National Cancer Institute

Precision Cancer Medicine Exceptional Responders NCI-MATCH

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Exceptional Responders Initiative

Phenotype to Genotype

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Exceptional Responders Initiative: Pilot Study

- 1-10% of patients respond well to drugs that do not go on to receive FDA approval for that indication
- Molecular mutations or changes in gene expression may explain these “exceptional responses”
- “Inactive” drugs are sometimes active in a subset of patients
- Could lead to development of predictive assays
- Improve biologic understanding for better therapeutics/diagnostic development

Exceptional Responders

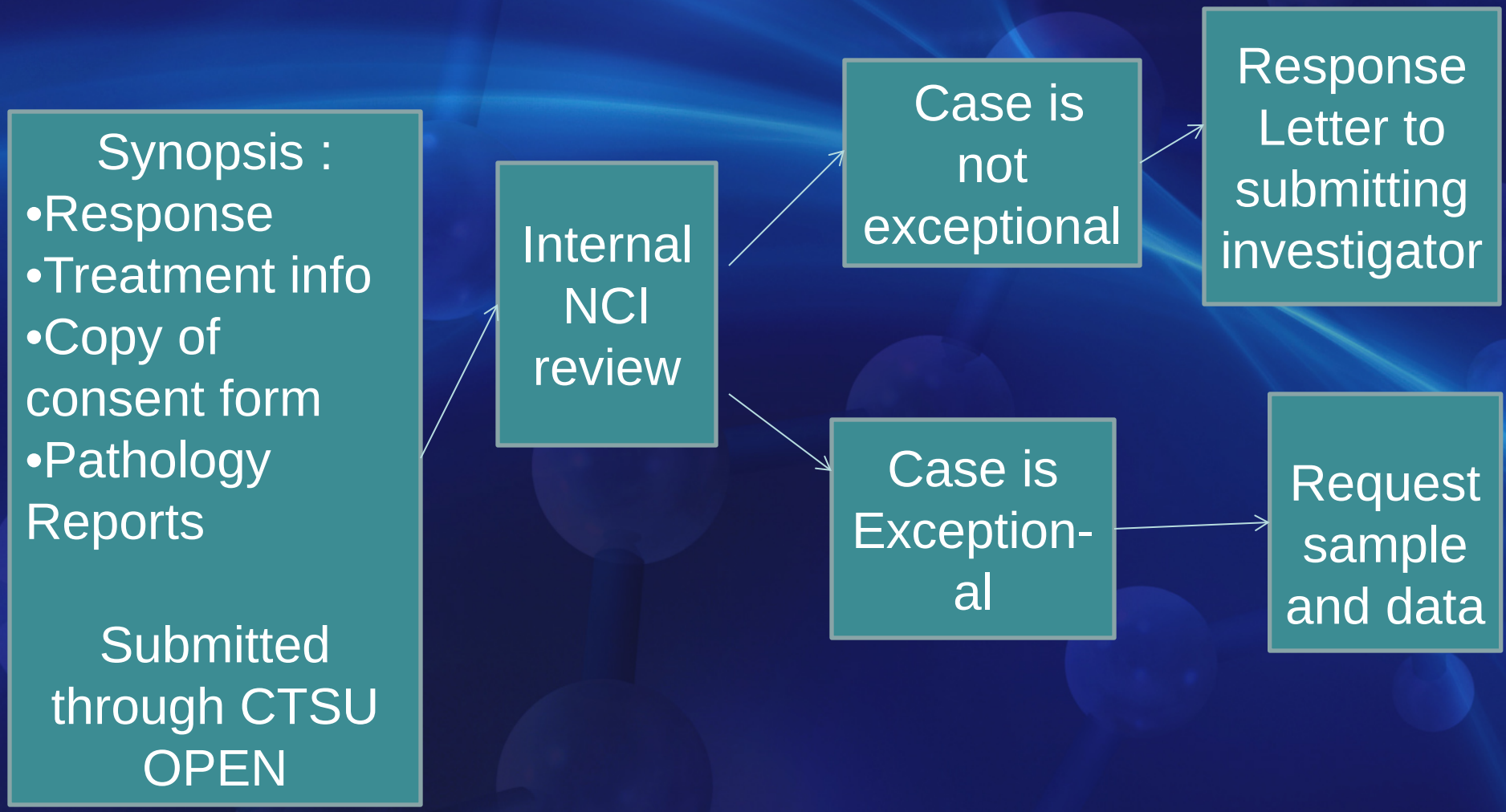
- Definitions
  - CR, or PR lasting at least 6 months
  - Drug did not go on to FDA approval in that indication due to insufficient activity
- Tissue
  - Prefer just before drug treatment; otherwise any prior
  - 50% tumor
  - FFPE, Frozen, core acceptable
  - Normal: blood or other

Solicitation of Exceptional Responders Cases

- Solicit Tissue Samples and Clinical Data
  - Letters to CTEP investigators for identified ER cases
  - Pharma
  - Cooperative Groups, U01s, and N01s
  - Cancer Centers
- Sites will be reimbursed for effort

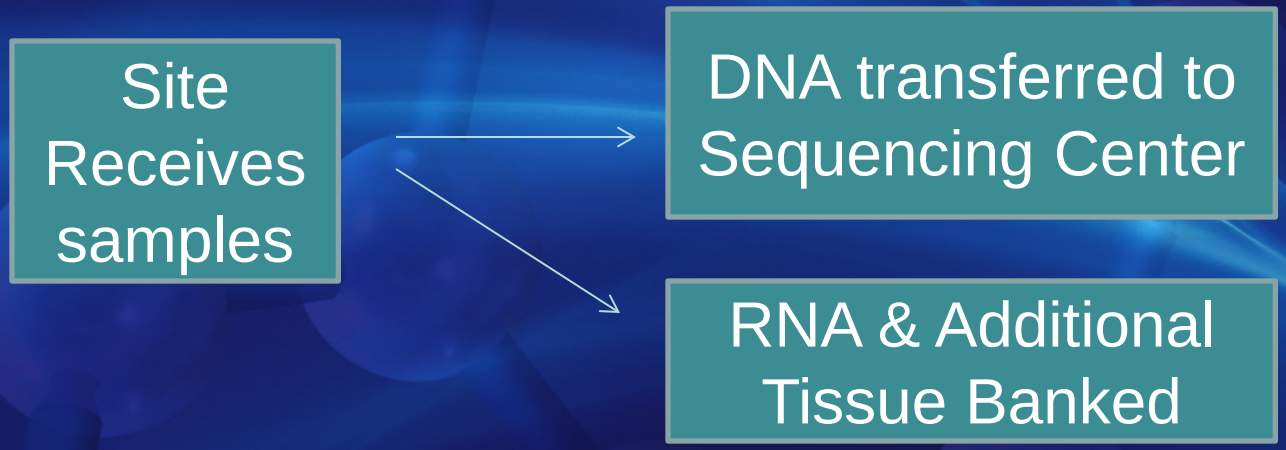
Screening of Potential ER Cases

Sites Submit Data through the CTSU's OPEN – Eligibility Stage



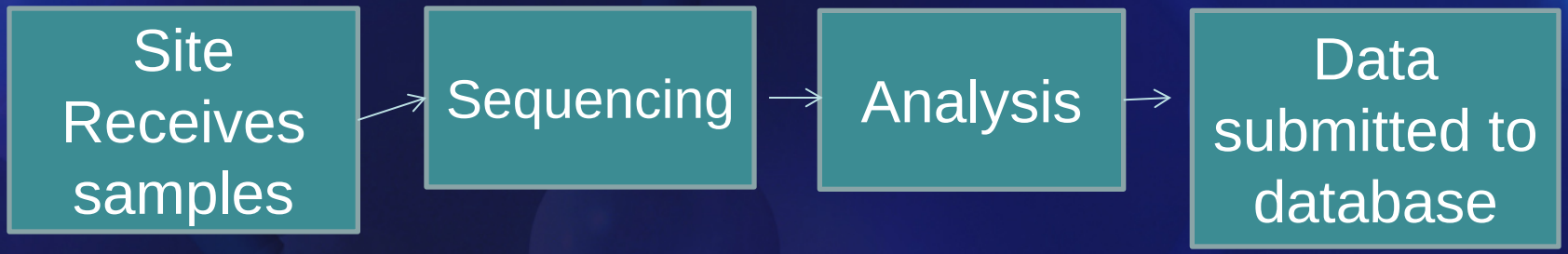
Sample Submission and Preparation

Central Biorepository: Nationwide Children's Hospital



Sequencing and Analysis of Samples

Contract Existing TCGA Sequencing Center



Timeline

Oct. 2013- Sept. 2015

Solicit exceptional cases and tissues

Dec. 2013- Sept. 2015

Sequencing and analysis

Jan. 2014 –Dec. 2015

Posting on controlled access website

Molecular Analysis for Therapy Choice (NCI-MATCH)

Genotype to Phenotype

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NCI-MATCH

- Umbrella protocol for multiple, single-arm phase II trials
  - Each molecular subgroup matched to a targeted agent
- IND for protocol template
  - Arms could be added or deleted without affecting other arms
- Initially focused on single-agents (commercial or experimental)
  - Combinations will be considered for targets that have validated combination targeted therapy
  - Need minimum dose/safety established in phase 1 trials
- Study will be reviewed by the CIRB

NCI MATCH

- Identify mutations/amplifications/translocations in patient tumor sample - eligibility determination
- Assign patient to relevant agent/regimen
- Tumor biopsies & sequencing at progression to illuminate resistance mechanisms
  - De-identified samples submitted to central labs
  - Whole-exome sequencing (research purposes) to detect nonambiguous germline variants

Eligibility

- Solid tumors and Lymphomas that have progressed following at least one line of standard therapy
  - Exclude histologies from a given arm if already FDA approved for that indication or lack of efficacy documented
- Tumor accessible for biopsy and patient willing to undergo biopsy
- At least 18 years of age
- Performance status ECOG 0-2
- Adequate organ function

Patient population considerations

- Target: at least 25% of total enrollment to be patients who have “rare” tumors
- “Common” defined as breast, NSCLC, colon, prostate
- Terminate enrollment to an arm if accrual on pace to require > 5 years to accrue

Levels of Evidence: Drugs

- Level 1: FDA approved; evidence of target inhibition, or proof of mechanism; demonstration that patient selection with CDx are more likely to respond
- Level 2: Agent met a clinical endpoint (objective response, PFS, or OS); with evidence of target inhibition; plausible evidence of a predictive or selection assay/analyte
- Level 3: Agent demonstrated evidence of clinical activity with evidence of target inhibition; some evidence of a predictive or selection assay/analyte
- Level 4: Preclinical evidence of anti-tumor activity and evidence of target inhibition; hypothesis for a predictive or selective assay/analyte

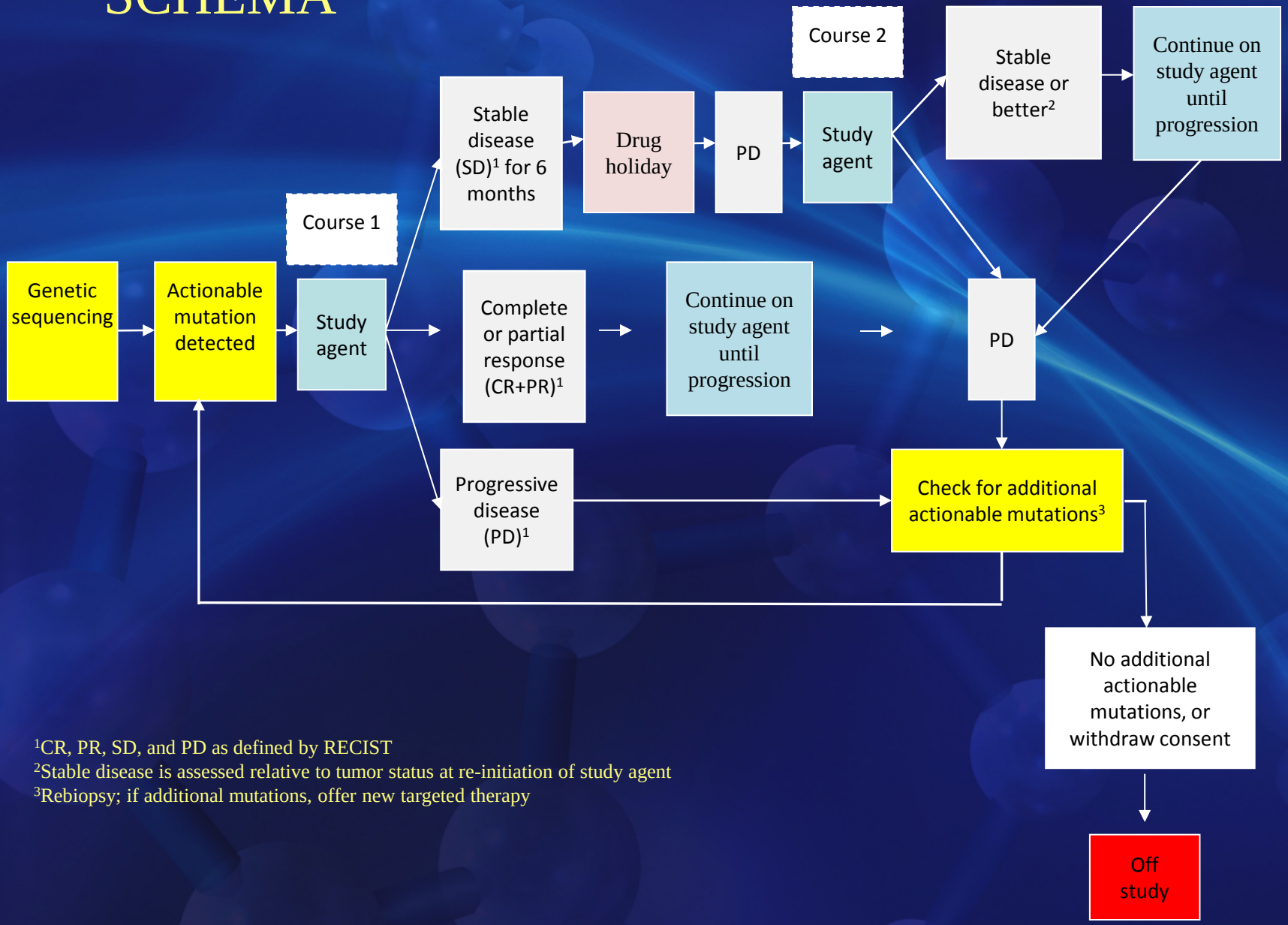
Levels of Evidence: genes

- Gene variants = target of an approved drug; and robust clinical data are lacking re: efficacy in certain cancer subtypes harboring that variant.
- Activating mutations in genes upstream of the molecular target of the agent in the associated signaling pathway(s)
- Inactivating mutations in genes that result in unique susceptibility to a specific molecular point of intervention (e.g., BRCA1 mutation and PARP inhibitors).
- Other genes of interest that have appropriate justification for inclusion based on scientific evidence regarding unique susceptibility to a specific molecular targeted therapy (potential future drug targets, potential biological/clinical interest).

Assays

- NGS: Ion Torrent PGM with custom Ampliseq panel of 200-300 actionable genes
- Validation in network of CLIA certified labs: RFP thru Leidos
- IHC, FISH?
- Rule driven treatment assignment

SCHEMA



[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

Statistical Design

(within each mutation-drug match)

- Dual Primary Endpoints: ORR 5% vs. 25% or PFS 6 months 15% vs 35%
- Simon 2-stage design 30 patients total
- Drug holiday for patients with stable disease
- Compare PFST1 to PFST2

ORR = proportion of patients with objective response (PR+CR) on initial course of study agent
PFS6 = proportion of patients alive and progression free at 6 months from initiation of study agent
PFST1 = Time until death or progression from start of drug holiday for a patient with stable disease at 6 months
PFST2 = Time until death or progression from therapy re-initiation for a patient who goes on drug holiday and progresses, but survives to have study agent re-initiated

Study Participation

- ECOG-ACRIN to lead with full cooperation of NCTN
  - individual PIs for each arm to rotate leadership positions
- Posted on CTSU
- CCOPs

Questions

- Exceptional responders:
  - Is whole exome sequencing or targeted sequencing likely to lead to more usable information?
  - Are there other types of patients or data that should be considered?

MATCH

- What hurdles are to be expected for this study with respect to accrual or willingness for clinicians to participate?

Other Questions /Comments