

# Use of blinded independent central review of PFS in definitive trials

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# Progression-free survival

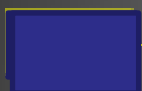
- Use of PFS an area of active debate.  
Not generally:
  - a measure of clinical benefit,
  - nor a surrogate for overall survival.
- For purposes of my talk, we agree that PFS is an important primary endpoint for regulatory approval.
- A trial with a PFS primary endpoint requires strong evidence that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

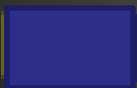
# What is Blinded Independent Central Review?

BICR		No		Yes		NA		NA
LE		No		No		Yes		NA



BICR PD information lost for this patient

BICR		No		No		?		?
LE		No		Yes		NA		NA



Week 6

Week 12

Week 18

Week 24

# 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

## 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

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

O. Amit <sup>a,\*</sup>, F. Mannino <sup>a</sup>, A.M. Stone <sup>b</sup>, W. Bushnell <sup>a</sup>, J. Denne <sup>c</sup>, J. Helderbrand <sup>d</sup>, H.U. Burger <sup>e</sup>

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

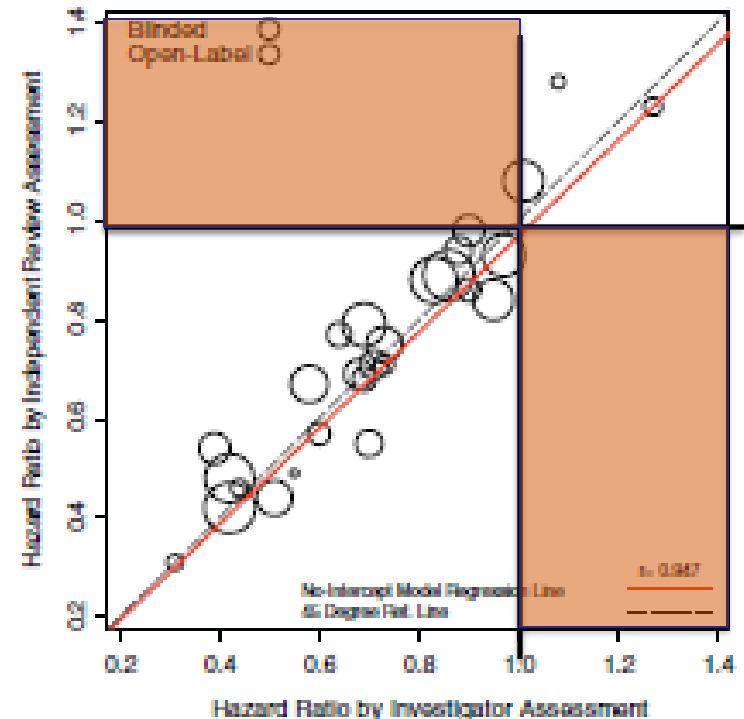


Fig. 1 - BICR versus LE HR by blinding status of trial.

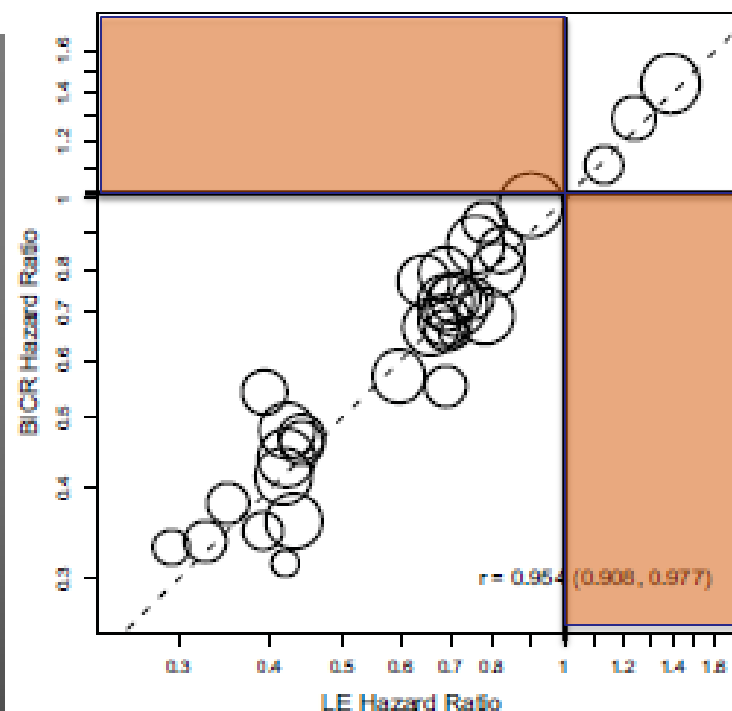
# Evaluation of Blinded Independent Central Review of Tumor Progression in Oncology Clinical Trials: A Meta-analysis

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& Regulatory Science  
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Richard Pazdur, MD<sup>2</sup>, and Rajeshwari Sridhara, PhD<sup>1</sup>

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

(A) PFS - Overall





# 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

# Options

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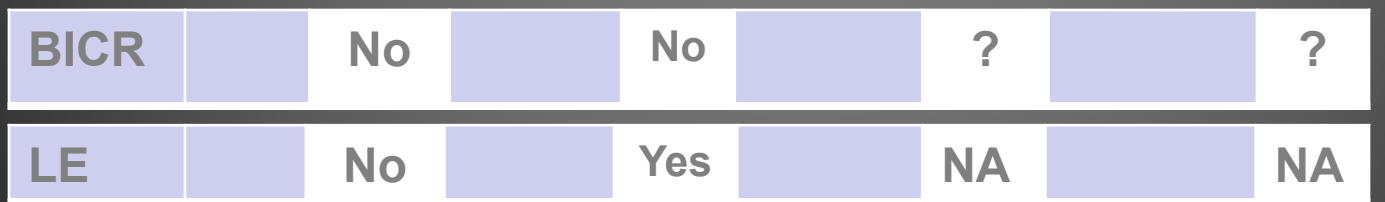
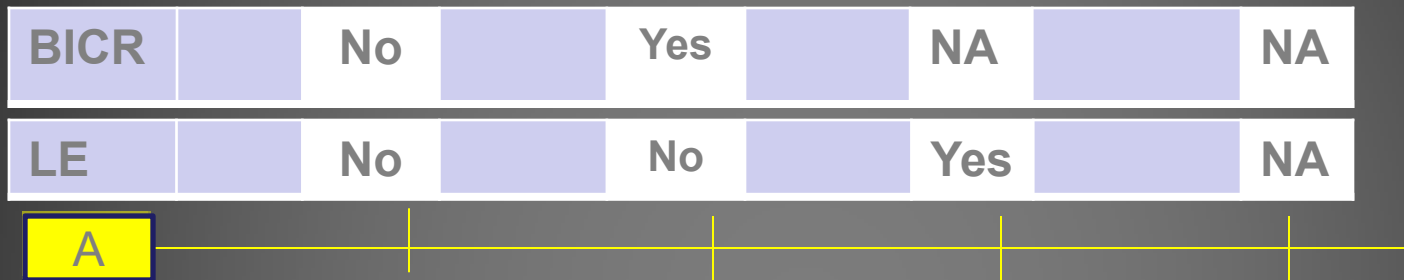
Use BICR on a subset as an audit of internal trial results

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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



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# 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.”

# EMA 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!

## NCI:

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## NIAID:

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