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DCTD RFAs

- Cancer Immunotherapy Trials Network (CITN)

- Cancer Immune Monitoring and Analysis Centers (CIMACs) (U24)
  &
  Cancer Immunological Data Commons (CIDC) for the CIMACs (U24)

Jeffrey Abrams, MD
William Merritt, PhD
Magdalena Thurin, PhD
Ming Song, PhD

Helen Chen, MD
Howard Streicher, MD
Elad Sharon, MD
James Zwiebel, MD

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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”**
- ✓ **Biomarkers and Database**

Clinical trials for Adoptive Cell Therapy

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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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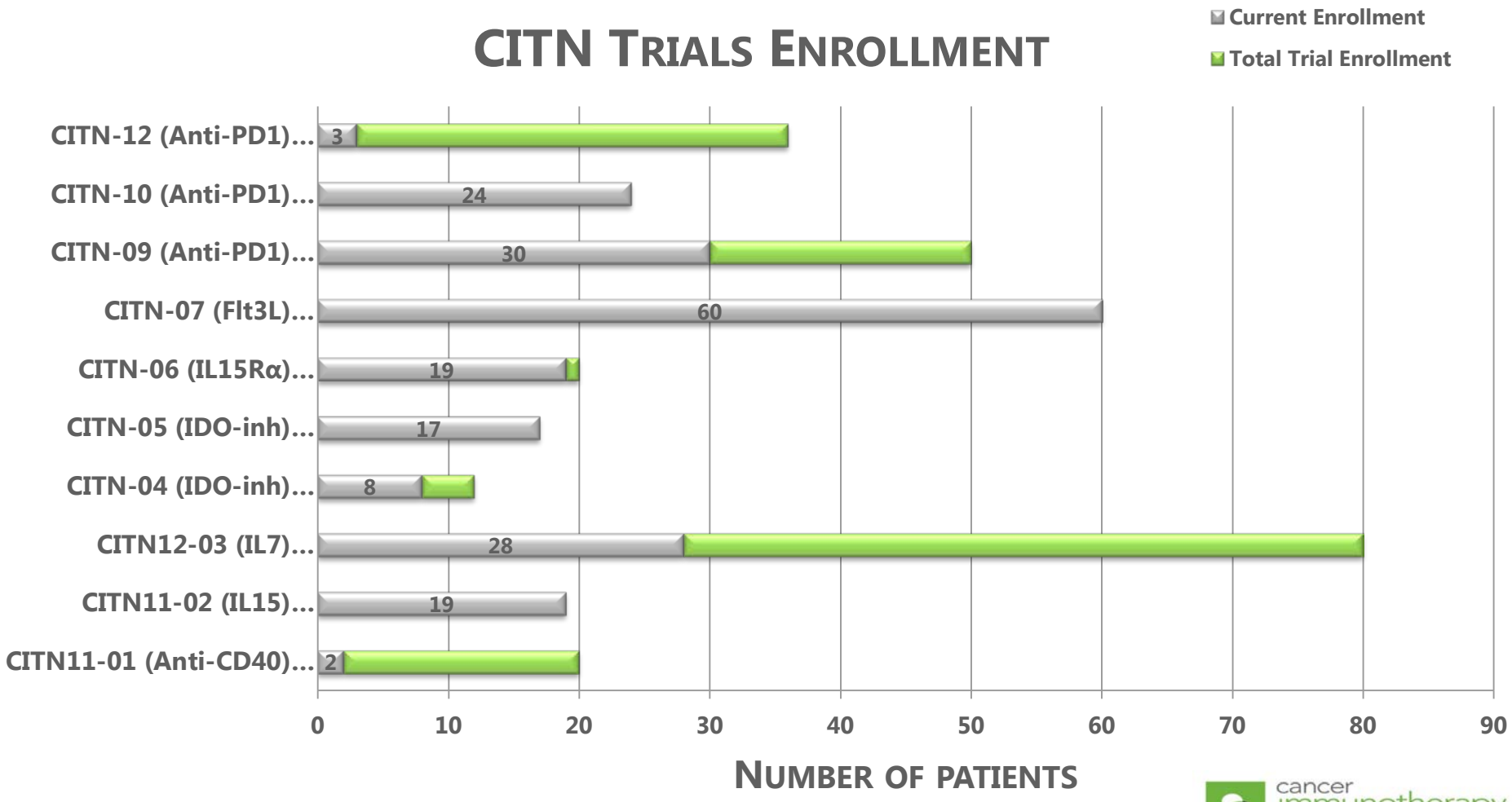
Current CITN Trials

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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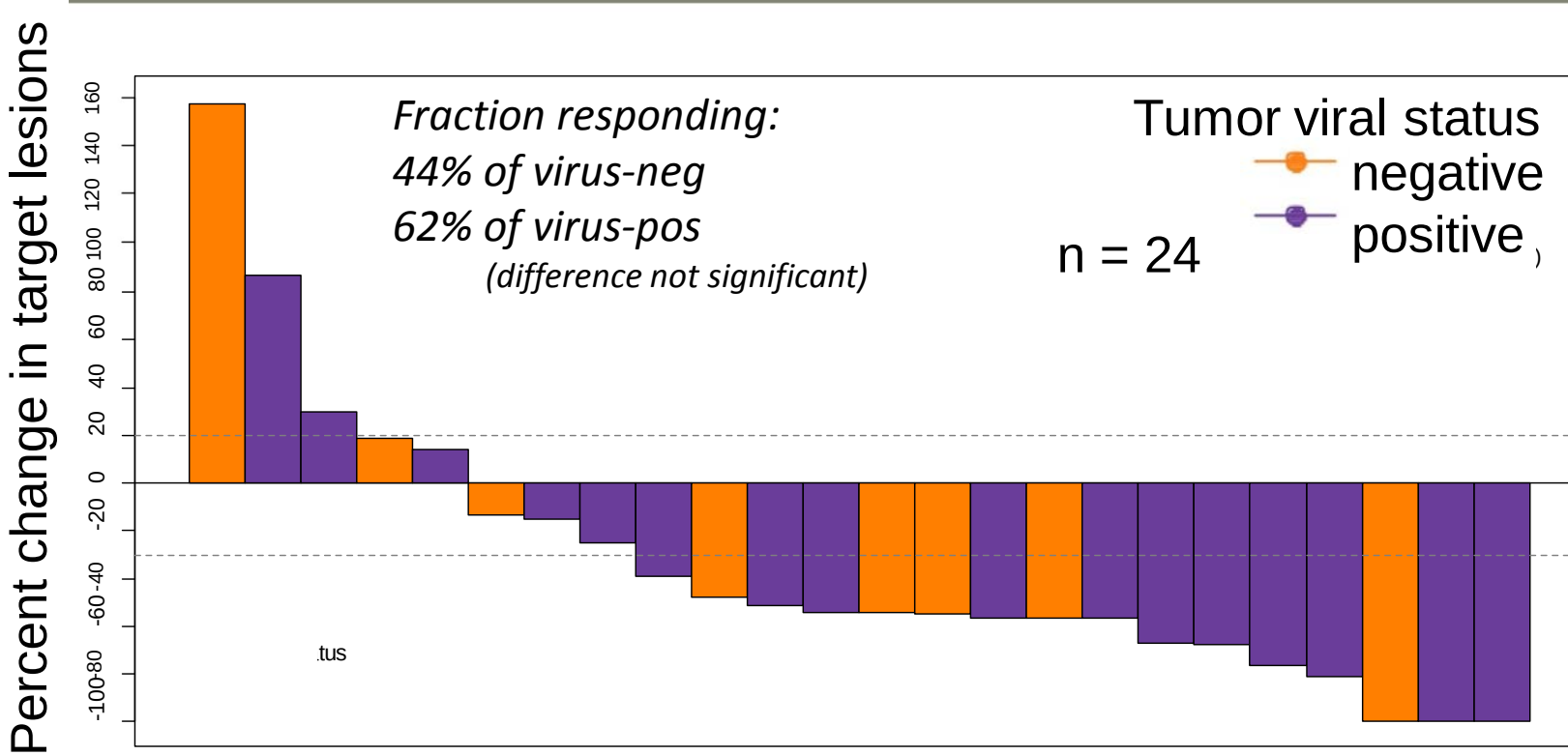
Responses to Pembrolizimab therapy in MCC



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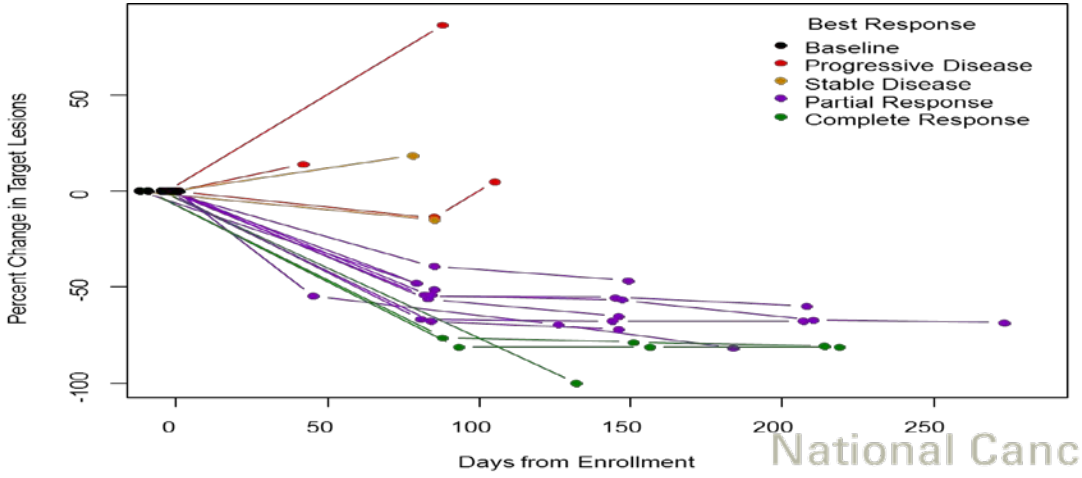
Pembrolizumab (anti-PD1) for Merkel Cell Carcinoma

- 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



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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 …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)	Proliferati… 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)

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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

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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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Cancer Immune Monitoring and Analysis Centers (CIMACs) (U24)
&
Cancer Immunological Data Commons (CIDC) for the CIMACs (U24)

Magdalena Thurin, Ph.D., CDP

Helen Chen, M.D., CTEP

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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Biomarkers are Critical to Further Development of Cancer Immunotherapy

- Immunotherapy has remarkable activity in a variety of cancers, but only a minority of patients benefit:
  - RR in most of the “responsive” tumors is 20-30%; Some tumors do not respond (pancreatic cancer, MMR+ colon cancer, myeloma).

- Strategies to optimize patients’ outcome will rely on:
  - Combination therapies to overcome intrinsic or acquired resistance.
  - Biomarkers – especially predictive markers to provide the right treatment to a given patient.

- Several categories of biomarkers can benefit immunotherapy:
  - Predictive of benefit from drug intervention and toxicity
  - Target modulation and rational design of combination therapy.
  - Response to therapy and monitoring.
  - Dose selection using pharmacogenomic markers.

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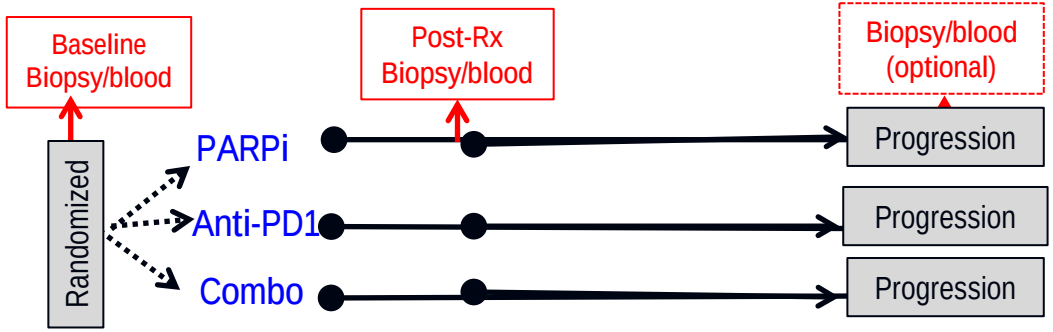
An example

- What is needed to achieve biomarker objectives in CTEP immunotherapy early phase trials?
- How can a network of laboratories with a data center help?

Several NCI-supported clinical trials are testing the combination of PD-1/PD-L1 and PARP inhibitors in tumors with DNA repair deficiencies

1. Trial A: Single arm study in ovarian ca and potentially other indications
2. Trial B: Phase II randomized trial in triple negative breast cancer with BRCA deficiency

One of the trial designs



3. Potential phase III trial … if efficacy signal is identified in an indication or molecular subset

- Hypothesis: PARP inhibitor may enhance response to anti-PD1; anti-PD-1 may sustain the duration of response to PARPi
- Primary endpoint: Clinical efficacy
- Common biomarker questions in PARPi + PD-1 trials
  - What is the baseline immune profile and mutational burden in BRCA deficient tumors?
  - Does PARP inhibition increase mutational burden/neoantigens, and influence immune infiltrate and clonality?
  - What markers are associated with response /resistance to PAPRi vs. Immunotherapy vs. the combo?

Planning of biomarker studies for PARPi + Anti-PD1 trials - Now:

Assays and panels of interest

- Tumor genomics and neoantigen analysis
  WES* and RNA-seq*; Prediction of class I/II neoantigens
- T-cell sequencing* (TCR sequencing)
- Functional profiling/signature: Cytokine panel; Nanostring
- In situ assays IHC, multiplex QIF (T cells* and B cell subsets, macrophages, dendritic cells, MDSC, NK cells)
- Tumor/blood: soluble single cell profiling using the 38-marker CyTOF panel

- **Current assay availability to individual trials**
  - Trial A site is experienced in QIF/IHC but not in WES; Trial B institute is well established for neoantigen analysis (WES, RNA Seq, T cell assays and informatics) but relatively weak in IHC
  - Both sites need assay development for other platforms
  - *Current approach:*
    - Trial A and B will collaborate under an ad hoc agreement … for QIF, neoantigen analysis
    - Seek expertise from other centers or companies … for nanostring, TCR sequencing.
    - Need lead time to validate other platforms (CyTOF)
    - Seek grants/supplements from multiple sources to support the work
    - No existing system for data deposit and integration across trials

A centrally supported, standing laboratory and informatics network will improve the efficiency and quality of biomarker studies for these and other immunotherapy trials

Planning of biomarker studies for PARPi + Anti-PD1 trials - Future:

Assays and panels of interest

- Tumor genomics and neoantigen analysis
  WES* and RNA-seq*; Prediction of class I/II neoantigens
- T-cell sequencing* (TCR sequencing)
- Functional profiling/signature: Cytokine panel; Nanostring
- In situ assays IHC, multiplex QIF (T cells* and B cell subsets, macrophages, dendritic cells, MDSC, NK cells)
- Tumor/blood: soluble single cell profiling using the 38-marker CyTOF panel

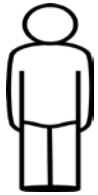
- **Potential role of Ca Immune Monitoring & Analysis Centers and Ca Immunological Data Commons**
  - Determine which assay and instruments are most appropriate for the biomarker question
  - Perform assays through designated labs in CIMAC
    - IHC/QIF; Multi-parametric flow cytometry; WES; TCR sequencing; Transcriptional profiling, RNA Seq, Nanostring

    (* Trial PI will pursue additional or alternate biomarker assays at their own institution when appropriate)
  - Establish and manage database for immune and tumor profiling data from CTEP trials
  - Perform within- and cross- trial analysis
    - For multiple PARPi + anti-PD-1 trials in different indications or with different agents; Comparison with chemotherapy + anti-PD1
  - If candidate markers are identified, the NETWORK will prepare for the next phase of biomarker development
    - Assay validation, cutoff optimization, CLIA qualification
    - Assist in design and perform assays for Clinical Validation

Role of informatics and computational support within and across trials

Analysis of the cancer-immune interplay within a single patient

(e.g. Mutation/Neoantigen profile with T cell phenotype/functional profile)



- Tumor Tissues
- Blood
- Imaging
- Clinical data

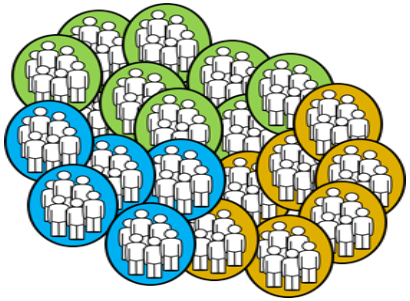
Data platforms:

- **Histopathology**: IHC, in situ hybridization, MALDI tissue imaging
- Multi-parametric flow cytometry;
- **DNA sequencing** of tumor and T cells (mutations, neoantigens, T cell clonality);
- **Transcriptional** profiling, RT-PCR, Nanostring, RNAseq;
- **Proteomics, epigenetics**;
- **Functional** assays (EliSpot, multimer binding, ELISA)

Single Trial Analysis

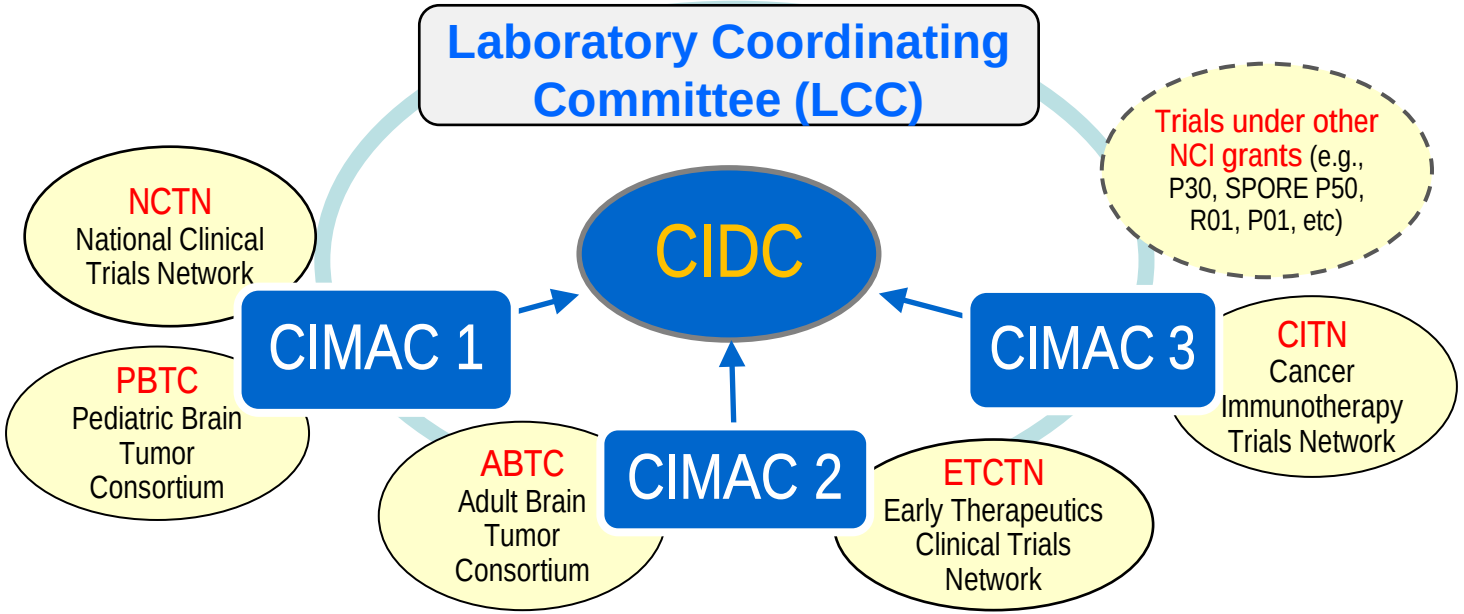
Clinical and I-O characterization & analysis

Network Analysis & IT



Multiple trial analysis

CIMACs (Laboratory Network of Cancer Immune Monitoring and Analysis Centers (U24) and CIDC (Cancer Immunologic Data Commons) (U24)



Up to 3 CIMACs and one CIDC, to support biomarker studies in CTEP approved Phase 0-2 trials

- Each CIMAC will have multi-disciplinary expertise to carry out immune-profiling and analysis
  - Will partner with pre-arranged Networks or Consortium
- CIDC will establish/manage data center to collect immune and tumor profiling results from CIMACs
- LCC (CIMACs/CIDC PIs and NCI) will coordinate resources and efforts among CIMACs (e.g. Sharing or upgrading major assay platforms; prioritizing or assigning biomarker service for non-CTEP trials)

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CIMACs - General Role

- Cancer Immune Monitoring and Analysis Centers (CIMACs) - up to 3 awards:
  - **Conduct correlative studies** and provide **immunoprofiling analyses** for specimens from NCI-supported clinical trials:
    - **NCI-supported Phase 1-2 clinical trial(s)** conducted within DCTD-supported networks/consortia (NCTN, ETCTN, CITN, PBTC, and ABTC).
    - Perform correlative studies **in NCI-supported clinical trials from outside** the established network/consortia (grant mechanism).

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CIMAC – Specific Functions

- Each “Center” in the network should be self-sufficient to conduct biomarker studies for a group of clinical trial sites and collaborate closely with **clinical investigators and study statisticians.**
- Provide service and **multidisciplinary expertise** (immunology, pathology, molecular biology) for:
  - **Use of well-defined**, fit-for-purpose assays for retrospective and prospective analysis.
  - **Scale-up assays** that need to be refined or that need to undergo analytic validation and clinical validation.
  - Some of the assay capacities may be **shared across the CIMACs.**
- Provide **computational biology and biostatistics** resources for high-throughput data analysis; specific projects require specific statistical tools and approaches.

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Cancer Immunologic Data Commons (CIDC)

- **Single site – responsible for quality and harmonization across CIMACs**
- **Bioinformatics Core** will:
  - Serve as a repository for collection of data on the studies completed by the CIMACs.
  - Collaborate with the CIMACs to facilitate standardization of **immunologic data collection** and fostering best practices among the CIMACs and their clinical collaborators.
  - Development of information resources and **sharing the data** with other investigators to promote secondary data analyses.
  - Collaboration with other **data centers** (e.g., Genomics Data Commons), whenever possible.

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CIDC - Administrative Core and LCC

- **CIDC Administrative Core** will be responsible for:
  - Logistical assistance in arranging network meetings, webinars and workshops.
  - Management of resources that are reserved for supporting studies from outside the pre-arranged alliances with clinical trials networks/consortia.

- **A Laboratory Coordinating Committee (LCC) -** a governing body of the network will be responsible for:
  - Strategic planning and prioritization of scientific questions regarding optimization of resources for correlative studies.
  - Overseeing and coordinating the integration efforts among CIMACs.
  - LCC will include representatives of the CIMACs, CIDC and the NCI.

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Network's Annual Budget

CIMACs U24

• Laboratory Centers*	$3,200K
• Scientific Leadership	$950K
• Network meetings/travel	$50K
• Direct Costs	$4,200K
• Total Costs	$6,500K

*Expected: 360 patients/year
(at $8,000/patient)

CIDC U24

• Scientific Leadership	$350K
• Bioinformatics Analysis	$150K
• Computers/Data Servers	$120K
• Database Systems Access	$20K
• Network meeting/travel	$10K
• Direct Costs	$650K
• Total Costs	$1,000K

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Questions for CTAC

- Are there improvements/changes to the CITN or CIMACs/CIDC that you would recommend?
- Do you think the CIMACs/CIDC will be able to partner effectively with NCI-supported clinical trial networks?