Gynecologic Cancer InterGroup

Endpoints in Gynecologic Cancer Clinical Trials

Keiichi Fujiwara

Saitama Medical University International Medical Center

GOTIC

GCIG Education Symposium, November 2017, Vienna

- AGENDA
  - Definition of Endpoint
  - Variation of Endpoint
    - Primary vs Secondary
    - Direct vs Surrogate
  - Suitable Endpoints for Gynecologic Cancer Clinical Trials from 5th OCCC
    - 1st Line
    - Recurrent Setting

- AGENDA
  - Definition of Endpoint
  - Variation of Endpoint
    - Primary vs Secondary
    - Direct vs Surrogate
  - Suitable Endpoints for Gynecologic Cancer Clinical Trials from 5th OCCC
    - 1st Line
    - Recurrent Setting

- Endpoint
  - Goal/Purpose of Clinical Trial
  - Depends on the Phase of Clinical Trial

- Phase 1
  - Safety
- Phase 2
  - Efficacy & Safety in Selective number of Patients
- Phase 3
  - True Efficacy

Endpoint of Phase I Trial

- To determine
  - Maximum Tolerable Dose (MTD) for the future trial
    - Whether or not the patient experiences a dose limiting toxicities (DLT)
  - Recomended Dose for Phase 2 Trials

Endpoint of Phase I Trial

- How?
  - The Traditional 3+3 Design
    - Too many patients with lower doses than MTD
  - Alternative Trial Designs such as Continuous Reassessment Model (CRM)
    - To accelerate the process
    - Good for Biologic Agents with low toxicity profiles

Endpoint of Phase 2 Trial

- To Provide
  - The testing ground for the development of definitive Phase 3 trials
    - Through the screening of new agents for antitumor activity
    - By piloting new treatment combination and schedules.
- Limitation
  - Small sample size compromising in Type I and II error cannot draw definitive conclusion

Endpoint of Phase 2 Trial

- How?
  - Single-Arm Phase 2 Designs
  - Muli-Arm Phase 2 Designs
    - Basket Trials
    - Umbrella Trials
- Using Short-Term Endpoints
  - Tumor Response for Cytotoxic Agents
  - 6-Month Survival for Target Therapies
    - Little Impact on Tumor Shrinkage

Endpoint of Phase 3 Trial

- To Compare the results with the Standard Therapy for
  - Superiority
    - Efficacy
      - OS
      - PFS
  - Equivalence or Noninferiority
    - Safety
    - PRO QOL
    - Cost-Benefit

- AGENDA
  - Definition of Endpoint
  - Variation of Endpoint
    - Primary vs Secondary
    - Direct vs Surrogate
  - Suitable Endpoints for Gynecologic Cancer Clinical Trials from 5th OCCC
    - 1st Line
    - Recurrent Setting

Primary vs Seconcary Endpoint for P3

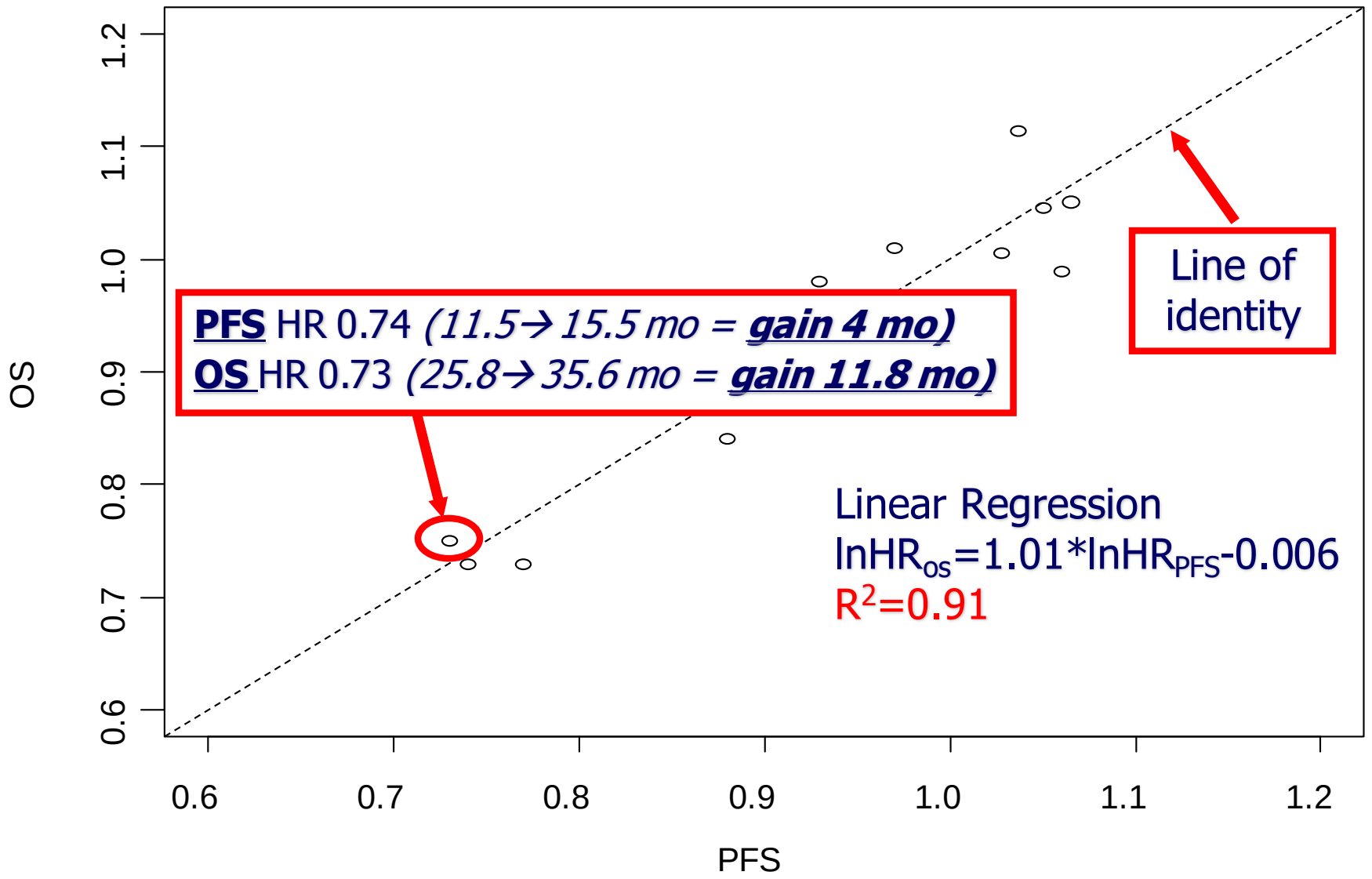
- Primary
  - OS or PFS for Superiority Trial
- Secondary
  - Safety
  - PRO QOL
  - Cost-Benefit

Surrogate Endpoints

- Although OS is the preferred primary endpoint
  - Not suitable in trials that takes longer time for diseases with good prognosis.
- Need endpoint that can surrogate OS
  - Which can measure with shorter time.
- Such as PFS or Tumor Response

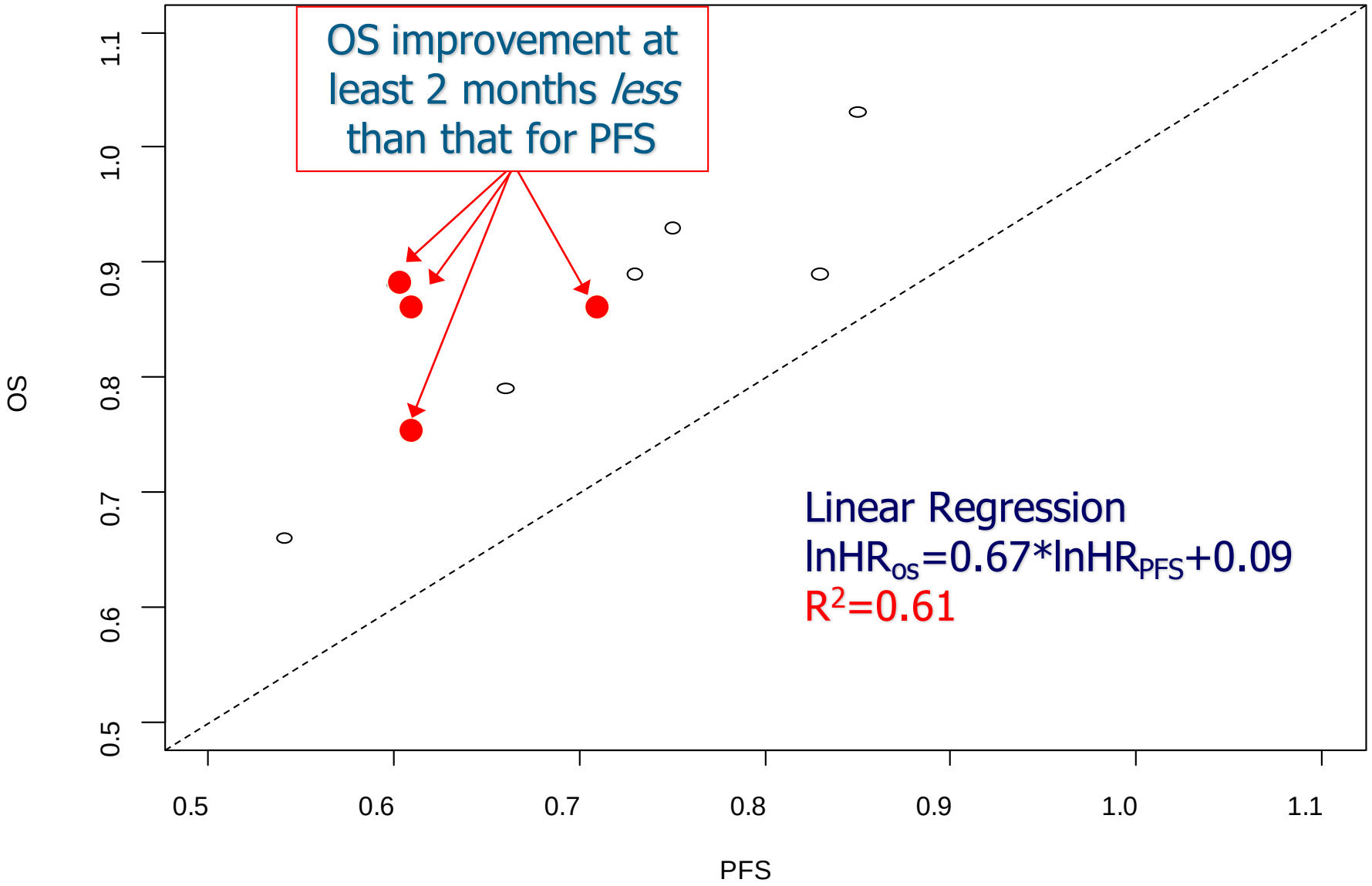
Hazard Ratios of PFS vs. OS:

Data from Platinum-based Chemotherapy Trials in Advanced OVCA



Hazard Ratios of PFS vs. OS:

Data from RCTs of Bevacizumab in Other Solid Tumors



Surrogate Endpoint

- Most useful in the context of Phase 2 trials, to screen agents for further randomized testing of effects on primary true endpoints.

- AGENDA
  - Definition of Endpoint
  - Variation of Endpoint
    - Primary vs Secondary
    - Direct vs Surrogate
  - Suitable Endpoints for Gynecologic Cancer Clinical Trials from 5th OCCC
    - 1st Line
    - Recurrent Setting

From 5th OCCC

- Trial Endpoints for 1st line intervention trial
  - OS is the preferred primary endpoint with or without a maintenance component.
  - PFS is an alternative primary endpoint, but if PFS is chosen OS must be measured as a secondary endpoint
  - PFS must be supported by additional endpoints, including
    - Predefined PRO
    - Time to first or second subsequent therapy.

From 5th OCCC

- Trial Endpoints for 1st line intervention trial
  - The increasing use of neoadjuvant chemotherapy provides opportunities for short-term trials to evaluate novel treatments prior to surgery
  - Translational endpoints in these 'window of opportunity' studies need to be better defined and validated.

From 5th OCCC

- Trial Endpoint in ROC
  - OS is the preferred endpoint for patient cohorts with an expected median OS ≤ 12 months.
  - PFS is an alternative, and it is the preferred endpoint when the expected median OS is >12 months.
  - However, PFS alone should not be the only endpoint and must be supported by additional endpoints
    - PRO: Patient Reported Outcomes
    - TSST: Time to Second Subsequent Therapy
    - TUDD: time until definitive deterioration of quality of life

Thank You !!