GCIG Harmonization Committee Stats Section

Leiden, December 2012

General Assembly Report

Chair: Jim Paul, SGCTG
Co-Chair: Byung Ho Nam, KGOG

GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

CANCER RESEARCH UK

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- Discussion on phase II trials for targeted agents with associated biomarker

- Review of consensus statement on designs for studies in rare cancers

- Discussion topics for futures meetings:-
  - The merits of PFS or OS as primary end-point
  - Futility boundaries
  - Response adaptive designs
  - Allowing/adjusting for treatment cross-over after progression in assessing effect of a new treatment on OS ✓

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Phase II Trials for Targeted Agents
-General Background Situation-

- We have a new targeted agent with associated biomarker to identify the “target” patient group (biomarker +ve)

- The preliminary choice of biomarker will be based on
  - Biological rationale
  - Laboratory data (in vitro/in vivo)
  - PD from phase I

- Nevertheless still uncertainty that biomarker is correct
  - Measuring the wrong thing
  - Have the wrong cut-off
  - Not required

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Phase II Trials for Targeted Agents
-General Background Situation-

- The phase II element of testing therefore should both
  - Provide a preliminary assessment of the worth of the drug
  - Provide a preliminary assessment of the worth of the biomarker
  - Allow exploratory analysis
    - To refine the definition of biomarker +ve
    - To identify other biomarkers

- To do this most reliably need to do phase II in biomarker +ve and biomarker –ve patients (overselecting in the rare group to keep numbers reasonable)

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Phase II Trials for Targeted Agents
-General Background Situation-

We wish to conduct a phase II to establish whether we should:-

- Go to a phase III in the “target” patient group (biomarker +ve) only
- Go to a phase III in all patients
  - Further assessment the biomarker (some evidence of effect in the biomarker –ve patients, but not as marked as in the biomarker +ve group)
  - Without the biomarker (no evidence that the effect of the new agent depends on the biomarker)

- Not go to phase III – no evidence of effect in biomarker +ve or –ve patients (back to drawing board look for another biomarker)

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Design 4: Randomized Phase II Trial Designs With Biomarkers

Boris Freidlin, Lisa M. McShane, Mei-Yin C. Polley, and Edward L. Korn

J Clin Oncol 30:3304-3309. © 2012 by American Society of Clinical Oncology

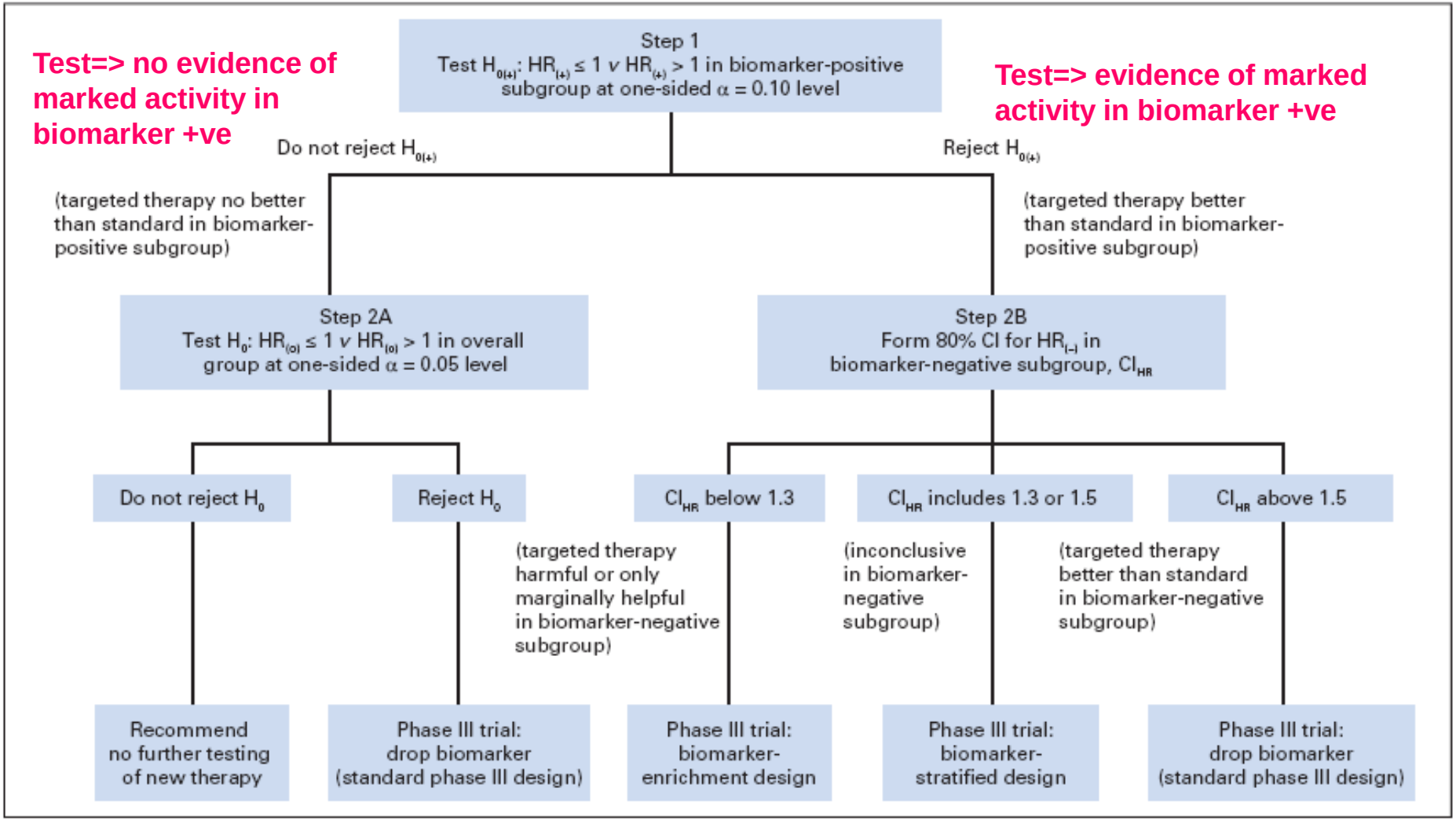

Fig 1. Decision algorithm for recommendation of phase III trial design based on the outcome of the proposed phase II biomarker trial design. H_0, null hypothesis in the overall group; $H_{0(+)}$, null hypothesis in the biomarker-positive subgroup; HR, hazard ratio; $HR_{(+)}$, HR of standard therapy relative to targeted therapy in biomarker-positive subgroup; $HR_{(-)}$, HR of standard therapy relative to targeted therapy in biomarker-negative subgroup; $HR_{(o)}$, HR of standard therapy relative to targeted therapy in overall group.