Overview of the Experimental Therapeutics Clinical Trials Network (ETCTN)

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NIH NATIONAL CANCER INSTITUTE

Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute, National Institutes of Health

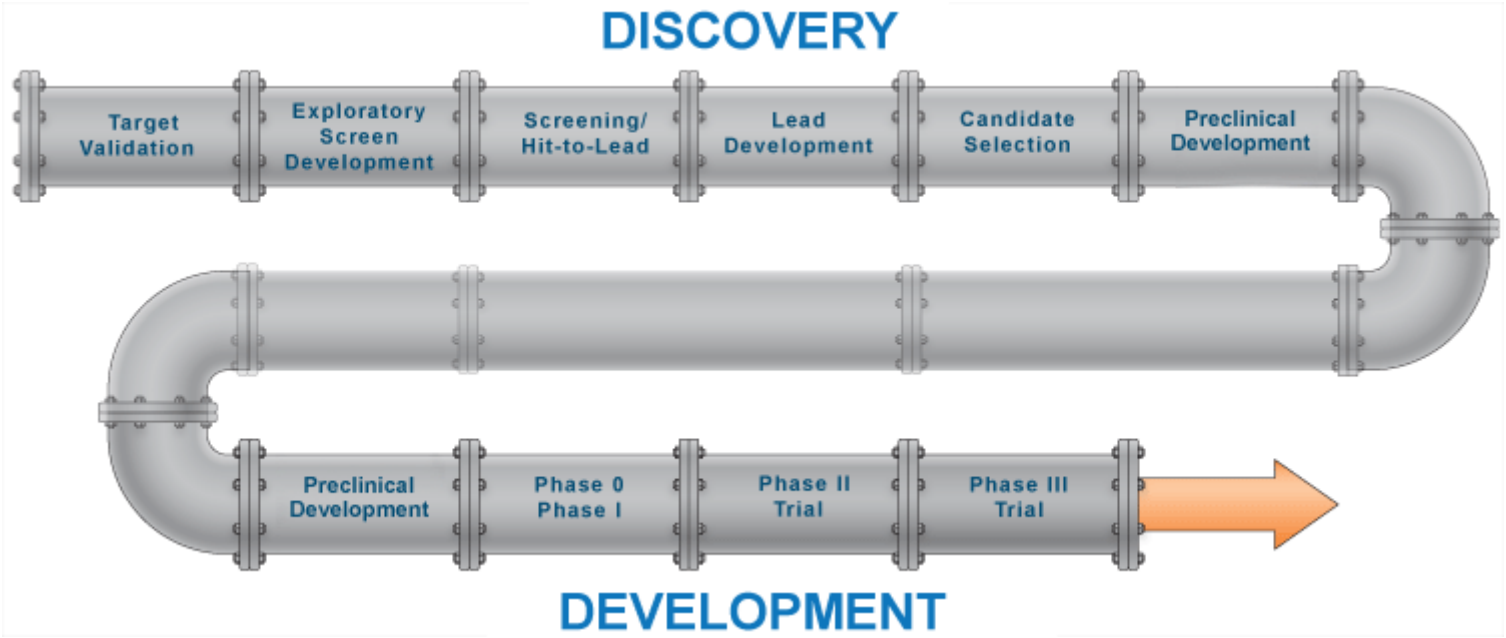
National Cancer Institute's Overall Drug Development Program

Cancer Therapy Evaluation Program (CTEP)

Role for the Experimental Therapeutics Clinical Trials Network (ETCTN)

- **For over seven decades,** NCI has done drug development and discovery in the public interest.
- **For over five decades**, NCI has coordinated relationships between Industry and Academia to help develop new cancer drugs.

- In the current iteration of this effort, two programs run in sequence to manage a portfolio of partnerships between NCI and Industry or Academia.
- **NCI Experimental Therapeutics (NExT) Program** is the program that selects agents for NCI-sponsored pre-clinical and clinical development.



- The **Experimental Therapeutics Clinical Trials Network (ETCTN)** is the clinical trials network that performs clinical studies of agents that are approved through NExT.
- In these partnerships, NCI
  - Assumes the regulatory responsibility for the trials (IND holder)
  - Pays for the clinical trials through cooperative grants (UM1) to ETCTN clinical trial sites
  - Works with ETCTN investigators and industry/academia partners to formulate the clinical development plan for the agent

- CTEP has access to novel agents from industry competitors, and therefore, can act as an honest broker for novel drug combination studies.
- Industry realizes that there are potential therapeutic indications that do not have high enough priority to compete for limited corporate resources.
- CTEP can expend public funds for clinical trials and regulatory support to advance the development of agents owned by Industry.
- CTEP has a network of experienced early-phase clinical trial investigators engaging its centralized clinical trial support systems.
- CTEP invests in correlative science studies to explore the pharmacodynamics of agents in clinical studies.

NCI: Why Extend Effort to Assist Industry Develop Its Agents

- NCI recognizes that there is a significant public interest in finding indications for new oncology drugs beyond those that may be the most profitable.
- NCI can advance the understanding of cancer biology and treatment through carefully designed clinical trials and through the correlative studies that are frequently and extensively incorporated into CTEP-sponsored ETCTN trials.

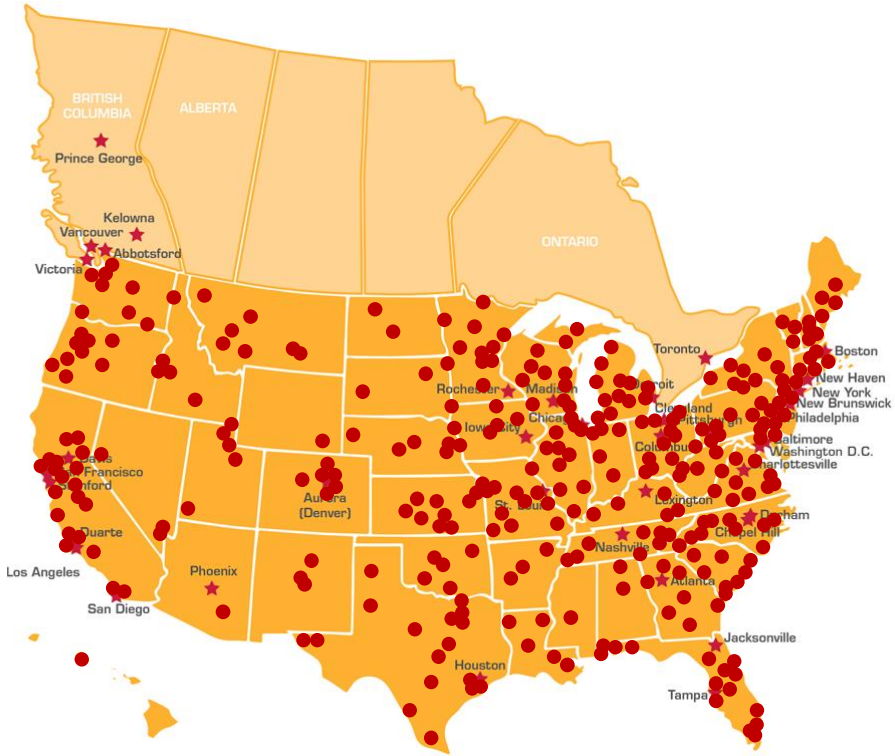
Goals and Objectives of the ETCTN

Cancer Therapy Evaluation Program (CTEP)

CTEP: Goals and Objectives of the ETCTN

- **Research and Develop New Cancer Treatments**
  - Explore dose and schedule in early treatment trials
  - Conduct trials of novel combination therapies
- **Study Tumor Characterization in Biomarker-driven Studies**
  - Interrogate molecular characterization: expression, sequence, and epigenetics
  - Validate biomarker assays in qualified laboratories
  - Incorporate functional imagining
- **Provide Enhanced Understanding of Cancer Biology**
- **Offer Education and Training for Early Career Investigators**

CTEP: Clinical Trials Networks



- Experimental Therapeutics Clinical Trials Network (ETCTN)
  - Studies phase 0, 1, or 2 clinical trials with biologic endpoints

★ Lead Academic Organization (LAO, 12) or affiliate (41) ○ Early Drug Development Opportunity Program (15)

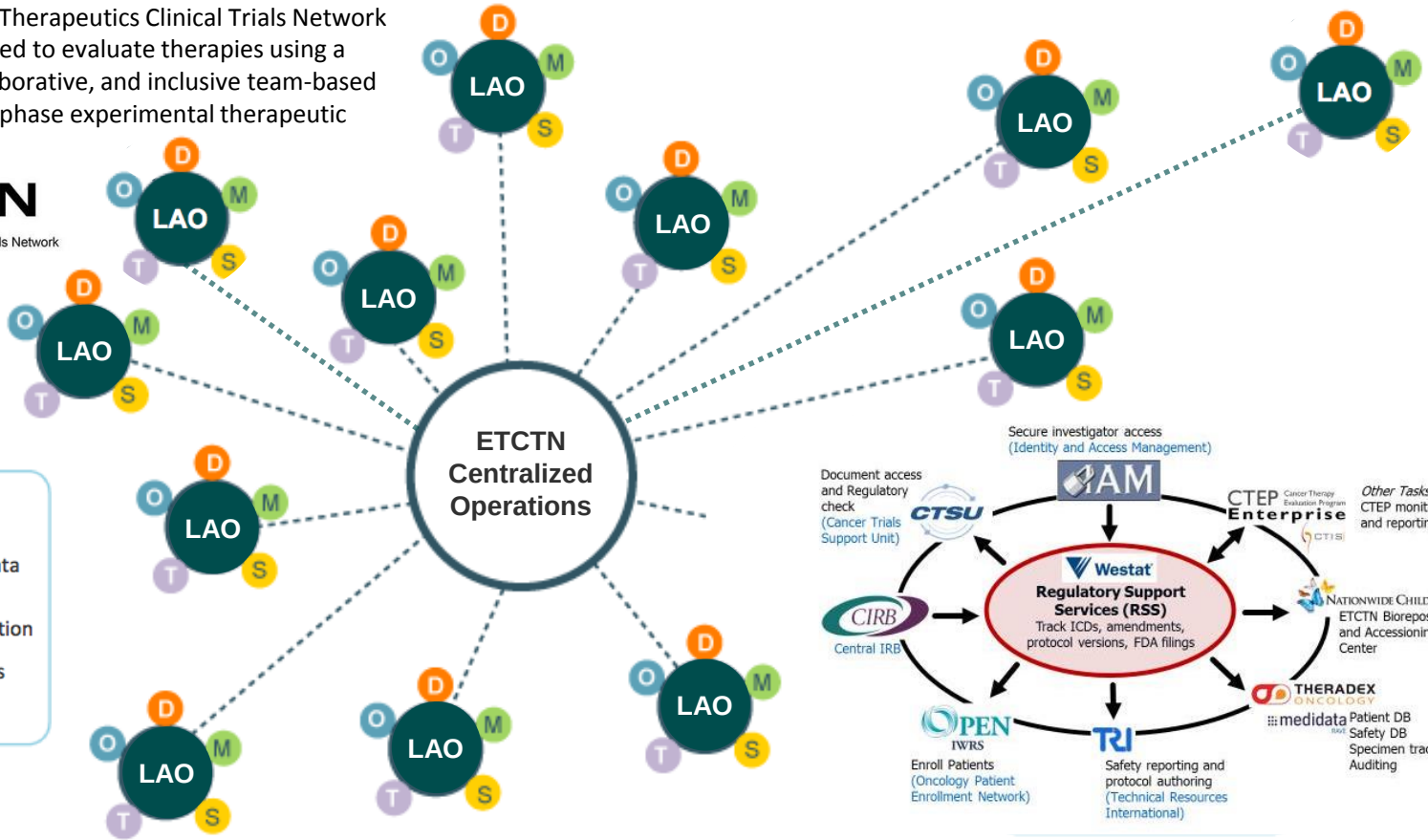
- National Clinical Trials Network (NCTN) – cooperative groups
  - Studies randomized phase 2 or 3 clinical trials with clinical endpoints

- Institutions include members of—Adult Brain Tumor Consortium (ABTC), Pediatric Brain Tumor Consortium (PBTC), and Cancer Immunotherapy Trials Network (CITN), NCI Community Oncology Program (NCORP)

CTEP: Experimental Therapeutics Clinical Trials Network (ETCTN) & Lead Academic Organization (LAO) infrastructure

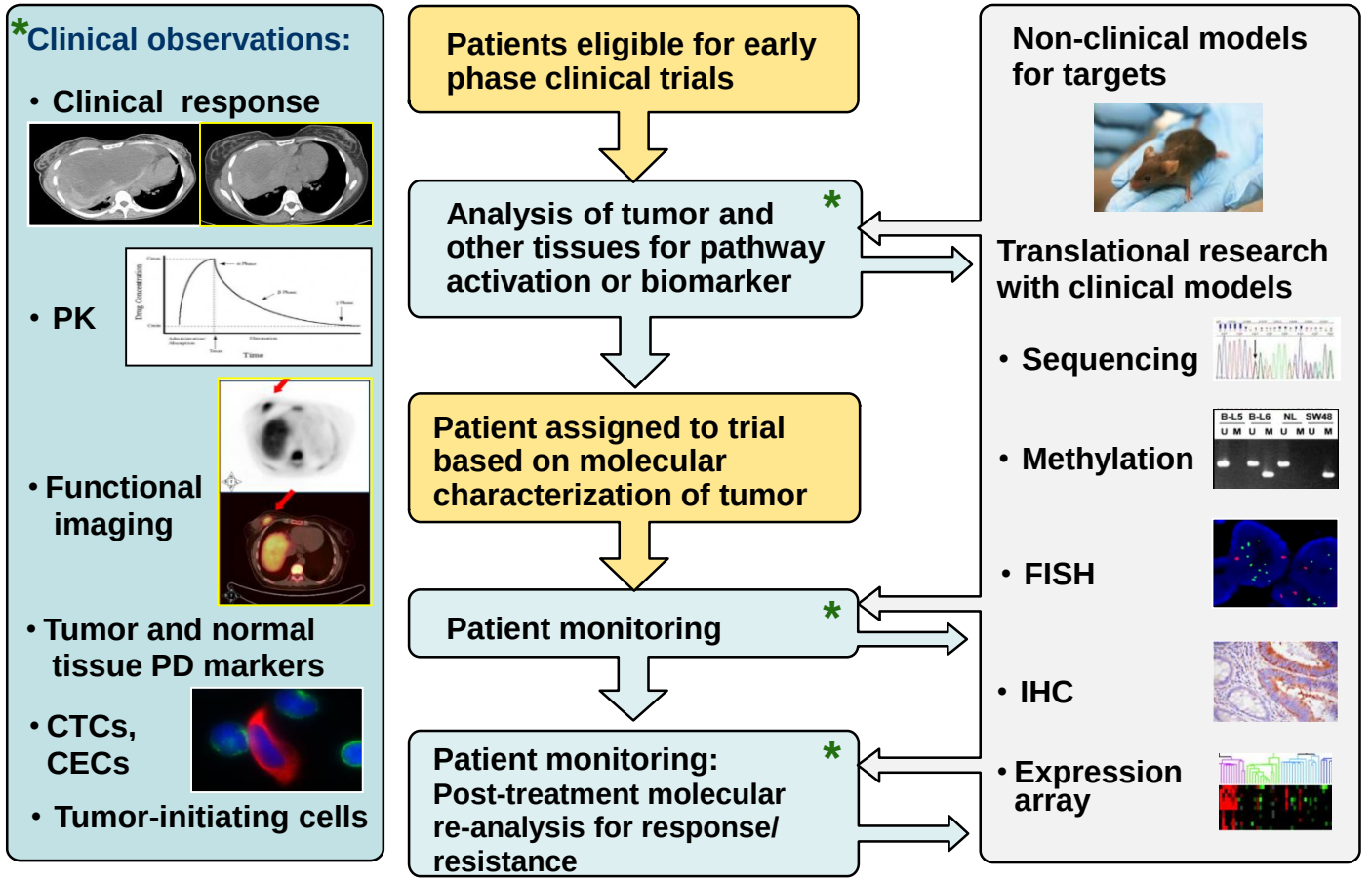
- The Experimental Therapeutics Clinical Trials Network (ETCTN) was created to evaluate therapies using a coordinated, collaborative, and inclusive team-based approach to early phase experimental therapeutic clinical trials.

ETCTN
Experimental Therapeutics Clinical Trials Network



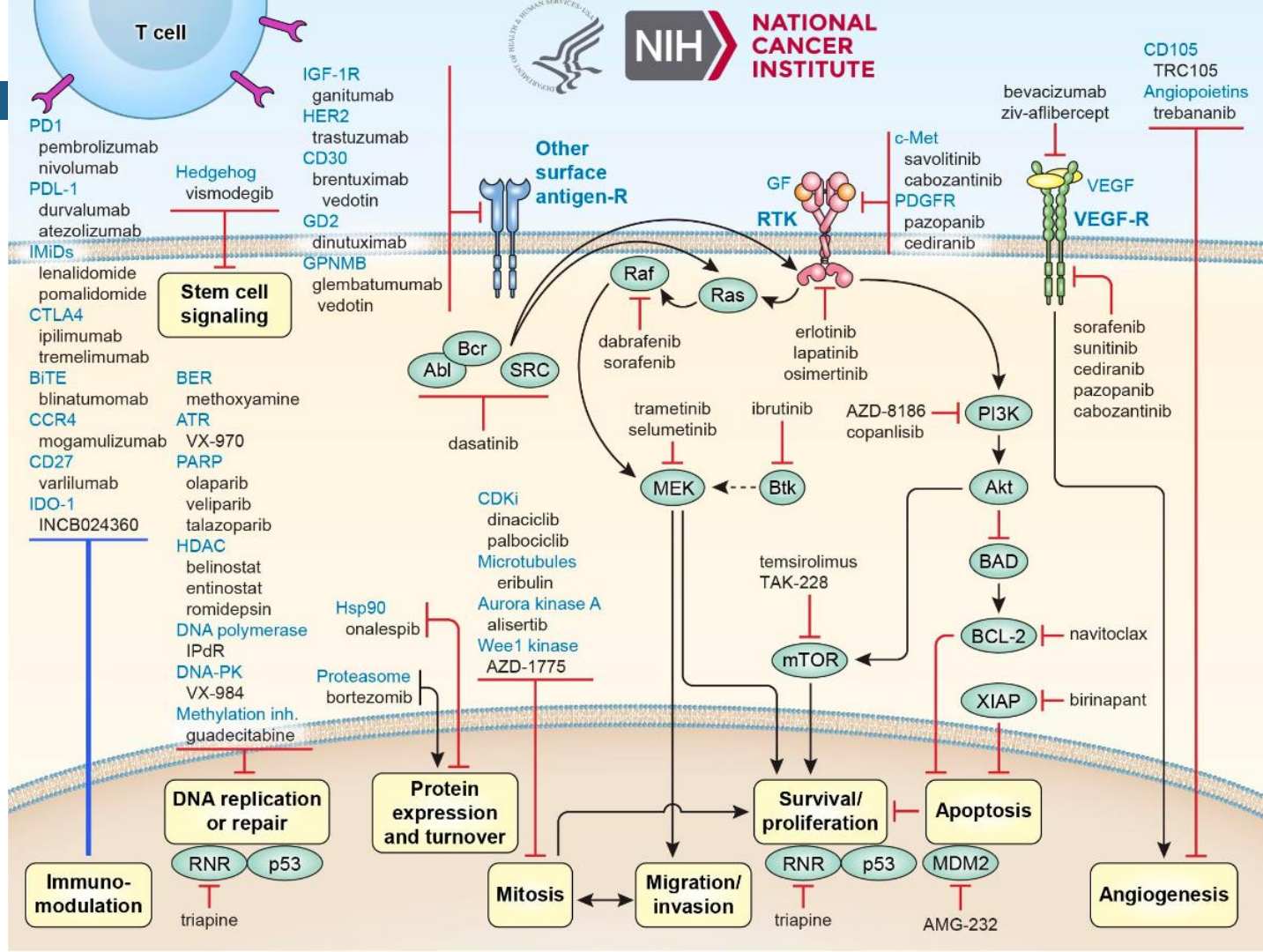
CTEP: Clinical Translational Research and Cancer Biology—Bedside to Bench and Back Again

- The objectives of the ETCTN are to:
- Conduct early clinical trials of NCI-IND agents in high priority areas of unmet medical needs
- Ensure efficient and timely activation and conduct of these clinical trials
- Integrate preclinical findings using clinical samples for biomarker analysis
- Promote collaboration among institutions and investigators
- Integrate molecular characterization, pharmacology, cancer biology, and imaging into clinical trials



CTEP: Current Portfolio

- 72 active agents under cooperative research and development agreement (CRADA)
- https://ctep.cancer.gov/industryCollaborations2/agreements_agents.htm



CTEP: Project Team Basics—sets the initial clinical development and biomarker plan for a new NExT agent

Step **1**

Project Team Formation

Step **1.1**

Project Team Member Applications Submitted

Available Roles:

A. Clinical Scientist
B. Translational Scientist
C. Clinical Pharmacologist
D. Cancer Biologist

Step **1.2**

CTEP Medical Officer Reviews Applications

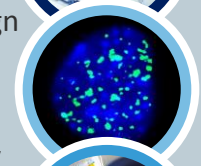
Step **1.3**

CTEP Selects Team Members

Step **1.4**

Initial Project Team WebEx Calls

Design



Biology

Pharmacology

Step **1.5**

Individual Project WebEx Calls

Step **1.6**

Investigational Drug Steering Committee Reviews Individual Projects

CTEP: Career Enhancement & Development for Early Career Investigators (03.2014 to 01.2018)

Activity	Number of LOIs (%)
Project Teams	13
Letters Of Intent (LOIs) solicited from Project Teams with an Early Career Investigator	45 (90)
LOIs with an Early Career Investigator 03.2014-01.2018	110 (45)
Unsolicited or pre-solicitation LOIs with an Early Career Investigator	60 (31)
Activated or transitioned ETCTN protocol with an Early Career Investigator	44 (60)

A Day in the Life of a ETCTN Trial Document

Cancer Therapy Evaluation Program (CTEP)

CTEP: Centralized Letter of Intent (LOI) Pathway Submission

Path: **PROJECT TEAM**
Letter of Intent (Solicited)

PHASE 1, 2, or 1/2
LETTER OF INTENT
Submission Form v8.1

National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

To complete the form electronically, use the mouse pointer or the Tab key to navigate. Select and enter text for each text field.

Lead LAO/Group/Institution[1]:	[Click and enter Lead LAO/Group; use Institution for non-ETCTN/non-Group trials]
Lead LAO/Group/Institution Code[1,2]:	[Click and enter Lead LAO/Group Code; use Institution Code for non-ETCTN/non-Group trials ONLY]
Other LAOs or Trial Team Sites[1,2]:	[Click and enter other LAOs, other Groups, and any non-LAO/non-Group Clinical Site/Institution Codes; list sites outside USA separately by country. If trial will involve all ETCTN LAOs, write "All ETCTN LAOs" (no codes needed)]
Title of LOI :	[Click here to enter Title]
LOI Version Submission Date:	[Click here to enter Date of submission to PIO]

Agent Information[2] *(duplicate rows as needed)*:	Name	NSC #	Source	Investigational?
Agent #1:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]
Agent #2:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]
Agent #3:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]
Agent #4:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]

Tumor Type: *(Click within the [ ] and type 'x' to indicate the tumor type)*	[ ] Solid Tumor [ ] Hematologic Malignancy (NOS) [ ] Disease-Specific
Disease-Specific[2]: *(Specify the Name and Code of the Study Disease)*	1. [Click and enter Disease Name] [Click and enter Disease Code] 2. [Click and enter Disease Name] [Click and enter Disease Code] 3. [Click and enter Disease Name] [Click and enter Disease Code]
Phase of Study:	[Click and enter Study Phase]
Estimated Monthly Accrual: *(**Note**: Projected accrual rates should be realistic. Actual accrual will be monitored and measured against this accrual estimate, and failure to meet accrual goals may result in study closure.)*	[Click and enter Accrual]
Proposed Sample Size:	Minimum: [Click and enter Size] Maximum: [Click and enter Size]
Earliest date the study can begin:	[Click and enter Date]
Projected Accrual Dates:	[Click and enter Date] to [Click and enter Date]

- There are two paths for CTEP support of clinical development ideas—Project Teams or Unsolicited Trials.

Competitive LOIs :

2

Test combinations in two disease-relevant cell lines

2

Test combinations in two disease-relevant xenograft models

Path: **UNSOLICITED TRIAL**
Letter of Intent (Unsolicited)

PHASE 1, 2, or 1/2
LETTER OF INTENT
Submission Form v8.1

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Lead LAO/Group/Institution Code[1,2]:	[Click and enter Lead LAO/Group Code; use Institution Code for non-ETCTN/non-Group trials ONLY]
Other LAOs or Trial Team Sites[1,2]:	[Click and enter other LAOs, other Groups, and any non-LAO/non-Group Clinical Site/Institution Codes; list sites outside USA separately by country. If trial will involve all ETCTN LAOs, write "All ETCTN LAOs" (no codes needed)]
Title of LOI :	[Click here to enter Title]
LOI Version Submission Date:	[Click here to enter Date of submission to PIO]

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Agent #3:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]
Agent #4:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]

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Phase of Study:	[Click and enter Study Phase]
Estimated Monthly Accrual: *(**Note**: Projected accrual rates should be realistic. Actual accrual will be monitored and measured against this accrual estimate, and failure to meet accrual goals may result in study closure.)*	[Click and enter Accrual]
Proposed Sample Size:	Minimum: [Click and enter Size] Maximum: [Click and enter Size]
Earliest date the study can begin:	[Click and enter Date]
Projected Accrual Dates:	[Click and enter Date] to [Click and enter Date]

CTEP: Document Workflows for ETCTN Letters of Intent (LOI)

Lead Protocol Organization	Contract Support (Interface between CTEP and Investigators)	CTEP Review	Additional Reviews (SC/BRC/CIRB/FDA)

Step **1**
Develop LOI

Step **4** Revise

Step **2** PIO* Reviews, Accepts, or Requests Changes

Step **3** **(LOI OEWG Start)**
Review in Protocol Review Committee For Decision

Step **3A** Review by Steering Committee

Revise & Resubmit

Disapprove **Approve**

Step **5** Review by Biomarker Review Committee

LOI/Concept Ends

Send Disapproval Letter

Step **6**
Develop Protocol
with ETCTN Centralized Protocol Writing Support (CPWS)

Send Approval Letter

*PIO = CTEP Protocol Information Office

CTEP: Centralized Protocol Writing Support (CPWS) Program

Lead Protocol Organization	Contract Support (Interface between CTEP and Investigators)	CTEP Review	Additional Reviews (SC/BRC/CIRB/FDA)

Step **7**
Develop Protocol
(after CTEP receives a drug commitment letter)

- The Centralized Protocol Writing Support (CPWS) Program was created to streamline the development of ETCTN protocol from LOI approval to protocol activation.

Step **7A**
CPWS Writes Initial Draft Protocol

Step **7B**
Teleconference

Step **7C**
Provide Clinical Data & Any Feedback

Step **7D**
Incorporate Clinical Data & Any Feedback

Step **7E**
Review & Approve

Approve Final

Step **8** ETCTN
CPWS protocol

CTEP: Document Workflows for Letters of Intent (LOI) or Concepts

ctep.cancer.gov

Lead Protocol Organization	Contract Support (Interface between CTEP and Investigators)	CTEP Review	Additional Reviews (SC/BRC/CIRB/FDA)

Step **8** ETCTN
CPWS protocol

Step **9** PIO Reviews, Accepts, or Requests Changes

Step **10**
Review in Protocol Review Committee For Decision

Step **11** Revise

Revise & Resubmit
Disapprove Approve

Step **12** Review by FDA, CIRB, BRC

Send Disapproval Letter

Protocol Ends

Step **13**
Activate Protocol

Amend Protocol

Send Approval Letter

Step **13A** PIO Reviews, Accepts, or Requests Changes to Amendment for Review

Step **13B**
Review in Protocol Review Committee For Decision

Revise & Resubmit
Disapprove Approve

Send Disapproval Letter

Activate Protocol

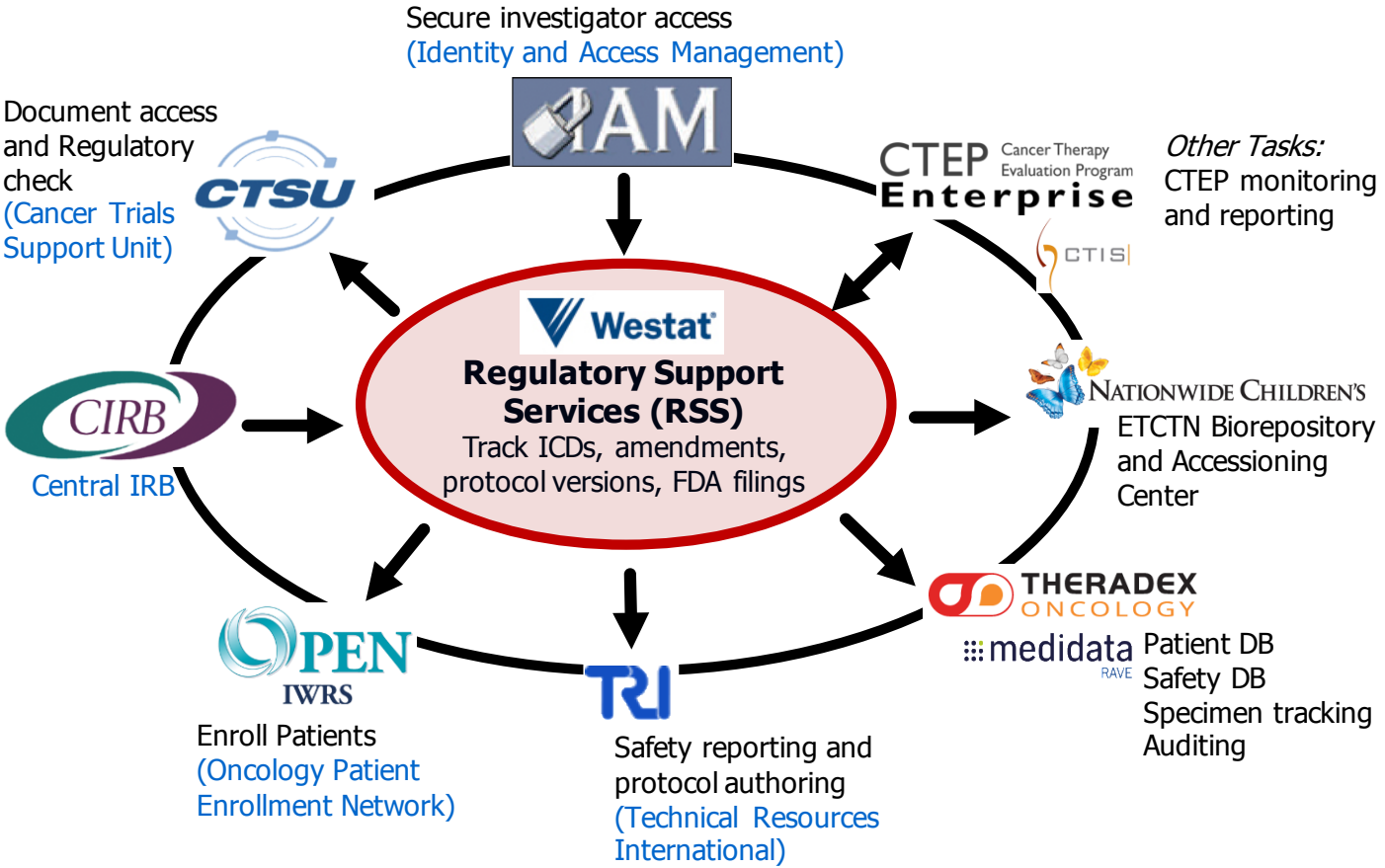
CTEP: What Challenges face the ETCTN?

- **Accrual**
  - Smaller patient populations to study arise due to molecularly-defined diseases
  - Need of a scalable/flexible program that can rapidly adapt to recruitment gaps
- **Biomarker-driven studies**
  - Tissue acquisition hurdles
  - Fit-for-purpose, validated assays
  - Functional imaging
- **Driving discovery to patients**
  - To and from bench to bedside collaborations
  - More predictive animal models to evaluate tumor heterogeneity

Sponsored Infrastructure

Cancer Therapy Evaluation Program (CTEP)

CTEP: ETCTN Supported Infrastructure



Medidata Rave

Cancer Therapy Evaluation Program (CTEP)

CTEP: ETCTN Medidata Rave

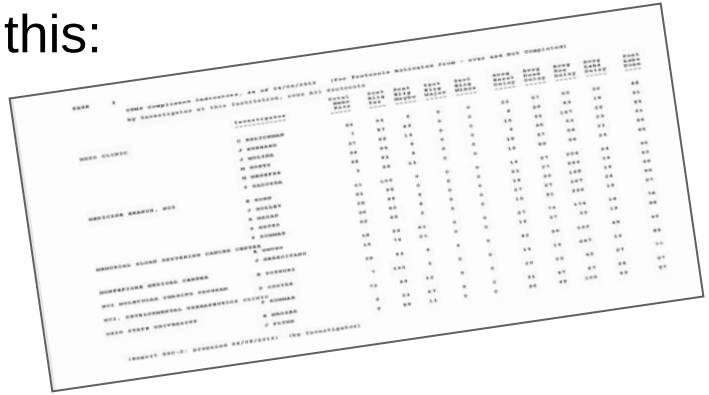
- Web based electronic data collection (EDC) to be used in all current and future CTEP studies
- CTEP-IAM account (user name and password) required to access Rave; must also have one of the Rave-specific roles identified.
  - Users must also be on the ETCTN site roster of a participating organization and have approval for a given trial at their site to manage data in Rave.
- All ETCTN studies will use the same standard Theradex eCRFs resulting in expedited study set-up following approval
- Built-in, real-time edit checks will minimize queries and after-the-fact data cleaning
- Queries entered by CTMS monitors and auditors can be resolved within Rave by site staff

Web Reporting

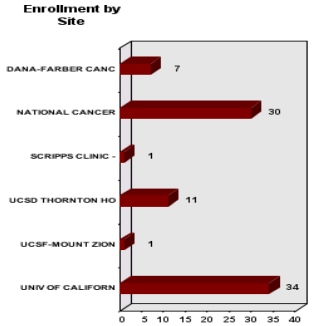
Cancer Therapy Evaluation Program (CTEP)

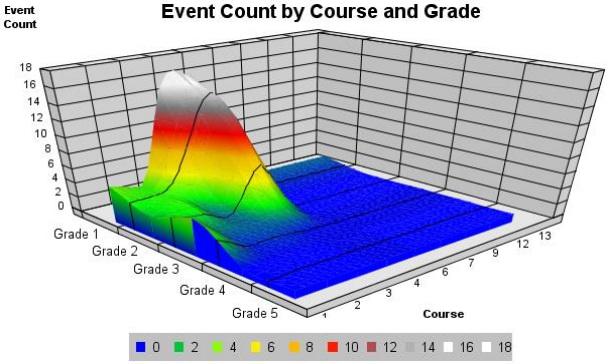
On August 1, 2013, Paper Reports were retired!

No more of this:



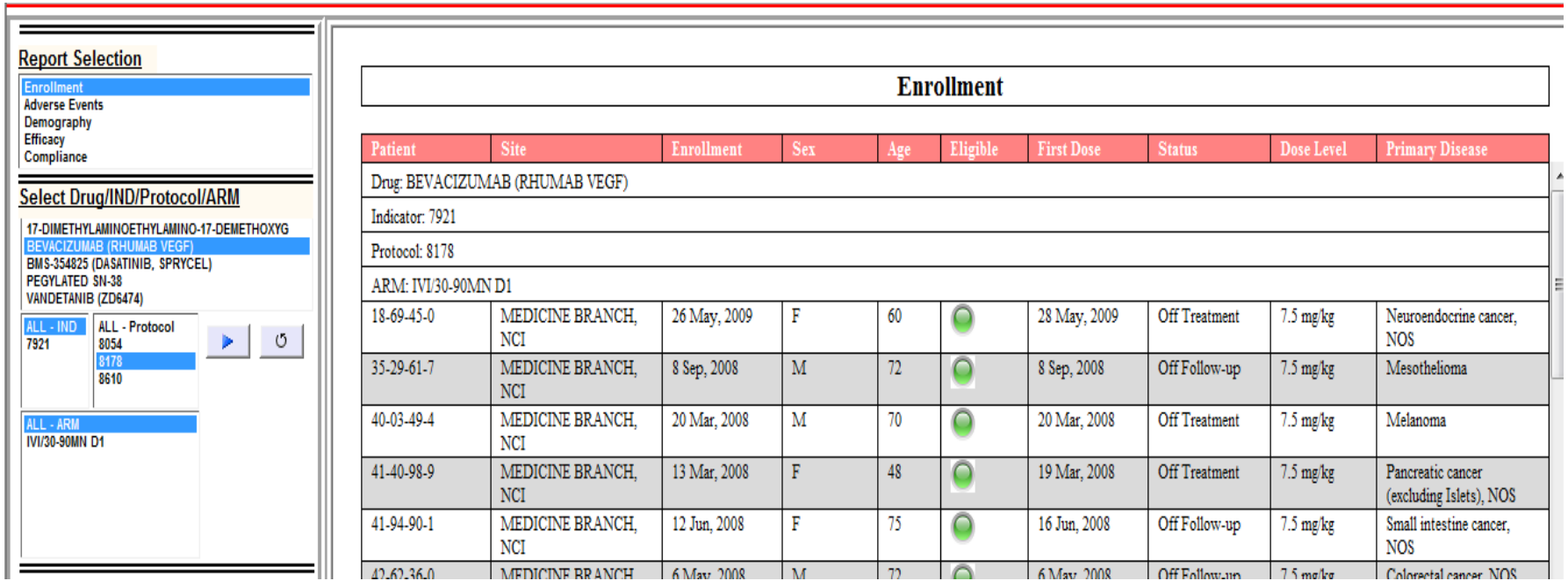
Now you can generate reports like this:





Compliance Overall for a Protocol

	Value	Percent
Number of Patients	51	
Number of Courses	101	
Investigator Eligible Patients	50	98.0%
Investigator Ineligible Patients	1	2.0%
Monitor Eligible Patients	49	96.1%
Monitor Ineligible Patients	2	3.9%
Monitor Missing Info	0	0.0%
Courses Evaluable	96	95.0%
Courses Complete	85	84.2%
Courses with Dose Modifications	47	46.5%
Courses with Significant Toxicities	70	69.3%
Average Lab Delay (Days)	69	
Labs Completed per Protocol	9644	81.3%



Enrollment

Patient	Site	Enrollment	Sex	Age	Eligible	First Dose	Status	Dose Level	Primary Disease
Drug: BEVACIZUMAB (RHUMAB VEGF)									
Indicator: 7921									
Protocol: 8178									
ARM: IVI/30-90MN D1									
18-69-45-0	MEDICINE BRANCH, NCI	26 May, 2009	F	60		28 May, 2009	Off Treatment	7.5 mg/kg	Neuroendocrine cancer, NOS
35-29-61-7	MEDICINE BRANCH, NCI	8 Sep, 2008	M	72		8 Sep, 2008	Off Follow-up	7.5 mg/kg	Mesothelioma
40-03-49-4	MEDICINE BRANCH, NCI	20 Mar, 2008	M	70		20 Mar, 2008	Off Treatment	7.5 mg/kg	Melanoma
41-40-98-9	MEDICINE BRANCH, NCI	13 Mar, 2008	F	48		19 Mar, 2008	Off Treatment	7.5 mg/kg	Pancreatic cancer (excluding Islets), NOS
41-94-90-1	MEDICINE BRANCH, NCI	12 Jun, 2008	F	75		16 Jun, 2008	Off Follow-up	7.5 mg/kg	Small intestine cancer, NOS
42-62-36-0	MEDICINE BRANCH	6 May, 2008	M	72		6 May, 2008	Off Follow-up	7.5 mg/kg	Colorectal cancer, NOS

CTEP: ETCTN Web Reporting Adverse Events

ctep_index1

Report Selection

Enrollment
Adverse Events
Demography
Efficacy
Compliance

Select Drug/IND/Protocol/ARM

17-DIMETHYLAMINOETHYLAMINO-17-DEMETHOXYG
BEVACIZUMAB (RHUMAB VEGF)
BMS-354825 (DASATINIB, SPRYCEL)
PEGYLATED SN-38
VANDETANIB (ZD6474)

ALL - IND
7921

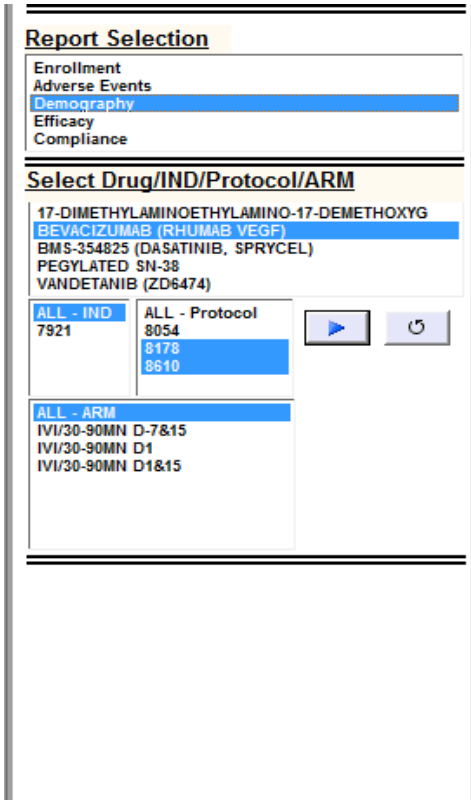
ALL - Protocol
8054
8178
8610

ALL - ARM
IVI/30-90MN D-7&15
IVI/30-90MN D1
IVI/30-90MN D1&15

Highest Grade by Patient N= 60

System Organ Class / Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
BLOOD/LYMPH DISORDERS	**1(1.7%)**					**1(1.7%)**
Anemia	1(1.7%)					1(1.7%)
GENERAL/ADM. SITE CONDITIONS		**2(3.3%)**				**2(3.3%)**
Fatigue		1(1.7%)				1(1.7%)
Pain		1(1.7%)				1(1.7%)
GI DISORDERS	**3(5.0%)**					**3(5.0%)**
Constipation	1(1.7%)					1(1.7%)
Dyspepsia	1(1.7%)					1(1.7%)
Dysphagia	1(1.7%)					1(1.7%)
INFECTIONS & INFESTATIONS		**1(1.7%)**				**1(1.7%)**
Wound infection		1(1.7%)				1(1.7%)
INVESTIGATIONS	**3(5.0%)**	**2(3.3%)**				**5(8.3%)**
AST increased	1(1.7%)					1(1.7%)
Activated PTT prolonged	1(1.7%)					1(1.7%)
Lymphocyte count decreased		1(1.7%)				1(1.7%)
Weight loss		1(1.7%)				1(1.7%)
White blood cell decreased	1(1.7%)					1(1.7%)
METABOLISM & NUTRITION	**4(6.7%)**	**2(3.3%)**				**6(10.0%)**
Anorexia	1(1.7%)					1(1.7%)

CTEP: ETCTN Web Reporting Demographics



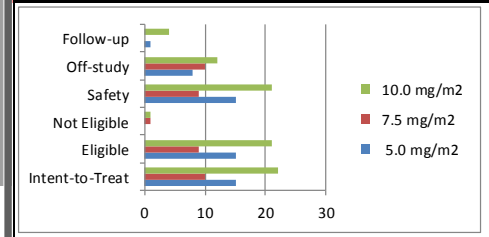
Study Population

	Dose Level					N = 47
	5.0 mg/m^2	7.5 mg/m^2	10.0 mg/m^2			Total
Intent-to-Treat	15 (31.9%)	10 (21.3%)	22 (46.8%)			47 (100.0%)
Eligible	15 (31.9%)	9 (19.1%)	21 (44.7%)			45 (95.7%)
Not Eligible		1 (2.1%)	1 (2.1%)			2 (4.2%)
Safety	15 (31.9%)	9 (19.1%)	21 (44.7%)			45 (95.7%)
Off-study	8 (17.0%)	10 (21.3%)	12 (25.5%)			30 (63.8%)
Follow-up	1 (2.1%)		4 (8.5%)			5 (10.6%)

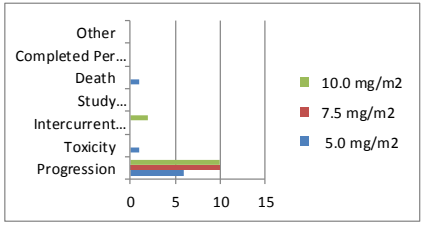
Study Disposition

	Dose Level					N = 47
	5.0 mg/m^2	7.5 mg/m^2	10.0 mg/m^2			Total
Progression	6 (12.8%)	10 (21.3%)	10 (21.3%)			26 (55.3%)
Toxicity	1 (2.1%)					1 (2.1%)
Intercurrent Illness			2 (4.2%)			2 (4.2%)
Study Terminated						
Death	1 (2.1%)					1 (2.1%)
Completed Per Protocol						
Other						

Population



Disposition



CTEP: ETCTN Web Reporting Efficacy Summary

Report Selection

- Enrollment
- Adverse Events
- Demography
- Efficacy
- Compliance

Select Drug/IND/Protocol/ARM

- 17-DIMETHYLAMINOETHYLAMINO-17-DEMETHOXYG
- BEVACIZUMAB (RHUMAB VEGF)
- BMS-354825 (DASATINIB, SPRYCEL)
- PEGYLATED SN-38
- VANDETANIB (ZD6474)

ALL - IND: 7921

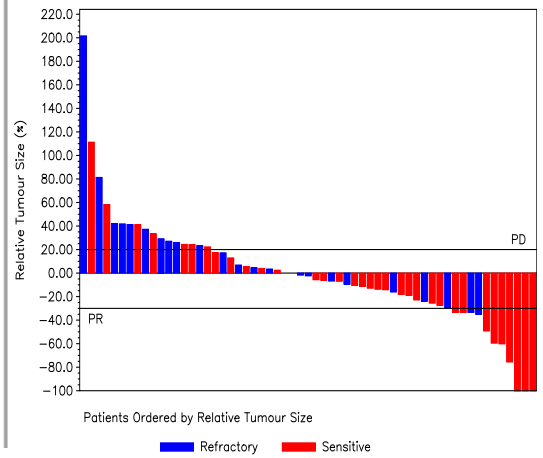
ALL - Protocol: 8054, 8178, 8610

ALL - ARM: IVI/30-90MN D-7&15, IVI/30-90MN D1, IVI/30-90MN D1&15

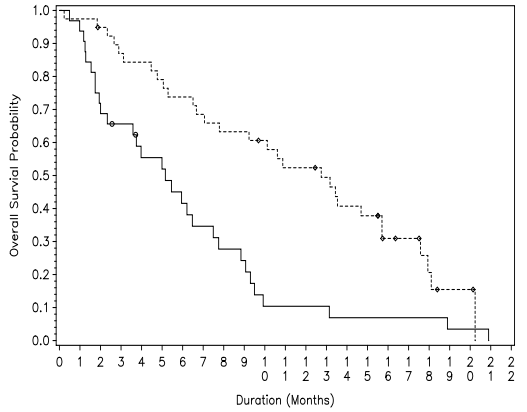
Best Response

	Dose Level					N = 47
	5.0 mg/m^2	7.5 mg/m^2	10.0 mg/m^2			Total
Complete Response	1 (2.1%)	2 (4.2%)	2 (4.2%)			5 (10.6%)
Partial Response	2 (4.2%)	1 (2.1%)	4 (8.5%)			7 (14.9%)
Stable Disease		3 (6.4%)	6 (12.8%)			9 (19.1%)
Disease Progression	10 (21.3%)	4 (8.5%)	6 (12.8%)			20 (42.6%)
Not Evaluable	2 (4.2%)		4 (8.5%)			6 (12.8%)

Waterfall Plot



Survival



ETCTN Education and Training

Cancer Therapy Evaluation Program (CTEP)

CTEP provides educational webinars for ETCTN members:

- For Leadership:
  - Kick-off and Overview
  - Rosters and Roles
  - Patient Enrollment
  - NCI CIRB
  - PIO Updates
  - Data Management
  - Biomarkers
  - Implementing Drug Project Teams
  - Web Reporting
- For Site Staff:
  - Introduction to the ETCTN, Centralized Services, and the CTSU Website
  - Patient Enrollment
  - Regulatory Processes
  - Data Management

- Educational Materials on the ETCTN-CTSU website contains links to the webinar recordings, checklists, and information sheets on 16 different topics. These include:

- Protocol Development
- Protocol Amendments
- Person Registration & CTEP-IAM
- Rosters & Roles
- CTSU
- Protocol Access & Communications
- Regulatory Processing
- Patient Education Materials
- The NCI CIRB
- Patient Enrollment
- Agent Ordering
- Data Management
- SAE Reporting
- CDUS Reporting
- Auditing and Monitoring
- Provider Education Materials

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