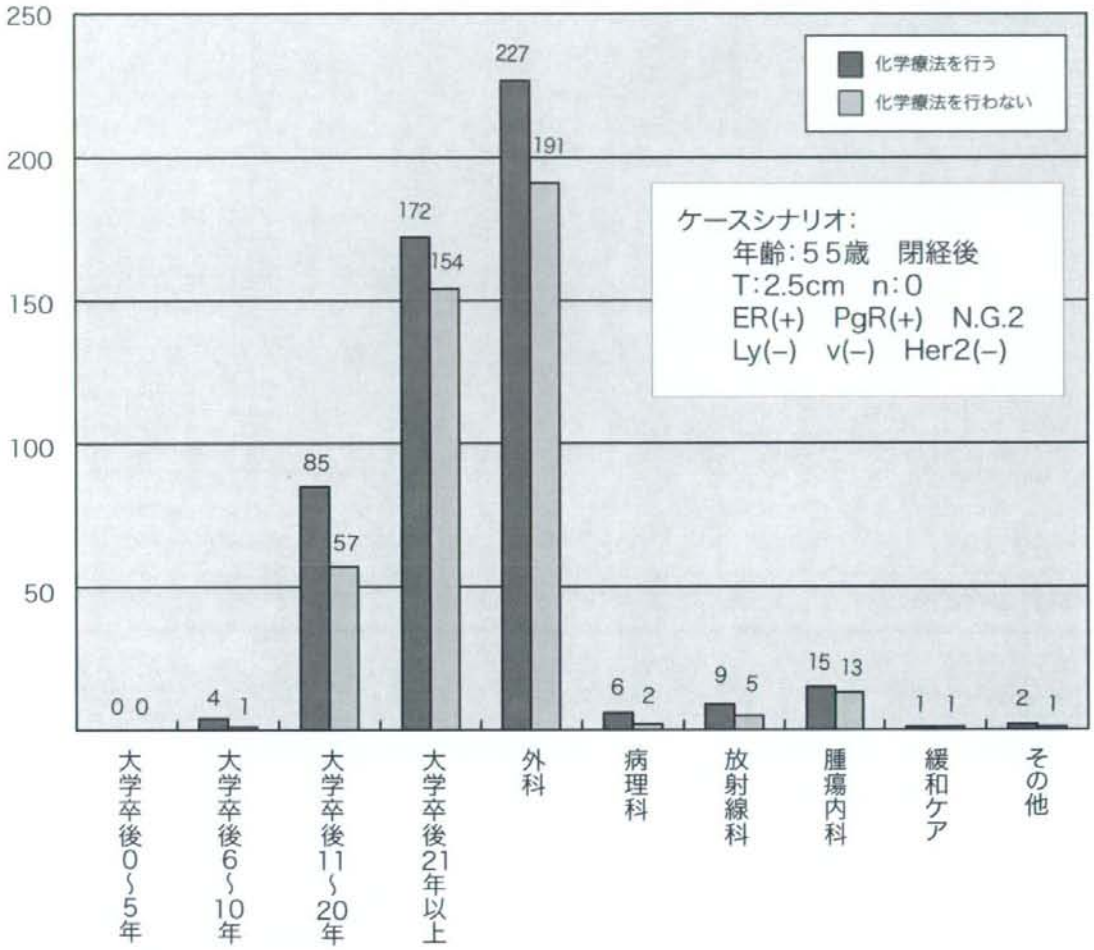
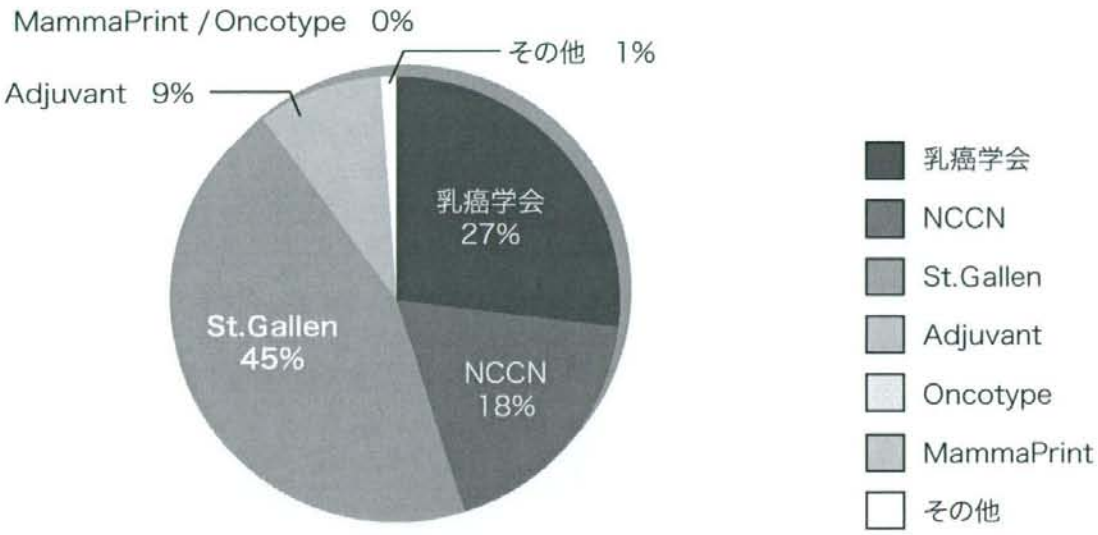
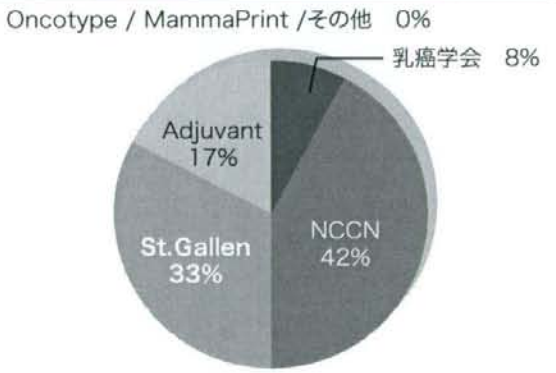

250
200
150
100
50
化学療法を行う
化学療法を行わない
ケースシナリオ:
年齢:55歳 閉経後
T:2.5cm n:0
ER(+) PgR(+) N.G.2
Ly(−) v(−) Her2(−)
0 0
4 1
85 57
172 154
227 191
6 2
9 5
15 13
1 1
2 1
大学卒後0〜5年
大学卒後6〜10年
大学卒後11〜20年
大学卒後21年以上
外科
病理科
放射線科
腫瘍内科
緩和ケア
その他

問8：化学療法の適用を決定するさい、何をよく参考にしますか（総数）

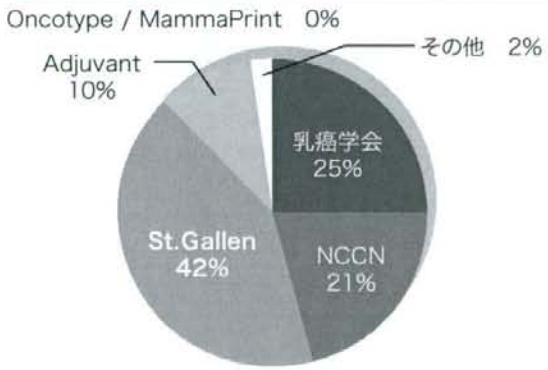


大学卒業年・専門科別

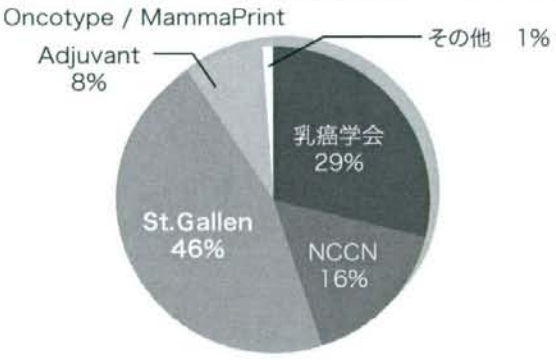
■大学卒後6～10年



■大学卒後11～20年

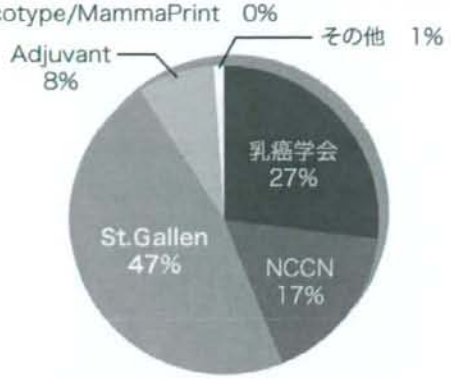


■大学卒後21年以上



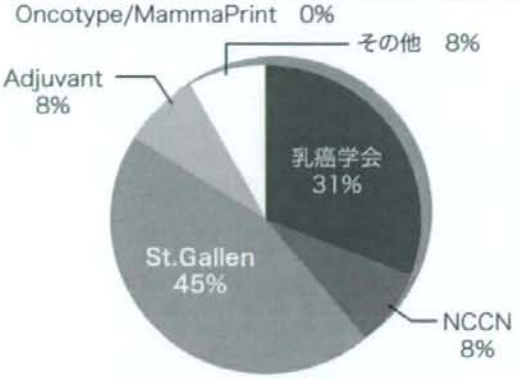
■外科

Oncotype/MammaPrint　0%



■病理科

Oncotype/MammaPrint　0%

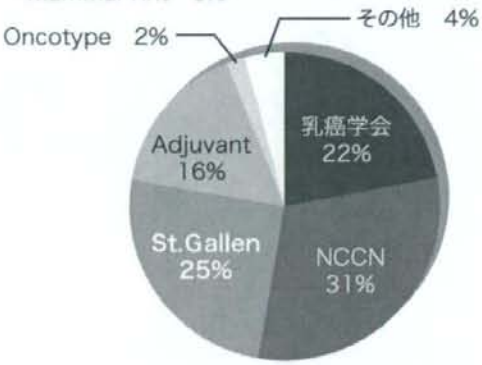


■放射線科

Adjuvant/Oncotype/MammaPrint　0%

■腫瘍内科

MammaPrint　0%

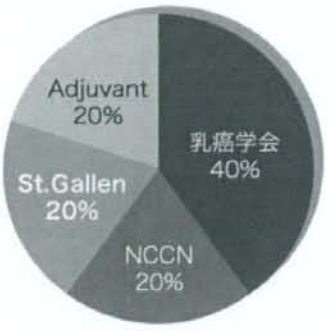


■緩和ケア

St.Gallen/Adjuvant/
Oncotype/MammaPrint　0%

■その他

Oncotype/MammaPrint/その他　0%



www.jccnb.net

NPO 法人日本乳がん情報ネットワーク
〒104-0044　東京都中央区明石町 11 番 3 号　築地アサカワビル
Tel：03-6278-0498　Fax：03-3543-4177

NCCN/JCCNB Seminar in Japan
～乳がん診療ガイドライン総括～

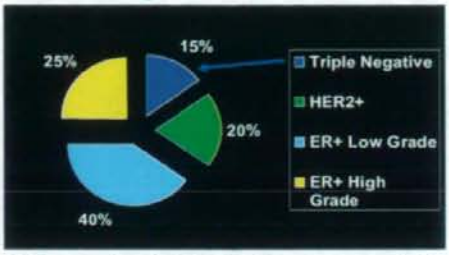
日　時：11 月 1 日（土）・11 月 2 日（日）
場　所：東京国際フォーラム　ホール B5、ホール D5
テーマ：乳がん診療ガイドライン総括

当日使用招聘者資料：
E.P.Winer (R.W.Carlson)
R.W.Carlson
R.L.Theriault
S.B.Edge
L.C.Collins

Triple Negative Breast Cancer

Eric P. Winer, MD
Dana-Farber Cancer Institute
Harvard Medical School
Boston, MA
October, 2008

Triple Negative Breast Cancer

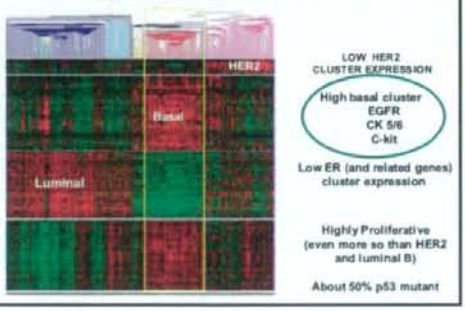


Only approximately 25,000-30,000 cases per year in U.S., but responsible for a disproportionate number of deaths

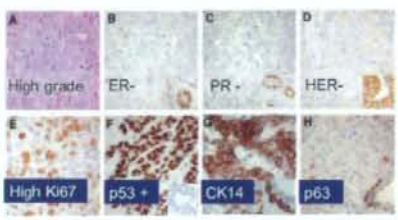
Triple Negative ≠ Basal-like

- Correlation is high, probably > 80%
- At present, clinical studies will use triple negative as a surrogate for basal-like as arrays are not available for clinical use
- As we search for targets, it is reasonable to explore basal clusters on array studies

Basal-like Breast Cancer: Gene Expression Characteristics

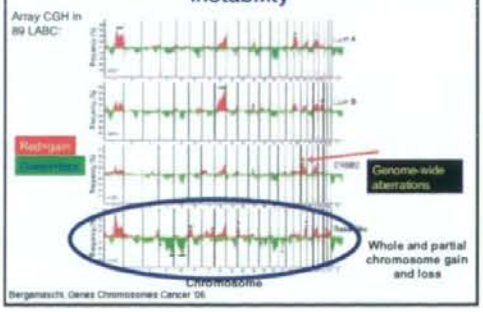


A Prototypical "Basal-like" Tumor

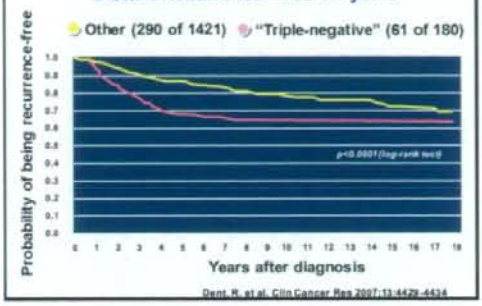


Courtesy of A. Richardson

Basal-like Breast Cancer and Genomic Instability

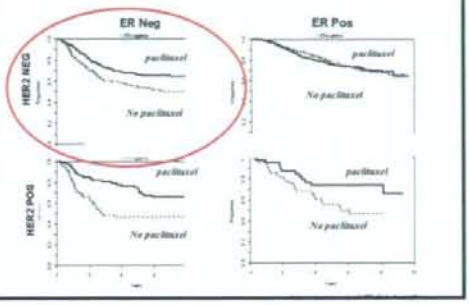


Henrietta Banting Breast Center
Distant Recurrence – F/U 8.1 years



Dent, R. et al. Clin Cancer Res 2007;13:4429-4434

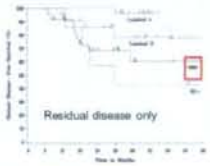
CALGB 9344 Disease-free Survival by ER and HER2



Basal-like Breast Cancer:Pathologic Response to Neoadjuvant Anthracycline/Taxane

Pathologic CR Rate

	T-FAC (N=82)*	AC-T (n=107)*
Luminal A/B	7%	7%
Normal-like	0	NA
HER2+/ER-	45%	36%
Basal-like	45%	26%

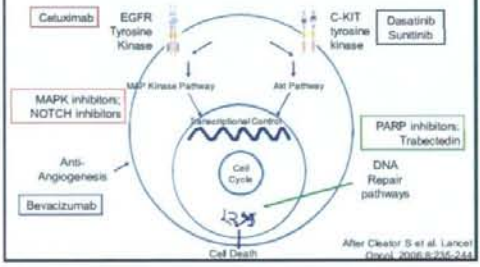


- Good outcome in pCR (>90% 5y DDFS)

- Residual disease in pts with triple negative disease associated with poor prognosis
- Additional therapy needed – what?

Rouzier, Clin Cancer Res'05; Carey, Clin Cancer Res'07

Triple-Negative Breast Cancers: Potential Therapeutic Targets

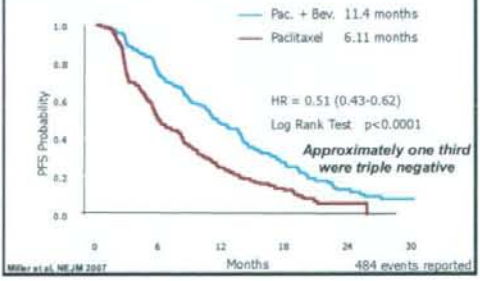


After Cleator S et al. Lancet Oncol. 2006;8:235-244

New Therapeutic Approaches

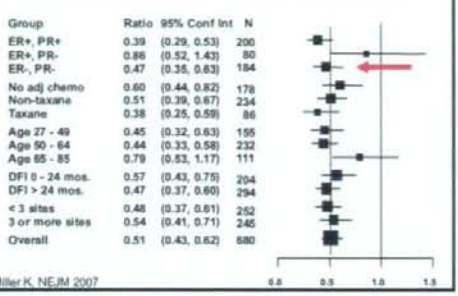
- Angiogenesis inhibitors
- Tyrosine kinase inhibitors
- Platinum-based chemotherapy
- PARP inhibition

Progression Free Survival
Paclitaxel vs Paclitaxel + Bevacizumab



Miller et al, NEJM 2007

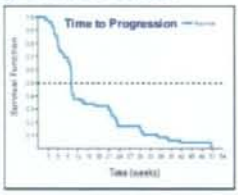
Bevacizumab in Clinical Subsets



Miller K, NEJM 2007

Phase II Trial of Sunitinib in Patients with Refractory Breast Cancer

- N=64
- ORR 7/64 = 11%
- ORR 3/20 = 15% in triple negative



- ?? VEGF-R inhibition vs c-kit inhibition vs both vs neither

Burstein et al, JCO 2008

EGFR Inhibitors in Breast Cancer

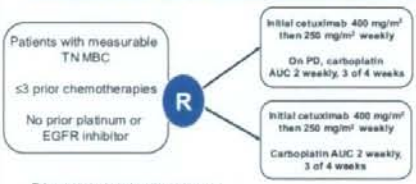
In unselected metastatic breast cancer, single agent EGFR inhibitors have not shown great activity:

• Phase II ZD1839 (Robertson)	2/27 PR	6/27 SD
• Phase II ZD1839 (Baselga)	0/31 PR	12/31 SD
• Phase II OSI-774 (Winer/Dickler)	1/69 PR	3/69 SD
• Phase II ZD1839 (Albain)	1/63 PR	7/63 SD

Summary RR: 2%

Cetuximab in Triple Negative MBC

Translational Breast Cancer Research Consortium (TBCRC) 001



Primary endpoint: objective response
Secondary endpoints: TTP, biomarker correlation with toxicity and response, OS
Cetuximab-alone arm failed to meet predetermined response criteria and was closed
Only arm 1a (cetuximab alone) and arm 1b (cetuximab alone, then cetuximab + carboplatin on progression) reported

Carey, SABCS 2007 (abstr 307)

TBCRC 001: Patient Characteristics

- 68% with visceral disease
- Line of therapy and prior rx
  - 46% 1st line
  - 54% 2nd/3rd line
  - 83% prior anthracycline
  - 64% prior taxane
- 44% EGFR+

Cetuximab in Triple Negative MBC: Clinical Efficacy

Best Response	Cetuximab Alone (n=31)
CR	0
PR	2 (6%)
SD	5 (16%)
Clinical Benefit	3 (105)

Carey, SABCS 2007 (abstr 307)

TBCRC 001: Clinical Efficacy

Includes patients initially treated with cetuximab and then treated with combination at time of progression

ITT population	Arm 2 (N=71)	Arm 2 + 1b (N=95)	
CR	1 (1.4%)	1 (1%)	Four patients on study Rx at 35, 39, 43, 99 weeks (1CR, 2PR, 1SD)
PR	11 (15%)	15 (16%)	
SD	16 (23%)	22 (23%)	
PD	37 (52%)	49 (52%)	
NE	6 (8%)	8 (8%)	No relationship of line of therapy and likelihood of clinical benefit
RR	*17%*	*17%*	
CB	*31%*	*29%*	

CB=PR or SD≥24wks

Carey et al, ASCO 2008

Shared Characteristics of Sporadic Basal-like Tumors and BRCA1 -/- Tumors

- ER- PR- Her2/Neu non-amplified
- Co-Cluster by Gene Profiling
- p53 mutant status
- Cytokeratin Expression
- Chromosome X Inactivation
- Genomic Instability

Pathologic Features
High Grade
Central Necrosis
Pushing Borders
Lymphocytic Infiltrate

DF/HCC SPORE: Neoadjuvant Cisplatin (CDDP) in Triple-Negative Breast Cancer

- N = 28
  - ≥ 2-cm stage II/III triple negative
- Single-agent cisplatin 75 mg/m² q3w x 4 cycles prior to surgery

Grade 4	
↑ LFT	1 pt
Grade 3	
Neutropenia	2 pts
Tinnitus	1 pt
Nausea	1 pt
Fatigue	1 pt
Hyperkalemia	1 pt
↑ LFT	1 pt

Pathologic CR	6 (22%)
Clinical CR	4 (14%)
Clinical PR	10 (36%)
Stable Disease	5 (17%)

Young age correlated with path CR p=0.04

2 patients with BRCA1 mutation, both with Path CR

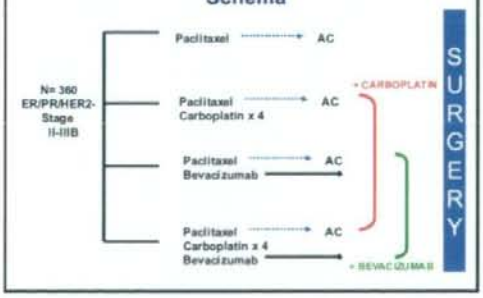
Garber et al Abs 3074, SABCS 2008

Cisplatin in Preop Setting in Patients With BRCA1-Related Breast Cancer

- Narod and colleagues studied neoadjuvant response to cisplatin in 10 patients with BRCA1 mutations
- Same regimen as in Garber trial
- 9/10 complete pathologic responses
- 10th patient did not complete neoadjuvant therapy

Byrski, T. et al., Breast Cancer Res Treat, Published online: 23 July 2008

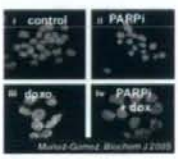
CALGB Triple Negative Neoadjuvant Trial Schema



The Potential Role of PARP Inhibition

- Loss of BRCA 1 or 2 → increased PARP dependence for DNA repair
- ? Augment efficacy of DNA-damaging agents
- PARP inhibitors are in clinical trials for both BRCA1 and Triple Negative

Cell Death Increased When PARP Inhibitor Added to Chemotherapy In BRCA2 Deficient Cells



Ongoing Studies PARP Inhibitors

- **Single agent trial of AZD 2281in patients with BRCA mutations**
- **Planned phase I of cisplatin plus AZD 2281**
- **Planned phase II of cisplatin plus AZD 2281 in preoperative setting for patients with triple negative disease**
- **Other agents in development from other companies**

Summary

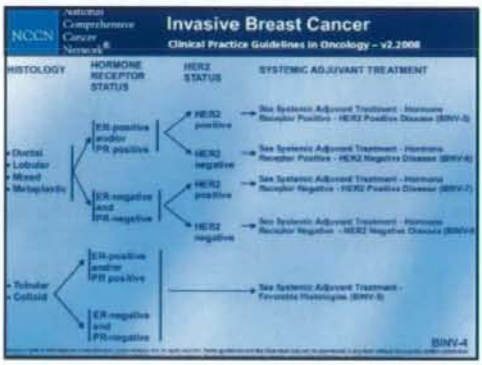
- Molecular characteristics of triple negative and basal-like disease are a subject of active investigation
- More heterogeneity in this tumor subset than once imagined
- EGFR remains an interesting therapeutic target with very limited suggestion that it may be useful for a subset
- Exploitation of angiogenesis inhibition likely to be important
- Platinum salts *MAY* play a role
- PARP inhibitors are of great interest, particularly in triple negative, BRCA1/2 associated disease

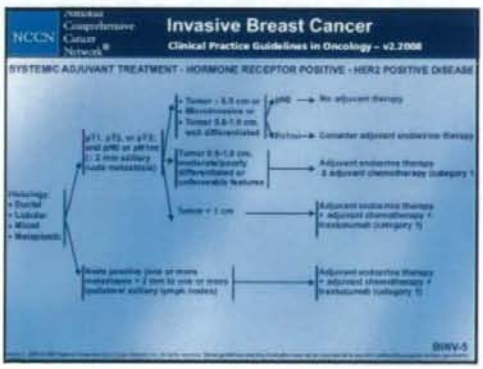
NCCN Guidelines Prognostic/Predictive Tools for Adjuvant Decision Making

Robert W. Carlson, M.D.
Chair, NCCN Breast Cancer Panel
and
Professor of Medicine
Stanford University

Biological Application of Adjuvant Therapy

- **Chemotherapy:** benefit in all endocrine and HER2 subtypes.
- **Trastuzumab:** active only in HER2 amplified or over-expressed disease
- **Endocrine therapies:** only effective in estrogen and/or progesterone receptor positive disease





Prognostic/Predictive Factors

	Prognostic	Predictive
Lymph nodes	Yes	
Tumor size	Yes	
Tumor type	Yes	
Tumor grade	Yes	
LVI	Yes	
Proliferation	Yes	
ER/PR status	Yes	Yes
HER2 status	Yes	Yes
Genomics	Yes	Yes

AdjuvantOnline Validation 10-Year DFS

Characteristic	Adjuvant Prediction (%)	Observed (%)
Age (years)		
20-35	67.9	54.3
36-50	69.8	67.8
51-65	70.5	71.2
66-75	71.7	72.3
>75	74.8	72.0
Tumor Grade		
1	82.8	82.7
2	74.5	73.4
3	63.9	62.1
Unknown	70.7	73.3

Olivotto et al. J Clin Oncol 23:2716,2005

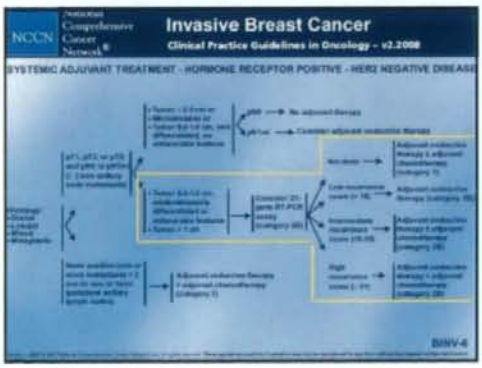
AdjuvantOnline Validation 10-Year DFS

Characteristic	Adjuvant Prediction (%)	Observed (%)
Tumor size, mm		
1-10	80.8	79.7
11-20	74.5	73.3
21-50	60.0	59.5
ER status		
Negative	65.5	66.1
Positive	72.0	69.6
Unknown	74.5	76.2

Olivotto et al. J Clin Oncol 23:2716,2005

AdjuvantOnline

- Pros
  - Widely available
  - Free of cost
  - Easy to use
  - Validated
  - Objective, unbiased
- Cons
  - Lack of HER2 and trastuzumab consideration
  - Mix of qualitative/quantitative factors
  - Lack of quality control over biomarkers input



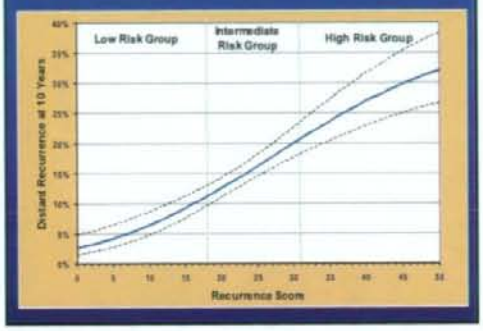
Gene Profiling Technology:

Oncotype DX™ Technology: Algorithm and Recurrence Score (RS)

RS = +0.47 x HER2 Group Score
-0.34 x ER Group Score
+1.04 x Proliferation Score
+0.10 x Invasion Group Score
+0.05 x CD68
-0.08 x GSTM1
-0.07 x BAG1

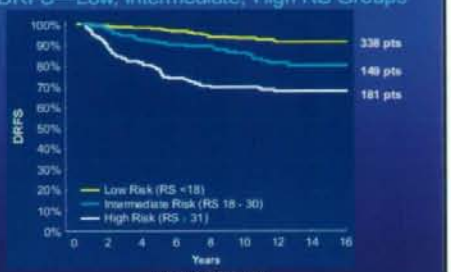
Recurrence Category	RS (0-100)
Low risk	<18
Intermediate risk	18-30
High risk	≥31

Recurrence Score as a Continuous Predictor



B14-Results

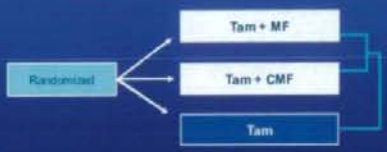
DRFS—Low, Intermediate, High RS Groups



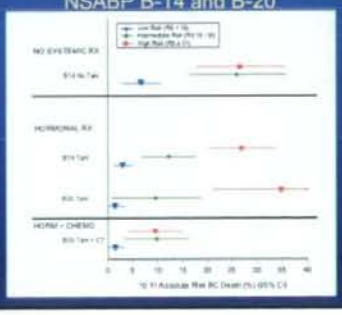
Park et al. SABCS 2003

RS as a predictive factor for benefit from tamoxifen: NSABP B-14

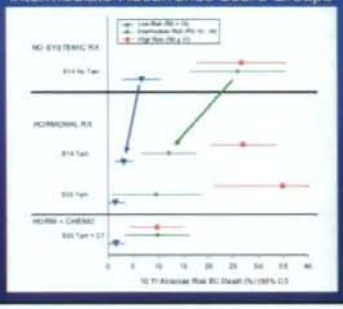
RS as a predictive factor for benefit from adjuvant chemotherapy: NSABP B-20



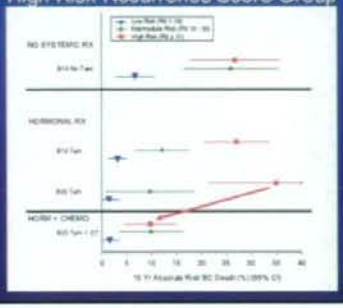
RS and Breast Cancer Death in NSABP B-14 and B-20



Largest Tamoxifen Benefit Observed in Low and Intermediate Recurrence Score Groups



Largest Chemotherapy Benefit Observed in High Risk Recurrence Score Group



NSABP B-20 Outcome by Recurrence Score

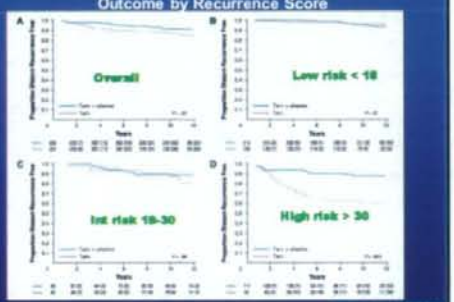
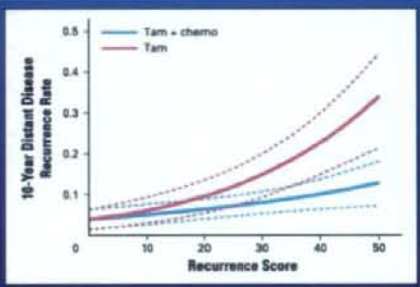


Fig 4. Linear fit of the likelihood of distant recurrence as a continuous function of recurrence score for the tamoxifen alone (TAM) and tamoxifen plus chemotherapy (TAM+ chemo) treatment groups



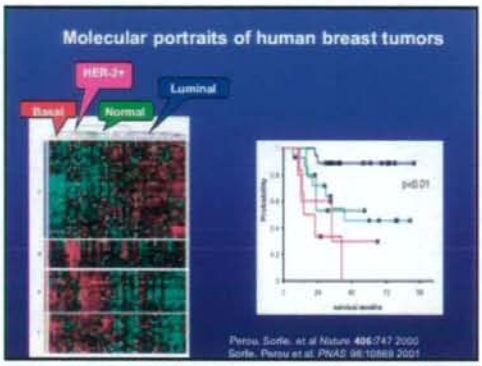
Park, S. et al. J Clin Oncol. 24:3726-3734 2006

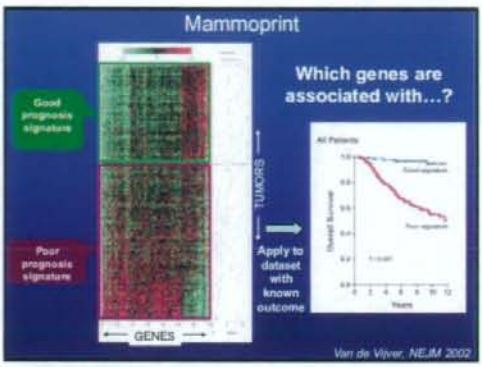
Use of 21-Gene RT-PCR Test

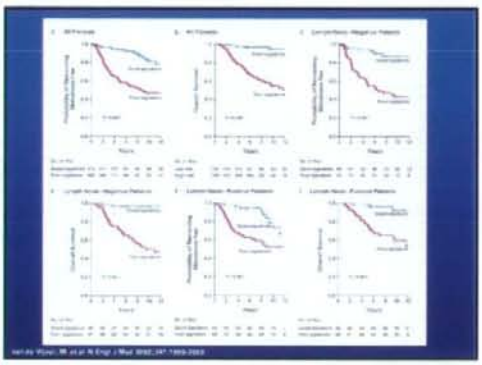
- Limited to ER+ node negative disease
- Validated only in tamoxifen treated patients with first generation chemotherapy
- Most HER2-positive disease has high RS
- Major use therefore is in ER+, HER2-negative, node negative disease.

21-Gene RT-PCR (OncotypeDX™)

- Pros
  - Highly reproducible
  - Quantitative
  - Based primarily upon known prognostic/predictive factors
  - Utilizes paraffin embedded tissue
- Cons
  - Expensive
  - Not clearly superior to assessment of ER/PR/HER2/Grade/Size/etc
  - Not US FDA approved

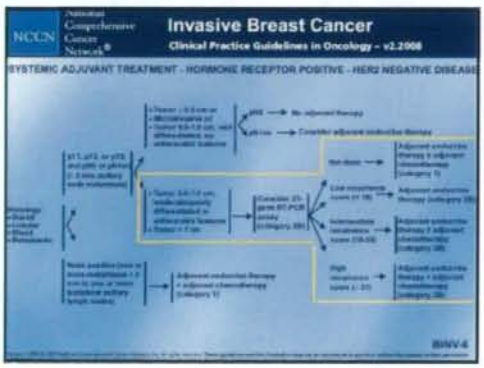






Mammoprint

- Pros
  - Appears prognostic
  - Widely separate groups
  - US FDA approved
- Cons
  - Currently requires fresh frozen tissue
  - Unknown regarding prediction
  - Expensive



Bisphosphonates and Breast Cancer

Bisphosphonates

- Analogues of pyrophosphate
- Carbon substitution makes them resistant to endogenous phosphatases in circulation
- Potent inhibitors of osteoclast growth, maturation and function
- Poorly absorbed via GI tract
- Structure function/potency relationship

Structure and Potency of Clinically useful Bisphophonates

Structure and Potency of Clinically useful Bisphophonates

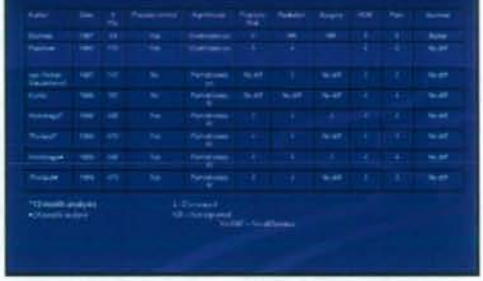
Bisphosphonate Mechanisms of Action

- Bind to hydoxyapatite crystals – inhibit breakdown
- Preferentially incorporated into active bone remodeling sites
- Promote osteoclast apoptosis – inhibit mevalonic acid pathway

Metastatic Breast Cancer

- Pamidronate
- Zoledronic acid
- Ibandronate
- Clodronate

Prospective randomized trials of bisphosphonates in bone metastasis from breast cancer



Prospective randomized trials of bisphosphonates in bone metastasis from breast cancer
References

Elomaa I, Blomqvist C, Porkka L, et al. Bone 1987;8:553

Paterson AHG, Powles TJ, Kanis JA et al. J Clin Oncol 1993;11:59

van Holten-Verzantvoort AT, Bijvoet OLM, Hermans J et al. Lancet 1987;2:983

Hortobagyi GN, Theriault RL, Porter L et al. N Engl J Med 1996;335:1785

Theriault RL, Lipton A, Leff R et al. Proc Am Soc Clin Oncol 1996;15:122 (abst)

Hortobagyi GN, Theriault RL, Lipton RL et al. J Clin Oncol 1999;17:846

Conte PF, Latreille J, Mauriac L et al. J Clin Oncol 1996;14:2552

Metastatic Breast Cancer

- Zoledronic acid vs pamidronate
- Randomized, double blind, trial
- 1648 patients
- Zoledronic acid 4 mg iv q 3-4 weeks OR
- Pamidronate 90 mg iv q 3-4 weeks
- Duration of study drug 24 months

Rosen et al. Cancer 2003;98:1735-1744

Metastatic Breast Cancer
Zoledronic Acid vs. Pamidronate

Combination of 2 randomized controlled trials 1130 patients – breast cancer – osteolytic bone mets

Zoledronic acid 4mg IV q 3-4 weeks OR

Pamadronate 90 mg IV q 3-4 weeks

12 month observation

Results:

Proportion with skeletal related events (SRE)

Zoledronic Acid	Pamidronate	
45%	45%	overall
48%	58%	lytic disease
Time to first SRE (days)		
310	174	

Rosen LS et al, Cancer 2004;100:36-43

Metastatic Breast Cancer
Zoledronic acid vs. Pamidronate – Long Term Efficacy

	Zoledronic Acid	Pamidronate	p value
SRE (%)	46%	49	NS
SRE (XRT)	19%	24%	0.037
Time to 1st SRE (days)	376	356	NS
Time to 1st SRE (days) br ca endocrine	415	370	0.047
SMR	9	1.49	0.125

NCCN Guideline Recommendation
BINV – I6 footnote "X"

- Pamidronate or zoledronic acid (with calcium 1200-1500mg and vitamin D 400-800 IU daily supplement) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis present, expected survival $\geq$ 3 months and creatinine $\leq$ 3.0 mg/dl..

Clinical Endpoints

- Decrease fracture risk
- Decrease need for radiation to bone
- Decrease need for surgery for bone
- Improve pain

Bisphosphonates and Metastases

- Established role in metastatic bone disease
  - Data sources
    - Randomized, placebo controlled trials
    - Randomized controlled trials
    - Meta analyses
    - Cochrane reviews

Patient Supplements

- Calcium 1200 – 1500 mg po daily
- Vitamin D 400 – 800 IU po daily
- Pre-administration assessment
  - Serum creatinine (adjust bisphosphonate per FDA black box)
  - **Dental evaluation and treatment as needed**

Weitzman R, Sauter N, Eriksen EF, Tarassoff PG, Lacerna LV, Dias R et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients--May 2006. *Crit Rev Oncol Hematol* 2007;62:148-52.

Guidelines Revision Recommended

- Bisphosphonate for bone metastasis. Pamidronate 90mg IV over not less than 2 hours monthly (FDA approved) ***OR*** Zoledronic acid 4mg IV over not less than 15 minutes monthly (FDA approved).
- Ibandronate 6mg IV over 1-2 hours monthly (not FDA approved)

Tripathy D, Body JJ, Bergström B. *Review of ibandronate in the treatment of metastatic bone disease: experience from phase III trials. Clin Ther* 2004;26:1947-59.

Pecherstorfer M, Rivkin S, Body JJ, Diel I, Bergström B. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. *Clin Drug Investig* 2006;26:315-22.

Bisphosphonates Cancer Treatment Induced Bone Loss (CTIBL)

- NCCN Guideline – None
- Background
  - Chemotherapy and ovarian ablation result in bone loss
  - Presumed mechanism hypoestrogenism
  - Aromatase inhibitors result in bone less and increased fracture risk

CTIBL – Studies with Bisphosphonates

Risedronate				
Study	**# Pt**	**End Point**	**Agents**	**Results**
DBRCT	53	BMD-LS, hip	Risedronate/placebo 30mg daily x 2 weeks, 10 weeks rest x 8 cycles	Improved BMD LS/hip with risedronate
DBRCT	87	BMD LS/hip	Risedronate 35 mg weekly/or placebo	Improved BMD LS/hip
DBRCT	216	BMD LS	Risedronate 35 mg/weekly or placebo	No difference in BMD LS at 12 mos
Ibandronate				
DBRCT	131	BMD	Ibandronate 50mg/placebo	Improved BMD LS/hip

CTIBL – Studies with Bisphosphonates References

Delmas PD, Balena R, [illegible] Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double blind, placebo-controlled study. J Clin Oncol 1997;15:955-62.

[illegible] Prevention of bone loss in survivors of breast cancer: A randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab [illegible]

[illegible] A phase III randomized, placebo-controlled, double-blind trial of risedronate for prevention of bone loss in premenopausal women undergoing adjuvant chemotherapy for breast cancer [illegible]

[illegible] results from ARIBON study [illegible]

CTIBL – Studies with Bisphosphonates

Pamidronate and Zoledronic Acid				
Type Study	# Pts	Endpoint	Agent	Result
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

CTIBL – Studies with Bisphosphonates References

[illegible] Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: a randomized controlled trial. J Clin Endocrinol Metab [illegible]

Gnant MF, [illegible] Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. J Clin Oncol 2007;25:820-8

Brufsky A, [illegible] Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. J Clin Oncol 2007;25:829-36

Bundred NJ, [illegible] Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. Cancer 2008;112:1001-10

Shapiro CL et al. J Clin Oncol [illegible]

Conclusions

- Bisphosphonates preserve BMD lumbar spine and hip in pre menopausal women with amenorrhea and/or ovarian failure.
- Bisphosphonates preserve BMD lumbar spine and hip in post menopausal women treated with an aromatase inhibitor.
- No data on fracture risk reduction

Recommended Guideline Modification *NOT APPROVED*

- Consider use of bisphosphonate in the adjuvant setting for preservation of BMD
  - Pre-menopausal women treated with gonadotoxic therapy – chemotherapy, ovarian ablation
  - Post - menopausal women treated with aromatase inhibitor

Recommended Guideline Modification *NOT APPROVED*

- Zoledronic acid 4mg IV q3 months for up to 12 months for pre menopausal women receiving gonadotoxic chemotherapy or treated with oophorectomy/ovarian suppression with or without an aromatase inhibitor in the adjuvant setting.
- Zoledronic acid 4mg IV q6 months for up to 5 years beginning with start of aromatase inhibitor adjuvant therapy.

Monitoring of Bone Health

- Monitor BMD at baseline, 12 months and annually
- Calcium 1200 – 1500 mg po daily
- Vitamin D 400 – 800IU daily
- Dental exam and treatment prior to bisphosphonate use
- Monitor serum creatinine per FDA recommendation

Adjuvant Bisphosphonate

- Potential to reduce recurrence and death from breast cancer
- Moot point if bisphosphonate used for BMD preservation

Oral Clodronate for Primary Breast Cancer

- 1069 patients
- Oral clodronate 1600 mg/day or placebo
- 2 years of therapy – start within 6 months
- Endpoint – bone relapse

Powles T et al. J Clin Oncol 2002; 20:3219-3224

Results Powles et al.

- During clodronate – significant decrease in bone mets
- Significant reduction in mortality during follow-up (23% reduction)

Powles T et al. J Clin Oncol 2002; 20:3219-3224
Ala S et al. Drug Safety 2003; 26:661-671

Reductions in New Metastases in Breast Cancer with Adjuvant Clodronate

- 302 patients primary breast cancer
- Bone marrow positive by cytokeratin (at least one cell)
- Clodronate 1600 mg daily or nil
- 2 years treatment
- Endpoints – distant mets, survival

Diel U et al. N Engl J Med 1998; 339:357

Results Diel et al.

Distant mets	21 clodronate	42 nil
Deaths	6 clodronate	22 nil
Bone mets	12 clodronate	25 nil
Median follow-up	36 months	

Diel U et al. N Engl J Med 1998; 339:357
Diel U et al. Cancer 2000;3080-3088