UNIVERSITÀ DI TORINO

Approccio critico all'evidenza scientifica

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Presidente eletto AIOM

AIOM ASSOCIAZIONE ITALIANA ONCOLOGIA MEDICA

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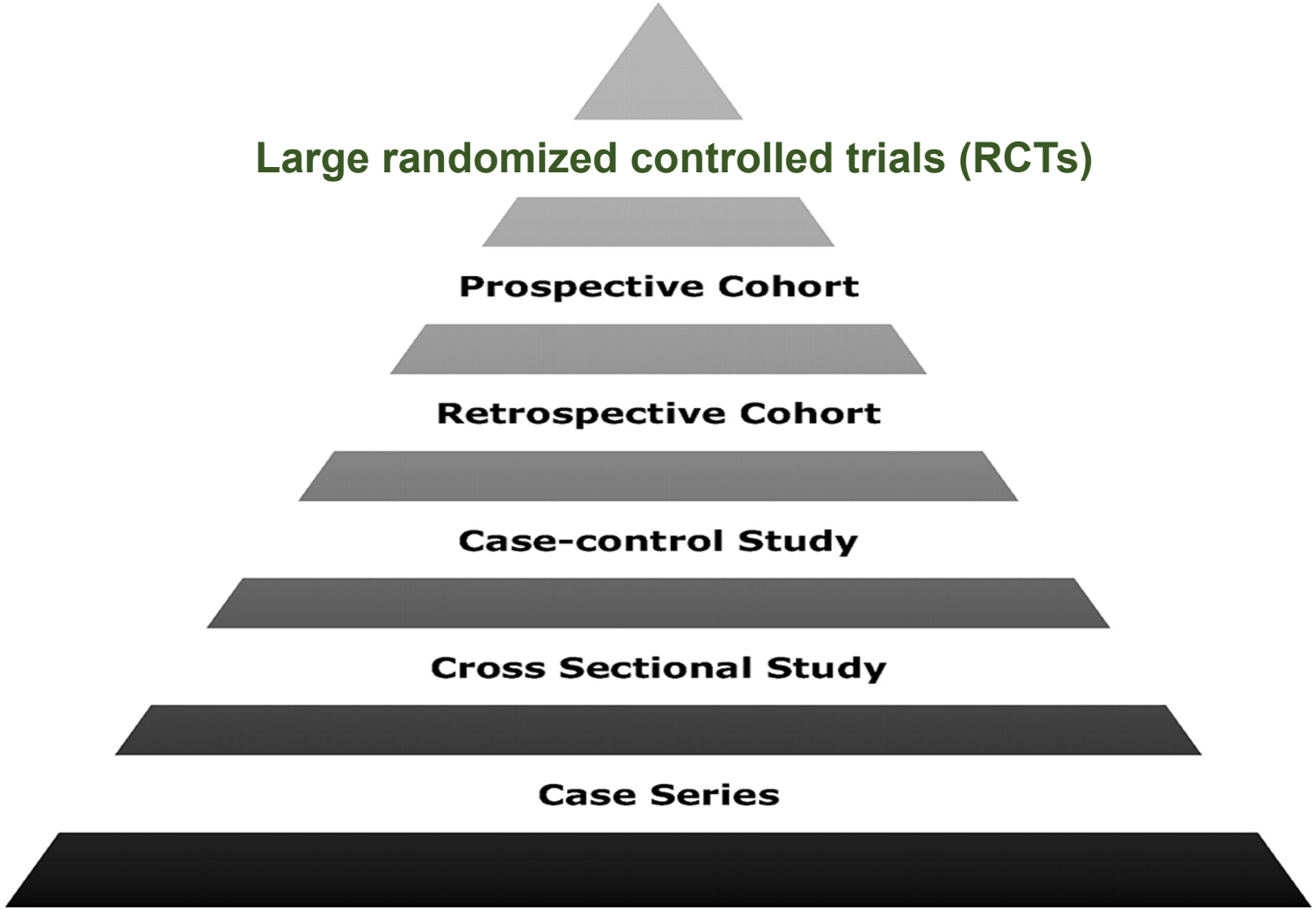
Disclosure
as of April 4, 2024

In the last 3 years I received:

- **Personal** honoraria for acting as consultant or participating to advisory boards:
  - Merck Sharp & Dohme, AstraZeneca, Takeda, Eisai, Janssen, Pfizer, Roche, Novartis, Merck, Amgen, GlaxoSmithKline

- **Institutional** research grant:
  - Tesaro - GlaxoSmithKline

La piramide dell'evidenza



Ho P M et al. Circulation 2008;118:1675-1684

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

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

Statistical significance vs clinical relevance: size of effect!

If a new treatment is to be introduced into clinical practice, **it should not be enough to show that it is 'better' than the standard therapy, regardless of the size of its effect**.

Instead, **it should be necessary to demonstrate that the effect is clinically worthwhile**, meaning as large as or larger than a specified threshold representing the minimal clinically worthwhile effect.

Floriani I, Garattini S, Torri V. Ann Oncol 2010
doi:10.1093/annonc/mdq266

Validity of results

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Internal validity

Is the research conducted correctly?

L’adeguatezza del braccio di controllo

European Journal of Cancer 189 (2023) 112920

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original research

Analysis of the adequacy of control arms in oncology randomised clinical trials published between 2017 and 2021: a meta-research study

Alessandro Rossi [a], Giacomo Aimar [b,c], Marco Audisio [d], Maristella Bungaro [e], Andrea Caglio [f], Raimondo Di Liello [g], Teresa Gamba [f], Piera Gargiulo [h], Eleonora Ghisoni [i], Pasquale Lombardi [j], Laura Marandino [k], Annapaola Mariniello [l,m], Chiara Paratore [d], Maria Lucia Reale [n], Federica Trastu [f], Valentina Tuninetti [f], Fabio Turco [m,o], Alessandra Fabi [a], Francesco Perrone [h], Massimo Di Maio [p,*,1,2]

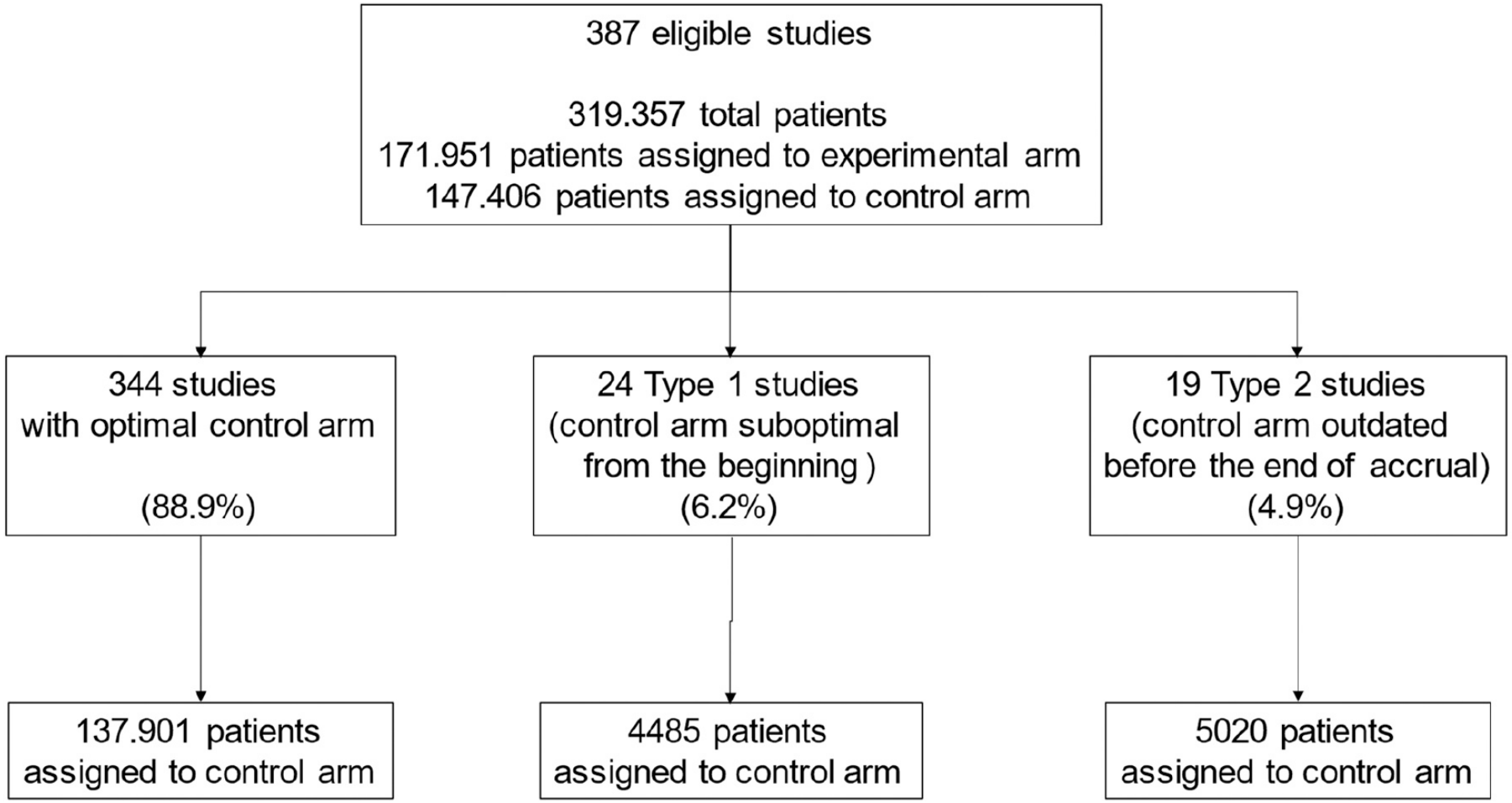
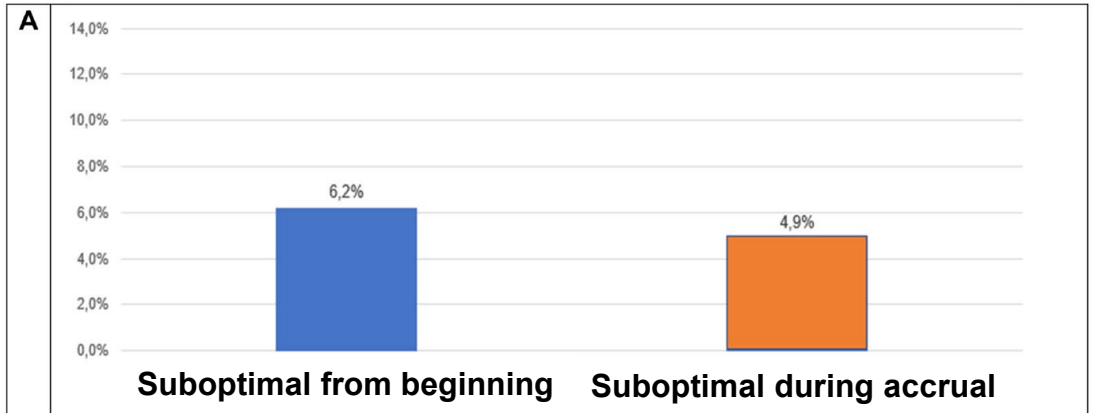
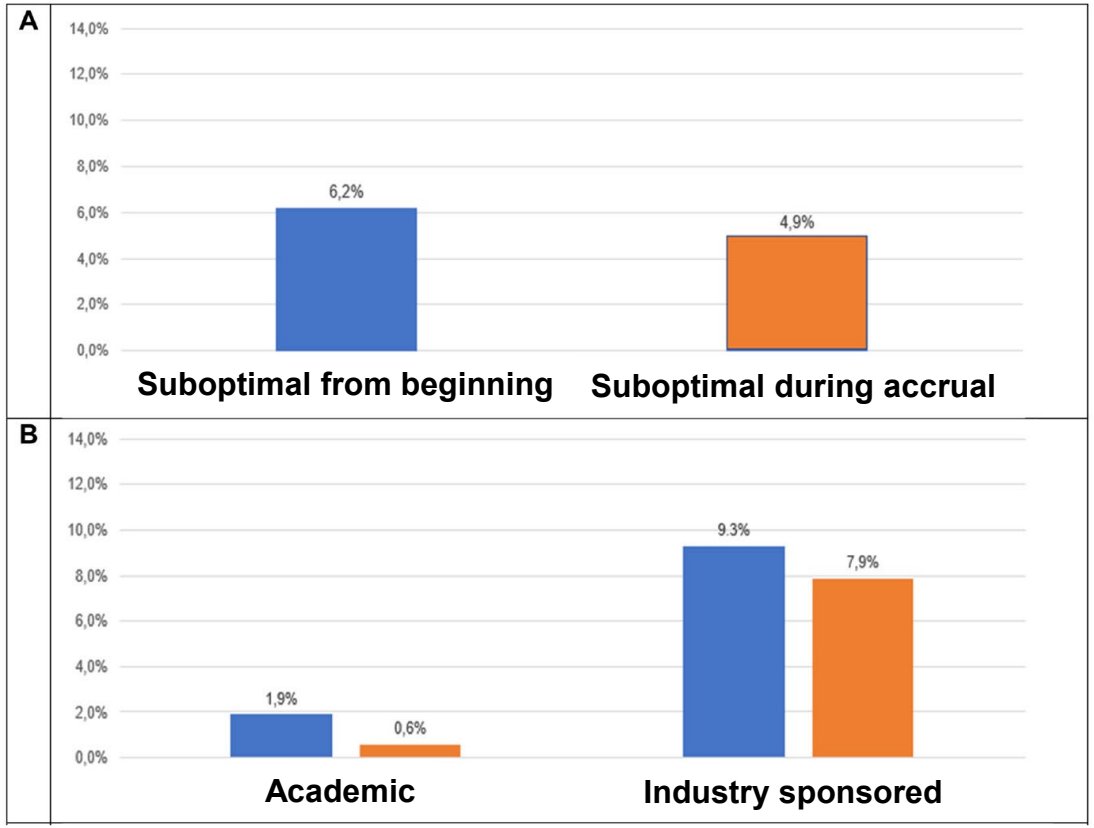


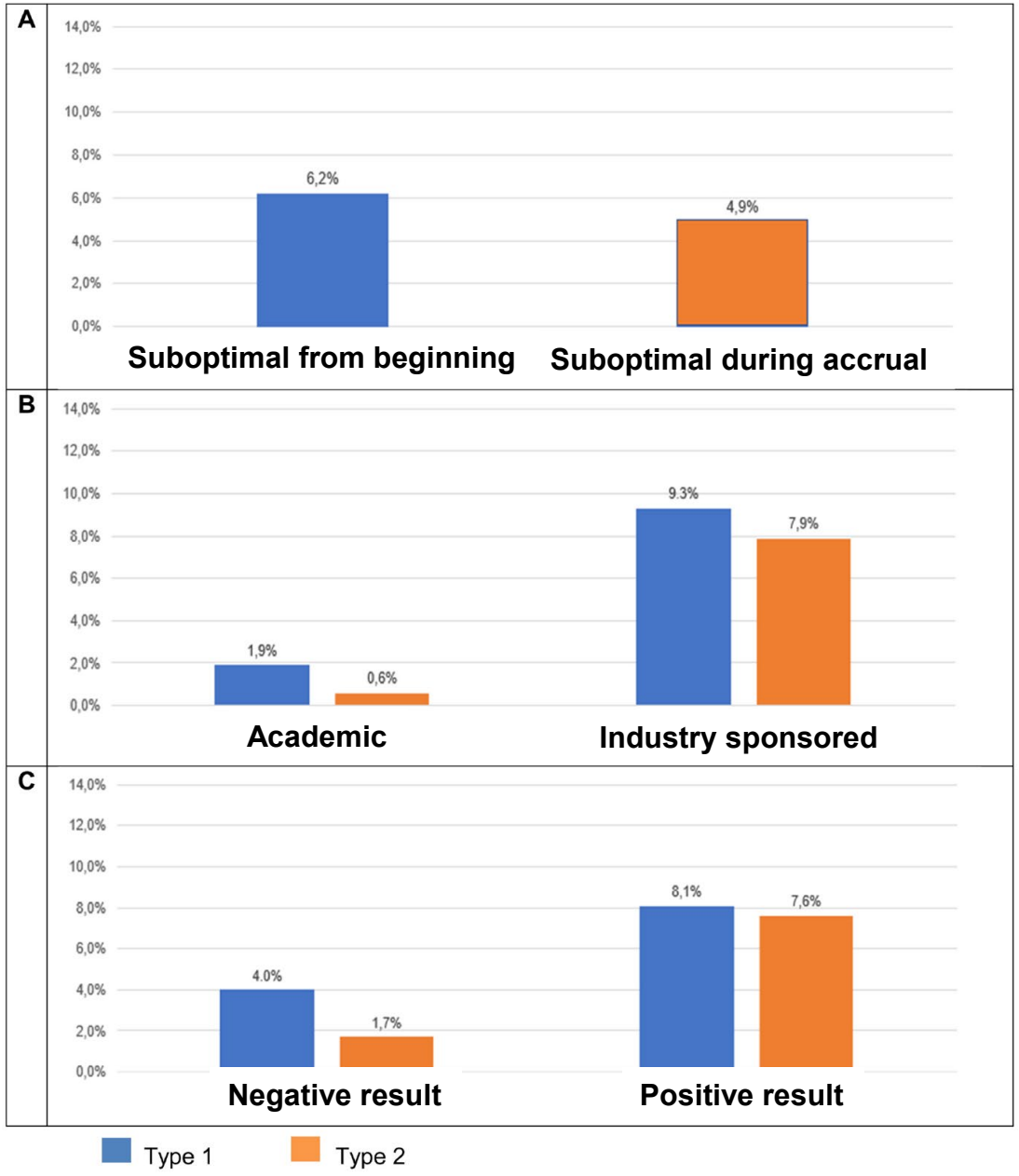
Fig. 2. Number of studies and number of patients assigned to control arm for each subgroup (studies with optimal control arm, studies with control arm suboptimal from the beginning, studies with control arm outdated before the end of the accrual).



Rossi A, et al. Eur J Cancer. 2023 Aug;189:112920.

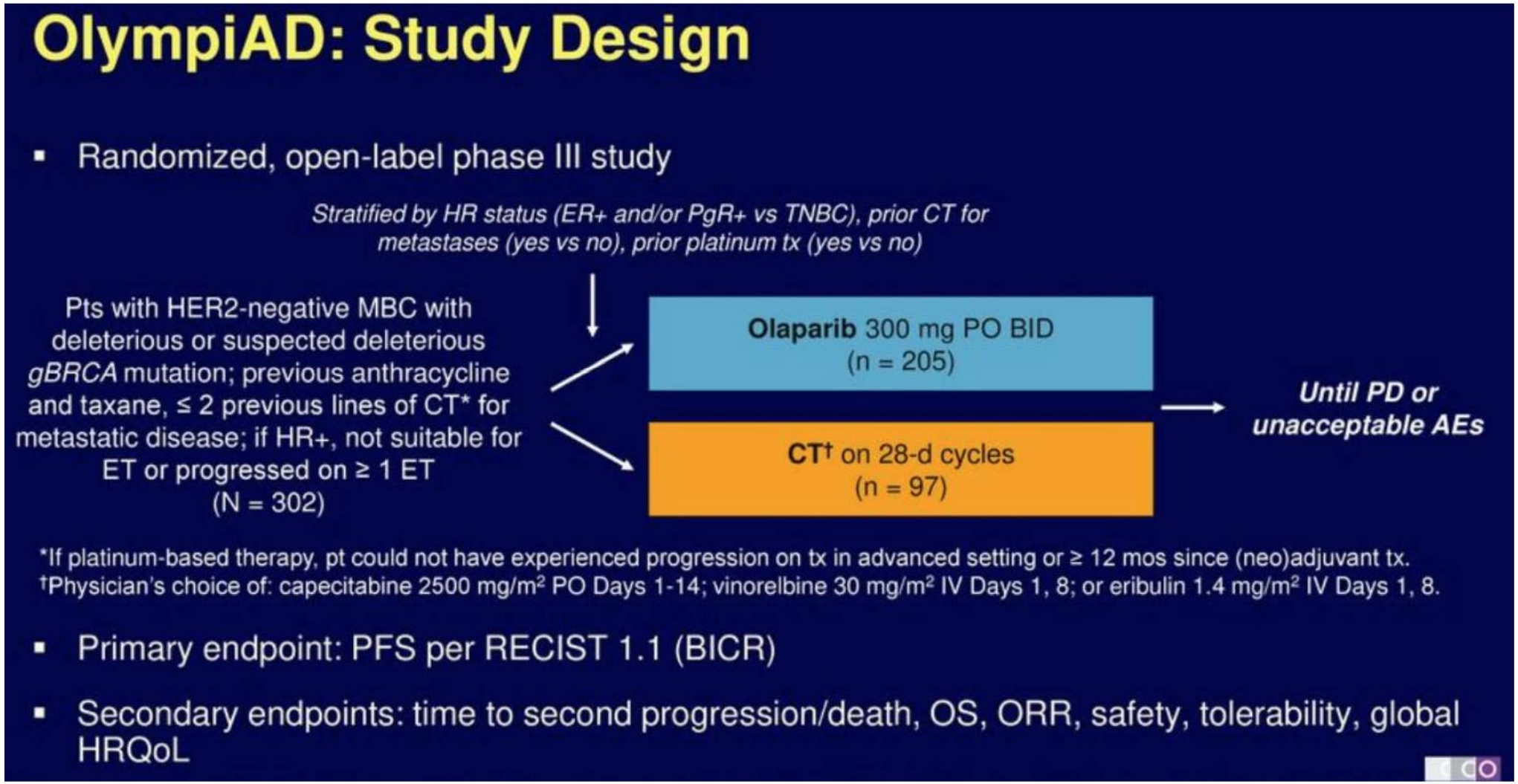


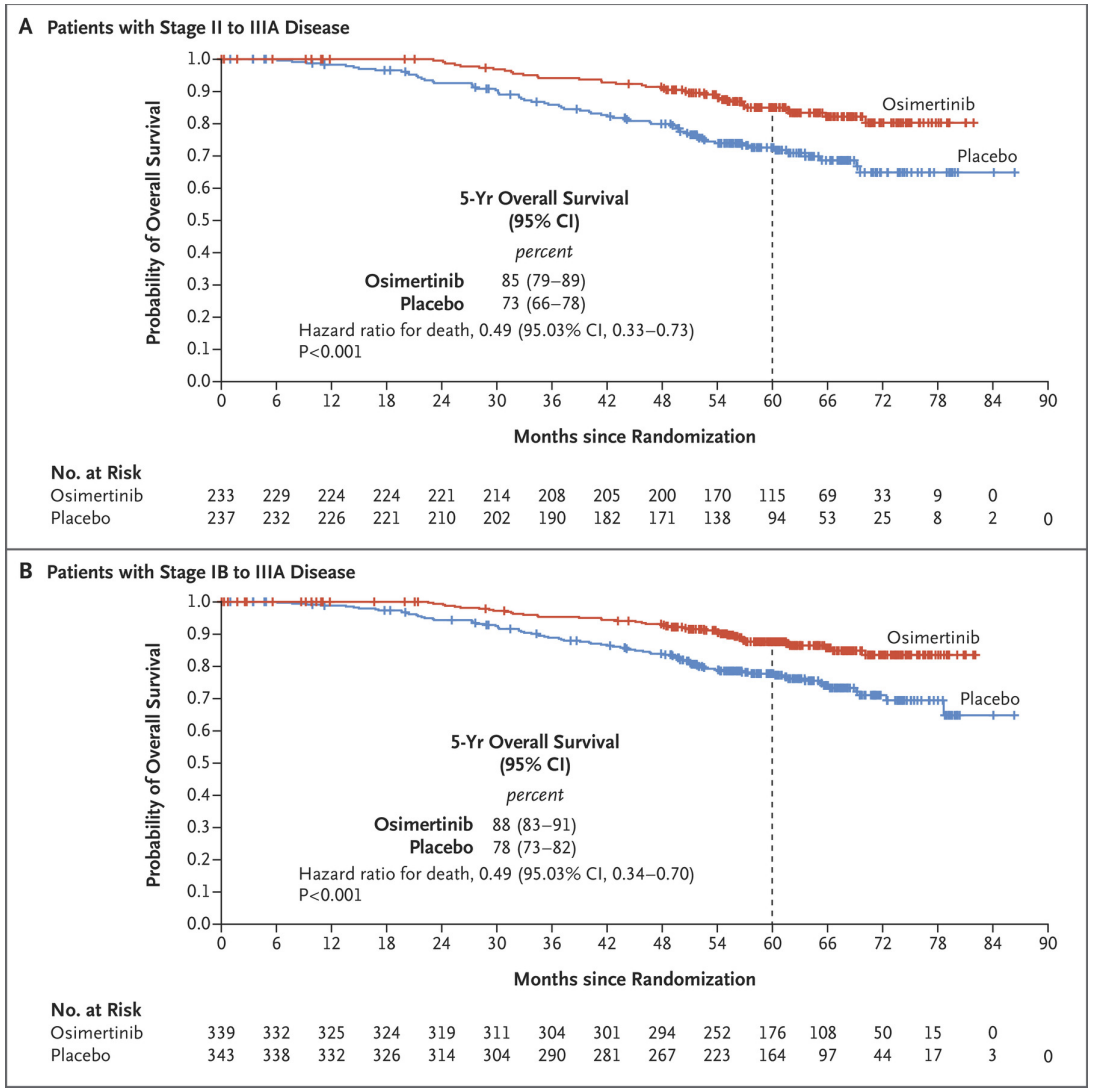
Rossi A, et al. Eur J Cancer. 2023 Aug;189:112920.



Rossi A, et al. Eur J Cancer. 2023 Aug;189:112920.

Il braccio di controllo: un esempio





Tsuboi M, et al; ADAURA Investigators. Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC. N Engl J Med. 2023 Jul 13;389(2):137-147.

Table S4. Summary of Subsequent Anticancer Treatments* Received in the Overall Population

	Osimertinib	Placebo
	number of patients (percent)	
All patients	**N = 339**	**N = 343**
Patients who received subsequent anticancer treatment*	n = 76 (22)	n = 184 (54)
EGFR-TKIs†	58 (76)	162 (88)
Osimertinib	31 (41)	79 (43)
Gefitinib	13 (17)	55 (30)
Afatinib	7 (9)	30 (16)
Erlotinib	6 (8)	24 (13)
Icotinib	2 (3)	15 (8)
Aumolertinib Mesilate	1 (1)	1 (1)
Aumolertinib	0	1 (1)
Dacomitinib	0	1 (1)
Other EGFR-TKI	0	1 (1)
Epitinib	0	1 (1)
Furmonertinib	0	1 (1)
Chemotherapy		
Platinum compounds†	20 (26)	43 (23)
Pemetrexed	13 (17)	37 (15)

Tsuboi M, et al; ADAURA Investigators. Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC. N Engl J Med. 2023 Jul 13;389(2):137-147.

Subsequent use of anticancer treatment in all the patients was 22% in the osimertinib group and 54% in the placebo group. The most common subsequent treatment in both groups was EGFR-TKIs (>75% of those who received subsequent treatment), most frequently osimertinib. A protocol amendment that allowed eligible patients to receive open-label osimertinib at recurrence was implemented after the primary analysis. The timing of this amendment, together with local practice, may have affected the frequency of osimertinib use as subsequent treatment. Data regarding the effect of subsequent osimertinib treatment on overall survival in the ADAURA trial are not available. Therefore, we cannot determine how subsequent osimertinib treatment in the post-recurrence context might have contributed to overall survival in the placebo group, although it is possible that this could have reduced the difference in overall survival seen between the osimertinib and placebo groups.

Tsuboi M, et al; ADAURA Investigators. Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC. N Engl J Med. 2023 Jul 13;389(2):137-147.

CORRESPONDENCE

Osimertinib in Resected *EGFR*-Mutated NSCLC

October 5, 2023
N Engl J Med 2023; 389:1341-1342
DOI: 10.1056/NEJMc2309385
Metrics

TO THE EDITOR

The results of the final analysis of the ADAURA trial, reported by Tsuboi et al. (July 13 issue),[1] show a relevant benefit in overall survival among patients with resected non–small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation who received adjuvant osimertinib. It is disappointing that less than half of the patients in the control group who had a relapse actually received osimertinib as the first subsequent treatment. The authors explain that this was due to the double-blind design, because the amendment allowing open-label osimertinib was implemented only after the primary analysis. Thus, many patients in the control (placebo) group were deprived of the most effective treatment for relapsed disease. The authors state that the use of osimertinib in some patients in the control group "could have reduced the difference in overall survival seen between the osimertinib and placebo groups." To be honest, the reasoning should be reversed, and this might have increased the difference in overall survival favoring the experimental group. Adequacy of the control group can be a problem not only when the treatment chosen as the comparator is not the reference standard[2] but also when subsequent lines of therapy are not effective.

Massimo Di Maio, M.D.
University of Turin, Turin, Italy
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Related Articles

ORIGINAL ARTICLE JUL 13, 2023
Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC
M. Tsuboi and Others

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The European Multidisciplinary Cancer Congress

Integrating basic & translational science, surgery, radiotherapy, medical oncology & care

STOCKHOLM, 23-27 SEPTEMBER 2011

Debate: This House Believes That Overall Survival is the Only Endpoint for Drug Approval
Stockholm, 27 September 2011

Overall survival is NOT the only endpoint for drug approval

Massimo Di Maio, MD
Medical oncologist
Clinical Trials Unit
National Cancer Institute, Napoli, Italy
dimaiomax@libero.it

A primary rationale for using PFS as an endpoint in cancer trials is that it could be considered as a **clinical benefit endpoint in itself**, provided that:

- **treatment effect is sufficiently large**
- **not only instrumental but clinical benefit**

VIEWPOINT

Biased Evaluation in Cancer Drug Trials—How Use of Progression-Free Survival as the Primary End Point Can Mislead

Ian F. Tannock, MD, PhD
Division of Medical Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada.

Gregory R. Pond, PhD
Department of Oncology, McMaster University, Hamilton, Ontario, Canada.

Christopher M. Booth, MD
Division of Cancer Care and Epidemiology, Departments of Oncology and Public Health Sciences, Queen's University, Kingston, Ontario, Canada.

The goal of any cancer treatment is to improve the duration and/or quality of patient survival. In recent years, only approximately 50% of the anticancer drugs approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have been shown to improve overall survival (OS) and/or a validated measure of quality of life (QoL). Most contemporary randomized clinical trials evaluating anticancer drugs use progression-free survival (PFS) as the primary end point.[1] Both the FDA and EMA accept a significant improvement in PFS for the registration of drugs for most types of cancer, although PFS is rarely a surrogate for OS. Designating PFS instead of OS as the primary end point may provide results more quickly: tumors progress before patients die, so "events" occur earlier, but the reduction in study time is usually modest.[2] For many new drugs that have been shown to improve PFS, subsequent analysis has demonstrated no improvement in OS or QoL, but these drugs are rarely withdrawn from the market.

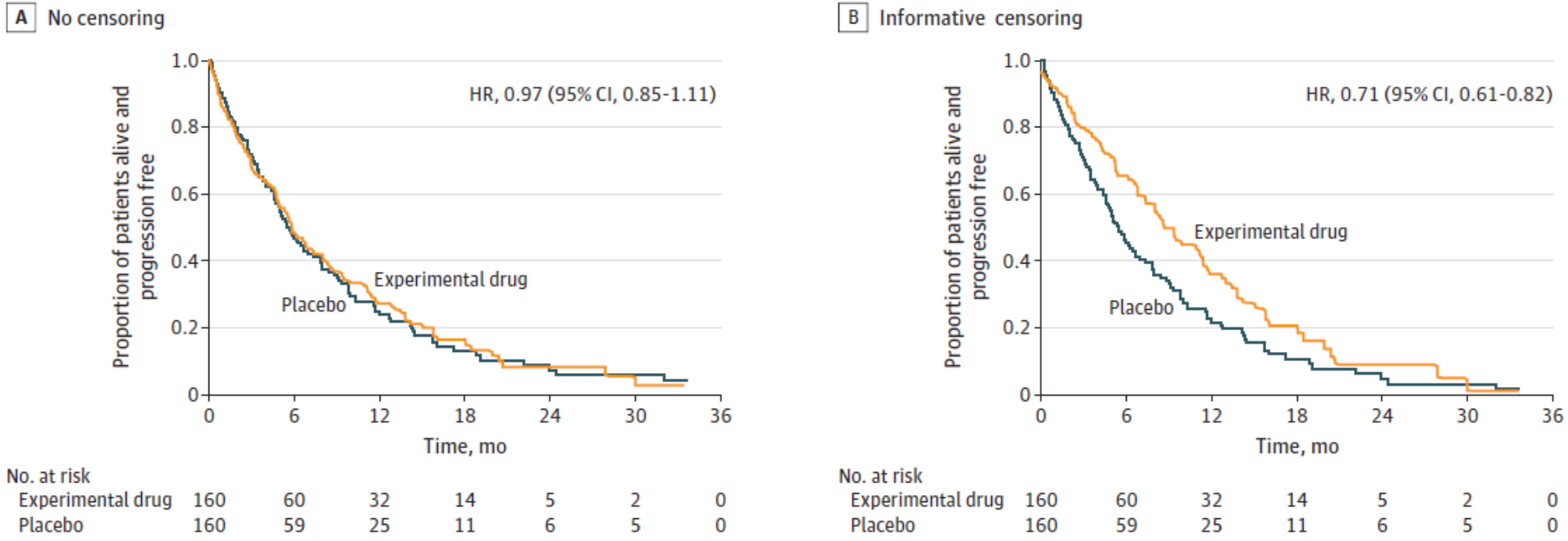
Important questions for clinicians interpreting trials with PFS as the primary end point include: (1) Can improvement in PFS itself indicate benefit? and (2) Are

gression-free disease to those at risk becomes a biased estimator, and the intention-to-treat principle is lost. The Figure illustrates how informative censoring can produce an artifactual difference between Kaplan-Meier PFS curves favoring the experimental group. In the Figure, A, the PFS curves are generated for a hypothetical clinical trial comparing the addition of an ineffective but nontoxic drug, or placebo, to standard therapy. Informative censoring did not occur in this hypothetical trial, and the PFS curves for the 2 groups are similar. In the Figure, B, the ineffective drug is hypothetically modeled to include toxicity such that 34 of 160 patients (21%) in the experimental group were censored before documenting progression. In this illustrative example, the censoring leads to a separation of the curves, with an apparent hazard ratio (HR) of 0.71 (95% CI, 0.61-0.82) in favor of the experimental treatment. Failure to account for informative censoring leads to bias and could even lead to the registration of an ineffective but toxic drug.

That uneven dropout rates can influence whether differences in PFS predict improvement in OS is illustrated by trials for women with estrogen receptor–positive advanced breast cancer. The BOLERO-2 (Breast

Tannock IF, Pond GR, Booth CM. Biased Evaluation in Cancer Drug Trials—How Use of Progression-Free Survival as the Primary End Point Can Mislead. *JAMA Oncol.* Published online March 10, 2022. doi:10.1001/jamaoncol.2021.8206

Figure. Kaplan-Meier Progression-Free Survival Plots for a Hypothetical Randomized Clinical Trial Comparing an Experimental Drug and a Placebo Added to Standard Treatment



A, The experimental drug is ineffective but nontoxic, and there is no censoring with 115 of 160 and 118 of 160 progression events in the experimental and control groups, respectively. The hazard ratio (HR) is 0.97 (95% CI, 0.85-1.11), indicating (appropriately) no benefit. B, The experimental drug is ineffective but toxic, so informative censoring occurs. In the experimental group, 34 patients (21% of total) withdraw from the trial before tumor progression is documented (censoring was modeled to occur within 6 months of randomization and 2 to 3 weeks before progression). With this change, progression events are recorded for only 81 patients in the experimental group but for 118 patients in the control group. The apparent median progression-free survival increases from 5.8 to 9.3 months for the experimental group, and the apparent HR is 0.71 (95% CI, 0.61-0.82).

Tannock IF, Pond GR, Booth CM. Biased Evaluation in Cancer Drug Trials—How Use of Progression-Free Survival as the Primary End Point Can Mislead. *JAMA Oncol.* Published online March 10, 2022. doi:10.1001/jamaoncol.2021.8206

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Ian Tannock et al,
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Lancet Oncology 2016; 16: e560-567

Underrating and underreporting of QoL and PROs in oncology

2012-2016

- 446 phase III trials
- 47.1% QoL not included among endpoints
- 38.1% QoL results collected but not presented in primary publications

Marandino et al, Ann Oncol 2018

Underrating and underreporting of QoL and PROs in oncology

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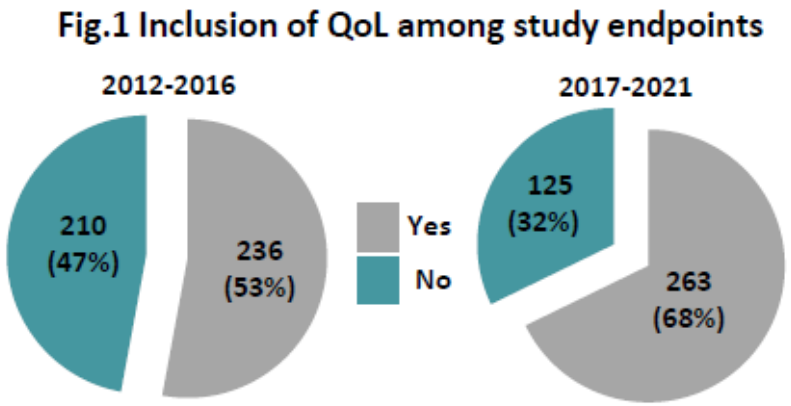
Marandino et al, Ann Oncol 2018

2017-2021

388 phase III trials



Marandino et al, BMJ Oncology 2023;2:e000021

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Marandino et al, Ann Oncol 2018

2017-2021

388 phase III trials

Fig.1 Inclusion of QoL among study endpoints

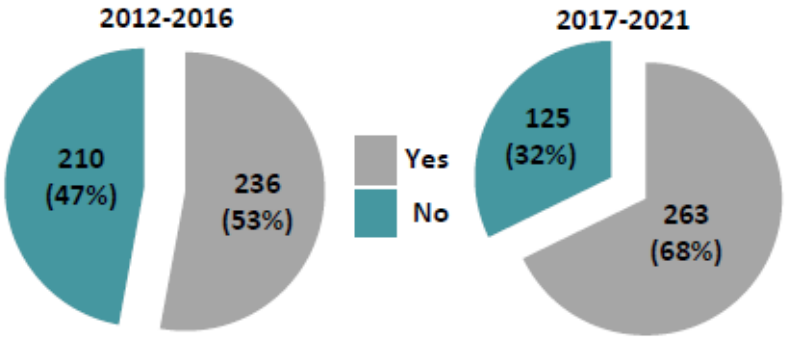
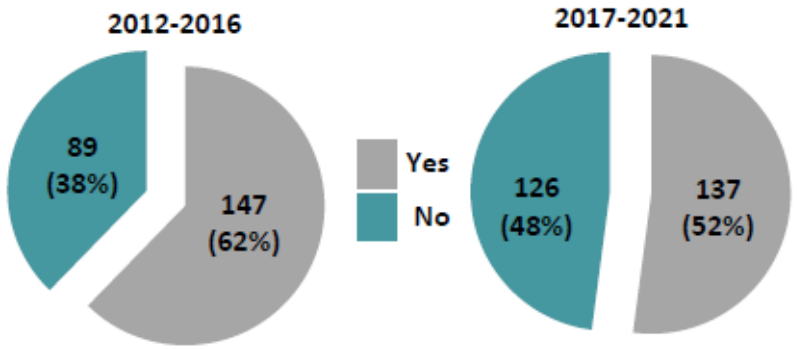
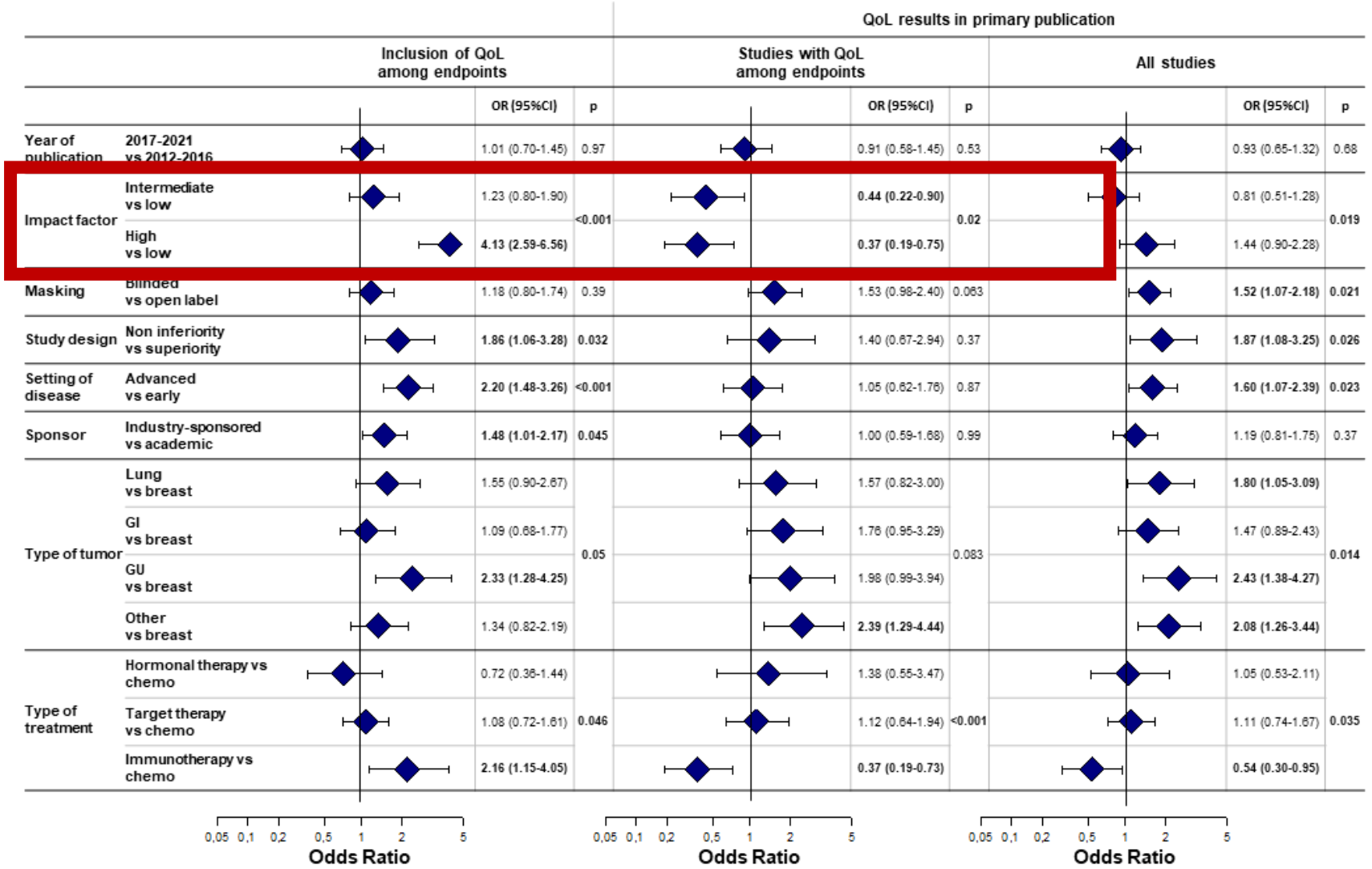


Fig.2 QoL results in primary study publication



Marandino et al, BMJ Oncology 2023;2:e000021



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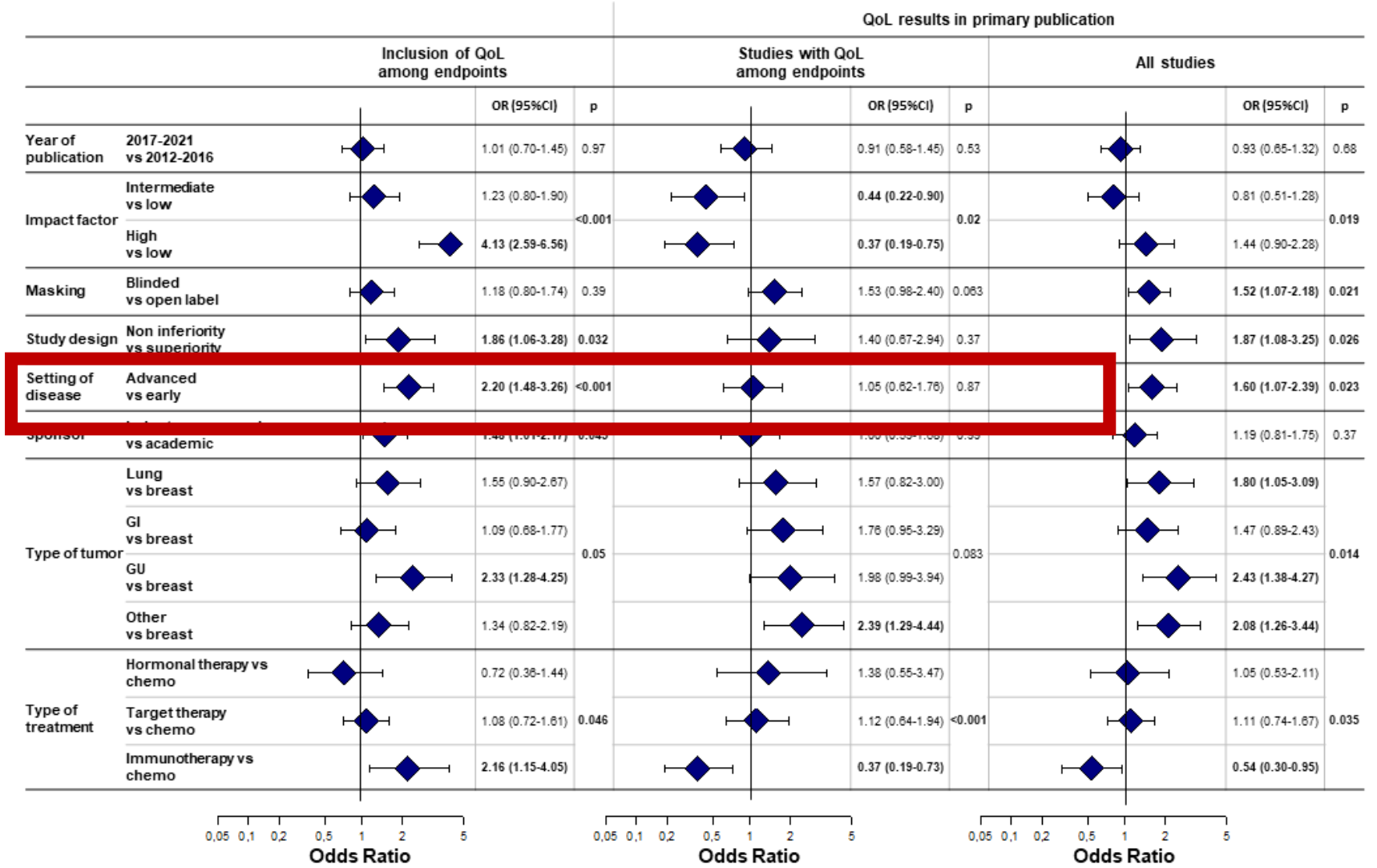
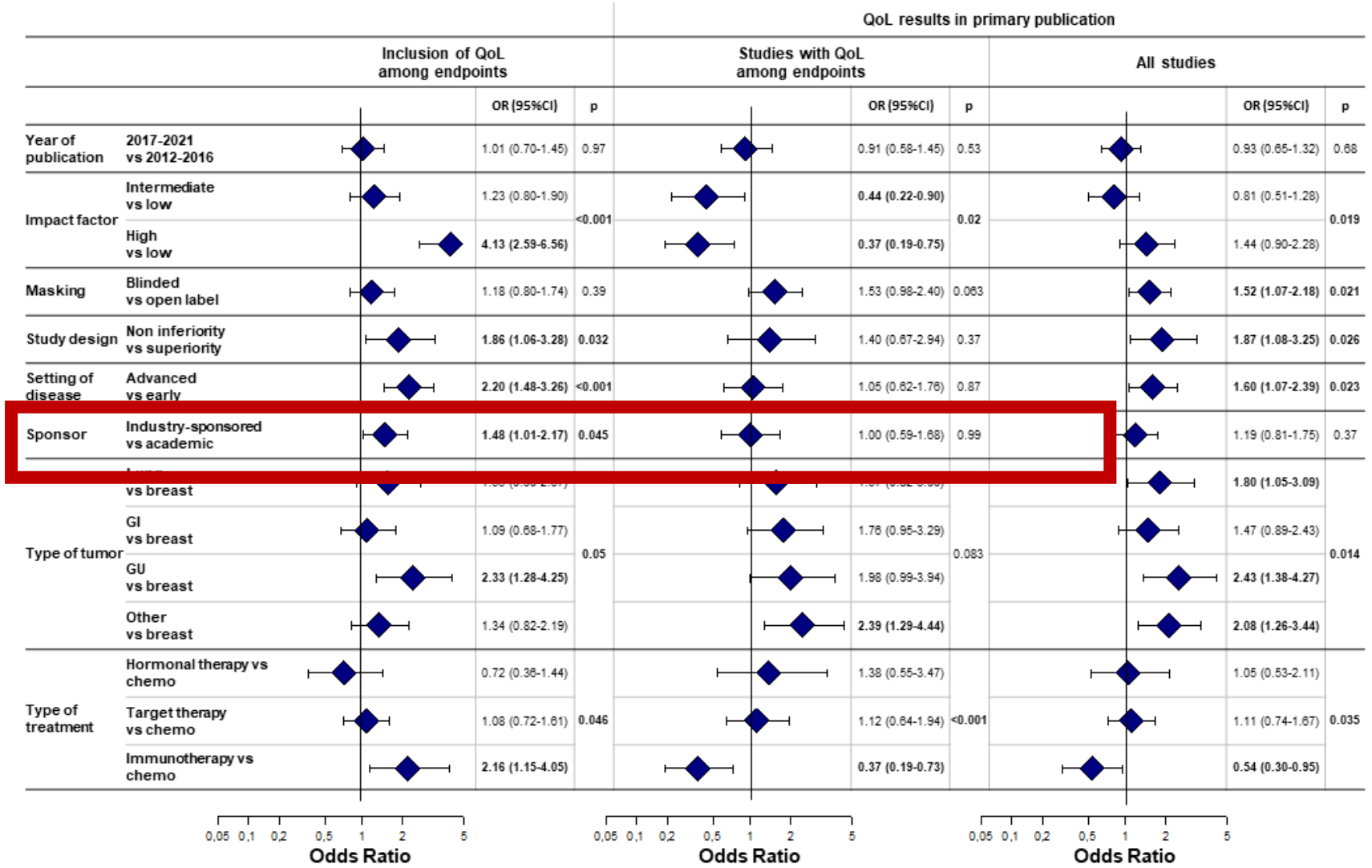
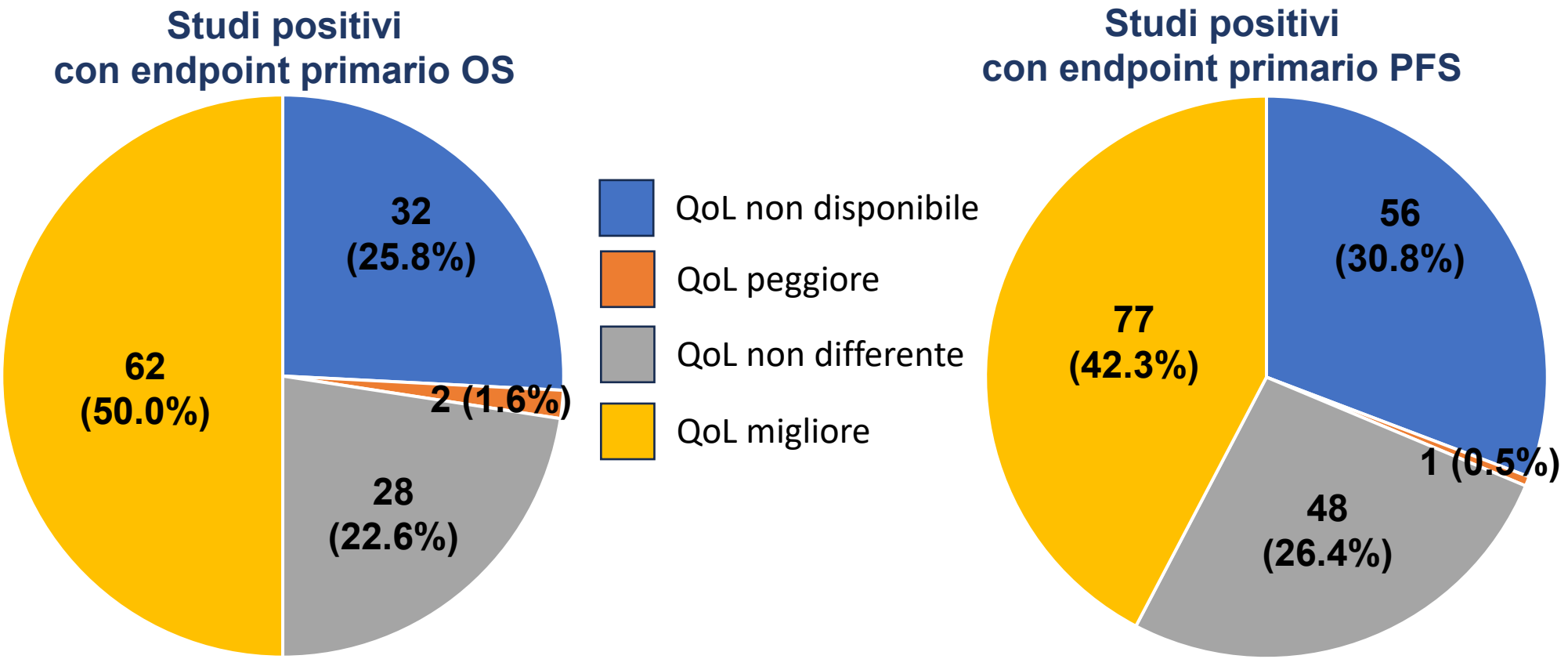


Marandino et al, BMJ Oncology 2023;2:e000021.



Marandino et al, BMJ Oncology 2023;2:e000021.

Associazione tra endpoint: OS, PFS, QoL



Paratore C, Schiavone R, …, Di Maio M
(unpublished data)

European Journal of Cancer 195 (2023) 113374

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original Research

Systematic review of adoption, reporting and impact of health-related quality of life in phase III non-inferiority trials of systemic oncology treatments

Sara Notarnicola [a,1], Lucrezia Zumstein [a,1], Jessica Paparo [a,1], Laura Marandino [b,2], Francesco Perrone [c], Massimo Di Maio [a,*,3,4]

[a] Department of Oncology, University of Turin, Ordine Mauriziano Hospital, Turin, Italy
[b] Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy
[c] Clinical Trial Unit, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italy

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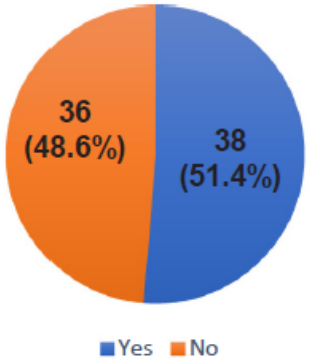
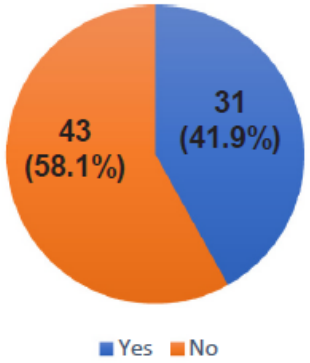
Trials demonstrating non-inferiority of the experimental arm (n=74)

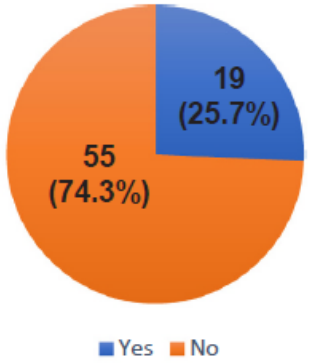
A. QoL included among endpoints



B. QoL results available in primary publication



C. QoL results supporting experimental treatment



Notarnicola S et al.
Eur J Cancer. 2023 Dec;195:113374. doi: 10.1016/j.ejca.2023.113374.

UNIVERSITÀ DI TORINO

Trials demonstrating non-inferiority of the experimental arm (n=74)

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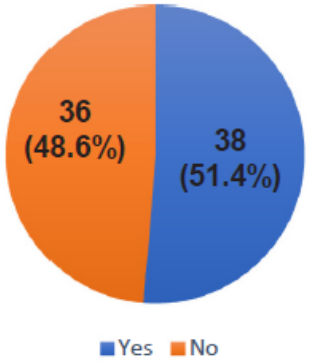
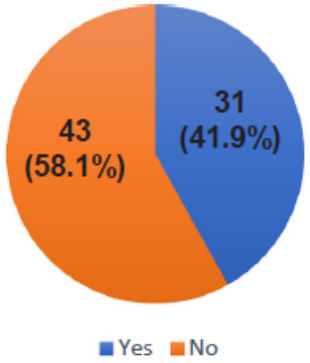
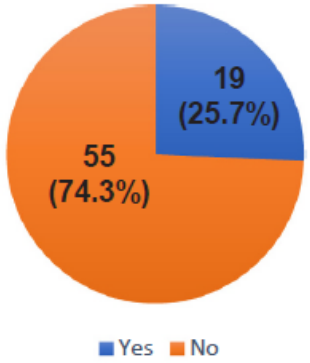


B. QoL results available in primary publication

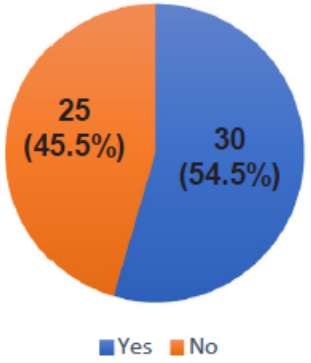


C. QoL results supporting experimental treatment

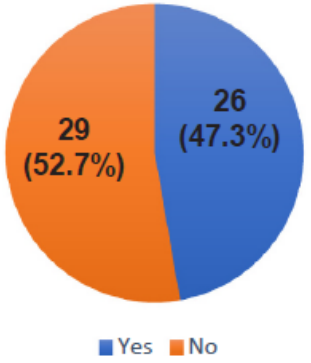


Trials testing the non-inferiority of different drugs, demonstrating non-inferiority of the experimental arm (n=55)

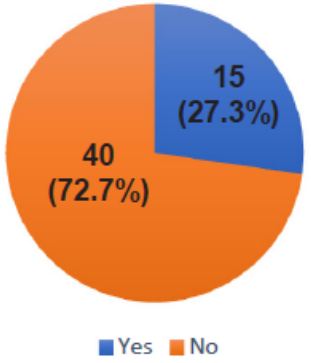
D. QoL included among endpoints



E. QoL results available in primary publication



F. QoL results supporting experimental treatment



Notarnicola S et al.
Eur J Cancer. 2023 Dec;195:113374. doi: 10.1016/j.ejca.2023.113374.

Validity of results

External validity

Are the results applicable to the real world?

Internal validity

Is the research conducted correctly?

Panel 1: Problems that might limit interpretation of randomised controlled trials

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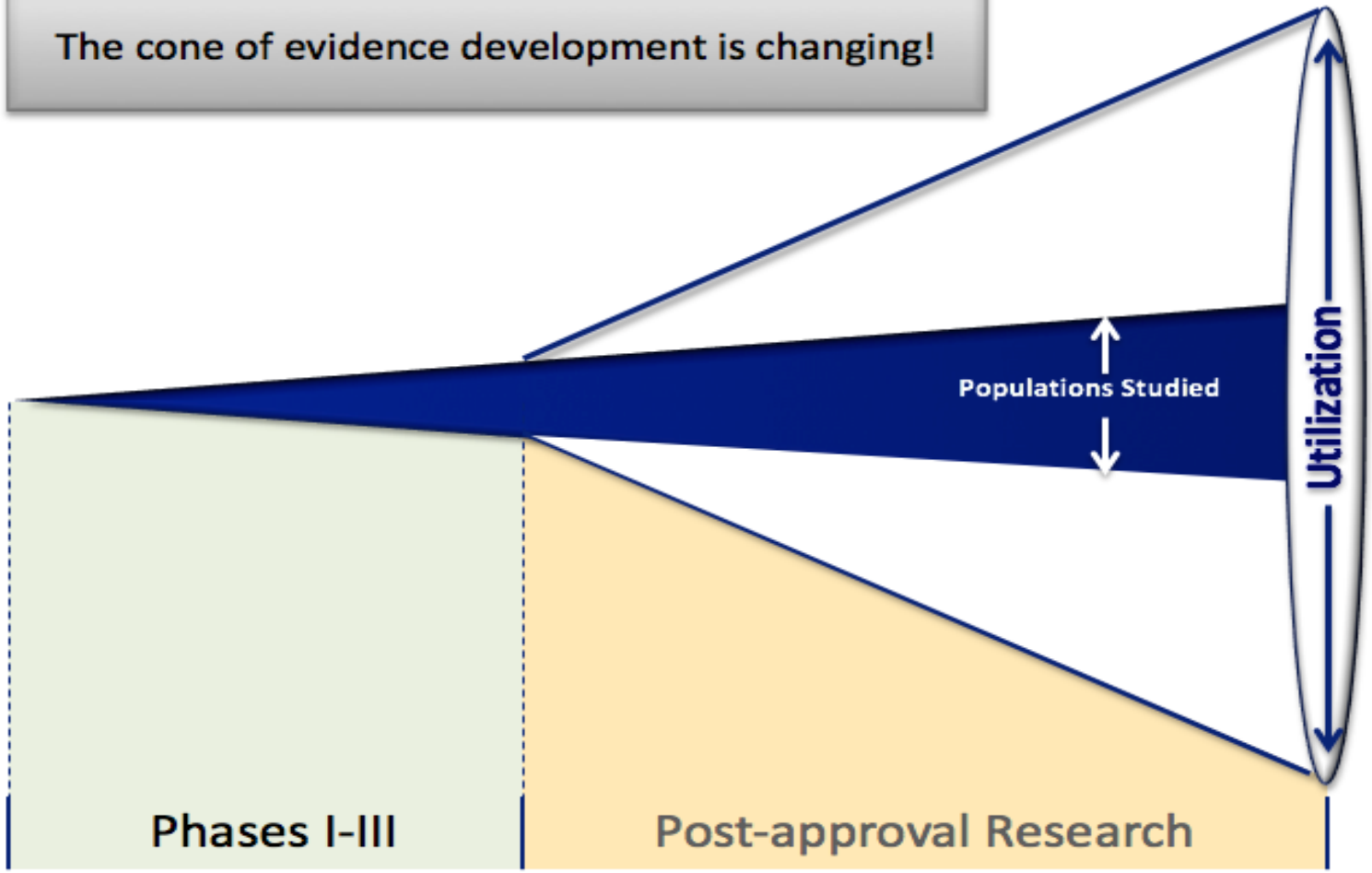
FDA analysis of Investigational New Drug Applications in 2015

- ~290 commercial IND submissions from 2015
  - 4% included pediatric patients
  - 60% required ECOG Performance status of 0-1
  - 77% excluded known, active or symptomatic CNS or brain metastases (47% allowed treated or stable brain metastases)
  - 84% excluded patients with known or active HIV (with only 2% allowing patients to enroll with adequate CD4 counts)
  - 74% excluded patients with history (or current) cardiovascular disease or risk (including angina pectoris, uncontrolled HTN, MI, CHF, arrhythmia)

Jin et al. JCO 2017

https://www.fda.gov/media/110332/download

The cone of evidence development is changing!



Variances in populations utilizing technology versus the populations studied

- Differing age groups (elderly, pediatrics)
- Race, ethnicity & gender variances
- Unstudied co-morbid conditions
- Differing concomitant drugs (including OTC)
- Lifestyle variances including smoking, dietary habits
- Differences in disease severity
- Varying levels of compliance

HealthCare

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Commentary

Real-World Evidence in Oncology: Opportunities and Limitations

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Real-world evidence • Clinical trials • Cancer treatments

Traditionally, randomized controlled clinical trials (RCTs) have been considered the highest level of evidence to define the efficacy of treatments, before their adoption in clinical practice. However, in oncology, like in other fields of medicine, the analysis of real-world evidence (RWE) to answer clinical and

and treat in daily clinical practice [4, 5]. This is due to stringent eligibility criteria, such as good performance status and absence of clinically relevant concomitant diseases. For instance, the analysis of the Investigational New Drugs applications submitted in 2015 to the U.S. Food and Drug Administration, for

ESMO daily REPORTER

An ESMO study reveals that poor quality of real-world data from oncology studies is still an issue

21 Oct 2023 | Targeted Therapy | Therapy | Clinical Research | Cancer Research | ESMO Congress 2023

ESMO Congress 2023 taking place in Madrid, Spain (20-24 October)

Scarcity of prospective data was reported as well as a limited use of real-world evidence as definitive evidence to regulatory approval decisions of targeted therapies in Europe

https://dailyreporter.esmo.org/esmo-congress-2023/digital-oncology/an-esmo-study-reveals-that-poor-quality-of-real-world-data-from-oncology-studies-is-still-an-issue

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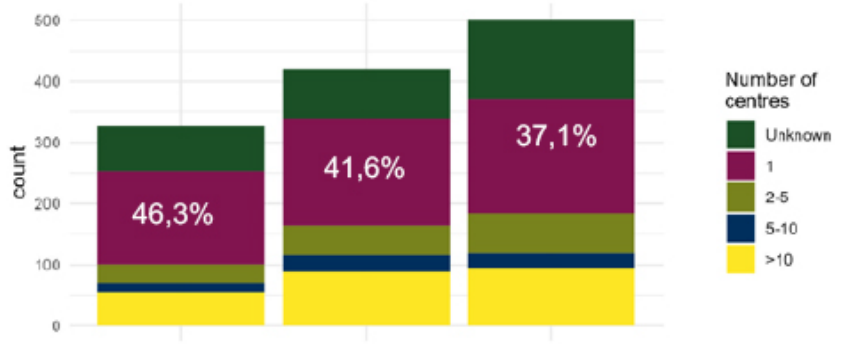
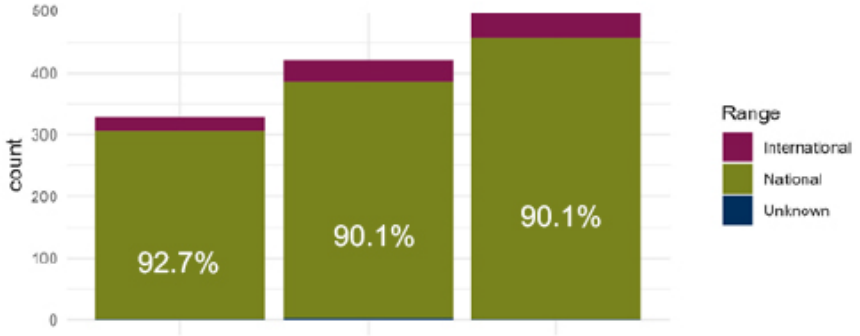
Results: Limiting Factors

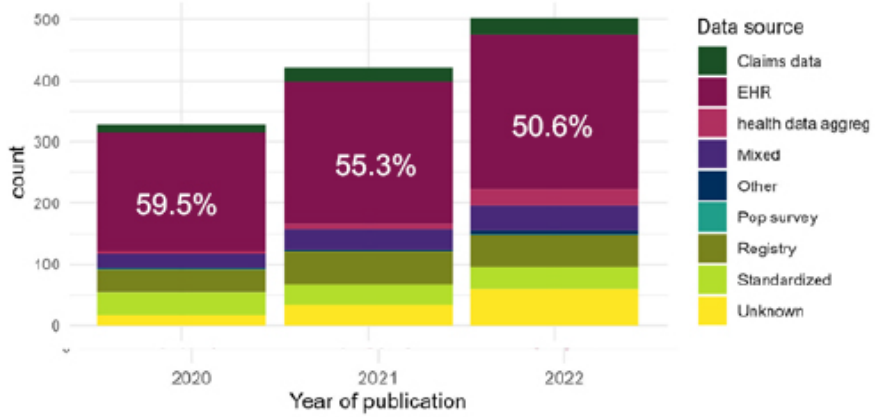
Number of Centre(s)



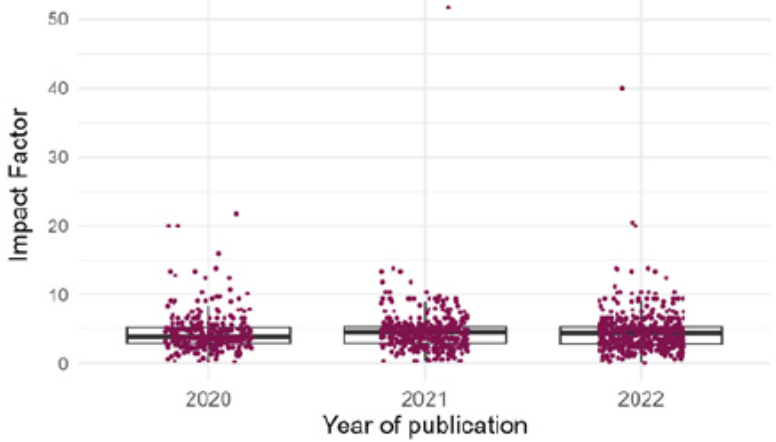
Study Range



Data Source



Impact Factor



Analysis of RWE publications on oncology targeted therapies (2020–2022) (ESMO Congress 2023, Abstract 1689O)

European Journal of Cancer 155 (2021) 136–144

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study

Jemma M. Boyle [a,1], Gemma Hegarty [b,1], Christopher Frampton [c], Elizabeth Harvey-Jones [d], Joanna Dodkins [d], Katharina Beyer [e], Gincy George [e], Richard Sullivan [d,f], Christopher Booth [g,2], Ajay Aggarwal [a,d,f,*,2]

Boyle et al, European Journal of Cancer 2021; 153:136-144

Table 1
Characteristics of the RWD studies (n = 293 for 45 drug indications) identified for FDA and EMA approved indications, including RWD studies included in the survival analyses (n = 224 for 37 drug indications).

	Observational RWD Studies		Observational RWD studies included in survival analyses	
	No.	**%**	**No.**	**%**
Country				
Italy	52	17.7	44	19.6
Japan	30	10.2	22	9.8
China	28	9.6	22	9.8
USA	26	8.9	16	7.1
France	22	7.5	18	8.0
Spain	15	5.1	12	5.4
Canada	14	4.8	9	4.0
South Korea	13	4.4	12	5.4
UK	8	2.7	6	2.7
Netherlands	8	2.7	8	3.6
Poland	7	2.4	5	2.2
Multi-country	14	4.8	9	4.0
Other individual country	56	19.1	41	18.3
Study Type				
Prospective	50	17.1	39	17.4
Retrospective	242	82.6	184	82.1
Unknown	1	0·3	1	0·4
Multicentre				
Yes	180	61.4	135	60.3
No	112	38.2	88	39.3
Unknown	1	0·3	1	0·4

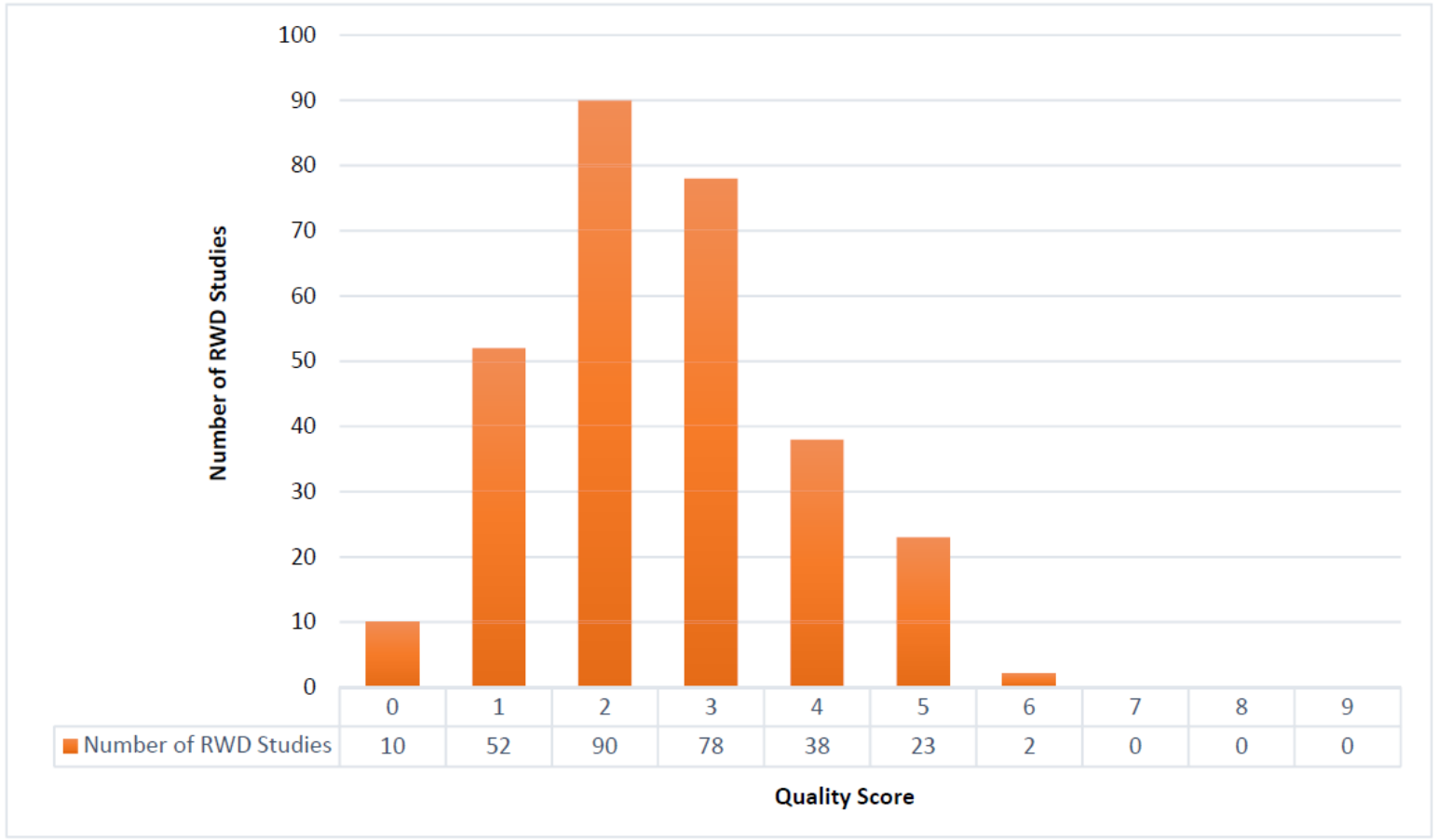


Fig. 1. Histogram of the distribution of total scores for RWD studies appraised using the Newcastle Ottawa Scale.

Le analisi di sottogruppo: Medicina di precisione o tortura dei dati?

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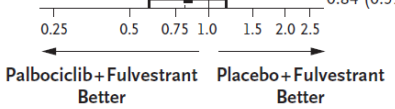
B Subgroup Analyses

Subgroup	No. of Patients (%)	Hazard Ratio for Death (95% CI)	Median Overall Survival (95% CI)		P Value for Interaction
			Palbociclib+ fulvestrant	Placebo+ fulvestrant	
			mo		
All patients					
Stratified analysis	521 (100)	0.81 (0.64–1.03)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Unstratified analysis	521 (100)	0.79 (0.63–1.00)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Sensitivity to previous hormonal therapy					0.12
Yes	410 (79)	0.72 (0.55–0.94)	39.7 (34.8–45.7)	29.7 (23.8–37.9)	
No	111 (21)	1.14 (0.71–1.84)	20.2 (17.2–26.4)	26.2 (17.5–31.8)	
Site of metastatic disease					0.44
Visceral	311 (60)	0.85 (0.64–1.13)	27.6 (24.4–31.2)	24.7 (20.8–31.8)	
Nonvisceral	210 (40)	0.69 (0.46–1.04)	46.9 (39.3–NE)	35.4 (24.6–NE)	
Menopausal status at study entry					0.25
Postmenopausal	413 (79)	0.73 (0.57–0.95)	34.8 (28.8–40.1)	27.1 (22.8–32.1)	
Premenopausal or perimenopausal	108 (21)	1.07 (0.61–1.86)	38.0 (24.4–NE)	38.0 (22.2–NE)	
Age					0.04
<65 yr	392 (75)	0.91 (0.70–1.20)	31.4 (27.4–39.3)	29.7 (24.0–38.0)	
≥65 yr	129 (25)	0.52 (0.33–0.82)	39.7 (30.7–47.0)	23.8 (20.0–33.8)	
Race or ethnic group					0.38
White	385 (74)	0.78 (0.60–1.01)	31.7 (27.6–38.9)	26.2 (21.4–32.1)	
Asian	105 (20)	1.04 (0.57–1.93)	43.7 (28.8–NE)	41.7 (29.7–NE)	
Black or other	29 (6)	0.47 (0.16–1.32)	37.3 (23.8–NE)	19.7 (4.4–NE)	
Hormone-receptor status					0.70
ER-positive and PR-positive	351 (67)	0.77 (0.57–1.03)	39.3 (32.0–45.7)	31.8 (24.0–39.1)	
ER-positive and PR-negative	142 (27)	0.86 (0.56–1.32)	27.6 (22.0–38.9)	24.3 (17.5–37.5)	
Disease-free interval					0.08
≤24 mo	62 (12)	1.31 (0.71–2.44)	19.9 (15.6–27.6)	20.3 (9.3–42.2)	
>24 mo	292 (56)	0.70 (0.52–0.96)	39.3 (31.7–44.5)	29.5 (22.8–38.1)	
Previous chemotherapy					0.66
Neoadjuvant or adjuvant treatment only	214 (41)	0.81 (0.56–1.17)	36.6 (28.9–42.3)	27.4 (22.2–39.5)	
Treatment for metastatic disease	177 (34)	0.91 (0.63–1.32)	25.6 (21.4–30.1)	26.2 (20.0–37.5)	
None	130 (25)	0.68 (0.41–1.15)	46.2 (36.5–NE)	29.7 (22.8–NE)	
Previous lines of therapy for metastatic disease					0.88
0	114 (22)	0.70 (0.43–1.14)	36.1 (27.6–43.7)	24.7 (19.5–34.6)	
1	225 (43)	0.86 (0.60–1.22)	38.0 (27.7–46.5)	33.8 (23.5–41.4)	
2	131 (25)	0.76 (0.48–1.22)	30.0 (23.0–40.1)	24.3 (20.0–29.7)	
≥3	51 (10)	0.64 (0.29–1.40)	34.8 (26.1–NE)	27.1 (5.3–NE)	
ESR1 mutation status					0.60
Positive	106 (20)	0.69 (0.43–1.12)	35.6 (23.6–42.0)	24.6 (19.7–33.0)	
Negative	289 (55)	0.85 (0.61–1.19)	36.5 (28.0–43.1)	31.8 (22.8–39.1)	
PIK3CA mutation status					0.64
Positive	133 (26)	0.74 (0.48–1.14)	28.6 (25.3–39.3)	22.2 (15.7–29.5)	
Negative	262 (50)	0.84 (0.59–1.18)	38.8 (28.9–44.5)	33.0 (24.3–41.6)	



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L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

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A che servono le analisi di sottogruppo?

- In uno studio con risultato complessivo positivo:
  - Il risultato è omogeneo in tutti i sottogruppi o ci sono alcuni pazienti che sembrano avere un beneficio minore?

- In uno studio con risultato complessivo negativo:
  - Ci sono sottogruppi che sembrano beneficiarsi del trattamento sperimentale?

Subgroup analyses in randomized phase III trials of systemic treatments in advanced solid tumours: a systematic review of trials published between 2017 and 2020

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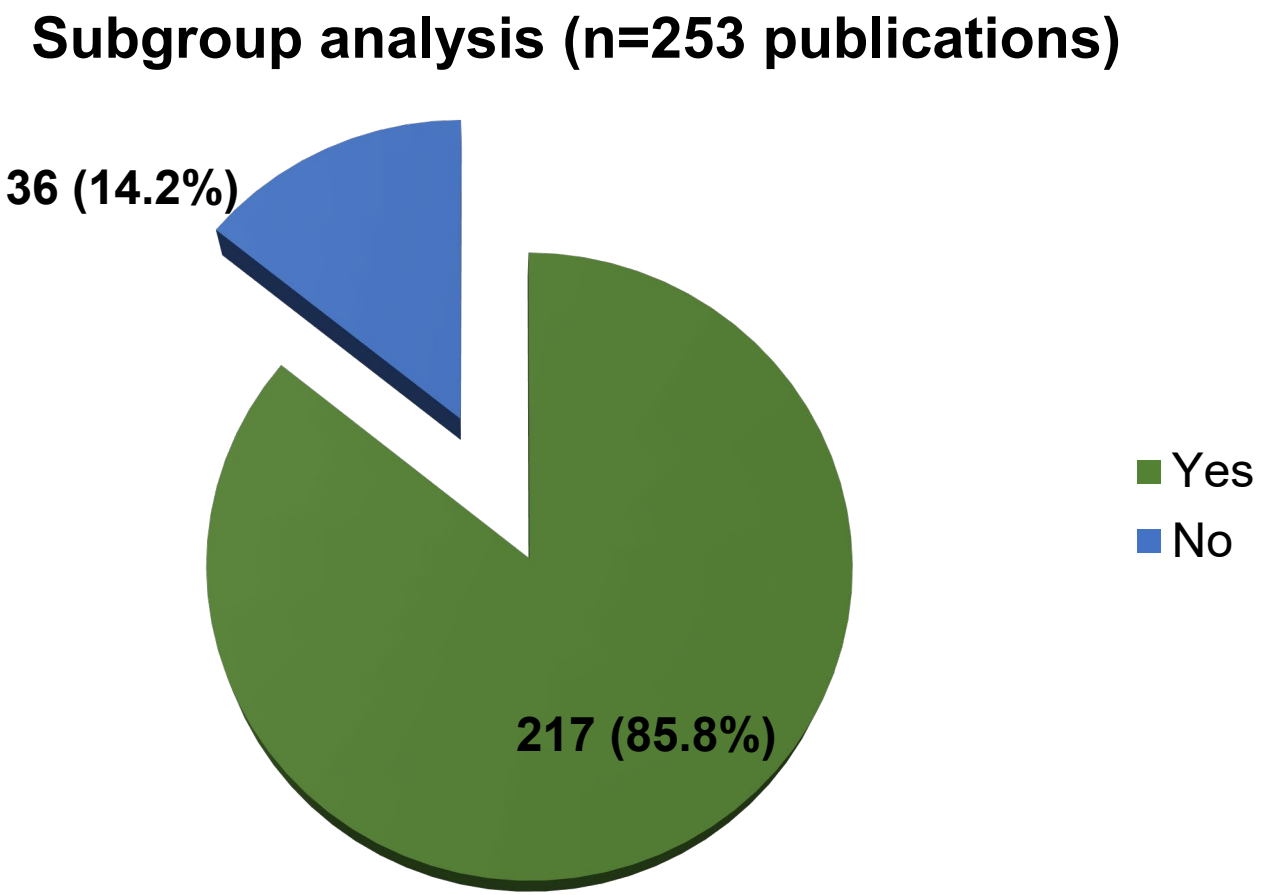
Inclusion criteria

- Phase III trials
- First publication Jan 2017 – Dec 2020
- Adult patients with solid tumors
- Locally advanced / metastatic cancer
- Systemic treatments
- Full publication in English

Paratore, Zichi et al, ESMO Open 2022 Dec;7(6):100593.

Subgroup analyses in randomized phase III trials of systemic treatments in advanced solid tumours: a systematic review of trials published between 2017 and 2020



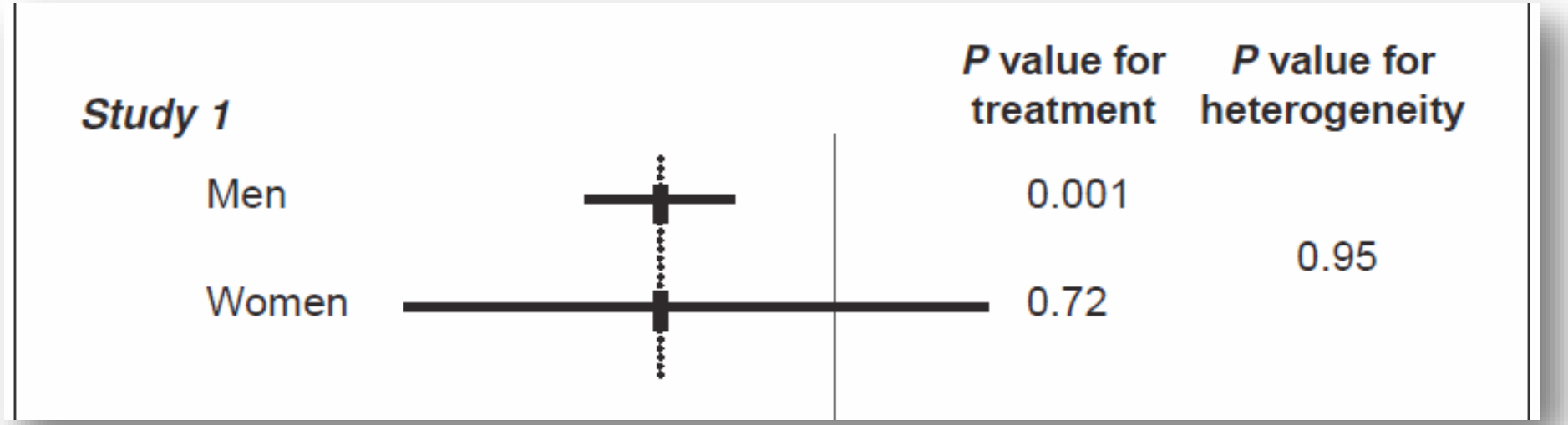
Paratore, Zichi et al, ESMO Open 2022 Dec;7(6):100593.

Subgroup analyses in randomized phase III trials of systemic treatments in advanced solid tumours: a systematic review of trials published between 2017 and 2020

	Number of variables	Number of subgroups
Forest plot of primary endpoint		
Median	**9**	**19**
Range	**(3 – 19)**	**(6 – 78)**
Forest plot of secondary endpoint		
Median	**8.5**	**20**
Range	**(1 – 19)**	**(2 – 43)**

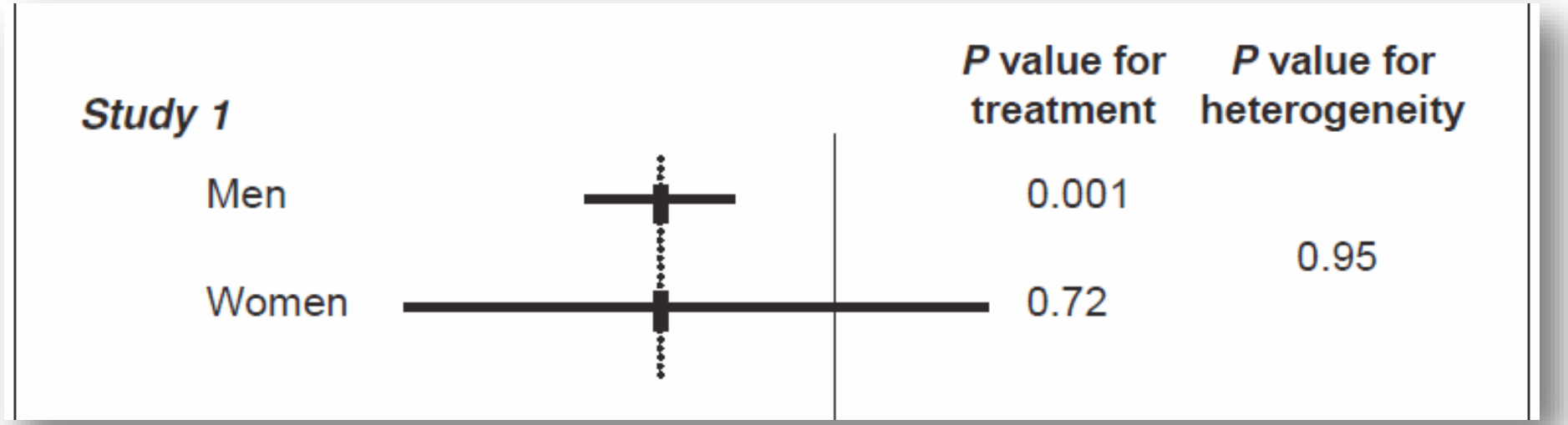
Paratore, Zichi et al, ESMO Open 2022 Dec;7(6):100593.

Come interpretare correttamente le analisi di sottogruppo?



Simes RJ et al, MJA 2004

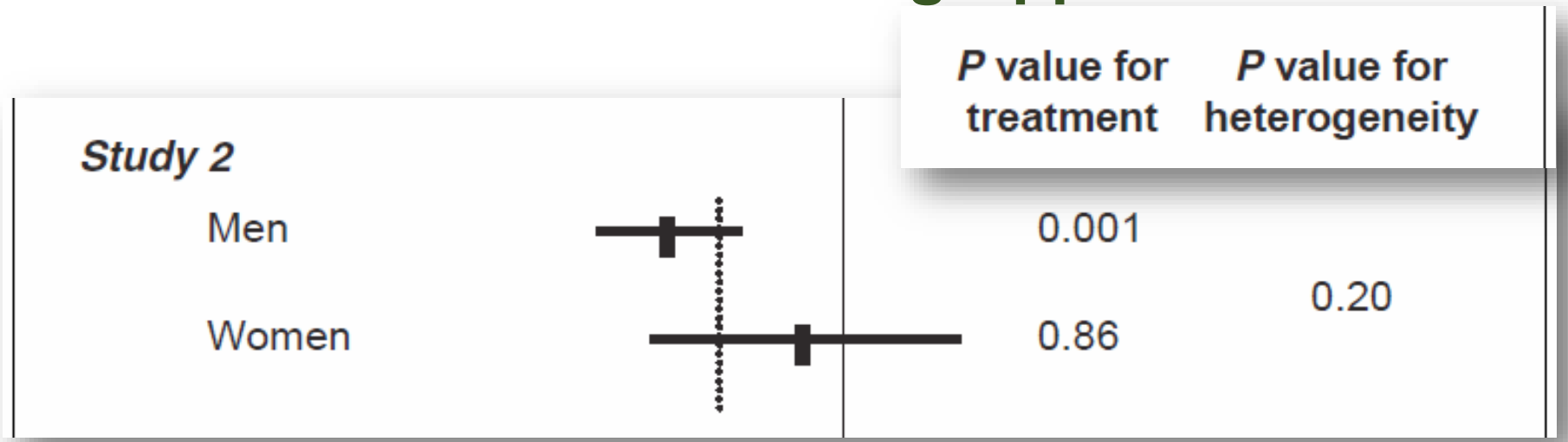
Come interpretare correttamente le analisi di sottogruppo?



In casi come questo, **NON E' CORRETTO AFFERMARE** che il trattamento sperimentale è più efficace negli uomini ma non nelle donne!

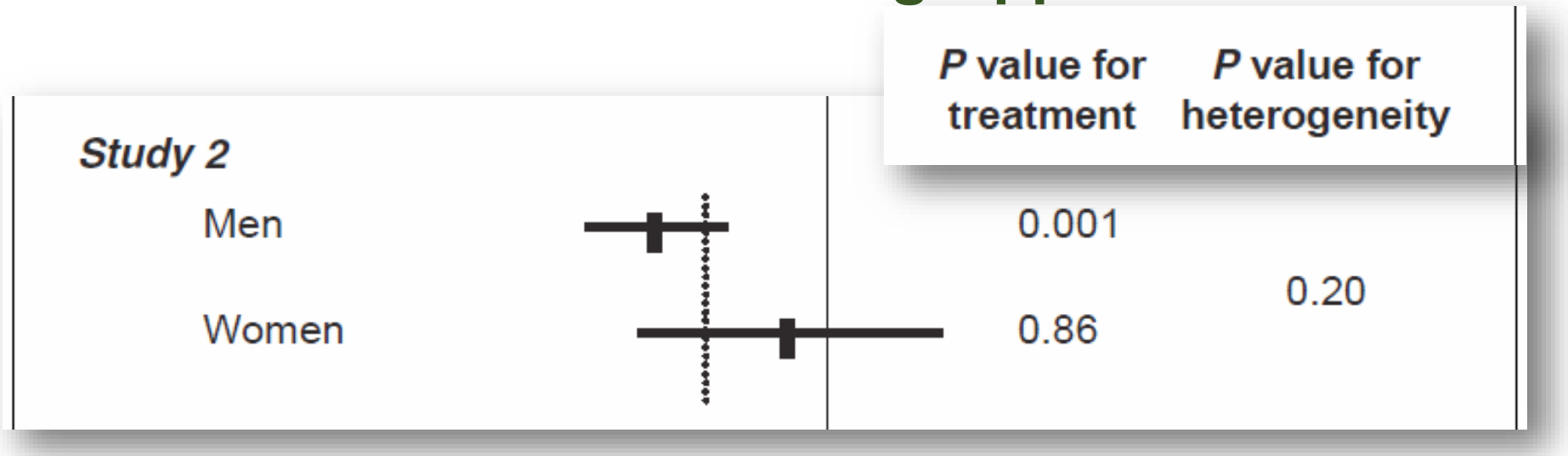
Simes RJ et al, MJA 2004

Come interpretare correttamente le analisi di sottogruppo?



Simes RJ et al, MJA 2004

Come interpretare correttamente le analisi di sottogruppo?

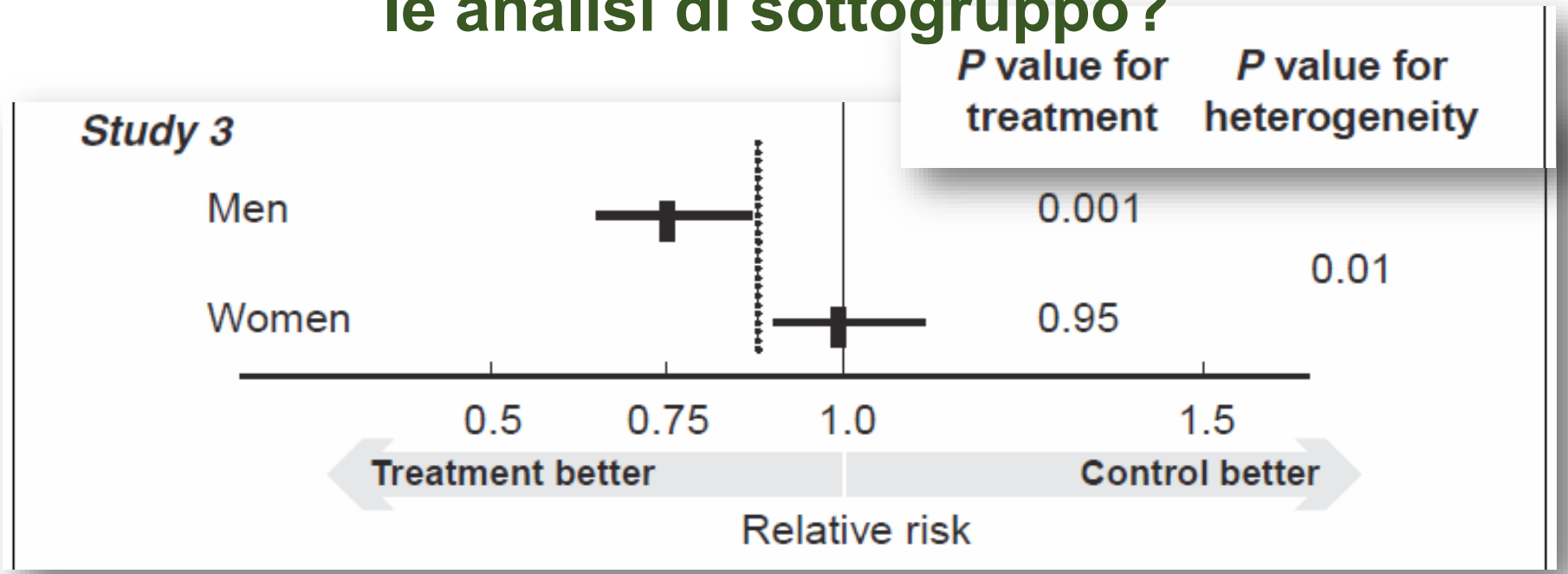


In casi come questi, è legittimo sospettare che l'effetto del trattamento possa essere diverso…

…ma sfortunatamente, non possiamo escludere che la differenza osservata sia dovuta al caso!

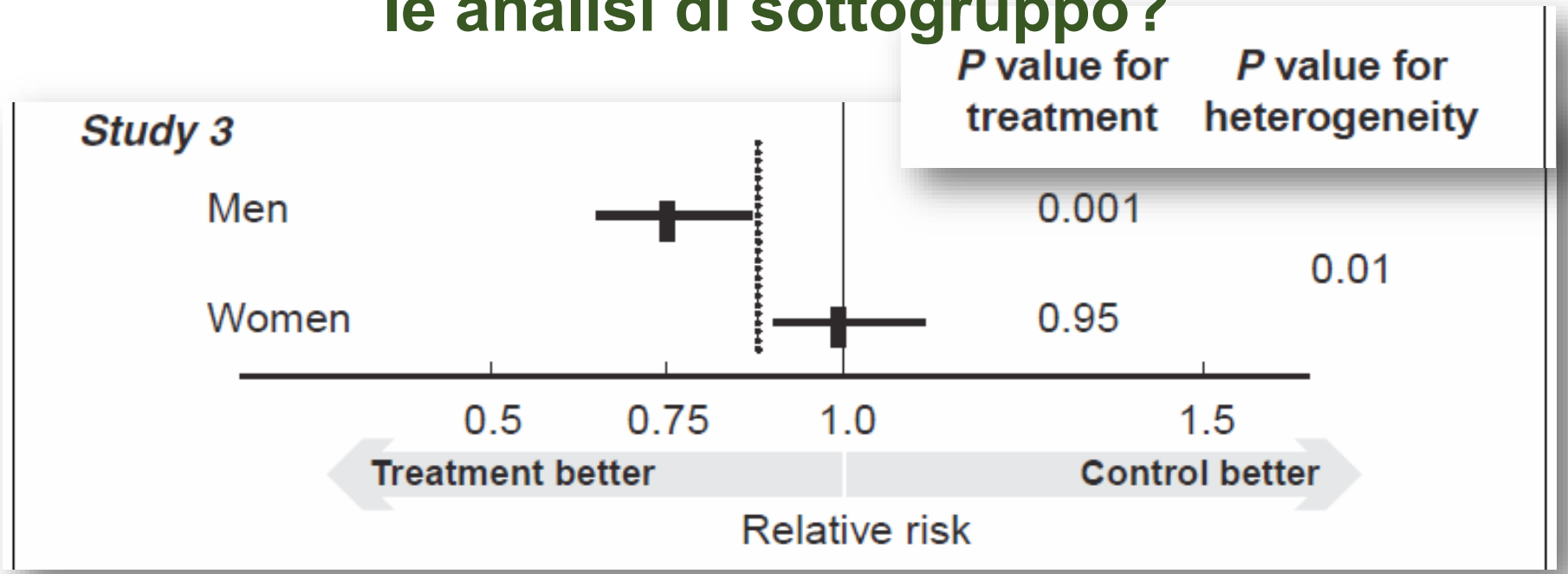
Simes RJ et al, MJA 2004

Come interpretare correttamente le analisi di sottogruppo?



Simes RJ et al, MJA 2004

Come interpretare correttamente le analisi di sottogruppo?



In casi come questo, è legittimo discutere l'eterogeneità di efficacia tra maschi e femmine.

Il test di interazione ci dice che è improbabile che la differenza sia dovuta al caso.

Approccio critico all'evidenza scientifica
Take home messages

- Molti (tutti?) punti cruciali dell'interpretazione e dell'analisi vanno affrontati in fase di disegno di studio.
- La validità del braccio di controllo (anche in termini di trattamenti ottimali post-progressione) ha importanti implicazioni metodologiche ed etiche.
- La scelta degli endpoint dovrebbe essere orientata alla dimostrazione di beneficio clinico.
- Nell'era dell'oncologia di precisione, le analisi di sottogruppo sono legittime, ma vanno interpretate con cautela.

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Approccio critico all'evidenza scientifica

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