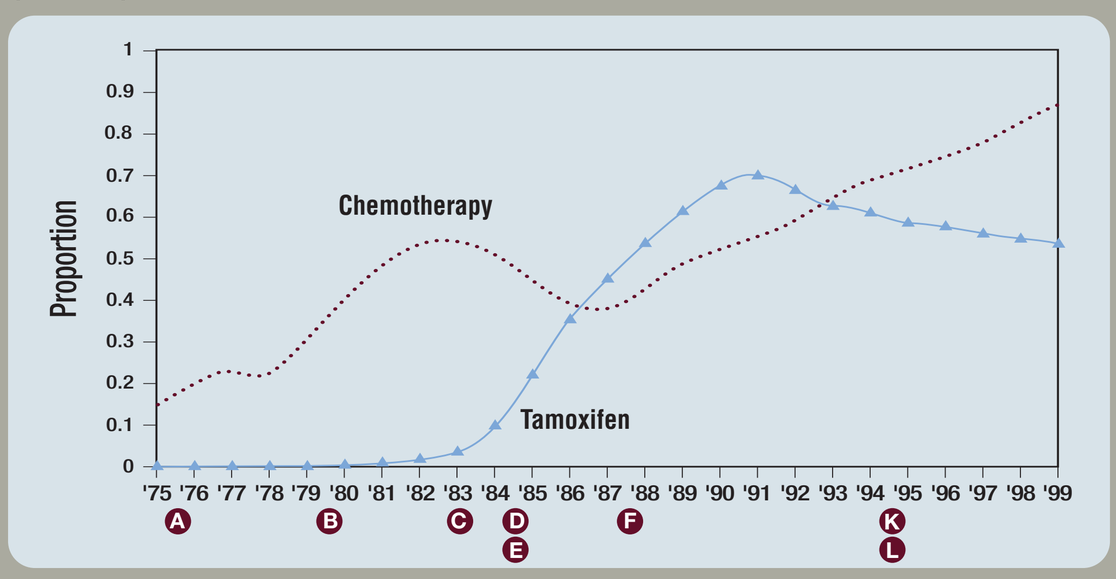
Research to Practice: Adjuvant Systemic Therapy

Considerable resources have been committed to conducting clinical trials that evaluate adjuvant systemic therapy; however, until recently, there were minimal patterns of care data available about how these therapeutic advances were being incorporated into community practice. A fascinating NCI initiative is now addressing this important question, and preliminary results suggest that the translation of research to clinical practice is a complex multifactorial process that warrants further investigation.

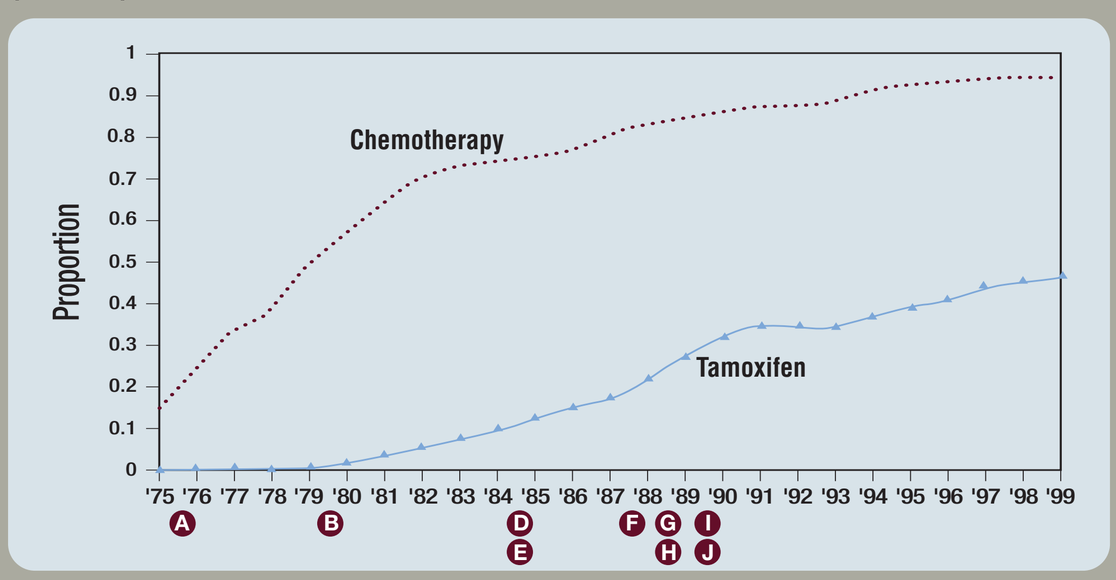
Benchmarks in the History of Adjuvant Systemic Therapy

- **A Bonadonna Publication**
  - *— Benefit for multi-agent chemo in premenopausal, N+*
- **B 1980 NIH Consensus Conference**
  - *— Multi-agent chemo recommended for premenopausal, N+*
- **C Novaldex Adjuvant Trial Organization (1983, 1984)**
  - *— Benefit for tamoxifen in postmenopausal, N+*
- **D 1985 Oxford Overview Meeting**
  - *— Benefit for multi-agent chemo in premenopausal, N+*
  - *— Benefit for tamoxifen in postmenopausal, N+*
- **E 1985 NIH Consensus Conference**
  - *— Multi-agent chemo recommended for premenopausal, N+*
  - *— Tamoxifen recommended for postmenopausal ER+, N+*
- **F 1988 NCI Clinical Alert**
  - *— Benefit to chemo and tamoxifen in node-negative tumors*
- **G US Intergroup study**
  - *— Benefit for multi-agent chemo in pre- and postmenopausal, high-risk N-*
- **H NSABP trials**
  - *— Benefit for multi-agent chemo in pre- and postmenopausal, ER-neg, N- and benefit to tamoxifen in pre- and postmenopausal ER+, N-*
- **I 1990 Oxford Overview Meeting**
  - *— Benefit for multi-agent chemo in pre- and postmenopausal, N- and benefit for tamoxifen in postmenopausal ER+, N-*
- **J 1990 NIH Consensus Conference**
  - *— Chemo and tamoxifen recommended for consideration for node-negative tumors greater than 1 cm*
- **K 1995 Oxford Overview Meeting**
  - *— Tamoxifen benefits premenopausal ER+*
- **L 1995 NCI Clinical Announcement**
  - *— No advantage for continuing tamoxifen beyond 5 years*

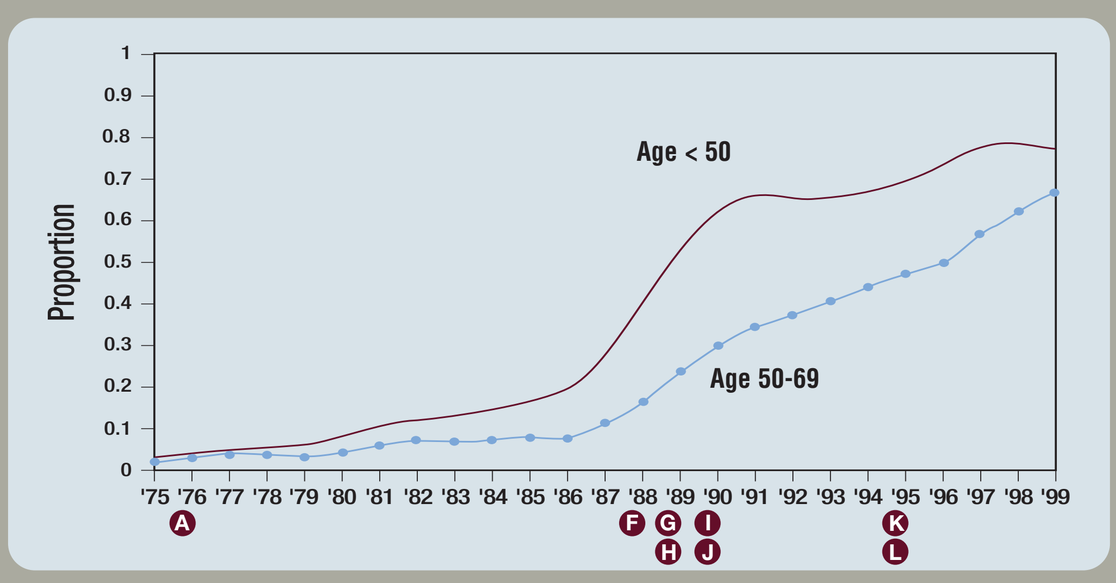
ADJUVANT THERAPY: WOMEN 50 TO 69-YEARS-OLD, STAGE II (NODE+)/IIIA BREAST CANCER



ADJUVANT THERAPY: WOMEN <50-YEARS-OLD, STAGE II (NODE+)/IIIA BREAST CANCER



ADJUVANT MULTI-AGENT CHEMOTHERAPY STAGE II, NODE-NEGATIVE BREAST CANCER PATIENTS



ADAPTED FROM: Mariotto et al. **Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999.** *J Natl Cancer Inst* 2002;94(21):1626-1634.

EVOLUTION OF BREAST CANCER TREATMENT

Those who don't know history are condemned to repeat it. For example, it is fascinating to see the evolution of the St Gallen consensus statements over time. At one point, we essentially said that node-negative patients should not receive adjuvant systemic therapy, but for the most recent consensus, we essentially did not exclude anyone with invasive breast cancer. Our interventions haven't changed much during that time, but what has evolved is our understanding of the risks and benefits of treatment and what our patients are willing to accept and, in fact, request. All of this is in constant evolution and what is absolutely true today may not be absolute tomorrow, and what is totally contraindicated today might become standard of care in just a few years.

—Gabriel Hortobagyi, MD

EFFECT OF 1988 NCI CLINICAL ALERT ON TREATMENT

"The proportions of patients with a negative lymph node status diagnosed after the May 1988 Clinical Alert who received adjuvant treatment (tamoxifen and/or multidrug chemotherapy) were significantly greater than predicted from treatment trends established before the Alert's release. Proportions of patients with positive lymph node status receiving adjuvant therapy subsequent to the Alert's release, in contrast, did not fall outside the projected confidence intervals for that group."

—Johnson TP et al. J Clin Oncol 1994;12(9):1783-8.

IMPACT OF THE META-ANALYSIS ON ADJUVANT TAMOXIFEN USE

It took a long time for tamoxifen to catch on in premenopausal women, because many opinion leaders in breast cancer in the early '90s were saying that it should not be given. They were concerned about its effects on estrogen levels. It was only when the 1995 overview data showed a convincing benefit that this attitude changed. This is an example where it took the meta-analysis and several smaller trials to convince people of benefits. In general, oncologists are early adapters. Once they have reasonably convincing evidence of a new treatment approach, they will use that approach.

—Jeff Abrams, MD

WHEN SHOULD PHYSICIANS CHANGE THEIR PRACTICE?

There are those who want to fast forward the clock and give their patients new and cutting-edge therapy as soon as it is available. I respect that. Others are more cautious and say, "This could be a Trojan horse, and we should wait until we are really sure before we routinely apply this." If we look back, many of us were very cautious about using adjuvant tamoxifen in the 1980s for node-negative patients and until about 1995 for premenopausal women, when the overview showed it was worthwhile. And I am sure I have had patients die of breast cancer needlessly… If I had just had a crystal ball and given them tamoxifen. I feel bad and have worried about that. The flip side is that there were people who were absolutely sure that high-dose chemotherapy — not just really high doses with transplant, but modestly high doses — would be better. So they fast forwarded the clock and began treating patients with those doses outside of clinical trials, because the clinical data looked interesting and promising. I also thought the data looked good, but randomized trials failed to demonstrate an advantage. I did not fast forward the clock there, and I feel good about the fact that I did not have patients die of leukemia or high-dose-related deaths, unless they agreed to be part of a trial. This is my philosophy, and I am admittedly cautious.

—Dan Hayes, MD

SELECT PUBLICATIONS

National Cancer Institute: Clinical alert from the National Cancer Institute. *Breast Cancer Res Treat* 1988;12:3-5.

Consensus Development Panel: **National Institutes of Health Consensus Development Conference statement: Adjuvant chemotherapy for breast cancer.** September 9-11, 1985. *CA Cancer J Clin* 36:42-47, 1986.

Early Breast Cancer Trialists' Collaborative Group: **Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: An overview of 61 randomized trials among 28,896 women.** *N Engl J Med* 1988;319:1681-1692.

Early Breast Cancer Trialists' Collaborative Group: **Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women—Parts 1, 2.** *Lancet* 1992;339:1-15,71-85.

NIH Consensus Conference: Treatment of early-stage breast cancer. *JAMA* 1991;265:391-395.

Harlan LC et al. **Adjuvant Therapy for Breast Cancer: Practice Patterns of Community Physicians.** *J Clin Oncol* 2002;20(7):1809-1817. Johnson TP et al. **Effect of a National Cancer Institute Clinical Alert on breast cancer practice patterns.** *J Clin Oncol* 1994;12(9):1783-8.

Lazovich D et al. **Breast conservation therapy in the United States following the 1990 National Institutes of Health Consensus Development Conference on the treatment of patients with early stage invasive breast carcinoma.** *Cancer* 1999;86:628-637.