

When overall survival cannot be the primary endpoint ...

Reflections on our challenges

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Why not always use overall survival as primary endpoint?

Overall Survival

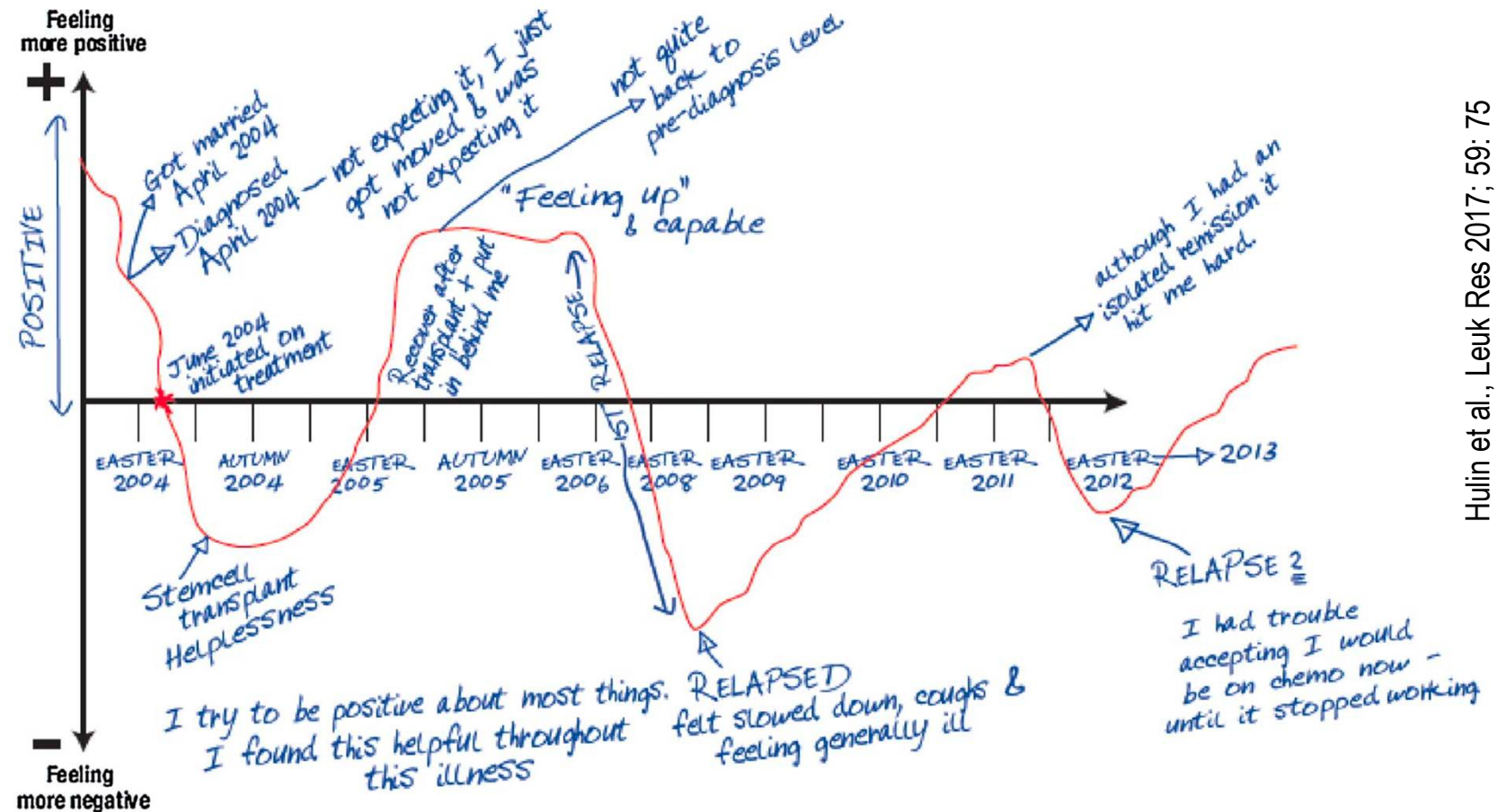
- It is the most important outcome for patients, direct clinical benefit
- Unambiguous, not subject to interpretation
- Alternative endpoints
 - do not always correlate with survival
 - the change in tumour size required progression may not be a relevant event for death
 - subject to assessment or timing bias

Alternative Endpoints (e.g. PFS)

- For some indications survival is too long to be captured in clinical trials
- Effective post-progression therapies may mask the effect of on overall survival
- Unintended treatment switching is not captured in overall survival
- Need to understand clinically meaningful improvements

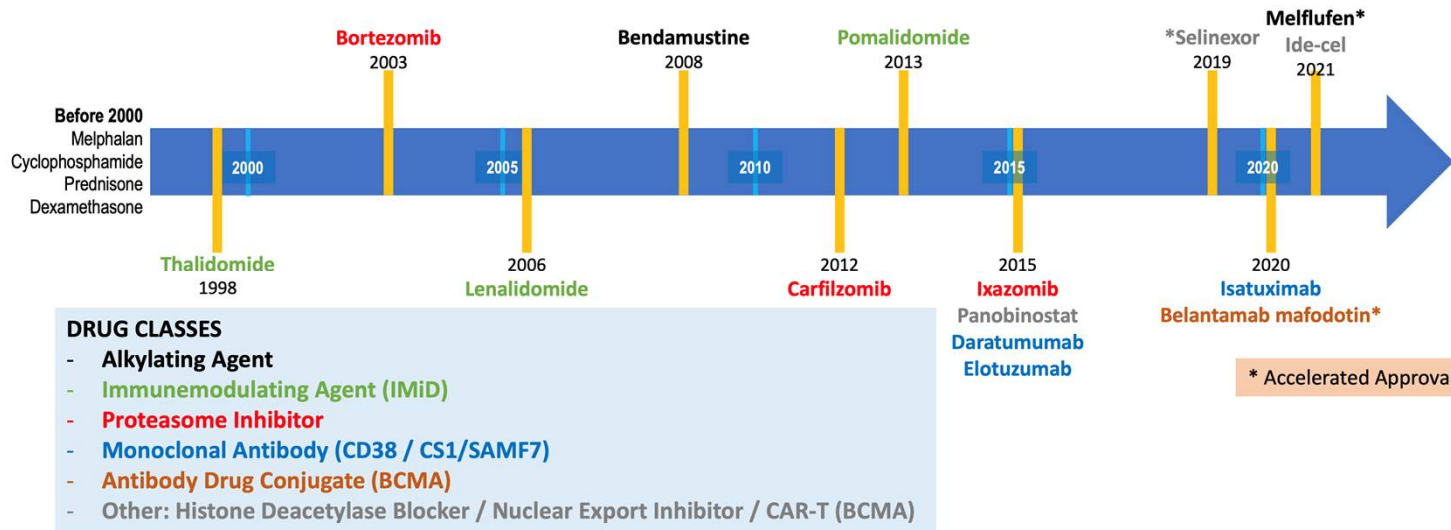
Patient's Perspective

- Need to expedite development and approval of treatments for serious and life-threatening diseases
- Changes in individual benefit-risk assessment in last-line therapy
- Progression is often a very negative event in the course of cancer therapy

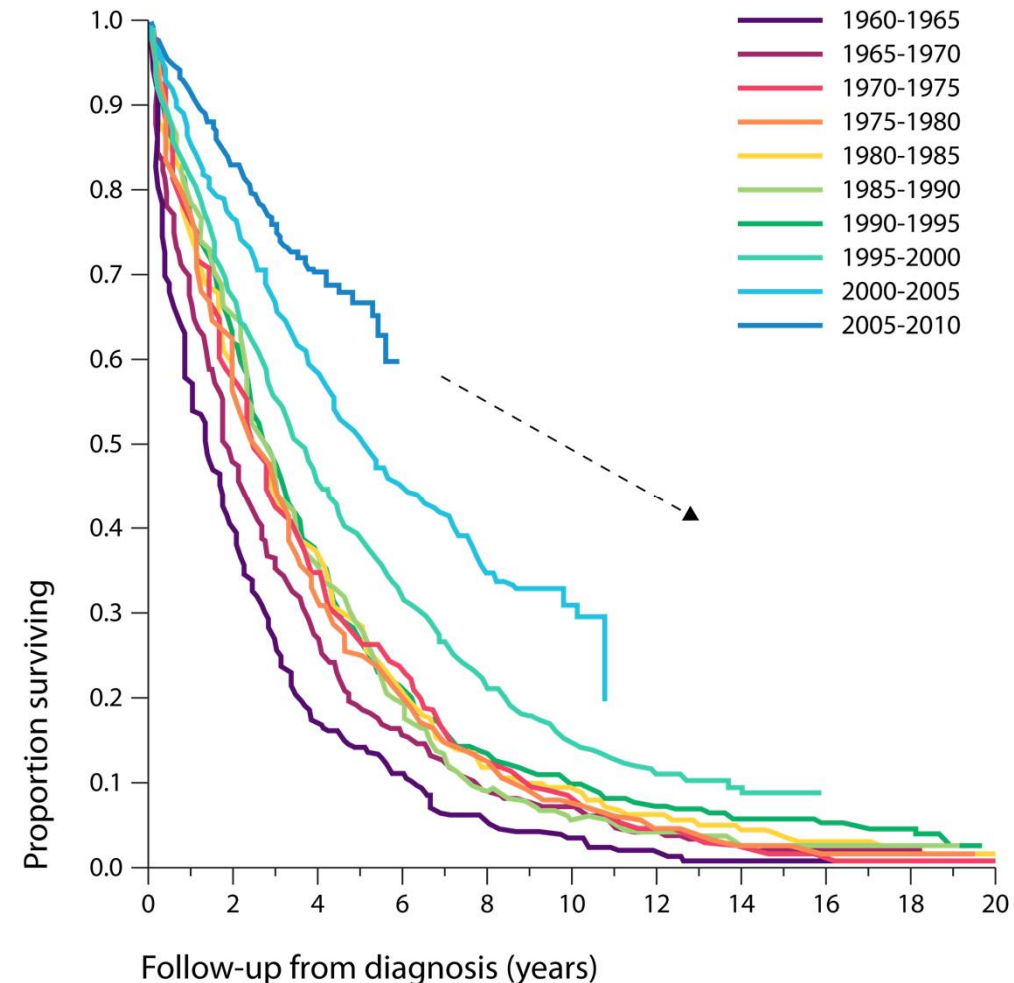


New approvals and overall survival in multiple myeloma

FDA/EMA Approval in Multiple Myeloma

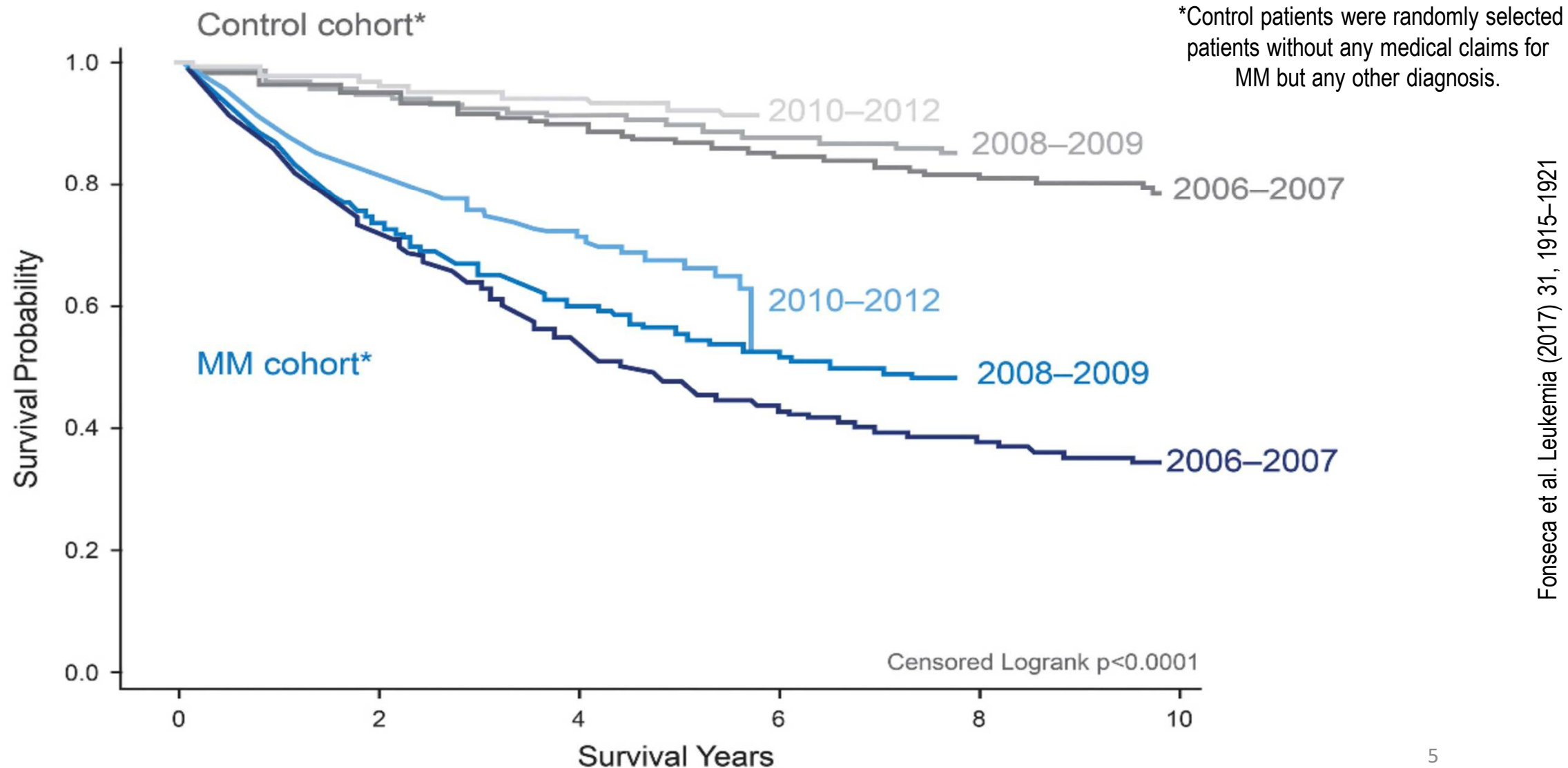


All approvals were based on studies with PFS/TTP or ORR/DoR as primary endpoint.



MM Overall Survival in US Population-Based Datasets

Truven Health Analytics MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases



Analysis

Endpoints in Clinical Trials

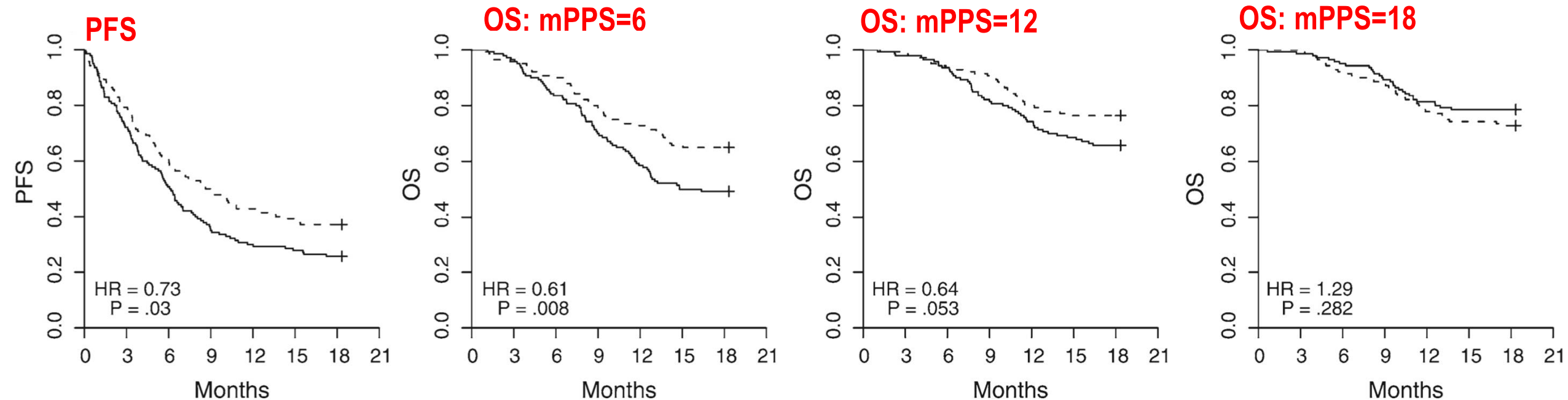
Established Endpoints

- Overall survival (OS)
- Progression-free survival (PFS)
- Disease-free or event-free survival (DFS, EFS)
- Objective response rate (PR+CR)
- Patient-reported endpoints (PRO)

Examples for Novel Endpoints

- Pathologic complete response (pCR)
- Measurable residual disease (MRD)
- CR at a certain time point (e.g. CR₃₀)
- Progression-free survival 2 (PFS2)
- ...

Post-Progression Survival (PPS)



“OS is a reasonable primary endpoint when median [PPS] is short but is too high a bar when median SPP is long, such as longer than 12 months.”

Progression-Free Survival 2 (PFS2)

PFS2 Definition (EMA):

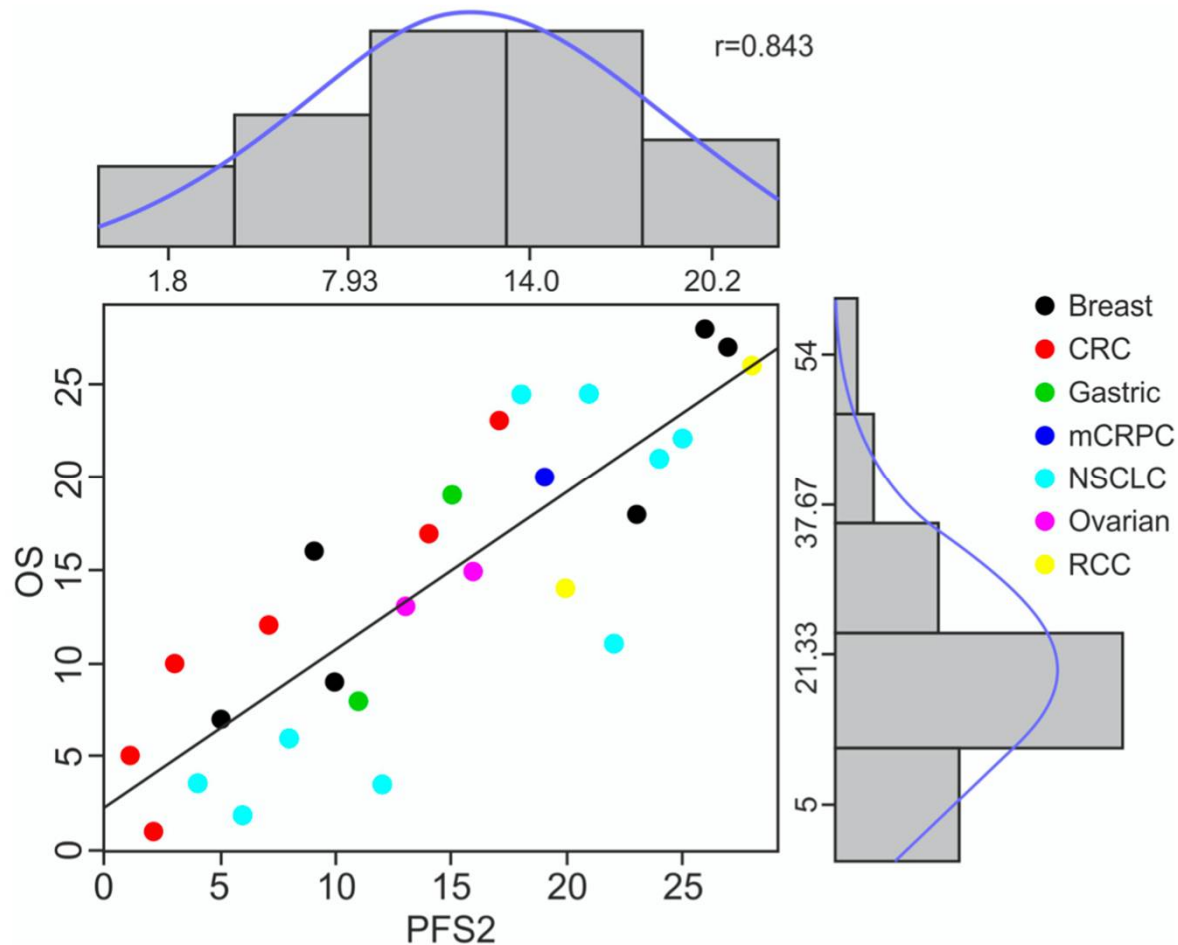
*Time from randomization to second objective disease progression, or death from any cause**



PFS: Progression-free survival, PPS: Post-progression survival

*EMA Guideline: Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man: Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials, December 13, 2012

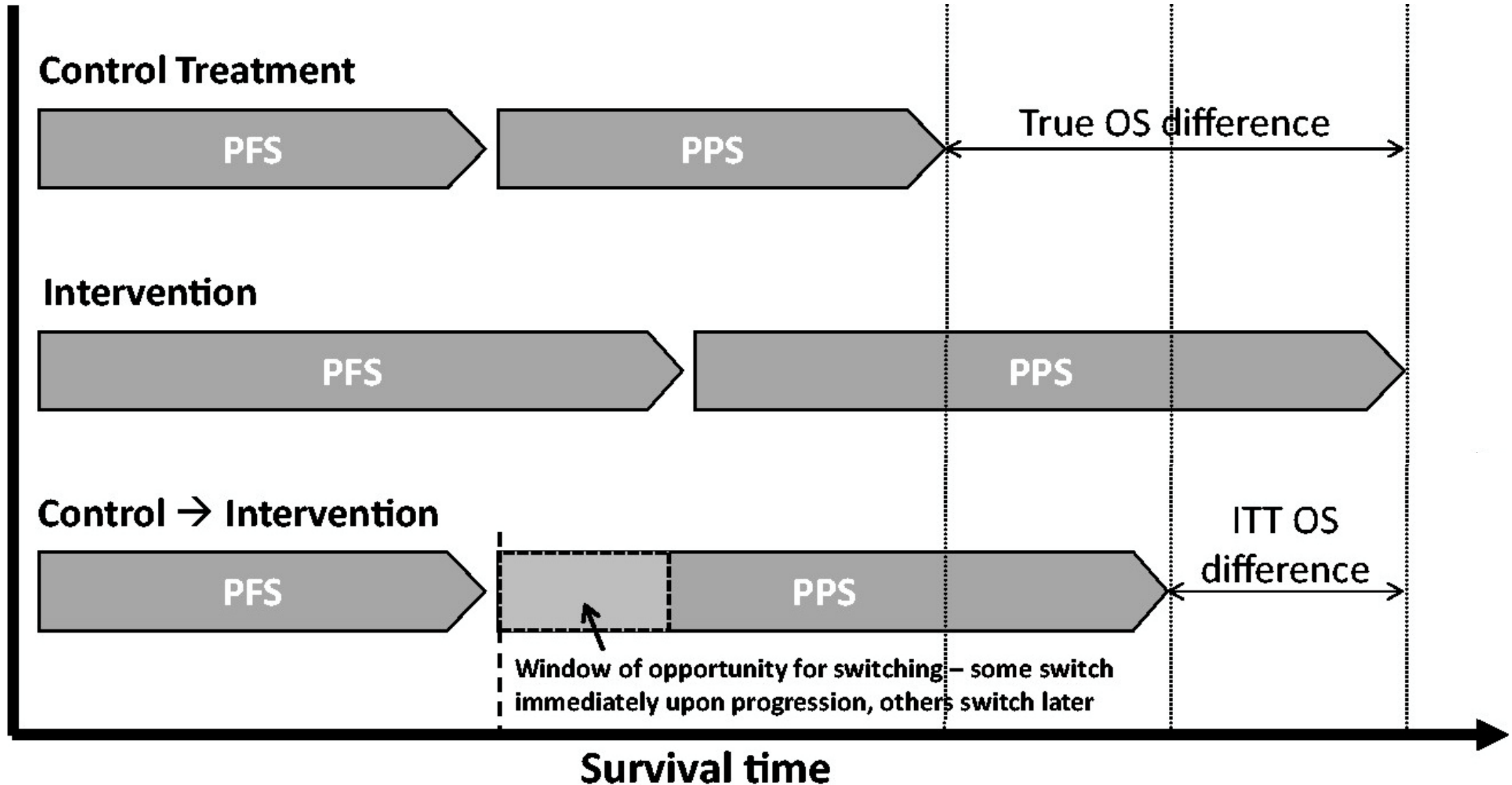
Assessment of PFS2 in Solid Tumors



- 15 studies (28 arms) in ovarian, gastric, colorectal, prostate, lung, renal and breast cancer
- A strong positive correlation for PFS2 and OS was found for all 15 studies, incl. 10 RCTs
- Results support the use of PFS2 to measure long-term clinical benefit when OS cannot be assessed
- However, the assessment of PD must be maintained in both arms during the post-progression period

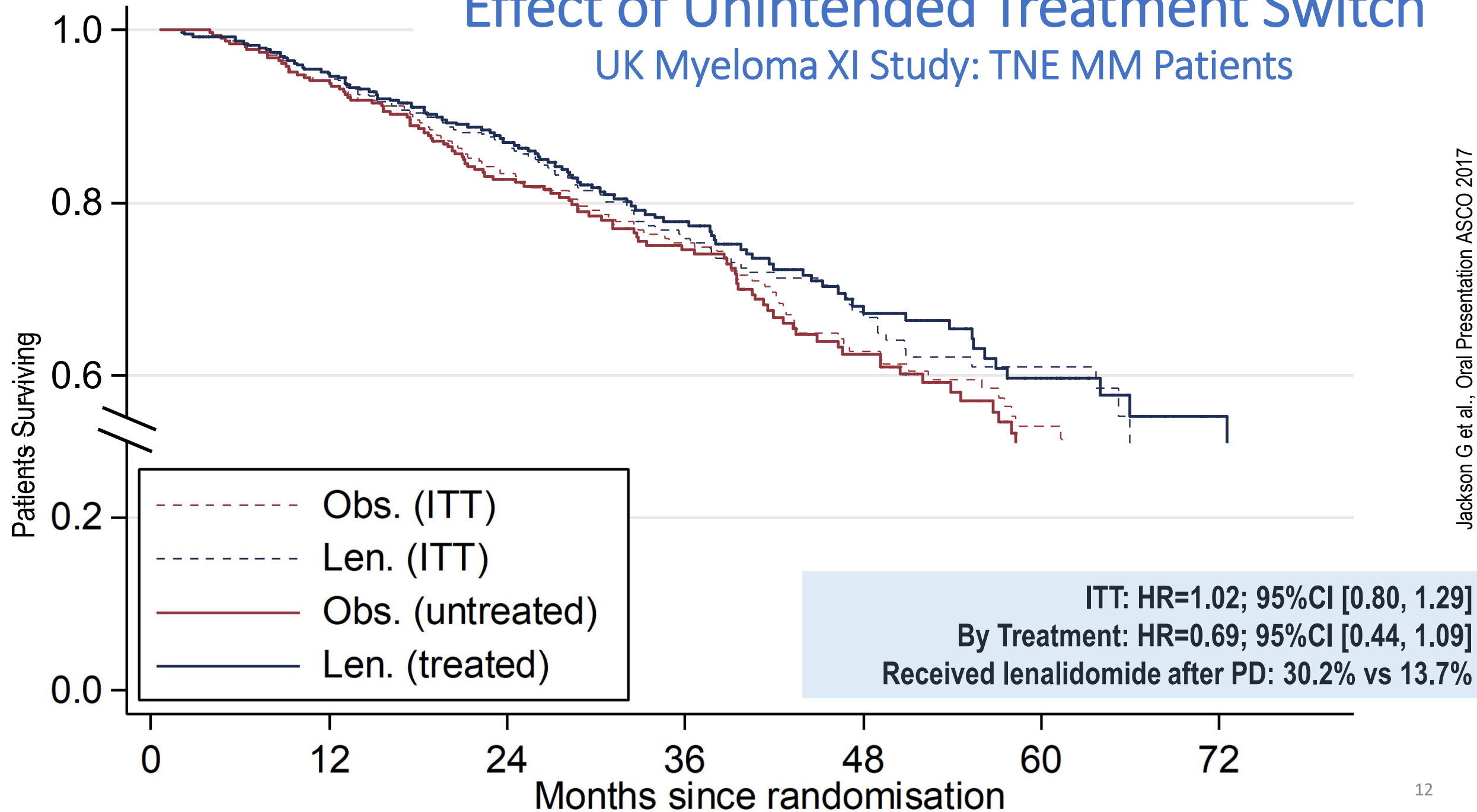
Effect of treatment-switching on overall survival

PFS: Progression-free survival; PPS: Post-progression survival

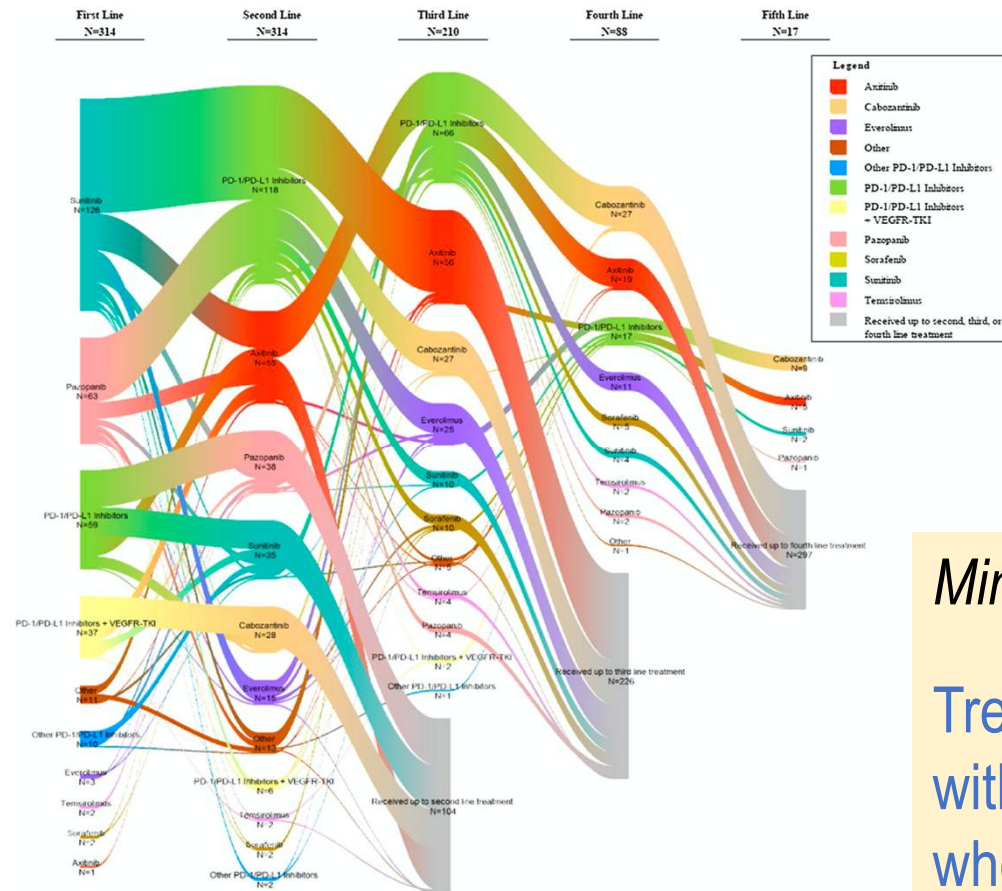


Effect of Unintended Treatment Switch

UK Myeloma XI Study: TNE MM Patients



The problem of subsequent therapy

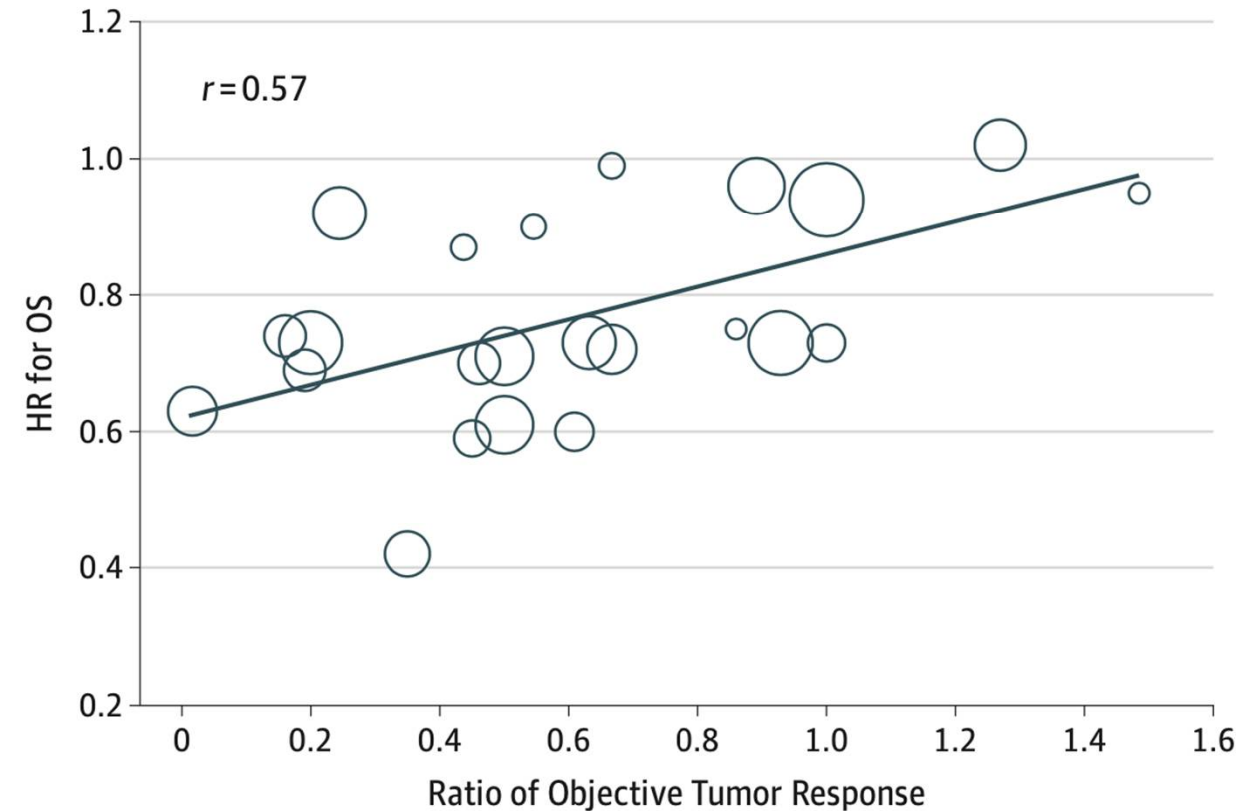


Minard/Sankey Flow Chart:

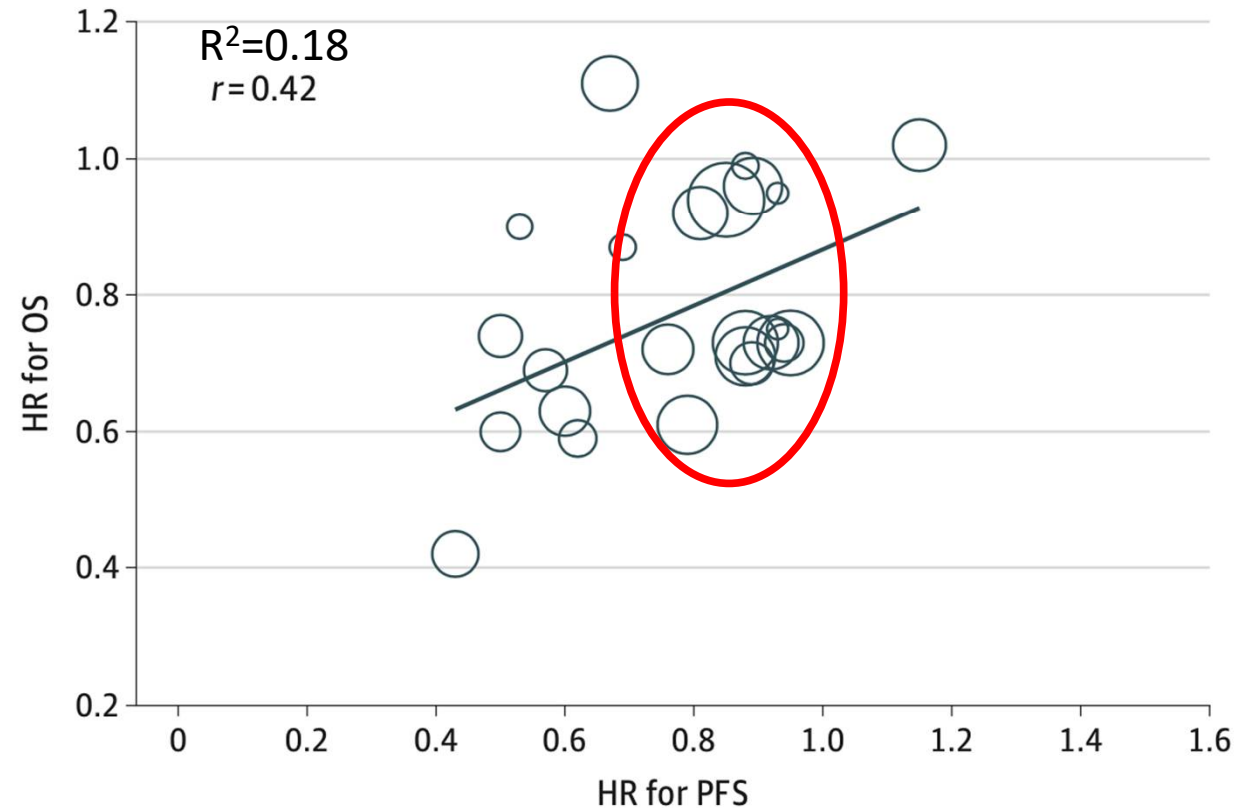
Treatment sequence of 314 patients with advanced renal cell carcinoma who received IO therapy in one line

Association between Endpoints for Immune Checkpoint Inhibitors in Solid Tumours

A Objective tumor response and HR for OS



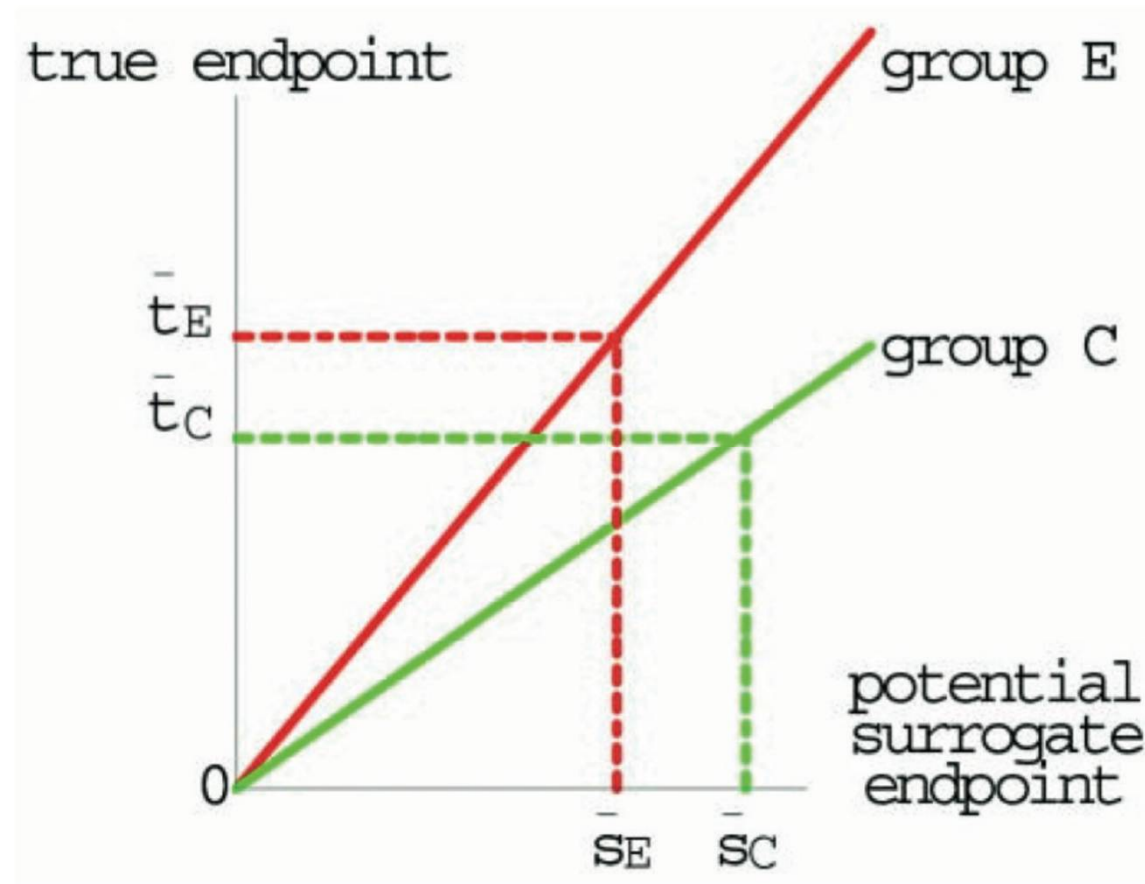
B HRs for PFS and OS



Development of New Endpoints

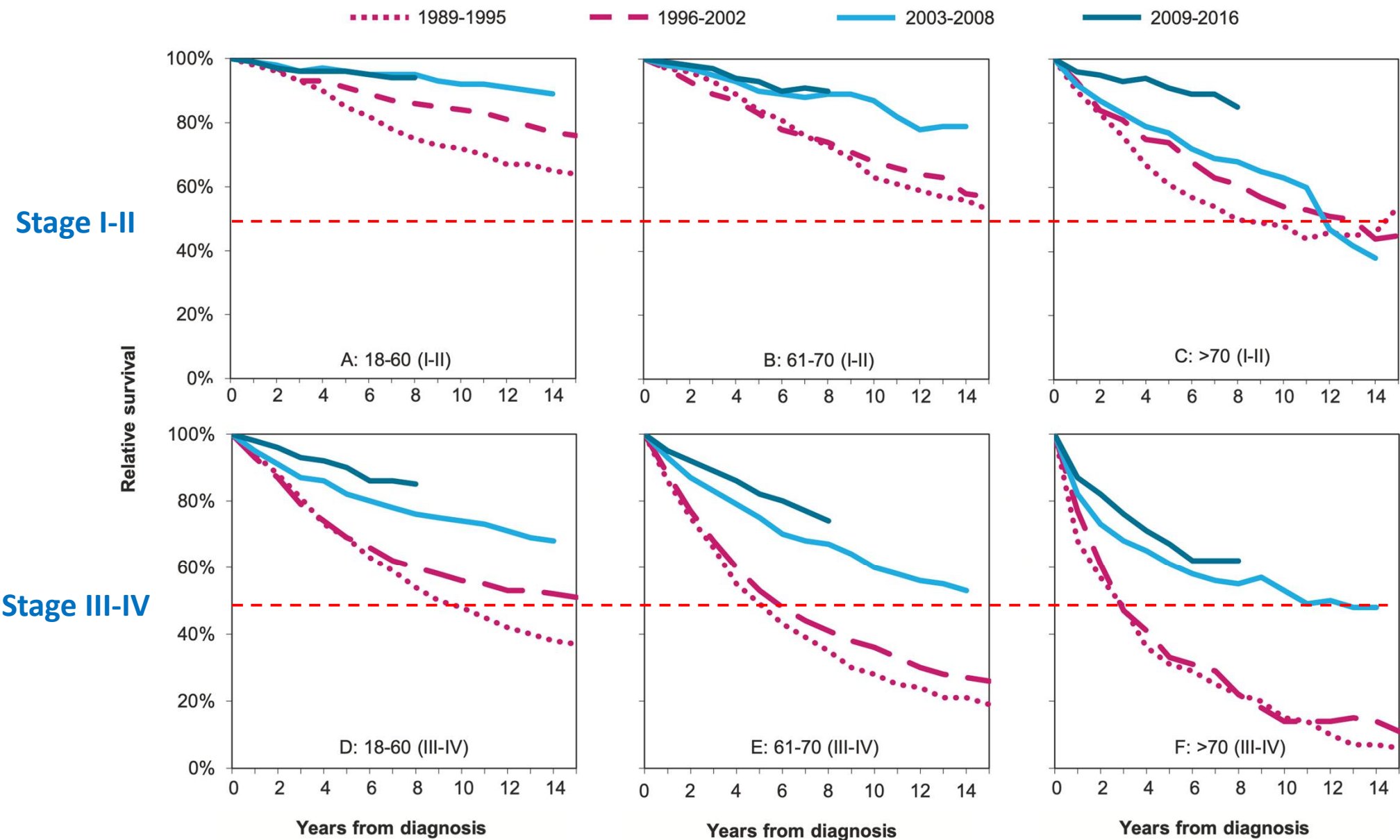
“A perfect correlate does not a surrogate make”

Need for a formal validation



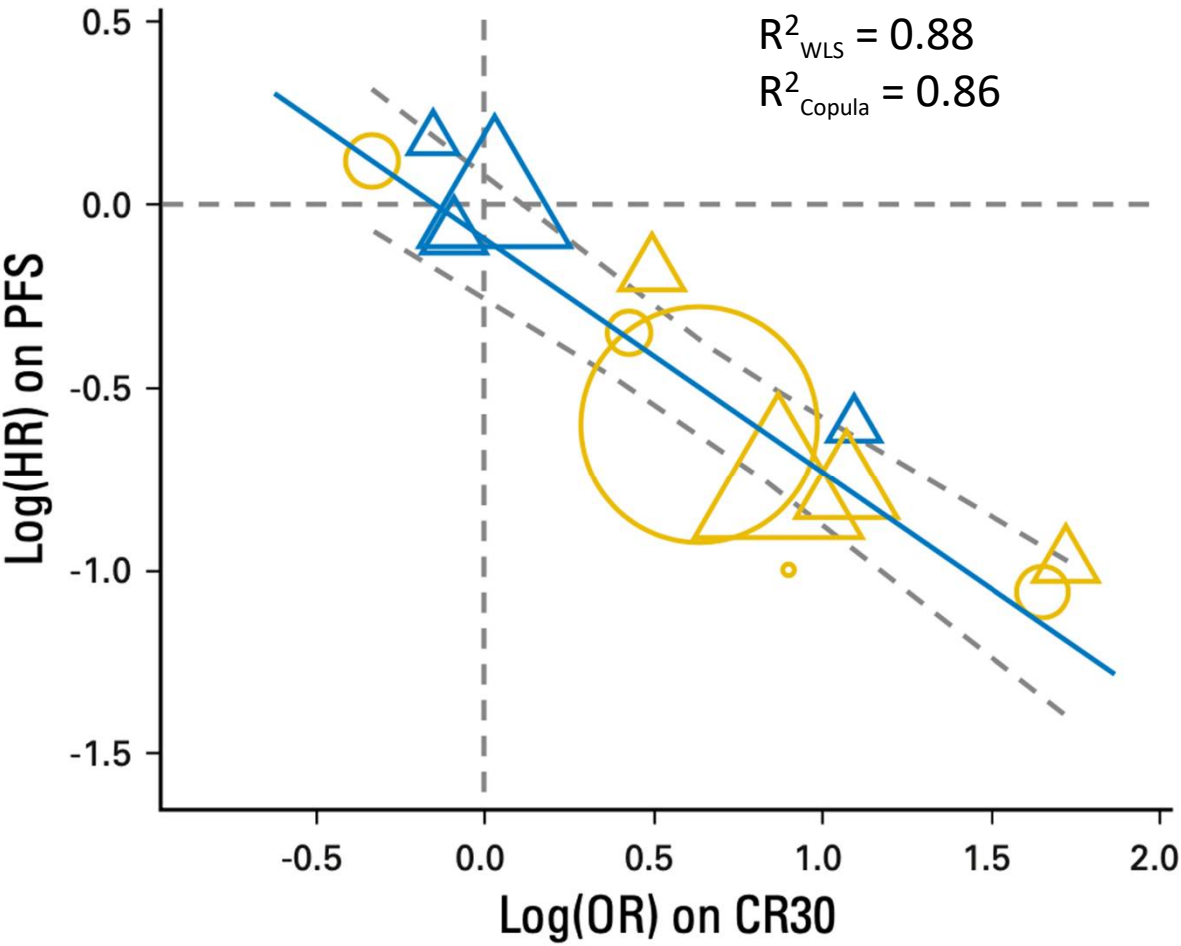
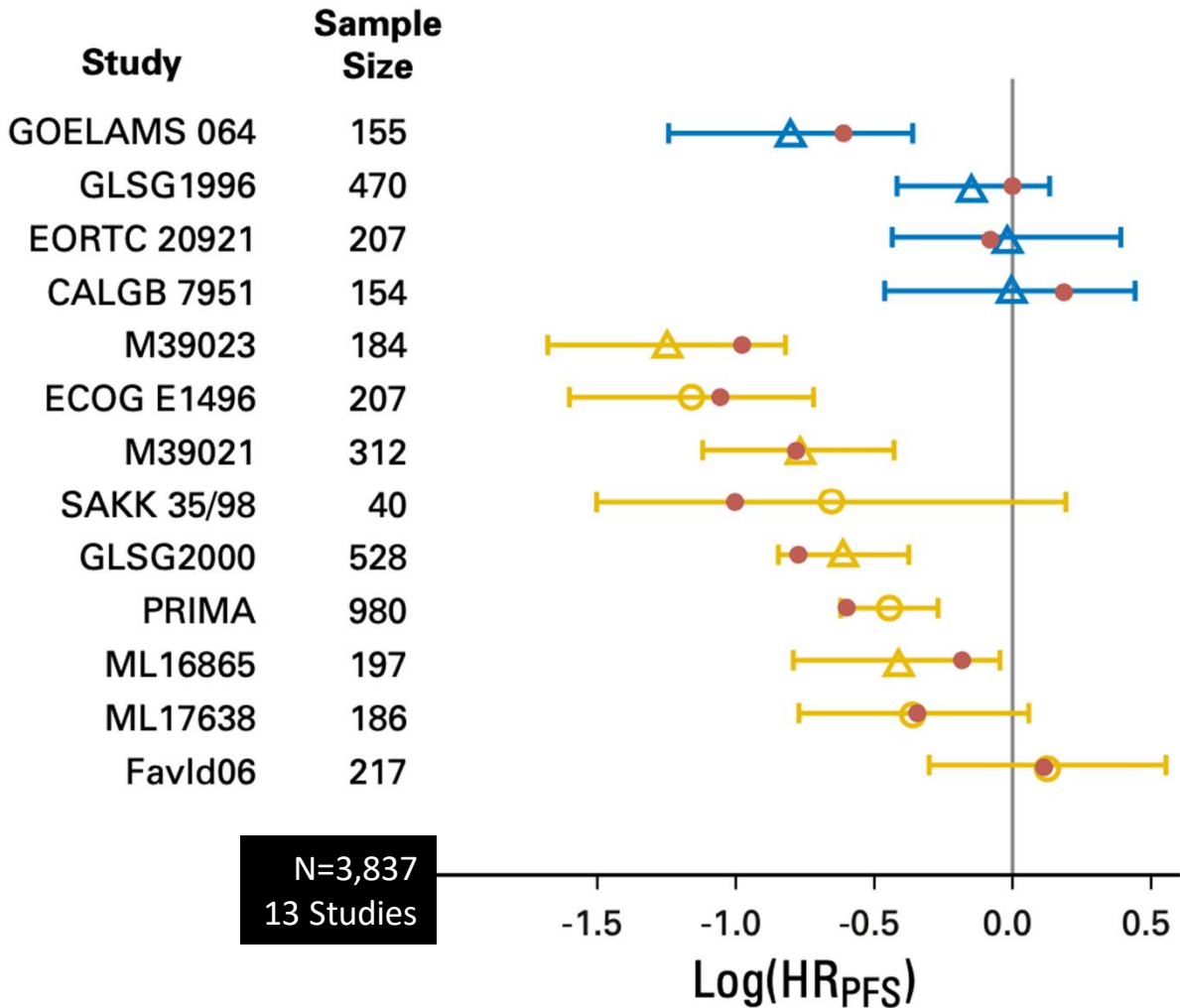
Follicular Lymphoma: Survival by Age, Stage, Tx Period

Population-based Dutch Registry Data



Use of CR rate at 30 mon in Follicular Lymphoma

Disease-specific median PFS: 6-8 years



Shi Q et al., J Clin Oncol 2016; 35: 552. Gold indicates rituximab trials; blue, non-rituximab trials; triangle, induction trial; and circle, maintenance trial.

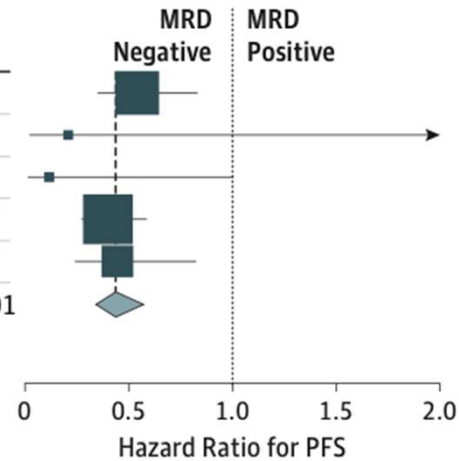
Measurable residual disease (MRD) in MM

Munshi et al., JAMA Oncol. 2017; 3: 28

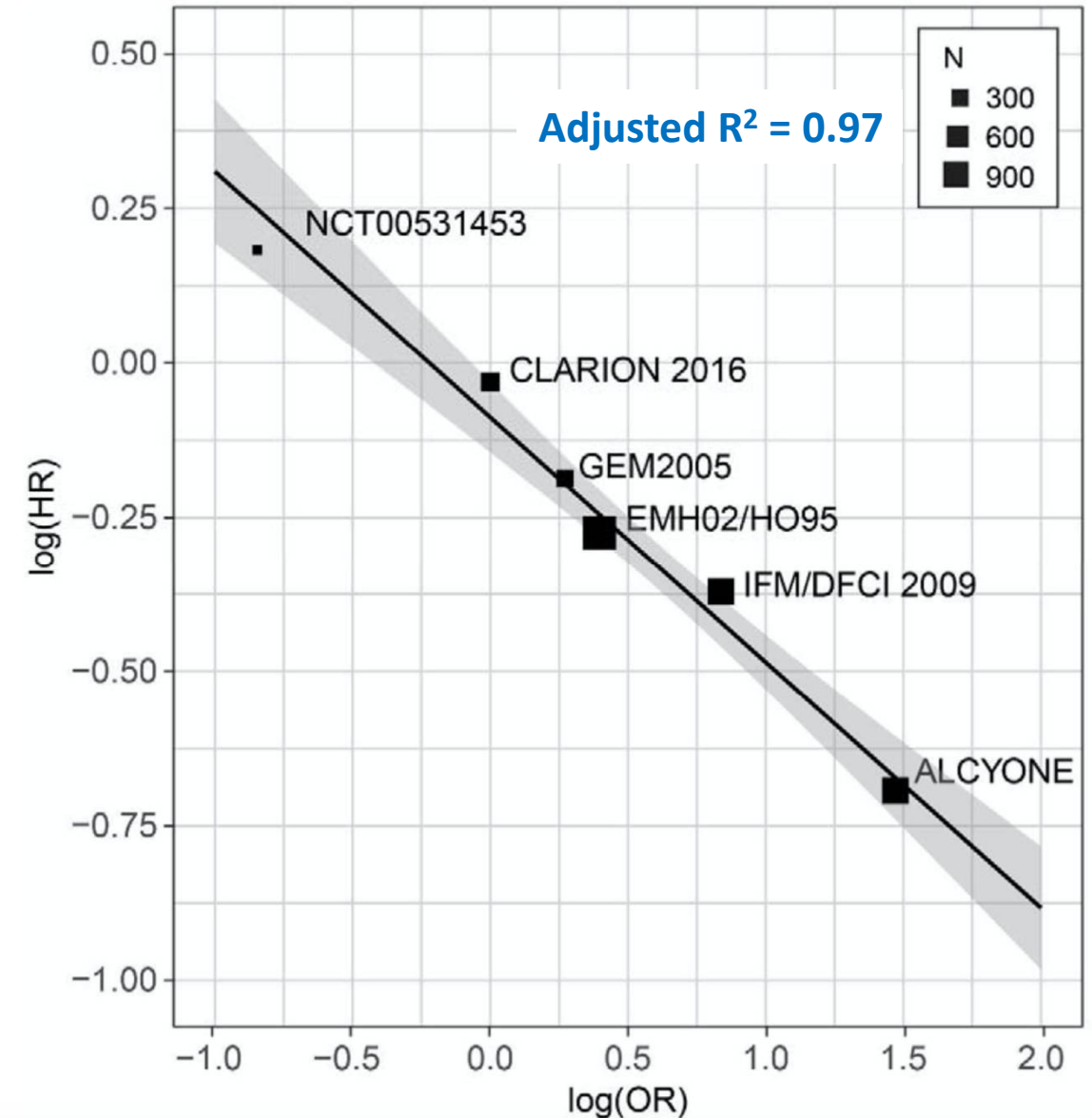
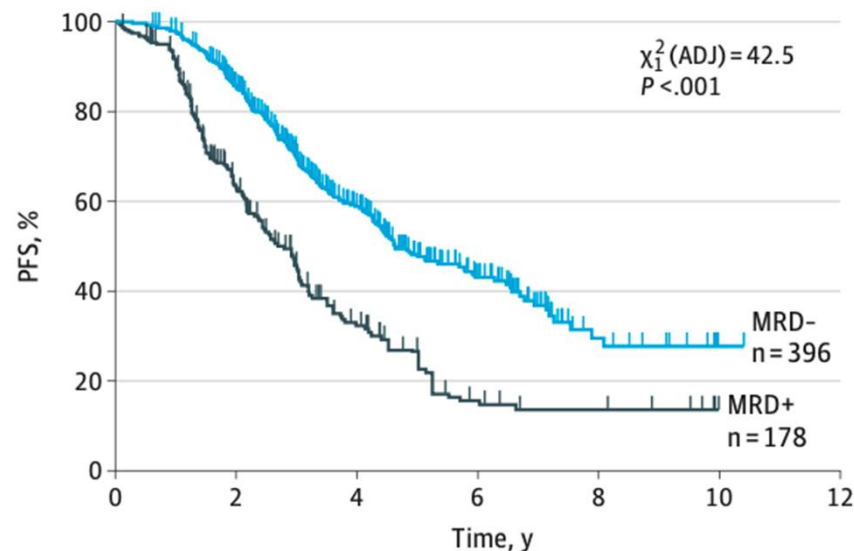
A CRs only: OS hazard ratio forest plot

Study

Rawstron et al,²⁸ 2002
 Swedin et al,⁸ 1998
 Paiva et al,²⁵ 2011
 Paiva et al,²⁶ 2012
 Fukumoto et al,³¹ 2016
 Overall HR, 0.44 95% CI, 0.34-0.56, $P < .001$



C CRs only: OS by MRD status



Avet-Loiseau H et al., Clin Lymphoma Myeloma Leuk. 2020; 20: e30

Summary

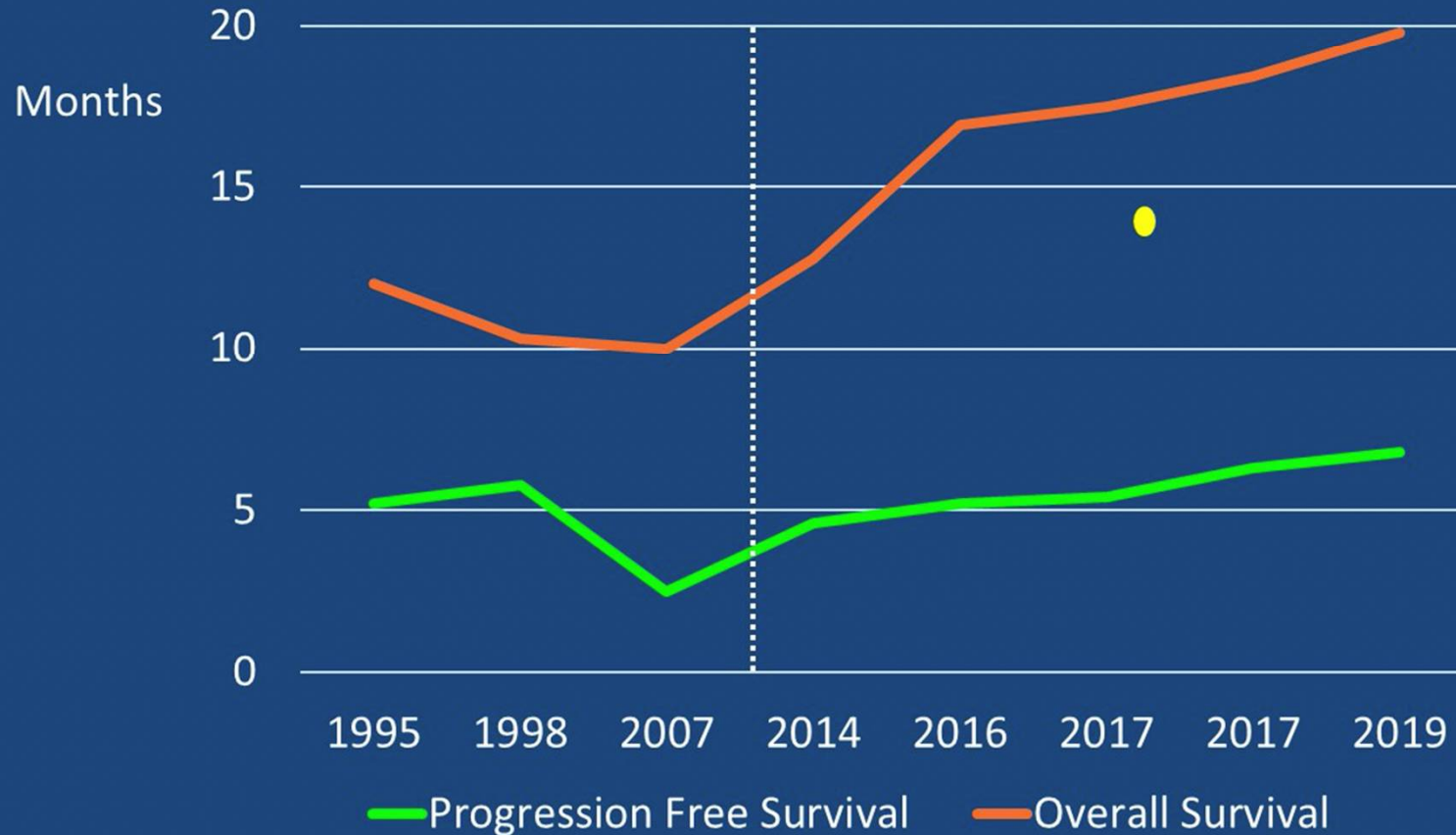
- Overall survival cannot serve as primary endpoint in all indications
 - Past successes leading to long OS times and larger choice of treatment alternatives lead to significant difficulties for new clinical trials
- Most important: The primary endpoint cannot be assessed in isolation of other endpoints or the disease context.
 - PFS plus OS (trend)
 - Other secondary endpoints, in some cases also PFS2, are also relevant
 - Safety and tolerability are always a key element
- Alternative endpoints are valid if correctly developed
 - Duration and available next-line treatments are key factors to understand the relationship between OS and alternate endpoints
 - New alternate endpoints must be carefully validated with evidence across different trials for the specific population and treatment modality
 - Specific biases, like measurement errors, assessment and attrition bias or informative censoring must be controlled
- Monitoring long-term trends in population-based registries is a valuable tool for the overall regulatory strategy and to identify if any systemic biases have occurred in past approvals

Backup



Discordant Evolution of PFS and OS in Soft-Tissue Sarcomas

Progression Free- and Overall Survival in metastatic STS treated with **Doxorubicin** 75 mg/m², in successive randomized phase 3 studies



- Note that GIST patients are not included since 2000
- GIST's are very insensitive to Doxorubicin

Verweij, Lancet, 2004

PRESENTED AT: **2019 ASCO**
ANNUAL MEETING

#ASCO19
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PRESENTED BY: Jaap Verweij

Santoro A et al, *JCO* 1995, Nielsen OS et al, *BJC* 1998, Lorrigan P et al, *JCO* 2007, Judson I et al. *Lancet Oncol* 2014, Ryan Ch et al. *J Clin Oncol* 2016, Seddon B et al. *Lancet Oncol* 2017, Tap WD et al, *Lancet Oncol* 2017, Chawla SP et al, *JCO* 2017

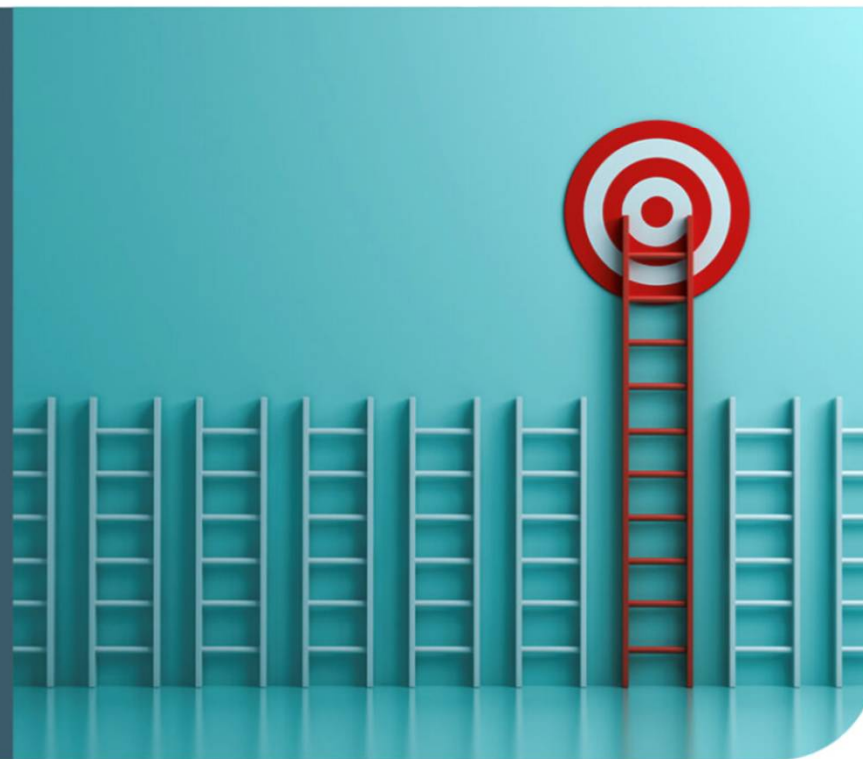


CDDF MULTI-STAKEHOLDER WORKSHOP

Endpoints in Cancer Drug Development

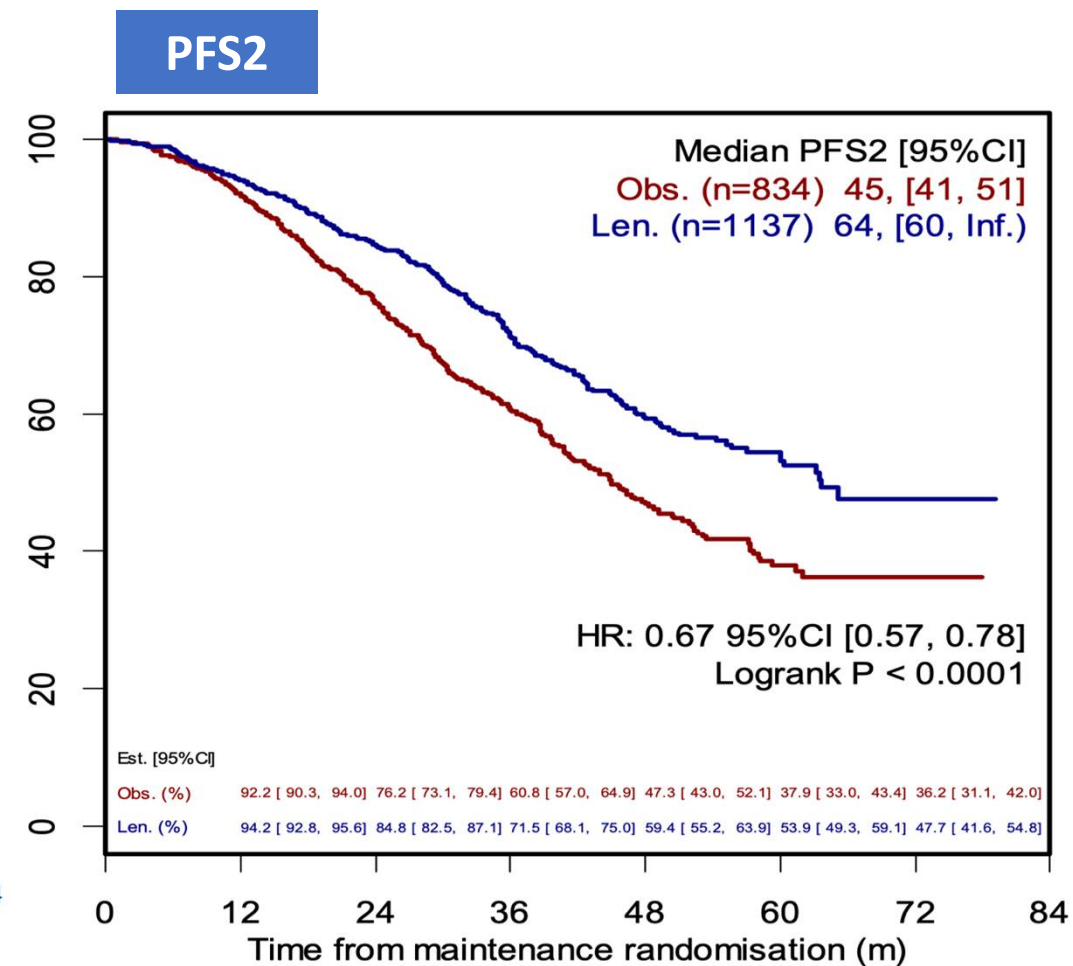
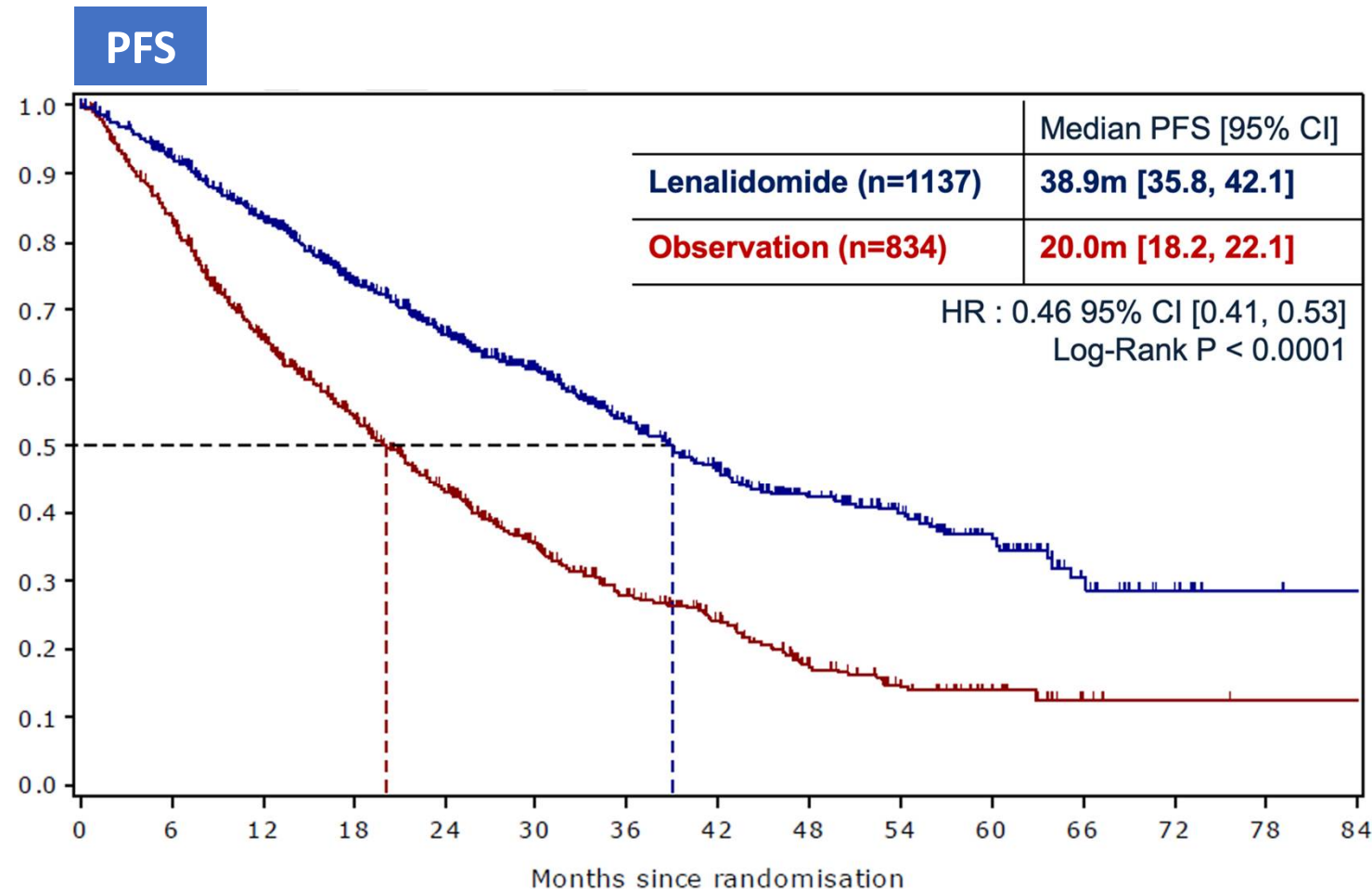
26 - 28 April 2021

ONLINE WORKSHOP

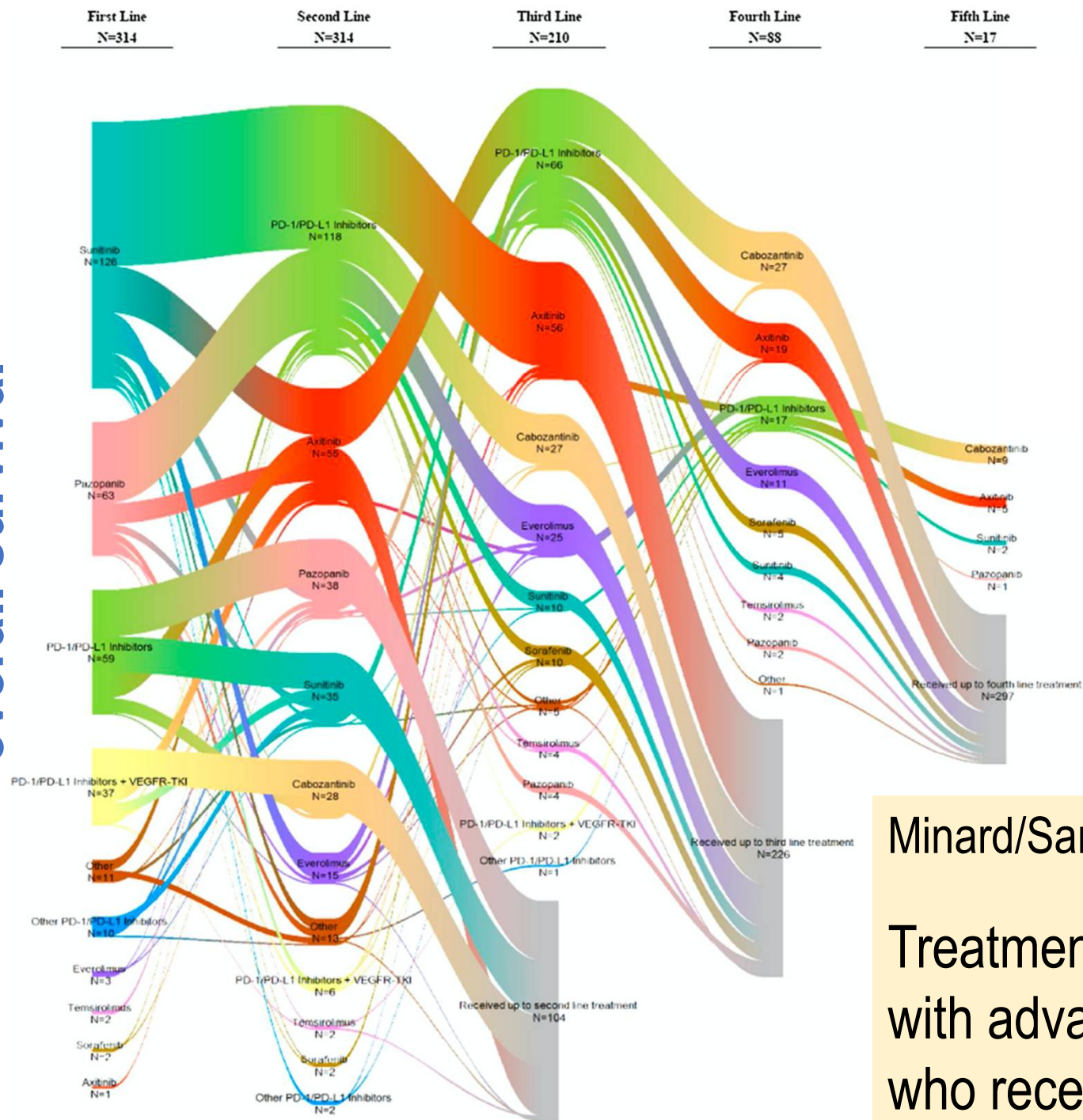


PFS and PFS2 in a large MM Trial

UK Myeloma XI Study



Effect of subsequent treatments on overall survival



Minard/Sankey Flow Chart:

Treatment sequence of 314 patients with advanced renal cell carcinoma who received IO therapy in one line



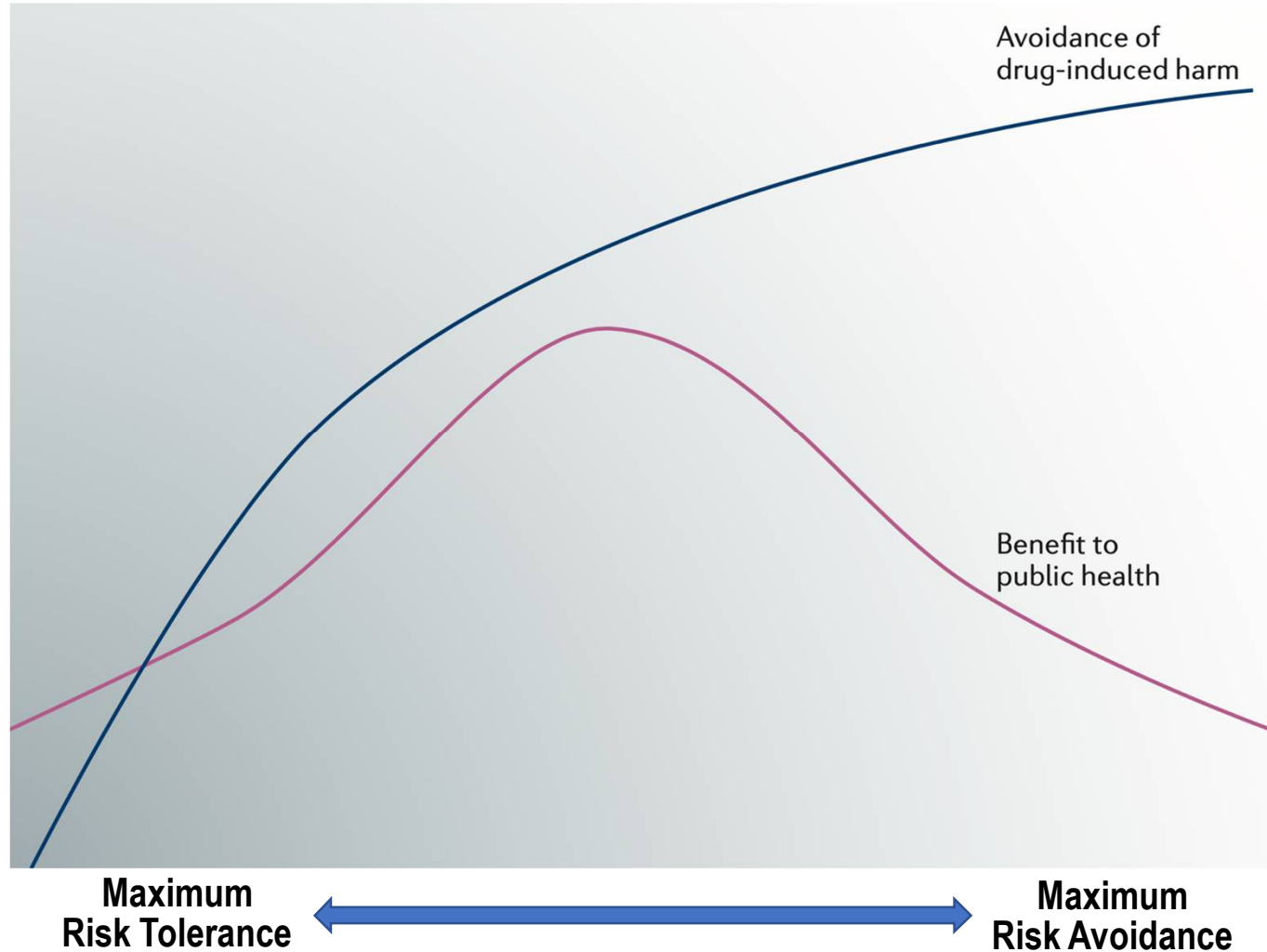
Kronos Bio Announces Phase III Trial of Entospletinib in *NPM1*-Mutated AML

SATURDAY, MARCH 13, 2021

Kronos Bio says it has reached an agreement with the U.S. Food and Drug Administration (FDA) to launch a phase III clinical trial evaluating its selective spleen tyrosine kinase inhibitor entospletinib for the treatment of patients with *NPM1*-mutated acute myeloid leukemia (AML) with a primary endpoint of measurable residual disease (MRD) negativity.

Kronos Bio's trial – the first to test a treatment's efficacy in patients with AML based on a faster endpoint of MRD-negativity instead of overall survival or time to relapse – will enroll 180 adult patients with newly diagnosed *NPM1*-mutated AML.

Balancing Risk Tolerance and Risk Avoidance



All stakeholders need to collaborate to balance

- *Patients' need for helpful treatment options*
- *Pharmaceutical innovation*
- *Avoidance of harm to patients and society*