Supplementary Material

Supplementary Tables

Supplementary table 1. Number of endocrine treatment switches during follow-up for all 2,295 patients included in this cohort, split by AI-endocrine treatment ratio at the end of follow-up.

Number of switches	AI <25%		25%≤AI≤75%		AI>75%		Total
	n	%	n	%	n	%	
0	448	71.8	0	0	348	60	796
1	97	15.5	1,047	96.0	227	39.1	1,371
2	76	12.2	30	2.7	5	0.9	111
3	3	0.5	14	1.3	0	0	17
Total	624	100	1,091	100	580	100	2,295

AI = Aromatase inhibitor

Supplementary table 2. Number and type of first RFS event split by age at diagnosis and AI-endocrine treatment ratio at the end of follow-up.*

	AI<25% (N=624)		25%≤AI≤75% (N=1,091)		AI>75% (N=580)	
	n	%	n	%	N	%
Local recurrence	21	11.4	14	11.9	3	4.1
Regional recurrence	12	6.5	8	6.8	3	4.1
Distant metastases	133	71.8	81	68.6	54	72.9
Death	19	10.3	15	12.7	14	18.9
Total number of events	185	100	118	100	74	100

AI = Aromatase inhibitor, RFS=Recurrence-Free Survival

* Number of RFS events that occurred first in the treatment groups as indicated. For example, in the group of patients who received an AI for less than 25% of their endocrine treatment duration, 185 RFS events occurred. Nineteen out of 185 events (10.3% of total number of RFS events) involved death as the first RFS event

Supplementary table 3. Adjusted hazard ratios for RFS and OS according to treatment groups defined by AI-endocrine treatment ratio when additional adjustments for Body Mass Index (BMI), total endocrine treatment duration, number of treatment switches, type of first endocrine treatment received, and including only women whose start or stop date of first endocrine treatment was known were made.

	Events	aHR	95% CI	p-value
Treatment effect adjusted for BMI				
RFS				
AI treatment duration*†				
AI<25%	185	1.00		
25%≤AI≤75%	118	0.86	0.65-1.13	0.283
AI> 75%	74	0.63	0.46-0.86	0.004
OS				
AI treatment duration*†‡				
AI<25%	127	1.00		
25%≤AI≤75%	62	0.33	0.22-0.50	<0.001
25%≤AI≤75% *(follow-up time - 5)		1.43	1.13-1.80	0.003
AI> 75%	47	0.51	0.35-0.74	<0.001
Treatment effect adjusted for total endocrine treatment duration				
RFS				
AI treatment duration*†				
AI<25%	185	1.00		
25%≤AI≤75%	118	0.86	0.65-1.13	0.270
AI> 75%	74	0.63	0.46-0.86	0.004
OS				
AI treatment duration*†‡				
AI<25%	127	1.00		
25%≤AI≤75%	62	0.65	0.43-0.99	0.047
25%≤AI≤75% *(follow-up time - 5)		1.31	1.04-1.65	0.021
AI> 75%	47	0.64	0.43-0.96	0.029
Treatment effect adjusted for number of treatment switches				
RFS				
AI treatment duration*†				
AI<25%	185	1.00		
25%≤AI≤75%	118	0.81	0.56-1.16	0.255
AI> 75%	74	0.59	0.43-0.81	0.001

OS				
AI treatment duration*†‡				
AI<25%	127	1.00		
25%≤AI≤75%	62	0.41	0.25-0.70	<0.001
25%≤AI≤75% *(follow-up time - 5)		1.39	1.10-1.76	0.006
AI> 75%	47	0.46	0.31-0.68	<0.001
Treatment effect adjusted for type of first endocrine treatment received				
RFS				
AI treatment duration*†				
AI<25%	185	1.00		
25%≤AI≤75%	118	0.86	0.65-1.13	0.274
AI> 75%	74	0.65	0.42-1.02	0.062
OS				
AI treatment duration*†‡				
AI<25%	127	1.00		
25%≤AI≤75%	62	0.33	0.22-0.50	<0.001
25%≤AI≤75% *(follow-up time - 5)		1.43	1.13-1.81	0.003
AI> 75%	47	0.60	0.36-1.02	0.058
Treatment effect when only including women with known start and stop dates of first endocrine treatment				
RFS				
AI treatment duration*†				
AI<25%	130	1.00		
25%≤AI≤75%	113	0.92	0.68-1.25	0.615
AI> 75%	54	0.76	0.53-1.10	0.151
OS				
AI treatment duration*†‡				
AI<25%	83	1.00		
25%≤AI≤75%	58	0.34	0.22-0.54	<0.001
25%≤AI≤75% *(follow-up time - 5)		1.46	1.12-1.91	0.005
AI> 75%	31	0.59	0.37-0.94	0.026

aHR = adjusted Hazard ratio, AI = Aromatase inhibitor, BMI = Body Mass Index, CI = Confidence interval, OS = Overall Survival, RFS = Recurrence-Free Survival

* The AI-endocrine treatment ratio, included in the model as a time-dependent variable, is defined as the percentage of total endocrine treatment duration (AI+tamoxifen) spent on AI treatment.

† All analyses were adjusted for age at diagnosis, trastuzumab use (included as a time-dependent variable), grade, positive lymph nodes, pT-stage, PR status, HER2 status and ovarian ablation (included as a time-dependent variable)

‡ Interaction between the 25%≤AI≤75% category and a follow-up time centered at 5-years was included to accommodate non-proportional hazards. For example at 5-years of follow-up patients in the model adjusted for BMI who had an AI-endocrine treatment ratio 25%≤AI≤75% had a smaller chance of an OS-

event then patients with an AI-endocrine treatment ratio AI<25% (adjusted-HR 0.33). The HR increases by 143% for each additional year of follow-up, so at 6-years of follow-up the hazard ratio for an AI-endocrine treatment ratio 25%≤AI≤75% versus AI<25%= = exp{ln(0.33)+(follow-up time-5)*ln(1.43)}=0.47.

Supplementary table 4. Adjusted hazard ratios for RFS and OS according to treatment groups defined by AI-endocrine treatment ratio in 497 women who received ovarian ablation at any stage during endocrine treatment

	Events	aHR	95% CI	p-value
RFS				
AI treatment duration*†				
AI<25%	38	1.00		
25%≤AI≤75%	29	1.08	0.61-1.90	0.800
AI> 75%	10	0.40	0.18-0.89	0.025
OS				
AI treatment duration*†‡				
AI<25%	25	1.00		
25%≤AI≤75%	17	0.59	0.23-1.54	0.283
25%≤AI≤75% *(follow-up time - 5)		2.04	1.06-3.92	0.034
AI> 75%	7	0.42	0.16-1.11	0.080

aHR = adjusted Hazard ratio, AI = Aromatase inhibitor, CI = Confidence interval, HER2=Human Epidermal growth factor Receptor-2, PR= progesterone receptor, OS = Overall Survival, RFS = Recurrence-Free Survival

* The AI-endocrine treatment ratio, included in the model as a time-dependent variable, is defined as the percentage of total endocrine treatment duration (AI+tamoxifen) spent on AI treatment.

† All analyses were adjusted for age at diagnosis, trastuzumab use (included as a time-dependent variable), grade, positive lymph nodes, pT-stage, PR status, HER2 status and ovarian ablation (included as a time-dependent variable)

‡ Interaction between the 25%≤AI≤75% category and a follow-up time centered at 5-years was included to accommodate non-proportional hazards. At 5-years of follow-up patients with an AI-endocrine treatment ratio 25%≤AI≤75% had a smaller chance of an OS-event then patients with an AI-endocrine treatment ratio AI<25% (adjusted-HR 0.59). The HR increases by 103% for each additional year of follow-up, so at 6-years of follow-up the hazard ratio for an AI-endocrine treatment ratio 25%≤AI≤75% versus AI<25%= = exp{ln(0.59)+(follow-up time-5)*ln(2.03)}=1.19.

Supplementary table 5. Adjusted hazard ratios for treatment groups by AI-endocrine treatment ratio using alternative AI-endocrine treatment ratio cut-offs for RFS and OS

	Events	aHR	95% CI	p-value
RFS				
AI treatment duration*†				
AI=0%	149	1.00		
0%< AI < 30%	42	0.69	0.48-1.00	0.051
30% ≤ AI ≤ 70%	106	0.83	0.61-1.13	0.230
70% < AI < 100%	30	0.60	0.39-0.93	0.022
AI=100%	50	0.52	0.35-0.76	<0.001
RFS				
AI treatment duration*†				
AI=0%	149	1.00		
0%< AI < 40%	54	0.64	0.45-0.91	0.012
40% ≤ AI ≤ 60%	72	0.97	0.69-1.36	0.866
60%< AI < 100%	52	0.67	0.46-0.97	0.033
AI=100%	50	0.52	0.36-0.76	<0.001
RFS				
AI treatment duration*†				
AI ≤ 50%	241	1.00		
AI > 50%	136	0.70	0.55-0.90	0.005
RFS				
AI treatment duration*†				
AI=0%	149	1.00		
0%< AI < 100%	178	0.74	0.57-0.97	0.029
AI=100%	50	0.52	0.36-0.76	<0.001
OS				
AI treatment duration*†‡				
AI=0%	107	1.00		
0%< AI < 30%	23	0.33	0.21-0.53	<0.001
30%≤ AI ≤ 70%	56	0.24	0.15-0.38	<0.001
30%≤ AI ≤ 70%* (follow-up time - 5)		1.49	1.16-1.91	0.002
70%< AI < 100%	18	0.42	0.25-0.71	0.001
AI=100%	32	0.36	0.23-0.57	<0.001
OS				
AI treatment duration*†‡				
AI=0%	107	1.00		
0%< AI < 40%	29	0.29	0.19-0.45	<0.001
0%< AI < 40%* (follow-up time - 5)		1.34	1.04-1.74	0.023
40% ≤ AI ≤ 60%	43	0.32	0.19-0.54	<0.001
40% ≤ AI ≤ 60%* (follow-up time - 5)		1.53	1.15-2.05	0.004
60%< AI < 100%	25	0.34	0.21-0.55	<0.001
AI=100%	32	0.36	0.23-0.57	<0.001
OS				
AI treatment duration*†				
AI ≤ 50%	159	1.00		
AI > 50%	77	0.52	0.38-0.70	<0.001

OS				
AI treatment duration*†‡				
AI= 0%	107	1.00		
0%< AI < 100%	97	0.32	0.23-0.44	<0.001
0%< AI < 100%* (follow-up time - 5)		1.25	1.03-1.52	0.021
AI=100%	32	0.36	0.23-0.57	<0.001

aHR = adjusted Hazard ratio, AI = Aromatase inhibitor, CI = Confidence interval, HER2 = Human Epidermal growth factor Receptor-2, PR = Progesterone receptor, OS = Overall Survival, RFS = Recurrence-Free Survival

* The AI-endocrine treatment ratio, included in the model as a time-dependent variable, is defined as the percentage of total endocrine treatment duration (AI+tamoxifen) spent on AI treatment.

† All analyses were adjusted for age at diagnosis, trastuzumab use (included as a time-dependent variable), grade, positive lymph nodes, pT-stage, PR status, HER2 status and ovarian ablation (included as a time-dependent variable)

‡ Interaction between the 25%≤AI≤75% category and follow-up time centered at 5-years was included to accommodate non-proportional hazards. For example at 5-years of follow-up patients with an AI-endocrine treatment ratio 30% ≤ AI ≤ 70% had a smaller chance of an OS-event then patients with an AI-endocrine treatment ratio AI=0% (adjusted-HR 0.24). The HR increases by 48% for each additional year of follow-up, so at 6-years of follow-up the hazard ratio for an AI-endocrine treatment ratio 30% ≤ AI ≤ 70% vs AI=0%= exp{ln(0.24)+(follow-up time-5)*ln(1.48)}=0.35.

Supplementary table 6: Adjusted hazard ratios for RFS and OS according to treatment groups defined by AI-endocrine treatment ratio and split by PR status.

		Events	aHR	95% CI	p-value	$p_{interactio}$§
RFS						
PR-	AI treatment duration*†					
	AI<25%	36	1.00			
	25%≤AI≤75%	17	1.04	0.52-2.09	0.909	
	AI> 75%	24	0.75	0.40-1.39	0.363	
PR+	AI treatment duration*†					0.710
	AI<25%	138	1.00			
	25%≤AI≤75%	92	0.82	0.60-1.13	0.221	
	AI> 75%	47	0.63	0.43-0.93	0.019	
OS						
PR-	AI treatment duration*†‡					
	AI<25%	29	1.00			
	25%≤AI≤75%	11	0.22	0.07-0.73	0.014	
	25%≤AI≤75%* (follow-up time - 5)		3.39	1.41-8.13	0.006	
	AI> 75%	14	0.46	0.21-0.98	0.045	
PR+	AI treatment duration*†					0.636
	AI<25%	91	1.00			
	25%≤AI≤75%	46	0.42	0.29-0.62	<0.001	
	AI> 75%	33	0.54	0.34-0.84	0.007	

aHR = adjusted Hazard ratio, AI = Aromatase inhibitor, CI = Confidence interval, PR= progesterone receptor, OS = Overall Survival, RFS = Recurrence Free Survival

* The AI-endocrine treatment ratio, included in the model as a time-dependent variable, is defined as the percentage of total endocrine treatment duration (AI+tamoxifen) spent on AI treatment.

† All analyses were adjusted for age at diagnosis, trastuzumab use (included as a time-dependent variable), grade, positive lymph nodes, pT-stage, HER2 status and ovarian ablation (included as a time-dependent variable)

‡ Interaction between the 25%≤AI≤75% category and a follow-up time centered at 5-years was included to accommodate non-proportional hazards. At 5-years of follow-up patients with PR- tumors and an AI-endocrine treatment ratio 25%≤AI≤75% had a smaller chance of an OS-event then patients with an AI-endocrine treatment ratio AI<25% (adjusted-HR 0.22). The HR increases by 339% for each additional year of follow-up, so at 6-years of follow-up the hazard ratio for an AI-endocrine treatment ratio 25%≤AI≤75% versus AI<25% = exp{ln(0.22)+(follow-up time-5)*ln(3.39)}=0.75.

§ The $p_{interaction}$ is based on a likelihood ratio test. A Cox model with an interaction term for AI treatment duration*PR status was compared with a Cox model that only contained the main effects of AI treatment duration and PR status.

Supplementary table 7: Adjusted hazard ratios for RFS and OS according to treatment groups defined by AI-endocrine treatment ratio and split by HER2 status.

		Events	aHR	95% CI	p-value	$p_{interaction}$§
RFS						
HER2-	AI treatment duration*†					
	AI<25%	159	1.00			
	25%≤AI≤75%	95	0.79	0.58-1.08	0.145	
	AI> 75%	35	0.64	0.43-0.93	0.022	
HER2+	AI treatment duration*†‡					0.540
	AI<25%	14	1.00			
	25%≤AI≤75%	8	1.16	0.42-3.23	0.767	
	25%≤AI≤75%* (follow-up time - 5)		1.64	0.99-2.72	0.055	
	AI> 75%	29	0.54	0.28-1.05	0.071	
OS						
HER2-	AI treatment duration*†‡					
	AI<25%	111	1.00			
	25%≤AI≤75%	48	0.28	0.18-0.45	<0.001	
	25%≤AI≤75%* (follow-up time - 5)		1.44	1.09-1.89	0.010	
	AI> 75%	21	0.48	0.30-0.79	0.003	
HER2+	AI treatment duration*†					0.656
	AI<25%	8	1.00			
	25%≤AI≤75%	4	0.88	0.24-3.14	0.840	
	AI> 75%	21	0.59	0.25-1.43	0.244	

aHR = adjusted Hazard ratio, AI = Aromatase inhibitor, CI = Confidence interval, HER2=Human Epidermal growth factor Receptor-2, OS = Overall Survival, RFS = Recurrence Free Survival

* The AI-endocrine treatment ratio, included in the model as a time-dependent variable, is defined as the percentage of total endocrine treatment duration (AI+tamoxifen) spent on AI treatment.

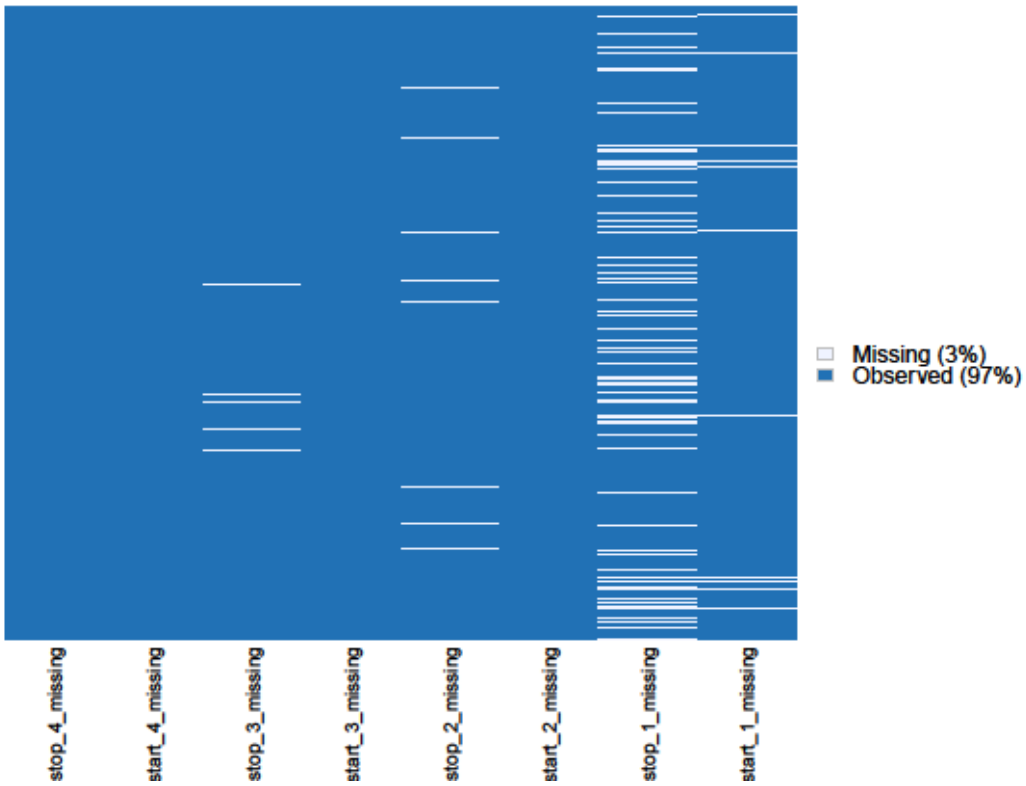
† All analyses were adjusted for age at diagnosis, trastuzumab use (included as a time-dependent variable), grade, positive lymph nodes, pT-stage, PR status and ovarian ablation (included as a time-dependent variable)

‡ Interaction between the 25%≤AI≤75% category and a follow-up time centered at 5-years was included to accommodate non-proportional hazards. For example at 5-years of follow-up patients with HER2- tumors and an AI-endocrine treatment ratio 25%≤AI≤75% had a smaller chance of an OS-event then patients with an AI-endocrine treatment ratio AI<25% (adjusted-HR 0.28). The HR increases by 144% for each additional year of follow-up, so at 6-years of follow-up the hazard ratio for an AI-endocrine treatment ratio 25%≤AI≤75% versus AI<25%= exp{ln(0.28)+(follow-up time-5)*ln(1.43)}=0.40.

§ The $p_{interaction}$ is based on a likelihood ratio test. A Cox model with an interaction term for AI treatment duration*HER2 status was compared with a Cox model that only contained the main effects of AI treatment duration and HER2 status

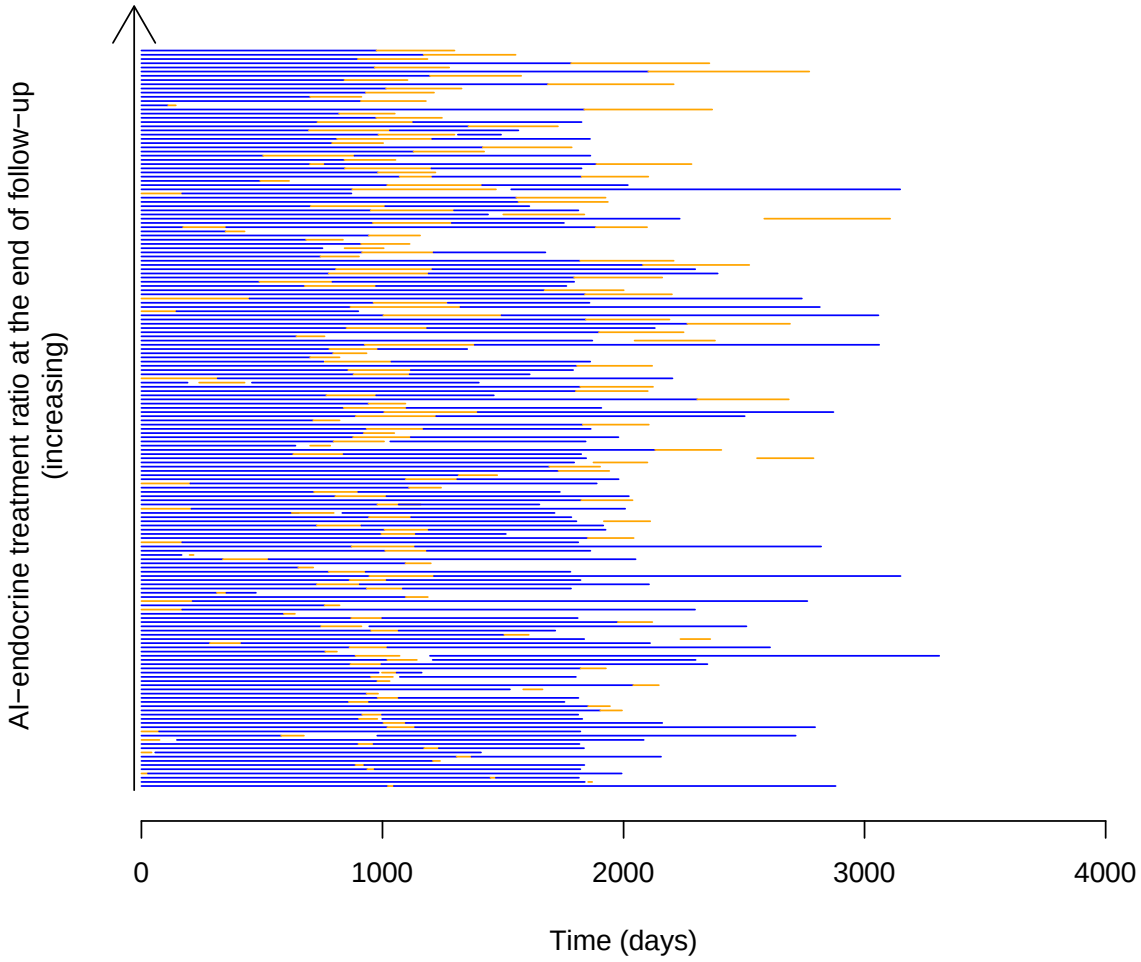
Supplementary Figures

Supplementary figure 1. Heatmap and table showing the number of women with missing endocrine treatment start dates and stop dates

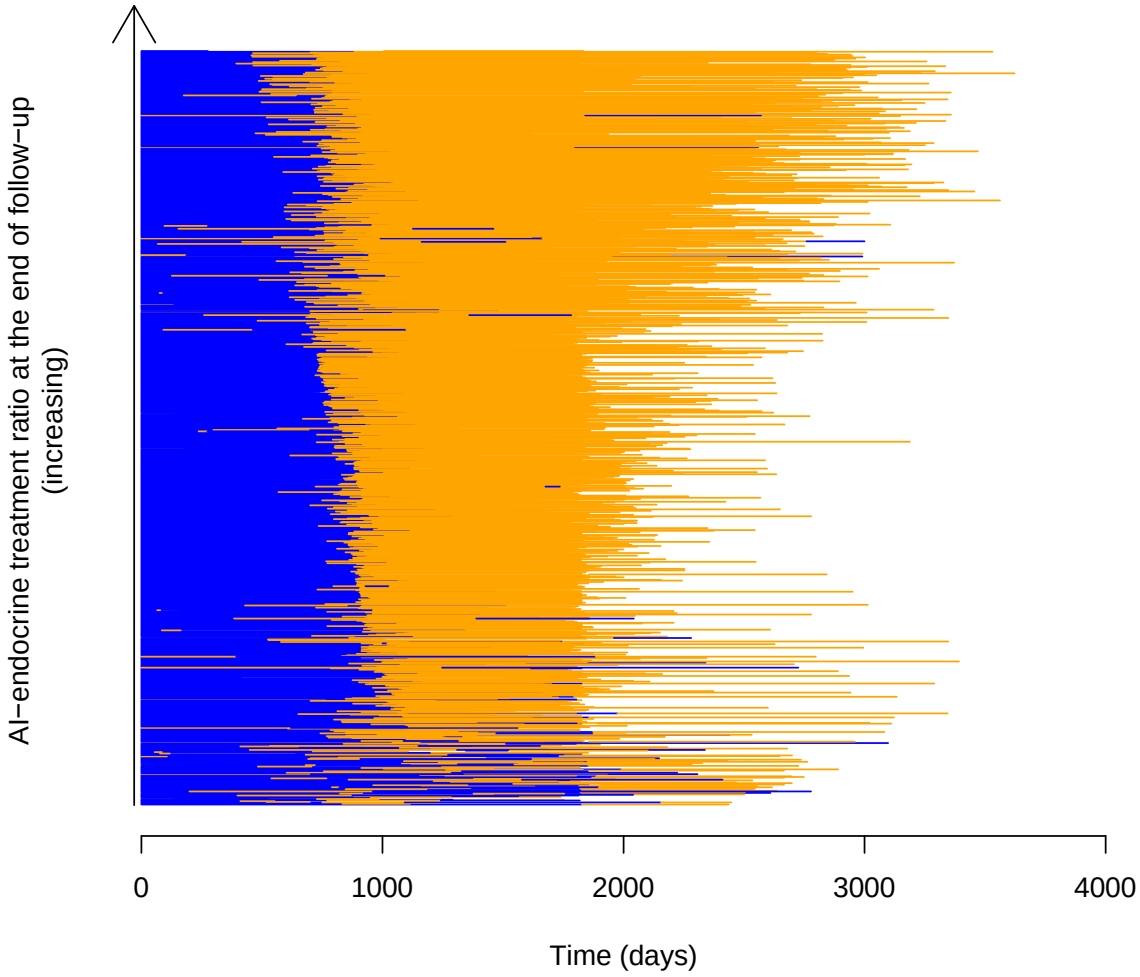


	Treatment 4		Treatment 3		Treatment 2		Treatment 1	
	Stop (n)	Start (n)	Stop (n)	Start (n)	Stop (n)	Start (n)	Stop (n)	Start (n)
Missing	0	0	32	0	25	4	422	109
Non-missing	17	17	96	128	1,474	1,495	1,873	2,186
Total	17		128		1,499		2,295	

Supplementary figure 2A. Line plot showing switches between tamoxifen (blue) and aromatase inhibitors (yellow) for all women (y-axes) with an AI-endocrine treatment ratio at the end of follow-up <0.25 and excluding women who only received tamoxifen.



Supplementary figure 2B. Line plot showing switches between tamoxifen (blue) and aromatase inhibitors (yellow) for all women (y-axes) with an AI-endocrine treatment ratio at the end of follow-up 0.25≤AI≤0.75



Supplementary figure 2C. Line plot showing switches between tamoxifen (blue) and aromatase inhibitors (yellow) for all women (y-axes) with an AI-endocrine treatment ratio at the end of follow-up >0.75 and excluding women who only received aromatase inhibitors