Challenges and open questions in hematology
Estimand aspects in the Gallium trial

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Gallium

- Phase III, 2-arm, randomized, open-label, parallel-group trial in 1st line follicular lymphoma (FL)
- Treatment regimen:
  - Obinutuzumab / Rituximab + backbone CT for 6 months.
  - If the patient responds then Obinutuzumab / Rituximab maintenance for another 2 years.
  - Otherwise follow-up as in maintenance without further treatment
- Primary endpoint:
  - Progression-free survival (PFS)
- Protocol definition: “time from randomization to earlier of progression or death”
- Assessment schedule: regular tumour assessments at months 3, 6, 10, 14, 18, 24, 30, 36, … Death dates also collected
- Trial read out prior to addendum:
  - Clinical cutoff 31st January 2016.
  - Marcus et al (2017), N Engl J Med; 377:1331-1344, https://pubmed.ncbi.nlm.nih.gov/28976863/

Protocol defined objective pre-addendum

The primary objective for this study is as follows:

- To evaluate the ***efficacy*** of obinutuzumab (GA101, RO5072759) plus chemotherapy followed by obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in patients with previously untreated advanced follicular lymphoma, ***as measured by investigator-assessed progression-free survival (PFS)***

How key trial results were reported

RESULTS

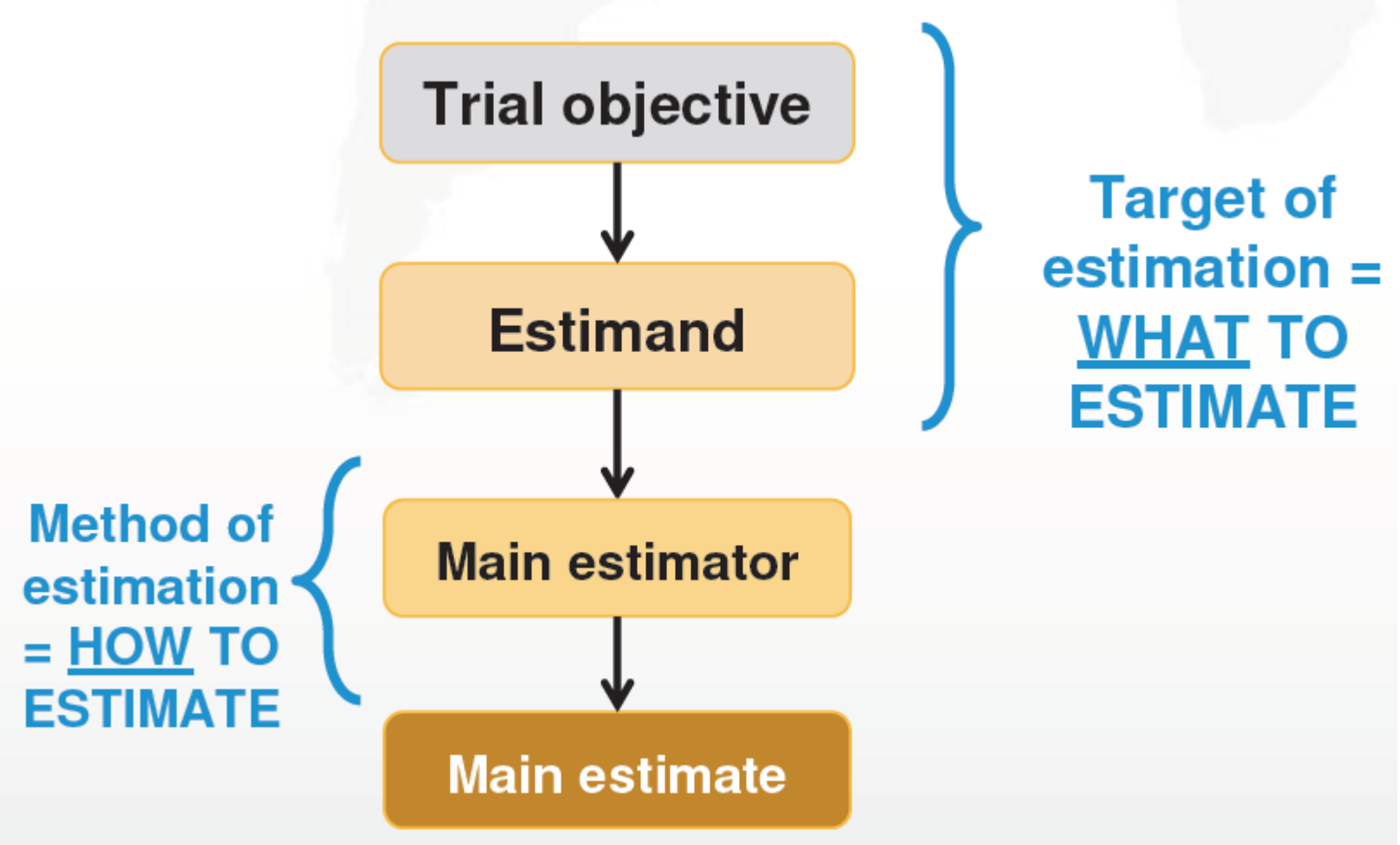
- A total of 1202 patients with follicular lymphoma underwent randomization (601 patients in each group). After a median follow-up of 34.5 months (range, 0 to 54.5), a planned interim analysis showed that obinutuzumab-based chemotherapy resulted in ***a significantly lower risk of progression, relapse, or death than rituximab-based chemotherapy*** (estimated 3-year rate of progression-free survival, 80.0% vs. 73.3%; hazard ratio for progression, relapse, or death, 0.66; 95% confidence interval [CI], 0.51 to 0.85; P = 0.001)

Marcus et al (2017)

Ambiguity remains, in the objective and reporting

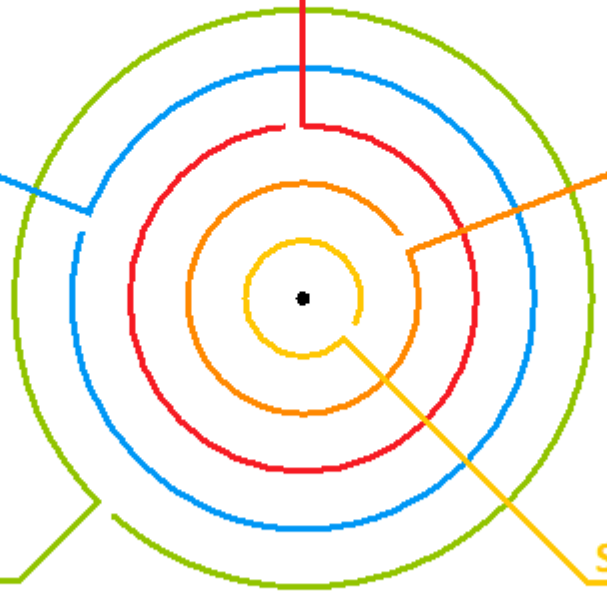
- Objective: How do we measure the effect?
- Definition of PFS:
  - Starting new anti-lymphoma therapy (NALT) prior to progression?
  - Withdrawal from trial treatment prior to progression?
  - «Relapse»: in paper, but not objective?

Estimand – target of estimation



ESTIMAND

TARGET OF ESTIMATION



VARIABLE

The variable (or endpoint) to be obtained for each patient

POPULATION

The population of patients targeted by the clinical question

INTERCURRENT EVENTS

Other intercurrent events (not already addressed by treatment, population, and variable) and how they are addressed

TREATMENT

The treatment condition of interest

SUMMARY

A population-level summary for the variable which provides a basis for treatment comparison

Taken from Degtyarev et al (2020).

Estimand components post-addendum

Treatments:

Experimental: *6 or 8 21-28 day cycles obinutuzumab D1 + C1D8, C1D15: 1000mg flat dose + site-specific choice of CT (CVP, Benda, CHOP) in induction followed in responding patients by 1000mg every 2 months until PD or up to 2y*

Control: *6 or 8 21-28 day cycles rituximab 375mg/m2 D1 + site-specific choice of CT (CVP, Benda, CHOP) in induction followed in responding patients by 375mg/m2 every 2 months until PD or up to 2y*

Population: *Patients with previously untreated follicular lymphoma (FL)*

Primary endpoint: *Progression-free survival (time from randomization to progression, relapse, or death)*

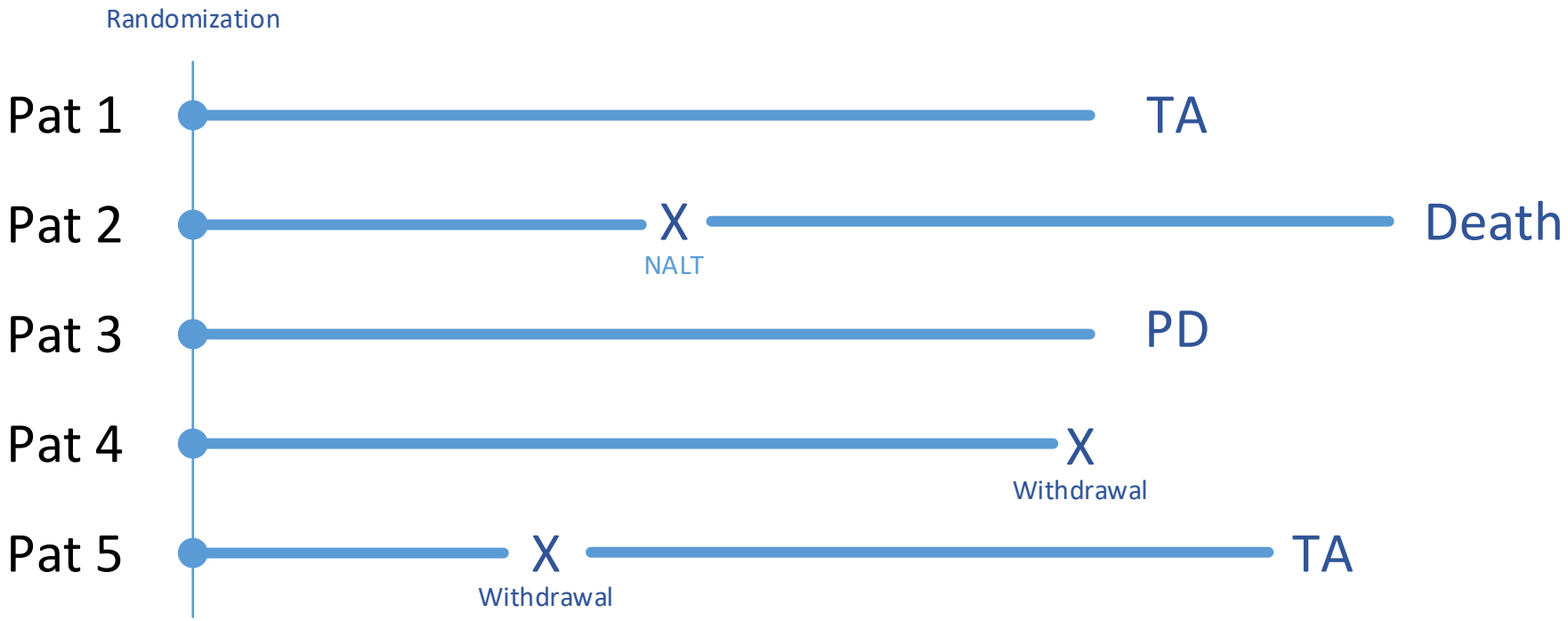
Intercurrent events:

NALT prior to progression

Withdrawal from trial treatment prior to progression

Summary measure: *Hazard ratio*

Handling of intercurrent events



TA – last valid tumor assessment → censored

Detailed trial objective post-addendum

The trial will compare 6 or 8 21-28 day cycles of obinutuzumab D1 + C1D8, C1D15: 1000mg + site-specific choice of CT (CVP, Benda, CHOP) in induction followed in responding patients by 1000mg every 2 months until PD or up to 2y with 6 or 8 21-28 day cycles of rituximab 375mg/m2 D1 + site-specific choice of CT (CVP, Benda, CHOP) in induction followed in responding patients by 375mg/m2 every 2 months until PD or up to 2y in patients with previously untreated follicular lymphoma

The primary comparison of interest is the hazard ratio of progression-free survival

The primary comparison of progression-free survival will be made regardless of whether patients withdraw from treatment or receive new-anti lymphoma therapy prior to disease progression

Benefits of estimand framework

- **Clinical trial objective** clarified in sufficient detail during trial planning
- Put objective in **Section 3** of protocol
- Estimand, endpoints, primary analysis, sample size, sensitivity analyses ~ follow from it
- Informs what data to collect:
  - Treatment policy → PD, death, tumor assessments also *after* intercurrent events
  - Date last known alive for OS also *after* intercurrent events
- Analysis, interpretation, and health authority interactions easier after unblinding
  - Likely less need for discussions

References

Degtyarev, E., Rufibach, K., Shentu, Y., Yung, G., Casey, M., Liu, F., Liu, Y., Sailer, O., Siegel, J., Sun, S., Tang, R., Zhou, J. *Assessing the impact of COVID-19 on the objective and analysis of oncology clinical trials – application of the estimand framework* (2020). Statistics in Biopharmaceutial Research, to appear. https://doi.org/10.1080/19466315.2020.1785543

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