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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I. Acknowledgment

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University of California at Los Angeles (UCLA), Los Angeles, CA; P.A. Ganz
University of Southern California, Los Angeles, CA; C.A. Russel
Scripps Clinic - La Jolla, La Jolla, CA; J.F. Kroener
University of California San Diego Moores Cancer Center, San Diego, CA; B.A. Parker
John Muir Medical Center, Concord, CA; J.T. Ganey
Kaiser Permanente - Fremont, Fremont, CA; L. Fehrenbacher
Alta Bates Hospital, Berkeley, CA; D.H. Irwin
Kaiser Permanente Santa Teresa (San Jose), Vallejo, CA; L. Fehrenbacher
Mercy General Hospital, Carmichael, CA; M. Javeed
Kaiser Permanente-San Francisco, Vallejo, CA; L. Fehrenbacher
Santa Rosa Memorial Hospital, Santa Rosa, CA; I.C. Anderson
Stanford University Medical Center, Stanford, CA; I.L. Wapnir
Kaiser Permanente, San Diego, CA; J.A. Polikoff
Glendale Memorial Hospital and Health Center, Glendale, CA; G. Al-Jazayrly
Penrose-Saint Francis Healthcare, Colorado Springs, CO; E.R. Pajon
Front Range Cancer Specialists, Fort Collins, CO; D. Medgyesy
Longmont United Hospital, Longmont, CO; E.R. Pajon
The Shaw Regional Cancer Center, Aurora, CO; A.D. Elias
Greenwich Hospital, Greenwich, CT; B.J. Drucker
Norwalk Hospital, Norwalk, CT; R.C. Frank
Stamford Hospital, Stamford, CT; I. Tepler
Eastern Connecticut Hematology and Oncology Associates, Norwich, CT; K. Jagathambal
Northwest Connecticut Oncology - Hematology Associates, Torrington, CT; D.S. Brandt
Georgetown University Hospital, Washington, DC; C. Isaacs
Washington Hospital Center, Washington, DC; A. Aggarwal
Sibley Memorial Hospital, Washington, DC; F. Barr
Christiana Healthcare Services - Christian Hospital, Newark, DE; D.D. Biggs
Memorial Cancer Institute, Hollywood, FL
Mount Sinai Medical Center CCOP, Miami Beach, FL; M.A. Schwartz
Holy Cross Hospital, Fort Lauderdale, FL; R.C. Lilienbaum
Sarasota Memorial Hospital, Sarasota, FL
Dekalb Medical Center, Atlanta, GA; T.E. Seay
Emory University, Atlanta, GA; R.M. O'Regan
Memorial Health University Medical Center, Savannah, GA; H.C. Lebos
Atlanta Regional CCOP, Atlanta, GA; T.E. Seay
Augusta Oncology Associates, Inc., Augusta, GA; M.R. Keaton
St. Joseph's/Candler Health System, Savannah, GA; M.A. Taylor
Mercy Medical Center - North Iowa, Mason City, IA; W.W. Bate
Medical Associates Clinic, Professional Corporation, Dubuque, IA; C. Holm
Loyola University Medical Center, Maywood, IL; K.S. Albain
Rush University Medical Center, Chicago, IL; M.A. Cobleigh
University of Chicago, Chicago, IL; H.L. Kindler
St. Anthony Medical Center, Rockford, IL; R.E. Nora
Decatur Memorial Hospital, Decatur, IL; J.L. Wade
Memorial Medical Center, Springfield, IL; J.L. Wade
Ingalls Memorial Hospital, Harvey, IL; M.F. Kozloff
Carle Cancer Center CCOP, Urbana, IL; K.M. Rowland
Community Regional Cancer Care North, Indianapolis, IN; R. Walling
Indiana University Medical Center, Indianapolis, IN; K.D. Miller
Fort Wayne Medical Oncology/Hematology Incorporated, Fort Wayne, IN; S.R. Nattam
Northern Indiana Consortium, South Bend, IN; R.H. Ansari
Cancer Center of Kansas - Wichita, Wichita, KS; S.R. Dakhil
Via Christi Regional Medical Center, Wichita, KS; S.R. Dakhil
Louisiana State University, Shreveport, LA; G.M. Mills
Tufts Medical Center, Boston, MA; J.K. Erban
Massachusetts General Hospital, Boston, MA; H.J. Burstein
Dana-Farber Cancer Institute, Boston, MA; H.J. Burstein
Beth Israel Deaconess Medical Center, Boston, MA; H.J. Burstein
North Shore Cancer Center, Salem, MA; K.J. Krag
Suburban Hospital, Bethesda, MD; C.B. Hendricks
Johns Hopkins University, Baltimore, MD; A.C. Wolff
Anne Arundel Medical Center, Annapolis, MD; S.P. Watkins
Kaiser Permanente - Shady Grove Medical Center, Rockville, MD; L.C. Hwang
Eastern Maine Medical Center, Bangor, ME; H.M. Segal
Mercy Hospital, Portland, ME; R.C. Inhorn
William Beaumont Hospital, Royal Oak, MI; D. Zakalik
University of Michigan Medical Center, Ann Arbor, MI; A.F. Schott
Wayne State University, Detroit, MI; R.T. Morris
Mid-Michigan Medical Center, Midland, MI; M.R. Hurtubise
Regions Hospital, Minneapolis, MN; D.J. Schneider
United Hospital, St. Paul, MN; P.J. Flynn
Duluth Clinic, Duluth, MN; R.J. Dalton
Mayo Clinic, Rochester, MN; J.N. Ingle
Saint Francis Regional Medical Center, Shakopee, MN; D.J. Schneider
Washington University School of Medicine, St Louis, MO; M.J. Naughton
Saint John's Regional Health Center, Springfield, MO; J.W. Goodwin
Missouri Baptist Medical Center, Saint Louis, MO; A.P. Lyss
Montana Cancer Consortium CCOP, Billings, MT; B.T. Marchello
University of North Carolina, Chapel Hill, NC; T.C. Shea
Mission Hospitals Inc, Asheville, NC; M.J. Messino
Forsyth Memorial Hospital, Winston-Salem, NC; J.O. Hopkins
Northeast Medical Center, Concord, NC; J.G. Wall
Hope, A Women's Cancer Center, Asheville, NC; D.J. Hertzel
Altru Hospital, Grand Forks, ND; T. Dentchev
Elliot Hospital, Manchester, NH; D. Weckstein
Dartmouth Hitchcock Medical Center, Lebanon, NH; P.A. Kaufman
Saint Barnabas Medical Center, Livingston, NJ; R.A. Michaelson
Cooper Hospital University Medical Center, Newark, NJ; D.D. Biggs
Cancer Institute of New Jersey, New Brunswick, NJ; D.L. Toppmeyer
Cancer Institute of New Jersey At Hamilton, Trenton, NJ; D.L. Toppmeyer
University of Nevada At Reno Washoe Medical Center, Reno, NV
Saint Vincent's Hospital and Medical Center of New York, New York, NY; P. Klein
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.

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<th>SOFT No chemotherapy</th>
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<th>SOFT Chemotherapy</th>
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<td>806 50.2</td>
<td>544 50.0</td>
<td>2346 50.0</td>
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<td>191 11.9</td>
<td>224 20.6</td>
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<td>68 7.2</td>
<td>289 18.0</td>
<td>312 28.7</td>
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<td>259 27.5</td>
<td>561 34.9</td>
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<td>45-49</td>
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<td>431 45.7</td>
<td>487 30.3</td>
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<td>1498 31.9</td>
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<td>79 4.9</td>
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<td>882 93.5</td>
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<td>891 94.5</td>
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<td>No chemotherapy SOFT</td>
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<td>Chemotherapy SOFT</td>
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Abbreviations: BCS=breast-conserving surgery; ER=estrogen receptor; IQR=interquartile range; PgR=progesterone receptor; OFS=ovarian function suppression; RT=radiotherapy.

<sup>1</sup>Other includes ER- and PgR-unknown, ER-unknown/PgR-positive, or ER- and PgR-negative.

<sup>2</sup>Other includes BCS without RT, or RT unknown.

<sup>3</sup>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.

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<td>Overall</td>
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</table>

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.

<table>
<thead>
<tr>
<th>Sites of First Disease-free Survival Event</th>
<th>Treatment Assignment</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exemestane+OFS</td>
<td>Tamoxifen+OFS</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>N Patients</td>
<td>2346</td>
<td>100.0</td>
</tr>
<tr>
<td>N disease-free survival events</td>
<td>216</td>
<td>9.2</td>
</tr>
<tr>
<td>Local</td>
<td>23</td>
<td>1.0</td>
</tr>
<tr>
<td>Contralateral breast</td>
<td>9</td>
<td>0.4</td>
</tr>
<tr>
<td>Regional ± above</td>
<td>9</td>
<td>0.4</td>
</tr>
<tr>
<td>Soft tissue / distant lymph nodes ± above</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>Bone ± above</td>
<td>54</td>
<td>2.3</td>
</tr>
<tr>
<td>Viscera ± above</td>
<td>75</td>
<td>3.2</td>
</tr>
<tr>
<td>Second (non-breast) invasive cancer*</td>
<td>38</td>
<td>1.6</td>
</tr>
<tr>
<td>Death without prior cancer event</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Death without prior cancer event, recurrence suspected</td>
<td>2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Status of Protocol-assigned Treatment</th>
<th>Cohort</th>
<th>Prior Chemotherapy</th>
<th>Treatment Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEXT</td>
<td>SOFT</td>
<td>TEXT</td>
</tr>
<tr>
<td></td>
<td>E+OFS</td>
<td>T+OFS</td>
<td>E+OFS</td>
</tr>
<tr>
<td>N Patients</td>
<td>N=526</td>
<td>N=527</td>
<td>N=470</td>
</tr>
<tr>
<td>Status overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuing</td>
<td>27.0</td>
<td>28.8</td>
<td>34.9</td>
</tr>
<tr>
<td>Completed</td>
<td>58.4</td>
<td>60.5</td>
<td>41.9</td>
</tr>
<tr>
<td>Stopped early</td>
<td>13.5</td>
<td>10.4</td>
<td>21.3</td>
</tr>
<tr>
<td>Never started</td>
<td>1.1</td>
<td>0.2</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>No. Patients</th>
<th>HR (95% CI)</th>
<th>P-Value*</th>
<th>No. Events</th>
<th>5-yr DFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>E+OFS</td>
<td>T+OFS</td>
<td>E+OFS</td>
<td>T+OFS</td>
<td>E+OFS</td>
</tr>
<tr>
<td>All Patients</td>
<td>2346</td>
<td>2344</td>
<td>0.72 (0.60-0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age at Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>231</td>
<td>290</td>
<td>0.84 (0.57-1.25)</td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>419</td>
<td>373</td>
<td>0.67 (0.46-0.96)</td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>748</td>
<td>775</td>
<td>0.73 (0.53-0.99)</td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td>731</td>
<td>767</td>
<td>0.71 (0.48-1.05)</td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>217</td>
<td>190</td>
<td>0.49 (0.24-0.99)</td>
<td></td>
</tr>
<tr>
<td>Lymph Node Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>1362</td>
<td>1350</td>
<td>0.60 (0.45-0.81)</td>
<td></td>
</tr>
<tr>
<td>pN+ 1-3</td>
<td>685</td>
<td>715</td>
<td>0.65 (0.48-0.89)</td>
<td></td>
</tr>
<tr>
<td>pN+ 4+</td>
<td>299</td>
<td>279</td>
<td>0.95 (0.70-1.29)</td>
<td></td>
</tr>
<tr>
<td>Tumor Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 cm</td>
<td>299</td>
<td>307</td>
<td>0.52 (0.26-1.04)</td>
<td></td>
</tr>
<tr>
<td>1-2 cm</td>
<td>1165</td>
<td>1151</td>
<td>0.82 (0.61-1.11)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.5 cm</td>
<td>759</td>
<td>756</td>
<td>0.76 (0.59-0.97)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>88</td>
<td>91</td>
<td>0.45 (0.23-0.90)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>35</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>478</td>
<td>489</td>
<td>0.70 (0.41-1.21)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1269</td>
<td>1258</td>
<td>0.75 (0.58-0.97)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>563</td>
<td>556</td>
<td>0.71 (0.54-0.92)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>36</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone Receptor Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+/PgR+</td>
<td>2061</td>
<td>2067</td>
<td>0.68 (0.56-0.83)</td>
<td></td>
</tr>
<tr>
<td>ER+/PgR-</td>
<td>207</td>
<td>213</td>
<td>0.80 (0.53-1.21)</td>
<td></td>
</tr>
<tr>
<td>ER-/PgR+</td>
<td>44</td>
<td>37</td>
<td>1.43 (0.43-5.06)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2017</td>
<td>2021</td>
<td>0.63 (0.52-0.76)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>286</td>
<td>279</td>
<td>1.25 (0.60-1.94)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>41</td>
<td>44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.