Design of Clinical Trials in the era of targeted agents: theory and practice

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What is a clinical trial?

• A clinical trial is a research study conducted in patients to answer specific questions about their treatment, diagnostic procedures or disease follow-up

• Clinical trials (also called interventional studies) are generally designed to determine whether new treatments could be both safe and effective.
• **Patients**
  - **Self interest:** Trial as a ‘last chance’ treatment, getting access to a treatment that would not otherwise be available
  - **Community:** A way of ‘giving something back’, while hoping that some benefit will come to them personally – and without too much risk from unpleasant side-effects

• **Scientists**
  - Understand disease and treatments
  - Improve patient care
  - Gather data and samples for further developments (diagnostic tests, biomarkers ...)

Target of a clinical trial

**Treatment**
- improve treatment (superiority)
- decrease morbidity/side effects

**Quality of Life**
- explore ways to improve comfort and the quality of life

**Screening**
- test the best way to detect certain diseases or health conditions

**Diagnostic**
- find better tests or procedures for diagnosing a particular disease or patient’s condition
The 4 phases of clinical research

Is the safe dose to give for the new treatment known in patients?

- Yes
  - Phase I needed (dose toxicities)
    - first-in-human trials
    - in a small group of people (e.g. 20-80)
    - to evaluate safety and determine safe dose range
    - 1 yr

- No
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    - in a small group of people (e.g. 20-80)
    - to evaluate safety and determine safe dose range
    - 1 yr

Is its activity against the tumor type of interest demonstrated? Or Is the efficacy of the new treatment worthy of direct comparison with standard treatment in the FASE III setting?

- Yes
  - Phase III needed (survival time)
    - in large groups of people (from several hundred to several thousand)
    - to determine efficacy by comparing to other standard or experimental interventions and monitor side effects
    - 2+ yrs
    - to monitor the effectiveness of the approved intervention in the general population
    - to collect information about any adverse effects associated with widespread use.

- No
  - Phase II needed (early efficacy measure e.g. response, 6-month PFS)
    - in a larger group of people (several hundred)
    - to determine activity and further evaluate safety.
    - 1-2 yrs
Clinical trial design with targeted therapy: Issues

- **New methodologies**
  - More “targets” (more or less)
  - More “patients” (sub-)groups

- **Re-assessment of trials’ end-points**
  - How do we deal with Phase I studies?
  - Is response adequate for Phase II?
  - Is randomized Phase II a reasonable approach?
  - Which kind of Phase III are required?
Traditional drug development according to Phases and Aims

Phase 1 → Phase 2 → Phase 3 → Phase 4

MTD
Safety Activity
Efficacy
Effectiveness Other

Modified – Di Maio M, Morabito A, Perrone F
Traditional drug development according to Phases and Aims

**Phase 1**

MTD

*Modified – Di Maio M, Morabito A, Perrone F*
Phase I

• 1\textsuperscript{st} stage of human experimentation with a new drug or combination

• **Goal:** “Determination of the maximal dose of drug, either alone or as part of a combination, that will, when administered by a specific schedule and route, produce an acceptable toxicity”

• **Population:** Advanced solid tumors unresponsive to standard therapies or for which there is no known effective treatment

• **Safety Endpoint:**
  - Dose-Limiting Toxicity (DLT): Grade 3-4 non hematological (except alopecia, nausea, vomiting that can be controlled with appropriate measures) or Grade 4 hematological toxicity
  - Maximum Tolerated Dose (MTD): Highest dose level which is associated with "acceptable" toxicity
Objectives of a phase I trial

• **Primary objective:**
  • Identify dose-limiting toxicities (DLTs) and the recommended phase II dose (RPTD)

• **Secondary objectives:**
  • Describe the toxicity profile of the new therapy in the schedule under evaluation
  • Assess pharmacokinetics (PK)
  • Assess pharmacodynamic effects (PD) in tumor and/or surrogate tissues
  • Document any preliminary evidence of objective antitumor activity
Definitions of key concepts in phase I trials

• **Dose-limiting toxicity (DLT):**
  • Toxicity that is considered unacceptable (due to severity and/or irreversibility) and limits further dose escalation
  
  • Specified using standardized grading criteria, e.g. Common Terminology Criteria for Adverse Event (CTCAE v4.0)
  
  • DLT is defined in advance prior to beginning the trial and is protocol-specific
  
  • Typically defined based on toxicity seen in the first cycle

• **Recommended phase II dose (RPTD or RD):**
  • Dose associated with DLT in a pre-specified proportion of patients (e.g. < 33%)
    – dose that will be used in subsequent phase II trials
# Cytotoxic vs Targeted

<table>
<thead>
<tr>
<th>Key differences</th>
<th>Traditional cytotoxic agents</th>
<th>Molecularly targeted agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Non-selective</td>
<td>Modulate a specific target</td>
</tr>
<tr>
<td>Effective dose</td>
<td>MTD</td>
<td>Non necessarily MTD</td>
</tr>
<tr>
<td>Route and schedule of administration</td>
<td>Often intermittent and intravenous</td>
<td>Often continuos and orally</td>
</tr>
<tr>
<td>Toxicity profile</td>
<td>Hematologic toxicity usually foreground</td>
<td>Non-hematologic toxicity usually foreground</td>
</tr>
<tr>
<td>Antitumor activity</td>
<td>Tumor shrinkage</td>
<td>Only tumor stabilization or delayed responses in some cases</td>
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</table>
Dose-effect model

Old-style cytotoxics...

- Usually have a **direct correlation** between dose and toxicity
- Over a threshold, **toxicity limits activity**
- Phase I aims to find out MTD as conducive to the highest efficacy
Phase I: MTD (maximum tolerated dose) or MTID (minimum target-inhibiting dose)?
Which ways to go forward?

- Development of prospective validation of biomarker-driven drugs in the EARLY PHASES

- Development of an easier/rapid analytical and statistical methodology to “push” drugs from the early phases to clinical practice
Key-Concepts for Clinical Trials
What do we assess in clinical trials?

- **Activity:**
  - Ability of the treatment to *induce modifications of the disease* thanks to which it is assumed that the patient may have a benefit: PHASE II

- **Efficacy:**
  - Ability of the treatment to induce a clinical benefit in patients who are administered in an experimental context: PHASE III

- **Effectiveness:**
  - Ability of a treatment to be effective in a *non-experimental, concrete and coincident with clinical practice*: are PHASE IV studies useful?
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Traditional drug development according to Phases and Aims

Phase 2

Safety Activity

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**Phase II**

**Goal:**
- A (early) signal of antitumor activity, which should translate into a clinical benefit for the patient
- Documentation of safety profile
- Support for the “go/no go” decision for the further development of the experimental treatment (phase III / phase II-III)

**Endpoints:**

- **For activity**
  - Response rate (for example, RECIST defined: complete response = disappearance of lesion(s), partial response = at least 30% decrease of the lesion)
  - Progression free percentage at some fixed time point
  - Biomarker based

- **For safety**
  - Rates of Side effects using CTC (standard grading scale for adverse events)

- **Feasibility** *(Protocol defined criteria to evaluate if the trial is feasible)*
Phase II

• **Population:**
  - Specific tumor type (Kidney, Breast, ...)
  - Relatively advanced disease
  - Specifically targeted population of patients (biomarker, ...)

• **Design:**
  - Single arm
  - Several arms (randomisation)
    - experimental arms
    - Use a control arm (Placebo / Observation / Standard treatment)
    - Or a combination of the above

If randomization, it may look like a Phase III design, but in any case it will avoid a randomized adequately powered phase III trial.

Phase II are not intended to directly impact on clinical practice (as phase III)
Objectives of Phase II Trials of Targeted Agents

- Determine whether there is a population of patients for whom the drug demonstrates sufficient anti-tumor activity to warrant a phase III trial

- Optimize the regimen in which the drug will be used in the phase III trial

- Optimize the target population for the phase III trial
Phase II: Appropriate Primary Endpoint

- Include secondary endpoints (biomarkers, PROs, imaging)
- Biomarkers
  - Do not enrich unless clinically validated
  - Consider adaptive designs
  - Consider multi-disease trials

Phase II: Targeted Agents

1. Conversely to Classical cytotoxics, targeted agents selectively hit a specific molecule/enzyme:
   - Their functional/clinical effects are directly related to the level of target inhibition

2. Targeted agents are “cytostatic” in nature:
   - They will slow down growth, but seldom shrink pre-existing tumor masses

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Phase II: Targeted Agents, particularly ATP-competitive kinase inhibitors, frequently hit multiple targets.

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Phase 3

Efficacy

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Phase III

- **Goal**: to determine the relative efficacy of the new treatment in terms of clinical benefit for the patient

- **Population**: Disease-oriented (specific patient population)

- **Comparative in nature** (**relative efficacy**)
  - to the natural history of the disease (control arm)
  - to the best current therapy (standard arm)

- **With objective to show**:
  - either **superiority**
    - Is the new treatment more effective than the standard? = Trial to show a difference in efficacy
  - or **non-inferiority**
    - Is the new treatment less aggressive, less invasive or less toxic than the standard but potentially ‘equally’ effective?
Phase III

- **Efficacy as primary endpoint:**
  - *Local control*: time from randomization to local failure (for localized disease treated locally: surgery or radiotherapy)
  - *Time to progression (TTP) or Disease-free interval (DFI)*: time from randomization to disease progression or recurrence
  - *Progression-free survival (PFS) or Disease-free survival (DFS)*: time from randomization to either progression/recurrence or death
  - *(Overall) Survival*: time from randomization to death from any cause

- **Secondary endpoints:**
  - Quality of life
  - Side effects
Randomized Phase III Clinical Trials

Eligible patients RANDOMISED

STANDARD Treatment

NEW Treatment

Treatment period

Follow-up period

Survival
Relapse-free survival
Response
Toxicity
Quality of life
Cost
Phase III Trials: questions

- The new drug is more effective than other drugs?
  - Superiority trial (is “statistically” relevant?)

- The use of the new drug determines a therapeutic benefit for patients?
  - Amount of the benefit (is “clinically” relevant?)

- The new drug is as effective as other drugs but with fewer side effects (or minor discomfort or lower costs)?
  - Non-inferiority trial

- What categories of patients may derive more benefit from the new drug?
  - Subgroups analysis
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Phase III Trials: ‘Sizing’ a trial for: Arm A (Experimental) vs Arm B (Control)

• **Superiority:**
  - A is better than B in terms of the primary outcome, and **this expected difference must be clinically relevant** (Minimum Clinically Relevant Benefit: $\Delta$)

• **Non-inferiority:**
  - A is **inferior** to B in terms of the primary outcome, but **not lower than a clinically pre-specified “margin” (M) which is considered clinically relevant**.

  ➢ **Ex.** You can accept a small degree of lower benefit, if patients experience better tolerability
Phase III Trials: Superiority and Non-inferiority

The choice of the non-inferiority margin must always be justified on both clinical and statistical grounds. It always needs to be tailored specifically to the particular clinical context and no rule can be provided that covers all clinical situations.

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European Medicines Agency London, 27 July 2005
Phase III Trials: Superiority and Non-inferiority

- **Non-inferiority randomized trial**
  - 2% variation in terms of absolute difference of recurrence
  - The 95% CI HR margins should not cross the 1.15 boundary
  - 1040 DFS events required for 80% power at 5% level
  - 4 years of accrual and at least 2 years of follow-up
  - HR were estimated from the stratified Cox model

- **Accrual target:** 3400 patients
Phase III Trials: Superiority and Non-inferiority

![Diagram showing the comparison of different treatments in Phase III trials. The diagram illustrates the comparison of treatments A, B, C, D, and E based on hazard ratio (HR) values. The horizontal axis represents HR values ranging from 0.85 to 1.6, and the vertical axis represents different trials. The diagram highlights the equivalence, superiority, non-inferiority, and inferiority of the treatments.]

*Pivot ESMO 2012*
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Phase III Trials: facing with complexity

A. Lung Adenocarcinoma
   - KRAS
   - EGFR
   - ALK
   - ROS1
   - MET
   - BRAF
   - NRAS
   - RET
   - MEEK1
   - PIK3CA

B. Lung Squamous Cancer
   - EGFR
   - FGFR
   - PIK3CA
   - ERBB2/3
   - TOR
   - MAPK

C. Breast Cancer
   - ERBB2
   - ERBB1
   - PIK3CA
   - PTEN
   - AKT
   - PTEN

D. Colorectal Cancer
   - KRAS
   - NRAS
   - ERBB2/3
   - BRAF
   - PIK3CA
   - PTEN

E. Melanoma
   - KIT
   - NF1
   - Other?
   - NRAS
   - BRAF
   - (PTEN and CDKN2A are frequently inactivated)

F. Head and Neck Squamous Cancer
   - CDKN2A
   - CCND1
   - EGFR
   - ERBB2

G. Ovarian Cancer
   - Percent
   - BRCA1/2
   - PIK3CA
   - PTEN
   - AKT
   - NF1
   - NRAS
   - CDKN2A
   - CCND1
   - CCNE1
   - BRAF
   - RAS
   - B1

H. Glioblastoma Multiforme
   - Percent
   - EGFR
   - ERBB2
   - FGFR1
   - MET
   - NF1
   - PIK3CA
   - CDK4
   - CDK6
   - BRAF
   - BRAF
   - DN1/2
Phase III Trials: the challenge of subgroup analyses

Ex.: if you test 10 subgroups, your F.P. chance is:

Probability That Multiple Subgroup Analyses Will Yield at Least One (Red), Two (Blue), or Three (Yellow) False Positive Results.

N ENGL J MED 354,16 WWW.NEJM.ORG APRIL 20, 2006
Many cancer treatments benefit only a small proportion of the patients to which they are administered.

By targeting treatment to the right patients:
1. Treated patients benefit
2. Treatment more cost-effective for society
3. More informative and successful clinical trials
Phase III Trials - attrition rates in biomarker analysis: The IPASS study

**1217 randomised patients (100%)**

**1038 biomarker consent (85%)**

**683 provided samples (56%)**

Sample not available, insufficient quantity to send, cytology only, sample at another site

Evaluable for:
- EGFR mutation: 437 (36%)
- EGFR gene copy number: 406 (33%)
- EGFR expression: 365 (30%)

CRUCIAL Role of Prospective Biobanking!
Phase III Trials: how to deal with the target

'Realize all' design
Biomarker-Stratified Design

'Marker status
M+
M-

RANDOMIZE

Experimental treatment
M+
M-

Standard treatment
M+
M-

'Strategy' ('customized') design
Biomarker-Strategy Design

'Marker status
M+
M-

Randomize

Experimental treatment

Standard treatment

'Targeted' design
Enrichment Design

'Marker status
M+
M-

Randomize

Experimental treatment

Standard treatment

Evaluating several treatments and biomarkers in mCRC: the Focus trial design

Seven principles of the FOCUS trial design

1. Evaluate multiple treatments and biomarkers in the same protocol
   - Including as many patients as possible with a given disease, with separate clinical questions for as marker-defined subgroups as are supported by current evidence

2. Assess ‘st first’ each treatment in the presumptive biomarker-enriched subset
   - (thus exploiting the putative link between biomarkers and novel treatments with corresponding mechanisms of action) but without assuming in the design that this association will be confirmed in later stages

3. Use randomized evidence with a control group for each biomarker/treatment cohort evaluation
   - Eliminating confounding resulting from prognostic biomarkers effects

4. Ensure rapid evaluation of each new treatment
   - Incorporating the flexibility of phase II and III components into each trial
   - Targeting a reasonably large treatment effect, with discontinuation of random assignment to treatments that are unpromising or overwhelmingly effective as early and reliably as possible

5. Allow the possibility of refining any biomarkers through the course of the trial
   - Either from internal data or more typically from data emerging from outside the trial

6. Allow the possibility of introducing a new biomarker and treatment pairing into the overall trial program when evidence warrants

7. Investigate new treatments in the earliest and most likely responsive settings that are clinically feasible
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Effectiveness of Bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV mCRC

Designing studies with Targeted Agents: What has changed (..is changing...)

- Treatment strategy and drug success depends on extensive pre-clinical and early clinical modeling
  - Depends on good science behind...!
- Thus:
  - Early phases are becoming (even more) crucial for drug development
    - By exploring potential biomarkers and surrogate
    - By generating additional hypotheses
      - to progress to Phase III
      - To go back to the lab!
Designing studies with Targeted Agents: What investigators expect

• “Winner” (drugs) of early studies after more reliable basic hypotheses and background:
  - Will be “tailored” on a specific molecular feature (biomarker-based design)
  - Will allow a real “bench to bedside” medicine
• With better early studies, few drugs will enter phase III studies
  - Increased chance to win over standard!
  - The chance to change clinical practice will increase!
Designing studies with Targeted Agents: What the Health Care Providers hope

• That the following trial for drug approval, will:
  - Be a “superiority” trial
  - Test big differences
  ✓ Less patient to be enrolled
  ✓ Shorted time to be completed
  - “Rapidly” provide useful informations for giving patients a clinically meaningful benefit
• To spare money and resources
The future of drug development?
Seeking evidence of activity of novel drugs in small groups of patients

• Given the growing fragmentation of all classic tumor types into small subgroups, it is essential to:
  - Obtain consensus regarding the best ways to establish the activity of new treatments in rare molecular subsets

• Randomized trials still provide us with the highest level of certainty
• What circumstances could make randomized studies more feasible?
  - Designing studies aiming for large differences between treatment arms (which is what would be expected for therapies targeting the subtype aberration)
  - Global collaboration (investigators’ networking)
  - Harmonization of rules and legislation with respect to clinical trials