

# " La terapia neoadiuvante nella neoplasia triple negative "

## CASO CLINICO

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Ospedale Infermi Rimini

Santarcangelo di Romagna

26 giugno 2010



# Caso Clinico



- Età: 59 anni
- Stato menopausale: postmenopausa (54 anni)
- Gravidanze a termine: 4
- Familiarità: 1° grado (madre all'età di 70 anni)
- Anamnesi patologica remota: nulla di rilevante
- Mastoplastica riduttiva bilaterale nel giugno 2006
- Comorbidità: assenti, no farmaci

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## ■ Anamnesi Oncologica:

**Marzo 2009:** accertamenti senologici per mastodinia sinistra. Presenza di addensamento mammario al QE sn con linfonodi palpabili

**Aprile 2009:** Mammografia: distorsione ghiandolare e addensamento al QE sn.  
Adenopatie visibili in regione ascellare

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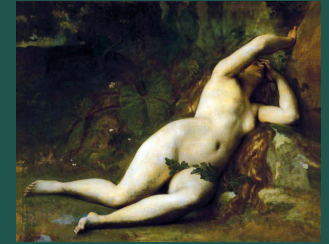


## ■ Anamnesi Oncologica:

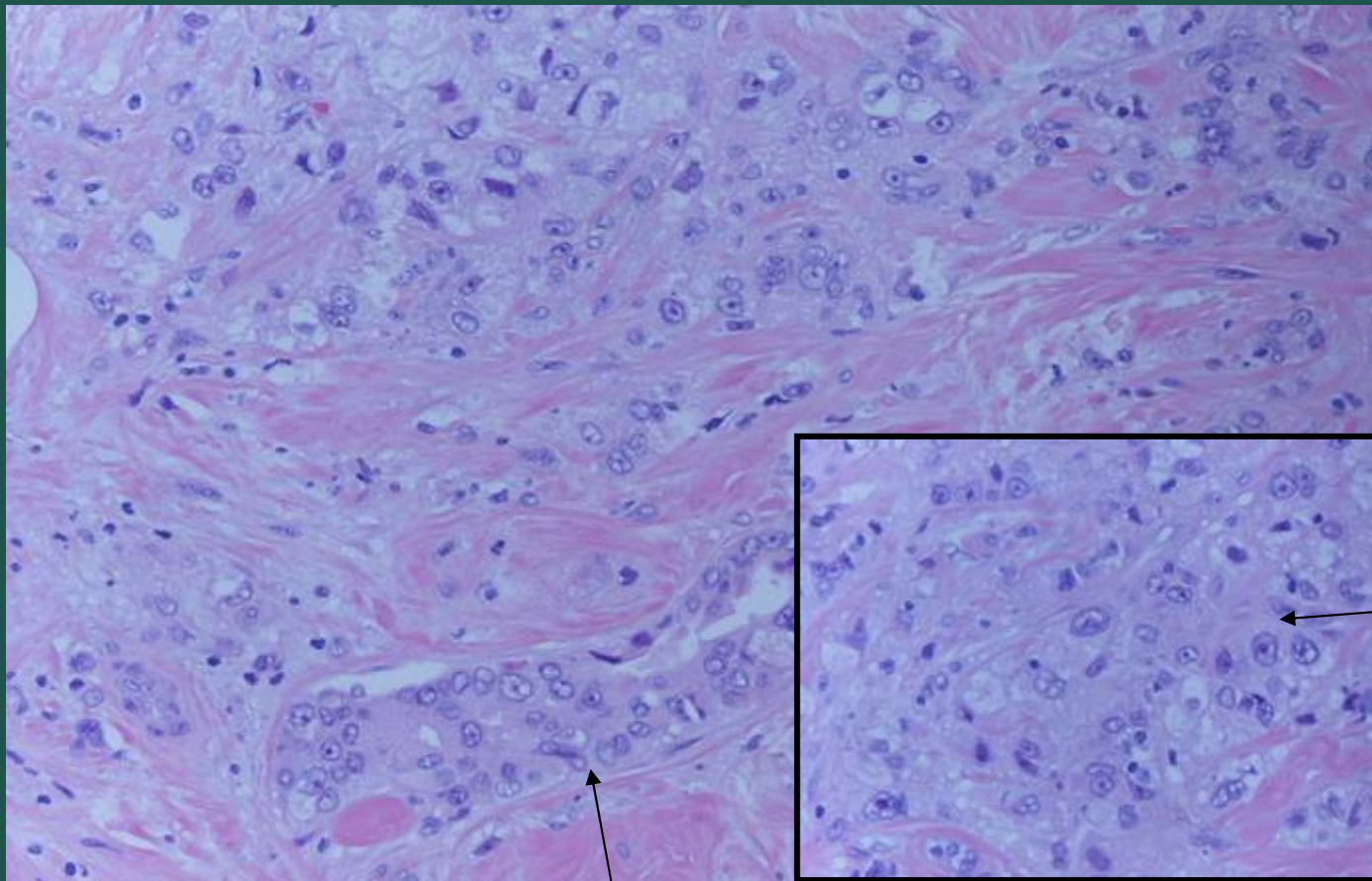
**Maggio 2009:** mammotomia con biopsia e diagnosi di

“ Carcinoma scarsamente differenziato costituito da voluminose cellule a citoplasma a tratti schiumoso. Numerose le mitosi e le immagini di invasione vascolare neoplastica ”

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■ Mammotome: carcinoma mammario scarsamente differenziato



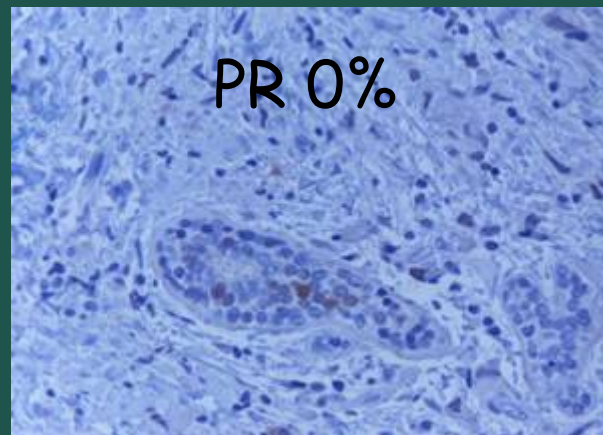
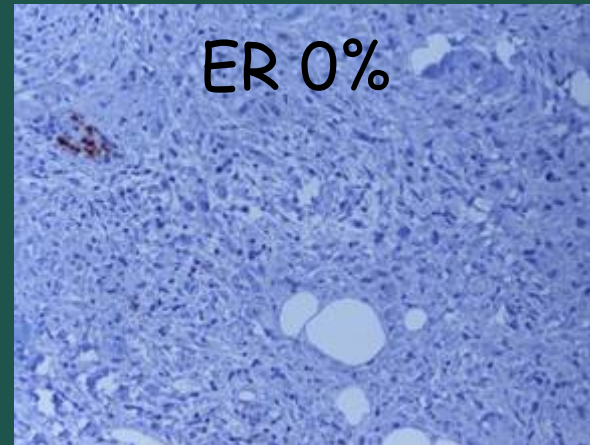
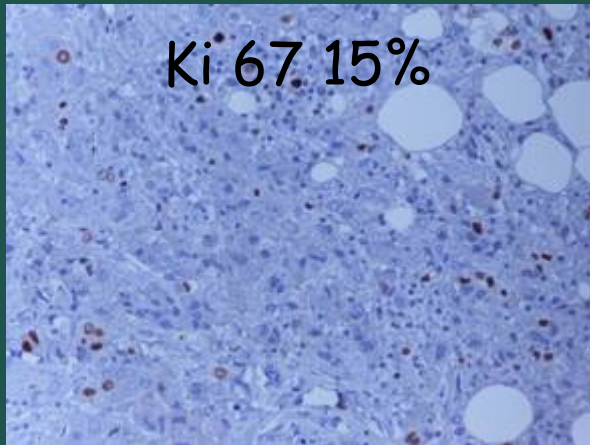
Voluminose  
cellule a  
citoplasma a  
tratti  
schiumoso

Invasione vascolare

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■ Mammotome: caratteristiche biologiche



HER2: assenza di amplificazione (FISH)

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## ■ Valutazione clinica oncologica per terapia primaria

- Neoplasia mammaria localmente avanzata

cT3(13 cm), cN1, M0

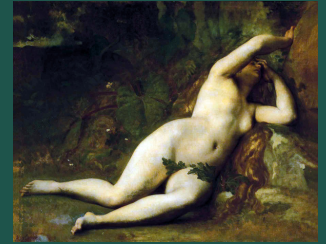
- PET scan: ipercaptazione mammaria sx e ascellare omolaterale.
- RX torace: negativo
- Ecografia addome: negativo

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- Quale scelta terapeutica ?
  - chirurgia
  - chemioterapia neoadiuvante, quali schemi terapeutici:
    - chemioterapia con regimi contenenti antracicline
    - combinazioni antracicline taxani
    - combinazioni contenenti derivati del platino
    - ruolo per terapie infusionali con fluoropirimidine / capecitabina

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## ■ La nostra scelta

*Giugno-Ottobre 2009*: chemioterapia neoadiuvante con schema ECF con programma di inserimento dei taxani in caso di insufficiente risposta dopo 4 cicli

⇒ 6 ECF

Remissione apparente completa clinica con negativizzazione alla PET

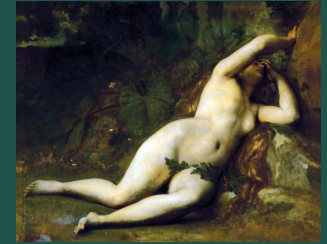
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## ■ Pro e contro la scelta dell'ECF

- Razionale per l'impiego del platino →  
Silver D.P. et al., JCO 2010  
Sirohi B. et al., Annals of Oncology 2008
- Razionale per una terapia infusionale →  
Smith I.E. et al., JCO 1995  
Smith I.E. et al., Annals of Oncology 2004
- Razionale per proseguire con capecitabina →  
Von Minckwitz G. et al., JCO 2010

# Caso Clinico



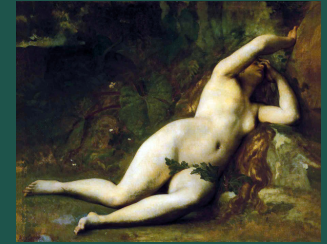
## Efficacy of Neoadjuvant Cisplatin in Triple-Negative Breast Cancer

*Daniel P. Silver, Andrea L. Richardson, Aron C. Eklund, Zhigang C. Wang, Zoltan Szallasi, Qiyuan Li, Nicolai Juul, Chee-Onn Leong, Diana Calogrias, Ayodele Buraimoh, Aquila Fatima, Rebecca S. Gelman, Paula D. Ryan, Nadine M. Tung, Arcangela De Nicolo, Shridar Ganesan, Alexander Miron, Christian Colin, Dennis C. Sgroi, Leif W. Ellisen, Eric P. Winer, and Judy E. Garber*

- Trial fase II, 28 pz., 4 CDDP 75 mg/mq ogni 21 giorni  
pCR 22% , Risposta Clinica 64 %

**Fattori predittivi di risposta al CDDP:** età giovane,  
bassa espressione BRCA1 mRNA, metilazione promotore  
BRCA1, mutazioni nonsense p53

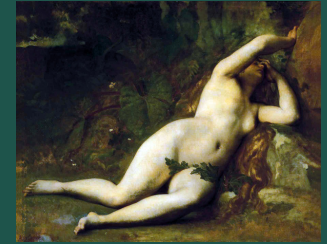
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## Fattori predittivi di risposta al trattamento:

Covariate	Miller-Payne 3,4,5 Responses			pCR		Clinical Response (CR and PR)	
	No. of Patients	Observed (%)	P*	Observed (%)	P*	Observed (%)	P*
All	28	50	—	21	—	64	—
Age, years			.001†		.13†		.46†
29-41 (Q1)	7	86		29		71	
42-49 (Q2)	7	71		43		71	
50-59 (Q3)	8	38		13		63	
60-69 (Q4)	6	0		0		50	
Tumor size, cm (by MRI)			.75†		.48†		.83†
Unknown	1	—		—		—	
2.0-2.7 (Q1)	6	50		17		67	
2.8-3.7 (Q2)	7	29		14		57	
3.8-4.5 (Q3)	8	88		25		75	
4.6-7.0 (Q4)	6	33		33		50	
Lymph nodes			1.00‡		1.00‡		.43‡
Negative	15	53		20		73	
Positive	13	46		23		54	
BRCA1 mRNA levels, arbitrary relative units			.03†		.79†		.65†
Unknown/NA	7	57		42		71	
0.00-0.03 (Q1)	5	100		0		80	
0.04-0.23 (Q2)	6	33		33		50	
0.25-0.44 (Q3)	5	40		0		60	
0.57-3.69 (Q4)	5	20		20		60	
BRCA1 methylation			.04‡		1.00‡		.40‡
Unknown/NA	5	80		60		80	
Negative	15	27		13		53	
Positive	8	75		13		75	
ΔNp63/TAp73 ratio			.39‡		.26‡		.66‡
Unknown	6	50		33		67	
> 2	9	67		33		56	
< 2	13	38		8		69	
Type of p53 mutation			.03‡		.78‡		.09‡
Unknown	6	50		33		67	
MSM	10	30		10		60	
NSM	6	100	.01§	33	1.00§	100	.23§
wt	6	33	.64¶	17	1.00¶	33	.14¶

# Caso Clinico



## Platinum-based chemotherapy in triple-negative breast cancer

B. Sirohi<sup>†</sup>, M. Arnedos, S. Popat, S. Ashley, A. Nerurkar, G. Walsh, S. Johnston & I. E. Smith\*

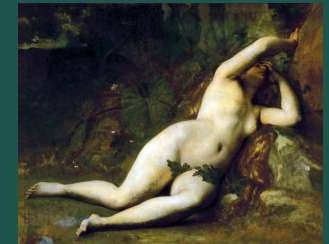
	Neo-adjuvant		P value
	Triple negative (N = 17)	Not triple negative (N = 77)	
Response rate			
CR	15 (88%)	39 (51%)	0.005 <sup>a</sup>
PR	2 (12%)	33 (43%)	
PD	0	5 (6%)	
Number of patients who underwent surgery	6 (35%)	54 (70%)	0.007
Path CR	1/6 (17%)	5/54 (9%)	0.5
Number relapsed	12 (71%)	51 (66%)	0.6
Pattern of recurrence			
Local	4 (24%)	16 (21%)	
Distant	7 (41%)	31 (40%)	0.9
Contralateral	1 (6%)	4 (5%)	
No recurrence	5 (29%)	26 (34%)	
Median OS (95% CI)	Undefined	Undefined	0.4
Median DFS (95% CI)	68 months (14–122)	90 months (56–123)	0.6

541 pz.  
↙ ↘  
ECF MVP

■ I regimi a base di platino aumentano RR

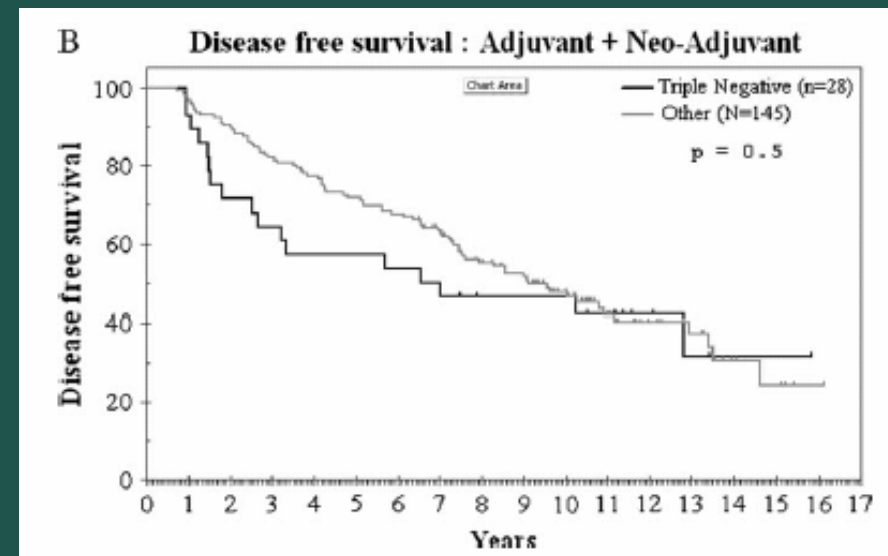
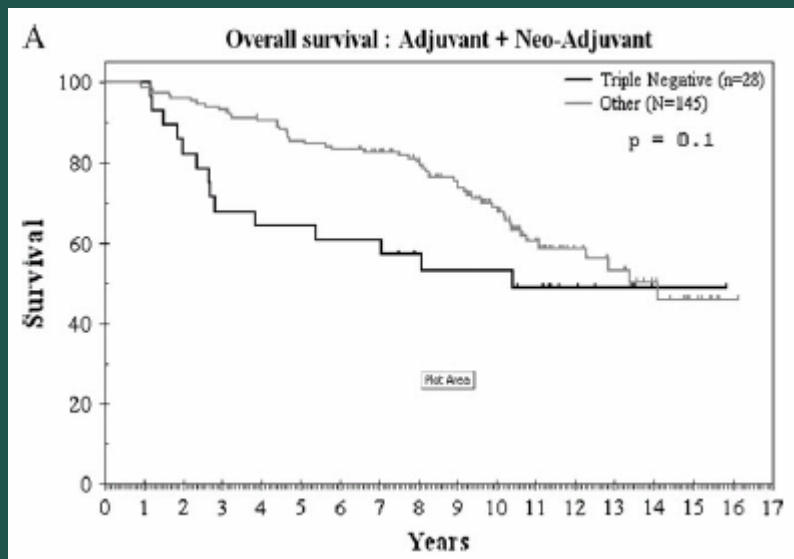
Annals of Oncology 2008

# Caso Clinico



## Platinum-based chemotherapy in triple-negative breast cancer

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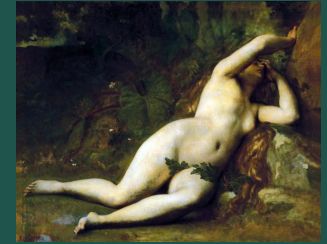


OS 5 ys: 64 % TN vs 85 % NTN

DFS 5 ys: 57 % TN vs 72 % NTN

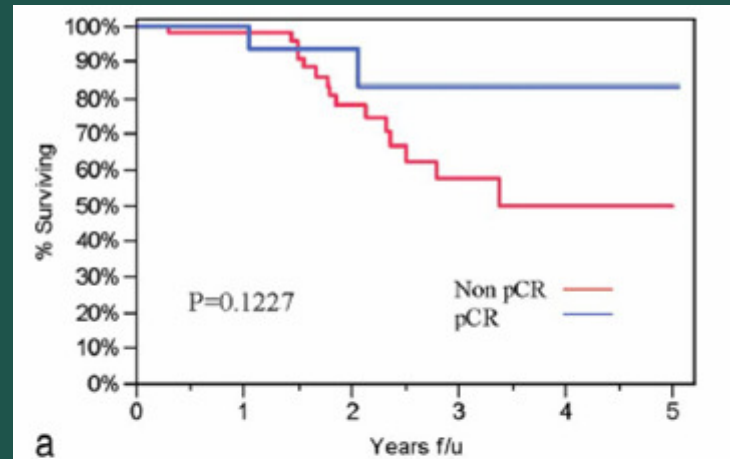
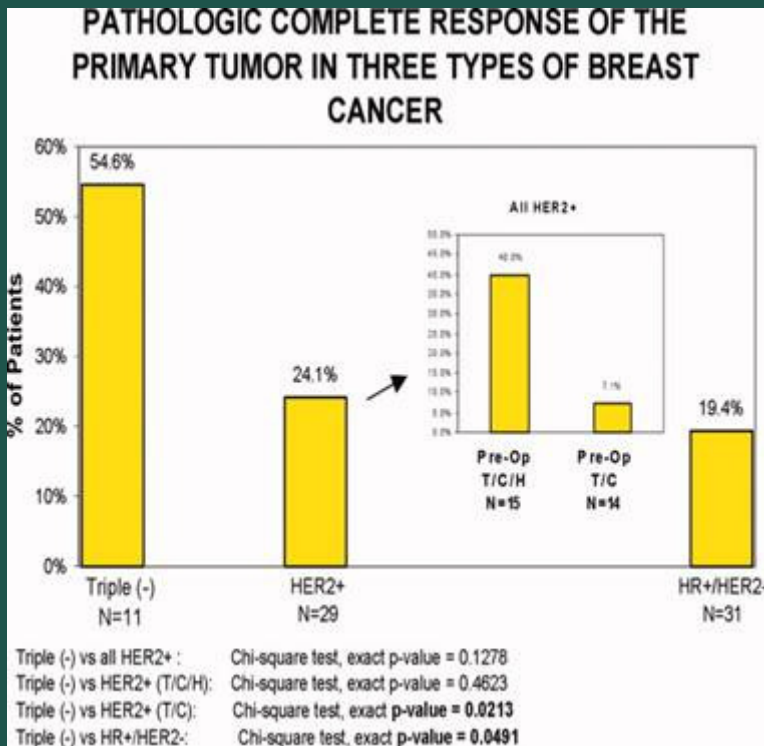
📊 Trend vs peggiore OS in EBC

# Caso Clinico



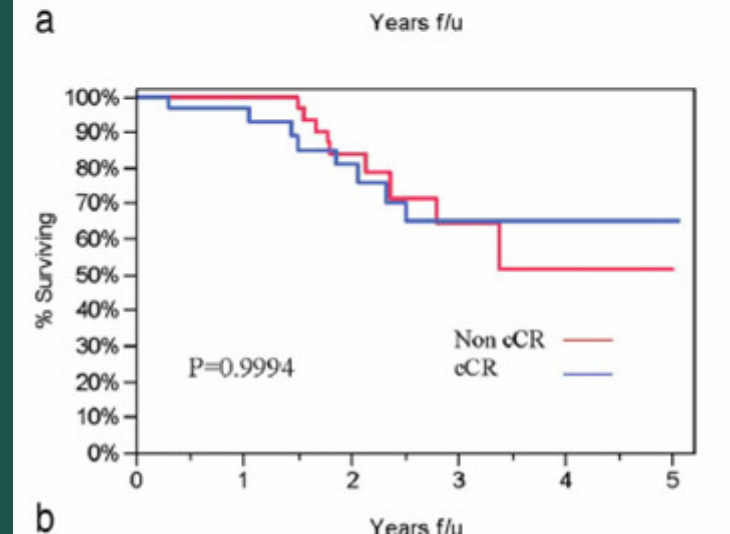
■ Carboplatino + Docetaxel : alti tassi pCR e RFS a 3 ys

- 74 pz., 4 cicli



pCR 83,3 %

Non pCR 58 %

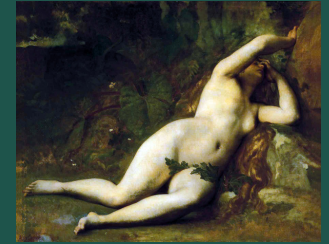


cCR 65 %

Non cCr 64,3 %

R. Chang et al., Cancer 2010

# Caso Clinico

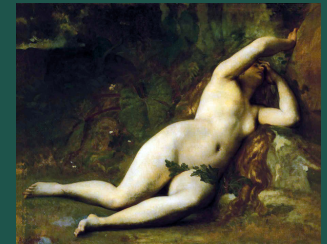


## High Complete Remission Rates With Primary Neoadjuvant Infusional Chemotherapy for Large Early Breast Cancer

By I.E. Smith, G. Walsh, A. Jones, J. Prendiville, S. Johnston, B. Gusterson, F. Ramage, H. Robertshaw, N. Sacks, S. Ebbs, J.A. McKinna, and M. Baum

- 50 pz., diametro tumorale mediano 6 cm. (range 3-12), 8 ECF
  - ORR 49 pz. (98 %), CRR 33 pz. (66 %), 3 pz (6 %) mastectomia
  - Cellularità tumorale ridotta nell' 81% delle pz. con ECF vs 36% con CMF o MMM ( $p < 0.02$ )
- ORR: 98 % ECF vs 70 - 80 % CMF - MMM**
- CRR: 66 % ECF vs 17 % CMF - MMM**

# Caso Clinico



## A novel continuous infusional 5-fluorouracil-based chemotherapy regimen compared with conventional chemotherapy in the neo-adjuvant treatment of early breast cancer: 5 year results of the TOPIC trial

Table 2. Response, axillary node involvement, relapse-free survival and overall survival

	AC (n = 215), %	Inf ECisF (n = 211), %	P value
Overall response	75	77	0.6 NS
Clinical CR	31	34	0.5 NS
PathCR	16	16	1.0
PathCR + residual DCIS	25	24	0.9
MR	17	16	1.0
NC	6	6	1.0
PD	2	1	0.7
Axillary node involvement	50	51	0.8
Survival (5 year median)	74	82	0.18
RFS (5 year median)	63	62	0.77

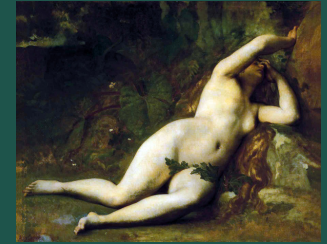
AC, doxorubicin and cyclophosphamide; CR, complete response; PathCR, pathological complete remission; DCIS, ductal carcinoma *in situ*; Inf ECisF, continuous infusional 5-fluorouracil with conventional cisplatin and epirubicin; MR, minor response; NC, no change; PD, progressive disease; RFS, relapse-free survival; NS, not significant.

426 pz., 6 cicli

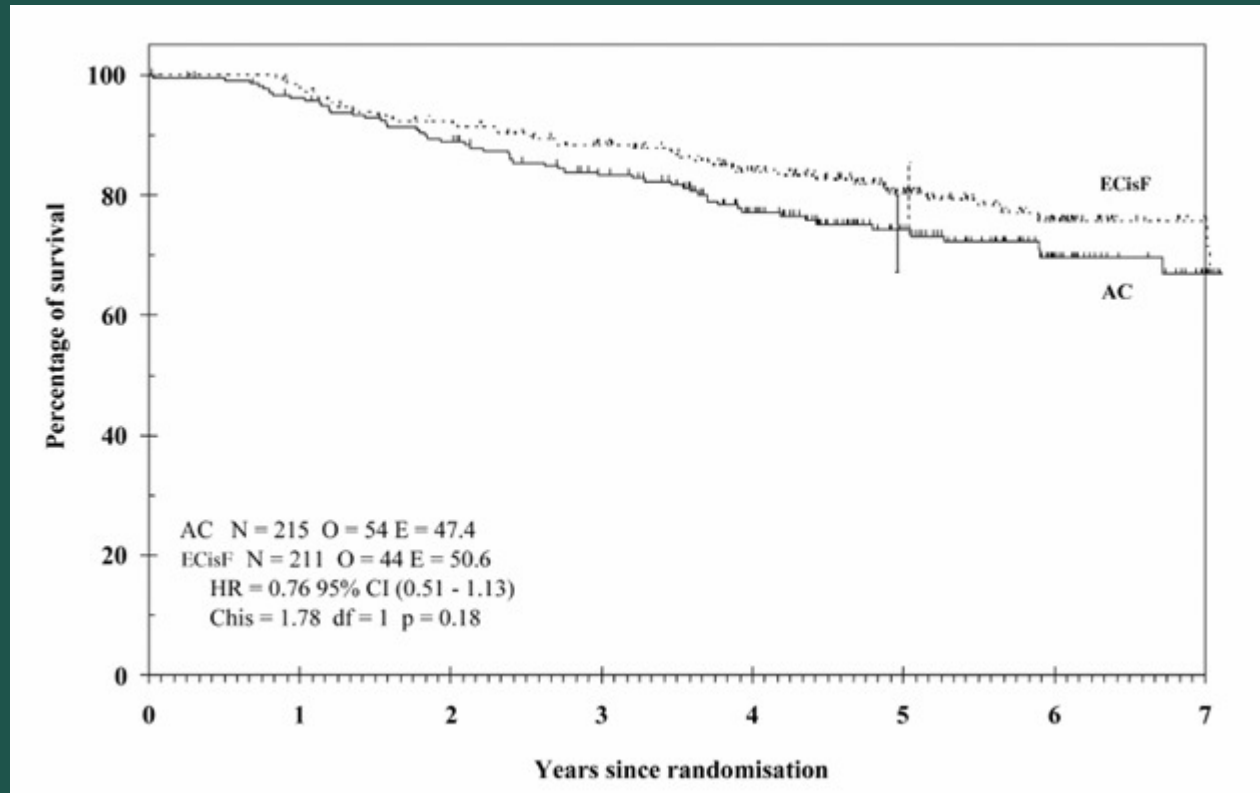
Smith I.E., et al.

Annals of Oncology 2004

# Caso Clinico



## TOPIC trial



OS 5 years:

➔ AC 74 %

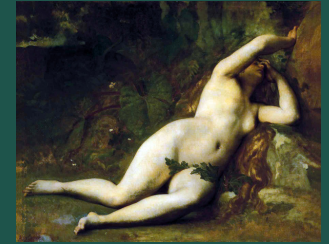
➔ ECF 82 %

P 0.18

Trend NS di aumentata sopravvivenza a favore di ECF

Smith I.E., et al. Annals of Oncology 2004

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" Tailored preoperative treatment of locally advanced triple negative breast cancer with epirubicin, cisplatin, and infusional fluorouracil followed by weekly paclitaxel "

- 30 pz., T2-T3, N0-3, ER/PR < 10 % , HER2 -
- Neoadiuvante: 4 ECF → 3 Paclitaxel sett.
- Adiuvante: CM metronomico
- End point primario: pCR. Secondari: CR, PR

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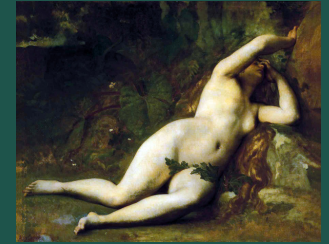
" Tailored preoperative treatment of locally advanced triple negative breast cancer with epirubicin, cisplatin, and infusional fluorouracil followed by weekly paclitaxel "

■ Risultati: pCR 12 pz. (40%)

OR 26 pz. (86%); PR 20 pz. (66%)

■ Conclusioni: ECF → Paclitaxel ha indotto un alto tasso di pCR e di negativizzazione dei linfonodi ascellari (80%)

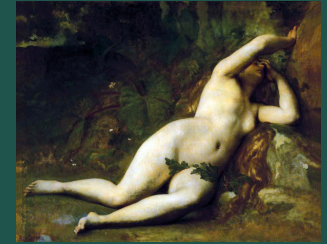
# Caso Clinico



“ Infusional fluorouracil, epirubicin and cisplatin followed by weekly paclitaxel plus bevacizumab in locally advanced breast cancer with unfavorable prognostic features”

- 30 pz cT2-4c, cN0-2, ER e PR < 10 % ; cT4d, ER e PR 0 %
- 4 ECF → 3 paclitaxel/weekly + bevacizumab
- OR 26 pz (87 %); SD 2 pz (7%); PD 2 pz (7 %)
- pCR 10 pz (33 %)

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VOLUME 28 · NUMBER 12 · APRIL 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

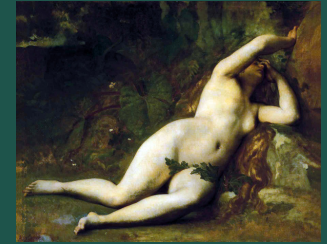
## Capecitabine in Addition to Anthracycline- and Taxane-Based Neoadjuvant Treatment in Patients With Primary Breast Cancer: Phase III GeparQuattro Study

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■ 1509 pz

■ 4 EC {  
4 docetaxel  
4 docetaxel + capecitabina  
4 docetaxel → capecitabina

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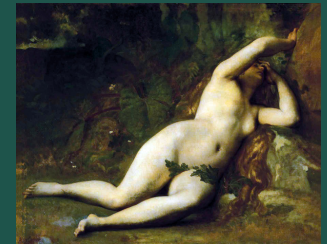
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- Risultati: pCR docetaxel 22,3 %  
docetaxel + capecitabina 19,5 %  
docetaxel → capecitabina 22,3 %

**Conclusioni:** la capecitabina concomitante o sequenziale ai regimi contenenti antracicline e taxani non ha riportato un beneficio maggiore in termini di pCR.

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## ■ CHT neoadiuvante; pCR % TNBC vs non-TN

	Year	Detection method	Regimen	No. of TNBC pts	TNBC pCR (%)	Non-TNBC pCR (%)
<b>Anthracycline</b>						
Le Toumeau et al. <sup>21</sup>	2007	IHC	Overall	96	29	13
			- Intensified FAC	- 56	- 47	
			- FEC	- 40	- 13	
Bidard et al. <sup>22</sup>	2008	IHC	FAC or FEC	120	17	4
<b>Anthracycline/taxane</b>						
Rouzier et al. <sup>23</sup>	2005	Molecular	T-FAC	22	45	18
Fernandez-Morales et al. <sup>24</sup>	2006	IHC	Anthracycline + taxane	23	39	12
Carey et al. <sup>20</sup>	2007	IHC	AC +/- taxane	34	27	11
Keam et al. <sup>25</sup>	2007	IHC	Docetaxel + Doxorubicin	47	17	3
Liedtke et al. <sup>3</sup>	2008	IHC	Overall	255	22	11
			- FAC/FEC/AC	- 70	- 20	
			- T-FAC/T-FEC	- 125	- 28	
			- Single agent taxane	- 17	- 12	
			- Other	- 43	- 14	
Esseman et al. <sup>26</sup>	2009	Molecular	AC → Paclitaxel	45	34	21
Wang et al. <sup>27</sup>	2009	IHC	Anthracycline + taxane	21	38	12
Straver et al. <sup>28</sup>	2009	Molecular	AC, or AT, or T/Capecitabine	38	34	12
<b>Platinum</b>						
Garber et al. <sup>29</sup>	2006	IHC	Cisplatin	22	23	n/ap
Sikov et al. <sup>30</sup>	2007	IHC	Carboplatin + paclitaxel	12	67	39
Torrise et al. <sup>4,31</sup>	2008	IHC	E/Cis/F → Paclitaxel	30	40	n/ap
Sirohi et al. <sup>32</sup>	2008	IHC	E/Cis/F	28	88 <sup>b</sup>	51 <sup>b</sup>
Leone et al. <sup>33</sup>	2009	IHC	Platinum + docetaxel +/- AC	125	34	n/av
Byrski et al. <sup>4,34</sup>	2009	IHC	Cisplatin	10	90	n/ap
<b>Other</b>						
Roche et al. <sup>35</sup>	2006	IHC	Ixabepilone	42	19	8%

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## ■ CHT NEOADIUVANTE: risultati

### ■ pCR by genic profile

### ■ 82 pz trattate in neoadiuvante con taxolo, doxorubicina, 5FU e Ciclofosfamide

	Classe molecolare				p-value
	Luminal (n=30)	Normal-like (n=10)	erbB2 (n=20)	Basal-like (n=22)	
ER+	30 (100%)	6 (60%)	11 (55%)	1 (5%)	<.001
HER2 +	1 (3%)	1 (10%)	16 (80%)	3 (14%)	<.001
Alto grado nucleare	11 (37%)	3 (30%)	16 (80%)	20 (91%)	<.001
pRC No	28 [93%(78-99)]	10 100%(29-100)]	11 [55%(32-77)]	12 [55%(32-76)]	
pRC Sì	2 [7%(1-22)]	0 [0%(0-31)]	9 [45%(23-68)]	10 [45%(24-68)]	<.001

La malattia con maggiore probabilità di risposta alla tp neoadiuvante è quella endocrino non responsiva

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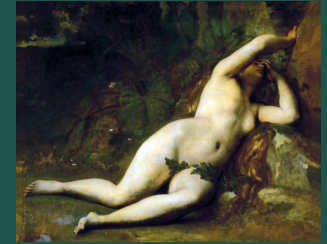
## Response to neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients

Response	No.	%
<b>Clinical response</b>		
Complete response	9	90
Partial response	1	10
No change	0	0
Progressive disease	0	0
<b>Pathologic response</b>		
Complete pathologic response	9	90
Partial response	1	10
No response	0	0
<b>Residual disease in breast</b>		
None	10	100
<1 cm	0	0
1-3 cm	0	0
4-9 cm	0	0
>9 cm	0	0
<b>Number of lymph nodes positive</b>		
0	9	90
1-3	1	10
4-9	0	0
>9	0	0

10 pz.

4 CDDP 75mg/mq

# Caso Clinico



## Efficacy of ixabepilone in ER/PR/HER2-negative (triple-negative) breast cancer

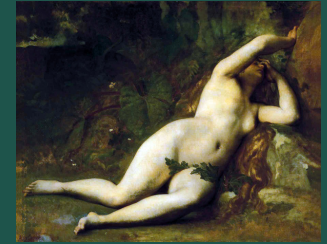
Edith A. Perez • Tejal Patel • Alvaro Moreno-Aspitia

Population	ER/PR/HER2-negative tumors (N = 42)	Non-ER/PR/HER2-negative tumors (N = 119)
Breast cancer $\geq 3$ cm not amenable to primary BCS	ORR <sup>b</sup> : 64%	ORR <sup>b</sup> : 60%
	pCR <sub>B</sub> : 26%	pCR <sub>B</sub> : 15%
	pCR <sub>BL</sub> : 19%	pCR <sub>BL</sub> : 8%

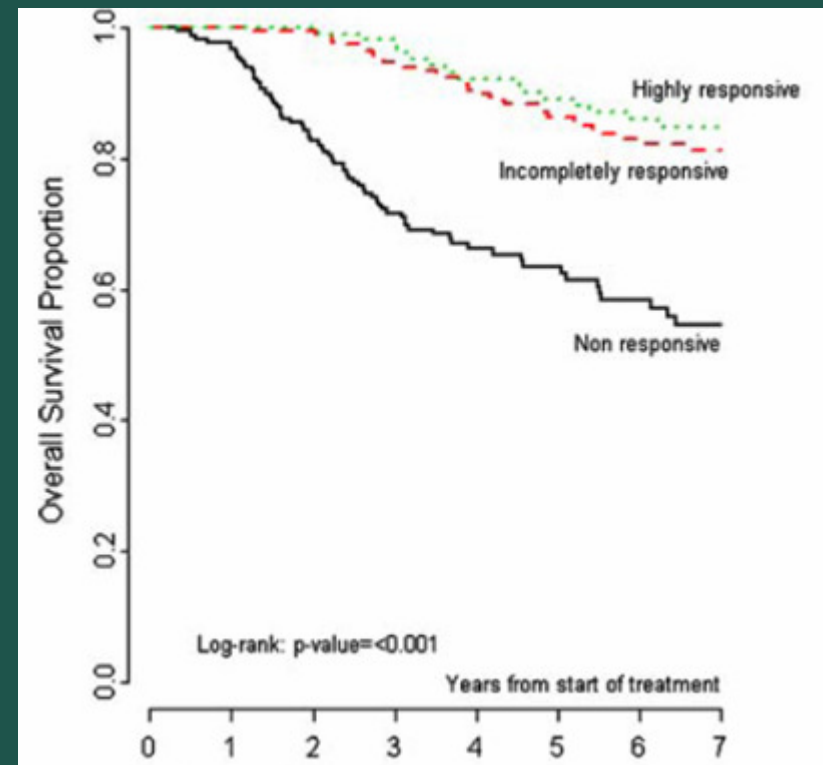
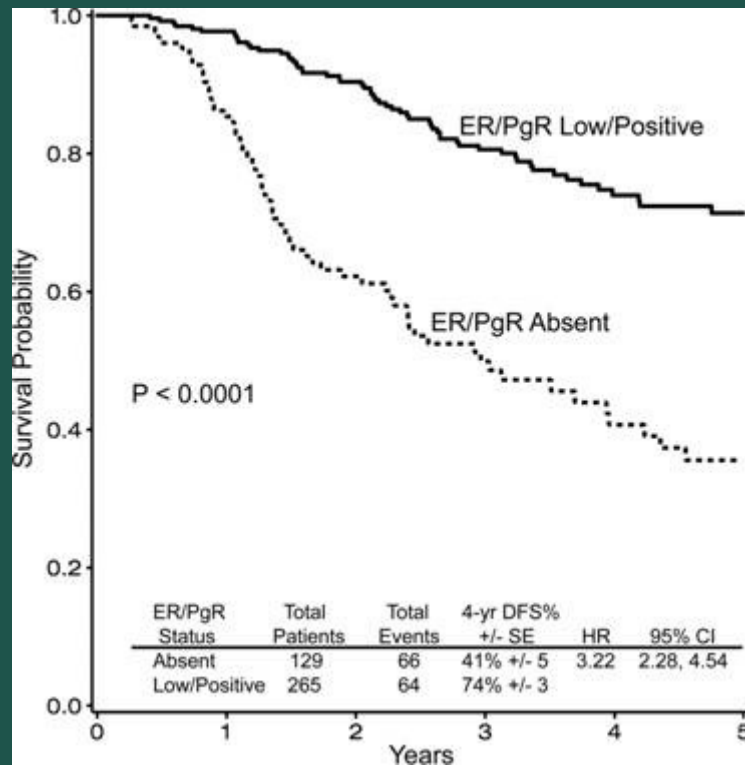
- Trial fase II, 40 mg./mq. ogni 21 giorni, 4 cicli
- pCR 26 % TN vs 15 % NTN

Breast Cancer Res. Treat. 2010

# Caso Clinico



## ■ OS by hormonal status



N 399; pCR ER+ 7.5%, ER – 33.3%  
P 0.0001

Colleoni M., Clin Cancer Res 2004

N 533 pz; pCR ER+ 0%, ER – 17.7%  
P < 0.001

Colleoni M., Breast Cancer Res Treat 2008

# Caso Clinico

risultati patologici



- **Novembre 2009** : quadrantectomia sn con diagnosi di "CDI, ypT2 ( 3 cm ), ypN1a ( 3/8 ), Mx."

**Biologia:**

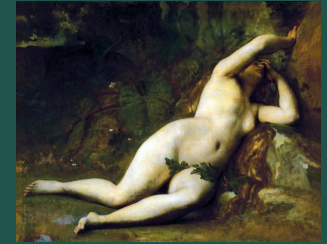
Grading: G3

IV: presenti e multiple

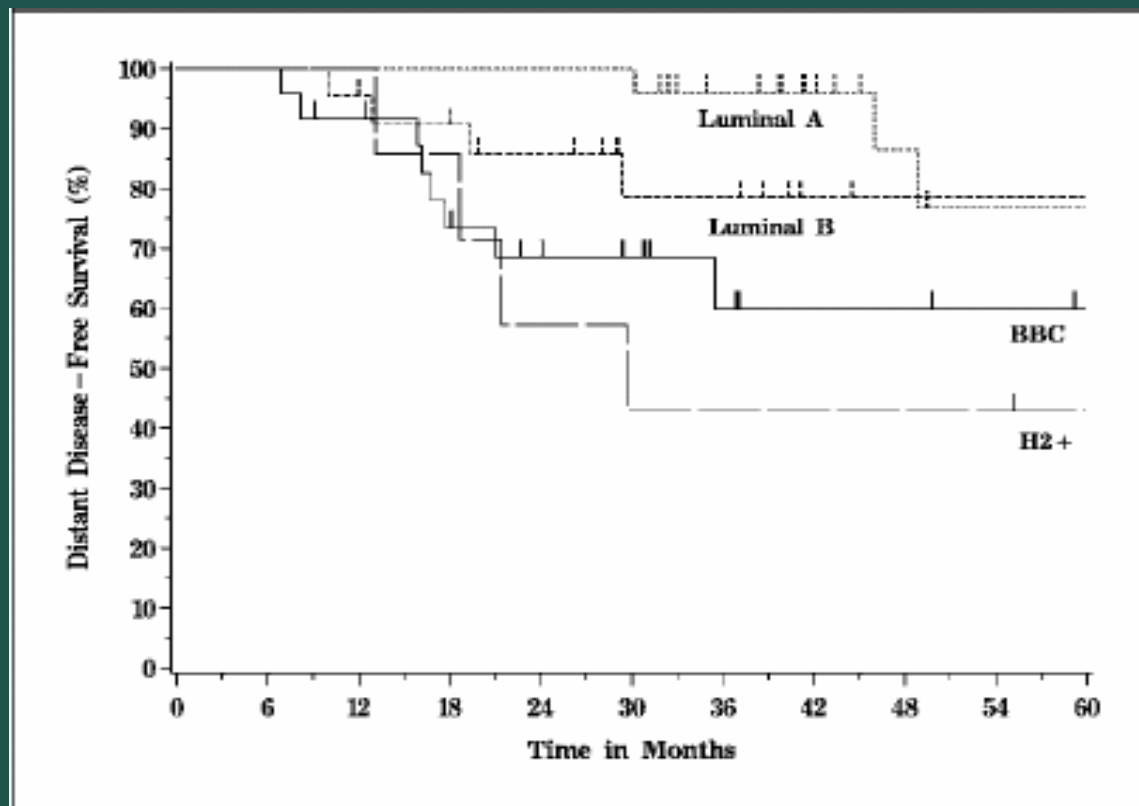
Ki67: 20 %

ER: 0 %; PR: 0 %; HER2: FISH assenza di amplificazione

# Caso Clinico



"The Triple Negative Paradox: primary tumor chemosensitivity of breast cancer subtypes "



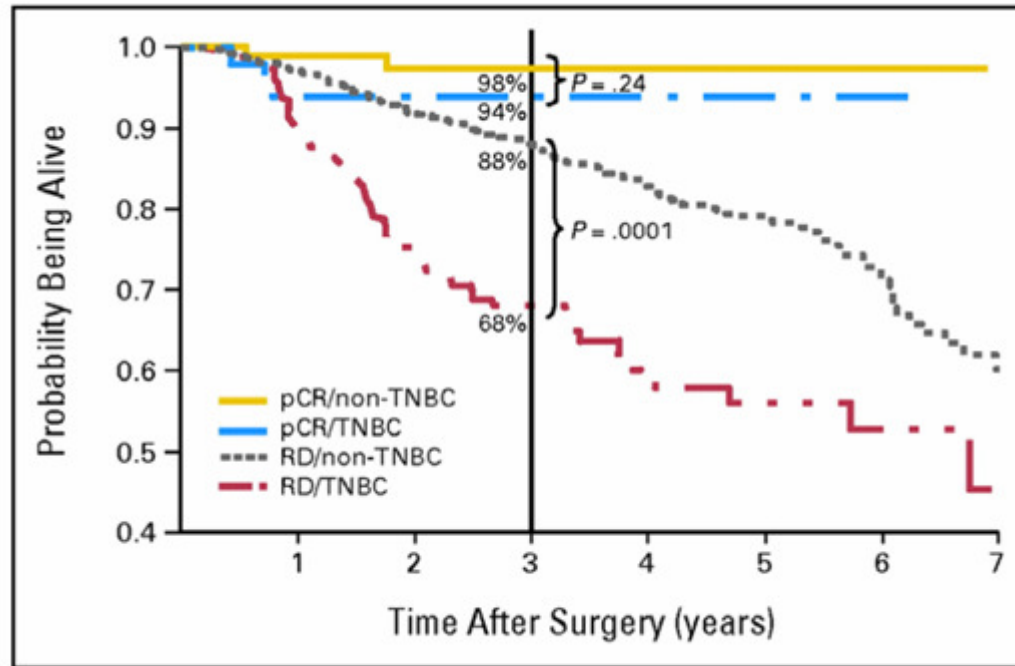
- DDFS nelle pz con residuo. Peggior prognosi nelle HER2 + e BBC

# Caso Clinico



## ■ TERAPIA NEOADIUVANTE

## ■ OS by pCR status in TN patients

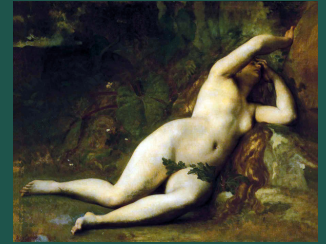


Liedtke, C. et al. J Clin Oncol; 26:1275-1281 2008

■ pCR → buona prognosi

■ RD → prognosi infausta specialmente se TN

# Caso Clinico



## ■ Terapia adiuvante?

Opzioni:

- niente
- Taxani
- CMF
- CM metronomico
- RT locoregionale

# Caso Clinico



■ La scelta terapeutica concordata con la paziente

- CM metronomico e radioterapia locoregionale
- A breve distanza dall'inizio del CM e alla rivalutazione clinica in corso di RT evidenza di progressione di malattia con comparsa di noduli cutanei con aspetti linfangitici

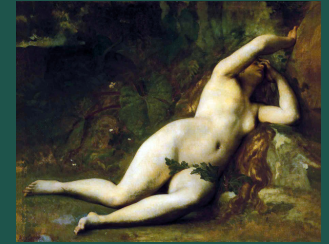
# Caso Clinico



■ Scelta della terapia alla progressione:

- Taxolo + Bevacizumab

# Conclusioni neoadiuvante TNBC



- Quale trattamento ottimale: schema e schedula ?
- Quale ruolo per i regimi con Platino ?

**Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006**

*Kaufmann M., et al. Annals of Oncology 2007*

**Neoadjuvant chemotherapy for “Triple Negative” breast cancer: a review of current practice and future outlook**

*Zeina N., Med. Oncol. 2010*

