



	Demographics at randomisation and tumour characteristics from the diagnostic core						Surgery details and tumour characteristics from surgery					
	Perioperative AI		Control		Total		Perioperative AI		Control		Total	
	(N=2976)		(N=1504)		(N=4480)		(N=2960)		(N=1497)		(N=4457)	
	n	%	n	%	n	%	n	%	n	%	n	%
Positive	..	..	..	..	..	..	317	11	152	10	469	11
Negative	..	..	..	..	..	..	2606	88	1316	88	3922	88
Unknown/Missing	..	..	..	..	..	..	37	1	29	2	66	1
<b>Hormone Receptor and HER2 status<sup>1</sup></b>												
HR+												
& HER2+	..	..	..	..	..	..	317	11	152	10	469	11
& HER2-	..	..	..	..	..	..	2601	88	1315	88	3916	88
& HER2 unknown	..	..	..	..	..	..	37	1	27	2	64	1
HR-												
& HER2-	..	..	..	..	..	..	4	<1	1	<1	5	<1
<b>Histological type</b>												
Ductal*	2404	81	1198	80	3602	80	2364	80	1199	80	3563	80
Lobular	428	14	224	15	652	15	454	15	236	16	690	16
Special type**2	105	4	58	4	163	4	124	4	50	3	174	4
DCIS/LCIS <sup>3</sup>	0	0	0	0	0	0	3	<1	2	<1	5	<1
Not breast cancer <sup>4</sup>	0	0	0	0	0	0	1	<1	0	0	1	<1
Not known	39	1	24	2	63	1	14	<1	10	1	24	1
<b>Tumour grade</b>												
G1	417	14	234	16	651	15	465	16	184	12	649	15

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	n	%	n	%	n	%	n	%	n	%	n	%
G2	1757	59	843	56	2600	58	1968	66	838	56	2806	63
G3	521	18	279	19	800	18	502	17	463	31	965	22
GX	0	0	1	<1	1	<1						
Not known***	278	9	145	10	423	9	17	1	6	<1	23	1
Missing	3	<1	2	<1	5	<1	8	<1	6	<1	14	<1
<b>Tumour size (cm)****</b>												
≤2	1666	56	870	60	2536	57	1372	46	671	45	2043	46
2 to 5	1238	42	599	40	1837	41	1448	49	745	50	2193	49
>5	54	2	28	2	82	2	129	4	74	5	203	5
Missing	18	1	7	<1	25	1	11	<1	7	<1	18	<1
<b>Definitive breast surgery</b>												
Mastectomy	..	..	..	..	..	..	1051	36	503	34	1554	35
Conservative surgery	..	..	..	..	..	..	1902	64	992	66	2894	65
Missing	..	..	..	..	..	..	7	<1	2	<1	9	<1
<b>Definitive axillary surgery</b>												
Yes	..	..	..	..	..	..	2911	98	1470	98	4381	98
Clearance	..	..	..	..	..	..	916	31	468	31	1384	31
Sampling	..	..	..	..	..	..	287	10	150	10	437	10

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	(N=2976)		(N=1504)		(N=4480)		(N=2960)		(N=1497)		(N=4457)	
	n	%	n	%	n	%	n	%	n	%	n	%
<i>SLNB</i>	..	..	..	..	..	..	1708	58	852	57	2560	57
No	..	..	..	..	..	..	42	1	25	2	67	2
Missing	..	..	..	..	..	..	7	<1	2	<1	9	<1
<b>Nodal status</b>												
N0	..	..	..	..	..	..	1815	61	892	60	2707	61
N1-3	..	..	..	..	..	..	801	27	434	29	1235	28
N4+	..	..	..	..	..	..	334	11	165	11	499	11
Missing	..	..	..	..	..	..	10	<1	6	<1	16	<1
<b>Vascular invasion</b>												
Yes	..	..	..	..	..	..	813	27	445	30	1258	28
No	..	..	..	..	..	..	1990	67	981	66	2971	67
Not reported	..	..	..	..	..	..	143	5	63	4	206	5
Missing	..	..	..	..	..	..	14	<1	8	1	22	<1
<b>Multi-focal disease</b>												
Yes	..	..	..	..	..	..	381	13	223	15	604	14
No	..	..	..	..	..	..	2563	87	1266	85	3829	86
Missing	..	..	..	..	..	..	16	1	8	1	24	1

\* Ductal includes patients with mixed ductal and lobular tumours

\*\* Special types on the diagnostic core include mucinous, papillary, tubular, metaplastic carcinoma, microcapillary, anaplastic with basaloid nuclear pattern

\*\*\* Some centres do not routinely report grade on the diagnostic core.

\*\*\*\* Pre-surgery this measurement is either by ultrasound or clinical examination. Patients are eligible if they have either a palpable tumour (clinical exam) of any size or a tumour with an ultrasound size of  $\geq 1.5$ cm. 618 patients had tumour size  $< 1.5$ cm, of which 607 confirmed the tumour was palpable.

<sup>1</sup> One patient (peri-op AI) with ER status unknown was HER2-; the remaining two patients (no peri-op AI) with ER status unknown also had HER2 status unknown

<sup>2</sup> Special types from surgery specimen include mucinous, papillary, tubular, endocrine cell carcinoma, pure special type, metaplastic carcinoma clear cell, basaloid carcinoma and tubular and cribriform.

<sup>3</sup> pre-surgical histological types for these patients were coded as ductal carcinoma

<sup>4</sup> pre-histological type was not known (this patient is recorded as ineligible)

Table 2: Table of disease-related first events and deaths

	Perioperative AI		Control		Total	
	(N=2976)		(N=1504)		(N=4480)	
	n	%	n	%	n	%
<b>Any disease-related first event</b>						
Yes	541	18	309	21	850	19
No	2435	82	1195	80	3630	81
<b>Event contributing to primary endpoint (TTR)</b>	<b>280</b>	<b>9</b>	<b>154</b>	<b>10</b>	<b>434</b>	<b>10</b>
Local recurrence (isolated)	25	1	13	1	38	1
Distant recurrence <sup>1</sup>	236	8	131	9	367	8
Breast cancer death <sup>2</sup>	19	1	10	1	29	1
<b>Other event</b>	<b>261</b>	<b>9</b>	<b>155</b>	<b>10</b>	<b>416</b>	<b>9</b>
Breast second primary cancer	26	1	24	2	50	1
Non-breast second primary cancer	136	5	80	5	216	5
Intercurrent death	99	3	51	3	150	3
<b>Total deaths</b>	<b>365</b>	<b>12</b>	<b>196</b>	<b>13</b>	<b>561</b>	<b>13</b>
<b>Breast cancer</b>	<b>201</b>	<b>7</b>	<b>110</b>	<b>7</b>	<b>311</b>	<b>7</b>
<b>Other (intercurrent deaths)</b>	<b>164</b>	<b>6</b>	<b>86</b>	<b>6</b>	<b>250</b>	<b>6</b>
Cardiovascular	41	1	25	2	66	1
Other cancer	59	2	35	2	94	2
Respiratory	37	1	15	1	52	1
Sepsis	14	<1	5	<1	19	<1
Other <sup>4</sup>	13	<1	6	<1	19	<1

If more than one “first event” reported on the same date, included in row here according to the following order of priority: distant recurrence, local recurrence, breast second primary cancer, non-breast second primary cancer, intercurrent death

<sup>1</sup>- Distant recurrence row includes patients where distant recurrence is reported within 6 weeks of local recurrence

<sup>2</sup>- Includes 25 patients (18 perioperative AI, 7 no perioperative AI) with unknown cause of death and no prior event. Note, one patient had a second primary before unknown cause of death and is not included here.

<sup>3</sup> conservatively counted as breast cancer deaths. Note: other cause of death following a non-breast second primary is not counted as a breast cancer death (N=1).

<sup>4</sup> other causes were as follows: Perioperative AI (N=13) – Accident (n=2) Acute kidney injury; Alzheimer’s; Ascending aortic aneurysm; Haematemesis secondary to gastric ulcer; Hepatic cirrhosis; Multi-organ failure; Myelofibrosis; Old age with vascular deterioration and chronic kidney disease; Portal hypertension, a fall, ascites, evidence of cirrhosis; Post-operative complications relating to pituitary tumour operation; Renal failure. Control (N=6) - Complications post laparotomy; Dementia; Diabetes mellitus; Meningioma; Subdural haematoma, Suicide

Table A4: Summary of disease-related endpoints

	Number of events (%)		Unadjusted HR (95%CI); p-value	Adjusted HR (95%CI); p-value	5 year survival estimate, % (95%CI)	
	Perioperative AI	Control			Perioperative AI	Control
RFS	385 (12.9)	207 (13.8)	0.94 (0.79, 1.11); 0.47	0.95 (0.79, 1.14); 0.59	87.9 (86.6, 89.1)	87.6 (85.7, 89.2)
TTLR	41 (1.4)	24 (1.6)	0.86 (0.52, 1.43); 0.57	0.92 (0.54, 1.56); 0.75	98.6 (98.1, 99.0)	98.5 (97.6, 99.0)
TTDR	262 (8.8)	147 (9.8)	0.90 (0.73, 1.10); 0.30	0.94 (0.75, 1.18); 0.59	91.7 (90.5, 92.6)	90.9 (89.2, 92.3)

Models adjusted for PR status (positive, negative, unknown), HER2 status positive, negative, unknown), pre-surgical tumour grade (G1, G2, G3), pathological tumour size (continuous), pre-surgical histological type (ductal, lobular, special type), nodal status (N0, N1-3, N4+), age at randomisation (continuous) and vascular invasion (yes, no).