Improving Clinical Trials to Advance the Success of Biomarker Driven Targeted Therapies

Prof Dr Christian Rolfo, MD, PhD, MBA
Head of Phase I – Early Clinical Trials Unit
Director of Clinical Trial Management Program
Oncology Department
Antwerp University Hospital
Center for Oncology Research (CORE), Antwerp University
Disclosures

• Novartis International Speaker Bureau for Lung Cancer
• Mylan: Scientific advisor for Lung Cancer Products
• Biocept: Research grant for Liquid Biopsy in NSCLC
• OncoDNA: Research collaboration exosomes project
• Oncompass: steering committee for Molecular Profile
• Boeringher Italy Speaker Bureau for Lung Cancer
• MSD International Speaker Bureau for Lung Cancer
New Treatment and Trial Paradigm

a
Past
Drugs
Which patients respond best?

Current and future
Determine molecular profile of the patient’s tumour
Determine which drugs are most appropriate

b
Past
Cytotoxic chemotherapies

Efficacy
PK
PD
Toxicity
MTD

Current and future
Molecular targeted therapies

Efficacy
Predictive biomarkers
PK
PD
Intermediate end-point biomarkers
Other molecular biomarkers
Molecular Matching in Early-Phase Trials

Examples of Tested Aberrations: $PIK3CA, PTEN, BRAF, RAS, EGFR, KIT, ALK, MET...$

Matched therapy

N=175
CR/PR = 27%

Therapy without matching

N=116
CR/PR = 5%

p<.0001
Matching the right biomarker with the right therapy...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker</th>
<th>Disease</th>
<th>Response rate in %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>BCR-ABL fusion</td>
<td>CML</td>
<td>77*</td>
<td>Druker et al., N Engl J Med 2001</td>
</tr>
<tr>
<td>Imatinib</td>
<td>KIT mutation</td>
<td>GIST</td>
<td>53</td>
<td>van Oosterom et al., Lancet 2001</td>
</tr>
<tr>
<td>Olaparib</td>
<td>BRCA 1, BRCA 2 mutations</td>
<td>Diverse cancers</td>
<td>39</td>
<td>Fong et al., N Engl J Med 2009</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF mutation</td>
<td>Melanoma</td>
<td>77**</td>
<td>Flaherty et al., N Engl J Med 2010</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>PTCH1 mutation</td>
<td>Basal cell cancer</td>
<td>55</td>
<td>Von Hoff et al., N Engl J Med 2010</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>EML4-ALK fusion</td>
<td>NSCLC</td>
<td>57</td>
<td>Kwak et al., N Engl J Med 2010</td>
</tr>
<tr>
<td>PI3K/AKT/mTOR inhibitors***</td>
<td>PIK3CA mutation</td>
<td>Diverse cancers</td>
<td>35</td>
<td>Janku et al. Mol Cancer Ther 2011</td>
</tr>
</tbody>
</table>
Clinical utility of a biomarker

Meric-Bernstam F et al. JCO 2013;31:1849-1857
Biomarker Development

**Clinical validity:**
The test result shows an association with a clinical outcome of interest.

**Analytical validity:**
The test’s performance is established to be accurate, reliable, and reproducible.

**Clinical utility:**
Use of the test results in a favorable benefit to risk ratio for the patient.
Timeline of biomarker development

- Biomarker development (ideal)
- Biomarker development (most targeted drugs)
- Biomarker development (some targeted drugs e.g. anti-EGFR MAb & KRAS)
Efficacy endpoints

• Tumor/Hematologic Response and Stable Disease (Clinical Benefit)
• Time to Progression or Progression-Free Survival
• Overall Survival
• Hazard Ratio

Safety endpoints

• Dose-limiting toxicities
• Specific toxicities, such as cardiac events or hemorrhage
Developing biomarker-specific end points in lung cancer clinical trials

Evaluating **overall survival improvement as a cancer clinical trials end point** is time-consuming and **costly**, but traditional **radiographic measurements** of tumours might not accurately **reflect clinical benefit due to confounding factors**

**Molecular imaging** aims to augment traditional radiographic measurements by differentiating malignant from normal tissues in order to **better capture biological or molecular responses to therapy**

**Circulating tumour factors**, such as proteins, DNA, and cells, hold great **promise as early predictors of therapeutic response** and disease recurrence

Tumour-derived factors present in the circulation might also enable early detection of molecular resistance markers and **provide information on tumour heterogeneity**
Developing biomarker-specific end points in lung cancer clinical trials

*Pharmacodynamic biomarkers* evaluate the biological, molecular, and functional effects of a drug on its target, potentially offering insights into mechanisms of action of new compounds and/or validating new targets.

Validation of specific biomarkers requires their broad inclusion in clinical trials for assessment of performance.
Phase 0 clinical trials: theoretical and practical implications in oncologic drug development

Lead discovery
Preclinical testing
Phase I
Phase II
Phase III
Phase IV

Target identification
Laboratory and animal studies
Clinical (in-human) studies
Synthesis
Target validation
Lead optimization

~5–6 years
IND application
~8–10 years
NDA Review and Approval

Coloma, Journal of Clinical Trials 2013:5 119–126
Phase 0 Clinical Trials: An Answer to Drug Development Stagnation?

First-in-human trial conducted prior to traditional Phase 1 study

Exploratory IND studies are clinical trials conducted early in phase

Small number of subjects (≈10-15)

Limited drug exposure
  - Low, non-toxic doses
  - Short duration (≈ ≤7 days)
  - One course only

No therapeutic intent

Phase 0 trials are not definitive studies
Phase 0 – Patient Recruitment and Ethical Considerations

Challenging, but not insurmountable

• Potential barriers to patient enrollment
  • No therapeutic intent or chance of benefit
  • Pre- and post-treatment tissue biopsies
  • Delay or exclusion from other trials or therapies

External concerns about ethics and availability of patients for study

• Institutional Ethics committee review and input
• IRB approval
• Informed Consent Process
  • Clearly explain the rationale for the study
  • Clearly describe the limited treatment and follow up period
  • Clearly state that there is absolutely no anticipated clinical benefit to the participant

• More straightforward than Phase 1
Traditional vision of Drug Development

Phase I
- Safety, tolerability
- Pharmacokinetics
- Pharmacodynamics
- Preliminary antitumor activity

Phase II
- Efficacy observed in selected tumor types, e.g. ORR, TTP, PFS

Phase III
- Meaningful benefit obtained in a randomized setting against existent standard e.g. OS
New Paradigm of Drug Development

Phase 1 trials

**Proof of Mechanism**
- Safety, tolerability – on target and off target effects
- Preliminary antitumor activity
- Evidence of target engagement in valid pharmacodynamic biomarkers

**Proof of Concept**

**Early**
- Predictive biomarkers explored
- Antitumor activity seen using surrogate endpoints e.g. ORR, TTP or PFS

**Late**
- Predictive biomarkers confirmed
- Proof of concept using a validated clinical endpoint e.g. OS

Courtesy of David Hong
Efficiency Gain From A Thoughtful Scientific/Regulatory Strategy

Unoptimized Strategy

Discovery

Preclinical Toxicology

Phase I

Phase II

Phase II

Phase III

Phase III

Regulatory Filing

Patent life

Adapted from Postel-Vinay et al., Annals of Oncol. 2016
Efficiency Gain From A Thoughtful Scientific/Regulatory Strategy

Discovery
Preclinical Toxicology
Phase I
Phase II
Phase III
Accelerated Approval

Time (Years)
Regulatory Filing
Patent life

Adapted from Postel-Vinay et al., Annals of Oncol. 2016
**ALKi Development Timeline: Rapid Success in a Short Time**

- **1994**
  - NPM-ALK discovered in ALCL

- **2007**
  - EML4-ALK discovered in NSCLC
  - Crizotinib phase III trial initiated

- **2009**
  - Crizotinib FDA-approved in first line

- **2011**
  - Crizotinib approved for pretreatment

- **2012**
  - Ceritinib Breakthrough Therapy designation request and granted 01/2013 and 03/2013

- **2013**
  - Ceritinib FDA approved for ALK+, crizotinib-resistant NSCLC

- **2014**
  - Ceritinib EMA CHMP positive opinion 26/02/2015

- **2015**
  - Alectinib approved in Japan
  - Crizotinib EMA approved for first-line. 10/2015
  - Ceritinib FDA Approved Dec 2015
Drug Development Paradigm (Better!)

- "System" Approach:
  - Neither simple, nor linear
  - Each component is part of a “whole” strategy
  - “Goal” driving earlier development steps: Iterative
    - Demonstrate clear, population specific benefit/risk
    - Efficient and timely as possible
    - Dynamic, responding to new knowledge
### The inverted Pyramid of Biomarker-Driven Trials

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Small</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient population</td>
<td>Large unselected</td>
<td>Small selected</td>
</tr>
</tbody>
</table>

- **Classic phase III**
- **Biomarker-driven phase I**

Evolving cancer treatments and concepts

- Evolving therapeutic concepts in oncology based on molecular biology understanding
  - Precision medicine
  - Cancer immunotherapy

From clinical oncology to molecular and immunological therapeutic approaches
Current strategy of clinical research is dominated by:

- Business
- Fashion
- Power

More and more “market and regulatory oriented” and less patients directed or based on unmet need in diseases or settings!
## 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</td>
<td>• Redundancy in the development of agents</td>
</tr>
<tr>
<td>• Often improvement in PFS but rarely in survival</td>
<td>• Many 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</td>
</tr>
<tr>
<td></td>
<td>• More and more biomarkers studies but limited validated biomarkers for clinical use</td>
</tr>
</tbody>
</table>

Still a huge gap between clinical research & the need in clinical practice
Need to Move to “One Patient – One Test”
Sequential Testing Is Not Sustainable

Not sustainable for labs (different platforms, sample preps), physicians (confusing), pharma (potential negative impact on drug access), regulators

1 Patient – 1 Test

Cobas EGFR mut test (Roche)

therascreen® EGFR (Qiagen)

Ceritinib

Tarceva (erlotinib)

Gilotrif (afatinib)

EFGR816

CO-1686

Buparlisib

Xalkori (crizotinib)

INC280

Zykadia

MEK162

VENTANA ALK (D5F3) Rabbit Monoclonal Primary Antibody assay

NGS Platform

Dako IHC test (?)

Alectinib

Pharma Ind. portfolio includes products for multiple genetic abnormalities
### Selected new designs in drug development

<table>
<thead>
<tr>
<th>New designs</th>
<th>Basket trials</th>
<th>Test the effect of one or more drugs on one or more single mutation in a variety of cancer types</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Umbrella</td>
<td>Test the impact of different drugs in different mutations in a single type of cancer</td>
</tr>
<tr>
<td>Genotype driven</td>
<td>Adaptative trial</td>
<td>based on modifying parameters of a clinical trial evaluating a treatment according to outcomes in participants</td>
</tr>
<tr>
<td></td>
<td>N of 1</td>
<td>Assessing the administration of an investigational agent over a short period of time</td>
</tr>
<tr>
<td></td>
<td>Windows of opportunity</td>
<td>Assessing the administration of an investigational agent over a short period of time</td>
</tr>
</tbody>
</table>
Hallmarks of Master Protocols

• One scoping study protocol
• Beneath: Separate parallel drug trials with
  ▪ Different biomarkers
  ▪ Different treatment designs
• Require collaboration of many stakeholders
  ▪ Academic
  ▪ Industry
    – Diagnostic
    – Pharmaceutical
  ▪ Regulatory
Why Master Protocols and not Separate Studies?

- Enhanced genomic screening efficiency
- Inclusion of wide array of molecular subtypes
- ↑ willingness of patients and HCPs to participate
- Deletion/insertion of new subprotocol by amendment instead of completely new protocol development
- ↑ and faster accrual c/w separate studies
- More rapid clinical development
- Better streamlined clinical development
Master Protocols: Higher Efficiency than separate studies if...

- Use of common genomic platform or diagnostic tests
- Screening for variants of multiple genomic targets in each tumor sample in each tumor sample (requires sufficient tumor material)
- Rapid inclusion of patients based on screening results
- Organizational setting that allows for addition/deletion of subprotocols
Hypothesis: The response to targeted therapy is determined by the underlying molecular variant and (largely) independent of histology.
<table>
<thead>
<tr>
<th>Prerequisites:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Drug must sufficiently inhibit target</td>
</tr>
<tr>
<td>2. Tumor must depend on target</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benefits:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Access to trial for patients with rare tumors (must have respective molecular marker)</td>
</tr>
<tr>
<td>▪ Testing must be done locally</td>
</tr>
<tr>
<td>▪ Small cohorts (usually single arm) may suffice to detect activity</td>
</tr>
<tr>
<td>▪ Quick results</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Challenges:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Molecular variant(s) may not be the only driver of tumor</td>
</tr>
<tr>
<td>▪ Contextual complexities in various histologies</td>
</tr>
<tr>
<td>▪ Single biomarkers may be inferior to multi-gene signature</td>
</tr>
<tr>
<td>▪ Structural variants may need to be complemented with functional studies</td>
</tr>
<tr>
<td>▪ Different tumor types have different prognoses: single primary endpoint (eg ORR) may skew results</td>
</tr>
</tbody>
</table>
MPACT, Molecular Profiling-based Assignment of Cancer Therapy

Flowchart:
- **Tumor biopsy from all patients for sequencing**
  - Mutation detected
    - Randomization (clinical team is blinded)
    - **Arm A**
      - Assign treatment identified to target mutation
      - Disease progression
    - **Arm B**
      - Assign treatment NOT identified to target mutation
  - Mutation not detected
    - Off study
Hypothesis: The response to targeted therapy is primarily determined by histologic context
Umbrella Trials: Pros and Cons

**Benefits:**
- Conclusions are specific for a given tumor type
  - Tumor heterogeneity limited to one tumor type
- For randomized substudies:
  - Potential to better understand the difference of targeted therapy vs SOC
  - Potential to differentiate between prognostic and predictive markers
  - Easier path to negotiate approval with regulatory agencies

**Challenges:**
- Requires:
  - Strong collaboration between academia and industry
  - Consistent marker profile, comparability of cohorts (bx, assay, Tx)
- Feasibility:
  - Subclassification into rare populations (particularly with rare cancers to start out with)
  - ↓ speed of accrual
  - Randomization requiring a larger sample size may be challenging
  - Appearance of new SOCs during trial conduct changes the environment
Lung-MAP Trial Arms for Treatment

Patients with squamous cell lung cancer

Tumor sample analyzed

Arm A

Arm B

Arm C

Arm D

Arm E

Tumor has none of the changes listed here

Tumor DNA has PIK3CA gene mutation

Tumor DNA has CCND1, D2, CDK4 gene mutation

Tumor DNA has FGFR gene amplification, mutation or fusion

Tumors contain high levels of c-Met protein

50% Chemo-therapy

50% Pemetrexed 4736

50% Chemo-therapy

50% GDC-0030 35

50% Chemo-therapy

50% Paclitaxel 145

50% Chemo-therapy

50% AZD 4547

50% Erlotinib 90

50% Rasburicase 54
Adaptative Design
Hallmarks of Bayesian Adaptative Design

- Randomized trial with Master Protocol
  - Subprotocols may leave or enter during trial
- Pts assigned to specific targeted therapy arms based on molecular signature
- Adaptative change of randomization based on treatment’s observed activity
  - ↑ randomization probability if activity is observed
  - ↓ randomization probability if unpromising activity
- Requirements to perform well:
  - Swift marker assessment
  - quick endpoint to inform adaptative randomization
  - slow accrual rate to ensure subsequent pts benefit from randomization adaption
Bayesian Adaptative Design: BATTLE-1 ("Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination")

**Table 1 Marker group definitions in BATTLE-1**

<table>
<thead>
<tr>
<th>Marker group</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EGFR</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

“+” is positive; “−” is negative; “x” is either positive, negative, or unknown; EGFR, epidermal growth factor receptor; BATTLE, Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination.

20 different treatment-by-biomarker subgroups, → Evaluation of performance of each treatment arm in each marker group.

Challenges in the recent clinical research methodology

• Challenges in Precision Medicine
• Challenges in early clinical trials methodology
• Challenges in more recently developed immunotherapy trials
Challenges in early clinical trials methodology

1. Inappropriate designs

2. Definition of dose-limiting toxicities and recommended doses and schedules are often inappropriate
Inappropriate designs in early clinical trials

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

X. Paoletti¹,²*, M. Ezzalfani³ & C. Le Tourneau³,⁴

¹Biostatistics and Epidemiology Department, Gustave Roussy, Villejuif; ²INSERM U1018, CESP, Paris-Sud University, Villejuif; ³INSERM/Institut Curie/Mines ParisTech U900, Paris; ⁴Department of Medical Oncology, Clinical Trial Unit, Institut Curie, Paris & Saint-Cloud, France

**Issues:** Inadequate period of toxicities observation, Inadequate DLT definition, Important toxicities at the RP2D, underestimation of the MTT toxicity profile.

- Statistical simulations demonstrated that new dose-escalation designs such as ATD and CRM type designs outperform the standard “3+3” design in phase I cancer clinical trials.

ATD: Accelerated titration design; CRM: Modified continual reassessment method
Efficiency of New Dose Escalation Designs in Dose-Finding Phase I Trials of Molecularly Targeted Agents

### Abstract

Christophe Le Tourneau\(^1,3\*\), Hui K. Gan\(^2\), Albiruni R. A. Razak\(^3\), Xavier Paoletti\(^4,5\)

\(^1\) Department of Medical Oncology, Institut Curie, Paris, France, \(^2\) Joint Austrian Oncology Unit, Austin Hospital, Melbourne, Australia, \(^3\) Department of Medical Oncology, Princess Margaret Hospital, Toronto, Canada, \(^4\) Department of Biostatistics, Institut Curie, Paris, France, \(^5\) Institut Curie / INSERM U900, Paris, France

**49% “3+3” design.**

**42% ATD**

**7% modified CRM**

**1%, pharmacologically guided DE**

<table>
<thead>
<tr>
<th>No. of trials</th>
<th>3+3</th>
<th>ATD</th>
<th>mCRM</th>
<th>PGDE</th>
<th>NS</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of patients per trial, median (range)</th>
<th>40</th>
<th>42 [14–92]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients exposed to drugs, median (range)</td>
<td>33</td>
<td>20 [0–68]</td>
</tr>
<tr>
<td>No. of patients exposed to dose levels, median (range)</td>
<td>0</td>
<td>9 [0–40]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not specified</td>
</tr>
<tr>
<td>Specified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (months) [range]</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MTD to starting dose ratio, mean [range]</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>No. of dose levels, median [range]</th>
</tr>
</thead>
</table>
Inappropriate recommended doses: The example of MKI?

- The use of antiangiogenic TKIs is challenging in clinical practice and often requires doses and/or schedules adaptation due to inappropriate RP2D in phase 1 trials.

- RP2D of anti angiogenic TKIs was defined (like chemotherapy) based on the toxicity burden during cycle 1.

⇒ New and innovative toxicity evaluation are needed (e.g., PRO CTC).

- Period of observation for DLT must be longer
- Adapted definitions for DLT including the burden of grade I/II
- Expansion cohorts exposed to different doses and/or schedules for an appropriate observation period.
A substantial proportion of drug-related dermatologic AEs occur after the traditional dose-limiting toxicity monitoring period of phase 1 Clinical trials.
Immunotherapy
1. **Optimal dose and schedule selection**
   > Minimal immunologically active dose (dose is not linearly associated with efficacy and toxicity)
   > Optimal dose for prolonged exposition

2. **Optimal sequence/rechallenge**
   > Maximize benefit for patients and minimize economic burden

3. **Identify resistant/sensitive disease to immunological approaches**
   > Biomarkers (immunoscore, Immunomics, ...)

4. **New patterns/definitions of tumor assessment and disease progression** *(Champiat et al., Clin Cancer Res 2016)*
Overall, what do we need?

1. More **innovative approaches and trials design** in drug development
   Individualizing clinical research

2. **Targeting what is unmet** need for patients

3. Limited and well designed **biomarkers studies (rather predictive of tumor resistance?!)** with high potential for clinical practice
A Phase 1b Study of ARGX-111 (C-met MAB) in Patients With Advanced Solid Cancer

Dose escalation  
Expansion cohort

Safety expansion cohort:  
3 mg/kg / 2 weeks (based on safety, biomarkers, PET results)

C1D1  
Dose level X

C2D15  
PET uptake ↓

C2D15  
stable or ↑  
PET uptake  
No toxicity

C3D1  
Dose level X

C3D1  
Dose level X + 1

Accelerated titration  
= PET-guided intra-patient dose escalation

Rolfo et al, J Clin Oncol 34, 2016 (suppl; abstr e14016)
More innovative approaches and trials design in drug development: Example

Platinum-R esophageal adc
Platinum-R esophageal scc
Platinum-R biliary tract cancer
Platinum-R wtRb bladder
Platinum-R wtRb endometrium

Platinum resistant
Unmet need settings
No standard second-line

CDK 4/6 inh

RECIST
FDG PET $D_0$ $D_3-D_0$
FDG PET $D_{10-D_{14}}$

Stop
if Metabolic Resistance & no Disease Control

Oncodistinct 002/MIME TRIAL: Multiorgan Metabolic imaging response assessment of a CDK4/6 inhibitor in solid tumors (other than breast)
Overall, what do we need?

Biomarkers results “on live” with high potential for clinical research and practice use
Data Tsunami
Stratified medicine creates multiple rare cancers
Multidisciplinary Molecular Tumour Board: a tool to improve Clinical Practice and selection accrual for Clinical Trials in Cancer Patients

Christian Rolfo, Andreia Coelho, Jose Ferri, Peter Van Dam, Amelie Dendooven, Christine Weyn, Marika Rasschaert, Lucas Van Houtven, Xuan Bich Trinh, Jan Van Meerbeeck, Roberto Salgado, Marc Peeters

Patrick Pauwels

On behalf of Molecular Tumour Board of Antwerp University Hospital, Edegem, Belgium.
Our New Way to Work . . . Molecular Tumor Board

Patient case is derived from his doctor

Molecular Tumor Board

Oncologist  Mol. Pathol  Gyneco  Thorax  Geneticist  Pediat  Nav. nurse

FFPE TUMOR SAMPLE
DNA EXTRATION

SEQUENCING LIBRARY PREPARATION
DNA Sequencing Capture

ANALYSIS PIPELINE
BASE SUBSTITUTIONS
SHORT INSERTIONS/DELETIONS
COPY NUMBER ALTERNATIONS
GENE FUSIONS

CLINICAL REPORT

Report with therapeutic proposal

Referral Doctor Discussion
Classification of mutations by treatment perspective

- **MUTATIONS**
  - MUTATED: 130 (69.9%)
  - NO MUTATED: 56 (30.1%)

- **DRIVER**
  - 75 (57.7%)

- **NO DRIVER**
  - DRUGGABLE: 21 (37.5%)
  - 55 (42.3%)
DISTRIBUTION BY TREATMENT: INCLUSION IN TRIAL vs MOLECULAR-BASED TREATMENT

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>FREQUENCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCLUDED IN TRIALS</td>
<td>22 (18)</td>
</tr>
<tr>
<td>PROPOSED BUT NOT INCLUDED</td>
<td>5 (3)</td>
</tr>
<tr>
<td>NOT INCLUDED</td>
<td>100 (79)</td>
</tr>
<tr>
<td>MOLECULAR-BASED TREATMENT</td>
<td>15 (12)</td>
</tr>
<tr>
<td>NO MOLECULAR BASED</td>
<td>85 (67)</td>
</tr>
</tbody>
</table>
Oncodistinct: A new model of clinical research collaboration based on the progress on molecular biology and methodological issues

Speed and quality trials

- Experts dedicated to clinical research
- Multidisciplinarity
  - Organ specialists
  - Radiation oncologists
  - Surgical oncology
  - Basic researchers
- Scientific Input
- Pharma and Academic labs
- Network of academic & non academic centers
- New therapeutic strategies
  - Studies meeting the unmet need of patients
  - Innovative and individualized designs
- Huge number of screened pts for gene/protein
- « Selected » Patients

Pharmas

Academic & non Academic trials

Satellite centers

Courtesy Prof. A. Awada
Oncodistinct studies investigate existing and **new therapies in all settings and are not dedicated to a specific trial phase** or tumor type (as the landscape changes). We are focusing on:

- New drugs in development from phase I to later phase trials
- Innovative trial designs
- Clinical settings with unmet medical need
- Development of immunotherapy and other new agents in the early settings
- Pertinent biomarkers studies with high potential for clinical practice
- “Proof of concept” studies

**Several studies are currently ready to start or under discussion and the first two Oncodistinct studies is planned to be launched in 2017.**
A New Clinical Research Network

A network of **8 comprehensive cancer centers** and **13 university hospitals and academic centers** dedicated to oncology care and research.

- University Hospital Brussels Belgium
- Institut Jules Bordet Brussels Belgium
- Antwerp University Hospital Belgium
- CHU Ambroise Paré, Mons Belgium
- Saint Elisabeth, Namur Belgium
- Centre Hospitalier de Luxembourg
- Oslo University Hospital Norway
- Erasmus MC Rotterdam Netherlands
- Centre Oscar Lambret, Lille France
- CHU Rouen France
- CHU Strasbourg France
- Hopital Saint Louis Paris France
- Centre Georges-François Leclerc Dijon France
- Institut Claudius Rigaud Toulouse France
- Institut Paoli Calmette Marseille France
- Institut Curie Paris France
- Hopital Paris Saint Joseph France
- Val d’Hebron Madrid Spain
- Istituto Nazionale dei Tumori Milan Italy
- American University of Beirut Lebanon
- Anhui Medical University Hospital China
Trial design depends on many additional parameters: Marker prevalence, strength of preliminary data, feasibility of real-time assessment, patient and operational resources.

• “Umbrella” and “basket” trials are increasingly the norm with targeted therapies and heterogeneous populations.

• Adaptive designs give flexibility, but at a cost.

Academia and industry as a partner

Don’t forget what the patients needs
Team members

**Oncology – Phase I Early Clinical Trials Unit**
Prof. Dr. Christian Rolfo -
Prof. Dr. Marc Peeters – head oncology and MOCA
Dr. Marika Rasschaert – Dr. Katrine De Block –
**Fellow:** Dr. Jose Ferri

**Rolfo Lab:**

**Exosomes:** Dr. Marco Giallombardo
  Dr. Pablo Reclusa Asiain
  Dr. Maria Elena Durendez

**tFree DNA:** Dr. Laura Sober – Karen Zwaenepoel

**Cell Lines & cMET:** Dr. Nele Van Der Steen

**Logistics:** Sam Van Gerwen, BsC

**Clinical Study –co:** Robrecht Lembrechts, BsC, PhD

**Molecular Pathology Unit**
Prof. Dr. Patrick Pauwels
Dr. Amelie Dendooven
Dr. Karen Zwaenepoel

**Tumor - Serum Bank**
Dr. Annemieke De Wilde
Dr. Sofie Goethals

**Next Generation Sequencing**
Dr. Christine Weyn – UZA
Dr. Suzanne Lambin
Dr. Ken Op De Beeck – UA

**Database:** Dr. Andreia Coelho

**Proteomics**
Prof. Inge Mertens
Prof. Geert Baggerman
Dr. Evelien Maes

MOCA 2014 Research Grant

Stichting tegen Kanker

Kennis / Ervaring / Zorg

vito vision on technology

Universiteit Antwerpen

UZA
Dank u voor uw aandacht

Thank you for your attention

christian.rolfo@uza.be