PHASE 1 CLINICAL TRIALS: DESIGNS AND CONSIDERATIONS

Sarit Assouline, MD, MSc, FRCPC
Associate professor, McGill University
Jewish General Hospital
Outline

- Introduction
- Goal of Phase I studies in oncology
- Standard 3+3 design
- Other designs
- Patient selection
- Expansion cohort
- Biomarkers

- Particular cases
  - Molecularly targeted therapies
  - Immunotherapy
  - Phase 1 combination studies
  - Pediatric phase 1 studies

- The investigator / investigative site
Preclinical

Phase I – Dose finding study

Phase II – Efficacy

Phase III – Randomized comparison to standard of care

New standard of care

≈ 5-7 years of testing
Phase I trial design

- **Primary objective**: determine dose and schedule
- **Endpoints**: safety, pharmacokinetics (PK), toxicity profile, modulation of target/biomarker
Objectives of phase 1 clinical trials.

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

- Controversial objectives:
  - Identification of specific target patient populations
  - Generation of preliminary evidence of target inhibition

Evidence of antitumor activity

Assumption: higher dose = greater clinical efficacy

Effect

Toxicity --

Anti-tumour

Dose

MTD

RP2D

c/o E. Eisenhauer
Primary objective of Phase I study is to determine the recommended phase 2 dose (RP2D) or maximum tolerated dose (MTD) in schedule evaluated.

- Assumption: higher dose = greater clinical efficacy

- Dose-escalation study to determine an acceptable level of dose-limiting toxicity (DLT) = MTD/RP2D
Dose Limiting Toxicity (DLT)

■ What is considered to be beyond the limit of tolerable toxicity
  ■ Severity – usually using the CTCAE V.4, grade 3 or 4
    AND
  ■ Duration – too long as to prohibit retreatment within a reasonable timeframe
    OR
  ■ Organ system involvement
    - Severe hematologic toxicity for patients with solid tumours (but ok for hematologic cancer)
    - Cardiotoxicity, renal or hepatic toxicity
    - Toxicity known to be associated with the agent (e.g. diarrhea, skin rash)
Ideal preclinical information

Drug

(Minimal) Blood level or other PK measure

(Optimal) Effect on target (normal/tumour)

In vivo effect on tumour

Effect on normal tissues (toxicology)

Dose

c/o E. Eisenhauer
Starting dose

- Safe, not overly conservative
- Dose by BSA* associated with 10% lethality in mice (MELD10) roughly equivalent to the human MTD
  - "allometric scaling" – toxicity as a function of body weight or surface area is assumed to be roughly constant across species
- Initial dose for Phase I trials is taken to be 1/10 the MELD10, or if smaller 1/3 the LD10 in the beagle dog.

*BSA = body surface area
Simulations show that for a wide variety of dose-toxicity curves, the probability is approximately 85-90% that the defined MTD will be associated with DLT probability of approximately 10-45%.
Classical dose escalation scheme

Modified Fibonacci sequence in which ever higher escalation steps have ever decreasing relative increments

<table>
<thead>
<tr>
<th>Dose level (cohort)</th>
<th>Dose increment</th>
<th>Dose (mg/m²)</th>
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<tbody>
<tr>
<td>1</td>
<td>Starting dose</td>
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<tr>
<td>2</td>
<td>100%</td>
<td>0.20</td>
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<td>3</td>
<td>67%</td>
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<td>4</td>
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<td>1.57</td>
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<td>9</td>
<td>33%</td>
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</table>

Dose limiting toxicities

Patient Cohort (patient nr. x1, x2, x3, …)

RD
Criticisms of standard design

1. The dose escalation is unnecessarily slow, leading to treatment of excessive numbers of patients at dose levels less likely to be efficacious

2. The MTD definition is unnecessarily imprecise in that it does not make adequate use of all the available first course toxicity data
   - 25% of oncology agents registered with the FDA are labeled at a dose different from that identified in phase I (Letourneau, JCO 2010;28:1401.).

3. Too few patients treated at the MTD
Accelerated titration design

Intracutaneous dose escalation

DLT, DLT

C

Dose

Time

SD, RD
Continual reassessment method for phase I trial design

Each patient is allocated to the dose most likely to be the MTD, according to the current state of the model. The model is “immediately” updated by incorporating first course toxicity data from each successive patient. The MTD is calculated from the final state of the model.

- Fewer patients treated at suboptimal dose.
- More precise estimate of the MTD.
  - DLT determined based on all available toxicity data.
- Ongoing computational efforts and communication with biostatistician.
Alternative Endpoints

- **Pharmacokinetics**
  - target AUC, minimum trough level, steady state level
  - Assures adequate drug delivery to tissues

- **Inhibition of target/pharmacodynamics**
  - In normal tissue
  - In tumor tissue
Graphical depiction of dose escalation methods for phase I cancer clinical trials

- **Up & down design**
- **Accelerated titration design**
- **Continual reassessment method**
- **Standard – 3+3**
- **Pharmacologically guided dose escalation**
- **Rule based**
- **Model based**
- **Escalation with overdose control**

Patient Selection

ALWAYS

■ Reasonable performance status (ECOG, Karnofsky)
■ Adequate organ function (liver, kidney, heart, marrow, nervous system)
■ Not pregnant
■ Consent and availability
■ (Ability to survive 1 month or 3 months)

SOMETIMES

■ Measurable disease
■ Eligibility for special drug administration
■ Specific tumor type ± biomarker (vs. all comers with cancer)
■ Restriction on number/type of prior therapies
Expansion cohort

- Gain more experience at the MTD
- Establish early signs of efficacy in different disease cohorts
  - *Pembrolizumab KEYNOTE001- phase I with dose expansion in metastatic melanoma and NSCLC-led to accelerated approval of drug (n=1200 pts)*
- Establish efficacy in cohort selected based on molecular target
  - *Ceritinib development – Phase 1 dose expansion in ALK positive NSCLC led to FDA approval*
- Safety expansion cohort
  - *Patients with poorer ECOG, CNS metastases, etc.*
Example of expansion cohort

Table 4 Dose Confirmation Rules

<table>
<thead>
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<th>Number of Toxicities</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
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</tbody>
</table>

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate = 30%
Noninformative prior is used: a=1; b=1;
k1=1; k2=1.5; pow=1 per [1]
Approval After Phase I: Ceritinib Runs the Three-Minute Mile

Bruce A. Chabner
Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

The old saw that phase I is all about safety and phase II is all about efficacy no longer applies. Phase I is all about Proof of Principle and efficacy, once a safe dose is reached.
Biomarkers

- Patient selection based on expression of molecular target
  - NSCLC, CML, Her2neu+ breast cancer
- Molecular profiling with NGS
  - Personalized medicine phase I programme (MD Anderson)
  - Molecular tumour boards

*Presence of an alternation in known oncogene does not necessarily imply it is the main driver*
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- Particular cases
  - Molecularly targeted therapies
  - Immunotherapy
  - Phase 1 combination studies
  - Pediatric phase 1 studies

- The investigator/investigative site
Molecularly targeted agents

The optimal dose is lower than the MTD

c/o E.Eisenhauer
Molecularly targeted agents (MTAs)

- Maximally administered dose (MAD) is determined instead of the MTD
- MTAs can demonstrate delayed or cumulative low-grade toxicities that are not captured within the DLT-assessment window
  - *Chronic toxicities due to drug target in normal tissues*
  - *20% of dose reductions with MTAs occur beyond the usual DLT-assessment period*

... 

- RP2D of MTAs should incorporate toxicity data from all cycles of therapy, as well as symptomatic grade 2 toxicities
- DLT window should be prolonged
- Efficacy endpoint can help in the process of dose escalation
Ponatinib

- **Phase 1**
  - DLT – amylase, lipase elevation and pancreatitis
  - Other toxicities – hematologic and rash
  - Median follow up 56 weeks
  - RP2D 45 mg daily
Table 4. Treatment-Related Adverse Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Chronic Phase CML&lt;br&gt;(N = 236)</th>
<th>Accelerated Phase CML&lt;br&gt;(N = 155)</th>
<th>Blastic Phase CML&lt;br&gt;(N = 48)</th>
<th>Ph-Positive ALL&lt;br&gt;(N = 11)</th>
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<tbody>
<tr>
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<td>Any Grade</td>
<td>Grade 1 or 2</td>
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<td><strong>Neurological events</strong></td>
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<td>Rash</td>
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<td>20 (11)</td>
<td>125 (82)</td>
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<td>Dry skin</td>
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<td>74 (27)</td>
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<td>Fatigue</td>
<td>51 (22)</td>
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<td><strong>Hematological events</strong></td>
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<tr>
<td>Thrombocytopenia</td>
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<td>75 (49)</td>
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<td>*Categorization of AOEs and VTEs is based on a broad collection of &gt;400 MedDRA preferred terms related to vascular ischemia or thrombosis;</td>
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<td><strong>Patient populations:</strong></td>
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<td>Serious adverse events</td>
<td>All grades</td>
<td>Serious adverse events</td>
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<td>CP-CML n=270</td>
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<td>Exposure-adjusted AOE, no. of patients with events per 100 patient-years</td>
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<td>VTEs</td>
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<td>2.0</td>
<td>1.8</td>
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15 month median follow-up

Median time to onset for AOE s in total and CP-CML patients was 11.5 (0.1–44.0) months and 14.1 (0.3–44.0) months, respectively.

Median time to onset for VTEs in total and CP-CML patients was 5.8 (0.1–40.1) months and 22.2 (2.0–40.1) months, respectively.

*Cortes et al, ASCO 2016 Abstract 7013

**Categorization of AOE s and VTEs is based on a broad collection of >400 MedDRA preferred terms related to vascular ischemia or thrombosis;**

*41 patients had >1 AOE; *72 patients had >1 serious AOE; *51 patients had >1 serious AOE; *71 patients had >1 serious AOE.

SAE s are serious adverse events

AOE s are arterial occlusive events
Inappropriate dose of multitargeted tyrosine kinase inhibitors: the original sin

Nuria Kotecki and Nicolas Penel

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Statistical controversies in clinical research: requiem for the 3 + 3 design for phase I trials

X. Paoliatti1,2,*, M. Ezzatfard3 & C. Le Tourneau3,4

1Biostatistics and Epidemiology Department, Gustave Roussy, Villejuif; 2INSERM U1018, CESP; Paris-Sud University, Villejuif; 3INSERM/Institut Curie/Mines Paris Tech-LIFL, Paris; 4Department of Medical Oncology, Clinical Trial Unit, Institut Curie, Paris & Saint-CLOUD, France

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The changing landscape of phase I trials in oncology

Kit Man Wong, Anna Capasso and S. Gail Eckhardt

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Headlines
MTAs- review of 84 studies from 2000 to 2010

- 49% used the 3+3 design
- 42% Accelerated titration design
- 7% continuous reassessment model
- 1% pharmacologically guided dose escalation

Word on immuno-oncology

Hoos, 2016
Immuno-oncology: immune checkpoint inhibitors

- 13 main phase 1 studies
  - 1 determined dose based on DLT
  - 10 maximum feasible dose
  - 2 PK parameters
- imAbs have limited potential for causing acute or cumulative toxicities
- immune-related adverse events (irAEs) occur at any time later in trial, therapy usually held if grade 2 or greater
  - affects drug exposure and thus should be considered as part of DLT definition
Overview of trial designs

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<th>Cytotoxic chemotherapy</th>
<th>Molecularly targeted agents</th>
<th>Immuno-stimulatory antibodies</th>
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<td>100-1000 immunologically</td>
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<td>selected patients</td>
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<td>PK/PD - biomarkers</td>
<td>Traditional PK</td>
<td>OIB</td>
<td>PK and pD-based dose</td>
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<td>dynamic biomarkers and</td>
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<td>Design</td>
<td>Traditional 3 + 3 dose-</td>
<td>3 + 3 dose-escalation</td>
<td>Accelerated titration/adaptive</td>
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<td>escalation design</td>
<td>design with large</td>
<td>design multiple parallel</td>
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<td>expansion cohorts in</td>
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<td>selected populations</td>
<td>long-term follow-up + drug</td>
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<td>rechallenge</td>
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<td>Drug approval</td>
<td>Based on later phase 2</td>
<td>Conditional of accelerated</td>
<td>Conditional of accelerated</td>
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<td></td>
<td>or 3 trials</td>
<td>approval based on large</td>
<td>approval based on histology</td>
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<td>molecularly selected</td>
<td>and immune-biomarker</td>
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<td>Conditional of accelerated</td>
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<td>Drug development timeframe</td>
<td>10 years</td>
<td>5-8 years</td>
<td>&lt;5 years</td>
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Figure 1. The evolving landscape of phase 1 trials—from cytotoxics to immunostimulatory monoclonal antibodies (mAbs). Many changes have been observed.

Postel-Vinay, Annals of Oncology, 2016
Phase 1 combination studies

- Combination with standard chemotherapy
  - Usually the chemotherapy is kept at a fixed dose, dose of molecularly targeted agent is varied

- Combination of two molecularly targeted agents
  - Testing synergistic target requires preclinical evidence supporting biological rationale
  - More complex because of synergistic or antagonistic PK/PD interactions
  - Overlapping toxicity

Paller C. NCI recommendation. Clinical Cancer Res. 2014
Pediatric Phase I studies

- Adult studies usually performed prior to pediatric studies, thus dose and toxicity already known
- Few toxic deaths in children
- Rare diseases with rapid progression – need to limit suspension of accrual

- Rolling six design – enrol 2 to 6 patients at a time, dose patient receives depend on number of enrolled patients, DLT rate, and number of patients who have completed the DLT window. De-escalation occurs when two or more DLT occur at a dose level, whereas escalation can be performed when 3/3, 4/4, 5/5, 5/6 or 6/6 patients are evaluated without DLT.

- CRM/Model based ensures fewer patients treated at lower doses

A. Doussau et al. / Contemporary Clinical Trials 47 (2016) 217–227
You and your site

- Multi-institutional phase I studies to expedite patient accrual
  - To accommodate the same number of patients, a site needs
    - More phase I studies
      - More personnel
      - More resources
      - More conference calls

- Greater interaction with CRO
  - To accommodate greater study coordination
  - To ensure quality of data as phase 1 may lead to drug approval

- More physicians involved in phase 1 research
  - Molecularly targeted studies are disease specific
  - Large studies with dose expansion cohorts
Outline

- Introduction
- Goal of Phase I studies in oncology
- Standard 3+3 design
- Other designs
- Patient selection
- Expansion cohort
- Biomarkers
- Particular cases
  - Molecularly targeted therapies
  - Immunotherapy
  - Phase 1 combination studies
  - Pediatric phase 1 studies
- The investigator /investigative site

Thank you. Questions?