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DCTD Immunotherapy Initiatives

- FY ‘ 17 - Renewal of Cancer Immunotherapy Trials Network (CITN) - $1.5M

- FY ‘17 – FOAs: 2 RFAs
  - U24: Cancer Immuno-therapy Monitoring and Analysis Centers - $6.5M
  - U24: Cancer Immunologic Data Commons - $1.5M

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Summary of the DCTD Cancer Immunotherapy Workshop

NCI Shady Grove, January 14-15, 2016

Helen Chen, M.D. CTEP, on Behalf of DCTD

A 1.5-day meeting with thought leaders in the field to discuss …

- Opportunities and gaps in cancer immunology/immunotherapy
- What NCI should do to facilitate further development

Speakers and invited guests

Extramural scientists

- **Jim Allison,** MD Anderson
- **Ira Mellman,** Genentech
- **Karolina Palucka,** Jackson Lab
- **Liz Jaffee,** Hopkins
- **Mario Sznol,** Yale
- **Padnanee Sharma,** MD Anderson
- **Mac Cheever,** Fred Hutchinson

Biomarker/informatics experts:

- **Kurt Schalper,** Yale
- **Elaine Mardis,** Wash University
- **Lisa Butterfield,** Pittsburg
- **Anna Wu,** UCLA
- **Atul Butte,** UCSF
- **Stan Hamilton,** MD Anderson
- **Diagnostic: Adaptive, NanoString, Nodality, Immudex**

Industry:

- **Merck, Incyte, AstraZeneca/MedImmune**

NCI Intramural Scientists

- **Steve Rosenberg, NCI**
- **Nick Restifo, NCI**
- **Jay Berzofsky**
- **Remy Bosselut**
- **Stephen Hewitt**

DCTD:

- J Doroshow, J Abrams, T Hecht
- **CTEP**: H Chen, H Streicher, E Sharon, J Zwiebel
- **Cancer Diagnostic Program**: M Thurin
- **Biologics Resource Branch**: S Creekmore, A Welch
- **Radiotherapy Development Program**: M Ahmed
- **BRP**: R Simon

Division of Cancer Biology:

- C Marks, S McCarthy, K Howcroft, D Singer

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What Should NCI Do?

Specific recommendations:

Basic science

- **Mouse Models**
- **Tumor Microenvironment**

Clinical Research

- ✓ **Clinical trials rich in “translation”**
- ✓ **Clinical trials for Adoptive Cell Therapy**
- ✓ **Biomarkers and Database**

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CITN AWARD to FHCRC

- A network composed of leading immunotherapists and institutions to design and implement early phase multi-site clinical trials.
- Awarded to FHCRC/Mac Cheever, PI: Sept. 2010
  - Funded the Central Operations and Statistical Center
  - 3 million/yr total costs for 5 years
  - Included a central Immunomonitoring Laboratory Core
  - Currently 32 sites

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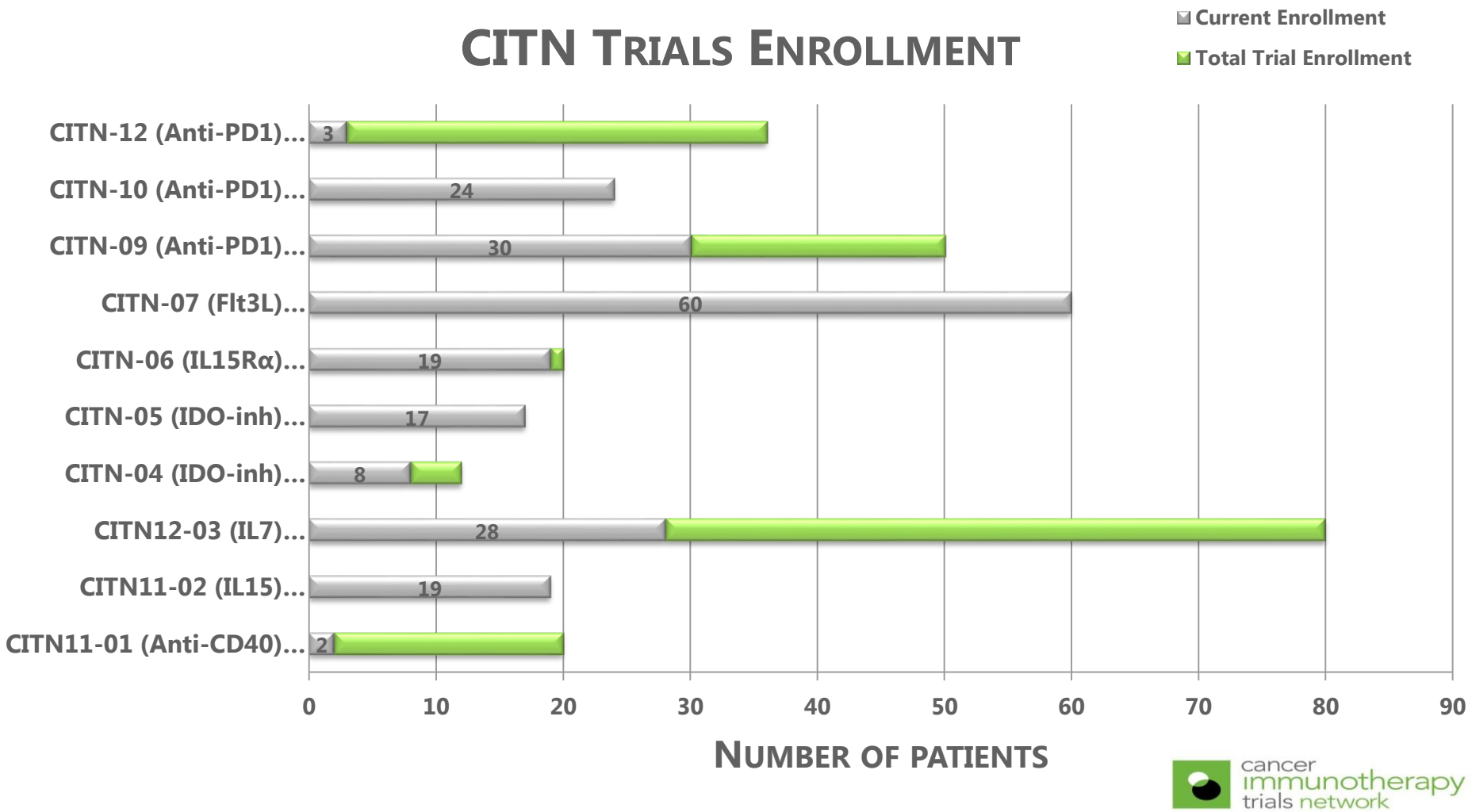
Current CITN Trials

1. **Anti-PD1**: in Merkel cell carcinoma, first systemic therapy
2. **Anti-PD1**: in mycosis fungoides, advanced, treatment failure
3. **Anti-PD1**: for advanced malignancy in HIV^+ patients
4. **Anti-CD40**: in pancreas cancer, neoadjuvant
5. **IL-15** (E. coli–derived, NCI): in NSCLC/H&N/renal/melanoma
6. **IL-15** (IL-15/IL-15Rα/Fc fusion protein): in melanoma
7. **IL-7**: in prostate cancer after Provenge vaccine
8. **IL-7**: in glioblastoma post-temozolomide (**ABTC trial**; *immune monitoring only)*
9. **IDO Inhibitor**: in melanoma with MELITAC 12.1 vaccine
10. **IDO Inhibitor**: in ovarian cancer, neoadjuvant
11. **Flt3-Ligand + Poly ICLC** + anti-DEC205-NY-ESO-1 vaccine: in melanoma, adjuvant

CITN Trials Enrollment



cancer immunotherapy trials network

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The NEW ENGLAND JOURNAL of MEDICINE

Available on-line at NEJM.org
Tuesday April 19

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)

Government
(NCI-CTEP-CITN)

Industry
(Merck)

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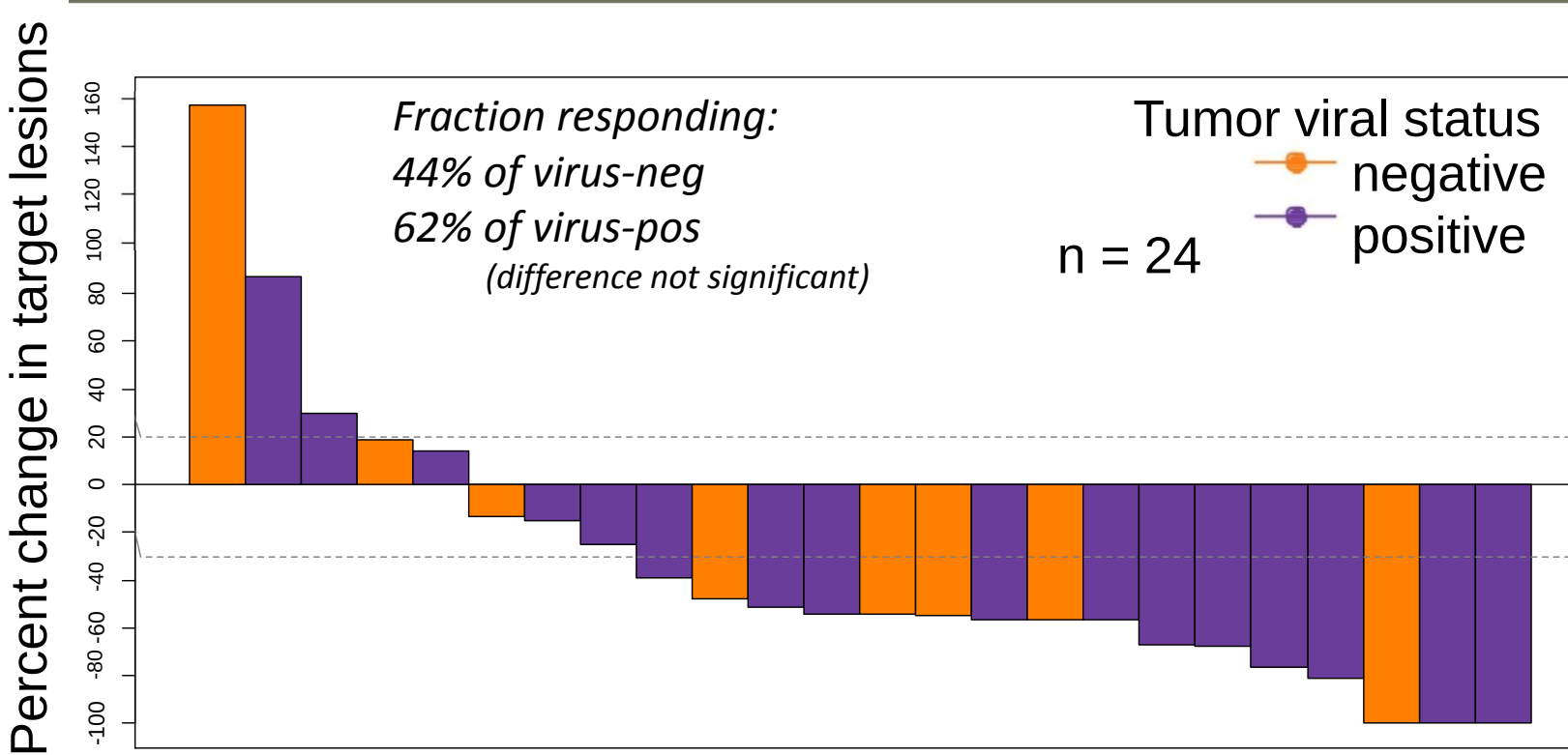
Responses to Pembrolizimab therapy in MCC



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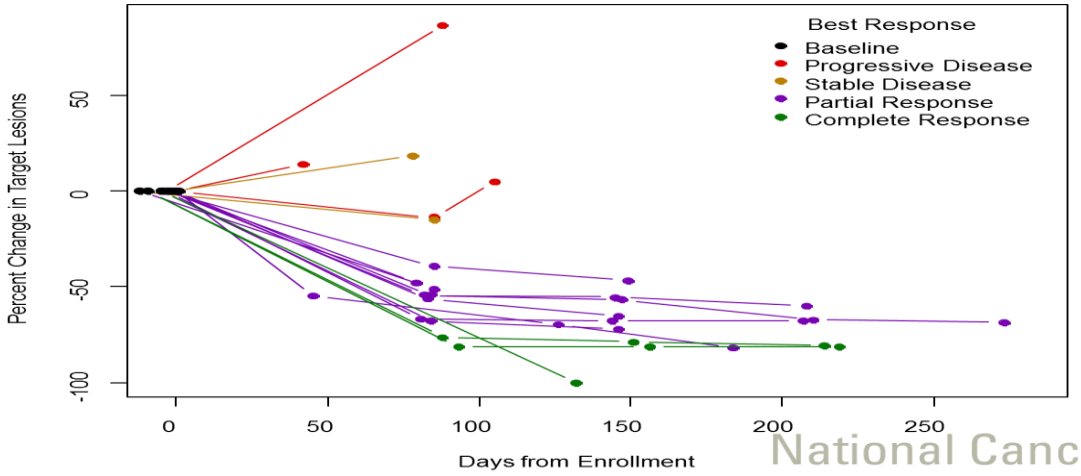
Pembrolizumab (anti-PD1) for Merkel Cell Carcinoma

- Phase II single arm, first line trial, at 7 CITN sites
- Responses (CR/PR) in 15 of 22 evaluable patients (68%); responses are rapid and appear more durable than chemotherapy
- **Presentation to European Cancer Congress, Sept. 2015; submitted "late-breaking" abstract for April AACR presentation**
- **Merck is applying to FDA for "breakthrough" designation for this indication**



Correlative Sciences Status Matrix: *Studies in Progress*

CITN-05
INCB024360

CITN-05
iIDO
ALC
Immunohistochemical Evaluation of Tumor Biopsies (CS 9.3.1)
Intra Tumor Kyn/Trp Ratios (CS 9.3.2)
Gene Expression Analyses of Tumor Biopsies, Ascites and PBMC (CS 9.3.3)
T-cell response: IFNγ ELISPOT (CS 9.3.4)
IDO inhibitor effects on CD8+ and CD4+ T cell subsets (CS 9.3.5)
Whole Blood Immunophenotyping (CS 9.3.6)
TCR Repertoire (CS 9.3.7)

Table 1. CITN Studies, Co … Matrix

Key: In Progress | Early Stage | In Progress w/o Ctrl Lab

CITN-02	CITN	CITN-06	CITN-07	CITN-09	CITN-10
IL-15	IL-	IL-15	Flt3L/CDX-1401	MK3475	MK3475
ALC	AL	ALC	ALC	ALC	ALC
Whole Blood Immunophenotyping (CS 9.2.1 and 9.2.2)	T-cell response ELISPOT	Whole Blood phenotyping (CS 2.1 and 9.2.2)	T-cell response: IFNγ ELISPOT (CS 9.1.1)	IHC Evaluation of Tumor Biopsiesc; Tumor PD-1 & PD-L1 Expr (CS #1)	Kyn/Trp Ratio (Special CS #1)
T-cell response: IFNγ ELISPOT (CS 9.2.3)	Proliferatio including Ki	sponse: IFNγ (CS 9.2.3)	Whole Blood Immunophenotyping (CS 9.2.2)	IHC: MCPyV protein expr (Anti-Tag); PCR: MCPyV DNA quantification (CS #2)	Skin Biopsy Analyses (CS #1, 2, 3)
NK cell function assays (CS 9.2.4)	Whole Immunopheno #3	ll Function (CS 9.2.4)	Circulating Tumor Cells (5.1)	Tetramer Phenotyping (Flow) (CS#3); Tetramer-sorted gene expression-PBMC (Nanostring) (CS#4)	Gene expression (PBMC; nanostring) (CS #3)
Serum Cytokine assays (Elisa) (CS 9.2.5)	PAP Ab, PA202 #4	Cytokines (CS 9.2.4)	PBMC Gene Expression (CS 9.1.2)	T-cell response: IFNγ ELISPOT: MCPyV other tumor Ags (CD8) -(CS#5)	Whole Blood Immunophenotyping & T cell function assays (CS #4)
Serum IL15, IL15 Receptor alpha and IL15 Antibody levels (CS 9.2.6)	TREC detecti	LT-803 (CS 9.2.6)	Antibody response: ELISA (5.1)	MCPyV Ab levels (CS #6)	Cytokine/Chemokine Analysis (serum ELISA) (CS #5)
	TCR deep seq #6		Anti-CDX-1401 Abs (NY-Eso-1) (5.1) - Both cohorts	Whole Blood Immunophenotyping (CS#7)	
	Kyn/Trp		Anti-CDX-301 antibodies (Flt3L) (5.1) - Cohort 1 only	Kyn/Trp ratio (CS #8)	
			CDX301 (Flt3L) serum level (CS 9.2.2) Cohort 1 only		
	ADA CY Immunogenic Study	genicity of ALT-803	IHC of T cell infiltrates and NY-ESO-1 Expr (CS 9.2.1)	HLA Typing	FNA (T cell characterization (Flow Cytometry)
	Circulating T (CTC) (Sect	yn/Trp Ratio	IHC of T cell infiltrates and NY-ESO-1 Expr (CS 9.2.1)		Circulating Sezary Cells
					Lymph Node Biopsy (Optional)

Other Results in Studies to Date

- **CITN-10: anti-PD1 in Mycosis Fungoides/Sezary Syndrome**
  - 8/24 PRs (33%) and 10/24 stable disease (42%)
  - Extensive immune/genomic correlates underway
  - **ASH 2016 abstract planned**
- **CITN11-02: NCI rhIL-15 for solid tumors**
  - 18-fold mean increase in NK cells & 2.7-fold mean increase in CD8 T cells at 3 μg/kg, day 15 cycle 1
  - **Presentation at May 2016 AAI meeting**
- **CITN-07: DC-targeting fusion vaccine plus/minus Flt3L**
  - Immune response change by Flt3L primary objective
  - Substantial increases in dendritic cells, NK cells, monocytes and antigen-specific T cell responses in Flt3L-treated patients
  - **ASCO 2016 poster presentation**

NCI-supported Immunotherapy Trials

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Between 2010 -2015

- **88 Phase I-III immunotherapy trials were activated in the DCTD Clinical Trial Network** (NCTN, ETCTN, CITN, and PBTC)
- **8 Phase III trials, 14 Randomized Phase 2 trials**
- **Clinical settings:** common, rare tumors; neoadjuvant, adjuvant and metastatic disease
- **Study regimens include single agent and novel combinations**

Check point inhibitors
- Anti- CTLA-4 (Ipilimumab, tremelimumab)
- Anti-PD-1 (Nivolumab, Pembrolizumab)
- Anti-PD-L1 (MEDI4736 and MPDL3280A)

Cytokine:
- IL-15
- IL-12

Vaccine
- CDX1401 (against NYSO-1)
- PSA PROSTVAC/TRICOM
- CEA TRICOM/PANVAC
- **Other:** peptide (gp100, HPV, RAS, P53, MART and others)

Oncolytic virus:
- T-VEC

T-cell engaging bispecific Ab
- CD19 BiTE (Blinatumomab)

Other immune modulators:
- IDO (INDB0243360) ~ 2 trials
- Lenalidomide, Pomalidomide: -
- FLT3 ligands
- Anti-CD27 mAb (CellDex)

Most randomized trials have mandatory collection of baseline tissues/blood
Many early clinical trials include serial biopsies
Definition of immunotherapy trials excludes MAbs directed at tumor targets or vasculature (e.g., cetuximab or bevacizumab)

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Why RENEW the CITN?

- Access to immunologic agents not in DCTD portfolio (eg. anti-CD40 and IL-7),
- 40% of CITN sites are not in ETCTN providing NCI access to wider pool of qualified immunotherapists,
- Translationally-rich trials
- Standing apparatus of immunotherapy sites is an attractive forum for investigators, and CITN is able to rapidly take advantage of new clinical opportunities in immunotherapy.

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CITN Renewal

- **Limited Competition RFA (UM1)**
- Integrate into existing CTEP/ETCTN processes:
  - Theradex to provide data management for all trials and utilize CTEP CIRB
  - CTSU to provide regulatory support system and website
- Subcontract/Member site composition limited to best 20 sites
- **Break out** immunomonitoring core to serve **ALL** NCI-sponsored networks/consortia (ie. CITN, ETCTN, ABTC and early NCTN trials) as a SEPARATE Network through a SEPARATE RFA

Next Directions in the CITN

Focus on Combinations (NCI-held or **not held**)

IL-15:

- Combinations:
  - IL-15 plus monoclonal antibody for enhanced ADCC (eg. with cituximab)
  - IL-15 with anti-PD1 (Merck)
- **Admune/Novartis IL-15 fusion protein** with NCI CCR (expansion cohort)

Other anti-PD1 trials:

- Anti-PD1 plus **IL-7** (Merck and Revimmune)
- Anti-PD1 failures – to biopsy, assess actionable reasons for failures

Other combinations:

- **Anti-CD137 (4-1BB)** plus trastuzumab (Pfizer) in breast cancer
- Intratumoral anti-CTLA4 plus local radiation plus anti-PD1 (Merck)

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CITN UM1 Budget

Operations and Statistical Office	$350K
Scientific Leadership	50K
Network Meetings and travel	30K
Treatment site support*	720K
Total Direct	**1150K**
Total Costs	**1500K**

*assume 120 patients/yr at $6,000/patient

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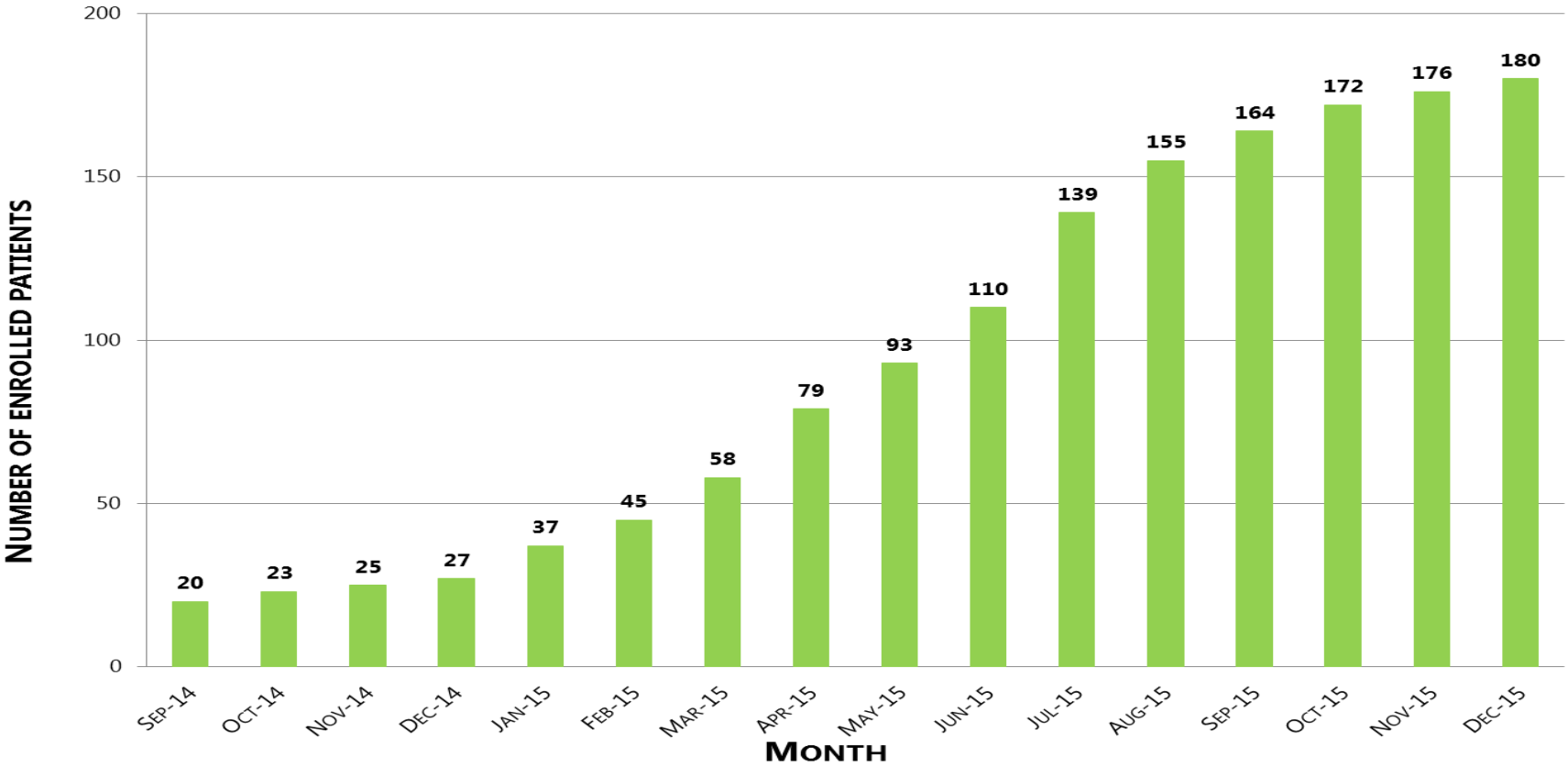
Extra Slides

CITN Trials Current Enrollment



Review of CITN by an External Panel

- Panel: Immunotherapy experts (5) plus medical oncologists outside of immunotherapy (2); Dr. Kim Lyerly, chair
- Overall recommendation (unanimous): support recompetition
  - Stellar team of investigators at major US immunotherapy sites
  - An infrastructure for coordinated areas of inquiry with a primary focus on immunotherapy, and for high quality and uniformed immunological assessment with the potential to expand the sophistication of analysis
  - Trial selection overall consistent with the aims of the network
  - Accrual appropriate given the focus on immunotherapy, emerging organizational capabilities, and need to address both CTEP and industry requirements
  - Enhances the existing clinical trials infrastructure and developmental therapeutics programs at the NCI
  - **Well poised to make contributions in the future**

Recommendations

- Infrastructure can be rate limiting as more protocols come on line: to *increase efficiency*, restructure to utilize the established infrastructure in CTEP

- Sites that are also ETCTN sites should engage appropriate investigators outside of the immunotherapy realm for testing combinations of targeted drugs with immuno-oncology agents

- Broaden leadership perspectives for decisions about future CITN trials