

Fox Chase Phase I Clinical Trial Program: An Overview

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Talk outline

- FCCC Phase I Program overview
- Optimal Phase I Collaborations
- Challenges and opportunities in the molecular therapeutics age

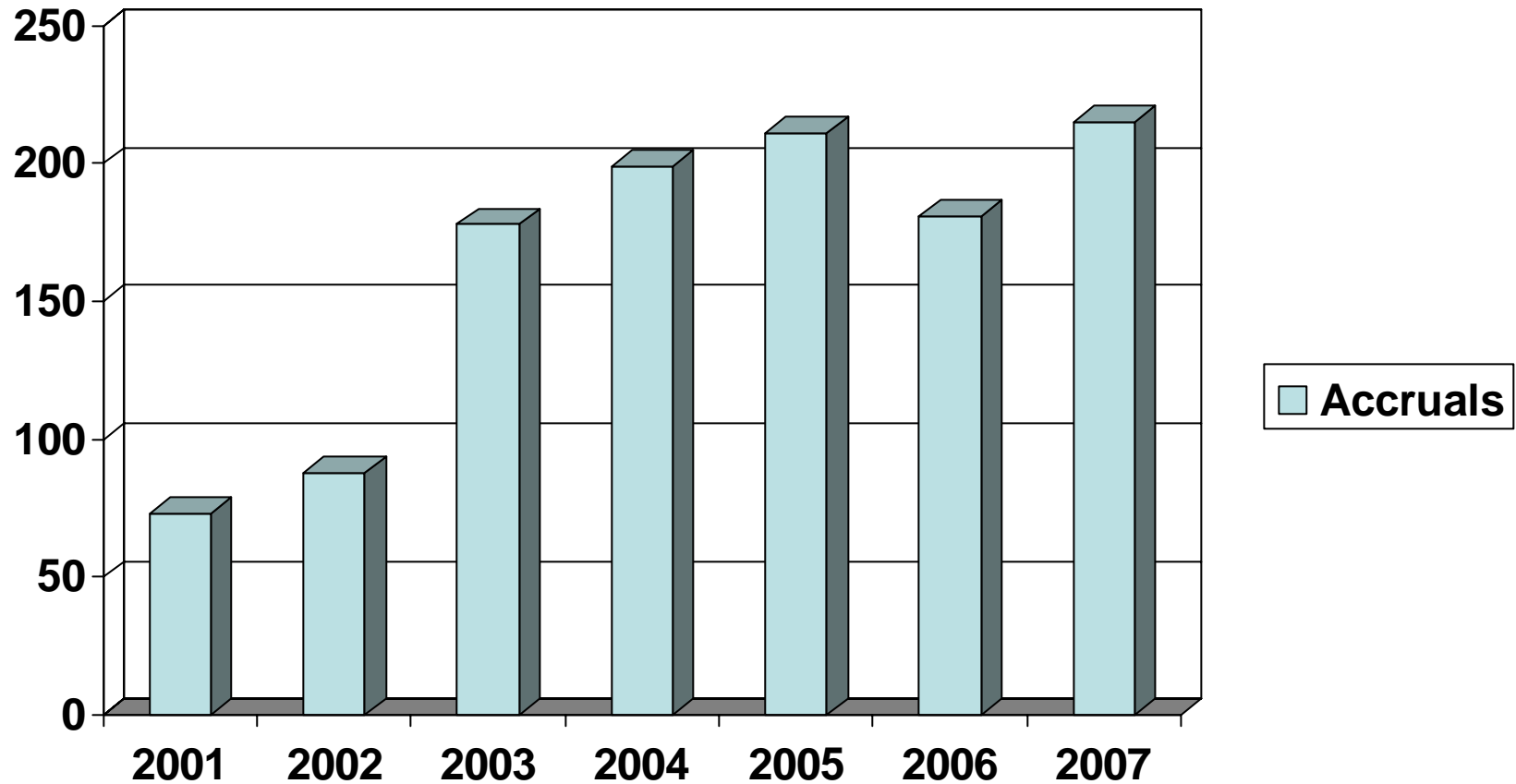
Program Goals & Objectives

- To develop more effective and less toxic therapies for the treatment of malignancy
- Identify potential biomarkers of drug effect
 - Blood tests (CTCs, proteomics, gene testing)
 - Imaging (DCE-MRI, PET)
- Pharmacokinetic and pharmacodynamic studies
- To provide a comprehensive menu of phase I studies to Fox Chase patients, Partners MDs, other referring physicians (tri-state and national)

Scope of Our Phase I Program

- Research interests: Diverse array of agents directed against the full spectrum of contemporary cancer targets
- Number of active studies: 24
- Number of planned studies: 12
- Important collaborations:
 - ECOG
 - RTOG
 - GOG
 - NCI
 - Pharmaceutical partners
 - Phase II Consortia (Princess Margaret, Fox Chase Network)

Phase 1 accruals by year



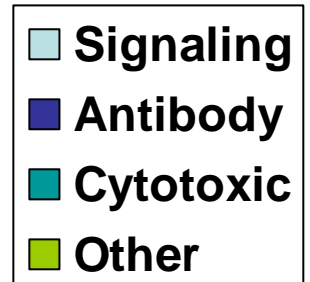
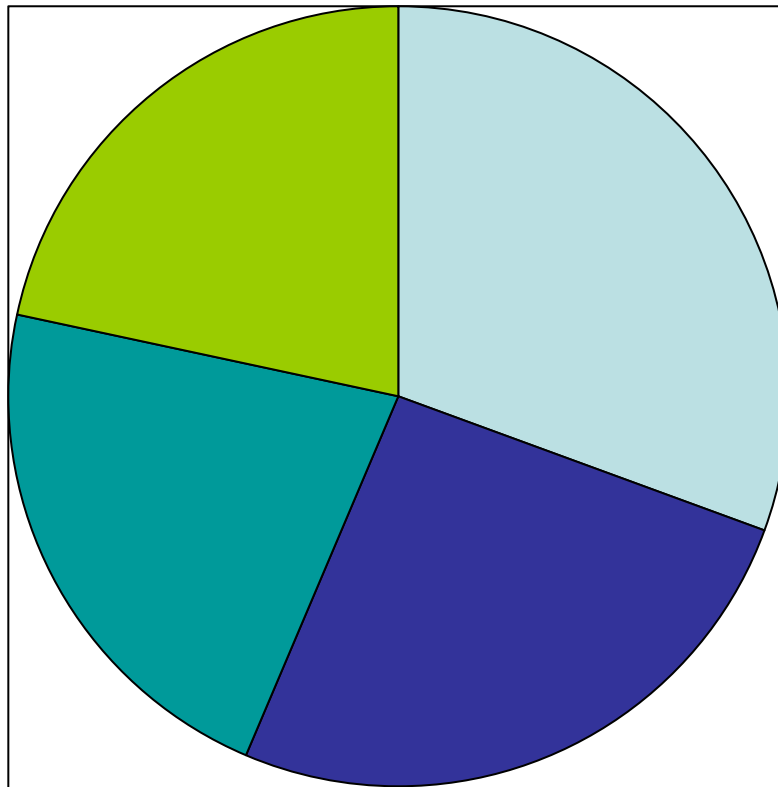
Phase I trial types

- New single agents
 - First-in-humans proof of concept trials
 - 3-4 per year at FCCC
- New schedule or dose of existing, usually not yet approved, agent
- Existing agents in combination
 - Novel agent added to a standard regimen (chemocombo)
- Multiple modalities
 - XRT plus new drug
 - Unlicensed drug plus unlicensed drug (unusual)
 - “All biologic” novel combinations (e.g., bevacizumab plus erlotinib)

Trials Menu Scope, 2008

- Broad array of agents directed against the full spectrum of contemporary cancer targets
 - Traditional DNA-interacting agents
 - Monoclonal antibodies
 - Small molecule enzyme inhibitors (TKIs)
 - Immunoconjugates
 - Other (chemosensitizers, pro-apoptotic agents, aurora kinase inhibitors, ksp inhibitors, etc.)

Present phase 1 composition



Phase I Team resources

- Research Team infrastructure:
 - Phase I Investigators: Two primary phase I PIs
 - Research Coordinators:
 - Four dedicated CRCs (RNs) paired with 4 data managers
 - Additional disease-specific teams assigned more disease-oriented studies
 - Other Personnel:
 - Regulatory: Four FTE (IRB, RRC, amendments, consent changes, 1572s, etc)
 - Contracts
 - Protocol Support Lab (5 FTE)
 - Clinical Research Unit Nursing
 - Inpatient Clinical research capabilities
 - Two dedicated Physician Assistants

Resources (cont.)

– Capabilities

- Protocol Support Lab
- New state of the art outpatient Clinical Research Unit
- Radiographic Imaging (PET, DCE-MRI, CT, Radionuclear imaging)
- Interventional Radiology
- Punch biopsies, FNA, Core needle biopsies

– Capacity management

- We currently enroll 200 phase I patients on protocol/year
- At our current capacity, this is steady state
- Plan to open one protocol for every one completed

– Study selection criteria:

- Scientific Merit/Feasibility
- Clinical Research Review (faculty interest)
- Research Review Committee
- IRB

Communication

– Internal communication:

- Weekly Phase I meetings
- E-mail
- Telephone
- Teleconferences with Sponsors
- Web-based resources for faculty and staff
- Face-to-face communication

Optimal Phase I Collaborations

Scientific/Translational

- Early review of protocol in development
- Protocol finalized after Research Review comments

Optimal Phase I Collaborations

Operations/Regulations

- Pre-planned monitoring visits
- On-site training of staff
- Off-site training of staff

Optimal Phase I Collaborations

Communications

- Scheduled biweekly teleconferences
- Minutes

Examples of Molecular Targets in Present and Upcoming Trials

- IGF1-R
- Novel anti-angiogenic targets
- PARP
- Kinesin spindle proteins
- “pan-TKIs” (Her1 and/or Her2, VEGFR)
- P-cadherin positive
- Tumors that are EGFR positive by IHC or FISH
- Mesothelin positive by IHC

Challenges

- Traditional Phase I designs are valid for novel chemotherapy drugs and some of the newer agents
- But, many targeted agents require assessment and incorporation of correlative endpoints or novel imaging modalities to get the dose and schedule right
 - Increasingly, no clear relationship between dose and toxicity
 - No DLT

Changing Expectations for Phase I

- DLTs and RP2D based on DLTs are often inadequate endpoints
 - May not be any DLTs
- Proof of mechanism
 - Does the agent interact with the target at clinically tolerable doses?
- Proof of principle
 - Does target interaction produce downstream events known/likely to produce, be associated with clinical efficacy?
- Preliminary evidence of clinical efficacy
 - Molecular imaging response (e.g., PET)
 - Objective radiographic response
 - Very prolonged stable disease (> 3 months)

Changing Patients in Phase I

- Molecular assessments may enrich phase 2 (and phase 1) studies with patients more likely to respond
 - But, how will we identify patients for these trials?
 - May require a new approach to disease classification
 - In some cases patient might be best served by early enrollment onto a trial (ex: GIST with exon 11 mutation)
- Tumor biopsies
 - Potentially important but difficult, expensive
 - Safety
 - Patient may progress early before the biopsy
 - Tissue assays need to be robust
 - Bias in patient selection

Novel endpoints

- **Imaging**
 - PET scanning
 - Tissue perfusion and blood volume
 - Glucose metabolism (FDG)
 - Cell division (FLT)
 - DCE-MRI
 - Blood flow
 - Changes in permeability
 - Tumor measurements in 3-D
- **PBMCs and CTCs**
- **Drug levels**
 - Saturable PK (cetuximab, bevacizumab)
- **Serum markers (apoptosis, sVEGFR, etc.)**

Fox Chase Phase I Team

