# Supplementary Appendix

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

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# Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

**Olivia Pagani, et al**

## SUPPLEMENTARY MATERIAL

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## III. Supplementary Methods, Tables and Figures

Premenopausal status: Eligibility for both trials included premenopausal status, defined by regular menses without exogenous hormones during the prior six months and/or estradiol level in the premenopausal range; patients who had completed chemotherapy prior to entry into SOFT were required to have a premenopausal estradiol level.

Study procedures: Patients were assessed with physical examination, menstrual and medication documentation every three months for the first year, then every six months until year 6 and annually thereafter. Annual mammography and bone densitometry were recommended. Blood tests and additional imaging were performed if medically indicated or according to local practice. Targeted adverse events and other grade 3 or higher adverse events were collected using Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Patients completed quality-of-life questionnaires consisting of linear analogue self-assessment (LASA) global and symptom-specific indicators at baseline, every six months for 2 years, and then annually in years 3 through 6.

Table S1. Patient, disease and treatment characteristics of 4690 patients randomized in TEXT and SOFT, overall and according to patient cohort as defined by trial and chemotherapy stratum. Number (%) of patients unless otherwise noted.

| **Characteristic** | **Cohort** | | | | | | | | **Overall** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **No chemo-therapy TEXT** | | **No chemo-therapy SOFT** | | **Chemo-therapy TEXT** | | **Prior Chemo-therapy SOFT** | | | |
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| *N Patients* | *1053* | *100* | *943* | *100* | *1607* | *100* | *1087* | *100* | *4690* | *100* |
| Treatment assignment | | | | | | | | | | |
| Exemestane+OFS | 526 | 50.0 | 470 | 49.8 | 806 | 50.2 | 544 | 50.0 | 2346 | 50.0 |
| Tamoxifen+OFS | 527 | 50.0 | 473 | 50.2 | 801 | 49.8 | 543 | 50.0 | 2344 | 50.0 |
| Age at randomization | | | | | | | | | | |
| <35 | 41 | 3.9 | 14 | 1.5 | 191 | 11.9 | 224 | 20.6 | 470 | 10.0 |
| 35-39 | 123 | 11.7 | 68 | 7.2 | 289 | 18.0 | 312 | 28.7 | 792 | 16.9 |
| 40-44 | 362 | 34.4 | 259 | 27.5 | 561 | 34.9 | 341 | 31.4 | 1523 | 32.5 |
| 45-49 | 406 | 38.6 | 431 | 45.7 | 487 | 30.3 | 174 | 16.0 | 1498 | 31.9 |
| ≥ 50 | 121 | 11.5 | 171 | 18.1 | 79 | 4.9 | 36 | 3.3 | 407 | 8.7 |
| Median [IQR] | 45 | [41-47] | 46 | [43-48] | 43 | [38-46] | 40 | [36-44] | 43 | [39-47] |
| Hormone receptor status | | | | | | | | | | |
| ER+ / PgR+ | 983 | 93.4 | 882 | 93.5 | 1380 | 85.9 | 883 | 81.2 | 4128 | 88.0 |
| ER+ / PgR- | 61 | 5.8 | 28 | 3.0 | 186 | 11.6 | 145 | 13.3 | 420 | 9.0 |
| ER+ / PgR unknown | 1 | 0.1 | 14 | 1.5 | 7 | 0.4 | 19 | 1.7 | 41 | 0.9 |
| ER- / PgR+ | 4 | 0.4 | 16 | 1.7 | 26 | 1.6 | 35 | 3.2 | 81 | 1.7 |
| Other[1] | 4 | 0.4 | 3 | 0.3 | 8 | 0.5 | 5 | 0.5 | 20 | 0.4 |
| HER2 status | | | | | | | | | | |
| Negative | 990 | 94.0 | 891 | 94.5 | 1318 | 82.0 | 839 | 77.2 | 4038 | 86.1 |
| Positive | 54 | 5.1 | 30 | 3.2 | 272 | 16.9 | 211 | 19.4 | 567 | 12.1 |
| Unknown/Not done | 9 | 0.9 | 22 | 2.3 | 17 | 1.1 | 37 | 3.4 | 85 | 1.8 |
| No. nodes positive | 835 | 79.3 | 865 | 91.7 | 542 | 33.7 | 470 | 43.2 | 2712 | 57.8 |

| Characteristic | Cohort | | | | | | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No chemo-therapy TEXT | | No chemo-therapy SOFT | | Chemo-therapy TEXT | | Prior Chemo-therapy SOFT | | | |
| N0 | | | | | | | | | | |
| N 1-3 | 216 | 20.5 | 78 | 8.3 | 688 | 42.8 | 418 | 38.5 | 1400 | 29.9 |
| N 4+ | 2 | 0.2 | 0 | 0.0 | 377 | 23.5 | 199 | 18.3 | 578 | 12.3 |
| Tumor size | | | | | | | | | | |
| <1 cm | 206 | 19.6 | 234 | 24.8 | 86 | 5.4 | 80 | 7.4 | 606 | 12.9 |
| 1-2 cm | 641 | 60.9 | 566 | 60.0 | 652 | 40.6 | 457 | 42.0 | 2316 | 49.4 |
| >2-5 cm | 188 | 17.9 | 130 | 13.8 | 756 | 47.0 | 441 | 40.6 | 1515 | 32.3 |
| >5 cm | 15 | 1.4 | 9 | 1.0 | 88 | 5.5 | 67 | 6.2 | 179 | 3.8 |
| Unknown | 3 | 0.3 | 4 | 0.4 | 25 | 1.6 | 42 | 3.9 | 74 | 1.6 |
| Tumor grade | | | | | | | | | | |
| 1 | 269 | 25.5 | 357 | 37.9 | 188 | 11.7 | 153 | 14.1 | 967 | 20.6 |
| 2 | 651 | 61.8 | 506 | 53.7 | 821 | 51.1 | 549 | 50.5 | 2527 | 53.9 |
| 3 | 121 | 11.5 | 61 | 6.5 | 589 | 36.7 | 348 | 32.0 | 1119 | 23.9 |
| Unknown | 12 | 1.1 | 19 | 2.0 | 9 | 0.6 | 37 | 3.4 | 77 | 1.6 |
| Months from surgery to randomization, median [IQR] | 1.5 | [1.1-1.9] | 1.8 | [1.3-2.4] | 1.2 | [0.9-1.6] | 8.0 | [5.7-10.1] | 1.6 | [1.1-2.7] |
| Local-regional treatment | | | | | | | | | | |
| Mastectomy, no RT | 272 | 25.8 | 233 | 24.7 | 406 | 25.3 | 219 | 20.1 | 1130 | 24.1 |
| Mastectomy with RT | 34 | 3.2 | 18 | 1.9 | 377 | 23.5 | 358 | 32.9 | 787 | 16.8 |
| BCS with RT | 727 | 69.0 | 670 | 71.0 | 797 | 49.6 | 492 | 45.3 | 2686 | 57.3 |
| Other[2] | 20 | 1.9 | 22 | 2.3 | 27 | 1.7 | 18 | 1.7 | 87 | 1.9 |
| Prior endocrine therapy[3] | | | | | | | | | | |
| No, not allowed | 1053 | 100.0 | -- | -- | 1607 | 100.0 | -- | -- | 2660 | 56.7 |
| No | -- | -- | 899 | 95.3 | -- | -- | 634 | 58.3 | 1533 | 32.7 |
| Yes | -- | -- | 44 | 4.7 | -- | -- | 453 | 41.7 | 497 | 10.6 |
| HER2-targeted therapy | | | | | | | | | | |
| Not HER2+ | 999 | 94.9 | 913 | 96.8 | 1329 | 82.7 | 866 | 79.7 | 4107 | 87.6 |
| HER2+, no therapy | 45 | 4.3 | 28 | 3.0 | 130 | 8.1 | 70 | 6.4 | 273 | 5.8 |
| HER2-targeted therapy | 9 | 0.9 | 2 | 0.2 | 148 | 9.2 | 151 | 13.9 | 310 | 6.6 |

Abbreviations: BCS=breast-conserving surgery; ER=estrogen receptor; IQR=interquartile range; PgR=progesterone receptor; OFS=ovarian function suppression; RT=radiotherapy,

[1]Other includes ER- and PgR-unknown, ER-unknown/PgR-positive, or ER- and PgR-negative.

[2]Other includes BCS without RT, or RT unknown.

[3]Oral endocrine therapy prior to randomization was allowed in SOFT while premenopausal status was (re)established; 3 patients had aromatase inhibitor, all others tamoxifen. In the SOFT prior chemotherapy cohort, average duration was 16 weeks (IQR, 10-22 weeks); in the SOFT no chemotherapy cohort, average duration was 5 weeks (IQR, 2-8 weeks).

Table S2. Patient, disease and treatment characteristics of 4690 patients randomized in TEXT and SOFT, overall and according to treatment assignment. Number (%) of patients unless otherwise noted.

| Characteristic | Treatment Assignment | | | | Overall | |
|---|---|---|---|---|---|---|
| | Exemestane +OFS | | Tamoxifen +OFS | | | |
| | N | % | N | % | N | % |
| *N Patients* | *2346* | *100* | *2344* | *100* | *4690* | *100* |
| Age at randomization | | | | | | |
| < 35 | 231 | 9.8 | 239 | 10.2 | 470 | 10.0 |
| 35-39 | 419 | 17.9 | 373 | 15.9 | 792 | 16.9 |
| 40-44 | 748 | 31.9 | 775 | 33.1 | 1523 | 32.5 |
| 45-49 | 731 | 31.2 | 767 | 32.7 | 1498 | 31.9 |
| ≥ 50 | 217 | 9.2 | 190 | 8.1 | 407 | 8.7 |
| Median [IQR] | 43 | [39-47] | 43 | [39-47] | 43 | [39-47] |
| Hormone receptor status | | | | | | |
| ER+ / PgR+ | 2061 | 87.9 | 2067 | 88.2 | 4128 | 88.0 |
| ER+ / PgR- | 207 | 8.8 | 213 | 9.1 | 420 | 9.0 |
| ER+ / PgR unknown | 22 | 0.9 | 19 | 0.8 | 41 | 0.9 |
| ER- / PgR+ | 44 | 1.9 | 37 | 1.6 | 81 | 1.7 |
| Other[1] | 12 | 0.5 | 8 | 0.3 | 20 | 0.4 |
| HER2 status | | | | | | |
| Negative | 2017 | 86.0 | 2021 | 86.2 | 4038 | 86.1 |
| Positive | 288 | 12.3 | 279 | 11.9 | 567 | 12.1 |
| Unknown/Not done | 41 | 1.7 | 44 | 1.9 | 85 | 1.8 |
| No. nodes positive | | | | | | |
| N0 | 1362 | 58.1 | 1350 | 57.6 | 2712 | 57.8 |
| N 1-3 | 685 | 29.2 | 715 | 30.5 | 1400 | 29.9 |
| N 4+ | 299 | 12.7 | 279 | 11.9 | 578 | 12.3 |
| Tumor size | | | | | | |
| <1 cm | 299 | 12.7 | 307 | 13.1 | 606 | 12.9 |
| 1-2 cm | 1165 | 49.7 | 1151 | 49.1 | 2316 | 49.4 |
| >2-5 cm | 759 | 32.4 | 756 | 32.3 | 1515 | 32.3 |
| >5 cm | 88 | 3.8 | 91 | 3.9 | 179 | 3.8 |
| Unknown | 35 | 1.5 | 39 | 1.7 | 74 | 1.6 |
| Tumor grade | | | | | | |
| 1 | 478 | 20.4 | 489 | 20.9 | 967 | 20.6 |
| 2 | 1269 | 54.1 | 1258 | 53.7 | 2527 | 53.9 |
| 3 | 563 | 24.0 | 556 | 23.7 | 1119 | 23.9 |
| Unknown | 36 | 1.5 | 41 | 1.7 | 77 | 1.6 |
| Local-regional treatment | | | | | | |
| Mastectomy, no RT | 560 | 23.9 | 570 | 24.3 | 1130 | 24.1 |
| Mastectomy with RT | 387 | 16.5 | 400 | 17.1 | 787 | 16.8 |
| BCS with RT | 1351 | 57.6 | 1335 | 57.0 | 2686 | 57.3 |
| Other[2] | 48 | 2.0 | 39 | 1.7 | 87 | 1.9 |
| Cohort | | | | | | |
| No chemotherapy TEXT | 526 | 22.4 | 527 | 22.5 | 1053 | 22.5 |
| No chemotherapy SOFT | 470 | 20.0 | 473 | 20.2 | 943 | 20.1 |
| Chemotherapy TEXT | 806 | 34.4 | 801 | 34.2 | 1607 | 34.3 |
| Prior chemotherapy SOFT | 544 | 23.2 | 543 | 23.2 | 1087 | 23.2 |

| Characteristic | Treatment Assignment | | | | Overall | |
|---|---|---|---|---|---|---|
| | Exemestane +OFS | | Tamoxifen +OFS | | | |
| HER2-directed therapy | | | | | | |
| Not HER2+ | 2046 | 87.2 | 2061 | 87.9 | 4107 | 87.6 |
| HER2+, no therapy | 133 | 5.7 | 140 | 6.0 | 273 | 5.8 |
| HER2-directed therapy | 167 | 7.1 | 143 | 6.1 | 310 | 6.6 |

Abbreviations: BCS=breast-conserving surgery; ER=estrogen receptor; IQR=interquartile range; PgR=progesterone receptor; OFS=ovarian function suppression; RT=radiotherapy,

[1]Other includes ER- and PgR-unknown, ER-unknown/PgR-positive, or ER- and PgR-negative.

[2]Other includes BCS without RT, or RT unknown.

Table S3. Sites of first disease-free survival event, overall and according to treatment assignment, after a median follow-up of 68 months.

| **Sites of First Disease-free Survival Event** | **Treatment Assignment** | | | | **Overall** | |
|---|---|---|---|---|---|---|
| | **Exemestane+OFS** | | **Tamoxifen+OFS** | | | |
| | N | % | N | % | N | % |
| *N Patients* | *2346* | *100.0* | *2344* | *100.0* | *4690* | *100.0* |
| N disease-free survival events | 216 | 9.2 | 298 | 12.7 | 514 | 11.0 |
| Local | 23 | 1.0 | 28 | 1.2 | 51 | 1.1 |
| Contralateral breast | 9 | 0.4 | 27 | 1.2 | 36 | 0.8 |
| Regional ± above | 9 | 0.4 | 30 | 1.3 | 39 | 0.8 |
| Soft tissue / distant lymph nodes ± above | 4 | 0.2 | 6 | 0.3 | 10 | 0.2 |
| Bone ± above | 54 | 2.3 | 65 | 2.8 | 119 | 2.5 |
| Viscera ± above | 75 | 3.2 | 105 | 4.5 | 180 | 3.8 |
| Second (non-breast) invasive cancer* | 38 | 1.6 | 32 | 1.4 | 70 | 1.5 |
| Death without prior cancer event | 2 | 0.1 | 5 | 0.2 | 7 | 0.1 |
| Death without prior cancer event, recurrence suspected | 2 | 0.1 | - | - | 2 | 0.0 |

Abbreviations: OFS=ovarian function suppression

*Gynecologic cancer occurred in 7 patients assigned to exemestane+OFS and 9 assigned to tamoxifen+OFS, including endometrial cancer in 2 and 5 patients, respectively.

Table S4. Status of patients on protocol-assigned treatment after 68 months median follow-up, overall and according to cohort and treatment assignment. After median follow-up 68 months, 14% of patients have stopped all protocol-assigned treatment early (including those who never started).

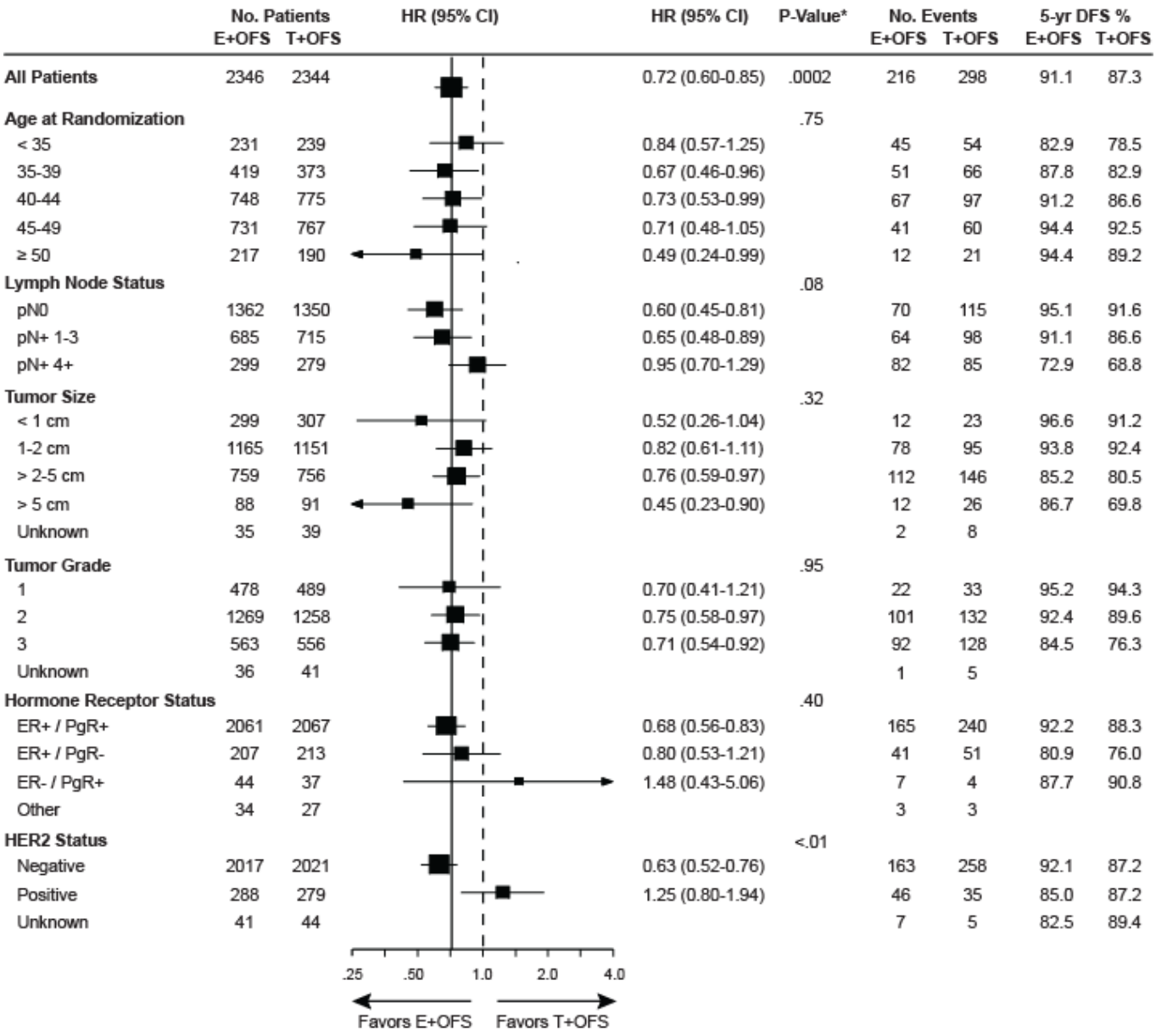
| **Status of Protocol-assigned Treatment** | **Cohort** | | | | | | | | **Treatment Assignment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **No chemotherapy TEXT** | | **No chemotherapy SOFT** | | **Chemotherapy TEXT** | | **Prior Chemotherapy SOFT** | | | | |
| | **E+OFS** | **T+OFS** | **E+OFS** | **T+OFS** | **E+OFS** | **T+OFS** | **E+OFS** | **T+OFS** | **E+OFS** | **T+OFS** | **Overall** |
| | **%** | **%** | **%** | **%** | **%** | **%** | **%** | **%** | **%** | **%** | **%** |
| ***N Patients*** | *N=526* | *N=527* | *N=470* | *N=473* | *N=806* | *N=801* | *N=544* | *N=543* | *N=2346* | *N=2344* | *N=4690* |
| **Status overall** | | | | | | | | | | | |
| Continuing | 27.0 | 28.8 | 34.9 | 39.3 | 21.0 | 24.2 | 39.3 | 36.3 | 29.4 | 31.1 | 30.2 |
| Completed | 58.4 | 60.5 | 41.9 | 48.0 | 64.1 | 64.9 | 47.4 | 52.7 | 54.5 | 57.7 | 56.1 |
| Stopped early | 13.5 | 10.4 | 21.3 | 11.4 | 13.8 | 10.1 | 12.5 | 10.7 | 14.9 | 10.6 | 12.8 |
| Never started | 1.1 | 0.2 | 1.9 | 1.3 | 1.1 | 0.7 | 0.7 | 0.4 | 1.2 | 0.6 | 0.9 |

Notes for Table S4:
E+OFS=exemestane (Aromasin® [Pfizer]) 25 mg orally daily with ovarian function suppression.
T+OFS=tamoxifen 20 mg orally daily with ovarian function suppression.
OFS: GnRH analogue (triptorelin 3.75 mg by intramuscular injection every 28±3 days), bilateral oophorectomy or bilateral ovarian irradiation (with biochemical confirmation of cessation of ovarian function after 2 months); 16% of patients have opted to undergo bilateral oophorectomy or bilateral ovarian irradiation at some point during adjuvant therapy.

In TEXT, all patients started OFS with GnRH analogue triptorelin for at least 6 months, after which patients could opt to undergo bilateral oophorectomy or ovarian irradiation at any time. If chemotherapy was administered, then triptorelin and chemotherapy started concomitantly; oral endocrine therapy started after chemotherapy was completed. If chemotherapy was not administered, then oral endocrine therapy started 6 to 8 weeks after initiation of triptorelin, to allow for a decline in ovarian estrogen production.

In SOFT, tamoxifen was to start at randomization, and exemestane was to begin 6 to 8 weeks after initiation of OFS; patients who had been taking tamoxifen at the time of randomization and were assigned to exemestane+OFS were permitted to continue tamoxifen until exemestane was initiated. The use of GnRH analogue, bilateral oophorectomy or bilateral ovarian irradiation was by patient preference and patients who began with GnRH analogue could opt to undergo surgery or irradiation at any time.

Figure S1. Cox proportional hazards model results of disease-free survival treatment comparison for all patients and according to subgroups. Median follow-up is 68 months. The solid vertical line is placed at 0.72, the hazard ratio estimate for all patients. The x-axis is scaled according to the natural logarithm of the hazard ratio. The size of the box is inversely proportional to the standard error of the hazard ratio.




*P-Value for “All Patients” is the stratified log-rank test; for other variables, P-Value is test of heterogeneity of the treatment effect across subgroups, using test of treatment-by-variable interaction from stratified Cox model, with “Unknown” or “Other” group omitted from the test.

Abbreviations: CI denotes confidence interval, E exemestane, ER estrogen receptor, HR hazard ratio, OFS ovarian function suppression, PgR progesterone receptor, T tamoxifen.

Figure S2. Kaplan-Meier estimates of (A,D) disease-free survival, (B,E) breast-cancer free interval and distant recurrence-free interval (C,F), according to treatment assignment, among cohorts of patients who did not receive chemotherapy. Median follow-up is 68 months. Abbreviations: CI=confidence interval; E=exemestane; HR=hazard ratio; OFS=ovarian function suppression;pts=patients; T=tamoxifen.

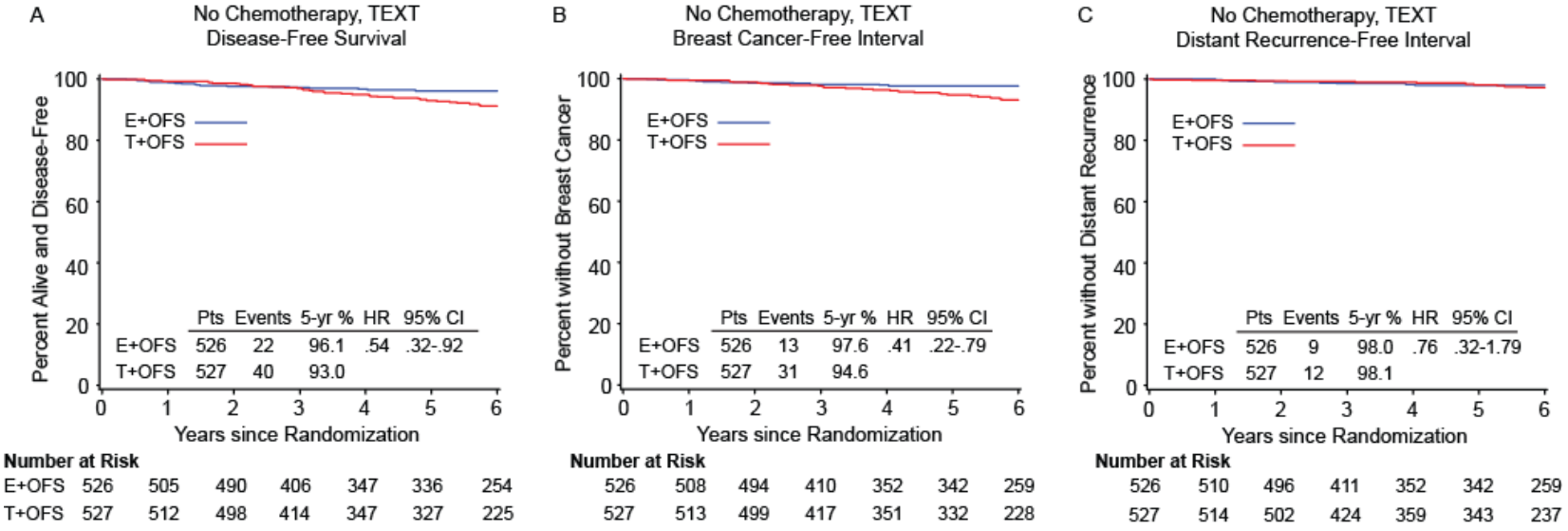


Figure S3. Kaplan-Meier estimates of (A,D) disease-free survival, (B,E) breast-cancer free interval and distant recurrence-free interval (C,F), according to treatment assignment, among cohorts of patients who were selected to receive chemotherapy. Median follow-up is 68 months. Abbreviations: CI=confidence interval; E=exemestane; HR=hazard ratio; OFS=ovarian function suppression; pts=patients; T=tamoxifen.