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Evidence-Based Medicine in Oncology Research

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Discussant: **Dr Luca Bertolaccini**, Thoracic Surgeon, European Institute of Oncology, Milan, Italy

Evidence-based medicine in oncology research

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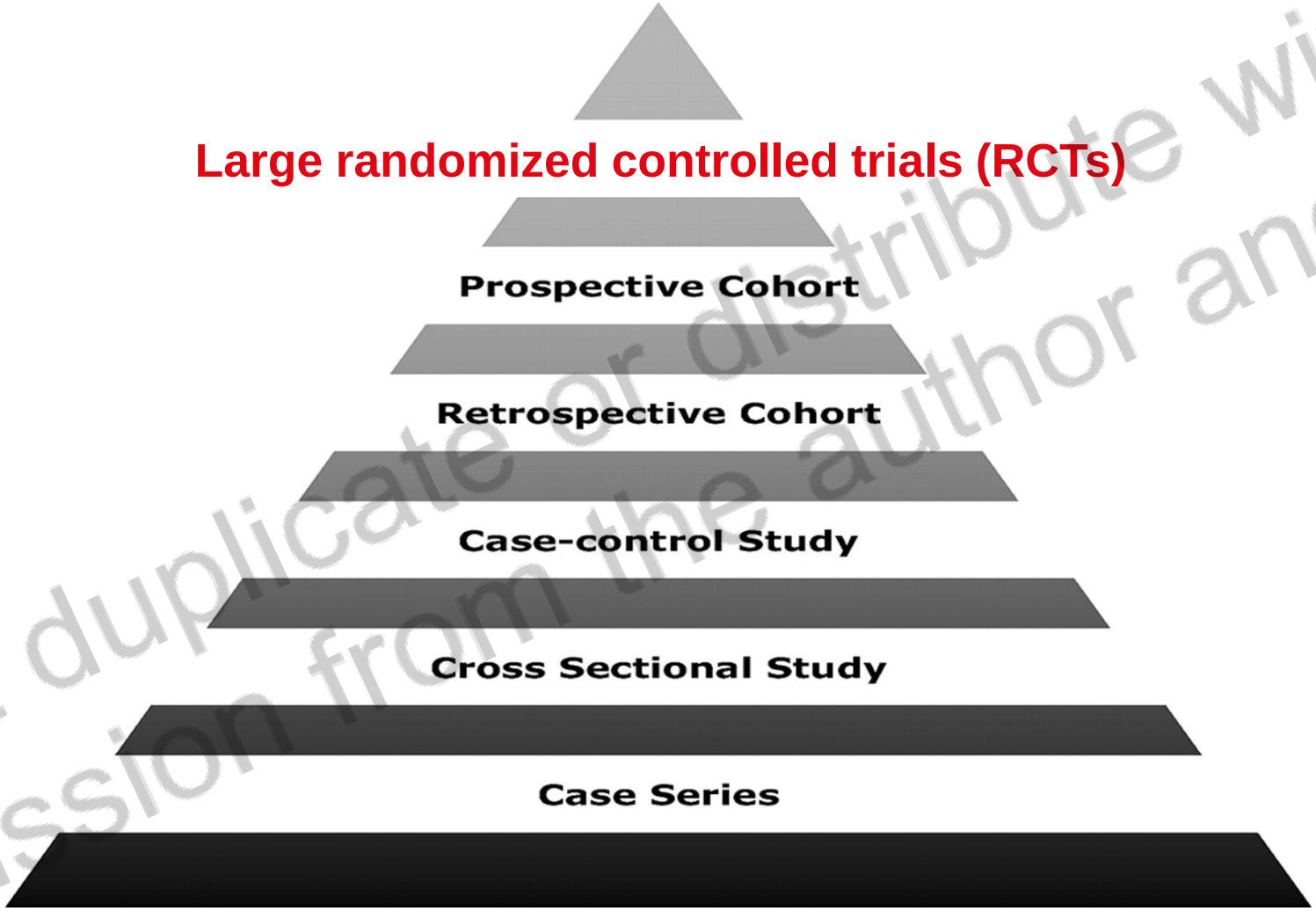
Potential conflicts of interest

	Sponsor
Personal (Honoraria for advisory board or consultant)	Novartis, Merck Sharp & Dohme, AstraZeneca, Pfizer, Eisai, Roche, Janssen, Astellas, Servier, Boehringer Ingelheim, Amgen, Merck Serono
Institutional (Research grant)	Tesaro - GlaxoSmithKline

The pyramid of evidence



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

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

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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

Internal validity

Is the research conducted correctly?

Please check the adequacy of control arm!

Research

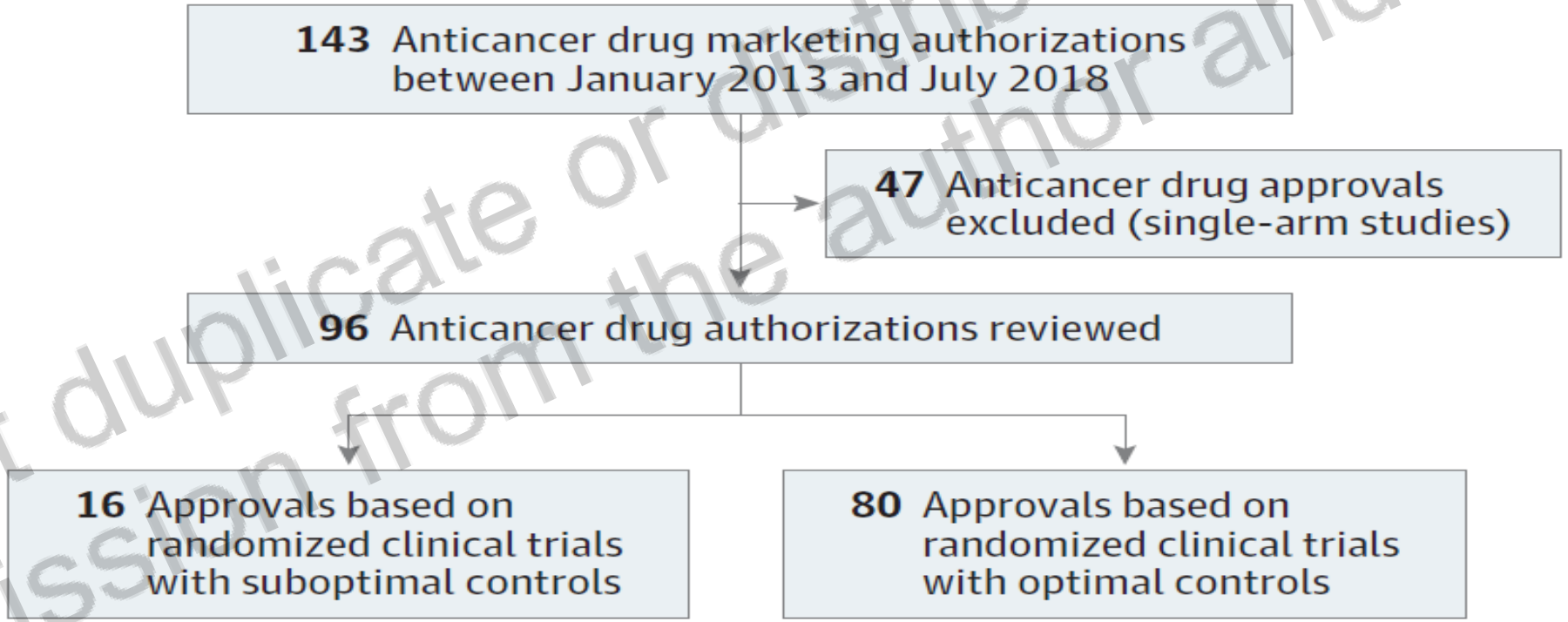
JAMA Oncology | Original Investigation

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.

Why control arm was considered sub-optimal?

- In 4 cases (25%), a treatment of proven efficacy was not allowed
- In 10 cases (63%), the treatment was already proven inferior compared to newer options
- In 2 cases (13%) patients assigned to control arm received a rechallenge with already used drugs

Hilal T, Sonbol MB, Prasad V. *JAMA Oncol.* Published online May 02, 2019.

Endpoints in oncology

Activity against the disease

- Objective tumor response
- Response duration
- TTP/PFS

Effect favouring the patient

- Overall survival
- Quality of life

- Toxicity

ASCO guide-lines J Clin Oncol 1996; 14: 671-679

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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
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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**

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Patient-reported outcomes

- A PRO (*patient-reported outcome*) is a **direct report of a patient's condition**, not interpreted nor modified from a clinician.

- PROs are considered the gold standard for the assessment of **subjective symptoms**, both in clinical practice and clinical trials.

Di Maio M, Basch E et al. Nat Rev Clin Oncol. 2016 May;13(5):319-25.
U.S. Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims.
European Medicines Agency. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 0: 1–9, 2018
doi:10.1093/annonc/mdy449
Published online 10 October 2018

REVIEW

Deficiencies in health-related quality-of-life assessment and reporting: a systematic review of oncology randomized phase III trials published between 2012 and 2016

L. Marandino[1,2], A. La Salvia[1,3], C. Sonetto[1,3], E. De Luca[1,4], D. Pignataro[1,3], C. Zichi[1,4], R. F. Di Stefano[1,3], E. Ghisoni[1,2], P. Lombardi[1,2], A. Mariniello[1,3], M. L. Reale[1,3], E. Trevisi[1,3], G. Leone[1,3], L. Muratori[1,3], M. Marcato[1,4], P. Bironzo[1,3], S. Novello[1,3], M. Aglietta[1,2], G. V. Scagliotti[1,3], F. Perrone[5†] & M. Di Maio[1,4*†]

[1]Department of Oncology, University of Turin, Turin; [2]Division of Medical Oncology, Candiolo Cancer Institute, FPO, IRCCS, Candiolo; [3]Division of Medical Oncology, San Luigi Gonzaga Hospital, Orbassano; [4]Division of Medical Oncology, Ordine Mauriziano Hospital, Turin; [5]Clinical Trials Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione Giovanni Pascale"-IRCCS, Napoli, Italy

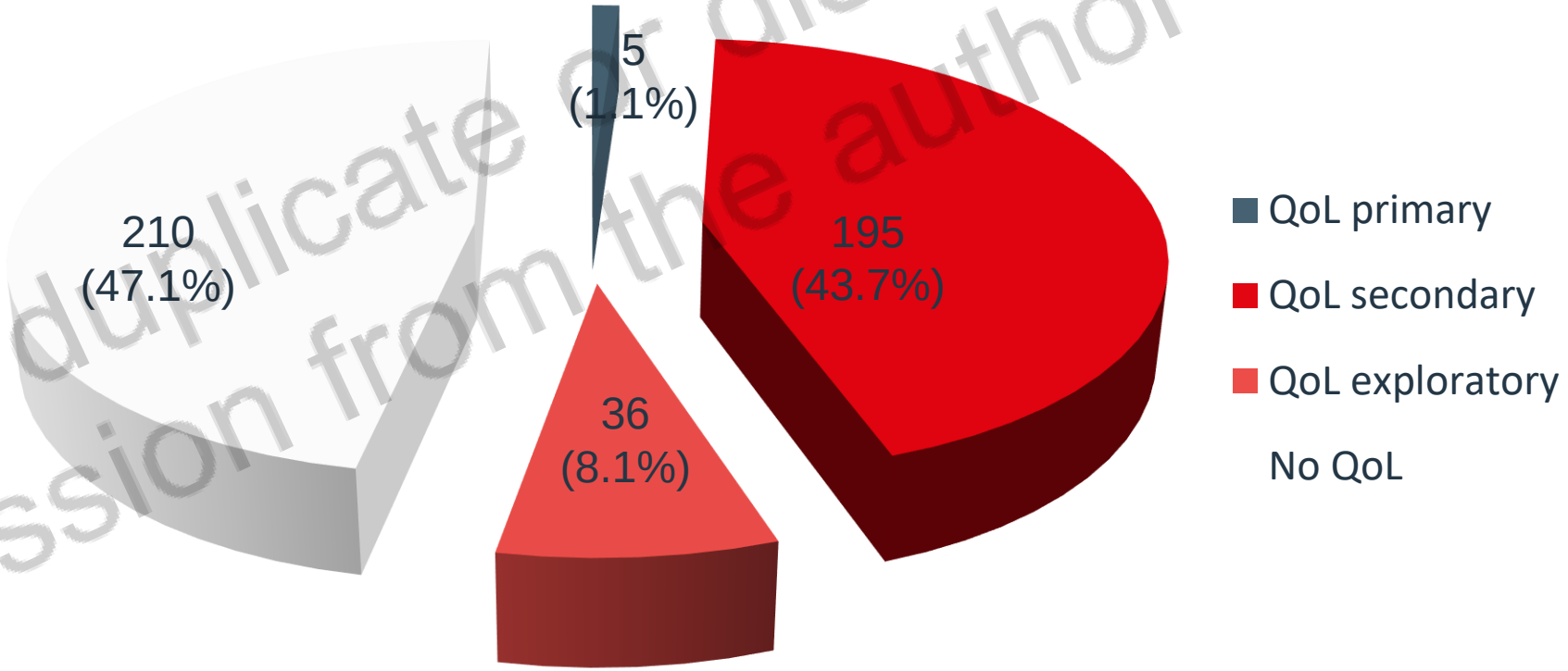
*Correspondence to: Prof. Massimo Di Maio, Department of Oncology, University of Turin and Division of Medical Oncology, Ordine Mauriziano Hospital, Via Magellano 1, 10128 Turin, Italy. Tel: +39-011-5082032; E-mail: massimo.dimaio@unito.it

†Both authors contributed equally as last authors.

Marandino L et al, Ann Oncol 2018 Dec 1;29(12):2288-2295.

Inclusion of QoL among study endpoints

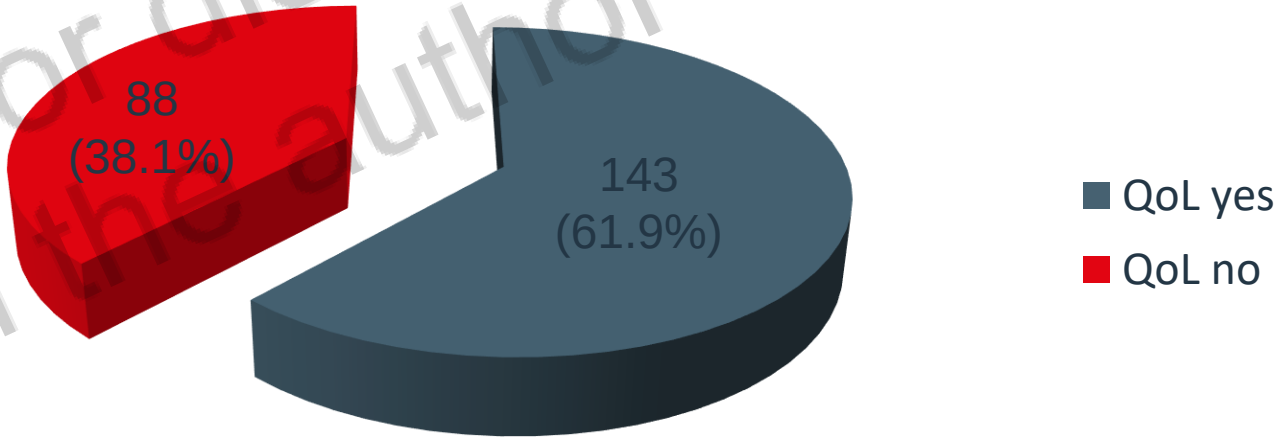
- **In the whole series (446 studies):**
  - QoL was primary endpoint in 5 trials (1.1%);
  - Qol was secondary endpoint in 195 trials (43.7%);
  - QoL was exploratory endpoint in 36 trials (8.1%).



Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295.

Presence of QoL results in the primary publication

- Out of 231 primary publications of trials with QoL as secondary/exploratory endpoint, QoL results were available in 143 (61.9%)



- QoL results: median of 12 rows (9.2%).

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295.

Time to secondary publication
(for trials with no QoL results in the primary publication)

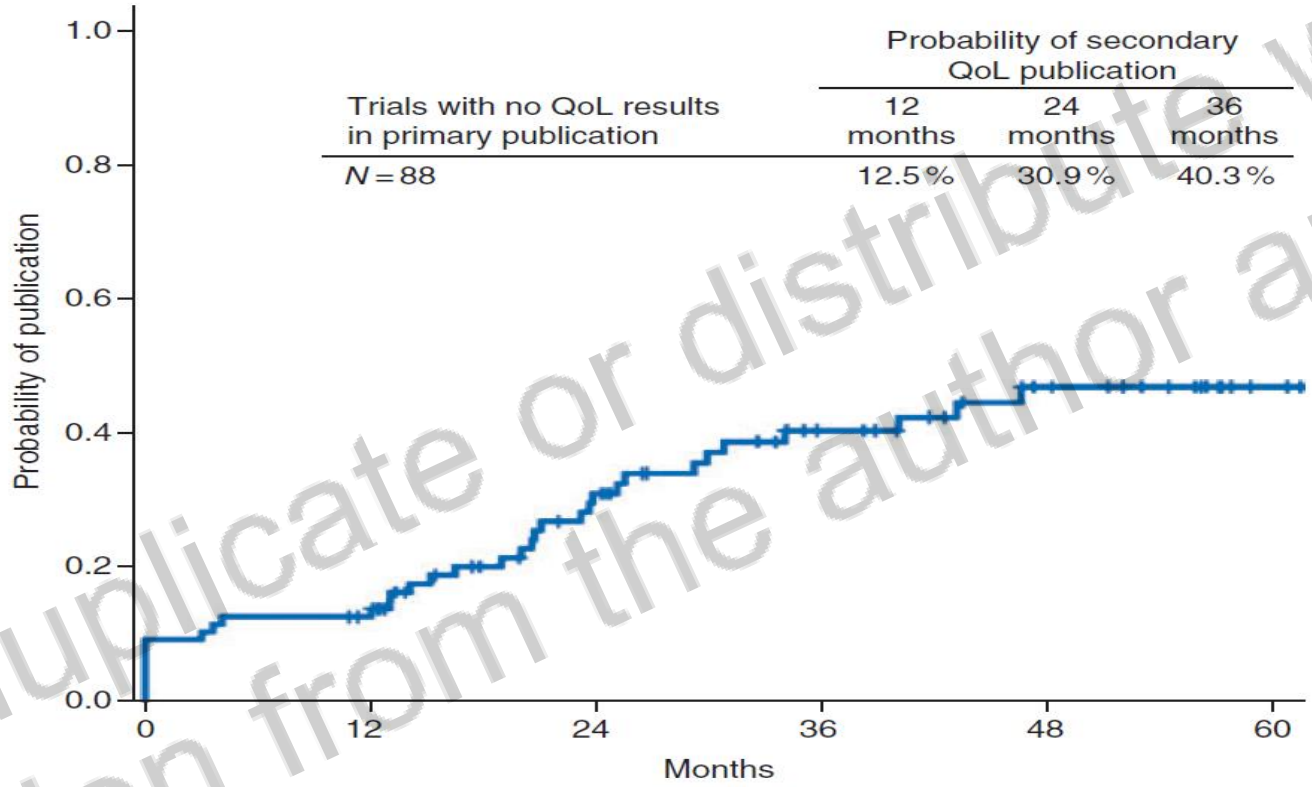
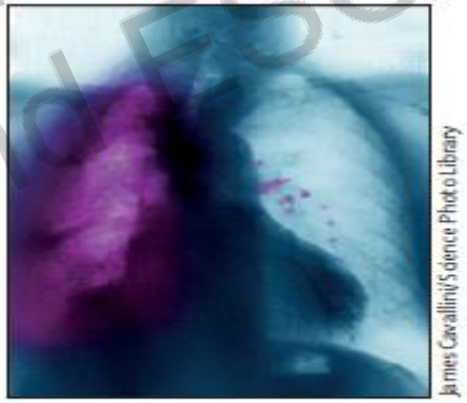


Figure 1. Kaplan–Meier curve of time to secondary publication with quality of life (QoL) results, for trials including QoL as a secondary/exploratory end point, but without any QoL result in the primary publication.

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295.

- Patient-reported outcomes and QOL results will allow a more complete definition of benefits and harms associated with the different treatments available for these patients.

- It is not surprising that both the ASCO framework and the ESMO magnitude of benefit scale to assess the value of anticancer treatments include QOL results among the parameters considered for the evaluation of study results.



Published Online
November 9, 2017
http://dx.doi.org/10.1016/
S1470-2045(17)30697-6

Di Maio M. Quality of life: an important element of treatment value. Lancet Oncol. 2017 Dec;18(12):1557-1558.

Validity of results

External validity

Are the results applicable to the real world?

Internal validity

Is the research conducted correctly?

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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

U.S. FOOD & DRUG ADMINISTRATION

"As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information."

Scott Gottlieb, FDA Commissioner
National Academies of Science, Engineering, and Medicine,
Examining the Impact of RWE on Medical Product Development,
September 19, 2017

"FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval."

Janet Woodcock, M.D., Director, CDER

https://www.fda.gov/media/120060/download

The Oncologist®

Commentary

Real-World Evidence in Oncology: Opportunities and Limitations

Massimo Di Maio,[a] Francesco Perrone,[b] Pierfranco Conte[c]

[a]Department of Oncology, University of Turin; Ordine Mauriziano Hospital, Torino, Italy; [b]Clinical Trial Unit, National Cancer Institute, IRCCS Fondazione Pascale, Napoli, Italy; [c]Department of Surgery, Oncology and Gastroenterology, University of Padova and Oncologia Medica 2, Istituto Oncologico Veneto, I.R.C.C.S., Padova, Italy

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

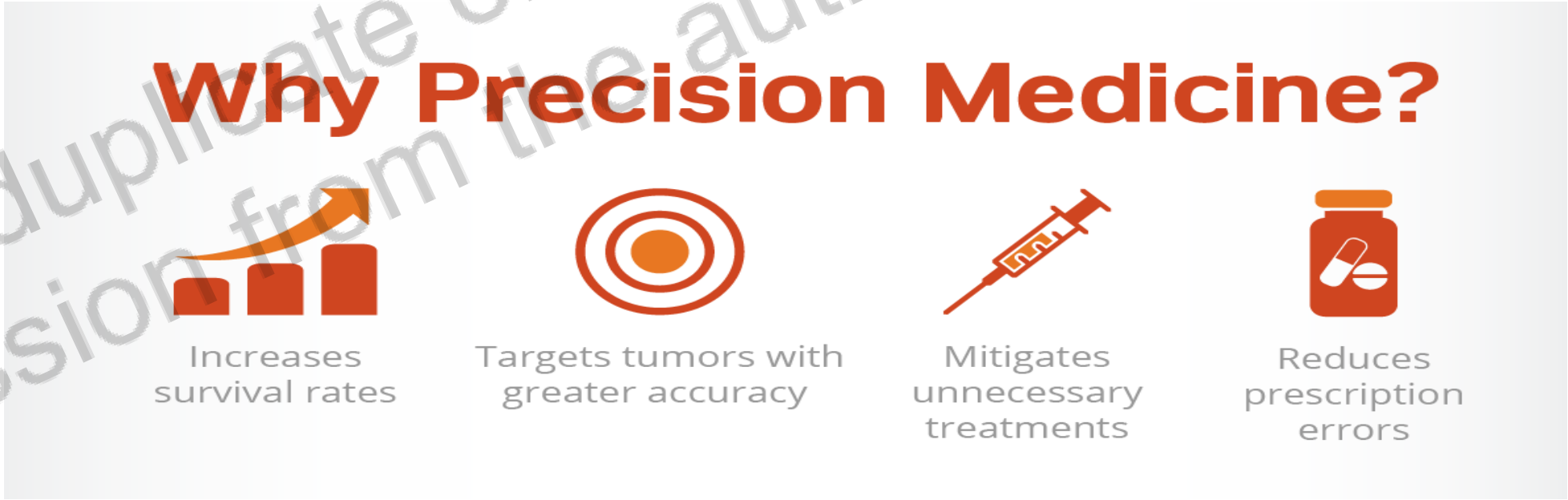
Key Words. Real-world evidence • Clinical trials • Cancer treatments

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

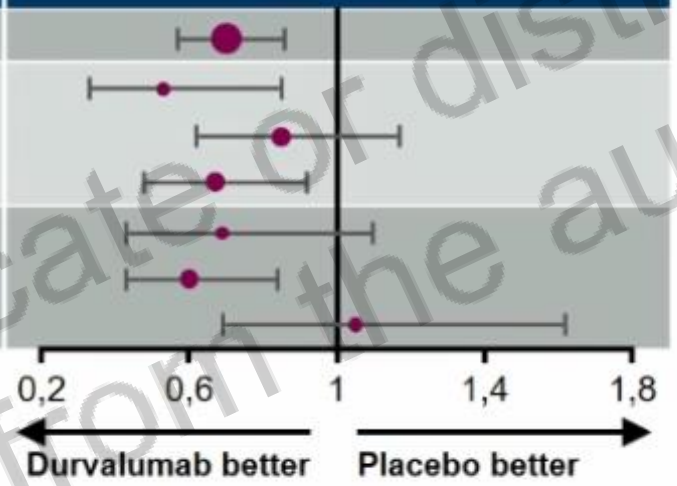
Di Maio, Perrone, Conte. The Oncologist 2020

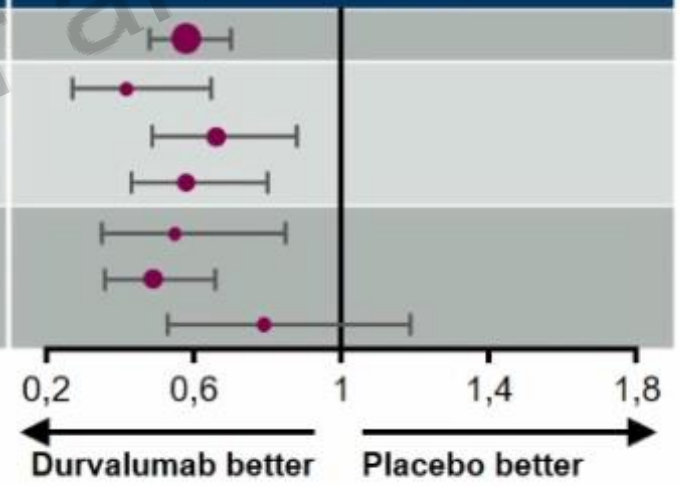
…even more than before, in the era of personalized medicine and precision oncology, **subgroup analysis** seems a valuable tool for optimizing treatment choices.



Subgroup analysis may impact regulatory decisions: Durvalumab in locally advanced NSCLC

		OS		PFS (BICR)	
		# events / # patients (%)	HR and 95% CI	# events / # patients (%)	HR and 95% CI
All patients		396/713 (55.5)		440/713 (61.7)	
PD-L1 status (pre-specified)	≥25%	76/159 (47.8)		92/159 (57.9)	
	<25%	164/292 (56.2)		181/292 (62.0)	
	Unknown	156/262 (59.5)		167/262 (63.7)	
PD-L1 status (post-hoc)	1–<25%	75/144 (52.1)		85/144 (59.0)	
	≥1%	151/303 (49.8)		177/303 (58.4)	
	<1%	89/148 (60.1)		96/148 (64.9)	





Faivre-Finn C, ESMO 2020
Annals of Oncology (2020) 31 (suppl_4): S1142-S1215

Subgroup analyses: why?

- Within a study with overall positive conclusions, subgroup analyses might help to better identify patients who benefit more, patients who benefit less or patients who don’t benefit at all.

Subgroup analyses: why?

- Within a study with overall positive conclusions, subgroup analyses might help to better identify patients who benefit more, patients who benefit less or patients who don't benefit at all.

- Within a study with overall negative conclusions, subgroup analyses might help to avoid **«throwing the baby out with the bath water»**, by identifying certain groups of patients in whom the experimental treatment appears to work.

Subgroup analyses: keywords

- Caution!
- Hypothesis generation
- Multiplicity: risks of false positive and false negative
- Look at consistency among studies
- Plausibility (but beware of belief bias!)
- Look at the interaction test!

Take home messages

- Randomized controlled trials are the gold standard for the production of evidence, but not all that glitters is gold!
- Please look at the adequacy of study design, control arm and study endpoints.
- Applicability of results to «real world» patients is not obvious.
- Subgroup analysis is legitimate to optimize treatment personalization, but please consider its risks!

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