Supplementary Appendix

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

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2. Eligibility criteria for pre-registration

Patients were required to have operable histologically confirmed adenocarcinoma of the female breast, completed primary surgical treatment, and meet the following criteria in order to preregister: (1) ER and/or PR-positive invasive breast cancer (as defined and determined by local or reference pathology laboratory), and Her2/neu negative by either fluorescent in-situ hybridization (FISH) or immunohistochemistry (as determined by local or reference pathology laboratory) (2) negative axillary nodes, as assessed by a sentinel lymph node biopsy, an axillary dissection, or both, (3) tumor size 1.1–5.0cm (or 5 mm-1.0 cm plus unfavorable histological features, defined as an intermediate or poor nuclear and/or histologic grade, or lymphovascular invasion), (4) within 84 days from the final surgical procedure required to adequately treat the primary tumor, including either a mastectomy or local excision plus an acceptable axillary procedure, and adequate (at least 1 mm if margin width specified) tumor-free margins of resection (for invasive and ductal carcinoma in-situ), (5) age ≥ 18 years and ≤ 75 years, (6) adequate organ function, including the following within 4 weeks prior to pre-registration - leukocyte count ≥ 3500/mm3 and platelets ≥ 100,000/mm3, serum creatinine ≤ 1.5mg/dL, serum aspartate transaminase (AST) ≤ 3-fold the upper institutional limits of normal, (7) disease-free of prior invasive malignancies for ≥ 5 years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, (8) signed informed consent.

Patients with a previous ipsilateral or contralateral invasive breast cancer or ductal carcinoma in situ, or with bilateral synchronous cancers, were not eligible, Patients who developed breast cancer after 8 or more weeks of receiving a selective estrogen-receptor modulator (SERM; e.g., tamoxifen, toremifene, raloxifene) or an aromatase inhibitor (e.g., anastrozole, letrozole, exemestane) for breast cancer prevention or a SERM for other indications (e.g., raloxifene for osteoporosis) were not eligible. Additional information regarding exclusion criteria are in the protocol document.

3. Preregistration and registration

A primary tumor sample was ordered within 3 days of preregistration by the enrolling site and sent to the Genomic Health laboratory (Redwood City, CA). Upon receipt of the Oncotype DX assay results, the enrolling site then proceeded with registration by taking the following steps: (1) faxed the Oncotype DX report to the ECOG Coordinating Center (with redaction of protected health information, and labelling with ECOG ID number obtained at preregistration), and (2) provided information for stratification variables (see section 4) required for randomization if indicated. Upon registration, chemotherapy treatment was either assigned or randomized based on the recurrence score results and randomization procedures described in section 4, if applicable.

4. Chemotherapy and endocrine therapy

Guidelines for chemotherapy and endocrine therapy treatment were provided in the protocol, as summarized below.

Chemotherapy regimens:

Regimen Name	Regimen Dose/Schedule	Regimen Schedule	No. of Cycles
Oral CMF	C 100 mg/m2/day PO x 14 days M 40 mg/m2 IV days 1, 8 F 600 mg/m2 IV days 1, 8	Every 4 weeks	6
IV CMF	C 600 mg/m2 IV M 40 mg/m2 IV F 600 mg/m2 IV	Every 3 weeks	6-8
Standard AC	A 60 mg/m2 IV C 600 mg/m2 IV	Every 3 weeks	4
Dose dense AC	A 60 mg/m2 IV C 600 mg/m2 IV Plus G-CSF	Every 2 weeks	4
Standard AC - T	A 60 mg/m2 and C 600 mg/m2 IV every 3 weeks x 4 cycles ⇒ T 175 mg/m2 every 3 weeks x 4 cycles	Every 3 weeks	8
Dose dense AC - T	A 60 mg/m2 and C 600 mg/m2 IV plus G-CSF every 2 weeks x 4 cycles ⇒ T 175 mg/m2 plus G-CSF every 2 weeks x 4 cycles	Every 2 weeks	8
FEC	F – 500 mg/m2 IV E – 50-100 mg/m2 IV C – 500 mg/m2 IV	Every 3 weeks	6
TAC	T - 75 mg/m2 A - 50 mg/m2 C - 500 mg/m2 **NOTE:** TAC should be used only in women </= 70 years of age	Every 3 weeks	4-6
TC	T - 75 mg/m2 C - 600 mg/m2	Every 3 weeks	4
Other protocol-specified regimens	Participating in other CTSU trials including chemotherapy	As specified in protocol	As specified in protocol

Endocrine Therapy – Years 1-5:

Menopausal Status	Regimen
Pre, Peri, or Post	Tamoxifen 20 mg PO daily
Post	Anastrazole (Arimidex) 1 mg PO daily
Post	Letrozole (Femara) 2.5 mg PO daily
Post	Exemestane (Aromasin) 25 mg PO daily
Pre or Peri	Participating in another CTSU study; as specified in treatment protocol
Post	Participating in another CTSU study; as specified in treatment protocol
Pre or Peri	Ovarian suppression (surgery, irradiation, or Gn RH analogue) may be used in conjunction with tamoxifen or an aromatase inhibitor, and may continue beyond 5 years.

Endocrine Therapy -Years 5-10

Menopausal Status at year 6	Treatment during years 1-5	Treatment years 6-10
Pre or Peri	Tamoxifen 20 mg PO daily	No further treatment
Post	Tamoxifen 20 mg/ PO daily	Any aromatase inhibitor
Post	Any aromatase inhibitor	No further treatment
Post	Any aromatase inhibitor	May continue aromatase inhibitor
Pre or Peri	Any treatment	Participating in CTSU study; as specified in protocol
Post	Any treatment	Participating in CTSU study; as specified in protocol

5. Low-risk (RS 0-10) & high-risk (RS 26 or higher) registries and RS distribution

Subjects with a recurrence score that was either low (RS 0-10 – arm A) or high (RS 26 or higher – arm D) were enrolled on prospective registry. Federal funding was provided for sites for the randomized arms (arms B and C) with a recurrence score of 11-25 and the low-risk registry (arm A). Enrollment to the high-risk registry (arm D) and subsequent followup was voluntary by the participating sites. This contributed to higher rates of no baseline/followup information and exclusion of registered subjects from the main analysis in arm D (341/1737 [19.6%]) than arm A (7 of 1629 [0.4%]), arm B (55 of 3458 [1.6%]), and arm C (131 of 3449 [3.8%]). This contributed to differences in recurrence score distribution of low (0-10), mid-range (11-25) and high (26 or higher) in the 10,273 registered subjects (15.9%, 67.2%, and 16.9%, respectively) compared with the 9719 subjects included in the main analysis (16.7%, 69.1%, and 14.3%, respectively).

6. Statistical methods

6A. Randomization procedures. Randomization was conducted centrally using permuted blocks within strata, with the strata defined by tumor size (2 cm or less vs. more than 2 cm), menopausal status (pre vs. post), planned chemotherapy (taxane-containing or not), planned radiation therapy (whole breast, no boost planned vs. whole breast, boost planned vs. partial breast irradiation planned vs. no planned radiation therapy for patients who had a mastectomy), and recurrence score group (11 to 15 vs. 16 to 20 vs. 21 to 25, which was added midway through the study).

6B. Study endpoints and statistical methods used for comparisons. The primary trial endpoint was invasive disease-free survival (iDFS), defined to be time from registration to first event, where the first event is any of ipsilateral breast tumor recurrence, local recurrence, regional recurrence, distant recurrence, contralateral second primary invasive cancer, second primary non-breast invasive cancer (excluding non-melanoma skin cancers), or death without evidence of recurrence. Secondary endpoints included: distant recurrence free interval (DRFI), defined as time from registration to date of distant recurrence of breast cancer, or of death with distant recurrence, if death is the first manifestation of distant recurrence; relapse free interval (RFI), defined as date from registration to first recurrence of breast cancer (ipsilateral breast, local-regional, or distant), or to the date of death with recurrence, if death is the first manifestation of recurrence; and overall survival (OS), defined as date from registration to death of any cause.

The primary comparisons of invasive disease-free survival and other pre-specified endpoints were stratified logrank tests using the randomization stratification variables. Hazard ratios were estimated from proportional hazards models, also stratified as in the randomization. Event-free rates were estimated using the Kaplan-Meier method, with confidence intervals computed using the log-log transform and Greenwood's variance. Non-inferiority tests were planned for DRFI and OS (but not RFI). The non-inferiority margins specified correspond to hazard ratios of 1.61 for DRFI and 1.46 for OS. The justification for these was based on absolute differences in 5-year rates. While both of these endpoints are short of the information needed for full power for these comparisons, the confidence intervals exclude these values and thus support conclusions of non-inferiority for these endpoints. The protocol also specified that a secondary analysis by treatment received would be performed (the as treated analysis), but did not specify the threshold for significance for this analysis (the appropriate threshold would be different, since the power of this comparison is not affected by nonadherence). As is often recommended for noninferiority comparisons, the comparison may be interpreted based on whether the confidence interval on the hazard ratio contains the noninferiority margin (1.322) or no difference (1.0). These comparisons are also stratified as in the randomization, but could still be biased because of differences in the group refusing chemo on arm C and the group receiving chemo on arm B.

6C. Adjustment in sample size for non-adherence. Based on data available as of October 30, 2008 (18 months after study activation), there were higher than anticipated rates of non-adherence to randomized treatment in both arms of the recurrence score 11 to 25 group (12% on average), including the chemoendocrine therapy arm (17% received no chemotherapy) and endocrine therapy alone arm (7% received chemotherapy). This required a 73% increase in the number of patients randomized relative to a design with 100% adherence (based on the Lachin-Foulkes correction), to ensure adequate power. Based on assuming accrual of 6,860 patients accrued over 3.81 years, of whom up to 5% would be ineligible, it was projected that 6517 eligible patients would be required.

6D. Interim monitoring. The first interim analysis was performed when at least 25% of the total planned number of invasive disease-free survival events were reported (N=209), and subsequent interim analyses were performed annually until either the criteria for early stopping were met or the total planned number of events for full information on invasive disease-free survival events (N=835) was achieved. At each interim analysis (and at the final analysis), the stratified log rank test statistic was computed. The stopping boundary for rejecting non-inferiority was based on a truncated version of the Lan-Demets error spending rate function corresponding to an O'Brien-Fleming shaped boundary with an overall one-sided type I error of 10%. At early analyses, the boundary was truncated at a level corresponding to a one-sided nominal significance of 0.002, and the boundary function was computed to maintain the type I error rate adjusting for the effects of the truncation and the effects of the early stopping in favor of non-inferiority. To allow for early stopping in favor of non-inferiority, the study was also monitored using conditional power for the primary assigned treatment comparison above and using repeated confidence interval (RCI) methodology. At each interim analysis, the conditional power of the log rank test for the primary comparison at a type I error rate of 10% (one-sided) was computed using simulations (incorporating the estimated distribution of treatment non-adherence). The two-sided 95% RCI on the log hazard ratio (for received endocrine vs. chemoendocrine therapy), was also computed. Since intention to treat and as treated analyses have well-known potential biases in the presence of treatment non-adherence, the hazard ratio in the subpopulation that would receive the assigned treatment if assigned to either arm was estimated using a full mixture likelihood approach and the RCI obtained by inverting the corresponding likelihood ratio test. The RCI used the critical value from the O'Brien-Fleming error spending rate function with an overall one-sided 2.5% error rate. If the conditional power of the assigned treatment analysis is less than 10% and the upper limit of the RCI lies below the minimum unacceptable log ratio of log (1.322), then the study will be stopped in favor of non-inferiority. This monitoring rule was deliberately chosen to be conservative, since the results must be convincing that the conclusion of non-inferiority is based on an adequate amount of information rather than on an underpowered comparison. Six interim analyses were conducted. The boundary for rejecting non-inferiority at the final analysis to control the overall significant level at 10% corresponds to a nominal one-sided significance level of 0.074. Median follow-up for invasive disease-free survival in the recurrence score 11 to 25 cohort was 91 months in arm B and 90 months in arm C, and for overall survival was 96 months in both arms.

6E. Impact of Incomplete followup information. Cumulative incidence analysis was used to examine the association of lost to follow-up with baseline factors. The patients who had no follow-up, who had some follow-up and subsequently withdrew consent for further follow-up, or for whom the institutions could not obtain further follow-up, were counted as lost to follow-up events, and DFS events were regarded as competing events. Overall, the 9-year cumulative incidence of lost to follow events was 12.2% on arm B and 14.7% on arm C (the arms here are the assigned groups). In arm C, there was a significant association of lost to follow-up with RS, with 9-year cumulative drop out of 16.6% for RS 11-15, 14.3% for RS 16-20, and 12.5% for RS 21-25, but there was no association with RS in arm B. This may be due to a similar association

with the decision to refuse assignment to chemo in arm C (which was higher for low RS patients), and patients refusing chemo being more likely to drop out from follow-up, too. The logrank tests and Cox models for treatment comparisons were stratified on the randomization factors, including grouped RS, tumor size, and menopause, and the validity of the analyses requires only that censoring be noninformative within strata, so the association with RS should not affect these. There was also an association with age/menopause in both arms, with the postmenopausal patients who were age <=50 having higher withdrawal rates (22.5% an arm C, 18.3% on arm B) than other groups. This is a small group, though.

Stratification does not protect against bias from differences in unobserved or unknown factors. For the primary comparison, the one-sided p-value is 0.13, vs. a threshold for rejecting noninferiority of 0.074. To explore whether differences in cases lost to follow-up on the two arms could affect the results, outcomes for cases with incomplete follow-up were simulated under some different scenarios. The average hazard rates were estimated within a reduced set of 12 strata defined by combinations of grouped RS, tumor size, and menopause (pooling data from arms B and C). These were then multiplied and divided by appropriate factors in arms B and C to give a specified treatment hazard ratio within each of the strata. These (constant) hazard rates were then used to generate additional follow-up for cases with incomplete follow-up (including those with no follow-up reported). For cases with DFS events in the original data, the observed data were used, and for cases with censored DFS times, a random DFS event time was generated given the observed follow-up and the stratum and arm. The calendar time of the 835th event was then determined (using the actual entry times), and follow-up on all cases was truncated at that time, giving a data set with 835 DFS events. The stratified logrank test was then calculated, and the 9-year Kaplan-Meier estimates obtained for both arms. This process was repeated 500 times in each scenario. In all scenarios, on average about 120 DFS events were from the generated additional follow-up and 715 from the original data (reflecting that there was substantial incomplete follow-up). The calculations were done with treatment hazard ratios (B vs. C) of 1.08 (which is the estimate from the observed data), 1.15, 1.20 and 1.30. The following table gives the average (over the 500 replicates) primary (one-sided) p-value, the proportion of samples where the p-value was < 0.074, the average difference in the 9-year DFS rates between the randomized arms, and the proportion of samples where the difference was >=3%.

Ratio	Average p-value	Proportion p<0.074	Average Difference in DFS rates (C – B)	Proportion Difference >= 3%
1.08	0.121	0.27	1.3%	0
1.15	0.102	0.41	1.4%	0
1.20	0.084	0.55	1.6%	0.004
1.30	0.064	0.68	1.7%	0.012

The results show that with a hazard ratio of 1.2 or greater for the additional data, the study likely would have rejected noninferiority for the primary comparison, but in all scenarios the overall difference is unlikely to be clinically meaningful. (This is due to the better than expected DFS rate, so the targeted hazard ratio corresponds to an absolute difference that is smaller than thought to be meaningful.)

***6F. Exploratory subset analysis*.** No subgroup interaction analyses were planned a-priori with the exception of the continuous RS by treatment analysis shown in Figures S5-10. Having concluded from the primary comparison that chemotherapy does not have a meaningful

benefit overall in the RS 11-25 population, the purpose of the subset analyses is to check for consistency in effects over the subsets and to consider whether the data suggest that some subgroups might still be benefitting from chemotherapy. Because of the smaller numbers, it is very difficult to establish non-inferiority in individual subgroups, and they generally do not provide adequate power for establishing superiority of chemotherapy, so these analyses should be primarily viewed as descriptive and exploratory. The effect of multiple testing also needs to be considered. For (re)establishing superiority of chemotherapy in subsets, invasive DFS is well established as a clinically meaningful endpoint for adjuvant therapies in breast cancer, and would be the appropriate endpoint to use here. The type I error for subset superiority comparisons would need to be controlled at an overall two-sided 5% level. With DFS comparisons in 32 subsets, a Bonferroni correction requires a p-value of 0.0016 for superiority in subsets. The most significant of the DFS subset comparisons had p=0.0018 in the age <= 50 subset, which is very close but not quite significant. This specific observation is of particular relevance, since the Early Breast Cancer Trialists' metaanalysis demonstrated that younger women derive greater benefit from adjuvant chemotherapy, which may be in part due to early menopause associated with cytotoxic therapy in older premenopausal women. While this difference is thus not conclusive, this and some of the other subsets do still suggest the possibility of benefit and we believe it is important to describe these findings. There was also an a-priori expectation that the benefit of chemotherapy, if any, would vary with RS, so giving these estimates is also important information, even if the evidence for benefit in some subsets is not conclusive

7. Supplemental tables 1-6

Table S1. Characteristics of patients by assigned treatment in intention-to-treat population

	Recurrence Score 0-10	**Recurrence Score 11 to 25**		**Recurrence Score 26 or Higher**
Study Arm	Arm A	Arm B	Arm C	Arm D
Assigned Treatment	Endocrine Therapy	Endocrine Therapy	Chemoendocrine Therapy	Chemoendocrine Therapy
Number	1619	3399	3312	1389
Age (years)				
Median (range)	58 (25-75)	55 (23-75)	55 (25-75)	56 (23-75)
</= 40	58 (4%)	154 (5%)	157 (5%)	79 (6%)
41-50	371 (23%)	985 (29%)	920 (28%)	330 (24%)
51- 60	563 (35%)	1235 (36%)	1206 (36%)	512 (37%)
61-70	518 (32%)	868 (26%)	895 (27)	395 (28%)
71-*75*	109 (7%)	157 (5%)	134 (4%)	73 (5%)
Menopausal Status				
Pre	478 (30%)	1212 (36%)	1203 (36%)	407 (29%)
Post	1141 (70%)	2187 (64%)	2109 (64%)	982 (71%)
Tumor size (cm)				
Median (interquartile	1.5 (1.2, 2.0)	1.5 (1.2, 2.0)	1.5 (1.2, 2.0)	1.7 (1.3, 2.3)
Mean – cm (+/- SD)	1.74 (+/-0.76)	1.71 (+/-0.81)	1.71 (+/-0.77)	1.88 (+/-0.99)
Distribution –no./total				
</= 1.0	202 (12%)	446 (13%)	423 (13%)	188 (14%)
1.1 - 2.0	1018 (63%)	2150 (63%)	2103 (64%)	741 (53%)
2.1 – 3.0	297 (18%)	640 (19%)	625 (19%)	348 (25%)
3.1 – 4.0	83 (5%)	122 (4%)	119 (4%)	91 (7%)
>/= 4.1	19 (1%)	41 (1%)	40 (1%)	20 (1%)
Unknown	0	0	2	1
Histologic grade				
Low	530 (34%)	959 (29%)	934 (29%)	89 (7%)
Intermediate	931 (59%)	1884 (57%)	1837 (57%)	590 (43%)
High	111 (7%)	439 (13%)	445 (14%)	681 (50%)
Unknown	47	117	96	29
ER expression				
Negative	5 (0%)	6 (0%)	3 (0%)	40 (3%)
Positive	1614 (100%)	3393 (100%)	3309 (100%)	1349 (97%)
PgR expression				
Negative	28 (2%)	267 (8%)	251 (8%)	405 (30%)
Positive	1555 (98%)	3072 (92%)	2989 (92%)	948 (70%)
Unknown	36	60	72	36
Clinical Risk				
Low	1227 (78%)	2440 (74%)	2359 (73%)	589 (43%)
High	345 (22%)	842 (26%)	855 (27%)	770 (57%)
Unknown	47	117	98	30

Primary Surgery				
Mastectomy	516 (32%)	935 (28%)	917 (28%)	368 (26%)
Breast	1103 (68%)	2464 (72%)	2395 (72%)	1021 (74%)
Adjuvant Chemo				
Yes	8 (0.5%)	185 (5.4%)	2704 (81.6%)	1300 (93.6%)
No	1611 (99.5%)	3214 (94.6%)	608 (18.4%)	89 (6.4%)
Recurrence score				
0-5	432 (27%)			
6-10	1187 (73%)			
11-15		1214 (36%)	1159 (35%)	
16-20		1368 (40%)	1344 (41%)	
21-25		817 (24%)	809 (24%)	
26-30				598 (43%)
31-35				315 (23%)
36-40				158 (11%)
41-50				202 (15%)
51-100				116 (8%)

Clinical risk group as defined in the MINDACT trial (Low risk defined by low grade and tumor size <=3cm, intermediate grade and tumor size <=2cm, and high grade and tumor size <=1cm; high risk defined as all other cases with known values for grade and tumor size).

Table S2. Treatment administered

	Recurrence Score 0-10	**Recurrence Score 11-25**		**Recurrence Score 26 or Higher**
	Arm A Endocrine Therapy	Arm B Endocrine Therapy	Arm C Chemoendocrine	Arm D Chemoendocrine
Total Number	1619	3319	3312	1389
Adjuvant Chemotherapy	(n=8)	(n=185)	(n=2704)	(n=1300)
CMF	1 (12%)	12 (6%)	183 (7%)	52 (4%)
Anthracycline w/o Taxane	0 (0%)	52 (28%)	774 (29%)	334 (26%)
Anthracycline and Taxane	2 (25%)	17 (9%)	181 (7%)	244 (19%)
Taxane & Cyclophosphamide	3 (38%)	95 (51%)	1515 (56%)	589 (45%)
Other or Type Not Specified	2 (25%)	9 (5%)	51 (2%)	81 (6%)
None	1611	3214	608	89
Endocrine Therapy (Premenopausal)	(n=478)	(n=1212)	(n=1203)	(n=407)
AI	32 (7%)	53 (4%)	110 (9%)	41 (10%)
OFS	17 (4%)	62 (5%)	33 (3%)	21 (5%)
OFS and AI	32 (7%)	124 (10%)	94 (8%)	31 (8%)
Tam	238 (50%)	558 (46%)	461 (38%)	177 (43%)
Tam and AI	146 (31%)	394 (33%)	482 (40%)	117 (29%)
Other	1 (0%)	5 (0%)	2 (0%)	1 (0%)
None Reported	12 (3%)	16 (1%)	21 (2%)	19 (5%)
Endocrine Therapy (Postmenopausal)	(n=1141)	(n=2187)	(n=2109)	(n=982)
AI	843 (74%)	1568 (72%)	1441 (68%)	695 (71%)
Tam	99 (9%)	170 (8%)	139 (7%)	79 (8%)
Tam and AI	180 (16%)	438 (20%)	483 (23%)	176 (18%)
Other	0 (0%)	0 (0%)	1 (0%)	1 (0%)
None Reported	19 (2%)	11 (1%)	45 (2%)	31 (3%)

Abbreviations: AI – aromatase inhibitor; OFS – ovarian function suppression; Tam – tamoxifenEndocrine therapy categories are based on whether any therapy of that type was given, with the exception of OFS. Endocrine therapy is classified as OFS for premenopausal patients if it is initiated within 2 years of entry and prior to any DFS events.

Table S3. Characteristics of patients with RS 11-25 according to treatment given

	Chemoendocrine (n=2889)	Endocrine (n=3822)
Age (years)		
<=40	152 (5%)	159 (4%)
41 to 50	859 (30%)	1046 (27%)
51 to 60	1060 (37%)	1381 (36%)
61 to 70	717 (25%)	1046 (27%)
71 to 75	101 (3%)	190 (5%)
Menopausal Status		
Pre	1112 (38%)	1303 (34%)
Post	1777 (62%)	2519 (66%)
Tumor Size (cm)		
<=1.0	344 (12%)	525 (14%)
1.1 to 2.0	1821 (63%)	2432 (64%)
2.1 to 3.0	583 (20%)	682 (18%)
3.1 to 4.0	107 (4%)	134 (4%)
>4.0	33 (1%)	48 (1%)
Unknown	1	1
Histologic Grade		
Low	767 (27%)	1126 (30%)
Intermediate	1608 (57%)	2113 (57%)
High	425 (15%)	459 (12%)
Unknown	89	124
ER Expression		
Negative	3 (0%)	6 (0%)
Positive	2886 (100%)	3816 (100%)
PgR Expression		
Negative	226 (8%)	292 (8%)
Positive	2600 (92%)	3461 (92%)
Unknown	63	69
Clinical Risk+		
High	806 (29%)	891 (24%)
Low	1993 (71%)	2806 (76%)
Unknown	90	125
Surgery		
Mastectomy	807 (28%)	1045 (27%)
Tumorectomy	2082 (72%)	2777 (73%)
Recurrence Score		
11-15	916 (32%)	1457 (38%)
16-20	1178 (41%)	1534 (40%)
21-25	795 (28%)	831 (22%)

Statistically significant differences: age (p=0.0005), menopausal status (p=0.0002), tumor size (p=0.05), histologic grade (p=0.0009), clinical risk (p<0.0001) and recurrence score (p<0.0001). +Clinical risk group as defined in the MINDACT trial (Low risk defined by low grade and tumor size <=3cm, intermediate grade and tumor size <=2cm, and high grade and tumor size <=1cm; high risk defined as all other cases with known values for grade and tumor size).

Table S4. Type of first invasive disease-free survival event by RS and assigned treatment

	Recurrence Score 0-10	Recurrence Score 11-25		Recurrence Score 26 or Higher
	Arm A Endocrine Therapy Alone	Arm B Endocrine Therapy Alone	Arm C Chemoendocrine Therapy	Arm D Chemoendocrine Therapy
No. of patients	1619	3399	3312	1389
Ipsilateral breast tumor recurrence	10	38	31	11
Other local-regional recurrence (+/- ipsilateral breast recurrence)	10	39	31	27
Distant recurrence (+/- ipsilateral breast or other local-regional recurrence)	28	107	92	80
Opposite breast cancer	29	44	48	9
Other second primary cancer	75	145	146	47
Death	33	63	52	15
Total no. of events (crude %)	185 (11.4%)	436 (12.8%)	400 (12.1%)	189 (13.6%)

Table S5. Type of first invasive disease-free survival event by treatment received for randomized cohort with RS 11-25

	Received Endocrine Therapy	Received Chemoendocrine Therapy
No. of patients	3822	2889
Ipsilateral breast tumor recurrence	43	26
Other local-regional recurrence (+/- ipsilateral breast recurrence)	45	25
Distant recurrence(+/- ipsilateral breast or other local-regional recurrence)	109	90
Opposite breast cancer	53	39
Other second primary cancer	168	123
Death	72	43
Total no. of events	490 (12.8%)	346 (12.0%)

Table S6. Type of first IDFS event for randomized patients by age, RS and arm

	RS 11-15		RS 16-20		RS 21-25	
	B	C	B	C	B	C
Age <=50 N	439	362	454	469	246	246
Ipsilateral breast tumor recurrence	8	7	10	4	6	1
Other local-regional recurrence (+/- ipsilateral breast recurrence)	3	3	8	8	8	5
Distant recurrence (+/- ipsilateral breast or other local-regional recurrence)	9	7	17	10	17	9
Opposite breast cancer	4	6	9	5	3	3
Other second primary cancer	16	8	16	9	5	6
Death	5	4	5	2	2	2
Total Events	45	35	65	38	41	26
Age 51-65 N	602	648	732	693	437	433
Ipsilateral breast tumor recurrence	1	4	5	6	5	4
Other local-regional recurrence (+/- ipsilateral breast recurrence)	4	7	7	3	7	4
Distant recurrence (+/- ipsilateral breast or other local-regional recurrence)	15	8	16	20	16	20
Opposite breast cancer	4	5	8	17	8	9
Other second primary cancer	13	32	38	35	20	14
Death	11	15	7	12	8	2
Total Events	48	71	81	93	64	53
Age 66-75 N	173	149	182	182	134	130
Ipsilateral breast tumor recurrence	0	2	3	2	0	1
Other local-regional recurrence (+/- ipsilateral breast recurrence)	1	0	1	1	0	0
Distant recurrence (+/- ipsilateral breast or other local-regional recurrence)	4	3	5	7	8	8
Opposite breast cancer	5	0	3	3	0	0
Other second primary cancer	18	15	12	14	7	13
Death	7	4	9	8	9	3
Total Events	35	24	33	35	24	25

8. Supplemental figures 1-13

Figure Labelling:

- **Assigned treatment (intention-to-treat analysis):** labelled as "**Arm B**" (RS 11-25 and randomized to endocrine therapy alone), "**Arm C**" (RS 11-25 and randomized to chemoendocrine therapy), "**Arm A"** (RS 0-10 and assigned to endocrine therapy alone), or "**Arm D**" (RS 26 or higher and assigned to chemoendocrine therapy)"
- **Treatment received (as-treated analysis):** labelled as "**Received endocrine therapy**" or "**Received Endocrine + Chemo**"

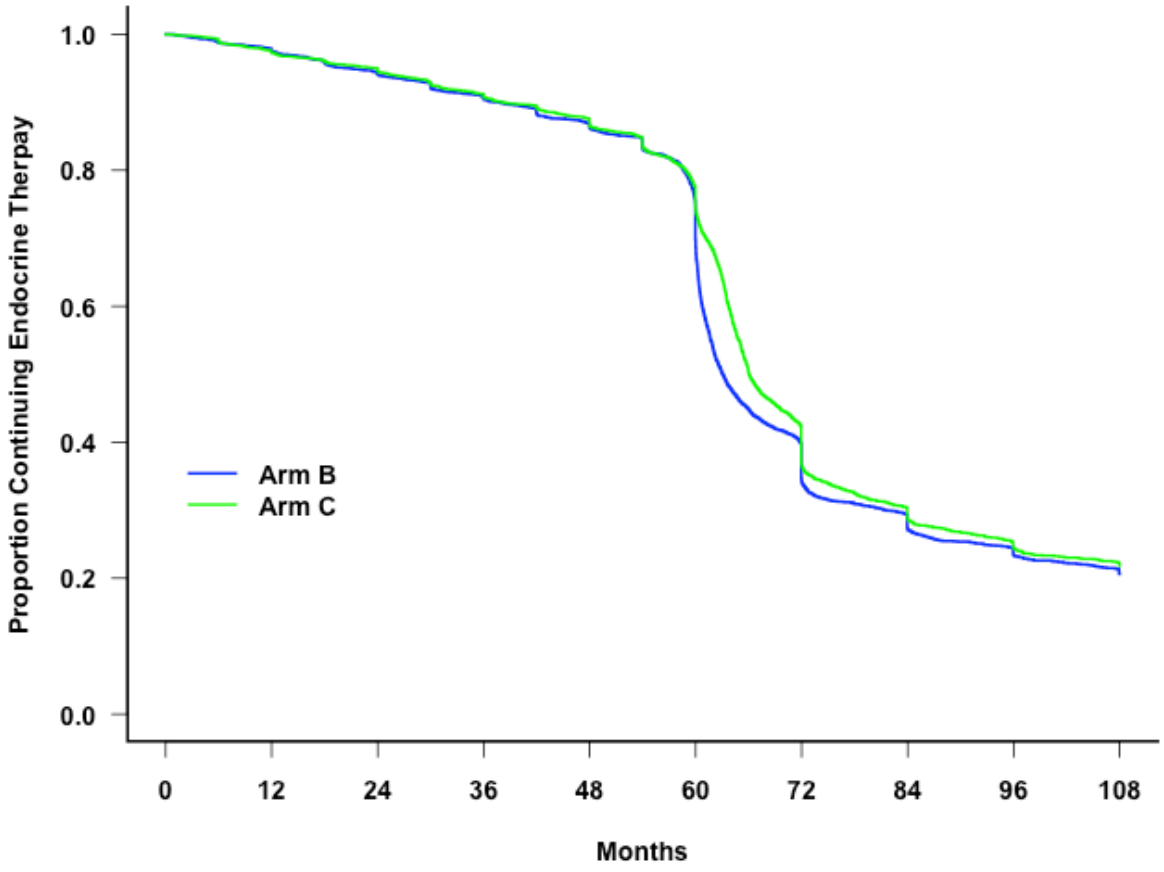
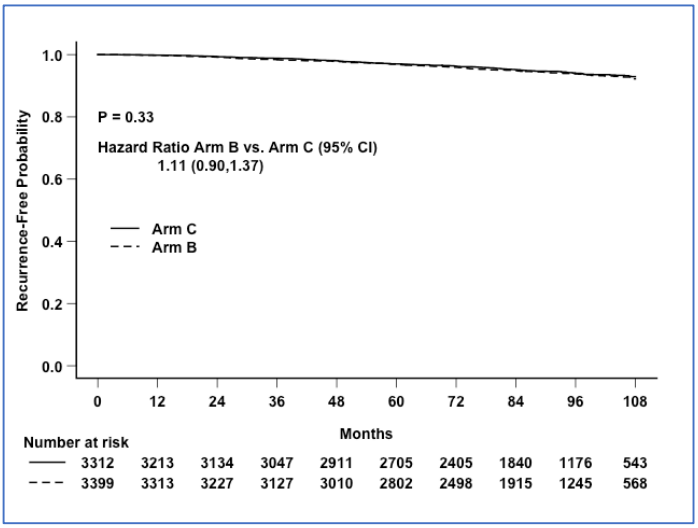


Figure S1. Duration of endocrine therapy by treatment arm in the RS 11 to 25 group in the intention-to-treat population (assigned treatment)



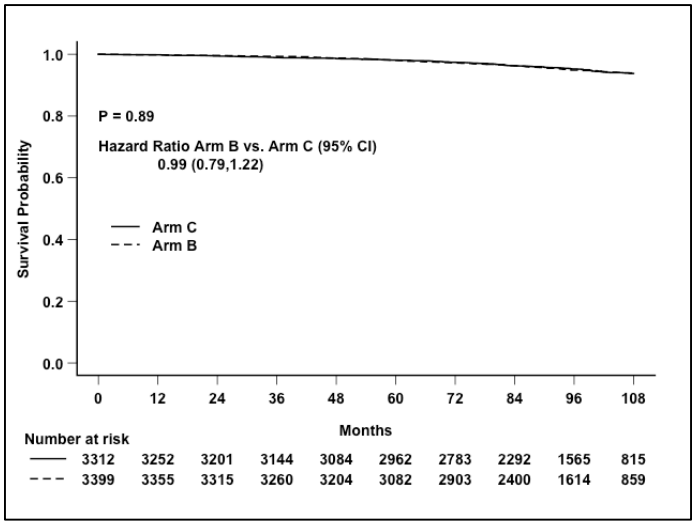


Figure S2a-b. Recurrence Score 11 to 25: Clinical Outcomes by Assigned Treatment Arm.

Kaplan Meier estimates by assigned treatment arm for endocrine therapy alone (arm B) chemoendocrine therapy (arm C) in the intention-to-treat analysis for freedom from breast cancer recurrence at a distant or local-regional site (a-left panel), and overall survival (b-right panel).

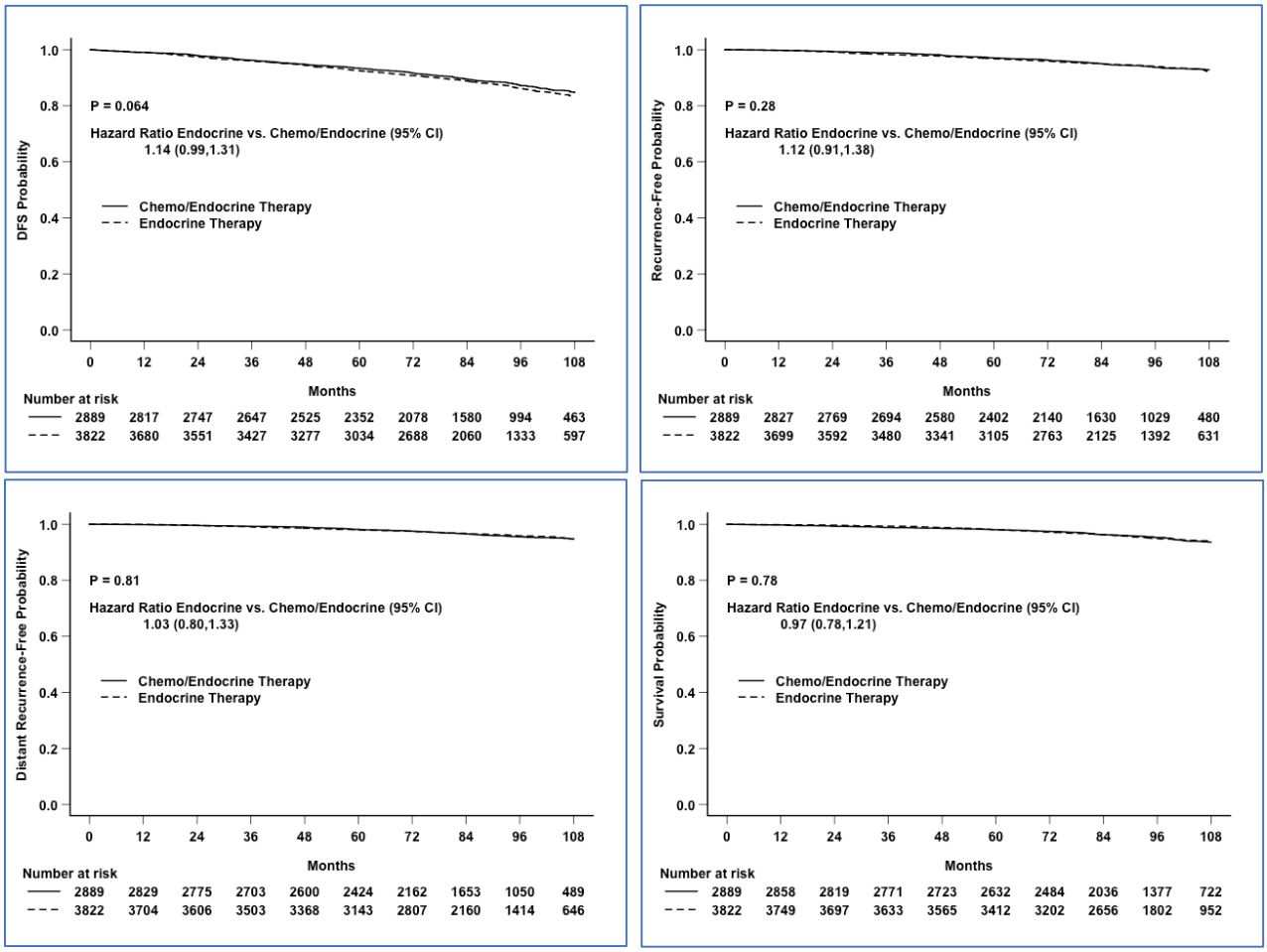


Figure S3. Clinical outcomes in RS 11-25 population by treatment received (as-treated analysis).

Kaplan Meier estimates by treatment for endocrine therapy alone and chemoendocrine therapy arms for (a-top left panel) invasive disease-free survival, (b-bottom left panel) freedom from breast cancer recurrence of breast cancer at a distant site, (c-top right panel) freedom from recurrence of breast cancer at a distant or local-regional site, and (d-bottom right) overall survival.

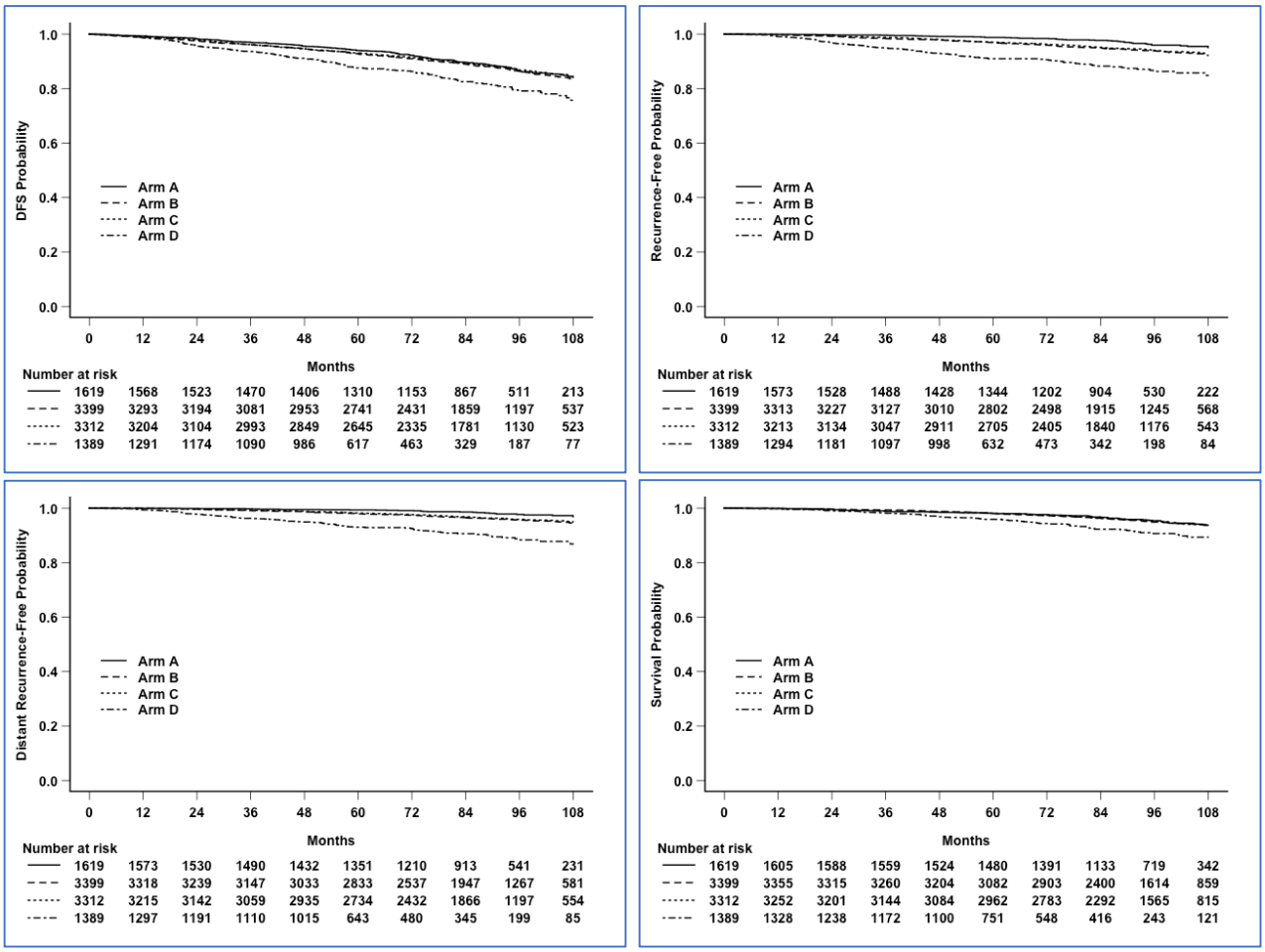


Figure S4. Clinical outcomes by assigned treatment in Arms A-D (intention-to-treat analysis).

Kaplan Meier estimates by recurrence score for (a-top left panel) invasive disease-free survival, (b-bottom left panel) freedom from breast cancer recurrence at a distant site, (c-top right panel) freedom from breast cancer recurrence at any, and (d-bottom right panel) overall survival ($p<0.0001$ for comparison of the 4 arms for all endpoints). (Arm A- RS 0-10 and assigned to endocrine therapy; arm B – RS 11-25 and randomized to endocrine therapy alone; arm C – RS 11-25 and randomized to chemoendocrine therapy; RS 26 or higher and assigned to chemoendocrine therapy).

Figures S5-10. Rate of Distant Recurrence by Recurrence Score as a Continuous Function.

The recurrence score was developed and validated specifically to be prognostic for distant recurrence, as described by Paik et al in the original B14 validation study, which included an analysis evaluating the association between continuous recurrence score (RS) and distant recurrence. We therefore also evaluated the relationship between continuous recurrence score and distant recurrence in TAILORx subjects.

As in the main analyses, proportional hazards models were fit. To check for nonproportionality, some models were fit separately for years 0 to 5 and for beyond 5 years. Differences were generally not significant. For example, for patients in the randomized subset, in a model with just continuous RS and treatment arm, the RS slope is 0.115 (standard error 0.024) during the first 5 years and 0.061 (0.022), p=0.10 for the null hypothesis that true slope is the same in both periods.

There are differences in the characteristics of those receiving chemotherapy (for analysis by treatment given), differences in the characteristics of arms A and D compared to B and C (for analyses including these cohorts), and there are also imbalances between randomized arms in some subsets. To avoid confounding with these other factors, most models also incorporated tumor size (<=2cm vs. > 2cm) and histologic grade (low vs. intermediate vs. high vs. not reported), which were the major prognostic factors for distant recurrence (in addition to RS). The models here were not stratified on the randomization stratification factors. RS was modeled either as a linear term or using a natural spline with 2 degrees of freedom. In all cases, model with the interaction between treatment (either assigned arm or treatment received) and RS (either linear or a natural spline) was fit, and the 9-year distant recurrence rate was estimated as a function of RS and treatment. For models incorporating tumor size and grade, the estimates given are for patients with tumor <=2cm and intermediate grade, since this constituted the largest group of trial participants for whom there is typically therapeutic equipoise (the estimates for other levels show similar patterns, but with absolute rates shifted up or down). The results are given in the figures S4-9.

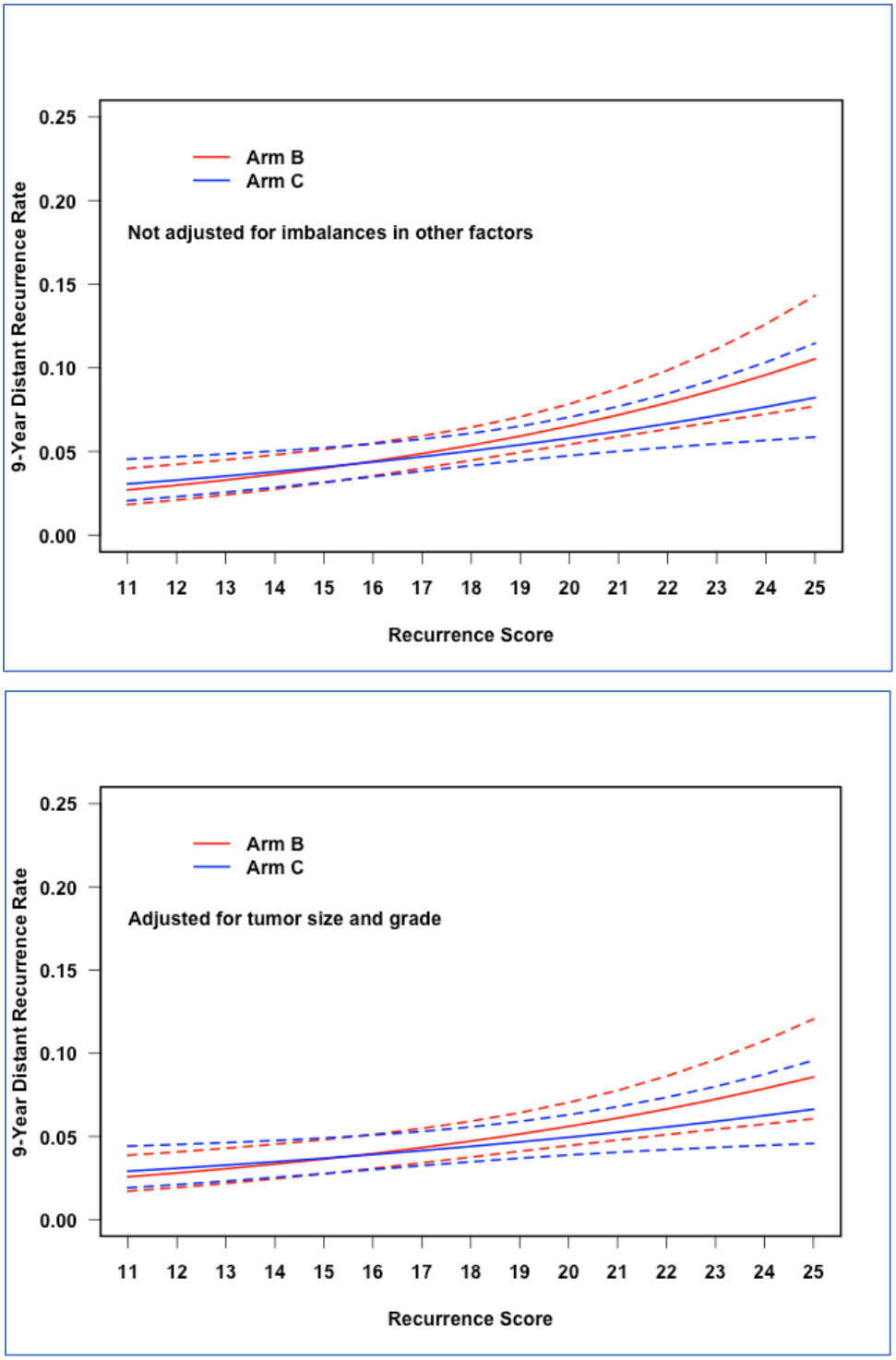


Figure S5. Continuous RS 11-25, distant recurrence, and assigned treatment.

9-year distant recurrence with pointwise 95% confidence intervals (dashed lines) by randomized arm and RS (model linear in RS).

Top panel: no adjustment for other factors. Bottom panel: adjusted for grade and tumor size, with the estimated rate given for intermediate grade and tumor size <=2cm.

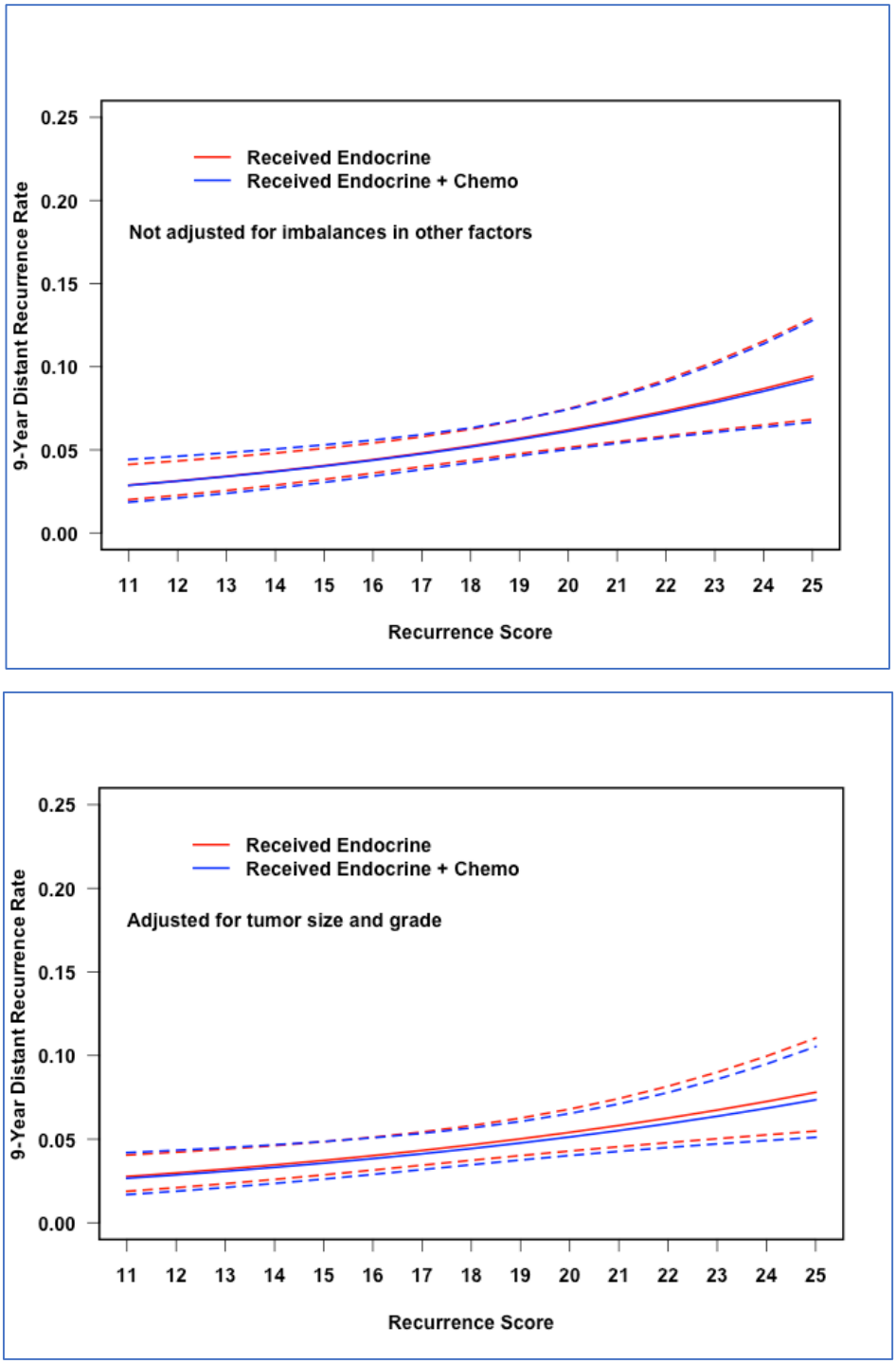
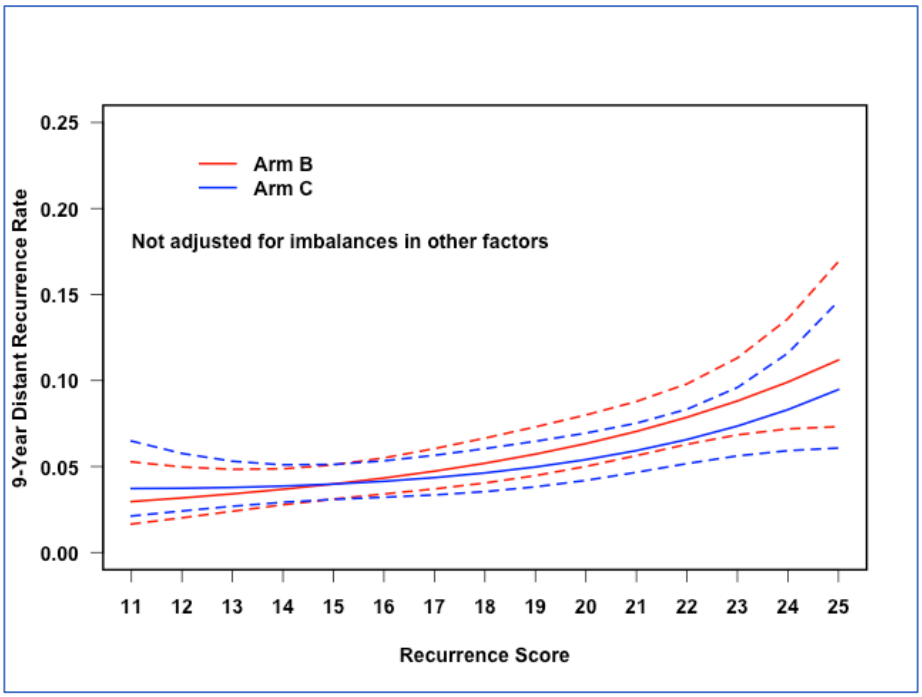


Figure S6. Continuous RS 11-25, distant recurrence, and treatment given (as-treated analysis).

9-year distant recurrence with pointwise 95% confidence intervals (dashed lines) by treatment received and recurrence score (model linear in RS), for the RS 11 to 25 population. Top panel: no adjustment for other factors. Bottom panel: adjusted for grade and tumor size, with the estimated rate given for intermediate grade and tumor size <=2cm.



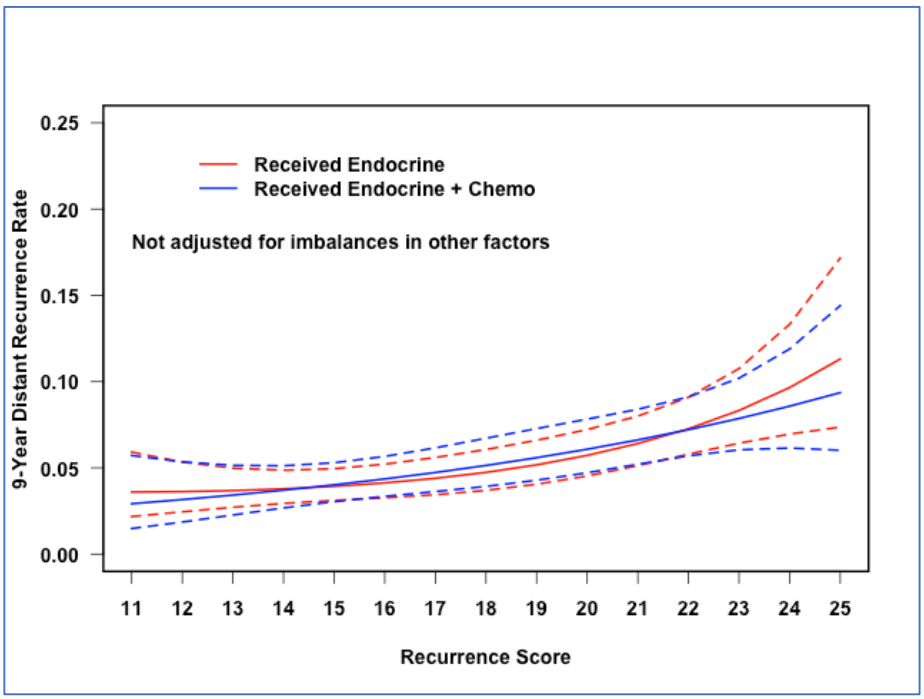
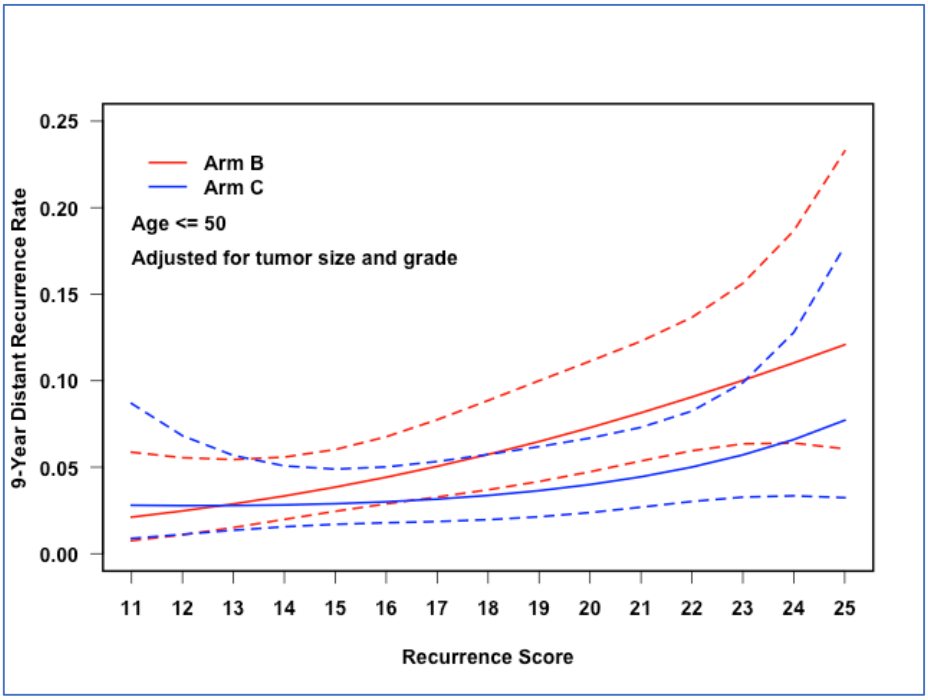


Figure S7. Continuous RS 11-25 and distant recurrence unadjusted for other factors (treatment assigned and treatment given).

9-year distant recurrence rates with pointwise 95% confidence intervals (dashed lines) by treatment and recurrence score (RS modeled with a natural spline with 2 degrees of freedom), for the RS 11 to 25 population.

Top panel by treatment arm assigned. Bottom panel by treatment received.



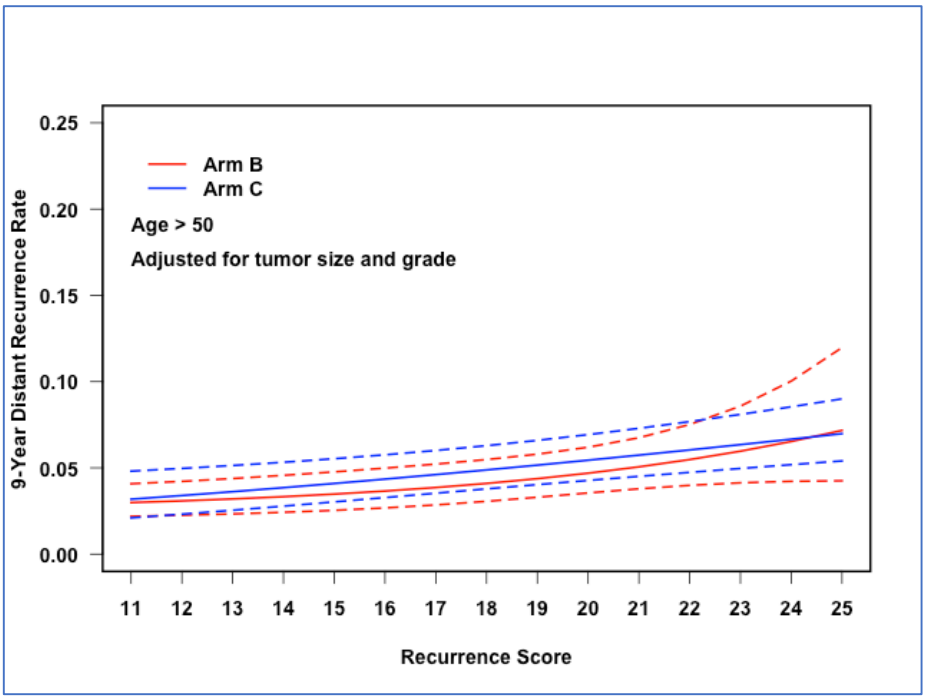


Figure S8. Continuous RS 11-25 and distant recurrence by age (</=50 vs. > 50 years). 9-year distant recurrence rates by treatment arm assignment, RS, and age (RS modeled with a natural spline with 2 degrees of freedom, adjusted for tumor size and grade).

Top panel, age <= 50 years. Bottom panel, age > 50 years.

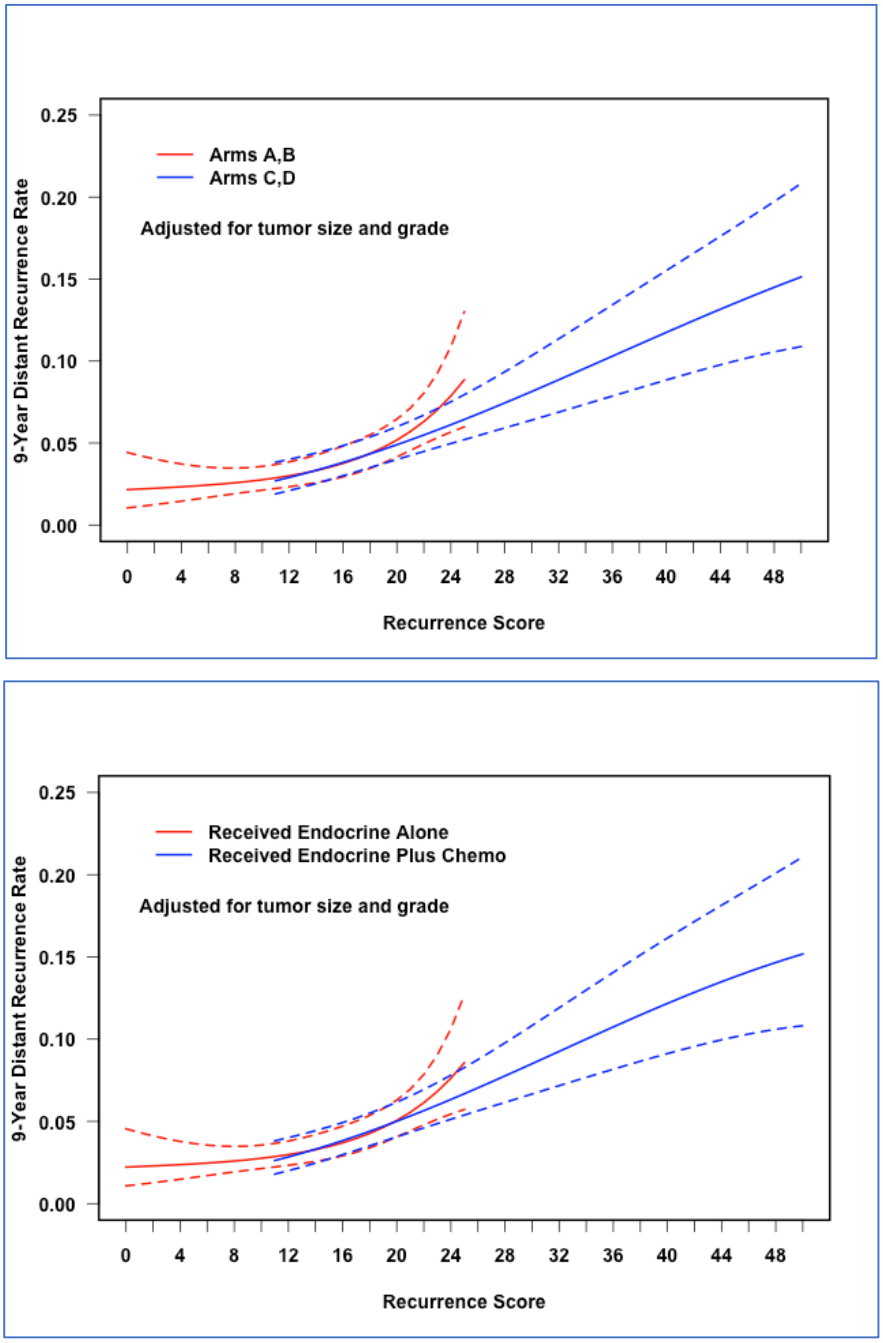


Figure S9. Continuous RS and distant recurrence in all treatment arms (by assigned treatment and treatment given).

9-year distant recurrence rates by treatment and recurrence score (RS modeled with a natural spline with 2 degrees of freedom), with the RS 0-10 and RS > 25 groups included with the randomized population. Top panel by treatment arm, adjusted for tumor size and grade. Bottom panel by treatment received, adjusted for tumor size and grade (8 patients with RS < 11 who received chemo and 89 patients with RS > 25 who did not are excluded from the treatment received analysis).

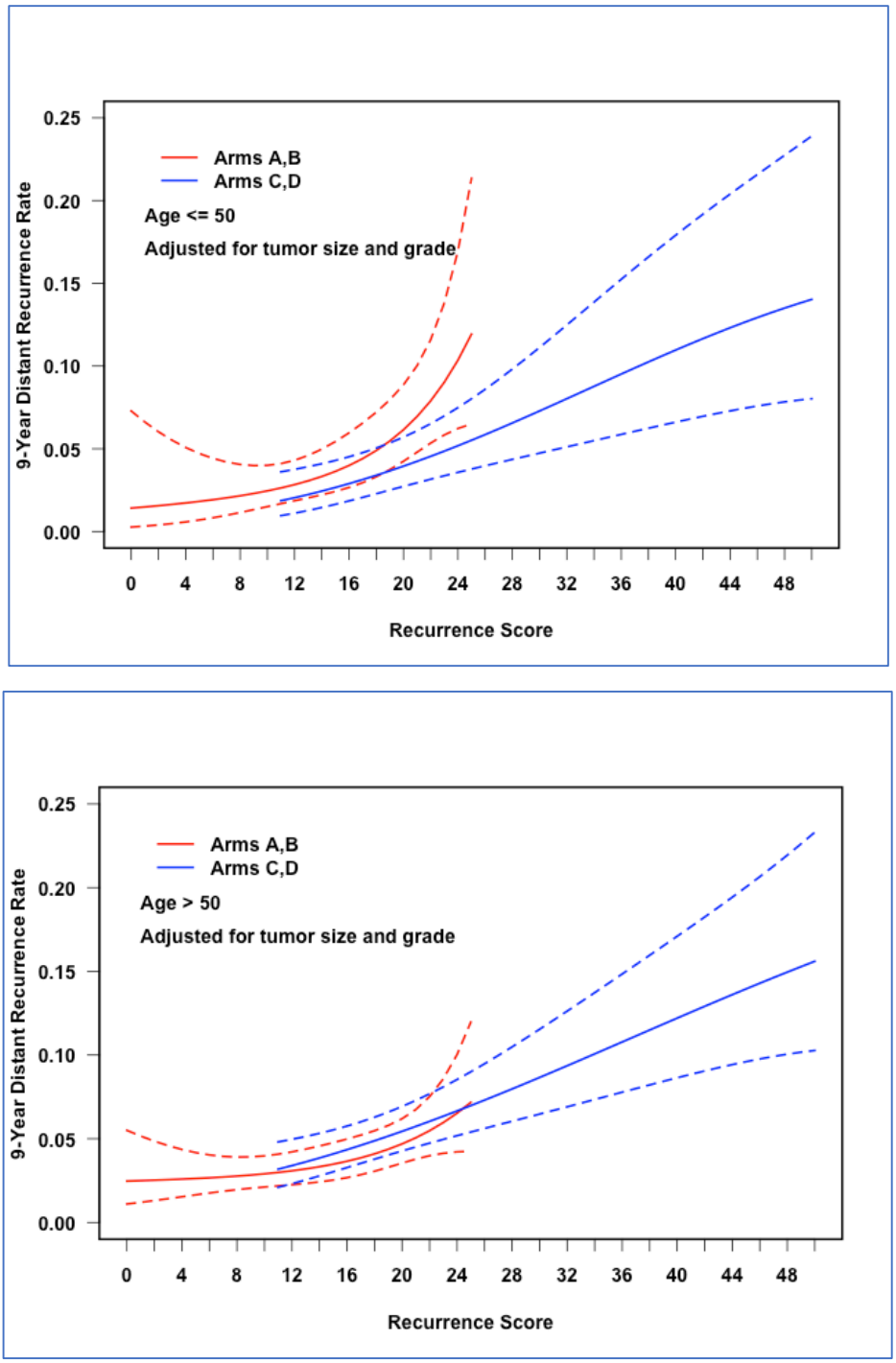
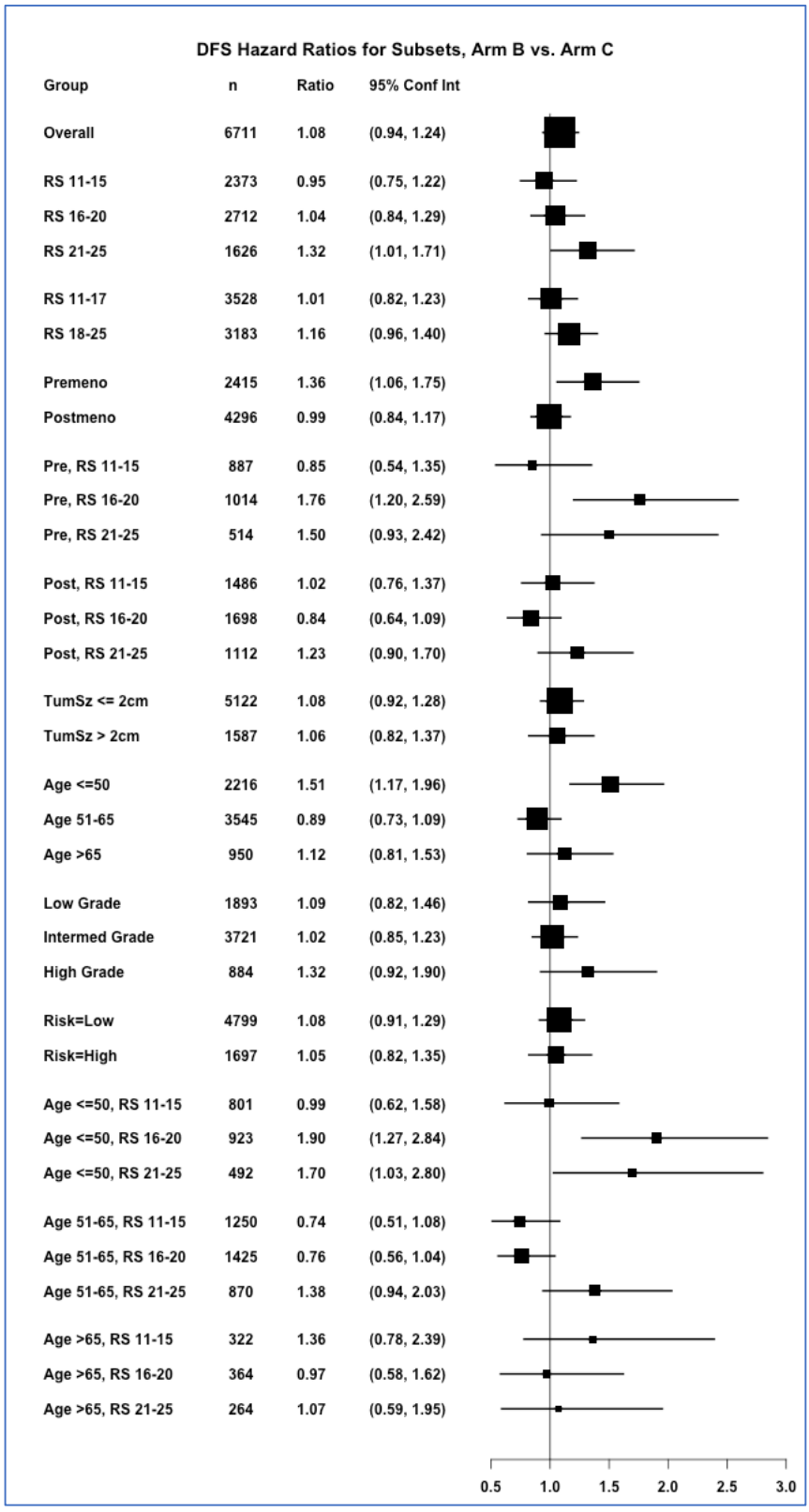


Figure S10. Continuous RS and distant recurrence in all assigned treatment arms by age (</= 50 years vs. > 50 years).

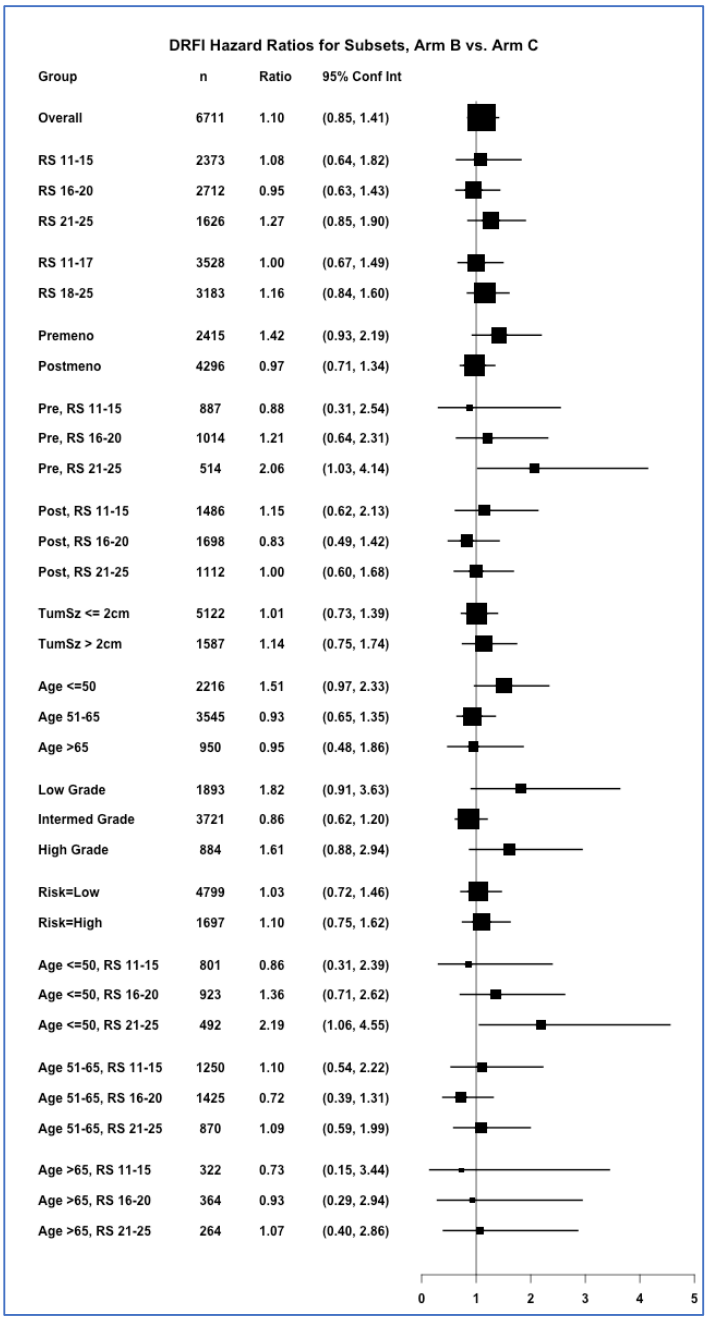
9-year distant recurrence rates by treatment arm, RS, and age (RS modeled with a natural spline with 2 degrees of freedom, adjusted for tumor size and grade), with the RS 0-10 and RS > 25 groups included with the randomized population.

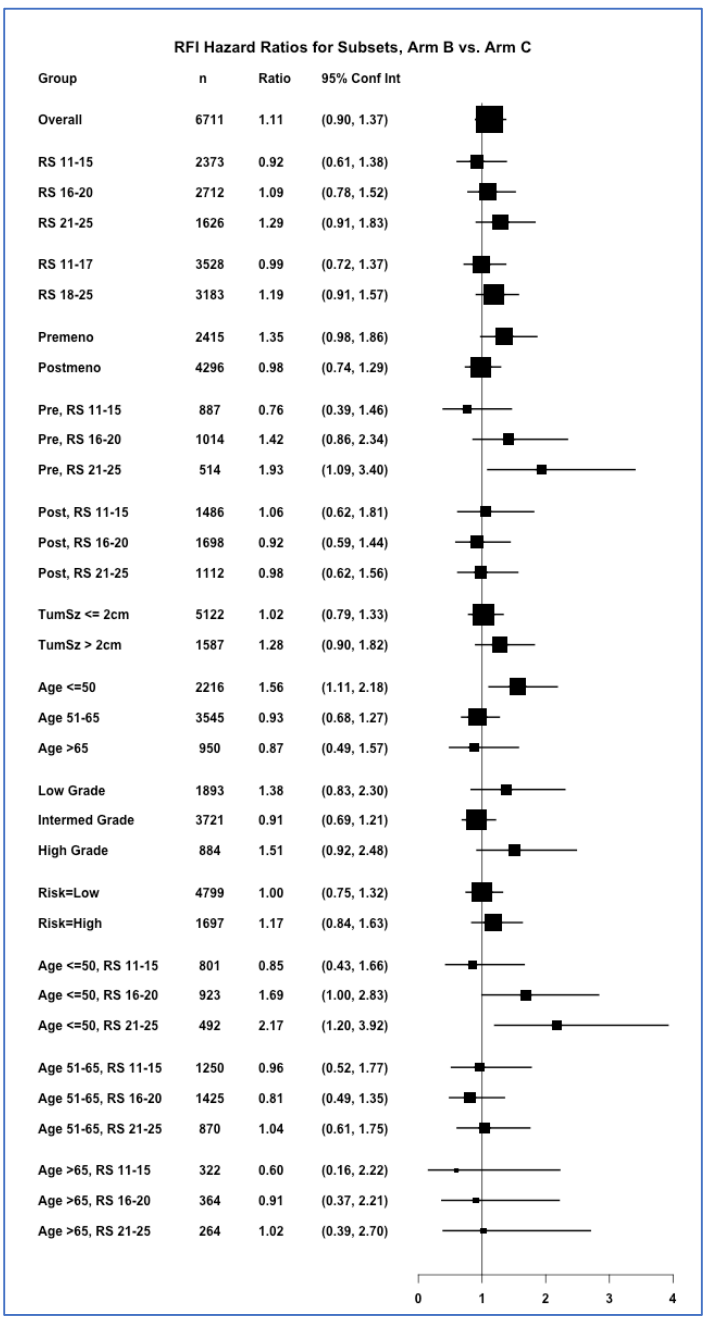
Top panel - age <= 50 years. Bottom panel - age > 50 years.

Figure S11. Recurrence Score 11 to 25: Subgroup Analysis for Comparison of Assigned Treatment Arms.



Forest plots showing comparison of outcomes by treatment arm for endocrine therapy alone (arm B) versus chemoendocrine therapy (arm C) for various covariates in the intention-to-treat analysis for invasive disease-free survival, freedom from breast cancer recurrence at a distant site, and freedom from breast cancer recurrence at a distant or local-regional site. Covariates included prespecified stratification factors, including menopausal status (pre, post), tumor size (</= 2 cm, > 2 cm), and categorical recurrence score (11-15, 16-20, 21-25), Other clinically relevant prognostic covariates examined included age (less than or equal to 50, 51-65, 66 or older), grade (low, intermediate, high), categorical recurrence score using other cutpoints (11-17, 18-25), and clinical risk group as defined in the MINDACT trial (low risk defined by low grade and tumor size <=3cm, intermediate grade and tumor size <=2cm, and high grade and tumor size <=1cm; high risk defined as all other cases with known values for grade and tumor size).


DRFI Hazard Ratios for Subsets, Arm B vs. Arm C
Group n Ratio 95% Conf Int
Overall 6711 1.10 (0.85, 1.41)
RS 11-15 2373 1.08 (0.64, 1.82)
RS 16-20 2712 0.95 (0.63, 1.43)
RS 21-25 1626 1.27 (0.85, 1.90)
RS 11-17 3528 1.00 (0.67, 1.49)
RS 18-25 3183 1.16 (0.84, 1.60)
Premeno 2415 1.42 (0.93, 2.19)
Postmeno 4296 0.97 (0.71, 1.34)
Pre, RS 11-15 887 0.88 (0.31, 2.54)
Pre, RS 16-20 1014 1.21 (0.64, 2.31)
Pre, RS 21-25 514 2.06 (1.03, 4.14)
Post, RS 11-15 1486 1.15 (0.62, 2.13)
Post, RS 16-20 1698 0.83 (0.49, 1.42)
Post, RS 21-25 1112 1.00 (0.60, 1.68)
TumSz <= 2cm 5122 1.01 (0.73, 1.39)
TumSz > 2cm 1587 1.14 (0.75, 1.74)
Age <=50 2216 1.51 (0.97, 2.33)
Age 51-65 3545 0.93 (0.65, 1.35)
Age >65 950 0.95 (0.48, 1.86)
Low Grade 1893 1.82 (0.91, 3.63)
Intermed Grade 3721 0.86 (0.62, 1.20)
High Grade 884 1.61 (0.88, 2.94)
Risk=Low 4799 1.03 (0.72, 1.46)
Risk=High 1697 1.10 (0.75, 1.62)
Age <=50, RS 11-15 801 0.86 (0.31, 2.39)
Age <=50, RS 16-20 923 1.36 (0.71, 2.62)
Age <=50, RS 21-25 492 2.19 (1.06, 4.55)
Age 51-65, RS 11-15 1250 1.10 (0.54, 2.22)
Age 51-65, RS 16-20 1425 0.72 (0.39, 1.31)
Age 51-65, RS 21-25 870 1.09 (0.59, 1.99)
Age >65, RS 11-15 322 0.73 (0.15, 3.44)
Age >65, RS 16-20 364 0.93 (0.29, 2.94)
Age >65, RS 21-25 264 1.07 (0.40, 2.86)
0 1 2 3 4 5


RFI Hazard Ratios for Subsets, Arm B vs. Arm C
Group n Ratio 95% Conf Int
Overall 6711 1.11 (0.90, 1.37)
RS 11-15 2373 0.92 (0.61, 1.38)
RS 16-20 2712 1.09 (0.78, 1.52)
RS 21-25 1626 1.29 (0.91, 1.83)
RS 11-17 3528 0.99 (0.72, 1.37)
RS 18-25 3183 1.19 (0.91, 1.57)
Premeno 2415 1.35 (0.98, 1.86)
Postmeno 4296 0.98 (0.74, 1.29)
Pre, RS 11-15 887 0.76 (0.39, 1.46)
Pre, RS 16-20 1014 1.42 (0.86, 2.34)
Pre, RS 21-25 514 1.93 (1.09, 3.40)
Post, RS 11-15 1486 1.06 (0.62, 1.81)
Post, RS 16-20 1698 0.92 (0.59, 1.44)
Post, RS 21-25 1112 0.98 (0.62, 1.56)
TumSz <= 2cm 5122 1.02 (0.79, 1.33)
TumSz > 2cm 1587 1.28 (0.90, 1.82)
Age <=50 2216 1.56 (1.11, 2.18)
Age 51-65 3545 0.93 (0.68, 1.27)
Age >65 950 0.87 (0.49, 1.57)
Low Grade 1893 1.38 (0.83, 2.30)
Intermed Grade 3721 0.91 (0.69, 1.21)
High Grade 884 1.51 (0.92, 2.48)
Risk=Low 4799 1.00 (0.75, 1.32)
Risk=High 1697 1.17 (0.84, 1.63)
Age <=50, RS 11-15 801 0.85 (0.43, 1.66)
Age <=50, RS 16-20 923 1.69 (1.00, 2.83)
Age <=50, RS 21-25 492 2.17 (1.20, 3.92)
Age 51-65, RS 11-15 1250 0.96 (0.52, 1.77)
Age 51-65, RS 16-20 1425 0.81 (0.49, 1.35)
Age 51-65, RS 21-25 870 1.04 (0.61, 1.75)
Age >65, RS 11-15 322 0.60 (0.16, 2.22)
Age >65, RS 16-20 364 0.91 (0.37, 2.21)
Age >65, RS 21-25 264 1.02 (0.39, 2.70)
0 1 2 3 4

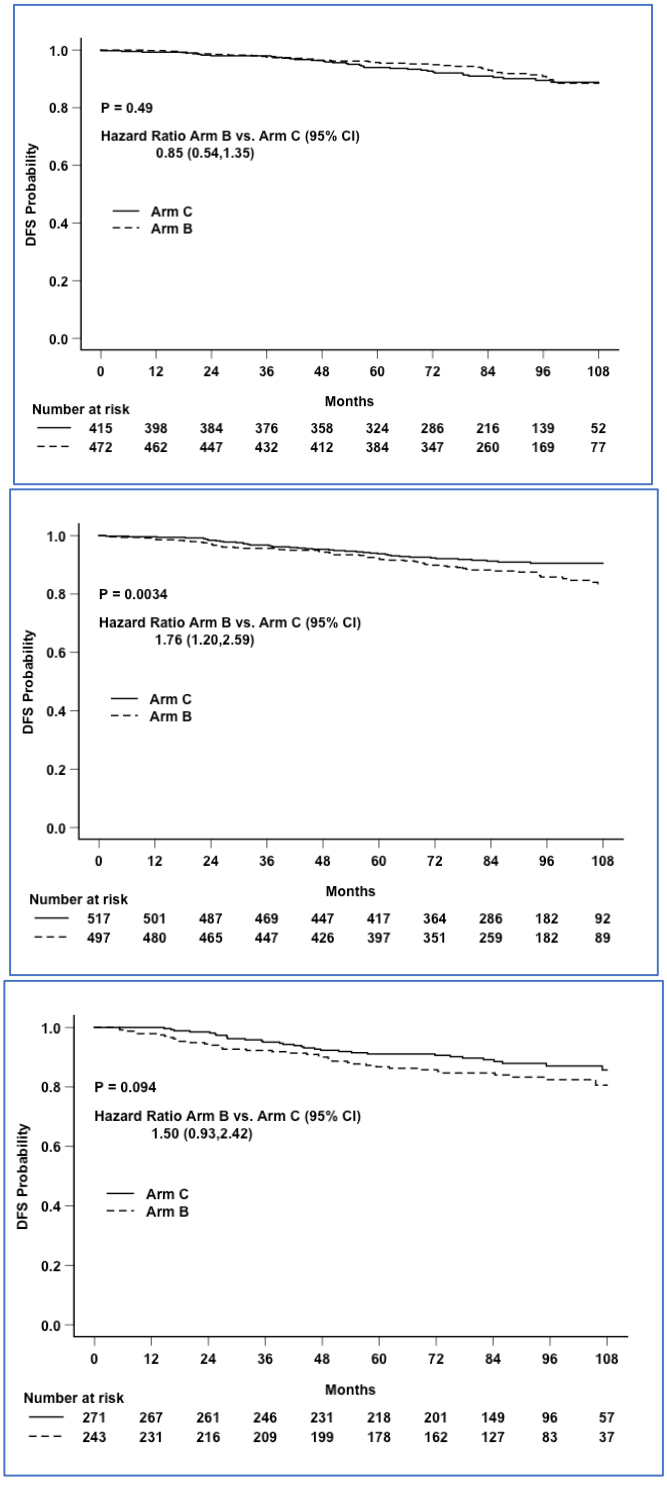


Figure S12. Invasive disease-free survival for premenopausal women with RS 11-15, 16-20, and 21-25 by assigned treatment (intention-to-treat analysis) Kaplan Meier estimates by treatment arm for arm B (endocrine therapy alone) and arm C (chemoendocrine therapy).

RS 11-15 (top), RS 16-20 (middle). RS 21-25 (bottom).

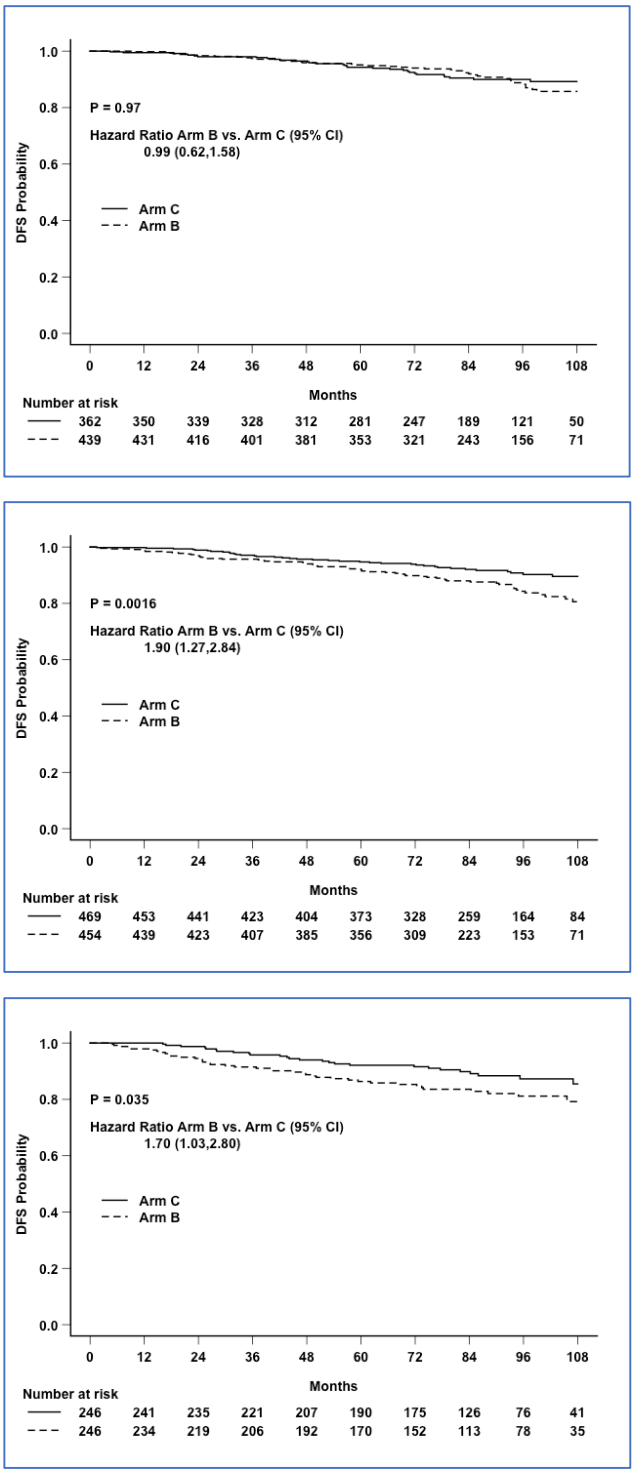


Figure S13. Invasive disease-free survival for women </= 50 years by assigned treatment (intention-to-treat analysis).

Kaplan Meier estimates by treatment arm for arm B (endocrine therapy alone) and arm C (chemoendocrine therapy).

RS 11-15 (top), RS 16-20 (middle), RS 21-25 (bottom).