Oncology Clinical Research Lifecycle

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Oncology Drug Development is Costly and High-Risk

![Diagram showing the stages of oncology drug development from Discovery to Mature Commercial, with phases labeled Preclinical, Clinical Development, Marketed, and Cash Flow "Valley of Death". Different funding sources are indicated: Grants, Private Finance, Angel Investors, Venture Capitalists, Stock Owners, and Commercial Revenue.]
Drug Selection Process

Need for Better Models to Identify Candidates

• Only 5% of oncology drugs entering human studies will make it to market
  – 75% of drug development costs are spent on failures
• Balance diverse characteristics
  – Activity against target
  – Activity against the disease process
  – Potent
  – Selective
  – Oral absorption
  – Ideal metabolism, distribution and elimination
  – Non-toxic to humans
• Sequential evaluation of drugs against target may be inefficient
• We have only scratched the surface of potential molecules
  – We have explored 50 therapeutic targets, but 10,000 potential
  – We have explored $10^7$ molecules, but $10^{64}$ potential
Steps for Oncology Drug Development

• Non-clinical studies; Investigational New Drug (IND)
• Phase I, II and III, marketing approval and phase IV.
• Drug development time (from first-in-human to approval)
  – Oncology: 8 years
  – Non oncology: 4-6 years
• Challenges in oncology drug development
  – Phase I development slower
    • Patients
    • Narrow therapeutic index of many agents
    • Incremental process required to safely identify a maximum tolerated dose (MTD)
    • Less-than-ideal pharmacokinetic or adverse event (AE) profile is tolerated
  – Phase II lack of activity is more common setting for discontinuing development
NON-CLINICAL SUPPORT
Non-Clinical Studies To Support Human Testing

• Essential studies in US
  – Rodent study to identify doses that produce life-threatening and non-life-threatening toxicity,
  – Non-rodent study to better characterize the tolerability of the drug in that species

• Important Studies
  – Safety pharmacology, toxicokinetic, pharmacokinetic, single/repeat dose toxicity, local tolerance, genotoxicity, carcinogenicity, reproduction toxicity and pharmacodynamic studies.

• Objective
  – Identify a safe starting dose for phase I trials in humans
  – Determination of potential drug toxicities

• Unique aspects with oncology
  – Top dose not necessarily limited by non-clinical dosing
  – Carcinogenicity studies
    • Not usually needed prior IND; sometimes occur after market
    • Important for drugs intended for chronic use, chemoprevention, or adjuvant therapy
Determination of Safe Human Starting Dose

- Body surface area (BSA, e.g. mg/m2)
  - Used to relate toxicity between species
  - DuBois: $\text{BSA} = 0.007184 \times \text{weight(kg)}^{0.425} \times \text{height(m)}^{0.725}$,
  - Mosteller: $\text{BSA} = \sqrt{\left(\frac{\text{height(cm)} \times \text{weight(kg)}}{3600}\right)}$.

- Calculation of starting dose
  - Determine the dose that is severely toxic to 10% of a rodent species (STD10)
  - Converted to the human equivalent dose on the basis of mg/m2
  - Apply a safety factor (for example one-tenth the STD10)
PHASE 1
Gelsinger Case

• Jesse Gelsinger 18 year-old, first person publicly identified as having died in a clinical trial for gene therapy
• Mild form of ornithine transcarbamylase deficiency
• Clinical trial aimed at developing a treatment for infants
• On September 13 1999, he was treated and suffered a massive immune response triggered by viral vector, led to multiple organ failure and brain death
• FDA investigation concluded that the scientists broke several rules of conduct:
  – Inclusion of Gelsinger despite having high ammonia levels that should have led to his exclusion from the trial
  – Failure to report that two patients had experienced serious side effects from the gene therapy
  – Failure to mention the deaths of monkeys given a similar treatment in the informed consent
London/Parexel Healthy Volunteer Study

• On 13 March 2006, healthy young volunteers took part in a clinical trial
• TGN1412, developed to fight autoimmune disease and leukemia by the company TeGenero based in Würzburg, Germany
• Six volunteers became violently ill minutes after having been injected with the drug
Dosing in Early Studies

• Dosing decisions
  – BSA often used in oncology
    • Relatively little correlation between BSA and organ function
  – Dose per body weight (mg/Kg)
  – Fixed dose

• Human dosing limit
  – Non-life-threatening settings: limit human exposure to maximum animal exposure
  – Life-threatening, incurable disease: top animal exposure may be exceeded if with careful, incremental dose escalation
Phase 1 Study Designs
Healthy Volunteer Study

Dose 1
6-drug, 2-placebo

Dose 2
6-drug, 2-placebo

Sentinel Subject

No DLT

Exceeds MTD
2+ DLTs

6-drug, 2-placebo
Phase 1 Study Designs
3+3 Design

- No DLT
- 1/3 DLT
- 2+/3 DLT
- 1/6 DLT
- 2+/6 DLT (MTD exceeded)
Trial Design: Ph 1: “Modified Toxicity Probability Interval”

- Rules conceptually similar to those used in the 3+3 design
  - Decisions of the mTPI design are based on posterior probabilities calculated under a coherent probability model
- Choice of target MTD and desired range
- Calculated prior to study start
- Decisions at intervals of less or more than 3
PHASE 2
Phase 2
Key Goals

• Identify ineffective or excessively toxic drugs using a minimum number of subjects
• Explore alternate dosing and indications
• Estimate safety and efficacy for phase 3 planning
• Fine-tune the recommended dose for a phase III trial population
• Opportunity for regulatory approval in settings of life-threatening disease with high unmet medical need
• Always consider the eventual indication
Common Phase 2 Design

- Single-Arm, or multiple arms with different doses
- Can have “reference” arm with no statistical comparison required (as opposed to formal control)
- Stopping rules, eg Simon 2-stage design

19 patients

- ≥4 responses → Add 30 patients
- ≤3 responses → Stop
- DLT rate >30% → Stop
Case Study: Assessing Value of Stable Disease

- RR: Placebo=0, Sorafenib=2%

- OS HR = 0.72
Case Study: Addressing Challenge of Combinations

PD on Iri
n=329

Iri + Cetux
23% RR

Cetux
11% RR

OS HR 0.91
Trial Design: Use of Waterfall Plots to Evaluate Efficacy

- Key information
  - Where chart crosses 0
  - Where is the median?
  - Proportion of patients with CR and/or PR

- Caution
  - Doesn’t include patients without scan (i.e., early PD or toxicity)
  - Doesn’t capture duration or any time dynamic
Trial Design: Immuno-Oncology Learnings

- MTD: Not identified in most Ph 1 trials of antibodies
  - 8% MTD; 15% PK data; 77% Max administered dose
  - Expansion cohorts with ~13% G3/4 toxicity (consistent with <MTD)
  - irAEs classically appear 8-10 weeks; Factor in RP2D determination

- Dosing: No clear consensus
  - Dose Response: No clear correlation
  - Schedule & Duration: Single dose vs defined # vs indefinite; Frequency
  - Route: Intratumoral vs IV vs SQ

- Expansion cohorts: Early enrichment strategy
  - Early molecular selection, potential for breakthrough design and AA
  - Dramatic increase in size of some Ph 1 studies
    - Need justification for sample size and robust stopping rules
  - TILs and PD-L1+ correlate with response, but not completely sensitive or specific
Trial Design: Immuno-Oncology Learnings (cont.)

- **Patient population**
  - With better safety profile, consider ECOG2 in Ph1 expansions
- **PK: Complexities with Antibodies**
  - Limitations on maximum volume
  - High-affinity antibodies with target-mediated elimination
  - Receptor-mediated endocytosis, concentration-dependent half-life, circulating forms of target receptor
- **PD**
  - Receptor occupancy (not dose correlated)
  - CD4/CD8/cytokines
  - Polymorphisms that might affect efficacy (eg FcγRIIIa for rituximab)
- **Efficacy**
  - mWHO
  - RECIST
  - irRC
    - Dissociated response
    - Delayed response
    - Pseudoprogression
  - Waterfall comparisons
  - Disease control

Postel-Vinay et al 2015
PHASE 3
Phase 3
Key Goals

• Definitively demonstrate the safety and efficacy of a treatment in a specific population
• Study an indication where new therapy is needed, or improvement is needed
• Gain regulatory approval for a treatment
Interpretation of Trial Results
Many Different Perspectives

- Principle Investigators
- Statistical leaders
- Data Monitoring Committee
- Regulators
- Payers
- Journal editors and reviewers
- Clinical experts
- Guidelines committees
- Physicians
- Patients
Oncology Endpoints

• Clinical Benefit Endpoints
  – Live longer
  – Feel better
  – Function better

• Surrogates
  – Tumor shrinkage
  – Delay in progression
Endpoints For Oncology Drug Approval by FDA

Response rate and Time-To-Event are most common endpoints

Martell 2013
Case Study: Phase 3 Design With Biomarker Classifier

**Endpoints**
- **Primary**
  - PFS

**Secondary**
- OS
- RR
- PROs
- CDx bridge
- Investigator-assessed PFS
- Time to Rx Failure

**Niraparib**
- **Choice**
  - Eribulin
  - Capecitabine
  - Gemcitabine
  - Vinorelbine

**Endpoints**
- **Primary**
  - PFS
- **Secondary**
  - CDx Bridge
  - OS
  - PRO

**Platinum sensitive ovarian ca in response**
- 180 \( gBRCA \)
- 192 \( Non-gBRCA \)

**Food effect**
- 21 \( Niraparib \)
- 2:1
- Placebo

**Endpoints**
- **Primary**
  - PFS

**Secondary**
- CDx Bridge
- OS
- PRO
Case Study: Quantify Value of Benefit

• National Institute for Health and Care Excellence (NICE) decides which drugs and treatments are available in UK

• Considerations:
  – Benefits patients
  – Help NHS meet its targets, eg improving survival rates
  – Value for money or cost effective

• Quality Adjusted Life Years (QALY)
  – Used to measure the benefit of a treatment based on duration and quality of life
  – Years of Life × Utility = QALY
    • Utility: Perfect health=1.0, bedridden=0.5

• Value of QALY = $55,000
  – If a treatment took someone from bedridden for a year to being out of bed for several hours each day (say utility 0.6) but cost more than $2,250/year, then not recommended
Market Forces Influence Drug Cost

Monthly Price Reductions after Loss of Exclusivity

Source: IMS Health, National Sales Perspectives, March 2015
PHASE 4
Phase 4 Development

- Include Phase 1, 2 and 3 designs
- Post marketing label expansion
- Advancing standards of care
- Combinations
- Special populations (e.g., liver or renal failure)
- New formulations
- Health economic studies
• The majority of approvals are for single agents

• 67% of most common indications list a combination as preferred in NCCN

Martell 2013
Challenges in Developing Combinations

- Hundreds of cpds in development; multi-target and specific
  - Monoclonal antibodies
  - Small molecules
  - Novel biologics
- High complexity of combination development
  - Contribution of each agent to safety and efficacy can’t be taken for granted
  - Potential overlapping toxicity
  - Greater complexity in study design and interpretation
  - Larger trial size
  - Delayed proof of concept
- Initial indication for most cancer compounds is as single agent
- More and more drugs targeting specific signaling pathways may require combinations as primary development strategy
General Strategies for Combinations

a) Multiple hits on same target
b) Multiple targets in same pathway
c) Multiple pathways
d) Target compensatory processes

Dancey and Chen, Nat. Rev. Drug Discov, 2006
Therapeutic Interventions Affecting T-Cell Function in Cancer

Regulate T effector and NK Cytolytic functions; prevent T-cell exhaustion

Release the brakes

- Anti-PD1
- Anti-PDL-1

Bring T cells into the tumor

- Anti-CTLA-4
- Immune activating cytokines
- IDO inhibitors
- Oncolytic viruses
- Targeted therapies

Combination treatment

- Vaccines
- Stereotactic radiosurgery
- Chemotherapy
- Adoptive cell therapy

Generation of T cells

Increase Tcell infiltration within the tumor; enhance Tcell proliferation

Promote antitumor T-cell activity
Case Study: Rare Diseases

• Basket study: enrollment based on biomarker classifier rather than histology
• Patients with disease associated with Abl, Kit or PDGFR across over 40 rare indications treated with imatinib
Database: Colorectal Cancer Survival in Diabetics from VA Database

- Over 20,000 patients with CRC, including >5,000 with DM + CRC
- Detailed data on HgA1c, creatinine, race, AJCC stage, BMI, comorbidity index, CRC treatment
- Metformin use associated with superior survival; Adjusted HR=0.82

Diabetics taking metformin have lower incidence of cancer and better surgical outcome following neoadjuvant therapy for breast cancer.
BIOMARKER DEVELOPMENT
Improved success for drugs with biomarkers

Non-Small Cell Lung Clinical Trial Success for Molecules With and Without Biomarkers

January 1998-January 2012  N=676 Trials and 199 Unique Compounds

<table>
<thead>
<tr>
<th>Phase</th>
<th>Biomarker</th>
<th>Non-Biomarker</th>
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<tbody>
<tr>
<td>Phase One</td>
<td>97%</td>
<td>43%</td>
</tr>
<tr>
<td>Phase Two</td>
<td>67%</td>
<td>40%</td>
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Source: Journal of Thoracic Oncology, 2014; 9 (2): 163
Biomarker validation and sequencing are critical
Case Study: Biomarker Classifier
Practical Considerations

Tumor Biopsy

| Individual Mutations | Mutation/methylation of DDR genes  
| DDR gene expression (mRNA, protein)  
| DDR activity (phospho-protein) |
|----------------------|----------------------------------|
| Outcome of HR Deficiency | DNA copy number aberrations  
| Microsatellite instability  
| LOH frequencies |
| Functional assessment | RAD51 foci formation  
| Sensitivity to DNA-damaging agents  
| Genetic complementation assays |
HRD Score vs Niraparib Sensitivity

- Sensitive to niraparib
- Resistant to niraparib

BRCA1 met
BRCA2 mut
BRCA1 mut
BRCA wt

Predicted non responders
HRD score
Predicted responders

Patient-Derived Xenografts
Challenges For Oncology Drug Development

Regulatory/Financial Interface

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<thead>
<tr>
<th>Historic</th>
<th>Present</th>
<th>Future</th>
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<tbody>
<tr>
<td>Indication Size</td>
<td>Cost/Indication</td>
<td>Off-Label Use</td>
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- **Historic**: Significant investment in research and development, but limited market size.
- **Present**: Higher costs and increased competition, with some market expansion.
- **Future**: Potential for significant growth and innovation, with continued investment and regulatory changes.
Thank You