the trial period was significantly lower in the 10-year group compared with the 5-year group (331 vs 397; p=0.01). Overall mortality was also significantly lower for the 10-year group (639 vs 722; p=0.01). The reductions in adverse breast cancer outcomes appeared to be relatively smaller earlier, with a recurrence rate ratio (RR) of 0.90 (95% CI, 0.79 to 1.02) during Years 5 to 9 and 0.75 (95% CI, 0.62 to 0.90) after Year 10, and breast cancer mortality RR of 0.97 (95% CI, 0.79 to 1.18) during Years 5 to 9 and 0.71 (95% CI, 0.58 to 0.88) after Year 10 [Davies C et al. *Lancet* 2012].

As the study of 10 years of tamoxifen compared with no tamoxifen has not yet been conducted, the authors combined data from the ATLAS trial and the EBCTCG meta-analysis (n=10,645), which compared 5 years of tamoxifen with no tamoxifen. The breast cancer death RR by period is shown in Table 1.

Table 1. Breast Cancer Death Rate Ratios: ER-Positive Disease by Period.

Tamoxifen	5 Years vs 0: EBCTCG Meta-Analysis (n=10,645)	10 Years vs 5: ATLAS Trial (n=6846)	10 Years vs 0: Estimated as a Product of RRs
Years 0–4	0.71‡ (0.62–0.80)	(1.0)	0.71‡ (0.62–0.81)
Years 5–9	0.66‡ (0.58–0.75)	0.97 (0.79–1.18)	0.64† (0.50–0.82)
Years 10+	0.73† (0.62–0.86)	0.71* (0.58–0.88)	0.52‡ (0.40–0.68)

*p=0.0016; †p=0.0001; ‡p<0.00001. ER=estrogen receptor; RR=rate ratio.

Endometrial cancer and pulmonary embolism mortality occurred in 0.2% of patients in the ATLAS trial and 0.2% of patients in the EBCTCG trial, indicating a total mortality of 0.4% with 10 years of tamoxifen compared with no tamoxifen. However, the reductions in breast cancer mortality by 9.1% in the EBCTCG meta-analysis and 2.8% in the ATLAS trial suggest an 11.9% total reduction with 10 years tamoxifen compared with no tamoxifen. Prof. Gray estimated the effects of 10 years of tamoxifen on 15-year mortality to have 30 times the benefits compared with not taking tamoxifen.

Combined data from ATLAS and the EBCTCG meta-analysis suggest that treatment with tamoxifen for 10 years decreases the rate of breast cancer mortality by approximately 33% in the first decade and 50% in the second decade after diagnosis. The authors proposed that, during Years 5 to 9, the smaller benefit from 10 years of tamoxifen compared with the later benefit from 5 years of tamoxifen was most likely due to the carryover effect of 5 years of tamoxifen.

Science Advisors' Statement

The findings of the ATLAS trial mirror the benefits of extended hormonal therapy in the National Cancer Institute of Canada Clinical Trials Group MA.17 [Goss PE et al. *J Clin Oncol* 2008] trial. The results of ATLAS should be discussed with patients receiving adjuvant tamoxifen therapy, and the benefits of extended tamoxifen therapy should be weighed against the small increased risk in side-effect morbidity.

CONFIRM Trial Final Analysis of Overall Survival: Fulvestrant 500 Versus 250 mg

Written by ***Toni Rizzo***

The Comparison of Fulvestrant 250 mg and 500 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing After Previous Endocrine Therapy [CONFIRM] trial compared treatment with 2 doses of fulvestrant (250 vs 500 mg) in postmenopausal women with locally advanced or metastatic estrogen receptor (ER)-positive breast cancer that had recurred or progressed after endocrine therapy. The primary analysis showed that progression-free survival (PFS) was significantly increased with fulvestrant 500 versus 250 mg [Di Leo A et al. *J Clin Oncol* 2010]. The final analysis of OS was presented by Angelo Di Leo, MD, Hospital of Prato, Prato, Italy.

In the CONFIRM trial, eligible patients were randomized to fulvestrant 250 mg (1 injection) plus placebo (1 injection; n=374) versus fulvestrant 500 mg (2 injections; n=362) on Days 0, 14, and 28, and every 28 days thereafter. The primary endpoint was PFS [Di Leo A et al. *J Clin Oncol* 2010]. The final analysis of OS was planned and conducted after 75% of the patients had died. After the primary analysis, patients receiving fulvestrant 250 mg were allowed to switch to 500 mg. The median age in both groups was 61 years and all patients were ER-positive. Eight (2.1%) of 374 patients in the fulvestrant 250-mg group switched to fulvestrant 500 mg.

At the first analysis, median PFS was 6.5 months with fulvestrant 500 mg versus 5.5 months with the 250-mg dose (HR, 0.80; 95% CI, 0.68 to 0.94; p=0.006). The first analysis of OS at 50% maturity showed that the median time to death was 25.1 months with fulvestrant 500 mg versus 22.8 months with fulvestrant 250 mg (HR, 0.84; 95% CI, 0.69 to 1.03; p=0.091) [Di Leo A et al. *J Clin Oncol* 2010].

The final analysis of OS at 75% maturity (full analysis set) demonstrated a median time to death of 26.4 months with fulvestrant 500 mg versus 22.3 months with 250 mg (HR,

0.81; 95% CI, 0.69 to 0.96; nominal p=0.016 [cannot be claimed as statistically significant]).

Serious adverse events (SAEs) were reported in 9.7% of patients taking fulvestrant 500 mg and 7.2% of those taking fulvestrant 250 mg. Treatment-related SAEs were reported in 2.2% of patients receiving 500 mg versus 1.1% receiving 250 mg. SAEs resulting in death during the whole treatment period occurred in 1.5% receiving 500 mg versus 2.0% receiving 250 mg.

Consistent with the previously reported PFS and OS data, the final OS analysis at 75% maturity showed that fulvestrant 500 mg is associated with a 4.1-month increase in median OS and a 19% reduction in the risk of death compared with fulvestrant 250 mg. Analysis of the first subsequent therapies does not support an imbalance between the 2 study arms. Only 2% of patients crossed over from 250 to 500 mg. However, activity for 500 mg after pretreatment with 250 mg is unknown. The safety results do not support a clinically relevant difference between fulvestrant 250 and 500 mg, and are consistent with the previously reported safety profile of fulvestrant 500 mg.

Neoadjuvant Chemotherapy in Women 35 and Under

Written by ***Emma Hitt, PhD***

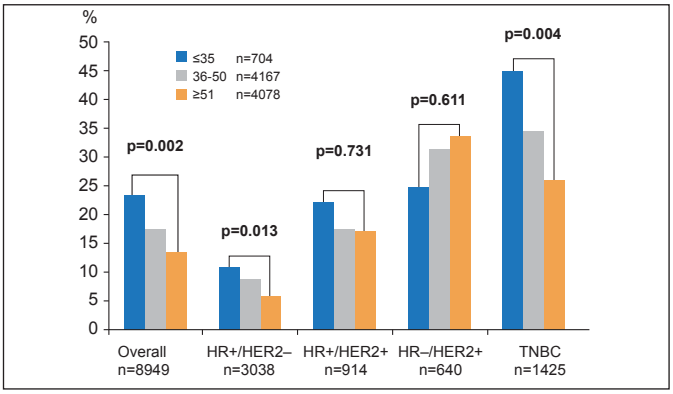
Evidence suggests that breast cancer in younger women may be clinically and etiologically distinct from older women [Bleyer A et al. *Nat Rev Cancer* 2010]. Breast cancer in young women demonstrates a worse prognosis and a more aggressive phenotype, higher proportions of high-grade and later-stage tumors, lower estrogen receptor (ER) positivity, and, in some studies, higher expression of human epidermal growth factor receptor 2 (HER2) [Bleyer A et al. *Nat Rev Cancer* 2010; Gnerlich JL et al. *J Am Coll Surg* 2009]. While some studies point to a unique breast cancer biology in young women, others have illustrated that the aggressive nature is the result of higher frequencies of aggressive breast cancer subtypes among younger patients. Sibylle Loibl, MD, PhD, German Breast Group, Neu-Isenburg, Germany, presented data on the response to neoadjuvant chemotherapy in women with breast cancer who are aged ≤35 years compared with older women.

The meta-analysis included 8949 patients with operable or locally advanced nonmetastatic breast cancer from 8 neoadjuvant German studies with follow-up. Patients were categorized into 3 age groups: ≤35 (n=704), 36 to 50 (n=4167), and ≥51 years (n=4078). All patients with endocrine responsive disease received adjuvant endocrine therapy. Subgroup analyses were conducted defined by hormone receptor (HR) and HER2 status.

Breast cancer subtype distribution was found to differ according to patient age group. Triple-negative breast cancer (TNBC) was more common in patients aged ≤35 than patients aged >35 years (26% vs 19%). In contrast, HR-positive/HER2-negative breast cancer was more common in patients aged >35 years compared with patients aged ≤35 years (37% vs 29%). HER2-positive tumors were similar in both age groups regardless of HR status.

The overall pathologic complete response (pCR) rate (defined as ypT0, ypN0) was significantly higher in patients aged ≤35 compared with patients aged ≥51 years (23% vs 13%; p=0.002; Figure 1). The only subgroups with pCR rates that were statistically higher for patients aged ≤35 years compared with patients aged ≥51 years were HR-positive/HER2-negative (11% vs 6%; p=0.013) and TNBC (45% vs 25%; p=0.004).

Figure 1. pCR Rates Overall and in Subgroups.



*HR and HER2-status not available for all patients. HER2=human epidermal growth factor receptor 2; HR=hormone receptor; TNBC=triple-negative breast cancer.
Reproduced with permission from S Loibl, MD, PhD.

The pCR rate was an independent predictor of disease-free survival (DFS) when the analysis was adjusted for age, tumor size, nodal status, histological type, grading, and clinical trial. DFS was significantly inferior in patients aged ≤35 compared with patients in the 36 to 50 (p=0.031) and the ≥51 year age groups (p=0.022). The difference was greater between age groups in patients who did not achieve pCR; patients aged ≤35 years had a 25% higher risk of relapse compared with the 36 to 50 (p=0.002) and ≥51 year age groups (p=0.001). In contrast to previous studies, patients aged ≤35 years with HR-positive/HER2-negative breast cancer who achieved a pCR had a better DFS compared with patients in the same age group who did not achieve pCR. Local recurrence-free survival was also significantly inferior in patients aged ≤35 years compared with patients in the 36 to 50 (p=0.017) and ≥51 years age groups (p=0.00018). Overall survival was not significantly different between the 3 age groups.