Consensus Recommendations

Clinical decision-making

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology

Paolo G. Casali
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RARE
CANCERS
EUROPE


ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology


EURORDIS
Rare Diseases Europe


EUROPEAN
CANCER
PATIENT
COALITION


EORTC
European Organisation for Research and Treatment of Cancer


Conticanet


EuroBoNeT


ECL
Association of European Cancer Leagues


cmlsupport
chronic myeloid leukaemia support group


IBTA
INTERNATIONAL
BRAIN TUMOUR
ALLIANCE


orphanet


FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI


CML AdvocatesNetwork


IEO
European Institute of Oncology


SIOPE
SIOP Europe


ESO
European
School
of
Oncology
Learning to care


EUROPEAN ONCOLOGY
NURSING SOCIETY


European
Society of
Pathology


NOVARTIS
ONCOLOGY


Pfizer
Oncology


sanofi aventis
Because health matters

Rare Tumours in Europe
CHALLENGES AND SOLUTIONS
6 November 2008 - Brussels

11.15 –13:15 PARALLEL BREAKOUT SESSIONS INCLUDING WORKING LUNCH

Workshop I

Rare tumours: Methodological and Regulatory Challenges

Chair: ***Paolo 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

Workshop II

Rare tumours: Organisational Challenges

Chair: ***Jean-Yves Blay***, *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

Workshop III

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

ESMO European Society for Medical Oncology

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]

European Action Against Rare Cancers

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.

U.S. Department of Health & Human Services

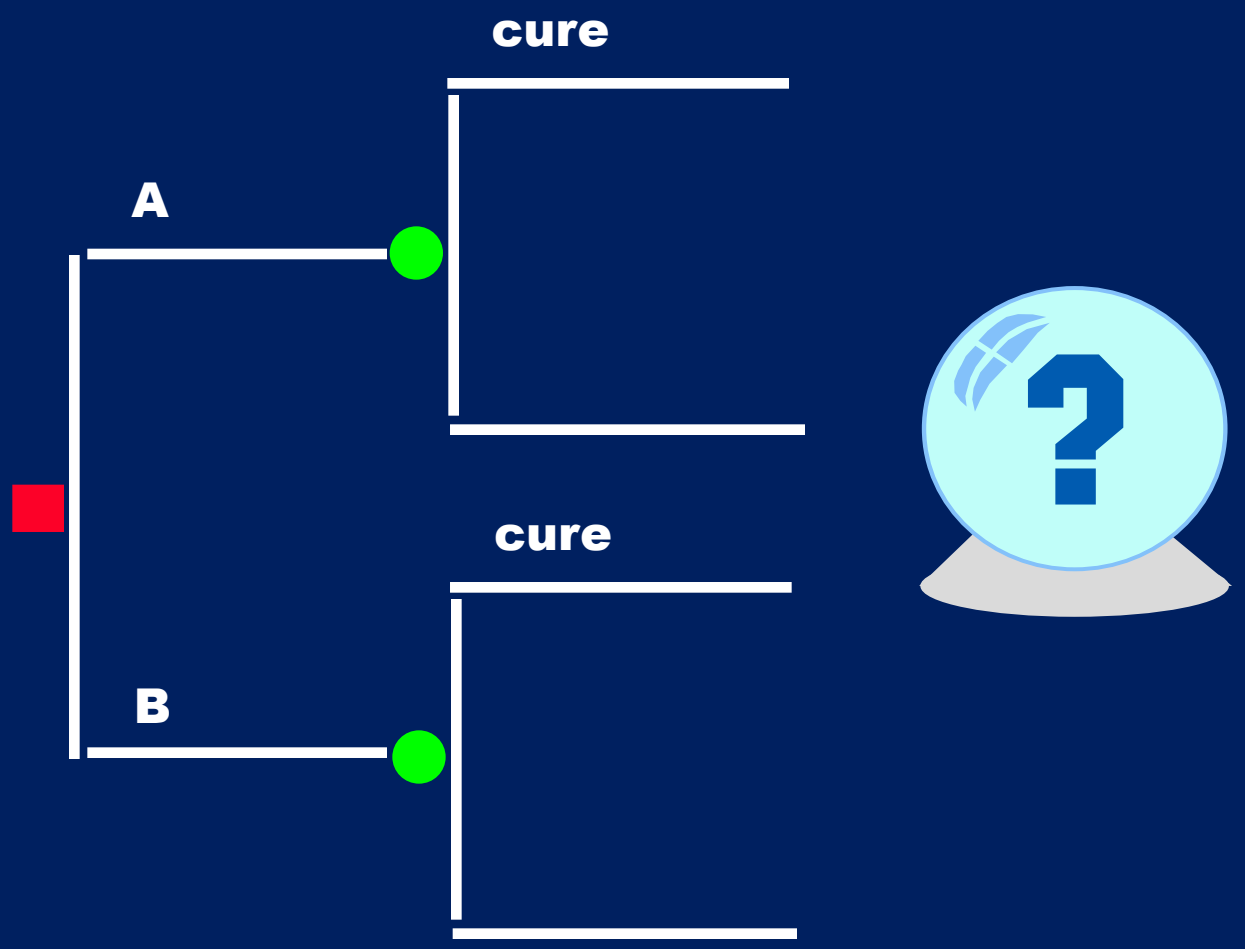
U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

Uncertainty



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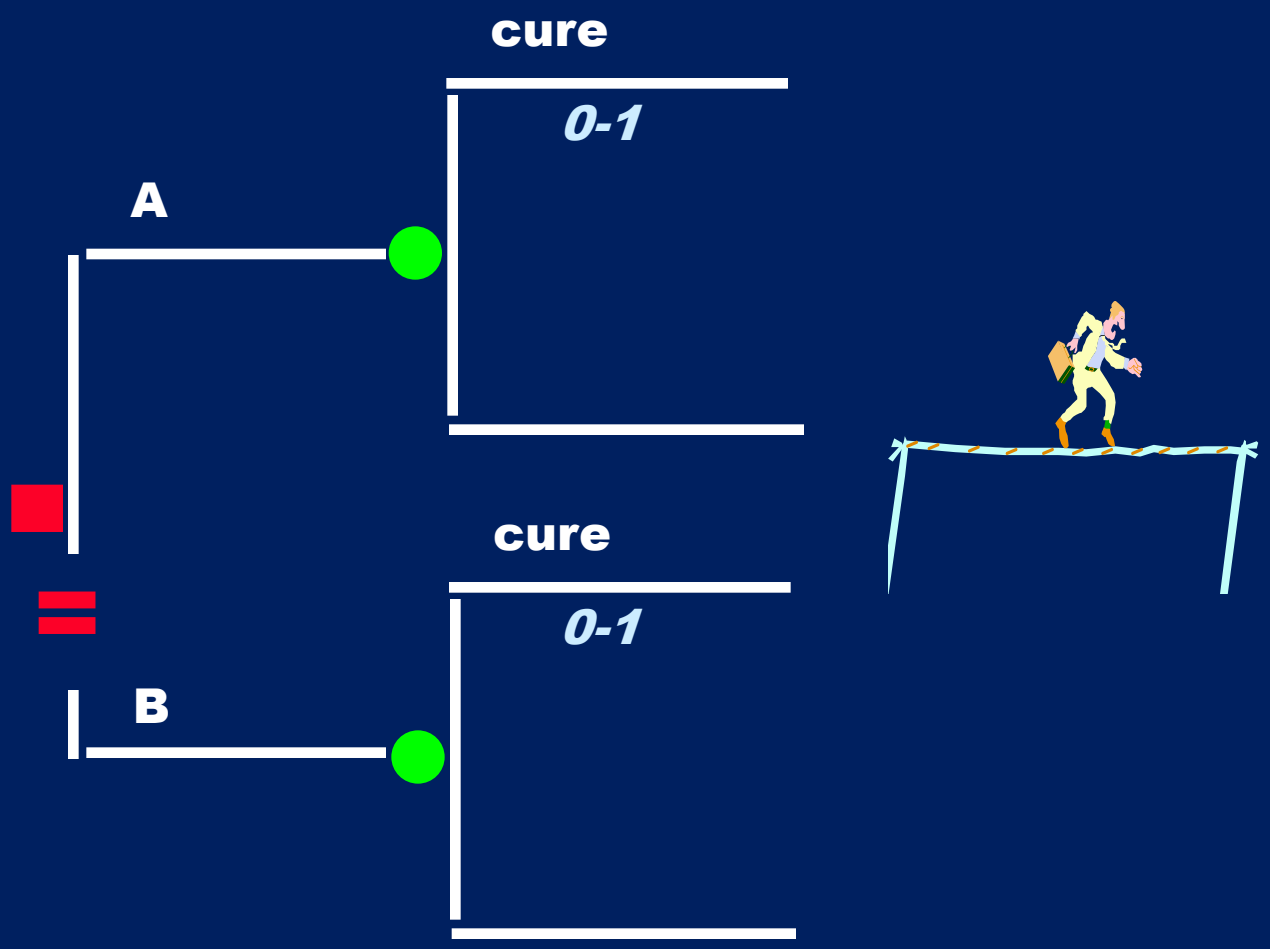

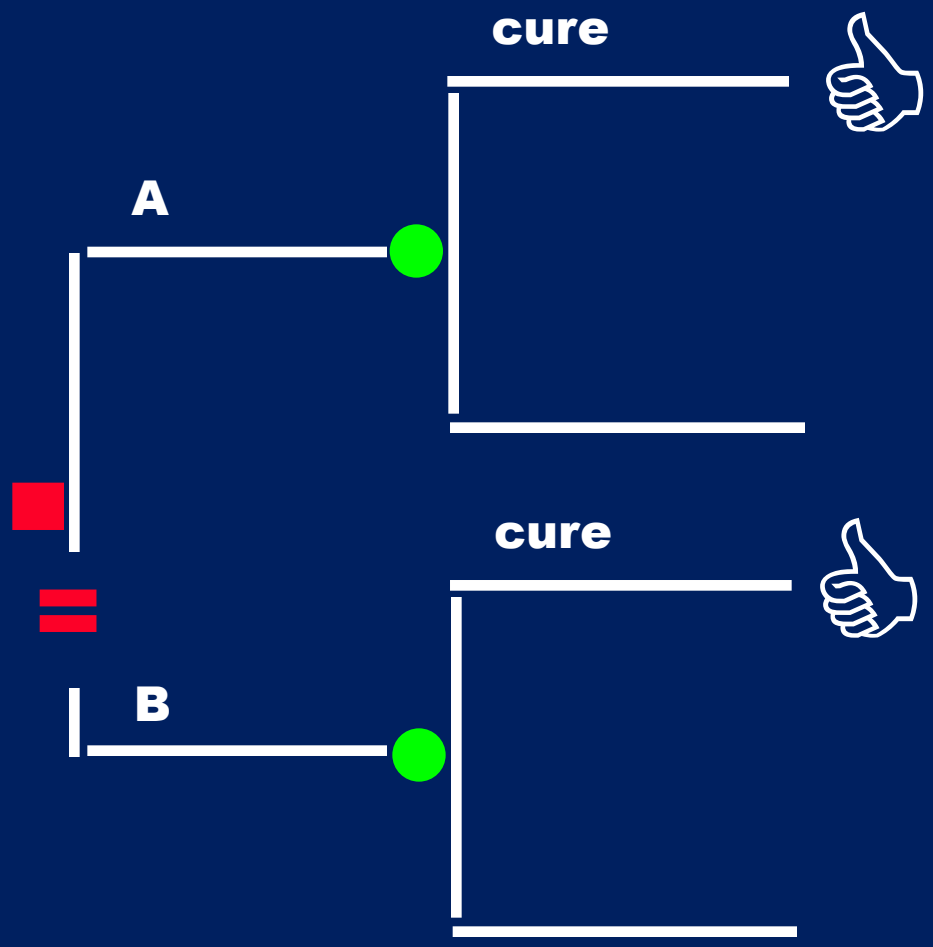
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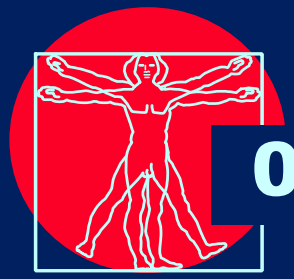
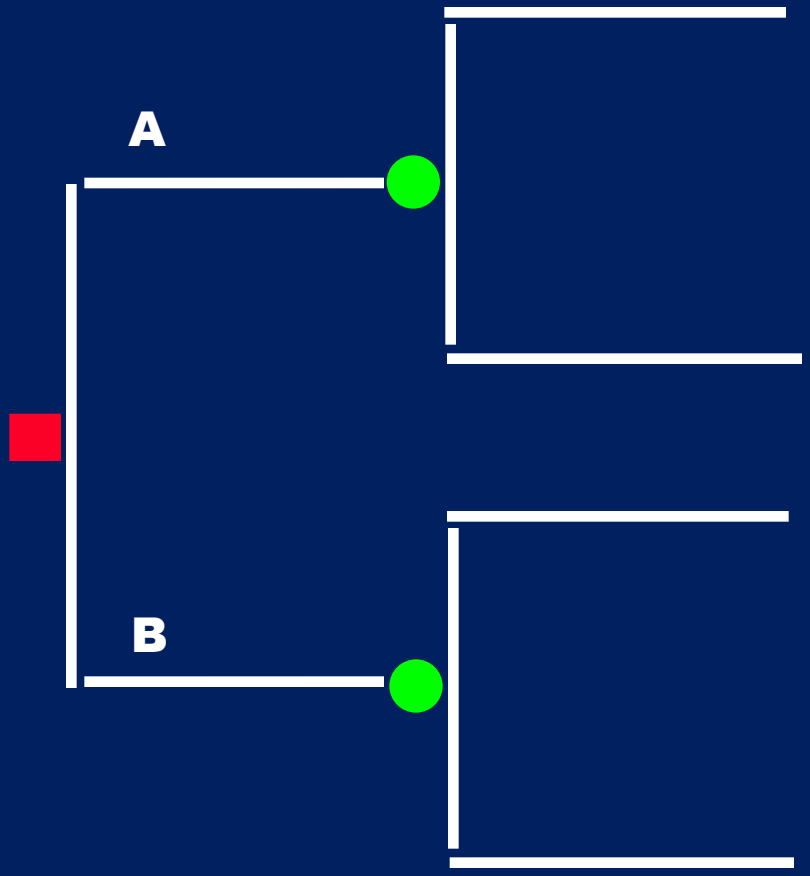
Utility





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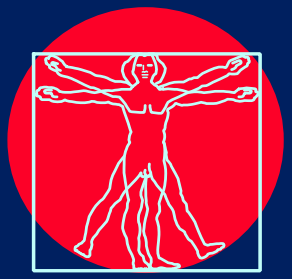

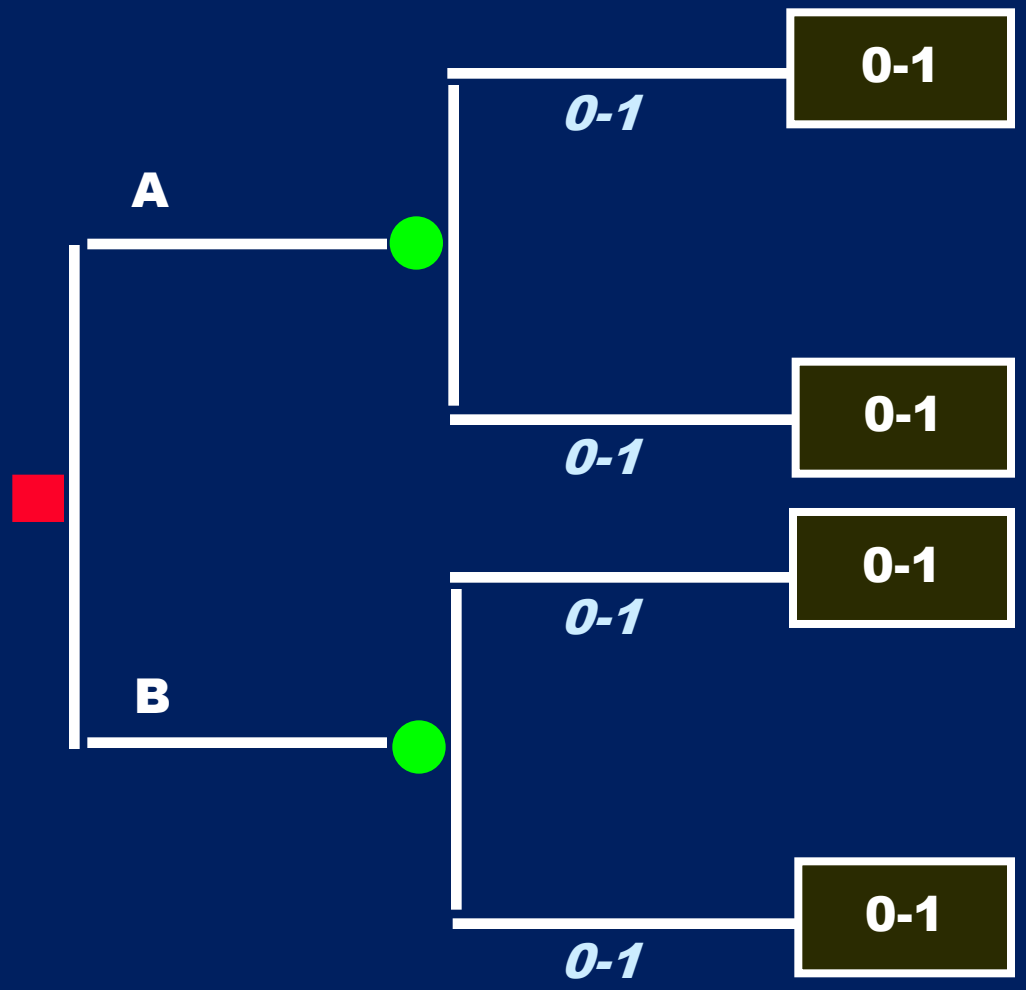

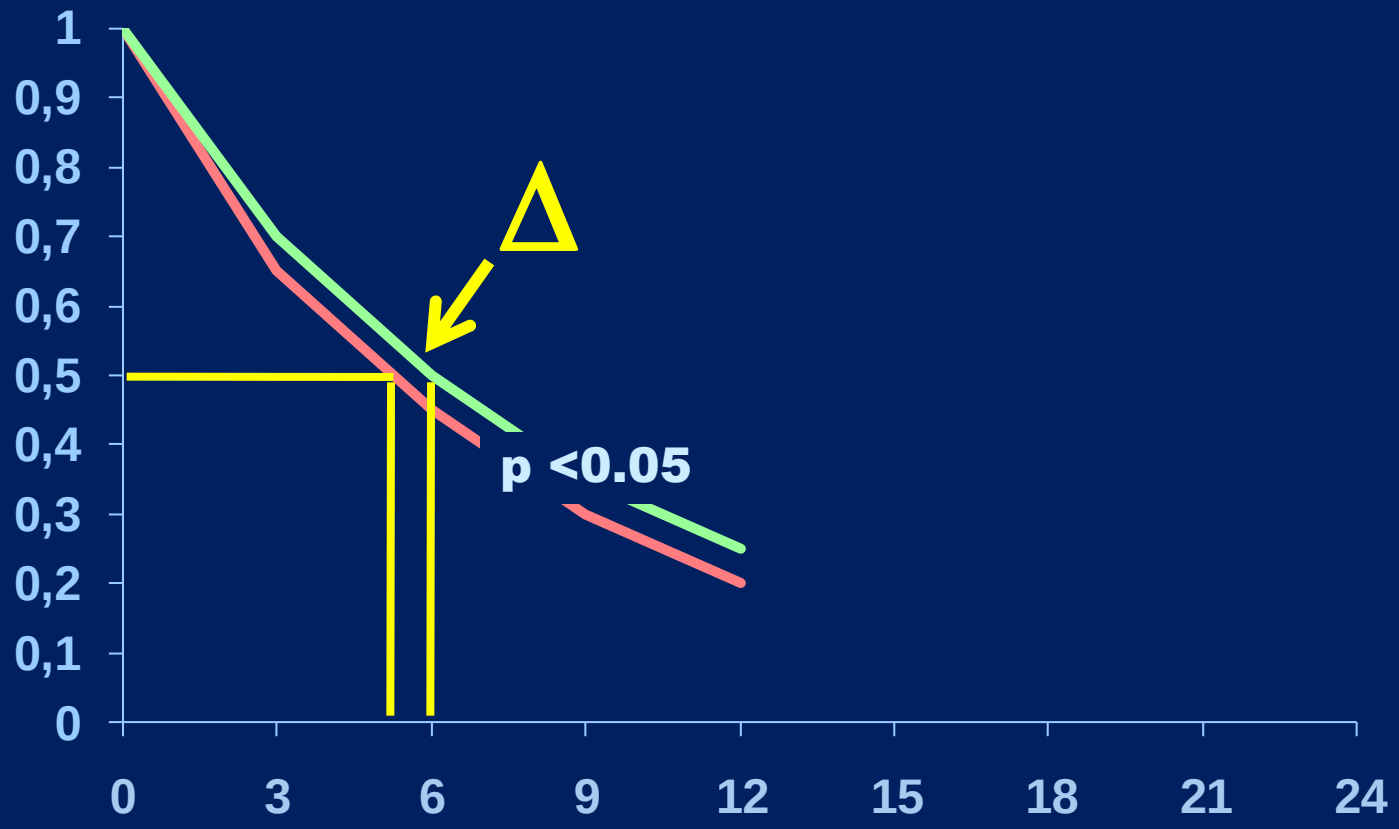
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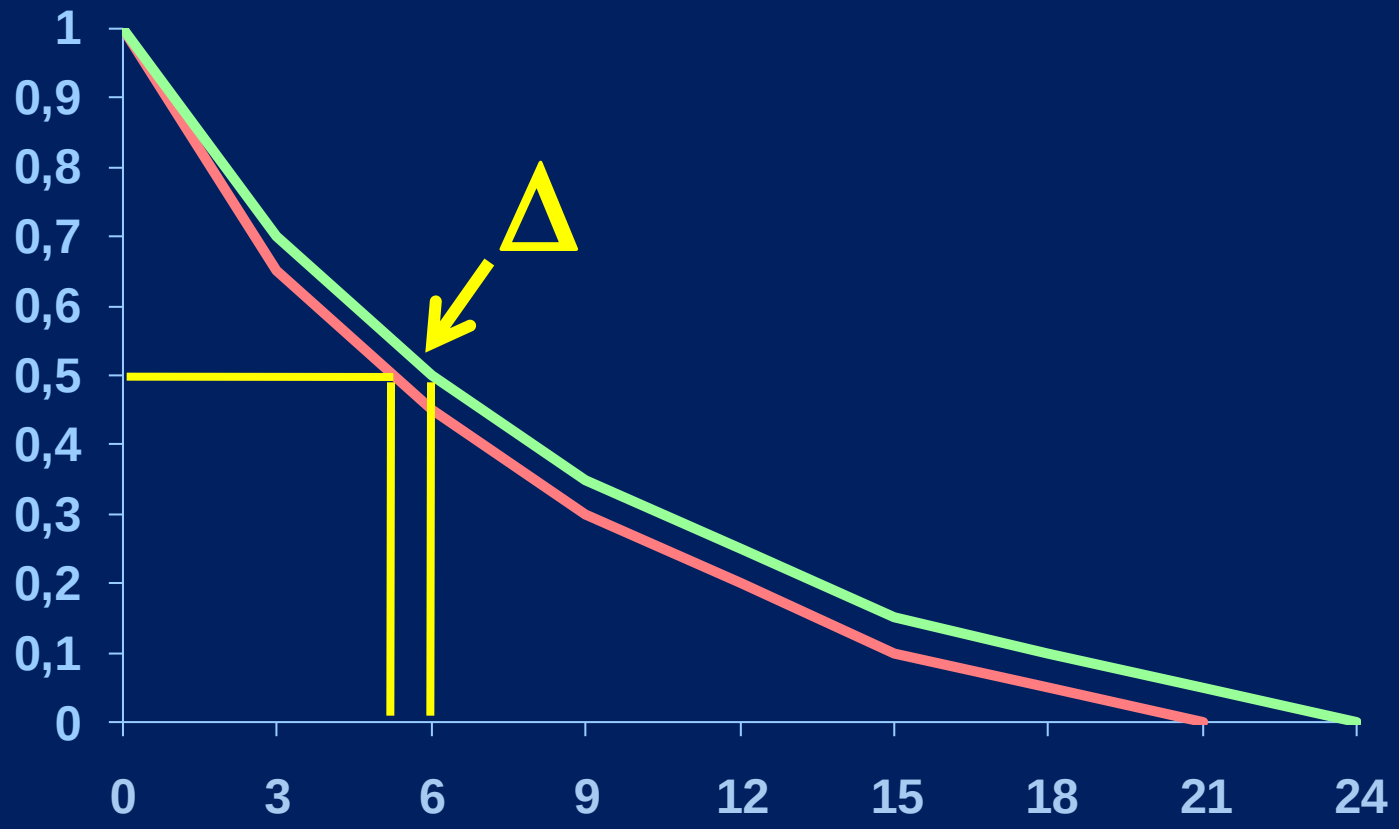
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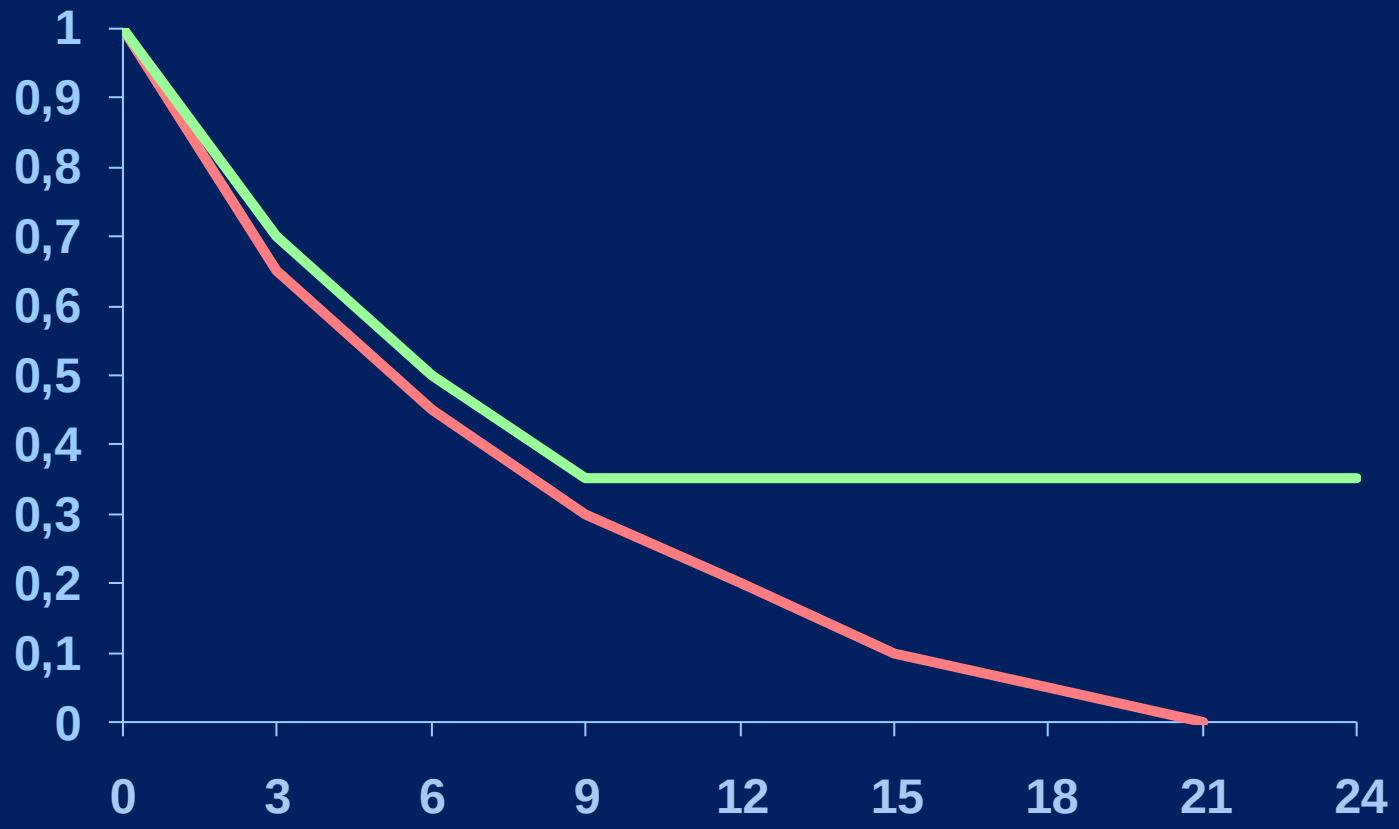
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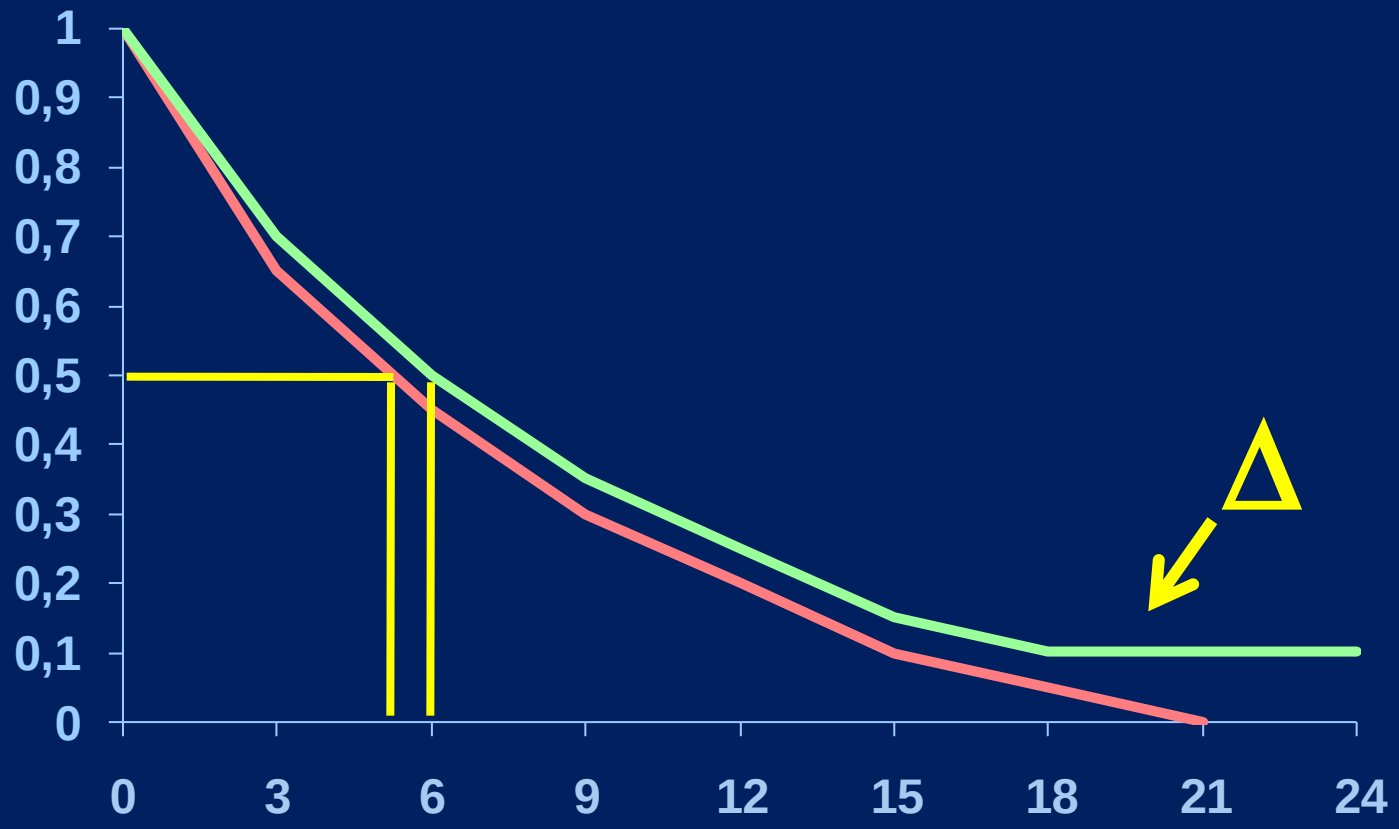
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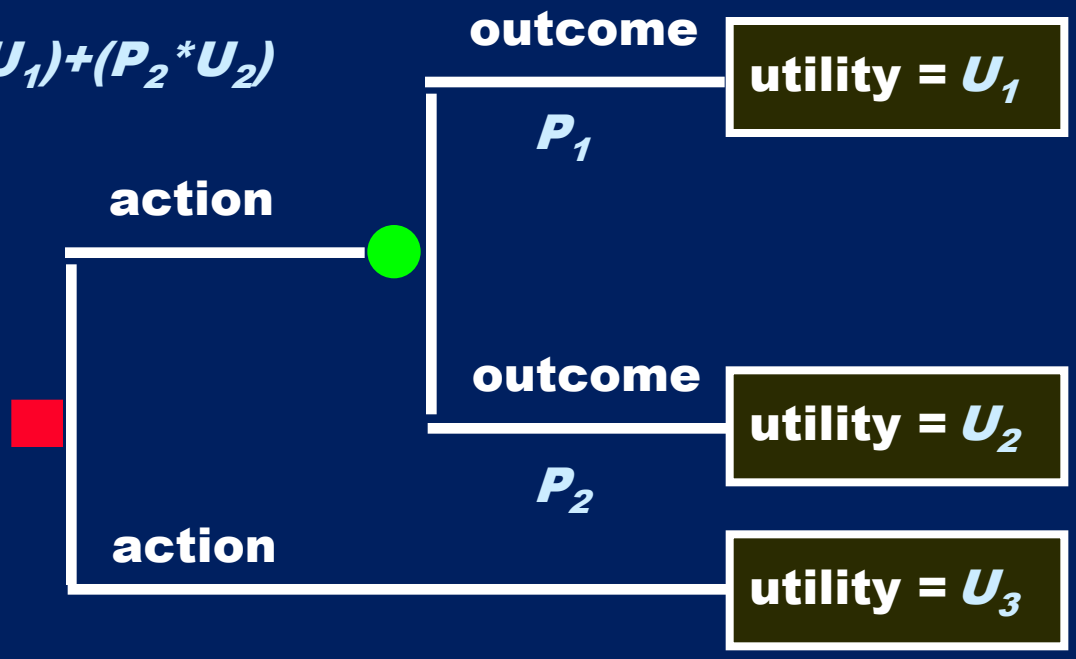
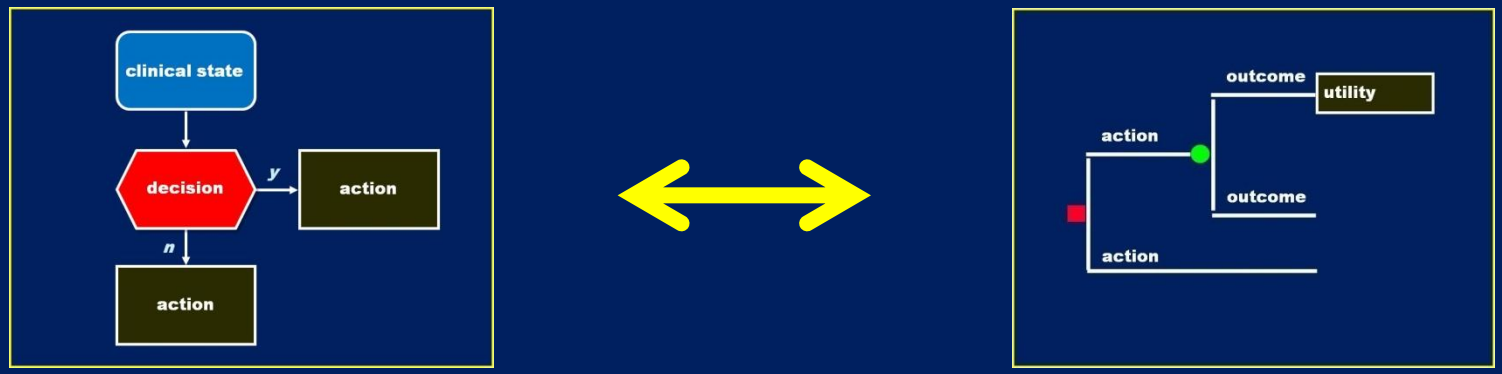
Decision analysis

$EU = (P_1 * U_1) + (P_2 * U_2)$



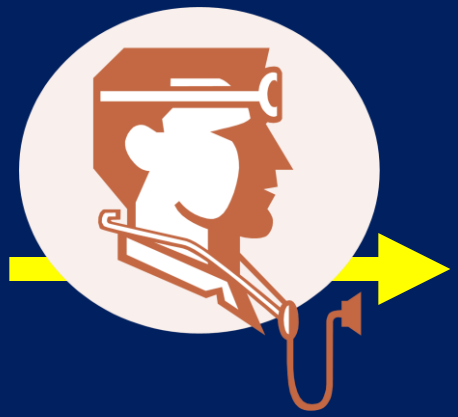
$EU = (1 * U_3)$

Clinical decision-making



R $p \leq 0.05$

$R < p \leq 0.05$



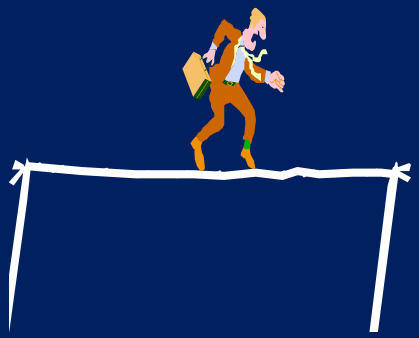
EDITORIALS

Demystify Statistical Significance—Time to Move on From the *P* Value to Bayesian Analysis

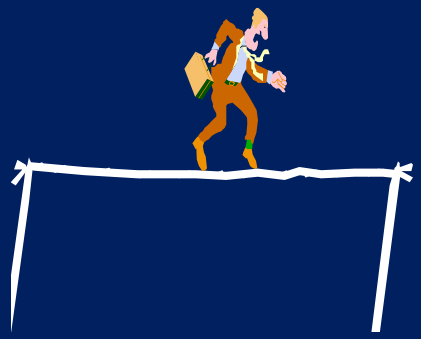
J. Jack Lee

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).

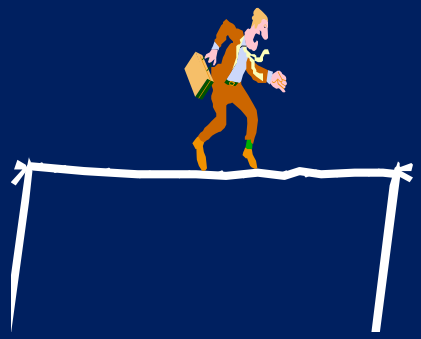
J Natl Cancer Inst 2011;103:2



risk

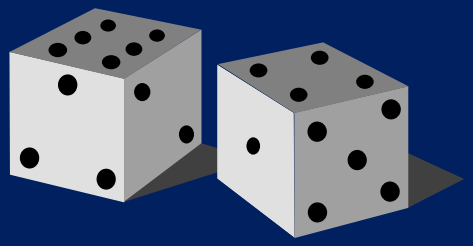


probability



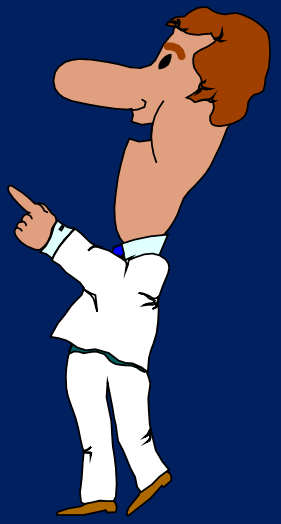
subjective probability

The notion of probability



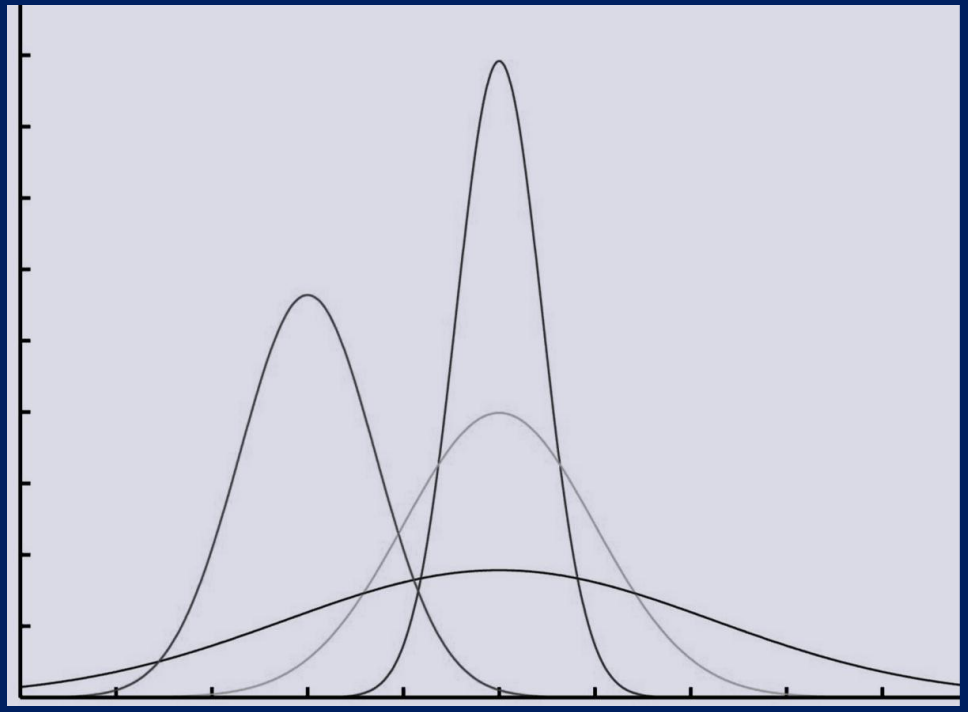
objective
frequency

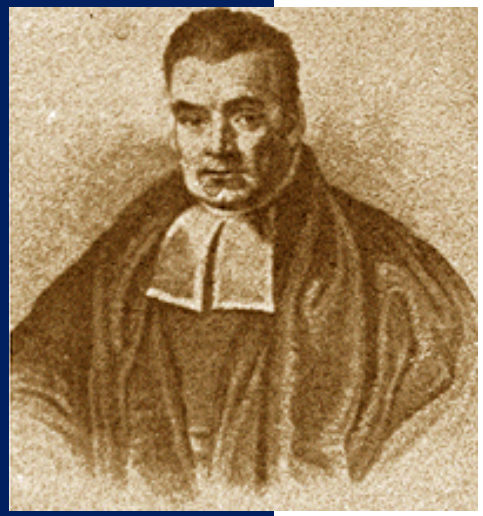
P[E]



degree of belief

Evidence from clinical studies…





PHILOSOPHICAL TRANSACTIONS:

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,

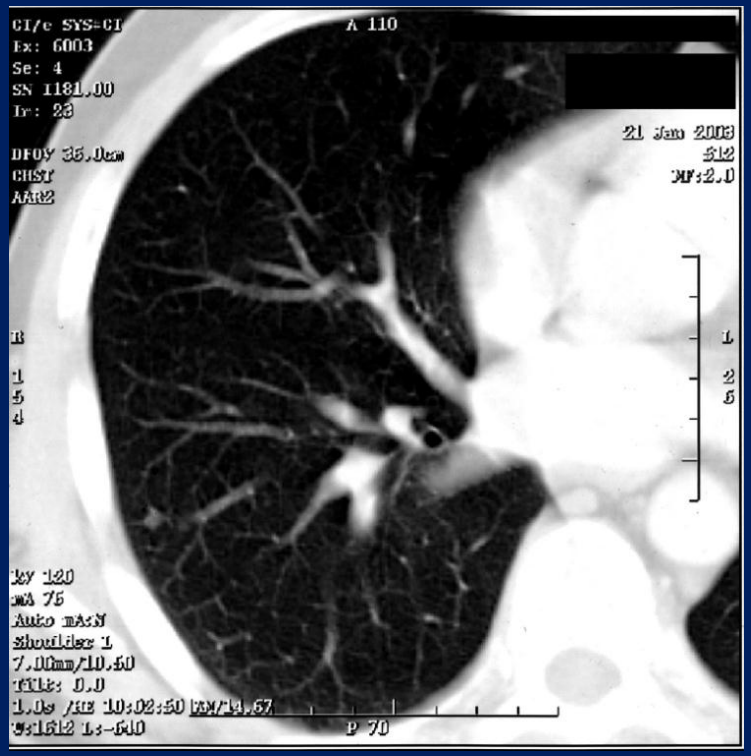
Read Dec. 23, 1763. I Now ſend you an eſſay which I have found among the papers of our deceaſed friend Mr. Bayes, and which, in my opinion, has great merit, and well deſerves to be preſerved. Experimental philoſophy, you will find, is nearly intereſted in the ſubject of it; and on this account there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

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

The Bayes theorem...

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

Mr. Bayes & Mr. Price. Phil Trans 1763;53:370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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 2 Proposed scores for assessing the validity of study relevant to small randomised controlled trial under design

Design	Validity score
Randomised controlled trial:	
No major flaws	1
Questionable quality	0.8
Major flaws	0.6
Non-randomised trial:	
Prospective controlled	0.4
Single arm study:	
With prespecified historical controls	0.3
No historical controls	0.2
Case study:	
Series	0.1
Single report	0.05

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

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

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

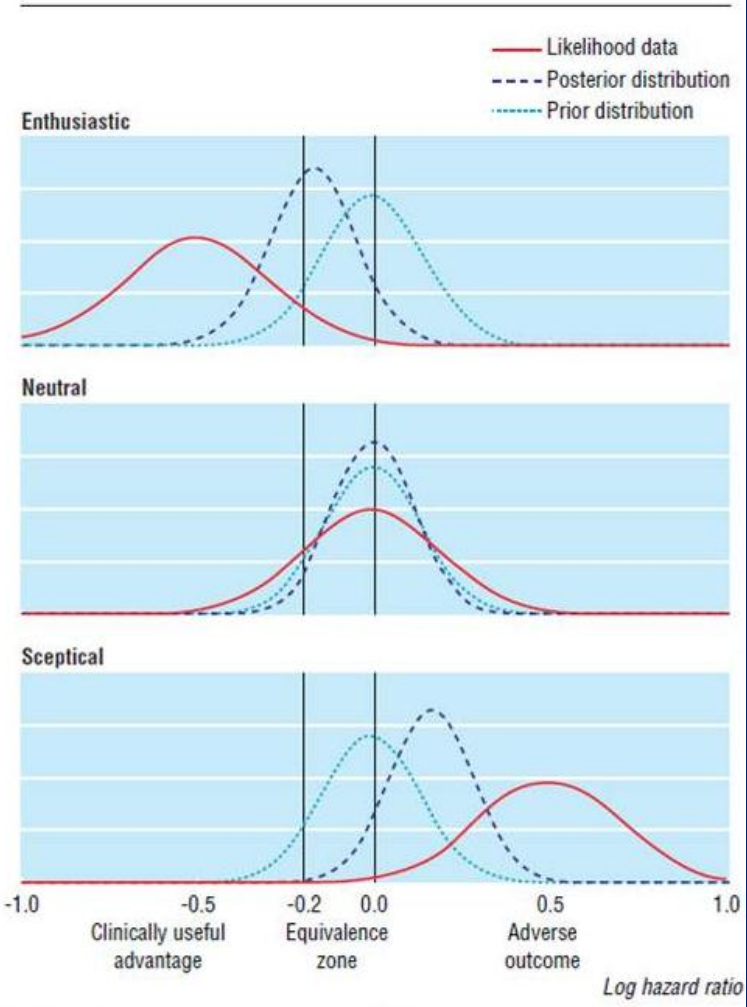
BMJ 2003;327:47

Education and debate

Strategy for randomised clinical trials in rare cancers

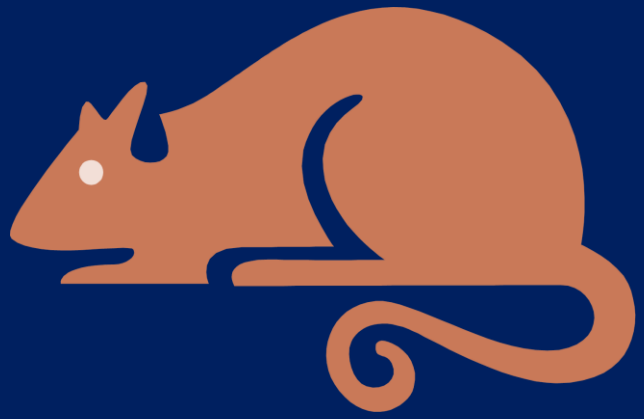
Say-Beng Tan, Keith B G Dear, Paolo Bruzzi, David Machin

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

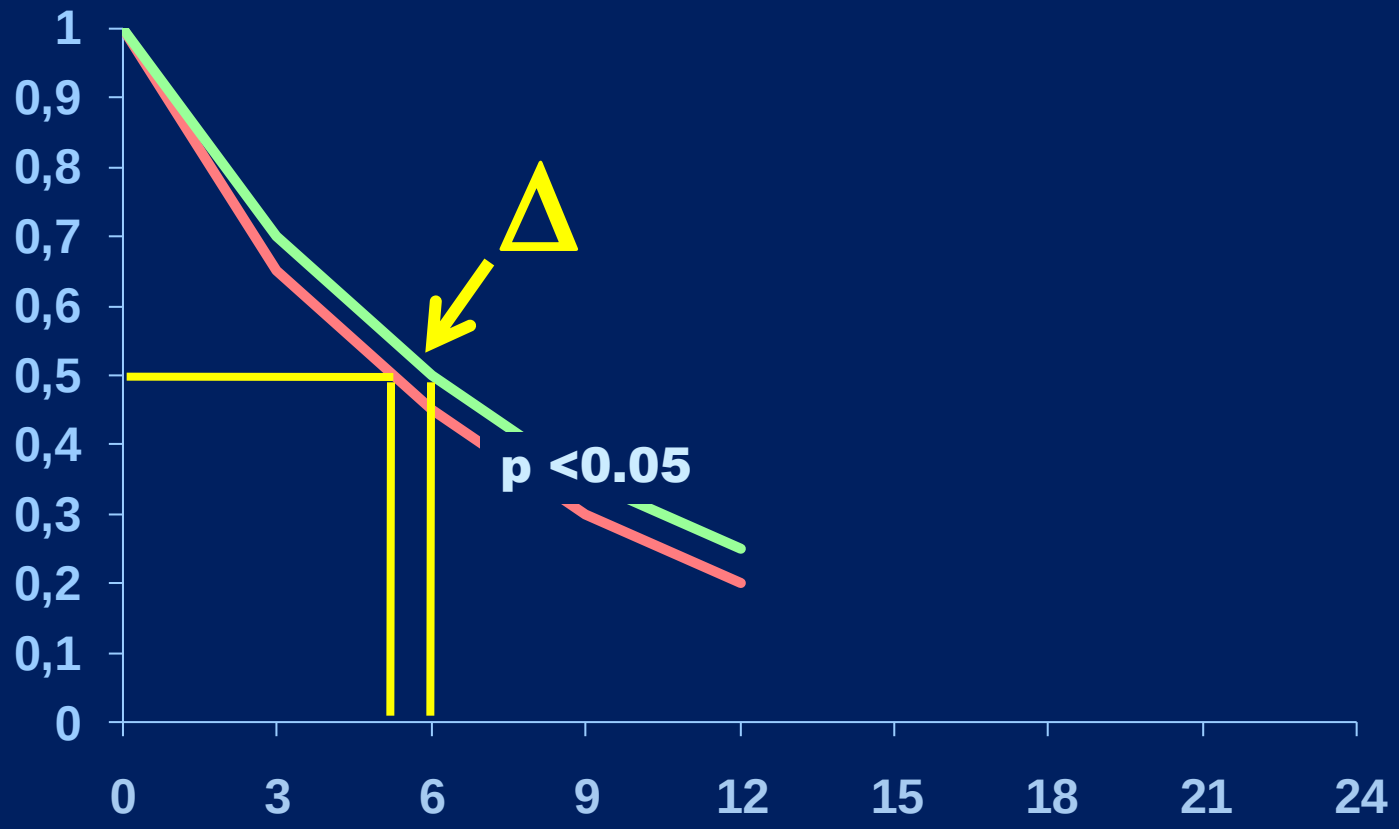


BMJ 2003;327:47

The preclinical rationale…



...is a prior probability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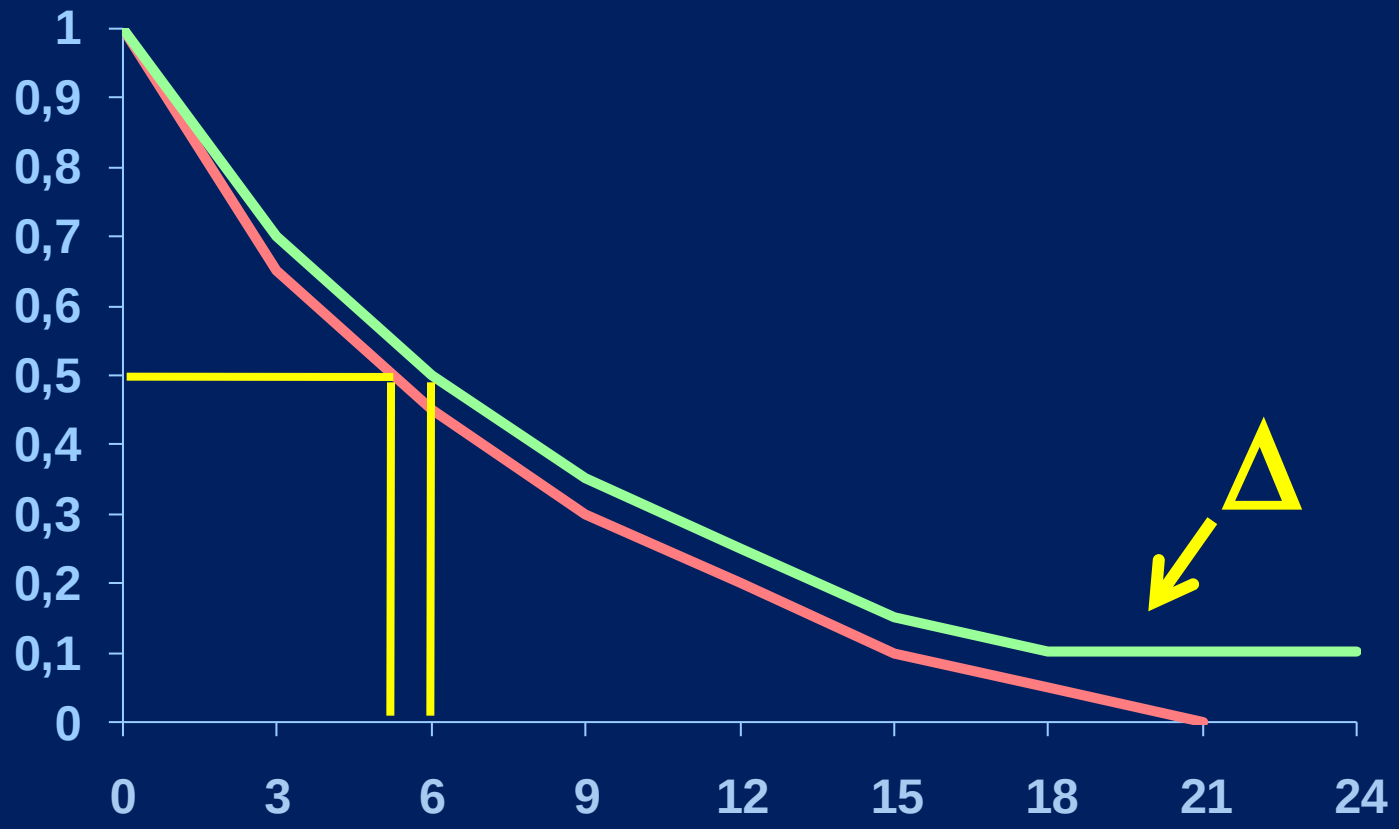
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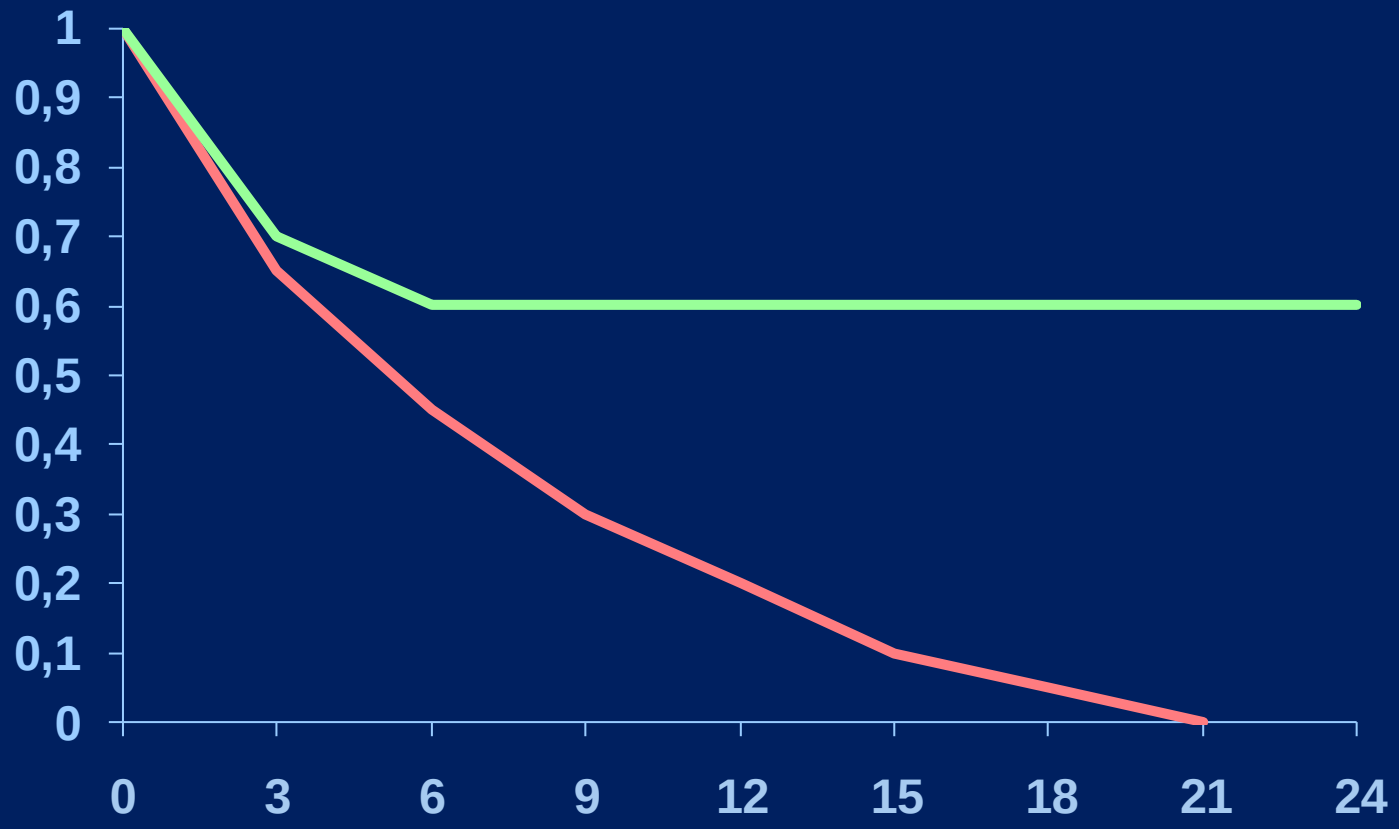
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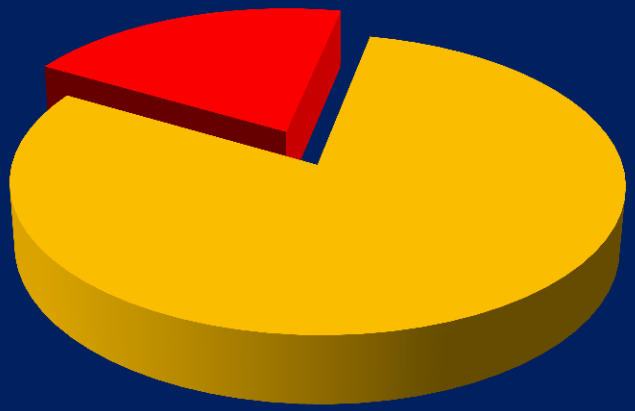
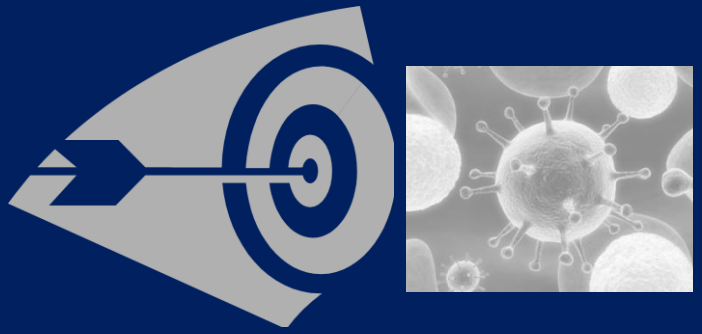
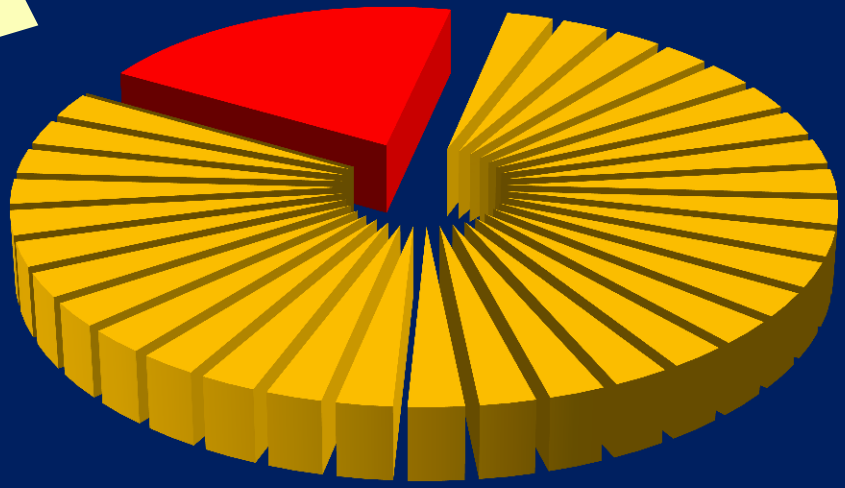
Quality of evidence…

Rare and frequent cancers…







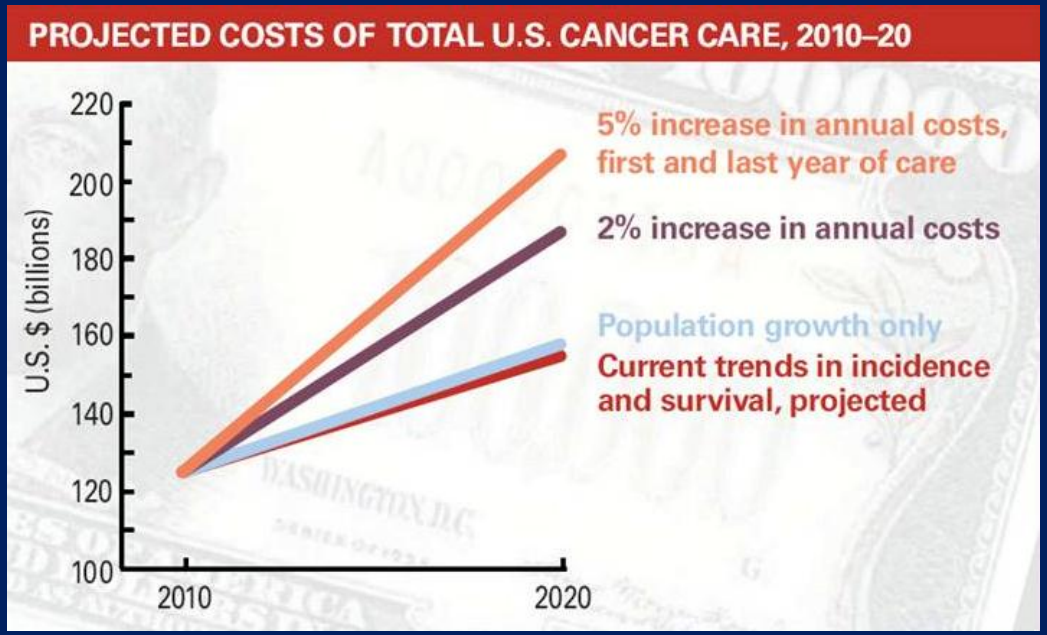
OPINION

Personalized medicine in oncology: the future is now

Richard L. Schilsky

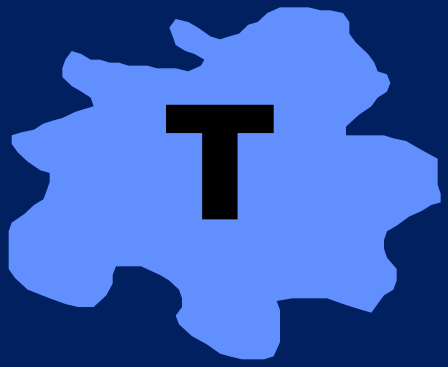
Abstract | Cancer chemotherapy is in evolution from non-specific cytotoxic drugs that damage both tumour and normal cells to more specific agents and immunotherapy approaches. Targeted agents are directed at unique molecular features of cancer cells, and immunotherapeutics modulate the tumour immune 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.

Nat Med 2010;9:363



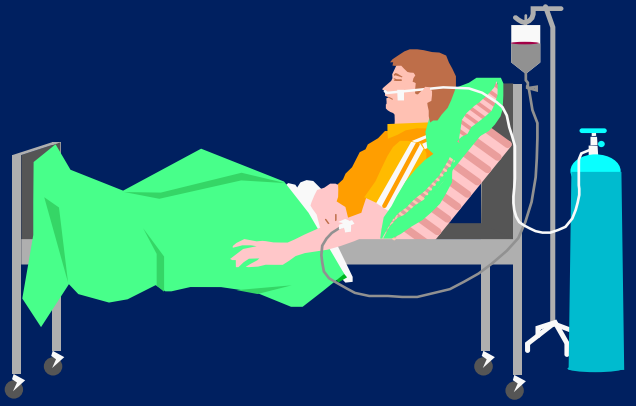
Malakoff D, Science 2011;331:1545

Surrogate end points



activity
(cancer outcomes)

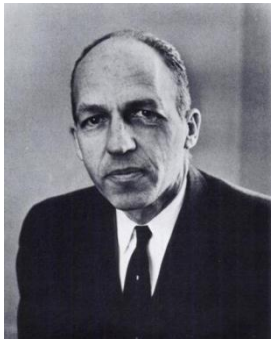
efficacy
(patient outcomes)



CLINICAL PHARMACOLOGY and THERAPEUTICS

volume 2 number 6 November-December 1961

Editorial



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

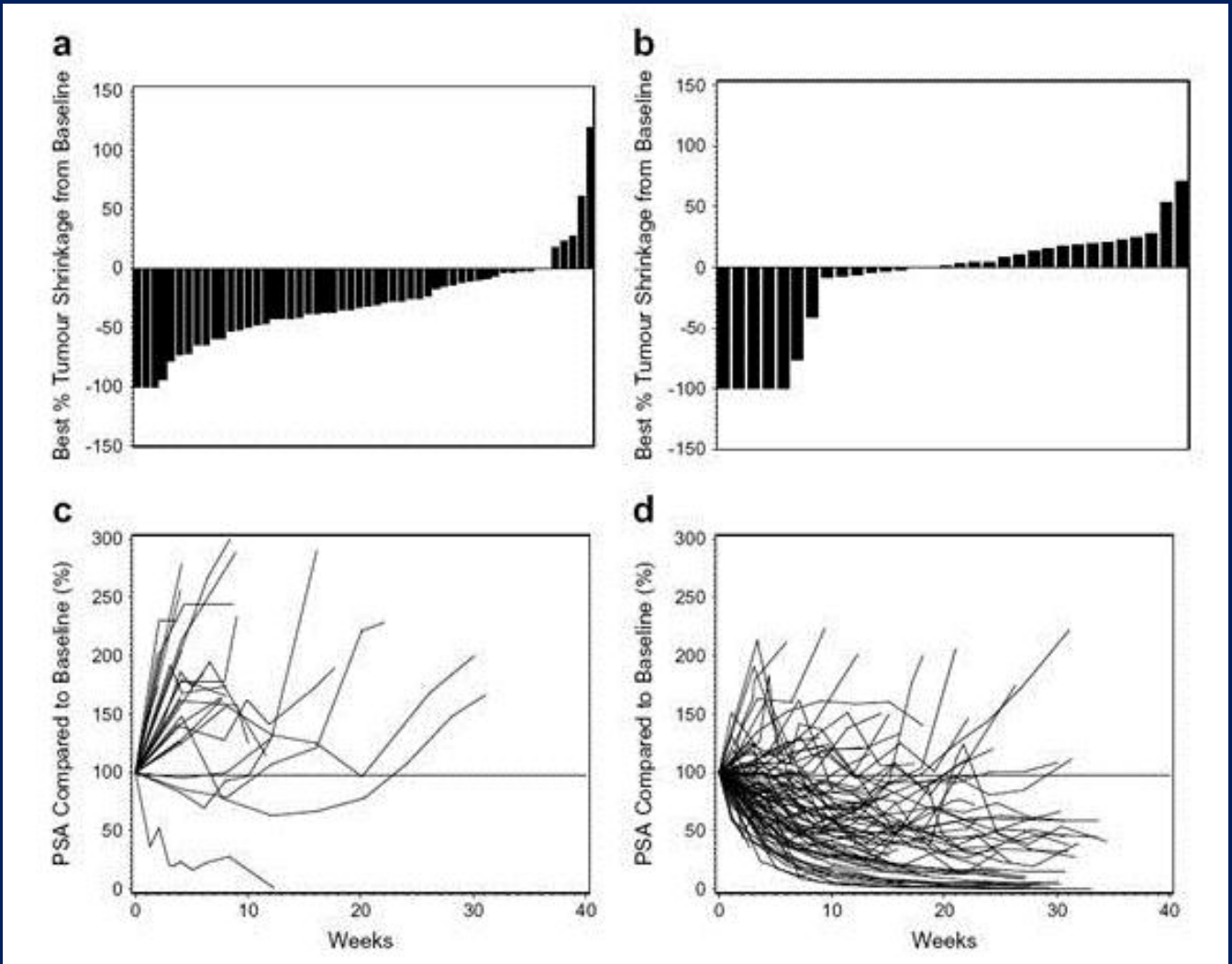
I-A* Distinct subjective benefit with favorable objective changes in all measurable criteria for 1 month or more.

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 unequivocal, 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 cancer may some day be applicable.

Karnofsky DA, 1961;6:709



Booth CM et al. Eur J Cancer 2008;44:25

Annals of Oncology 9: 1047–1052, 1998.

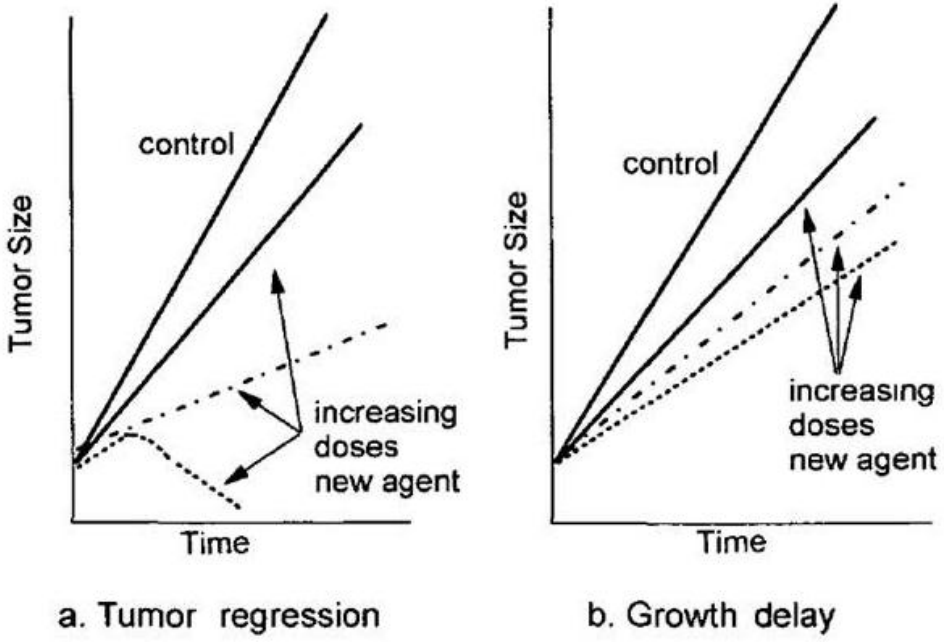
Special article

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

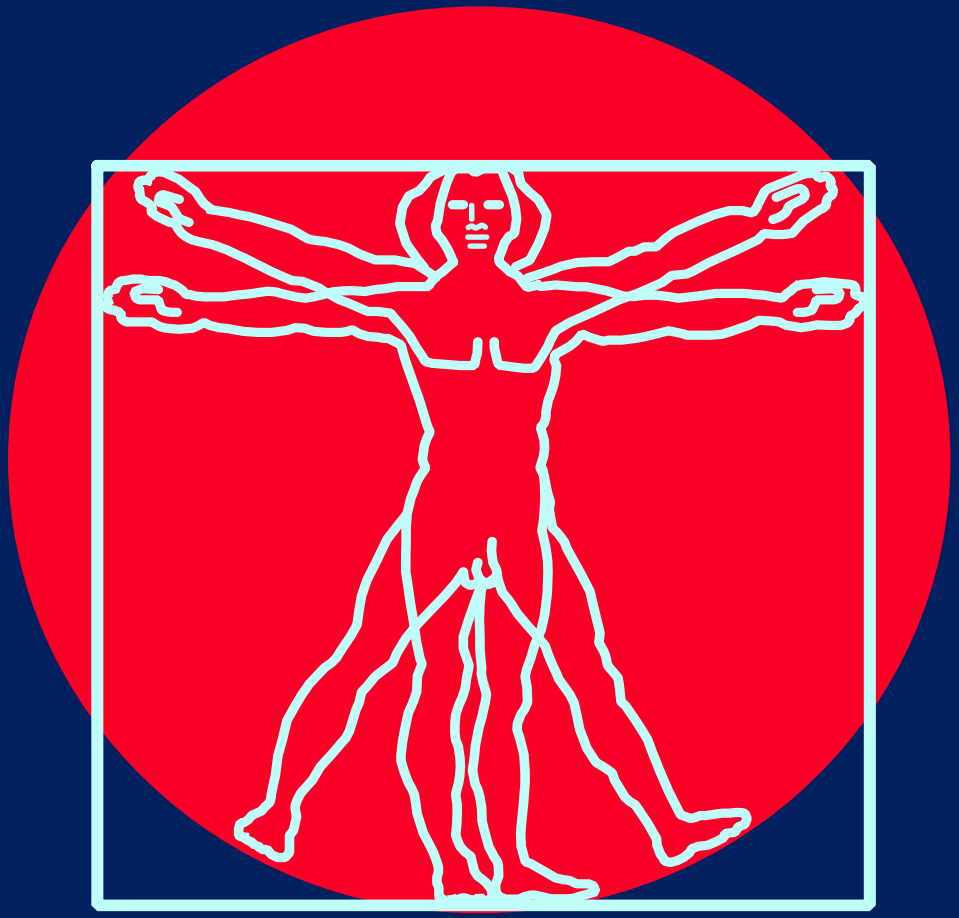
The Michel Clavel lecture, held at the 10th NCI-EORTC Conference on New Drugs in Cancer Therapy, Amsterdam, 16–19 June 1998

E. A. Eisenhauer

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



«Individualized» medicine



European Action Against Rare Cancers

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