

# Phase III Randomized Adjuvant Study of Tamoxifen Alone Versus Sequential Tamoxifen and Anastrozole in Postmenopausal Women with Hormone-Responsive Breast Cancer: N-SAS BC03 Study.

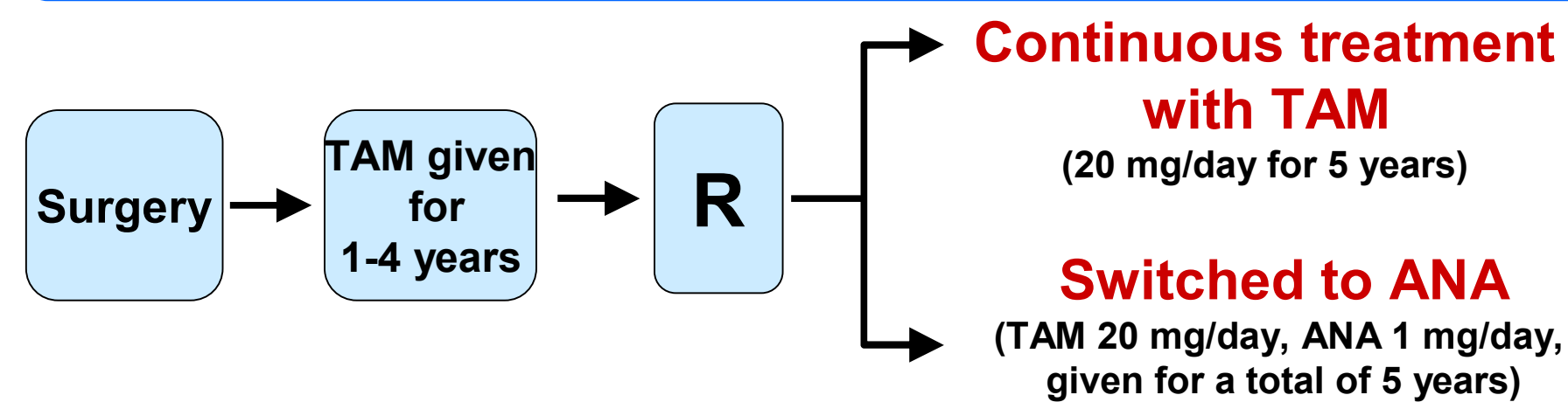
Aihara T<sup>1</sup>, Takatsuka Y<sup>2</sup>, Osumi S<sup>3</sup>, Aogi K<sup>3</sup>, Hozumi Y<sup>4</sup>, Imoto S<sup>5</sup>, Mukai H<sup>5</sup>, Iwata H<sup>6</sup>, Watanabe T<sup>7</sup>, Shimizu C<sup>7</sup>, Nakagami K<sup>8</sup>, Tamura M<sup>9</sup>, Ito T<sup>10</sup>, Masuda N<sup>11</sup>, Ogino N<sup>12</sup>, Hisamatsu K<sup>13</sup>, Mitsuyama S<sup>14</sup>, Abe H<sup>15</sup>, Yamaguchi T<sup>16</sup> and Ohashi Y<sup>16</sup>.

<sup>1</sup>Aihara Hospital; <sup>2</sup>Kansai Rosai Hospital; <sup>3</sup>Shikoku Cancer Hospital; <sup>4</sup>Jichi Medical University; <sup>5</sup>National Cancer Center Hospital East; <sup>6</sup>Aichi Cancer Center Hospital; <sup>7</sup>National Cancer Center Hospital; <sup>8</sup>Shizuoka General Hospital; <sup>9</sup>Hokkaido Cancer Center; <sup>10</sup>Rinku General Medical Center; <sup>11</sup>Osaka National Hospital; <sup>12</sup>Saiseikai Tondabayashi Hospital; <sup>13</sup>Hiroshima City Asa Hospital; <sup>14</sup>Kitakyushu Municipal Medical Center; <sup>15</sup>Shiga University of Medical Science, Shiga; <sup>16</sup>University of Tokyo.

## Background

Clinical trials conducted in Western countries have shown that improved disease-free survival (DFS) is associated with the use of aromatase inhibitors (AIs) instead of tamoxifen (TAM) in postmenopausal women with early breast cancer (1-5). Pharmacogenetic differences in drug-metabolizing genes may cause ethnic differences in response or tolerability to AIs, as well as TAM. In fact, improved DFS in response to extending treatment with letrozole after 5 years treatment of TAM has not been confirmed in women from minority groups (6). Therefore, assessment of the efficacy of AIs in non-white women is warranted. We report the results of switching adjuvant therapy from TAM to anastrozole (ANA) in postmenopausal Japanese women with breast cancer enrolled in an open-label, randomized clinical trial (N-SAS BC03 study).

## Study Design



## Objectives and Endpoints

- To determine whether postoperative adjuvant therapy with TAM for 1 to 4 years, followed by switching to ANA for a total treatment period of 5 years, is superior to continuous treatment with TAM for 5 years in postmenopausal women with hormone-responsive early breast cancer.
- Primary endpoints: disease-free survival and adverse events.
- Secondary endpoints: relapse-free survival, overall survival, health-related quality of life (HRQOL).

## Patients

No. of registered=eligible pts (706)		Patient enrollment period: Nov 2002 – Dec 2005	
TAM	ANA	Median follow-up period: 42 (range, 3.2-60)months	
352	354		
No. of analyzed pts (696)		No. of pts without drug administration	
TAM	ANA	TAM	ANA
349	347	3	7

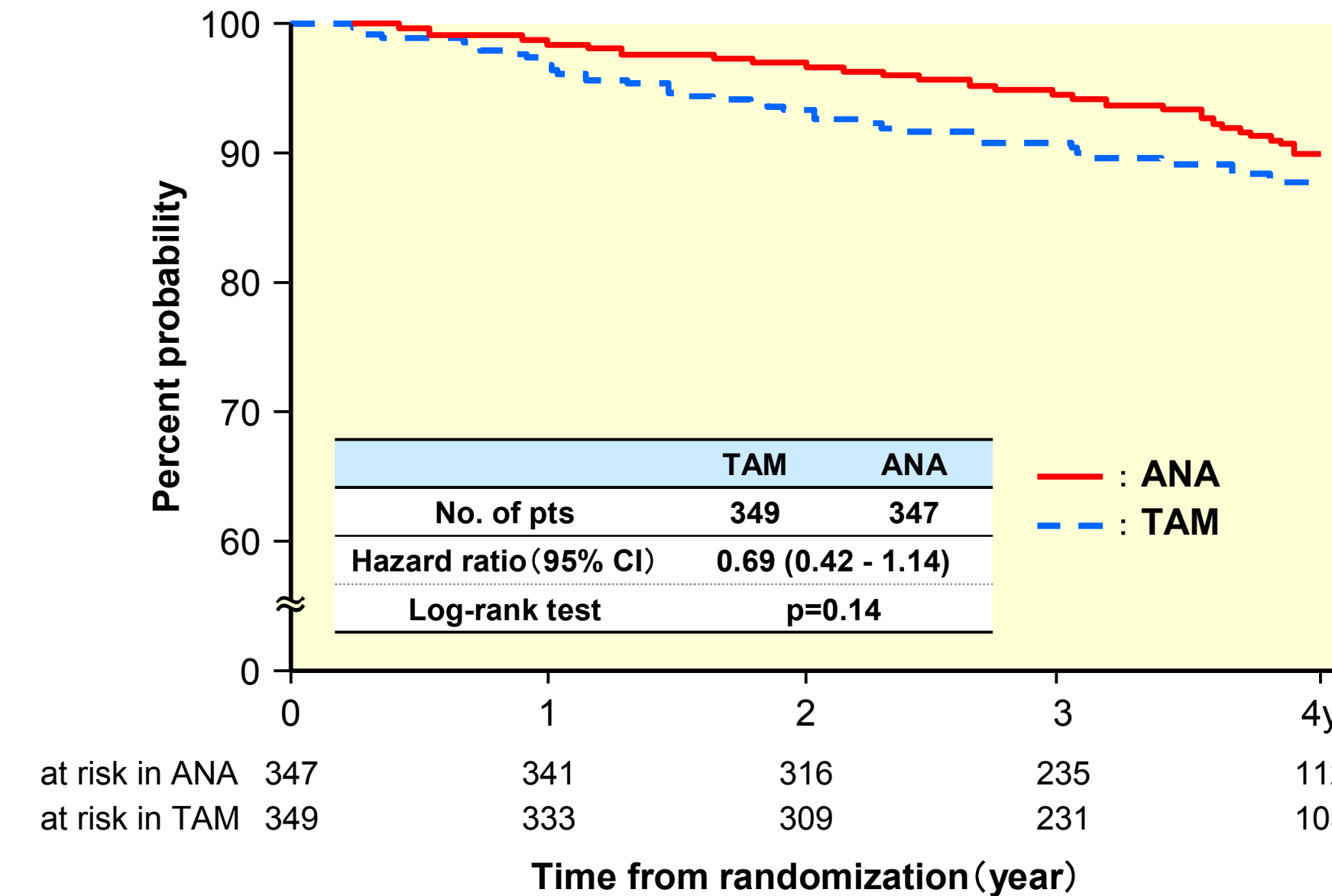
	TAM (n=349)	ANA (n=347)
Age (mean±sd)	60.2±7.4	59.5±7.4
<b>Stage</b>		
I	142	148
IIA	134	123
IIB	50	51
IIIA	12	12
IIIB	11	13
<b>Pathological tumor size</b>		
< 3cm	276	276
≥ 3cm	73	71
<b>Nodal status</b>		
0	210	206
1 - 3	99	102
4 - 9	30	22
10 -	10	17
<b>ER</b>		
Positive	325	322
Negative	24	25
<b>PR</b>		
Positive	273	272
Negative	76	75
<b>Type of Surgery</b>		
Breast-conserving surgery	181	182
Mastectomy	168	165
<b>HER2</b>		
0, 1+, 2+	164	163
3+	13	13
Unknown	172	169
<b>Chemotherapy</b>		
+	186	187
-	163	160

## Adverse Events(%)

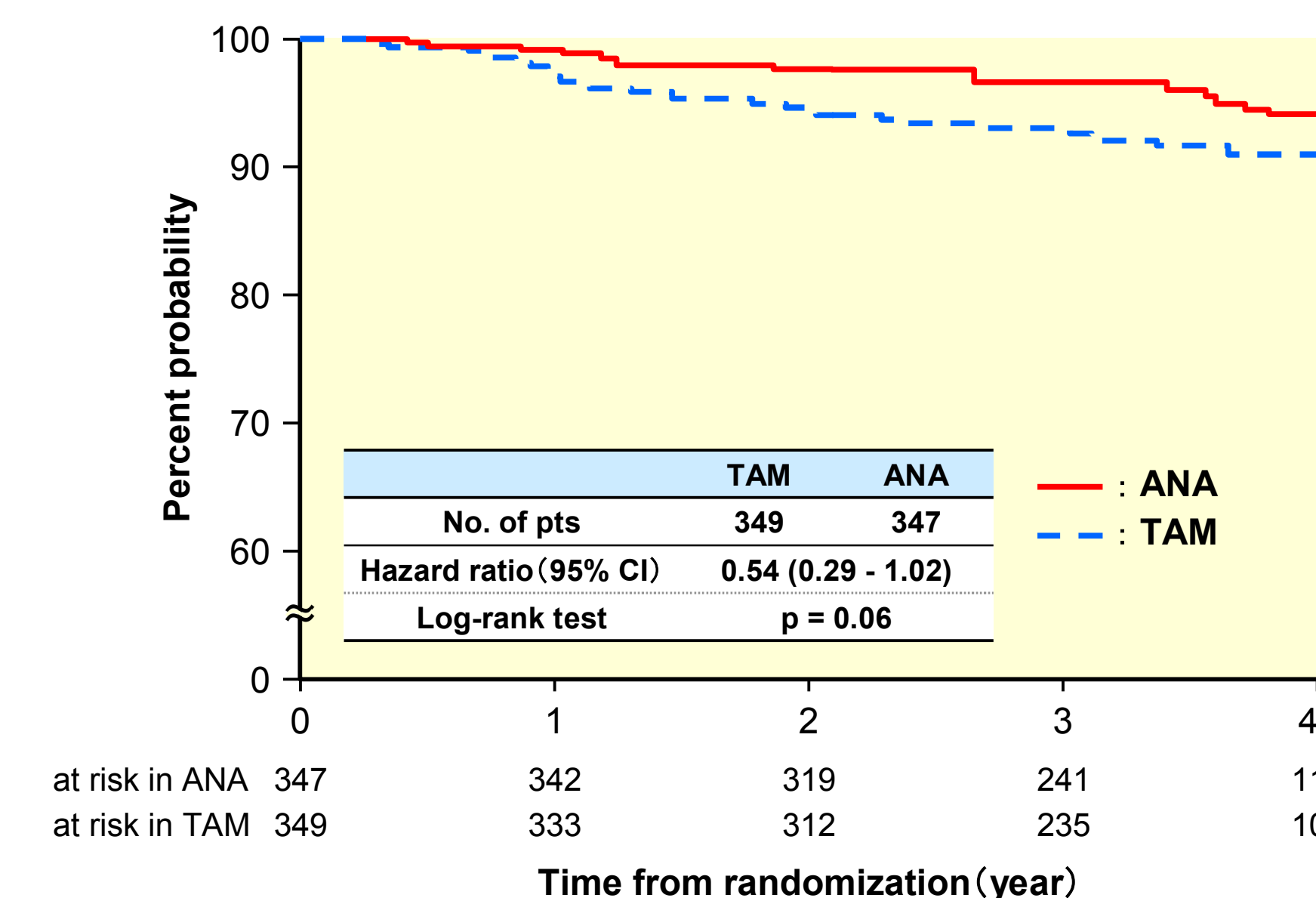
	TAM		ANA	
	≥Grade1	≥Grade3	≥Grade1	≥Grade3
Leukopenia	21.8	0.0	21.0	0.0
AST, ALT	28.4	0.6	31.1	1.4
Anorexia	5.7	0.0	5.5	0.0
Nausea & vomiting	6.3	0.0	7.2	0.0
Hot flash	44.7	0.0	36.3	0.0
Fatigue	25.5	0.0	26.5	0.0
Mood fluctuations	18.1	0.0	20.5	0.0
Headache	16.0	0.0	18.2	0.0
Joint pain (arthralgia)	31.8	0.6	50.4	2.3
Genital bleeding	8.0	0.0	9.2	0.0
Vaginal discharge	24.4	0.0	16.1	0.0
Heart disease	0.9	0.9	0.6	0.6
Thrombosis/Embolism	0.0	0.0	0.3	0.3
Endometrial cancer	0.3	0.3	0.0	0.0
Contralateral breast ca.	0.9	0.9	0.6	0.6

## Efficacy

### Disease-free Survival



### Relapse-free Survival



## Summary

- After a median follow-up of 42 months (range, 3.2-60), the number of events related to DFS was 26 in the ANA group as compared with 37 in the TAM group; the number of events related to RFS was 15 in the ANA group as compared with 27 in the TAM group.
- The unadjusted hazard ratio was 0.69 (95% confidence interval, 0.42 to 1.14; P=0.14 by the log-rank test) for DFS and 0.54 (95% confidence interval, 0.29 to 1.02; P=0.06 by the log-rank test) for RFS, both in favor of ANA.
- There was no difference in OS (p=0.59).
- Hot flashes and vaginal discharge were more common in the TAM group, whereas arthralgia was more common in the ANA group, similar to the results in white women.

## Conclusion

- Switching from TAM to ANA was confirmed to be associated with a lower disease recurrence rate than continuing TAM in postmenopausal Japanese women with breast cancer, consistent with the findings of previous studies.
- Side effect profiles were similar in both groups.
- Liver dysfunction was more frequent in the ANA group.
- High rates of thrombosis or endometrial cancer did not occur in the TAM group, probably because of the low baseline risk in Japanese women.

## References

- Baum M, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*. 2002 22;359(9324):2131-9.
- Thürlimann B, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005 29;353(26):2747-57.
- Jakesz R, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet*. 2005 6-12;366(9484):455-62.
- Coombes RC, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med*. 2004 11;350(11):1081-92.
- Boccardo F, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol*. 2005 1;23(22):5138-47.
- Moy B, et al. Clinical outcomes of ethnic minority women in MA.17: a trial of letrozole after 5 years of tamoxifen in postmenopausal women with early stage breast cancer. *Ann Oncol*. 2006 17(11):1637-43.