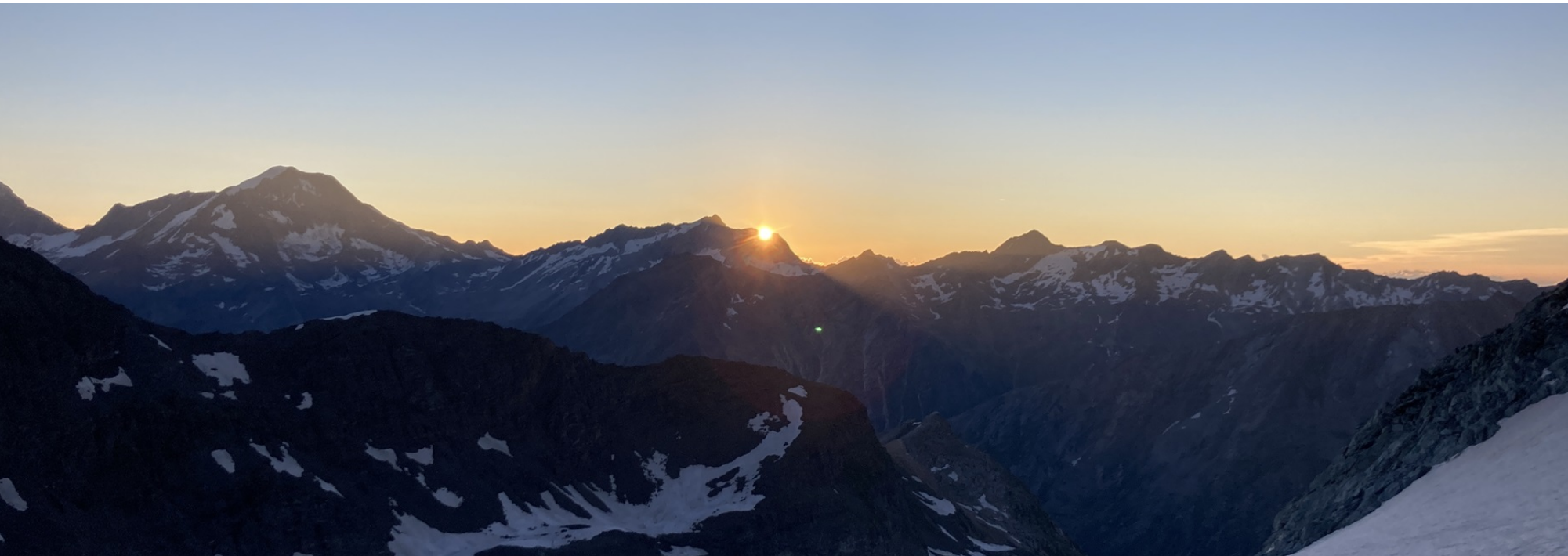
CLL11 – a trial tailored to answer questions from many stakeholders efficiently

Kaspar Rufibach

EFSPI regulatory statistics workshop 2024, Basel



Every successful drug development program has many parents.

Gabi Bieska, Elina Asikanius, Uli Burger, Jörg Maurer.

I have not been involved in the design and running of this trial!

Who can we convince once the data is in?

Regulators are not the only stakeholder.

CLL11 was a platform trial!

Closed testing efficient for multiarm trials.

You need good drug developers!

Impact

Approval and reimbursement of **GAZYVA** in **chronic lymphocytic leukemia** (CLL).

1st Breakthrough Therapy-designated drug to receive FDA approval, Lee et al. (2014).

Clinical publication: Goede et al. (2014).

Statistical publication: Asikanius et al. (2016). Simulation code as supplementary material.

No impact:

More frequent use of closed testing in multiarm trials.

Context at design stage

Context at design stage

CI + Gazyva

2nd generation anti−CD20, experimental

Context at design stage

Chlorambucil

approved standard in Germany (only!)

Cl + Gazyva

2nd generation anti−CD20, experimental

Context at design stage

Chlorambucil

approved standard in Germany (only!)

Cl + MabThera

1st generation anti−CD20, not approved, off−label use

Cl + Gazyva

2nd generation anti−CD20, experimental

2-arm trial G vs. C:

Regulator ☺
Patients ☹
Scientific community / treating physicians ☹
HTA ☹

How to efficiently design a 3-arm trial?

Null hypotheses and type I error protection

Pairwise null hypotheses:

$$\begin{aligned} H_{0,\text{G vs. C}} &: \text{HR}_{\text{G/C}} = 1, \\ H_{0,\text{R vs. C}} &: \text{HR}_{\text{R/C}} = 1, \\ H_{0,\text{G vs. R}} &: \text{HR}_{\text{G/R}} = 1. \end{aligned}$$

All hypotheses of interest.

Design must **strongly** protect **familywise error rate** (FWER):

$$P(\text{reject at least one true null hypothesis}) \leq \alpha$$

irrespective of which null hypothesis are true.

Primary endpoint: **progression-free survival**.

Closed testing:

General principle to construct testing strategy that protects FWER.

$$\boxed{H_{0,\text{G vs. C}} : \mathrm{HR}_{\text{G/C}} = 1} \quad \boxed{H_{0,\text{R vs. C}} : \mathrm{HR}_{\text{R/C}} = 1} \quad \boxed{H_{0,\text{G vs. R}} : \mathrm{HR}_{\text{G/R}} = 1}$$

$$\Uparrow$$

$$H_{0,\text{G vs. C}} \cap H_{0,\text{G vs. C}} \cap H_{0,\text{G vs. C}}$$

$$\Uparrow$$

$$\boxed{H_{0,\text{global}} : \mathrm{HR}_{\text{G/C}} = \mathrm{HR}_{\text{R/C}} = \mathrm{HR}_{\text{R/G}} = 1}$$

Reject $H_{0,\text{global}}$ at $\alpha \Rightarrow$ each individual hypothesis **can be tested at α**.

If you have enough power to test $H_{0,\text{global}}$ – virtually **free lunch**!

Assumptions

Global significance level: $\alpha = 0.05$.

Alternative hypotheses and power for sample size planning:

- **98%** power to detect $\mathrm{HR}_{\mathrm{G/C}} = 12/27 = \mathbf{0.444}$,
- 80% power to detect $\mathrm{HR}_{\mathrm{R/C}} = 12/20 = \mathbf{0.600}$,
- 80% power to detect $\mathrm{HR}_{\mathrm{G/R}} = 20/27 = \mathbf{0.741}$.

Why 98%?

- Futility and efficacy interim for R vs. C at final analysis of G vs. C $\Rightarrow$ 30% adequate information fraction to perform interim at.
- Enough **safety follow up** for C for benefit-risk.
- Randomization to arm G expected to have terminated at G vs. C analysis cutoff.

Four potential strategies

1. **Three separate trials**:
   - Each at $\alpha = 0.05$.
   - Distribute patients on three trials $\Rightarrow$ use each patient for **one** comparison only.
2. **One 3-arm trial with Bonferroni correction**:
   - Each comparison at $\alpha = 0.0167$.
   - All patients in same trial $\Rightarrow$ use each patient for **two** comparisons.
3. **One 3-arm trial with closed testing, wait until last comparison mature**:
   - Test $H_{0,\text{global}}$ once targeted number of events for **latest** comparison reached.
4. **One 3-arm trial with closed testing, each comparions analyzed once mature**:
   - Test $H_{0,\text{global}}$ once targeted number of events for **first** comparison is reached.
   - Perform other pairwise comparisons once targeted number of events reached.

Metrics

- **Time to regulatory approval of Gazyva**: determined by first cutoff G vs. C.
- **Time to make patients / scientific community / HTA happy**: determined by cutoff G vs. R.

Consideration:

- Closed test in Strategies 3 and 4 induces **power loss** for each pairwise comparison. Quantify power loss, mainly for G vs. R.

Time to regulatory approval for Gazyva

	G vs. C: 0.444	R vs. C: 0.600	G vs. R: 0.741
Three separate trials	**34.4**	39.2	hopeless
Bonferroni	**21.4**	24.3	90.1
Closed testing – last mature	**47.4**	47.4	47.4
Closed testing – first mature	**18.6**	19.4	51.0

Time to make patients / HTA happy

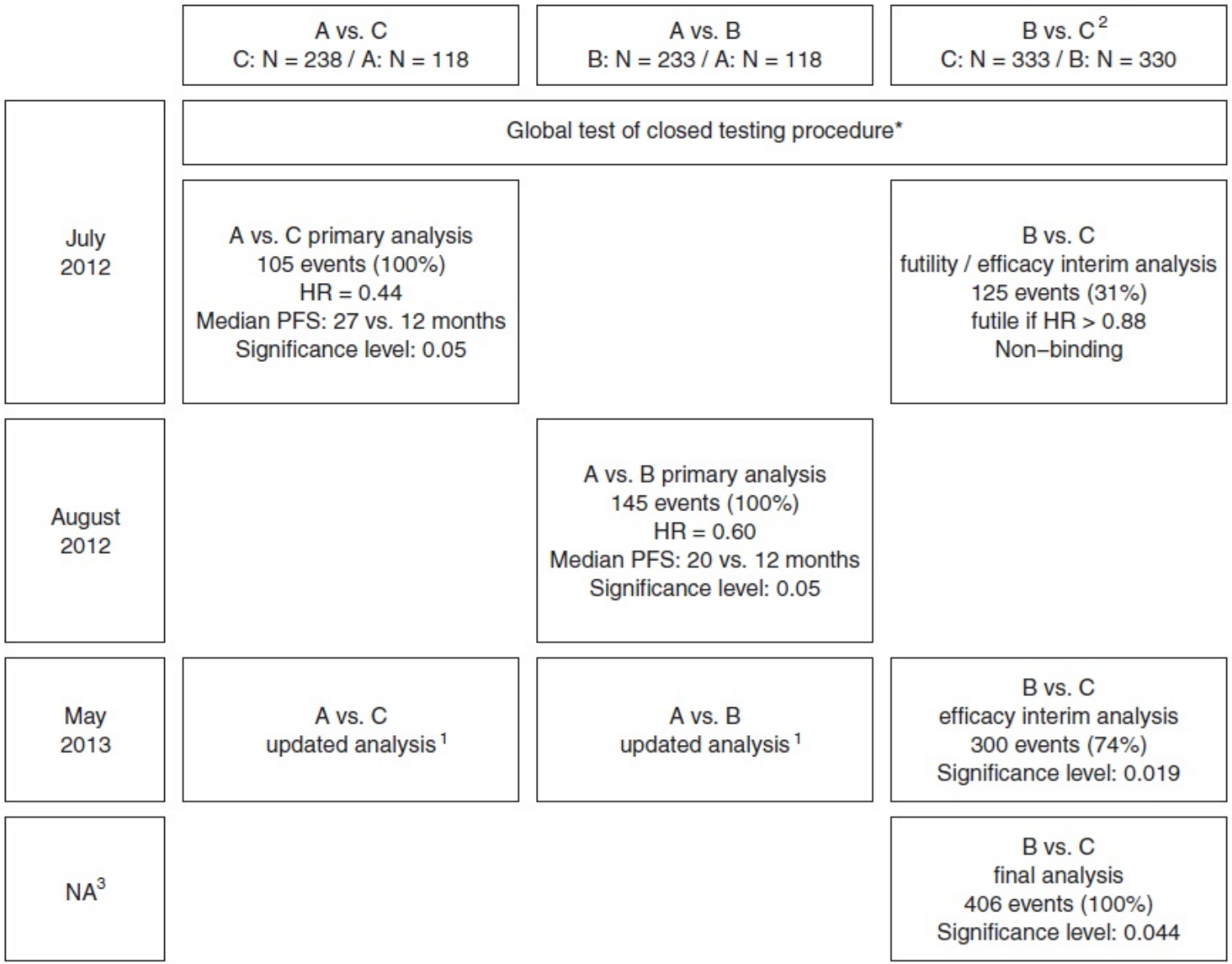
	G vs. C: 0.444	R vs. C: 0.600	**G vs. R: 0.741**
Three separate trials	34.4	39.2	**hopeless**
Bonferroni	21.4	24.3	**90.1**
Closed testing – last mature	47.4	47.4	**47.4**
Closed testing – first mature	18.6	19.4	**51.0**

Last scenario:

- Slight **power loss (1.7%)** compared to 2-arm trial for G vs. R comparison due to global test.
- Compensate through **17** more events.
- Corresponds to **3.8** months delay compared to 2-arm trial.

G vs. R stopped at interim analysis for efficacy.

To pull this off you need good drug developers!


A vs. C
C: N = 238 / A: N = 118
A vs. B
B: N = 233 / A: N = 118
B vs. C[2]
C: N = 333 / B: N = 330
Global test of closed testing procedure*
July 2012
A vs. C primary analysis
105 events (100%)
HR = 0.44
Median PFS: 27 vs. 12 months
Significance level: 0.05
B vs. C
futility / efficacy interim analysis
125 events (31%)
futile if HR > 0.88
Non–binding
August 2012
A vs. B primary analysis
145 events (100%)
HR = 0.60
Median PFS: 20 vs. 12 months
Significance level: 0.05
May 2013
A vs. C
updated analysis[1]
A vs. B
updated analysis[1]
B vs. C
efficacy interim analysis
300 events (74%)
Significance level: 0.019
NA[3]
B vs. C
final analysis
406 events (100%)
Significance level: 0.044

Operational aspects in CLL11

Operational bias:

- Hazard ratios became known over time: $\mathrm{HR}_{\mathrm{G/R}} = \mathrm{HR}_{\mathrm{G/C}}/\mathrm{HR}_{\mathrm{R/C}}$! (under some assumptions).
- Treatment schedule in CLL11 rather fixed once started.
- Define analysis timepoints not only through PFS cutoffs: e.g. all patients needed to be randomized to G prior to cutoff for G vs. C.

Further operational aspects:

- Multiple final / interim analyses on different sets of patients.
- iDMC for interim analyses in G vs. R.
- Independent response review: even more important after G vs. C was unblinded.

Who can we convince once the data is in?

Regulators are not the only stakeholder.

CLL11 was a platform trial!

Closed testing efficient for multiarm trials.

You need good drug developers!

Thank you for your attention.

kaspar.rufibach@gmail.com

Slides can be downloaded on

www.kasparrufibach.ch

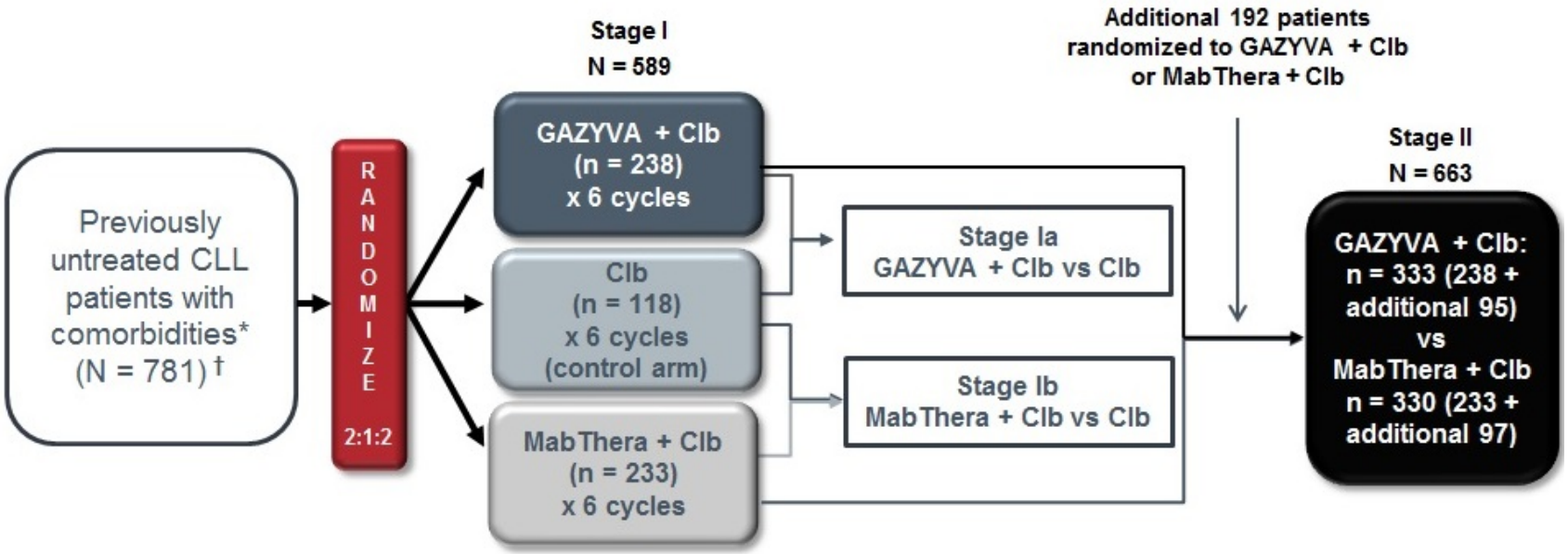
References I

- Asikanius, E., Rufibach, K., Bahlo, J., Bieska, G. and Burger, H. U. (2016). Comparison of design strategies for a three-arm clinical trial with time-to-event endpoint: Power, time-to-analysis, and operational aspects. *Biometrical journal. Biometrische Zeitschrift* **58** 1295–1310.
- Goede, V., Fischer, K., Busch, R., Engelke, A., Eichhorst, B., Wendtner, C. M., Chagorova, T., de la Serna, J., Dilhuydy, M. S., Illmer, T., Opat, S., Owen, C. J., Samoylova, O., Kreuzer, K. A., Stilgenbauer, S., Dohner, H., Langerak, A. W., Ritgen, M., Kneba, M., Asikanius, E., Humphrey, K., Wenger, M. and Hallek, M. (2014). Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N. Engl. J. Med.* **370** 1101–1110.
- Lee, H. Z., Miller, B. W., Kwitkowski, V. E., Ricci, S., DelValle, P., Saber, H., Grillo, J., Bullock, J., Florian, J., Mehrotra, N., Ko, C. W., Nie, L., Shapiro, M., Tolnay, M., Kane, R. C., Kaminskas, E., Justice, R., Farrell, A. T. and Pazdur, R. (2014). U.s. Food and drug administration approval: obinutuzumab in combination with chlorambucil for the treatment of previously untreated chronic lymphocytic leukemia. *Clin. Cancer Res.* **20** 3902–3907.

Backup

CLL11 design

Primary endpoint: **progression-free survival** (PFS).



Assumptions

Global significance level: $\alpha = 0.05$.

Assumed effect sizes:

- $\mathrm{HR}_{\mathrm{G/C}} = 12/27 = \mathbf{0.444}$,
- $\mathrm{HR}_{\mathrm{R/C}} = 12/20 = \mathbf{0.600}$,
- $\mathrm{HR}_{\mathrm{G/R}} = 20/27 = \mathbf{0.741}$.

Assumptions:

- $n = 640$ patients in each strategy.
- Randomize 1:2:2.
- 20pts/m for 2m, 40pts/m for 15m.

Methods

Strategies 1, 2:

- **Compute** number of necessary events.
- **Compute** cutoffs for analyses based on that.

Strategies 3, 4:

- **Unadjusted** analysis: **Compute** number of necessary events and cutoff.
- **Adjusted** analysis: Global test gates pairwise tests. Increase number of necessary events from unadjusted analysis until **simulations** (10^6 runs) yield targeted power.

Analysis cutoffs

			G vs. C	R vs. C	G vs. R
Hazard ratio			0.444	0.600	0.741
Strategy 1:		computed #required events	111	136	349
Three separate trials		computed cutoff (months)	**34.4**	39.2	–
Strategy 2:		computed #required events	136	181	465
3-arm with Bonferroni		computed cutoff (months)	**21.4**	24.3	90.1
Strategy 3:	unadj.	computed #required events	275	303	349
3-arm with		computed cutoff (months)	47.2	47.2	47.2
closed testing	adj.	ass. (G vs. R)/resulting (R/G vs. C) #events	276	303	350
		cutoff (months) corresponding to #events	**47.4**	47.4	47.4
Strategy 4:	unadj.	computed #required events	111	136	349
3-arm with		computed cutoff (months)	18.6	19.4	47.2
closed testing	adj.	assumed #required events	111	136	366
		cutoff (months) corresponding to #events	**18.6**	19.4	51.0
	power	simulated power corresponding to #events	0.974	0.807	0.800
		simulated unadj. power corresp. to #events	0.988	0.809	0.817

Patients for each comparison:

- Strategy 1: 64/128; 64/128; 128/128.
- Strategies 2-4: 128/256; 128/256; 256/256.

Results - power loss

Detailed results in backups.

			G vs. C	R vs. C	G vs. R
Hazard ratio			0.444	0.600	0.741
Strategy 1: **Three separate trials**		computed #required events	111	136	349
		computed cutoff (months)	34.4	39.2	–
Strategy 2: **3-arm with Bonferroni**		computed #required events	136	181	465
		computed cutoff (months)	21.4	24.3	90.1
Strategy 3: **3-arm with closed testing**	unadj.	computed #required events	275	303	349
		computed cutoff (months)	47.2	47.2	47.2
	adj.	ass. (G vs. R)/resulting (R/G vs. C) #events	276	303	350
		cutoff (months) corresponding to #events	47.4	47.4	47.4
Strategy 4: **3-arm with closed testing**	unadj.	computed #required events	111	136	349
		computed cutoff (months)	18.6	19.4	47.2
	adj.	assumed #required events	111	136	366
		cutoff (months) corresponding to #events	18.6	19.4	51.0
	power	simulated power corresponding to #events	0.974	0.807	**0.800**
		simulated unadj. power corresp. to #events	0.988	0.809	**0.817**

Patients for each comparison:

- Strategy 1: 64/128; 64/128; 128/128.
- Strategies 2-4: 128/256; 128/256; 256/256.

Results

Results: with CLL11 strategy,

- save between $\sim$ 3**m** and $\sim$ 29**m** to first cutoff,
- $\sim$ 2% **power loss** for G vs. R, corresponding to **17 events** or $\sim$ 4**m**.

Explore strategy based on closed testing in multi-arm trials.

Paper compares strategies with respect to

- operational complexity,
- operational bias,
- difficulty of inference in pairwise comparisons,
- type I error protection for secondary endpoints.
- Sensitivity analysis: CLL11 assumed quite large effect sizes. Strategy also feasible for smaller effect sizes?

Operational aspects in CLL11

Operational bias: Information from ongoing CT causes changes to participant pool, investigator or patient behavior, or other clinical aspects that affect conduct such that conclusions about efficacy or safety are impacted by differences in data collected post public availability of interim results.

CLL11:

- G vs. C became available quickly.
- Treatment schedule in CLL11 rather fixed once started.
- Define analysis timepoints not only through PFS cutoffs: e.g. all patients needed to be randomized to G prior to cutoff for G vs. C.

Further operational aspects:

- Multiple final / interim analyses on different sets of patients.
- iDMC for interim analyses in G vs. R.
- Independent response review: even more important after G vs. C was unblinded.

R version and packages used to generate these slides:

R version: R version 4.4.1 (2024-06-14 ucrt)

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

Other packages: reporttools / xtable

This document was generated on 2024-08-29 at 17:19:12.