5 Minute JournalClub

Outcomes of Women Who Were Premenopausal at Diagnosis in the MA17 Trial of Extended Letrozole After Five Years of Tamoxifen

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year where published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Identify the efficacy and safety of extended aromatase inhibitor therapy after five years of tamoxifen in patients with early-stage breast cancer who were premenopausal at diagnosis and became postmenopausal during the tamoxifen therapy.

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5 MinuteJournalClub

IN THIS ISSUE:

In 1990, I traveled to Bethesda for an NCI Consensus Conference on breast cancer, and managed to arrange a joint interview with the King and Queen of tamoxifen, Mike Baum and Helen Stewart. Both of these noted investigators were in town presenting findings from Phase III randomized trials they led demonstrating what the chemo-oriented oncology world of that era had a very hard time swallowing — namely that a fairly nontoxic treatment then employed for palliation of metastatic disease could, if used as adjuvant therapy, have an impressive impact on breast cancer recurrence and death.

Working on the other side of the pond, Mike managed to pull off two trials in the UK while Helen ran the landmark Scottish study, and their data demonstrated the benefit of tamoxifen in both pre- and postmenopausal patients. However, there was another key European hormonal player whose work was considered the gold standard for evidence — the soon-to-be-knighted Sir Richard Peto, who was able to convince (without email or the web) virtually every investigator who had previously done a randomized trial in early breast cancer to provide individual patient data that the Oxford minions then "cleaned up" and wove into forest plots that ultimately defined treatment standards in that era of smaller trials.

This laborious work became in 1985 the first breast cancer Worldwide Overview, in which Peto clearly demonstrated that postmenopausal patients treated with tamoxifen experienced a major survival benefit. However, even by 1990 the Overview did not demonstrate an OS advantage in premenopausal women, and for this reason many investigators cautioned against prescribing Tam to younger women. However, Mike, Helen and Sir Richard all knew that the most likely explanation for the lack of a survival benefit was not that the agent didn't work in that setting, but more likely that not

enough events had yet been observed, simply because there are fewer pre- than postmenopausal patients.

During that 1990 interview conducted at an ancient Holiday Inn across from the NIH, Helen, and particularly Mike, were totally apoplectic about the premenopausal issue and almost jumped across the table imploring listeners to treat these patients with a relatively safe and well-tolerated agent that had the potential to cut the relapse rate in half.

However, Patterns of Care studies at that time (yes, we did those then) demonstrated that younger women pretty much weren't receiving adjuvant tamoxifen until 1995, when more events were eventually accrued to the Overview, and Mike and Helen's assertions played out exactly as predicted. In an instant, Tam became standard for premenopausal patients with ER-positive tumors. I remember doing some pretty scary mental math back then adding up the number of young women who likely died during the 10 years spanning the 1985 and 1995 Overviews, when premenopausal patients finally received the blessings of the evidence-based pontiffs.

These nightmares returned a few months ago in San Antonio, when Paul Goss presented a **new analysis** from the historic MA17 study of letrozole after five years of adjuvant tamoxifen. To enter the trial, patients had to be postmenopausal at the randomization point but could have been premenopausal at the time of diagnosis, and in that subset, the effect of a delayed AI was equal to and perhaps even greater than it was in primary postmenopausal patients.

In the seven years since first presenting MA17, Paul has continually professed his belief that ER-positive breast cancer is a lifelong remitting and relapsing disease not unlike follicular lymphoma, and that the potential impact of prolonged endocrine treatment may be far greater than most realize. His pioneering work has demonstrated that hormonal interventions many years after diagnosis can profoundly impact clinical outcome, and he has cautioned us not to look at the breast cancer "golf ball" 10 yards off the tee but when "it lands on the fairway 20 years later."

Paul points out that the biologic model of ER-positive disease is unlikely to be different in pre- and postmenopausal patients, but our Patterns of Care studies demonstrate that premenopausal patients rarely receive more than five years of hormone therapy, and there is a lack of clinical research and a lot of confusion about management of patients who cease menses during tamoxifen — in some cases after chemo — and of the uncommon but important scenario of a woman who is still premenopausal after five years of tamoxifen.

And so it goes. More fodder for debates, roundtables and publications, but in the back of my head an old tune plays, and it brings back bad memories.

Next up on 5-Minute Journal Club...well, this marks the conclusion of our short and hopefully sweet review of the best from San Antonio. Please take a moment and tell us candidly what you liked and didn't like about this craziness and check out our new **web-video-slide program** in six tumor types, "Year in Review," profiling the most important papers and publications of the past year.

Neil Love, MD
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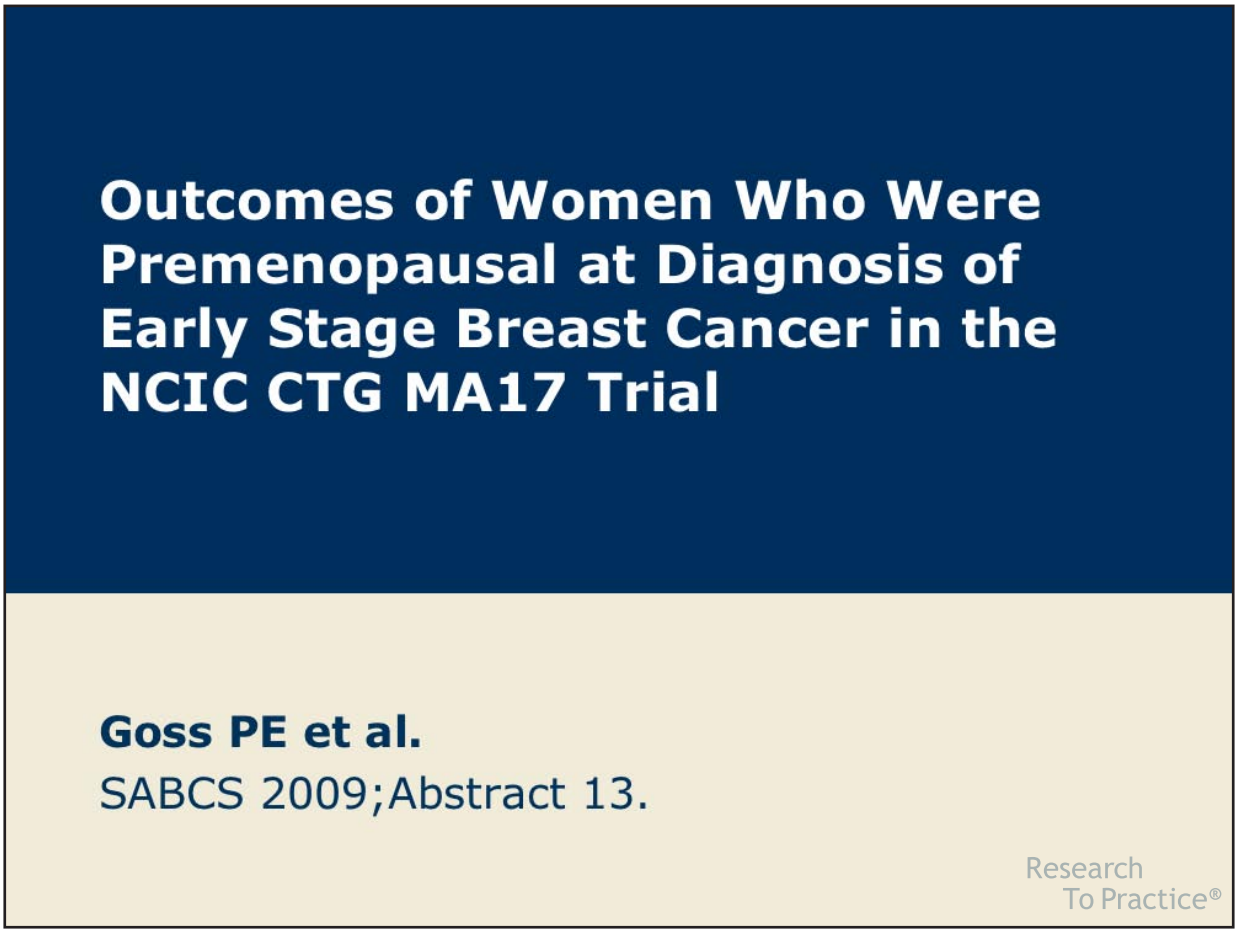
Outcomes of Women Who Were Premenopausal at Diagnosis in the MA17 Trial of Extended Letrozole After Five Years of Tamoxifen

Presentation discussed in this issue

Goss PE et al. **Outcomes of women who were premenopausal at diagnosis of early stage breast cancer in the NCIC CTG MA17 trial.** San Antonio Breast Cancer Symposium 2009;**Abstract 13**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Rowan T Chlebowski, MD, PhD (12/30/09)



Introduction

- Extended aromatase inhibitor (AI) therapy is a standard of care for postmenopausal women with hormone receptor-positive (HR+) breast cancer who have received 5 years of tamoxifen (*NEJM* 2003;349:1793, *JCO* 2008;26:1965).
- Five years of tamoxifen therapy remains a common standard adjuvant hormonal therapy in premenopausal patients.
- A substantial proportion of premenopausal patients with estrogen receptor-positive breast cancer recur after 5 years of tamoxifen therapy (SABCS 2007;Abstract P-1).
- **Current study objective**:
  - Assess the benefit of extended aromatase inhibitor therapy after five years of tamoxifen in women who are premenopausal at the time of diagnosis and become postmenopausal during tamoxifen.

Goss PE et al. SABCS 2009;Abstract 13.

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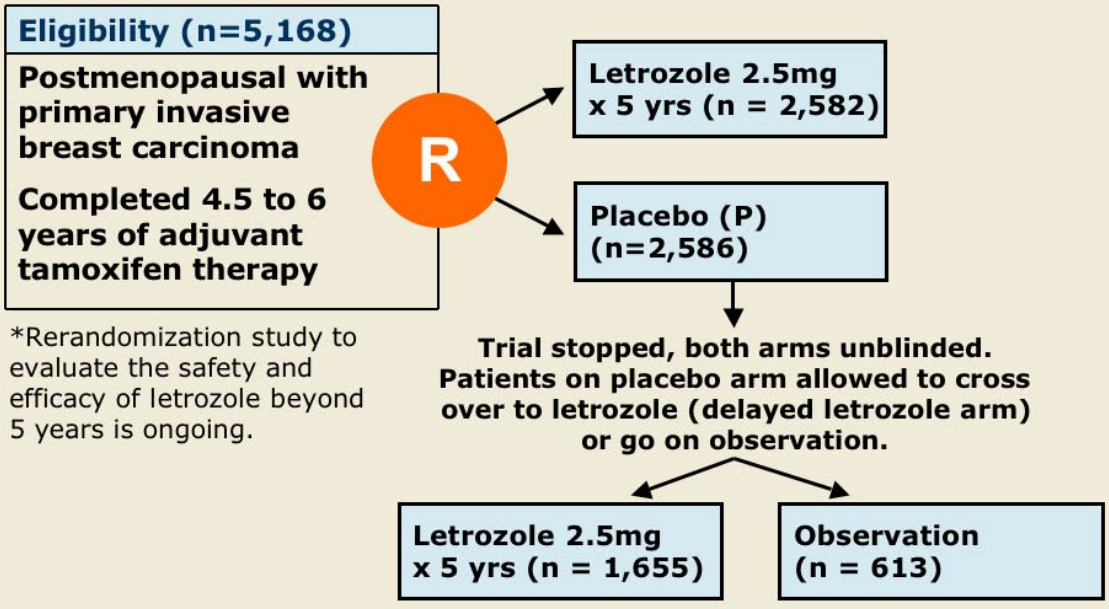
NCIC CTG MA17: Trial Schema*



*Rerandomization study to evaluate the safety and efficacy of letrozole beyond 5 years is ongoing.

Goss PE et al. SABCS 2009;Abstract 13.

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MA17: Patient Menopausal Status at Primary Diagnosis

- **Premenopausal (n=889)**
  - < 50 years of age with menses, but underwent subsequent bilateral oophorectomy when tamoxifen therapy started.
  - < 50 years of age with menses, but became amenorrheic during adjuvant chemotherapy or on tamoxifen.
- **Postmenopausal (n=4,277)**
  - ≥ 50 years of age without menses at diagnosis.
  - < 50 years of age without menses and considered postmenopausal at diagnosis.
  - Considered postmenopausal in terms of menopausal LH/FSH levels.

Goss PE et al. SABCS 2009;Abstract 13.

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Premenopausal Patients Have a Worse Prognosis

Patient Characteristic	Premenopausal (n=889)	Postmenopausal (n=4,227)	*p*-value
Median age at diagnosis	~45 yrs	~60 yrs	<0.0001
Node-positive	56%	44%	<0.001
Both ER- and PR-positive	77%	74%	0.02
Chemotherapy	80%	38%	<0.0001
Mastectomy	55%	50%	0.003
Letrozole treatment	48%	51%	0.14

Goss PE et al. SABCS 2009;Abstract 13.

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Absolute Differences in Four-Year Disease-Free Survival Rates (Letrozole versus Placebo)

	Premenopausal (n=889)	Postmenopausal (n=4,277)
All patients	10.1% HR=0.25; $p<0.0001$	3.3% HR=0.69; $p=0.0008$

In years 0 through 4 post completion of tamoxifen, premenopausal patients had a greater treatment benefit from letrozole than postmenopausal patients.

- **Premenopausal: 10.1% absolute decrease in disease recurrence (75% risk reduction)**
- **Postmenopausal: 3.3% absolute decrease in disease recurrence (31% risk reduction)**

Goss PE et al. SABCS 2009;Abstract 13.

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Absolute Differences in Four-Year DFS Rates in Node-Positive BC (Letrozole versus Placebo)

	Premenopausal (n=501)	Postmenopausal (n=1,857)
Node-positive	9.6% HR=0.37; $p=0.008$	7.0% HR=0.68; $p=0.03$

In patients with node-positive disease (years 0 to 4 post completion of tamoxifen), premenopausal patients had a greater treatment benefit from letrozole than postmenopausal patients.

- **Premenopausal: 9.6% absolute decrease in disease recurrence (63% risk reduction)**
- **Postmenopausal: 7.0% absolute decrease in disease recurrence (32% risk reduction)**

Goss PE et al. SABCS 2009;Abstract 13.

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Absolute Differences in Four-Year DFS Rates in Node-Negative BC (Letrozole versus Placebo)

	Premenopausal (n=375)	Postmenopausal (n=2,192)
Node-negative	11.5% HR=0.00; p=0.005	1.1% HR=0.58; p=0.04

In patients with node-negative disease (years 0 to 4 post completion of tamoxifen), premenopausal patients had a greater treatment benefit from letrozole than postmenopausal patients.

- **Premenopausal: 11.5% absolute decrease in disease recurrence (100% risk reduction)**
- **Postmenopausal: 1.1% absolute decrease in disease recurrence (42% risk reduction)**

Goss PE et al. SABCS 2009;Abstract 13.

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Absolute Differences in Five-Year DFS Rates (Delayed Letrozole vs Observation)

	Premenopausal (n=425)	Postmenopausal (n=1,957)
DFS	8.2% HR=0.39; p=0.007	3.0% HR=0.36; p=0.0003

In patients who delayed (up to six years post completion of tamoxifen) extended AI therapy, premenopausal patients had a greater treatment benefit from letrozole than postmenopausal patients.

- **Premenopausal: 8.2% absolute decrease in disease recurrence (61% risk reduction)**
- **Postmenopausal: 3.0% absolute decrease in disease recurrence (64% risk reduction)**

Goss PE et al. SABCS 2009;Abstract 13.

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Absolute Differences in Five-Year Distant DFS Rates (Delayed Letrozole vs Observation)

	Premenopausal (n=425)	Postmenopausal (n=1,957)
Distant DFS	5.9% HR=0.15; *p*=0.02	2.2% HR=0.45; *p*=0.03

In patients who delayed (up to six years post completion of tamoxifen) extended AI therapy, premenopausal patients had a greater treatment benefit from letrozole than postmenopausal patients.

- **Premenopausal: 5.9% absolute decrease in distant disease recurrence (85% risk reduction)**
- **Postmenopausal: 2.2% absolute decrease in distant disease recurrence (55% risk reduction)**

Goss PE et al. SABCS 2009;Abstract 13.

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Treatment-Related Toxicities

Adverse Event	Premenopausal		*p*-value
	Letrozole (n=424)	Placebo (n=465)	
Arthralgia	24%	16%	0.004
Vaginal bleeding	10%	16%	0.01

Adverse Event	Postmenopausal		*p*-value
	Letrozole (n=2,157)	Placebo (n=2,120)	
Hot flushes	55%	50%	0.001
Arthralgia	25%	21%	0.002
Myalgia	15%	12%	0.007
Alopecia	5%	3%	0.003

Goss PE et al. SABCS 2009;Abstract 13.

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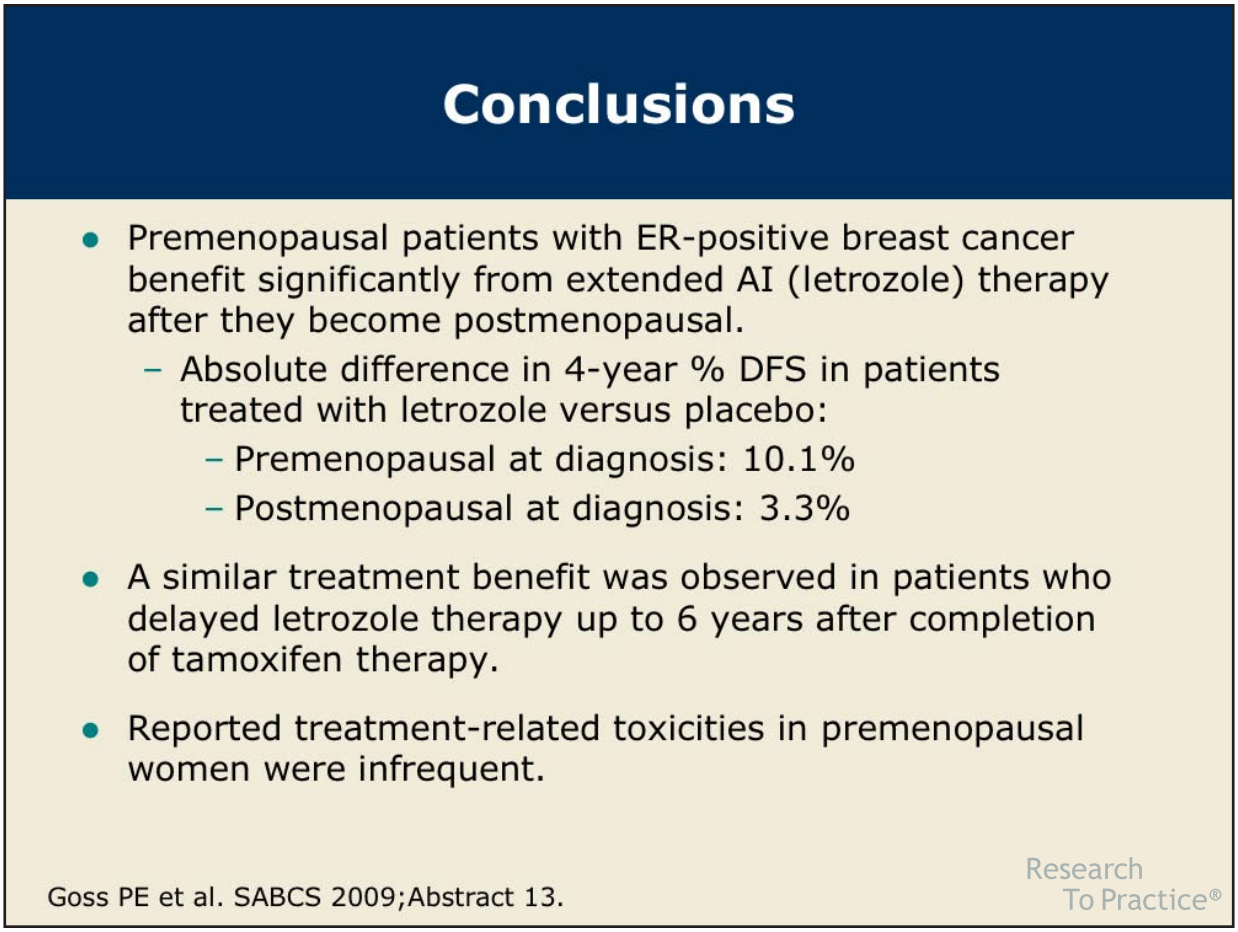

DR CHLEBOWSKI: Paul Goss reexamined data from the MA17 trial, in which patients who were described as postmenopausal were randomly assigned to either letrozole or placebo after five years of tamoxifen.

Postmenopausal is defined as an absence of menstruation for 12 months without intervention that could influence menstruation, such as chemotherapy, tamoxifen or marathon running.

Approximately 900 women, who were on average 45 years old and premenopausal at the time of their original diagnosis, were allowed entry into the trial after becoming amenorrheic with chemotherapy and/or tamoxifen, and thereby considered to be "postmenopausal".

It is interesting that in this group of patients who received delayed letrozole, the women who were premenopausal at diagnosis had a substantially greater reduction in risk of recurrence — 75 percent — compared to the risk reduction with delayed letrozole observed in postmenopausal women at postunblinding of the study — 30 percent.

I believe the explanation for this is that women who undergo normal menopause experience a gradual hormonal adjustment, because the perimenopause period lasts for about five years, and so the effect of hormonal adjustment from treatment on

the tumor is not as great relative to what it would be in premenopausal women who become postmenopausal with chemotherapy and added tamoxifen.

DR LOVE: What criteria in terms of menopausal status would you require in order to switch to an AI after five years of tamoxifen?

DR CHLEBOWSKI: I would require women to be at least 45 years old at the time of diagnosis and to have been receiving tamoxifen for five years. They would have to be amenorrheic from chemotherapy and maintain their amenorrheic status while receiving tamoxifen.

Dr Chlebowski is Professor of Medicine at the David Geffen School of Medicine at UCLA and Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center in Torrance, California.