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Molecular Analysis for Therapy Choice (NCI-MATCH)

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NCI-MATCH rationale

- Molecularly targeted therapy benefits patients with defined molecular features:

  within individual tumor types:

  - imatinib in CML (bcr-abl)
  - imatinib in GIST (CKIT & PDGFRα)
  - erlotinib in NSCLC (EGFR)
  - crizotinib in NSCLC (EML4-ALK)

  and, across tumor types:

  - trastuzumab in breast & gastric (Her-2)
  - vemurafenib in melanoma, thyroid & NSCLC, but not colon cancer (BRAF)

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NCI MATCH

- Identify mutations/amplifications/translocations in patient tumor sample - eligibility determination
- Assign patient to relevant agent/regimen
- Need to sequence large numbers of tumors and need to have large numbers of targeted treatments
- 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

NCI-MATCH SCHEMA

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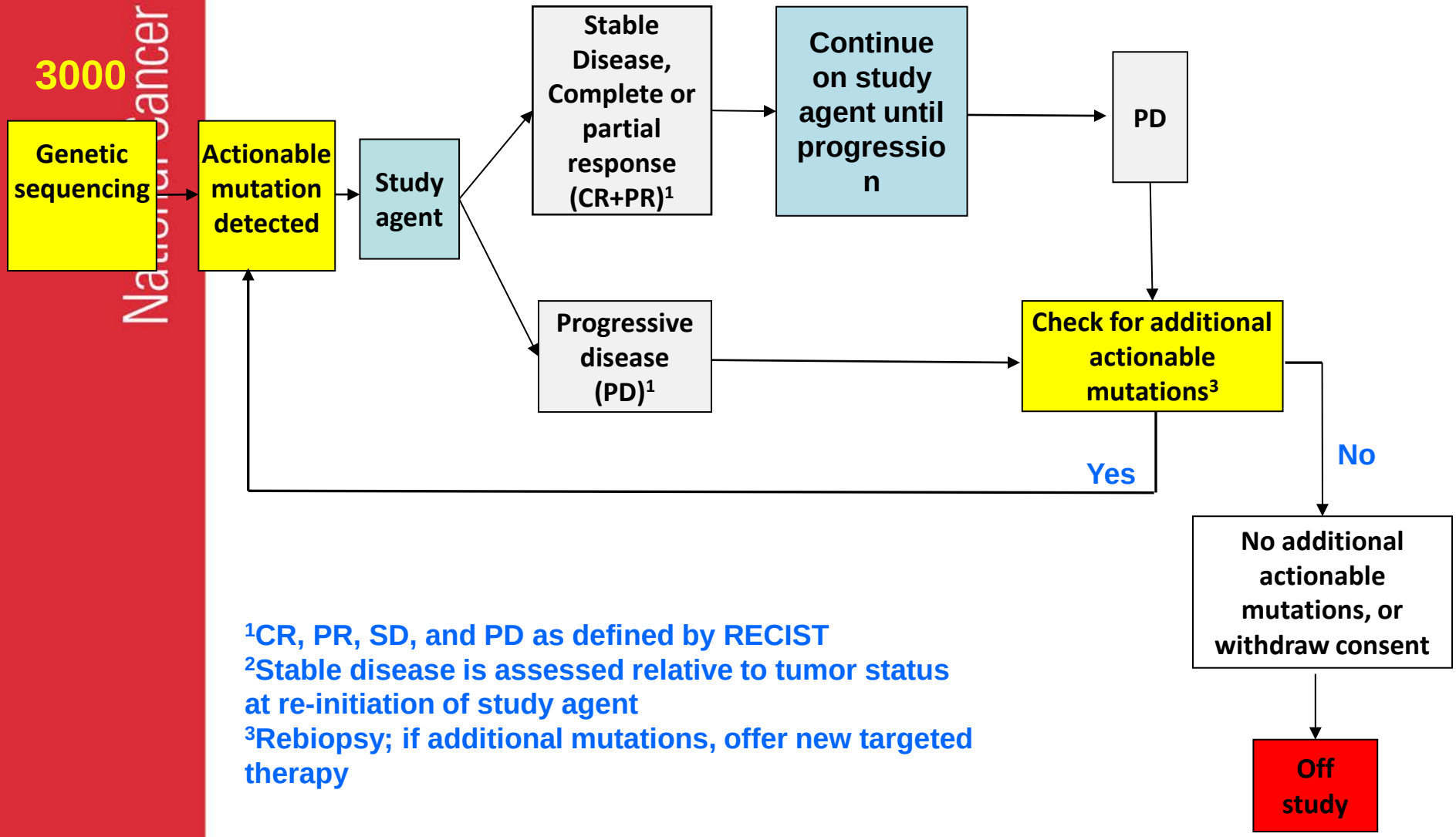
3000



[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

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NCI-MATCH

- Umbrella protocol for multiple, single-arm phase II trials
  - Each molecular subgroup matched to a targeted agent
- CTEP-IND for protocol template
  - Arms could be added or deleted without affecting other arms
  - Device discussions with CDRH
- 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

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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

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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

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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**

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

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Study Participation

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

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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

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Levels of Evidence: genes

- Credentialed for selection of an approved treatment target in a particular malignancy (e.g., ERBB2 amplification and trastuzumab; BRAFV6003 and vemurafenib)
- Credentialed for selection of an approved treatment target in any malignancy but robust clinical data are lacking re: efficacy in other cancer subtypes harboring that variant.
- Gene/variant is an eligibility criteria for an ongoing clinical trial
- N of 1: response (e.g. TSC1, everolimus)
- Preclinical data
  - a. Response in at least 2 xenografts with the mutation AND no response in 2 xenografts without the mutation OR
  - b. Response in several cell lines with the mutation AND no response in cell lines without the mutation

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Team Approach

- Agent & Gene Selection Committee vetting actionable genetic alterations and most robust agents
  - May need to recruit additional agents
  - Essential targets/pathways include: RTK, MAPK & PI3K
- Genetic platform developed and validated at NCI-Frederick & responses to RFA being review for extramural diagnostic centers

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Over 40 drugs pledged

COMPANY

- Abbvie
- Amgen
- Ariad
- Biomarin
- BMS
- Boehringer Ingelheim
- Clovis

COMPANY

- Genentech
- JNJ
- Millenium
- Pfizer
- Sanofi
- Tesaro
- Tracon
- Verastem

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In progress

- Currently 20 “arms”
- EGFR, HER2, MET, BRAF, NF1, GNAQ, GNA11, TSC1/2, PTEN, Patch, NF2, ALK, ROS, FGFR

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Eligibility Assays

- NGS: Ion Torrent PGM with custom Ampliseq panel of 200-300 actionable genes
  - Single nucleotide variants
  - Amplifications
  - Selected translocations
- Validation in network of CLIA certified labs: RFP thru Leidos
- IHC, FISH as needed
- Rule driven treatment assignment

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NGS Assay Details

- Central pre-analytic pathology laboratory
  - Biopsy receiving, specimen processing, H&E assessment, enrichment (if needed) & extraction of nucleic acids
  - Shipment to MATCH Clinical Laboratory Network for NGS assay
- Standardized SOPs for targeted Ion Torrent AmpliSeq NGS Assay
- Standard Assay report (CLIA)

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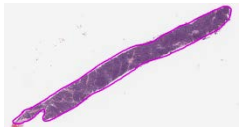
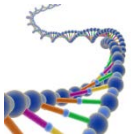
Workflow and Turnover Time of the Assay System



Tissue Fixation Path Review

Tumor content >50%



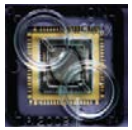
Nucleic Acid Extraction

DNA yield > 20 ng

Library/Template Prep

Library yield > 10 pM

Test fragments: A/D > 80% AQ17, Read Length > 90 bp
Reads per sample: >350, 000
Read Length: 140-160 bp
Coverage: " >80% of amplicons coverage >450X
Positive: detect all true positive variants
Negative: detect no false positive aMOI
NTC: total reads < 2% of lowest sample library read



Sequencing

Data Analysis

aMOI Report Review

Final Report

aMOI = actionable mutation of interest

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In progress

- Nomination of investigators to guide optimal target/agent selection
  - Will become authors and PIs of study arm
- Continued engagement with patient advocates to ensure that design is responsive to patients' needs/concerns
- Develop master protocol including elements that pertain to all arms
  - Tissue submission, result reporting, response criteria, QOL

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