Phase I trials in patients: new approaches and designs in Oncology

Session 5: How to be prepared

Nuria Kotecki, MD
Clinical Trial Conduct Unit
Institut Jules Bordet, Brussels Belgium
Executive officer – Oncodistinct network

Eufemed, 17th May 2019
OUTLINE

- Evolving landscape in oncology: New drugs and new cancer types definitions
- Current status for new drug development and phase 1 trials in oncology
- Challenges for clinical research in oncology
- What do we need in drug development methodology?
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- What do we need in drug development methodology?
The molecular and immune biology of cancer cells is better understood

Hanahan et Weinberg, Cell, 2000
Hanahan et Weinberg, 2011
Evolving therapeutic concepts in oncology based on molecular/immune biology understanding

From empirical oncology to molecular and immunological therapeutic approaches
Common cancers are now rare

A. Lung Adenocarcinoma

B. Lung Squamous Cancer

C. Breast Cancer

D. Colorectal Cancer

E. Melanoma

F. Head and Neck Squamous Cancer

G. Ovarian Cancer

H. Glioblastoma Multiforme

Garraway LA, J Clin Oncol 2013;31:1806-1814
OUTLINE

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- What do we need in drug development methodology?
Classical approach of drug development

Drug discovery

Preclinical
- Activity
- PK/PD
- Toxicology (in vitro/in vivo)

Clinical
- Phase I (dose-finding trial)
- Phase II (efficacy)
- Phase III (registration)
- Clinical practice

PRECLINICAL validation
Classical approach of drug development

<table>
<thead>
<tr>
<th>Steps</th>
<th>Purpose</th>
<th>Number of compounds</th>
<th>Number of patients</th>
<th>Estimated Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Research</td>
<td>Identify Potential New Medicines</td>
<td>&gt; 10,000</td>
<td>10s</td>
<td>8-10 Years</td>
</tr>
<tr>
<td>Lead Identification &gt; Optimisation</td>
<td>Safety Dose PK/PD</td>
<td>1 - 2 Years</td>
<td>100s</td>
<td>1 - 2 Years</td>
</tr>
<tr>
<td>Phase I</td>
<td>Activity Safety PK/PD</td>
<td>2 - 4 Years</td>
<td>1000s</td>
<td>1 Year</td>
</tr>
<tr>
<td>Phase II</td>
<td>Efficacy Superiority</td>
<td>2 - 5 Years</td>
<td></td>
<td>Until Patent Expiration</td>
</tr>
<tr>
<td>Phase III Pivotal randomised</td>
<td>Obtain Marketing Authorisation</td>
<td>1 - 2 Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>Establish Market</td>
<td>1 Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Launch</td>
<td>Expand Market</td>
<td></td>
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<tr>
<td>Global Optimization / NILEX</td>
<td></td>
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</table>

Major endpoints in phase 1 trials

- **Dose Limiting Toxicity**: Occurrence of severe toxicities during the first cycle of systemic cancer therapy.

- **Maximum Tolerated Dose**: The highest dose of a drug or treatment that does not cause unacceptable side effects.

- **Recommended Phase II Dose**
Considerations for the evolution of phase I oncology trials

Evolution of phase I oncology trials

- Biomarker selection
- Basket trials
- Umbrella trials
- Exploratory objectives

- Patient selection

- Dose-escalation designs

- 3+3 design
  - ATD
  - CRM

- Integrating precision cancer medicine

- Increase genomic sequencing
- Molecular tumor boards

- Adapted DLT definitions

- Regulatory changes

- Combinations studies

- Breakthrough designations

Adapted from Wong et al. Nature Reviews 2016
Considerations for the evolution of phase I oncology trials

- 3+3 design
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Dose-escalation designs

Patient selection

Biomarker selection
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Basket trials

Umbrella trials

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Evolution of phase I oncology trials

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Adapted DLT definitions

Regulatory changes

Adapted from Wong et al. Nature Reviews 2016
Phase 1 published from 01/2014 to 06/2015

### Trial sponsorship

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Trials (%) (N=224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic</td>
<td>106 (47.0)</td>
</tr>
<tr>
<td>Industry</td>
<td>118 (53.0)</td>
</tr>
</tbody>
</table>

### Expansion cohort

<table>
<thead>
<tr>
<th>Expansion cohort</th>
<th>Yes</th>
<th>No</th>
</tr>
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<tr>
<td></td>
<td>64 (28.6)</td>
<td>160 (71.4)</td>
</tr>
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</table>

#### Treatments

- TKI
- Monoclonal Antibody
- Immunotherapy
- Chemotherapy
- Hormonal Therapy
- Others

Italiano A et al, NEJM 2018
Considerations for the evolution of phase I oncology trials

Adapted from Wong et al. Nature Reviews 2016

- Patient selection
  - Biomarker selection
  - Basket trials
  - Umbrella trials
  - Exploratory objectives

- Combinations studies
- Evolution of phase I oncology trials
- Dose-escalation designs
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- Patient selection
- Regulatory changes
- Breakthrough designations

- Integrate precision cancer medicine
- Increase genomic sequencing
- Molecular tumor boards

- Adapted DLT definitions
Dose escalation methods for phase I cancer clinical trials.

- Accelerate drug development
- Limited number of patients treated at a suboptimal dose
- Integrate drug mechanism of action and target activation
Typical dose–toxicity and dose–efficacy curves for cytotoxic agents

- Hypothesis: Toxicity and efficacy increase when the dose is increasing
- MTD considered as the optimal dose
- Still true in the era of MTA/IO ??

Dose escalation methods for phase I cancer clinical trials.

- Simple up and down design
- 3+3 design
- Accelerated titration design
- Pharmacologically guided DE
- Modified continual reassessment method
- Escalation with overdose control

Considerations for the evolution of phase I oncology trials

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- Combinations studies
  - Breakthrough designations
- Regulatory changes
- Adapted DLT definitions
- Integrate precision cancer medicine
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- Dose-escalation designs
- 3+3 design
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  - CRM

Adapted from Wong et al. Nature Reviews 2016
Adapted DLT definitions

- **New toxicities** *(including long term toxicities):*
  - Extended DLT period
  - Better definition of the induced toxicity in relation to the study drug
  - Use of expansion cohorts
  - Consider the clinical importance of each grade and toxicity type

Adapted from Paoletti X, Eur J Cancer. 2014
Considerations for the evolution of phase I oncology trials

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Adapted from Wong et al. Nature Reviews 2016
SELECTED NEW DESIGNS IN DRUG DEVELOPMENT BASED ON MOLECULAR BIOLOGY OR ON STRATEGY

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<td>Basket trials</td>
<td>Test the effect of one drug on single mutation in a variety of cancer types</td>
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<td>Test the impact of different drugs in different mutations in a single type of cancer</td>
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|                   | Adaptive trial | Allows the modification of some parameters of the trial as data accrue, e.g. sample size reassessment, stop for early efficacy/ futility, drop an arm with necessity to have an active IDMC.  
A platform trial is a type of adaptive trial designed to evaluate multiple treatments efficiently. |
|                   | Windows of opportunity | Assessing the administration of an investigational agent over a short period of time |
|                   | Randomized discontinuation design | phase I: all patients are openly treated with the medication  
phase II: Those who have responded are randomly assigned to continue the same treatment or switch to placebo. particularly useful in studying the effect of long-term, non-curative therapies |
|                   | N of 1 trials | Clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions. |
Novel precision medicine trial designs

**Umbrella trial**
- 1 type of cancer
- Different genetic mutations (● ● ●)
- Test drug 1
- Test drug 2
- Test drug 3

**Basket trial**
- Multiple types of cancer
- 1 common genetic mutation (●)
- Test drug
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ADAPTIVE DESIGN

Adaptive trials offer a more flexible way to deal with drug performance over the course of a study. I-SPY 2 uses a design called Bayesian, in which patient allocation is shifted according to treatment response.

Colours represent different biomarker profiles.

**DRUG A**
- Outcome better than control
- Outcome same as control

**DRUG B**
- Subsequent recruitment favours profiles that benefit
- Discontinue drug B

**CONTROL**
- Drug B shows no improvement over control for any biomarker
- Randomized recruitment to control arm continues

Modified recruitment creates potential for drug to reach endpoint faster, and informs phase III design.
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- **Patient selection**
  - Biomarker selection
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  - Exploratory objectives

- **Regulatory changes**
  - Breakthrough designations

- **Combinations studies**

- **Evolution of phase I oncology trials**

  - **Dose-escalation designs**

  - **3+3 design**
  - ATD
  - CRM

  - **Integrate precision cancer medicine**

  - Increase genomic sequencing
  - Molecular tumor boards

  - **Adapted DLT definitions**

  - **Regulatory changes**

Adapted from Wong et al. Nature Reviews 2016
The Belgian Molecular Profiling Program of Metastatic Cancer for Clinical Decision and Treatment Assignment

A BSMO master protocol “PRECISION 1 and 2”

BSMO 2014-2

Precision 1
- Investigate benefits of approach
- Interinstitutional Molecular tumor board

Precision 2
- Establish new evidence on efficacy in specific genotype-cancer type associations
Considerations for the evolution of phase I oncology trials

Adapted from Wong et al. Nature Reviews 2016
RECENT DEVELOPMENTS IN THE CLINICAL RESEARCH METHODOLOGY AND REGULATORY CHANGES

Phase I → Phase II → Phase III 

Drug Approval 7-10 years

Accelerated Approval (e.g., Crizotinib in ALK translocated NSCLC)

Phase I/II → Phase III 

~5 years

Adapted from Postel Vinay et al. Annals of Oncol. 2016
The NEW ENGLAND

A Percent Change in Tumor Burden

- Disease progression
- Stable disease
- Partial response
- Complete response

Percent Change from Baseline

-30%

Patient No.

and A. John Iafrate, M.D., Ph.D.
Number of patients enrolled in recent phase I trials having led to conditional approval or breakthrough designations

Postel-Vinay S et al, Annals of Oncology 2016
# EVOLVING METHODOLOGY OF EARLY PHASE TRIALS FROM CYTOTOXICS TO IMABS

<table>
<thead>
<tr>
<th></th>
<th>Cytotoxic chemotherapy</th>
<th>Molecular-targeted agents</th>
<th>Immunostimulatory antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients number</strong></td>
<td>30-50 unselected pts</td>
<td>30-200 “molecularly” selected pts</td>
<td>100-1000 “immunologically” selected pts</td>
</tr>
<tr>
<td><strong>MTD</strong></td>
<td>MTD reached</td>
<td>MTD unconstantly reached</td>
<td>MTD rarely reached</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>3+3</td>
<td>3 + 3 with large expansion cohorts</td>
<td>Accelerated titration/Adaptive designs/ Multiple expansion cohorts</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td>Safety</td>
<td>Safety and activity</td>
<td>Safety and activity</td>
</tr>
</tbody>
</table>

Adapted from Postel Vinay et al. Annals of Oncol. 2016
Encouraging Trends in Modern Phase 1 Oncology Trials

224 trials between 01/2014-06/2015

ORR : 19.8%

Factors significantly associated with an RR:

- Trials investigating a single tumor type
- Presence of a tumor biology eligibility criterion
- Combination of treatments
- Presence of an expansion cohort

Italiano et al. NEJM 2018
OUTLINE

- Evolving landscape in oncology: New drugs and new cancer types definitions
- Current status for new drug development and phase 1 trials in oncology
- Challenges for clinical research in oncology
- What do we need in drug development methodology?
Challenges in early clinical trials methodology (2 examples)

1. Still inappropriate designs\(^1,\,^2\)

2. Definition of DLT and recommended doses and schedules are often inappropriate\(^3\)

1. X. Paoletti et al. 2014
2. C. Le Tourneau et al 2009
3. N. Kotecki et al COON 2017
Inappropriate dose of multitargeted tyrosine kinase inhibitors: the original sin

Nuria Kotecki and Nicolas Penel

Purpose of review
The use of antiangiogenic tyrosine kinase inhibitors (TKIs) is challenging and often requires dose adaptation and transient or definitive treatment interruption. We believe that the inappropriate recommended dose of TKI is related to no optimal study designs in the early development of the drug.

Recent findings
As an example of this, we described herein some pitfalls made in the successive development of sunitinib, sorafenib, regorafenib, and pazopanib, but there are several other examples of early drugs development illustrating this issue.

Summary
Regarding the antiangiogenic TKI mechanism of action, we strongly feel that innovative approaches are needed such as extended dose-limiting toxicity period or a better definition of the induced toxicity. Furthermore, before classic phase II/III trials, an intermediate step may be needed to better define the recommended phase II dose, such as a randomized phase I/II trial with several expansion cohorts.

Keywords
antiangiogenic, dose, optimal study designs, tyrosine kinase inhibitors
Challenges in precision medicine

LIMITED AVAILABILITY OF BIOMARKERS IN CLINICAL PRACTICE

More and more biomarkers studies (Pubmed search: 42636!) but very few were validated for clinical use.

>> Importance of selective and well designed clinical trials integrating high level of translational research with potential for clinical practice.

>> Importance of using a proper statistical strategy for validation.

>> Need for quality assurance and reproducibility.
Challenges in precision medicine

- High promotion of Precision Medicine among medical team and patients
  - but
- Limited number of actionable/targetable mutations
- Limited access or not available clinical trials or marketed targeted agents
  - High attrition rate and ethical issues

Adapted from Massart et al. Cancer Discovery 2017

MOSCATO-01
- 1110 pts included from 11/2011 to 03/2016
- 411 pts with targetable mutations
  - 49%
- 119 treated pts
  - 19%
Tumor-Agnostic treatment for cancer

Example of TRK fusions

- Can be harbored by 1% of all cancers
- Targeted treatments are very potent

The New England Journal of Medicine

Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri,
M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati,
M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik,
J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski,
F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed,
M. Ladan, B.B. Tuch, K. Ebbat, S. Cruickshank, N.C. Ku, M.C. Cox,
D.S. Hawkins, D.S. Hong, and D.M. Hyman
Tumor-Agnostic treatment for cancer

*Example of TRK fusions*

**FDA approves larotrectinib for solid tumors with NTRK gene fusions**

Novembre 2018
Tumor-Agnostic treatment for cancer

Example of TRK fusions

- How can patients be screened without universal molecular screening?
- **Is recruitment possible in clinical trials without clinical and genomic data sharing?**
MatchMiner
Developed at Dana Farber Cancer Institute
Challenges for immunotherapy trials

Optimal dose and schedule selection

- Minimal immunologically active dose (dose is not linearly associated with efficacy and toxicity)
- Optimal dose for prolonged exposure

Optimal sequence/rechallenge

- Maximize benefit for patients and minimize economic burden

Identify resistant/sensitive disease to immunological approaches

- Biomarkers (immunoscore, Immunomics, …)

New patterns/definitions of tumor assessment and disease progression

Combinations issues
Current strategy of solid cancers clinical research is dominated by:

More “market and regulatory oriented” trials and less patients directed or based on unmet need in diseases or settings!
Huge redundancy in the development of agents: Number of active trials with PD1/PDL1 Ab
Evolution of PD-1/PDL-1 trials by different cancer types
High cost and attrition rate
Current strategy of clinical research

- New chemotherapy agents are less and less developed (except antibody drugs conjugates (ADC)) but chemotherapy has proven to cure patients

- Molecular-targeted therapies (and ADC) have been developed but rarely have cured patients (except for endocrine agents and trastuzumab in breast cancer)

- Recently the hype of immunotherapy slows significantly the development of other anti-cancer treatments
Does the current design of oncology trials meet the need of patients?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Several new anticancer agents reached clinical practice much faster than in the past</td>
<td>• still Inappropriate design and DLT definitions</td>
</tr>
<tr>
<td>• Often improvement in PFS (but rarely in survival (metastatic setting))</td>
<td>• Commonly used endpoints are not relevant for immunotherapy or other new agents</td>
</tr>
<tr>
<td>• Often improvement in DFS (but rarely in OS (early setting))</td>
<td>• Redundancy in the development of agents</td>
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<tr>
<td></td>
<td>• Competitive trials in the same setting</td>
</tr>
<tr>
<td></td>
<td>• Few studies looking to a therapeutic strategy</td>
</tr>
<tr>
<td></td>
<td>• Few studies in unmet need clinical settings or focusing on rares cancers</td>
</tr>
<tr>
<td></td>
<td>• More biomarkers studies but limited validated biomarkers for clinical use</td>
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Still a huge gap between clinical research & the need in clinical practice!!
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What do we need in drug development methodology?

1. More innovative approaches and trials design in drug development

2. Targeting unresolved scientific questions and settings of unmet need for patients

3. More selective and well designed biomarkers studies with clinical utility integrating high level translational research approaches

4. Creating new models of clinical research networks and collaboration between pharma, cooperative groups and investigators
What do we need in drug development methodology?

- Good biological rationale
- Focus on unmet medical need
- Efficient and pragmatic Clinical research network
ACADEMIC MODEL OF CLINICAL RESEARCH COLLABORATION BASED ON THE PROGRESS ON MOLECULAR BIOLOGY AND METHODOLOGICAL ISSUES

- Scientific Input
- Experts dedicated to clinical research
- Network of academic & non academic centers
- Pharmas
- Pharma and Academic labs
- Satellites centers
- Huge number of screened pts for gene/protein
  « Selected » Patients
- New therapeutic strategies
  Studies meeting the unmet need of patients
  Innovative and individualized designs
- Academic & non Academic trials

Speed and quality academic and non academic trials

www.oncodistinct.net
A new model of clinical research collaboration
“working together and not as different groups”

Academic centres, non-academic centres with expertise in research, early and late drug developers, monospecialized and multispecialized investigators, clinicians, laboratory workers and patients

Scientific input
High number of screened patients
Speed in performance of trials
Able to perform early (2-3 centres) to late phase trials within the network (several centres)
Aknowledgements

Pr Ahmad Awada
Dr Philippe Aftimos
Dr Christiane Jungels
And the Oncodistinct network investigators