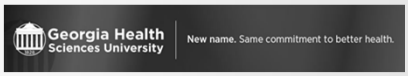
2011 GASCO Annual Meeting
Best of ASCO Review

Breast Cancer Abstracts:
Prevention & Adjuvant Therapy



Thomas A. Samuel, MD

Associate Professor of Medicine
Georgia Health Sciences University
Director, GHSU Clinical Breast Cancer Program
Member, GHSU Cancer Center
August 27, 2011

Disclosure

- ***Potential Conflicts of Interest:***
  - *Principal Investigator:*
    - *Novartis*
    - *ImClone*
    - *Exelesis*
  - *Sub-Investigator:*
    - *GHSU MB-CCOP*
  - *Speaker's Bureau:*
    - *Novartis*
    - *GlaxoSmithKline*

"We do not know what we mean by cure because there is a great difference between cure and long-term survival. "

Dr. Arthur Holleb
American Cancer Society

Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

- **Prevention**:
  - Abs # LBA-504- Goss, PE et al. (NCIC MAP.3)
- **Adjuvant Therapy:**
  - Abs# 1004- Budd, GT et al. (SWOG S0221)
  - Abs# LBA-1003- Whelan, TJ et al. (NCIC MA.20)
  - ACOSOG Z11- Giuliano, AE et al. (*JAMA* 2011)
  - Abs# 1000- Schneider, BP et al. (ECOG E5103)

Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

- **Prevention**:
  - Abs # LBA-504- Goss, PE et al. (NCIC MAP.3)
- **Adjuvant Therapy:**
  - Abs# 1004- Budd, GT et al. (SWOG S0221)
  - Abs# LBA-1003- Whelan, TJ et al. (NCIC MA.20)
  - ACOSOG Z11- Giuliano, AE et al. (*JAMA* 2011)
  - Abs# 1000- Schneider, BP et al. (ECOG E5103)

Exemestane for Breast-Cancer Prevention in Postmenopausal Women

Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., José E. Alés-Martínez, M.D., Ph.D., Angela M. Cheung, M.D., Ph.D., Rowan T. Chlebowski, M.D., Ph.D., Jean Wactawski-Wende, Ph.D., Anne McTiernan, M.D., John Robbins, M.D., Karen C. Johnson, M.D., M.P.H., Lisa W. Martin, M.D., Eric Winquist, M.D., Gloria E. Sarto, M.D., Judy E. Garber, M.D., Carol J. Fabian, M.D., Pascal Pujol, M.D., Elizabeth Maunsell, Ph.D., Patricia Farmer, M.D., Karen A. Gelmon, M.D., Dongsheng Tu, Ph.D., Harriet Richardson, Ph.D., for the NCIC CTG MAP.3 Study Investigators

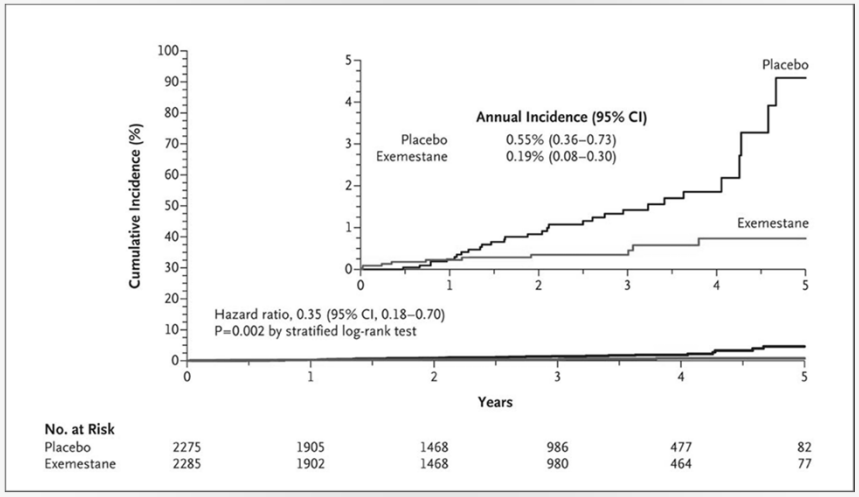
N Engl J Med
Volume 364(25):2381-2391
June 23, 2011

The NEW ENGLAND JOURNAL of MEDICINE

MAP.3 Study Overview

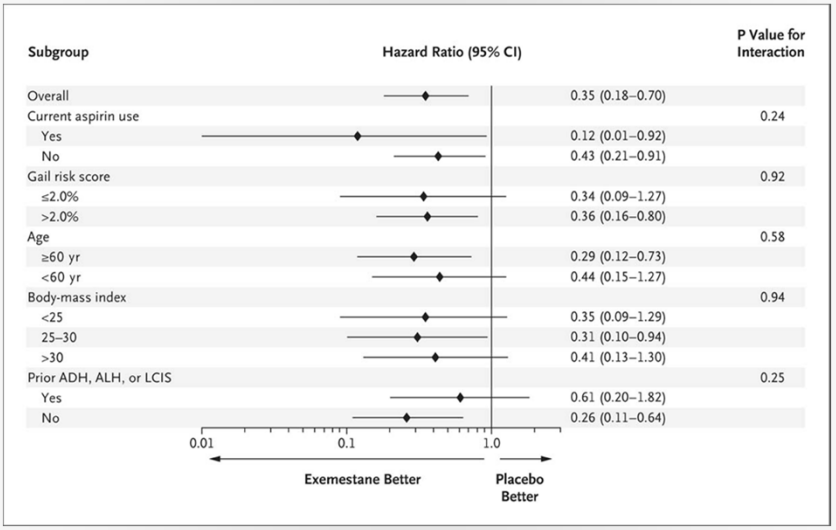
- In postmenopausal women at increased risk for breast cancer, exemestane reduced the annual incidence of invasive breast cancer by 65% after a median follow-up of only 3 years.
- Exemestane caused no serious toxic effects and only minimal changes in quality of life.

Cumulative Incidence of Invasive Breast Cancer.



Goss PE et al. N Engl J Med 2011;364:2381-2391

Hazard Ratios for the Development of Invasive Breast Cancer, According to Planned Subgroup Analysis.



Goss PE et al. N Engl J Med 2011;364:2381-2391

Incidence of Invasive and Preinvasive Breast Events by Treatment Group.

Table 2. **Incidence of Invasive and Preinvasive Breast Events by Treatment Group.***

Type of Event	Exemestane (N = 2285)		Placebo (N = 2275)		Hazard Ratio (95% CI)†	P Value‡
	No. of Cases	Annual Incidence (%)	No. of Cases	Annual Incidence (%)		
Invasive breast cancer						
All cases	11	0.19	32	0.55	0.35 (0.18–0.70)	0.002
ER-positive	7	0.12	27	0.46	0.27 (0.12–0.60)	<0.001
ER-negative	4	0.07	5	0.09	0.80 (0.21–2.98)	0.74
PR-positive	5	0.09	20	0.34	0.26 (0.10–0.69)	0.004
PR-negative	6	0.10	12	0.20	0.50 (0.19–1.33)	0.16
HER2/neu-positive	0	0.00	6	0.10	NA	NA
HER2/neu-negative	10	0.17	26	0.44	0.40 (0.19–0.82)	0.01
HER2/neu unknown	1	NA	0	NA	NA	NA
T stage 1	8	0.14	28	0.48	0.29 (0.13–0.65)	0.001
T stages 2 to 4	3	0.05	3	0.05	0.98 (0.20–4.86)	0.98
T stage X	0	NA	1	NA	NA	NA
Node-positive	3	0.05	9	0.15	0.33 (0.09–1.71)	0.08
Node-negative	7	0.12	22	0.38	0.33 (0.14–0.78)	0.008
Node unknown	1	NA	1	NA	NA	NA
M stage 0	11	0.19	30	0.51	0.38 (0.19–0.75)	0.004
M stage X1	0	NA	2	NA	NA	NA
DCIS§	9	0.16	14	0.24	0.65 (0.28–1.51)	0.31
Invasive breast cancer and DCIS§	20	0.35	44	0.77	0.47 (0.27–0.79)	0.004
ADH, ALH, and LCIS	4	0.07	11	0.20	0.36 (0.11–1.12)	0.08

* ADH denotes atypical ductal hyperplasia, ALH atypical lobular hyperplasia, CI confidence interval, DCIS ductal carcinoma in situ, ER estrogen receptor, HER2 human epidermal growth factor receptor type 2, LCIS lobular carcinoma in situ, NA not available (i.e., not calculated because of small number of events), and PR progesterone receptor.
† The hazard ratio is for the comparison of exemestane with placebo.
‡ P values were obtained with the use of a stratified log-rank test.
§ Women with prior DCIS at baseline were excluded.

Goss PE et al. N Engl J Med 2011;364:2381-2391

Side Effects during Treatment, According to Severity.

Table 3. **Side Effects during Treatment, According to Severity.***

Side Effect	Exemestane (N = 2240)					Placebo (N = 2248)					P Value
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	
		no.			*no. (%)*		*no.*			*no. (%)*	
Any	464	931	536	32	1963 (88)	557	877	437	30	1901 (85)	0.003
Cardiac: hypertension	119	109	112	1	341 (15)	124	118	109	3	354 (16)	0.65
Endocrine											
Hot flashes	489	344	67		900 (40)	450	225	43		718 (32)	<0.001
Fatigue	342	150	31	2	525 (23)	305	135	25		465 (21)	0.03
Sweating	284	201	1		486 (22)	263	169	1		433 (19)	0.046
Insomnia	117	98	15		230 (10)	127	55	7		189 (8)	0.04
Constitutional and gastrointestinal											
Diarrhea	77	32	9		118 (5)	58	16	1		75 (3)	0.002
Heartburn	223	92	17		332 (15)	200	79	10		289 (13)	0.06
Nausea	137	15	3		155 (7)	102	18	2		122 (5)	0.04
Musculoskeletal: arthritis	102	113	30	2	247 (11)	96	83	17		196 (9)	0.01
Neurologic											
Dizziness	145	35	9		189 (8)	152	48	9		209 (9)	0.32
Mood alteration or depression	123	90	19	4	236 (11)	128	98	8	1	235 (10)	0.96
Pain											
Back	106	77	21	2	306 (9)	119	80	23		222 (10)	0.45
Extremity	67	68	17	1	153 (7)	60	54	8		122 (5)	0.054
Joint	294	293	75	3	665 (30)	308	264	33	1	606 (27)	0.04
Muscle	69	62	16		147 (7)	111	67	14		192 (9)	0.01
Upper respiratory: cough	196	28	10		234 (10)	224	31	11		266 (12)	0.14
Sexual function: vaginal dryness	209	142	1		352 (16)	219	124			343 (15)	0.68
Secondary-end-point toxic effects											
Clinical skeletal fracture					149 (6.7)					143 (6.4)	0.72
New osteoporosis					37 (1.7)					30 (1.3)	0.39
Cardiovascular events					106 (4.7)					111 (4.9)	0.78
Other solid tumors or hematologic malignant lesions					43 (1.9)					38 (1.7)	0.58

* The grades of severity are based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, as follows: 0 indicates none, 1 mild (intervention not needed), 2 moderate (requiring minimal or noninvasive intervention and limiting age-appropriate activities of daily living), 3 severe (medically significant, requiring hospitalization, and limiting self-care activities of daily living), 4 life-threatening, and 5 death (related to the adverse event).

Conclusions

- Exemestane significantly reduced invasive breast cancers in postmenopausal women who were at moderately increased risk for breast cancer.
- During a median follow-up period of 3 years, exemestane was associated with no serious toxic effects and only minimal changes in health-related quality of life.

Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

- **Prevention**:
  - Abs # LBA-504- Goss, PE et al. (NCIC MAP.3)
- **Adjuvant Therapy:**
  - Abs# 1004- Budd, GT et al. (SWOG S0221)
  - Abs# LBA-1003- Whelan, TJ et al. (NCIC MA.20)
  - ACOSOG Z11- Giuliano, AE et al. (*JAMA* 2011)
  - Abs# 1000- Schneider, BP et al. (ECOG E5103)

First analysis of SWOG S0221: A phase III trial comparing chemotherapy schedules in high-risk early breast cancer.

G. T. Budd, W. E. Barlow, H. C. F. Moore, T. J. Hobday, J. A. Stewart, C. Isaacs, M. Salim, J. K. Cho, K. Rinn, K. S. Albain, H. K. Chew, G. V. Burton, T. D. Moore, G. Srkalovic, B. A. McGregor, L. E. Flaherty, R. B. Livingston, D. Lew, J. Gralow, G. N. Hortobagyi

Abs# 1004

AC+G Regimen: Background (1)

- U. Washington Adjuvant Experience
  - Dox 24 mg/m2/wk + Cyclo 60 mg/m2/d po + GCSF days 2-7
  - 85% 5 year disease-free survival in node+ breast cancer when followed by weekly paclitaxel
- S9625: Locally Advanced SWOG Phase II
  - 26% pCR rate to neo-adjuvant AC+G (without taxane)
- S0012: Locally Advanced SWOG Phase III
  - AC+G vs AC q 3 wk x 5, followed by weekly paclitaxel
  - 24% pCR vs 21% overall (p=0.45)
  - 27% pCR vs 12% in inflammatory cancer (p=0.06)

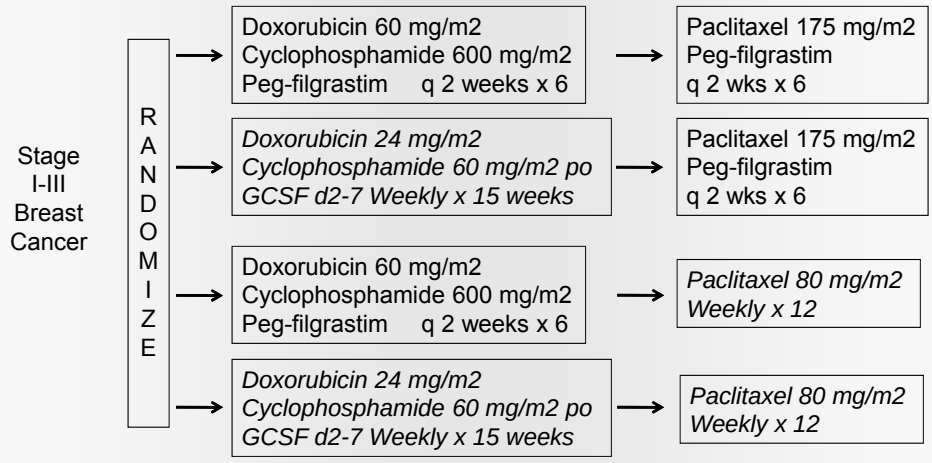
AC+G Regimen: Background (2)

- Some features of "Metronomic Chemotherapy"
  - Possible anti-angiogenic as well as cytotoxic effects
  - Frequent, modest doses of cytotoxic chemotherapy
  - But, hematopoietic growth factors required

S0221: Eligibility

- Female or Male (19 males actually enrolled)
- Histologically Proven Stage I-III Invasive Breast Cancer
- "High Risk," defined as
  - Node+ (N1-3)
  - Any Primary Tumor ≥2 cm
  - Tumor ≥1 cm if
    - ER- and PR-
    - ER+ or PR+ if Recurrence Score ≥26
- HER2+ tumors allowed
  - Trastuzumab given with paclitaxel after 11/15/2006

S0221: Schema
2 x 2 Factorial Design



S0221: Statistical Design

- 3250 pts to be randomized equally to the 4 arms of a 2x2 factorial design
- Primary Endpoint: Disease-free survival (DFS)
  - Power to detect HR 0.82 when comparing each weekly factor to q2 week arms
- First interim analysis (of 6 planned) after 30% of anticipated events
  - Test of efficacy: one-sided p-value ≤ 0.0001
  - Test of "futility": Lower bound of 99.5% CI for the hazard ratio > 0.82 suggesting a benefit to weekly therapy would not be found

S0221: 1st Interim Analysis

- At the first interim analysis, the prescribed 99.5% confidence interval boundary for futility for the AC+G arm was crossed, excluding the hypothesis that the hazard ratio was 0.82 or better in favor of the AC+G arm.
- No boundary was crossed for the paclitaxel comparison and there was no significant interaction of the two factors.
- DSMC recommended suspending randomization to the AC factor – recommendation accepted by SWOG and NCI

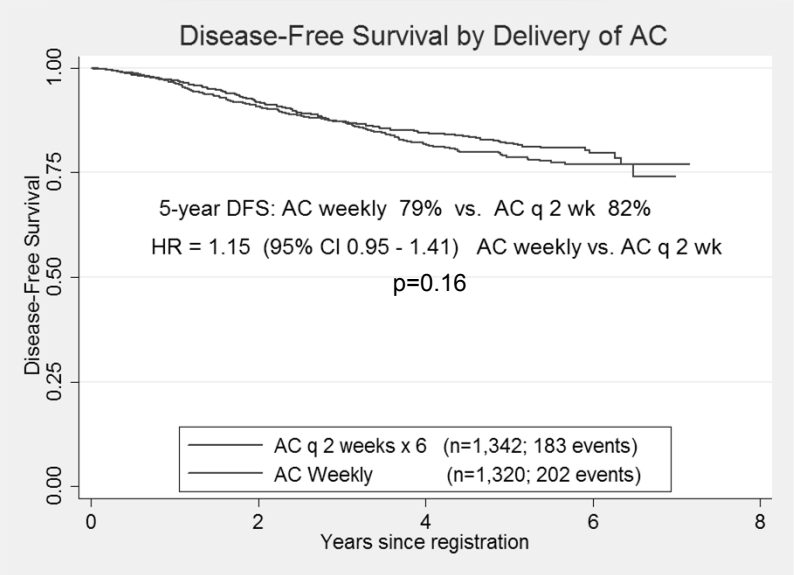
Current Results for AC (ddAC vs. wAC+G)

- Results collapsed over paclitaxel arms
- The arms are balanced for standard prognostic factors
- Results presented:
  - Population characteristics
    - 2716 randomized patients
  - Disease-free survival to date by AC arm
    - 2662 eligible patients with follow-up
  - Major subset analyses
  - Overall survival to date by AC arm
  - Toxicity
    - 2480 patients with complete Toxicity Evaluation

Patient Characteristics

Characteristic	Continuous AC+G	AC q 2 weeks x 6	Total
Randomized	1341	1375	2716
Known ineligible or withdrew consent	21 (1.6%)	33(2.4%)	54 (2.0%)
Analyzed	1320	1342	2662
Black race	155 (11.7%)	147 (11.0%)	302 (11.3%)
Age			
Median (years)	50	51	51
Range (years)	21-79	23-86	21-86
Menopausal status			
Pre	620 (47.5%)	627 (47.6%)	1247 (47.6%)
Post	685 (52.5%)	689 (52.4%)	1374 (52.4%)
Unknown/NA(males)	15	26	41
Node +	1016 (77.3%)	1016 (76.2%)	2032 (76.7%)
Node -	298 (22.7%)	318 (23.8%)	616 (23.3%)
ER-/PR-	431 (32.8%)	442 (33.1%)	873 (33.0%)
ER+ or PR+	883 (67.2%)	892 (66.9%)	1775 (67%)
HER2+	231 (17.7%)	243 (18.4%)	474 (18.0%)

S0221: Updated Interim Analysis



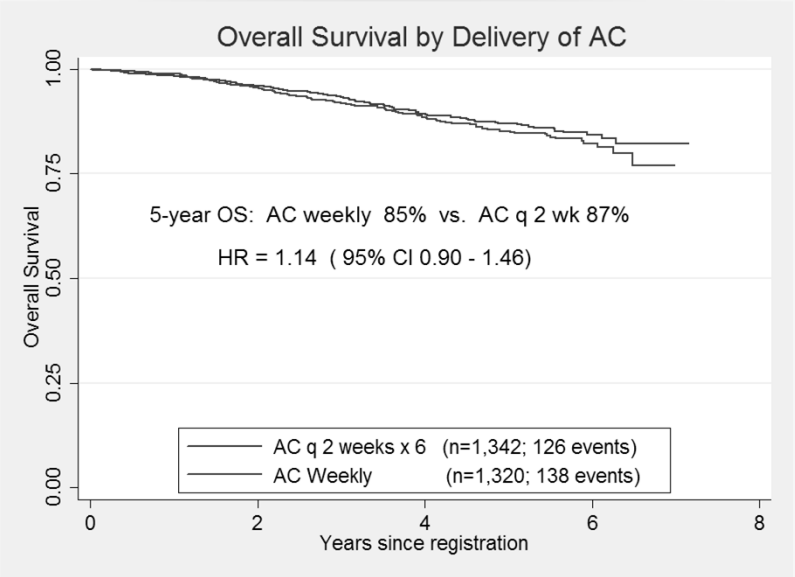
S0221: First Interim Analysis

DFS Subset Analysis

Subgroup	HR (Weekly vs. Q 2 week)	95% CI
All	1.15	0.95 – 1.41
Receptor Positive	1.14	0.87 – 1.50
Receptor Negative	1.21	0.89 – 1.63
Node Negative	1.44	0.85 – 2.42
Node Positive	1.09	0.88 – 1.36
HER2 Positive	1.19	0.73 – 1.93

Adjusted for paclitaxel administration

S0221: Updated Interim Analysis



S0221 Toxicity: First Interim Analysis - 2480 patients

Hemoglobin: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
9%	**0.6%**	5%	0.25%	<0.001
WBC: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
8%	**12%**	11%	4%	0.001
Neutrophils: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
8%	18%	15%	8%	0.09
Platelets: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
2%	0.8%	3%	0.4%	0.6

S0221 Toxicity: First Interim Analysis - 2480 patients

Infection – Febrile Neutropenia: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
5%	**1%**	1.7%	0.25%	<0.001
Infection – Non-Neutropenic: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
2.8%	0.08%	2.4%	0.33%	0.84
Grade 5: 0.08%		Grade 5: 0.16%		

S0221 Toxicity: First Interim Analysis - 2480 patients

Mucositis: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
2%	0	**8%**	**0.2%**	<0.001
Dermatologic/Hand-Foot Syndrome: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
2%	0	**15%**	**2%**	<0.001

S0221 Toxicity: First Interim Analysis - 2480 patients

Cardiac: AC Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
0.9%	**0.2%**	0.4%	0	0.046
Grade 5: 0.08%				
Cardiac: Both AC and Paclitaxel Segments				
Q 2 Week		**Weekly**		
3	4	3	4	p-value
1.7%	**0.5%**	0.5%	0	<0.001
Grade 5: 0.3%				

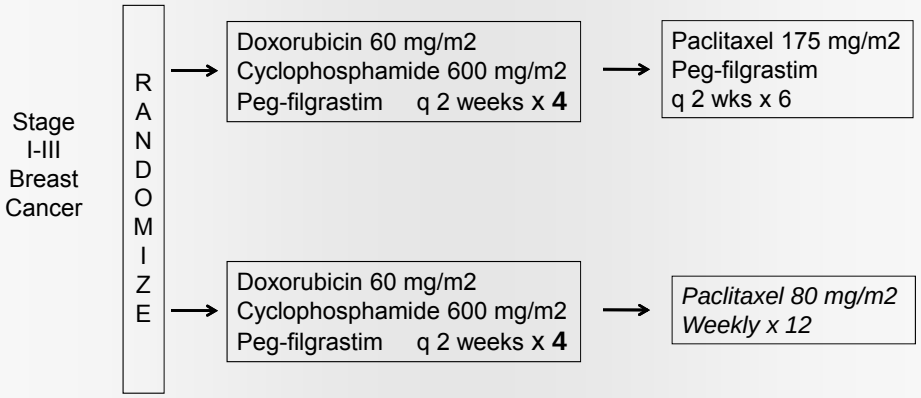
S0221 Toxicity: First Interim Analysis - 2480 patients

- Treatment-Related Deaths: 13/2480
  - Infection: 4
  - Cardiac: 3
  - Pulmonary: 1
  - Multi-organ Failure: 2
  - Sudden Death: 2
  - Liver Failure: 1
- Secondary Leukemia/MDS
  - AC q 2 wk: 11
  - AC+G: 10

S0221 Conclusions

- The toxicities of continuous AC+G and q 2 week AC differ
  - Weekly produces more stomatitis, dermatologic toxicity
  - Q 2 weeks produces more myelosuppression, cardiac toxicity
- Continuous AC+G is not superior to q 2 week AC and is not recommended for routine use
- The optimal dose and schedule of paclitaxel administration warrants determination
  - Changes in dose and schedule can significantly affect the toxicity and efficacy of chemotherapy

S0221: Revised Schema for remaining 534 patients



Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

- **Prevention**:
  - Abs # LBA-504- Goss, PE et al. (NCIC MAP.3)
- **Adjuvant Therapy:**
  - Abs# 1004- Budd, GT et al. (SWOG S0221)
  - Abs# LBA-1003- Whelan, TJ et al. (NCIC MA.20)
  - ACOSOG Z11- Giuliano, AE et al. (*JAMA* 2011)
  - Abs# 1000- Schneider, BP et al. (ECOG E5103)

NCIC CTG MA.20:

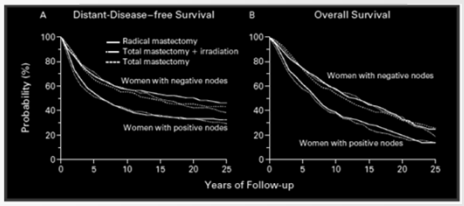
An intergroup trial of regional nodal irradiation in early breast cancer.

T. J. Whelan, I. Olivotto, I. Ackerman, J. W. Chapman, B. Chua, A. Nabid, K. A. Vallis, J. R. White, P. Rousseau, A. Fortin, L. J. Pierce, L. Manchul, P. Craighead, M. C. Nolan, J. Bowen, D. R. McCready, K. I. Pritchard, M. N. Levine, and W. Parulekar

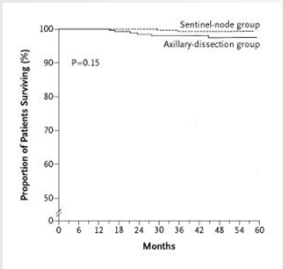
Abs# LBA-1003

NCIC MA.20

- Designed to ask question:
  - ***Does more regional radiation reduce systemic failure and reduce BC-related mortality?***
- Prior trials have shown more axillary surgery does not improve survival outcomes



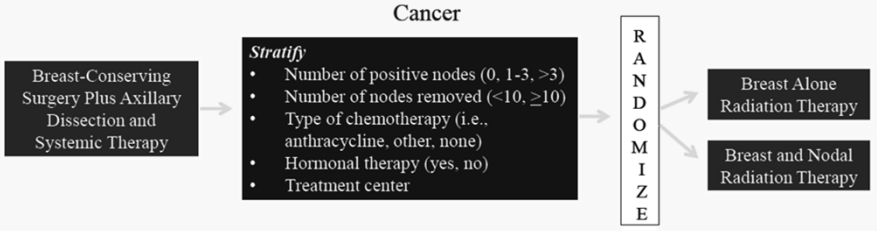
NSABP B-4 Fisher et al. NEJM 2002;347:1233-41.



Veronesi et al. NEJM 2003;349:546-53.

NCIC MA.20:

MA20 Study Schema: A Phase III Study of Regional Radiation Therapy in Early-Stage Breast Cancer

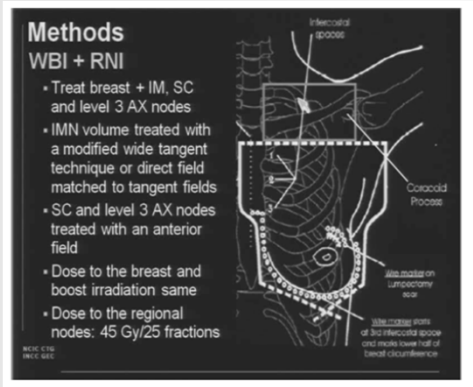


Inclusion Criteria

- Invasive, female breast cancer
- Breast conserving surgery plus Level I, II axillary dissection (or SLN only if node negative)
- Systemic therapy with chemotherapy, hormones, or both
- Moderate to high risk of regional recurrence on the basis of:
  - -Involved axillary nodes
  - -Or if node-negative, patients must have tumors ≥2.0 cm in diameter, have <10 nodes dissected, and have either grade 3 histology, estrogen receptor-negative disease, or the disease present in lymphovascular spaces in the breast

NCIC MA.20

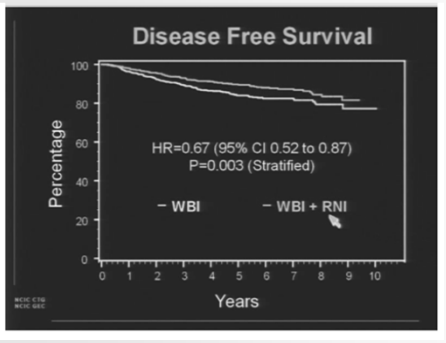
- Planned accrual=1822 (actual n=1832)
  - WBI= 916
  - WBI + RNI= 916
- Powered to detect 5% improvement in survival at 5 years
- Based upon interim results, DSMC advised results to be released



Whelan et al. ASCO 2011 LBA1003

NCIC MA.20 Results

	WBI only (%)	WBI + RNI (%)	p
Isolated LR DFS*	94.5	96.8	.02
DDFS	87	92.4	.002
DFS	84	89.7	.003
OS	90.7	92.3	.07



Whelan et al. ASCO 2011 LBA1003

***identical IBR in each group**
67% of recurrences were in the axilla

NCIC MA.20 Adverse Events

	WBI only (%)	WBI + RNI (%)	p
XRT Dermatitis	40	50	<.001
Pneumonitis > grade 2	0.2	1.3	.01
Lymphedema	4.1	7.3	.004

Whelan et al. ASCO 2011 LBA1003

NCIC MA.20 Conclusions

Trial Conclusions:

- RNI, added to WBI increased DFS at 5 yrs with a reduction in both locoregional and distant recurrence
- Trend toward OS benefit
- RNI associated with increased pneumonitis & lympedema

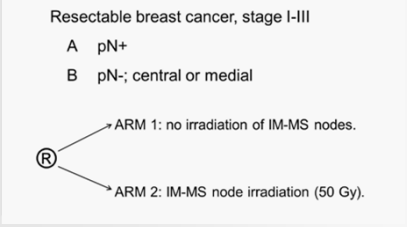
Whelan et al. ASCO 2011 LBA1003

NCIC MA.20 Clinical Implications

Clinical Implications:

- Pts with 1-3 LN+:
  - RNI needed
  - Not candidates for partial breast XRT
  - Not candidates for hypofractionation
  - May need PMRT
    - Complicates reconstruction
    - More pts treated

- EORTC 22922/10925 asks similar question: (n=4004)



Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

- **Prevention**:
  - Abs # LBA-504- Goss, PE et al. (NCIC MAP.3)
- **Adjuvant Therapy:**
  - Abs# 1004- Budd, GT et al. (SWOG S0221)
  - Abs# LBA-1003- Whelan, TJ et al. (NCIC MA.20)
  - ACOSOG Z11- Giuliano, AE et al. (*JAMA* 2011)
  - Abs# 1000- Schneider, BP et al. (ECOG E5103)

ACOSOG Z0011

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis
A Randomized Clinical Trial

Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall L, Morrow M

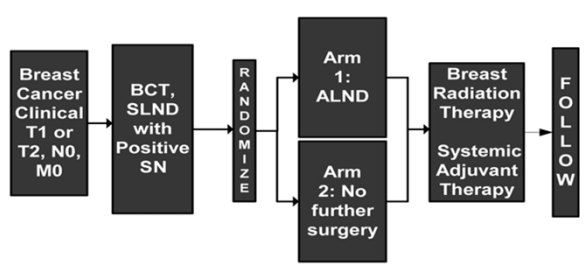
JAMA. 2011 Feb 9;305(6):569-75.

ACOSOG Z0011

- Hypothesis:

SLND alone achieves similar locoregional control and survival as Level I and II ALND for H&E SN node-positive women.

ACOSOG Z0011



•**Eligibility: (n=891)**

- •***Clinical T1 T2 N0*** **breast cancer**
- **•H&E-detected metastases in SN (AJCC 5th edition)**
- **•Lumpectomy with whole breast irradiation**
- **•Adjuvant systemic therapy by choice**

•**Ineligibility**

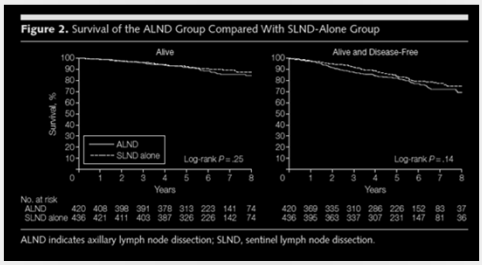
- ***•Third field (nodal irradiation) or APBI***
- ***•Metastases in SN detected by IHC***
- ***•Matted nodes***
- ***•3 or more involved SN***

ACOSOG Z0011

- Target accrual=1900
- Primary endpoint was overall survival as a measure of noninferiority of the experimental arm (i.e. SLND alone)
  - 500 deaths needed for 90% power
- Accrual closed early at DMSC recommendation ***(n=891)***
  - Lower than expected mortality (94 deaths at 6.3 yrs median follow-up)
  - Would take 20+ years to complete at target accrual
- Adjuvant systemic therapy (ctx or endo) given to most women
  - 96% in ALND group
  - 97% in SLND group
- WBI given to most women
  - 88.9% in ALND group
  - 89.6% in SLND group
  - ***No data on RNI***
- **Adjusted HR:**
  - OS= 0.87 (p= .03)
  - DFS= 0.88 (p= .47)

ACOSOG Z0011 Results

- **No significant difference in DFS between patients treated with SLND (83.9%) or ALND (82.2%)**
- **No significant difference in OS between patients treated with SLND (92.5%) or ALND (91.8%)**
- **Only older age, ER-, and lack of adjuvant systemic therapy - *not operation* - were associated with worse OS by multivariable analysis.**

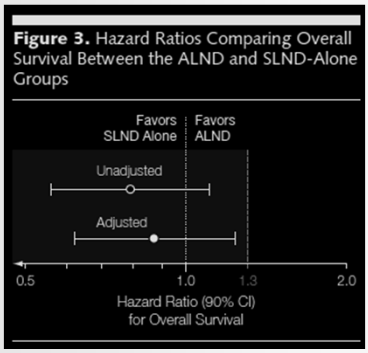


Giuliano et al. JAMA 2011 Feb 9;305(6):569-75.

ACOSOG Z0011 Conclusions

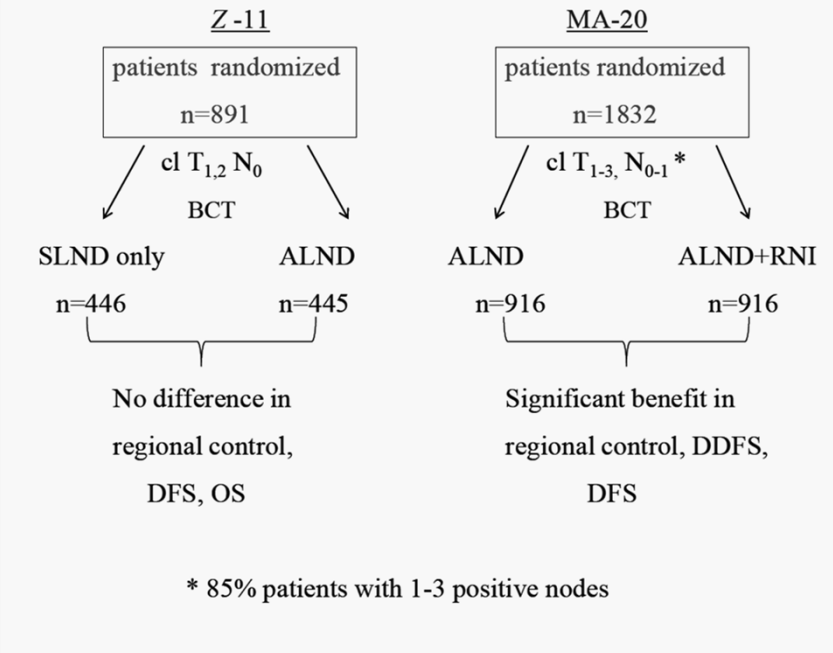
"In this prospective randomized study SLND alone provided excellent locoregional control and survival comparable to completion ALND."

"This study does not support the routine use of ALND in early nodal metastatic breast cancer. The role of this operation should be reconsidered."



Giuliano et al. JAMA 2011 Feb 9;305(6):569-75.

Is this practice changing ?



Z11 v. MA.20

- MA.20 completed accrual, Z11 did not
  - Z11 still subject Type I error that SLND is inferior to ALND though not likely
  - Not adequately powered to prove hypothesis
- Greater tumor burden in MA.20
- No comment on XRT fields in Z11

- Need more info:
  - MA.20 outcomes data by #LN+ & micromets
  - Z11 outcomes data by extent of nodal disease
  - Z11 XRT fields
  - Both trials- need longer follow-up

Is Z11 or MA.20 practice changing?
Maybe…
•Less surgery ok with cN0 disease
•Regional axillary XRT improves outcomes

Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

- **<u>Prevention</u>**:
  - Abs # LBA-504- Goss, PE et al. (NCIC MAP.3)
- **<u>Adjuvant Therapy:</u>**
  - Abs# 1004- Budd, GT et al. (SWOG S0221)
  - Abs# LBA-1003- Whelan, TJ et al. (NCIC MA.20)
  - ACOSOG Z11- Giuliano, AE et al. (*JAMA* 2011)
  - Abs# 1000- Schneider, BP et al. (ECOG E5103)

Genetic associations with taxane-induced neuropathy by a genome-wide association study (GWAS) in E5103.

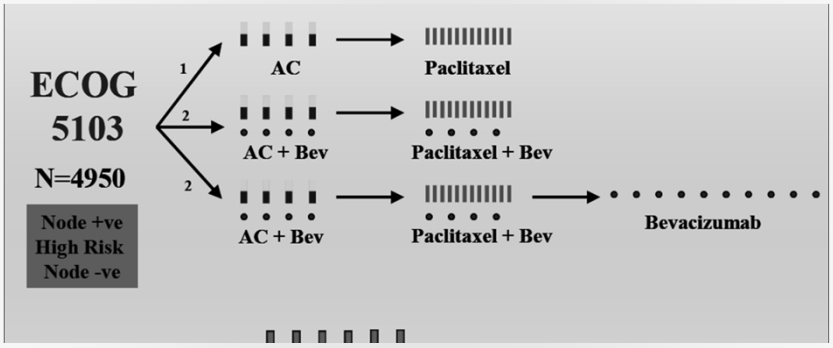
B. P. Schneider, L. Li, K. Miller, D. Flockhart, M. Radovich, B. A. Hancock, N. Kassem, T. Foroud, D. L. Koller, S. S. Badve, Z. Li, A. H. Partridge, A. M. O'Neill, J. A. Sparano, C. T. Dang, D. W. Northfelt, M. L. Smith, E. Railey, G. W. Sledge

Abs# 1000

ECOG 5103 GWAS Rationale

- Taxane-induced peripheral neuropathy
  - Most common non hematological toxicity
  - Can be severe, irreversible, and function limiting
- Weekly paclitaxel (e.g. E1199) causes highest incidence of neuropathy
- No known predictive biomarkers to predict at-risk populations for neuropathy

ECOG 5103 Schema



Will the addition of bevicizumab to a standard adjuvant chemotherapy regimen of AC-T improve survival outcomes?

ECOG 5103 GWAS study

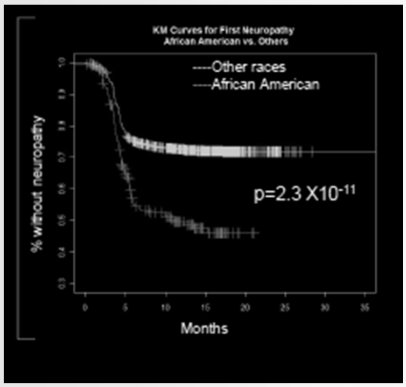
- Biomarker assessment:
  - N=2204 evaluable
  - Peripheral blood germline DNA analysis
  - Data presented related to
    - CTC v3: grade 2-4 peripheral neuropathy phenotypic data
    - Event: Time to first neuropathy n=613
  - Median follow-up= 15 months.

ECOG 5103 GWAS study

- Comparison of time to neuropathy to genotypic analysis using standard Cox regression models and corrected for various co-variates
  - ER status, grade, age, tumor laterality, & race
- No statistical difference in time to neuropathy between three arms

ECOG 5103 GWAS study

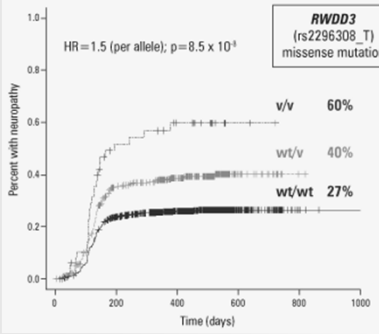
- Clinical predictors of neuropathy:
  - Advanced age-
    - 12.9% increase with each 10yrs (p=.004)
  - African-American race-
    - HR=2.1 ($p=2.3X10^{-11}$)



ECOG 5103 GWAS study

- Missence SNP in RWDD3 increases risk of neuropathy
- RWDD3 involved in sumoylation of cellualr factors important in stress response system (e.g. HIF1-a, I-kappa-b)

Fig. 1. Missense SNP in *RWDD3*



ECOG 5103 GWAS study

- Other SNPs also noted to have associations with increased risk of neuropathy-
  - ***TECTA SNP variant:***
    - wt/wt- 28% risk at 15 mos
    - wt/v- 30% risk at 15 mos
    - v/v- 55% risk at 15 mos
    - HR=2.07; p= 3.15 $X10^{-7}$
  - 15 total SNPs in 12 genes found with $p<10^{-7}$

ECOG 5103 GWAS study

- **Clinical implications:**
  - Need replication/validation of these studies *(ongoing)*
  - Need some kind of interventional, prospective study
    - ? in African-Americans or other at-risk populations for neuropathy

Not ready for prime-time but thought provoking…stay tuned…

Georgia Health Sciences University
New name. Same commitment to better health.

GHSU Multidisciplinary Breast Cancer Program

Surgical Oncology	Medical Oncology	Radiation Oncology
		
D. Scott Lind, MD	Thomas Samuel, MD	Catherine Ferguson, MD

Georgia Health Sciences University

New name. Same commitment to better health.

GHSU Multidisciplinary Breast Cancer Program

GHSU Cancer Center Phase I Trials Unit:

Pam Bourbo

Nicole Aenchbacher, RN, BSN

GHSU Cancer Center MB-CCOP Unit:

Melanie Kumrow

GHSU Breast Cancer Risk Assessment Program

To all our patients & families