DRUGS DEVELOPMENT METHODOLOGY

The unavoidable break with the past

Ahmad Awada has reported no conflicts of interest
Nuria Kotecki has reported no conflicts of interest
Alex A Adjei has reported no conflicts of interest
Guillem Argiles has reported no conflicts of interest
Dirk Arnold has reported consulting and advisory services, speaking or writing engagements, public presentations for Roche, Merck Serono, Bayer Healthcare, Servier, BTG, Terumo, Sanofi Oncology and Eli Lilly
Jean-Yves Blay has reported to have received research support and honoraria from Roche, BMS GSK, Novartis, Pharmamar, MSD, Lilly, Ignyta and Deciphera
Olivier Collignon has reported no conflicts of interest
Christian Dittrich has reported no conflicts of interest
Felip Janku has reported to have a research support from Novartis, Deciphera, Symphogen, Piquor, Roche, BioMed Valley Discoveries and Upsher-Smith Laboratories; he is on the Scientific Advisory Boards of Deciphera, Illumina and Guardant Health, he provides paid consulting for Immunoment, IFM Therapeutics and Trovagene and has ownership interest in Trovagene.
Denis Lacombe has reported no conflict of interest
Nicolas Penel has reported no conflicts of interest
Josep Tabernero has reported to have served on Advisory Boards for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho and Takeda
DRUGS DEVELOPMENT METHODOLOGY IN SOLID TUMOURS

The unavoidable break with the past

KEY POINTS: What do we need in drug development methodology?

- Targeting settings with unmet need for patients
- More innovative approaches and trials design in drug development with the aim to individualise clinical research
- Selective and well-designed biomarker studies (rather predictive of intrinsic tumour resistance?!?) with high potential for clinical utility
- New ways of collaboration and functioning between pharma, cooperative groups and on-site investigators
- Creating new models of clinical research networks, taking into consideration the recent molecular biology advances
OUTLINE

1. Research in oncology: Historical view and current strategy
2. Does the current design of oncology trials meet the need of patients?
3. Recent developments in the clinical research methodology
4. Challenges of the recent clinical research methodology
5. What do we need?
1. RESEARCH IN ONCOLOGY

Historical view and current strategy
RESEARCH IN ONCOLOGY
A historical view

Clinical research focused on public health questions

Building clinical trial methodologies

Drug-oriented clinical research

Drug- and target-oriented clinical research
DRUG-/TARGET-ORIENTED CLINICAL RESEARCH IN SOLID CANCERS

Percentage of the studies at the Jules Bordet Institute in June 2017

Pharmaceutical industry-based clinical research: 70%

Academic clinical research in «partnership» with the pharmaceutical industry: 20%

«Pure» academic research: 10%

Number of patients: Pharma (450); Academic (377)
CLASSICAL APPROACH OF DRUG DEVELOPMENT

EVOLVING THERAPEUTIC CONCEPTS IN ONCOLOGY
Based on molecular biology understanding

- Chemotherapy
  - Molecular-targeted agents
  - Immunotherapy
- Cytotoxic/cytostatic concept
- Pathway/target-based concept
- Biological concept

From empirical oncology to molecular and immunological therapeutic approaches
TYPES OF CLINICAL TRIALS
In advanced breast cancer (2007–2011)

- Cytotoxic (21%)
- Targeted therapies-based (72%)
- Immunotherapies (7%)

CURRENT STRATEGY OF BREAST CANCER CLINICAL RESEARCH

New chemotherapy agents are less and less developed (except antibody drug conjugates [ADC]) but chemotherapy is proven to cure patients – A very risky developmental strategy

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 has slowed down significantly the development of other anticancer treatments

From empirical oncology to molecular and immunological therapeutic approaches
CURRENT STRATEGY OF SOLID CANCER

Clinical research is dominated by:

- Business
- Fashion
- Power

More “market and regulatory oriented” trials and less patient-directed or based on unmet need in diseases or settings!
2. DOES THE CURRENT DESIGN OF ONCOLOGY TRIALS MEET THE NEED OF PATIENTS?
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 (the interval from Phase I to registration has shortened from ~8–10 years to &lt;5 years nowadays)</td>
<td>♦ Redundancy in the development of agents</td>
</tr>
<tr>
<td>♦ Often improvement in PFS (but rarely in survival [metastatic settings])</td>
<td>♦ Commonly used endpoints are not relevant for immunotherapy</td>
</tr>
<tr>
<td>♦ Often improvement in early DFS (but rarely in OS [early settings])</td>
<td>♦ Many competitive trials in the same setting</td>
</tr>
<tr>
<td></td>
<td>♦ Few studies looking at a therapeutic strategy</td>
</tr>
<tr>
<td></td>
<td>♦ Few studies in unmet need clinical settings or focusing on rare cancers</td>
</tr>
<tr>
<td></td>
<td>♦ More and more biomarker studies but limited validated biomarkers for clinical use</td>
</tr>
<tr>
<td></td>
<td>♦ Principles of analytical validation and clinical utility are often not properly taken into account in drug development models</td>
</tr>
</tbody>
</table>

Still a huge gap between clinical research and the need in clinical practice
3. RECENT DEVELOPMENTS IN THE CLINICAL RESEARCH METHODOLOGY
NO CLEAR FRONTIER BETWEEN PHASE I, PHASE II AND PHASE III

Drug approval

Phase I

Phase II

Phase III

7–10 years

0

Accelerated approval (e.g. crizotinib in ALK translocated NSCLC)

Phase I/II

Phase III

~5 years

0

## 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 monoclonal antibodies (imAbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients number</strong></td>
<td>30–50 unselected patients</td>
<td>30–200 “molecularly” selected patients</td>
<td>100–1000 “immunologically” selected patients</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>IV &gt; Oral</td>
<td>Oral &gt; IV</td>
<td>IV</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>

MTD, maximum tolerated dose

EVOLUTION OF CLINICAL RESEARCH LANDSCAPE

Adjuvant setting (1)

PAST

♦ Large RCTs
♦ Thousands of unselected patients
♦ Small benefits

PRESENT and FUTURE

♦ «Selected» groups of patients* (challenging)
♦ Number of patients is variable
♦ Large benefits requested!
♦ Need of biomarkers for selection/surrogate markers for efficacy

*By clinical, pathological or molecular criteria
## EVOLUTION OF CLINICAL RESEARCH LANDSCAPE

### Metastatic setting (2)

<table>
<thead>
<tr>
<th><strong>PAST</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ RCTs</td>
</tr>
<tr>
<td>♦ Hundreds of unselected patients</td>
</tr>
<tr>
<td>♦ OS is the main endpoint (less PFS)</td>
</tr>
<tr>
<td>♦ Small benefits</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PRESENT and FUTURE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ RCTs or single arm trials aiming to demonstrate a large effect on ORR based on historical controls</td>
</tr>
<tr>
<td>♦ Need for databases of historical control arms</td>
</tr>
<tr>
<td>♦ Selected groups of patients*</td>
</tr>
<tr>
<td>♦ Basket and umbrella studies</td>
</tr>
<tr>
<td>♦ Lower number of patients treated but huge number screened</td>
</tr>
<tr>
<td>♦ PFS as preponderate endpoint</td>
</tr>
<tr>
<td>♦ Large benefits requested!</td>
</tr>
</tbody>
</table>

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*By clinical, pathological or molecular criteria*
SELECTED NEW DESIGNS IN
DRUG DEVELOPMENT
Based on molecular biology or on strategy

<table>
<thead>
<tr>
<th>Genotype driven</th>
<th>New designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basket trials</td>
<td>Test the effect of one drug on single mutation in a variety of cancer types</td>
</tr>
<tr>
<td>Umbrella</td>
<td>Test the impact of different drugs in different mutations in a single type of cancer</td>
</tr>
<tr>
<td>Adaptive trial</td>
<td>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. <strong>A platform trial</strong> is a type of adaptive trial designed to evaluate multiple treatments efficiently</td>
</tr>
<tr>
<td>Windows of opportunity</td>
<td>Assessing the administration of an investigational agent over a short period of time</td>
</tr>
<tr>
<td>Randomised discontinuation design</td>
<td>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</td>
</tr>
<tr>
<td>N of 1 trials</td>
<td><strong>Clinical</strong> trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions</td>
</tr>
</tbody>
</table>

IDMC, Independent Data Monitoring Committee
4. CHALLENGES OF THE RECENT CLINICAL RESEARCH METHODOLOGY
CHALLENGES OF THE RECENT CLINICAL RESEARCH METHODOLOGY

Challenges of early clinical trials methodology

Challenges of precision medicine

Challenges of more recently-developed immunotherapy trials
CHALLENGES OF EARLY CLINICAL TRIALS METHODOLOGY (2 EXAMPLES)

1. Inappropriate designs$^{1,2}$

2. Definition of dose-limiting toxicities and recommended doses and schedules are often inappropriate$^{3}$

The desperate hunt for biomarkers:

More and more biomarker studies (Pubmed search: 42,636!) 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 for reproducibility and interpretation of complex datasets
<table>
<thead>
<tr>
<th>Target</th>
<th>Tumour</th>
<th>Inhibitor</th>
<th>Predictive markers of sensitivity/resistance</th>
<th>Disease setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>Breast</td>
<td>Tamoxifen, aromatase inhibitors (AI), fulvestrant</td>
<td>ER expression, ER mutation (resistance)</td>
<td>Adjuvant and advanced disease</td>
</tr>
<tr>
<td>EGFR</td>
<td>Head and neck</td>
<td>Cetuximab</td>
<td>-</td>
<td>Locally-advanced head and neck cancer</td>
</tr>
<tr>
<td>EGFR</td>
<td>NSCLC</td>
<td>Gefitinib/erlotinib/afatinib/ osimertinib</td>
<td>EGFR activating mutation, EGFR T790M mutation</td>
<td>Metastatic NSCLC</td>
</tr>
<tr>
<td>EGFR</td>
<td>NSCLC squamous</td>
<td>Necitumumab</td>
<td>EGFR expression</td>
<td>Metastatic squamous NSCLC</td>
</tr>
<tr>
<td>K-/N-Ras B-Raf</td>
<td>Colorectal</td>
<td>Cetuximab, panitumumab</td>
<td>K-/N-Ras mutations/B-Raf mutation (resistance)</td>
<td>Metastatic colorectal cancer</td>
</tr>
<tr>
<td>HER-2/neu</td>
<td>Breast</td>
<td>Trastuzumab, pertuzumab, lapatinib, neratinib, T-DM1 trastuzumab</td>
<td>HER-2/neu amplification</td>
<td>Breast: Adjuvant and advanced disease, Gastric: Metastatic disease</td>
</tr>
</tbody>
</table>
LIMITED AVAILABILITY OF BIOMARKERS IN CLINICAL PRACTICE (2)

<table>
<thead>
<tr>
<th>Target</th>
<th>Tumour</th>
<th>Inhibitor</th>
<th>Predictive markers of sensitivity</th>
<th>Disease setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>NSCLC, colorectal, renal, breast, ovary, cervix</td>
<td>Bevacizumab, aflibercept (colon)</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Hepatocellular, colorectal, gastric, NSCLC</td>
<td>Sorafenib, regorafenib, ramucirumab, ramucirumab</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>VEGF(R); M-TOR</td>
<td>Renal</td>
<td>MTKs, bevacizumab everolimus, temsirolimus</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>VEGFR; M-TOR'</td>
<td>Neuroendocrine (pancreas), soft tissue sarcomas</td>
<td>Sunitinib, everolimus, pazopanib</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>VEGFR, RET</td>
<td>Thyroid</td>
<td>Vandetanib, sorafenib lenvatinib</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>M-TOR</td>
<td>Breast</td>
<td>Everolimus</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>CDK 4/6</td>
<td>Breast</td>
<td>Palbociclib, ribociclib, abemaciclib</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
</tbody>
</table>
### LIMITED AVAILABILITY OF BIOMARKERS IN CLINICAL PRACTICE (3)

<table>
<thead>
<tr>
<th>Target</th>
<th>Tumour</th>
<th>Inhibitor</th>
<th>Predictive markers of sensitivity/resistance</th>
<th>Disease setting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIT</strong></td>
<td><strong>GIST</strong></td>
<td>Imatinib, sunitinib, regorafenib</td>
<td>KIT mutation</td>
<td>High risk or metastatic GIST</td>
</tr>
<tr>
<td>EML4-ALK/ROS1</td>
<td><strong>NSCLC</strong></td>
<td>Crizotinib, ceritinib, alectinib, crizotinib</td>
<td>EML4-ALK translocation</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td><strong>RANKL</strong></td>
<td>Bone metastases, giant cell tumours</td>
<td>Denosumab</td>
<td></td>
<td>Advanced disease</td>
</tr>
<tr>
<td>Hedgehog</td>
<td>Basal cell carcinoma</td>
<td>Vismodegib</td>
<td>PTCH mutations</td>
<td>Advanced disease</td>
</tr>
<tr>
<td><strong>BRAF, MEK</strong></td>
<td>Melanoma</td>
<td>Vemurafenib, dabrafenib, trametinib</td>
<td>BRAF mutation on V600</td>
<td>Advanced disease</td>
</tr>
<tr>
<td><strong>PARP</strong></td>
<td>Breast, ovary (BRCA tumours)</td>
<td>Olaparib, niraparib, rucapanib</td>
<td>BRCA mutation</td>
<td>Advanced disease</td>
</tr>
<tr>
<td><strong>CTLA4</strong></td>
<td>Melanoma</td>
<td>Ipilimumab</td>
<td></td>
<td>Advanced disease</td>
</tr>
<tr>
<td><strong>PD-1/PD-L1</strong></td>
<td>Melanoma, NSCLC, RCC, gastric, head and neck, urothelial, …</td>
<td>Nivolumab, pembrolizumab,...</td>
<td>PD-L1 protein in NSCLC</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>Prostate</td>
<td>Abiraterone, enzalutamide,</td>
<td></td>
<td>Advanced disease</td>
</tr>
</tbody>
</table>
CHALLENGES OF PRECISION MEDICINE (2)

High promotion of precision medicine among medical team and patients

but

Limited number of actionable/targetable mutations

Limited access or unavailable clinical trials or marketed targeted agents

High attrition rate

Ethical issues

MOSCATO-01

1110 patients included from 11/2011 to 03/2016

411 patients with targetable mutations

49%

119 treated patients

19%

Adapted from Massard C, et al., Cancer Discov 2017;7:586–95
1. Optimal dose and schedule selection
   Minimal immunologically active dose (dose is not linearly associated with efficacy and toxicity)
   - Optimal dose for prolonged exposure

2. Optimal sequence/re-challenge
   Maximise benefit for patients and minimise economic burden

3. Identify resistant/sensitive disease to immunological approaches
   Biomarkers (immunoscore, immunomics, …)

4. New patterns/definitions of tumour assessment and disease progression
   (Champiat S, et al., Clin Cancer Res 2016;23:1920–8)

5. Combinations issues
5. WHAT DO WE NEED?
OVERALL, WHAT DO WE NEED?

1. Continue to perform pivotal trials (regulatory purpose)
2. More innovative approaches and trial designs in drug development → Individualising clinical research!
3. Targeting the unmet need for patients in the context of nosological fragmentations of the diseases
4. More selective and well-designed biomarker studies (rather predictive of tumour resistance, such as K/N-Ras mutations in colorectal cancer) with high potential for clinical practice
5. Creating new models of clinical research networks (e.g. Oncodistinct.net…) and collaboration between pharma, cooperative groups and investigators
WHAT DO WE NEED?

- Biomarkers
  - Biological rationale
- Focus on unmet medical need
- Efficient and pragmatic
  - Clinical research network
**CLINICAL RESEARCH INDIVIDUALISATION: EXAMPLE**

A Phase Ib 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)

**Accelerated titration**

= PET-guided intrapatient dose escalation

- C1D1 Dose level X
- C2D15 PET uptake ↓
- C2D15 stable or ↑ PET uptake No toxicity
- C3D1 Dose level X
- C3D1 Dose level X + 1

clinicaltrials.gov: ClinicalTrials.gov Identifier: NCT02055066
MORE INNOVATIVE APPROACHES AND TRIAL DESIGNS 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

CDK 4/6 inh

Platinum resistant

Unmet need settings

No standard second-line

STOP if metabolic resistance and no disease control

Oncodistinct 002/MIME TRIAL: Multiorgan Metabolic imaging response assessment of a CDK4/6 inhibitor in solid tumours (other than breast)
TARGETING UNMET NEED FOR PATIENTS

Brain METS – Example

A Phase II trial to evaluate a HER2-targeted investigational agent crossing the BBB for prevention of subsequent CNS event in HER2 advanced breast cancer (ABC)

Local therapy includes: WBRT, stereotactic radiotherapy, surgery

The time period between the 2 local treatments should be known (T2/T1 > 1.3)
BIOMARKERS RESULTS

“ON LIVE” with high potential for clinical research and practice use: Biocartis platform as an example

Idylla™: fully automated, real-time PCR
Offer fast and easy access to molecular biomarker results (blood, tumour…)
Time frame of 35 to 150 minutes
Analyse both RNA and DNA

Available cartridges:
EGFR mutation assay,
BRAF mutation test
KRAS mutation test
NRAS-BRAF-EGFRS492R mutation assay
tctBRAF mutation assay
tcKRAS mutation assay
NRAS-BRAF mutation test

Others under preparation
A NEW ACADEMIC MODEL OF CLINICAL RESEARCH COLLABORATION

Based on the progress on molecular biology and methodological issues

- New therapeutic strategies
- Studies meeting patients' unmet needs
- Innovative and individualized designs
- "Selected" patients
- Experts dedicated to clinical research
- Multidisciplinary: Organ specialists, Radiation oncologists, Surgical oncology, Basic researchers
- Academic labs
- Pharmas
- Network of academic and non academic centres
- Huge number of screened patients for gene/protein

Fast and good quality of academic and non academic trials

Academic and non academic trials

Satellites centres

New therapeutic strategies
Studies meeting patients’ unmet needs
Innovative and individualised designs

Huge number of screened patients for gene/protein
THANK YOU!