EXTENDED ENDOCRINE TREATMENT IN BREAST CANCER

RASNA GUPTA

OBJECTIVES

- 5 year vs 10 years of endocrine treatment in adjuvant setting
- Common toxicities of Adjuvant treatment
- When to refer back to Cancer Centre

Adjuvant Endocrine Agents:

Tamoxifen

- Current standard of care in premenopausal women.
- Useful regardless of menopausal status
- In postmenopausal women:
  - Reduces recurrence by 37 – 54%
  - Reduces death by 11 – 33%
- Long-term side effects characterized
- Carryover effect documented
- Utility in sequence with AIs in post-menopausal women.

Early Breast Cancer Trialists, Lancet 2005.

Adjuvant Endocrine Agents:

Aromatase Inhibitors

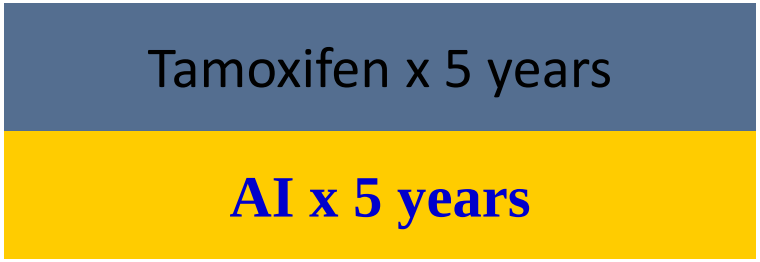
- Current standard of care in post-menopausal women
- Inhibit peripheral conversion of androgens to estrogens by the aromatase enzyme
- 3 agents: anastrazole, letrozole, exemestane.

Key Issues in Adjuvant Endocrine Therapy for Postmenopausal Women

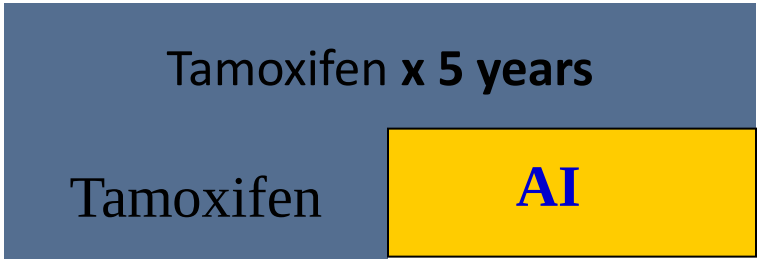
- 2/3 of breast cancers are ER/PR+
- 3/4 of post-menopausal women have ER/PR+ tumors
- When to start or stop an AI
- Whether and how to use tamoxifen
  - Tumor features (ER, PR, HER2)
  - Clinical factors (patient preference, comorbidities)
  - Pharmacogenomic factors
  - Concurrent medication factors
- Minimizing side effects, esp. bones
- Late sequelae – good or bad – of AI therapy

ADJUVANT TRIALS

AIS IN POSTMENOPAUSAL WOMEN



Upfront vs Tamoxifen



Sequential vs Tamoxifen

Extended Rx, AI vs Placebo

ASCO GUIDELINES

"The Panel believes that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen. Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options."

Winer, et al JCO 2004

DURATION OF THERAPY

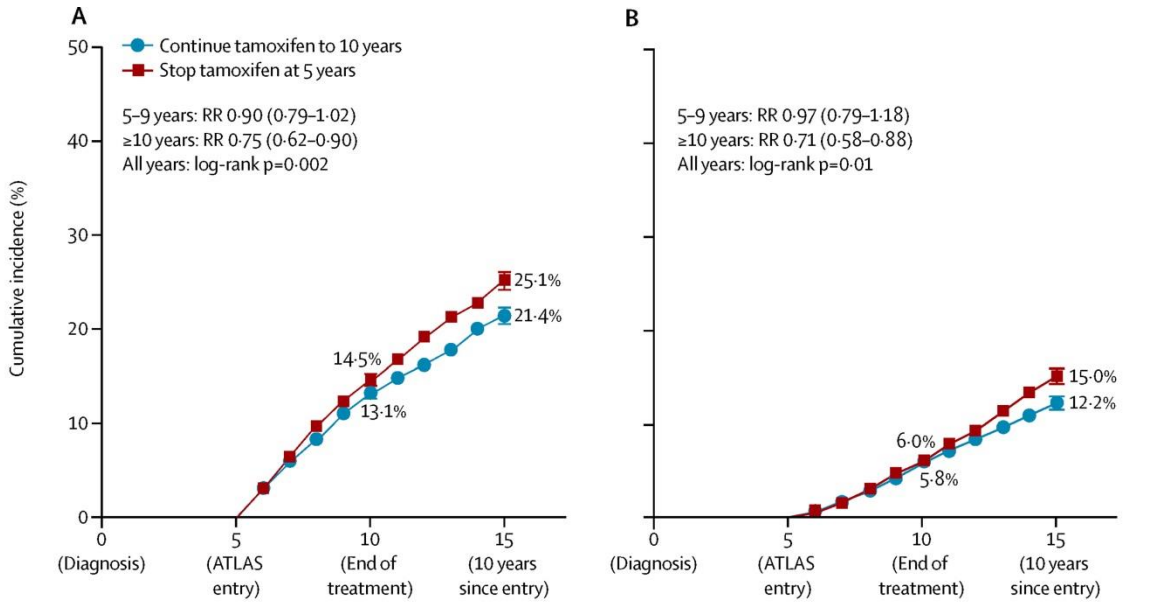
Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomized trial

Dr Christina Davies, et al

The Lancet
Volume 381, Issue 9869, Pages 805-816 (March 2013)
DOI: 10.1016/S0140-6736(12)61963-1

Recurrence (A) and Breast Cancer Mortality (B) for 6846 Women

- Taking adjuvant tamoxifen for 10 years results in fewer recurrences than taking it for 5 yrs.
- Increase in incidences of endometrial cancer and pulmonary embolus, but reduced the rate of ischemic heart disease.



	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	–24·8/224·7	–29·1/94·7	–2·1/12·5	–3·2/94·0	–27·2/77·5	–2·5/10·6

The Lancet 2013 381, 805-816DOI: (10.1016/S0140-6736(12)61963-1)

MA.17R: Reduced Risk of Recurrence with Extending Adjuvant Letrozole Beyond 5 Yrs in Postmenopausal Women with Early-Stage Breast Cancer.

Glen Goss et al.

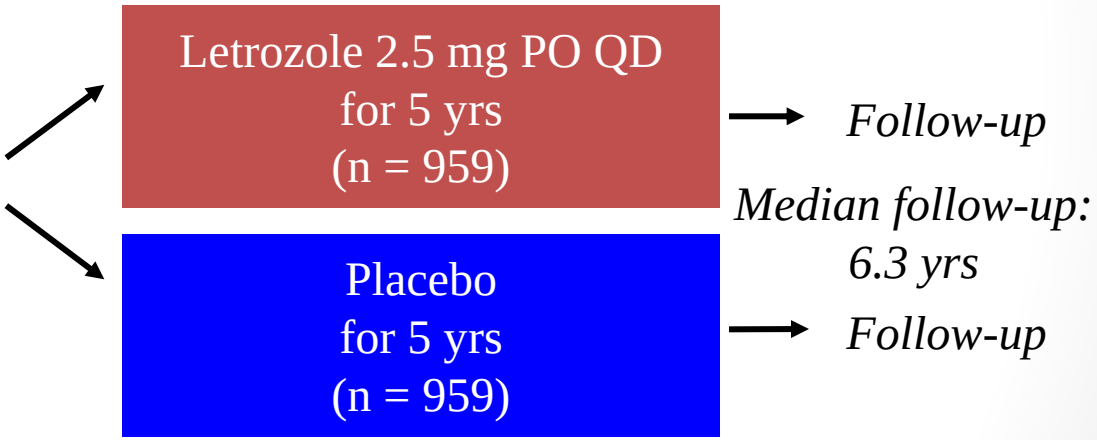
MA.17R Extended Letrozole: Background

- 5 yrs of AI therapy, either initially or after 2-5 yrs of tamoxifen, standard of care for postmenopausal women with HR-positive early breast cancer
  - Based largely on results of Canadian Cancer Trials Group MA.17 trial, which compared 5 yrs of letrozole vs placebo following 5 yrs of tamoxifen[1,2]
  - DFS and OS outcomes superior with letrozole
- Extending AI treatment with letrozole to 10 yrs may further reduce risk of breast cancer recurrence.

1. Goss PE, et al. N Engl J Med. 2003;349:1793-1802. 2. Jin H, et al. J Clin Oncol. 2012;30:718-721.

MA.17R: STUDY DESIGN

Postmenopausal pts with ER+ and/or PgR+ breast cancer who completed 4.5-6 yrs of letrozole 2.5 mg PO QD ± prior tamoxifen (N = 1918)



- Primary endpoint: DFS (from randomization)
- Secondary endpoints: OS, CBC, safety, QoL

Goss PE, et al. ASCO 2016.

MA.17R: DFS and OS After Median Follow-up of 6.3 Yrs

DFS Outcomes	Letrozole	Placebo	HR (95% CI)	*P* Value
Overall 5-yr DFS, %	95	91	0.66 (0.48-0.91)	.01
Events, n (%)	67 (7.0)	98 (10.2)		
New contralateral breast cancers, n (%)	13 (1.4)	31 (3.2)		.007
Locoregional recurrences, n	19	30		
Distant recurrences, n	42	53		
Bone recurrences, n	28	37		

Goss PE, et al. ASCO 2016. Abstract LBA1.

MA.17R: FRACTURES DURING TREATMENT

- Bone health and bone protection similar between arms at baseline

Bone Events, %	Letrozole (n = 959)	Placebo (n = 959)	*P* Value
Bone fracture	14	9	.001
Location of bone fracture			
▪ Spine	1.8	0.9	.12
▪ Wrist	2.8	1.7	.09
▪ Pelvis	0.1	0.7	.08
▪ Hip	0.7	0.6	.79
▪ Femur	0.9	0.4	.17
▪ Tibia	0.5	0.4	.74
▪ Ankle	2.0	1.2	.14
▪ Other	7.1	5.0	.06
New-onset osteoporosis	11	6	< .0001

Goss PE, et al. ASCO 2016.

MA.17R: CONCLUSIONS

- MA.17R first study to demonstrate benefit of extending AI treatment beyond 5 yrs.
  - Letrozole treatment for 10 yr decreased risk of disease recurrence by 3-4%
    - Majority of benefit in reduction of contralateral breast cancer.
  - No new toxicities observed.
  - Bone health remains important in weighing risks/benefits.
  - Treatment extension did not adversely impact QoL.
- OS not improved by extending letrozole beyond 5 yrs.

Goss PE, et al. ASCO 2016. Abstract LBA1.t

MA.17R: SAFETY

Adverse Event, %	Letrozole (n = 959)	Placebo (n = 959)	*P* Value
Hot flashes/flushes	38	37	NS
Arthralgia	53	50	NS
Myalgia	28	25	NS
Bone pain	18	14	.01
Vaginal dryness	11	10	NS
Elevated alkaline phosphatase	12	9	.01
Elevated ALT	11	14	.02
Cardiovascular event	12	10	NS

Goss PE, et al. ASCO 2016. Abstract LBA1.

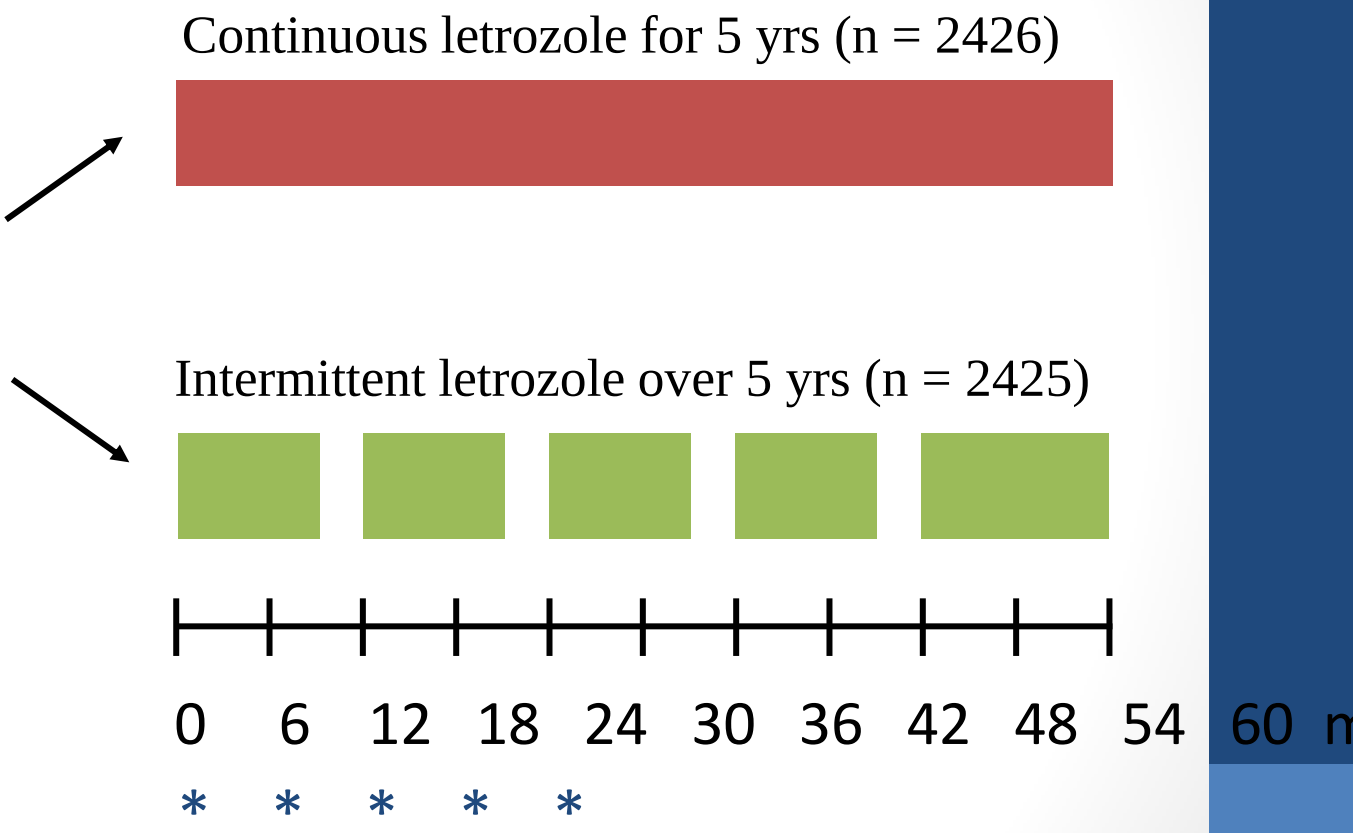
BACKGROUND

- SOLE: randomized phase III trial evaluating use of intermittent letrozole as option to prolong sensitivity to endocrine treatment[4]

1. Goss PE, et al. N Engl J Med. 2003;349:1793-1802. 2. Mamounas T, et al. SABCS 2016. Abstract S1-05. 3. Song RX, et al. J Natl Cancer Inst. 2001;93:1714-1723. 4. Colleoni M, et al. ASCO 2017. Abstract 503.
5. Sabnis GJ, et al. Cancer Res. 2008;68:4518-4524.

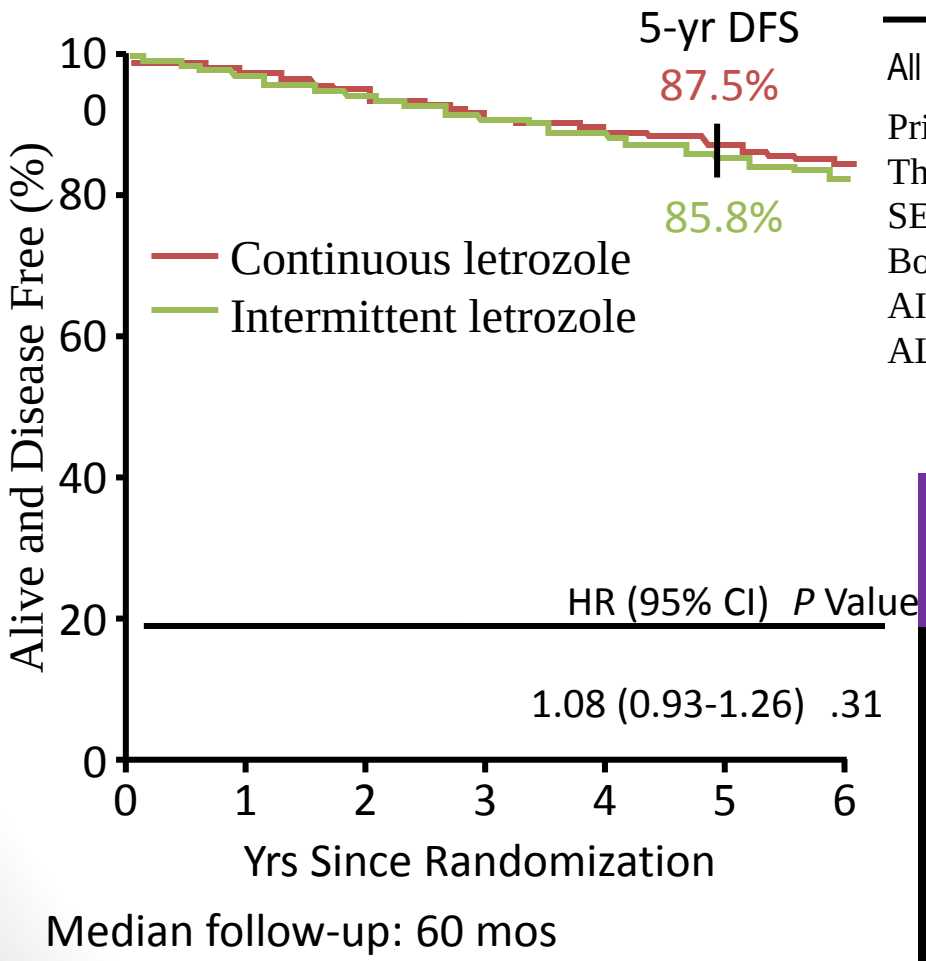
CONTINUOUS VS INTERMITTENT LETROZOLE AFTER ENDOCRINE TX IN BREAST CANCER (SOLE)

Postmenopausal women with clinically disease free HR+ lymph node-positive early BC who have completed 4-6 yrs of adjuvant endocrine therapy (N = 4851)

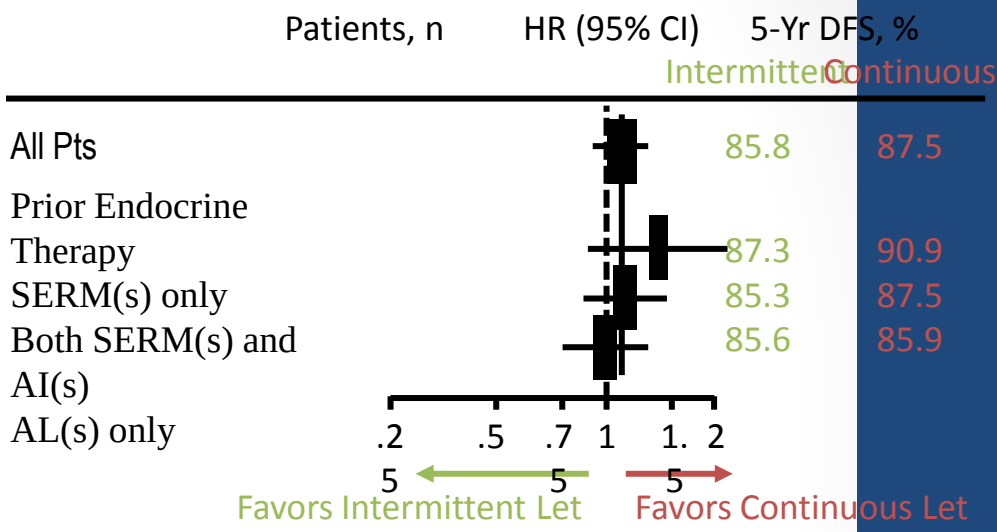


Colleoni M, et al. ASCO 2017. Abstract 503.

SOLE: DISEASE FREE SURVIVAL



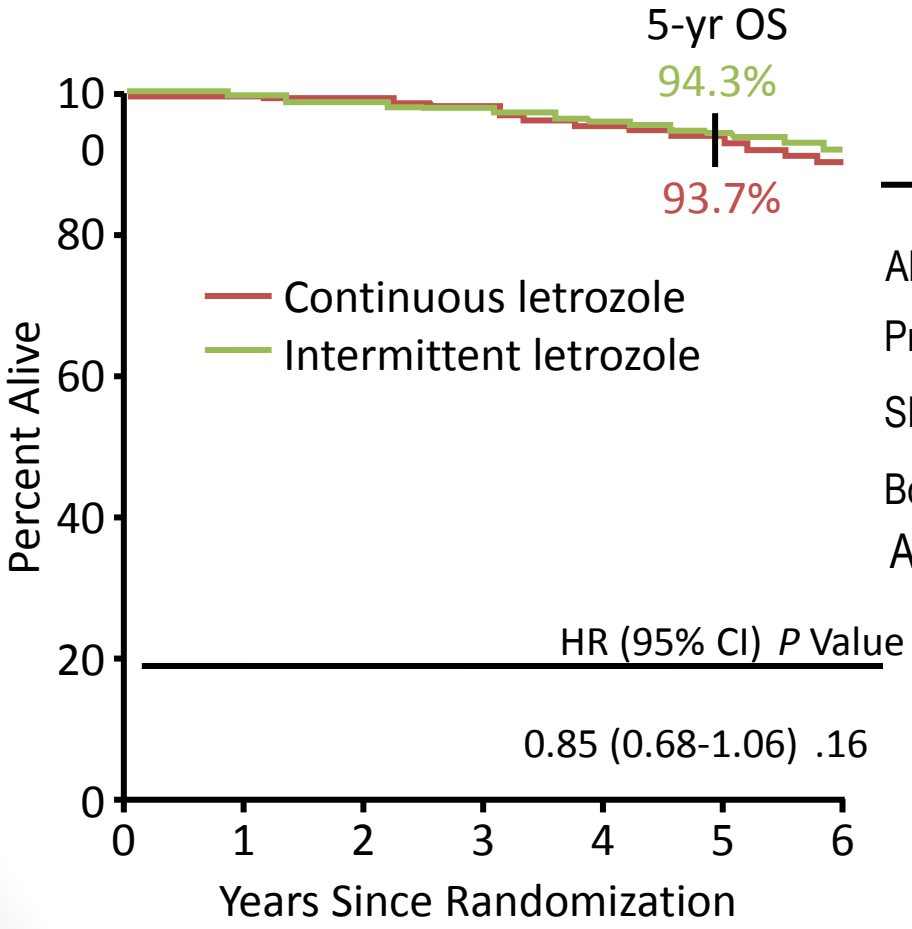
Median follow-up: 60 mos

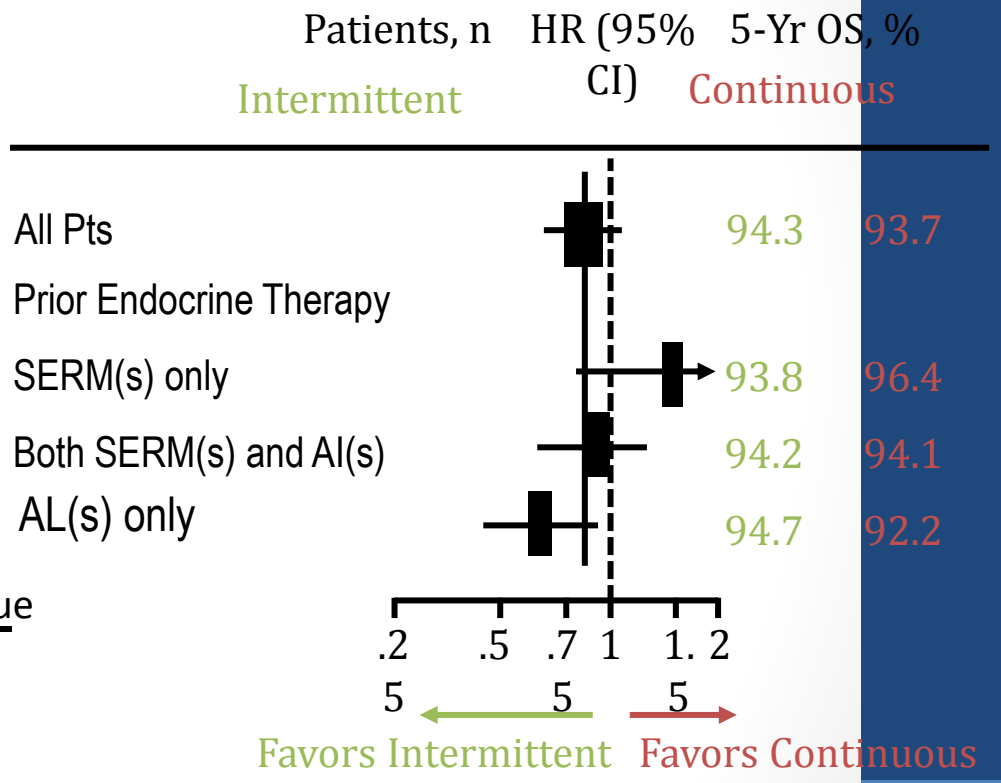


DFS Event, %	Continuous Let (n = 2426)	Intermittent Let (n = 2425)
DFS event	13.1	14.3
BC event as first site	8.9	8.7
Second malignancy (nonbreast)	3.1	3.9
Death without cancer event	0.9	1.4
Death, incomplete information	0.3	0.3

Colleoni M, et al. ASCO 2017.

SOLE: OS





Median follow-up: 60 mos

Colleoni M, et al. ASCO 2017. Abstract 503.

SOLE: CONCLUSIONS

- Extended intermittent letrozole did not improve DFS vs continuous dosing in postmenopausal women with HR+ breast cancer.
- No change in safety profile with intermittent vs continuous dosing.

Colleoni M, et al. ASCO 2017. Abstract 503.

NSABP B-42:
BACKGROUND

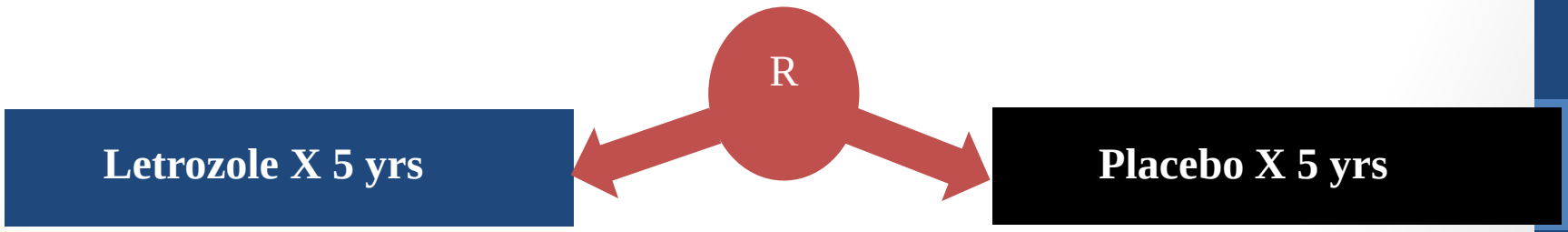
- NSABP B - 42 aimed to determine whether 5 years of letrozole vs. placebo improves disease-free survival in patients who have completed 5 years of hormonal therapy with either an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor.

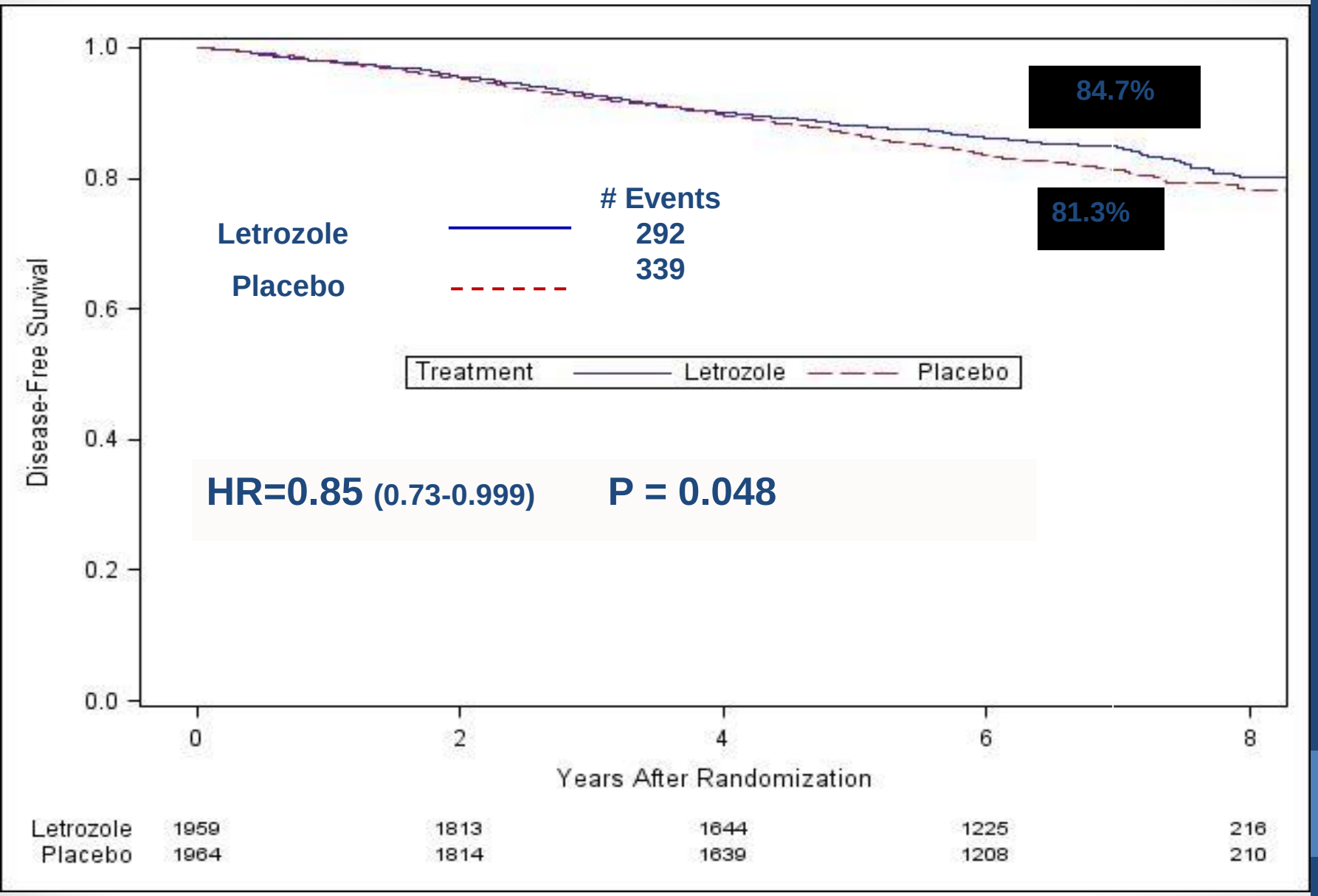
NSABP B-42: SCHEMA

- Postmenopausal Pts with ER+ or PR+ Breast Cancer
- Stage I, II, or IIIa invasive BC at diagnosis
- Disease-free After 5 Years of Endocrine Therapy

AI X 5 yrs or **TAM X ≤ 3 yrs → AI to Complete 5 yrs**

Stratification:
Pathological nodal status (Negative, Positive)
Prior adjuvant TAM (Yes, No)
Lowest BMD T score: spine, hip, femur (>-2.0, ≤ -2.0 SD)




1.0
0.8
0.6
0.4
0.2
0.0
Disease-Free Survival
84.7%
81.3%
Events
Letrozole
292
Placebo
339
Treatment
Letrozole
Placebo
HR=0.85 (0.73-0.999)
P = 0.048
0
2
4
6
8
Years After Randomization
Letrozole 1959 1813 1644 1225 216
Placebo 1964 1814 1639 1208 210

NSABP B-42: DFS FIRST EVENTS BY TREATMENT

	Placebo (n=1964)		Letrozole (n=1959)	
First event	#	%	#	%
Distant Recurrence	87	4.4	61	3.1
Local Recurrence	33	1.7	36	1.8
Second Primary Ca	171	8.7	134	6.8
Opposite Breast	59	3.0	30	1.5
Non-Breast	112	5.7	104	5.3
Death	48	2.4	61	3.1
Total First Event	339	17.3	292	14.9

NSABP B-42: SUMMARY

- The beneficial effect of extended letrozole therapy on DFS did not reach statistical significance (15% reduction)
- No significant difference in overall survival
- Extended letrozole provided:
  - Statistically significant improvement in Breast cancer–free interval event rate (29% reduction)
  - Statistically significant reduction in the rate of Distant recurrence rate R (28% reduction)
- Letrozole did not significantly increase risk of osteoporotic fractures but risk of arterial thrombotic events was elevated for letrozole after 2.5 years

OTHER NEGATIVE TRIALS

- Phase 3 DATA study.

- 1,912 postmenopausal women who had received 2 to 3 years of adjuvant tamoxifen randomized to either 3 or 6 years of anastrozole.

- Five-year adapted disease-free survival (disease-free survival beyond 3 years after randomization to aromatase inhibitor therapy) was 83.1% for patients receiving 6 additional years of anastrozole and 79.4% for those receiving 3 years.
- - The hazard ratio was 0.79 (P = .07).

OTHER NEGATIVE TRIALS

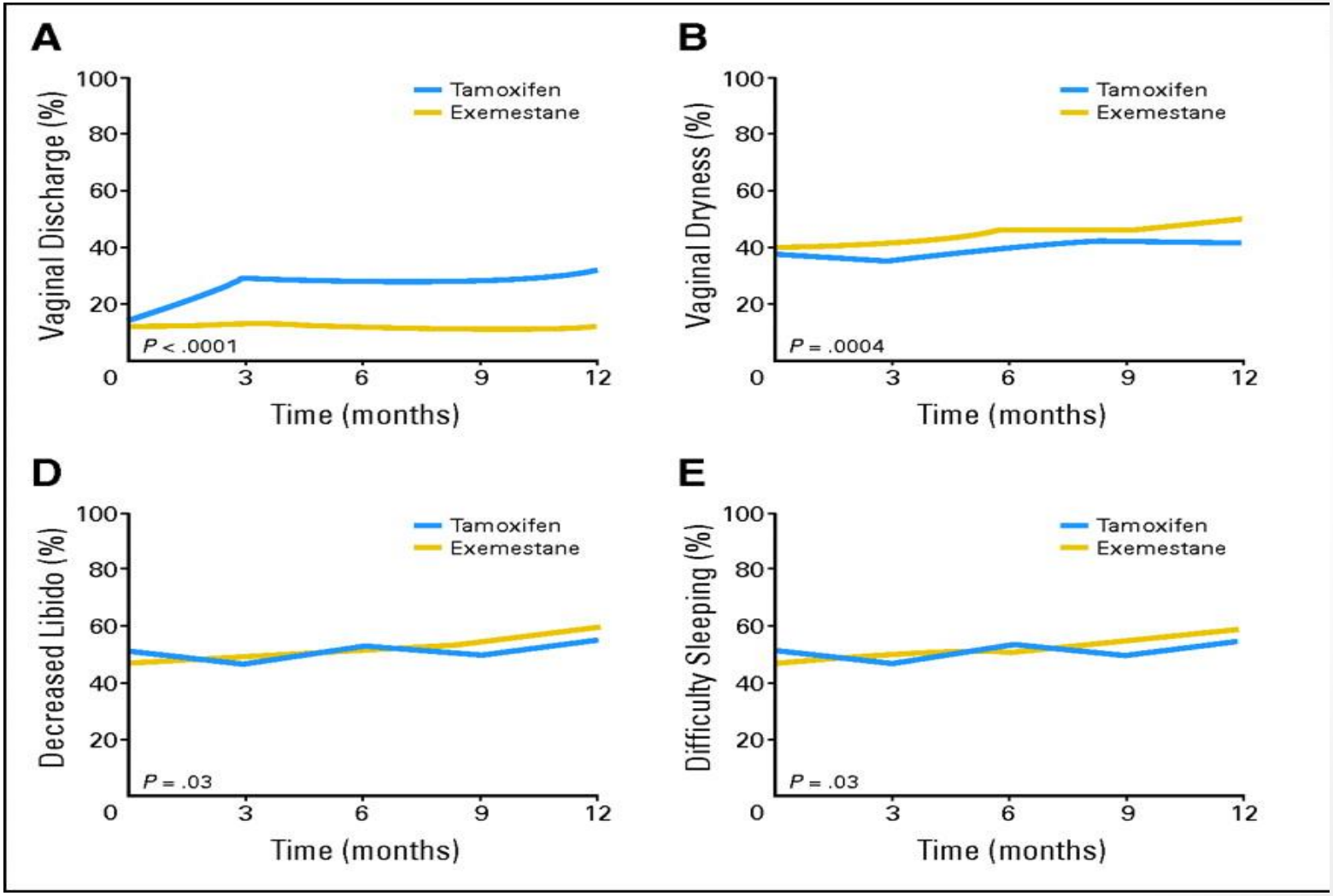
Phase III IDEAL trial.

- The 1,824 postmenopausal patients were randomized to letrozole for 2.5 years or 5 more years of extended therapy after receiving 5 years of adjuvant tamoxifen (10%) or aromatase inhibitor(30%).
- The 5-year disease-free survival rate was 88.4% in patients receiving 2.5 more years of treatment and 87.9% for those receiving 5 additional years (HR = .96, *P* = .70).
- Overall survival rates were 93.5% and 92.6%, respectively (HR = 1.08, *P* = .59).
- There was a significant difference in the prevention of second primary breast cancers (HR = 0.37, *P* = .008), but this represented a small (1%) absolute risk reduction.

AI TOXICITIES

- Arthralgias
- Sexual Dysfunction
- Osteoporosis

AI TOXICITIES



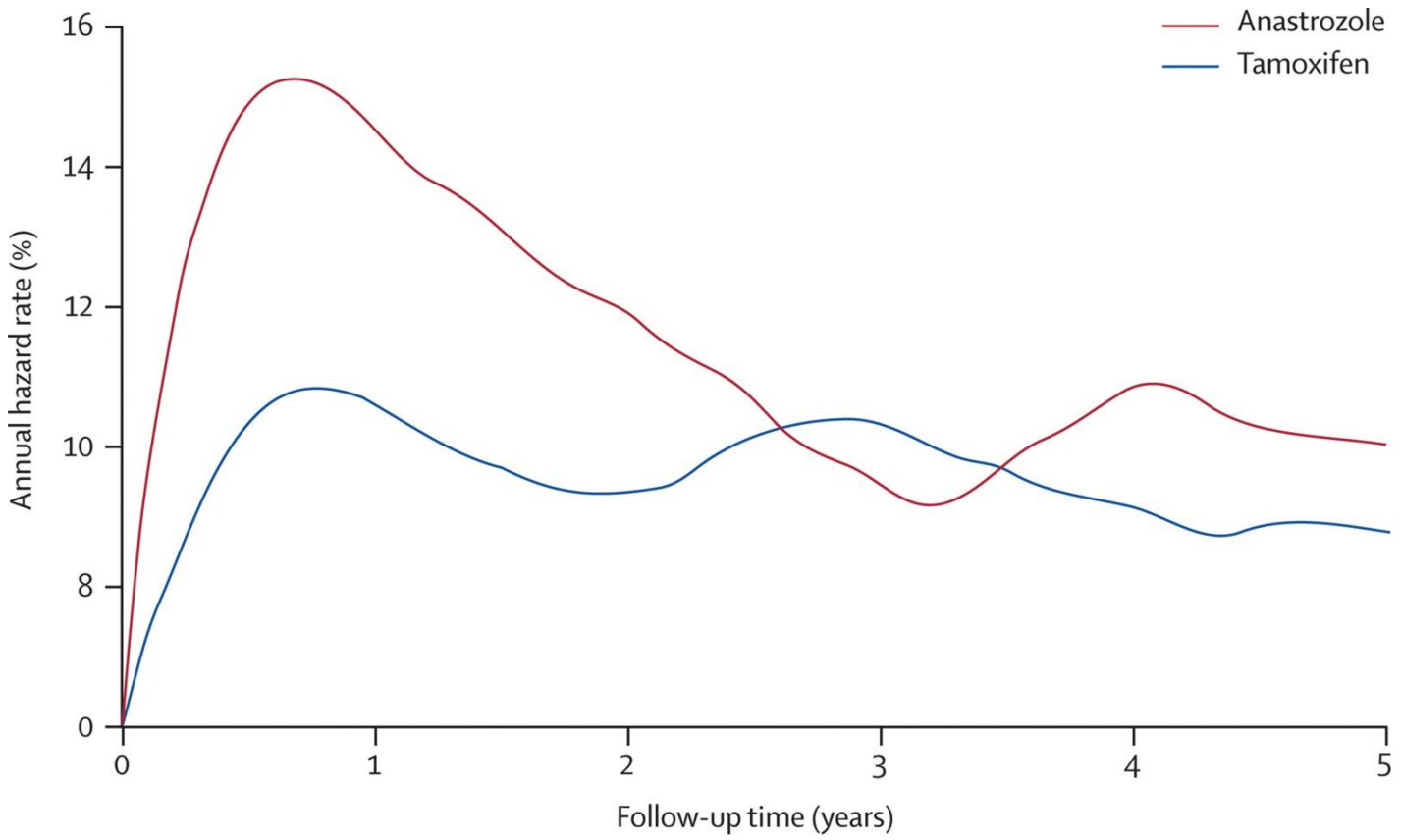
TEAM Trial
Jones, S. E. et al. J Clin Oncol; 25:4765-4771 2007

AI ARTHRALGIA SYNDROME

Common complaint

- Symmetric
- Hands, feet, pelvis/hip, arms
- Pathognomonic criteria:
  - “I aged overnight.” “I feel like an old lady.”
  - Squeezing hands/joints gesture
- Etiology unclear

ATAC
Arthralgia Incidence over Time



Sestak, et al. Lancet Oncology 2008

Diagnosis: AI-associated joint symptoms

Pts referred to Rheumatology at Michigan and Hopkins

Diagnosis	Number of patients (%)
Bursitis	8 (21.1%)
Trochanteric	6 (15.8%)
Carpal tunnel syndrome	8 (21.1%)
Osteoarthritis	11 (28.9%)
Knee	3 (7.9%)
Hand	2 (5.3%)
Tendonitis	14 (36.8%)
Rotator cuff/shoulder	8 (21.2%)
Wrist	3 (7.9%)
Elbow	2 (5.3%)
Patellofemoral syndrome	7 (18.4%)

AI ARTHRALGIA SYNDROME

Practical Suggestions

1. Alert patients to this side effect
2. Reassure patients that this is not associated with destructive arthritis and that most cases are mild and abate over time
3. Encourage weight reduction and regular exercise
4. For more severely affected patients, suggest AI withdrawal to gauge relationship to treatment
5. Options: tamoxifen, other AIs, none

FRACTURE RATES IN ADJUVANT AI TRIALS

	Aromatase Inhibitor	Tamoxifen / Placebo	% Increase	Reference
ATAC	340 (11%)	237 (7.7%)	43%	Howell et al 2005
BIG 1-98	228 (5.8%)	162 (4.1%)	41%	Thurlimann et al 2005
IES	162 (7.0%)	111 (4.9%)	45%	Coombes et al 2006
ABCSG/ ARNO	34 (2.0%)	16 (1.0%)	113%	Jakesz et al 2005
MA.17	137 (5.3%)	119 (4.6%)	15%	Perez et al 2006

Bone Health Guidelines

- Consider bone health when choosing adjuvant endocrine therapies
- Check BMD at baseline when initiating AI therapy
- Recheck BMD at 1-2 years
- Initiate therapy for osteporosis / osteopenia according to standard guidelines derived from normal postmenopausal patient experience
- Interventions that “work” in general population with osteopenia / osteoporosis also work in breast cancer survivors

CONCLUSIONS

- Careful assessment of potential risks and benefits is required before recommending extended letrozole therapy, including:
  - Patient and tumor characteristics (age, nodal status)
  - Existing co-morbidities
  - Information on bone mineral density
  - Tolerance of the AI in the initial 5 years
- Genomic classifiers that predict risk of late recurrence and/or benefit from extended endocrine therapy may help to further individualize the recommendation for extended aromatase inhibitor therapy

THANKS