Precision Cancer Medicine

Exceptional Responders

NCI-MATCH

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Exceptional Responders Initiative

Phenotype to Genotype
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

National Cancer Institute
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

Synopsis:
- Response
- Treatment info
- Copy of consent form
- Pathology Reports

Submitted through CTSU OPEN

Internal NCI review

Case is not exceptional

Response Letter to submitting investigator

Case is Exceptional

Request sample and data
Sample Submission and Preparation

Central Biorepository: Nationwide Children’s Hospital

Site Receives samples

DNA transferred to Sequencing Center

RNA & Additional Tissue Banked

Sequencing and Analysis of Samples

Contract Existing TCGA Sequencing Center

Site Receives samples

Sequencing

Analysis

Data submitted to database
Timeline

Oct. 2013- Sept. 2015
Solicit exceptional cases and tissues

Dec. 2013- Sept. 2015
Sequencing and analysis

Posting on controlled access website
Molecular Analysis for Therapy Choice (NCI-MATCH)

Genotype to Phenotype
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
Genetic sequencing → Actionable mutation detected → Study agent → Complete or partial response (CR+PR)\(^1\) → Stable disease (SD)\(^1\) for 6 months → Drug holiday → PD → Study agent → Stable disease or better\(^2\) → Continue on study agent until progression

Stable disease or better\(^2\) → Continue on study agent until progression → Check for additional actionable mutations\(^3\) → No additional actionable mutations, or withdraw consent → Off study

Progressive disease (PD)\(^1\) → Course 2 → PD

\(^1\)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?
• What hurdles are to be expected for this study with respect to accrual or willingness for clinicians to participate?