Basics in clinical trials design

Monica Arnedos MD
Breast Unit
Gustave Roussy
France
monica.arnedos@gustaveroussy.fr
The History of interventional clinical trials

1st clinical trial: 1747 Clinical trial on scurvy

A CLINICAL TRIAL OF SANOCRYSIN IN PULMONARY TUBERCULOSIS

J. BURNS AMBERSON, JR., B. T. McMAHON AND MAX PINNER

Obviously, the matching could not be precise, but it was as close as possible, each patient having previously been studied independently by two of us. Then, by a flip of the coin, one group became identified as group I (sanocrysin-treated) and the other as group II (control). The members of the separate groups were known only to the nurse in charge of the ward and to two of us. The patients themselves were not aware of any distinction in the treatment administered.

American Review of Tuberculosis 1931; 4: 401-35
## Traditional approach

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-30 people</td>
<td></td>
<td>Less than 100 people</td>
<td>Generally, from 100 to thousands of people</td>
<td>Several hundred to several thousand people</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
</tr>
<tr>
<td>• To find a safe dosage</td>
</tr>
<tr>
<td>• To decide how the agent should be given</td>
</tr>
<tr>
<td>• To observe how the agent affects the human body</td>
</tr>
<tr>
<td>Phase 2</td>
</tr>
<tr>
<td>• To determine if the agent or intervention has an effect on a particular cancer</td>
</tr>
<tr>
<td>• To see how the agent or intervention affects the human body</td>
</tr>
<tr>
<td>Phase 3</td>
</tr>
<tr>
<td>• To compare the new agent or intervention (or new use of a treatment) with the current standard</td>
</tr>
<tr>
<td>Phase 4</td>
</tr>
<tr>
<td>• To further evaluate the long-term safety and effectiveness of a new treatment</td>
</tr>
</tbody>
</table>
### Traditional approach

#### The Drug Development and Approval Process

<table>
<thead>
<tr>
<th>Preclinical Testing</th>
<th>Clinical Trials</th>
<th>Post-Clinical Trials</th>
<th>Total Years for Drug Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Step 3</strong></td>
<td><strong>Step 6</strong></td>
<td><strong>Step 7</strong></td>
</tr>
<tr>
<td>Laboratory/ Preclinical Testing</td>
<td>File IND¹ application with FDA²</td>
<td>File NDA³ or BLA⁴ with FDA</td>
<td>FDA Approval</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td><strong>Purpose</strong></td>
<td><strong>Purpose</strong></td>
<td><strong>Purpose</strong></td>
</tr>
<tr>
<td>Assess safety and biological activity in the laboratory and in animal models</td>
<td>Obtain FDA approval to begin clinical testing in humans after promising results in laboratory</td>
<td>Determine what dosage is safe, how treatment should be given</td>
<td>Evaluate effectiveness, looks for side effects</td>
</tr>
<tr>
<td>All anticancer drugs (average number of years)</td>
<td>4.4 years</td>
<td></td>
<td>8.6 years</td>
</tr>
<tr>
<td>All drugs* (average number of years)</td>
<td>3.8 years</td>
<td></td>
<td>10.4 years</td>
</tr>
</tbody>
</table>

---

¹IND = Investigational New Drug  
²FDA = Food and Drug Administration  
³NDA = New Drug Application  
⁴BLA = Biologics License Application
People who participate in Phase 1 trials are those who have no known effective treatment options, or they have already tried other treatment options.

When a phase 2 trial begins, it is not yet known if the agent tested works against the specific cancer being studied.

In phase 3 trials, participants have an equal chance to be assigned to one of two or more groups (...). Placebos are almost never used in cancer clinical trials.
Traditional approach

• Issues
  – Lengthy
  – Costly: estimated cost of bringing new drug to the market $800 million to $2 billion\textsuperscript{1}
  – In 2000, a new medical compound entering Phase 1 had 5 to 8% chance of eventually reaching the market and around 45% of the Phase 3 programs do not have the optimum dose\textsuperscript{2}

• Need to evolve to adapt to molecular pre-screening

Molecular landscape of breast cancer

Stephens et al, Nature 2012
Integration of biomarkers in clinical trial designs

Lawrence et al, Nature 2014; 505: 495
How clinical research is evolving to become more efficient and to adapt to this new era of targeted therapy?
I. implementing strategies to reduce time and number of patients

II. adapting clinical trials design to molecular pre-screening for targeted therapies

III. application of new measures by the regulatory agencies

IV. exploiting new scenarios
Alternatives for Phase 1 design

3+3 design

- Easy to implement and safe
- Slow with many patients treated at subtherapeutic doses

Accelerated titration design: escalation with overdose control

- Rapid and greater proportion of patients at higher doses
- Interpatient dose escalation may mask cumulative or delayed toxicities
Modification of Phase 1 trials

Conventional Objectives

- Determination of dose and schedule for phase II trials
- Safety and toxicity evaluation
- Pharmacokinetic assessments

Newer Objectives

- Generation of preliminary evidence of target inhibition
- Identification of specific target patient populations

Enriched Phase Ib trials (expansion cohorts)
Phase 1/1b trials

A Phase 1 Study of MM-141 (anti-IGF1R/HER3 antibody) in Patients With Advanced Solid Tumors (NCT01733004)

- **Arm A**: monotherapy in all tumor types (n=15)
  - 3+3 design

- **Arm B**: Breast cancer Everolimus + endocrine therapy (n=12)

- **Arm C**: Pancreatic cancer nab-paclitaxel + gemcitabine (n=11)

- **Arm D**: HCC Monotherapy (n=3)
  - 3+3 design + biomarkers

Second cohort (D+1)
Phase 2 trials

Objectives:
- To test the efficacy of a new drug
- Go or no-Go to phase III trials

Primary objective: ↓ORR, PFS

Cross-over or not
Factorial (treatment A, treatment B, treatment A+B, placebo)
Other designs for randomized trials (randomized selection design “pick the winner”)
**Phase 3 trials**

**Objective:** to compare the therapy with the standard-of-care, to determine if a new treatment is superior to the standard therapy

**Primary objective:** PFS, ↓OS

**EMBRACE Trial**
- 762 advanced BC patients
- 2:1
- Eribulin n=508
- TPC n=254

**CLEOPATRA Trial**
- Patients with HER2-positive MBC (N = 808)
- Placebo + trastuzumab
- Docetaxel* ≥6 cycles recommended
- Pertuzumab + trastuzumab
- Docetaxel* ≥6 cycles recommended

*Cortes et al, Lancet 2011; 377: 914–23*

Standard clinical research

Phase 2
- Treatment A
- Treatment B
- Combination
- Control

Phase 3
- Treatment B
- Control

Data analysis
Planning of phase 3
Phase 2 results

Improvement: Adaptive designs
**Seamless adaptive designs**

**Advantages:** shorter duration time, flexible, allows many simultaneous treatment arms and modifications

**Requirements:** use complicated bayesian approach, frequent interim analysis with a proactive role of the IDMC
I. implementing strategies to reduce time and number of patients

II. adapting clinical trials design to molecular pre-screening for targeted therapies

III. application of new measures by the regulatory agencies

IV. exploiting new scenarios
Background and Assumptions

- **Targeted therapy**: treatment designed to affect a particular biologic pathway, mutation, receptor, etc
- A **bioassay** \((M)\) is used to judge presence or absence of the target A prognostic or predictive biomarker
- \(M\) can be measured on the eligible patients: Two groups based on the biomarker \((M^-\text{ and } M^+)\)
- Targeted therapy is assumed a priori to work primarily in patients with the target \((M^+)\)
Things to consider

• How certain is the assumption that the treatment effect will be limited to M+ patients?
• How appropriate is the binary classification into M+ and M-? Is the classification based on a continuous measurement?
• What is the prevalence of M+ patients?
• How accurate is the assay?
**Traditional design**

- **No pre-selection**
  - **Treatment**
  - **Control**

**Advantages**
- Simple
- Addresses a broad population question

**Disadvantages**
- Large sample size
- Potentially unnecessary treatment for M- patients
- Cannot assess prospectively effect in M+ or M- patients
- Risk of being negative if effect only limited in M+

**Example: BOLERO-2 trial**

- 724 women with ER+ HER2- metastatic breast cancer, with exposure to prior AI
  - Everolimus 10 mg/day + Exemestane 25 mg/day (N = 485)
  - Placebo + Exemestane 25 mg/day (N = 239)
Targeted design

Prescreening population for clinical trial

Biomarker

M -

M +

R

Treatment

Control

Buyse, Michiels et al, Expert Rev Mol Diag 2011
Targeted design

Prescreening population for clinical trial

Example: HERA trial

HER2+ early BC patients
n=3401

- Trastuzumab 1 year
  (n=1703)
- Trastuzumab 2 years
  (n=1701)
- No treatment
  (n=1698)

Advantages
- Requires many fewer patients
- Avoids potentially unnecessary treatment for M-

Disadvantages
- Cannot assess effect in M- patients
- Slow accrual
- Less efficient than randomize-all design if drug has some activity in M- patients
Biomarker-stratified design

Prescreening population for clinical trial

- Biomarker
  - M -
  - M +
  - R

- Treatment
- Control
- Treatment
- Control
Biomarker-stratified design

Example: Marvel trial

- Preregistration (n = 1,196 with tumor tissue)
- Central pathology review and EGFR evaluation by FISH (FISH status blinded) (n = 956 with assay results)

  - FISH+ (estimated approximately 30%; n = 286)
    - Randomization (1:1)
      - Erlotinib (n=143)
      - Pemetrexed (n=143)
  - FISH– (estimated approximately 70%; n = 670)
    - Randomization (1:1)
      - Erlotinib (n=335)
      - Pemetrexed (n=335)

Advantages
- Test of predictive ability of biomarker (interaction)

Disadvantages
- Power of “interaction test” is very low, huge sample sizes are required
- Potential for overtreatment of M- patients
- Biomarker often unknown or poorly defined for prospective stratification

- Test of predictive ability of biomarker (interaction)
- Power of “interaction test” is very low, huge sample sizes are required
- Potential for overtreatment of M- patients
- Biomarker often unknown or poorly defined for prospective stratification
Adaptive parallel
Biomarker-stratified design

HER2 negative / HR positive LA/mBC patients

Randomisation & Stratification:
FGF pathway amplified vs non-amplified

- **Fulvestrant + dovitinib**
  - 45 patients FGF Amplified
  - 30 patients FGF Non-Amplified

- **Fulvestrant + placebo**
  - 45 patients FGF Amplified
  - 30 patients FGF Non-Amplified

Primary Endpoints
PFS per local assessment in FGF amplified and in all pts regardless of FGF status

Secondary Endpoints
ORR, DOR, OS, Safety, PK profile, PS, PRO

Exploratory Endpoints
Biomarker correlation with clinical outcome

Treat until PD, unacceptable toxicity, death or discontinuation for any other reason

Clinical Trial terminated earlier due to low recruitment FGF-Amplified patients
Classical screening

Patient in Progressive Disease

- Determination of molecular alteration A
  - If positive: Inclusion in Clinical Trial A
  - If negative: Determination of molecular alteration B

- Determination of molecular alteration B
  - If positive: Inclusion in Clinical Trial B
  - If negative: C

- D

- ...

Similar studies in parallel for different types of tumors

Problems:

Tumor Tissue
Patient in Progressive Disease
The umbrella trials

Molecular testing

Same tumor type or different tumor types

- Molecular alteration A
  - Drug A
  - Randomized or not versus standard treatment

- Molecular alteration B
  - Drug B

- Molecular alteration C
  - Drug C

Treatment based on single molecular alteration or molecular profile
The BATTLE Program

End-point: PFS at 8 weeks - DCR

SAFIR02 trial

- 210 randomised, around 400 screened
- **Hypothesis:** median PFS 3 to 6 months

- **Target:** defined by 1st generation virtual cell (CCLE)

- **Chemotherapy:** 6–8 cycles
- **Biopsy metastatic site:** next generation sequencing
- **Array CGH**

- **Her2-negative metastatic breast cancer no more than 1 line chemotherapy**

- **Followed up but not included**

- **SOC**
  - R
  - AZD2014
  - AZD4547
  - AZD5363
  - AZD8931
  - Bras A: targeted therapy
  - Vandetanib
  - Selumetinib
  - Casodex
  - olaparib

- **Sponsor:** UNICANCER
- **Funding:** French charity
- **Pharma partner:** AZ
NCI-MATCH
(Molecular Analysis for Therapy Choice)

Refractory Advanced Solid Tumors/Lymphomas
ORR (5% vs. 25%)
PFS (6 months: 15% vs. 35%)

40+ agents pledged with at least RP2D

The basket trials

Molecular testing

Breast cancer
NSCLC
Colon cancer

M+

Breast cancer
NSCLC
Colon cancer

Examples:
VE_BASKET (NCT01524978): vemurafenib in BRAF-mutated solid tumors and multiple myeloma
AcSé Crizotinib (NCT02034981): crizotinib in alterations MET, ROS1, ALK
I. implementing strategies to reduce time and number of patients

II. adapting clinical trials design to molecular pre-screening for targeted therapies

III. application of new measures by the regulatory agencies

IV. exploiting new scenarios
Drug approval based on Phase 1/2 data

**FDA Accelerated approval** to some new drugs for serious and life-threatening illnesses that lack satisfactory treatments before measures of effectiveness required for approval are available

**Crizotinib** received accelerated approval for treatment of ALK-positive locally-advanced or metastatic NSCLC based on two Phase 1 trials

In May 2012 the FDA issued draft guidance suggesting that pCR could be used as an endpoint in neoadjuvant early-stage high risk breast cancer trials for accelerated approval under certain conditions.
Drug approval neoadjuvant setting

Approval of docetaxel + trastuzumab + pertuzumab as neoadjuvant treatment in HER2+ BC

I. implementing strategies to reduce time and number of patients

II. adapting clinical trials design to molecular pre-screening for targeted therapies

III. application of new measures by the regulatory agencies

IV. exploiting new scenarios
Pre-operative setting: Phase 0 trials

Pre-surgical treatment (Biological window trial)

- In accordance with the FDA
- Administration of shorter periods of time
- In early disease
- Lower number of patients
- Provides pharmacodynamics and pharmacokynetics
- Validation of biomarkers

PRIMARY AIM: To evaluate the biological effect of the drug on the target
Trials in the pre-operative setting

**Diagram:**
- **Baseline**:
  - ER+ breast tissue
  - Biopsy

- **Surgery**:
  - c. 2 weeks
  - 4,486 patients randomised to perioperative AI Rx (letrozole or anastrozole) vs. no perioperative Rx
  - Biopsy or excision biopsy

**Randomization 3:1**
Palbociclib vs no treatment

- Breast US
- 14 days
- Breast US

**NFS d10**
Further reading

• Le Tourneau et al, *Dose Escalation methods in Phase I clinical trials*. JNCI 2009; 101: 708
• Ivy et al, *Approaches to Phase 1 clinical trial design focused on safety, efficiency and selected patient population*. CCR 2010; 16:1726
• Seymour et al, *The design of Phase II clinical trials testing cancer therapeutics*. CCR 2010; 16: 1764
• Kummar et al, *Application molecular profiling in clinical trials for advanced metastatic cancers*. JNCI 2015; 107(4):djv003