

(CONFRONTO SULLE PROPOSTE PER IL
TRATTAMENTO DEL CARCINOMA TRIPLO NEGATIVO)

TUMORE TRIPLO NEGATIVO: UNA MALATTIA?

Ornella Garrone, Michela Donadio

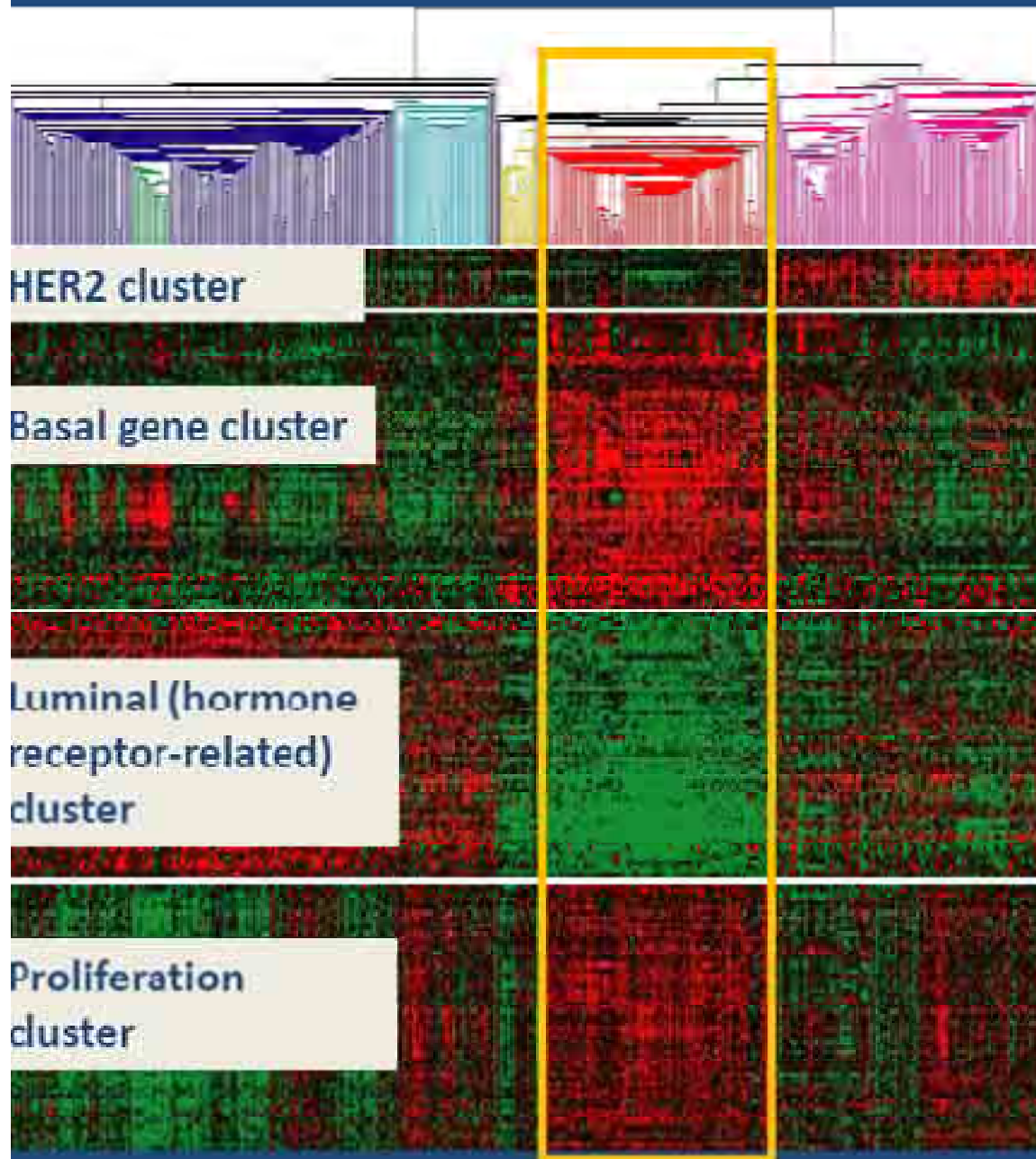
ASO S. Croce e Carle Cuneo

Ospedale S. Giovanni Battista Torino

TRIPLE NEGATIVE: Definition and Clinical Features

- \approx 15% of invasive cancer
- Immunohistochemically negative for ER and PgR
- Lack of overexpression or amplification of the HER 2 gene
- Lack of targeted therapies
- Immunohistochemical surrogate of basal like breast cancer

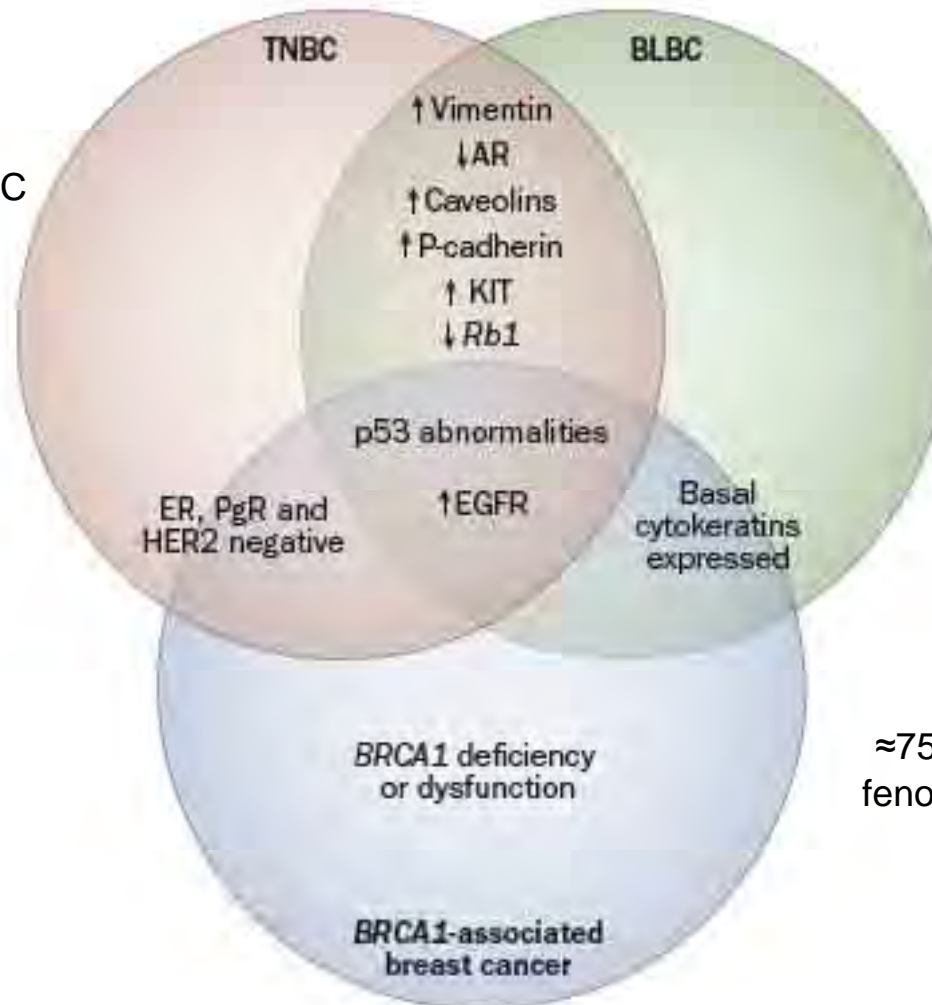
The Picture of Basal-like Breast Cancer



- Low ER (and related genes) expression
- Low HER2 cluster expression
→ usually “triple negative”
- High basal cluster
 - basal cytokeratins
 - EGFR
 - c-kit
 - others...
- Very proliferative
- Often p53 mutant
- Evidence of genomic instability

Concordanza BLBC e TNBC $\approx 75\%$

$\approx 10-35\%$ TN non BLBC
 $\approx 40-80\%$ TN esprime
marcatori basali



$\approx 45\%$ BLBC non TN

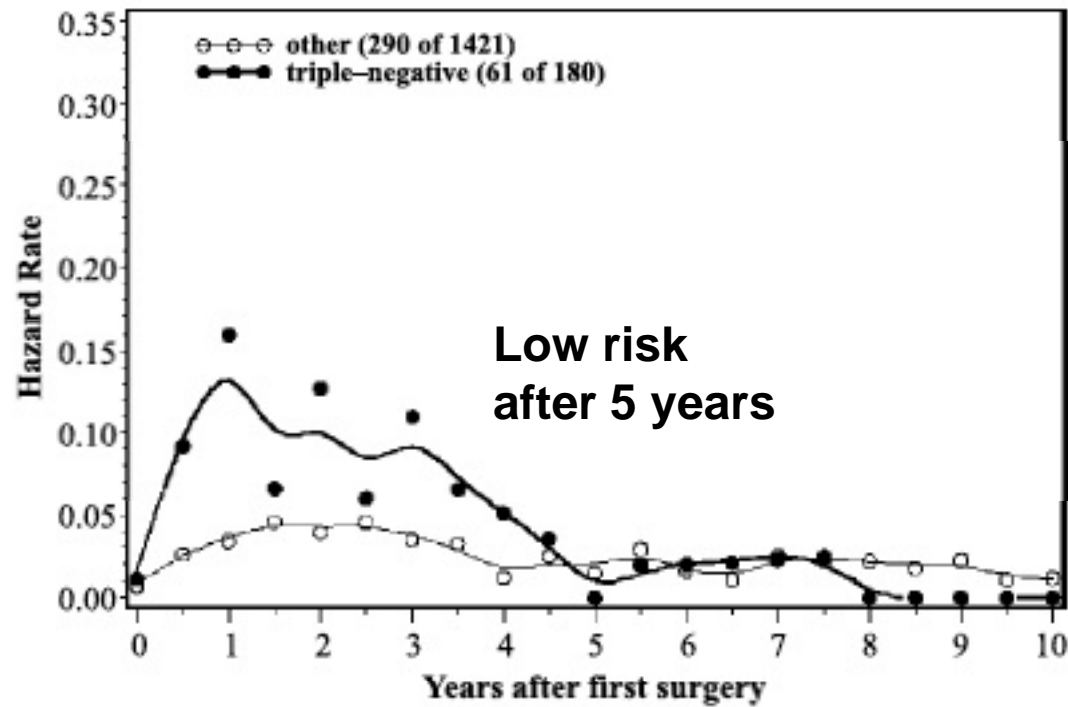
$\approx 75\%$ dei tumori hanno
fenotipo TN o BL

TNBC epidemiology

Key points

Younger patients
Premenopausal
Increased body weight
African Americans
Advanced stage
High grade

Triple negative behavior



Risk of relaps over time

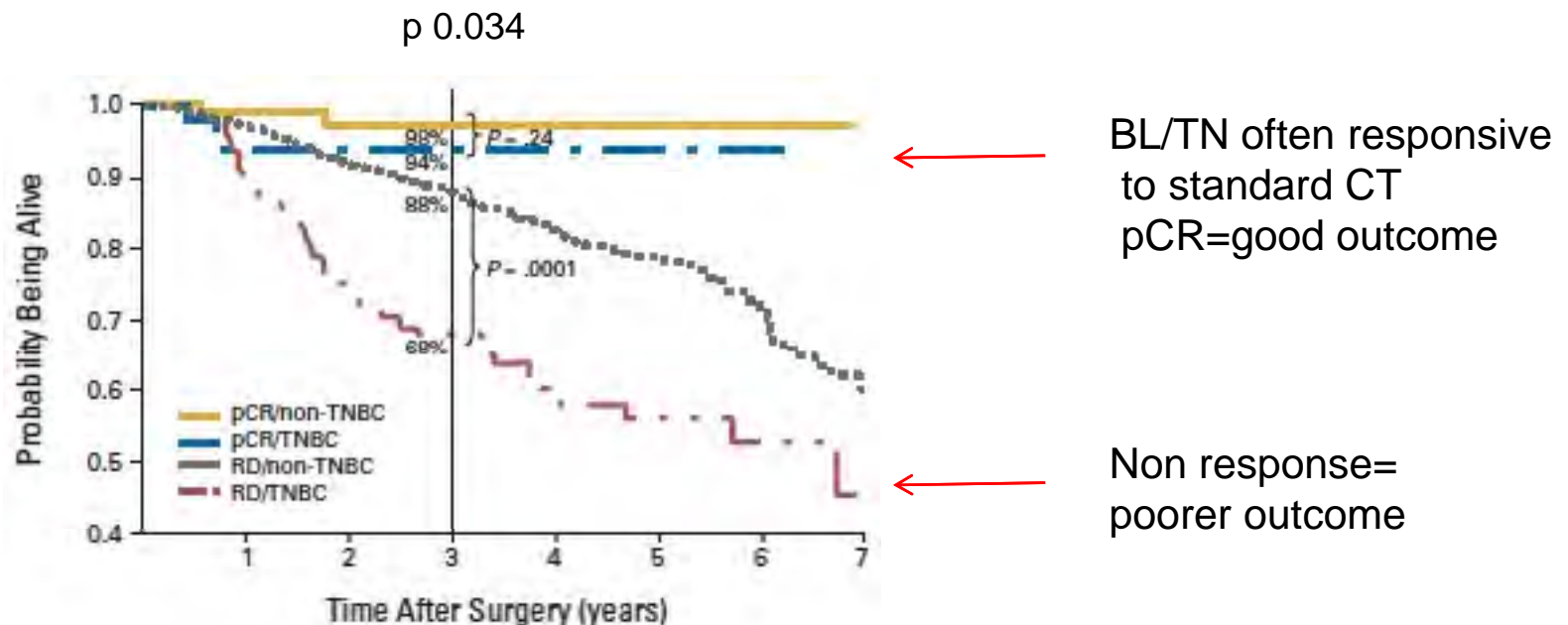
Triple negative behavior

Sites	N	Bone	Soft tissue	Viscera*
TNBC	79	13%	13%	74%
ER+	123	39%	7%	54%
HER2+	78	7%	12%	81%

* Lung (40%), Brain (30%), Liver (20%)

Triple negative paradox

Regimen	TNBCC	Non-TNBCC
FAC/FEC/AC (308)	20%	5%
TFAC/TFEC (588)	28%	17%
Taxanes (58)	12%	2%
Other (164)	14%	7%
Total (1118)	22%	11%



Platinum-Based Chemotherapy: Rationale

Triple negative disease
(≈20% of breast cancer cases)



Basal-like phenotype
(50-80% of triple negative)



BRCA 1 loss-of-function
(≈80% of basal-like)

Mechanisms of DNA Repair

Environmental factors
(UV, radiation, chemicals)

Normal physiology
(DNA replication, ROS)

Chemotherapy
(alkylating agents, antimetabolites)

Radiotherapy

DNA DAMAGE



---> **Cell Death**

MAJOR DNA REPAIR PATHWAYS

Single Strand Breaks

- Nucleotide excision repair
- Base excision repair
 - PARP1

Replication Lesions

- Base excision repair
 - PARP1

Double Strand Breaks

- Non-homologous end-joining
- Homologous recombination
 - BRCA1/BRCA2
- Fanconi anemia pathway
- Endonuclease-mediated repair

DNA Adducts/Base Damage

- Alkyltransferases
- Nucleotide excision repair
- Base excision repair
 - PARP1

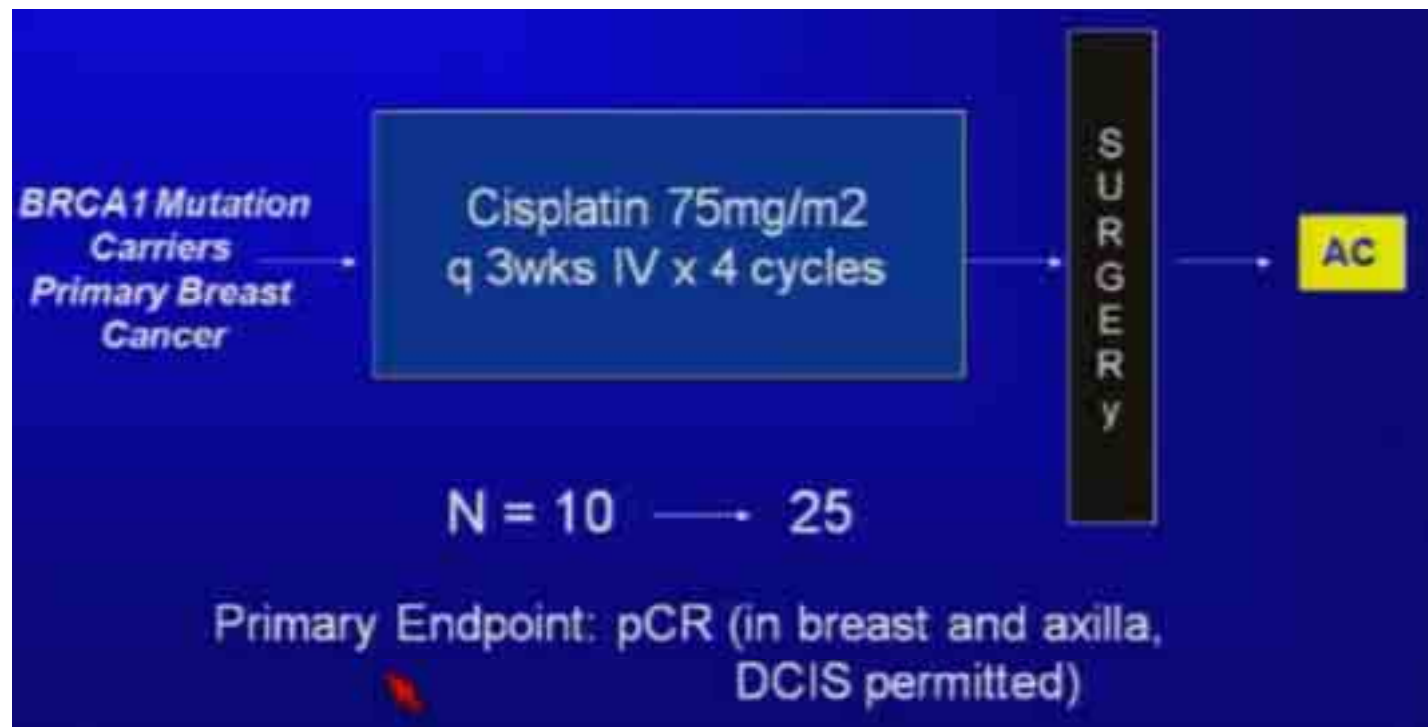
28 stage II-III TNBC; CDDP 75 mg/m² for 4 cycles every 3 weeks
pCR 22%

B

5

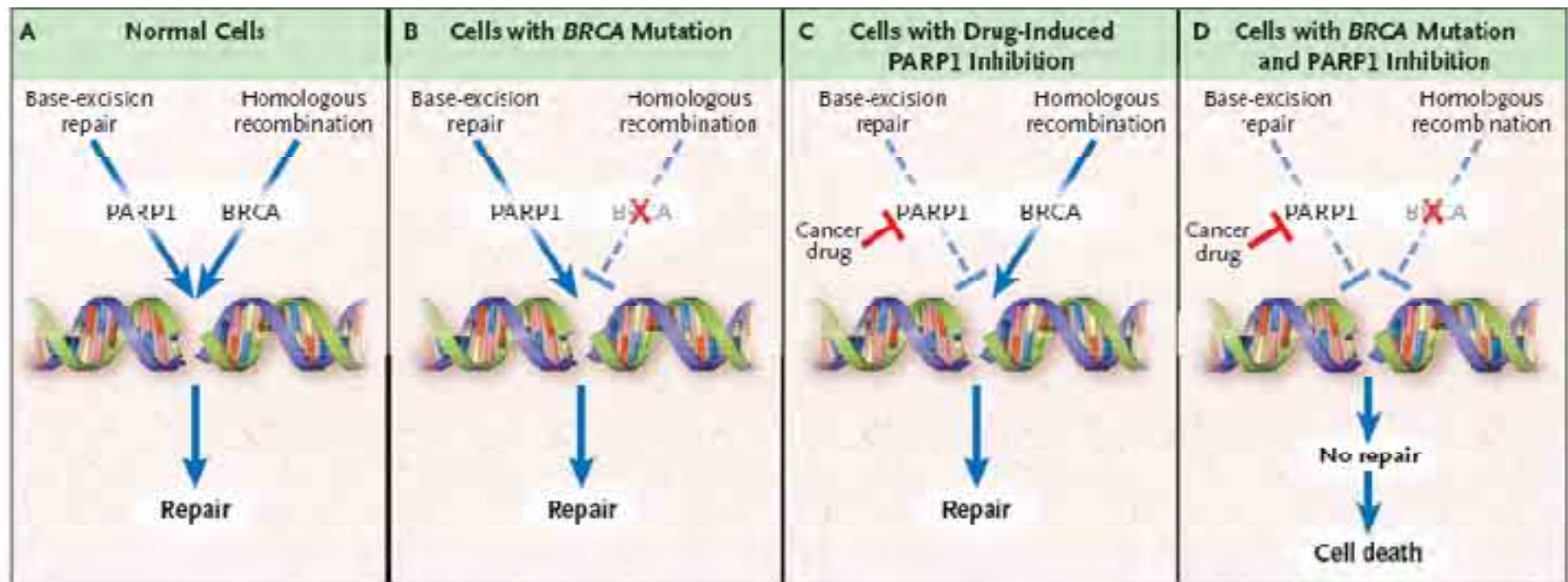
	Resistant										Sensitive																
Response Score	Progress	1					2					3					4					5					
Sample No.	15 21 26 27	4 6 12 13 16	14 20 22 24 28					1 11 23 25					2 7 8 10					3 5 9 17 18 29									
i) BRCA1 Mutation	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>				
ii) Low BRCA1 mRNA	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>					<input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>				
iii) BRCA1 methylation	<input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>					<input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>				
iv) $\Delta Np63/TAp73 > 2$	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>				
v) p53 NSM	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>					<input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/>				

Neoadjuvant cisplatin in BRCA1 mutant patients



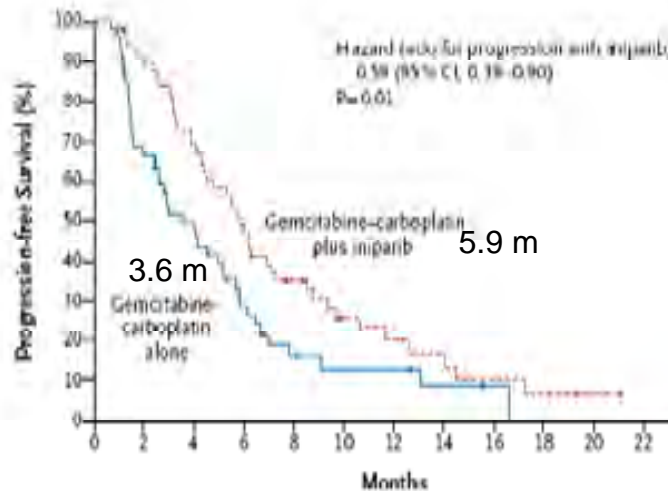
pCR 72%

Rationale for combining PARP inhibitors in BRCA deficient tumors: syntetic lethality



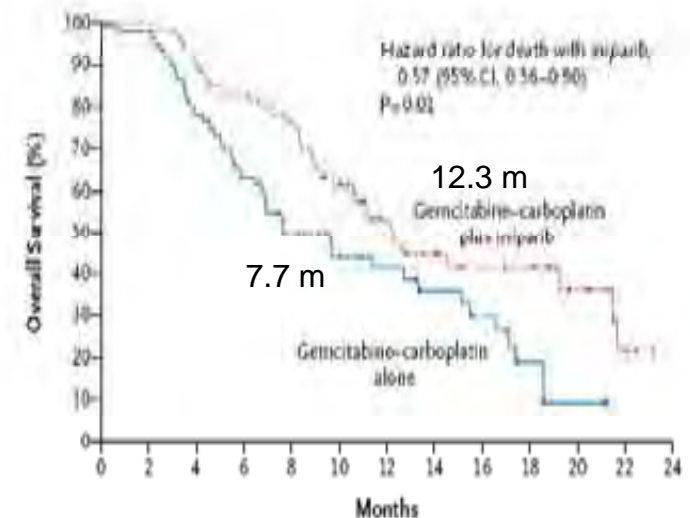
Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Progression-free Survival

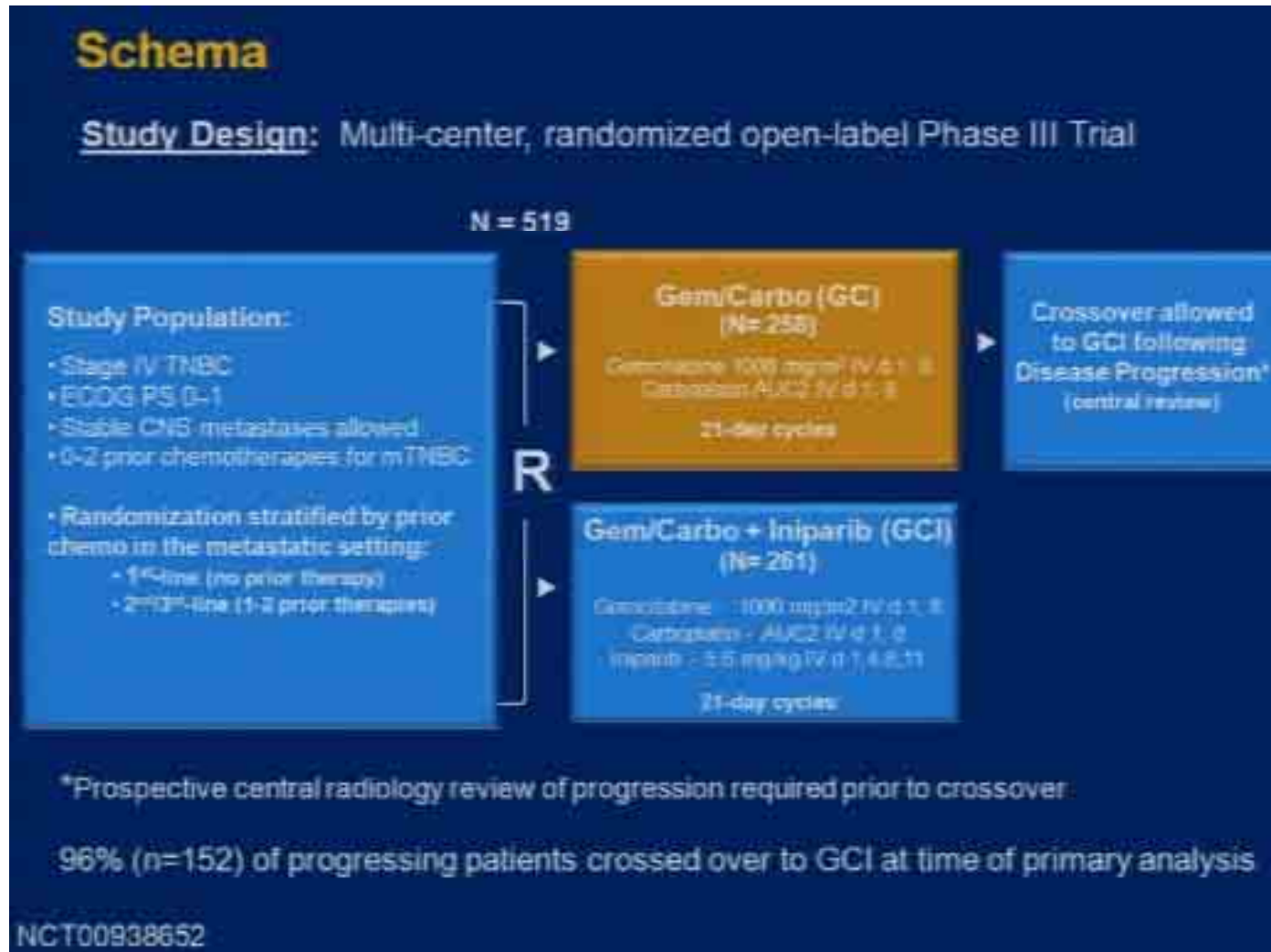


Iniparib-gemcitabine-carboplatin improved the rate of clinical benefit from 34% to 56% (P = 0.01) and the rate of overall response from 32% to 52% (P = 0.02)

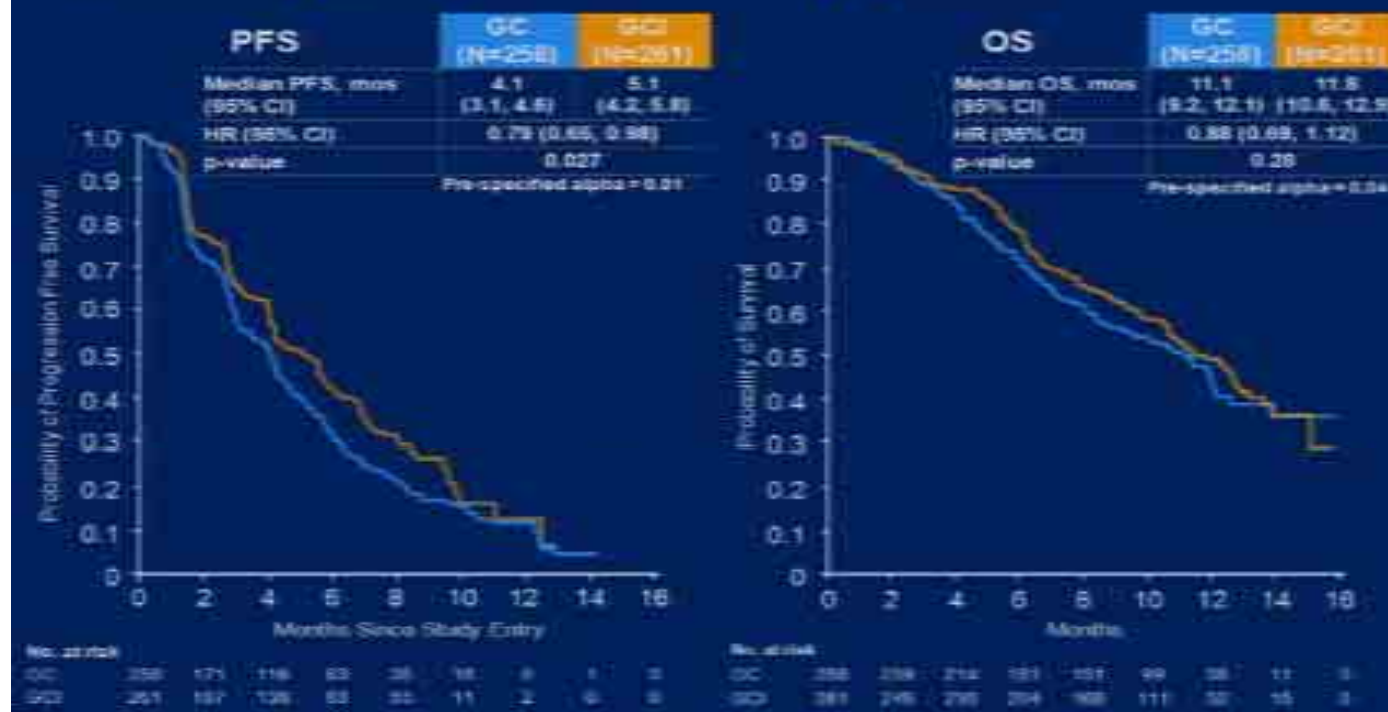
Overall Survival



Phase III confirmatory trial



Efficacy Endpoints – ITT population

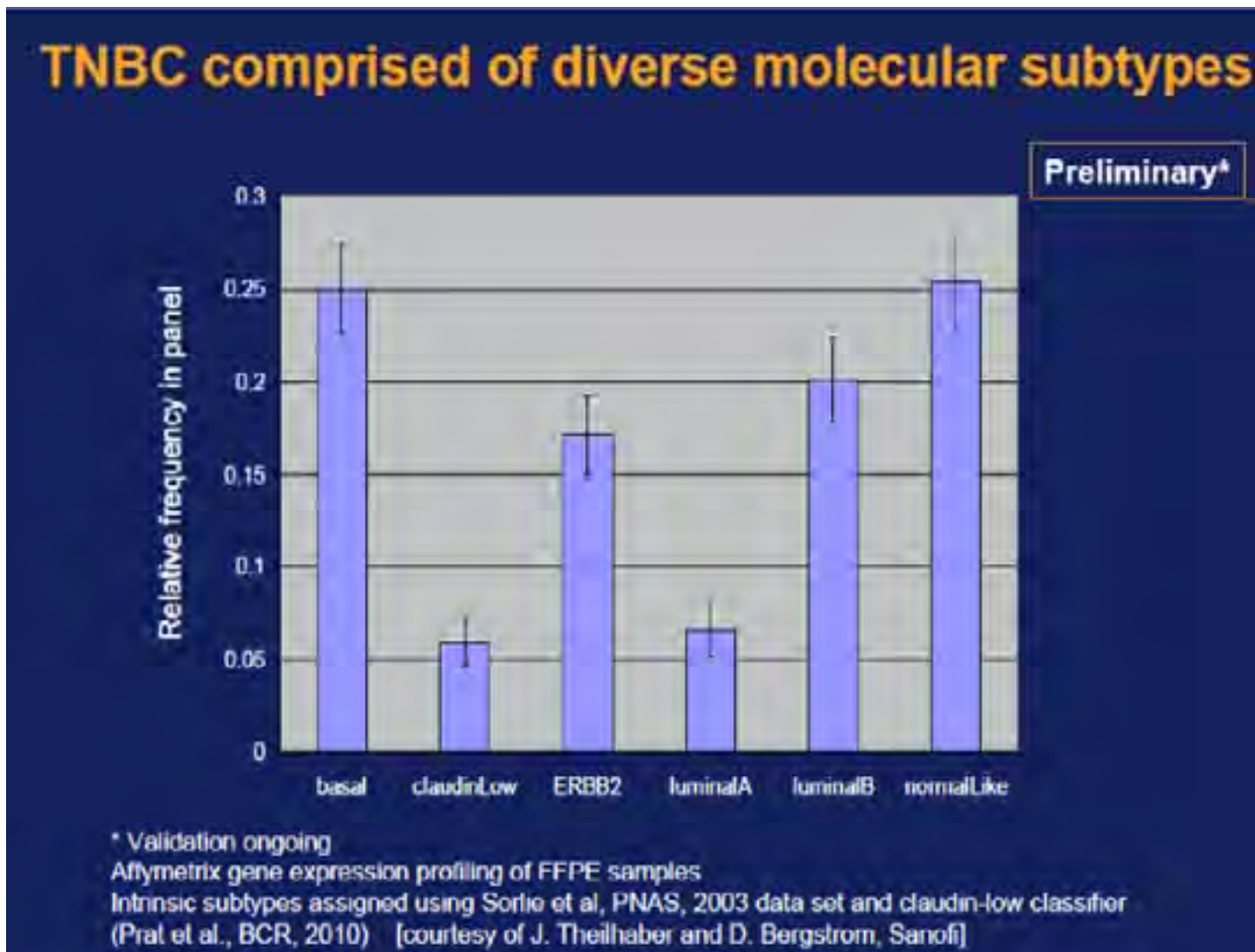


Lo studio non ha raggiunto i criteri di significatività per gli endpoints coprimari OS e PFS.

PFS 4,1 versus 5,1 mesi (HR 0.79; p=0.027)

OS 11,1 versus 11,8 mesi (HR 0.88; p=0.28)

What was really enrolled?



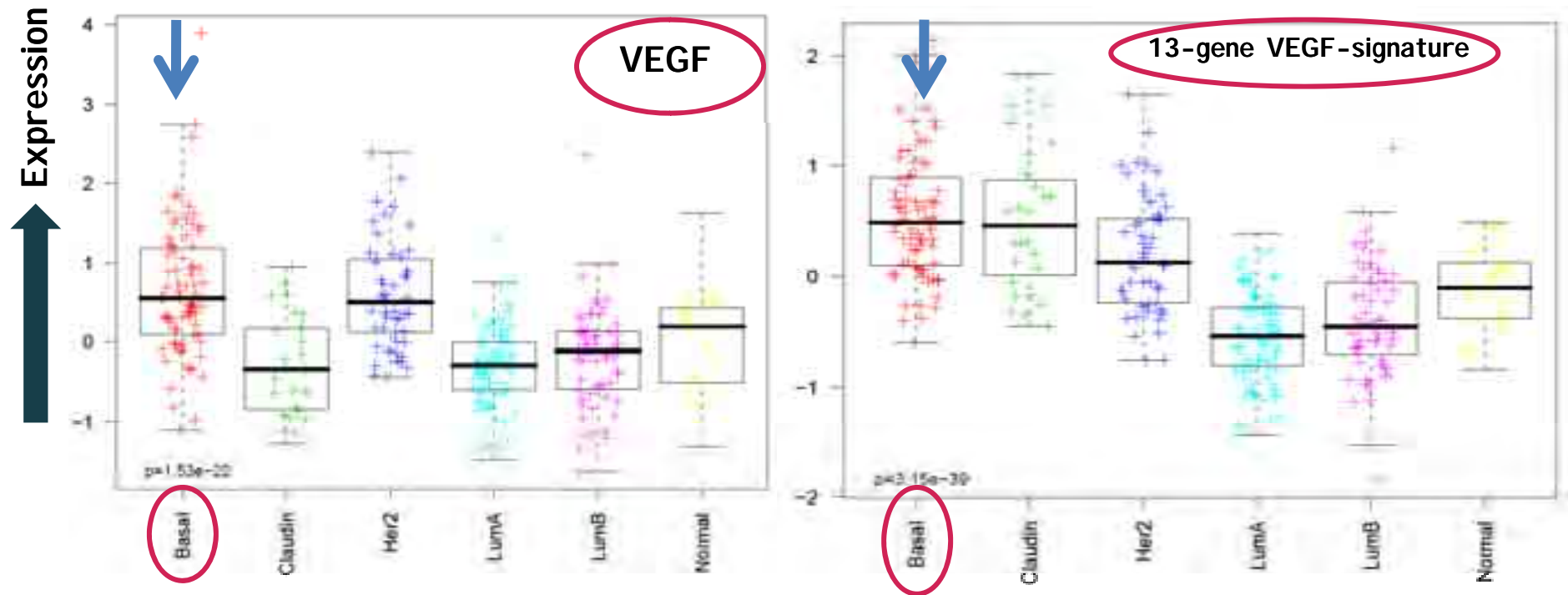
Phase III study of chemo +/- iniparib

Iniparib* (BSI-201)

A novel, investigational, anti-cancer agent

- In triple negative breast cancer cell lines¹⁻⁴:
 - Induces cell cycle arrest in the G2/M phase
 - Induces double strand DNA damage γ -H2AX foci but does not inhibit PARP 1 and 2 at physiologic drug concentrations
 - Potentiates cell-cycle arrest induced by DNA damaging agents, including platinum and gemcitabine
- Physiologic targets of iniparib and its metabolites are under investigation

Hypoxia-related Features and Basal-like Tumors



TNBC is highly proliferative and requires extensive angiogenesis to support rapid growth and metastasis (? Role for bevacizumab)

META-ANALYSIS OF PATIENTS WITH TRIPLE-NEGATIVE BREAST CANCER FROM THREE RANDOMIZED TRIALS OF FIRST-LINE BEVACIZUMAB AND CHEMOTHERAPY TREATMENT FOR METASTATIC BREAST CANCER

J O Shaughnessy¹, G Romieu², V Diéras³, M Bartsch⁴, A-A Duenne⁵, DW Miller⁶

San Antonio Breast Cancer Symposium; December 8–12, 2010

Figure 1. Kaplan-Meier estimate of PFS (TNBC subgroup)

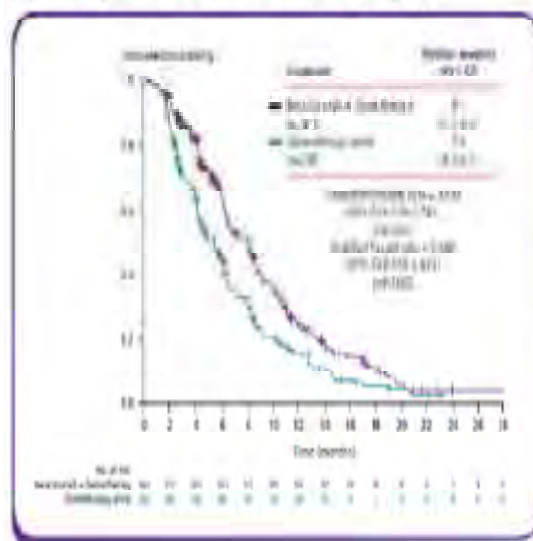
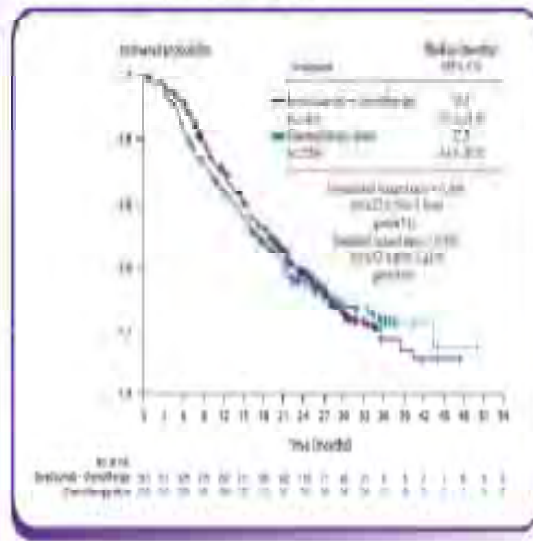
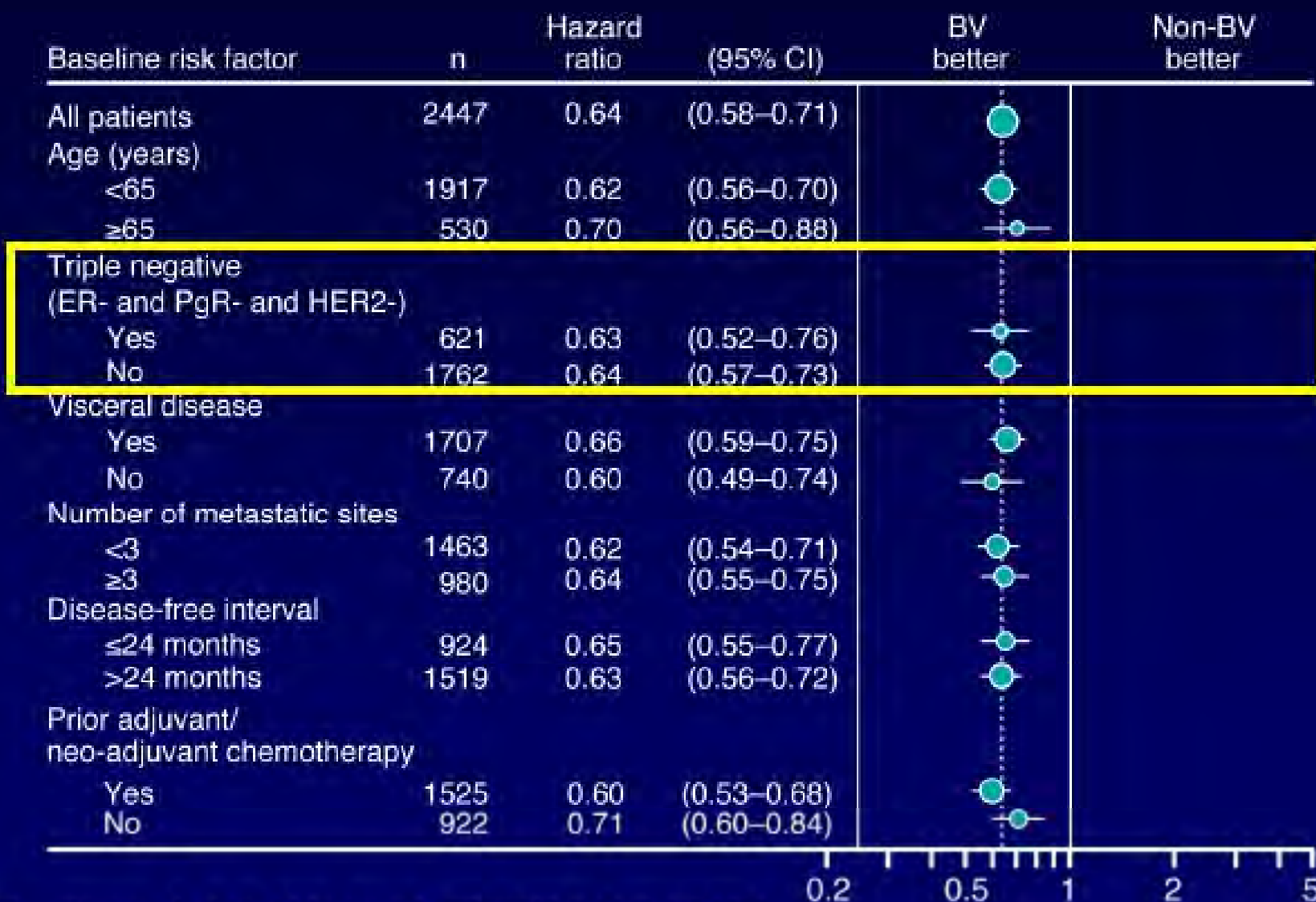


Figure 2. Overall survival (TNBC subgroup)



- 621 TNBC pts from E2100, RIBBON, AVADO trials
- PFS benefit, but no OS benefit

Analysis of PFS by Subgroups



Panoramica degli studi in Italia

Setting	Titolo dello studio	Stato dello studio
Avanzato	Studio clinico di fase II con Dasatinib (BMS-354825) in pazienti affette da carcinoma della mammella TN in fase avanzata	Chiuso
Avanzato	Studio multicentrico, randomizzato, in aperto per la valutazione di SAR240550, un inibitore della poli (ADP-ribosio) polimerasi-1 (PARP-1) somministrato 2 volte a settimana, in combinazione con gemcitabina/carboplatino in pazienti con tumore della mammella metastatico TN (mTNBC)	Aperto
Avanzato	Studio randomizzato di fase II con cetuximab e cisplatino nel trattamento del carcinoma mammario metastatico ER-negativo, PgR-negativo, HER2 negativo (basal like)	Chiuso

TNBC: Adjuvant setting

Chemotherapy is the only option for TNBC

Subtype	Type of therapy	Notes on therapy
Luminal A	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status or other indicator of risk: see text).
Luminal B (HER2 negative)	Endocrine \pm cytotoxic therapy	Inclusion and type of cytotoxics may depend on level of endocrine receptor expression, perceived risk and patient preference.
Luminal B (HER2 positive)	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
HER2 positive (non luminal)	Cytotoxics + anti-HER2	Patients at very low risk (e.g. pT1a and node negative) may be observed without systemic adjuvant treatment.
Triple negative (ductal)	Cytotoxics	
Special histological types		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine nonresponsive	Cytotoxics	Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

St. Gallen 2011

Fattori che indicano la necessità della chemioterapia:

- Istologia G3: **SI 95,5%**
- Ki 67 > 14%: **SI 68,8%**
- Low hormone receptor status (<50%): **SI 68,1%**
- HER2 +: **SI 95,7%**
- **Tripli negativi:** **SI 97,7%**
- Quasi tutti N+: **SI 40,4%** **NO 59,6%**
- > 3 N+ : **SI 88,4%** **NO 9,3%**
- Invasione linfovascolare: **SI 40,4** **NO 48,9%**

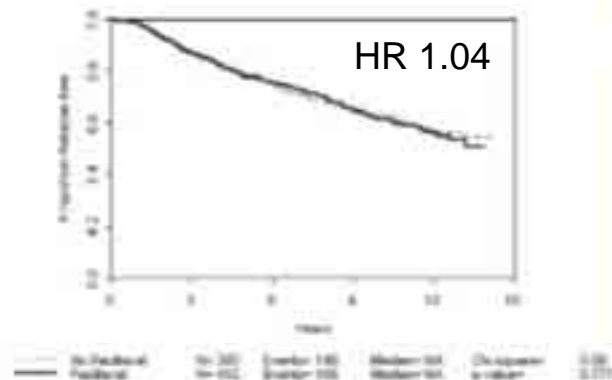
Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

Should the CT for invasive ductal TNBC contain:

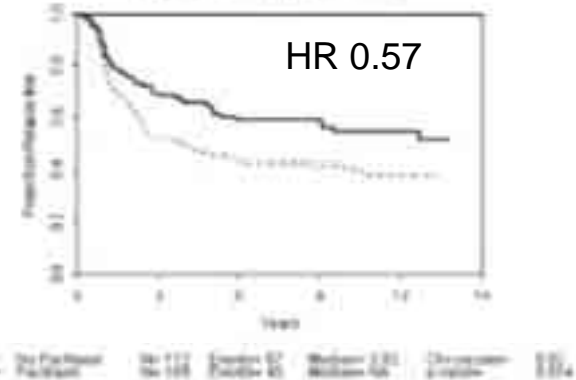
- anthracycline and taxane? 82% Yes**
- alkylating agents (such as CMF)? 92% Yes**
- platinum? 65% No**
- Should dose-dense (e.g. weekly paclitaxel) regimen CT be considered?
52% Yes – 48% No**
- Should antiangiogenic treatment be added to CT for « basal like »?
88% No**

Benefit from Stronger chemotherapy according to subtype (CALGB 9344)

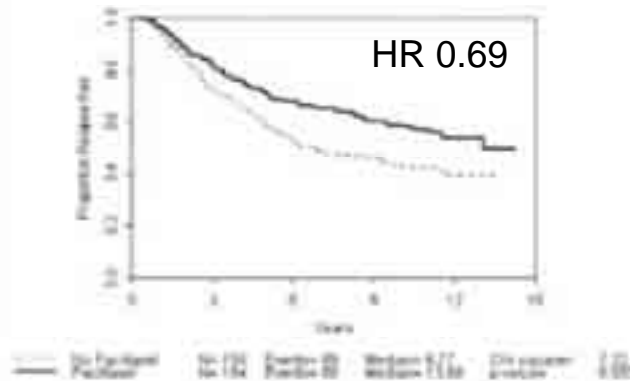
Luminal A by paclitaxel



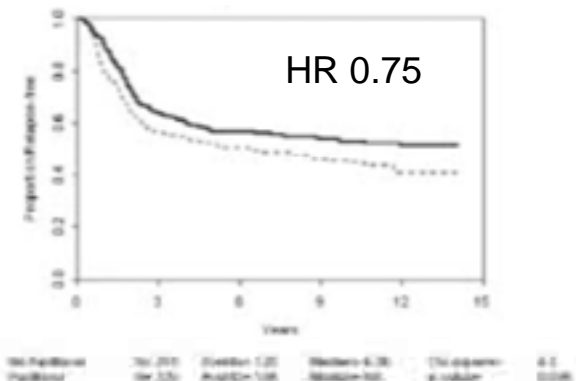
HER2/ER- by paclitaxel



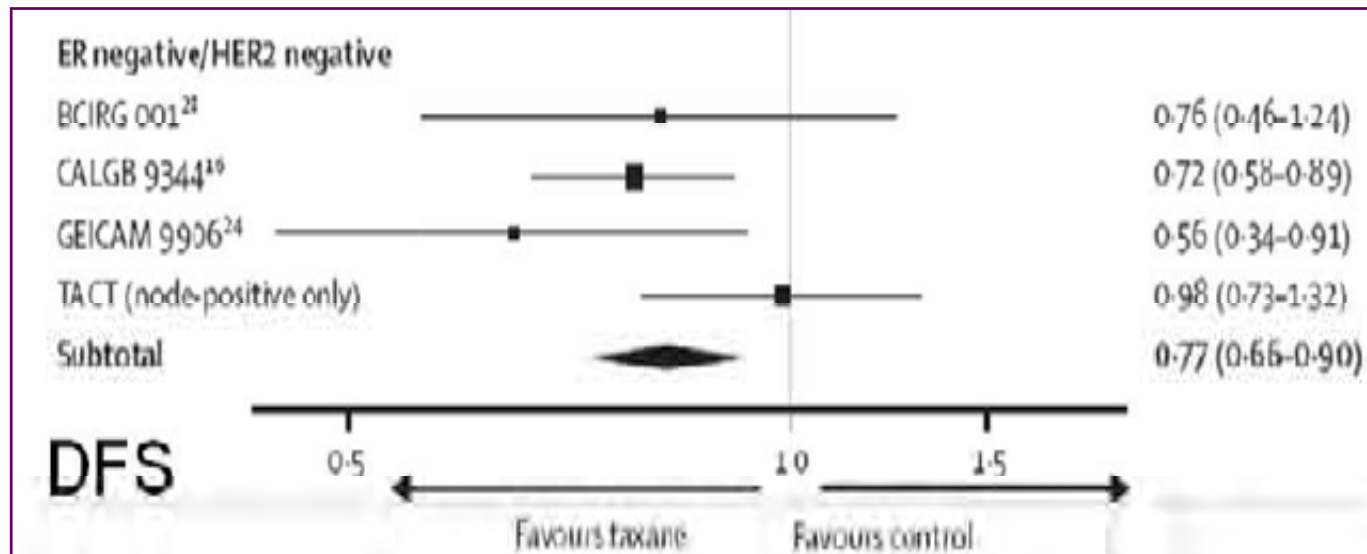
Luminal B by paclitaxel



Core-basal by paclitaxel



Taxanes vs Anthra in Triple negative BC



TRIAL	YEARS OF ACCRUAL	AGENTS
BCIRG 001 ¹	1997-1999	TAC vs FAC
CALGB 9344 ²	1994-1999	4 x AC vs 4 x AC + 4 x P
GEICAM 9906 ³	1999-2002	6 x FEC vs 4 x FEC + 8 x P weekly
TACT ⁴	2001-2003	FEC-D or E-CMF vs FEC-D

1. Martin M, NEJM 2005
2. Hayes DF, NEJM 2007
3. Martin M, J Nat Cancer Inst 2008
4. Ellis, Lancet, 2009

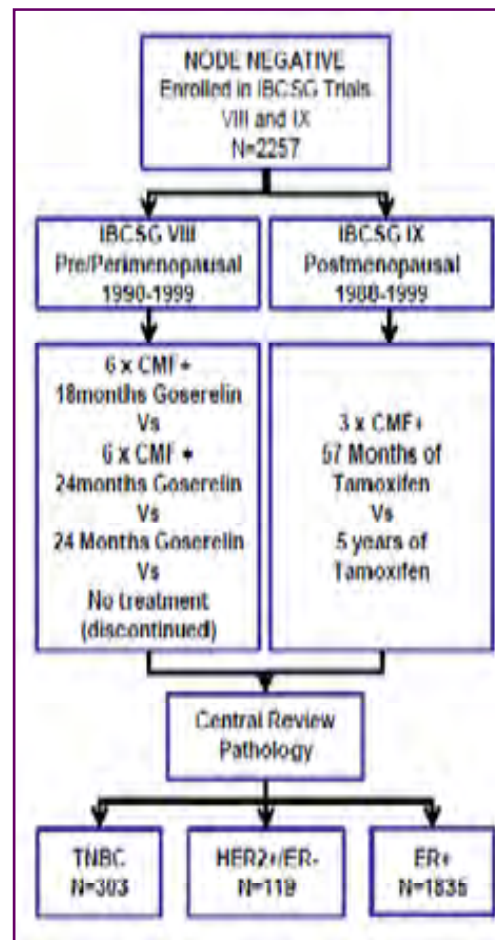
A meta-analysis of phase III trials evaluating the predictive value of HER2 and topoisomerase II alpha in early breast cancer patients **treated with CMF or anthracycline-based adjuvant therapy**

Anthracycline-based therapy in TNBC

Results of central testing in a subgroup of the published meta-analysis: some benefit in patients with HER2 negative but also high-proliferating breast cancer

In the TN group (294 pts), the DFS HR was 0.77 (0.54-1.09), suggesting that benefit from Anthracyclines might not be confined to HER2+ pts.

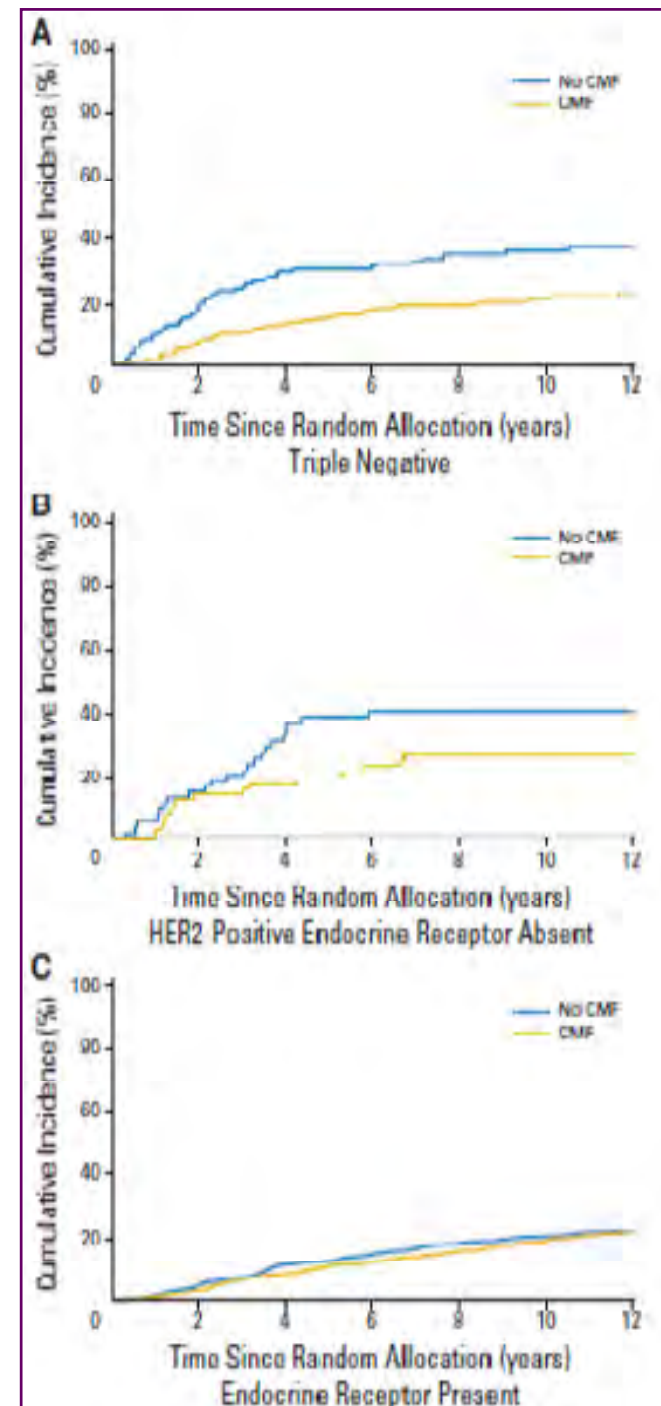
Classical Cyclophosphamide, Methotrexate, and Fluorouracil Chemotherapy Is More Effective in Triple-Negative, Node-Negative Breast Cancer: Results From Two Randomized Trials of Adjuvant Chemoendocrine Therapy for Node-Negative Breast Cancer



303 pts TN

Subtype	HR for Relapse	95% CI	P
TNBC	0.46	0.29-0.73	0.009
HER2+/ER-	0.58	0.29-1.17	0.24
ER+	0.90	0.74-1.11	-

Colleoni JCO, 2010



Dose Dense Chemotherapy in TNBC

Dose-Dense Chemotherapy in Nonmetastatic Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials

3 trials enrolled 3337 patients compared DD chemotherapy with a conventional CT schedule (similar agents)

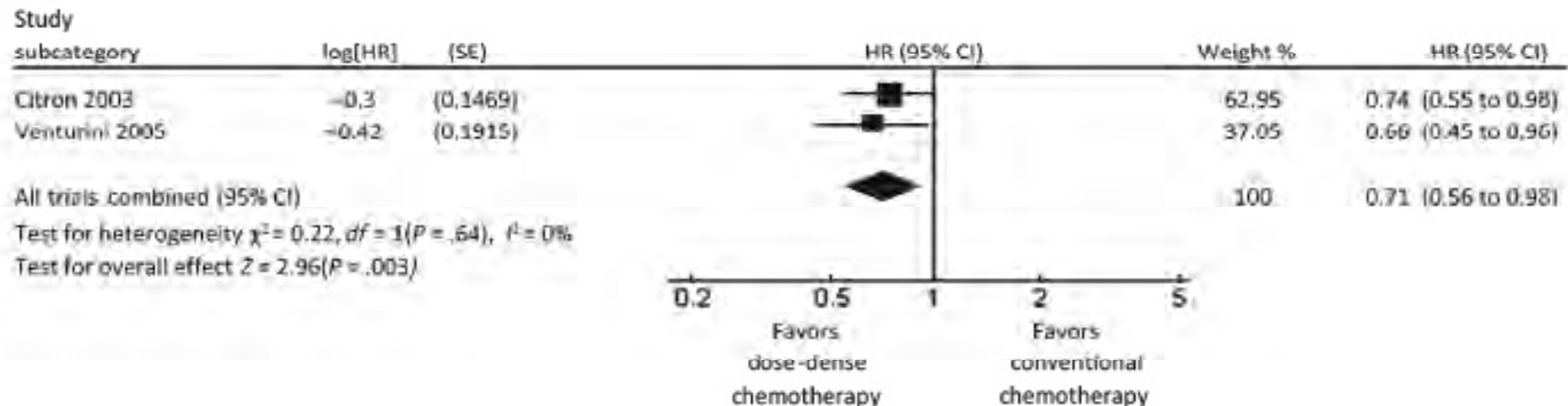
Table 1. Conserved dose-dense chemotherapy trials*

First author, year (reference)	Study location	Treatment setting	Treatment protocol†	Treatment interval, ‡ d	Number of patients	Follow-up, mo	Median age, y	Stage				Number of events	
								Tumor size	Nodal status, %	ER status, %	PR status, %	DFS	OS
Venturini, 2005 (7)	Italy	Adjuvant	ECF	14	604	216	50	<2 cm: 49;	Neg: 38;	Pos: 52;	Pos: 39;	168	104
			ECF	21	610		<70§	2.1–5.0 cm: 45; 5 cm: 5	Pos: 64	Neg: 41	Neg: 48	191	118
Citron, 2003 (6)	United States	Adjuvant	ATC	14	493	78	50	<2 cm: 20;	1–3 pos: 29;	Pos: 32.1;	ND	230	168
			AC then T	14	494			>2 cm: 20	4–9 pos: 14; 10 pos: 6	Neg: 17			
			ATC	21	495			<2 cm: 18;	1–3 pos: 29;	Pos: 32.3;	ND	278	202
			AC then T	21	501			>2 cm: 29	4–9 pos: 14; 10 pos: 6	Neg: 0.5			
Baldini, 2003 (8)	Italy	Neoadjuvant, adjuvant	CEF × 3 then surgery radiation then CMF	14	77	60	52	IB–IC: 25; IIIA: 20; IIIB: 50		Pos: 18.6; Neg: 8.0	Pos: 12.6; Neg: 22.0	29	22
			CEF × 3 then surgery radiation then CMF CEF intercalated × 6	21	73		50			Pos: 22; Neg: 0.8	Pos: 17.3; Neg: 34	37	24

7 trials compared DD CT with regimen that use standard intervals but with different agent and/or dosage (modified DD CT trials)

DFS for ER- PATIENTS

Dose-dense chemotherapy results in better overall and disease-free survival, particularly in women with hormone receptor–negative breast cancer



No benefit in pts with ER+

Additional data from randomized controlled trials are needed before dose-dense chemotherapy can be considered as the standard of care.

Bonilla L. JNCI 2010

Dose-Dense and/or Metronomic
Schedules of Specific Chemotherapies
Consolidate the Chemosensitivity of
Triple-Negative Breast Cancer: A
Step Toward Reversing Triple-
Negative Paradox

Dose dense: Weekly paclitaxel

Weekly paclitaxel significantly improved the 5-year progression-free hazard rate by 40% in hormone receptor–negative (including triple-negative subset) breast cancer and 20% in hormone receptor–positive subsets compared with these subsets treated with once-every-3-weeks scheduling.

Sparano JA, Engl J Med 2008

“For patients with triple-negative tumors, optimally scheduled doxorubicin and cyclophosphamide (once every 2 weeks) and paclitaxel (once weekly) should be standard”

Mehta RS, JCO 2008

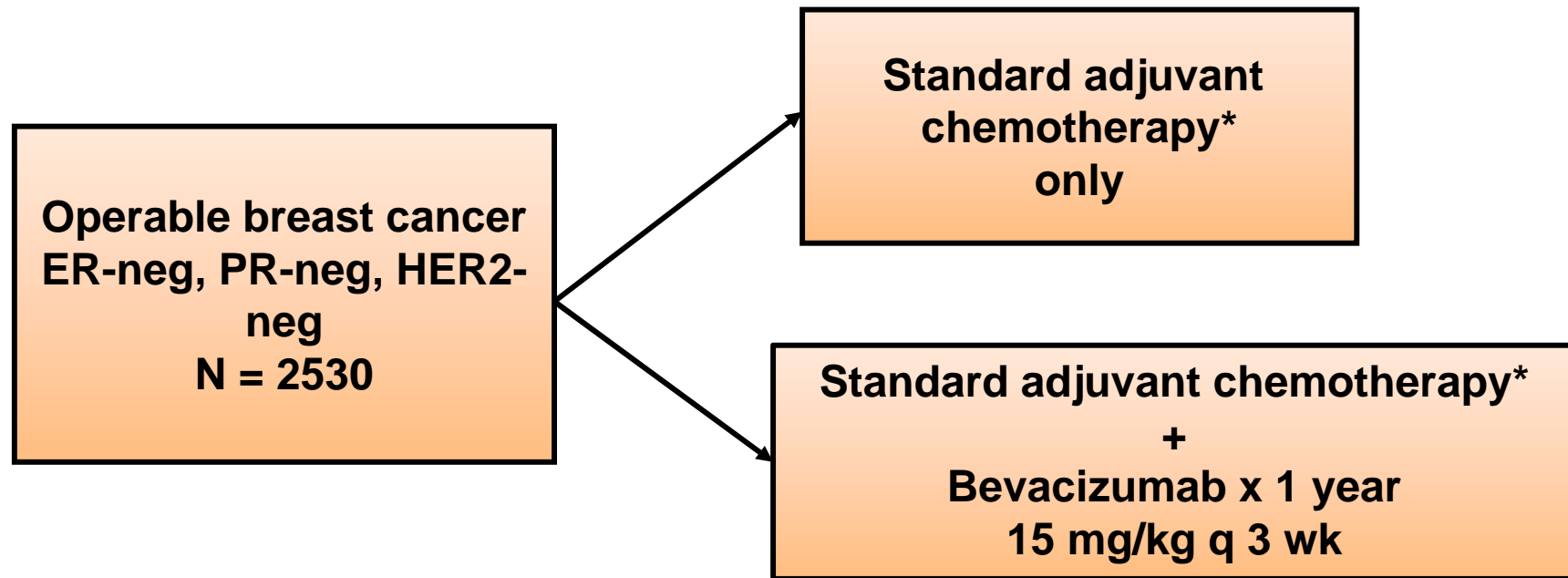
Antiangiogenic treatment in TNBC

Panoramica degli studi in Italia

Setting	Titolo dello studio	Stato dello studio
Avanzato	Studio randomizzato di fase II con ixabepilone in monoterapia e ixabepilone in combinazione con cetuximab nel trattamento di prima linea in donne affette da tumore della mammella localmente avanzato non operabile o metastatico TN (negatività di ER, PgR, HER2)	Chiuso
Adiuvante	Sperimentazione internazionale multicentrica in aperto a due bracci di fase III trial su bevacizumab come adiuvante nel tumore mammario TN	Chiuso
Adiuvante	Studio di fase II di CT preoperatoria con carboplatino, paclitaxel e bevacizumab (Ca, Pa, Be) in pazienti con carcinoma mammario operabile o localmente avanzato TN (ER, PgR, HER2 negativo)	Aperto
Adiuvante	Doxorubicina liposomiale pegilata (Caelyx), cisplatino e 5-FU in i.c. (CCF) seguiti da terapia metronomica con ciclofosfamide, capecitabina e sorafenib (CCS) come trattamento preoperatorio del carcinoma mammario localmente avanzato TN	Chiuso

BEATRICE

Phase III Trial of Adjuvant Bevacizumab Therapy in TNBC



Primary endpoint: Invasive DFS

***anthracycline / taxane or taxane only**

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

Conclusions

For TNBC (usual ductal type) the panel supported the **inclusion of anthracyclines and taxanes**, and an **alkylating agent** (typically cyclophosphamide) **but did not support** the routine use of cisplatin or carboplatin

A slim majority agreed that DD CT should be considered

Panel was strongly opposed to the inclusion of antiangiogenic therapies

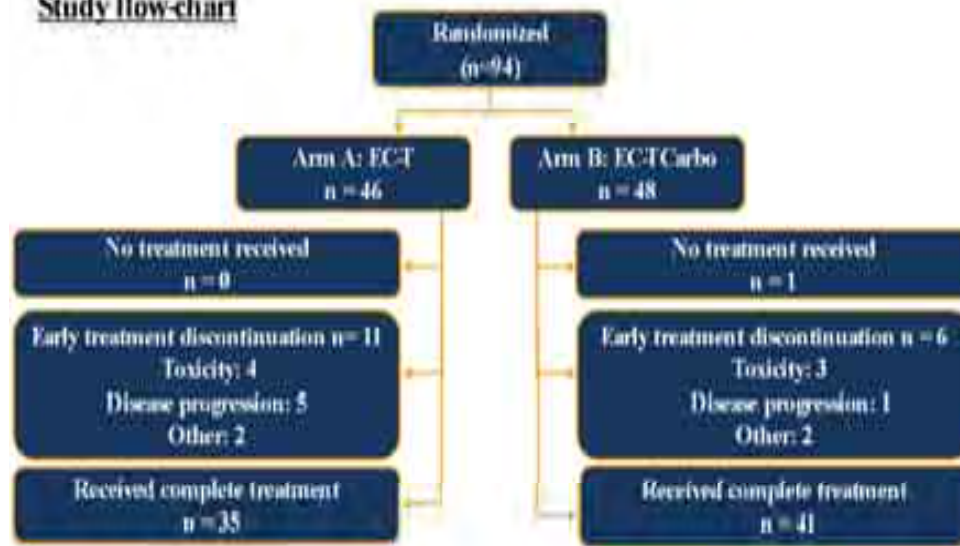
TNBC: Neoadjuvant setting

Neoadjuvant platinum in BRCA/TNBC : High pCR

PATIENTS	AUTHOR	REGIMEN	N	RESULTS
BRCA1	Byrski et al 2008	Cisplatin alone	10	90% pCR
BRCA 1	Gronwald et al 2009	Cisplatin alone	25	72% pCR
TNBC	Silver et al 2010	4xcisplatin q3w	28	pCR 22% Low BRCA1 mRNA expression associated with good response
TNBC	Torrisi et al 2008	4xEpirubicin/cisplatin/5- FU→3xpaclitaxel q3w	30	pCR 40%; ORR 86%
TNBC	Ryan et al 2009	4xcisplatin/bevacizumab q3w	55	Response rate 36%
TNBC	Frasci et al 2009	8xcisplatin/epirubicin/pacl itaxelq1w+GCSF	74	pCR 62%
TNBC	Sikov et al 2007	4xTaxotere/carboplatin q3w	10	pCR 50%
TNBC	Leone et al 2009	4xTaxotere/carboplatin or cisplatin with 4xAC q3w or without	125	pCR 40 vs 29%

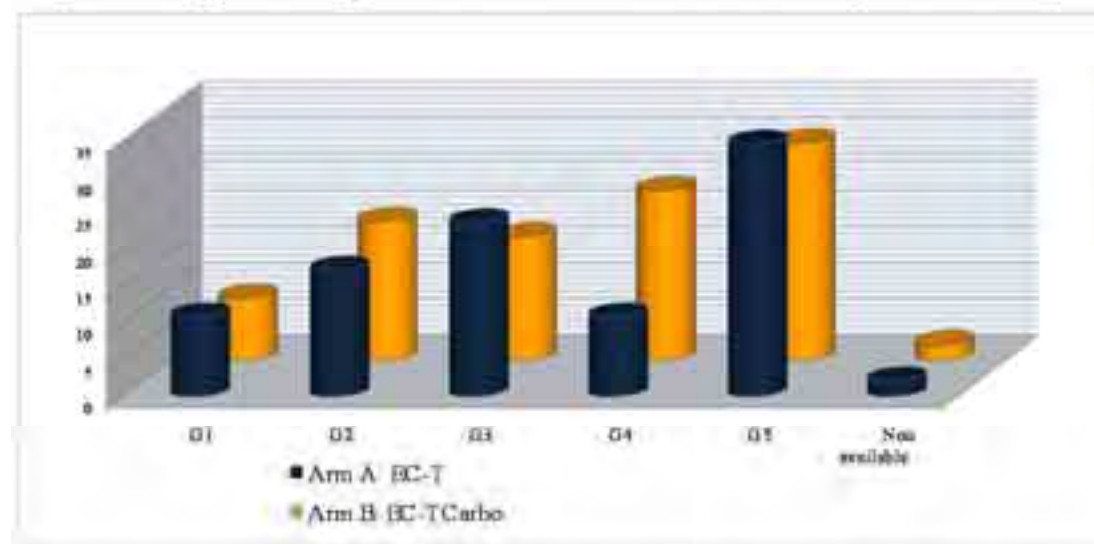
Neoadjuvant Chemo w/wo carboplatin

Study flow-chart



Geicam 2006/03 (ER-, PgR-, HER2-, CK 5/6+ and/or EGFR+)

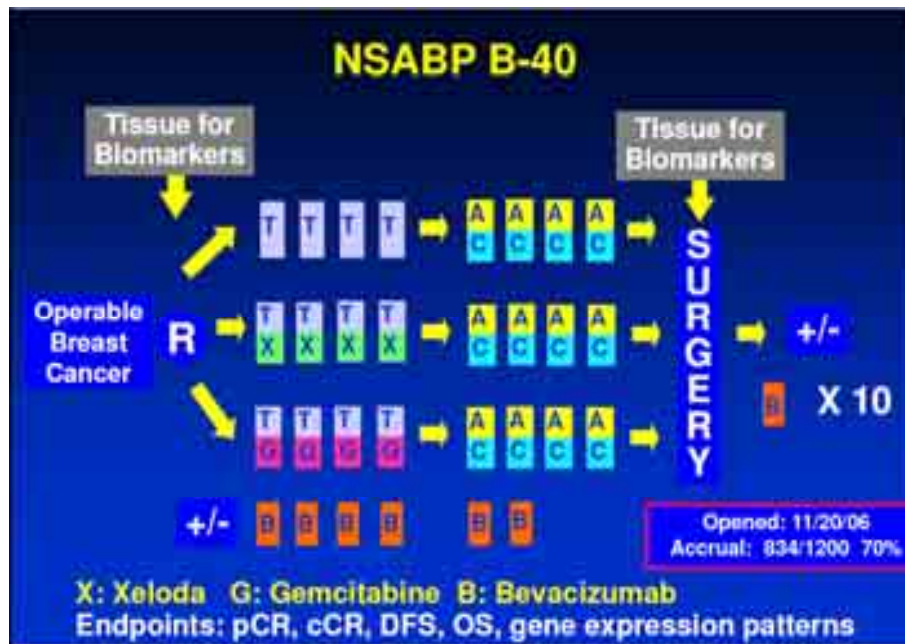
Pathological Response in Breast: Miller & Payne Criteria



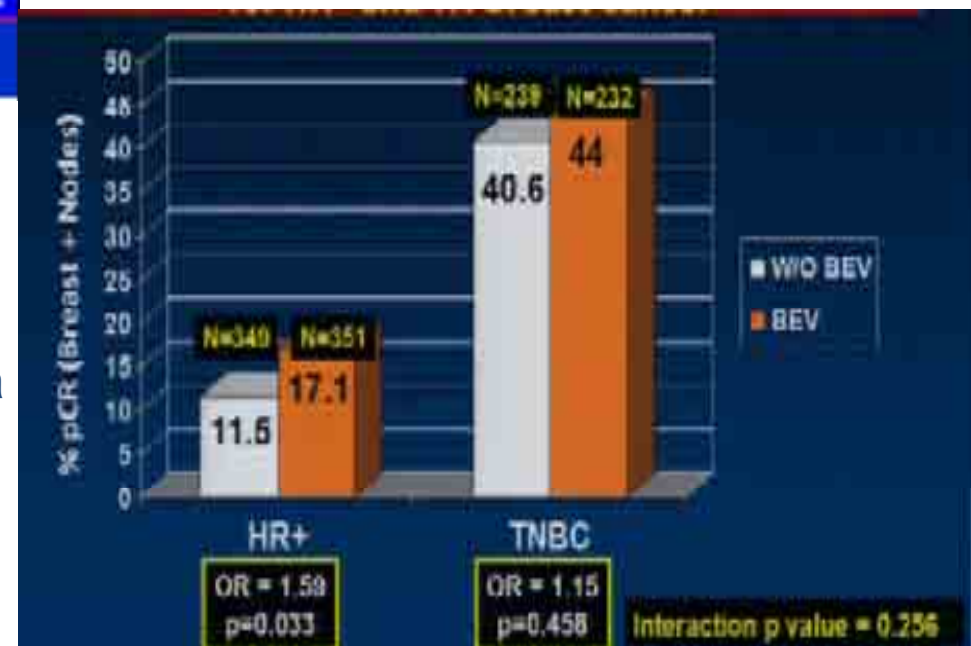
pCR rates are not superior with the addition of carboplatin

Antiangiogenic treatment in TNBC: Neoadjuvant setting

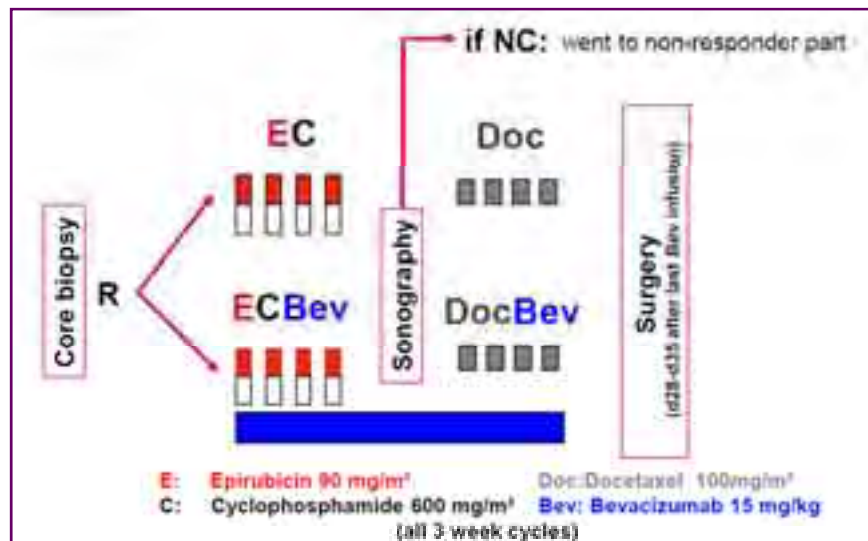
The NSABP B-40 neoadjuvant trial



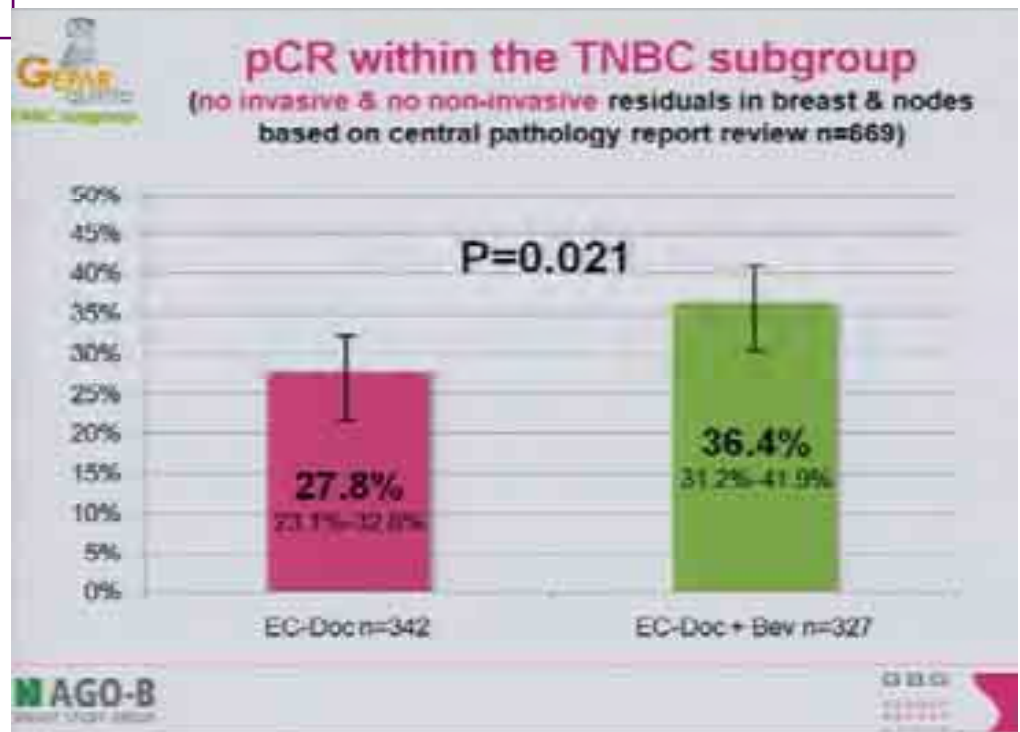
pCR rates in the breast and the axilla



Bevacizumab with EC-Docetaxel in TNBC

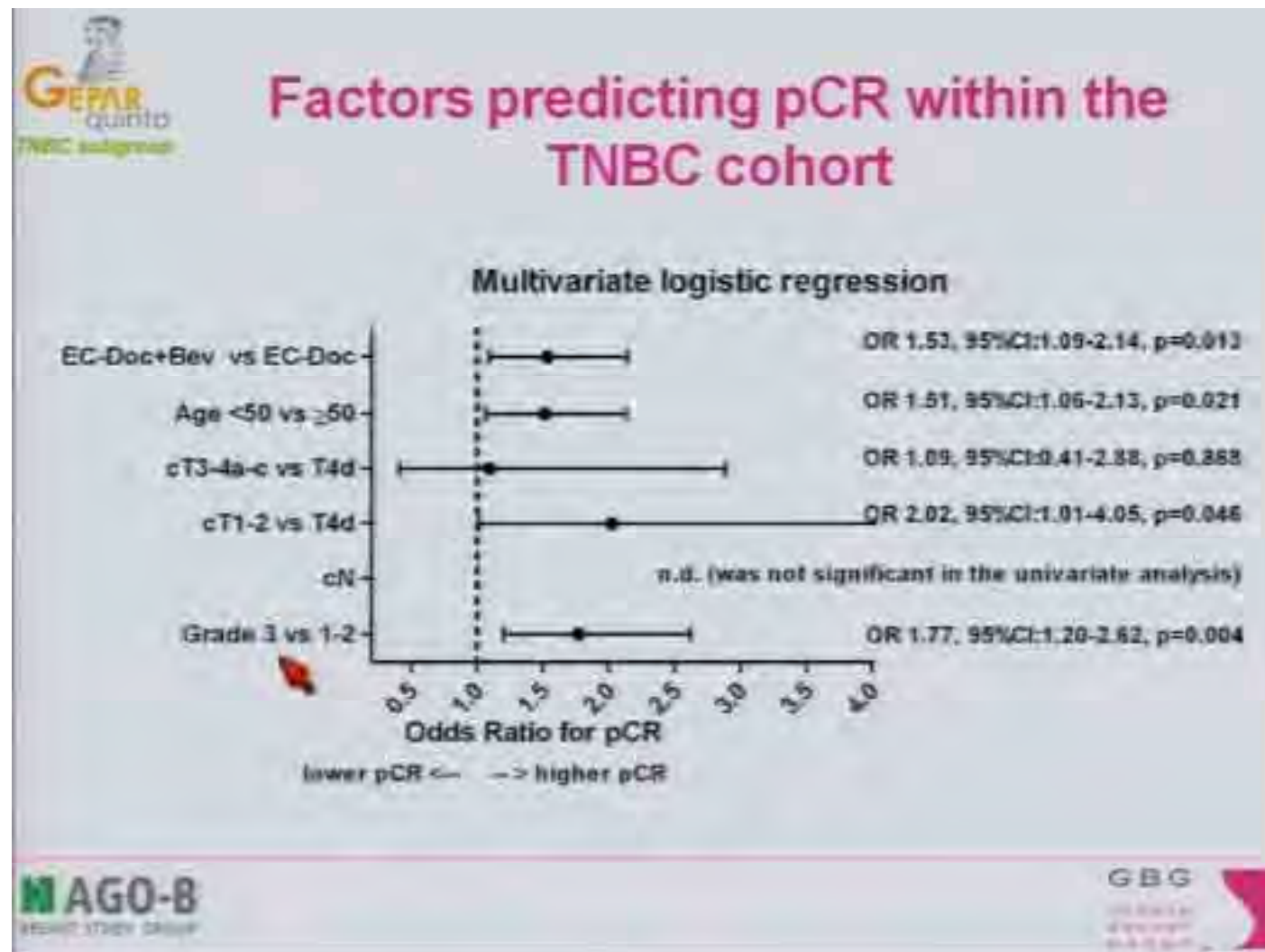


Von Minckwitz et al, SABCS 2010



Gerber, ASCO 2011, abstr 1006

Predictive factors of pCR



TNBC

PROTOCOLLI DI STUDIO NAZIONALI

Sperimentazione internazionale multicentrica in aperto a due bracci di Fase III trial su bevacizumab come adiuvante nel tumore mammario TRIPLO NEGATIVO

**Studio di fase II di chemioterapia preoperatoria con carboplatino, paclitaxel e bevacizumab (Ca.Pa.Be.)
in pazienti con carcinoma mammario operabile o localmente avanzato
TRIPLO NEGATIVO**

Studio di fase II di chemioterapia preoperatoria con carboplatino, paclitaxel e bevacizumab (Ca.Pa.Be.) in pazienti con carcinoma mammario triplo negativo operabile o localmente avanzato

PAESI COINVOLTI NELLA SPERIMENTAZIONE: Italia

POPOLAZIONE PREVISTA: 43 soggetti in Italia

CENTRI PARTECIPANTI ITALIANI ()

A.O. UNIVERSITARIA POLICLINICO DI MODENA, OSPEDALE DI CARPI (MO), OSPEDALE DI S. MARIA NUOVA REGGIO NELL'EMILIA, UNIVERSITA' DEGLI STUDI DI UDINE

LO STUDIO E' APERTO DAL 20 GENNAIO 2011 : **DURATA ACCRUAL IN ITALIA:** 2 ANNI

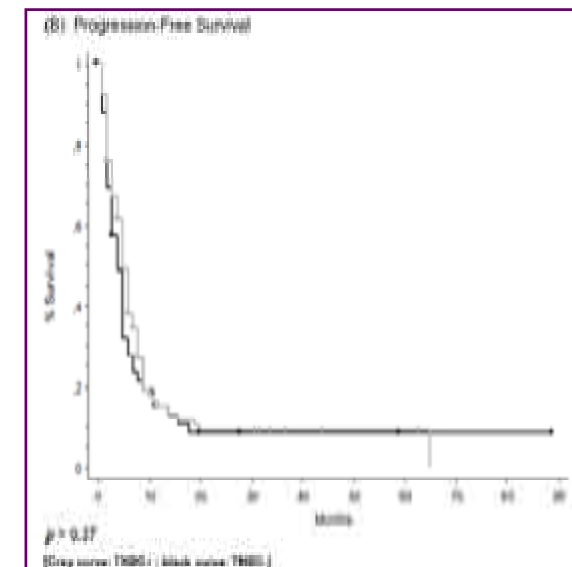
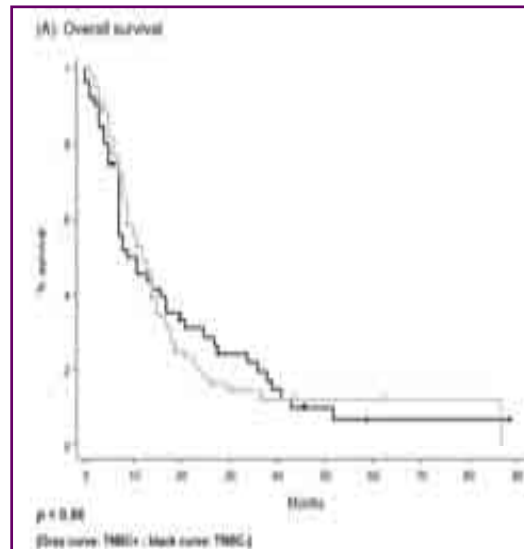
OBIETTIVI

- Valutare l'attività di questo regime in termini di tasso di risposte patologiche complete (pCR rate)
- Valutare la sicurezza di questa combinazione
- Valutare la % di chirurgia conservativa
- Valutare le risposte obiettive cliniche
- Valutare il tempo a ripresa di malattia e la sopravvivenza globale
- Valutare il cambiamento indotto da trattamento sul ki67, sulla pathway di EGFR e su altri marcatori molecolari caratterizzanti la malattia triplo negativa
- Studiare un profilo di espressione genica tumorale in grado di predire la risposta, ed i cambiamenti indotti dalla terapia sul profilo di espressione genica.
- Studiare una possibile correlazione sul genotipo VEGF (SNPs) con la risposta, la tollerabilità e con la prognosi
- Studiare la possibilità di una valutazione precoce della risposta con lo studio in DCE-MRI.

Chemotherapy in metastatic TNBC

Platinum-based chemotherapy in metastatic triple-negative breast cancer: the Institut Curie experience

CT regimens	N (%)
CDDP 50 mg/m ² d2-d3 Ifosfamide 1500 mg/m ² d1-d3 d1 = d21	101 (70.6%)
Carboplatin AUC5 d1 Ifosfamide 1500 mg/m ² d1-d3 d1 = d28	8 (5.6%)
CDDP 50 mg/m ² d2-d3 Ifosfamide 1500 mg/m ² d1-d3 Bevacizumab 15mg/m ² d1 d1 = d21	6 (4.2%)
CDDP 75 mg/m ² d2-d3 Gemcitabine 1250 mg/m ² d1 and d8 d1 = d21	4 (2.8%)
CDDP 75 mg/m ² d1 Cyclophosphamide 75 mg/m ² d1 d1 = d21	3 (2.1%)
CDDP 75 mg/m ² d1 Docetaxel 75 mg/m ² d1 d1 = d21	6 (4.2%)
NAP1 (NAvelbine Platine Ifosfamide): CDDP 50 mg/m ² d2-d3 Ifosfamide 1500 mg/m ² d1-d3	11 (7.7%)
Vinorelbine 25 mg/m ² d1-d8 d1 = d28, three cycles then High Dose Chemotherapy HDCT (Mephalan + Thiotepa) and autologous bone marrow transplantation	



	N	Response rate	Clinical benefit (PR + SD)
ER- /HER2- (TNBC)	93	31 (33.3%)	49.5%
ER+/HER2-	33	6 (18.2%)	39.4%
ER+/HER2+	8	3 (37.5%)	62.5%
ER- /HER2+	9	2 (22.2%)	33.3%

Total N= 143
TNBC= 93

CONCLUSIONI

Chemioterapia Adiuvante/Neo = Trattamento RE neg
Farmaci di riferimento A-T

BRCA1 mut/disfunzionale

Ruolo del Cisplatino?

Bevacizumab

Dati non definitivi

Parp-I

Con il corretto target

...TNBC nel 2011...

