**Table 1. Study Characteristics**

| EN#  Study (Year)  Quality | Design  Study Period  Location/Setting | Inclusion/Exclusion Criteria  Study N | Treatment Description | Follow-Up |
| --- | --- | --- | --- | --- |
| EN# 1499  Swain (2010)  NSABP B-30 Trial  (long term amenorrhea (menstrual history) data reported in EN# 1828 (Ganz, 2011) abstracted concurrently)  Good | RCT  1999-2004  184 Cancer Centers in North America | Inclusion: invasive adenocarcinoma (tumor stage T1, T2, or T3, clinical nodal stage N0 or N1, and metastasis stage M0); primary surgery with total mastectomy or lumpectomy plus axillary nodal dissection with margins of resection that were histologically free of invasive tumor or ductal carcinoma in situ; evidence of tumor in at least one lymph node required; randomization must have occurred within 84 days after the final surgery  Exclusion: bilateral breast cancer, previous therapy for breast cancer, current administration of hormone therapy  or raloxifene, previous anthracycline containing or taxane-containing chemotherapy for any malignant condition, pregnancy, and grade 2 or higher peripheral neuropathy  Women with surgical or natural menopause were excluded from the MH study after the baseline questionnaire.  N=5351 Randomized (NSABP study)  N=2445 (menstrual history substudy) | **A=doxorubicin (Adriamycin), C=cyclophosphamide, T=docetaxel**  (i) Sequential ACT Regimen: four cycles of doxorubicin at a dose of 60 mg per square meter of body-surface area plus cyclophosphamide at a dose of 600 mg per square meter every 3 weeks, followed by four cycles of docetaxel at a dose of 100 mg per square meter every 3 weeks  (ii) AT Regimen: four cycles of doxorubicin at a dose of 60 mg per square meter plus docetaxel at a dose of 60 mg per square meter every 3 weeks (MODIFIED: doxorubicin at a dose of 50 mg per square meter and docetaxel at a dose of 75 mg per square meter)  (iii) Concurrent ACT: four cycles of doxorubicin at a dose of 60 mg per square meter plus cyclophosphamide at a dose of 600 mg per square meter plus docetaxel at a dose of 60 mg per square meter every 3 weeks (MODIFIED: doxorubicin at a dose of 50 mg per square meter, cyclophosphamide at a dose of 500 mg per square meter, and docetaxel at a dose of 75 mg per square meter)  Patients with HR positive tumors received TAM for 5 years upon completion of chemotherapy. | B-30 Study:  Median 73 months  LTFU: 87 patients (2%)  Seq. ACT: 30  AT: 31  Con. ACT: 26  MH Substudy:  24 months post chemo  LTFU: 79 patients  Seq. ACT: 25  AT: 27  Con. ACT: 27 |
| EN# 1496  Su (2009)  Good | Retrospective Cohort  2004-2008  Single Institution (Rena Rowan Breast Center at UPenn; age-matched controls recruited from the Penn Ovarian Aging Study at UPenn)  United States | Inclusion: Stage I-III breast cancer; premenopausal at cancer diagnosis; treatment with cyclophosphamide-based adjuvant chemotherapy; presence of a uterus and at least one ovary; initiation of adjuvant chemo at least 1-4 years prior to enrollment (hormonal chemo was not included in exclusion criteria)  Exclusion: hormonal contraceptives or hormone replacement therapy  N (Assessment 1)=237 women total (127 patients, 110 controls)  N (Assessment 2)=111 patients | **A=doxorubicin (Adriamycin), C=cyclophosphamide, T=docetaxel, F=Fluorouracil**  Intervention description: cyclophosphamide-based regimens  Assessment 1: AC 38%, AC/T 54%, FAC 3%, Other 3%  Assessment 2: AC 37%, AC/T 56%, FAC 3%, Other 4%  Control description: no cancer, no chemotherapy | Median: 5.2 years post chemotherapy  LTFU at Assessment 2: 13% of patients (16/127) |
| EN# 1529  Del Mastro (2011)  PROMISE-GIM6 Trail  Fair+ | RCT  Oct 2003-Oct 2010  Multicenter (16 cancer centers)  Italy | Inclusion: premenopausal women; early stage breast cancer (stages I-III); candidate for neoadjuvant or adjuvant chemo; aged 18-45 years  Exclusion: previous chemotherapy, or radiation, for cancers prior to the study; evidence of distant metastases; other malignancies in the 5 years prior to enrollment (except basal or squamous cell carcinoma of the skin or adequately treated in situ carcinoma of the cervix); and pregnancy or lactation  Number Analyzed:  *Primary Analysis*  n=281  *Secondary Analysis*  n=260 | Intervention description: adjuvant or neoadjuvant treatment with anthracycline-based,anthracycline plus taxane–based, or CMF-based chemotherapy (100 mg/m2 of oral cyclophosphamide on days 1-14 or 600 mg/m2 of intravenous cyclophosphamide on days 1 and 8; 40 mg/m2 of methotrexate on days 1 and 8; and 600 mg/m2 of fluorouracil on days 1 and 8).  PLUS monthly Triptorelin injections (3.75 mg) during chemotherapy  Control description: adjuvant or neoadjuvant treatment with anthracycline-based, anthracycline plus taxane–based, or CMF-based chemotherapy (100 mg/m2 of oral cyclophosphamide on days 1-14 or 600 mg/m2 of intravenous cyclophosphamide on days 1 and 8; 40 mg/m2 of methotrexate on days 1 and 8; and 600 mg/m2 of fluorouracil on days 1 and 8).  No Triptorelin | Median FU: 12 months post-chemotherapy  LTFU:  Total: 13/260 (5.0%)  IG: 7/139 (5.0%)  CG: 6/121 (4.9%) |
| EN# 1387  Han (2009)  Fair+ | Prospective Cohort  2002-2007  Single Istitution (National Cancer Center Hospital Korea)  South Korea | Inclusion: premenopausal women; early stage breast cancer (stages I-III); treated with one of three specified chemo regimens: TX/AC, AC followed by T, or FAC between 2002-2005 at the study institution; younger than 50 years  Exclusion: patients who lacked information about their menstrual history; history of hysterectomy, bilateral oophorectomy, or ovarian suppression (with GnRH; patients who received incomplete chemo regimens; relapse within 12 months  N=285 | (i) TX/AC regimen: preoperative docetaxel 75 mg/m2 on day 1 plus capecitabine 1,000 mg/m2 orally twice daily on days 1–14, every 3 weeks for four cycles, or doxorubicin 60 mg/m2 plus cyclophosphamide 600 mg/m2 (AC)  on day 1 every 3 weeks for four cycles. Postoperatively,patients were crossed over to the other therapy  (ii) AC + T regimen: AC regimen followed by paclitaxel 175 mg/m2 on day 1, every 3 weeks for four cycles  (iii) FAC regimen: 5-fluorouracil 500 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2 on day 1 every 3 weeks for six cycles.  The TX/AC and AC followed by T regimens were regarded as taxane-based whereas the FAC regimen was considered to be non-taxane based.  Chemotherapy, No. (%)  TX/AC: 122  AC followed by T: 34  FAC: 129 | Median: 40 months post-chemo  LTFU: NR |
| EN# 1214  International Breast Cancer Study Group (2006)  IBCSG Trial 13-93  Fair+ | RCT  May 1993-August 1999  Setting NR  Coordinating centers in Switzerland and Australia | Inclusion: premenopausal\*, node-positive breast cancer, not suitbale for endocrine therapy alone, BC Stage I-III, surgical resection of the primary tumor  Exclusion: pregnancy or lactation, inadequate surgery, menopausal, advanced disease, other cancers, advanced comorbidities  \*Premenopausal defined as:  1) normal menstrual period within 6 months prior to randomization  2) previous hysterectomy, no HRT, < 40 yrs OR >40 w/ premenopausal FSH levels  3) receiving HRT, <49, menstrual period w/in 6 months prior to randomization | Intervention description: 5years of tamoxifen + four 21-day courses of doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) IV on day 1 or epirubicin (90mg/m2) and cyclophosphamide (600 mg/m2) IV on day 1, followed by immediate or delayed (16 week gap) three 28-day courses of classic CMF  Control description: no tamoxifen + four 21-day courses of doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) IV on day 1 or epirubicin (90mg/m2) and cyclophosphamide (600 mg/m2) IV on day 1, followed by immediate or delayed (16 week gap) three 28-day courses of classic CMF  N=1246 Analyzed | Median FU: 7 years  LTFU: NR |
| EN# 1009  Tormey (1992)  Eastern Cooperative Oncology Group Trial  Fair+ | RCT  1982-1991  Two-tiered randomized study  United States | Inclusion: premenopausal women w/ breast carcinomas (< or equal to 5 cm); axillary lymph node involvement with one or more nodes; ER +; normal bone scan; diagnostic biopsy within 4 weeks of surgery; randomization within 6 weeks of surgery; white blood cell count >4000/mm; platelet count >100,000/mm; creatinine < 1.5 mg/dL, normal AST and alkaline phosphatase, bilirubin < 1.5 mg%; fasting glucose <9.7mmol/L; no previous or cooccurring malignancy  Exclusion: tumor or nodal fixation, arm edema, skin ucleration, evidence of inflammatory cancer, evidence of metastatic disease; medical conditions that preclude treatment  N (randomized)=658 | Two induction regimens consisting of 12 cycles of therapy beginning 1-6 weeks after mastectomy:  CMFPT - 28 day CMF regimen with prednisone and twice daily Tamoxifen: oral cyclo 100 mg/m days 1-14, IV methotrexate 40 mg/m days 1 and 8, IV fluorouracil 600 mg/m days 1 and 8, oral predinsone 40 mg/m days 1-14, oral Tam 10mg twice daily  ALTER - CMFPT regimen plus fluoxymesterone (H) 10 mg twice daily in odd numbered cycles, prednisone omitted after cycle 3. Even numbered cycles consisted 22-day courses of IV vinblastine 4.5 mg/m, IV adriamycin (dox) 45 mg/m, IV thiotepa 12 mg/m, and twice daily Tam (VATHT)  After 12 cycles of induction patients were randomized to either continue Tam or to observation for 4 years. | Median FU:  Induction – 5.1 years post chemo  Maintenance – 4.1 years after induction  LTFU: NR |
| EN# 1640  Munster (2012)  Fair | RCT  2003-2010  Single Institution – Moffit Cancer Center at the University of South Florida  United States | Inclusion: premenopausal women; early stage breast cancer (stages I-III); planned adjuvant or neoadjuvant cehmotherapy; younger than 45 years; FSH level less than 40 mIU/mL; 2 menstrual periods within 6 months prior to enrollment  Exclusion: pregnancy or lactation, prior chemotherapy, or bilateral oophorectomy/ovarian irradiation before enrollment; history of other cancers; personal or familial history of premature ovarian failure; plan to undergo oophorectomy or hysterectomy in w/in 2 years; use of oral contraceptives  N (randomized)=49 | Intervention description: [(neo) adjuvant chemotherapy regimens (four cycles of doxorubicin plus cyclophosphamide [AC], four cycles of doxorubicin plus cyclophosphamide  followed by four cycles of a taxane [AC3T], or six cycles with fluorouracil plus epirubicin [FEC] or doxorubicin plus cyclophosphamide [FAC]). Womenwith estrogen receptor (ER) –positive tumors were offered tamoxifen for 5 years.] + monthly Triptorelin injections throughout chemotherapy  Control description: [(neo) adjuvant chemotherapy regimens (four cycles of doxorubicin plus cyclophosphamide [AC], four cycles of doxorubicin plus cyclophosphamide  followed by four cycles of a taxane [AC3T], or six cycles with fluorouracil plus epirubicin [FEC] or doxorubicin plus cyclophosphamide [FAC]). Womenwith estrogen receptor (ER) –positive tumors were offered tamoxifen for 5 years.] NO TRIPTORELIN | Median FU:  18 months (range 5-43 months)  Patients w/out resumption of menses followed for at least 24 months  LTFU: 0 |
| EN# 1568  Park (2011)  Fair  (May need to exclude since Ovarian Failure measures are not reported by treatment regimen) | Retrospective Cohort  2001-2010  Single Institution – National Cancer Center Hospital  South Korea | Inclusion: premenopausal women; early stage breast cancer (stages I-III); surgical removal of breast cancer; received chemotherapy  Exclusion: hysterectomy after chemotherapy; no recorded menstrual data; GnRH during adjuvant endocrine treatment use of oral contraceptives  N (Analyzed)=872 | (i) anthracycline based: doxorubicin 60 plus cyclophosphamide 600 mg/m2 on day 1 every 3 weeks for four cycles (AC) and 5-FU 500, doxorubicin 50, and cyclophosphamide 500 mg/m2 on day 1 every 3 weeks for six cycles (FAC);  (ii) taxane-containing: doxorubicin 50 plus taxotere 75 mg/m2 onday 1 every 3 weeks for six cycles (AT) and doxorubicin 60 plus cyclophosphamide 600 mg/m2 on day 1 every 3 weeks for four cycles, followed by taxotere 75 mg/m2 on day 1 and/or capecitabine 2000 mg/m2 on day 1 to 14 every 3 weeks for four cycles [AC-T(X)];  (iii) cyclophosphamide 600 mg/m2 on day 1, methotrexate 40 mg/m2 on day 1 and 8, and 5-FU 600 mg/m2 on day 1 and 8 every 3 weeks for six cycles (CMF). | Median FU: 6.2 years  LTFU: NR |
| EN# 1467  Jung (2010)  Fair | Prospective Cohort  January 1995-July 2009  Multiple Institution  South Korea | Inclusion: premenopausal women; histologically proven early stage breast cancer (stages I-III); treated with surgery and adjuvant chemo; disease free for 12 months post-chemo;  Exclusion: previous chemotherapy, or radiation, for cancers prior to the study; evidence of distant metastases or other malignancies; perimenopausal or menopausal women  N=241 | CMF regimen was administered to patients with 0–3 axillary lymph nodes involved, according to the following schedule: cyclophosphamide 500 mg/m2 intravenous (i.v.) bolus injection on day 1 and day 8; methotrexate 50 mg/m2 i.v. bolus injection on day 1 and day 8; and 5-FU 500 mg/m2 i.v. bolus injection on day 1 and day 8.  Treatment was repeated every 4 weeks for 6 cycles.  FAC regimen was given to patients with more advanced breast cancer (more than 3 axillary lymph nodes involved). The FAC regimen was administered, according to the following schedule: 5-FU 500 mg/m2 intravenous (i.v.) bolus injection on day 1 and day 8; adriamycin 40 mg/m2 i.v. bolus injection on day 1; and cyclophosphamide500 mg/m2 i.v. bolus injection on day 1 and day 8. Treatment was repeated every 4 weeks for 6 cycles. | Median FU: 108.9 months  LTFU: NA |
| EN# 1399  Kim (2009)  Fair | Retrospective Cohort  2003-2008  Single Institution (Korea Cancer Center Hospital)  South Korea | Inclusion: premenopausal women; early stage breast cancer (stages I-III); diagnosed between 2003-2006 at the study institution; younger than 45 years  Exclusion: previous chemotherapy, or radiation, for cancers prior to the study; history of hysterectomy, oophorectomy, or ovarian suppression; patients who received incomplete chemo regimens; patients with poor memory of their menstrual changes  N=324 | CMF - cyclophosphamide/methotrexate/5-fluorouracil  AC, AC+T - doxorubicin/cyclophosphamide followeed by a taxane  TA - anthracycline plus taxane  FAC - 5-fluorouracil/doxorubucin/cyclophosphamide | Median FU: 31.3 months  LTFU: NR |
| EN# 1255  Whoon (2006)  Fair | Retrospective Cohort  1992-2007  Single Institution (Asan Medical Center)  South Korea | Inclusion: premenopausal at diagnosis; early stage breast cancer (stages I-III); treated with adjuvant chemo; age 35 years or younger  Exclusion: patients who lacked information (or poor memory) about their menstrual history; lost to follow-up; death  N=160 | (i) CMF regimen (cyclophosphamide-based) consisted of 6 cycles of a combination of cytoxan (600 mg/m2, intravenous [i.v.]), methotraxate (40 mg/m2, i.v.), and 5-fluorouracil (600 mg/m2, i.v.) on days 1 and 8 of every 3 week cycle,or 12 cycles of cytoxan (100 mg/m2, per oral, days 1 to 14), methotraxate (40 mg/m2, i.v., days 1 and 8), and 5-fluorouracil (600 mg/m2, i.v., days 1 and 8) every 4 weeks.  (ii) The AD regimen (anthracycline-based) consisted of 4 cycles of i.v. cytoxan (600 mg/m2) and doxorubicin (60 mg/m2) on day 1 every 3 weeks (AC regimen), or 6 cycles of i.v. cytoxan (600 mg/m2), doxorubicin (60 mg/m2), and 5-fluorouracil (600 mg/m2) on day 1 every 3 weeks (CAF regimen). | Median FU: 54 months  LTFU: NR |
| EN# 1245  Roche (2006)  French Adjuvant Study Group 06 Randomized trial  Fair- | RCT  1990-1998  Multiple institutions (14 French centers)  France | Inclusion: premenopausal at diagnosis; early stage breast cancer (stages I-III); operable breast cancer (received mastectomy or BCS and axillary dissection); ER/PR positive; treated with adjuvant chemo; age 50` years or younger; WHO performance status <2; normal haematologic (granulocyte count >2.109/l, platelet count >100.109/l), hepatic (bilirubin <35 lmol/l) and renal (serum creatinine level <130 lmol/l) functions; and no cardiac dysfunction [baseline left ventricular ejection fraction (LVEF) ‡50%]  Exclusion: evidence of metastases; history of cardiac dysfunction or previous cancer; a serious underlying medical illness or psychiatric disorder; inflammatory or locally advanced breast cancer before surgery; previous radiation therapy, hormonotherapy or chemotherapy for breast cancer; or if treatment start exceeded 42 days from initial surgery for breast cancer  N=331 | TAM - LHRHa Group: triptorelin 3.75 mg/month intramuscularly (i.m.) plus tamoxifen 30 mg/day orally for 3 years (TAMLHRHa). Locoregional radiotherapy commenced within 6 weeks after initial surgery  FEC-50 Group: fluorouracil 500 mg/m2, epirubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 intravenously (i.v.) every 21 days for six cycles, without hormonal treatment. Locoregional radiotherapy commenced within 30 days after the last  chemotherapy cycle | Median FU:  LTFU: 2 patients |

**Table 2. Outcomes**

| EN#  Study (Year)  Quality | Study Arm | N Analyzed | Chemotherapy Induced Amernorrhea (CIA) | Resumption of Menses | Hormone Levels (FSH, Inhibin B, Estradiol E2, Antimullerian Hormone AMH) |
| --- | --- | --- | --- | --- | --- |
| EN# 1499  Swain (2010)  NSABP B-30 Trial  (long term amenorrhea (menstrual history) data reported in EN# 1828 (Ganz, 2011) abstracted concurrently)  Good | Sequential ACT Regimen: 4 cycles of doxorubicin at a dose of 60 mg per m2 of body-surface area + cyclophosphamide at a dose of 600 mg per m2 every 3 weeks, followed by four cycles of docetaxel at a dose of 100 mg per m2 every 3 weeks | MH Substudy:  692 | CIA definition: no report of menses within 15 months after randomization  12 months: 83.3%  (~576/692)  18 months: 70%  (~484/692)  24 months: 65%  (~450/692) | NR | NR |
| AT Regimen: 4 cycles of doxorubicin at a dose of 60 mg per m2 + docetaxel at a dose of 60 mg per m2 every 3 weeks (MODIFIED: doxorubicin at a dose of 50 mg per m2 and docetaxel at a dose of 75 mg per square meter) | 752 | 12 months: 47.1%  (~354/752)  18 months: 35%  (~263/752)  24 months: 32%  (~241/752) | NR | NR |
| Concurrent ACT: 4 cycles of doxorubicin at a dose of 60 mg per m2 + cyclophosphamide at a dose of 600 mg per square meter + docetaxel at a dose of 60 mg per m2 every 3 weeks (MODIFIED: doxorubicin at a dose  of 50 mg per m2, cyclophosphamide at a dose of 500 mg per m2, and docetaxel at a dose of 75 mg per m2) | 705 | 12 months: 67.2%  (~474/705)  18 months: 60%  (~423/705)  24 months: 57%  (~402/705) | NR | NR |
| EN# 1496  Su (2009)  Good | Intervention Group: cyclophosphamide-based regimens  Assessment 1 (A1): AC 38%, AC/T 54%, FAC 3%, Other 3%  Assessment 2 (A2): AC 37%, AC/T 56%, FAC 3%, Other 4% | A1: 127  A2: 111 | CIA Overall  A1: 55% (70/127)  A2: 56% (62/111)  % w/CIA by # of cyclo cycles at A1  <=4 cycles: 57%  >4 cycles:67%  % w/CIA by Chemo regimen\*  Taxanes: 53%  No Taxanes: 67%  \*percentages related to reciept of taxanes during treatment between CIA and No CIA groups do not sum correctly  % w/CIA by chemo schedule  Every 2 weeks (dose dense: 49%  Every 3 weeks: 66% | NR | AMH, pg/mL (mean)  IG (A1): 53.1  *CIA: 39.1*  *No CIA: 131.6*  Inhibin B, pg/mL (mean)  IG (A1): 12.7  *CIA: 7.7*  *No CIA: 25.3*  FSH, IU/L (mean)  IG (A1): 35.6  *CIA: 52.9*  *No CIA: 17.4* |
| Control Group: no cancer, no chemotherapy | 110 | NA | NR | AMH, pg/mL (mean): 99.5  Inhibin B, pg/mL (mean): 38.5  FSH, IU/L (mean): 13.3 |
| EN# 1529  Del Mastro (2011)  PROMISE-GIM6 Trail  Fair+ | Intervention Group (IG): anthracycline-based, anthracycline + taxane, or CMF-based chemo (100 mg/m2 of oral cyclo on days 1-14 or 600 mg/m2 IV cyclo on days 1 and 8; 40 mg/m2 of methotrexate on days 1 and 8; and 600 mg/m2 of fluorouracil on days 1 and 8)  PLUS monthly Triptorelin injections (3.75 mg) during chemotherapy | Primary Analysis: 148  Secondary Analysis: 139 | *Primary Analysis*  CIA, No.(%):  IG: 139/148 (93.9)  *Secondary Analysis*  Early Menopause, No. (%):  IG: 11/139 (7.9) | Resumption of menses:  IG: 88/139 (63.3) | No.(%) w/Premenopausal levels of E2 without resumption of menses:  CG: 18/139 (14.9)  No.(%) w/Premenopausal levels of FSH without resumption of menses and without premenopausal levels of E2:  IG: 14/139 (10.1) |
| Control Group (CG): anthracycline-based, anthracycline + taxane, or CMF-based chemo (100 mg/m2 of oral cyclo on days 1-14 or 600 mg/m2 IV cyclo on days 1 and 8; 40 mg/m2 of methotrexate on days 1 and 8; and 600 mg/m2 of fluorouracil on days 1 and 8)  No Triptorelin | Primary Analysis:133  Secondary Analysis: 121 | *Primary Analysis*  CIA, No.(%):  CG: 121/133 (90.9)  *Secondary Analysis*  Early Menopause, No. (%):  CG: 31/121 (25.6) | Resumption of menses:  CG: 60/121 (49.6) | No.(%) w/Premenopausal levels of E2 without resumption of menses:  CG: 18/121 (14.9)  No.(%) w/Premenopausal levels of FSH without resumption of menses and without premenopausal levels of E2:  CG: 12/121 (9.9) |
| EN# 1387  Han (2009)  Fair+ | TX/AC regimen: preoperative docetaxel 75 mg/m2 on day 1 plus capecitabine (AC) 1,000 mg/m2 orally twice daily on days 1–14, every 3 weeks for four cycles, or doxorubicin 60 mg/m2 plus cyclophosphamide 600 mg/m2 (AC) on day 1 every 3 weeks for four cycles. Postoperatively,patients were crossed over to the other therapy | 122 at baseline\*  \*Outcomes are reported as percentages for each FU point by treatment regimen. The denominator for each regimen is not known for each time point. | 6 months (n=285): 97.5%  12 months (n=285): 90.2%  24 months (n=273): 71.2%  36 months (n=236): 66.7% | NR | NR |
| AC + T regimen: AC regimen followed by paclitaxel 175 mg/m2 on day 1, every 3 weeks for four cycles | 34 at baseline\* | 6 months (n=285): 88.2%  12 months (n=285): 73.5%  24 months (n=273): 64.5%  36 months (n=236): 73.3% | NR | NR |
| FAC regimen: 5-fluorouracil 500 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2 on day 1 every 3 weeks for six cycles. | 129 at baseline\* | 6 months (n=285): 81.4%  12 months (n=285): 72.1%  24 months (n=273): 63.7%  36 months (n=236): 58.9% | NR | NR |
| EN# 1214  International Breast Cancer Study Group (2006)  IBCSG Trial 13-93  Fair+ | Intervention Group: 5years of tamoxifen + four 21-day courses of doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) IV on day 1 or epirubicin (90mg/m2) and cyclophosphamide (600 mg/m2) IV on day 1, followed by immediate or delayed (16 week gap) three 28-day courses of classic CMF | 624 | CIA = no report of menses within 15 months after randomization (first 5 follow-up reports). The denominator reflects the # of patients LTFU  476/538 (88%) | 11% of the 918 women (entire study) who experienced CIA resumed menses | NR |
| Control Group: four 21-day courses of doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) IV on day 1 or epirubicin (90mg/m2) and cyclophosphamide (600 mg/m2) IV on day 1, followed by immediate or delayed (16 week gap) three 28-day courses of classic CMF  NO Tamoxifen | 622 | CIA = no report of menses within 15 months after randomization (first 5 follow-up reports). The denominator reflects the # of patients LTFU  442/527 (84%) | 11% of the 918 women (entire study) who experienced CIA resumed menses | NR |
| EN# 1009  Tormey (1992)  Eastern Cooperative Oncology Group Trial  Fair+ | CMFPT: 28 day CMF regimen with prednisone and twice daily Tamoxifen: oral cyclo 100 mg/m days 1-14, IV methotrexate 40 mg/m days 1 and 8, IV fluorouracil 600 mg/m days 1 and 8, oral predinsone 40 mg/m days 1-14, oral Tam 10mg twice daily | 263 | 176/263 (67%) |  |  |
| ALTER: CMFPT regimen plus fluoxymesterone (H) 10 mg twice daily in odd numbered cycles, prednisone omitted after cycle 3. Even numbered cycles consisted 22-day courses of IV vinblastine 4.5 mg/m, IV adriamycin (dox) 45 mg/m, IV thiotepa 12 mg/m, and twice daily Tam (VATHT) | 270 | 178/270 (66%) |  |  |
| TAM: Patients rerandomized to continue Tamoxifen for 4 years | 201 | 3/201 (1.5%) | 36/201 (18%) |  |
| OBS: Patients rerandomized to observation for four years | 195 | 5/195 (2.5%) | 30/195 (15%) |  |
| EN# 1640  Munster (2012)  Fair | Intervention Group: [(neo) adjuvant chemotherapy regimens (four cycles of [AC], four cycles of  [AC+T], or six cycles with [FEC] or [FAC])]  + monthly Triptorelin injections throughout chemotherapy | 26 | NR | Menses Maintained Throughout: 1/26  Resumed: 22/26  Not Resumed: 3/26 | **Mean Serum FSH Levels**  Baseline  <35 years:3.9  35-39 years:4.9  >39:6.4  >18 Months  <35 years:7  35-39 years:15.2  >39: 20.3  **Mean Inhibin B Levels:**  Baseline  <35 years: 66.2  35-39 years: 63.5  >39: 23.8  >18 Months  <35 years: 9.9  35-39 years: 19.8  >39: 12.9 |
| Control Group: [(neo) adjuvant chemotherapy regimens (four cycles of [AC], four cycles of  [AC+T], or six cycles with [FEC] or [FAC])]  NO TRIPTORELIN | 21 | NR | Menses Maintained Throughout: 5/21  Resumed:14/21  Not Resumed: 2/21 | **Mean Serum FSH Levels**  Baseline  <35 years:3.9  35-39 years: 4.8  >39: 4.5  >18 Months  <35 years: 1.8  35-39 years: 15.2  >39: 20.3  **Mean Inhibin B Levels:**  Baseline  <35 years: 11.1  35-39 years:67.0  >39: 71.8  >18 Months  <35 years: 6.5  35-39 years:11.8  >39: 9.4 |
| EN# 1568  Park (2011)  Fair  (May need to exclude since Ovarian Failure measures are not reported by treatment regimen) |  |  |  |  |  |
| EN# 1467  Jung (2010)  Fair | CMF regimen cyclophosphamide 500 mg/m2 intravenous (i.v.) bolus injection on day 1 and day 8; methotrexate 50 mg/m2 i.v. bolus injection on day 1 and day 8; and 5-FU 500 mg/m2 i.v. bolus injection on day 1 and day 8.  Treatment was repeated every 4 weeks for 6 cycles. | 188 | No CIA  CMF(n=100)  No menstrual change: 36 (36%)  Oligomenorrhea: 21 (21%)  CIA  CMF (n=100)  Definitive Amernorrhea: 43 (43%)  Temporary Amenorrhea (RM): 0 | NR | NR |
| FAC regimen 5-FU 500 mg/m2 intravenous (i.v.) bolus injection on day 1 and day 8; adriamycin 40 mg/m2 i.v. bolus injection on day 1; and cyclophosphamide 500 mg/m2 i.v. bolus injection on day 1 and day 8. Treatment was repeated every 4 weeks for 6 cycles. | 53 | No CIA  FAC (n=23)  No menstrual change: 6 (26.1%)  Oligomenorrhea: 2 (8.7%)  CIA  FAC (n=23)  Definitive Amernorrhea: 15 (65.2%)  Temporary Amenorrhea (RM): 0 | NR | NR |
| EN# 1399  Kim (2009)  Fair | CMF - cyclophosphamide/methotrexate/5-fluorouracil | 242 | CIA: 197/242 (81.4%)  No CIA: 45/242 (18.6%) | 30/197 (15.2%) | NR |
| Anthracycline or Taxane containing regimens - AC, AC+T - doxorubicin/cyclophosphamide followeed by a taxane  TA - anthracycline plus taxane  FAC - 5-fluorouracil/doxorubucin/cyclophosphamide | 82 | CIA: 64/82 (78.0%)  No CIA:18/82 (22.0%) | 47/64 (73.4%) | NR |
| EN# 1255  Whoon (2006)  Fair | CMF regimen (cyclophosphamide-based) consisted of 6 cycles of a combination of cytoxan (600 mg/m2, intravenous [i.v.]), methotraxate (40 mg/m2, i.v.), and 5-fluorouracil (600 mg/m2, i.v.) on days 1 and 8 of every 3 week cycle,or 12 cycles of cytoxan (100 mg/m2, per oral, days 1 to 14), methotraxate (40 mg/m2, i.v., days 1 and 8), and 5-fluorouracil (600 mg/m2, i.v., days 1 and 8) every 4 weeks. | 80 | CMF Regimen (n=80)  No CIA: 68.8% (55/80)  Temporary CIA: 25% (20/80)  Permanent CIA: 6.2% (5/80) | NR | NR |
| AD regimen (anthracycline-based) consisted of 4 cycles of i.v. cytoxan (600 mg/m2) and doxorubicin (60 mg/m2) on day 1 every 3 weeks (AC regimen), or 6 cycles of i.v. cytoxan (600 mg/m2), doxorubicin (60 mg/m2), and 5-fluorouracil (600 mg/m2) on day 1 every 3 weeks (CAF regimen). | 80 | AD Regimens  AC (n=53)  No CIA: 62.3% (33/53)  Temporary CIA: 33.9% (18/53)  Permanent CIA: 3.8% (2/53)  CAF (n=27)  No CIA: 48.1% (13/27)  Temporary CIA: 40.8% (11/27)  Permanent CIA: 11.1% (3/27) | NR | NR |
| EN# 1245  Roche (2006)  French Adjuvant Study Group 06 Randomized trial  Fair- | TAM - LHRHa Group: triptorelin 3.75 mg/month intramuscularly (i.m.) plus tamoxifen 30 mg/day orally for 3 years (TAMLHRHa). Locoregional radiotherapy commenced within 6 weeks after initial surgery | 164 | No CIA: 0 (0)  CIA: 164/164 (100%)  -Temporary CIA: 95/164 (58%)  -Permanent CIA: 69/164 (42%) | NR | NR |
| FEC-50 Group: fluorouracil 500 mg/m2, epirubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 intravenously (i.v.) every 21 days for six cycles, without hormonal treatment. Locoregional radiotherapy commenced within 30 days after the last  chemotherapy cycle | 168 | No CIA: 65/168 (38%)  CIA: 104/168 (62%)  -Temporary CIA: 52/104 (50%)  -Permanent CIA: 52/104 (50%) | NR | NR |