Understanding objectives and endpoints in Clinical Cancer Trials (Incl. Role of PRO Patient Reported Outcomes and Quality of Life aspects)

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COI

- NOVARTIS
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- NESTLE
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- IPSEN
- BAYER
- CHUGAI
- ERYTECH

Introduction

- **Design of clinical trials requires** :
  - Primary outcome with corresponding primary endpoint
  - Endpoint ≠ objective (but related)
  - Conclusion based on the Primary objective = why do this trial ?
  - **Hypotheses**:
    - To improve the primary endpoint
    - Difference / equivalence/ superiority/non inferiority

- **Should be Clinically meaningful for the patients in Phase III**:
  - Therapeutic strategy should demonstrated a clinical benefit

Introduction

- **Endpoint refers to an outcome measure in clinical trial for primary and secondary objectives of the study**.
  - Outcomes measured during the course of the trial
  - Endpoints served to define and to answer the question (Friedman, Furberg, and DeMets)

Introduction

- Appropriate choice of endpoint as primary Depend on . . .
  - Phase of the trial (II, III, IV etc..)
  - Disease, cancer localization
  - Treatment setting (progressive, adjuvant, palliative etc ..)
  - Therapy
  - Feasibility

- Key Requirements for Drugs Approval (FDA) or to change practice :
  - Demonstration of efficacy = Clinical benefit with acceptable safety in adequate and well-controlled studies
    - Longer Life
    - Better Life (Health related Quality of life)
    - With Safety
    - And acceptable Cost

Introduction

Cancer Outcomes Research

Joseph Lipscomb, Molla S. Donaldson, Neeraj K. Arora, Martin L. Brown, Steven B. Clauser, Arnold L. Potosky, Bryce B. Reeve, Julia H. Rowland, Claire F. Snyder, Stephen H. Taplin

- In order for an endpoint to achieve its potential to improve cancer care delivery, 3 prerequisites apply
  - **Technically sound** (reproducibility, validity etc..)
  - **Persuasive evidence about the effect of interventions on those outcomes**, with due attention to the causal linkages among intermediate, Clinical, and final Outcome
  - The **willingness and ability to translate findings into information that decision makers find understandable and compelling**.

→ **Should be used at the Meso (trials), Micro (clinician-patient decision making) and Macro (Population surveillance of trends) levels**

(Lipscomb J, et al. Cancer outcomes research. J Natl Cancer Inst 2004)

Introduction

Different type of endpoints :

- Clinical vs. surrogate
- Landmark vs. time-to-event
- Binary vs. continuous
- Single event vs. Composite
- Objective vs subjective

The Oncologist

Endpoints for Assessing Drug Activity in Clinical Trials

RICHARD PAZDUR

Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Maryland, USA

Endpoints

- **Overall survival**:
  - To improve length of survival time is a major goal of cancer = gold standard for phase III trials.
  - Time from clinical trial randomization until death from any cause.
  - Direct measure of **clinical benefit** for the patients
  - Calculated with precision.
  - Could take time to be evaluated, requiring relatively large and/or lengthy clinical trials.

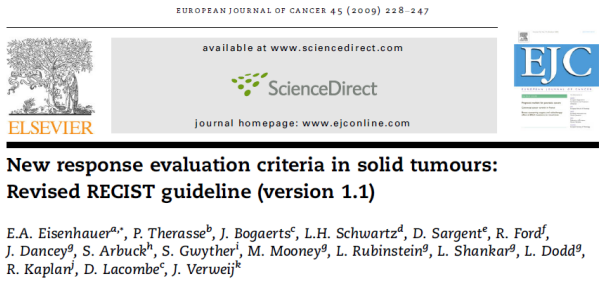
Definition	Time from randomization until death from any cause
Pros	• Measure of direct benefit • Easy to measure (Unbiased)
Cons	• It may require large population and follow-up • It includes deaths unrelated to cancer • It may be affected by crossover or subsequent therapies
Censor	• Last date subjects was seen alive

Endpoints

- **Disease-free survival (DFS)**:
  - "the time from randomization until recurrence of tumor, second cancer or death from any cause whichever occur first (FDA 2007).
  - "Although overall survival is a conventional endpoint for most adjuvant settings, DFS can be an important endpoint in situations where survival may be prolonged, making a survival endpoint impractical." (FDA 2007).
  - **To be used DFS should be surrogate of OS as** in some cancer localization : Colon, gastric, head & neck.
  - **DFS needs to be evaluated carefully** — a patient's quality of life (QOL) in the period of extended DFS is an important consideration for payers, provides, and patients alike

Endpoints

- **Tumor Response**
  - Measuring tumor shrinkage to assess if treatment is having an effect on the tumor.
  - **Primary endpoint in Phase II trials** but is often measured in Phase I and III trials as well as secondary objectives.
  - **Response is not an endpoint for adjuvant clinical trials** where the primary tumor has been « removed » surgically since in that case there are no detectable tumors to measure.
  - RECIST criteria were commonly used with classification as Complete Response, Partial response, Stability, Progressive
  - With immunotherapy and some biotherapy RECIST criteria reflecting tumor shrinkage may not be the most appropriate metric :IRECIST, CHOI criteria etc


EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

ELSEVIER

EJC

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer[a,*], P. Therasse[b], J. Bogaerts[c], L.H. Schwartz[d], D. Sargent[e], R. Ford[f], J. Dancey[g], S. Arbuck[h], S. Gwyther[i], M. Mooney[g], L. Rubinstein[g], L. Shankar[g], L. Dodd[g], R. Kaplan[j], D. Lacombe[c], J. Verweij[k]

Endpoints

- **Progression Free survival & time to progression:**
  - Measures the length of time that a patient is both alive and without worsening of their cancer. These are typical endpoints for phase II and III.
  - **This is not a direct measure of clinical benefit**
  - **Time to Tumor Progression (TTP)** is defined as the time from randomization to time of progressive disease.
  - **The progression- free survival (PFS)** duration is defined as the time from randomization to objective tumor progression or death (all causes)

Definition	Time from randomization until radiolagical tumor progression
Pros	• Requires smaller sample size • Not affected by crossover or subsequent therapies • Based on objective and quantitative assessment
Cons	• Measurement may be subject to bias • Requires frequent radiologic assessment (e.g. every 6 weeks) and same or similar among treatment arms • In some settings can be difficult to validate
Censor	• Last date radiological tumor assessment

Guidance for Industry
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Endpoints

- **Patient-Reported Outcomes (PRO)**

  - **Any report of the status of a patient's health condition assess directly from the patient, without interpretation of the patient's response by a clinician or anyone else.**
    - Fatigue (MFI20), Pain (BPISF)
    - Then PRO include Health related Quality of life / Quality of life

  - **Improvement of PRO is considered a direct clinical benefit and may be an appropriate endpoint for regular approval** (FDA).
    - FDA drug approvals have used patient symptom assessments and/ or physical signs representing symptomatic improvement as primary efficacy endpoints.

Brief Pain Inventory

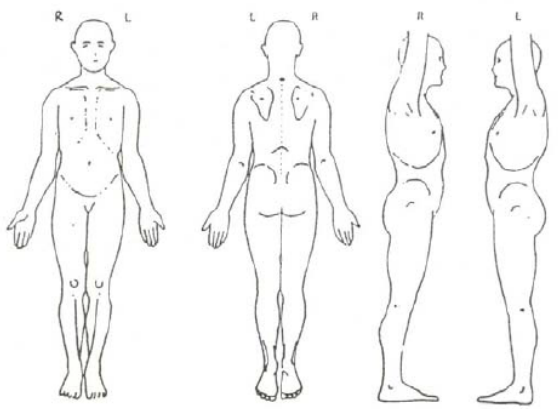
Dec 2006

Pain Interference: _____

Date: _____

Name: _____

1. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts most.



2. Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

3. Please rate your pain by circling the one number that best describes your pain at its least in the last week.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain on average.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

6. What treatments or medications are you receiving for your pain?

_____

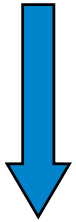
_____

Endpoints

- WHO definition of Health (1948) : «Health is a state of complete **physical, mental and social well-being** and **not merely the absence of disease or infirmity** »

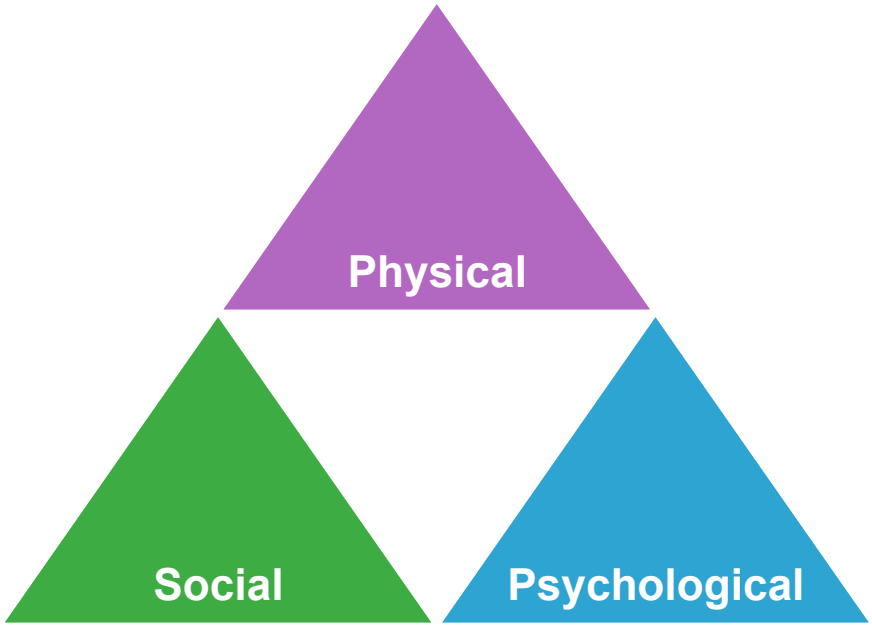
How to assess this definition of Health ?

- **Health related Quality of life** : multidimensional concept including at **least physical, mental and social dimensions and symptoms related to the treatment**



HRQoL to assess perceived health in all dimensions by the patients

Key components of HRQoL instruments



Endpoints

- **Health related Quality of Life:**
  - ***Multidimensional concept to assess indirectly health perceived by patients according the health defined by WHO in 1948***
  - Based on subjective measures of how well the patient is functioning and enjoying life. This takes into account both benefits of treatment and loss of quality of life due to the side effects of treatment, progression etc.
  - HRQOL is assessed with validated questionnaire like EORTC QLC30 for cancer patients with added modules specific of cancer localization & treatments (BR23, ELD14, OV28….etc)
  - HRQOL is typically an endpoint of phase III and now of phase II
  - Improvement in signs or symptoms must clearly distinguish between tumor symptoms and drug toxicity.
  - Patient-reported outcomes are optimally evaluated in randomized, blinded trials by the patients.

HRQOL is prognostic of OS duration in numerous cancer localizations

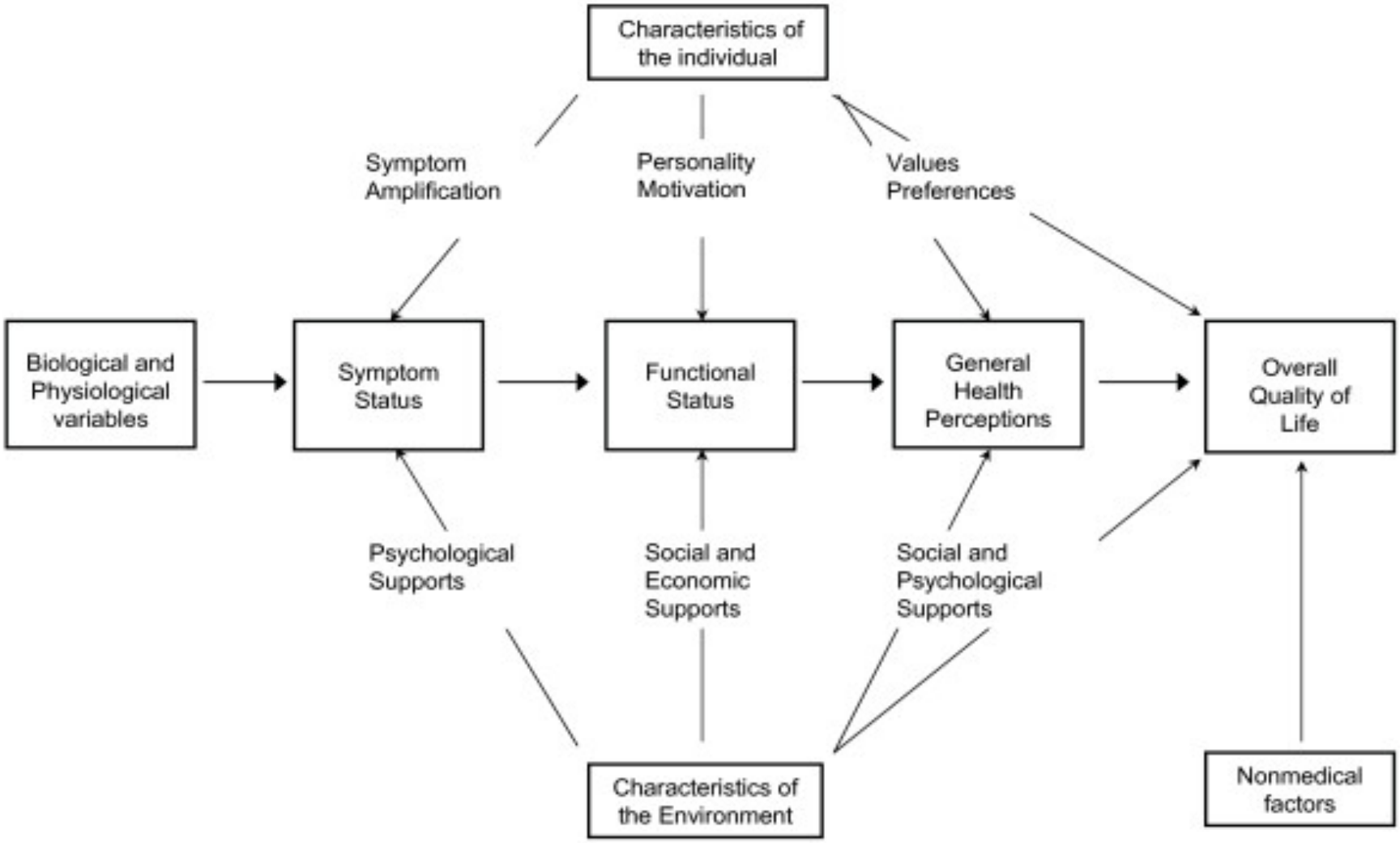


Figure 1 : **A causal pathway model of health-related quality of life.**
The horizontal arrows indicate the main, but not exclusive, direction of causality.
Wilson IB, Cleary PD. JAMA 1995;273:59–65

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

a manner as the situation allows." A proper internal

1988;i:1373-4.

Review

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EXPERT REVIEWS

Impact of response shift on longitudinal quality-of-life assessment in cancer clinical trials

Expert Rev. Pharmacoeconomics Outcomes Res. 11(5), 549–559 (2011)

Zeinab Hamidou[1,2], Tienhan Sandrine Dabakuyo[1,2] and Franck Bonnetain[†1,2]

The assessment of longitudinal change in subjective patient-reported outcomes such as health-related quality of life (HRQoL) is a key component of many clinical and research evaluations. A major goal of measuring patient-reported HRQoL is to determine to what extent changes in HRQoL reports over time represent true changes in HRQoL due to treatment or cancer and to what extent they reflect measurement error. Indeed, the subjective assessment of HRQoL change

Measuring quality of life

Is quality of life determined by expectations or experience?

Alison J Carr, Barry Gibson, Peter G Robinson

Summary points

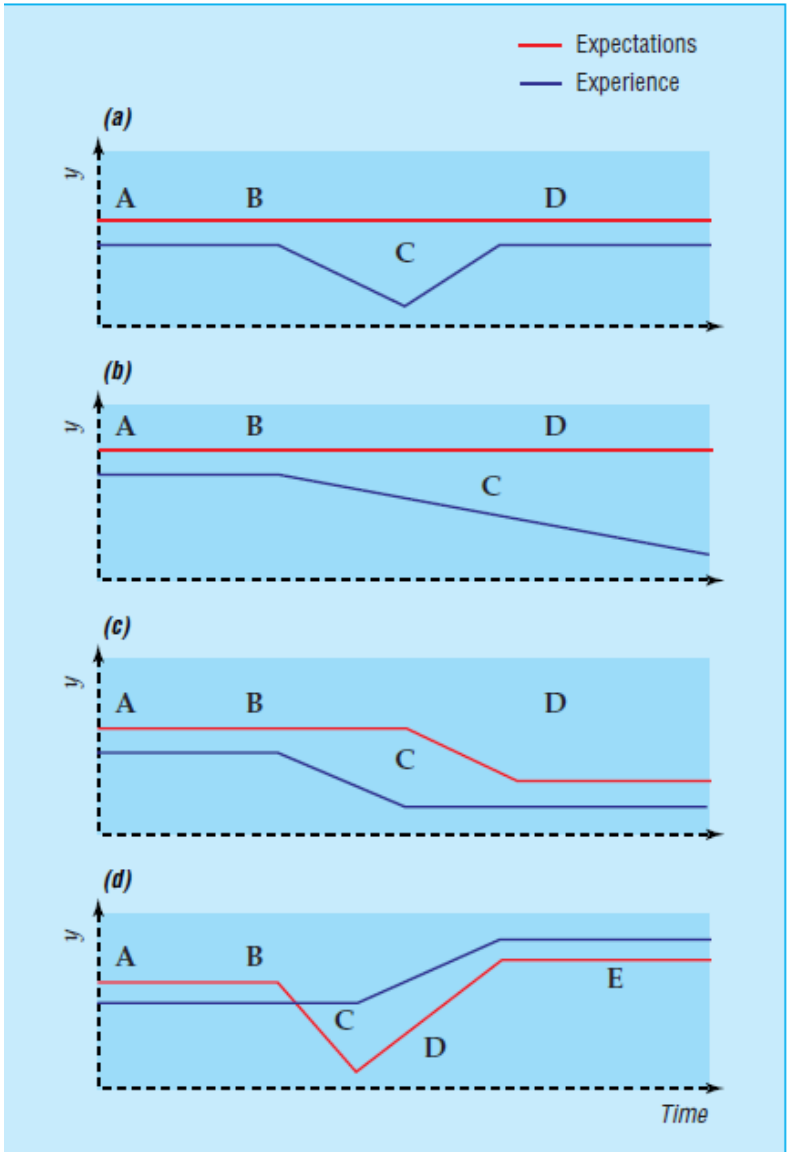
Health related quality of life is the gap between our expectations of health and our experience of it

Perception of quality of life varies between individuals and is dynamic within them

People with different expectations will report that they have a different quality of life even when they have the same clinical condition

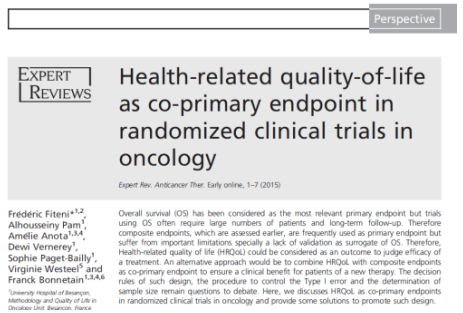
People whose health has changed may report the same level of quality of life when measures are repeated

Current measures do not take account of expectations and cannot distinguish between changes in the experience of disease and changes in expectations of health



Endpoint classification according to the clinical benefit for the patients

- Clinical benefit meaning should be reaffirmed
- What is a composite endpoint ?
- What is a surrogate endpoint ?


Perspective

EXPERT REVIEWS

Health-related quality-of-life as co-primary endpoint in randomized clinical trials in oncology

Expert Rev. Anticancer Ther. Early online, 1–7 (2015)

Frédéric Fiteni*[1,2], Alhousseiny Pam[1], Amélie Anota[1,3,4], Devi Vernerey[1], Sophie Paget-Bailly[1], Virginie Westeel[5] and Franck Bonnetain[1,3,4,6]

[1]University Hospital of Besançon, Methodology and Quality of Life in Oncology Unit, Besançon, France

Overall survival (OS) has been considered as the most relevant primary endpoint but trials using OS often require large numbers of patients and long-term follow-up. Therefore composite endpoints, which are assessed earlier, are frequently used as primary endpoint but suffer from important limitations specially a lack of validation as surrogate of OS. Therefore, Health-related quality of life (HRQoL) could be considered as an outcome to judge efficacy of a treatment. An alternative approach would be to combine HRQoL with composite endpoints as co-primary endpoint to ensure a clinical benefit for patients of a new therapy. The decision rules of such design, the procedure to control the Type I error and the determination of sample size remain questions to debate. Here, we discusses HRQoL as co-primary endpoints in randomized clinical trials in oncology and provide some solutions to promote such design.


VOLUME 27 · NUMBER 17 · JUNE 10 2009

JOURNAL OF CLINICAL ONCOLOGY

STATISTICS IN ONCOLOGY

Issues in Using Progression-Free Survival When Evaluating Oncology Products

Thomas R. Fleming, Mark D. Rothmann, and Hong Laura Lu


VOLUME 27 · NUMBER 33 · NOVEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Call for Clarity in the Reporting of Benefit Associated With Anticancer Therapies

There was considerable heterogeneity in definition of clinical benefit among the 51 trials with a tumor-centered end point. In 45 articles stable disease was used in combination with complete and/or partial response; in three further studies stable disease was used alone.

Endpoint classification in oncology

VOLUME 27 · NUMBER 17 · JUNE 10 2009
JOURNAL OF CLINICAL ONCOLOGY | STATISTICS IN ONCOLOGY

Issues in Using Progression-Free Survival When Evaluating Oncology Products

Thomas R. Fleming, Mark D. Rothmann, and Hong Lan Lu

- **<u>Clinical endpoints</u> = <u>Patient centered endpoints</u>**
  - Characteristic or variable that reflects how a patient feels (QoL), functions (QoL, PRO), or survives (OS): **OS, Health related Quality of Life (QoL), fatigue, pain**

- **<u>Biomarkers</u> = <u>tumor centered endpoints</u>**
  - A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention: **PFS, DFS, RECIST**

- **<u>« Surrogate Endpoints »</u> :**
  - A biomarker that is intended to substitute for a clinical endpoint = for a « patient center endpoints »
  - A surrogate endpoint is expected to predict clinical benefit : ***surrogate validation using meta analysis approaches and should be done by cancer localization & treatment modalities***

Ref : Temple, JAMA 1999;282:790.

Ref : Biomarkers Definitions Working Group, Clin Pharmacol Ther 2001;69:89.

Guidance for Industry
Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Endpoint classification for FDA

The Oncologist

The Role of the U.S. Food and Drug Administration Review Process: Clinical Trial Endpoints in Oncology

Amy E. McKee,[a] Ann T. Farrell,[a] Richard Pazdur,[a] Janet Woodcock[b]

[a]Office of Oncology Drug Products, [b]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA

Key Words. Effectiveness • Endpoint • Approval

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated a surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies

- 1st : OS

- 2nd : PRO & HRQOL

Guidance for Industry

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Additional copies are available from:

Office of Training and Communications
Division of Drug Information, HFD-240

Table 1, continued

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit • Not a comprehensive measure of drug activity • Only a subset of patients who benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression-Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Composite endpoint

- One Endpoint based on at least 2 events, components
- Combination of various clinical events that might happen
- Ex with PFS : including local progression, metastases or death (all causes), where any one of those events would count as part of the composite endpoint

Mainer CL. Clinical Trials Dictionary, 1996.

ELSEVIER

Journal of Clinical Epidemiology 58 (2005) 785–790

Journal of Clinical Epidemiology

Powering our way to the elusive side effect: A composite outcome 'basket' of predefined designated endpoints in each organ system should be included in all controlled trials

Peter Tugwell[a,b,c,*], Maria G. Judd[a], Jim F. Fries[d], Gurkirpal Singh[e], George A. Wells[c]

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[b]*Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada*
[c]*Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada*
[d]*Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, USA*
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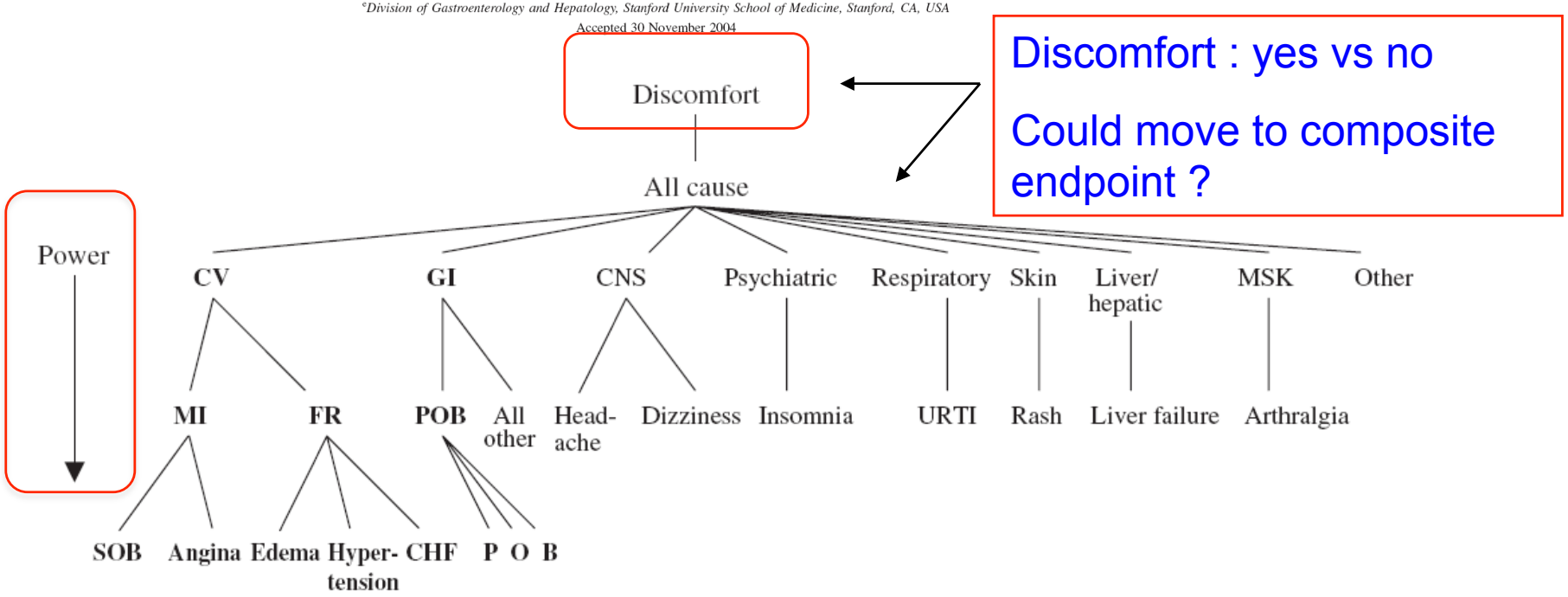
Accepted 30 November 2004



Discomfort : yes vs no

Could move to composite endpoint ?

Fig. 2. Hierarchy of toxicity data collection for discomfort. *Abbreviations:* CHF, congestive heart failure; CNS, central nervous system; CV, cardiovascular; FR, fluid retention; GI, gastrointestinal; MI, myocardial infarction; MSK, musculoskeletal; POB, perforation, obstruction, and bleeding; SOB, shortness of breath; URTI, upper respiratory tract infection. Arrow indicates decreasing power.

Composite endpoint

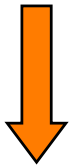
BMJ

RESEARCH

Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review

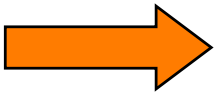
Gloria Cordoba, researcher,[1] Lisa Schwartz, professor,[2] Steven Woloshin, professor,[2] Harold Bae, researcher,[2] Peter C Gøtzsche, professor[1]

- Advantages
  - To improve rate of event
  - To improve statistical power
  - To reduce trial duration and or number of patient



- **But each of component should be clinically meaningful**
- Important to look at effects on each of the components
- Similar effects (certainly, direction of effects) should be seen on all components

- **No one component should dominate the endpoint**
- **If it does, this might limit the licensed indication**



Definition is a key component

BMJ

RESEARCH

Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review

Gloria Cordoba, researcher,[1] Lisa Schwartz, professor,[2] Steven Woloshin, professor,[2] Harold Bae, researcher,[2] Peter C Gøtzsche, professor[1]

WHAT IS ALREADY KNOWN ON THIS TOPIC

- When trial results are reported as a composite outcome, the effect is often smallest for the most important component of the outcome and biggest for the less important components
- Clinician driven outcomes are predictive of a statistically significant result for the composite outcome
- Individual outcomes may be selected for inclusion in the composite to ensure statistical significance

WHAT THIS STUDY ADDS

- Changes in the definition of composite outcomes during a trial are common and suggest biased reporting
- Pivotal data are often missing, ambiguous, or uninterpretable

CONS composite endpoints:

- **To reach statistical significance**
- **Smallest effect for the most important component**

Cite this article as: BMJ, doi:10.1136/bmj.39136.682083.AE (published 2 April 2007)

BMJ

RESEARCH

Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials

Ignacio Ferreira-González, research fellow,[1] Jason W Busse, research associate,[3] Diane Heels-Ansdell, statistician,[3] Victor M Montori, associate professor,[5] Elie A Akl, assistant professor,[6]

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical trialists use composite end points, outcomes that capture the number of patients who have one or more of several events, to increase event rates and statistical power

When the gradient of importance to patients is large, and the more important events are uncommon and show negligible treatment effects, use of composite end points can be misleading

WHAT THIS STUDY ADDS

Almost half of a sample of recent prominently published cardiovascular trials used composite end points, which were often inadequately reported and showed large gradients in importance to patients

End points of least importance to patients typically contributed most events

Composite end points, as currently used in cardiovascular trials, may often be misleading

Definition of composite endpoint is then crucial

VOLUME 26 · NUMBER 22 · AUGUST 1 2008

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Table 2. Distribution of Selected Key Points Related to Time-to-Event End Points or to Articles Reported in Cancer Randomized Clinical Trials Published in 2004 in Eight Major Journals

Key Point	Survival End Points (n = 267) No.	%	Articles (n = 125) No.	%
Starting point	203	76	98	78
Event of interest	197	70	99	79
Censor	125	47	73	58
All 3 key points	113	42	65	52
Survival estimation or effect size*	248	93	119	95†
Precision	163	61	94	67
No. of events	172	65	90	72
No. of patients at risk	119	45	66	53
All 4 key points	73	27	40	32
All key points	33	12	10	8

*Effect size, hazard ratio or difference in median survival times.
†Survival estimation (n = 113, 90%), effect size (n = 91, 73%).

To allow comparison of the results between trials

Survival End Point Reporting in Randomized Cancer Clinical Trials: A Review of Major Journals

Simone Mathoulin-Pelissier, Sophie Gourgou-Bourgade, Franck Bonnetain, and Andrew Kramar

Table 3. Reported Definitions for the Time-to-Event End Points From 10 Articles With All Seven Key Points Reported (according to starting point, events of interest, and censor)

Term	No. of Articles*	Cancer Site	Starting Point	Events of Interest	Censor
Overall survival	3	Pancreas Breast Ovaries	Randomization (or treatment start)	Death from any cause	Lost to follow-up (censored at the date of last contact)
Overall survival	5	Colorectal Prostate Melanoma Stomach Pancreas	Randomization (or treatment start)	Death	Clinical cut-off Lost to follow-up (censored at the date of last contact)
Disease-free survival	1	Melanoma	Randomization	Relapse or death	Alive without relapse at last follow-up
Progression-free survival	5	Ovaries Colorectal Lymphoma Prostate Pancreas	Randomization (or end of induction treatment)	Progression or death	Last disease assessment or last follow-up without progression
Time-to-progression	1	Pancreas	Randomization (or treatment start)	First objective documentation of tumor progression or time of death as result of progressive disease in the absence of previous documentation of objective progressive disease	No objective evidence of tumor progression and patients were off study; death > 30 days after last treatment evaluation (last dose for chemotherapy); death resulting from causes unrelated to the main studied cancer

*Total > 10 because one article had several end points.

Breast Cancer Res Treat (2008) 109:567–572
DOI 10.1007/s10549-007-9681-x

EPIDEMIOLOGY

The in- or exclusion of non-breast cancer related death and contralateral breast cancer significantly affects estimated outcome probability in early breast cancer

R. A. Nout · W. E. Fiets · H. Struikmans · F. R. Rosendaal · H. Putter · J. W. R. Nortier

Table 2 Definitions of outcome.

Overall survival	Time from surgery until death from any cause
Disease specific survival	Time from surgery until death related to breast cancer. Death not related to breast cancer is censored (Kaplan–Meier analysis) or treated as competing event (competing risk analysis).
Disease free interval	Time from surgery until recurrent disease.[a] Death not related to breast cancer is censored (Kaplan–Meier analysis) or treated as competing event (competing risk analysis).
Disease free survival	Time from surgery until recurrent disease[a] or death from any cause.

[a] In the definition of recurrent disease local recurrence, regional recurrence, and distant metastasis are considered events; contralateral breast cancer is ignored, treated as event or censored (Kaplan–Meier analysis) / treated as competing event (competing risk analysis)

Table 3 Estimated 10-year survival according to definition of survival determined both by Kaplan–Meier method and the competing risk analysis.

Survival definition	10-year Survival (%)					
	All patients		No adjuvant systemic therapy		Adjuvant systemic therapy	
	KM	CR	KM	CR	KM	CR
Overall survival	68.0		75.8		58.6	
Disease specific survival	79.3	80.6	85.3	86.2	71.9	73.7
Disease free survival						
Contralateral BC ignored	59.3		65.8		51.2	
Contralateral BC censored	58.6	59.4	64.9	66.0	51.1	51.6
Contralateral BC event	55.5		59.9		50.2	
Disease free interval						
Contralateral BC ignored	69.4	70.9	74.6	75.8	63.0	64.9
Contralateral BC censored	68.9	70.9	73.9	75.9	63.2	65.4
Contralateral BC event	64.8	66.5	67.6	69.2	61.3	63.4

KM: Kaplan–Meier method; CR: competing risk analysis; BC: breast cancer

DFS at 10 years from 55.5 to 59.3% !

ARTICLE IN PRESS

European Journal of Cancer (2012) xxx, xxx–xxx

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Protocol of the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project: Formal consensus method for the development of guidelines for standardised time-to-event endpoints' definitions in cancer clinical trials

Carine A. Bellera [a,b,*], Marina Pulido [a,b], Sophie Gourgou [c], Laurence Collette [d], Adélaïde Doussau [b,e,f], Andrew Kramar [g], Tienhan Sandrine Dabakuyo [h], Monia Ouali [d], Anne Auperin [i], Thomas Filleron [j], Catherine Fortpied [d], Christophe Le Tourneau [k], Xavier Paoletti [l], Murielle Mauer [d], Simone Mathoulin-Pélissier [a,b,f,o], Franck Bonnetain [m,n,o]

Annals of Oncology Advance Access published March 27, 2015

review

Annals of Oncology 00: 1–7, 2015
doi:10.1093/annonc/mdv106

Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (*Definition for the Assessment of Time-to-event Endpoints in CANcer trials*)†

S. Gourgou-Bourgade[1,2*], D. Cameron[3], P. Poortmans[4], B. Asselain[5], D. Azria[6], F. Cardoso[7], R. A'Hern[8], J. Bliss[8], J. Bogaerts[9], H. Bonnefoi[10], E. Brain[11], M. J. Cardoso[7], B. Chibaudel[12], R. Coleman[13], T. Cufer[14], L. Dal Lago[15], F. Dalenc[16], E. De Azambuja[15], M. Debled[10], S. Delaloge[17], T. Filleron[16], J. Gligorov[18], M. Gutowski[19], W. Jacot[20], C. Kirkove[21], G. MacGrogan[10], S. Michiels[22,23], I. Negreiros[24], B. V. Offersen[25], F. Penault Llorca[26,27], G. Pruneri[28,29], H. Roche[16], N. S. Russell[30], F. Schmitt[31,32], V. Servent[33], B. Thürlimann[34], M. Untch[35], J. A. van der Hage[36], G. van Tienhoven[37], H. Wildiers[38,39], J. Yarnold[40], F. Bonnetain[41], S. Mathoulin-Pélissier[42,43], C. Bellera[42,43] & T. S. Dabakuyo-Yonli[44]

European Journal of Cancer (2014) 50, 2983–2993

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Guidelines for time-to-event end-point definitions in trials for pancreatic cancer. Results of the DATECAN initiative (Definition for the Assessment of Time-to-event End-points in CANcer trials) ☆

Franck Bonnetain [a,*], Bert Bonsing [b], Thierry Conroy [c], Adelaide Dousseau [d], Bengt Glimelius [e], Karin Haustermans [f], François Lacaine [g], Jean Luc Van Laethem [h], Thomas Aparicio [i], Daniela Aust [j], Claudio Bassi [k], Virginie Berger [l], Emmanuel Chamorey [m], Benoist Chibaudel [n], Laeticia Dahan [o], Aimery De Gramont [n], Jean Robert Delpero [p], Christos Dervenis [q], Michel Ducreux [r], Jocelyn Gal [s], Erich Gerber [t], Paula Ghaneh [u], Pascal Hammel [v], Alain Hendlisz [w], Valérie Jooste [x], Roberto Labianca [y], Aurelien Latouche [z], Manfred Lutz [aa], Teresa Macarulla [ab], David Malka [r], Muriel Mauer [ac], Emmanuel Mitry [ad], John Neoptolemos [ae], Patrick Pessaux [af], Alain Sauvanet [ag], Josep Tabernero [ab], Julien Taieb [ah], Geertjan van Tienhoven [ai], Sophie Gourgou-Bourgade [aj], Carine Bellera [ak], Simone Mathoulin-Pélissier [ak], Laurence Collette [ac]

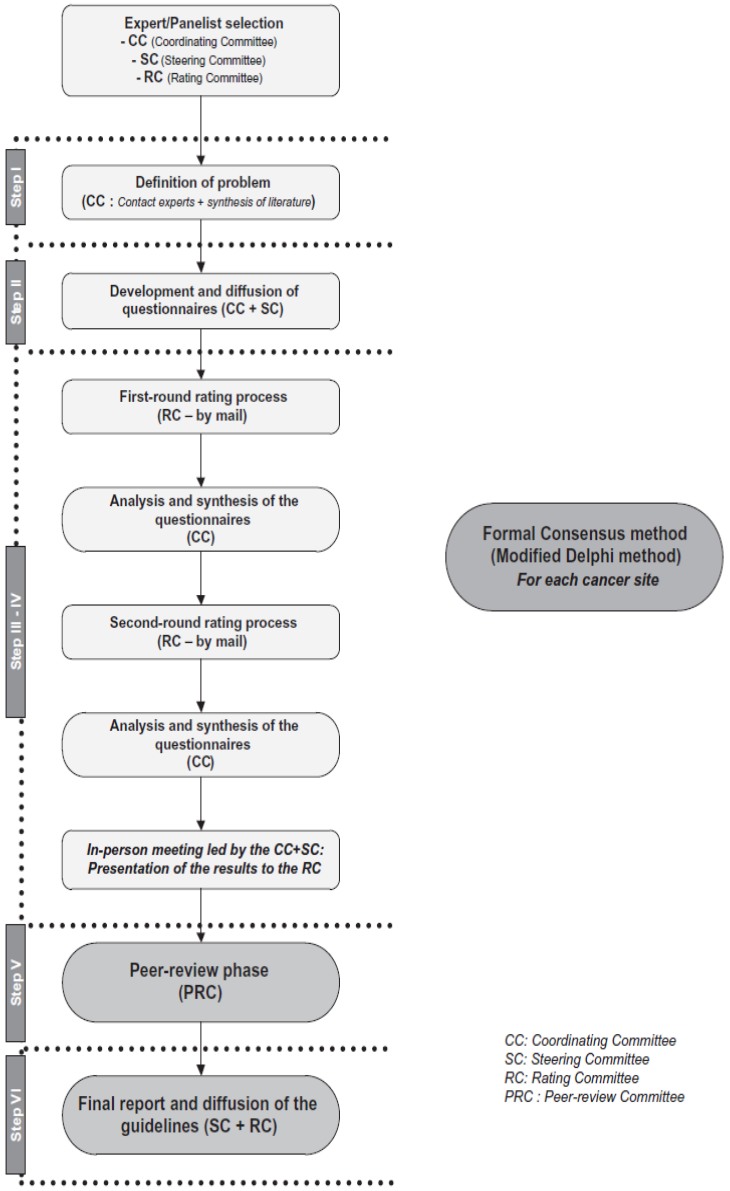
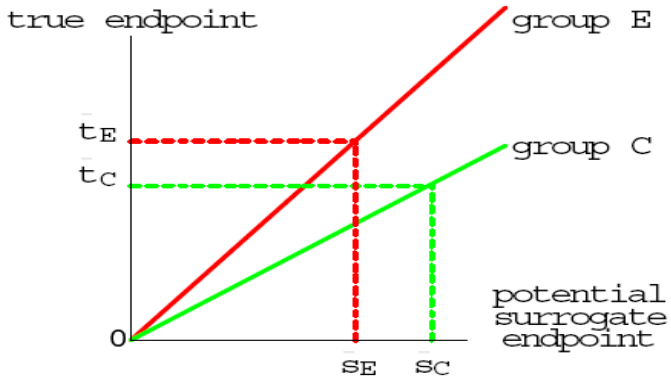


Fig. 1. The formal consensus of the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project.

Surrogacy/surrogate endpoints

- Clinical benefit required surrogacy :
  - Impact of treatment on the surrogate (PFS, DFS etc..) should predict effect of treatment on the clinical endpoints (OS, HRQOL etc)
  - **A simple correlation is not sufficient** : if tumor shrinkage was correlated with OS ≠ surrogacy




BMC Medical Research Methodology

BioMed Central

Research article

Open Access

A perfect correlate does not a surrogate make

Stuart G Baker*[1] and Barnett S Kramer[2]

Address: [1]Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, USA and [2]Office of Disease Prevention, National Institutes of Health, USA

Email: Stuart G Baker* - sb16i@nih.gov; Barnett S Kramer - KramerB@OD.NIH.GOV

* Corresponding author

Published: 09 September 2003

BMC Medical Research Methodology 2003, **3**:16

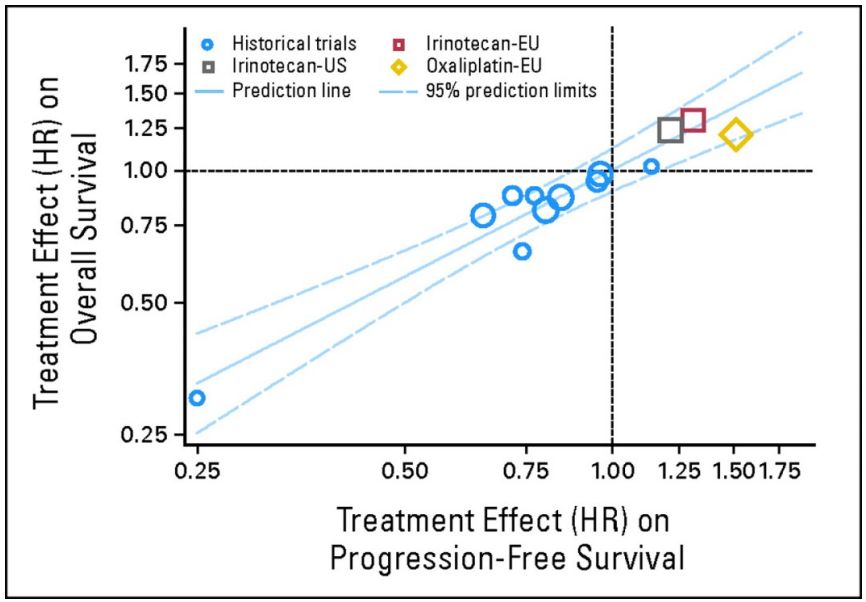
Received: 10 July 2003

Accepted: 09 September 2003

  - **Surrogate evaluation should be done by cancer localization, setting, type of treatment etc and then always done a posteriori**
  - Gold standard for validation : Meta-analytic approach

91.Fleming TR: Surrogate endpoints and FDA's accelerated approval process. Health Aff (Millwood) 24:67-78, 2005

PFS as surrogate of OS in mCRC ?



VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Progression-Free Survival Is a Surrogate for Survival in Advanced Colorectal Cancer

Marc Buyse, Tomasz Burzykowski, Kevin Carroll, Stefan Michiels, Daniel J. Sargent, Langdon L. Miller, Gary L. Elfring, Jean-Pierre Pignon, and Pascal Piedbois

PFS « surrogate » of OS for chemotherapies
But since
ASCO 2013 PFS could not be considered as a good « surrogate » for biotherapies

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

Progression-Free Survival: Meaningful or Simply Measurable?

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

See accompanying articles on pages 1114 and 1122

VOLUME 33 · NUMBER 1 · JANUARY 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Individual Patient Data Analysis of Progression-Free Survival Versus Overall Survival As a First-Line End Point for Metastatic Colorectal Cancer in Modern Randomized Trials: Findings From the Analysis and Research in Cancers of the Digestive System Database

Qian Shi, Aimery de Gramont, Axel Grothey, John Zalcberg, Benoist Chibaudel, Hans-Joachim Schmoll, Matthew T. Seymour, Richard Adams, Leonard Saltz, Richard M. Goldberg, Cornelis J.A. Punt, Jean-Yves Douillard, Paulo M. Hoff, Joel Randolph Hecht, Herbert Hurwitz, Eduardo Díaz-Rubio, Rainer Porschen, Niall C. Tebbutt, Charles Fuchs, John Souglakos, Alfredo Falcone, Christophe Tournigand, Fairooz F. Kabbinavar, Volker Heinemann, Eric Van Cutsem, Carsten Bokemeyer, Marc Buyse, and Daniel J. Sargent

See accompanying editorial on page 4 and article on page 36

- Interest for the patients to improve PFS without OS improvement ?

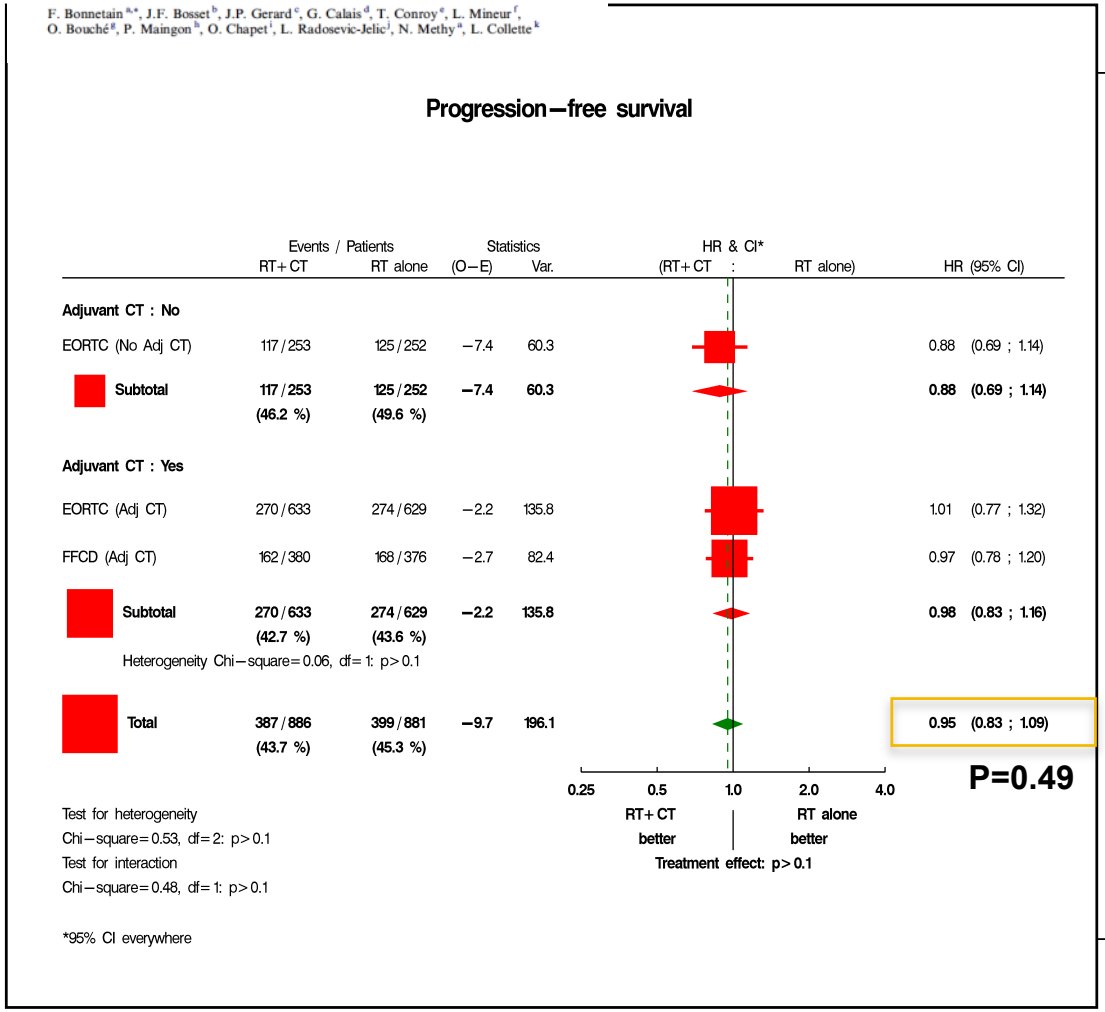
Class (n. of trials)	Overall (22)	Targeted (12)	Non-strategy (18)	Superiority (16)
Pt level				
Rank corr.	.51 (.50 - .52)	.55 (.54 - .56)	.53 (.52 - .54)	.51 (.50 - .52)
Trt arm level [6m PFS vs. 12m OS rates]				
R^2_{WLS}	.69 (.58 - .79)	.70 (.48 - .91)	.73 (.62 - .83)	.71 (.59 - .83)
Trial level [HR_{PFS} vs. HR_{OS}]				
R^2_{WLS}	.54 (.33 - .75)	.52 (.24 - .80)	.54 (.32 - .76)	.51 (.24 - .77)
R^2_{Copula}	.46 (.24 - .68)	.45 (.16 - .75)	.48 (.24 - .71)	.54 (.31 - .78)
Concordance	67%	64%	68%	63%

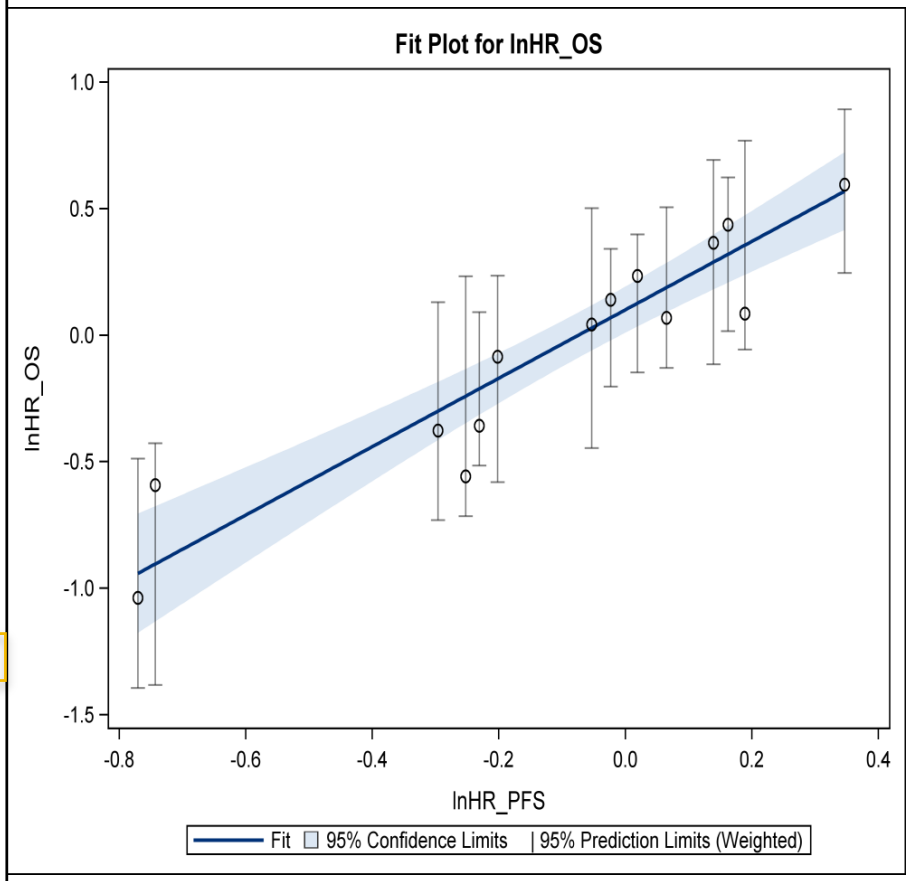
ARTICLE IN PRESS
European Journal of Cancer (2012) xxx, xxx–xxx
Available at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: www.ejconline.com
EJC
ELSEVIER

Surrogacy of PFS for OS in T3-T4 Rectal Cancer

What is the clinical benefit of preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer in a pooled analysis of EORTC 22921 and FFCD 9203 trials: Surrogacy in question?

F. Bonnetain [a,*], J.F. Bosset [b], J.P. Gerard [c], G. Calais [d], T. Conroy [e], L. Mineur [f], O. Bouché [g], P. Maingon [h], O. Chapet [i], L. Radosevic-Jelic [j], N. Methy [a], L. Collette [k]





3 year PFS Rates :

- CRT = 64.3% (95% CI: 61.0-67.5%)
- RT = 60.6% (95% CI: 57.2-63.9%)

PFS
Trial-level association
R^2 = 0.88 (95% CI 0.77 – 1)

DFS is still surrogate in adjuvant colon cancer

VOLUME 25 · NUMBER 29 · OCTOBER 10 2007

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

End Points for Colon Cancer Adjuvant Trials: Observations and Recommendations Based on Individual Patient Data From 20,898 Patients Enrolled Onto 18 Randomized Trials From the ACCENT Group

Daniel J. Sargent, Smitha Patiyil, Greg Yothers, Daniel G. Haller, Richard Gray, Jacqueline Benedetti, Marc Buyse, Roberto Labianca, Jean Francois Seitz, Christopher J. O'Callaghan, Guido Francini, Axel Grothey, Michael O'Connell, Paul J. Catalano, David Kerr, Erin Green, Harry S. Wieand, Richard M. Goldberg, and Aimery de Gramont

From the Departments of Health Sciences Research and Medical Oncology, North Central Cancer Treatment Group, Mayo Clinic, Rochester, MN; Biostatistics Center, National Surgical Adjuvant Breast and Bowel Project Statistical Center and Operations

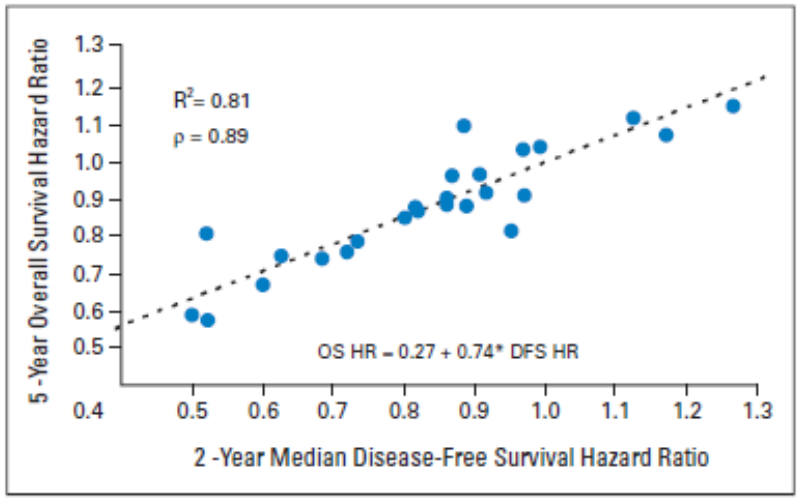


Fig 3. Hazard ratios (HRs) for 2-year median disease-free survival (DFS) *v* 5-year overall survival (OS) for 25 within-trial comparisons.

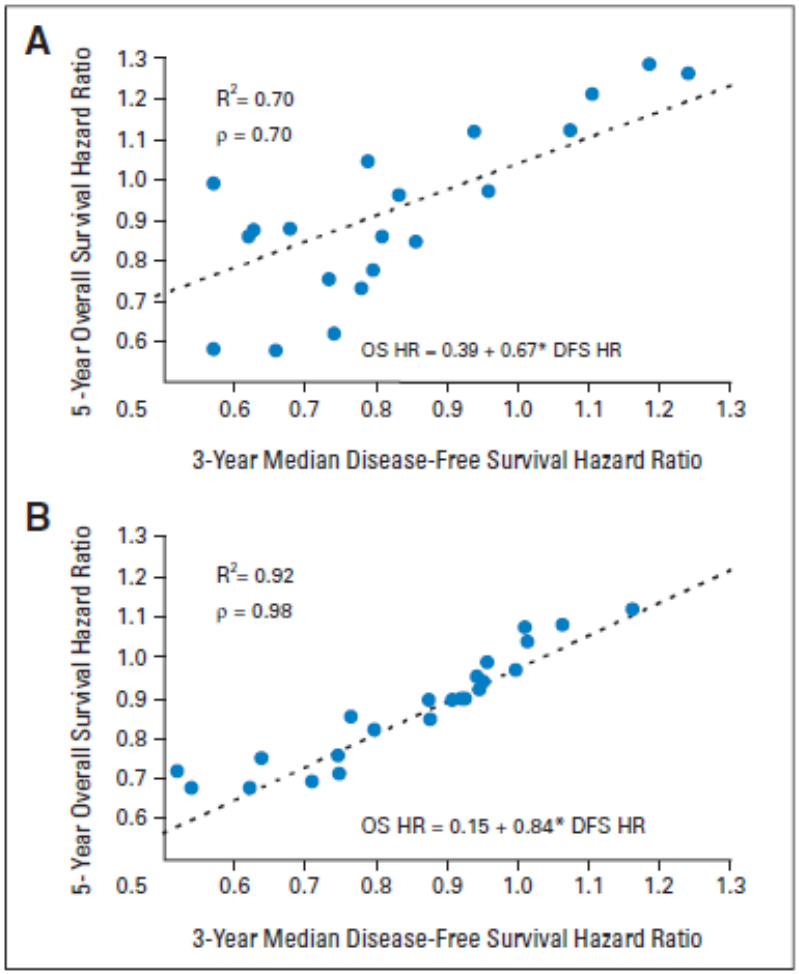


Fig 2. Hazard ratios (HRs) for 3-year disease-free survival (DFS) *v* 5-year overall survival (OS) by stage for 25 within-trial comparisons. (A) Stage II patients; (B) stage III patients.

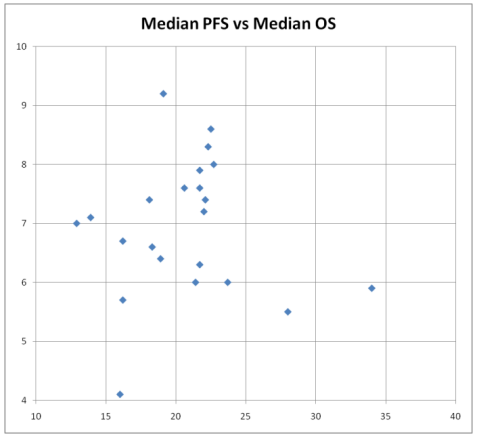
PFS as surrogate in breast cancer

Evaluation of Tumor Response, Disease Control, Progression-Free Survival, and Time to Progression As Potential Surrogate End Points in Metastatic Breast Cancer

Tomasz Burzykowski, Marc Buyse, Martine J. Piccart-Gebhart, George Sledge, James Carmichael, Hans-Joachim Lück, John R. Mackey, Jean-Marc Nabholtz, Robert Paridaens, Laura Biganzoli, Jacek Jassem, Marijke Bontenbal, Jacques Bonneterre, Stephen Chan, Gul Atalay Basaran, and Patrick Therasse

- ✓ At the individual level PFS et OS:

The rank correlation coefficient between PFS and survival was 0.688 (95% CI, 0.686 to 0.690), which indicated a moderate correlation between these end points. The rank correlation coefficient between TTP and survival was 0.682 (95% CI, 0.680 to 0.684).



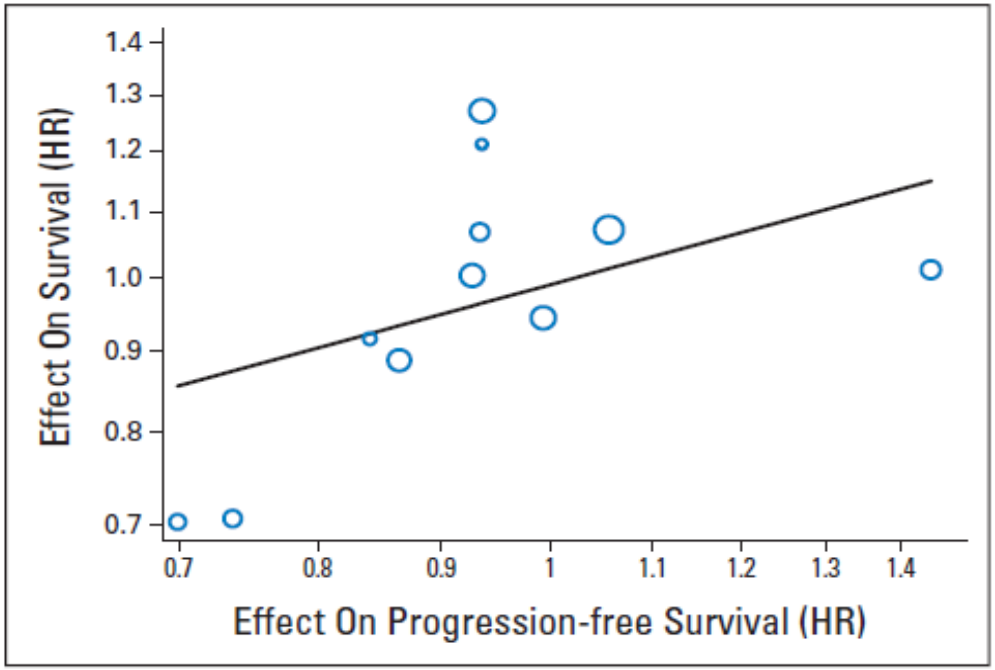
PFS in breast cancer

Evaluation of Tumor Response, Disease Control, Progression-Free Survival, and Time to Progression As Potential Surrogate End Points in Metastatic Breast Cancer

Tomasz Burzykowski, Marc Buyse, Martine J. Piccart-Gebhart, George Sledge, James Carmichael, Hans-Joachim Lück, John R. Mackey, Jean-Marc Nabholtz, Robert Paridaens, Laura Biganzoli, Jacek Jassem, Marijke Bontenbal, Jacques Bonneterre, Stephen Chan, Gul Atalay Basaran, and Patrick Therasse

- ✓ At the trial level

PFS is not surrogate of OS in mBC



The rank correlation coefficient between the treatment effects on PFS and survival was 0.48 (95% CI, −0.34 to 1.30; Fig 3). For the treatment effects on TTP and survival, the ρ was 0.49 (95% CI, −0.32 to 1.30; plot not shown). As with the result obtained for tumor response and disease control, both estimates indicated a weak and imprecisely estimated association between treatment effects for PFS and TTP on one hand and for survival on the other hand.

REVIEW

Disease-Free Survival as a Surrogate for Overall Survival in Adjuvant Trials of Gastric Cancer: A Meta-Analysis

Koji Oba, Xavier Paoletti, Steven Alberts, Yung-Jue Bang, Jacqueline Benedetti, Harry Bleiberg, Paul Catalano, Florian Lordick, Stefan Michiels, Satoshi Morita, Yasuo Ohashi, Jean-pierre Pignon, Philippe Rougier, Mitsuru Sasako, Junichi Sakamoto, Daniel Sargent, Kohei Shitara, Eric Van Cutsem, Marc Buyse, Tomasz Burzykowski; on behalf of the GASTRIC group

Manuscript received February 12, 2013; revised July 25, 2013; accepted July 25, 2013.

Correspondence to: Koji Oba, PhD, Translational Research and Clinical Trial Center, Hokkaido University Hospital, Kita 14, Nishi 5, Kita-ku, Sapporo, Hokkaido 0608648, Japan (e-mail: k.oba@huhp.hokudai.ac.jp).

DOI:10.1093/jnci/djt337

JNCI Journal of the National Cancer Institute Advance Access published October 9, 2013

BRIEF COMMUNICATION

Progression-Free Survival as a Surrogate for Overall Survival in Advanced/Recurrent Gastric Cancer Trials: A Meta-Analysis

Xavier Paoletti, Koji Oba, Yung-Jue Bang, Harry Bleiberg, Narikazu Boku, Olivier Bouché, Paul Catalano, Nozomu Fuse, Stefan Michiels, Markus Moehler, Satoshi Morita, Yasuo Ohashi, Atsushi Ohtsu, Arnaud Roth, Philippe Rougier, Junichi Sakamoto, Daniel Sargent, Mitsuru Sasako, Kohei Shitara, Peter Thuss-Patience, Eric Van Cutsem, Tomasz Burzykowski, Marc Buyse; on behalf of the GASTRIC group

Manuscript received February 10, 2013; revised July 25, 2013; accepted July 25, 2013.

We used a meta-analytic validation approach (3,4,7). OS was defined as the time from randomization to death from any cause or to the last follow-up. PFS was the time to tumor progression or death from any cause or time to the last follow-up assessment. A detailed description of statistical methods used is provided in the Supplementary Material (available online). For external validation, we applied the identified relation to predict the hazard ratio (HR) for OS (HR_{OS}) from the hazard ratio for PFS (HR_{PFS}) in randomized trials published since 2000 for which we had not

VOLUME 27 · NUMBER 33 · NOVEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Call for Clarity in the Reporting of Benefit Associated With Anticancer Therapies

Christopher M. Booth, Pavlo Ohorodnyk, and Elizabeth A. Eisenhauer

National Cancer Institute of Canada Clinical Trials Group, Queen's University, Kingston, Ontario, Canada

Despite its original definition, in the modern era of targeted therapy clinical benefit is often used in this journal and elsewhere to describe a decrease in tumor size or stable disease for a minimum period of time.[5-8] We suggest that whether such patients experience

in the duration and/or quality of survival.

Ultimately, the goal of all of our therapies is to improve either the quality or quantity of survival for patients with cancer. We hope that the *Journal of Clinical Oncology* and other investigators consider the proposed changes in language in an effort to more clearly communicate the true benefits of our therapies to patients, clinicians, and policy makers.

The real objective of the treatment is to improve Survival duration and/or Quality of life

Outcomes and endpoints in cancer trials: bridging the divide

Michelle K Wilson, Deborah Collyar, Diana T Chingos, Michael Friedlander, Tony W Ho, Katherine Karakasis, Stan Kaye, Mahesh K B Parmar, Matthew R Sydes, Ian F Tannock, Amit M Oza

Cancer is not one disease. Outcomes and endpoints in trials should incorporate the therapeutic modality and cancer *Lancet Oncol* 2015; 16

The key priorities in the treatment of cancer are to enable affected individuals to live longer or better, and ideally both, than they would without therapy.[1] The discussion of outcomes and endpoints in oncology trials needs to take into account cancer type and therapeutic modality as these parameters affect the expectations of both clinicians and patients. Our accompanying Review[2] discussed the

Outcomes and endpoints in trials of cancer treatment: the past, present, and future

Michelle K Wilson, Katherine Karakasis, Amit M Oza

Cancer treatment should allow patients to live better or longer lives, and ideally, both. Trial endpoints should show *Lancet Oncol* 2015; 16: e32–42

However, PFS as the primary outcome measure in trial design and analysis carries a risk of drawing invalid conclusions about the long-term efficacy of a drug, particularly if it is not a true surrogate endpoint for that disease site. Evidence from large randomised controlled trials that does not show improved overall survival or quality of life in patients in addition to PFS raises the question of the value of incorporating such a treatment into clinical practice

The time has come for the oncology community to challenge traditional trial design and develop new, validated endpoints that reflect clinical benefit rather than deviations in tumour size. Trial endpoints must keep pace with the evolution of clinical trial designs. By

+Model
JVS 336 1–6
ARTICLE IN PRESS

Journal of Visceral Surgery (2013) xxx, xxx–xxx

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www.em-consulte.com/en

REVIEW

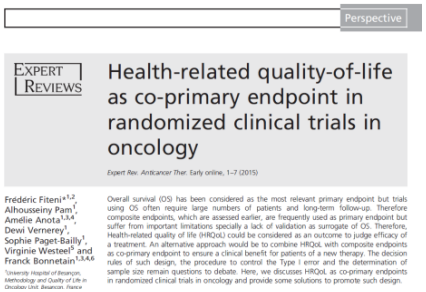
Endpoints in cancer clinical trials

F. Fiteni[a], V. Westeel[a], X. Pivot[a], C. Borg[a], D. Vernerey[b], F. Bonnetain[b,*]

[a] University Hospital of Besançon, Department of Medical Oncology, 3, boulevard Fleming, 25000 Besançon, France
[b] Methodology and quality of Life in Oncology unit (EA 3181) & quality of Life and cancer clinical research plateform, CHU de Besançon, 2, place Saint-Jacques, 25000 Besançon, France

So where are we going = co-primary endpoints
- Patient centered endpoints : SG & QdV
- Tumor Centered endpoint: PFS, DFS etc

- HrQoL should be a co-primary endpoint with tumor centered endpoint to be in line with :
  - Trials duration and sample size
  - Demonstration of clinical benefit for the patient



Perspective

EXPERT REVIEWS

Health-related quality-of-life as co-primary endpoint in randomized clinical trials in oncology

Expert Rev. Anticancer Ther. Early online, 1–7 (2015)

Frédéric Fiteni*[1,2], Alhousseiny Pam[1], Amélie Anota[1,3,4], Devi Vernerey[1], Sophie Paget-Bailly[1], Virginie Westeel[5] and Franck Bonnetain[1,3,4,6]

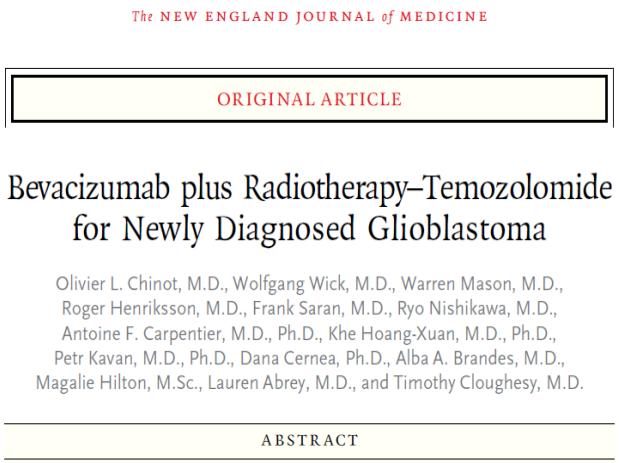
[1]University Hospital of Besançon, Methodology and Quality of Life in Oncology Unit, Besançon, France

Overall survival (OS) has been considered as the most relevant primary endpoint but trials using OS often require large numbers of patients and long-term follow-up. Therefore composite endpoints, which are assessed earlier, are frequently used as primary endpoint but suffer from important limitations specially a lack of validation as surrogate of OS. Therefore, Health-related quality of life (HRQoL) could be considered as an outcome to judge efficacy of a treatment. An alternative approach would be to combine HRQoL with composite endpoints as co-primary endpoint to ensure a clinical benefit for patients of a new therapy. The decision rules of such design, the procedure to control the Type I error and the determination of sample size remain questions to debate. Here, we discuss HRQoL as co-primary endpoints in randomized clinical trials in oncology and provide some solutions to promote such design.

New challenge to implement such design in oncology

Two phase III RCT in glioblastoma for regular approval of Bevacizumab

- Two me too trials:
  - STUPP + /- Bevacizumab in Glioblastoma



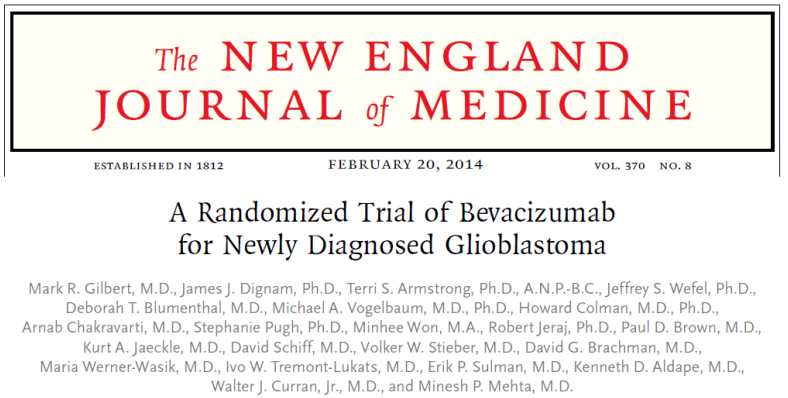
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

Olivier L. Chinot, M.D., Wolfgang Wick, M.D., Warren Mason, M.D., Roger Henriksson, M.D., Frank Saran, M.D., Ryo Nishikawa, M.D., Antoine F. Carpentier, M.D., Ph.D., Khe Hoang-Xuan, M.D., Ph.D., Petr Kavan, M.D., Ph.D., Dana Cernea, Ph.D., Alba A. Brandes, M.D., Magalie Hilton, M.Sc., Lauren Abrey, M.D., and Timothy Cloughesy, M.D.

ABSTRACT



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 20, 2014 VOL. 370 NO. 8

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.A., Robert Jeraj, Ph.D., Paul D. Brown, M.D., Kurt A. Jaeckle, M.D., David Schiff, M.D., Volker W. Stieber, M.D., David G. Brachman, M.D., Maria Werner-Wasik, M.D., Ivo W. Tremont-Lukats, M.D., Erik P. Sulman, M.D., Kenneth D. Aldape, M.D., Walter J. Curran, Jr., M.D., and Minesh P. Mehta, M.D.

  - No effect on OS
  - Positive effect on PFS
  - While OS and PFS were co-primary (« single sufficient ») no impact was observed on OS : patient clinical benefit is questionnable for regulatory approval
  - Then HrQOL was regarded as primary endpoint but Different results for HrQOL

Published Ahead of Print on March 17, 2014 as 10.1200/JCO.2013.51.4489
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.4489

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial

Eric Pujade-Lauraine, Felix Hilpert, Béatrice Weber, Alexander Reuss, Andres Poveda, Gunnar Kristensen, Roberto Sorio, Ignace Vergote, Petronella Witteveen, Aristotelis Bamias, Deolinda Pereira, Pauline Wimberger, Ana Oaknin, Mansoor Raza Mirza, Philippe Follana, David Bollag, and Isabelle Ray-Coquard

Author affiliations appear at the end of this article.

Published online ahead of print at

Processed as a Rapid Communication manuscript; see accompanying editorial doi: 10.1200/JCO.2013.54.7299; listen to the podcast by Dr Iasonos at www.jco.org/podcasts

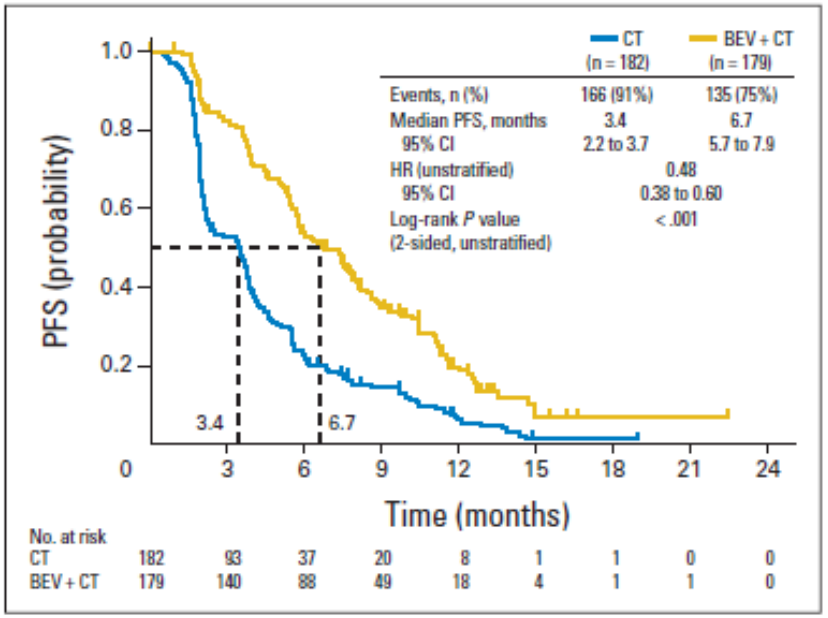


Fig 2. Progression-free survival (PFS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

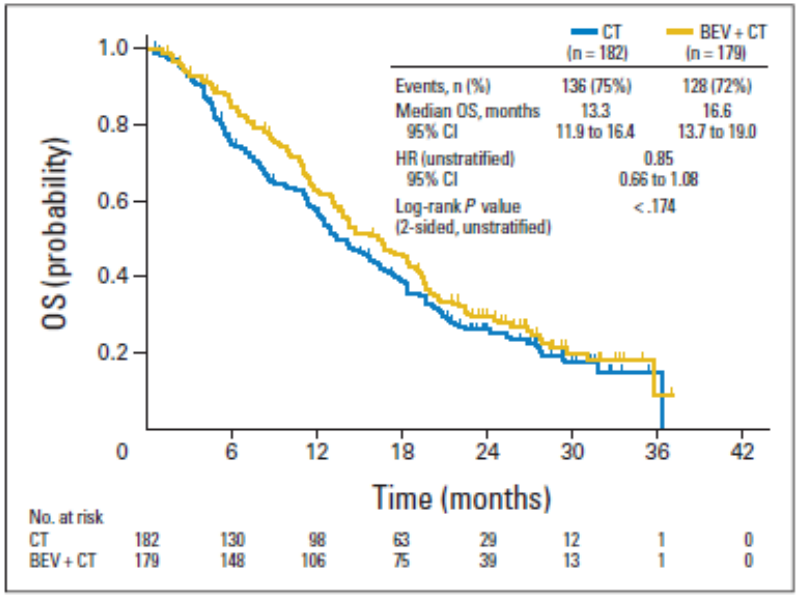


Fig 3. Overall survival (OS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

Published Ahead of Print on March 31, 2014 as 10.1200/JCO.2013.51.4240
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.4240

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Patient-Reported Outcome Results From the Open-Label Phase III AURELIA Trial Evaluating Bevacizumab-Containing Therapy for Platinum-Resistant Ovarian Cancer

Martin R. Stockler, Felix Hilpert, Michael Friedlander, Madeleine T. King, Lari Wenzel, Chee Khoon Lee, Florence Joly, Nikolaus de Gregorio, José Angel Arranz, Mansoor Raza Mirza, Roberto Sorio, Ulrich Freudensprung, Vesna Sneller, Gill Hales, and Eric Pujade-Lauraine

Martin R. Stockler, Madeleine T. King, Chee Khoon Lee, The University of Sydney; Michael Friedlander, Prince of Wales Clinical School, University of New South Wales, Sydney, Australia; Felix Hilpert, Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) and Klinik für Gynäkologie

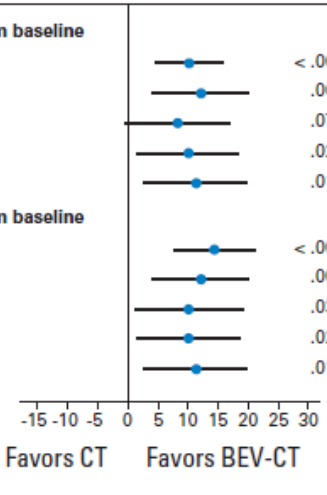
Listen to the podcast by Dr Iasonos at www.jco.org/podcasts

Conclusion

Bevacizumab increased the proportion of patients achieving a 15% improvement in patient-reported abdominal/GI symptoms during chemotherapy for platinum-resistant ovarian cancer.

A

Subscale	CT (n = 182) No.	%	BEV-CT (n = 179) No.	%	Difference, % (95% CI)	P
Main analysis	**Patients achieving a ≥ 15% improvement from baseline**					
Physical functional	3 of 170	1.8	20 of 167	12.0		< .001
Role functional	17 of 170	10.0	37 of 167	22.2		.003
Emotional functional	26 of 168	15.5	39 of 164	23.8		.072
Social functional	21 of 167	12.6	37 of 163	22.7		.020
Global health status/QoL score	22 of 169	13.0	40 of 164	24.4		.011
Sensitivity analysis	**Patients achieving a ≥ 10% improvement from baseline**					
Physical functional	6 of 170	3.5	30 of 167	18.0		< .001
Role functional	17 of 170	10.0	37 of 167	22.2		.003
Emotional functional	27 of 168	16.1	43 of 164	26.2		.031
Social functional	21 of 167	12.6	37 of 163	22.7		.020
Global health status/QoL score	22 of 169	13.0	40 of 164	24.4		.011



Co-primary endpoints

Walter Offen (Chair)
Eli Lilly and Company
Christy Chuang-Stein
Pfizer
Alex Dmitrienko
Eli Lilly and Company
Gary Littman
Wyeth
Jeff Maca
Novartis
Laura Meyerson

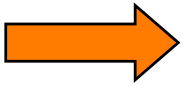
Multiple Co-primary Endpoints: Medical and Statistical Solutions
A Report From the Multiple Endpoints Expert Team of the Pharmaceutical Research and Manufacturers of America

- Which methodology

- Key point: decision rules

- «***alternative* primary endpoint or single sufficient** »
  - Treatment will be declared as efficient if at least one endpoint is clinically and statistically significant
  - Alpha type (false +) should be controlled

- « ***multiples co-primary endpoints*** »
  - Treatment will be declared as efficient if the two endpoint are clinically and statistically significant
  - To control statistical power (false -)



Co-primary could be composite endpoints

original article

Annals of Oncology
doi:10.1093/annonc/mdq687

EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors

A. G. Pallis[1*], A. Ring[2], C. Fortpied[3], B. Penninckx[4], M. C. Van Nes[5], U. Wedding[6], G. vonMinckwitz[7], C. D. Johnson[8], L. Wyld[9], A. Timmer-Bonte[10], F. Bonnetain[11], L. Repetto[12], M. Aapro[13], A. Luciani[14] & H. Wildiers[15] on behalf of the European Organisation for Research

Besides the 'classical' efficacy end points (overall survival, time to tumor progression, progression-free survival), cancer clinical trials in the older patients should have an assessment of the impact of treatment on QoL, functional status and independence of the patient. These issues could be incorporated either as co-primary end points or as composite end points (in combination with efficacy end points)

FULL PAPER

BJC

British Journal of Cancer (2013), 1–7 | doi: 10.1038/bjc.2013.407

Keywords: health-related quality of life; elderly; European Organisation for Research and Treatment of Cancer QLQ-C30; module validation study

International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer

S Wheelwright*[,1], A-S Darlington[2], D Fitzsimmons[3], P Fayers[4,5], J I Arraras[6], F Bonnetain[7], E Brain[8], A Bredart[9], W-C Chie[10], J Giesinger[11], E Hammerlid[12], S J O'Connor[13], S Oerlemans[14,15], A Pallis[16], M Reed[17], N Singhal[18], V Vassiliou[19], T Young[20], C Johnson[1] on behalf of the EORTC Quality of Life Group

Published Ahead of Print on September 9, 2013 as 10.1200/JCO.2013.49.6125
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.49.6125

JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology Position Article

Hans Wildiers, Murielle Mauer, Athanasios Pallis, Andrea Luciani, Giuseppe Curigliano, Martine Extermann, and Ulrich Wedding, European Organisation for Research and Treatment of Cancer, Brussels; Hans

Hans Wildiers, Murielle Mauer, Athanasios Pallis, Arti Hurria, Supriya G. Mohile, Andrea Luciani, Giuseppe Curigliano, Martine Extermann, Stuart M. Lichtman, Karla Ballman, Harvey Jay Cohen, Hyman Muss, and Ulrich Wedding

In Ederly cancer patients

HrQOL should be co-primary / composite endpoint

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

Maha Hussain, M.D., Catherine M. Tangen, Dr.P.H., Donna L. Berry, Ph.D., R.N., Celestia S. Higano, M.D., E. David Crawford, M.D., Glenn Liu, M.D., George Wilding, M.D., Stephen Prescott, M.D., Subramanian Kanaga Sundaram, M.D., Eric Jay Small, M.D., Nancy Ann Dawson, M.D., Bryan J. Donnelly, M.D., Peter M. Venner, M.D., Ulka N. Vaishampayan, M.D., Paul F. Schellhammer, M.D., David I. Quinn, M.D., Ph.D., Derek Raghavan, M.D., Ph.D., Benjamin Ely, M.S., Carol M. Moinpour, Ph.D., Nicholas J. Vogelzang, M.D., and Ian M. Thompson, Jr., M.D.

The coprimary objectives were to assess whether intermittent therapy was noninferior to continuous therapy with respect to survival, with a one-sided test with an upper boundary of the hazard ratio of 1.20, and whether quality of life differed between the groups 3 months after randomization.

N Engl J Med 2013;368:1314-25.
DOI: 10.1056/NEJMoa1212299

HrQOL as clinical endpoint

- Primary or co-primary endpoints in oncology

- To demonstrate that new therapeutic strategies reach a clinical benefit for the patient

- To individualize treatment based on HrQOL

Thank you for your attention