Cancer Drug Development

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• Drugs are only useful if they are available to patients (marketed)
• Drugs are only useful to patients when doctors know how to use them
• Doctors rely on clinical trials data to know how to use drugs
• Clinical drug development is the ‘orderly’ process of producing data which defines the safety and efficacy of a new drug/agent
Milestones in Drug Development Prior to Clinical Trials

- Discovery of target, molecule, or anti-cancer activity
- Optimization against target/define mechanism of action
- Assay development (measure drug and effect on target)
- In vitro activity
- In vivo activity (appropriate models, dose, schedule, combinations)
- Pharmacokinetics
- Pharmacodynamics
- Route of Administration (PO/IV/SQ/other)
- Metabolism/Activity of Metabolites
- Toxicology (relevance of species)/Vesicant effects
- Characterization of human tumors for expression and relevance of target
- Mechanisms of Drug Resistance
- Chemistry/synthesis
- Production (yield, identity, purity, contaminants, potency)
- Solubility/Formulation/Stability/Storage/Diluent and tubing compatibility
- Distribution after administration
- Drug Interactions
- Business Issues
  - Indications and market size, drug development plan
  - Patent protection
  - Competition
  - Positioning
  - Cost and Financing of Development
  - Pricing
  - Return on Investment
• Study of new drugs in patients requires an Investigational New Drug Application to the FDA
• Pre-IND meetings with FDA are strongly recommended to assure they agree with planned toxicology and initial trial design
• Rules governing conduct of investigational drug studies are covered under CFR Title 21 section 312
• The IND sponsor and study investigator have clear regulatory responsibilities
  – Documentation
    • Qualification of investigators and sites
    • IRB approvals
    • Site and FDA communications
    • Control of investigational drug
  – Monitoring for safety and compliance with the protocol and federal rules
  – Adverse Event Reporting
  – Modification of research plan based on ongoing review of safety and activity data
  – Amendments
  – Annual reports
Clinical Development – Phase 1

- Dose (optimal or maximal tolerated dose)
- Schedule
- Safety
- Pharmacokinetics, drug distribution
- Pharmacodynamics
- Biologic activity and effect on target
- Imaging
- Exploration of combinations based on:
  - clinical activity
  - knowledge of mechanism and tumor biology or other preclinical studies (drug synergy)
  - Combination phase 1 trials usually begin concurrent with or after phase 2 trials
Trial Designs for Phase 1

• FDA guidance for starting dose based on toxicology in two species (rat and dog, monkeys for some biologics)
• Standard design
  – Dose escalation in modified Fibonacci scheme
  – 3-6 per cohort
  – Continue escalating until 2 DLT in a cohort
  – MTD is highest dose cohort in which no more than 1 patient of 6 develops DLT

• Accelerated titration designs
  – Single-patient cohorts, 100% dose escalation until one grade 2 event, then standard design of 3-6/cohort, 40% dose escalation between cohorts until MTD

• Continuous dose reassessment models
Clinical Development – Phase 2

• Screen for disease activity
  – Single agent and combinations
  – Endpoints include rates of disease regression, progression-free survival, or survival
  – Endpoints depend on drug and indication, other available treatment
  – Endpoints influence study design

• Further characterize safety and feasibility
• Additional dose-ranging studies (dose versus effect)
• Correlations between biological activity and clinical outcome (effect on target versus outcome)
• Baseline host/tumor characteristics versus clinical outcome and biological effect on target
  – Tumor biology/characteristics (expression of target, mechanisms of resistance)
  – Drug metabolism or host features (polymorphisms in target gene or metabolic phenotype, pharmacogenetics)
  – Influence patient selection for further development
Typical Trial Designs for Phase 2

• Demonstrate sufficient activity to continue development or proceed to larger phase 3 trials
• Statistical designs minimize false negative, accept higher rate of false positive because existing therapies are poor and do not want to miss potentially active drug
• Single-arm, two stages
  – Response rate with 95% confidence intervals
  – Response usually defined as tumor regression (PR/CR based on RECIST), but also can include prolonged stable disease
  – Differentiate response rate probability p0 from probability p1
  – Comparison to well-defined historical controls
• Randomized trials
  – Comparison of regimens or doses
  – Usually small numbers per arm in cancer, not powered to detect small or reasonable differences
  – Preferable when drug is expected to increase progression-free survival (cytostatic) with low rate of tumor regression
Clinical Development – Phase 3

- Trials which are designed to demonstrate efficacy (true patient benefit) and isolate the effect of the new drug
- Comparisons are usually made against standard treatment
  - New drug + standard treatment vs. standard treatment ($Xyz$ vs. $yz$) or;
  - New drug versus standard treatment ($X$ vs. $yz$) or;
  - $Xz$ versus $yz$
- Endpoints are true measures of benefit or **validated** surrogates of benefit
  - Increased survival
  - Decrease in symptoms
  - Possible surrogates: tumor regression and progression-free survival, tumor markers or markers of biological effect
- Trials must be well-controlled
  - Almost always, randomized
  - Adequately designed (placebos and blinding as appropriate, particularly if progression-free survival is an endpoint)
  - Powered to detect statistically significant differences
  - Differences from control should be clinically meaningful and reasonable
  - High-level statistical input into design and analysis is mandatory
• Non-clinical studies should continue throughout clinical development
  – Define mechanism of action
  – Refine dose and schedule
  – Mechanisms of resistance
  – Optimal combinations (schedule issues important)
  – New indications
  – NDA directed studies (ie, carcinogenicity)

• Clinical development continues post-marketing
  – Expand in indicated ‘market’
  – Improve outcome and patient selection
  – Improve treatment for disease
  – Test activity in other indications
  – Registration studies for secondary indications
Roster of Players in Cancer Drug Development

- FDA
- NCI
  - Developmental Therapeutics Program
  - Cancer Therapy Evaluation Program
- Drug companies
  - Big Pharma
  - Biotechnology companies
- Contract Research Organizations
- Grant agencies other than NCI (ACS, DOD)
- Investors/Funds/Venture Capital
- Clinical Investigators and Scientists
- Institutional Review Boards
- Institutional Scientific Review Committees
- Institutional Quality Assurance and Compliance Committees
- Site Grants and Contracts
- Other Review Organizations
  - GCRC
  - Biosafety
  - Radiation Research
  - Recombinant DNA Advisory Committee
- Site research team (nurses, study nurses, data and study coordinators, data entry personnel, pharmacists, statisticians, bioinformatics, surgeons, pathologists, scientists)
- Patients and patient advocates
- Public and the Media
Clinical Protocols

- SCHEMA
- OBJECTIVES
- BACKGROUND
- PATIENT SELECTION
- REGISTRATION PROCEDURES
- TREATMENT PLAN
- DOSING DELAYS/DOSE MODIFICATIONS
- ADVERSE EVENTS REPORTING, SAFETY MONITORING, AND COMPLIANCE
- PHARMACEUTICAL INFORMATION
- CORRELATIVE/SPECIAL STUDIES
- STUDY CALENDAR AND MONITORING
- MEASUREMENT OF EFFECT
- STATISTICAL CONSIDERATIONS
- REFERENCES
- APPENDICES
Running the Gauntlet for an Investigator-Initiated Trial

- Idea and/or preclinical data
- Commitment for drug
- IND issues
- Funding commitment
- Write the protocol
- Write the informed consent
- Approval of protocol and consent from IND sponsor
- Submission Form for Institutional Scientific Review Committee
- Approval from Institutional Scientific Review Committee
- Write HIC application
- Approval from HIC
- Grants and Contracts (CDA, budget, CTA)
  - Hospital, CTO, sponsor, grant agency, etc.
- Case Report Forms and Database
- Pharmacy issues
- Coordination of study execution and procedures
- Training of staff
After Study Activation

- Identify and screen patients
- Coordinate tissue sampling and storage
- Protocol compliance (follow study treatment and monitoring)
- Monitor for safety and accrual
- Report adverse events
- Report safety and other data to Institutional Monitoring Committees and other sponsors (IND, funding agency, etc.) (frequency determined by site or sponsor)
- Annual Reports to HIC and Monitoring Committees
- Audits and Monitoring Visits
- Review and assess outside IND safety reports
- Amendment creation and submission
- Assure collection of data and accuracy of database
- Weekly meetings with staff for study issues and coordination
- Response audits
- Analyze clinical and preclinical data
- Write and submit publications
Why Participate in Clinical Cancer Research and Drug Development?

• Most current treatments are not effective or are toxic
• Investigational drugs and approaches are the only means to improve outcome
• Investigational treatments offer a chance for benefit or improved benefit compared to standard treatment in many patients
• Observations made in treatment of patients with investigational treatments can lead to new insights and ideas for improved treatment or can drive laboratory investigations in new directions