**Table 1. Study Characteristics**

| EN#  Study (Year)  Trial Name  Quality | Design  Study Period  Location/Setting | Inclusion/Exclusion Criteria  Study N | Adjuvant ChemotherapyTreatment Description | Follow-Up |
| --- | --- | --- | --- | --- |
| EN#1399  Martin (2010)  *Spanish Breast Cancer Research Group (GEICAM) Trial 9805*  Good | RCT (two-arm)  6/1999 – 3/2009  Spain, Poland and Germany | Inclusion: women ages 18-70 who had undergone primary surgery for unilateral operable breast carcinoma (tumor stage T1, T2, T3) and had negative axillary lymph nodes (>10 nodes examined). Patients were also required to meet one or more of the 1998 St. Gallen consensus recommendations for patients with operable node-negative breast cancer (tumor size >2cm, hormone receptor negative, histologic grade of 2 or 3, or age <35 years)  N=1060 | TAC: docetaxel 75 mg/m2 IV + doxorubicin 50 mg/m2 IV + cyclophosphomide 500 mg/m2 IV every 21 days x 6 cycles  FAC: fluorouracil 500 mg/m2 IV + doxorubicin 50 mg/m2 IV + cyclophosphomide 500 mg/m2 IV) every 21 days x 6 cycles | Median: 77 months  LTFU: NR |
| EN#1263  Francis (2008)  *Breast International Group (BIG 02-98) Trial*  Good | RCT (four-arm)  6/1998 – 3/2006  Australia, South America, Europe | Inclusion: women ages 18-70 with operable, clinical stage T1-3 invasive breast cancer; required to have resected tumors with clear margins and at least one positive axillary lymph node among a minimum of eight dissected lymph nodes  Exclusion: supraclavicular lymph node involvement; distant metastases; previous cancers; neuropathy of grade 2 or higher; other serious medical conditions  N=2,887 women | A🡪CMF (sequential control): doxorubicin 75 mg/m2 IV every 21 days for 4 cycles followed by CMF for 3 cycles  AC🡪CMF (concurrent control): doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 IV every 21 days for 4 cycles followed by CMF for 3 cycles  A🡪T🡪CMF (sequential docetaxel): doxorubicin 75 mg/m2 IV every 21 days for 3 cycles followed by doxetaxel 100 mg/m2 IV every 21 days for 3 cycles followed by CMF for 3 cycles  AT🡪CMF (concurrent docetaxel): doxorubicin 50 mg/m2 IV + docetaxel 75 mg/ (with docetaxel commencing 1 hour after doxorubicin) every 21 days for 4 cycles followed by CMF for 3 cycles  *CMF regimen*: cyclophosphamide 100 mg/m2 orally (days 1-14) + methotrexate 40 mg/m2 IV (days 1 and 8) + fluorouracil 600 mg/m2 IV (days 1 and 8) every 28 days for 3 cycles | Median: 62.5 months  LTFU: 2.1% (61/2887) |
| EN#1265  Goldstein (2008)  *North American Breast Cancer Intergroup Trial E2197*  Good | RCT (two-arm)  7/1998 – 1/2007  North America | Inclusion: women with operable, histologically confirmed adenocarcinoma of the breast with either histologically involved lymph nodes (1-3) or tumor size was greater than 1.0 cm; adequate hematologic, hepatic, cardiac and renal function; must have been free of prior invasive malignancies for >5 years with the exception of curatively treated basal cell or squamous cell carcinoma of the skin or cervix; no prior chemo or radiation (except for DCIS)  Exclusion: patients with T4 or N2-3 breast cancers  N=2,952 | Arm 1 (AT): doxorubicin 60 mg/m2 IV + docetaxal 60 mg/m2 IV every 21 days for 4 cycles  Arm 2 (AC): doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 every 21 days for 4 cycles | Median: 79.5 months  LTFU: 2.8% (83/2952) |
| EN#1214  Ferguson (2007)  Good | Systematic Review | Inclusion: unconfounded RCTs; women with histologically confirmed operable breast cancer (stage I to IIIA); studies that included both women receiving neoadjuvant and adjuvant chemotherapy, only if reported separately  Exclusion: protocol-only studies; studies without outcome measure of interest; women who received neoadjuvant chemotherapy  N=21,191 women (11 studies) | Any chemotherapy regimen containing a taxane (paclitaxel and docetaxel) compared to non-taxane containing regimens | Range: 43 – 69 months (median) |
| EN#1141  Venturini (2005)  Good | RCT (two-arm)  11/1992 – 9/2004  Italy | Inclusion: women with histologically confirmed breast cancer; undergone radical mastectomy or BCS in addition to axillary lymph node dissection; lymph node-positive disease with no more than 10 involved nodes or high risk of recurrence (defined as age 35 years or younger, hormone receptor negative, tumor size of at least 2cm, poor histologic grade and/or high proliferative rate; women younger than age 70 years must have received no prior chemotherapy and have no evidence of distant metastases, and have adequate hematologic, renal and hepatic function  N=1,214 women | Arm 1 (FEC dose-dense): fluorouracil 600 mg/m2 + epirubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 14 days for 6 cycles, with the addition to filgrastim  Arm 2 (FEC): fluorouracil 600 mg/m2 + epirubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 21 days for 6 cycles | Median: 124.8 months  LTFU: 10.8% |
| EN#1035  Bernard-Marty (2003)  Good | RCT (three-arm)  6/1988 – 12/1996 | Inclusion: women less than 70 years of age with histologically confirmed, node-positive breast cancer; performance status <1 on the Eastern Cooperative Oncology Group scale; LVEF within normal limits; WBC of 4000/m3 or higher; neutrophil count 2000/m3 or higher; platelet count 100,000/mmg3 or higher; total bilirubin level 1.2 mg/dL or less; serum creatinine level 1.5 mg/dL or less; no distant metastases; no history of previous cancer except carcinoma in-situ of the cervix and basal cell skin cancer; no previous medical or radiation therapy for BC  N=777 women | Arm 1 (EC): Epirubicin 60 mg/m2 IV on day 1 and cyclophosphamide 500 mg/m2 IV on day 1) cycles every 21 days for eight cycles  Arm 2 (HEC): Epirubicin 100 mg/m2 IV on day 1 and cyclophosphamide 830 mg/m2 IV on day 1) cycles every 21 days for eight cycles  Arm 3 (CMF – Control): Cyclophosphamide 100 mg/m2 orally days 1-14; methotrexate 40 mg/m2 IV days 1 and 8; 5-fluorouracil 600 mg/m2 IV days 1 and 8 for every 28 days for six cycles | Median: 71-75 months  LTFU: 2.96% |
| EN#961  Fisher (1999)  *NSABP B25 Trial*  Good | RCT (three-arm)  4/1992 – 12/1998  37 institutions in the U.S. and Canada | Inclusion: women with primary, operable breast cancer; one or more histologically proven positive axillary nodes  Exclusion: metastatic disease  N=2,534 women | Arm 1: Doxorubicin 60 mg IV every 21 days x 4 courses + cyclophosphamide 2400 mg IV on day 1 of course 1 and course 2  Arm 2: Doxorubicin 60 mg IV every 21 days x 4 courses + cyclophosphamide 2400 mg IV on day 1 of course 1-4  Arm 3 (Control): Doxorubicin 60 mg IV every 21 days x 4 courses + cyclophosphamide 1200 mg IV every 21 days x 4 courses | Mean: 55.2 months  LTFU: 3.9% |
| EN#1586  Shulman (2012)  *Cancer and Leukemia Group B (CALGB) 40101*  Fair+ | RCT (four-arm)  5/2000 – 2/2008  U.S. | Inclusion: women with operable breast cancer with 0-3 positive axillary nodes  N=3,871 | Arm 1 (AC x4): doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 IV for 4 cycles  Arm 2 (AC x6): doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 IV for 6 cycles  Arm 3 (T x4): paclitaxel 80 mg/m2 IV (when given weekly) or 175 mg/m2 IV (when given every 2 weeks) for 4 cycles  Arm 4 (T x6): paclitaxel 80 mg/m2 IV (when given weekly) or 175 mg/m2 IV (when given every 2 weeks) for 6 cycles  *Note: AC regimens were initially administered every 3 weeks and T regimens weekly (3 weeks of T was considered 1 cycle). The protocol was amended partway through so that both AC and T were administered every 2 weeks instead* | Median: 63.6 months  LTFU: 1% |
| EN#1131  Praga (2005)  Fair+ | Retrospective cohort  6/1995 – 12/2001 | Inclusion: Women with early stage breast cancer, defined as node positive or negative; enrolled onto one of nineteen clinical trials  Exclusion: previous treatment; distant metastases  N=10,111 | Arm 1: epirubicin-containing regimens  Arm 2: non-epirubicin-containing regimens | Median: 60 months  LTFU: NR |
| EN#1028  Schrama (2002)  Fair+ | RCT  4/1991 – 12/1995  Single institution in the Netherlands | Inclusion: women younger than 60 years of age with breast cancer (operable according to classic Haagensen criteria and with extensive axillary node metastases); performance status of 0 or 1 on the WHO scale; normal bone marrow, renal and hepatic function  Exclusion: axillary dissection; distant metastases  N=81 | Arm 1 (High-dose chemotherapy): ***Pre-surgery*** - FEC (5-fluorouacil 500 mg IV + epirubicin 120 mg IV + cyclophosphomide 500 mg IV) x 3 courses; ***Post-surgery*** - FEC x 1 course + filgrastim 300 ug + peripheral-blood progenitor cell (PBPC) collection followed by high-dose chemothrapy after 3 weeks (cyclophosphomide 6 g + thiotepa 480 mg + carboplatin 1600 mg, divided over 4 days) + PCPC support (anti-emetics and antibiotics)  Arm 2 (Control): ***Pre-surgery*** - FEC (5-fluorouacil 500 mg IV + epirubicin 120 mg IV + cyclophosphomide 500 mg IV) x 3 courses; ***Post-surgery***- FEC x 1 course | Median: 82.8 months  LTFU: NR |
| EN# 974  Chaplain (2000)  Fair+ | Retrospective cohort (registry-based)  1/1982 – 12/1998  France | Inclusion: women with breast cancer who received curative surgical treatment; ages 84 years and younger  Exclusion: distant metastases; unknown surgical treatment; older than 85 years of age  N=3,093 women | Protocols containing mitoxantrone or anthracyclines | Follow-up ended at the date of recurrence/event, last known follow-up date, 85th birthday, or 12/31/1998 |
| EN#1587  Simone (2012)  *NCI Breast Conservation trial*  Fair | RCT  1979 – 1987  U.S. | Inclusion: pathologically confirmed invasive breast tumors 5 cm or less with clinically negative or positive axillary lymph nodes  Exclusion: metastatic disease, previous cancer, poor operative risk, multi-centric disease  N=247 | All patients received AC, but the regimen changed over the treatment period  1979: doxorubicin 30 mg/m2 IV + cyclophosphamide 150 mg/m2 IV every 28 days for 12 cycles  1983: doxorubicin 30 mg/m2 IV + cyclophosphamide 200 mg/m2 IV every 28 days for 12 cycles  1985: doxorubicin 40 mg/m2 IV + cyclophosphamide 200 mg/m2 IV every 21 days for 9 cycles | Median: 308.4 months |
| EN#1598  Vici (2012)  *Gruppo Oncologio Italia Meridionale (GIOM) 9902*  Fair | RCT  4/1999 – 10/2005  Italy | Inclusion: women ages 18-70 years; defininte primary surgery plus axillary dissection for operable (T1-T3) breast cancer within 6 weeks; histologically proven axillary lymph node involvement (at least 5 nodes removed); WHO performance status less than 2; adequate hematologic, hepatic, renal, and cardiac function  Exclusion: pregnancy; locally advanced or metastatic BC; previous chemo, hormonal therapy, radiotherapy, or other cancers (except basal cell skin carcinoma or in situ cervical cancer) or contralateral breast cancers; documented history of cardiac disease; preexistent neuropathy or any other severe illness or medical condition  N=750 women | Arm 1 (EC): epirubicin 120 mg/m2 IV + cyclophosphamide 600 mg/m2 IV every 21 days for 4 cycles  Arm 2 (D🡪EC): docetaxel 100 mg/m2 IV every 21 days for 4 cycles followed by epirubicin 120 mg/m2 IV + cyclophosphamide 600 mg/m2 IV every 21 days for 4 cycles | Median: 64 months  LTFU: 2.9% |
| EN#1106  Campone (2005)  *French Adjuvant Study Group*  Fair | Retrospective cohort  1986 – 2001  France | Inclusion: operable breast cancer; WHO performance status <2; normal hematological, hepatic, cardiac, and renal function; enrollment in one of eight FASG trials  Exclusion: Evidence of metastases; documented history of cardiac disease or previous cancer (except treated basal cell and squamous cell carcinoma or the skin or cancer of the uterine cervix); serious underlying medical illness or psychiatric disorder; inflammatory or locally advanced breast cancer before surgery; previous radiation therapy, hormonal therapy or chemotherapy for BC; start of treatment exceed 42 days from initial surgery for BC  N=2,603 women | Epirubicin-based treatment  FEC 50, 75, or 100: fluorouracil 500 mg/m2 + epirubicin 50, 75, or 100 mg/m2 + cyclophosphamide 500 mg/m2 forevery 21 days for 3 or 6 cycles  E weekly: epirubicin 30 mg on days 1, 8, and 15 every 28 days for 6 cycles  E-VNR: epirubicin 50 mg/m2 on day 1 + vinorelbine 25 mg/m2 on days 1 and 8 every 21 days for 6 cycles | Median: 96 months  LTFU: NR |
| EN#1042  Crump (2003)  *NCIC-CTF Adjuvant Chemotherapy Trials*  Fair | Retrospective cohort  12/1989 – 5/2002  Canada | Inclusion: premenopausal women; node-positive or high-risk node negative; enrollment in one of four NCIC-CTF trials  Exclusion: Distant metastases; documented history of cardiac disease or previous cancer (except treated basal cell and squamous cell carcinoma of the skin or cancer of the cervix, endometrium, colon or thyroid treated more than 5 years before study entry and presumed cured); inadequate renal function; serious underlying medical illness or psychiatric disorder; inflammatory or locally advanced BC before surgery; microscopic evidence of residual tumor at the resection margin or the total mastectomy; gross tumor that remained in the axilla postsurgery; previous radiation therapy or chemotherapy for BC; more than 10 weeks from initial surgery for BC  N=1,451 women | Depending on the trial, women received one of the following regimens:  CEF x6: cyclophosphamide 75 mg/m2 orally on days 1-14 + epirubicin 60 mg/m2 IV on days 1 and 8 + fluorouracil 500 mg/m2 IV on days 1 and 8 every month for 6 cycles  CEF+G-CSF: cyclophosphamide 700 mg/m2, 900 mg/,m2 or 1,100 mg/m2 + epirubicin 7 mg/m2 + fluorouracil 500 mg/m2 IV every 14 days for 12 cycles, supported by granulocyte colony-stimulating factor (G-CSF)  CMF x6: cyclophosphamide 100mg/m2 orally on days 1-14 + methotrexate 40 mg/m2 IV on days 1 and 8 + fluorouracil 600 mg/m2 IV on days 1 and 8 every month for six cycles  AC: doxorubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 3 weeks for 4 cycles | Varied, depending on the trial  Range (median): 58.8 – 108 months  LTFU: NR |
| EN#970  Bergh (2000)  *Scandinavian Breast Group (SBG) 9401*  Fair | RCT (2 arm)  3/1994 – 3/1998  Sweden | Inclusion: women 60 years of age or younger with histologically confirmed breast cancer; expected 5-year RFS of 30% or less and a life expectancy exceeding 3 months; eight or more involved axillary lymph nodes or five or more positive lymph nodes and negative hormone receptors; either nuclear anaplasia grade 2-3 (or equivalent high risk criterion) or a high S-phase fraction  Exclusion: Distant metastases or previous cancer (excluding cervical carcinoma in-situ or contralateral breast cancer); treatment with cytokine within 4 weeks of enrollment; inadequate psychological function; complicated serious disease or uncontrolled infection; pregnancy or lactation; known hypersensitivity to E-coli-derived proteins; enrollment in other drug studies  N=525 women | Arm 1 (Tailored FEC): all patients randomized to this group start on Step 1; based on hematological toxicity, dose adjustments were made - escalation, reduction, or unaltered.  *Step -2*: fluorouracil 600 mg IV + epirubicin 38 mg IV + cyclophosphamide 450 mg IV  *Step -1:* fluorouracil 600 mg IV + epirubicin 60 mg IV + cyclophosphamide 600 mg IV  ***Step 1****:* fluorouracil 600 mg IV + epirubicin 75 mg IV + cyclophosphamide 900 mg IV  *Step 2*: fluorouracil 600 mg IV + epirubicin 90 mg IV + cyclophosphamide 1200 mg IV + mesna 720 mg IV  *Step 3*: fluorouracil 600 mg IV + epirubicin 105 mg IV + cyclophosphamide 1500 mg IV + mesna 900 mg IV  *Step 4*: fluorouracil 600 mg IV + epirubicin 120 mg IV + cyclophosphamide 1800 mg IV + mesna 1080 mg IV  Arm 2 (high-dose FEC+CTCb): fluorouracil 600 mg IV + epirubicin 60 mg IV + cyclophosphamide 600 mg IV x 2 courses followed by fluorouracil 600 mg IV + epirubicin 60 mg IV + cyclophosphamide 1200 mg IV + 5 ug/kg G-CSF followed by high dose chemotherapy after 3-4 weeks (cyclophosphamide 6000 mg + thiotepa 500 mg + carboplatin 800 mg) | Median: 34.3 months (relapse)  Median: 38.3 months (survival)  LTFU: 0.76% |
| EN#  Liu (2008)  *CALBG 9141*  Fair- | Prospective cohort (pilot study)  2/1993 – 4/1994 | Inclusion: women with histologically confirmed, operable carcinoma of the breast and at least one involved axillary lymph node, adequate end-organ function, and an ECOG performance status of 0-2.  N=172 women | Arm 1 (AC 🡪T): doxorubicin 37.5 mg/m2 IV + cyclophosphamide 2000 mg/m2 IV every 21 days for 5 cycles followed by paclitaxel 175 mg/m2 IV every 21 days for 4 cycles | Median: 141.6 months  LTFU: NR |

**Table 2. Outcomes**

| EN#  Study (Year)  Quality | Study Arm | N Analyzed | Incidence of Any Solid Tumor | Incidence of AML | Incidence of MDS | Incidence of Other Type of Secondary Malignancy | Secondary Malignancy-Related Death |
| --- | --- | --- | --- | --- | --- | --- | --- |
| EN#1399  Martin (2010)  *Spanish Breast Cancer Research Group (GEICAM) Trial 9805*  Good | TAC: docetaxel 75 mg/m2 IV + doxorubicin 50 mg/m2 IV + cyclophosphomide 500 mg/m2 IV every 21 days x 6 cycles | 539 | 2.4% (13/539)  *Contralateral BC: 0.74% (*4/539)  *Endometrial*: 0.19% (1/539)  Ovarian: 0.37% (2/539)  *Other*: 1.1% (6/539) | NR | NR | NR | NR |
| FAC: fluorouracil 500 mg/m2 IV + doxorubicin 50 mg/m2 IV + cyclophosphomide 500 mg/m2 IV) every 21 days x 6 cycles | 521 | 5.0% (26/521)  *Contralateral* BC: 1.9% (10/521)  *Endometrial*: 0.77% (4/521)  *Ovarian*: 0.19% (1/521)  *Other*: 1.9% (10/521)  *Unknown*: 0.19% (1/521) | NR | NR | NR | NR |
| EN#1263  Francis (2008)  Good | A🡪CMF (sequential control): doxorubicin 75 mg/m2 IV every 21 days for 4 cycles followed by CMF for 3 cycles | 481 | NR | Leukemia or MDS: 0.3% (3/968) | | Second primary cancer: 2.1% (10/481) | NR |
| AC🡪CMF (concurrent control): doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 IV every 21 days for 4 cycles followed by CMF for 3 cycles | 487 | NR | Second primary cancer: 1.6% (8/487) | NR |
| A🡪T🡪CMF (sequential docetaxel): doxorubicin 75 mg/m2 IV every 21 days for 3 cycles followed by doxetaxel 100 mg/m2 IV every 21 days for 3 cycles followed by CMF for 3 cycles | 960 | NR | Leukemia or MDS: 0.1% (2/1919) | | Second primary cancer: 1.9% (18/960) | NR |
| AT🡪CMF (concurrent docetaxel): doxorubicin 50 mg/m2 IV + docetaxel 75 mg/ (with docetaxel commencing 1 hour after doxorubicin) every 21 days for 4 cycles followed by CMF for 3 cycles | 959 | NR | Second primary cancer: 1.5% (14/959) | NR |
| EN#1265  Goldstein (2008)  *North American Breast Cancer Intergroup Trial E2197*  Good | Arm 1 (AT): doxorubicin 60 mg/m2 IV + docetaxal 60 mg/m2 IV every 21 days for 4 cycles | 1,441 | NR | AML/MDS: .049% (7/1441) | | Nonbreast second primary: 4.0% (57/1441) | NR |
| Arm 2 (AC): doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 every 21 days for 4 cycles | 1,441 | NR | AML/MDS: 0.49% (7/1441) | | Nonbreast second primary: 2.7% (39/1441) | NR |
| EN#1214  Ferguson (2007)  Good | Any chemotherapy regimen containing a taxane (paclitaxel and docetaxel) compared to | 7,093 | NR | Secondary Leukemia/ myelodysplasia: 0.35% (25/7093) | | NR | NR |
| Non-taxane containing regimens | 7,056 | NR | Secondary Leukemia/ myelodysplasia: 0.33% (23/7056) | |  |  |
| EN#1141  Venturini (2005)  Good | Arm 1 (FEC dose-dense): fluorouracil 600 mg/m2 + epirubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 14 days for 6 cycles, with the addition to filgrastim | 604 | 4.8% (29/604)  *Breast: 2.0% (12/604)* | 0 | 0 | NR | NR |
| Arm 2 (FEC): fluorouracil 600 mg/m2 + epirubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 21 days for 6 cycles | 610 | 4.6% (28/610)  Breast: 2.3% (14/610) | 0 | 0 | NR | NR |
| EN#1035  Bernard-Marty (2003)  Good | Arm 1 (EC): Epirubicin 60 mg/m2 IV on day 1 and cyclophosphamide 500 mg/m2 IV on day 1) cycles every 21 days for eight cycles | 267 | 3.0% (8/267)  *Contralateral BC: 1.5% (*4/267)  *Uterine*: 0.37% (1/267)  *Thyroid*: 0.37% (1/267)  *Melanoma*: 0.37% (1/267) | 0% | NR | *CLL*: 0.37% (1/267) | 0% |
| Arm 2 (HEC): Epirubicin 100 mg/m2 IV on day 1 and cyclophosphamide 830 mg/m2 IV on day 1) cycles every 21 days for eight cycles | 255 | 4.3% (11/255)  *Contralateral BC*: 2.0% (5/255)  *Ovary (epithelial):* 0.78% (2/255)  *Cervix (squamous):* 0.39% (1/255)  *Thyroid*: 0.39% (1/255)  *Lung*: 0.39% (1/255)  *Glioblastoma*: 0.39% (1/255) | 1.2% (3/255) | NR | *Lymphoma*: 0.39% (1/255)  *CLL*: 0.39% (1/255) | 1.2% (3/255, all due to AML) |
| Arm 3 (CMF – Control): Cyclophosphamide 100 mg/m2 orally days 1-14; methotrexate 40 mg/m2 IV days 1 and 8; 5-fluorouracil 600 mg/m2 IV days 1 and 8 for every 28 days for six cycles | 255 | 4.3% (11/255)  *Contralateral BC:* 2.7% (7/255)  *Colorectal carcinoma: 0.78% (*2/255)  *Thyroid:* 0.39% (1/255)  *Melanoma:* 0.39% (1/255) | 0% | NR | 0% | 0% |
| EN#961  Fisher (1999)  *NSABP B-25*  Good | Arm 1: Doxorubicin 60 mg IV every 21 days x 4 courses + cyclophosphamide 2400 mg IV on day 1 of course 1 and course 2 | 845 | NR | 0.59% (5/845) | 0.59% (5/845) | NR | NR |
| Arm 2: Doxorubicin 60 mg IV every 21 days x 4 courses + cyclophosphamide 2400 mg IV on day 1 of course 1-4 | 847 | NR | 0.71% (6/847) | 0.24% (2/847) | NR | NR |
| Arm 3 (Control): Doxorubicin 60 mg IV every 21 days x 4 courses + cyclophosphamide 1200 mg IV every 21 days x 4 courses | 842 | NR | 0.48% (4/842) | 0% (0/842) | NR | NR |
| EN#158  Shulman (2012)  *Cancer and Leukemia Group B (CALGB) 40101*  Fair+ | Arm 1 (AC x4): doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 IV for 4 cycles | 795 | NR | 0.1% (1/795) | | NR | 0.32% (5/1584) |
| Arm 2 (AC x6): doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 IV for 6 cycles | 789 | NR | 0.63% (5/789) | | NR |
| Arm 3 (T x4): paclitaxel 80 mg/m2 IV (when given weekly) or 175 mg/m2 IV (when given every 2 weeks) for 4 cycles | 798 | NR | 0 | |  | 0 |
| Arm 4 (T x6): paclitaxel 80 mg/m2 IV (when given weekly) or 175 mg/m2 IV (when given every 2 weeks) for 6 cycles | 789 | NR | 0 | |  |  |
| EN#1131  Praga (2005)  Fair+ | Arm 1: epirubicin-containing regimens | 7,110 |  | 0.39% (28/7110) | | NR | NR |
| Arm 2: non-epirubicin-containing regimens | 2,686 |  | 0.07% (2/2686) | | NR | NR |
| EN#1028  Schrama (2002)  Fair+ | Arm 1 (High-dose chemotherapy): ***Pre-surgery*** - FEC (5-fluorouacil 500 mg IV + epirubicin 120 mg IV + cyclophosphomide 500 mg IV) x 3 courses; ***Post-surgery*** - FEC x 1 course + filgrastim 300 ug + peripheral-blood progenitor cell (PBPC) collection followed by high-dose chemothrapy after 3 weeks (cyclophosphomide 6 g + thiotepa 480 mg + carboplatin 1600 mg, divided over 4 days) + PCPC support (anti-emetics and antibiotics) | 41 | 4.9% (2/41)  *Basal cell carcinoma:* 2.4% (1/41)  *Adenoma of the colon:* 2.4% (1/41) | NR | 4.9% (2/41) | NR | NR |
| Arm 2 (Control): ***Pre-surgery*** - FEC (5-fluorouacil 500 mg IV + epirubicin 120 mg IV + cyclophosphomide 500 mg IV) x 3 courses; ***Post-surgery***- FEC x 1 course | 40 | 2.5% (1/40)  *Adenoma of the colon:* 2.5% (1/40) | NR | 0% (0/40) | NR | NR |
| EN#  Chaplain (2000)  Fair+ | Anthracycline-containing regimens | 341 | NR | NR | NR | NLAL/RAEB-t: 0.29% (1/341) | NR |
| EN#1587  Simone (2012)  *NCI Breast Conservation Trial*  Fair | AC-based regimens | 237 | NR | NR | NR | Non-breast cancer: 10.5% (25/237) | NR |
| EN#1598  Vici (2012)  *Gruppo Oncologio Italia Meridionale (GIOM) 9902*  Fair | Arm 1 (EC): epirubicin 120 mg/m2 IV + cyclophosphamide 600 mg/m2 IV every 21 days for 4 cycles | 374 | 1.1% (4/374)  *Pancreas: 0.27% (1/374)*  *Thyroid: 0.27% (1/374)*  *Endometrium: 0.53% (2/374)* | 0 | 0 | NH-lymphoma: 0.27% (1/374) | 0.8% (3/374) |
| Arm 2 (D🡪EC): docetaxel 100 mg/m2 IV every 21 days for 4 cycles followed by epirubicin 120 mg/m2 IV + cyclophosphamide 600 mg/m2 IV every 21 days for 4 cycles | 376 | 1.1% (4/376)  *Skin: 0.27% (1/376)*  *Ovary: 0.27% (1/376)*  *Peritoneum: 0.27% (1/376)*  *Colon-rectum: 0.27% (1/376)* | 0 | 0 | 0 | 0 |
| EN#1106  Campone (2005)  *French Adjuvant Study Group*  Fair | Epirubicin-based treatment  FEC 50, 75, or 100: fluorouracil 500 mg/m2 + epirubicin 50, 75, or 100 mg/m2 + cyclophosphamide 500 mg/m2 forevery 21 days for 3 or 6 cycles  E weekly: epirubicin 30 mg on days 1, 8, and 15 every 28 days for 6 cycles  E-VNR: epirubicin 50 mg/m2 on day 1 + vinorelbine 25 mg/m2 on days 1 and 8 every 21 days for 6 cycles | 2,603 | NR | 0.23% (6/2603) | NR | ALL: 0.08% (2/2603) | 0.19% (5/2603; 3 due to AML and 2 due to ALL) |
| EN#1042  Crump (2003)  *NCIC-CTF Adjuvant Chemotherapy Trials*  Fair | CEF x6: cyclophosphamide 75 mg/m2 orally on days 1-14 + epirubicin 60 mg/m2 IV on days 1 and 8 + fluorouracil 500 mg/m2 IV on days 1 and 8 every month for 6 cycles | 539 | NR | 0.92 (5/539) | NR | Acute leukemia: 1.30% (7/539)  ALL: 0.37% (2/539) | 0.74% (4/539, all due to AML) |
| CEF+G-CSF: cyclophosphamide 700 mg/m2, 900 mg/,m2 or 1,100 mg/m2 + epirubicin 7 mg/m2 + fluorouracil 500 mg/m2 IV every 14 days for 12 cycles, supported by granulocyte colony-stimulating factor (G-CSF) | 97 | NR | 0 | NR | 0 | 0 |
| CMF x6: cyclophosphamide 100mg/m2 orally on days 1-14 + methotrexate 40 mg/m2 IV on days 1 and 8 + fluorouracil 600 mg/m2 IV on days 1 and 8 every month for six cycles | 678 | NR | 0.15% (1/678) | NR | 0 | 0.15% (1/678, due to AML) |
| AC: doxorubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 3 weeks for 4 cycles | 231 | NR | 0.87% (2/231) | NR | NR | 0.43% (1/231, due to AML) |
| EN#970  Bergh (2000)  *Scandinavian Breast Group (SBG) 9401*  Fair | Arm 1 (Tailored FEC): all patients randomized to this group start on Step 1; based on hematological toxicity, dose adjustments were made - escalation, reduction, or unaltered.  ***Step 1****:* fluorouracil 600 mg IV + epirubicin 75 mg IV + cyclophosphamide 900 mg IV | 251 | 4.38% (11/251)  *Contralateral Breast cancer:* 3.59% (9/251)  *Rectal carcinoma:* 0.40% (1/251)  *Basal carcinoma of the skin*: 0.40% (1/251) | 1.20% (3/251) | 0.79% (2/251) | NR | 2.79% (7/251; all due to AML or MDS) |
| Arm 2 (high-dose FEC+CTCb): fluorouracil 600 mg IV + epirubicin 60 mg IV + cyclophosphamide 600 mg IV x 2 courses followed by fluorouracil 600 mg IV + epirubicin 60 mg IV + cyclophosphamide 1200 mg IV + 5 ug/kg G-CSF followed by high dose chemotherapy after 3-4 weeks (cyclophosphamide 6000 mg + thiotepa 500 mg + carboplatin 800 mg) | 274 | NR | NR | NR | NR | NR |
| EN#  Liu (2008)  Fair- |  |  |  |  |  |  |  |

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL=chronic lymphocytic leukemia; MDS=myelodysplastic syndrome