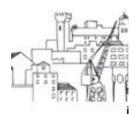
Paziente Oligometastatico Successive Terapie Sistemiche? (Breast Cancer. Why?)

P Pronzato
Roma, 18.11.2012







	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 Treatment intent Type of treatment	high (90%) curative locoregional + adjuvant systemic	medium (50%) curative locoregional + adjuvant systemic	zero? curative? systemic + local?	zero palliative systemic

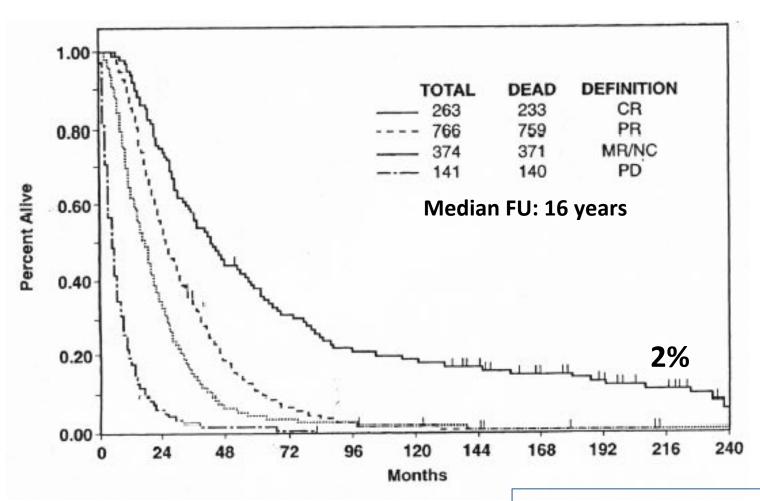
Treatment End Points

MBC: Treatment End Points

- Prolongation of Survival
- Improvement of Quality of Life

And Cure?

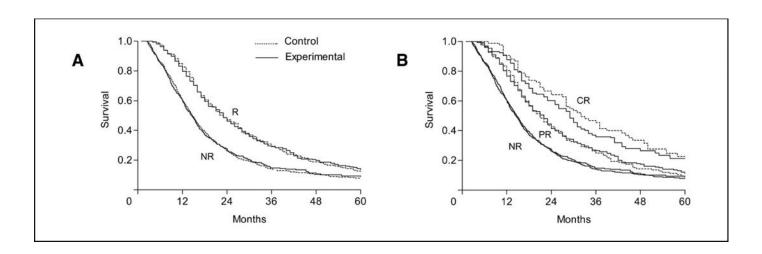
Overall Survival according to response to front line CT in MBC



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)



Is MBC Survival improving?

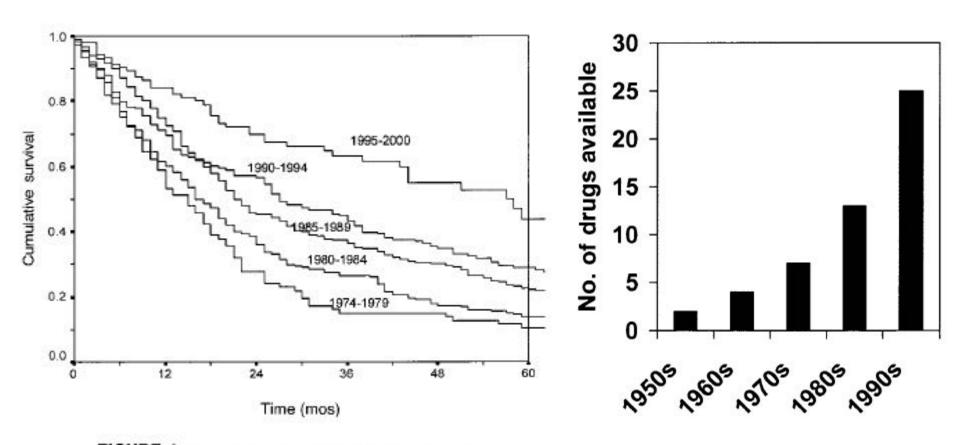


FIGURE 1. Overall survival from time of recurrence.

 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+</p>

Guide Lines

Waiting for....

- Chemotherapy prolongs survival for isolated local or regional recurrence of breast cancer.
 The CALOR trial (Chemotherapy as Adjuvant for Locally 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





Cancer Network* Invasive Breast Cancer

NCCN Guidelines Index Breast Cancer Table of Contents Discussion

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE Initial treatment with lumpectomy Total mastectomy + axillary lymph node staging if level I/II axillary dissection not previously done kk + radiation therapy Local only Initial treatment with mastectomy + level I / II Surgical resection if possible II recurrence axillary dissection and prior radiation therapy Initial treatment with mastectomy Surgical resection if possible + radiation therapy to no prior radiation therapy chest wall and supraclavicular and infraclavicular nodes Consider Surgical resection if possible + radiation therapy if systemic possible to chest wall, supraclavicular and Axillary recurrence Regional therapy infraclavicular nodes, and axilla only Radiation therapy if possible to chest wall and Supraclavicular recurrence Local and supraclavicular and infraclavicular nodes regional Radiation therapy if possible to chest wall, recurrence Internal mammary node recurrence supraclavicular and infraclavicular nodes, and internal mammary nodes Add denosumab. ER and/or PR positive: HER2 negative See BINV-18 Bone disease present zoledronic acid, or ER and/or PR positive: HER2 positive b pamidronateⁱⁱ Systemic ER and PR negative, or ER and/or PR positive disease^{II,}J and endocrine refractory; HER2 negative b Bone disease not present ER/PR negative or ER and/or PR positive ee BINV-20 and endocrine refractory; HER2 positiveb bSee Principles of HER2 Testing (BINV-A). Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given Surgery, radiation, or regional chemotherapy (e.g., intrathecal

Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis is present, expected survival is ≥3 months, and renal function is adequate. Patients should undergo a dental examination with preventive dentistry prior to initiation of this therapy. The optimal schedule and duration of denosumab, zoledronic acid, or pamidronate are unknown.

ISee NCCN Palliative Care Guidelines.

kik In women with a local breast recurrence after breast-conserving surgery who had a prior sentinel lymph node biopsy, a repeat SNB may be technically possible. The accuracy of repeat SNB is unproven, and the prognostic significance of repeat SNB after mastectomy is unknown and its use is discouraged.

If not technically resectable, consider systemic therapy to best response, then resect if possible.

Note: All recommendations are category 2A unless otherwise indicated.

9. Pathologic fracture

10. Cord compression

12. Chest wall disease

11. Localized painful bone or

soft-tissue disease

8. Impending pathologic fracture

± hyperthermia (category 3) if radiation therapy used

methotrexate) indicated for localized clinical scenarios:

1. Brain metastas es

4. Pieural effusion 5. Pericardial effusion

2. Leptomeningeal disease

3. Chorold metastases

6. Billiary obstruction

7. Ureteral obstruction

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-17

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

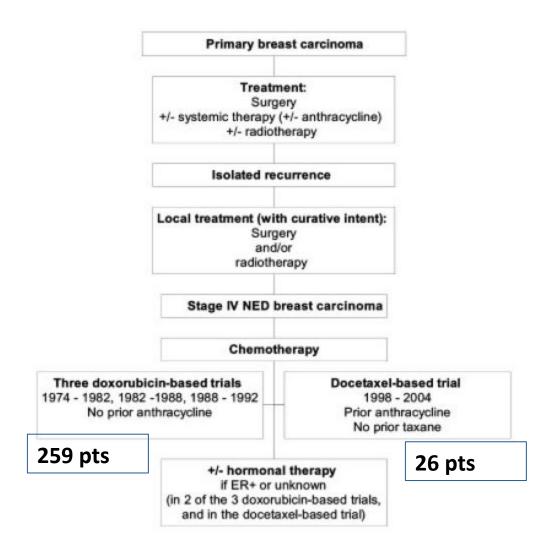
F. Cardoso ^{a,*}, A. Costa ^b, L. Norton ^c, D. Cameron ^d, T. Cufer ^e, L. Fallowfield ^f, P. Francis ^g, J. Gligorov ^h, S. Kyriakides ⁱ, N. Lin ^j, O. Pagani ^k, E. Senkus ^l, C. Thomssen ^m, M. Aapro ⁿ, J. Bergh ^o, A. Di Leo ^p, N. El Saghir ^q, P.A. Ganz ^r, K. Gelmon ^s, A. Goldhirsch ^t, N. 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 96% (25) Yes (26 voters) opinion

- 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)

Results



EO Hanrahan, Cancer 2005

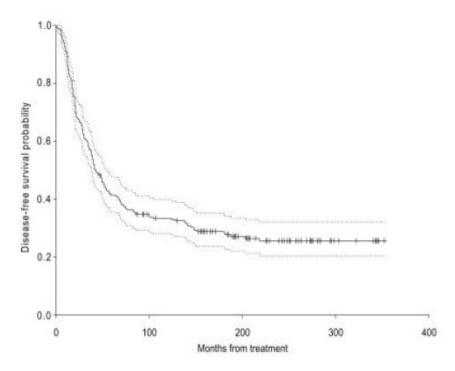


FIGURE 4. This chart illustrates the duration and probability of disease-free survival for the three doxorubicin-based studies combined. Dotted lines indicate 95% confidence intervals.

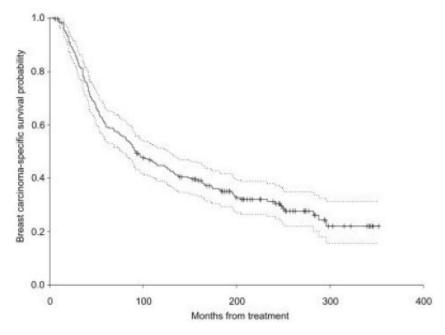


FIGURE 6. This chart illustrates the duration and probability of breast carcinoma-specific survival for the three doxorubicin-based studies combined. Dotted lines indicate 95% confidence intervals.

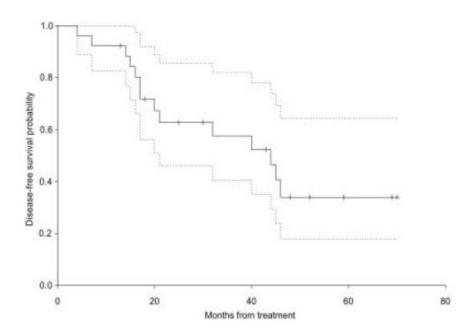


FIGURE 2. This chart illustrates the duration and probability of disease-free survival for the docetaxel-based study. Dotted lines indicate 95% confidence intervals.

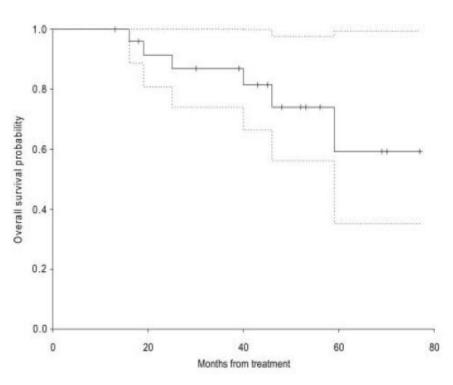
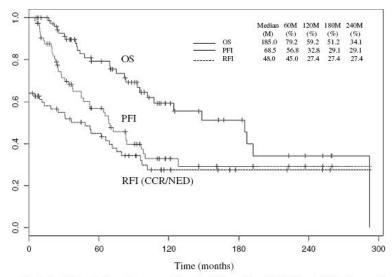


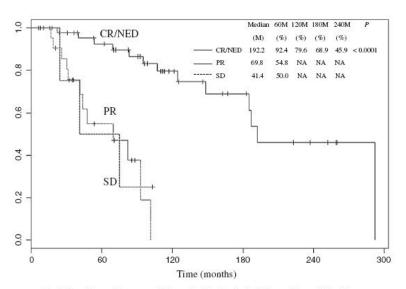
FIGURE 3. This chart illustrates the duration and probability of overall survival for the docetaxel-based study. Dotted lines indicate 95% confidence

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



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

Decision Making Process

Decision Drivers

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

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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.

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.

Believing in Local Therapies



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

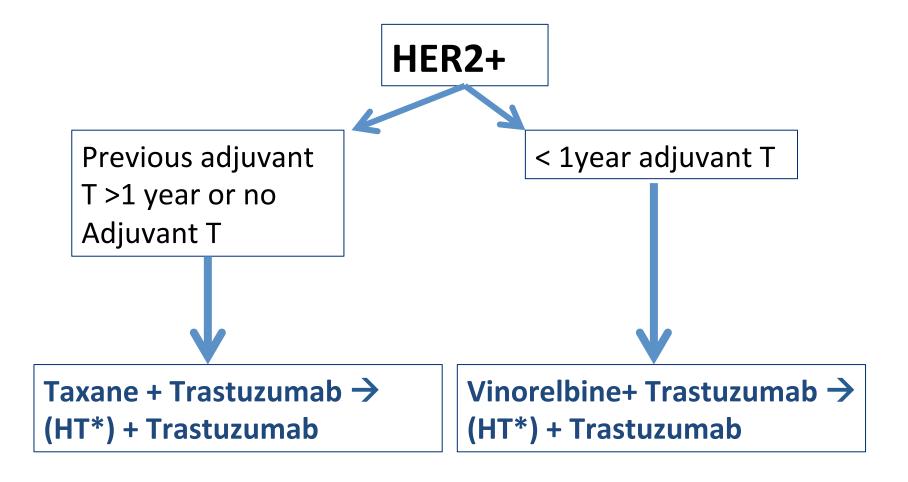
- HR+ → HR- Hold HT
- HR- \rightarrow HR+ Add HT

How long?

- The answer is easy at (least apparently) for
 - HT
 - "Adjuvant Style CT"

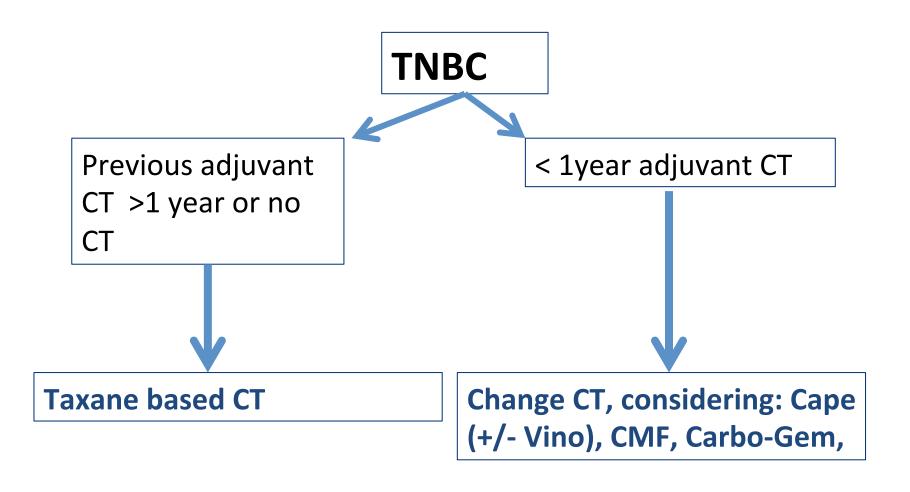
- The answer is difficult (or no answer) for
 - Trastuzumab
 - Other CT
 - Bevacizumab

Temptative algorythm 1

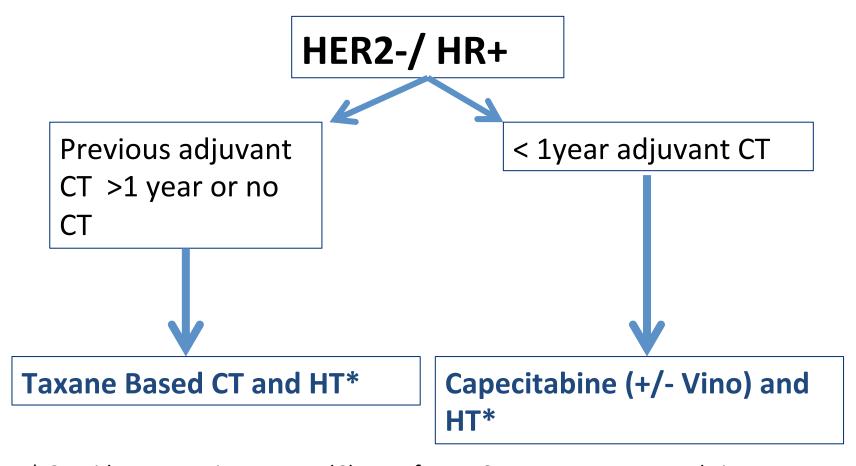


^{*} Change from NSAI to Exemestane and vice versa; change from Tam to AI in postm

Temptative algorythm 2

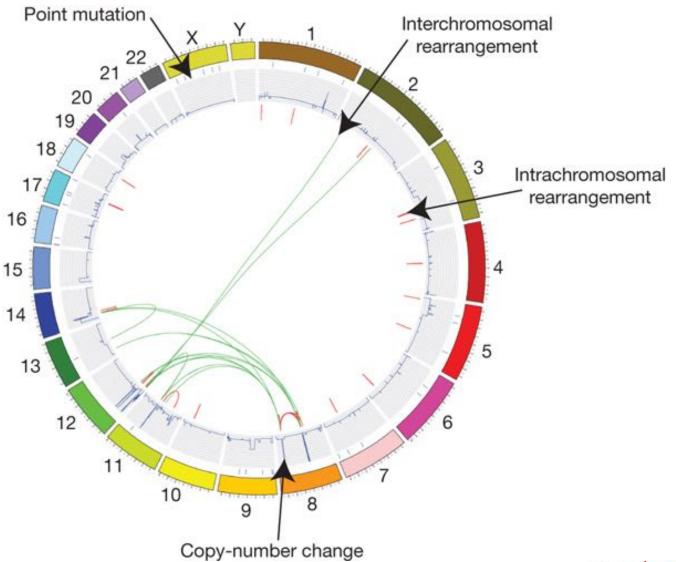


Temptative algorythm 3

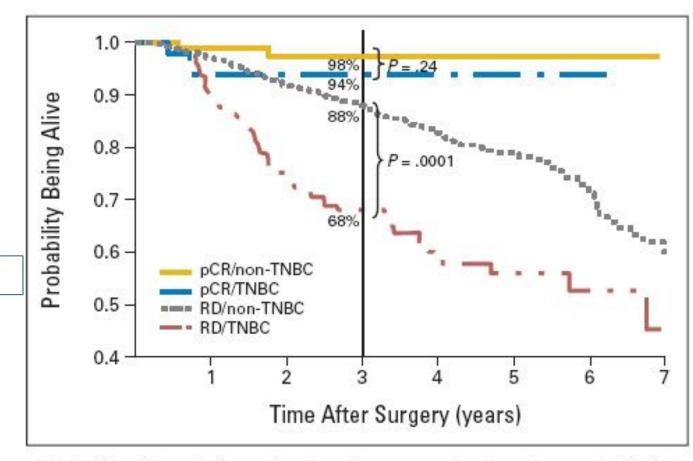


^{*} Consider concomitant HT and Change from NSAI to Exemestane and vice versa; change from Tam to AI in postm

A Role for "Neo"? YES







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