median

Imaging fundamentals

Imaging in oncology clinical trials

Overview

The drug development process

Stage	Goal
1. Basic research	Target identification
2. Discovery/lead optimization	Identify suitable molecule or prototype to interact with target
3. Preclinical studies	Mechanism of action, proof of principle in animals
4. Phase I	Dosage, pharmacodynamics, safety, proof of concept
5. Phase II	Efficacy and safety
6. Phase III	Efficacy and safety; regulatory submission
7. Phase IV	Real world use, additional safety if required by regulatory agencies

Common terms and acronyms

- **Randomized:** each patient's treatment assignment is left to chance.
- **Controlled:** the treatment group receiving the drug is compared to a group given either an active control (established drug; also known as an active comparator) or a placebo (sugar pill; negative control).
- **Double-blinded:** researchers, patients, and imaging readers are unaware of the patients' treatment group throughout the evaluation period.
- **Open-label:** a study in which there is no blinding; participants and researchers are aware of the treatment being given, and there is no placebo group.
- **IND:** Investigational New Drug.
- **NDA:** New Drug Application.

Oncology trial design

The primary endpoint in most oncology trials is patient survival:

- Overall Survival (OS): clinical endpoint; considered gold standard; not always practical due to high patient numbers and required time.
- Progression-free Survival (PFS): measures time from treatment initiation to beginning of disease progression; most commonly used oncology endpoint.

Another important oncology trial endpoint:

- Objective Response Rate (ORR): proportion of patients with a reduction in tumor burden by a predefined amount.

Disease progression is defined according to the chosen response criteria:

- The most widely used response criteria for solid tumors is RECIST1.1, which assesses tumor size by CT or MRI.
  - Tumor growth = disease progression; Tumor shrinkage = response to treatment
- In RECIST1.1, tumor response is categorized according to defined parameters:
  - CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
- Immunotherapies have their own unique response criteria: iRECIST, irRC and irRECIST.
  - Immunotherapies typically exhibit a delayed response and tumors can enlarge prior to disease stabilization.
  - Tumor growth does not automatically define disease progression; imaging is performed again after 12 weeks to test for response.

Clinical trial phases: Overview of the Clinical Trials Process

	Preclinical testing		Phase 1	Phase 2	Phase 3	
Subjects	Laboratory and animal studies		20–100 Healthy volunteers	100–300 Patient volunteers	1,000–3,000 Patient volunteers	
Purpose	Assess safety & biological activity	FILE IND	Safety & dosage	Safety, dosing & efficacy	Safety, verify effectiveness & side effects	FILE NDA
Avg Time	1 - 6 Years		1.8 Years	2.1 Years	2.5 Years	
Probability of moving to next phase			62.8% of INDs	24.6% of INDs	40.1% of INDs	
	10,000 →	250 →		50 →	5 →	1

www.fdareview.org/03_drug_development.php
www.bio.org - Clinical Development Success Rates 2006 - 2015

Imaging in clinical trials

Clinical trials attempt to answer the following questions:

- *Is the drug safe?*
- *What happens to the drug in the body?*
- *What happens to the body when the drug is taken*
- *Is the drug clinically effective?*
- *How should the drug best be administered?*

Clinical trial phases (continued)

Preclinical & FIM	• Preclinical testing involves animal and laboratory studies. – Is the drug effective in living organisms? – Is the compound biologically active?	• At the conclusion of preclinical testing, an investigational new drug application (IND) must be filed with the regulatory agency – then the First in Man (FIM) Studies.
Phase I ~1–2 Years	• Phase I evaluates drug safety and a safe dosing range: clinical efficacy is generally limited to establishing proof of principle. – Sometimes, Phase I is divided into Ia and Ib. Phase Ia studies are usually performed on healthy volunteers and phase Ib is on patients with cancer. – Tumor size can also be used as a safety parameter, as any new drug that results in tumor growth will not proceed through the clinical trial process. • Pharmacokinetic (PK) and pharmacodynamic (PD) data is collected. –PK and PD: The evaluation and quantification of what the body does to a drug over time, tested at many doses (absorption, distribution, metabolism, and elimination).	• Imaging in Phase I can be used to: – Evaluate extent of cancer using CT or MRI. – Identify patient populations most likely to respond to treatment. – Assess PK using PET. – Test drug safety: kidney or liver damage using MRI. – Make go/no go decisions on whether or not to proceed in clinical testing. – Test novel imaging endpoints.
Phase II ~2 Years	• Drug is given to a larger group of patients who have cancer. – Does the drug work in the disease population? – At what dose is the drug effective? – Drug is tested at several doses using placebo controlled or active comparator design to determine the optimal dose to carry into Phase III studies.	• Imaging studies in Phase II can be used to: – Detect early changes to pathophysiology as it relates to efficacy or safety. – Stratify patients into treatment groups. – Identify patient populations most likely to respond. – Evaluate imaging biomarkers. – Make go/no go decisions regarding move to Phase III.
Phase III ~3-5 Years	• Confirm efficacy results in a larger population: determine clinically meaningful drug benefit and requires the greatest amount of time, financial resources, strategic planning. –Is the drug working and safe? • Identify adverse events: establishes a benefit-to-risk ratio (BRR) for the patient. – BRR influences the decision to approve the drug for first-line, second-line, or salvage therapy. – BRR must be comparable or better than current therapies in order to gain first-line treatment status.	• After Phase III testing, a new drug application (NDA) is filed with the regulatory agency. –The NDA contains all data from preclinical and Phase I-III studies; an NDA can be thousands of pages long and may require as long as 1-2 years to be reviewed by the regulatory agency. • Imaging in Phase III is used to determine disease progression as an indicator of clinical benefit. – This typically includes measuring changes in tumor size after treatment (compared to baseline) using CT or MRI for solid tumors; can also include measuring glucose metabolism by PET/CT (e.g., for lymphoma). – The way in which disease progression is measured is determined by response criteria, which are specific to type of tumor and/or drug class.
Phase IV	After review and approval of the NDA, Phase IV postmarketing studies are initiated; also called post-marketing surveillance. • Phase IV studies are conducted after the drug has already been approved by the regulatory agency to confirm safety and efficacy with long-term use.	• Collects additional information for patients and healthcare providers that was not generated in Phase III trials. – Phase IV studies must use current prescribing instructions. – Used to study specific populations, monitor a longterm safety parameter, investigate a new efficacy endpoint, or explore new indications. – Regulatory agencies can make approval contingent upon Phase IV studies that address specific safety concerns. – Phase IV imaging studies are used to further assess or confirm efficacy and safety.

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