

INTRODUZIONE ALLA RICERCA INDIPENDENTE FOCUS SULL'IMMUNO-ONCOLOGIA



**Dall'idea alla costruzione dello studio:
cosa «mettere in conto» e gli errori da evitare**

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Il filo conduttore: La buona ricerca clinica

Una buona ricerca clinica deve essere:

- 1. Scientificamente rilevante**
- 2. Metodologicamente corretta**
- 3. Eticamente accettabile**

La costruzione di uno studio valido

Validità interna
La ricerca è condotta
correttamente?

Dimensionamento del campione

Discutere l'ipotesi è fondamentale per poter ragionare su un dimensionamento adeguato dello studio



Fattori che influenzano la numerosità del campione in una sperimentazione clinica



Dimensionamento del campione

- Uno studio troppo piccolo ha altissima probabilità di produrre un risultato inconclusivo



Dimensionamento del campione

- Uno studio troppo piccolo ha altissima probabilità di produrre un risultato inconclusivo



- Uno studio troppo grande rispetto alle potenzialità degli sperimentatori ha altissima probabilità di non raggiungere il dimensionamento necessario

La costruzione di uno studio valido: l'appropriatezza del braccio di controllo

Research

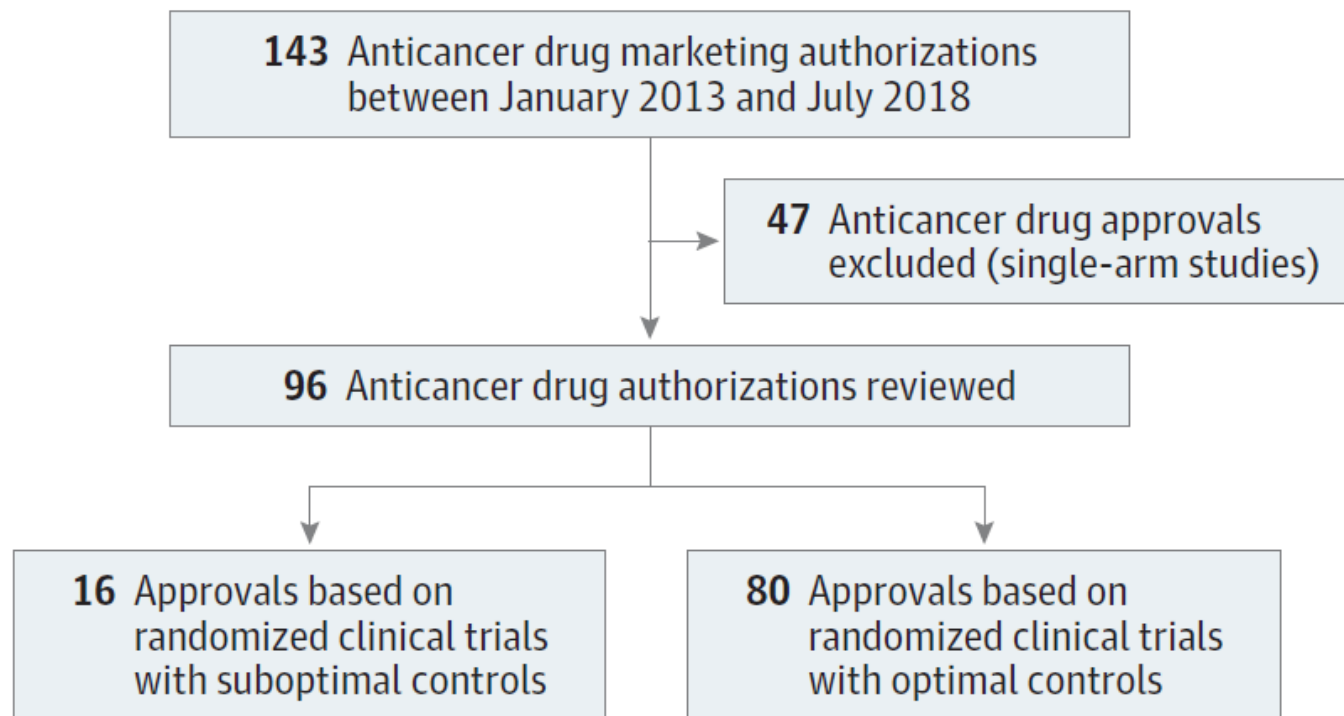
JAMA Oncology | **Original Investigation**

Analysis of Control Arm Quality in Randomized Clinical Trials Leading to Anticancer Drug Approval by the US Food and Drug Administration

Talal Hilal, MD; Mohamad Bassam Sonbol, MD; Vinay Prasad, MD, MPH

Hilal T, Sonbol MB, Prasad V. *JAMA Oncol*. Published online May 02, 2019.
doi:10.1001/jamaoncol.2019.0167

Figure 1. Flowchart of All Cancer Drug Approvals From January 1, 2013, to July 31, 2018



Hilal T, Sonbol MB, Prasad V. *JAMA Oncol*. Published online May 02, 2019.
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Perché il braccio di controllo è stato giudicato subottimale?

- In 4 casi (25%), NON era consentito un trattamento che invece risulta di provata efficacia
- In 10 casi (63%), il trattamento era già dimostrato inferiore rispetto ad altri trattamenti disponibili
- In 2 casi (13%) il trattamento di controllo prevedeva il rechallenge di farmaci già usati

Hilal T, Sonbol MB, Prasad V. *JAMA Oncol*. Published online May 02, 2019.
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Panel 1: Problems that might limit interpretation of randomised controlled trials

Some randomised controlled trials might:

- Ask questions of commercial rather than clinical interest
- Be based on inadequate preclinical and early clinical studies
- Use surrogate endpoints that do not reflect patient benefit (ie, duration or quality of survival)
- Fail to assess or inadequately assess health-related quality of life or patient-reported outcomes even though the goals of treatment are palliative
- Show statistically significant but clinically irrelevant results
- Be analysed and reported prematurely
- Underestimate the toxicity of new treatments
- Be subject to biased reporting, both in the primary publication and by the media
- Select patients who do not represent those seen in everyday practice

Ian Tannock et al,

Relevance of randomised controlled trials in oncology, Lancet Oncology 2016; 16: e560-567

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Methodological issues in QoL evaluation in clinical trials

- Choice of the questionnaire
- Choice of timing of administration
- Management of missing data
- Multiplicity of items
- Modality of analysis
- Definition of clinically relevant differences

La costruzione di uno studio valido

Validità esterna

I risultati sono applicabili
al «real world»?

Validità interna

La ricerca è condotta
correttamente?

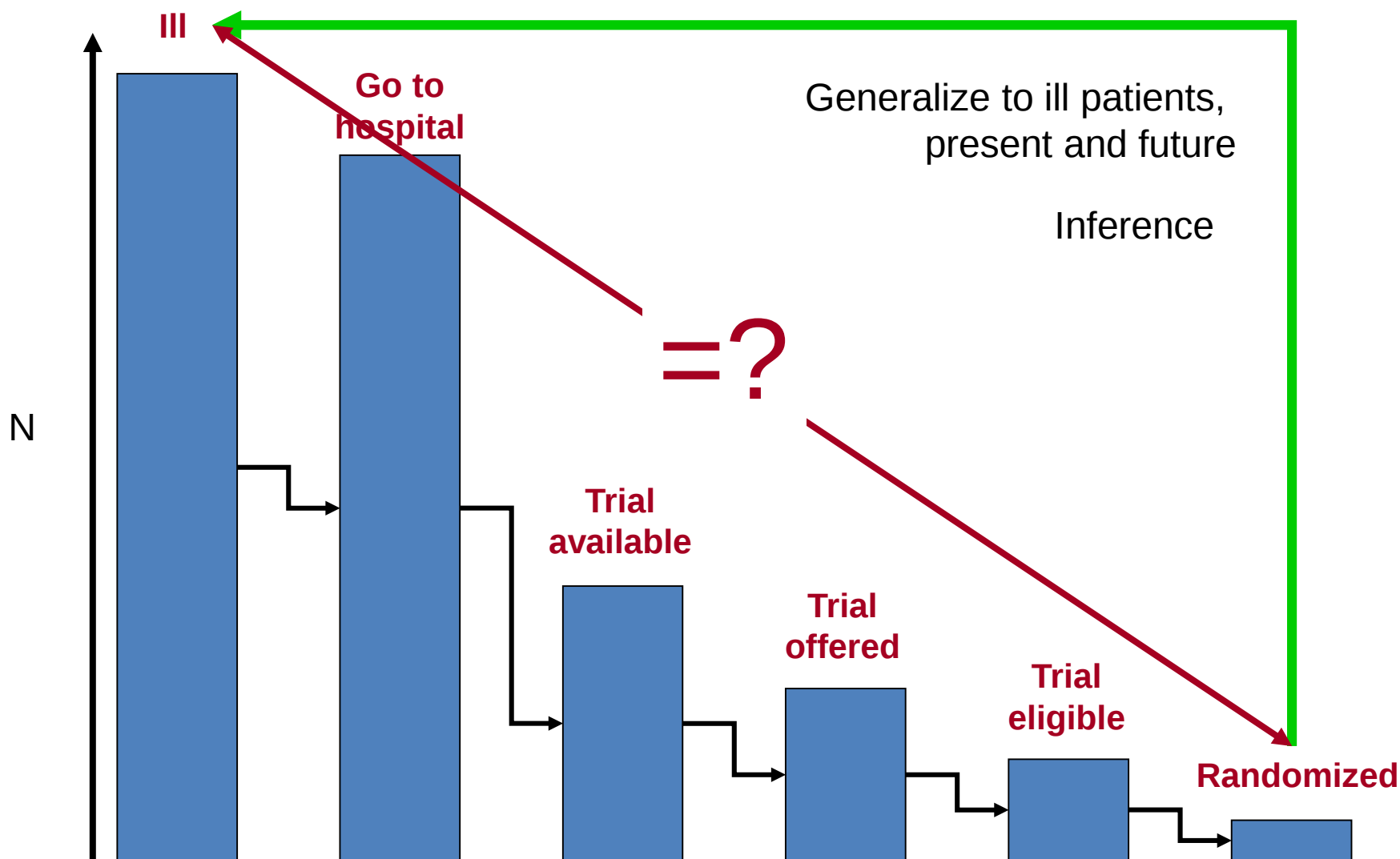
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Validità esterna?



Cortesia di Francesco Perrone

Modernizing Eligibility Criteria for Clinical Trials

Julia A. Beaver, MD
Director DOP1, OHOP, FDA

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement

Edward S. Kim, Suanna S. Bruinooge, Samantha Roberts, Gwynn Ison, Nancy U. Lin, Lia Gore, Thomas S. Uldrick, Stuart M. Lichtman, Nancy Roach, Julia A. Beaver, Rajeshwari Sridhara, Paul J. Hesketh, Andrea M. Denicoff, Elizabeth Garrett-Mayer, Eric Rubin, Pratik Multani, Tatiana M. Prowell, Caroline Schenkel, Marina Kozak, Jeff Allen, Ellen Sigal, and Richard L. Schilsky

Le analisi di sottogruppo: croce e delizia!

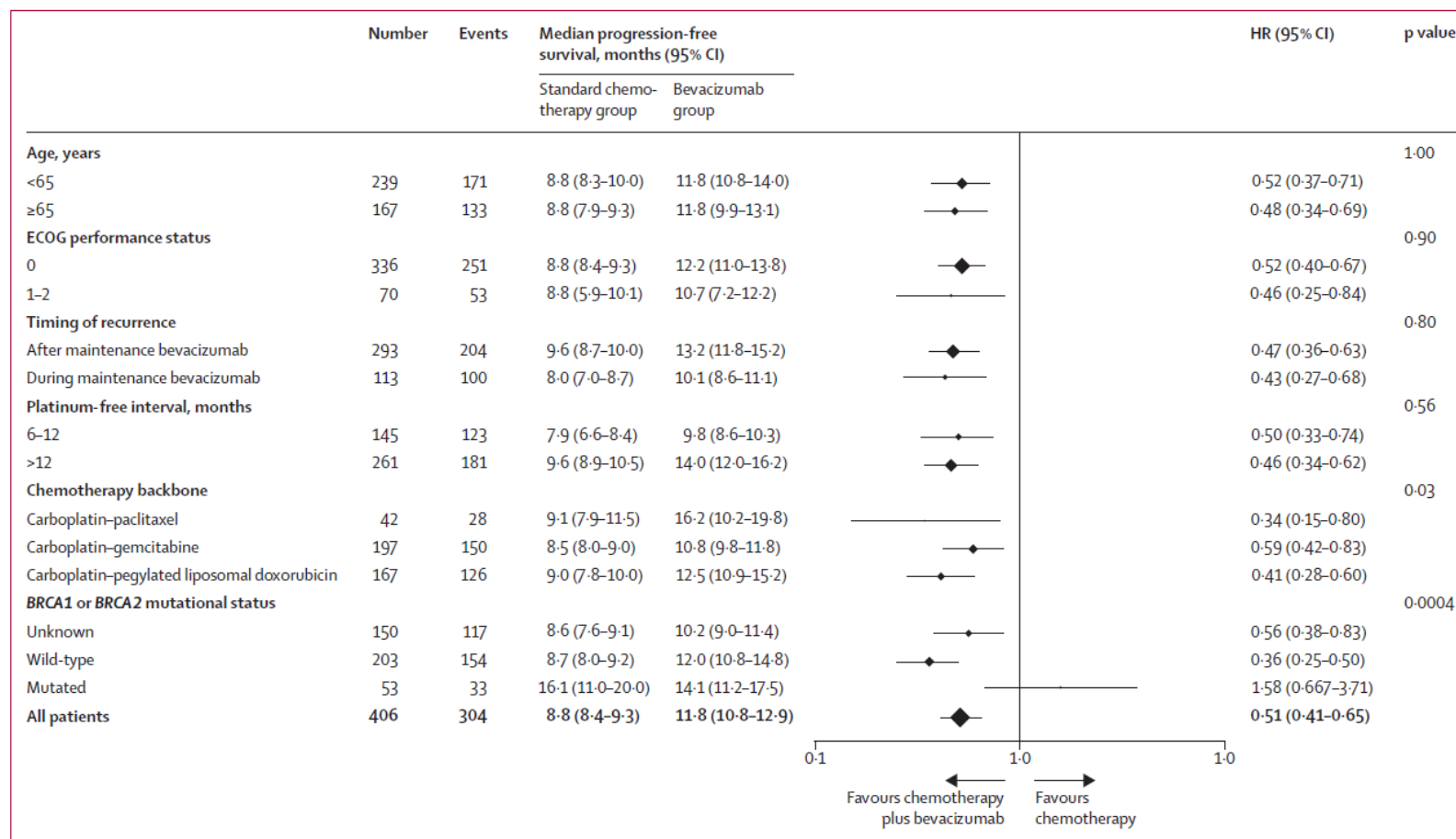


Figure 3: Forest plot of subgroup analysis of progression-free survival

The size of symbols is proportional to the number of patients in each subgroup. Interaction p values were calculated by the likelihood-ratio test of two nested models, with and without interaction. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio.

Le analisi di sottogruppo: la regola d'oro è pianificare!



Figure 3: Forest plot of subgroup analysis of progression-free survival

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