Designing First-in-Human Trials for Small Molecules and Biologics

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Learning Objectives

- Better understand important key design elements of first-in-human trials
- Gain insight to lay the foundation for future clinical development beyond the initial dose finding component of a FIH trial
- Learn other helpful tips to successfully navigating the process of FDA IND submission and review

First-In-Human Study

- Patient population
- Dose finding design
- Safety monitoring
- Risk mitigation measures
- Adequacy to inform future drug development
- Informed consent/investigator brochure

FIH Trials --- First Things First!!

- *Begin with the end in mind* (Stephen Covey)
  - Know your drug
  - Identify your goals
  - Design trial accordingly
  - Clearly communicate the above!!
    - Protocol
    - General Investigational Plan
    - Investigator Brochure

Typical FIH Goals - Oncology

- Evaluate toxicity
- Identify
  - maximum tolerated dose (MTD)
  - optimal biologic dose (OBD)
  - recommended phase 2 dose (RP2D)
- Explore antitumor activity at RP2D

Patient Population

- Eligibility criteria should reflect:
  - Seriousness of the disease
  - Available therapies
  - Known toxicities and/or toxicity in animals
  - Drug mechanism of action and metabolism (if known)
  - Recovery from prior treatment
  - Special populations (e.g., pediatric patients)

For some targeted therapies

- Tumors with biomarker of interest
- Sufficient tumor specimen for testing

Dose Limiting Toxicity (DLT)

- Guides dose escalation, de-escalation, and MTD identification
- Should be clearly defined based on severity or other important criteria (e.g., duration)
  - NCI Common Terminology Criteria for Adverse Events (NCI CTCAE)
  - Justify unusual criteria
- Context is important
  - Healthy volunteer vs. late stage cancer
  - Monitoring as outpatient vs. hospital or ICU
  - Continuous dosing, long half-life, or immunotherapies may require extended DLT period of observation

Dose Escalation Designs

- Rule-based
  - 3+3
  - Accelerated titration
  - not the only option!!

- Model-based
  - Modified toxicity probability (mTPI)
  - Continual Reassessment Methods (CRM)
  - Escalation with overdose control (EWOC)

Dosing/Dose Escalation Considerations

- Is the starting dose safe?
  - Generally based on toxicology data (preclinical) for FIH trial

- In a dose-escalation study, what is the *next* dose?
  - Half-log increments for biological drugs
  - Percentiles for small molecules
    - Fixed, modified Fibonacci, etc.
  - Expected dose/toxicity relationship important to consider
  - Intra-patient dose escalation permitted under certain conditions

Additional thoughts about dose-finding…

- RP2D and MTD not necessarily the same!
- RP2D considerations:
  - MTD
  - PK/PD
  - Toxicities beyond DLT period
  - Additional patient tolerability information (e.g., PRO-CTCAE)

- And… RP2D not necessarily = optimal dose
- Continued dose refinement strongly recommended early

Safety Monitoring

- Provide detailed schedule of events

- Consider available pre-clinical data and clinical data for drugs with same/similar mechanism

- Consider half-life

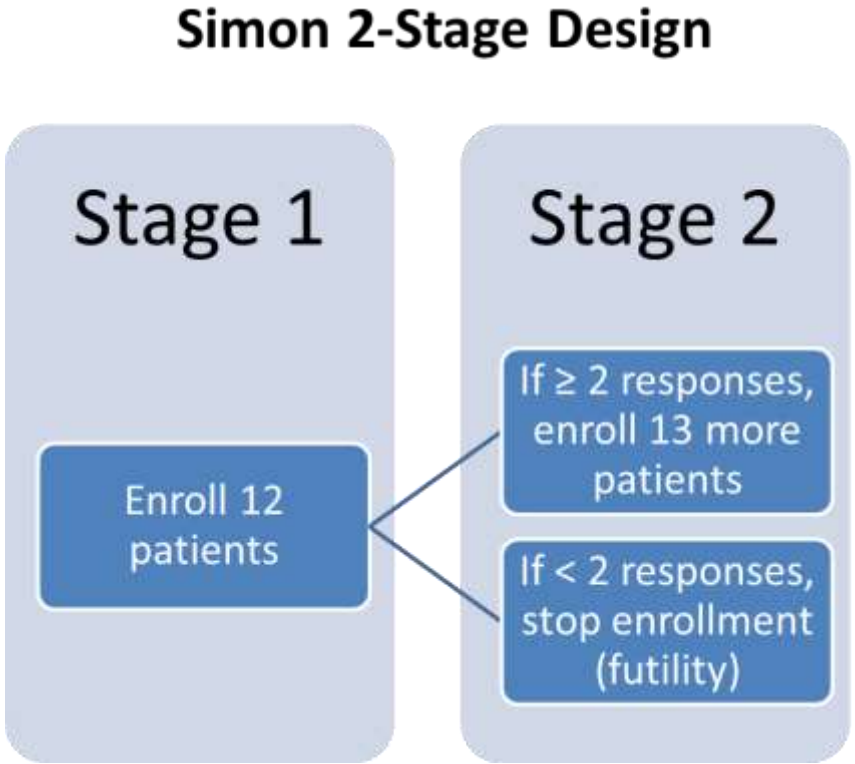
- FIH studies typically need frequent assessments, particularly early on

Other Risk Mitigation Measures

- Dose modification for toxicities
- Treatment and study stopping rules
- Safety monitoring committee procedures

Expansion Cohorts

- Typically multiple
- Proof-of-concept
- Early efficacy data
- Generally no more than 40 patients per cohort for solid tumors
- Consider further dose refinement/optimization
- Consider different patient populations (e.g., pediatric)

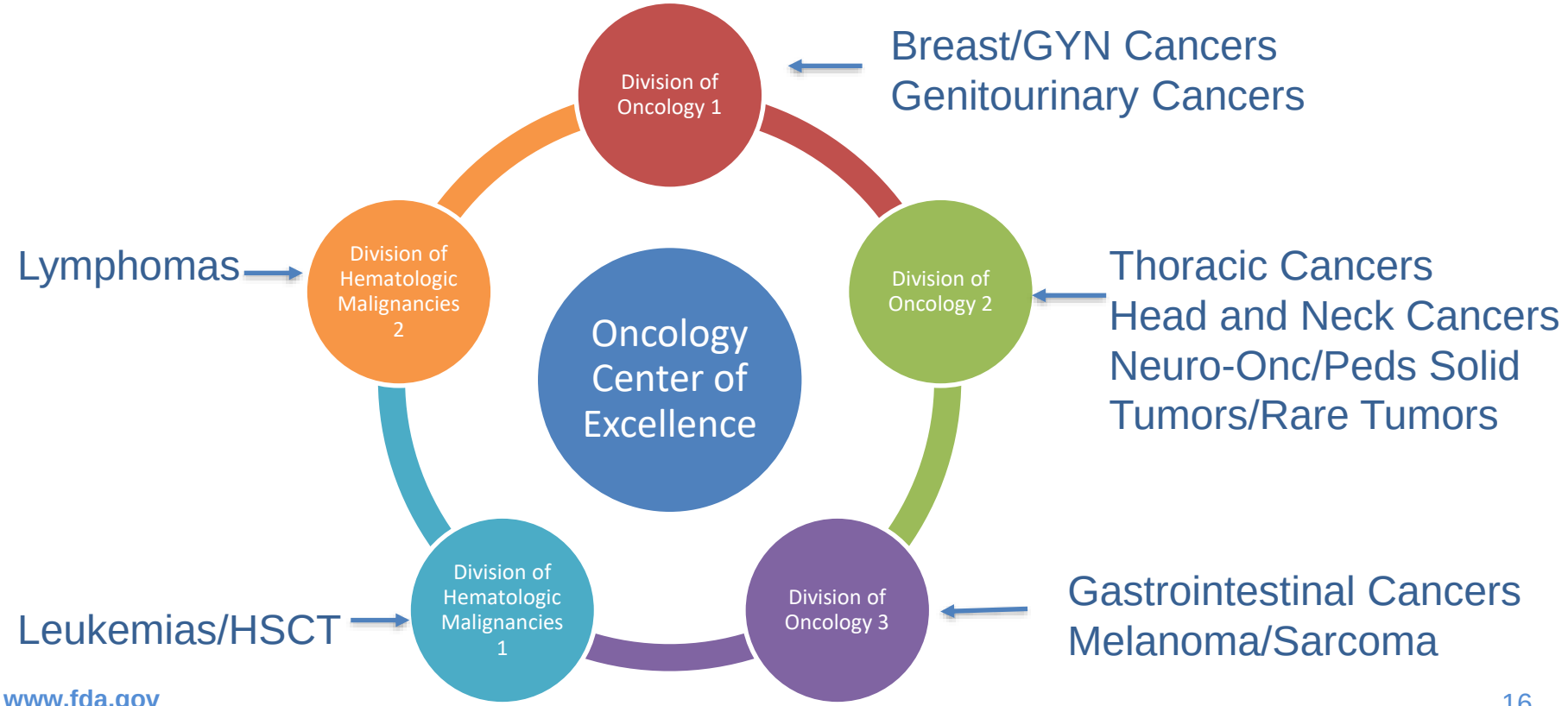


FDA Review FIH INDs

Oncology Center of Excellence

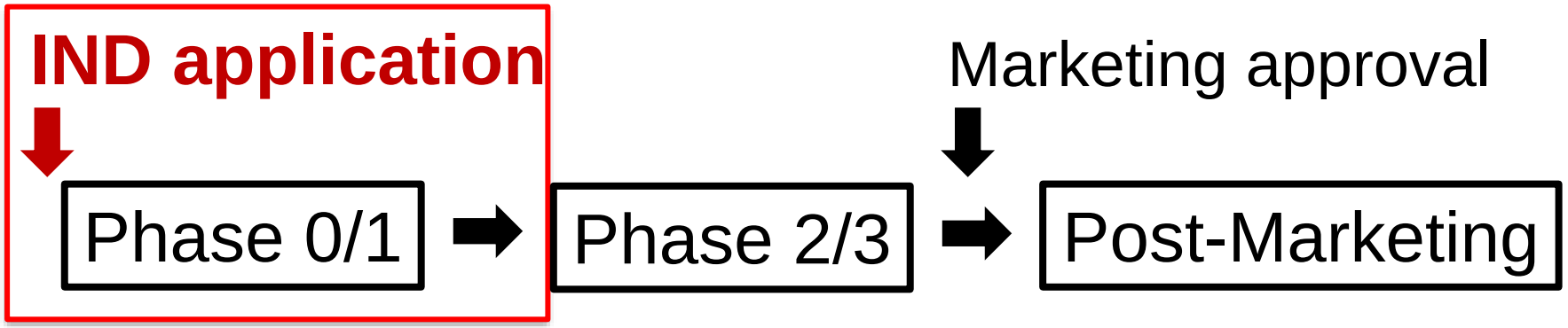
> 100 Oncologists

Office of Oncologic Diseases: Clinical Divisions



IND Application

- Regulatory review spans drug development and starts with the IND
- Purpose: Protection of clinical trial participants and evaluation of quality of scientific study in later phases



FDA IND Review Process

- 30-day Safety Review
- Determines if IND is "safe to proceed" or placed "on hold"
- Allowed to proceed if:
  - Does not pose an unreasonable or significant risk of illness or injury
  - Is adequately designed to meet its stated objectives

Multi-Disciplinary Regulatory Review

Non-Clinical Pharmacology
& Toxicology

Clinical Team
(Oncology Expertise)

Project
Management

Clinical Pharmacology

Product Quality

Statistics

FDA Review Process

- IND discussed at safety meeting (~ week 3) with Division Leadership
- You may receive **Information Requests** for revisions or clarifications.
  - Deficiencies: these changes must be made
  - Comments: suggestions to think about
- 30 days is up!
  - The IND may proceed (no news is good news)
  - The IND will be put on full or partial **Clinical Hold**: you may not start the study

Pre-IND ("Type B") Meeting

- Likely to result in smoother process for original INDs
- Discuss an IND prior to submission
  - Scheduled within 60 days of request
  - Meeting includes the team that will review your application
  - Written responses or teleconference
- Include:
  - Specific questions
  - Provide detailed information/context for topics you want addressed

Summary/Key Points- FIH Trials

- FIH trials should serve patients first
- Primary focus: preserve patient safety
- Lay the foundation for future development
  - No one-size-fits-all approach
  - RP2D/antitumor activity
  - Identification of patient populations/tumor types for future investigation
- Dose-finding does not end at Phase 1
- Consider Pre-IND meeting to facilitate IND application process

Resources

- https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

- https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp
  - https://www.fda.gov/media/72730/download
  - https://www.fda.gov/media/72752/download

Resources

- https://www.fda.gov/about-fda/oncology-center-excellence/oncology-center-excellence-guidance-documents
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluating-cancer-drugs-patients-central-nervous-system-metastases
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/inclusion-older-adults-cancer-clinical-trials
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-vitro-diagnostics-oncology-trials-streamlined-submission-process-study-risk
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expansion-cohorts-use-first-human-clinical-trials-expedite-development-oncology-drugs-and-biologics
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-inclusion-adolescent-patients-adult-oncology-clinical-trials
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-minimum-age-considerations-inclusion-pediatric-patients

U.S. FOOD & DRUG ADMINISTRATION

Questions?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