Precision Medicine Needs Randomized Trials

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Louvain-la-Neuve, Belgium
The changing face of oncology trials

- Increasing knowledge on the biological features of cancer
- Availability of a growing number of targeted therapies*
- Changing regulatory environment

*Monoclonal antibodies, inhibitors of protein kinases, growth factors and other signaling molecules, and various forms of immunotherapy
Some recent approvals

Crizotinib

Pembrolizumab

Table 1. Efficacy data

<table>
<thead>
<tr>
<th>Study 1001</th>
<th>Study 1005</th>
</tr>
</thead>
<tbody>
<tr>
<td>INV</td>
<td>IRC</td>
</tr>
<tr>
<td>N = 116</td>
<td>N = 105</td>
</tr>
<tr>
<td>Response rate&lt;sup&gt;a&lt;/sup&gt; (95% CI)</td>
<td>71 (61.2%; 55 (52.4%; 52%-70%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>2</td>
</tr>
<tr>
<td>Partial response</td>
<td>69</td>
</tr>
<tr>
<td>Duration of response (partial response)</td>
<td>48.1 wks</td>
</tr>
<tr>
<td>Median (range)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(4.1+ to 76.6+)</td>
</tr>
</tbody>
</table>

<sup>a</sup>REGIST v1.0 in Study 1001 and v1.1 in Study 1005.

<sup>b</sup>The Kaplan–Meier method with censored values (+).

Clin Cancer Res 2014;20:2029-34
Journal for Immunotherapy of Cancer 2015; 3:36
Seamless transition
Basis for FDA approvals

Review of Oncology and Hematology Drug Product Approvals at the US Food and Drug Administration Between July 2005 and December 2007

Rajeshwari Sridhara, John R. Johnson, Robert Justice, Patricia Keegan, Aloka Chakravarty, Richard Pazdur

Thirty-seven of the 53 indications were based on data from randomized studies. These randomized studies included 17 “add-on” studies in which the investigational drug plus standard chemotherapy was compared with the standard chemotherapy alone, four studies in which placebo was the comparator, and four studies in which best supportive care was the comparator (Table 1). The study sample sizes in the randomized studies ranged from 87 patients for the use of eculizumab in paroxysmal nocturnal hemoglobinuria to 19747 patients for the use of raloxifene for the reduction in risk of invasive breast cancer. The remaining 16 indications were based on data from single-arm studies with no comparison group. In these studies, the sample sizes ranged from 18 patients for the use of imatinib mesylate in dermatofibrosarcoma protuberans to 232 patients for the use of nilotinib hydrochloride monohydrate in chronic-phase chronic myeloid leukemia (Table 1). Forty-four of the 53 indications were based on results from a single study.
Evolution

2002

Chemotherapy
All-comers
No treatment effect

2010

Targeted therapy
EGFR-mutated
Large treatment effect

Evidence favoring precision medicine

### Published phase II trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Response Rate (%)</th>
<th>Meta-analysis</th>
<th>Pooled analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Not personalized</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

### Median Progression-Free Survival (months, 95% CI)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Personalized</th>
<th>Meta-analysis</th>
<th>Pooled analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Not personalized</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

### Median Overall Survival (months, 95% CI)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Personalized</th>
<th>Meta-analysis</th>
<th>Pooled analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Not personalized</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

### FDA-approved agents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>RRR (95% CI)</th>
<th>PFS N</th>
<th>HR (95% CI)</th>
<th>OS N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personalized</td>
<td>14</td>
<td>3.82 (2.51 to 5.82)</td>
<td>13</td>
<td>0.41 (0.33 to 0.51)</td>
<td>13</td>
<td>0.71 (0.61 to 0.83)</td>
</tr>
<tr>
<td>Non-personalized</td>
<td>37</td>
<td>2.08 (1.76 to 2.47)</td>
<td>38</td>
<td>0.59 (0.53 to 0.65)</td>
<td>33</td>
<td>0.81 (0.77 to 0.85)</td>
</tr>
<tr>
<td>P (univariate)</td>
<td>.009</td>
<td></td>
<td>.004</td>
<td></td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>P (meta-regression)*,†</td>
<td>.03</td>
<td></td>
<td>&lt;.001</td>
<td></td>
<td>.07</td>
<td></td>
</tr>
</tbody>
</table>

Precision medicine is compelling
Is rationale enough?

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sébastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sabin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators

Lancet Oncol 2015;16:1324-34
Let’s not forget toxicity

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<table>
<thead>
<tr>
<th>Patients who received molecularly targeted agents (n=100*)</th>
<th>Patients who received cytotoxic chemotherapy (n=91†)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2 necessitating drug interruption or delay†</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Any event§</td>
<td>12 (12%)</td>
</tr>
</tbody>
</table>

*Lancet Oncol 2015;16:1324-34*
Recent ethical concerns

Early Accelerated Approval for Highly Targeted Cancer Drugs
Bruce A. Chabner, M.D.

If patients with incurable disease who have the right biomarker for response are informed of these impressive early results, they will want and perhaps deserve access to the new drug and may not accept random assignment to a modestly effective and toxic standard agent. The phase 3 trial may lack equipoise in the eyes of both physicians and patients.

Historical debate (the 70’s)

1972
CONTROLLED STUDIES IN CLINICAL CANCER RESEARCH
Thomas C. Chalmers, M.D., Jerome B. Block, M.D., and Stephanie Lee, M.A.
RANDOMIZE THE FIRST PATIENT!

1974
NON-RANDOMIZED CONTROLS IN CANCER CLINICAL TRIALS
Edmund A. Gehan, Ph.D., and Emil J. Freireich, M.D.

2009
The Need for Large-Scale Randomized Evidence
Without Undue Emphasis on Small Trials,
Meta-analyses, or Subgroup Analyses
Charles H. Hennekens, MD, DrPH
David DeMets, PhD

2014
Improving the Drug Development Process
More Not Less Randomized Trials
Benjamin Djulbegovic, MD, PhD
Iztok Hozo, PhD
John P. A. Ioannidis, MD, DSc

2016
Evaluating interventions for Ebola: The need for randomized trials
Thomas R Fleming¹ and Susan S Ellenberg²
The case of AZT for HIV infection

THE EFFICACY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

Survival

Nineteen subjects in the placebo group and 1 in the AZT group died during the study (P<0.001 by the Cox regression model).

Figure 1. Proportion of Patients in Whom Opportunistic Infections Developed during the Study (Kaplan–Meier Product–Limit Method). The left panel shows infection among patients with AIDS who were receiving AZT or placebo (PCB), and the right panel shows infection among those with AIDS-related complex (ARC).

Perils of non-randomized evidence

- Selection bias
- Unknown confounders
- Stage migration
- Temporal trends in supportive care etc.
- Different populations between early- and late-phase trials
Benefits of randomization

• Controls selection bias and the problems of historical/contemporary comparisons
• Provides an internal control for all efficacy and safety outcomes
• Allows reliable conclusions about small benefits on important clinical endpoints
• Disentangles the prognostic vs. predictive impact of molecular alterations
• Allows validation of predictive/surrogate biomarkers
Randomization vs. what?

– Experimental vs. standard of care (SOC)
– Experimental vs. treatment of physician’s choice (TPC)
– SOC ± experimental
– TPC ± experimental
– Single agent vs. combination
– Different doses
– Different schedules
– Different durations (e.g., randomized discontinuation)
– Immediate vs. delayed administration
Drug/biomarker pair is the key

- Rituximab and CD20
- Trastuzumab/lapatinib and HER-2
- Imatinib/dasatinib/nilotinib and BCR-Abl/KIT
- Erlotinib/gefitinib/afatinib and EGFR activating mutations
- Osimertinib and EGFR T790M mutation
- Cetuximab/panitumumab and KRAS
- Crizotinib/ceritinib/alectinib and ALK-EML
- Vemurafenib/dabrafenib and BRAF
- Pembrolizumab and MSI-H/MMR deficiency
Validation of biomarkers

To validate a predictive biomarker

• Randomized trials are needed

Validation of biomarkers

To validate a predictive biomarker

• Randomized trials are needed
• Randomized trials are needed on biomarker+ and biomarker- patients

Validation of biomarkers

To validate a predictive biomarker

• Randomized trials are needed
• Randomized trials are needed on biomarker+ and biomarker- patients
• Large randomized trials are needed (because interaction tests lack power)

Validation of biomarkers

To validate a surrogate biomarker-based endpoint (e.g. circulating tumor DNA),
- Randomized trials are needed
- Large randomized trials are needed
- Several randomized trials are needed (to confirm that the treatment effect on the surrogate is predictive of the treatment effect on the true endpoint)

Randomize as soon as possible
When can we forgo randomization?

Role of randomized phase III trials in an era of effective targeted therapies

Manish R. Sharma and Richard L. Schilsky

Box 1 | Six criteria for targeted therapies to be approved without a phase III trial

- Preclinical studies should confirm that the drug targets a driver of the malignant phenotype
- An analytically validated assay should be available to identify which tumors have the intended target
- The drug should be studied in a population of patients that are selected on the basis of having the target
- The response rate and average response duration should indicate a clinically meaningful improvement over that which would be expected based on historical data for the existing standard of care in the same subset of selected patients
- These two outcome measures (response rate and response duration) must be interpreted in the context of the disease setting
- There should be no life-threatening safety concerns about the drug based on the total body of available data
Randomization in phase I

- As soon as expansion cohorts kick off
- To different doses/schedules, preferably with a SOC control arm
  - If SOC not available, any treatment other than the investigational therapy (including agents of the same class)
- Early stopping for outstanding activity, based on interim analyses of biomarkers
Randomization in phase II

- To select regimens more likely to succeed in phase III
- Whenever indicated, include assessment of biomarkers
- Early stopping for outstanding efficacy, based on interim analyses of intermediate endpoints
Randomization in phase III

- Important to include a true control (best treatment patients would receive outside of trial)
- Early stopping for outstanding efficacy, based on interim analyses of surrogate endpoints