Clinical Trial Design

Fang-Shu Ou, Ph.D.
Faculty Statistician
Alliance Statistics and Data Center

New Investigator Day-Long Course, May 11, 2017

Objectives

- Disease-specific information
- Phases of clinical trials
- Randomized trials
  - Placebo-controlled
  - Blinding
- Objectives and endpoints
- Interim analysis
- Sample size

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Disease-specific information

- Eligibility
  - Disease (solid tumor vs. hematology)
  - The stage of the disease
  - Any specific molecular profile

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Trial Phases – I/II/III

- Phase I – first in human
  - Goal: Patient safety, dose finding
  - Designs: single arm, dose-escalation
    - 3+3 cohort design
    - Continual reassessment method (CRM)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Trial Phases – I/II/III *(cont.)*

- Phase II
  - Goal: Patient safety, early efficacy
  - Designs: single arm vs. multiple arms
    non-randomized vs. randomized
  - Single arm typically is non-randomized
    - Simon's single-arm 2-stage design
  - Randomized Phase II is the best if possible

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Trial Phases – I/II/III *(cont.)*

- Phase III
  - Goal: confirm efficacy
  - Designs: randomized
    - How many arms?
    - What is the randomization ratio between arms?
    - Blinded?
    - Placebo-controlled?

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Randomization

- Treatment assigned by chance
- Goal:
  - Avoid bias in treatment assignment
  - Patients in different arms are comparable
  - Comparison and inference across arms is valid
  - Typically 1:1 randomized
  - 2:1 will require slightly larger sample sizes

Randomization is preferred when possible.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Issue of Lack of Randomization

- Observational study of 656 consecutive patients
- Tested association of biomarker (MSI, dotted lines) with chemotherapy benefit
- Chemo seems to be very beneficial for pts with MSI
- Problem: Non-randomized: Treated pts median 13 years younger than untreated!

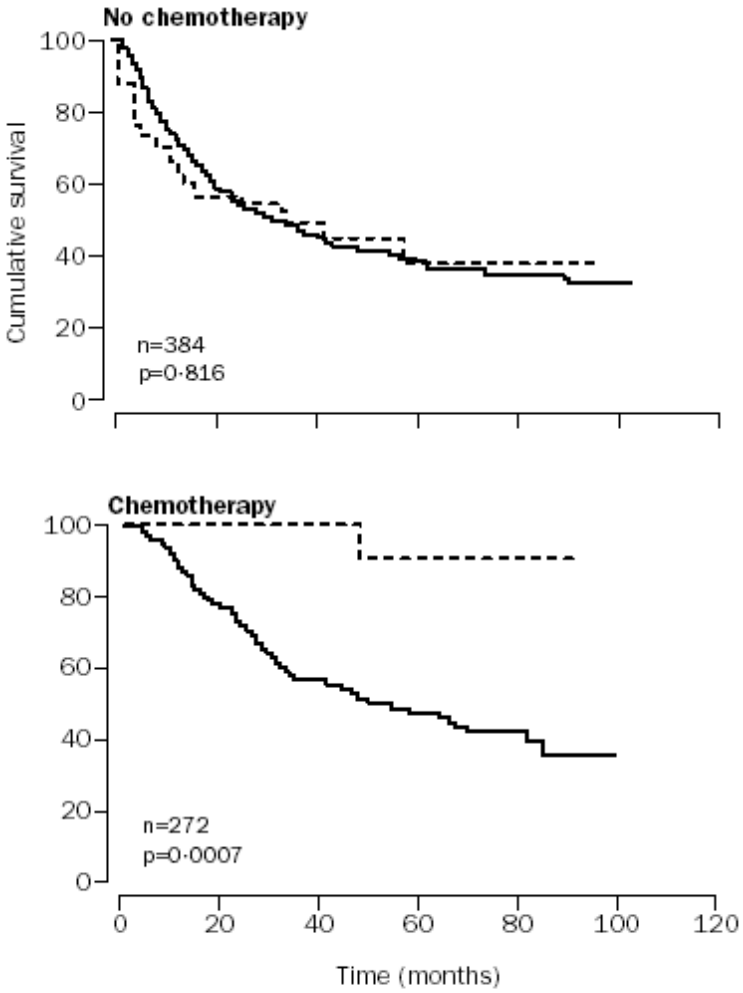


Figure 5: **Kaplan-Meier survival curves for patients with and without MSI**

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Blinding

- Treatment assignment is masked from patients/treating physicians
  - Open label: no blinding
  - Single-blind: patients
  - Double-blind: patients AND treating physician
- Goal:
  - Avoid bias due to knowledge of treatment

Double-blind is preferred when possible.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Issues with Lack of Blinding

- Canadian cooperative trial of cyclophosphamide and plasma exchange
  - 3-arm study including a placebo arm
- Blinded and un-blinded neurologists evaluated disease course
- Blinded evaluation => No difference between groups
- Un-blinded evaluation => one of the treatment arms is superior

The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial; Noseworthy et. al; Neurology; 1994; (44) 116

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Placebo-controlled

- The control arm is a placebo
  - Typically used when the standard of care is observation
- Patient advocates and treating physicians may dislike it
  - 2:1 randomization
  - Cross-over study

Placebo-controlled is preferred when possible.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Placebo-controlled *(cont.)*

- Examples of placebo-controlled study
  - CORRECT study, in patients with previously treated metastatic colorectal cancer
    - 2:1 randomization was used
  - RADIANT-2 study, in patients with advanced, progressive NET with carcinoid symptoms
    - 1:1 randomization and cross-over was used

Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial; Grothey A. et al.; Lancet, 2013; 381 (9863); 303-312

Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study; Pavel et al.; Lancet, 2011; 378 (9808); 2005-2012

Endpoints and Objectives

- Endpoints
  - Must be measurable
  - Must be sensitive to the effect of treatment
  - Clinically relevant

- Objective
  - The over-arching goal for the study

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Endpoints and Objectives *(cont.)*

- Different types of endpoints
  - Time-to-event endpoints
    - Disease-free survival
    - Progression-free survival
    - Overall survival
  - Binary endpoints
    - Best objective response rate (CR/PR)
    - Overall survival **rate** at 18 months

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Endpoints and Objectives *(cont.)*

- Null hypothesis ($\mathbf{H_o}$)
  - What we currently know
  - For example, the median overall survival is 15 months
- Alternative hypothesis ($\mathbf{H_1}$)
  - What we expect the experimental agent can achieve
  - For example, the median overall survival is 20 months
  - It can be presented as a hazard ratio, 0.75.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Endpoints and Objectives *(cont.)*

- Clinically relevant effect size
  - Hazard ratio = 0.75
  - Median PFS: 7 months vs. 9.3 months
  - Median PFS: 9 years vs. 12 years

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Interim analysis

- Definition - An analysis conducted prior to the planned final analysis

- Possible actions:
  - Continue as planned
  - Modify the trial
  - Permanently close down the trial

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Interim analysis *(cont.)*

- Why stop early?
  - One treatment convincingly superior or inferior
  - Treatments convincingly not different
  - Excessive toxicity
  - Extremely slow accrual
  - External evidence (e.g., other trials) leading to scientific irrelevance

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Interim analysis *(cont.)*

- What does it cost me?
  - Pausing the accrual (optional)
  - Interim analysis requires an increased sample size
    - Efficacy – inflate type I error (alpha)
    - Futility – inflate type II error (beta)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Sample size

- What else does a statistician need to know until I can have a sample size?
  - Type I error rate (= α)
  - Power (=1- β)
  - Budget constraints
  - Total study length
  - Accrual rate (especially for time-to-event endpoint)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

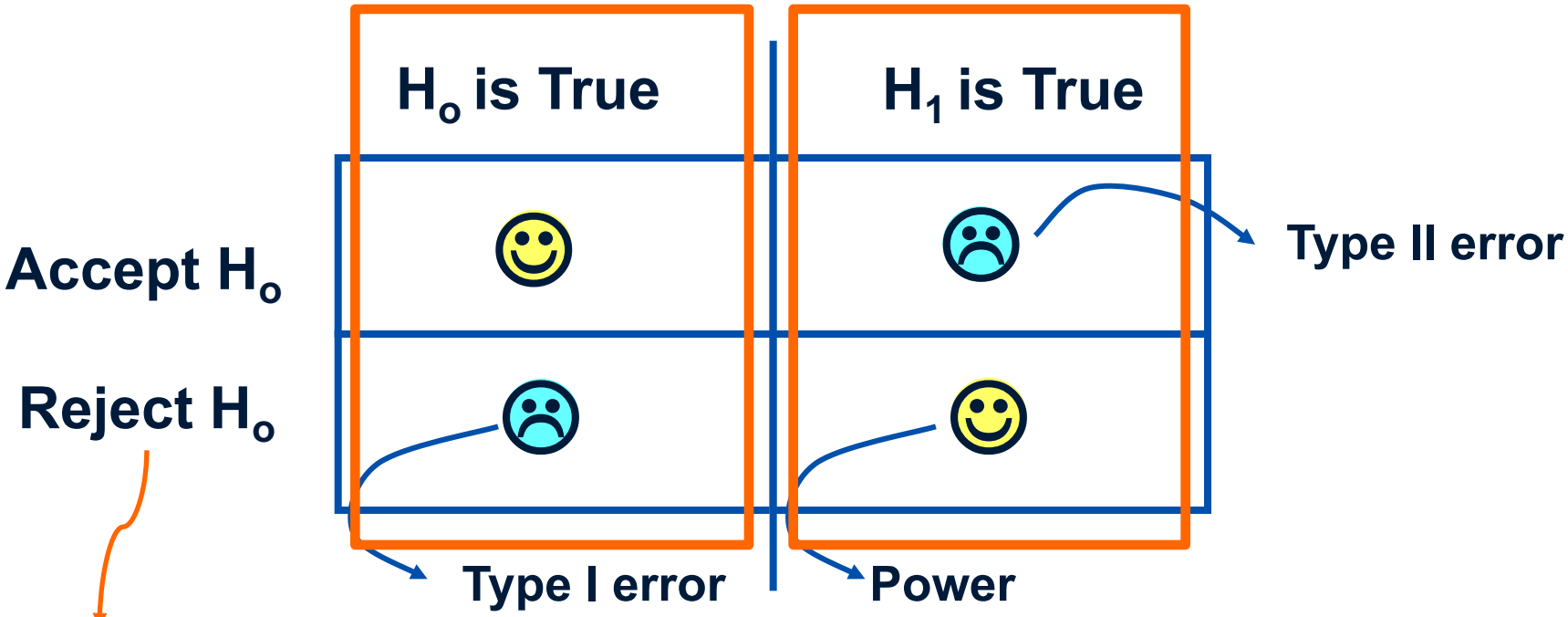
Sample size *(cont.)*

- Type I error rate (α)
  - The possibility of declaring the experimental agent is efficacious when it is not (false-positive rate)

- Power (=1- β)
  - The possibility of declaring the experimental agent is efficacious when it is truly so (true positive rate)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Sample size *(cont.)*



α =probability of Type I error (level of significance)

β =probability of Type II error

$1-\beta$ =Power

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Sample size *(cont.)*

- Type I error (α), common choices
  - Single-arm phase II: one-sided 0.05, 0.1, and 0.15
  - Randomized phase II: one-sided 0.1, 0.15, and 0.2
  - Phase III: one-sided 0.025 and 0.005 (equivalent to two-sided 0.05 and 0.01)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Sample size *(cont.)*

- Power (1- β), common choices
  - Single-arm phase II: 0.8 and 0.85
  - Randomized phase II: 0.80, 0.85, 0.90
  - Phase III: 0.90

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Sample size *(cont.)*

- Budget constraints and total study length
  - Budget limits often determine the sample size
  - Study length also comes into play
    - Slow accrual study
    - Studies in rare disease
- Accrual rate (time-to-event endpoint)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Conclusion

- Designing a clinical trial is a team effort
- Involve your statistician early and often

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Questions?

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY