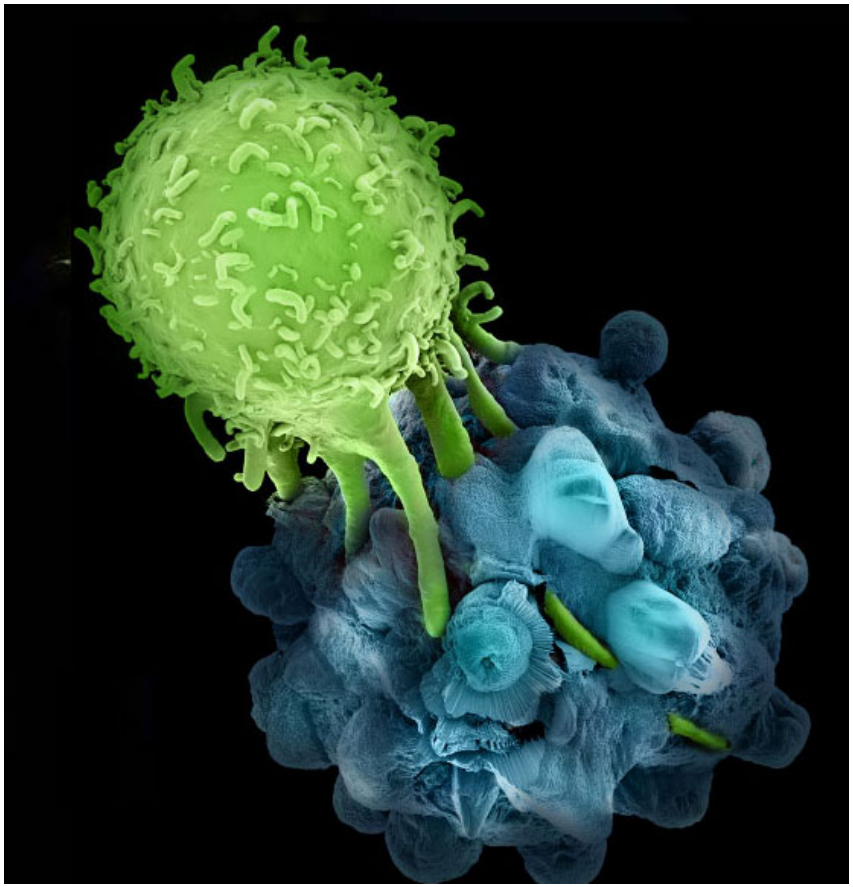
Cancer Immunotherapy Trials Network

SITC 29th Annual Meeting

(November 08, 2014)



Martin A “Mac” Cheever MD
PI: CITN
Member: FHCRC
mcheever@fredhutch.org

cancer immunotherapy trials network

NCI funded: Cancer Immunotherapy Trials Network (CITN)

- Brings together cancer immunologists from 32 foremost universities & cancer centers in North America
  - To design and conduct innovative early phase trials for patients with cancer (www.CITNinfo.org).
  - To provide the infrastructure essential for collaboration
  - To gain access to top-ranked agents not broadly available for testing
    - By focusing on prioritized agents
    - By capitalizing on
      - Prominence of Member Site Principal Investigators (PIs) &
      - Partial trial funding from the NCI
      - Focus on helping industry achieve their goals

cancer immunotherapy trials network

Focus: Remains in Line with "Field" Priority

Ranked Agents (2007) & Updated (2013)

- Agent Criteria
  - Potential for use in cancer therapy
  - Perceived need by multiple, independent clinical investigators
  - Potential use in more than one clinical setting (i.e., against different tumor types or as part of multiple therapy regimens)
  - Not broadly available for testing in patients
  - Not commercially available or likely to be approved for commercial use in the near future

cancer immunotherapy trials network

Ranked Priority Immunotherapy Agents: 2007 vs. 2013 and Availability

COLOR CODE
Agent in CITN
Agent not being manufactured
Agent in early phase trials & not available yet
Agent not selected yet for CITN trials

Ranked Priority Immunotherapy Agents	2013	Increase	2007
Anti-PD1 & Anti-PD-L1	1	+++	2
Anti-CD40/anti-CD40L	2	+++	4
IL-15	3		1
IL-12	4		3
Anti-OX-40	5	+++	16
IL-7	6		5
Anti-LAG3	7	+++	20
IDO inhibitor	8		7
Anti-TGF-beta	9		9
Anti-CD137	10		8
CpG	11	---	6
Anti-GITR	12		12
Poly I:C/Poly ICLC	13		15
Anti-IL10/anti-IL10R	14	---	10
Resiquimod/853A	15		18
Flt3L	16	---	11
Anti-B7-H4	17		17
MPL	18	---	14
CCL21 Adenovirus	19	---	13
LIGHT or LIGHT vector	20		19

<u>Anti-PD-1 (#1)</u>
(Merck)
	Check point inhibitor	• **Merkel Cell Carcinoma**
		• Single arm trial; first systemic therapy
		  • Simon Two Stage design
		  • 24 Patients
		  • Pembrolizumab
		• Protocol approved by CTEP & Merck
		• IND allowed
		• To be activated in November
		• **PI: Nghiem (Fred Hutch/UW);**
		• **Co-PD Kohrt (Stanford)**
		  • Daud (UCSF)
		  • Friedlander (Mt. Sinai)
		  • Gibney (Moffitt)
		  • Kluger (Yale)
		  • Kudchakar (Emory)
		  • Lipson (Johns Hopkins)
		  • Olencki (Ohio State)
		  • Reddy (Stanford)
		  • Rudrapatna (Minnesota)
		  • Tawbi (Pittsburgh)

<u>Anti-PD-1 (#1)</u>
(Merck)
	Check point inhibitor	• **Mycosis fungoides**
		• Single arm; advanced disease; Simon two stage
		• 24 Patients
		• Pembrolizumab
		• Protocol approved by CTEP & Merck
		• IND allowed
		• Trial activated
		• First patient – December
		
		• **PI: Kohrt (Stanford)**
		  • Kim (Stanford)
		  • Porcu (Ohio State)
		  • Foss (Yale)
		  • Sokol (Moffitt)
		  • Shustov (Fred Hutch/U of Washington)
		  • Shanbhag (Johns Hopkins)
		  • Rook (Penn)
		  • Horwitz (MSKCC)

cancer immunotherapy trials network

<u>Anti-CD40 (#2)</u>
(Roche)
	DC activator	• **Neoadjuvant resectable pancreas cancer**
		• Anti-CD-40
		• RO7009789 (Roche)
		• Same as: CP-870,893 (Pfizer)
		• Co-Funded by Pancreatic Cancer Action Network and SU2C
		• Protocol activated 2011
		• Franchise sold x 2
		• Current: Protocol amendment submitted to CTEP
		  • Change gem + CD40 to Gem + Nab-paclitaxel + anti-CD40
		• IND amendment pending (Vonderheide)
		• Trial likely to re-open in February
		
		• **PI: Vonderheide (Penn)**
		  • O'Dwyer (Penn)
		  • Jaffee (Johns Hopkins)

cancer immunotherapy trials network

<u>IL-15 (#3)</u>
(NCI
E. Coli derived
	T cell & NK cell growth factor	• **Phase I: NSCLC/ SCCHN/ Renal/ Melanoma**
		• First in man sub-Q outpatient regimen - solid tumors for combining with vaccines, antibodies and other agents;
		• Trial Open at 5 sites (CTEP limit)
		• 3 dose escalation cohorts filled: (0.25, 0.5, 1.0 mcg/kg)
		  • Fourth cohort (2 mcg/kg) expanded to 6 pts with one DLT (pancreatitis)
		  • Cohort 5 (3 mcg/kg) to open
		
		• **PI: Miller (U Minnesota)**
		  • Kohrt (Stanford)
		  • Sondel / McNeel (Wisconsin)
		  • Thompson (UW]
		  • Waldmann & Conlon (NCI)

cancer immunotherapy trials network

<u>IL15/IL15Ra/Fc fusion (#3)</u>
(Altor)
	T cell & NK cell growth factor	• **First in man: Advanced melanoma**
		• Co-funded by Melanoma Research Alliance & Altor;
		• Trial Activated
		• On third dose cohort (1 mcg/kg)
		  • Four patients to date
		
		• **PI: Margolin (Stanford/ Fred Hutch/Washington)**
		  • Daud (UCSF)
		  • Ernstoff (Cleveland)
		  • Lewis (Dartmouth)
		  • Lee (Fred Hutch/ U of Washington)
		  • Holtan (Minnesota)
		  • Kaufman (Rutgers)
		  • Waldmann/Conlon (NCI)

cancer immunotherapy trials network

<u>IL-7 (#6)</u>
CYT107 (RevImmune) +
sipuleucel-T (Dendreon)
	Homeostatic T cell growth factor	• **Prostate cancer - Advanced asymptomatic**
		• **Sipuleucel-T + IL-7 (CYT107) (10 mcg/kg weekly x 4)**
		• June 2013: Trial activated / Cytheris bankrupt
		• Oct 2013 Assets purchased by Cognate BioServices/ RevImmune
		• Protocol revision approved by CTEP & FDA
		• IND allowed (CITN/Cheever – sponsor)
		• First patient January 2015
		
		• **PI: Fong (UCSF)**
		• **Co-PI Ferrari (NYU)**
		  • Kucuk (Emory)
		  • Seigne (Dartmouth)
		  • Yu (Fred Hutch/ U Washington)
		  • Harrison (Duke)
		  • Galsky (Mt. Sinai)
		  • Monk (Ohio State)
		  • Curti (Providence, Oregon)
		  • Millard (UCSD)
		  • Stadler (U Chicago)
		  • Pollack (U Miami)
		  • Appleman (Pittsburgh)

<u>IL-7 (#6)</u> CYT107 (RevImmune) + Infectious disease vaccines	Homeostatic T cell growth factor	• **Breast & Colon Cancer - Post – adjuvant chemotherapy > age 60** • IL7 pre & post 6 infectious disease vaccines • Trial likely to re-open in February/ March with already vialed IL7 • **PI: Gress (NCI) with Sportes (GRU)** • **Co-PI: Perales (MSKCC);**

cancer immunotherapy trials network

<u>IDO Inhibitors (#8)</u> (Incyte)	IDO Inhibition	• **Neoadjuvant ovarian cancer**
		• INCB024360
		• To evaluate inhibition on ascites & tumor microenvironment
		• Trial activated
		• IND sponsor (NCI)
		• Accrual began August
		  • 2 patients enrolled
		  • Entry criteria loosened
		
		• **PI: Odunsi (Roswell)**
		• **Co-PI: Geller (Minn)**

cancer immunotherapy trials network

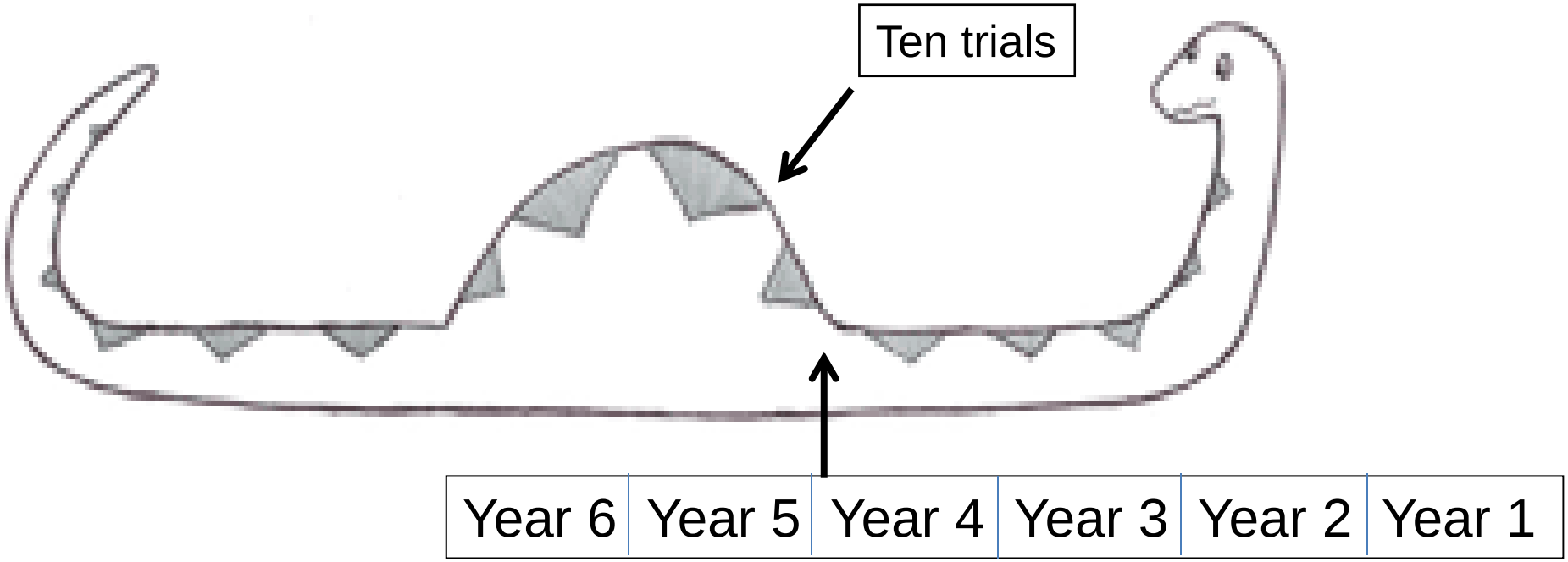
<u>IDO Inhibitors (#8)</u> (Incyte)	IDO Inhibition	• **Advanced melanoma**
		• INCB024360
		• To evaluate inhibition +/- peptide vaccine on tumor microenvironment
		• IND Sponsor (CITN/Cheever)
		• Slow accrual: One patient enrolled
		  • Multiple screen failures
		  • Entry criteria loosened
		
		• **PI: Slingluff (UVA)**
		• **Co-PI, Ernstoff (Cleveland)**
		  • Tyler (Duke)
		  • Delman & Lawson (Emory)

cancer immunotherapy trials network

<u>Flt3-Ligand (#16)</u> + (Celldex)
 	
<u>Poly ICLC (#13)</u> + (Oncovir)
	Dendritic cell growth factor
	
	TLR3 agonist
		• **Melanoma (Adjuvant)**
		• Flt3L x 7 days to grow DC
		• + poly ICLC to activate DC
		• + anti-DEC205-NY-ESO-1 vaccine targets DC
		• Immune Monitoring in collaboration with Cancer Vaccine Consortium (CVC)
		• IND (CTEP)
		• Trial opened: September 2014
		• Three patients accrued – waiting safety hiatus to continue accrual
		
		• **PI: Bhardwaj (NYU)**
		  • Albertini (Wisconsin)
		  • Chapman (MSKCC)
		  • Curti (Providence Portland)
		  • Ernstoff (Cleveland)
		  • Feun (Miami)
		  • Gastman (Cleveland)
		  • Gibney (Moffitt)
		  • Hanks (Duke)
		  • Kohrt (Stanford)
		  • Lee (Fred Hutch/Washington)
		  • Pavlick (NYU)

Trial Accrual

"Pig in Python"



Funded accrual = 214
Accrual to date = 24
Projected accrual = 300+

cancer immunotherapy trials network

Pig in Python: Why?

- "Deliberateness of Prioritization"
  - Primary Focus on Agents Prioritized by Field and heretofore not available!
  - Agent concepts all started at the same time
- Delays: "Every unhappy trial is unhappy in its own way"
  - (Agent #1) Anti-PD1: Ponderous administrative and legal demands (sequential development of 2 LOIs and 3 protocols for same trial over 2 years)(for two trials, i.e. 4 LOIs and 6 "finalized" protocols)
  - (Agent # 2) Anti-CD40: Owned by 3 companies since protocol approval
  - (Agent #3) IL15: NCI manufacture, purification, vialing, IB, IND; Safety hiatus post each dose escalation
  - (Agent #7) IL7: Cytheris agreed; > 50 legal documents negotiated by the Fred Hutch; trial opened; Cytheris bankrupt; franchise purchased by second company (RevImmune); hiatus for RevImmune to organize regulatory information; amended protocol amended; new IND

cancer immunotherapy trials network

So - What have we learned?

cancer immunotherapy trials network

Patience!

Future Goals

- Funded for 15 trials
  - 5 additional iterative trials with same agents
  - Protocol amendments as much as possible
- Focus on serial biopsies: to "Mine failures to inform next steps"

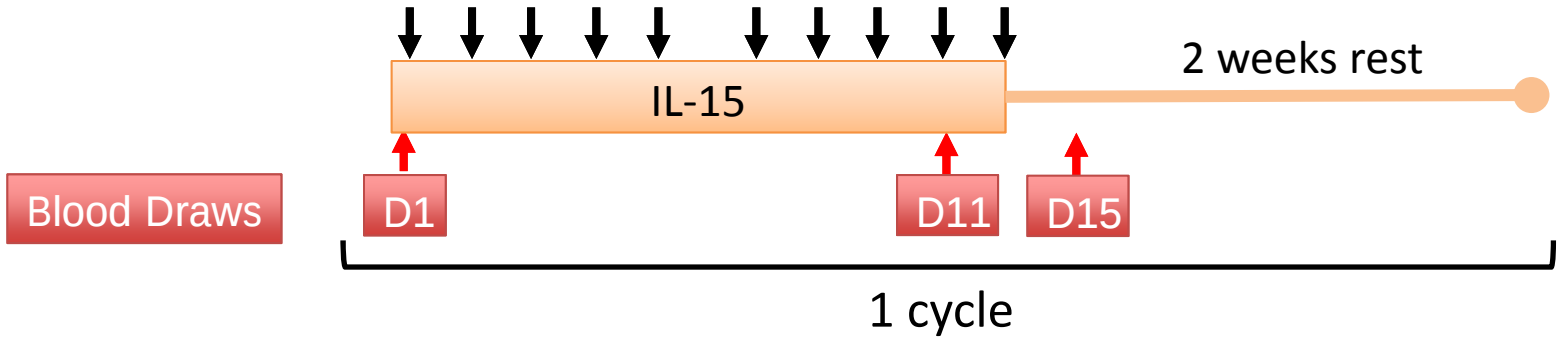
cancer immunotherapy trials network

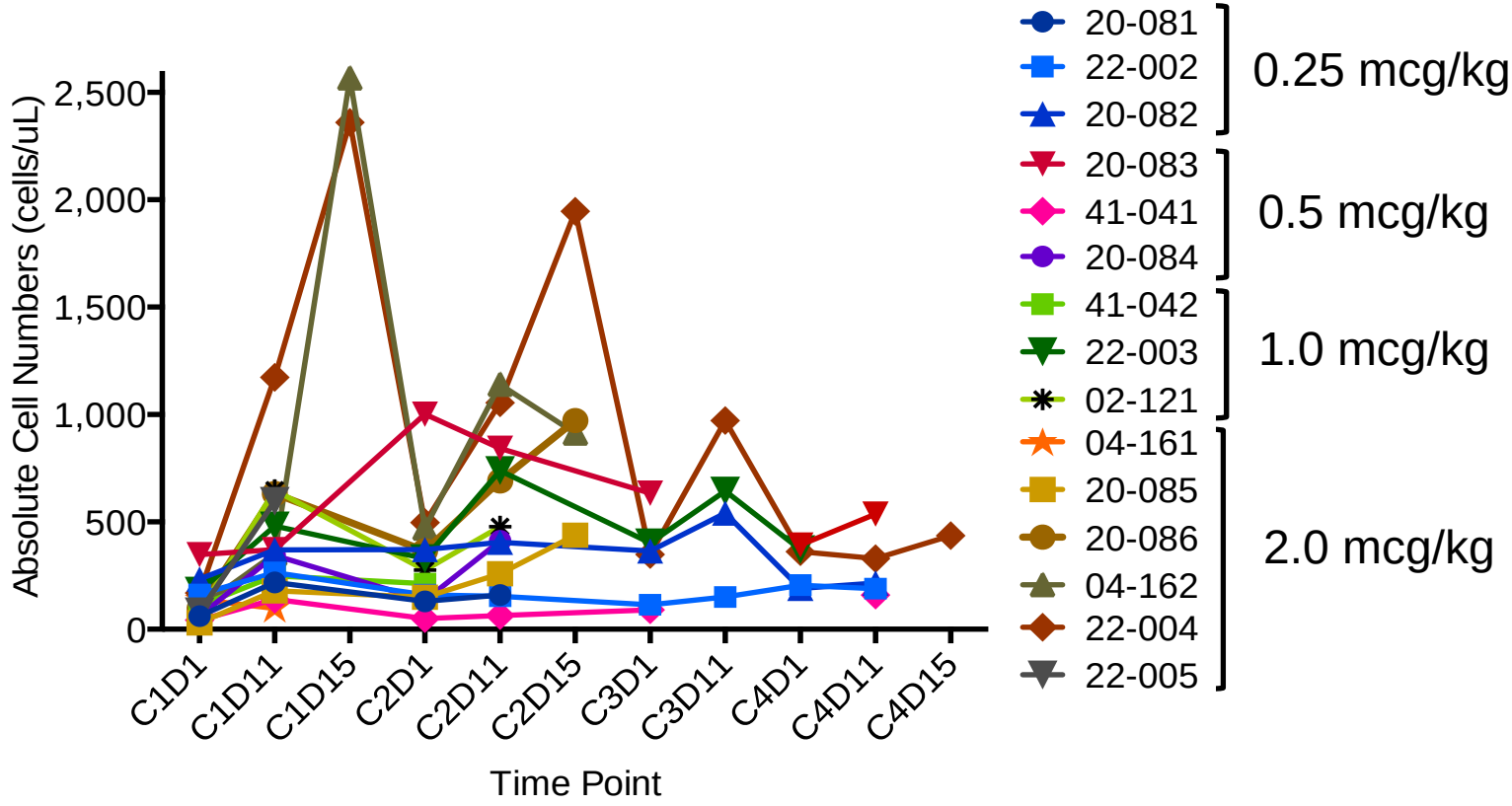
Trials with Three Priority Agents

- **IL15**
  - **PI: Jeff Miller MD; U of Minnesota**
- Flt3L
  - PI: Nina Bhardwaj MD PhD; Mt Sinai
- Anti-PD-1
  - PI: Holbrook Kohrt MD PhD; Stanford

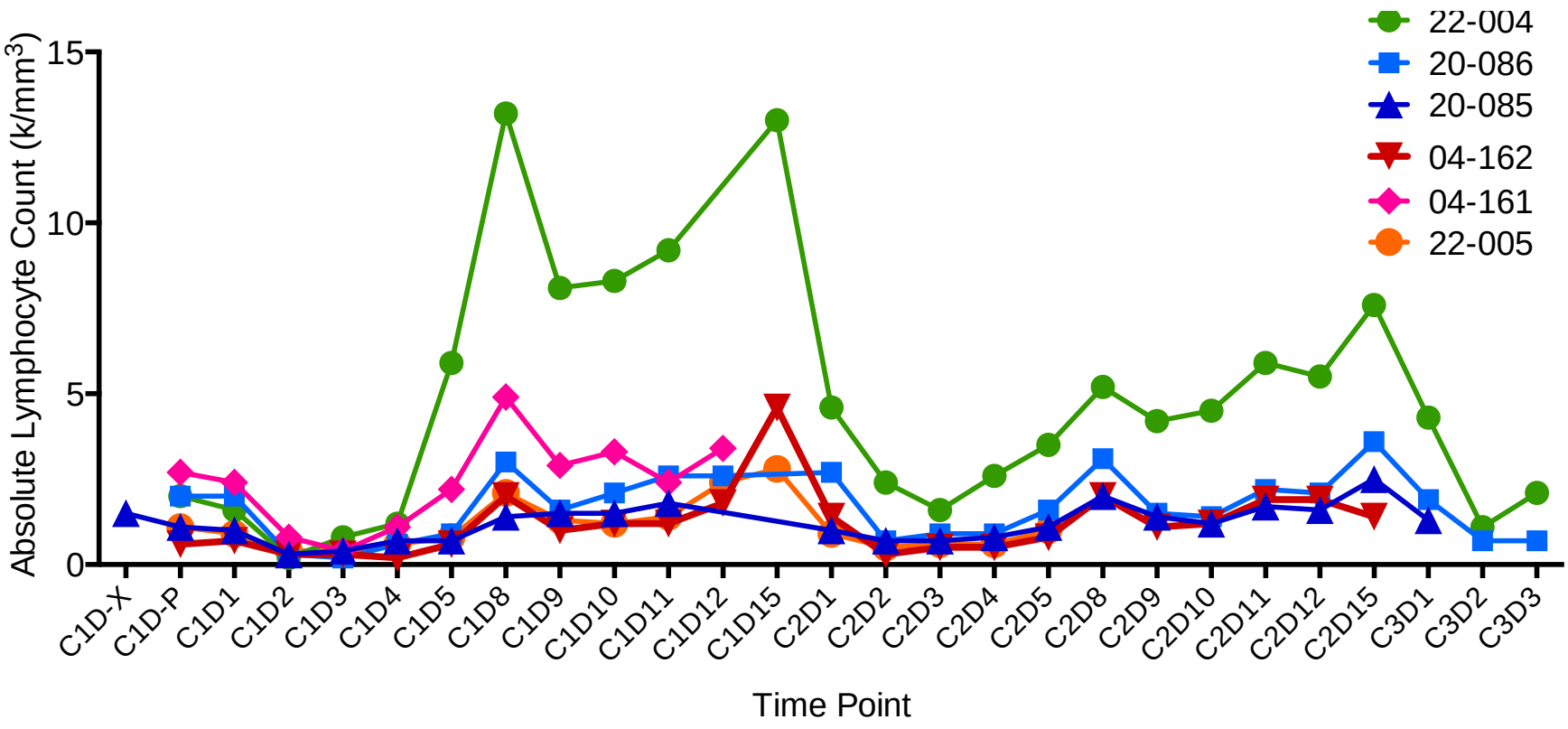
cancer immunotherapy trials network

CITN11-02: Phase I Dose Escalation Study of SQ IL-15 (E.coli)

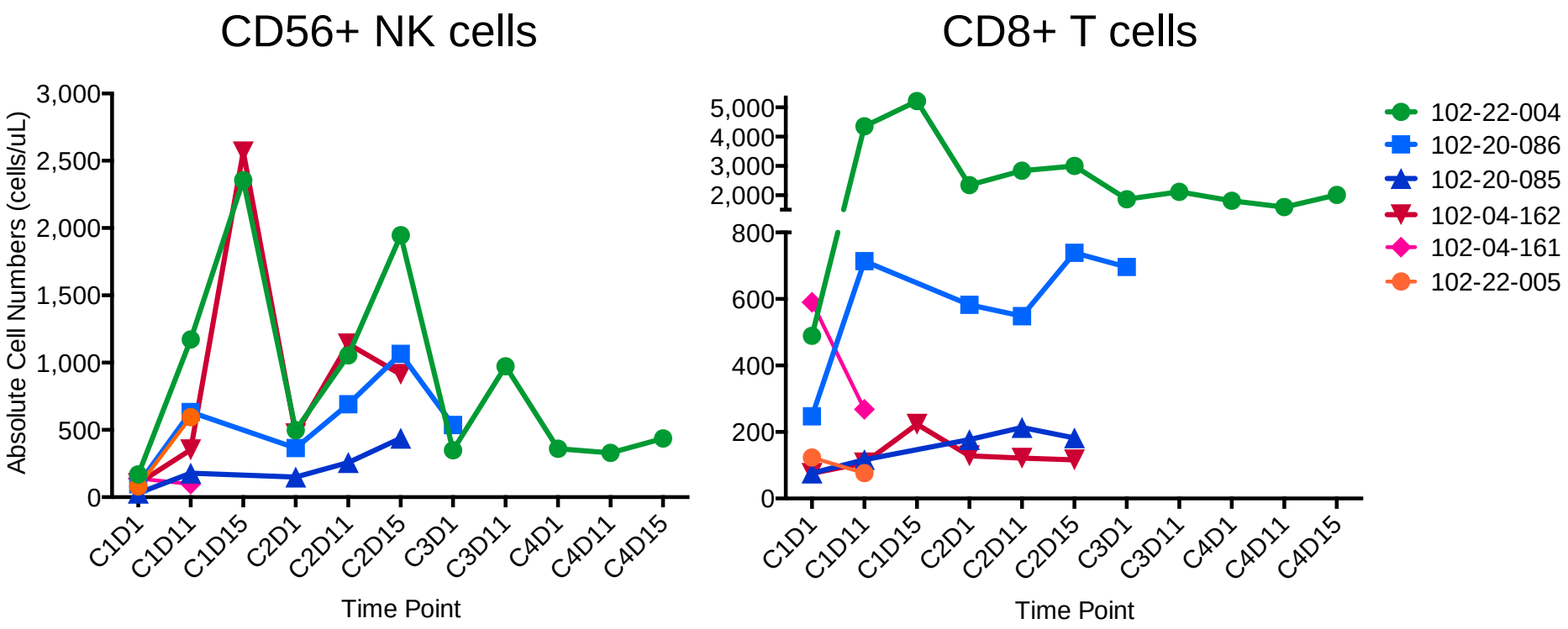




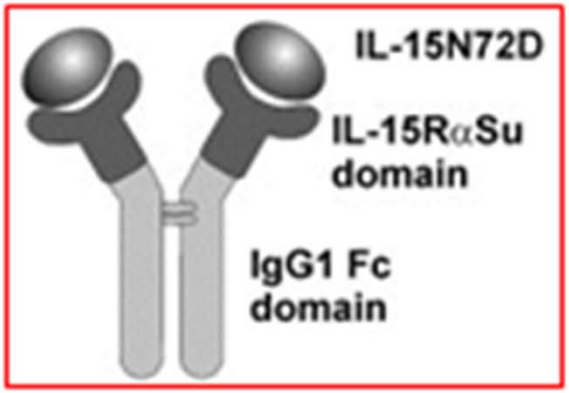
Absolute Lymphocyte Count in the 2mcg Dose Cohort



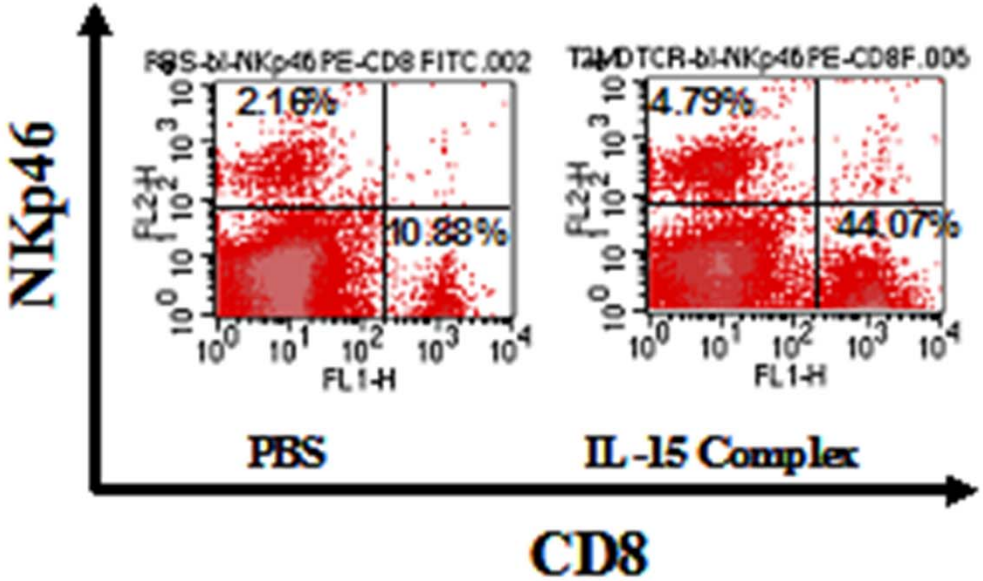
NK and T cell Frequencies: 2 mcg/kg/dose



Interleukin-15:Interleukin-15αSu/Fc Fusion Complex (Altor-803)



ALT-803 stimulated CD8+ T cells & NK cells responses in murine PBMC [Injected IP days 0, 3: test day 7]



ALT803 in CITN-06 (Kim Margolin)

Pts: advanced melanoma after at least 1 survival-enhancing Rx

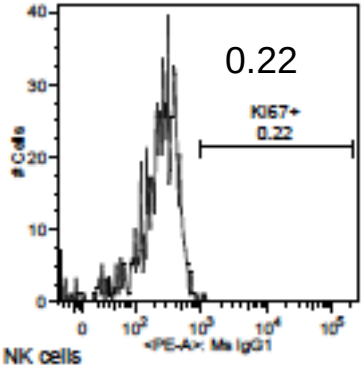
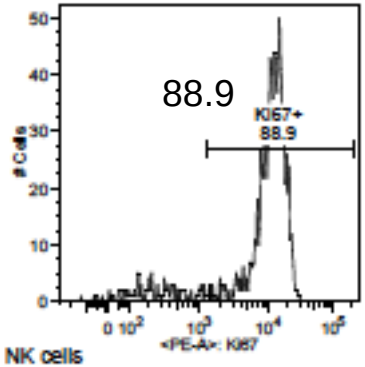
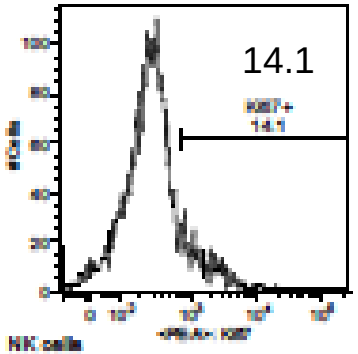
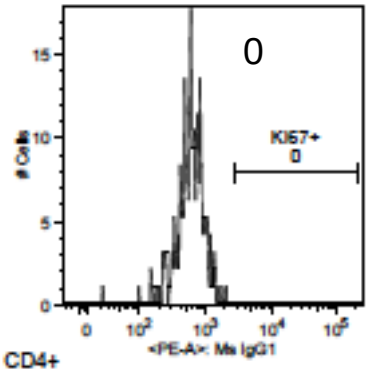
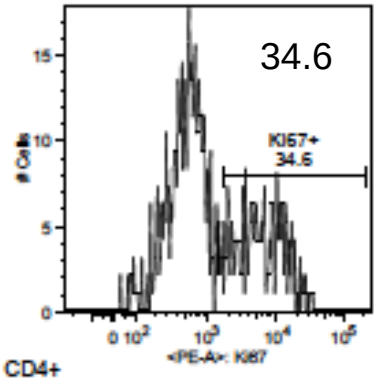
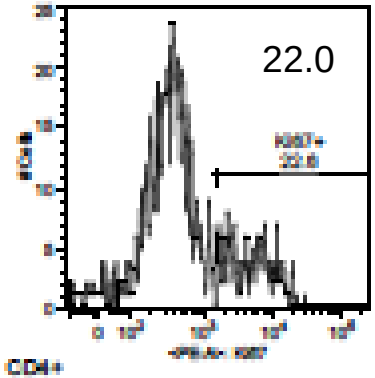
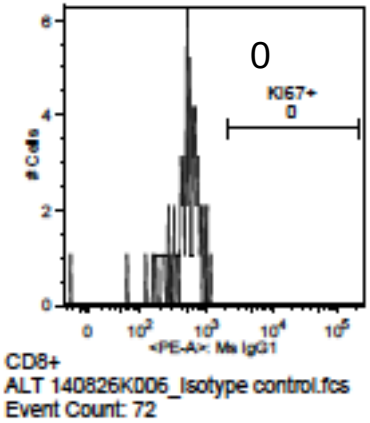
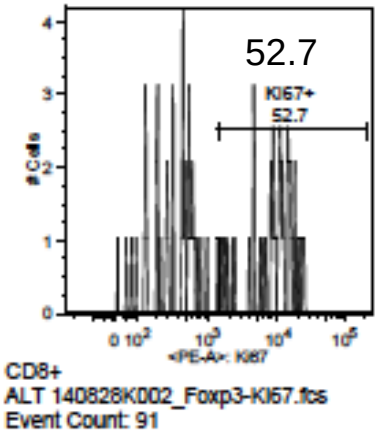
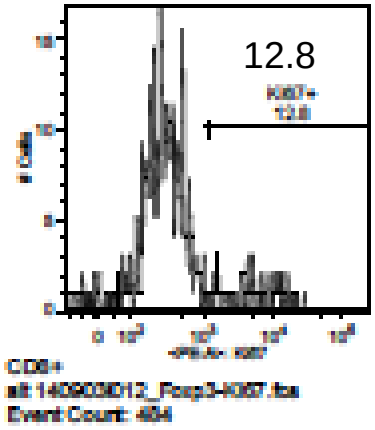
Doses: .3, 1, 3, 6, 10 µg/kg weekly x 4 of 6

Ph I/expansion: DLT/MED/correlates and clinical activity

ALT803 in heme malignancies
Jeffrey Miller

- Pts
  - Heme malignancies
  - Relapse post matched allo-HCT
- Dose/schedule
  - 1, 3, 6, 10, 20, 30 µg/kg
  - weekly x 4
- Phase I and expansion
  - DLT/MTD/MED
  - Correlate, clinical activity

X-Axis
%Ki67+

	Isotype Control	Day 3	Day 7
NK			
CD4			
CD8			

Conclusion: IL-15 safely increases NK and T cells

The Future: Enhancing IL-15 immunity ± intact antibody, BiTEs (CD3 directed) or BiKEs (CD16 directed) and other variables being considered:

1. **± Anti-CD137**
2. **± IDO inhibitor**
3. **± anti-PDL1 ± CTLA4**
4. **± anti-CD40L**
5. **± ADAM17 inhibitor**

Trials with Three Priority Agents

- IL15
  - PI: Jeff Miller MD; U of Minnesota
- **Flt3L**
  - **PI: Nina Bhardwaj MD PhD; Mt Sinai**
- Anti-PD-1
  - PI: Holbrook Kohrt MD PhD; Stanford

cancer immunotherapy trials network

CITN-07-FLT3L

A PHASE II OPEN LABEL MULTICENTER RANDOMIZED STUDY OF CDX-1401, A DENDRITIC CELL TARGETING NY-ESO-1 VACCINE IN PATIENTS WITH RESECTED MELANOMA PRETREATED WITH RECOMBINANT CDX-301, A RECOMBINANT Flt3 LIGAND

Nina Bhardwaj, MD, PhD

Director of Immunotherapy

Professor of Medicine, Division of Hematology & Oncology Tisch Cancer Institute

Icahn School of Medicine at Mount Sinai

OBJECTIVES

PRIMARY OBJECTIVE:

- To determine whether the immune response to NY-ESO-1 by vaccination with CDX-1401 + poly-ICLC is increased by prior expansion of circulating DC by therapy with Flt3L.

SECONDARY OBJECTIVES:

- To assess the effects on immune responses to other tumor antigens associated with melanoma and memory viral responses.
- To assess effects on frequency and phenotype of T cells and innate immune cells
- To assess the safety, tolerability, and clinical efficacy of the vaccine regimens.

PROTOCOL DESIGN

PHASE II

Stage IIIB,C; IV Resected melanoma

COHORT 1

N=30

CYCLES 1 and 2:

Days 1-7: CDX-301 (Flt-3 L) SQ- 25mcg/kg/day

Day 8: CDX-301 (Flt-3 L) SQ- 25mcg/kg/day +
CDX 1401 (Anti-DEC-205-NY-ESO-1) 1 mg SQ/ID + Poly-ICLC 2mg SQ

Day 9: CDX-301 (Flt-3 L) SQ- 25mcg/kg/day + Poly-ICLC 2mg SQ

Day 10:CDX-301 (Flt-3 L) SQ- 25mcg/kg/day

CYCLES 3 and 4:

Day 1: CDX 1401 (Anti-DEC-205-NY-ESO-1) 1 mg SQ/ID + Poly-ICLC 2mg SQ

Day 2: Poly ICLC 2 mg SQ

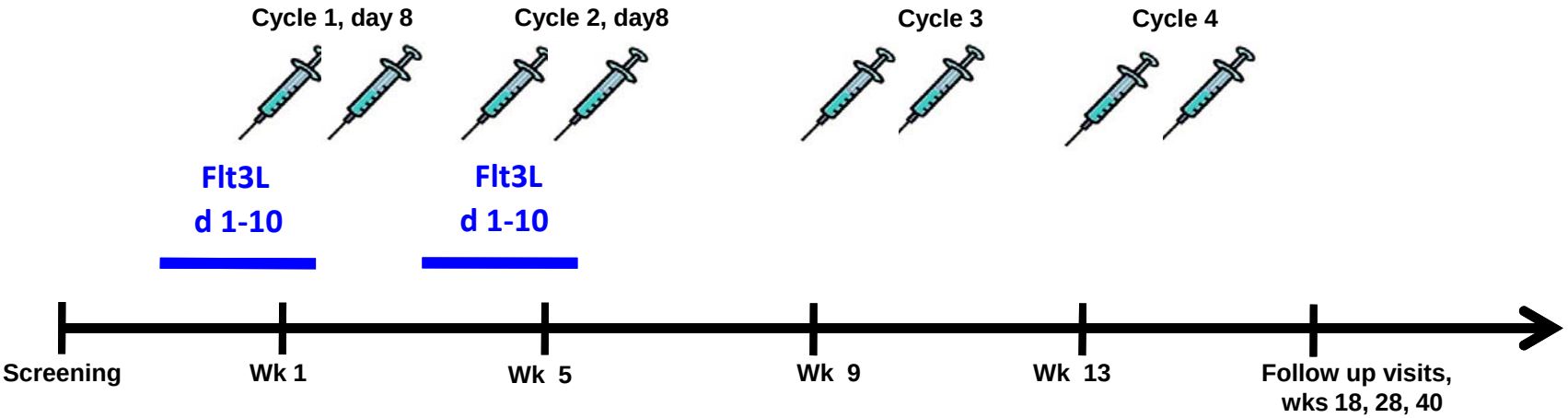
N=30

COHORT 2

CYCLES 1 thru 4:

Day 1: CDX 1401 (Anti-DEC-205-NY-ESO-1) 1 mg SQ/ID + Poly-ICLC 2mg SQ

Day 2: Poly ICLC 2 mg SQ



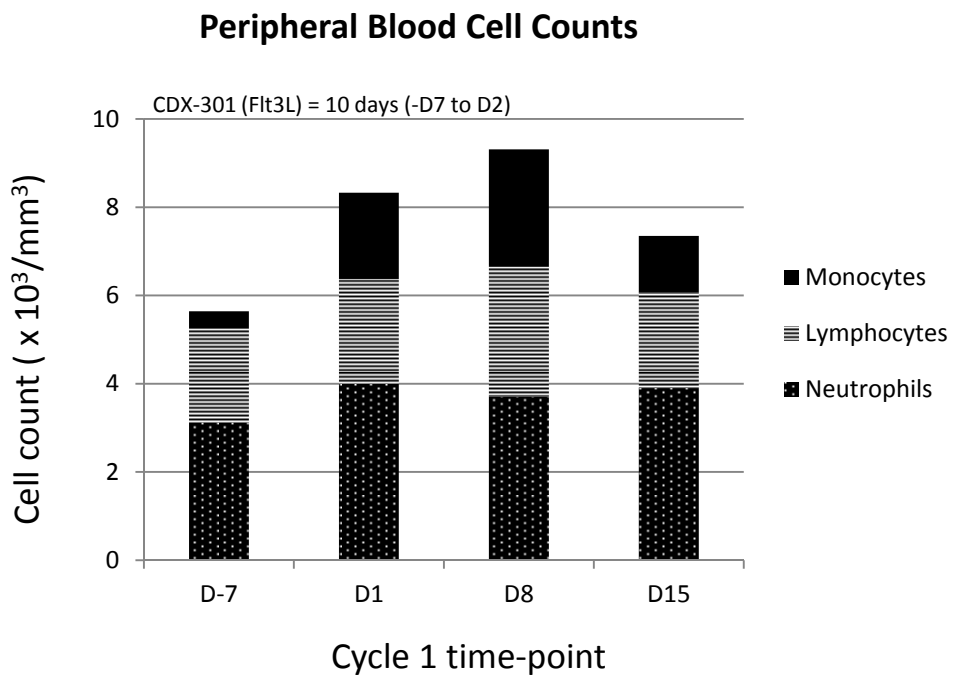
CITN-07:

2 subjects enrolled, third on Monday

- Subject 1 has entered cycle 2

- Grade 1 injection site reactions, flu-like symptoms

Subject 107-21-001



EXPECTED RESULTS

1. Flt3L will enhance the immunogenic potential of Dec-205-NY-ESO-1 vaccine + Hiltonol.

2. Flt3L arm will expand DC frequencies in vivo.

3. Flt3L arm will expand NK and monocytes in vivo.

4. Combination of Flt3L/Dec-205 vaccine/Hiltonol will be safe.

Trials with Three Priority Agents

- IL15
  - PI: Jeff Miller MD; U of Minnesota
- Flt3L
  - PI: Nina Bhardwaj MD PhD; Mt Sinai
- **Anti-PD-1**
  - **PI: Holbrook Kohrt MD PhD; Stanford**

cancer immunotherapy trials network

RESCUING PD-1 FAILURES

DESIGNING THE OPTIMAL TRIAL

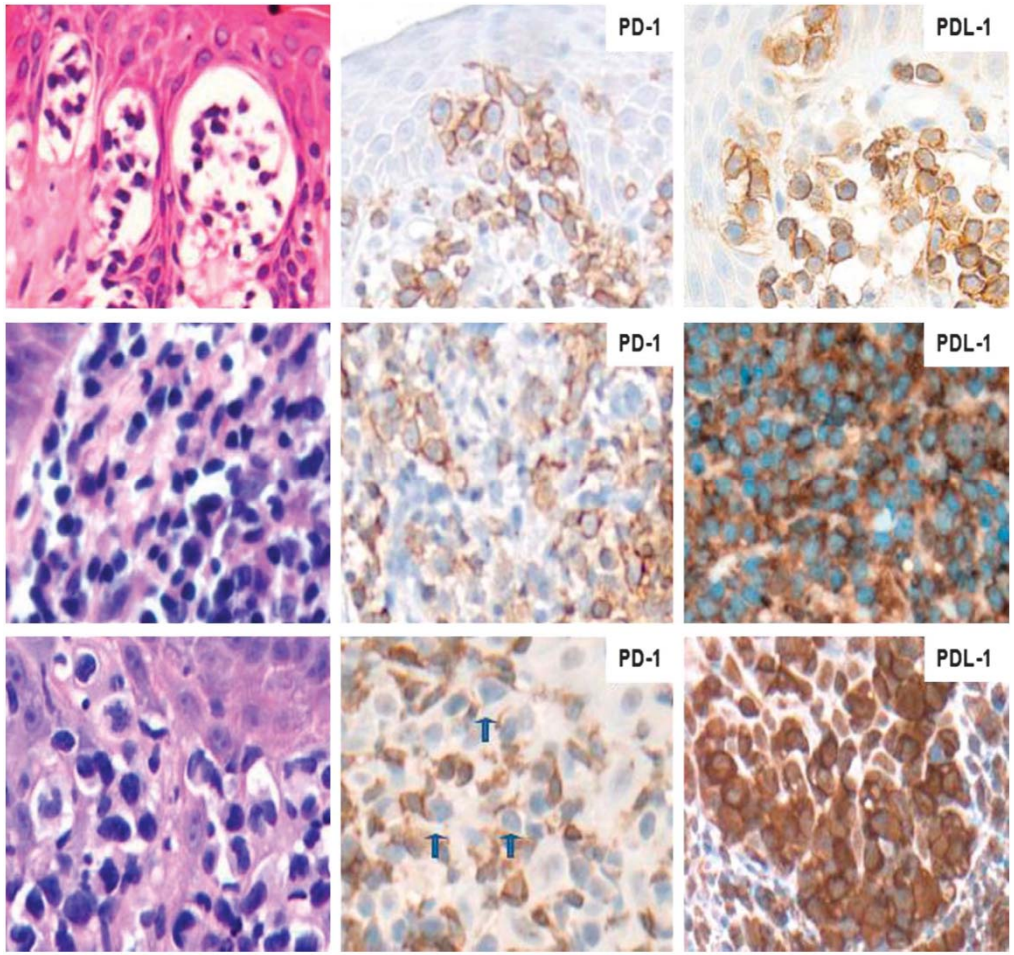
Holbrook Kohrt, MD PhD

Stanford Cancer Institute

Anti-PD1 Therapy in Mycosis Fungoides

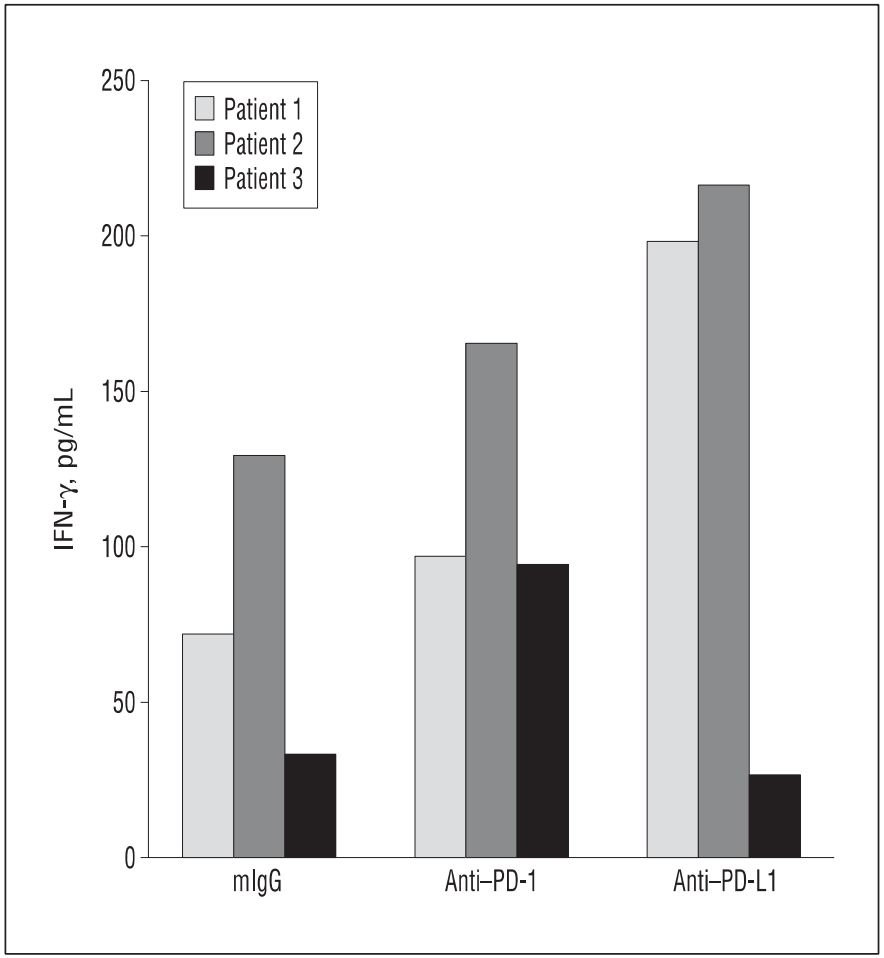
Biology Predicts Response to PD1/PD-L1 Blockade

High PD1+ and PDL1+ Tumor & TIL Expression



Kantekure 2012

Functional Role of PD1/L1 Blockade



Samimi 2010

Preliminary Signals of Efficacy

Yet, No Complete Responses

Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)→ aPD-L1 → PR → PD ~16 cycles

pre-treatment (11/20/2012)

C8D1 (4/23/2013)

Preliminary Signals of Efficacy

Yet, No Complete Responses

Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)→ aPD-L1 → PR → PD ~16 cycles

pre-treatment (11/20/2012)

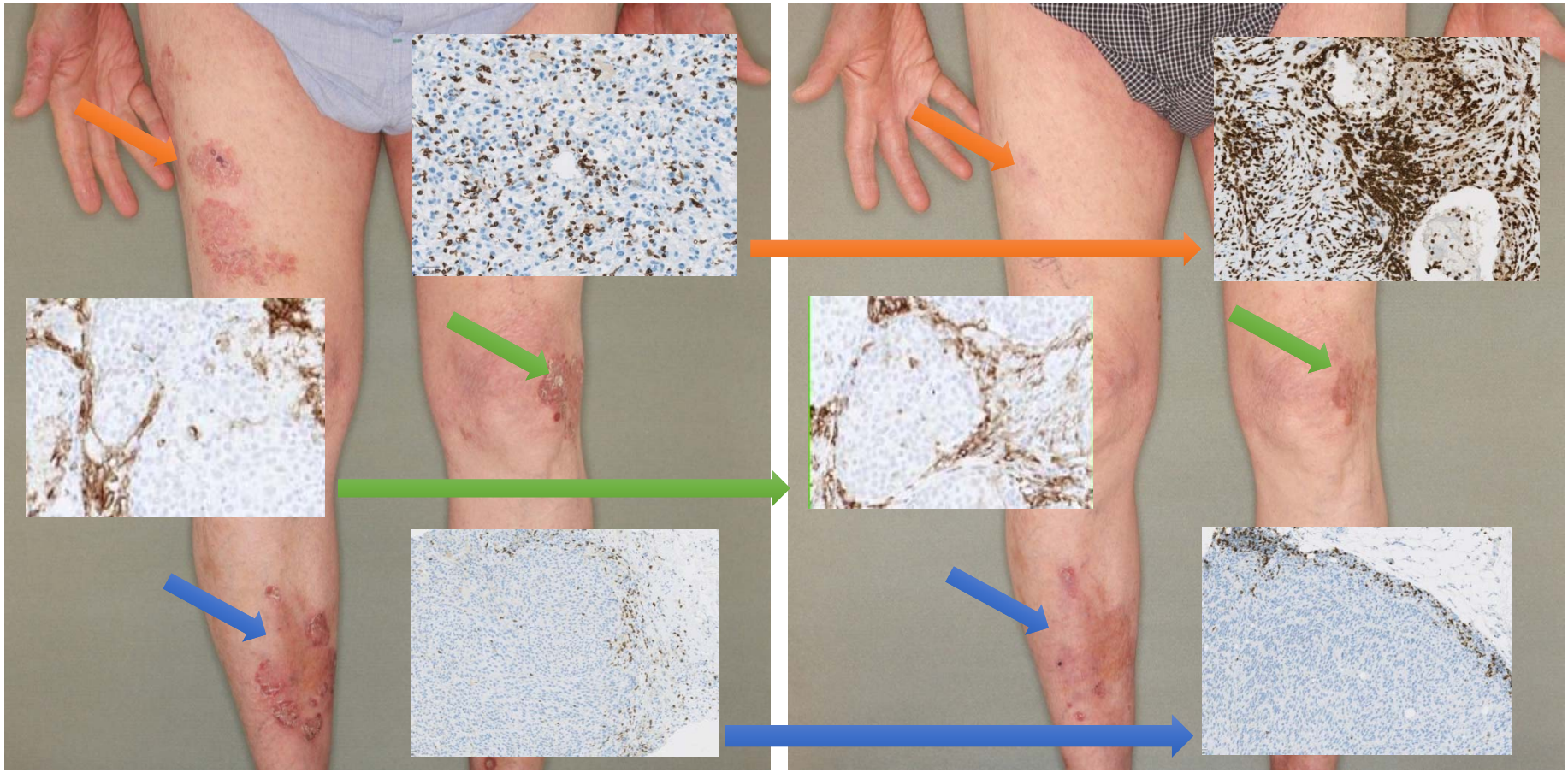
C8D1 (4/23/2013)

Preliminary Signals of Efficacy

Yet, No Complete Responses

Stage IB MF (h/o phototx, bexarotene, anti-CD4 mAb, forodesine, CpG+RT, lenalidomide, sapacitabine, enzastaurin, TSEBT)→ aPD-L1 → PR → PD ~16 cycles

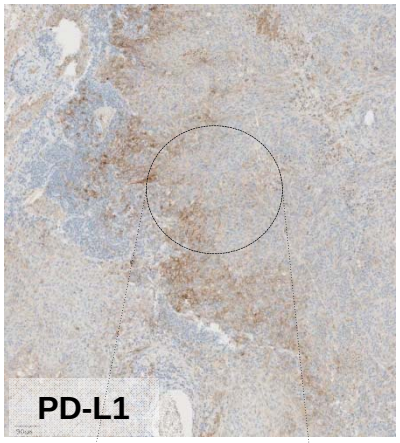
pre-treatment (11/20/2012) **C8D1 (4/23/2013)**

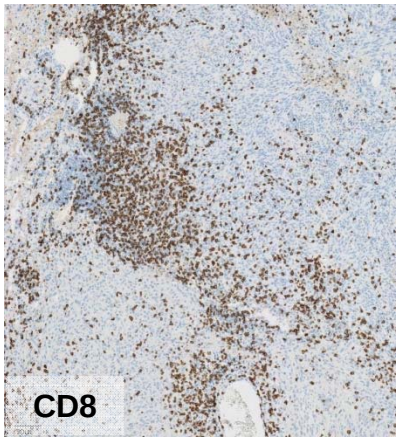


OBJECTIVE: IDENTIFY AND INDIVIDUALIZE THERAPIES WHICH INDUCE OR AUGMENT RESPONSES TO PD-1 BASED ON THE OBSERVED TUMOR BIOLOGY AT PROGRESSION

HYPOTHESIS: THERAPY NEEDED TO INDUCE PD-L1 & TUMOR RESPONSE CAN BE DETERMINED BASED ON TUMOR AND IMMUNE PROFILE AT PROGRESSION

At Progression

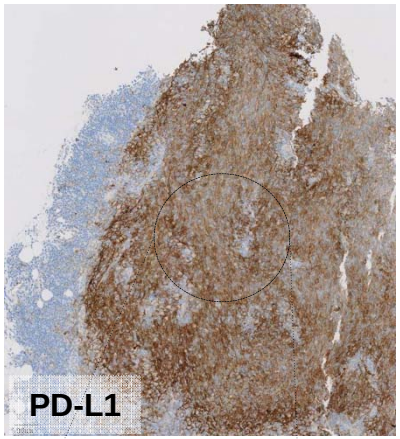


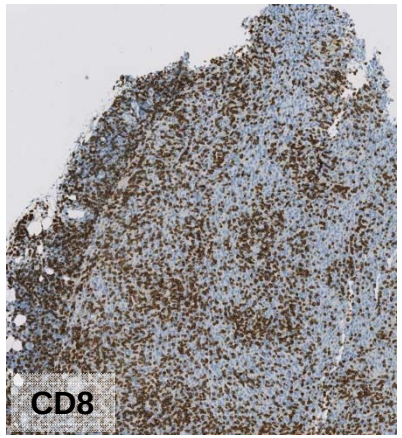


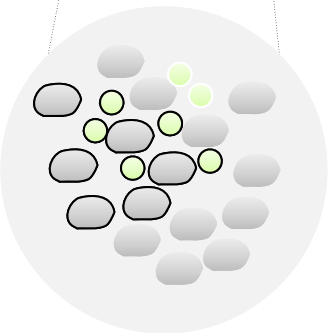
Anti-PD-1 RESCUE TX

Anti-PD-1 Cont'd

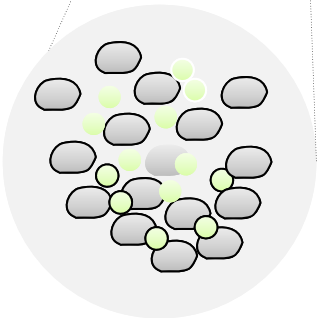
Following RESCUE TX







Focal PD-L1 expression may represent interface between cancer cells and immune cells



Activated T cells release IFNγ and may induce PD-L1 expression in neighboring tumor cells

- Tumor cells
- PD-L1 expressing tumor cells
- TIL/Immune cells

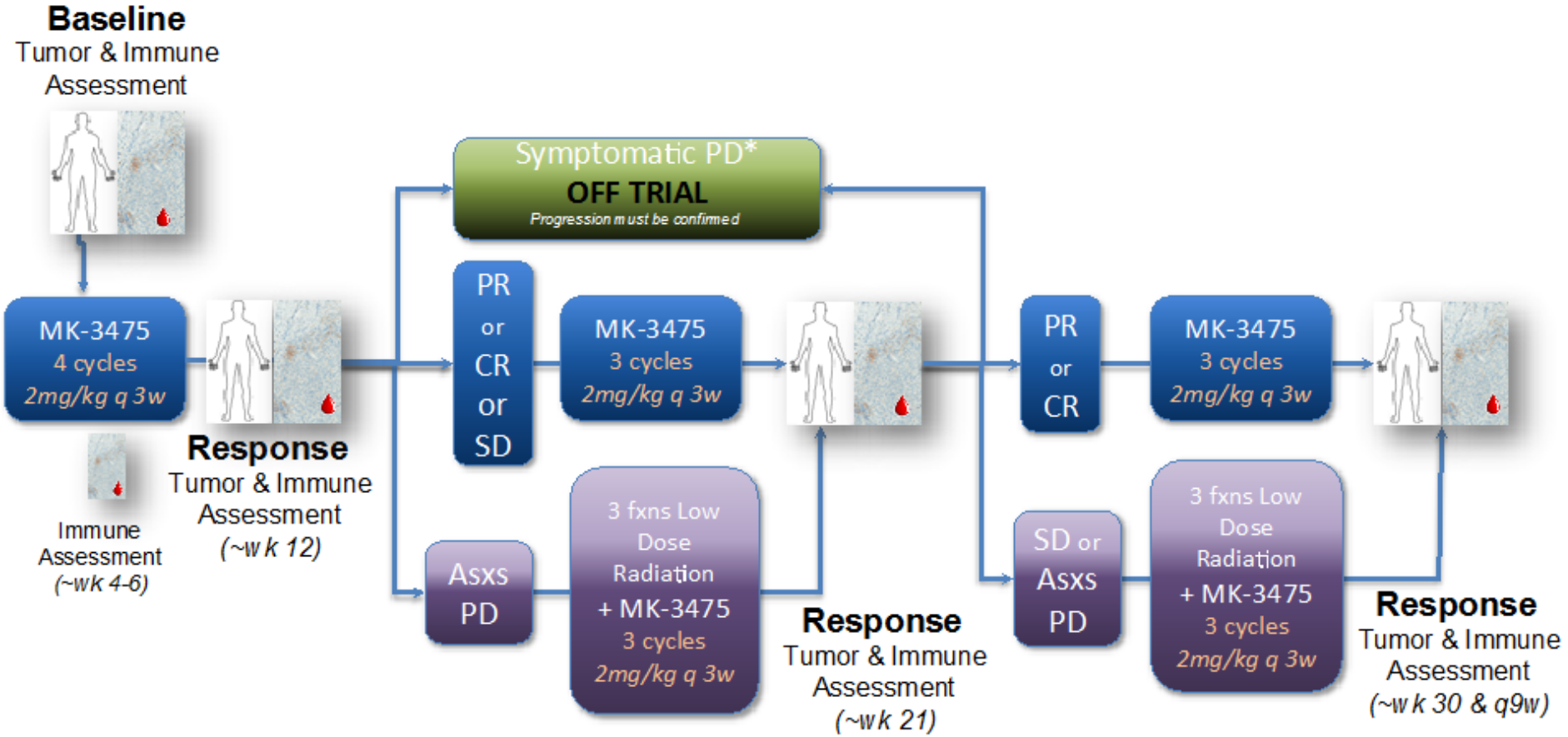
Kohrt, H. SITC 2013.

A POTENTIAL OPTIMAL TRIAL DESIGN

cancer immunotherapy trials network

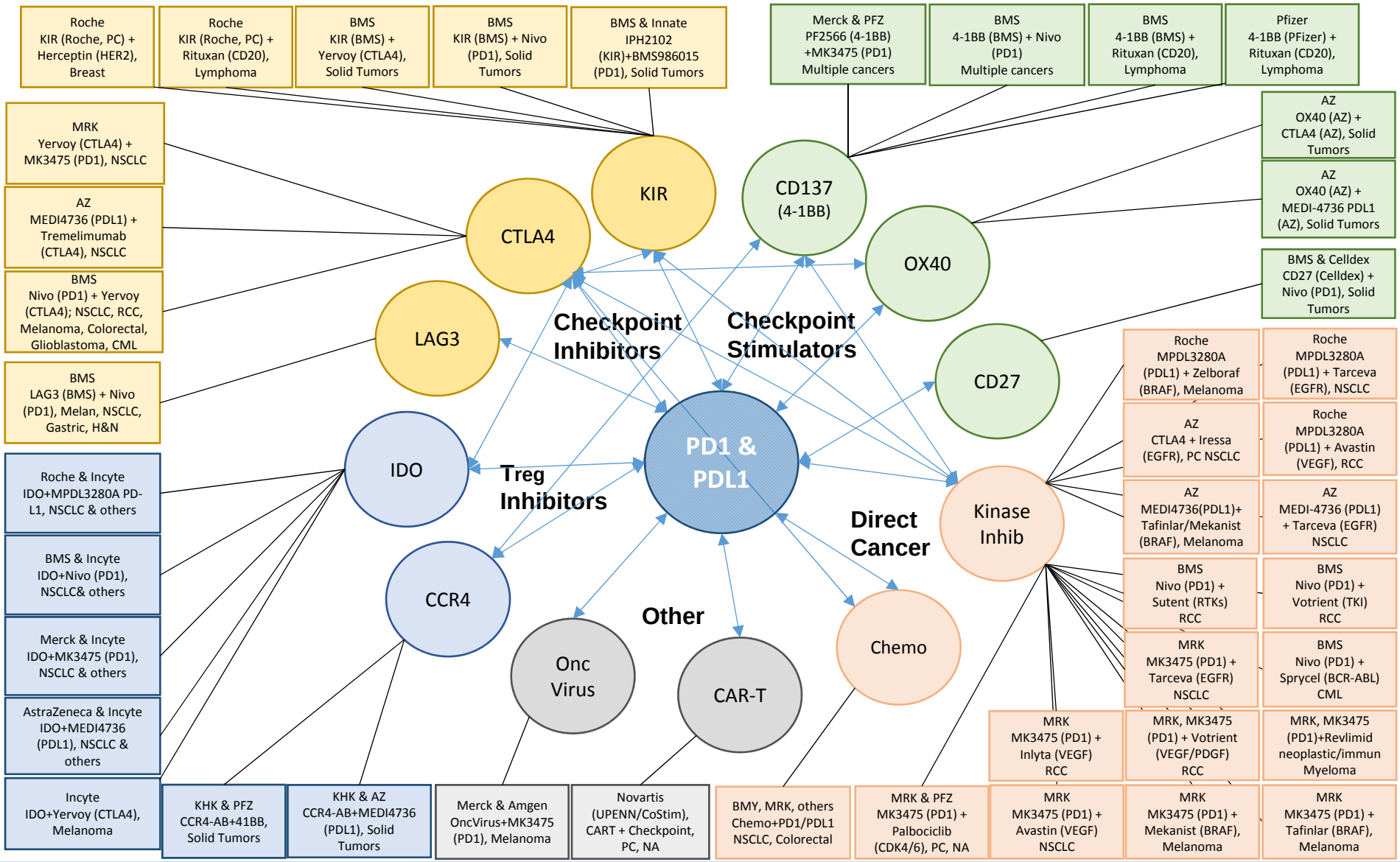
OPTIMAL

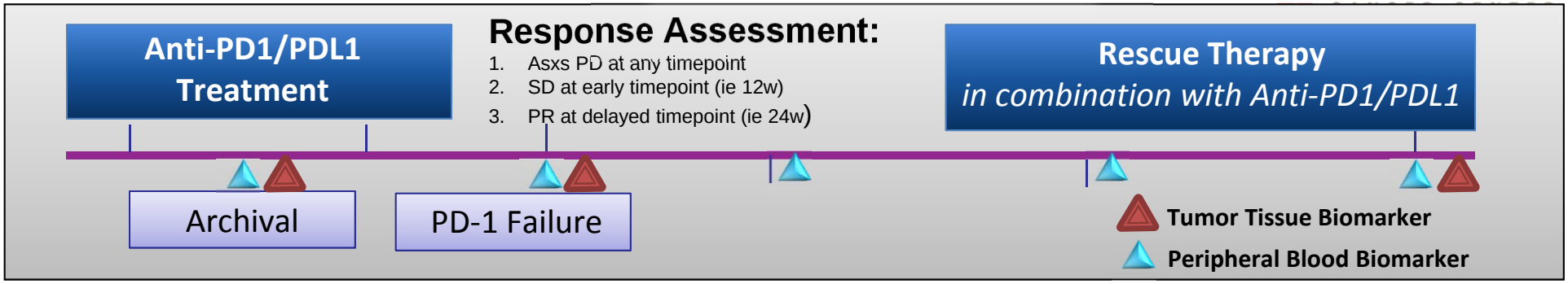
Optimizing PD-1 Therapy In Mycosis Fungoides with Addition of Low-dose XRT



A Plethora of Potential Combinations

Missed or Captured Opportunities?

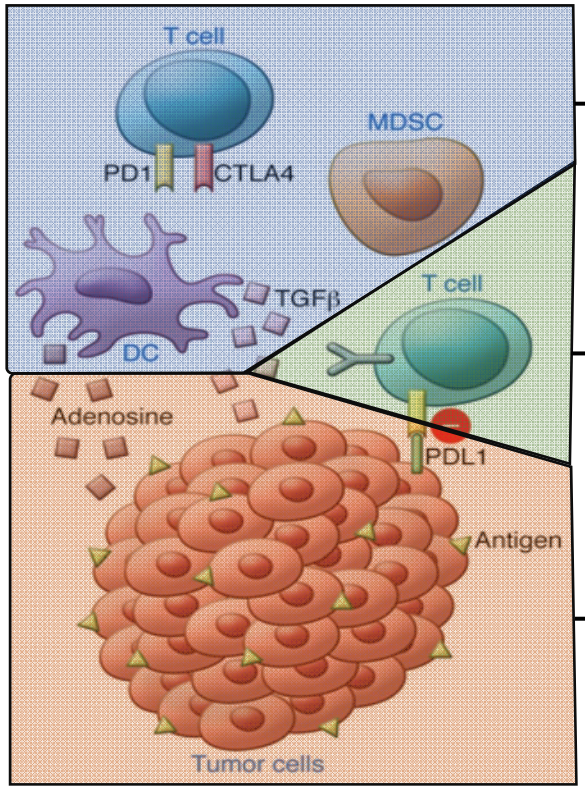


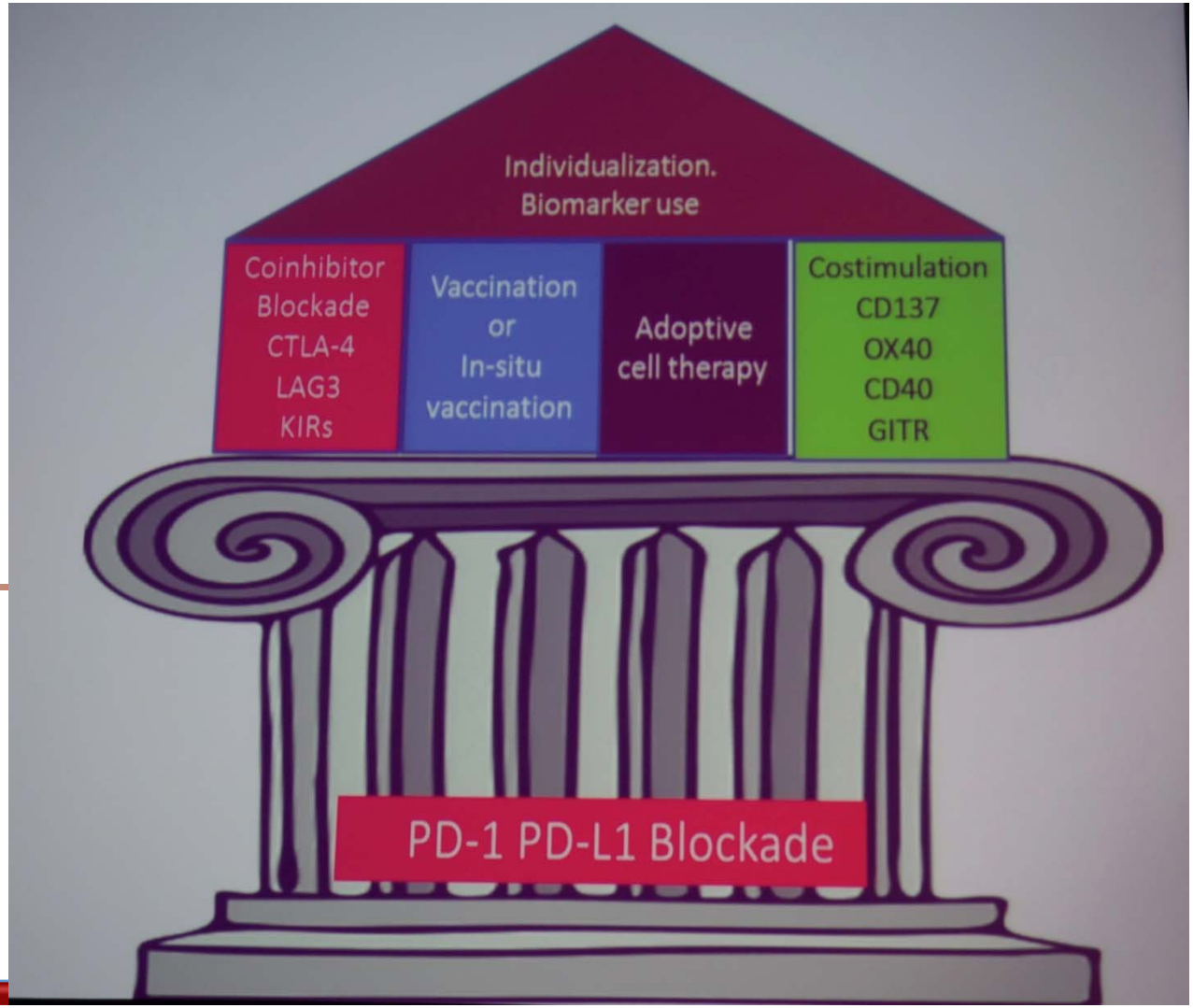


Biomarker Assessment

Tumor Tissue & PBMC

Analysis Guides Selection of Rescue Therapy





Thanks!!!

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

cancer immunotherapy trials network

Future of Immunotherapy

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