When overall survival cannot be the primary endpoint

An EU regulatory perspective

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From Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6; ”CHMP Anticancer Guideline”)

- **“Confirmatory trials should demonstrate that the investigational product provides *clinical benefit*.“**
- **“There should thus be *sufficient evidence* available demonstrating that the chosen primary endpoint can provide a valid and *reliable measure of clinical benefit* in the patient population described by the inclusion criteria”**
- **But what is *sufficient evidence* to demonstrate that a non-overall survival endpoint is a *reliable measure of clinical benefit*?**

Established measures of clinical benefit according to the CHMP Anticancer Guideline

- **“There are a number of clinical endpoints, which are considered as adequate primary endpoints in confirmatory clinical trials to measure clinical benefit”**
- **“These typically include Overall Survival (OS), Progression Free Survival (PFS) Event Free Survival (EFS), and Disease Free Survival (DFS)”**
- **“Selected patient-reported outcomes (PROs), such as symptom control, could also constitute clinically relevant and valid primary endpoints, provided high data quality is ensured”**

The rationale for PFS as an endpoint capturing clinical benefit (CHMP Anticancer Guideline)

- **”An effect on prolonging PFS of sufficient magnitude (…) is considered in itself a clinically relevant effect:**
- ***because documented progression of the disease is generally assumed to be associated with subsequent onset or worsening of symptoms, worsening of quality of life, and the need for subsequent treatments generally associated with lower efficacy and worse toxicity*”**
- **No demonstration of a correlation of PFS and OS, or of PFS and documented symptomatic benefit, is required in the specific case**
- **There is no assumption of the surrogacy of PFS for OS**
- **“No signs of a detrimental effect on OS should be present”. Consequently, OS is viewed as a safety endpoint in this case.**

The PFS paradox

- **PFS is the most common registrational endpoint for anticancer therapies**
- **Still, in scientific advice for sponsors, EU regulators generally encourage the use of OS rather than PFS, as primary endpoint, in situations where post progression survival is short**
- **However, the shorter post progression survival, the more correlated PFS and OS are anticipated to be**
- **HTA's have frequently questioned whether a PFS gain is "itself a clinically relevant effect"**
- **Nowithstanding this, PFS will remain an important endpoint to capture clinical benefit in randomized controlled cancer trials**

The CHMP Anticancer Guideline on PFS2

- **“In order to capture possible negative effects on next-line therapy and to outbalance tolerability and toxicity concerns related to therapy, it is expected that time from randomisation to PFS2 in the experimental arm show no detrimental effect compared to the control arm”**
- **Understood by EU regulators as a sort of safety endpoint; a surrogate for OS**
- **The measurement of PFS2 is generally not necessary, and is most often not captured directly**
- **Determination requires continued systematic monitoring for progression in trials, following a PFS event, which otherwise concludes systematic monitoring for progressive disease**

Objective Response rate (ORR) / Duration of Response (DoR) and single arm trials

- **"Resorting to non-randomized trials should be duly justified – for instance (…) a large treatment effect on endpoints such as ORR and DoR, likely to *translate in true clinical benefit*".**
- **As opposed to a gain in PFS, objective responses are not themselves considered clinical benefit**
- **However, "ORR, despite all its shortcomings related to patient-selection, etcetera, is a rather convincing measure of anti-tumour activity as for most tumours, spontaneous regression fulfilling criteria for at least partial response is a rare phenomenon"**
- **ORR is primarily used as registrational endpoint in late line settings, or rare cancers, *since it is the only endpoint that isolates drug effects in single arm trials***
- **Remains controversial among EU regulators how this measure captures clinical benefit**

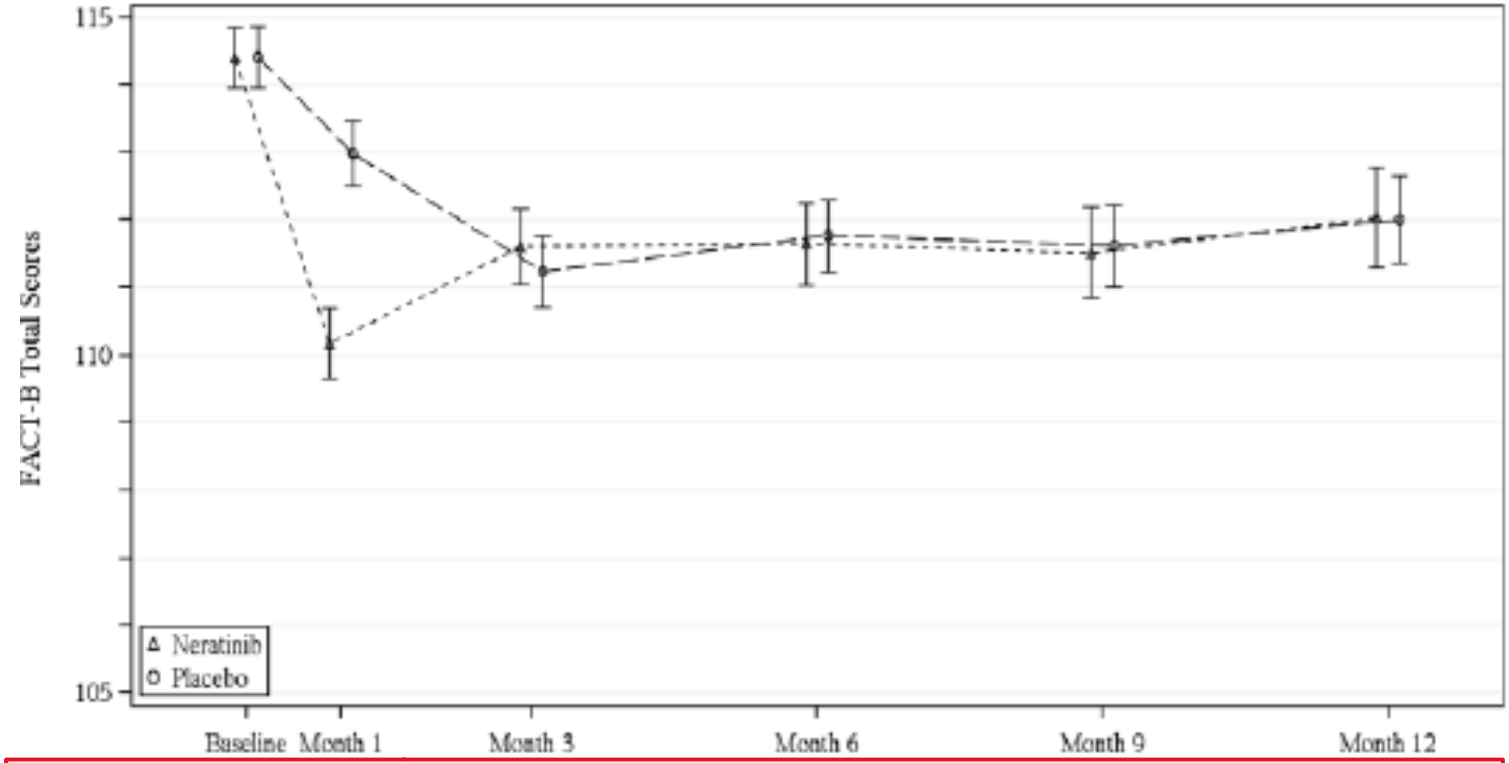
Patient Reported Outcomes (PROs)

- **“Selected PROs, such as symptom control, could also constitute clinically relevant and valid primary endpoints, provided high data quality is ensured”**
- **“PROs can provide important patient perspectives on the disease and the treatment received”**
- **“Clinical studies to support regulatory submissions are encouraged to include relevant PRO measures, as secondary or exploratory outcomes or as primary outcomes when justified, using carefully validated tools”**

However…

- **PRO outcomes are generally not subject to type 1 error control in trial protocols (sponsor's decision)**
- **There are frequently no satisfactory considerations on how to handle intercurrent events in the analysis (e.g., death, change of therapy)**
- **There is frequently very considerable amounts of missing data**
- **Can we rely on PRO's in open-label studies?**
- **How to assess "equivalence claims" (no deterioration of health-related quality of life in add-on study) when assay sensitivity is uncertain?**

An adjuvant setting example: what is the estimand?



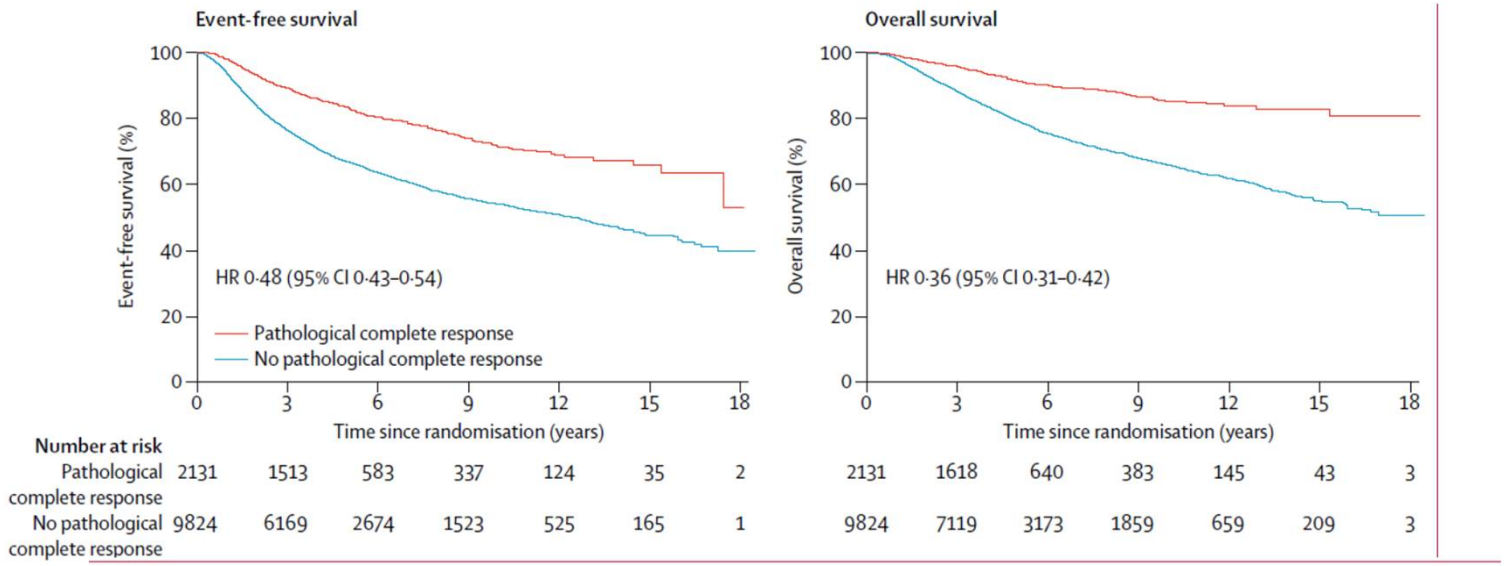
Number of Patients:

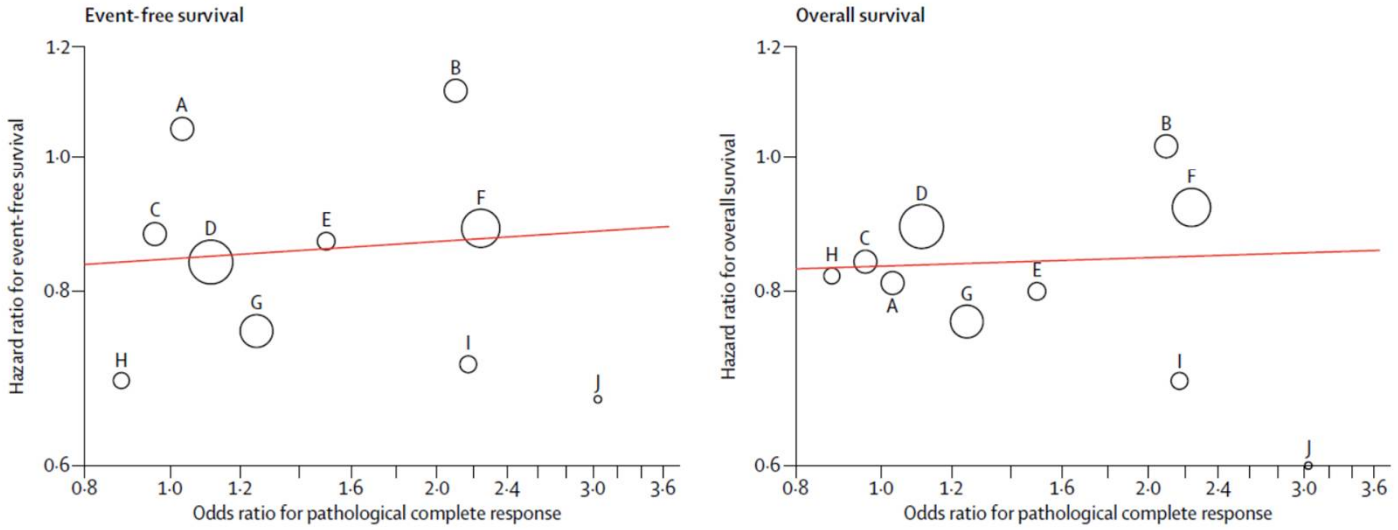
Neratinib	1264	1201	987	853	716	611
Placebo	1273	1274	1236	1135	978	853

Beyond ORR…

- **Major Molecular Response (MMR) is accepted as registrational endpoint in CML**
- **There are CHMP guidelines on Pathological Complete Response (pCR) as well as on Minimal Residual Disease (MRD) in several hematological conditions**
- **Generally difficult to view as clinical benefit per se**
- **Consequently, surrogacy for PFS/DFS or OS must be established**
- ***What is surrogacy*?**

pCR as a surrogate endpoint (Cortazar et al, 2014)





Patient- and trial level surrogacy

- **Patient level surrogacy does not isolate the causal effect of the drug on the time dependent endpoint, through its effect on the surrogate marker.**
- **Rather, it compares outcomes in patients with good and with poor prognosis**
- **To establish a trial-level surrogate, one needs to show that the between-arm differences in the surrogate endpoint accurately capture or predict the between-arm differences in the relevant, time-dependent endpoint**
- **Patient level surrogacy may be demonstrated, but data on trial level surrogacy absent or not convincing**

Concluding reflections

- **The anticancer drug development- as well as treatment paradigm, is based on the notion of impacting tumor growth**
- **Thus, clinical benefit is anticipated to be mediated through drug effects on tumor kinetics**
- **Drug impact on tumor burden is, in many settings, a parameter that can be reproducibly quantified**
- **Consequently, it is reasonable to base conclusions on clinical benefit on a measure of drug impact of tumor growth, when data on the impact of treatment on OS are absent or inconclusive**
- **The magnitude of drug impact on tumor growth that is considered to represent clinical benefit, may be a matter of communal agreement based on clinical practice and summary understanding, rather than on conclusive scientific inference**