Molecular Analysis for Therapy Choice (NCI MATCH)

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Classification of Cancer

Traditional Methods (Solid Tumors)

1. Anatomic location of the primary cancer
   – Breast, lung, colon, prostate, etc.
2. Histologic Classification
   – Adenocarcinoma, squamous, sarcoma, urothelial, transitional
3. Grading (low, intermediate, high)
   – (cell differentiation, other known risk factors)

Traditional Drug Development Process

- **Discovery** (Identify promising agents)
- **Pre-Clinical (Laboratory)** 3-6 years
  – In Vitro: establish chemical structure, drug classification, mechanism of action.
  – Animal testing (Pharmacology)
    - Activity against implanted cancer cell lines
- **Clinical Trials (Phase 0 – 3)** 6-8 years
  – Multiple phase 2 trials, each limited to one specific primary cancer type (All comers).
  – Phase 3 determined by the best response rate of the primary cancer at the phase 2 testing
- **FDA Review of NDA** (1-2 years)

Traditional Drug Development Process

- 10,000 agents screened
  - 250 enter pre-clinical testing
    - 5 enter human testing
      - 1 new drug will get FDA approval
- 10-15 years to develop one new drug
- $800 to $1 billion (Includes cost of failures)

Cancer is a Disease of Genes Gone Awry

- A cell carries the entire set of genetic instructions – the genome – that makes an entire organism
- Cancer is genetic in its origin and is triggered by altered genes.
- Genes that control the orderly replication of cells become damaged (mutation) allowing the cell to reproduce without restraint
  - Germ cell mutations are inherited (10%)
  - Somatic cell mutations are random, or in response to injuries from environmental agents as radiation or chemicals (90%)

What are Biomarkers to Drug Development

- A biomarker is defined as any characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological response to a therapeutic intervention
- Genetic alterations in the cancer cell that promote tumor growth and tumor progression provide a unique molecular fingerprint of the tumor cells that is different from normal cells
- If these "qualitative" differences can be accurately identified and validated as being required by the tumor to survive but not the normal cell, drugs may be developed to "**target**" the biomarker to kill only the cancerous cells.

Validation of Molecular Biomarkers

- Genomic studies of the same cancer types have often identified discordant biomarker candidates and patterns
- FDA: All diagnostic devices (IVD) used to make treatment decisions in a clinical trial are investigational and are considered as a significant risk device that must be validated as an accepted indicator of the process of interest in carefully designed clinical trials.
  - Must demonstrate in clinical trials that the marker accurately predicts the clinical endpoint of interest
  - Erroneous IVD companion diagnostic device results could lead to withholding appropriate therapy or to administering inappropriate therapy.

Types of Biomarkers

- Biomarkers may be substances that are produced by the body in response to cancer growth or by the cancer tissue itself and may be detected in blood, urine, or tissue samples
  - Enzymes and isoenzymes
  - Hormones
  - Immunoglobulins
  - Antigens
  - Receptors
  - Oncogene products
  - Genetic markers

Classification of Biomarkers in Clinical Practice "Personalized Medicine"

- Screening and Diagnostic - used to improve cancer screening and detection, monitor for recurrence (PSA to screen for prostate cancer)
- Prognostic - Predict relative risk, develop risk-adapted treatment regimens (Oncotype-DX)
- Predictive – Select targeted drugs most likely to benefit (Her2/neu in breast cancer)

The Cancer Genome Atlas (TCGA) Pan-Cancer Initiative

- Tumors arising in several difference tissue types share the same oncogenic signature
  - "Suggest" that different primary cancers with the same oncogenic signatures may be responsive to the same agents targeting the mutation.
- Molecular profiling identified treatable targets in 80% of 1,400 patients with cancer of unknown primary (CUP)
  - Biomarkers identified suggested drugs not traditionally considered for treatment of CUP

The Evolving Paradigm for Developing Precision Medicine

- **Genomics of Exceptional Responders**
  (Phenotype to Genotype)
  - Tumor from patients who had an exceptional response to a drug that did not show adequate benefit in the general patient population of a specific cancer type to justify its continued development
- **NCI-MATCH Clinical trial**
  (Genotype to Phenotype)
  - Screen for molecular features that may predict response to a drug with a given mechanism of action

MATCH Trial Design

- Designed as a Master Screening Trial to identify patients with tumors that have mutations/ amplifications in pathways targetable by existing therapeutic agents.
  - Goal = Molecularly profile 3000 patients with a multianalyte validated targeted NGS assay to identify 1000 patients with actionable targets
- Serves as an "umbrella" for multiple single-arm phase II trials each designed to match an identified molecular lesion of interest to a matching targeted drug defined to work on the specific mutation in a phase II setting
  - Plan to screen for as many as 15 actionable mutations with available targeting agents per patient. Identified targets/agents will be dynamic during conduct of trial.

Molecular Analysis for Therapy Choice

- **Rationale for MATCH Trial Design**:
  - The most efficient way to assess tumor context in relation to genotype and therapeutic response is a phase 2 evaluation that assigned therapy on the basis of genetic alterations predicted to correlate with efficacy, regardless of tumor type
- **MATCH Hypothesis**:
  - Patients with tumor mutations/amplifications in one of the genetic pathways of interest are more likely to derive clinical benefit if treated with agents targeting that specific pathway when compared to historically standard therapies chosen without regard to molecular characteristics

Molecular Eligibility Assessment

- NCI to contract CLIA certified labs for genetic analysis; will assure standard SOP and concordance
- Each 500 patients will have set number of slots for common vs. uncommon histologies
  - Ratio could be revised based on the balance of patients enrolled onto the drug treatment part of the study
  - Common: breast, NSCLC, colon, prostate, (lymphoma?)
- Target enrollment of 25% of patients who have “rare” tumor enrolled for treatment

Eligibility Criteria

- Patients with solid tumors whose disease has progressed following at least one line of standard therapy
  - Exclude histologies for which agent is approved by the FDA or had shown convincing lack of efficacy with an agent
- Tumor accessible to biopsy and patient willing to undergo biopsy (Note: Biopsy at progression will be requested but not mandatory)
- at least 18 years of age
- performance status ECOG 0-2
- adequate organ function
- agent specific exclusion criteria, if applicable, will be included in the eligibility criteria

Trial Logistics

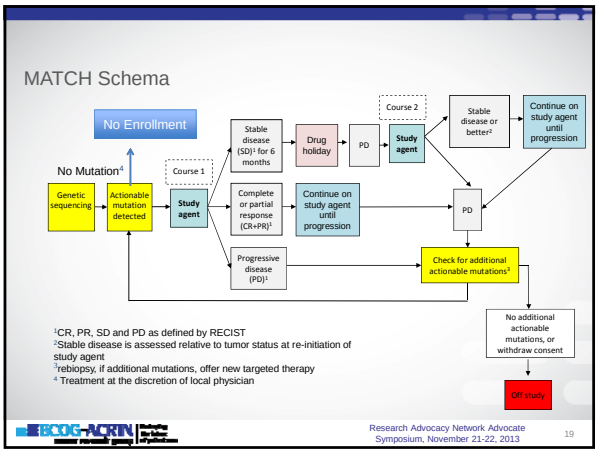
- ECOG Lead: Will be on the CTSU menu of trials
- Composed of Multiple single arm phase II trials
- Single IND (IDE) for protocol template (We hope)
  - Arms may be added or deleted during the conduct of the trial without affecting other arms
- Initially only single agents then consider combination arms in the future
- May include use of approved agents for off-label indications or investigational agents
- Central IRB will be required
- Desired start July 2014

Selection of targeting drugs

- Agents selected could be commercially available or investigational but would have at minimum *dose/safety established* in phase 1 trials
  - Level 1: FDA approved different tumor
  - Level 2: Data from clinical trials in similar molecular abnormality; investigational drug
  - Level 3: plausible preclinical evidence that drug works against given tumors with a given molecular abnormality

Sites that May Participate in MATCH

- ECOG-ACRIN is the designated lead Group
- All member sites of the National Clinical Trials Network (NCTN) Cooperative Groups
- NCI designated Cancer Centers
- CCOPs
- Special participants may request to Join but all sites need to have track record of receiving CTEP investigational agents


MATCH Schema
No Enrollment
No Mutation[4]
Genetic sequencing
Actionable mutation detected
Course 1
Study agent
Stable disease (SD)[1] for 6 months
Drug holiday
PD
Course 2
Study agent
Stable disease or better[2]
Continue on study agent until progression
Complete or partial response (CR+PR)[1]
Continue on study agent until progression
PD
Progressive disease (PD)[1]
Check for additional actionable mutations[3]
No additional actionable mutations, or withdraw consent
Off study
[1]CR, PR, SD and PD as defined by RECIST
[2]Stable disease is assessed relative to tumor status at re-initiation of study agent
[3]rebiopsy, if additional mutations, offer new targeted therapy
[4] Treatment at the discretion of local physician
ECOG-ACRIN
Research Advocacy Network Advocate Symposium, November 21-22, 2013
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