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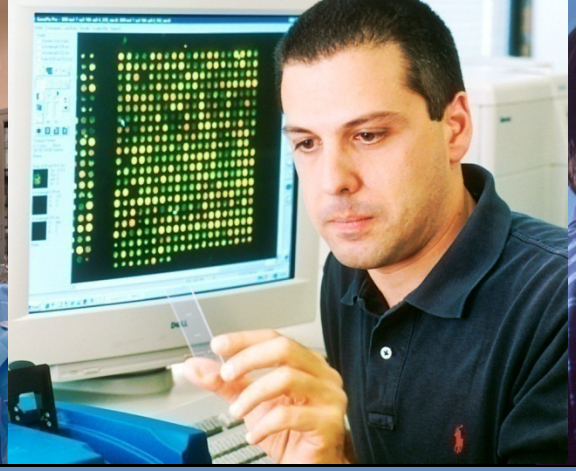


CTEP/NCI's Role in Registration Trials

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Implementing a National Cancer Clinical Trials System for the 21st Century:
IOM Session # 6
Washington, DC
February 12, 2013

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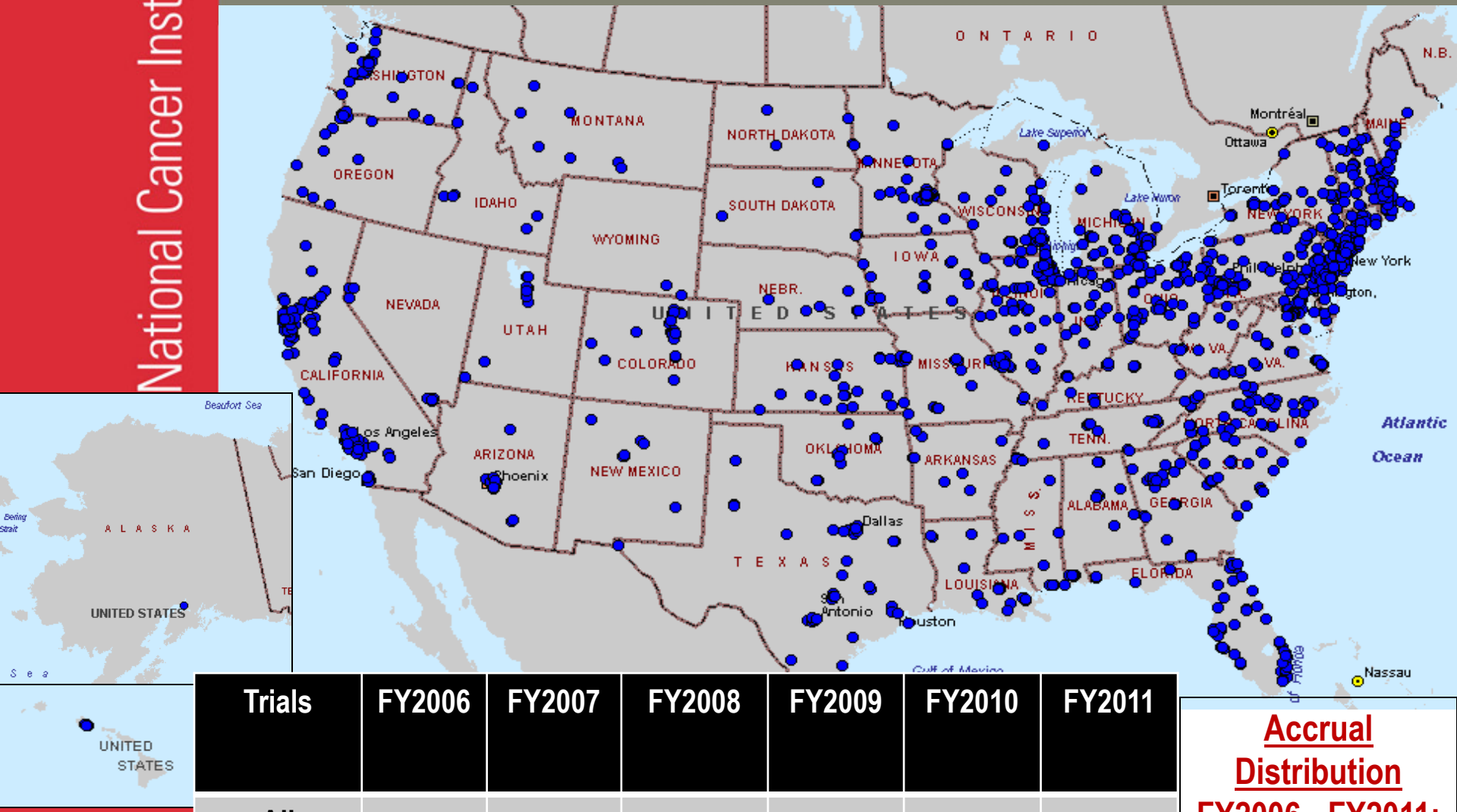
Overview of the Current Program



Trials	FY2006	FY2007	FY2008	FY2009	FY2010	FY2011
All Phases: Treatment Trials	27,263	24,289	25,540	29,063	23,299	19,462

Accrual Distribution FY2006 - FY2011:

Phase 3: 82.0%

Phase 2: 15.3%

Phase 1/Pilot: 2.6%

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Selected NCI/CTEP-sponsored Trials Contributing to FDA-approved Indications for New Oncology Agents

- **1991 - 1994**
  - Fludarabine phosphate (SWOG)
  - Pentostatin (CALGB, SWOG)
  - Paclitaxel (GOG, CALGB, ECOG, NCCTG, SWOG)
  - Melphalan IV (CALGB)
  - Pegasparginase (POG)
- **2001 - 2004**
  - Imatinib mesylate (COG, SWOG)
  - Letrozole (NCIC, Intergroup)
  - Oxaliplatin (NCCTG, Intergroup)
  - Taxotere (SWOG)
- **2005 - 2008**
  - Nelarabine (COG, CALGB)
  - Bevacizumab (ECOG, Intergroup)
  - Herceptin (NSABP, NCCTG, Intergroup)
  - Imatinib mesylate/ GIST-adjuvant (ACOSOG)
  - Rituximab (ECOG, Intergroup)
  - Bortezomib (Memorial Sloan-Kettering)
- **2009 – 2012**
  - Bevacizumab/ RCC (CALGB)
  - Romidepsin (CCR)
  - Dasatinib (SWOG)
  - Imatinib mesylate (ACOSOG)

Year FDA Approval of Indication in Agent Label	Agent	Supplemental Indication Unless Otherwise Noted	Related Cooperative Group Trial Number(s)
BLA Currently in Preparation	Anti-GD2 Antibody ch14.18	Use in "high-risk" neuroblastoma (Primary indication for the agent)	COG: ANBL0032
2009	Bevacizumab	Use in 1st-line therapy in advanced renal cell carcinoma in combination with interferon alpha	CALGB-90206
2008	Imatinib mesylate	Use as adjuvant therapy after resection of primary GIST	ACOSOG-Z9001
2006	Bevacizumab	Second-line therapy in advanced colorectal cancer in combination with FOLFOX	E3200
2006	Bevacizumab	Use in 1st-line therapy in advanced NSCLC in combination with chemotherapy	E4599
2006	Imatinib mesylate	Use in pediatric newly diagnosed CML	COG: AAML0123
2006	Rituximab	Use in Diffuse Large B-cell Lymphoma	E4494
2006	Rituximab	Use in Non-Hodgkins Lymphoma	E1496
2006	Thalidomide	Use in newly diagnosed Multiple Myeloma	E1A00
2006	Trastuzumab	Use in combination with adjuvant chemotherapy in operable HER2-positive breast cancer	NSABP-B-31 and NCCTG-N9831
2005	Nelarabine	Use in T-cell ALL and T-cell lymphoblastic lymphoma that has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens (Primary indication for the agent)	P9673 and CALGB-59901

Year Publication (or Abstract or Announcement) of Negative Results	Cancer Site	Trial Number	Experimental Agent or Regimen	Result - Indication
2011	Brain Cancer: Glioblastoma	RTOG-0525	Dose-dense temozolomide	Conducted internationally by the RTOG, EORTC and NCCTG, it randomized 833 patients—largest GBM trial reported to date. No statistical difference was observed between standard and dose dense temozolomide arms median OS or median PFS, or by methylation status.
2011	Head & Neck Cancer (SCCA)	RTOG-0522	Concurrent accelerated RT plus cisplatin with cetuximab	The study showed that the addition of cetuximab to standard chemoradiation did not improve progression-free survival or overall survival.
2010	Colon Cancer	N0147	Cetuximab in combination with adjuvant chemotherapy	In this randomized phase 3 trial, the addition of Cetuximab to chemotherapy (mFOLFOX6) was of no benefit for patients with resected stage III KRAS wild-type colon cancer.
2010	Colon Cancer	NSABP-C-08	Bevacizumab in combination with adjuvant chemotherapy	Bevacizumab for 1 year with chemotherapy (mFOLFOX6) did not significantly prolong disease-free survival in stage II and III colon cancer.

Overview of Changes to the NCI Clinical Trials System for Registration Trials

- National Clinical Trials Network (NCTN)
  - Trial Efficiency and Quality
- NCI Central IRB
- CRADA and Intellectual Property Agreements
- New Trial Designs for Registration

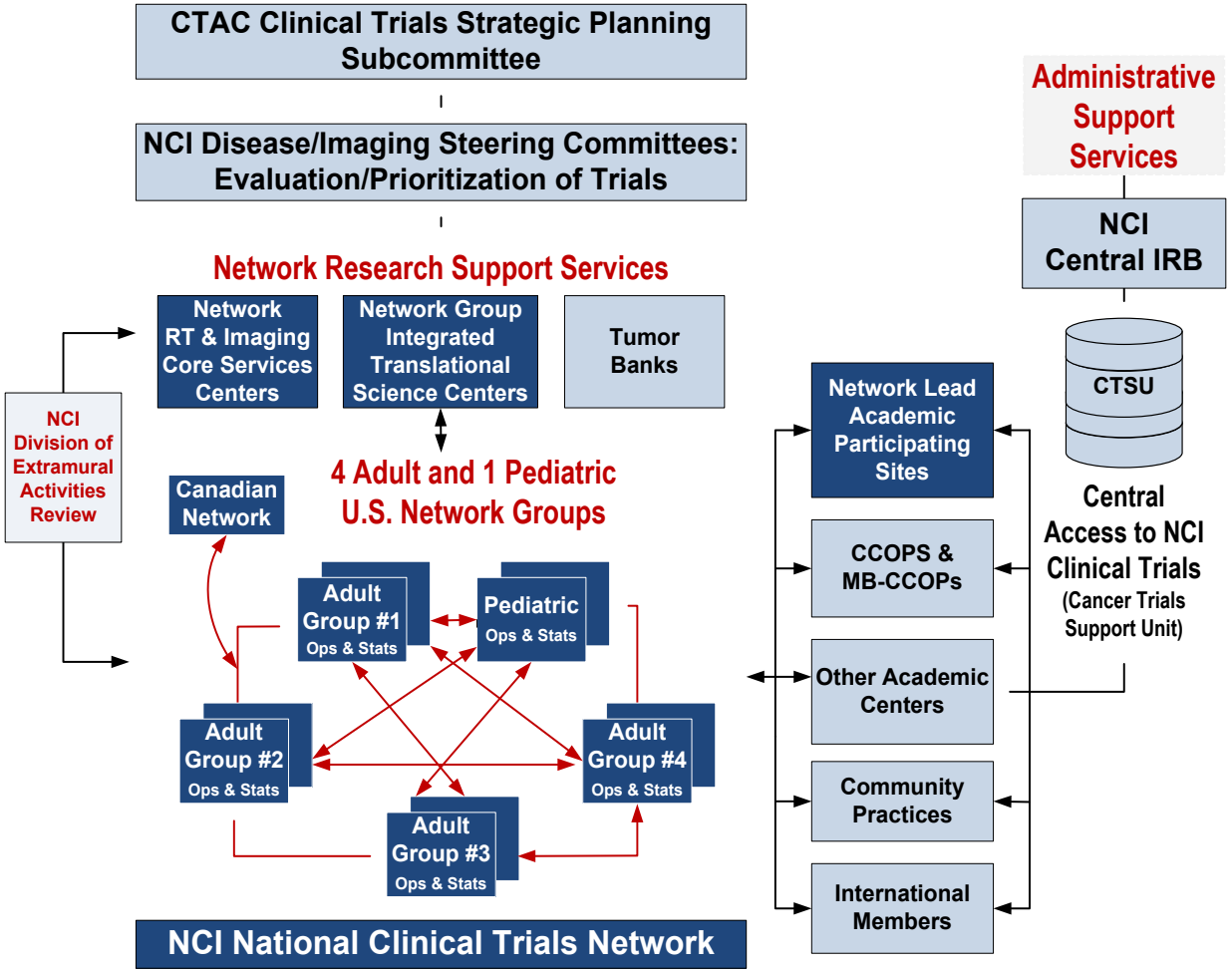
IOM Goal 1: Improve Speed & Efficiency of the Design, Launch, and Conduct of Clinical Trials

Recommendation 1: *Facilitate some consolidation of Group "front-office" operations by reviewing & ranking Groups with defined metrics on similar timetable & by linking funding to review scores*

Progress:

- New Program with up to 4 adult & 1 pediatric Network Groups
- Peer-review focused on overall research strategy, collaboration, & operational efficiency
- Support for trials designed with integral molecular screening
- Integrated translational science & Lead Academic Participating Site awards
- Core RT/Imaging services
- Strategic planning & trial prioritization at national level
- Adult and pediatric Central IRBs
- Common IT data mgt system
- Centralized 24/7 patient registration

New Program: NCI National Clinical Trials Network (NCTN)



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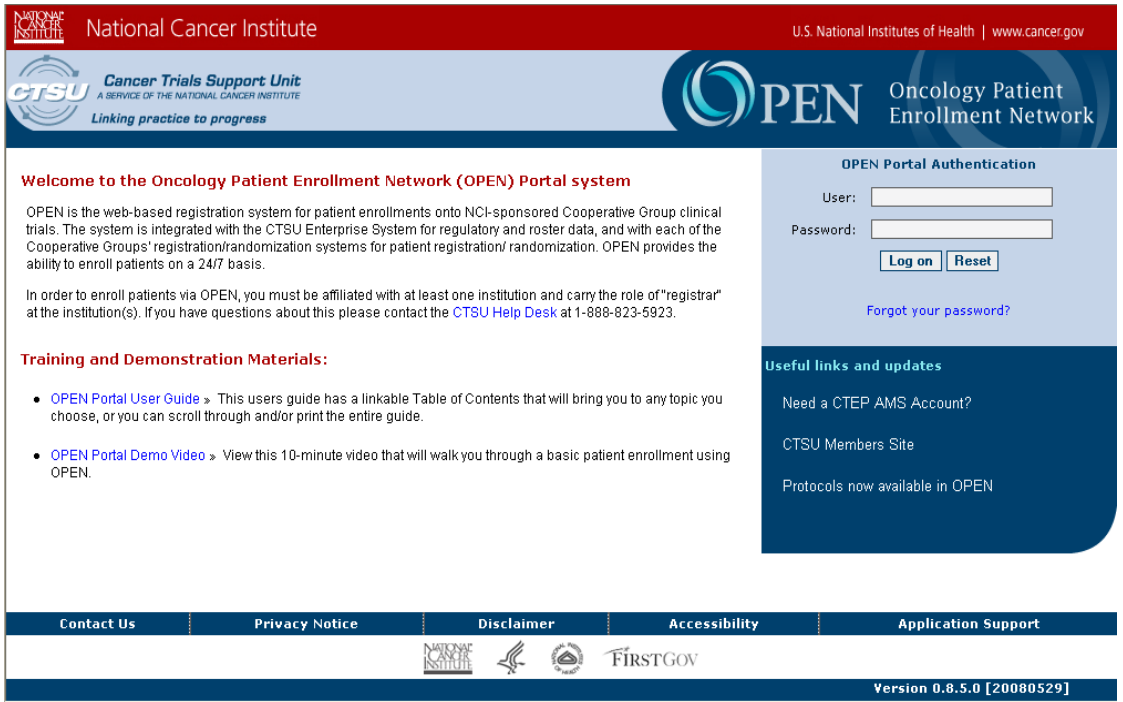
CTSU: A National Infrastructure for Patient Enrollment on NCI-Supported Clinical Trials

Cancer Trials Support Unit (CTSU) has expanded centralized administrative & regulatory functions for clinical trials

- Over 57,000 patients enrolled via CTSU since 2002
- Cross-Group accrual available for all phase 3 & select phase 2 tx trials
- Expansion of services to other NCI trial networks & collaborative trials
- Provides a range of critical services in support of the national system

- ✓ Patient registration
- ✓ Accrual reimbursement
- ✓ Protocol Coordination
- ✓ Clinical Data Operations
- ✓ Regulatory Support Service
- ✓ Financial Management
- ✓ Site Auditing
- ✓ Site QA
- ✓ CTSU Help Desk
- ✓ CTSU Web Site
- ✓ Education & Trial Promotion

As of 2011, 24/7 enrollment for all Group Tx trials



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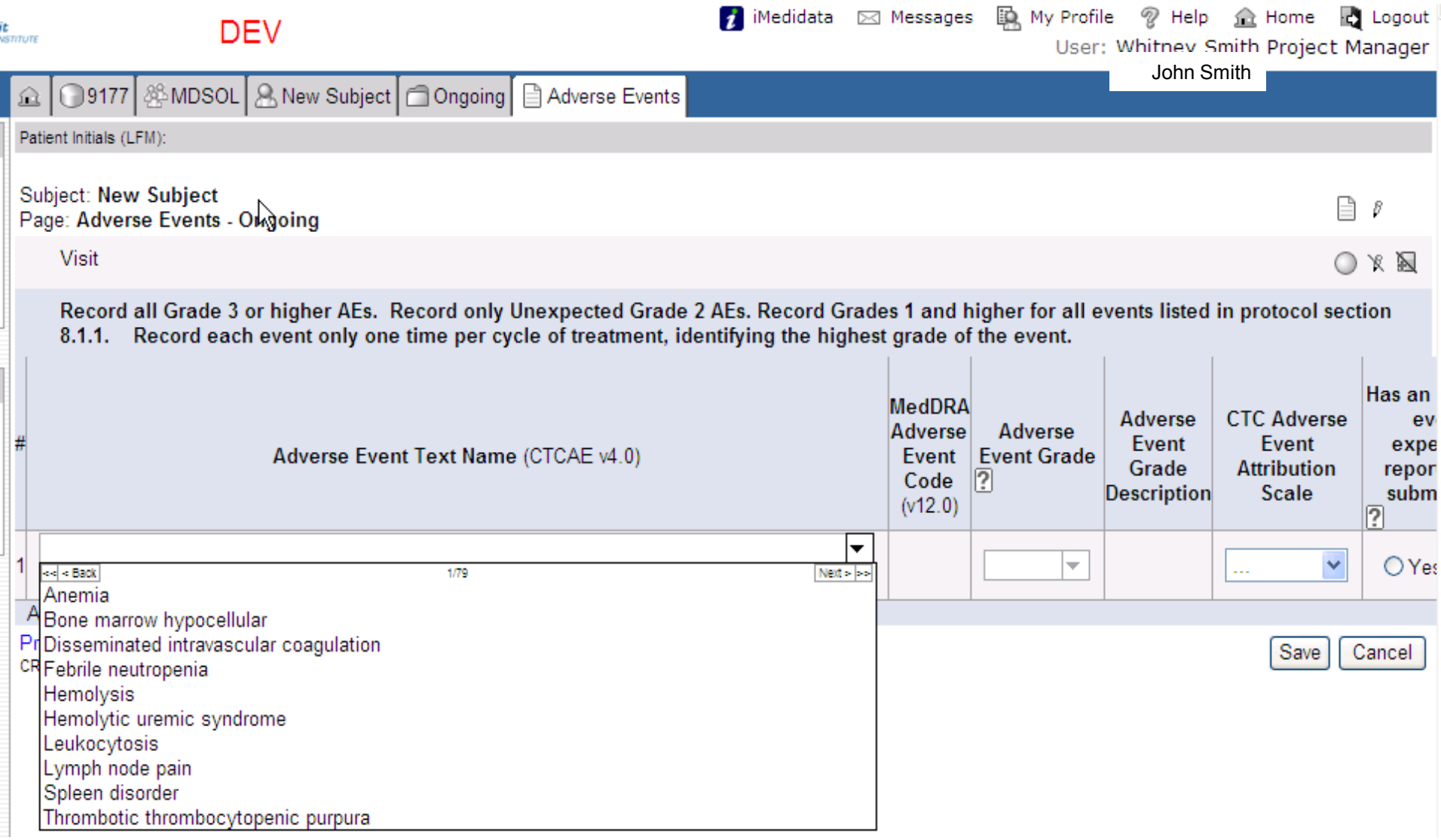
Common IT Data Management System (CDMS)

- **Electronic tool(s) or processes that support**
  - ✓ Data collection: Remote Data Capture (RDC)
  - ✓ Data coding: Standard libraries - Common Toxicity Criteria
  - ✓ Data management: Discrepancy, delinquency, communication, correction & preparation of data for analysis
- **Core benefits of CDMS on NCI-supported multicenter trials**
  - ✓ Reduces training costs & cost of overall cost of data management
  - ✓ Reduces risk of data delinquency and/or discrepancy
  - ✓ Reduces time/effort to correct/complete data
  - ✓ Reduces delays in obtaining Science and Safety results & improves trial management & decision-making
- **Other Benefits to NCI-supported multicenter trials**
  - ✓ Supports/complements transformation of Groups into new 'Network' program
  - ✓ Meets FDA & other Federal requirements for e- data capture, security & transfer
  - ✓ Promotes data sharing
  - ✓ Sets stage for further infrastructure improvements such as integration with expedited Serious AE reporting, remote auditing, electronic filing for FDA reports

Medidata RAVE® Toxicity (Adverse Event) Page



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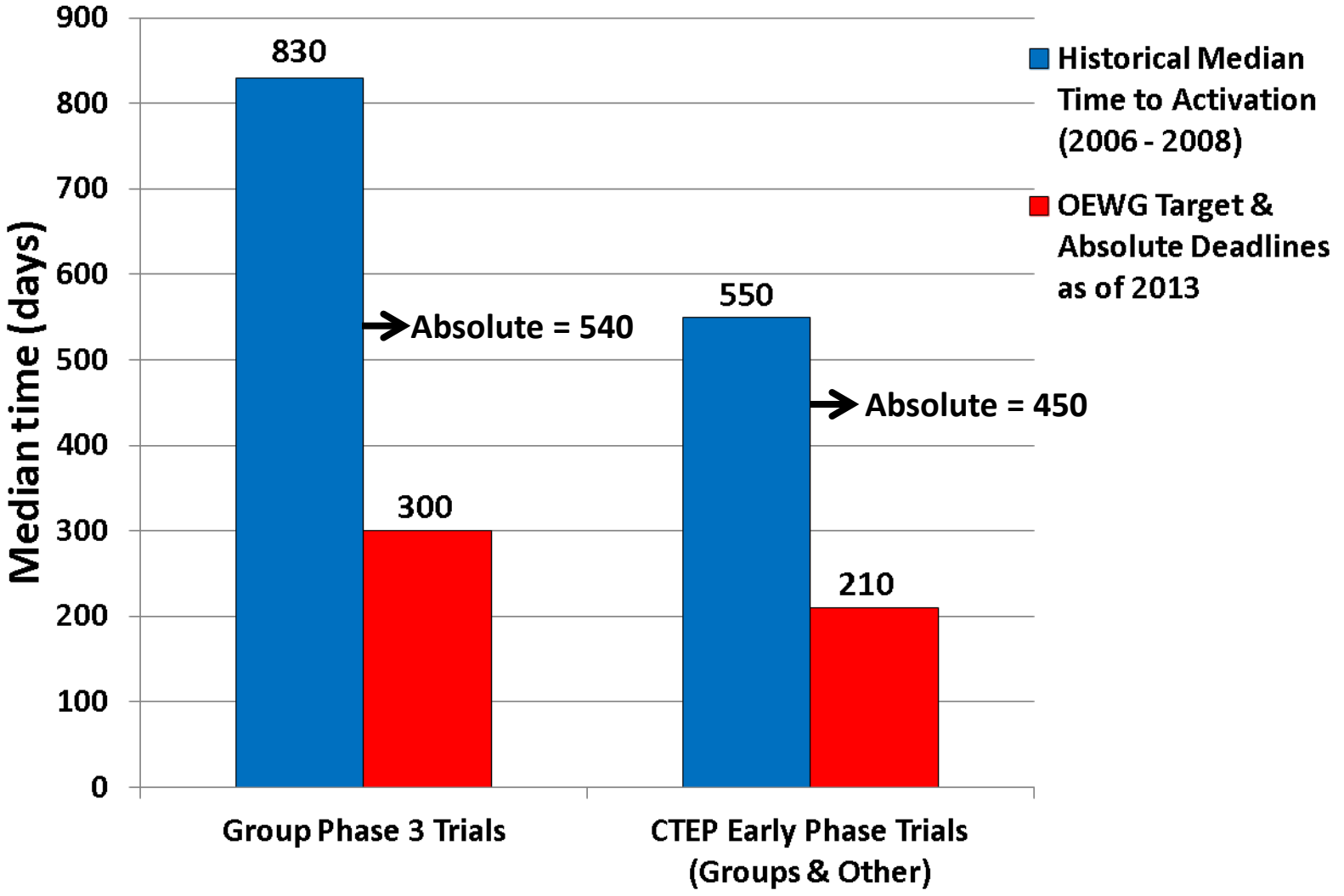
Implementation of Operational Efficiency Timelines



Protocol terminated if absolute timelines not achieved

Update on Implementation

- **In March 2010, the OEWG provided recommendations to the NCI on strategies to decrease the time required to activate NCI-sponsored clinical trials**

- **A major component of the recommendations was the creation of target timelines and absolute deadlines for studies to go from Concept/LOI submission to activation (activation defined as study open to patient enrollment) with revision of absolute deadlines in April 2012**

  - **Phase 1 and 2 Studies:**
    - **Target Timeline – 210 days (7 months)**
    - **Absolute Deadline – ~~540 days~~ Now 450 days (15 months)**

  - **Phase 3 Studies:**
    - **Target Timeline – 300 days (10 months)**
    - **Absolute Deadline – ~~730 days~~ Now 540 days (18 months)**

Comprehensive Changes Undertaken to Improve Trial Initiation Timelines

	Change	Implementation
Target Timeline	**An ideal goal, achievable if all partners function optimally**	**7 months for phase 1-2 trials and 10 months for phase 3 trials**
Absolute Deadline	**An immoveable date by which the trial must be open to patient enrollment**	**18 months for phase 1-2 trials and 24 months for phase 3 trials***
Staffing Additions	**New positions created to manage protocol timelines and to assist physicians with protocol authorship, revisions, and editing**	
Process Improvement	**Implementation of uniform templates for protocol development and for reviewers' comments**	**Requirement for prompt teleconferences to resolve scientific and regulatory review issues at each step of review**
Information Technology	**Creation of a website to track all phases of protocol's life cycle**	

***The absolute timelines were revised in April 2012 to be more stringent – 15 months for phase 1-2 trials and 18 months for phase 3**

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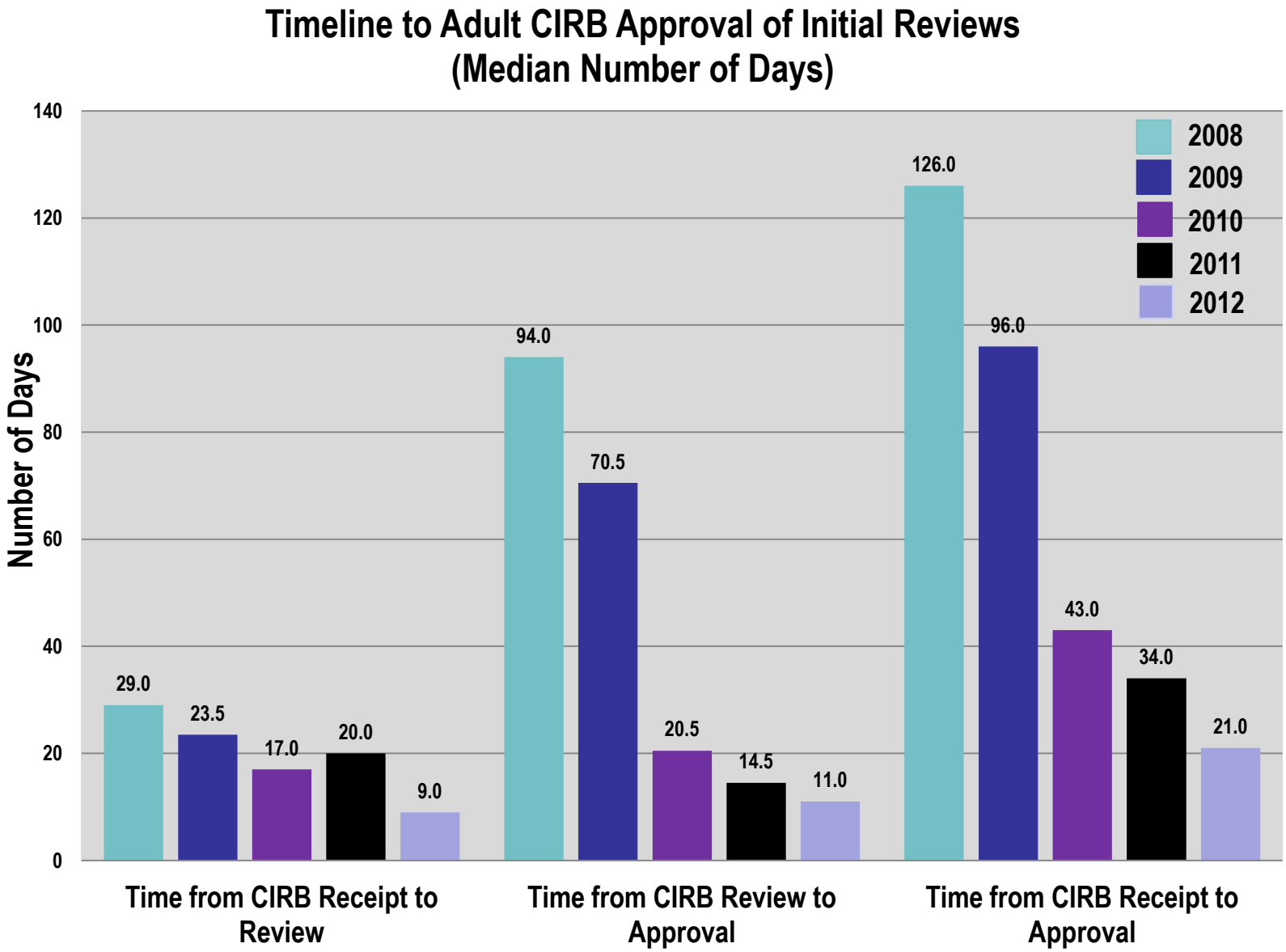
NCI CIRB: Changes in Initial Review Timeline



Intellectual Property Terms for Investigational Agent Combinations

Single Agent Studies

- Collaborator receives a non-exclusive, royalty-free license for internal research purposes only.
- Collaborator has first rights to negotiate an exclusive or non-exclusive royalty-bearing license.

Combination Agent Studies

- Each Collaborator receives a non-exclusive, royalty-free license for all purposes, including commercial purposes, to any combination IP.
- Still can negotiate a co-exclusive or exclusive license for Collaborator agent IP.

Changing Times – Today's Landscape

- Entrance of molecularly targeted agents into clinical trials has changed relationships among parties. Trials depend more on defining targets and developing biomarkers.
- Prior IP Option and most of our collaborative agreements (and funding agreements) were silent as to the disposition of agent-treated human tumor samples and rights related to them. The IP framework surrounding agent-treated samples and the associated clinical data have become increasingly important.

Revised IP Option for CTEP-sponsored Trials

A. The IP Option described in this Section A would apply to inventions that would be described in patent disclosures that claim the use and/or the composition of the Agent(s) and that are conceived or first actually reduced to practice pursuant to clinical or non-clinical studies utilizing the NCI CTEP provided Agent(s)("Section A Inventions"):

(i) a **royalty-free**, worldwide, **non-exclusive license for commercial purposes**; and

(ii) a time-limited **first option to negotiate an exclusive, or co-exclusive**, if applicable, world-wide, **royalty-bearing license for commercial purposes**.

What are examples of Section A Inventions?

- Alternate uses for agents, the “Minoxidil and Viagra” scenarios.
- Dosing schedules, unique administration techniques that improve efficacy.
- In general, inventions that would fall under the scope of Section A would be very rare.

Revised IP Option for CTEP-sponsored Trials

- **B. The IP Option described in this Section B would apply to inventions not covered by Section A, but are nevertheless conceived or first actually reduced to practice pursuant to clinical or non-clinical studies utilizing the CTEP-provided Agent(s). It also applies to inventions that are conceived or first actually reduced to practice pursuant to NCI CTEP-approved studies that use non-publicly available clinical data or specimens from patients treated with the CTEP-provided Agent (including specimens obtained from NCI CTEP-funded tissue banks) ("Section B Inventions").**

Revised IP Option (continued)

- (i) **Nonexclusive**, nontransferable, **royalty-free**, world-wide license to all Institution Inventions for **research purposes only**; and
- (ii) "A nonexclusive, royalty-free, world-wide license to disclose and to promote Section B Inventions that are necessary or required by a regulatory authority for marketing authorization of the Agent or required to be on a product insert or other promotional material regarding the Agent or useful for informing Healthcare providers and patients regarding use of the Agent"

What are examples of Section B Inventions?

- Assays/Diagnostics – Possibly broad in array
- New scientific methods or techniques
- The scope of inventive material is much broader under Section B, however the license grant is much narrower.

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Molecular Profiling in NCI-sponsored Clinical Treatment Trials

DCTD, CCG, CBIIT, OD

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Two examples

- ALCHEMIST
- Master Protocol in Advanced Lung Cancer

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ALChEMIST

Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial

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Drug Biomarkers in Lung Adenocarcinoma

TKI-sensitizing EGFR mutations:

10% in Western population

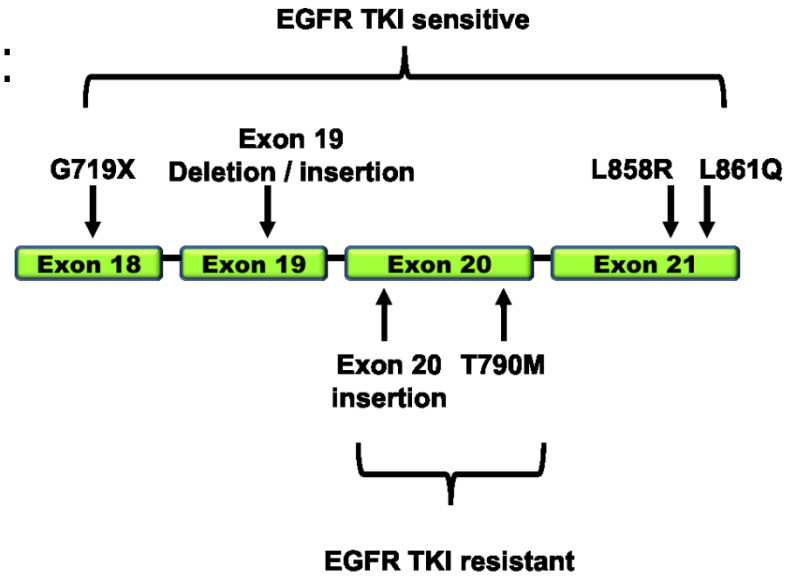
Up to 50% in Asian population

Enriched in:

- females
- non-smokers
- younger patients

Multiple tests in clinical use

No FDA-approved clinical assay

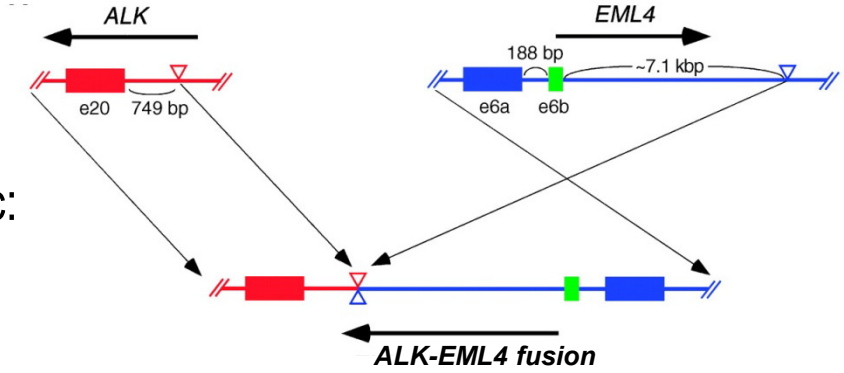


ALK Rearrangement

5-7% in Western population

FDA approved companion diagnostic:

Vysis Break Apart FISH probe



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National Trial for Molecular Characterization of Early Stage, Adenocarcinoma of the Lung

Eligibility:

- Diagnosis of Adenocarcinoma
- Clinical stage I, II, or III deemed resectable
- Pathologic stage I, II, or III that:
    - has been successfully resected
    - adequate tissue available
    - +/- local test for EGFR mutation or ALK rearrangement
- Patient Consent to allow
    - donation of de-identified cancer information for research
    - performance of central testing for adjuvant study referral
    - 5 year follow-up: treatment and outcome
    - contact regarding follow-up biopsy if cancer recurs
    - (optionally) re-contact if no recurrence at end of study

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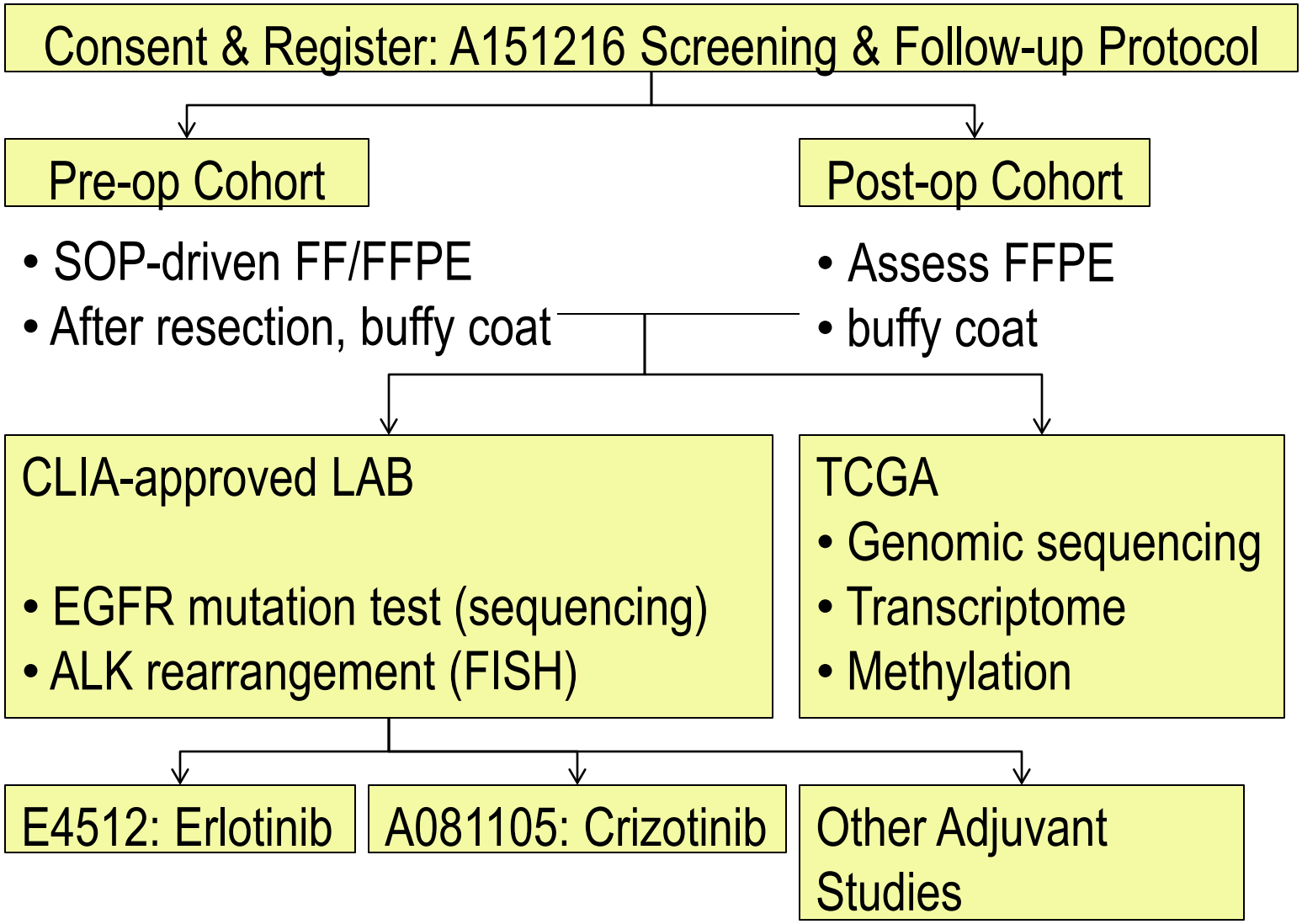
Tissue Flow



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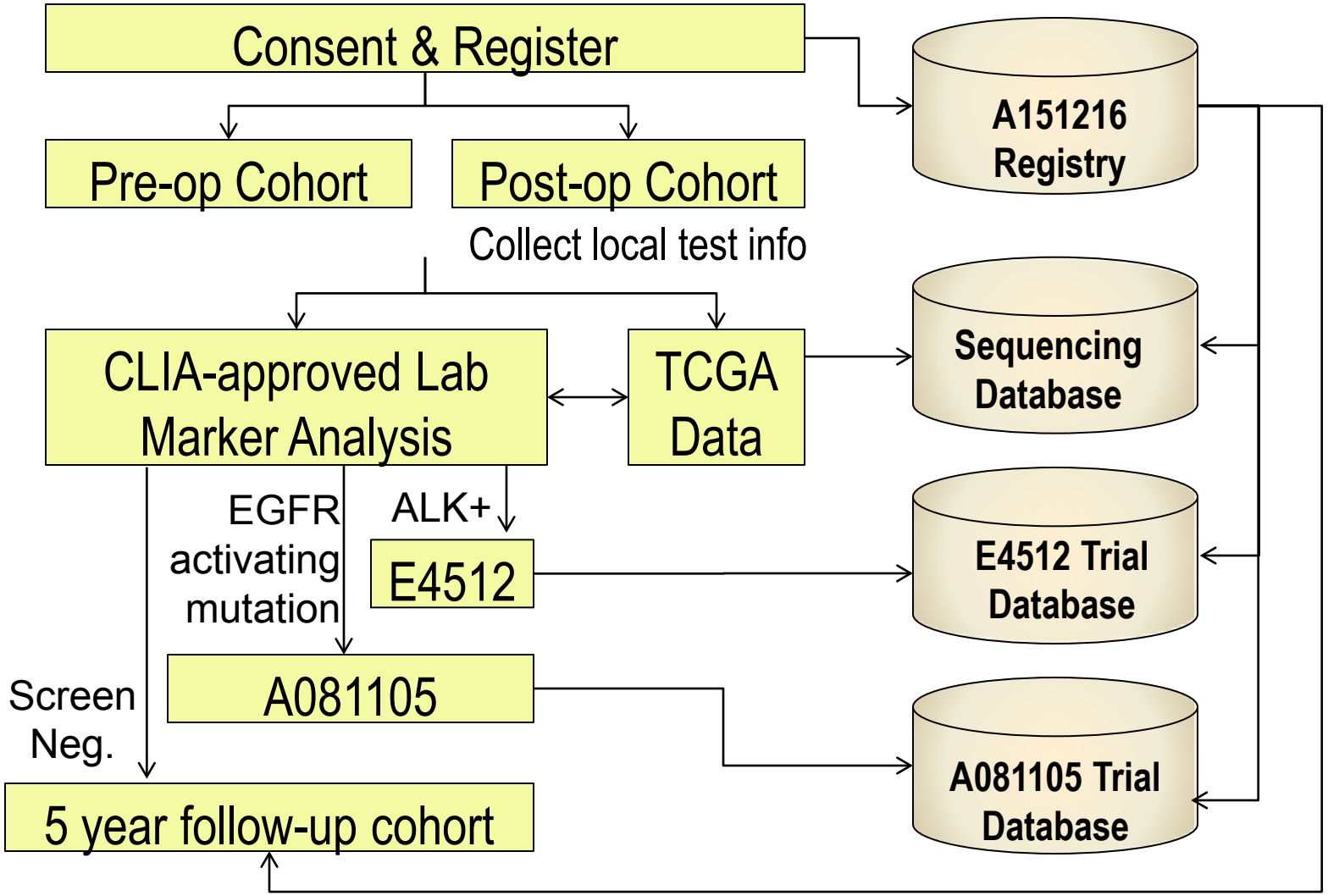
Data Flow



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ALChEMIST – Beyond Treatment Endpoints

- Opportunity to collect epidemiologic info spanning tobacco, diet, alcohol and work exposures
- TCGA (GDAC centers) to perform molecular profiling studies on large cohort (~ 7000 pts) with ability to re-profile at relapse in about 50% (“natural genomic history”)
- Opportunity to develop a molecular profiling report for physicians that will meet with FDA approval
- Development of approach to sharing unexpected germline mutations for cancer risk with patients screened in this trial

Master Protocol: Advanced NSCLC

- Multi-arm, multi-marker/drug “master protocol” Phase 2-3 trial
  - Randomized, Controlled
  - Multiple new therapies are tested simultaneously in a specific disease setting
  - Designed to allow FDA approval of new therapeutics
  - Assigns patients to experimental treatment vs standard-of-care control arm on the basis of specific biomarkers

Advantages of Master Protocol Multi-Drug Registration Trial Design

- Grouping multiple studies reduces the overall screen failure rate
- Single master protocol will result in process and operational efficiency gains
  - Provides consistency
  - Trial infrastructure will be in place
  - Bring safe and effective drugs to patients faster

Trial Design – Drugs and Biomarkers

- A trial steering committee will evaluate each application to determine whether a drug/biomarker pair can enter the trial
- **Drugs**
  - Ready to enter a phase 2-3 confirmatory trial
  - **Each drug must have clinical data demonstrating activity in a responsive patient group**
  - Patient group can be identified by assessment of biomarker in patient tumor biopsies

Trial Design – Biomarkers and Screening

- **Each compound's biomarker is based on analytically validated test/platform** suitable for a pivotal trial
- This trial could use common screening platform that assays multiple biomarkers
  - If predictive biomarker is in a CLIA-approved platform, it could be considered adequate for patient selection and randomization
    - **Would require Investigational Device Exemption (IDE) prior to trial start**
    - **If new drug shows clinical benefit in selected patient population the biomarker could be analyzed and given FDA clearance**

Lung Cancer: Example Squamous Cell Carcinoma Mutation Incidence

Gene	Event Type	Frequency
FGFR1	Amplification	20-25%
FGFR2	Mutation	5%
PIK3CA	Mutation	9%
PTEN	Mutation-Deletion	18%
CCND1	Amplification	8%
CDKN2A	Deletion/Mutation	45%
PDGFRA	Amplification-Mutation	9%
EGFR	Amplification	10%
MCL1	Amplification	10%
BRAF	Mutation	3%
DDR2	Mutation	4%
MET	High copy-amplification	11%
ERBB2	Amplification	2%

Use of a Multi-marker Platform

- Advantages
  - Conserves tumor samples
  - Testing protocols easier to standardize
  - Sponsors would not be responsible for designing their own diagnostic
- Considerations
  - Have not yet been used in registration trial
  - The process **would require close communication with the FDA** to determine its applicability

Master Protocol Multi-Drug Phase 2/3 Design