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Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer:

A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE—Estrogen receptor-positive (ER+) tumors of the breast are generally highly responsive to endocrine treatment. Although endocrine therapy is the mainstay of adjuvant treatment for ER+ breast cancer, the role of endocrine therapy in the neoadjuvant setting is unclear.

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OBJECTIVE—To evaluate the effect of neoadjuvant endocrine therapy (NET) on the response rate and the rate of breast conservation surgery (BCS) for ER+ breast cancer.

DATA SOURCES—Based on PRISMA guidelines, a librarian-led search of PubMed and Ovid MEDLINE was performed to identify eligible trials published from inception to May 15, 2015. The search was performed in May 2015.

STUDY SELECTION—Inclusion criteria were prospective, randomized, neoadjuvant clinical trials that reported response rates with at least 1 arm incorporating NET (n = 20). Two authors independently analyzed the studies for inclusion.

DATA EXTRACTION AND SYNTHESIS—Pooled odds ratios (ORs), 95% CIs, and *P* values were estimated for end points using the fixed- and random-effects statistical model.

RESULTS—The analysis included 20 studies with 3490 unique patients. Compared with combination chemotherapy, NET as monotherapy with aromatase inhibitors had a similar clinical response rate (OR, 1.08; 95% CI, 0.50–2.35; $P = .85$; n = 378), radiological response rate (OR, 1.38; 95% CI, 0.92–2.07; $P = .12$; n = 378), and BCS rate (OR, 0.65; 95% CI, 0.41–1.03; $P = .07$; n = 334) but with lower toxicity. Aromatase inhibitors were associated with a significantly higher clinical response rate (OR, 1.69; 95% CI, 1.36–2.10; $P < .001$; n = 1352), radiological response rate (OR, 1.49; 95% CI, 1.18–1.89; $P < .001$; n = 1418), and BCS rate (OR, 1.62; 95% CI, 1.24–2.12; $P < .001$; n = 918) compared with tamoxifen. Dual combination therapy with growth factor pathway inhibitors was associated with a higher radiological response rate (OR, 1.59; 95% CI, 1.04–2.43; $P = .03$; n = 355), but not clinical response rate (OR, 0.76; 95% CI, 0.54–1.07; $P = .11$; n = 537), compared with endocrine monotherapy. The incidence of pathologic complete response was low (<10%).

CONCLUSIONS AND RELEVANCE—Neoadjuvant endocrine therapy, even as monotherapy, is associated with similar response rates as neoadjuvant combination chemotherapy but with significantly lower toxicity, suggesting that NET needs to be reconsidered as a potential option in the appropriate setting. Additional research is needed to develop rational NET combinations and predictive biomarkers to personalize the optimal neoadjuvant strategy for ER+ breast cancer.

Endocrine therapy is the mainstay of treatment for estrogen receptor-positive (ER+) breast cancer. At approximately 75% of all breast cancers, ER+ constitutes the most common subtype of the disease.[1,2] Conceptually, endocrine therapy strategies include 2 approaches. The first approach inhibits the production of estrogen (ligand) so no ligand is available to activate the receptor. This strategy is used by aromatase inhibitors (AI), which block the aromatase enzyme and lower estrogen levels in postmenopausal women, or by luteinizing hormone-releasing hormone agonists, which reduce estrogen production by the ovaries and lower estrogen levels in premenopausal women. The second approach targets the estrogen receptor itself and is used by drugs such as tamoxifen, a selective estrogen receptor modulator, or fulvestrant, a selective estrogen receptor degrader.

Although medical therapy for localized breast cancer is primarily used in the adjuvant setting, it can also be effectively used in the neoadjuvant (preoperative) setting. Neoadjuvant therapy for breast cancer is generally established as a therapeutic option for selected high-risk breast cancers, such as tumors 2 cm or greater, and for locally advanced disease

(including tumors initially ineligible for resection). The use of neoadjuvant therapy offers several clinical and research advantages. In patients with large tumors, neoadjuvant therapy is likely to reduce the tumor size and can make some patients candidates for breast conservation surgery (BCS) rather than mastectomy.[3] Given that the primary tumor remains intact during therapy, the neoadjuvant treatment approach allows for monitoring of treatment response and discontinuation of inactive therapy in the event of disease progression, thereby saving the patient exposure to potentially toxic therapy. From a research perspective, the preoperative setting has become recognized as a human in vivo system to explore biomarker development and the efficacy of therapies, including novel agents.[4] A number of studies[5] have shown that the benefit of chemotherapy is similar whether treatment is given in the adjuvant or neoadjuvant setting.

Although the role of neoadjuvant chemotherapy (NACT) is well established in localized breast cancer, the role of neoadjuvant endocrine therapy (NET), as monotherapy and in combination with other therapies, remains unclear. Owing to concern for delayed time to response compared with cytotoxic chemotherapy, NET was initially used to treat elderly patients with ER+ breast cancer, particularly those who were not considered good candidates for systemic chemotherapy or surgery, because NET in general is well tolerated.[6–10] Since 2001, a number of studies[11–24] have explored the efficacy of NET in a more general population and demonstrated considerable response rates in patients with ER+ breast cancer, suggesting that NET could be a significantly less toxic alternative to NACT. However, these studies had small sample sizes with low power, which limited their ability to make robust conclusions to guide clinical application. Moreover, considerable debate remains on the optimal choice of endocrine therapy. Consequently, NET is used infrequently in clinical practice. To address these issues, we conducted a comprehensive systematic review and meta-analysis to evaluate and compare the efficacy of various NETs, including combination strategies, for ER+ breast cancer.

Methods

Based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[25] a librarian-led systematic search restricted to English-language studies in PubMed and Ovid MEDLINE was performed in May 2015 to identify eligible trials published from inception to May 15, 2015. The search strategy is detailed in eMethods in the Supplement. Gray literature was not included. Inclusion criteria were prospective, randomized, neoadjuvant clinical trials that had at least 1 NET arm and reported response rates. Studies including patients with any neoplasm other than female breast cancer were excluded, as were studies analyzing unresectable or metastatic breast cancer. This meta-analysis of readily available literature did not require institutional review board approval, and each respective study detailed their consent procedures.

Data extraction was performed independently by two of us (L.M.S. and A.G.), with very good interobserver agreement ($\kappa = 0.95$). The response rate was the primary end point of interest. Data on pathologic complete response (pCR) rate and rates of BCS were also collected when available. *Response rate* was defined as the probability of achieving a complete response and/or a partial response, determined by serial clinical or radiological

measurement, as reported by the study under consideration. A *pCR* was defined as no residual malignant lesion detected by pathologic examination of the resected tissue.

Pooled odds ratios (ORs) and *P* values were estimated for end points using the Mantel-Haenzel method and considering a fixed- and random-effects statistical model, with analyses repeated using the Peto 1-step OR method to account for rare events.[26] Meta-analyses were conducted with the computer program Review Manager (RevMan; version 5.1 for Windows; Nordic Cochrane Centre). The 95% CIs were calculated and presented in forest plots. Statistical heterogeneity was evaluated with the χ^2 test, and inconsistency was estimated using the I^2 statistic.[27] Differences between studies regarding eligibility criteria, patient population, potential bias, and treatment-delivered arms were discussed. The quality of the selected randomized clinical trials was assessed based on the instrument developed by Jadad et al[28] (eTable 1 in the Supplement). Sensitivity analyses were conducted to evaluate the effect of various variables on outcomes and to evaluate trends. A *P* value of .05 was considered statistically significant.

Results

A total of 477 potential studies were identified by the systematic search. Studies that were duplicated (n = 200) were excluded, and we reviewed abstracts for the remaining 277 studies. Of these, a total of 27 randomized clinical trials were selected for full review. Seven trials were excluded for incomplete data (n = 1), duplication (n = 1), and lack of comparisons of interest (n = 5). Ultimately, 20 trials met the criteria for inclusion, with 3490 unique patients. The PRISMA diagram detailing the inclusion process is shown in eFigure 1 in the Supplement. The PubMed search was repeated in April 2016, and 1 additional study of interest was found.[29]

Study Characteristics

The selected studies[22–24, 30–46] were published from January 2001 to December 2014. The sample sizes ranged from 44 to 374 and featured a broad patient population. Eighteen studies (90%)[22–24, 31–33, 35–46] included postmenopausal women only; 1 study (5%)[30] included premenopausal and postmenopausal women, and 1 study (5%)[34] focused entirely on premenopausal women. The selected trials compared NACT vs NET and tamoxifen vs AIs, used different durations of AI therapy, and administered NET with additional agents. Details on the selected studies are shown in the Table.

NET vs NACT

Pooled data of trials comparing NET monotherapy with AI and combination NACT for localized breast cancer demonstrated no significant difference in the clinical response rate (OR, 1.08; 95% CI, 0.50–2.35; *P* = .85; n = 378), radiological response rate (OR, 1.38; 95% CI, 0.92–2.07; *P* = .12; n = 378), pCR (OR, 1.99; 95% CI, 0.62–6.39; *P* = .25; n = 378), or BCS rate (OR, 0.65; 95% CI, 0.41–1.03; *P* = .07; n = 334), as outlined in Figure 1. Alternative statistical models demonstrating consistent results are found in eFigure 2 in the Supplement.[30–32]

However, toxicity was significantly increased in the NACT arm in all 3 studies (eTable 2 in the Supplement). Alba et al[30] reported a reduction in grade 3 (severe) to 4 (life-threatening) adverse events (OR, 0.11; 95% CI, 0.03–0.35; $P \leq .001$) favoring NET. Semiglazov et al[32] reported increased rates of neutropenia, febrile neutropenia, and cardiotoxicity with chemotherapy. Palmieri et al[31] reported statistically significant increases in alopecia, nausea, vomiting, stomatitis, and anemia with NACT. One trial[33] compared NET plus chemotherapy with NACT alone. This trial included patients with ER+ and ER-negative tumors, but in the subgroup analysis focused on those with ER+ tumors, a statistically significant benefit accrued for the clinical response rate ($P = .007$) and pCR ($P = .04$) by adding endocrine therapy.

Different Types of NET

Seven trials compared NET plus AIs vs tamoxifen.[22–24, 34–37] The pooled analysis demonstrated a highly statistically significant benefit favoring the AI over tamoxifen for the clinical response rate (OR, 1.69; 95% CI, 1.36–2.10; $P < .001$; n = 1352) and radiological response rate (OR, 1.49; 95% CI, 1.18–1.89; $P < .001$; n = 1418), as outlined in Figure 2A and B and eFigure 3 in the Supplement. The IMPACT study (Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen)[23] compared a third treatment arm in which patients received a combination of tamoxifen and letrozole vs tamoxifen alone, with no significant difference in the clinical response rate (OR, 1.15; 95% CI, 0.67–2.00; $P = .61$) and radiological response rate (OR, 1.48; 95% CI, 0.79–2.79; $P = .22$) between the 2 groups. No difference was seen in the pCR rate (OR, 1.42; 95% CI, 0.38–5.33; $P = .60$;n = 633), although the total number of events was small and only 3 studies[22, 34, 36] reported pCR (Figure 2C). For the BCS rate, a statistically significant benefit favored AI over tamoxifen (OR, 1.62; 95% CI, 1.24–2.12; $P < .001$; n = 918) (Figure 2D). For all studies, toxicity was low with both treatment strategies.

One study[38] compared durations of exemestane, 25 mg/d, for 6 and 4 months and reported no difference between the 2 groups in clinical response rates. Another study[39] compared 3 different AIs and reported no significant difference in clinical response rates among patients who received letrozole and anastrozole compared with those who received exemestane (95 of 127 [74.8%] vs 85 of 123 [69.1%] vs 78 of 124 [62.9%], respectively) and similar biological activity based on changes in the Ki67 proliferative index and the preoperative endocrine prognostic index. In addition, surgical outcomes were improved in all 3 groups, with 81 of 159 patients (50.9%) who were considered mastectomy-only candidates at the start of treatment undergoing BCS and 157 of 189 patients (83.1%) who were marginal candidates for BCS undergoing BCS.[39]

One study[40] compared fulvestrant dosages of 500 and 250 mg/mo for 16 weeks before surgery. Results demonstrated no significant difference in tumor response by ultrasonography in the intent-to-treat population (OR, 1.30; 95% CI, 0.64–2.64; $P = .47$) but higher biological activity for the 500-mg vs the 250-mg doses, consistent with observations in the metastatic setting. Our updated search revealed 1 study[29] that compared neoadjuvant anastrozole with fulvestrant, which showed similar response rates (33 of 56 [58.9%] vs 28 of

52 [53.8%], respectively) and BCS rates (33 of 56 [58.9%] vs 26 of 52 [50.0%], respectively).

NET as Monotherapy vs Dual Therapy

Agents used in combination with NET in the studies were everolimus,[41] celecoxib,[42] zoledronic acid,[43] gefitinib,[44, 45] dual endocrine therapy with AI plus tamoxifen,[23] and lapatinib.[46] As seen in Figure 3A and B, the analysis of monotherapy vs dual therapy showed no difference in terms of clinical response rate (OR, 0.91; 95% CI, 0.70–1.19; $P = .50$; n = 941) although with significant heterogeneity, but dual therapy was associated with a higher radiological response rate (OR, 1.49; 95% CI, 1.11–2.02; $P = .008$; n = 758), with similar results seen with alternative statistical models (eFigure 4 in the Supplement). Of the trials looking at NET with an additional agent considered to be a growth factor pathway inhibitor, dual therapy was associated with a higher radiological response rate (OR, 1.59; 95% CI, 1.04–2.43; $P = .03$; n = 355) but not clinical response rate (OR, 0.76; 95% CI, 0.54–1.07; $P = .11$; n = 537), which had significant heterogeneity compared with endocrine monotherapy (Figure 3C and D), with similar results noted using alternative statistical models (eFigure 4 in the Supplement). The incidence of a pCR in any arm was low overall (<10%), with resultant low numbers not suitable for intergroup comparisons. Rates of conversion to BCS were not uniformly reported. An additional study[44] testing gefitinib plus an AI was not suitable for direct comparison because gefitinib plus placebo represented the control arm. This small study (n = 56) showed that the addition of an AI resulted in greater tumor size reduction with a minimal increase in treatment-related adverse events.

Discussion

This comprehensive systematic review and meta-analysis suggests that NET, even as monotherapy, is associated with similar response rates to NACT given as combination therapy but with lower toxicity. The incidence of pCR was uniformly low, consistent with other neoadjuvant studies in ER+ breast cancer.[47] As demonstrated, neoadjuvant AIs are more effective than tamoxifen. Our study also suggests that dual combination therapy might be superior to monotherapy.

Although NACT is more widely used for fit patients than NET, both therapies have similar efficacy and low toxicity, and NET needs to be reconsidered as a potential option. In terms of choice of NET, results of this analysis mirror those seen in the adjuvant setting, with superior results for letrozole over tamoxifen in the neoadjuvant trial PO24 and the adjuvant trial BIG (Breast International Group) 1–98.[22, 48] Notably, similar to the adjuvant trial ATAC (Arimidex, Tamoxifen, Alone or in Combination), combining tamoxifen and an AI was not found to be beneficial in the neoadjuvant IMPACT trial.[23, 49] Similarly, the 1 study solely focusing on premenopausal women, the STAGE study,[34] demonstrated 6 months of ovarian suppression plus an AI was more effective in reducing tumor size than tamoxifen, which supported results seen in the adjuvant setting in the SOFT (Suppression of Ovarian Function Plus Either Tamoxifen or Exemestane Compared With Tamoxifen Alone) and TEXT (Triptorelin With Either Exemestane or Tamoxifen) trials.[50]

In the traditional treatment paradigm in ER+ breast cancer, endocrine therapy and chemotherapy were not combined because endocrine therapy might have a negative effect on concurrent chemotherapy by arresting the cell cycle in the G_O phase and limiting the sensitivity of cancer cells to cytotoxic chemotherapy.[51, 52] However, as reviewed above, combination treatment with NET plus chemotherapy compared with NACT alone showed a statistically significant benefit to adding endocrine therapy for the clinical response rate and pCR, which challenges the notion that, at least in certain instances, endocrine therapy might not negatively affect the therapeutic efficacy of concurrent chemotherapy.[33] With the remarkable therapeutic success seen in the metastatic setting with the combination of endocrine therapy and cyclindependent kinase (CDK) 4/6 inhibition, which also affects the cell cycle, and the growing appreciation of tumor heterogeneity, it might be time to revisit the dogma of never combining endocrine therapies with cell cycle-specific therapies.[53, 54]

Another traditional treatment paradigm that might warrant reconsideration is the general recommendation that NET should not be offered to premenopausal women and that NACT should be preferred. This area is understudied. Most of the randomized trials reviewed in this analysis focused on postmenopausal women. A potential concern is the time (approximately 4 weeks) needed for the combination of AI and luteinizing hormone-releasing hormone agonists to induce estradiol suppression.[30] This concern further underscores the importance of other novel endocrine therapies and biomarker-driven trials in premenopausal ER+ breast cancer. Furthermore, the use of targeted agents in combination with NET for premenopausal women has not been well studied and should be evaluated further to balance efficacy with potential toxicities, including long-term toxicities of chemotherapy in young breast cancer survivors.

Determination of the correct patient population for NET remains in question. Tools such as Oncotype Dx Breast Recurrence Score and the Breast Cancer Index have been validated in the adjuvant setting and could be explored in the neoadjuvant setting as a potential mechanism to predict response to endocrine therapy.[55, 56] In addition, biopsies performed during the course of treatment can provide valuable information regarding treatment response. Data from the IMPACT trial suggest that 2- to 4-week tumor Ki67 expression during endocrine therapy is predictive of long-term outcomes.[57] The Alliance for Clinical Trials in Oncology cooperative group has designed a phase 3 neoadjuvant clinical trial (ALTERNATE)[58] randomizing postmenopausal women with localized ER+ invasive breast cancer to anastrozole, fulvestrant, or their combination to assess a biomarker-driven treatment strategy and identify women with a low risk for disease recurrence. In this trial, biopsies are performed during NET, and patients with Ki67 expression greater than 10% are switched to chemotherapy. This strategy allows early assessment of endocrine therapy-responsive vs -unresponsive disease, which could obviate the need for chemotherapy in select settings.

The neoadjuvant setting might serve as an attractive model for drug development in ER+ breast cancer. The trials comparing endocrine monotherapy with combination therapy suggest superior radiological response rates, but the low number of trials, different drugs, and nonselective inhibitors limit specific conclusions. Several ongoing trials are combining endocrine therapy with selective inhibitors of the PI3K/Akt/mTOR/D-cyclin-CDK4/6

pathways in the neoadjuvant setting, such as letrozole with or without the PI3K inhibitor taselisib (LORELEI)[59] and letrozole with or without the CDK4/6 inhibitor palbociclib (PALLET).[60] Preliminary analysis of a phase 2 trial examining palbociclib combined with anastrozole as neoadjuvant therapy for stage 2 or 3 ER+ breast cancer showed that the addition of a CDK4/6 inhibitor significantly lowers Ki67, suggesting that the addition of CDK4/6 inhibition can improve the efficacy of NET.[61]

This study has several limitations. First, to avoid mixing studies with different treatment arms and to limit heterogeneity, only studies with similar arms were combined, and some pooled analyses were therefore restricted to 2 to 3 studies with resultant small sample sizes. Second, some of the studies comparing NET vs NACT used different radiological modalities to assess the radiological response rate. Sensitivity analysis including only the studies reporting the radiological response rate by ultrasonography demonstrated similar results (OR, 1.20; 95%CI, 0.75–1.92; $P = .45$). Although the response rate was not assessed uniformly in all trials, most used Response Evaluation Criteria in Solid Tumors (RECIST), and no evidence of major publication bias was found (eFigure 5 in the Supplement). Third, the definition of ER+ varied among some of the studies. The PO24 and IMPACT trials demonstrated higher response rates in patients with higher ER expression.[22, 23] In addition, the studies do not report survival data. Survival is a difficult end point for NET studies given the recommended use of adjuvant endocrine therapy, varying adherence with adjuvant endocrine therapy, differing use of adjuvant chemotherapy, and the long-term follow-up needed for late recurrences in ER+ breast cancer. Semiglazov et al[32] reported the local recurrence rate after a mean follow-up of less than 36 months (3.3% and 3.4% of patients who received endocrine therapy and chemotherapy, respectively). Last, conclusions regarding improved rates of BCS are limited overall because determining eligibility for BCS is subjective by nature and depends on several variables, including patient preference.

Conclusions

Neoadjuvant endocrine therapy can be a safe and effective option for localized ER+ breast cancer. Given the low toxicity associated with NET, reconsideration of NET as a worthwhile treatment option in the neoadjuvant setting is reasonable, particularly as combination therapy, similar to NACT in combination, for the correct patient population. Determining the correct patient population for NET remains an unanswered question, and will be best addressed by additional studies incorporating NET with strong biomarker-driven hypotheses. Neoadjuvant endocrine therapy also provides the opportunity to examine mechanisms of endocrine resistance, to optimize and compare endocrine therapies, and to investigate combination approaches with novel targeted therapies that may delay or prevent endocrine resistance. Further studies examining predictive biomarkers are needed to personalize optimal NET plus targeted therapy combinations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Is neoadjuvant endocrine therapy (NET), as monotherapy and in combination with other therapies, an effective treatment option for localized estrogen receptor-positive (ER+) breast cancer?

Findings

In this meta-analysis of 20 randomized clinical trials with a total sample size of 3490 women, NET, even as monotherapy, was associated with response rates similar to those of neoadjuvant combination chemotherapy but with lower toxicity.

Meaning

Neoadjuvant endocrine therapy is a reasonable treatment option for localized ER+ breast cancer, and additional studies are needed to develop rational endocrine therapy combinations and predictive biomarkers to optimize NET strategies.

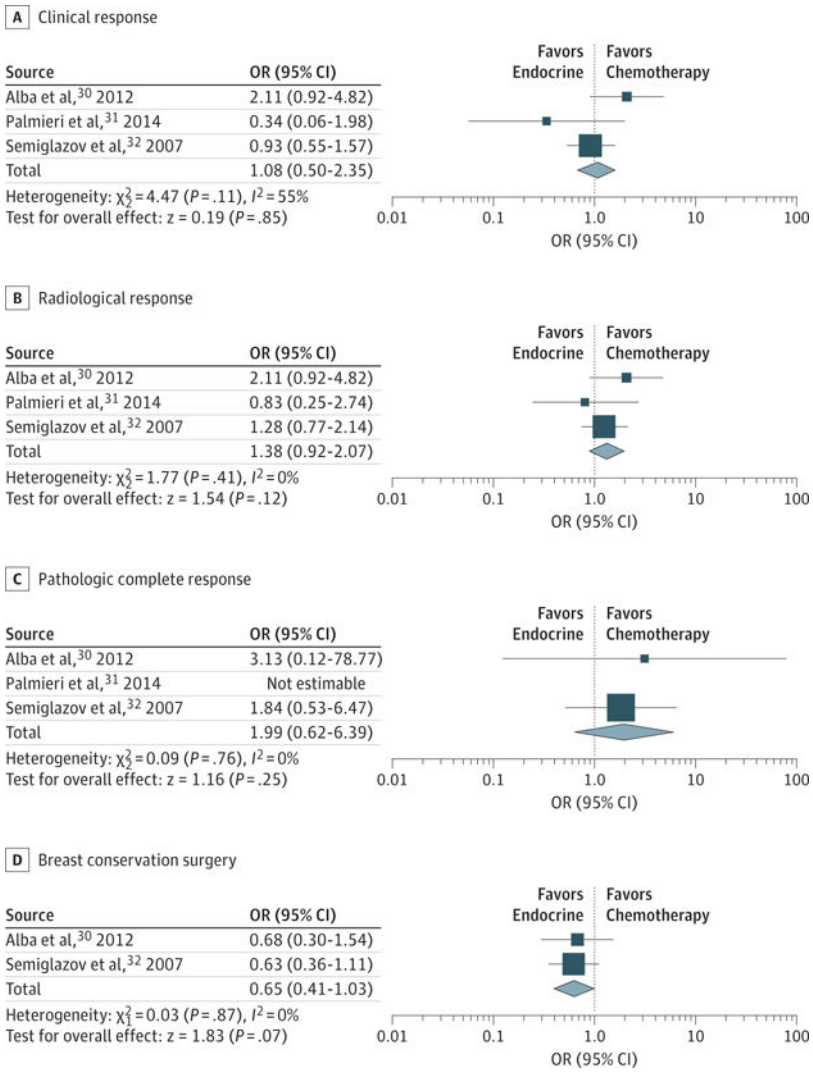

Figure 1. Neoadjuvant Hormone Therapy vs Neoadjuvant Cytotoxic Chemotherapy

Fixed-effects odds ratios (ORs) are calculated using the Mantel-Haenszel test with nonevent as the reference. Error bars represent 95% CI. Different marker sizes indicate the weight given to the specific study.

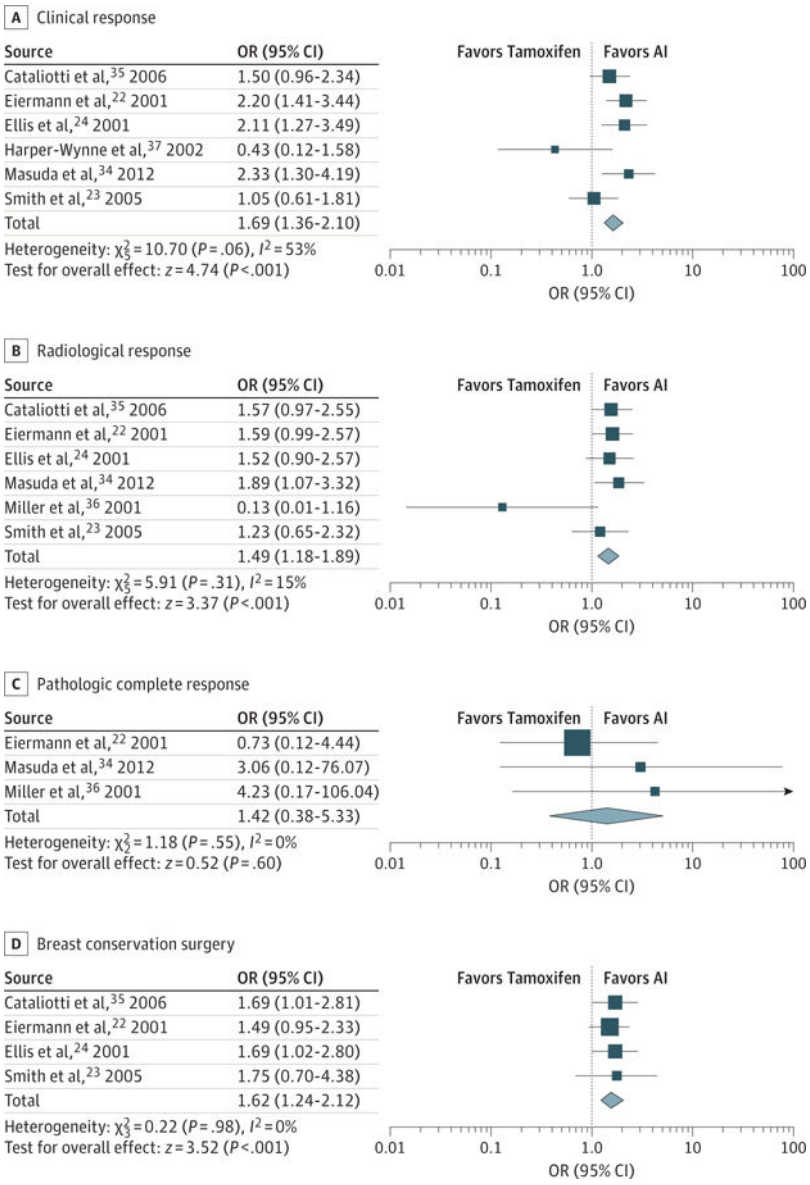

Figure 2. Neoadjuvant Aromatase Inhibitors (AIs) vs Neoadjuvant Tamoxifen

Fixed-effects odds ratios (ORs) are calculated using the Mantel-Haenszel test with nonevent as the reference. Error bars represent 95% CI. Different marker sizes indicate the weight given to the specific study.

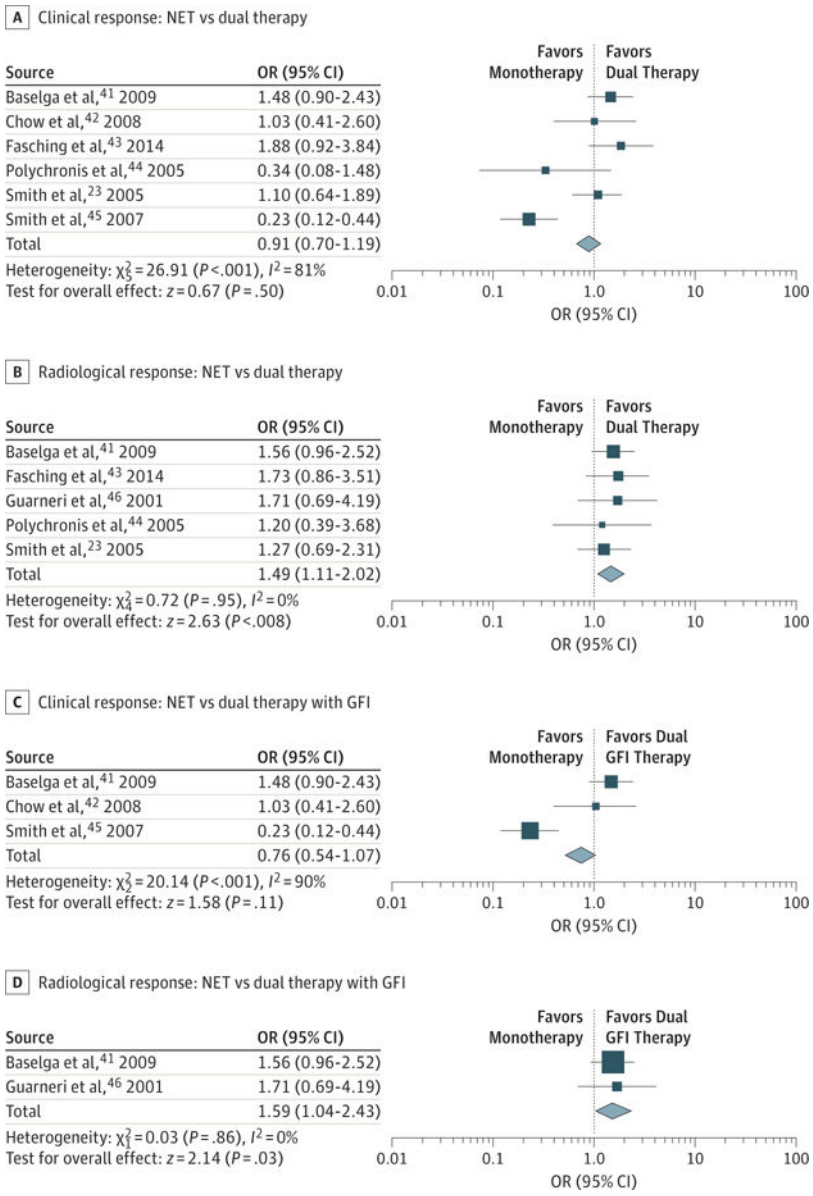

Figure 3. Neoadjuvant Endocrine Therapy as Monotherapy vs Dual Therapy

For comparison of aromatase inhibitors with dual therapy, dual therapy includes tamoxifen, zoledronic acid, everolimus, celecoxib, gefitinib, or lapatinib. Fixed-effects odds ratios (ORs) are calculated using the Mantel-Haenszel test with nonevent as the reference. Error bars represent 95% CI. Different marker sizes indicate the weight given to the specific study. GFI indicates growth factor pathway inhibitor.

Table

Summary of the Clinical Trials Included in the Meta-analysis[a]

Source (Trial Name)	Experimental Arm Therapy	Experimental Arm Therapy Duration, wk	Control Arm Therapy	Control Arm Therapy Duration, wk	Total No. of Participants for Comparisons	Primary End Point
Endocrine Therapy vs Chemotherapy						
Alba et al,[30] 2012 (GEICAM/2006–03)	Exemestane, 25 mg/d, plus goserelin, 3.6 mg/mo if premenopausal	24	EC-T: epirubicin, 90 mg/m^2, plus cyclophosphamide, 600 mg/m^2 × 4 cycles q21d Docetaxel, 100 mg/m^2 × 4 cycles q21d plus goserelin, 3.6 mg/mo if premenopausal	24	95	OR by MRI based on RECIST criteria
Palmieri et al,[31] 2014 (NEOCENT)	Letrozole, 2.5 mg/d	18–23	FEC: fluorouracil, 500–600 mg/m^2, plus epirubicin, 75–100 mg/m^2, plus cyclophosphamide, 500–600 mg/m^2 × 6 cycles q21d; switched to docetaxel, 100 mg/m^2 after 3 cycles if SD or PD (n = 11)	18	44	Feasibility OR (by US or mammography based on RECIST criteria) was a secondary end point
Semiglazov et al,[32] 2007	Anastrozole, 1 mg/d Exemestane, 25 mg/d	12	Doxorubicin, 60 mg/m^2, plus paclitaxel, 200 mg/m^2 × 4 cycles q21d	12	239	OR by clinical palpation (PR defined as regression >50%) OR by US/mammography was a secondary end point
Different Types of Endocrine Therapy						
Eiermann et al,[22] 2001 (PO24)	Letrozole, 2.5 mg/d	16	Tamoxifen, 20 mg/d	16	324	OR by clinical palpation OR by US/mammography was a secondary end point
Smith et al,[23] 2005 (IMPACT)	Anastrozole, 1 mg/d Anastrozole, 1 mg/d plus tamoxifen, 20 mg/d	12	Tamoxifen, 20 mg/d	12	330	OR by caliper assessment based on WHO criteria OR by US was a secondary end point
Masuda et al,[34] 2012 (STAGE)	Anastrozole, 1 mg/d, plus goserelin, 3.6 mg/mo	24	Tamoxifen, 20 mg/d, plus goserelin, 3.6 mg/mo	24	197	OR by caliper assessment OR by US, MRI, or CT based on RECIST criteria was a secondary end point
Cataliotti et al,[35] 2006 (PROACT)	Anastrozole, 1 mg/d	12	Tamoxifen, 20 mg/d	12	314[b]	OR based on US by RECIST criteria
Ellis et al,[24] 2001	Letrozole, 2.5 mg/d	16	Tamoxifen, 20 mg/d	16	250	OR byclinical assessment based on WHO criteria OR by US/ mammography was a secondary end point

Source (Trial Name)	Experimental Arm Therapy	Experimental Arm Therapy Duration, wk	Control Arm Therapy	Control Arm Therapy Duration, wk	Total No. of Participants for Comparisons	Primary End Point
Miller et al,[36] 2001	Anastrozole, 1 mg/d (n = 12) or 10 mg/d (n = 11)	12	Tamoxifen, 40 mg/d	12	112	OR by caliper assessment and by US based on percentage reduction in tumor volume
Harper-Wynne et al,[37] 2002	Vorozole, 2.5 mg/d	12	Tamoxifen, 20 mg/d	12	53	Biological differences, including OR by US, and clinical assessment based on percentage change in tumor volume
Endocrine Therapy With Growth Factor Pathway Inhibitors						
Guarneri et al,[46] 2014	Letrozole, 2.5 mg/d, plus lapatinib, 1500 mg/d	24	Letrozole, 2.5 mg/d, plus placebo	24	92	OR based on US by RECIST criteria
Baselga et al,[41] 2009	Letrozole, 2.5 mg/d, plus everolimus, 10 mg/d	16	Letrozole, 2.5 mg/d, plus placebo	16	270	OR based on palpation by WHO criteria OR also assessed by US/ mammography
Chow et al,[42] 2008 (CAAN)	Exemestane, 25 mg/d, plus celecoxib, 400 mg twice daily	12	Exemestane, 25 mg/d, plus letrozole, 2.5 mg/d	12	79	OR by caliper assessment based on UICC criteria
Smith et al,[45] 2007	Anastrozole, 1 mg/d, plus gefitinib, 250 mg/d (combined 2 arms, gefitinib 14 vs 16 weeks)	16	Anastrozole, 1 mg/d	16	206	Change in Ki67 Secondary end point was OR (modality not specified) based on UICC/WHO criteria
Studies Without Direct Comparisons for Meta-analysis						
Hojo et al,[38] 2013 (PTEX46)	Exemestane, 25 mg/d	24	Exemestane, 25 mg/d	16	51	OR by caliper assessment based on RECIST criteria
Kuter et al,[40] 2012 (NEWEST)	Fulvestrant, 500 mg/mo, plus 500 mg on d 14 of mo 1	16	Fulvestrant, 250 mg/mo	16	211	OR by 3-dimensional US assessment (PR defined as regression ≥65%)
Ellis et al,[39] 2011 (ACOSOG Z1031)	Exemestane, 25 mg/d	16–18	Letrozole, 2.5 mg/d Anastrozole, 1 mg/d	16–18	374	OR by clinical assessment based on WHO criteria
Polychronis et al,[44] 2005	Gefitinib, 250 mg/d, plus anastrozole, 1 mg/d	4–6	Gefitinib, 250 mg/d, plus placebo	4–6	56	Change in Ki67 Secondary end points included clinical and US assessments
Fasching et al,[43] 2014 (FemZone)	Letrozole, 2.5 mg/d, plus intravenous zoledronic acid, 4 mg q4w	24	Letrozole, 2.5 mg/d	24	131	OR by mammography based on RECIST criteria
Mohammadianpanah et al,[33] 2012	Letrozole, 2.5 mg/d, plus fluorouracil, 600 mg/m^2, doxorubicin, 60 mg/m^2, and cyclophosphamide, 600 mg/m^2 (FAC), q21d	9–13	Fluorouracil, 600 mg/m^2, doxorubicin, 60 mg/m^2, and cyclophosphamide, 600 mg/m^2 (FAC), q21d	9–13	62 (ER+)	OR by caliper assessment and US based on RECIST criteria pCR

Abbreviations: CT, computed tomography; ER+, estrogen receptor positive; MRI, magnetic resonance imaging; OR, overall response rate; pCR, pathologic complete response; PD, progressive disease; PR, partial response; q4w, every 4 weeks; q21d, every 21 days; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UICC, Union for International Cancer Control; US, ultrasonography; WHO, World Health Organization.

[a] All study participants were postmenopausal except for the study by Alba et al,[30] in which participants were premenopausal and postmenopausal.

[b] Excluded patients who received hormone therapy plus chemotherapy.

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