Ruolo delle antracicline convenzionali e liposomiali nel rechallange di I linea del MBC; wALT trial (fase I-II)

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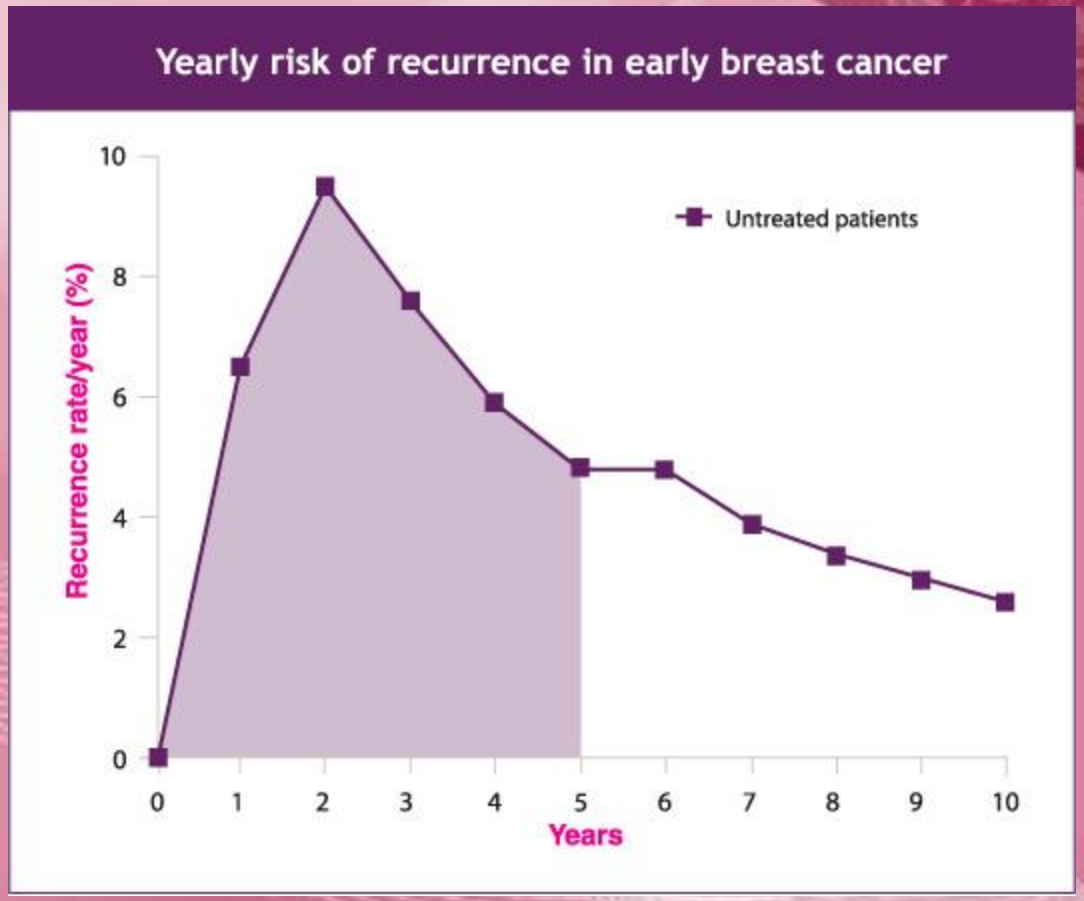
ROMA, 12 Novembre 2008

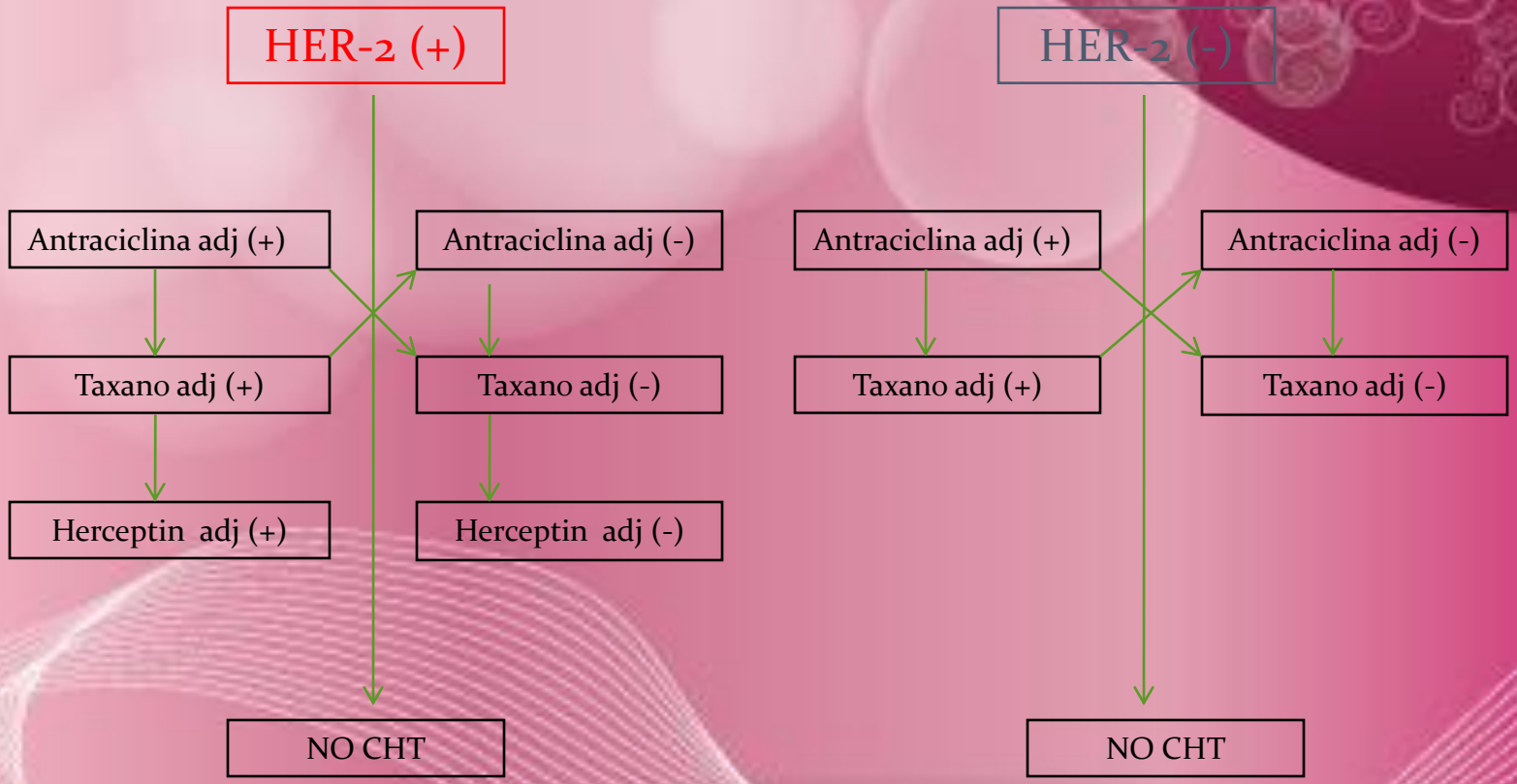
MBC: chi è la paziente in I linea?

- Pz Naïve (metastatica al momento della I diagnosi)
- Pz con Recidiva locale
- Pz con Metastasi a distanza (singola sede di metastasi o plurimetastatica)

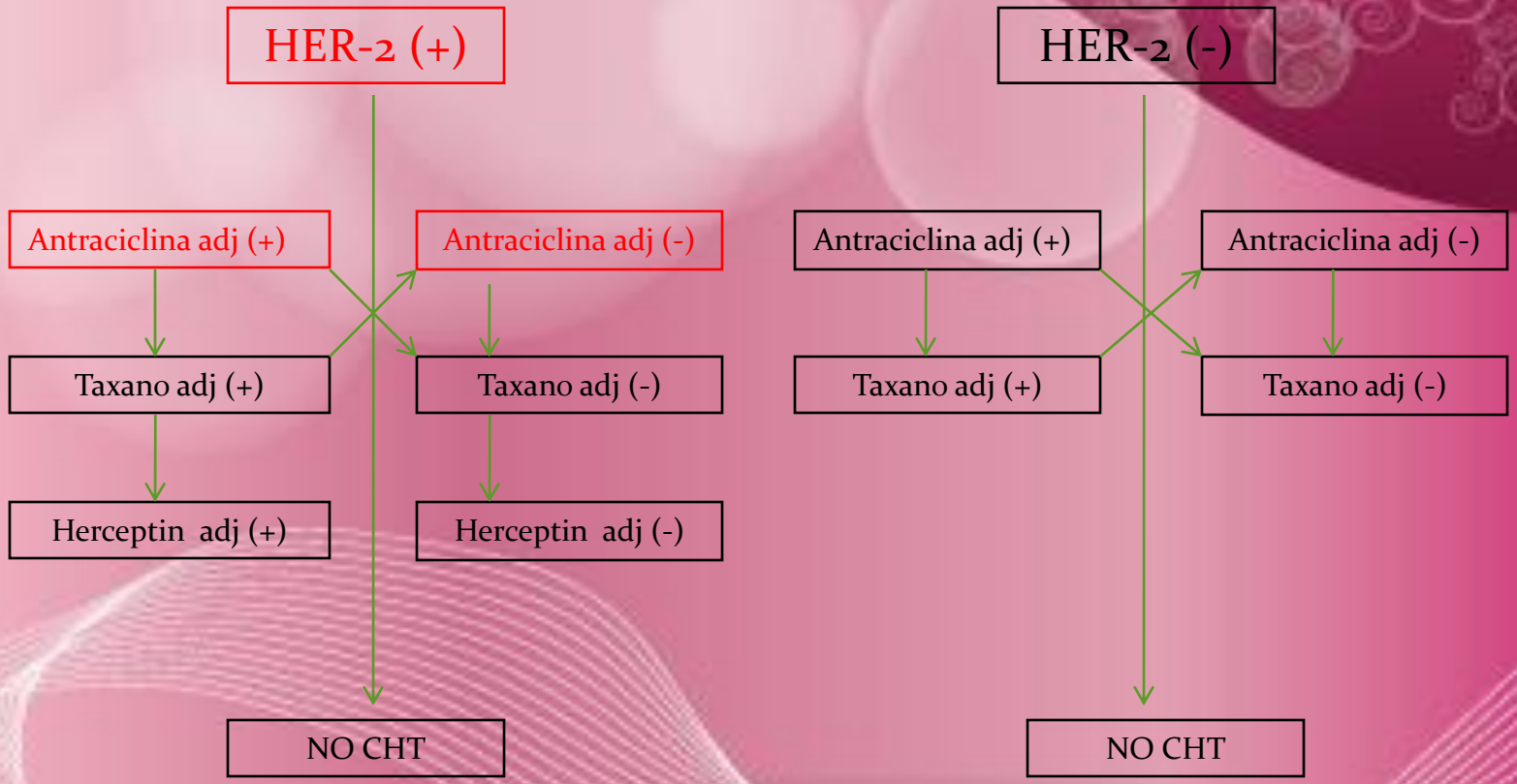
…attendere la recidiva: quando?



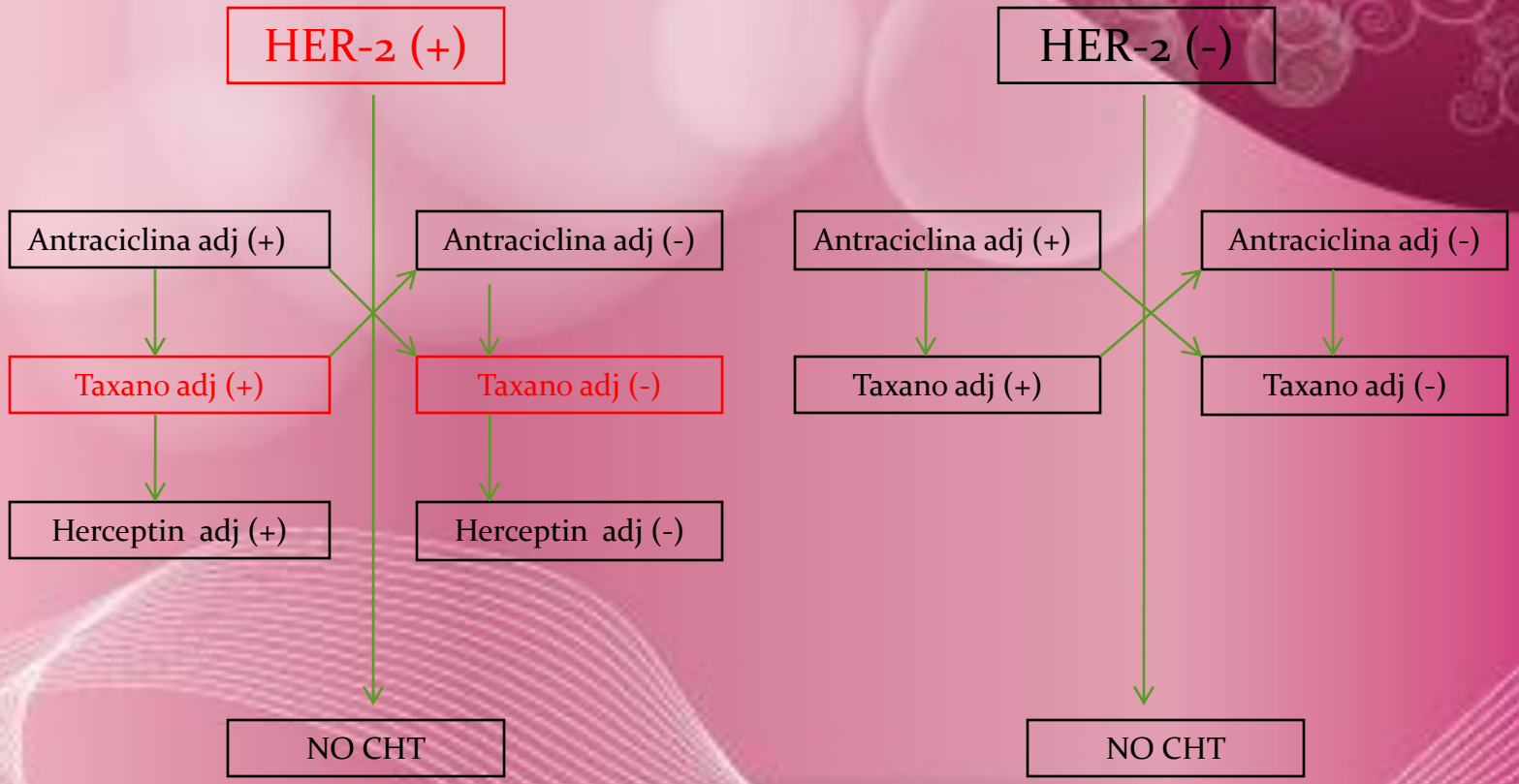
MBC: chi è la paziente in I linea? HER2(+) vs HER2(-)



MBC: chi è la paziente in I linea? ANTRA adj (+) vs ANTRA adj (-)

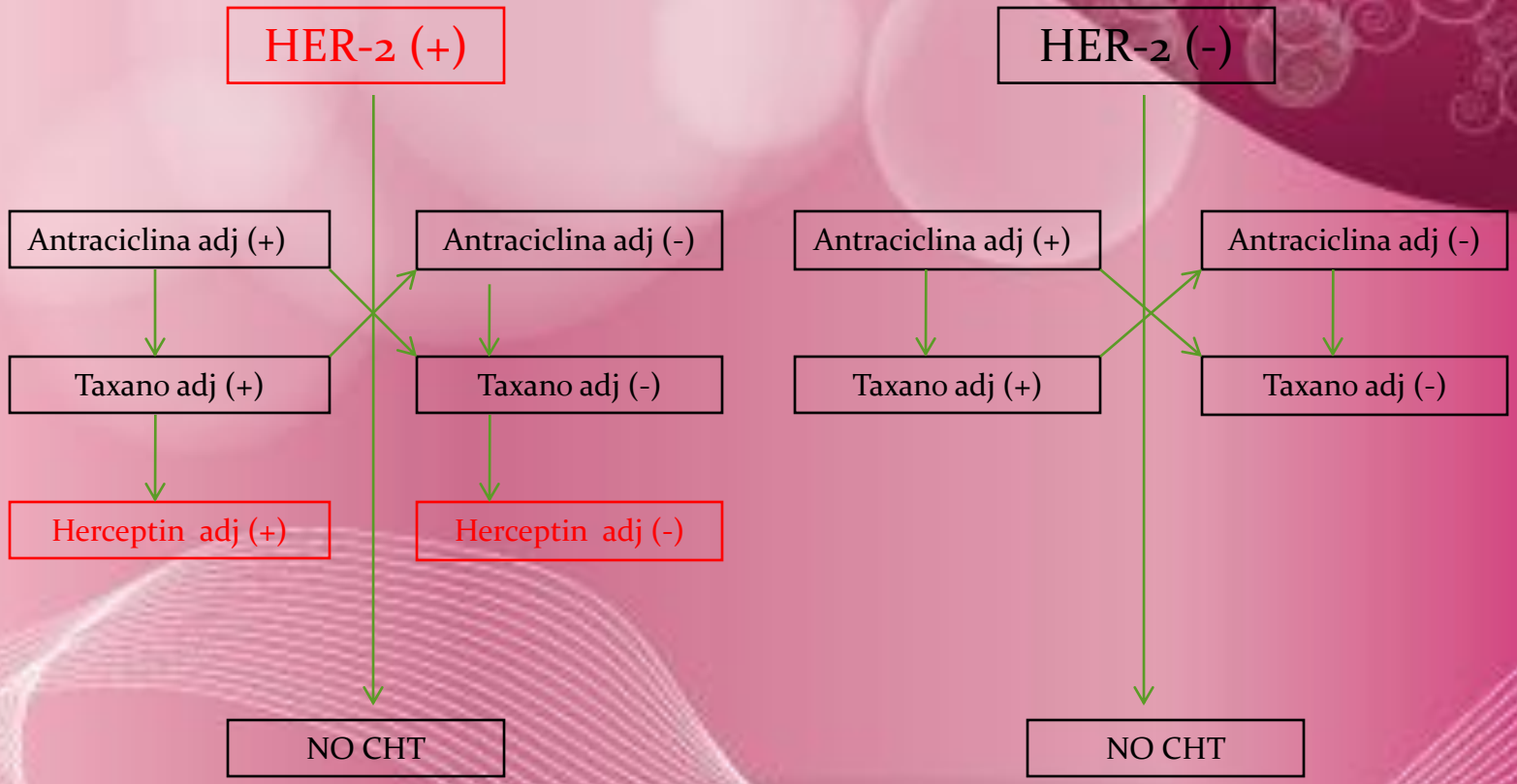


MBC: chi è la paziente in I linea? TAXANO (+) vs TAXANO(-)

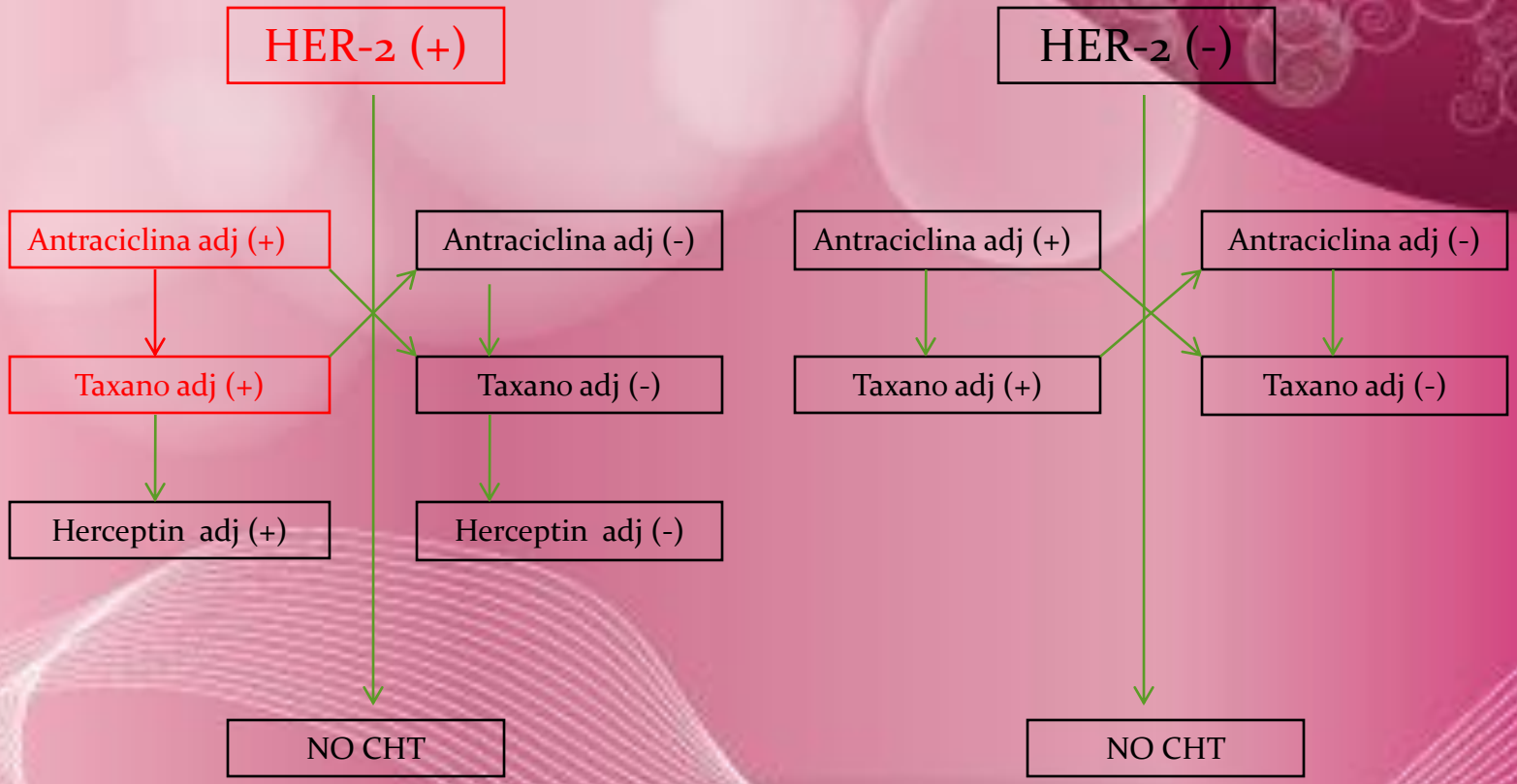


MBC: chi è la paziente in I linea?

HERCEPTIN adj (+) vs HERCEPTIN adj (-)



MBC: chi è la paziente in I linea?



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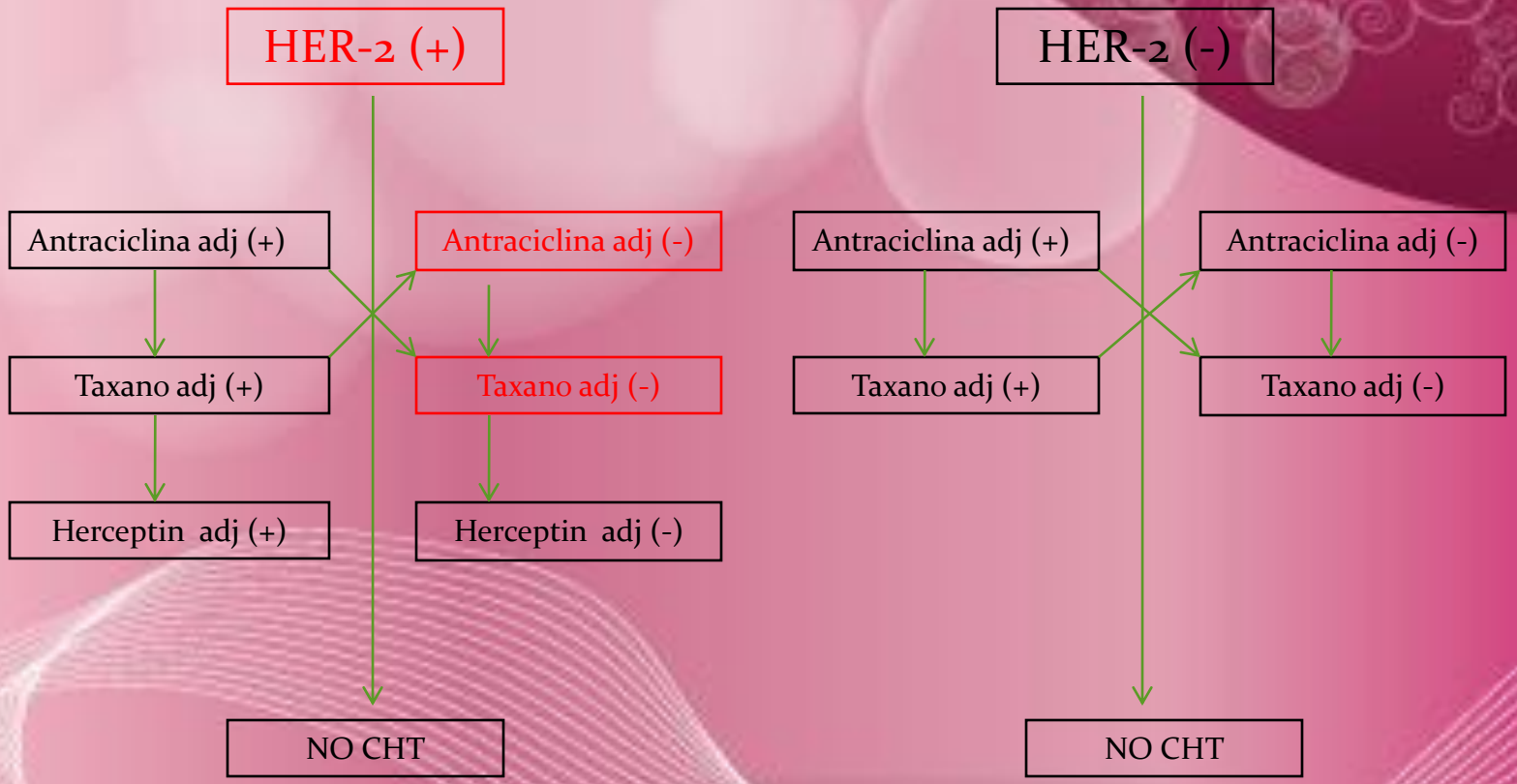

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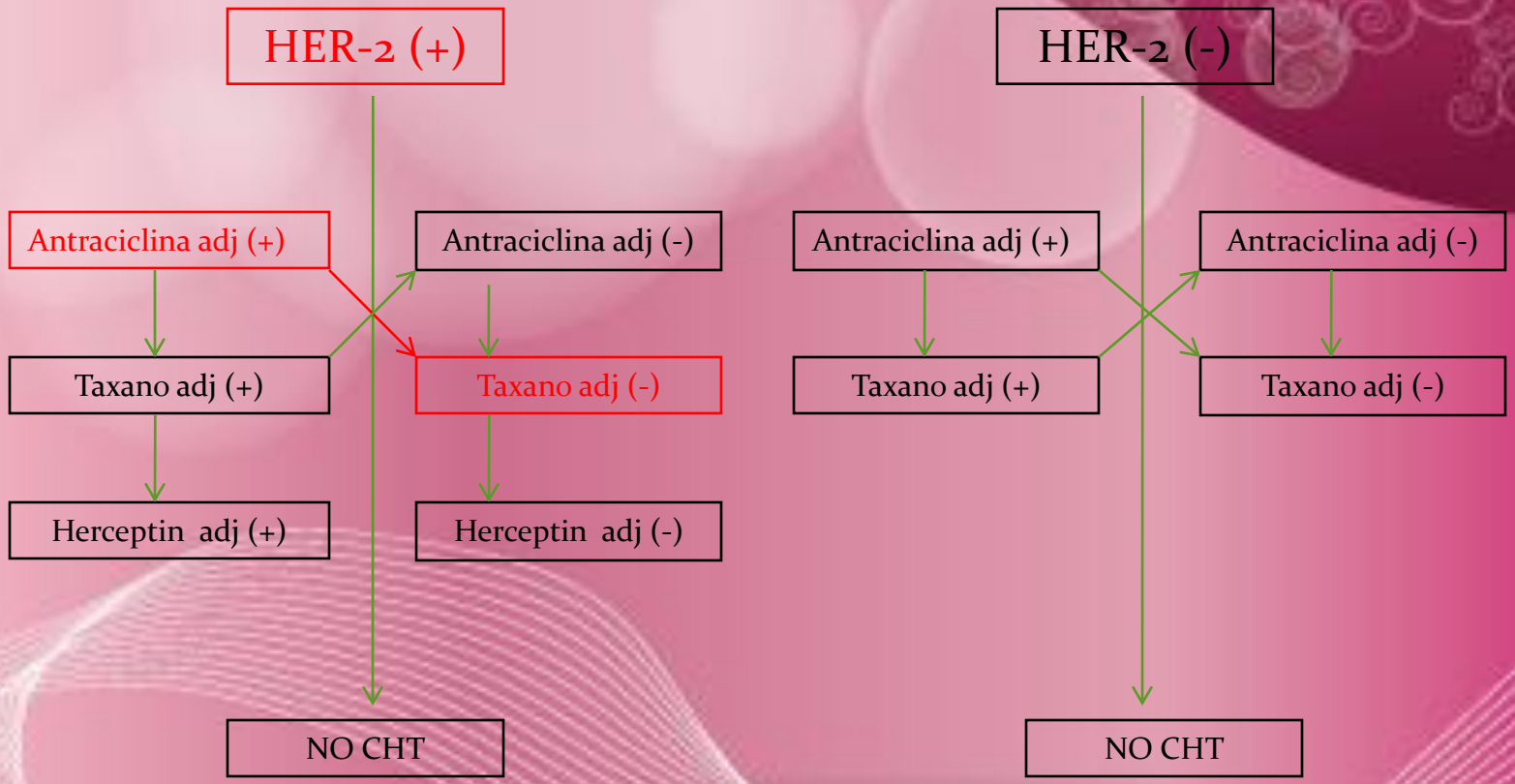
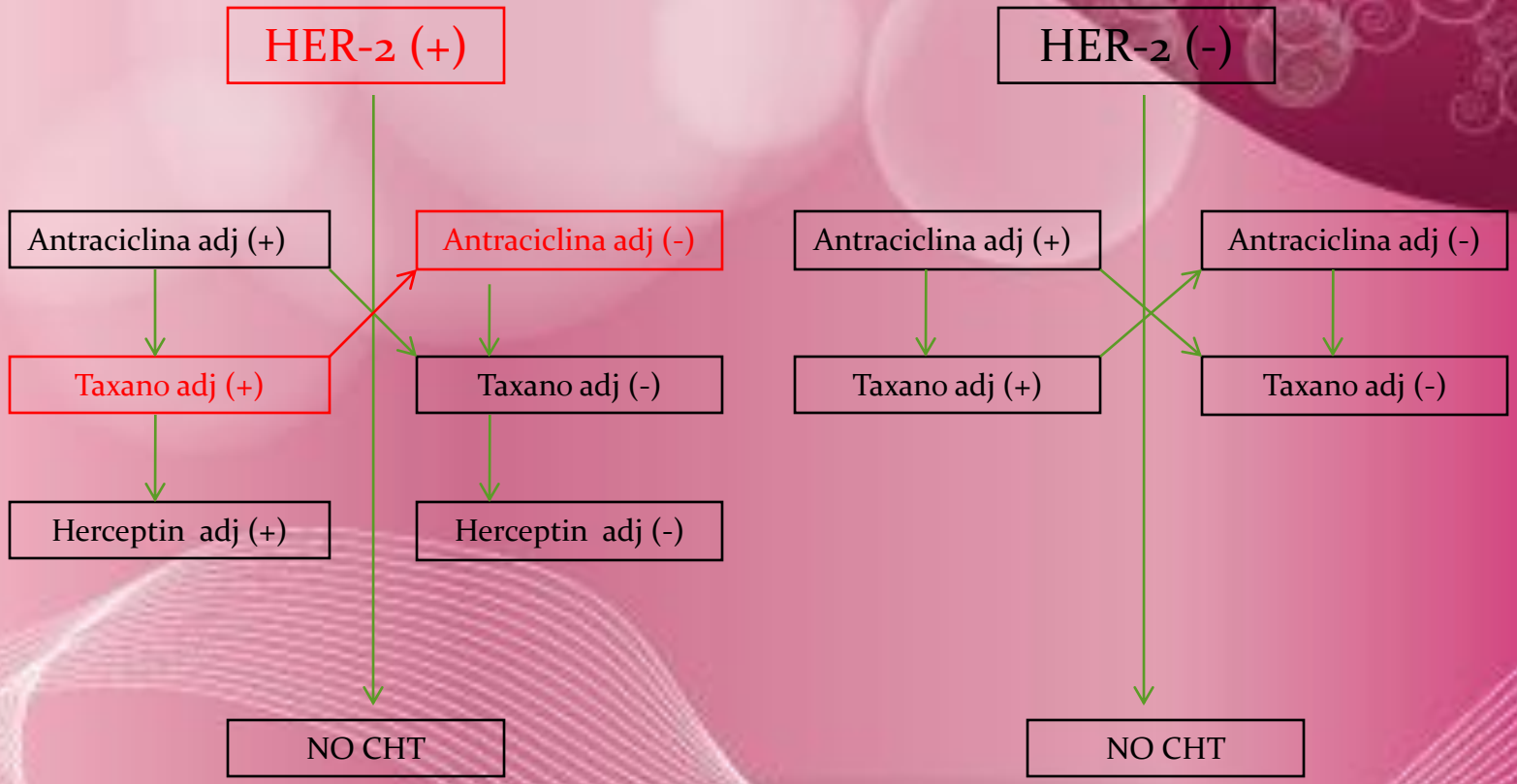


MBC: chi è la paziente in I linea?



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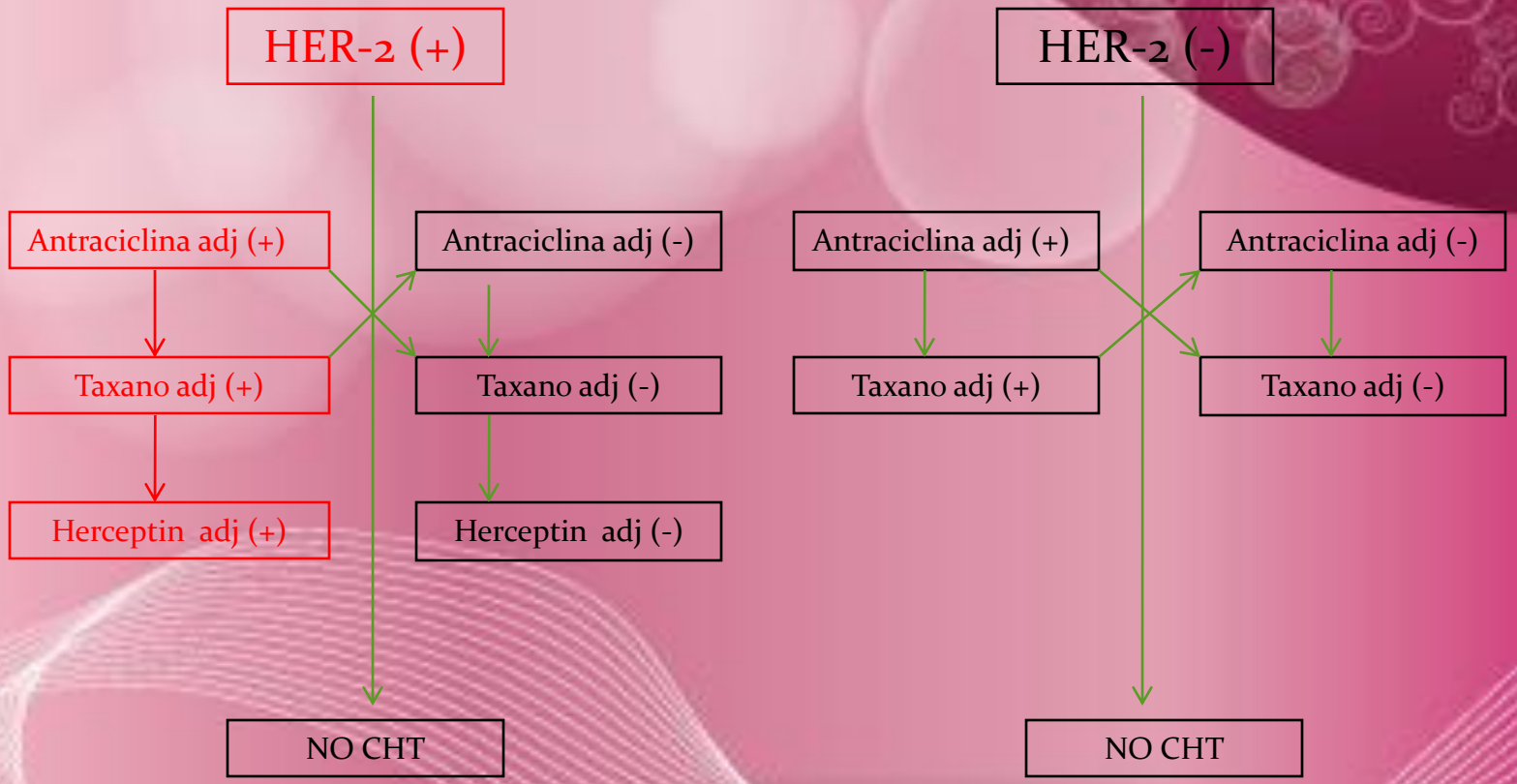
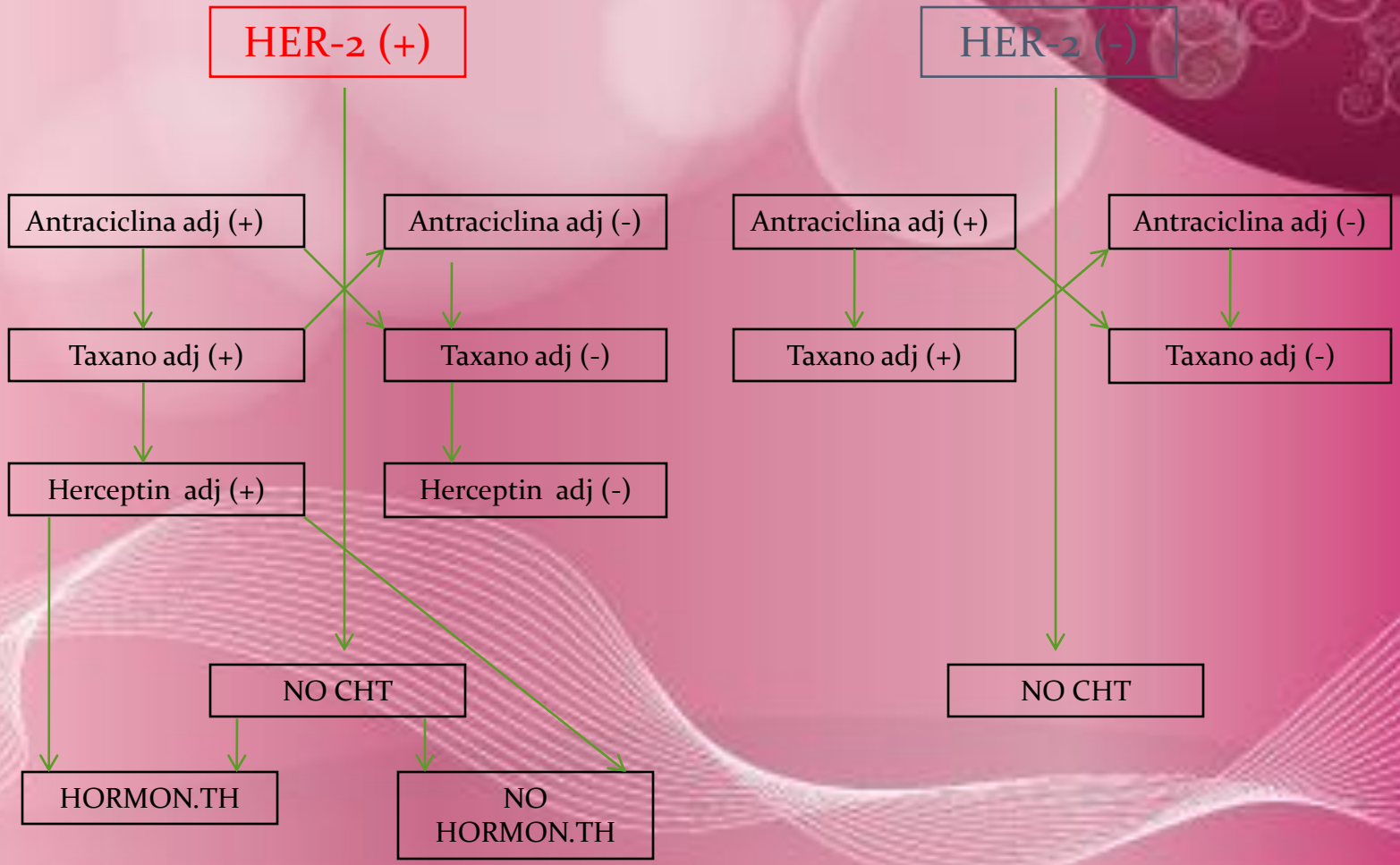


MBC: chi è la paziente in I linea? HER2(+) vs HER2(-)



Non un profilo di MBC, ma tanti!

MBC

Sopravvivenza a 5 anni: 20%

Sopravvivenza media: 12 to 24 months

Le risposte ai trattamenti di I linea sono spesso elevate, ma non sostenute.

Le linee successive hanno un outcome progressivamente peggiore

QUALE MIGLIOR STRATEGIA DI I LINEA?

1. Ormonoterapia o CHT?
2. MonoCHT o PoliCHT?
3. Combinazione o sequenziale?
4. Re-challenge o no re-challenge ?

5. Biologico?

SAPER SCEGLIERE…

Conoscere la prognosi, valutare i fattori predittivi di risposta e scegliere il trattamento…

Fattori prognostici e fattori predittivi

“A prognostic factor is a measurable clinical or biological characteristic associated with a disease-free or overall survival period in the absence of adjuvant therapy, whereas a predictive factor is any measurable characteristic associated with a response or lack of a response to a specific treatment”.

BC

Fattori prognostici: numero dei linfonodi coinvolti, dimensioni del tumore, grado istologico e stato recettoriale

Fattori predittivi: HER-2, ciclina E, p 27, ploidia, S-Phase, p53

La CHT adj (ove indicata)…

… aumenta la DFS del 23%

…aumenta la OS del 15%

Le antracicline sono il farmaco d'elezione.

L' aggiunta del taxano nelle N(+) migliora la DFS e la OS

FAC (o FEC) adj riducono il rischio di morte del 38% nelle pazienti con EBC di etá < 50 aa e del 20% in quelle 50<aa<69 .

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. **Lancet 2005**; 365:1687–1717.

ANTRACICLINA SI, ANTRACICLINA NO!

TAXANO SI, TAXANO NO!

Rechallenge: QUANDO?

Clin Breast Cancer. 2007 Dec;7(11):841-9

Evolving nonendocrine therapeutic options for metastatic breast cancer: how adjuvant chemotherapy influences treatment. **Conte P Guarneri V Bengala C**

Recidiva < 12 mesi dalla fine della CHT adj: NO RECHALLENGE

Recidiva > 12 mesi dallafine della CHTadj: SI RECHALLENGE

A CHI?!

(1964)

STANDARD in HER-2 (+) MBC

- TAXANO+TRASTUZUMAB (M77001)

Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first line treatment: The M77001 study group. J Clin Oncol 2005;23:4265– 4274.

- VINORELBINA + TRASTUZUMAB

Chan A. A review of the use of trastuzumab (Herceptin) plus vinorelbine in metastatic breast cancer. Ann Oncol 2007;18:1152–1158.

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ANTRACICLINE RE-CHALLENGE IN HER(-) MBC

Table 2 Activity of first-line anthracycline-containing regimens and prior adjuvant therapy

Study	*n* of patients	Adjuvant treatment	First-line chemotherapy			
			Type	OS (mos)	TTP (mos)	RR (%)
Kardinal et al. (1988) [6]	425	Chemotherapy naive ($n = 379$)	CAF	19.6	10.6	59
		CMF-like ($n = 32$) or L-PAM ($n = 10$) or anthracycline based ($n = 2$) or others ($n = 2$)		17.5	9.4	50
Venturini et al. (1996) [7]	326	Chemotherapy naive ($n = 144$)	CEF	21.1[a]	11.4[a]	58[a]
		CMF-like ($n = 143$)		15.3	8.8	43
		Anthracycline based ($n = 39$)		15.8	6.6	44
Pierga et al. (2001) [8]	1,430	Chemotherapy naive ($n = 992$)	Anthracycline based	26[a]	14[a]	66[a]
		CMF-like ($n = 190$) or anthracycline based ($n = 165$)		19	10	56
Gennari et al. (2004) [9]	291	Chemotherapy naive ($n = 101$)	ET	27.5	12.5	68
		CMF ($n = 109$)		23.8	11	63
		Anthracyclines ($n = 81$)		20.2	10.2	67

[a] Statistically significant difference.

Abbreviations: CAF, cyclophosphamide, doxorubicin, and fluorouracil; CEF, cyclophosphamide, epirubicin, and fluorouracil; CMF, cyclophosphamide, methotrexate, and fluorouracil; ET, epirubicin and paclitaxel; L-PAM, melphalan; OS, overall survival; RR, response rate; TTP, time to progression

Conclusioni (1)

- Pz pre-trattati in adj hanno un peggior outcome

- L'utilizzo dell'antraciclina in I linea in pz che avevano ricevuto CMF o antraciclina in adj non ha mostrato differenze significative in termini di risposte e sopravvivenza

???

Conclusioni (2)

Pacilio C, Morabito A, Nuzzo F et al. Is epirubicin effective in first-line chemotherapy of metastatic breast cancer (MBC) after an epirubicin containing adjuvant treatment? A single centre phase III trial. Br J Cancer 2006;94:1233–1236.

SOLO 1 STUDIO sul RECHALLENGE!!

Gli autori di una revisione critica concludono che non sussistono, ad oggi, i presupposti del re-challenge con antracicline in pz pre-trattate in adj o neo-adj

(LIVELLO DI EVIDENZA 2b,B)

Table 1. Levels of evidence and grades of recommendation by Oxford Centre for Evidence-Based Medicine (May 2001)

Level	Type of evidence
1a	From a systematic review of multiple, well-designed, high-power, randomized, controlled trials
1b	From at least one well-designed,

Grade	Grading of recommendation
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

???

Taxani in I LINEA MBC

Quali evidenze?

The Oncologist®

Breast Cancer

First-Line Chemotherapy for HER-2–Negative Metastatic Breast Cancer Patients Who Received Anthracyclines as Adjuvant Treatment

ALESSANDRO MORABITO,[a] MARIA CARMELA PICCIRILLO,[a] KATIA MONACO,[a] CARMEN PACILIO,[b] FRANCESCO NUZZO,[b] PAOLO CHIODINI,[c] CIRO GALLO,[c] ANDREA DE MATTEIS,[b] FRANCESCO PERRONE,[a] FOR THE NCI NAPLES BREAST CANCER GROUP

[a]Clinical Trials Unit and [b]Medical Oncology C, National Cancer Institute, Naples, Italy; [c]Department of Medicine and Public Health, Second University of Naples, Italy

Key Words. Metastatic breast cancer • Adjuvant anthracyclines • First-line chemotherapy • Taxanes

Disclosure: No potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

Table 4. Regimens evaluated in phase III clinical trials dedicated to anthracyclines-pretreated metastatic breast cancer patients

Study	# of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)	Main differences in toxicity profile
Nabholtz et al. (1999) [25]*	392	First and second	Docetaxel (D) versus vinblastine + mitomycin (VM)	11.4,[a] 8.7	4.7,[a] 2.7	30,[a] 11.6	More neutropenia with D and thrombocytopenia with VM
Sjöström et al. (1999) [26]*	289	First and second	Docetaxel (D) versus methotrexate + fluorouracil (MF)	10.4, 11.1	6.3,[a] 3.0	42,[a] 21	More leukopenia, neuropathy edema, asthenia, and skin toxicity with D
O'Shaughnessy et al. (2002) [35]*	511	First, second, and third	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30	More stomatitis, diarrhea, and HFS with CD and neutropenic fever, myalgia, and arthralgia with D
Albain et al. (2004) [39]***	529	First	Gemcitabine + paclitaxel (GP) versus paclitaxel (P)	18.5,[a] 15.8	5.4,[a] 3.5	39,[a] 25	More hematological toxicity with GP
Jones et al. (2006) [27]*	449	First and second	Paclitaxel (P) versus docetaxel (D)	12.7, 15.4[a]	3.6, 5.7[a]	25, 31	More hematological and nonhematological toxicities with D
Chan et al. (2005) [40]**	305	First and second	Gemcitabine + docetaxel (GD) versus capecitabine + docetaxel (CD)	NR	8.1, 8.1	32, 32	More diarrhea, mucositis, HFS, and drug-related discontinuation with CD
Miller et al. (2005) [34]**	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 5.1	28.2,[a] 14.2	More hypertension, proteinuria, and neuropathy with PB
Bergh et al. (2006) [37]*	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,? 19	9.3,[a] 7.7	68,[a] 40	More HFS and stomatitis with CD
Soto et al. (2006) [38]*	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]	More alopecia in the combination arms
Marcoux et al. (2006) [47]*	114	Salvage	Gemcitabine + vinorelbine (GV) versus capecitabine (C)	NR	3.7, 5.8	25.8, 24.1	More hematological toxicity with GV; more common HFS with C
Pacilio et al. (2006) [10]	51	First	Epirubicin + docetaxel (ED) versus docetaxel (D)	18, 21	9, 11	72, 79	More leukopenia, nausea, and stomatitis with ED
Batist et al. (2006) [22]	68	First	Nonpegylated liposomal doxorubicin (M) versus doxorubicin (A) (pooled data)	16, 15	4.5, 3.4	31,[a] 11	More cardiac toxicity with A
Martin et al. (2007) [46]	252	First, second, and third	Gemcitabine + vinorelbine (GV) versus vinorelbine (V)	NR	6.3,[a] 4.1	37,[a] 25	More hematological toxicity with GV
Vahdat et al. (2007) [49]**	752	Second and third	Ixabepilone + capecitabine (IC) versus capecitabine (C)	NR	5.8,[a] 4.2	35,[a] 14	More hematologic toxicity, peripheral neuropathy, and myalgia with IC

[a]Statistically significant difference.
[b]Pro fit study.
*Study reported only as abstract as of December 2006.
Abbreviations: HFS, hand–foot syndrome; HR, hazard ratio; NR, not reported; OS, overall survival; RR, response rate; TTP, time to progression.

Study	*n* of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)	Main differences in toxicity profile
O'Shaughnessy et al. (2002) [35][b]	511	First, second, and third	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30	More stomatitis, diarrhea, and HFS with CD and neutropenic fever, myalgia, and arthralgia with D
Beslija et al. (2006) [37][c]	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,[a] 19	9.3,[a] 7.7	68,[a] 40	More HFS and stomatitis with CD
Soto et al. (2006) [38][c]	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]	More alopecia in the combination arms
Miller et al. (2005) [54][b,c]	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 6.1	28.2,[a] 14.2	More hypertension, proteinuria, and neuropathy with PB

VIVA MAMMA INDUSTRIA….

Antracicline liposomiali: esiste un razionale nel rechallenge?

Pooled analysis di 2 studi randomizzati prospettici di Fase III (LDC vs AC; LD vs A)

Batist G, Harris L, Azarnia N et al. Improved anti-tumor response rate with decreased cardiotoxicity of non-pegylated liposomal doxorubicin compared with conventional doxorubicin in first-line treatment of metastatic breast cancer in patients who had received prior adjuvant doxorubicin: Results of a retrospective analysis. Anticancer Drugs 2006;17:587–595.

Batist G, Ramakrishnan G, Rao CS et al. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol 2001;19:1444 –1454.

Harris L, Batist G, Belt R et al. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicentre trial as first-line therapy of metastatic breast carcinoma. Cancer 2002;94:25–36.

…there may be…

"The results of this analysis indicate that patients with breast cancer who relapse later than 6 months after anthracycline treatment in the adjuvant setting may respond to anthracycline-based treatment of metastatic disease and, furthermore, that there may be greater benefit from non-PLD, either alone or in combination with cyclophosphamide, as first-line treatment in the metastatic setting compared with conventional doxorubicin".

…there may be…

ORR (31% versus 11%; *p* .04)

mTTF (4.2 versus 2.1 mesi; *p* *.001)*

LD *ct* vs convenzionale Doxo *ct* (*p* *.001)*

Max recommended cumulative dose LD is >1.260 mg/m2

Pooled analysis di 2 sottogruppi di 2 studi differenti!!

“NON CI SONO DATI DEFINITIVI….”

“SERVONO PIU’ STUDI…..”

…e io cosa faccio alla Sig.ra Rossi che ha un MBC e che devo trattare domani?

Autore	CHT	TTP	RR	OS
Theodoulou (2002)	LD+Trastuzumab			
Cortes (2004)	LD+Trastuzumab+Docetaxel	28.5 mesi	92%	-
Schimdt (2005)	LD+gemcitabina+Docetaxel			
Valero-Buzdar (1999)	LD+Ciclophosphamide+5-FU'			

CARDIOTOSSICITA’

CHF

Doxorubicina:

5% : CD 400 mg/mq,

16% : CD 500 mg/mq

26% :CD 550 mg/mq

Epirubicina:

37% ogni 100 mg/mq

Doxo *c* : Epi *c* = 1 : 1.8

MCD= 5% rischio di sviluppo di cardiotossicitá

- Adriamicina 550 mg/mq
- Epirubicina 900 mg/mq

esempio:

pz trattata con CEF75 adj e sup. corp. 1,7:

Epi CD per 6 cicli: 765 mg (rimanenti alla MCD: 765 mg)

JNCI Journal of the National Cancer Institute 2008 100(15):1058-1067;
ARTICLES

New Insight Into Epirubicin Cardiac Toxicity: Competing Risks Analysis of 1097 Breast Cancer Patients

Marianne Ryberg, Dorte Nielsen, Giuliana Cortese, Gitte Nielsen, Torben Skovsgaard, Per Kragh Andersen

Results: A total of isk factors for cardiotoxicity inclu (hazard ratio per every 100 mg/n val = 1.21 to 1.61), patient age, predisp tinal irradiation, or antil isk factors for death from all othe esser dosages of epirubicin, increas otherapy, and patient age. **The cu s a 5% risk of cardiotoxicity wa dependent on risks of both card**

CARDIOTOSSICITA’

Trastuzumab *c: 7-9 %*

Antraciclina + Trastuzumab

TTP (7.4 vs 4.6) , p< . 001

OS (25.1 vs 20.3), p< .0046

Cardiotossicitá nel braccio A+H: 27%

Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783–792.

Dall'HERA trial ad oggi..

Trial (last follow-up)	Regimen[a]	N	Efficacy				Cardiac events		
			DFS		OS		Severe CHF	Systolic dysfunction	Trastuzumab discontinuation
			%	HR versus control (*P* value)	%	HR versus control (*P* value)			
HERA (24 months) [3, 20, 21]	Any Ctx[b]	1693	74	–	90	–	0	0.5%[c]	
	Any Ctx[b] → H	1694	81	0.64 (0.0001)	92	0.66 (0.0115)	0.6%	3.0%[c]	4.3%
NCCTG N9831 and NSABP B-31	AC → T	1679	67	–	91	–	0.8%[d]	17%[e]	–
(24 months) [4, 22]	AC → TH	1672	85	0.48 (<0.0001)	87	0.67 (0.015)	4.1%[d]	34%[e]	19%
BCIRG-006 (second interim	AC → T	1073	77	–	86	–	0.4%	10%[f]	–
analysis at 36 months) [5]	AC → TH	1074	83	0.61 (<0.0001)	92	0.59 (0.004)	1.9%	18.1%[f]	Not yet published
	TCH	1075	82	0.67 (0.0009)	91	0.66 (0.017)	0.4%	8.6%[f]	Not yet published
FinHER (36 months) [6]	T or V → FEC[g]	116	78	–	90	–	4%	3%[e]	–
	T or V + H → FEC +H[g]	115	89	0.42 (0.01)	96	0.41 (0.07)	0	0	Not reported

Study	Drug	No. of patients	ORR (%)	Response duration (months)	TTF (months)	TTP (months)	Cardiac toxicity (%)	CHF (No.)
3	MC	80	46	10	5.7	7.7	12	0
	EC	80	39, NS	7.7, $P = 0.005$	4.4, $P = 0.007$	5.6, $P = 0.02$	10, NS	0

Myocet vs Epirubicina

Study	Drug	No. of patients	ORR (%)	OS (months)	Cardiac toxicity (%)	CHF (No.)
1	MC	142	43	19	6	0
	AC	155	43	16, NS	21, $P = 0.0001$	5, $P = 0.02$
2	M	108	26	16	13	2
	A	116	26	20, NS	29, $P = 0.0001$	9, $P = 0.0001$

Myocet vs Doxorubicina

LD e PLD + trastuzumab

Study	Treatment	*N*	Efficacy results	Safety results
Nonpegylated LD				
Theodoulou et al. [59]	LD 60 mg/m^2 i.v. every 3 weeks H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	37	OR: 58%; SD: 16%	CHF: one patient; asymptomatic cardiotoxicity: 1 patient; grade 4 neutropenic fever: 2/203 cycles; grades 3–4 nausea 2/37 patients (5.4%)
PLD				
Chia et al. [60]	PLD 50 mg/m^2 i.v. every 4 weeks; H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	30	OR: 52%; SD: 38%; PPS: 12.0 months	CHF: none; asymptomatic cardiotoxicity: 3 patients; grade 3 mucositis: 1/30 patients (3%); grade 3 PPE: 9/30 patients (30%); grades 3–4 neutropenia: 8/30 patients (27%)
Wolff et al. [61]	HER2-negative patients; PLD 30 mg/m^2 i.v. every 3 weeks; T 60 mg/m^2 i.v. every 3 weeks	41	OR: 40%; TTP: 10.5 months	CHF: none; grades 1–2 cardiotoxicity—cycle 8: 9/22 patients (41%); ≥30 days post-treatment: 1/9 patients (11%)
	HER2-positive patients; PLD 30 mg/m^2 i.v. every 3 weeks; T 60 mg/m^2 i.v. every 3 weeks; H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	48	OR: 46%; TTP: 13.1 months	CHF: none; grades 1–2 cardiotoxicity—cycle 8: 10/18 patients (56%); ≥30 days post-treatment: 12/18 patients (67%); increased incidence grades 2–3 PPE in this arm
Stickeler et al. [62]	PLD 40 mg/m^2 i.v. every 4 weeks; H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	15	CB: 42.9%; OS: 16.2 months	CHF: none; asymptomatic cardiotoxicity: 3/15 patients (20%)
Andreopoulou et al. [63]	PLD 30 mg/m^2 i.v. every 3 weeks; H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	12	CB: 67%	CHF: one patient (grade 3); asymptomatic cardiotoxicity (grade 2): 3 patients (25%); grade 3 neutropenia: 2/12 patients (17%); grade 3 hypersensitivity: 2/12 patients (17%); grade 3 mucositis: 1/12 patients (8%); grade 3 rash: 1/12 patients (8%); grade 3 esophagitis: 1/12 patients (8%)

HER2(+) vs HER2(-)

Gli HER2(+) ris HER2(-), no!

Journal of Clinical Oncology, Vol 26, No 5 (February 10), 2008: pp. 736-744

REVIEW ARTICLE

HER-2 and Topoisomerase II As Predictors of Response to Chemotherapy

Kathleen I. Pritchard, Hans Messersmith, Leela Elavathil, Maureen Trudeau, Frances O'Malley, Bindi Dhesy-Thind

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HER2 overexpression or amplification has been shown to be associated with a poor prognostic effect in women with breast cancer. At least eight analyses based on randomized trials have examined the relationship between *HER2* and the differential effect of anthracycline compared with non–anthracycline-containing regimens. Only three of these studies were sufficiently powered to show a significant interaction between *HER2* and anthracycline- versus non–anthracycline-containing treatments, but because all of the study results tended to be in the same direction, it is not surprising that three recent meta-analyses of published data have suggested that **anthracycline-containing regimens provide more benefit than non–anthracycline-containing regimens in women whose tumors are overexpressed or amplified (positive) for *HER2***. Since topoisomerase II is a known target of the anthracyclines, it has been postulated that this relationship is actually based on the proximity of *HER2* to the topoisomerase II gene (*TOP2A*) in the 17q chromosome. At least four recent studies have suggested that deletion and amplification of the *TOP2A* gene are associated with poor prognosis and are predictive of greater response to anthracycline-containing than to non–anthracycline-containing regimens. However, in at least one of those studies, *HER2* positivity was as or more predictive. Although it has been suggested that *HER2* positivity is predictive of better response to higher-dose anthracycline-containing regimens compared with standard anthracycline-containing regimens and to taxane- compared with non–taxane-containing regimens, these relationships have not been robust or consistent. Additional studies will be required to clarify these relationships.

ARTICLE

HER2 Status and Efficacy of Adjuvant Anthracyclines in Early Breast Cancer: A Pooled Analysis of Randomized Trials

Alessandra Gennari , Maria Pia Sormani , Paolo Pronzato , Matteo Puntoni , Mariantonietta Colozza , Ulrich Pfeffer , Paolo Bruzzi

Background
Adjuvant chemotherapy with anthracyclines improves disease-free and overall survival compared with non – anthracycline-based adjuvant chemotherapy regimens in the treatment of early breast cancer. The role of *HER2 status as a marker of anthracycline responsiveness has been explored by subset analyses* within randomized clinical trials, with inconsistent results. We performed a pooled analysis of the interaction between *HER2 status and the efficacy of adjuvant anthracyclines based on the published* subset data.

Methods
We searched literature databases to identify randomized trials that compared anthracycline-based with non – anthracycline-based adjuvant chemotherapy regimens in the treatment of early breast cancer and reported efficacy data according to *HER2 status. Log hazard ratios (HRs) for disease-free and overall survival* were pooled across the studies according to *HER2 status by inverse variance weighting. A pooled* test for treatment by *HER2 status interaction was performed by weighted linear meta-regression. All* statistical tests were two-sided.

Results
Eight studies (with 6564 randomly assigned patients, of whom 5354 had *HER2 status information available)* were eligible for this analysis. In *HER2 -positive disease (n = 1536 patients), anthracyclines were* superior to non – anthracycline-based regimens in terms of disease-free (pooled HR of relapse = 0.71; 95% confidence interval [CI] = 0.61 to 0.83; *P < .001) and overall (pooled HR of death from any cause = 0.73;* 95% CI = 0.62 to 0.85; *P < .001) survival. In HER2 -negative disease (n = 3818 patients), anthracyclines did* not improve disease-free (HR = 1.00; 95% CI = 0.90 to 1.11; *P = .75) or overall (HR = 1.03; 95% CI = 0.92 to* 1.16; *P = .60) survival. The test for treatment by HER2 status interaction yielded statistically significant* results: for disease-free survival, the chi-square statistic for interaction was 13.7 (*P < .001), and for overall* survival, it was 12.6 (*P < .001).*

Conclusions **The added benefits of adjuvant chemotherapy with anthracyclines appear to be confined to women who have *HER2 overexpressed or amplified breast tumors.***

J Natl Cancer Inst 2008;100: 14 – 20

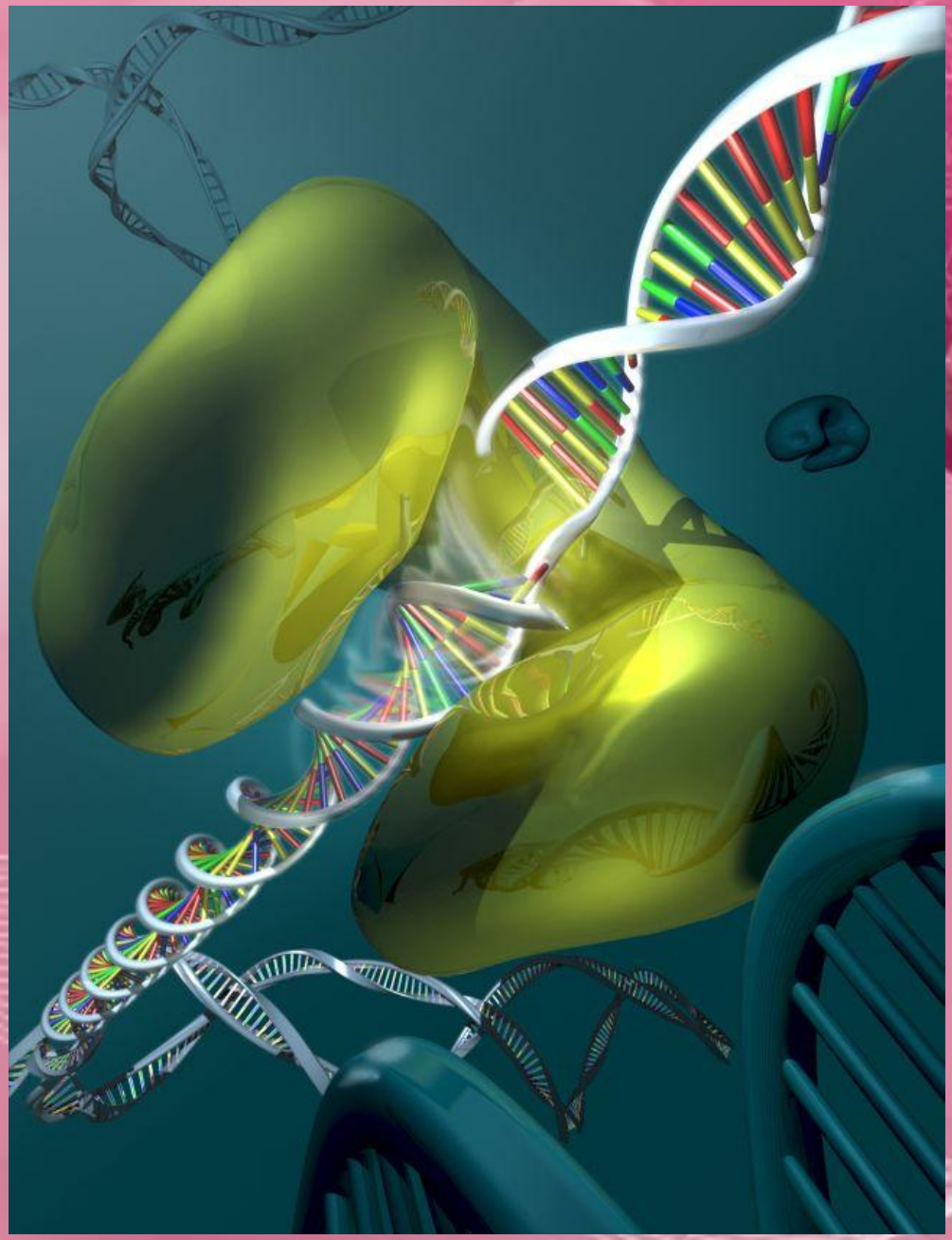

BAD NEWS

ASCO American Society of Clinical Oncology

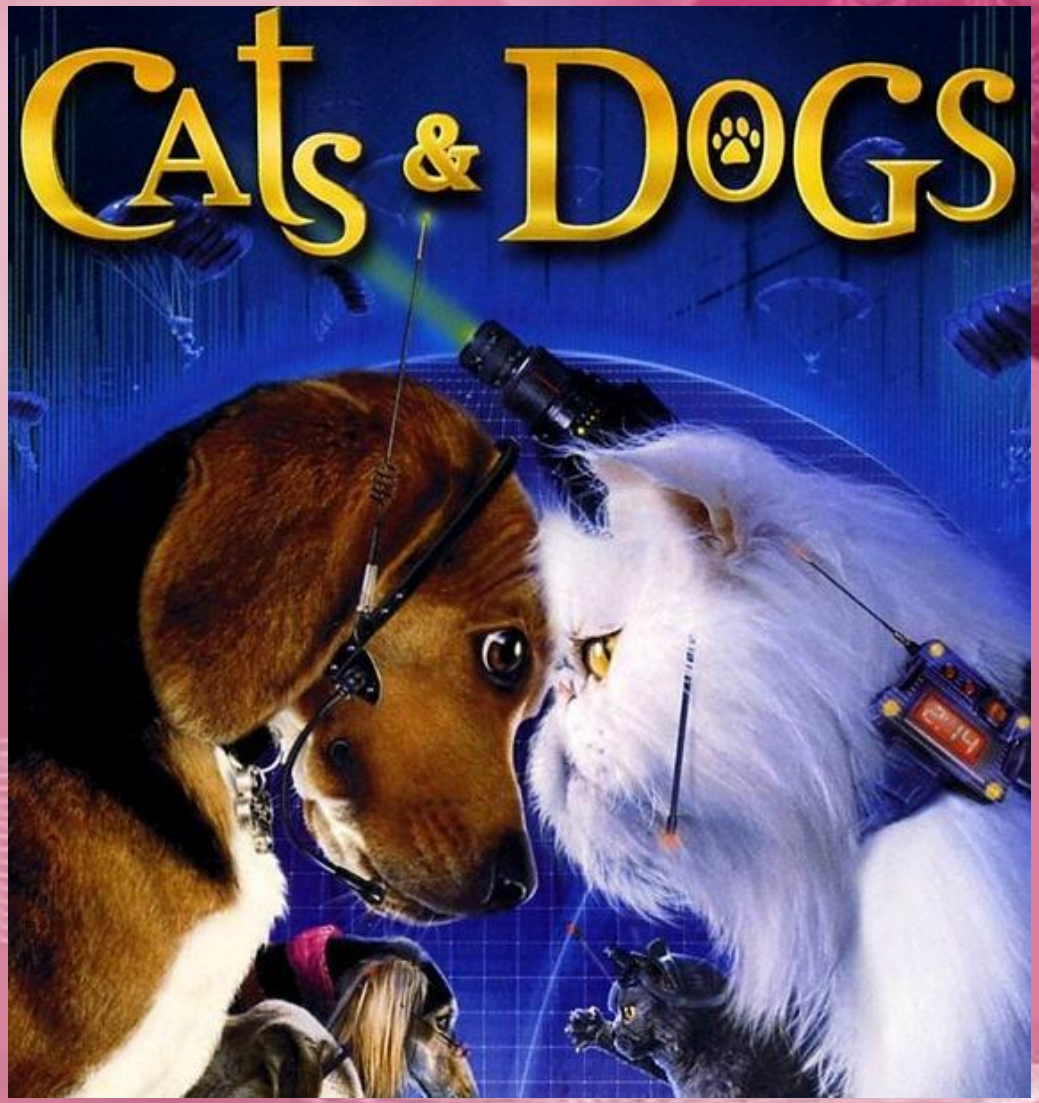
HER2(-) BC e antracicline

A. Di Leo, ASCO 2008

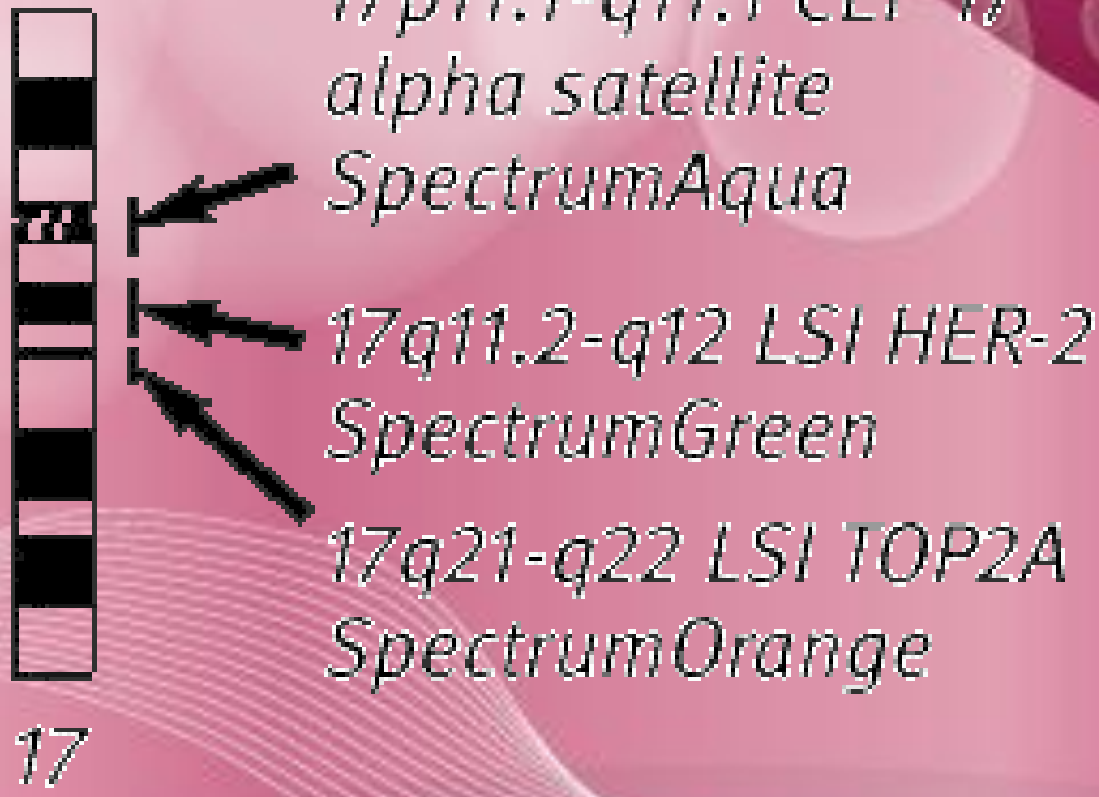
- Un'analisi di 8 studi ha evidenziato che le pz HER2(-) non beneficiano di un trattamento con antracicline (JCO 2008, Pritchard & Co.)
- Pooled analysis di 8 trial randomizzati: nessun beneficio per le pz HER2(-) dal trattamento con antracicline (J Natl Cancer Inst 2008, Gennari & Co)
- L'amplificazione della **TOPO 2α** si riscontra raramente negli HER2(-)



HER2 e TOPOISOMERASI 2α

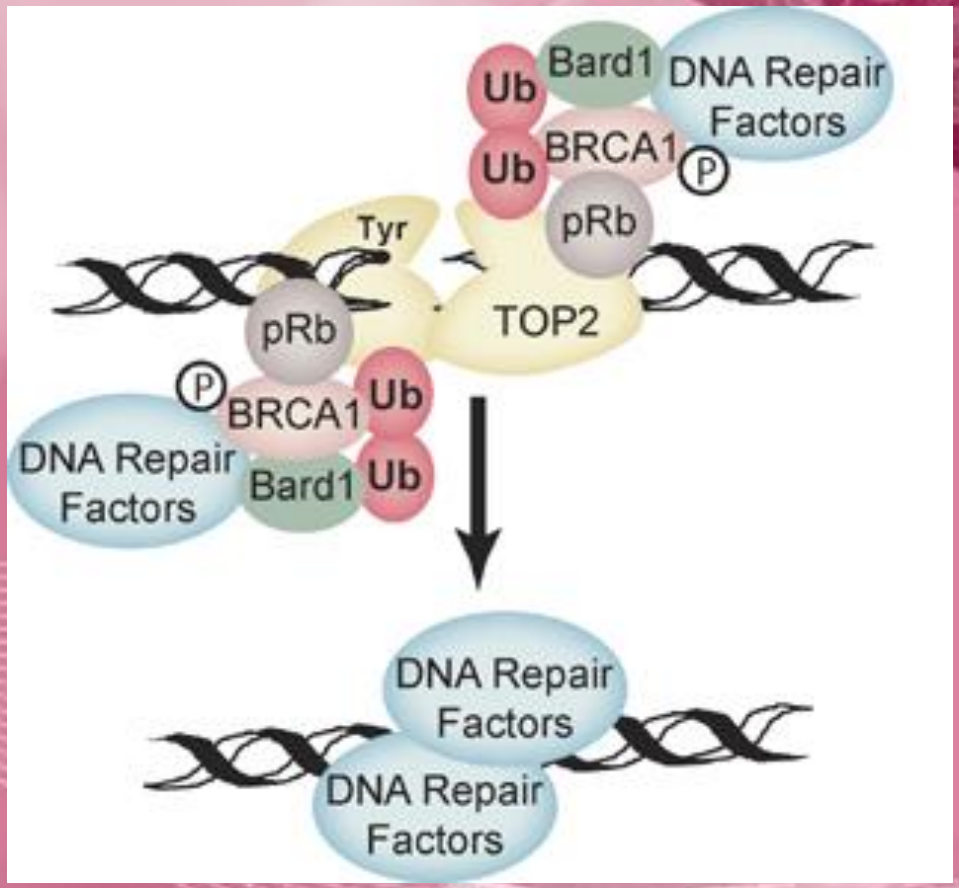


HER2 e TOPOISOMERASI IIα




...E NON
FINISCE QUI!
CAVA

HER2 – TOPO2α – BRCA 1/2



BRCA1- and BRCA2-Deficient Cells Are Sensitive to Etoposide-Induced DNA Double-Strand Breaks via Topoisomerase II

Alejandro D. Treszezamsky,1 Lisa A. Kachnic,2 Zhihui Feng,1,3 Junran Zhang,1,3 Chake Tokadjian,1 and Simon N. Powell1,3

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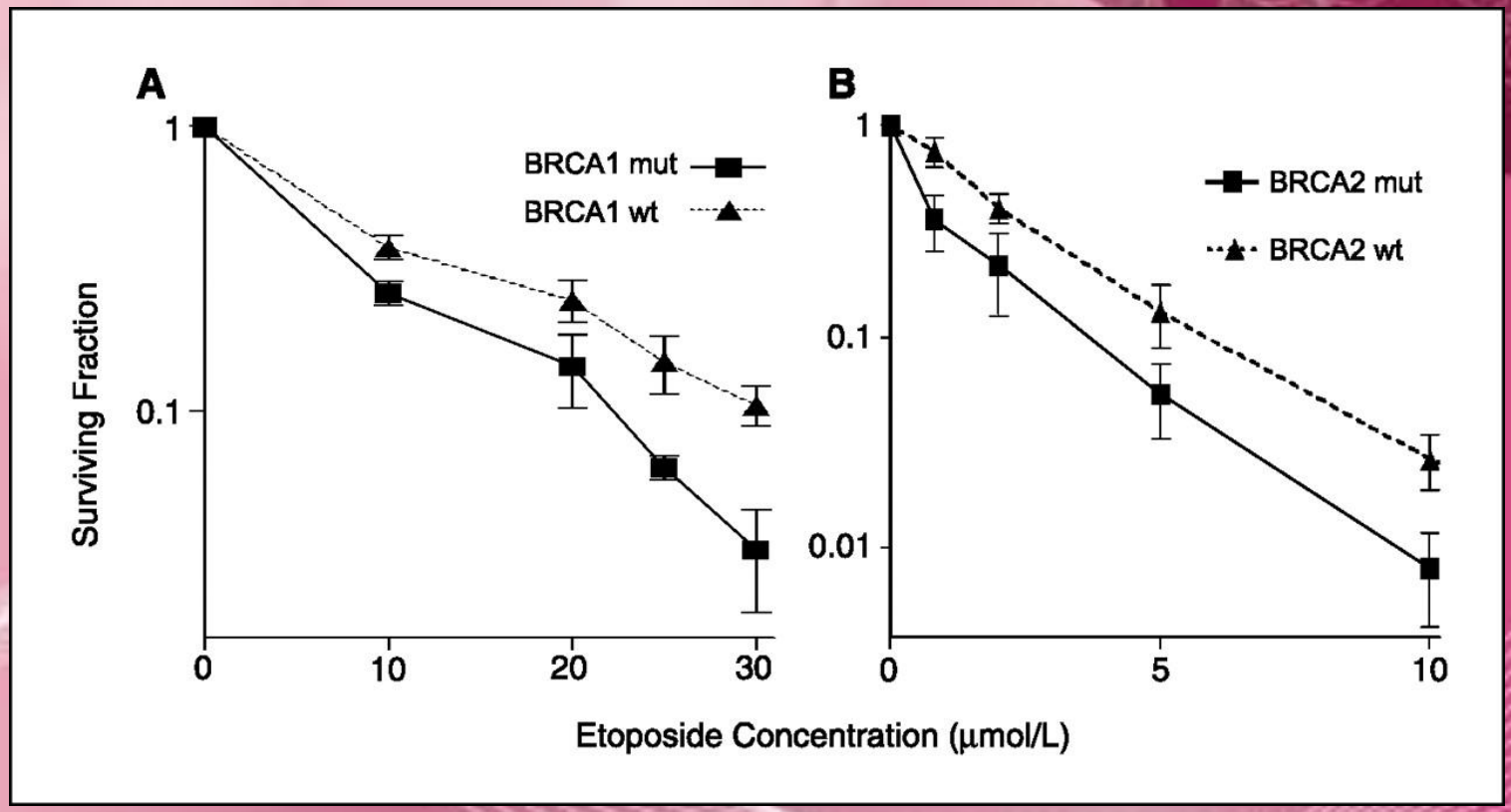
Center, Boston, Massachusetts; and 3Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri

Abstract

The function of BRCA1 and BRCA2 in DNA repair could affect the sensitivity of cells to cytotoxic agents, and would therefore be an important component of planning therapy for breast and ovarian cancers. Previously, both BRCA1- and BRCA2- deficient tumors were shown to be sensitive to mitomycin C, and the mechanism was presumed to be a defect in the repair of interstrand crosslinks by homologous recombination. Here, we show that **both BRCA1 and BRCA2 determine the sensitivity to the cytotoxic drug,** etoposide, using genetic complementation of BRCA-deficient cells. Etoposide is known to bind to topoisomerase II and prevent the resolution of the ''cleavable complex,'' in which one DNA duplex is passed through a second duplex. The specificity of this BRCAdependent sensitivity was confirmed by the use of aclarubicin, which is a catalytic inhibitor of topoisomerase II and prevents the formation of the cleavable complex. In the presence of aclarubicin, the differential sensitivity of BRCA-proficient and BRCA-deficient cells was lost. Thus, etoposide requires the presence of topoisomerase II to show specific sensitization in the absence of the function of BRCA1 or BRCA2. We conclude that homologous recombination is used in the repair of DNA damage caused by topoisomerase II poisons. Overall, these results suggest that etoposide is a potentially useful drug in the treatment of BRCA-deficient human cancers. [Cancer Res 2007;67(15):7078–81]

BRCA-Syndrome (?)



Research article

Open Access

c-erbB2 and topoisomerase IIα protein expression independently predict poor survival in primary human breast cancer: a retrospective study

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This article is online at: http://breast-cancer-research.com/content/7/3/R374

P.Fritz et al.; BCRT 2005, 7:R374-R384

Materials and methods

Patients and pathological data

Tumor tissue was analyzed for protein expression of c-erbB2 and topoisomerase IIα from 225 patients with primary invasive breast cancer who underwent surgery from 1986 to 1998 at the Department of Gynaecology, Robert Bosch Hospital, Stuttgart, Germany. The local ethics committee was informed

P.Fritz et al.; BCRT 2005, 7:R374-R384

Table 4

Clinical characteristics of patients with and without overexpression of c-erbB2 and topoisomerase IIα

Parameter	Value			
Topoisomerase overexpression	Absent	Absent	Present	Present
c-erb B2 overexpression	Absent	Present	Absent	Present
Stage, *n* (%)				
I	29 (24.2)	3 (15.0)	6 (11.1)	2 (10.0)
II	59 (49.1)	7 (35.0)	36 (66.6)	11 (55.0)
III	29 (24.2)	9 (45.0)	9 (16.7)	6 (30.0)
IV	3 (2.5)	1 (5)	3 (5.6)	1 (5.0)
Total[a]	120	20	54	20
Receptor status, *n* (%)				
ER or PR positive	92 (79.3)	12 (57.1)	32 (58.2)	10 (52.6)
PR and PR negative	24 (20.7)	9 (42.9)	23 (41.8)	9 (47.4)
Total[b]	116	21	55	19

[a]214 patients with complete data were analyzed for stage; [b]211 patients with complete data were analyzed for receptor status. ER, estrogen receptor; PR, progesterone receptor.

P.Fritz et al.; BCRT 2005, 7:R374-R384

Prognostic impact of c-erbB2 overexpression

Tumors with an immunoreactive score exceeding 2 or 3 were considered to overexpress c-erbB2. Accordingly, 43 (19.1%) of the patients showed overexpression of this oncogene. Patients with c-erbB2 overexpression showed a similar distribution of age, stage, histological criteria, and receptor status to that of the c-erbB2 negative subgroup (data not shown).

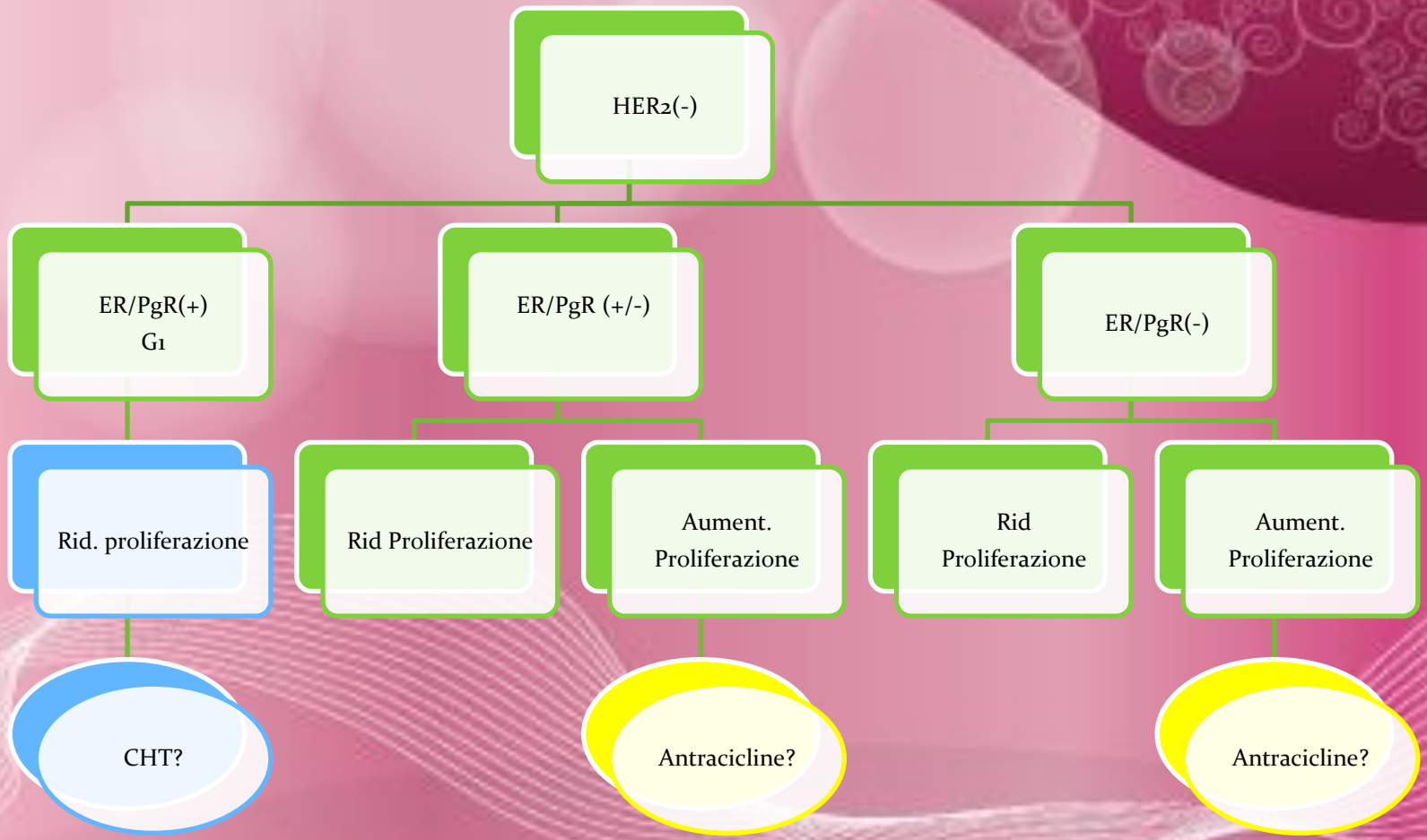
However, the former patients were characterized by a significantly inferior survival in a univariate statistical analysis (log rank 17.94; $P < 0.0001$). The median overall survival time of patients with tumors overexpressing c-erbB2 was 55 months, with a 5-year survival rate of 46.0%. In contrast, median survival time was not reached in the c-erbB2 negative group. The 5-year survival in this group was 78.3% (Fig. 1a). Patients with c-erbB2-overexpressing tumors received no significant benefit from anthracycline-based adjuvant therapy, and even had the worst prognosis of all groups analyzed (log rank 10.17; $P = 0.001$; see below).

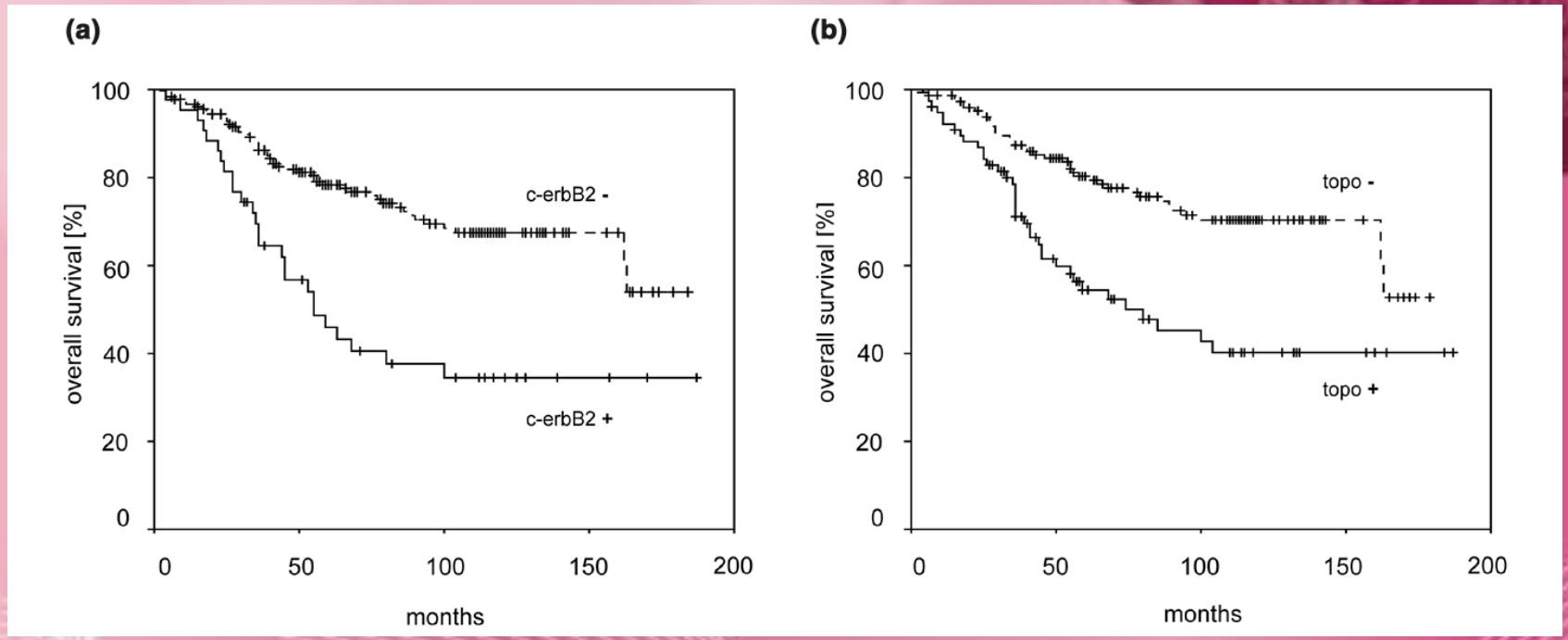
c-erb-B2(+) pz: mOS: 55 mesi 5y-OS(46%) [nessun vantaggio dall'aggiunta delle antracicline adj per HER2(+)]

c-erb-B2(-) pz: mOS:ns 5y-OS (78.3%)

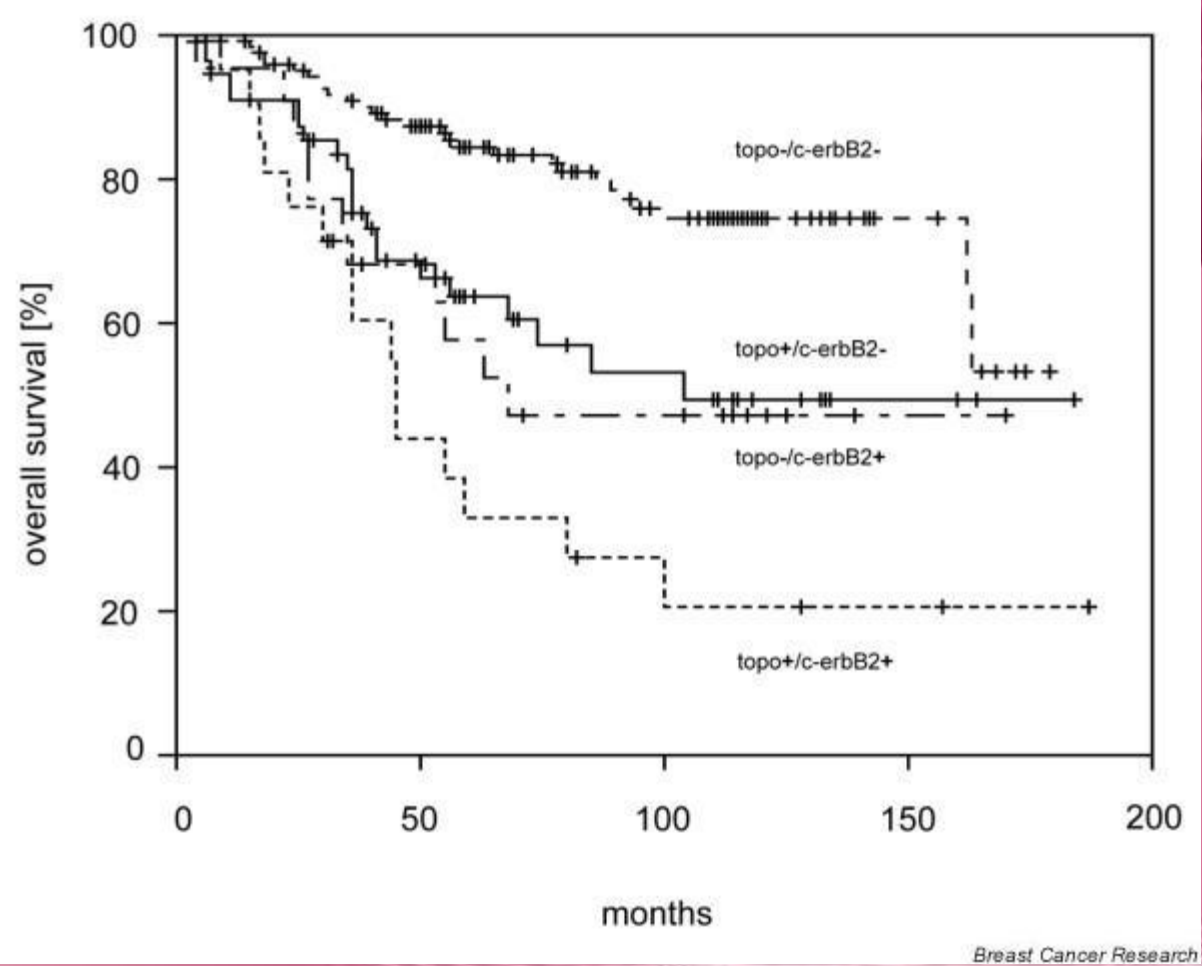
P.Fritz et al.; BCRT 2005, 7:R374-R384

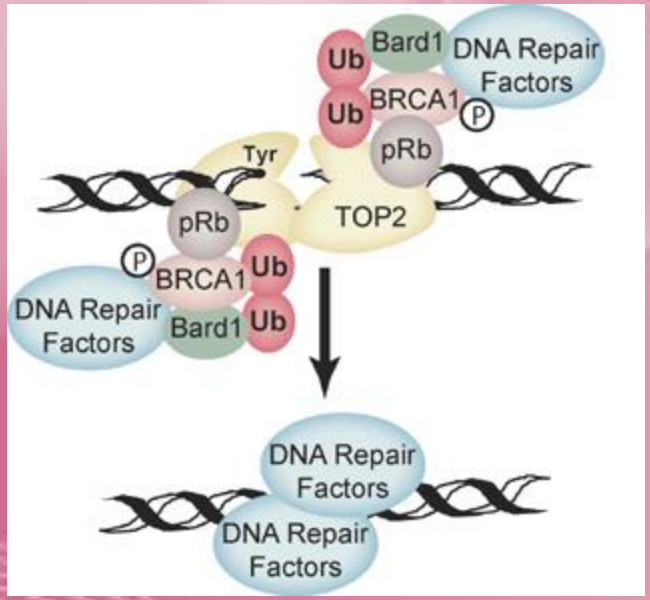
Chiave di lettura: tanti HER2(-)





P.Fritz et al.; BCRT 2005, 7:R374-R384


100
80
60
40
20
0
overall survival [%]
0
50
100
150
200
months
topo-/c-erbB2-
topo+/c-erbB2-
topo-/c-erbB2+
topo+/c-erbB2+
Breast Cancer Research


Ub
Bard1
DNA Repair Factors
Ub
BRCA1
P
pRb
Tyr
TOP2
pRb
P
BRCA1
Ub
DNA Repair Factors
Bard1
Ub
DNA Repair Factors
DNA Repair Factors

Conclusion

Our data suggest that protein expression of topoisomerase IIα is a prognostic factor that is independent of c-erbB2, stage, and histological grading. In addition, the results of this exploratory study indicate that anthracycline treatment is not capable of reversing the negative prognostic influence of the expression of topoisomerase IIα or c-erbB2. Nevertheless, because of the small number of patients remaining in these subgroups, no firm conclusion can be made about the predictive value of topoisomerase IIα or c-erbB2 regarding sensitivity to anthracyclines. Our results support the view that studying the deregulation of either the *topoisomerase IIα* gene or topoisomerase IIα protein might yield different results depending on the method applied. This should be considered when planning prospective studies on the predictive and prognostic value of topoisomerase IIα.

P.Fritz et al.; BCRT 2005, 7:R374-R384

La co-amplificazione della TOPO-IIα e di HER-2 non produce differenze significative in termini di DFS nei bracci con e senza antracicline, ma, un'analisi per sottogruppi ha dimostrato che, l'amplificazione della stessa, produce un significativo peggioramento nel braccio trattato con antracicline. (BCIRG 006,II interim analysis).

Ergo, non sono gli HER2 (-)a rispondere male alle antracicline, ma é il profilo della malattia, associata alla amplificazione della TOPO-II , ad avere una prognosi peggiore. QUINDI l'HER2 non è un fattore PREDITTIVO!

review

Annals of Oncology 19: 1530–1539, 2008
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Anthracycline–trastuzumab regimens for HER2/neu-overexpressing breast cancer: current experience and future strategies

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Anthracycline–trastuzumab-containing regimens demonstrate significant clinical activity in human epidermal growth factor receptor 2 (HER2)-positive breast cancer; however, the utility of this strategy is limited by unacceptably high rates of significant cardiotoxicity, particularly with concurrent administration. Anthracycline-induced cardiotoxicity is thought to be mediated primarily through increased myocardial oxidative stress, modified partly by the activity of neuregulins. Trastuzumab-induced cardiotoxicity is thought to be mediated by the ErbB/neuregulin system, with exposure to trastuzumab partly blocking the protective effect of neuregulins on the myocardium. As a result, trastuzumab increases the risk of anthracycline-induced cardiotoxicity. Several strategies have been adopted in attempts to minimize cardiotoxicity, including patient selection on the basis of preexisting cardiac risk, monitoring of cardiac function during treatment, and early management of cardiac dysfunction. The use of less cardiotoxic anthracyclines may be one strategy to lessen the risk of cardiotoxicity. Liposomal doxorubicin products offer similar efficacy compared with conventional doxorubicin, with significantly less cardiotoxicity, and have been successfully used in combination with trastuzumab in the metastatic and neo-adjuvant setting. Clinical trials are currently underway to assess the safety of pegylated liposomal doxorubicin during concurrent administration with trastuzumab compared with standard sequential treatment using conventional doxorubicin in the adjuvant setting.

Key words: adjuvant therapy, anthracyclines, breast cancer, cardiotoxicity, HER2+, pegylated liposomal doxorubicin, trastuzumab

Rayson, Annals of Oncology 19; 1530-1539, 2008

Study	Treatment	*N*	Efficacy			Safety	
			PFS	Response rate	Median survival	Cardiotoxicity[a]	Other toxic effects (liposomal versus conventional)
O'Brien et al. [57]	PLD 50 mg/m^2 every 4 weeks	254	6.9 months, HR = 1.00	NR	NR	4% (no cases of CHF) HR = 3.16 ($P < 0.001$)	Alopecia: 20% versus 66%; nausea: 37% versus 53%; vomiting: 19% versus 31%; stomatitis: 22% versus 15%; mucositis: 23% versus 13%; neutropenia: 4% versus 10%; PPE: 48% versus 2%
	Doxorubicin 60 mg/m^2 every 3 weeks	255	7.8 months	NR	NR	19%	
Harris et al. [58]	LD 75 mg/m^2 every 3 weeks	108	NR	26%	16 months	13% (two cases of CHF) HR = 3.56 ($P = 0.0001$)	Alopecia: 81% versus 88%[b]; nausea/vomiting: 13% versus 24%[c]; stomatitis/ mucositis: 9% versus 14%[c]; neutropenia: 50% versus 58%[d]; PPE: one case with LD
	Doxorubicin 75 mg/m^2 every 3 weeks	116	NR	26%	20 months ($P = 0.09$)	29%	

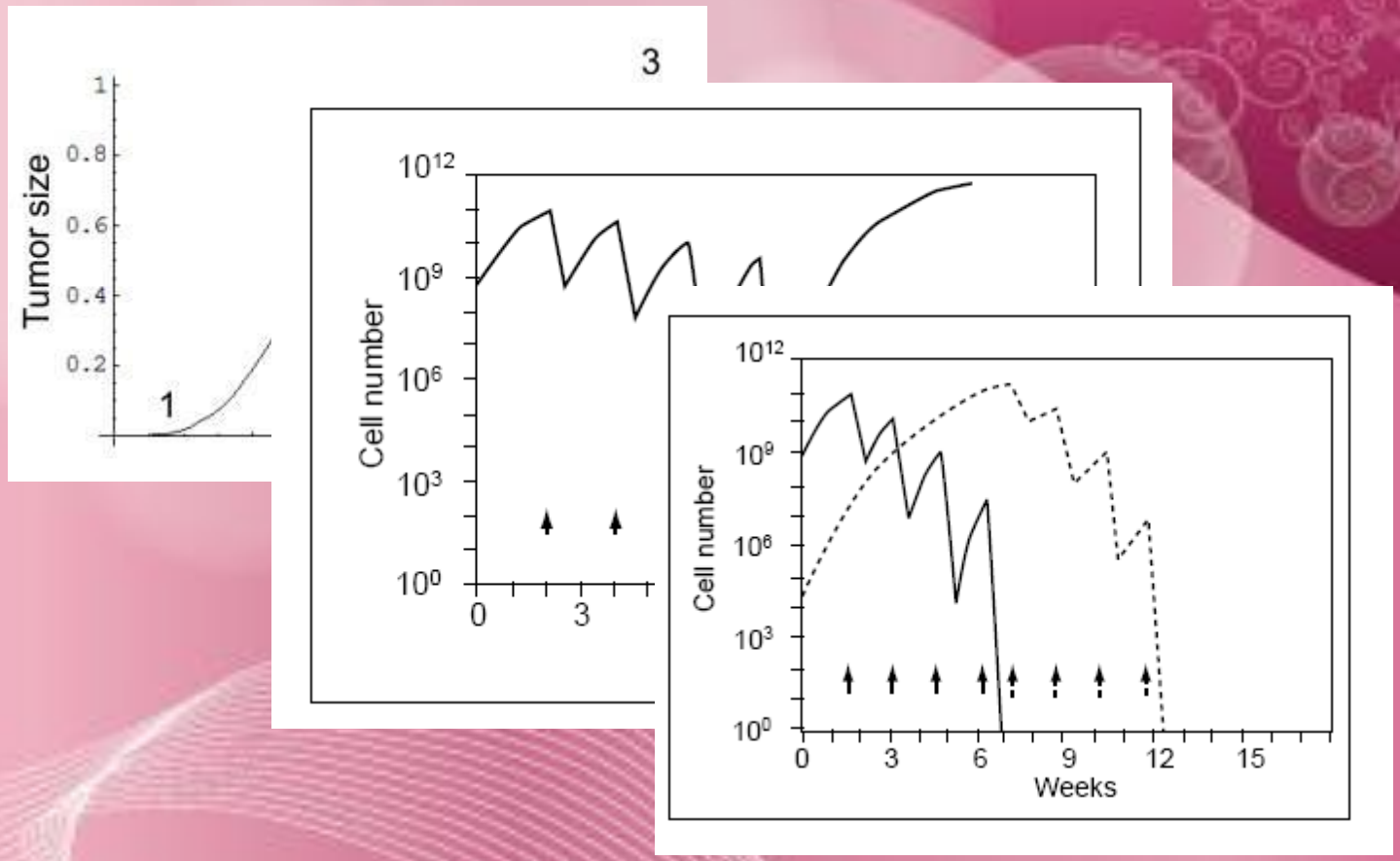
Rayson, Annals of Oncology 19; 1530-1539, 2008

SAPIENZA
UNIVERSITÀ DI ROMA

w-ALT TRIAL (Fase I-II)
Combinazione settimanale di antraciclina Liposomiale (AL) e taxano (T) nella I linea del carcinoma mammario

PROTOCOLLO "DI SERI"

Perchè la malattia metastatica è inguaribile?



Resistenza assoluta o resistenza relativa?

Come superare le resistenze….

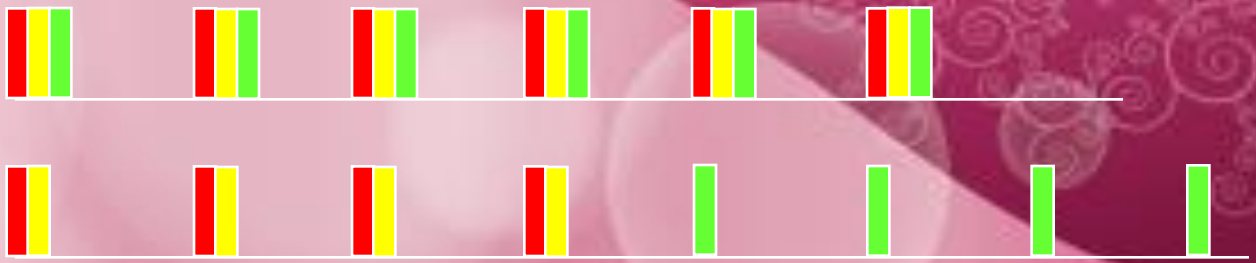
- Aumento di dose (regimi *dose-dense*)
- Formulazioni diverse di citotossici con comprovata efficacia (es.: liposomiale)
- Utilizzo di coadiutori anti-MDR

Regimi chemioterapici

Trisettimanale convenzionale

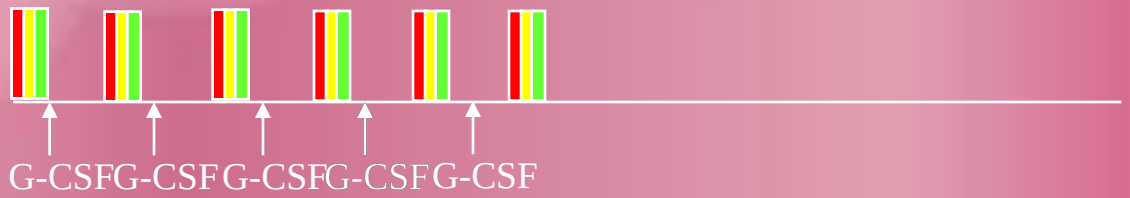
Combinazione

Sequenziale



Dose Dense- Stesso dosaggio ogni 2 settimane+ G-CSF

Dose-dense



Metronomica – Dosaggio giornaliero + G-CSF

Metronomica

DISEGNO DELLO STUDIO

Disegno dello Studio (2002-2007)

Trisettimanale convenzionale

Combinazione standard

AL 60 mg/m^2 q3w

Paclitaxel 135 mg/m^2 q3w o **Docetaxel** 75 mg/m^2 q3w

wALT TRIAL

6 cicli

AL 25 mg/m^2 d1,8,15 q4w

Paclitaxel 50 mg/m^2 d1,8,15 q4w o **Docetaxel** 30 mg/m^2 d1,8,15 q4w

FASE I (solo per Taxol)

End point primario: MTD e DLT

Pz arruolate: n° 6

n°1 pz trattata con: 20 mg/mq wLD e 45 mg/mq wTaxol per 3 settimane /4

n°1 pz trattata con: 25 mg/mq wLD e 45 mg/mq wTaxol per 3 settimane/4

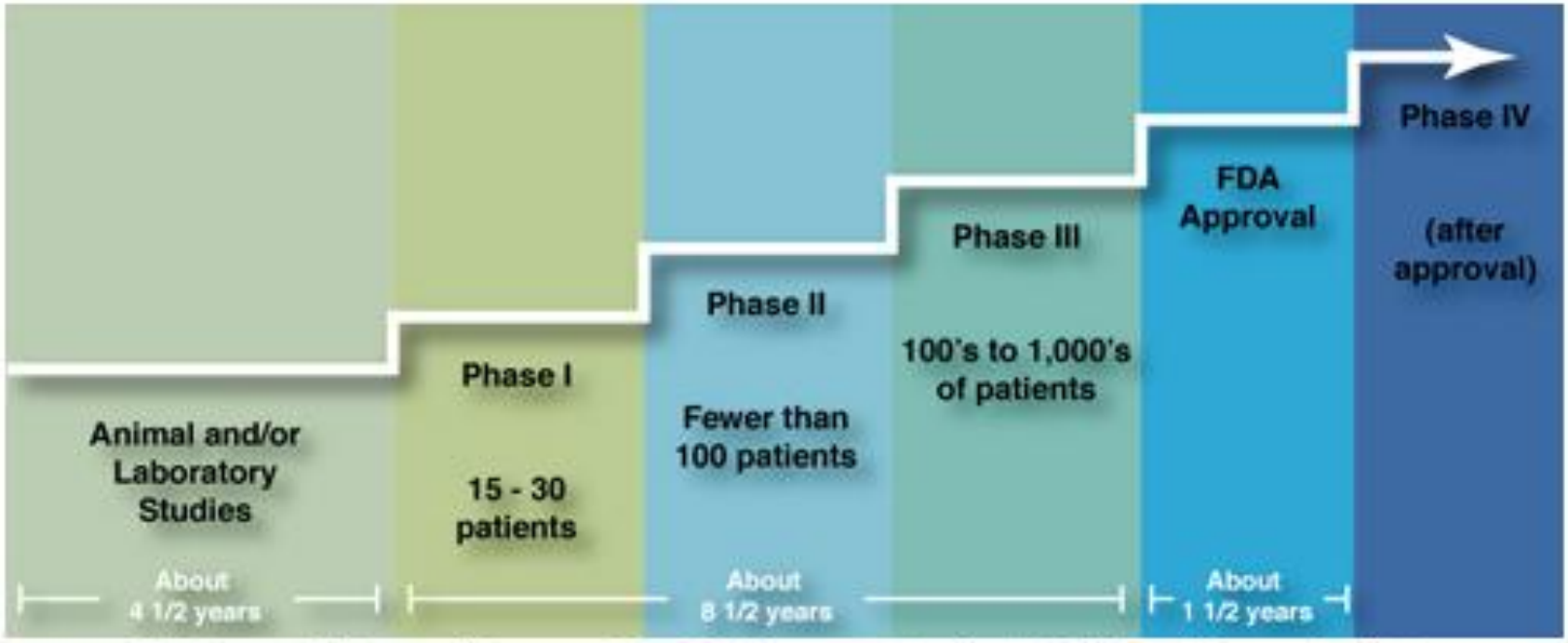
n°1 pz trattata con: 30 mg/mq wLD e 45 mg/mq wTaxol per 3 settimane/4 (DLT; leuconeutropenia G4)

n°1 pz trattata con: 25 mg/mq wLD e 45 mg/mq wTaxol per 3 settimane/4

n°1 pz trattata con: 25 mg/mq wLD e 50 mg/mq wTaxol per 3 settimane/4

n°1 pz trattata con: 25 mg/mq wLD e 50 mg/mq wTaxol per 3 settimane/4

Non eseguiti dosaggi dei farmaci su prelievi ematici ed urinari per impossibilità tecnica.



The Drug and Approval Process in the 1990s as reported by the National Cancer Institute.

Profilo pazienti

Profilo pazienti	N (%)
Totale	48
Età	
Media	55.8 anni
Mediana	**56**
Range	45-65
(ECOG) PS	
0	**31**
1	12
2	5
Istologia	
Duttale	32
Lobulare	7
Misto	9
Profilo recettoriale	
ER(+)	**40**
PgR(+)	**39**
HER2(+)*	**29**

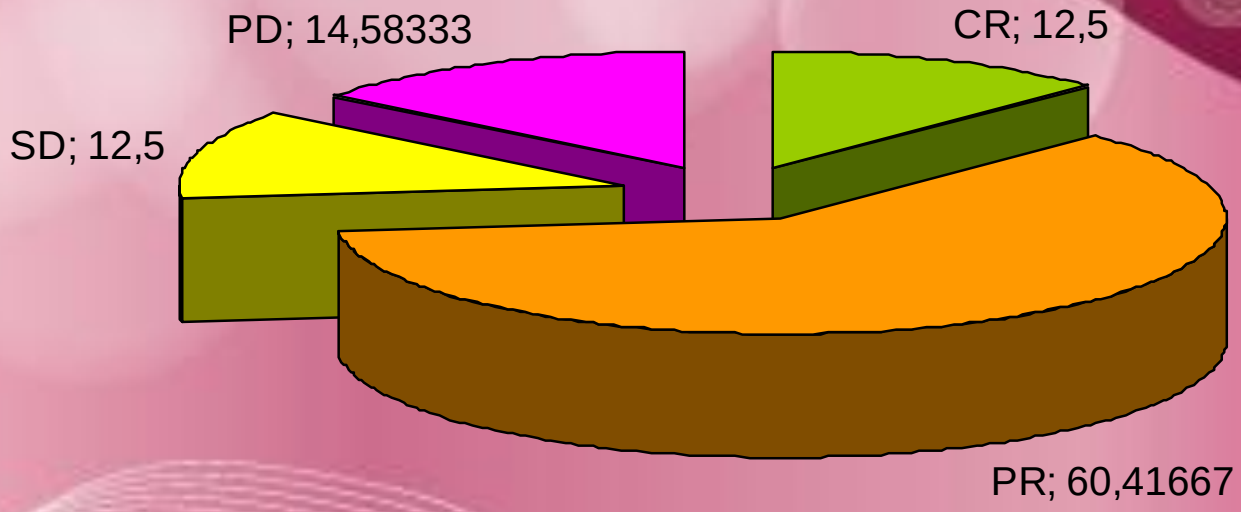
Precedente trattamento adiuvante	
Antracicline	48
Taxani	12
Ormonoterapia	40
Trastuzumab adiuvante	6
Metastasi	
1	16
≥ 2	**32**
Sedi di metastasi	
Tessuti molli	5
Linfonodi	10
Epatiche	29
Polmonari	4
Cerebrali	2
Ossee	34

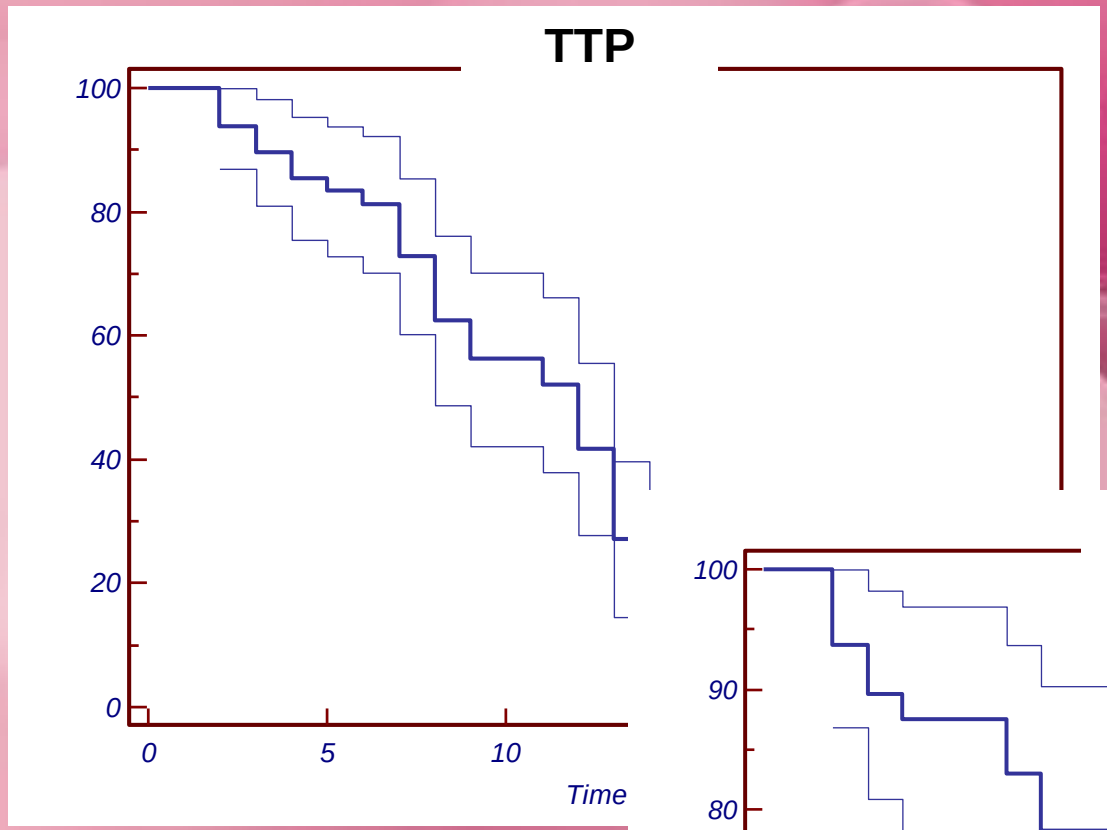
Obiettivi

- End-point primario: ORR
- End-point secondari:
  - TTP
  - OS (2y)
  - Tossicità

Beneficio clinico: Tot, Paclitaxel vs Docetaxel

	Pz (n=48)	**Paclitaxel (n=28)**	**Docetaxel (n=20)**
CR	12.5%	14.2%	10%
PR	60.41%	67.85%	50%
SD	12.5%	3.5%	25%
PD	14.59%	14.2%	15%
Beneficio complessivo	85.41%	85.71%	85%
TTP	10.68 mesi	10.60 mesi	10.80 mesi
OS (2y) ***(intent to treat)***	21.60 mesi	21.71 mesi	21.45 mesi

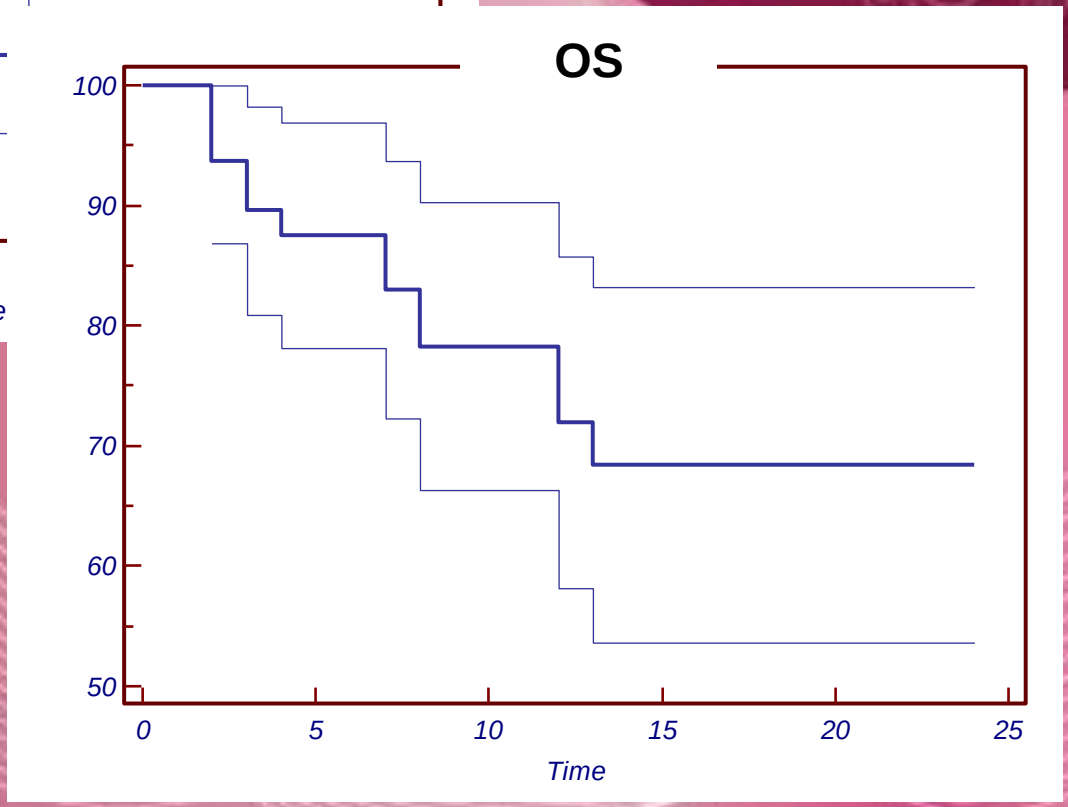

PD; 14,58333
CR; 12,5
SD; 12,5
PR; 60,41667



mTTP: 10.68 mesi

mOS (2y): 21.60

OS: 65.6%



Tossicità

	Pz (n=48)		Somministrazioni (n=762)	
Grado (WHO)	**1-2 (%)**	**3-4 (%)**	**1-2 (%)**	**3-4 (%)**
Leucopenia	**39 (81.25)**	**36 (75)**	251 (32.93)	169 (22.17)
Neutropenia	**34 (70.80)**	**33 (68.75)**	202 (26.50)	158 (20.73)
Trombocitopenia	7 (14.51)	-	102 (13.38)	60 (7.87)
Anemia	28 (58.33)	24 (50)	154 (20.20)	94 (12.33)

	Pz (n=48)		Somministrazioni (n=762)	
Grado (WHO)	**1-2 (%)**	**3-4 (%)**	**1-2 (%)**	**3-4 (%)**
Mucosite	17 (35.41)	10 (20.83)	153 (20.07)	67 (8.7)
Febbre n.n.	3 (6.25)	-		
Neuropatia	19 (39.58)	2 (4.16)	114 (14.96)	154 (20.20)
Alopecia	29 (60.41)		-	
Astenia	27 (56.25)	4 (8.3)	154 (20.20)	42 (5.5)
Nausea/Vomito	17 (35.41)	-	40 (5.2)	-
Onicolisi	16 (33.33)		-	
Edema	15 (31.25)		-	
Reazioni allergiche	6 (12.5)		-	

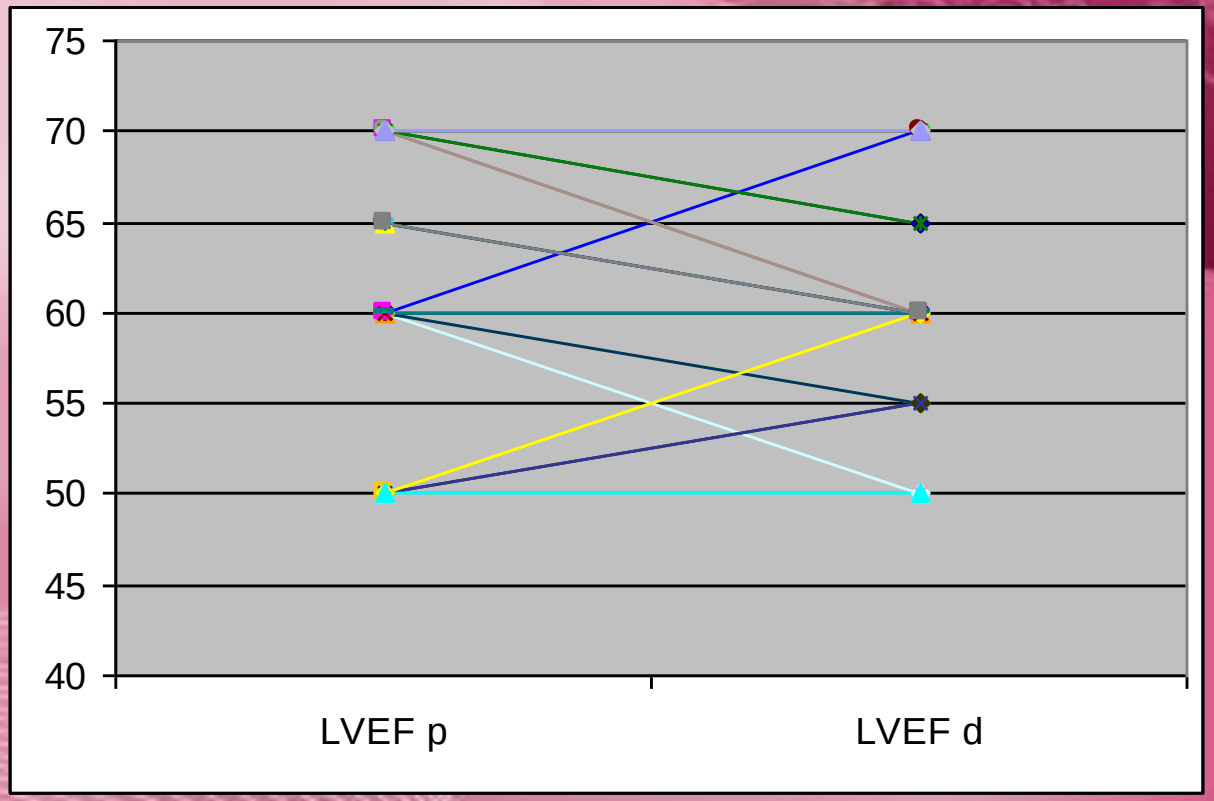
Docetaxel vs Paclitaxel

	Docetaxel		Paclitaxel		*p*
	G1/2	**G3/4**	**G1/2**	**G3/4**	
Onicolisi	-	11 (22.91%)	-	5 (10.41%)	< .0001
Mucosite	9 (18.75%)	6 (12.53%)	8 (16.6%)	4 (8.3%)	< .0001
Neuropatia sensoriale	12 (25%)	5 (10.41%)	7 (14.58%)	5 (10.41%)	< . 001

Dose cumulativa di antracicline ricevuta in adiuvante (adj)

	Pz (n°)	Tot cicli somministrati in adj	Dose cumulativa media
Epirubicina	18	95	340 mg/mq
Doxorubicina	30	159	379 mg/mq
Tot	48		

Cardiotossicità



Riduzione della LVEF: 29.16% dei pazienti (13 pz)

Mai riduzione della LVEF > 10%

Nessuna HFS

HER2(+) vs HER2(-)

Escludendo le 6 pazienti trattate con Herceptin adj:

TTR (23 pz HER2+) vs (19 pz HER2-): 34.2 vs 36.7 mesi (*p ns)*

PRO E CONTRO

PRO

- Significativo beneficio clinico
- Miglioramento del TTP rispetto ai regimi trisettimanali
- Buon profilo di tossicità

CONTRO

- Studio monocentrico
- Trastuzumab ???
- Firma molecolare??
- Topoisomerasi 2α ?
- Costi?
- Continuare a risposta??

Concludendo… (1)

Valutare attentamente:

- il profilo biologico di malattia alla ripresa (identificare eventuali cambiamenti rispetto al primitivo) {stato di HER2, ER,PgR; sede e numero di metastasi}
- i trattamenti giá somministrati in adj
- il tempo trascorso dall'ultimo trattamento adj –neoadj (≤ 12 mesi)
- il PS della paziente e le aspettative della stessa

Concludendo …..(2)

- Considerare rechallenge (ANTRA o TAX) se recidiva > 12 mesi
- Considerare l'utilizzo di combinazioni meno tossiche e farmaci con miglior distribuzione tissutale (LD)
- Attenzione alla dose massima cumulativa
- Il profilo di HER2 non é predittivo di risposta a taxani o antracicline
- Evitare la combinazione di ANTRA con Herceptin; se necessario, eseguire il trattamento sequenziale (programmare ecocardio di rivalutazione sistematica)

Riflessioni per il futuro…

- Utilizzeremo ancora le antracicline, fra alcuni anni?
- Le formulazioni liposomiali potranno sostituire quelle convenzionali?
- K.Pretchard, ASCO 2008,sessione plenaria
  "…quantunque noi del board siamo tutti convinti che, tra qualche anno, l'utilizzo delle antracicline diminuirá drammaticamente, ad oggi, restano la pietra miliare della terapia del BC sia adj che metastatico"

ASCO in pillole…

K.Pretchard, ASCO 2008,sessione plenaria

"…quantunque noi del board siamo tutti convinti che, tra qualche anno, l'utilizzo delle antracicline diminuirá drammaticamente, ad oggi, restano la pietra miliare della terapia del BC sia adj che metastatico"

… 2 ore piú tardi, in sessione plenaria, A.Di Leo

" …ad oggi non conosciamo ancora realmente i fattori predittivi di risposta alle antracicline su cui c'é e ci sará ancora molto da lavorare".

GRAZIE