Redesign of the Early Experimental Therapeutics Program: NCI Early Phase Therapeutics Network

NCI-Clinical Trials and Translational Research Advisory Committee

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Challenges for an Early Phase Therapeutics Network

Accrual

- Newer agents may be very active in tumors with a mutation(s)
- However, smaller patient populations with the mutation marker must be identified
- Studies will require multi-site/multi-disciplinary participation if biomarker driven
- A sizable/flexible program that can rapidly adapt to accrual needs is required
- Develop resources that address scientific and IRB review

Biomarkers

- Validated assays in qualified labs

Translation

- Understand MOA and mechanism of resistance
- POC and POM, molecular characterization
- Technology expertise
DCTD/CTEP Goals for an Early Phase Therapeutics Network

- *Optimize Integration* of Experimental Therapeutics with NCI/DCTD-funded Assets/Programs
- Development of interdisciplinary teams
- Promote collaboration between preclinical and clinical investigators
- *Molecular characterization* of patient tumors to enable evaluation of POM, POC, combinations, resistance
- Resources for collection (with biopsies), tumor banking, and analysis
AGENTs

Special Emphasis Panel (SEP)

NCI Review, Analysis and Funding Allocation

Cancer Therapy Evaluation Program (CTEP)

Investigational Drug Steering Committee (IDSC)

U01 / N01 sites

NCI Experimental Therapeutics Program (NExT)

prioritizes agents for NCI development

membership: DCTD, DTP, CTEP / IDB, CCR
development plan, agreements / CRADA

LOI solicitation

Clinical Trials

National Cancer Institute
High Priority Targets and Agents

**Survival / Proliferation**
- Ras
- Raf
- MEK
- PI3K
- Akt
- mTOR
- Bcl-2
- XIAP
- Btk
- PCI-32765
- CD105
- TRC105

**Angiogenesis**
- VEGF-R
- VEGF
- Bcr-Abl
- IGF-1R
- HER2
- c-Kit
- sertatinib
- sorafenib
- c-Met
- Z-endoxifen
- PDGFR
- FLT3
- RET
- bFGFR
- selumetinib

**Mitosis**
- mTOR
- CDKs
- dinaciclib
- microtubules
- bortezomib
- CDKs
- dinaciclib
- microtubules
- bortezomib

**Protein Turnover**
- proteasome
- bortezomib
- CHK1
- SCH 900776
- Aurora kinase A
- MLN 8237
- Wee1 kinase
- MK-1775

**Apoptosis**
- temsirolimus
- FdCyd
- THU
- obatoclax
- venetoclax
- navitoclax
- AT-101
- lapatinib
- cetuximab
- EGFR

**Migration / Invasion**
- ceramide
- fenretinide
- dasatinib
- sorafenib
- imatinib
- sunitinib
- gefitinib
- gefitinib
- lapatinib
- cetuximab
- bevacizumab
- VEGF Trap

**Immuno-modulation**
- CTLA4
- ipilimumab
- ticilimumab
- CD22
- HA22
- Hsp90
- AT 13387
- PU-H71

**DNA Repair / Epigenetics**
- PARP
- Veliparib
- HDAC
- belinostat
- entinostat
- vorinostat
- LMP400/776
- Topoisomerases
- Alkylation
- Dimethane sulfonate
- Methylation inh.
- FdCyd/THU

**Other**
- Notch
- RO4929097
- Vismodegib
- Hedgehog
- LMP400/776
- Alkylation
- Dimethane sulfonate
- Methylation inh.
- FdCyd/THU

**Topoisomerases**
- LMP400/776
- Alkylation
- Dimethane sulfonate
- Methylation inh.
- FdCyd/THU

**Bcr-Abl**
- IMC-A12
- linsitinitib
- pertuzumab
- trastuzumab

**BTK**
- PCI-32765
How is the System Evolving?

- **Team Science** focused approach

- **Molecular profiling** of patient tumors from early experimental therapeutics clinical trials

- **Enhanced collaboration**, both within NCI/DCTD (PD Lab, CRADA collaboration, CDP, CIP, RRP) and with other NCI-sponsored programs, including SPORES, Centers, mouse models consortia, grantees (P01s)
Translational Clinical Research: Bedside to Bench and Back

Patients eligible for early phase clinical trials

Analysis of tumor and other tissues for pathway activation or resistance / other

Patient assigned to trial based on molecular characterization of tumor

Patient monitoring

Patient monitoring: Post-treatment molecular reanalysis

Non-clinical models for targets

Translational Research with “clinical” models

• Methylation status
• Sequencing
• Expression arrays
• FISH
• IHC

$\star = $ clinical observation

National Cancer Institute
NCI Early Phase Therapeutics Network

Team Science:

Investigational Agent Specific

- Clinical Scientists
  - Early Trials – Clinical Trials Network (ET-CTN) Investigators
- NCI/DCTD
- Translational Scientists
  - SPOREs
  - P01s/Imaging Networks
- NCI/DCTD
- Cancer Biology Scientists
  - NCI/DCB
Summary for Discussion

• Redesigned ET-CTN should learn from every clinical trial performed
• Each patient’s tumor should be molecularly characterized to inform current and future drug development
• ET-CTN focus should be primarily on defining POM, POC, target engagement, comprehensive multi-phase tumor evaluation
• NCI funds many translational and cancer biological grants and Designated Cancer Centers that should be leveraged in this effort
• NCI’s early drug development effort should be scientifically-focused and complement the pharmaceutical industry whose primary goal is drug approval

What is the most effective way to integrate/implement our collaborative strategy?