Combined Tamoxifen and Luteinizing Hormone-Releasing Hormone (LHRH) Agonist Versus LHRH Agonist Alone in Premenopausal Advanced Breast Cancer: A Meta-Analysis of Four Randomized Trials

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Purpose: **The logic behind the application of luteinizing hormone-releasing hormone (LHRH) agonists in combination with tamoxifen in premenopausal women is that LHRH agonists on the one hand suppress the tamoxifen-induced stimulation of the pituitary-ovarian function and, on the other hand, seem as effective as surgical castration. This meta-analysis combines all randomized evidence to compare the combined treatment with LHRH agonist alone with respect to overall survival, progression-free survival, and objective response in premenopausal women with advanced breast cancer.**

Patients and Methods: **Four clinical trials randomizing a total of 506 premenopausal women with advanced breast cancer to LHRH agonist alone or to the combined treatment of LHRH agonist plus tamoxifen were identified. Meta-analytic techniques were used to analyze individual patient data from these trials.**

Results: **With a median follow-up of 6.8 years, there was a significant survival benefit (stratified log-rank test, *P* = .02; hazards ratio [HR] = 0.78) and progression-free survival benefit (stratified log-rank test, *P* = .0003; HR = 0.70) in favor of the combined treatment. The overall response rate was significantly higher on combined endocrine treatment (stratified Mantel Haenszel test, *P* = .03; odds ratio = 0.67).**

Conclusion: **The combination of LHRH agonist plus tamoxifen is superior to LHRH agonist alone in premenopausal women with advanced breast cancer. Therefore, if a premenopausal woman with advanced breast cancer is thought to be suitable for endocrine treatment, it is proposed that the combination of a LHRH agonist plus tamoxifen be considered as the new standard treatment.**

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THE MOST POWERFUL hormone-stimulating breast tumor growth is estradiol; hence, its deprivation/antagonism, by either medical or surgical means, is particularly important in treating the disease. For many years, the classical endocrine manipulation for premenopausal patients with advanced breast cancer has been surgical oophorectomy, which removed both functioning ovaries.[1] An alternative to this is to medically suppress the function of the ovaries by using an luteinizing hormone-releasing hormone (LHRH) agonist. In the premenopausal woman the pituitary gland is stimulated by pulses of LHRH, producing pulsatile secretion of gonadotrophins and maintaining the cyclical activity of the gonads. Chronic administration of an LHRH agonist, using a long-term depot formulation, results in an initial stimulation of gonadotrophin release, which is quickly followed by a fall in gonadotrophin secretion and a subsequent decrease in the circulating estrogen concentrations to postmenopausal levels.[2] Therefore, although in vitro work has demonstrated that LHRH agonists have some direct antitumor effects[3-6] and there is evidence of specific LHRH binding sites in primary human breast cancers,[6,7] the principal mechanism of action of LHRH agonist treatment is still by medical castration.

A series of phase II studies with different LHRH agonists, including goserelin ([TM]Zoladex[/TM], Zeneca) and buserelin ([TM]Suprefact[/TM] Hoechst, Frankfurt, Germany), have demonstrated the activity of these agents in premenopausal women with advanced breast cancer.[2,8] Furthermore, a randomized study of premenopausal women with estrogen receptor (ER)–positive or ER-unknown advanced breast cancer and another randomized study of premenopausal women with ER-positive and/or progesterone receptor–positive metastatic breast cancer showed that treatment with

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the LHRH agonist, goserelin, provided a clinical benefit similar to surgical oophorectomy in terms of both progression-free and overall survival, but without the need for surgery and all the ensuing complications.[9,10]

Tamoxifen is now considered to be the standard first-line therapy for postmenopausal patients with advanced breast cancer. Although the recent overview by the Early Breast Cancer Trialists' Collaborative Group shows a clear benefit for adjuvant tamoxifen in terms of both survival and reduction in recurrence in premenopausal women with ER-positive tumors or tumors of unknown ER status,[11] the use of tamoxifen in premenopausal women with advanced disease has not been demonstrated so clearly.[12] Clinical experience of tamoxifen in premenopausal women is less than in the postmenopausal setting, and relatively few patients (< 400) have been included in phases II and III trials. Tamoxifen is generally accepted as an alternative to surgical oophorectomy in premenopausal patients on the basis of two relatively small comparative studies (total of 160 patients including ER-negative patients).[13,14] Although no significant differences between the treatments were shown, it is not possible to draw any definite conclusions about the equivalence of tamoxifen to oophorectomy.[7,15] Furthermore, in premenopausal women, tamoxifen can result in stimulation of pituitary-ovarian function, sometimes accompanied by high peaks in plasma estradiol levels, together with gonadotrophin levels that are either unchanged or slightly increased.[7,15-18] The possible deleterious effects resulting from such high circulating estradiol concentrations competing with tamoxifen for ER binding sites has been a matter of debate and potential concern for a number of years.[16]

The application of LHRH agonists in combination with other endocrine agents such as tamoxifen in premenopausal women has provoked a great deal of interest.[7,17,19-22] Endocrine studies have demonstrated that coadministration of an LHRH agonist completely suppresses the stimulatory effects of tamoxifen on pituitary-ovarian function and results in postmenopausal levels of circulating estrogens.[7,19-22] Hence, by combining an LHRH agonist with tamoxifen, it is possible to induce a so-called maximal estrogen blockade. Early reports indicated that the combination of goserelin or buserelin with antiestrogen therapy increased the duration of response as assessed in nonrandomized studies.[19,22]

During the past 5 years, three randomized trials have shown that the addition of tamoxifen to LHRH agonist treatment results in either a positive trend or a significant improvement in response rates and/or duration of response and/or overall survival in premenopausal women with advanced breast cancer (or specific subgroups thereof).[9,23,24] Furthermore, more recently, a fourth such trial has commenced in Japan. The meta-analysis described here was conducted to give an overview of the results of all known randomized trials comparing an LHRH agonist alone with the combination of an LHRH agonist plus tamoxifen, with the aim of investigating whether combined endocrine therapy is more effective than an LHRH agonist alone in the treatment of premenopausal women with advanced breast cancer.

Table 1. Trials Included

	LHRH Agonist Alone	LHRH Agonist + Tamoxifen	Total
International study	159	159	318
EORTC study	54	53	107
Italian study	24	24	48
Japanese study	19	14	33
Total	256	250	506

Such a meta-analysis has the advantage of increasing the power of the statistical comparisons to detect treatment differences.[25,26] The data verification, analysis, and drafting of the publication was carried out independently by the Meta-Analysis Unit of the European Organization for Research and Treatment of Cancer (EORTC) Data Center in conjunction with the principal investigators representing each of the individual trials.

PATIENTS AND METHODS

Eligibility

A literature search was carried out to identify all randomized trials, both published and unpublished, that compared an LHRH agonist alone with the combination of an LHRH agonist plus tamoxifen in premenopausal patients with advanced breast cancer (patients had either measurable distant metastases or locally advanced disease). Abstract books of meetings were reviewed. Furthermore, all collaborators, leaders in the use of combined endocrine therapy, were well aware of ongoing trials and research in this area. They were well informed by different pharmaceutical companies about trial plans with various LHRH agonists.

Trials

Four relevant trials were identified, as listed in Table 1: an international trial,[23] an EORTC trial,[24] an Italian trial,[9] and a Japanese study (unpublished). All trials commenced in 1988, with the exception of the Japanese trial, which started in 1994 and is still open to patient accrual. The trials differed slightly from each other with respect to both the hormonal treatment regimen used and the eligibility criteria. These differences are summarized below (Table 2).

Treatment Regimens

The EORTC study included three treatment arms: (1) LHRH agonist alone, (2) tamoxifen alone, and (3) LHRH agonist plus tamoxifen. LHRH agonist treatment consisted of buserelin 6.6 mg of subcutaneous (SC) depot, administered every 6 weeks for the first 12 weeks and every

Table 2. Treatment Regimens and Eligibility Criteria

	International Trial	EORTC Trial	Italian Trial	Japanese Trial
Start accrual	1988	1988	1988	1994
Treatment regimens	LHRH agonist LHRH agonist + tamoxifen	LHRH agonist LHRH agonist + tamoxifen Tamoxifen	LHRH agonist LHRH agonist + tamoxifen Ovarian ablation Ovarian ablation + tamoxifen	LHRH agonist LHRH agonist + tamoxifen
LHRH agonist	Goserelin 3.6 mg SC depot once every 4 weeks	Buserelin 6.6 mg SC depot first 12 weeks every 6 weeks, then every 8 weeks	Goserelin 3.6 mg SC depot once every 4 weeks	Goserelin 3.6 mg SC depot once every 4 weeks
Tamoxifen	20 mg twice daily	20 mg twice daily	30 mg daily	20 mg daily
Menopausal status definition	Menstrual cycle at least once during last year	Menstrual cycle at least once every 3 months	Menstrual cycle at least once during last year	Regular menstrual cycles
Prior endocrine therapy	No adjuvant endocrine therapy during last 6 months	No adjuvant endocrine therapy during last year	No prior endocrine therapy for advanced disease	No adjuvant endocrine therapy during last 4 weeks
Prior chemotherapy	No adjuvant chemotherapy during last 6 months	No adjuvant chemotherapy during last 6 months	No prior chemotherapy for advanced disease	No adjuvant chemotherapy during last 4 weeks
Receptor status	ER+ and ER− ER unknown	ER+ and/or PR+ Unknown and DFI > 2 years	ER+ ER unknown	ER+ ER unknown

Abbreviation: DFI, disease-free interval.

8 weeks thereafter. The dose of tamoxifen was 40 mg: 20 mg twice daily. Only treatment arms 1 and 3 were used in the meta-analysis.

The Italian study had a two-by-two factorial design and contained four treatment arms: (1) ovarian ablation (by surgical oophorectomy or ovarian irradiation), (2) LHRH agonist alone, (3) ovarian ablation plus tamoxifen, and (4) LHRH agonist plus tamoxifen. LHRH agonist treatment consisted of goserelin 3.6 mg SC depot, once every 4 weeks. The dose of tamoxifen was 30 mg daily. Only treatment arms 2 and 4 were used in the meta-analysis.

The International study (ICI/Zeneca 2302) had only two treatment arms: (1) LHRH agonist and (2) LHRH agonist plus tamoxifen. LHRH agonist treatment consisted of goserelin 3.6 mg SC depot, once every 4 weeks. The dose of tamoxifen was 40 mg: 20 mg twice daily. Both treatment arms were used in the meta-analysis.

The Japanese study also had only two treatment arms: (1) LHRH agonist and (2) LHRH agonist plus tamoxifen. LHRH agonist treatment consisted of goserelin 3.6 mg SC depot, once every 4 weeks. The dose of tamoxifen was 20 mg daily. Both treatment arms were used in the meta-analysis.

Menopausal Status

Only premenopausal patients were eligible, but menopausal status was defined differently in the four trials. A menstrual period had to occur at least once every 3 months in the EORTC trial and at least once during the last year in the international and Italian studies, whereas the Japanese trial only specified regular menstrual cycles.

Prior Treatment

Although the treatment was first-line treatment for advanced disease in all trials, each of the trials had slightly different inclusion criteria with respect to previous hormonal therapy and/or chemotherapy. In the EORTC trial, patients had no adjuvant endocrine therapy during the previous year or chemotherapy during the previous 6 months. Patients should not have received hormonal therapy or chemotherapy in the previous 6 months in the international trial. In the Italian trial, no prior hormonal or chemotherapy for advanced disease was allowed. Finally, in the Japanese trial, no hormonal therapy, chemotherapy, or immunotherapy should have been given in the previous 4 weeks.

Receptor Status

In the EORTC trial, patients were only eligible if their tumors were ER-positive and/or progesterone receptor–positive or, in those cases where the tumor receptor status was unknown, the patient must have had a disease-free interval of more than 2 years. In both the Italian and the Japanese trials, only those patients with positive or unknown ER status were considered eligible. Receptor status was not used as an eligibility criterion in the international trial.

Data Collection: Individual Patient Data

For all patients within each of the trials, the following individual patient data were requested:

1. *Treatment assigned by randomization:* LHRH agonist or LHRH agonist plus tamoxifen, and the date of randomization.

2. *Potential prognostic factors*: date of birth, ER status (ER-positive if > 10 fmol/mg cytosol protein, ER-negative if < 10 fmol, and ER-unknown if not assessed), disease-free interval (time interval between treatment of the primary tumor and disease recurrence), prior adjuvant chemotherapy, adjuvant hormonal therapy or surgical ovarian ablation, and disease sites: soft tissue disease, bone metastases, and/or visceral metastases. The dominant site of metastases was classified using a hierarchical system with visceral metastases, where present, being considered to be the dominant site, followed by bone; soft tissue was considered to be the dominant site if neither visceral nor bone metastases were present.

3. *End points:* The primary end point was duration of survival from randomization onto the trial, with progression-free survival and objective response as the secondary end points. The date of death, or the date when last known to be alive, and the date of progression were collected. The criteria for assessing objective response were based on the Union International Contre le Cancer (UICC) response criteria[27] except in the

Table 3. Patient Characteristics by Trial

Characteristic	International Trial		EORTC Trial		Italian Trial		Japanese Trial		Overall	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years										
Median	42		43		42		45		42	
Range	24-56		28-58		32-54		32-51		24-58	
ER status										
Positive	194	61	62	58	39	81	18	55	313	62
Negative	67	21	12	11*	0	0	0	0	79	16
Unknown	57	18	33	31	9	19	15	45	114	22
DFI										
< 2 years	146	46	38	35	22	46	13	39	219	43
≥ 2 years	138	43	64	60	26	54	20	61	248	49
Unknown	34	11	5	5	0	0	0	0	39	8
Adjuvant chemotherapy										
Yes	91	29	32	30	29	60	18	55	170	33
No	222	70	69	64	17	36	14	42	322	64
Unknown	5	1	6	6	2	4	1	3	14	3
Adjuvant hormone therapy										
Yes	8	2	4	4	1	2	18	55	31	6
No	305	96	98	91	45	94	14	42	462	91
Unknown	5	2	5	5	2	4	1	3	13	3
Dominant site of disease										
Soft tissue	58	18	26	24	11	23	13	40	108	21
Bone	152	48	46	43	33	69	11	33	242	48
Visceral	108	34	35	33	4	8	9	27	156	31

*Eleven patients ER−/PR+ and one patient ER−/PR−.

Japanese study, which used the response criteria for advanced/recurrent breast cancer described in the 12th edition of *General Rules for Clinical and Pathological Recording of Breast Cancer*.[28] Complete and partial responders were taken together as responders, whereas no change or progression were classified as nonresponders.

The data were checked both for internal consistency and for the distribution of the prognostic factors over the two treatment arms.

Statistical Methods

All analyses used the intent-to-treat principle, including all patients according to the treatment group assigned at the time of randomization. Treatment effects were compared only within a trial. The observed minus expected number of events and its variance were calculated in each trial and then summed across all trials. The trial was always used as a stratification factor, and all tests were two-sided.[29,30]

The duration of survival and progression-free survival curves were estimated using the Kaplan-Meier technique[31,32] and compared using the stratified log-rank test with the Mantel variance.[32] The overall hazards ratio (HR) and its 95% confidence interval were obtained, based on the stratified log-rank statistic.

The objective response rate was compared using the stratified Mantel-Haenszel χ^2 test for combining two-by-two tables.[33] The overall treatment effect is given by the typical odds ratio (OR) with its 95% confidence interval.

The meta-analysis results are presented graphically in Forest plots. The main analysis comparing the two treatment arms was stratified by trial. For each trial, an OR or HR and its 99% confidence interval were calculated. χ^2 tests for heterogeneity and interactions were used to detect differences in treatment effect between trials and prognostic subgroups, respectively.[30] As interaction tests have generally low power, a nonsignificant interaction test between a prognostic factor and the treatment is not a proof that there is no interaction. Therefore, we performed exploratory analyses to check whether the treatment differences were in the same direction in the different prognostic subgroups instead of looking for differences between the subgroups.

RESULTS

Patient Characteristics

In total, 506 patients were entered onto the two arms of interest, 256 on LHRH agonist alone and 250 on the combination of LHRH agonist plus tamoxifen (Table 1). Seventy-nine percent of patients received goserelin as the LHRH agonist, and 21% received buserelin. The median follow-up was 6.8 years in all the trials combined. The Japanese trial had, however, a median follow-up of only 2 years.

The key patient characteristics by trial are listed in Table 3. Age was similar in all the trials and ranged from 24 to 58 years, with a median of 43 years. Overall, 62% of patients were ER-positive, 16% ER-negative, and 22% were of unknown ER status. None of the patients in the Italian or the Japanese trials were ER-negative, but the percentage of patients with an unknown receptor status was at least 18% (in the international trial), rising to 45% in the Japanese

Table 4. Patient Characteristics by Treatment Group

Characteristic	LHRH Agonist Alone		LHRH Agonist + Tamoxifen		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	42		43		43	
Range	24-58		28-56		24-58	
ER status						
Positive	152	59	161	65	313	62
Negative	38	15	41	16	79	16
Unknown	66	26	48	19	114	22
DFI						
$<$ 2 years	115	45	104	42	219	43
$\geq$ 2 years	122	48	126	50	248	49
Unknown	19	7	20	8	39	8
Adjuvant chemotherapy						
Yes	92	36	78	31	170	33
No	154	60	168	67	322	64
Unknown	10	4	4	2	14	3
Adjuvant hormone therapy						
Yes	17	7	14	6	31	6
No	230	90	232	93	462	91
Unknown	9	3	4	1	13	3
Location of disease						
Soft tissue	58	23	50	20	108	21
Bone	126	49	116	46	242	48
Visceral	72	28	84	34	156	31

trial. Between one third and one half of the patients had a disease-free interval of less than 2 years (disease-free interval is defined as the time interval between treatment of the primary tumor and disease recurrence).

In the EORTC and international trials, most patients did not receive adjuvant chemotherapy before entry (probably because of node negativity), whereas the majority of patients in the Italian and Japanese trials did so (Table 3). Overall, only 6% of these premenopausal women received adjuvant hormonal therapy.

Almost one half of the patients in the international and EORTC trials had bone metastases as the dominant site at diagnosis of advanced disease, with visceral metastases being the next most frequent. In the Italian trial, two thirds of the patients had bone metastases as the dominant site, whereas in the Japanese trial, patients were more or less equally divided over the three groups. Overall, patient characteristics were well balanced across the two treatment groups (Table 4).

Survival

Figure 1 presents the Kaplan-Meier curves for the overall duration of survival by treatment. Stratifying by study, there is a significant difference ($P = .02$) in favor of the combined treatment (Fig 2). With an HR equal to 0.78 and an associated 95% confidence interval of 0.63 to 0.96, there is a 22% reduction in the hazard of death for the combined treatment group. Although the test for heterogeneity between trials is not significant at the 5% level, such tests have relatively low power. The *P* value of .08 indicates that there might be differences between the different trials, the Japanese trial with 33 patients having a much more extreme treatment effect than the international trial with 318 pa-

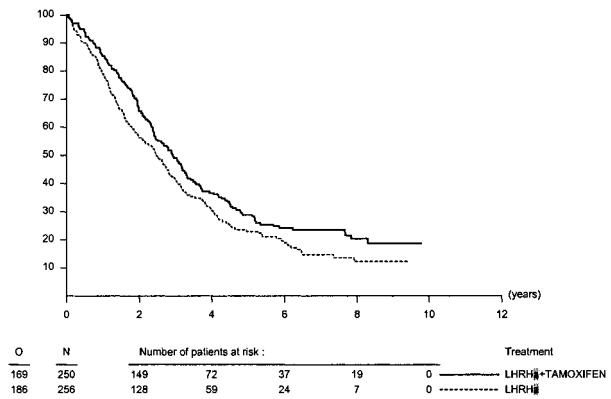

Fig 1. Overall survival curves for LHRH agonist and LHRH agonist + tamoxifen.

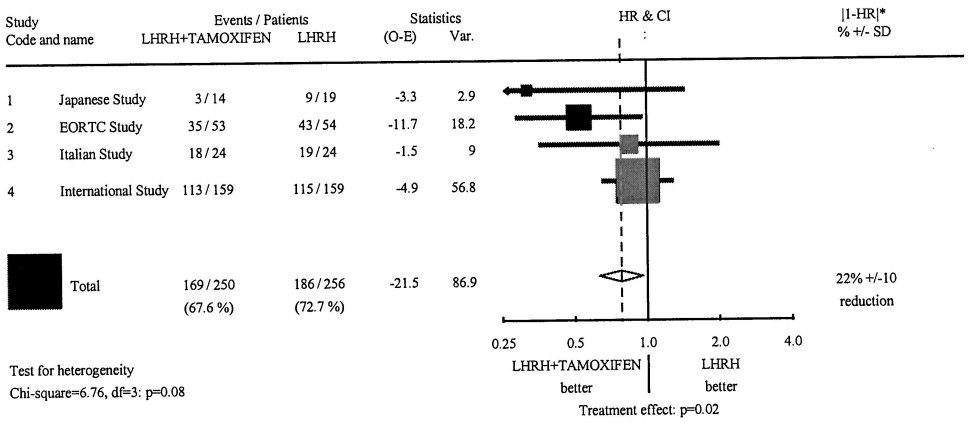

Fig 2. Overall survival stratified by study.

tients. The treatment effect goes in the same direction for all four trials. Subgroup analyses were performed based on the ER status (Fig 3A), disease-free interval (Fig 3B), and dominant site of disease (Fig 3C). In each of the subgroups of these variables, there is a consistent trend in favor of the combined treatment.

Progression-Free Survival

Kaplan-Meier curves for the duration of progression-free survival are presented by treatment group in Fig 4. Stratifying by study, there is a significant treatment effect (P = .0003) in favor of the combined hormonal treatment (Fig 5). With an HR equal to 0.70 and an associated 95% confidence interval of 0.58 to 0.85, there is a 30% reduction in the hazard of progression/death for the combined treatment group. The results in the four studies are more homogeneous for this end point (P = .5) than for survival. For the subgroup analysis based on the ER status, the treatment effect is in the same direction within each of the ER subgroups (Fig 6).

Objective Response

For 18 patients, the objective response was unknown (EORTC study: five on combined treatment, seven on LHRH agonist alone; Italian study: four on combined treatment, two on LHRH agonist alone). We took the conservative approach and classified these patients as nonresponders.

The overall response rate was 76 (30%) of 256 on LHRH agonist alone and 97 (39%) of 250 on the combined treatment, again demonstrating a statistically significant difference (P = .03) in favor of the combined treatment (Fig 7). The typical OR was 0.67 with an associated 95% confidence interval of 0.46 to 0.96, corresponding to a reduction in odds of nonresponse for the combined treatment group of 33%. The test for heterogeneity between trials was not significant. For the subgroup analysis based on the ER status, the treatment effect is once again in the same direction in each of the ER subgroups (Fig 8). The objective response rate for ER+ patients alone was 50 (33%) of 152 on LHRH agonist alone and 68 (42%) of 161 on the combined treatment.

Duration of Objective Response

The combined treatment was associated with a durable response. The meta-analysis demonstrated that the median duration of response in patients receiving combined treatment was 602 days, compared with a median of 350 days in those receiving LHRH agonist alone (based on 97 objective responders in the combined treatment and 76 in the LHRH agonist alone). Table 5 summarizes the results for survival, progression-free survival, and objective response.

DISCUSSION

The meta-analysis, combining the results of four randomized, comparative trials, included more than 500 patients with 355 deaths at the time of analysis. The maturity of three of the four trials (overall death rate, 70%) means that the conclusions of this meta-analysis are unlikely to alter with time. It represents the largest randomized cohort of premenopausal breast cancer patients treated with pharmacologic endocrine therapies for advanced disease.

Using combined endocrine treatment to produce maximal estrogen blockade resulted in both a clinically relevant and statistically significant reduction in the risk of dying or progression/death (a 22% lower risk of dying and a 30% lower risk of progression/death) compared with the LHRH agonist–alone group. Although the treatment differences in the individual studies for progression-free survival were

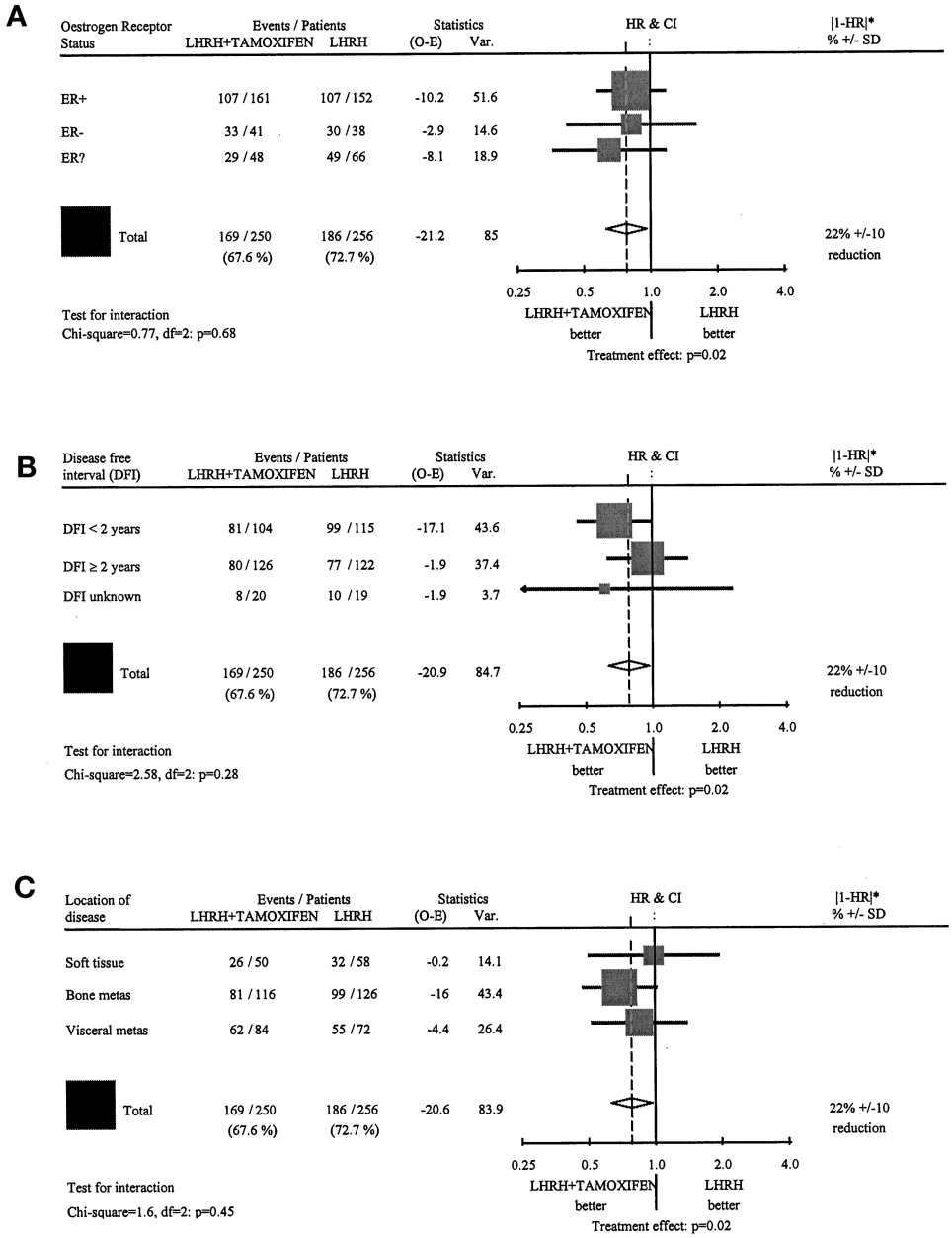

Fig 3. Overall survival by ER status (A), disease-free interval (B), and dominant site of disease (C).

much more homogeneous than for the survival end point, there was no significant heterogeneity between trials. Individually, only the EORTC trial showed a significant difference at the 1% level for both progression-free survival and overall survival. In the EORTC trial, the median time to progression/death in the LHRH agonist–alone group was 6.3 months and was increased to 9.7 months in the combined treatment group ($P = .008$), whereas the median time to death was increased from 2.5 years to 3.7 years in favor of the combined treatment group ($P = .006$).[24] In the international trial, the median time to progression/death in the LHRH agonist–alone group was 5.3 months and was prolonged to 6.4 months in the combined treatment group ($P = .03$), whereas the median time to death was 2.4 years and 2.7 years in the two treatment groups, respectively ($P = .25$).[23] The Japanese trial is unpublished, and the Italian trial did not show separate results for the two relevant treatment arms.

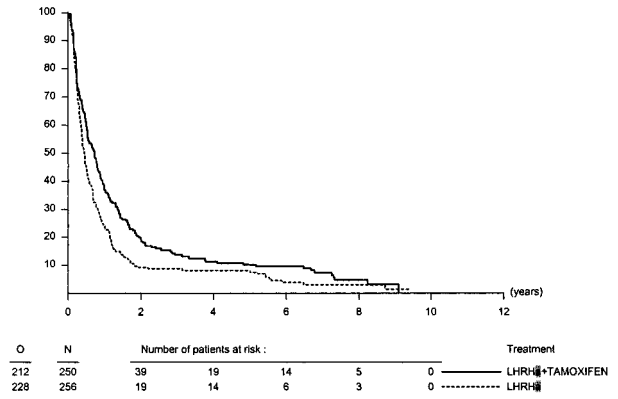

Fig 4. Progression-free survival curves for LHRH agonist and LHRH agonist + tamoxifen.

Although in each individual study the odds of having an objective response on the combined treatment were higher than those for LHRH agonist alone, none showed a statistically significant difference between the treatment groups. The published results showed that the objective response was higher, but not significantly so, in the combined treatment arm as compared with the LHRH agonist–alone group in all three published trials (EORTC: OR = 0.56, P = .17; international: OR = 0.76, P = .24; Italian: OR = 0.46, P = .23).

The meta-analysis, however, showed a statistically significant difference in favor of LHRH agonist plus tamoxifen, with an objective response of 39% compared with 30% for LHRH agonist alone (OR, 0.67; P = .03). Furthermore, the combined treatment seems to be associated with a highly durable response in these advanced breast cancer patients (median of 602 days compared with 350 days in those receiving LHRH agonist alone).

As the meta-analysis only compared two randomized treatment regimens, LHRH agonist alone versus LHRH agonist plus tamoxifen, a direct comparison of the combination with tamoxifen could not be specifically addressed. However, the EORTC study, consisting of three treatment arms, showed no difference between LHRH agonist and tamoxifen (progression-free survival: HR = 1.1, P = .71; survival: HR = 1.2, P = .33), whereas combining LHRH agonist and tamoxifen was superior to tamoxifen alone[24] (progression-free survival: HR = 1.5, P = .05; survival: HR = 1.63, P = .03).

The results of this meta-analysis indicate that in women with advanced breast cancer treated by hormonal manipulation, the combination of an LHRH agonist plus tamoxifen is preferable to LHRH agonist alone. Such combination is probably also of great value in women with primary breast cancer, as discussed by Klijn et al[24] and Davidson.[34] For instance, these authors referred to four trials that showed that such endocrine treatment is at least as effective or more effective than standard adjuvant chemotherapy.

Although the subgroup analyses on the primary end point for ER status, disease-free interval, and dominant metastatic site should be considered as exploratory in nature as a result of the relatively small patient numbers and the multiple comparisons performed, a trend for improved survival in favor of the combined treatment, consistent with the overall conclusion, was seen for each of the subgroups. None of the tests for interaction are significant; however, the tests for interaction lack power and there are few patients in some of the subgroups. Therefore, the magnitude of the treatment effect might vary over subgroups, but more data are needed to further investigate this.

One obvious question that arises is whether the same benefits observed with combined hormonal therapy could be achieved by using the two treatments sequentially. However, premenopausal patients are unlikely to be given a second endocrine therapy after progressing on the first, unless the duration of response has been relatively long or

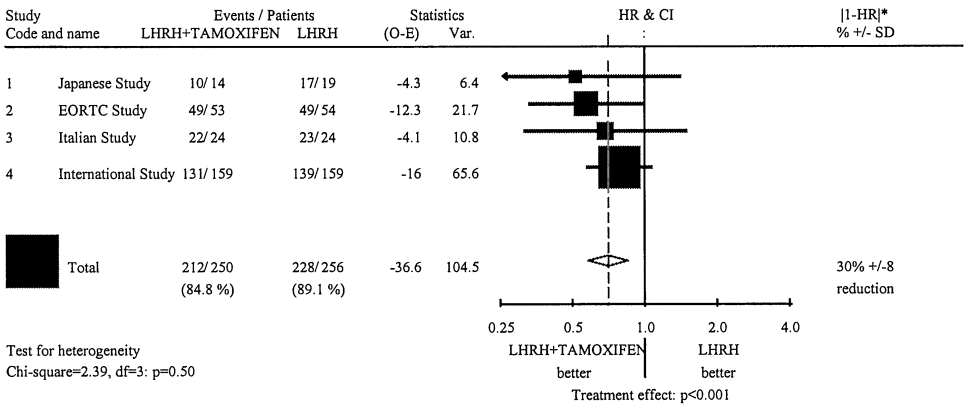

Fig 5. Progression-free survival stratified by study.

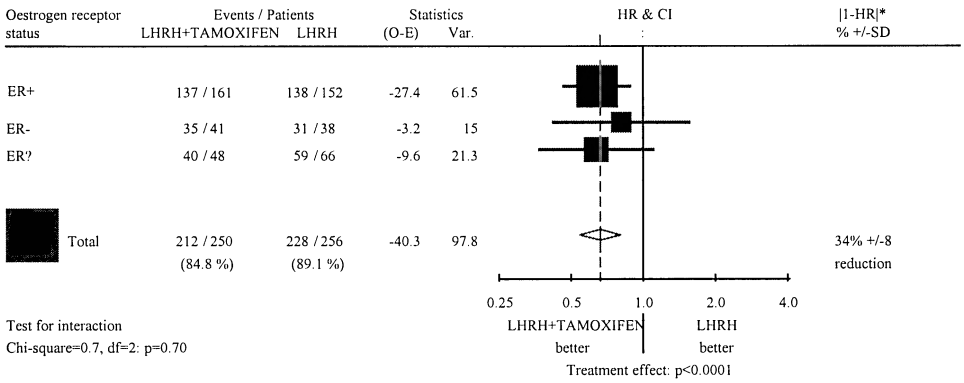

Fig 6. Progression-free survival by ER status.

the tumor burden was low, and the option more often preferred in such cases would be chemotherapy. For example, in the international study, although it was stipulated that all patients in the LHRH agonist–alone arm would receive tamoxifen after first progression, only just fewer than one half (71 of 159) actually did so.[23] It is therefore better to treat with combined therapy up front.

The meta-analysis did not analyze differences in tolerability between the two treatment arms. Data from the largest trial, the international trial, representing 63% of the total patient population (318 of 506), demonstrated that the combination of goserelin plus tamoxifen was well tolerated, and no additional safety issues were associated with the combined therapy as compared with goserelin alone. The incidence of elicited pharmacologic effects (ie, hot flushes, vaginal discharge or soreness, and impact on sexual activity) was similar for both LHRH agonist alone and the combination of LHRH agonist plus tamoxifen. Furthermore, there were no clinically significant differences in hematology or biochemistry parameters between the two treatment groups.[23]

The analysis has shown the advantages of combining hormonal agents, each separately effective in breast cancer and which have different methods of action: LHRH agonist reduces the serum estradiol, and tamoxifen is a peripheral estrogen antagonist. It seems likely that similar combinations will have similar advantages. Therefore, the results of comparing a combination of an aromatase inhibitor with tamoxifen with lower estrogen levels in postmenopausal women and tamoxifen will be also of great interest.

In conclusion, therefore, on the basis of improved survival, progression-free survival, and objective response, the results of this meta-analysis provide a solid rationale to prefer the combination of an LHRH agonist plus tamoxifen for a premenopausal woman with advanced breast cancer who is to be treated by endocrine therapy.

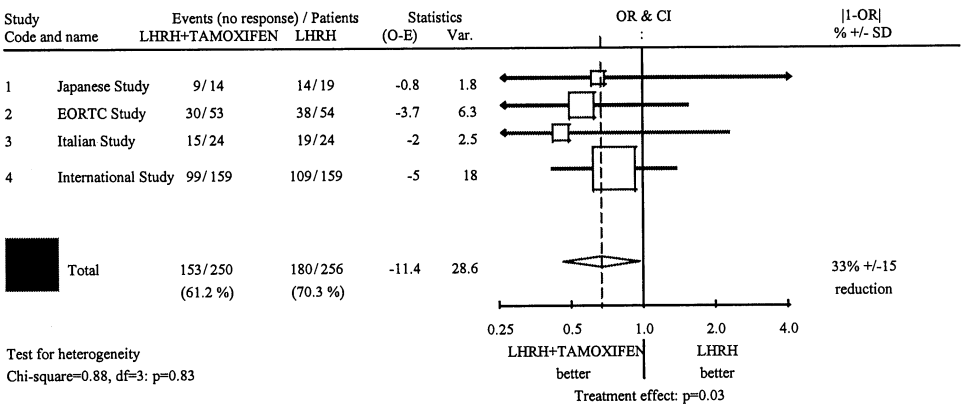

Fig 7. Objective response rate stratified by study.

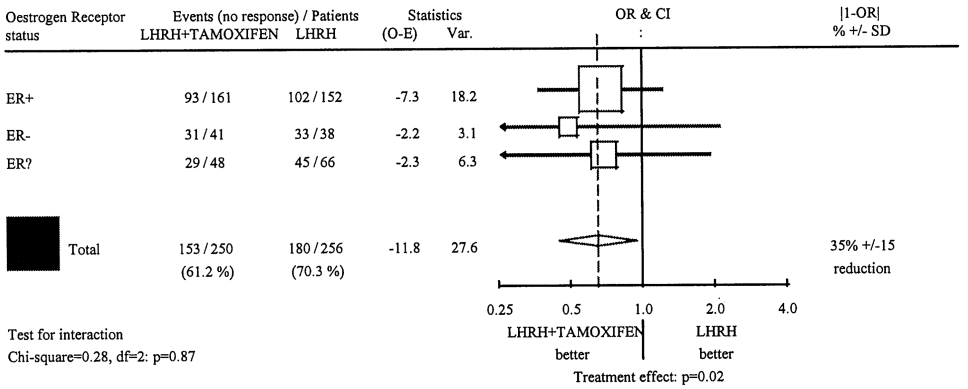

Fig 8. Objective response rate by ER status.

Table 5. Summary of Results by Treatment Group

End Point	LHRH Agonist Alone (n = 256)	LHRH Agonist Plus Tamoxifen (n = 250)	HR/OR	95% CI	Log-Rank *P*
Median survival, years	2.5	2.9	0.78	0.63-0.96	.02
Median progression-free survival, months	5.4	8.7	0.70	0.58-0.85	.0003
Objective response, %	29.7	38.8	0.67	0.46-0.96	.03

Abbreviation: CI, confidence interval.

APPENDIX
Participants

EORTC study. J.G.M. Klijn (Rotterdam, the Netherlands); L.V.A.M. Beex (Nijmegen, the Netherlands); L. Mauriac (Bordeaux, France); J.A. van Zijl (Tygerberg, South Africa); C. Veyret (Rouen, France); J. Wildiers (Leuven, Belgium); J. Jassem (Gdansk, Poland); M. Piccart (Brussels, Belgium); J. Burghouts (Den Bosch, the Netherlands); D. Becqaert (Antwerp, Belgium); C Seynaeve (Rotterdam, the Netherlands); F. Mignolet (Brussels, Belgium); L. Duchateau (Brussels, Belgium); R. Sylvester (Brussels, Belgium); M. Namer (Nice, France); J.P. Julien (Rouen, France); J. Garcia Conde (Valencia, Spain); M. Dunser, R. Margreiter (Innsbruck, Austria); T. Tjabbes (Zwolle, the Netherlands); K.J. Roozendaal (Amsterdam, the Netherlands); P.C. van der Velden (Dirksland, the Netherlands); J.W.R. Nortier (Utrecht, the Netherlands).

International study. R. Blamey (Nottingham, UK); A. Howell (Manchester, UK); J. Forbes (Waratah, Australia); M. Kaufmann (Heidelberg, Germany); B. Nordenskjold (Linkoping, Sweden); S. Kvinnsland (Trondheim, Norway); R.G. Wilson (Newcastle-on-Tyne, UK); W. Jonat (Hamburg, Germany); U.R. Kleeberg (Hamburg, Germany); W. Eiermann (Munchen, Germany); J. Hilfrich (Mainz, Germany); H.K. Weitzel (Berlin, Germany); U. Glas (Stockholm, Sweden); L.E. Rutqvist (Stockholm, Sweden); C. Rudenstam (Goteborg, Sweden); S. Sander (Gavle, Sweden); S. Ryden (Angelholm, Sweden); P. Honsson (Helsingborg, Sweden); P.E. lonning (Bergen, Norway); L Loven (Kristianstad, Sweden); I.S. Russell (Victoria, Australia); C. Olweny (Adelaide, Australia); J.J. Byrne (Nedlands, Australia); R.D. Snyder (Fitzroy, Australia); A.S. Coates (Camperdown, Australia); R.M. Lowenthal (Hobart, Australia); P.N. Jeal (Melbourne, Australia); D.N. Dalley (Darlinghurst, Australia); F. Janicke (Munchen, Germany); W. Kleine (Freiburg, Germany); R.Th. Michel (Frankfurt, Germany).

Italian study. F. Boccardo, L. Canobbio, D. Amoroso, A. Rubagotti (Genova, Italy); C. Bumma (Torino, Italy); M. D'Aprile (Latina, Italy); A. De Matteis (Napoli, Italy); A. Di Carlo (Palermo, Italy); G. Francini, R. Petrioli (Siena, Italy), U. Folco (Pietra Ligure, Italy); E. Calligioni (Aviano, Italy); P. Gallotti (Vigevano, Italy); M. Lopez (Roma, Italy); M. Mesiti (Messina, Italy); P. Pacini (Firenze, Italy); M. Sassi (Reggio Emilia, Italy); P. Sismondi, P. Zola (Torino, Italy)

Japanese study. M. Ogita (Sapporo, Japan); M. Okazaki (Sapporo, Japan); T. Watanabe (Fukushima, Japan); T. Satomi (Iwaki, Japan); C. Hatazawa (Aomori, Japan); N. Okuyama (Tokyo, Japan); T. Koyama (Tokyo, Japan); M. Kobayashi (Kawasaki, Japan); T. Shimizu (Yokohama, Japan); T. Tabei (Kita adachi-gun, Japan); M. Sano, H. Makino (Niigata, Japan); J. Ando (Utsunomiya, Japan); M. Kimura (Ota, Japan); T. Takeuchi (Nagoya, Japan); H. Aoyama (Nagoya, Japan); H. Koyama (Osaka, Japan); E. Shin, G. Chou (Osaka, Japan); T. Yasumura (Kyoto, Japan); K. Miyauchi (Sakai, Japan); Y. Takatsuka (Amagasaki, Japan); N. Tsuzi (Okayama, Japan); M. Shiramizu, H. Tashiro (Fukuoka, Japan); R. Nishimura (Kumamoto, Japan); M. Tanaka (Kurume, Japan).

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