MHRA
Regulating Medicines and Medical Devices

Regulatory Issues in Survival Analysis

Dr Yolanda Barbachano

Medicines and Healthcare Products Regulatory Agency

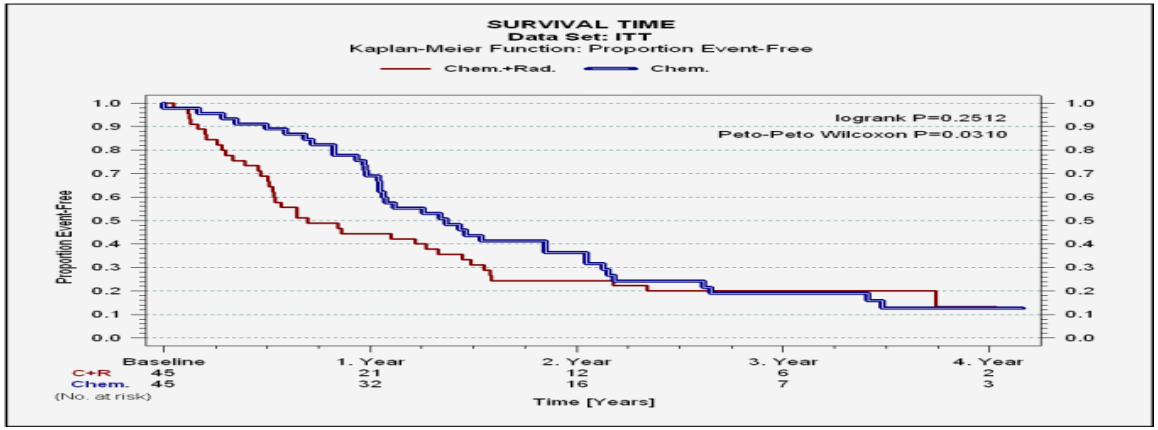
Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MHRA.

Main Issues

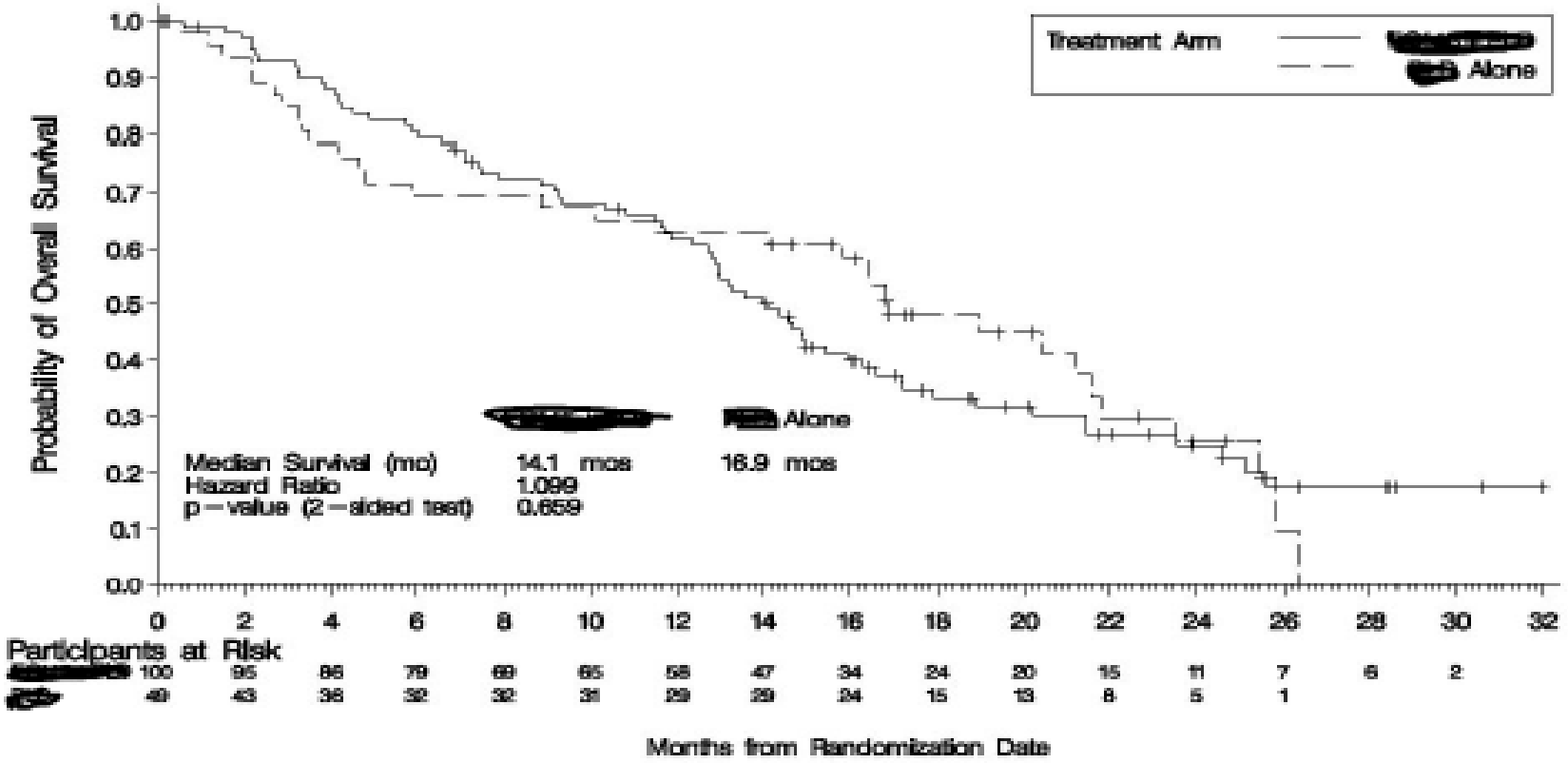
- Summary statistics
- Interim analyses
- Missing data
- Switching treatments

Summary Statistics



- Median time to event
- Percentage of subjects event-free at time t
- Hazard ratio

Non-proportional hazards



Proportional hazards

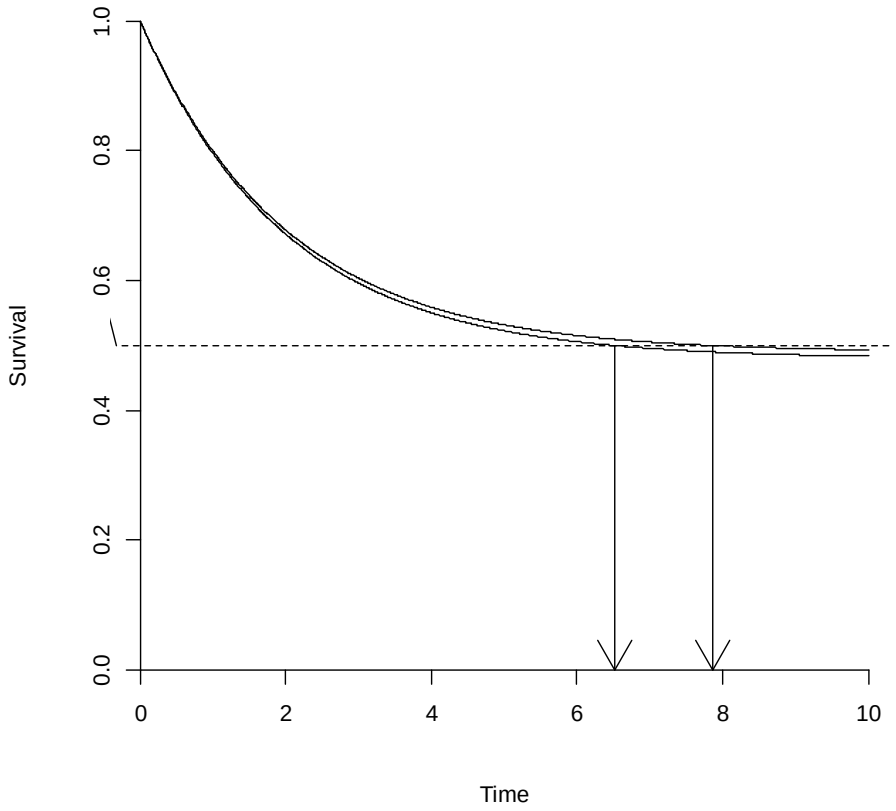
- Hazard ratio useful statistic – but not good enough on its own

- Can be misleading on its own – and can't be compared with other hazard rates without context. For example – hazard ratio of 0.5 – looks impressive???

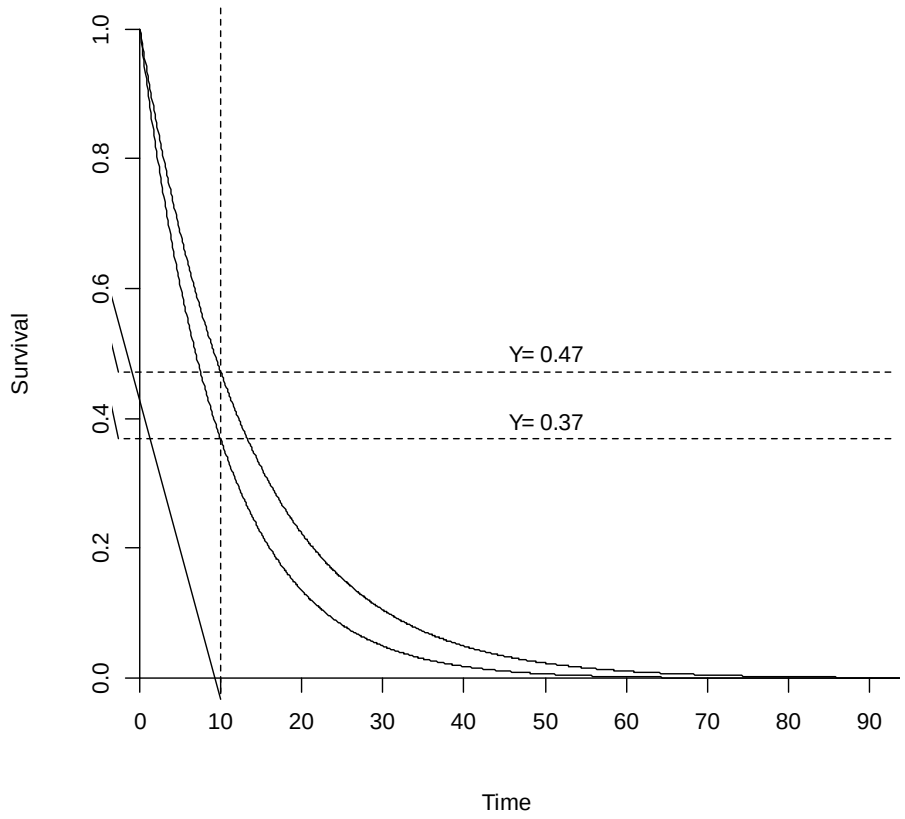
- Halving risk from 0.9 to 0.45 more impressive than from 0.002 to 0.001 – the latter will hardly save any events…

- So more information is needed…

Slowly declining curves

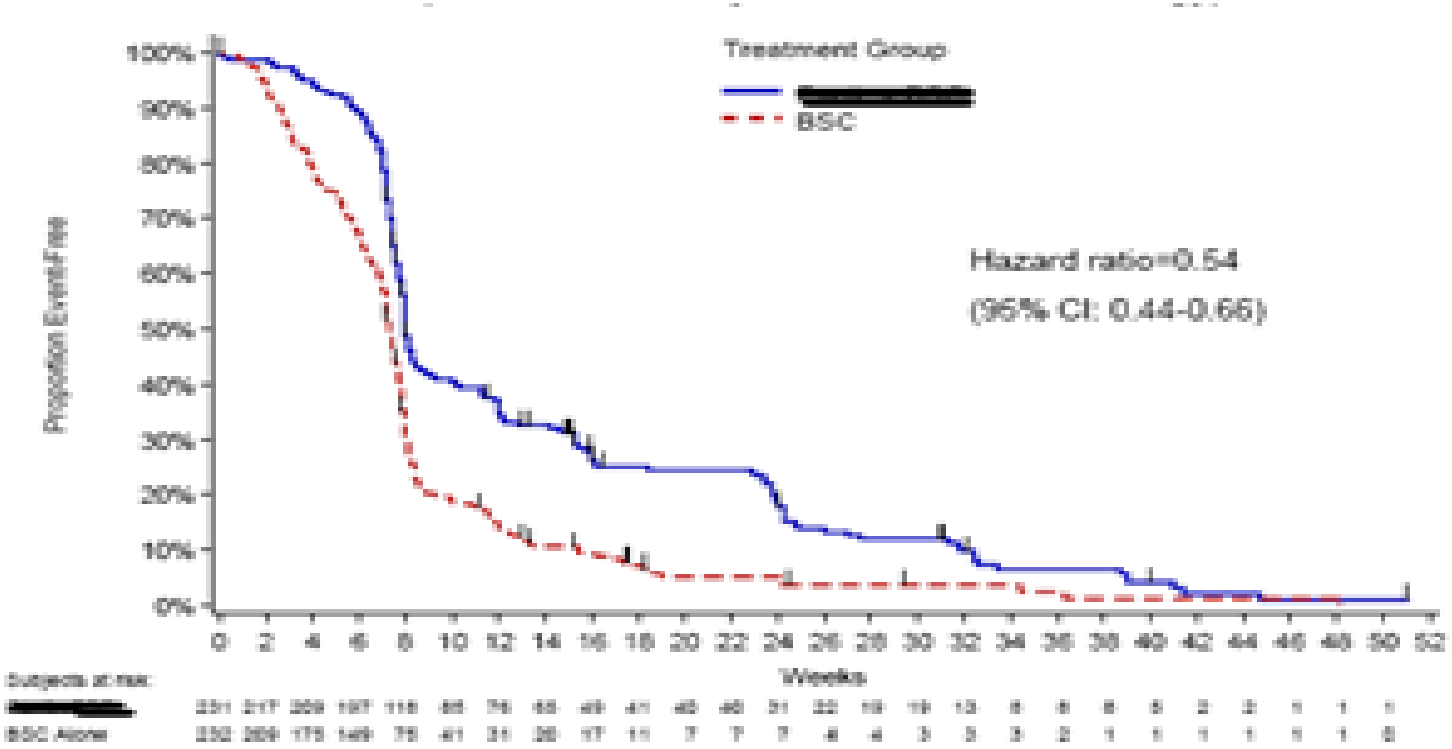


Quickly declining curves



Example

Kaplan-Meier Estimate of Progression-free Survival by Randomized Treatment (All Enrolled Analysis Set, Central Radiology)



Cardiovascular studies

- Typically primary endpoint is a composite of death and hospitalisation analysed using time-to-first event approach.
- However patients often have multiple hospitalisations as well as terminal events
- Each recurrent HF hospitalisation substantially increases the risk of death

- New approaches to analysis include joint frailty models and the win ratio.

Interim Analyses

- More of a concern in oncology than heart disease – much smaller studies
- Usually only 1 pivotal study
- Often open label

- If study stops – very limited data set for B/R assessment
- Results need to be as robust and convincing as possible

Interim Analyses

When planning - need to consider:

- No use stopping for PFS if OS is needed
- If any subgroups of interest will have enough representation
- If more follow up/patients are needed anyway – e.g. safety endpoints

Interim Analyses

- If study stops for success at interim – limited data for benefit-risk assessment
- Results at this point should be representative of whole population
- Fewer patients with long follow up - better than many patients with short follow up

- E.g. If 1000 patients are randomised and 250 events are required for the final analysis (25% maturity), then interim when 125 events have been observed on the first 500 patients randomised

Missing Data

- Often overlooked in time to event trials
- But censored patients considered to have similar survival to those continuing
- Important to know if censoring ‘informative’ or ‘non-informative’
- Imbalance in informative censoring gives cause for concern

Non-informative censoring

- Censoring caused by the study design:
- Study finished and event not reached
- Planned 2-year follow-up only – event not reached
- Study planned for certain number of events
- Imbalance in non-informative censoring is not a concern – just reflects different efficacy of treatment (so usually good if more censoring in treatment group).

Informative censoring

- The fact a patient is censored gives information about the chances of having an event. Censoring not caused by the study design:
- Took rescue medication (maybe should count as event?)
- Trial withdrawal
- Moved away
- Patient lost to follow-up??

Informative censoring

- It is not possible to judge if censoring is informative – e.g. could decision to move away be based on progress of condition?

- Safest policy to assume all informative unless caused directly by trial design.

- Imbalance in informative censoring is cause for concern – could lead to bias

Sensitivity analyses

- Sometimes some patients are censored, but it might also be a reasonable approach to say they may have had an event

- e.g. rescue medication use, adverse event causes discontinuation

- Sensitivity analysis can provide reassurance that the censoring had no real influence on the results

Interval censoring

- This can arise in trials where events can only be seen at visits (e.g. PFS). So we know the event occurred – but we don't know exactly when, only a range.

- Doesn't cause important bias as long as the visit schedule is the same for both groups and is strictly followed.

- If there are lots of unscheduled visits bias can be caused (especially in an open trial).

- A sensitivity analysis where all events assigned to next scheduled visit can correct this.

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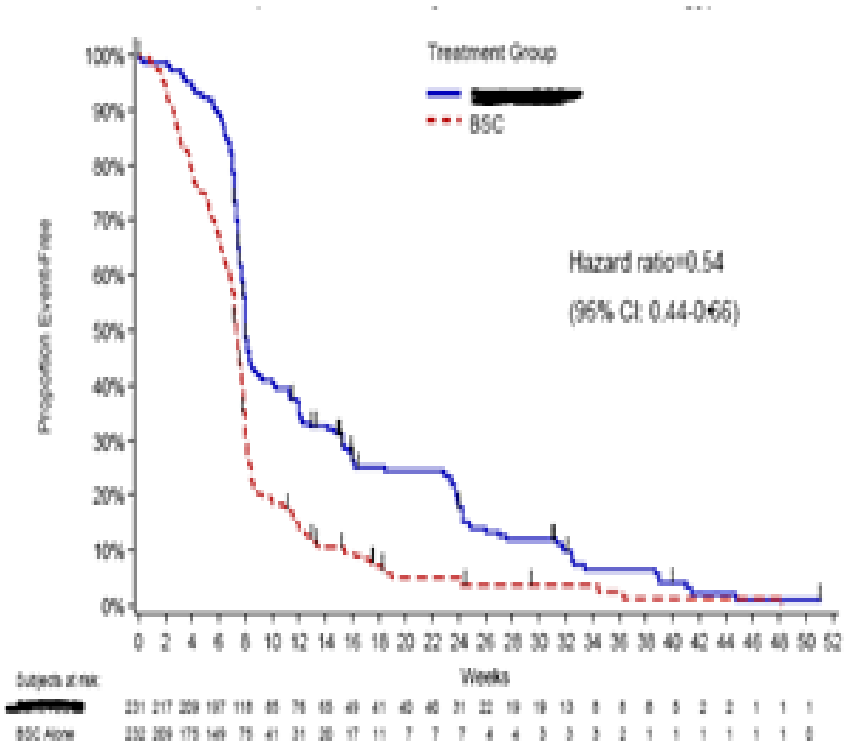
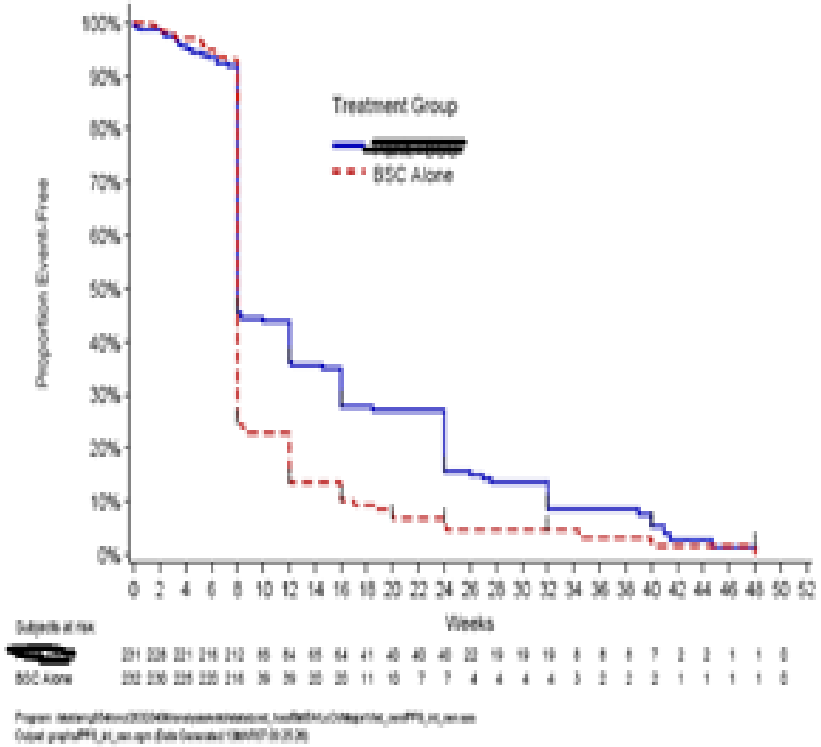


Kaplan-Meier Estimates of Progression-free Survival Imputing Radiologic Progression at the Closest Scheduled Assessment Time Point



Switching Treatments

- Mainly an oncology problem
- Often both PFS and OS are needed to demonstrate a positive B/R – however patients often treated with different treatments at PD:
  - Patients on control swap to investigational
  - Patients on both treatments go to next line therapy as per local guidelines
- No longer comparing just new versus control

Switching Treatments

- Ideally both OS and PFS show benefit of new drug regardless of switching
- But often the benefit in PFS is no longer seen in OS – switching usually blamed
- Modelling approaches to try and correct for this are of limited use - rely on unrealistic assumptions
- Improvement in PFS would be expected to create improvement is OS unless subsequent treatment very unbalanced (which needs explaining)

Switching Treatments

- Occasionally the opposite happens: More treatment effect on OS than PFS

- Could be the result of a very efficacious next line treatment

- Patients with shorter PFS swap earlier – making a bad treatment look good

Conclusions

- Important to consider shape of curve – summary statistics
- Interim analyses: limited but representative dataset
- Consider possible bios by informative sensoring
- Inconsistencies between PFS and OS need to be investigated. Not enough to blame switching.