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How to do a critical appraisal of scientific papers

Expert: **Dr Bostjan Seruga**, Institute of Oncology Ljubljana, Ljubljana,Slovenia

Discussant: **Dr Arnoud Templeton**, St. Claraspital Basel, Basel,Switzerland

How to do a critical appraisal of scientific papers

Expert: Boštjan Šeruga, MD, PhD

Division of Medical Oncology, Institute of Oncology Ljubljana and University of Ljubljana, Slovenia

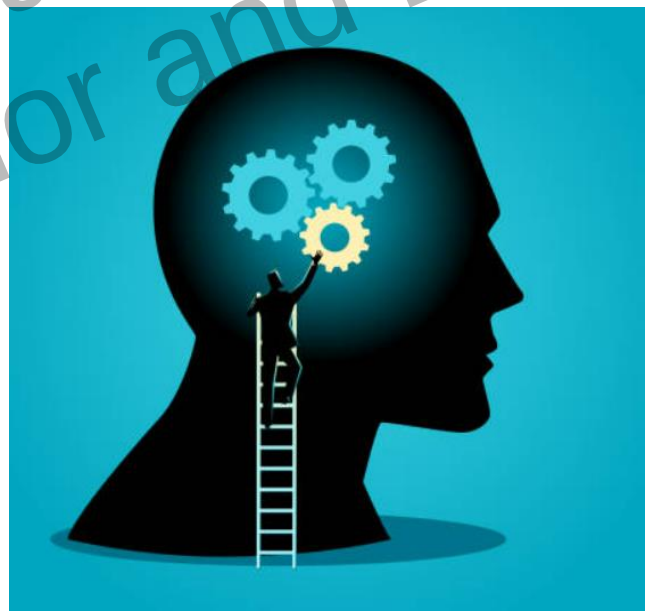
Discussant: Arnoud J. Templeton, MD

Department of Oncology, St. Claraspital Basel and University of Basel, Switzerland

Why can our critical thinking be compromised?

Lack of knowledge
and necessary skills

Exhaustion



Other influence our thinking
(despite having knowledge and skills)

What is conflict of interest (COI)? (=clash between requirements and interests)

Financial

- Payments from pharamaceutical industry influence our perscribing practice
- Experts on guidelines committees have substantial financial COI
- Declaring COI may not prevent bias

Intrinsic

- Engage and publish research to achieve career advancement
- Receive accolades from peers and professional societies
- Be competitive for grant funding

Daylian and Detsky, JAMA 2008; Booth and Detsky, BMJ 2019; Tannock and Joshua, Ann Oncol 2019; Gray et al, JCO 2007

Why to use toxic and expensive cancer drugs?

- To improve quality of life (QoL)

and/or

- To improve overall survival (OS)

These are patients-centered outcomes (i.e. relevant endpoints)

- Unfortunatly, cancer trials do not necessarily measure these outcomes
- Surrogate measures (endpoints) are not a direct measure of clinical benefit

Significant P-value usually defines a "positive" RCT

The P-value is a number, calculated from a statistical test, that describes how likely you are to have found a particular set of observations if the null hypothesis were true.

P-values and significance testing are often misunderstood and misused

P-value

- P-value does not measure the probability that a hypothesis is true, or the probability that the data were produced by the chance alone
- Scientific and policy decisions should not be based only on p< 0.05
- A P-value, or statistical significance, does not measure a size of an effect or the importance of a result
- By itself, a P-value does not provide a good measure of evidence regarding the model or hypothesis

American Statistical Association

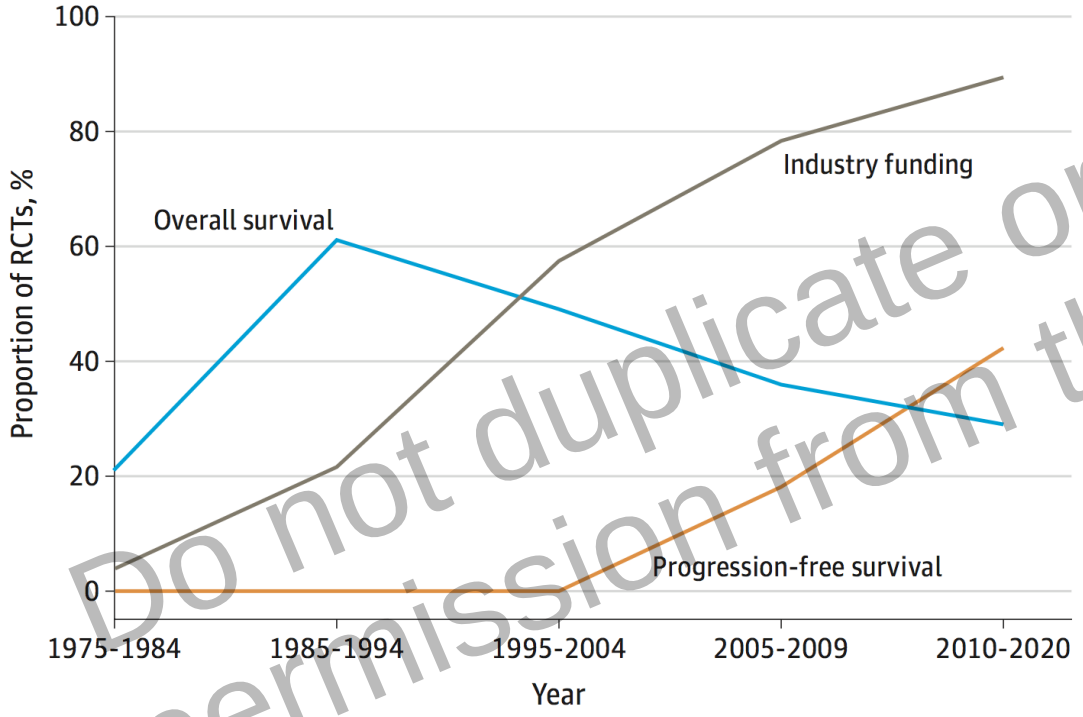
What are relevant questions about a ”positive" randomized clinical trial (RCT)?

- What is the endpoint?
- What is the effect size?
- What is tolerability?
- How do all these matter to patients in everyday clinics?

Evolution of the Randomized Clinical Trial in the Era of Precision Oncology

Joseph C. Del Paggio, MD; John S. Berry; Wilma M. Hopman, MA; Elizabeth A. Eisenhauer, MD; Vinay Prasad, MD; Bishal Gyawali, MD, PhD; Christopher M. Booth, MD

N=602 RCTs



- **Contemporary RCTs largely measure putative surrogate endpoints such as progression-free survival (PFS)**
- **They are almost exclusively funded by the pharmaceutical industry**

JAMA Oncology May 2021 Volume 7, Number 5

Progression-Free Survival: Meaningful or Simply Measurable?

Christopher M. Booth and Elizabeth A. Eisenhauer, *NCIC Clinical Trials Group, Queen's University, Kingston, Ontario, Canada*

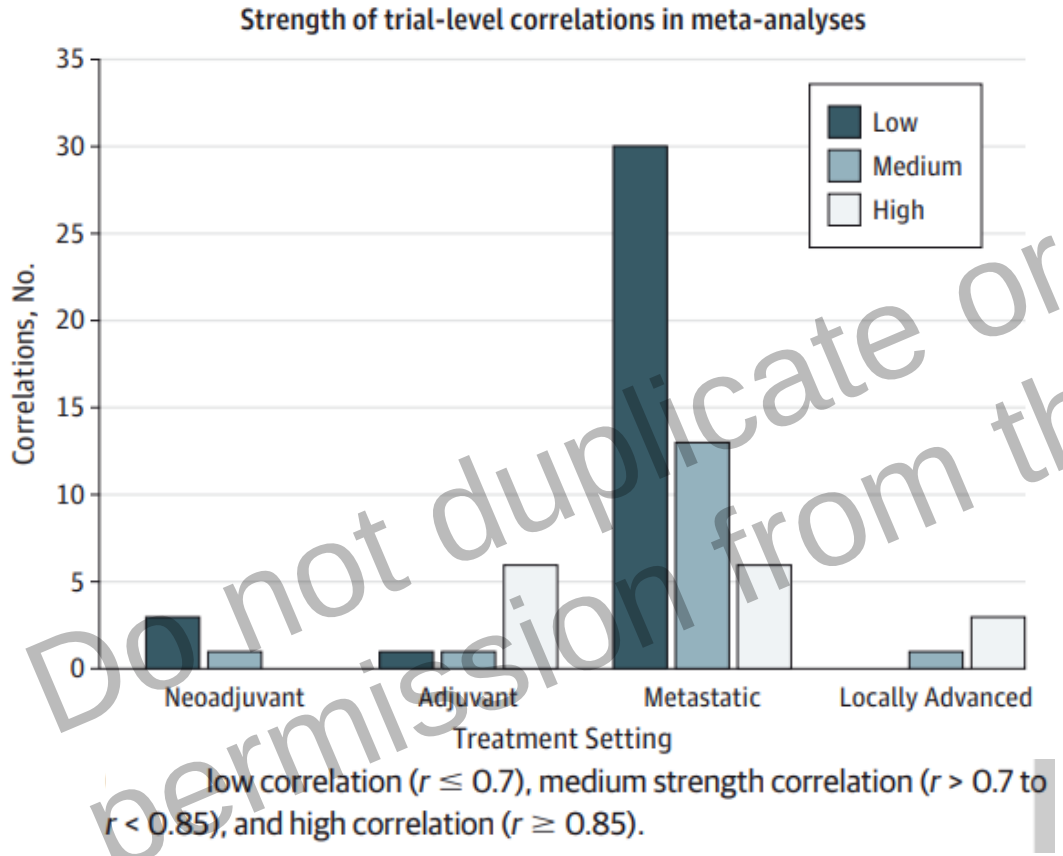
- **Disease progression was intended for use in clinical trials to screen new drugs**
- **It was intended to describe what happens to tumor during therapy – not to infer a meaningful benefit to a patient from those changes**
- **What improvement in PFS (and other similar endpoints) means for patients?**
  - **Is their prognosis (OS) improved?**
  - **Is their HRQoL improved?**

VOLUME 30 · NUMBER 10 · APRIL 1 2012
JOURNAL OF CLINICAL ONCOLOGY

The Strength of Association Between Surrogate End Points and Survival in Oncology

A Systematic Review of Trial-Level Meta-analyses

Vinay Prasad, MD, MPH; Chul Kim, MD, MPH; Mauricio Burotto, MD; Andrae Vandross, MD



low correlation ($r \leq 0.7$), medium strength correlation ($r > 0.7$ to $r < 0.85$), and high correlation ($r \geq 0.85$).

- 36 articles in which 65 specific correlations between a surrogate end point and survival were identified
- 52% correlations were of low strength ($r \leq 0.7$), 25% were of medium strength ($r > 0.7$ to $r < 0.85$), and 23% were highly correlated ($r \geq 0.85$) with survival
- All validation studies use only a subset of available trials.

JAMA Internal Medicine August 2015

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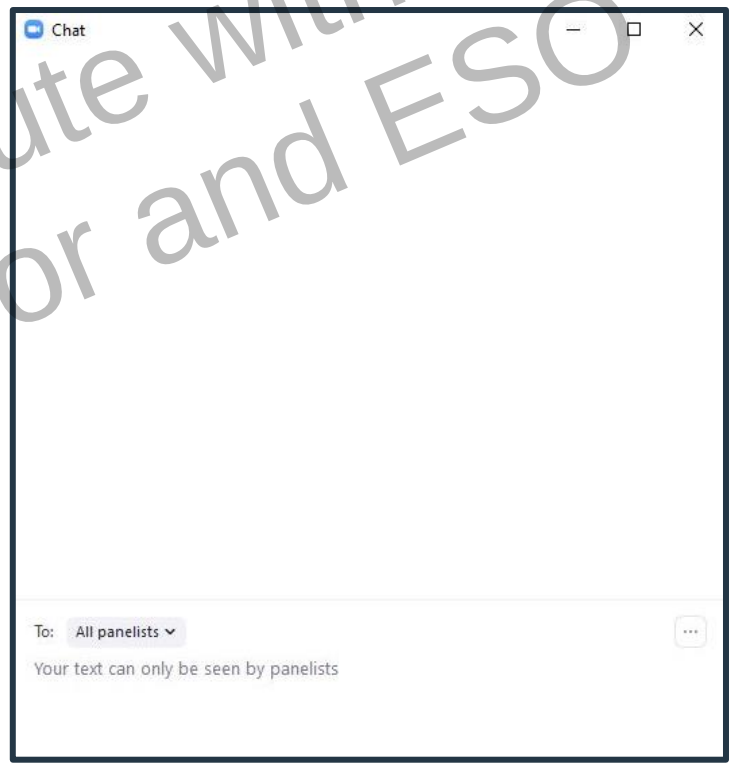

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Why surrogate endpoint may not predict outcomes in clinically relevant endpoint (OS)?

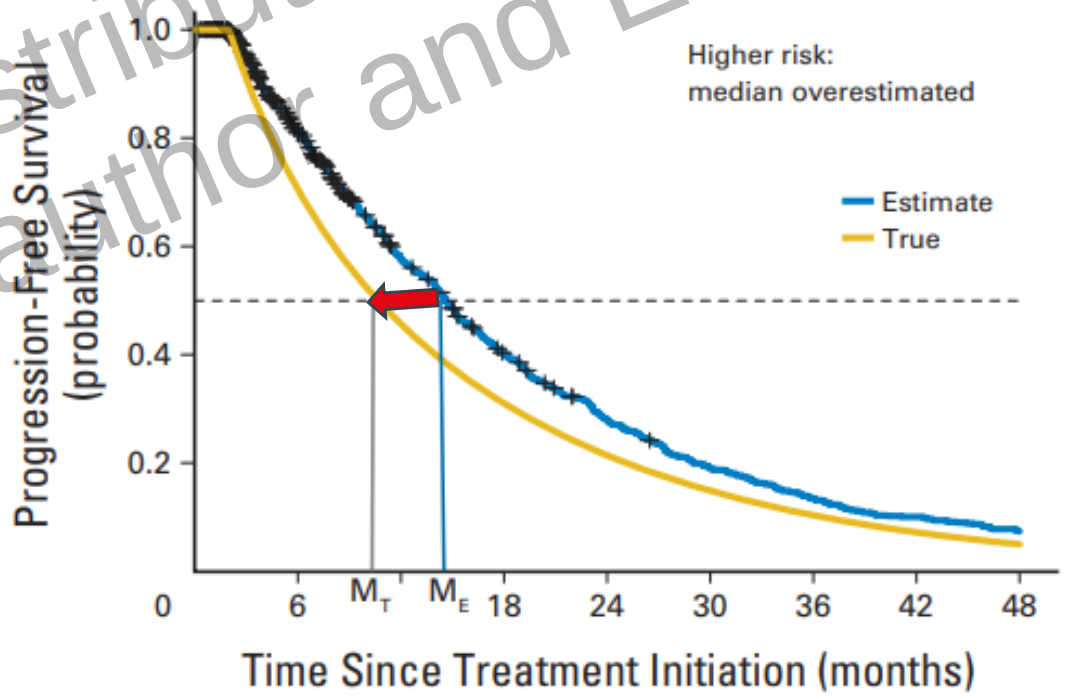
- **Technical factors - PFS is not measured appropriately/accurately**
  - **measurement bias, evaluatuon bias, attrition bias, informative censoring**

- **Surrogate endpoint does not predict OS, drug may change relationship between surrogate endpoint and OS**
  - **Surrogate endpoint may not have a causal role in the hard endpoint (e.g. pCR), off target effect independent of the disease process, post-progression disease growth is accelerated**

Kemp and Prasad, BMC Medicine, 2017

What is informative censoring?

- Patients may be taken off study before progression for reasons such as: toxicity, patient or physician preference, initiation of nonprotocol therapy
- Informative censoring occurs when censored patients are at a different risk for treatment failure than those who remain on study (they are not censored at random)
- If informative censoring is differential (occurs more often in the treatment than in the control group), then the efficacy of the intervention may be falsely over-estimated

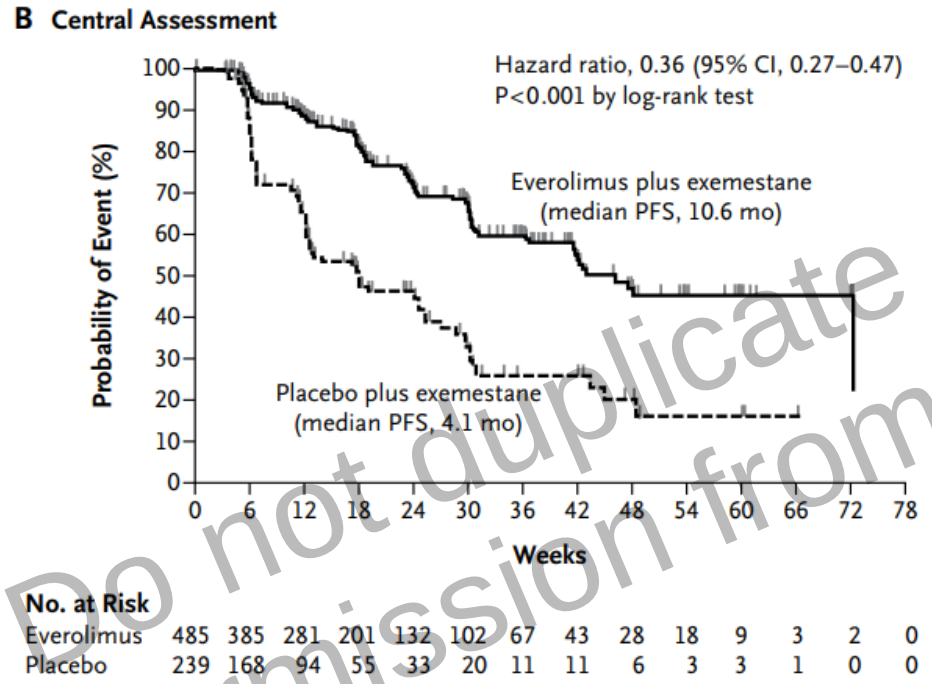


Campigotto and Weller, J Clin Oncol, 2014; Templeton et al, Nat Rev Clin Oncol, 2020

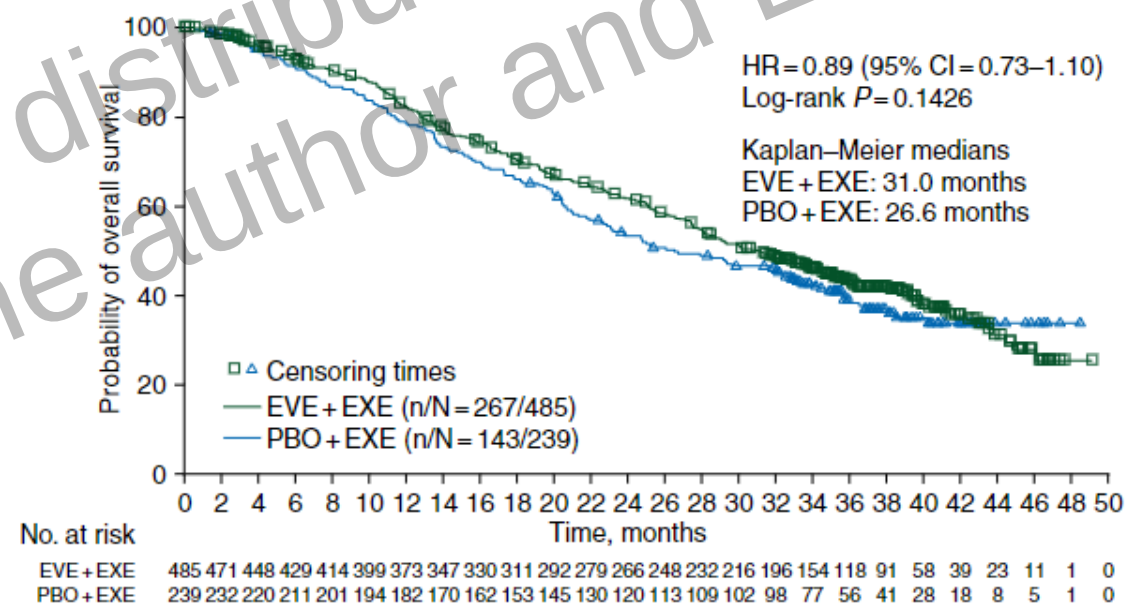
Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D.,

PFS



OS



26.8% and 6.1% of the patients receiving everolimus and placebo, respectively, withdrew from the study prior to progression owing mainly to treatment-related adverse events.

Baselga et al, NEJM 2012

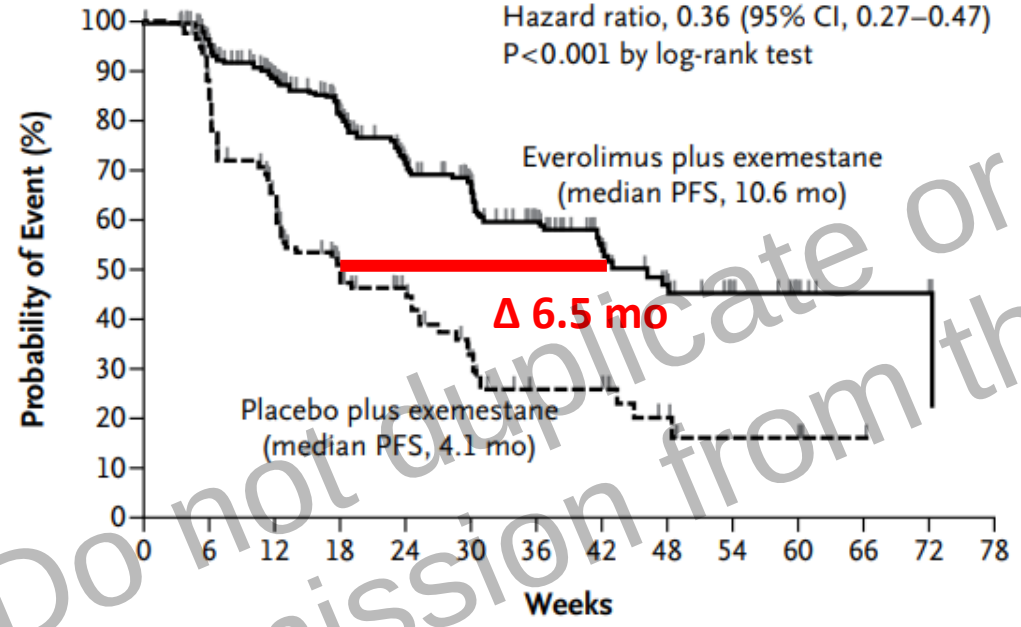
Piccart et al, NEJM 2014

Influence of censoring on conclusions of trials for women with metastatic breast cancer

Arnoud J. Templeton [a,1], Olga Ace [a,1], Eitan Amir [a], Francisco Vera-Badillo [a], Alberto Ocana [b], Gregory R. Pond [c], Ian F. Tannock [a,*]

B Central Assessment

PFS



No. at Risk

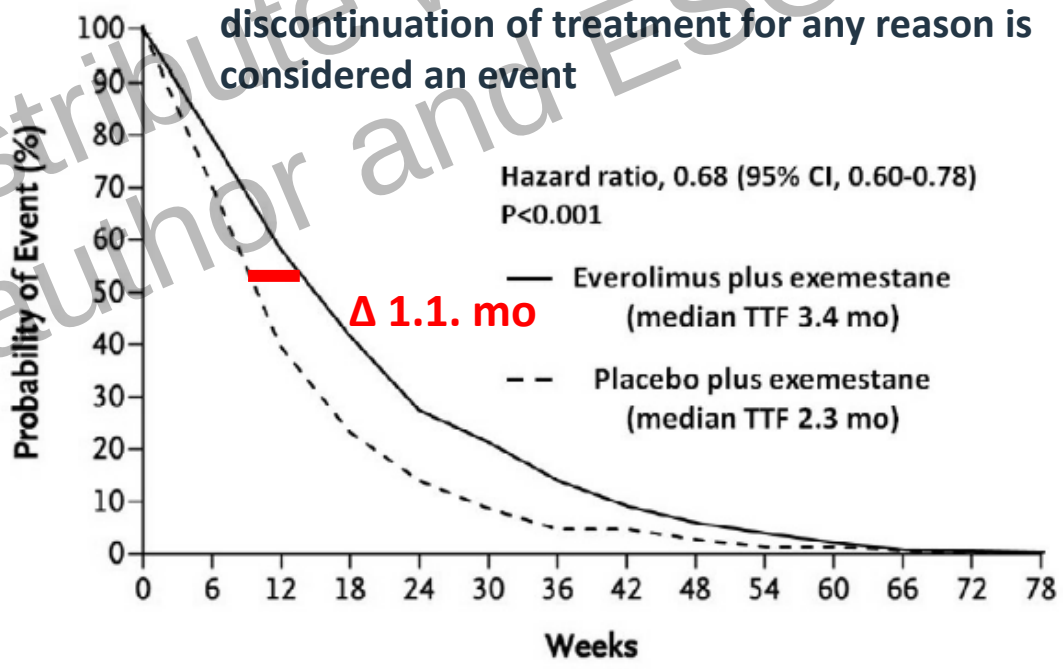
Everolimus	485	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

Baselga et al, NEJM 2012

B

Time-to-treatment-failure (TTF)

discontinuation of treatment for any reason is considered an event



No. at Risk

Everolimus	458	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

Templeton et al, EJC 2015

Informative censoring of surrogate end-point data in phase 3 oncology trials

- Of 73 oncologic RCTs with significant surrogate time-to-event endpoints
  - 33 (45%) RCTs reported significant benefit in OS (concordant trials)
  - 40 (55%) RCTs did not reported significant benefit in OS (discordant trials)
- Significant differential censoring in surrogates was 43% (17/40) and 51% (17/33) in discordant and concordant trials, respectively.
  - significant censoring imbalance in the experimental arm occurred only in discordant trials (15% vs 0%, p=0.033) while excessive censoring in control arm occured more often concordant trials (28% vs. 52%, p=0.036)
- After sensitivity analysis, 50% and 15% of the discordant and concordant trials lost their statistical significance in the surrogate

S. Gilboa et al. / European Journal of Cancer 153 (2021)

Solutions to reduce bias of informative censoring

- OS rather than surrogate endpoint is the primary endpoint
- Analysing intention-to-treat population
- Time-to-Treatment Failure (TTF) as an endpoint (it can be compared to other surrogate endpoints
  - TTF includes discontinuation of treatment as failure
- Transparent reporting of censoring
- Sensitivity analyses
  - Worst case (assuming all censored patients had progression)
  - Best case (assuming none of the censored patients had progression)

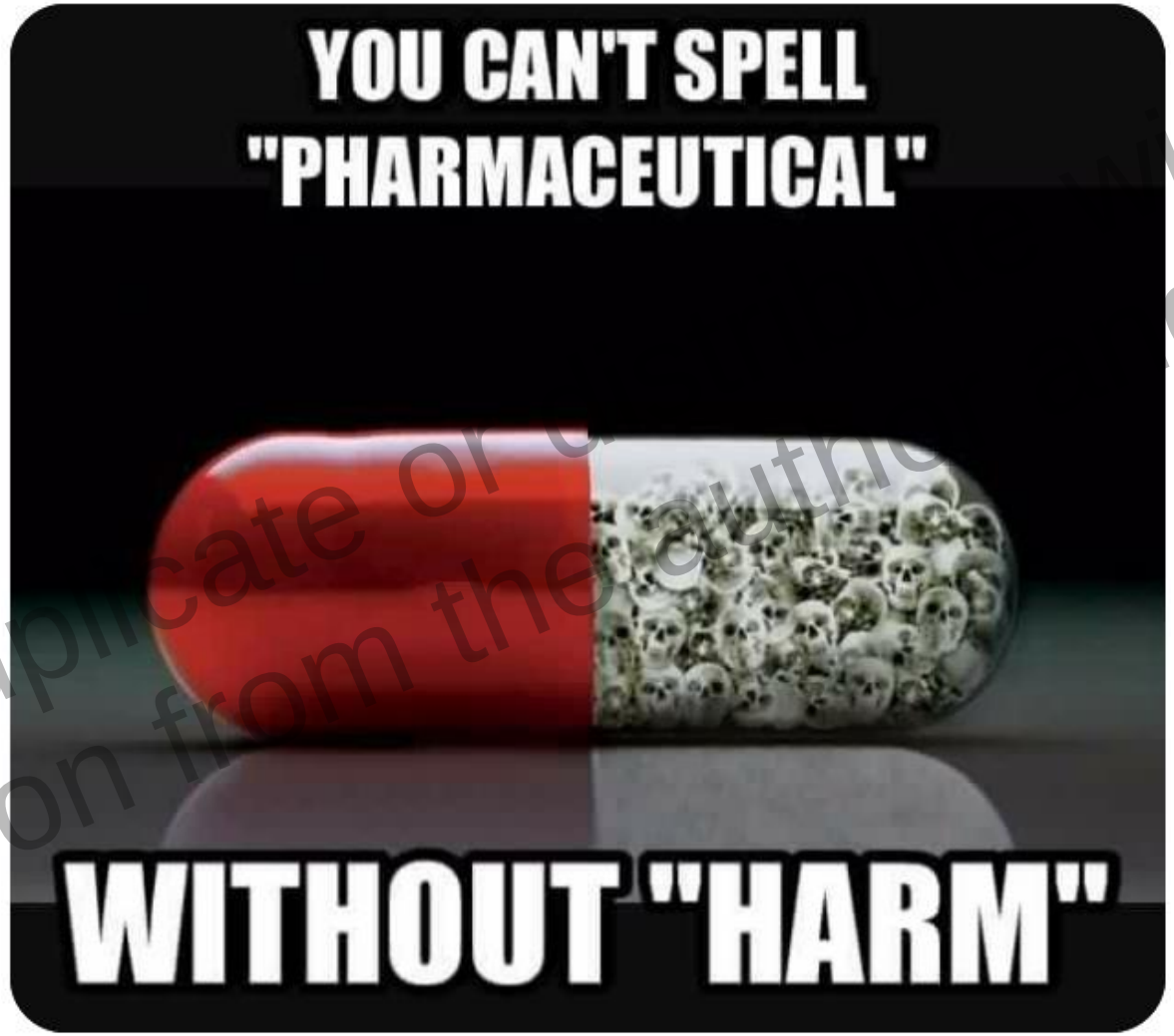
Templeton et al, Nat Rev Clin Oncol 2020

Association between progression-free survival and patients' quality of life in cancer clinical trials

Thomas J. Hwang [1,2] and Bishal Gyawali [1,2]

- 325 RCTs in advanced or metastatic solid tumors published between 2010-2015
- 190 (54%) RCTs included QoL endpoint, 147 RCTs reported QoL outcomes
- The association between PFS and improvement in global QoL was weak (r=0.34; AUC =0.72)

Int. J. Cancer: **144,** 1746–1751 (2019)



Under-Reporting of harm in clinical trials

- Patients in daily practice are older and have more comorbidities
- Under-reporting of harm in clinical trials because of
  - Under-reporting of symptomatic adverse events by physicians
  - Inadequate reporting
  - Short follow-up misses long-term toxicities and serious toxicities which may only become apparent in post-marketing phase

Seruga et al, Lancet Oncology 2016

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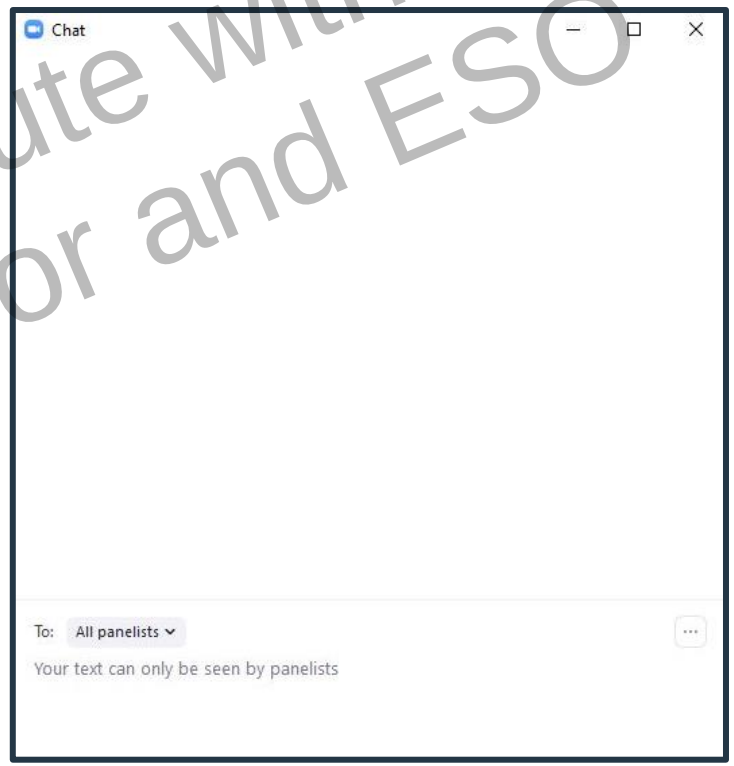

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Univerza v Ljubljani

How good are physicians in reporting of harm in clinical trials?

- **Physician‘s reporting of symptomatic AEs lacks reliability**
  - Agreement between different physicians is moderate at best; different symptoms ratings can affect treatment decisions
- **Physicians under-report the incidence and severity of symptoms compared to reports of patients**
- **Physician‘s reports better predict unfavourable clinical events (e.g. death, ER visits) than patient‘s reports**
  - Patient‘s reports better reflect underlying daily health status than clinician reports

Atkinson et al, Qual Life Res, 2012

Pakhomow et al, Am J Manag Care, 2008; Basch et al, JNCI, 2009

Reporting of Serious Adverse Drug Reactions of Targeted Anticancer Agents in Pivotal Phase III Clinical Trials

Bostjan Seruga, Lynn Sterling, Lisa Wang, and Ian F. Tannock

Updated drug labels for 12 targeted agents	NOT reported in initial drug labels	NOT reported in pivotal RCTs
All Serious ADRs N=76	49%	39%
Potentially fatal ADRs N=38	58%	39%

ADR: Adverse Drug Reaction; RCT; Randomized Clinical Trial

VOLUME 29 · NUMBER 2 · JANUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

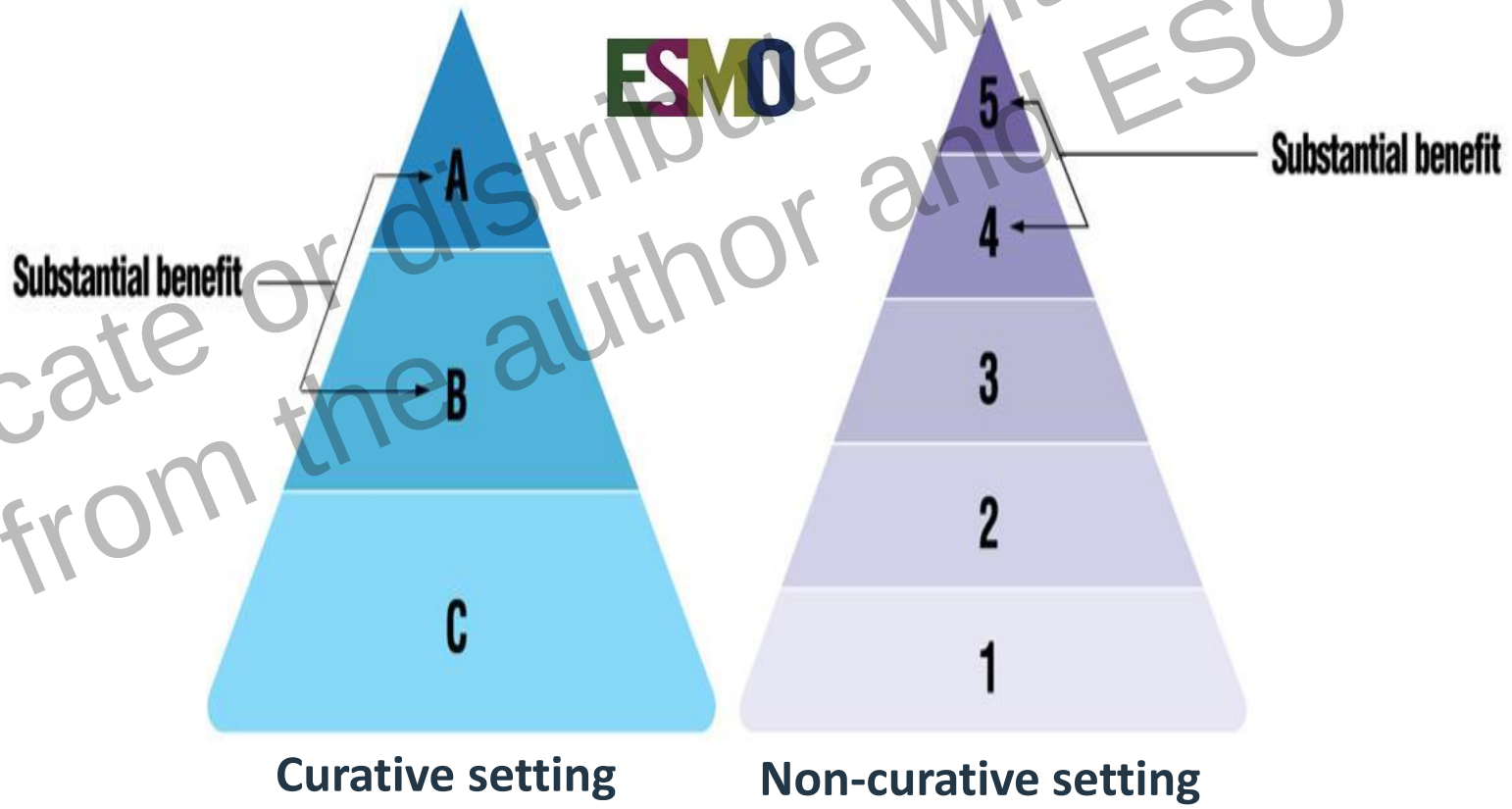
Impact of underreporting of toxicity

- Patients
  - do not know what symptoms to expect
  - prolongation of life by potentially toxic treatments might not always be a priority for patients
- Regulators (and payers)
  - may not appropriately balance risks and benefits
  - underestimates of the costs of managing harm

An important step forward: Clinical value scales

Clinical value and not statistical significance should be used as a criterion of importance

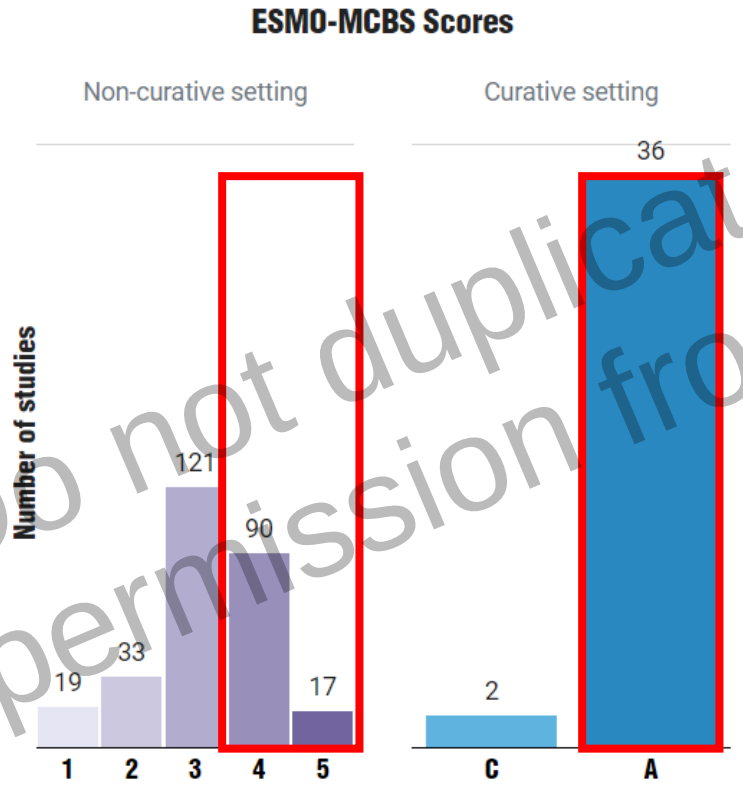
Clinical value scale emphasizes improvements in duration and quality of survival



Cherny et al, Ann Oncol, 2017

Only a minority of studies evaluating drugs in non-curative setting demonstrate clinical value

Studies evaluating cancer medicines approved by EMA since 2016 and by FDA since 2020



Non-curative setting:
107/280 (38,2%) of studies evaluating agents approved by EMA score 4 or 5

Curative setting:
36/38 (94,7%) of studies evaluating agents approved by EMA score A

ESMO-MCBS Scorecards
https://www.esmo.org/guidelines

Do Contemporary Randomized Controlled Trials Meet ESMO Thresholds for Meaningful Clinical Benefit?

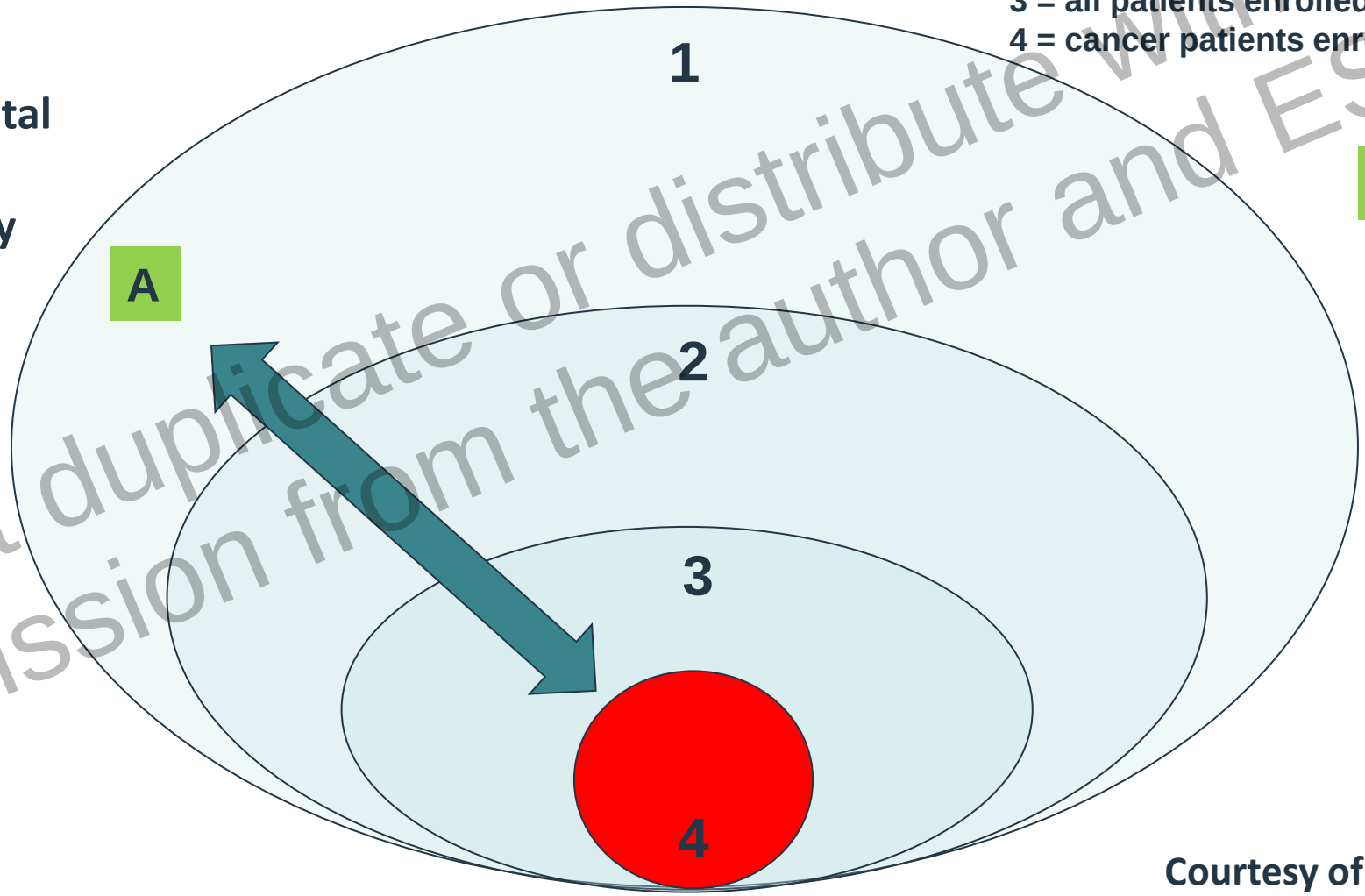
- **277 RCTs evaluating systemic therapy for breast cancer, NSCLC, CRC, and pancreatic cancer published 2011-2015 reviewed**
- **Experimental therapy was statisticaly superior to the control arm in 138 RCTs (50%)**
  - **of these, results of only 43 (31%) RCTs met the ESMO-MCB clinical benefit treshold**
- **Among the 226 RCTs for which the ESMO-MCBS could be applied, 31% (70/226) were designed to detect an effect size that could meet ESMO-MCBS thresholds.**

Del Paggio et al, Ann Oncol, 2017

Efficacy – Effectiveness Gap

1 = all patients with cancer
2 = all patients without comorbidities
3 = all patients enrolled into trials
4 = cancer patients enrolled into pivotal trial

Can results from the pivotal clinical trial be applied to our patient in everyday clinical practice?



A our patient in everyday clinic

MIND THE GAP

Courtesy of Dr. A. Templeton

Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials*

A. J. Templeton[1], F. E. Vera-Badillo[1], L. Wang[2], M. Attalla[1], P. De Gouveia[1], R. Leibowitz-Amit[1], J. J. Knox[1], M. Moore[1], S. S. Sridhar[1], A. M. Joshua[1], G. R. Pond[3], E. Amir[1] & I. F. Tannock[1]*

Patients treated with 3-weekly docetaxel (2001-2011)	Routine practice N=314	Clinical trials N=43	TAX 327 N=335	p
Median # of cycles	6	8	9.5	< 0.001
Median OS (mo)	13.6	20.4	19.3	< 0.001
Febrile neutropenia	9.6%	0	3%	< 0.001
Death during therapy	4%	0%	3%	ns

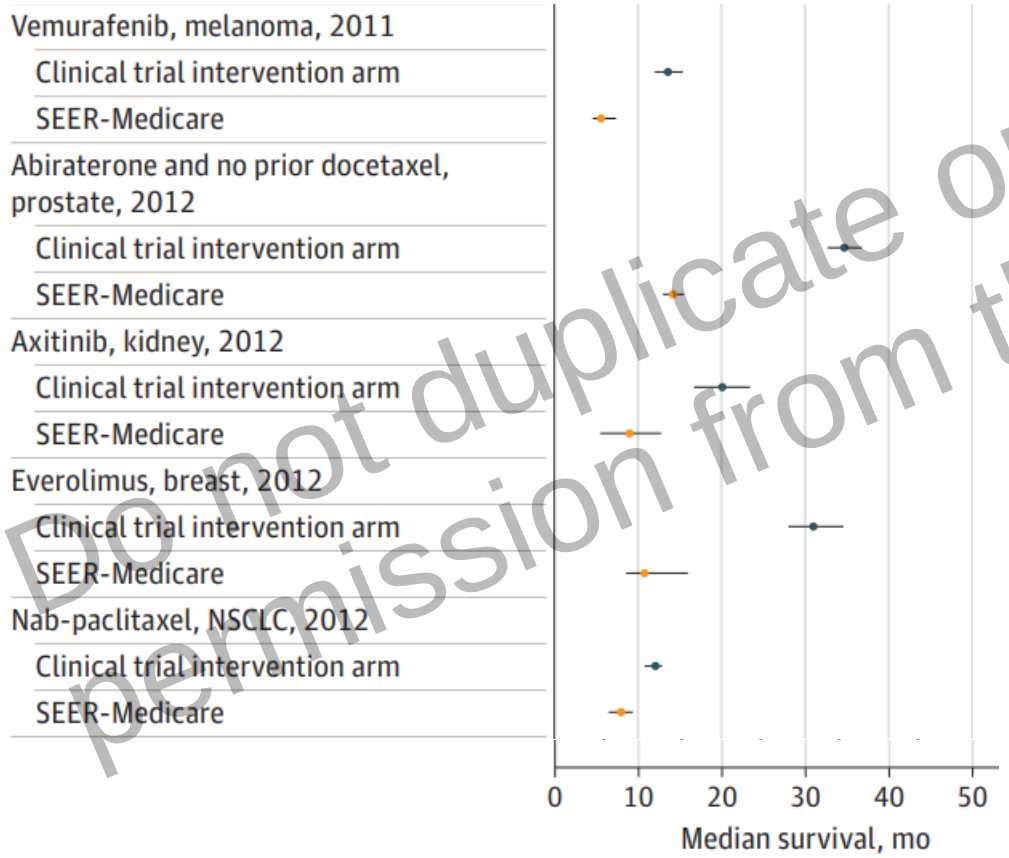
Annals of Oncology 24: 2972–2977, 2013
doi:10.1093/annonc/mdt397
Published online 14 October 2013

Original Investigation | Oncology

Assessment of Outcomes Associated With the Use of Newly Approved Oncology Drugs in Medicare Beneficiaries

Angela K. Green, MD, MSc; Michael Curry, MS; Niti Trivedi, MPH; Peter B. Bach, MD, MAPP; Sham Mailankody, MBBS

Compared > 11,000 trial patients with > 9,000 SEER-Medicare patients



- Median age in SEER-Medicare 72.7 yrs (vs. 61 yrs in trial patients)
- Median OS among SEER-Medicare patients was shorter than among patients in the clinical trial intervention arm (-6.3 mo)
- Dose reductions or single perscriptions were more common among SEER-Medicare patients

JAMA Network Open. 2021

Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies

A. Srikanthan [a], F. Vera-Badillo [b], J. Ethier [a], R. Goldstein [a], A.J. Templeton [c], A. Ocana [d], B. Seruga
E. Amir [a,*]

- **86 protocols written between 1987 and 2012 analysed for eligibility criteria**
- **Proportion of screened patient, who were excluded from trials increased from 9% to 18% over a 10 year period (*P* for trend <0.001)**
- **Increasing frequency of exclusion of patients with: prior cerebrovascular events, coagulation/bleeding disorders, prior gastrointestinal bleeding, cardiac co-morbidities, based on concurrent medication**
- **Decreasing frequency of exclusion in: upper age limit usage and leukopenia**

Cancer Treat Rev, 2016

Conclusions

- For various reasons our critical thinking can be compromised
- Cancer trials often do not directly measure and report patient-centered outcomes
- While presentation of benefit of new anticancer therapy may be overly optimistic, harm may be underreported in RTCs
- Consider clinical value of new therapies and generalizability of results of RCTs in everyday clinical practice

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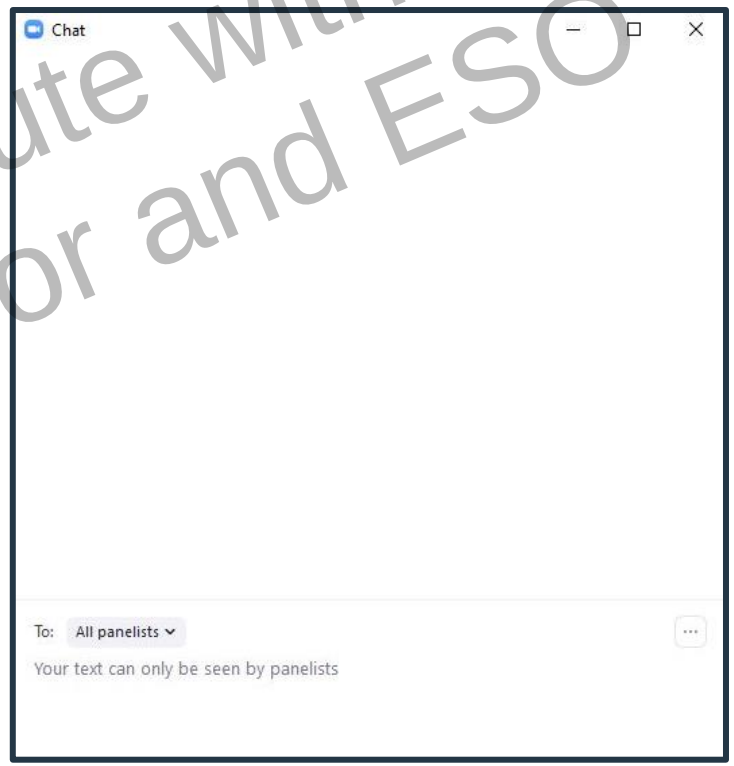
e-Session

Question & Answer Session



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will take place on 27th April 2022, at the same time

Things about early breast cancer that keep us up at night

Expert: **Prof Olivia Pagani**, Riviera-Chablais Hospital, Rennaz, Switzerland

Discussant: **Dr Elzbieta Senkus**, Medical University of Gdansk, Gdansk, Poland

Thank you!

for participating in this
ESCO-session
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