Targeted Agents In Breast Cancer

Wonderful Music With New Instruments

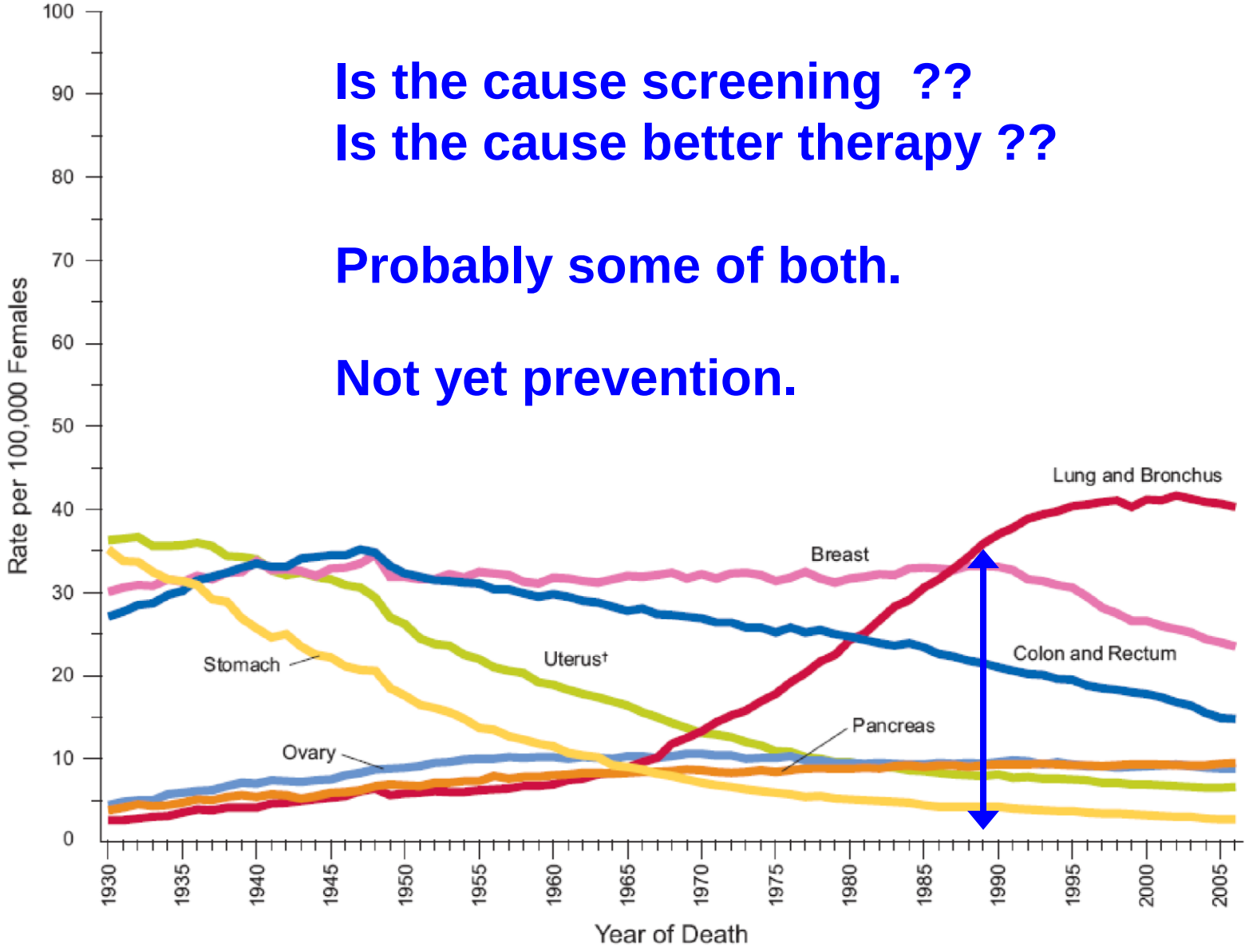
Trends In Cancer Mortality In Women in US

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

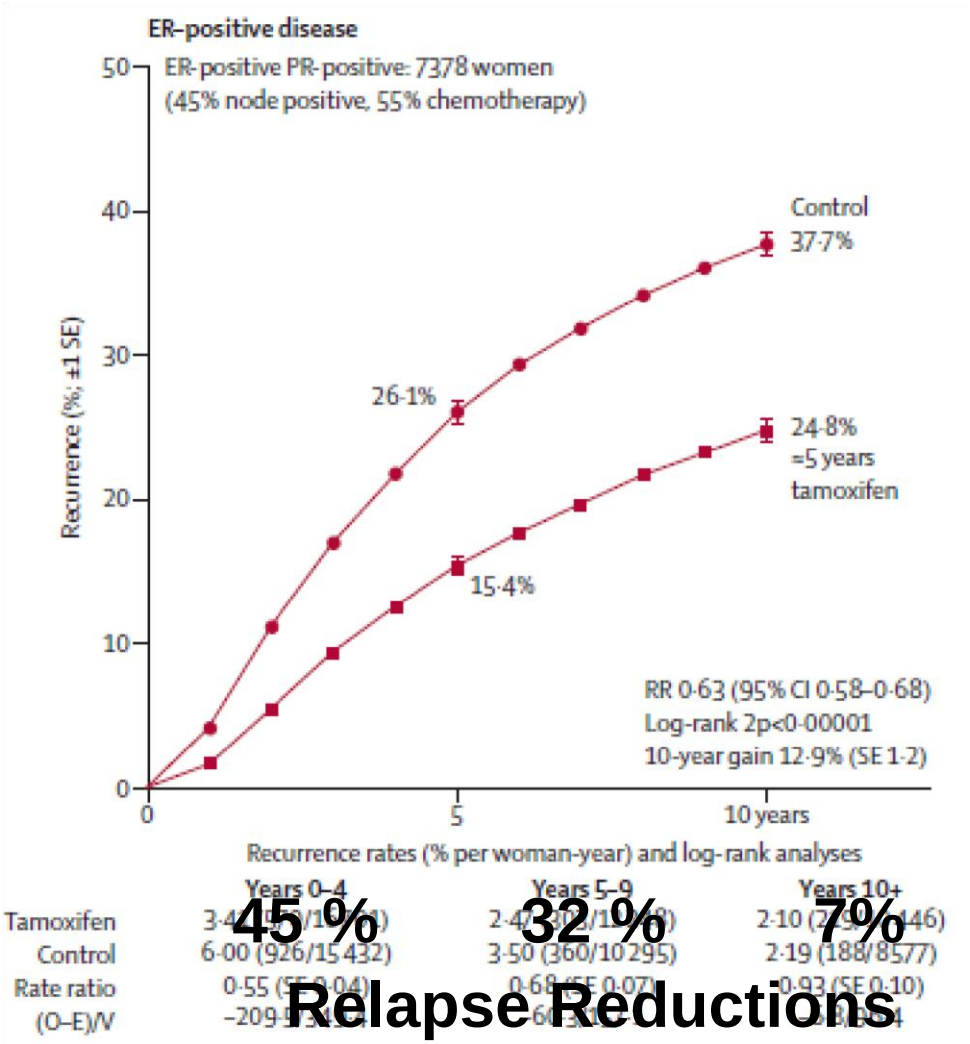
Tamoxifen: An Agent Targeting The Estrogen Receptor.

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

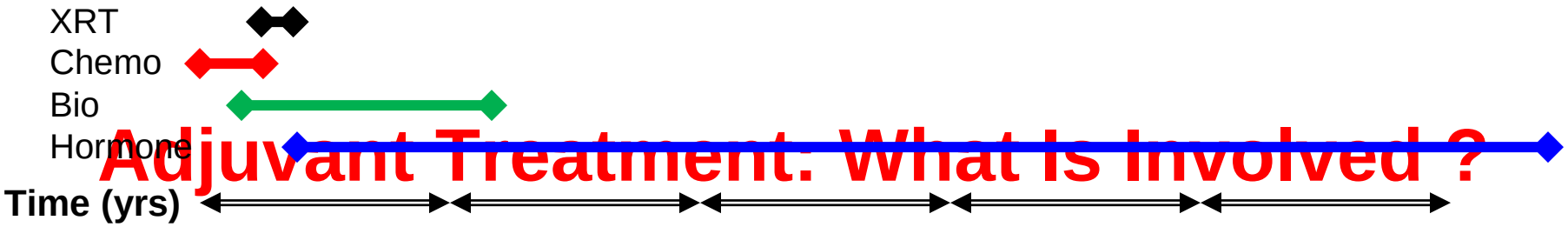
Lots of variations but this is a common way.

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

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

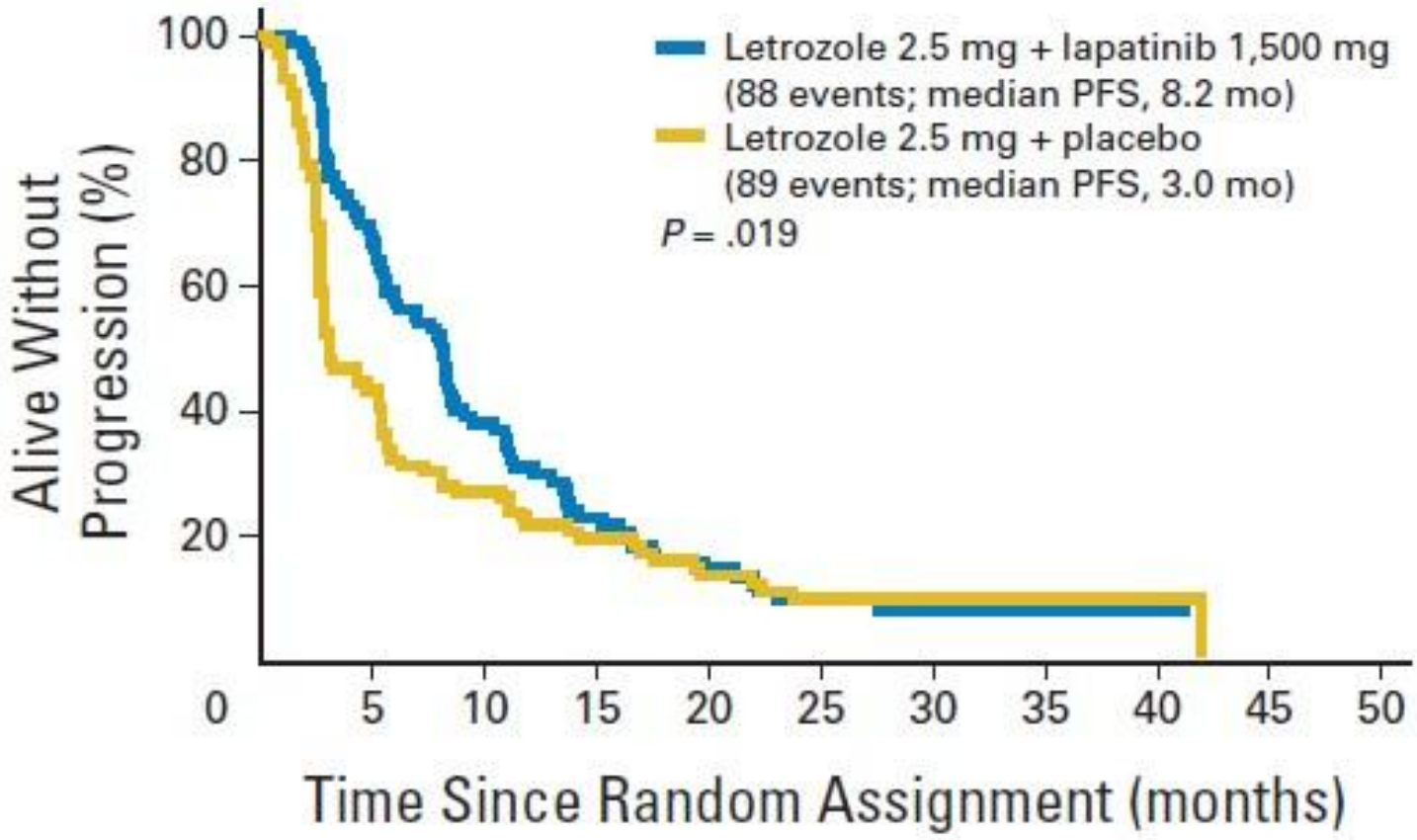
Biological Therapy: 1 year
Only if Her2 positive
Usually low toxicity antibodies.

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

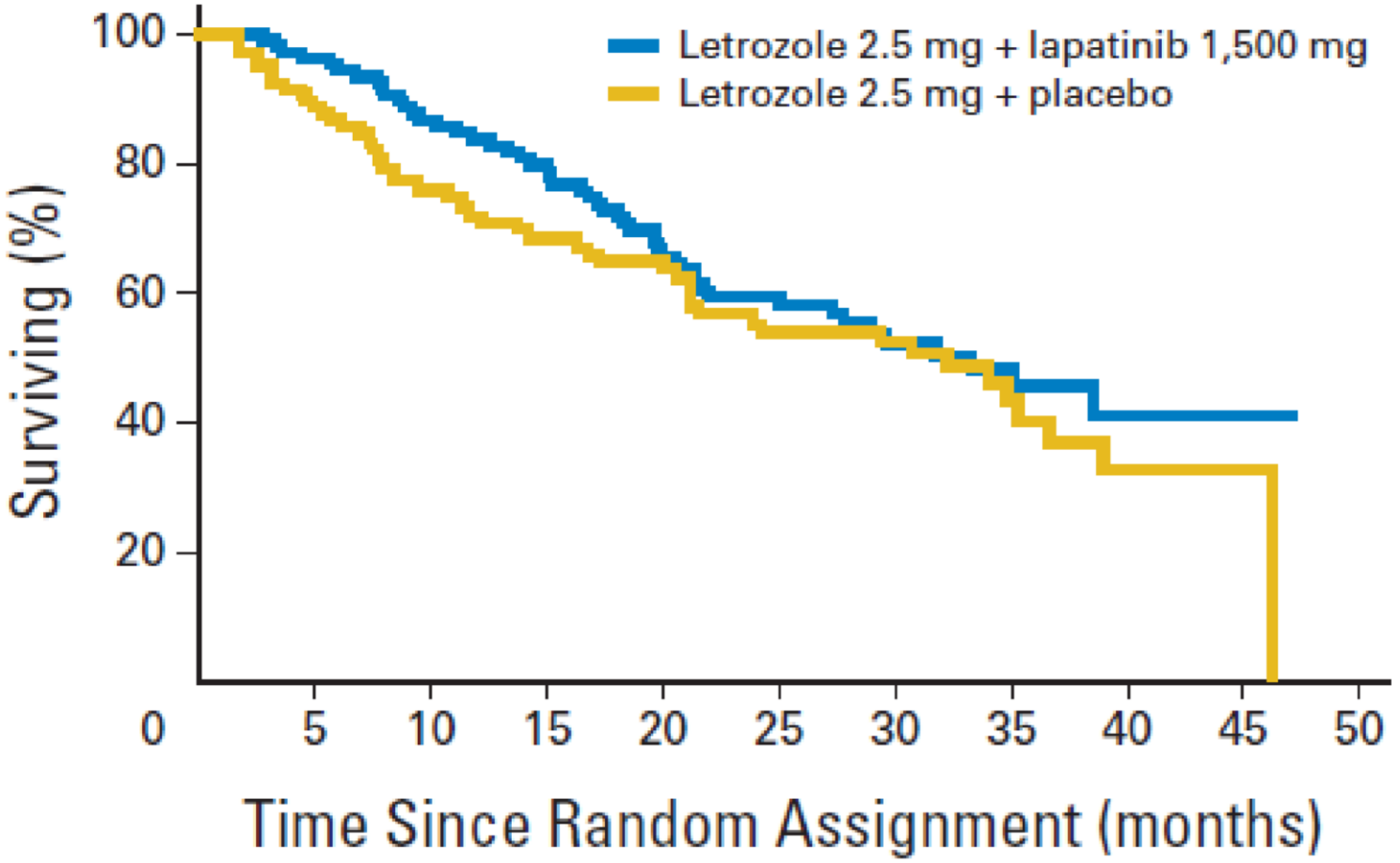


Adjuvant Treatment: What Is Involved ?

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

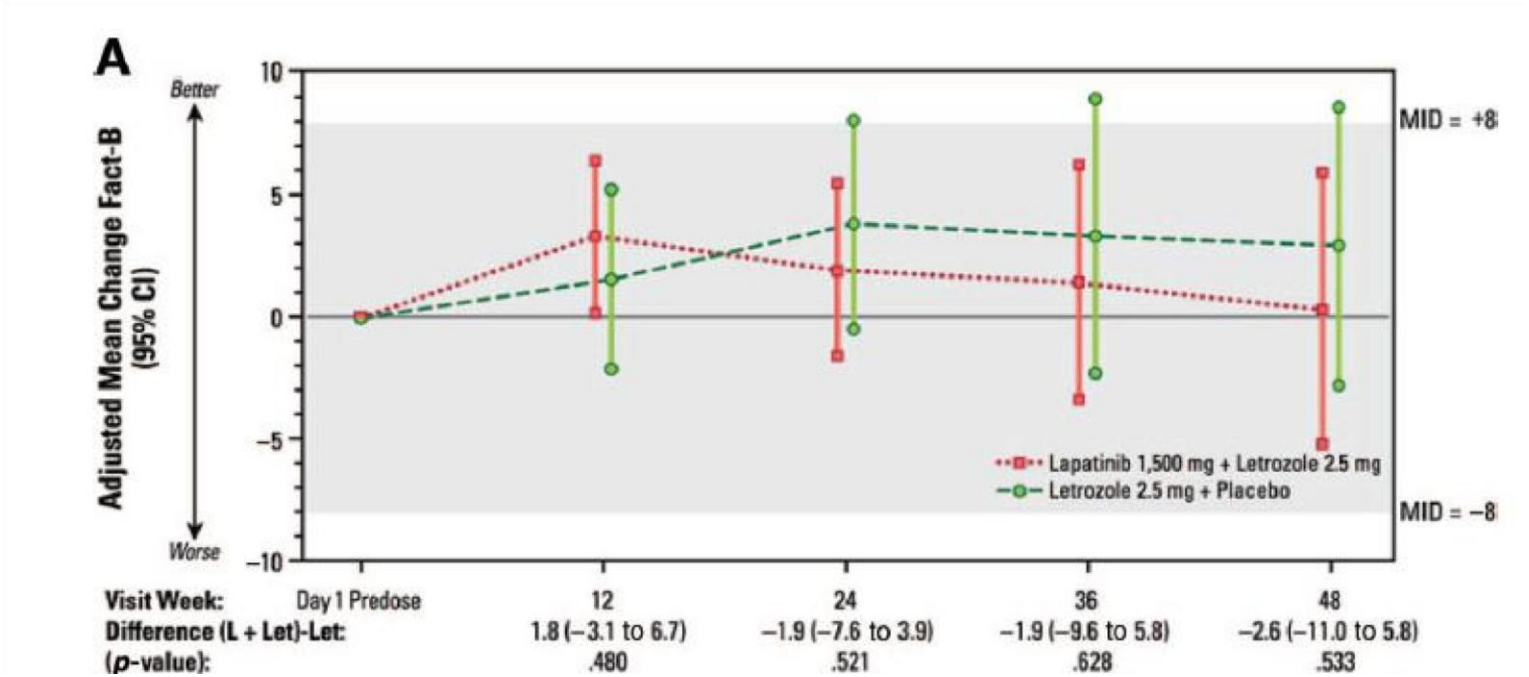


OS Results of A Trial
Letrozole + Lapatinib vs Letrozole



QOL Results of A Trial

Letrozole + Lapatinib vs Letrozole



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

AI's +/- Everolimus

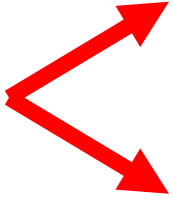
Neoadjuvant Study

Letrozole + Everolimus (Better Response)
More Toxicity

Letrozole Gr 3/4 23 %

1st Line MBC Study

Exemestane + Everolimus (Pending)



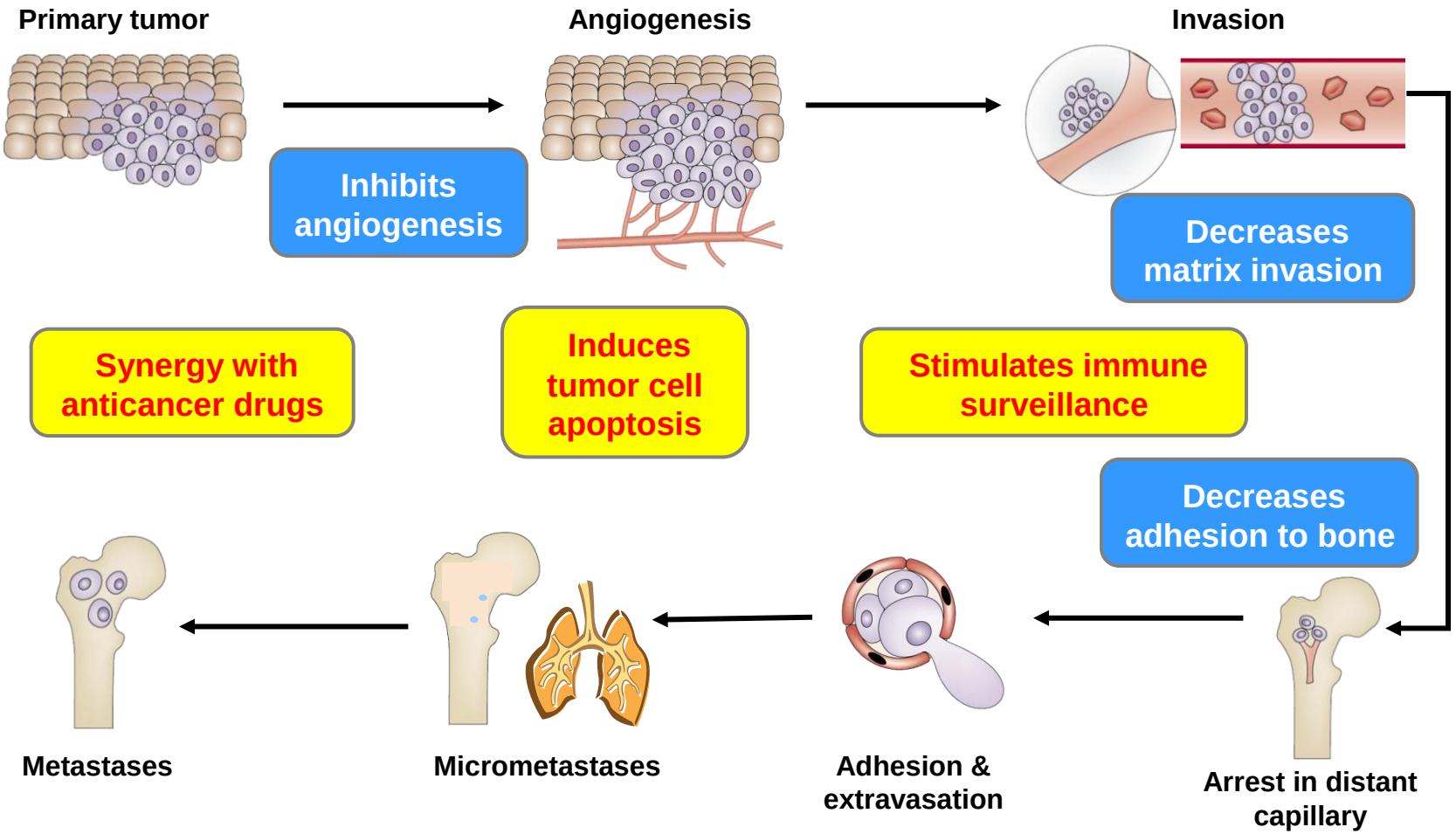
Exemestane

Bisphosphonates ? !

Not really a
Specifically Targeted Agents

Can Zoledronic Acid (An Osteoporosis Treatment) Improve Outcomes?

Inhibition of Multiple Steps in Tumor Cell Metastasis



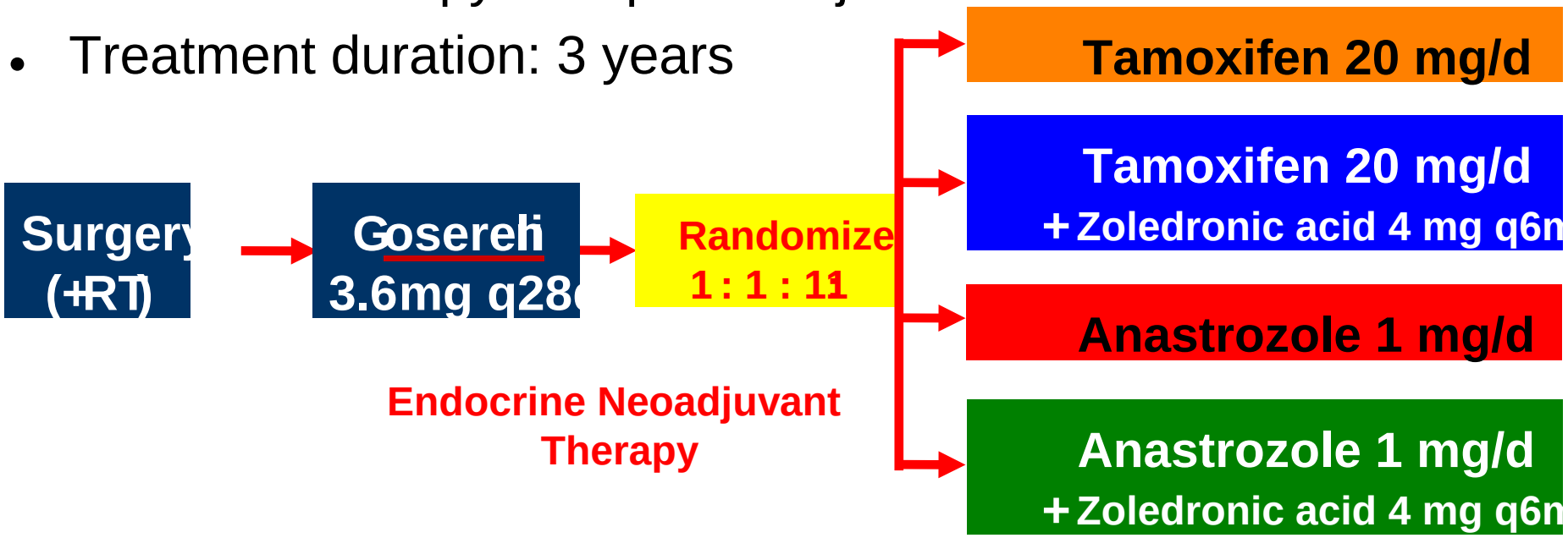
Adapted from Mundy GR, et al. *Nat Rev Cancer*. 2002;2:584-593.

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)

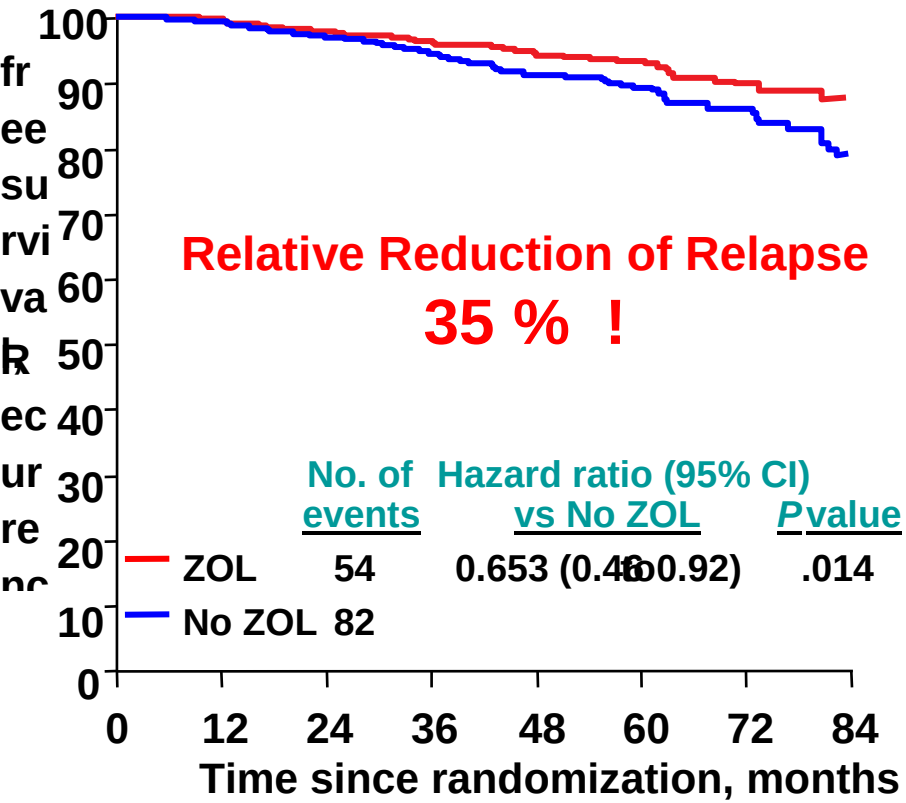
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



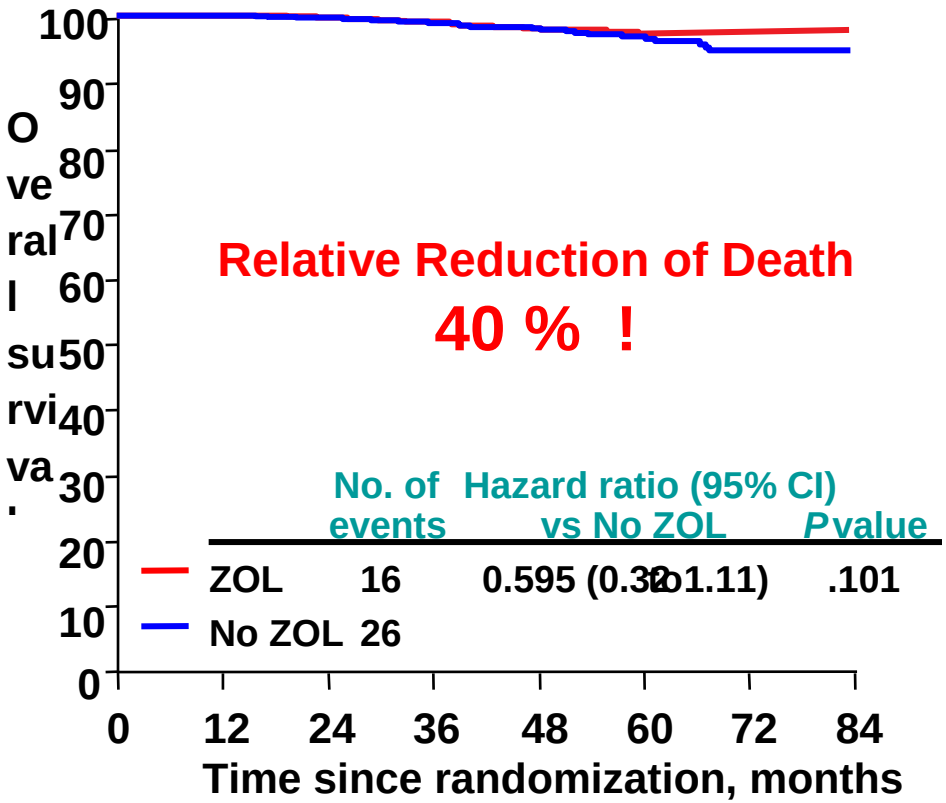
- Stage I&II, <10 positive nodes

Secondary Endpoints: ZOL vs No ZOL

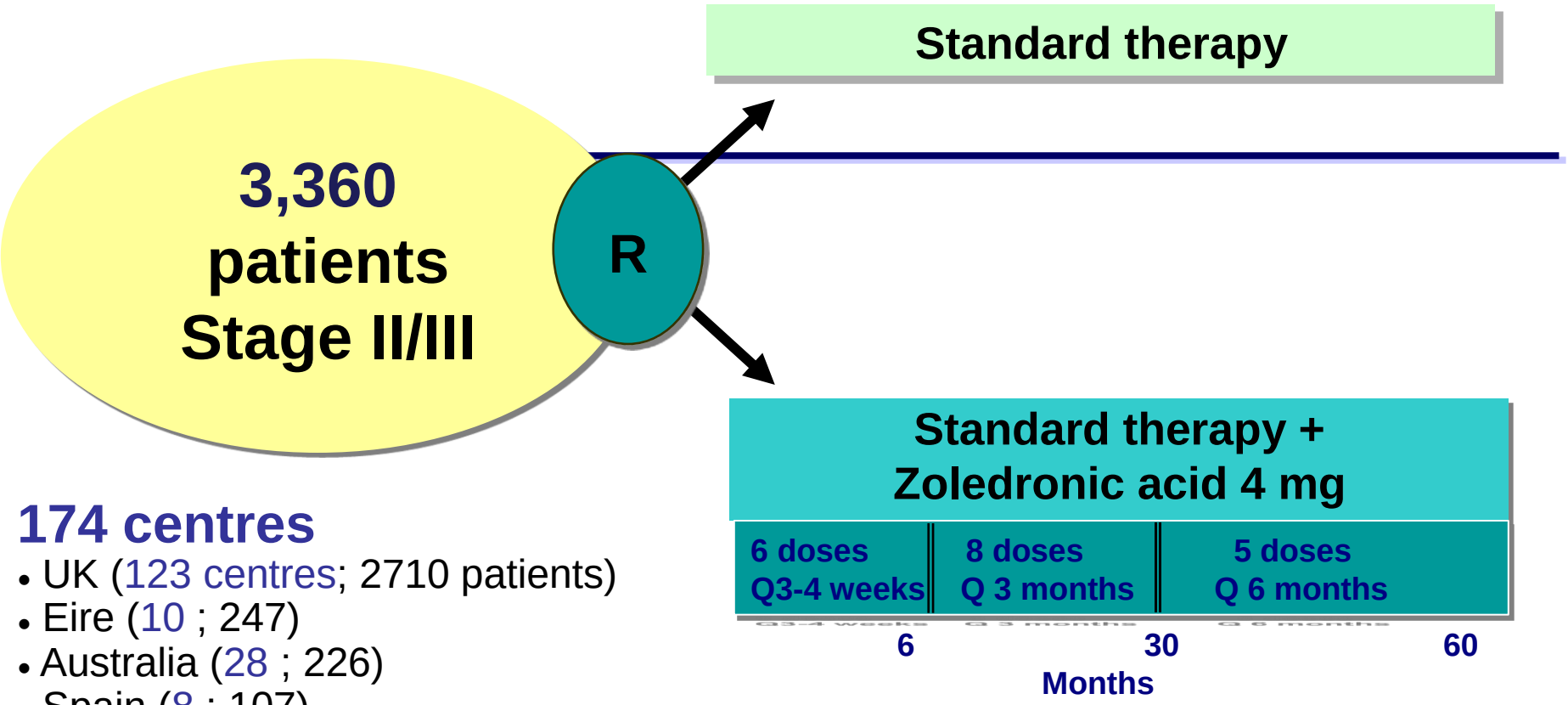
RFS



OS



Accrual September 2003 - February 2006



174 centres

- UK (123 centres; 2710 patients)
- Eire (10 ; 247)
- Australia (28 ; 226)
- Spain (8 ; 107)

AZURE: Study Design

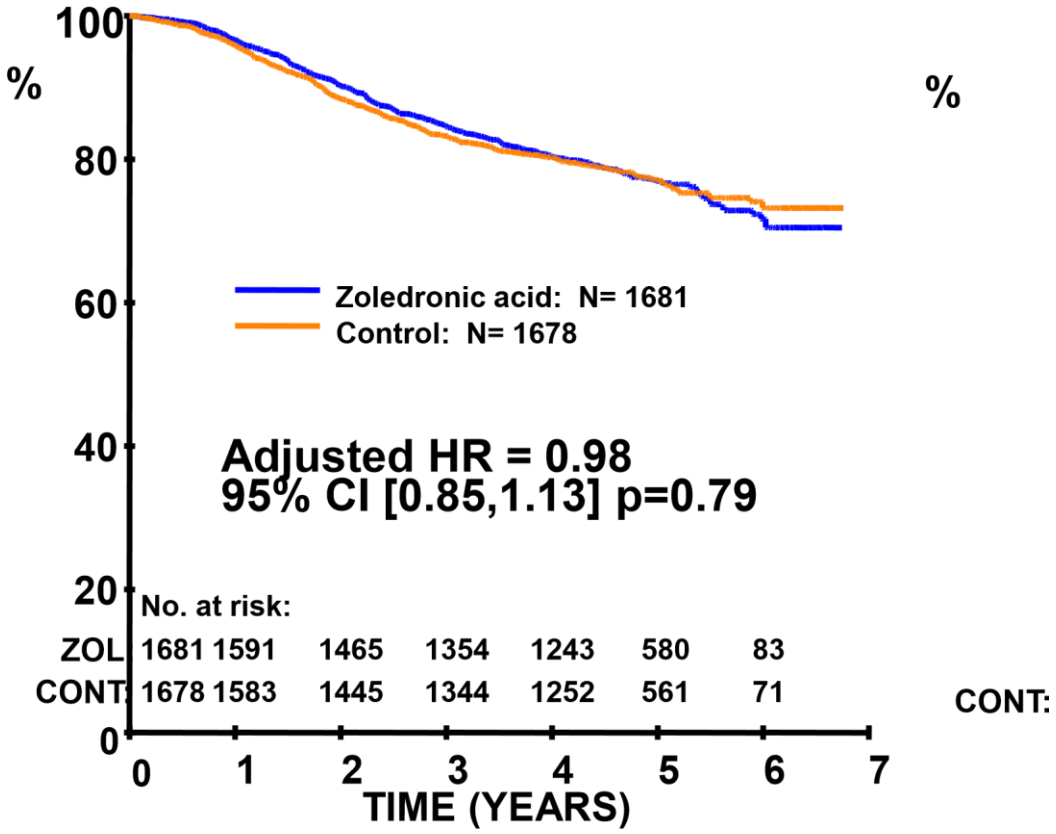
- Portugal (1 ; 32)
- Thailand (2 ; 25)

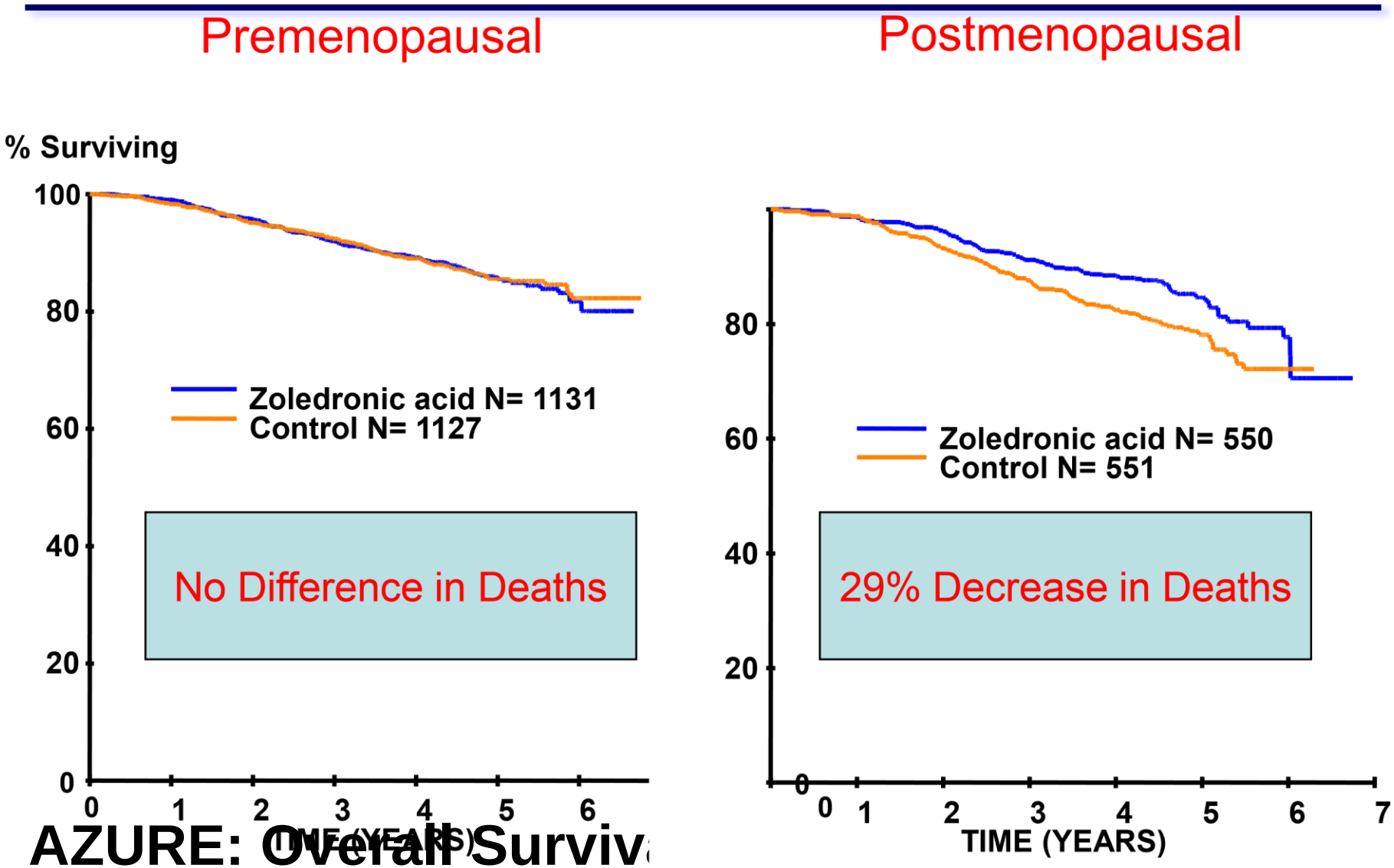
Treatment duration 5 years

- Taiwan (2 ; 13)

AZURE: Disease Free Survival NO EFFECT ! BIG SURPRISE

The University Of Sheffield.


100
%
80
60
40
20
0
%
Zoledronic acid: N= 1681
Control: N= 1678
Adjusted HR = 0.98
95% CI [0.85,1.13] p=0.79
No. at risk:
ZOL 1681 1591 1465 1354 1243 580 83
CONT 1678 1583 1445 1344 1252 561 71
CONT:
0 1 2 3 4 5 6 7
TIME (YEARS)



AZURE: Overall Surviv

There Are Many Promising Ideas

Some of these will be good