Paziente Oligometastatico Successive Terapie Sistemiche? (Breast Cancer. Why?)

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Roma, 18.11.2012

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	Early disease	Locally advanced disease	Oligometastatic disease	Metastatic disease
Disease extend	small primary tumor, no lymph node metastases	large primary tumor, lymph node metastases	solitary or few metastatic lesions	multiple organ involvement
Chance of cure	high (90%)	medium (50%)	zero?	zero
Treatment intent	curative	curative	curative?	palliative
Type of treatment	locoregional + adjuvant systemic	locoregional + adjuvant systemic	systemic + local?	systemic

K Dellas, Breast Care 2011

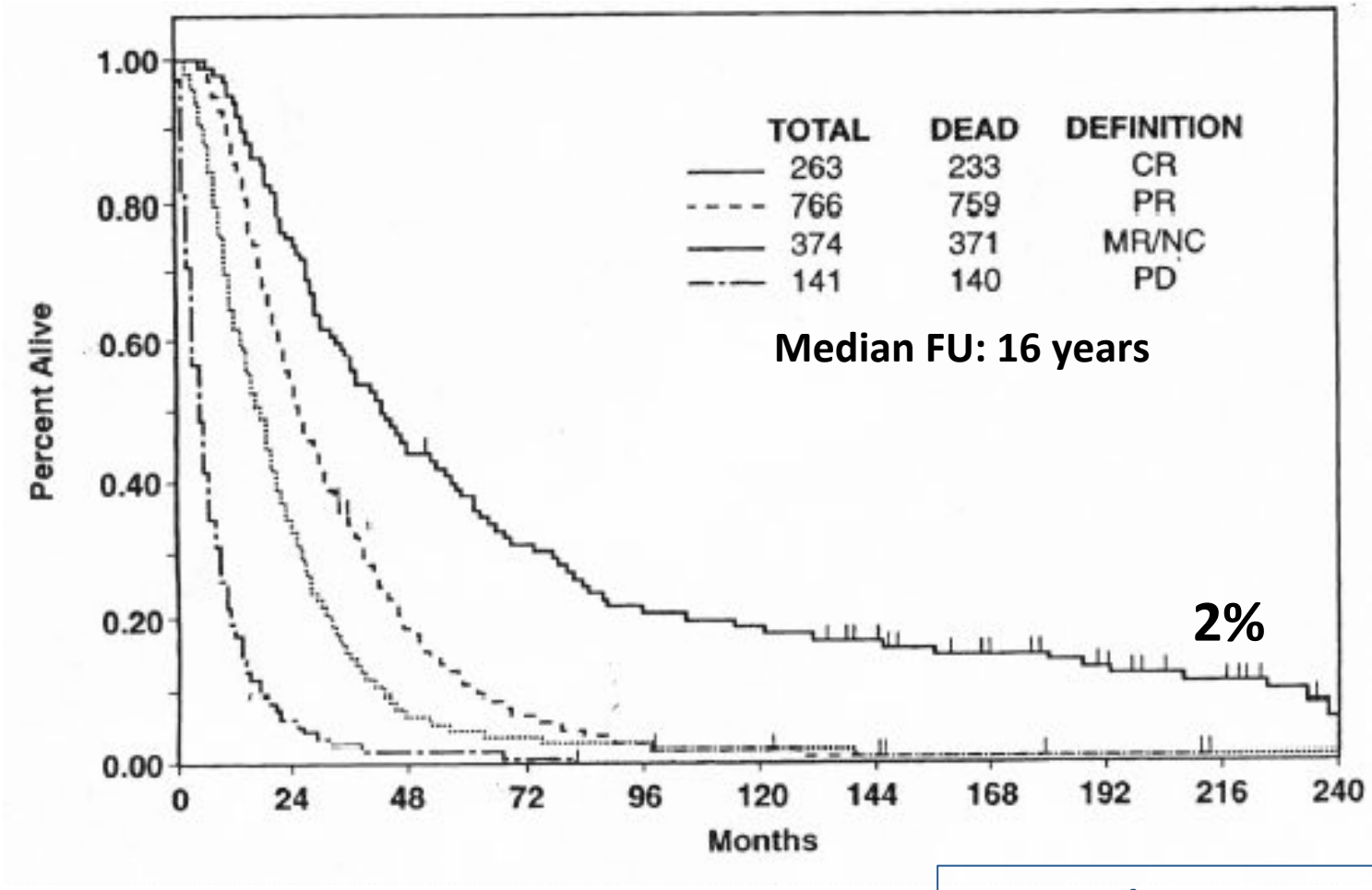
Treatment End Points

MBC : Treatment End Points

- **Prolongation of Survival**
- **Improvement of Quality of Life**

- **And Cure?**

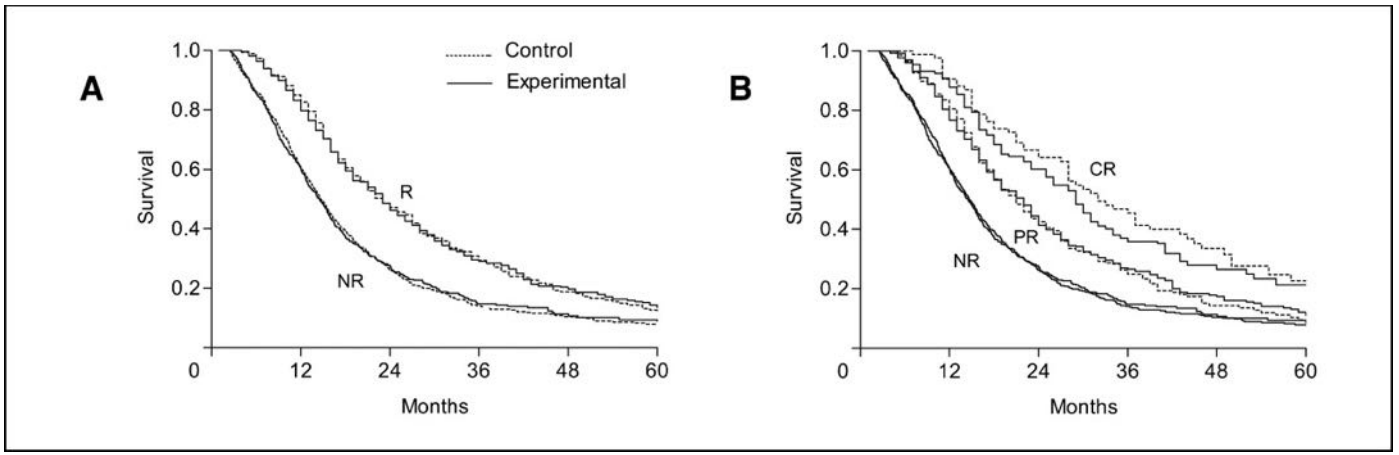
Overall Survival
according to response to front line CT in MBC



PA Greenberg, JCO 1996

Effect of Tumor Response on Survival

- **Tumor response is a highly significant predictor of survival** (p <0.0001)
- Compared with no response:
  - CR, HR 0.48 (95% CI, 0.40 to 0.57)
  - PR, HR 0.69 (95% CI, 0.62 to 0.77)
- Median survival time:
  - **CR, 28.8 months (95% CI, 25.4 to 45.3)**
  - **PR, 21.3 months (95% CI, 19.2 to 22.4)**
  - **No response, 14.6 months (95% CI, 13.9 to 15.4)**



P Bruzzi, JCO 2005

Is MBC Survival improving ?

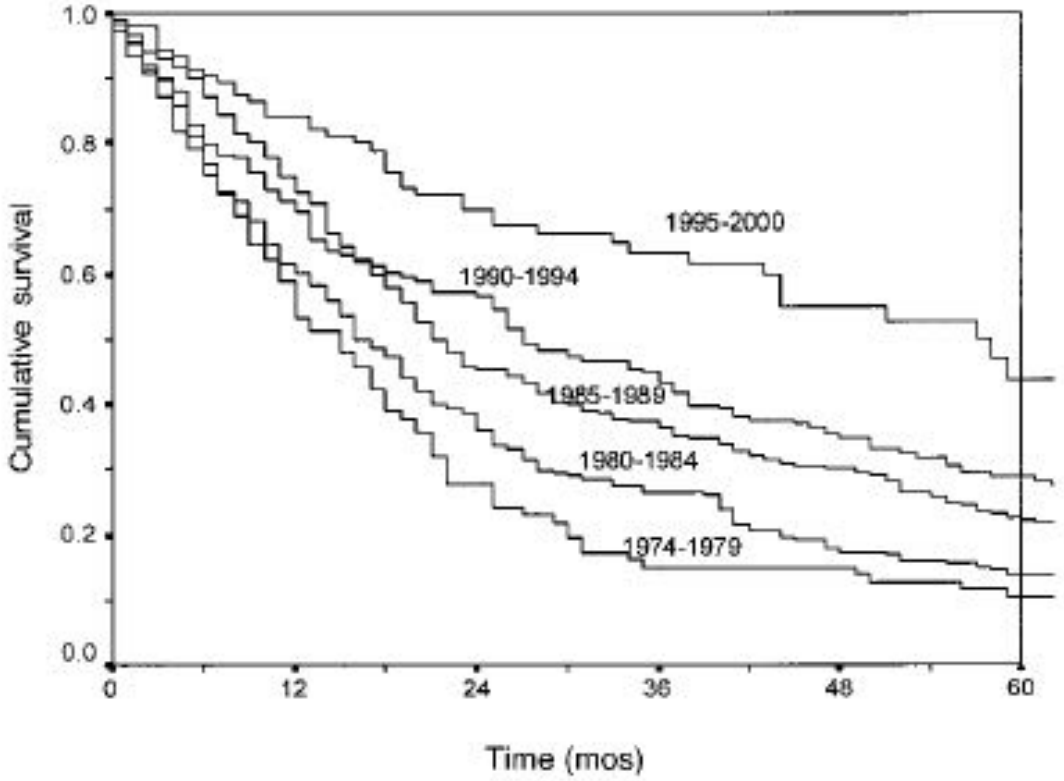
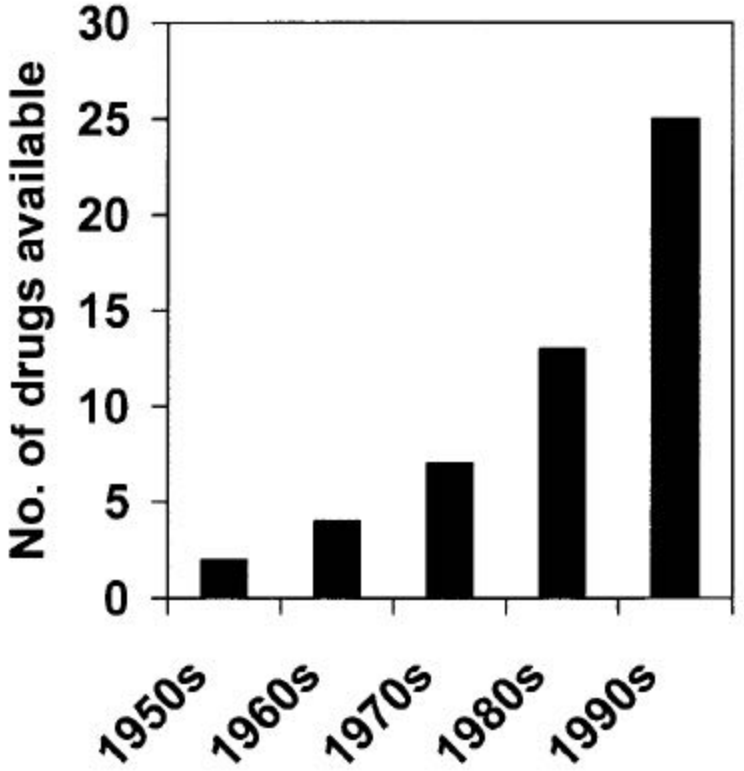


FIGURE 1. Overall survival from time of recurrence.



S Giordano, Cancer 2004

- **Is so unexpected to find a 5% 10-yr OS (from relapse) ? among**
  - **HR+/HER2- (independently from extension and achievement of CR)**
  - **HER2+ responding (even <CR) to anti- HER2+**

Guide Lines

Waiting for….

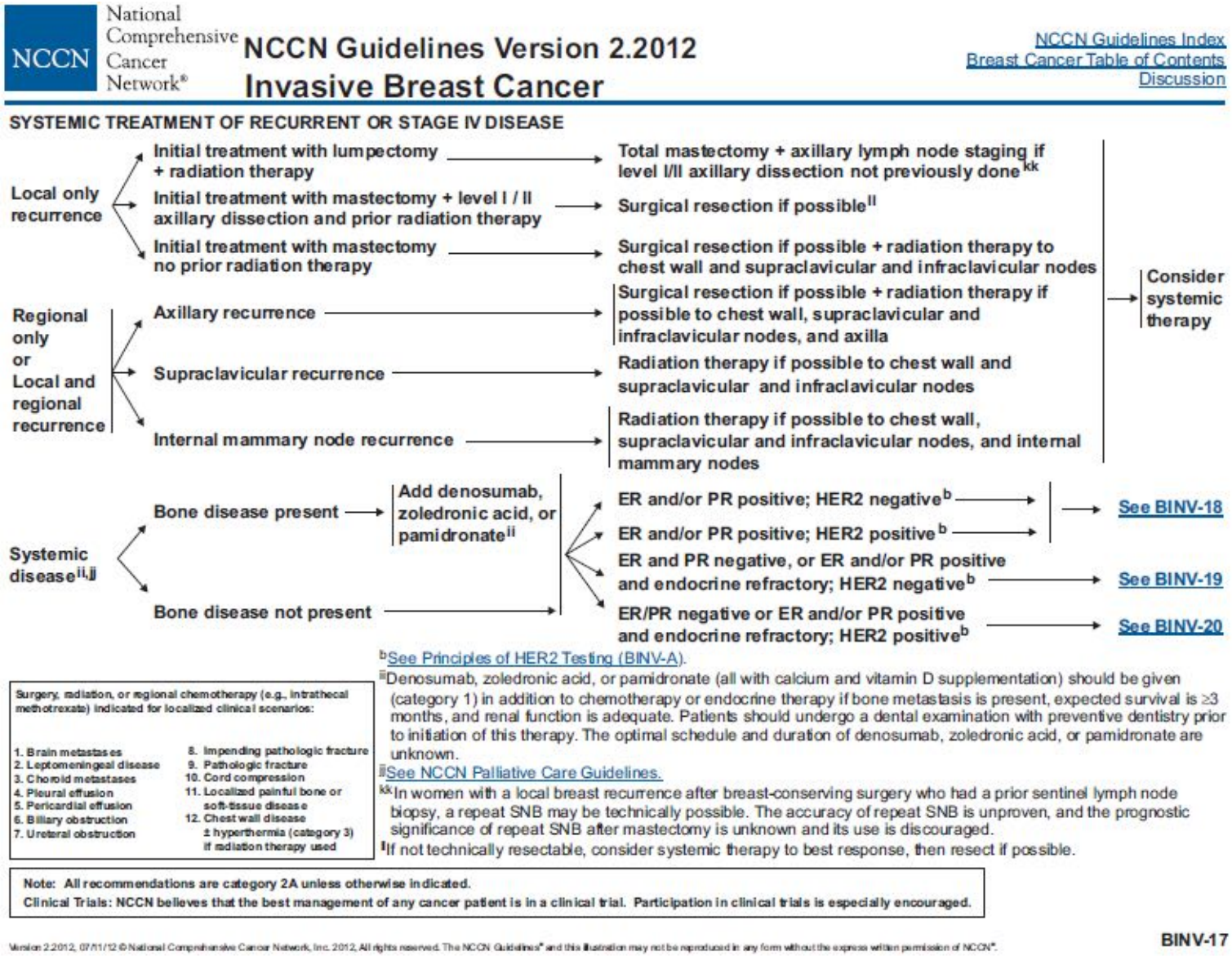
- **Chemotherapy prolongs survival for isolated local or regional recurrence of breast cancer. The CALOR trial (Chemotherapy as Adjuvant for Locallly Recurrent Breast Cancer); IBCSG 27-02; NSABP B-37; BIG 1-02**
  - **S Aebi**
  - **Scheduled at San Antonio, December 6**

Metastatic Breast Cancer

- ***Is still valid the paradigm that MBC is uncurable?***

- ***Is oligometastatic disease (aggressively treated) uncurable?***

NCCN Guidelines v3_2012



NCCN Guidelines v2_2012, Breast Cancer- www.nccn.org

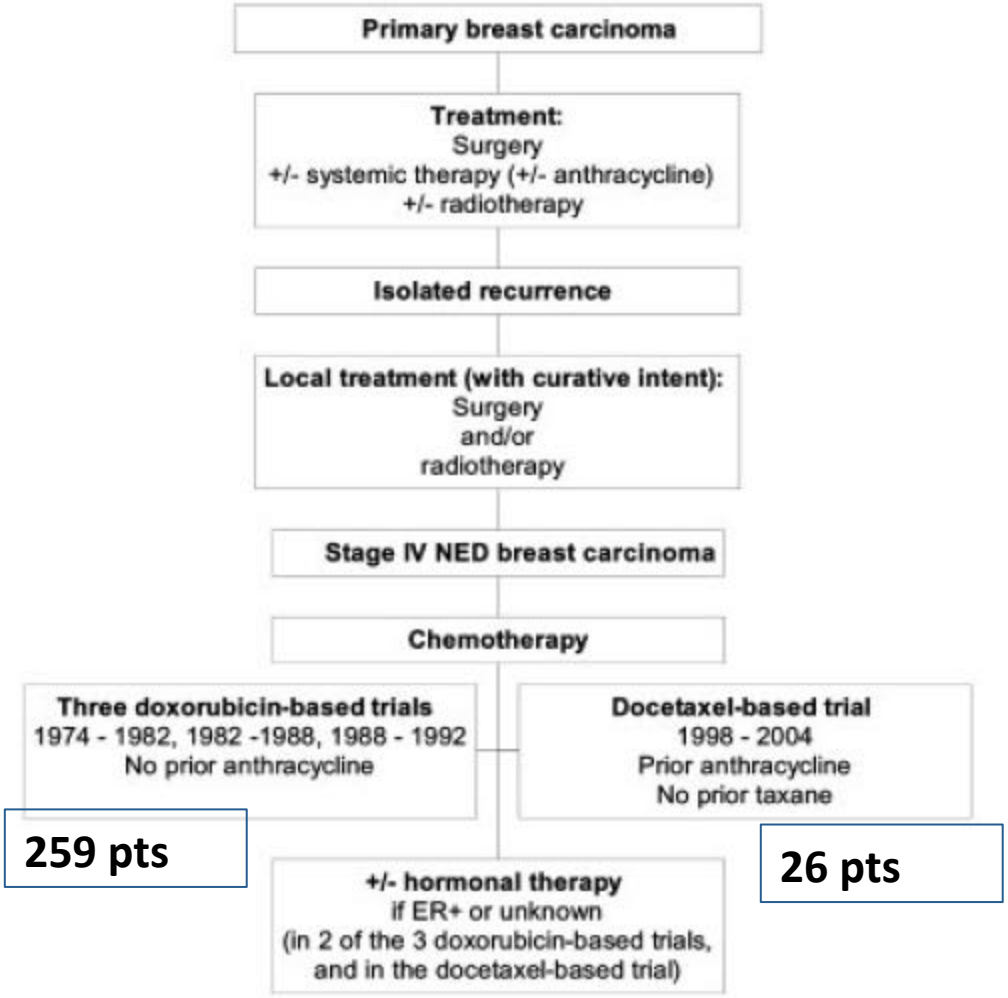
1st International consensus guidelines for advanced breast cancer (ABC 1)

F. Cardoso [a,*], A. Costa [b], L. Norton [c], D. Cameron [d], T. Cufer [e], L. Fallowfield [f], P. Francis [g], J. Gligorov [h], S. Kyriakides [i], N. Lin [j], O. Pagani [k], E. Senkus [l], C. Thomssen [m], M. Aapro [n], J. Bergh [o], A. Di Leo [p], N. El Saghir [q], P.A. Ganz [r], K. Gelmon [s], A. Goldhirsch [t], N. Harbeck [u], N. Houssami [v], C. Hudis [w], B. Kaufman [x], M. Leadbeater [y], M. Mayer [z], A. Rodger [aa], H. Rugo [bb], V. Sacchini [cc], G. Sledge [dd], L. van't Veer [ee], G. Viale [ff], I. Krop [gg], E. Winer [gg]

17) A small but very important subset of patients with MBC, for example those with oligo-metastatic disease, can achieve complete remission and a long survival. A multimodal approach should be considered for these selected patients. A prospective clinical trial addressing this specific situation is needed.	Expert opinion	96% (25) Yes (26 voters)
18) The true value of the removal of the primary tumour in patients with stage IV breast cancer is currently unknown. However, it can be considered in selected patients. Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (e.g. attaining clear margins and addressing disease in the axilla) as in patients with early stage disease. Prospective clinical trials to confirm the value of this approach, the best candidates and timing are currently ongoing.	2 B	100% Yes (29 voters)

F Cardoso, The Breast 2012

Results



EO Hanrahan, Cancer 2005

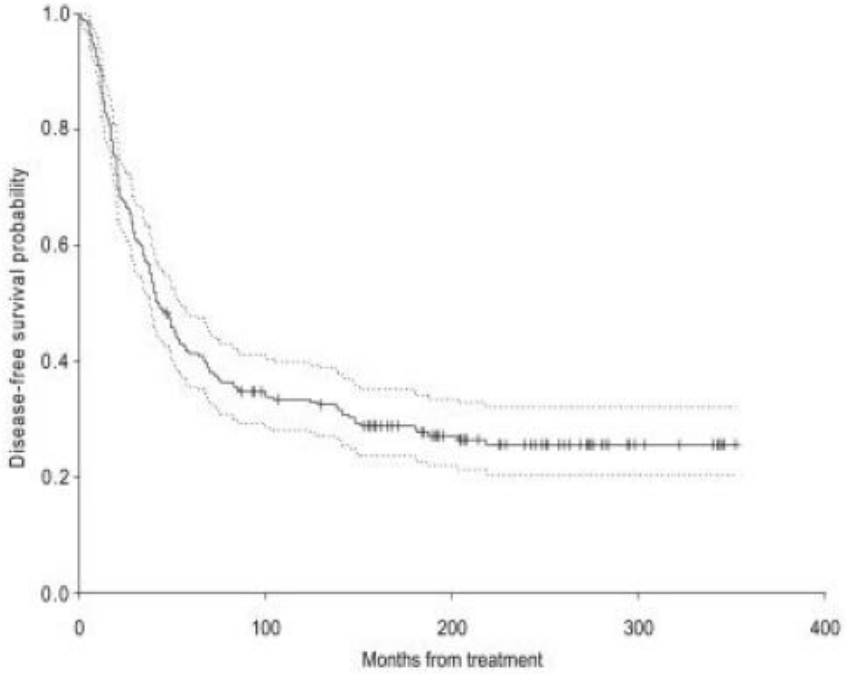


FIGURE 4. This chart illustrates the duration and probability of disease-free survival for the three doxorubicin-based studies combined. Dotted lines indicate 95% confidence intervals.

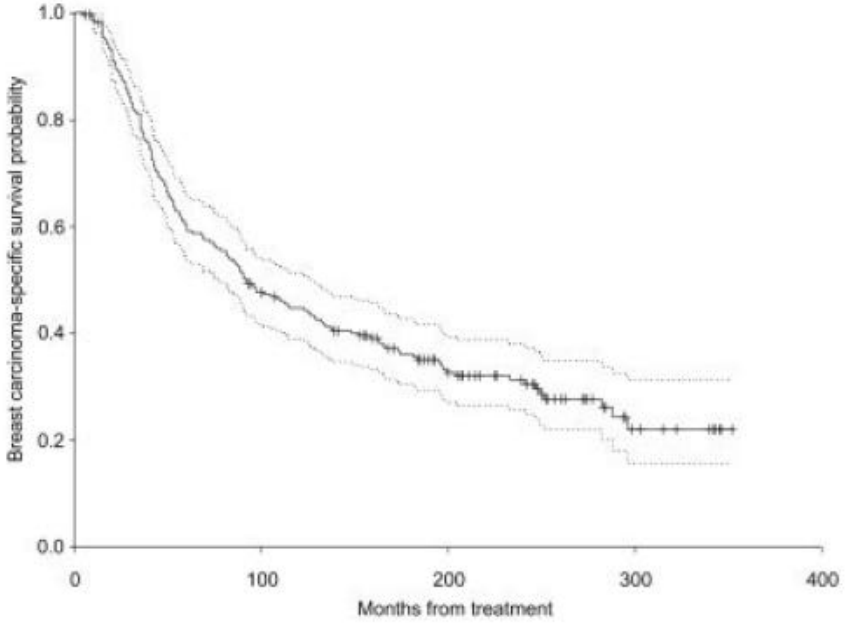


FIGURE 6. This chart illustrates the duration and probability of breast carcinoma-specific survival for the three doxorubicin-based studies combined. Dotted lines indicate 95% confidence intervals.

EO Hanrahan, Cancer 2005

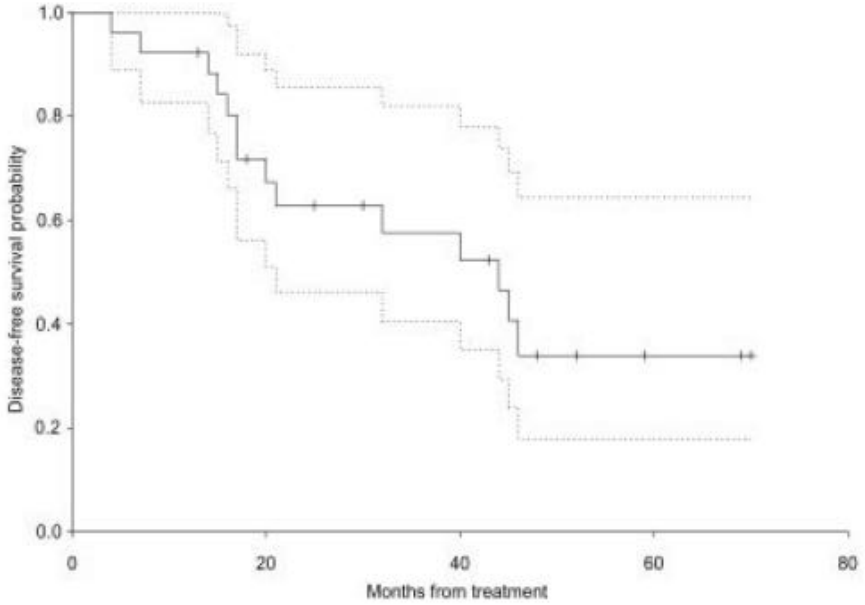


FIGURE 2. This chart illustrates the duration and probability of disease-free survival for the docetaxel-based study. Dotted lines indicate 95% confidence intervals.

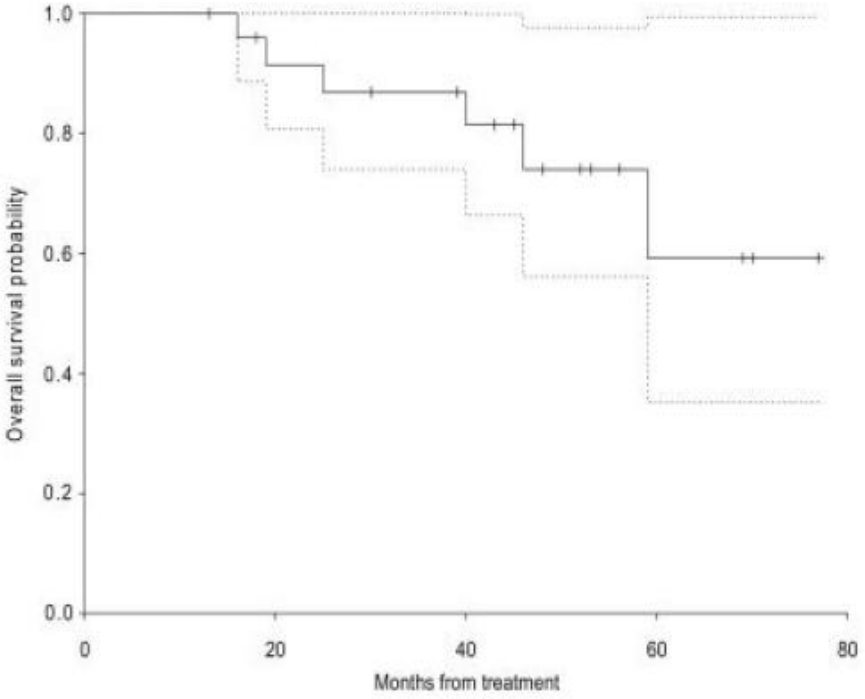
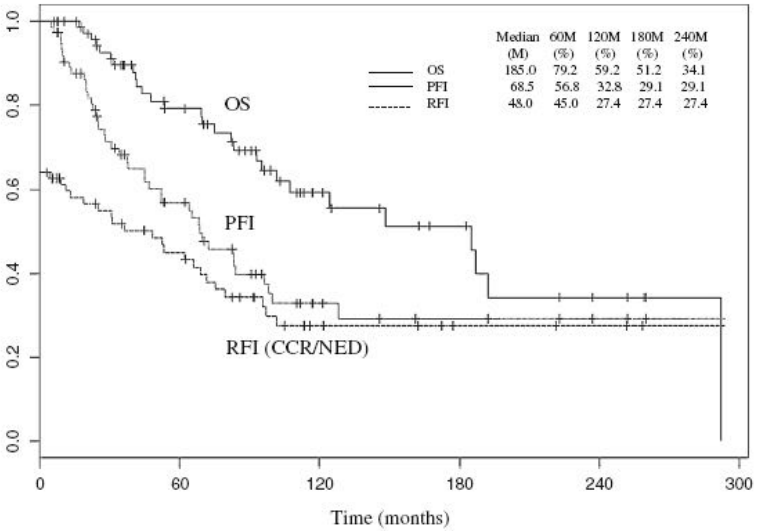


FIGURE 3. This chart illustrates the duration and probability of overall survival for the docetaxel-based study. Dotted lines indicate 95% confidence

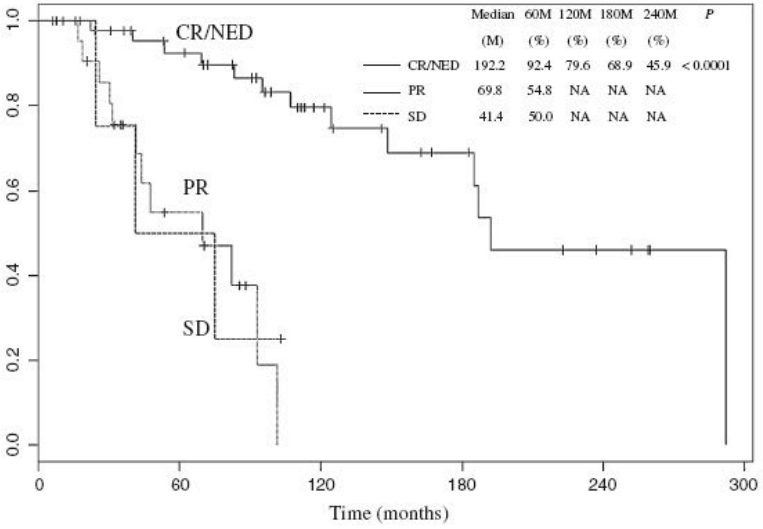
EO Hanrahan, Cancer

Fig. 1 Estimated overall survival, progression-free interval, and relapse-free interval by multidisciplinary treatment



Abbreviations: CCR : continuing complete response, M : months, NED : no evidence of clinical disease, OMBC : oligometastatic breast cancer, OS : overall survival, PFI : progression-free interval, RFI : relapse-free interval, y : year

Fig. 2 Estimated overall survival by response to multidisciplinary treatment



Abbreviations: CR : complete response, M(m) : months, NA:not applicable, NED : no evidence of clinical disease, OS : overall survival, PR : partial response, SD : stable disease

T Kobayashi, BCRT 2012

Decision Making Process

Decision Drivers

- Extent of Disease
- **HER2**
- **ER and PgR**
- Life Expectancy (age and comorbidities)
- Pretreatments

Decision Drivers

- **Extent of Disease**
- **HER2**
- **ER and PgR**
- **Life Expectancy (age and comorbidities)**
- **Pretreatments**

Process

- Staging
- Local Therapy
- Systemic Therapy
  - "Adjuvant Style"
  - "MBC Style"

Believing in Local Therapies

Table 2. Resection of pulmonary metastases from breast cancer*

First author (reference)	No. of patients	Median OS (mo)	5-y OS (%)
Friedel, 2002 (70)	467	35	35
Planchard, 2004 (69)	125	50	45
Friedel, 1994 (71)	91	ND	27
Murabito, 2000 (72)	62 (28 complete resection)	Complete resection: 79; incomplete resection: 15.5	Complete resection: 80
McDonald, 1994 (73)	60	42	37.8
Livartowski, 1998 (74)	40	70	54
Tanaka, 2005 (75)	39	32	30.8
Lanza, 1992 (76)	37	47	49.5
Staren, 1992 (77)	33	58 (single metastasis)	36
Girard, 1994 (78)	32	ND	ND
McCormack, 1978 (79)	28	20	15
Rena, 2007 (80)	27	ND	38
Ludwig, 2003 (81)	21	96.9	53
Mountain, 1978 (82)	21	27	14

* ND = no data; OS = overall survival.

O Pagani, The Breast 2012

Believing in Local Therapies

Table 3. Resection of liver metastases from breast cancer*

First author (reference)	No. of patients	Median OS (mo)	5-y OS (%)
Adam, 2006 (83)	85	46†	41†
Pocard, 2001 (84)	65	ND	46 (4-y)
Elias, 2003 (85)	54	34	34
Pocard, 2000 (86)	52	42	65 (3-y)
Raab, 1998 (87)	34	27	18.4
Sakamoto, 2005 (88)	34	36	21
Vlastos, 2004 (89)	31	63	61
Yoshimoto, 2000 (90)	25	42†	33†
Elias, 1995 (91)	21	38.2†	24†
Ercolani, 2005 (92)	21	40.3	25
Singletary, 2003 (13)	21	40 (DFS)	55 (3-y DFS)
Pocard, 1997 (93)	21	ND	60

* DFS = disease-free survival; ND = no data; OS = overall survival.

† Since diagnosis of liver metastases.

O Pagani, The Breast 2012

Believing in Local Therapies

Breast Care

Review Article · Übersichtsarbeit

Breast Care 2011;6:363–368
DOI: 10.1159/000333115

Published online: October 13, 2011

Does Radiotherapy Have Curative Potential in Metastatic Patients? The Concept of Local Therapy in Oligometastatic Breast Cancer

Kathrin Dellas

Relative and Absolute Risk Reduction

	Deaths without Adjuvant	Red RR 20%	Deaths in spite of Adjuvant
100	40	-8	32

NNT: 100/8 = 12.5

Relative and Absolute Risk Reduction

Selecting pts on the base of individual risk

	Deaths without Adjuvant	Red RR 20%	Deaths in spite of Adjuvant
100	80	-16	64

NNT: 100/16 = 6.25

Which Systemic Therapy?

List of Agents

- **Hormonotherapy**
  - **Tamoxifen**
  - **Anastrozole or Letrozole**
  - **Exemestane**
  - **Fulvestrant HD**

- **Anti-HER2**
  - **Trastuzumab**
  - **Lapatinib**
  - **TDM1**
  - **Pertuzumab**

- **Chemotherapy**
  - **Anthracycline (incl liposomial)**
  - **Taxane (incl nab-paclitaxel)**
  - **Capecitabine**
  - **Vinorelbine**
  - **Eribulin**

- **Bevacizumab**

Since the risk is high…..

- **HER2+**
  - **Trastuzumab + CT → Trastuzumab + HT**
- **TNBC**
  - **“Adjuvant Style” POLICT (anthra → Tax)**
  - **Other CT (MonoCT, Cape-Vin, Carbo-Gem)**
  - **Pac + Beva**
- **HR+ / HER2-**
  - **HT +/- CT**

And the Bio Shifts?

- **HER2+ → HER2- Hold Trastuzumab**
- **HER2- → HER2+ Add Trastuzumab**

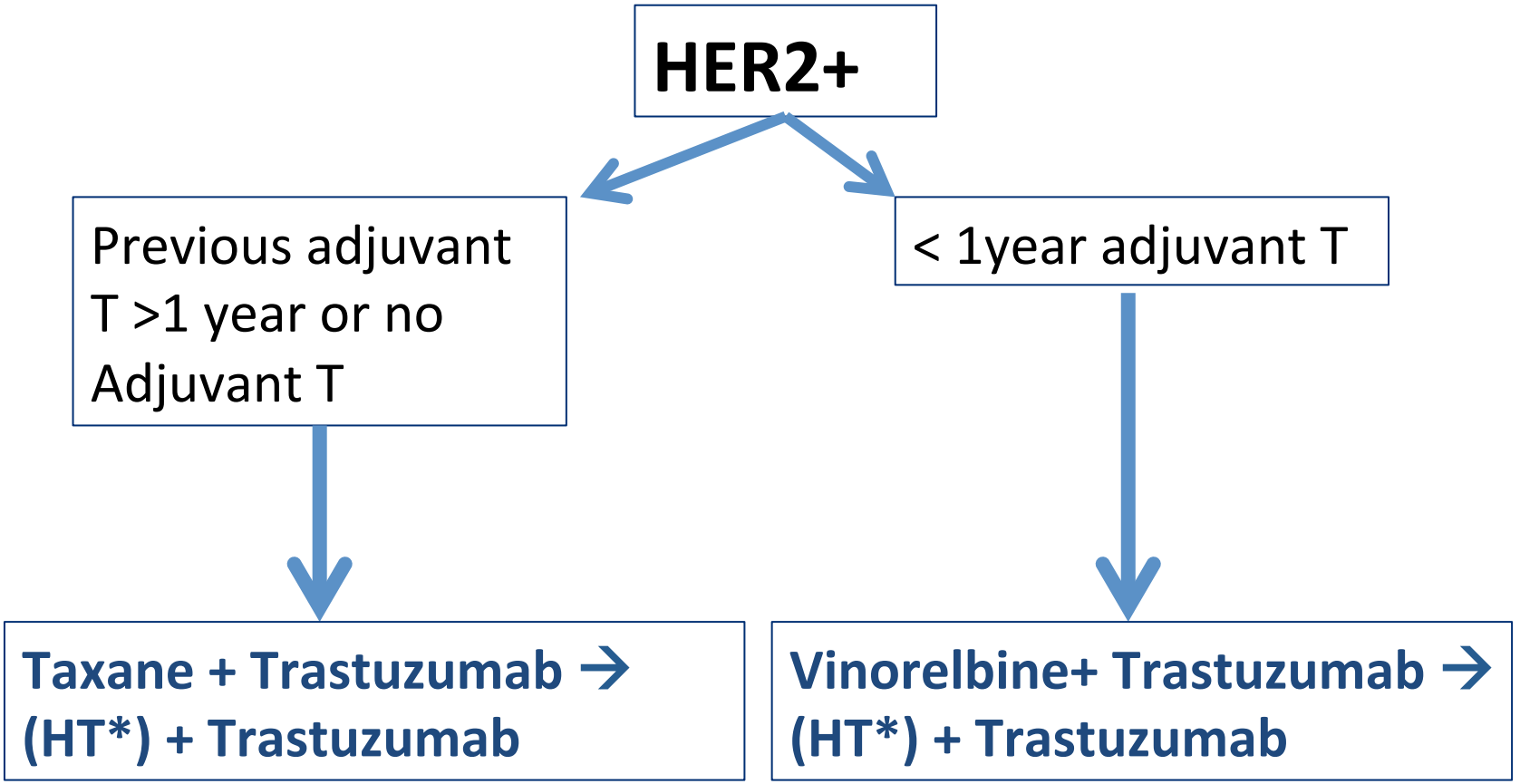
- **HR+ → HR- Hold HT**
- **HR- → HR+ Add HT**

How long?

- **The answer is easy at (least apparently) for**
  - **HT**
  - **“Adjuvant Style CT”**

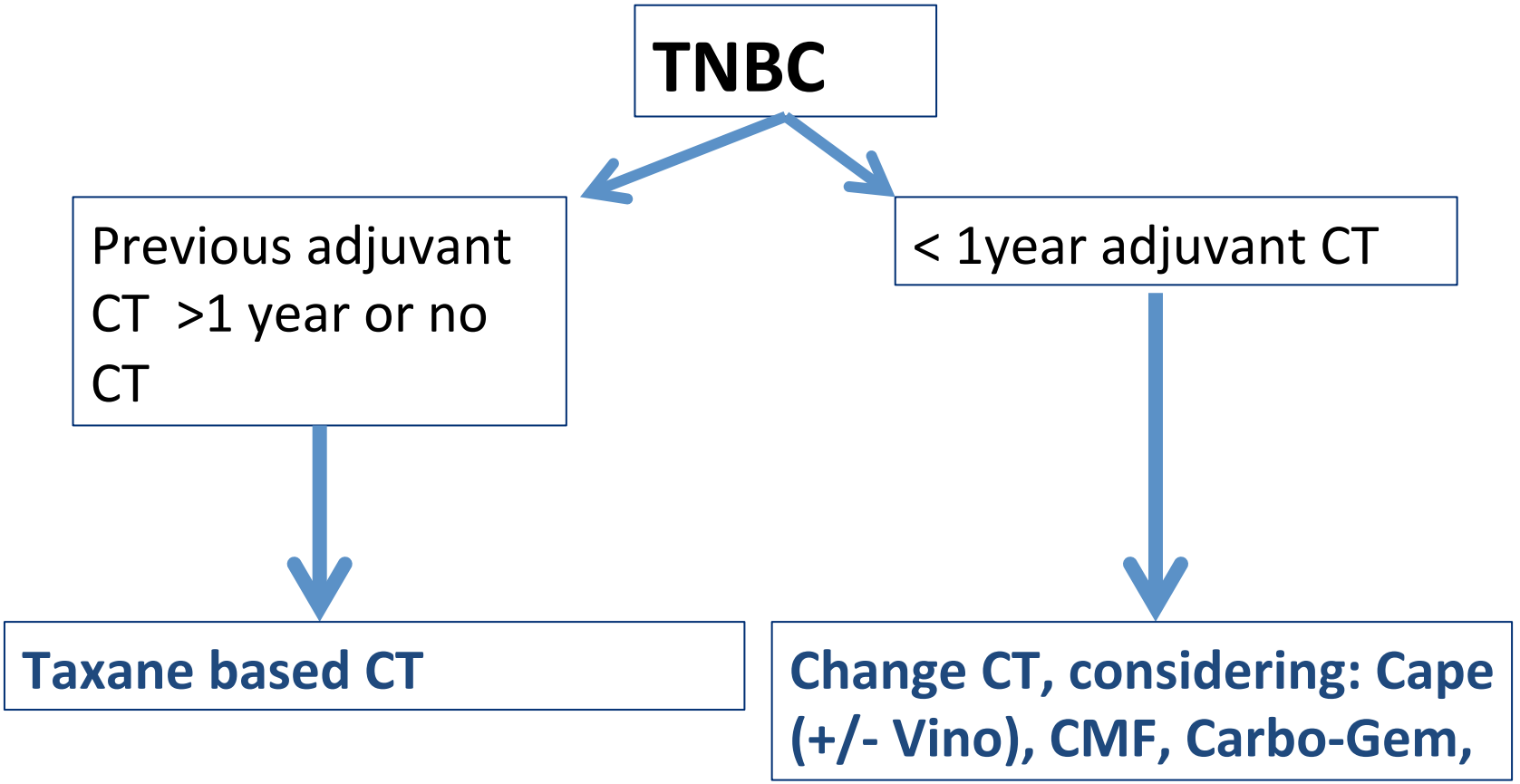
- **The answer is difficult (or no answer) for**
  - **Trastuzumab**
  - **Other CT**
  - **Bevacizumab**

Temptative algorythm 1

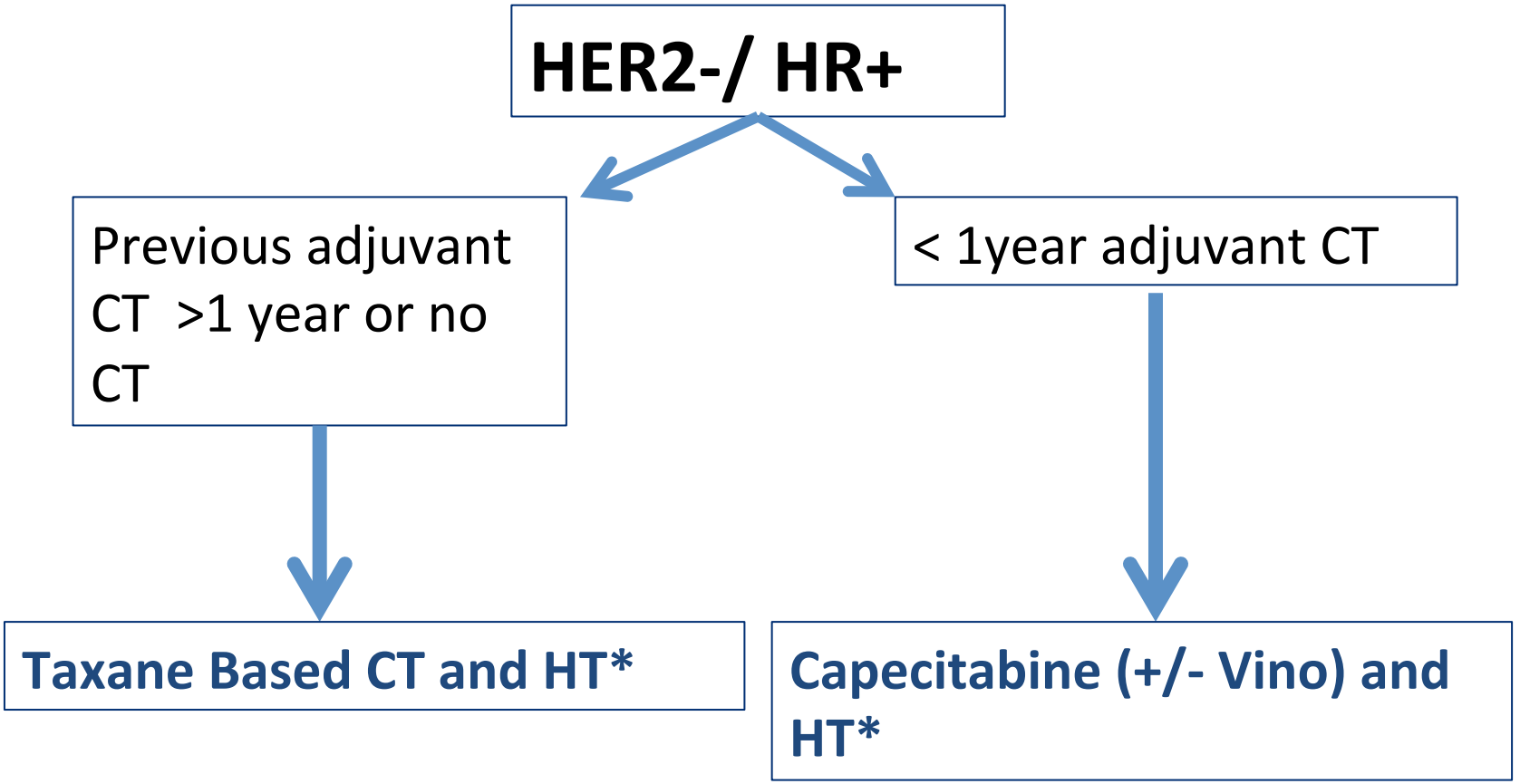


* Change from NSAI to Exemestane and vice versa; change from Tam to AI in postm

Temptative algorythm 2



Temptative algorythm 3



* Consider concomitant HT andChange from NSAI to Exemestane and vice versa; change from Tam to AI in postm

A Role for “Neo”?
YES

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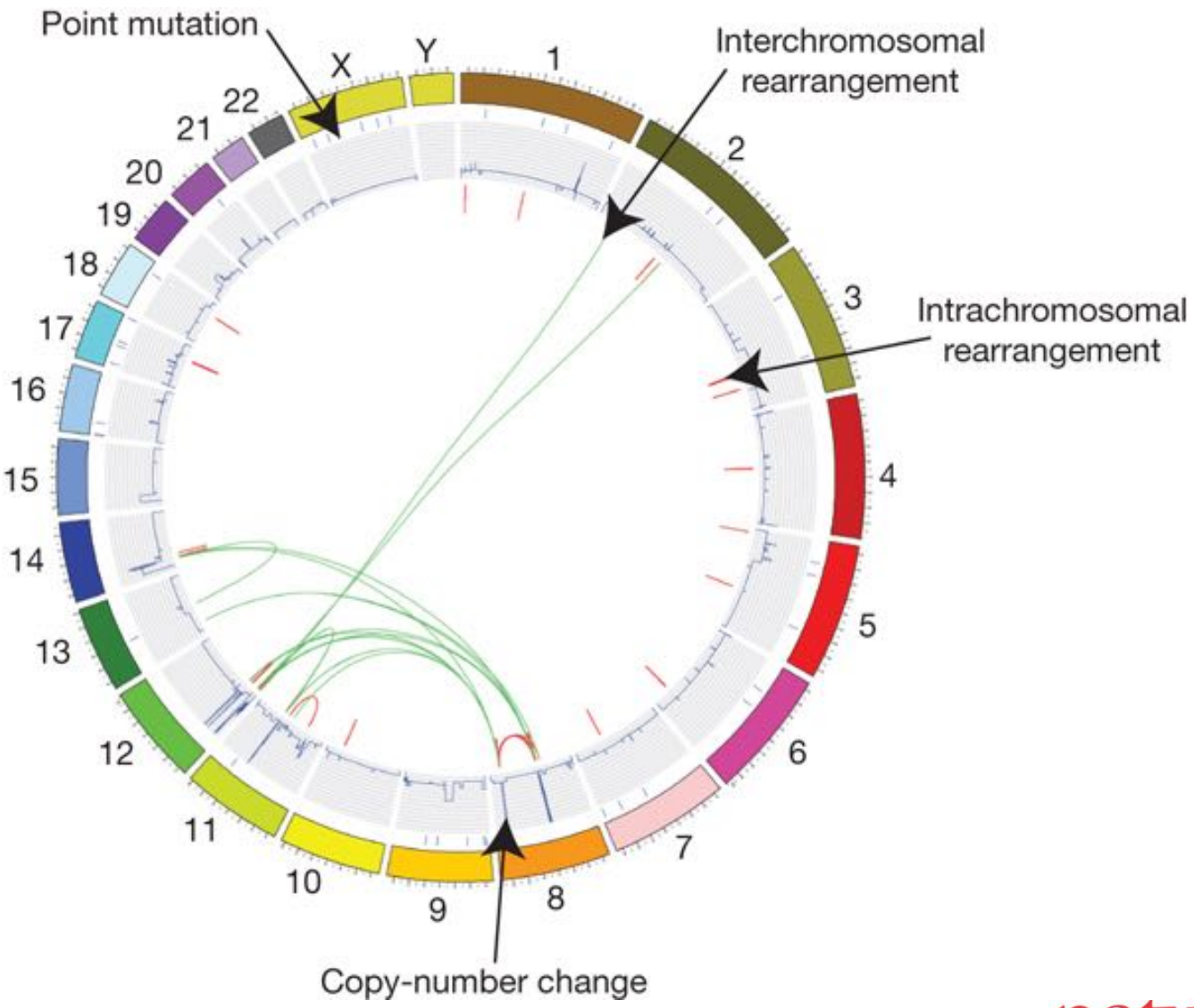

MR Stratton *et al. Nature* **458**, 719-724 (2009) doi:10.1038/nature07943

2008

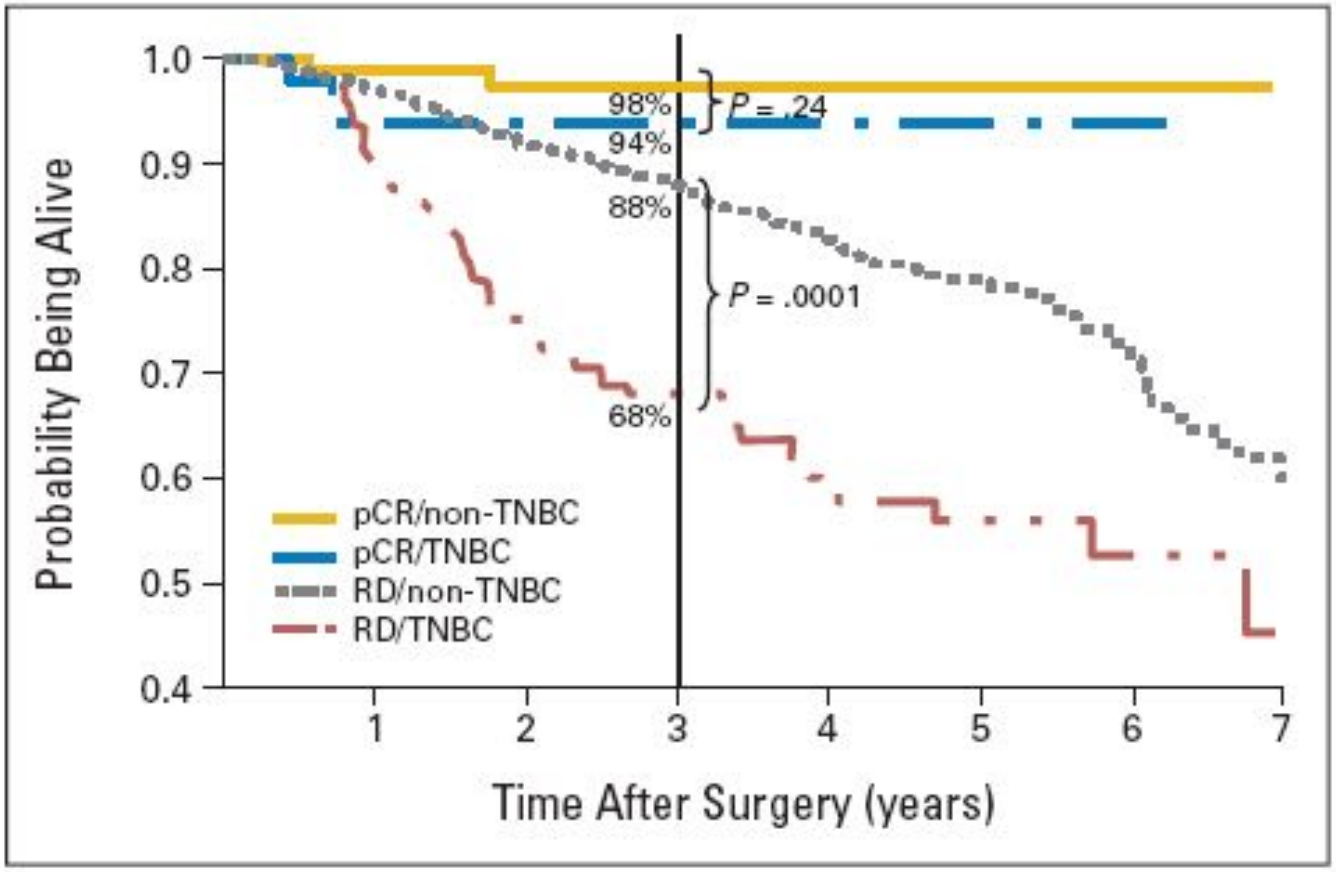

Fig 2. Overall survival as a function of response to chemotherapy (pathologic complete response [pCR] *v* residual disease [RD]) and triple-negative status (triple-negative breast cancer [TNBC] *v* non-TNBC).

Conclusions

The reasonable approach

- Consider "True" Oligometastatic Disease as a story apart
- After Local Treatment, Consider an "Adjuvant Style" Systemic Treatment based on HER2/HR and pretreatments
- If Systemic Treatment is started, Consider at a point the Local Treatment and a susbequent Systemic also on the basis of a Response