Precision Medicine in Oncology Field: From the new early clinical trials to the new personnalised combinations

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• Disclosure form:

• Consultant or advisory role (fees) or meeting invitation from Roche, MSD, Pfizer, AZ, BMS, PFO and Gilead
Classical drug development paradigm before 2000
From small unselected patients....

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PURPOSE</strong></td>
<td>Find MTD</td>
<td>Define Activity</td>
</tr>
<tr>
<td><strong>EMPHASIS</strong></td>
<td>Safety</td>
<td>Activity</td>
</tr>
<tr>
<td><strong>ENDPOINT</strong></td>
<td>Toxicity (DLT)</td>
<td>Response (ORR)</td>
</tr>
<tr>
<td><strong>N (patients)</strong></td>
<td>20-60</td>
<td>20-200</td>
</tr>
<tr>
<td><strong>Registration value</strong></td>
<td>Null</td>
<td>Limited</td>
</tr>
</tbody>
</table>
The revolution in drug development is a change in nature and goals of early phases: From the traditional « one size fits all » strategy to biomarker driven trials.

### Phase I/II

<table>
<thead>
<tr>
<th>PURPOSE</th>
<th>Define MTD and Activity (rapid dose escalation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPHASIS</td>
<td>Safety &amp; <strong>Activity</strong> &amp; Biomarkers</td>
</tr>
<tr>
<td>ENDPOINT</td>
<td><strong>Toxicity &amp; Response</strong> (all and selected) &amp; Preliminary Survival: to achieve the proof of concepts</td>
</tr>
<tr>
<td>N (patients)</td>
<td>100-1000 + (large selected patients)</td>
</tr>
<tr>
<td>Registration value</td>
<td>Real (conditional approvals, breakthrough)</td>
</tr>
</tbody>
</table>

### Phase III

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Compare with SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphasis</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Survival (PFS, OS)</td>
</tr>
<tr>
<td>N (patients)</td>
<td>200-2000</td>
</tr>
<tr>
<td>Registration value</td>
<td>Major (confirmatory)</td>
</tr>
</tbody>
</table>

JC Soria, 2017
The revolution in drug development has profound implications:

- Previous phase 1 replaced by phase 1-2 trials expansion cohorts
  - Median Duration 8 to 10 years

A dramatic reduction in drug development from >10y to <5y between the 1st in man to the drug registration

Percentage of costs of R&D*:

- Preclinical: 29%
- Phase I: 9%
- Phase II: 17%
- Phase III: 40%
- Approval Process: 5%

Duration is shortened (2-5 years)

Global cost: $1.8 billion

Global cost: $? (lower?)

Courtesy of JC Soria

Burock S, EJC 2013
Paul S, Nat Rev Drug Discovery 2010
Working hypothesis

• Targeting mechanisms that lead to cancer progression can improve patient’s outcome

• These mechanisms are individual

• Goal: to identify the mechanism of cancer progression at the individual level, in order to target it
Precision Medicine: Concept: Identify the targets to be treated in each patient

**BASKET PROGRAM**

### AcSé program

**Principles**

- **Drug X Project**
  - Molecular diagnosis of drug X targets
  - Academic Sponsor
  - Phase 2 Clinical trial
  - INCa molecular genetic centers
  - Molecular testing task force
  - Steering committee
  - IDMC

- **Crizotinib Project**
  - Molecular diagnosis ALK, MET, ROS1
  - INCa molecular genetic centers
  - Molecular testing task force
  - Steering committee
  - IDMC

- **Vemurafenib Project**
  - Molecular diagnosis B-RAF
  - INCa molecular genetic centers
  - Molecular testing task force
  - Steering committee
  - IDMC

- **Drug Y Project**
  - Molecular diagnosis B-RAF
  - INCa molecular genetic centers
  - Molecular testing task force
  - Steering committee
  - IDMC

**Provided by pharmaceutical firms**

### Validated projects

- **Crizotinib Project**
  - Active since July 2013
- **Vemurafenib Project**
  - Active since October 2014
- **Drug Y Project**
  - IDMC

### Molecular diagnosis process

- **Single test from INCa platforms**
  - Non small cell lung cancer (NSCLC)
  - Ovarian cancer
  - Cholangiocarcinoma
  - Thyroid cancer
  - Prostatic cancer
  - Bladder cancer
  - Sarcoma/GIST
  - Multiple myeloma
  - Chronic Lymphocytic Leukemia (CLL)
  - Hairy cell leukaemia (HCL)

- **Molecular pangenomic programs**
  - Inclusion/Exclusion criteria
  - Consent form

### Cohorts

A/ Pathology cohorts “one pathology, BRAF mutation” diagnosed by INCa molecular genetic centers
1. NSCLC, V600 mutated
2. Ovarian, V600 mutated
3. Cholangiocarcinoma, V600 mutated
4. Thyroid cancer, V600 mutated
5. Prostatic cancer, V600 mutated
6. Bladder cancer, V600 mutated
7. Sarcoma / GIST, V600 mutated
8. Multiple Myeloma, V600 mutated
9. Chronic Lymphocytic Leukemia (CLL), V600 mutated
10. Hairy Cell Leukemia (HCL) V600 mutated (this excludes Hairy Cell Leukemia variant types, marginal zone splenic lymphoma (MZL), splenic red pulp lymphoma (SRPL) patients)

B/ Miscellaneous malignancies

Patients harboring BRAF genomic alterations ONLY tested via emerging biomarkers programs or molecular pangenomic programs:
- With any other non-predefined pathology harboring a V600 mutation
- Same or other non-predefined pathology harboring non V600 activating mutations
- Same or other non-predefined pathology harboring BRAF amplifications

JY Blay, Lyon
Next generation of clinical trials: big hope for cancer and HIV cure

• Single agent in well defined entities
• Combinations on single pathways
• Combinations on different pathways
• Molecular treatment and immunotherapy combinations
• Rotations to prevent emergence of clonal resistance
• Multiplication of clinical trials!
Conclusions

Personalized medicine in cancer treatments: progress and limits

• Nosological fragmentation

• Target driver alterations
  – The previous paradigm 2000-2015

• Integrate complexity and heterogeneity in clinical research
  – The next paradigm 2016-2025

• Measuring tumor cell heterogeneity

• Histology, molecular complexity, stroma, patient, time

• Need to integrate this complexity

• Pharmacodynamic and pharmacokinetics

• Patient compliance and patient reported outcome (PRO)

• International collaborations

• Circulating DNA and TC: to monitor response and track drug resistance