

## Terapia sistemica adiuvante Il contributo della ricerca Italiana

### Lo studio HOBEO

Francesco Perrone

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# DISCLOSURE INFORMATION

- Personal financial interests, for advisory role or speaker activities
  - Bayer, Janssen Cilag, Pierre Fabre, Astra Zeneca, Celgene, Incyte, Sandoz, Bristol Myers Squibb, Ipsen, Eli Lilly
- Institutional financial interests, for financial support to research activities
  - Astra Zeneca, Bayer, Roche, Merck, Pfizer, Incyte, Sanofi, BioClin, Tesaro.



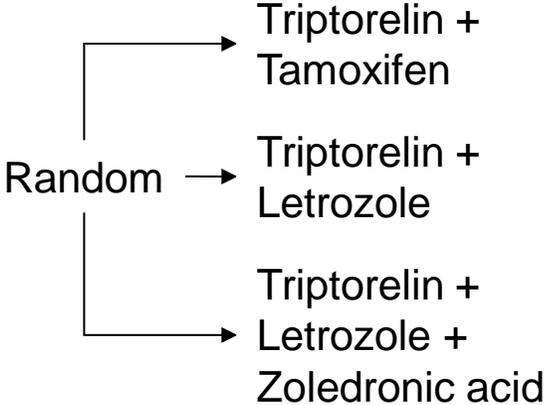
# HOBQE...

- **H**ormonal **B**one effects of **E**ndocrine adjuvant treatment of breast cancer...
- Un percorso, un programma più che un semplice studio
- O, se volete, un *adaptive trial ante litteram*



# HOBEOE 1

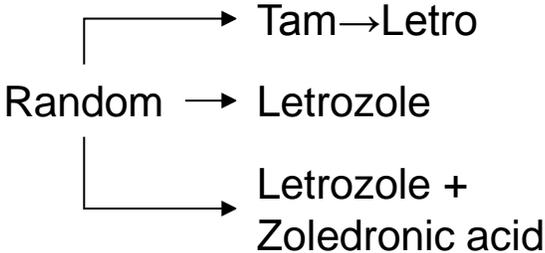
## Premenopausal patients



Single centre

1yr Bone Health

## Postmenopausal patients



2004

First patient in

2009

Sample size for bone health analysis reached (N=500)



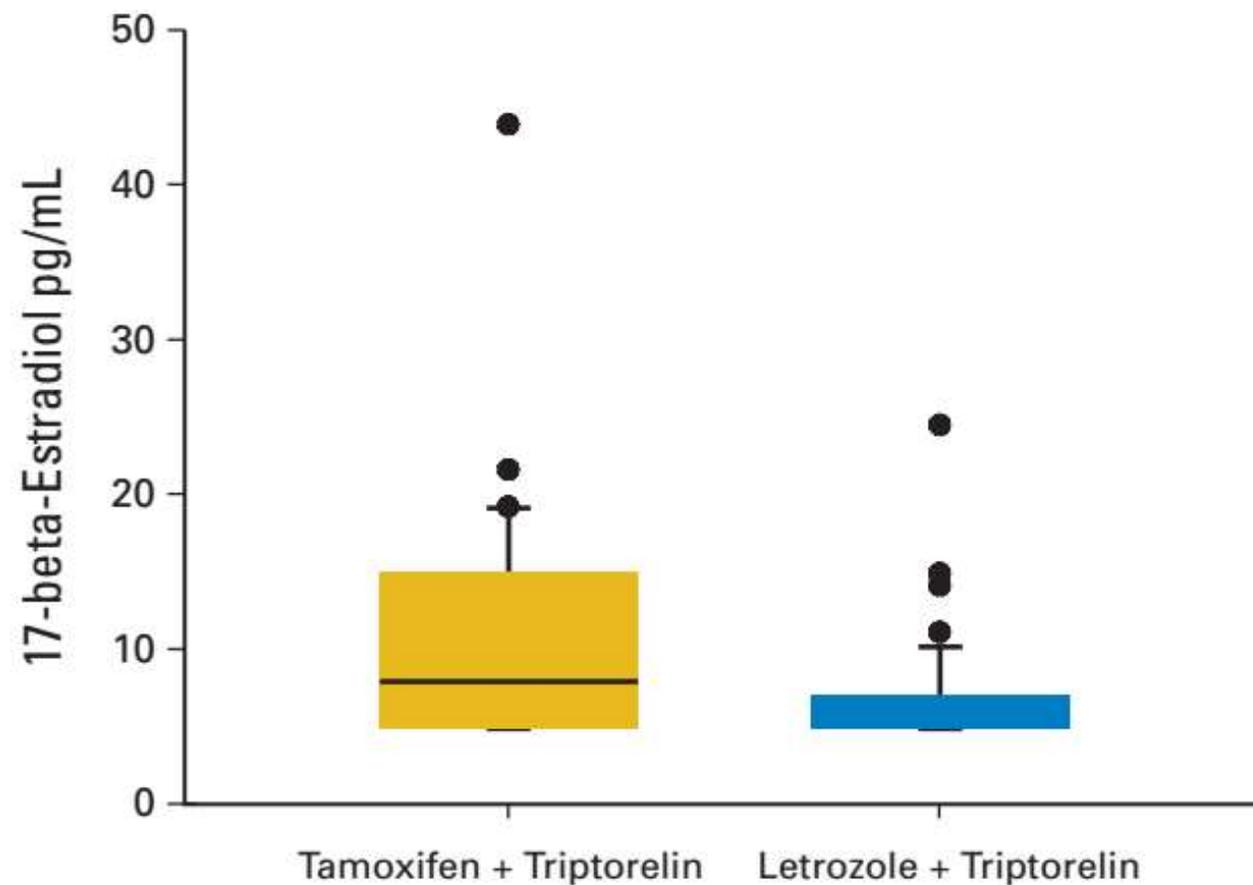
# HOBQE1 - prodotti

- Plenaria AIOM 2011
- Pubblicazioni
  - JCO 2008: hormonal effects in premenopausal patients
  - JCO 2009: hormonal effects in postmenopausal patients
  - Annals of Oncology 2012: primary analysis on bone health
  - EBCTCG
    - 2 metanalisi (Lancet Oncology 2016)
    - 1 lavoro prognosi (NEJM 2017)



## Endocrine Effects of Adjuvant Letrozole + Triptorelin Compared With Tamoxifen + Triptorelin in Premenopausal Patients With Early Breast Cancer

*Emanuela Rossi, Alessandro Morabito, Ermelinda De Maio, Francesca Di Rella, Giuseppe Esposito, Adriano Gravina, Vincenzo Labonia, Gabriella Landi, Francesco Nuzzo, Carmen Pacilio, Maria Carmela Piccirillo, Giuseppe D'Aiuto, Massimiliano D'Aiuto, Massimo Rinaldo, Gerardo Botti, Ciro Gallo, Francesco Perrone, and Andrea de Matteis*

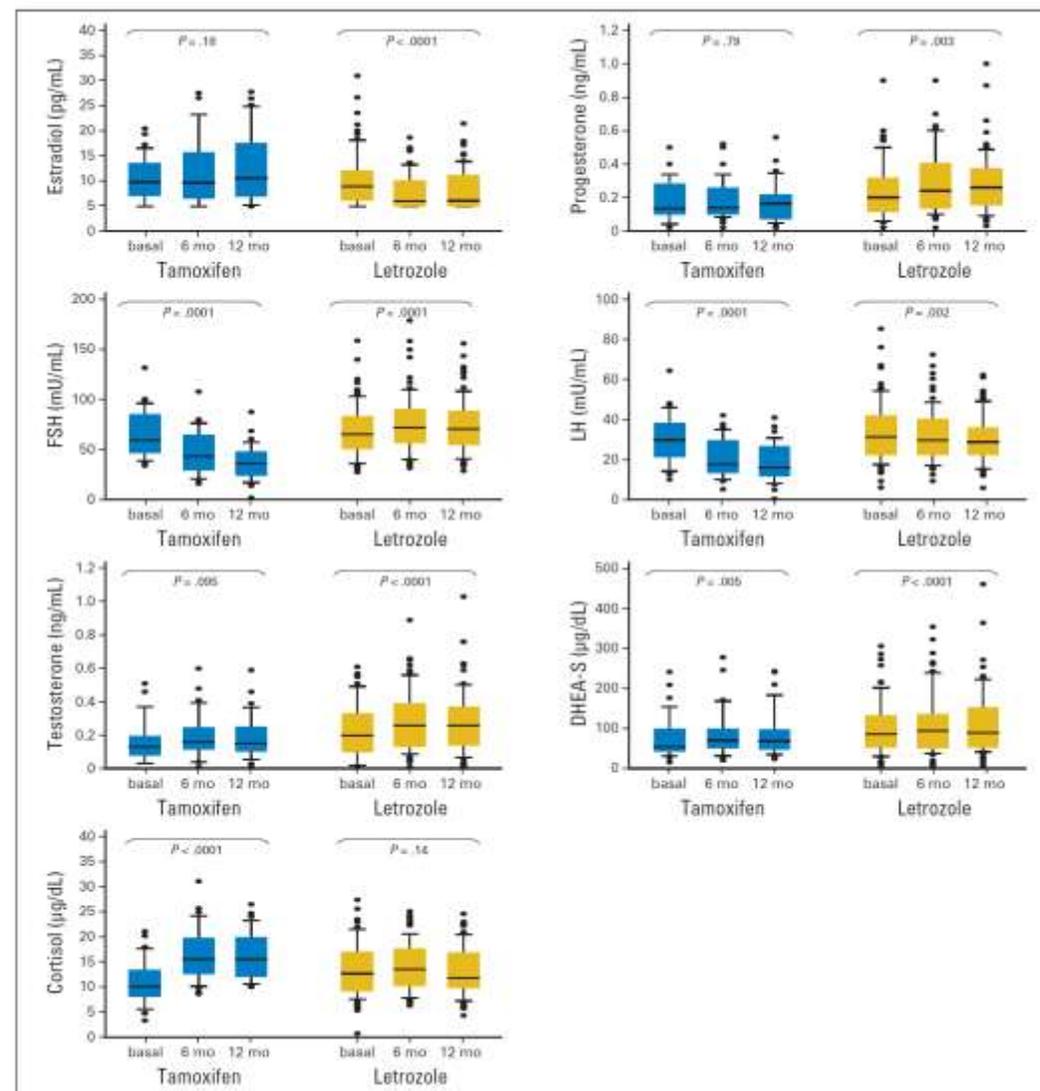


## Endocrine Effects of Adjuvant Letrozole Compared With Tamoxifen in Hormone-Responsive Postmenopausal Patients With Early Breast Cancer: The HOBEO Trial

Emanuela Rossi, Alessandro Morabito, Francesca Di Rella, Giuseppe Esposito, Adriano Gravina, Vincenzo Labonia, Gabriella Landi, Francesco Nuzzo, Carmen Pacilio, Ermelinda De Maio, Massimo Di Maio, Maria Carmela Piccirillo, Gianfranco De Feo, Giuseppe D'Aiuto, Gerardo Botti, Paolo Chiodini, Ciro Gallo, Francesco Perrone, and Andrea de Matteis

### Conclusion

Adjuvant letrozole and tamoxifen result in significantly distinct endocrine effects. Such differences can explain the higher efficacy of letrozole as compared with tamoxifen.



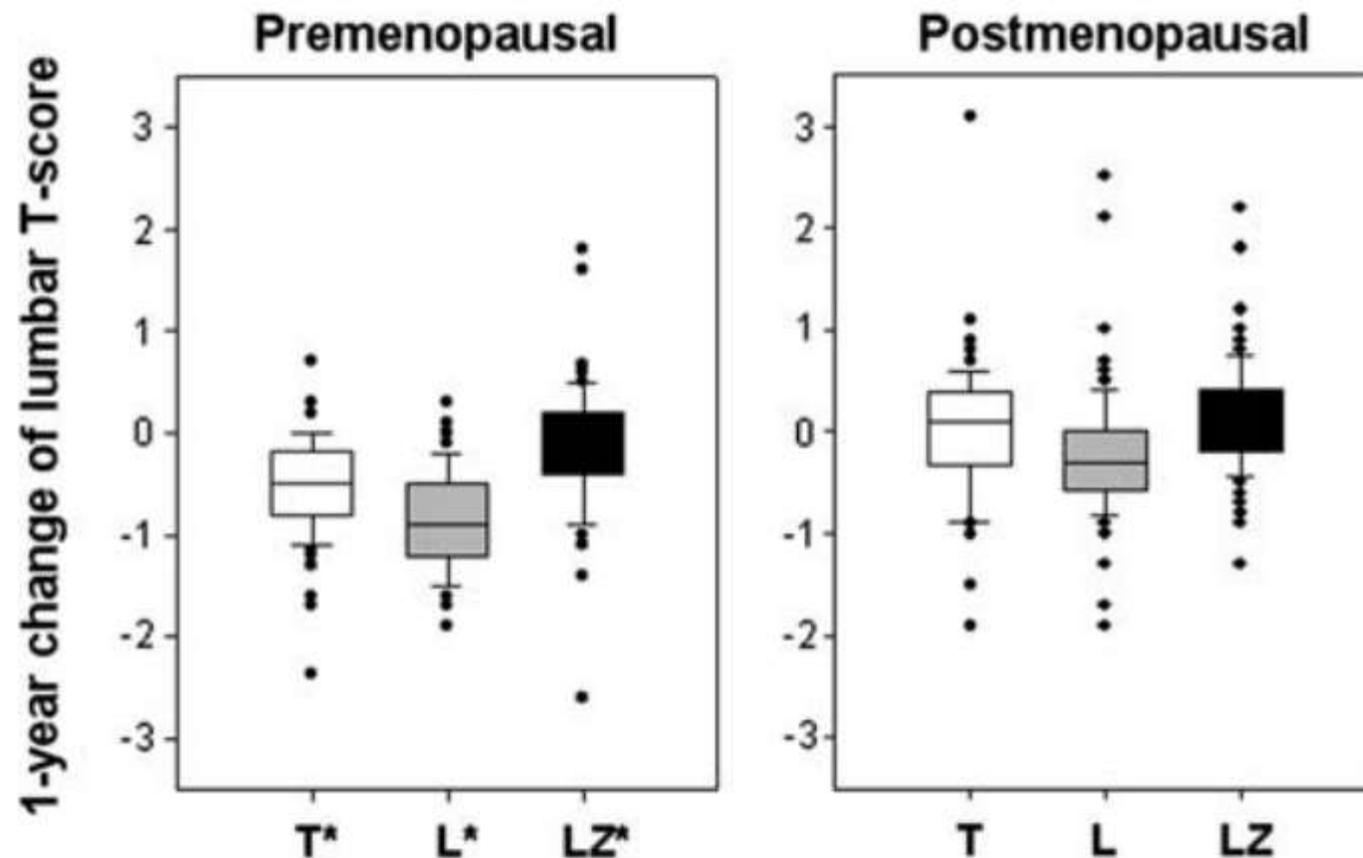
## **Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: the randomized phase 3 HOBEO study**

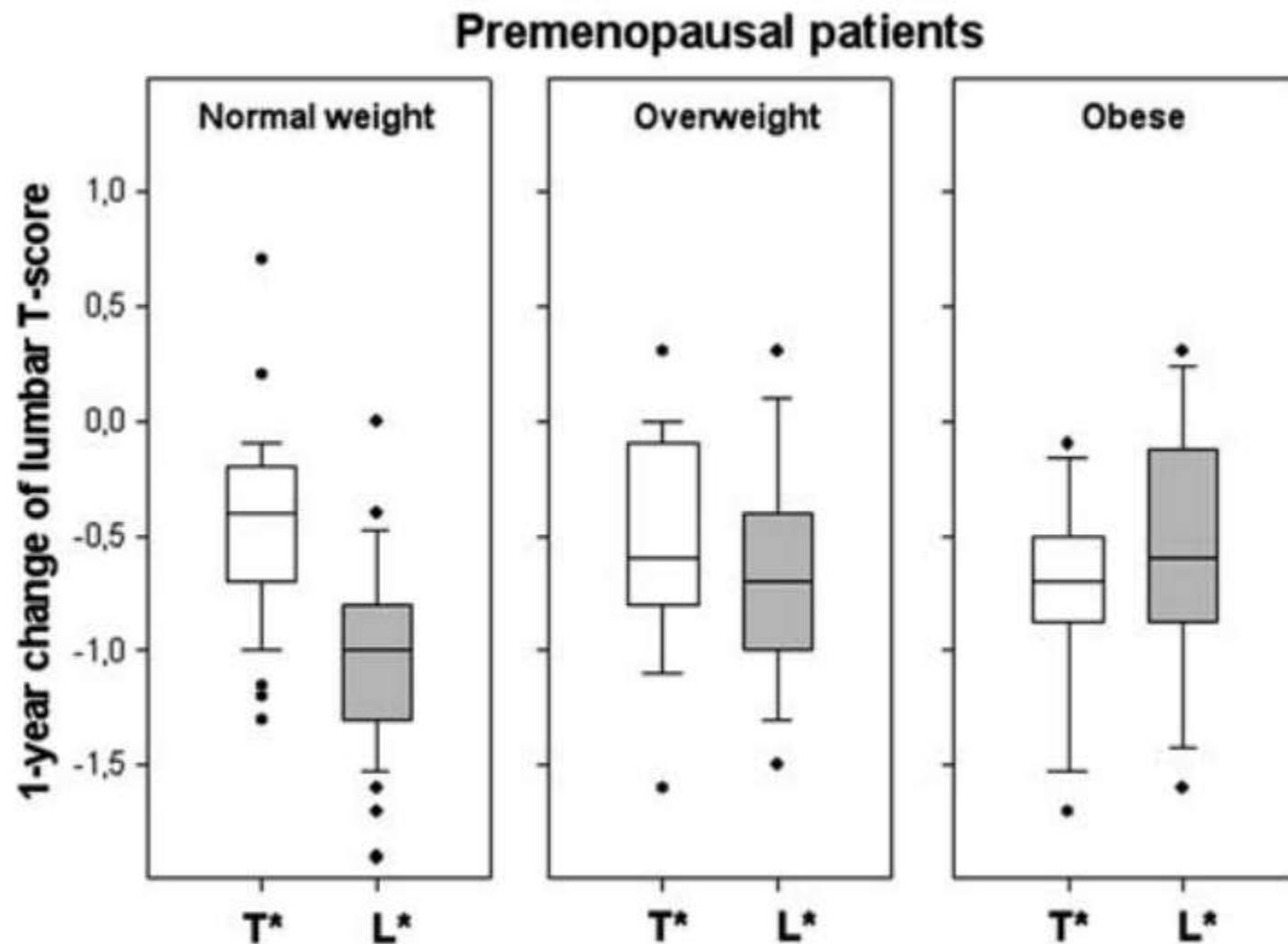
F. Nuzzo<sup>1</sup>, C. Gallo<sup>2</sup>, S. Lastoria<sup>3</sup>, M. Di Maio<sup>4</sup>, M. C. Piccirillo<sup>4</sup>, A. Gravina<sup>1</sup>, G. Landi<sup>1</sup>, E. Rossi<sup>1,5</sup>, C. Pacilio<sup>1</sup>, V. Labonia<sup>1</sup>, F. Di Rella<sup>1</sup>, A. Bartiromo<sup>3</sup>, G. Buonfanti<sup>1</sup>, G. De Feo<sup>4</sup>, G. Esposito<sup>6</sup>, R. D'Aniello<sup>7</sup>, P. Maiolino<sup>7</sup>, S. Signoriello<sup>2</sup>, E. De Maio<sup>4,†</sup>, V. Tinessa<sup>8</sup>, G. Colantuoni<sup>5</sup>, M. De Laurentiis<sup>1</sup>, M. D'Aiuto<sup>9</sup>, M. Di Bonito<sup>10</sup>, G. Botti<sup>10</sup>, P. Giordano<sup>4</sup>, G. Daniele<sup>4</sup>, A. Morabito<sup>4</sup>, N. Normanno<sup>11</sup>, A. de Matteis<sup>1</sup> & F. Perrone<sup>4\*</sup>

**Conclusions:** In the HOBEO (HOrmonal BOne Effects) trial, the positive effect of zoledronic acid on BMD largely counteracts damage produced by letrozole as compared with tamoxifen. Letrozole effect is lower among overweight/obese premenopausal patients.



**Figure 1.** Distribution of 1-year change from baseline of lumbar T-score by treatment arm in the whole study population (top) and according to menopausal status (bottom). Asterisk indicates plus triptorelin. Horizontal lines of box plots represent 5th, 25th, 50th, 75th, 95th percentile of the distribution; points outside horizontal lines show outlier values. L, letrozole; LZ, letrozole + zoledronic acid; T = tamoxifen.





**Figure 2.** Distribution of 1-year change from baseline of lumbar T-score by baseline body mass index and treatment arm, among premenopausal (top) and postmenopausal patients (bottom). Asterisk indicates plus triptorelin. Horizontal lines of box plots represent 5th, 25th, 50th, 75th, 95th percentile of the distribution; points outside horizontal lines show outlier values. L, letrozole; LZ, letrozole + zoledronic acid; T, tamoxifen.

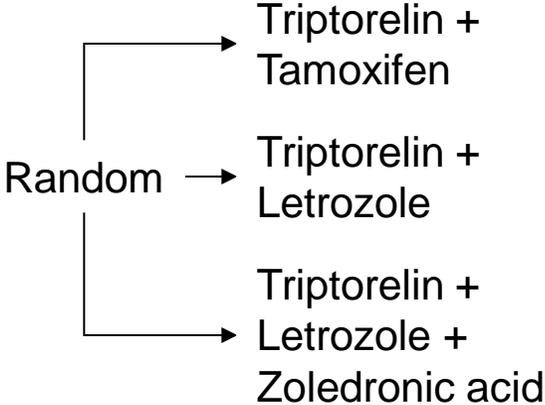
## Quindi, nel 2009

- In premenopausa (con triptorelina)
  - Letrozolo sopprime estrogeni più di tamoxifen (come atteso)
  - Gli effetti tossici sull'osso sembrano correlati al BMI (più evidenti nelle pazienti normopeso)
  - L'acido zoledronico li annulla completamente
- Dati incerti sulla efficacia di acido zoledronico
- Nessuno studio in corso nel mondo con letrozolo in premenopausa
  - SOFT&TEXT in corso con exemestane (positivi)
  - ABCSG-12 in corso con anastrozolo (aveva già dato un risultato negativo)

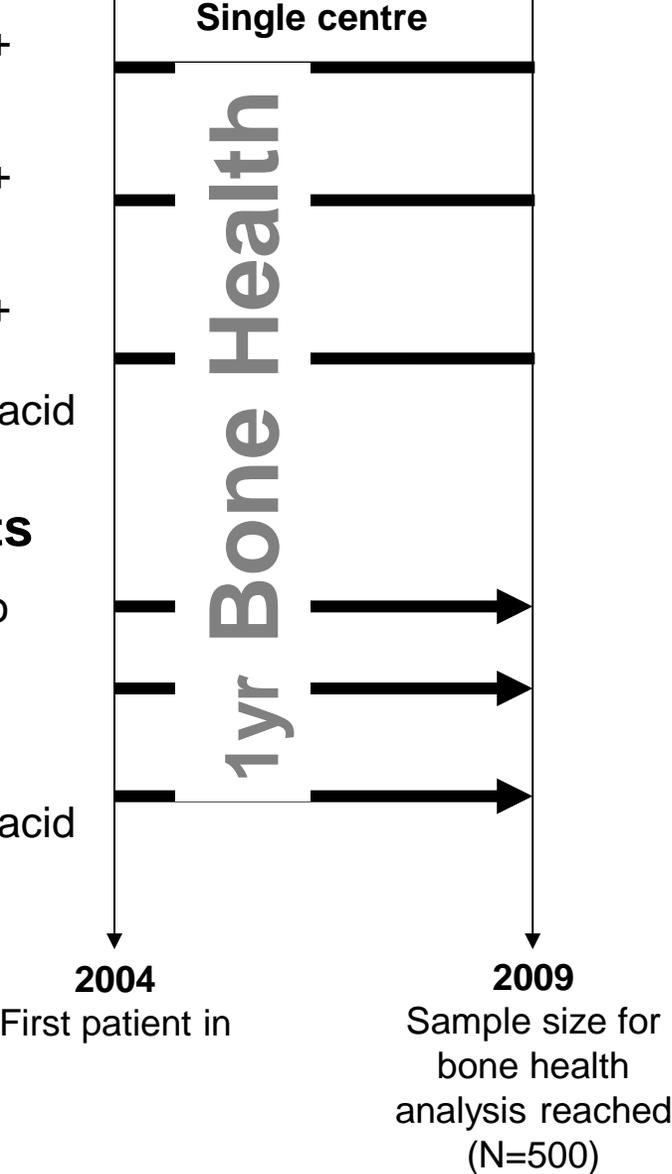
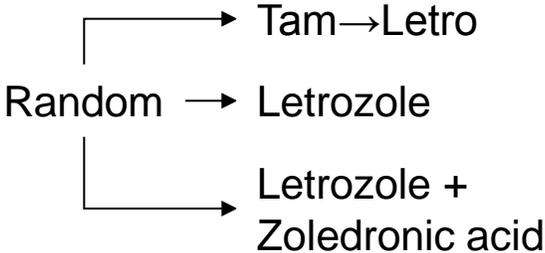


# HOBQE 1

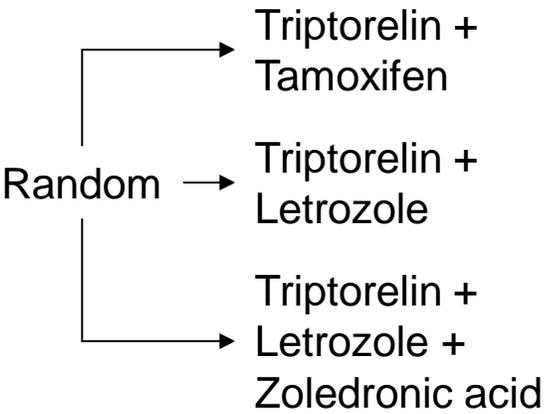
## Premenopausal patients



## Postmenopausal patients



**Premenopausal patients**



**HOB OE 1**

**HOB OE 2**

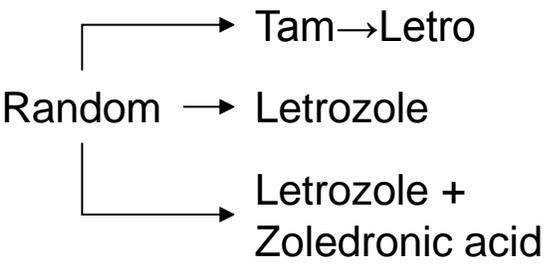
amendment #7 - September 2009

Single centre

Multicentre

1yr Bone Health

**Postmenopausal patients**



2004

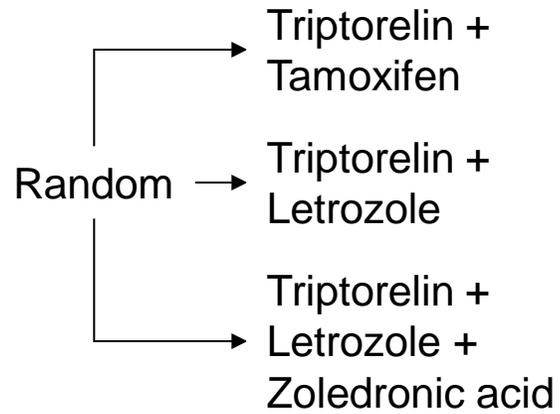
First patient in

2009

Sample size for bone health analysis reached (N=500)



# Premenopausal patients



## HOBEO 1

## HOBEO 2

amendment #7 - September 2009

Single centre

Multicentre

1yr Bone Health

DFS

# Postmenopausal patients



2004  
First patient in

2009  
Sample size for  
bone health  
analysis reached  
(N=500)

2015  
Sample size for  
DFS analysis in  
premenopausal  
reached (N=1065)





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Original Research

# Adjuvant zoledronic acid and letrozole plus ovarian function suppression in premenopausal breast cancer: HOBEO phase 3 randomised trial



Francesco Perrone <sup>a,\*</sup>, Michelino De Laurentiis <sup>b</sup>, Sabino De Placido <sup>c</sup>, Michele Orditura <sup>d</sup>, Saverio Cinieri <sup>c</sup>, Ferdinando Riccardi <sup>f</sup>, Angela Stefania Ribocco <sup>e</sup>, Carlo Putzu <sup>h</sup>, Lucia Del Mastro <sup>i,j</sup>, Emanuela Rossi <sup>k</sup>, Vincenza Tinessa <sup>l</sup>, Anna Maria Mosconi <sup>m</sup>, Francesco Nuzzo <sup>b</sup>, Francesca Di Rella <sup>b</sup>, Adriano Gravina <sup>b</sup>, Giovanni Iodice <sup>b</sup>, Gabriella Landi <sup>b</sup>, Carmen Pacilio <sup>b</sup>, Valeria Forestieri <sup>c</sup>, Rossella Lauria <sup>c</sup>, Agnese Fabbri <sup>n</sup>, Toni Ibrahim <sup>o</sup>, Ermelinda De Maio <sup>p</sup>, Sandro Barni <sup>q</sup>, Stefania Gori <sup>r</sup>, Vittorio Simeon <sup>s</sup>, Laura Arenare <sup>a</sup>, Gennaro Daniele <sup>a</sup>, Maria Carmela Piccirillo <sup>a</sup>, Nicola Normanno <sup>l</sup>, Andrea de Matteis <sup>b</sup>, Ciro Gallo <sup>s</sup>



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Editorial

# New evidence and hope for young patients with breast cancer



Michael Gnant  
*Medical University of Vienna, Vienna, Austria*

## The HOBEO-2 multicenter randomized phase 3 trial in premenopausal patients with hormone-receptor positive early breast cancer comparing Triptorelin plus either Tamoxifen or Letrozole or Letrozole + Zoledronic acid.

Francesco Perrone, Michelino De Laurentiis, Sabino De Placido, Anna Diana, Palma Fedele, Carmela Mocerino, Francesca Martella, Carlo Putzu, Lucia Del Mastro, Emanuela Rossi, Vincenza Tinessa, Jennifer Foglietta, Francesca Di Rella, Adriano Gravina, Giovanni Iodice, Carmen Pacilio, Valeria Forestieri, Laura Arenare, Gennaro Daniele, Andrea de Matteis, Ciro Gallo



# Aim and design

- To compare Letrozole and Zoledronic acid + Letrozole to Tamoxifen (always associated with Triptorelin) in terms of disease-free survival in premenopausal patients with early breast cancer

**RANDOM**  
**1:1:1**

- **T - Tamoxifen** 20 mg/day for 5 yrs + **Triptorelin** 3.75 mg, q4 wks, 5 yrs
- **L - Letrozole** 2.5 mg/day for 5 yrs + **Triptorelin**
- **ZL - Zoledronic acid** 4 mg i.v. every 6 months for 5 yrs + **Letrozole + Triptorelin**



# Sample size calculation

- Primary endpoint: disease-free survival – DFS
  - Defined as the occurrence of locoregional or distant recurrence or contralateral invasive breast cancer or ductal carcinoma in situ or second malignancy other than breast or death for any cause
- To recognize a hazard ratio (HR) of 0.60
  - 3-arm log-rank test
  - 80% power, two-tailed alpha 0.05
  - 166 events required and 1050 patients planned (350 per arm)
- April 2018: analysis plan changed from event-driven to time-driven (at 5yrs median follow-up)
  - EBCTCG request and IDMC suggestion, with blinded data



# Statistical analysis

- Analysis based on intention-to-treat
- Null hypothesis of three-arm equivalence first tested with unstratified log-rank test
- If the global test was statistically significant at the 0.05 level
  - pairwise comparisons allowed using the Bonferroni-Holm adjustment
  - increasing alpha levels (0.0167, 0.025, 0.05) to preserve the family-wise alpha error of 0.05



# Selection of patients

- Major inclusion criteria
  - $\geq 18$  years old
  - histologically confirmed breast cancer
  - ER+ or PgR+
  - last menstrual cycle within 12 months prior to the randomization date
  - previous adjuvant chemotherapy and concomitant adjuvant trastuzumab were allowed
  - written informed consent
- Major exclusion criteria
  - evidence of active bone fracture
  - previously received tamoxifen or an aromatase inhibitor
  - abnormal kidney and liver function
  - need of or ongoing invasive dental therapy



## Study conduct

- Sponsor: National Cancer Institute, Naples, Italy
- Supporters: Novartis (drugs supply), AIRC (funding 2004-2007)
- Enrolment: March 2004 - August 2015
- Centres: 16 Italian institutions
- Data lock: June 30, 2018 (64 months median follow-up)

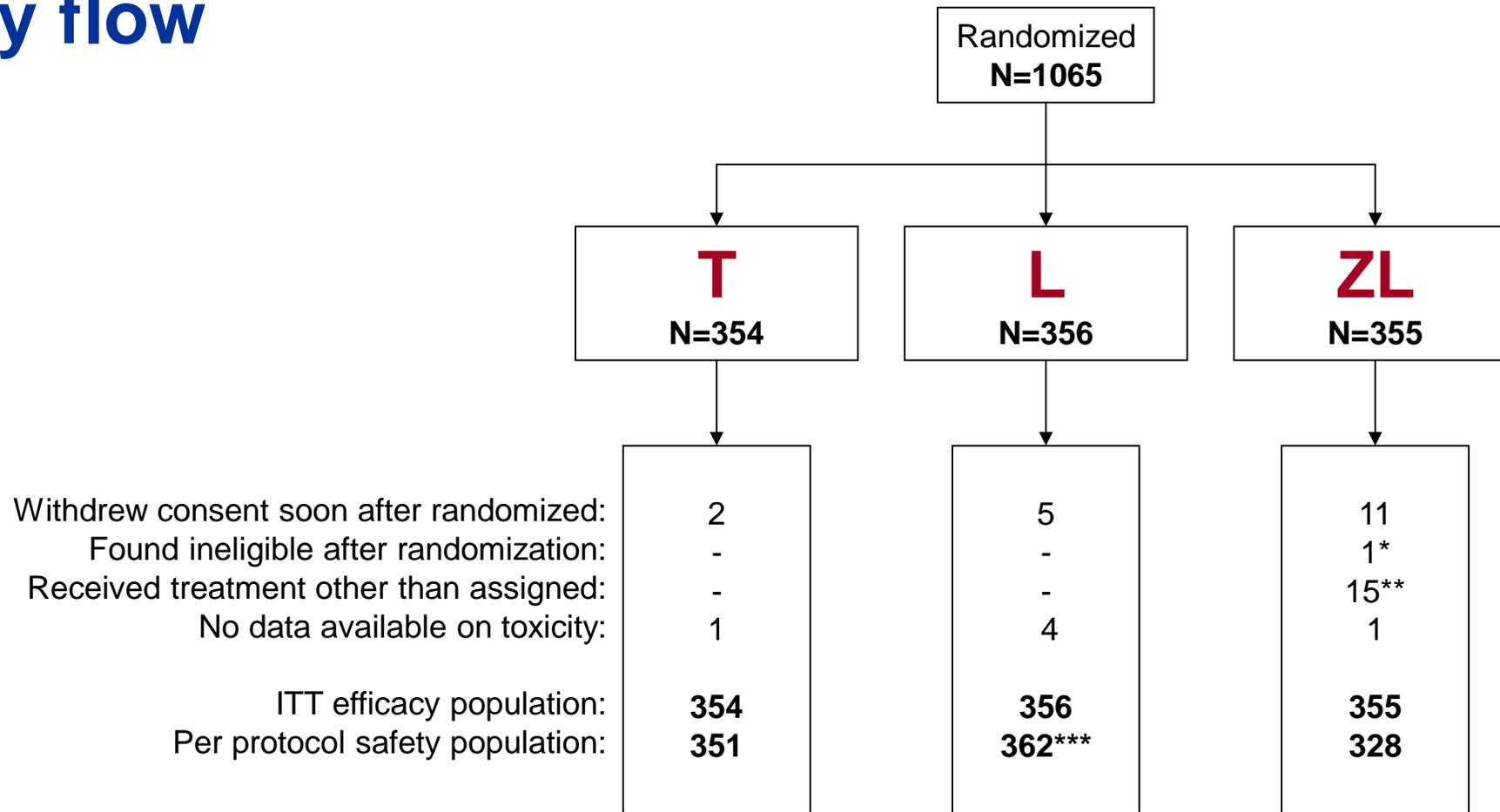
**Clinicaltrials.gov: NCT00412022**



<b>Centro</b>	<b>Codice</b>	<b>Tamoxifen + Triptorelin</b>		<b>Letrozole + Triptorelin</b>		<b>Zoledronic acid + Letrozole + Triptorelin</b>		<b>Totali</b>
		<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	
Istituto Nazionale Tumori, Napoli	93	183	33,5	182	33,3	181	33,2	<b>546</b>
Oncologia Medica - Federico II , Napoli	47	57	32,8	59	33,9	58	33,3	<b>174</b>
Oncologia Medica Università "Luigi Vanvitelli"	171	22	34,9	20	31,7	21	33,3	<b>63</b>
U.O.C. Oncologia Medica - Ospedale Perrino, Brindisi	344	21	35,6	18	30,5	20	33,9	<b>59</b>
Ospedlae Cardarelli, Napoli	63	19	33,3	19	33,3	19	33,3	<b>57</b>
Ospedale S.Maria Annunziata Bagno a Ripoli - Firenze	431	13	35,1	13	35,1	11	29,7	<b>37</b>
Cattedra di Oncologia Medica Università di Sassari	19	9	29,0	12	38,7	10	32,3	<b>31</b>
IST Genova	547	9	31,0	10	34,5	10	34,5	<b>29</b>
Oncologia Medica - S. Giuseppe Moscati , Avellino	68	6	28,6	7	33,3	8	38,1	<b>21</b>
Oncologia Medica –Rummo, Benevento	6	4	33,3	3	25,0	5	41,7	<b>12</b>
Oncologia Medica S. Maria della Misericordia Perugia	40	4	33,3	3	25,0	5	41,7	<b>12</b>
Oncologia - Ospedale Belcolle, Viterbo	315	2	22,2	4	44,4	3	33,3	<b>9</b>
IRST di Meldola	222	3	42,9	1	14,3	3	42,9	<b>7</b>
Oncologia - Azienda UsI Toscana Nord Ovest, Livorno	179	2	50,0	2	50,0	0	0,0	<b>4</b>
Oncologia Medica - Treviglio (BG)	148	0	0,0	2	100,0	0	0,0	<b>2</b>
Oncologia Medica, S.Cuore Don Calabria , Negrar (VR)	380	0	0,0	1	50,0	1	50,0	<b>2</b>
<b>Totale</b>		<b>354</b>		<b>356</b>		<b>355</b>		<b>1065</b>



# Study flow



\* Previous Hodgkin disease

\*\* Received letrozole+triptorelin only

\*\*\* Including patients receiving letrozole+triptorelin only in the Zoledronic acid arm



# Baseline characteristics (1)

	<b>T</b> (N=354)	<b>L</b> (N=356)	<b>ZL</b> (N=355)
<b>Age at randomisation - no. (%)</b>			
median	44.7	44.9	45.2
(interquartile range)	(41.3-48.0)	(40.8-48.0)	(40.9-48.1)
≤ 40	65(18.4)	73(20.5)	78(22.0)
>40 - ≤50	245(69.2)	241(67.7)	240(67.6)
>50	44(12.4)	42(11.8)	37(10.4)
<b>Body Mass Index – no. (%)</b>			
Median	24.8	24.8	22.7
(interquartile range)	(22.1-27.8)	(22.1-27.4)	(22.7-28.0)
≤25	168(47.5)	165(46.3)	154(43.4)
>25 - ≤30	94(26.6)	102(28.7)	109(30.7)
>30	50(14.1)	47(13.2)	47(13.2)
Missing	42(11.9)	42(11.8)	45(12.7)
<b>Previous chemotherapy – no. (%)</b>			
No	132(37.3)	133(37.4)	133(37.5)
Yes	222(62.7)	223(62.6)	222(62.5)



## Baseline characteristics (2)

	T	L	ZL
	(N=354)	(N=356)	(N=355)
<b>Pathologic Tumor category – no. (%)</b>			
pT1	243(68.6)	239(67.1)	239(67.3)
pT2	92(26.0)	99(27.8)	95(26.8)
pT3	8(2.3)	10(2.8)	10(2.8)
pT4	4(1.1)	3(0.8)	2(0.6)
pTx or unknown	7(2.0)	5(1.4)	9(2.5)
<b>Pathologic nodal status – no. (%)</b>			
pN0	193(54.5)	196(55.1)	194(54.6)
pN1	111(31.4)	109(30.6)	110(31.0)
pN2	34(9.6)	38(10.7)	35(9.9)
pN3	16(4.5)	13(3.7)	16(4.5)
<b>Grading – no. (%)</b>			
G1	36(10.2)	33(9.3)	26(7.3)
G2	195(55.1)	177(49.7)	204(57.5)
G3	112(31.6)	128(36.0)	117(33.0)
Missing	11(3.1)	14(3.9)	8(2.3)



# Baseline characteristics (3)

	<b>T</b> (N=354)	<b>L</b> (N=356)	<b>ZL</b> (N=355)
<b>PgR status – no. (%)</b>			
positive	344 (97.2)	341 (95.8)	346 (97.5)
negative	9 (2.5)	10 (2.8)	8 (2.3)
unknown	1 (0.3)	5 (1.4)	1 (0.3)
<b>HER-2 status – no. (%)</b>			
positive	56 (15.8)	42 (11.8)	47 (13.2)
negative	295 (83.3)	313 (87.9)	306 (86.2)
unknown	3 (0.8)	1 (0.3)	2 (0.6)



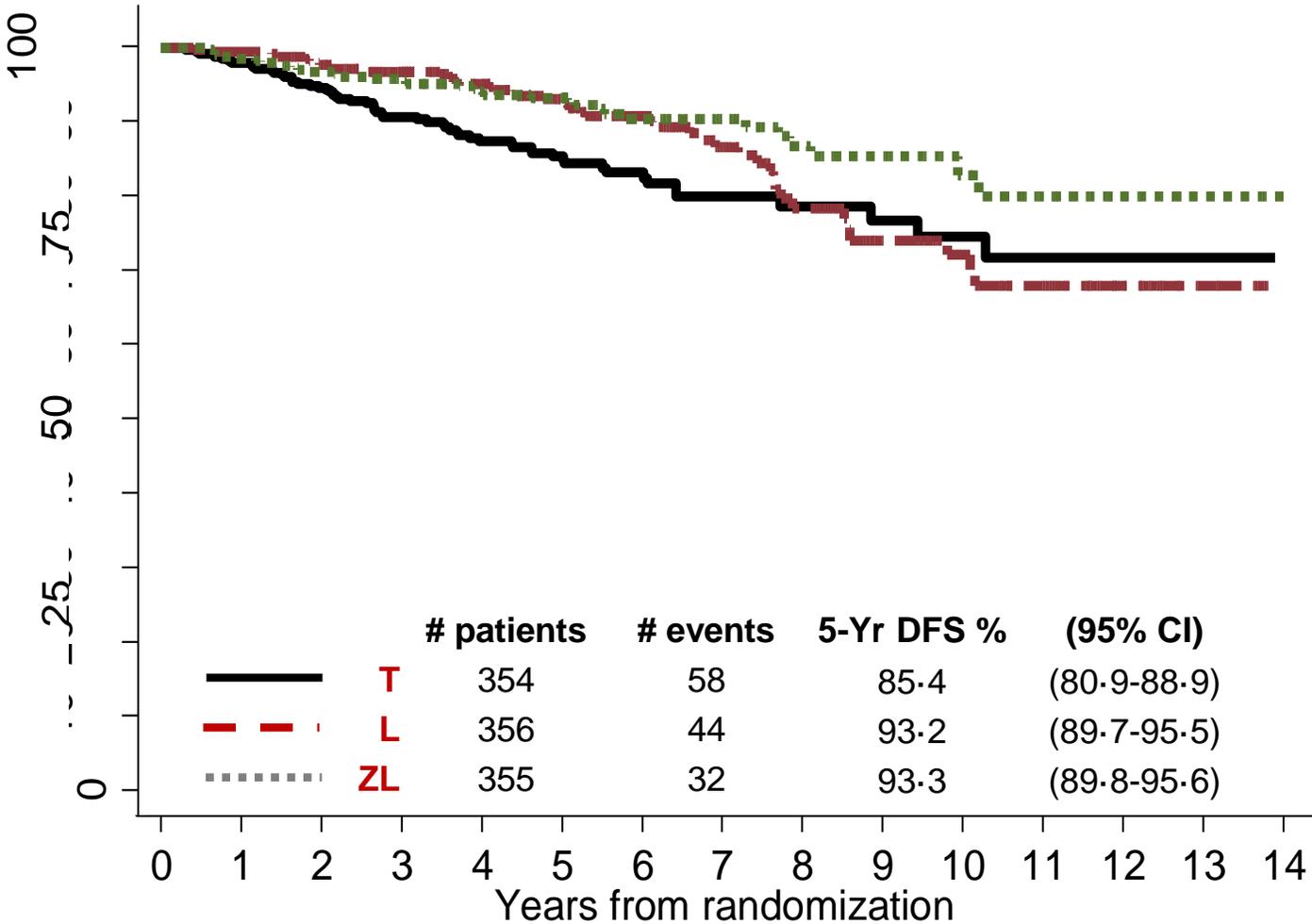
# Events

	<b>T</b> <b>(N=354)</b>	<b>L</b> <b>(N=356)</b>	<b>ZL</b> <b>(N=355)</b>
<b>DFS events</b> – no. (%)	58 (16.4)	44 (12.4)	32 (9.0)
Component of DFS event* – no. (%)			
Locoregional	11 (3.1)	13 (3.7)	4 (1.1)
Distant	37 (10.5)	27 (7.6)	19 (5.4)
Not including bone	20 (5.6)	17 (3.4)	6 (1.7)
Including bone	17 (4.8)	11 (3.1)	13 (3.7)
Contralateral breast cancer	6 (1.7)	7 (2.0)	3 (0.8)
Second non-breast cancer	7 (2.0)	4 (1.1)	6 (1.7)
Death without cancer	1 (0.3)	0 (0.0)	0 (0.0)
<b>Deaths</b> – no. (%)	17 (4.8)	11 (3.1)	8 (2.3)

\* associations are possible



# DFS

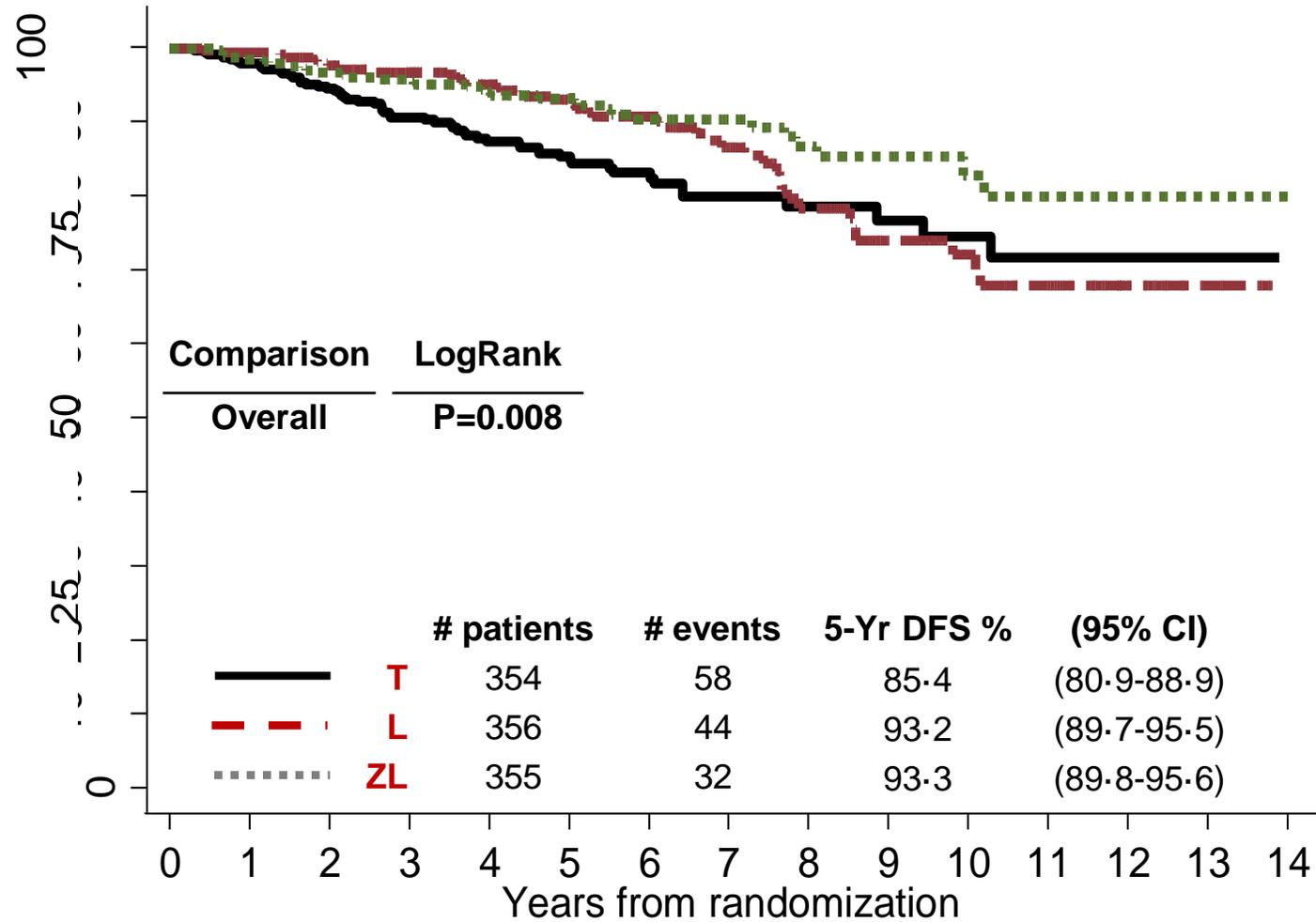


Number at risk

T	354	346	326	288	226	189	113	73	56	39	27	18	12	4	0
L	356	348	340	311	259	218	132	89	60	47	35	26	15	4	0
ZL	355	333	323	298	252	210	131	90	65	43	31	25	14	5	1



# DFS

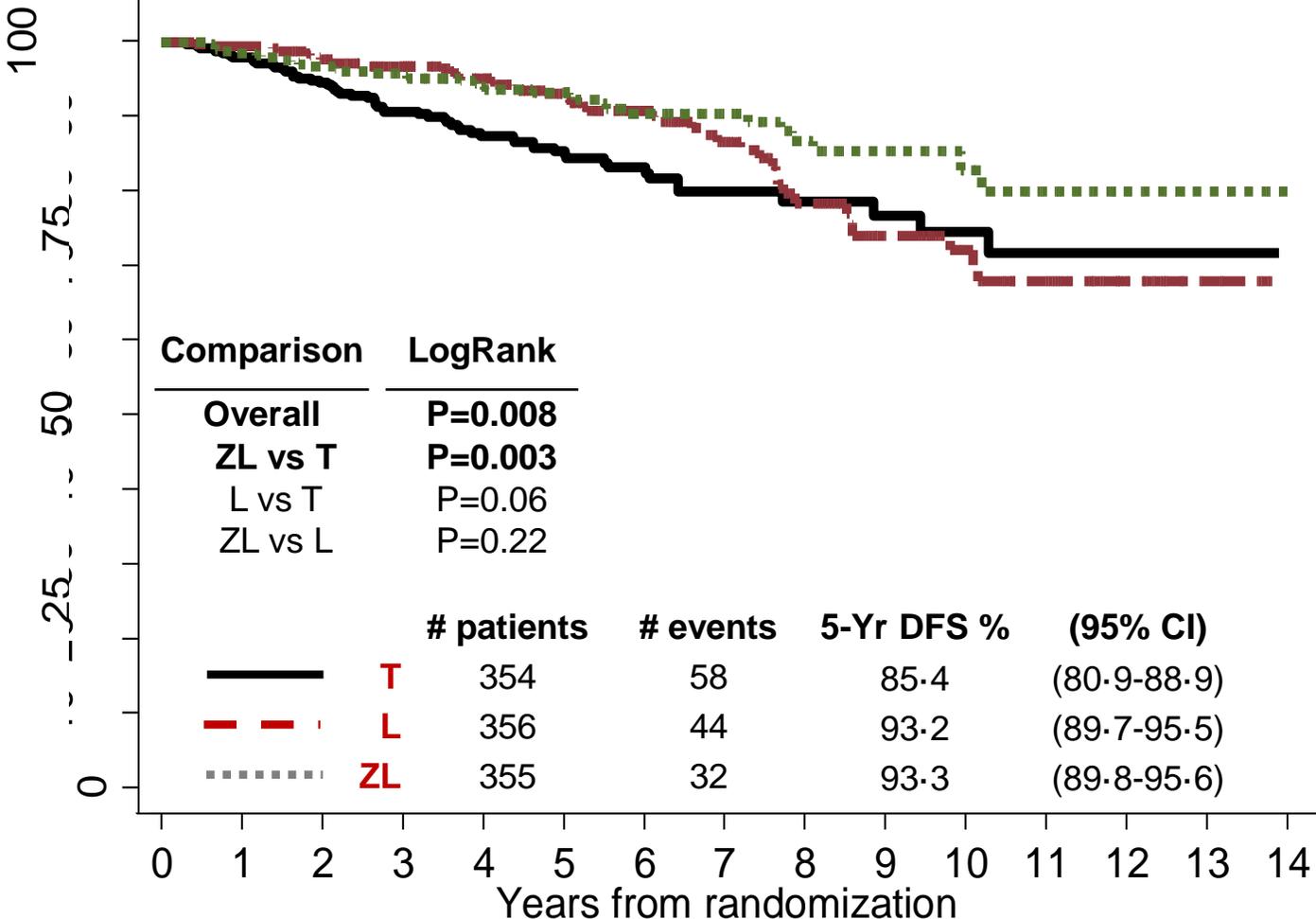


Number at risk

T	354	346	326	288	226	189	113	73	56	39	27	18	12	4	0
L	356	348	340	311	259	218	132	89	60	47	35	26	15	4	0
ZL	355	333	323	298	252	210	131	90	65	43	31	25	14	5	1



# DFS

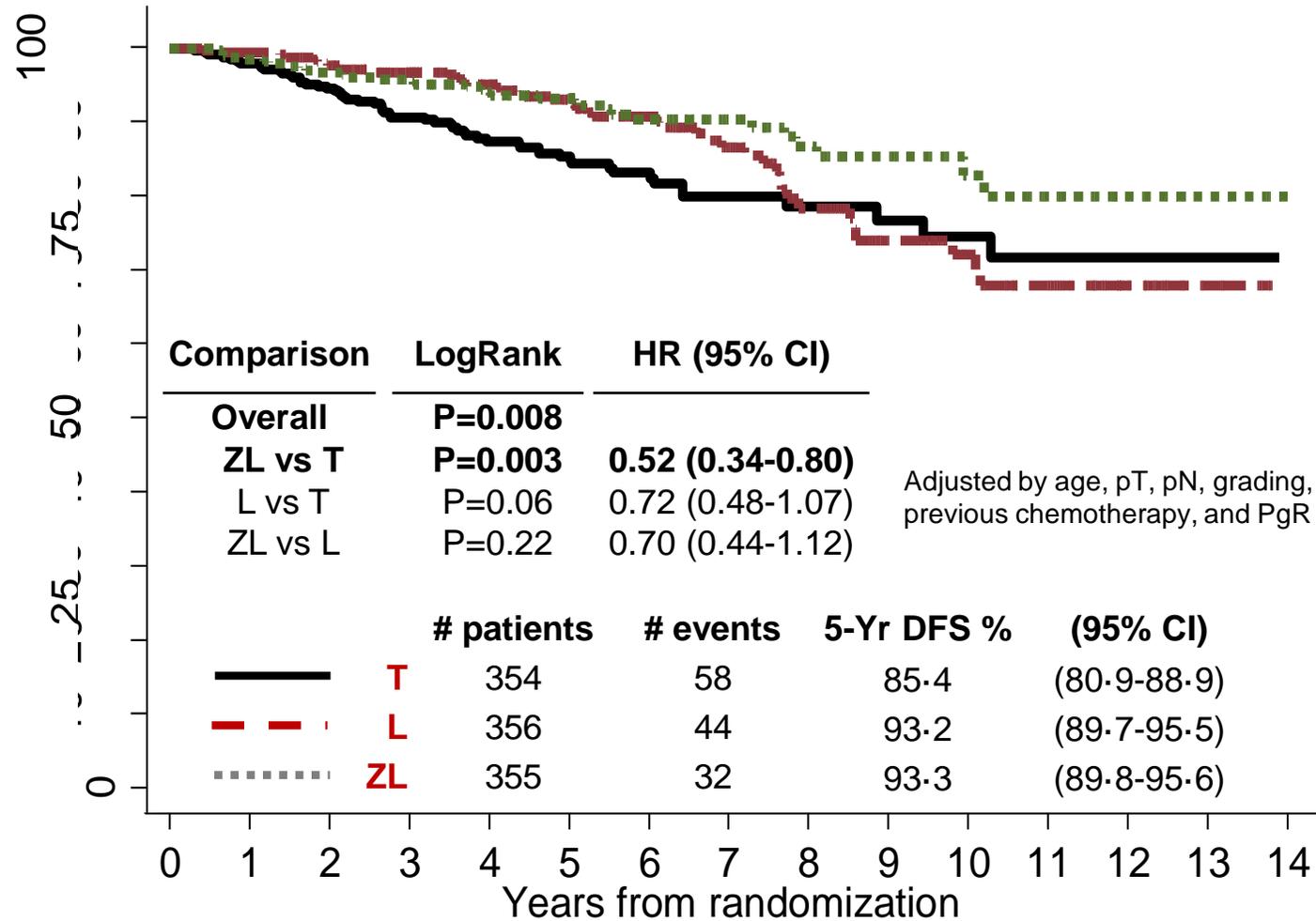


Number at risk

T	354	346	326	288	226	189	113	73	56	39	27	18	12	4	0
L	356	348	340	311	259	218	132	89	60	47	35	26	15	4	0
ZL	355	333	323	298	252	210	131	90	65	43	31	25	14	5	1



# DFS



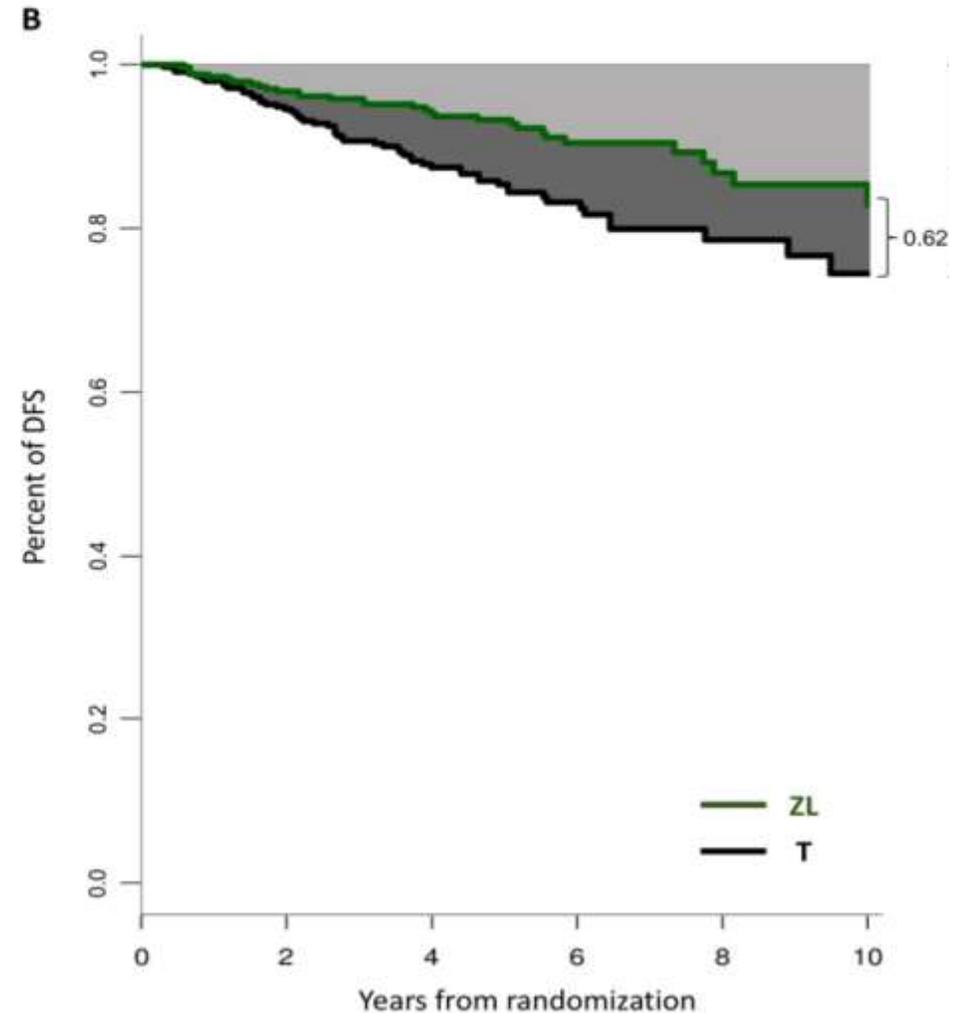
## Number at risk

T	354	346	326	288	226	189	113	73	56	39	27	18	12	4	0
L	356	348	340	311	259	218	132	89	60	47	35	26	15	4	0
ZL	355	333	323	298	252	210	131	90	65	43	31	25	14	5	1

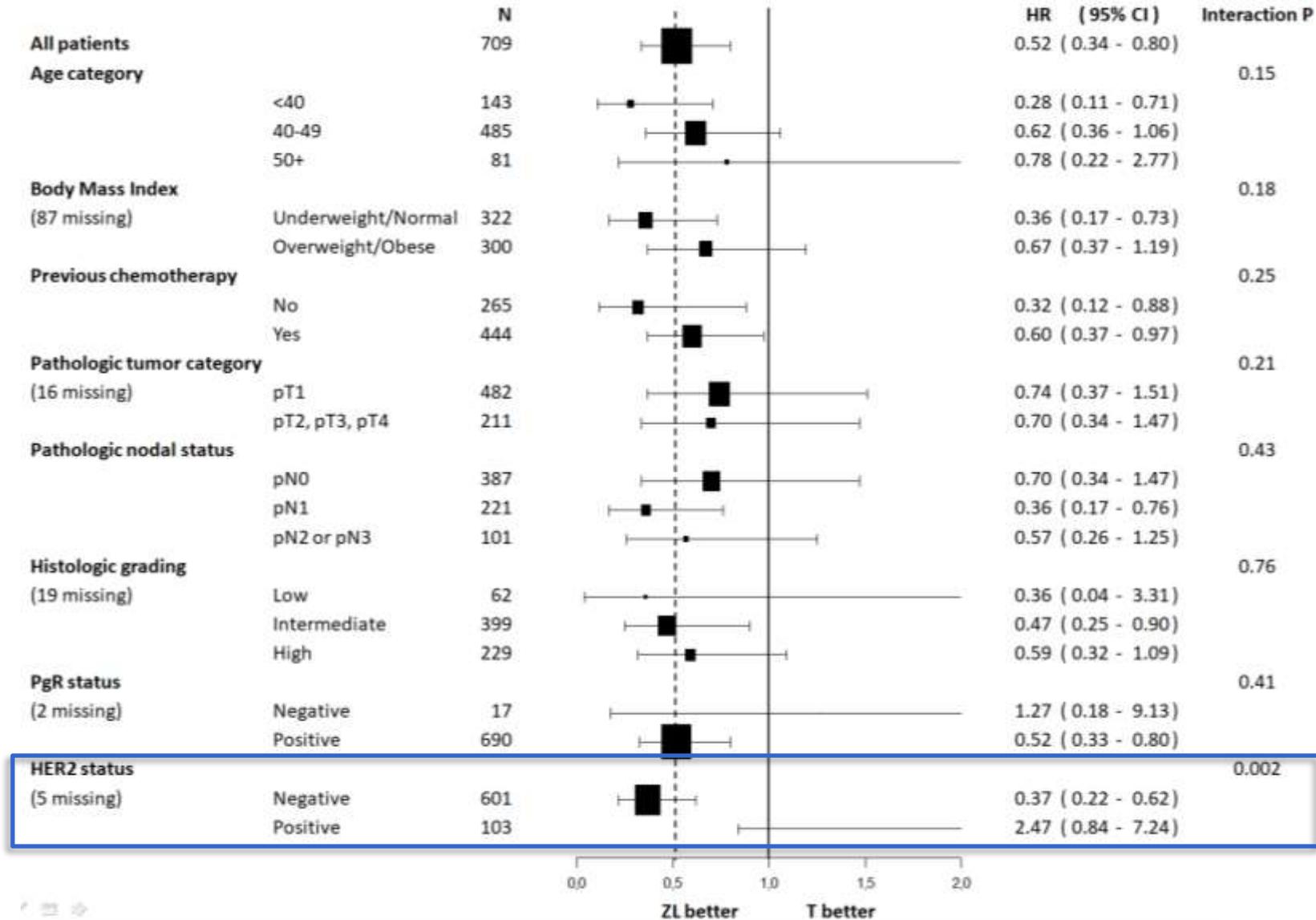


# Restricted mean DFS analysis

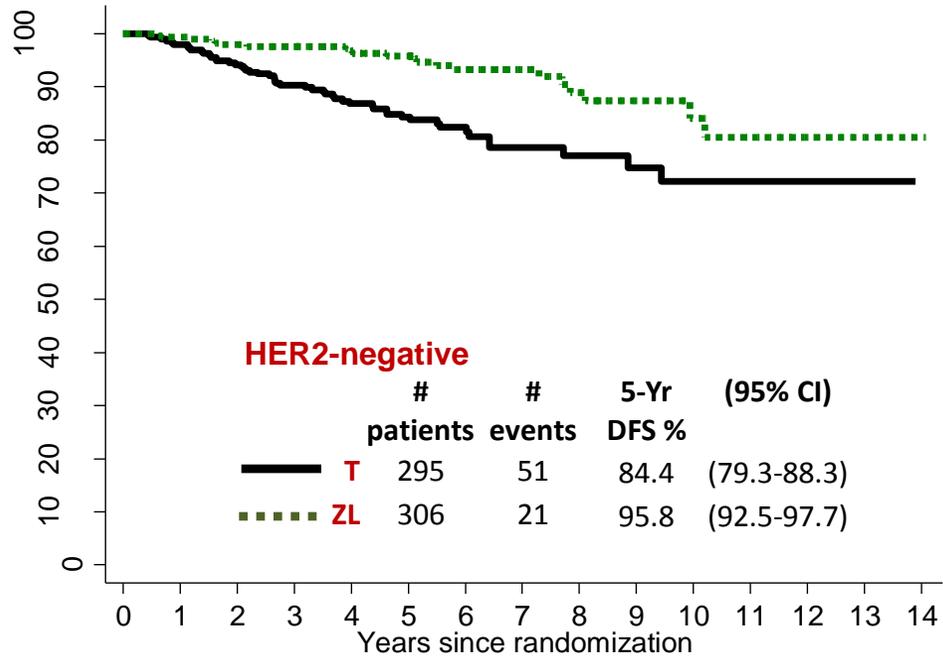
The absolute mean gain in DFS expectancy with ZL vs T estimated by the difference between RMSTs was equal to 0.6 years at 10 years; this gain was equal to 45% of the maximum achievable benefit at 10 years



# DFS Subgroup analyses: ZL vs T

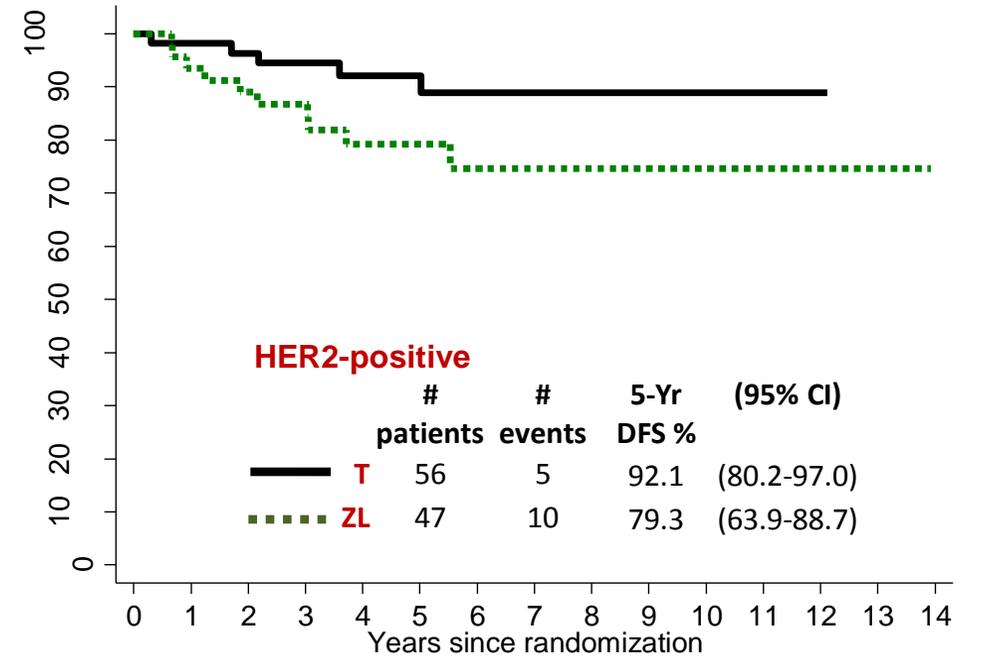


# DFS (ZL vs T) by HER2 status



Number at risk

T	295	289	270	241	188	158	96	60	46	32	21	15	10	4	0
ZL	306	289	282	260	223	187	118	81	57	35	25	19	10	4	1

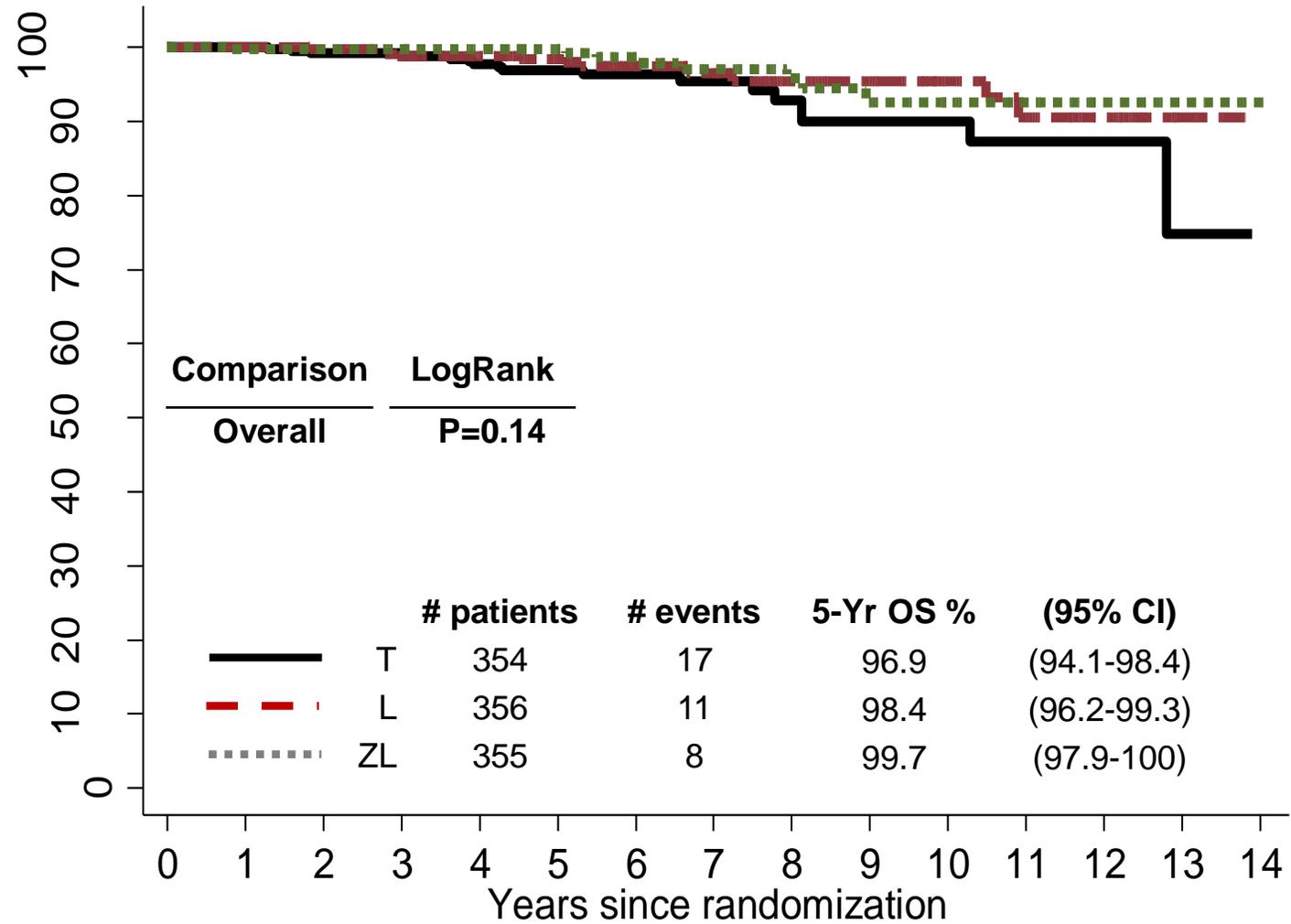


Number at risk

T	56	54	53	45	36	29	15	11	8	5	4	2	1	0	0
ZL	47	42	39	37	29	23	13	9	8	8	6	6	4	1	0



# OS



## Number at risk

T	354	353	341	312	252	214	131	90	69	50	35	25	18	5	0
L	356	350	346	314	267	228	140	99	71	58	46	34	21	6	0
ZL	355	337	333	307	265	220	142	98	73	48	34	29	15	5	1

Figure S5



# Compliance

	<b>T</b> <b>(N=354)</b>	<b>L</b> <b>(N=356)</b>	<b>ZL</b> <b>(N=355)</b>
Consent withdrawal soon after randomization	2 (0.6)	5 (1.4)	11 (3.1)
Treatment never started	0 (0.0)	0 (0.0)	<b>15 (4.2)</b>
Treatment stopped because of DFS event	<b>46 (13.0)</b>	19 (5.3)	19 (5.4)
Treatment stopped because of toxicity	20 (5.6)	24 (6.7)	<b>44 (12.4)</b>
Treatment stopped because of refusal	6 (1.7)	2 (0.6)	<b>15 (4.2)</b>
Treatment stopped lost to follow-up	5 (1.4)	5 (1.4)	1 (0.3)
Treatment stopped for other or undefined reasons	12 (3.4)	1 (0.3)	9 (2.5)
Treatment completed per protocol	174 (49.2)	211 (59.3)	164 (46.2)
Treatment ongoing	89 (25.1)	89 (25.0)	77 (21.7)



# Rate of selected adverse events

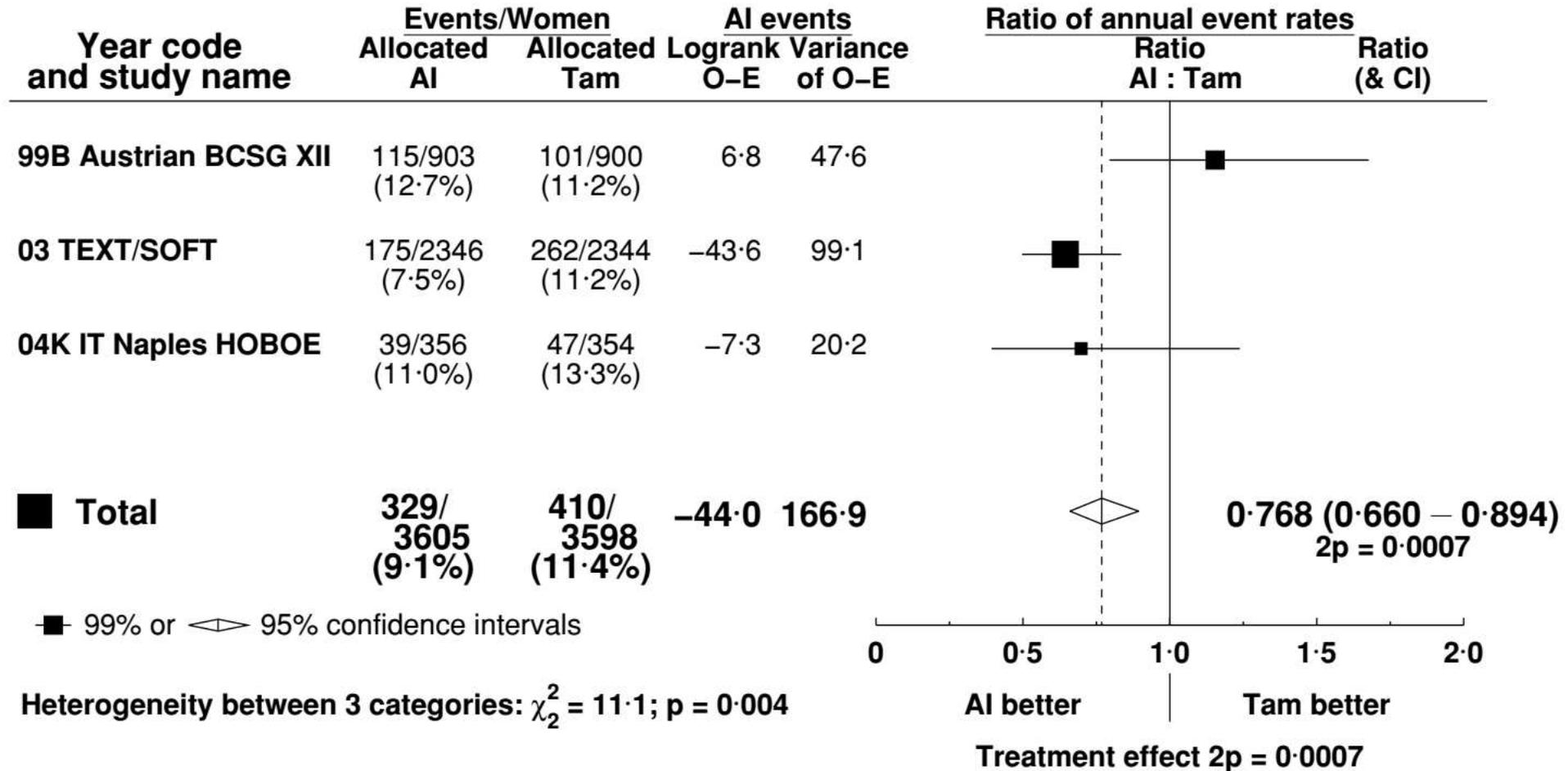
CTC term	T (N=351)		L (N=362)		ZL (N=328)		P*
	Any (≥1)	Severe (≥3)	Any (≥1)	Severe (≥3)	Any (≥1)	Severe (≥3)	
Fever	-	-	0.8	-	13.7	0.6	<0.0001
Hypercholesterolemia	20.2	-	30.4	-	25.6	0.3	0.006
Arthralgia	21.9	-	45.0	3.0	45.7	2.7	<0.0001
Bone pain	15.4	-	29.0	0.3	26.8	2.4	0.0001
Osteonecrosis	-	-	-	-	1.2	1.2	0.01
Neuropathy – sensory	7.7	-	13.0	0.3	14.3	0.3	0.02
Endometrial abnormalities	6.8	0.3	3.0	-	2.4	-	0.005
Vaginal dryness	11.7	-	20.7	-	19.8	-	0.002

\* exact Kruskal Wallis non-parametric analysis of variance of the worst reported grade



# AlvT\_premenop: Aromatase inhibitor VERSUS tamoxifen:

## RECURRENCE analysis of published data for ABCSG XII and TEXT/SOFT (all patients):



ABCSG XII: Annals of Oncology 26: 313–320, 2015 doi:10.1093 – table 1.

TEXT/SOFT: N Engl J Med 2014; 371:107-118 DOI: 10.1056/NEJMoa1404037 – figure 2b

HOBOE data (May 31, 2018)

09:47:45 7 November 2018

Not for publication or citation



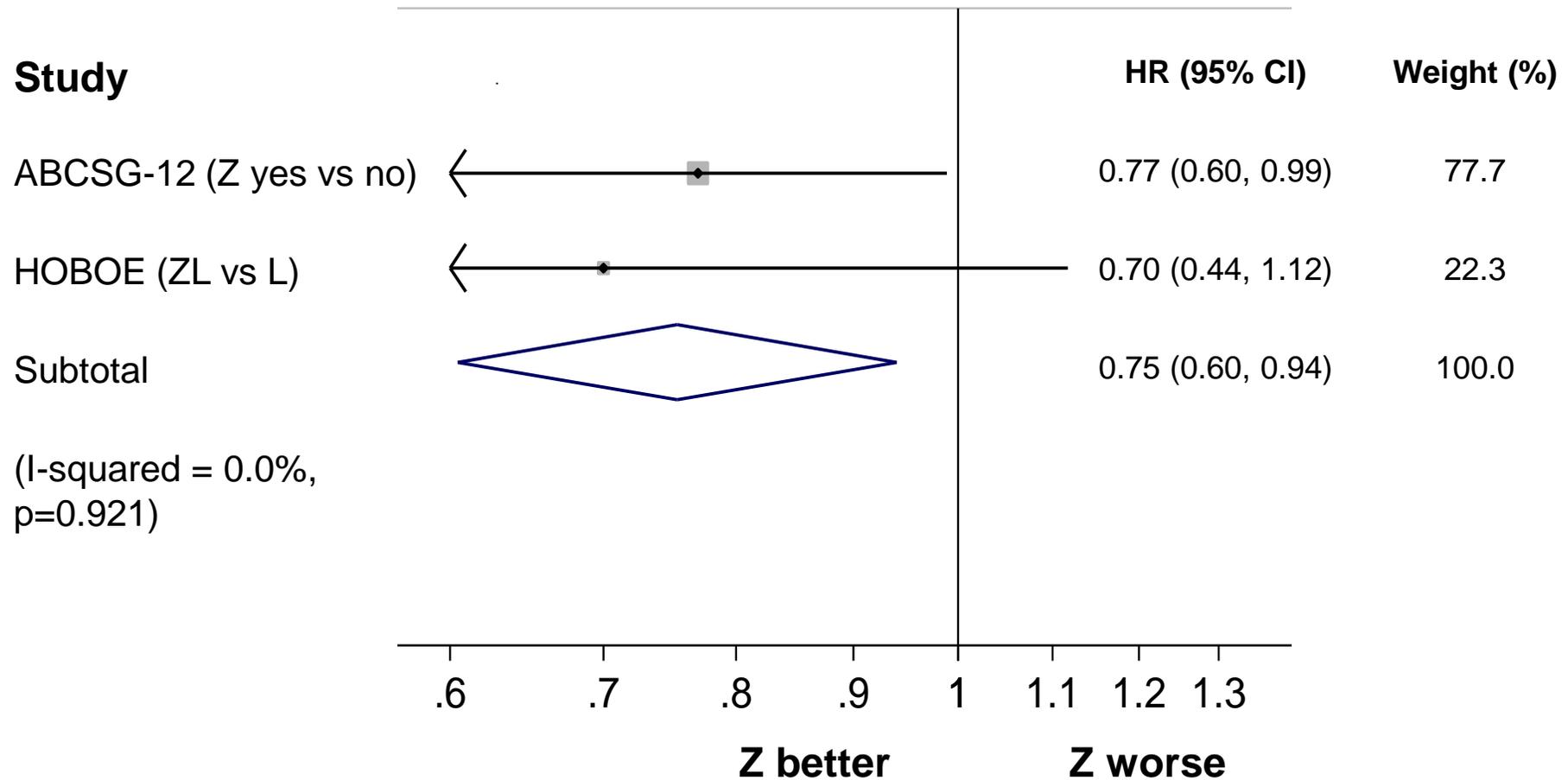


Figure A7



# Conclusions

- HOBOE shows that Zoledronic acid plus Letrozole significantly improves DFS of premenopausal early breast cancer patients with hormone-receptor positive tumors, undergoing ovarian suppression with triptorelin
- Compliance with Zoledronic acid plus Letrozole is problematic
- Toxicity of Zoledronic acid plus Letrozole and of Letrozole alone is worse as compared to tamoxifen



# Acknowledgments

## The patients and their families

**Co-investigators** - MC Piccirillo, G Daniele, M Di Maio, A Morabito, C Schettino, L Arenare, A Del Giudice, J Bryce, G De Feo, MT Ribeco, A Gimigliano, S Bevilacqua, F Perrone, A De Matteis, F Nuzzo, A Gravina, M De Laurentiis, C Pacilio, F Dirella, G Iodice, G Landi, V Labonia, G Buonfanti, M Licenziato, N Normanno, A De Luca, R Tortoriello, F Avino, R Cerra, A Fucito, I Donzelli, MT Melucci, M Rinaldo, G D’Aiuto, M D’Aiuto, R Thomas, I Capasso, M Di Bonito, G Botti, F La Vecchia, MP Curcio, M Staiano, F Collina, M Cantile, M Cerrone, P Maiolino, R D’Aniello, P Muto, V Ravo, S Lastoria, F Di Gennaro, T Petrosino, MR Rubulotta, P Vallone, SV Setola, S Filice, A Gallipoli D’Errico, A Petrillo, E Cavalcanti, D Cerasuolo; S De Placido, V Forestieri, R Lauria, G Arpino, M Giuliano, C De Angelis; M Orditura, F Ciardiello, A Diana, C Gallo, S Signoriello, P Chiodini, G Signoriello, V Simeon, L Guizzaro; F Riccardi, G Carteni, C Mocerino, M Trunfio (Napoli). S Cinieri, P Fedele, L Orlando (Brindisi). A Ribeco, F Martella (Firenze). C Putzu, G Sanna (Sassari). L Del Mastro, C Bighin (Genova). E Rossi, G Colantuoni (Avellino). V Tinessa, P Federico (Benevento). AM Mosconi, J Foglietta (Perugia). A Fabbri, L Moschetti (Viterbo). T Ibrahim (Meldola). E De Maio (Livorno). S Barni (Treviglio). S Gori, M Turazza (Negrar).

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Grazie per l'attenzione

