

CLINICAL TRIAL ENDPOINTS

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DISCLOSURES

- ◆ Ian Tannock has reported no conflict of interest relevant to this presentation
- ◆ Steinar Aamdal has reported no conflict of interest
- ◆ Dirk Arnold has reported to have received honoraria for educational activities/Advisory role from Roche, Merck-Serono, Bayer, Servier, BTG
- ◆ Urania Dafni has reported no conflict of interest
- ◆ Ulrich Keilholz has reported to be a member of the Speakers Bureau of BMS, Astra Zeneca, MSD, Merck, GSK, Novartis, Roche, Amgen, Pfizer and has served as consultant for all these companies
- ◆ Morten Mau-Sørensen has reported no conflict of interest
- ◆ Piotr Rutkowski has reported no conflict of interest related to this ppt. However he has received honoraria from Novartis, Roche, GSK, MSD, BMS, Pfizer, Bayer and Amgen and he has served as a member of Advisory Board for Novartis, Roche, Magen, Bayer, MSD and BMS
- ◆ Stefan Sleijfer has reported no conflict of interest

ENDPOINTS NEED TO MATCH THE PURPOSE OF THE TRIAL



Phase 1: Evaluate toxicity

Study drug disposition (pharmacokinetics, PK)

Proof of concept that drug inhibits its target (pharmacodynamics, PD)

Determine dose and schedule for Phase 2

Phase 2: Estimate anti-tumour efficacy

Further define toxicity

Further PD studies

Phase 3: Compare outcomes reflecting patient benefit with usual standard of care

ENDPOINTS APPROPRIATE FOR OTHER TYPES OF TRIAL



Phase 0: Trials in which a (usually) low dose of a drug is given. Appropriate endpoints are measures of drug disposition and target inhibition

Phase 4: Post-marketing studies. Appropriate endpoints are those of efficacy and toxicity under real-life conditions

Trials of local therapy: In addition to endpoints used in trials of systemic therapy, other appropriate endpoints may include:

- Local relapse-free survival

- Functional effects

- Completeness of resection

ENDPOINTS IN PHASE I AND PHASE II TRIALS



- While the primary goal of phase I trials is to evaluate toxicity and tolerance (and PK and PD) agents that show no signs of activity rarely succeed in later trials.
- The primary goal in phase II is to determine if there is sufficient evidence of *anti-tumour activity* to undertake further studies in phase III (very expensive in terms of human and €€€ resources).
- Appropriate endpoints for phase II include measures of anti-tumour activity such as **Overall Response Rate (ORR)** or reduction of a tumour marker (e.g. PSA response rate).
- **Progression-free survival (PFS)** or **percent without progression at a given time** are also appropriate endpoints in phase II trials, especially if they are randomised.
- Identification of **biomarkers** is important in early phase trials. New endpoints such as reduction in circulating tumour cells (**CTCs**) are under investigation

TUMOUR RESPONSE AS AN ENDPOINT



- ◆ **Evaluation of Tumour response** has been standardised using (modified) “Response Evaluation Criteria in Solid Tumours” (**RECIST**).
- ◆ **Stable Disease (SD)** is reported frequently as an endpoint with the implication that it reflects an anti-tumour effect of a drug rather than a criterion to continue treatment.
 - ◆ While long-term SD (e.g. > 6 months) might imply anti-tumour effects, a tumour **growing steadily with a volume doubling time of ≥ 2 months (typical for human tumours) will satisfy SD ≥ 1 month.**
- ◆ **Endpoints used in Phase II trials do not measure benefit to patients.** Tumour shrinkage is rarely correlated with endpoints of patient benefit such as Overall Survival (OS) or Quality of Life (QoL)
 - ◆ “**Clinical benefit rate**” (CR+PR+SD) should **not** be used. It has no implication of “clinical benefit”.

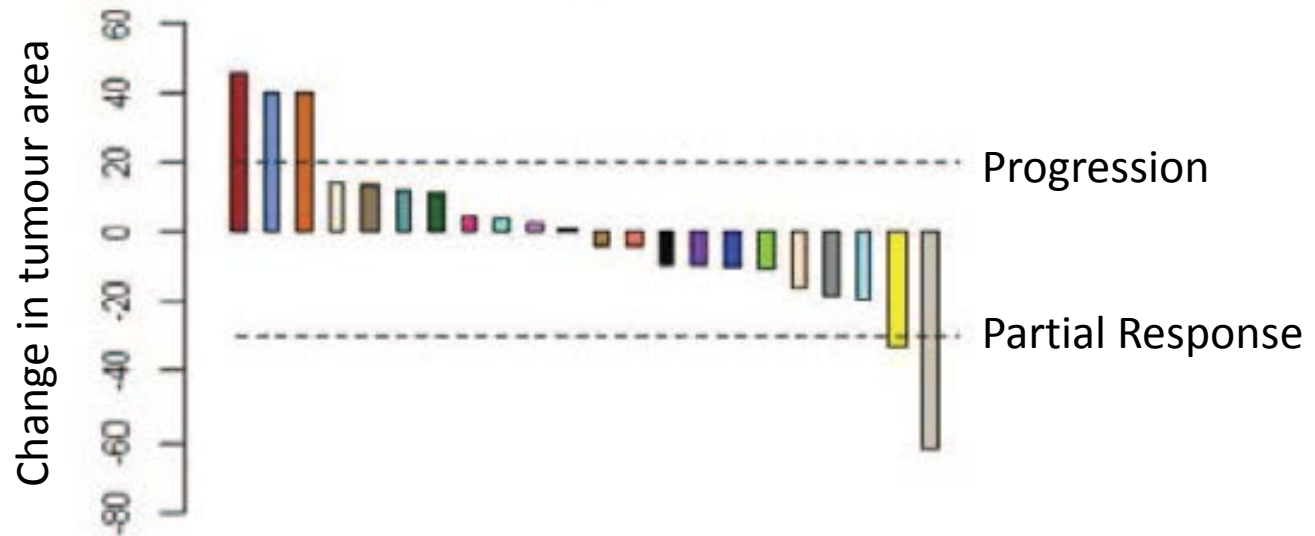
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TUMOUR RESPONSE: MEASUREMENT ERROR AND WATERFALL PLOTS



- Despite standardisation by RECIST, evaluation of ORR is subject to **measurement error**
- **Waterfall plots** are now in common use to demonstrate maximal changes in tumour size among patients in phase II trials

Example:



- Waterfall plots are also subject to errors of tumour measurement

ENDPOINTS IN PHASE III TRIALS

- ◆ The goal of Phase 3 trials is to compare outcomes reflecting patient benefit with the usual standard of care.
- ◆ There are essentially only 2 ways in which patients may benefit from treatment:
 - ◆ They either live longer or they live better.
- ◆ Thus the most appropriate endpoints of phase III trials are:
 - ◆ Overall Survival (OS)
 - ◆ Quality of Life (QoL)
- ◆ Any other endpoint is a surrogate endpoint, and should be shown to predict OS or QoL.

SURROGATE ENDPOINTS IN PHASE III TRIALS



- ◆ While OS is a preferred endpoint and not subject to bias, the survival time for patients with many types of cancer is (fortunately) quite long. This is especially true for trials of adjuvant therapy.
- ◆ **Disease-Free Survival (DFS)**, also known as Relapse-Free Survival (RFS), is often used as a primary endpoint in phase III trials of adjuvant therapy.
- ◆ **Progression-Free Survival (PFS)** is used commonly as a primary endpoint in phase III trials evaluating treatment of metastatic cancer.
 - ◆ Since the size of a trial is determined by the number of “events”, and recurrence or progression of cancer usually occurs before death, trials with DFS or PFS as the primary endpoint can be evaluated earlier, and require a smaller sample.
 - ◆ Some investigators also prefer these endpoints because they are not influenced by subsequent therapies.

CRITERIA FOR ESTABLISHING “SURROGACY”

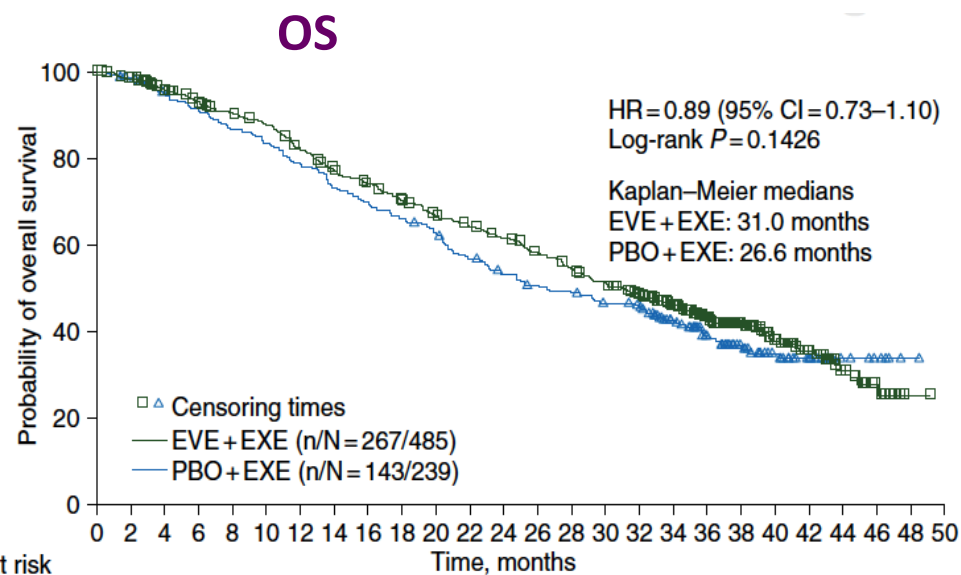
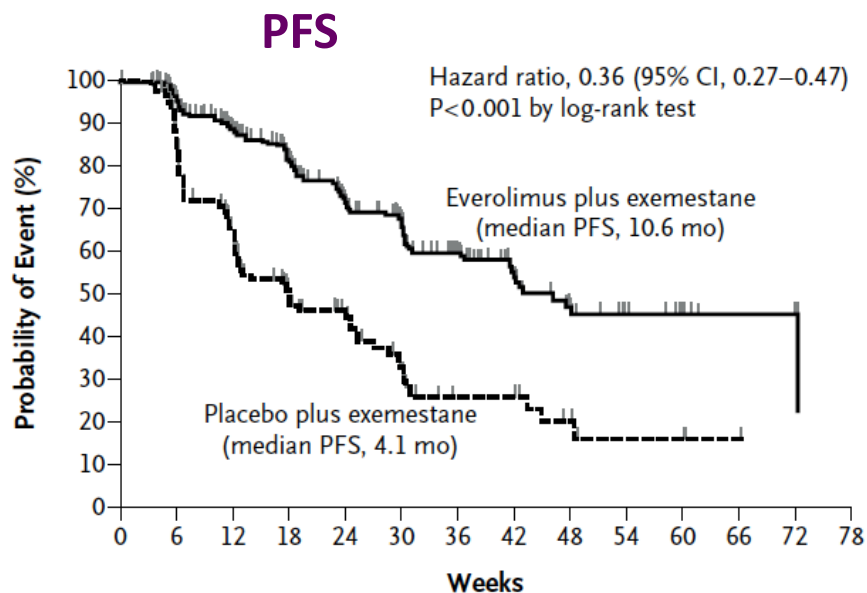


- Surrogacy of an endpoint such as PFS for OS requires that a patient with longer PFS will have longer OS. **It is not sufficient that PFS be correlated with OS.**
- A valid surrogate for OS should satisfy the **Prentice criteria**:
 - The treatment has an effect on survival time.
 - The treatment has an effect on the surrogate.
 - The surrogate is associated with survival time.
 - The treatment effect on survival is captured by the surrogate.
- It is rare that endpoints such as DFS or PFS have been shown to be true surrogates for OS

RELATIONSHIP BETWEEN PFS, DFS AND OS

- Although DFS and PFS may be correlated with OS, changes in DFS or PFS frequently do not predict subsequent improvements in OS.

Example: Bolero-2 study of exemestane +/- everolimus for postmenopausal women with metastatic ER+ breast cancer after progression on non-steroidal Aromatase Inhibitor



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ADVANTAGES AND DISADVANTAGES OF DFS OR PFS AS ENDPOINTS IN PHASE III TRIALS



Advantages

- ◆ “Events” occur earlier, so trials can be reported earlier, potentially accelerating availability of active new treatments
- ◆ Greater number of “events” allows smaller trials
- ◆ Not subject to effects of subsequent treatment

Disadvantages

- ◆ Not measures of patient benefit
 - ◆ Delayed tumour progression, but with toxicity causing detriment in QoL, and no improvement in OS, does not convey clinical benefit
- ◆ Subject to bias
 - ◆ Uncertainty of time of relapse or progression
 - ◆ Censoring bias – imbalanced withdrawal of patients who are censored prior to relapse or progression

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HAZARD RATIOS

- ◆ For time to event endpoints (OS, DFS and PFS) it is common to report the difference between experimental and control curves as a **Hazard Ratio (HR)**.
- ◆ **Use of HR implies “proportional hazards”:**
 - ◆ i.e. the ratio between events occurring in any given time interval with experimental compared to control treatment is constant
 - ◆ HR is not meaningful where survival curves are not of similar shape
- ◆ If $HR < 1$ and the 95% confidence interval excludes 1, there is a statistically significant effect of the experimental treatment as compared to control.
- ◆ **Statistical significance is not the same as clinical significance.**
- ◆ It is common to analyse actuarial survival curves when many patients have not had an “event” (relapse, progression or death). The tails of the curves are poorly defined and HR will change with time – usually becoming closer to 1.0



Thank you!