

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplemental material to Cardoso, van 't Veer, Bogaerts et al

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2 Reason registered/screened but not enrolled

Table S 1: Reason enrollment was not successful (screening failure)

Reason for screening failure	All screening failures (N=4595) N (%)
MammaPrint not feasible (mostly <50%/<30% tumor cells)	1182 (26%)
Patient/investigator decision	899 (20%)
Ineligible : LN status	772 (17%)
Inadequate/absent sample	768 (17%)
Ineligible: other	447 (10%)
Unknown or other	527 (11%)

3 Risk corrections post enrollment

Table S 2: Risk corrections post enrollment

C-risk/G-risk at enrollment	Corrected C-risk/G-risk					Total (N=6693) N (%)
	C-low/G-? (N=1) N (%)	C-low/G-low (N=2744) N (%)	C-low/G-high (N=592) N (%)	C-high/G-low (N=1550) N (%)	C-high/G-high (N=1806) N (%)	
	C-low/G-low	1 (100.0)	2600 (94.8)	3 (0.5)	30 (1.9)	
C-low/G-high	0 (0.0)	95 (3.5)	580 (98.0)	0 (0.0)	15 (0.8)	690 (10.3)
C-high/G-low	0 (0.0)	44 (1.6)	0 (0.0)	1450 (93.5)	3 (0.2)	1497 (22.4)
C-high/G-high	0 (0.0)	5 (0.2)	9 (1.5)	70 (4.5)	1788 (99.0)	1872 (28.0)

Legend: For 275 patients (4%) the C and/or G risk supplied at enrollment was corrected later during the trial as shown in the table.

Table S 3: Reason for clinical risk change

Reason for clinical risk assessment change	Total (N=103) N (%)
change in tumor size	21 (20.2)
change in tumor grade	19 (18.3)
change in ER status	4 (3.8)
change in HER2 status	12 (11.5)
change in Nodal status	24 (23.1)
clinical risk of LN2/3+ was miscalculated as LN 4/9+	6 (5.8)
clinical risk of 12% was miscalculated as low risk	6 (5.8)
other/combination	11 (10.6)

Legend: For 103 patients the clinical risk status was corrected post-enrollment based on updated patient and tumor characteristics that were received from the site during the study as shown in the table. The patient with unknown genomic risk post enrollment (C-low/G-?) is classified under C-low/G-low (risk per enrollment) in the analyses per corrected risk. For 38 of those 103 patients the clinical risk assessment supplied at time of enrollment lead to an inappropriate treatment strategy allocation. By 'inappropriate' we mean a treatment strategy ('CT' versus 'no CT') that would not be considered as an option for the patient per MINDACT protocol. For example, for patients belonging to the discordant risk groups, both 'CT' and 'no CT' are considered appropriate treatment strategies while for the C-low/G-low group 'CT' would be an inappropriate treatment strategy. Out of these 38 patients, 21 have received an inappropriate treatment as defined in MINDACT: 3 patients were under-treated (did not receive CT when they should have) and 18 were over-treated (received CT when they should not have, as per protocol definition); 5 of the over-treated patients had a change in both clinical and genomic risk.

Table S 4: Reason for genomic risk change

Reason for clinical risk assessment change	Total (N=177) N (%)
Change in RNA extraction solution	153 (86.4)
Sample swap	5 (2.8)
other/combination	19 (10.7)

Legend: For 177 patients the genomic risk status was corrected post-enrollment for reasons tabulated above.

For 56 of these 177 patients, the genomic risk result supplied at time of enrollment lead to an inappropriate treatment strategy allocation. Among these 56 patients, 37 received an inappropriate treatment strategy, as per protocol definition: 2 patients were under-treated (did not receive CT when they should have) and 35 were over-treated (received CT when they should not have); 5 of the over-treated patients had a change in both clinical and genomic risk.

Table S 5: Sensitivity analysis excluding period of shift in risk due to change in RNA extraction solution

PTS population (excluding G-risk shift period): C-high/G-low – no CT					
	Allocated Treatment strategy	Patients (N)	Observed Events (O)	% at 5 Year(s) (95% CI)	Standard error of the 5 year rate
DMFS	no CT	549	33	94.0 (91.5, 95.8)	0.0109

PPS population (excluding G-risk shift period): C-high/G-low						
	Allocated Treatment strategy	Patients (N)	Observed Events (O)	% at 5 Year(s) (95% CI)	Hazard ratio * (95% CI)	p-value **
DFS	CT	503	32	93.3 (90.3, 95.4)	0.57 (0.37,0.87)	0.009
	no CT	542	61	88.8 (85.7, 91.3)	1.00	
DMFS	CT	503	18	96.5 (94.1, 97.9)	0.60 (0.34,1.06)	0.080
	no CT	542	33	94.0 (91.4, 95.8)	1.00	
OS	CT	503	8	98.8 (97.1, 99.5)	0.54 (0.23,1.26)	0.154
	no CT	542	17	97.0 (94.9, 98.2)	1.00	

PPS population (excluding G-risk shift period): C-low/G-high						
	Allocated Treatment strategy	Patients (N)	Observed Events (O)	% at 5 Year(s) (95% CI)	Hazard ratio * (95% CI)	p-value **
DFS	CT	183	14	92.7 (86.8, 96.0)	0.69 (0.34,1.39)	0.297
	no CT	198	20	90.3 (84.6, 93.9)	1.00	
DMFS	CT	183	9	96.3 (91.8, 98.3)	0.86 (0.35,2.14)	0.749
	no CT	198	11	94.1 (89.2, 96.9)	1.00	
OS	CT	183	3	98.7 (94.7, 99.7)	0.45 (0.11,1.85)	0.267
	no CT	198	7	96.7 (92.7, 98.5)	1.00	

Legend: Because of the temporary shift in the 70-gene risk (from the 24th of May 2009 until the 30th of January 2010) all risk groups as enrolled are somewhat biased due to incorrect risk assessment in the full period (from end of May 2009 to January 2010). Therefore 2 additional patient populations (sensitivity analysis) were defined in the

SAP: one for the analyses of CT vs no CT in the discordant groups (PPS) and one for the primary test (PTS). These populations correspond to the PP1 and PT populations respectively, but exclude all patients enrolled during this G-risk shift period.

* Hazard ratios were calculated with the use of a Cox model after adjustment for the factors used in stratification for randomization assignments.

** values were calculated by means of the Wald test in the adjusted Cox Model.

4 Outcome in the 4 risk groups

Table S 6: Outcome in terms of DMFS, DFS and OS for the 4 risk groups (per corrected risk)

	Corrected Risk	Patients	Observed Events	% at 5 Year(s) (95% CI)
DMFS	C-low/G-low	2745	77	97.6 (96.9, 98.1)
	C-low/G-high	592	32	94.8 (92.4, 96.4)
	C-high/G-low	1550	82	95.1 (93.8, 96.2)
	C-high/G-high	1806	171	90.6 (89.0, 92.0)
DFS	C-low/G-low	2745	211	92.8 (91.7, 93.7)
	C-low/G-high	592	58	90.3 (87.3, 92.6)
	C-high/G-low	1550	137	91.4 (89.7, 92.8)
	C-high/G-high	1806	266	85.3 (83.4, 87.0)
OS	C-low/G-low	2745	47	98.4 (97.8, 98.9)
	C-low/G-high	592	19	97.2 (95.5, 98.3)
	C-high/G-low	1550	39	97.6 (96.6, 98.3)
	C-high/G-high	1806	103	94.7 (93.4, 95.7)

	Type of first event*	
DMFS	distant metastasis	266 (73.5)
	death	96 (26.5)
DFS	distant metastasis	242 (36.0)
	Loco-regional recurrence	110 (16.4)
	2nd primary cancer	282 (42.0)
	death	38 (5.7)

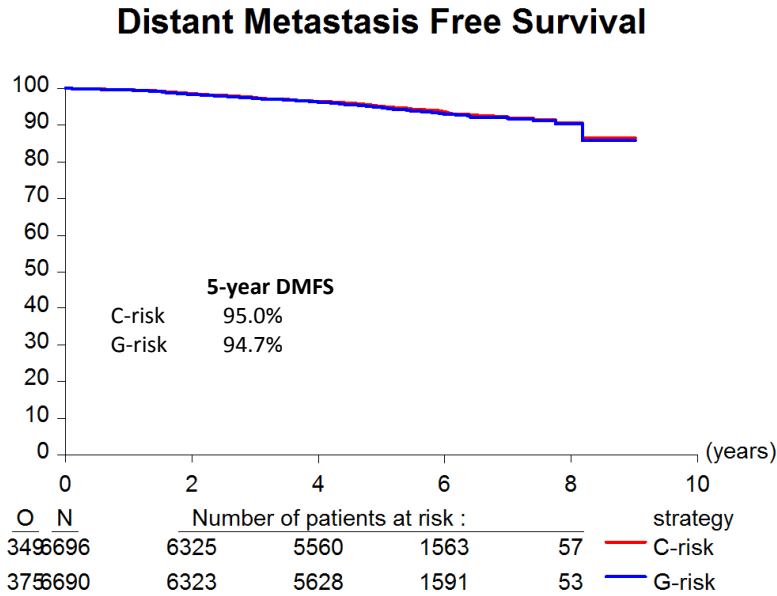
* Patients who experience multiple events at the same time (within a 1 month window), are classified into the first applicable category according to the following priority list:

1. distant metastases
2. locoregional recurrence
3. new 2nd primary cancer
4. death (due to any cause)

Legend: This figure reports the outcome in terms of DMFS, DFS and OS for the 4 risk groups C-low/G-low, C-low/G-high, C-high/G-low and C-high/G-high. The analysis includes all enrolled patients and the risk groups are based on corrected risk (Figure 1B).

5 Distant Metastasis Free Survival according to the genomic and clinical risk treatment strategy

Figure S 1: DMFS according to the genomic and clinical risk treatment strategy

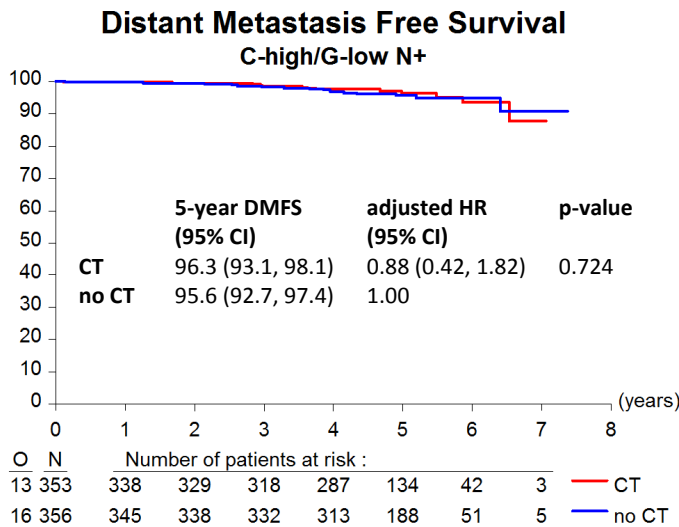
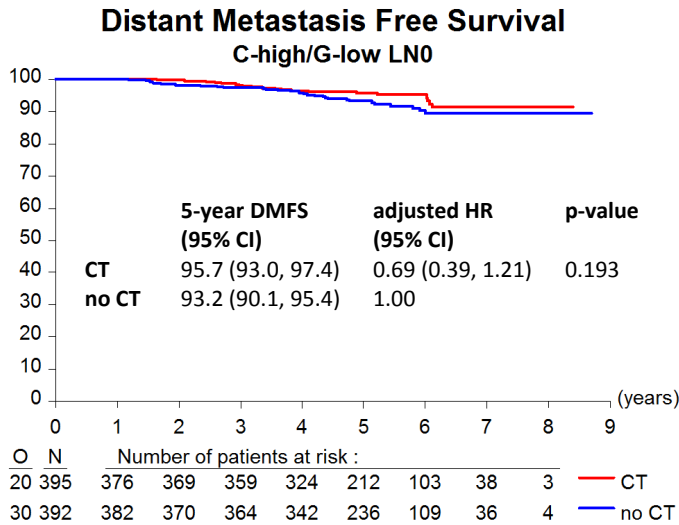


Legend: This analysis estimates the outcome if all patients were treated according to C-risk or G-risk respectively. Using risk at time of enrollment, the C-risk strategy group consists of the groups C-low/G-low, C-low/G-high randomized to 'no CT', C-high/G-low randomized to 'CT' and C-high/G-high. The G-risk strategy consists of C-low/G-low, C-low/G-high randomized to 'CT', C-high/G-low randomized to 'no CT' and C-high/G-high. To have an unbiased estimate, the discordant patients (who were randomized) are doubly weighted, because they are underrepresented by a factor 2 in the resulting sample. Therefore comparison by means of classical statistical inference is incorrect and only the estimates of the 5-year DMFS are shown.

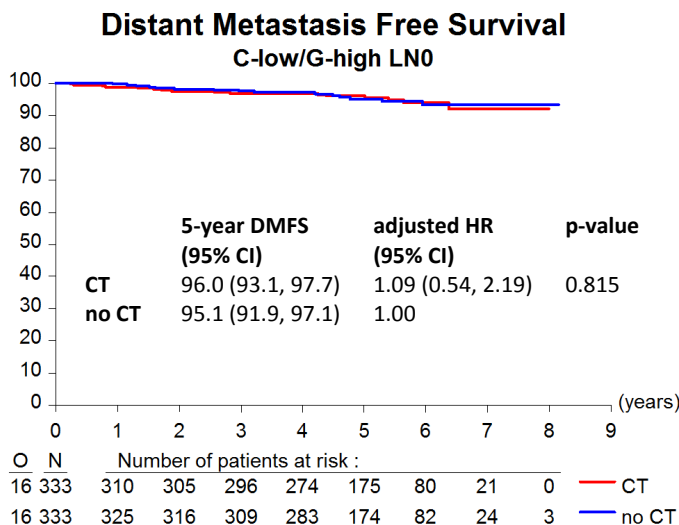
6 DMFS for CT versus no CT in the two discordant risk groups (ITT1 population), by nodal status

Figure S 2: DMFS CT versus no CT in the two discordant risk groups (ITT1 population) by nodal status

A. C-high/G-low discordant risk group



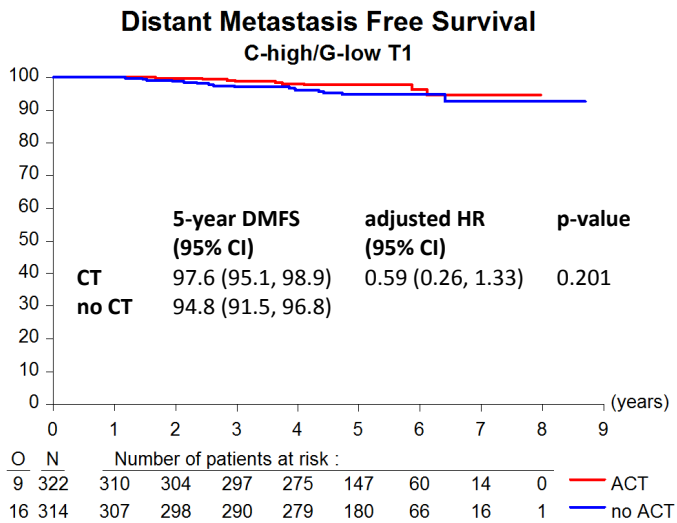
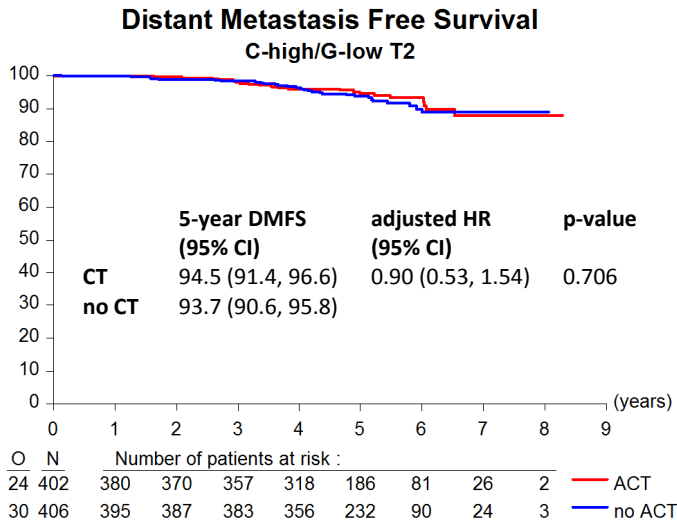
B. C-low/G-high discordant risk group



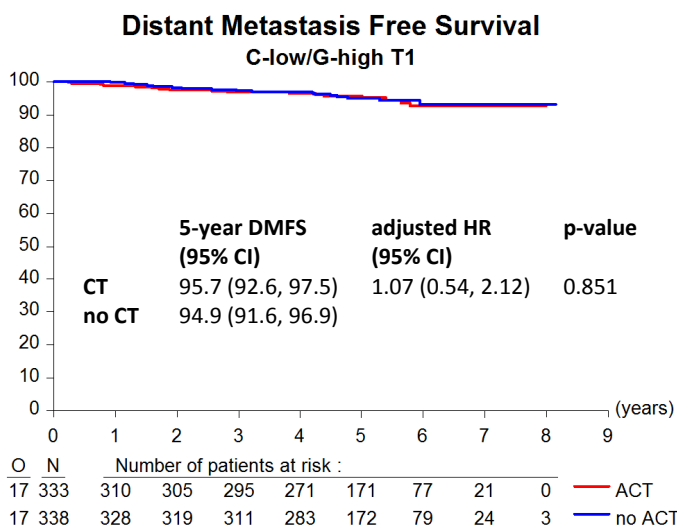
Of note: the group of node-positive patients in the C- low/G-high group is too small to be analyzed

7 DMFS for CT versus no CT in the two discordant risk groups (ITT1 population), by tumor size

Figure S 3: DMFS CT versus no CT in the two discordant risk groups (ITT1 population) by tumor status
A. C-high/G-low discordant risk group



B. C-low/G-high discordant risk group



Of note: the group of T2 patients in the C- low/G-high group is too small to be analyzed

8 Analyses within the subgroup of HR+/HER2-/LN0 patients

Table S 7: Corrected risk in the subgroup of HR+/HER2-/LN0 patients

HR+/HER2-/LN0- subgroup	
Corrected risk (clinical/genomic)	Total (N=4225) N (%)
C-low/G-low	2464 (58.3)
C-low/G-high	452 (10.7)
C-high/G-low	716 (16.9)
C-high/G-high	593 (14.0)

Legend: The HR+/HER2-/LN0 subgroup consists out of 4225 patients (63% of the AP population). Among the 4425 HR+/HER2-/LN0 patients, 3180 (75%) have a low genomic risk.

Table S 8: Outcome per corrected risk in the subgroup of HR+/HER2-/LN0 patients

HR+/HER2-/LN0 subgroup				
	Corrected risk	Patients (N)	Observed Events (O)	% at 5 Years (95% CI)
DFS	C-low/G-low	2464	193	92.7 (91.5, 93.7)
	C-low/G-high	452	43	90.6 (87.2, 93.2)
	C-high/G-low	716	67	91.5 (89.1, 93.4)
	C-high/G-high	593	79	86.4 (83.0, 89.1)
DMFS	C-low/G-low	2464	68	97.6 (96.9, 98.2)
	C-low/G-high	452	26	94.3 (91.4, 96.3)
	C-high/G-low	716	44	94.9 (92.8, 96.3)
	C-high/G-high	593	56	90.9 (88.0, 93.2)
OS	C-low/G-low	2464	41	98.5 (97.8, 98.9)
	C-low/G-high	452	16	97.1 (94.9, 98.4)
	C-high/G-low	716	22	97.0 (95.3, 98.1)
	C-high/G-high	593	30	95.5 (93.4, 96.9)
DMFI*	C-low/G-low	2464	43	98.4 (97.8, 98.9)
	C-low/G-high	452	16	96.2 (93.7, 97.8)
	C-high/G-low	716	35	96.3 (94.6, 97.5)
	C-high/G-high	593	48	91.8 (89.0, 93.9)

* See section 10 for the definition of distant metastasis free interval (DMFI).

Table S 9: Outcome by genomic risk when following genomic treatment strategy (G-low versus G-high), in the subgroup of HR+/HER2-/LN0 patients

HR+/HER2-/LN0 subgroup				
	Genomic risk at enrollment	Allocated Treatment strategy		% at 5 Years
DFS	Genomic Low	Follow g-risk	no ACT	92.0
	Genomic High	Follow g-risk	ACT	89.0
DFMS	Genomic Low	Follow g-risk	no ACT	96.7
	Genomic High	Follow g-risk	ACT	93.0
OS	Genomic Low	Follow g-risk	no ACT	97.8
	Genomic High	Follow g-risk	ACT	96.1
DMFI*	Genomic Low	Follow g-risk	no ACT	97.8
	Genomic High	Follow g-risk	ACT	94.6

* See section 10 for the definition of distant metastasis free interval (DMFI).

Legend: This analysis estimates the outcome for G-low patients and G-high patients, if all patients' chemotherapy decision would be decided by G risk (thus no chemo for G-low and chemo for G-high). To do this, all patients whose treatment allocation was consistent with such strategy are selected (so excluding the discordant ones who were randomized the other way). This analysis is similar to the one in Figure S1, but now reporting only for genomic risk, stratified by G-low versus G-high. To have an unbiased estimate, the discordant ones who were randomized into the strategy are doubly weighted, because they are underrepresented by a factor 2 in the resulting sample. No statistical inference between the two groups will be done (since randomized patients allocated to follow G-risk are doubly weighted), but the efficacy in both groups will be assessed by means of the 5-year estimate of DFS, DMFS, OS and DMFI.

Figure S 4 DMFS by genomic risk when following genomic treatment strategy (G-low versus G-high), in the subgroup of HR+/HER2-/LN0 patients

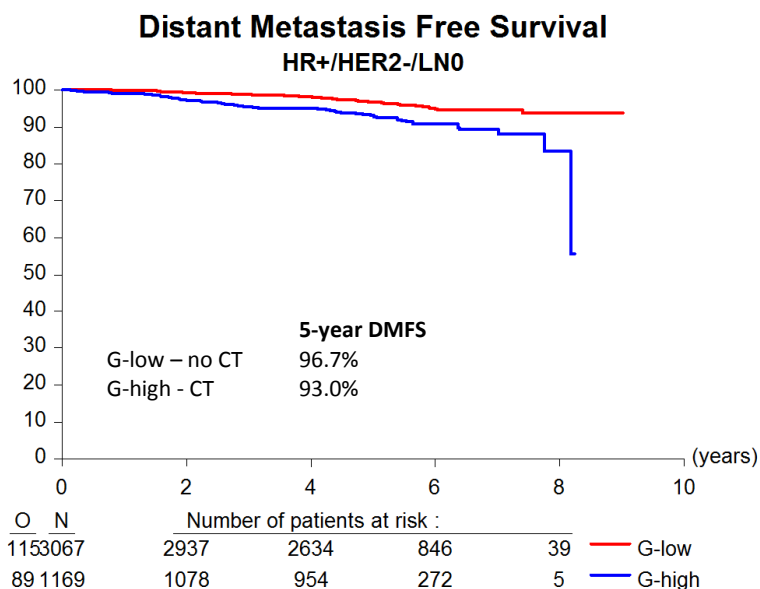
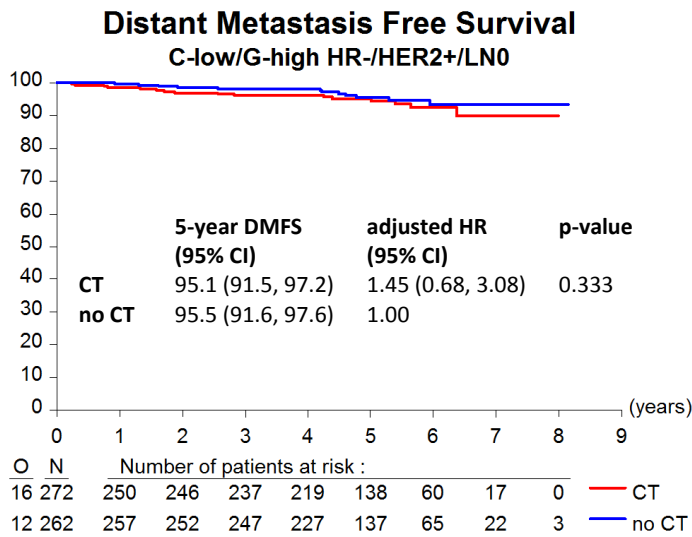
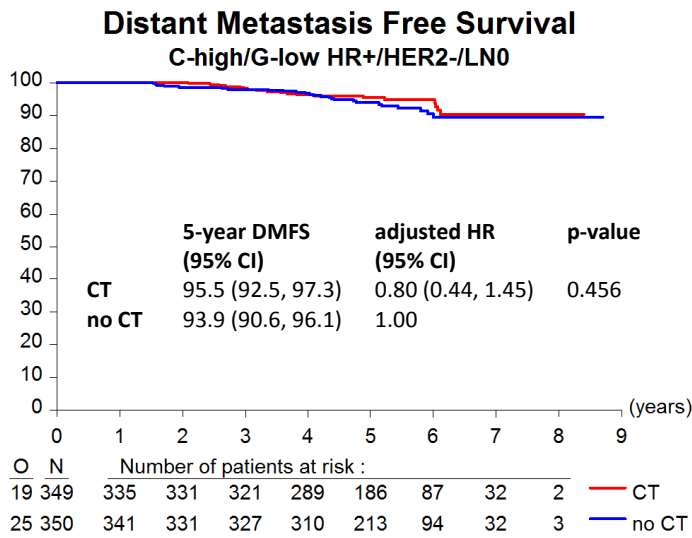


Figure S 5: DMFS for CT versus no CT in the two discordant risk groups (ITT1 population), in the HR+/HER2-/LN0 subgroup



9 Multivariate analysis

Table S 10: Multivariate analysis for DMFS in all enrolled patients

Final model for DMFS (After backward selection) (N=6643)						
Factor	Levels	Interactions with chemo	N		Hazard Ratio (95% CI)	P-value
C-risk	low		3325		1.00	0.026
	high		3318		1.49 (1.05, 2.13)	
G-risk	low		4273		1.00	<0.001
	high		2370		2.41 (1.79, 3.26)	
LN status	LN-		5253		1.00	0.063
	LN+		1390		1.28 (0.99,1.67)	
T status	≤ 1 cm		915		1.00	<0.001
	1-2 cm		3853		1.18 (0.78, 1.79)	
	2-5 cm		1798		1.92 (1.20, 3.06)	
	> 5cm		77		0.32 (0.04, 2.39)	
CT and HER2 status interaction	HER2 negative	No CT	5998	3654	1.00	CT effect: <0.001 HER2 effect: 0.967 Interaction effect between HER2 and CT: 0.012
		CT		2344	0.56 (0.40, 0.78)	
	HER2 positive	No CT	645	176	1.00	
		CT		469	0.24 (0.13,0.49)	
HR status	negative		1436		1.00	0.114
	positive		5207		0.82 (0.63, 1.05)	
grade	1		1487		1.00	0.060
	2		3627		1.49 (1.04, 2.13)	
	3		1529		1.68 (1.08, 2.63)	
surgery	Mastectomy		1205		1.00	0.015
	Breast conserving surgery		5438		0.74 (0.58, 0.94)	

Legend: The focus of this analysis is on determining the extent to which 70-gene signature risk assessment may or may not replace other risk factors. Because key prognostic factors were used to decide on chemotherapy, chemotherapy (no CT, CT) will be included in all models below. In the population of all enrollment patients DMFS will be subjected to a full multivariate analysis, using the following conventions:

All variables listed below will be put into a multivariate Cox proportional hazards model, together with chemotherapy and chemotherapy-variable interactions, and the final model will be built using backward selection (until all $p < 0.05$), while keeping chemotherapy and the factors to be retained (as listed below) in the model at all times. Variables will be included or excluded with their full categorization without regrouping or selection of categories.

The variables to be considered, and their categories, are:

- Age (<35, 35-49, 50-70)
- Baseline WHO performance status (WHO 0, WHO >0)

- Menopausal status
- Type of surgery (breast conserving surgery, radical mastectomy)
- Type of node evaluation (SNB, full axillary clearance)

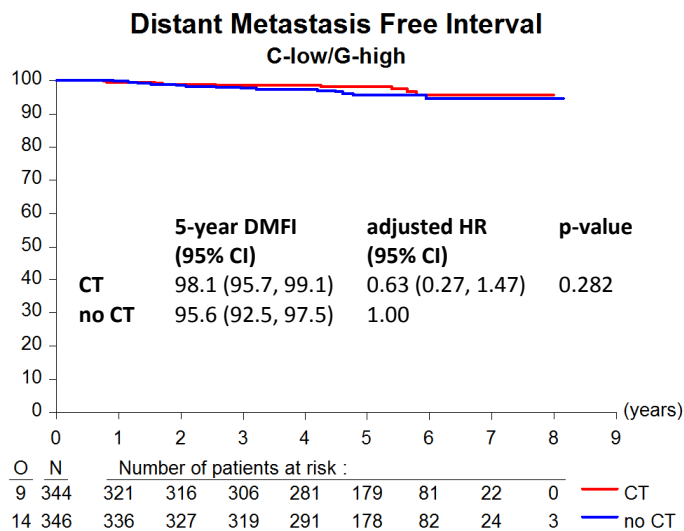
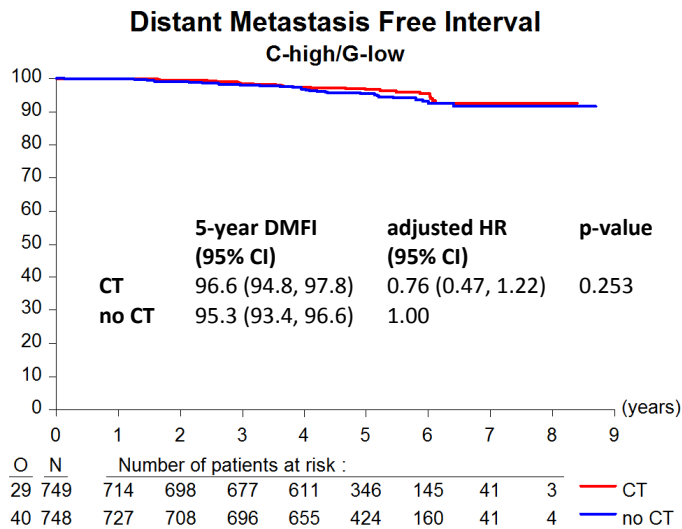
The below variables will be retained in all models:

- Tumor size (0-1 cm, >1-2 cm, >2-5 cm, >5 cm)
- Differentiation (grade I, grade II, grade III)
- Nodal involvement (yes, no)
- HER-2 status (positive, negative)
- ER-PgR status (Positive (ER and/or PgR), Negative (both))
- Clinical-pathological risk assessment (C-risk) (low, high)
- 70-gene signature risk assessment (G-risk) (low, high)

The central pathology results for ER, PgR, HER2 and grade will be used when available (local pathology will be used otherwise). Patients with a missing value for any of the above factors are removed from the multivariate model when this model includes that factor.

10 Distant Metastasis Free Interval

Figure S 6: DMFI for CT versus no CT in the two discordant risk groups (ITT1 population)



Legend: For the endpoint of distant metastasis free interval (DMFI) only distant metastatic recurrences and deaths due to breast cancer progression or treatment toxicity will be considered events. Patients with unknown cause of death are also considered to have an event for DMFI. Patient with another cause of death (cardiovascular disease, other chronic disease, second primary cancer or other) are censored on their death date. If the patient is alive without an event, the censoring date will be the last examination date. Patients ineligible due to M1 status at baseline are censored at time 0 (1 patient).

11 Compliance to randomized treatment

Table S 11: Compliance to randomized treatment as assessed by medical review

	C-low/G-low (N=2745)	C-low/G-high (N=592)	C-high/G-low (N=1550)	C-high/G-high (N=1806)	Total (N=6693)
	N (%)	N(%)	N(%)	N (%)	N (%)
Treatment non-compliance					
no issue	2627 (95.7)	482 (81.4)	1244 (80.3)	1707 (94.5)	6059 (90.5)
Treatment allocation = CT but no CT given	0 (0.0)	58 (9.8) *	115 (7.4) **	71 (3.9)	244 (3.6)
Treatment allocation = no CT but CT given	37 (1.3)	36 (6.1) *	83 (5.4) **	0 (0.0)	156 (2.3)
Unknown whether CT given	3 (0.1)	4 (0.7)	9 (0.6)	19 (1.1)	35 (0.5)
Other	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)
Risk change – compliance not defined	78 (2.8)	12 (2.0)	99 (6.4)	9 (0.5)	198 (3.0)
Reason Treatment allocation = CT but no CT given		N=58	N=115	N=71	N=244
patient refusal		52 (89.7)	95 (82.6)	64 (90.1)	211 (86.5)
PI decision		4 (6.9)	13 (11.3)	2 (2.8)	19 (7.8)
patient refusal + PI decision		0 (0.0)	3 (2.6)	1 (1.4)	4 (1.6)
ineligible		1 (1.7)	0 (0.0)	2 (1.8)	3 (1.2)
Other		1 (1.7)	4 (4.3)	2 (1.8)	7 (2.9)
Reason Treatment allocation = no CT but CT given	N=37	N=36	N=83		N=156
patient refusal	19 (51.4)	14 (38.9)	45 (54.2)		78 (50.0)
PI decision	13 (35.1)	19 (52.8)	26 (31.3)		58 (37.2)
patient refusal + PI decision	1 (2.7)	1 (2.8)	3 (3.6)		5 (3.2)
Missing	4 (10.8)	2 (5.6)	9 (10.8)		15 (9.6)

* 592 patients had corrected C-low/G-high risk.

Among those 592, 296 were allocated to CT at time of registration of which 58 were non-compliant (19.6%).

Among those 592, 296 were allocated to no CT at time of registration of which 36 were non-compliant (12.2%).

** 1550 patients had corrected C-high/G-low risk.

Among those 1550, 793 were allocated to CT at time of registration of which 115 were non-compliant (14.5%).

Among those 1550, 757 were allocated to no CT at time of registration of which 83 were non-compliant (11.0%).

Legend: The blue cells correspond to the patients that are considered non-compliant. For a clarification of the non-compliance rates in the C-low/G-high and C-high/G-low group refer to the footnotes * and **.

12 Agreement between local and central pathology

Table S 12: Agreement for all patients with available central pathology

	Concordance (95% CI)	Kappa (95% CI)	Positive Agreement	Negative Agreement	PPV	NPV	N
ER	97.8% (97.5 – 98.2)	0.897 (0.879 - 0.915)	98.2	94.8	99.3	87.3	5787
PgR	90.0% (90.2 – 91.7)	0.729 (0.707 – 0.750)	91.7	87.8	97.0	71.1	5734
HER2	96.6% (96.1 – 97.0)	0.796 (0.768 – 0.823)	80.4	98.2	82.5	98.0	5746

13 Clinical risk assessment according to modified Adjuvant!Online

Table S 13: Classification of patients according to clinical risk assessment by the modified version of Adjuvant!Online

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
		1-3 positive nodes	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
	1-3 positive nodes	N-	Any size	C-high	
			poorly differentiated or undifferentiated	N-	≤ 1 cm
	1.1-5 cm	C-high			
	1-3 positive nodes	N-	Any size	C-high	
			HER2 positive	well differentiated OR moderately differentiated	N-
	2.1-5 cm	C-high			
	1-3 positive nodes	N-		Any size	C-high
				poorly differentiated or undifferentiated	N-
1.1-5 cm	C-high				
1-3 positive nodes	N-	Any size	C-high		
		HER2 negative	well differentiated	N-	≤ 2 cm
2.1-5 cm	C-high				
1-3 positive nodes	N-		Any size	C-high	
			moderately differentiated OR poorly differentiated or undifferentiated	N-	≤ 1 cm
1.1-5 cm	C-high				
1-3 positive nodes	N-		Any size	C-high	
		HER2 positive	well differentiated OR moderately differentiated	N-	≤ 1 cm
1.1-5 cm	C-high				
1-3 positive nodes	N-		Any size	C-high	
			poorly differentiated or undifferentiated	Any	Any size

14 DMFS, DFS and OS for CT versus no CT in the two discordant risk groups (ITT1 population)

Table S 14: DMFS, DFS and OS for CT versus no CT in the two discordant risk groups (ITT1 population).

C-high/G-low Intent-to-Treat population (ITT)							
	Treatment strategy followed		Patients (N)	Observed Events (O)	% at 5 Year(s) (95% CI)	Hazard Ratio* (95% CI)	p-value**
DMFS	Follow c-risk	CT	749	34	95.9 (94.0, 97.2)	0.78 (0.50,1.21)	0.267
	Follow g-risk	no CT	748	46	94.4 (92.3, 95.9)		
DFS	Follow c-risk	CT	749	54	92.9 (90.5, 94.7)	0.71 (0.50,1.01)	0.055
	Follow g-risk	no CT	748	78	90.1 (87.5, 92.1)		
OS	Follow c-risk	CT	749	14	98.4 (97.0, 99.1)	0.69 (0.35,1.35)	0.278
	Follow g-risk	no CT	748	22	97.0 (95.4, 98.1)		

C-low/G-high Intent-to-Treat population (ITT)							
	Treatment strategy followed		Patients (N)	Observed Events (O)	% at 5 Year(s) (95% CI)	Hazard Ratio* (95% CI)	p-value**
DMFS	Follow g-risk	CT	344	18	95.8 (92.9, 97.6)	1.17 (0.59,2.28)	0.657
	Follow c-risk	no CT	346	17	95.0 (91.8, 97.0)		
DFS	Follow g-risk	CT	344	28	92.1 (88.3, 94.6)	0.87 (0.53,1.45)	0.603
	Follow c-risk	no CT	346	34	90.1 (86.1, 93.0)		
OS	Follow g-risk	CT	344	11	97.1 (94.5, 98.5)	1.28 (0.54,3.02)	0.578
	Follow c-risk	no CT	346	10	97.8 (95.5, 99.0)		

Legend: These results compliment the Kaplan Meier curves in Figure 2 in the main paper.

* Hazard ratios were calculated with the use of a Cox model after adjustment for the factors used in stratification for randomization assignments.

** values were calculated by means of the Wald test in the adjusted Cox Model.

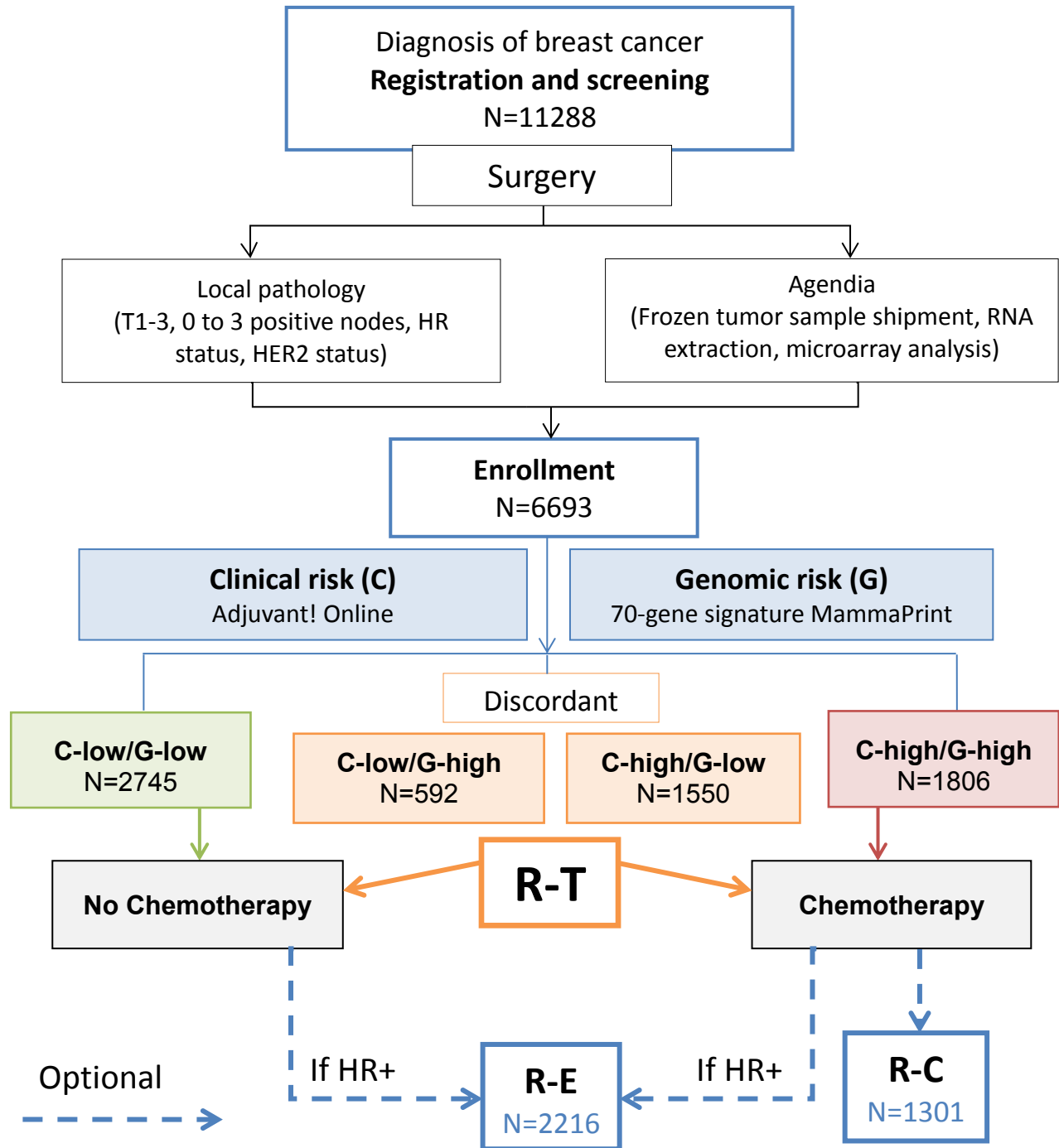
15 DMFS in the C-high/G-low risk group in the different analysis populations

Table S 15: DMFS the C-high/G-low risk group in the different analysis populations

Analysis Population (see main paper Figure 1)	Treatment strategy followed	Number of patients	Number of events	5-year distant- metastasis-free- survival (95% CI)	difference
Primary Test population	Genomic risk: No chemo	644	38	94.7% (92.5-96.2)	/
Intent-to-Treat population (C-high/G-low)	Genomic risk: No chemo	748	46	94.4% (92.3, 95.9)	1.5 %
	Clinical risk: chemo	749	34	95.9% (94.0, 97.2)	
Per Protocol population (C-high/G-low)	Genomic risk: No chemo	636	37	94.8 (92.6, 96.3)	1.9%
	Clinical risk: chemo	592	22	96.7 (94.7, 98.0)	

16 The MINDACT study design

Figure S 7: The MINDACT study design.



Note that patient numbers for the risk groups correspond to the numbers in the corrected risk groups.

Legend: Patients with invasive early stage BC were screened for the trial. Eligible patients were women between ages 18 and 70, with histologically proven primary non-metastatic (M0) invasive BC (clinical T1, T2 or operable T3), initially LN0 only, and as of August 2009, up to 3 LN+. Clinical risk (C) was determined by a modified version of Adjuvant! Online (version 8.0 with HER2 status). Genomic risk (G) is determined by the 70-gene-signature. Patients with low-risk disease according to both C and G results were advised not to receive adjuvant CT, while for those with high-risk disease by both tests, CT was proposed. Patients with discordant results were randomized to have their treatment decision (R-T) based on either the C or the G result (i.e., CT or no CT). The R-T randomization used a

minimization technique stratified for institution, risk group (C-low/G-high vs. C-high/G-low), HR status (ER+ and/or PgR+ vs. ER and PgR neg), nodal involvement (yes, no), age (<50 vs. ≥50), HER2 status (HER2+ vs. HER2 neg vs. unknown), axillary treatment (sentinel node only vs. dissection), and type of surgery (mastectomy vs. breast conservation). Two additional (optional) randomizations were implemented: patients assigned to adjuvant CT (either randomly due to discordant results or due to high-risk concordance of both tests) could be randomized to an anthracycline containing regimen or docetaxel plus capecitabine (R-C). The anthracycline arm was different for patients with LNO BC and for patients with LN+ disease, as standard therapies were different for each subgroup at that time. For LNO disease, anthracycline-based without taxanes regimens were used and included: FAC (cyclophosphamide, doxorubicin and 5-fluorouracil), FEC (cyclophosphamide, epirubicin and 5-fluorouracil), CAF (d1+8), CEF (d1+8) or E-CMF (4 cycles of single-agent epirubicin, followed by 4 cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF)). For LN+ disease, the standard regimen was a sequence of 3 cycles of FEC 100 followed by 3 cycles of docetaxel.

Patients with HR+ BC could be further randomized to either 2 years of tamoxifen followed by 5 years of letrozole or 7 years of up-front letrozole (R-E). For this randomization, pre-menopausal women had to also receive a GnRH analogue.