Progression-Free Survival by Local Investigators vs. Blinded Independent Central Review in Hormone-Positive, HER2-Negative Metastatic Breast Cancer: A Systematic Review and Meta-Analysis

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BACKGROUND AND OBJECTIVES

- Progression-free survival (PFS) is a widely accepted primary endpoint in breast cancer trials; however, it remains susceptible to assessment bias.
- To reduce this risk of bias, blinded independent central review (BICR) is often incorporated into randomized clinical trial designs.
- Emerging evidence has suggested discordance between investigator- and BICR-assessed PFS, with BICR often producing more optimistic estimates.
- Here we present a meta-analysis comparing BICR- and investigator-PFS in RCTs of patients with hormone receptor–positive, HER2-negative (HR+/HER2–) metastatic breast cancer (mBC) following progression on CDK4/6 inhibitor (CDK4/6i) therapy.

METHODS

- We conducted a systematic review and meta-analysis including phase II and III RCTs of patients with HR+/HER2– mBC and progression following CDK4/6i.
- Eligible studies required or permitted prior CDK4/6i use and reported PFS assessed by both local investigators and BICR.
- For each trial, we calculated a discrepancy index (DI)—the ratio of hazard ratios (HR) for BICR- vs investigator-PFS—and the absolute difference in median PFS (mPFS) between the two assessments. A pooled DI was estimated using a mixed-effects model.
- Subgroup analysis of trials requiring prior CDK4/6i and meta-regression by bone-only disease, visceral metastases, control arm type (endocrine/targeted therapy vs chemotherapy), study design (open-label vs double blinded), and primary endpoint (investigator- vs BICR-PFS) were performed.

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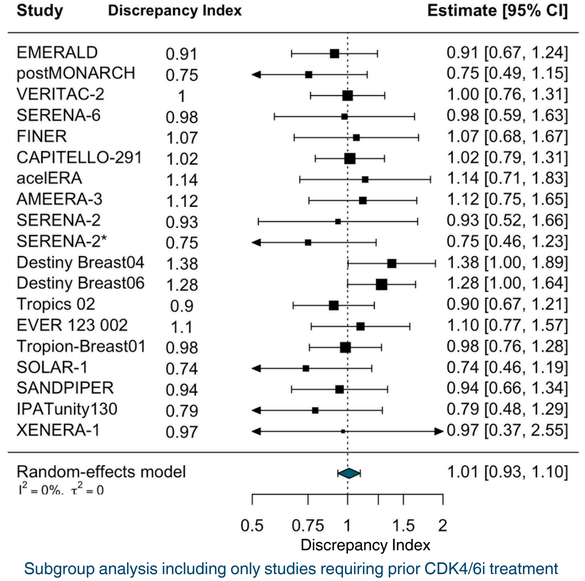
RESULTS

Table 1. Main characteristics and results of the studies included.

Study	Intervention	Control	% on prior CDK4/6i	Primary PFS Assessment
EMERALD	Elacestrant (n=239)	Fulvestrant or AI (n=238)	100	BICR
postMONARCH	Abemaciclib + fulvestrant (n=182)	Fulvestrant (n=186)	100	Investigator
VERITAC-2	Vepdegestat (n=313)	Fulvestrant (n=311)	100	BICR
SERENA-6	Camizestrant + CDK4/6i (n=157)	AI + CDK4/6i (n=158)	100	Investigator
FINER	Ipatasertib + fulvestrant (n=125)	Fulvestrant (n=125)	100	Investigator
CAPITELLO-291	Capivasertib + fulvestrant (n=355)	Fulvestrant (n=353)	69.1	Investigator
acelERA	Giredestrant (n=151)	Fulvestrant or AI (n=152)	41.9	Investigator
AMEERA-3	Amcenestrant (n=143)	Fulvestrant, AI or tamoxifen (n=147)	79.0	BICR
SERENA-2	Camizestrant (n=147)	Fulvestrant (n=73)	51.0	Investigator
Destiny Breast04	Trastuzumab Deruxtecan (n=331)	Chemotherapy (n=163)	70.4	BICR
Destiny Breast06	Trastuzumab Deruxtecan (n=436)	Chemotherapy (n=430)	90.4	BICR
Tropics 02	Sacituzumab Govitecan (n=272)	Chemotherapy (n=271)	99.0	BICR
EVER 123002	Sacituzumab govitecan (n=166)	Chemotherapy (n=165)	48.6	BICR
Tropion-Breast01	Datopotamab Deruxtecan (n=365)	Chemotherapy (n=367)	82.5	BICR
SOLAR-1	Alpelisib + fulvestrant (n=169)	Fulvestrant (n=172)	59.0	Investigator
SANDPIPER	Taselisib + fulvestrant (n=340)	Fulvestrant (n=176)	29.0	Investigator
IPATunity130	Ipatasertib–paclitaxel (n=146)	Placebo–paclitaxel (n=76)	25.6	Investigator
XENERA-1	Xentuzumab + everolimus + exemestane (n=52)	Everolimus + exemestane (n=51)	75.7	BICR

Figure 1. Forest-plot for the discrepancy index.

No statistically significant difference was observed between investigator- and BICR-assessed PFS overall.



Subgroup analysis including only studies requiring prior CDK4/6i treatment showed a pooled DI of 0.94 (95% CI, 0.80–1.11; p = 0.81).

Figure 2. Forest Plot of meta-regression analyses.

Findings were consistent across meta-regression analyses (all p>0.05).

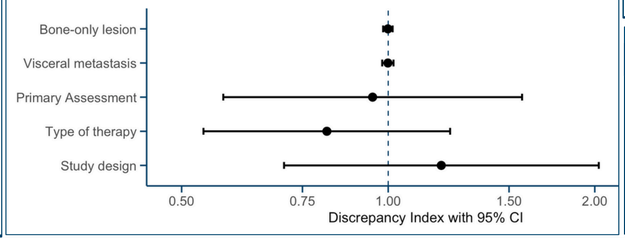
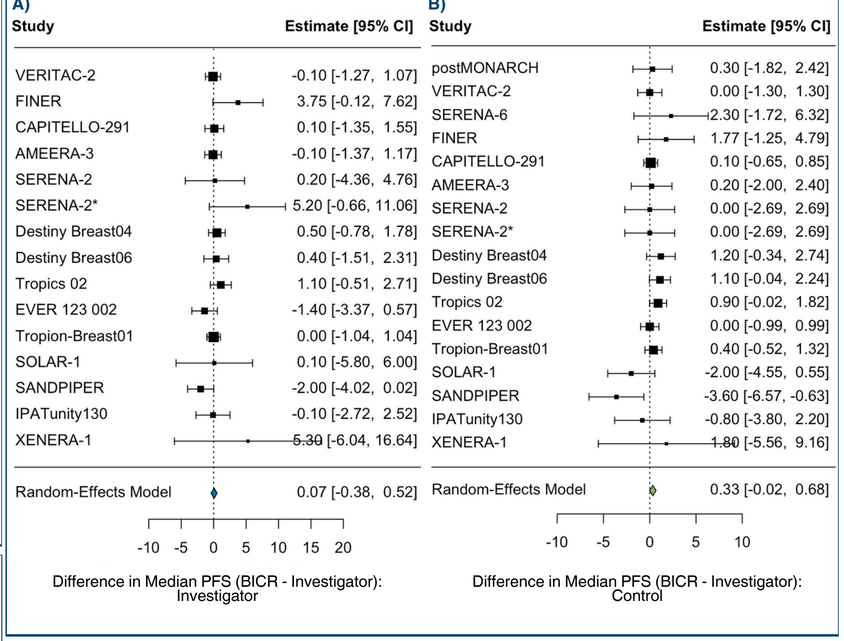


Figure 3. Forest plot of differences in mPFS assessed by BICR versus local investigators in A) intervention and B) control groups.

In intervention arms, the pooled difference was 0.07 months (95% CI: –0.38 to 0.52; p = 0.76), showing no significant discrepancy. In control arms, the pooled difference was 0.33 months (95%CI 0.02-0.68; p=0.06), indicating a non-significant trend toward larger discrepancies.



CONCLUSION

- Several recent RCTs in HR+/HER2– mBC have shown a trend toward longer mPFS with BICR, likely due to investigators incorporating additional clinical data, leading to censoring and exclusion from BICR analysis.
- However, our meta-analysis found no statistically significant differences between the two methods in this patient population.
- This consistency was demonstrated across meta-regression analyses adjusting for potential effect modifiers and in outlier trials suggesting that both approaches yield comparable PFS estimates.

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