DEBATE: NUEVOS TRATAMIENTOS EN CÁNCER DE MAMA

POSICIONAMIENTO Y ALGORITMO TERAPÉUTICO

Dr. Pedro Sánchez Rovira

Complejo Hospitalario de Jaén.

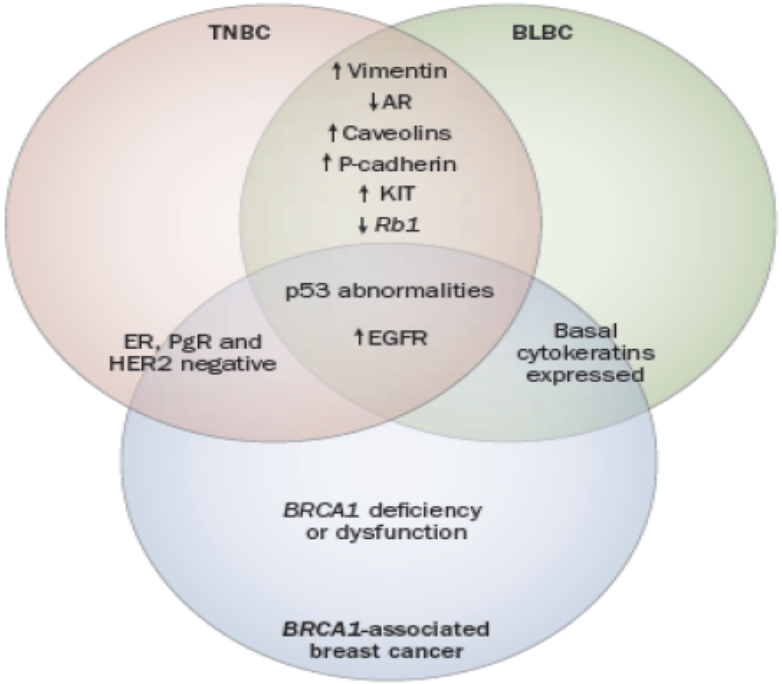
CÁNCER DE MAMA TRIPLE NEGATIVO

Triple Negativo

Marcador	Reactividad
R Estrógenos	-
R Progestetrona	-
Her2	-
EGFR (receptor de Factor de Crecimiento)	+
Citoqueratinas basales (5/6)	+

FENOTIPOS RECEPTORES ESTROGENOS NEGATIVOS

FENOTIPO TN / Basal

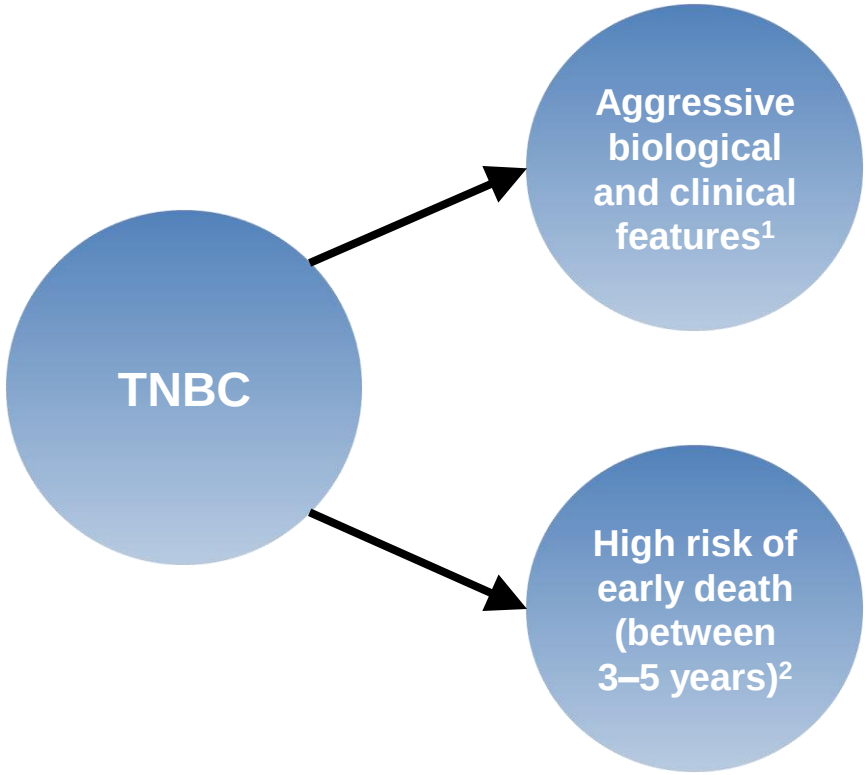


- TN y Basal **no equivalentes**.
- **Ca mama en BRCA1** frec. TN y/o Basal
- Puede **defectos BRCA1** en carcinomas TN / Basales esporádicos
- Frecuentes **recidivas y metástasis** tempranas.
- No tto específico

Carey, L et al. Nature Reviews 201

FACTORES PRONÓSTICOS Y PREDICTIVOS

TNBC prognosis is poor

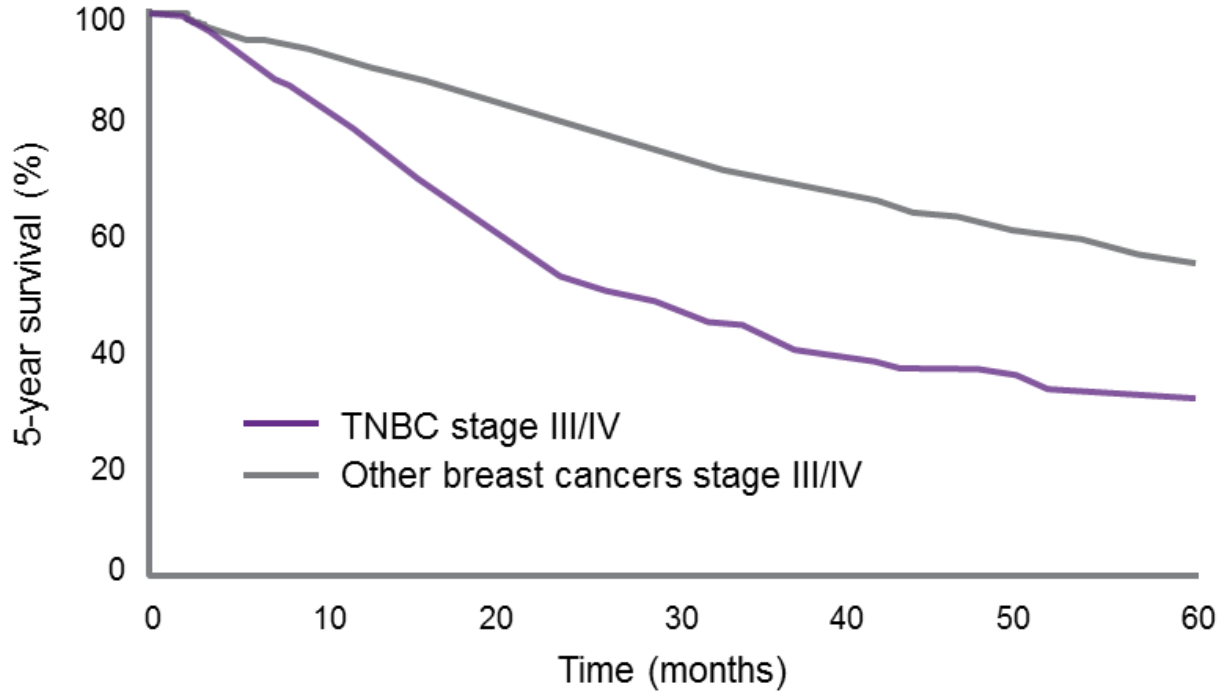


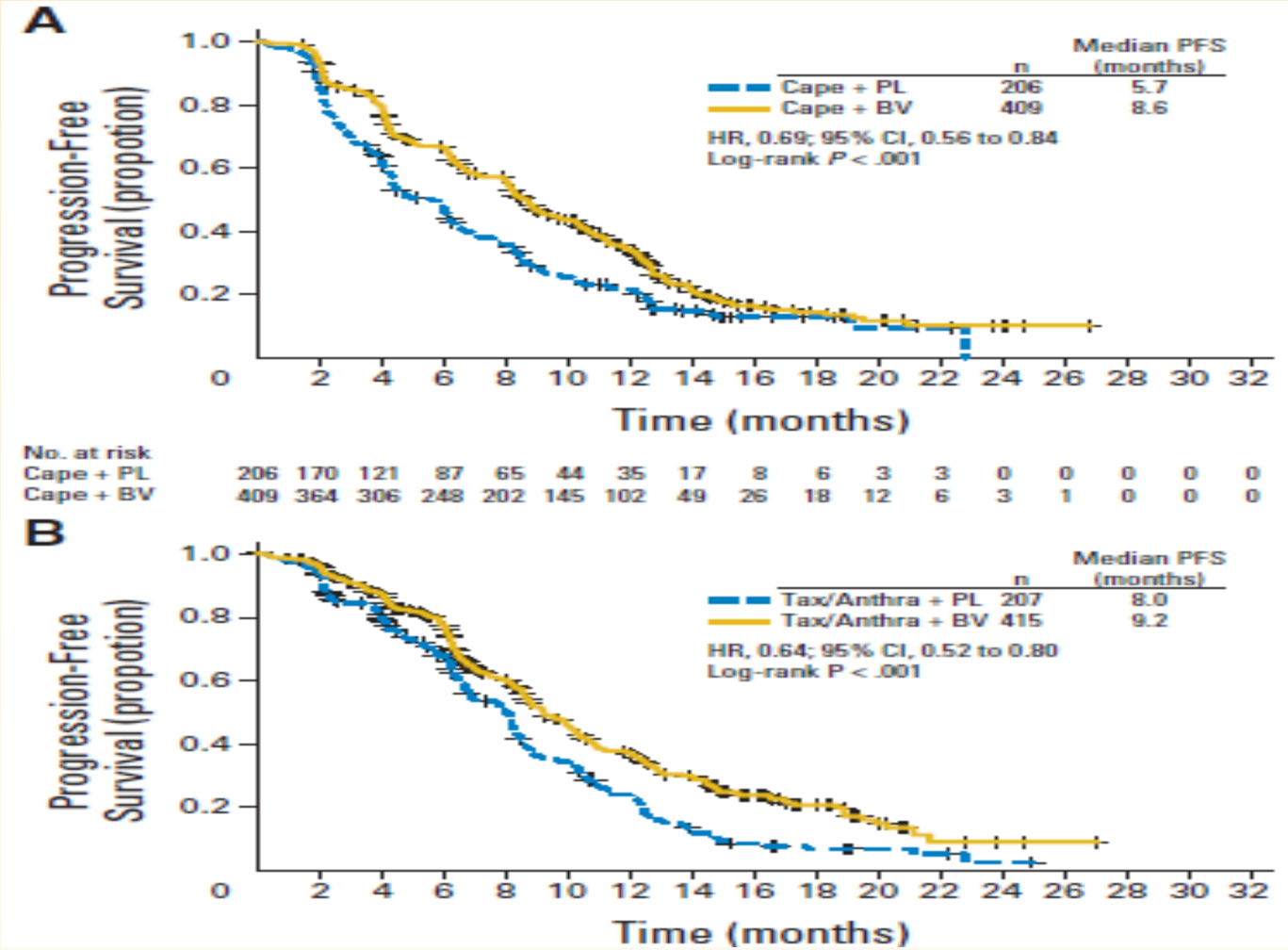
- Large, high-grade tumours
- Greater propensity to metastasise to viscera

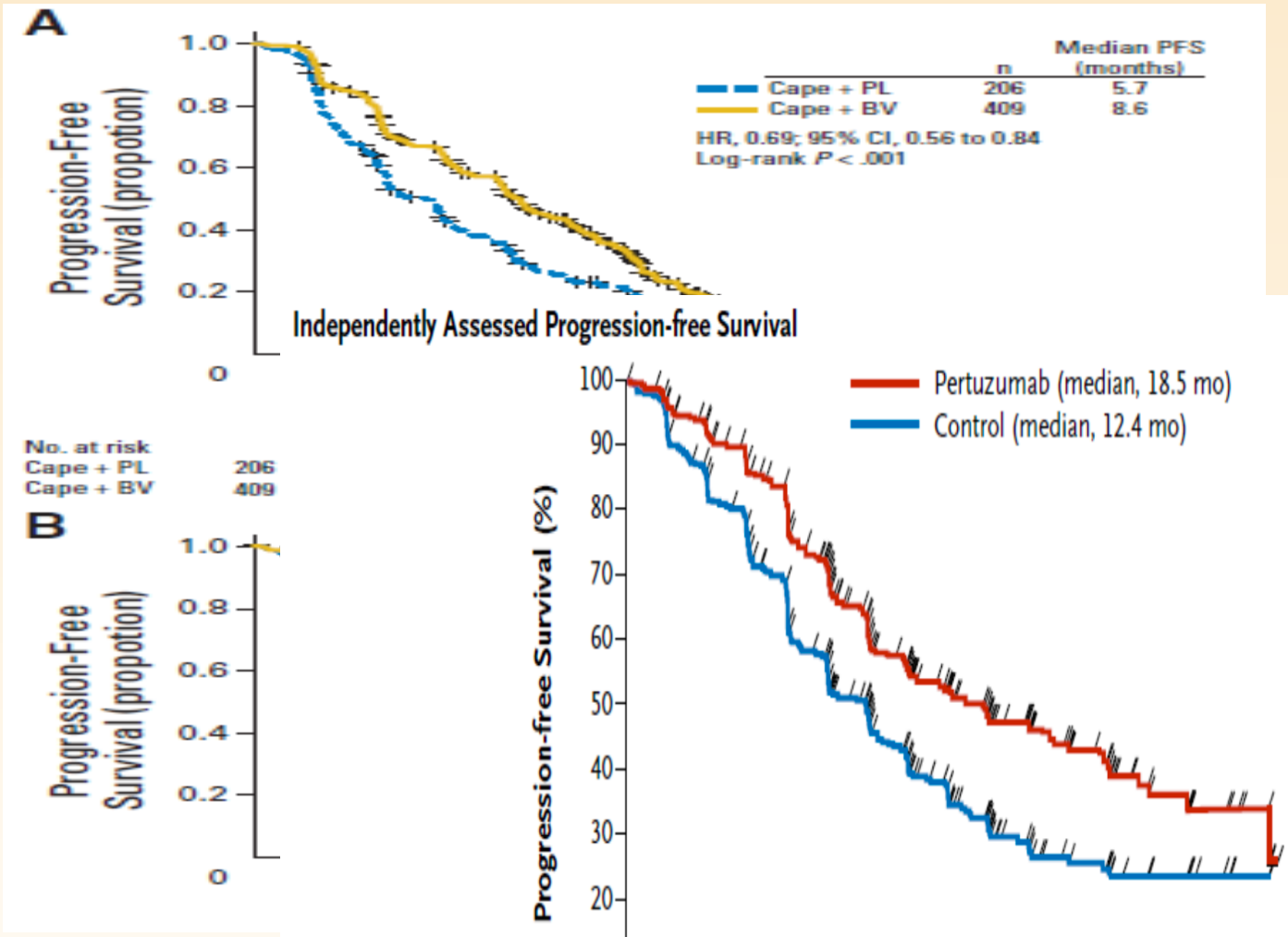
- Rapid rise in risk of recurrence following diagnosis
- Peak risk of recurrence at 1–3 years
- Rapid progression from distant recurrence to death

1. Foulkes, et al. N Engl J Med 2010; 2. Dent, et al. Clin Cancer Res 2007

Survival for women with TNBC is worse than for other subtypes of stage III/IV disease[1]




A
Progression-Free Survival (propotion)
1.0
0.8
0.6
0.4
0.2
0
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Time (months)
Median PFS
n (months)
Cape + PL 206 5.7
Cape + BV 409 8.6
HR, 0.69; 95% CI, 0.56 to 0.84
Log-rank P < .001
No. at risk
Cape + PL 206 170 121 87 65 44 35 17 8 6 3 3 0 0 0 0 0
Cape + BV 409 364 306 248 202 145 102 49 26 18 12 6 3 1 0 0 0
B
Progression-Free Survival (propotion)
1.0
0.8
0.6
0.4
0.2
0
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Time (months)
Median PFS
n (months)
Tax/Anthra + PL 207 8.0
Tax/Anthra + BV 415 9.2
HR, 0.64; 95% CI, 0.52 to 0.80
Log-rank P < .001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No. at risk
Cape + PL 206
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B
Progression-Free Survival (propotion)
1.0
0.8
0.6
0.4
0.2
0

Independently Assessed Progression-free Survival
Pertuzumab (median, 18.5 mo)
Control (median, 12.4 mo)
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Months
Hazard ratio, 0.62
(95% CI, 0.51–0.75)
P<0.001

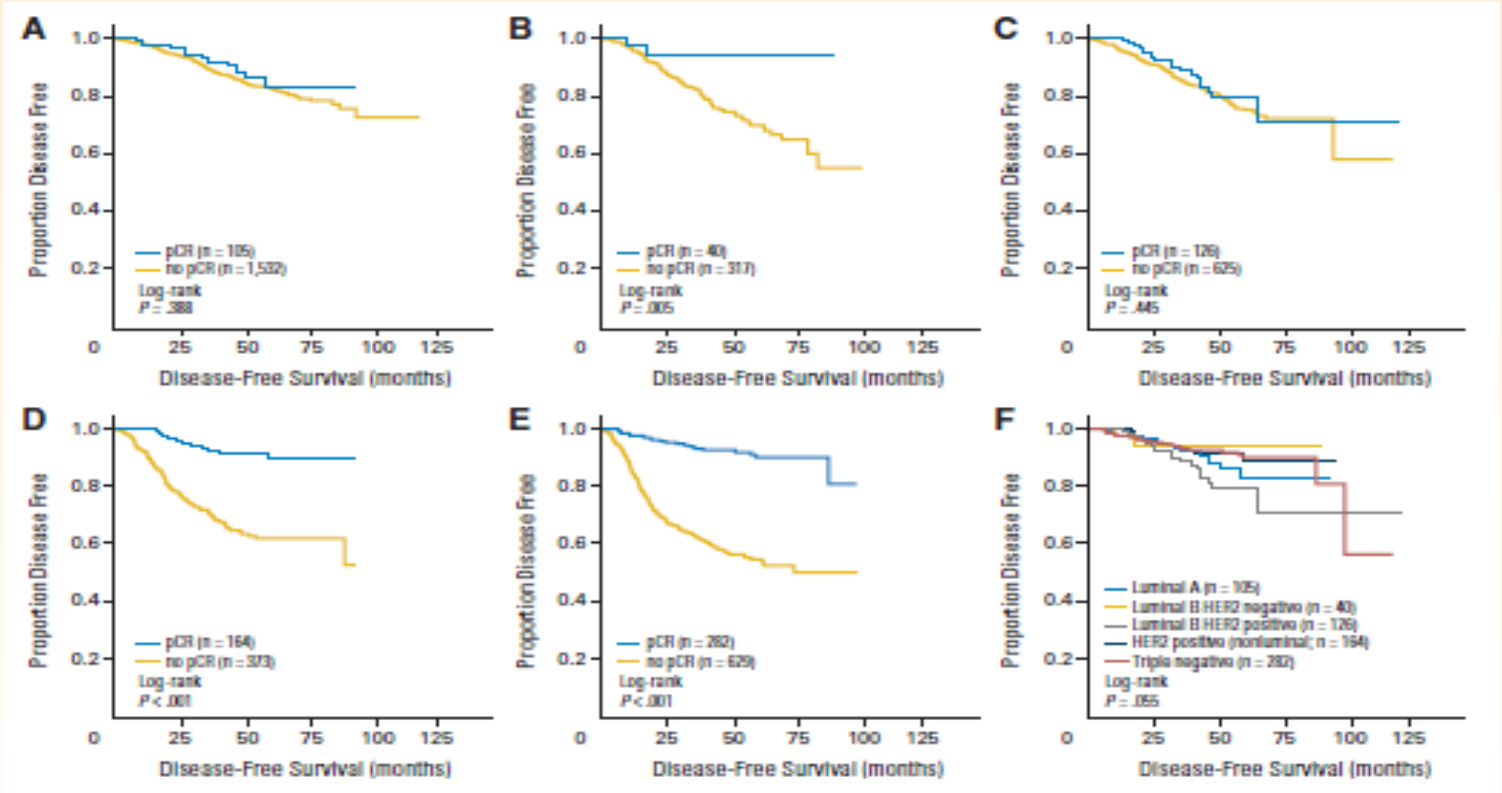
VOLUME 30 · NUMBER 15 · MAY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes

Gunter von Minckwitz, Michael Untch, Jens-Uwe Blohmer, Serban D. Costa, Holger Eidtmann, Peter A. Fasching, Bernd Gerber, Wolfgang Eiermann, Jörn Hilfrich, Jens Huober, Christian Jackisch, Manfred Kaufmann, Gottfried E. Konecny, Carsten Denkert, Valentina Nekljudova, Keyur Mehta, and Sibylle Loibl



TRATAMIENTO
PRÁCTICA CLÍNICA

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other first-line agents for HER2-positive disease:

Trastuzumab alone or with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[3]

[1]There is no compelling evidence that combination regimens are superior to sequential single agents.

[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

[3]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

special article

Annals of Oncology 00: 1–18, 2014
doi:10.1093/annonc/mdu385

ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

F. Cardoso[1*], A. Costa[2,3], L. Norton[4], E. Senkus[5], M. Aapro[6], F. André[7], C. H. Barrios[8], J. Bergh[9], L. Biganzoli[10], K. L. Blackwell[11], M. J. Cardoso[12], T. Cufer[13], N. El Saghir[14], L. Fallowfield[15], D. Fenech[16], P. Francis[17], K. Gelmon[18], S. H. Giordano[19], J. Gligorov[20], A. Goldhirsch[21], N. Harbeck[22], N. Houssami[23], C. Hudis[24], B. Kaufman[25], I. Krop[26], S. Kyriakides[27], U. N. Lin[26], M. Mayer[28], S. D. Merjaver[29], E. B. Nordström[30], O. Pagani[31], A. Partridge[32], F. Penault-Llorca[33], M. J. Piccart[34], H. Rugo[35], G. Sledge[36], C. Thomssen[37], L. van't Veer[38], D. Vorobiof[39], C. Vrieling[40], N. West[41], B. Xu[42] & E. Winer[26]

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Guideline statements	LoE	Consensus
Sequential monotherapy is the preferred choice for MBC. Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.	IA	96% (25) yes 4% (1) abstain (26 voters)

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Guideline statements	LoE	Consensus
Sequential monotherapy is the preferred choice for MBC. Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.	IA	96% (25) yes 4% (1) abstain (26 voters)
For *triple-negative LABC*, anthracycline- and taxane-based chemotherapy is recommended as an initial treatment.	IA	85.3% (35) yes 9.7% (4) abstain (41 voters)

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Guideline statements	LoE	Consensus
Sequential monotherapy is the preferred choice for MBC. C should be reserved rapid clinical progr threatening viscera for rapid symptom control.	IA	96% (25) yes
For *triple-negative LA* anthracycline- and based chemotherap recommended as ar treatment.		

Guideline statements	LoE	Consensus
In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, and who do not need combination chemotherapy, single-agent capecitabine, vinorelbine, or eribulin are the preferred choices.	IB	77.1% (27) yes 20.0% (7) abstain (35 voters)
Additional choices include gemcitabine, platinum agents, taxanes, and liposomal anthracyclines.		
The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.		

Clin Transl Oncol (2013) 15:1004–1010
DOI 10.1007/s12094-013-1095-0

CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guidelines for the management of metastatic breast cancer 2013

A. Llombart Cussac · J. de la Haba Rodríguez · A. Ruiz Simón · I. Álvarez López · J. Cortés Castán

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CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guidelines for the management of metastatic breast cancer 2013

A. Llombart Cussac · J. de la Haba Rodríguez ·
A.

First-line therapy

Both anthracyclines and taxanes are the most active agents in MBC, and they remain the best option even among

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First-line therapy

Both anthracyclines and taxanes are the most active agents in

Taxanes and anthracyclines may be not adequate options in patients preexposed in early stages to both agents and relapsing shortly after. Capecitabine, an oral fluoropyrimidine, was specifically approved after progression to anthracyclines and taxanes. Moreover, the excellent tolerability profile of capecitabine makes it suitable in many other first-line situations like elderly or fragile patients, very low burden or asymptomatic disease [12].

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Both anthracyclines and taxanes are the most active agents in

Taxanes and anthracyclines may be not adequate options in patien

relapsing

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racycline

profile of

line situa

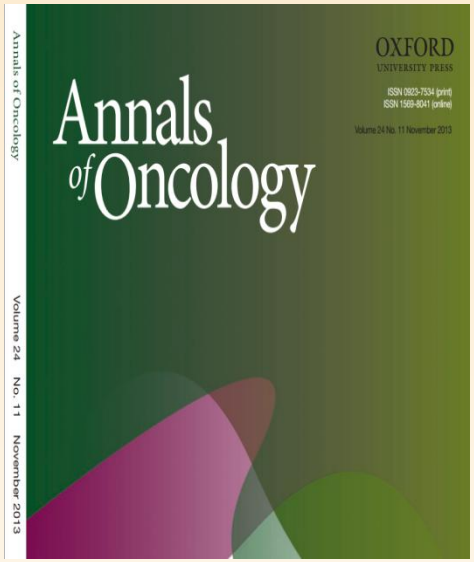
burden o

Second and late lines

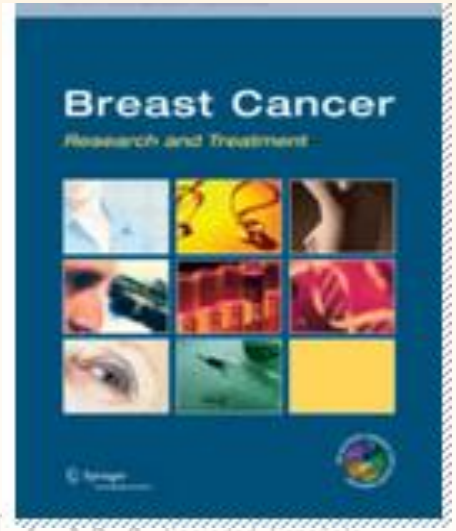
There is no limit to the number of therapy lines to be proposed. However, maintenance of a good quality of life is principal and can be best achieved with prompt amelioration of symptoms [3].

A large number of agents have shown activity in MBC and may be suitable for selected patients. However, the ability to influence survival is modest and there is little justification for highly toxic regimens. Good options are: rechallenging with an alternative taxane (standard or nab-paclitaxel), or anthracycline (liposomal), or introducing agents with different mechanisms of action like vinorelbine (oral or IV), capecitabine or eribuline.

BEVACIZUMAB



First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic **breast cancer**: pooled and subgroup analyses of data from 2447 patients. Miles DW, Diéras V, Cortés J, Duenne AA, Yi J, O'Shaughnessy J.Ann Oncol. 2013 Nov;24(11):2773-80.



Breast Cancer Res Treat. 2012 Jun;133(3):1067-75.
Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial. Brufsky A[1], Valero V, Tiangco B, Dakhil S, Brize A, Rugo HS, Rivera R, Duenne A, Bousfoul N, Yardley DA.

GEICAM investigación en cáncer de mama

En mujeres con cáncer de mama metastásico, triple negativas, el tratamiento con antraciclinas, taxanoso capecitabina + bevacizumab 10 mg/kg cada 2 semanas ó 15 mg/kg cada 3 semanas, comparado con la quimioterapia parece ser más eficaz en mejorar la supervivencia libre de progresión de la enfermedad pero no para mejorar la supervivencia global. En ambos grupos la frecuencia de efectos adversos grado 3 ó 4 sería alrededor del 50% (André 2012).

En mujeres con cáncer de mama metastásico, triple negativas, el tratamiento con taxanos, gemcitabina, capecitabina o vinorelbina + bevacizumab 10 mg/kg cada 2 semanas ó 15 mg/kg cada 3 semanas, comparado con la quimioterapia + placebo, parece ser más eficaz en mejorar la supervivencia libre de progresión de la enfermedad, la supervivencia global y la respuesta al tratamiento. Las pacientes tratadas con quimioterapia + bevacizumab presentarían una mayor frecuencia de efectos adversos grado 3 ó 4 (neutropenia, hipertensión y proteinuria) (Brufsky 2011).

special article

Annals of Oncology 00: 1–18, 2014
doi:10.1093/annonc/mdu385

ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

special article

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ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

Bevacizumab combined with chemotherapy as first- or second-line therapy for MBC provides only a moderate benefit in PFS and no benefit in overall survival. The absence of known predictive factors for bevacizumab efficacy renders recommendations on its use difficult. Bevacizumab can only therefore be considered as an option in selected cases in these settings and is not recommended after a first/second line.

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Clin Transl Oncol
DOI 10.1007/s12094-013-1084-3

CLINICAL GUIDES IN ONCOLOGY

SEOM Clinical Guidelines for the systemic treatment of early breast cancer 2013

special article

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Clin Transl Oncol
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CLINICAL GUIDES IN ONCOLOGY

SEOM Clinical Guidelines for the systemic treatment of early breast cancer 2013

Bevacizumab, a humanized anti-VEGF monoclonal antibody, is the only biological agent approved for HER2-negative MBC patients. In combination with paclitaxel or capecitabine, bevacizumab strongly increases responses and progression-free survival [13]. Its toxicity profile, hypertension, proteinuria, and hemorrhagic events are manageable with no increase in toxic deaths [14]. In the absence of predictive markers, bevacizumab could be considered for selected patients with aggressive or symptomatic disease [3].

CARBOPLATINO

Study	n	Regimen	Eligibility	pCR Breast & Axilla (%)
Randomized trials				
Alba[21]	94	Epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 21 d x 4 cycles followed by docetaxel 100 mg/m^2 every 21 d x 4 or docetaxel 75 mg/m^2 + carboplatin AUC 6 every 21 d x 4 cycles	Stage II-III ER-, PR-, HER2- and CK 5/6 or EGFR-positive breast cancer	30% with Cp, 30% no Cp
von Minckwitz[22]	315	Paclitaxel 80 mg/m^2 every 7 d + nonpegylated liposomal doxorubicin 20 mg/m^2 every 7 d + bevacizumab 15 mg/kg IV every 21 d ± carboplatin AUC 1.5 every 7 d x 18 cycles	Stage II-III TNBC	59% with Cp, 38% no Cp
Sikov[29]	443	Paclitaxel 80 mg/m^2 every 7 d x 12 cycles followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 wk x 4 cycles ± carboplatin AUC 6 every 21 d x 4 cycles (with paclitaxel) ± bevacizumab 10 mg/kg every 2 wk x 9 cycles (with paclitaxel and doxorubicin/cyclophosphamide)	Stage II-III TNBC	54% with Cp, 41% no Cp, 52% with bev, 44% no bev
Single-arm trials				
Gronwald[17]	25	Cisplatin 75 mg/m^2 IV every 21 d x 4 cycles	Stage I-III *BRCA1*-mutant breast cancer (80% TNBC)	72%
Silver[19]	28	Cisplatin 75 mg/m^2 IV every 21 d x 4 cycles	Stage IIA-IIIC TNBC (T ≥ 1.5 cm)	21%
Ryan[20]	51	Cisplatin 75 mg/m^2 IV every 21 d x 4 cycles + bev 15 mg/kg IV every 3 wk x 3 cycles	T1-3 TNBC	15%
Telli[23]	80	Gemcitabine 1000 mg/m^2 IV d 1,8 + carboplatin AUC 2 IV d1,8 + iniparib 5.6 m/kg IV d 1, 4, 8, 11 every 21 d x 6 cycles	Stage I-IIIA TNBC or *BRCA1/2*-mutant breast cancer (T ≥ 1 cm)	36%, *BRCA*^{wt} = 33%, *BRCA*^{mut} = 56%

CARBOPLATINO

ONCOLOGY LETTERS 5: 983-991, 2013

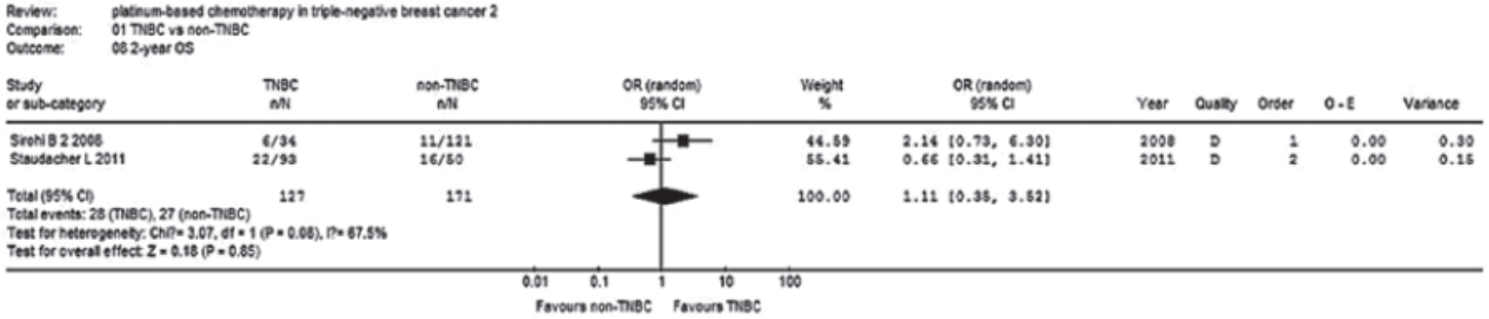
Platinum-based chemotherapy in triple-negative breast cancer: A meta-analysis

MIAO LIU, QIN-GUO MO, CHANG-YUAN WEI, QING-HONG QIN, ZHEN HUANG and JIE HE

Breast Surgery Department of Tumor Hospital, Guangxi Medical University, Nanning, Gaungxi 530021, P.R. China

CARBOPLATINO

ONCOLOGY LETTERS 5: 983-991, 2013



Brea

Figure 7. 2-year overall survival rate: advanced/metastatic.

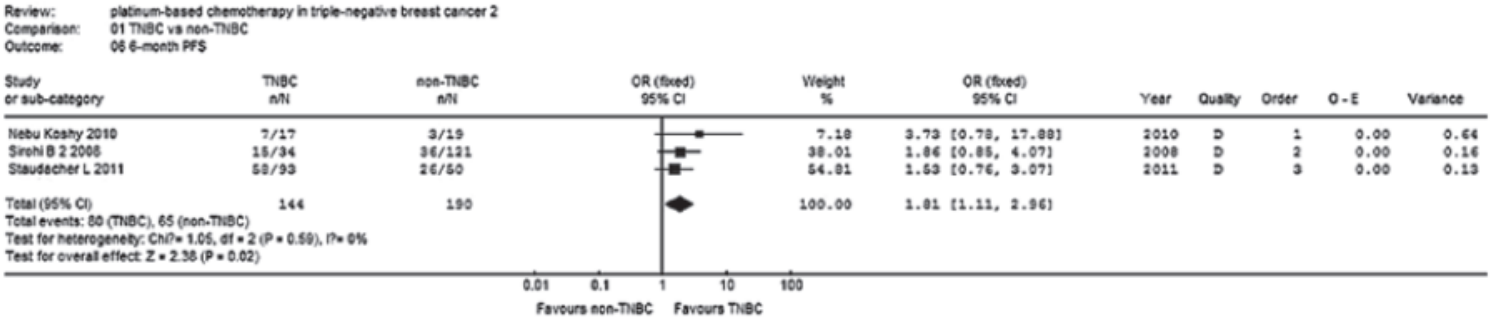


Figure 8. 6-month progression-free survival rate: advanced/metastatic.

Las pacientes con cáncer de mama metastásico triple negativas tratadas con quimioterapia basada en platinos (cisplatino 25-50 mg/m2 o carboplatino AUC= 5 ó cualquiera de ellos en combinación con gencitabina 1.000 mg/m2) parecen presentar un beneficio similar a las pacientes no triple negativas en términos de supervivencia y respuesta al tratamiento y podrían presentar un beneficio superior en términos de supervivencia libre de progresión de la enfermedad.Los efectos adversos grado 3 ó 4 más importantes son la neutropenia febril, leucopenia, neutropenia, anemia, trombopenia, hiponatremia, alopecia, nausea/vómito, diarrea y astenia (Liu 2013).

special article

Annals of Oncology 00: 1–18, 2014
doi:10.1093/annonc/mdu385

ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

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ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

Guideline statements	LoE	Consensus
In patients with ***BRCA*-*associated triple-negative or endocrine-resistant MBC*** previously treated with an anthracycline and a taxane (in the adjuvant or metastatic setting), a platinum regimen may be considered, if the patient is not included in a clinical trial. All other treatment recommendations are similar to sporadic MBC.	IC	82.5% (33) yes 12.5% (5) abstain (40 voters)

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Clin Transl Oncol
DOI 10.1007/s12094-013-1084-3

CLINICAL GUIDES IN ONCOLOGY

SEOM Clinical Guidelines for the systemic treatment of early breast cancer 2013

special article

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CLINICAL GUIDES IN ONCOLOGY

SEO
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There is a great debate about the place of platine compounds in mostly MBC triple-negative patients. With no phase III data, the combination of carboplatine and gemcitabine has been accepted as control arm by EMA and FDA [11]. The combination is active in patients resistant to anthracyclines and taxanes and it is an acceptable option in young patients with aggressive symptomatic disease. As gemcitabine single agent has very little activity in this setting, it makes sense to preserve it for this combination.

review

Annals of Oncology
doi:10.1093/annonc/mds067

Targeting triple-negative breast cancer: optimising therapeutic outcomes

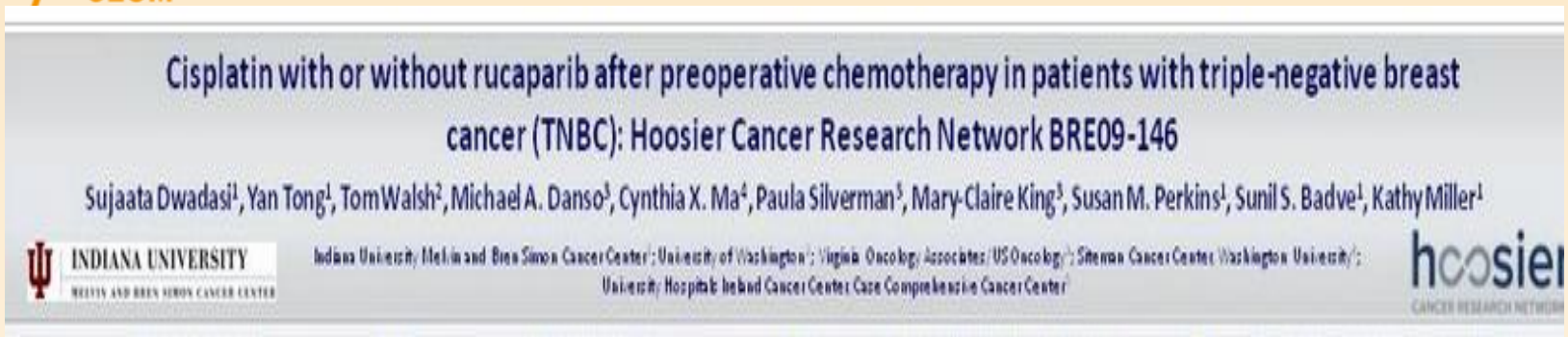
K. Gelmon[1,2*], R. Dent[3,4], J. R. Mackey[5,6], K. Laing[7,8], D. McLeod[9] & S. Verma[10,11]

PARP inhibitors							
O'Shaughnessy [31], Rd phase II	First-line+ (0–3 prior regimens)	Gemcitabine 1000 mg/m^2 d1, 8, q3w; carboplatin AUC 2 d1, 8, q3w; iniparib 5.6 mg/kg d1, 4, 8, 11, q3w	61	56 (34–76)	52 ($P = 0.02$)	5.9; 0.59 [0.39–0.90] ($P = 0.01$)	12.3; 0.57 [0.36–0.90] ($P = 0.01$)
		Gemcitabine 1000 mg/m^2 d1, 8, q3w; carboplatin AUC 2 d1,8, q3w[d]	62	53 (26–80)	32	3.6	7.7
O'Shaughnessy [37], Rd phase III	First-line+ (0–2 prior regimens)	Gemcitabine 1000 mg/m^2 d1,8, q3w; carboplatin AUC 2 d1,8, q3w; iniparib 5.6 mg/kg d1, 4, 8, 11, q3w	261	53	34	5.1; 0.79 [0.65–0.98] ($P = 0.027$)[f]	11.8; 0.88 [0.69–1.12] ($P = 0.28$)[g]
		Gemcitabine 1000 mg/m^2 d1, 8, q3w; carboplatin AUC 2 d1, 8, q3w[e]	258	54	30	4.1	11.1

Phase III study evaluating safety and efficacy of the addition of veliparib plus carboplatin versus the addition of carboplatin to standard neoadjuvant chemotherapy in subjects with early-stage triple-negative breast cancer (TNBC).

Gunter Von Minckwitz MD

Opened in Jan 2014. **NCT02032277**



With a median follow-up of 9 months, 1-yr DFS was similar (~76%) in both treatment groups. BROCA identified deleterious mutations in 22/101 (22%) pts (8 BRCA 1, 12 BRCA 2, 2 BRIP1). 1-yr DFS in the 22 pts with mutations was ~85% compared to 79% without mutations. Whole transcriptome sequencing of paired pre vs. post preoperative chemotherapysamples will be reported separately (Radovich et al, ASCO 2014). **Conclusions: The addition of low dose rucaparib (current phase II monotherapy dose 600 mg orally twice daily) did not impact the toxicity of cisplatin or improve 1-yr DFS**. Comparison to predicted DFS based on residual cancer burden (RCB) is planned to investigate potential benefit from cisplatin. Genetic testing was underutilized in this high risk population with only 30% of BRCA1 and BRCA2 mutations identified as part of routine clinical care. Clinical trial information: **NCT01074970**.

La evidencia disponible proviene de ensayos clínicos aleatorizados de fase 2 ó 3, no ciegos o con escasa potencia estadística por lo que la mayoría de los resultados son imprecisos y la calidad de la evidencia es baja.

Se debe destacar que no existen suficientes pruebas científicas que permitan identificar un tratamiento adecuado para estas pacientes. ***Todos los resultados se basan en análisis de subgrupos de las estrategias valoradas en otros ensayos clínicos.***

Los efectos adversos son frecuentes en las pacientes tratadas con quimioterapia basada en platinos, inhibidores PARP, antiangiogénicos, o nuevos agentes. Sin embargo, ninguno de los autores de los estudios evaluados en este informe destacó particularmente la toxicidad sobre los beneficios en términos de eficacia del tratamiento.

Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-)

Guidelines Breast
Version 2014.1

www.ago-online.de

	Oxford / AGO LoE / GR		
➢ Cytotoxic therapy as for ER pos. HER2 neg. patients			++
➢ Experimental therapies within studies			++
➢ Platinum-based regimen	4	C	+/-
➢ Bevacizumab added to cytotoxic therapy	2b	B	+

Guidelines Breast
Version 2014.1

www.ago-online.de

Further Information

References

MBC HER2 negative: Cytotoxic Therapy After *Taxane and Anthracycline* Treatment

	Oxford / AGO LoE / GR		
➢ Experimental therapies within studies			++
➢ Capecitabine	2b	B	++
➢ Eribulin	1b	B	++
➢ Vinorelbine	2b	B	++
➢ (Peg)-liposomal Doxorubicin	2b	B	+
➢ Gemcitabine + Cisplatin / Carboplatin	2b	B	+/-
➢ Gemcitabine + Capecitabine	2b	B	+/-
➢ Gemcitabine + Vinorelbine*	1b	B	-
➢ Ixabepilone + Capecitabine*	1b	B	-

PERSPECTIVAS DE FUTURO

Triple-negative breast cancer: bridging the gap from cancer genomics to predictive biomarkers

Ther Adv Med Oncol
2014, Vol. 6(3) 88–100
DOI: 10.1177/1758834013519843

S. Lindsey Davis, S. Gail Eckhardt, John J. Tentler and Jennifer R. Diamond

Table 2. Biomarker evaluations with classical chemotherapeutic agents in the treatment of triple-negative breast cancer in the neoadjuvant setting.

Chemotherapy regimen	Potential biomarker(s)	pCR rate	Method of testing	Type of study
Docetaxel and epirubicin [Li *et al*. 2011]	Basal-like markers negative Nm23-H1 positive	72.7% 53.8%	IHC	Prospective
Cisplatin [Byrski *et al*. 2010]	*BRCA1* mutation	83%	PCR	Retrospective
Docetaxel and doxorubicin [Keam *et al*. 2011]	High Ki-67	18.2%	IHC	Retrospective
Anthracycline-based therapy [Bidard *et al*. 2008]	p53 positive	22.5%*	IHC	Retrospective
TAC [Von Minckwitz *et al*. 2011]	High cytoplasmic PARP	41%	IHC	Retrospective
Anthracycline and taxane combinations [Darb-Esfahani *et al*. 2012]	High *TMSB15A* expression	47.2% and 36.8%**	qRT-PCR	Retrospective
Various regimens [Dennison *et al*. 2013]	High *LDHB* expression	45.5% and 36.6%**	Microarray	Retrospective
Anthracycline or taxane-based therapy [Ono *et al*. 2012]	High tumor-infiltrating lymphocytes	37%	Histopathologic evaluation	Retrospective

* Not statistically significant increase.

Published OnlineFirst March 27, 2013; DOI: 10.1158/0008-5472.CAN-12-1699

Cancer Research

Review

Genetic Susceptibility to Triple-Negative Breast Cancer

Kristen N. Stevens[1], Celine M. Vachon[1], and Fergus J. Couch[1,2]

Published OnlineFirst March 27, 2013; DOI: 10.1158/0008-5472.CAN-12-1699

Review

Geneti

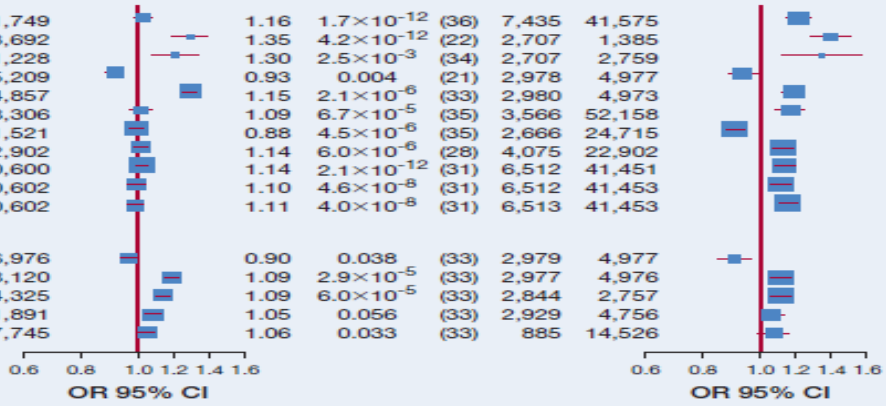
Kristen N.

A ER-positive

SNP	Chr.	Locus	OR	P	Ref.	Cases	Controls
Triple-negative risk: Strong evidence							
rs10069690	5	*TERT*	1.03	0.011	(36)	27,074	41,749
rs2046210[a]	6	*ESR1*	1.26	7.1×10^{-10}	(22)	3,654	3,692
rs12662670[b]	6	*ESR1*	1.17	2.4×10^{-3}	(34)	4,310	11,228
rs10483813[c]	14	*RAD51L1*	0.90	1.3×10^{-9}	(21)	16,693	35,209
rs3803662	16	*TOX3*	1.26	9.6×10^{-60}	(33)	19,420	34,857
rs8170	19	19p13	0.99	0.38	(35)	25,649	48,306
rs8100241	19	19p13	0.99	0.61	(35)	12,267	21,521
rs22843378	20	*RALY/EIF2S2*	1.01	0.67	(28)	9,965	22,902
rs4245739	1	*MDM4*	0.99	0.56	(31)	25,225	40,600
rs12710696	2	2p24.1	1.01	0.53	(31)	25,225	40,602
rs11075995	16	*FTO*	1.02	0.083	(31)	25,220	40,602
Triple-negative risk: Marginal evidence							
rs17468277[d]	2	*CASP8*	0.96	0.058	(33)	17,805	36,976
rs13387042	2	2q35	1.16	8.5×10^{-30}	(33)	19,310	38,120
rs889312	5	*MAP3K1*	1.11	9.3×10^{-14}	(33)	18,835	34,325
rs3817198	11	*LSP1*	1.07	1.4×10^{-5}	(33)	17,427	31,891
rs1982073	19	*TGFB1*	1.04	0.011	(33)	11,495	27,745

B ER-negative

OR	P	Ref.	Cases	Controls
1.16	1.7×10^{-12}	(36)	7,435	41,575
1.35	4.2×10^{-12}	(22)	2,707	1,385
1.30	2.5×10^{-3}	(34)	2,707	2,759
0.93	0.004	(21)	2,978	4,977
1.15	2.1×10^{-6}	(33)	2,980	4,973
1.09	6.7×10^{-5}	(35)	3,566	52,158
0.88	4.5×10^{-6}	(35)	2,666	24,715
1.14	6.0×10^{-6}	(28)	4,075	22,902
1.14	2.1×10^{-12}	(31)	6,512	41,451
1.10	4.6×10^{-8}	(31)	6,512	41,453
1.11	4.0×10^{-8}	(31)	6,513	41,453
0.90	0.038	(33)	2,979	4,977
1.09	2.9×10^{-5}	(33)	2,977	4,976
1.09	6.0×10^{-5}	(33)	2,844	2,757
1.05	0.056	(33)	2,929	4,756
1.06	0.033	(33)	885	14,526



C Triple-negative

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rs12662670[b]	6	*ESR1*	1.33	1.1×10^{-4}	(37)	2,707	2,759
rs10483813[c]	14	*RAD51L1*	0.86	3.0×10^{-4}	(37)	2,978	4,977
rs3803662	16	*TOX3*	1.17	3.1×10^{-6}	(37)	2,980	4,973
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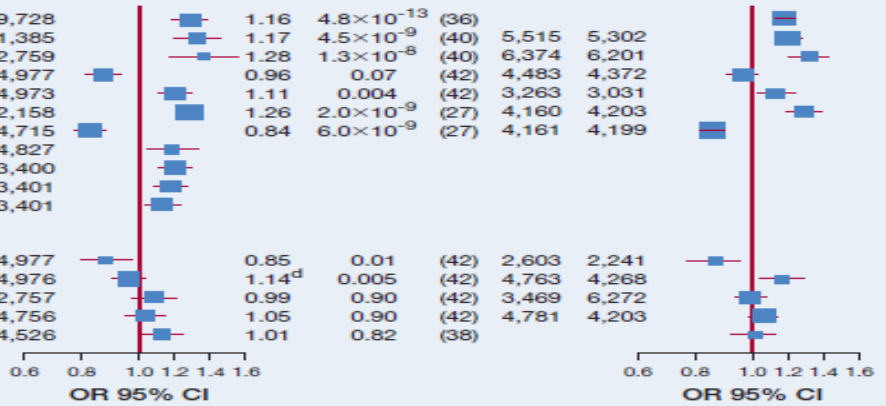
1.16	4.8×10^{-13}	(36)		
1.17	4.5×10^{-9}	(40)	5,515	5,302
1.28	1.3×10^{-8}	(40)	6,374	6,201
0.96	0.07	(42)	4,483	4,372
1.11	0.004	(42)	3,263	3,031
1.26	2.0×10^{-9}	(27)	4,160	4,203
0.84	6.0×10^{-9}	(27)	4,161	4,199
0.85	0.01	(42)	2,603	2,241
1.14[d]	0.005	(42)	4,763	4,268
0.99	0.90	(42)	3,469	6,272
1.05	0.90	(42)	4,781	4,203
1.01	0.82	(38)		



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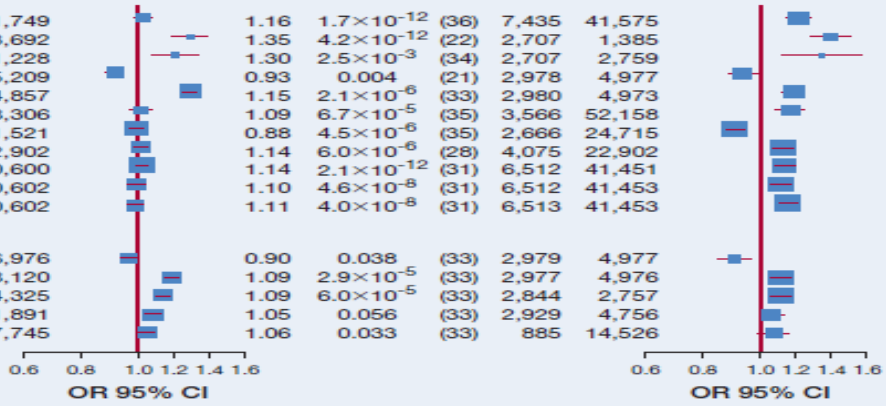

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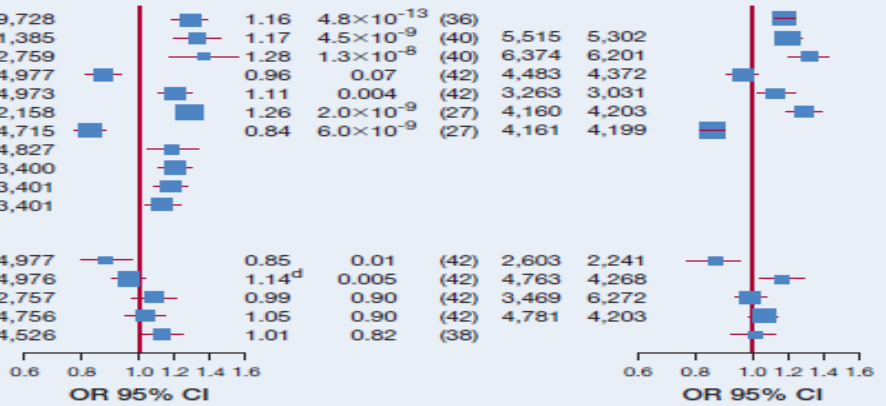


19p13.1 locus and the MDM4 locus has been associated with TNBC, but not other forms of breast cancer, suggesting that these are TNBC-specific loci

The Oncologist®

Breast Cancer

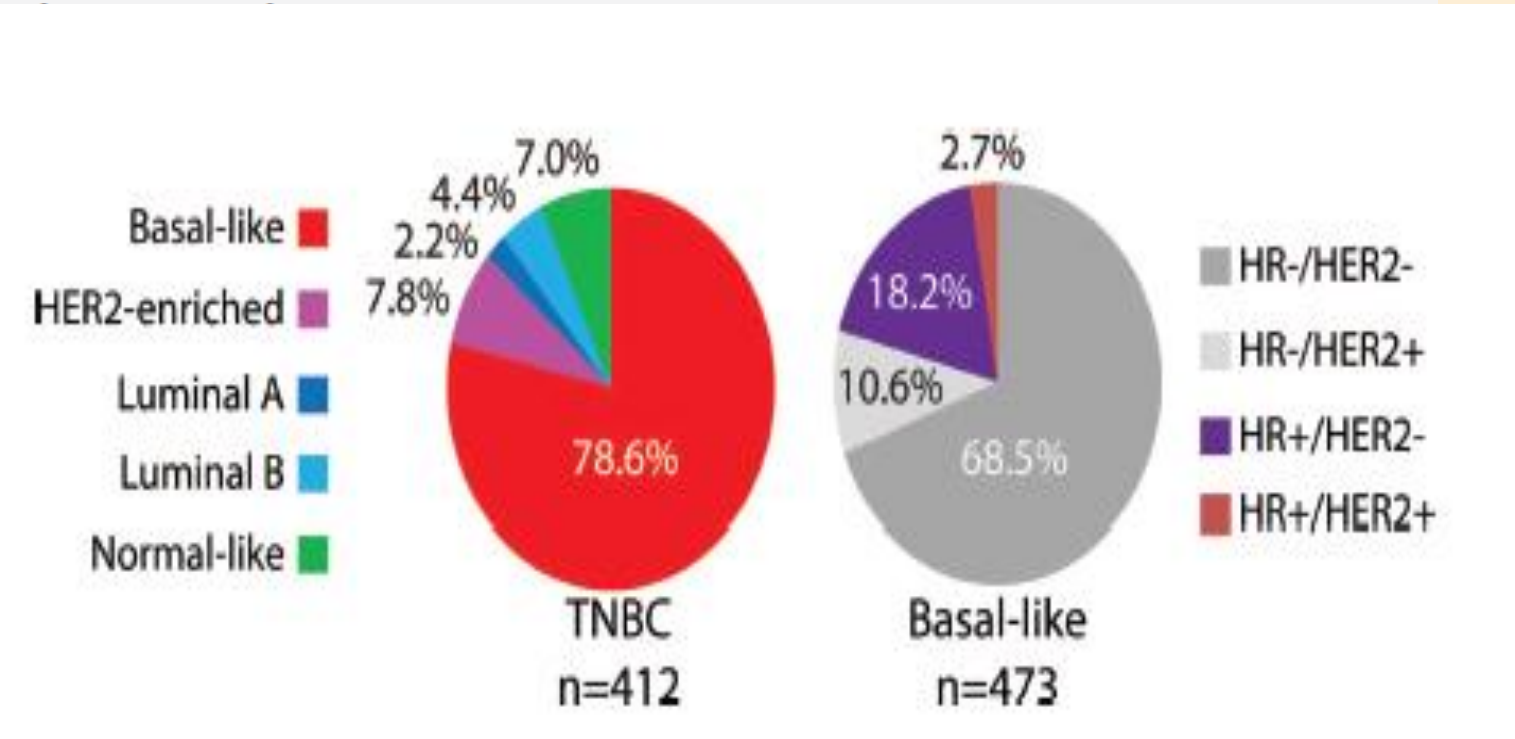
Molecular Characterization of Basal-Like and Non-Basal-Like Triple-Negative Breast Cancer

ALEIX PRAT,[a,b,c] BARBARA ADAMO,[b,c] MAGGIE C.U. CHEANG,[d] CAREY K. ANDERS,[d] LISA A. CAREY,[d] CHARLES M. PEROU[d,e,f]

The Oncologist®

Breast Cancer

Molecular Characterization of Basal-Like and Non-Basal-Like



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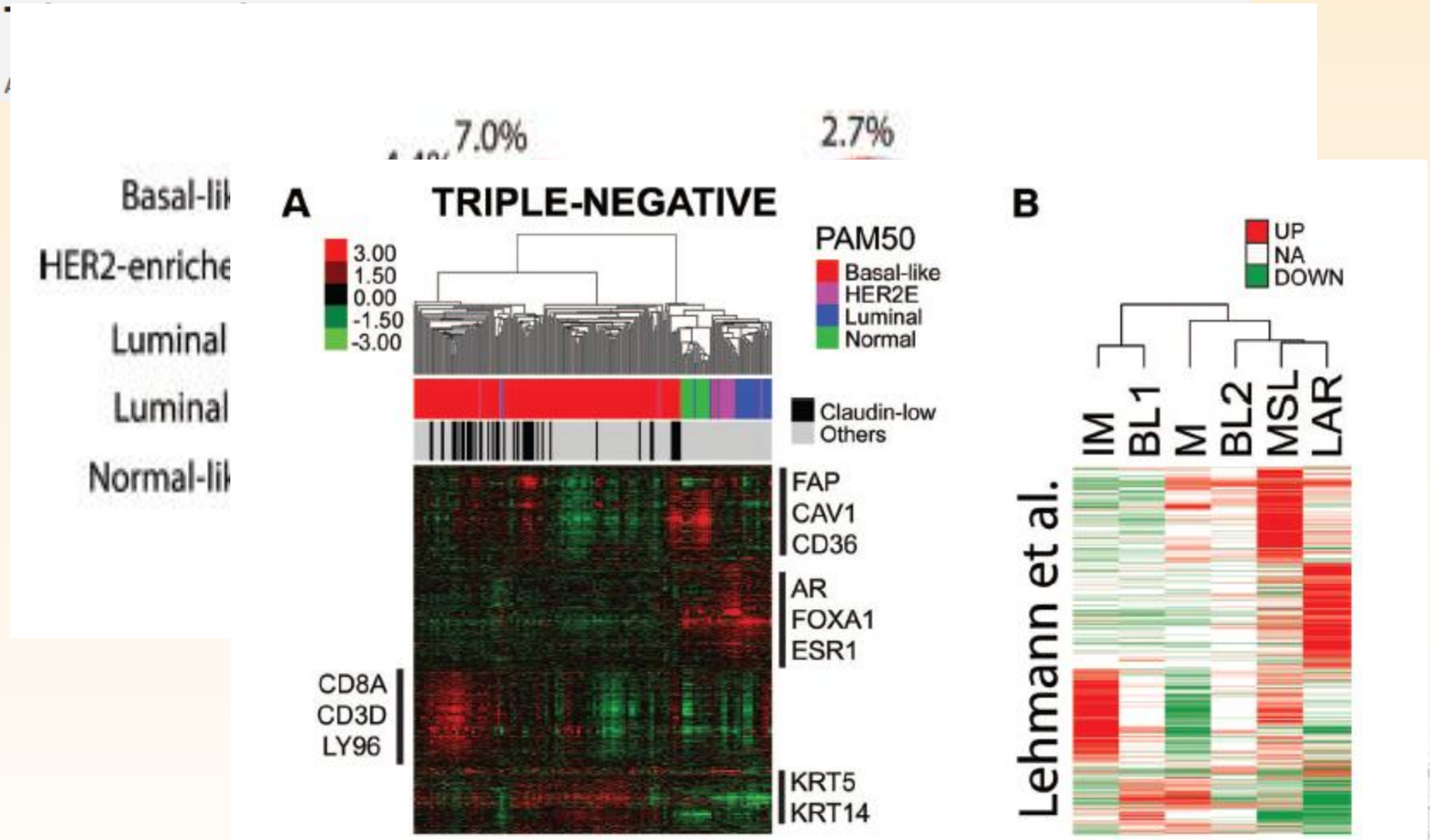


Triple Negative Subtype GE Patterns are Reproducible

UNS Unclassified

BL1 Basal-like 1

BL2 Basal-like 2

IM Immunomodulatory

M Mesenchymal

MSL Mesenchymal/Stem-like

LAR Luminal/Androgen receptor

Lehmann BD, et al.
J Clin Invest. 2011

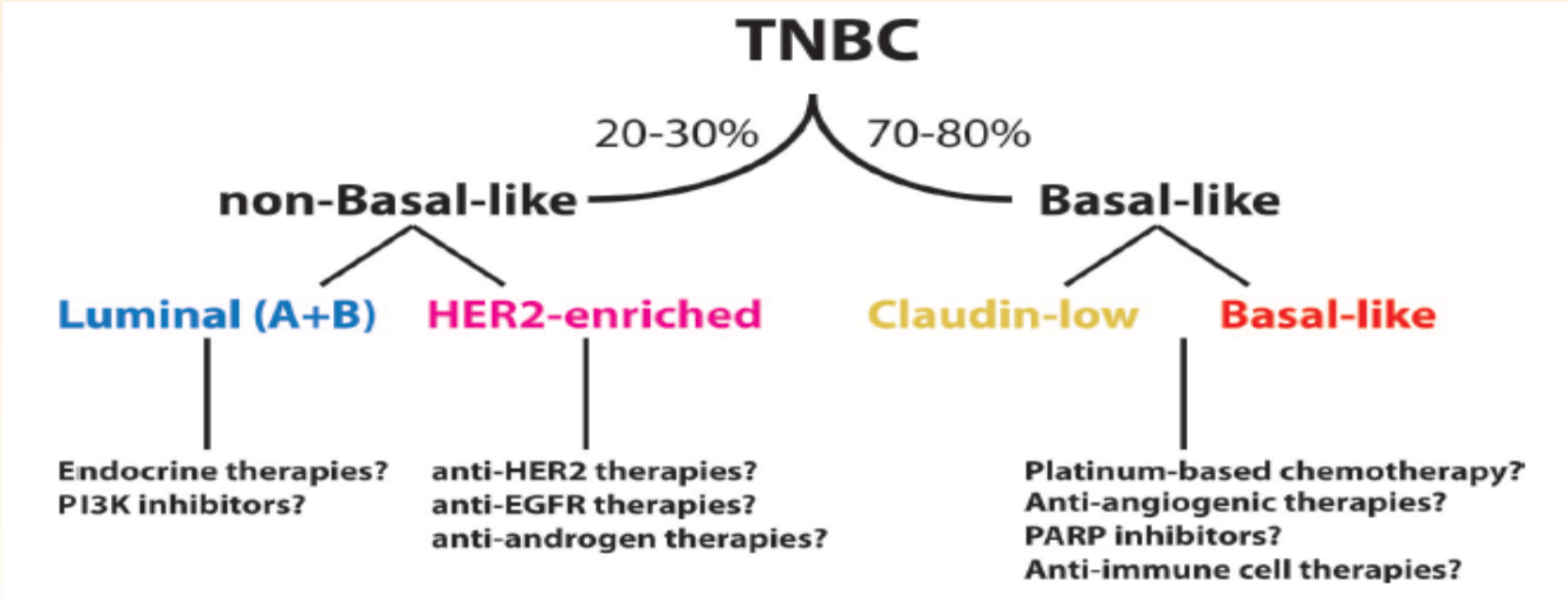
The Oncologist®

Breast Cancer

Molecular Characterization of Basal-Like and Non-Basal-Like Triple-Negative Breast Cancer

ALEIX PRAT,[a,b,c] BARBARA ADAMO,[b,c] MAGGIE C.U. CHEANG,[d] CAREY K. ANDERS,[d] LISA A. CAREY,[d] CHARLES M. PEROU[d,e,f]

[a]Translational Genomics Unit, [b]Breast Cancer Unit, and [c]Medical Oncology Department, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [d]Lineberger Comprehensive Cancer Center, [e]Department of Genetics, and [f]Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, North Carolina, USA



BEATRICE Trial: Biomarker Results

- Biomarker analysis performed to investigate potential predictive markers of benefit from adjuvant bevacizumab
- Sub-study included 45% of total patient population
- Evaluated correlation of biomarkers with invasive disease-free survival

Baseline Plasma Concentration	HR*	*P*-Value
Median VEGF-A		
High	0.81	.7415
Low	0.89	
3rd Quartile VEGF-A		
High	0.64	.3551
Low	0.92	
Median VEGFR-2		
High	.61	.0291
Low	1.24	

* HR < 1.0 indicates CT plus Bev better than CT alone

Carmeliet et al., SABCS 2012, abstract P3-06-34

Clinical Cancer Research

Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes

Hiroko Masuda, Keith A. Baggerly, Ying Wang, et al.

Clin Cancer Res Published OnlineFirst August 15, 2013.

Clinical Cancer Research

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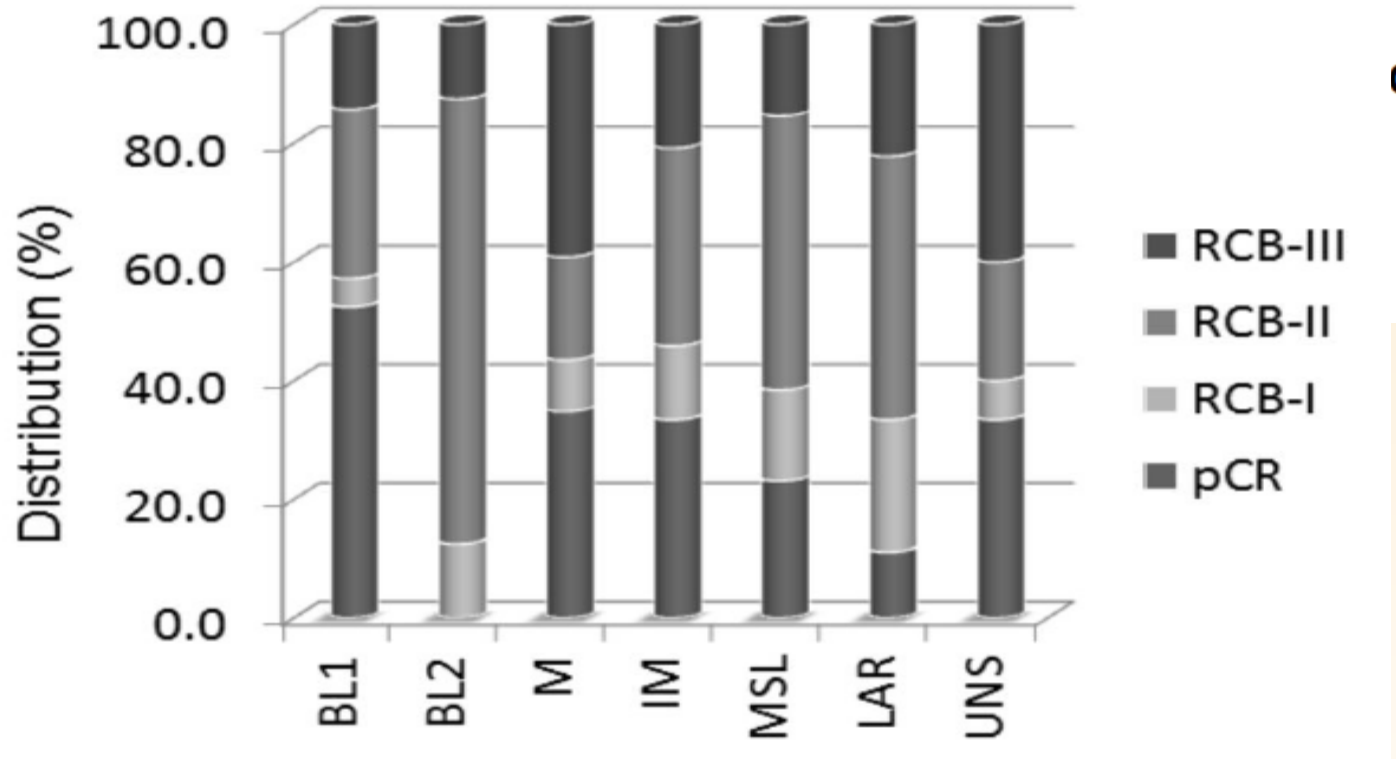

Clinical Cancer Research

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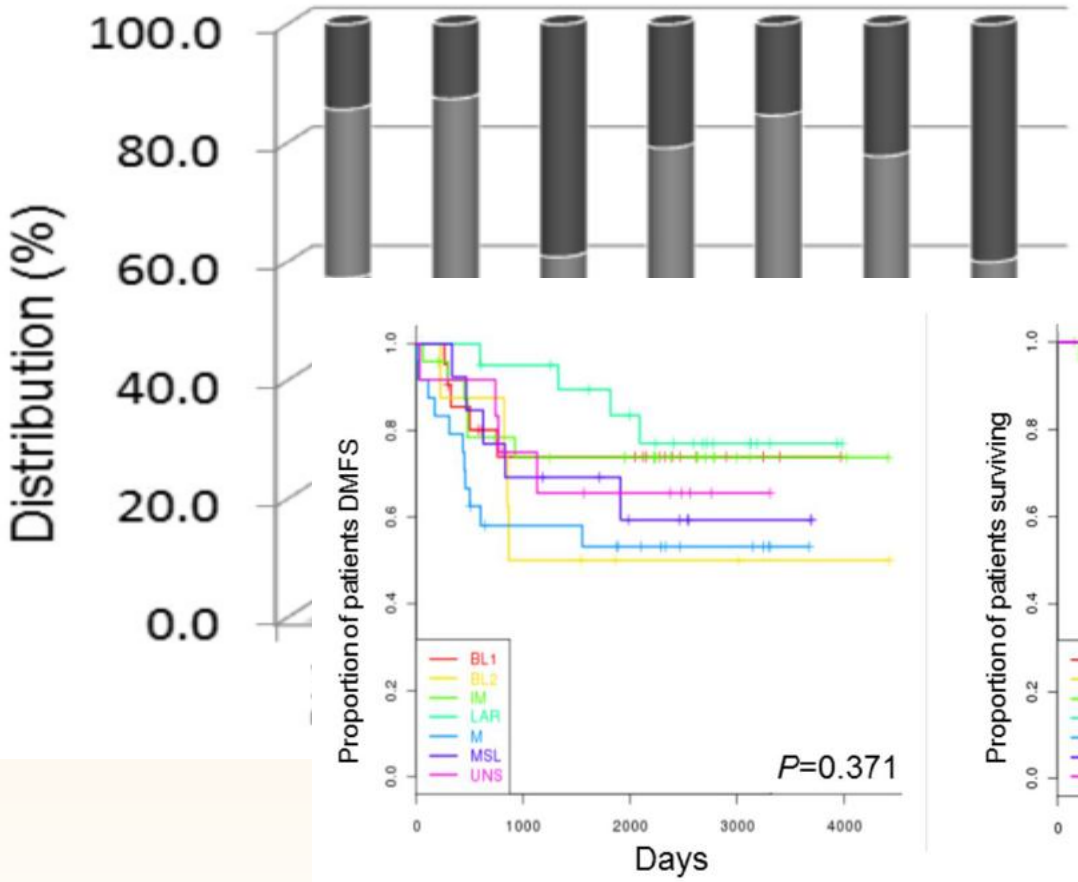
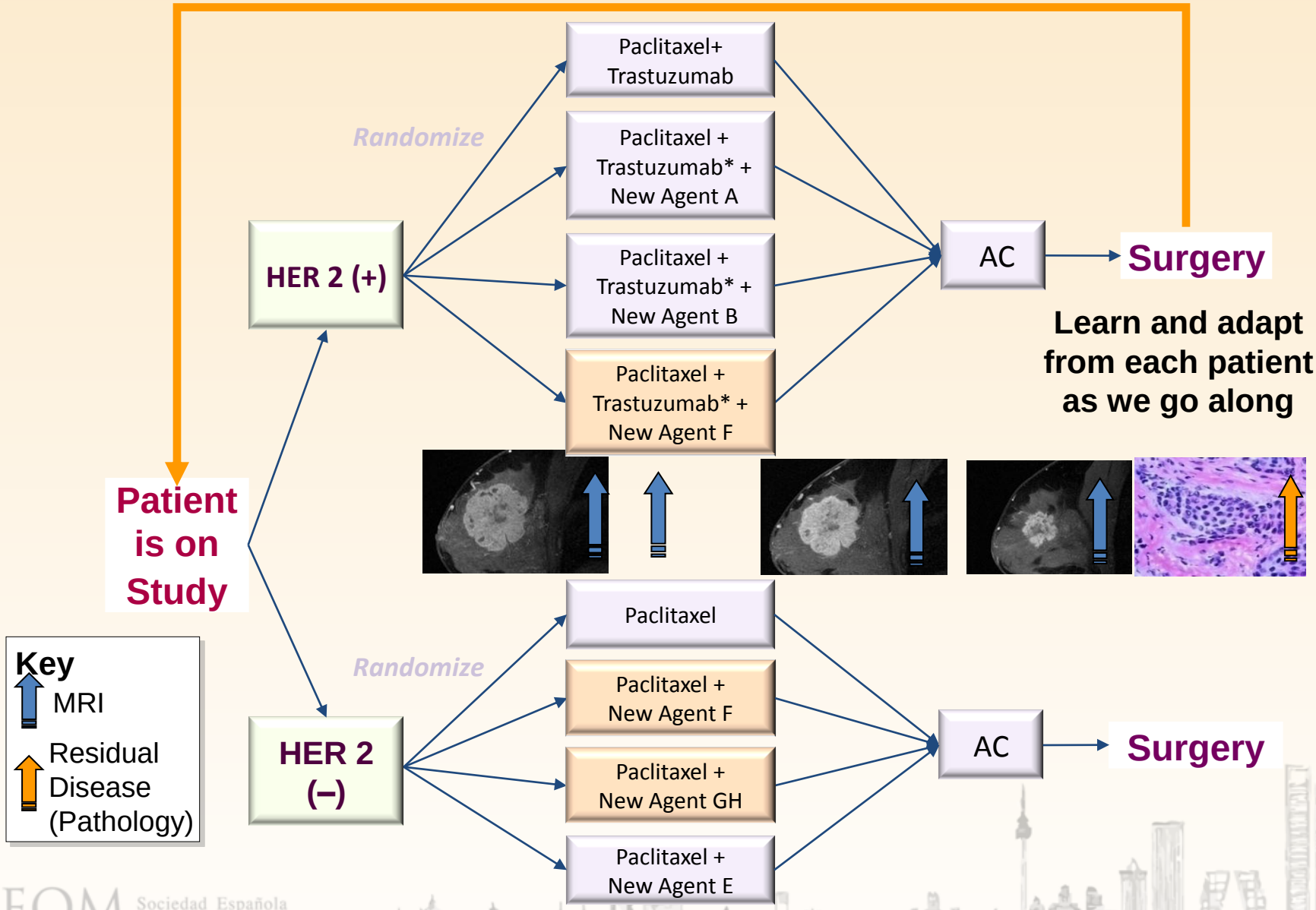


Triple-negative breast cancer subtypes and pathologic complete-response rate to neoadjuvant chemotherapy: Results from the GEICAM/2006-2003 study.

Results: From the 94 enrolled pts, we processed 46 pre-treatment tumor samples in a central lab and isolated high-quality RNA for microarray analysis in 39 (42%); 7 samples are still pending to be analyzed. Tumors were classified as follows: 4 BL1, 2 BL2, 8 IM, 5 LAR, 3 M, 3 ML with 7 pts that couldn't be assigned to any subtype and were not included in this analysis. Three (75%) of the BL1 subtype pts achieved a pCR (p-value=0.075). In contrast, IM and LAR achieved the lowest pCR rates (12% and 20%, respectively). In the carboplatin-treated patients, 100% of BL1 patients showed pCR (p-value=0.033) in contrast with none of the IM and LAR pts. **Conclusions:** Our preliminary findings suggest that TNBC subtypes can predict tumor response to neoadjuvant CHT, supporting their potential clinical utility in diagnosis, treatment selection and drug development, bringing TNBC pts a step closer to personalized medicine.

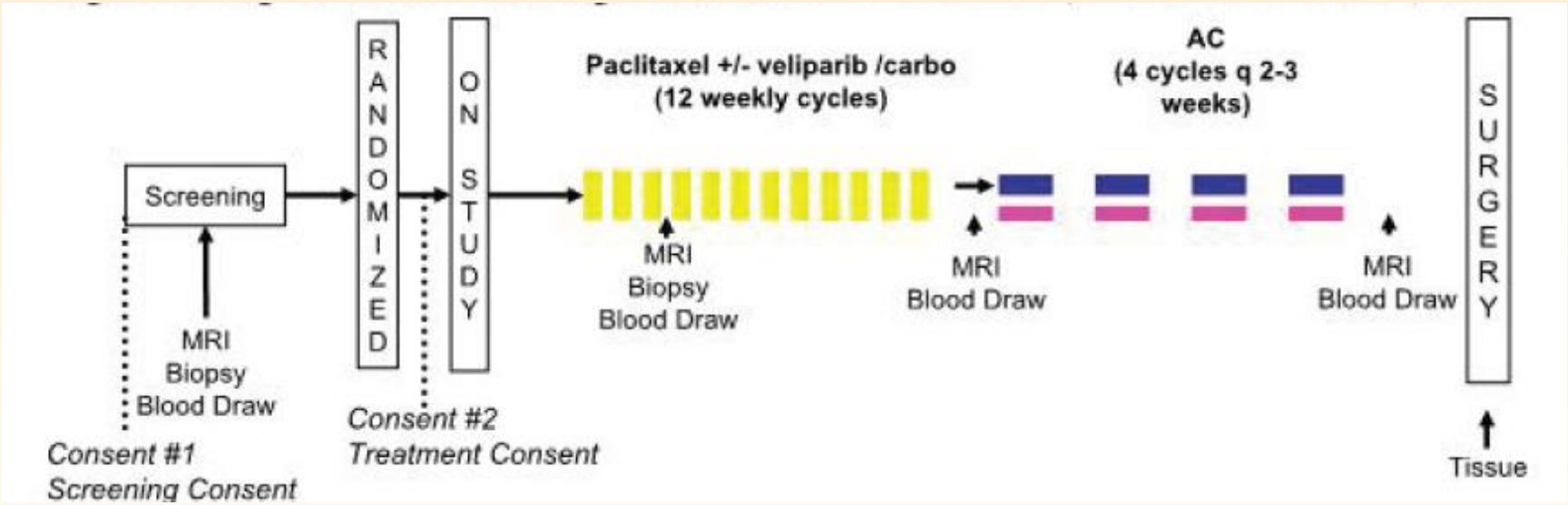
I-SPY 2 TRIAL:

Learn, Drop, Graduate, and Replace Agents Over Time



*Investigational agent may be used in place

Veliparib/carboplatino más tratamiento neoadyuvante estandar para pacientes triple negativas: I-SPY 2 TRIAL



I-SPY 2: the first graduate

Rugo et al, #S5-02, SABCS, 2013

- Primary end point: pCR
- Graduate regimens have >85% Bayesian predictive probability of success in a 300-pts biomarker-linked neoadjuvant phase III trial
- Veliparib+carbo met the 85% predictive probability criterion in HR-/HER2- and all HER2- pts

%	pCR	p V+Cb better	p of successful phase III
All HER2-	35 vs 20	97%	71%
HR+/HER2-	14 vs 15	44%	16%
TNBC	52 vs 24	99%	92%

- V/Cb graduated with a TNBC signature and recommended for future trial
- Biomarker study? (lesson from iniparib)

Therapeutic Advances in Medical Oncology *Review*

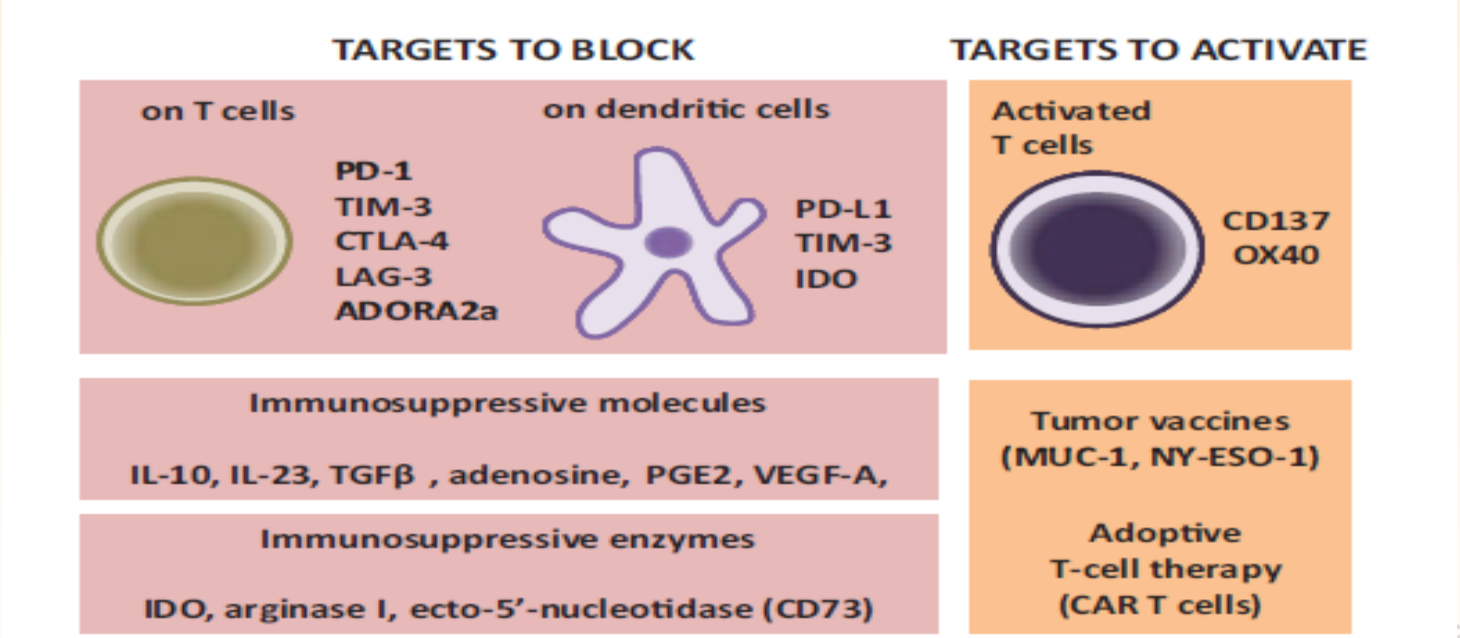
Immunotherapeutic approaches in triple-negative breast cancer: latest research and clinical prospects

Ther Adv Med Oncol

(2013) 5(3) 169–181

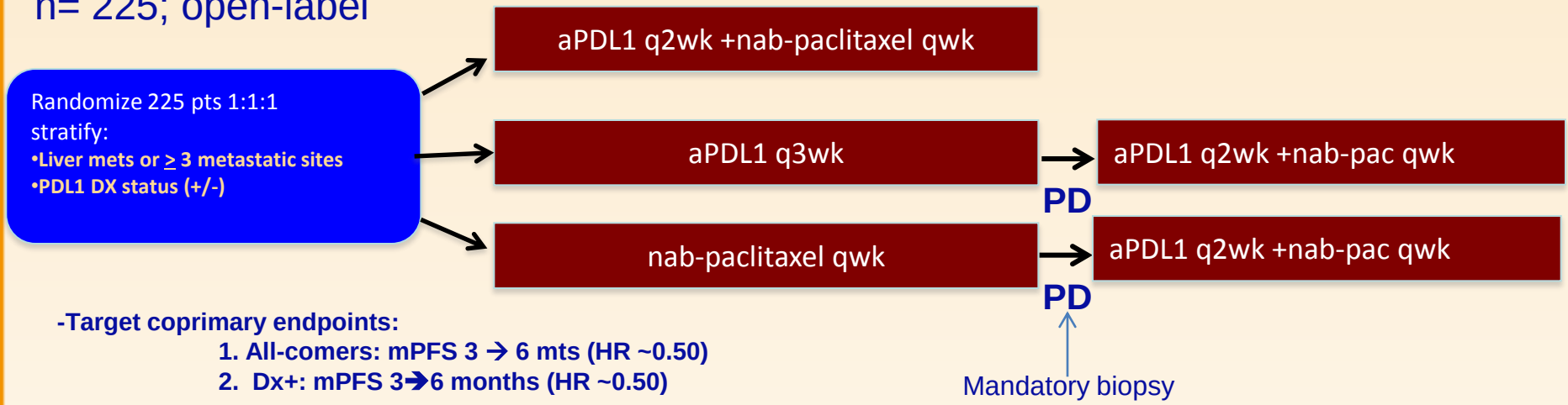
DOI: 10.1177/1758834012475152

John Stagg and Bertrand Allard



Phase II design

n= 225; open-label



-Target coprimary endpoints:

1. **All-comers: mPFS 3 → 6 mts (HR ~0.50)**
2. **Dx+: mPFS 3→6 months (HR ~0.50)**

Rationale: 2L mTNBC due to current aPDL1 monotherapy and wide bevacizumab use in EU;PFS in all comers, but powered for Dx+ question
Key eligibility: mTNBC, tissue mandatory
Primary endpoint: PFS (RECIST1.1) in all comers and Dx+
Other: PFS (mRECIST) all comers and Dx+, OS, ORR, DOR

	All Comers		Dx +	
	per comparison	3-arm total	per comparison	3-arm total
IA #1 (12M)	30	45	NA	
IA #2 (20M)	100	150	20	30
Final (24M)	125	188	25	38

Note: If subgroup analysis shows no benefit in all comers at IA #1, team will assess value in developing/enrolling **only PDL1+ IHC 2,3** patients to Ph II – and present rationale to DRC

Cancer Discov. 2014 February ; 4(2): 232–245. doi:10.1158/2159-8290.CD-13-0286.

Molecular profiling of the residual disease of triple-negative breast cancers after neoadjuvant chemotherapy identifies actionable therapeutic targets

Justin M. Balko[1,4], Jennifer M. Giltnane[2,4], Kai Wang[8], Luis J. Schwarz[1,5,6], Christian D. Young[1], Rebecca S. Cook[3,4], Phillip Owens[3], Melinda E. Sanders[2,4], Maria G. Kuba[2], Violeta Sánchez[1], Richard Kurupi[1], Preston D. Moore[1], Joseph A. Pinto[5], Franco D. Doimi[5], Henry Gómez[6], Dai Horiuchi, Andrei Goga, Brian D. Lehmann[9], Joshua A. Bauer[9], Jennifer A. Pietenpol[4,9], Jeffrey S. Ross[8], Gary A. Palmer[8], Roman Yelensky[8], Maureen Cronin[8], Vincent A. Miller[8], Phillip J. Stephens[8], and Carlos L. Arteaga[1,3,4]

Cancer Discov. 2014 February ; 4(2): 232–245. doi:10.1158/2159-8290.CD-13-0286.

Molecular
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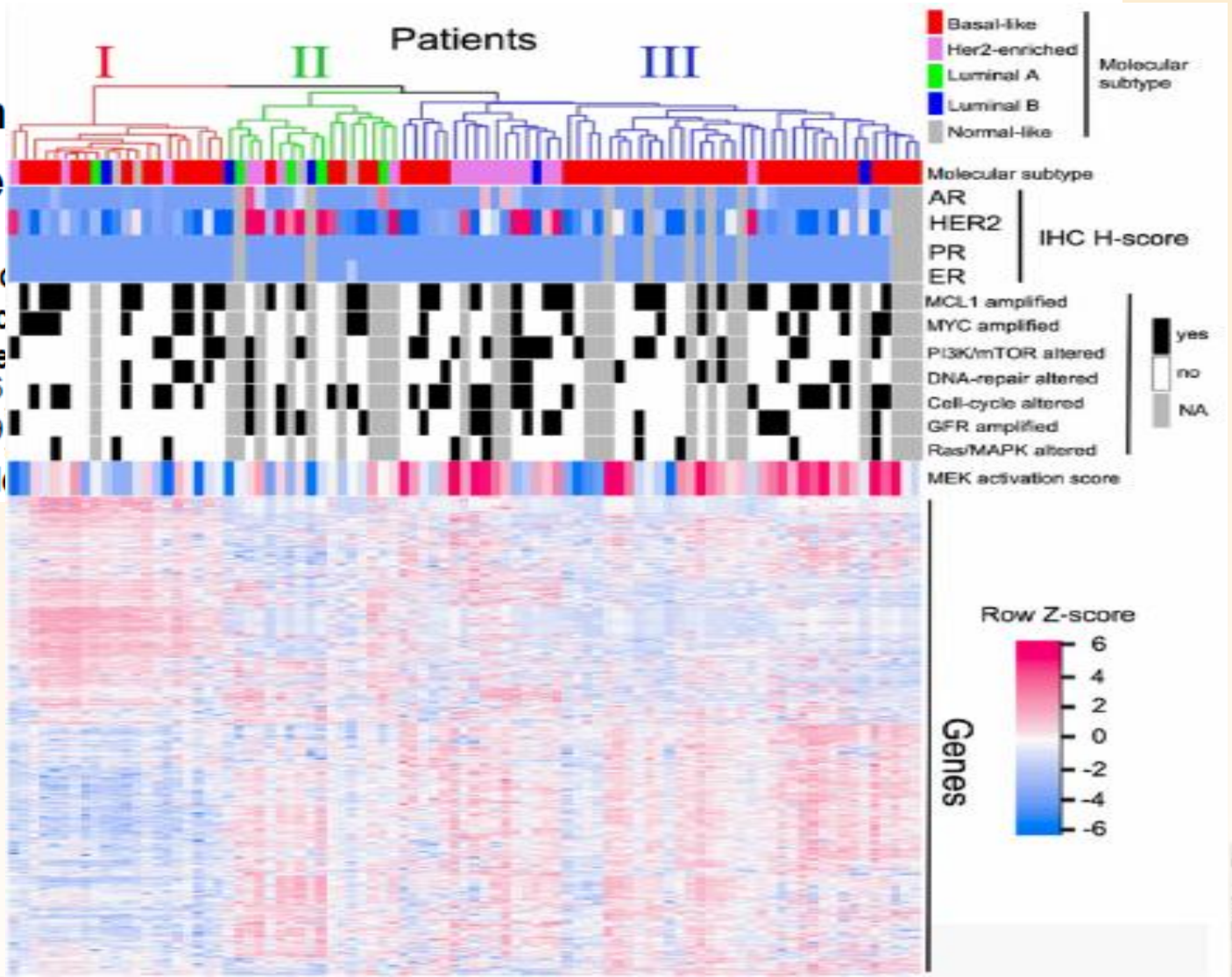


TERAPIAS DIRIGIDAS

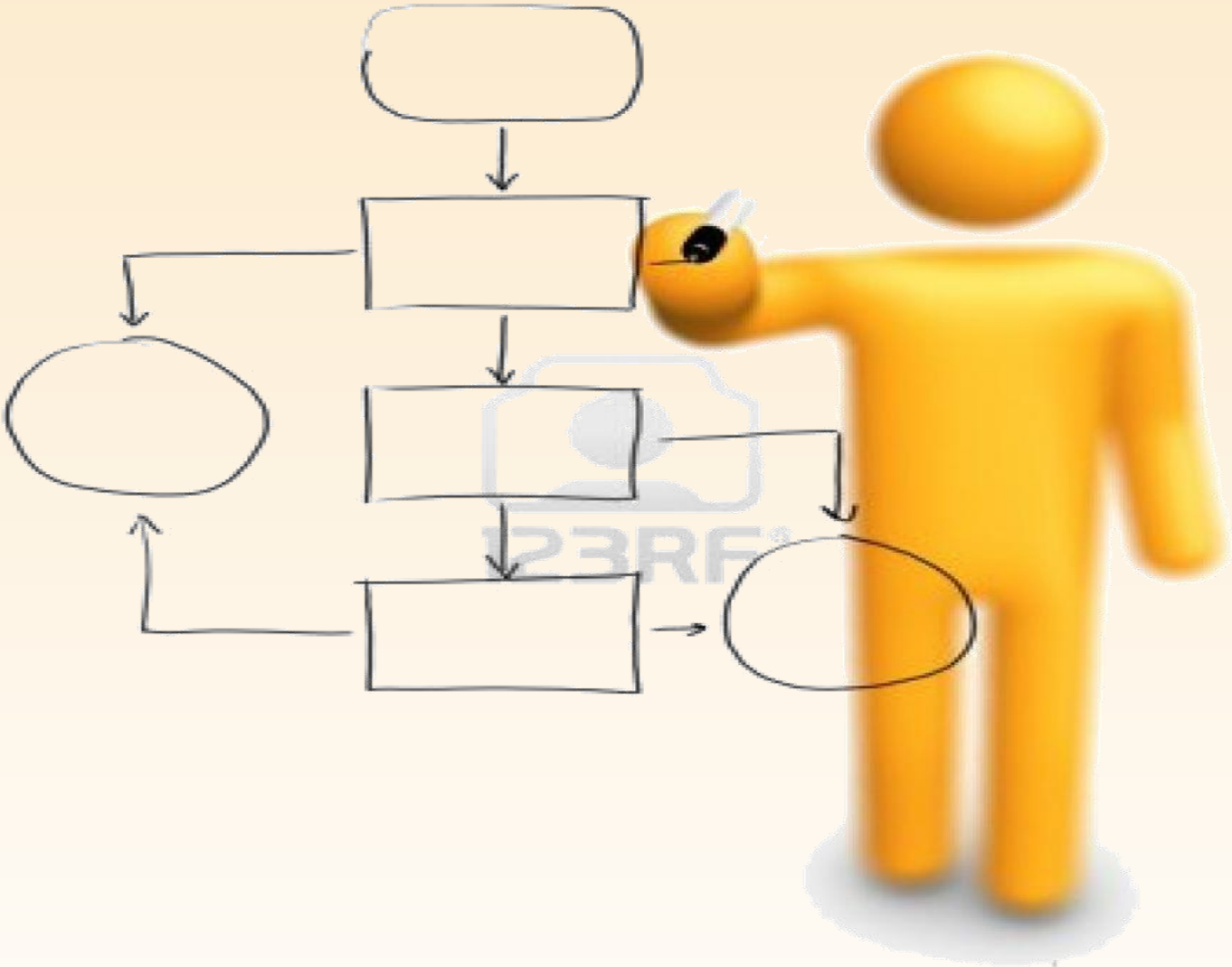
TNBC subtypes	Molecular characteristics	Potential therapies
Basal-like 1	Cell cycle function Proliferation DNA damage response	Chemotherapy PARP inhibitor
Basal-like 2	Cell cycle function Proliferation Growth factor signaling	Chemotherapy PARP inhibitor
Mesenchymal	EMT Cell motility Differentiation Proliferation	Src inhibitor PI3K pathway inhibitor Wnt pathway inhibitor
Mesenchymal stem-like	EMT Cell motility Differentiation Growth factor signaling Angiogenesis	Src inhibitor PI3K pathway inhibitor Wnt pathway inhibitor
Luminal androgen receptor	AR signaling Luminal cytokeratine	AR antagonist Hsp90 inhibitor PI3K pathway inhibitor
Immunomodulatory	Immune cell processes	Immune targeted agents

AR, androgen receptor; EMT, epithelial mesenchymal transition; PARP, poly ADP ribose polymerase; TNBC, triple-negative breast cancer.

CONCLUSIONES

- EL CÁNCER DE MAMA TRIPLE NEGATIVO CONSTITUYE UN GRUPO HETEROGENEO DE SUBTIPOS CON DISTINTOS MECANISMOS BIOMOLECULARES.
- DEBEMOS PONER EN MARCHA LOS MECANISMOS NECESARIOS PARA LA IMPLEMENTACIÓN DEL DIAGNÓSTICO MOLECULAR EN ESTE SUBGRUPO DE PACIENTES.
- CON ELLO, EL TRATAMIENTO BASADO EN LA COMBINACIÓN DE ANTRACICLINAS Y TAXANOS PODRÍA INDIVIDUALIZARSE (INCLUSIÓN DE PLATINOS, ANTIANGIOGÉNICOS, INHIBIDORES DE PARP…)
- CONSTITUYE UNO DE LOS PRINCIPALES DESAFIOS EN CÁNCER DE MAMA QUE NOS OBLIGA A PARTICIPAR EN LAS DISTINTAS LINEAS DE INVESTIGACIÓN.

GRACIAS




Lo siento pero hemos cambiado el algoritmo
TOON Refugee