

# NCI Exceptional Responders Initiative

Phenotype to Genotype

September 2014

# 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.

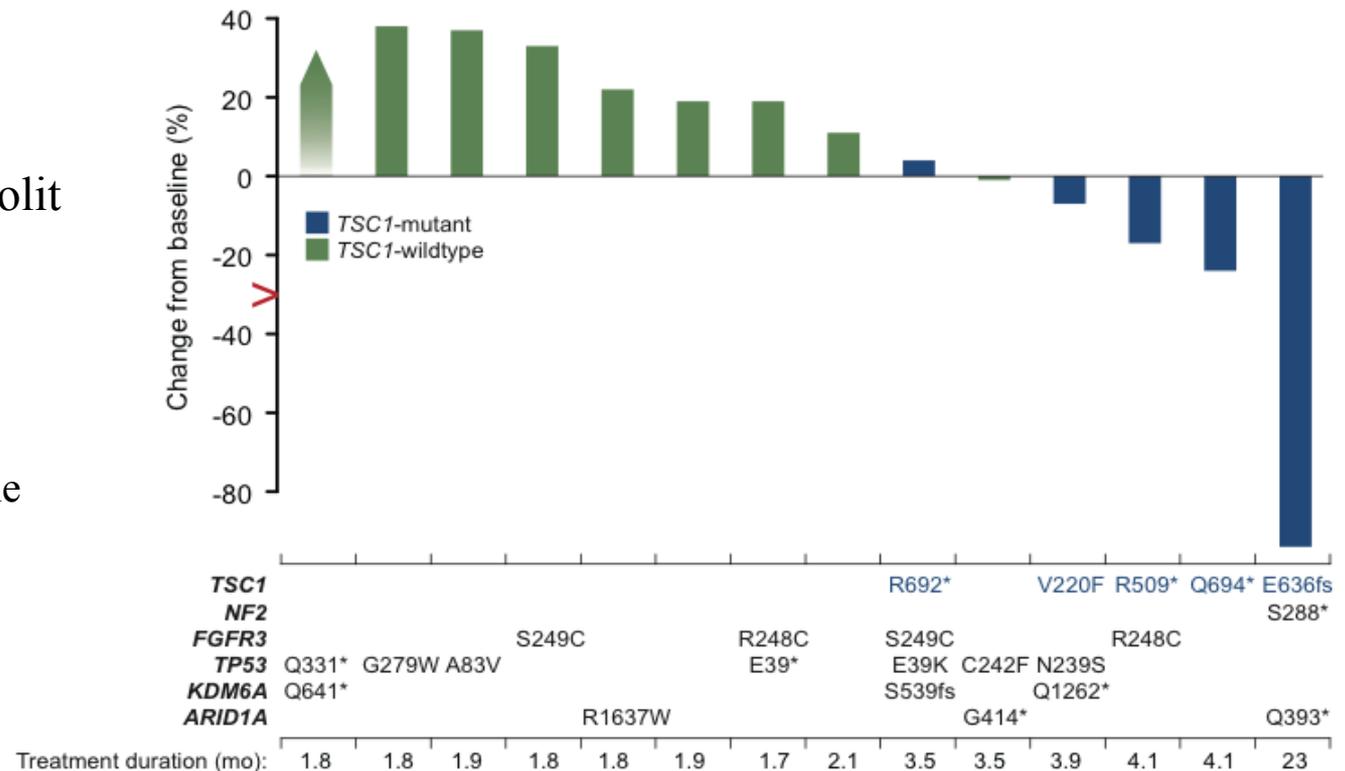
# TSC1 mutation correlates with clinical benefit in patient with metastatic bladder cancer

The graph below illustrates best overall response of 14 bladder cancer patients treated with everolimus. The bars note whether tumor grew or shrank.

Patients with TSC1-mutant tumors (blue bars) stayed on everolimus longer than those with TSC1-wildtype tumors and the time before their cancer recurred was longer. Some patients with TSC1-mutant tumors had responses, one exceptional.

(Source:  
Iyer/Berger/Taylor/Solit  
*Science* 2012 article)

Red hatchmark notes the  
threshold for partial  
response.



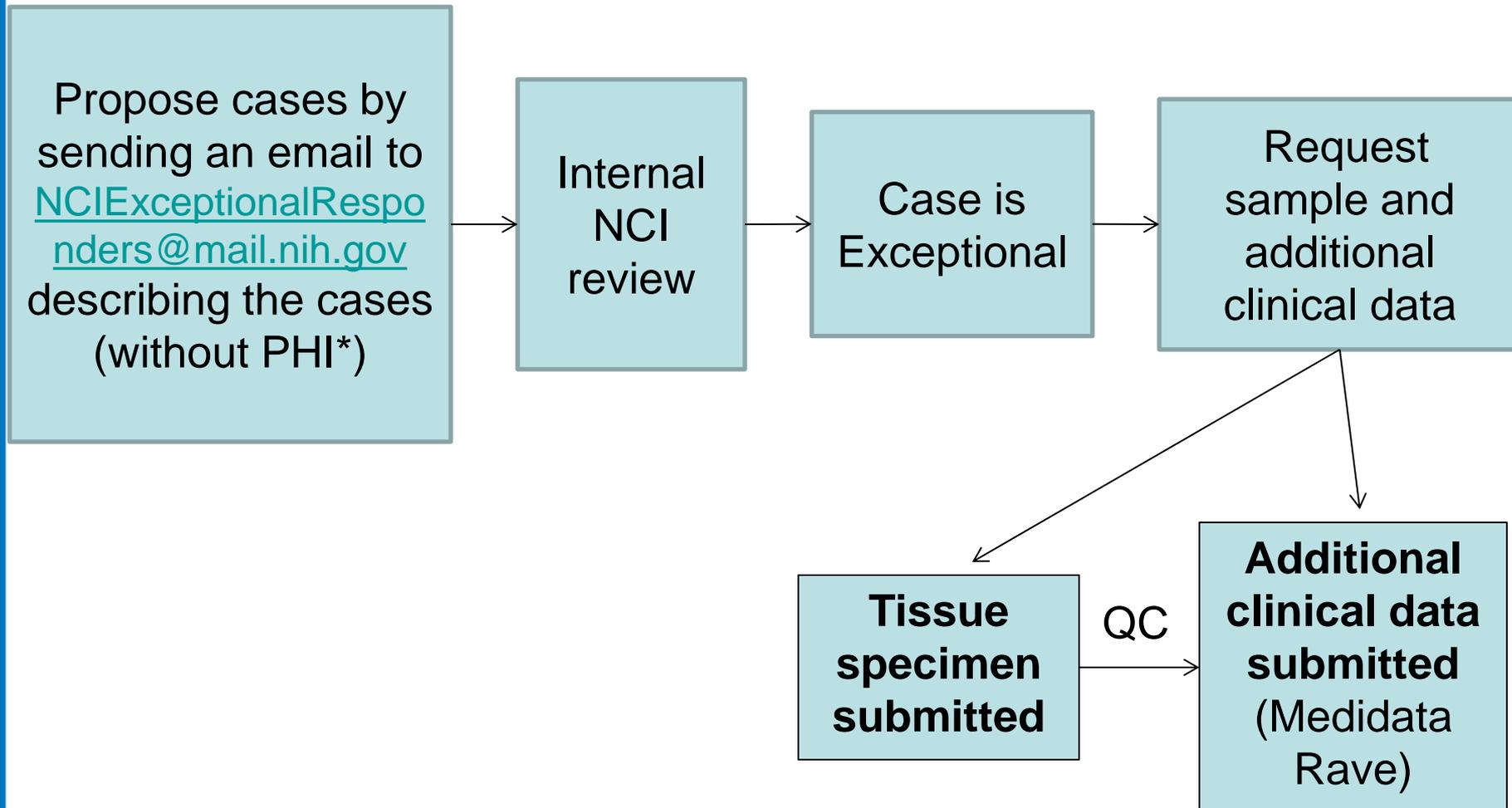
# Exceptional Responders: Objectives

- To identify molecular indicators in malignant tissues from patients who were exceptional responders on clinical trials or other systemic cancer treatments, using whole exome, targeted, and mRNA sequencing, and potentially molecular characterization methods.
- To explore associations between the identified molecular indicators and the putative mechanism of action of the treatment received by the patient.
- To test the feasibility of identifying "exceptional responders", obtaining the relevant tumor and normal tissue and clinical data, and performing whole exome sequencing on these samples.

# Exceptional Responders: Definition

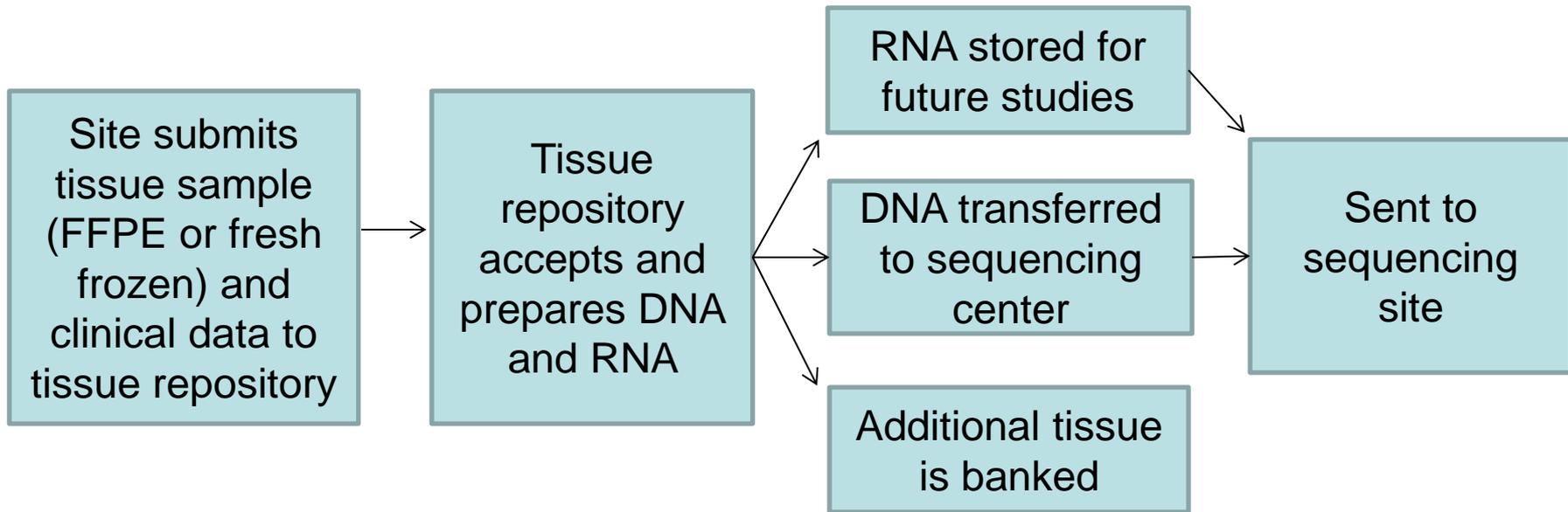
- **Definition of “Exceptional Responder”:**
  - Complete Response, or
  - Partial Response lasting at least 6 months
  - Drug did not go on to FDA approval in that indication due to insufficient activity or not expected to have CR or PR  $\geq$  6 months in  $>$  10% of patients
- **Tissue**
  - Tumor tissue: Prefer just before drug treatment; otherwise any prior
  - At least 50% tumor
  - FFPE, frozen, core acceptable
  - Normal tissue: blood or other

# Screening of Potential Exceptional Responder Cases

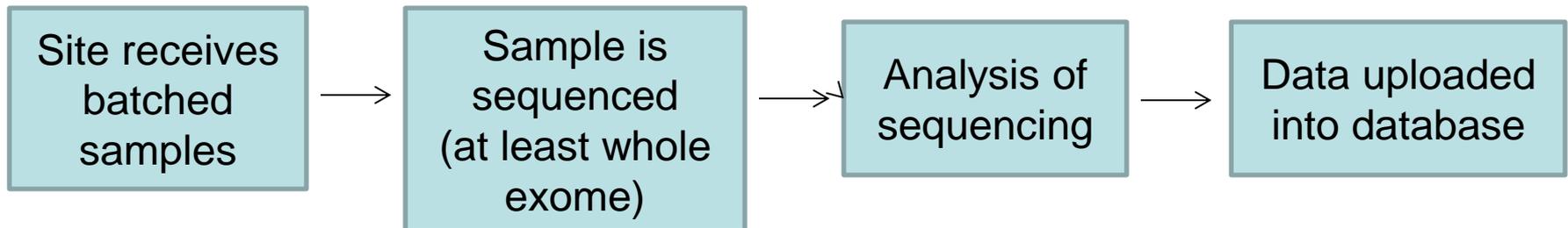


\*PHI = protected health information

# Submission and Preparation of Samples



# Sequencing and Analysis of Samples



# Logistics

- Protocol approved by the NCI Central IRB.
- Available on CTSU.
- Cases proposed by email and reviewed.
- Cases approved as “exceptional” will enter clinical data through OPEN and Medidata Rave.
- Provisions for non-CTEP investigators to participate.

