1033IL/0027/0030 ISE

TABLE T23.7 SUBJECTS WITH MEASURABLE AND NO MEASURABLE DISEASE AT ENTRY - COMBINED
(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N =511		N =510		N =1021	
	N	%	N	%	N	%
MEASURABLE DISEASE	418	81.8	426	83.5	844	82.7
NO MEASURABLE DISEASE	93	18.2	84	16.5	177	17.3

MEASURABLE DISEASE INCLUDES SUBJECTS WITH ANY BIDIMENSIONALLY OR UNIDIMENSIONALLY MEASURABLE LESIONS

NO MEASURABLE DISEASE INCLUDES SUBJECTS WITH EITHER NO LESIONS OR NON-MEASURABLE DISEASE ONLY

1033IL/0027/0030 ISE

TABLE T23.8.1 SITE OF METASTATIC DISEASE AT ENTRY - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

SITE OF DISEASE	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N = 511		N = 510		N = 1021	
	N	%	N	%	N	%
SKIN	235	46.0	233	45.7	468	45.8
LYMPH	208	40.7	212	41.6	420	41.1
BONE	268	52.4	256	50.2	524	51.3
VISCERAL	186	36.4	211	41.4	397	38.9
LUNG	150	29.4	168	32.9	318	31.1
LIVER	45	8.8	61	12.0	106	10.4
ABDOMEN	17	3.3	13	2.5	30	2.9
OTHER	1	0.2	3	0.6	4	0.4
NO EVALUABLE DISEASE	4	0.8	2	0.4	6	0.6

SUBJECTS WITH METASTATIC DISEASE MAY APPEAR IN MORE THAN ONE ROW

PLEURAL EFFUSIONS ARE CONSIDERED VISCERAL LUNG DISEASE

1033IL/0027/0030 ISE

TABLE T23.8.2 EXTENT OF METASTATIC DISEASE AT ENTRY - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

EXTENT OF DISEASE		ANASTROZOLE		TAMOXIFEN		TOTAL	
		N = 511		N = 510		N = 1021	
		N	%	N	%	N	%
EXTENT COVARIATE	SOFT TISSUE AND/OR LUNG DISEASE ONLY	194	38.0	181	35.5	375	36.7
	ALL OTHER DISEASE COMBINATIONS	317	62.0	329	64.5	646	63.3
NO VISCERAL DISEASE	SOFT TISSUE ONLY	146	28.6	139	27.3	285	27.9
	BONE ONLY	101	19.8	86	16.9	187	18.3
	BONE AND SOFT TISSUE ONLY	74	14.5	72	14.1	146	14.3
VISCERAL DISEASE	NO EVIDENCE OF LIVER INVOLVEMENT	141	27.6	150	29.4	291	28.5
	LIVER INVOLVEMENT	45	8.8	61	12.0	106	10.4
NO EVALUABLE DISEASE	NO EVALUABLE DISEASE	4	0.8	2	0.4	6	0.6

PLEURAL EFFUSIONS ARE CONSIDERED VISCERAL LUNG DISEASE

1033IL/0027/0030 ISE

TABLE T24 REASON FOR WITHDRAWAL OF TRIAL TREATMENT - COMBINED

(SUBJECTS INCLUDED : ALL TREATED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

PRIMARY REASON FOR WITHDRAWAL	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N = 506		N = 511		N = 1017	
	N	%	N	%	N	%
DEATH	12	2.4	5	1.0	17	1.7
DISEASE PROGRESSION (INVESTIGATOR'S OPINION)	287	56.7	319	62.4	606	59.6
PATIENT LOST TO FOLLOW UP	2	0.4	1	0.2	3	0.3
ADVERSE EVENT	23	4.5	22	4.3	45	4.4
PROTOCOL NON-COMPLIANCE	8	1.6	9	1.8	17	1.7
PATIENT UNWILLING TO CONTINUE	12	2.4	17	3.3	29	2.9
OTHER REASON	13	2.6	10	2.0	23	2.3
TOTAL	357	70.6	383	75.0	740	72.8

1033IL/0027/0030 ISE

TABLE T26.1.1 DURATION OF TREATMENT - COMBINED

(SUBJECTS INCLUDED : ALL TREATED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

DURATION OF TREATMENT (DAYS)	ANASTROZOLE	TAMOXIFEN
	N = 506	N = 511
MEDIAN	263	244
MIN	2	3
MAX	1195	1260

1033IL/0027/0030 ISE

TABLE T26.1.2 DURATION OF TREATMENT IN WEEKS - COMBINED

(SUBJECTS INCLUDED : ALL TREATED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

DURATION OF TREATMENT (WEEKS)	ANASTROZOLE		TAMOXIFEN	
	N = 506		N = 511	
	N	%	N	%
<0 TO 12	77	15.2	84	16.4
<12 TO 24	95	18.8	117	22.9
<24 TO 48	114	22.5	127	24.9
<48 TO 96	168	33.2	125	24.5
>96	52	10.3	58	11.4

1033IL/0027/0030 ISE

TABLE T26.1.3 DURATION OF FOLLOW-UP TO DATE LAST SEEN ALIVE - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WHO WERE ALIVE AT DATA CUTOFF)

DURATION OF FOLLOW-UP (DAYS)	ANASTROZOLE	TAMOXIFEN	TOTAL
	N = 373	N = 383	N = 756
MEDIAN	547	567	554
MIN	0	35	0
MAX	1194	1260	1260

1033IL/0027/0030 ISE

TABLE T26.2.1 PROGRESSION STATUS - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

SUBJECT STATUS		ANASTROZOLE		TAMOXIFEN		TOTAL	
		N = 511		N = 510		N = 1021	
		N	%	N	%	N	%
NOT PROGRESSED	ALIVE NO PROGRESSION	148	29.0	125	24.5	273	26.7
PROGRESSED	TOTAL PROGRESSED	363	71.0	385	75.5	748	73.3
	PROGRESSION DURING TREATMENT	316	61.8	330	64.7	646	63.3
	PROGRESSION AFTER TREATMENT WITHDRAWAL	17	3.3	21	4.1	38	3.7
	DEATH BEFORE PROGRESSION	30	5.9	34	6.7	64	6.3

1033IL/0027/0030 ISE

TABLE T26.2.3 MEDIAN TIME TO PROGRESSION - COMBINED

(SUBJECTS INCLUDED: ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

	ANASTROZOLE	TAMOXIFEN
	N = 511	N = 510
TIME TO PROGRESSION (DAYS)	259	212

MEDIAN TIMES TO EVENT WERE ESTIMATED USING KAPLAN-MEIER METHOD

1033IL/0027/0030 ISE

TABLE T26.2.5 TIME TO PROGRESSION : ANALYSIS RESULTS - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

TAMOXIFEN:ANASTROZOLE	HAZARD RATIO	LOWER 95% CONFIDENCE LIMIT
PRIMARY ANALYSIS	1.13	1.00
SECONDARY ANALYSIS (ADJUSTED)	1.12	1.00
SECONDARY ANALYSIS (UNADJUSTED)	1.13	1.00

A HAZARD RATIO >1 INDICATES THAT ANASTROZOLE IS ASSOCIATED WITH A LONGER TIME TO PROGRESSION THAN IS TAMOXIFEN

THE PRIMARY ANALYSIS WAS PERFORMED USING A COX REGRESSION MODEL INCLUDING FACTORS FOR TREATMENT, AGE, PREVIOUS HORMONAL THERAPY, ER/PR STATUS AND EXTENT OF DISEASE AT ENTRY USING TRIAL AS A STRATIFICATION FACTOR.

THE SUPPORT ANALYSIS (ADJUSTED) WAS PERFORMED USING A COX REGRESSION MODEL INCLUDING FACTORS FOR TREATMENT, AGE, PREVIOUS HORMONAL THERAPY, ER/PR STATUS AND EXTENT OF DISEASE AT ENTRY USING TRIAL AS AN ADDITIONAL COVARIATE.

THE SUPPORT (UNADJUSTED) ANALYSIS WAS PERFORMED USING A COX REGRESSION MODEL INCLUDING TREATMENT FACTOR ONLY.

1033IL/0027/0030 ISE

TABLE T26.3.1 BEST OBJECTIVE RESPONSE - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

OVERALL OBJECTIVE RESPONSE RATE	BEST OBJECTIVE RESPONSE	ANASTROZOLE		TAMOXIFEN		TOTAL	
		N = 511		N = 510		N = 1021	
		N	%	N	%	N	%
RESPONSE	COMPLETE RESPONSE	24	4.7	21	4.1	45	4.4
	PARTIAL RESPONSE	124	24.3	117	22.9	241	23.6
	TOTAL	148	29.0	138	27.1	286	28.0
NON RESPONSE	STABLE DISEASE >=24 WEEKS	144	28.2	127	24.9	271	26.5
	STABLE DISEASE < 24 WEEKS	16	3.1	12	2.4	28	2.7
	PROGRESSION	203	39.7	233	45.7	436	42.7
	TOTAL	363	71.0	372	72.9	735	72.0

1033IL/0027/0030 ISE

TABLE T26.3.3 BEST OBJECTIVE RESPONSE : MEASURABLE DISEASE - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITH MEASURABLE DISEASE AT ENTRY)

OVERALL OBJECTIVE RESPONSE RATE	BEST OBJECTIVE RESPONSE	ANASTROZOLE		TAMOXIFEN		TOTAL	
		N = 418		N = 426		N = 844	
		N	%	N	%	N	%
RESPONSE	COMPLETE RESPONSE	45	10.8	43	10.1	88	10.4
	PARTIAL RESPONSE	108	25.8	99	23.2	207	24.5
	TOTAL	153	36.6	142	33.3	295	35.0
NON RESPONSE	STABLE DISEASE >=24 WEEKS	88	21.1	74	17.4	162	19.2
	STABLE DISEASE < 24 WEEKS	19	4.5	16	3.8	35	4.1
	PROGRESSION	158	37.8	194	45.5	352	41.7
	TOTAL	265	63.4	284	66.7	549	65.0

RESPONSE BASED ON MEASURABLE DISEASE ASSESSMENTS ONLY

ST97

1033IL/0027/0030 ISE

TABLE T26.3.4 BEST OBJECTIVE RESPONSE BY EXTENT OF DISEASE - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

EXTENT OF DISEASE = SOFT TISSUE AND/OR LUNG DISEASE ONLY

OVERALL OBJECTIVE RESPONSE RATE	BEST OBJECTIVE RESPONSE	ANASTROZOLE N = 194		TAMOXIFEN N = 181		TOTAL N = 375	
		N	%	N	%	N	%
RESPONSE	COMPLETE RESPONSE	20	10.3	13	7.2	33	8.8
	PARTIAL RESPONSE	66	34.0	58	32.0	124	33.1
	TOTAL	86	44.3	71	39.2	157	41.9
NON RESPONSE	STABLE DISEASE >=24 WEEKS	37	19.1	38	21.0	75	20.0
	STABLE DISEASE < 24 WEEKS	6	3.1	5	2.8	11	2.9
	PROGRESSION	65	33.5	67	37.0	132	35.2
	TOTAL	108	55.7	110	60.8	218	58.1

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TABLE T26.3.4 BEST OBJECTIVE RESPONSE BY EXTENT OF DISEASE - COMBINED
(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

EXTENT OF DISEASE = ALL OTHER DISEASE COMBINATIONS

OVERALL OBJECTIVE RESPONSE RATE	BEST OBJECTIVE RESPONSE	ANASTROZOLE N = 317		TAMOXIFEN N = 329		TOTAL N = 646	
		N	%	N	%	N	%
RESPONSE	COMPLETE RESPONSE	4	1.3	8	2.4	12	1.9
	PARTIAL RESPONSE	58	18.3	59	17.9	117	18.1
	TOTAL	62	19.6	67	20.4	129	20.0
NON RESPONSE	STABLE DISEASE >=24 WEEKS	107	33.8	89	27.1	196	30.3
	STABLE DISEASE < 24 WEEKS	10	3.2	7	2.1	17	2.6
	PROGRESSION	138	43.5	166	50.5	304	47.1
	TOTAL	255	80.4	262	79.6	517	80.0

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TABLE T26.3.5 CLINICAL BENEFIT - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

CLINICAL BENEFIT	BEST OBJECTIVE RESPONSE	ANASTROZOLE		TAMOXIFEN		TOTAL	
		N = 511		N = 510		N = 1021	
		N	%	N	%	N	%
BENEFIT	COMPLETE RESPONSE	24	4.7	21	4.1	45	4.4
	PARTIAL RESPONSE	124	24.3	117	22.9	241	23.6
	STABLE DISEASE >=24 WEEKS	144	28.2	127	24.9	271	26.5
	TOTAL	292	57.1	265	52.0	557	54.6
NO BENEFIT	STABLE DISEASE < 24 WEEKS	16	3.1	12	2.4	28	2.7
	PROGRESSION	203	39.7	233	45.7	436	42.7
	TOTAL	219	42.9	245	48.0	464	45.4

TABLE T26.3.6 OBJECTIVE RESPONSE RATE : ANALYSIS RESULTS - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

ANASTROZOLE:TAMOXIFEN	ODDS RATIO	LOWER 95% CONFIDENCE LIMIT
PRIMARY ANALYSIS	1.06	0.83
SECONDARY ANALYSIS (UNADJUSTED)	1.10	0.87

ANASTROZOLE-TAMOXIFEN	ESTIMATED DIFFERENCE IN RESPONSE RATES	LOWER 95% CONFIDENCE LIMIT
PRIMARY ANALYSIS	1.08	-3.49
SECONDARY ANALYSIS (UNADJUSTED)	1.90	-2.58

THE PRIMARY ANALYSIS WAS PERFORMED USING A LOGISTIC REGRESSION MODEL INCLUDING FACTORS FOR TREATMENT, AGE, PREVIOUS HORMONAL THERAPY, ER/PR STATUS AND EXTENT OF DISEASE AT ENTRY USING TRIAL AS AN ADDITIONAL COVARIATE

THE SUPPORT (UNADJUSTED) ANALYSIS WAS PERFORMED USING A LOGISTIC REGRESSION MODEL INCLUDING TREATMENT FACTOR ONLY

RESPONDERS ARE THOSE SUBJECTS WITH A BEST OBJECTIVE RESPONSE OF COMPLETE RESPONSE (CR) OR PARTIAL RESPONSE (PR)

AN ODDS RATIO >1 FAVORS ANASTROZOLE WHEREAS <1 FAVORS TAMOXIFEN

A DIFFERENCE IN RESPONSE RATES >0 FAVORS ANASTROZOLE WHEREAS <0 FAVORS TAMOXIFEN

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TABLE T26.4.1 REASONS FOR TREATMENT FAILURE - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

PRIMARY REASON FOR TREATMENT FAILURE	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N = 511		N = 510		N = 1021	
	N	%	N	%	N	%
DEATH	8	1.6	6	1.2	14	1.4
DISEASE PROGRESSION (OBJECTIVE)	316	61.8	329	64.5	645	63.2
DISEASE PROGRESSION (INVESTIGATOR'S OPINION)	28	5.5	29	5.7	57	5.6
PATIENT LOST TO FOLLOW UP	2	0.4	1	0.2	3	0.3
ADVERSE EVENT	21	4.1	21	4.1	42	4.1
PROTOCOL NON-COMPLIANCE	5	1.0	8	1.6	13	1.3
PATIENT UNWILLING TO CONTINUE	7	1.4	14	2.7	21	2.1
NEVER STARTED RANDOMIZED TREATMENT	3	0.6	1	0.2	4	0.4
OTHER REASON	12	2.3	9	1.8	21	2.1
TOTAL	402	78.7	418	82.0	820	80.3

DISEASE PROGRESSION (INVESTIGATOR'S OPINION) REFERS TO PROGRESSION NOT CONFIRMED BY THE CRITERIA SET IN THE PROTOCOL

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TABLE T26.4.2 MEDIAN TIME TO TREATMENT FAILURE - COMBINED

(SUBJECTS INCLUDED: ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

	ANASTROZOLE	TAMOXIFEN
	N = 511	N = 510
TIME TO TREATMENT FAILURE (DAYS)	208	176

MEDIAN TIMES TO EVENT WERE ESTIMATED USING KAPLAN-MEIER METHOD

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TABLE T26.4.3 TIME TO TREATMENT FAILURE : ANALYSIS RESULTS - COMBINED
(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

TAMOXIFEN:ANASTROZOLE	HAZARD RATIO	LOWER 95% CONFIDENCE LIMIT
PRIMARY ANALYSIS	1.13	1.01
SECONDARY ANALYSIS (ADJUSTED)	1.13	1.01
SECONDARY ANALYSIS (UNADJUSTED)	1.13	1.01

A HAZARD RATIO >1 INDICATES THAT ANASTOZOLE IS ASSOCIATED WITH A LONGER TIME TO TREATMENT FAILURE THAN IS TAMOXIFEN

THE PRIMARY ANALYSIS WAS PERFORMED USING A COX REGRESSION MODEL INCLUDING FACTORS FOR TREATMENT, AGE, PREVIOUS HORMONAL THERAPY, ER/PR STATUS AND EXTENT OF DISEASE AT ENTRY USING TRIAL AS A STRATIFICATION FACTOR.

THE SUPPORT ANALYSIS (ADJUSTED) WAS PERFORMED USING A COX REGRESSION MODEL INCLUDING FACTORS FOR TREATMENT, AGE, PREVIOUS HORMONAL THERAPY, ER/PR STATUS AND EXTENT OF DISEASE AT ENTRY USING TRIAL AS AN ADDITIONAL COVARIATE.

THE SUPPORT (UNADJUSTED) ANALYSIS WAS PERFORMED USING A COX REGRESSION MODEL INCLUDING TREATMENT FACTOR ONLY.

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TABLE T26.5.1 DURATION OF RESPONSE FROM RANDOMIZATION - COMBINED

(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITH A COMPLETE OR PARTIAL RESPONSE)

DURATION OF RESPONSE (DAYS)	ANASTROZOLE	TAMOXIFEN
	N = 148	N = 138
MEDIAN	498	524
MIN	63	83
MAX	1194	1124

MEDIAN TIMES TO EVENT WERE ESTIMATED USING KAPLAN-MEIER METHOD

1033IL/0027/0030 ISE

TABLE T26.5.2 DURATION OF RESPONSE FROM FIRST DOCUMENTATION OF OBJECTIVE RESPONSE - COMBINED
(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITH A COMPLETE OR PARTIAL RESPONSE)

DURATION OF RESPONSE (DAYS)	ANASTROZOLE	TAMOXIFEN
	N = 148	N = 138
MEDIAN	378	406
MIN	34	54
MAX	1027	1037

MEDIAN TIMES TO EVENT WERE ESTIMATED USING KAPLAN-MEIER METHOD

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TABLE T26.5.3 DURATION OF CLINICAL BENEFIT - COMBINED

(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITH A COMPLETE RESPONSE, PARTIAL RESPONSE, OR STABLE DISEASE >= 24 WEEKS)

DURATION OF CLINICAL BENEFIT (DAYS)	ANASTROZOLE	TAMOXIFEN
	N = 292	N = 265
MEDIAN	483	445
MIN	63	77
MAX	1194	1260

MEDIAN TIMES TO EVENT WERE ESTIMATED USING KAPLAN-MEIER METHOD

ST107

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TABLE T26.6.1 SURVIVAL STATUS - COMBINED

(SUBJECTS INCLUDED : ALL RANDOMIZED SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

SURVIVAL STATUS	ANASTROZOLE		TAMOXIFEN		TOTAL	
	N = 511		N = 510		N = 1021	
	N	%	N	%	N	%
ALIVE	373	73.0	383	75.1	756	74.0
DEAD	138	27.0	127	24.9	265	26.0

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TABLE T26.6.3 SURVIVAL AT TWO YEARS - COMBINED

(SUBJECTS INCLUDED: ALL RANDOMIZED SURJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030)

	ANASTROZOLE	TAMOXIFEN
	N = 511	N = 510
PROPORTION ALIVE AT TWO YEARS (%)	65.2	69.4

SURVIVAL WAS ESTIMATED USING KAPLAN-MEIER METHOD

TABLE T28.1 THE PROPORTION OF SUBJECTS WHO RECEIVED FURTHER BREAST CANCER THERAPY - COMBINED
(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITHDRAWN FROM TRIAL TREATMENT)

THERAPY		ANASTROZOLE N = 357		TAMOXIFEN N = 383		TOTAL N = 740	
		N	%	N	%	N	%
RADIOTHERAPY	YES	107	30.0	105	27.4	212	28.6
	NO	250	70.0	278	72.6	528	71.4
CHEMOTHERAPY	YES	142	39.8	158	41.3	300	40.5
	NO	215	60.2	225	58.7	440	59.5
HORMONAL THERAPY	YES	172	48.2	222	58.0	394	53.2
	NO	185	51.8	161	42.0	346	46.8
OTHER THERAPIES	YES	83	23.2	78	20.4	161	21.8
	NO	274	76.8	305	79.6	579	78.2

TABLE T28.2 DURATION OF FURTHER BREAST CANCER THERAPY - COMBINED

(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITHDRAWN FROM TRIAL TREATMENT)

THERAPY	DURATION (DAYS)	ANASTROZOLE	TAMOXIFEN
		N = 357	N = 383
RADIOTHERAPY (SESSIONS PER PATIENT)	TOTAL TREATED	107	105
	N	106	97
	MEAN	15	15
	MEDIAN	10	11
	SD	14.4	12.4
	MIN	0	0
	MAX	77	66
CHEMOTHERAPY (CYCLES PER PATIENT)	TOTAL TREATED	89	97
	N	88	96
	MEAN	8	6
	MEDIAN	6	6
	SD	6.3	6.3
	MIN	0	0
	MAX	40	31
TAMOXIFEN	TOTAL TREATED	116	27
	N	58	13
	MEAN	171	139
	MEDIAN	141	94
	SD	133.4	176.7

(CONTINUED)

N = NUMBER OF SUBJECTS FOR WHICH DURATION COULD BE CALCULATED

TABLE T28.2 DURATION OF FURTHER BREAST CANCER THERAPY - COMBINED

(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITHDRAWN FROM TRIAL TREATMENT)

THERAPY	DURATION (DAYS)	ANASTROZOLE	TAMOXIFEN
		N = 357	N = 383
TAMOXIFEN	MIN	0	10
	MAX	735	574
ANASTROZOLE	TOTAL TREATED	17	110
	N	6	42
	MEAN	267	156
	MEDIAN	220	118
	SD	165.8	135.5
	MIN	82	9
	MAX	540	608
MEGESTROL	TOTAL TREATED	42	42
	N	23	22
	MEAN	95	161
	MEDIAN	88	101
	SD	63.1	173.8
	MIN	6	-1
	MAX	279	819
PAMIDRONIC ACID	TOTAL TREATED	38	38
	N	11	18
	MEAN	126	117

(CONTINUED)

N = NUMBER OF SUBJECTS FOR WHICH DURATION COULD BE CALCULATED

TABLE T28.2 DURATION OF FURTHER BREAST CANCER THERAPY - COMBINED
(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITHDRAWN FROM TRIAL TREATMENT)

THERAPY	DURATION (DAYS)	ANASTROZOLE	TAMOXIFEN
		N = 357	N = 383
PAMIDRONIC ACID	MEDIAN	55	110
	SD	190.0	108.5
	MIN	0	0
	MAX	664	338
MEDROXYPROGESTERONE	TOTAL TREATED	16	20
	N	10	13
	MEAN	182	183
	MEDIAN	205	135
	SD	134.0	138.6
	MIN	10	18
	MAX	420	410
CLODRONIC ACID	TOTAL TREATED	21	14
	N	11	4
	MEAN	105	219
	MEDIAN	92	242
	SD	80.0	75.3
	MIN	2	112
	MAX	257	279
HORMONE THERAPY, NOT OTHERWISE SPECIFIED	TOTAL TREATED	12	13

(CONTINUED)

N = NUMBER OF SUBJECTS FOR WHICH DURATION COULD BE CALCULATED

TABLE T28.2 DURATION OF FURTHER BREAST CANCER THERAPY - COMBINED
(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITHDRAWN FROM TRIAL TREATMENT)

THERAPY	DURATION (DAYS)	ANASTROZOLE	TAMOXIFEN
		N = 357	N = 383
HORMONE THERAPY, NOT OTHERWISE SPECIFIED	N	8	11
	MEAN	159	178
	MEDIAN	110	118
	SD	192.0	179.6
	MIN	16	56
	MAX	605	678
LETROZOLE	TOTAL TREATED	6	17
	N	3	10
	MEAN	92	129
	MEDIAN	119	79
	SD	52.9	133.9
	MIN	31	28
	MAX	126	474
AMINOGLUTETHIMIDE	TOTAL TREATED	6	14
	N	3	12
	MEAN	119	396
	MEDIAN	70	410
	SD	106.0	230.2
	MIN	47	51

(CONTINUED)

N = NUMBER OF SUBJECTS FOR WHICH DURATION COULD BE CALCULATED

TABLE T28.2 DURATION OF FURTHER BREAST CANCER THERAPY - COMBINED
(SUBJECTS INCLUDED : ALL SUBJECTS IN TRIALS 1033IL/0027 AND 1033IL/0030 WITHDRAWN FROM TRIAL TREATMENT)

THERAPY	DURATION (DAYS)	ANASTROZOLE	TAMOXIFEN
		N = 357	N = 383
AMINOGLUTETHIMIDE	MAX	241	725
FORMESTANE	TOTAL TREATED	6	14
	N	4	7
	MEAN	70	139
	MEDIAN	80	136
	SD	59.0	62.7
	MIN	0	40
	MAX	119	249
MASTECTOMY	TOTAL TREATED	5	10
	N	5	10
	MEAN	0	0
	MEDIAN	0	0
	SD	0.0	0.0
	MIN	0	0
	MAX	0	0

N = NUMBER OF SUBJECTS FOR WHICH DURATION COULD BE CALCULATED

APPENDIX A

Supplementary general information

Differences in protocol inclusion and exclusion criteria between Trials 0030 and 0027

Trial 1033IL/0030	Trial 1033IL/0027
Inclusion criteria	
Women who have a bilateral oophorectomy classed as postmenopausal and included in trial	Not specified in protocol
Treatment with adjuvant chemotherapy allowed up to 6 months before entry into the trial	Allows treatment with adjuvant chemotherapy before entry without time limit
Allows subjects who were treated for malignancy, but were disease-free and off therapy for ≥5 years, and who the investigator considered "cured"	Not allowed
Written informed consent	Written informed consent preferred, but witnessed verbal consent allowed
For hormone receptor status, original hormone receptor status was acceptable if the hormone receptor status of the recurrent tumor was unavailable	Statement not included in protocol
Exclusion criteria	
Subjects who have relapsed while on previous hormonal therapy	Not specified in protocol
Subjects with liver function tests (AST or ALT) >x5 upper limit of reference range	Subjects with liver function tests (AST or ALT) >x3 upper limit of reference range
Subjects who have received hormone replacement therapy within 6 weeks prior to entry	Not specified in protocol
Subjects who have had a bone marrow transplant before randomization	Not specified in protocol
Subjects treated with any of the therapies mentioned in section 6 of the protocol either concurrently or within 4 weeks before randomization	Subjects treated concurrently with any of the therapies mentioned in section 6 of the protocol

DISEASE STAGING OF PATIENTS WITH DISEASE LIMITED TO SOFT TISSUE

Trial Treatment group Number of randomized patients	Stage of disease			
	Stage IV[a]	Stage III	Stage II[b]	Stage I[c]
Trial 0030				
Anastrozole n=171	0001/0008 0008/0003 0012/0011 0013/0001 0032/0001 0035/0003 0049/0006 0066/0002 0079/0001 0080/0039 0084/0011 0085/0004 0145/0001	0015/0004 0091/0001	0016/0001 0103/0004	0052/0001
Tamoxifen n=182	0008/0002 0009/0001 0012/0004 0012/0005 0021/0002 0023/0001 0023/0002 0035/0004 0049/0008 0056/0001 0063/0001 0064/0001 0073/0001 0080/0021 0080/0034 0096/0003 0097/0006 0106/0002 0115/0001 0119/0002 0125/0003 0125/0006 0130/0001 0135/0001 0149/0002	0066/0003 0066/0005 0074/0001 0080/0038	0015/0003 0031/0002 0084/0003 0116/0001	NA

Trial Treatment group Number of randomized patients	Stage of disease			
	Stage IV[a]	Stage III	Stage II[b]	Stage I[c]
Trial 0027				
Anastrozole n=340	0007/0002 0007/0004 0011/0003 0021/0013 0024/0003 0025/0001 0032/0002 0032/0003 0032/0005 0032/0006 0035/0001 0048/0102 0052/0004 0057/0002 0069/0001 0069/0002 0071/0001 0078/0001 0079/0001 0079/0101 0080/0102 0098/0009 0098/0016 0110/0002	0005/0001 0005/0002 0006/0001 0011/0007 0013/0002 0013/0006 0015/0102 0016/0001 0020/0003 0020/0004 0021/0003 0021/0004 0021/0006 0021/0007 0021/0010 0023/0001 0025/0006 0025/0008 0025/0012 0026/0002 0026/0003 0026/0006 0026/0008 0026/0009 0026/0010 0026/0015 0026/0102 0026/0103 0027/0003 0031/0002 0031/0003 0031/0005 0031/0007 0032/0012 0039/0004 0045/0001 0045/0002 0045/0010 0045/0103 0046/0004 0046/0005 0047/0002	0011/0004 0012/0002 0012/0005 0013/0001 0021/0011 0025/0002 0027/0004 0027/0007 0027/0008 0039/0003 0046/0002 0051/0115 0052/0007 0054/0003 0064/0006 0098/0013 0112/0002 0114/0004	NA

Trial Treatment group Number of randomized patients	Stage of disease			
	Stage IV[a]	Stage III	Stage II[b]	Stage I[c]
Trial 0027 (continued) Anastrozole n=340 (continued)		0047/0004 0047/0005 0047/0007 0047/0104 0054/0002 0054/0005 0054/0007 0064/0001 0064/0003 0064/0008 0072/0001 0073/0001 0073/0004 0073/0005 0073/0006 0073/0009 0075/0001 0076/0003 0080/0004 0082/0002 0082/0003 0082/0007 0082/0008 0082/0009 0086/0001 0086/0004 0086/0006 0086/0008 0098/0001 0098/0005 0098/0007 0099/0002 0099/0004 0099/0006 0099/0007 0100/0001 0100/0004 0105/0002 0110/0003 0114/0001 0114/0005 0114/0009 0114/0106 0115/0001		

Trial Treatment group Number of randomized patients	Stage of disease			
	Stage IV[a]	Stage III	Stage II[b]	Stage I[c]
Trial 0027 (continued)				
Tamoxifen n=328	0010/0001 0011/0001 0012/0001 0012/0003 0013/0003 0013/0004 0015/0002 0031/0006 0032/0004 0032/0007 0048/0103 0053/0001 0081/0002	0007/0003 0010/0002 0011/0002 0011/0006 0012/0006 0012/0007 0013/0005 0015/0001 0019/0001 0019/0002 0020/0002 0021/0002 0021/0005 0021/0008 0021/0009 0024/0002 0025/0003 0025/0004 0025/0005 0025/0009 0025/0011 0025/0118 0026/0001 0026/0004 0026/0007 0026/0012 0026/0013 0031/0001 0031/0008 0032/0008 0032/0010 0032/0011 0038/0001 0045/0006 0046/0006 0047/0001 0047/0003 0047/0006 0047/0008 0047/0103 0047/0105 0051/0004	0020/0001 0021/0012 0027/0001 0027/0002 0027/0005 0027/0006 0064/0002 0078/0003 0082/0005 0084/0001 0100/0002 0113/0006	NA

Trial Treatment group Number of randomized patients	Stage of disease			
	Stage IV[a]	Stage III	Stage II[b]	Stage I[c]
Trial 0027 (continued)		0052/0003		
		0054/0006		
Tamoxifen		0064/0004		
n=328		0064/0005		
(continued)		0065/0103		
		0073/0002		
		0073/0003		
		0073/0007		
		0073/0008		
		0079/0002		
		0079/0005		
		0080/0003		
		0082/0001		
		0082/0004		
		0082/0006		
		0086/0002		
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		0098/0006		
		0098/0012		
		0098/0014		
		0099/0001		
		0099/0003		
		0100/0003		
		0105/0001		
		0114/0002		
		0114/0003		
		0114/0008		
		0114/0010		
		0114/0011		
		0114/0102		
		0114/0104		

[a] Patients with recurrent breast cancer were considered to be stage IV. Patients with metastatic disease outside soft tissue are stage IV, but are not listed in this table.

[b] These patients may have actually been stage III if axillary lymph nodes were fixed, or if breast tumor was associated with edema, skin ulceration, or other properties which would make it a T4 lesion, but this information was not collected.

[c] This patient may have actually been stage III if the breast tumor was associated with edema, skin ulceration, or other properties which would make it a T4 lesion, but this information was not collected.

Disease staging was based on the 3rd edition of the American Joint Committee (AJC) staging system (Harris. 1991).

REFERENCE

Harris JR. Staging and prognostic factors. In: Harris JR, Hellman S, Henderson IC, Kinne DW, editors. Breast Diseases. 2nd edition. Philadelphia: JB Lippincott, 1991. Chapter 15.

APPENDIX B

Supplementary statistical information

1 SUPPLEMENTARY STATISTICAL INFORMATION

1.1 Time to disease progression

Table 1 summarizes the progression status as of the data cutoff date (10 March 1999) for all randomized subjects in Trials 0027 and 0030, separately and combined, by trial treatment.

Table 1 Progression status of randomized subjects

Progression status	Number (%) of subjects					
	Trial 0027		Trial 0030		Combined trials	
	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Randomized subjects	340	328	171	182	511	510
Alive without progression[a]	91 (26.8)	81 (24.7)	57 (33.3)	44 (24.2)	148 (29.0)	125 (24.5)
Progression during treatment	216 (63.5)	209 (63.7)	100 (58.5)	121 (66.5)	316 (61.8)	330 (64.7)
Progression after treatment withdrawal	15 (4.4)	18 (5.5)	2 (1.2)	3 (1.6)	17 (3.3)	21 (4.1)
Death before progression	18 (5.3)	20 (6.1)	12 (7.0)	14 (7.7)	30 (5.9)	34 (6.7)

[a] Includes subjects who were continuing treatment and subjects withdrawn from treatment.

A total of 748 (73.3%) subjects had disease progression. The subjects who were randomized to anastrozole treatment appeared to have a lower progression rate and longer estimated median time to progression (71.0% and 259 days, respectively) than did subjects who were randomized to tamoxifen treatment (75.5% and 212 days, respectively).

For time to progression, formal treatment comparisons were made using a Cox regression model to assess that anastrozole was noninferior to tamoxifen. The Cox regression model was used in 3 ways: (1) the adjusted analysis with treatment factor and the 4 baseline prognostic covariates (extent of disease, previous hormonal therapy, ER and PR status, and age) using 'trial' as a stratification factor; (2) the adjusted analysis with treatment factor and the 4 baseline prognostic covariates using 'trial' as an additional covariate; and (3) the unadjusted analysis with treatment factor only. As stated in the statistical analysis plan, the primary analysis is (1) and the other 2 analyses are considered as supportive.

In order for all subjects to be included in the adjusted analysis, missing covariates had to be dealt with. No subjects had missing values for age. For ER/PR receptor status any missing values were taken to be 'unknown'. Subjects with missing values for both ER and PR receptor status were therefore assigned to the category 'all other combinations'. Subjects with missing baseline disease assessments were categorized as having 'no evaluable disease' and these subjects were

included in the extent of disease category 'all other disease combinations'. Two subjects who were randomized to anastrozole (Subject from Trial 0027 and Subject from Trial 0030) had no information as to whether they had received previous hormonal therapy. The most common covariate category was assigned for them, therefore these 2 subjects were included in the 'no' category for the previous hormonal therapy category. These covariate categories were also used in all subsequent analyses.

The trial-by-treatment interaction was tested using the Cox regression model with factors for trial, treatment, 4 baseline prognostic covariates, and the trial-by-treatment interaction. The statistical evidence of significant trial-by-treatment interaction was observed at p=0.0169. As stated in the statistical analysis plan, a likelihood ratio test developed by Gail and Simon (1985) was then used to further examine the nature of the interaction (quantitative or qualitative). To test the quantitative trial-by-treatment interaction, the weighted mean difference (D bar) in hazard ratio between two trials was 0.1160. The test statistic of no quantitative interaction (H) was 5.5640, and p-value from the chi-square distribution with 1 degree of freedom for H was 0.0183. Therefore, we conclude that the quantitative trial-by-treatment interaction is present. To test the qualitative trial-by-treatment interaction, the estimated to be 0.0054 and the was estimated to be 8.0330. Since the min =0.0054 is less than the critical value of 2.71 we conclude that there is no qualitative trial-by-treatment interaction and combined analysis can be performed.

The assumptions of the Cox regression model and proportionality were also investigated. The p-value of 0.60 from a Wald chi-squared statistic for a time-dependent explanatory variable showed that there was no evidence of a departure from proportionality. For the adjusted analyses, a global test was performed to check the inclusion of the 4 treatment-by-covariate interactions. The p-value from a log likelihood ratio test was 0.46 from the primary adjusted analysis with 'trial' as a stratum, and the p-value was 0.47 from the support adjusted analysis with 'trial' as an additional covariate. Therefore, the inclusion of the interaction terms was not statistically significant.

Table 2 summarizes the statistical analysis of time to disease progression for Trials 0027 and 0030, separately and combined.

Table 2 Statistical analysis of time to disease progression in Trials 0027 and 0030, separately and combined

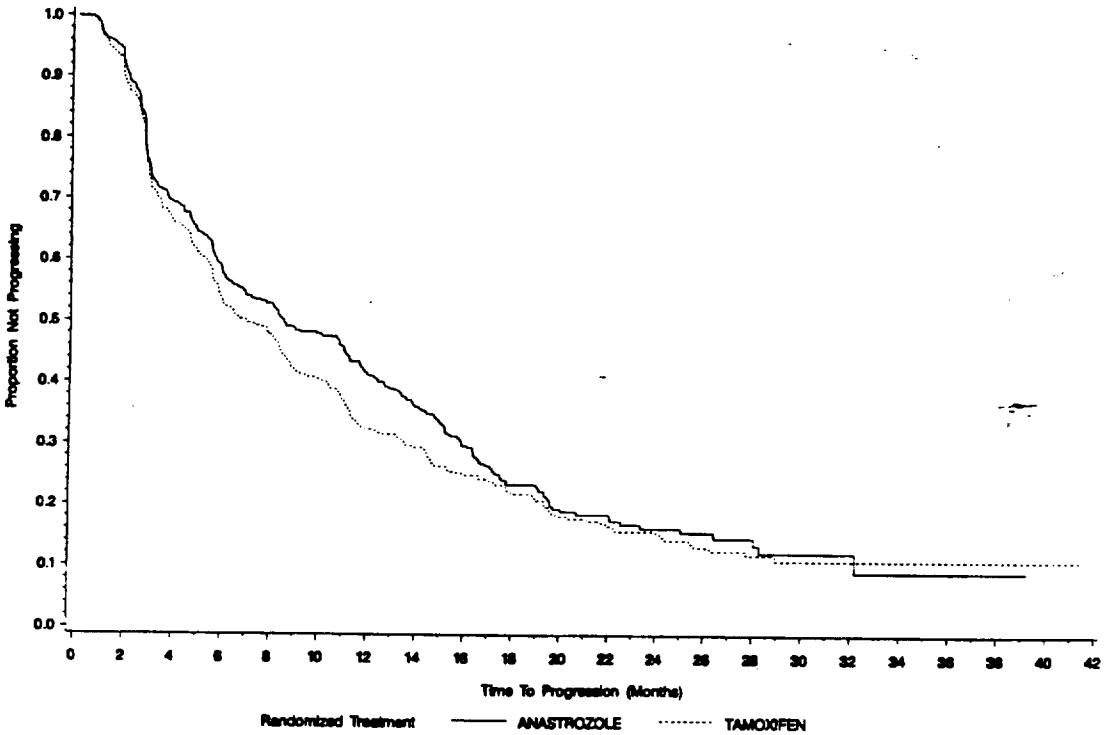
Comparison	Statistical analysis	
	Hazard ratio[a]	Lower 95% CL
Tamoxifen:anastrozole		
Trial 0027		
Adjusted analysis[b]	0.99	0.86
Unadjusted analysis[c]	1.01	0.87
Trial 0030		
Adjusted analysis[b]	1.44	1.16
Unadjusted analysis[c]	1.42	1.15
Combined trials		
Primary analysis (adjusted)[d]	1.13	1.00
Support analysis (adjusted)[e]	1.12	1.00
Support analysis (unadjusted)[c]	1.13	1.00

[a] Hazard ratio >1.00 indicates that anastrozole is associated with longer time to progression than is tamoxifen.
[b] The primary analysis (adjusted) was performed for individual trials using a Cox regression model including factors of treatment, extent of disease at entry, previous hormonal therapy, estrogen/progesterone receptor status, and age.
[c] The support analysis (unadjusted) was performed using a Cox regression model including treatment factor only.
[d] The adjusted analysis was repeated for combined trials using trial as a stratification factor - primary analysis.
[e] The adjusted analysis was repeated for combined trials by adding trial as an additional covariate - support analysis.
CL Confidence limit.

From the primary analysis, the hazard ratio of 1.13 favors anastrozole. The lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen:anastrozole) was 1.00, which was greater than the statistical criterion of 0.8 to declare noninferiority. The similar results have been observed from the 2 support analyses; the hazard ratios were 1.12 and 1.13 from the support adjusted analysis and the support unadjusted analysis, respectively. The lower 95% confidence limit for the hazard ratio was 1.00 from the 2 supporting analyses. The consistent results show that anastrozole is noninferior to tamoxifen in terms of time to progression.

The Kaplan-Meier plot of time to progression is presented in Figure 1.

Figure 1 Kaplan-Meier probability of time to progression



1.2 Objective response

Table 3 summarizes the tumor responses for all randomized subjects in Trials 0027 and 0030, separately and combined, by trial treatment.

Table 3 Objective response for all subjects in Trials 0027 and 0030, separately and combined

Objective response	Number (%) of subjects					
	Trial 0027		Trial 0030		Combined trials	
	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Responders	112 (32.9)	107 (32.6)	36 (21.1)	31 (17.0)	148 (29.0)	138 (27.1)
Complete response (CR)	19 (5.6)	16 (4.9)	5 (2.9)	5 (2.7)	24 (4.7)	21 (4.1)
Partial response (PR)	93 (27.4)	91 (27.7)	31 (18.1)	26 (14.3)	124 (24.3)	117 (22.9)
Non-responders	228 (67.1)	221 (67.4)	135 (78.9)	151 (83.0)	363 (71.0)	372 (72.9)
Stable disease (SD)	88 (25.9)	83 (25.3)	72 (42.1)	56 (30.8)	160 (31.3)	139 (27.3)
≥24 weeks	79 (23.2)	75 (22.9)	65 (38.0)	52 (28.6)	144 (28.2)	127 (24.9)
<24 weeks	9 (2.6)	8 (2.4)	7 (4.1)	4 (2.2)	16 (3.1)	12 (2.4)
Progression (PROG)	140 (41.2)	138 (42.1)	63 (36.8)	95 (52.2)	203 (39.7)	233 (45.7)

The objective response rate was defined as the proportion of subjects showing best objective response of complete response (CR) or partial response (PR). The best objective response rate of complete or partial response was similar for subjects treated with anastrozole (29.0%) and for subjects treated with tamoxifen (27.1%). The percentage of subjects with a best response rate of stable disease greater than or equal to 24 weeks was greater in subjects treated with anastrozole (28.2%) compared with subjects treated with tamoxifen (24.9%).

For objective response rate, formal treatment comparisons were made using a logistic-regression model to assess that anastrozole was noninferior to tamoxifen. The logistic-regression model was used in 2 ways: (1) the adjusted analysis with treatment factor and the 4 baseline prognostic covariates using 'trial' as an additional covariate; and (2) the unadjusted analysis with treatment factor only. As stated in the statistical analysis plan, the primary analysis is (1) and the other analysis is considered as supportive. The baseline prognostic covariates included in adjusted logistic regression model are the same as described for time to progression.

The trial-by-treatment interaction was tested using the logistic regression model with factors for treatment, 4 baseline prognostic covariates, and the trial-by-treatment interaction. There was no statistical evidence of trial-by-treatment interaction (p=0.25).

For the adjusted model, a global test was performed to check the inclusion of the 4 treatment-by-covariate interactions. Inclusion of the interaction terms was not statistically significant, with a log likelihood p-value of 0.77.

The logistic regression used in SAS only generates the estimated odds ratio . The following formula was used to convert the odds ratio to a difference in response rates (RR):

Where is the odds ratio (anastrozole/tamoxifen), is the observed number of responders in the tamoxifen group and is the observed number of nonresponders in the tamoxifen group.

To determine the difference in response rates and the associated confidence limit, the values for the estimated odds ratio and the lower 1-sided 95% confidence limit of the odds ratio were substituted into the above equation. This gave the difference in response rates between anastrozole and tamoxifen and the corresponding lower confidence limit, assuming that the response rate for tamoxifen was fixed at the observed response rate in this treatment group.

Table 4 summarizes the statistical analysis of objective response rate in Trials 0027 and 0030, separately and combined, by trial treatment.

Table 4 Statistical analysis of objective response rate in Trials 0027 and 0030, separately and combined

Comparison	Statistical analysis			
	Odds ratio[a]	Lower 95% CL	Difference in response rate[b]	Lower 95% CL
Anastrozole:tamoxifen				
Trial 0027				
Adjusted analysis[c]	0.95	0.72	−1.01	−6.74
Unadjusted analysis[d]	1.01	0.77	0.32	−5.37
Trial 0030				
Adjusted analysis[c]	1.38	0.87	5.01	−1.90
Unadjusted analysis[d]	1.30	0.83	4.02	−2.47
Combined trials				
Primary analysis (adjusted)[e]	1.06	0.83	1.08	−3.49
Support analysis (unadjusted)[d]	1.10	0.87	1.90	−2.58

[a] Odds ratio less than 1.00 indicates that anastrozole is associated with lower response rate than is the tamoxifen.
[b] Difference in response rate (anastrozole - tamoxifen) was calculated from odds ratio using the formula stated in this section.
[c] The primary analysis (adjusted) was performed for individual trials using a logistic regression model including factors of treatment, site of disease at entry, previous hormonal therapy, estrogen/progesterone status, and age.
[d] The support analysis (unadjusted) was performed using a logistic regression model including treatment factor only.
[e] The adjusted analysis was repeated for combined trials by adding trial as an additional covariate.
CL Confidence limit.

From the primary (adjusted) analysis, the estimated difference in response rate of 1.08 favors anastrozole. The lower 1-sided 95% confidence limit for the difference in response rate (anastrozole - tamoxifen) was -3.49% from the adjusted analysis, which was greater than the statistical criterion of -10% to declare noninferiority. The same results were observed from the unadjusted analysis, with an estimated difference in response rate of 1.90 and the lower 95% confidence limit of –2.58%. Therefore, it can be concluded that anastrozole is noninferior to tamoxifen for objective response rate.

1.3 Time to treatment failure

Table 5 summarizes the reasons for treatment failure for all randomized subjects in Trials 0027 and 0030 combined by trial treatment up to the date of the last objective response assessment before the data cutoff date. For the majority of subjects who reached treatment failure in each treatment group across trials, the reason for treatment failure was disease progression.

Table 5 Reasons for treatment failure for subjects in Trials 0027 and 0030 combined

Reason	Number (%) of subjects[a]					
	Trial 0027		Trial 0030		Combined trials	
	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Death without evidence of progression	5 (1.5)	3 (0.9)	3 (1.8)	3 (1.6)	8 (1.6)	6 (1.2)
Disease progression (objective)	216 (63.5)	208 (63.4)	100 (58.5)	121 (66.5)	316 (61.8)	329 (64.5)
Treatment stopped because of disease progression (investigator's opinion)	15 (4.4)	16 (4.9)	13 (7.6)	13 (7.1)	28 (5.5)	29 (5.7)
Subject lost to follow-up	2 (0.6)	1 (0.3)	0	0	2 (0.4)	1 (0.2)
Adverse event	13 (3.8)	15 (4.6)	8 (4.7)	6 (3.3)	21 (4.1)	21 (4.1)
Protocol noncompliance	3 (0.9)	6 (1.8)	2 (1.2)	2 (1.1)	5 (1.0)	8 (1.6)
Unwilling to continue	5 (1.5)	10 (3.0)	2 (1.2)	4 (2.2)	7 (1.4)	14 (2.7)
Never started randomized treatment	2 (0.6)	1 (0.3)	1 (0.6)	0	3 (0.6)	1 (0.2)
Other reason	6 (1.8)	6 (1.8)	6 (3.5)	3 (1.6)	12 (2.3)	9 (1.8)
Total number of subjects with treatment failure	267 (78.5)	266 (81.1)	135 (78.9)	152 (83.5)	402 (78.7)	418 (82.0)

Of the 1021 subjects who were randomized in this trial, 702 (68.8%) subjects had treatment failure resulting from disease progression (645 [63.2%] subjects from the objective algorithm and 57 [5.6%] subjects from the investigator's opinion). One hundred and four (10.2%) subjects were withdrawn from trial treatment for reasons other than disease progression, and 14 (1.4%) subjects died before progression.

A total of 820 (80.3%) subjects had treatment failure. A smaller percentage of subjects who were randomized to anastrozole treatment (78.7%) had treatment failure when compared with subjects who were randomized to tamoxifen treatment (82.0%). Subjects who were randomized to anastrozole treatment also had a longer estimated median time to treatment failure (208 days) when compared with subjects who were randomized to tamoxifen treatment (176 days).

Formal treatment comparisons were analyzed using a Cox regression model in the same way that was done for time to progression.

The trial-by-treatment interaction was tested using the Cox regression model with factors for treatment, 4 baseline prognostic covariates, and the trial-by-treatment interaction. There was no statistical evidence of trial-by-treatment interaction (p=0.07).

The assumptions of the Cox regression model and proportionality were also investigated. The p-value of 0.96 from a Wald chi-squared statistic for a time-dependent explanatory variable showed that there was no evidence of a departure from proportionality. For the adjusted model with "trial" as an additional covariate, a global test was performed to check the inclusion of the 4 treatment-by-covariate interactions. The p-value from a log likelihood ratio test was 0.57 from both the primary adjusted analysis with "trial" as a stratum and the support adjusted analysis with "trial" as an additional covariate. Therefore, the inclusion of the interaction terms was not statistically significant.

Table 6 summarizes the statistical analysis of time to treatment failure in Trials 0027 and 0030, separately and combined, by trial treatment.

Table 6 Statistical analysis of time to treatment failure in Trials 0027 and 0030, separately and combined

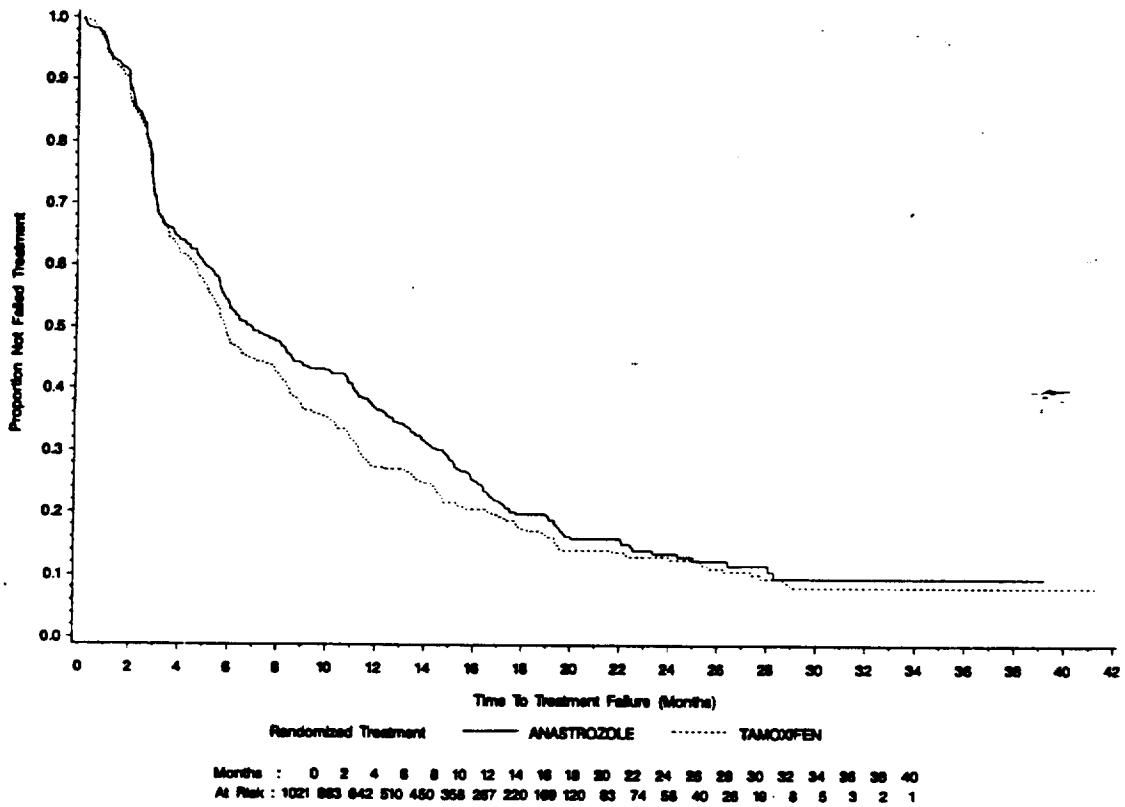
Comparison	Statistical analysis	
	Hazard ratio[a]	Lower 95% CL
Tamoxifen:anastrozole		
Trial 0027		
Adjusted analysis[b]	1.03	0.89
Unadjusted analysis[c]	1.04	0.90
Trial 0030		
Adjusted analysis[b]	1.35	1.11
Unadjusted analysis[c]	1.33	1.10
Combined trials		
Primary analysis (adjusted)[d]	1.13	1.01
Support analysis (adjusted)[e]	1.13	1.01
Support analysis (unadjusted)[c]	1.13	1.01

[a] Hazard ratio >1.00 indicates that anastrozole is associated with longer time to progression than is tamoxifen.
[b] The primary analysis (adjusted) was performed for individual trials using a Cox regression model including factors of treatment, extent of disease at entry, previous hormonal therapy, estrogen/progesterone receptor status, and age.
[c] The support analysis (unadjusted) was performed using a Cox regression model including treatment factor only.
[d] The adjusted analysis was repeated for combined trials using trial as a stratification factor - primary analysis.
[e] The adjusted analysis was repeated for combined trials by adding trial as an additional covariate - support analysis.
CL Confidence limit.

The hazard ratio and the associated lower 1-sided 95% confidence limit (tamoxifen:anastrozole) was the same from these 3 analyses (the primary analysis and the 2 support analyses). The hazard ratio of 1.13 favors anastrozole. The lower 1-sided 95% confidence limit was 1.01, which was greater than the statistical criterion of 0.8 to declare noninferiority; thus proving that anastrozole is noninferior to tamoxifen in terms of time to progression.

The Kaplan-Meier plot of time to treatment failure is presented in Figure 2.

Figure 2 Kaplan-Meier probability of time to treatment failure



1.4 Time to death (survival)

Table 7 summarizes the survival status for all randomized subjects in Trials 0027 and 0030, separately and combined, by trial treatment.

Table 7 Survival status for subjects in Trials 0027 and 0030, separately and combined

Survival status	Number (%) of subjects[a]					
	Trial 0027		Trial 0030		Combined trials	
	Anastrozole 1 mg (n=340)	Tamoxifen 20 mg (n=328)	Anastrozole 1 mg (n=171)	Tamoxifen 20 mg (n=182)	Anastrozole 1 mg (n=511)	Tamoxifen 20 mg (n=510)
Alive[a]	249 (73.2)	254 (77.4)	124 (72.5)	129 (70.9)	373 (73.0)	383 (75.1)
Dead	91 (26.8)	74 (22.6)	47 (27.5)	53 (29.1)	138 (27.0)	127 (24.9)

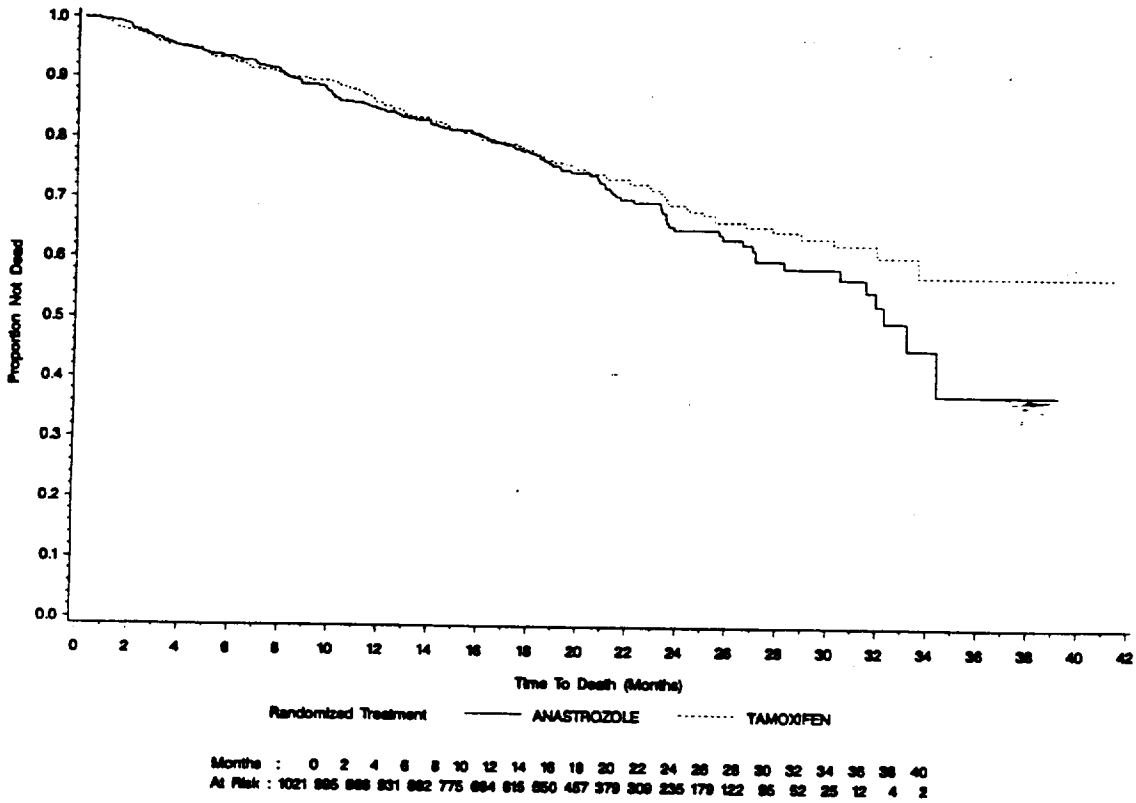
[a] Data for these subjects were censored at the last known observation.

The death rate was similar for the treatment groups (138 [27.0%] subjects who were randomized to anastrozole treatment and 127 [24.9%] subjects who were randomized to tamoxifen treatment had died at the time of data cutoff).

The percentage of subjects who were alive longer than 2 years after trial treatment ended was 65.2% for subjects who were randomized to anastrozole treatment and 69.4% for subjects who were randomized to tamoxifen treatment. A statistical analysis of survival was not performed because only 265 (26.0%) subjects in this trial had died at the time of data cutoff.

The Kaplan-Meier plot of time to death is presented in Figure 3.

Figure 3 Kaplan-Meier probability of time to death



Zeneca ZD1033 (anastrozole, ARIMIDEX™)

ZENECA'S RESPONSIBLE MEDICAL OFFICER APPROVAL

Integrated Summary of Safety Information

This document falls within the goals of the International Clinical Plan, meets Zeneca standard practices, and is suitable for inclusion in the regulatory submission.

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CLINICAL STRATEGY LEADER APPROVAL

Integrated Summary of Safety Information

This document falls within the goals of the International Clinical Plan, meets Zeneca standard practices, and is suitable for inclusion in the regulatory submission.

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Zeneca ZD1033 (anastrozole, ARIMIDEX™)

GLOBAL PROJECT STATISTICIAN APPROVAL

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Zeneca ZD1033 (anastrozole, ARIMIDEX™)

Supplemental New Drug Application

Integrated Summary of Safety Information

28 September 1999

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EXECUTIVE SUMMARY

Overview

This Integrated Summary of Safety (ISS) provides an overview of the safety data from the first-line clinical trial program for anastrozole (ZD1033, ARIMIDEX™), a selective aromatase inhibitor for use in the treatment of postmenopausal women with advanced breast cancer.

The anastrozole clinical trial program summarized in this document is comprised of 2 core controlled trials (Trials 1033IL/0030 and 1033IL/0027) and 4 additional clinical pharmacology trials (Trials 1033NY/0001, 1033IL/0032, 1033IL/0033, and 1033IL/0035). Data from 2 ongoing trials (Trials 1033JP/0027 and 1033CZ/0001) and Trial A-15-12 (which used a different system for the coding of adverse events) were not included in the integrated analyses.

Baseline characteristics and extent of exposure

At the time of data cutoff for this ISS (10 March 1999), a total of 1017 postmenopausal women with advanced breast cancer were given trial treatment. This included 506 subjects who were given anastrozole and 511 subjects who were given tamoxifen in the core controlled clinical trials and 88 postmenopausal women (75 of whom were given 1 mg anastrozole and 13 of whom were given 10 mg of anastrozole) and 16 healthy men (all of whom were given 7 mg [7 × 1 mg] anastrozole for 1 day followed by 1 mg daily) in the additional clinical trials.

In the core controlled trials, the mean and distribution of age, body mass index, weight, and height were similar between the treatment groups. The majority of subjects were Caucasian, with other ethnic groups each contributing less than 4% of the trial population in the controlled clinical trials. Slightly more than one-half of the subjects in the controlled trials were more than 65 years of age. At the time of data cutoff, subjects in the core controlled trials were exposed to anastrozole at the therapeutic dose of 1 mg daily for up to 1195 days. The durations of both exposure and follow-up were similar between the 2 treatment groups.

Summary of safety

- The most frequently reported adverse event was vasodilatation. Other commonly reported adverse events were nausea, asthenia, and various types of pain. Overall, the most commonly reported drug-related adverse events were vasodilatation, nausea, and asthenia. These events were also common in the anastrozole second-line program and were not unexpected given the known safety profile of the drug.

- The only other individual adverse event, besides vasodilatation, for which the difference between treatment groups was greater than 4% was leukorrhea, which occurred in 1.8% of subjects who were given anastrozole and 6.1% of subjects who were given tamoxifen.

- In the core controlled trials, the overall incidence of joint-related symptoms (such as arthritis, arthralgia, and arthrosis) in subjects who were given anastrozole was approximately twice that reported in subjects who were given tamoxifen. The mechanism of any association of anastrozole with joint-related symptoms is unknown; no subject withdrew from the trials because of joint-related symptoms.

- In the categories of prespecified adverse events expected from the pharmacological action of anastrozole and tamoxifen, higher incidences of thromboembolic disease depression, tumor flare, gastrointestinal disturbances, lethargy, and vaginal bleeding occurred more frequently in subjects who were given the tamoxifen, but these did not reach statistical significance. Vaginal dryness, weight gain, and hot flushes were reported by a greater proportion of subjects who were given anastrozole, but the differences did not reach statistical significance. Only gastrointestinal disturbances and hot flushes were reported by more than 5% of subjects who were given anastrozole.

- In the core controlled trials, vasodilatation (hot flushes) was more common in subjects ≤65 years of age in both treatment groups. Conversely, the incidence of hypertension was higher in subjects >65 years of age in both treatment groups. Anastrozole was well tolerated in postmenopausal women, regardless of age.

- Review of adverse events with regard to concomitant medications did not suggest any medication-treatment interactions. In addition, there was no increased risk from either anastrozole or tamoxifen in subjects with mild-to-moderate abnormalities in hepatic biochemistry.

- In the core controlled trials, 26.1% subjects had died by the time of data cutoff. Most deaths were related to breast cancer and the incidence of death from breast cancer was similar between the 2 treatment groups. Most of the non-breast cancer related deaths were from cardiovascular disease or respiratory disease. In cases where adverse events

led to death, none of the primary causes of death were attributable to anastrozole or tamoxifen in either the core or additional clinical trials.

- The incidences of adverse events that led to withdrawal were low and similar between the 2 treatment groups. There were no notable differences between the 2 treatment groups for the occurrence of specific adverse events that led to withdrawal.
- The overall incidence of serious adverse events in the core controlled trials was similar between the treatment groups. More subjects who were given tamoxifen had serious adverse events related to the cardiovascular system. The most common individual serious adverse events were pathological fracture, nausea, and dyspnea. Most serious adverse events were not related to trial treatment.
- No concerns regarding drug safety or pharmacology were raised by the analysis of laboratory results, whether by mean values or from the Zeneca-defined laboratory abnormalities.

Overall conclusions and prescribing recommendations

The safety profile of anastrozole in postmenopausal women with advanced breast cancer, as established in the second-line clinical trial program, was confirmed in the first-line clinical trial program. The data from the core controlled trials demonstrate that anastrozole was well tolerated; adverse events were usually mild-to-moderate with only a few withdrawals resulting from undesirable effects. The pharmacological action of anastrozole in lowering estrogen levels may give rise to certain expected effects; these include hot flushes and vaginal dryness. Anastrozole may be associated with gastrointestinal disturbances (anorexia, nausea, constipation, vomiting, diarrhea), asthenia, joint pain/stiffness, somnolence, headache, or rash.

There was a low incidence of venous and arterial thromboembolic disease. The low incidence of vaginal bleeding and vaginal discharge was consistent with the known pharmacology of anastrozole, which would be predicted to have no estrogenic effect, and no effect on the endometrium. Despite the lack of estrogenic activity, there was no increase in myocardial infarction or pathological fracture when compared with tamoxifen. Anastrozole was associated with an increase in symptoms related to the joints, but a mechanism of action is uncertain. The lack of withdrawals resulting from joint-related symptoms indicates these events were tolerable to patients who were being treated for advanced breast cancer and their physicians.

Overall, anastrozole was well tolerated as a first-line agent for the treatment of advanced breast cancer in postmenopausal women. The pharmacology of anastrozole and resulting safety profile may be a clinical advantage in certain patients, such as those with a history of thromboembolic disease, or an intact uterus. This, together with the efficacy data, establishes the value of anastrozole for the treatment of advanced breast cancer in postmenopausal women.

On the basis of the data presented in this ISS, it is recommended that the following safety-related addition be made to the prescribing information for ARIMIDEX:

Possible adverse reactions: ARIMIDEX may be associated with joint pain/stiffness.