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23 **Appendices**

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27 ***Number of patients per participating hospital***

28 Included patients were treated between 1990 and 2000 at the Netherlands Cancer Institute-Antoni van Leeuwenhoek  
29 Hospital (N=683), Erasmus Medical Center-Daniel den Hoed Clinic (N=320), which are cancer centers; Leiden University  
30 Medical Center (N=205), an academic hospital; and Medisch Spectrum Twente Hospital (N=839), PAMM Laboratories (N=221),  
31 Albert Schweitzer Hospital (N=191), Rijnland Hospital (N=86), Viecuri Hospital (N=74), Diaconessenhuis Leiden (N=50), and  
32 Elkerliek Hospital (N=41), which are regional hospitals.

33 An update of the clinical and follow-up data revealed that 19 patients included in the current study were 50 years at  
34 diagnosis, and therefore did not meet the eligibility criterion of below 50 years. This shift in age was due to adjustment of the  
35 date of diagnosis (histological confirmation). Given the small number of patients concerned and the fact that the results remained  
36 the same irrespective of whether these patients were included or not, we decided to keep them in the analyses.

37

38 ***Procedures***

39 Data categorization: age at diagnosis (continuous), tumor size (continuous for PREDICT and for Adjuvant! categorized  
40 as: 0.0-1.0 cm, 1.1-2.0 cm, 2.1-3.0 cm, 3.1-5.0 cm or >5.0 cm), tumor grade (categorized as: Grade 1, Grade 2, Grade 3 or  
41 undefined if missing), number of positive axillary lymph nodes (continuous for PREDICT and for Adjuvant! categorized as: 0  
42 positive nodes, 1-3 positive nodes, 4-9 positive nodes or >9 positive nodes), ER-status (categorized as: positive, negative or  
43 undefined if missing).

44 For Adjuvant! if tumor diameter (in mm) was missing, patients were categorized using pathological T-stage if available  
45 (T1 was categorized as having a tumor of 1.1-2.0 cm, T2 was categorized as having a tumor of 3.1-5.0 cm and T3 was  
46 categorized as having a tumor of >5.0 cm). For Adjuvant! patients with missing data on the number of positive axillary lymph  
47 nodes were categorized using pathological N-stage if available (N0 was categorized as having 0 positive nodes, N1 was  
48 categorized as having 1-3 positive nodes, N2 was categorized as having 4-9 positive nodes and N3 was categorized as having >9  
49 positive nodes). We used weighed mean imputed values to calculate PREDICT survival estimates for missing values of grade  
50 (imputed value: 2.25), tumor size in mm (if pT1a-b: 5mm; pT1c: 1.5mm; pT2: 40mm; pT3: 50mm), and number of positive  
51 axillary lymph nodes (if pN1: 2 positive nodes; pN2: 7 positive nodes; pN3: 10 positive nodes). The T, N, and M were  
52 determined according to Dutch guidelines at the time of diagnosis; for combining these three factors in the stage variable, the  
53 AJCC TNM staging guidelines of 2002 were used.

54 According to the clinical cut-off points endorsed in the Dutch breast cancer guideline for immunohistochemical  
55 staining of receptors, a tumor was considered receptor negative using the following cut-offs: ER= ≤10%; PR= ≤10%; Her2-  
56 score= 0 or 1+) (21;26;27). Receptor status data was included from Tissue Micro Arrays (TMA) if data from pathology reports  
57 was not available, for ER the data source was N<sub>TMA</sub>= 757 and N<sub>pathology reports</sub>= 1316, and for Her2 data source was N<sub>TMA</sub>= 817 and  
58 N<sub>pathology reports</sub>= 308. Patients with a tumor that did not express ER, PR and Her2 were considered to have a triple negative tumor.  
59 Within the time period that patients in this cohort had been diagnosed (i.e. 1990-2000), it was not yet standard practice to  
60 routinely assess cell-surface Her2 protein expression by immunohistochemistry (Her2-status missing for N= 1,639 (60%)). Her2  
61 was mostly included from analyses of TMA using Her2 immunohistochemistry, however, the number of copies of the Her2-gene  
62 was not quantified using an in situ hybridization technique (e.g., FISH, CISH or SISH) for patients with an equivocal Her2  
63 immunohistochemistry (i.e. 2+ score) to definitively determine Her2-status (N= 60 (2%)). We opted to include patients with  
64 equivocal Her2 immunohistochemistry in our analyses and treat them as having Her2-negative disease, based on Kaplan-Meier  
65 curves analyses that showed that their survival pattern was similar to those with immunohistochemistry Her2-negative disease  
66 (data not shown).

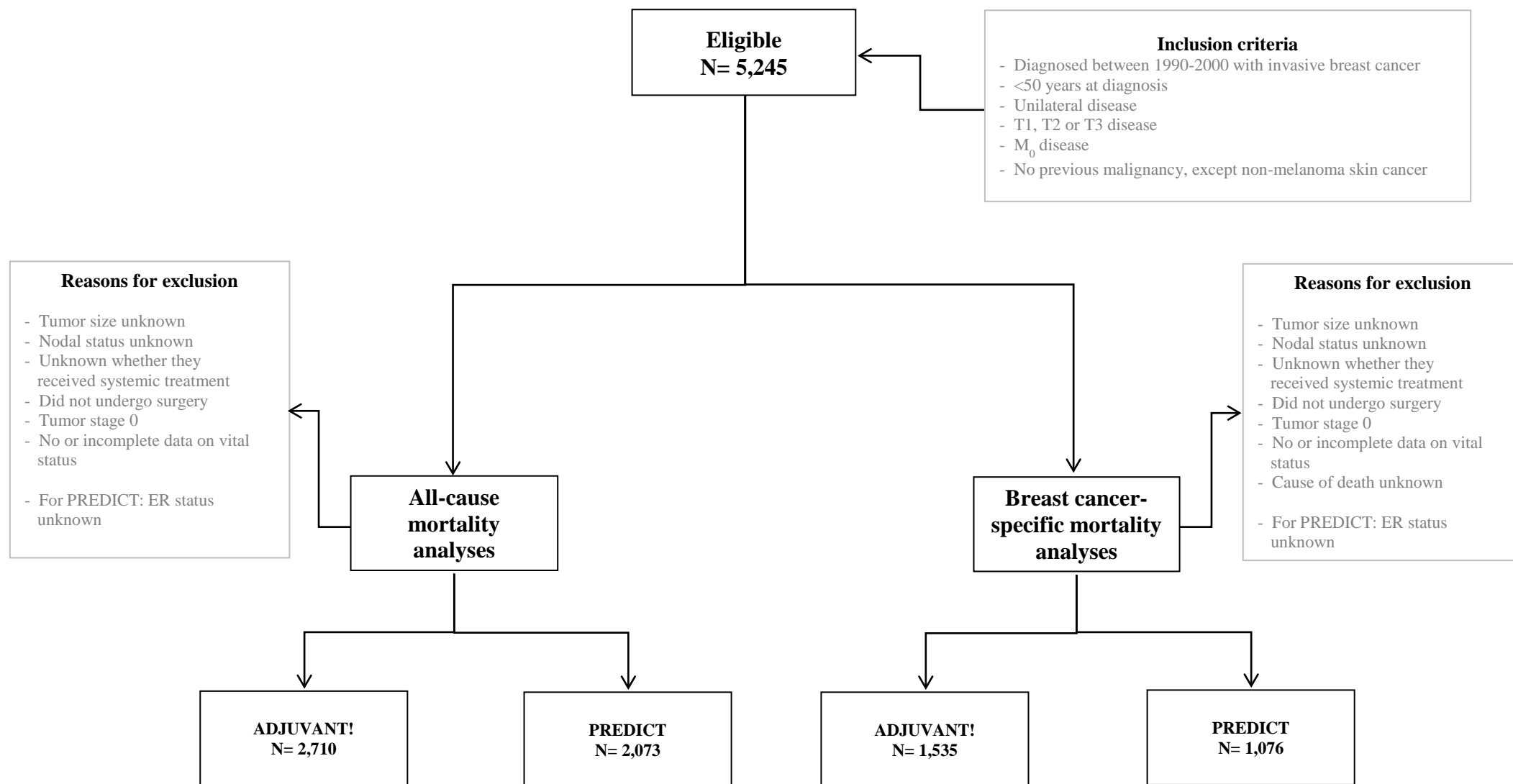
67 Angiolymphatic-invasion, i.e., tumor formation in blood and/or lymph blood vessels, was only available for reviewed  
68 tumor H&E slides. A breast pathologist (H. Peterse, NKI-AVL) scored the tumors as follows: 0=none, 1=1-3 vessels in the whole  
69 slide, 2=more than three vessels in the whole slide.

70 Adjuvant systemic treatment was categorized as: none, first generation (if treated with cyclophosphamide -  
71 methotrexate - fluorouracil (CMF), cyclophosphamide - doxorubicin or epirubicin (AC or EC) (four cycles) or if type  
72 chemotherapy regime was unknown and the patient also received endocrine therapy) and second generation (if treated with  
73 fluorouracil (5FU) - doxorubicin or epirubicin - cyclophosphamide (FEC or FAC) (six cycles), others). In the Adjuvant! analysis  
74 sample (N=2,710), in total 1,058 patients received first generation chemotherapy and 47 patients received second-generation  
75 chemotherapy. In the PREDICT analysis sample (N=2,073), in total 800 patients received first generation chemotherapy and 24  
76 patients received second-generation chemotherapy. In this population, endocrine treatment only consisted of Tamoxifen.

77 ***Analyses***

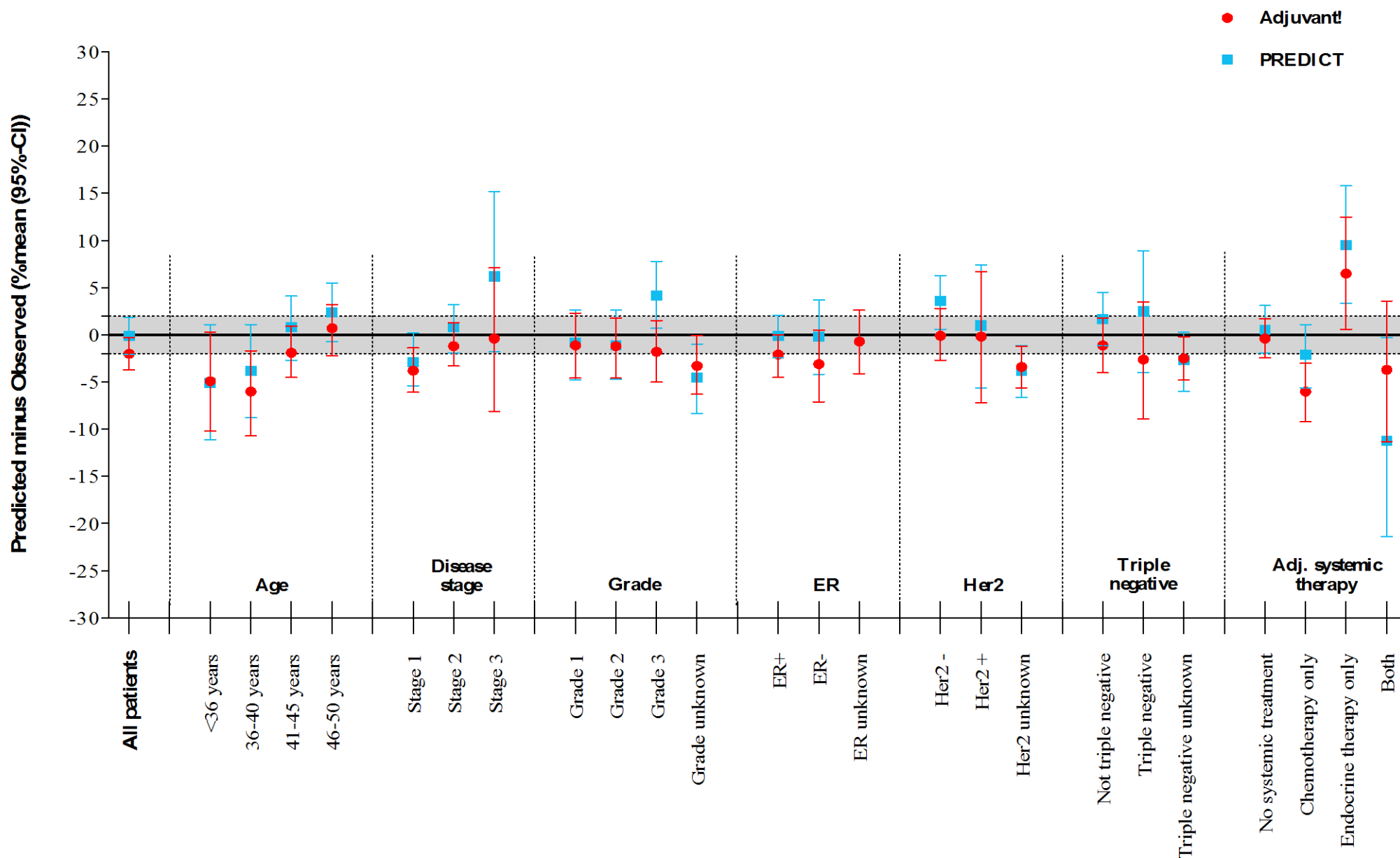
78 The following hospitals had no data on cause of death and were thus excluded from the breast cancer-specific mortality  
79 estimates, namely: Elkerliek (N=41), Viecuri (N=74), PAMM Laboratories (N=221) and Medisch Spectrum Twente (N=839).

**Appendix Figure 1 Flowchart of patient selection**



T<sub>1</sub>= tumors size ≤20 mm; T<sub>2</sub>= tumors size between 21-50 mm; T<sub>3</sub>= tumors size >50 mm; M<sub>0</sub>= no distant metastases; ER= estrogen receptor status.  
The number of people excluded for each reason for exclusion is not reported as patients were almost always excluded for multiple reasons.

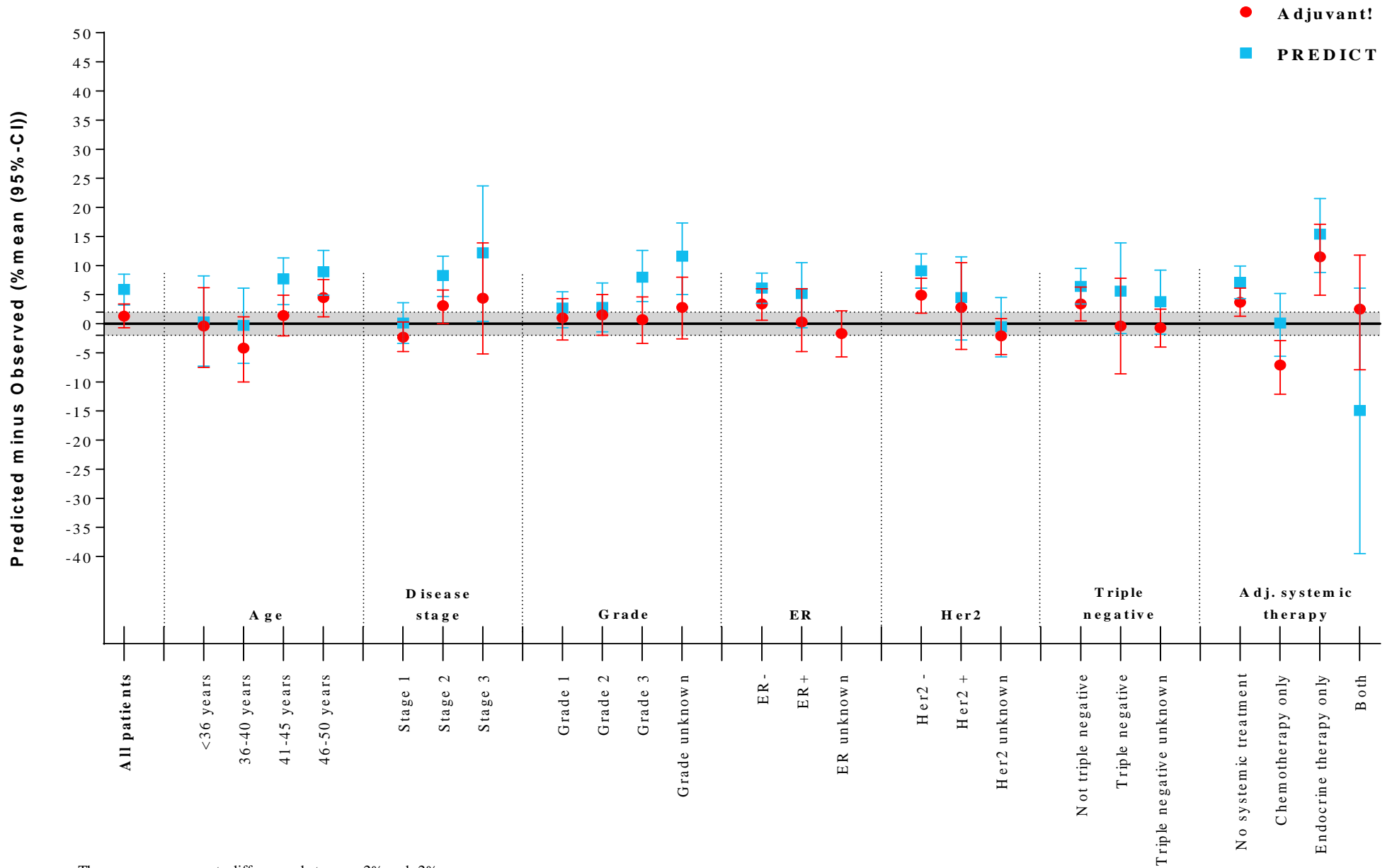
**Appendix Figure 2 Overview of Adjuvant! and PREDICT estimates of all-cause mortality by prognostic factors for patients diagnosed between 1990-2000**



The grey area represents differences between +2% and -2%

For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 1.

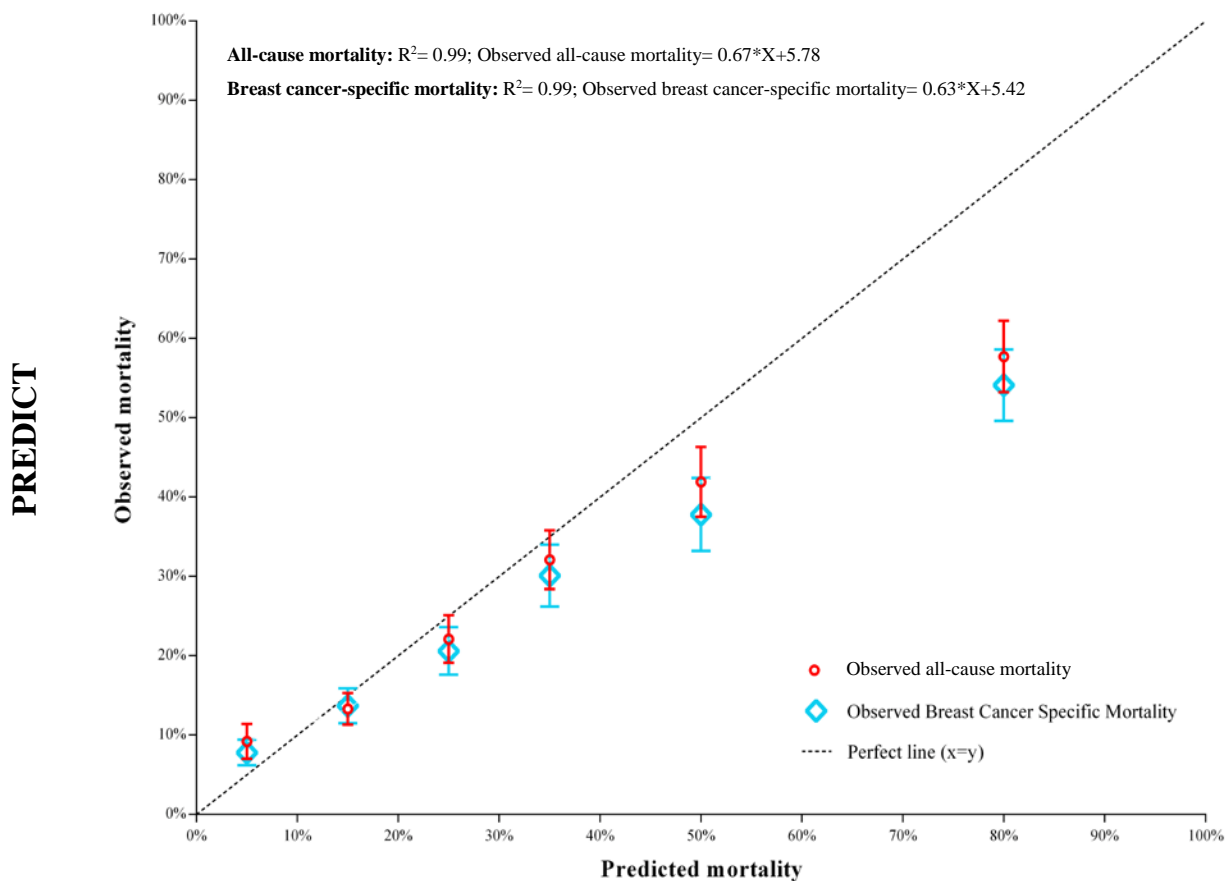
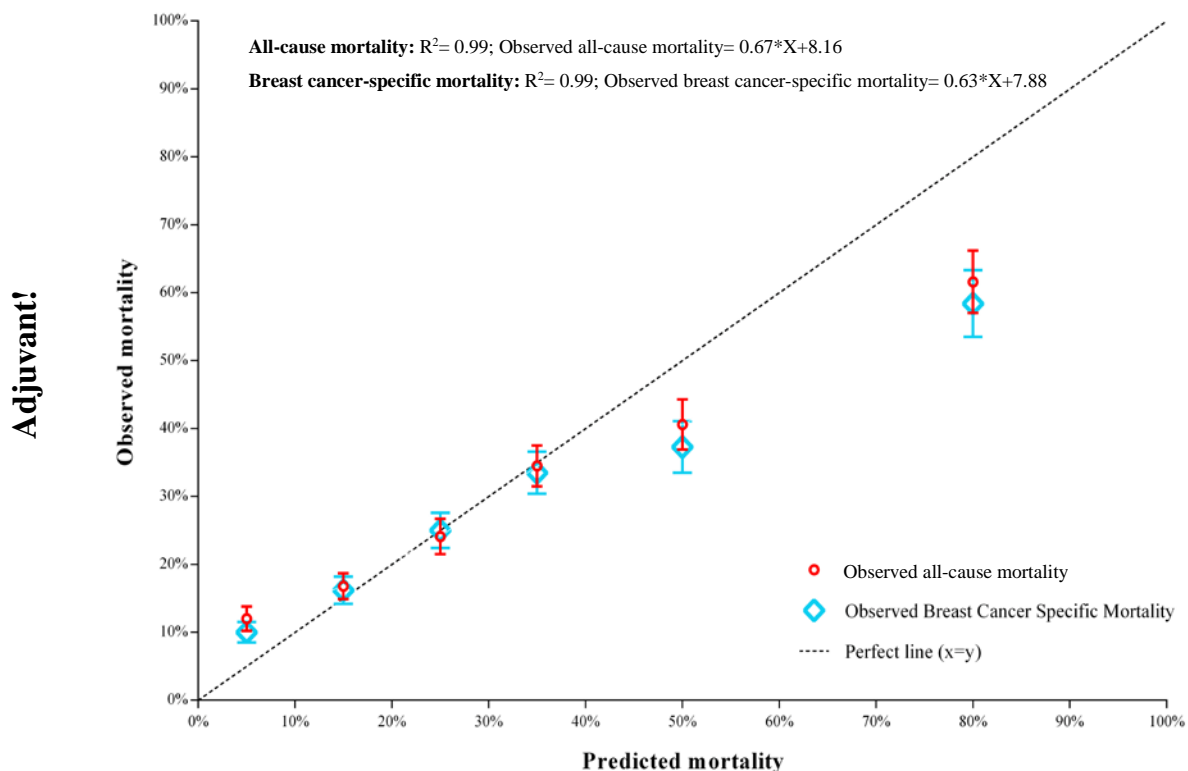
Appendix Figure 3 Overview of Adjuvant! and PREDICT's estimates of breast cancer-specific mortality by prognostic factors for patients diagnosed between 1990-2000



The grey area represents differences between +2% and -2%

For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 1.

Appendix Figure 4 Observed vs. Predicted 10-year all-cause and breast cancer-specific mortality for patients diagnosed between 1990-2000 (without updated adjuvant systemic therapy receipt data)



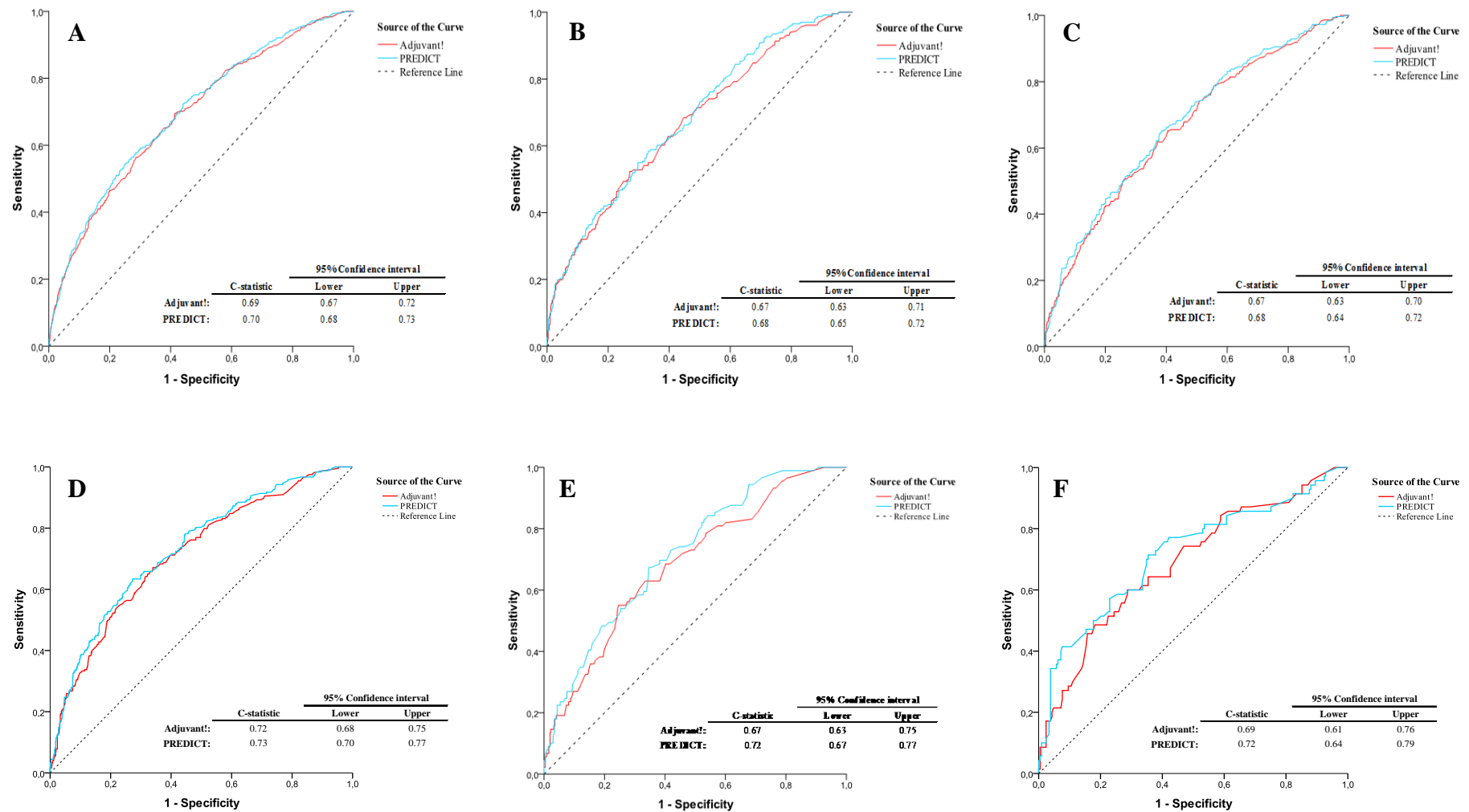
The analysis of Adjuvant!'s calibration contains N= 1,535 patients, and in the PREDICT analysis we included N= 1,076 patients.

Deciles with <100 patients were merged, namely 40% to 60% and 60% to 100%.

Error bars are standard errors (SE).

For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 2.

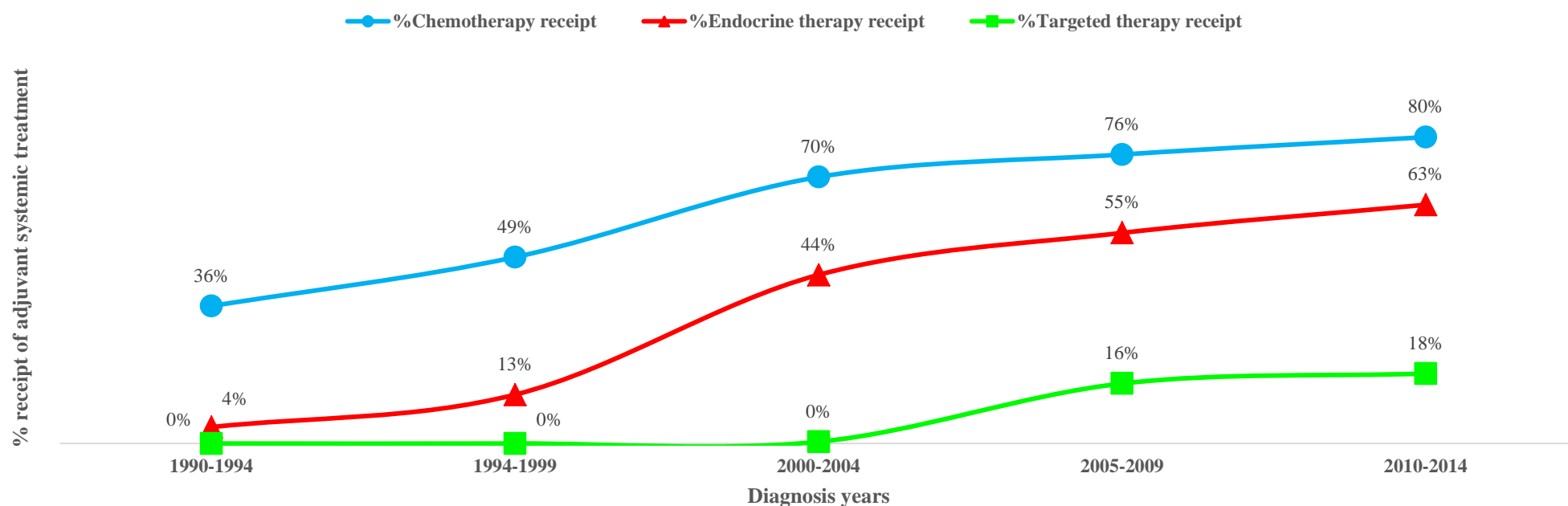
## Appendix Figure 5 Discriminatory accuracy of Adjuvant! and PREDICT in patients diagnosed between 1990-2000



All ROC-curves are based on patients diagnosed between 1990 up to 2000 included in the PREDICT analyses (N=2,073). For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 3.

**A** ROC-curve 10-year all-cause mortality (N=2,073); **B** ROC-curve 10-year all-cause mortality for patients not treated with adjuvant systemic therapy (N=1,061); **C** ROC-curve 10-year all-cause mortality for patients with unknown Her2-status (N=964); **D** ROC-curve 10-year breast cancer-specific mortality (N=1,076); **E** ROC-curve 10-year breast cancer-specific mortality for patients not treated with adjuvant systemic therapy (N= 591); **F** ROC-curve 10-year breast cancer-specific mortality for patients with unknown Her2-status (N=279).

**Appendix Figure 6 Netherlands Cancer Registry data on the trends in use of adjuvant systemic therapy among stage I-III breast cancer patients aged <50 years diagnosed between 1990-2014**

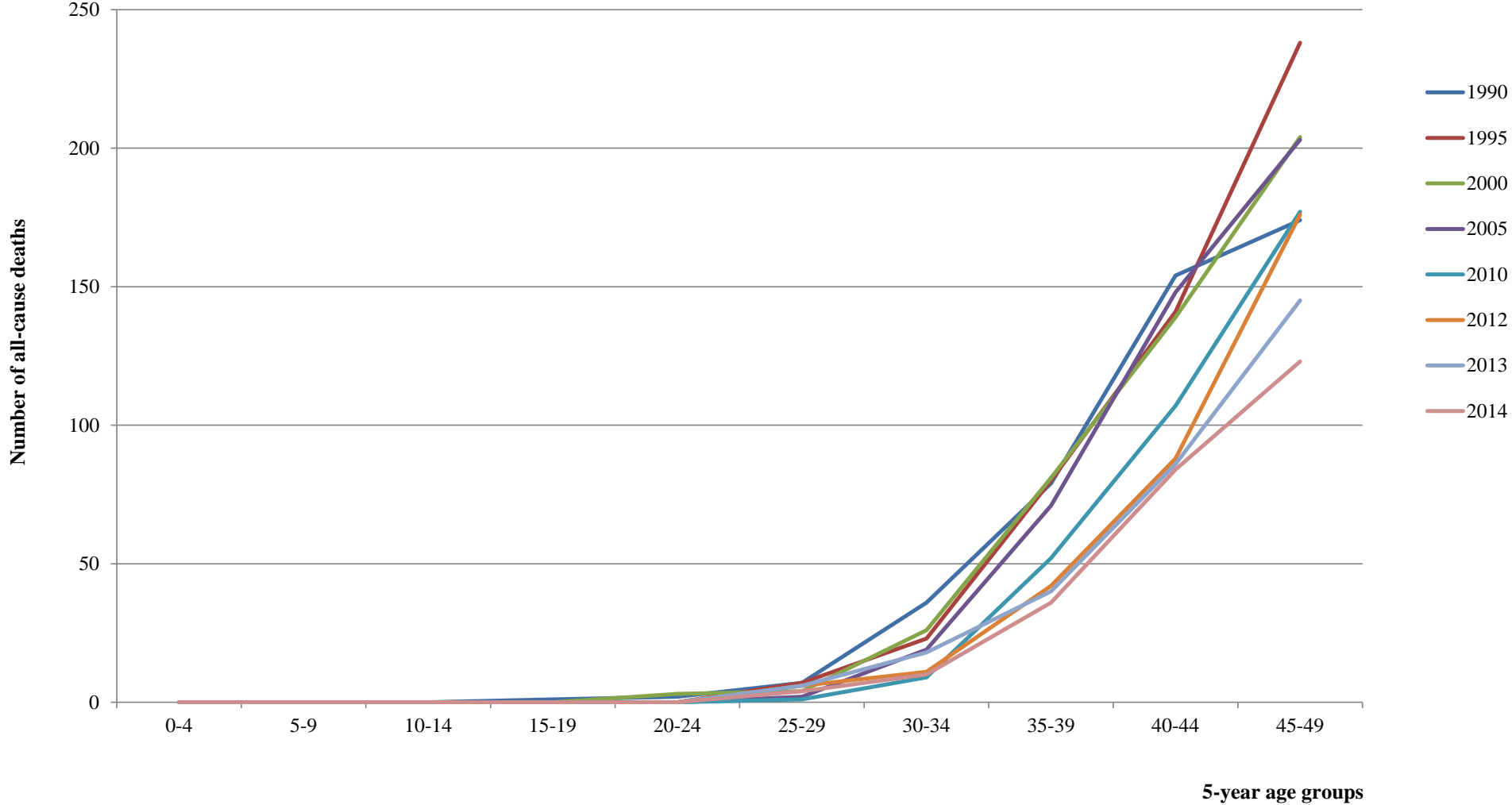


Diagnosis years	Total population	Total number of patients who received:								
		Neo-adjuvant chemotherapy	Adjuvant chemotherapy	Neo-adjuvant and adjuvant chemotherapy	Neo-adjuvant endocrine therapy	Adjuvant endocrine therapy	Neo-adjuvant and adjuvant endocrine therapy	Neo-adjuvant targeted therapy	Adjuvant targeted therapy	Neo-adjuvant and adjuvant targeted therapy
1990-1994	10.269	109	3.582	9	4	438	0	0	0	0
1994-1999	11.451	207	5.357	29	18	1.449	0	0	0	0
2000-2004	12.907	599	8.374	42	18	5.684	4	1	58	0
2005-2009	13.983	1.555	8.933	101	30	7.674	14	239	1.888	72
2010-2014	13.887	3.215	7.749	184	71	8.592	25	633	1.722	191

Source: Netherlands Cancer Registry, managed by Netherlands Comprehensive Cancer Organisation (IKNL)© March 2016



**Appendix Figure 7 Netherlands Cancer Registry data on mortality rates among breast cancer patients for the period 1990-2014**



Source: Netherlands Cancer Registry, managed by Netherlands Comprehensive Cancer Organisation (IKNL) © January 2016

<b>Appendix Table 1 Overview of subsets used in the analyses</b>				
	<b>Adjuvant! analyses</b>		<b>PREDICT analyses</b>	
	<b>Subset diagnosed between 1990-2000</b>		<b>Subset diagnosed between 1990-2000</b>	
	<i>all-cause mortality</i>	<i>breast cancer-specific mortality</i>	<i>all-cause mortality</i>	<i>breast cancer-specific mortality</i>
<b>Number of patients:</b>	2,710	1,535	2,073	1,076
<b>Mean FUP in years (SE):</b>	13.5 (0.12)	8.7 (0.07)	13.5 (0.14)	8.6 (0.08)
<b>FUP range in years:</b>	0 to 23	0 to 10	0 to 23	0 to 10
<b>Mean age in years (SE):</b>	42 (0.10)	43 (0.14)	42 (0.12)	43 (0.17)
<b>Age in years (range):</b>	23 to 50	23 to 50	23 to 50	23 to 50
<b>Number of patients per age category (%):</b>				
<35	328 (12)	189 (12)	254 (12)	132 (12)
36-40	447 (17)	255 (17)	353 (17)	183 (17)
41-45	936 (35)	538 (35)	716 (35)	379 (35)
46-50	999 (37)	553 (36)	750 (36)	382 (36)
<b>Number of patients per stage (%):</b>				
1	925 (34)	534 (35)	690 (33)	365 (34)
2	1,614 (60)	891 (58)	1,256 (61)	638 (59)
3	171 (6)	110 (7)	127 (6)	73 (7)
unknown	0	0	0	0

<b>Appendix Table 2: Distribution of prognostic characteristics by age at diagnosis for patients diagnosed between 1990-2000 (N (row%))</b>						
	≤35 years N <sub>col</sub> = 254	36-40 years N <sub>col</sub> = 353	41-45 years N <sub>col</sub> = 716	46-50 years N <sub>col</sub> = 750	N <sub>row</sub>	P*
<b>ER-status</b>						
ER +	127 (9)	225 (16)	517 (36)	581 (40)	1,450	<b>&lt;0.001</b>
ER -	127 (20)	128 (21)	199 (32)	169 (27)	623	
Unknown	0	0	0	0	0	
<b>Her2-status</b>						
Her2 -	105 (12)	155 (17)	307 (34)	331 (37)	898	0.093
Her2 +	36 (17)	41 (19)	70 (33)	64 (30)	211	
Unknown	113	157	339	355	964	
<b>Tumor grade</b>						
Grade 1	16 (6)	36 (14)	88 (34)	121 (46)	261	<b>&lt;0.001</b>
Grade 2	46 (9)	86 (17)	180 (35)	206 (40)	518	
Grade 3	123 (17)	145 (20)	246 (34)	215 (30)	729	
Unknown	69	86	202	208	565	
<b>Tumor size</b>						
0.1-1.0 cm	29 (11)	47 (19)	86 (34)	92 (36)	254	0.326
1.1-2.0 cm	85 (11)	132 (17)	279 (35)	300 (38)	796	
2.1-3.0 cm	54 (12)	85 (18)	168 (36)	162 (35)	469	
3.1-5.0 cm	64 (15)	63 (15)	142 (33)	159 (37)	428	
>5 cm	22 (18)	26 (21)	41 (33)	37 (29)	126	
Unknown	0	0	0	0	0	
<b>Positive nodes</b>						
0	122 (12)	149 (15)	372 (37)	360 (36)	1,003	<b>0.046</b>
1-3	77 (11)	134 (19)	220 (32)	258 (37)	689	
4-9	36 (13)	49 (18)	98 (36)	90 (33)	273	
>9	19 (18)	21 (19)	26 (24)	42 (39)	108	
Unknown	0	0	0	0	0	
<b>Disease stage</b>						
Stage 1	72 (10)	108 (16)	260 (38)	250 (36)	690	0.085
Stage 2	164 (13)	216 (17)	413 (33)	463 (37)	1,256	
Stage 3	18 (14)	29 (23)	43 (34)	37 (29)	127	
Unknown	0	0	0	0	0	
<b>Surgery</b>						
Breast conserving	104 (10)	192 (18)	377 (36)	380 (36)	1,053	<b>0.032</b>
Mastectomy	150 (15)	160 (16)	338 (33)	369 (36)	1,017	
Unknown	0	1	1	1	3	
<b>Adjuvant systemic treatment</b>						
None	104 (11)	144 (15)	369 (38)	349 (36)	966	<b>&lt;0.001</b>
Chemotherapy only	125 (16)	157 (20)	257 (33)	249 (32)	788	
Endocrine therapy only	3 (3)	6 (6)	26 (26)	66 (65)	101	
Both	22 (10)	46 (21)	64 (29)	86 (39)	218	
Unknown	0	0	0	0	0	

ER= estrogen receptor; Her2= Her2neu receptor  
This table is based on the patients included in the PREDICT analyses (N= 2,073). It is based on updated adjuvant systemic treatment data. In the new data patients were mainly reallocated to having received systemic treatment instead of not having done so, and having received chemotherapy instead of only endocrine therapy.  
If row percentage does not add up to 100%, this is due to the rounding at the first decimal.  
\*P-values for Chi-square tests (not including unknown).

**Appendix Table 3 Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)**

	<i>10-year all-cause mortality</i>					<i>10-year breast cancer-specific mortality</i>				
	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P
<b>Overall</b>	2073 (100)	27.2	28.3	-1.1 (-3.2 to 0.9)	0.28	1076 (100)	22.6	25.8	3.2 (0.8 to 5.6)	<b>0.007</b>
<b>Age (years)</b>										
≤ 35	254 (12)	26.6	33.2	-6.6 (-12.5 to -0.1)	<b>0.04</b>	132 (12)	33.0	30.7	-2.3 (-10.6 to 5.2)	0.52
36-40	353 (17)	25.3	30.2	-4.9 (-10.0 to 0.0)	0.06	183 (17)	31.1	27.9	-3.2 (-9.5 to 4.0)	0.35
41-45	716 (35)	27.5	27.5	0.0 (-3.2 to 3.3)	0.99	379 (35)	19.8	25.7	5.9 (1.8 to 10.0)	<b>0.003</b>
46-50	750 (36)	27.7	26.4	1.3 (-1.8 to 4.3)	0.39	382 (36)	17.5	23.1	5.6 (1.6 to 9.2)	<b>0.01</b>
<b>Her2-status</b>										
Negative	898 (43)	29.9	27.7	2.2 (-0.6 to 5.0)	0.15	628 (58)	18.3	24.5	6.2 (3.3 to 9.1)	<b>0.001</b>
Positive	211 (10)	38.9	39.6	-0.7 (-8.2 to 6.1)	0.85	169 (16)	34.3	36.8	2.5 (-4.9 to 9.4)	0.49
Unknown	964 (47)	21.9	26.3	-4.4 (-7.3 to -1.4)	<b>0.01</b>	279 (26)	25.1	22.0	-3.1 (-8.2 to 1.8)	0.22
<b>ER-status</b>										
Positive	1450 (70)	23.5	24.5	-1.0 (-3.2 to 1.1)	0.38	785 (73)	18.2	21.9	3.7 (1.0 to 6.4)	<b>0.01</b>
Negative	623 (30)	35.9	37.2	-1.3 (-5.2 to 2.3)	0.52	291 (27)	34.4	36.1	1.7 (-3.5 to 7.5)	0.54
<b>Triple negative</b>										
Not triple negative	971 (47)	28.7	28.2	0.5 (-2.1 to 3.3)	0.72	727 (68)	20.9	25.1	4.2 (1.0 to 6.9)	<b>0.01</b>
Triple negative	207 (10)	37.6	36.9	0.7 (-6.7 to 7.2)	0.84	136 (13)	33.1	34.9	1.8 (-6.7 to 9.1)	0.64
Unknown	895 (43)	23.1	26.4	-3.3 (-6.5 to -0.5)	<b>0.03</b>	213 (20)	21.6	22.0	0.4 (-5.4 to 5.9)	0.89
<b>Tumor Grade</b>										
Grade 1	261 (13)	9.1	10.1	-1.0 (-5.0 to 3.0)	0.63	176 (16)	6.3	6.9	0.6 (-3.3 to 3.8)	0.72
Grade 2	518 (25)	19.5	21.6	-2.1 (-6.0 to 1.4)	0.25	342 (32)	17.5	18.5	1.0 (-2.9 to 4.7)	0.63
Grade 3	729 (35)	44.0	41.4	2.6 (-1.1 to 6.2)	0.16	442 (41)	35.3	39.9	4.6 (-0.1 to 9.0)	<b>0.05</b>
Unknown	565 (27)	20.8	25.9	-5.1 (-8.6 to -1.2)	<b>0.01</b>	116 (11)	13.8	21.6	7.8 (1.1 to 13.9)	<b>0.02</b>

Table is based on updated adjuvant systemic treatment data.

ER= estrogen receptor; Her2= Her2neu receptor

<sup>a</sup> = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.

- = Due to the small number of cases, we were unable to calculate this value.

<sup>a</sup> P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

**Appendix Table 3 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)**

	<i>10-year all-cause mortality</i>					<i>10-year breast cancer-specific mortality</i>				
	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P
<b>Stage</b>										
Stage 1	690 (33)	11.0	14.0	-3.0 (-5.7 to -0.2)	<b>0.04</b>	365 (34)	12.9	12.3	-0.6 (-4.3 to 2.6)	0.77
Stage 2	1256 (61)	32.8	32.8	0.0 (-3.1 to 1.9)	0.62	638 (59)	25.4	30.2	4.8 (1.6 to 8.0)	<b>0.01</b>
Stage 3	127 (6)	64.9	61.2	3.7 (-4.6 to 12.7)	0.42	73 (7)	46.6	54.5	7.9 (-4.0 to 19.5)	0.17
<b>Tumor size</b>										
0.1-1.0 cm	254 (12)	8.7	12.8	-4.1 (-8.8 to 0.5)	<b>0.09</b>	155 (14)	11.0	9.8	-1.2 (-6.8 to 3.4)	0.64
1.1-2.0 cm	796 (38)	14.9	19.7	-4.8 (-7.9 to -1.9)	<b>0.001</b>	358 (33)	19.0	17.5	-1.5 (-5.8 to 2.3)	0.47
2.1-3.0 cm	469 (23)	31.0	31.7	-0.7 (-5.4 to 3.2)	0.74	261 (24)	24.1	29.4	5.3 (0.0 to 10.7)	<b>0.06</b>
3.1-5.0 cm	428 (21)	44.5	40.7	3.8 (-0.8 to 8.4)	0.11	224 (21)	29.0	36.4	7.4 (1.0 to 13.8)	0.27
>5 cm	126 (6)	68.0	58.6	9.4 (0.3 to 18.0)	<b>0.04</b>	78 (7)	38.5	52.6	14.1 (3.2 to 25.5)	<b>0.02</b>
<b>Positive nodes</b>										
0	1003 (48)	14.1	17.0	-2.9 (-5.4 to -0.5)	<b>0.02</b>	544 (51)	15.4	15.2	-0.2 (-3.5 to 2.9)	0.85
1-3	689 (33)	28.3	29.6	-1.3 (-4.9 to 1.8)	0.44	380 (35)	23.9	29.5	5.6 (0.6 to 9.6)	<b>0.02</b>
4-9	273 (13)	53.6	49.7	3.9 (-2.0 to 9.8)	0.20	112 (10)	38.4	48.5	10.1 (1.2 to 19.3)	<b>0.03</b>
>9	108 (5)	75.1	70.9	4.2 (-4.1 to 12.8)	0.36	40 (4)	62.5	69.8	7.3 (-7.5 to 23.3)	0.32
<b>Morphology</b>										
IDC	1569 (76)	27.8	29.5	-1.7 (-3.8 to 0.6)	0.15	812 (75)	24.3	27.5	3.2 (0.2 to 6.1)	<b>0.03</b>
ILC	204 (10)	21.3	25.1	-3.8 (-9.8 to 2.3)	0.23	105 (10)	21.0	20.0	-1.0 (-9.3 to 6.7)	0.81
IL/DC	109 (5)	32.4	29.5	2.9 (-6.7 to 11.2)	0.50	52 (5)	15.4	24.4	9.0 (-1.7 to 17.7)	<b>0.09</b>
Tubular carcinoma	64 (3)	13.8	10.0	3.8 (-3.0 to 8.4)	0.22	25 (2)	0.0	5.6	-	-
Mucinous carcinoma	23 (1)	31.0	24.2	6.8 (-11.1 to 19.4)	0.39	14 (1)	14.3	20.0	5.7 (-15.7 to 14.4)	0.57
Medular	46 (2)	44.6	28.8	15.8 (4.4 to 24.5)	<b>0.02</b>	25 (2)	16.0	27.4	11.4 (-4.4 to 22.6)	0.14
Comedo carcinoma	23 (1)	26.5	32.8	-6.3 (-27.2 to 12.8)	0.55	14 (1)	21.4	26.9	5.5 (-17.8 to 20.7)	0.60
Other	35 (2)	16.0	22.3	-6.3 (-23.4 to 8.8)	0.42	29 (3)	24.1	19.0	-5.1 (-21.5 to 9.6)	0.52

Table is based on updated adjuvant systemic treatment data.

ER= estrogen receptor; Her2= Her2neu receptor

<sup>a</sup> = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.

- = Due to the small number of cases, we were unable to calculate this value.

\* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

**Appendix Table 3 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)**

	<i>10-year all-cause mortality</i>					<i>10-year breast cancer-specific mortality</i>				
	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P
<b>Angiolymphatic invasion</b>										
No angiolymphatic invasion	502 (24)	26.5	24.9	1.6 (5.3 to -2.3)	0.40	336 (31)	17.0	20.2	3.2 (-1.0 to 7.1)	0.12
Angiolymphatic invasion in up to 3 vessels	278 (13)	25.9	28.6	-2.7 (-8.1 to 2.7)	0.36	68 (6)	22.1	28.6	6.5 (-4.3 to 15.8)	0.21
Extensive angiolymphatic invasion	140 (7)	36.2	40.6	-4.4 (-13.1 to 4.4)	0.32	36 (3)	47.2	47.3	0.1 (-17.6 to 16.5)	0.99
Unknown	1153 (56)	26.7	28.2	-1.5 (-4.3 to 1.0)	0.26	636 (59)	24.2	27.2	3.0 (-0.1 to 6.2)	<b>0.07</b>
<b>Type of surgery</b>										
Breast conserving surgery	1053 (51)	19.0	21.8	-2.8 (-5.5 to -0.3)	<b>0.04</b>	575 (53)	20.0	19.8	-0.2 (-3.5 to 3.3)	0.93
Mastectomy	1017 (49)	35.6	35.0	0.6 (-2.5 to 3.6)	0.70	500 (46)	25.6	32.7	7.1 (2.7 to 10.7)	<b>0.001</b>
Unknown	3 (0.1)	7.7	20.5	-	-	1 (0)	0.0	11.3	-	-
<b>Radiotherapy</b>										
No	450 (22)	22.2	24.3	-2.1 (-6.2 to 2.0)	0.30	225 (21)	20.9	23.1	2.2 (-3.4 to 7.7)	0.43
Yes	1623 (78)	28.5	29.4	-0.9 (-3.1 to 1.4)	0.45	851 (79)	23.0	26.5	3.5 (0.6 to 6.3)	<b>0.03</b>
<b>Systemic treatment</b>										
None	966 (47)	18.4	19.8	-1.4 (-3.9 to 3.9)	0.28	496 (46)	13.3	16.9	3.6 (0.4 to 6.7)	<b>0.03</b>
Chemotherapy only	788 (38)	35.5	36.8	-1.3 (-4.6 to 2.1)	0.46	377 (35)	35.0	36.1	1.1 (-3.7 to 5.7)	0.63
Endocrine therapy only	101 (5)	38.1	32.4	5.7 (-2.8 to 14.0)	0.20	62 (6)	14.5	25.9	11.4 (1.4 to 19.4)	<b>0.02</b>
Endocrine therapy and chemotherapy	218 (11)	30.0	32.9	-2.9 (-9.1 to 3.2)	0.40	141 (13)	25.5	29.2	3.7 (-3.6 to 10.8)	0.32

Table is based on updated adjuvant systemic treatment data.

ER= estrogen receptor; Her2= Her2neu receptor

<sup>a</sup> = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.

- = Due to the small number of cases, we were unable to calculate this value.

\* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

**Appendix Table 4 Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)**

	<i>10-year all-cause mortality</i>					<i>10-year breast cancer-specific mortality</i>				
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P*
<b>All patients</b>	2,710 (100)	26.7	28.7 (0.9)	-2.0 (-3.7 to -0.3)	<b>0.023</b>	1,535 (100)	24.3	23.0 (1.1)	1.3 (-0.7 to 3.4)	0.232
<b>Age (years)</b>										
≤ 35	328 (12.1)	34.4	39.3 (2.6)	-4.9 (-10.2 to 0.3)	0.066	189 (12.3)	33.1	33.5 (3.5)	-0.4 (-7.5 to 6.2)	0.908
36-40	447 (16.5)	28.0	34.0 (2.3)	-6.0 (-10.7 to -1.7)	<b>0.009</b>	255 (16.6)	26.2	30.4 (2.8)	-4.2 (-10 to 1.2)	0.136
41-45	936 (34.5)	25.1	27.0 (1.4)	-1.9 (-4.5 to 0.9)	0.182	538 (35.0)	22.9	21.5 (1.8)	1.4 (-2.1 to 4.9)	0.459
46-50	999 (36.9)	25.1	24.4 (1.4)	0.7 (-2.2 to 3.2)	0.638	553 (36.0)	21.8	17.3 (1.7)	4.5 (1.2 to 7.6)	<b>0.009</b>
<b>Her2-status</b>										
Negative	911 (33.6)	25.4	25.5 (1.4)	-0.1 (-2.7 to 2.8)	0.964	633 (41.2)	22.5	17.6 (1.5)	4.9 (1.8 to 7.8)	<b>0.002</b>
Positive	214 (7.9)	40.5	40.7 (3.4)	-0.2 (-7.2 to 6.7)	0.963	170 (11.1)	37.5	34.7 (3.7)	2.8 (-4.4 to 10.5)	0.447
Unknown	1,585 (58.5)	25.6	29.0 (1.1)	-3.4 (-5.6 to -1.2)	<b>0.004</b>	732 (47.7)	22.8	24.9 (1.6)	-2.1 (-5.3 to 0.9)	0.179
<b>ER-status</b>										
Positive	1,450 (53.5)	23.4	25.5 (1.1)	-2.1 (-4.5 to 0.0)	0.062	785 (51.1)	21.1	17.7 (1.4)	3.4 (0.6 to 6.0)	<b>0.017</b>
Negative	623 (23.0)	35.4	38.5 (2.0)	-3.1 (-7.1 to 0.5)	0.106	291 (19.0)	33.7	33.4 (2.8)	0.3 (-4.8 to 6.0)	0.915
Unknown	637 (23.5)	25.7	26.4 (1.8)	-0.7 (-4.1 to 2.6)	0.717	459 (29.9)	23.8	25.5 (2.0)	-1.7 (-5.7 to 2.2)	0.422
<b>Triple negative</b>										
Not triple negative	972 (35.9)	26.6	27.7 (1.5)	-1.1 (-4.0 to 1.8)	0.466	727 (47.4)	23.8	20.4 (1.5)	3.4 (0.5 to 6.3)	<b>0.029</b>
Triple negative	207 (7.6)	33.6	36.2 (3.3)	-2.6 (-8.9 to 3.5)	0.456	136 (8.9)	31.7	32.1 (3.9)	-0.4 (-8.6 to 7.8)	0.918
Unknown	1,639 (60.5)	25.8	28.3 (1.2)	-2.5 (-4.8 to -0.2)	0.034	672 (43.8)	23.3	24.0 (1.7)	-0.7 (-4.0 to 2.5)	0.653
<b>Tumor Grade</b>										
Grade 1	328 (12.1)	10.8	11.9 (1.8)	-1.1 (-4.6 to 2.3)	0.540	229 (14.9)	8.1	7.1 (1.7)	1.0 (-2.8 to 4.3)	0.555
Grade 2	644 (23.8)	21.9	23.1 (1.7)	-1.2 (-4.6 to 1.8)	0.465	459 (29.9)	19.2	17.7 (1.8)	1.5 (-2.0 to 5.0)	0.412
Grade 3	915 (33.8)	35.8	37.6 (1.7)	-1.8 (-5.0 to 1.5)	0.286	607 (39.5)	34.1	33.4 (2.0)	0.7 (-3.4 to 4.6)	0.746
Unknown	823 (30.4)	26.6	29.9 (1.6)	-3.3 (-6.3 to -0.1)	<b>0.040</b>	240 (15.6)	24.8	22.0 (2.7)	2.8 (-2.6 to 8.0)	0.307
<b>Stage</b>										
Stage 1	925 (34.1)	11.6	15.4 (1.2)	-3.8 (-6.1 to -1.4)	<b>0.005</b>	534 (34.8)	9.8	12.1 (1.4)	-2.3 (-4.8 to 0.3)	0.093
Stage 2	1,615 (59.6)	32.4	33.6 (1.2)	-1.2 (-3.3 to 1.3)	0.315	892 (58.1)	29.8	26.7 (1.5)	3.1 (0.0 to 5.8)	<b>0.042</b>
Stage 3	170 (6.3)	54.9	55.3 (3.9)	-0.4 (-8.1 to 7.1)	0.915	109 (7.1)	50.7	46.3 (4.7)	4.4 (-5.2 to 13.9)	0.337
<b>Tumor size</b>										
0.1-1.0 cm	363 (13.4)	10.2	14.9 (1.9)	-4.7 (-8.4 to -0.9)	<b>0.015</b>	221 (14.4)	7.0	11.0 (2.2)	-4.0 (-8.5 to -0.1)	0.061
1.1-2.0 cm	1,036 (38.2)	17.9	22.8 (1.3)	-4.9 (-7.5 to -2.4)	<b>0.002</b>	540 (35.2)	15.3	17.4 (1.6)	-2.1 (-5.3 to 1.2)	0.193
2.1-3.0 cm	582 (21.5)	33.2	33.2 (1.9)	0.0 (-3.9 to 3.7)	0.987	347 (22.6)	30.6	25.9 (2.4)	4.7 (0.2 to 9.5)	0.053
3.1-5.0 cm	560 (20.7)	38.3	37.9 (2.0)	0.4 (-3.4 to 4.3)	0.823	314 (20.5)	35.0	31.8 (2.7)	3.2 (-2.3 to 8.2)	0.238
>5 cm	169 (6.2)	55.3	49.1 (4.0)	6.2 (-2.1 to 13.7)	0.121	113 (7.4)	52.4	40.0 (4.8)	12.4 (2.9 to 21.5)	<b>0.014</b>

For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable.

ER= estrogen receptor; Her2= Her2neu receptor

- = Due to the small number of cases, we were unable to calculate this value.

\* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

**Appendix Table 4 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)**

	<i>10-year all-cause mortality</i>					<i>10-year breast cancer-specific mortality</i>				
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
<b>Positive nodes</b>										
0	1,348 (49.7)	16.0	19.4 (1.1)	-3.4 (-5.6 to -1.3)	<b>0.002</b>	544 (26.2)	15.6	15.1 (1.5)	0.5 (-2.4 to 3.4)	0.748
1-3	869 (32.1)	28.7	30.8 (1.6)	-2.1 (-5.3 to 0.9)	0.171	380 (18.3)	31.9	22.7 (2.1)	9.2 (4.8 to 13.3)	<b>0.001</b>
4-9	347 (12.8)	46.4	45.5 (2.7)	0.9 (-4.6 to 6.3)	0.740	112 (5.4)	55.1	37.8 (4.7)	17.3 (7.7 to 25.6)	<b>0.001</b>
>9	146 (5.4)	67.0	61.6 (4.1)	5.4 (-3.4 to 13.3)	0.189	40 (1.9)	77.5	62.5 (7.8)	15.0 (0.1 to 30.3)	0.066
<b>Morphology</b>										
IDC	2,038 (75.2)	28.9	30.7 (1.0)	-1.8 (-3.9 to 0.2)	0.081	812 (39.2)	29.7	23.6 (1.5)	6.1 (3.2 to 9.0)	<b>0.003</b>
ILC	272 (10)	25.0	26.5 (2.6)	-1.5 (-6.7 to 3.4)	0.584	105 (5.1)	22.1	19.4 (4.0)	2.7 (-5.2 to 10.4)	0.477
IL/DC	129 (4.8)	25.8	25.6 (3.8)	0.2 (-7.2 to 7.5)	0.960	52 (2.5)	26.9	15.4 (5.0)	11.5 (1.4 to 21.1)	<b>0.048</b>
Tubular carcinoma	78 (2.9)	10.3	6.4 (2.8)	3.9 (-2.1 to 8.9)	0.196	25 (1.2)	5.7	-	-	-
Mucinous carcinoma	31 (1.1)	19.9	16.1 (6.6)	3.8 (-10.1 to 15.4)	0.581	14 (0.7)	20.0	14.3 (9.3)	5.7 (-20.0 to 14.4)	0.566
Medular	58 (2.1)	27.4	12.1 (4.3)	15.3 (6.6 to 23.3)	<b>0.016</b>	25 (1.2)	27.8	16.0 (7.4)	11.8 (-5.5 to 23.6)	0.125
Comedo carcinoma	40 (1.5)	26.7	37.5 (7.5)	-10.8 (-25.7 to 3.4)	0.161	14 (0.7)	26.9	21.4 (10.8)	5.5 (-19.7 to 20.7)	0.624
Other	49 (1.8)	21.5	26.5 (6.3)	-5.0 (-17.4 to 7.5)	0.444	29 (1.4)	19.3	24.1 (8.1)	-4.8 (-22.4 to 10.6)	0.541
Unknown	15 (0.6)	24.9	13.3	-	-	0	-	-	-	-
<b>Angiolymphatic invasion</b>										
No angiolymphatic invasion	557 (20.6)	22.4	23.0 (1.8)	-0.6 (-4.4 to 2.5)	0.747	336 (16.2)	20.6	16.0 (2.0)	4.6 (0.6 to 8.7)	<b>0.030</b>
Angiolymphatic invasion in up to 3 vessels	355 (13.1)	26.7	28.7 (2.5)	-2.0 (-7.0 to 2.6)	0.404	68 (3.3)	29.0	22.1 (4.9)	6.9 (-3.4 to 16.5)	0.165
Extensive angiolymphatic invasion	159 (5.9)	36.0	45.3 (3.9)	-9.3 (-16.9 to -1.5)	<b>0.013</b>	36 (1.7)	48.7	45.7 (8.7)	3.0 (-13.8 to 19.4)	0.729
Unknown	1,639 (60.5)	27.3	29.0 (1.1)	-1.7 (-3.9 to 0.5)	0.127	636 (30.7)	30.2	23.7 (1.7)	6.5 (3.3 to 9.8)	<b>0.001</b>
<b>Type of surgery</b>										
Breast conserving surgery	1,365 (50.4)	20.6	23.7 (1.1)	-3.1 (-5.3 to -0.8)	<b>0.008</b>	575 (27.7)	20.7	19.6 (1.6)	1.1 (-2.2 to 4.3)	0.503
Mastectomy	1,340 (49.4)	33.0	33.9 (1.3)	-0.9 (-3.5 to 1.8)	0.494	500 (24.1)	35.9	24.7 (2.0)	11.2 (7.1 to 14.9)	<b>0.001</b>
Unknown	5 (0.2)	18.6	20.0	-	-	1 (0.1)	-	-	-	-
<b>Radiotherapy</b>										
No	614 (22.7)	23.0	25.2 (1.7)	-2.2 (-5.6 to 1.2)	0.188	225 (10.9)	24.0	19.8 (2.6)	4.2 (-1.3 to 9.0)	0.120
Yes	2,096 (77.3)	27.8	29.7 (1.0)	-1.9 (-3.9 to 0.0)	0.059	851 (41.1)	28.8	22.5 (1.5)	6.3 (3.6 to 9.4)	<b>0.001</b>
<b>Systemic treatment</b>										
None	1,395 (51.5)	20.3	20.7 (1.1)	-0.4 (-2.4 to 1.7)	0.693	591 (28.5)	21.7	14.6 (1.5)	7.1 (4.3 to 9.9)	<b>0.001</b>
Chemotherapy only	935 (34.5)	33.5	39.5 (1.6)	-6.0 (-9.2 to -3.0)	<b>0.001</b>	317 (15.3)	35.7	35.6 (2.7)	0.1 (-5.6 to 5.2)	0.965
Endocrine therapy only	210 (7.7)	33.6	27.1 (3.0)	6.5 (0.6 to 12.5)	<b>0.036</b>	149 (7.2)	35.0	19.6 (3.2)	15.4 (8.8 to 21.5)	<b>0.001</b>
Endocrine therapy and chemotherapy	170 (6.3)	33.4	37.1 (3.7)	-3.7 (-11.3 to 3.6)	0.310	19 (0.9)	27.2	42.1 (11.7)	-14.9 (-39.5 to 6.1)	0.239

For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable.

ER= estrogen receptor; Her2= Her2neu receptor

- = Due to the small number of cases, we were unable to calculate this value.

\* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.