Coming of age : treatment and outcomes in older patients with breast cancer

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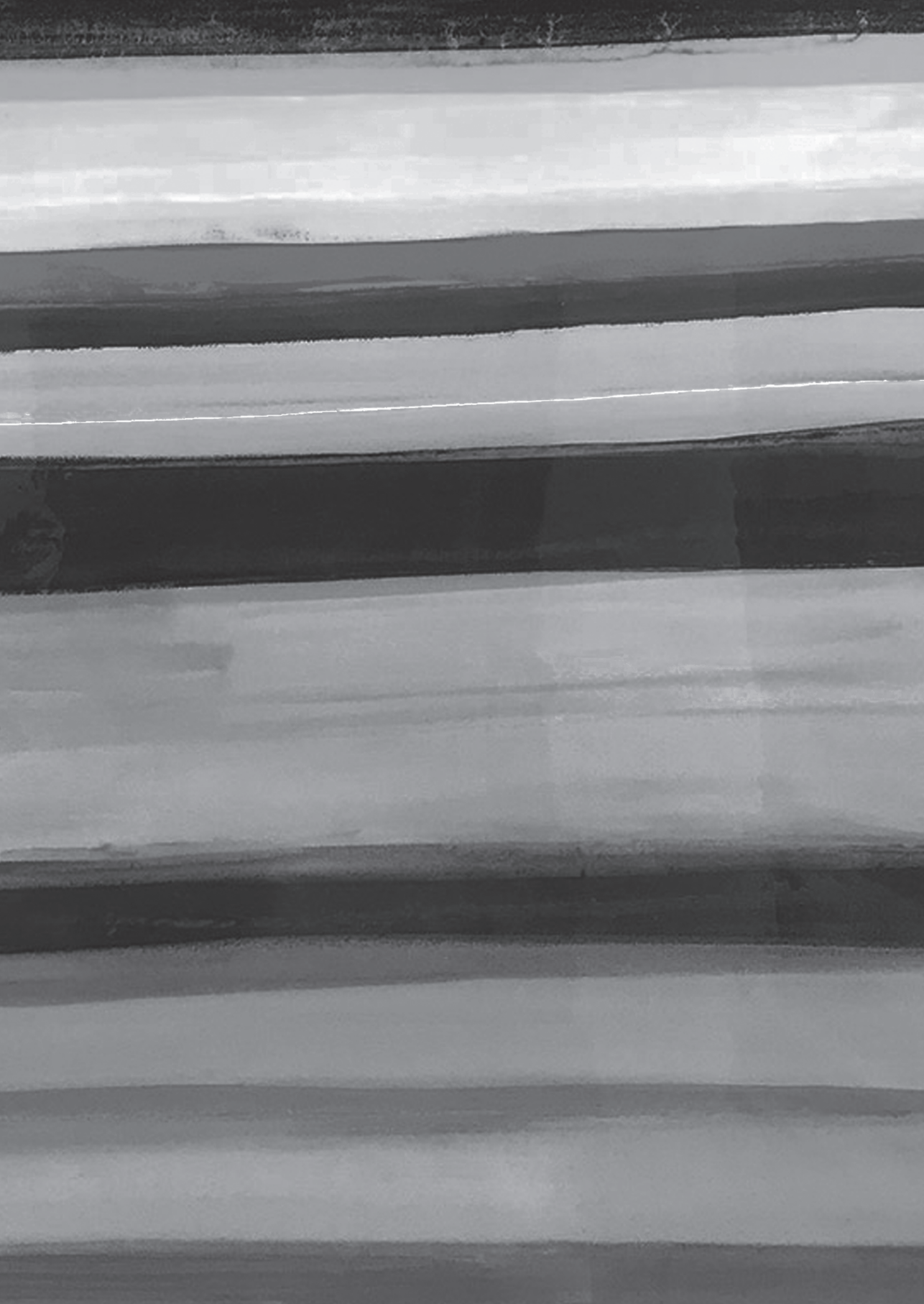

CHAPTER 3

Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial

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ABSTRACT

Background: After five years of median follow-up, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial observed no difference in disease free survival between exemestane monotherapy and a sequential scheme of tamoxifen followed by exemestane in postmenopausal patients with early-stage, hormone receptor positive (HR+) breast cancer. As recurrence risk in HR+ breast cancer remains linear beyond five years after diagnosis, long-term follow-up outcomes of this trial were analysed.

Methods: The TEAM trial, a multicenter phase III open-label randomised controlled trial, included postmenopausal patients with early stage HR+ positive breast cancer from nine countries between 2001 and 2006. Patients were randomly allocated in a 1:1 ratio by a computer-generated random permuted block method to either five years of open-label exemestane monotherapy (25 mg daily) or a sequential scheme of tamoxifen (20 mg daily) followed by exemestane for a total duration of five years. Randomisation was performed centrally in each country. Long term follow-up data for disease recurrence and survival was collected in six participating countries and analyzed by intention-to-treat. The primary endpoint was disease free survival (DFS) at ten years of follow-up. The trial is registered with ClinicalTrials.gov, NCT00279448, NCT00032136; NTR 267; Ethics Commission Trial 27/2001.

Findings: 6120 patients were included in the current intention-to-treat analysis. Median follow-up was 9·8 years (interquartile range 8·0-10·3). During follow-up, 921 (30%) of 3075 patients in the exemestane arm and 929 (31%) of 3045 patients in the sequential arm experienced a DFS event. DFS at ten years was 67% (95% CI 65-69) for the exemestane arm and 67% (95% CI 65-69) for the sequential arm (hazard ratio (HR) 0·96, 95% CI 0·88-1·05, p=0·39).

Interpretation: The long-term findings of the TEAM trial confirm that both exemestane alone and sequential therapy with upfront tamoxifen are equally effective as adjuvant endocrine therapy in postmenopausal HR+ early breast cancer patients. These results validate the opportunity to individualize adjuvant endocrine strategy accordingly, based on patient preferences, comorbidities and tolerability.

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RESEARCH IN CONTEXT

Evidence before this study

We performed a search in PubMed MEDLINE (OVID-version), Embase (OVID-version), and Cochrane, limited to articles published before March 1st 2017. For the search, we combined the terms 'long-term follow-up', 'aromatase inhibitors', 'tamoxifen', 'sequential therapy', 'postmenopausal women', and 'hormone receptor positive breast cancer', also using various synonyms and related terms. This resulted in 104 papers, of which five were relevant results from randomised clinical trials. The majority of these trials studied long-term follow-up of other adjuvant endocrine therapy regimes, such as five years of tamoxifen versus anastrozole in the ATAC trial, or tamoxifen monotherapy versus sequential therapy in the IES trial. Furthermore, our search strategy identified a recent meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), comparing all major regimes including an aromatase inhibitor (AI) with each other, a sequential scheme or with tamoxifen alone, for the longest follow-up available. In this meta-analysis, the comparison between AI monotherapy and tamoxifen followed by AI was limited to seven years of follow-up; hence, none of the included trials had ten-years data available.

Added value of this study

This study is the first trial to report on ten-year follow-up of randomizing patients between five years of AI monotherapy or sequential therapy with upfront tamoxifen followed by an AI. After ten years, no significant differences in either DFS or OS between both schedules were observed. However, we did observe a small difference in disease recurrence, in favour of patients treated with exemestane monotherapy (20% versus 22% with sequential scheme).

Implications of all the available evidence

For postmenopausal patients with early-stage, HR+ breast cancer five years of tamoxifen monotherapy, AI monotherapy, or sequential treatment with upfront tamoxifen are valid investigated treatment schedules to prevent relapse after surgery. Earlier, the EBCTCG meta-analysis showed that both the sequential strategy and AI monotherapy are superior to tamoxifen monotherapy after ten years of follow-up. The current analysis of the TEAM trial shows that at ten years of follow-up, both the sequential scheme with upfront tamoxifen and AI monotherapy are equal with regard to DFS and OS. Therefore, both strategies are equally effective treatment options for postmenopausal patients with HR+ early breast cancer.

INTRODUCTION

For more than three decades, tamoxifen has been the hallmark for adjuvant treatment in women with hormone receptor positive (HR+) breast cancer, leading to a proportional risk reduction in recurrence of breast cancer and death by 40% and 26% respectively.[1] Over the last ten years, aromatase inhibitors (AI), given either for five years or for two to three years after two to three years of tamoxifen, have shown superior efficacy over tamoxifen alone, further reducing the proportional risk of breast cancer recurrence by approximately 30% over five years of follow-up.[2]

HR+ patients who remain disease free after five years of adjuvant endocrine treatment, still face a substantial risk of recurrence (11% and 20% ten and fifteen years after diagnosis, respectively[3,4]), indicating the importance of long-term follow-up for trials comparing adjuvant endocrine treatment strategies.

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) phase III trial compared five years of exemestane with a sequential scheme of 2·5 years of tamoxifen followed by 2·5 years of exemestane. After five years of median follow-up, no significant difference for disease free survival (DFS), overall survival (OS) and relapse free survival (RFS) was observed between the two treatment strategies.[5] The current analysis of the TEAM trial is the first study to present ten-year outcomes of the efficacy of five years of AI (exemestane) versus sequential therapy (tamoxifen followed by exemestane).

METHODS

Study design and participants

The TEAM trial is a phase III open-label randomised controlled trial that enrolled postmenopausal women with histologically confirmed breast adenocarcinoma and locally assessed estrogen- (ER) and/or progesterone-receptor-positive (PgR) disease who had completed local treatment with curative intent between 2001 and 2006.[5] There were no age-related restrictions for inclusion. Other eligibility criteria were an ECOG performance status of 0 or 1, adequate hematological parameters (PLT > $100x10^9$/L, WBC > $3x\ 10^9$/L), renal (creatinine <1.5 ULN) and liver function (ASAT or ALAT <2.5 ULN). Exclusion criteria included: earlier adjuvant endocrine therapy or neo-adjuvant chemotherapy, uncontrolled cardiac disease, other malignancies or other serious illnesses interfering with subject compliance, adequate informed consent or study participation.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio centrally in each country by use of a computer-generated random permuted block method with stratification per country. Treatment allocation was not masked to participants, those prescribing the medication, those assessing outcomes and analysing the data. Patients were enrolled by the local clinicians in the participating hospitals.

Procedures

Endocrine treatment was started within ten weeks after completion of surgery and end of chemotherapy if indicated, and was administered orally daily for five years in both treatment arms. Patients were initially assigned either to exemestane (25 mg once a day) for a duration of five years or tamoxifen (20 mg once a day, orally) for a duration of five years. After the publication of the IES trial,[6] the the protocol was amended. Patients assigned to tamoxifen were switched after 2·5 to three years to exemestane therapy for a total duration of five years of treatment. Dose reductions were not allowed. Patient visits were required every 3 months during the first year, and every 6 months during the remaining active treatment period. Study endpoints and adverse events were recorded during each visit during active treatment. performed mammography was performed yearly, laboratory tests and other radiological evaluations were performed as determined by local guidelines.

The original study was conducted in 566 hospitals in nine countries. For the current pre-planned long term follow-up analysis, we only included patients who were enrolled in countries where follow-up was collected for at least two additional years after the five years of endocrine therapy in the context of the study. For this reason, patients from Japan (n=184), France (n=1,230), and the United States (n=2,232) were excluded from analyses (Figure 1). Data were collected in the

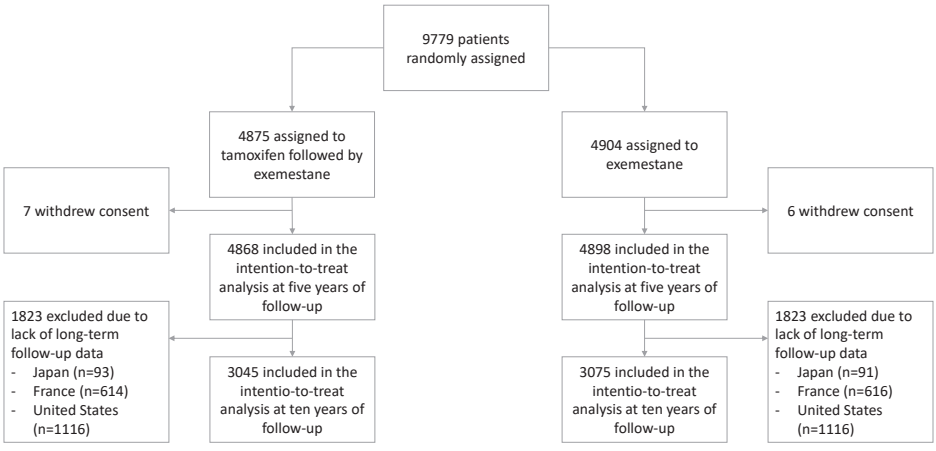

Figure 1: trial profile

different countries and sent as a batch per country to Leiden, and thereafter merged into one database. Information on cause of death was gathered on the case report form and thereafter categorized into ten pre-specified groups. Classification of cause of death was verified by the TEAM central datacenter. Late side effects after five years of endocrine therapy in this current analysis were not recorded. Database cutoff was set at February 19, 2016.

Outcomes

The primary endpoint was disease free survival (DFS), defined as the time from randomisation to disease recurrence or death from any cause. Disease recurrence was defined as disease recurrence (locoregional or distant) or a new primary breast cancer. Ductal carcinoma in situ was not considered as recurrent disease. Secondary outcomes were overall survival (OS) defined as time from randomization to time of death due to any cause, recurrence free interval (RFI) defined as time from randomisation to recurrence or time of death due to breast cancer if no recurrence was reported before death and distant recurrence free interval (DRFI) defined as time from randomisation to distant recurrence or time of death due to breast cancer if no recurrence was reported before death. Patients with distant metastases at time of death were categorized as death due to breast cancer.

Statistical analysis

All patients who were randomly assigned to treatment, except those who withdrew consent before start of treatment, were included in the intent-to-treat population. All analyses were performed in the intent-to-treat population. A power calculation was performed before study initation for analyses after five years of follow-up, and has been described extensively previously.[5] All tests were two-sided and a p-value of less than or equal to 0·05 was considered statistically significant. Kaplan-Meier estimates of DFS and OS were calculated for each treatment group. DFS and OS were compared between treatment groups using log-rank tests and stratified by country and additional stratification factors within countries (nodal status (positive versus negative), PgR status (positive versus negative), adjuvant chemotherapy (yes versus no)). All hazard ratios (HRs) were calculated with a Cox regression analysis using the same stratification factors as the log-rank tests. Cumulative incidence of recurrence and subdistribution hazard ratios (sHRs) for RFI and DRFI were calculated using the Fine and Gray model for competing risks, taking other causes of death into account as competing events.[7] Proportional differences were tested using Pearson's χ^2 test. All time-to-event curves were truncated after ten years of follow-up, while HRs and sHRs include all events until database cutoff.

Additional analyses

Predefined subgroup analyses were performed for DFS. Interaction between treatment and prognostic factors was tested for effect modification using the Cox proportional hazard model. A post-hoc analysis was performed to study the relation between treatment and breast

cancer specific mortality (BCSM) and other cause mortality (OCM). Cumulative incidence of recurrence and sHRs were calculated using the Fine and Gray model for competing risks.

An additional five year conditional survival analysis for DFS using the Cox proportional hazard model was performed as a post-hoc analysis to compare treatment groups for late disease recurrences, and subgroup analyses were performed to test interaction between treatment and prognostic factors for late recurrences. Furthermore, to estimate the influence of HER2 positive patients included in this study population, analyses were repeated post-hoc after exclusion of the HER2 positive patients. Kaplan Meier estimates were calculated for ten year DFS for each treatment arm in the remaining population.

For this long-term follow up analysis, patients from countries that did not collect long-term follow-up data were excluded. To assess whether findings from this study could be generalized to the original population various additional post-hoc analyses were performed. First, baseline clinicopathological factors between the in- and excluded patients were compared. Second, DFS at five years after randomisation was compared between the in-and excluded patients. Third, treatment effect between the in- and excluded patients at five years was tested for interaction. Last, a sensitivity analysis was performed to compare treatment arms for DFS with complete follow up time for the original TEAM population. Patients from countries that did not collect outcomes after five years were censored.

Statistical analyses were performed using R 3.3.0 version using the *survival*, *prodlim* and *cmprsk* packages.

The study was conducted in compliance with the guidelines of the Declaration of Helsinki, International Conference on Harmonization and Good Clinical Practice. Appropriate approvals from the ethical committee were obtained. All patients provided written informed consent. This study is registered in France with ClinicalTrials.gov, NCT00279448; the Netherlands and Belgium with Netherlands Trial Register, NTR 267; the UK and Ireland with ClinicalTrials.gov, NCT00032136; and Germany with Ethics Commission Trial, 27/2001.

Role of the funding source

The TEAM trial was initially funded by an unrestricted grant from Pfizer. Collection of long term follow-up was funded by the Dutch Cancer Foundation (UL 2010-4674). Funding sources had no role in the study design, data collection, analysis, interpretation of the data, writing of the manuscript, or the decision to publish. Study investigators listed as authors were involved in data interpretation writing the report and the decision to submit. The corresponding author had full access to all of the data and the final responsibility to submit for publication. All authors had access to the raw data.

RESULTS

In the original TEAM trial, 9766 patients were included in the intention-to-treat population between January 16th 2001 and January 31st 2006.[5] Overall, 6120 (63%) patients from six countries were included in the current intention-to-treat population and analyzed for the primary and secondary outcomes (Figure 1). Median follow-up was 9·8 years (IQR 8·0-10·3) and median age at diagnosis was 63·8 years (IQR 57·8-70·8). Baseline characteristics were similar between both treatment arms (Table 1).

Table 1. Baseline characteristics of patients in the intention to treat population

	Tamoxifen followed by exemestane (n=3045)		**Exemestane (n=3075)**	
	N	%	N	%
Age (years)				
< 50	102	3.3	109	3.5
50-59	948	31.1	926	30.1
60-69	1193	39.2	1180	38.4
≥ 70	802	26.3	860	28.0
Histological grade				
G1 (well)	301	9.9	315	10.2
G2 (moderate)	1569	51.5	1599	52.0
G3-G4 (poor)	930	30.5	905	29.4
Unknown	245	8.0	256	8.3
Tumour (T) stage				
T0,Tis	1	0.0	1	0.0
T1	1500	49.3	1526	49.6
T2	1321	43.4	1363	44.3
T3, T4	216	7.1	175	5.7
Tx, unknown	7	0.2	10	0.3
Nodal (N) stage				
N0	1295	42.5	1308	42.5
N1	1538	50.5	1562	50.8
N2-3	201	6.6	195	6.3
Unknown	11	0.4	10	0.3
Metastasis (M) stage				
M0 (no distant metastasis)	3041	99.9	3069	99.8
M1 (distant metastasis)	2	0.1	5	0.2
Not assessed	2	0.1	1	0.0
Estrogen-receptor status				
Positive	2970	97.5	3014	98.0
Negative	75	2.5	58	1.9
Unknown	0	0.0	3	0.1
Progesterone-receptor status				
Positive	2163	71.0	2215	72.0
Negative	535	17.6	535	17.4
Unknown	347	11.4	325	10.6

Table 1. Baseline characteristics of patients in the intention to treat population *(continued)*

	Tamoxifen followed by exemestane (n=3045)		Exemestane (n=3075)	
	N	%	N	%
Most extensive surgery				
Mastectomy	1464	48.1	1409	45.8
Wide local excision	1577	51.8	1663	54.1
No resection	0	0.0	1	0.0
Unknown	4	0.1	2	0.1
Time from surgery to initiation of hormone treatment (months)				
< 3	1882	62.5	1886	61.8
3 to 6	628	20.8	694	22.7
≥ 6	502	16.7	472	15.5
Unknown	33	1.1	23	0.7
Adjuvant radiotherapy				
Yes	2053	67.4	2114	68.7
No	984	32.3	950	30.9
Unknown	8	0.3	11	0.4
Adjuvant chemotherapy				
Yes	1112	36.5	1141	37.1
No	1933	63.5	1934	62.9
Unknown	0	0	0	0
Country				
Netherlands	1379	45.3	1374	44.7
Germany	723	23.7	748	24.3
United Kingdom and Ireland	639	21.0	636	20.7
Greece	100	3.3	107	3.5
Belgium	204	6.7	210	6.8

During the ten year study period, 921 (30%) of 3075 patients in the exemestane group and 929 (31%) of 3045 patients in the sequential group experienced a DFS event (Table 2). The Kaplan-Meier-estimated ten year DFS percentage was 67% (95% CI 65-69) for the exemestane arm and 67% (95% CI 65-69) for the sequential arm (HR 0·96, 95% CI 0·88-1·05, p=0·39, Figure 2A). Treatment effect was consistent between all subgroups and no significant interaction was observed between treatment and clinicopathological factors (Figure 3). Overall, hazard ratios were similar to those of the previous report after five years of median follow-up.[5]

Table 2. Disease-free survival events*

	Tamoxifen followed by exemestane (n=3045)		Exemestane (n=3075)	
	N	%	N	%
Total	929	30.5	921	30.0
Locoregional recurrence only**	71	2.3	52	1.7
Distant metastases	502	16.5	470	15.3
New primary breast cancer***	50	1.6	45	1.5
Intercurrent deaths	306	10.0	354	11.5

* only first events for DFS were recorded **Includes ipsilateral breast cancer. ***Without distant metastasis.

During follow-up, 733 (24%) of 3075 patients in the exemestane arm died and 727 (24%) of 3045 patients in the sequential arm (Table 3). Overall survival after ten years was 74% (95% CI 72-75)in the exemestane group and 73% (95% CI 72-75) in the sequential group (HR 0·98, 95% CI 0·89-1·09, p=0·74, Figure 2B). BC recurrence occurred in 567 (18%) of 3075 patients in the exemestane arm and 623 (20%) of 3045 patients in the sequential arm during follow-up. Cumulative incidence for BC recurrences after ten years of follow up was slightly lower in the exemestane group (20%, 95% CI 19-22) than in the sequential group (22%, 95% CI 20-24) (sHR for RFI 0·88, 95% CI 0·79-0·99, p=0·03, Figure 4A). Distant recurrences occurred in 468 (15%) of 3075 patients in the exemestane arm and 497 (16%) of 3045 patients

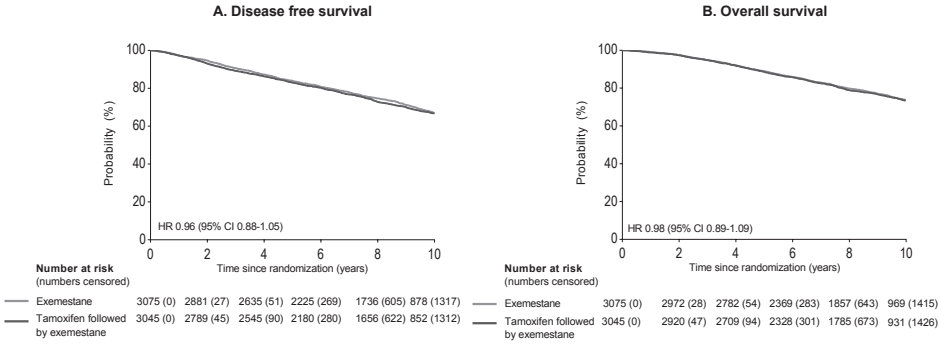

Figure 2: Disease free survival (A) and overall survival (B)

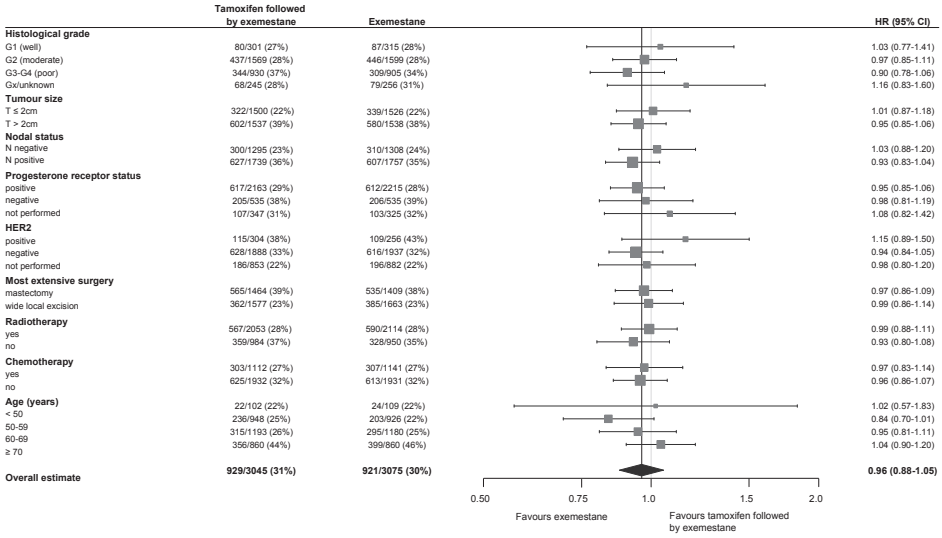

Figure 3: Subgroup analysis of disease free survival
Numbers are number of events by numbers at risk at time of randomization (n/N(%)). The gray line represents a hazard ratio of 1.00, the black line is the overall hazard ratio of 0.96

in the sequential arm. No difference in cumulative incidence for distant recurrence was observed for exemestane alone versus sequential therapy (16% (95% CI 15-18) versus 18% (95% CI 16-19) respectively, sHR for DRFI 0·91, 95% CI 0·80-1·03, p=0·15, Figure 4B).

Table 3. Causes of death

	Tamoxifen followed by exemestane (n=3045)		Exemestane (n=3075)	
	N	%	N	%
Death due to breast cancer*	419	13.8	377	12.3
Death due to other causes	308	10.1	356	11.6
Second malignant disease	72	2.4	85	2.8
Endometrial cancer	2	0.1	1	0.0
Cardiac related	45	1.5	61	2.0
Thromboembolism	5	0.2	11	0.4
Pulmonary related	18	0.6	20	0.7
Cerebral related	16	0.5	23	0.7
Vascular related	2	0.1	4	0.1
Other	91	3.0	95	3.1
Unknown reason	57	1.9	57	1.9

*Death due to breast cancer was defined as death due to breast cancer as recorded or if distant metastasis were present at time of death

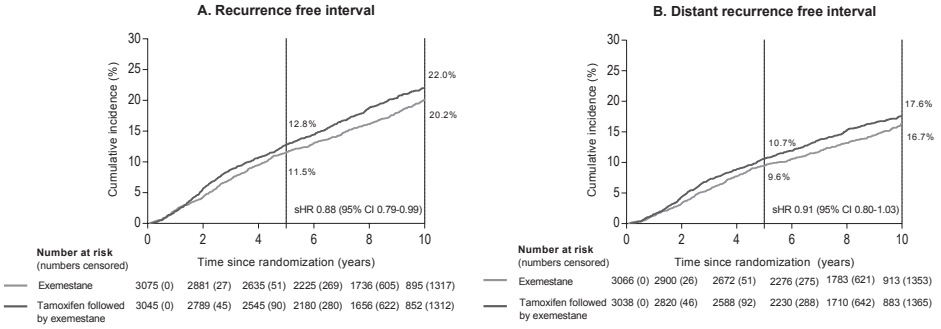

Figure 4: Cumulative incidence of recurrences (A) and distant recurrences (B)

Additional analyses

In the exemestane arm, 377 (12%) of 3075 patients died due to breast cancer and in the sequential arm 419 (14%) of 3045 patients died due to breast cancer (Table 3). Cumulative incidence for BCSM after ten years of follow-up was 13·5% (95% CI 12·3-14·9) in the exemestane arm and 15·4% (95% CI 13·0-16·9) in the sequential arm (sHR 0·88, 95% CI 0·77-1·01, p=0·07, Figure 5). Death due to other causes than BC occurred in 356 (12%) of

3075 patients in the exemestane arm and 308 (10%) of 3045 patients in the sequential arm (Table 3). Cumulative incidence for OCM was 12·8% (95% CI 11·5-14·2) in the exemestane arm and 11·3% (95% CI 10·0-12·6) in the sequential arm (sHR 1·14, 95% CI 1·00-1·31, p=0·08, Figure 5). No significant differences for cause of death were observed between the treatment arms. The number and types of new primary non-breast cancers are shown in Table 4. Endometrial cancer occurred more frequently in the sequential arm than in the exemestane arm (23 (0·8%) of 3045 patientsversus 7 (0·2%) of 3075 patients, respectively). Other second, non-breast cancers were not different between both treatment arms (Table 4).

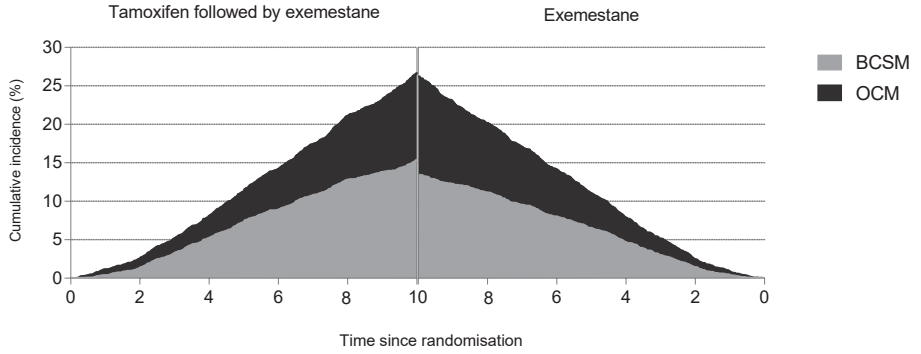

Figure 5: Stacked cumulative incidence of breast cancer specific mortality (BCSM) and other cause mortality (OCM) by treatment arm
Cumulative incidence function for cause of death stacked on top of each other by the two treatment arms. Sum of the two functions represents all-cause mortality.

Table 4. Non-breast cancers

	Tamoxifen followed by exemestane (n=3045)		Exemestane (n=3075)	
	N	%	N	%
Non-breast cancers				
Colorectal	40	1.3	52	1.7
Lung	32	1.1	37	1.2
Endometrial	23	0.8	7	0.2
Other	132	4.3	140	4.6

One patient in the sequential arm developed two colorectal tumours; five patients in the sequential arm and six patients in the exemestane arm developed more than one non-breast cancer tumour.

Five years after randomization, 2470 (80%) of 3075 patients in the exemestane arm and 2385 (78%) of 3045 patients in the sequential arm were alive and disease free. 431 (17%) of 2470 patients in the exemestane arm and 423 (18%) of 2385 patients in the sequential arm experienced a DFS event in the remaining follow up period. DFS at ten years was 80% (95%

CI 78-82) in the exemestane arm and 81% (95% 79-82) in the sequential arm (HR 0·98, 95% CI 0·86-1·13, p=0·82). This effect was consistent among all subgroups and no significant interaction was observed between treatment and clinicopathological factors (webappendix, page 1).

For the repeated analysis excluding the HER2 positive patients, 560 HER2 positive patients (9 %) were excluded from the original trial population. In the remaining HER2 negative or HER2 unknown population, 812 (29%) of 2819 patients assigned to the exemestane arm and 814 (30%) of 2741 patients assigned to the sequential arm experienced a DFS event. DFS at ten years was 68% (95% CI 66-70) for patients in the exemestane arm and 67% (95% CI 66-69) for patients in the sequential arm. This was not significantly different compared to the results of the total study population.

Patients from countries that did not collect long-term follow-up had more favourable tumour characteristics at baseline (webappendix, page 2). DFS at five years for patients included in the long-term follow-up analysis was lower than that of excluded patients (DFS 84%, 95% CI 83-84 and DFS 90%, 95% CI 89-91, respectively). Treatment effect for DFS at five years was comparable between patients included in the long-term follow-up analysis and patients that were excluded (HR 0·96 (95% CI 0·88-1·06) and HR 1·01 (95% CI 0·84-1·22), respectively, p-value for interaction = 0·66). Treatment effect for the original TEAM population was comparable to the results of the long-term follow-up study (HR 0·97, 95% CI 0·90-1·06).

DISCUSSION

To our knowledge, this is the first trial reporting ten year outcomes of five years of AI monotherapy compared to five years sequential therapy with upfront tamoxifen, showing that after ten years of median follow-up both exemestane monotherapy and the sequential scheme are equally effective treatment strategies for postmenopausal patients with HR+ early breast cancer. No significant differences between the treatment arms were observed for DFS and OS, although a small benefit was observed for exemestane monotherapy with regard to cumulative incidence of recurrences. An additional analysis looking into cause of death suggests a lower breast cancer specific mortality but a higher other cause mortality for exemestane monotherapy compared to sequential therapy.

The results from this ten year analysis of the TEAM trial are consistent with the long-term analysis of the BIG 1-98 trial. After a median follow-up of 8·0 years, this study reported no differences between letrozole and sequential therapy (tamoxifen followed by letrozole) for DFS (HR 1·07, 0·92-1·25) and OS (HR 1·10, 0·90-1·33).[8] The TEAM results reported

in this study represent a much larger patient cohort and after a longer follow-up period, thereby strengthening the results reported from the BIG 1-98 trial. Furthermore, our results are in line with findings from the EBCTCG meta-analysis, including all trials investigating the value of AI versus tamoxifen regimens in postmenopausal HR+ breast cancer patients. They observed a very small benefit regarding recurrences rates of AI monotherapy over the sequential scheme with upfront tamoxifen after a median follow-up period of seven years (recurrence rate 14·5% versus 13·8%), but observed no benefit with respect to OS in this same time period.[2] In view of the current ten year results of the TEAM trial and data from the BIG 1-98 trial and EBCTCG meta-analysis, both the sequential scheme with upfront tamoxifen and AI monotherapy are equally effective strategies.

When considering cause of death, results of the current analyses suggest that there might be a small benefit of exemestane therapy on breast cancer-specific mortality, although the percentage of distant metastasis was not significantly different (Figure 4B). Interestingly, this beneficial effect of exemestane on breast cancer-specific mortality seems to be counterbalanced by an increase in non-breast cancer related mortality leading to similar overall survival rates. In the TEAM trial report after five years of median follow-up, significantly more cardiovascular adverse events were observed in the patients receiving exemestane alone.[5] After ten years of follow-up, death due to cardiac cause or vascular cause was higher in the exemestane arm (n=65) than in the sequential arm (n=47). In addition, more patients died due to a thromboembolic cause in the exemestane arm (n=11) than in the sequential arm (n=5) (Table 3). Unfortunately, this trial was not designed to show a significant difference in cause of death. A recently published meta-analysis showed a significantly higher risk for cardiovascular events for patients treated with AI monotherapy compared to upfront tamoxifen followed by an AI (RR 1·16, 95% CI 1·03-1·31). It has been suggested that the occurrence of more cardiovascular events in patients receiving an AI compared to patients receiving tamoxifen is most likely explained by the protective effect of tamoxifen on cardiovascular outcomes.[9,10] The increased risk of death with an AI has also been observed in the ABCSG-12 trial, investigating zoledronic acid versus no zoledronic acid with adjuvant tamoxifen or anastrozol (in combination with LHRH analogues) in premenopausal BC patients. Anastrozol and tamoxifen (in combination with LHRH analogues) were equally effective for disease free survival after eight years of follow-up but a significantly worse overall survival for anastrozol was observed.[11] Overall, these findings suggest that although AI might be more favorable for breast cancer related outcomes, it lacks the cardioprotective effect of tamoxifen, which might be preferred for patients with a relatively low risk breast cancer and high risk cardiovascular profile. Further long-term research is necessary to confirm these observations and to better define subgroups with high risk for cardiovascular diseases that might benefit from upfront tamoxifen.

An important remaining question is whether it is possible to select some subgroups for which there is a more clear benefit for either upfront tamoxifen or AI use. In the BIG 1-98 trial, patients with a poor prognosis (using ER and PgR status, HER2 status, Ki-67 index and clinical prognostic factors) appeared to have more benefit regarding DFS from letrozole monotherapy compared to any other treatment strategy.[12] A meta-analysis, comparing tamoxifen and AI monotherapy (either for five or two to three years), suggested that HER2-negative tumors would benefit more from AI monotherapy.[13] However, this study evaluated only the period in which the active treatment was different between both arms. Our analysis, covering 10 years of follow-up and comparing the sequential scheme with AI monotherapy in a large cohort, failed to identify any clinicopathological subgroup that would benefit more from either the sequential treatment or AI monotherapy. Therefore, the identification of a subgroup for which there is a more clear benefit of either therapy remains challenging. In the context of the TEAM pathology study, we plan to combine clinicopathological factors with biomarkers. This will hopefully identify biomarkers that will allow for better stratification.

With no evident improvement in disease related outcomes and overall survival nor a clear benefit for a specific subgroup for either AI monotherapy or sequential therapy, the choice of therapy might depend on safety and tolerability not only during but also after completion of treatment. The TEAM five-year analysis showed that the use of tamoxifen is associated with an increase in gynaecological- and thromboembolic side effects, whereas exemestane was more often associated with musculoskeletal disorders like arthralgia, osteoporosis and subsequent fractures.[5] In the current analyses, after ten years of median follow-up and five years after treatment completion, more endometrial cancers were still observed in the sequential than in the exemestane arm, although absolute numbers were low (23 versus 7, Table 4). Further analysis showed that median time to diagnosis of endometrial cancer was 7·0 years after randomization in this study for patients who received the sequential therapy. This suggests a long-term carry-over effect of tamoxifen use. Reassuringly, deaths due to endometrial cancer did not occur more frequently in one of the groups (Table 3). Unfortunately, no other long-term adverse events on the abovementioned items were collected in the context of the TEAM study. In the ATAC trial, fractures were more common during treatment in the anastrozole arm compared to the tamoxifen arm, but were similar after treatment completion at ten years of follow-up, suggesting no carry-over effect after treatment completion.[14] Although some evidence from side studies of the TEAM trial and the BIG 1-98 trial suggest poorer cognitive functioning in patients receiving tamoxifen compared to patients using an AI,[15,16] it remains unclear whether tamoxifen also affects long term cognitive functioning. Quality of life did not appear to be different between AIs and tamoxifen in several trials.[17-19] However, no quality of life data from these trials are available after completion of therapy. It would be worthwhile to develop a cardiovascular

risk and potentially other risk profiles, enabling to select the appropriate therapy regimen for a particular patient.

Another relevant unanswered question is the optimal length of adjuvant endocrine therapy, which is currently being studied in several trials.[20] Of note, 435 (16%) of the 2,753 Dutch patients in this analysis continued with letrozole beyond five years in the context of the prospective phase-III Investigation on the Duration of Extended Adjuvant Letrozole treatment (IDEAL) trial (randomization between 2·5 or five years of extended therapy with letrozole).[21] TEAM trial patients that continued in the IDEAL trial were equally distributed among both treatment arms of the TEAM trial and were equally randomised for either 2·5 or five years of extended therapy in the IDEAL trial. Differences between the two treatment arms in the TEAM trial are therefore not likely explained by the extended therapy. However, extended therapy could have affected the ten year results at a similar rate for both arms and possibly have led to an underestimation of recurrence rates. Given the equivalence of sequential therapy (tamoxifen followed by AI) compared with AI therapy for the first five years of adjuvant endocrine therapy, it will be highly interesting whether upfront tamoxifen or AI monotherapy during five years has a differential benefit in patients who will receive extended endocrine therapy.

During the inclusion period of the TEAM trial (study closure January 31, 2006), adjuvant trastuzumab was not yet administered as the first reports on the efficacy of adjuvant trastuzumab therapy only became available mid-2005.[22,23] In the current patient cohort, only a minority of patients had HER2 positive breast cancer (n=560, 9%). Our subgroup analysis did not show any difference in treatment effect between patients with HER2-negative, HER2-positive or unknown HER2 status, and no significant interaction between subgroups was observed (Figure 3). Further, repeated analyses excluding the HER2 positive patients were consistent with the findings in the total cohort. Given these results, the findings of the total study cohort may be considered reliable estimates of outcome for HER2 negative/HR+ patients.

Some countries that did not collect long-term follow-up (such as the United States and Japan) included relatively more low-risk patients in the TEAM trial (wepappendix, page 2). As a result, these patients had a significantly higher DFS at five years after randomization compared to patients included in the current long-term follow-up analysis. However, as subgroup analysis in this study showed that prognostic factors did not influence treatment effect (Figure 2), it is not expected to affect the findings of the current analyses. Moreover, no significant interaction for treatment was found between patients included in this long-term follow-up analysis and excluded patients . Therefore, we expect that results for treatment comparison in the current study cohort are representative for the original TEAM

population. Furthermore, a sensitivity analysis that included both the included patients and excluded patients (with five years of follow-up) yielded consistent results. Despite the decreased number of patients included in the current analyses, the power to detect differences between treatment arms for the primary endpoint was sufficient as the number of events due to longer follow-up time increased compared to the five year evaluation of this study (current analysis: n=1850, Table 2; previous report: n=1428,[5] respectively).

There are some other limitations that we are aware of. Firstly, we did not collect long-term adverse events for the current analyses. Secondly, as mentioned previously, extended adjuvant therapy either inside or outside a study protocol could have possibly led to an underestimation of disease recurrence. Finally, we collected data on cause of death and although cause of death classification is more reliable in clinical trial settings, it could have been subject to misclassification.

In conclusion, both the sequential scheme with upfront tamoxifen and exemestane monotherapy for five years are equally effective adjuvant treatment options for postmenopausal, hormone-receptor-positive breast cancer patients, with comparable survival rates after ten years of median follow-up. This allows the possibility for shared decision making between the clinician and patient, balancing individual patient characteristics and preferences, side effect profiles, and tolerability. Future studies will hopefully show which subgroup, if any, benefits more from either strategy, and whether extension of any of these strategies is worthwhile.

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Supplementary Table 1. Subgroup analysis of disease free survival for patients who remained disease free at five years after randomization

	n	N	HR (95% CI)
Histological grade			
G1 (well)	96	525	1.14 (0.76-1.71)
G2 (moderate)	415	2594	0.98 (0.81-1.19)
G3-G4 (poor)	278	1398	0.90 (0.72-1.15)
Gx/unknown	65	383	0.99 (0.72-1.92)
Tumour size			
T ≤2cm	347	2537	1.09 (0.88-1.34)
T >2cm	504	2273	0.93 (0.81-1.27)
Nodal status			
negative	304	2167	1.01 (0.81-1.27)
positive	548	2676	0.96 (0.81-1.14)
Progesterone receptor status			
positive	611	3564	0.97 (0.83-1.14)
negative	153	764	1.17 (0.85-1.61)
not performed	90	527	0.81 (0.53-1.24)
HER2			
positive	87	408	1.01 (0.67-1.55)
negative	617	3087	0.96 (0.82-1.12)
not performed	150	1360	1.09 (0.79-1.50)
Most extensive surgery			
mastectomy	479	2128	0.91 (0.76-1.09)
wide local excision	375	2724	1.12 (0.91-1.37)
Radiotherapy			
yes	542	3377	1.06 (0.90-1.26)
no	311	1467	0.87 (0.70-1.10)
Chemotherapy			
yes	261	1797	1.10 (0.86-1.40)
no	593	3058	0.93 (0.80-1.10)
Age (years)			
<50	19	166	0.91 (0.37-2.25)
50-59	200	1560	0.88 (0.67-1.17)
60-69	278	1942	0.88 (0.67-1.17)
≥70	357	1187	1.12 (0.69-1.11)
Overall estimate	**854**	**4855**	**0.98 (0.86-1.13)**

n: number of events, N: numbers at risk at time of randomization, hazard ratio (HR) and corresponding 95% confidence intervals (95% CI) for sequential therapy (reference) and exemestane monotherapy.

Supplementary Table 2. Baseline characteristics of patients in the original TEAM population, patients included for the current analysis and patients excluded for the current analysis

	Original TEAM population (n=9766)		Included for ten year analysis (n=6120)		Excluded for ten year analysis (n=3646)		
	N	%	N	%	N	%	P value*
Age (years)							
< 50	331	3.4	211	3.4	120	3.3	0.44
50-59	3017	30.9	1874	30.6	1143	31.3	
60-69	3731	38.2	2373	38.8	1358	37.2	
≥ 70	2687	27.5	1662	27.2	1025	28.1	
Histological grade							
G1 (well)	1677	17.2	616	10.1	1061	29.1	<0.001
G2 (moderate)	4797	49.1	3168	51.8	1629	44.7	
G3-G4 (poor)	2438	25.0	1835	30.0	603	16.5	
Unknown	854	8.7	501	8.2	353	9.7	
Tumour (T) stage							
T0,Tis	6	0.1	2	0.0	4	0.1	<0.001
T1	5690	58.3	3026	49.4	2664	73.1	
T2	3592	36.8	2684	43.9	908	24.9	
T3, T4	457	4.7	391	6.4	66	1.8	
Tx, unknown	21	0.2	17	0.3	4	0.1	
Nodal (N) stage							
N0	5112	52.3	2603	42.5	2509	68.8	<0.001
N1	4110	42.1	3100	50.7	1010	27.7	
N2-3	478	4.9	396	6.5	82	2.2	
Unknown	66	0.7	21	0.3	45	1.2	
Metastasis (M) stage							
M0 (no distant metastasis)	9725	99.6	6110	99.8	3615	99.1	<0.001
M1 (distant metastasis)	8	0.1	7	0.1	1	0.0	
Not assessed	33	0.3	3	0.0	30	0.8	
Estrogen-receptor status							
Positive	9586	98.2	5984	97.8	3602	98.8	0.001
Negative	176	1.8	133	2.2	43	1.2	
Unknown	4	0.0	3	0.0	1	0.0	
Progesterone-receptor status							
Positive	7300	74.7	4378	71.5	2922	80.1	<0.001
Negative	1725	17.7	1070	17.5	655	18.0	
Unknown	741	7.6	672	11.0	69	1.9	

Supplementary Table 2. Baseline characteristics of patients in the original TEAM population, patients included for the current analysis and patients excluded for the current analysis (*continued*)

	Original TEAM population (n=9766)		**Included for ten year analysis (n=6120)**		**Excluded for ten year analysis (n=3646)**		
	N	%	N	%	N	%	P value*
Most extensive surgery							
Mastectomy	4333	44.4	2873	46.9	1460	40.0	<0.001
Wide local excision	5423	55.5	3240	52.9	2183	59.9	
No resection	3	0.0	1	0.0	2	0.1	
Unknown	7	0.1	6	0.1	1	0.0	
Time from surgery to initiation of hormone treatment (months)							
< 3	5100	52.2	3768	61.6	1332	36.5	<0.001
3 to 6	2661	27.2	1322	21.6	1339	36.7	
≥ 6	1912	19.6	974	15.9	938	25.7	
Unknown	93	1.0	56	0.9	37	1.0	
Adjuvant radiotherapy							
Yes	6697	68.6	4167	68.1	2530	69.4	<0.001
No	2976	30.5	1934	31.6	1042	28.6	
Unknown	93	1.0	19	0.3	74	2.0	
Adjuvant chemotherapy							
Yes	3514	36.0	2253	36.8	1261	34.6	<0.001
No	6252	64.0	3867	63.2	2385	65.4	
Unknown	0		0		0		

* **P** value corresponds to proportional distribution of patients included in the current analysis versus patient excluded in the current analysis