Re-inventing NCI-Supported Early Phase Clinical Trials

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Causes of Phase II Failures: 2008-2010

- Efficacy: 51%
- Strategic: 29%
- Safety: 19%
- PK/Bioavail: 1%

Overall Phase II Success Rate 18% (2008-2009)

Current U01 Experimental Therapeutics Program:

- Current budget: \( \sim \$8.87 \text{ M} / \text{yr} \)
- Annual accrual across 14 sites: 898 – 1290 / yr
- Average number of open trials: 120
- Active INDs: 80
- Anticipated INDs in 2012: 15
Challenges for NCI-Supported Early Phase Clinical Trials

- **Accrual**
  - New agents may be very active in tumors with specific mutations or other defined genotypes
  - However, smaller patient populations with the specific molecular characteristics must be identified
  - Studies will require multi-site participation if biomarker-driven
  - A program of sufficient breadth and flexibility capable of rapidly adapting to variable accrual needs is required versus current focus on single site trials
  - Develop resources that can support scientific requirements and IRB review in early phase trials across sites

- **Biomarkers**
  - Validated assays in qualified labs; cannot continue without them

- **Translation**
  - Understanding MOA and mechanism of resistance in humans
DCTD: Transitioning to the Future

• Choose agents for NCI’s early trials only if time frame allows for the development of an appropriately qualified molecular marker.

• Develop agents that can be brought to the clinic under conditions that could demonstrate POM in Phase 0/1 or POC in Phase II/III [No tissue, No marker, No study].

• Facilitate the transfer of the full range of tumor biology expertise that exists uniquely in NCI’s major translational programs into the NExT pipeline through the development of a new Early Phase Network.

• Provide the essential core laboratory resources to ensure that for every clinical trial supported by DCTD we will understand at its conclusion why it succeeded or why it did not.
How Should the NCI’s Early Phase Network Change?

• Serve as nexus for enhanced collaboration across NCI-sponsored programs: Centers, SPORES, PO1s, Mouse Models
  ✓ Provide broader access to critical pharmacodynamic and clinical genomic core resources for early phase clinical trials utilizing facilities in Frederick and/or extramural core laboratories
  ✓ Ensure standardization of clinical genomic and molecular marker testing, as well as data handling, storage, and analysis in concert with the NCI’s overall clinical genomics program

• Reprogramming of current resources to a smaller number of early phase clinical sites performing fewer trials should support:
  ✓ Critical imaging studies
  ✓ Repetitive biopsies for molecular characterization
  ✓ Core tissue handling and storage resources specifically for early phase trials (not currently available)
  ✓ Utilization of translational cores now funded by NCI Center, PO1, and SPORE grants by early phase trialists
What Do We Need To Do?

- Develop a national consensus around a re-defined early phase clinical trials model
- Enhance the capacity of the new NCI-Frederick-based molecular characterization laboratory and/or the clinical assay development network initiated with ARRA funds (a collaboration comprised of both academic and molecular diagnostics concerns) in the area of specific multi-analyte assays (i.e., next generation sequencing panels of targeted mutations or exome-capture sequencing)
- Develop the additional data acquisition, storage, and analysis capabilities in concert with the extramural community to support a modern early phase network that will conduct trials at multiple sites based on the availability of an expanding range of molecular information (that must ultimately be placed in a confidential, but widely accessible database)
- Work with Industry partners to establish how molecular characterization data will be developed, utilized, and shared over multiple, sequential clinical trials involving a variety of agents (from different companies) that a single patient may enter
Concerns

- Fewer, but better resourced, sites will be required to perform substantially more sophisticated clinical investigations; however, the network sites will all have to interact with a much larger group of academic/industry collaborators than currently
- Many more, and more complicated, components to the new network
- A database sufficient to hold new clinical genomic information will need to be established; quantitatively and qualitatively different than current capabilities
- A molecular analysis and reporting pipeline will need to be developed and validated
- New core of (probably extramural) bio-informaticians will need to be recruited to participate in this effort
- Pharma collaborators will have to agree to sharing patient response data and permitting NCI and affiliates to use this for future research (clinical) studies

Initiating a pilot program at the Clinical Center to test new approaches to many of these concerns