

Best of ASCO 2008 Breast Cancer

Lou Fehrenbacher MD
September 6, 2008

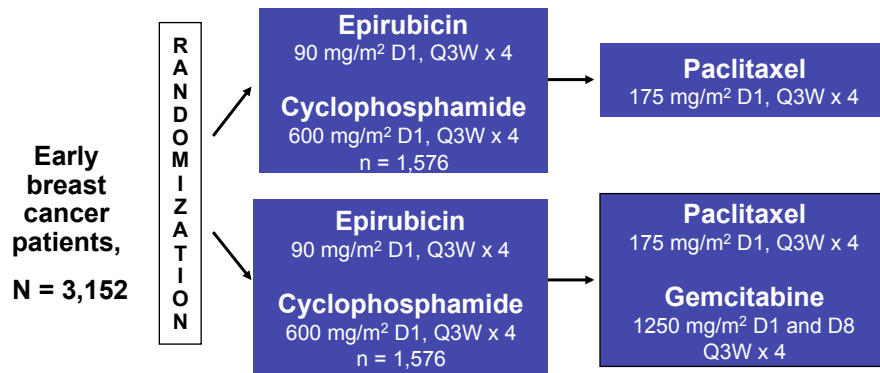
Best of ASCO 2008 Breast Cancer

- **Adjuvant Therapy**
 - tANGO: A randomized phase III trial of gemcitabine in paclitaxel-containing, epirubicin/cyclophosphamide-based, adjuvant chemotherapy for women with early stage breast cancer. **Abstract#506**. C.J. Poole
 - CALGB 49907: Standard chemotherapy (CMF or AC) versus capecitabine in early stage breast cancer patients aged 65 and older: Results of CALGB/CTSU 49907. **Abstract #507**. H.B. Muss
 - Vit D Deficiency: Frequency of vitamin D deficiency at breast cancer diagnosis and association with risk of distant recurrence and death in a prospective cohort study of T1-3, N0-1, M0 Breast Cancer. **Abstract #511**. P.J. Goodwin
 - Zoledronic acid: Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with endocrine-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12. **Abstract #LBA4**. M. Grant.
- **Metastatic Disease**
 - HER2(-) AVADO: Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer. **Abstract #LBA1011**. Miles, D.
 - HER2(+) A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+metastatic breast cancer progressing on trastuzumab therapy. **Abstract #1015**. J. O'Shaughnessy
 - HER2(+) Results of a phase II trial of trastuzumab and pertuzumab in patients with HER2+ metastatic breast cancer who had progressed during trastuzumab therapy. **Abstract #1026**. K.A.Gelmon
- **Pathophysiology**
 - Discordant Primary vs Metastatic: Molecular changes in the primary breast cancer versus the relapsed/metastatic lesion from a large population based database and tissue microarray series. **Abstract #1000**. R. MacFarlane
 - CTC/DTC's/Stem Cells- Multiple, if time permits

tANGO- Does Adding Gemcitabine to Adjuvant Chemorx Improve Outcomes?

- Poole, C., et.al.,
- Abstract #506, British/Irish Coop Effort
- Implications for Pending NSABP B-38 with an arm of ACx4, TGx4
- Does Addition of gemcitabine to paclitaxel, as in EC-TG add benefit to EC-T alone, or only toxicity

Phase III tAnGo Trial: Study Design

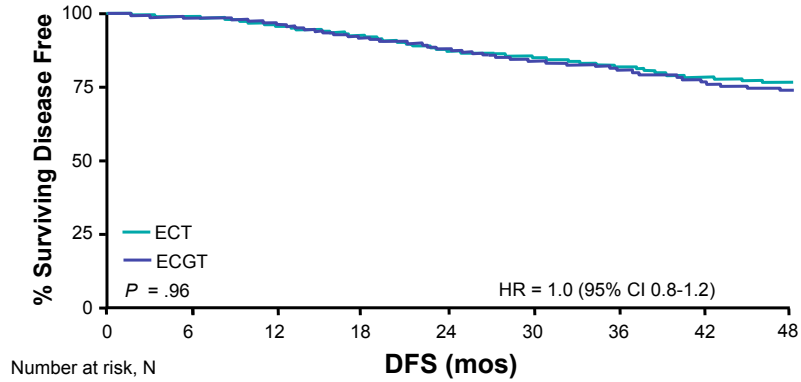


A British Irish Cooperative effort.

Poole CJ, et al. ASCO 2008. Abstract #506.

Phase III tAnGo Trial Disease-Free Survival: ECT Vs ECGT

No significant difference between treatments



	0	6	12	18	24	30	36	42	48
ECT	1571	1545	1479	1392	1156	834	533	162	86
ECGT	1570	1550	1488	1385	1158	813	531	154	88

Poole CJ, et al. ASCO 2008. Abstract 506.

Toxicity

Toxicity data are available from 3104 (99%) eligible pts (1554, 1550) through 23843 cycles (12016, 11827).

	%pts reporting severe grades	ECT	EC-GT	p
There were slight excesses in the number of pts reporting severe toxicities throughout EC-GT (p<0.05).	Neutropenia	27%	34%	<0.0001
	Infection	9%	13%	0.0007
	Fatigue	10%	13%	0.003
	Vomiting	7%	9%	0.03
	Anaemia	1%	2%	0.04
	Nausea	7%	8%	0.05
	Constipation	2%	3%	0.05
	Fever	3%	5%	0.06
	Diarrhoea	2%	3%	0.09
	Thrombocytopenia	<1%	1%	0.12
Neutropenic Sepsis was suffered by 5% EC-T & 6% EC-GT patients	Cough	<1%	<1%	0.18
	Superficial Thrombophlebitis	<1%	<1%	0.18
	DVT	<1%	1%	0.21
	Myalgia/arthralgia	12%	13%	0.27
	Neuro-sensory	4%	5%	0.31
	Stomatitis	2%	2%	0.41
	Dyspnoea	2%	3%	0.46
	Skin	1%	2%	0.65
	Alopecia	96%	95%	0.84

tANGO- Does Adding Gemcitabine to Adjuvant Chemorx Improve Outcomes?

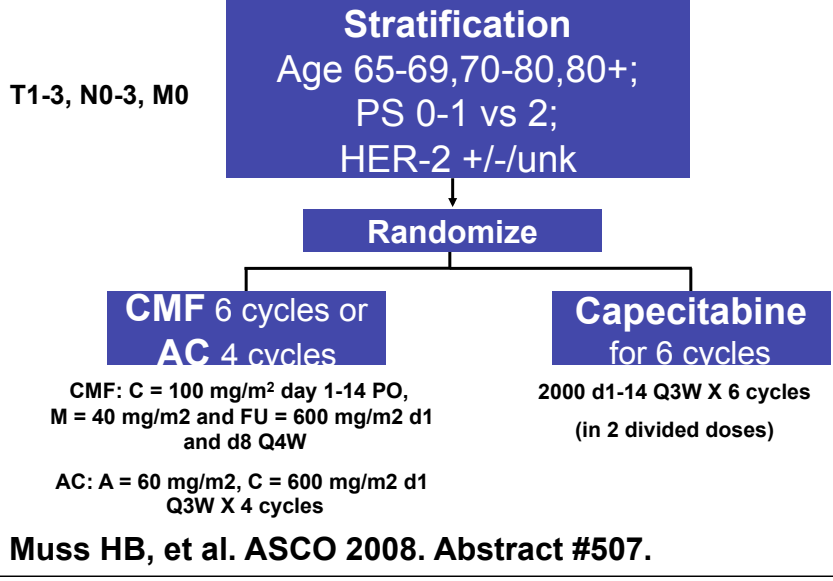
- **NO**
- Poole, C., et.al.,
- Abstract #506, British/Irish Coop Effort
- Negative Implications for Pending NSABP B-38 with an arm of ACx4, TGx4
- Addition of gemcitabine to paclitaxel, as in EC-TG does not add benefit to EC-T alone, only toxicity

CMF or AC vs Capecitabine in Adjuvant Chemorx for Breast Cancer Patients 65yo+

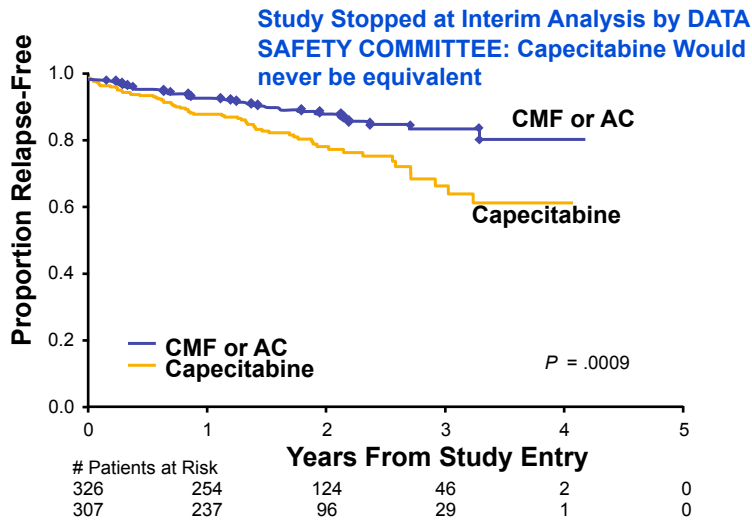
- Abstract 507
- Muss, H.,
- CALGB 49907, CTSU Intergroup Study
- Is Capecitabine equal in efficacy to CMF or AC in adjuvant chemotherapy for breast cancer in women 65+? Does it have a clear toxicity advantage?

CALGB 49907 Design: CMF or AC Vs Capecitabine in EBC Pts > 65 Yrs

T1-3, N0-3, M0

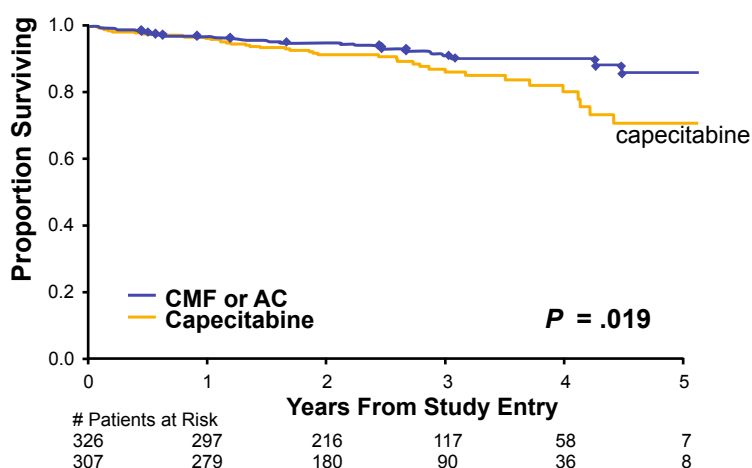


CALGB 49907: Relapse-Free Survival By Treatment Arm



Muss HB, et al. ASCO 2008. Abstract 507.

CALGB 49907 Overall Survival By Treatment Arm



Muss HB, et al. ASCO 2008. Abstract 507.

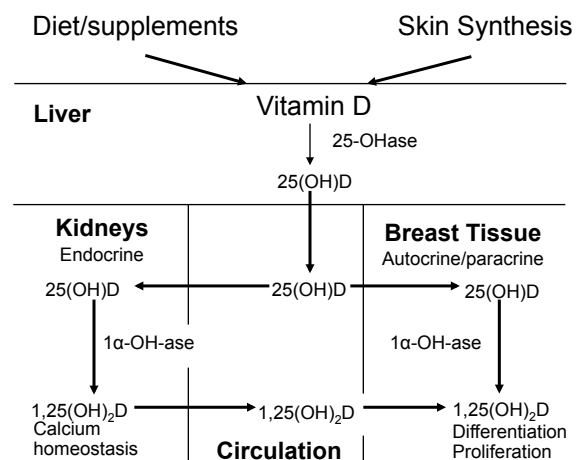
CMF or AC vs Capecitabine in Adjuvant Chemorx for Breast Cancer Patients 65yo+

- Abstract 507
- Muss, H.,
- CALGB 49907, CTSU Intergroup Study
- Capecitabine was INFERIOR to CMF or AC in adjuvant chemotherapy for breast cancer in women 65+. Worse DFS and OS, with no clear toxicity advantage
- Unplanned Subset analysis suggests particular inferiority in ER Negative tumors

Vitamin D Deficiency is Common at Breast Cancer Diagnosis and Is Associated with a Significantly Higher Risk of Distant Recurrence and Death in a Prospective Cohort Study of T1-3, N0-1, M0 Breast Cancer

- Abstract #511
- Goodwin, P. Sunnybrook, Toronto
- 512 women with newly dx. Breast cancer at academic institution in a northern latitude
- Mean age 51

Frequency of Vitamin D Deficiency at Breast Cancer Diagnosis: Background

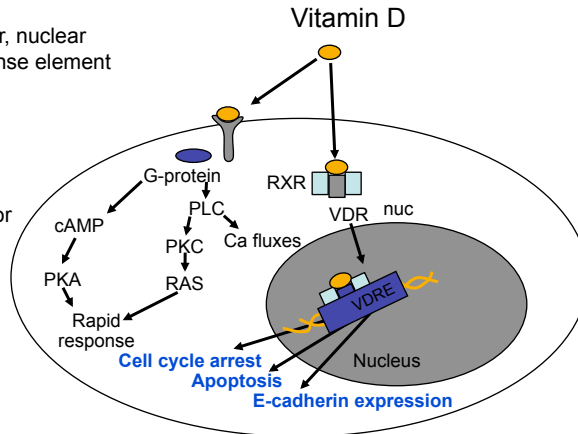


Goodwin PJ, et al. ASCO 2008. Abstract 511.

Vitamin D Deficiency in Breast Cancer

Cellular Effects in Breast Cancer

VDR – Vitamin D receptor, nuclear
 VDRE – Vitamin D response element
 cAMP – Cyclic AMP
 PKA – Protein kinase A
 PKC – Protein kinase C
 PLC – Phospholipase C
 RAS – GTPase, pathway
 RXR – Retinoid X receptor



Goodwin PJ, et al. ASCO 2008. Abstract 511.

Freq of Vit D Deficiency at BC Diagnosis and Risk of Recurrence: Study Design

Locoregional Breast Cancer T1-3, N0-1, M0
 ▪ Dx 1989 to 1996 (Toronto - latitude 43° 40')
 ▪ n = 512 women in **COHORT**

Blood – frozen at -80°C*
 Diet, Physical Activity, Clinical Data

Systemic Treatment
 (if any)

Annual Follow-up to 2007
 ▪ Distant recurrence
 ▪ Death
 Mean 11.6 years

* Analysed for 25-OH vitamin D in 2007

Vitamin D Deficiency in Breast Cancer

25-OH Vitamin D Levels at Diagnosis (Toronto – latitude 43° 40')

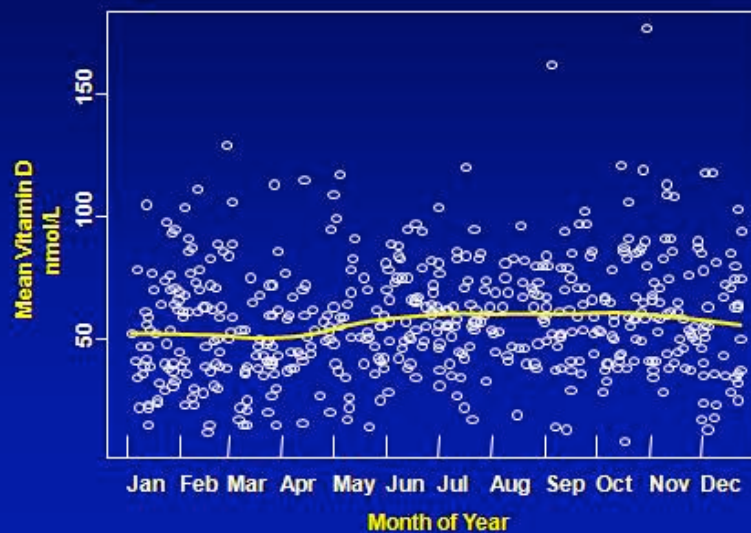
Mean: 58.1 ± 23.4 nmol/L

Range: 8-177 nmol/L

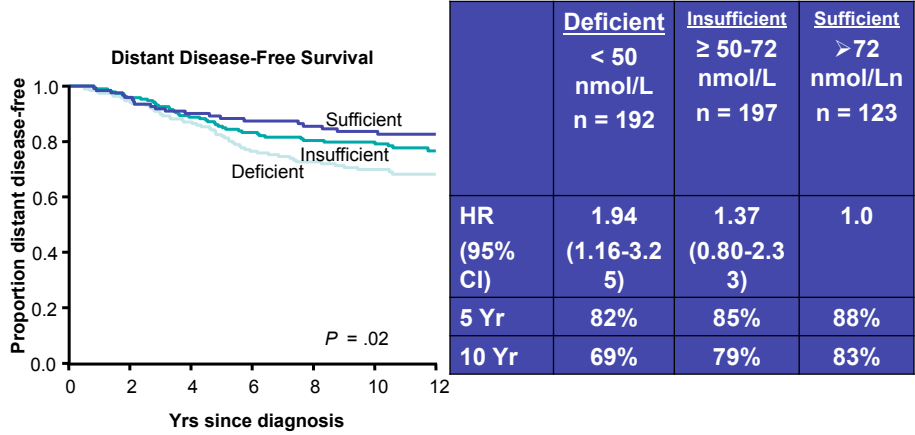
	nmol/L	ng/ml	#	%
Deficient	< 50	< 20	192	37.5
Insufficient	50-72	20-29	197	38.5
Sufficient	> 72-374	30-150	123	24.0
Toxic	> 374	>150	0	0

Vitamin D Deficiency in Breast Cancer

25-OH Vitamin D Levels at Diagnosis



Distant Disease-Free Survival by Vitamin D Level in EBC



Goodwin PJ, et al. ASCO 2008. Abstract 511.

Vitamin D Deficiency in Breast Cancer

Patient Factors Associated with Vitamin D Level

Factor	#	Mean Vitamin D (nmol/L)	p-value
Age	< 50 years	296	0.006
	≥ 50 years	216	
BMI	≤ 25 kg/m ²	280	0.004
	> 25-30 kg/m ²	149	
	> 30 kg/m ²	83	
Vitamin D Supplement	Yes	110	< 0.0001
	No	362	

Correlations (Spearman)

Factor	r	p-value
Retinol	0.18	0.0001
Vitamins B, C, E, riboflavin	0.16 < r < 0.25	< 0.05
Grains/cereals	0.13	0.005
Alcohol	0.16	0.0005*
Physical Activity	0.03	0.56
Insulin	-0.16	< 0.0004

* Not linear – highest levels with 5-10 drinks/week

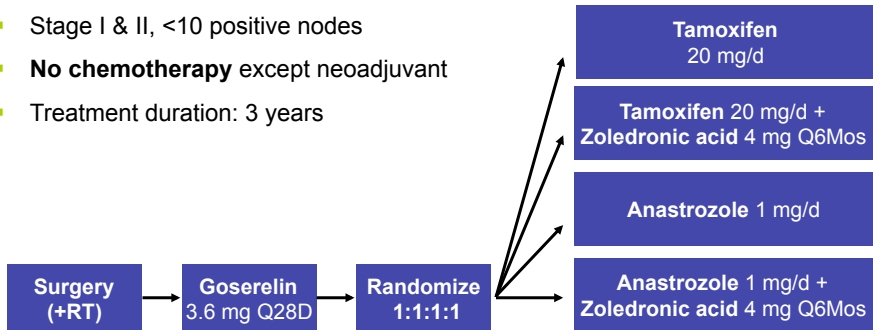
Vitamin D Deficiency in Breast Cancer

Conclusions

1. Vitamin D deficiency/insufficiency was common at breast cancer diagnosis. Only 24% had levels considered sufficient.
2. Vitamin D deficiency was associated with higher grade tumors.
3. Vitamin D deficiency was associated with an increased risk of distant recurrence and death.
4. Replication is recommended; an RCT of vitamin D supplementation may be indicated if results are replicated.
5. Caution is recommended in applying these results in the clinical situation – it is premature to advise breast cancer patients to use vitamin D supplementation in doses higher than recommended for bone health. Consideration should be given to measuring vitamin D levels in blood to ensure they are in a healthy range.

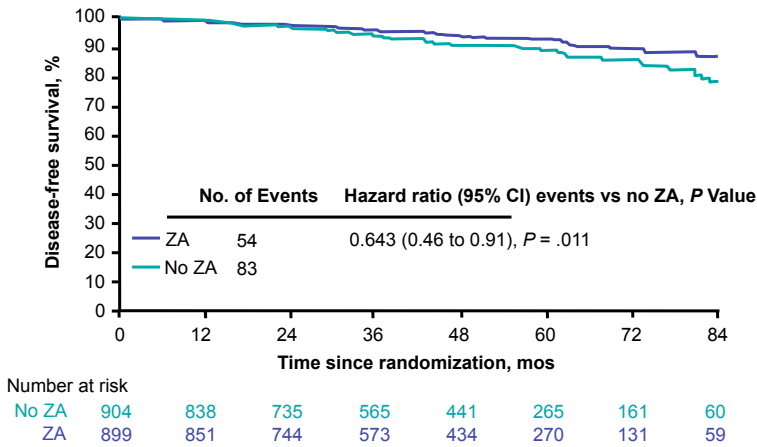
Ovarian Suppression Plus TAM or ANA +/- ZA: ABCSG-12 Trial Design

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



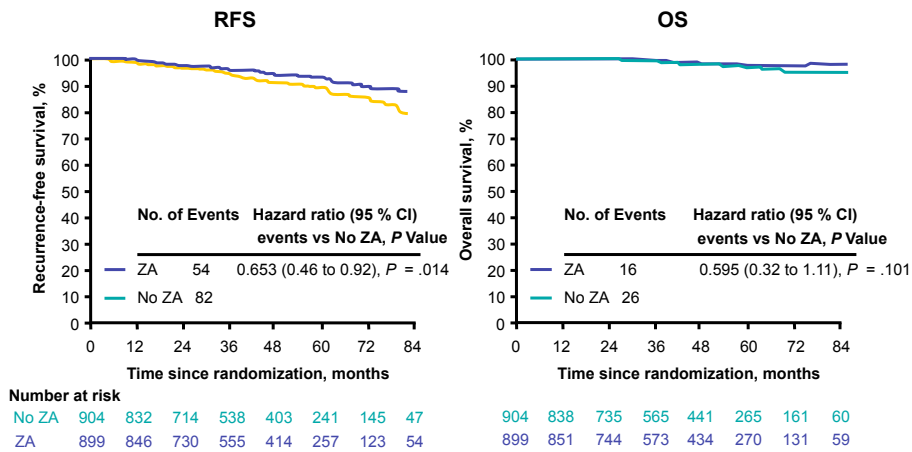
Gnant M, et al. ASCO 2008. Abstract LBA4.

Disease-Free Survival: ZA Vs No ZA



Gnant M, et al. ASCO 2008. Abstract LBA4.

Secondary Endpoints: ZA Vs No ZA



Gnant M, et al. ASCO 2008. Abstract LBA4.

Ovarian Suppression Plus TAM or ANA +/- ZA: ABCSG-12 Implications

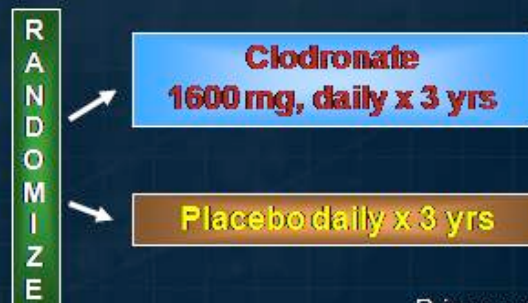
- Is the data sufficient to use bisphosphonates to reduce recurrence risk in pre or post menopausal breast cancer patients
 - Not used with chemorx
 - No survival advantage seen to date
 - Major larger studies pending results
 - Austrian study-
 - Premenopausal
 - Ovarian suppression + hormonal
 - No chemorx
 - Provocative, particularly with emerging physiologic effects
- Enroll patients into S-0307

Gnant M, et al. ASCO 2008. Abstract LBA4.

Breast Cancer: Adjuvant Clodronate

NSABP B34/CTSU

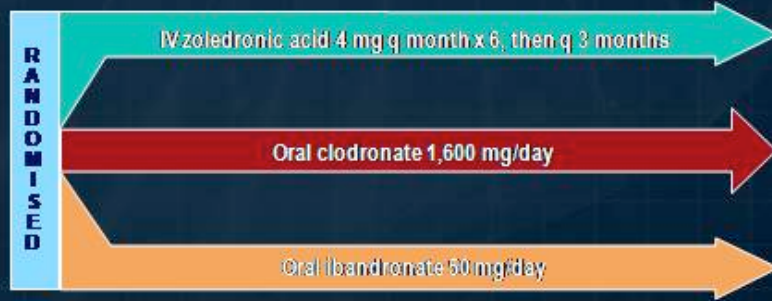
- 3200 patients with stage I, II breast cancer; may receive chemotherapy, hormonal therapy, both or neither. Accrual completed March 31, 2004



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Primary endpoint
Disease-free survival

SWOG 0307/Intergroup Trial



Target accrual
4,500 patients* with stage I, II, or IIIA breast cancer receiving standard systemic therapy

ASCO Annual '08 Meeting

Breast Cancer: 2408/AZURE

Primary End-point:

- Disease-Free Survival (DFS) & Bone Metastases-Free Survival



*Follow-up: 10 years for recurrence and survival

ASCO Annual '08 Meeting

AVADO: A Randomized Double Blind Study of Bevacizumab in Combination with Docetaxel as First Line Treatment of Patients with HER2 Negative Recurrent or Metastatic Breast Cancer: Safety and Efficacy

Question: Does the addition of Bevacizumab add Clinical Benefit to patients treated with docetaxel in first line metastatic breast cancer?

- Abstract LBA1011
- Miles, D. from Middlesex, U.K.
 - Acknowledged advisory, consultancy, and honoraria from Roche
- Sponsored by Roche
- Performed in Europe
- ASCO discussant: Kathy Albain,
 - Advisory Board Consultant to Genentech

AVADO Study Design

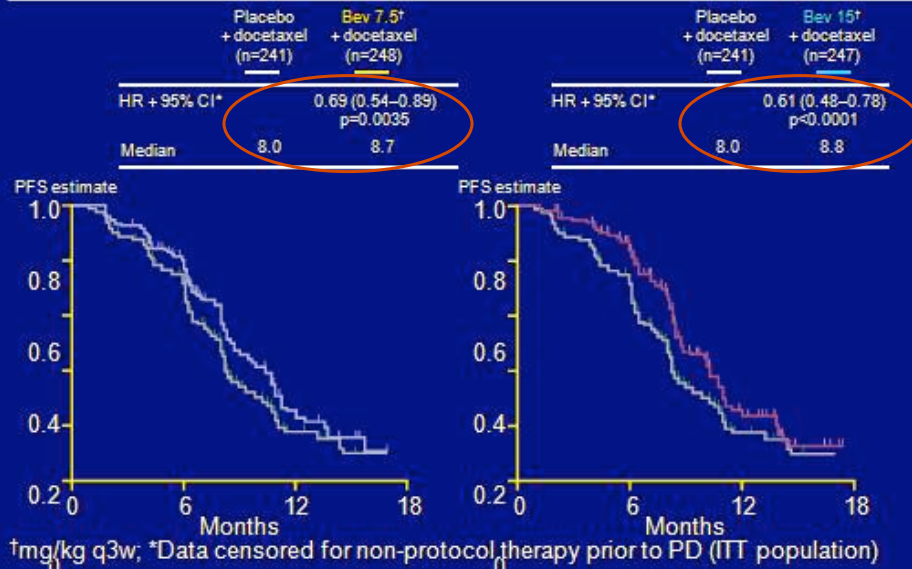
- **Metastatic Breast Cancer,**
 - newly diagnosed, without prior metastatic chemorx.
- **To receive IV Docetaxel 100 mg/m² q3wks and randomized to**
 - 1) placebo,
 - 2) 7.5 mg/m² Bevacizumab q3wks, or
 - 3) 15 mg/m² Bevacizumab q3wks.
 - 4) Option to receive Bevacizumab 2nd line
- **Primary End Point: Progression Free Survival**

AVADO: response (patients with measurable disease), %

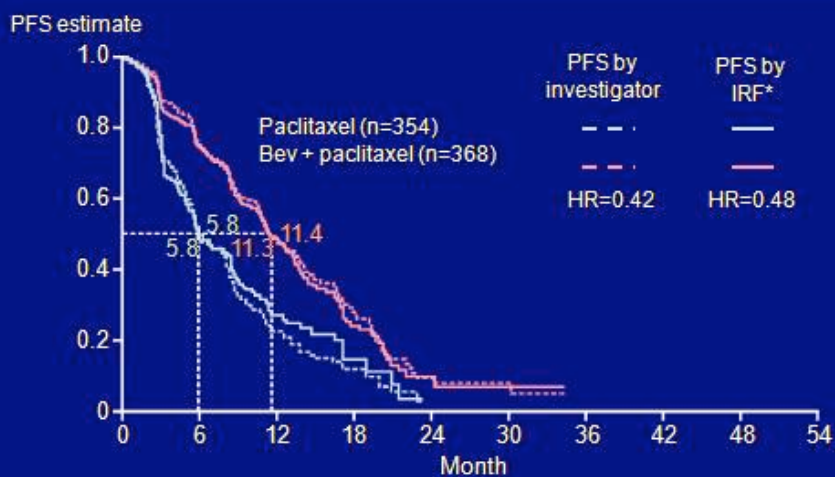
	Placebo + docetaxel (n=207)	Bev 7.5† + docetaxel (n=201)	Bev 15† + docetaxel (n=206)
Overall response rate	44	55	63
p value (vs control)	–	0.0295	0.0001
Best response			
CR	1	3	1
PR	44	52	62
SD	39	35	25
PD	12	5	4

†mg/kg q3w

AVADO: progression-free survival (stratified analysis)



E2100: significant progression-free survival increase confirmed by Independent Review Facility (IRF)



*Scans available for 90% of patients. Cameron D. EJC Suppl. 2008; Avastin SmPC 2008

AVADO Conclusions

- Both Bevacizumab doses of 2.5mg/kg/wk and 5mg/kg/wk increased PFS from 8.0 months (non Bev) to 8.7 and 8.8 months respectively. This was statistically significant. It is less clear if this 21 day difference is clinically significant.
- Survival data is immature.
- The PFS difference of 0.7 -0.8 months is quite dissimilar to the 5.5 month difference seen with weekly paclitaxel plus bevacizumab
- The benefit of adding bevacizumab to non weekly paclitaxel regimens appears unclear and may not be warranted. Ongoing trials including the Ribbon trials may provide answers to this question.
-

A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy

Abstract 1015

J.O'Shaughnessy, K.L.Blackwell, H.Burstein, A.M.Storniolo, G.Sledge, J.Baselga, M.Koehler, S.Laabs, A.Florance, D.Roychowdhury

- Abstract#1015 O'Shaughnessy, J.
 - Consultant to GSK
- Study performed in US and Europe
- Insightful for the ALLTO Adjuvant HER2+ Breast Cancer International Study

Phase III Study to Test if Total HER2+ Blockade Improves Clinical Outcome

Key Inclusion

- HER2+(FISH+/ IHC3+) MBC
- Progression on
 - Anthracycline
 - Taxane
 - Trastuzumab
- Progression on most recent trastuzumab regimen

Stratification Factors

- Visceral Disease
- Hormone Receptor

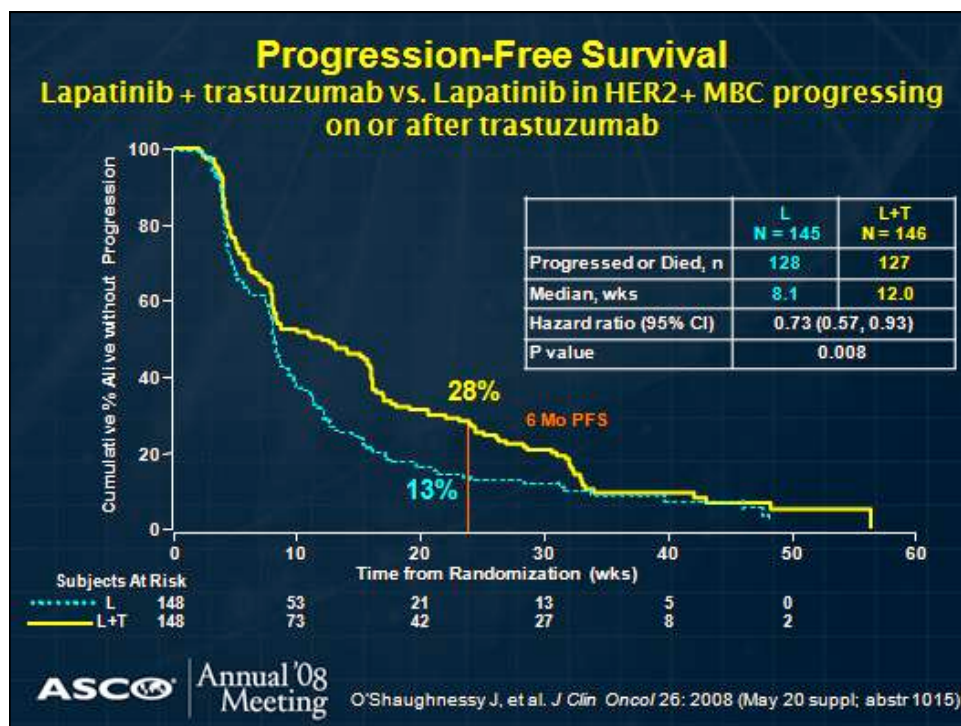
R A N D O M I Z A T I O N

- Lapatinib 1500 mg/day PO N=148
- Lapatinib 1000 mg/day PO Trastuzumab 4 → 2 mg/kg IV qw N=148

Crossover if PD after 4wk therapy (N=73)

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Study conducted and funded by GlaxoSmithKline ⁶

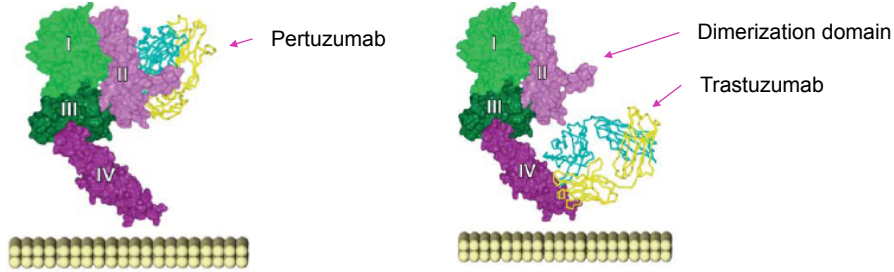


**Results of a Phase II Trial of
trastuzumab and pertuzumab in HER2+
patients with metastatic breast cancer
who had progressed during
trastuzumab therapy**

ASCO 2008 Abstract #F1026

K.A. Gelmon, P. Fumoleau, S. Verma,
A.M. Wardley, P.F. Conte, D. Miles, L. Gianni,
V.A. McNally, G. Ross, J. Baselga

Pertuzumab and trastuzumab bind to distinct epitopes on HER2 extracellular domain



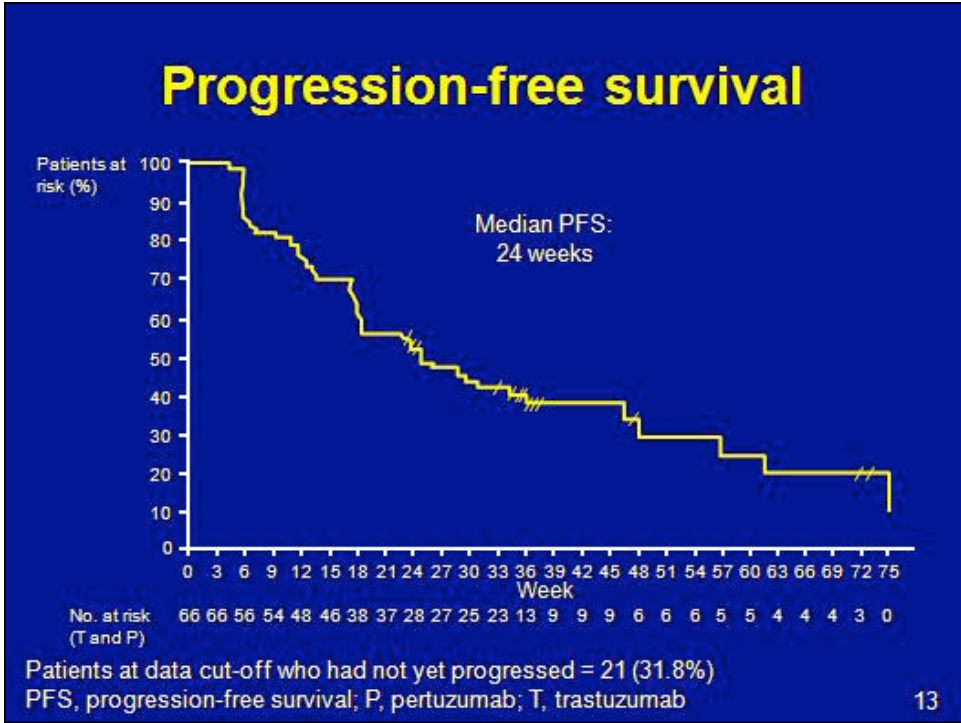
- Activates antibody-dependent cellular cytotoxicity (ADCC)
- Has a major effect on role of HER2 as a co-receptor with HER3 or EGFR
- Inhibits multiple HER-mediated signaling pathways

- Activates ADCC
- Prevents HER2 domain cleavage
- Inhibits HER2-mediated signaling pathways

Encouraging efficacy results

Response	n (%) (n=66)
Complete response ^a	5 (7.6)
Partial response ^a	11 (16.7)
Stable disease for ≥ 8 cycles (approx. 6 months)	17 (25.8)
Objective response rate	16 (24.2)
Clinical benefit rate^b	33 (50.0)

^aMedian duration of response was 25.1 weeks (12.4-66.6)
^bAt data cut-off 21 (31.8%) patients have not yet progressed



CLEOPATRA TOC4129g/WO20698: Phase III study of pertuzumab/trastuzumab in HER2+ MBC

HER2+ MBC
N = 800

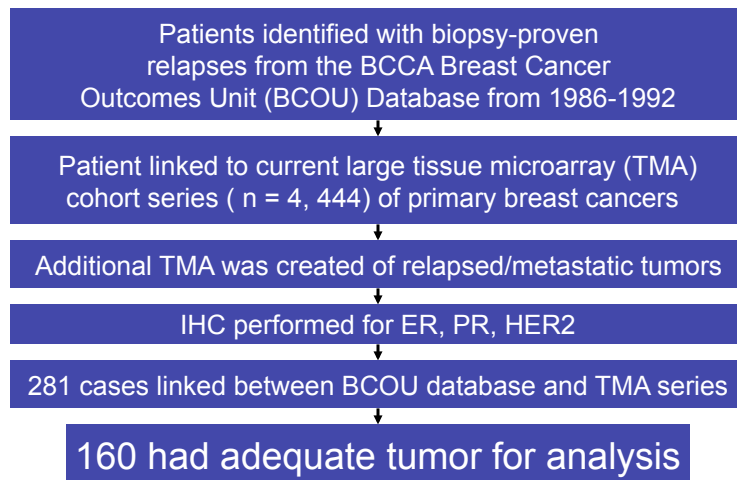
Docetaxel + trastuzumab + placebo

Docetaxel + pertuzumab + trastuzumab

An international Phase III randomized, double-blind, placebo-controlled study (approximately 250 sites worldwide)

- Enrolment stratified:
- Prior treatment for breast cancer
 - Geographic region of enrolment

Studying Molecular Changes in Primary Vs Metastatic Lesions: Study Design Schema



MacFarlane R, et al. ASCO 2008. Abstract 1000.

Changes in Primary Vs Metastatic Lesions: Results and Summary

Results:

- 160 tumor blocks with adequate tissue:
 - 115 (72%): no changes in ER/PR or HER2 status
- Of the 45 (28%) tumors with changes in receptor status:
 - 11(7%): local recurrence
 - 34(21%): regional or distant relapse:
 - 11 went from ER/PR+ to ER/PR-
 - 14 went from ER/PR- to ER/PR+
 - 3 went from HER2- to HER2+
 - 6 went from HER2+ to HER2-

Summary:

- Biopsies of relapsed/metastatic breast cancer should be performed routinely because of changes in ER/PR or HER2 receptor status

MacFarlane R, et al. ASCO 2008. Abstract 1000.