Update: NCI-MATCH Trial, NCI Patient-Derived Models Repository

James H. Doroshow, M.D.
Deputy Director for Clinical& Translational Research
National Cancer Institutes of Health

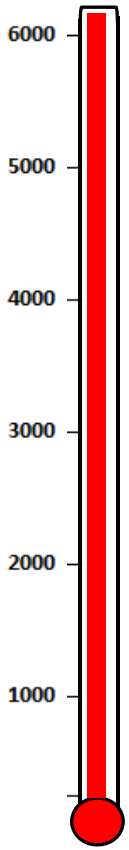
NIH NATIONAL CANCER INSTITUTE

NCAB-BSA Meeting
June 20, 2017

Topics for Discussion

- NCI MATCH Trial
- NCI Patient-Derived Models Repository

NCI-MATCH Testing and Enrollment as of 6/18/17



6398 patients with tumor samples (N=6000)

5482 patients had received their test results

983 had a gene abnormality matching an available treatment

And proceeded to be further evaluated for the specific eligibility for the arm to which they matched

660 patients had enrolled for treatment

NOTE: These are strictly numbers reflecting a point in time and cannot be used to calculate overall rates; some are assigned and still in evaluation for eligibility for an arm; estimated 72% of those assigned will enroll

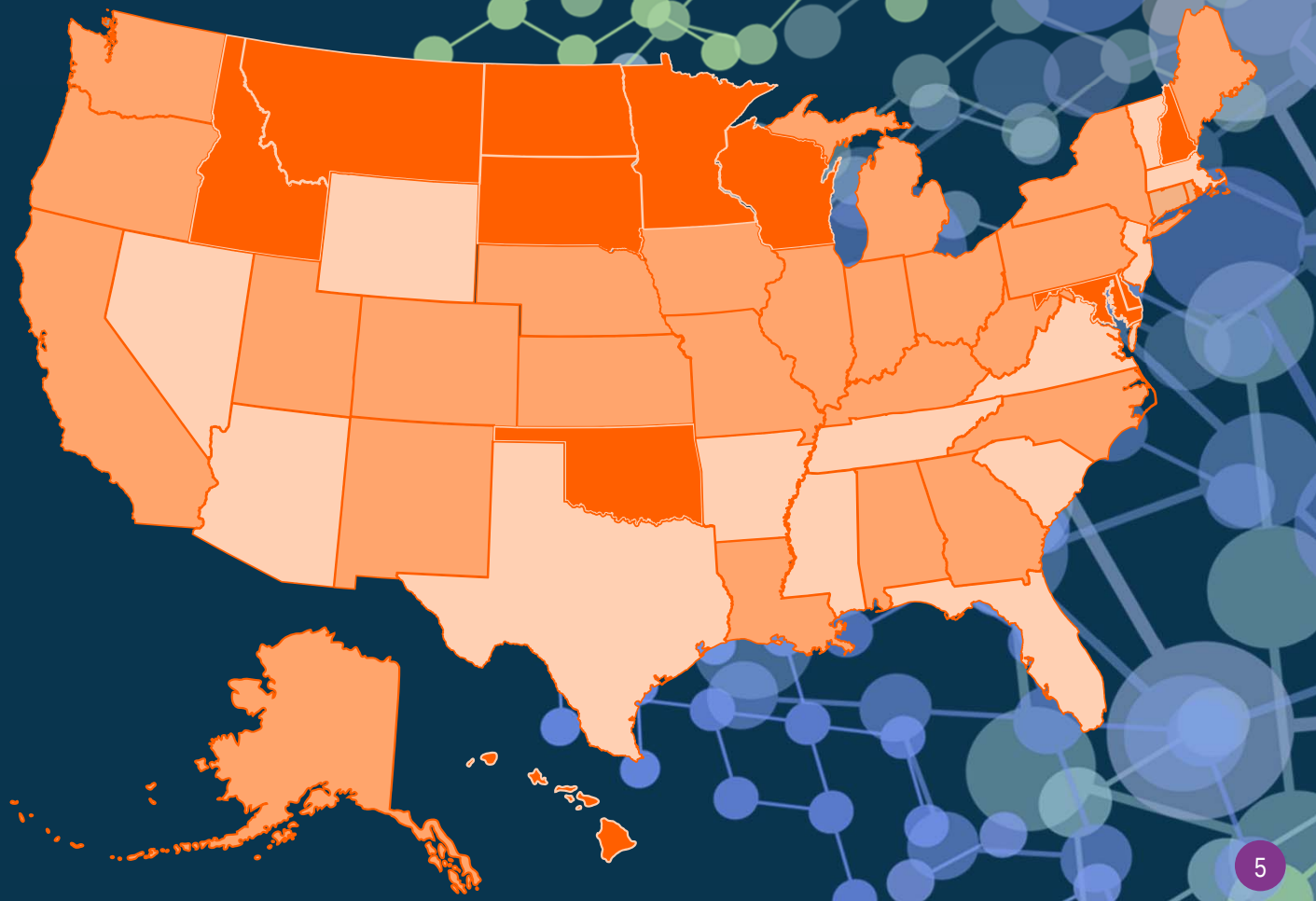
Current: as of June 18, 2017

- **25 treatment arms; ≈ 50% fully accrued; ≈ 25% well on the way; ≈ 25% will need additional accrual from 'rare variant study'**
- **Assay success rate 94%**
- **Median assay turnaround time 16 days**
- **Toxicity acceptable**
- **Objective responses have been observed**

NCI "MATCH" CANCER TREATMENT TRIAL: STATE BY STATE ENROLLMENT

ENROLLMENT PER 1 MILLION POPULATION

- **30 – 65**
- **>8 – <30**
- **FEWER than 8**



MATCH = Molecular Analysis for Therapy CHoice

States with Enrollment of more than 30 patients per 1 Million Population

- Delaware
- Hawaii
- Idaho
- Maryland
- Minnesota
- Montana
- New Hampshire
- North Dakota
- Oklahoma
- South Dakota
- Wisconsin

NCI-MATCH Expanded to 25 Arms May 31, 2016

Arm / Target	Drugs(s)
A EGFR mut	Afatinib
B HER2 mut	Afatinib
C1 MET amp	Crizotinib
C2 MET ex 14 sk	Crizotinib
E EGFR T790M	AZD9291
F ALK transloc	Crizotinib
G ROS1 transloc	Crizotinib
H BRAF V600	Dabrafenib+trametinib
I PIK3CA mut	Taselisib
N PTEN mut	GSK2636771
P PTEN loss	GSK2636771
Q HER 2 amp	Ado-trastuzumab emtansine

Arm / Target	Drug(s)
R BRAF nonV600	Trametinib
S1 NF1 mut	Trametinib
S2 GNAQ/GNA11	Trametinib
T SMO/PTCH1	Vismodegib
U NF2 loss	Defactinib
V cKIT mut	Sunitinib
W FGFR1/2/3	AZD 4547
X DDR2 mut	Dasatinib
Y AKT1 mut	AZD 5363
Z1A NRAS mut	Binimetinib
Z1B CCND1,2,3 amp	Palbociclib
Z1D dMMR	Nivolumab
Z1I BRCA 1/2	AZD1775

Red = accrued 35 patients;
Green = nearing 35 patient

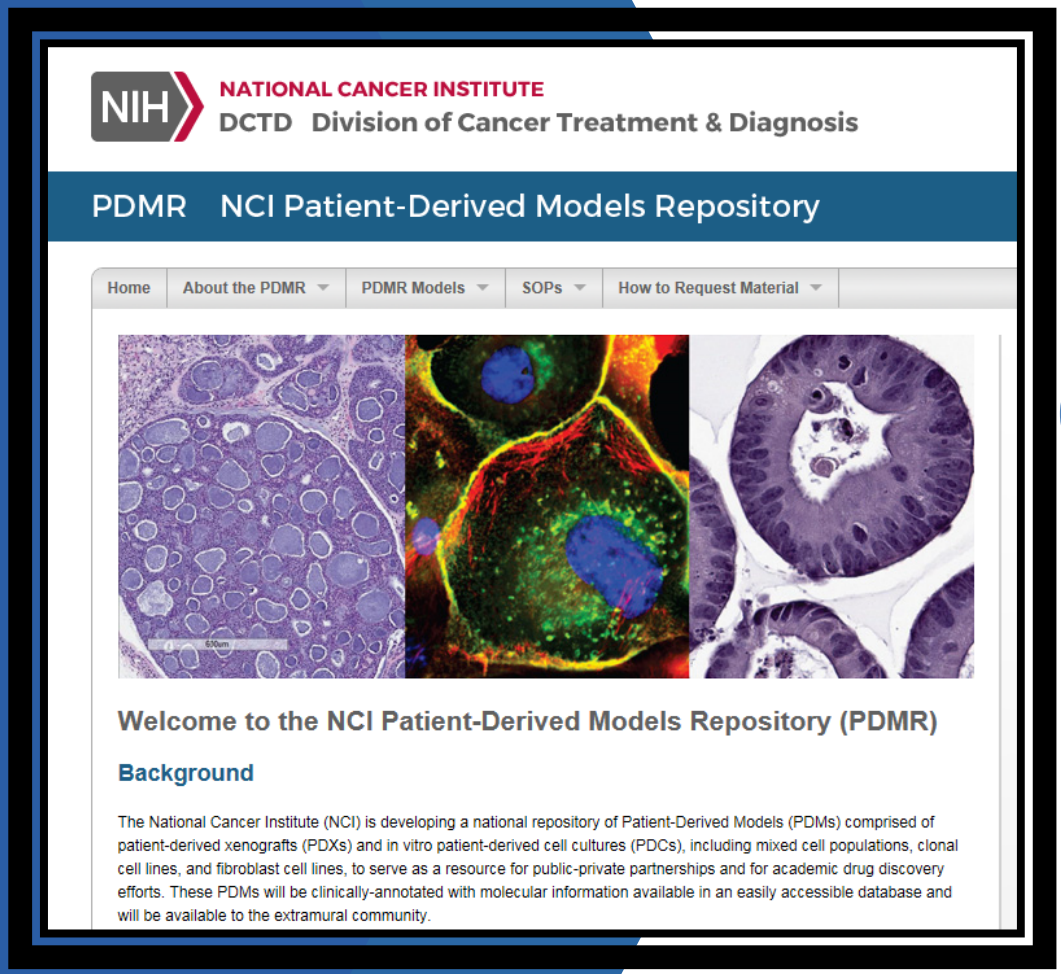
ECOG-ACRIN cancer research group | NIH NATIONAL CANCER INSTITUTE

Arms added: March 13, 2017

- EAY131-J: Herceptin + Perjeta/HER2 Amp **(to follow Arm Q)**.
- EAY131-L: MLN0128/mTOR Mutations (**New target**)
- EAY131-M: MLN0128/TSC1/TSC2 Mutations (**New target**)
- EAY131-Z1C: Palbociclib/CDK4/CDK6 Amplification (**New target**)
- EAY131-Z1E: Loxo 101/NTRK Fusions (**New target**)
- EAY131-Z1I: AZD1775/BRCA1, BRCA2 mutations ***(New target)***

Rare variant initiative (Began May 2017)

- Several arms are not expected to fill even with sequencing 6000 patient tumors, due to the rarity of the variant in the population
- However, good evidence exists these variants are drivers and may respond to drugs in NCI MATCH
- Tumor sequencing is now more commonly done in clinical practice
- Enrichment: Initially, four additional CLIA certified labs will participate in finding these patients and letting their doctors know they may be eligible for NCI MATCH
  - 2 commercial labs
    - Foundation Medicine Inc
    - Caris
  - 2 clinical labs (using their own, non-MATCH assay)
    - MD Anderson Cancer Center
    - Memorial Sloan Kettering Cancer Center
  - Results will be verified with the MATCH assays retrospectively
  - Soon, a process for qualifying other commercial and academic sequencing labs will be posted to encourage additional accrual to this phase of NCI-MATCH

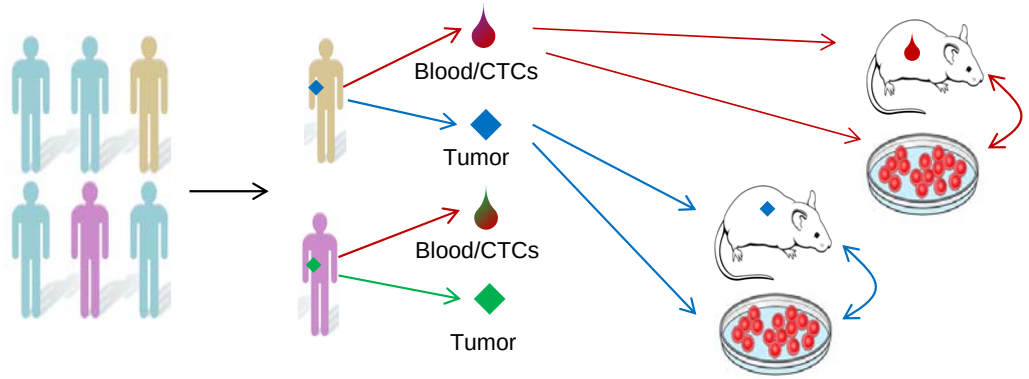


NCI's Patient-Derived Models Repository (PDMR): Open for 3 weeks

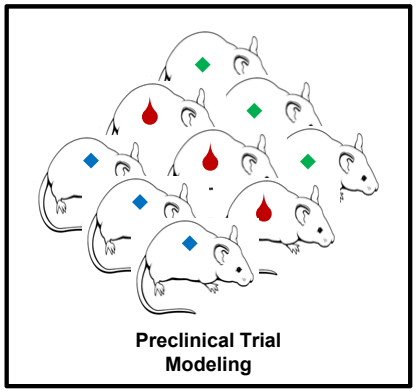
https://pdmr.nci.gov

NCI Patient-Derived Models Repository: Multiple Avenues for Discovery

Develop PDX Models and PDC (Tumor & Fibroblast) Lines
DNA, RNA, Protein, WES, RNASeq, Targeted Sequencing

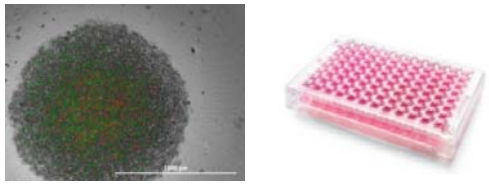


Tumor/Patient Heterogeneity

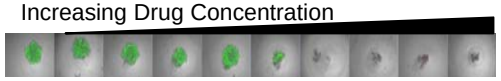


Preclinical Trial Modeling

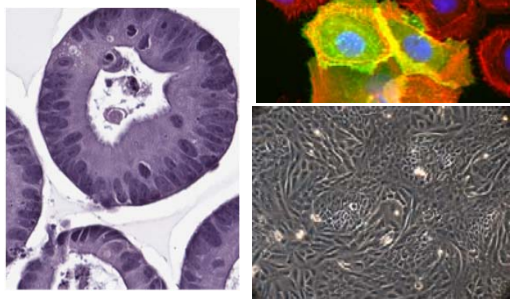
3D Culture, 3D Pharmacodynamics



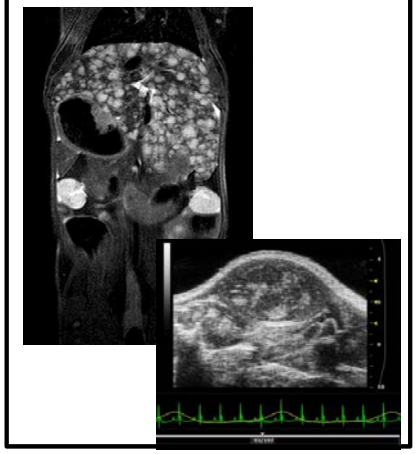
Increasing Drug Concentration



2D and Organoid Cultures

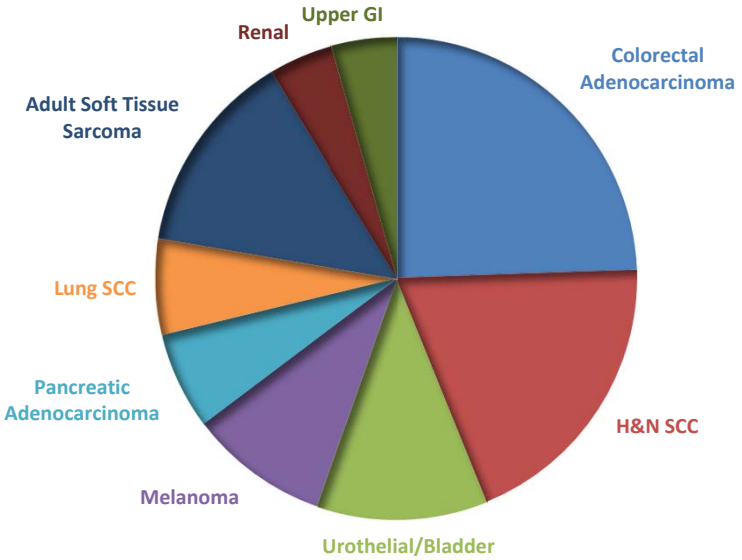


Live Tumor Imaging



National Cancer Institute
Patient-Derived Models Repository

NCI Patient-Derived Models Repository (PDMR) Initial Distribution Types



- PDX Pathology Confirmed
- Whole Exome Sequence, NCI Cancer Gene Panel, and RNASeq Available
- Human Pathogen Screening and STR Profile Available
- Confirmed Re-growth from Cryopreserved Fragments

Distribution Groups (N=100 Models)
Colorectal Adenocarcinoma
Head & Neck Squamous Cell Carcinoma • Pharyngeal, Laryngeal, Lip/oral cavity, NOS
Urothelial/Bladder
Melanoma
Pancreatic Adenocarcinoma
Lung Squamous Cell Carcinoma
Adult Soft Tissue Sarcoma • Ewings, Leiomyosarcoma, Malignant fibro. histiocytoma, Fibrosarcoma, Non-Rhabdosarcoma NOS, Rhabdosarcoma NOS
Renal
Upper GI • Stomach, Sm. Intest, GIST, Appendiceal

NATIONAL CANCER INSTITUTE
PATIENT-DERIVED MODELS REPOSITORY

Questions?

NCI Virtual Drug Formulary: Development

- Created a system within the NCI that leverages our existing mechanisms to provide PIs with Investigational agents for investigator held INDs
- The program:
  - ✓ Agent menu; 8 week turn-around time for Pharma review (approval or not) of proposals
  - ✓ Utilizes pre-existing agreements/infrastructure that current Pharmaceutical Collaborators are already familiar with
- Agents provided for both clinical and pre-clinical studies
- INDs held by investigators/institutions, not CTEP/NCI; no NCI funding for trials
- Agreement terms standardized or pre-approved so as to substantially decrease the transactional costs of study initiation; NCI funds drug distribution and tracking of trials
- Launched January 2017; As of May 2017: **26** agents from **7** companies:

  Agents: Alectinib; Atezolizumab; Bevacizumab; Cobimetinib; Durvalumab; Ensartinib; Ipilimumab; Larotrectinib; LY3039478; Mogamulizumab; Nivolumab; Obinutuzumab; Pertuzumab; Prexasertib; Savolitinib; Selumetinib;Trastuzumab; Tremelimumab; Vemurafenib; Vismodegib; Vistusertib; AZD1775; AZD5069; AZD5363; AZD8186; MEDI9447

  Companies: Bristol-Myers Squibb; Eli Lilly; Genentech; Astra-Zeneca; Kyowa Hakko Kirin; Loxo; Xcovery

NCI Virtual Drug Formulary

- Access to investigational drugs for investigator initiated studies is difficult and time consuming, often the cost-benefit of negotiating an agreement with a Pharmaceutical Collaborator is prohibitive or so difficult and time consuming that the study is never initiated.
- This process is especially burdensome for multi-agent combinatorial studies, and more burdensome still when one or both of those agents are investigational and proprietary to different collaborators.
- Major roadblock to precision medicine clinical trials