Comparison of clinical development plans for a confirmatory trial with subpopulation selection

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Question

Setup:

- Phase I done $\Rightarrow$ bring new drug efficiently to registration.
- Primary endpoint: **overall survival** (OS).
- **Binary** biomarker $\Rightarrow$ defines potential subpopulation.

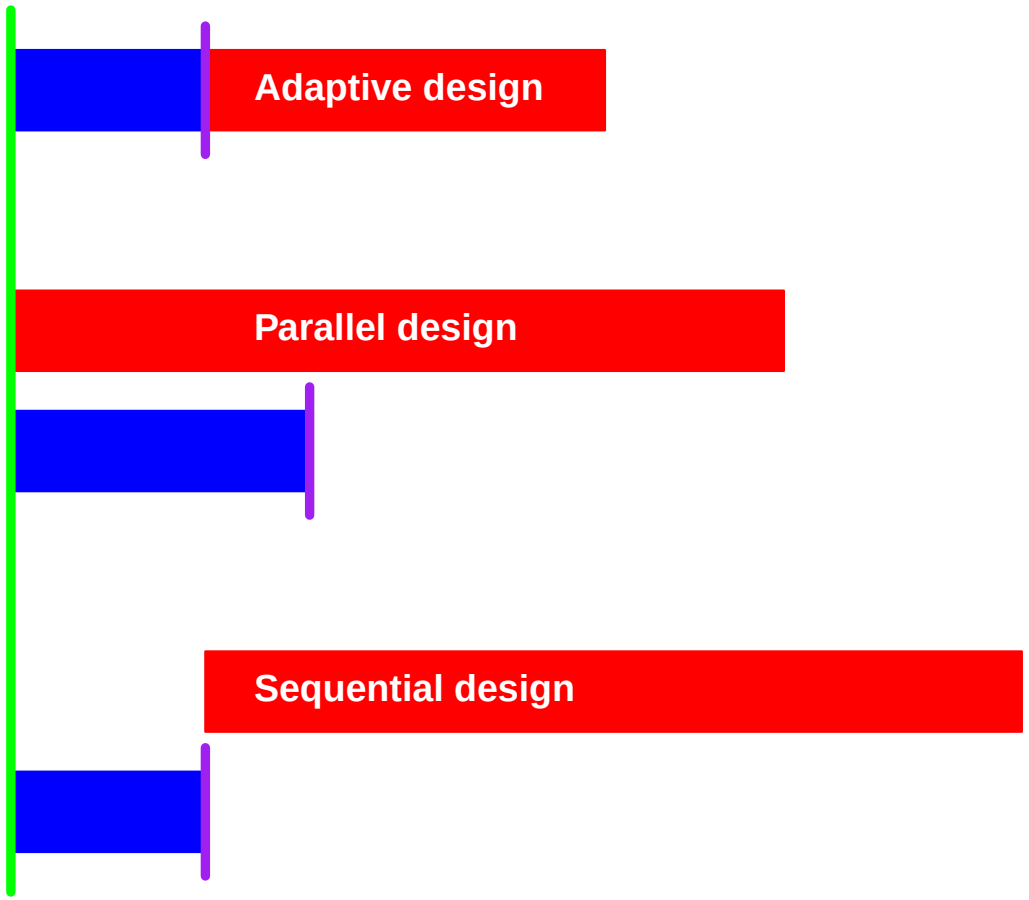
Questions to be asked in clinical trial:

1. Effect in full population?
2. Effect in subpopulation?
3. Effect in full and subpopulation, but enhanced in subpopulation?

Select at interim which scenario to pursue:

- Based on **quick** endpoint, e.g. progression-free survival (PFS).
- Maintain integrity of trial, i.e. protect (overall) type I error, for each way forward after interim.

Potential clinical development plans



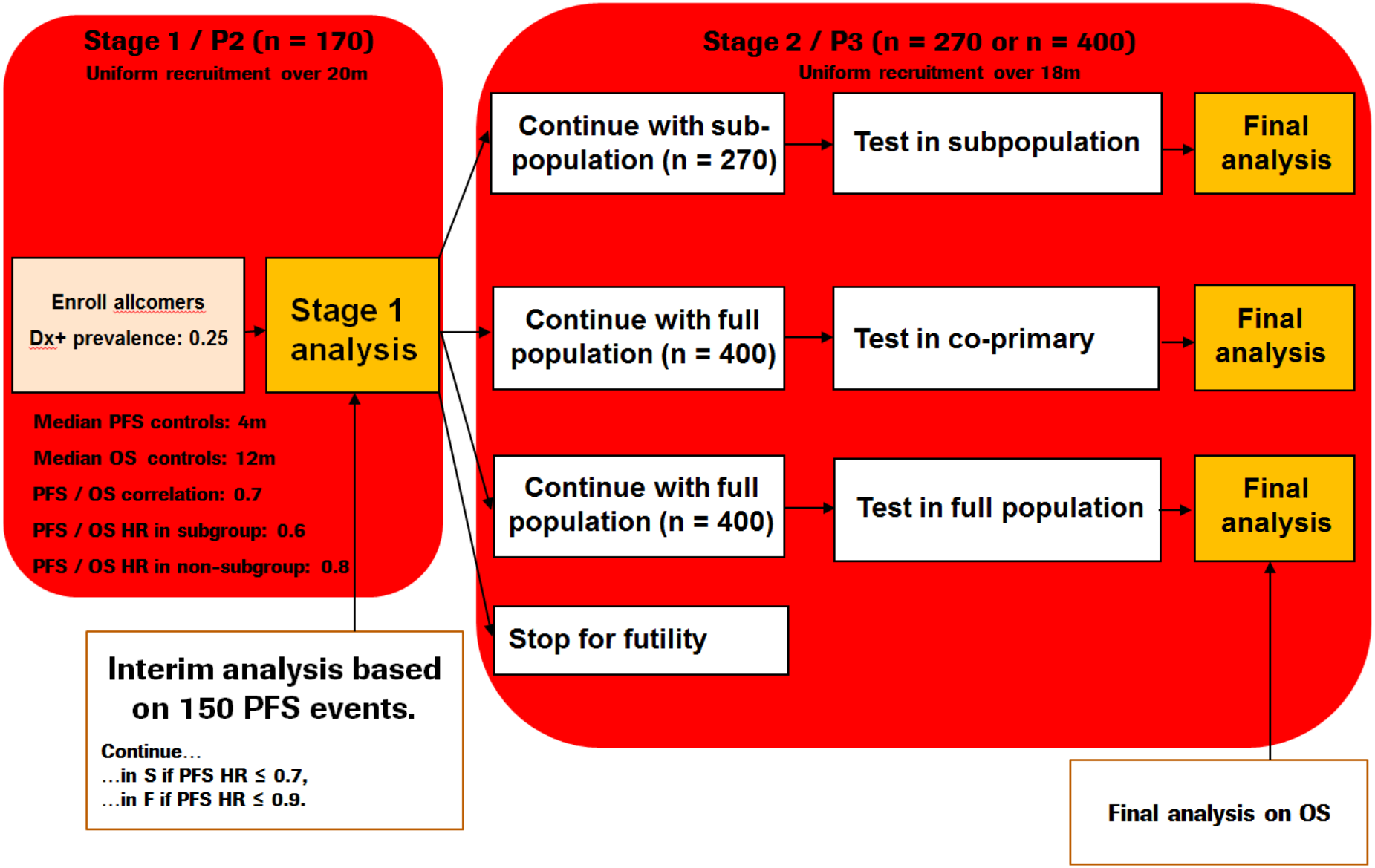
Final analysis combines data from Stage 1 & Stage 2.

Trial final analysis uses data from P3 only. P3 informed by P2 results.

Trial final analysis uses data from P3 only.

- Stage 1 = Phase II
- Stage 2 = Phase III
- Randomization
- Interim analysis

Base case assumptions



Base case assumptions

Base case assumptions:

- **Realistic** scenario in oncology.
- Interim decision instantaneously.
- **No white space** between Phase 2 and Phase 3 in sequential.
- **Accrual rate kept constant** in parallel $\Rightarrow$ longer recruitment time, as we need to fill two trials $\Rightarrow$ delayed interim.
- Exponential PFS and OS times with pre-specified correlation, Michael and Schucany (2002).

Base case assumptions

Interim decision rule: Set targets for PFS hazard ratio at interim:

- Continue in F if PFS hazard ratio ≤ 0.9.
- Continue in S if PFS hazard ratio ≤ 0.7.

Features:

- Easy interpretable and communicable.
- Corresponds to decision based on z-statistic since variance used to normalize based on pre-specified fixed number of events.

Co-primary endpoint: Correct for multiplicity using Hochberg's correction, as for adaptive design. See Jenkins et al. (2011). **Fair** comparison.

Power & timelines

Tune **recruitment** and **cutoffs** such that:

- Adaptive & sequential: Recruitment to Phase II / Stage I has finished prior to PFS interim cutoff.
- Parallel: Recruitment to Phase II has finished prior to PFS interim cutoff.
- Recruitment to Phase III / Stage II has finished prior to OS final cutoff.

Tune **number of events** such that:

- Sum of power to reject either null hypothesis is $\geq 80\%$.
- Stage I and II OS cutoffs are aligned.
- Cutoffs for OS final analysis are aligned in full and subpopulation.

Sequential and parallel: need more events as we do not reuse Phase 2 data.

Metrics

"Traditional" metric in statistical literature: assumptions $\Rightarrow$ power.

Metrics useful when **planning a study**:

1. Define targeted power (80%).
2. Vary patient numbers and/or recruitment rate (# centers) and explore
   - Time to interim PFS cutoff,
   - Time to final OS cutoff,

   among designs that reach targeted power.

"Traditional model": sequential design

Applicable if **not yet well-defined subgroup** at start of Phase 2:

- Still more than one marker to explore after Phase 1.
- Marker still under development.

Biomarker-unrelated: want to make **fully informed** decision at end of Phase 2.

Run randomized Phase 2, analyze data, decide whether to continue with a Phase 3

- in F and analyze in F only,
- in F and analyze in F and S (co-primary),
- in S only,
- without a Phase 3 (stop for futility).

Phase 3:

- Separate trial, do **not re-use data from Phase 2** in final analysis.
- Power: taking into account Phase 2! Power of entire program.
- Get result at final analysis of this trial.
- To get 80% power $\Rightarrow$ need more events $\Rightarrow$ need to wait longer.

Resulting timelines

	Sequential Seamless
PFS interim	26.7m
Final OS for Phase 2 patients	Phase 2 data
	not used
Phase 3 Final OS: F only or co-primary	163.4m
Phase 3 Final OS: S only	157.2m
Power	68%

Parallel Phase II/III design

Applicable if

- **complicated** marker $\Rightarrow$ ongoing assay development and/or cutoff determination.
- **Prevalence** of biomarker subgroup unclear.

Start Phase 2 & Phase 3 at same time. Analyze Phase 2 PFS data and inform Phase 3 whether to

- continue in F and analyze in F only,
- continue in F and analyze in F and S (co-primary),
- continue in S only,
- stop for futility.

Phase 3: still separate trial, Phase 2 data only used to inform Phase 3 $\Rightarrow$ external to Phase 3. **Accepted by regulators**.

Get result at final analysis of Phase 3 by analyzing all Phase 3 data.

Resulting timelines

	Sequential Seamless	Parallel Phase 2 & Phase 3
PFS interim	26.7m	42.3m
Final OS for Phase 2 patients	Phase 2 data not used	separate Phase 2 data used to inform Phase 3
Phase 3 Final OS: F only or co-primary	163.4m	74.3m
Phase 3 Final OS: S only	157.2m	73.5m
Power	68%	80%

Adaptive seamless design

Various approaches in literature: Brannath et al. (2009), Jenkins et al. (2011), Mehta et al. (2014).

We chose Jenkins et al. (2011) for our comparisons:

- Reasonably **simple** methodologically.
- Parameters to be determined are **easy to interpret and communicate**.
- Decision rule **transparent** and simple.
- PFS in Phase 2, OS in Phase 3 $\Rightarrow$ reflects a **realistic** sequential Phase 2 / Phase 3 scenario.

Phase 2 = Stage 1, Phase 3 = Stage 2.

Details in backup.

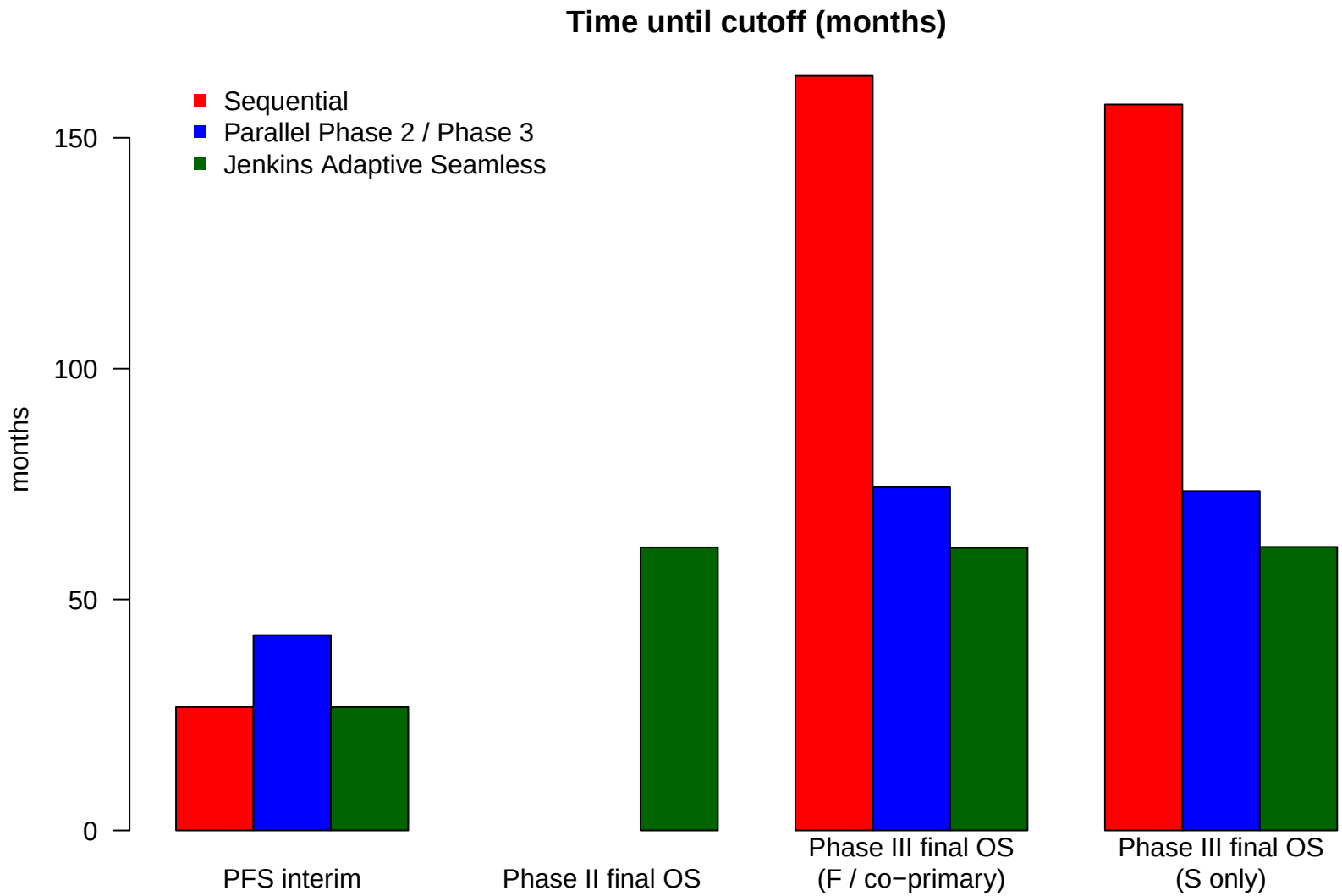
Resulting timelines

	Sequential Seamless	Parallel Phase 2 & Phase 3	Adaptive Seamless
PFS interim	26.7m	42.3m	26.7m
Final OS for Phase 2 patients	Phase 2 data not used	separate Phase 2 data used to inform Phase 3	61.3m
Phase 3 Final OS: F only or co-primary	163.4m	74.3m	61.2m
Phase 3 Final OS: S only	157.2m	73.5m	61.4m
Power	68%	80%	80%

Comments:

- Adaptive design: **tune parameters** so that design has desired features (power, cutoffs).
- Cutoffs for adaptive **aligned**.
- **Massive gain** in time for adaptive: re-use OS data of Stage 1 patients.
- Principle **broadly applicable**, not only for subpopulation selection. GATSBY trial: dose selection at interim. `http://clinicaltrials.gov/show/NCT01641939`

Resulting timelines



Drivers for the trial duration differences?

Sequential **slow**: Start P3 only once P2 is finished. Phase 2 OS data not re-used.

Adaptive faster than Parallel:

- We assume same accrual **rate** in Parallel Phase 2 & 3, but need to fill two trials $\Rightarrow$ interim decision 15.6m later.
- Recruitment rates: Stage 1: 8.5/m; Stage 2: 15/m (S only), 22.2/m (F or co-primary). Parallel **recruits longer at slower rate**. Might compensate through higher Operational effort, e.g. more centers.
- F or co-primary longer for sequential compared to parallel: in parallel, early recruited patients in Phase 3 already started to have events. Sequential: start recruitment from scratch after interim.
- p-value combination for adaptive entails small power loss $\Rightarrow$ duration increase for adaptive (compared to parallel).

Conclusions for timing

Substantial time gains Adaptive $>$ Parallel $>$ Sequential.

Adaptive uses less patients than parallel and is still faster.

Adaptive offers opportunity to substantially accelerate development.

Status of biomarker

Statistical literature: "Assume we have a biomarker that defines S" - typically not realistic **after Phase 1**:

- Biomarker hypothesis not very strong yet.
- Prevalence: Data in limited and highly selected number of patients so far only.
- Most binary biomarkers rely on dichotomizing continuous measurement $\Rightarrow$ estimation of cutoff that determines biomarker positive and negative notoriously difficult.
- Assay performance may vary between Phase I and Phase II/III, or across populations.
- Assay interpretation only consistent for specialized labs $\Rightarrow$ extension to more routine diagnostic?
- Adaptive $\Rightarrow$ filing strategy defined after Phase I $\Rightarrow$ risky.

Sponsor might not feel comfortable to start an adaptive enrichment Phase II/III trial that will potentially run for years, with being blinded to interim decision.

See Rufibach et al. (2015) for detailed discussion.

Overall conclusions

Substantial time gains Adaptive $>$ Parallel $>$ Sequential.

If

- stable binary biomarker and
- accurate idea about subgroup prevalence

after Phase 1 available $\Rightarrow$ opportunity to substantially accelerate development through use of adaptive seamless design.

Outlook: evaluate combination of PFS and OS information for interim decision in Jenkins' design, Brückner et al. (2017).

Acknowledgments

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Jenkins' adaptive seamless design

Null hypotheses: $H_0^{\mathrm{F}}, H_0^{\mathrm{S}}$, and H_0^{FS} (no OS difference in neither F nor S). Protect **familywise error rate**.

Put together building blocks of "standard" statistical methods to set up adaptive trial design.

Raw p-values:

- $p_1^{\mathrm{F}}, p_1^{\mathrm{S}}$: From OS data of pts recruited in Stage 1, computed at end of Stage 2.
- $p_2^{\mathrm{F}}, p_2^{\mathrm{S}}$: From OS data of pts recruited in Stage 2, computed at end of Stage 2.

p-value for co-primary hypothesis via **Hochberg procedure**: under positive dependence compute multiplicity corrected p-value for H_0^{FS}:

$$p_i^{\mathrm{FS}} \quad = \quad \min[2\min\{p_i^{\mathrm{F}}, p_i^{\mathrm{S}}\}, \max\{p_i^{\mathrm{F}}, p_i^{\mathrm{S}}\}], \ i = 1, 2.$$

Hochberg (1988).

Jenkins' adaptive seamless design

Phase 2 PFS (used for interim decision) and Phase 2 OS data (used in final analysis) **correlated** $\Rightarrow$ **inverse Normal *p*-value combination** to combine Stage 1 and Stage 2 OS *p*-values:

Co-primary case – when considering both H_0^F and H_0^S

Testing H_0^F: $w_1 \Phi^{-1}(1 - p_1^F) + w_2 \Phi^{-1}(1 - p_2^F)$

Testing H_0^S: $w_1 \Phi^{-1}(1 - p_1^S) + w_2 \Phi^{-1}(1 - p_2^S)$

Testing H_0^{FS}: $w_1 \Phi^{-1}(1 - p_1^{FS}) + w_2 \Phi^{-1}(1 - p_2^{FS})$

F only case – when considering H_0^F only

Testing H_0^F: $w_1 \Phi^{-1}(1 - p_1^F) + w_2 \Phi^{-1}(1 - p_2^F)$

Testing H_0^{FS}: $w_1 \Phi^{-1}(1 - p_1^{FS}) + w_2 \Phi^{-1}(1 - p_2^F)$

S only case – when considering H_0^S only

Testing H_0^S: $w_1 \Phi^{-1}(1 - p_1^S) + w_2 \Phi^{-1}(1 - p_2^S)$

Testing H_0^{FS}: $w_1 \Phi^{-1}(1 - p_1^{FS}) + w_2 \Phi^{-1}(1 - p_2^S)$

Table 1 in Jenkins et al. (2011). Weights appropriately pre-specified. Need to test all hypotheses involved in closed test.

Jenkins' adaptive seamless design

Bauer and Posch (2004):

IF

selection of Stage 2 population is affected by PFS of Stage 1 subjects

AND

OS follow-up of Stage 1 subjects contributes to their Stage 2 logrank statistic

THEN

this statistic might not have desired null distribution.

Solution in Jenkins et al. (2011): Pre-specify length of OS follow-up of Stage 1 patients $\Rightarrow$ Stage 1 follow up not allowed to be affected by interim outcome $\Rightarrow$ combination test p-values **independent** and **uniform** under H_0.

Jenkins' adaptive seamless design

Closed testing for overall assessment for co-primary case: reject H^{F} only if H^{FS} is rejected, same for S.

Interim decision rule: easy interpretable and communicable.

Set targets for PFS hazard ratio at interim. Our base case:

- Continue in F if PFS hazard ratio ≤ 0.9.
- Continue in S if PFS hazard ratio ≤ 0.7.

Corresponds to decision based on z-statistic since variance used to normalize based on pre-specified fixed number of events.

Jenkins' adaptive seamless design

Biased estimates at final analysis. Assess bias via simulation.

Entire set-up pre-specified in protocol.

Building blocks put together such that overall significance level is controlled $\Rightarrow$ design feasible from regulatory perspective, but requires more discussion $\Rightarrow$ timelines.

Operationally more complex: follow-up of Stage 1 patients pre-specified, need quick interim decision (same for parallel), more upfront interactions with HAs, ...

Interim decision taken by iDMC!

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 3.3.1 (2016-06-21)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages:

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