Challenges in Accelerating the Drug Development Paradigm in Oncology

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Changes in Drug Development

• Two dominant therapeutic directions
  – Targeted (molecularly specified) agents
    • Small molecules, monoclonal antibodies
  – Immunotherapeutics
    • Multiple agents, targets, approaches

• “Seamless” drug development
  – Evolution of the continuous phase I trial
Seamless Drug Development

• Blurring of phases of trials/removal of later phase trials
  – Bendamustine, crizotinib, osimertinib
• Pembrolizumab
  – Phase I initiated 2011
  – Early activity signals led to rapid expansion of cohorts
  – Total phase I population = 1200 patients
  – Led to approval in 2 diseases and a companion diagnostic
• More efficient enrollment, lower total sample size in development

Seamless Drug Development

- Design concerns emerge

Questions Regarding the Design of Large First-in-Human Cancer Trials.

- Is there a compelling rationale for including multiple expansion cohorts?
- Is the sample-size range consistent with the stated objectives and end points?
- Is there an appropriate statistical analysis plan for all stated end points?
- Are the eligibility criteria appropriately tailored to the expansion cohorts?
- Is there a defined end to the trial, in terms of both efficacy and futility?
- Is there a system in place to communicate with all investigators in a timely fashion?
- Does the informed consent reflect the current knowledge of safety and efficacy of the investigational drug and other agents in the same class?
- If the trial may be used for regulatory approval, is there an independent oversight committee?
- If the trial may be used for regulatory approval, has there been communication with regulatory agencies?

Seamless Drug Development – Mind the Gap(s)

- Decreased trial population
- Rapid acceleration of dose derivation and adoption for licensing trials
- Clinical pharmacology studies
# Oral Agents – New Molecular Entities

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Dose Finding

Determination of dose for registration-directed studies

Phase 1 + Phase 2

Registration-directed studies

Commercial access

Limited learning about variability of exposure following a fixed dose

Requirements for post-marketing studies in special populations and refined exposure-response analyses
Process of Dose Finding

• Preclinical toxicity data
• Formulation
  – Optimization of dissolution, pH dependence
    • Increasing need for acidic GI environment
• Phase 1 dose derivation
  – Oral more fixed than IV therapies
  – Food effects ignored early or require fasting
  – Aimed at the maximum tolerated dose (MTD) in the first cycle
• MTD often the only dose evaluated in phase 2 and beyond
• Trials define dose for a population, individual dose adjustment is empiric
Limitations to the Current Approach

• Dose-exposure-effect relationships are rarely well defined a priori
• High rates of dose reductions in subsequent trials
• Fails to identify patients who may benefit from lower and higher doses
• Targeted agents – the optimal biologic dose (OBD) may not = MTD
Limitations to the Current Approach

• Chronic therapy-limiting adverse events may not be incorporated in dose decisions
• Application of MTD to subsequent combinations, populations questionable
• Multiple schedules are rarely explored in a comparative fashion
  – Continuous dosing of oral agents for activity not necessarily needed
Late Toxicities with Targeted Agents

Case Study #1

- Drug X is a multi-kinase inhibitor
- FDA approved dose = MTD from single agent phase 1 trial
- In phase 3, 86.4% required at least one dose modification (interruption, reduction, discontinuation)
  - 2 dose reductions allowed (70% and 40% of starting dose)
Case Study #1

- **PK/PD**
  - High fat meal increases AUC by 57%
  - $T_{1/2} = 55$ hours
    - Accumulates 5-fold at 21 days
  - Efficacy: No relationship between exposure (AUC) and PFS
  - Safety: Increased exposure = decreased time to first dose modification, increased QTc

- Post-marketing requirement to study lower doses
Case Study #2

- Drug Y is another multikinase inhibitor
- Dose – 4 tablets daily
- PK
  - Parent $t_{1/2} = 14-58$ hr, M2 metabolite = $14-32$ hr, M5 metabolite = $32-70$ hr
  - Different formulation in clinical trials versus marketed one
    - Higher M2 and M5 exposure
  - Undergoes enterohepatic cycling (3 peaks at 4, 8, and 24 hours)
  - Parent and metabolites highly albumin-bound (99.5%)
  - M2 and M5 exposure higher in those > 65 years and in women
  - High fat meal increases parent AUC by 48%
Case Study #2

- Dose interruptions in 61%, 38% reduced due to AEs
- Two post-marketing pharmacology commitments
- Three post-marketing trials (CYP probe trial after repeated dosing, QT prolongation study, and renal impairment)
- Intrapatient variability for metabolites = 46% and 64%
- FDA clin pharm review – “A population PK analysis has not been completed, therefore covariates contributing to variability are unknown”
Post-Approval Clinical Trial Commitments – Oral Agents

• Often clinical pharmacology studies
• Since 2011
  – 28 new approvals
    • 11 accelerated
  – 78 postmarketing requirement trials
    • 5 dose finding
    • 30 drug-drug interaction
      – CYP and gastric pH effects
    • 19 hepatic impairment, 7 renal impairment
    • 2 food effects

accessdata.fda.gov/scripts/cder/daf
clinicaltrials.gov
Methods to Improve Dose Precision

• Precision - getting the dose right for the majority of populations
• Formulation improvement
• Earlier complete understanding of food effects and concomitant medications
• Application of physiologically based pharmacokinetic models
  – Sparse PK collection in later stage trials
• Approve multiple doses for differing populations, optimally defined by clinical variables
Proposed Phase 2 Dose Model