Hormonal Therapy for Breast Cancer Bone Health and Survivorship

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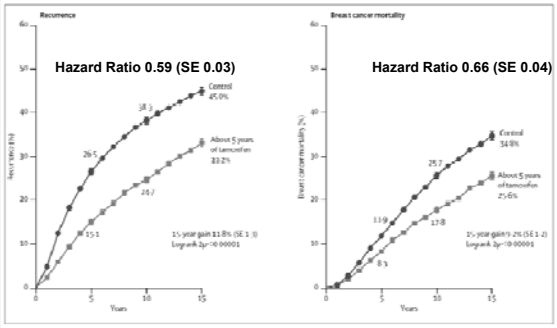
Financial Disclosure

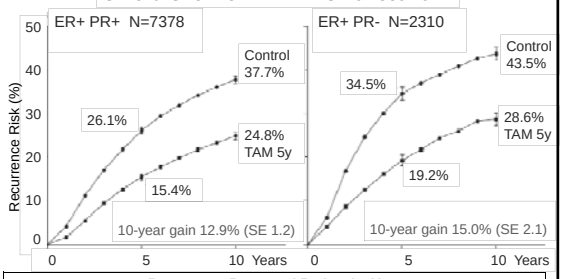
- I have no significant relationships to disclose.

Benefits of Adjuvant Tamoxifen (5 yrs, ER+)



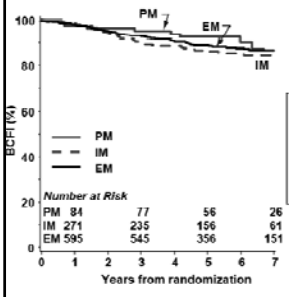
EBCTG Lancet 2005

Oxford Overview – EBCTG Lancet 2011



Recurrence Rates and Ratios by Year								
Years	1 to 4	5 to 9	10+	overall	1 to 4	5 to 9	10+	overall
Tamoxifen	3.41	2.47	2.10	P<0.00001	4.42	2.58	1.49	P<0.00001
Control	6.00	3.50	2.19		8.52	3.02	1.52	
Rate ratio	0.55	0.68	0.93	0.63	0.50	0.84	0.92	0.60

Outcome by CYP2D6 Genotype: BIG 1-98 Trial

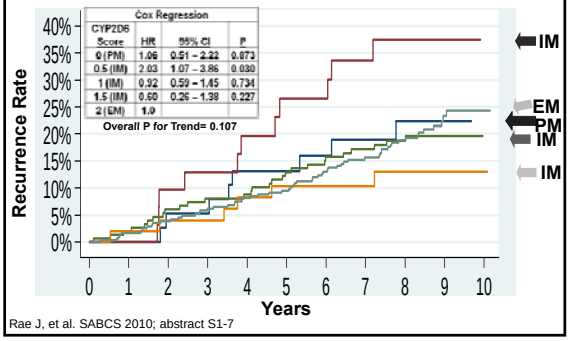


Tamoxifen
No Chemotherapy

	N	Events	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
PM	86	8	.71 (.34-1.46)	.58 (.28-1.21)
IM	277	40	1.22 (.83-1.79)	.95 (.50-1.40)
EM	610	75	1	1
			P=0.32	P=0.35

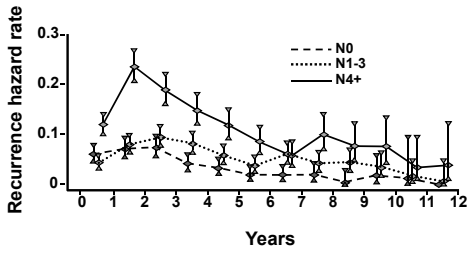
Leyland-Jones B, et al. SABCS 2010, Abstr S1-8

CYP2D6 Score in ATAC Trial Recurrence in Tamoxifen Arm



Rae J, et al. SABCS 2010; abstract S1-7

Long-Term Recurrence Hazard Rates for Breast Cancer After Primary Therapy



Saphner et al. J Clin Oncol. 1996

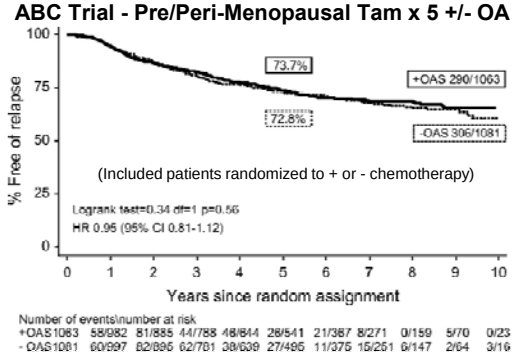
Relative Risk of Recurrence for 10 Versus 5 Years of Adjuvant Tamoxifen: aTTom/ATLAS and Other Trials

Trial	Events/Women		Odds ratio (95% CI)
	~ 10 years	~ 5 years	
aTTom	437/3468	456/3484	0.95 (0.83 – 1.09)
ATLAS	739/5750	825/5750	0.87 (0.78 – 0.96)
Scottish	37/137	36/145	1.05 (0.65 – 1.70)
NSABP B-14	78/592	63/576	1.23 (0.88 – 1.72)
ECOG	14/72	28/66	0.41 (0.22 – 0.78)

Relative Risk of Recurrence in aTTom and ATLAS Trials Based on Follow-up Time			
	Events/Women		Odds ratio (95% CI)
	~ 10 years	~ 5 years	
Years 0-1	512/9218	529/9234	0.96 (0.85 – 1.08)
Years 2-4	469/8754	541/8706	0.84 (0.74 – 0.95)
Years 5+	195/8290	211/8171	0.88 (0.72 – 1.07)

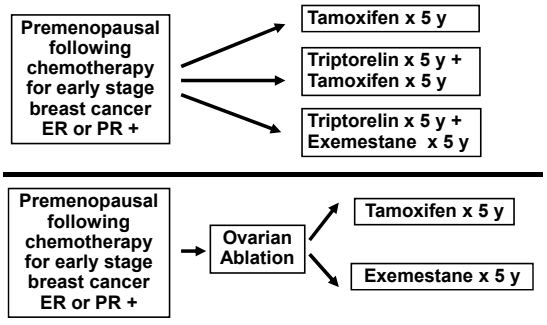
Gray et al, ASCO 2008, abstract # 513

Does Ovarian Ablation (OA) Add to Tamoxifen? ABC Trial - Pre/Peri-Menopausal Tam x 5 +/- OA

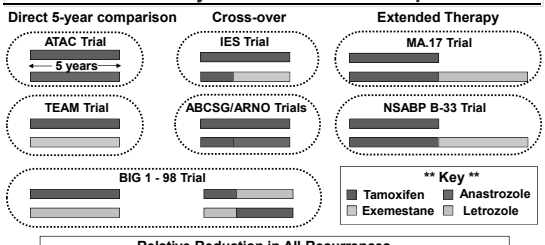


The Adjuvant Breast Cancer Trials Collaborative Group, JNCI 2007

SOFT and TEXT Trials



Clinical Trials of Adjuvant Tamoxifen Compared to AIs



Relative Reduction in All Recurrences		
17 - 19%	27 - 40%	43%
Absolute Reduction in All Recurrences (at 3-6 years)		
2 - 4%	3 - 5%	6%

Based on data from ATAC and BIG 1-98 for direct comparison; IES and ABCSG/ARNO for cross-over; MA.17 for extended therapy

ATAC – 100 Month Disease-free survival Curves shown for HR+ patients

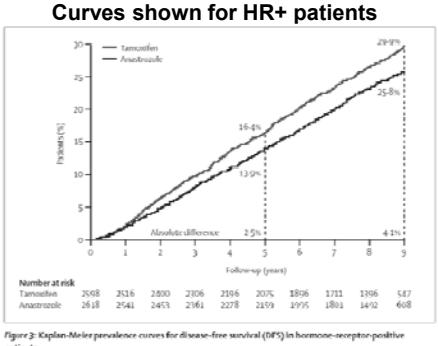
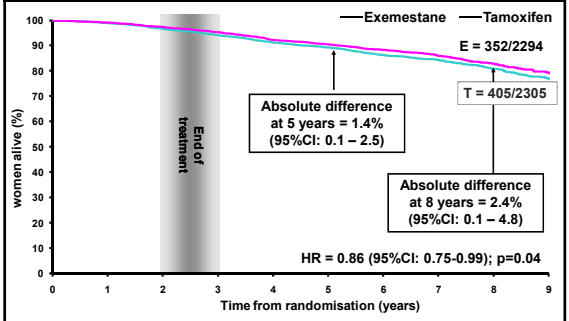


Figure 3: Kaplan-Meier prevalence curves for disease-free survival (DFS) in hormone-receptor-positive patients

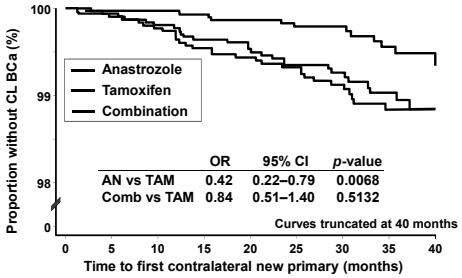
ATAC Trialists' Group Lancet Oncol 2008

Exemestane Intergroup Study (EIS) Overall Survival – ER+/unknown



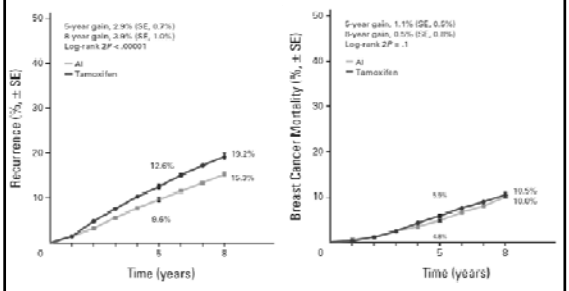
Coombes RC, et al. ECCO15/ESMO34, 2009

Analysis of the Incidence of New (Contralateral) Breast Primaries: ATAC Trial



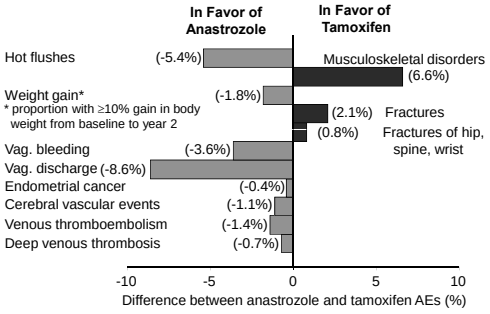
Howell A, et al Lancet 2005

Meta-Analysis of Tamoxifen vs. AI Studies N ≈ 19,000 Patients



Dowsett M, et al J Clin Oncol 2010

ATAC Trial: Significant Difference in Pre-defined Adverse Events



ATAC Trialists' Group Lancet Oncol 2008

MA/27 Adjuvant Exemestane vs. Anastrozole: Efficacy

Median follow-up 4.1 years

	HR (Stratified)	*P* Value
Event-Free Survival	1.02 (0.87-1.18)	.85
Node negative	1.04 (0.85-1.27)	.726
Node positive/unknown	0.99 (0.79-1.23)	.896
No adjuvant chemotherapy	1.01 (0.84-1.23)	.894
Adjuvant chemotherapy	1.02 (0.80-1.29)	.887
Overall Survival	0.93 (0.77-1.13)	.64
Distant Disease–Free Survival	0.95 (0.76-1.18)	.46
Disease-Specific Survival	0.93 (0.70-1.24)	.62

Goss P et al. SABCS 2010; abstract S1-1.

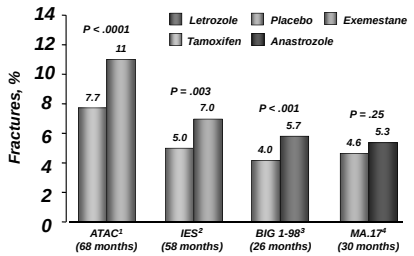
Adjuvant Exemestane vs. Anastrozole: Significantly Different AEs (All Grades[a])

Adverse Event	Exemestane (n = 3761)	Anastrozole (n = 3759)	*P* Value
Vaginal Bleeding	40 (1%)	61 (2%)	.04
ALT	53 (1%)	23 (1%)	.001
AST	47 (1%)	19 (1%)	.001
Bilirubin	59 (2%)	24 (1%)	< .0001
Masculinization	36 (1%)	11 (0%)	< .0001
Atrial Fibrillation	72 (2%)	46 (1%)	.02
Hypertriglyceridemia	80 (2%)	124 (3%)	.002
Hypercholesterolemia	577 (15%)	665 (18%)	.01
Osteoporosis	1171 (31%)	1304 (35%)	.001

[a] Grade 1/2: 70%

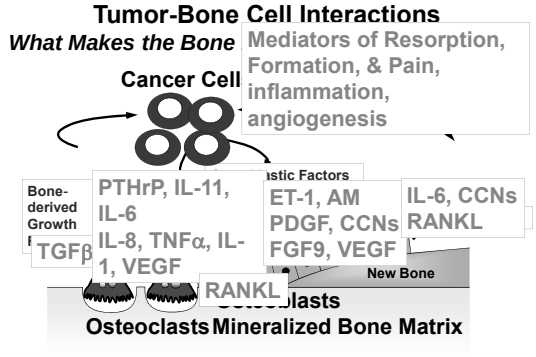
Goss P et al. SABCS 2010; abstract S1-1.

Fracture Risk with Adjuvant Aromatase Inhibitors



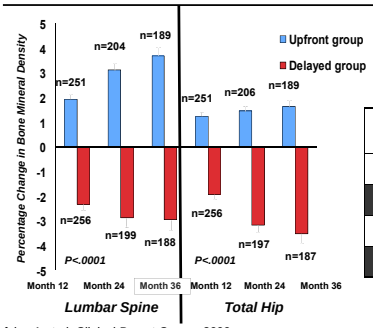
1. Howell et al. Lancet. 2005; 365:60-62; 2. Coleman et al. Lancet Oncol 2007; 8:119-127
3. Thurlimann et al. N Engl J Med. 2005; 353:2747-2757;
4. Goss et al. J Natl Cancer Inst. 2005; 97:1262-1271

Tumor-Bone Cell Interactions



Mundy Nature Reviews Cancer 2002; Roodman NEJM 2004

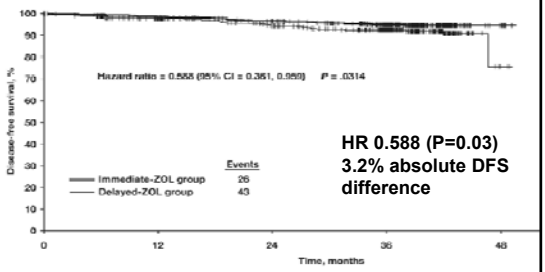
Z-FAST Trial : Upfront vs. Delayed Zoledronate in AI-Treated Patients



Upfront Group	Delayed Group
Total Fractures	
17 (5.7%)	19 (6.3%)
Recurrences @ 36 mo	
9 (3.0%)	19 (6.3%)

Brufsky A et al. Clinical Breast Cancer 2009

ZO-FAST Trial: 36 mo fu N=1065

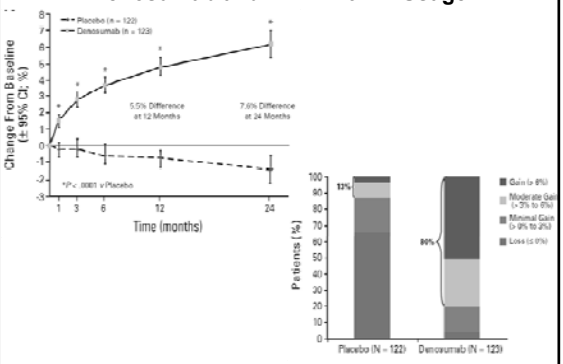


HR 0.588 (P=0.03)
3.2% absolute DFS difference

- **Fewer bone metastases: 1.7% vs 3.2%**
- **Fewer recurrences:**
- **Local 0.4% vs 1.9%, Distant 3.8 v 5.6**

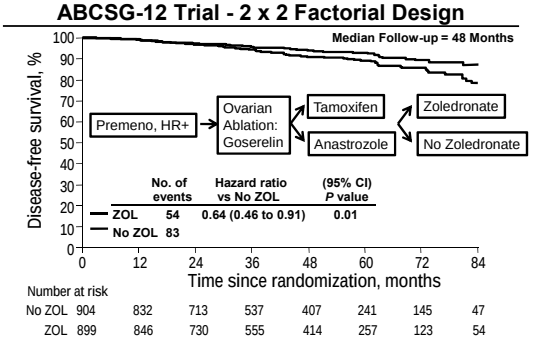
Eidtmann H, et al. Ann Oncol 2010

Denosumab and BMD with AI Usage



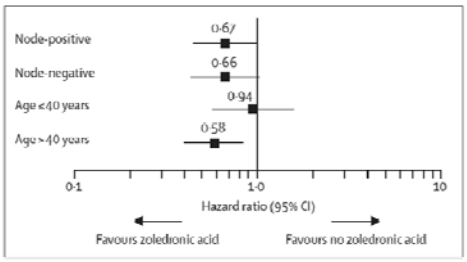
Ellis GK et al. J Clin Oncol 2008

Adjuvant Zoledronate: Disease-Free Survival ABCSG-12 Trial - 2 x 2 Factorial Design



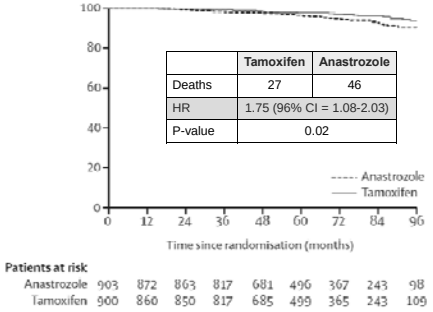
Gnant M et al. NEJM 2009

Adjuvant Zoledronate: Disease-Free Survival ABCSG-12 Trial – Follow-up, 62 Months



Gnant M et al. Lancet 2011

Adjuvant Zoledronate: Disease-Free Survival ABCSG-12 Trial – Follow-up, 62 Months



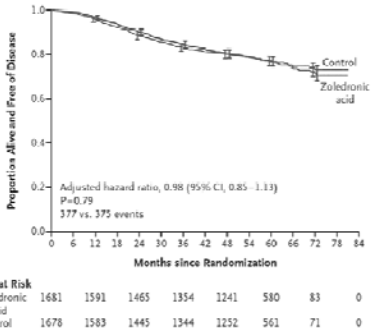
	Tamoxifen	Anastrozole
Deaths	27	46
HR	1.75 (96% CI = 1.08-2.03)	
P-value	0.02	

Patients at risk

Anastrozole	903	872	863	817	681	496	367	243	98
Tamoxifen	900	860	850	817	685	499	365	243	109

Gnant M et al. Lancet 2011

AZURE: Disease-Free Survival

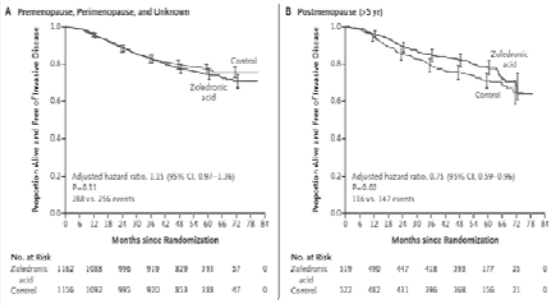


No. at Risk

Zoledronic acid	1681	1591	1465	1354	1241	580	83	0
Control	1678	1583	1445	1344	1252	561	71	0

Colman R, et al, NEJM 2011

AZURE: Overall Survival by Menopausal Status



Colman R, et al, NEJM 2011

S0307 Intergroup/NSABP: Phase III Comparison of 3 Bisphosphonates as Adjuvant Therapy for Breast Cancer

PIs: J Gralow, A Paterson

- Patients: stage I, II, III breast cancer patients receiving "standard" systemic therapy
- Treatment: (3 years)

Clodronate 1,600 mg po qd

vs.

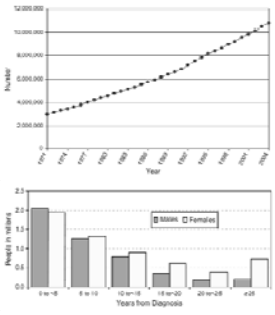
Ibandronate 50 mg po qd

vs.

Zoledronic acid 4 mg IV q month x 6, followed by q3 month

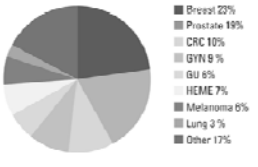
N = 6,000
Closed to accrual 2-1-10

Breakdown of ~11 Million Cancer Survivors in the U.S.



Rowland JH and Bellizzi KM. Heme Onc Clinic N Am 2008

Ganz PA and Hahn EE. J Clin Oncol 2008



Breast Cancer Survivorship: Key Topics

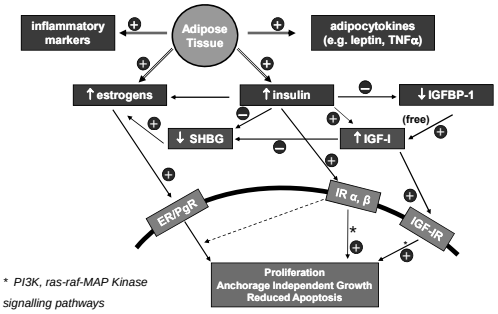
- Survivorship plans
- Does surveillance for recurrence affect outcome?
- Physical and physiological
  - Fertility
  - Menopausal symptoms
  - Bone health
  - Long term effects (cardiac, second cancers)
- Do diet and physical activity affect recurrence risk?
- Emotional and psychosocial
- Vocational, occupational and legal
- Costs (individual and societal)

Survivorship Plan: What and Why

- 2005 – Institute of Medicine publishes *"From Cancer Patient to Cancer Survivor: Lost in the Transition"*
- This was followed by complementary reports from the CDC, Lance Armstrong Foundation and President's Cancer Panel
- These documents provided directives for developing treatment summaries so that proper surveillance and care could be implemented by the broad medical community – such summaries would include:
  - Name/contact of all cancer providers
  - Surgical, imaging and laboratory procedures
  - Details of pathology, biomarkers
  - Complete summary of all radiation and systemic treatments
  - Recommended follow-up, monitoring and interventions

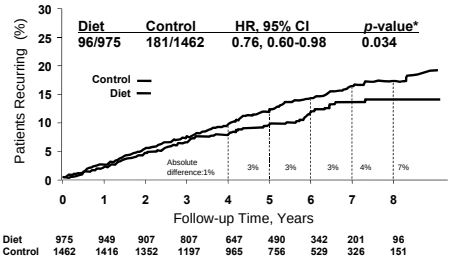
Pathways of Obesity and Breast Cancer

Interactions of Estrogen and Insulin/IGF Mechanisms



* *PI3K, ras-raf-MAP Kinase signalling pathways*

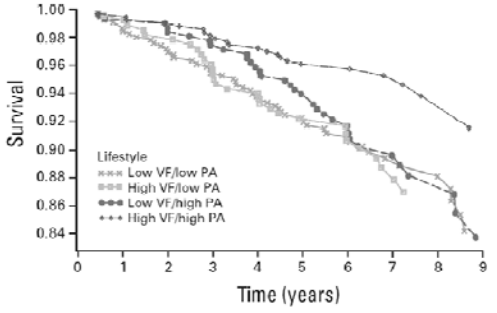
Randomized Trial of Low Fat vs Control Diet After Early Stage Breast Cancer (WIN Study)



* From adjusted Cox proportional hazards model including: stratification factors, ER status, tumor size, and surgery (mastectomy/lumpectomy), p value = 0.067 by unadjusted log rank test

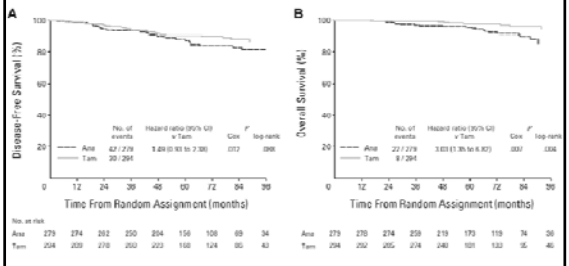
Chlebowski R et al. JNCI 2006

WHEL Study Control Group: Effect of Dietary Vegetable/Fiber (VF) and Physical Activity (PA) after a Diagnosis of Early Stage Breast Cancer



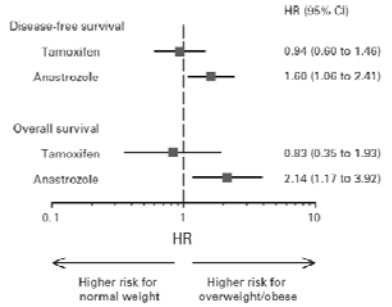
Pierce JP et al. J Clin Oncol 2007

Effect of Obesity and Outcome Tam vs Anastrozole ABCSG-12 Trial



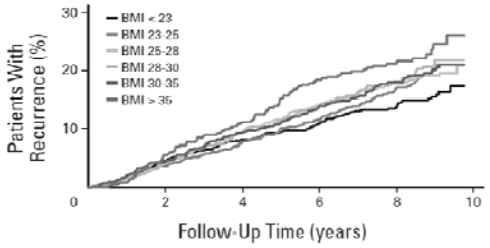
Pfeiler G, et al. J Clin Oncol 2011

Effect of Obesity and Outcome Tam vs Anastrozole ABCSG-12 Trial



Pfeiler G, et al. J Clin Oncol 2011

Effect of Obesity and Outcome Tam vs Anastrozole ATAC Trial

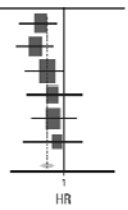


Sestak I, et al. J Clin Oncol 2010

Effect of Obesity and Outcome Tam vs Anastrozole ATAC Trial

All Recurrences

BMI	Anastrozole No.	Anastrozole %	Tamoxifen No.	Tamoxifen %	HR*	95% CI
< 23	55	11.3	79	16.5	0.64	0.45 to 0.91
23-25	66	13.2	81	20.9	0.58	0.41 to 0.82
25-28	90	16.2	114	19.7	0.76	0.57 to 1.00
28-30	54	16.6	63	19.8	0.83	0.57 to 1.20
30-35	72	16.3	92	19.2	0.84	0.61 to 1.14
> 35	39	19.7	50	21.8	0.76	0.49 to 1.16
All	366	14.8	479	19.4	0.73	0.63 to 0.83



Sestak I, et al. J Clin Oncol 2010

Outcomes in Obese vs. Nonobese Patients in E1199 According to Breast Cancer Tumor Type

	Disease-Free Survival		Overall Survival	
	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value
Overall	1.10 (0.96-1.26)	.14	1.13 (0.96-1.33)	.15
HR+/HER2–	1.23 (1.02-1.49)	.035	1.46 (1.15-1.85)	.002
HER2+	1.07 (0.77-1.47)	.70	0.89 (0.60-1.31)	.55
TNBC	1.01 (0.77-1.33)	.93	1.05 (0.77-1.43)	.75

[a] Multivariate analysis

Recently Opened NCIC/CTSU Trial

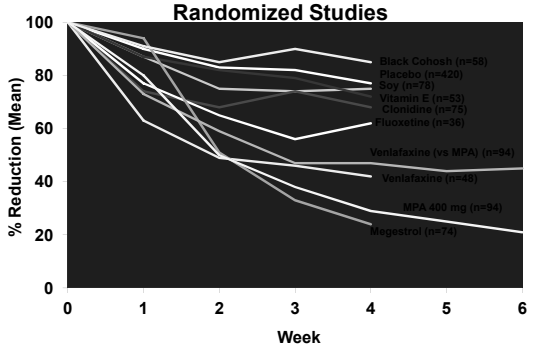
T1–3, N0-3,M0
Invasive breast cancer
Surgically removed +/-
Radiation/systemic therapy

→ Metformin 850 mg bid x 5 years

→ Placebo bid x 5 years

Sparano J, et al. SABCS 2010; abstract S2-1

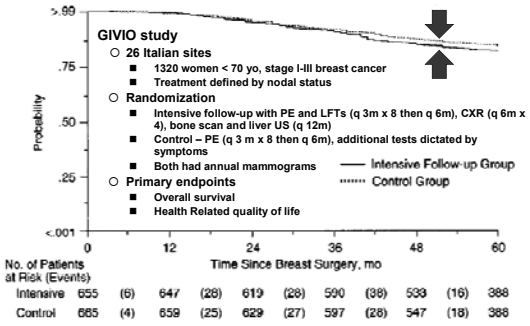
Mean Hot Flash Score Reduction Randomized Studies



Does Surveillance and Early Detection of Recurrence Matter?

- **Justifications:**
  - Early detection results in more effective treatment
  - Patients are reassured – does this improve quality of life?
  - Investigational endpoint
    - Monitor effectiveness of adjuvant therapy
- **Disadvantages:**
  - Aggressive screening results in overtreatment of early disease
  - Routine testing creates anxiety and need for additional tests
  - Increased costs to patients without benefit

GIVIO Trial



GIVIO Investigators. JAMA 1994

Consensus Recommendations for Follow-up After Early Stage Breast Cancer

- Annual mammography, monthly breast self exam
- Other routine cancer screening
- Regular clinic visits for H and P
  - Every 3-6 months for 3 years, every 6 months for 2 years, then yearly
- Health care maintenance
  - Bone and cardiovascular health
- No routine testing (labs or imaging). Testing as indicated by clinical findings.
- Resources:
  - NCCN guidelines (www.nccn.org)
  - ASCO guidelines (www.ASCO.org)
  - American Cancer Society

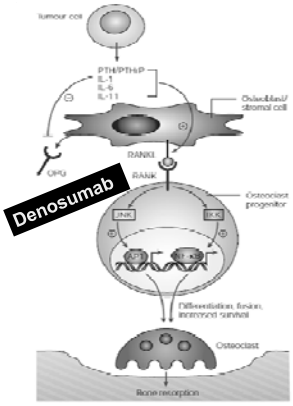
Bisphosphonate Effects on Skeletal Related Events in Breast Cancer Bone Metastases

	% pts with SRE	
Placebo	65% 24 months [1]	
Pamidronate	46%	
Pamidronate	49% 24 months [2]	
Zoledronic Acid	46%	(p = not sig)
Placebo	50% 12 months [3]	
Zoledronic Acid	30%	

[1] Lipton A et al, Cancer, 2000
[2] Rosen LS et al, Cancer, 2003
[3] Kohno N et al, J Clin Oncol 23, 2005

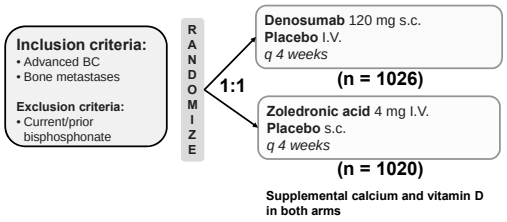
The RANK-RANK Ligand system in osteolytic bone metastases

Tumor ➔ PTHrp ➔RANK Ligand ➔ binds to receptor RANK ➔ osteoclast activation➔ bone resorption



Mundy GR. Nat Rev Cancer 2002

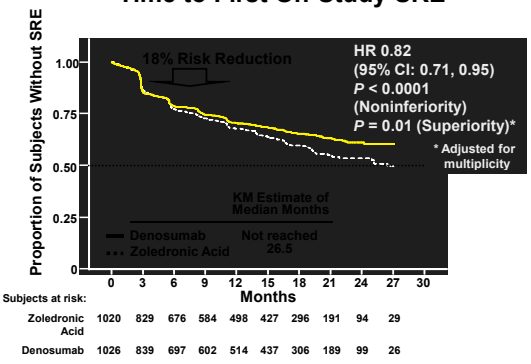
Denosumab vs. Zoledronic Acid for the Prevention of Skeletal-Related Events (SREs) From Breast Cancer Metastases



- **Primary endpoint: time to first on-study SRE (noninferiority)**
- **Secondary endpoints include: time to first on-study SRE (superiority), time to first and subsequent on-study SRE (superiority)**

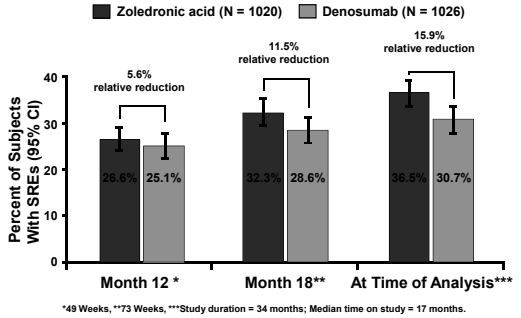
Stopeck A et al. J Clin Oncol 2010

Time to First On-Study SRE



Stopeck A et al. J Clin Oncol 2010

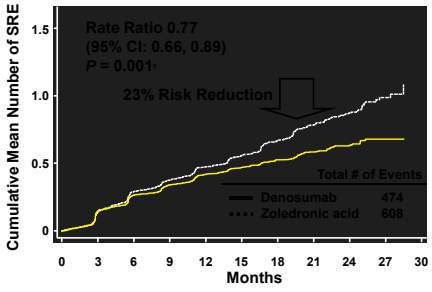
Proportion of Subjects Experiencing an SRE



*49 Weeks, **73 Weeks, ***Study duration = 34 months; Median time on study = 17 months.

Stopeck A et al. J Clin Oncol 2010

Time to First-and-Subsequent On-Study SRE (Multiple Event Analysis)



Stopeck A et al. J Clin Oncol 2010

Denosumab vs. Zoledronic Acid for the Prevention of SREs: Safety

Adverse Event	Denosumab (n = 1020)	Zoledronic Acid (n = 1013)
Overall	977 (96%)	985 (97%)
Serious	453 (44%)	471 (46%)
Acute Phase Reactions*	106 (10%)	277 (27%)
Pyrexia	9 (1%)	116 (11.5%)
Bone pain	13 (1.3%)	36 (4%)
Renal-Related Toxicities	50 (5%)	86 (8.5%)
Serious	2 (< 1%)	15 (1.5%)
ONJ†	20 (2%)	14 (1.4%)

* Within 3 days of treatment administration
† Osteonecrosis of the jaw; *P* = .39

Stopeck A et al. J Clin Oncol 2010

Recommendations for Bone Monitoring and Treatment

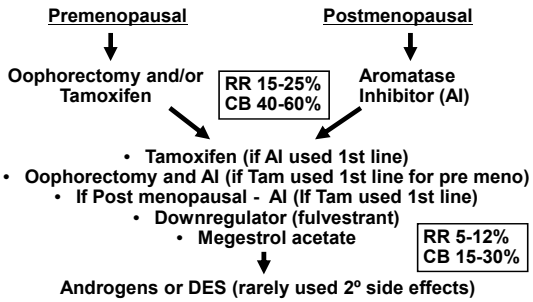
- Baseline bone health assessment
  - Dual energy x-ray absorptiometry (DEXA) Scan
  - Clinical factors (body mass, ethnicity, smoking history, prior personal or family history of fracture
- Follow-up bone health assessment
- Calcium, vitamin D replacement for all patients
- Anti-resorptive therapy (typically bisphosphonate) for:
  - T-score < -2.5 to -2.0
  - T-score or < 1.0 with additional risk factors
  - If DEXA scan not available, >1 clinical risk factors

Updated ASCO Guidelines for Bone Modifying Agents (BMA) in MBC

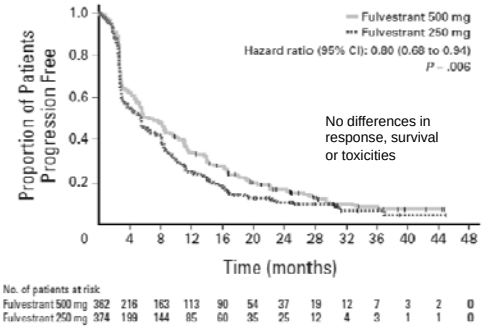
- BMAs are recommended for patients with metastatic breast cancer with evidence of bone destruction.
  - Denosumab 120 mg subQ every 4 weeks
  - Pamidronate 90 mg i.v. every 3 to 4 weeks
  - Zoledronic acid 4 mg i.v. every 3 to 4 weeks
- One BMA is not recommended over another
- Monitor creatinine level
- All patients should have a dental examination and preventive dentistry before using a BMA.
- At onset of cancer bone pain, provide standard of care for pain management and start BMAs.
- Use of biochemical markers to monitor BMA use is not recommended for routine care.

Van Poznak C et al. J Clin Oncol 2011

Hormonal Therapy Algorithm for Advanced Breast Cancer

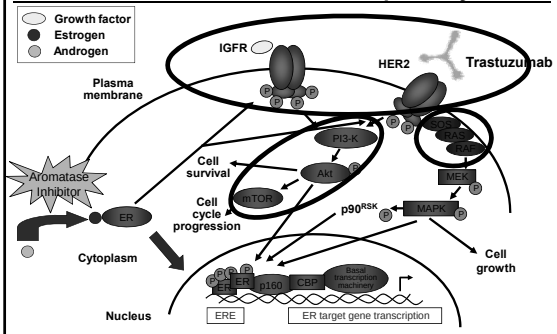


Dose of Fulvestrant and Outcome: CONFIRM Trial



Di Leo A et al. J Clin Oncol 2010

Cross-talk between signal transduction and endocrine pathways



Adapted from Johnston 2005

Randomized Phase II Trial of Tamoxifen +/- Everolimus

Inclusion criteria:
- HR$^+$/HER2$^-$ MBC
- Postmenopausal
- Prior AI

Stratify by:
- Primary vs. secondary hormone resistance

RANDOMIZE

Tamoxifen 20 mg/day **Everolimus** 10 mg/day **(n = 54)**

Tamoxifen 20 mg/day **(n = 57)**

Primary endpoint: CBR (CR + PR + SD at 6 months)
Secondary endpoints including: TTP, OS, ORR, safety

Bachelot et al. SABCS 2010; abstract S1-6

Randomized Phase II Trial of Tamoxifen +/- Everolimus: Results

Combination therapy significantly improved:
- **CBR: 61% vs. 42%; *P* = .045**
- **OS: HR 0.32 (95% CI, 0.15-0.68); *P* = .0019**

	Tamoxifen/ Everolimus (n = 54)	Tamoxifen (n = 57)	HR (95% CI)	*P* Value
Time to Progression	8.6 months	4.5 months	0.53 (0.35-0.81)	.0026
Primary Hormone Resistance (n = 54)	5.4 months	3.9 months	0.74 (0.42-1.3)	NR
Secondary Hormone Resistance (n = 56)	17.4 months	5.0 months	0.38 (0.21-0.71)	NR

Bachelot et al. SABCS 2010; abstract S1-6