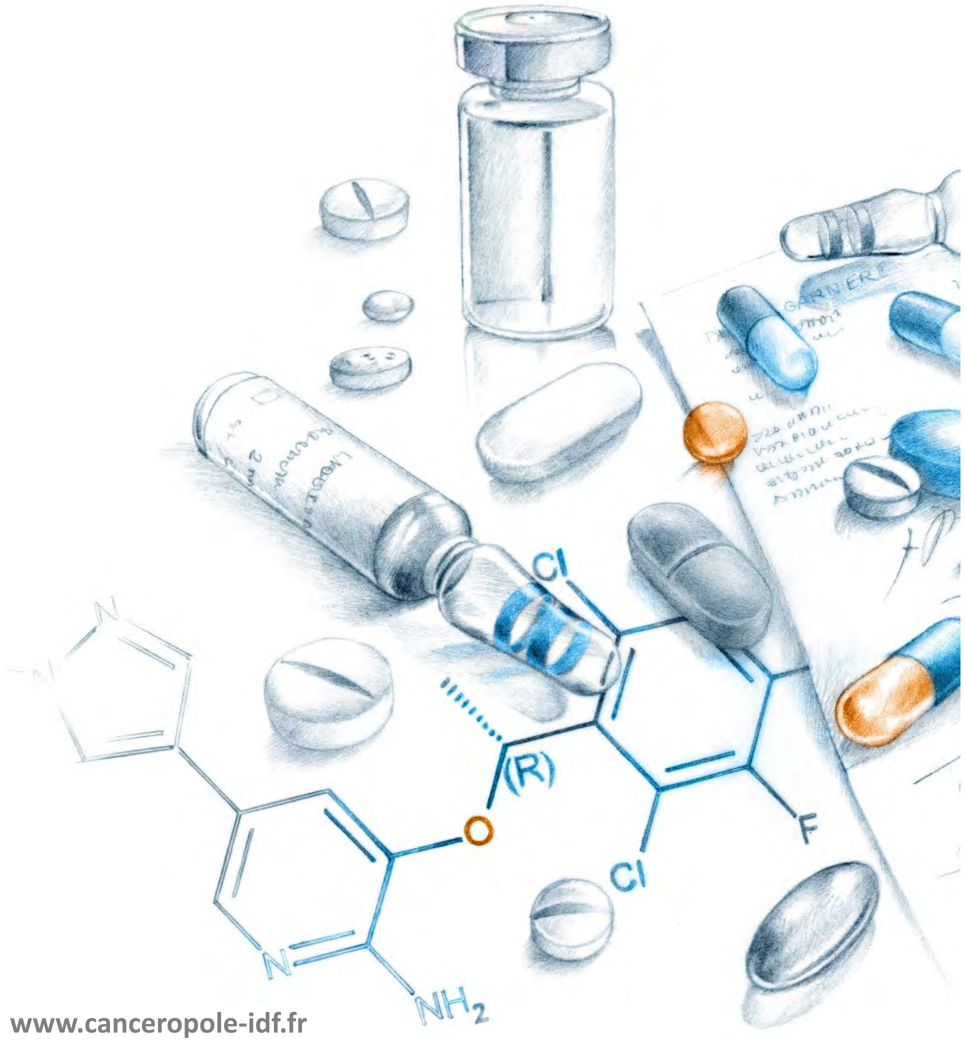
Cancéropôle Île-de-France

FÉDÉRER LA RECHERCHE ET L'INNOVATION MÉDICALE EN CANCÉROLOGIE

Critère de jugement, bénéfice clinique et niveau de preuve en cancérologie



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Cancers rares : faciliter l'accès aux thérapies innovantes
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- CHUGAI
- EISAI

Introduction

- *Essai clinique* :
  - objectif principal : conclusion
  - critère de jugement ad hoc
- *Emettre des hypothèses* :
  - Améliorer d'une quantité n le critère de jugement
  - Supériorité / Non infériorité
- ***Sens clinique*** **pour le patient** **dans les essais** :
  - Le traitement ou la prise en charge apporte un bénéfice tangible pertinent pour les patients

G Model
CANRAD-2654; No. of Pages 4
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Cancer/Radiothérapie xxx (2010) xxx–xxx

ELSEVIER MASSON
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Mise au point

Qualité de vie relative à la santé et critères de jugement en cancérologie

Health related quality of life and endpoints in oncology

F. Bonnetain

Unité de biostatistiques et d'épidémiologie, EA 4184, plateforme de recherche clinique qualité de vie et cancer, centre Georges-François-Leclerc, 1, rue du Pr-Marion, 21079 Dijon cedex, France

Published Ahead of Print on March 17, 2014 as 10.1200/JCO.2013.53.8009
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.53.8009

JOURNAL OF CLINICAL ONCOLOGY — ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

Lee M. Ellis, David S. Bernstein, Emile E. Voest, Jordan D. Berlin, Daniel Sargent, Patricia Cortazar, Elizabeth Garrett-Mayer, Roy S. Herbst, Rogerio C. Lilenbaum, Camelia Sima, Alan P. Venook, Mithat Gonen, Richard L. Schilsky, Neal J. Meropol, and Lowell E. Schnipper

Lee M. Ellis, University of Texas MD
Anderson Cancer Center, Houston, TX;

See accompanying editorial doi: 10.1200/JCO.2013.54.5277

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 29 · NUMBER 17 · JUNE 10 2011

JOURNAL OF CLINICAL ONCOLOGY — STATISTICS IN ONCOLOGY

Overall Survival As the Outcome for Randomized Clinical Trials With Effective Subsequent Therapies

Edward L. Korn, Boris Freidlin, and Jeffrey S. Abrams

Introduction

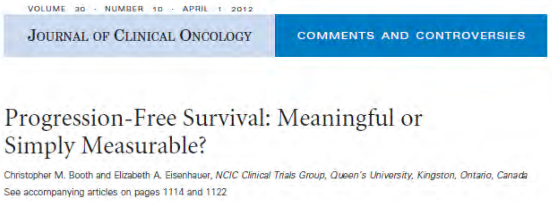
- **Critère de jugement = Endpoint :**
  - **Mesure faite durant un essai pour les objectifs principaux et secondaires.**
  - Les critères de jugement servent à définir et à répondre à une question/un objectif
  - (Friedman, Furberg, and DeMets)

Introduction

- Le choix du critère dépend . . .
  - Phase de l’essai (II, III, IV etc..)
  - Maladie, localisation du cancer, Cancer Rare
  - “Treatment setting” : progressive, adjuvant, palliative etc ..
  - Thérapies
  - Faisabilité de sa mesure

- 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

Critères de Jugement et essais cliniques en Cancérologie



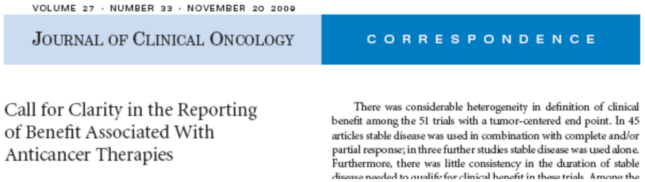
VOLUME 30 · NUMBER 10 · APRIL 1 2012

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Progression-Free Survival: Meaningful or Simply Measurable?

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

See accompanying articles on pages 1114 and 1122



VOLUME 27 · NUMBER 33 · NOVEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY | CORRESPONDENCE

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

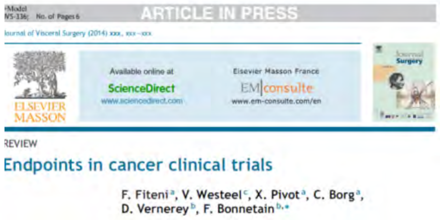
There was considerable heterogeneity in definition of clinical benefit among the 51 trials with a tumor-centered end point. In 45 articles stable disease was used in combination with complete and/or partial response; in three further studies stable disease was used alone. Furthermore, there was little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

- **Critère clinique** : une caractéristique qui est le reflet de ce que le patient **perçoit (QoL),** d'une **fonction (QoL/ PRO)** ou d'une **survie (SG)** **= critères centrés sur le patient**

- **Marqueurs biologiques** : une caractéristique qui est objectivée par une mesure quantitative et évaluée comme un indicateur du processus pathogénique ou de la réponse pharmacologique à une intervention thérapeutique : **PFS/ DFS/ RECIST** etc. … = **critères centrés sur la tumeur**

- **Critère substitutif (« Surrogate Endpoint »)** : un marqueur biologique intermédiaire qui a pour objet de se substituer à un critère clinique. Un critère intermédiaire doit prédire le bénéfice clinique des traitements évalués = évaluation statistique

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



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Journal of Visceral Surgery (2014) xxx, xxx—xxx

Available online at ScienceDirect www.sciencedirect.com
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REVIEW

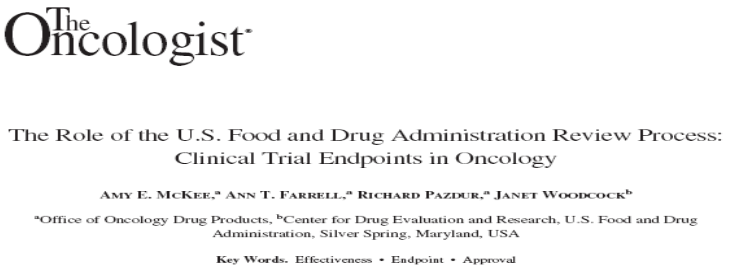
Endpoints in cancer clinical trials

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

Ref : Temple, JAMA 1999;282:790.

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

Critères de Jugement pour la FDA



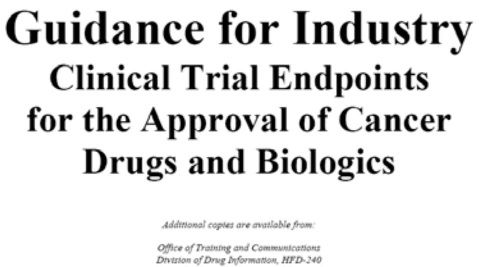
The Oncologist

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



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

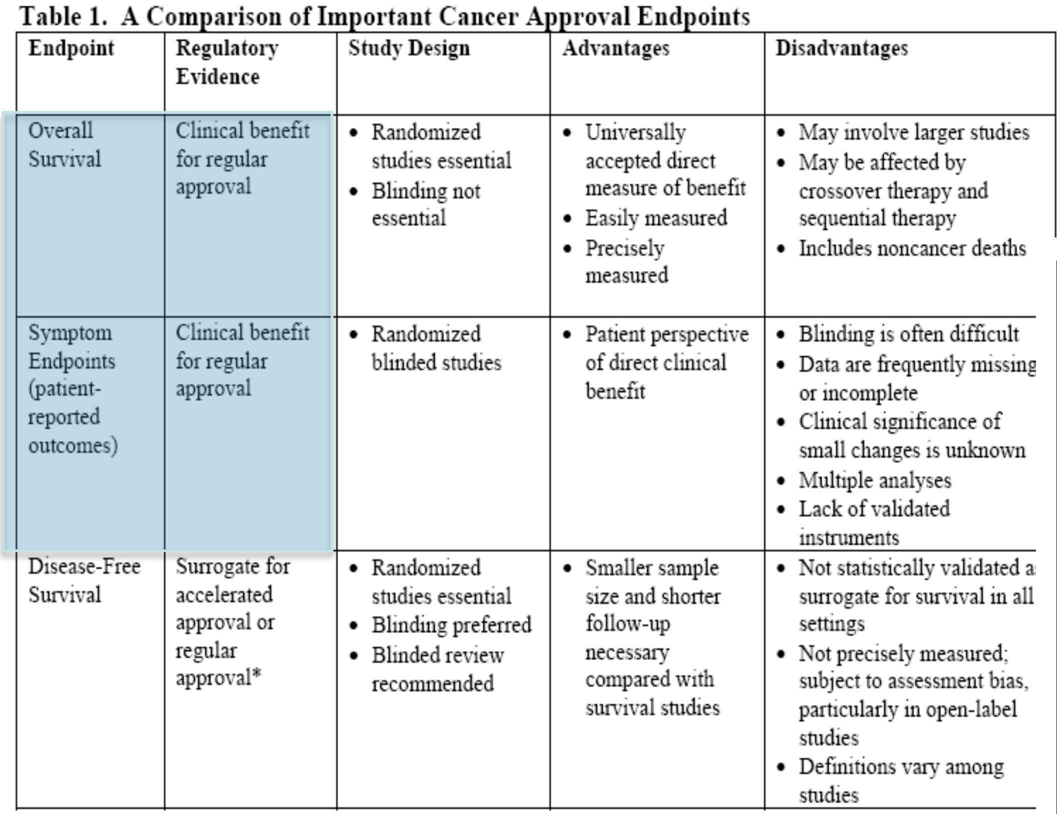


Table 1. A Comparison of Important Cancer Approval Endpoints

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

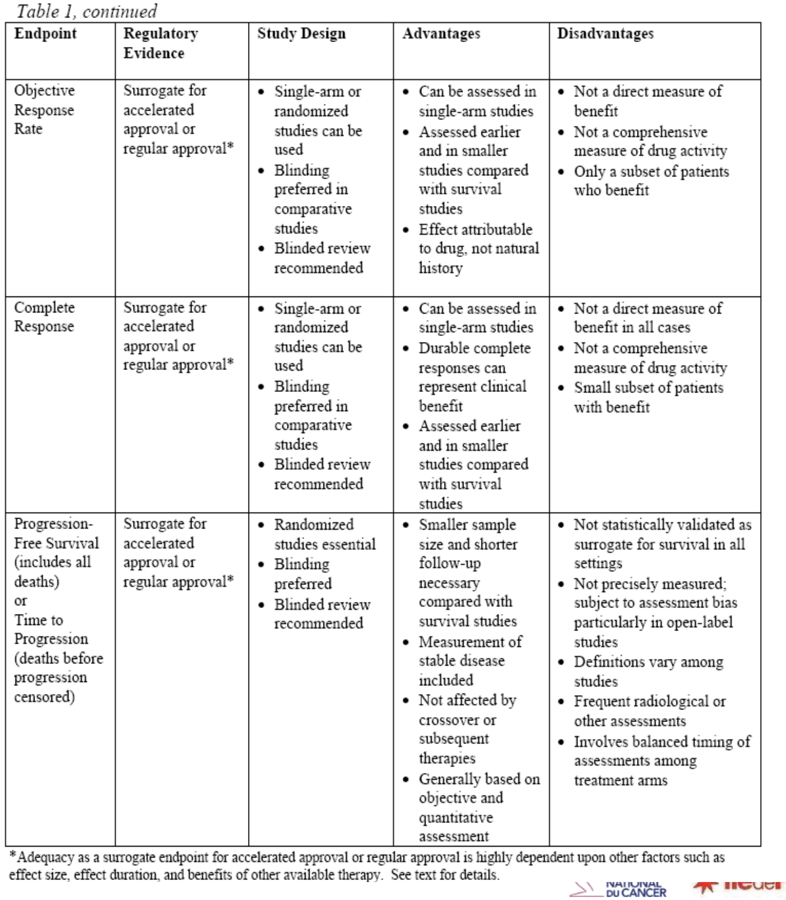


Table 1, continued

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.

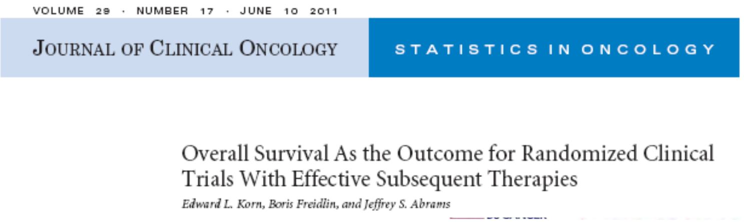
- 1er : Survie globale
- 2nd : QOL / PRO

Pourquoi utiliser d'autres critères que la SG ?

- **Survie Globale** :
  - Critère reflétant bénéfice clinique pour le patient
  - Décès objectifs
  - Mesure précise du temps d'occurrence
  - Exhaustivité
  - Définition précise/reproductible quel que soit le pays
  - Durée d'étude longue : meilleure évaluation de EI

- **Limites de la Survie globale pour les essais**
  - Effectifs requis pour observer les événements (adjuvant)
  - Durée d'étude longue (situation adjuvante)
  - Problèmes des lignes de traitements consécutives (situation avancée) : mais correspond aux standards et équilibré entre les bras de traitement

Pour avoir des Essais cliniques positifs ?



VOLUME 29 · NUMBER 17 · JUNE 10 2011

JOURNAL OF CLINICAL ONCOLOGY | STATISTICS IN ONCOLOGY

Overall Survival As the Outcome for Randomized Clinical Trials With Effective Subsequent Therapies

Edward L. Korn, Boris Freidlin, and Jeffrey S. Abrams

Critères composites comme alternatives à l'OS?

Critères composites comme alternatives à l'OS?

- Santé/ Maladie = complexité :
  - Définition OMS ≠ absence de maladie
  - Critère binaire absence/ présence d'une maladie X/ d'un symptôme pourrait ne pas correspondre à la réalité

↓

- **Critères composites**
- **Critères conjoints**

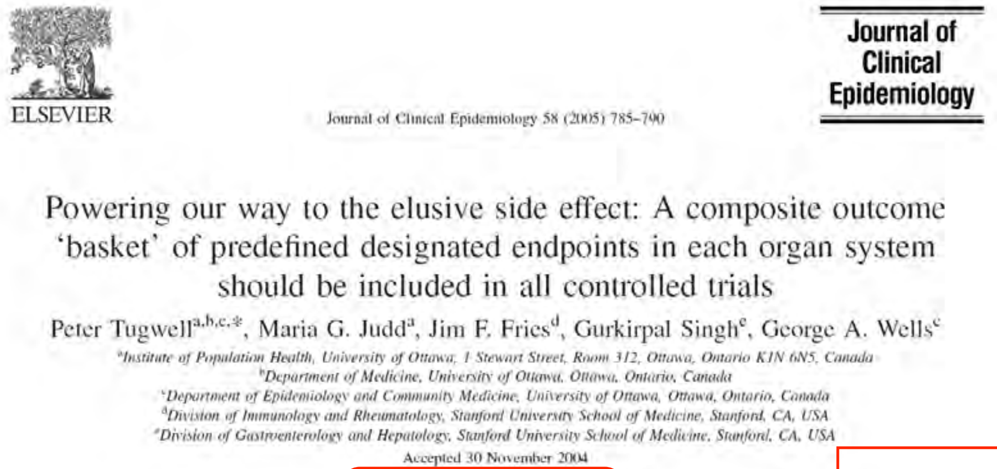
Deux concepts différents

Mais

Des objectifs analogues

↓

Critères de jugement combinés


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]

[a]Institute of Population Health, University of Ottawa, 1 Stewart Street, Room 312, Ottawa, Ontario K1N 6N5, Canada
[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
[e]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

Accepted 30 November 2004

Inconfort : oui vs non

non composite ?

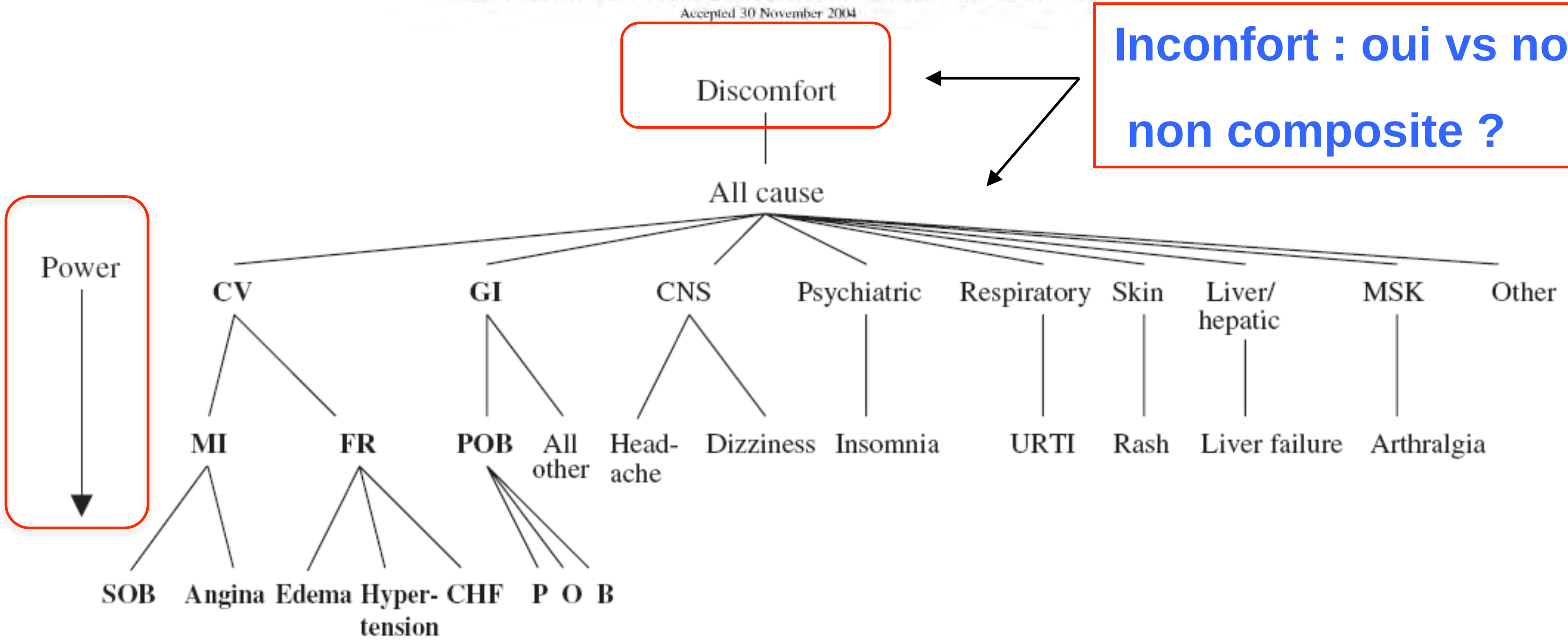
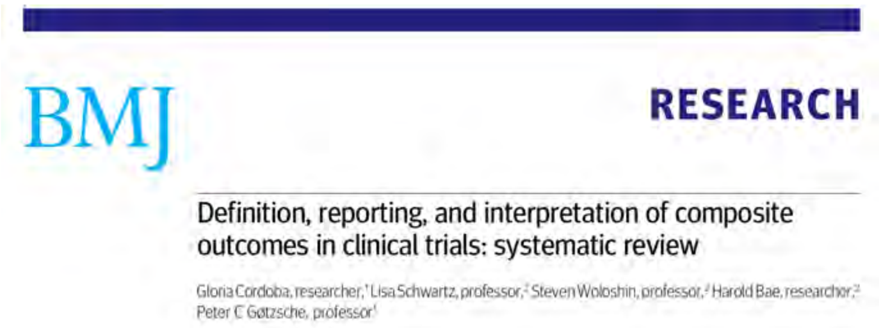

Discomfort
All cause
Power
CV
GI
CNS
Psychiatric
Respiratory
Skin
Liver/ hepatic
MSK
Other
MI
FR
POB
All other
Head-ache
Dizziness
Insomnia
URTI
Rash
Liver failure
Arthralgia
SOB
Angina
Edema
Hyper-tension
CHF
P
O
B

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.

Les critères composites


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]

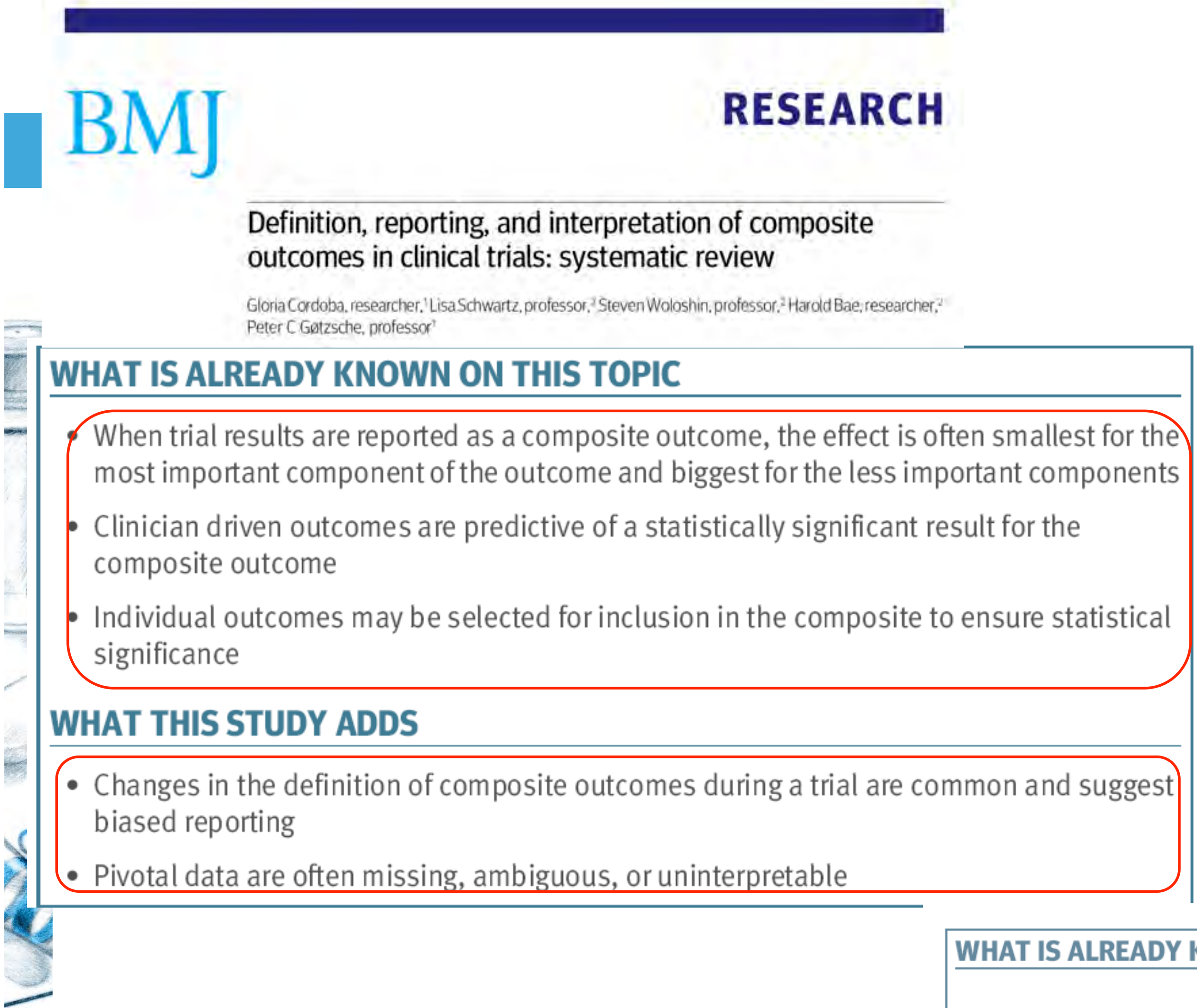
- **Avantages des critères composites**
  - Augmenter les taux d'événements
  - Augmenter la puissance statistique

- **Mais les composantes du critère doivent avoir une importance équivalente d'un point de vue clinique**

- Process d'évolution pathologique et au regard de la réponse pharmacologique analogues : ie **impact du traitement analogue sur chacune des composantes du critère composite**

Importance de la définition

Neaton JD et al, *Stat Med* 1994 & Yusuf S and Negassa A, Amer Heart J 2002.



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

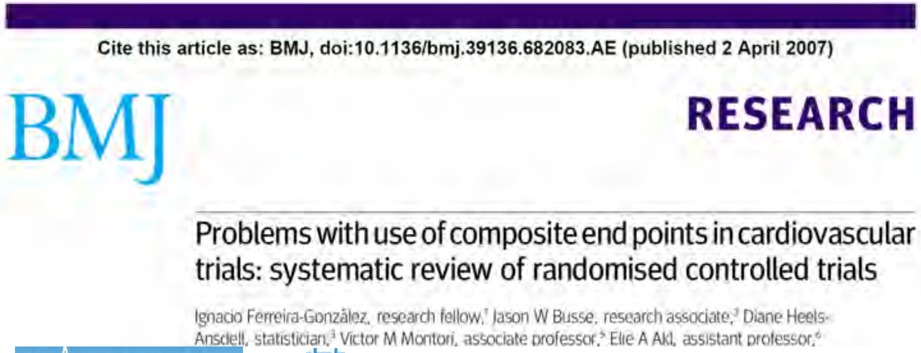
WHAT THIS STUDY ADDS

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

Critères composites :

- Avoir des résultats statistiquement significatifs

- Mais discutable eg contribution plus forte d'événements peu pertinents pour le patient



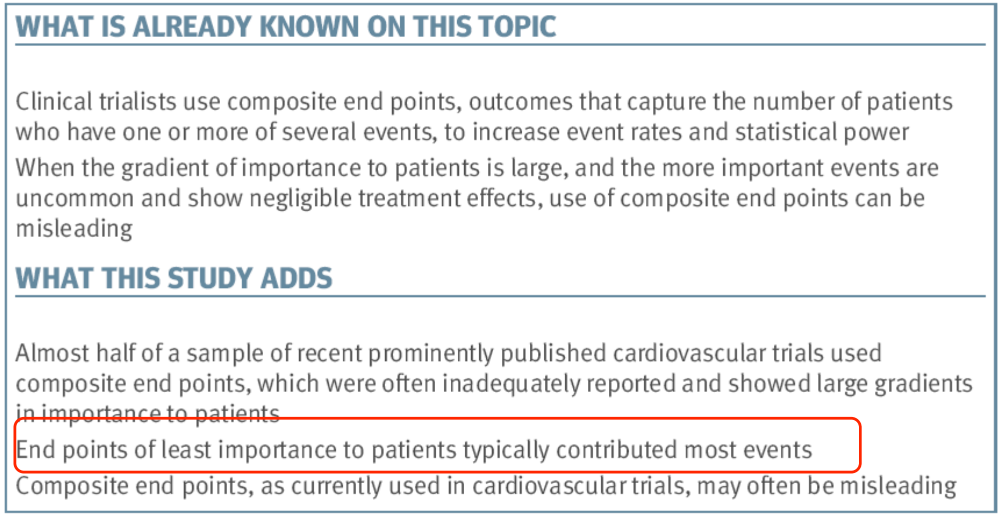
Cite this article as: BMJ, doi:10.1136/bmj.39136.682083.AE (published 2 April 2007)

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,[2] 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

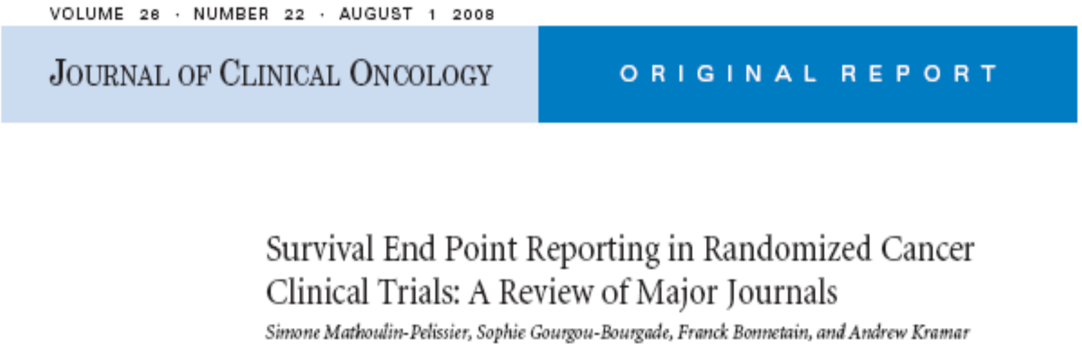
Composite end points, as currently used in cardiovascular trials, may often be misleading

Qualités requises des critères composites et interprétation

Montori VM et al, BMJ 2005.

- **Chacune des composantes doit avoir une importance analogue pour le patient**;
  - Pertinence clinique
- **Chacune des composantes doivent avoir une fréquence d'occurrence analogue**.
  - Est-ce que le critère le moins et les plus important ont la même fréquence
  - Reporter la fréquence de chacun des événements
- **Le traitement doit avoir un effet analogue sur chacune des composantes**.
  - Est-ce que les mécaniques biologiques, cliniques sous jacentes sont équivalentes
- **Les données de chacune des composantes doivent être recueillies jusqu'à la fin de l'essai**.
- **Chacune des composantes doit être analysée séparément comme critère secondaire**.
  - Est-ce que les estimations ponctuelles de réduction du risque et IC à 95% sont suffisamment proches

Critères de jugement composites & définitions



VOLUME 26 · NUMBER 22 · AUGUST 1 2008

JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

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

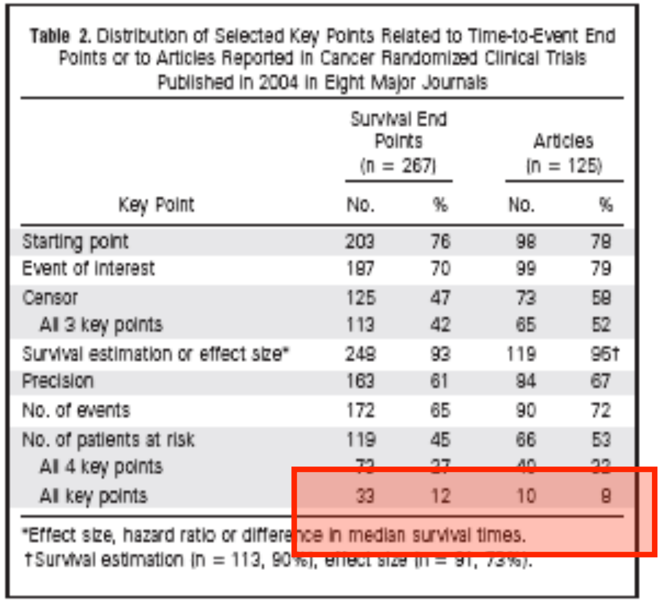


Table 2. Distribution of Selected Key Points Related to Time-to-Event End Points or to Articles Reported in Cancer Randomized Clinical Trials Published in 2004 in Eight Major Journals

Key Point	Survival End Points (n = 267)		Articles (n = 125)	
	No.	%	No.	%
Starting point	203	76	98	78
Event of interest	187	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	84	67
No. of events	172	65	90	72
No. of patients at risk	119	45	66	53
All 4 key points	72	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%).

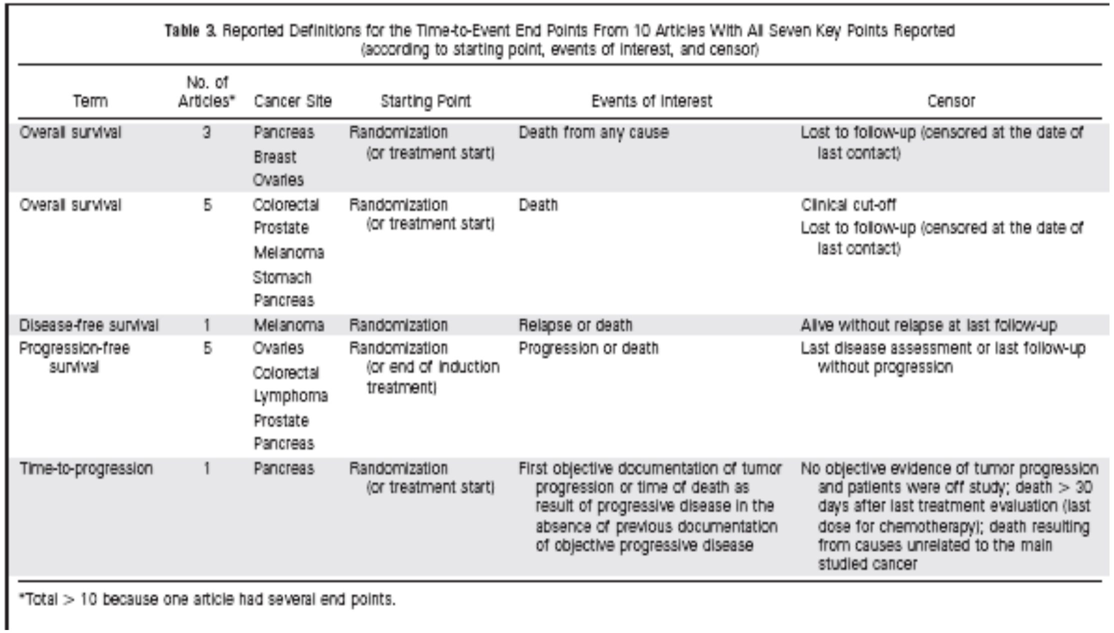
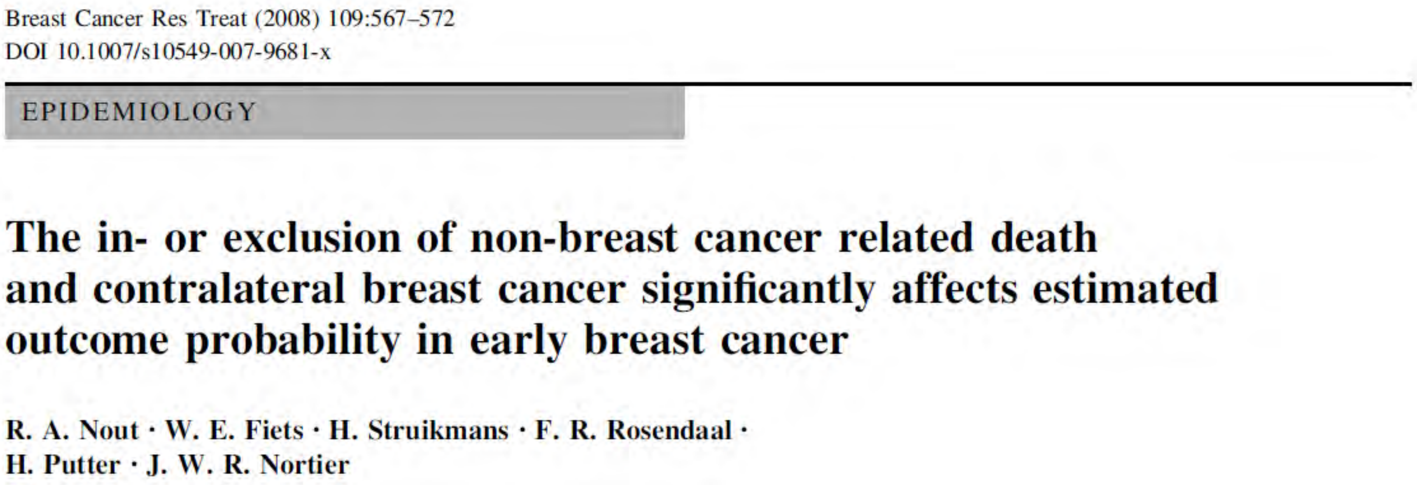


Table 3. Reported Definitions for the Time-to-Event End Points From 10 Articles With All Seven Key Points Reported (according to starting point, events of interest, and censor)

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

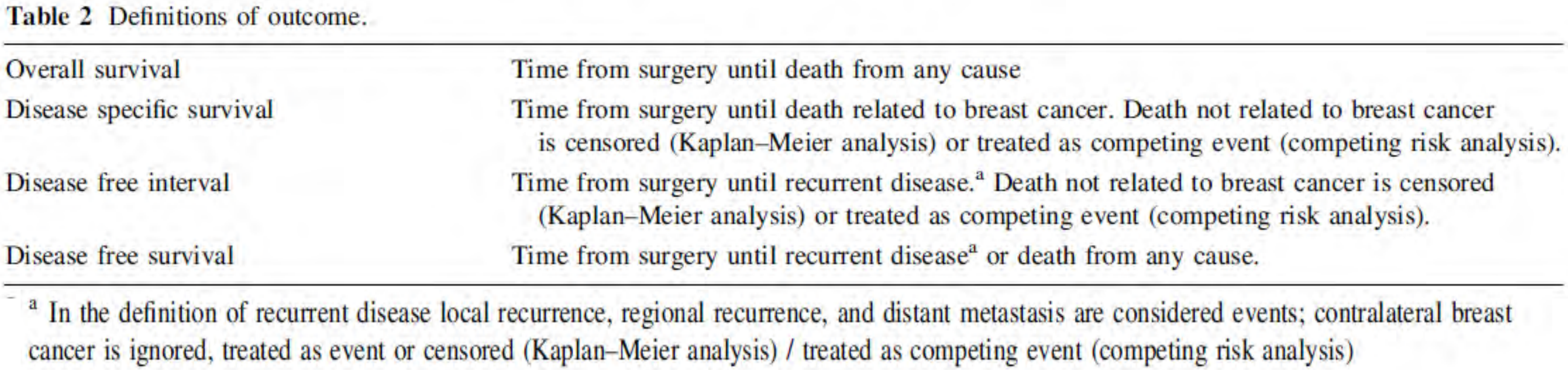


Table 2 Definitions of outcome.

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)

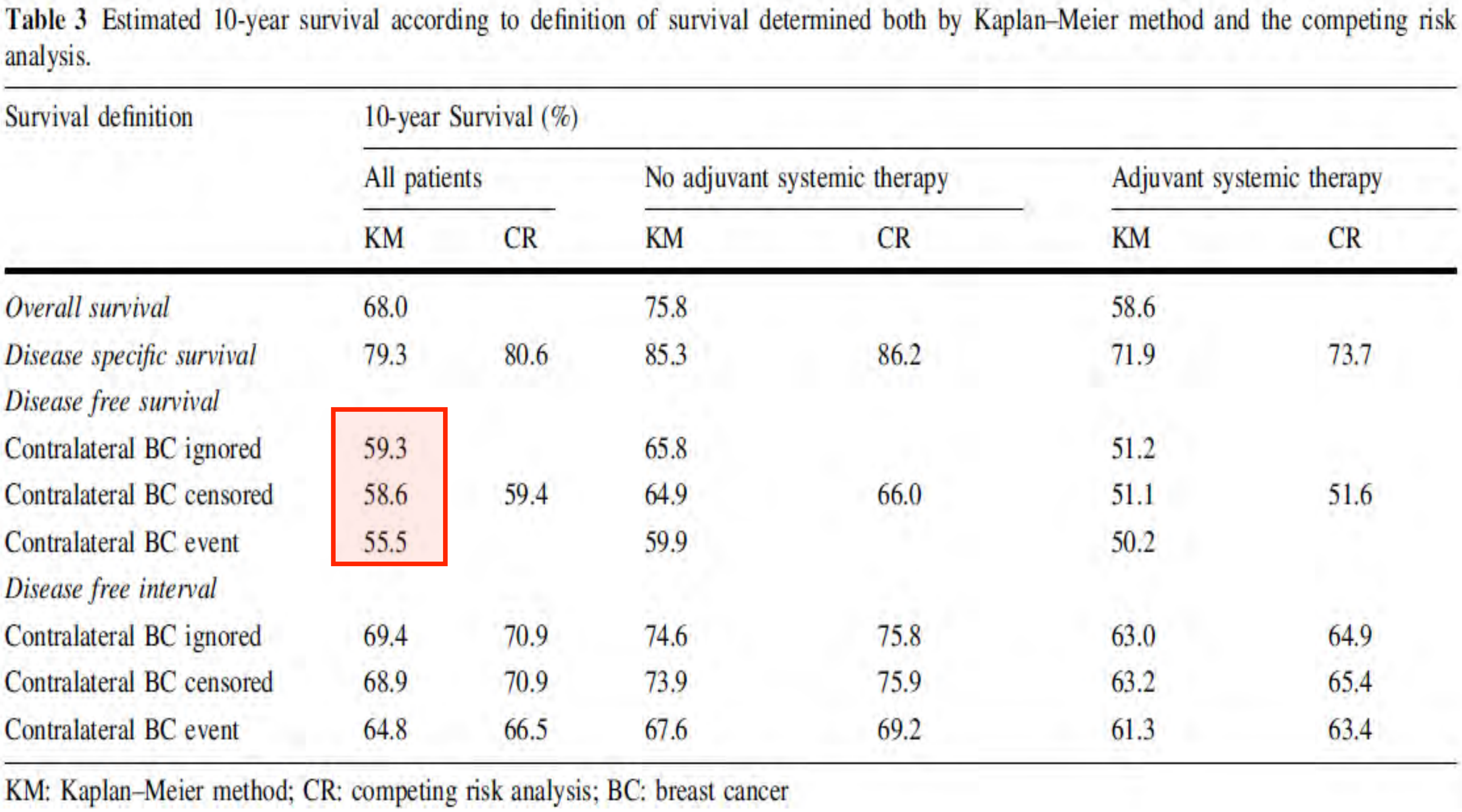
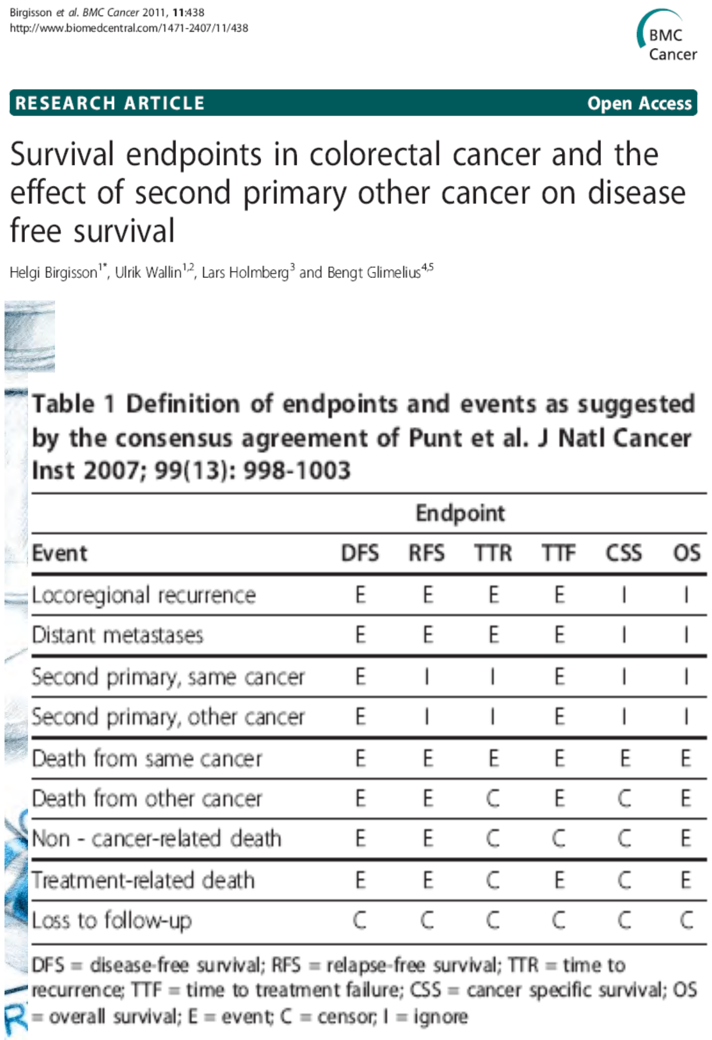


Table 3 Estimated 10-year survival according to definition of survival determined both by Kaplan–Meier method and the competing risk analysis.

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

Taux de DFS à 10 ans selon la définition varie de 55.5 to 59.3%



Birgisson *et al. BMC Cancer* 2011, **11**:438
http://www.biomedcentral.com/1471-2407/11/438

BMC Cancer

RESEARCH ARTICLE **Open Access**

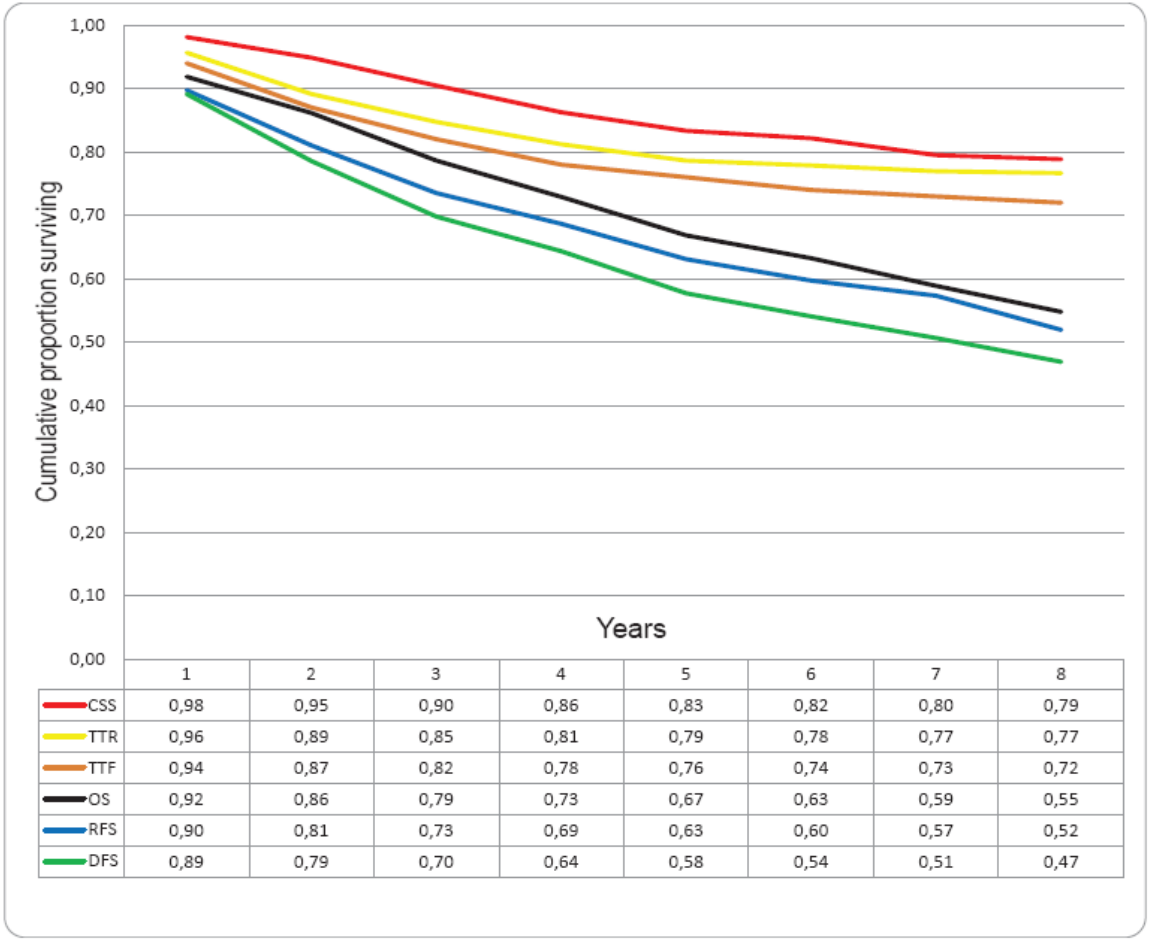
Survival endpoints in colorectal cancer and the effect of second primary other cancer on disease free survival

Helgi Birgisson[1*], Ulrik Wallin[1,2], Lars Holmberg[3] and Bengt Glimelius[4,5]

Table 1 Definition of endpoints and events as suggested by the consensus agreement of Punt et al. J Natl Cancer Inst 2007; 99(13): 998-1003

	Endpoint					
Event	DFS	RFS	TTR	TTF	CSS	OS
Locoregional recurrence	E	E	E	E	I	I
Distant metastases	E	E	E	E	I	I
Second primary, same cancer	E	I	I	E	I	I
Second primary, other cancer	E	I	I	E	I	I
Death from same cancer	E	E	E	E	E	E
Death from other cancer	E	E	C	E	C	E
Non - cancer-related death	E	E	C	C	C	E
Treatment-related death	E	E	C	E	C	E
Loss to follow-up	C	C	C	C	C	C

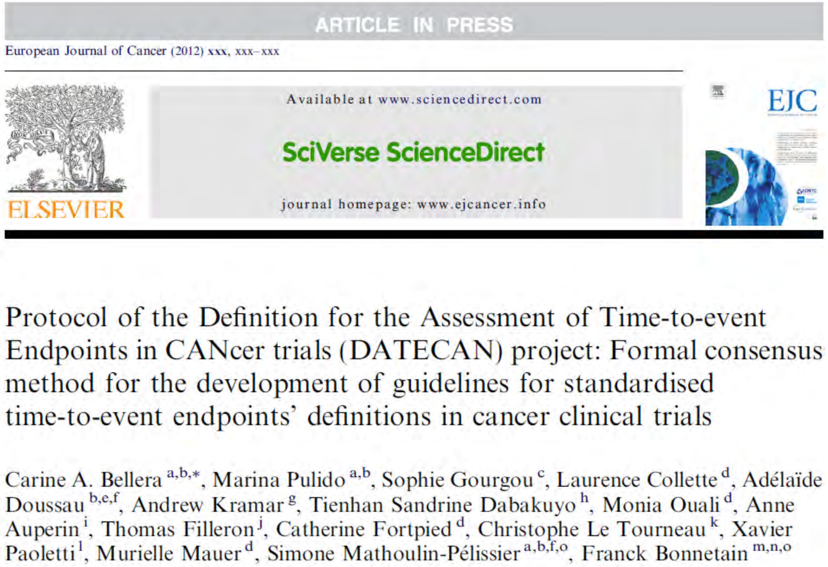
DFS = disease-free survival; RFS = relapse-free survival; TTR = time to recurrence; TTF = time to treatment failure; CSS = cancer specific survival; OS = overall survival; E = event; C = censor; I = ignore



	1	2	3	4	5	6	7	8
CSS	0,98	0,95	0,90	0,86	0,83	0,82	0,80	0,79
TTR	0,96	0,89	0,85	0,81	0,79	0,78	0,77	0,77
TTF	0,94	0,87	0,82	0,78	0,76	0,74	0,73	0,72
OS	0,92	0,86	0,79	0,73	0,67	0,63	0,59	0,55
RFS	0,90	0,81	0,73	0,69	0,63	0,60	0,57	0,52
DFS	0,89	0,79	0,70	0,64	0,58	0,54	0,51	0,47

Figure 1 Comparison of different survival endpoints in patients treated with curative intention for colorectal cancer, disease stages I-III (n = 332). CSS: cancer specific survival; TTR: time to recurrence; TTF = time to treatment failure; OS: overall survival; RFS: relapse-free survival; DFS: disease-free survival.

Différence entre survie sans maladie et survie sans récidive ?


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]

Fait:
- Sein
- Sarcome/GIST
- Pancréas
- Rein

En cours:
- Tête & cou
- œsophage estomac
- Poumon
- mCRC

4 C.A. Bellera et al. / European Journal of Cancer xxx (2012) xxx–xxx

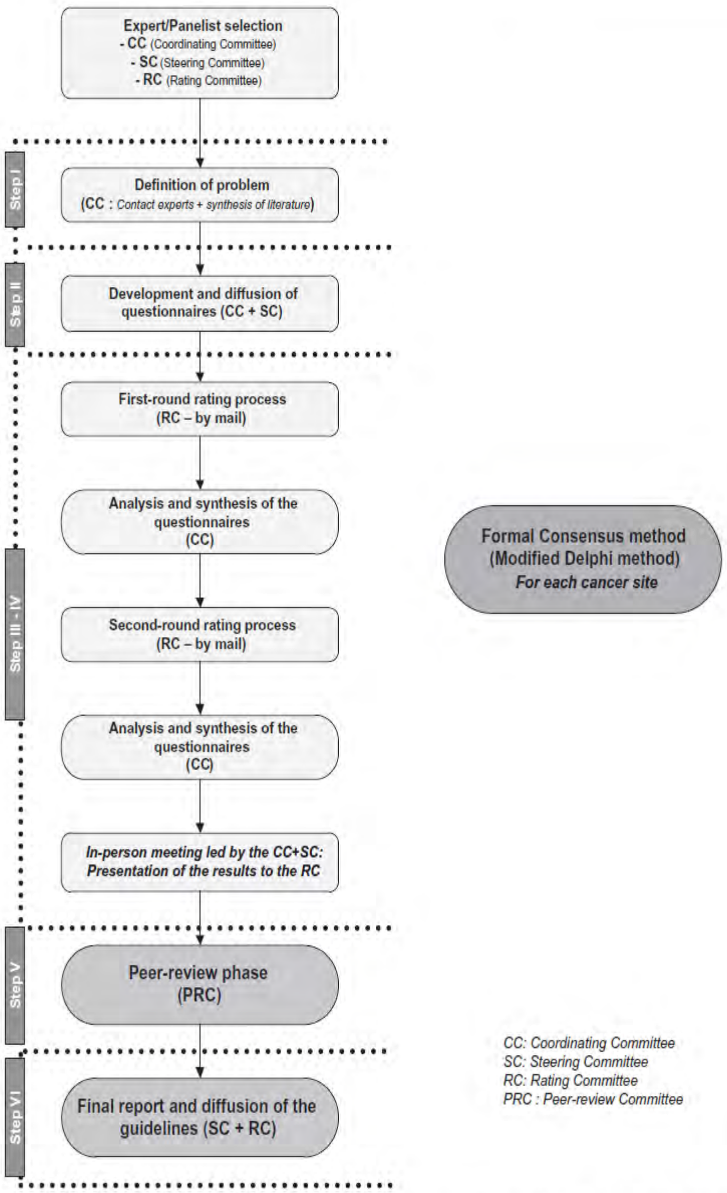
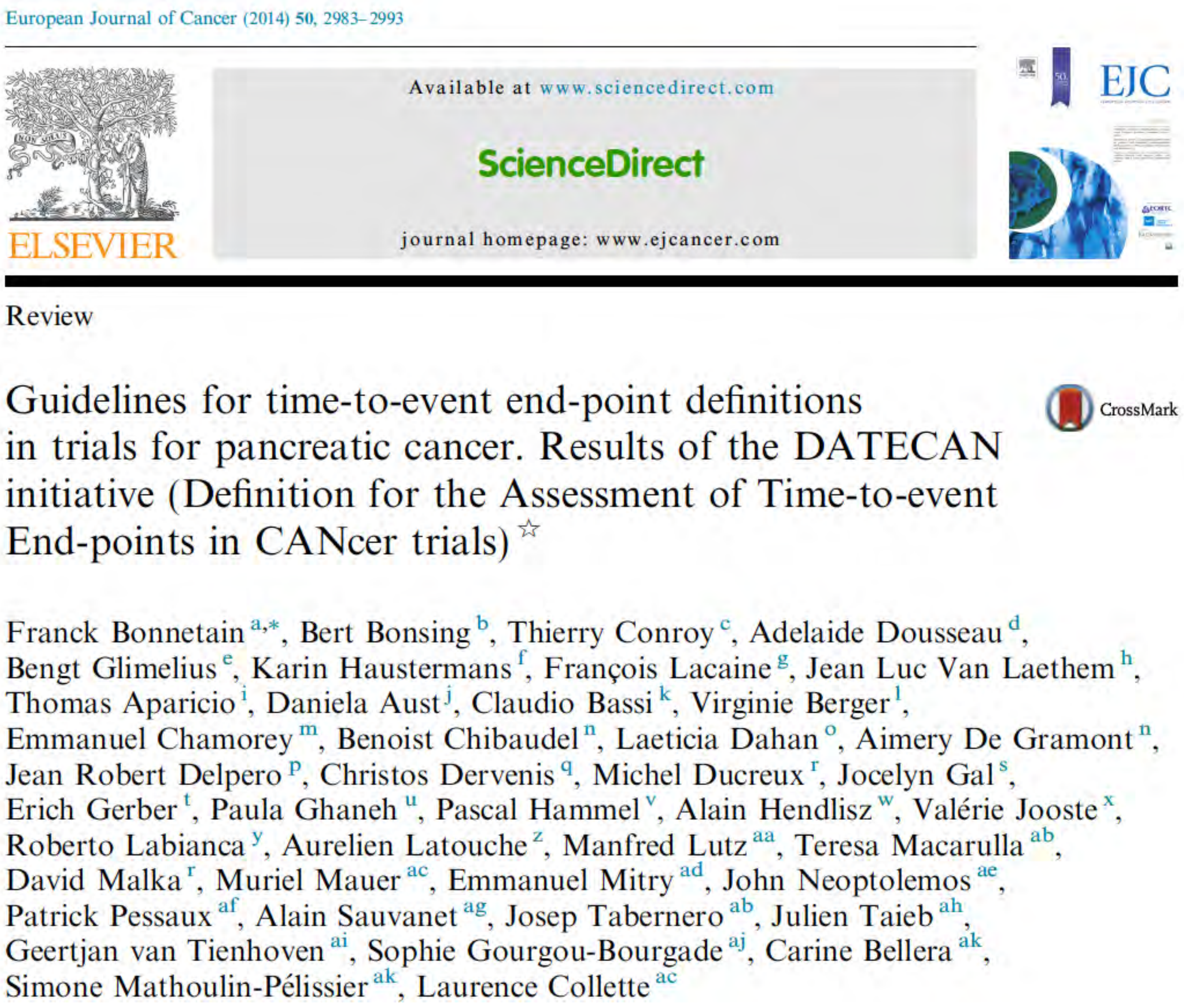

Expert/Panelist selection
- CC (Coordinating Committee)
- SC (Steering Committee)
- RC (Rating Committee)
Step I
Definition of problem
(CC : Contact experts + synthesis of literature)
Step II
Development and diffusion of questionnaires (CC + SC)
Step III - IV
First-round rating process
(RC – by mail)
Analysis and synthesis of the questionnaires
(CC)
Second-round rating process
(RC – by mail)
Analysis and synthesis of the questionnaires
(CC)
In-person meeting led by the CC+SC:
Presentation of the results to the RC
Step V
Peer-review phase
(PRC)
Step VI
Final report and diffusion of the guidelines (SC + RC)
Formal Consensus method
(Modified Delphi method)
For each cancer site
CC: Coordinating Committee
SC: Steering Committee
RC: Rating Committee
PRC : Peer-review Committee

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



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

ELSEVIER

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

EJC

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)☆

CrossMark

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]

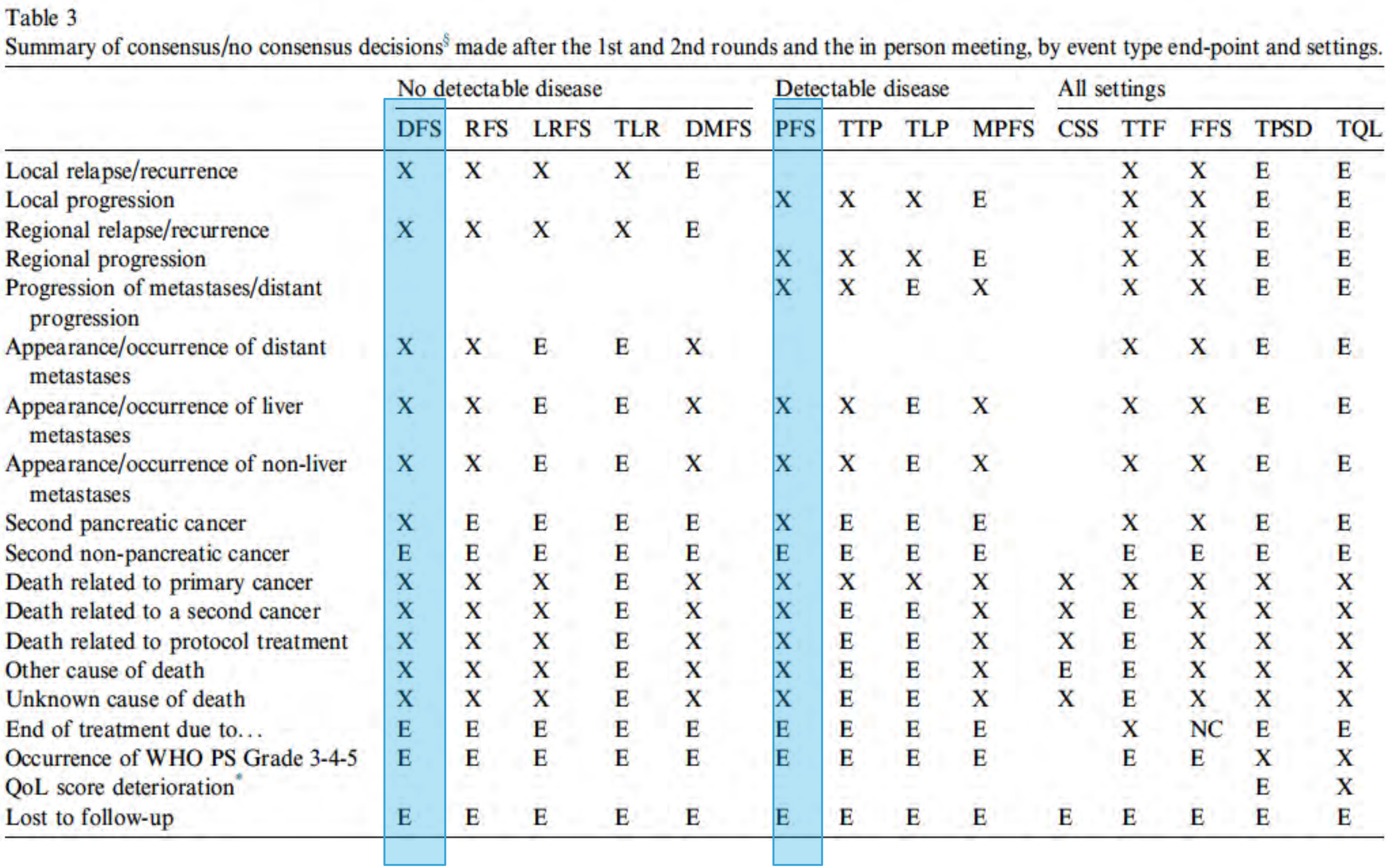
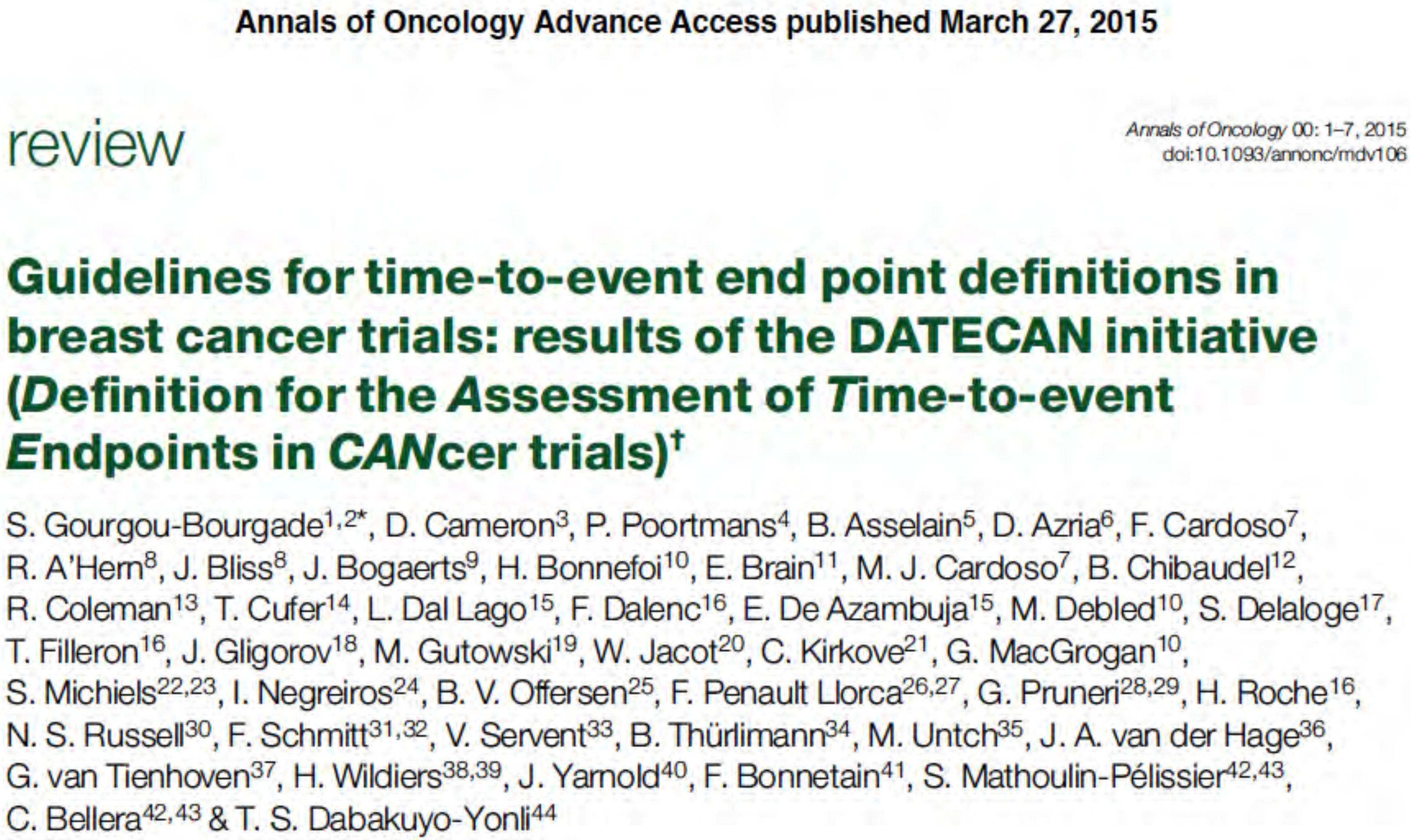


Table 3

Summary of consensus/no consensus decisions[§] made after the 1st and 2nd rounds and the in person meeting, by event type end-point and settings.

	No detectable disease					Detectable disease				All settings				
	DFS	RFS	LRFS	TLR	DMFS	PFS	TTP	TLP	MPFS	CSS	TTF	FFS	TPSD	TQL
Local relapse/recurrence	X	X	X	X	E						X	X	E	E
Local progression						X	X	X	E		X	X	E	E
Regional relapse/recurrence	X	X	X	X	E						X	X	E	E
Regional progression						X	X	X	E		X	X	E	E
Progression of metastases/distant progression						X	X	E	X		X	X	E	E
Appearance/occurrence of distant metastases	X	X	E	E	X						X	X	E	E
Appearance/occurrence of liver metastases	X	X	E	E	X	X	X	E	X		X	X	E	E
Appearance/occurrence of non-liver metastases	X	X	E	E	X	X	X	E	X		X	X	E	E
Second pancreatic cancer	X	E	E	E	E	X	E	E	E		X	X	E	E
Second non-pancreatic cancer	E	E	E	E	E	E	E	E	E		E	E	E	E
Death related to primary cancer	X	X	X	E	X	X	X	X	X	X	X	X	X	X
Death related to a second cancer	X	X	X	E	X	X	E	E	X	X	E	X	X	X
Death related to protocol treatment	X	X	X	E	X	X	E	E	X	X	E	X	X	X
Other cause of death	X	X	X	E	X	X	E	E	X	E	E	X	X	X
Unknown cause of death	X	X	X	E	X	X	E	E	X	X	E	X	X	X
End of treatment due to…	E	E	E	E	E	E	E	E	E		X	NC	E	E
Occurrence of WHO PS Grade 3-4-5	E	E	E	E	E	E	E	E	E		E	E	X	X
QoL score deterioration*													E	X
Lost to follow-up	E	E	E	E	E	E	E	E	E	E	E	E	E	E



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 (*D*efinition for the *A*ssessment of *T*ime-to-event *E*ndpoints in *CAN*cer 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]

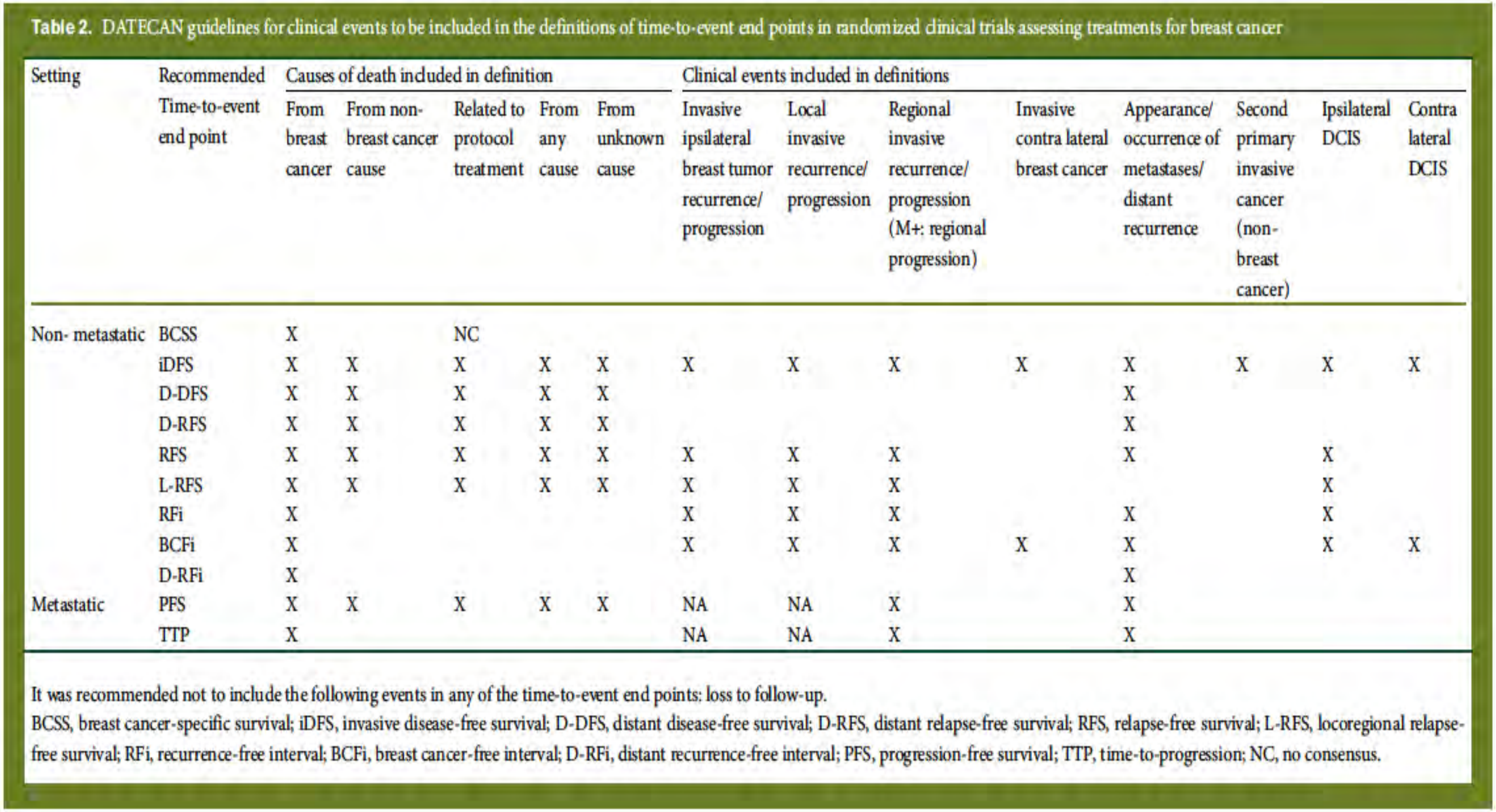


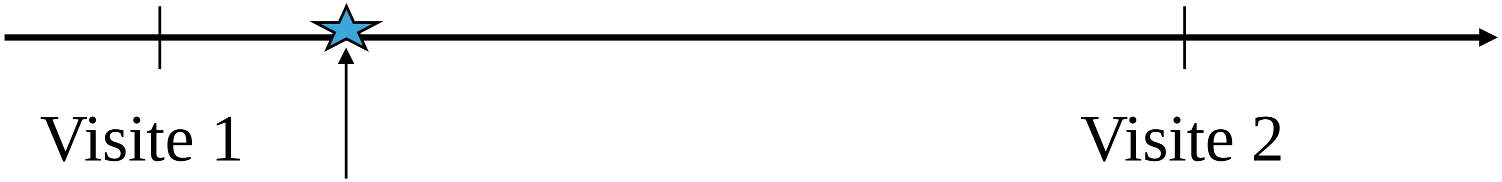
Table 2. DATECAN guidelines for clinical events to be included in the definitions of time-to-event end points in randomized clinical trials assessing treatments for breast cancer

Setting	Recommended Time-to-event end point	Causes of death included in definition					Clinical events included in definitions							
		From breast cancer	From non-breast cancer cause	Related to protocol treatment	From any cause	From unknown cause	Invasive ipsilateral breast tumor recurrence/ progression	Local invasive recurrence/ progression	Regional invasive recurrence/ progression (M+: regional progression)	Invasive contra lateral breast cancer	Appearance/ occurrence of metastases/ distant recurrence	Second primary invasive cancer (non-breast cancer)	Ipsilateral DCIS	Contra lateral DCIS
Non- metastatic	BCSS	X		NC										
	iDFS	X	X	X	X	X	X	X	X	X	X	X	X	X
	D-DFS	X	X	X	X	X					X			
	D-RFS	X	X	X	X	X					X			
	RFS	X	X	X	X	X	X	X	X		X		X	
	L-RFS	X	X	X	X	X	X	X	X				X	
	RFi	X					X	X	X		X		X	
	BCFi	X					X	X	X	X	X		X	X
	D-RFi	X									X			
Metastatic	PFS	X	X	X	X	X	NA	NA	X		X			
	TTP	X					NA	NA	X		X			

It was recommended not to include the following events in any of the time-to-event end points: loss to follow-up.

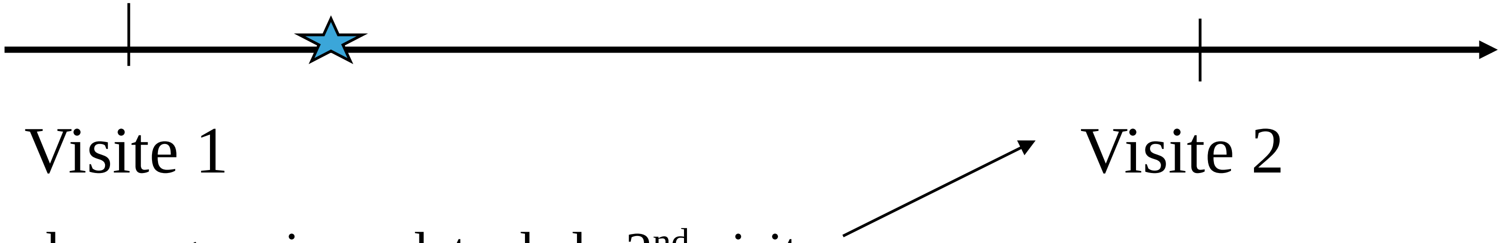
BCSS, breast cancer-specific survival; iDFS, invasive disease-free survival; D-DFS, distant disease-free survival; D-RFS, distant relapse-free survival; RFS, relapse-free survival; L-RFS, locoregional relapse-free survival; RFi, recurrence-free interval; BCFi, breast cancer-free interval; D-RFi, distant recurrence-free interval; PFS, progression-free survival; TTP, time-to-progression; NC, no consensus.

Survie Globale



La date de décès = la date réelle d’occurrence

Survie Sans Progression

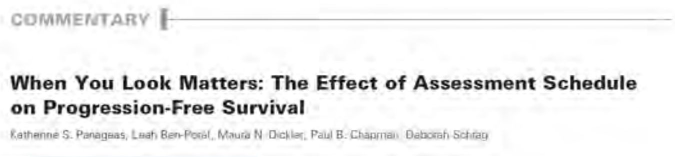


La date de progression =date de la 2nd visite

Surestimation de la SSP

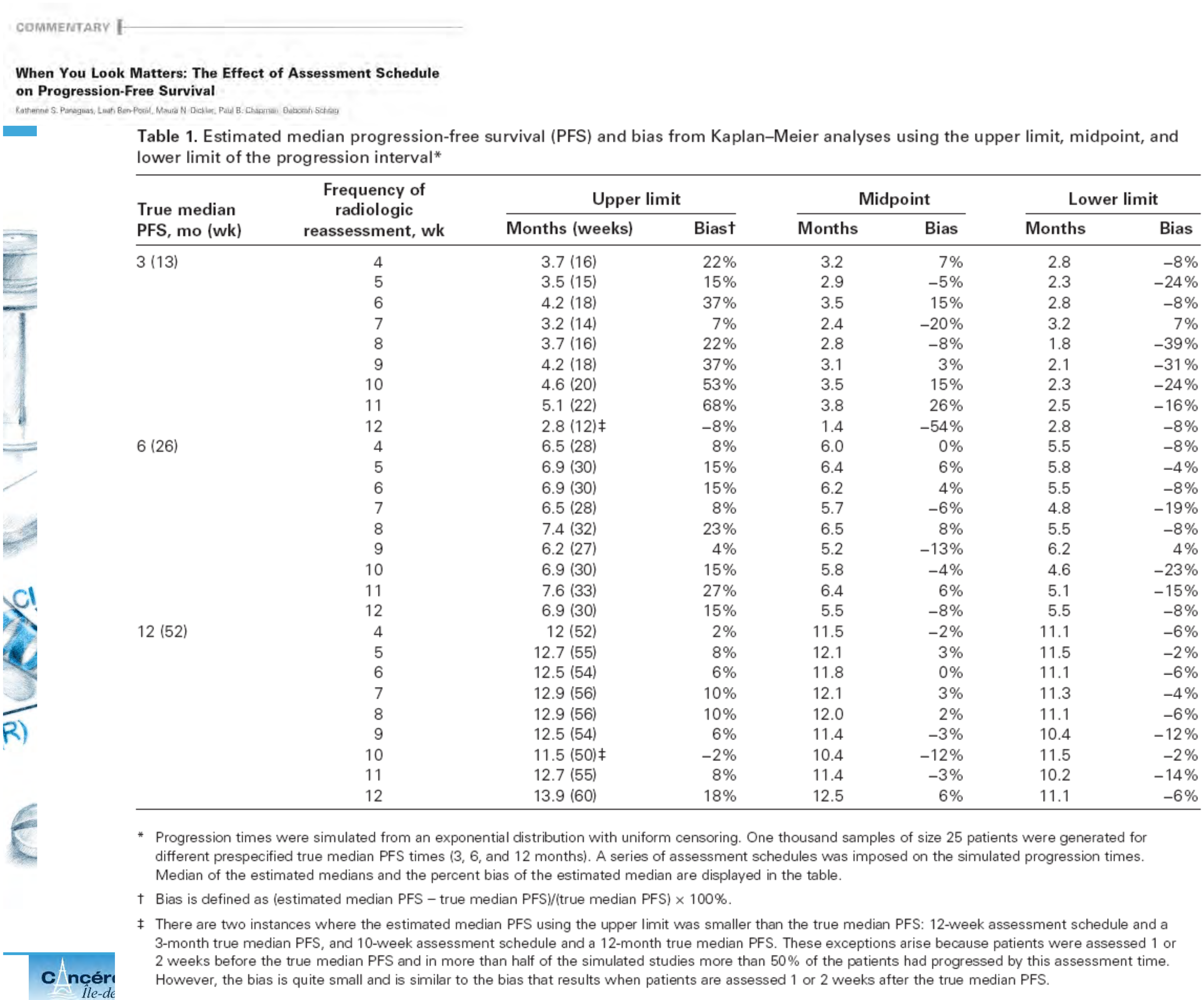
Biais si décès précoce

Kaplan Meier non optimal car censure par intervalle intervalle


COMMENTARY

When You Look Matters: The Effect of Assessment Schedule on Progression-Free Survival

Katherine S. Panageas, Leah Ben-Porat, Maura N. Dickler, Paul B. Chapman, Deborah Schrag



COMMENTARY

When You Look Matters: The Effect of Assessment Schedule on Progression-Free Survival

Katherine S. Panageas, Leah Ben-Porat, Maura N. Dickler, Paul B. Chapman, Deborah Schrag

Table 1. Estimated median progression-free survival (PFS) and bias from Kaplan–Meier analyses using the upper limit, midpoint, and lower limit of the progression interval*

True median PFS, mo (wk)	Frequency of radiologic reassessment, wk	Upper limit		Midpoint		Lower limit	
		Months (weeks)	Bias†	Months	Bias	Months	Bias
3 (13)	4	3.7 (16)	22%	3.2	7%	2.8	−8%
	5	3.5 (15)	15%	2.9	−5%	2.3	−24%
	6	4.2 (18)	37%	3.5	15%	2.8	−8%
	7	3.2 (14)	7%	2.4	−20%	3.2	7%
	8	3.7 (16)	22%	2.8	−8%	1.8	−39%
	9	4.2 (18)	37%	3.1	3%	2.1	−31%
	10	4.6 (20)	53%	3.5	15%	2.3	−24%
	11	5.1 (22)	68%	3.8	26%	2.5	−16%
	12	2.8 (12)‡	−8%	1.4	−54%	2.8	−8%
6 (26)	4	6.5 (28)	8%	6.0	0%	5.5	−8%
	5	6.9 (30)	15%	6.4	6%	5.8	−4%
	6	6.9 (30)	15%	6.2	4%	5.5	−8%
	7	6.5 (28)	8%	5.7	−6%	4.8	−19%
	8	7.4 (32)	23%	6.5	8%	5.5	−8%
	9	6.2 (27)	4%	5.2	−13%	6.2	4%
	10	6.9 (30)	15%	5.8	−4%	4.6	−23%
	11	7.6 (33)	27%	6.4	6%	5.1	−15%
	12	6.9 (30)	15%	5.5	−8%	5.5	−8%
12 (52)	4	12 (52)	2%	11.5	−2%	11.1	−6%
	5	12.7 (55)	8%	12.1	3%	11.5	−2%
	6	12.5 (54)	6%	11.8	0%	11.1	−6%
	7	12.9 (56)	10%	12.1	3%	11.3	−4%
	8	12.9 (56)	10%	12.0	2%	11.1	−6%
	9	12.5 (54)	6%	11.4	−3%	10.4	−12%
	10	11.5 (50)‡	−2%	10.4	−12%	11.5	−2%
	11	12.7 (55)	8%	11.4	−3%	10.2	−14%
	12	13.9 (60)	18%	12.5	6%	11.1	−6%

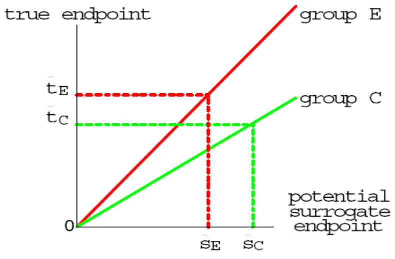
* Progression times were simulated from an exponential distribution with uniform censoring. One thousand samples of size 25 patients were generated for different prespecified true median PFS times (3, 6, and 12 months). A series of assessment schedules was imposed on the simulated progression times. Median of the estimated medians and the percent bias of the estimated median are displayed in the table.

† Bias is defined as (estimated median PFS − true median PFS)/(true median PFS) × 100%.

‡ There are two instances where the estimated median PFS using the upper limit was smaller than the true median PFS: 12-week assessment schedule and a 3-month true median PFS, and 10-week assessment schedule and a 12-month true median PFS. These exceptions arise because patients were assessed 1 or 2 weeks before the true median PFS and in more than half of the simulated studies more than 50% of the patients had progressed by this assessment time. However, the bias is quite small and is similar to the bias that results when patients are assessed 1 or 2 weeks after the true median PFS.

Critères « potentiellement » substitutif en Cancérologie

- Bénéfice / critère clinique si substitutif :
  - Utilisés comme critères de jugement final si prédit le bénéfice clinique (ie SG et ou Qualité de Vie)
  - **Corrélation pas suffisante** : le fait que l'évolution tumorale soit associée à la durée de la survie ne veut pas dire qu'elle la prédit



BMC Medical Research Methodology

Research article

A perfect correlate does not a surrogate make

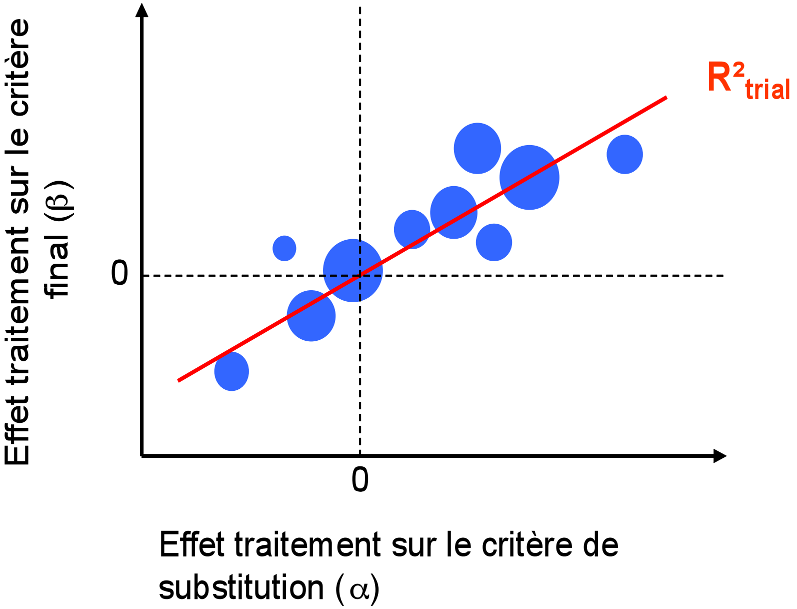
Stuart G Baker*1 and Barnett S Kramer2

BioMed Central
Open Access

  - **Substitutivité dépendante de la situation, du stade et du type de chimiothérapie**
  - Effets larges nécessaires sur SSP pour avoir un impact clinique pertinent pour la SG

Évaluation d'un critère de substitution

- Évaluation à partir d'un seul essai
  - Critères de Prentice
  - Proportion de l'effet traitement sur le critère final expliquée par le critère de substitution
- Approche méta-analytique



Validation of surrogate endpoint by Burzykowski, Molenberghs, Buyse method

Pour valider un critère substitutif :

- 1 - Forte correlation au niveau individuelle entre le critère candidat et le vrai critère clinique

ET

- 2 - Forte correlation entre l'effet du traitement sur le critère candidat et l'effet du traitement sur le critère final (R2> 0.75)
- Le 1er est très fréquent, le second est plus rare

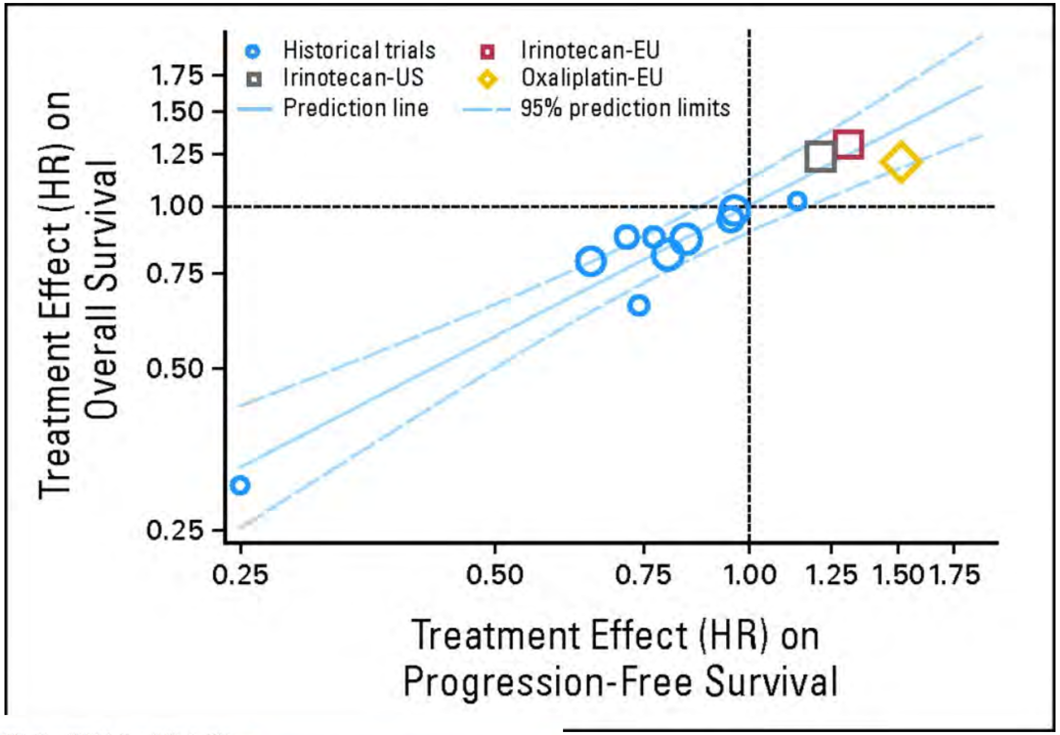
Ref: Buyse et al, Biostatistics 2000; Burzykowski et al, Applied Statistics 2001

Critères de Jugement et essais cliniques en Cancérologie

- Classification de Fleming (2005)
  - *Niveau 1* :Critère de jugement mesurant un réel bénéfice clinique pour le patient (SG et QdV)
  - *Niveau 2* :Un critère de substitution validé, selon l'approche méta-analytique (de tels critères sont rares) ;
  - *Niveau 3* :Un critère de substitution non validé, mais qui a néanmoins raisonnablement des chances de prédire le bénéfice clinique souhaité, sur des considérations statistiques et cliniques.
  - *Niveau 4* :Une mesure biologique corrélée au critère clinique.

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

PFS comme critère de jugement substitutif de l'OS dans le CCRm?



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 » de OS pour
chimiothérapie
Mais depuis
ASCO 2013 PFS mauvais
« surrogate » pour
biothérapies

VOLUME 30 · NUMBER 10 · APRIL 1 2012

JOURNAL OF CLINICAL ONCOLOGY — COMMENTS AND CONTROVERSIES

Progression-Free Survival: Meaningful or Simply Measurable?

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

See accompanying articles on pages 1114 and 1122

- Comment évaluer le bénéfice clinique pour le patient ?
- Contexte Economique

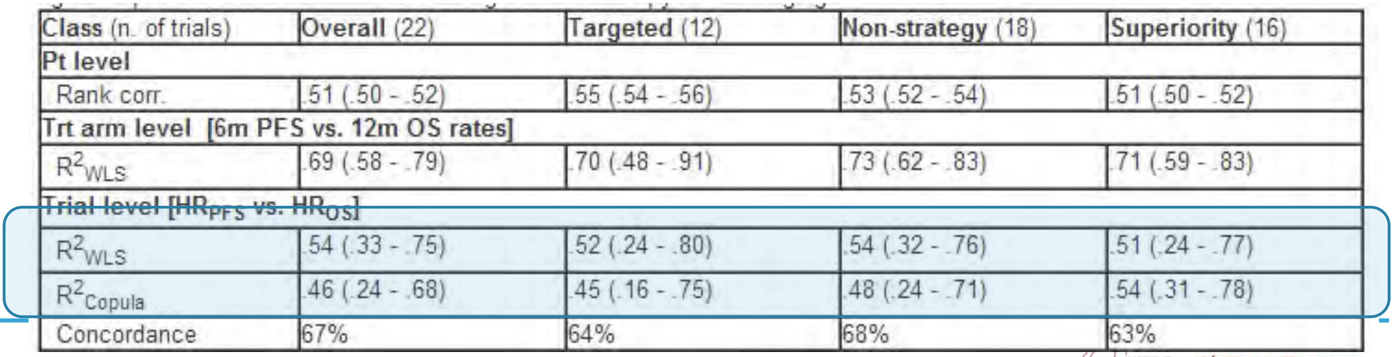
VOLUME 33 · NUMBER 1 · JANUARY 1 2015

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 Diaz-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



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%

Fleming et al. ***J Clin Oncol 27:2874-2880; 2009 ESSAIS CCRm soumis à la FDA***

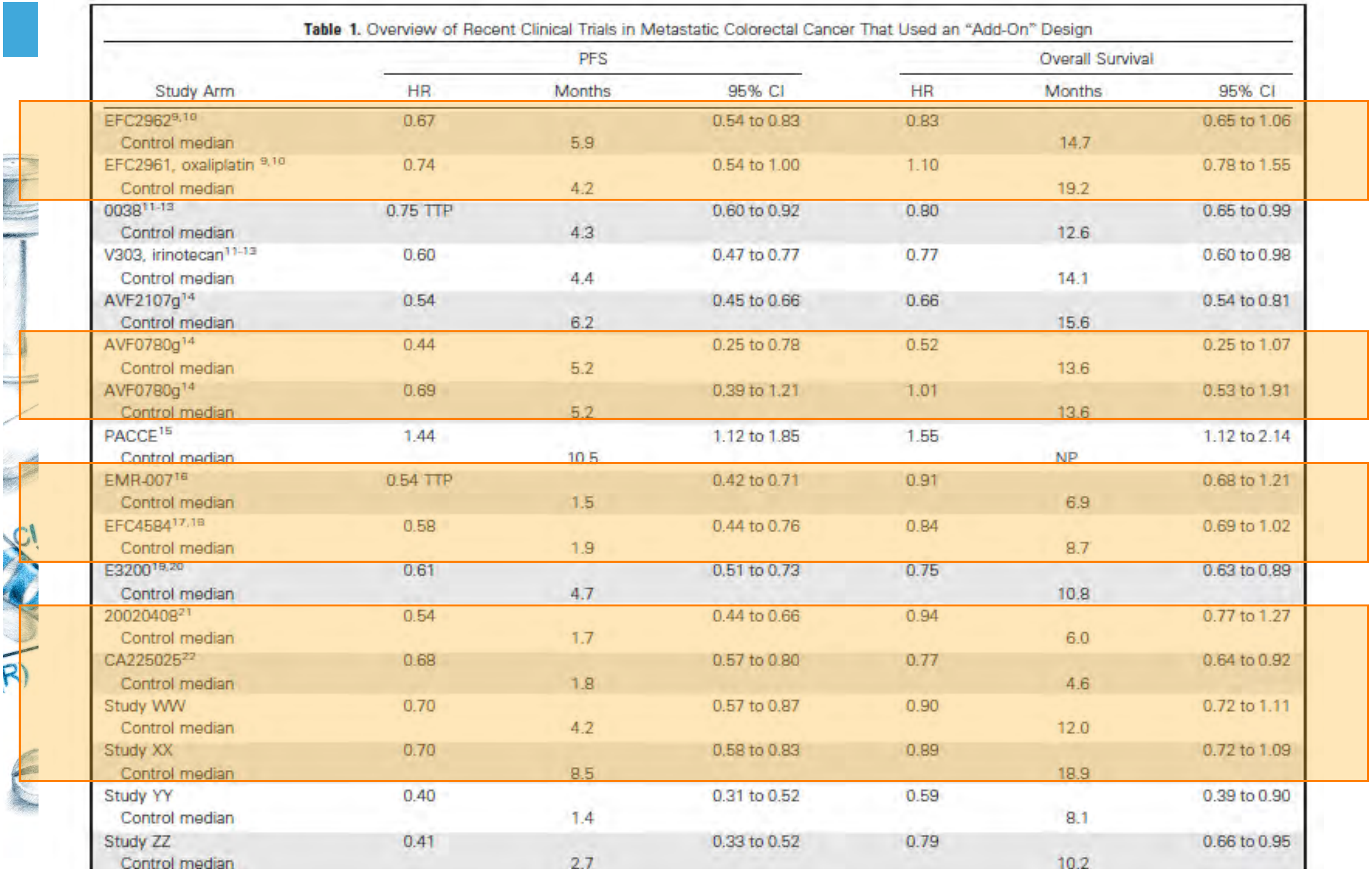
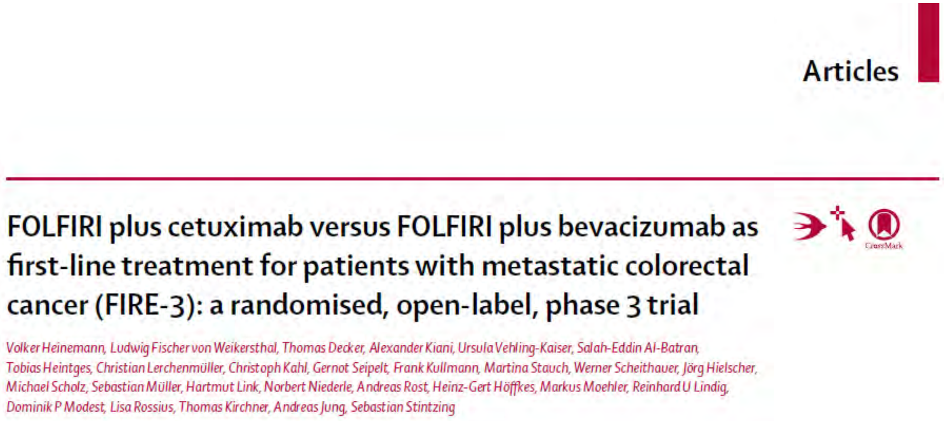


Table 1. Overview of Recent Clinical Trials in Metastatic Colorectal Cancer That Used an "Add-On" Design

	PFS			Overall Survival		
Study Arm	HR	Months	95% CI	HR	Months	95% CI
EFC2962[9,10]	0.67		0.54 to 0.83	0.83		0.65 to 1.06
Control median		5.9			14.7	
EFC2961, oxaliplatin [9,10]	0.74		0.54 to 1.00	1.10		0.78 to 1.55
Control median		4.2			19.2	
0038[11-13]	0.75 TTP		0.60 to 0.92	0.80		0.65 to 0.99
Control median		4.3			12.6	
V303, irinotecan[11-13]	0.60		0.47 to 0.77	0.77		0.60 to 0.98
Control median		4.4			14.1	
AVF2107g[14]	0.54		0.45 to 0.66	0.66		0.54 to 0.81
Control median		6.2			15.6	
AVF0780g[14]	0.44		0.25 to 0.78	0.52		0.25 to 1.07
Control median		5.2			13.6	
AVF0780g[14]	0.69		0.39 to 1.21	1.01		0.53 to 1.91
Control median		5.2			13.6	
PACCE[15]	1.44		1.12 to 1.85	1.55		1.12 to 2.14
Control median		10.5			NP	
EMR-007[16]	0.54 TTP		0.42 to 0.71	0.91		0.68 to 1.21
Control median		1.5			6.9	
EFC4584[17,18]	0.58		0.44 to 0.76	0.84		0.69 to 1.02
Control median		1.9			8.7	
E3200[19,20]	0.61		0.51 to 0.73	0.75		0.63 to 0.89
Control median		4.7			10.8	
20020408[21]	0.54		0.44 to 0.66	0.94		0.77 to 1.27
Control median		1.7			6.0	
CA225025[22]	0.68		0.57 to 0.80	0.77		0.64 to 0.92
Control median		1.8			4.6	
Study WW	0.70		0.57 to 0.87	0.90		0.72 to 1.11
Control median		4.2			12.0	
Study XX	0.70		0.58 to 0.83	0.89		0.72 to 1.09
Control median		8.5			18.9	
Study YY	0.40		0.31 to 0.52	0.59		0.39 to 0.90
Control median		1.4			8.1	
Study ZZ	0.41		0.33 to 0.52	0.79		0.66 to 0.95
Control median		2.7			10.2	

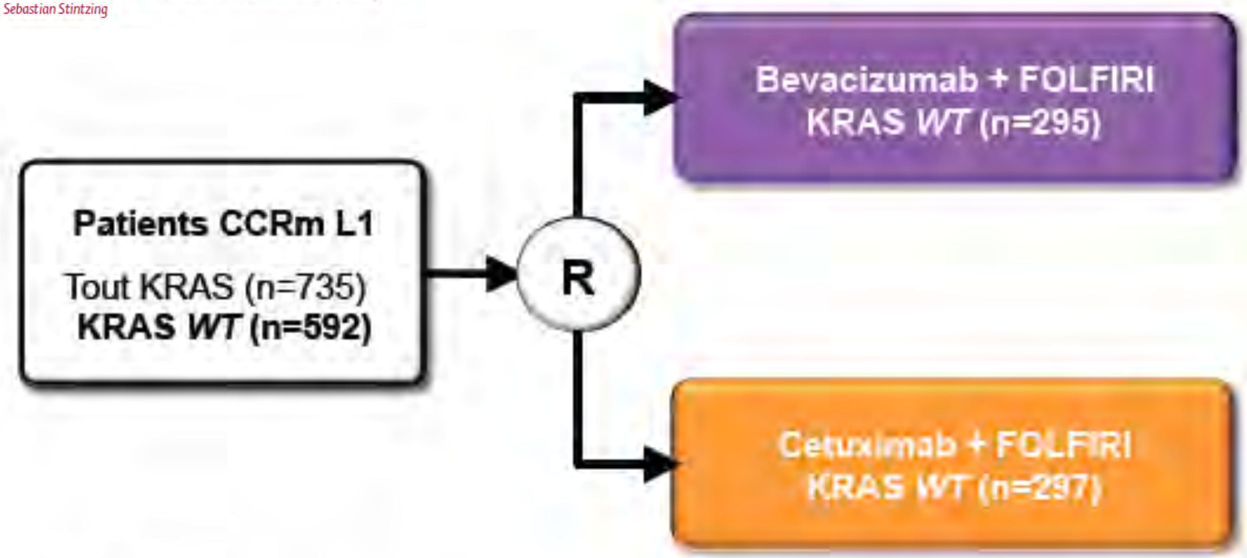
10/ 17 (60%) pas d'impact sur OS malgré une amélioration PFS HR < 0.80



Articles

FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial

Volker Heinemann, Ludwig Fischer von Weikersthal, Thomas Decker, Alexander Kiani, Ursula Vehling-Kaiser, Salah-Eddin Al-Batran, Tobias Heintges, Christian Lerchenmüller, Christoph Kahl, Gernot Seipelt, Frank Kullmann, Martina Stauch, Werner Scheithauer, Jörg Hielscher, Michael Scholz, Sebastian Müller, Hartmut Link, Norbert Niederle, Andreas Rost, Heinz-Gert Höffkes, Markus Moehler, Reinhard U Lindig, Dominik P Modest, Lisa Rossius, Thomas Kirchner, Andreas Jung, Sebastian Stintzing



Patients CCRm L1

Tout KRAS (n=735)

KRAS *WT* (n=592)

Bevacizumab + FOLFIRI
KRAS *WT* (n=295)

Cetuximab + FOLFIRI
KRAS *WT* (n=297)

- **Critère principal** : RO
- **Critères secondaires** : SSP, SG, taux de résection secondaire R0, tolérance
- **Promoteur** : Université de Munich (soutien Merck)

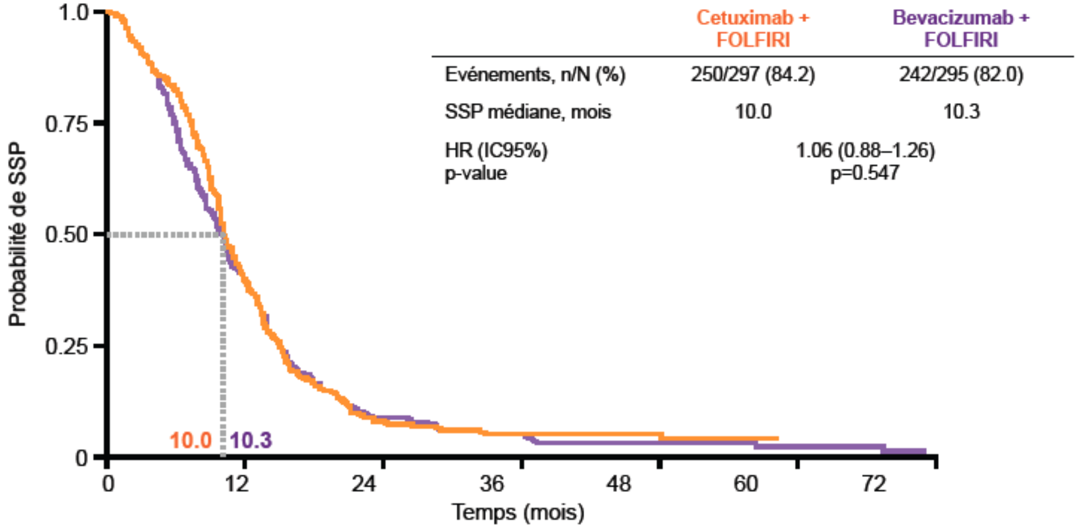
→ **Choix critère principal non pertinent car ce n'est pas un critère clinique**

Heinemann V et al. ASCO 2013 (abst. LBA3506)

Etude FIRE-3 (Ph.III)
Résultat principal : réponse objective (RO)

Population en ITT* (n=592)	Cetuximab + FOLFIRI (n=297)	Avastin + FOLFIRI (n=295)
RO (95% CI), %	62.0 (56.2–67.5)	58.0 (52.1–63.7)
Odds ratio	1.18 (0.85-1.64)	
p-value‡	0.183	

Etude FIRE-3 (Ph.III)
Résultat secondaire : Survie Sans Progression



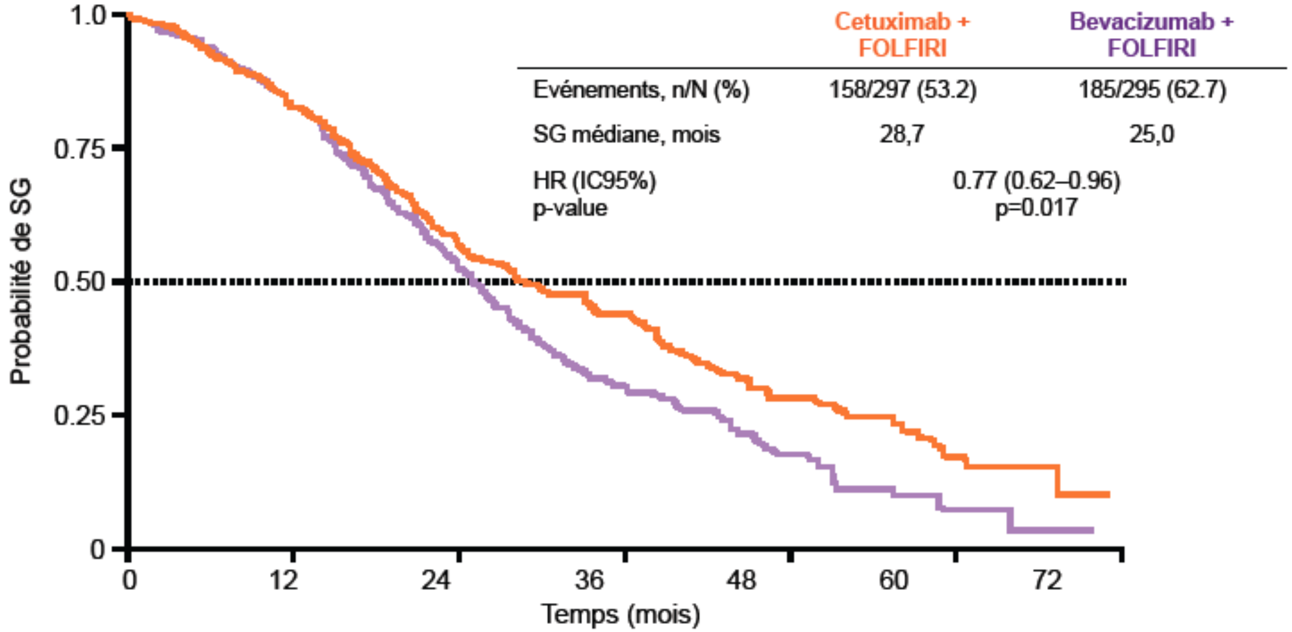
	Cetuximab + FOLFIRI	Bevacizumab + FOLFIRI
Evénements, n/N (%)	250/297 (84.2)	242/295 (82.0)
SSP médiane, mois	10.0	10.3
HR (IC95%) p-value	1.06 (0.88–1.26) p=0.547	

Patients à risque

297	100	19	10	5	3
295	99	15	6	4	

Heinemann V et al. ASCO 2013 (abst. LBA3506)

Etude FIRE-3 (Ph.III)
Résultat secondaire : Survie Globale



	Cetuximab + FOLFIRI	Bevacizumab + FOLFIRI
Evénements, n/N (%)	158/297 (53.2)	185/295 (62.7)
SG médiane, mois	28,7	25,0
HR (IC95%) p-value	0.77 (0.62–0.96) p=0.017	

Patients à risque

297	218	111	60	29	9
295	214	111	47	18	2

Durée médiane de suivi >30 mois dans les deux bras de traitement

Heinemann V et a

Confirmation que PFS, RO ne sont pas substitutifs de OS

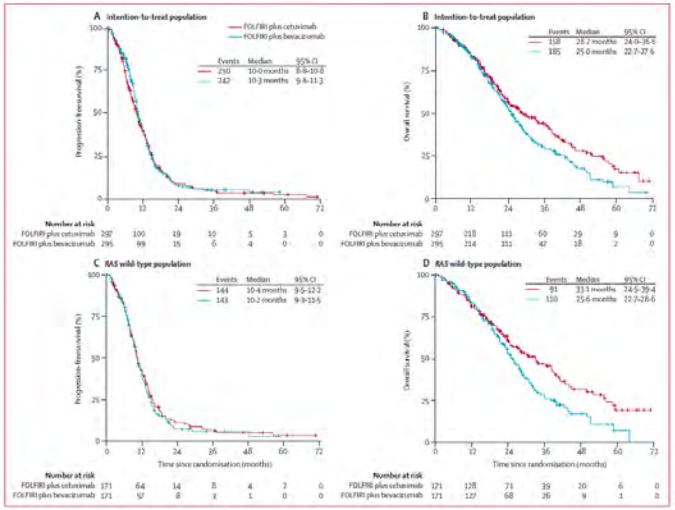
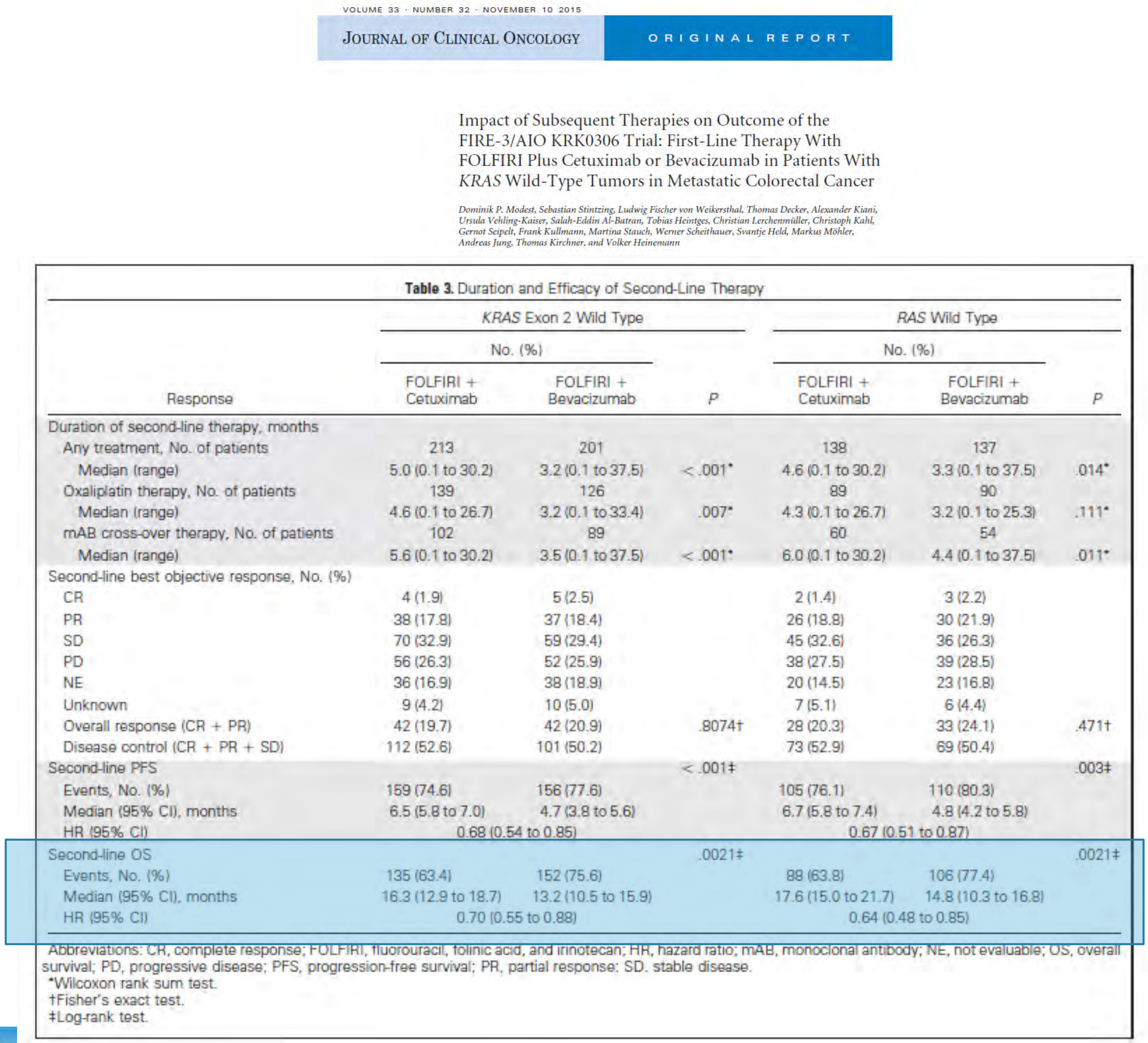


Figure 2: Kaplan-Meier estimates of progression-free and overall survival
In the intention-to-treat (A and B) and RAS wild-type (C and D) populations, according to treatment group. FOLFIRI=fluorouracil, folinic acid, and irinotecan.



VOLUME 33 · NUMBER 32 · NOVEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Subsequent Therapies on Outcome of the FIRE-3/AIO KRK0306 Trial: First-Line Therapy With FOLFIRI Plus Cetuximab or Bevacizumab in Patients With *KRAS* Wild-Type Tumors in Metastatic Colorectal Cancer

Dominik P. Modest, Sebastian Stintzing, Ludwig Fischer von Weikersthal, Thomas Decker, Alexander Kiani, Ursula Vehling-Kaiser, Salah-Eddin Al-Batran, Tobias Heintges, Christian Lerchenmüller, Christoph Kahl, Gernot Seipelt, Frank Kullmann, Martina Stauch, Werner Scheithauer, Svantje Held, Markus Möhler, Andreas Jung, Thomas Kirchner, and Volker Heinemann

Table 3. Duration and Efficacy of Second-Line Therapy

	KRAS Exon 2 Wild Type			*RAS* Wild Type		
	No. (%)			No. (%)		
Response	FOLFIRI + Cetuximab	FOLFIRI + Bevacizumab	*P*	FOLFIRI + Cetuximab	FOLFIRI + Bevacizumab	*P*
Duration of second-line therapy, months						
Any treatment, No. of patients	213	201		138	137	
Median (range)	5.0 (0.1 to 30.2)	3.2 (0.1 to 37.5)	< .001*	4.6 (0.1 to 30.2)	3.3 (0.1 to 37.5)	.014*
Oxaliplatin therapy, No. of patients	139	126		89	90	
Median (range)	4.6 (0.1 to 26.7)	3.2 (0.1 to 33.4)	.007*	4.3 (0.1 to 26.7)	3.2 (0.1 to 25.3)	.111*
mAB cross-over therapy, No. of patients	102	89		60	54	
Median (range)	5.6 (0.1 to 30.2)	3.5 (0.1 to 37.5)	< .001*	6.0 (0.1 to 30.2)	4.4 (0.1 to 37.5)	.011*
Second-line best objective response, No. (%)						
CR	4 (1.9)	5 (2.5)		2 (1.4)	3 (2.2)	
PR	38 (17.8)	37 (18.4)		26 (18.8)	30 (21.9)	
SD	70 (32.9)	59 (29.4)		45 (32.6)	36 (26.3)	
PD	56 (26.3)	52 (25.9)		38 (27.5)	39 (28.5)	
NE	36 (16.9)	38 (18.9)		20 (14.5)	23 (16.8)	
Unknown	9 (4.2)	10 (5.0)		7 (5.1)	6 (4.4)	
Overall response (CR + PR)	42 (19.7)	42 (20.9)	.8074†	28 (20.3)	33 (24.1)	.471†
Disease control (CR + PR + SD)	112 (52.6)	101 (50.2)		73 (52.9)	69 (50.4)	
Second-line PFS			< .001‡			.003‡
Events, No. (%)	159 (74.6)	156 (77.6)		105 (76.1)	110 (80.3)	
Median (95% CI), months	6.5 (5.8 to 7.0)	4.7 (3.8 to 5.6)		6.7 (5.8 to 7.4)	4.8 (4.2 to 5.8)	
HR (95% CI)	0.68 (0.54 to 0.85)			0.67 (0.51 to 0.87)		
Second-line OS			.0021‡			.0021‡
Events, No. (%)	135 (63.4)	152 (75.6)		88 (63.8)	106 (77.4)	
Median (95% CI), months	16.3 (12.9 to 18.7)	13.2 (10.5 to 15.9)		17.6 (15.0 to 21.7)	14.8 (10.3 to 16.8)	
HR (95% CI)	0.70 (0.55 to 0.88)			0.64 (0.48 to 0.85)		

Abbreviations: CR, complete response; FOLFIRI, fluorouracil, folinic acid, and irinotecan; HR, hazard ratio; mAB, monoclonal antibody; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
*Wilcoxon rank sum test.
†Fisher's exact test.
‡Log-rank test.

Original Article

Quality of Life in Patients With K-*RAS* Wild-Type Colorectal Cancer

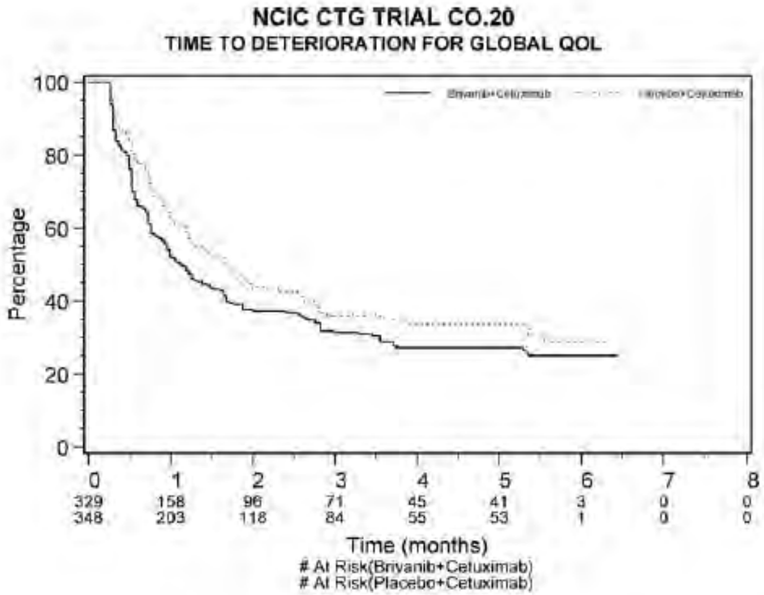
The CO.20 Phase 3 Randomized Trial

Jolie Ringash, MD[1]; Heather-Jane Au, MD[2]; Lillian L. Siu, MD[3]; Jeremy D. Shapiro, MD[4]; Derek J. Jonker, MD[5];
John R. Zalcberg, MD[6]; Malcolm J. Moore, MD[7]; Andrew Strickland, MD[8]; Rami Kotb, MD[9]; Mark Jeffery, MD[10];
Thierry Alcindor, MD[11]; Siobhan Ng, MD[12]; Muhammad Salim, MD[13]; Sabe Sabesan, MD[14]; Jay C. Easaw, PhD[15];
Jenny Shannon, MD[16]; Fabyolla El-Tahche, PhD[17]; Ian Walters, MD[18]; Dongsheng Tu, PhD[19];
Christopher J. O'Callaghan, DVM[19]; on behalf of the NCIC Clinical Trials Group and
the Australasian Gastrointestinal Trials Group

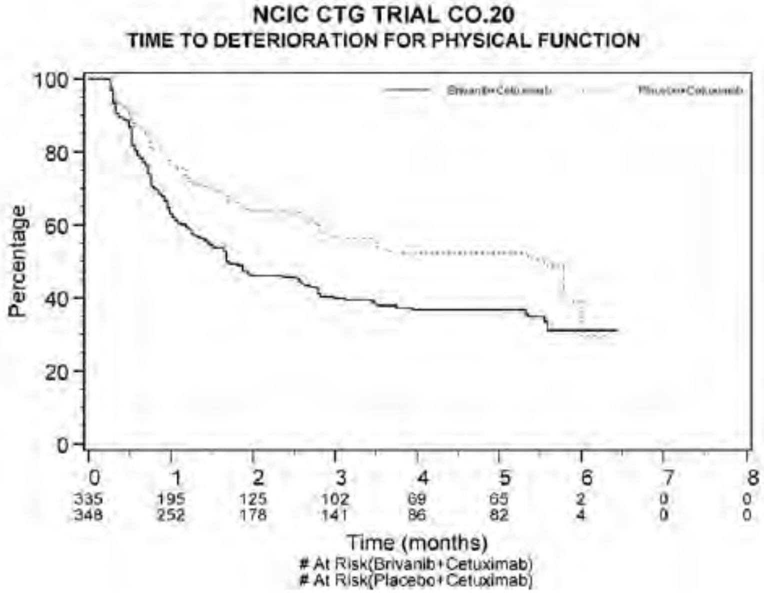
Cancer January 15, 2014

The primary QoL hypothesis was that the combined treatment (CET/BRIV) would delay deterioration in QoL scores; specifically, the time to deterioration by ≥10 points on the Physical Function (PF) and GHS scales of the EORTC QLQ-C30 would be longer in this arm compared with the CET/placebo arm. PF and GHS were chosen as the scales most likely to be sensitive to the effects of chemotherapy and to best reflect the global QoL experience. The previous CO.17 study had demonstrated a me-

> patients who received CET/placebo. Although BRIV was found to significantly delay disease progression, this benefit led to neither an improvement in OS nor patient QoL (indeed, QoL deteriorated more quickly). If better sup-



NCIC CTG TRIAL CO.20
TIME TO DETERIORATION FOR GLOBAL QOL



NCIC CTG TRIAL CO.20
TIME TO DETERIORATION FOR PHYSICAL FUNCTION

vs 11%), hypertension, rash, diarrhea, abdominal pain, dehydration, and anorexia. **CONCLUSIONS:** Compared with CET/placebo, the combination of CET/BRIV worsened time to QoL deterioration for patients with K-*RAS* wild-type, chemotherapy-refractory, metastatic colorectal cancer on the PF and GHS scales of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30. This result may be due to higher rates of fatigue and gastrointestinal adverse events. *Cancer* **2014;120:181-9.**

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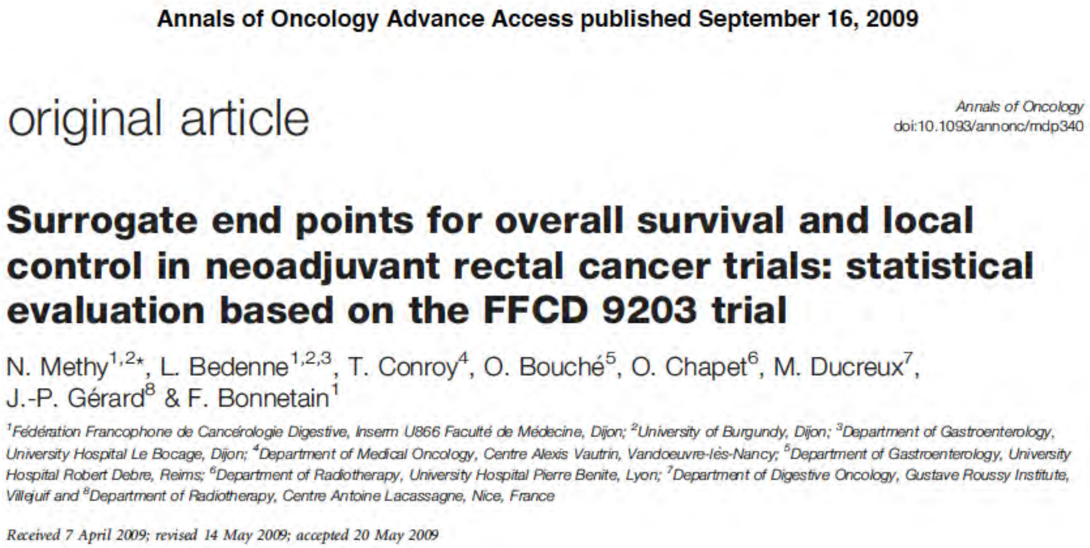


Annals of Oncology Advance Access published September 16, 2009

original article

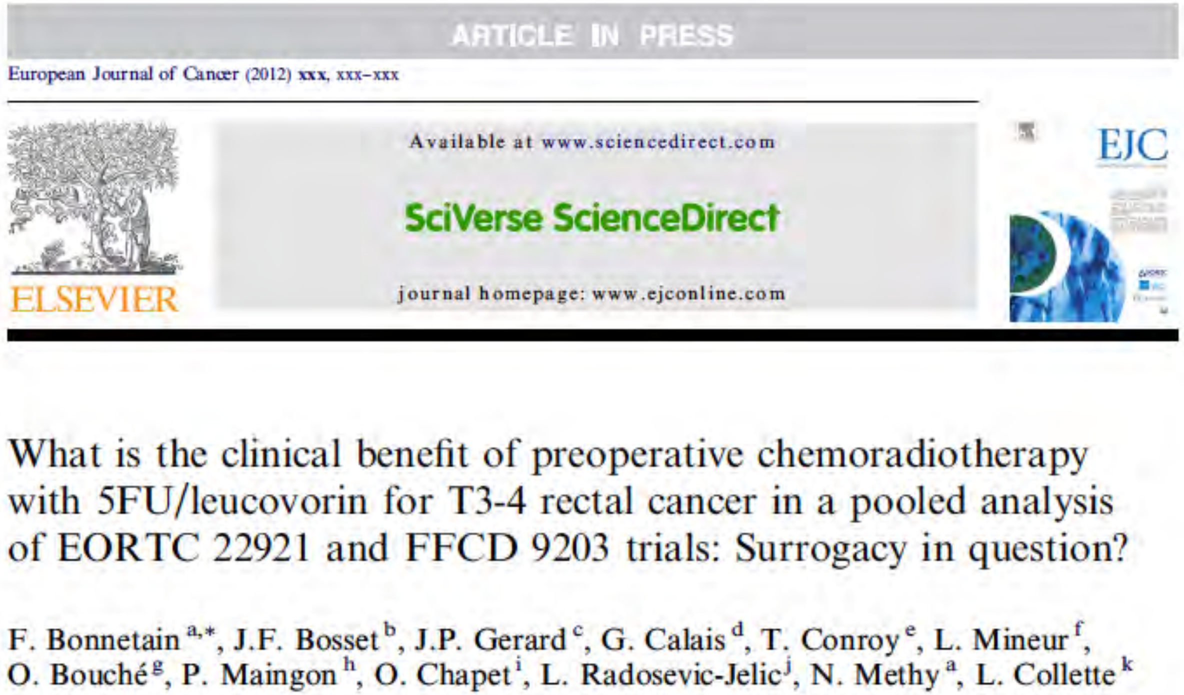
Annals of Oncology
doi:10.1093/annonc/mdp340

Surrogate end points for overall survival and local control in neoadjuvant rectal cancer trials: statistical evaluation based on the FFCD 9203 trial

N. Methy[1,2*], L. Bedenne[1,2,3], T. Conroy[4], O. Bouché[5], O. Chapet[6], M. Ducreux[7],
J.-P. Gérard[8] & F. Bonnetain[1]

[1]Fédération Francophone de Cancérologie Digestive, Inserm U866 Faculté de Médecine, Dijon; [2]University of Burgundy, Dijon; [3]Department of Gastroenterology, University Hospital Le Bocage, Dijon; [4]Department of Medical Oncology, Centre Alexis Vautrin, Vandoeuvre-lès-Nancy; [5]Department of Gastroenterology, University Hospital Robert Debre, Reims; [6]Department of Radiotherapy, University Hospital Pierre Benite, Lyon; [7]Department of Digestive Oncology, Gustave Roussy Institute, Villejuif and [8]Department of Radiotherapy, Centre Antoine Lacassagne, Nice, France

Received 7 April 2009; revised 14 May 2009; accepted 20 May 2009



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

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EJC

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]

Table 4. Prentice criteria and PTE for local control, among patients with gross complete resection ($n = 674$)

	Candidate surrogate end point (S) for time to local recurrence					
	ypT[a]	ypT0	T downstaging[b]	ypN	CRM[c]	Tumor regression[a]
Treatment effect on local recurrence (RT–CT versus RT)						
HR (95% CI)	0.50 (0.31 to 0.80)					
β	−0.70					
P	0.004					
Treatment effect on local recurrence, adjusted for S (RT–CT versus RT)						
HR (95% CI)	0.52 (0.32 to 0.84)	0.52 (0.32 to 0.83)	0.52 (0.32 to 0.84)	0.51 (0.32 to 0.83)	0.52 (0.27 to 0.97)	0.54 (0.33 to 0.88)
β_S	−0.66	−0.67	−0.66	−0.67	−0.67	−0.62
P	0.008	0.007	0.008	0.007	0.041	0.013
PTE (%) = $1 - \beta_S/\beta$ (95% CI)	6.8 (−8.8 to 28.7)	4.9 (−6.6 to 16.8)	6.2 (−4.7 to 26.4)	4.8 (−6.4 to 24.7)	4.9 (−80.7 to 105.3)	12.1 (−0.9 to 40.7)

β and β_S, Cox coefficients; CI, confidence interval; CRM, circumferential resection margin; HR, hazard ratio; PTE, proportion of treatment effect; RT, radiotherapy; RT–CT, radiotherapy and chemotherapy.

[a] Introduced in Cox models as dichotomous covariables.

[b] T was considered dowstaged when ypT stage (from 0–3) was lower than clinical stage (3 or 4).

[c] Considered as positive if the microscopic tumor extension reached the margin.

original article

Annals of Oncology 21: 518–524, 2010
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Published online 16 September 2009

Surrogate end points for overall survival and local control in neoadjuvant rectal cancer trials: statistical evaluation based on the FFCD 9203 trial

N. Methy[1,2*], L. Bedenne[1,2,3], T. Conroy[4], O. Bouché[5], O. Chapet[6], M. Ducreux[7],
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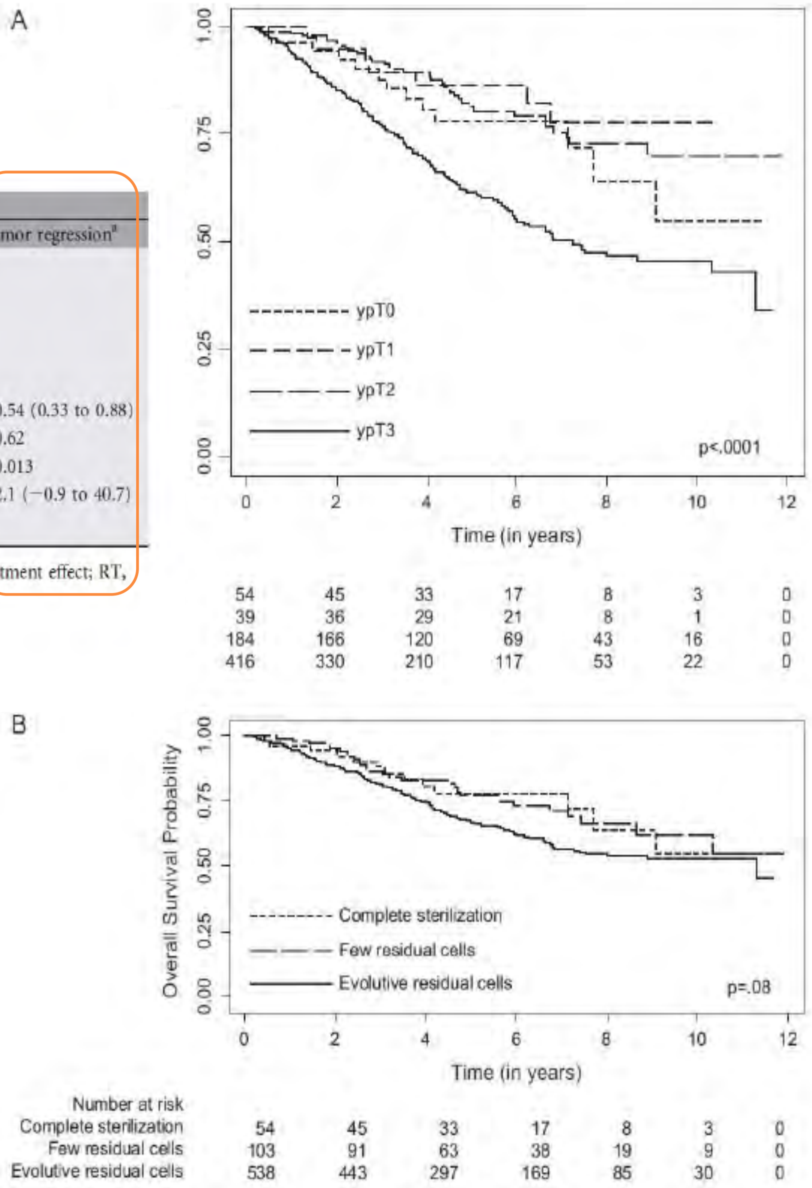
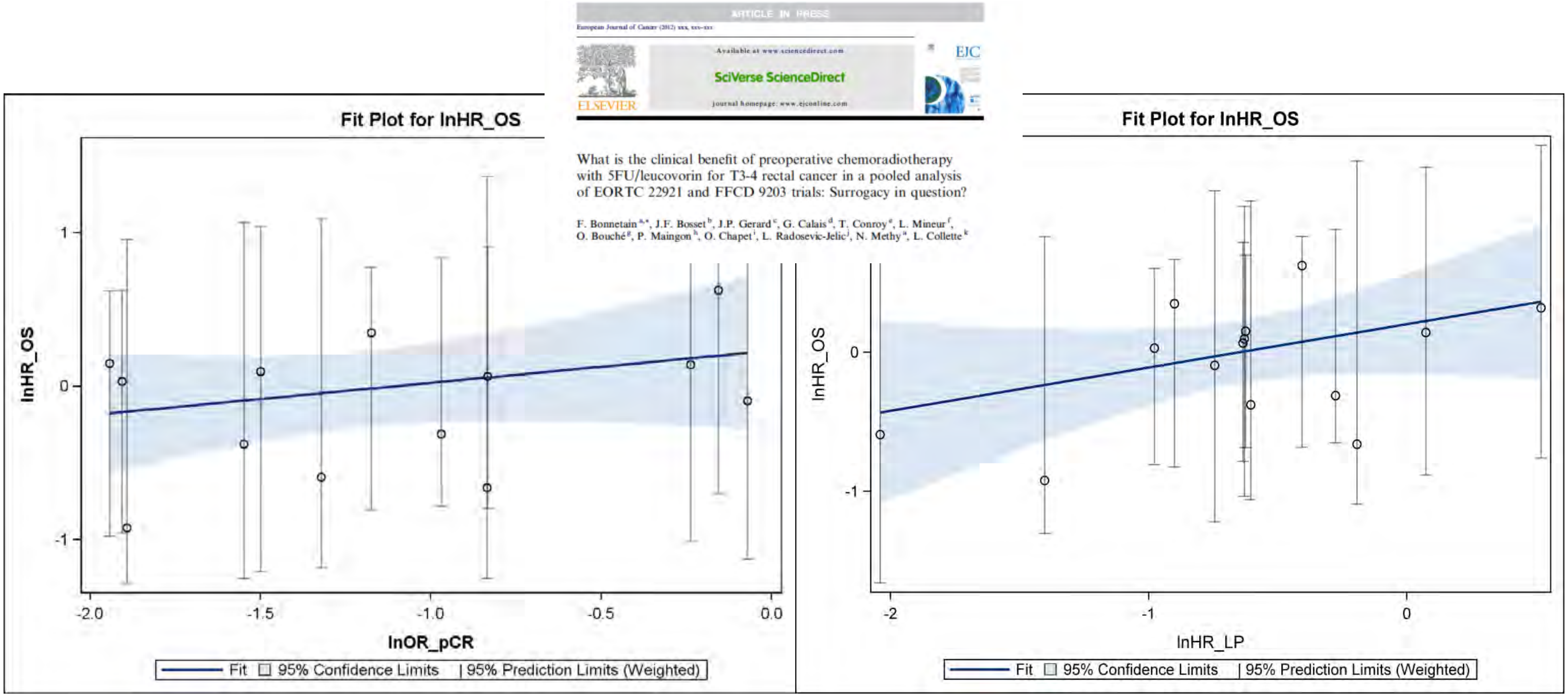


Figure 1. Prognostic value of ypT stage (A) and tumor regression grade (B) for overall survival.

pCR et LC comme surrogate de OS dans le cancer du rectum T3-T4 ?(Bonnetain et al, ASCO 2011 et EJC 2012)



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

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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]

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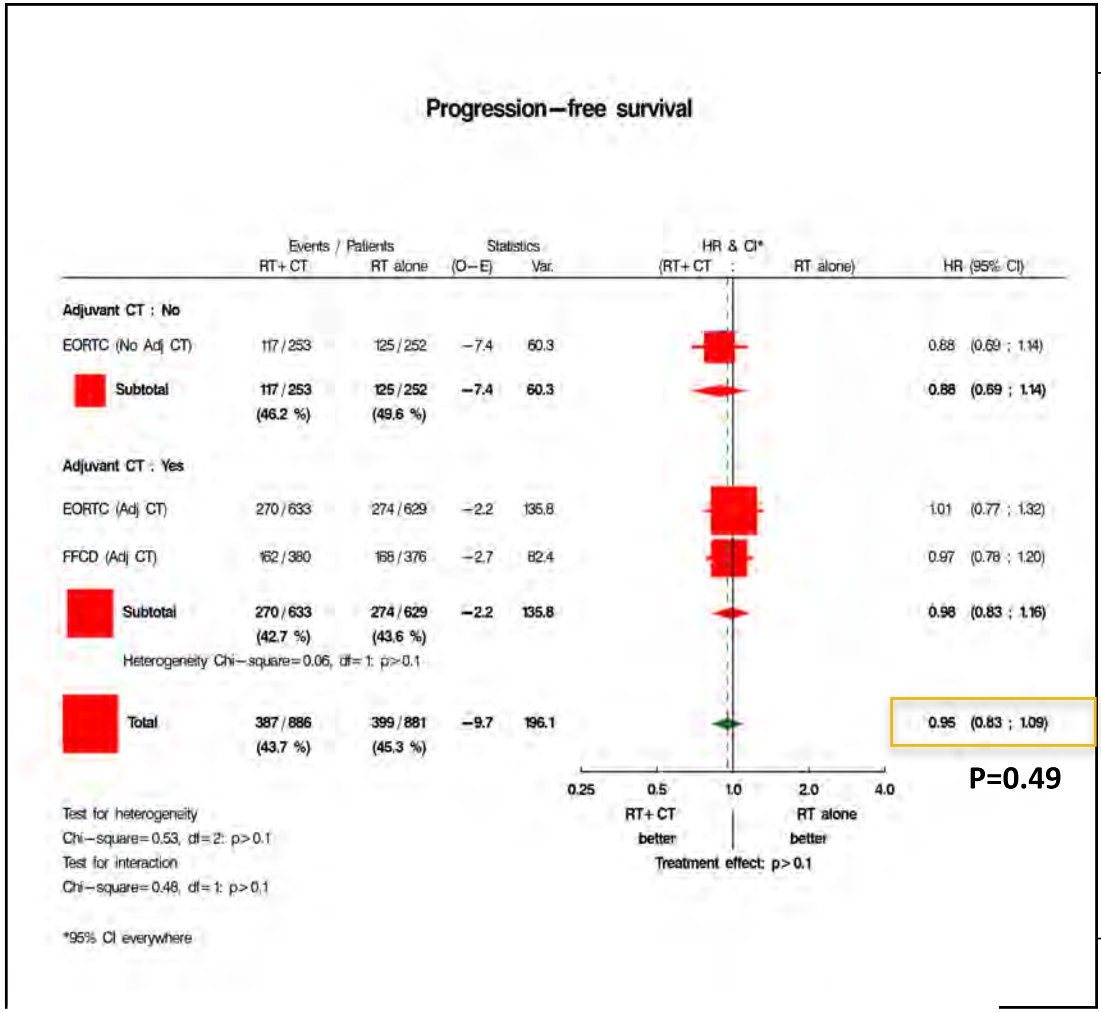
EJC
Fit Plot for lnHR_OS
lnHR_OS
1
0
-1
-2.0
-1.5
-1.0
-0.5
0.0
lnOR_pCR
Fit
95% Confidence Limits
95% Prediction Limits (Weighted)
Fit Plot for lnHR_OS
lnHR_OS
0
-1
-2
-1
0
lnHR_LP
Fit
95% Confidence Limits
95% Prediction Limits (Weighted)

pCR
Trial-level association
R² = 0.11 (95% CI : 0.0 to 0.44)

LC
Trial-level association
R² = 0.17 (95% CI : 0 to 0.52)

R² < 0.75 Mauvais surrogates pour OS

Results : Surrogacy of PFS for OS weighted linear regression



Progression–free survival

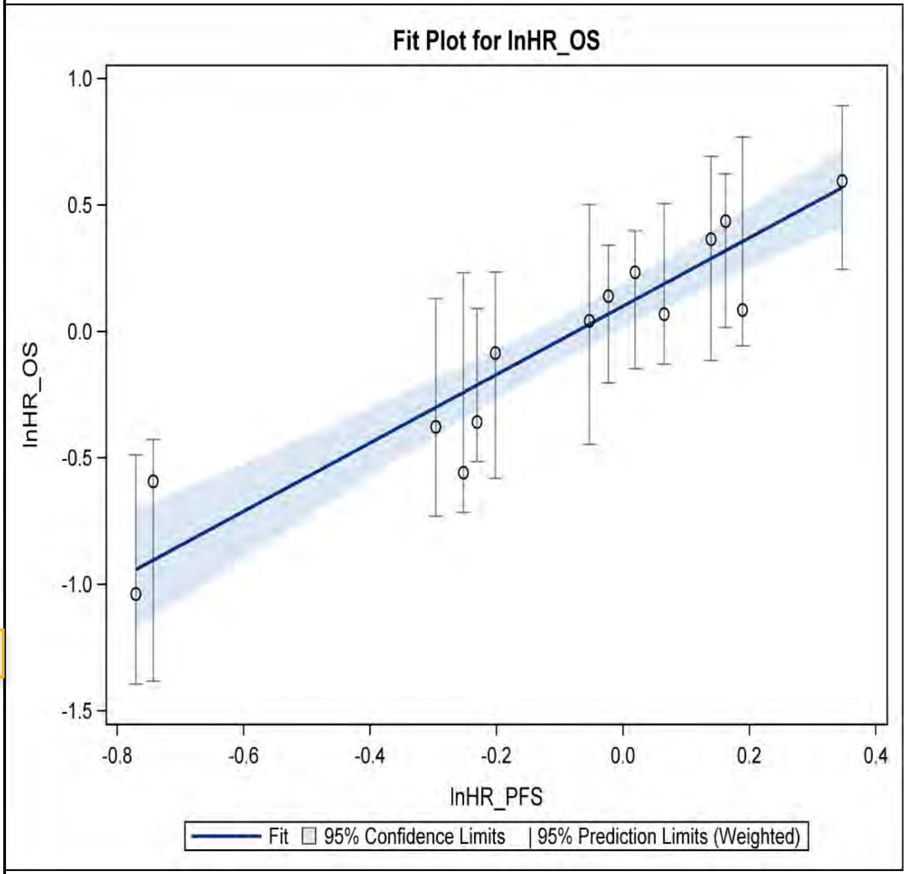
	Events / Patients		Statistics		
	RT+ CT	RT alone	(O–E)	Var.	HR (95% CI)
Adjuvant CT : No					
EORTC (No Adj CT)	117 / 253	125 / 252	−7.4	60.3	0.88 (0.69 ; 1.14)
Subtotal	**117 / 253** **(46.2 %)**	**125 / 252** **(49.6 %)**	**−7.4**	**60.3**	**0.88 (0.69 ; 1.14)**
Adjuvant CT : Yes					
EORTC (Adj CT)	270 / 633	274 / 629	−2.2	135.8	1.01 (0.77 ; 1.32)
FFCD (Adj CT)	162 / 380	168 / 376	−2.7	82.4	0.97 (0.78 ; 1.20)
Subtotal	**270 / 633** **(42.7 %)**	**274 / 629** **(43.6 %)**	**−2.2**	**135.8**	**0.98 (0.83 ; 1.16)**
Heterogeneity Chi–square=0.06, df=1: p>0.1					
Total	**387 / 886** **(43.7 %)**	**399 / 881** **(45.3 %)**	**−9.7**	**196.1**	**0.95 (0.83 ; 1.09)**

HR & CI*
(RT+ CT : RT alone)
0.25
0.5
1.0
2.0
4.0
RT+ CT better
RT alone better
Treatment effect: p>0.1

P=0.49

Test for heterogeneity
Chi–square=0.53, df=2: p>0.1
Test for interaction
Chi–square=0.48, df=1: p>0.1

*95% CI everywhere



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)

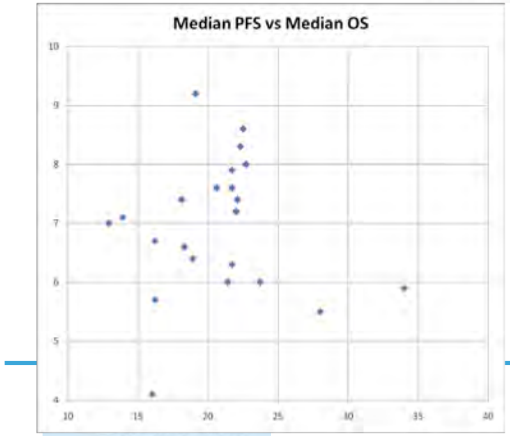
PFS substitutif de l’OS dans mBC ?

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

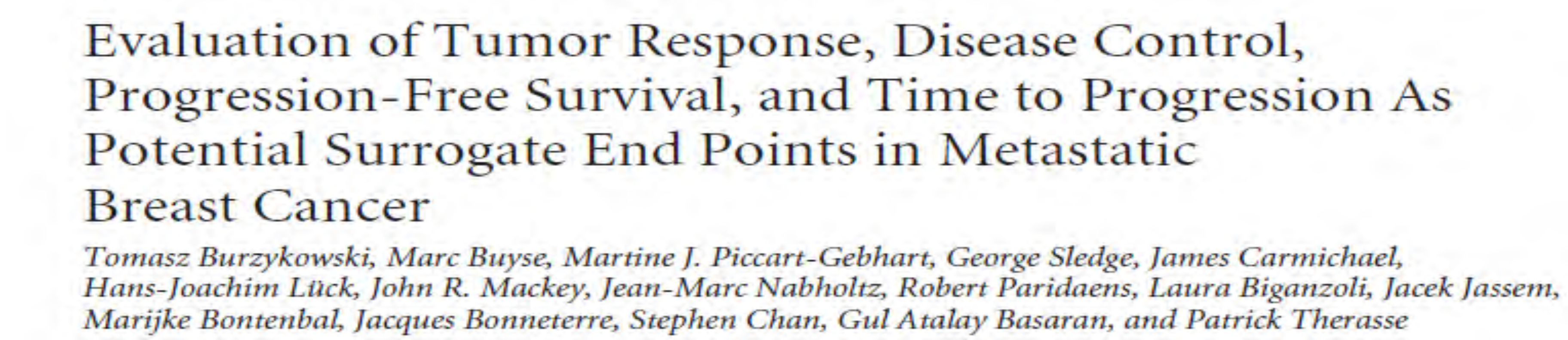
Tomasz Burzykowski, Marc Buyse, Martine J. Piccart-Gebhart, George Sledge, James Carmichael, Hans-Joachim Lück, John R. Mackey, Jean-Marc Nabholtz, Robert Paridaens, Laura Biganzoli, Jacek Jassem, Marijke Bontenbal, Jacques Bonneterre, Stephen Chan, Gul Atalay Basaran, and Patrick Therasse

- ✓ au niveau individuel entre 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).



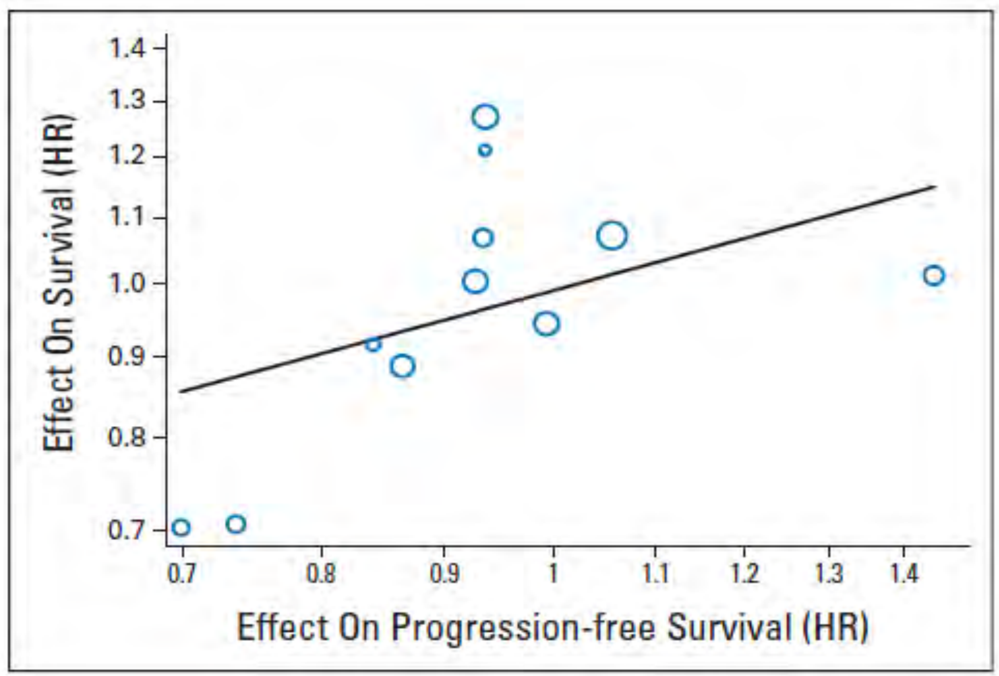
PFS substitutif de l’OS dans mBC ?

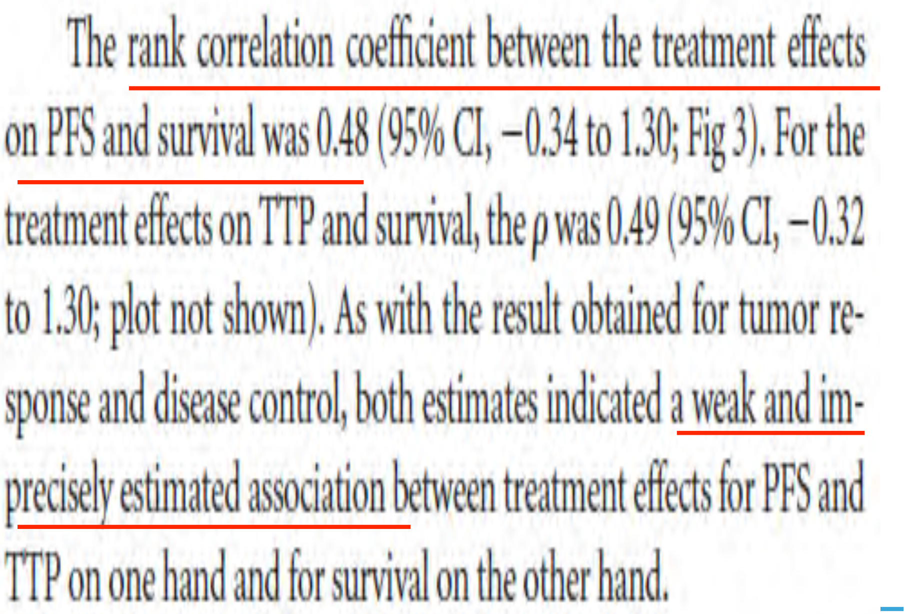


Evaluation of Tumor Response, Disease Control, Progression-Free Survival, and Time to Progression As Potential Surrogate End Points in Metastatic Breast Cancer

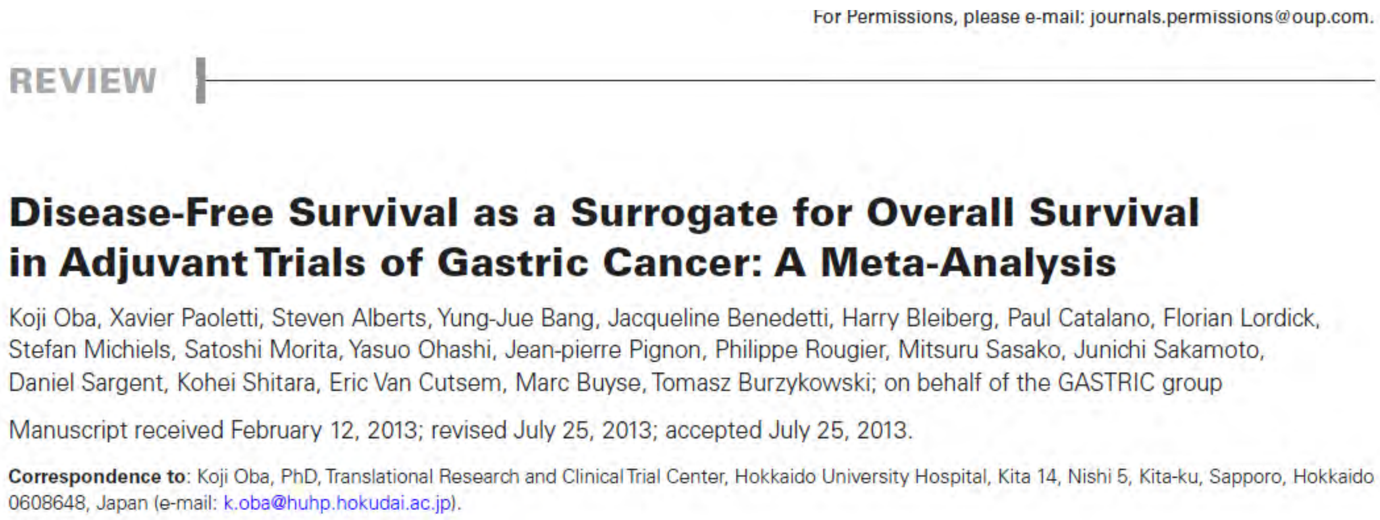
Tomasz Burzykowski, Marc Buyse, Martine J. Piccart-Gebhart, George Sledge, James Carmichael, Hans-Joachim Lück, John R. Mackey, Jean-Marc Nabholtz, Robert Paridaens, Laura Biganzoli, Jacek Jassem, Marijke Bontenbal, Jacques Bonneterre, Stephen Chan, Gul Atalay Basaran, and Patrick Therasse

✓ corrélation entre l’effet du traitement sur PFS et l’effet du traitement OS:





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.



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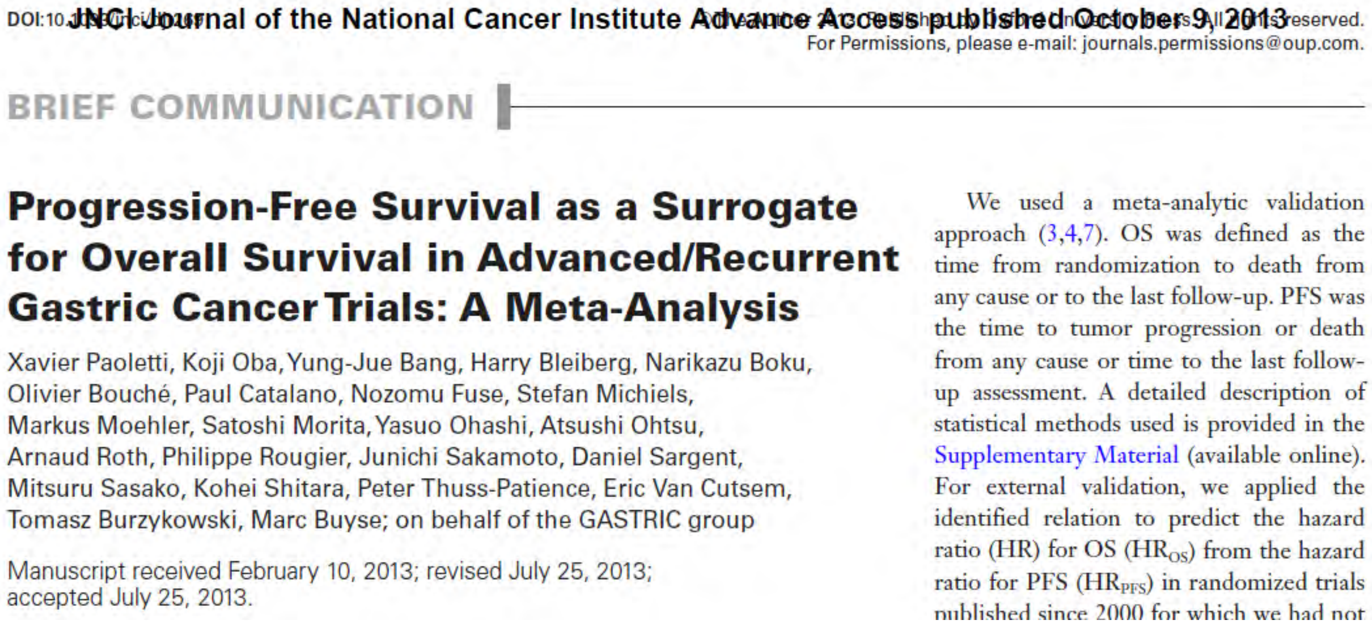
REVIEW

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.[illegible] **JNCI Journal of the National Cancer Institute Advance Access published October 9, 2013** [illegible] reserved.

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BRIEF COMMUNICATION

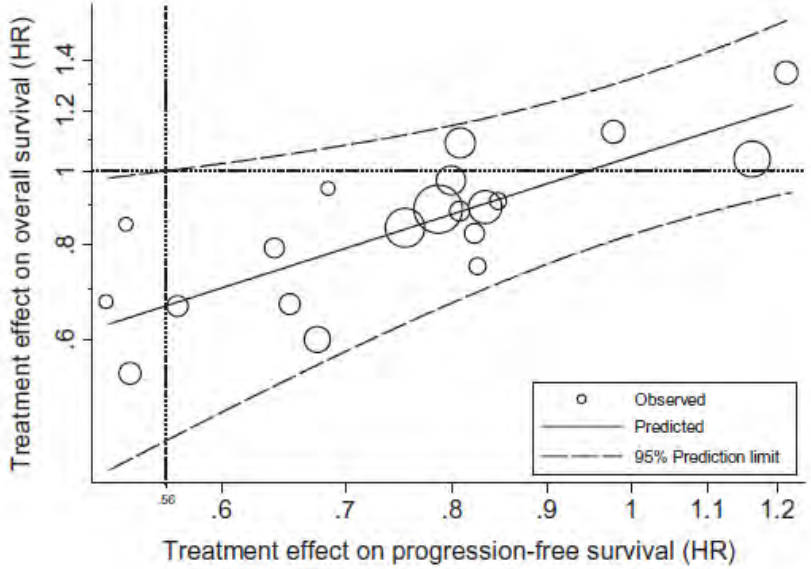
Progression-Free Survival as a Surrogate for Overall Survival in Advanced/Recurrent Gastric Cancer Trials: A Meta-Analysis

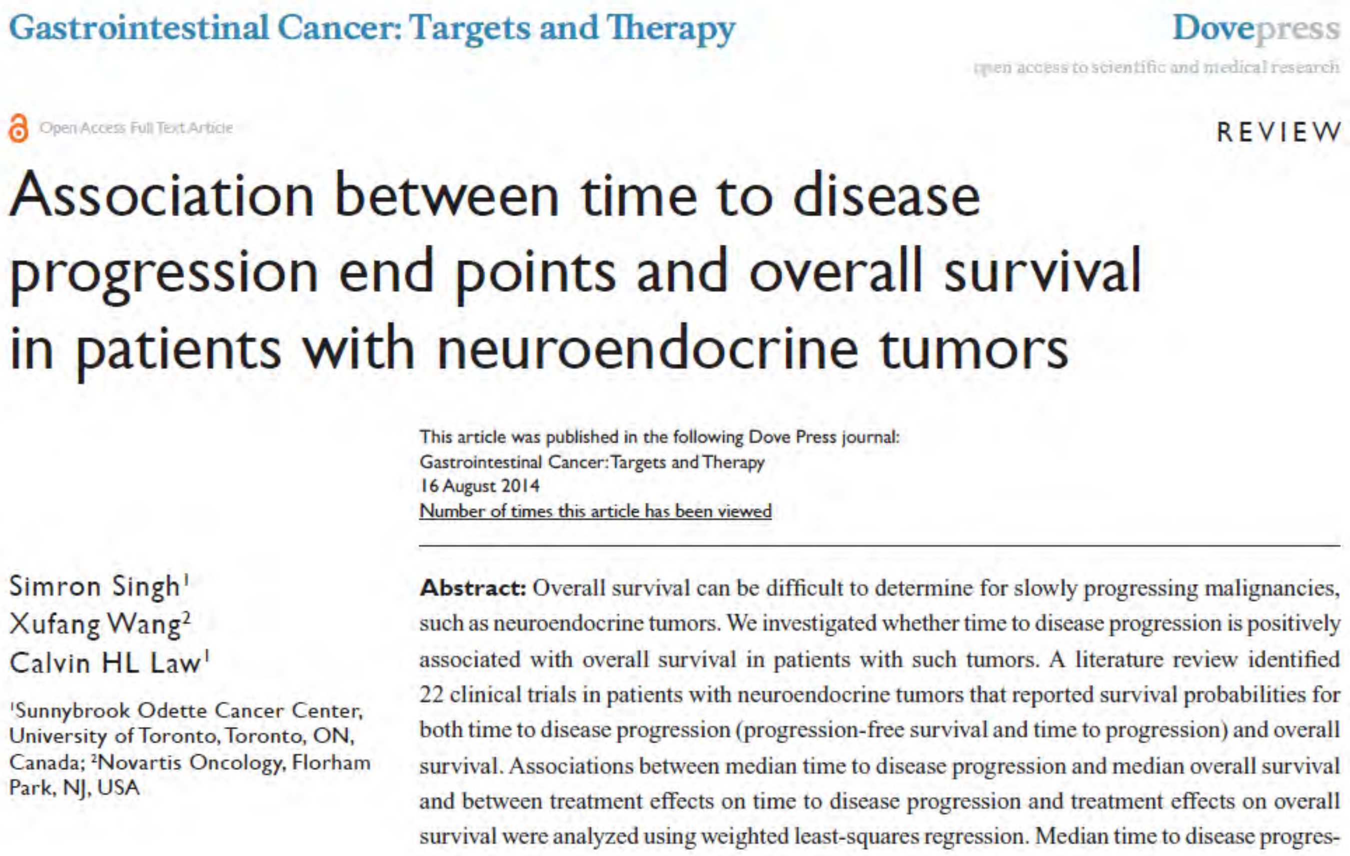
Xavier Paoletti, Koji Oba, Yung-Jue Bang, Harry Bleiberg, Narikazu Boku, Olivier Bouché, Paul Catalano, Nozomu Fuse, Stefan Michiels, Markus Moehler, Satoshi Morita, Yasuo Ohashi, Atsushi Ohtsu, Arnaud Roth, Philippe Rougier, Junichi Sakamoto, Daniel Sargent, Mitsuru Sasako, Kohei Shitara, Peter Thuss-Patience, 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

The individual-level association, as measured by the rank correlation coefficient, was 0.853 (95% CI = 0.852 to 0.854), indicating substantial correlation between PFS and OS for a given patient. The association at the trial level between log HR_{OS} and log HR_{PFS} was only moderate, with a coefficient of determination, R^2, adjusted for the estimation errors (31), of 0.61 (95% CI = 0.04 to 1.00). The large confidence interval reflects the uncertainty around this estimate. The linear regression model that relates the treatment effect on PFS and on OS adjusted for estimations errors was





Gastrointestinal Cancer: Targets and Therapy

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REVIEW

Association between time to disease progression end points and overall survival in patients with neuroendocrine tumors

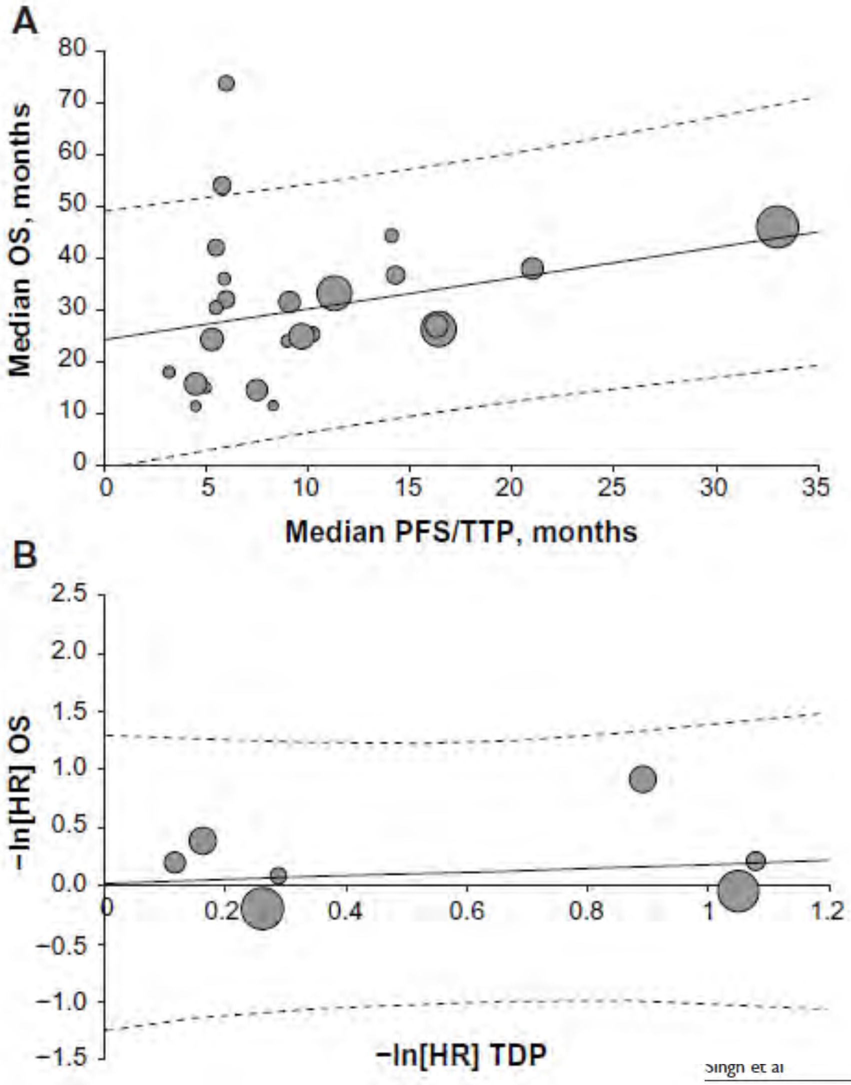
This article was published in the following Dove Press journal:
Gastrointestinal Cancer: Targets and Therapy
16 August 2014
Number of times this article has been viewed

Simron Singh[1]
Xufang Wang[2]
Calvin HL Law[1]

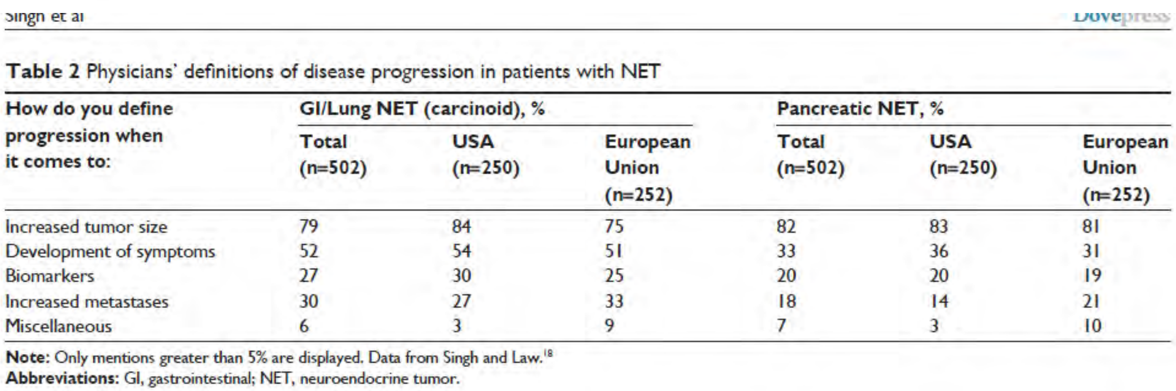
[1]Sunnybrook Odette Cancer Center, University of Toronto, Toronto, ON, Canada; [2]Novartis Oncology, Florham Park, NJ, USA

Abstract: Overall survival can be difficult to determine for slowly progressing malignancies, such as neuroendocrine tumors. We investigated whether time to disease progression is positively associated with overall survival in patients with such tumors. A literature review identified 22 clinical trials in patients with neuroendocrine tumors that reported survival probabilities for both time to disease progression (progression-free survival and time to progression) and overall survival. Associations between median time to disease progression and median overall survival and between treatment effects on time to disease progression and treatment effects on overall survival were analyzed using weighted least-squares regression. Median time to disease progres-

Meta-analyse de données de littérature
Confusion entre PFS et TDP



OS (coefficient on −ln[HR] 0.151; 95% CI −0.843, 1.145; *P*=0.713, Figure 2B). Similar to the analysis of the association between median TDP and median OS, the low R^2 of 0.030 suggests that the HR for TDP explains a relatively small proportion of the variability in the HR for OS. If the RADIANT-2 and RADIANT-3 studies[13,37] were excluded from the linear regression because of the high degree of crossover, the coefficient increased to 0.413 and the R^2 increased nearly 10-fold to 0.273; however, the relationship between risk reduction for median TDP and risk reduction for median OS remained statistically insignificant (*P*=0.366).



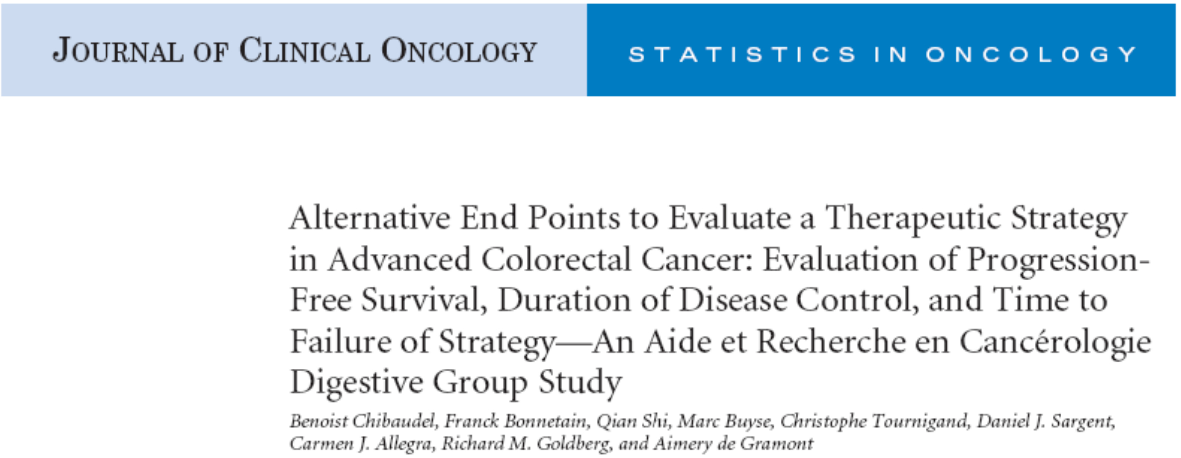
Singh et al Dovepress

Table 2 Physicians' definitions of disease progression in patients with NET

How do you define progression when it comes to:	GI/Lung NET (carcinoid), %			Pancreatic NET, %		
	Total (n=502)	USA (n=250)	European Union (n=252)	Total (n=502)	USA (n=250)	European Union (n=252)
Increased tumor size	79	84	75	82	83	81
Development of symptoms	52	54	51	33	36	31
Biomarkers	27	30	25	20	20	19
Increased metastases	30	27	33	18	14	21
Miscellaneous	6	3	9	7	3	10

Note: Only mentions greater than 5% are displayed. Data from Singh and Law.[18]
Abbreviations: GI, gastrointestinal; NET, neuroendocrine tumor.

Critères composites pour essais de stratégie



Journal of Clinical Oncology | STATISTICS IN ONCOLOGY

Alternative End Points to Evaluate a Therapeutic Strategy in Advanced Colorectal Cancer: Evaluation of Progression-Free Survival, Duration of Disease Control, and Time to Failure of Strategy—An Aide et Recherche en Cancérologie Digestive Group Study

Benoist Chibaudel, Franck Bonnetain, Qian Shi, Marc Buyse, Christophe Tournigand, Daniel J. Sargent, Carmen J. Allegra, Richard M. Goldberg, and Aimery de Gramont

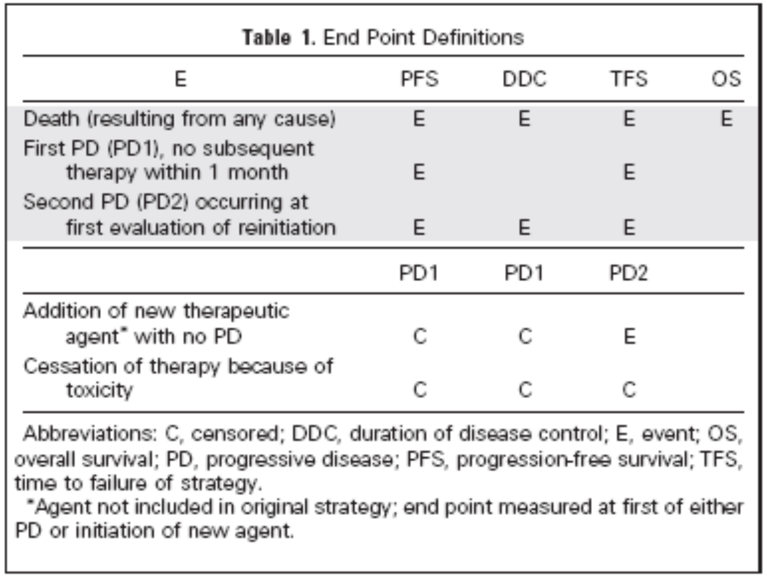


Table 1. End Point Definitions

E	PFS	DDC	TFS	OS
Death (resulting from any cause)	E	E	E	E
First PD (PD1), no subsequent therapy within 1 month	E		E	
Second PD (PD2) occurring at first evaluation of reinitiation	E	E	E	
	PD1	PD1	PD2	
Addition of new therapeutic agent* with no PD	C	C	E	
Cessation of therapy because of toxicity	C	C	C	

Abbreviations: C, censored; DDC, duration of disease control; E, event; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TFS, time to failure of strategy.

*Agent not included in original strategy; end point measured at first of either PD or initiation of new agent.

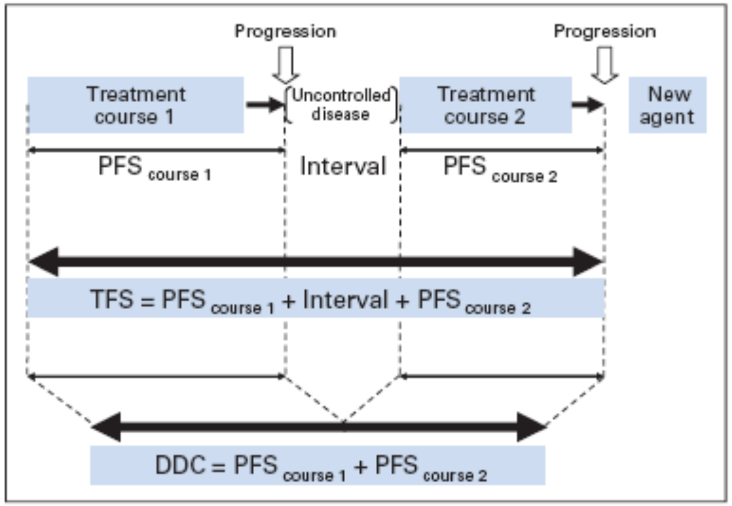

Progression
Progression
Treatment course 1
Uncontrolled disease
Treatment course 2
New agent
PFS course 1
Interval
PFS course 2
TFS = PFS course 1 + Interval + PFS course 2
DDC = PFS course 1 + PFS course 2

Fig 1. General definitions. DDC, duration of disease control; PFS, progression-free survival; TFS, time to failure of strategy.

Critères composites pour essais de stratégie

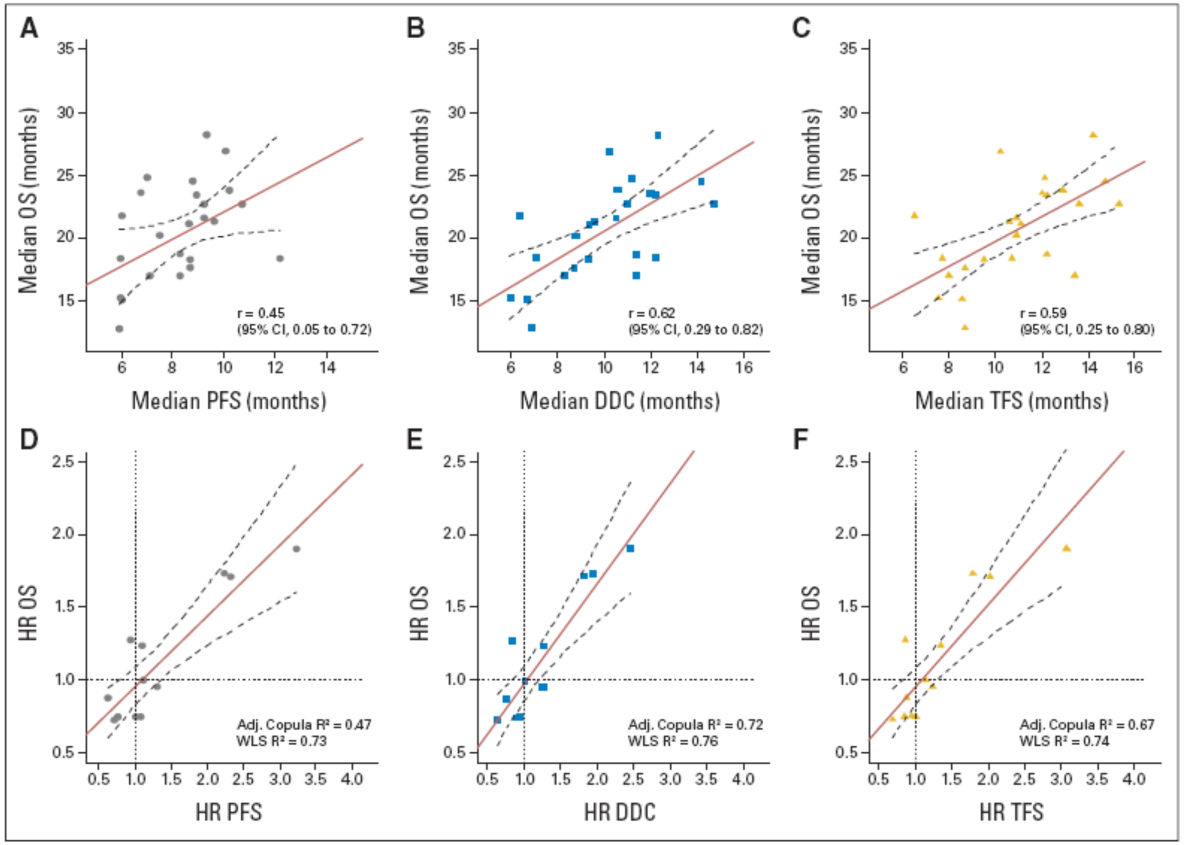
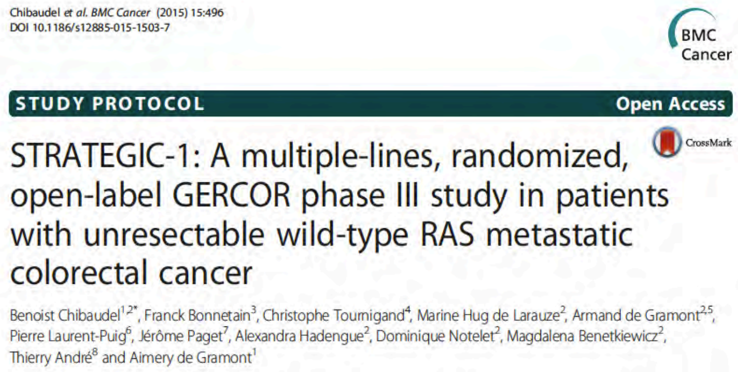


Fig 3. Association between potential surrogate end points (progression-free survival [PFS], duration of disease control [DDC], and time to failure of strategy [TFS]) and overall survival (OS) in terms of (A, B, C) median time and (D, E, F) hazard ratio (HR). Adj, adjusted; WLS, weighted least square.


Chibaudel *et al. BMC Cancer* (2015) 15:496
DOI 10.1186/s12885-015-1503-7

BMC Cancer

STUDY PROTOCOL **Open Access**

STRATEGIC-1: A multiple-lines, randomized, open-label GERCOR phase III study in patients with unresectable wild-type RAS metastatic colorectal cancer

Benoist Chibaudel[1,2*], Franck Bonnetain[3], Christophe Tournigand[4], Marine Hug de Larauze[2], Armand de Gramont[2,5], Pierre Laurent-Puig[6], Jérôme Paget[7], Alexandra Hadengue[2], Dominique Notelet[2], Magdalena Benetkiewicz[2], Thierry André[8] and Aimery de Gramont[1]

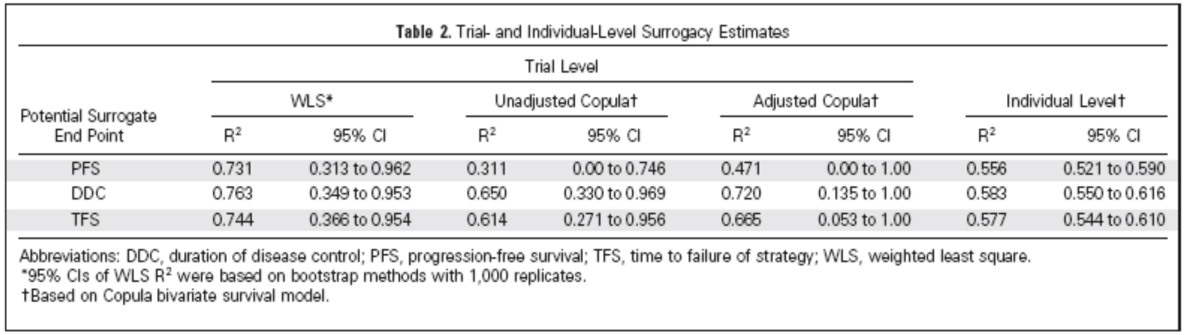
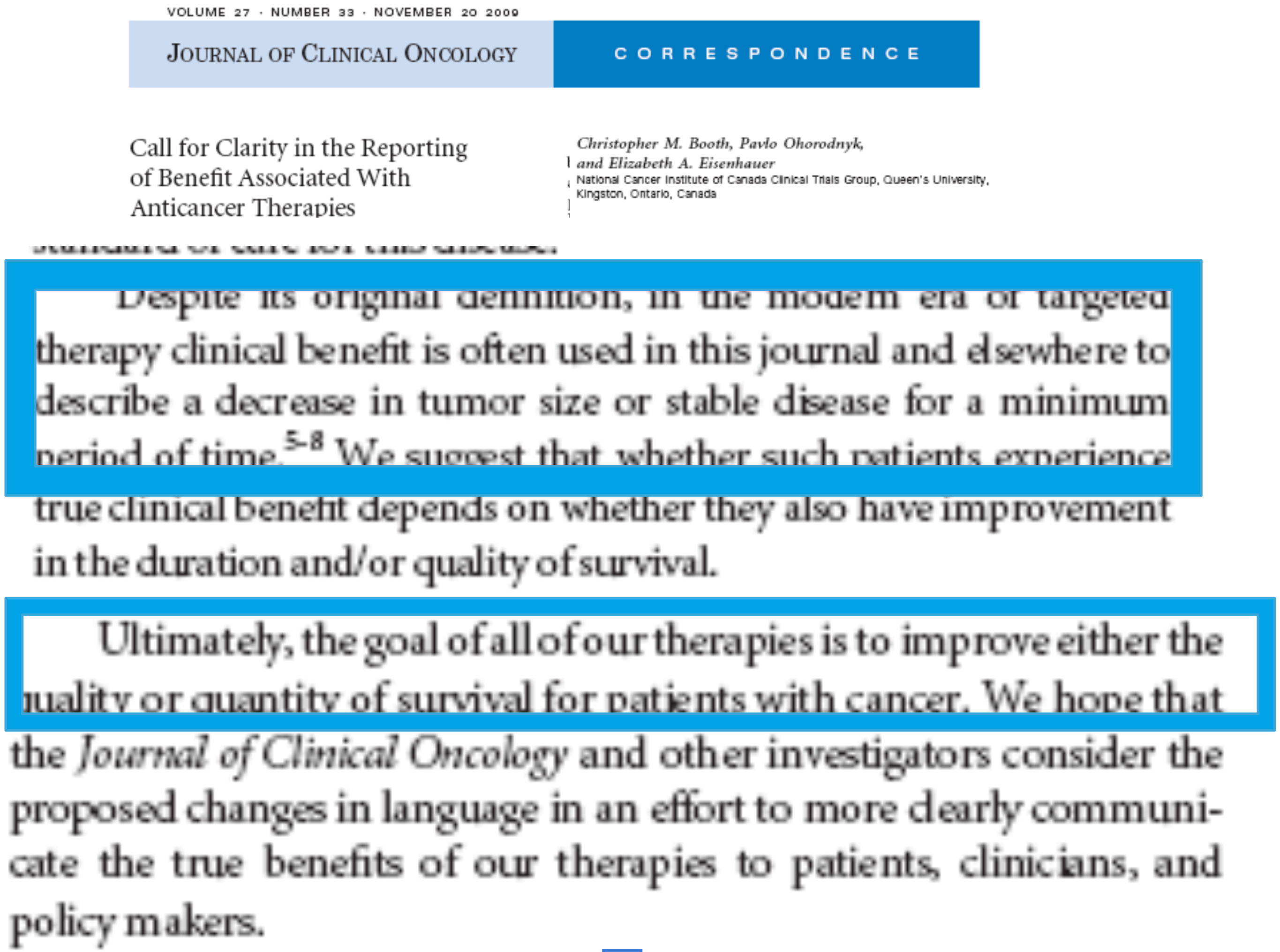


Table 2. Trial- and Individual-Level Surrogacy Estimates

Potential Surrogate End Point	Trial Level						Individual Level†	
	WLS*		Unadjusted Copula†		Adjusted Copula†			
	R^2	95% CI	R^2	95% CI	R^2	95% CI	R^2	95% CI
PFS	0.731	0.313 to 0.962	0.311	0.00 to 0.746	0.471	0.00 to 1.00	0.556	0.521 to 0.590
DDC	0.763	0.349 to 0.953	0.650	0.330 to 0.969	0.720	0.135 to 1.00	0.583	0.550 to 0.616
TFS	0.744	0.366 to 0.954	0.614	0.271 to 0.956	0.665	0.053 to 1.00	0.577	0.544 to 0.610

Abbreviations: DDC, duration of disease control; PFS, progression-free survival; TFS, time to failure of strategy; WLS, weighted least square.
*95% CIs of WLS R^2 were based on bootstrap methods with 1,000 replicates.
†Based on Copula bivariate survival model.



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

standard of care for this disease.

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 true clinical benefit depends on whether they also have improvement in the duration and/or quality of survival.

Ultimately, the goal of all of our therapies is to improve either the uality 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.

Réel objectif d'un traitement améliorer la quantité et ou la qualité de la survie

+Model
JVS 336 1–6
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Journal of Visceral Surgery (2013) xxx, xxx—xxx

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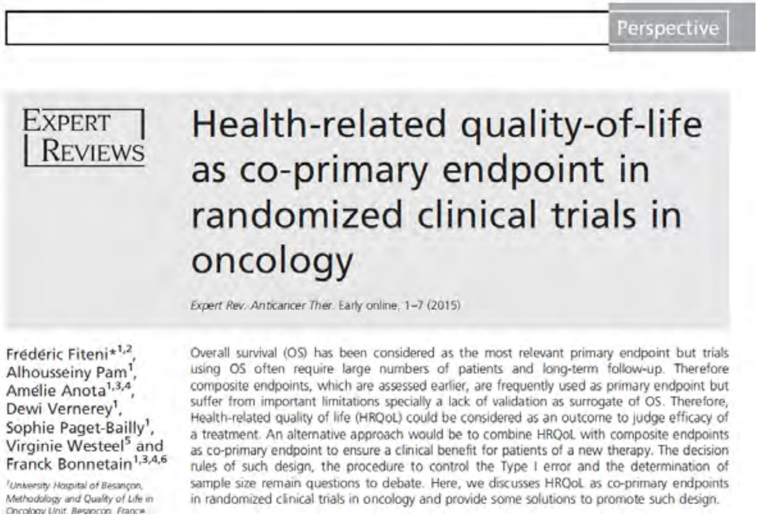
REVIEW

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 Me
25000 Besançon, France
[b] Methodology and quality of Life in Oncology unit (
clinical research plateform, CHU de Besançon, 2, pla



Perspective

EXPERT REVIEWS

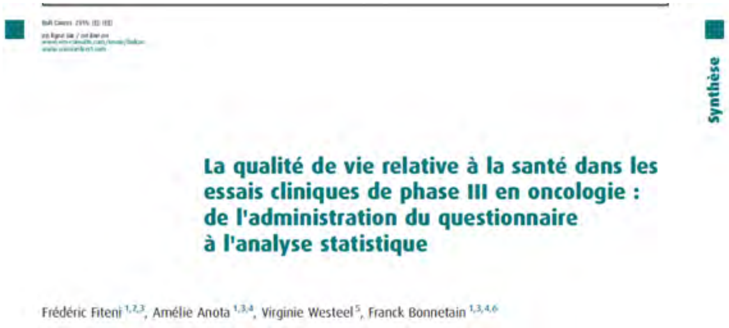
Health-related quality-of-life as co-primary endpoint in randomized clinical trials in oncology

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

Frédéric Fiteni*[1,2], Alhousseiny Pam[1], Amélie Anota[1,3,4], Dewi 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.

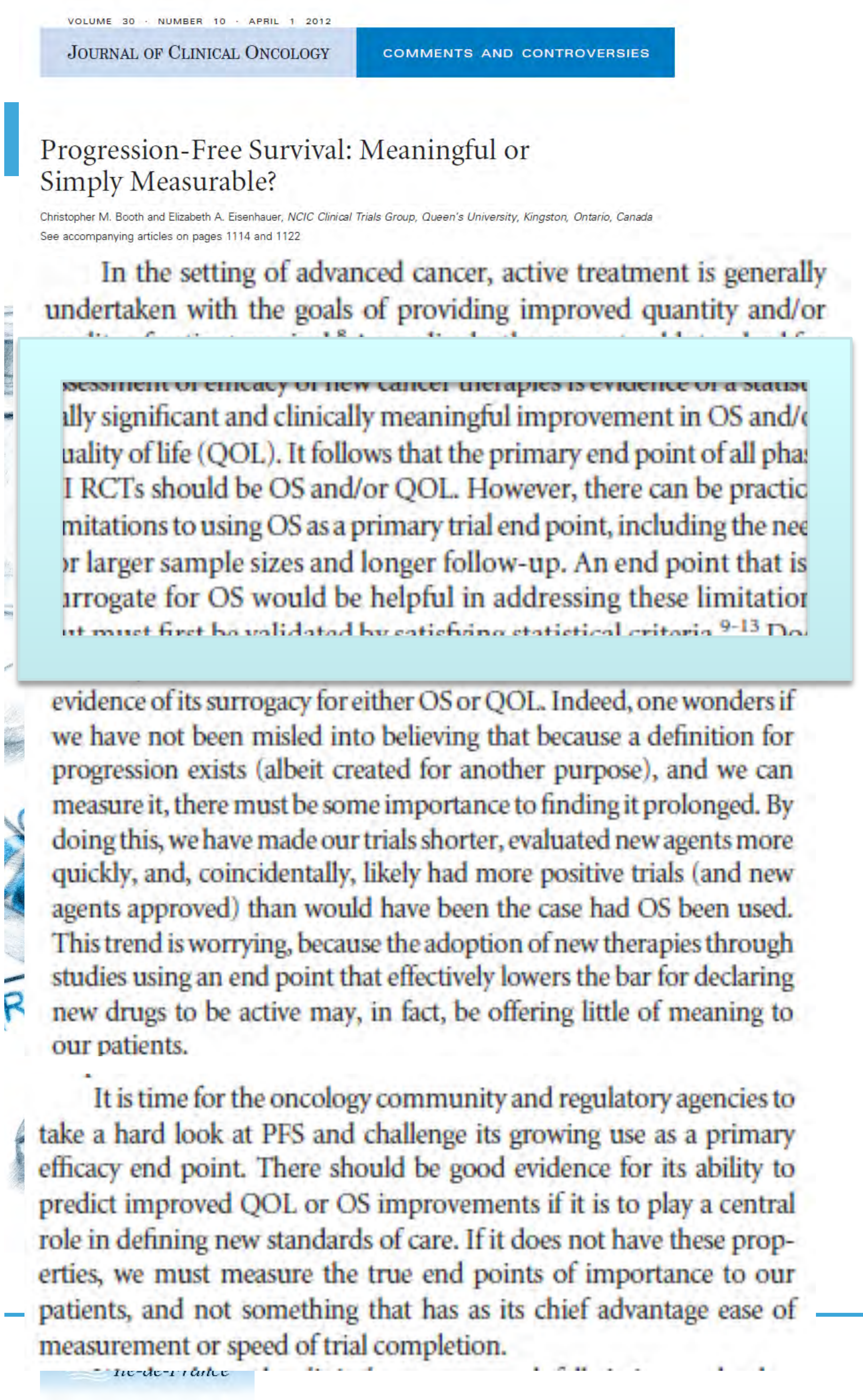


Synthèse

La qualité de vie relative à la santé dans les essais cliniques de phase III en oncologie : de l'administration du questionnaire à l'analyse statistique

Frédéric Fiteni[1,2,3], Amélie Anota[1,3,4], Virginie Westeel[5], Franck Bonnetain[1,3,4,6]

- Critères centrés sur le patient : SG & QdV
- Critères centrés sur la tumeur : PFS, DFS etc



VOLUME 30 · NUMBER 10 · APRIL 1 2012

JOURNAL OF CLINICAL ONCOLOGY COMMENTS AND CONTROVERSIES

Progression-Free Survival: Meaningful or Simply Measurable?

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

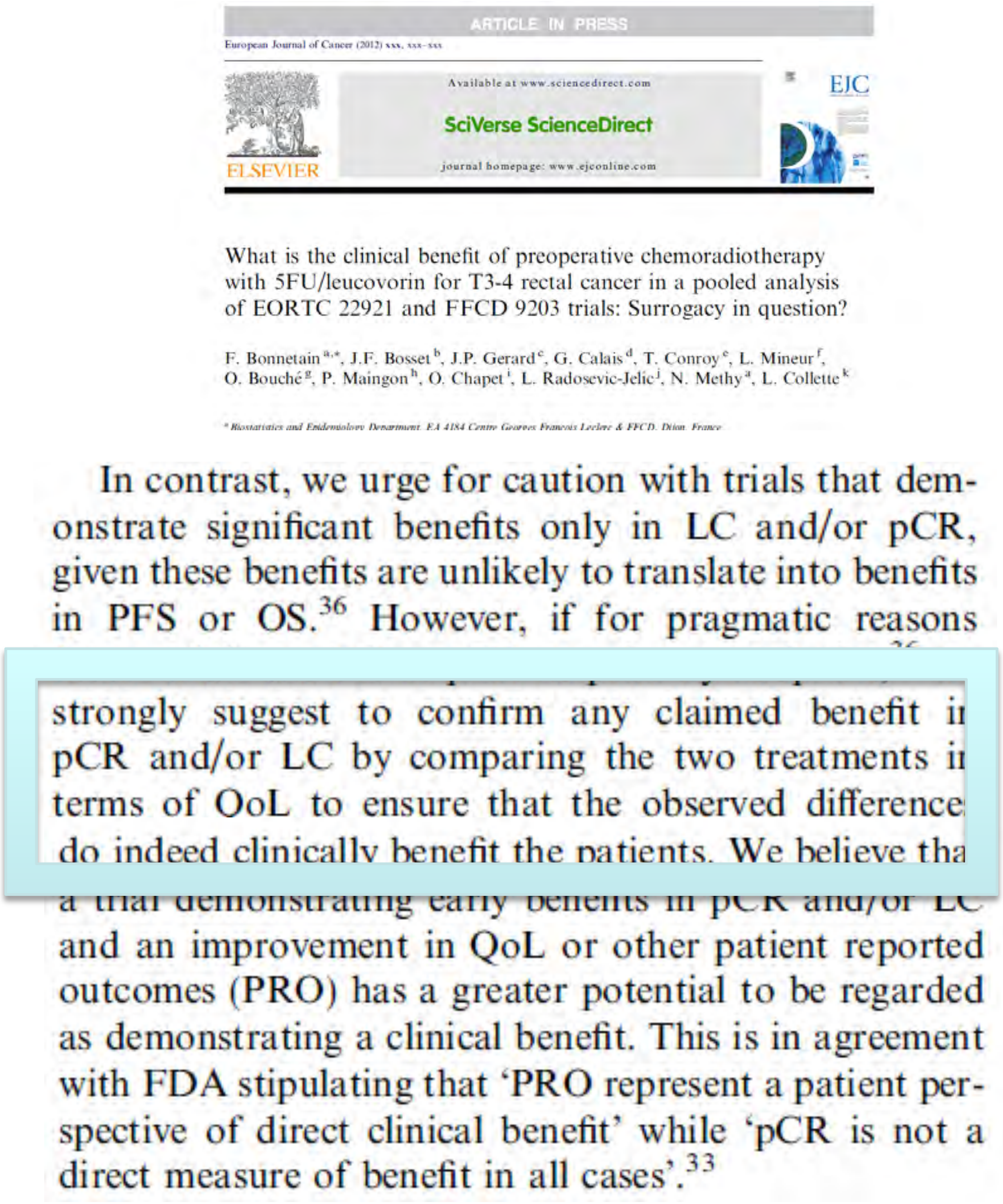
See accompanying articles on pages 1114 and 1122

In the setting of advanced cancer, active treatment is generally undertaken with the goals of providing improved quantity and/or

ssessment of efficacy of new cancer therapies is evidence of a statist
lly significant and clinically meaningful improvement in OS and/
uality of life (QOL). It follows that the primary end point of all pha
I RCTs should be OS and/or QOL. However, there can be practic
mitations to using OS as a primary trial end point, including the nee
r larger sample sizes and longer follow-up. An end point that is
urrogate for OS would be helpful in addressing these limitatio
ut must first be validated by satisfying statistical criteria.[9-13] Do

evidence of its surrogacy for either OS or QOL. Indeed, one wonders if we have not been misled into believing that because a definition for progression exists (albeit created for another purpose), and we can measure it, there must be some importance to finding it prolonged. By doing this, we have made our trials shorter, evaluated new agents more quickly, and, coincidentally, likely had more positive trials (and new agents approved) than would have been the case had OS been used. This trend is worrying, because the adoption of new therapies through studies using an end point that effectively lowers the bar for declaring new drugs to be active may, in fact, be offering little of meaning to our patients.

It is time for the oncology community and regulatory agencies to take a hard look at PFS and challenge its growing use as a primary efficacy end point. There should be good evidence for its ability to predict improved QOL or OS improvements if it is to play a central role in defining new standards of care. If it does not have these properties, we must measure the true end points of importance to our patients, and not something that has as its chief advantage ease of measurement or speed of trial completion.



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

Available at www.sciencedirect.com

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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?

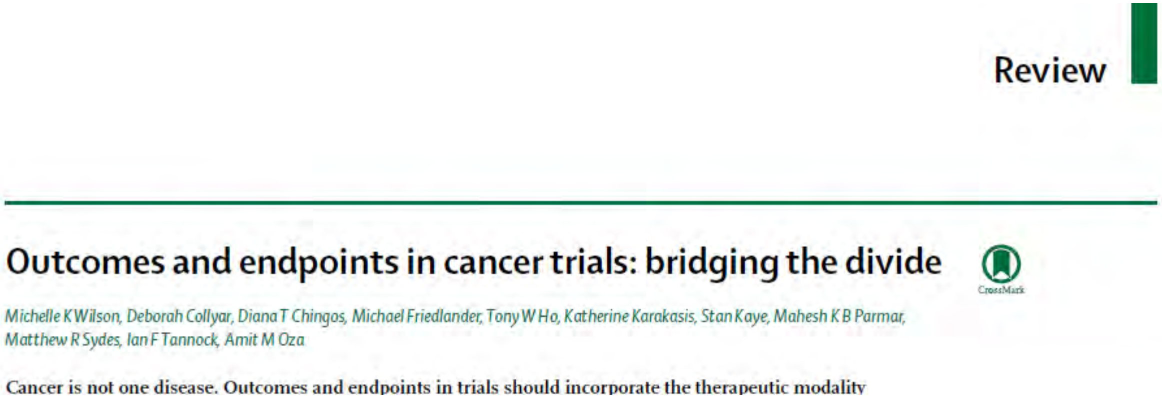
F. Bonnetain[a,*], J.F. Bosset[b], J.P. Gerard[c], G. Calais[d], T. Conroy[e], L. Mineur[f],
O. Bouché[g], P. Maingon[h], O. Chapet[i], L. Radosevic-Jelic[j], N. Methy[a], L. Collette[k]

[a] *Biostatistics and Epidemiology Department, EA 4184 Centre Georges Francois Leclerc & FFCD, Dijon, France*

In contrast, we urge for caution with trials that demonstrate significant benefits only in LC and/or pCR, given these benefits are unlikely to translate into benefits in PFS or OS.[36] However, if for pragmatic reasons

strongly suggest to confirm any claimed benefit i
pCR and/or LC by comparing the two treatments i
terms of QoL to ensure that the observed difference
do indeed clinically benefit the patients. We believe tha

a trial demonstrating early benefits in pCR and/or LC and an improvement in QoL or other patient reported outcomes (PRO) has a greater potential to be regarded as demonstrating a clinical benefit. This is in agreement with FDA stipulating that 'PRO represent a patient perspective of direct clinical benefit' while 'pCR is not a direct measure of benefit in all cases'.[33]

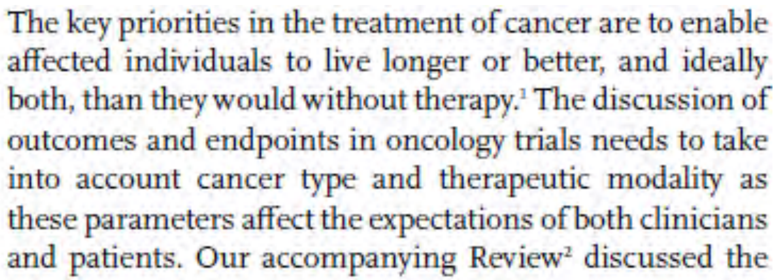


Review

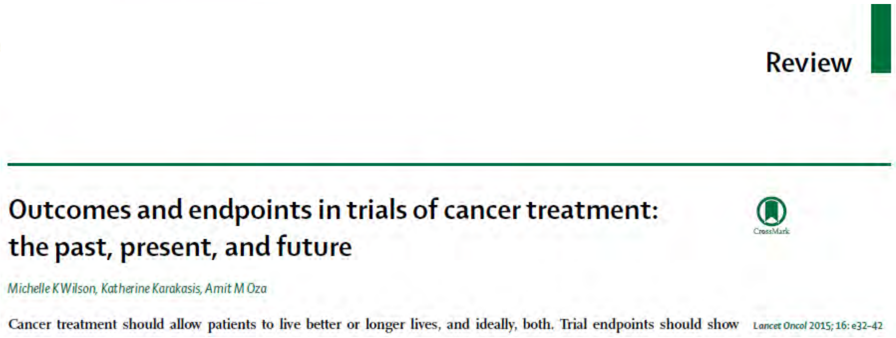
Outcomes and endpoints in cancer trials: bridging the divide

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



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



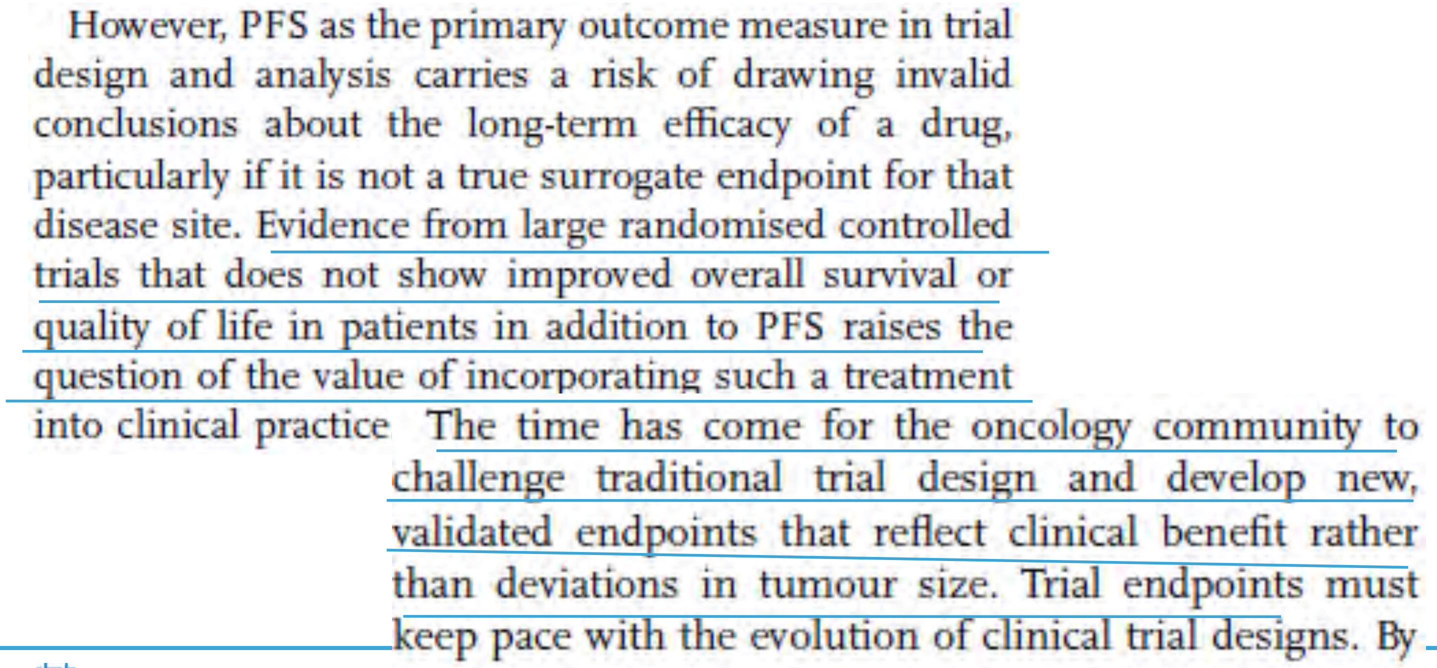
Review

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

Michelle K Wilson, Katherine Karakasis, Amit M Oza

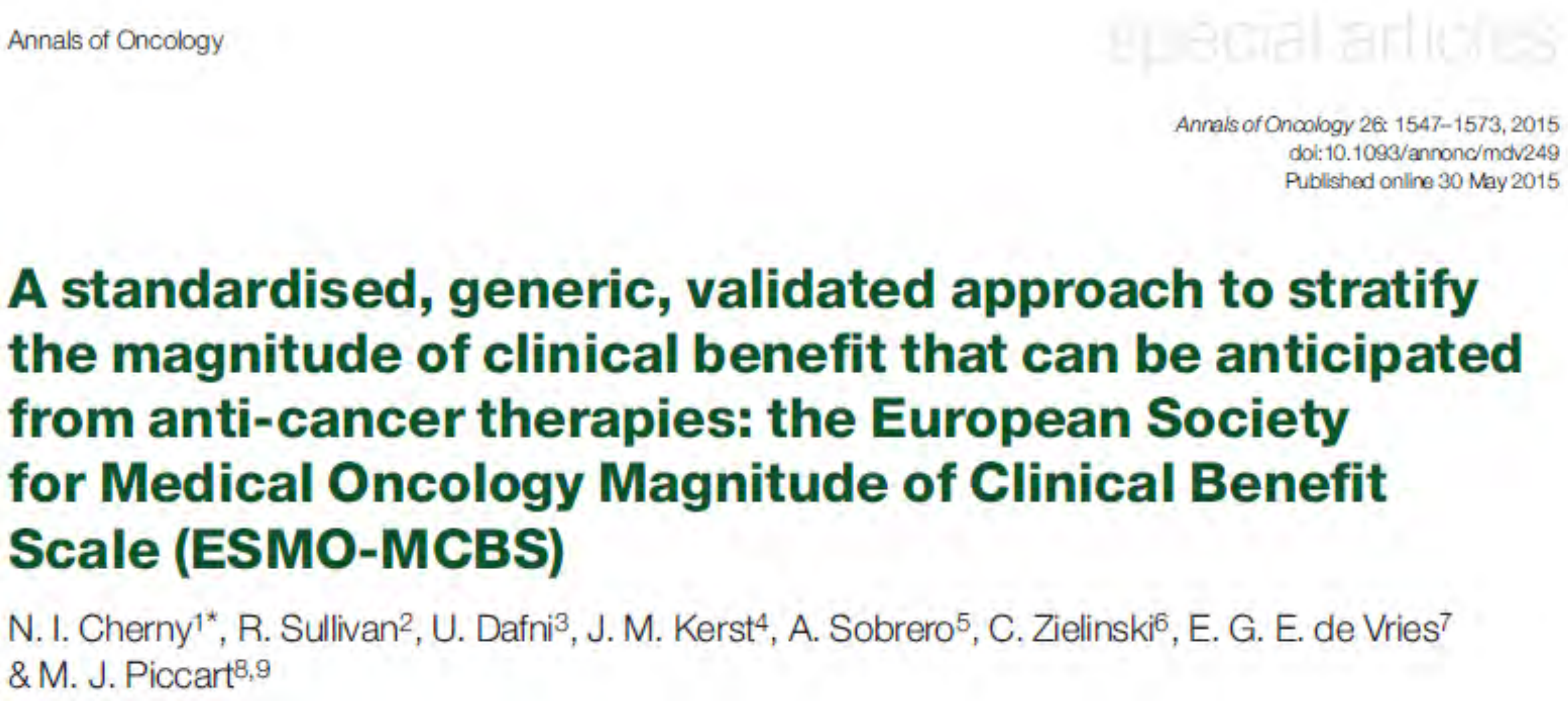
Lancet Oncol 2015; 16: e32–42

Cancer treatment should allow patients to live better or longer lives, and ideally, both. Trial endpoints should show



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



Annals of Oncology

special articles

Annals of Oncology 26: 1547–1573, 2015
doi:10.1093/annonc/mdv249

Published online 30 May 2015

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

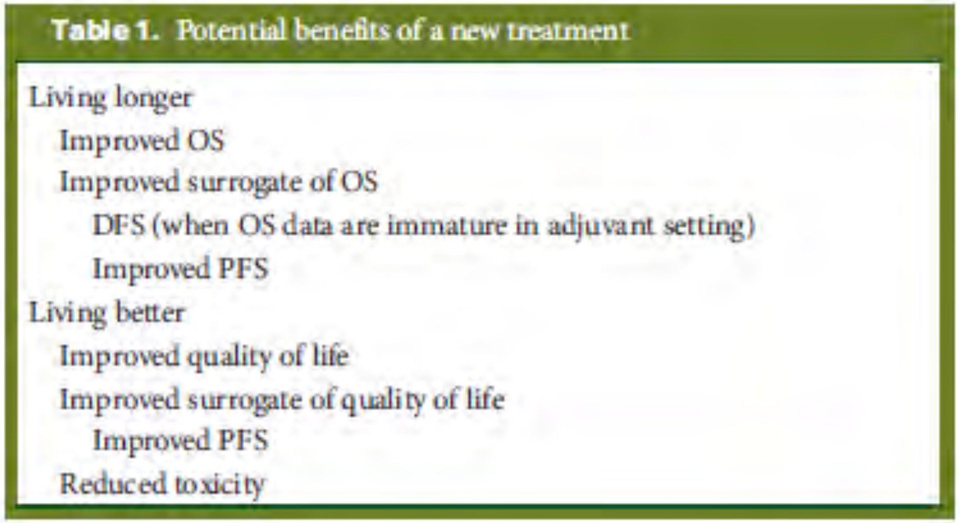


Table 1. Potential benefits of a new treatment

- Living longer
  - Improved OS
  - Improved surrogate of OS
    - DFS (when OS data are immature in adjuvant setting)
    - Improved PFS
- Living better
  - Improved quality of life
  - Improved surrogate of quality of life
    - Improved PFS
  - Reduced toxicity

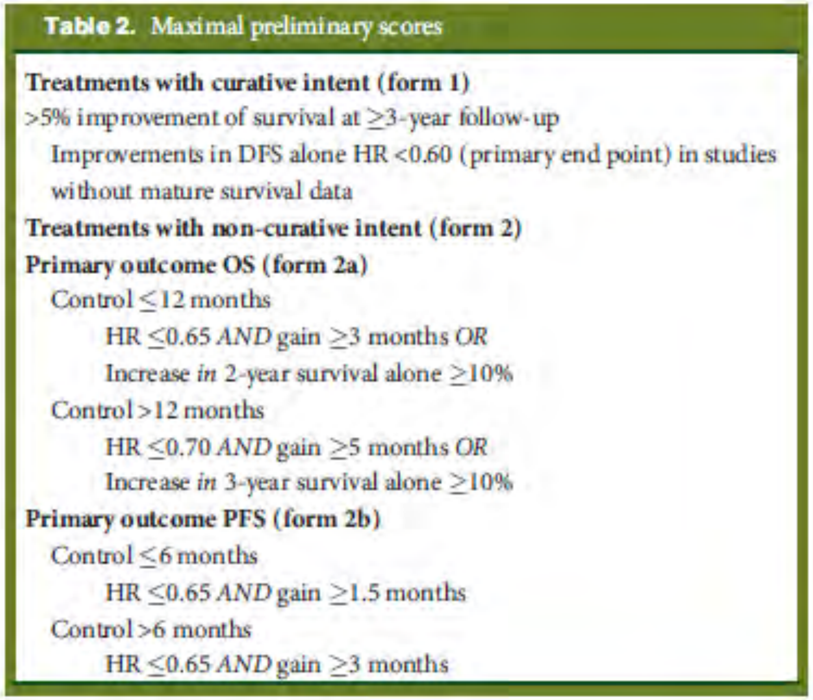


Table 2. Maximal preliminary scores

Treatments with curative intent (form 1)
>5% improvement of survival at ≥3-year follow-up
Improvements in DFS alone HR <0.60 (primary end point) in studies without mature survival data
Treatments with non-curative intent (form 2)
Primary outcome OS (form 2a)
Control ≤12 months
HR ≤0.65 *AND* gain ≥3 months *OR*
Increase *in* 2-year survival alone ≥10%
Control >12 months
HR ≤0.70 *AND* gain ≥5 months *OR*
Increase *in* 3-year survival alone ≥10%
Primary outcome PFS (form 2b)
Control ≤6 months
HR ≤0.65 *AND* gain ≥1.5 months
Control >6 months
HR ≤0.65 *AND* gain ≥3 months

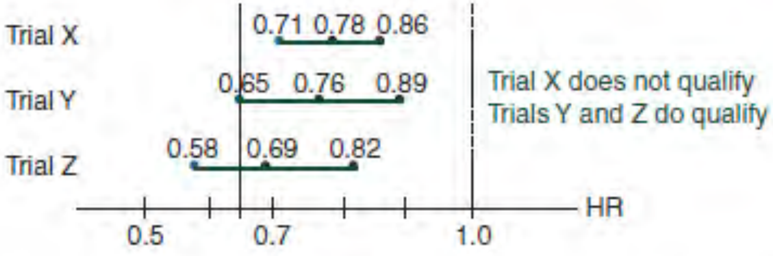
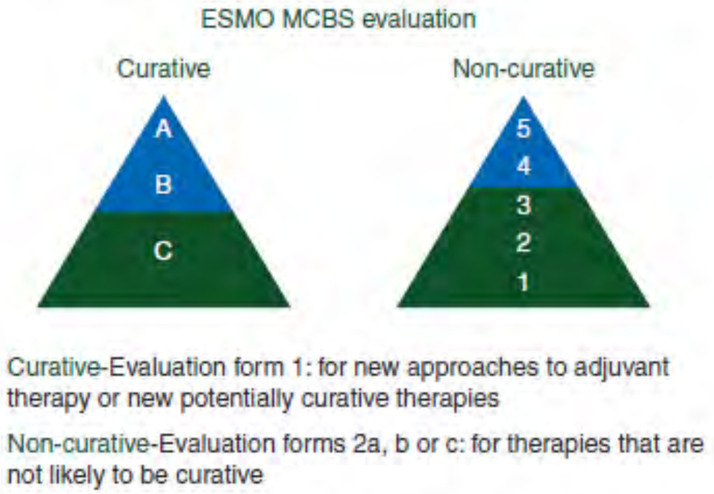


Figure 1. Use of threshold HR in the ESMO-MCBS exemplified for HR threshold of 0.65.



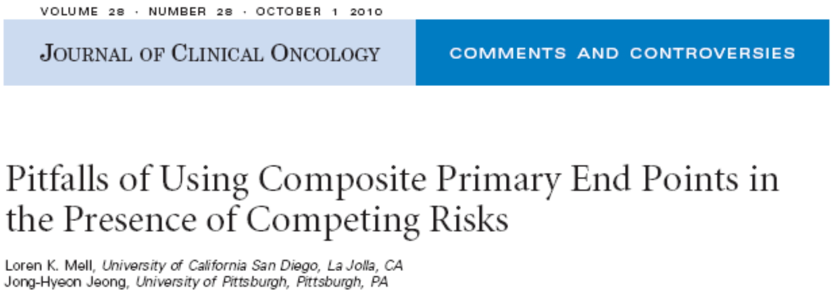
Curative-Evaluation form 1: for new approaches to adjuvant therapy or new potentially curative therapies

Non-curative-Evaluation forms 2a, b or c: for therapies that are not likely to be curative

Figure 3. Visualisation of ESMO-MCB scores for curative and non-curative setting. A & B and 5 and 4 represent the grades with substantial improvement.

Les critères conjoints

- Limites des critères composites
  - Prime à la signification statistique vs sens clinique

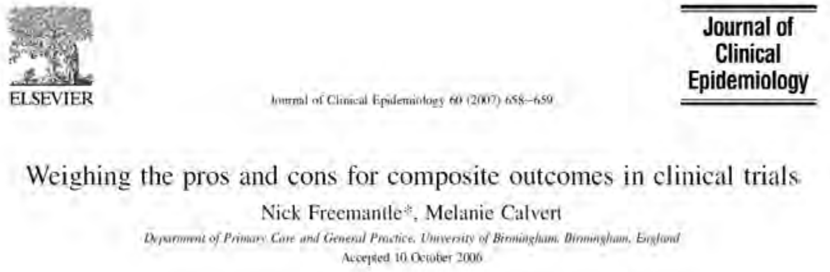


VOLUME 28 · NUMBER 28 · OCTOBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Pitfalls of Using Composite Primary End Points in the Presence of Competing Risks

Loren K. Mell, *University of California San Diego, La Jolla, CA*
Jong-Hyeon Jeong, *University of Pittsburgh, Pittsburgh, PA*



ELSEVIER

Journal of Clinical Epidemiology 60 (2007) 658–659

Journal of Clinical Epidemiology

Weighing the pros and cons for composite outcomes in clinical trials

Nick Freemantle*, Melanie Calvert

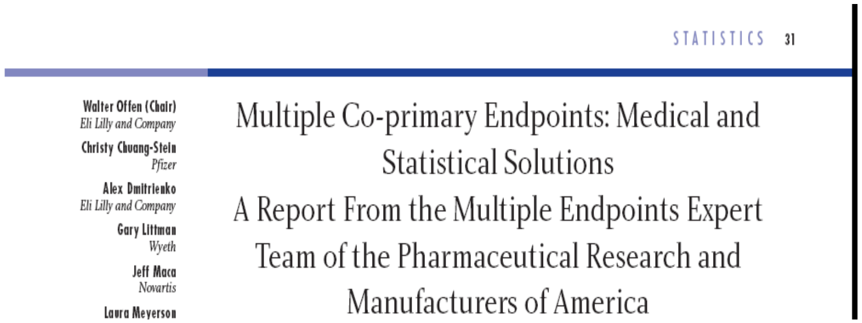
Department of Primary Care and General Practice, University of Birmingham, Birmingham, England

Accepted 10 October 2006

- Une des solutions possibles
  - « designer » l'essai sur certaines composantes en les considérant comme des co-critères principaux
  - Induit un calcul d'effectif adapté pour les risques d'erreur

Formuler des objectifs et des hypothèses explicites

Les critères conjoints



STATISTICS 31

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

- Quelles définitions pour les critères conjoints

- Dépend des Règles décisionnelles

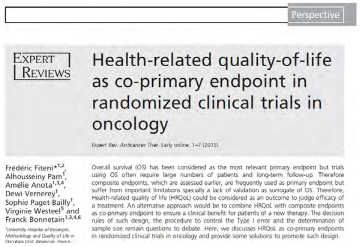
- «***alternative* primary endpoint or single sufficient** »
  - Intervention efficace si effet sur au moins un des co critères principaux
  - Contrôle du risque alpha

- « ***multiples co-primary endpoints*** »
  - Intervention efficace si effet sur l’ensemble des co critères principaux :
  - Effet requis pour l’ensemble des co-critères

Les co-critères peuvent être aussi des critères composites

• HrQoL comme co-critère de jugement principal avec PFS ? :

- Respecter les contraintes de durée des essais et le nombre de patients
- Mais démonstration d'un bénéfice clinique en sus d'un bénéfice tumoral



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], Dewi 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.

» Implique de répondre à des challenges méthodologiques pour analyses de la HRQOL (Bonnetain F et al, JCO 2016 in Press)?

- » 1 – Standardisation des analyses et du report (CONSORT PRO)
- » 2 –Resultats et analyses cliniquement compréhensibles
- » 3 – Formulation d'hypothèses possible pour calcul du NSN pour HRQOL

Qual Life Res
DOI 10.1007/s11136-013-0583-6

QUANTITATIVE METHODS SPECIAL SECTION

Time to health-related quality of life score deterioration as a modality of longitudinal analysis for health-related quality of life studies in oncology: do we need RECIST for quality of life to achieve standardization?

Amélie Anota · Zeinab Hamidou · Sophie Paget-Bailly · Benoist Chibaudel · Caroline Bascoul-Mollevi · Pascal Auquier · Virginie Westeel · Frederic Fiteni · Christophe Borg · Franck Bonnetain

Accepted: 12 November 2013
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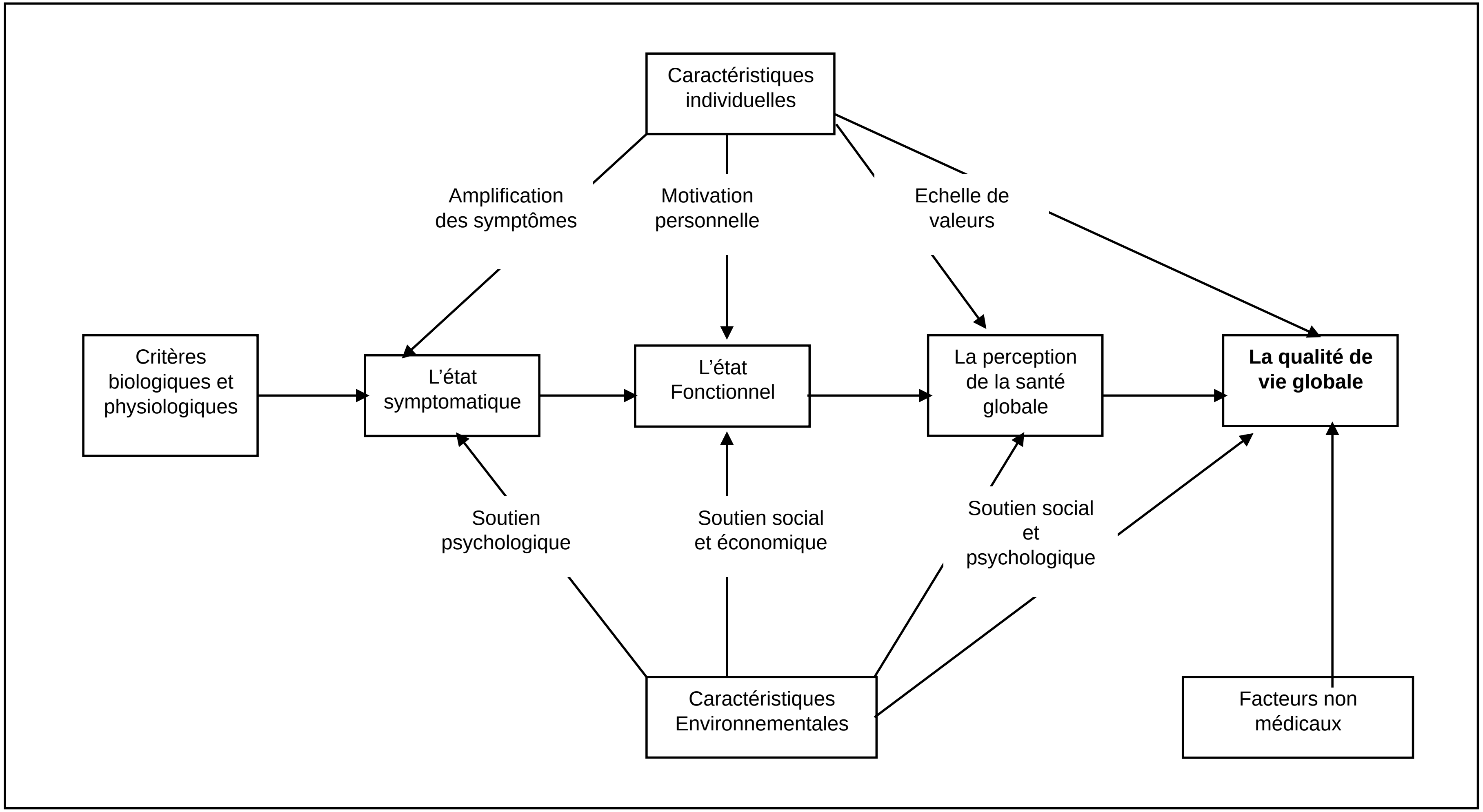
Statistical Challenges in the Analysis of Health-Related Quality of Life in Cancer Clinical Trials

Franck Bonnetain (1,2,3), Frédéric Fiteni (1,2,4), Fabio Efficace (5), Amélie Anota (1,2,3)

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

Besançon, France

Bonnetain F et al,
JCO 2016 in Press



Caractéristiques individuelles

Amplification des symptômes

Motivation personnelle

Echelle de valeurs

Critères biologiques et physiologiques

L'état symptomatique

L'état Fonctionnel

La perception de la santé globale

La qualité de vie globale

Soutien psychologique

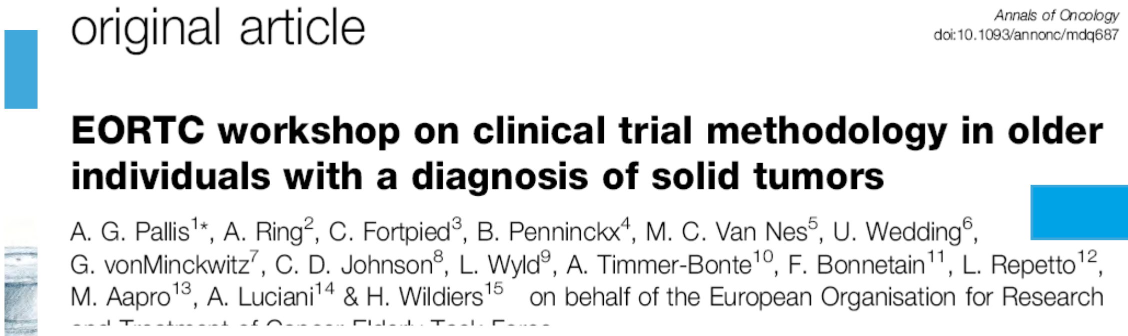
Soutien social et économique

Soutien social et psychologique

Caractéristiques Environnementales

Facteurs non médicaux

Figure 1 : Relation dynamique entre 5 critères de jugement en santé d'après Wilson et Cleary {Wilson & Cleary, 1995}.

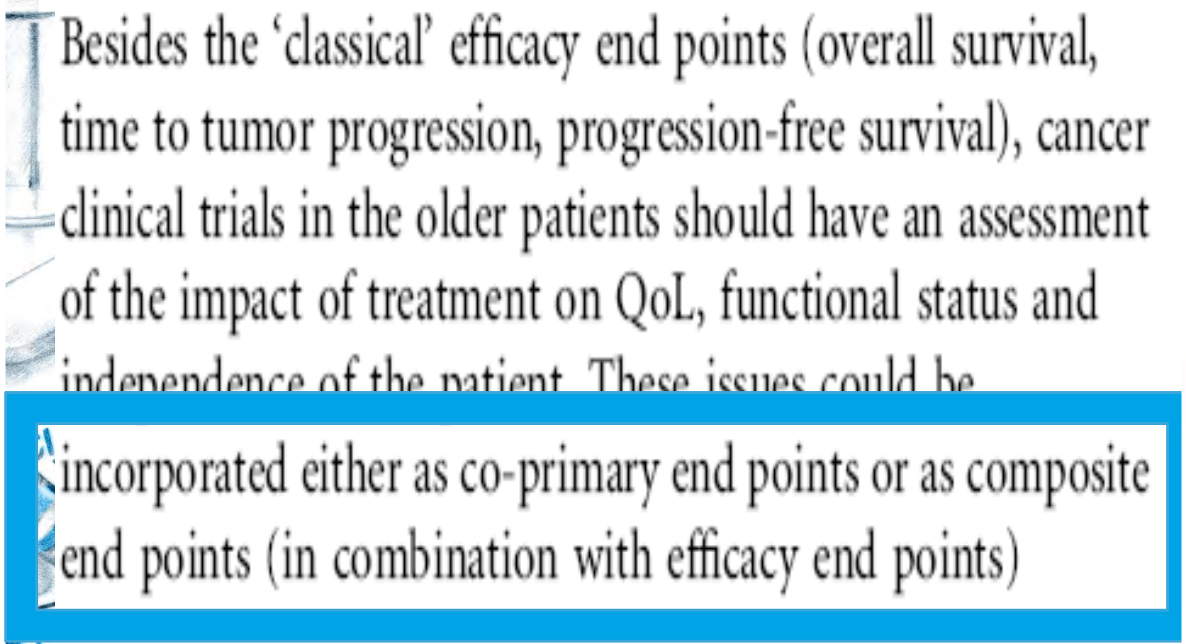


original article

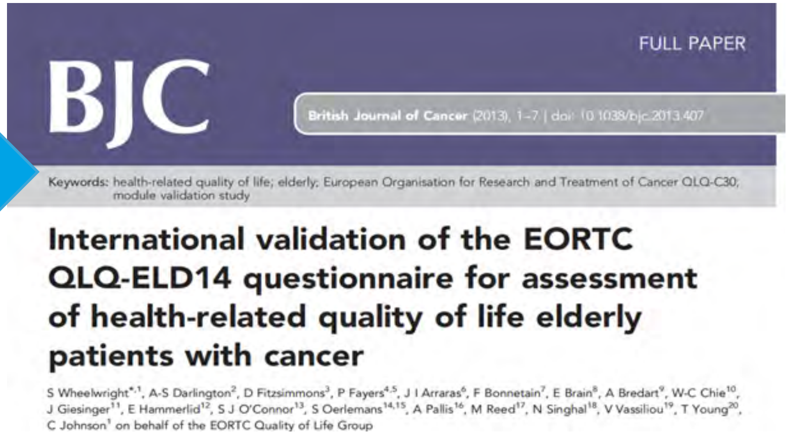
Annals of Oncology
doi:10.1093/annonc/mdq687

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

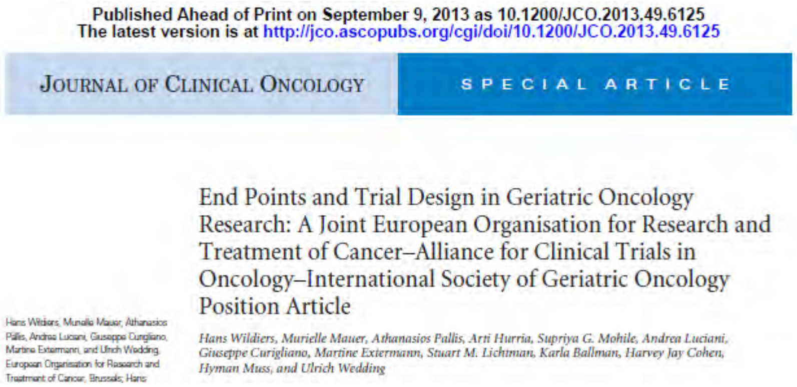
BJC

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

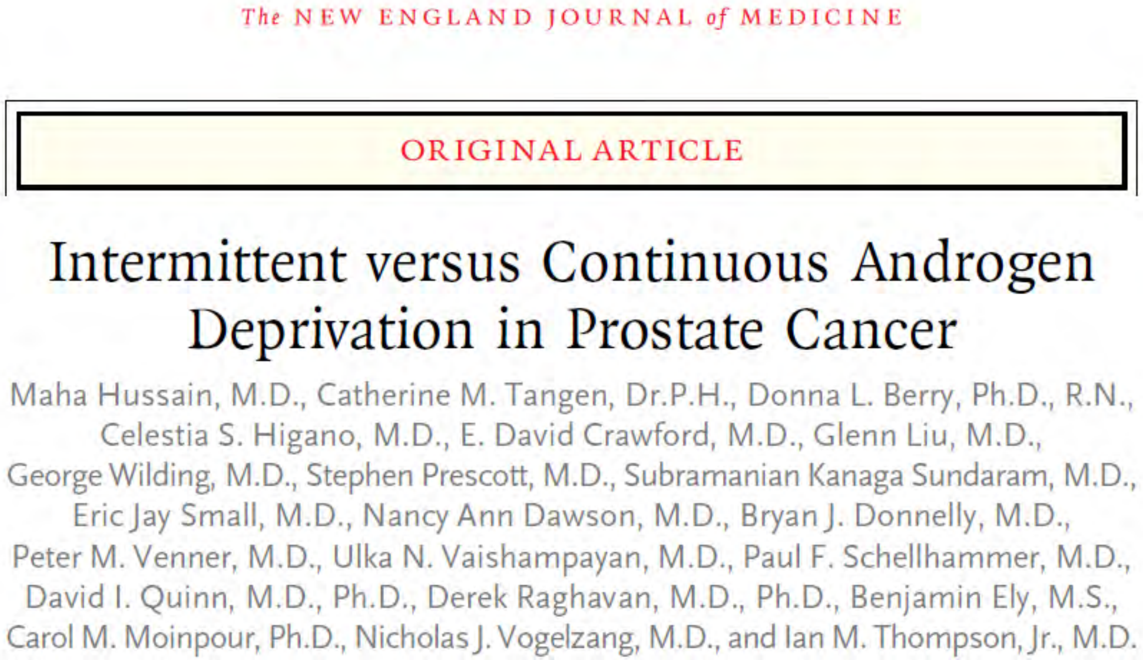
End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology Position Article

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

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

Pour les essais en oncogériatrie

HrQOL should be co-primary / composite endpoint

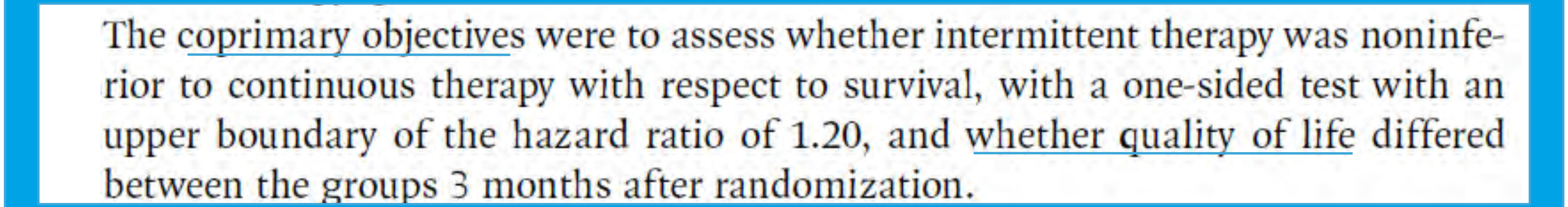


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

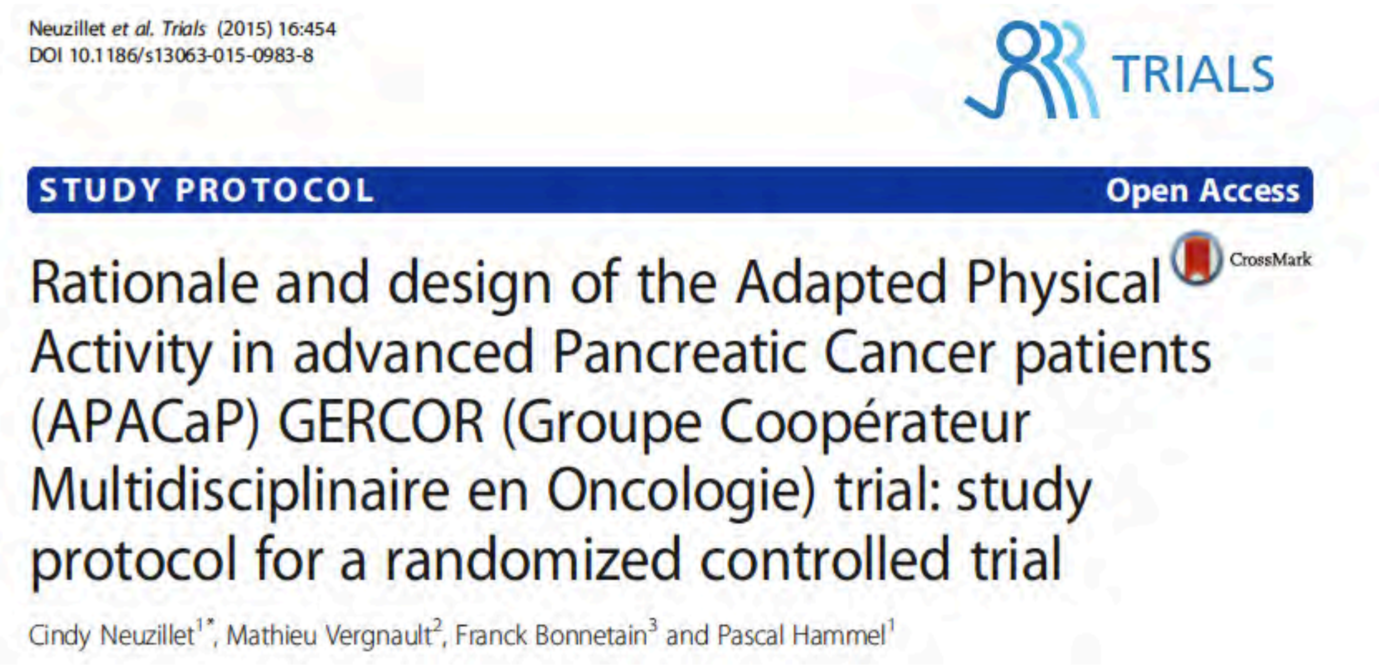
Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

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



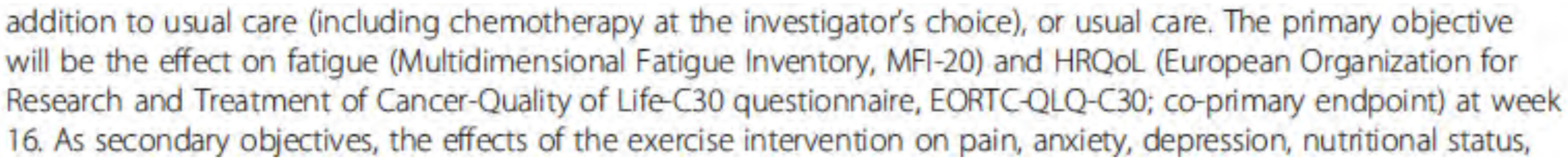
Neuzillet *et al. Trials* (2015) 16:454
DOI 10.1186/s13063-015-0983-8

TRIALS

STUDY PROTOCOL **Open Access**

Rationale and design of the Adapted Physical Activity in advanced Pancreatic Cancer patients (APACaP) GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) trial: study protocol for a randomized controlled trial

Cindy Neuzillet[1*], Mathieu Vergnault[2], Franck Bonnetain[3] and Pascal Hammel[1]



addition to usual care (including chemotherapy at the investigator's choice), or usual care. The primary objective will be the effect on fatigue (Multidimensional Fatigue Inventory, MFI-20) and HRQoL (European Organization for Research and Treatment of Cancer-Quality of Life-C30 questionnaire, EORTC-QLQ-C30; co-primary endpoint) at week 16. As secondary objectives, the effects of the exercise intervention on pain, anxiety, depression, nutritional status,

Conclusions

- Critères de plus en plus complexes
  - Limites des critères tumoraux et des critères composites
  - Cancer ≠ tumeur
  - Maladie systémique

- Avenir
  - Co-critères orientés tumeurs et patients (HRQOL / PRO) :
    - oncogériatrie,
    - ovaire metastatique,
    - essais de NI
    - Soins de supports
  - Critères composites validés

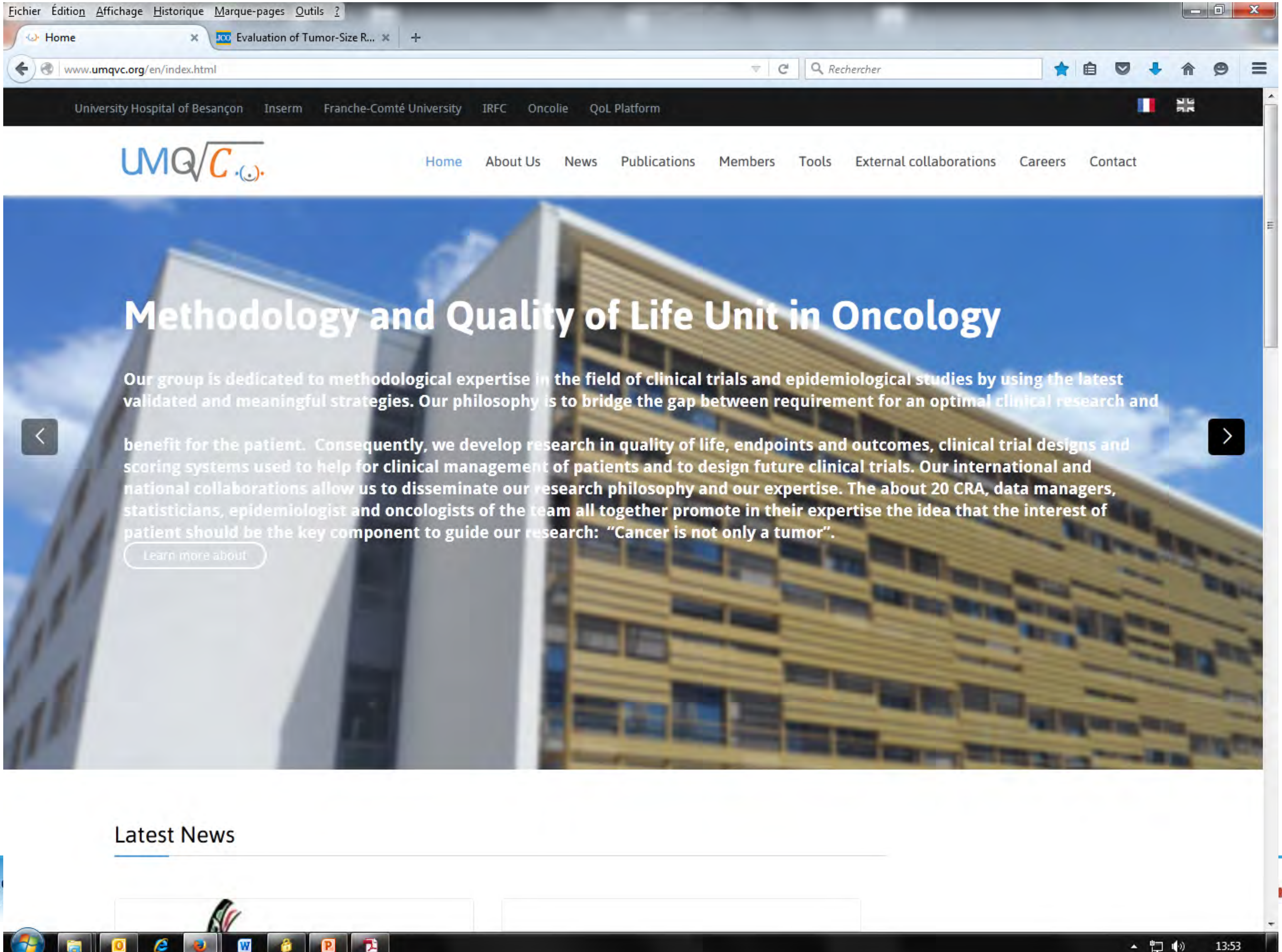
Quelques perspectives

- DATECAN 1 & 2
  - – Consensus définitions poursuivis
  - – Méthodes pour valider critères composites

- EORTC QOL :
  - – SISAQOL
  - – qRECIST

- ARCAD = Co-primary QoL/PFS
  - – Position paper pour considérer la QdV comme co-critères de jugement principal dans les essais mCRC
  - – Générer des hypothèses sur QdV pour planifier

Merci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Methodology and Quality of Life Unit in Oncology

Our group is dedicated to methodological expertise in the field of clinical trials and epidemiological studies by using the latest validated and meaningful strategies. Our philosophy is to bridge the gap between requirement for an optimal clinical research and

benefit for the patient. Consequently, we develop research in quality of life, endpoints and outcomes, clinical trial designs and scoring systems used to help for clinical management of patients and to design future clinical trials. Our international and national collaborations allow us to disseminate our research philosophy and our expertise. The about 20 CRA, data managers, statisticians, epidemiologist and oncologists of the team all together promote in their expertise the idea that the interest of patient should be the key component to guide our research: “Cancer is not only a tumor”.

Latest News