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Original Research

Optimal adjuvant endocrine treatment of ER+/HER2+ breast cancer patients by age at diagnosis: A population-based cohort study

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Abstract ***Background:*** Prior randomised controlled trials on adjuvant hormonal therapy included $HER2_{any}$ patients; however, a differential effect of aromatase inhibitors (AIs) versus tamoxifen (TAM) may have been missed in ER+/HER2+ patients that comprise 7–15% of all breast cancer patients.

In addition, a woman's hormonal microenvironment may influence sensitivity to TAM and AIs in the adjuvant setting, which changes during menopausal transition, a process that takes years. We studied the efficacy of AIs versus TAM in ER+/HER2+ breast cancer patients grouped by age at diagnosis as a proxy for menopausal status using treatment and outcome data from the nationwide population-based Netherlands Cancer Registry (NCR).

Patients and methods: All women diagnosed between 2005 and 2007 with endocrine-treated, $T_{any}N_{any}M_0$, ER+/HER2+ breast cancer were identified through the NCR (n = 1155).

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Patients were divided by age at diagnosis: premenopausal (≤45 years; $n = 326$), perimenopausal (45<years≤55; $n = 304$) and postmenopausal (>55 years; $n = 525$). A time-dependent variable, indicating whether AI or TAM was received for >50% of endocrine treatment duration, was applied to subdivide groups by predominant treatment received. Recurrence-free survival (RFS) and overall survival (OS) were assessed using Kaplan–Meier survival estimation and Cox regression. Hazard ratios (HRs) were adjusted for chemotherapy, trastuzumab, age at diagnosis, N-status, grade, pT-stage and ovarian ablation.

Results: During follow-up, 237 recurrences and 182 deaths occurred. Perimenopausal women derived significant RFS and OS benefit from AI compared with TAM, HR 0.47 (95% CI 0.25–0.91; $P = 0.03$) and HR 0.37 (95% CI 0.18–0.79; $P = 0.01$), respectively, whereas premenopausal women derived no benefit from AI compared with TAM. Treatment effects differed significantly between these age groups (interaction $P = 0.03$ and $P = 0.02$, respectively). Among postmenopausal women a small but non-significant AI benefit was observed.

Conclusion: AI treatment, preferably without any TAM treatment, was associated with the best RFS and OS outcome in ER+/HER2+ perimenopausal breast cancer patients.

1. Background

Tamoxifen (TAM) was the standard adjuvant endocrine treatment for all oestrogen receptor (ER) positive breast cancers until aromatase inhibitors (AIs) showed superiority over TAM in the treatment of ER+ postmenopausal patients [1]. Premenopausal patients were expected to derive a similar benefit from AI treatment. Indeed, results from the combined SOFT/TEXT analysis confirmed that the AI exemestane plus ovarian ablation (OA) significantly improved disease-free survival (DFS), breast cancer-free interval and distant metastasis-free survival when compared with TAM plus OA and TAM alone [2,3].

Studies on the crosstalk between the ER and human epidermal growth factor receptor 2 (HER2) pathways, however, resulted in the discovery of a differential endocrine treatment response between ER+/HER2– and ER+/HER2+ preclinical breast cancer models, suggesting that ER+/HER2+ cell lines are resistant to TAM [4–7]. Clinical studies confirmed the benefit of AI over TAM in postmenopausal ER+/HER2+ patients, although the difference was not significant [8–10]. In premenopausal ER+/HER2+ patients, TAM plus OA resulted in a non-significant better outcome than AI plus OA [3]. Perimenopausal patients were excluded from all these trials. Patients aged 45–55 years at diagnosis were included, but only when menopausal status was confirmed [11].

We hypothesise that the hormonal microenvironment influences tumourigenesis and endocrine treatment sensitivity. Since menopausal transition is a process in time, we were interested to study the relative efficacy of AIs versus TAM in ER+/HER2+ breast cancer patients by age at diagnosis using treatment and outcome data from the population-based Netherlands Cancer Registry (NCR).

2. Methods

2.1. Patient selection

The nationwide population-based prospective NCR has registered all newly diagnosed, histologically confirmed, Dutch cancer patients from 1989 onwards. Detailed information on patient, tumour and treatment characteristics are collected from hospital records by trained registrars. Vital status data are available through annual linkage with the municipal population registry, conducted once a year. Information on the cause of death is not available. Disease recurrence data, which are not systematically recorded in the NCR, were complemented by NCR registrars by returning to the hospital records.

Using the NCR, we identified all women without a prior malignancy who were diagnosed between 2005 and 2007 with a $T_{any}N_{any}M_0$, ER+/HER2+, endocrine-treated, invasive breast cancer.

According to Dutch guidelines, tumours were considered ER+ when ≥10% of tumour cells stained positive on immunohistochemistry (IHC). For HER2, tumours scoring positive on in-situ hybridisation, 3+ on IHC or positive on polymerase chain reaction were considered HER2+. Endocrine treatment was defined as TAM or AI treatment with or without OA achieved through surgery or chemical ablation.

2.2. Statistical analysis

To take switches between TAM and AI into account, we calculated the cumulative treatment duration for both

modalities, starting from the date of treatment initiation until the date of treatment discontinuation. When the exact date of treatment initiation was missing, date of diagnosis or end date of previous endocrine treatment was used instead. Similarly, when the exact date of treatment discontinuation was missing, start date of subsequent endocrine treatment, disease recurrence, death or end of follow-up (FUP) was used.

The two endocrine treatment modalities were compared by investigating the AI treatment duration relative to the cumulative endocrine treatment duration in a time-dependent manner. In other words, at any event time during FUP, we calculated the AI-endocrine treatment ratio = (AI treatment duration/(AI+TAM treatment duration) × 100%) (Supplemental Fig. 1). Our main analyses used an AI-endocrine treatment ratio dichotomised at 50%. In addition, the AI-endocrine treatment ratio was treated as a continuous variable to assess trend. The AI-endocrine treatment ratio was evaluated by age at diagnosis using ≤45 years (premenopausal), 45<years≤55 (perimenopausal), >55 years (postmenopausal) as age cut-offs for menopausal status, in our main analyses. Heterogeneity of treatment effects by age at diagnosis was evaluated by likelihood ratio tests. We used OA as a time-dependent covariate. OA achieved through chemical ablation was, therefore, only taken into account when endocrine treatment was given concurrently. Patients receiving endocrine treatment after surgical ablation were also considered OA treated.

FUP time was used as the time scale to evaluate recurrence-free survival (RFS) and overall survival (OS). FUP-time calculation was performed with left truncation at the start of the first endocrine treatment. RFS time was calculated to death from any cause, invasive ipsilateral, local, regional or distant recurrence, whichever occurred first [12]. OS time was calculated until death from any cause. RFS and OS were assessed using an extended Kaplan–Meier survival estimator for time-dependent covariates [13]. Patients without RFS and OS events at the end date of FUP or patients lost to FUP were censored. Cox regression modelling using FUP as the time scale was performed to estimate hazard ratios (HRs), 95% confidence intervals (CIs) and *p*-values. Factors included treatment group, chemotherapy, trastuzumab, age at diagnosis, lymph node status, grade, pathological T stage and OA. The proportionality of hazards was evaluated using Schoenfeld residuals and the assumptions were fulfilled.

Sensitivity analyses were performed including the number of treatment switches, type of first treatment received (TAM vs AI) and excluding women with missing start date of the first endocrine treatment. In addition, four alternative AI-endocrine treatment ratio cut-offs and five alternative age cut-offs were evaluated.

Statistical analyses were performed using R version 3.2.1 and StataSE 13.

3. Results

3.1. Study population

Of 1155 women diagnosed with ER+/HER2+ invasive breast cancer between 2005 and 2007, 326 women were premenopausal (≤45 years), 304 were perimenopausal (45<years≤55) and 525 were postmenopausal (>55 years). Baseline characteristics are shown by age and AI-endocrine treatment ratio at the end of FUP (Table 1).

The majority of women received an AI for the largest part of their endocrine treatment duration, regardless of age at diagnosis. OA frequencies in combination with AIs were as expected for the different age groups (Table 1). Forty-five percent of patients (524/1155) received one type of endocrine treatment only. Most patients switching endocrine treatments switched once, 488/1155 (42.3%; Supplemental table 2).

Most tumours were ≤T2, grade 3 and accompanied by at least one lymph node metastasis (Table 1). Treatment included chemotherapy for 99.1% (323/326) and 92.4% (281/304) of premenopausal and perimenopausal patients compared with 32% (168/525) for postmenopausal patients. Similarly, trastuzumab treatment was given to 87.1% (284/326), 81.9% (249/304) and 27% (142/525) of premenopausal, perimenopausal and postmenopausal ER+/HER2+ breast cancer patients, respectively (Table 1).

3.2. Recurrence-free survival

Most RFS events concerned distant metastases (Supplemental table 3).

In premenopausal women, 5-year RFS was 88% in predominantly AI-treated patients and 90% in those who mainly received TAM (adjusted HR 1.32; 95% CI 0.69–2.52; $P = 0.40$; Fig. 1, Table 2). In perimenopausal women, AI treatment significantly improved 5-year RFS in comparison to TAM (90% versus 78%; adjusted HR 0.47; 95% CI 0.25–0.91; $P = 0.03$; $p_{trend} \leq 0.01$).

We found evidence for treatment-effect heterogeneity of TAM versus AI between premenopausal and perimenopausal women (interaction $P = 0.03$), indicating that perimenopausal women but not premenopausal women derived a statistically significant RFS benefit from AI treatment versus TAM. It was unclear whether this effect was in part due to the addition of OA since the interaction-*P*-values between women treated with an AI versus those who received AI + OA were 0.458 for premenopausal women and 0.16 for perimenopausal women, respectively (Supplemental table 4).

In postmenopausal women mainly receiving an AI did not significantly improve RFS in comparison to TAM (5-year rates: 77% versus 73%; adjusted HR 0.86; 95% CI 0.56–1.34; $P = 0.51$).

Table 1
Baseline characteristics of all 1155 ER+/HER2+, endocrine-treated Dutch breast cancer patients according to age at diagnosis and treatment status at the end of follow-up.

Variable	Premenopausal (≤45 years at diagnosis) $n = 326$				Perimenopausal (>45−≤55 years at diagnosis) $n = 304$				Postmenopausal (>55 years at diagnosis) $n = 525$			
	TAM		AI		TAM		AI		TAM		AI	
	$N = 119$	100%	$N = 207$	100%	$N = 49$	100%	$N = 255$	100%	$N = 59$	100%	$N = 466$	100%
Mean age (range)	38.0 (24−45)		39.4 (21−45)		49.1 (46−55)		50.5 (46−55)		71.2 (56−96)		67.7 (56−94)	
Mean RFS FUP (years)(range)	6.0 (0.67−7.92)		6.3 (1.3−7.9)		5.5 (1.8−7.9)		6.2 (1.4−7.9)		4.7 (0.3−7.8)		5.6 (0.3−7.9)	
Mean OS FUP (years)(range)	6.3 (1.00−7.92)		6.6 (1.6−7.9)		6 (3.5−7.9)		6.4 (1.8−7.9)		5 (0.3−7.8)		5.8 (0.3−7.9)	
pT-stage												
$1,1_a,1_b,1_c$	65	54.6%	86	41.5%	22	44.9%	113	44.3%	23	39%	213	45.7%
2	42	35.3%	91	44%	24	49.0%	117	45.9%	34	57.6%	222	47.6%
3	3	2.5%	6	2.9%	1	2.0%	10	3.9%	1	1.7%	18	3.9%
$4,4_a,4_b,4_c,4_D$	0	0%	1	0.5%	0	0%	2	0.8%	1	1.7%	5	1.1%
Unknown	9	7.6%	23	11.1%	2	4.1%	13	5.1%	0	0%	8	1.7%
Grade												
I	4	3.4%	10	4.8%	1	2.1%	7	2.7%	2	3.4%	15	3.2%
II	26	21.8%	62	30%	18	36.7%	77	30.2%	20	33.9%	168	36.1%
III	72	60.5%	110	53.1%	27	55.1%	147	57.7%	33	55.9%	253	54.3%
Unknown	17	14.3%	25	12.1%	3	6.1%	24	9.4%	4	6.7%	30	6.4%
Positive lymph nodes												
0	45	37.8%	77	37.2%	22	44.9%	108	42.3%	23	39%	214	45.9%
1−3	49	41.2%	82	39.6%	19	38.8%	81	31.8%	20	33.9%	171	36.6%
4−9	19	16%	35	16.9%	5	10.2%	47	18.4%	6	10.2%	43	9.2%
>10	6	5%	12	5.8%	3	6.1%	17	6.7%	6	10.2%	28	6%
Unknown	0	0%	1	0.5%	0	0%	2	0.8%	4	6.8%	10	2.1%
Chemotherapy												
Yes	119	100%	204	98.6%	41	83.7%	240	94.1%	15	25.4%	153	32.8%
No	0	0%	3	1.4%	8	16.3%	15	5.9%	44	74.6%	313	67.2%
Trastuzumab												
Yes	102	85.7%	182	87.9%	38	77.6%	211	82.7%	13	22%	129	27.7%
No	17	14.3%	25	12.1%	11	22.4%	44	17.3%	46	78%	337	72.3%
Ovarian ablation												
Yes[a]	76	63.9%	155	74.9%	7	14.3%	35	13.7%	0	0%	4	0.9%
• Surgery	18		67		3		15		0		3	
• GnRH	71		121		5		28		0		1	
No	43	36.1%	52	25.1%	42	85.7%	220	86.3%	59	100%	462	99.1%

Abbreviations: TAM, tamoxifen; GnRH, gonadotropin-releasing hormone agonist; AI, aromatase inhibitor; FUP, follow-up; RFS, recurrence-free survival; OS, overall survival.
Women are considered TAM or AI treated based on the AI: endocrine treatment duration ratio. A woman belongs to the TAM group if the AI: endocrine treatment duration (AI+TAM) ratio is ≤0.50 and to the AI group if the AI: (AI+TAM) is ratio>0.5.

[a] Numbers may not add-up because some patients received a GnRH before their surgery.

3.3. Overall survival

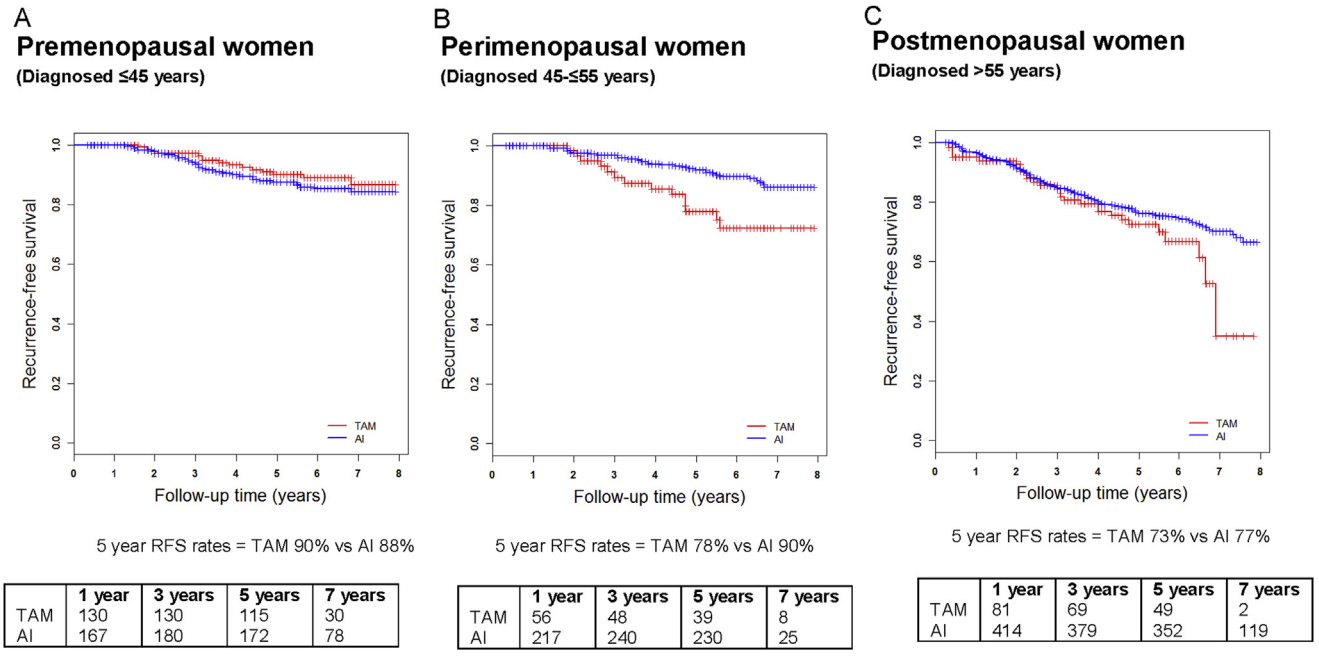
Premenopausal women did not derive significant OS benefit when mainly AI treated compared with predominantly TAM treated (5-year rates 97% versus 95%; adjusted HR 1.44; 95% CI 0.63–3.31; $P = 0.39$; Fig. 2, Table 3). Perimenopausal women on the other hand derived a significant OS benefit from AI compared with TAM (5-year rates: 96% versus 87%; adjusted HR 0.37; 95% CI 0.18–0.79; $P = 0.01$; $p_{trend} = 0.01$). The AI treatment effect significantly differed between perimenopausal and premenopausal women (interaction $P = 0.02$). At present it is unclear whether addition of OA played a role in this observation, since the test for interaction was not significant (Supplemental table 5). Nevertheless, for the whole group of ER+/HER2+ breast cancer patients, addition of OA conferred a survival benefit (Table 2). Most OS events were observed in postmenopausal women. Predominant AI treatment did not significantly improve OS in postmenopausal women when compared with mainly TAM treatment (5-year rates: 81% versus 75%; adjusted HR 0.78; 95% CI 0.46–1.32; $P = 0.36$).

3.4. Sensitivity analysis

Similar results were obtained in sensitivity analyses using different cut-offs for the AI-TAM ratios (Supplemental table 6A–6H), number of treatment switches, type of first treatment received and excluding 55 patients with missing start date of the first endocrine treatment (data not shown). Using five different cut-offs for age at diagnosis yielded similar patterns, with HRs favouring TAM for premenopausal women (the youngest age categories) and AI for perimenopausal and postmenopausal women. The strongest differential TAM and AI treatment effect was found for the age cut-offs presented (premenopausal [≤45 years], perimenopausal [45<years≤55], postmenopausal [>55 years]; Supplemental table 1A–1B).

4. Discussion

The hormonal environment changes during menopausal transition, a process that takes several years. We hypothesised that a woman's hormonal microenvironment influences the relative endocrine treatment sensitivity to TAM and AIs in the adjuvant setting. Here, we studied the relative efficacy of AIs versus TAM in ER+/HER2+ breast cancer patients grouped by age at diagnosis. We focused on ER+/HER2+ patients, since a differential effect of AIs versus TAM may have been missed in ER+/HER2+ patients that comprise only 7–15% of all breast cancer patients. To interpret our results, in light of current literature, women ≤45 years at diagnosis can be considered enriched for premenopausal



	1 year	3 years	5 years	7 years
TAM	130	130	115	30
AI	167	180	172	78

	1 year	3 years	5 years	7 years
TAM	56	48	39	8
AI	217	240	230	25

	1 year	3 years	5 years	7 years
TAM	81	69	49	2
AI	414	379	352	119

Fig. 1. Kaplan–Meier curves showing the RFS of ER+/HER2+ Dutch breast cancer patients according to age at breast cancer diagnosis and endocrine treatment received (TAM or AI)*.A. Premenopausal (≤45 years at diagnosis)B. Perimenopausal (between 45 and 55 years at diagnosis)C. Postmenopausal (>55 years at diagnosis). *Women are considered TAM or AI treated based on the AI: endocrine treatment duration ratio. A woman belongs to the TAM group if the AI: endocrine treatment duration (AI + TAM) ratio is ≤0.50 and to the AI group if the AI: (AI + TAM) is ratio >0.5. AI, aromatase inhibitor, ER, oestrogen receptor, HER2, human epidermal growth factor receptor 2, RFS, recurrence-free survival, TAM, tamoxifen.

Table 2
Multivariate Cox regression for RFS in 1155 ER+/HER2+, endocrine-treated, Dutch breast cancer patients.

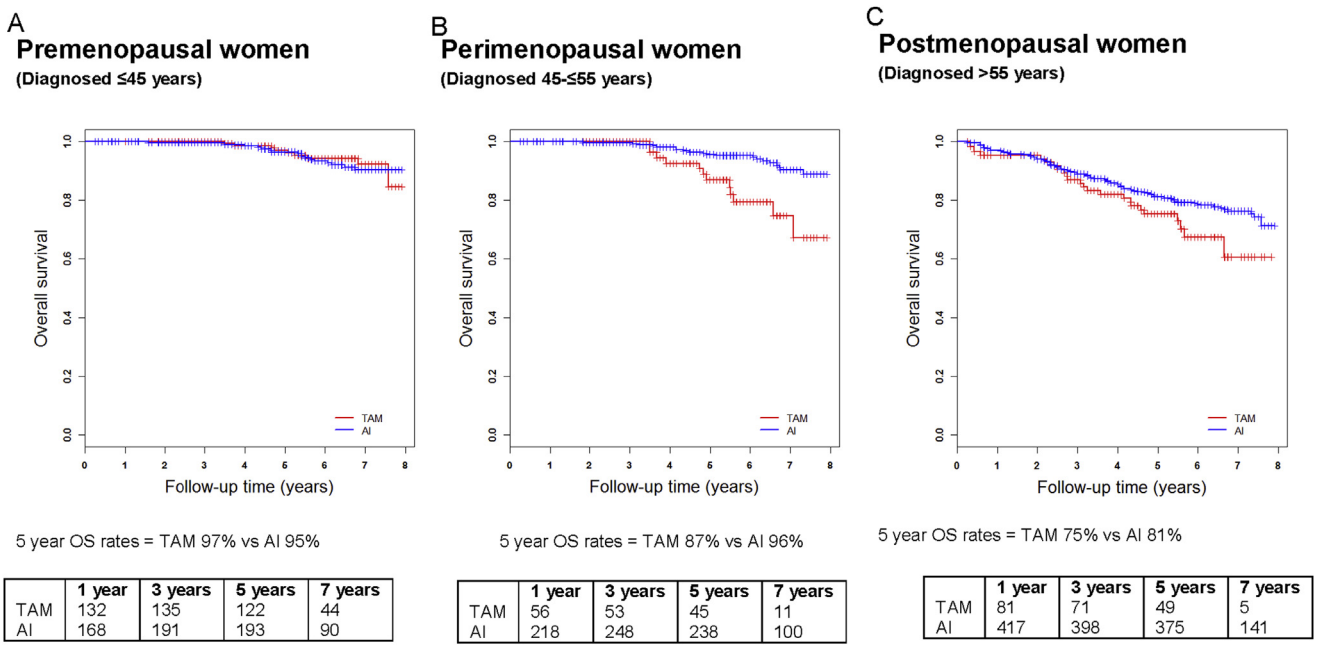
Variable	Nr events	HR	CI	*p*-value	*p*-trend	*p*-interaction
TAM vs AI						
Premenopausal (≤45 years at diagnosis)						
TAM	15	1.00				
AI	29	1.32[a]	0.69–2.52	0.40	0.51	
Perimenopausal (>45–≤55 years at diagnosis)						0.03[a]
TAM	14	1.00				
AI	30	0.47[a]	0.25–0.91	0.03	<0.01	
Postmenopausal (>55 years at diagnosis)						
TAM	26	1.00				
AI	123	0.86	0.56–1.34	0.51	0.76	
Age						
≤45						
45–55			0.85–3.98	0.12		
>55			0.61–2.80	0.50		
Chemotherapy						
No	129	1.00				
Yes	108	0.38	0.22–0.65	<0.01		
Trastuzumab						
No	145	1.00				
Yes	92	0.81	0.49–1.33	0.40		
Grade						
I	6	0.79	0.36–1.74	0.56		
II	86	1.08	0.82–1.43	0.58		
III	120	1.00				
NA	25	1.46	0.79–2.72	0.23		
Positive lymph nodes						
0	66	1.00				
1–3	89	1.88	1.35–2.62	<0.01		
4–9	41	3.20	2.08–4.93	<0.01		
>10	34	5.49	3.53–8.53	<0.01		
pT-stage						
1, 1A, 1B, 1C	84	1.00				
2	131	1.46	1.10–1.94	<0.01		
3	11	1.08	0.54–2.16	0.82		
4, 4A, 4B, 4C, 4D	3	1.51	0.38–6.11	0.56		
NA	8	1.03	0.40–1.31	0.95		
Ovarian ablation						
No	208	1.00				
Yes	29	0.80	0.49–1.31	0.38		

Abbreviations: AI, aromatase inhibitor; TAM, tamoxifen; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.
Women are considered TAM or AI treated based on the AI: endocrine treatment duration ratio. A woman belongs to the TAM group if the AI: endocrine treatment duration (AI + TAM) ratio is ≤0.50 and to the AI group if the AI: (AI + TAM) is ratio >0.5.
[a] A p-value for interaction was calculated to determine whether the AI and TAM treatment comparison differed significantly between women ≤45 years at diagnosis and those diagnosed 45<years≤55.

patients, women diagnosed at <45 to ≤55 years considered enriched for perimenopausal patients and women >55 years at diagnosis considered enriched for postmenopausal patients. We found that perimenopausal women derived significant RFS and OS benefit from an AI compared with TAM, HR 0.47 (95% CI 0.25–0.91; $P = 0.03$) and HR 0.37 (95% CI 0.18–0.79; $P = 0.01$), respectively.

For treatment purposes oncologists consider most perimenopausal women (aged 45–55 years) premenopausal and treat them accordingly. After natural menopause these patients are considered postmenopausal. To date, no clinical trial was conducted comparing TAM and AI in this patient subset.

Our results are best understood in light of similar results from the NCIC CTG MA17 trial [14]. They investigated whether 5 years of letrozole was superior to placebo after 4.5–6 years of prior TAM use. Patients were postmenopausal at randomisation and stratified by menopausal status at diagnosis. Women who were premenopausal at diagnosis but postmenopausal at randomisation were considered perimenopausal. These patients derived a more pronounced DFS benefit from letrozole when compared with placebo (HR 0.26; 95% CI 0.13–0.55; $P = 0.0003$) than those who were postmenopausal at diagnosis (HR 0.67; 95% CI 0.51–0.89; $P = 0.006$; interaction $P = 0.03$) [14]. The mechanism underlying this finding is unknown but the observation



	1 year	3 years	5 years	7 years
TAM	132	135	122	44
AI	168	191	193	90

	1 year	3 years	5 years	7 years
TAM	56	53	45	11
AI	218	248	238	100

	1 year	3 years	5 years	7 years
TAM	81	71	49	5
AI	417	398	375	141

Fig. 2. Kaplan–Meier curves showing the OS of ER+/HER2+ Dutch breast cancer patients according to age at breast cancer diagnosis and split by endocrine treatment received (TAM or AI)*. A. Premenopausal (≤45 years at diagnosis). B. Perimenopausal (between 45 and 55 years at diagnosis). C. Postmenopausal (>55 years at diagnosis).*Women are considered TAM or AI treated based on the AI: endocrine treatment duration ratio. A woman belongs to the TAM group if the AI: endocrine treatment duration (AI + TAM) ratio is ≤0.50 and to the AI group if the AI: (AI + TAM) is ratio >0.5. AI, aromatase inhibitor, ER, oestrogen receptor, HER2, human epidermal growth factor receptor 2, OS, overall survival, TAM, tamoxifen.

fits with our hypothesis that a changing hormonal (micro)environment influences the sensitivity of breast cancer cells to either adjuvant TAM or AI.

Studies that compared TAM and AI in premenopausal ER+ breast cancer patients were often conducted in HER2-patients or did not take HER2 status into account [15,16]. An exception are the combined SOFT/TEXT analyses, where subgroup analysis of the HER2+ patients revealed that TAM plus OA significantly improved DFS when compared with TAM only, HR 0.42 (95% CI 0.22–0.80) [2]. When exemestane plus OA was compared with TAM plus OA, the difference in DFS proved non-significant, HR 1.25 (95% CI 0.80–1.94) [3]. Another study, published in 2003, also reported TAM plus OA as a very effective treatment for premenopausal ER+/HER2+ breast cancer patients, although no comparison with AIs was made [17].

Although the RFS results of SOFT/TEXT and our study are very comparable, patient populations differ. Premenopausal status was confirmed for all patients in SOFT/TEXT while we studied age at diagnosis. Another difference with SOFT/TEXT pertains to the administration of chemotherapy. While 83.1% (196/236) ER+/HER2+ patients in SOFT/TEXT received chemotherapy, 99.1% of premenopausal women in our cohort did.

The high chemotherapy use in our cohort might have led to 10%–70% of patients experiencing chemotherapy-induced amenorrhoea (CIA) or chemotherapy-induced menopause (CIM) [18]. The incidence of CIA and CIM likely explains why a proportion of premenopausal and perimenopausal women in our study did not receive OA while on AI treatment.

In our study, there was an impression of better survival in premenopausal and perimenoapusal women when an AI was combined with OA as opposed to an AI without OA, although the difference was not significant. For the whole group of ER+/HER2+ breast cancer patients in our study, addition of OA to TAM or AI conferred a substantial survival benefit. In the SOFT/TEXT subgroup analyses of premenopausal ER+/HER2+ patients, superiority of OA added to TAM has been shown [2]. Therefore, addition of ovarian function suppression to endocrine therapy is advised [19].

Most trials on the differential effectiveness of AI and TAM were conducted in postmenopausal patients that included low numbers of ER+/HER2+ patients [11]. Our findings are consistent with results from the adjuvant BIG1-98 trial that reported a non-significant DFS benefit for AI-treated ER+/HER2+ patients compared with those receiving TAM (HR 0.62; 95% CI 0.37–1.03) [8]. Other studies failed to find a difference or reported on the superiority of AI over TAM in these patients [10,11,20,21].

Our study has some limitations. Although this study is the largest in its kind, sample size and event rates were

Table 3
Multivariate Cox regression for OS in 1155 ER+/HER2+, endocrine-treated, Dutch breast cancer patients.

Variable	Nr events	HR	CI	*p*-value	*p*-trend	*p*-interaction
TAM vs AI						
Premenopausal (≤45 years at diagnosis)						
TAM	9	1.00				
AI	17	1.44[a]	0.63–3.31	0.39	0.47	
Perimenopausal(>45–≤55 years at diagnosis)						0.02[a]
TAM	12	1.00				
AI	20	0.37[a]	0.18–0.79	0.01	0.01	
Postmenopausal (>55 years at diagnosis)						
TAM	23	1.00				
AI	101	0.78	0.46–1.32	0.36	0.28	
Age						
≤45	26	1.00				
45–55	32	1.90	0.79–4.59	0.15		
>55	124	1.35	0.56–3.24	0.51		
Chemotherapy						
No	107	1.00				
Yes	75	0.30	0.16–0.55	<0.01		
Trastuzumab						
No	116	1.00				
Yes	66	0.98	0.56–1.71	0.951		
Grade						
I	3	0.45	0.13–1.56	0.21		
II	66	0.94	0.68–1.31	0.72		
III	95	1.00				
NA	18	1.11	0.51–2.40	0.80		
Positive lymph nodes						
0	44	1.00				
1–3	72	2.36	1.61–3.48	<0.01		
4–9	31	3.95	2.32–6.71	<0.01		
>10	27	5.91	3.48–10.04	<0.01		
pT-stage						
1, 1A, 1B, 1C	65	1.00				
2	85	1.47	1.05–2.05	0.03		
3	16	1.17	0.52–2.59	0.71		
4, 4A, 4B, 4C, 4D	10	1.88	0.40–8.89	0.43		
NA	6	1.84	0.63–5.33	0.26		
Ovarian ablation						
No	178	1.00				
Yes	4	0.13	0.04–0.38	<0.01		

Abbreviations: AI, aromatase inhibitor; TAM, tamoxifen; HR, hazard ratio; CI, confidence interval; OS, overall survival.
Women are considered TAM or AI treated based on the AI: endocrine treatment duration ratio. A woman belongs to the TAM group if the AI: endocrine treatment duration (AI + TAM) ratio is ≤0.50 and to the AI group if the AI: (AI + TAM) is ratio >0.5.
[a] A p-value for interaction was calculated to determine whether AI and TAM treatment comparison differed significantly between women ≤45 years at diagnosis and those diagnosed 45<years≤55.

still relatively low. In addition, no significant AI benefit was observed in postmenopausal women. This might be a real effect, caused by a differential endocrine sensitivity of ER+/HER2+ breast cancers when compared with ER+/HER2-breast cancers. However, it may also be a result of residual confounding by indication as Dutch clinical guidelines recommend AIs for all high risk postmenopausal patients which might have diminished the positive effect of AI versus TAM treatment on patient outcome [22].

In conclusion, ER+/HER2+ perimenopausal breast cancer patients (diagnosed 45<years≤55) derived significant RFS and OS benefit from treatment with mainly AIs when compared with predominantly TAM. AI treatment, not tamoxifen, should therefore be the treatment of choice for ER+/HER2+ breast cancer patients in this age group.

The optimal treatment for premenopausal patients (aged <45 years) seems to be TAM (+OA) and for postmenopausal patients (aged >55 years) an AI, although no significant difference between the two treatments was observed in these age categories.

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Conflict of interest statement

GSS has received institutional research support funding from Roche. SCL is an advisory board member for Cergentis, Novartis, Roche and Sanofi and received research support funding from Amgen, AstraZeneca, Bristol-Myers Squibb (BMS), Genentech, Roche and Sanofi. All remaining authors have declared no conflicts of interest.

Ethics approval

This project was approved by the Medical Ethical Committee of the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital (PTC12.1262/NBCP).

Contributions

SCL and SS conceived the study. The study was designed by GMHED, KJ, GSS, MH and SCL. All data were analysed by KJ and MH and interpreted by all authors. GMHED drafted the manuscript. All authors listed, critically reviewed and approved the manuscript before submission.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2017.11.010.

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