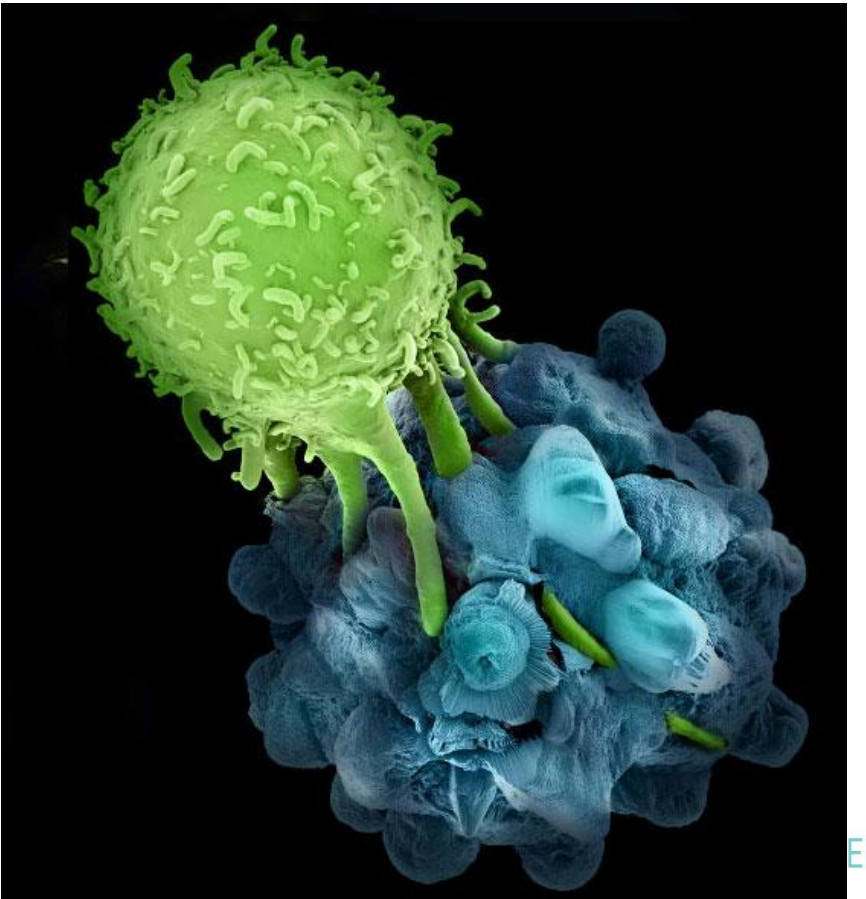

SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
sitc
Society for Immunotherapy of Cancer

# Cancer Immunotherapy Trials Network (CITN)

## *Progress Report*

***(November 11, 2017)***



Martin A. “Mac” Cheever MD
PI: Cancer Immunotherapy Trials Network
Member: Fred Hutch
Professor: U of Washington
mcheever@fredhutch.org

ER IMMUNOTHERAPY WORLDWIDE

cancer immunotherapy trials network

# Presenter Disclosure Information

*Martin A. "Mac" Cheever*

No Conflicts

Many biases

# CITN Renewal

# CITN Renewal


- 5 years from September 1st 2017
- Increased budget for pediatric immunotherapy trials
  - Folded-in scientists from St. Baldrick's/SU2C Pediatric Immunotherapy Dream Team (PCDT)
  - Crystal Mackall, Paul Sondel, John Maris
  - Very different cancer biology
    - Relative paucity of nonsynonymous somatic mutations
    - Single-agent anti-PD1 therapy has shown little evidence for antitumor activity in Phase I trials
    - FOCUS: "synthetic immunotherapies" (e.g., mAbs, bispecific Abs, CAR T cells)
- Laboratory correlative studies from outstanding collaborating CIMACs (Cancer Immune Monitoring and Analysis Centers)
  - Primary: Stanford (PI: Holden Maecker)
  - Secondary: Mt Sinai (PI: Sacha Gnjatic)

cancer immunotherapy trials network

# CITN Renewal Core Focus: Remains the Same

- Trials with agents central to effective immune responses
  - Ongoing trials with:
    - Dendritic cell activator (anti-CD40)
    - Dendritic cell growth factor (Flt3L)
    - T-cell and NK cell activator & growth factor (IL-15)
    - Homeostatic T-cell growth factor (IL-7)
    - Agent to inhibit suppressive enzymes (IDO inhibitor)
    - Vaccine adjuvant (poly ICLC)
    - Checkpoint inhibitor (anti-PD1)
    - Innate activators (IFN-gamma)
- **Still remarkably few academic investigator initiated trials for all agents except anti-PD1/PD-L1**

cancer immunotherapy trials network

# Progress from Six CITN Trials

- Three trials with anti-PD1 (pembrolizumab) in orphan diseases
  - Merkel cell carcinoma: first systemic therapy
  - Mycosis fungoides/Sezary syndrome: advanced, treatment failure
  - HIV & advanced malignancy

- Three trials with agents that induce growth of cells central to an effective immune response
  - IL-15/IL-15Ra/Fc (ALT-803): subcutaneous dose escalation in solid tumors
  - IL-7: prostate cancer after Sipuleucel-T (Provenge, Dendreon)
  - Flt3-Ligand: Flt3-Ligand (CDX-301) + Poly ICLC (Hiltonol) + anti-DEC205-NY-ESO-1 vaccine (CDX-1401): melanoma, adjuvant

cancer immunotherapy trials network

The NEW ENGLAND JOURNAL of MEDICINE

Publication: June 2016
Data cutoff: Feb 2016

ORIGINAL ARTICLE

# PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma

Paul T. Nghiem, M.D., Ph.D., Shailender Bhatia, M.D., Evan J. Lipson, M.D., Ragini R. Kudchadkar, M.D., Natalie J. Miller, B.A., Lakshmanan Annamalai, D.V.M., Ph.D, Sneha Berry, M.S., Elliot K. Chartash, M.D., Adil Daud, M.B., B.S., Steven P. Fling, Ph.D., Philip A. Friedlander, M.D., Harriet M. Kluger, M.D., Holbrook E. Kohrt, M.D., Ph.D.,* Lisa Lundgren, M.S., Kim Margolin, M.D., Alan Mitchell, M.Sc., Thomas Olencki, D.O., Drew M. Pardoll, M.D., Ph.D., Sunil A. Reddy, M.D., Erica M. Shantha, M.D., William H. Sharfman, M.D., Elad Sharon, M.D., M.P.H., Lynn R. Shemanski, Ph.D., Michi M. Shinohara, M.D., Joel C. Sunshine, M.D., Ph.D., Janis M. Taube, M.D., John A. Thompson, M.D., Steven M. Townson, Ph.D., Jennifer H. Yearley, D.V.M., Ph.D., Suzanne L. Topalian, M.D., and Martin A. Cheever, M.D.

Key collaborations:

- Academic
  8 universities
- Industry
  Merck
- Government
  NCI-CTEP

cancer immunotherapy trials network

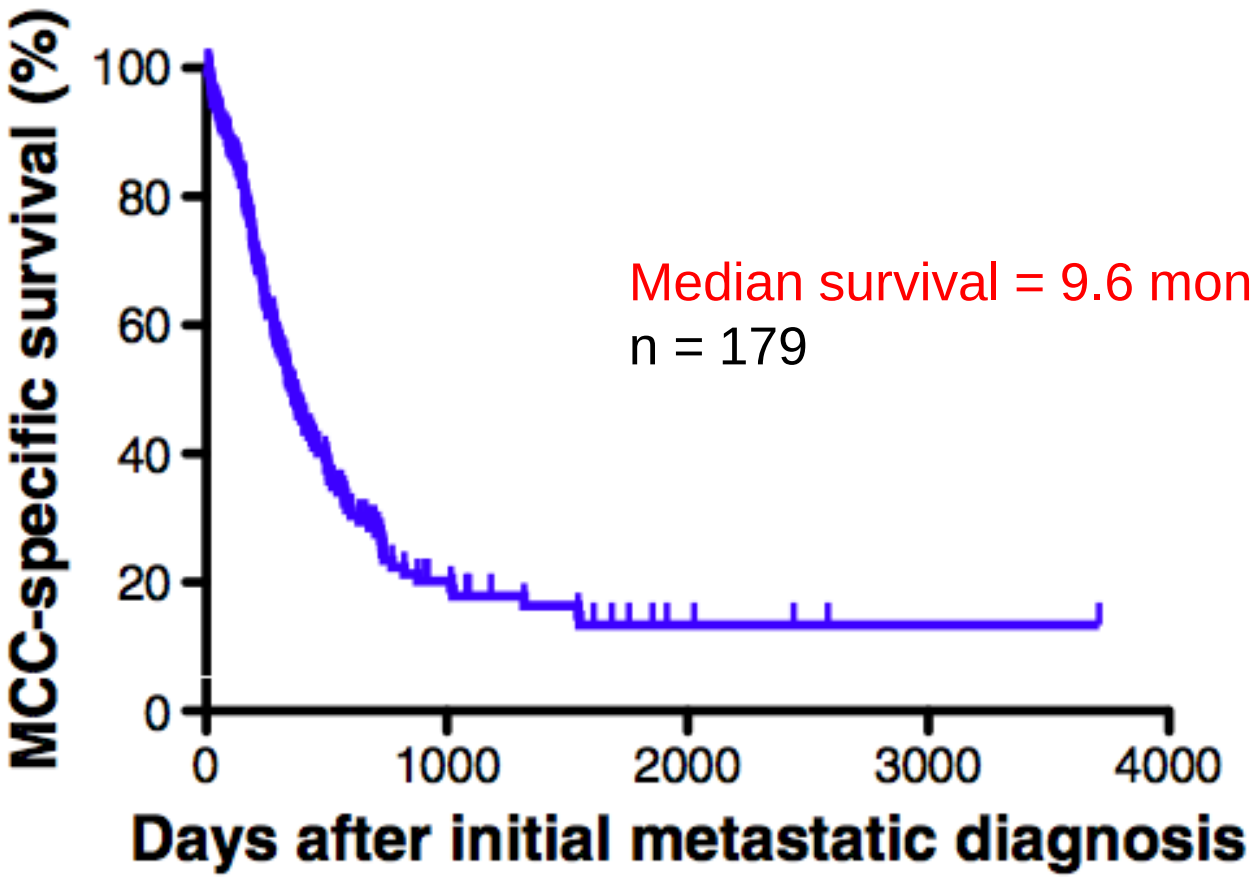
Metastatic MCC → platinum + etoposide

Initial responses common (53%) → poor durability:

>50% of patients progress by 3 months

>90% of patients progress by 10 months

*Lyer, et al, J Clin Oncol 32:5s, 2014 (suppl; abstr 9091)*



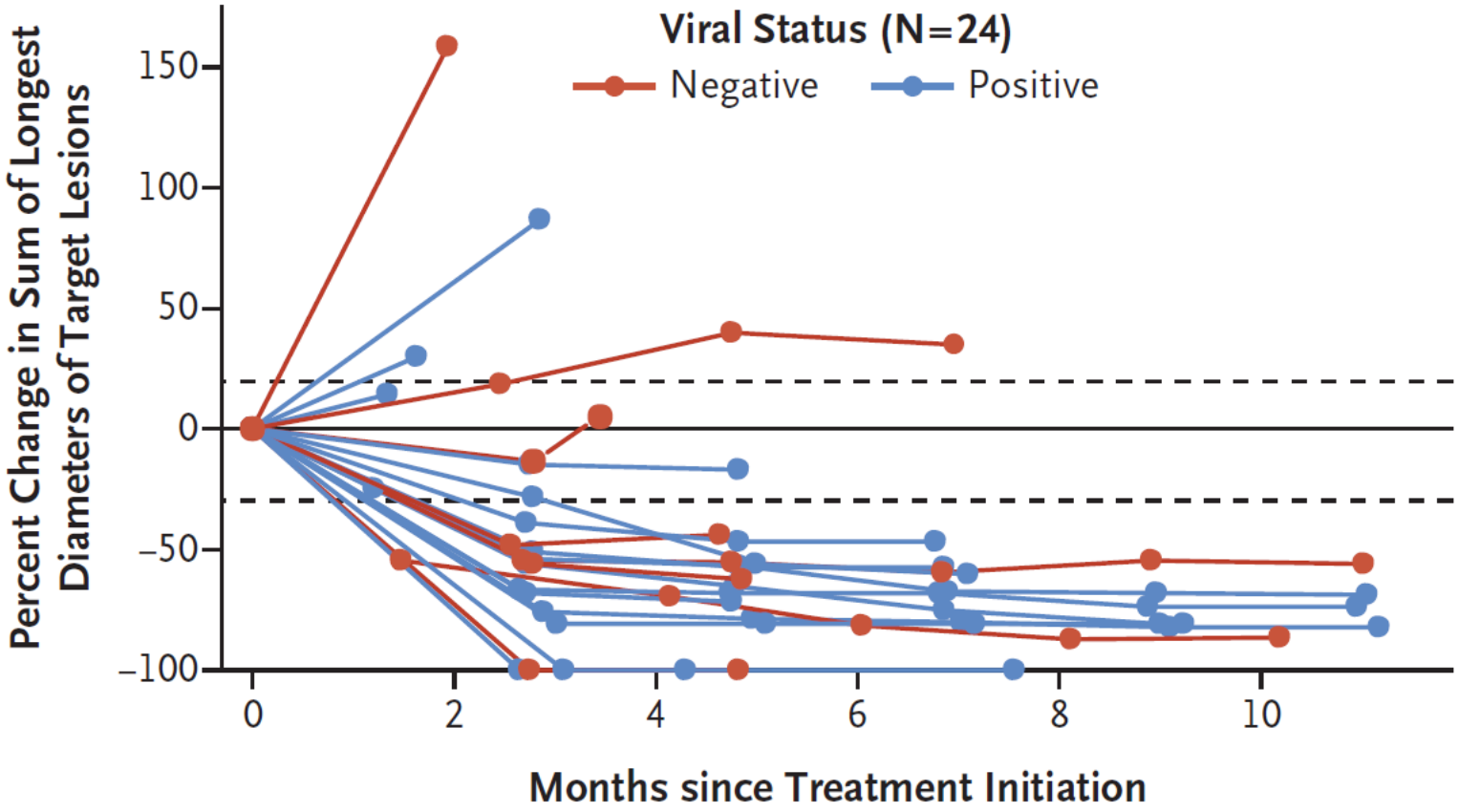

Median survival = 9.6 months

n = 179

**Miller, et al**, *Curr Treat Options Onc,* 2013

# Responses often rapid, then stable

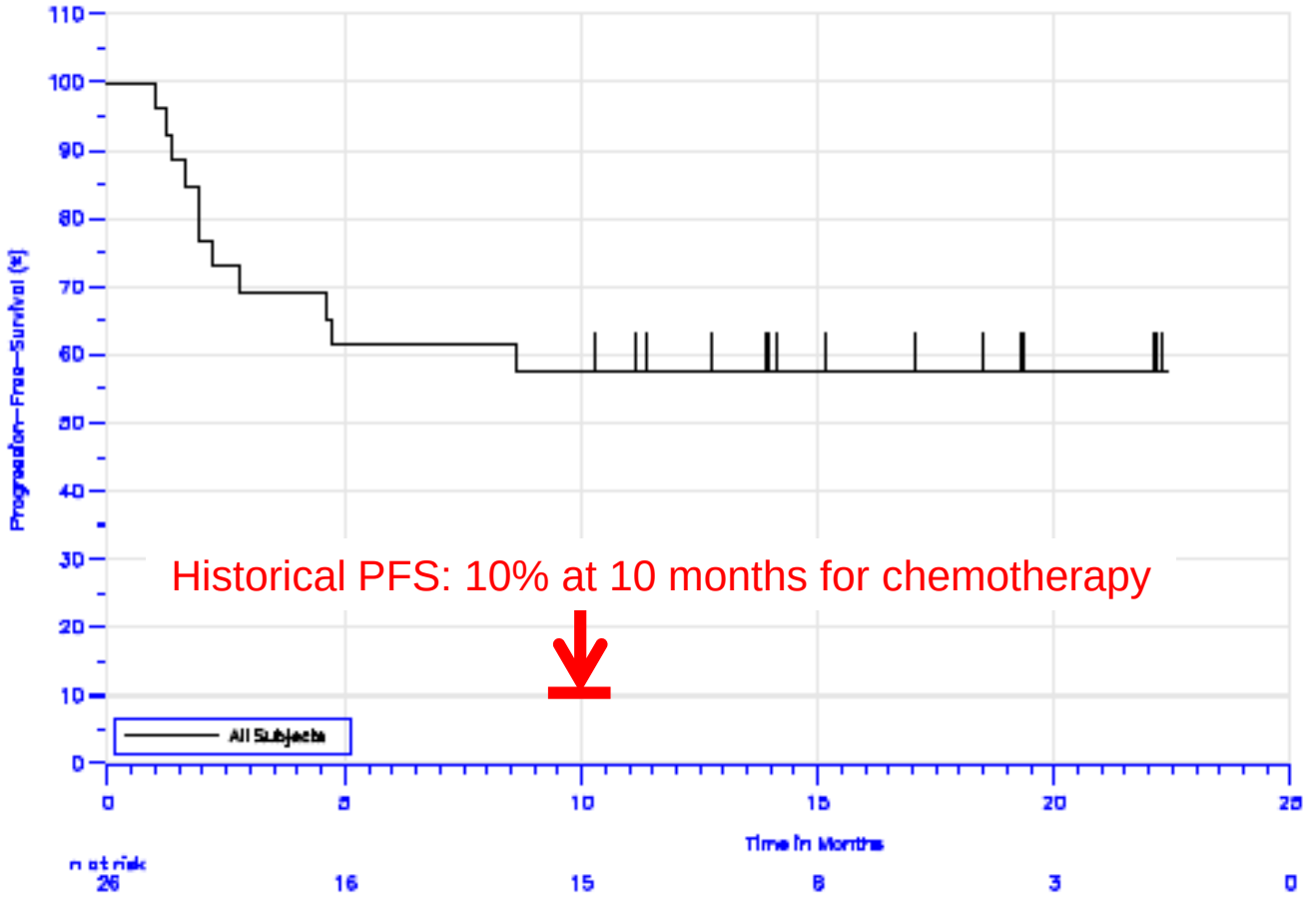
Data cutoff: Feb 2016




cancer immunotherapy trials network

# First 26 patients: Kaplan-Meier Estimates of Progression Free Survival

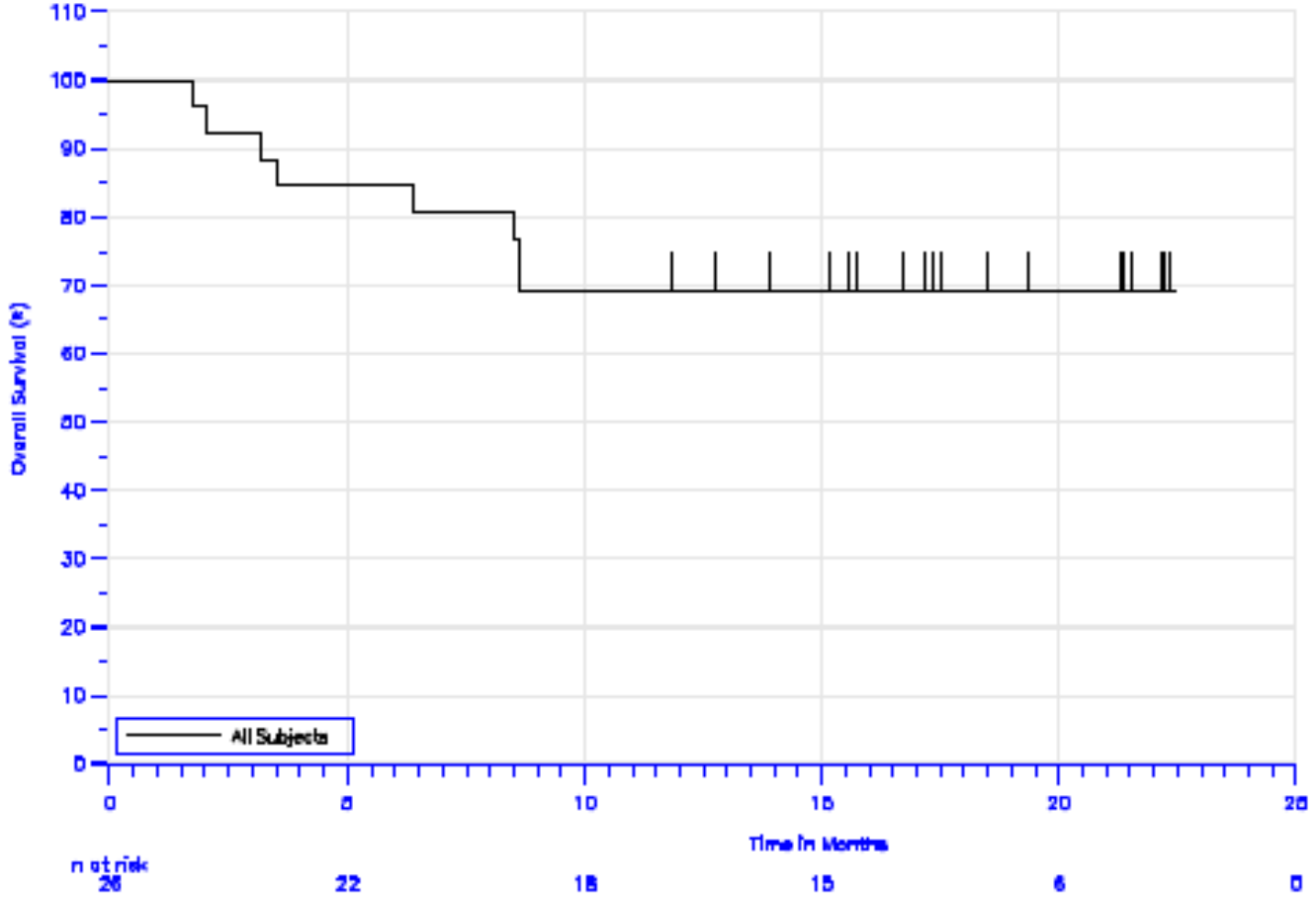
(ASaT Population)(Data Cutoff December, 2016)




(Data Cutoff Date: 06DEC2016).

# First 26 patients: Kaplan-Meier Estimates of Overall Survival

(ASaT Population)(Data Cutoff December, 2016)




(Data Cutoff Date: 06DEC2016).

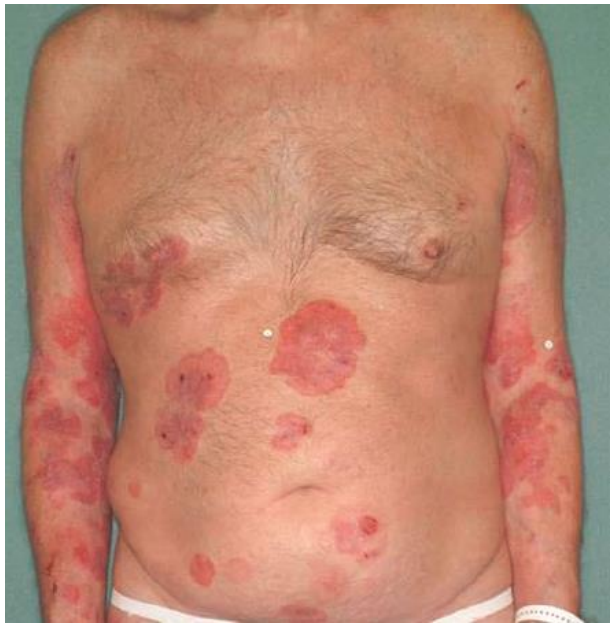
**[Change in NCCN Guidelines]**

**[Expanded to 50 patients: Fully accrued]**

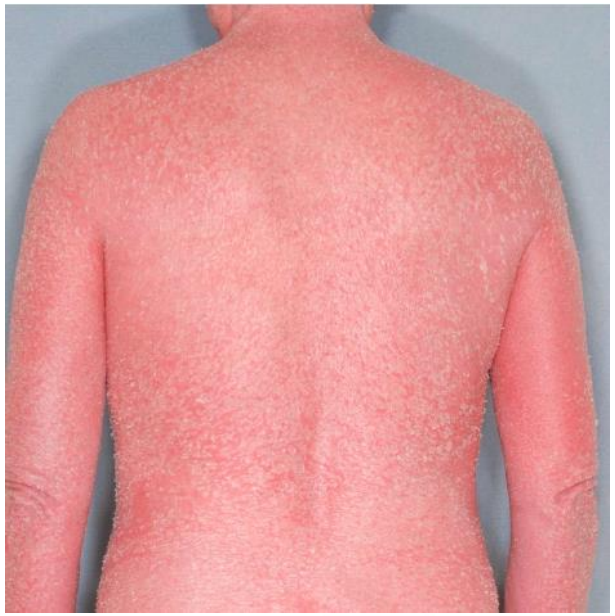
# Mycosis Fungoides & Sezary Syndrome

- Mycosis Fungoides and Sezary Syndrome are the 2 most common subtypes of cutaneous T cell lymphoma (CTCL)
  - 4% of all non-Hodgkin's lymphoma (~3,000 new US cases per year)
  - Classically, a cancer of malignant CD4 memory T cells

Mycosis Fungoides



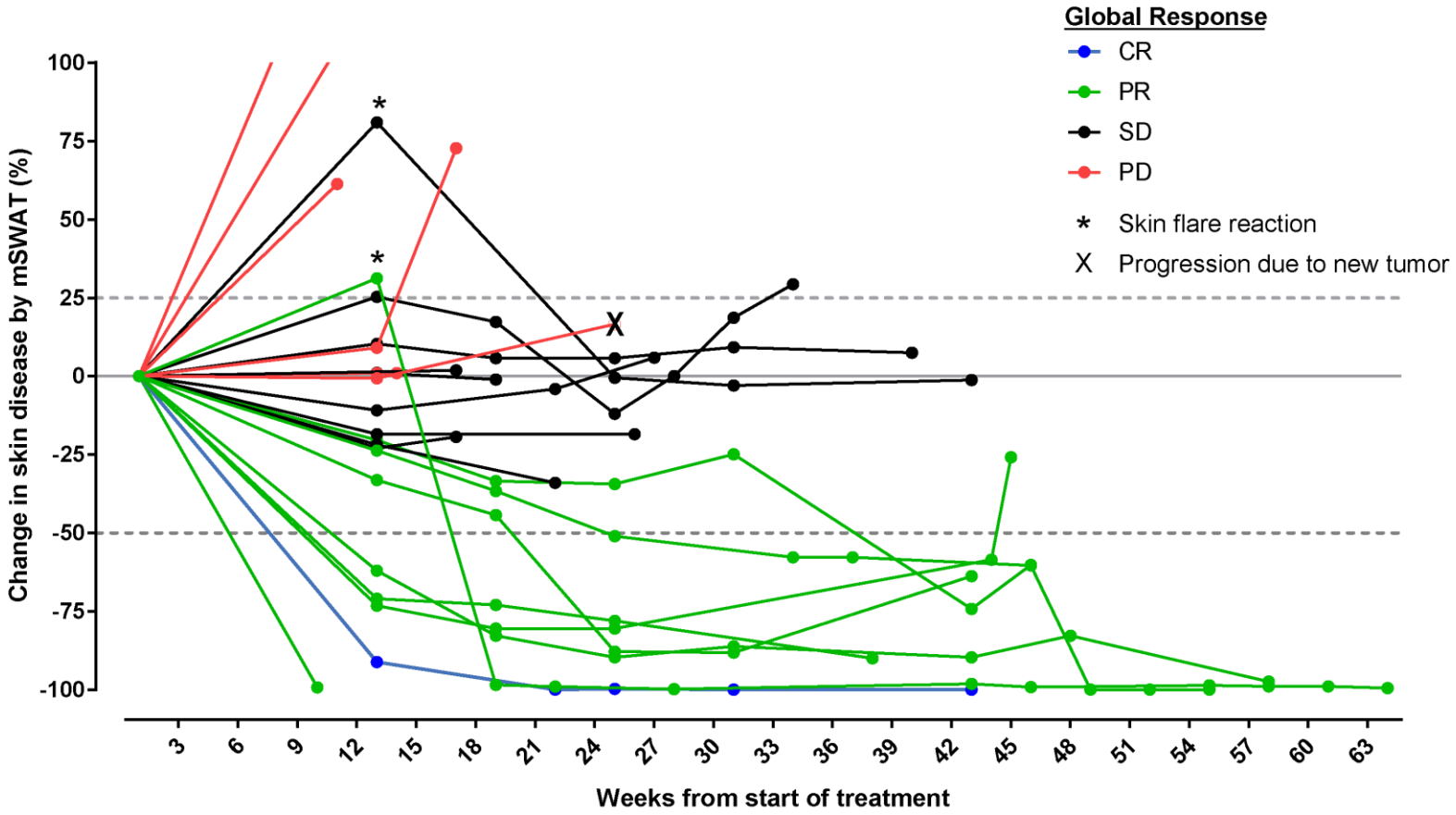
Sezary Syndrome



cancer immunotherapy trials network

# Anti-PD1 (pembrolizumab) in relapsed/refractory CTCL (mycosis fungoides/Sezary syndrome)

(PI: Youn Kim, MD)




**[Overall response rate: 38%]**

**[Change in NCCN Guidelines]**

cancer immunotherapy trials network

# Opened follow on trial: pembrolizumab + IFN-gamma 1b

## (PI: Michael Khodadoust MD)

- Anti-PD1 and IFN-gamma
  - Both have activity in mycosis fungoides
  - Synergistic mechanisms
    - IFN-gamma activates T cells
    - Anti-PD1 unleashes T cells
- Endogenous IFN-gamma is essential for Th1 immune responses
  - Drives T cell responses
  - Stimulates DCs & macrophages to upregulate MHC
  - Enhanced antigen presentation
  - Enhanced CD8+ T cell and NK cell cytotoxicity
  - Increased Th1 immune activity
  - Reduced Th2 immune activity
- Exogenous is limited by downstream induction of PD-L1

cancer immunotherapy trials network

# Anti-PD1 in patients with HIV & advanced malignancy (PI: Tom Uldrick MD)

- Patients with HIV have been excluded from FDA approval trials for pembrolizumab, nivolumab, atezolizumab and avelumab
  - Safety data in this patient population is imperative for treating physicians and clinical investigators

cancer immunotherapy trials network

# To date, pembrolizumab has an acceptable safety profile in patients with HIV

- 36 patient trial
  - HIV+ patients on highly effective anti-retroviral therapy (cART) who also have cancer
- 30 patients accrued
  - 18 patients reported on yesterday (Tom Uldrick)
- Three cohorts based on CD4 counts
  - Cohort 1: 100-199 CD4+ T cells/mcL
  - Cohort 2: 200-350 CD4+ T cells/mcL
  - Cohort 3: >350 CD4+ T cells/mcL
- Outcome:
  - Acceptable safety profile
  - $CD4^+$ T-cells counts may increase on pembrolizumab
  - HIV control is maintained on antiretroviral therapy
- Conclusions:
  - Anti-PD1 therapy should be considered in patients with HIV and malignancies with FDA-approved indications
  - Patients with HIV who meet appropriate eligibility criteria for a given cancer should be included in immunotherapy studies
  - Studies evaluating strategies to treat HIV that incorporate checkpoint inhibitors are warranted

cancer immunotherapy trials network

# Caveat to acceptable safety profile in patients with HIV

- One patient with advanced Kaposi sarcoma died
  - He had had elevated level of KSHV and died with disseminated KSHV
- Revised conclusions:
  - Patients with unexplained KSHV viremia or KSHV-associated multicentric Castleman disease require special consideration and should probably be excluded
  - Physicians should be aware of the possibility of emergent KSHV-associated multicentric Castleman disease in Kaposi sarcoma patients and early treatment is advised

- Follow on Trial:
  - Cohort 4:  Anti-PD1 as first systemic therapy for Kaposi sarcoma not amenable to local therapy

cancer immunotherapy trials network

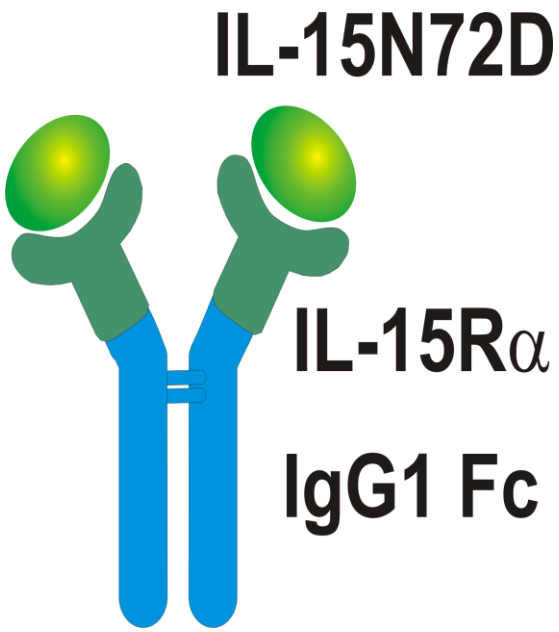
# Progress from CITN Trials

- Three trials with anti-PD1 (pembrolizumab) in orphan diseases
  - Merkel cell carcinoma: first systemic therapy
  - Mycosis fungoides/Sezary syndrome: advanced, treatment failure
  - HIV & advanced malignancy

- Three trials with agents that induce growth of cells central to an effective immune response
  - IL-15/IL-15Ra/Fc (ALT-803): subcutaneous dose escalation in solid tumors
  - IL-7: prostate cancer after Sipuleucel-T (Provenge, Dendreon)
  - Flt3-Ligand: Flt3-Ligand (CDX-301) + Poly ICLC (Hiltonol) + anti-DEC205-NY-ESO-1 vaccine (CDX-1401): melanoma, adjuvant

cancer immunotherapy trials network

# ALT-803: IL-15:IL5Ra-Fc Fusion Complex




Agent

- Increased binding to IL15Ra from N72D mutation
- Serum half-live = 25 hours

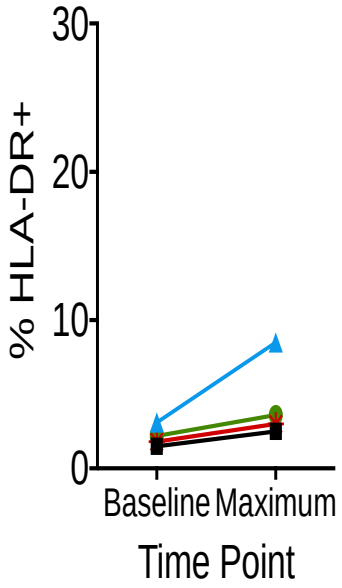
Trial Outline

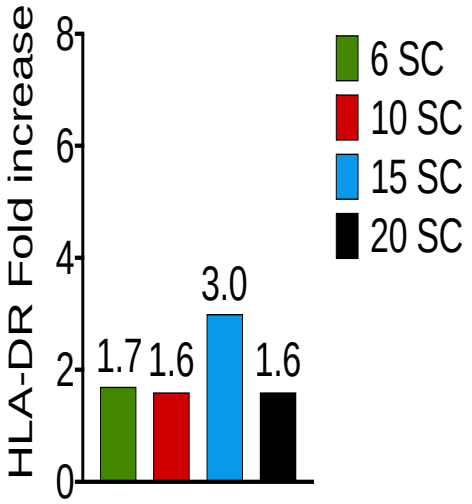
- Patients with solid tumors
- Dose escalation (4 dose levels)
- Subcutaneous administration
- Dosed weekly for 4 consecutive weeks
- of every 6-week cycle

cancer immunotherapy trials network

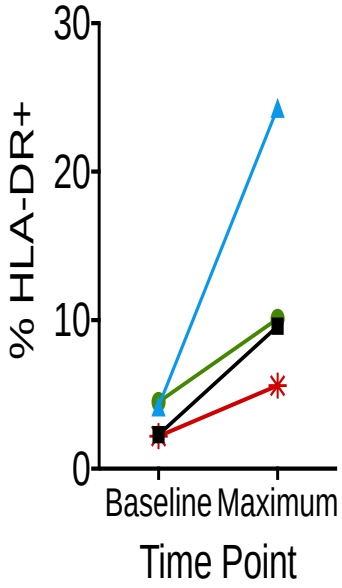
# Effect of subcutaneous ALT-803 on T cell HLA-DR Expression

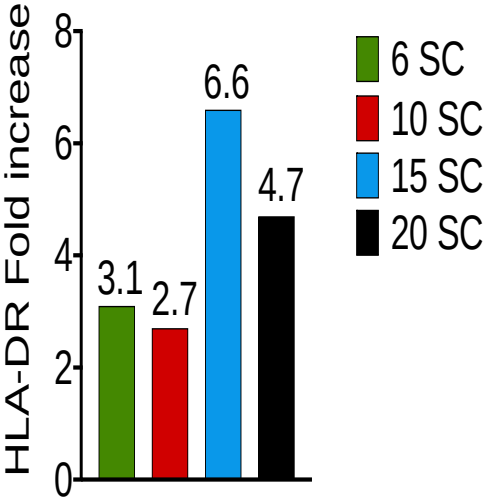
CD4+



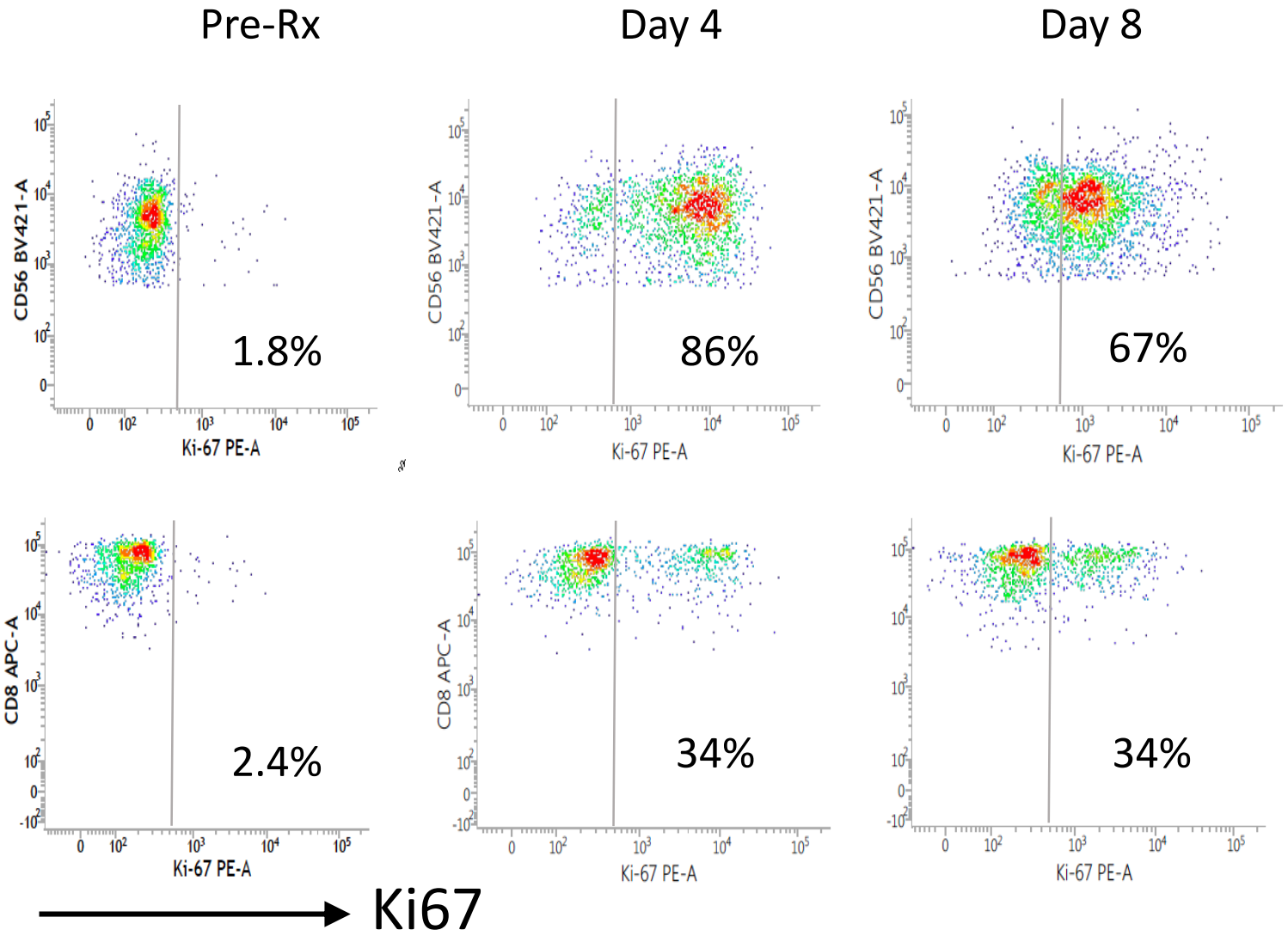




CD8+



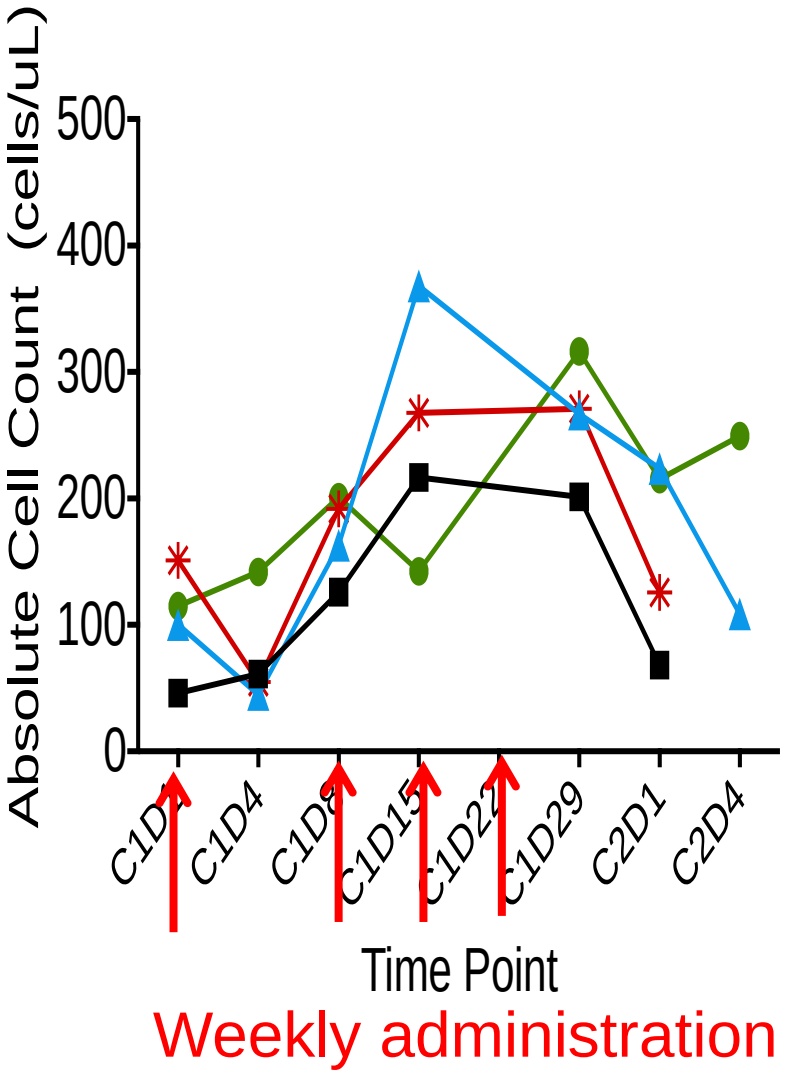
# Ki67+ cells – representative patient

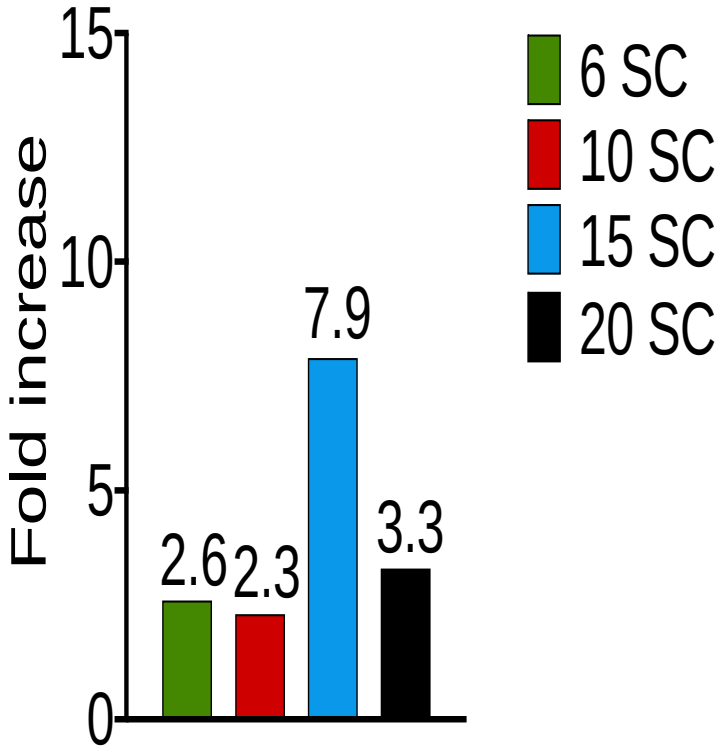



Subject 18: 15mcg/kg SC

Altor BioScience

# Effect of subcutaneous ALT-803 on Circulating Total CD3-CD56+ NK cells: By Dose Cohort



# Follow on trials:

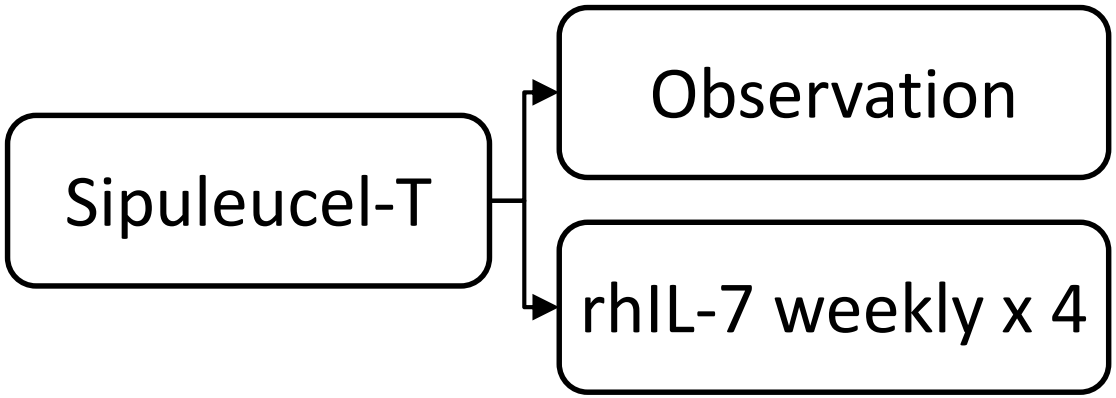
- Rescue anti-PD1/PD-L1 failure with ALT-803
  - IL-15/IL-15Ra/Fc (ALT-803) + anti-PD1 (pembrolizumab): to rescue HNSCC
  - IL-15/IL-15Ra/Fc (ALT-803) + anti-PD1 (pembrolizumab): to rescue melanoma

- Significance of the trial?
  - Largest single category of cancer patient will be patients on anti-PD1/PD-L1 + "X" and growing tumors
  - Anti-PD1/PD-L1 is effective in subsets of every type of cancer
    - >1,000 anti-PD1/PD-L1 trials, many combined with "X"
    - Many "X"s will be effective
  - There will never be a "standard" anti-PD1/PD-L1 therapy
  - East coast "X" will be different than West coast "X"
    - Like Tupac vs. Notorious B.I.G.
- Need biologically driven trials to address the issue of PD-1 failure

cancer immunotherapy trials network

# Recombinant glycosylated human interleukin-7 (CYT107) after sipuleucel-T (Provenge®) for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer

(PI: Lawrence Fong, MD, UCSF)
(Co-PI: Russell Szmulewitz, MD, University of Chicago)

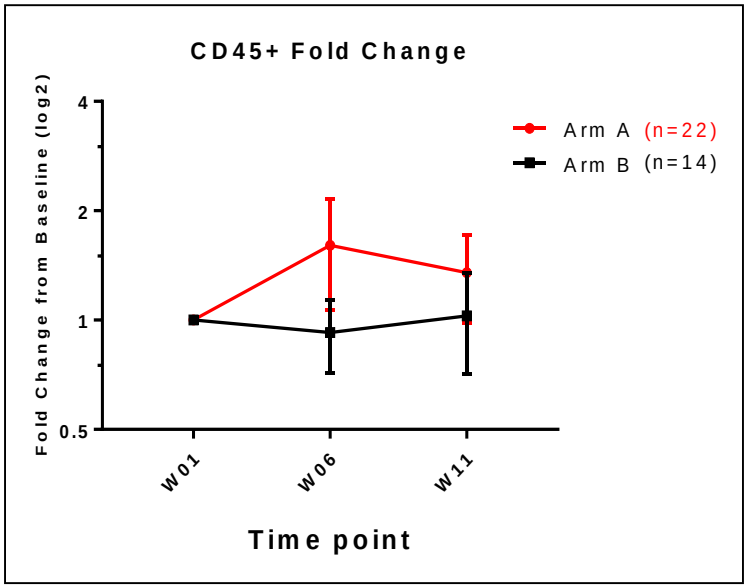


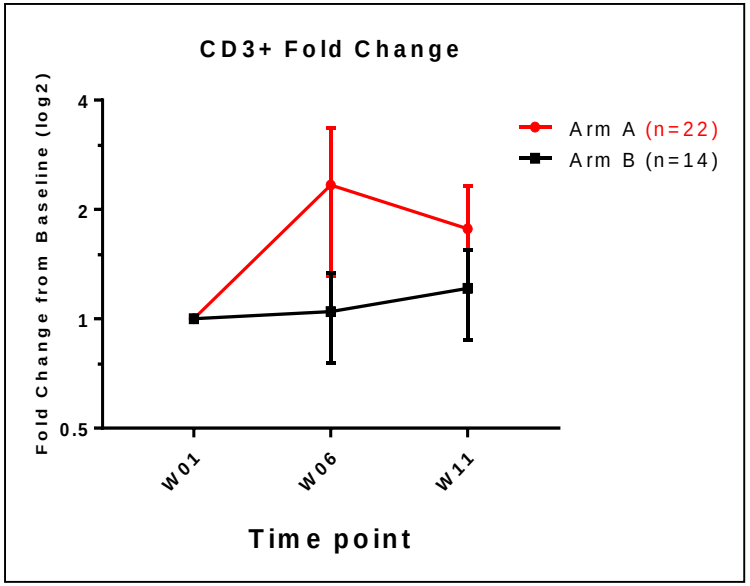

Accrual = 54
(as of 11/09/17)

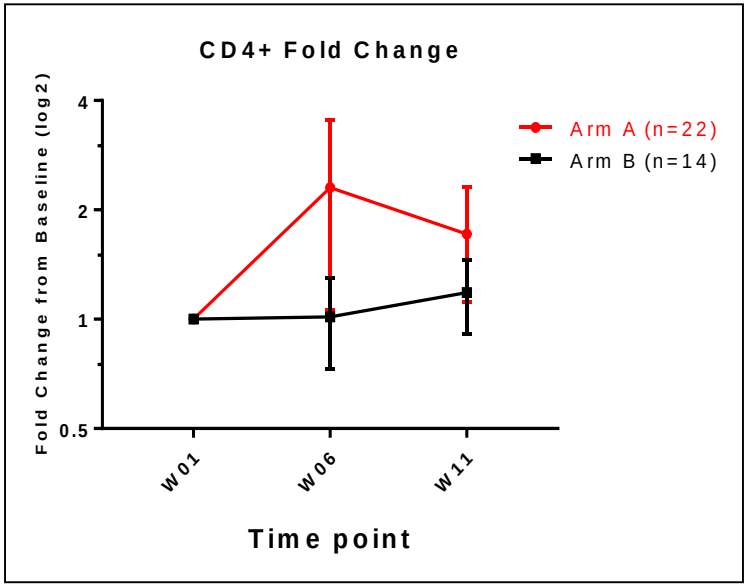
10 µg/kg of subcutaneous CYT107

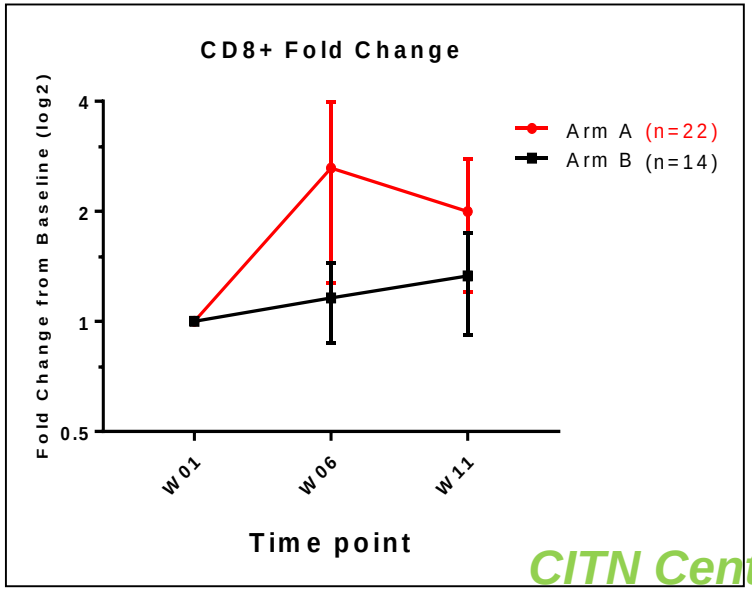
cancer immunotherapy trials network

# Comparison between Arms of Fold-Increase from Baseline of Lymphocytes and T cells in Whole Blood



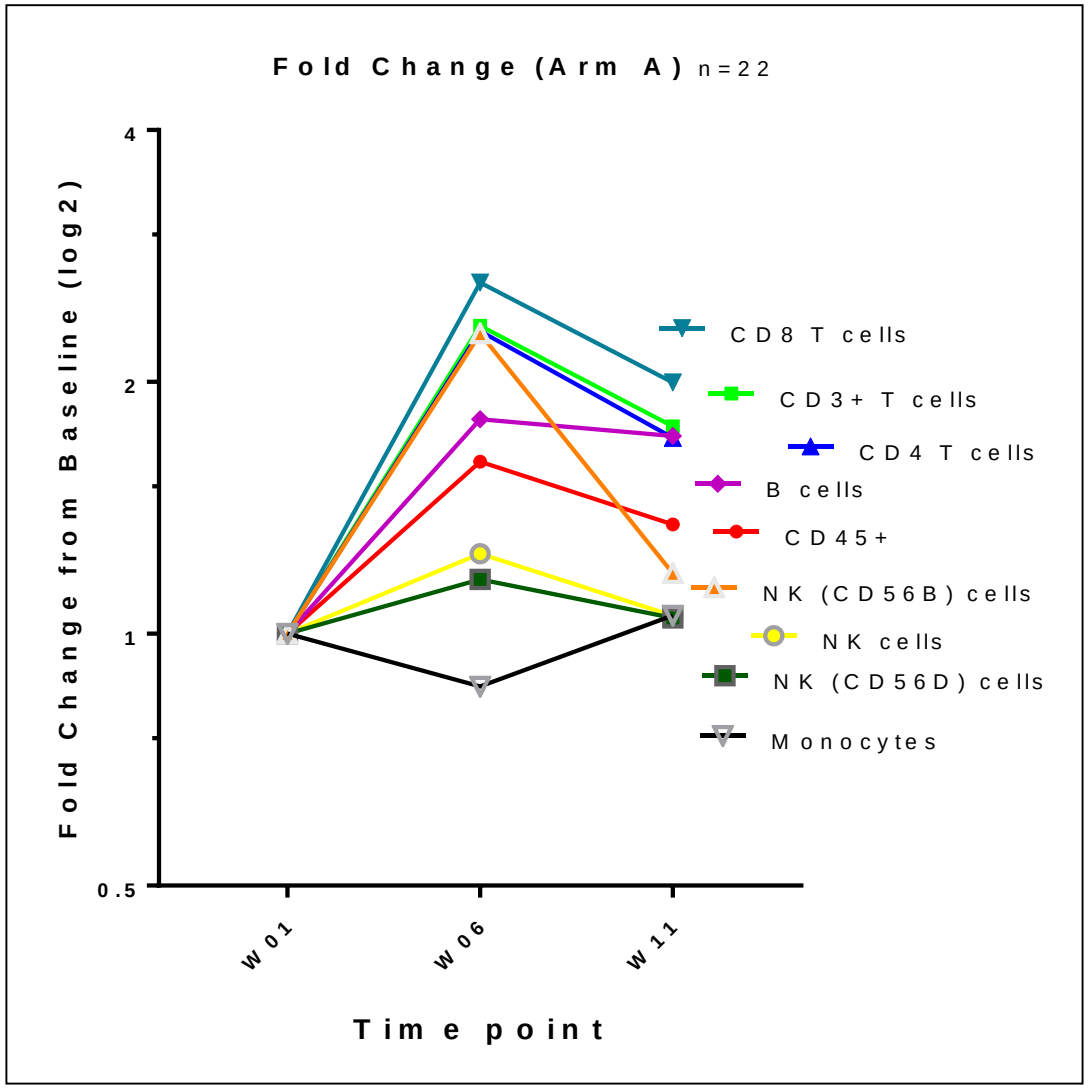



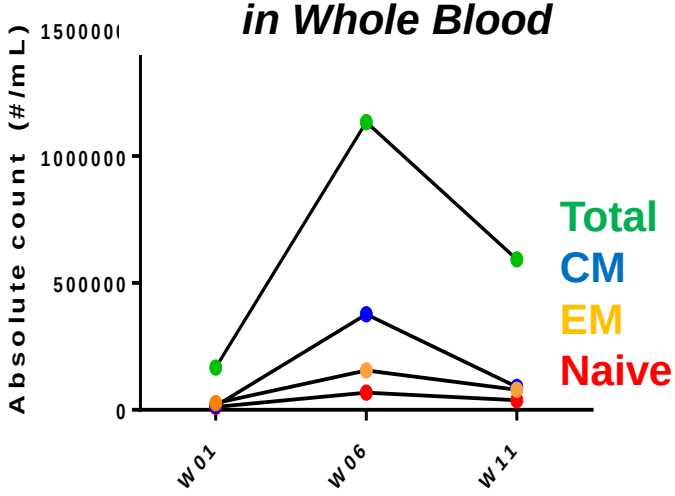




CITN Central Lab

# Comparison between Arms of Fold-Increase from Baseline of all PBMC subsets in Whole Blood



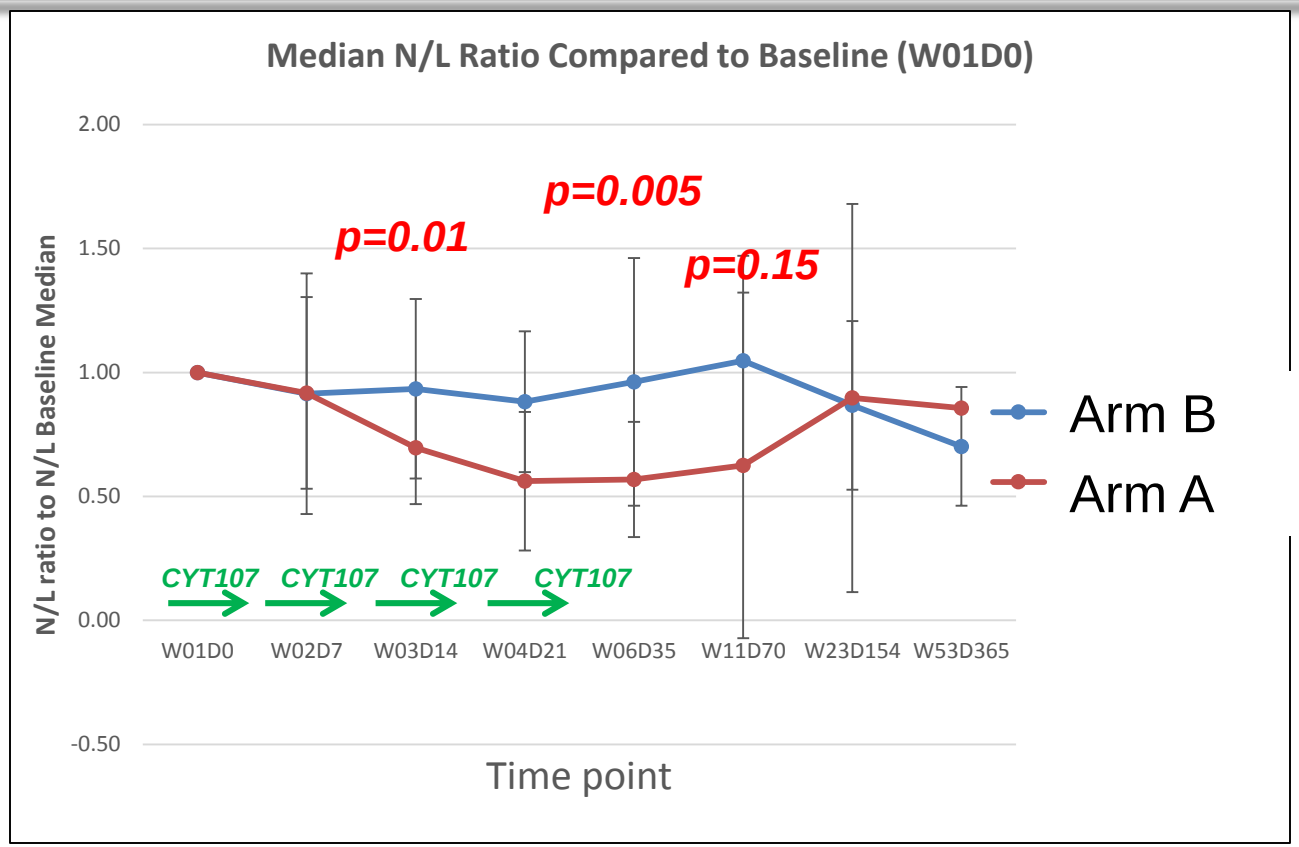

***Single Patient Vignette***
***Est absolute #s***
***in Whole Blood***




cancer immunotherapy trials network

# Change from Baseline in Neutrophil: Lymphocyte Ratio

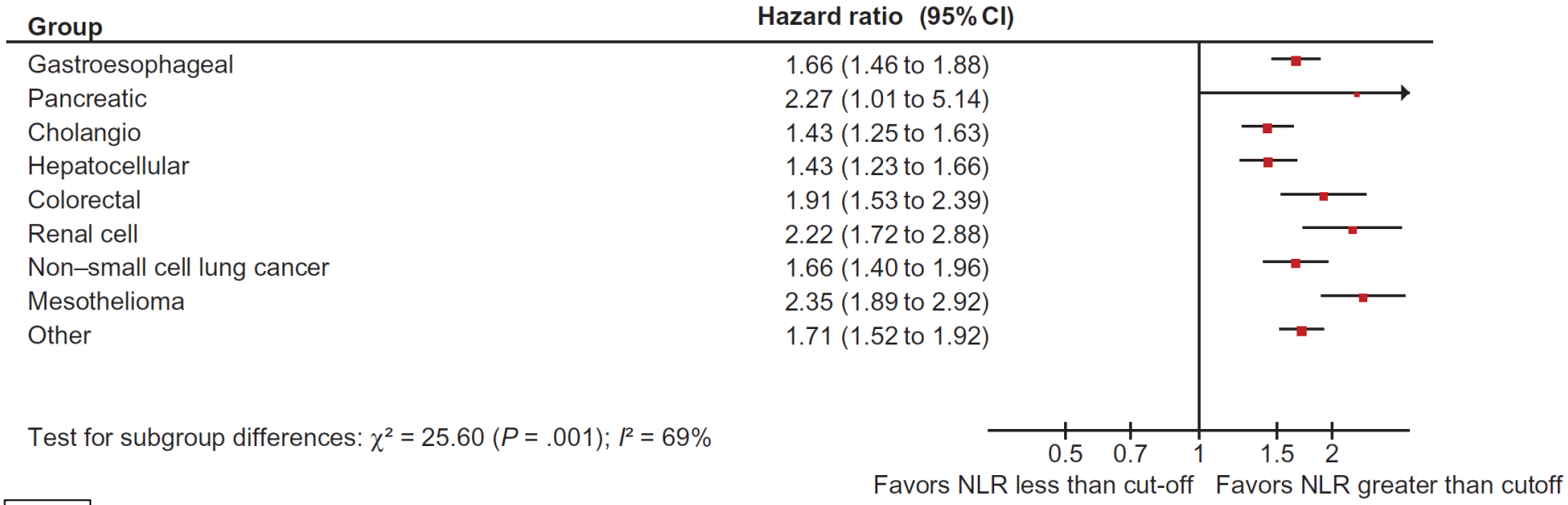
## *(Median calculated from CBC)*




cancer immunotherapy trials network

# Meta-Analysis: Neutrophil-to-Lymphocyte Ratio

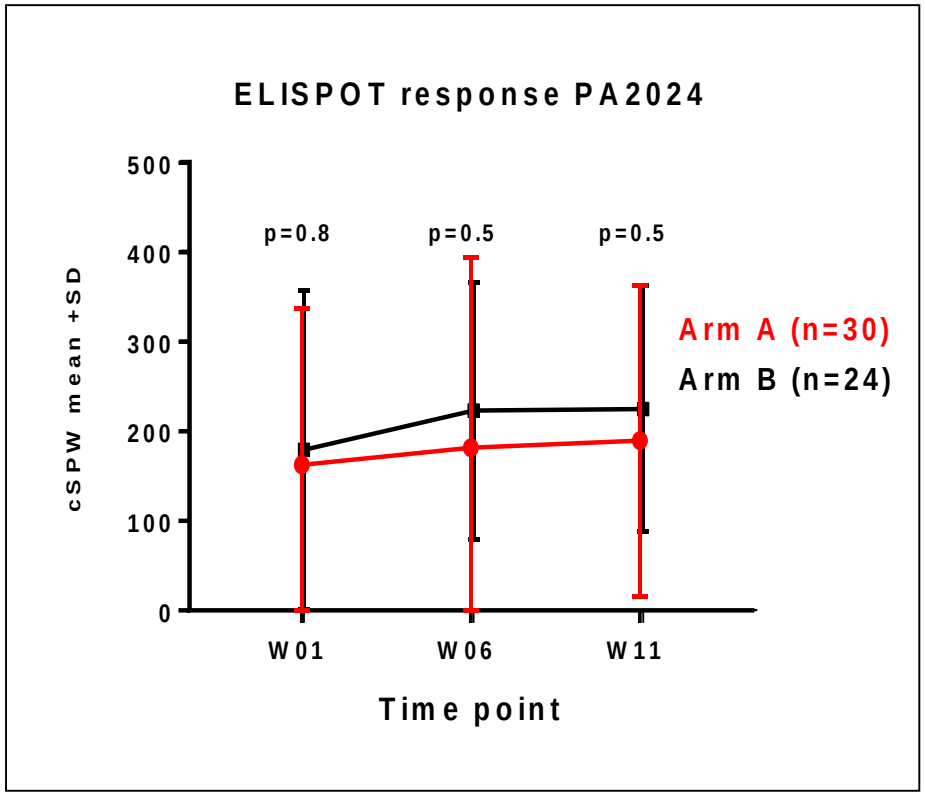
- **One hundred studies (40,559 patients)**
- Median cutoff for NLR was 4
  - For OS: NLR greater than the cutoff was associated with a hazard ratio of 1.81 (95% CI = 1.67 to 1.97; *P* < .001)
  - For CCS, PFS and DFS: Hazard ratios were 1.61, 1.63, and 2.27, respectively (all *P* < .001).
    - Effect observed in all disease subgroups, sites, and stages



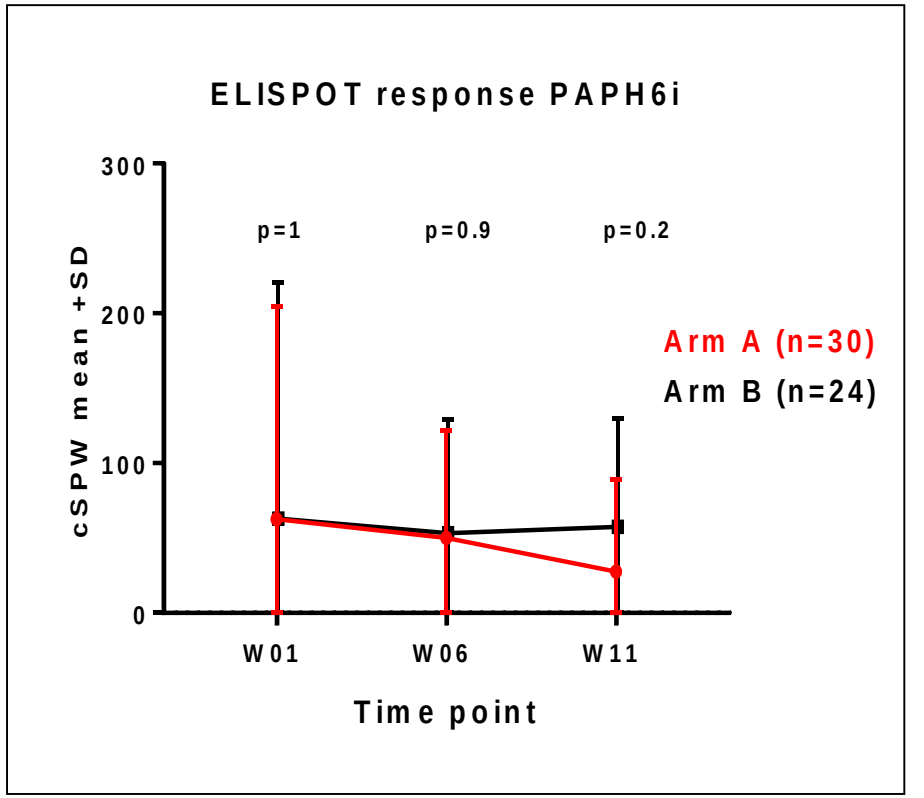

[Templeton et al. NLR JNCI 2014]

# T cell Immune Responses against PA2024 and PAP Elispot Analyses (cSPW/300K PBMC)

PA2014 is the vaccine




PAPH6i is human PAP

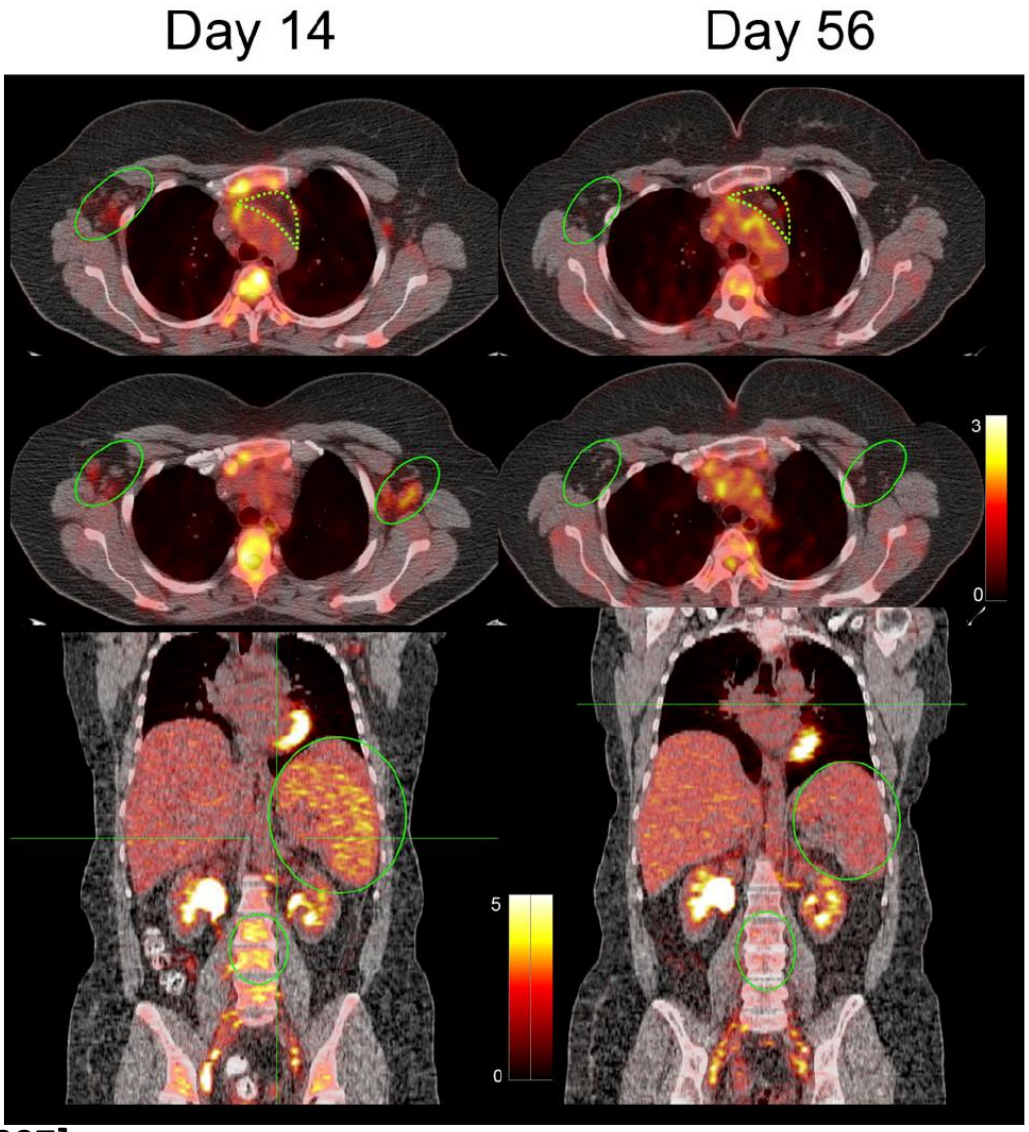



cancer immunotherapy trials network

# IL-7 increases T cells in lymph nodes, spleen & marrow as well as peripheral blood

**PET-CT imaging of lymphoid organs & increased metabolic activity after rhIL-7**

**Increased metabolic Activity = pink Maximal = yellow**




[Sportès (Mackall) et al J. Exp. Med. 1681:2007]

# IL-7 Conclusions

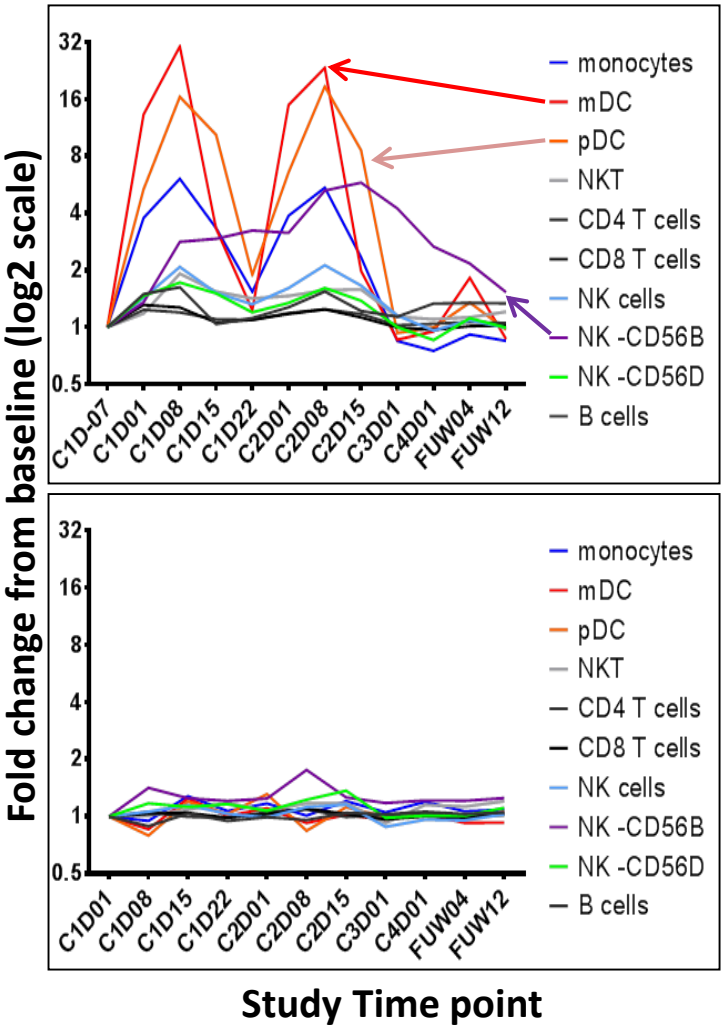
- IL-7 is well tolerated following sipuleucel-T
- IL-7 induces and expansion of circulating T cells in prostate cancer patients (mCRPC).
  - CD4, CD8
  - Naïve, CM, EM
- There is no significant difference in the ELISPOT responses to PA2024, PAP

- Follow on trials
  - To determine whether doubling T cell number will increase efficacy of anti-PD-L1
    - IL-7 + anti-PD-L1 (atezolizumab): bladder cancer
  - To determine whether reversing the NLR and increasing T cell levels will improve the prognosis of patients with high NLR

cancer immunotherapy trials network

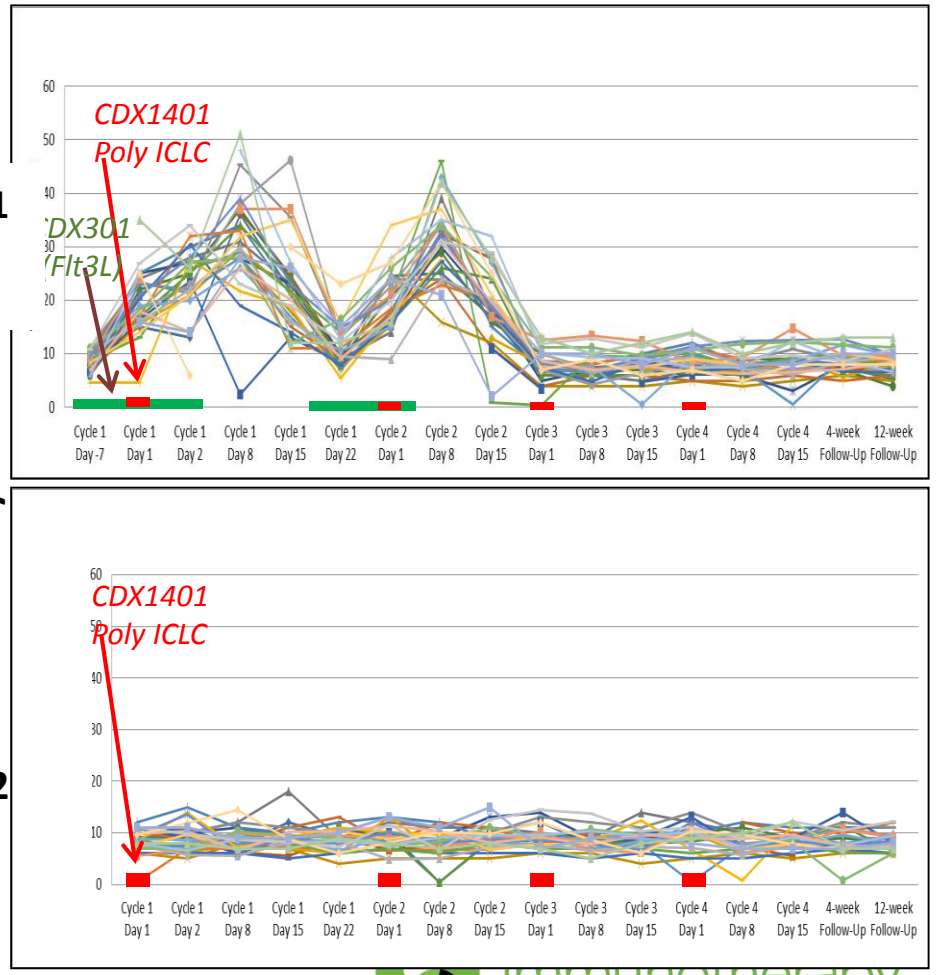
# Adjuvant melanoma vaccine: Flt3-Ligand + Poly ICLC + anti-DEC205-NY-ESO-1 vaccine (PI: Nina Bhardwaj MD PhD)

## Fold-increase over baseline of innate immune cells




<Cohort 1

<Cohort 2



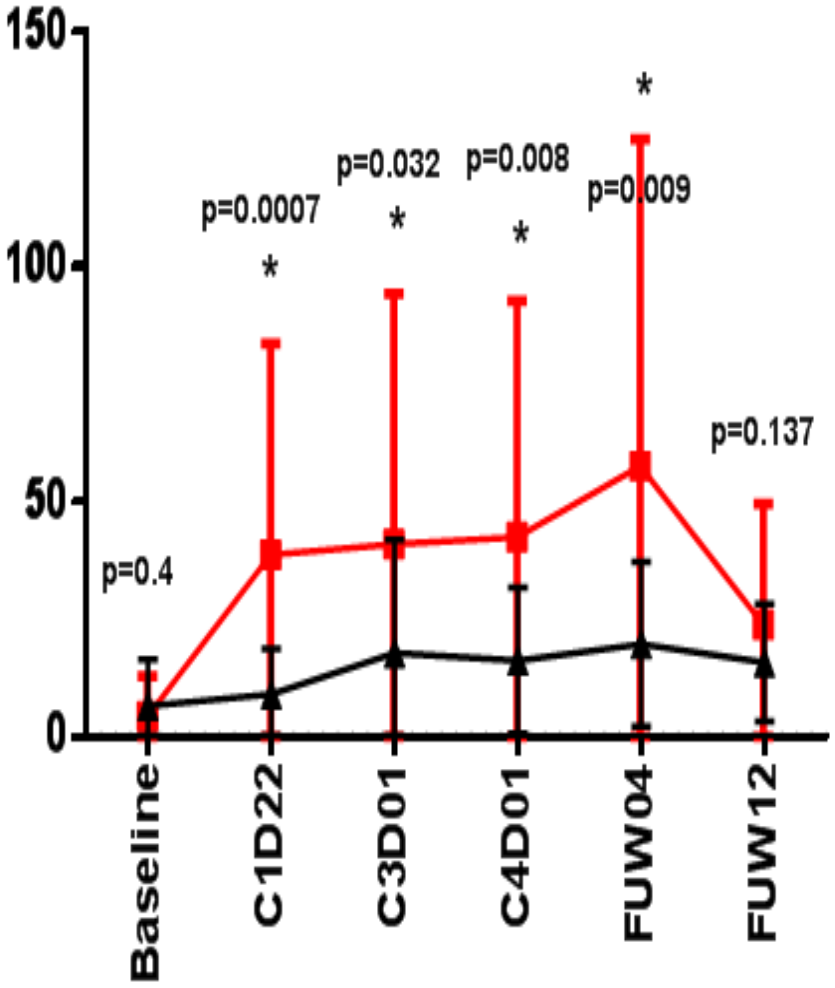
# A Dendritic Cell Targeting NYESO-1 Vaccine Significantly Augments Early and Durable Immune Responses in Melanoma Patients Pretreated with Human Flt-3 Ligand

(5:30 – 5:45 p.m. Today)


- Nina Bhardwaj, MD, PhD – *The Tisch Cancer Institute at The Icahn School of Medicine at Mount Sinai*


cancer immunotherapy trials network

# Anti-NY-ESO-1 specific T cell responses in Cohort 1 subjects are more robust, detected earlier and in more subjects




cancer immunotherapy trials network

# Thanks!!!


- CITN Site PIs & Investigators
- SITC
  - Bernie Fox
  - Tom Gajewski
  - Franco Marincola
  - Howard Kaufman
  - Lisa Butterfield
  - Tara Withington - Executive Director
- CTEP
  - Bill Merritt - Project Officer
  - Howard Streicher - Senior Investigator
  - Elad Sharon – Senior Investigator
- Patients – Past, current & future!

cancer immunotherapy trials network

# Immunotherapy Today

"I'M ALWAYS LIKE THIS, AND MY FAMILY WAS WONDERING IF YOU COULD PRESCRIBE A MILD DEPRESSANT."

cancer immunotherapy trials network