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Figure S1. Distribution of Recurrence Scores by Menopausal Status

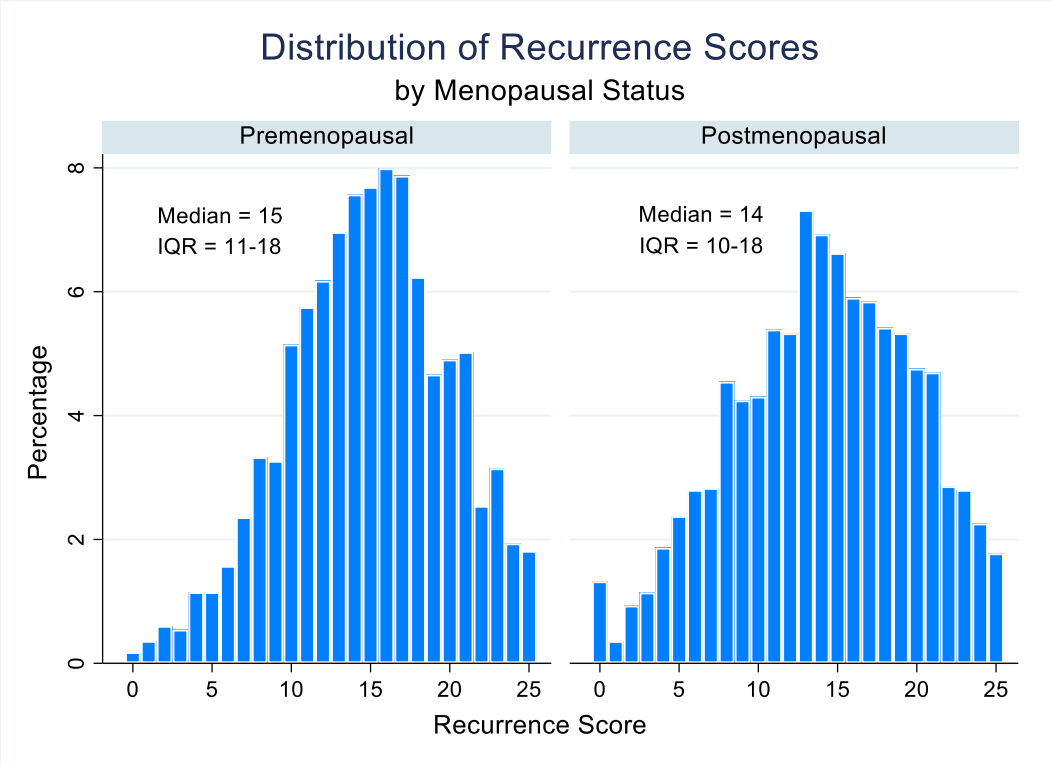
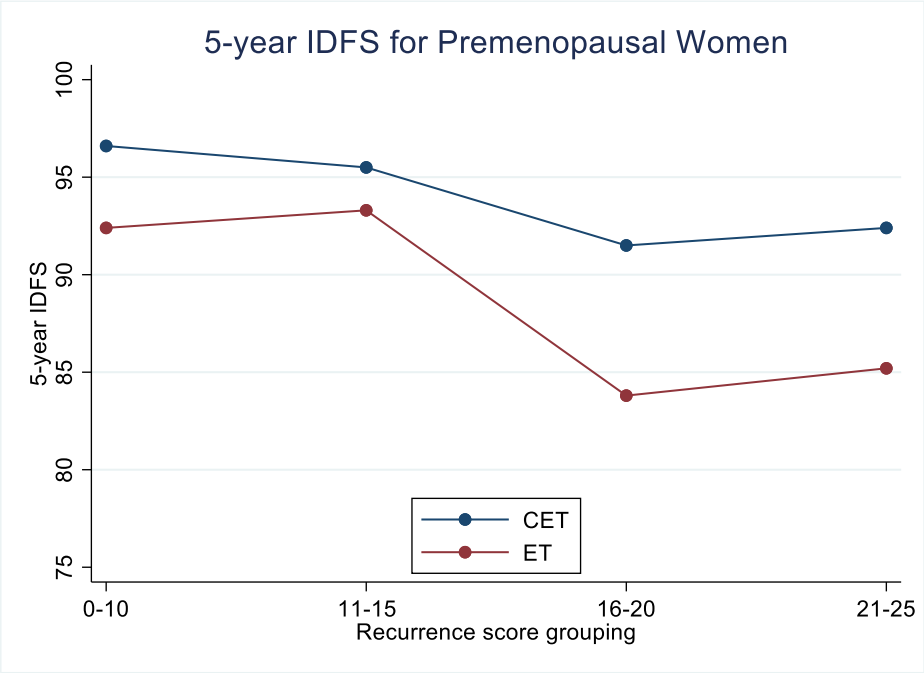


Figure S2. Five-year Invasive Disease-Free Survival when defined as a) Premenopausal Women or b) Women Aged 50 or less

A.



B.

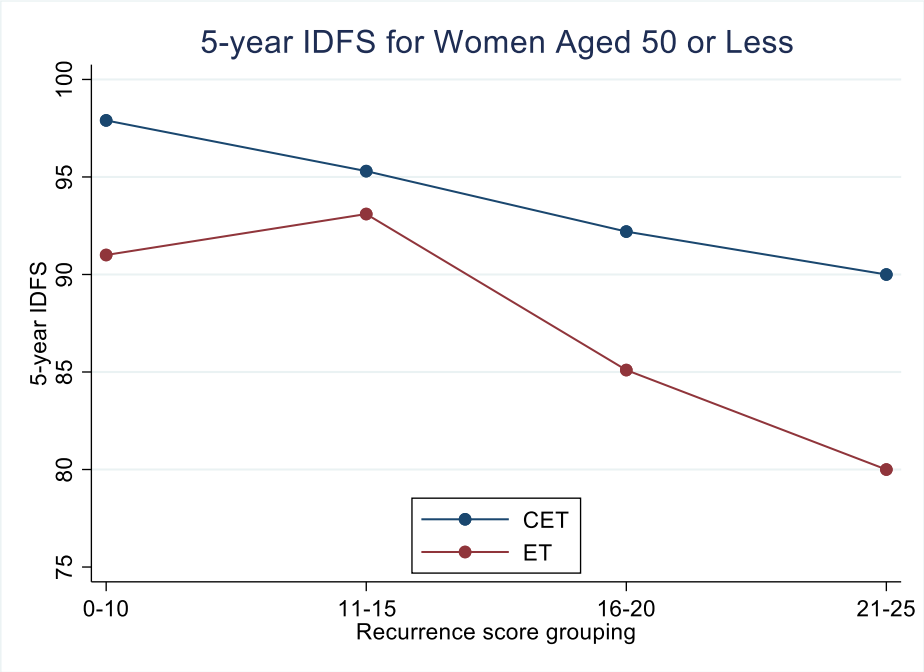
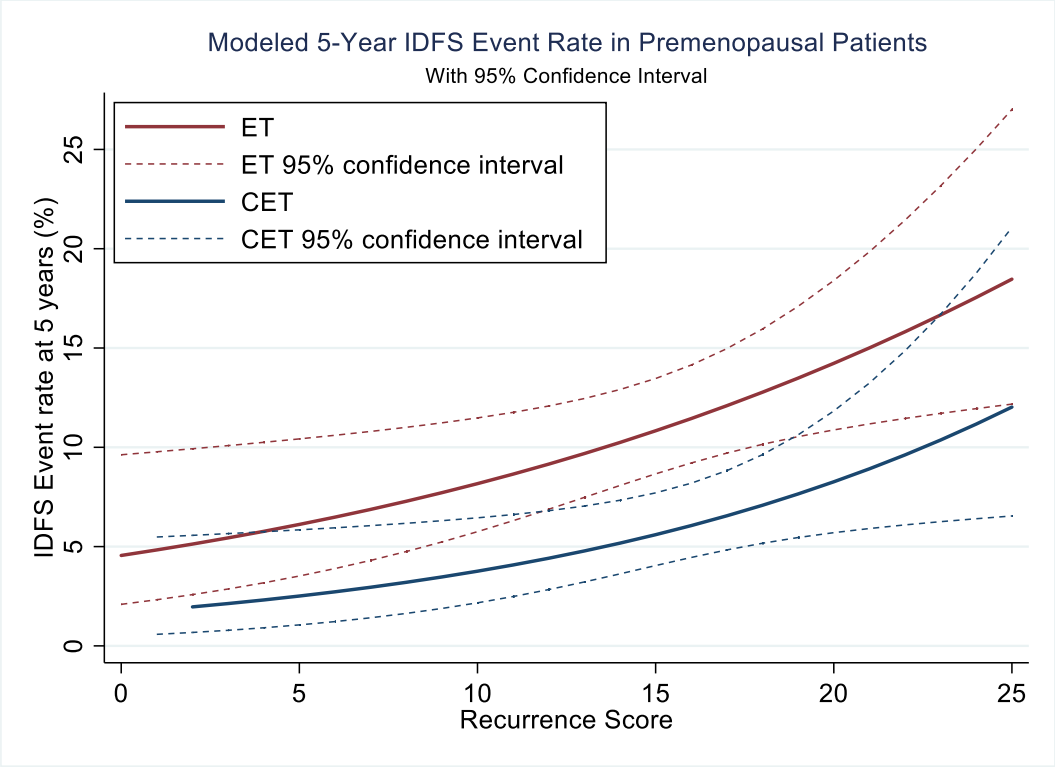


Figure S3. Modeled 5-year IDFS Event Rates for Premenopausal Women by Assigned Treatment Arm

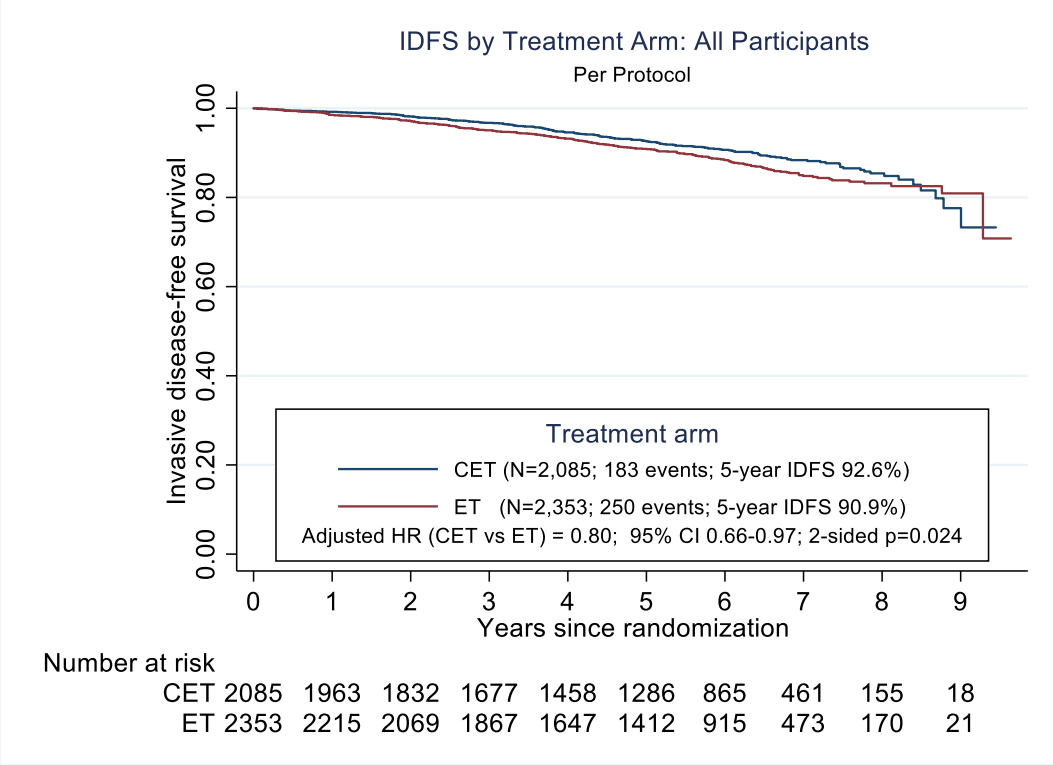


Based on flexible parametric modeling using proportional odds link and model terms for assigned treatment arm, continuous Recurrence Score, and the interaction of treatment arm and RS.

Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002 Aug 15;21(15):2175-97. doi: 10.1002/sim.1203. PMID: 12210632.

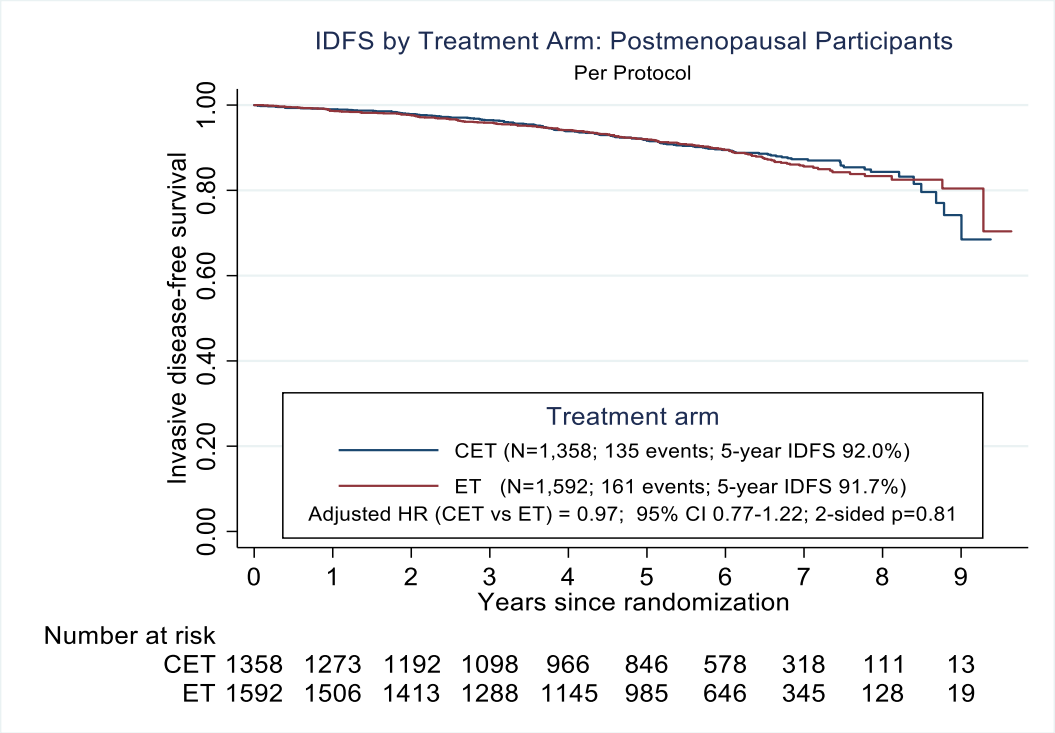
Figure S4. Invasive Disease-Free Survival among Patients with a Recurrence-Score ≤ 25 in all Participants and by Menopausal Status (Per Protocol Population)

4A. Invasive Disease-Free Survival in All Participants by Treatment Arm



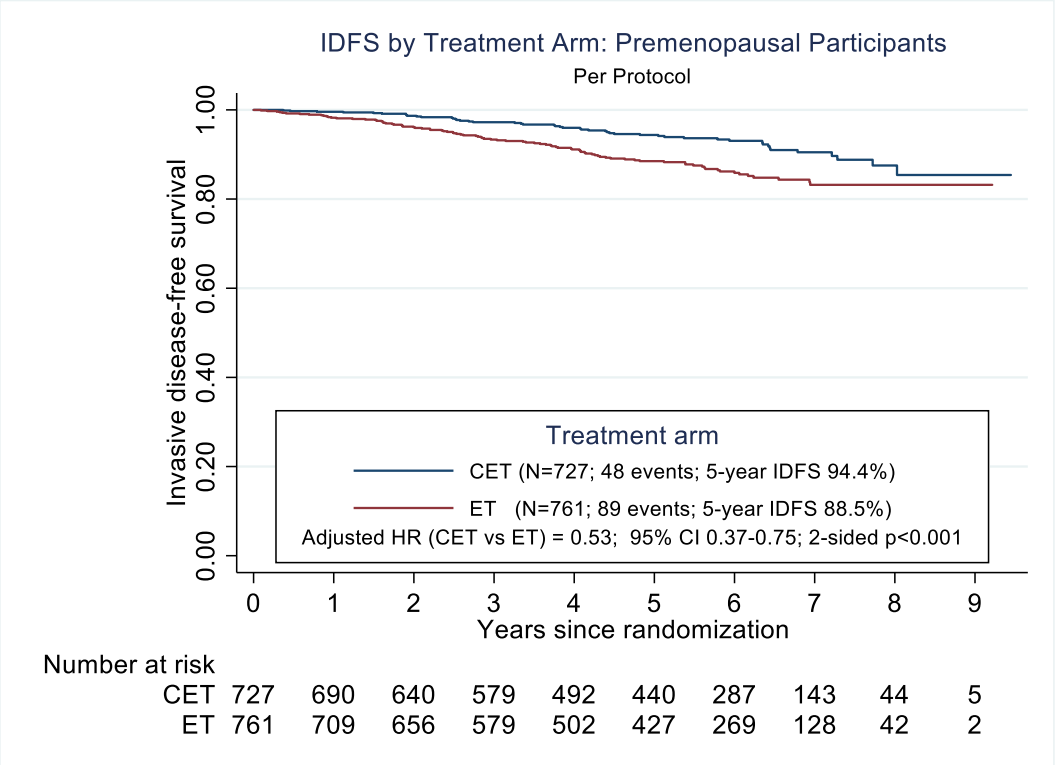
Treatment	Accepted assigned treatment	Did not accept assigned treatment	Total
ET	2,353 (94.2%)	144 (5.8%)	2,497
CET	2,085 (83.8%)	402 (16.2%)	2,487
Overall	4,438 (89.0%)	546 (11.0%)	4,984

4B. Invasive Disease-Free Survival in Postmenopausal Women by Treatment Arm



Treatment	Accepted assigned treatment	Did not accept assigned treatment*	Total
ET	1,592 (95.3%)	79 (4.7%)	1,671
CET	1,358 (81.9%)	300 (18.1%)	1,658
Overall	2,950 (88.6%)	379 (11.4%)	3,329

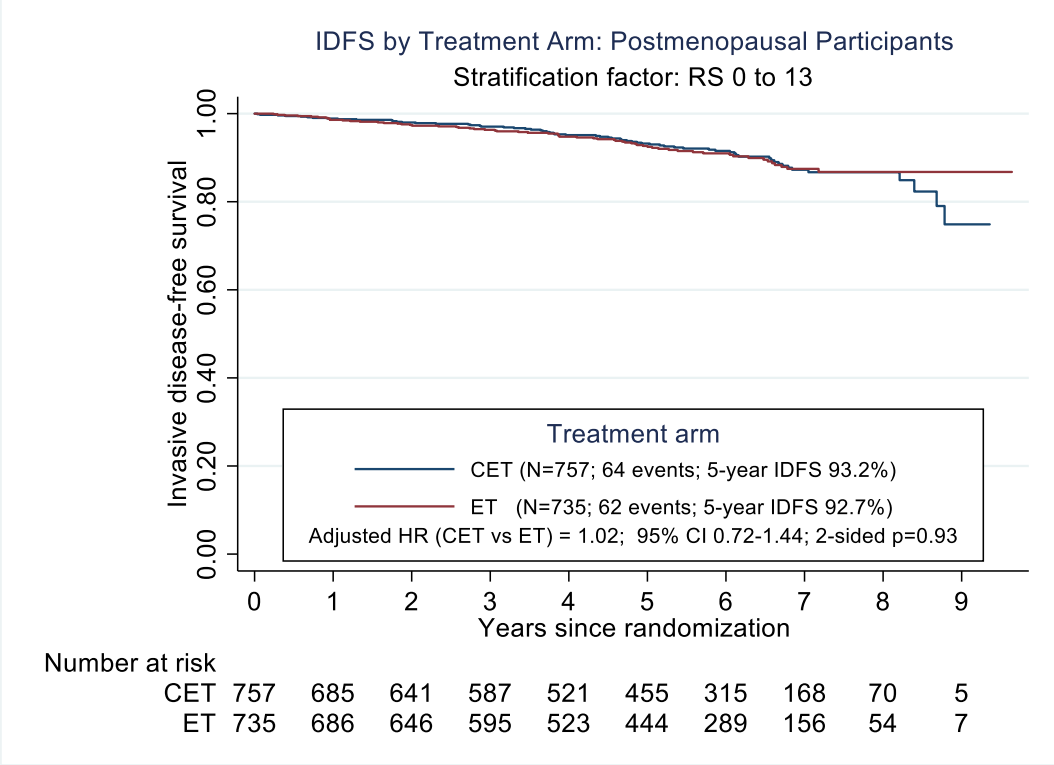
4C. Invasive Disease-Free Survival in Premenopausal Women by Treatment Arm



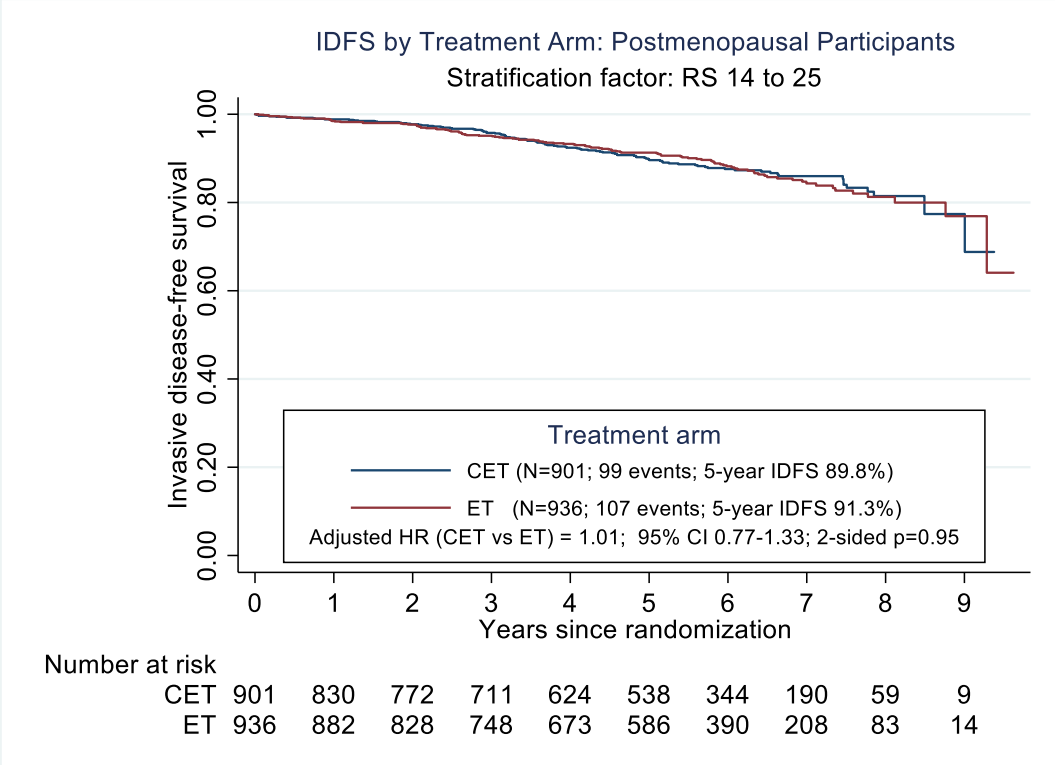
Treatment	Accepted assigned treatment	Did not accept assigned treatment	Total
ET	761 (92.1%)	65 (7.9%)	826
CET	727 (87.7%)	102 (12.3%)	829
Overall	1,488 (89.9%)	167 (10.1%)	1,655

Figure S5. Invasive Disease-Free Survival Stratified by Recurrence Score Category and Menopausal Status in a Post-Hoc Analysis

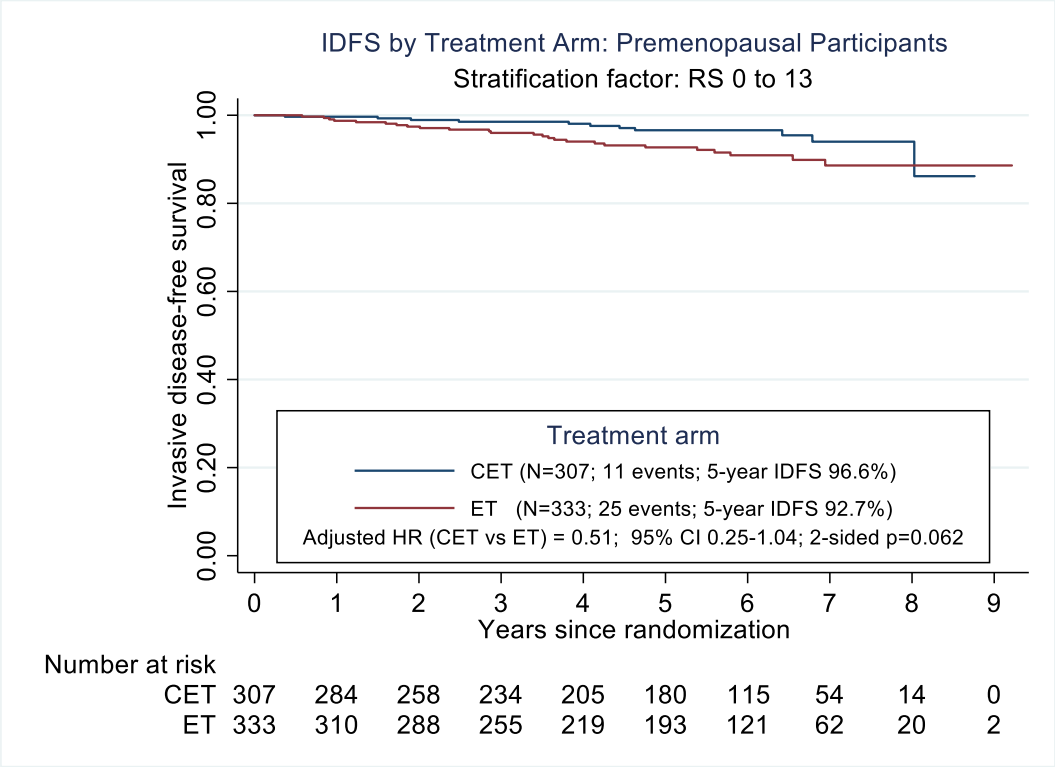
5A. Invasive Disease-Free Survival in Postmenopausal Patients with Recurrence Score 0-13



5B. Invasive Disease-Free Survival in Postmenopausal Patients with Recurrence Score 14-25



5C. Invasive Disease-Free Survival in Premenopausal Patients with Recurrence Score 0-13



5D. Invasive Disease-Free Survival in Premenopausal Patients with Recurrence Score 14-25

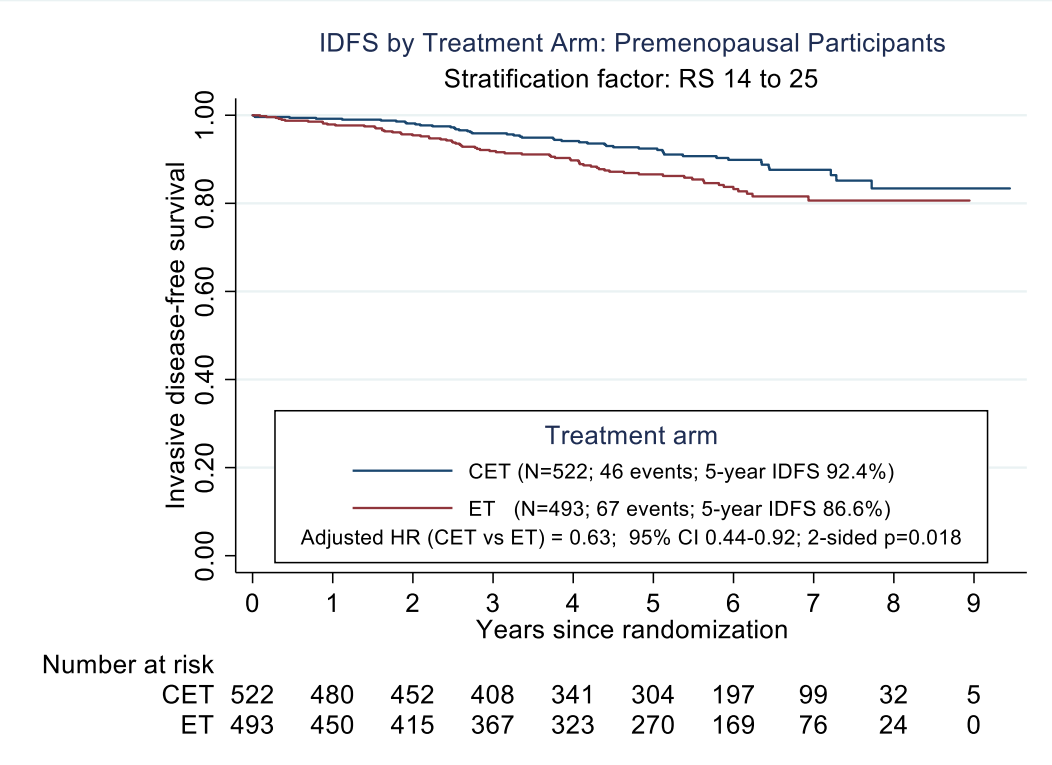
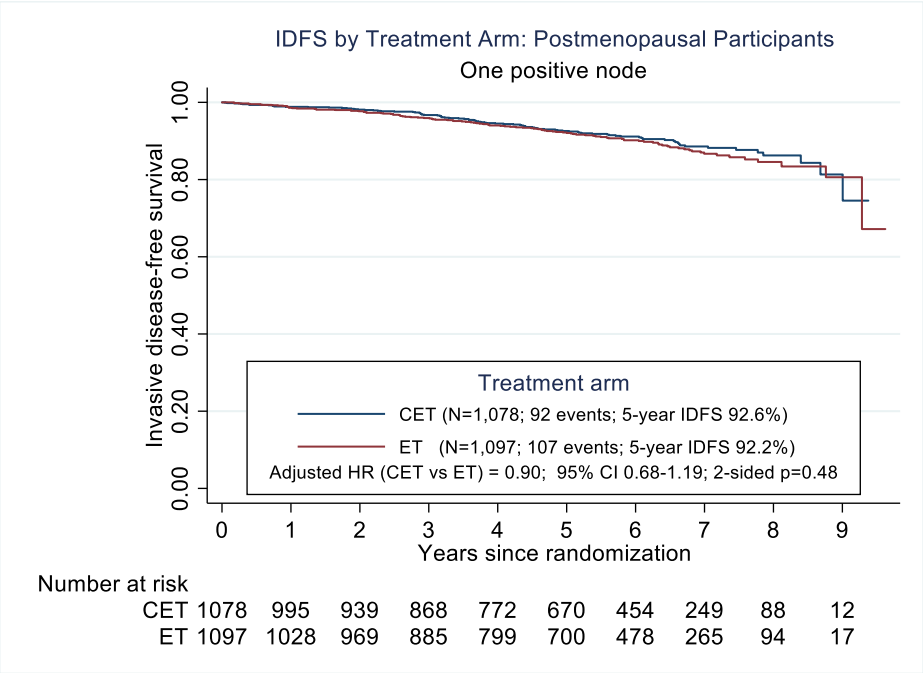
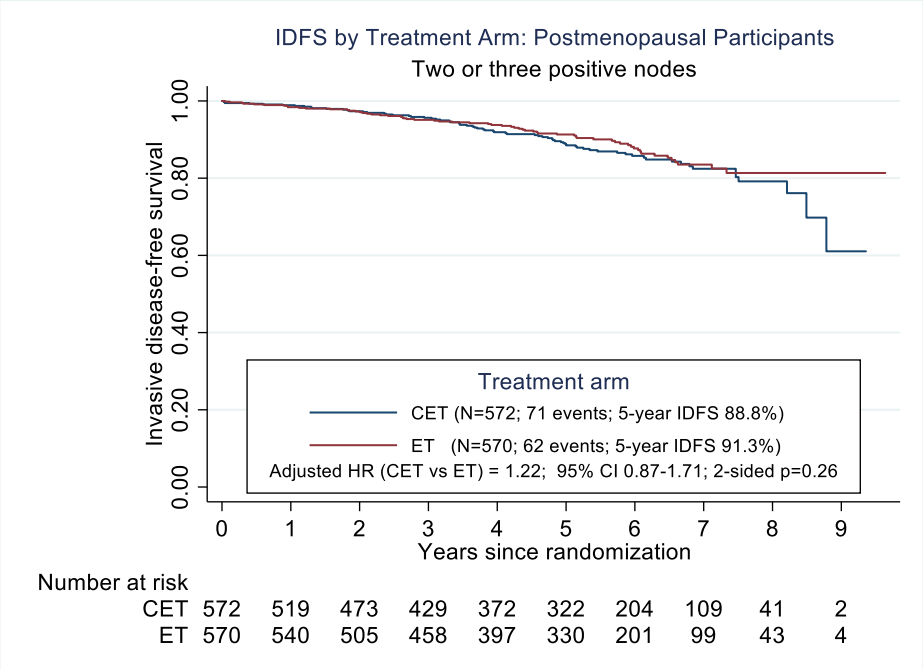


Figure S6. Invasive Disease-Free Survival Stratified by Number of Nodes and Menopausal Status

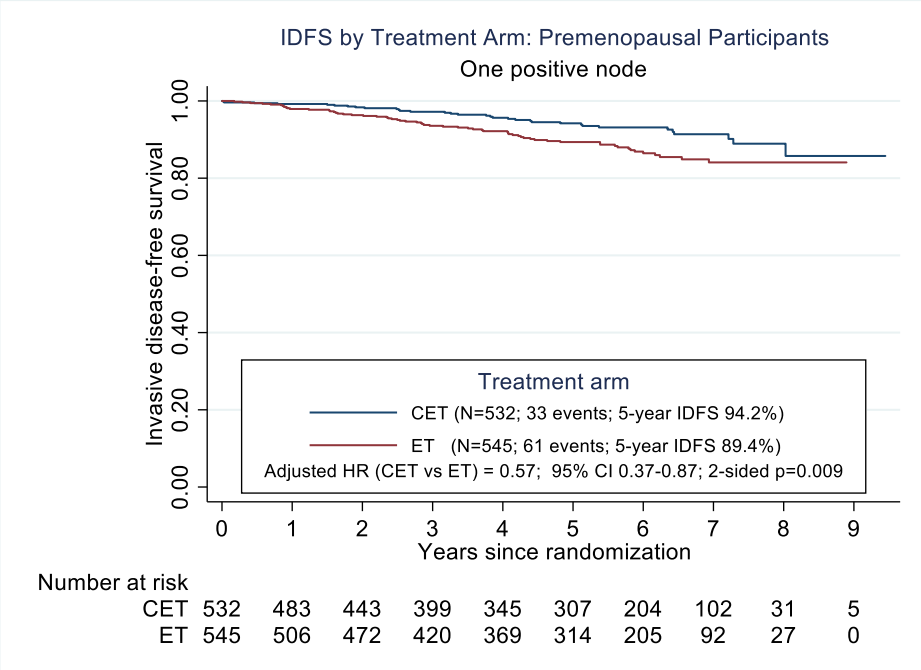
S6A. Invasive Disease-Free Survival in Postmenopausal Patients with 1 Lymph Node



6B. Invasive Disease-Free Survival in Postmenopausal Patients with 2-3 Lymph Nodes



6C. Invasive Disease-Free Survival in Premenopausal Patients with 1 Lymph Node



6D. Invasive Disease-Free Survival in Premenopausal Patients with 2-3 Lymph Nodes

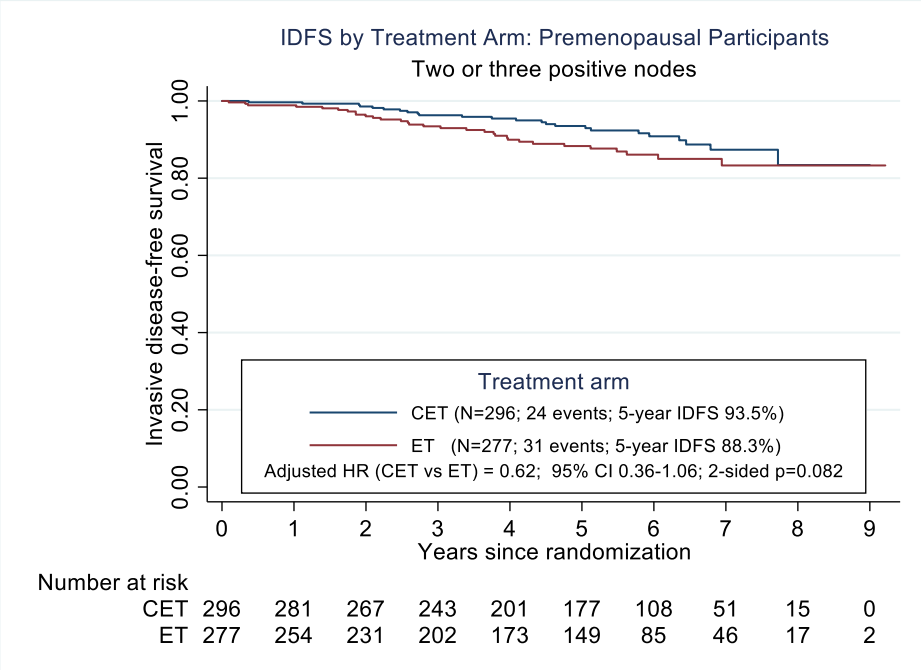
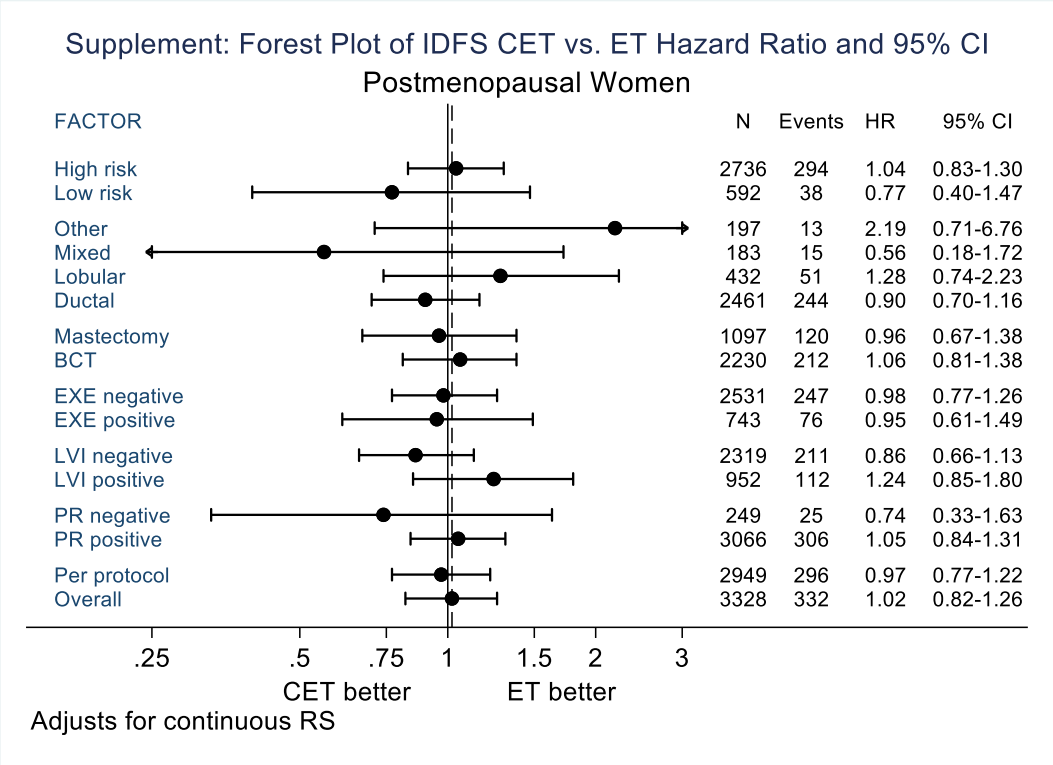
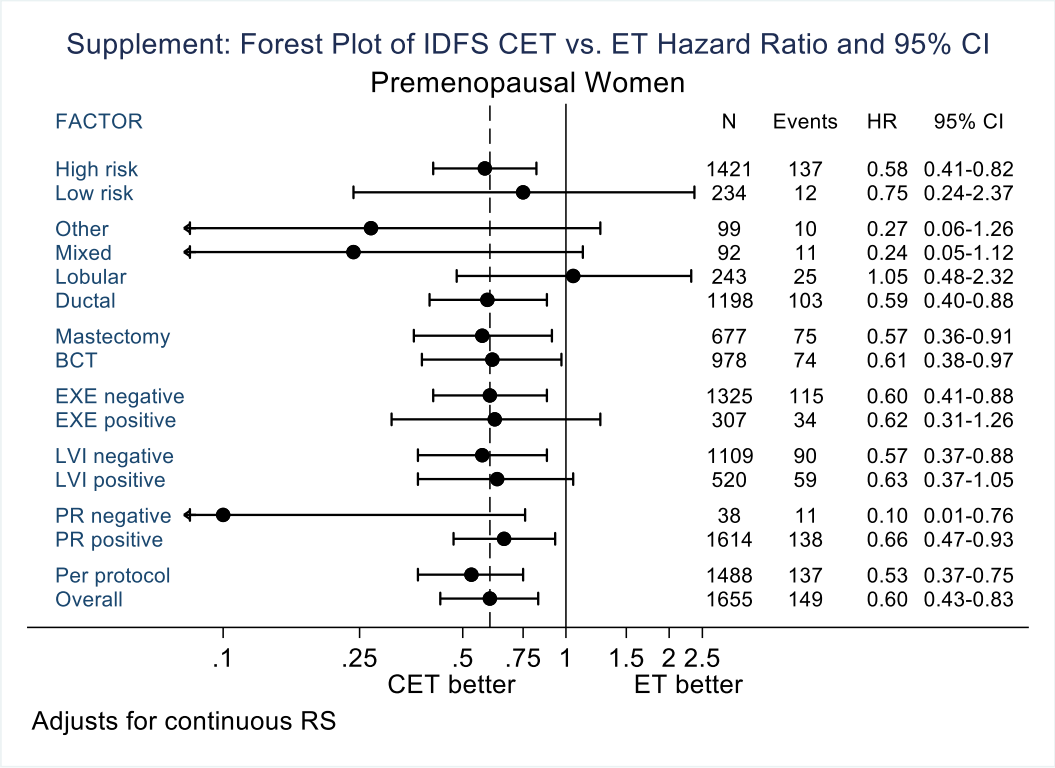


Figure S7. Forest Plot of Invasive Disease-Free Survival with Additional Subgroups



Low risk is tumor size < 2cm AND Grade 1, using a modified version of Adjuvant! Online. High risk is everything else

Arrowheads indicate that the confidence interval extends beyond the boundaries of the 0.25 to 3.0 range



Low risk is tumor size < 2cm AND Grade 1, using a modified version of Adjuvant! Online. High risk is everything else

Arrowheads indicate that the lower confidence bound is below the minimum value for the graph

Table S1. Baseline Participant Characteristics with Additional Variables

	Total (n=5018)		Endocrine Therapy Alone (n=2507)		Chemo and Endocrine Therapy (n=2511)	
RACE						
White	3295	65.7%	1628	64.9%	1667	66.4%
Black	251	5.0%	121	4.8%	130	5.2%
Asian	324	6.5%	170	6.8%	154	6.1%
Other/Unknown	1148	22.9%	588	23.5%	560	22.3%
ETHNICITY						
Hispanic	622	12.4%	325	13.0%	297	11.8%
Non-Hispanic	3426	68.3%	1695	67.6%	1731	68.9%
Unknown	970	19.3%	487	19.4%	483	19.2%
MEDIAN AGE (RANGE)	57.5 (18.3 – 87.6)		57.2 (18.3 – 86.0)		57.9 (28.0 – 87.6)	
AGE CATEGORY						
< 40 years	147	2.9%	80	3.2%	67	2.7%
40-49 years	1077	21.5%	547	21.8%	530	21.1%
50-59 years	1675	33.4%	838	33.4%	837	33.3%
60-69 years	1538	30.6%	761	30.4%	777	30.9%
≥ 70 years	581	11.6%	281	11.2%	300	12.0%
MENOPAUSAL STATUS						
Pre-menopausal	1665	33.2%	831	33.2%	834	33.2%
Post-menopausal	3353	66.8%	1676	66.8%	1677	66.8%
RECURRENCE SCORE						
0-13	2147	42.8%	1071	42.7%	1076	42.9%
14-25	2871	57.2%	1436	57.3%	1435	57.1%
AXILLARY SURGERY						
Axillary lymph node dissection (with or without sentinel node mapping)	3140	62.6%	1571	62.7%	1569	62.5%
Sentinel node biopsy without axillary lymph node dissection	1878	37.4%	936	37.3%	942	37.5%
HORMONE RECEPTOR STATUS						
ER+ and PR+	4701	94.3%	2349	94.2%	2352	94.3%
ER+ and PR-	286	5.7%	144	5.8%	142	5.7%
Not reported	31					
TUMOR SIZE						
T1	2923	58.3%	1470	58.6%	1453	57.9%
T2	1843	36.7%	912	36.4%	931	37.1%
T3	252	5.0%	125	5.0%	127	5.1%

	Total		Endocrine Therapy Alone		Chemo and Endocrine Therapy	
	(n=5018)		(n=2507)		(n=2511)	
HISTOLOGIC GRADE						
Low	1218	24.3%	607	24.3%	611	24.4%
Intermediate	3215	64.3%	1580	63.2%	1635	65.3%
High	507	10.1%	279	11.2%	228	9.1%
Unknown	63	1.3%	34	1.4%	29	1.2%
Not reported	15					
HISTOLOGY						
Invasive ductal carcinoma	3673	74.6%	1840	74.8%	1833	74.4%
Invasive lobular carcinoma	674	13.7%	316	12.9%	358	14.5%
Invasive mixed ductal/lobular	278	5.6%	146	5.9%	132	5.4%
Other	299	6.1%	157	6.4%	142	5.8%
Not reported	94					
EXTRANODAL EXTENSION						
No/Unknown	3874	78.7%	1932	78.5%	1942	78.8%
Yes	1051	21.3%	528	21.5%	523	21.2%
Not reported	93					
CLINICAL RISK						
High risk	4182	83.3%	2101	83.8%	2081	82.9%
Low risk	836	16.7%	406	16.2%	430	17.1%

Clinical Risk: Low risk is tumor size < 2cm AND Grade 1, using a modified version of Adjuvant! Online. High risk is everything else

ER = Estrogen Receptor; PR = Progesterone Receptor

Table S2. Treatment Administered and Exploratory Analyses within Treatment Arm

Table S2A. Treatment administered by menopausal status and randomized arm

	Premenopausal		**Postmenopausal**	
	Chemoendocrine Therapy	Endocrine Therapy	Chemoendocrine Therapy	Endocrine Therapy
Total Number	829	826	1658	1671
Adjuvant Chemotherapy	(n=721)	(n=53)	(n=1332)	(n=53)
Anthracycline w/o Taxane	35 (5%)	1 (2%)	35 (3%)	3 (6%)
Anthracycline and Taxane	387 (54%)	25 (47%)	522 (39%)	19 (36%)
Taxane & Cyclophosphamide	298 (41%)	25 (47%)	758 (57%)	30 (57%)
Other	1 (<1%)	2 (4%)	17 (1%)	1 (2%)
None/Not Reported	108	773	326	1618
Endocrine Therapy*	(n=805)	(n=810)	(n=1579)	(n=1644)
AI	44 (5%)	16 (2%)	1339 (85%)	1414 (86%)
OFS and AI	20 (2%)	37 (5%)	4 (<1%)	8 (<1%)
OFS and Tam	26 (3%)	94 (12%)	2 (<1%)	3 (<1%)
OFS, Tam, and AI	5 (1%)	23 (3%)	1 (<1%)	2 (<1%)
Tam	673 (84%)	611 (75%)	144 (9%)	133 (8%)
Tam and AI	10 (1%)	20 (2%)	47 (3%)	69 (4%)
Other	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
None	26 (3%)	8 (1%)	39 (2%)	14 (1%)
Not Reported	24	16	79	27

* During first 12 months after randomization; restricted to patients included in the survival analyses

Treatment reporting

Chemotherapy type with start and stop dates was expected to be reported for both treatment arms in order to capture any chemotherapy that was administered regardless of treatment arm assignment. Type of endocrine therapy administered was recorded at 6, 12, 18, 24, 30, 36, 48, and 60 months. Use of ovarian function suppression was also recorded at those follow-up visits as well as the occurrence of regular menstrual periods for women who reported being premenopausal at registration for the trial.

Exploratory analyses of treatment and outcomes

Since all treatment is post-randomization, the analyses must be landmarked to start survival time follow-up after a designated treatment period or alternatively use time-dependent Cox regression analyses. Given that current median follow-up is only 5.1 years, extensive analyses of endocrine use requires additional follow-up. Below, 12-month landmarked analyses of some treatment comparisons are presented based only on treatment within the first year. These analyses are exploratory and preliminary, do not adjust for multiplicity, and may lack power due to small numbers. Furthermore, selection of treatment type within the randomized arm depends on clinical factors and such factors are adjusted for in these analyses.

Table S2B. Exploratory analyses of treatment or patient characteristics and association with IDFS within menopausal status and assigned arm

Menopausal status	Assigned Arm	Inclusion criteria	Group 1	Group 2	HR (1 vs. 2) 95% CI
Postmenopausal	CET	Received chemo in 12 months	Anthracycline & taxane (n=477)	Taxane & cyclophosphamide (n=724)	0.89 (0.60-1.32)
Premenopausal	CET	Received chemo in 12 months	Anthracycline & taxane (n=356)	Taxane & cyclophosphamide (n=289)	0.93 (0.50-1.72)
Premenopausal	CET	Received chemo in 12 months	No periods in 12 months (n=481)	Periods during 12 months (n=188)	0.82 (0.43-1.55)
Premenopausal	CET	Received chemo in 12 months & Age <50	No periods in 12 months (n=316)	Periods during 12 months (n=145)	0.91 (0.42-1.99)
Premenopausal	ET	Received endocrine therapy in 12 months	OFS in 12 months (n=144)	No OFS in 12 months (n=594)	0.71 (0.38-1.30)
Premenopausal	ET	Received endocrine therapy in 12 months & Age <50	OFS in 12 months (n=112)	No OFS in 12 months (n=416)	0.60 (0.30-1.20)

All analyses are landmarked starting at 12 months post-randomization. Analyses are adjusted for age, RS, tumor size, and grade.

Table S3. Analysis of Invasive Disease-Free Survival in the Overall Population

Table S3A. Primary Analysis: Test of the Interaction of Chemotherapy (Predictive Effect) with Recurrence-Score

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.67	0.17	0.38 - 1.18
RS (per unit change)	1.05	0.0001	1.02 - 1.07
Menopausal status	1.07	0.48	0.88 - 1.30
Chemotherapy x RS Interaction	1.02	0.35	0.98 - 1.05

RS=Recurrence-Score, CI=Confidence Interval

Table S3B. Primary Analysis: Test of the Prognostic Effect of Chemotherapy adjusting for Recurrence-Score

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.86	0.10	0.72 - 1.03
RS (per unit change)	1.05	<0.0001	1.04 - 1.07
Menopausal status	1.07	0.49	0.88 - 1.30

Table S3C. Test of the Interaction of Chemotherapy with the Stratification Factor Menopausal Status

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.59	0.002	0.43 - 0.83
RS (per unit change)	1.05	<0.0001	1.04 - 1.07
Menopausal status	0.84	0.19	0.65 - 1.09
Chemotherapy x Menopausal Status	1.71	0.008	1.15 – 2.54

Table S4. Analysis of Invasive Disease-Free Survival in the Postmenopausal Population

Table S4A. Test of the Interaction of Chemotherapy (Predictive Effect) with Recurrence-Score in Postmenopausal Women

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.81	0.54	0.42 - 1.57
RS (per unit change)	1.04	0.003	1.01 - 1.07
Chemotherapy x RS Interaction	1.01	0.48	0.97 - 1.06

RS=Recurrence-Score, CI=Confidence Interval

Table S4B. Test of Chemotherapy Benefit Adjusting for Recurrence-Score in Postmenopausal Women

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	1.02	0.89	0.82 - 1.26
RS (per unit change)	1.05	<0.0001	1.03 - 1.07

Table S4C. Test of Chemotherapy Benefit Adjusting for Recurrence-Score and Other Prognostic Variables in a Multivariable Model for Postmenopausal Women

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	1.03	0.79	0.83 - 1.28
RS (per unit change)	1.05	<0.0001	1.03 - 1.07
Positive nodes 2 vs 1	1.22	0.12	0.95 – 1.57
Positive nodes 3 vs 1	1.55	0.013	1.10 – 2.20
Grade 2 vs 1	1.30	0.08	0.97 – 1.73
Grade 3 vs 1	1.74	0.003	1.20 – 2.53
Tumor size 2-5 cm vs < 2 cm	1.47	0.001	1.17 – 1.84
Tumor size >5 cm vs < 2 cm	1.96	0.004	1.24 – 3.11
Age (per year)	1.02	0.02	1.00 – 1.03

Harrell's c-statistic for fit = 0.63

Table S5. Analysis of Invasive Disease-Free Survival in the Premenopausal Population

Table 5A. Test of the Interaction of Chemotherapy (Predictive Effect) with Recurrence-Score in Premenopausal Women

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.31	0.057	0.09 - 1.04
RS (per unit change)	1.05	0.018	1.01 - 1.09
Chemotherapy x RS Interaction	1.04	0.26	0.97 - 1.12

RS=Recurrence-Score, CI=Confidence Interval

Table 5B. Test of Chemotherapy Benefit Adjusting for Recurrence-Score in Premenopausal Women

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.60	0.002	0.43 – 0.83
RS (per unit change)	1.06	0.0002	1.03 - 1.10

Table S5C. Test of Chemotherapy Benefit Adjusting for Recurrence-Score and Other Prognostic Variables in a Multivariable Model for Premenopausal Women

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.60	0.002	0.43 – 0.83
RS (per unit change)	1.06	0.001	1.02 - 1.09
Positive nodes 2 vs 1	1.15	0.46	0.80 – 1.67
Positive nodes 3 vs 1	1.00	0.99	0.56 – 1.80
Grade 2 vs 1	1.34	0.21	0.85 – 2.12
Grade 3 vs 1	1.46	0.22	0.80 – 2.65
Tumor size 2-5 cm vs < 2 cm	1.52	0.02	1.08 – 2.13
Tumor size >5 cm vs < 2 cm	1.48	0.25	0.76 – 2.88
Age (per year)	0.97	0.03	0.94 - 1.00

Harrell's c-statistic for fit = 0.64

Table S6. Baseline Characteristics by Menopausal Status

	Total (n=5018)		Premenopausal (n=1665)		Postmenopausal (n=3353)	
RACE						
White	3295	65.7%	981	58.9%	2314	69.0%
Black	251	5.0%	57	3.4%	194	5.8%
Asian	324	6.5%	188	11.3%	136	4.1%
Other/Unknown	1148	22.9%	439	26.4%	709	21.1%
ETHNICITY						
Hispanic	622	12.4%	231	13.4%	391	11.7%
Non-Hispanic	3426	68.3%	1071	64.3%	2355	70.2%
Unknown	970	19.3%	363	21.8%	607	11.7%
MEDIAN AGE (RANGE)	57.5 (18.3 – 87.6)		47.3 (27.8 – 65.7)		62.9 (18.3 – 87.6)	
AGE CATEGORY						
< 40 years	147	2.9%	142	8.5%	5	0.2%
40-49 years	1077	21.5%	1012	60.8%	65	1.9%
50-59 years	1675	33.4%	507	30.5%	1168	34.8%
60-69 years	1538	30.6%	4	0.2%	1534	45.8%
≥ 70 years	581	11.6%	0	0%	581	17.3%
RECURRENCE SCORE						
0-13	2147	42.8%	645	38.7%	1502	44.8%
14-25	2871	57.2%	1020	61.3%	1851	55.2%
AXILLARY SURGERY						
Axillary lymph node dissection (with or without sentinel node mapping)	3140	62.6%	1105	66.4%	2035	60.7%
Sentinel node biopsy without axillary lymph node dissection	1878	37.4%	560	33.6%	1318	39.3%
HORMONE RECEPTOR STATUS						
ER+ and PR+	4701	94.3%	1620	97.8%	3081	92.5%
ER+ and PR-	286	5.7%	37	2.2%	249	7.5%
Not reported	31					
POSITIVE NODES						
1 node	3275	65.5%	1084	65.3%	2191	65.6%
2 nodes	1266	25.3%	427	25.7%	839	25.1%
3 nodes	460	9.2%	149	9.0%	311	9.3%
Not reported	17					
TUMOR SIZE						
T1	2923	58.3%	938	56.3%	1985	59.2%
T2	1843	36.7%	621	37.3%	1222	36.4%
T3	252	5.0%	106	6.4%	146	4.4%
HISTOLOGIC GRADE						
Low	1218	24.3%	361	21.7%	857	25.6%
Intermediate	3215	64.3%	1122	67.6%	2093	62.6%
High	507	10.1%	159	9.6%	348	10.4%
Unknown	63	1.3%	18	1.1%	45	1.4%
Not reported	15					

	Total (n=5018)		Premenopausal (n=1665)		Postmenopausal (n=3353)	
HISTOLOGY						
Invasive ductal carcinoma	3673	74.6%	1199	73.2%	2474	75.3%
Invasive lobular carcinoma	674	13.7%	243	14.8%	431	13.1%
Invasive mixed ductal/lobular	278	5.6%	95	5.8%	183	5.6%
Other	299	6.1%	100	6.1%	199	6.1%
Not reported	94					
EXTRANODAL EXTENSION						
No/Unknown	3874	78.7%	1330	81.2%	2544	77.4%
Yes	1051	21.3%	307	18.8%	744	22.6%
Not reported	93					
CLINICAL RISK						
High risk	4182	83.3%	1427	85.7%	2755	82.2%
Low risk	836	16.7%	238	14.3%	598	17.8%

Clinical Risk: Low risk is tumor size < 2cm AND Grade 1, using a modified version of Adjuvant! Online. High risk is everything else

ER = Estrogen Receptor; PR = Progesterone Receptor

Table S7. Type of First Invasive Disease-Free Survival Event by Treatment Assigned for Randomized Postmenopausal Patients with Recurrence Score 25 or less (N=3,329)

	ARM NAME				Total	
	CET N = 1658		ET N = 1671			
	N	Percentage	N	Percentage	N	Percentage
IDFS EVENT TYPE						
Any Distant Recurrence	44	27.0%	46	27.2%	90	27.1%
Local/Regional Recurrence	12	7.4%	16	9.5%	28	8.4%
Opposite Breast (recurrence or new primary)	12	7.4%	9	5.3%	21	6.3%
Non-Breast New Primary	44	27.0%	51	30.2%	95	28.6%
Recurrence not Classified	10	6.1%	6	3.5%	16	4.8%
Death not due to Recurrence or Second Primary	41	25.1%	41	24.3%	82	24.7%
Total	163		169		332	

CET = Chemotherapy Followed by Endocrine Therapy
ET = Endocrine Therapy Alone
IDFS = Invasive Disease-Free Survival

Table S8. Type of First Invasive Disease-Free Survival Event by Treatment Assigned for Randomized Premenopausal Patients with Recurrence-Score 25 or less (N=1655)

	ARM NAME				Total	
	CET N = 829		ET N = 826			
	N	Percentage	N	Percentage	N	Percentage
IDFS EVENT TYPE						
Any Distant Recurrence	27	47.4%	49	53.3%	76	51.0%
Local/Regional Recurrence	10	17.5%	18	19.6%	28	18.8%
Opposite Breast (recurrence or new primary)	5	8.8%	9	9.8%	14	9.4%
Non-Breast New Primary	11	19.3%	10	10.9%	21	14.1%
Recurrence not Classified	0	0%	1	1.1%	1	00.7%
Death not due to Recurrence or Second Primary	4	7.0%	5	5.4%	9	6.0%
Total	57		92		149	

CET = Chemotherapy Followed by Endocrine Therapy
ET = Endocrine Therapy Alone
IDFS = Invasive Disease-Free Survival

Table S9. Any Invasive Disease-Free Survival Event by Treatment Assigned for Randomized Patients with Recurrence-Score 25 or less (N=4984)

	ARM NAME					
	CET N = 2487		ET N = 2497		Total	
	N	Percentage	N	Percentage	N	Percentage
IDFS EVENT TYPE						
Any Distant Recurrence	71	32.3%	95	36.4%	166	34.5%
Local/Regional Recurrence	22	10.0%	34	13.0%	56	11.6%
Opposite Breast (recurrence or new primary)	17	7.7%	18	6.9%	35	7.3%
Non-Breast New Primary	55	25.0%	61	23.4%	116	24.1%
Recurrence not Classified	10	4.5%	7	2.7%	17	3.5%
Death not due to Recurrence or Second Primary	45	20.5%	46	17.6%	91	18.9%
Total	220		261		481	

CET = Chemotherapy Followed by Endocrine Therapy
ET = Endocrine Therapy Alone
IDFS = Invasive Disease-Free Survival

Table S10. Number of Patients with a Given Type and Grade of Adverse Event
Postmenopausal Patients

Adverse Events Unlikely or Not Related to Treatment Excluded
Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed
Data as of March 26, 2021

	Chemo and Endocrine Therapy (n=1336) Grade				Endocrine Therapy Alone (n=1577) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
Abdominal pain	1331	5	0	0	1577	0	0	0
Alkaline phosphatase increased	1335	1	0	0	1577	0	0	0
Allergic reaction	1334	2	0	0	1576	1	0	0
ALT increased	1334	2	0	0	1576	1	0	0
Anemia	1321	14	1	0	1577	0	0	0
Anorexia	1334	2	0	0	1577	0	0	0
Anxiety	1334	2	0	0	1576	1	0	0
Arthralgia	1298	38	0	0	1546	31	0	0
Atrial fibrillation	1333	3	0	0	1576	1	0	0
Back pain	1336	0	0	0	1576	1	0	0
Blood/lymph disorder-Other	1333	3	0	0	1577	0	0	0
Bone marrow hypocellular	1335	1	0	0	1577	0	0	0
Bone pain	1327	9	0	0	1575	2	0	0
Breast infection	1335	1	0	0	1577	0	0	0
Cataract	1336	0	0	0	1576	1	0	0
Catheter related infection	1335	0	1	0	1577	0	0	0
CD4 lymphocytes decreased	1334	2	0	0	1577	0	0	0
Chest wall pain	1336	0	0	0	1576	1	0	0
Colitis	1333	3	0	0	1577	0	0	0
Constipation	1333	3	0	0	1577	0	0	0
Dehydration	1327	9	0	0	1577	0	0	0
Depression	1333	3	0	0	1573	4	0	0
Dermatitis radiation	1334	2	0	0	1575	2	0	0
Device related infection	1334	1	1	0	1577	0	0	0
Diarrhea	1311	25	0	0	1575	2	0	0
Dizziness	1334	2	0	0	1576	1	0	0
Dry mouth	1335	1	0	0	1577	0	0	0
Dyspareunia	1335	1	0	0	1576	1	0	0
Dyspnea	1334	2	0	0	1577	0	0	0
Ear pain	1334	2	0	0	1577	0	0	0
Edema limbs	1335	1	0	0	1577	0	0	0
Ejection fraction decreased	1335	0	1	0	1577	0	0	0
Erythroderma	1335	1	0	0	1576	1	0	0
Esophagitis	1334	2	0	0	1577	0	0	0
Fatigue	1295	41	0	0	1570	7	0	0

	Chemo and Endocrine Therapy (n=1336) Grade				Endocrine Therapy Alone (n=1577) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
Febrile neutropenia	1282	42	12	0	1576	0	1	0
Fever	1334	1	1	0	1577	0	0	0
Flank pain	1335	1	0	0	1577	0	0	0
Flu like symptoms	1335	1	0	0	1577	0	0	0
Gastric hemorrhage	1335	1	0	0	1577	0	0	0
Gastric ulcer	1335	1	0	0	1577	0	0	0
Gen disorders/admin site cond	1334	2	0	0	1577	0	0	0
Generalized muscle weakness	1332	4	0	0	1577	0	0	0
GGT increased	1335	1	0	0	1577	0	0	0
GI disorders-Other, specify	1335	0	0	1	1577	0	0	0
Hand-Foot syndrome	1330	6	0	0	1577	0	0	0
Headache	1331	5	0	0	1577	0	0	0
Heart failure	1335	1	0	0	1577	0	0	0
Hematuria	1335	1	0	0	1577	0	0	0
Hot flashes	1332	4	0	0	1565	12	0	0
Hyperglycemia	1324	12	0	0	1576	1	0	0
Hypertension	1330	6	0	0	1571	6	0	0
Hypokalemia	1331	5	0	0	1577	0	0	0
Hyponatremia	1334	2	0	0	1577	0	0	0
Hypotension	1334	2	0	0	1576	1	0	0
Infections/infestations-Other	1334	2	0	0	1577	0	0	0
INR increased	1336	0	0	0	1576	1	0	0
Insomnia	1330	6	0	0	1573	4	0	0
Kidney infection	1335	1	0	0	1577	0	0	0
Leukocytosis	1333	3	0	0	1577	0	0	0
Localized edema	1335	1	0	0	1577	0	0	0
Lung infection	1330	4	2	0	1577	0	0	0
LV systolic dysfunction	1335	1	0	0	1577	0	0	0
Lymphedema	1336	0	0	0	1576	1	0	0
Lymphocyte count decreased	1318	17	1	0	1577	0	0	0
MS/connective tissue disorder	1335	1	0	0	1577	0	0	0
Mucositis oral	1316	20	0	0	1577	0	0	0
Myalgia	1316	20	0	0	1569	8	0	0
Myocardial infarction	1334	2	0	0	1577	0	0	0
Nausea	1322	14	0	0	1577	0	0	0
Neck pain	1334	2	0	0	1577	0	0	0
Neoplasms, all	1334	1	1	0	1577	0	0	0
Nervous sys disorders-Other	1335	1	0	0	1577	0	0	0
Neutrophil count decreased	1230	38	68	0	1577	0	0	0
Osteoporosis	1335	1	0	0	1577	0	0	0
Pain	1335	1	0	0	1577	0	0	0
Pain in extremity	1336	0	0	0	1576	1	0	0

	Chemo and Endocrine Therapy (n=1336) Grade				Endocrine Therapy Alone (n=1577) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
Paresthesia	1334	2	0	0	1577	0	0	0
Peripheral ischemia	1336	0	0	0	1576	1	0	0
Peripheral motor neuropathy	1334	2	0	0	1577	0	0	0
Peripheral sensory neuropathy	1317	18	1	0	1575	2	0	0
Platelet count decreased	1334	2	0	0	1577	0	0	0
Pleuritic pain	1335	1	0	0	1577	0	0	0
Pneumonitis	1330	6	0	0	1577	0	0	0
Pruritus	1333	3	0	0	1576	1	0	0
Rash maculo-papular	1331	5	0	0	1575	2	0	0
Renal/urinary disorders-Other	1335	1	0	0	1577	0	0	0
Repro system/breast ds-Oth	1335	1	0	0	1577	0	0	0
ROM decreased	1335	1	0	0	1577	0	0	0
RT recall reaction, derm	1334	2	0	0	1577	0	0	0
Secondary Leukemia	1335	0	1	0	1577	0	0	0
Sepsis	1331	0	4	1	1577	0	0	0
Sinus tachycardia	1335	1	0	0	1577	0	0	0
Skin infection	1331	5	0	0	1577	0	0	0
Skin ulceration	1335	0	1	0	1577	0	0	0
Skin/subq tissue ds-Other	1331	5	0	0	1573	4	0	0
Stroke	1334	1	1	0	1575	1	0	1
Supraventricular tachycardia	1335	1	0	0	1576	1	0	0
Syncope	1333	3	0	0	1577	0	0	0
Thromboembolic event	1331	4	1	0	1576	1	0	0
Tinnitus	1335	1	0	0	1577	0	0	0
Typhlitis	1335	0	0	1	1577	0	0	0
Upper GI hemorrhage	1335	0	1	0	1577	0	0	0
Upper respiratory infection	1335	1	0	0	1577	0	0	0
Urinary tract infection	1332	4	0	0	1577	0	0	0
Urticaria	1335	1	0	0	1577	0	0	0
Vaginal dryness	1336	0	0	0	1573	4	0	0
Vaginal hemorrhage	1336	0	0	0	1576	1	0	0
Vomiting	1322	14	0	0	1577	0	0	0
Watering eyes	1334	2	0	0	1577	0	0	0
Weight gain	1334	2	0	0	1577	0	0	0
Weight loss	1334	2	0	0	1577	0	0	0
White blood cell decreased	1287	31	18	0	1577	0	0	0
Wound dehiscence	1335	1	0	0	1577	0	0	0
MAX. GRADE ANY ADVERSE EVENT	967	274	92	3	1488	87	1	1

Table S11. Number of Patients with a Given Type and Grade of Adverse Event
Premenopausal Patients

Adverse Events Unlikely or Not Related to Treatment Excluded
Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed
Data as of March 26, 2021

	Chemo and Endocrine Therapy (n=717) Grade				Endocrine Therapy Alone (n=751) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
Abdominal pain	715	2	0	0	751	0	0	0
Acute kidney injury	716	1	0	0	751	0	0	0
Allergic reaction	713	4	0	0	751	0	0	0
ALT increased	715	2	0	0	750	1	0	0
Anemia	712	4	1	0	751	0	0	0
Arthralgia	710	7	0	0	747	4	0	0
AST increased	717	0	0	0	750	1	0	0
Back pain	716	1	0	0	751	0	0	0
Blood/lymph disorder-Other	716	1	0	0	751	0	0	0
Bone pain	711	6	0	0	748	3	0	0
Breast infection	716	1	0	0	751	0	0	0
Bronchial infection	716	1	0	0	751	0	0	0
Catheter related infection	715	2	0	0	751	0	0	0
Chest pain - cardiac	716	1	0	0	751	0	0	0
Colitis	715	2	0	0	751	0	0	0
Constipation	716	1	0	0	751	0	0	0
Death NOS	717	0	0	0	750	0	0	1
Dehydration	715	2	0	0	751	0	0	0
Depression	717	0	0	0	749	2	0	0
Dermatitis radiation	715	2	0	0	749	2	0	0
Device related infection	715	2	0	0	751	0	0	0
Diarrhea	711	6	0	0	750	1	0	0
Dizziness	716	1	0	0	751	0	0	0
Dry skin	716	1	0	0	751	0	0	0
Dyspepsia	716	1	0	0	751	0	0	0
Erythema multiforme	716	1	0	0	751	0	0	0
Esophagitis	716	1	0	0	751	0	0	0
Fatigue	711	6	0	0	749	2	0	0
Febrile neutropenia	689	27	1	0	751	0	0	0
Fever	716	1	0	0	751	0	0	0
Gastrointestinal pain	716	1	0	0	751	0	0	0
GGT increased	716	1	0	0	751	0	0	0
Hand-Foot syndrome	716	1	0	0	751	0	0	0
Headache	715	2	0	0	750	1	0	0
Hemorrhoids	716	1	0	0	751	0	0	0

	Chemo and Endocrine Therapy (n=717) Grade				Endocrine Therapy Alone (n=751) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
Hot flashes	709	8	0	0	749	2	0	0
Hyperglycemia	713	4	0	0	751	0	0	0
Hyperhidrosis	716	1	0	0	751	0	0	0
Hypertension	716	1	0	0	751	0	0	0
Hypotension	716	1	0	0	751	0	0	0
Infections/infestations-Other	716	1	0	0	751	0	0	0
Injection site reaction	716	1	0	0	751	0	0	0
Insomnia	714	3	0	0	751	0	0	0
Irregular menstruation	714	3	0	0	750	1	0	0
Leukocytosis	716	0	1	0	751	0	0	0
Lipase increased	716	1	0	0	751	0	0	0
Localized edema	717	0	0	0	750	1	0	0
Lymphedema	716	1	0	0	751	0	0	0
Lymphocyte count decreased	715	2	0	0	751	0	0	0
Menorrhagia	717	0	0	0	750	1	0	0
Mucositis oral	714	3	0	0	751	0	0	0
Muscle weakness lower limb	716	1	0	0	751	0	0	0
Myalgia	713	4	0	0	751	0	0	0
Myelitis	716	1	0	0	751	0	0	0
Nausea	710	7	0	0	751	0	0	0
Neoplasms, all	716	1	0	0	751	0	0	0
Neutrophil count decreased	674	19	24	0	750	1	0	0
Pain	716	1	0	0	751	0	0	0
Pain in extremity	715	2	0	0	751	0	0	0
Peripheral motor neuropathy	715	1	1	0	751	0	0	0
Peripheral sensory neuropathy	715	2	0	0	751	0	0	0
Platelet count decreased	716	1	0	0	751	0	0	0
Pneumonitis	715	2	0	0	751	0	0	0
Premature menopause	716	1	0	0	751	0	0	0
Pruritus	715	2	0	0	751	0	0	0
Rash acneiform	716	1	0	0	751	0	0	0
Rash maculo-papular	714	3	0	0	751	0	0	0
Secondary Leukemia	715	0	1	1	751	0	0	0
Skin infection	713	4	0	0	751	0	0	0
Skin/subq tissue ds-Other	717	0	0	0	750	1	0	0
Stroke	717	0	0	0	750	0	0	1
Suicidal ideation	716	1	0	0	751	0	0	0
Surg/medical procedures-Oth	715	2	0	0	747	4	0	0
Thromboembolic event	713	3	1	0	748	3	0	0
Urticaria	714	3	0	0	751	0	0	0
Uterine hemorrhage	717	0	0	0	750	1	0	0
Vaginal hemorrhage	716	1	0	0	751	0	0	0

	Chemo and Endocrine Therapy (n=717) Grade				Endocrine Therapy Alone (n=751) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
Vascular access complication	716	1	0	0	751	0	0	0
Vomiting	712	5	0	0	751	0	0	0
Watering eyes	715	2	0	0	751	0	0	0
Weight gain	715	2	0	0	750	1	0	0
White blood cell decreased	701	12	4	0	751	0	0	0
MAX. GRADE ANY ADVERSE EVENT	574	111	31	1	723	27	0	1