Predictive value of Progesterone Receptor expression in Advanced Breast Cancer. Systematic Review and Meta-analysis

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Abstract

Introduction and objectives: Endocrine therapy (ET) is the standard treatment for patients with luminal (HR+/HER2–) metastatic breast cancer (MBC). However, the predictive value of progesterone receptor (PR) expression in this setting remains controversial. This study aimed to evaluate PR expression as a predictive biomarker of progression-free survival (PFS) in patients with luminal MBC treated with ET.

Materials and methods: A systematic search was conducted in PubMed, MEDLINE, and EMBASE to identify clinical trials (CTs) that included patients with luminal MBC treated with ET (either as monotherapy or in combination) and reported PR status. Data were analyzed using STATA v.12. A meta-analysis of proportions was performed to estimate pooled PR prevalence, and weighted means and frequencies were calculated. PFS according to PR status was the primary outcome.

Results: Following the screening of 1,144 studies, 46 clinical trials (published between 1997 and 2024) met the eligibility criteria.

Trial characteristics: phase II (40%) or phase III (48.9%); randomized design (71.7%); evaluated endocrine therapy (ET) either as monotherapy with parenteral SERDs (34.8%), or in combination with CDK4/6 inhibitors (39.1%) or PIK3CA/AKT/mTOR pathway inhibitors (26.1%). None of the trials investigating oral SERDs (N=31) reported PR status and were excluded from the meta-analysis. Patient characteristics (N=16,921): predominantly women (99.8%); median age 63 years (range 23–98); postmenopausal (89%) or premenopausal (10.9%); majority from Western countries (80%); visceral metastases in 48.2%, and bone-only disease in 19.1%; prior lines of therapy: none (23.9%) or ≤1 (28.3%). Most tumors were ER-positive (93.0%) and PR-positive (72.4%). The median follow-up across trials was 18.5 months. The predictive value of PR expression for PFS was reported in 25% of ET-only trials, 50% of ET+CDK4/6 trials, and 25% of ET+PIK3CA/AKT/mTOR trials. A statistically significant benefit was observed in patients with both PR-positive and PR-negative tumors who received combination therapy, compared to those treated with endocrine monotherapy (either fulvestrant or aromatase inhibitors [AIs]). Among patients receiving ET alone, clinical benefit was observed exclusively in those with PR-positive tumors. Overall heterogeneity across and within subgroups was consistent.

Conclusion: PR is an accessible and standardized biomarker that may have predictive relevance in ET-based treatment strategies. In ET monotherapy settings, clinical benefit was higher in patients with PR-positive tumors. In contrast, in combination regimens, outcomes were independent of PR status.

Introduction and Objective

Endocrine therapy (ET) is the standard treatment for patients with **luminal (HR+/HER2-) metastatic breast cancer (MBC)**. However, the **predictive value of progesterone receptor (PR)** expression in this setting **remains controversial**.

PR has traditionally been considered a marker of estrogen receptor (ER) pathway integrity, and its absence may influence tumor biology and response to therapy.

Our aim was to evaluate **PR expression as a predictive biomarker of progression-free survival (PFS) in luminal MBC treated with ET, including both monotherapy and combination regimens.**

Material and Methods

A **systematic review and meta-analysis** were conducted in accordance with PRISMA guidelines and registered in PROSPERO (CRD42024616344).

A systematic search of PubMed, MEDLINE, and EMBASE (last update December 2024) was performed to identify **prospective clinical trials** including adult patients with luminal MBC treated with **ET,** either as **monotherapy or in combination with CDK4/6 or PI3K/AKT/mTOR inhibitors**. Trials reporting PR expression and clinical outcomes such as PFS, overall survival (OS), objective response rate (ORR), or clinical benefit rate (CBR) were eligible. Data were extracted on study design, patient characteristics, treatment regimens, and PR/ER status.

Statistical analyses were conducted using Stata version 12, applying random-effects models and evaluating heterogeneity with the I^2 statistic. A meta-analysis of proportions was performed to estimate PR prevalence; Weighted means and frequencies were calculated. PFS according to PR status was the primary outcome.

Results

A total of **1,144 records were screened,** and 45 clinical trials published between 1997 and 2024 met the inclusion criteria, comprising 16,921 patients with hormone receptor-positive (HR+)/HER2-negative MBC.

Most studies were **phase II (42.2%)** or **phase III (53.3%)** with a randomized design (71.7%) and **evaluated ET as monotherapy with parenteral SERDs (34.8%), ET combined with CDK4/6 inhibitors (39.1%) or ET combined with PI3K/AKT/mTOR inhibitors (26.1%)**. None of the trials investigating oral SERDs (N=31) reported PR status and were therefore excluded from the meta-analysis**. The characteristics of the included clinical trials are shown in Table 1.**

Among the **16,921 patients** included, the vast majority were **women** (99.8%), **postmenopausal** (89%) or premenopausal (10.9%); with a median age of **63 years** (range 23–98), most of them from Western countries (80%). They had visceral metastases in 48.2%, and bone-only disease in 19.1%; prior lines of therapy: none (23.9%) or ≤1 (28.3%).

The **prevalence of PR positivity was 72.0%** (95% CI: 69.2–75.6), with no significant differences among therapeutic subgroups: **ET monotherapy (69.6%), ET + CDK4/6 inhibitors (75.7%), and ET + PI3K/AKT/mTOR inhibitors (71.2%) (p=0.23).** Estrogen receptor (ER) positivity was consistently high, with a prevalence of 93.0% (95% CI: 88.1–98.0). **PR prevalence among groups is shown in Figure 1.** The median follow-up across trials was 18.5 months.

As shown Figure 2, a **statistically significant benefit was achieved in combination regimens**—including CDK4/6 or PI3K/AKT/mTOR inhibitors—both PR-positive and PR-negative subgroups, with hazard ratios uniformly favoring combination therapy over endocrine monotherapy.

In contrast, in **endocrine monotherapy trials** (either fulvestrant or aromatase inhibitors [AIs]), **clinical benefit was observed only in PR-positive tumors**, whereas PR-negative disease showed no significant PFS advantage.

Overall heterogeneity across and within subgroups was consistent with the use of random-effects models.

Conclusions

PR is an accessible and standardized biomarker that may have predictive relevance in ET-based treatment strategies. In ET monotherapy settings, clinical benefit was greater in patients with PR-positive tumors, whereas in combination regimens outcomes appeared independent of PR status.

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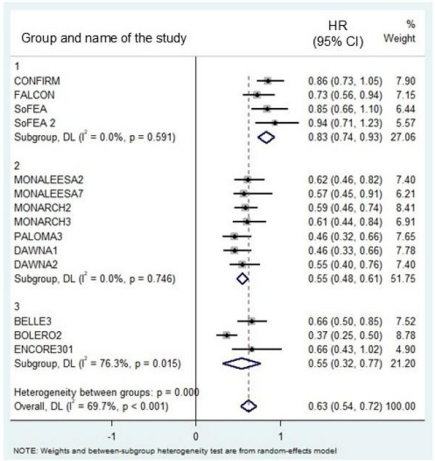
References

References supporting the findings of this study are available from the corresponding author upon reasonable request

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Figure 1. Forest-plot including clinical trials with specific predictive information (PFS) according to PR+ (A) or PR- (B) status. Group 1: ET. Group 2: ET + i.CDK4/6. Group 3: ET + i.PI3K/AKT/mTOR.

A. PR+



B. PR-

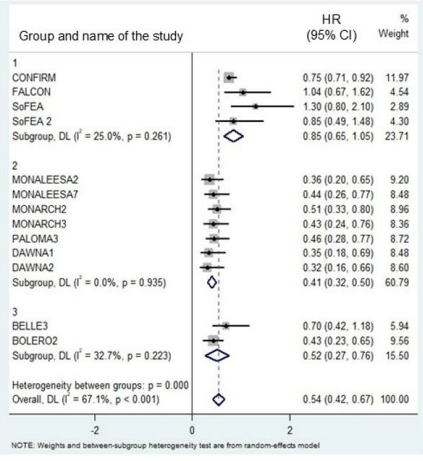
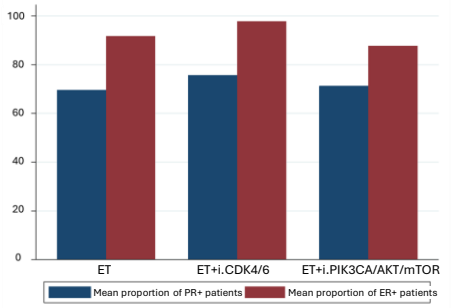


Table1. Clinical trial characteristics.

Variable		N	%
Phase	Ib/II	19	42,22
	III/IIIb	24	53,33
	IV	2	4,44
Randomization	Yes	33	71,74
	No	13	28,26
Double blind	Yes	23	50,0
	No	23	50,0
Control arm	Yes	37	80,43
	No	9	19,57
Main objective	CBR	6	13,04
	ORR	8	17,39
	PFS	29	63,04
	TTP	3	6,52

Figure 2. PR prevalence among groups.



Abbreviations:
Hazard Ratio (HR). Confidence Interval 95% (CI95%). Progesterone Receptor (PR). Estrogen Receptor (ER). Endocrine Therapy (ET). i.CDK4/6 (CDK4/6 inhibitors). i.PIK3CA/AKT/mTOR (PIK3CA/AKT/mTOR inhibitors). Clinical Benefit Rate (CBR). Objective Response Rate (ORR). Progression Free Survival (PFS). Time To Progression (TTP).