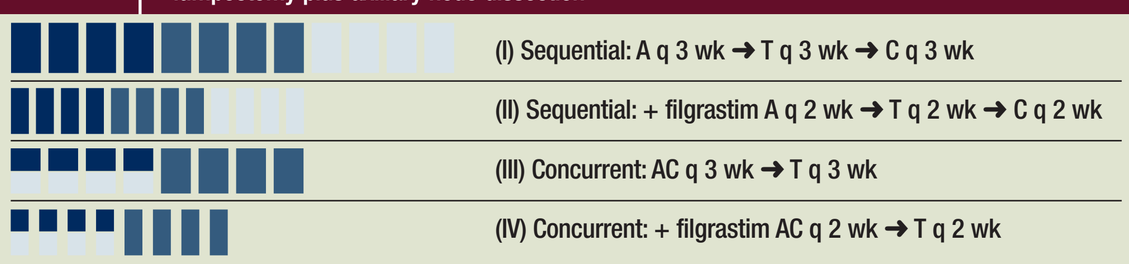
Dose-Dense Adjuvant Chemotherapy

A number of randomized trials — including NSABP B-22 and other studies using autologous stem cell support — have failed to demonstrate an advantage to dose-intensive chemotherapy. A dose-dense chemotherapy regimen involves a strategy where closer-than-normal dosing intervals are utilized, often facilitated by hemotopoietic growth factor support, i.e., filgrastim. Several Phase II trials have assessed different dose-dense regimens as adjuvant therapy in women with node-positive breast cancer. As a result, major Phase III randomized trials are evaluating the role of dose-dense adjuvant chemotherapy. CALGB 9741 is closed to accrual, and initial results were presented at the San Antonio Breast Cancer Symposium in December, suggesting a disease-free and survival advantage in the dose-dense randomization arms.

PHASE III RANDOMIZED STUDY OF SEQUENTIAL CHEMOTHERAPY USING DOXORUBICIN, PACLITAXEL, AND CYCLOPHOSPHAMIDE OR CONCURRENT DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL AT 14- AND 21-DAY INTERVALS IN WOMEN WITH NODE-POSITIVE STAGE II OR IIIA BREAST CANCER Closed Protocol
Protocol IDs: CLB-9741, E-C9741, NCCTG-C9741, SWOG-C9741
Projected Accrual: 2,000 patients

Eligibility:	Operable, stage II or IIIA adenocarcinoma of the breast (T0-3, N1-2, and M0) surgically treated by either a modified radical mastectomy or a lumpectomy plus axillary node dissection



SOURCE: NCI Physician Data Query, December 2002 and adapted from presentation, M Citron, San Antonio Breast Cancer Symposium 2002.

Three-year results of CALGB 9741, a phase III randomized study comparing dose-dense versus conventional scheduling and sequential versus combination adjuvant chemotherapy for node-positive breast cancer

Parameters	Dose-dense Scheduling	Conventional Scheduling	P Value
Disease-free survival	85%	81%	RR = 0.74 (p = 0.007)
Overall survival	92%	90%	RR = 0.69 (p = 0.014)

SOURCE: Citron M et al. **Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs. combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALBG 9741, INT C9741).** *Breast Cancer Res Treat* 2002; Abstract 15.

SELECT PHASE II DOSE-DENSE ADJUVANT CHEMOTHERAPY TRIALS

Reference	Eligibility	Number of Patients	Chemotherapy Regimen	Results
Hudis 1999	≥4 positive lymph nodes	71	A q 21 days x 4 → C q 14 days x 3 + (filgrastim days 3-10 of each cycle)	5 years: 52% DFS, 60% OS
Hudis 1999	≥4 positive lymph nodes	42	A q 14 days x 3 → T q 14 days x 3 → C q 14 days x 3 (filgrastim days 3-10 of each cycle)	4 years: 78% DFS
Fountzilas 2001	T1-T3; ≥10 positive lymph nodes	49	E q 2 wks x 3 → T q 2 wks x 3 → CMF q 2 wks x 3 (filgrastim days 2-10 of each cycle)	3 years: 72% DFS, 90% OS
Ellis 2002	Node+ and HER2+ or ER/PR - or ≥4 positive lymph nodes	52	[A ± F q wk] x 20-24 wks + C qd x 20 wks + filgrastim each day of treatment with C	5 years: 85% DFS, 86% OS

A = doxorubicin; T = paclitaxel; C = cyclophosphamide; E = epirubicin; M = methotrexate; F = 5-fluorouracil; DFS = disease-free survival; OS = overall survival

SELECT PUBLICATIONS

Citron M et al. **Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs. combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALBG 9741, INT C9741).** *Breast Cancer Res Treat* 2002.

Ellis GK et al. **Dose-dense anthracycline-based chemotherapy for node-positive breast cancer.** *J Clin Oncol* 2002;20(17):3637-3643.

Fornier MN et al. **Doxorubicin followed by sequential paclitaxel and cyclophosphamide versus concurrent paclitaxel and cyclophosphamide: 5-year results of a phase II randomized trial of adjuvant dose-dense chemotherapy for women with node-positive breast carcinoma.** *Clin Cancer Res* 2001;7(12):3934-3941.

Fountzilas G et al. **Dose-dense adjuvant chemotherapy with epirubicin monotherapy in patients with operable breast cancer and ≥10 positive axillary lymph nodes. A feasibility study.** *Oncology* 1998;55(6):508-512.

Fountzilas G et al. **Dose-dense sequential adjuvant chemotherapy with epirubicin, paclitaxel and CMF in high-risk breast cancer.** *Oncology* 2001;60(3):214-220.

Hudis C et al. **5-year results of dose-intensive sequential adjuvant chemotherapy for women with high-risk node-positive breast cancer: A phase II study.** *J Clin Oncol* 1999;17(4):1118-1126.

Hudis C et al. **Sequential dose-dense doxorubicin, paclitaxel, and cyclophosphamide for resectable high-risk breast cancer: Feasibility and efficacy.** *J Clin Oncol* 1999;17(1):93-100.

Razis E et al. **Dose-dense sequential chemotherapy with epirubicin and paclitaxel in advanced breast cancer.** *Cancer Invest* 2001;19(2):137-144.

Trudeau ME. **Optimizing adjuvant breast cancer chemotherapy: Rationale for the MA.21 study.** *Oncology (Huntingt)* 2001;15(5 Suppl 7):7-13.

Untch M et al. **Dose-dense and sequential strategies in adjuvant breast cancer therapy.** *Oncology (Huntingt)* 2001;15(5 Suppl 7):14-20.

DEFINITION OF DOSE-DENSE CHEMOTHERAPY

"The delivery of multiple cycles of chemotherapy using the shortest possible intervals is therefore hypothesized to minimize tumor regrowth between one cycle and the next. This is called 'dose-dense' chemotherapy, herein an increase in dose-intensity is obtained by shortening the intervals between treatments and not, as has been done previously, by simply increasing dose levels."

—Hudis C et al. J Clin Oncol 1999;17:1118-1126.

"The concept of 'dose intensity' (DI) in the management of breast cancer has been widely explored by medical oncologists during the last decade… DI can be increased either by dose escalation or by reducing the interval between cycles, a concept termed 'dose density.' The administration of drugs at an adequate dosing at shorter time intervals, i.e. every 2 weeks, became feasible with the introduction of hemopoietic growth factors into the clinical practice…Sequential chemotherapy and dose-dense chemotherapy are two concepts that greatly influenced the design of adjuvant clinical trials in breast cancer during the last decade. The design of such trials was mostly empirical although it was based on mathematical and experimental evidence stressing the superiority of dose-dense sequential chemotherapy over conventional chemotherapy."

—Fountzilas G et al. Oncology 2001;60:214-220.

INTERGROUP TRIAL 9741

This study was designed with input from all members of the breast Intergroup and coordinated by the CALGB. It had a two-by-two factorial design. The two parameters were dose-density — giving drugs every two weeks instead of every three weeks using G-CSF — and combination versus sequential therapy. The doses were the same optimal doses derived from previous clinical trial experience. The only difference was the schedules.

—Larry Norton, MD

CLINICAL APPLICABILITY OF DOSE-DENSE ADJUVANT CHEMOTHERAPY

Dose-dense adjuvant chemotherapy in a nonprotocol setting is a reasonable option. This trial, which accrued over 2,000 patients, shows improved efficacy, decreased death rates and reduced toxicity; therefore, there's no reason not to use dose-dense therapy at this time.

I believe in dose-dense therapy because I've seen its evolution in the laboratory and the clinic for 25 years, and I believe it has a solid basis. However, no individual can stand up and say this is the new standard of care. We have to see how people are going to utilize this in the community.

I would not be shocked to find this approach widely accepted and used, but whether it becomes a new standard of care needs to be defined by the community.

—Larry Norton, MD

ACCEPTANCE OF DOSE DENSITY IN CLINICAL PRACTICES

Dose-dense therapy is definitely a therapeutic option for high-risk patients with breast cancer at this time. I always present patients with their options, and I like to hear what they have to say. In general, patients want the treatment with the most potential for cure. Many want to receive the treatment quickly — in fact, that's one of the most common reasons patients express for wanting dose-dense therapy.

I was initially embargoed from revealing the results of CALGB 9741, but now I discuss it with patients. I give them my take on the literature and my recommendation. I've been surprised how positively dose-dense therapy has been received. As I talk to physicians, I find they are often already using or at least considering it.

— Marc Citron, MD