

Letrozole after Tamoxifen

A Patient's Guide to
"Extended Adjuvant Therapy"

Objectives

- Define “adjuvant therapy”
- Discuss menopause
- Review what estrogen does and why it matters in breast cancer
- Talk about the benefits and side effects of tamoxifen
- Discuss what new drug research has shown in the treatment of breast cancer

Objectives

- To provide you with the information about a new medication called Letrozole (Femara[®])
 - What is Letrozole?
 - Who should consider Letrozole treatment?
 - How does Letrozole work?
 - What does the research show about Letrozole?
 - What are the side effects of Letrozole?

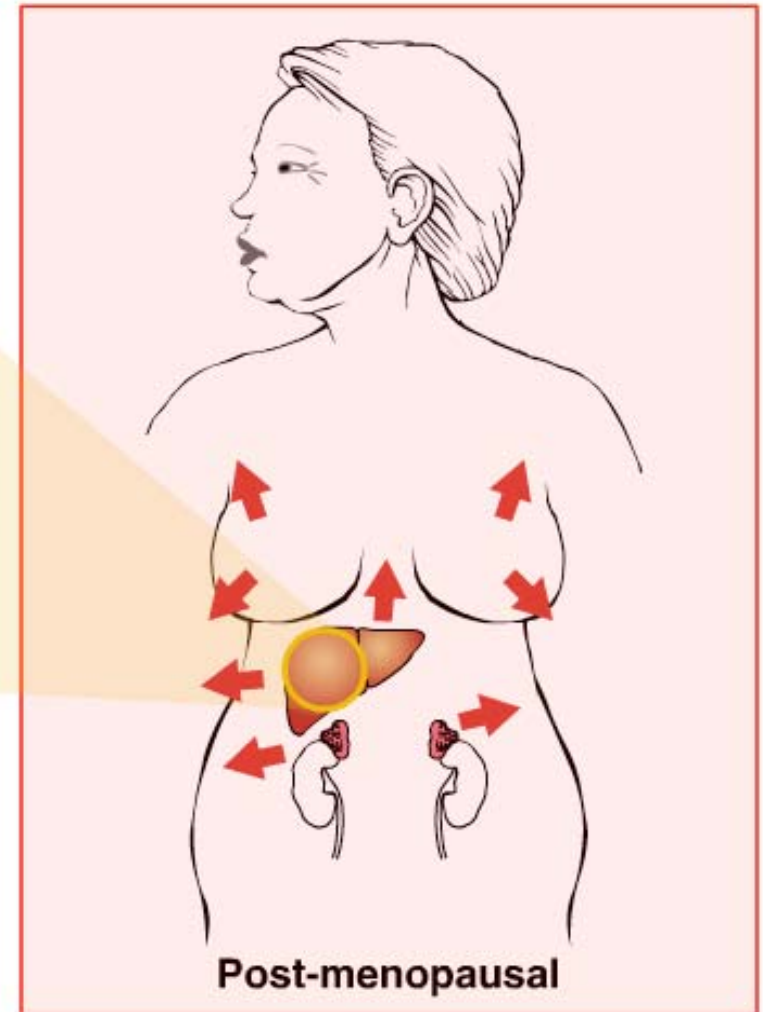
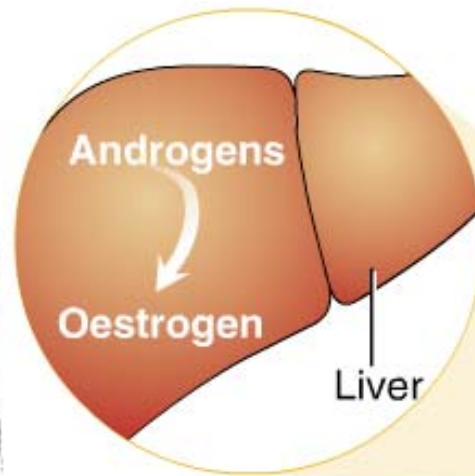
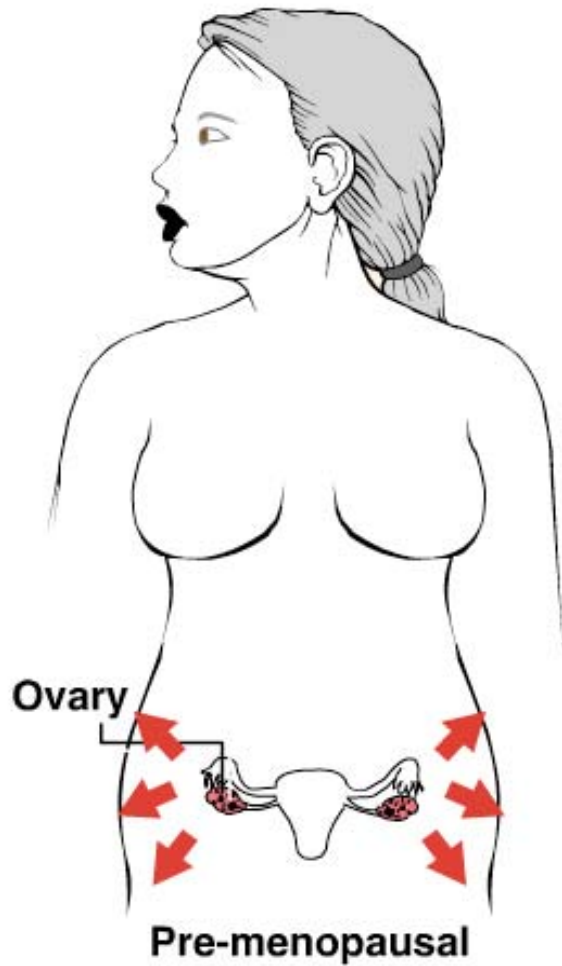
What is "Adjuvant" Therapy?

Treatment given after the surgeon has removed all visible breast cancer



Premenopausal

Post menopausal



Menopause

- Estrogen is present in ALL women in regardless of a women's menopausal status
- Women who are post menopausal make a small amount of estrogen through the conversion of "male like" hormones to "female like" hormones.
- This conversion is done by an enzyme called aromatase.

Menopause

- Most women are post menopausal by age 55. However, menopause can occur earlier than 55 years of age.
- Women who have had chemotherapy may go through menopause at a younger age
- Menopausal status for women between 45-55 can be confirmed by a blood test.

Menopause

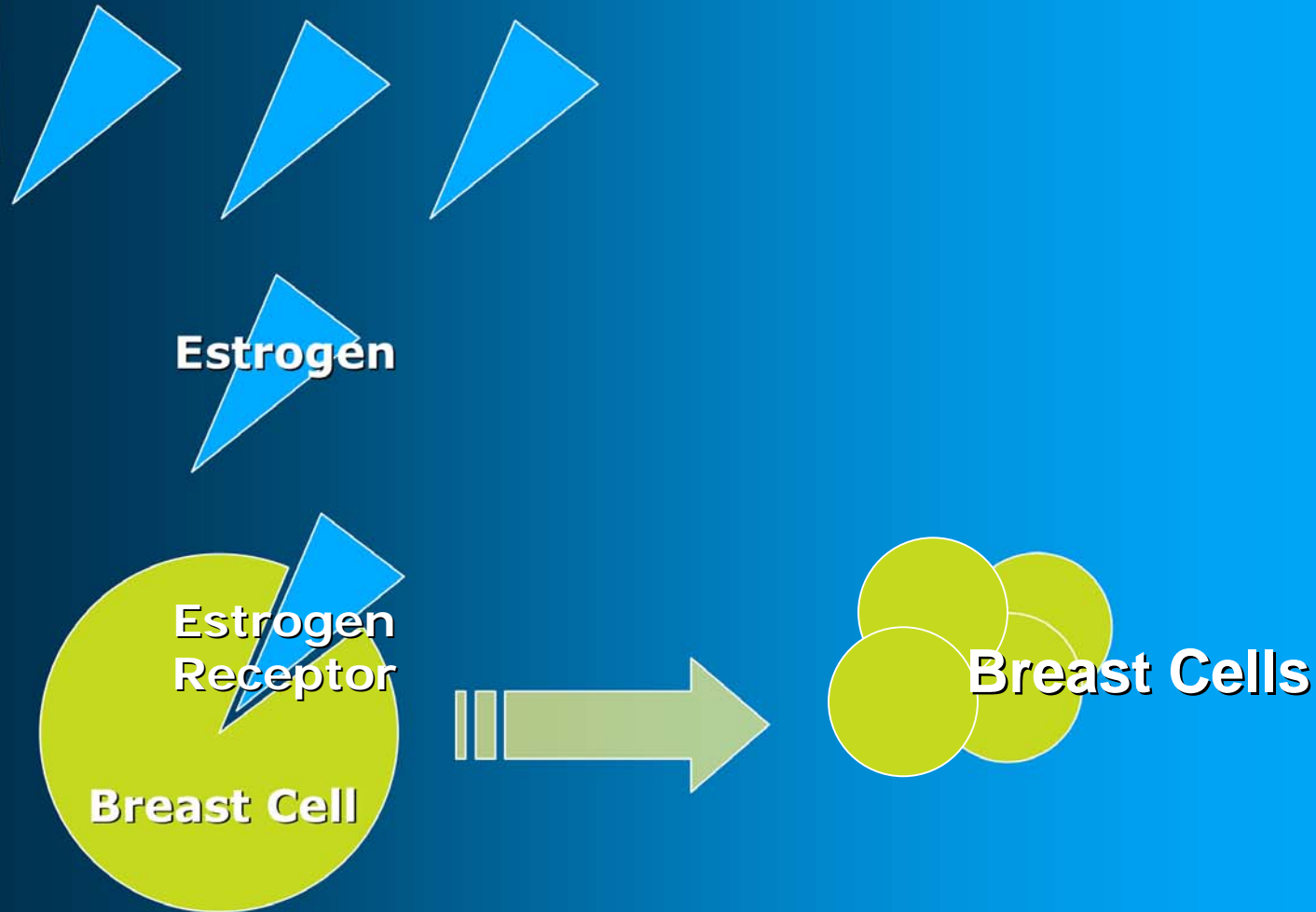
- Women who have had both ovaries surgically removed are definitely post menopausal
- If you have had a menstrual cycle in the past 10 months you are NOT post menopausal and this treatment is NOT going to be effective for you.

Breast Cancer Treatment Target

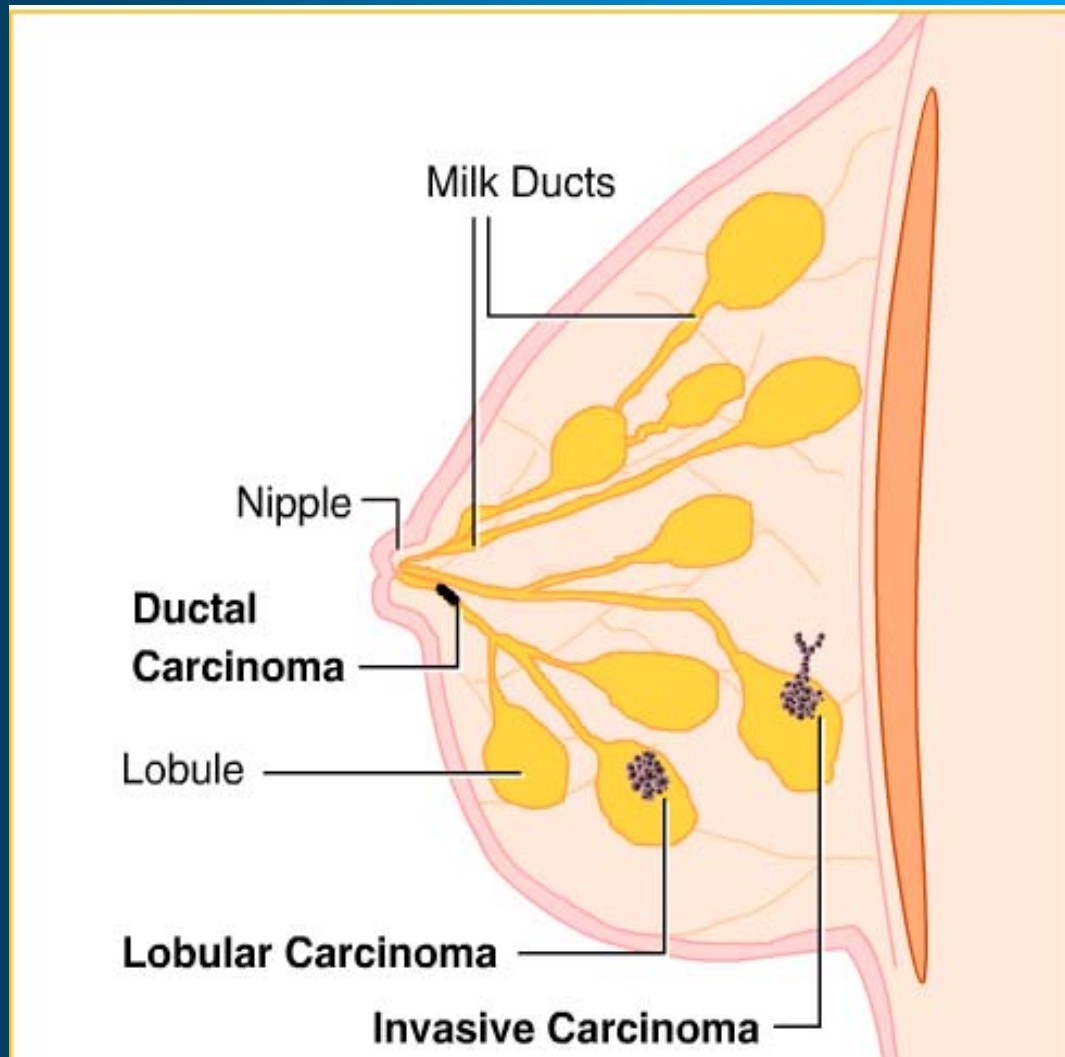


Target = Estrogen encourages
growth of breast cells and
increases risk of breast cancer
recurrence

Estrogen's Effects on Breast



Breast Cancer



Breast Cancer

- In 2006, an estimated 22,300 women will be diagnosed with breast cancer.
- Since 1994, death rates for breast cancer have been declining steadily.
- Declining death rates are, in part, due to increased early detection as well as new/better treatment options.

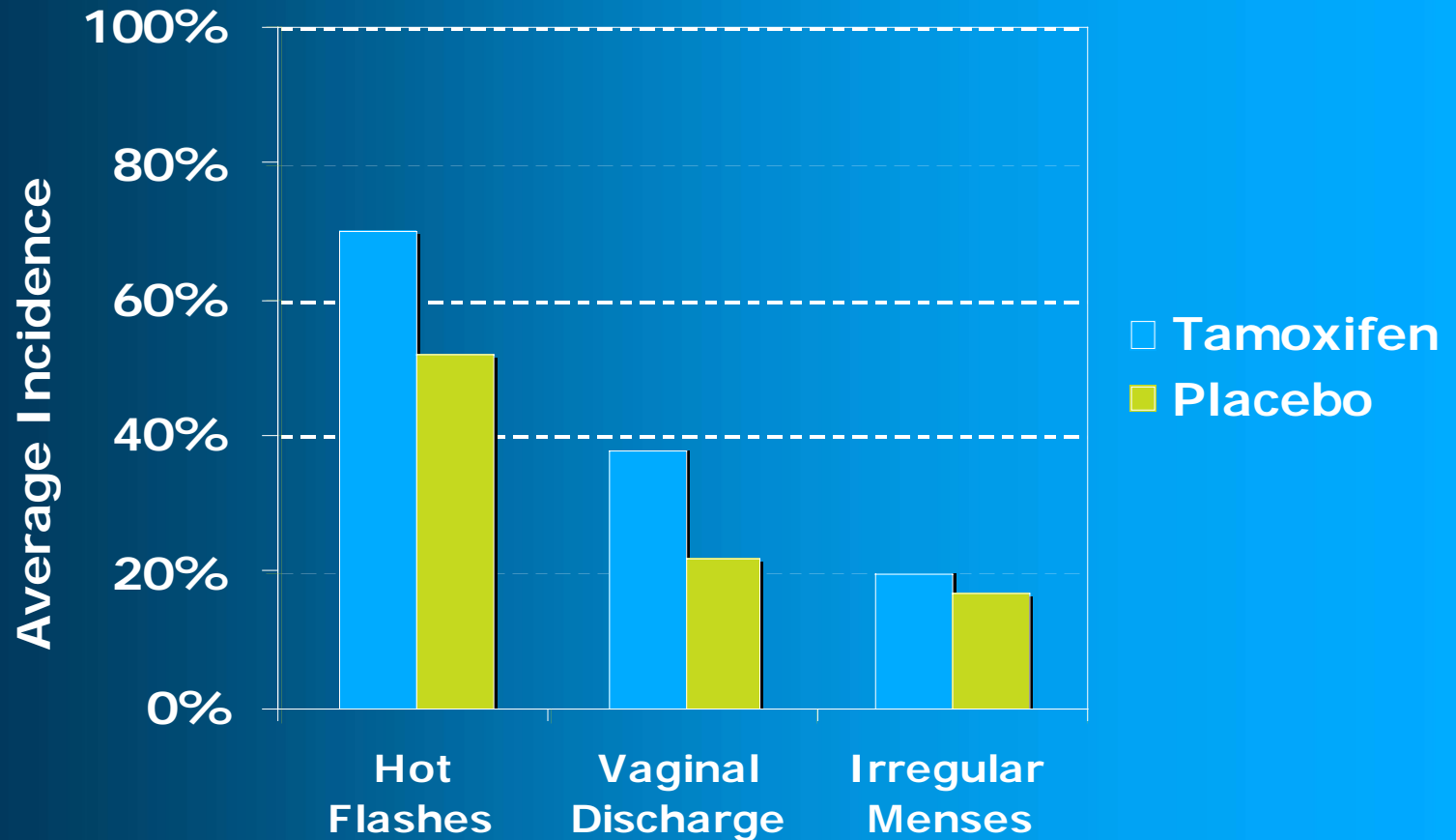
Tamoxifen

- Tamoxifen has been part of breast cancer treatment for almost 30 years
- Tamoxifen has been shown to improve overall survival anywhere from 5-11% depending on the stage of breast cancer
- Over 71 trials have been done showing the benefit of Tamoxifen for women with estrogen sensitive breast cancer.

Tamoxifen

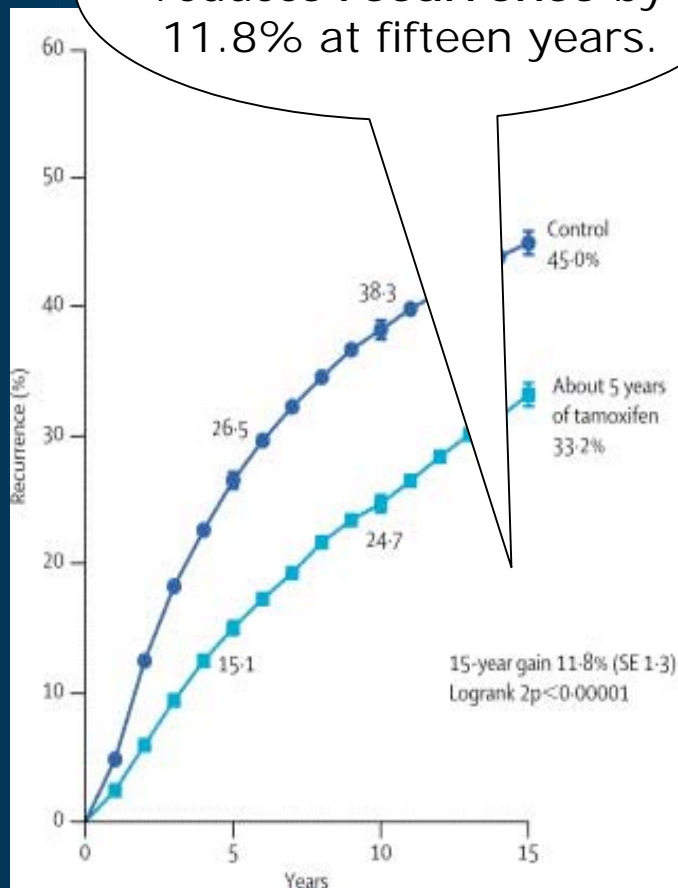
- Pill taken once a day for five years
- Beneficial effects
 - Reduces the chance of breast cancer recurrence
 - Prevents osteoporosis
 - Reduces blood cholesterol
- Unfavorable effects
 - Increases the risk of endometrial cancer
 - Increases the risk of blood clots
 - Menopausal symptoms such as hot flashes, and vaginal dryness or discharge.

Side Effects of Tamoxifen

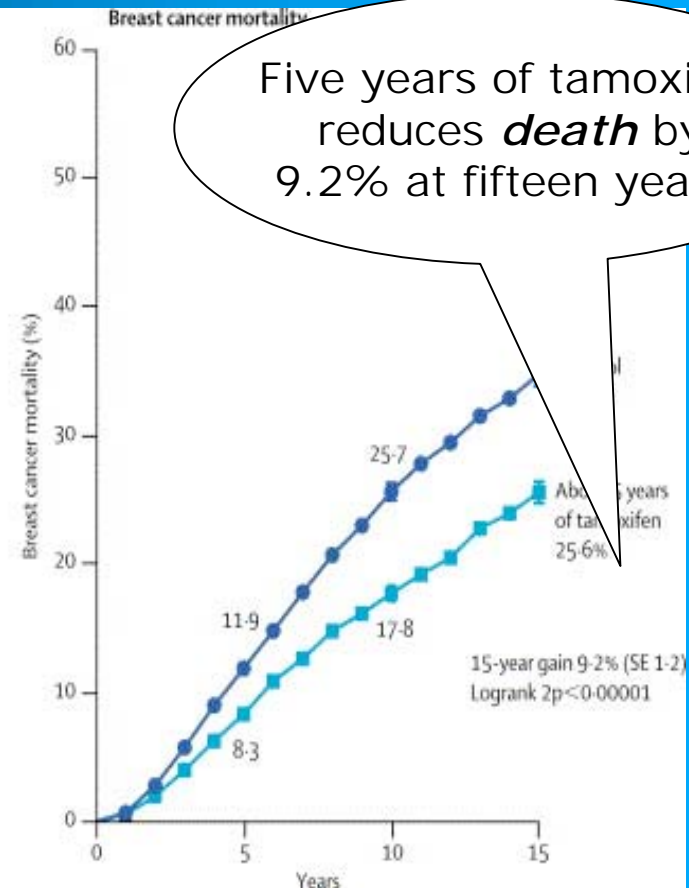


Tamoxifen reduces death and recurrence rates

Five years of tamoxifen reduces *recurrence* by 11.8% at fifteen years.



Five years of tamoxifen reduces *death* by 9.2% at fifteen years.



What is Letrozole?

- Letrozole is a pill that belongs to a family of drugs called Aromatase Inhibitors (AI's)
- There are three drugs in the "family" of Aromatase Inhibitors:
 - Letrozole (Femara®)
 - Exemestane (Aromasin®)
 - Anastrozole (Arimidex®)

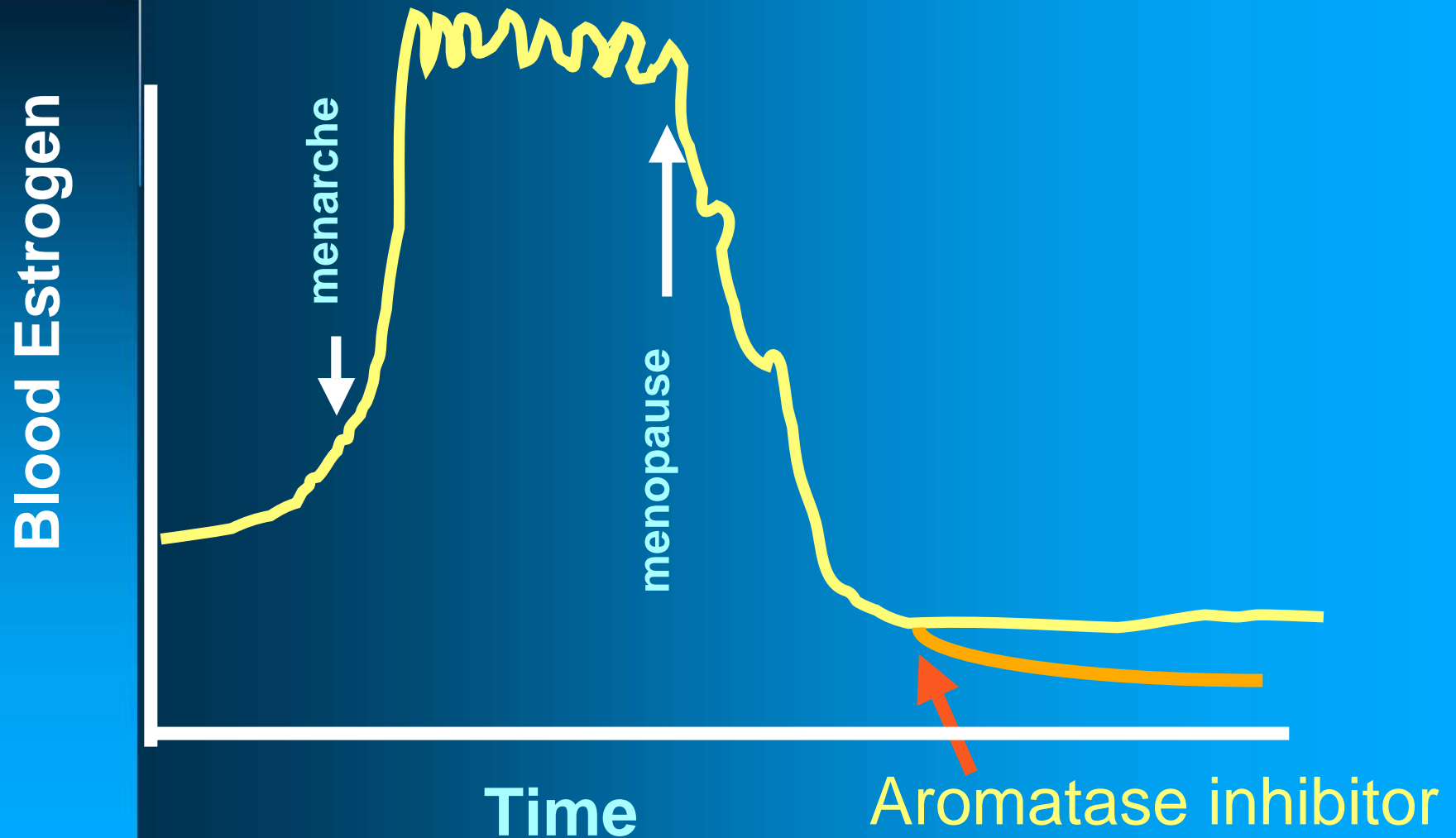
What is an Aromatase Inhibitor (AI)?

- AI's are drugs that work by limiting the ability of the enzyme called aromatase to create estrogen
- Estrogen can act as a "fuel" to spark breast cancer growth
- AI's almost completely suppress estrogen levels in post menopausal women.

Aromatase Inhibitors

- Letrozole is the only drug being used to reduce the risk of recurrence after 5 years of Tamoxifen.
- A number of studies have been done using various AI's. Today, we will be focusing ONLY on the research involving Letrozole.

Aromatase Inhibitors and Estrogen



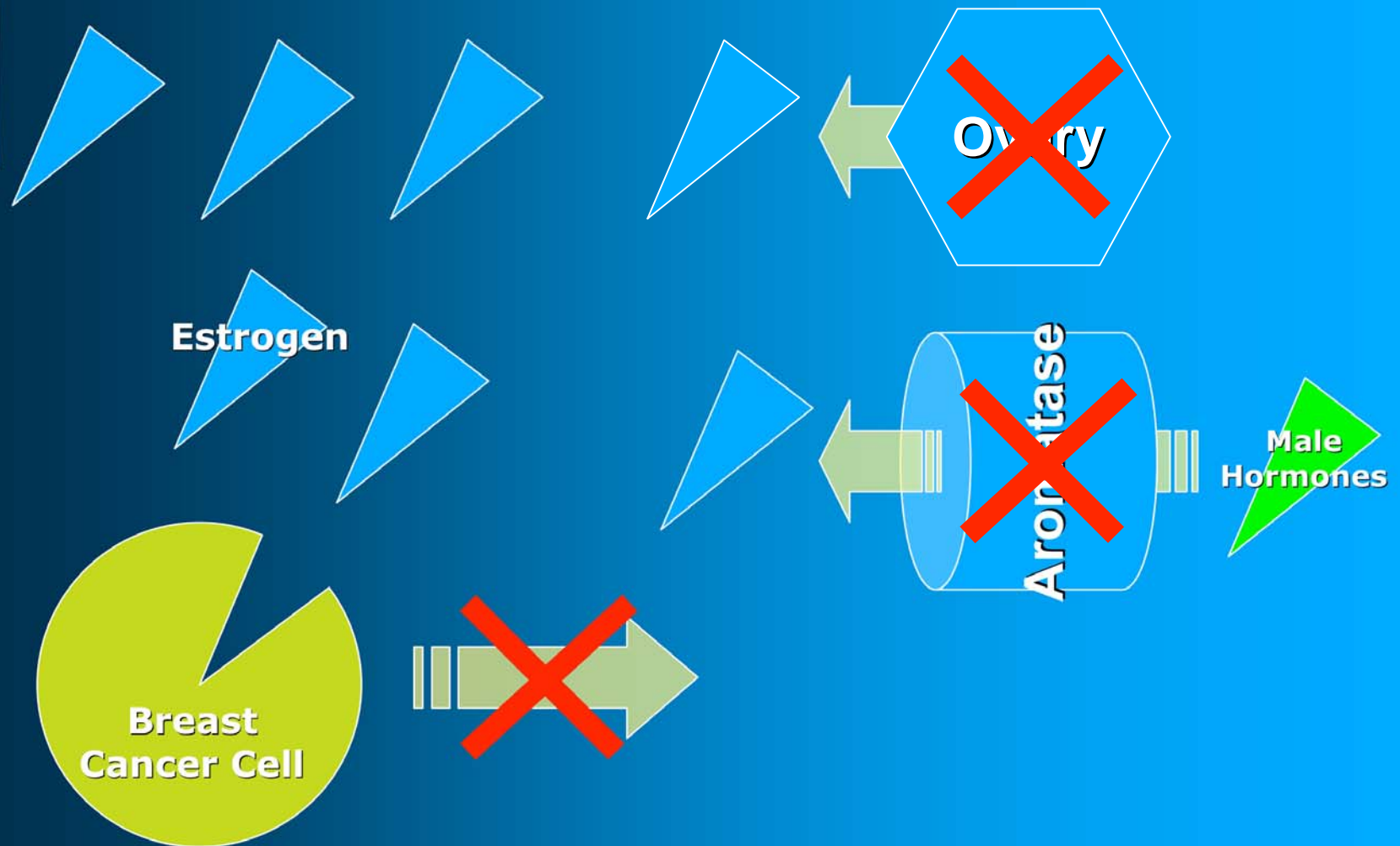
Who Should Consider Letrozole Treatment?

- Post Menopausal women only
- Women who have taken 4.5 to 5 years of Tamoxifen (or already finished)
- Women who didn't have spread or return of their breast cancer since they were originally diagnosed

How does Letrozole work?

- Letrozole works by preventing the conversion of male hormones to female hormones
- By preventing the conversion of male hormones to estrogen, there is a further depletion of estrogen
- For the drug to work, you **MUST** be post menopausal

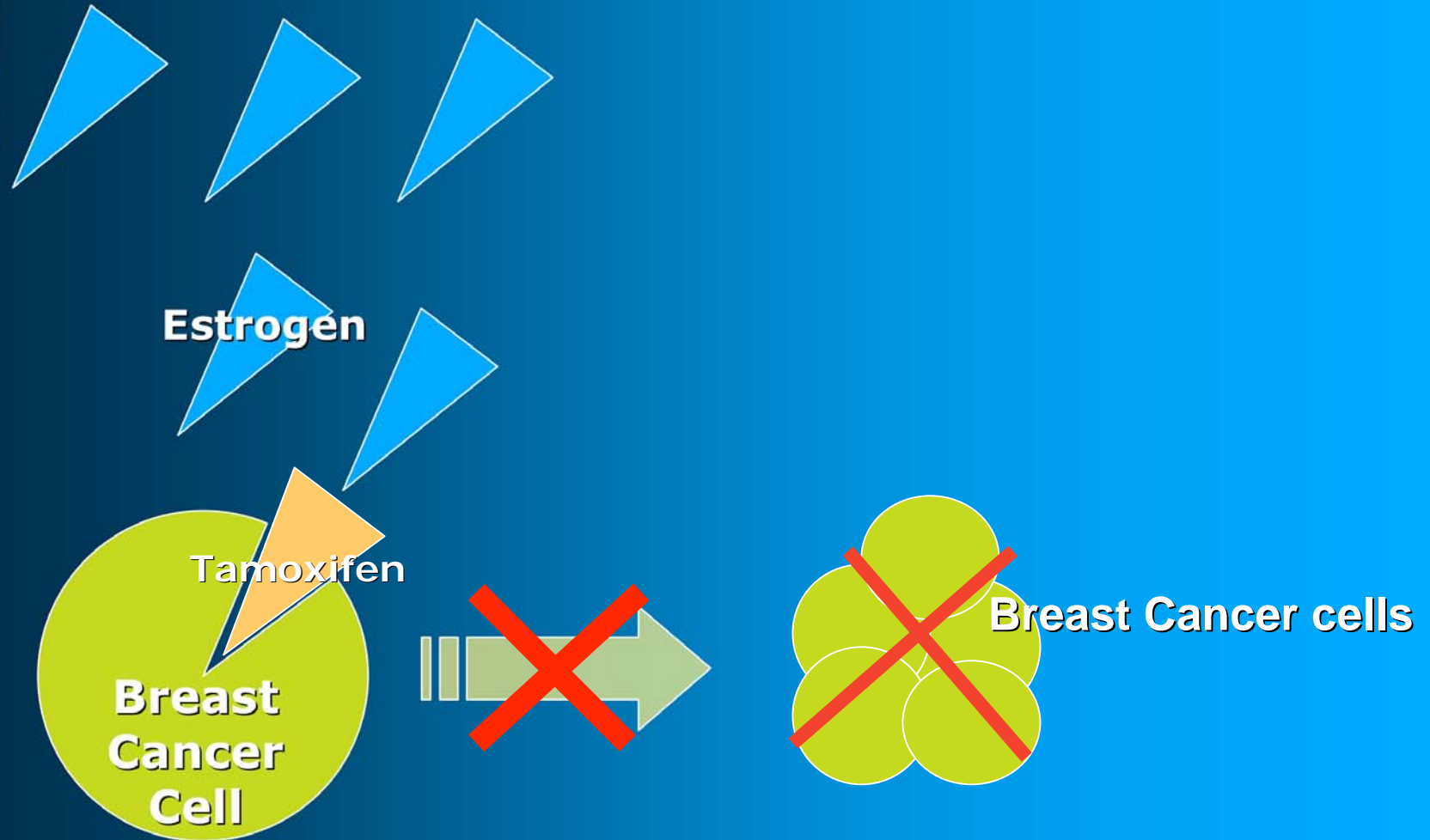
How does Letrozole work?



How is Letrozole different than Tamoxifen?

- Letrozole suppresses the production of estrogen in post menopausal women
- Tamoxifen has no effect on the PRODUCTION of estrogen. Tamoxifen prevents the binding of estrogen to the estrogen receptors of the cancer cells and, therefore, blocks the stimulation of the tumor.

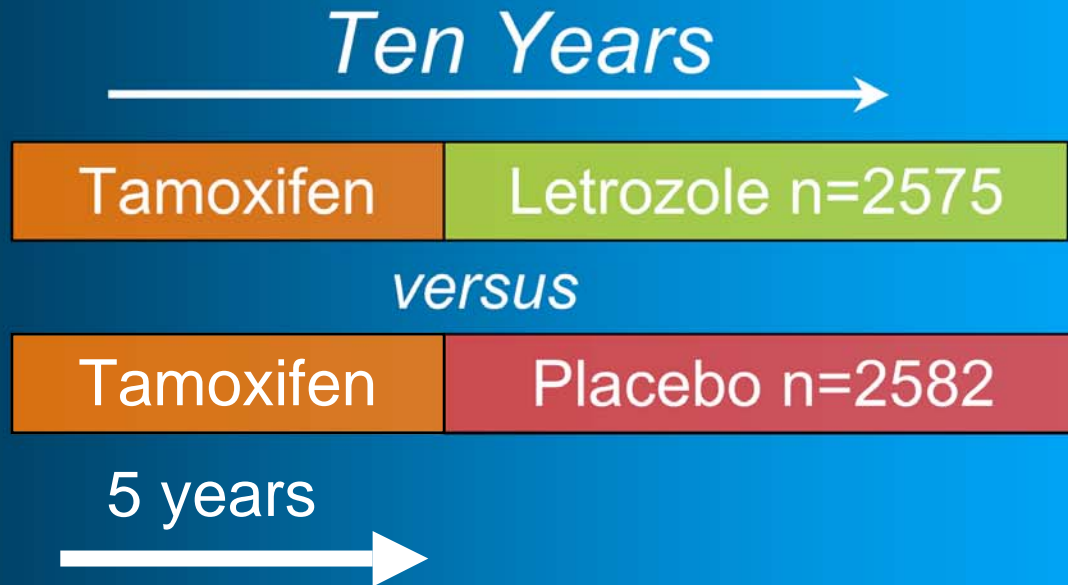
How does Tamoxifen work?



"MA17" Trial

- Randomized 5,187 post-menopausal females with estrogen sensitive breast cancer to receive
 - Letrozole pill once a day
 - Placebo pill once a dayafter about five years of tamoxifen
 - 46% node negative
 - 46% also received chemotherapy
- Median follow-up of 30 months
- Double blind randomized placebo controlled trial

"MA₁₇" Trial



Definitions

- Disease-free survival defined as time when a women started on the trial to:
 - A recurrence of breast cancer,
 - New breast cancer, or
 - Death from any cause
- Overall survival defined as time from randomization to death from any cause

Disease Free Survival vs. Overall Survival

The difference between these two points in time is known as a disease free survival advantage

Diagnosis

Death

Delaying the point in time in which a woman died because of treatment is known as an overall survival advantage

Results

- By taking Letrozole after Tamoxifen, there was an absolute reduction in recurrence of breast cancer by 4.6% (a "disease-free survival advantage")
- In total, 155 women taking placebo had their disease recur compared to 92 of the women who took Letrozole

Results - Put another way....

- After an average of four years, about 6% of women who took the placebo had a recurrence but only 3.5% of the women who took Letrozole had a recurrence.

Overall Survival

- There was no statistically significant overall survival advantage for women who took Letrozole.
- After the first analysis of the data, it appeared that women with node-positive breast cancer had a survival advantage by taking Letrozole. These results were published in the *Journal of the National Cancer Institute*.

Overall Survival

- However, a subsequent unplanned Health Canada analysis (with a slightly longer follow-up) showed the survival advantage for women with node-positive breast cancer was no longer present.
- We are unsure if women with node-positive breast cancer benefit more than those with node-negative breast cancer.

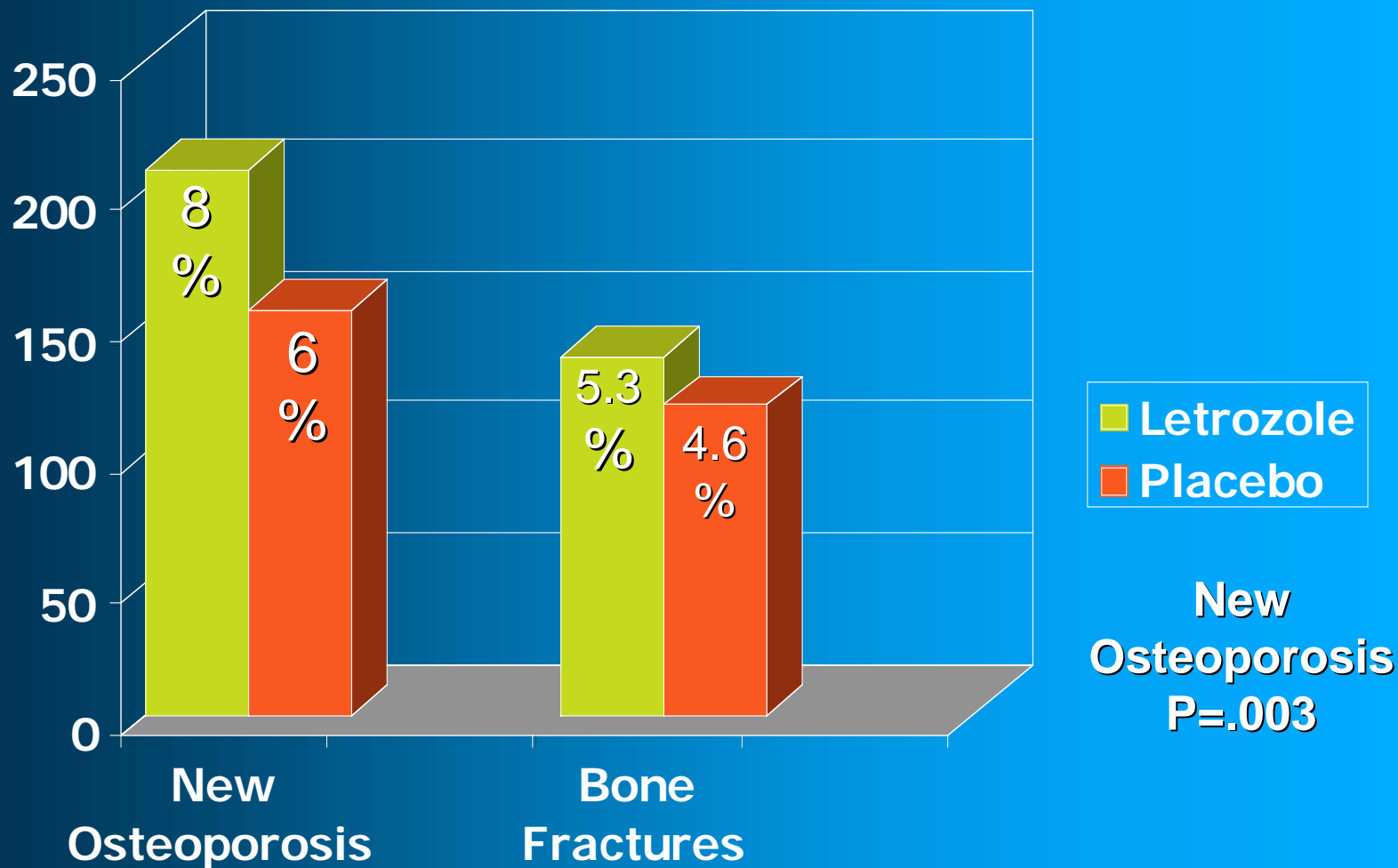
Issues with the Study

- This study was stopped early because an independent data safety monitoring committee concluded that, based on the early results, Letrozole was beneficial when compared to placebo and therefore women on the study should have the chance to receive it.

Letrozole Side Effects

Adverse Effects	Letrozole (<i>n</i> = 2,572)	Placebo (<i>n</i> = 2,577)	<i>p</i> value
Hot flashes	58%	54%	0.003
Arthralgia (aches/pains)	25%	21%	<0.001
Vaginal bleeding	6%	8%	0.005
Osteoporosis (bone thinning)	8.1%	6.0%	0.003
Lipid levels (cholesterol or blood fat levels)	16%	16%	<i>NS</i>

Patients who Developed Osteoporosis or Bone Fractures



Bone Health Recommendations

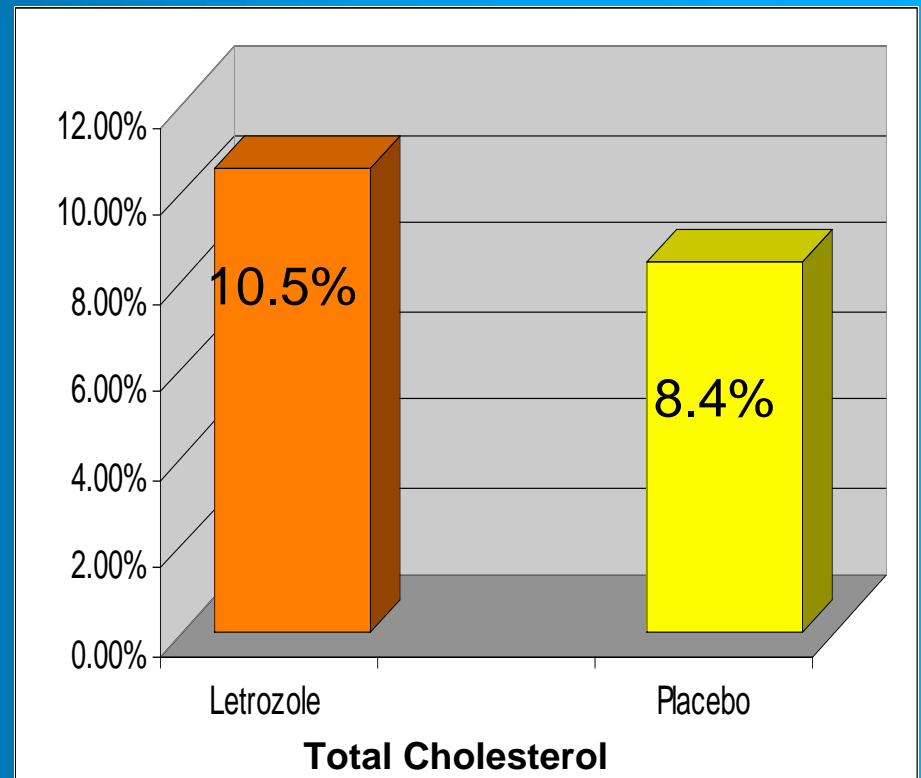
- All women who wish to take Letrozole should have bone density testing done prior to starting on Letrozole
- Bone density should then be done once a year
- Exercise, Calcium, and Vitamin D are recommended for all post menopausal women
- Women with low bone density may also require bone strengthening drugs (Fosamax[®] or Didrocal[®])

Blood Lipid Levels

- Tamoxifen helps lower blood cholesterol
- Women who switched to Letrozole after 5 years of Tamoxifen can have modest increases in their cholesterol levels
- Having high cholesterol and other cardiac (heart) risk factors may increase a woman's chance of heart attack or stroke; however, this was not seen in the MA17 trial

Blood Lipid Levels

- Changes in blood cholesterol levels were not statistically significant between treatment groups



Incidence of Cardiovascular Deaths

- 9 out of 2582 Letrozole patients suffered a cardiovascular death (0.3%)

Compared to

- 13 out of 2586 Placebo patients (0.5%)

Incidence of Fatal Stroke

- 2 out of 2582 patients taking Letrozole suffered strokes (0.07%)

Compared to

- 4 out of 2586 patients taking placebo (0.15%)

Total Cardiovascular Events

- The total number of cardiovascular events seen when comparing Letrozole to placebo was:
- 149 women who took Letrozole cardiovascular events
- Compared to
- 144 women who received placebo
- This was not statistically significant

Lipid Recommendations

- Just to be on the safe side:
 - Blood cholesterol (lipid) levels need to be checked prior to starting Letrozole
 - Lipid levels should be checked every year by your family doctor and treated, if needed.

Summary:

- Women who are post menopausal and have completed 5 years of Tamoxifen can consider taking Letrozole
 - There is a disease-free survival advantage to Letrozole
 - No unequivocal overall survival advantage has been shown

Summary:

- Letrozole is a pill that is taken once a day
- Side effects include hot flashes, aches and pains, changes in bone density, and changes in blood cholesterol levels

Summary:

- 3 years of Letrozole is currently paid for by the Alberta Cancer Board
 - The study intended to treat women with Letrozole for 5 years
 - The study was stopped early with an average treatment time of 30 months

Next Steps

- If you would like to consider treatment with Letrozole, please call the cancer center.
- You **MUST** complete a bone density and have blood work **BEFORE** your appointment (we will explain how to do these tests and where you can get them done)

Questions?

Call your Cancer Center