Chemotherapy in Breast Carcinoma

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Breast Cancer Global & Indian Scene

- High rates: 86-104/100,000 in developed countries – exception- Japan
- Risk of developing breast cancer during life time of woman 1 in 14 (upto age 70)
- Decreasing mortality in USA due to early diagnosis and management.

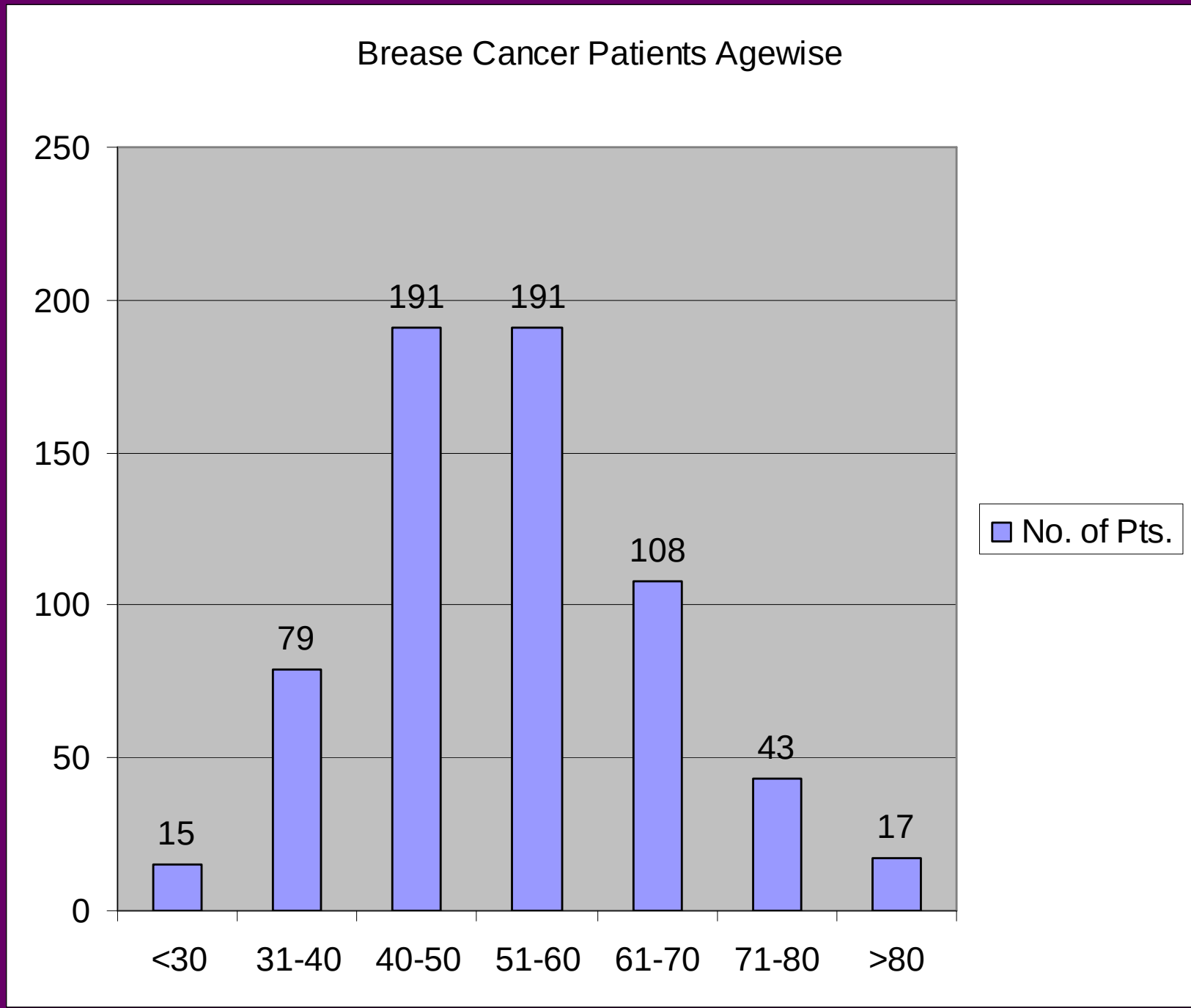
- 20-30/100000 in various population based registries.Lower rates in rural population
- 70,000 to 80,000 new cases per year. About 10% will be below age of 40.Average age:49
- Higher rate than Cancer cervix in Urban population of Bombay, Delhi, Trivendrum and Ahmedabad
- 12-26% cancer in women in hospital registries

Natural history –if untreated

- Average survival from 1st symptom- 44 months
- Median survival- 2.5 years
- 5 year survival- 22%
- 10 year survival – 5%
- Above data on the basis of tumor doubling time
- Biology of breast cancer-Aggressive or slowly progressive

Breast Cancer-Priority Heath Problem

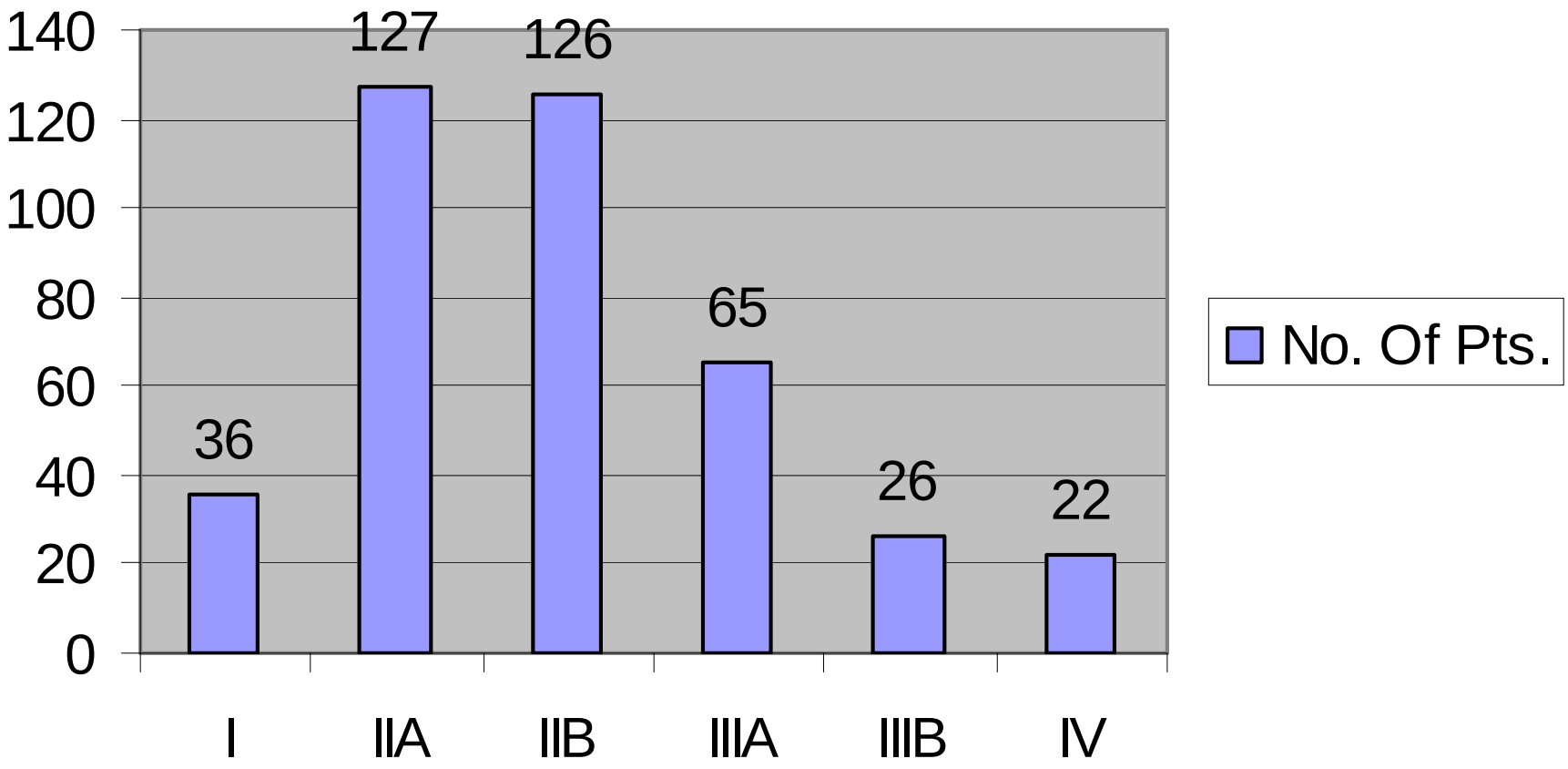
- **80 to 85% of women after developing their Breast cancer die of their Breast cancer**
- Mueller & Jeffries- Ann.Sur.1975


Brease Cancer Patients Agewise
250
200
150
100
50
0
191
191
108
79
43
17
15
<30
31-40
40-50
51-60
61-70
71-80
>80
No. of Pts.

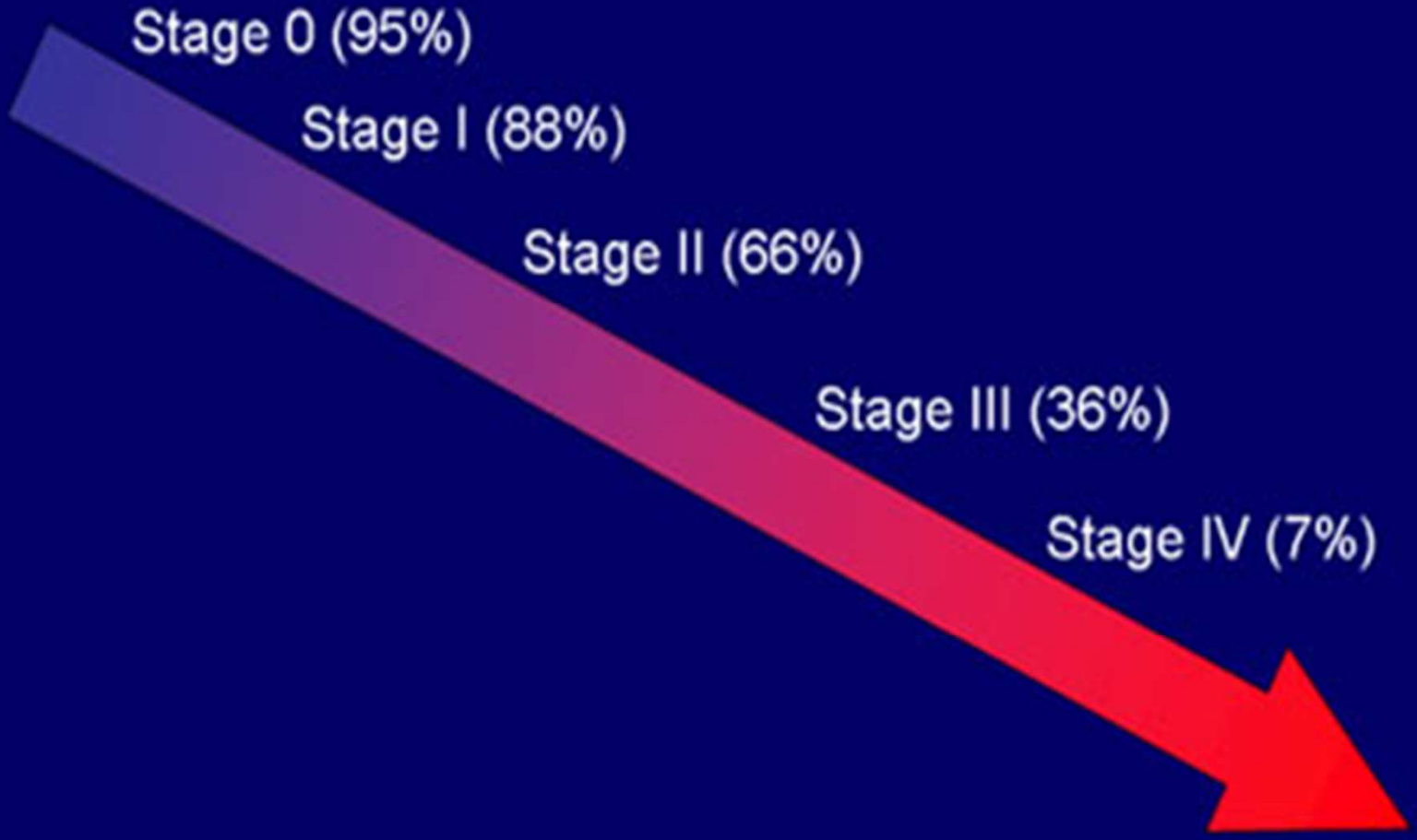
Breast Cancer - Stage at Presentation

–	India	West	Survival
• Stage 0-	?	12.4%	98%
• Stage I-	4% to 8%	41.8%	90%
• Stage II-	40% to 57%	33.1%	70%
• Stage III-	28 % to 41%	8.0%	50%
• Stage IV-	6% to 14%	4.7%	4.7%

- 39% IIIB and IV in illiterate-against 19% in educated


Dr. Pankaj Shah's Clinic
Stagewise Distribution
140
120
100
80
60
40
20
0
36
127
126
65
26
22
I
IIA
IIB
IIIA
IIIB
IV
No. Of Pts.

5-Year Survival Rates by Stage



Medline Plus. *Breast Cancer*. http://www.nlm.nih.gov/medlineplus/ency/article/000913.htm. Accessed January 2008.

Management of Breast Cancer

- **Ideal example of joint management by all three disciplines.**

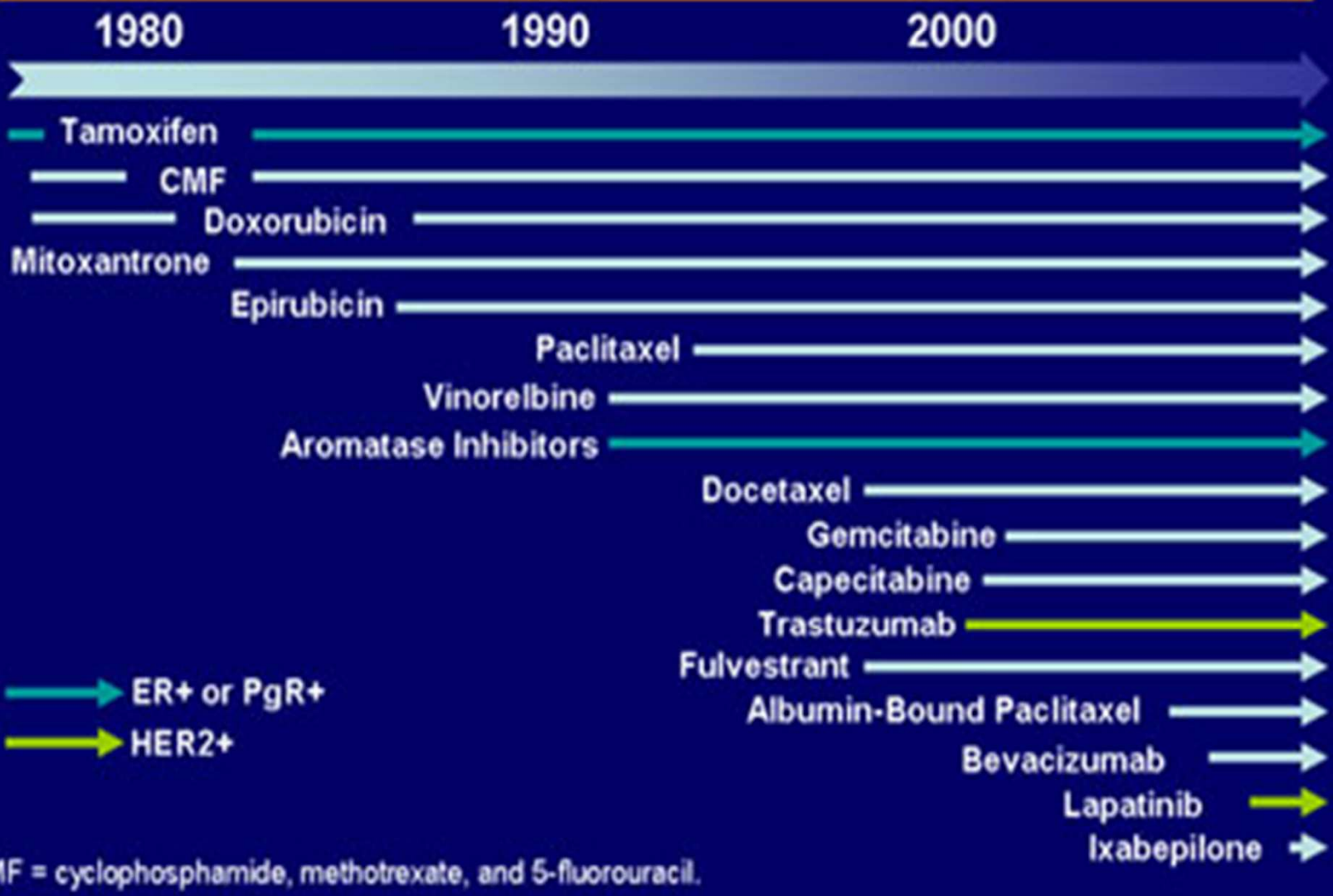
Goals of Therapy

- Mainly Systemic disease with local presentation
- Early disease= To prevent recurrence – Adjuvant therapy
- For locally advanced disease- Neoadjuvant therapy
- For advanced disease palliation

Treatment Sequences

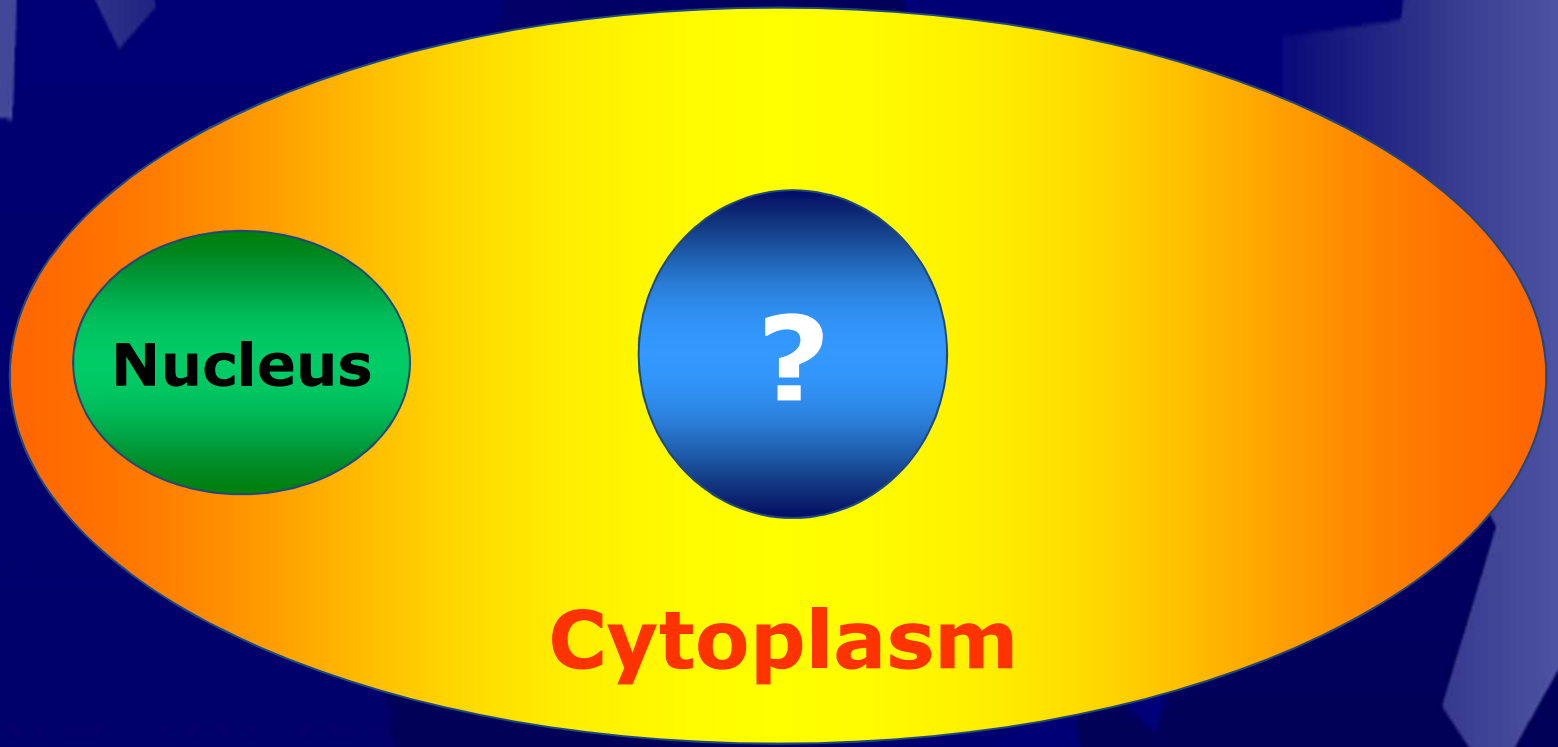
- Optimum yet to determine
- Local surgery with AND -> Adjuvant CT as per need or FNAC → Neoadjuvant CT→Surgery or RT → CT

Advances in Treatment



CMF = cyclophosphamide, methotrexate, and 5-fluorouracil.

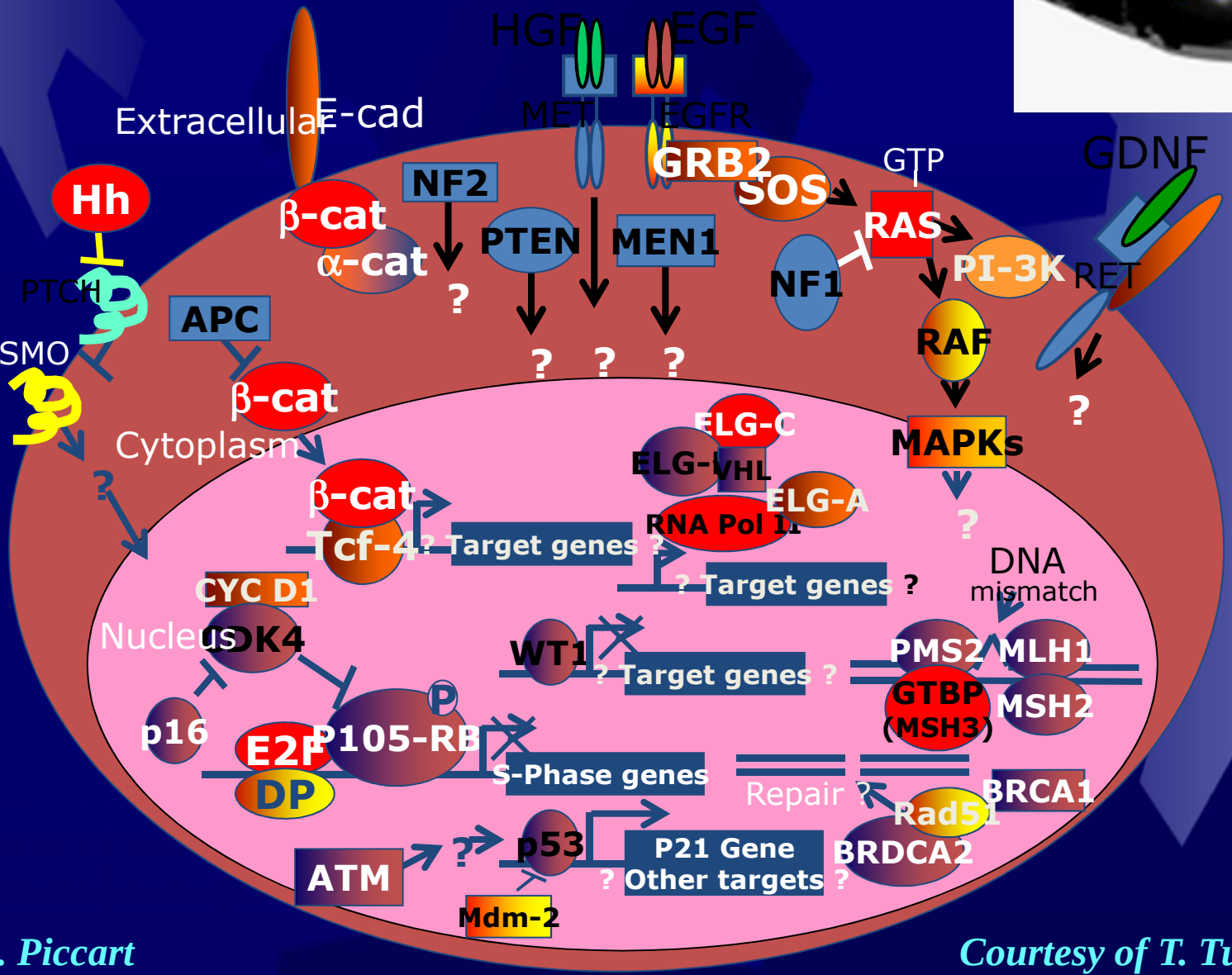
The Cancer Cell in 1975



M.J. Piccart

Courtesy of T. Tursz

The Cancer Cell in 2007!!



M.J. Piccart

Courtesy of T. Tursz

Prognostic and Predictive Factors

- Prognostic factors
  - Predict natural history
    - Nodal status
    - Tumor size
    - LVI
    - Grade
    - HER2 status*
    - ER/PgR*
    - Age
    - Recurrence score*
- Predictive factors
  - Predict response to therapy
    - ER/PgR*
    - HER2*
    - Recurrence score*

*Both prognostic and predictive

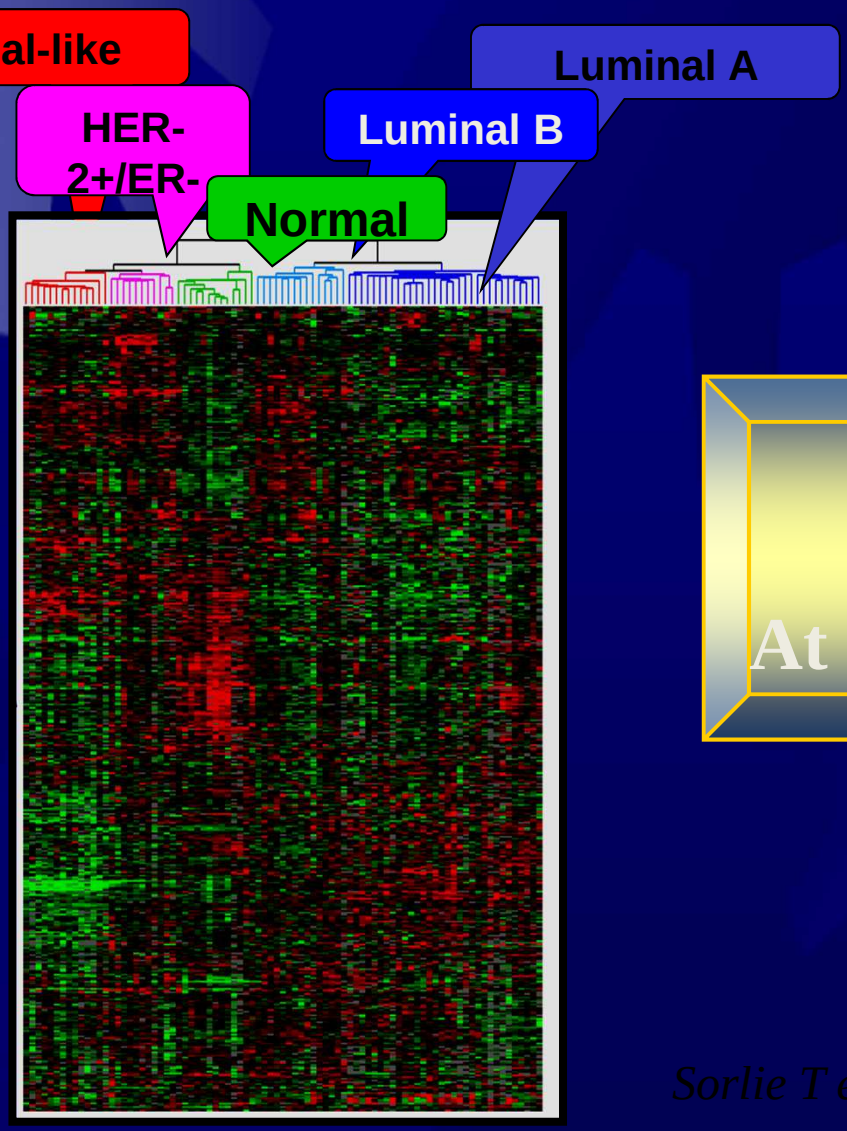
LVI = lymphovascular invasion; ER = estrogen receptor; PgR = progesterone receptor.

Rugo. ASCO, 2005. Abstract 3009. Adapted from slide presentation.

Definition of risk categories for patients with node-negative breast cancer

Risk category	Definition
Low risk	Node negative AND all of the following features: • pathological tumour size <2 cm • pathological tumour grade 1 • absence of peritumoural vascular invasion • *HER2/neu* gene neither over-expressed nor amplified • age >35 years
Intermediate risk	Node negative AND at least one of the following features: • pathological tumour size >2 cm • pathological tumour grade 2–3 • presence of peritumoural vascular invasion • *HER2/neu* gene overexpressed or amplified • age <35 years
High risk	Node positive (1–3 nodes involved) AND *HER2/neu* gene neither overexpressed nor amplified Node positive (1–3 nodes involved) AND *HER2/neu* gene over-expressed or amplified Node positive (4 or more involved nodes)

BREAST CANCER CLASSIFICATION USING GENE EXPRESSION PROFILING



Breast cancer

=

At least 4 distinct diseases!

Sorlie T et al, PNAS 2001

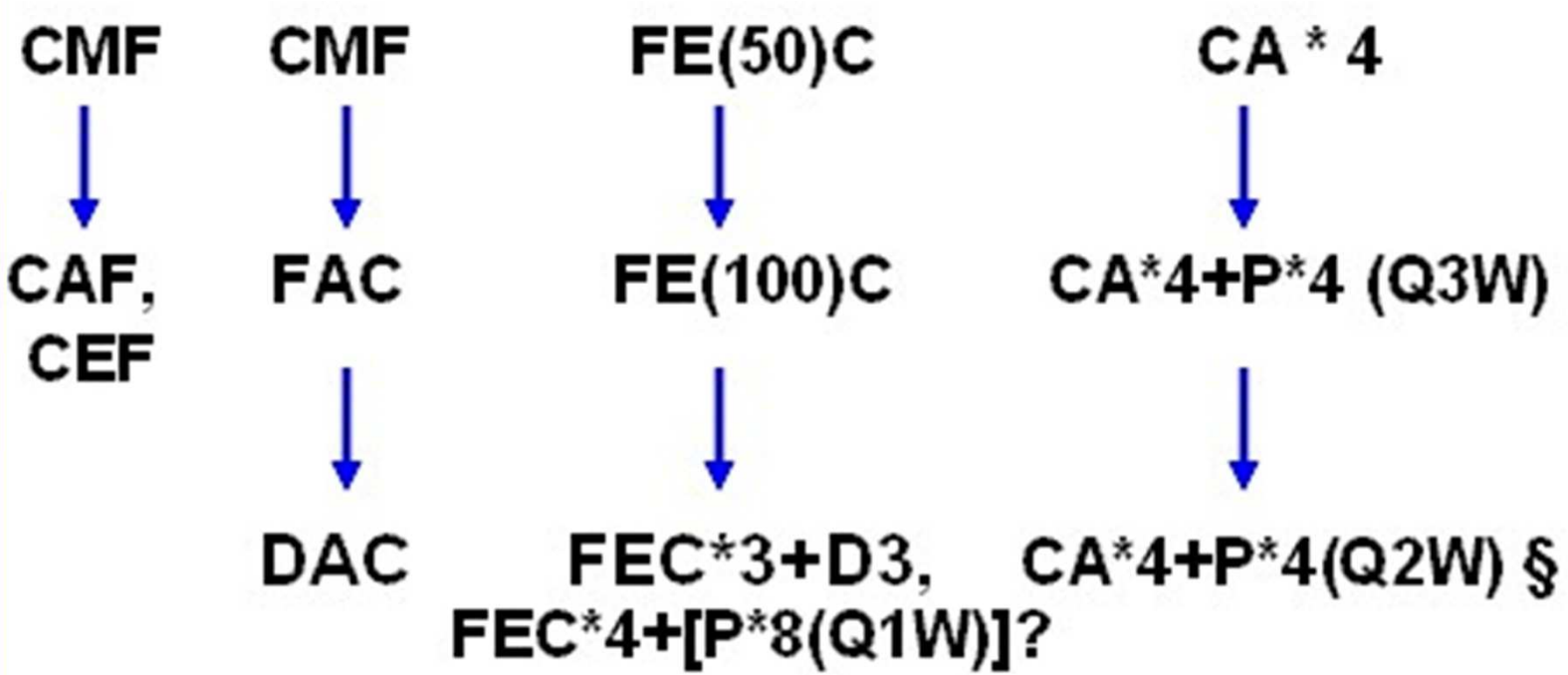
M.J. Piccart

Courtesy of Lisa CAREY

Chemotherapy in carcinoma breast

- Adjuvant
- Neoadjuvant
- Chemotherapy in metastatic cancer

The Generations
(Lineages and Chains of Inference)



P = paclitaxel; D = docetaxel; A = doxorubicin; E = epirubicin

§ Exploratory analyses suggest may be less effective in ER+ cases

? Hazard ratios consistent with designation but p values for OS not < 0.05

Adjuvant chemotherapy

CMF, first generation, 1970s

Cyclophosphamide
Methotrexate
5-FU

Benefit in

-Older individual with early stage carcinoma Breast
-Distant recurrence
-Survival

Table 1: Proportional Risk Reduction of Adverse Outcome
For Patients Treated with Polychemotherapy: Overall Effectiveness

	N=*	% Proportional Risk Reduction (standard error)ϕ	
Regimen		Recurrence	Death
CMF	4103/4047	24 (3)	14 (4)
CMF + extra cytotoxics	1622/1596	20 (2)	15 (5)
Other polychemotherapy	3701/3719	25 (4)	17 (4)
Average Polychemotherapy	9426/9362	24 (2)	15 (2)

* Number of patients in the trials who received polychemotherapy vs the number who did not.

ϕ Two times the SE defines the ~ limits of the 95% confidence interval.

Adjuvant chemotherapy

- **CAF or CEF, 2nd generation, 1980s**
  - Cyclophophamide
  - Adramycin(or Epirubicin)
  - 5-FU

  - More toxic than CMF
  - CAF better than CMF in high-risk group
    - Axilla LN+
    - LN-, but tumor large or other risk factor

Table 5. Proportional Risk Reduction of Adverse Outcome for Patients Treated with Adjuvant Anthracycline vs Non-Anthracycline Regimens

	N=	% Proportional Risk Reduction (standard error)	
Regimen		Recurrence	Death
With Anthracyclines vs without	3477/3473	12 (4)	11 (5)

What have we learned?

- Standard regimens are CMF and CAF
- Anthracycline (e.g. Adriamycin) containing regimens are superior to those that lacks it
- High dose therapy did not improve overall survival
  - Increased morbidity and mortality

Hamilton, et al., J Clin Oncol 23:1760, 2005.

After 200+ RCTs -

- Combination therapy is superior to single agents
- 4 to 6 months produced optimal results
  - Longer treatment with the same regimen did NOT provide incremental gains
- Hormone receptor-positive patients benefit from sequential chemotherapy plus endocrine therapy
  - Additive therapeutic effect

Third Generations Regimen

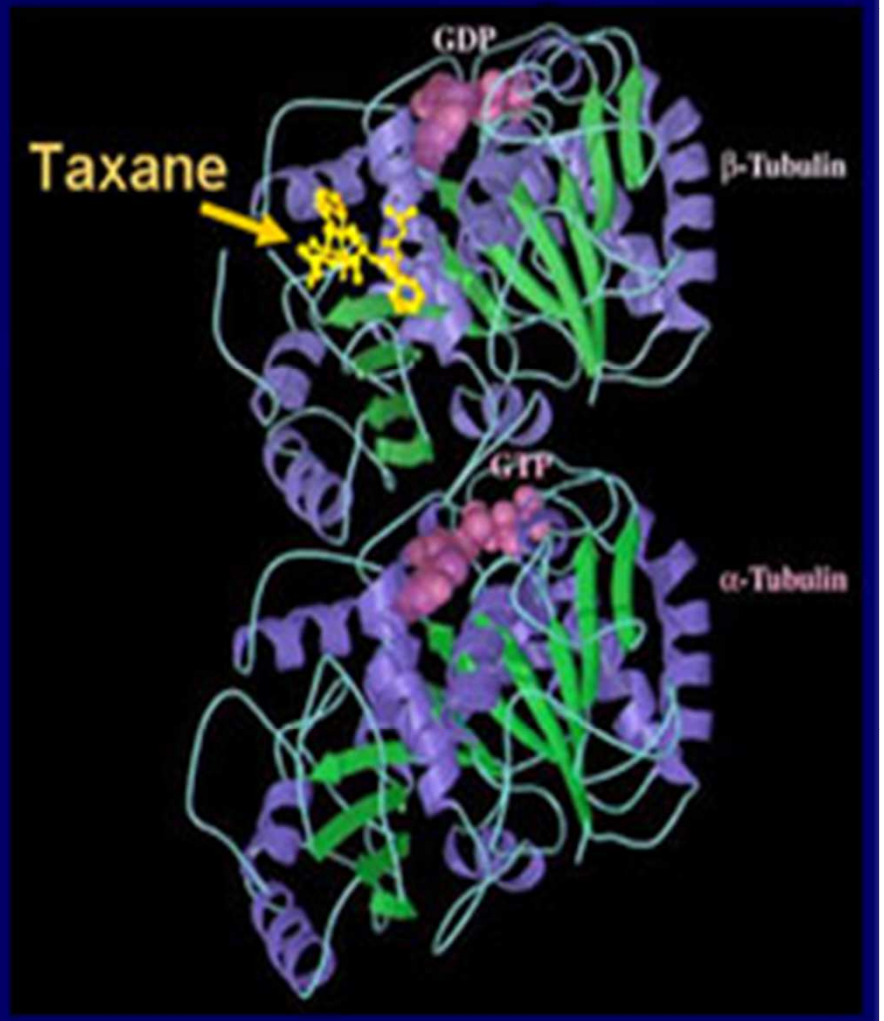
Taxanes as Adjuvant Therapy in BC

- Taxane use in stage I-III BC significantly improves disease-free survival and overall survival
  - Recurrence is still a substantial problem
- Emergence of molecular resistance to taxanes:
  - Increases population requiring alternate therapy
  - Decreases efficacy to other chemotherapies by cross-resistance

BC = breast cancer.

Taxane Mechanism of Action (Paclitaxel, Docetaxel)

- Stabilize microtubules and promote polymerization
- Arrest cellular division at G2/M checkpoint, inducing apoptosis
- Reversibly bind β-tubulin subunits



Downing and Nogales. *Cell Struct Funct*. 1999;24:269.
Esteva et al. *Oncologist*. 2001;6:133.

Taxanes

- 1st Trial CALGB 9344: AC ± placlitaxel(T)
- 3,121 node-positive patients
- Median follow-up of 69 months
  - 5 yr DFS: 70% v 65%, p=0.0023
  - 5 yr OS: 80% v 77%, p=0.0064

Henderson, et al., J Clin Oncol 21:976, 2003

Docetaxel (Taxotere) Trial

- BCIRG 001 Trial
  - 1,491 node-positive patients
  - TAC X6 v FAC X6
  - 5 yr outcome
    - DFS: 75% v 68%
    - OS: 87% v 81%
  - Increased morbidity
    - Febrile neutropenia 10X control arm
    - Neurotoxicity

Nabholz, et al., Proc ASCO 21:36, 2002

Dose-dense Regimen

- Theoretical premise:

  "Full doses of drug, given at the highest possible frequency, will produce the highest degree of cell kill"

- CALGB 9741
  - 2,005 node-positive patients
  - 2 X 2 factorial design
    - A → T → C every 3 weeks
    - A → T → C every 2 weeks + G-CSF
    - AC → T every 3 weeks
    - AC → T every 2 weeks + G-CSF

CALGB 9741

- Median follow-up of 36 months
- Dose dense regimen
  - 4 yr DFS: 82% v 75%
  - Significant OS in favor of dose-dense arm
  - Low rate of neutropenic fever and cardiac toxicity
  - Increased rate of anemia

Citron, et al., J Clin Oncol 21:1431,2003.

Overall survival in the paclitaxel adjuvant trials

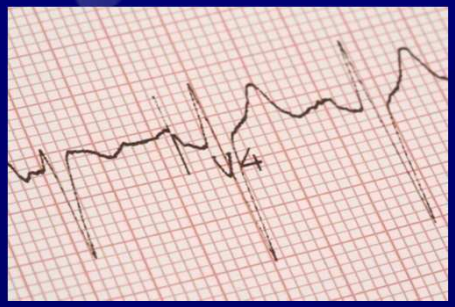
Trial	No.	Follow-up	Regimen	Overall survival HR	Overall survival *p*	5-year absolute OS (%)
CALGB 9344	3121	69	AC x 4 → T x 4	0.82 (0.71–0.98)	0.006	80 77
NSABP B-28	3060	64	AC x 4 → T x 4 AC x 4	0.93 (0.78–1.12)	0.46	85 85

- TAC is a very effective adjuvant regimen for patients with node-positive breast cancer:
  - Significant improvement of DFS and OS over FAC
  - TAC significantly improved DFS irrespective of nodal, menopausal, HER2 and hormonal status

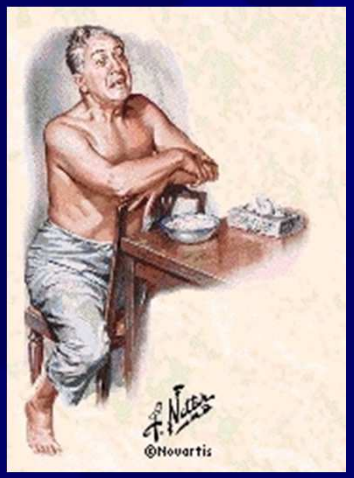
Conclusions

- Taxanes have improved the effectiveness of several adjuvant regimens
- Until now the backbone of these regimens has been an anthracycline
- Recent evidence relates effectiveness of anthracyclines to topoisomerase IIa
- There are now 2 non-anthracycline regimens that challenge the assumption that anthracyclines are needed to treat breast cancer

Cardiovascular Side Effects of Modern Cancer Therapy



Arrhythmia



Cardiac Dysfunction
Heart Failure

Thromboembolism

AP / MI

Hypertension

Overall Conclusions

- Two adjuvant breast trials have demonstrated the efficacy of non-anthracycline regimens:
  - ✓ USO 9735: TC > AC (HER2 status unknown)
  - ✓ BCIRG 006: efficacy of TCH in HER2-positive patients
- Molecular data from BCIRG 006 puts the role of anthracyclines in adjuvant breast cancer treatment into question
- Anthracyclines cause significant cardiotoxicity, which is augmented with trastuzumab
- Optimal way to prevent cardiotoxicity is to eliminate the key stressor: anthracyclines

Adjuvant Endocrine Therapy

- All with ER positive tumors require ET
- Premenopausal women- Tamoxifen
- Postmenopausal women- Aromatase inhibitors

Endocrine Therapy

- Gold Standard: Tamoxifen (Nolvadex)
  - Anti-estrogen receptor
  - 5 years treatment of ER+/PR+ breast cancer
  - Relative risk reduction of 25%
    - Node-positive: 10% improvement in 10-yr survival
    - Node-negative: 5% improvement in 10-yr survival
  - Lower toxicity profile compared to chemotherapy

Aromatase Inhibitors (AIs)

- Conversion of androgenic substrates to estradiol
  - Enzyme complex - aromatase
    - Highly expressed in ovarian follicles in premenopausal women
- AIs blocks aromatase activity
- Postmenopausal women:
  - Residual estrogen production by peripheral conversion
    - Subcutaneous fat, liver, muscle
  - AIs suppress circulating estrogen by 98+%

AIs and Breast Cancer

- Estrogen and receptor positive breast carcinoma
  - Tamoxifen binds estrogen receptors and exerts anti-estrogenic effect
  - AIs block peripheral estrogen conversion in postmenopausal women
  - Reduction in estrogen results in cancer growth inhibition
- AIs have minimal effect on breast cancer in premenopausal women in clinical trials

Adverse Effects: AIs v Tamoxifen

- Lower incidence
  - Hot flashes
  - Vaginal bleeding and discharge
  - Venous thromboembolism
  - Endometrial cancer
- Higher risk for
  - Musculoskeletal symptoms
  - Fractures associated with osteoporosis

ATAC Trialists' Group Lancet 359:2313, 2002.

Baum, et al., Cancer 98:1802, 2003.

Fulvestrant

- Pure estrogen antagonist
- Monthly intramuscular injection
- Activity in tamoxifen resistant and AI-resistant advanced breast cancer.

Role of Ovarian ablation\suppression

- Premenopausal women
- Can be achieved through surgery or ovarian irradiation or through the use of LHRH agonists.
- No added advantage over tamoxifen.
- Useful in Premenopausal women who retain menstruation after chemotherapy.

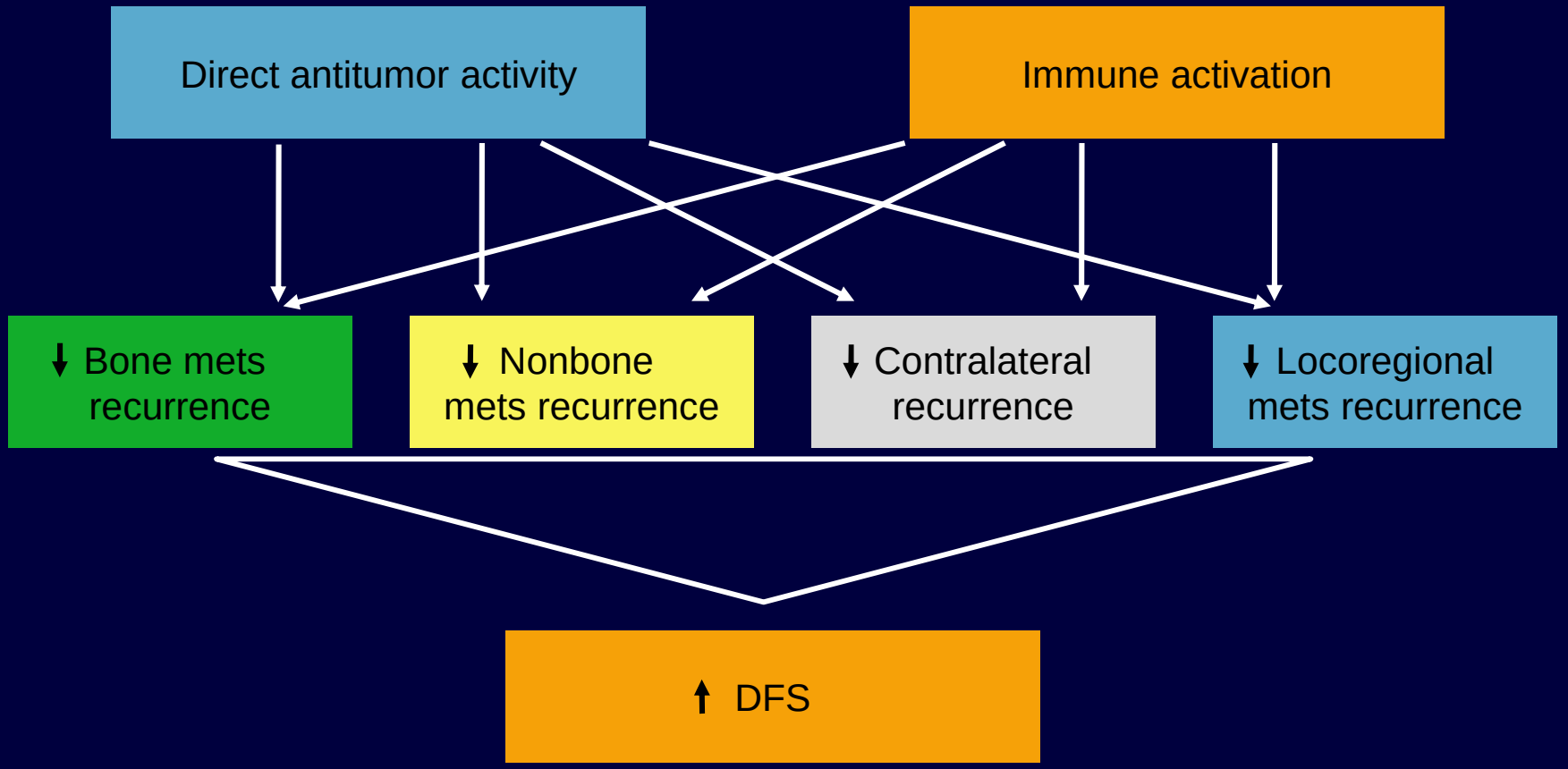
Take Home Message

- In postmenopausal women, AIs appears to be superior to Tamoxifen
  - Reducing/delaying cancer recurrence
  - Lowering contralateral second primary cancer
  - Slightly better adverse effects profile except for osteoporosis
- Should be considered for women having difficulties with Tamoxifen
- Should be considered in addition to 5 years of Tamoxifen

Role of Biphosphonates

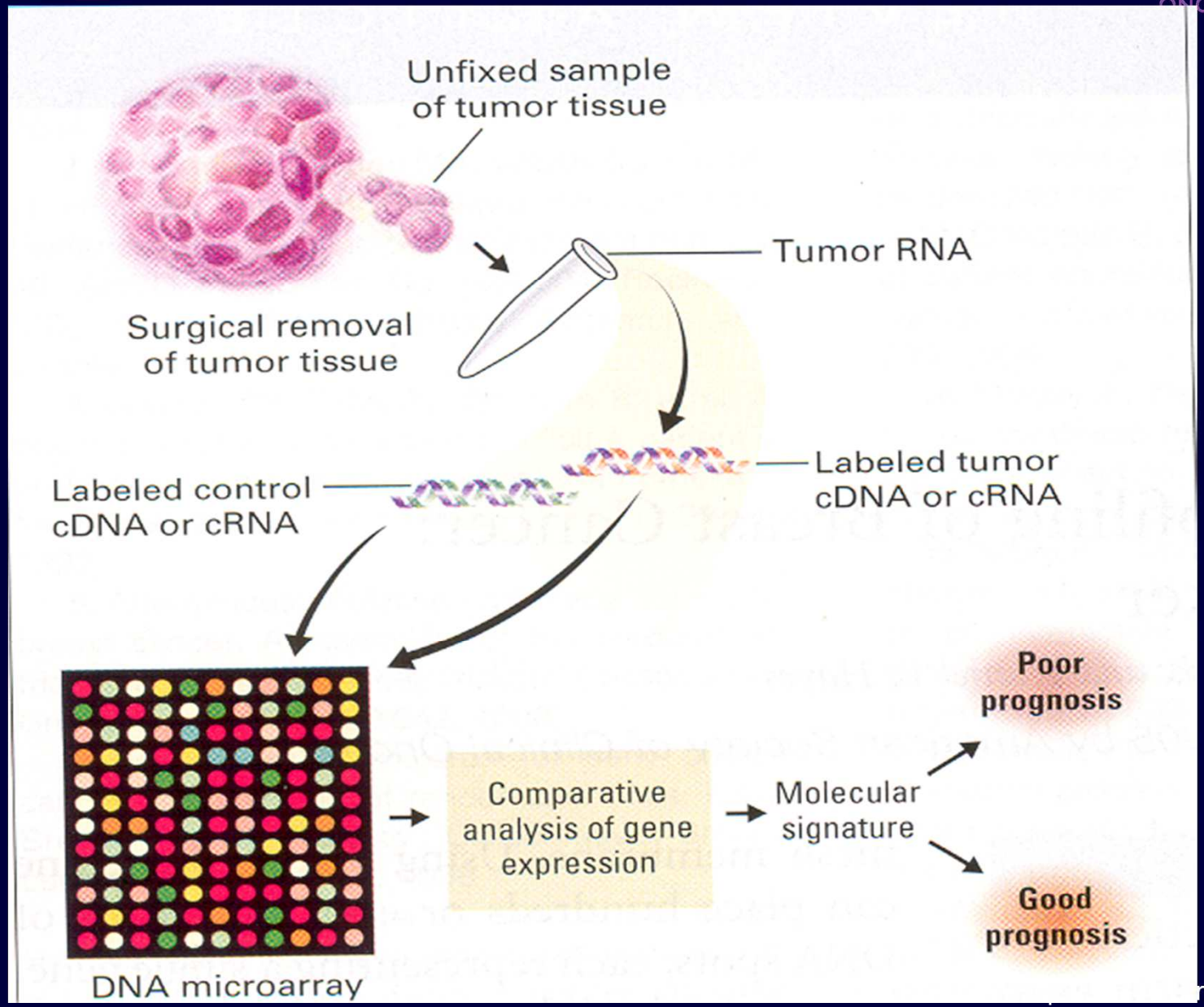
- **Premenopausal women with hormone-responsive, stage I and II breast cancer: ABCSG-12 study.**
- Endocrine therapy plus ZOL significantly reduces the risk of DFS events by 36% and the risk of RFS events by 35% compared with endocrine therapy alone in premenopausal women with endocrine-responsive BC.

ZA-Mediated Mechanisms Contributing to Improved DFS



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

Gene Expression Profiling



Oncotype Dx
Mammoprint (70 Gene Panel)

Refined NSABP / Genomic Health Gene Set

Proliferation Genes
Ki67, STK15, Survivin, Cyclin B1, MYBL2

ER Related Genes
ER, PR, Bcl2, SCUBE2

Her2 Related Genes
Her2, GRB7

Invasion Related Genes
Stromolysin 3, Cathepsin L2

Other Cancer Related Genes
GSTM1, CB68, BAG 1

Reference Genes
Beta-Actin, GAPDH, RPLPO, GUS, TRFC

Refined NSABP / Genomic Health Gene Set

1.04 * Proliferation Gene Group Score

-0.34 * ER Group Score

+0.47 * Her2 Group Score

+0.10 * Invasion Group Score

-0.08 * GSTM1 + 0.05 * CD68 – 0.07 * BAG1

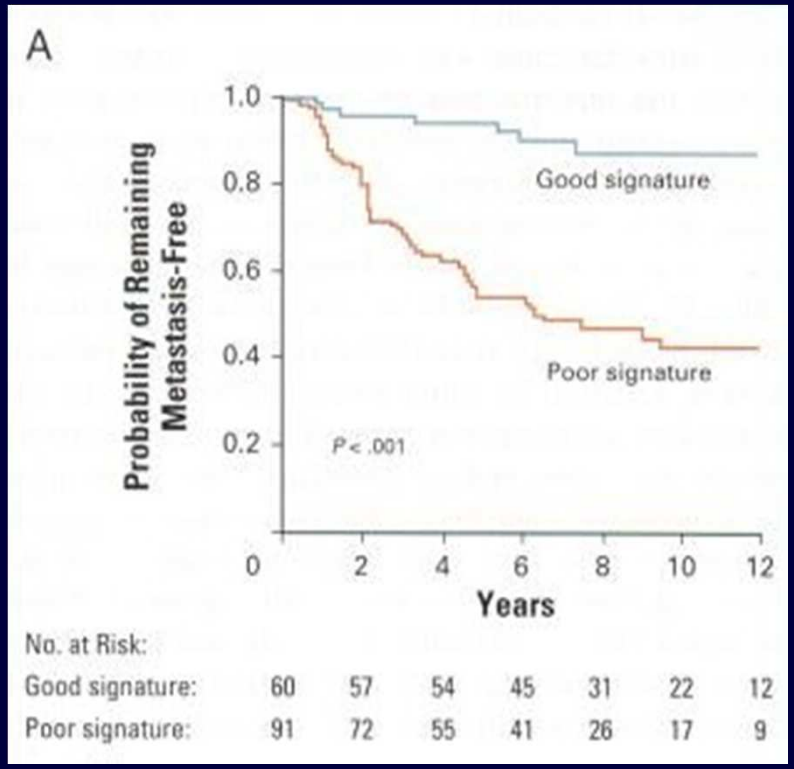
Prognostic Score

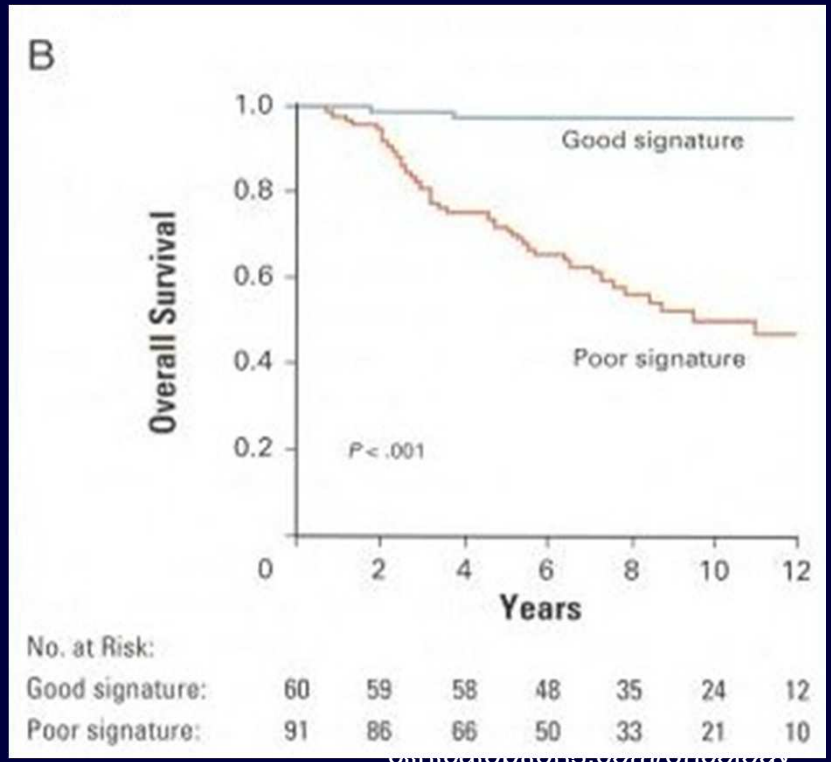
Low Risk < 18

Intermediate Risk 18 - 30.9

High Risk ≥ 31

Survival Analysis by Gene Expression profiling for lymph-node-negative breast cancer patients





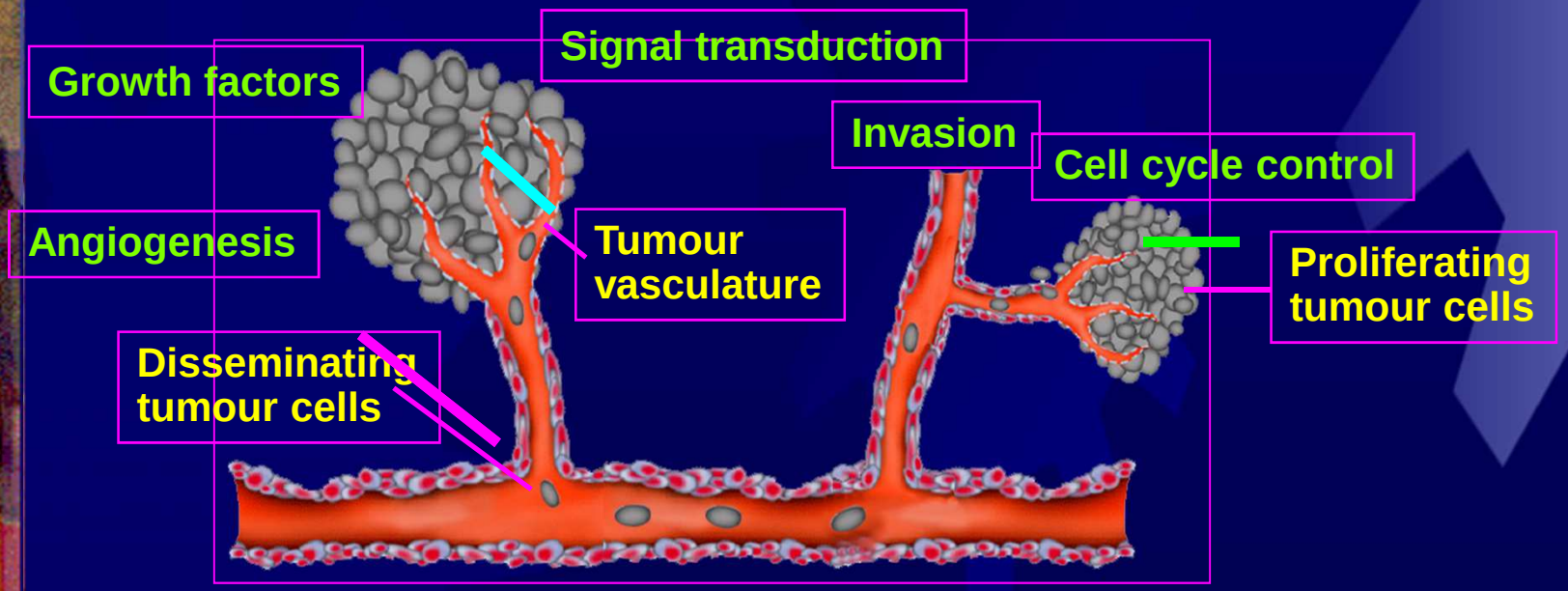
Triple-Negative Breast Cancer

- More aggressive clinical course than other forms of breast cancer
- Increased likelihood of distant recurrence
- Increase in node positivity
- Tendency to develop visceral metastases early in the course of their disease

A NEW WAVE OF SUCCESSFUL TARGETED THERAPEUTICS!!!!

Targeted therapy in cancer

- Many more biologic processes understood at a molecular level in the host (the body's response to the cancer) as well as those in the tumour itself



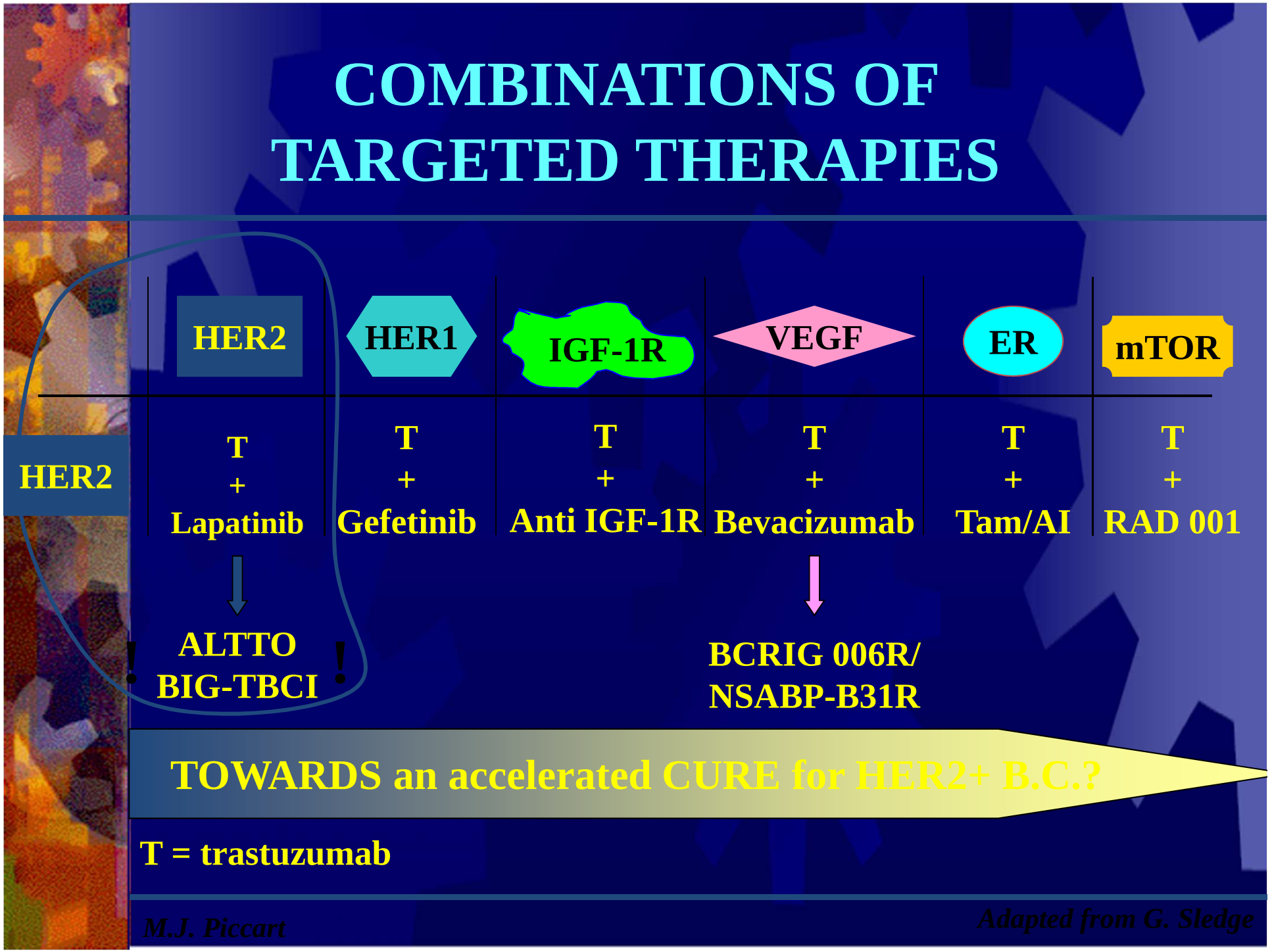
A summary of four adjuvant trials of trastuzumab at time of interim analysis

Study	Eligibility – all patients HER-2+ and had adjuvant chemotherapy	No.	Study design	Median follow-up
NSABP-31	LN-positive	1021 1022	**Group 1**: AC x 4 → paclitaxel x 4 **Group 2**: AC x 4 → paclitaxel x 4 plus weekly trastuzumab for 12 months	28 months
N9831	LN-positive and high risk LN-negative	1633 1633	**Group A**: AC x 4 → weekly paclitaxel x 12 **Group B**: AC x 4 → weekly paclitaxel x 12 → weekly trastuzumab for 12 months* **Group C**: AC x 4 → weekly paclitaxel x 12 *plus* weekly trastuzumab for 12 months	18 months
HERA	LN-positive or LN-negative (tumour >1 cm) and completed adjuvant chemotherapy	1694 1694 1693	**Group A**: 3 weekly trastuzumab for 24 months* **Group B**: 3 weekly trastuzumab for 12 months **Group C**: observation	12 months
BCIRG-006	LN-positive or high-risk node negative disease	1073 1074 1075	**Group 1**: AC x 4 → docetaxel x 4 **Group 2**: AC x 4 → docetaxel x 4 *plus* weekly trastuzumab then 3 weekly for 12 months **Group 3**: docetaxel plus carboplatin x 6 *plus* weekly trastuzumab then 3 weekly for 12 months	23 months

A summary of the endpoints of the adjuvant trials (NSABP B-31 and N9831, and HERA)

Endpoints	Number of events		HR	*p* value
	T	Control		
B-31 and N9831*				
DFS	133	261	0.48 (0.39–0.59)†	<0.0001
OS	62	92	0.67 (0.48–0.93)‡	0.015
HERA				
DFS	127	220	0.54 (0.43–0.67)	<0.0001
OS	29	37	–	NS

COMBINATIONS OF TARGETED THERAPIES



THE ALTTO TRIAL

8000 women with HER2 positive breast cancer

CHEMOTHERAPY

- **Trastuzumab x 1y**
- **Lapatinib x 1y**
- **Trastuzumab ↓ then lapatinib**
- **Trastuzumab combined with lapatinib**

With a huge translational research effort!

(e.g. tumor / blood collection → back to the lab!)

M.J. Piccart

- **ER +ve/ PR +ve, Her2 neu +ve=** chemotherapy + Harmonal + Transtuzumab
- **ER +ve/ PR +ve, Her2 neu -ve=** chemotherapy + Harmonal
- **ER +ve/ PR + ve, Her2 neu + ve=** chemotherapy + Transtuzumab
- **ER -ve/ PR -ve, Her2 neu -ve=** chemotherapy

Neoadjuvant Chemotherapy (cont.)

- Goals
  - Decrease tumor size
  - Minimize surgery
  - Establish tumor sensitivity
- Appropriate treatments
  - Chemotherapy
  - Tamoxifen or aromatase inhibitors
  - Radiation therapy

Factors Influencing Decision to Use Neoadjuvant Chemotherapy in Operable Breast Cancer

- Does the patient need adjuvant chemotherapy based on information known prior to surgery?
- Would neoadjuvant chemotherapy potentially alter the extent of resection?
- Does the patient desire breast preservation?
- Would treatment benefit from knowledge of in vivo chemosensitivity?

Advantages

- Higher rate of breast conservation
  - Convert some “inoperable” breast cancer to potentially curative surgical candidates
- Response in real time
  - Lack of response – change regimen
- Prognosis can be refined by degree of residual disease
  - Pathologic clinical response had much higher DFS and OS

Wolmark, et al., JNCI 30:96, 2001.

Conclusions

- Neoadjuvant chemotherapy is recommended for patients with locally advanced disease
- A taxane should be included in the regimen
- Ongoing trials will help determine appropriate regimens and the benefit of targeted therapies in this setting

Trials of Neoadjuvant Trastuzumab: Summary of Efficacy

- Preoperative clinical responses observed
  - Overall response rate, 70% to 90%
  - Clinical complete response, 15% to 30%
  - Pathologic complete response, approximately 18%
- Responses higher for patients with 3+ expression of HER2

Metastatic Breast Cancer

- Chronic disease
- MS of MBC-2 to 3 yrs/5-10% live more than10yr.
- 3% to 25% can achieve CR/PR and can be rendered disease free and progression free for more than 5 yrs.
- Optimal sequential use of all modalities can lead to maximum palliation,delay progression and death as much as possible

When to initiate CT in MBC ?

- Difficult decision
- There is no evidence that CT should be initiated as soon as MBC is identified
- Optimal duration of CT also varies on the basis of clinical situation and patient preferences

Chemotherapy Regimens for MBC: 2008 NCCN Recommendations

Representative Single Agents

- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin
- Paclitaxel
- Docetaxel
- Capecitabine
- Vinorelbine
- Gemcitabine
- Albumin-bound paclitaxel

Combination Regimens

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

MBC = metastatic breast cancer; F = fluorouracil; A = doxorubicin; C = cyclophosphamide; E = epirubicin; T = paclitaxel; M = methotrexate.

National Comprehensive Cancer Network. Breast Cancer. Clinical Practice Guidelines in Oncology – v.2.2008.

First-Line MBC: Single-Agent Response Rates

Treatment	ORR (%)
Docetaxel[1] (75-100 mg/m^2)	40-68
Paclitaxel[1] (175-250 mg/m^2 3-24 h)	32-62
Doxorubicin[2]	43
Capecitabine[3]	30
Vinorelbine[4]	35-53
Gemcitabine[5]	18-37
Cyclophosphamide[2]	36
Fluorouracil[2]	28
Methotrexate[2]	26
Mitoxantrone[2]	27

ORR = overall response rate.

1. Esteva et al. *Oncologist*. 2001;6:133.
2. Sledge. *Cancer Control*. 1999;6:17.
3. O'Shaughnessy et al. *Ann Oncol*. 2001;12:1247.
4. Vogel and Nabholtz. *Oncologist*. 1999;4:17.
5. Seidman. *Oncology*. 2001;60(3):189.

Other Modalities Used in the Treatment of Metastatic Breast Cancer

- Monoclonal antibody therapy
  - Trastuzumab
- Bisphosphonate therapy
  - Pamidronate
- Radiation therapy

Monoclonal Antibody Therapy for Breast Cancer: Conclusions

- Bevacizumab improves PFS when added to paclitaxel for treatment of locally recurrent or metastatic disease
  - Improved overall survival and overall response
  - Increased hypertension, proteinuria, neuropathy with bevacizumab
- Adjuvant trastuzumab improves survival outcomes
- Trastuzumab added to paclitaxel as adjuvant therapy following doxorubicin/cyclophosphamide prolongs disease-free and overall survival
  - Concurrent trastuzumab/paclitaxel appears superior to sequential
- Increased cardiac toxicity in patients receiving trastuzumab + paclitaxel: within 4% acceptable range

Changes in Primary Vs Metastatic Lesions: Results and Summary

Results

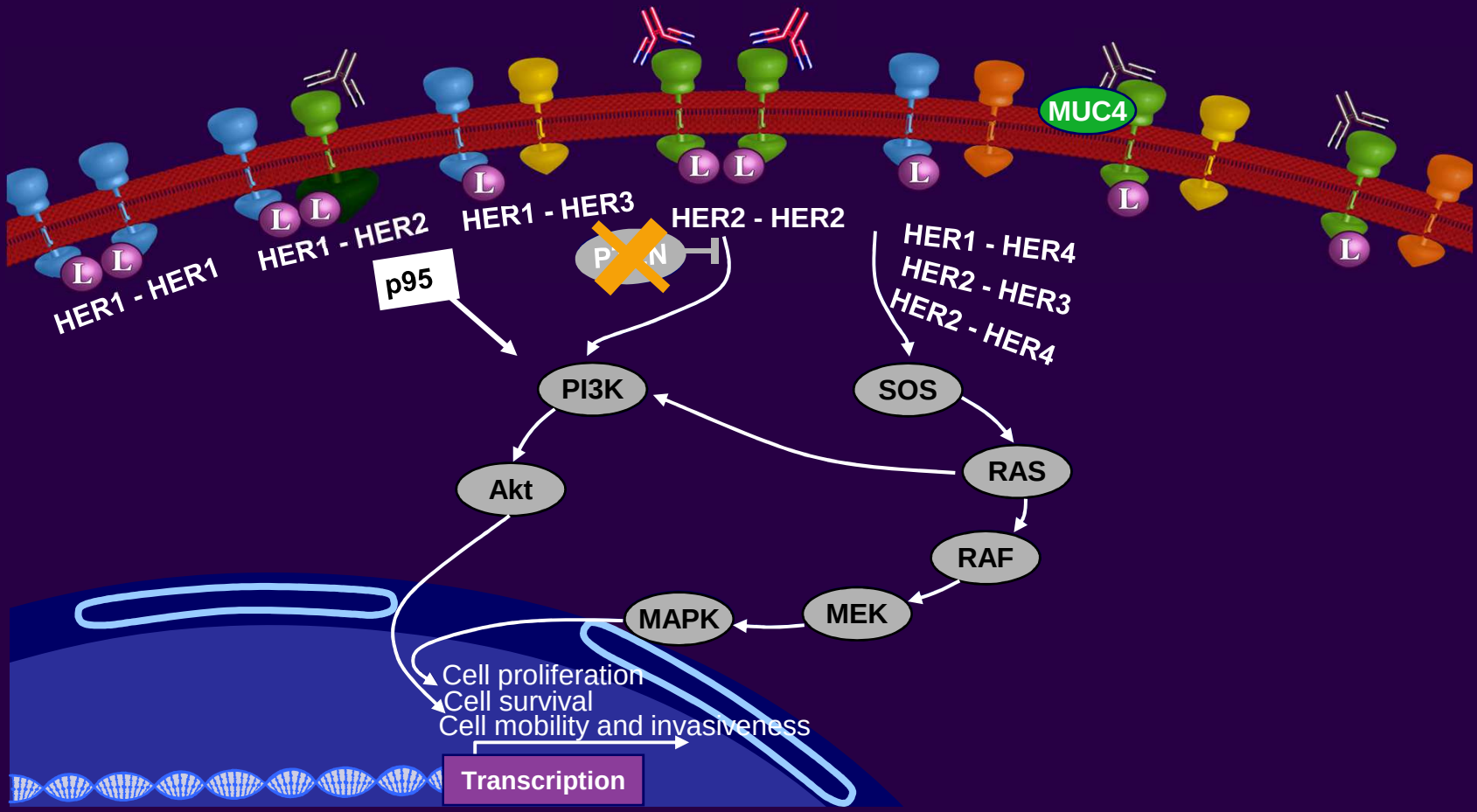
- 160 tumor blocks with adequate tissue
  - 115 (72%): no changes in ER/PgR or HER2 status
- Of the 45 (28%) tumors with changes in receptor status
  - 11(7%): local recurrence
  - 34 (21%): regional or distant relapse
    - 11 went from ER/PgR+ to ER/PgR-
    - 14 went from ER/PgR- to ER/PgR+
    -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

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

Total Blockade of HER2 May Provide Greater Antitumor Activity and Overcome Resistance



O'Shaughnessy J, et al. ASCO 2008. Abstract 1015.

Treatment Efficacy: Lapatinib vs Lapatinib + Trastuzumab

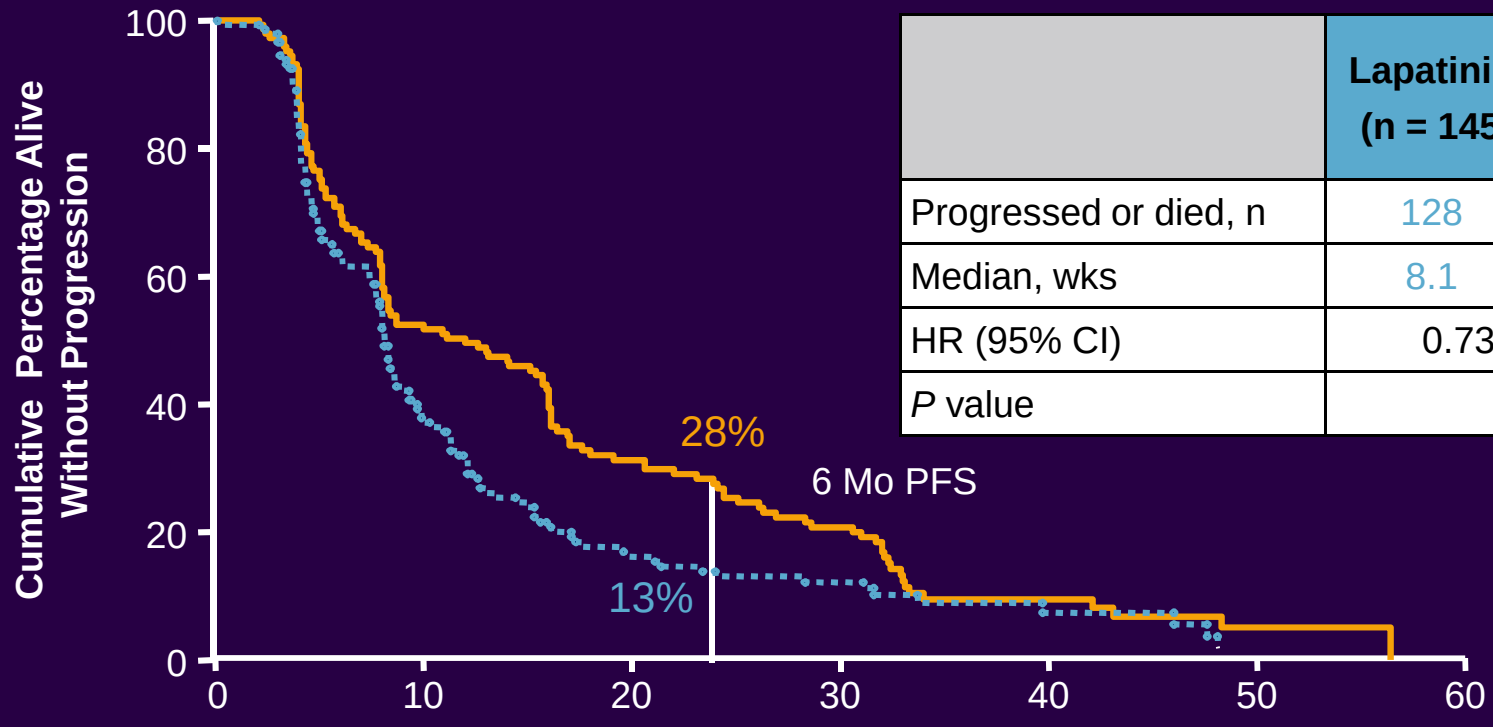
Clinical Response	Lapatinib (n = 145)	Lapatinib + Trastuzumab (n = 146)
Response rate, %* (95% CI)	6.9 (3.4-12.3)	10.3 (5.9-16.4)
Odds ratio (95% CI)	1.5 (0.6-3.9) *P* = .46	
Clinical benefit rate, %† (95% CI)	12.4 (7.5-18.9)	24.7 (17.9-32.5)
Odds ratio (95% CI)	2.2 (1.2-4.5) *P* = .01	

*Confirmed CR + PR.
†CR + PR + SD ≥ 6 mos.

O'Shaughnessy J, et al. ASCO 2008. Abstract 1015.

CLINICAL CARE OPTIONS ONCOLOGY

PFS: Lapatinib vs Lapatinib + Trastuzumab



	Lapatinib (n = 145)	Lapatinib + Trastuzumab (n = 146)
Progressed or died, n	128	127
Median, wks	8.1	12.0
HR (95% CI)	0.73 (0.57- 0.93)	
P value	.008	

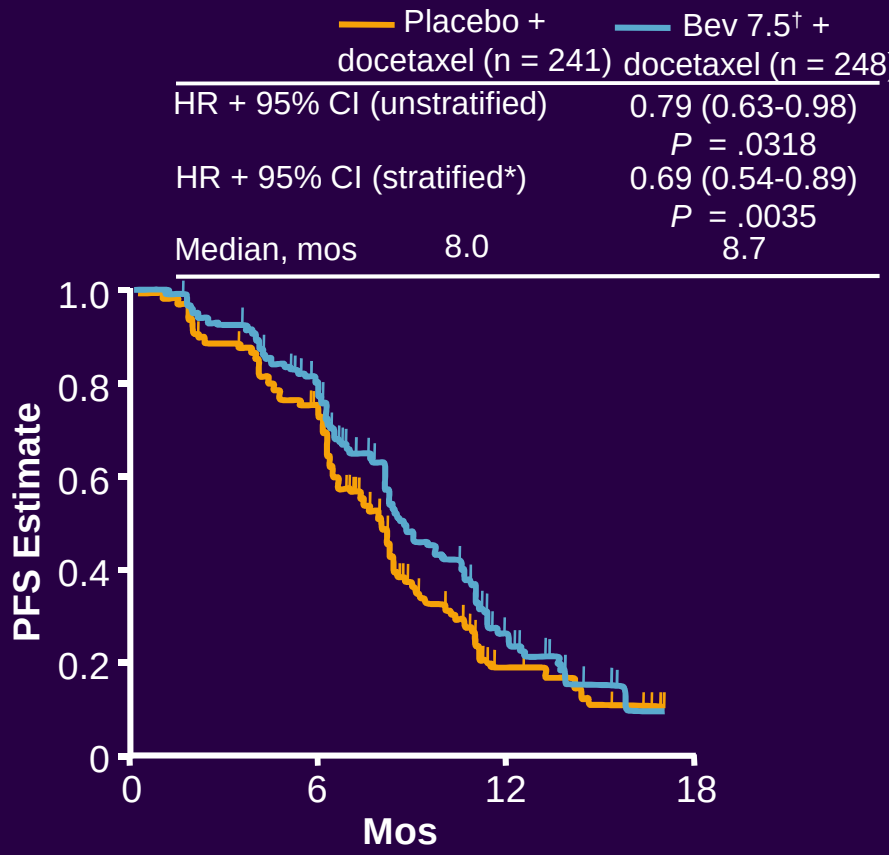
Subjects at Risk

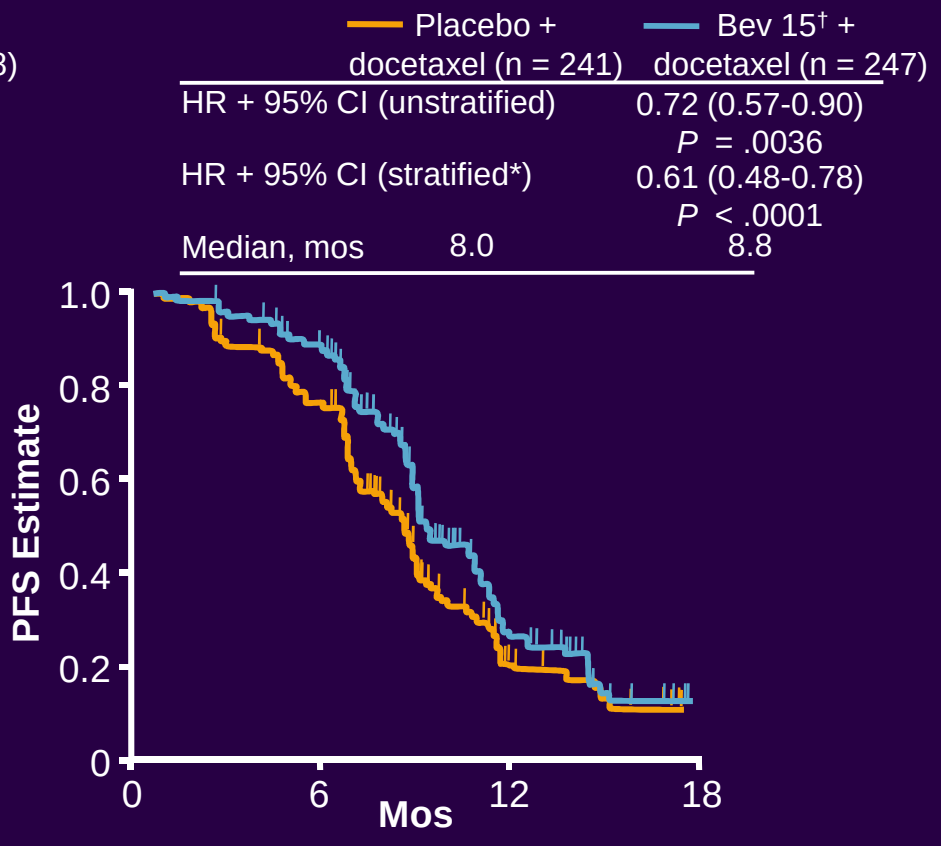
Lapatinib	148	53	21	13	5	0
Lapatinib + Trastuzumab	148	73	42	27	8	2

O'Shaughnessy J, et al. ASCO 2008. Abstract 1015.

CLINICAL CARE OPTIONS ONCOLOGY

AVADO Trial PFS: by Bevacizumab Dose





*Data censored for non-protocol therapy prior to PD.
†mg/kg Q3W.

Miles D, et al. ASCO 2008. Abstract LBA1011.

Rationale for New Agents

- MBC remains an important medical problem
- Anthracyclines and taxanes are the standard of care
  - Increasing use in the adjuvant setting
  - Drug resistance
- Need for new agents
  - Capecitabine approved for use after failure of anthracyclines and/or taxanes
    - ORRs 9% to 14% in phase 3 studies[1,2]
  - Limited efficacy of other agents used in MBC

1. Miller et al. *J Clin Oncol.* 2005;23:792.
2. Geyer et al. *N Engl J Med.* 2006;355:2733.

Treatment options for bone metastases

- **Radiotherapy- treatment of choice for painful bone met. No impact on survival**
- **Cytotoxic chemotherapy and hormonal therapy tend to prolong survival modestly**
- **Biphosphonates, gallium nitrate and calcitonin as osteoclast inhibitor**

Bisphosphonates in bone metastases

- Pain relief
- Decrease in bone metastases related complications
- Healing of bone met. Lesions
- Preliminary results suggest use of bisphosphonate in patients without over bone met can reduce incidence of bone met.

Radioactive isotopes

- FDA approved :Stronium 89,Samarium 153
- Under active clinical investigations: tin117,yttrium90,rhenium -186,holmium 60
- Produce substantial pain relief in 50% to 80% of patients
- Major toxicity myelosupression
- Useful whensymptomatic multiple osseous met inpatient receiving 2nd or 3rd line of systemic therapy

Defining "High Risk" Patients

- What exactly is the relative risk when there is a family history of breast cancer?
  - One family member with postmenopausal breast cancer
    - 2-3 fold relative risk elevation
  - "high risk" family
    - Multiple 1st degree relatives
    - Pre-menopausal breast cancer
    - Bilateral breast cancer
    - Male breast cancer
    - Ovarian cancer

The BReast CAncer (BRCA) Genes

- 5 to 10% of breast cancer are hereditary
  - BRCA1
  - BRCA2
- 50% to 80% lifetime risk
- Tumor suppressor genes
  - Involved in cell cycle control
- In addition to breast cancer
  - BRCA1 mutation is associated with 50% risk for ovarian cancer
  - BRCA2 mutation is associated with increased risk for male breast CA

BRCA Genes

- Who should be considered for BRCA testing?
  - 2 first degree relatives
  - One first degree relative
    - Premenopausal
    - Bilateral
  - Ovarian cancer
  - Multiple breast cancer, including male breast cancer
- Offered with complete genetic/social counseling

Chemoprevention

- NSABP BPCT-1
  - 13,388 women randomized to receive tamoxifen versus placebo
  - At median follow-up of 54 months
    - 49% reduction of invasive breast cancer
    - 50% reduction of non-invasive breast cancer
  - Caveats
    - No reduction in ER negative carcinomas
    - Overall survival was not a measured outcome
      - We Don't Know If The Breast Cancer Reduction Translates into Cancer Death Reduction
    - Increased risk for
      - endometrial cancer (RR = 4 in age>50)
      - DVT (RR = 1.7)
      - PE (RR=3.0)

Fisher, JNCI, 1999

STAR Chemoprevention Trial (Study of Tamoxifen against Raloxifene)

- Tamoxifen vs. Raloxifene
  - both are approved medications that selectively block estrogen receptors
  - estrogen receptors are present on many tissues - breast, bone, uterus, blood vessels, and many others
  - Tamoxifen - breast cancer medication
  - Raloxifene - anti-osteoporosis medication
- Compare the 2 groups of women for development of breast cancer, possible side effects or other benefits

Mean follow-up of 3.9 years,
Raloxifene vs Tamoxifen.

-no difference in invasive cancer.
- -More cases of noninvasive cancer
- -84% reduction in endometrial hyperplasia
-statistically significant reduction in the number of hysterectomies.
-reduced endometrial cancers. -
-Significantly fewer thromboembolic events and cataracts.

Cost of chemotherapy

Drug	Cost(Rs)
Inj Cyclophosphamide 1 gm	30
Inj Methotrexate 50 mg	19
Inj 5fluorouracil 500mg	235
Inj Adriamycin 50mg	345
Inj Docetaxel 120mg	3000-10000
Inj Paclitaxel 300mg	2200- 8000
Inj Transtuzumab 440mg	1,05000
Inj Epirubicin 50mg	1350
Tab Cepecitabine 500mg	68

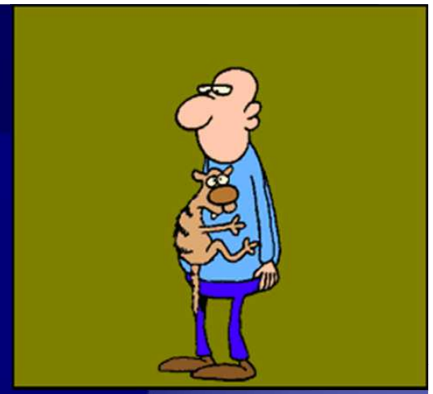
Average BSA- 1.5

Chemotherapy	Cost(Rs)
One cycle of CMF	550
One cycle of FAC	1250
One cycle of TAC	5000-12000
One cycle of FEC	4500

Hormonal therapy

- Tamoxifen 2 Rs
- LetraZOLE 5 RS
- Anastrazole – 40 Rs
- Lupride
- Fulvestrant 20000 Rs

Future Perspectives



- ANATOMICAL STAGING - → MOLECULAR STAGING
- BIOLOGY OF BREAST CANCER → NEW PROGNOSTIC & PREDICTIVE FACTORS.

- PREDICTIVE ONCOLOGY → PREDICTS RESPONSE OF INDIVIDUAL PATIENT TO CT, RT & BIOLOGICAL THERAPY.

ONE SHOE FITS ALL HYPOTHESIS DOES NOT HOLD TRUE ANYMORE

THANK YOU