Consensus Recommendations

Clinical decision-making

Paolo G. Casali
paolo.casali@istitutotumori.mi.it
<table>
<thead>
<tr>
<th>Time</th>
<th>Parallel Breakout Sessions Including Working Lunch</th>
</tr>
</thead>
</table>
| 11.15   | **Rare tumours: Methodological and Regulatory Challenges**  
Chair: **Paola Casali**, ESMO  
Co-Chair: **Jan Liliemark**, Swedish Medicines Agency  
- The orphan drugs approval process - Filippo De Braud, European Institute of Oncology  
- Current guidelines on efficacy assessment in the EU - Iordanis Gravanis, EMEA  
- Strategies for rare tumours in medical statistics - Paolo Bruzzi, National Institute for Cancer Research of Genoa  
- A parliamentary perspective - Jolanta Dickute, MEP  
Discussion |
| 12.15   | **Rare tumours: Organisational Challenges**  
Chair: **Jean-Yves Bley**, Conticanet  
Co-Chair: **Bertram Wiedenman**, Charité University Hospital Berlin  
- The challenge of rare tumours treatment in the EU - Peter Hohenberger, University of Heidelberg  
- The role of patient advocacy groups - Jan Geissler, European Cancer Patient Coalition  
- Developing networks in hematology - Rüdiger Hehlmann, Leukemia Network  
- Examples of overcoming the barriers - Thor Alvegard, Scandinavian Sarcoma Group & Markus Wartenberg, Sarcoma Patients EuroNet  
Discussion |
| 13.15   | **Rare tumours: Patient Access Challenges**  
Chair: **Kathy Redmond**, Cancer World  
Co-Chair: **Flaminia Macchia**, Eurordis  
- Challenges and barriers: An overview - Yann Le Cam, Eurordis  
- Living with a rare tumour: a patient story - Ella Pybus, Meningioma UK  
Discussion |
Improving Rare Cancer Care in Europe
Recommendations on Stakeholder Actions and Public Policies

Whereas

A. Rare cancers\(^1\) belong to the group of rare diseases that are normally defined as diseases with a prevalence of less than 50 out of 100,000. Even when defined more conservatively by taking into account some peculiarities of natural history and prognosis (e.g. by selecting those cancers with an incidence rate around or lower than 5/100,000/year), rare cancers represent about 20% of all cases of malignant neoplasms, including all cancers affecting children and teenagers and many affecting young adults;

B. There are significant variations in incidence and mortality rates for different types of rare cancers. There are also significant survival differences for the same types of rare cancers between the EU member states;\(^2\)
Recommendations Addressing Regulatory Barriers in Rare Cancer Care

We:

1. Acknowledge that while the process for establishing the efficacy of new medicines is in principle the same for all cancers, the strength of the evidence – intended as level and quality of evidence and statistical precision – that is achievable in common cancers is difficult to achieve in rare conditions and, therefore, a higher degree of uncertainty should be accepted for regulatory as well as clinically informed decision-making.
Uncertainty

A

B

cure

cure

?
Risk

A

B

0-1

cure

0-1

cure
Utility
Decision analysis

\[ EU = (P_1 * U_1) + (P_2 * U_2) \]

\[ EU = (1 * U_3) \]
Clinical decision-making
$R < P \leq 0.05$
$R < p < 0.05$
Demystify Statistical Significance—Time to Move on From the P Value to Bayesian Analysis

J. Jack Lee

Correspondence to: J. Jack Lee, PhD, Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, 1400 Pressler St, Unit 1411, Houston, TX 77030 (e-mail: jjlee@mdanderson.org).
risk
probability
subjective probability
The notion of probability

objective frequency

$P[E]$ degree of belief
Evidence from clinical studies...
LII. An Essay towards solving a Problem in the Doctrine of Chances. By the late Rev. Mr. Bayes, F. R. S. communicated by Mr. Price, in a Letter to John Canton, A. M. F. R. S.

Dear Sir,

Read Dec. 23, 1763. I now send you an essay which I have found among the papers of our deceased friend Mr. Bayes, and which, in my opinion, has great merit, and well deserves to be preferred. Experimental philosophy, you will find, is nearly interested in the subject of it; and on this account there seems to be particular reason for thinking that a communication of it to the Royal Society cannot be improper.
The Bayes theorem...

\[ P[A|B] = P[A] \times \frac{P[B|A]}{P[B]} \]

Mr. Bayes & Mr. Price. Phil Trans 1763;53:370
Education and debate

Strategy for randomised clinical trials in rare cancers
Say-Beng Tan, Keith B G Dear, Paolo Bruzzi, David Machin

Proving that a new treatment is more effective than current treatment can be difficult for rare conditions. Data from small randomised trials could, however, be made more robust by taking other related research into account.

Table 1 Proposed scales and scores for assessing the three components of pertinence of study relevant to small randomised controlled trial under design

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Treatment</th>
<th>Endpoint</th>
<th>Component score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same disease and stage</td>
<td>Same as proposed standard and experimental treatments</td>
<td>Overall survival</td>
<td>1</td>
</tr>
<tr>
<td>Same disease, different stage or type of patient</td>
<td>Same standard treatment, similar experimental treatment (eg different dose)</td>
<td>PFS, DFS, or EFS; adjustment factor available</td>
<td>0.9</td>
</tr>
<tr>
<td>Different site, same biology/histology</td>
<td>Similar standard and experimental treatments</td>
<td>PFS, DFS, or EFS; adjustment factor unavailable</td>
<td>0.8</td>
</tr>
<tr>
<td>Same site, different biology/histology</td>
<td>Response rate validated as a surrogate endpoint</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Different site, some similarity</td>
<td>Some similarity in standard or experimental treatment, or both</td>
<td>Response rate not validated as surrogate endpoint</td>
<td>0.3</td>
</tr>
<tr>
<td>Different disease</td>
<td>Unrelated treatments</td>
<td>Unrelated endpoints</td>
<td>0</td>
</tr>
</tbody>
</table>

DFS—disease-free survival, PFS—progression-free survival, EFS—event-free survival.

Table 2 Proposed scores for assessing the validity of study relevant to small randomised controlled trial under design

<table>
<thead>
<tr>
<th>Design</th>
<th>Validity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trial:</td>
<td></td>
</tr>
<tr>
<td>No major flaws</td>
<td>1</td>
</tr>
<tr>
<td>Questionable quality</td>
<td>0.8</td>
</tr>
<tr>
<td>Major flaws</td>
<td>0.6</td>
</tr>
<tr>
<td>Non-randomised trial:</td>
<td></td>
</tr>
<tr>
<td>Prospective controlled</td>
<td>0.4</td>
</tr>
<tr>
<td>Single arm study:</td>
<td></td>
</tr>
<tr>
<td>With prespecified historical controls</td>
<td>0.3</td>
</tr>
<tr>
<td>No historical controls</td>
<td>0.2</td>
</tr>
<tr>
<td>Case study:</td>
<td></td>
</tr>
<tr>
<td>Series</td>
<td>0.1</td>
</tr>
<tr>
<td>Single report</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Education and debate

Strategy for randomised clinical trials in rare cancers
Say-Beng Tan, Keith B G Dear, Paolo Bruzzi, David Machin

Proving that a new treatment is more effective than current treatment can be difficult for rare conditions. Data from small randomised trials could, however, be made more robust by taking other related research into account.
The preclinical rationale...
...is a prior probability
$p < 0.05$
Quality of evidence...
Rare and frequent cancers...
Personalized medicine in oncology: the future is now

Richard L. Schilsky

Abstract | Cancer chemotherapy is in evolution from non-specific cytotoxic drugs that damage both tumour and normal cells to more specific agents and immunotherapy approaches. Targeted agents are directed at unique molecular features of cancer cells, and immunotherapeutics modulate the tumour immune response; both approaches aim to produce greater effectiveness with less toxicity. The development and use of such agents in biomarker-defined populations enables a more personalized approach to cancer treatment than previously possible and has the potential to reduce the cost of cancer care.
PROJECTED COSTS OF TOTAL U.S. CANCER CARE, 2010–20

5% increase in annual costs, first and last year of care
2% increase in annual costs
Population growth only
Current trends in incidence and survival, projected

Malakoff D, Science 2011;331:1545
Surrogate end points

T

activity
(cancer outcomes)

efficacy
(patient outcomes)
Editorial

Category I. Clinical benefit with favorable objective changes in all measurable criteria of disease.

I-A" Distinct subjective benefit with favorable objective changes in all measurable criteria for 1 month or more.

I-B" Objective regression of all palpable or measurable neoplastic disease for 1 month or more in a relatively asymptomatic patient who is able to carry on his usual activities without undue difficulty. The observed tumor regression should be unprejudiced, and it is suggested that all lesions be reduced at least 50 per cent in bulk. This category applies as long as the regression persists and ends if any lesion, old or new, recurs.

I-C Complete relief of symptoms, if any, and regression of all manifestations resulting from the active disease for 1 year or more. The relation to the frequency of therapy is not relevant if the disease does not recur between courses of therapy.

Category II. Interruption or slowing in progression of disease without definite evidence of subjective or objective improvement. No criteria are presently available to classify this type of response. Statistical evidence of prolongation of survival time in specific patterns of outcome may some day be applicable.
Special article

Phase I and II trials of novel anti-cancer agents: Endpoints, efficacy and existentialism

The Michel Clavel lecture, held at the 10th NCI-EORTC Conference on New Drugs in Cancer Therapy, Amsterdam, 16–19 June 1998

E. A. Eisenhauer

Investigational New Drug Program, NCIC Clinical Trials Group, Queen's University, Kingston, Ontario, Canada

---

a. Tumor regression

b. Growth delay
«Individualized» medicine
European Action Against Rare Cancers

Paolo G. Casali
paolo.casali@istitutotumori.mi.it