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

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2nd EORTC Cancer Clinical Research Methodology Course for Patient Advocates, Brussels

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COI

- NOVARTIS
- MERCK SERONO
- CELGENE
- AMGEN
- ROCHE
- NESTLE
- INTEGRAGEN
- IPSEN
- BAYER
- CHUGAI
- CHUGAI
- ERYTECH
Introduction

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

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

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

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

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

• In order for an endpoint to achieve its potential to improve cancer care delivery, 3 prerequisites apply

  – **Technically sound** (reproducibility, validity etc..)

  – **Persuasive evidence about the effect of interventions on those outcomes**, with due attention to the causal linkages among intermediate, Clinical, and final Outcome

  – The **willingness and ability to translate findings into information that decision makers find understandable and compelling.**

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

Introduction

Different type of endpoints:

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

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

<table>
<thead>
<tr>
<th>Definition</th>
<th>Time from randomization until death from any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pros</td>
<td>• Measure of direct benefit&lt;br&gt;• Easy to measure (Unbiased)</td>
</tr>
<tr>
<td>Cons</td>
<td>• It may require large population and follow-up&lt;br&gt;• It includes deaths unrelated to cancer&lt;br&gt;• It may be affected by crossover or subsequent therapies</td>
</tr>
<tr>
<td>Censor</td>
<td>• Last date subjects was seen alive</td>
</tr>
</tbody>
</table>
Endpoints

• **Disease-free survival (DFS):**

  – “the time from randomization until recurrence of tumor, second cancer or death from any cause whichever occur first (FDA 2007).

  – “Although overall survival is a conventional endpoint for most adjuvant settings, DFS can be an important endpoint in situations where survival may be prolonged, making a survival endpoint impractical.” (FDA 2007).

  – **To be used DFS should be surrogate of OS as** in some cancer localization: Colon, gastric, head & neck.

  – **DFS needs to be evaluated carefully** — a patient’s quality of life (QOL) in the period of extended DFS is an important consideration for payers, provides, and patients alike.
Endpoints

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

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

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

• **Patient-Reported Outcomes (PRO)**

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

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

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

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

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

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

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

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

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

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

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

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

   ________________________________
Endpoints

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

  How to assess this definition of Health?

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

HRQoL to assess perceived health in all dimensions by the patients
Key components of HRQoL instruments

- Physical
- Social
- Psychological
Endpoints

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

**HRQOL is prognostic of OS duration in numerous cancer localizations**
Figure 1: A causal pathway model of health-related quality of life. The horizontal arrows indicate the main, but not exclusive, direction of causality. Wilson IB, Cleary PD. JAMA 1995;273:59–65
EORTC QLQ-C30 (version 3)

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

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

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

**During the past week:**

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

*Please go on to the next page*
Measuring quality of life
Is quality of life determined by expectations or experience?
Alison J Carr, Barry Gibson, Peter G Robinson

Summary points

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

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

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

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

Current measures do not take account of expectations and cannot distinguish between changes in the experience of disease and changes in expectations of health
Endpoint classification according to the clinical benefit for the patients

• Clinical benefit meaning should be reaffirmed

• What is a composite endpoint?

• What is a surrogate endpoint?
Endpoint classification in oncology

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

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

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

## Endpoint classification for FDA

### Table 1. A Comparison of Important Cancer Approval Endpoints

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

**- 1st : OS**

**- 2nd : PRO & HRQOL**

### Guidance for Industry

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

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

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

• One Endpoint based on at least 2 events, components

• Combination of various clinical events that might happen

• Ex with PFS: including local progression, metastases or death (all causes), where any one of those events would count as part of the composite endpoint

Mainer CL. Clinical Trials Dictionary, 1996.
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 Tugwell¹,²,³, Maria G. Judd,⁴,⁵ Jim F. Fries,⁴,⁵ Guiskirpal Singh,⁶ George A. Wells²,³

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²Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada
³Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada
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⁵Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

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Discomfort: yes vs no
Could move to composite endpoint?

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

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

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

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

Definition is a key component
CONS composite endpoints:
- To reach statistical significance
- Smallest effect for the most important component

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
Definition of composite endpoint is then crucial to allow comparison of the results between trials.
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.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>Time from surgery until death from any cause</td>
</tr>
<tr>
<td>Disease specific survival</td>
<td>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).</td>
</tr>
<tr>
<td>Disease free interval</td>
<td>Time from surgery until recurrent disease.⁷ Death not related to breast cancer is censored (Kaplan-Meier analysis) or treated as competing event (competing risk analysis).</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>Time from surgery until recurrent disease⁷ or death from any cause.</td>
</tr>
</tbody>
</table>

⁷ 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.

<table>
<thead>
<tr>
<th>Survival definition</th>
<th>10-year Survival (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>No adjuvant systemic therapy</td>
<td>Adjuvant systemic therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KM</td>
<td>CR</td>
<td>KM</td>
<td>CR</td>
</tr>
<tr>
<td>Overall survival</td>
<td>68.0</td>
<td>75.8</td>
<td>58.6</td>
<td></td>
</tr>
<tr>
<td>Disease specific survival</td>
<td>79.3</td>
<td>80.6</td>
<td>85.3</td>
<td>86.2</td>
</tr>
<tr>
<td>Disease free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral BC ignored</td>
<td>59.3</td>
<td>65.8</td>
<td>51.2</td>
<td></td>
</tr>
<tr>
<td>Contralateral BC censored</td>
<td>58.6</td>
<td>59.4</td>
<td>64.9</td>
<td>66.0</td>
</tr>
<tr>
<td>Contralateral BC event</td>
<td>55.5</td>
<td>59.9</td>
<td>50.2</td>
<td></td>
</tr>
<tr>
<td>Disease free interval</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral BC ignored</td>
<td>69.4</td>
<td>70.9</td>
<td>74.6</td>
<td>75.8</td>
</tr>
<tr>
<td>Contralateral BC censored</td>
<td>68.9</td>
<td>70.9</td>
<td>73.9</td>
<td>75.9</td>
</tr>
<tr>
<td>Contralateral BC event</td>
<td>64.8</td>
<td>66.5</td>
<td>67.6</td>
<td>69.2</td>
</tr>
</tbody>
</table>

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

**DFS at 10 years from 55.5 to 59.3% !**
Protocol of the Definition of 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, Marina Paludo, Sophie Gourgou, Laurence Collette, Adelaide Doussau, Andrew Kramar, Tienhan Sandrine Dabakuyo, Monia Ouadi, Anne Auperin, Thomas Filleron, Catherine Fortpié, Christophe Le Tourneau, Xavier Pauketat, Murielle Mauer, Simone Mathoulin-Péllissier, Franck Bonnetain

Annals of Oncology Advance Access published March 27, 2015

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


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)


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

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

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

91. Fleming TR: Surrogate endpoints and FDA’s accelerated approval process. Health Aff (Millwood) 24:67-78, 2005
PFS as surrogate of OS in mCRC?

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

- Interest for the patients to improve PFS without OS improvement?
Surrogacy of PFS for OS in T3-T4 Rectal Cancer

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
R² = 0.88 (95% CI 0.77 – 1)
DFS is still surrogate in adjuvant colon cancer

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


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

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

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

✓ At the individual level PFS et OS:

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

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

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

- At the trial level

PFS is not surrogate of OS in mBC

The rank correlation coefficient between the treatment effects on PFS and survival was 0.48 (95% CI, −0.34 to 1.30; Fig 3). For the treatment effects on TTP and survival, the ρ was 0.49 (95% CI, −0.32 to 1.30; plot not shown). As with the result obtained for tumor response and disease control, both estimates indicated a weak and imprecisely estimated association between treatment effects for PFS and TTP on one hand and for survival on the other hand.
**Disease-Free Survival as a Surrogate for Overall Survival in Adjuvant Trials of Gastric Cancer: A Meta-Analysis**

Koji Oba, Xavier Paoletti, Steven Albarts, Yung-Jue Bang, Jacqueline Benedetti, Harry Bleiberg, Paul Catalano, Florian Lordick, Stefan Michiels, Satoshi Morita, Yasuo Ohashi, Jean-pierre Pignon, Philippe Rougier, Mitsuji 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).

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

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.\textsuperscript{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 quality or quantity of survival for patients with cancer. We hope that the Journal of Clinical Oncology and other investigators consider the proposed changes in language in an effort to more clearly communicate the true benefits of our therapies to patients, clinicians, and policy makers.

The real objective of the treatment is to improve Survival duration and/or Quality of life.
Outcomes and endpoints in cancer trials: bridging the divide

Michelle K Wilson, Deborah Collyer, Diana T Changas, Michael Friedlander, Tony W Hsia, Katherine Kanakis, Stan Kaye, Mehesh K B Parmar, Matthew R Sydes, Ian Tannock, Amit M Oza

Cancer is not one disease. Outcomes and endpoints in trials should incorporate the therapeutic modality and cancer.

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. 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 discussed the

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

Michelle K Wilson, Katherine Kanakis, Amit M Oza

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
So where are we going = co-primary endpoints
- Patient centered endpoints : SG & QdV
- Tumor Centered endpoint: PFS, DFS etc
• HrQoL should be a co-primary endpoint with tumor centered endpoint to be in line with:

  – Trials duration and sample size

  – Demonstration of clinical benefit for the patient

New challenge to implement such design in oncology
Two phase III RCT in glioblastoma for regular approval of Bevacizumab

- Two me too trials:
  - STUPP +/- Bevacizumab in Glioblastoma
    - No effect on OS
    - Positive effect on PFS
    - While OS and PFS were co-primary (« single sufficient ») no impact was observed on OS: patient clinical benefit is questionable for regulatory approval
    - Then HrQOL was regarded as primary endpoint but Different results for HrQOL
Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial


Processed as a Rapid Communication manuscript; see accompanying editorial doi: 10.1200/JCO.2013.54.7295; listen to the podcast by Dr Iasonas at www.jco.org/podcasts

![Graph 1](image1.png)

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

![Graph 2](image2.png)

**Fig 2.** Overall survival (OS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.
Patient-Reported Outcome Results From the Open-Label Phase III AURELIA Trial Evaluating Bevacizumab-Containing Therapy for Platinum-Resistant Ovarian Cancer

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

• Which methodology

• Key point: decision rules

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

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

Co-primary could be composite endpoints
EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors

A. G. Pallis\textsuperscript{1*}, A. Ring\textsuperscript{2}, C. Fortpiad\textsuperscript{3}, B. Penninck\textsuperscript{4}, M. C. Van Nes\textsuperscript{5}, U. Wedding\textsuperscript{6}, G. von Minckwitz\textsuperscript{7}, C. D. Johnson\textsuperscript{8}, L. Wyld\textsuperscript{9}, A. Timmer-Bonte\textsuperscript{10}, F. Bonneta\textsuperscript{11}, L. Repetto\textsuperscript{12}, M. Aapro\textsuperscript{13}, A. Luciani\textsuperscript{14} & H. Wilders\textsuperscript{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).

In Elderly cancer patients
HrQOL should be co-primary / composite endpoint
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.

DOI: 10.1056/NEJMoa1212299
HrQOL as clinical endpoint

- Primary or co-primary endpoints in oncology

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

- To individualize treatment based on HrQOL
Thank you for your attention