

# Targeted Agents In Breast Cancer

Wonderful Music With New Instruments

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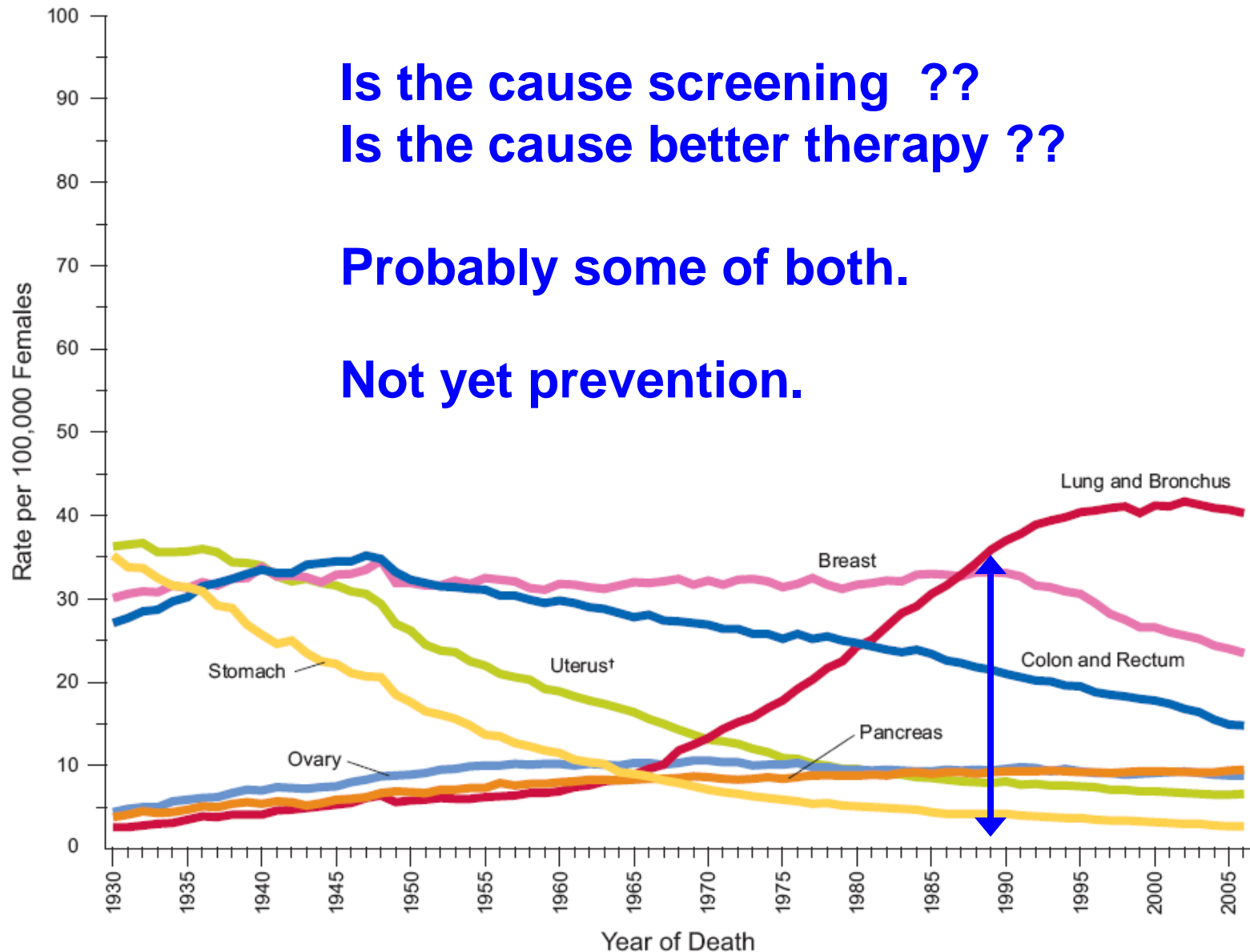
# Trends In Cancer Mortality In Women in US

## At This Rate We Will Beat Breast Cancer In 2040

Is the cause screening ??  
Is the cause better therapy ??

Probably some of both.

Not yet prevention.



# Targeted Agents In Breast Cancer

## Accelerated Progress

1. Its expression is only found to a limited extent in normal adult tissues
2. Its expression in cancer correlates with its anti-cancer effects.
3. It can be combined with other agents without unexpected toxicity

# Targeted Agents In Breast Cancer

## Why All The Excitement Now

1. Knowledge about metabolic, signalling, and control pathways is advancing
2. Methodologies for detecting and quantitating macromolecules are improving
3. Methods for screening large libraries of compounds are maturing.

# Targets In Breast Cancer

## **The Estrogen Receptor. ER**

*(Discovery late 1970s)*

# Targets In Breast Cancer

## The Grandmother of Them All The Estrogen Receptor.

Restricted expression in tissues in the adult.

Toxicity issues: Expression in endometrium  
Expression in bone  
Expression in CNS

Methodologies for detecting  
Still an issue

# Targets In Breast Cancer

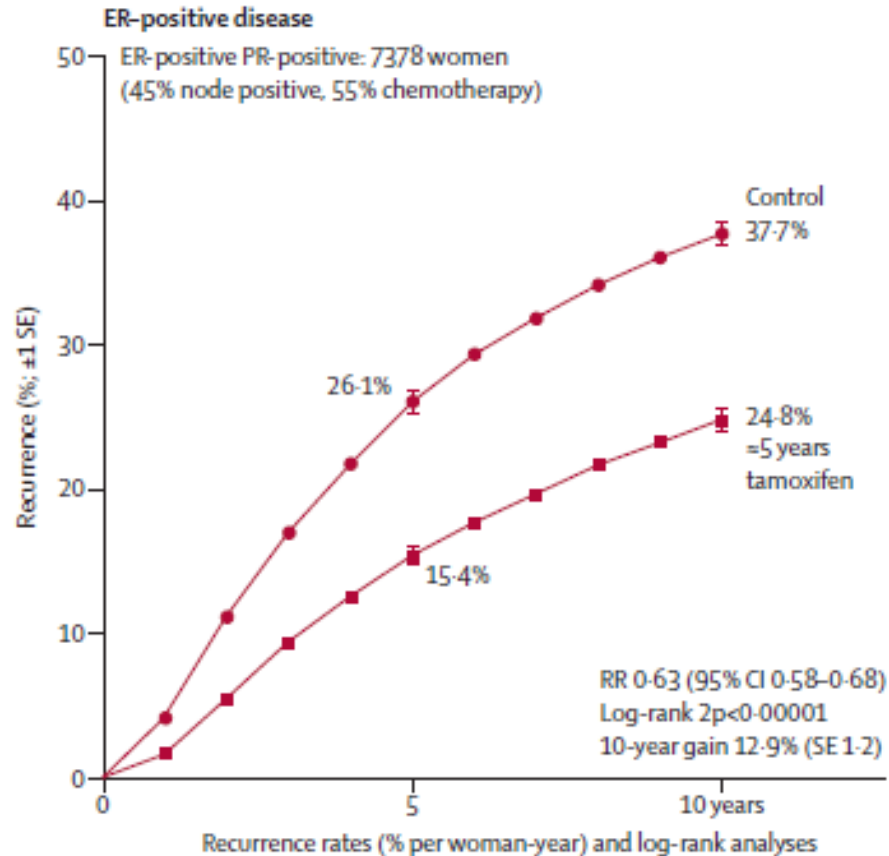
## Tamoxifen: An Agent Targeting The Estrogen Receptor.

### Useful In

Metastatic Disease	50 % RR
Adjuvant Therapy	40 % HR
Prevention	40 % RR

# Targets In Breast Cancer

## Tamoxifen Effects Are Long Term



**45 %      32 %      7%**  
**Relapse Reductions**

# Targets In Breast Cancer

**HER2**

*(Discovery late 1980s)*

# Targets Agents In Breast Cancer

## Second Major Target Her2

Restricted expression in the adult  
Expression in heart ?

Methodologies for detecting  
Still an issue

In adjuvant therapy do Her2  
“negative“ cases respond

## NSABP B-47

### Chemotherapy With or Without Trastuzumab After Surgery in Treating Women With Invasive Breast Cancer

**Groups:** Arm 1. DC q3w \* 6

Arm 2. AC qw2 or 3w \* 4 then P qw \* 12

Arm 3. DC and **Trastuzumab** q3w \* 6 and then **Tras.** q3w \* 11

Arm 4. AC qw2 or 3w \* 4 then P and **Tras.** qw \* 12 then **Tras.** Q3w \* 12

#### Eligibility

1. HER2 0 or 1 by IHC. If Her2 = 2, FISH negative. If Her2 = 3 ineligible
2. Node positive. If Node Negative. N0 with ER/PgR negative or Grade 3

# Targets/Agents In Breast Cancer

## Active Classes (1990's)

### **HER2-targeted agents**

Pertuzumab and trastuzumab-maytansine immunoconjugate)

### **VEGF-targeted agents**      aflibercept

anti-VEGF monoclonal antibody bevacizumab

### **Dual EGFR/HER2-targeted agents**

afatinib [BIBW 2992] and neratinib,

### **Multitargeted tyrosine kinase inhibitors**

sunitinib, pazopanib

### **Mammalian target of rapamycin (mTOR)**

everolimus

### **Poly (ADPribose) polymerase 1 inhibitors**

iniparib, olaparib.

# Targets In Breast Cancer

## Development of A New Agent

Metastatic Disease  
NeoAdjuvant Therapy

Adjuvant Therapy

Prevention

# Adjuvant Treatment: What Is Involved ?

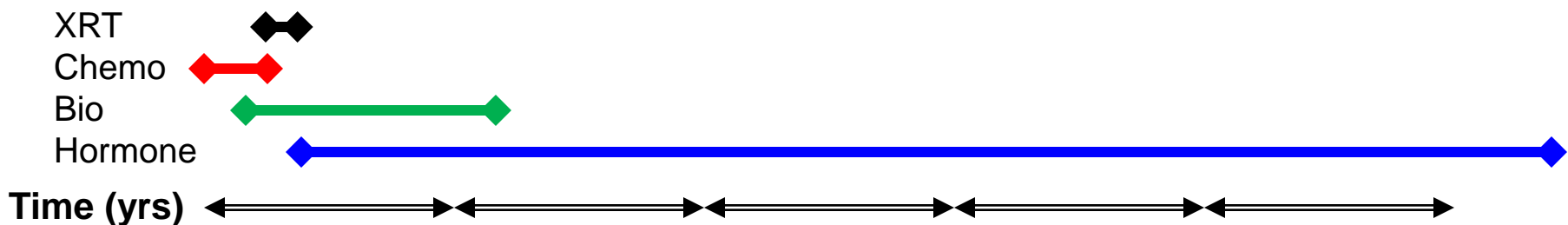
Lots of variations but this is a common way.

Radiation: 4-6 weeks  
High risk of local recurrence  
Inconvenient, bothersome.

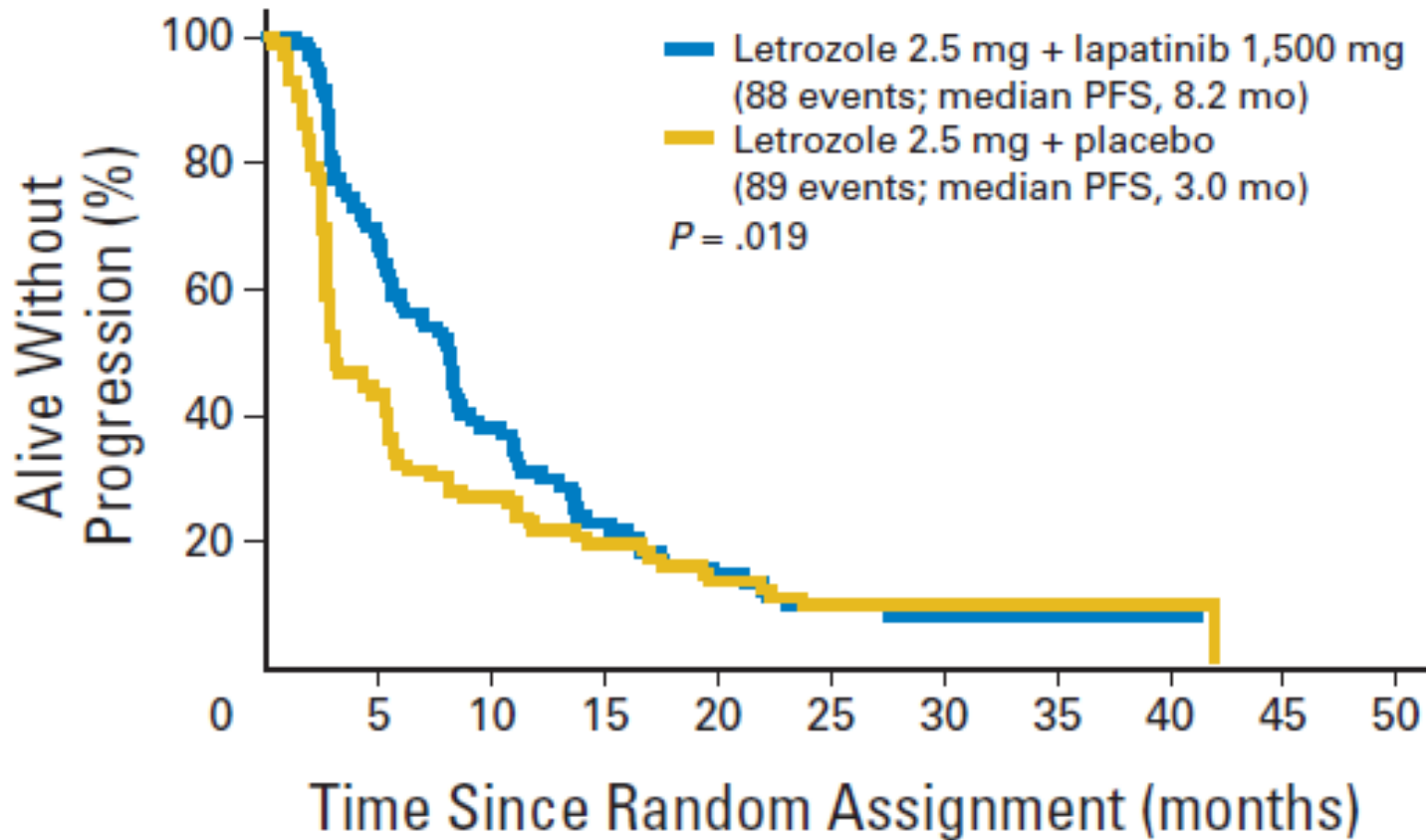
Chemotherapy: 3-6 months  
Unacceptable risk of dying of cancer  
Tolerable, but obnoxious.

Biological Therapy: 1 year  
Only if Her2 positive  
Usually low toxicity antibodies.

Hormone therapy: 5 years  
Only if ER (estrogen receptor positive)  
Usually low toxicity pills.

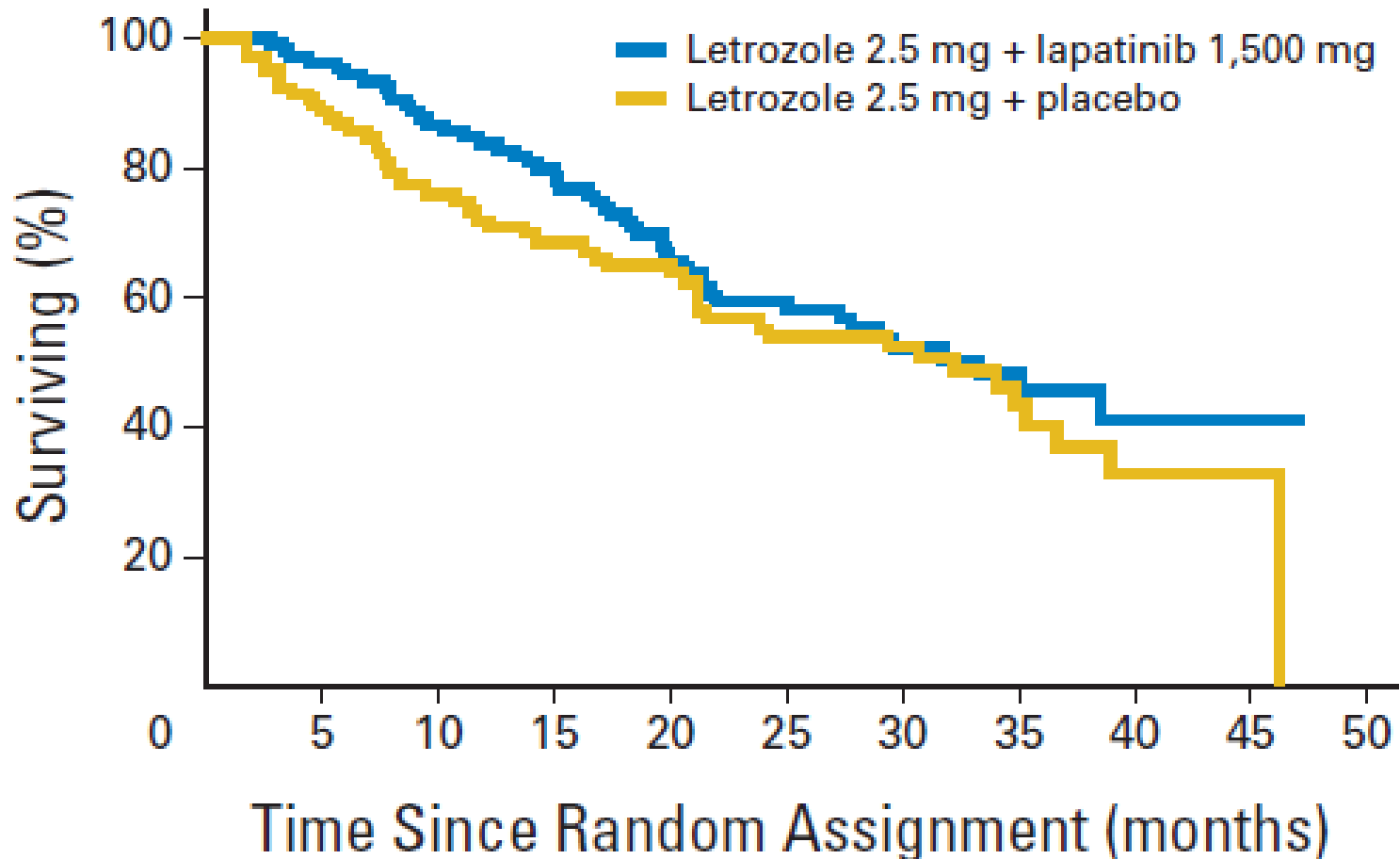


# PFS Results in MBC of A Trial Letrozole + Lapatinib vs Letrozole



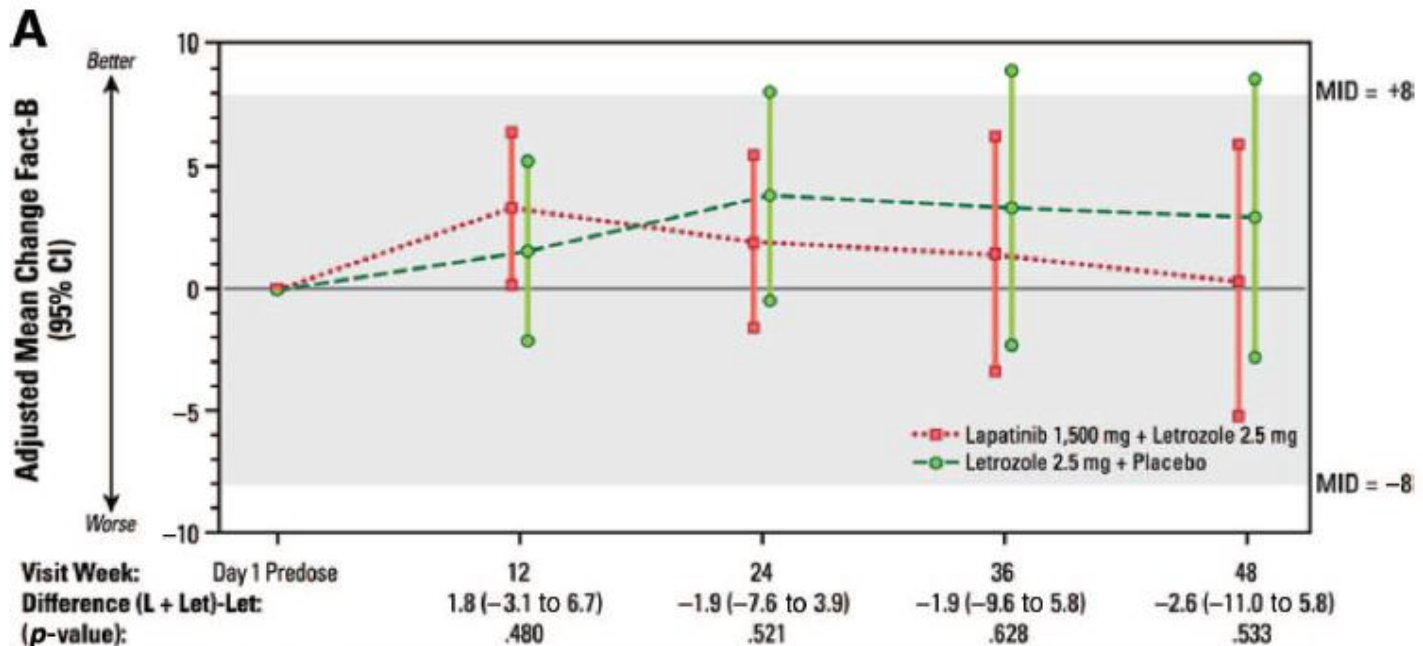
# OS Results of A Trial

## Letrozole + Lapatinib vs Letrozole



# QOL Results of A Trial


## Letrozole + Lapatinib vs Letrozole




10% of the L + L patients had Grade 3 / 4 diarrhea

# AI's +/- Everolimus

## Neoadjuvant Study




Letrozole + Everolimus (Better Response)  
More Toxicity




Letrozole Gr 3/4 23 % vs 4 %)

## 1<sup>st</sup> Line MBC Study



Exemestane + Everolimus (Pending)



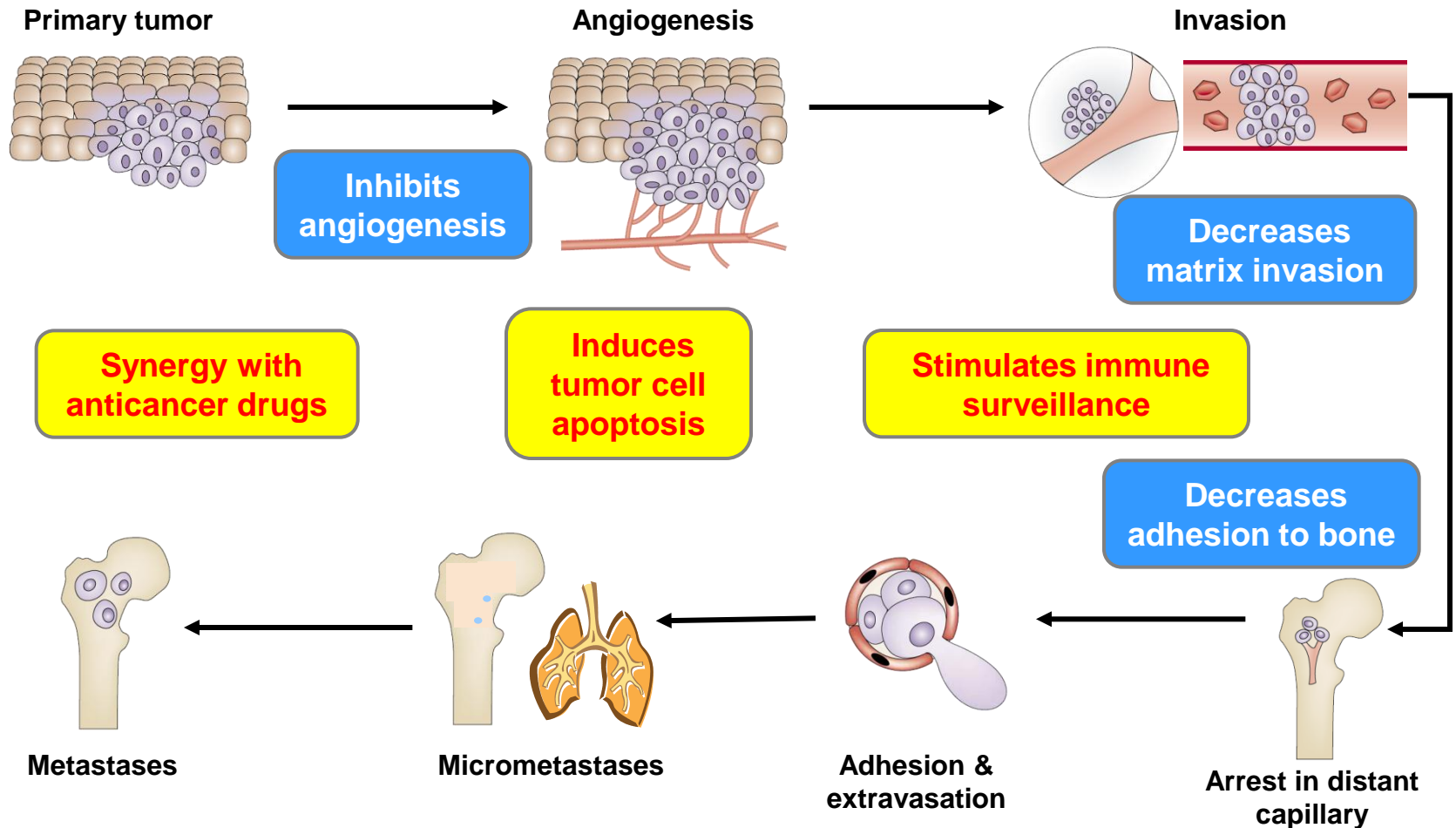
Exemestane

**Bisphosphonates ? !**

**Not really a  
Specifically Targeted Agents**

# Can Zoledronic Acid (An Osteoporosis Treatment) Improve Outcomes?

## Inhibition of Multiple Steps in Tumor Cell Metastasis

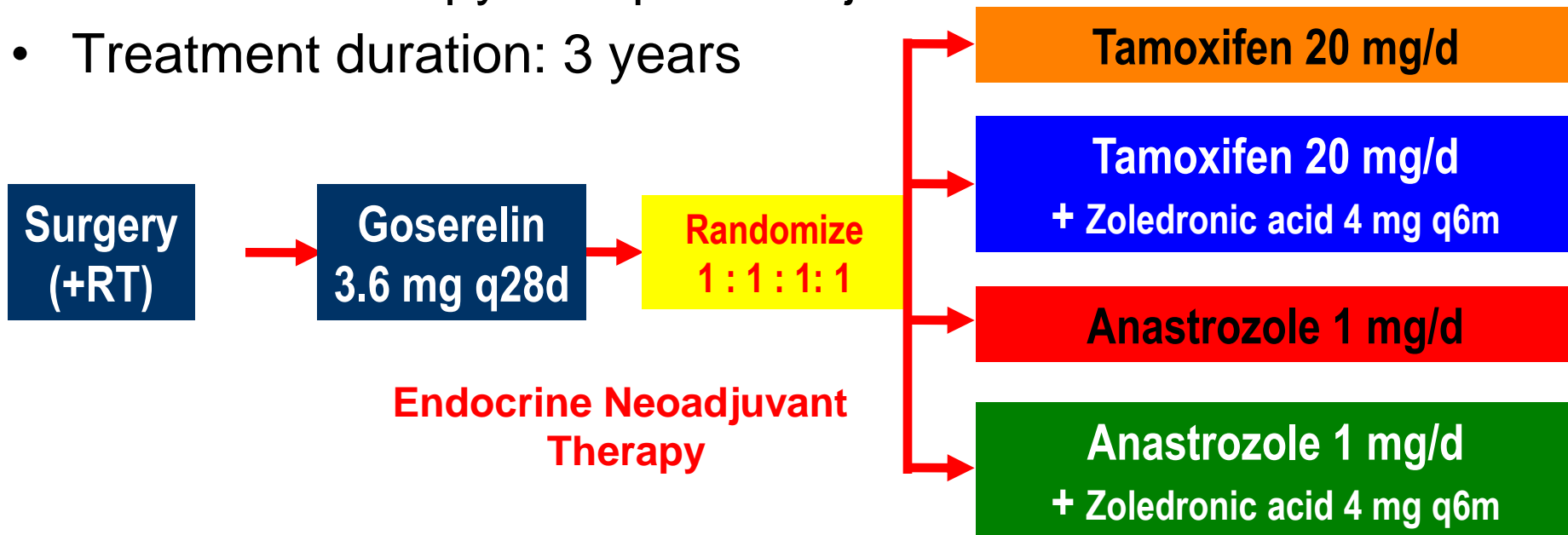


Adapted from Mundy GR, et al. *Nat Rev Cancer*. 2002;2:584-593.

# Austrian BC Study Group 12 Trial Design

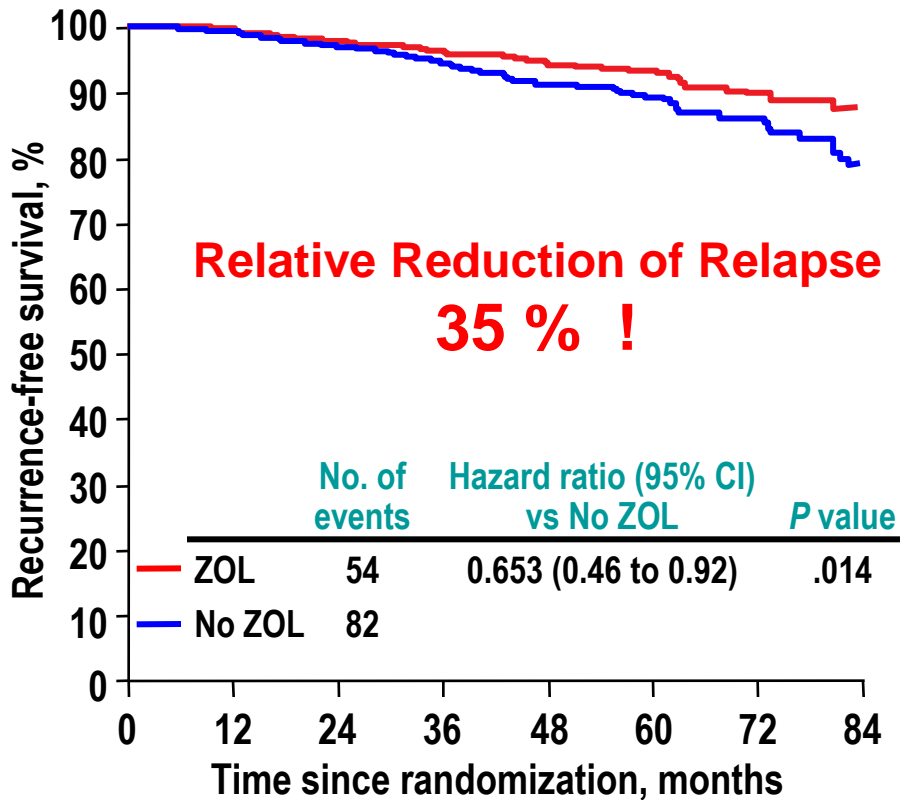
Results Presented in 2008

- Accrual 1999-2006
- 1,803 **premenopausal** breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years

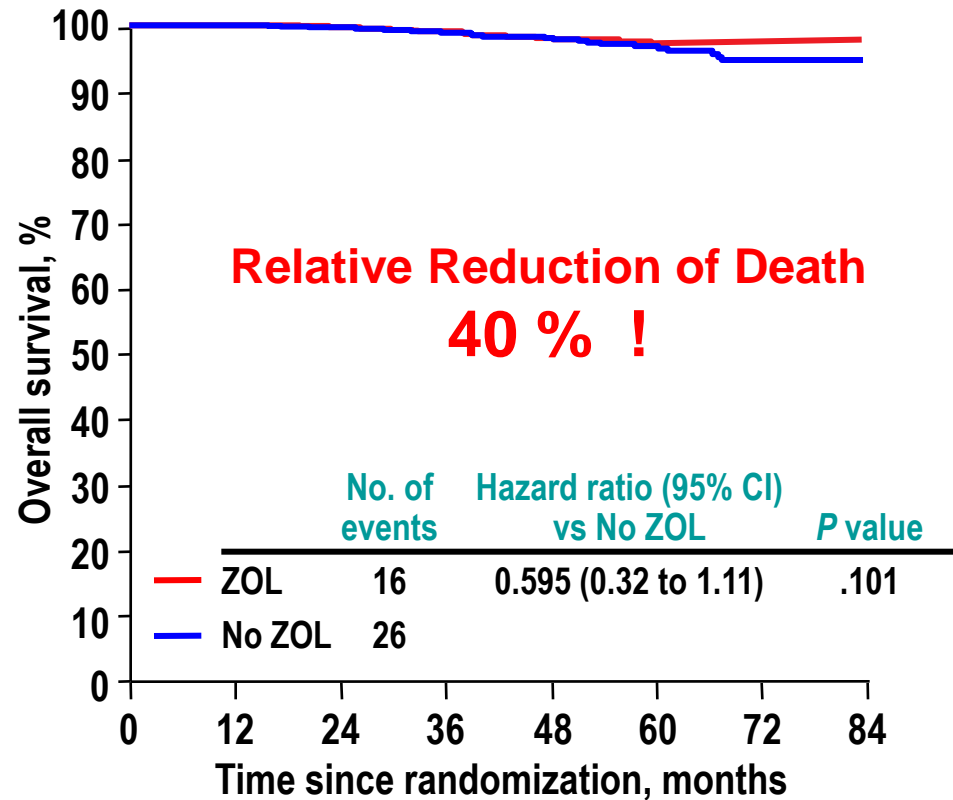


# Secondary Endpoints: ZOL vs No ZOL

## RFS

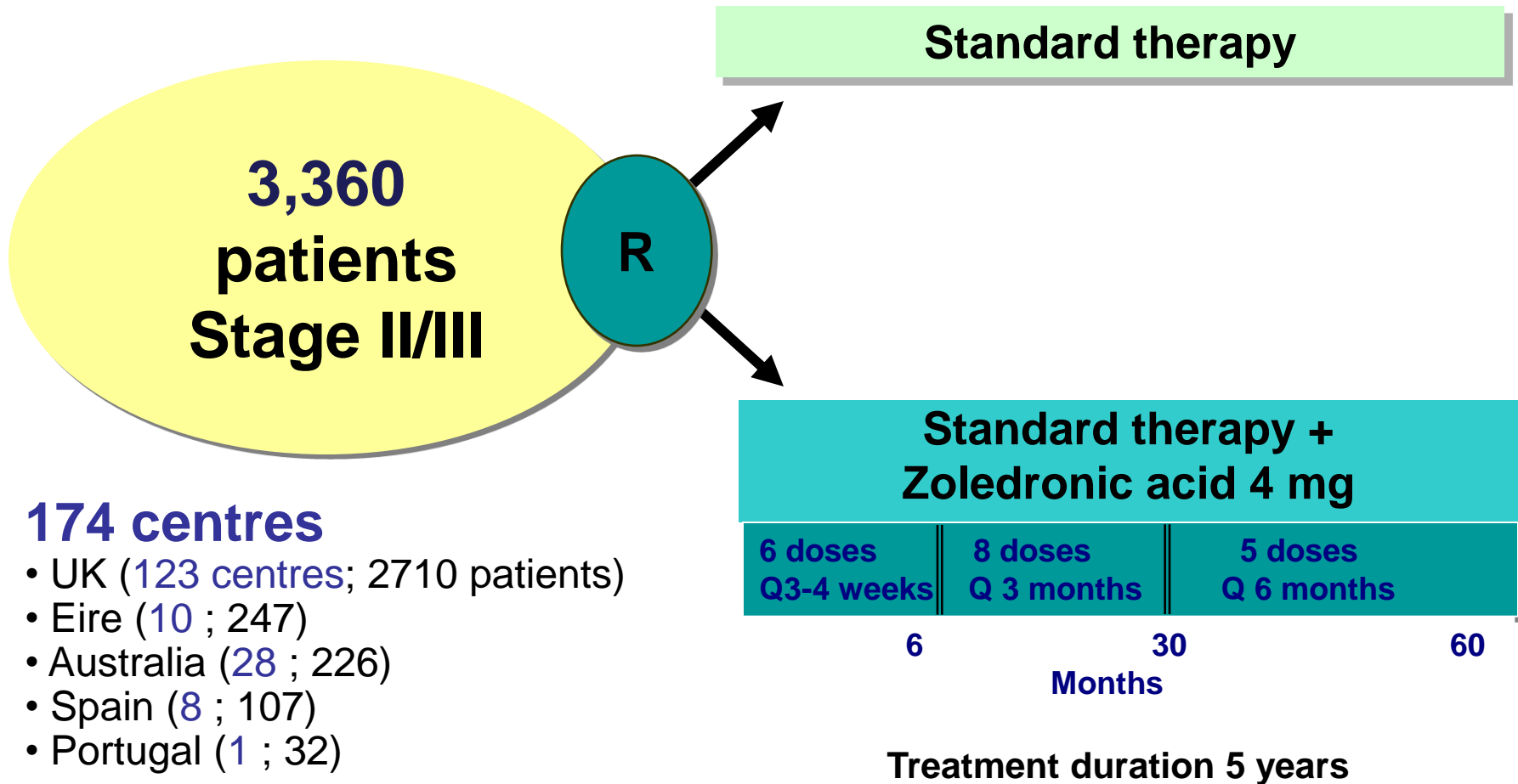


## OS



# AZURE: Study Design

Accrual September 2003 - February 2006

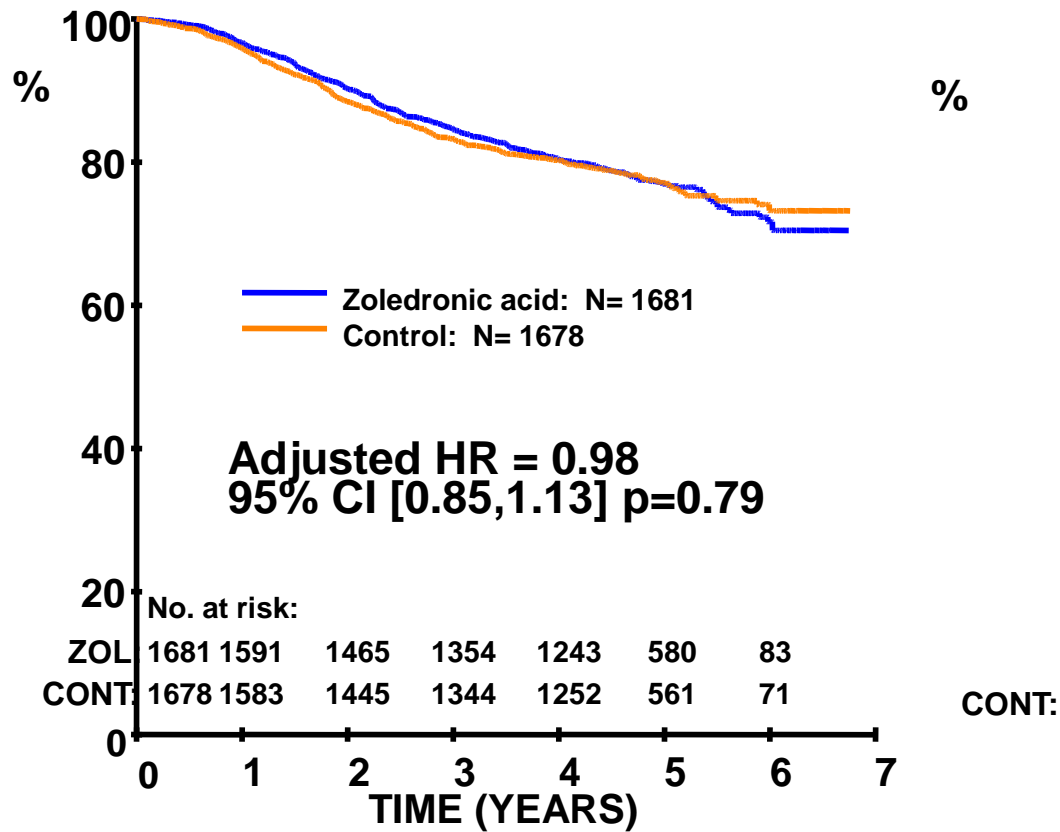


## 174 centres

- UK (123 centres; 2710 patients)
- Eire (10 ; 247)
- Australia (28 ; 226)
- Spain (8 ; 107)
- Portugal (1 ; 32)
- Thailand (2 ; 25)
- Taiwan (2 ; 13)

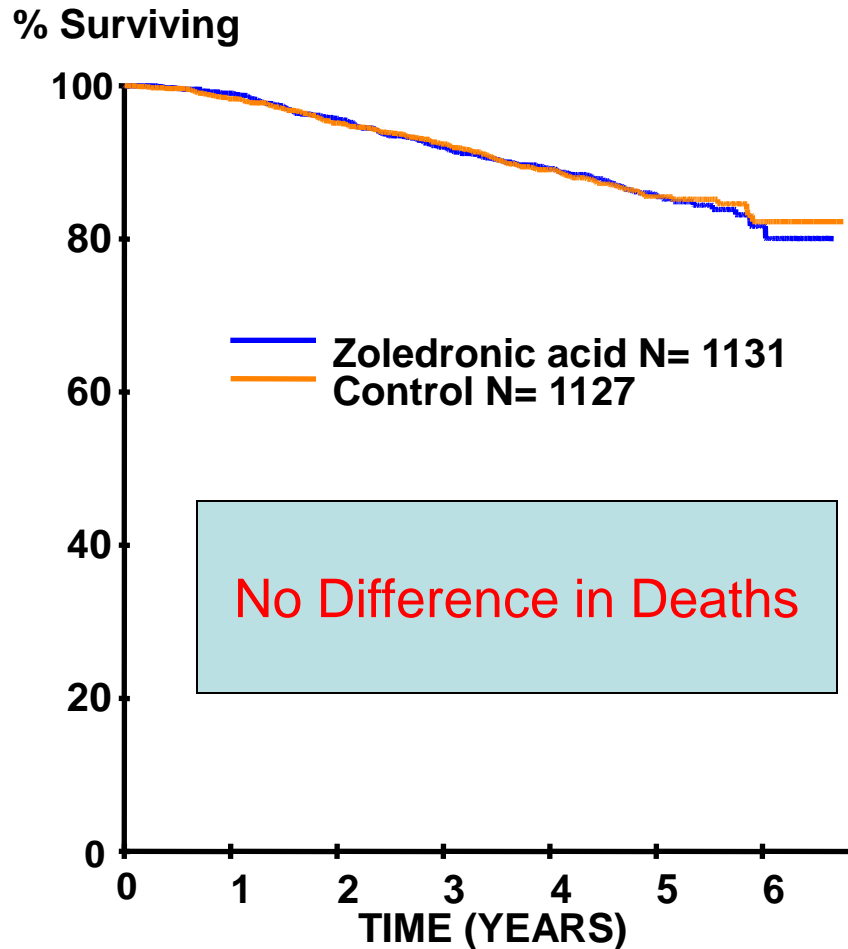
# AZURE: Disease Free Survival

## NO EFFECT ! BIG SURPRISE

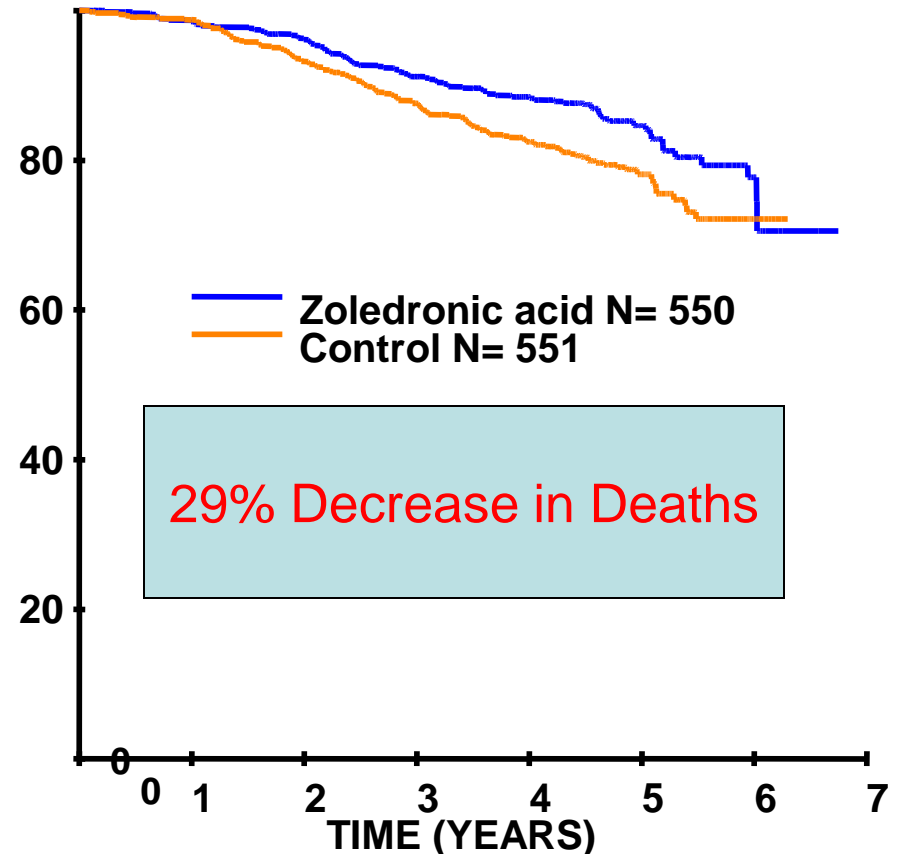


# AZURE: Overall Survival by Menopausal Status

## Premenopausal



## Postmenopausal



**There Are Many Promising Ideas**

**Some of these will be good**