# Follow-up time in clinical trials with a time-to-event endpoint: Redefining the question(s)

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*ISCB43, Newcastle, 22nd August 2022*

Paper written within Oncology estimand WG

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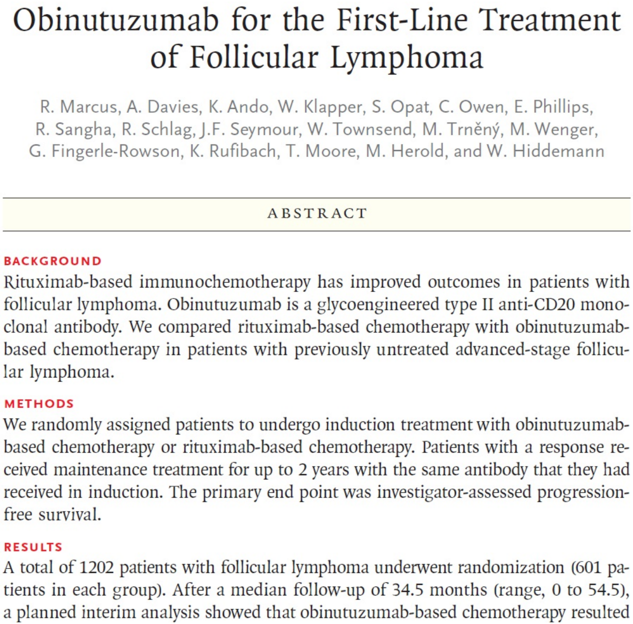

# Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

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## ABSTRACT

### BACKGROUND

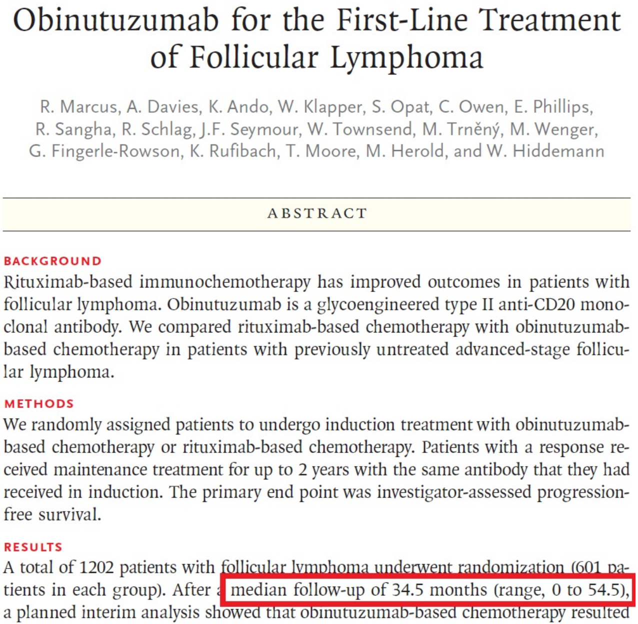
Rituximab-based immunochemotherapy has improved outcomes in patients with follicular lymphoma. Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody. We compared rituximab-based chemotherapy with obinutuzumab-based chemotherapy in patients with previously untreated advanced-stage follicular lymphoma.

### METHODS

We randomly assigned patients to undergo induction treatment with obinutuzumab-based chemotherapy or rituximab-based chemotherapy. Patients with a response received maintenance treatment for up to 2 years with the same antibody that they had received in induction. The primary end point was investigator-assessed progression-free survival.

### RESULTS

A total of 1202 patients with follicular lymphoma underwent randomization (601 patients in each group). After a median follow-up of 34.5 months (range, 0 to 54.5), a planned interim analysis showed that obinutuzumab-based chemotherapy resulted



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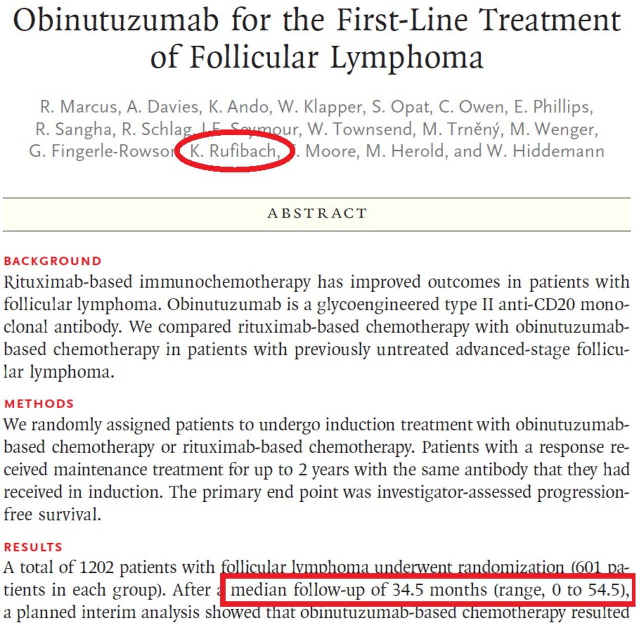

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# What do these 34.5 months mean?

**What do these 34.5 months mean?**

**What can we conclude from it?**

**Nothing!**

**Nothing!**

**Do not report such numbers at all!**

# What do trialists believe 34.5 months means?

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**Shuster (1991): interviews with oncologists.**

# Median of...

# Median of...

**”Follow-up among those who did not have the event yet.”**

**Median of...**

**"Follow-up among those who did not have the event yet."**

**"Follow-up of all patients."**

**Median of...**

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**”Follow-up of all patients.”**

**”Time from trial entry to clinical cut-off date.”**

**Median of...**

**”Follow-up among those who did not have the event yet.”**

**”Follow-up of all patients.”**

**”Time from trial entry to clinical cut-off date.”**

**”Censoring distribution, estimated through inverse KM.”**

# What do trialists want to know?

# ”Maturity” of the estimated survival function.

**”Maturity” of the estimated survival function.**

**”Stability” of the estimated survival function.**

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**Time interval where Kaplan-Meier estimate is ”valid”.**

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**”Stability” of the estimated survival function.**

**Time interval where Kaplan-Meier estimate is ”valid”.**

**”Quality” of follow-up.**

# ”Maturity”?

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## ”Validity”?

**”Maturity”?**

**”Stability”?**

**”Validity”?**

**”Quality”?**

**”Maturity”?**

**”Stability”?**

**”Validity”?**

**”Quality”?**

**Trials compared based on vague concept of ”follow-up”.**

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- Inspiration from estimand framework to **start with scientific question(s)** trialists want answers to.

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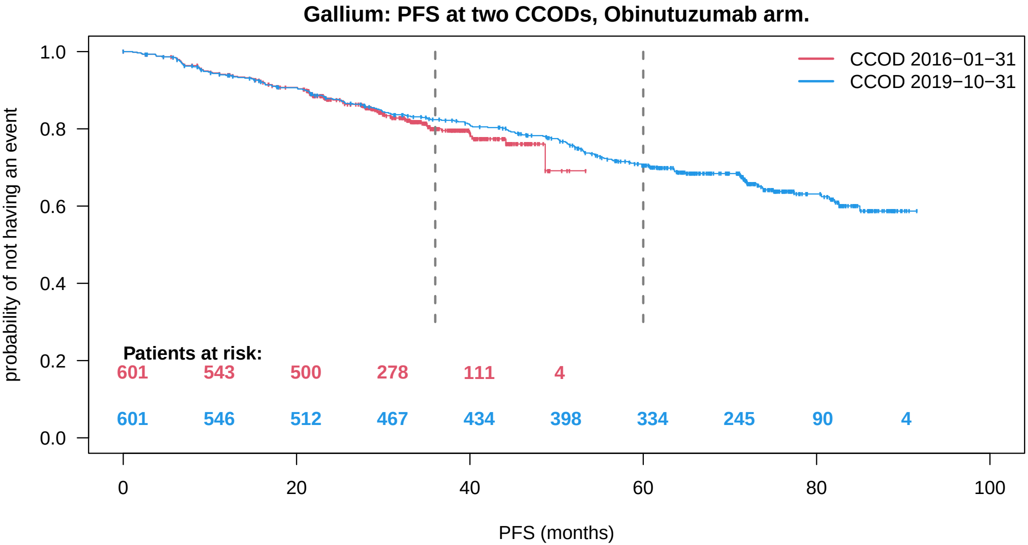
Proposal:

- Inspiration from estimand framework to **start with scientific question(s)** trialists want answers to.
- Analyze existing quantities.
- Extend considerations to 2-sample case. Separately for PH and non-PH.

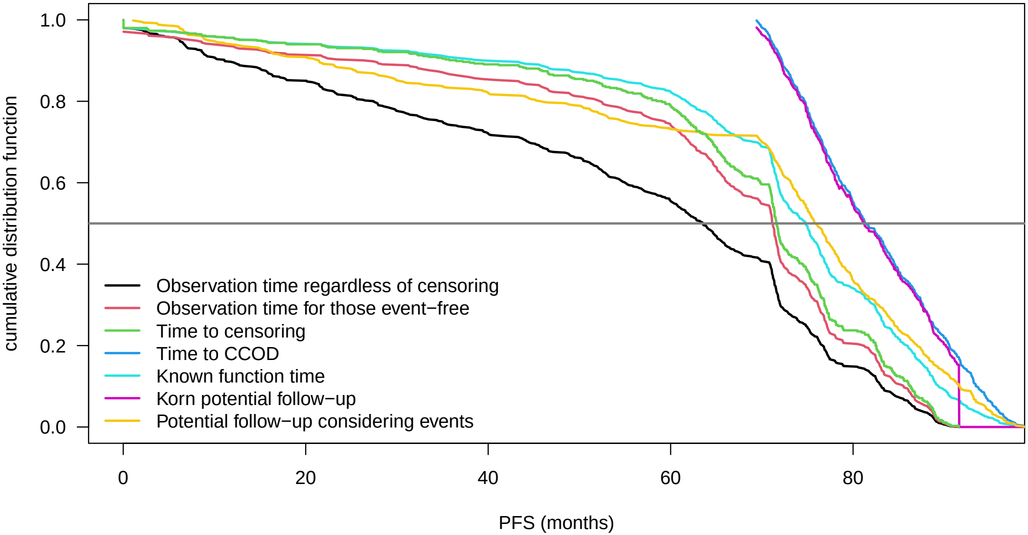
# One-sample case



# Commonly used quantities

| Follow-up quantifier | Patient subset | Primary event | Censoring: administrative | Censoring: LTFU | CCOD |
|---|---|---|---|---|---|
| **Observation time regardless of censoring** | | event | event | event | ignored |
| **Observation time for those censored** | censored | ▨ | event | event | ignored |
| | event | excluded | | | |
| **Time to censoring** | | censored | event | event | ignored |
| **Time to CCOD, Potential follow-up** | | ignored | ignored | ignored | event |
| **Known function time** | censored | ▨ | event | event | ignored |
| | event | ignored | ▨ | ▨ | event |
| **Korn's potential follow-up time** | | Generalization of time to censoring, estimates P(under follow-up at $t$), distinguishes lost-to-follow-up and administrative censoring. | | | |
| **Potential follow-up considering events** | censored | ▨ | ignored | ignored | event |
| | event | event | ▨ | ▨ | ignored |

# One-sample case, second CCOD



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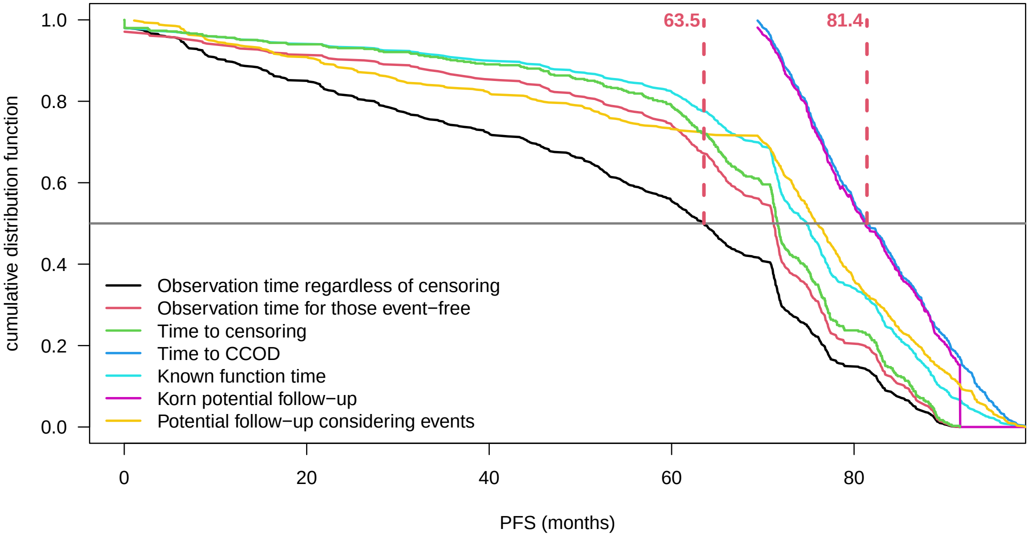

## What do trialists **really** want to know?

| Term | Question | How to best answer |
|---|---|---|

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| **Precision** | How precise is estimate of underlying true survival function $S_X$? | Pointwise CIs or confidence bands. |

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| **Stability** | How much can KM estimate possibly change in future data snapshot? | Consider all currently censored patients to either (1) have event day after censoring or (2) being censored at latest observed event time. Betensky (2015). |

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| **Information** | How much of information necessary to achieve targeted power for hypothesis test, either for milestone timepoint or median, has been collected? | Power depends on inverse of variance of parameter of interest. |

**No ”measure of follow-up” needed whatsoever!**

# Two-sample case

Why different from one-sample case?

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- Interest in **relative** effect.

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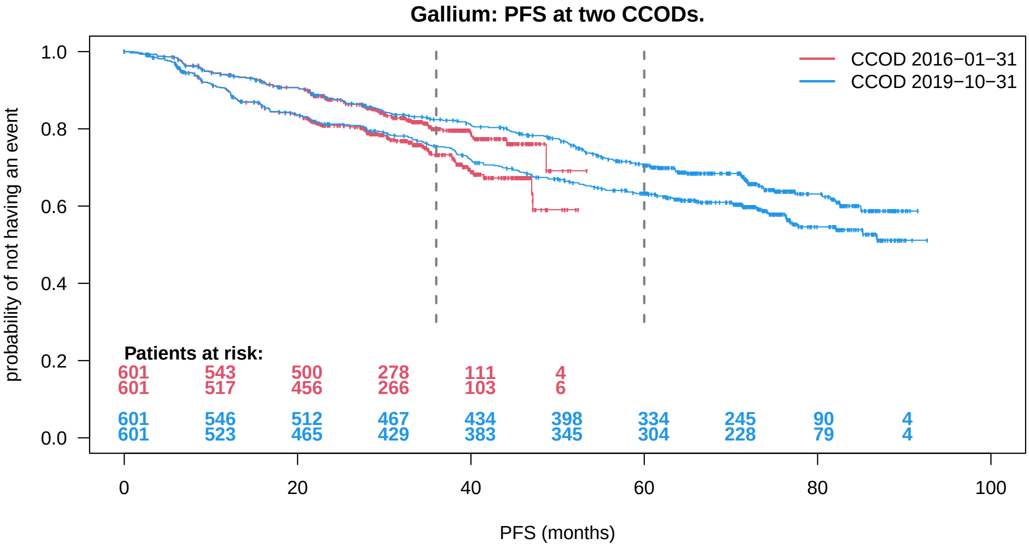
Why different from one-sample case?

- Interest in **relative** effect.
- Proportional (PH) vs. non-proportional hazards (NPH).

# Two-sample case - PH



## What does power of logrank (any) test depend on **in general**?

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**Inverse of variance of parameter of interest.**

**Only under PH and for unweighted logrank test proportional to #events!**

| Term | Question | How to best answer |
|---|---|---|
| **Precision** | How precise is HR estimate? | CI. |
| **Stability** | How much can HR estimate change in future data snapshot? | If PH assumption applies then estimate of HR will (on average) simply become more precise over time. |
| **Information** | How much of information necessary to achieve targeted power for hypothesis test for HR within group-sequential design has already been collected? | Information fraction $d_{\text{int}}/d_{\text{fin}}$. |
| **PH (reliability)** | Do hazard functions remain proportional? | Standard tools to assess PH, e.g. plot nonparametric estimates of (cumulative) hazard functions over time, and ratio thereof, or hypothesis tests. |
| **Censoring pattern** | Is censoring distribution same in both arms? Are distributions of censoring reasons same in both arms? | Plot nonparametric estimates of censoring distribution per arm, potentially split by censoring reason. |

**”We need enough FU for safety.”**

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**HTA assessments: use FU to assess ”Evidence base sufficient for evidence synthesis?”**

# Vague questions!

**Vague questions!**

**No FU-quantifier whatsoever can answer these questions!**

**Vague questions!**

**No FU-quantifier whatsoever can answer these questions!**

**Formulate questions precisely!**

**More follow-up is better in any case!**

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**Depends on quantity of interest.**

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PH vs. NPH:

- Assumption matters for stability!
- NPH: need to chose effect measure.
- Information depends on #events (PH) or many more quantities (NPH).

**Do not provide a quantification of follow-up.**

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**Not only useless, but confusing.**

# Resources

Paper: https://arxiv.org/abs/2206.05216.

Markdown with all code: https://oncoestimand.github.io/quantFU/quantFU.html.

Oncology estimand WG: http://www.oncoestimand.org.

# Thank you for your attention.

**kaspar.rufibach@roche.com**
**http://go.roche.com/dss-mco**

**http://www.kasparrufibach.ch**
**numbersman77**
**numbersman77**

# References I

Betensky, R. A. (2015). Measures of follow-up in time-to-event studies: Why provide them and what should they be? *Clin Trials*, **12**(4), 403–408.

Shuster, J. J. (1991). Median follow-up in clinical trials. *J. Clin. Oncol.*, **9**(1), 191–192.

# Backup

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- Exclusively relying on PH to ”predict” future course of the trial: **strong and statistically motivated assumption**.

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Stability cannot be assessed using whatever measure of follow-up!

# Results for Gallium (PH)

# Precision, stability, information

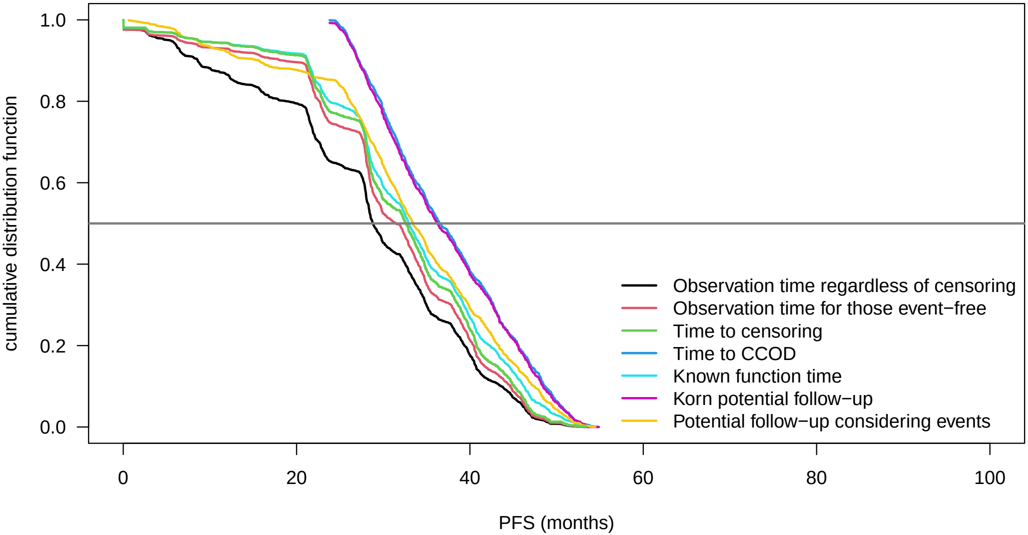
| | CCOD 2016-01-31 | CCOD 2019-10-31 |
|---|---|---|
| HR | 0.66 | 0.76 |
| 95% CI | [0.51, 0.85] | [0.62, 0.92] |
| Number of events $d$ | 245 | 419 |
| Proportion of patients with event | 20.4% | 34.9% |

Table: Key efficacy results for Gallium.

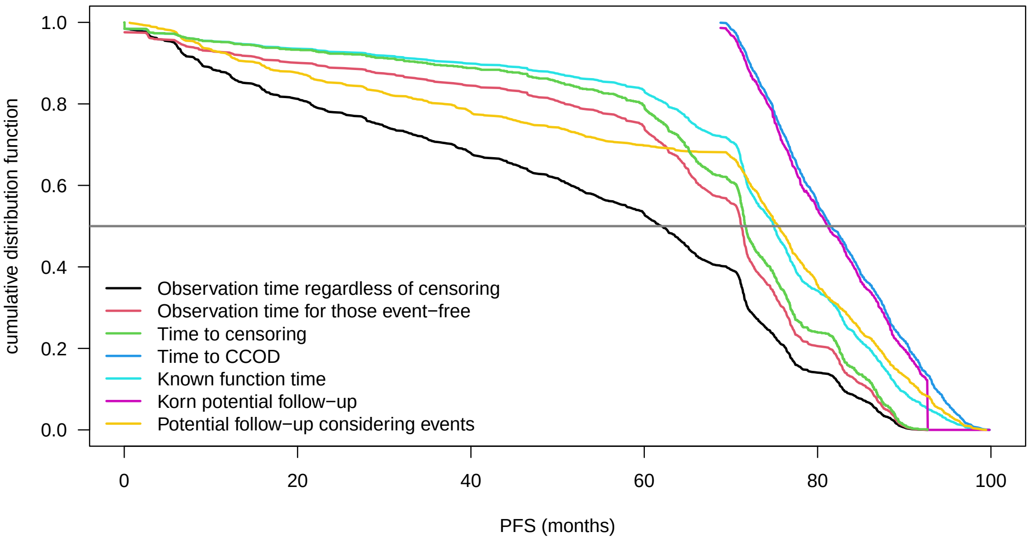
| milestone | treatment arm | CCOD 2016-01-31 | CCOD 2019-10-31 |
|---|---|---|---|
| 36 | Rituximab | 0.73 [0.66, 0.80] | 0.76 [0.71, 0.79] |
| 36 | Gazvya | 0.80 [0.73, 0.85] | 0.82 [0.79, 0.86] |
| 36 | Difference Obinutuzumab - Rituximab | 0.07 [0.01, 0.12] | 0.07 [0.02, 0.12] |
| 60 | Rituximab | - | 0.63 [0.58, 0.68] |
| 60 | Gazvya | - | 0.70 [0.65, 0.75] |
| 60 | Difference Obinutuzumab - Rituximab | - | 0.07 [0.02, 0.13] |

Table: Milestone KM estimates for Gallium.

# Quantification of follow-up, CCOD1



# Quantification of follow-up, CCOD2



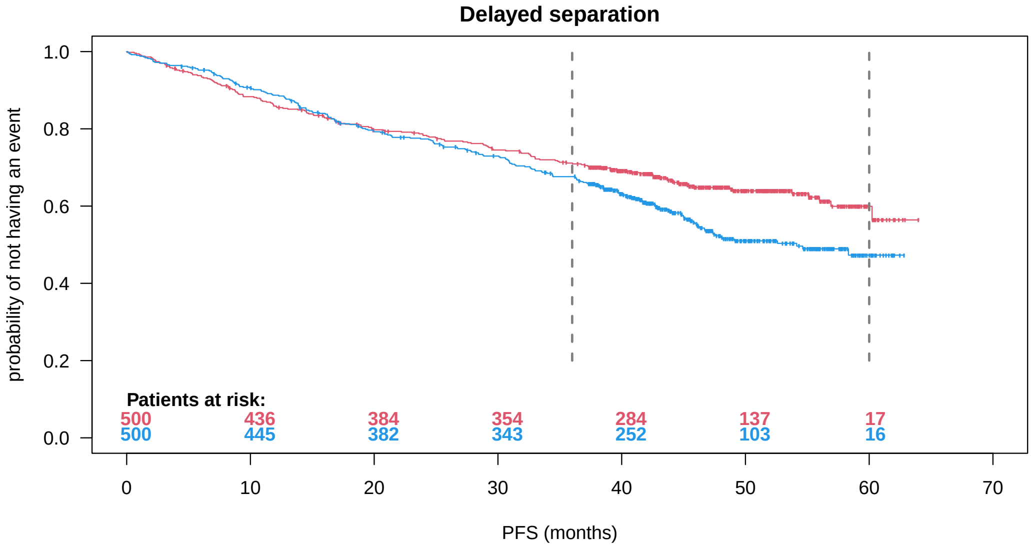
# Quantification of follow-up

| Quantity | CCOD 2016-01-31 | CCOD 2019-10-31 | $\Delta$ | $\Delta$% |
|---|---|---|---|---|
| Observation time regardless of censoring | 28.8 | 62.0 | 33.2 | +115% |
| Observation time for those event-free | 31.5 | 71.2 | 39.8 | +126% |
| Time to censoring | 32.6 | 71.7 | 39.1 | +120% |
| Time to CCOD | 36.5 | 81.5 | 45.0 | +123% |
| Known function time | 32.9 | 75.0 | 42.0 | +128% |
| Korn potential follow-up | 36.2 | 81.2 | 44.9 | +124% |
| Potential follow-up considering events | 33.4 | 75.5 | 42.1 | +126% |

Table: Different quantifications of follow-up for Gallium, in months.

# Delayed separation example

# Two-sample case - NPH: delayed separation



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**No hope #events tells us everything!**

# Illustration for RMST

Variance of RMST depends on:

- total number of patients,
- randomization ratio,
- KM estimate of the pooled sample,
- estimated censoring distribution in each arm (which can be taken as pooled if random censoring is assumed),
- observed number of events at $t_0$,
- observed number of patients still at risk at $t_0$.

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| **Information** | How much of information necessary to achieve targeted power for hypothesis test for effect of interest has already been collected, if group-sequential design is used? | Not only related to #events / information fraction.<br>Effect measure specific. |

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| **PH** | Not applicable. | |

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| **PH** | Not applicable. | |
| **Censoring pattern** | Same as in PH scenario. | |

# Trial design

Assumptions:

- Base event rate: 0.012, corresponding to median time-to-event of 60 months.
- Piecewise exponential survival with no effect between 0 and 12 months, HR $=$ 0.65 thereafter.
- In both arms: probability LTFU follows exponential distribution calibrated such that probability amounts to 0.025 at 12 months. Corresponds to median time-to-LTFU of 329 months.
- After ramp-up of 6 months we recruit 42 patients / month until maximal number of 1000 patients.

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CCOD after 389 events: power of

- 80.5% for unweighted logrank test,
- 69.7% using RMST difference based on KM estimates between arms, with data-driven restriction time $t_0$ of lower of two maximal observed times (events and censored) in each arm.
- Based on 10000 simulated trials.

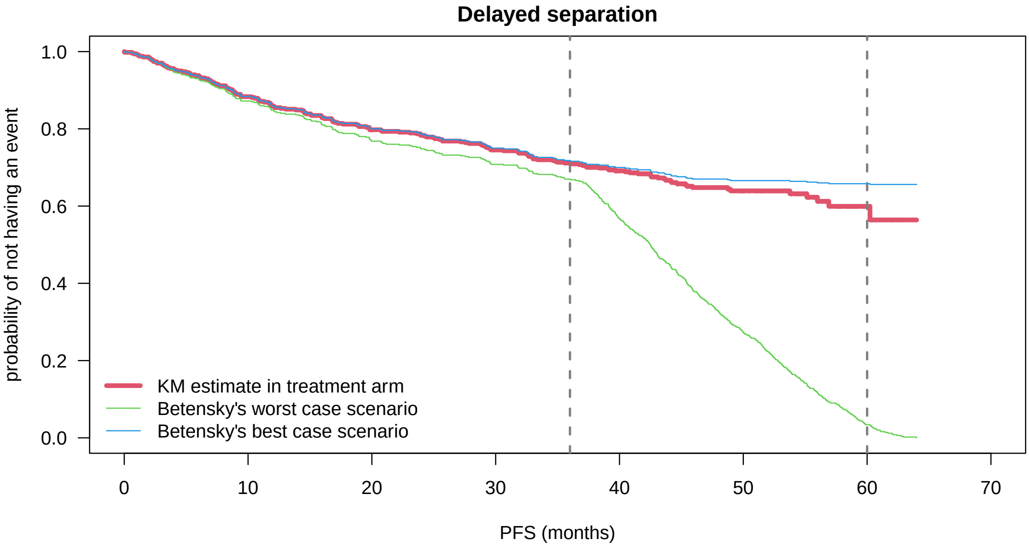
# Precision

| milestone | treatment arm | KM estimates and 95% CIs |
|---|---|---|
| 36 | Control arm | 0.68 [0.62, 0.73] |
| 36 | Treatment arm | 0.71 [0.66, 0.76] |
| 36 | Difference treatment - control | 0.04 [-0.03, 0.09] |
| 60 | Control arm | 0.47 [0.30, 0.65] |
| 60 | Treatment arm | 0.60 [0.46, 0.73] |
| 60 | Difference treatment - control | 0.13 [0.05, 0.21] |

Table: Milestone estimates for delayed separation example.

Difference of RMST between arms: 2.82 months between arms with 95% CI from -0.35 to 5.98.

# Stability


Delayed separation
probability of not having an event
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
PFS (months)
KM estimate in treatment arm
Betensky's worst case scenario
Betensky's best case scenario

*Doing now what patients need next*

**R version and packages used to generate these slides:**

R version: R version 4.1.1 (2021-08-10)

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

Other packages: reporttools / xtable / rpact / survminer / ggpubr / survival / forcats / stringr / dplyr / purrr / readr / tidyr / tibble / ggplot2 / tidyverse

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