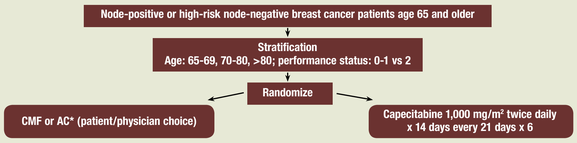
# CALGB-49907: Adjuvant Chemotherapy in Elderly Women

**Relatively few randomized trials of adjuvant chemotherapy have included substantial numbers of elderly women, so a relative paucity of research data exists with regard to the risks and benefits of this intervention. This is particularly problematic in older women with estrogen receptor-negative tumors who will not receive endocrine therapy. Another common clinical dilemma is the elderly woman with an estrogen receptor-positive tumor for whom the incremental benefits and risks of chemotherapy in addition to endocrine treatment must be considered. An important related trial being led by Dr Hyman Muss, CALGB-49907, randomly assigns elderly women with primary breast cancer to either the orally administered fluoropyrimidine prodrug capecitabine, or AC or CMF chemotherapy. In addition to evaluating disease-free and overall survival, a number of key quality-of-life endpoints are being evaluated.**

### CALGB-49907: ADJUVANT CMF OR AC VERSUS CAPECITABINE IN WOMEN AGE 65 AND OLDER




*Patients whose LVEF is not within lower limits of normal must receive CMF, not AC. All ER/PR-positive patients receive tamoxifen or an aromatase inhibitor for five years.

**Objectives**
- Primary: Relapse-free survival
- Secondary:
  - Overall survival
  - Toxicities
  - Quality of life
  - Comorbidity and functional status
  - Adherence to capecitabine

**Comparing capecitabine to IV therapy: key issues**
- Oral agent
- Targets tumor tissue (potential therapeutic index gain)
- Known efficacy in metastatic setting
- Known toxicity: No cardiac damage
- Major drug interaction is with warfarin
- Potential better quality of life
- Less reliance on caregiver

SOURCES: NCI Physician Data Query, October 2004; Budman DR. *Breast Cancer Update Grand Rounds* 2004(8).

### SUMMARY OF EFFICACY: SINGLE-AGENT CAPECITABINE VERSUS STANDARD CHEMOTHERAPY IN METASTATIC DISEASE

| Efficacy | Capecitabine versus CMF as first-line therapy (n=93) | | Capecitabine versus paclitaxel as second-line therapy (n=41) | |
|---|---|---|---|---|
| | Capecitabine | CMF | Capecitabine | Paclitaxel |
| Response rate (95% CI) | 30% (19-43) | 16% (5-33) | 36% (17-59) | 26% (9-51) |
| Complete response | 5% | 0% | 14% | 0% |
| Median time to disease progression (95% CI) | 4.1 months (3.2-6.5) | 3.0 months (2.4-4.8) | 3.0 months (1.4-6.6) | 3.1 months (2.5-6.5) |
| Median survival | 19.6 months | 17.2 months | 9.4 months | 9.4 months |

CI = confidence interval

DERIVED FROM: Biganzoli L et al. **Moving forward with capecitabine: A glimpse of the future.** *Oncologist* 2002;7(Suppl 6):29-35.

### PROPORTION OF ELDERLY PATIENTS (AGE ≥65) IN SWOG TRIALS AS COMPARED WITH THE PROPORTION OF ELDERLY PATIENTS WITH CANCER IN THE UNITED STATES*

| Type of cancer | Percent of US cancer cases occurring in patients age 65 and older | Percent of enrolled patients age 65 and older |
|---|---|---|
| Breast | 49 | 9 |
| Brain | 44 | 19 |
| Colorectal | 72 | 40 |
| Leukemia | 63 | 27 |
| Lung | 66 | 39 |
| Myeloma | 70 | 25 |
| All types | 63 | 25 |

*The differences between the two groups were significant ($p < 0.001$) for all types of cancer listed.

SOURCE: Hutchins LF et al. **Underrepresentation of patients 65 years of age or older in cancer-treatment trials.** *N Engl J Med* 1999;341(27):2061-7.

### UNDERREPRESENTATION OF ELDERLY WOMEN IN RECENT CALGB ADJUVANT TRIALS

| Trial regimens | Total accrued | Age 70 and older |
|---|---|---|
| CLB-8541 CAF in three different doses | 1,572 | 150 (10%) |
| CLB-9344 AC ± T | 3,170 | 182 (6%) |
| CLB-9741 A → T → C vs AC → T in a q2wk vs q3wk schedule | 2,005 | 162 (8%) |

C = cyclophosphamide; A = doxorubicin; F = fluorouracil; T = paclitaxel

SOURCE: CALGB-49907 Protocol.

### RATES OF OFFERING AND ACCEPTING CLINICAL TRIAL PARTICIPATION IN WOMEN

| Mean age (years) | Offered protocol | Consented when offered |
|---|---|---|
| 50.4 | 51% | 56% |
| 76.5 | 35% | 50% |

SOURCE: Kemeny M et al. **Barriers to clinical participation by older women with breast cancer.** *J Clin Oncol* 2003;21(12):2268-75.

## SELECT PUBLICATIONS


Bouchardy C et al. **Undertreatment strongly decreases prognosis of breast cancer in elderly women.** *J Clin Oncol* 2003;21(19):3580-7.

Du X, Goodwin JS. **Patterns of use of chemotherapy for breast cancer in older women: Findings from Medicare claims data.** *J Clin Oncol* 2001;19(5):1455-61.

Extermann M et al. **What threshold for adjuvant therapy in older breast cancer patients?** *J Clin Oncol* 2000;18(8):1709-17.

Gagnon B et al. **Pattern of care at the end of life: Does age make a difference in what happens to women with breast cancer?** *J Clin Oncol* 2004;22(17):3458-65.

Kemeny MM et al. **Barriers to clinical trial participation by older women with breast cancer.** *J Clin Oncol* 2003;21(12):2268-75.

Mandelblatt JS et al. **Predictors of long-term outcomes in older breast cancer survivors: Perceptions versus patterns of care.** *J Clin Oncol* 2003;21(5):855-63.

O'Shaughnessy JA et al. **Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer.** *Ann Oncol* 2001;12(9):1247-54.

Talbot DC et al. **Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines.** *Br J Cancer* 2002;86(9):1367-72.




### CALGB-49907: CAPECITABINE VERSUS AC/CMF IN THE ELDERLY

One of the exciting trials we have ongoing in North America is CALGB-49907. This is a trial that essentially compares standard chemotherapy — four cycles of AC or CMF with oral cyclophosphamide — to six cycles of capecitabine for elderly patients. Physicians can select the standard chemotherapy for patients randomly assigned to that arm. We're excited about the trial and like to believe it's an equivalence study, as some background data suggest that oral capecitabine is as good as standard therapy. It would be nice if we had an oral regimen because I think people would rather be at home than in our clinics all the time.

What's nice about this trial is we have a quality-of-life endpoint, and we're collecting data from approximately the first 300 patients. We also are using a very clever computerized pill bottle for the patients receiving capecitabine. The bottle has a computer chip in the lid and every time the patient opens the bottle to take a dose, the computer chip registers it. We're also going to collect tumor blocks to see if we can predict how these older patients do with chemotherapy.

*— Hyman B Muss, MD*

### EFFICACY OF CAPECITABINE IN THE ELDERLY

"A recent randomized phase II trial, comparing single-agent capecitabine and CMF as first-line therapy in patients with metastatic breast cancer who were 55 years and older (median age 69 years), demonstrated the response rate to capecitabine alone (25 percent) at a dose of 2510 mg/m² per day for 14 days, every three weeks was superior to intravenous CMF (16 percent). Grade 3 or 4 hand-foot syndrome was seen in 16 percent of patients on capecitabine and none on CMF, Grade 3 or 4 diarrhea in 8 percent with capecitabine and 3 percent with CMF, and Grade 3 or 4 hematological toxicity in 20 percent with capecitabine and 47 percent with CMF. In another Phase II randomized trial comparing capecitabine in the same dose and schedule as above with paclitaxel 175 mg/m² every three weeks, the response rate was 36 percent for 22 patients on capecitabine and 21 percent for 22 patients on paclitaxel. These data suggest that the efficacy of capecitabine in patients with metastatic disease is similar to CMF or paclitaxel."

*— CALGB-49907 PROTOCOL*

### RATIONALE FOR CALGB-49907

Why would the CALGB want to conduct this trial? Capecitabine has the advantage of oral administration, and it targets tumor tissue. My major interest for the last 15 years has been clinical pharmacology and drug development, and this is an interesting drug because it's changing the way we think in oncology. We are trying to target tissue and diminish toxicity rather than just using an active drug. Capecitabine has known efficacy and doesn't cause cardiac damage, which is a major issue as patients get older.

*— Daniel R Budman, MD*

### ACCRUAL AND IMPORTANCE OF CALGB-49907

Hyman Muss has made some changes to try to make the eligibility more streamlined and easier for physicians and patients to participate in the study. Unfortunately, we ran into toxicity problems in two patients in the capecitabine arm. These cases were evaluated by the data monitoring committee and one case was thought to be related to an enzyme deficiency. The other case was thought to be an unfortunate late toxicity in which the patient didn't contact the physician in a timely fashion.

New rules have been written into the trial to ensure toxicity problems do not occur again. We strongly believe that this trial will address a very good question: How does an oral agent compare to traditional intravenous chemotherapy? In patients with metastatic disease, capecitabine has been shown to be better than CMF, so we might even have an efficacy advantage.

*— Jeffrey Abrams, MD*