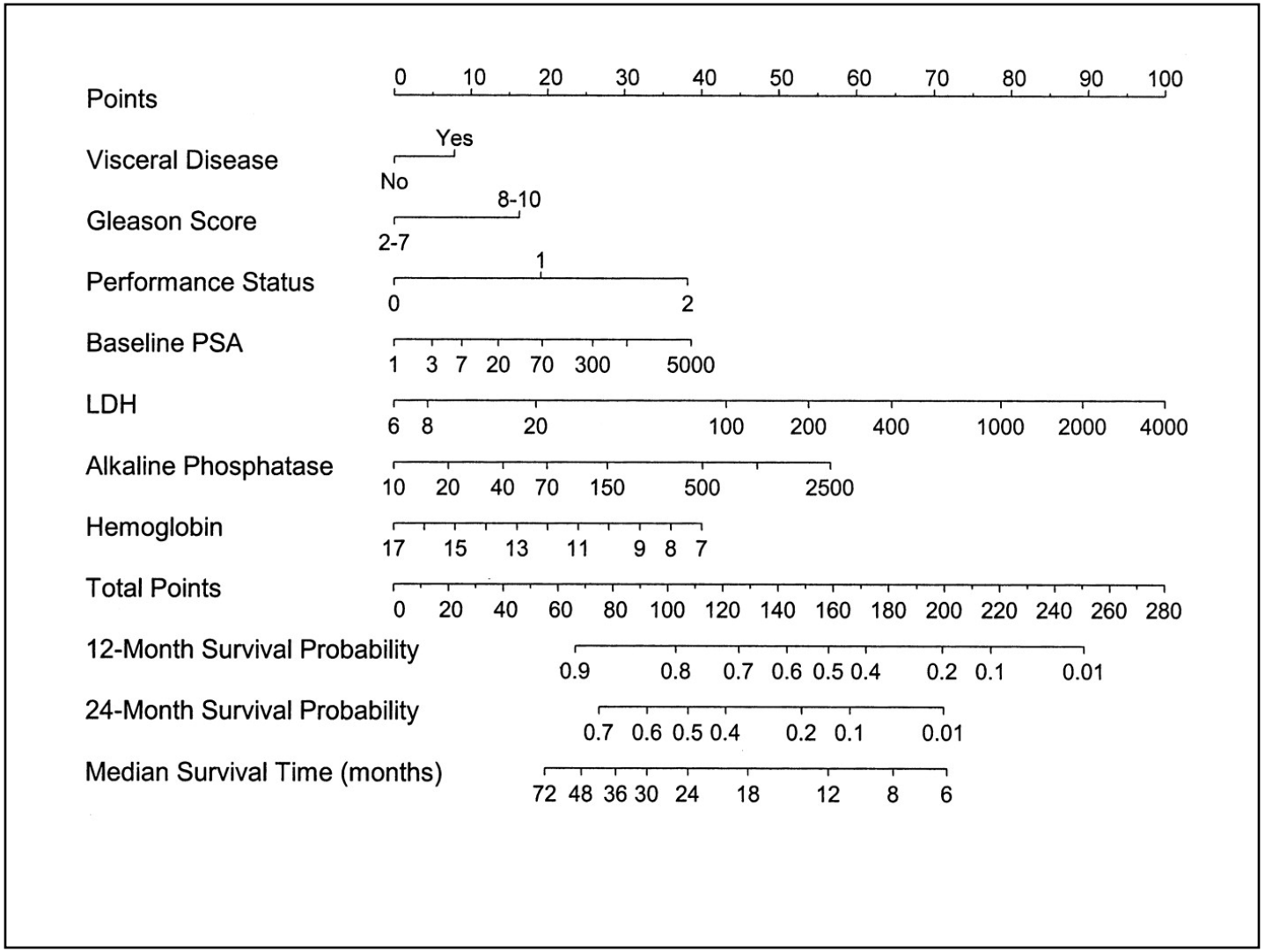
PSA-TRICOM - PHASE I/II CLINICAL TRIAL: STUDY DESIGN



- Androgen refractory
- Metastatic disease



HALABI NOMOGRAM TO PREDICT SURVIVAL

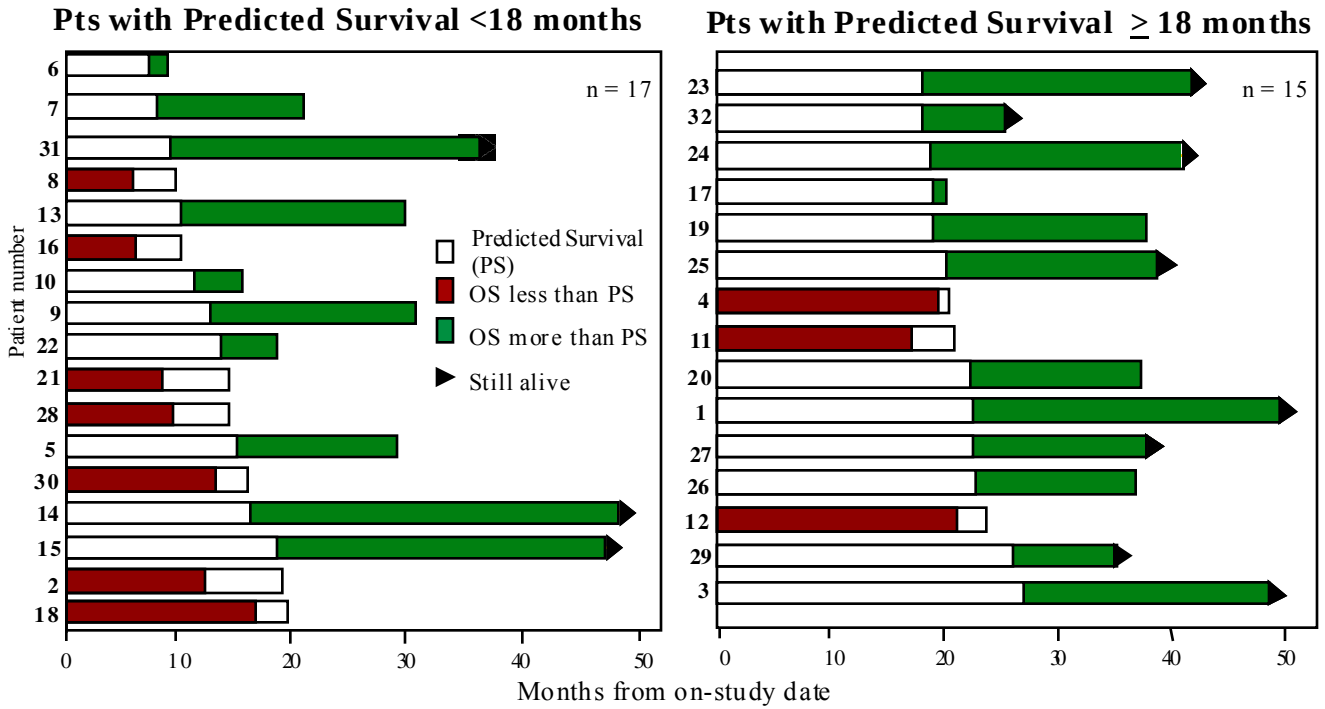


Halabi, et al., J. Clin Oncol, 2003

OVERALL SURVIVAL IN PSA-TRICOM CLINICAL TRIAL

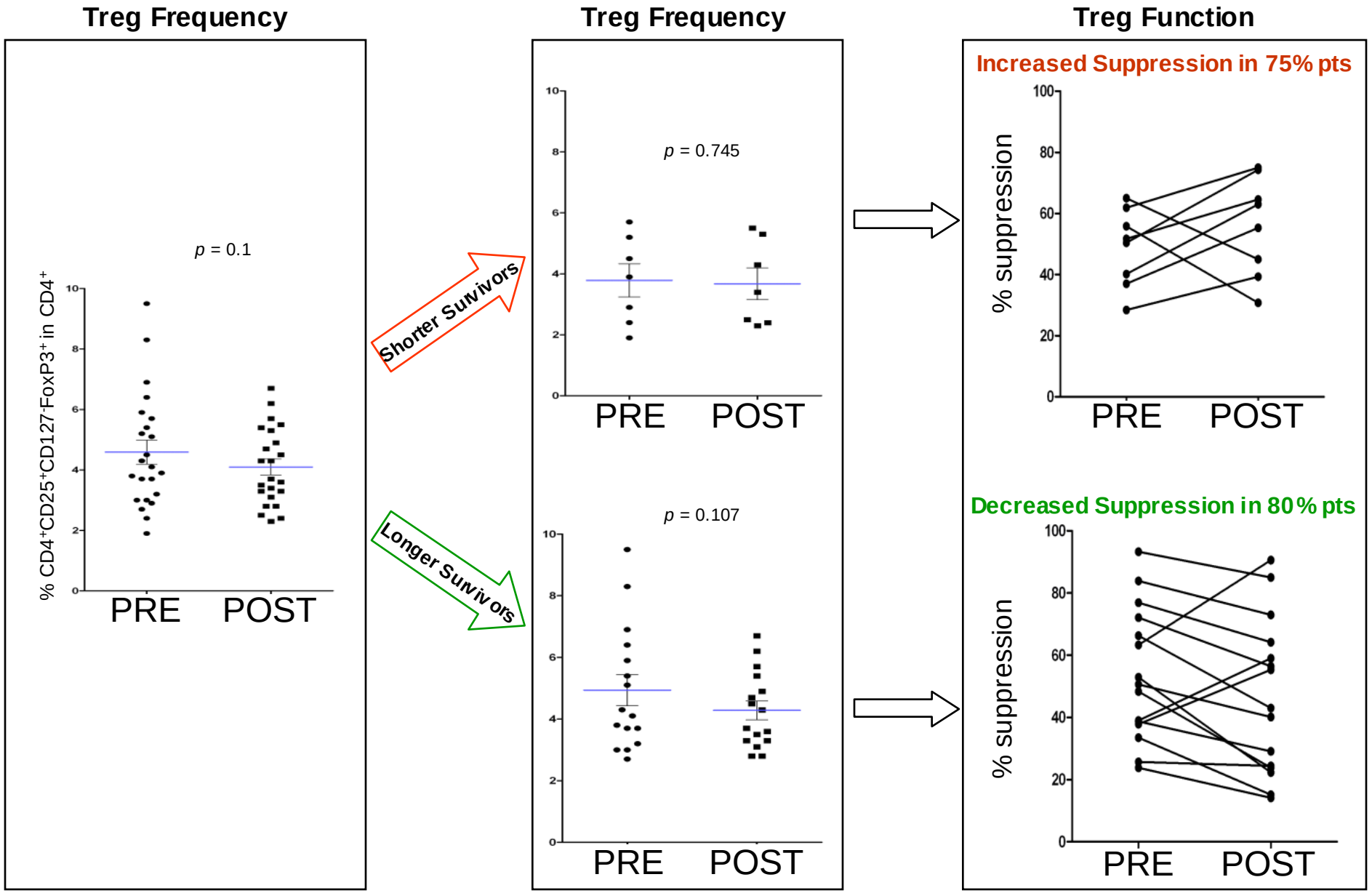
Patient Group	Median PS (mos)	Actual Median OS (mos)	Difference in Survival (mos)	Patients with OS longer than PS	
All	17.4	26.6	9.2	22/32	*p*=0.05*
<18 PS	12.3	14.6	2.3	10/17	*p*=0.63*
≥18 PS	20.9	Not reached (8/15 alive at 44.6 mos+)	23.7+	12/15	*p*=0.035*

*two-tailed p-value is listed.



Immunologic and Prognostic Factors Associated with Overall Survival Employing a Poxviral-based PSA Vaccine in Metastatic Castrate-resistant Prostate Cancer.
Gulley JL, et al. *Cancer Immunol Immunother*, 2009.

T-REG ($CD4^+CD25^+CD127^-FoxP3^+$) FUNCTION CORRELATES WITH OVERALL SURVIVAL



POSSIBLE ROLE OF CTLA-4 EXPRESSION ON T-REGS

Zheng Y, Manzotti CN, Burke F, Dussably L, Qureshi O, Walker LS, Sansom DM.

Acquisition of suppressive function by activated human CD4+ CD25- T cells is associated with the expression of CTLA-4 not FoxP3.

J Immunol. 2008 Aug 1;181(3):1683-91.

Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, Nomura T, Sakaguchi S.

CTLA-4 control over Foxp3+ regulatory T cell function.

Science. 2008 Oct 10;322(5899):271-5.

Miyara M, Yoshioka Y, Kitoh A, Shima T, Wing K, Niwa A, Parizot C, Taflin C, Heike T, Valeyre D, Mathian A, Nakahata T, Yamaguchi T, Nomura T, Ono M, Amoura Z, Gorochov G, Sakaguchi S.

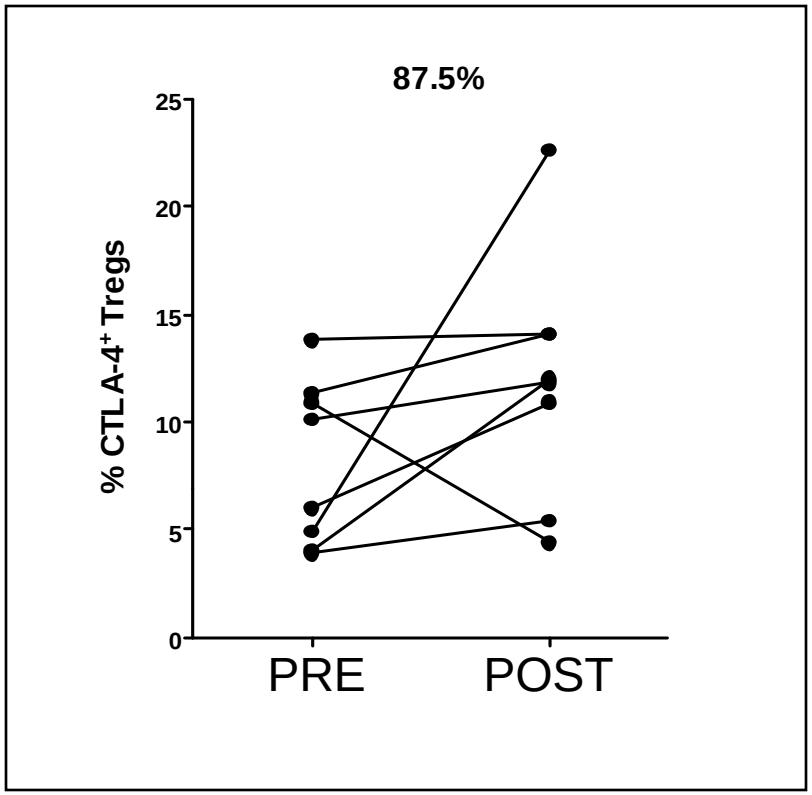
Functional delineation and differentiation dynamics of human CD4+ T cells expressing the FoxP3 transcription factor.

Immunity. 2009 Jun 19;30(6):899-911.

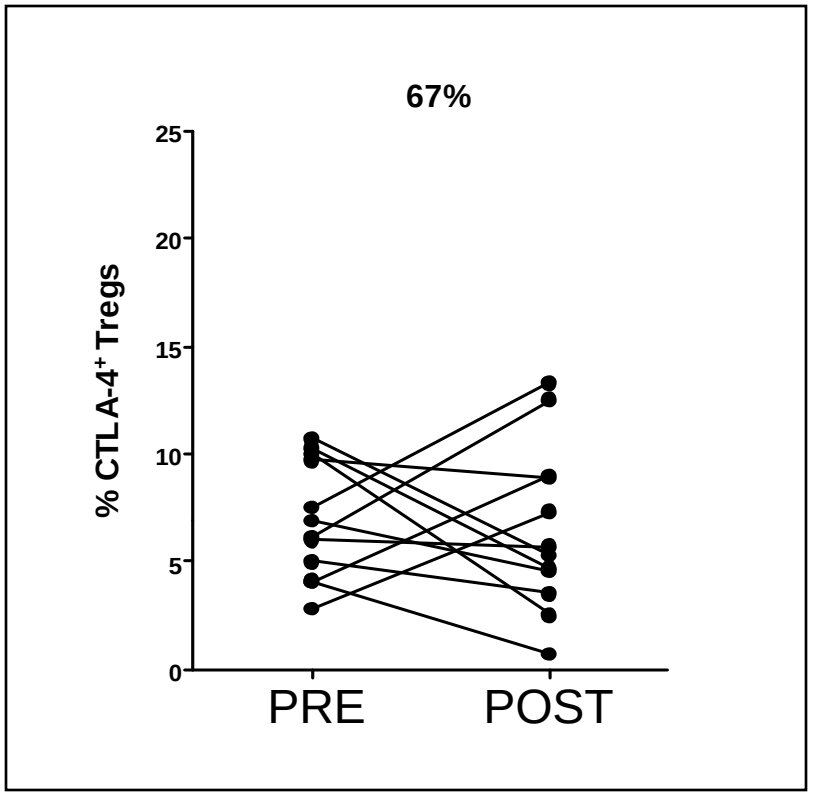
$CD4^{+}$ $CD25^{+++}$ $FoxP3^{hi}$ $CD45RA^{-}$ ($CTLA\text{-}4^{hi}$ DR^{hi}) activated Tregs (aTregs) Suppressive +++

CORRELATION BETWEEN CTLA-4 EXPRESSION ON T-REGS AND T-REG SUPPRESSIVE FUNCTION

INCREASED SUPPRESSION

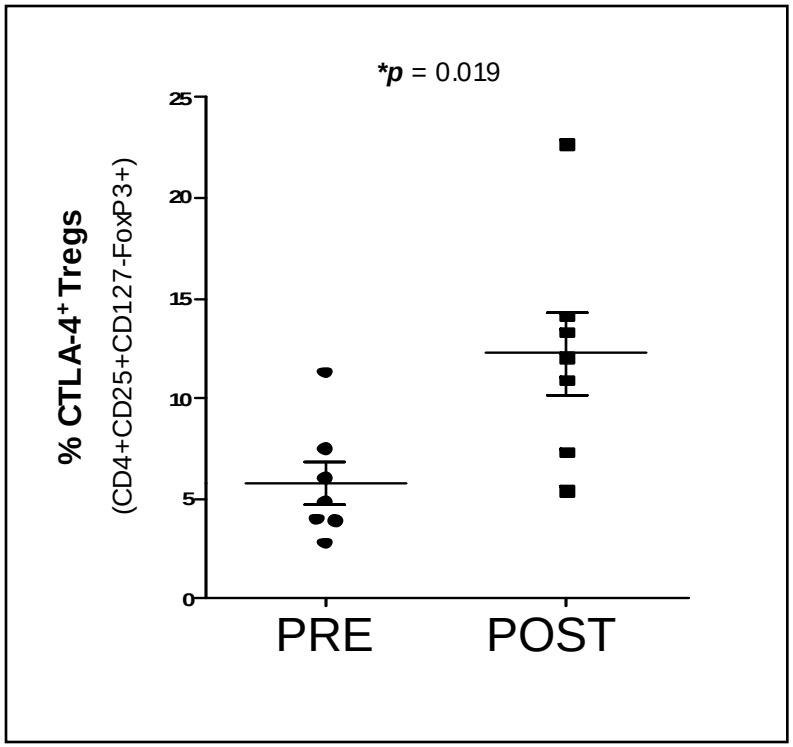


DECREASED SUPPRESION

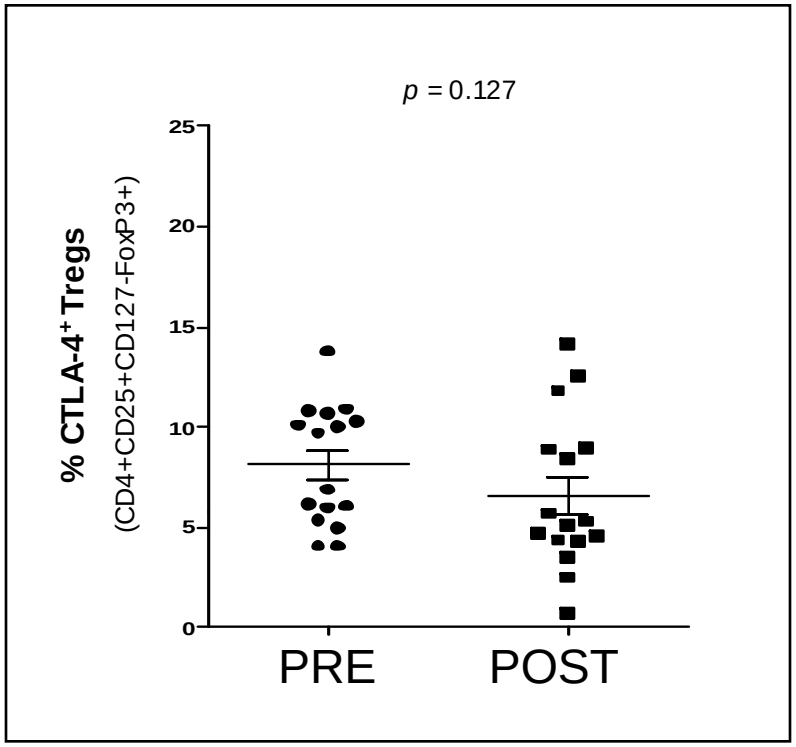


CORRELATION BETWEEN CTLA-4 EXPRESSION ON T-REGS AND PATIENT SURVIVAL

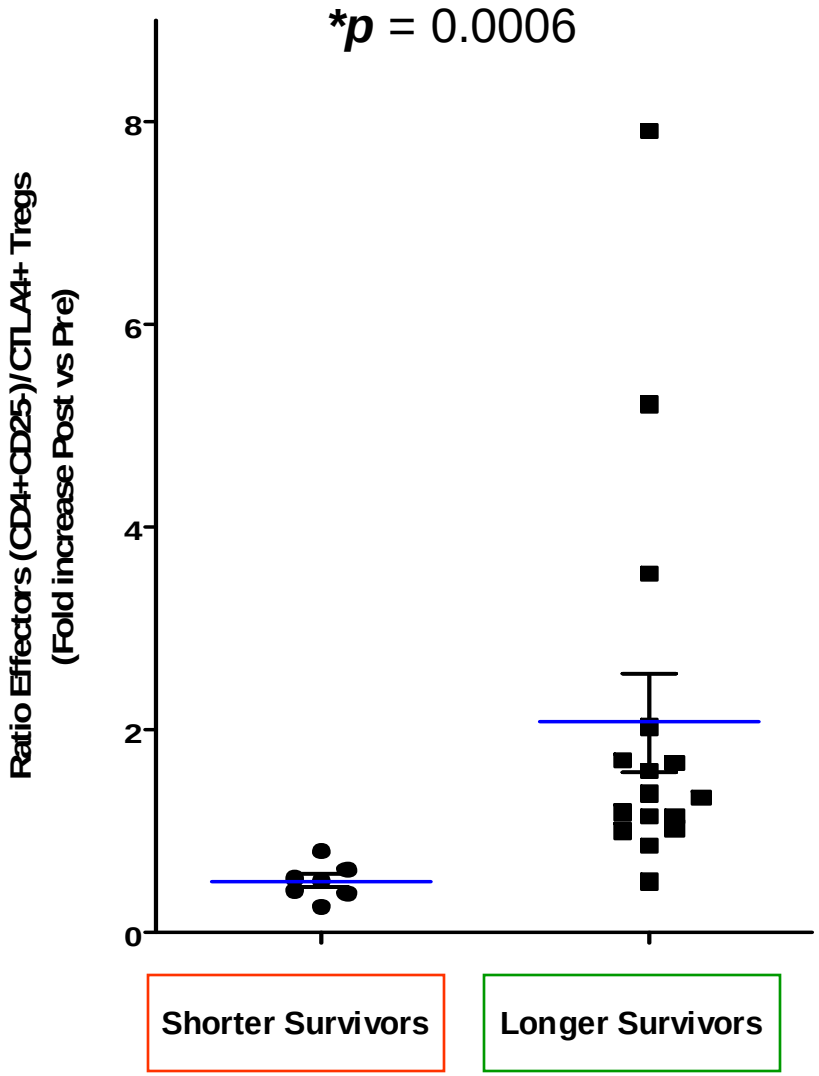
SHORTER SURVIVORS



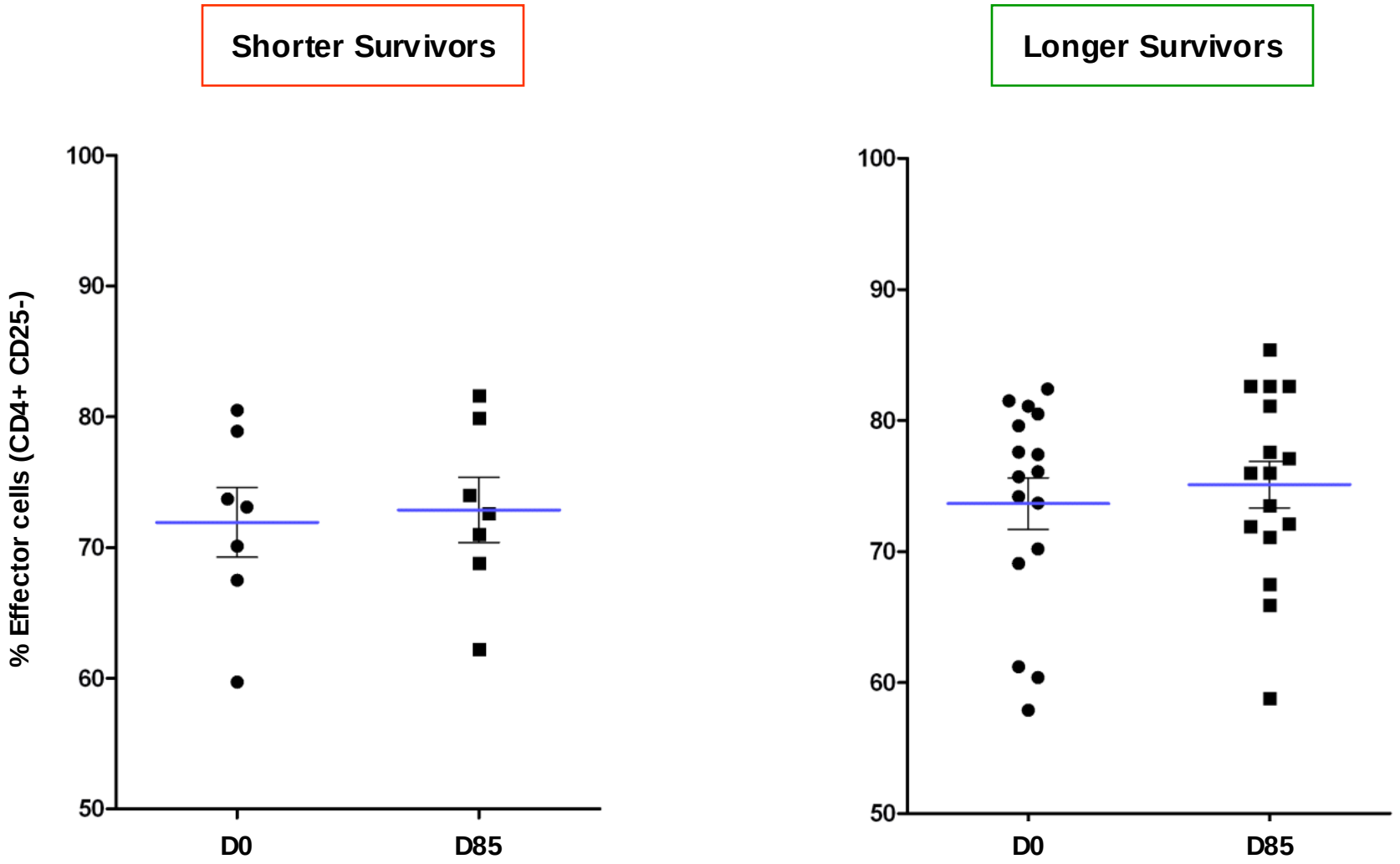
LONGER SURVIVORS



CORRELATION BETWEEN PATIENT SURVIVAL AND EFFECTOR/CTLA4^{+} EXPRESSING T-REG RATIO



NO DIFFERENCE IN THE % OF EFFECTOR CELLS IN SHORTER AND LONGER SURVIVORS



CONCLUSIONS

1. **No difference in Treg numbers pre- and post-vaccination**

2. **Significant correlations between:**

   - **Treg suppressive function and overall survival**
   - **Frequency of CTLA-4 expressing Tregs and Treg suppressive function**
   - **Patient survival and the ratio between effectors and CTLA4 expressing Tregs**

These data suggest that the clinical benefit of vaccine immunotherapy with PSA-TRICOM can be due in part to a decreased Treg suppressive activity post vaccination

Further studies are ongoing to confirm and extend this observation

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