Use of blinded independent central review of PFS in definitive trials

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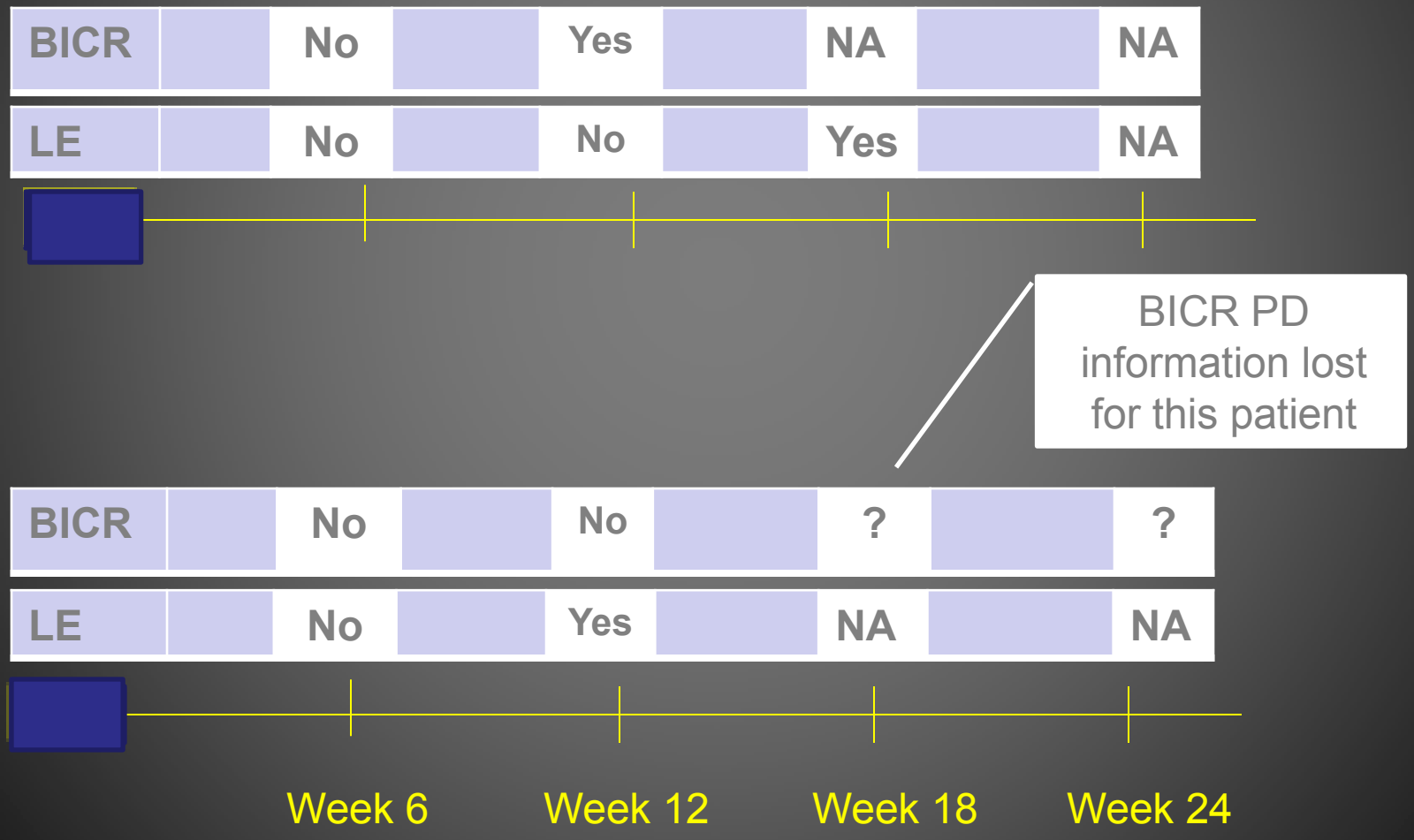
Progression-free survival

- Use of PFS an area of active debate. Not generally:
  - a measure of clinical benefit,
  - nor a surrogate for overall survival.
- For purposes of my talk, we agree that PFS is an important primary endpoint for regulatory approval.
- A trial with a PFS primary endpoint requires strong evidence that treatment effect is large.

Concerns about PFS assessments by site

- Progression assessments vary by reader
- Discrepancy rates in timing and presence of progression are high (typically > 30%)
- Concern about potential reader bias from local evaluators, who know treatment assignment, has lead to requirement for blinded independent central review

What is Blinded Independent Central Review?



The potential bias trade-off

Estimation of true effect on PFS remains elusive:

- Local evaluations: suspicion of subjective bias
- Blinded independent central review: potential informative censoring

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STATISTICS IN ONCOLOGY

Blinded Independent Central Review of Progression-Free Survival in Phase III Clinical Trials: Important Design Element or Unnecessary Expense?

Lori E. Dodd, Edward L. Korn, Boris Freidlin, C. Carl Jaffe, Lawrence V. Rubinstein, Janet Dancey, and Margaret M. Mooney

- Blinded Independent Central Review does not eliminate concerns about biased treatment effect estimates.
  - Potential for informative censoring is possible pitfall of BICR
  - Discrepancy rates between BICR reads can be high too
- Meta-analysis of published trials (7) reporting both BICR and LE showed similar treatment effects.
  - In spite of high discrepancy rates, both approaches produced similar conclusions about treatment efficacy

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Blinded independent central review of progression in cancer clinical trials: Results from a meta-analysis ☆

O. Amit [a,*], F. Mannino [a], A.M. Stone [b], W. Bushnell [a], J. Denne [c], J. Helterbrand [d], H.U. Burger [e]

- 27 randomized phase III trials in solid tumors
- Both local evaluation and BICR
- Correlation between hazard ratios: 0.95

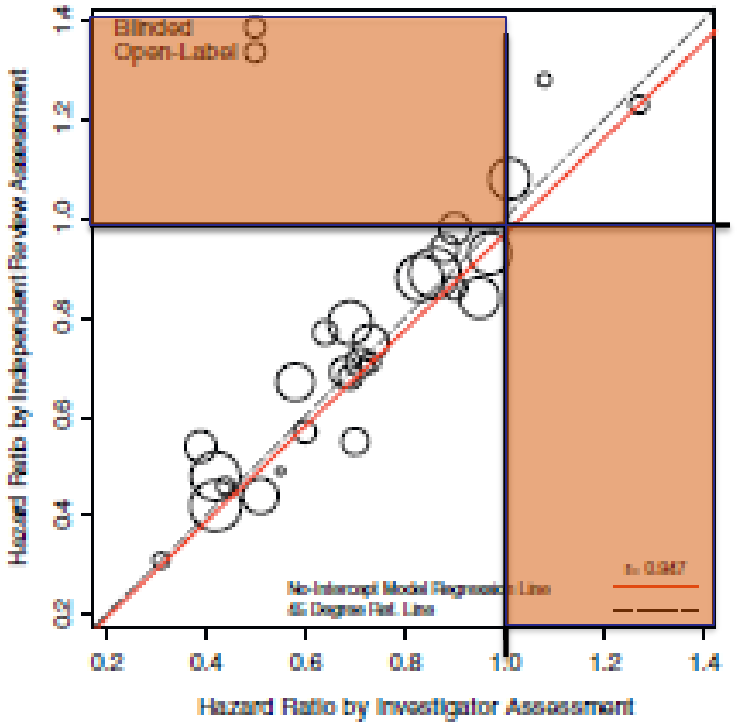

Fig. 1 – BICR versus LE HR by blinding status of trial

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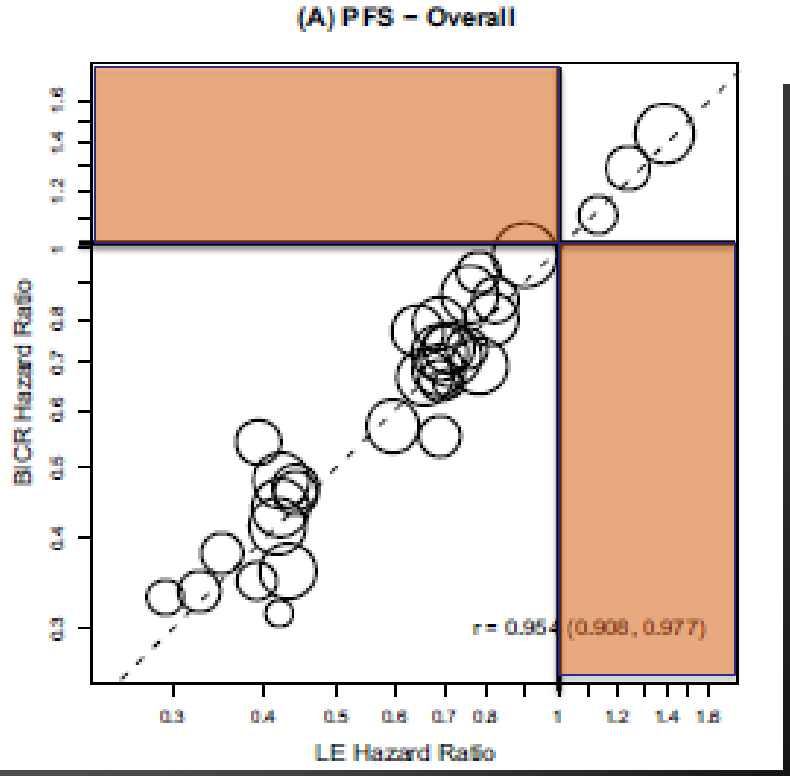
Evaluation of Blinded Independent Central Review of Tumor Progression in Oncology Clinical Trials: A Meta-analysis

Jenny J. Zhang, PhD[1], Huanyu Chen, PhD[1], Kun He, PhD[1], Shenghui Tang, PhD[1], Robert Justice, MD[2], Patricia Keegan, MD[2], Richard Pazdur, MD[2], and Rajeshwari Sridhara, PhD[1]

- 33 randomized phase III trials in solid tumors
- Both investigator assessment and blinded independent central review
- Correlation between hazard ratios: 0.91



Options

Use overall survival	• Clinically meaningful endpoint and time of death not subjective
Use complete-case BICR	• Costly, time-consuming, and rarely necessary
Use local evaluations	• Double-blinded trials. • Ensure local radiologists are suitably trained and blinded to treatment assignment
Use BICR on a subset as an audit of internal trial results	• Two published audit methods • Less effort than complete-case BICR but adds cost, time, and complexity

Local Evaluations

Double-blinded trials: BICR not required.

- Concerns about side-effects revealing treatment assignment may limit use of double-blinding
- BUT, a partially blinded trial (e.g., >90% of subjects) may have greater value than an unblinded trial. (An area worthy of research)

Unblinded trials: blind local evaluator to treatment assignment and assure appropriate training

- Would this be more burdensome than BICR?
- Aside: Extent to which local reads are evaluated with knowledge of treatment assignment is unknown

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Two published audit methods:

- Method A: On a subset demonstrate BICR hazard ratio is statistically significant and clinically meaningful. (Dodd et al., Biometrics 2011)
- Method B: Compare discrepancy rates (between BICR and LE) between treatment arms (Amit et al. 2011)
  - If difference between arms is high, this suggests bias.

Differential discordance

July 24, 2012 ODAC meeting

- All committee members agreed that an audit approach should be considered
- Members advised against complete elimination of BICR
  - Presence of audit cited as mechanism for preventing bias
  - Need for "threat" of full BICR
- No recommendations for specific audit method
  - "Methodology not "ripe" yet."

EMEA guidelines

- Open to audit concept
- “In general the confidence in the quality of the trial will increase if the trial results from the BICR do not differ from the investigator assessments to any important degree.”
- “Procedures for independent review shall be defined prospectively…”

Two audit methods

- Forthcoming paper from FDA retrospectively compares the two approaches in 26 randomized phase 3 registration trials. (Zhang et al, in revision)
  - Demonstrates feasibility of this approach, but prospective evaluation still needed.
  - One case (carcinoid) in which differential discrepancy rate consistently failed to identify bias when it should have.

Moving forward

- Collection and storage of all images a requirement for regulatory approval
- Practical details regarding audit implementation requires more consideration
  - Sampling with site stratification?
  - In settings with known difficulties with interpretation, should we consider interim monitoring of discrepancy rates (ignoring treatment assignment)?

Moving forward

- BICR audit may be best strategy today but technological advances may offer alternative solutions:
  - real-time BICR reads
  - ensure local reviews are blinded
- Dr. Harrington, ODAC meeting: “If there is a truth, it’s the way treatments will be administered in the clinic once approved.”
  - True effect of drug on PFS endpoint may be best estimated in double-blinded trial

Thanks to my collaborators!

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