



3er. Taller Internacional Multidisciplinario de Cáncer de Mama y 1 er.
Simposio de Cáncer Ginecológico
7 de Abril de 2019, Córdoba

Dr. Ernesto Korbenfeld

Caso Clínico:
Carcinoma de Mama
Triple Negativo.Cuál es
el mejor tratamiento
sistémico ?

AGENDA

- Introducción
- Neoadyuvancia vs. Adyuvancia
- Esquema de Quimioterapia
- Futuro cercano...
Incorporación de la Inmunoterapia ?

1. Introducción: Cáncer de Mama Triple Negativo

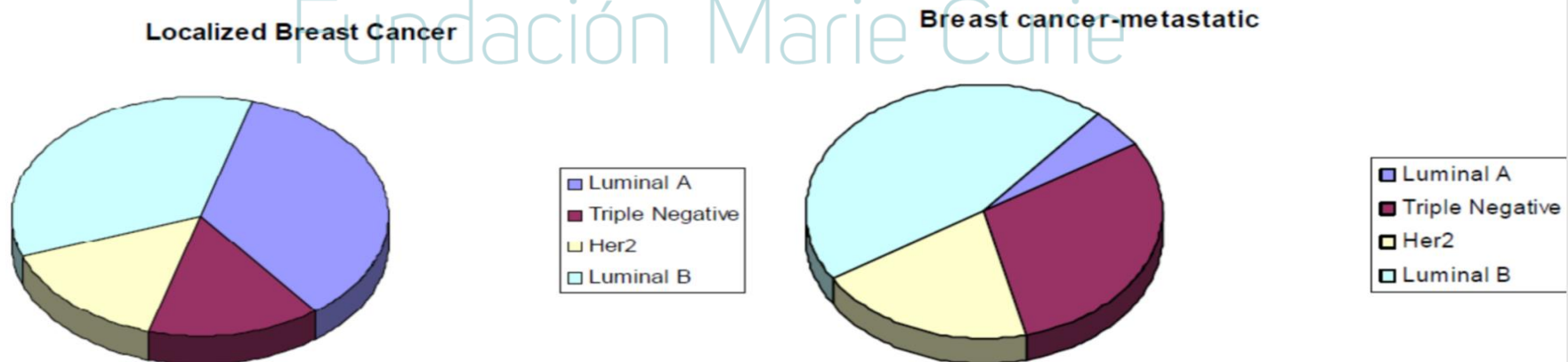
SUBGRUPO HETEROGÉNEO

Aprox. 15 % de carcinomas mamarios

Desproporcionada tasa de recaídas y mortalidad

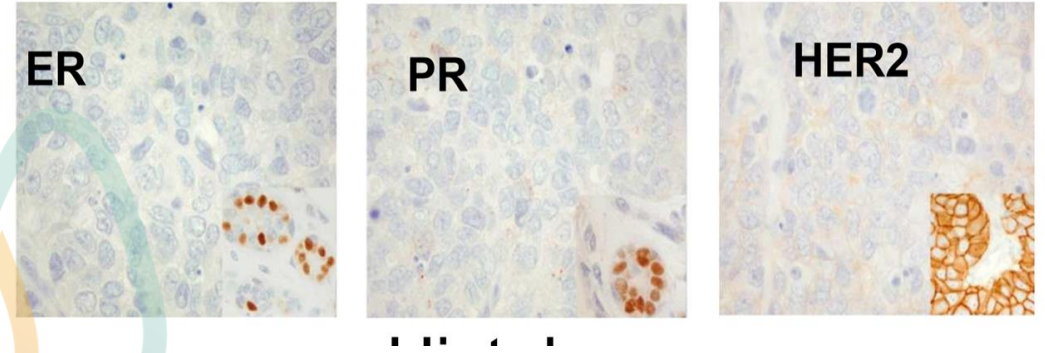
Ausencia de Terapias Blanco-Específicas (excepto en pacientes con mutaciones de BRCA1 /2, 20% de tumores TN)

La Quimioterapia constituye el tratamiento sistémico



1. Introducción: Definición

Immunohistochemistry



-
- ER and PR <1% nuclear
 - HER2 “negative”:
IHC 0 or 1+
staining or 2+ IHC
staining with
negative FISH

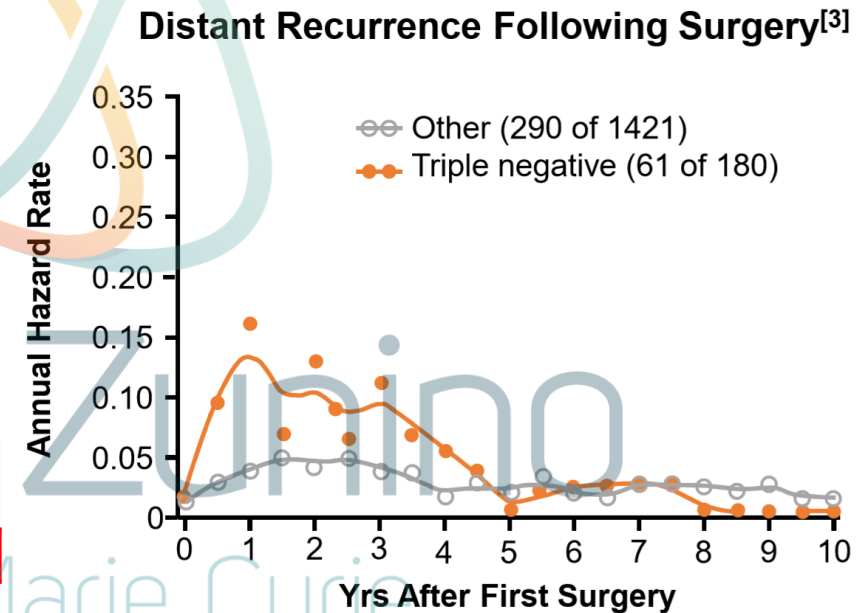
1. Introducción: Principales Características Clínicas

- Mayor proporción en Mujeres Premenopáusica
 - Predominantes en mujeres de raza negra e hispánicas
 - La mayoría tienen un curso clínico agresivo
 - A menudo se presentan como tumores del intervalo
 - Alto índice de proliferación: $ki67 > 20\%$
 - GH3
 - Mayor riesgo de recurrencia a distancia y recaída local
 - Mayor compromiso visceral y en SNC en pacientes con enfermedad avanzada
 - Rápida progresión desde la aparición de la metástasis y la muerte
 - La mayoría de las muertes ocurre dentro de los 5 años
- Relación con la obesidad

1. Introducción: Principales Características Clínicas

- Relapse pattern^[1]
 - Short disease-free interval
 - Increase in visceral mets
 - Differs from luminal:
 - CNS mets in 46% of cases

Rate of Recurrence ^[2]	n	Bone, %	Soft Tissue, %	Viscera, %
TNBC	79	13	13	74
ER+	123	39	7	54
HER2+	78	7	12	81



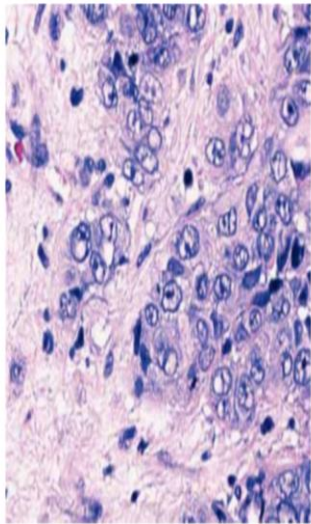
1. Lin NU, et al. Cancer. 2008;113:2638-2645. 2. Liedtke C, et al. J Clin Oncol. 2008;26:1275-1281. 3. Dent R, et al. Clin Cancer Res. 2007;13:4429-4434.

1. Introducción: Características Patológicas

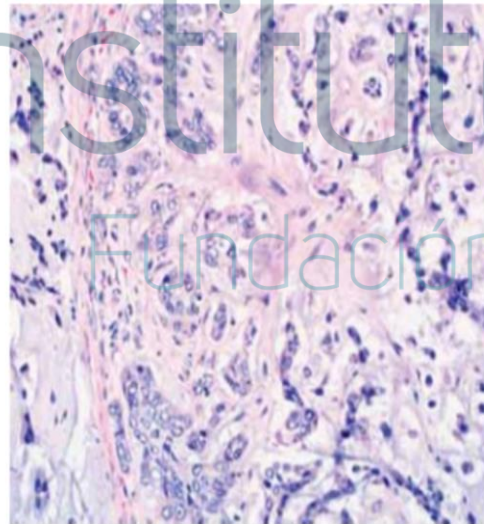
1. Tipos Histológicos de pobre pronóstico

Carcinoma ductal Infiltrante de alto grado, NOS

Necrosis, proliferación fibrosa, infiltrado linfocitario intratumoral y peritumoral. Ausencia de CDIS

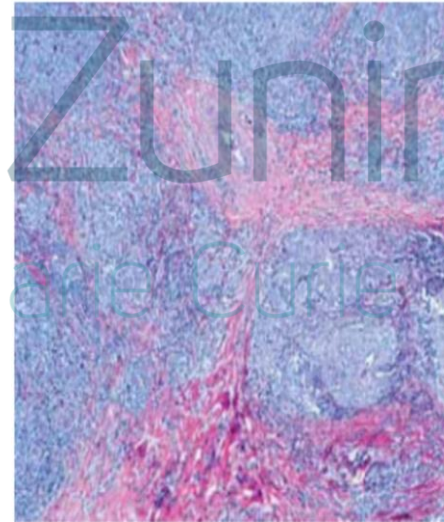


Carcinoma Metaplásico: diferenciación escamosa, condroide o cél. ahusadas. Pobre pronóstico

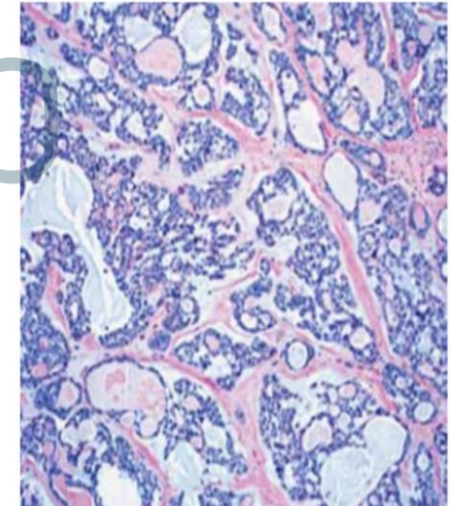


2. Tipos Histológicos de buen pronóstico

Carcinoma Medular: alto grado mitótico, denso infiltrado linfocitario. Mejor pronóstico



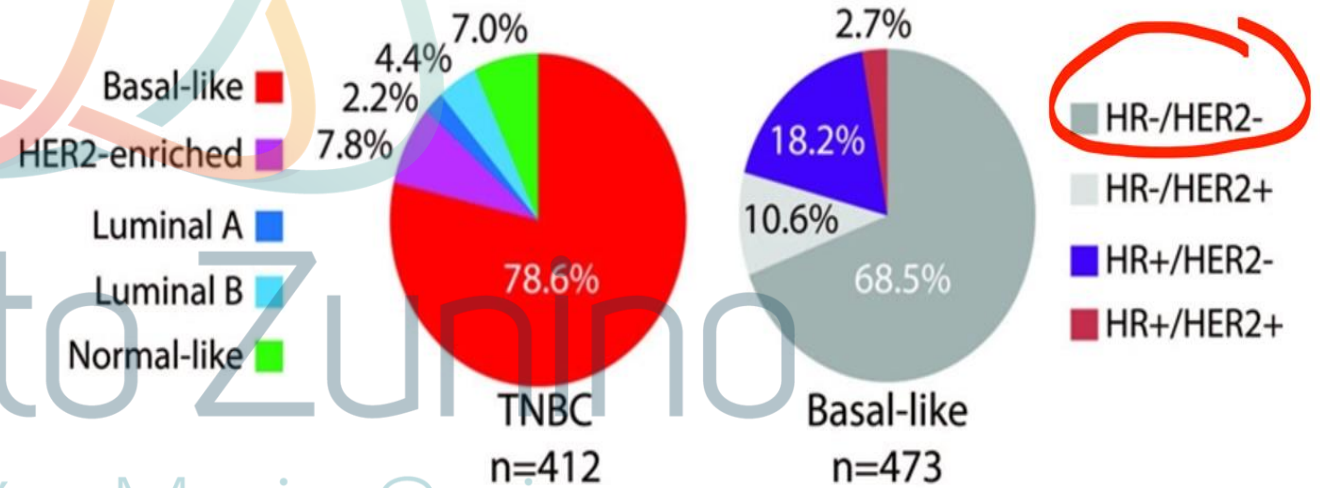
Tumores Adenoide-quístico: Bajo grado. Componente epitelial y mioepitelial. p63 y c-kit +. Buen pronóstico



Instituto Zunino
Fundación Marie Curie

1. Introducción: Clasificación Molecular

Cáncer de mama triple negativo



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

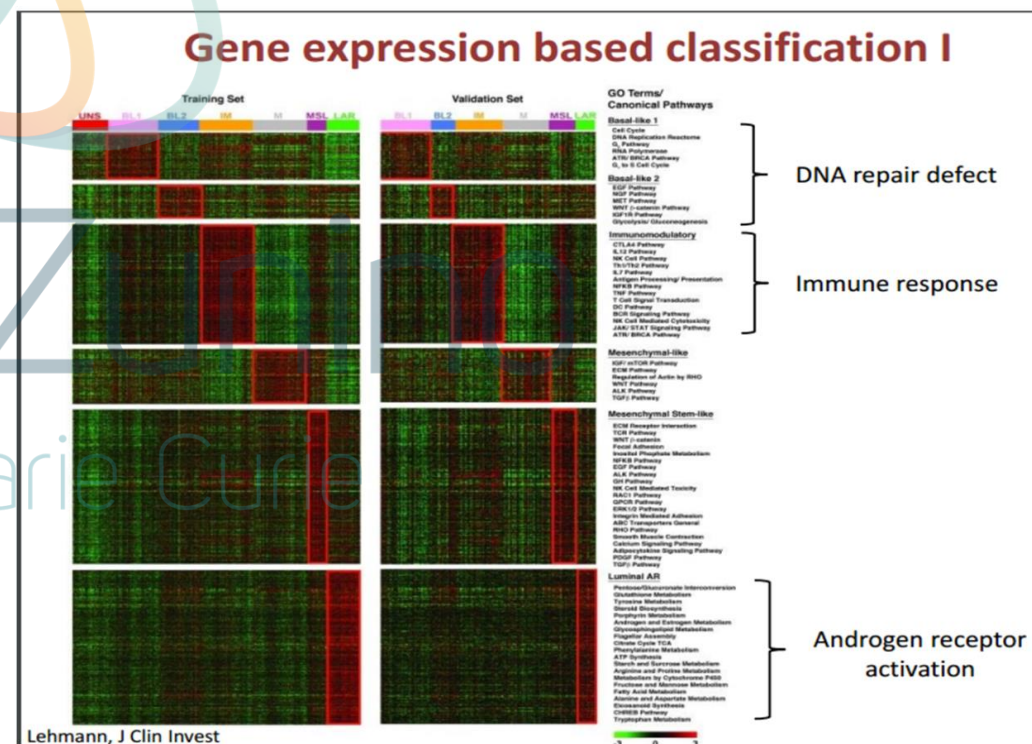
Oncologist, Feb2013, Vol. 18 Issue 2, p123-133, 11p, 5 Diagrams, 1 Chart, 2 Graphs
Graph; found on p125

1. Introducción: Clasificación molecular de Tumores TN

Classification of TNBC into 6 different subtypes



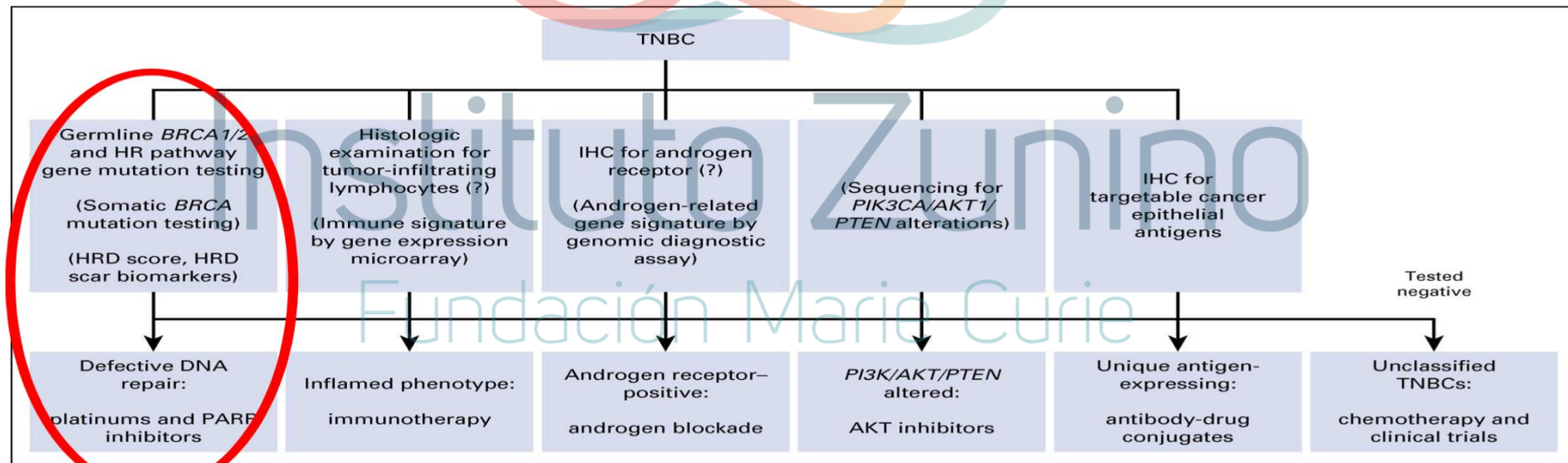
Lehmann et al. J Clin Invest 2011



Lehmann. J Clin Invest

1. Introducción: Nuevas modalidades de tratamiento en tumores TN

Are There Any Clinically Relevant Subgroups of Triple-Negative Breast Cancer in 2018?



Jack J. Chan; Tira J.Y. Tan; Rebecca A. Dent
Journal of Oncology Practice May 11, 2018

2. Potenciales Ventajas de la Terapia Neoadyuvante

1. Mejorar el “downstaging” tumoral

- A. Tumores irresecables→ Tumores resecables
- B. Mastectomía→ Cirugía Conservadora
- C. VAG→ Ganglio Centinela
- D. Mejoría de los resultados cosméticos
- E. Reduce la morbilidad de la cirugía

2. Temprano inicio del Tratamiento Sistémico

3. Evaluación “in vivo ” de la respuesta tumoral. Permite mejorar la estimación pronóstica (RCp vs. no RCp; Carga Tumoral Residual, presencia de TILs)

4. Provee la oportunidad de evaluar marcadores pronósticos subrogantes de respuesta al tratamiento

2. Potenciales ventajas de la Terapia Neoayuvante

5. Mejor selección de las terapias adyuvantes de acuerdo o no si alcanzó RCp (TN capecitabine ; Her2+ TDM-1)
6. Permite tiempo para el testeo genético y considerar las opciones quirúrgicas
7. Acorta el tiempo para la aprobación de nuevas drogas por las entidades regulatorias
8. Mejora la confianza de la paciente al observar la disminución/desaparición del tumor

2. Un Equipo Multidisciplinario es Esencial para la planificación de la Estrategia Terapéutica

Surgical, medical and radiation oncologists involved in treatment plan design

Staging studies may be needed before treatment initiation



Additional imaging studies/interventions may be necessary to better define the extent of loco-regional disease and plan therapy

Discussions of the benefits of neoadjuvant vs. adjuvant treatment from each speciality's standpoint

Early involvement of plastic surgeons and geneticists further facilitates the treatment plan

Diferentes Objetivos en Enfermedad Temprano vs. Metastásica

Early BC

The ultimate goal of eBC treatment is to **cure patients**¹

If unsuccessful



Metastatic BC

Treatment goal = **optimise survival and quality of life**²



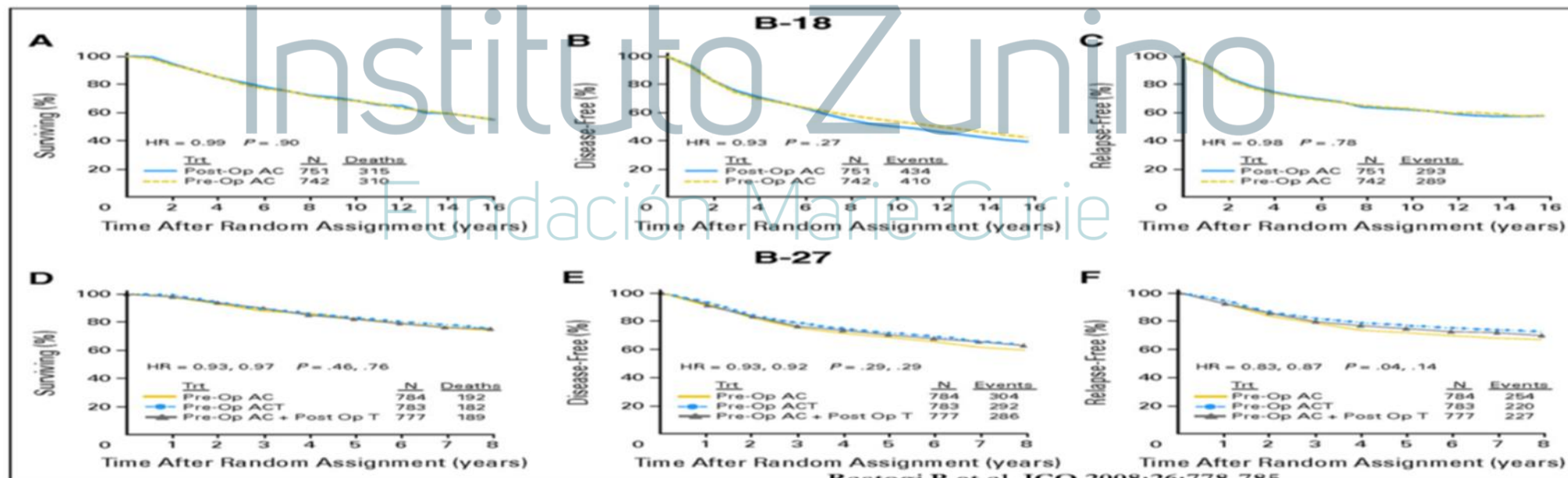
Failure of eBC treatment leads to more patients having, and dying of, mBC

Important to treat patients with eBC as early as possible; delaying treatment with anti-HER2 therapy leads to increased risk of disease recurrence or death³ and thus more cases of mBC

2. Potenciales Ventajas de la Terapia Neoadyuvante

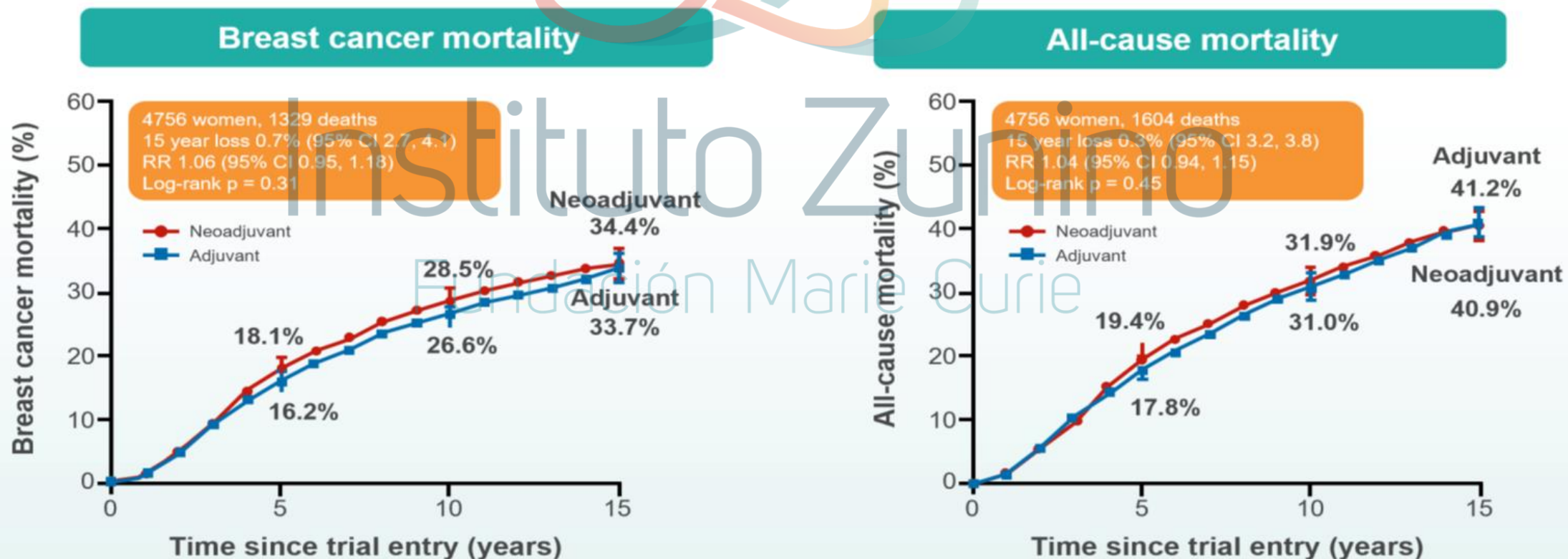
NSABP B 18 y NSABP B 27

NSABP B 18 y NSABP B 27



2. Potenciales Ventajas de la Terapia Neoadyuvante

Meta-analysis of ten randomised trials in BC* showed that mortality rates are similar with neoadjuvant or adjuvant chemotherapy only



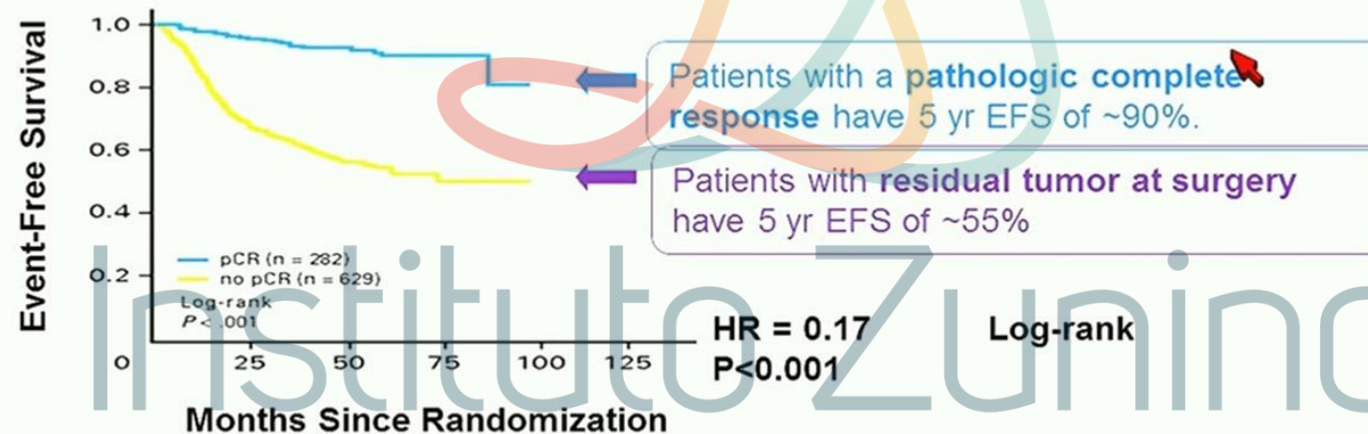
2. Paciente con TN T2N1 MO: Neoadyuvancia o Adyuvancia ?

St Gallen Consensus 2017

Table 5. Adjuvant systemic treatment recommendations for triple negative and <i>HER2</i> positive early breast cancer			
Subtypes according to clinical-pathologic and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
Ductal triple negative pT1a node negative		No routine adjuvant chemotherapy for stage pT1a pN0.	
Higher T and N stage	<u>Neoadjuvant therapy for stage II or III is suggested as initial treatment approach.</u> Chemotherapy should include anthracycline and taxanes	Dose-dense adjuvant chemotherapy preferred by only a minority of the consensus panel	No consensus on post-neoadjuvant treatment in case of residual disease. In <i>BRCA1/2</i> associated cancers, the Panel was evenly split on whether to recommend (neo)adjuvant platinum chemotherapy though agreed that such patients should receive alkylating chemotherapy.

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

Pathologic Complete Response Correlates With Event-Free Survival



FDA (2012) and EMA (2014) guidance recognize pCR as a surrogate endpoint potentially suitable for approval of new therapy

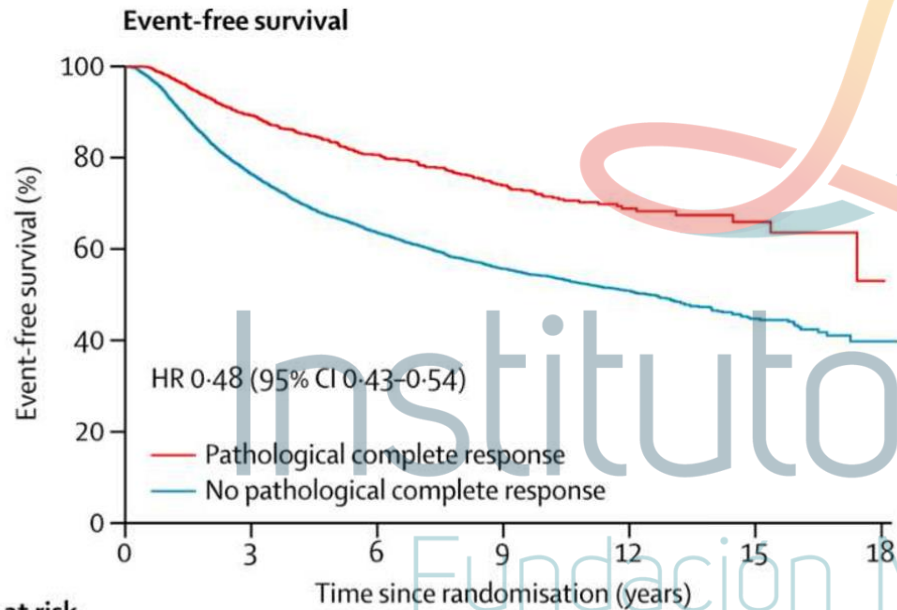
SLIDES ARE THE PROPERTY OF THE AUTHOR, PERMISSION REQUIRED FOR REUSE.

von Minckwitz G et al. JCO 2012.

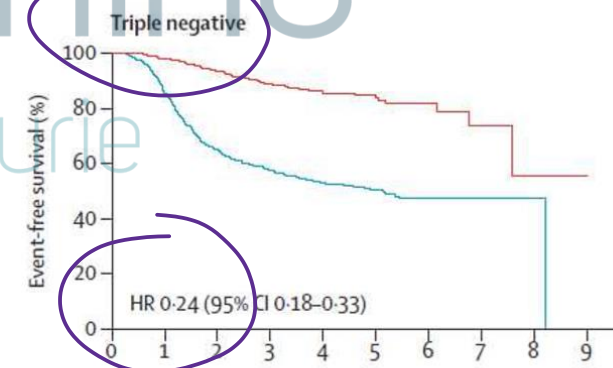
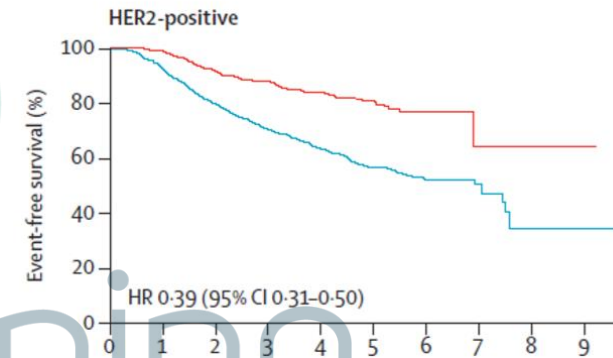
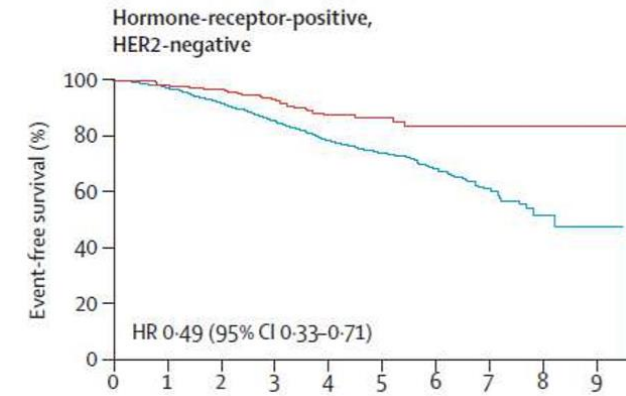
PRESENTED AT: ASCO Annual '15 Meeting

pCR and EFS

- FDA Meta Analysis (Cortazar et al, Lancet 2014)
 - >11K patients from 12 neoadjuvant trials
 - Median follow-up for EFS: 5.4 years



Number at risk	0	3	6	9	12	15	18
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1

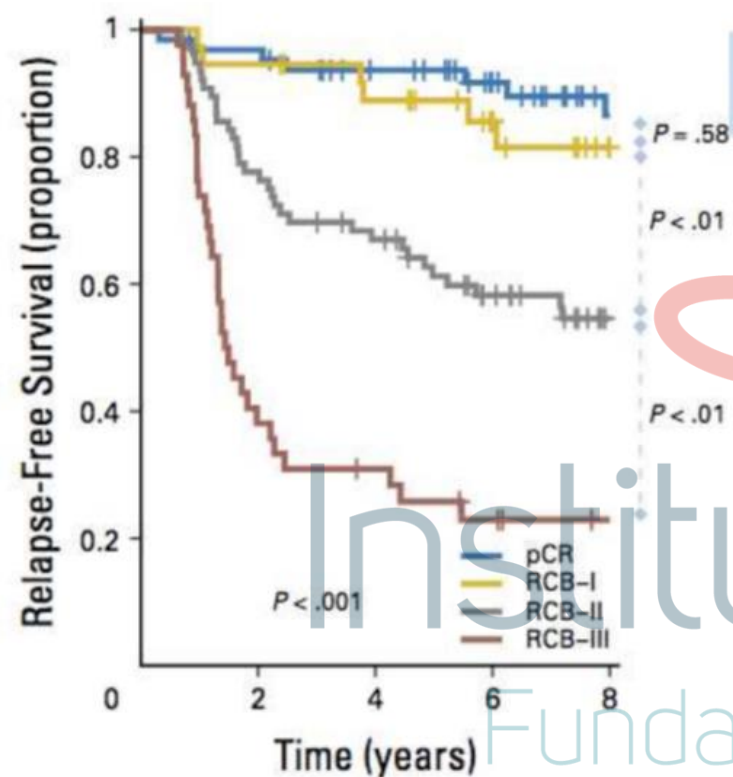


2. Respuesta Patológica Completa (RCp): Definiciones

Definitions of pCR		
		
Breast pCR	Total pCR	GBG pCR
ypT0/is	ypT0/is ypN0	ypT0 ypN0
• No invasive tumor in the breast	• No invasive tumor in the breast • Node negative at definitive surgery	• No invasive tumor in the breast • Node negative at definitive surgery • No remaining <i>in situ</i> disease

TNM (tumor, nodes, metastasis) classification; y=status post initial therapy; p=confirmed by pathology after initial treatment; T=tumor; N=nodes; is=in situ; GBG=German Breast Group.

Quantity of Residual Disease (Residual Cancer Burden) is prognostic



No. at risk:

	0	2	4	6	8
pCR	64	61	53	43	29
RCB-I	37	35	31	23	13
RCB-II	76	59	49	36	23
RCB-III	42	16	12	8	5

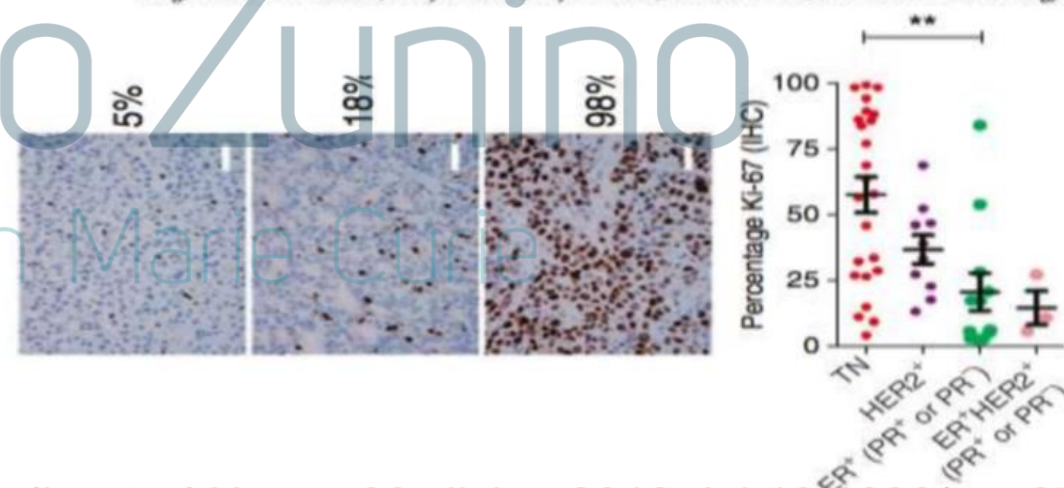
VOLUME 35 • NUMBER 10 • APRIL 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

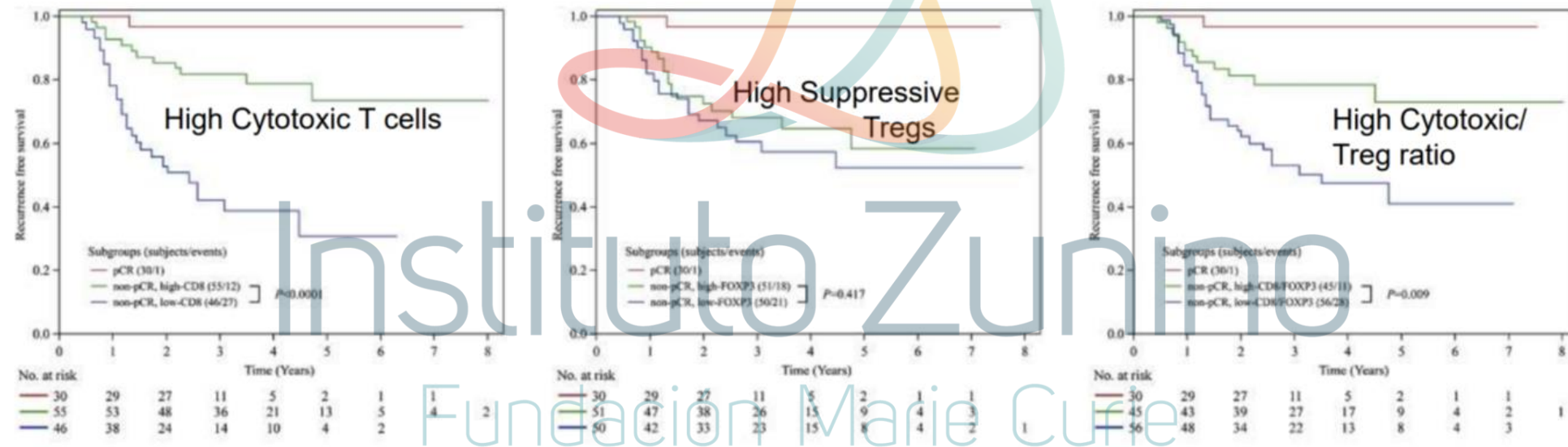
Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype

W. Fraser Symmans, Caimiao Wei, Rebekah Gould, Xian Yu, Ya Zhang, Mei Liu, Andrew Walls, Alex Bousamra, Maheshwari Ramineni, Bruno Sinn, Kelly Hunt, Thomas A. Buchholz, Vicente Valero, Aman U. Buzdar, Wei Yang, Abenaa M. Brewster, Stacy Moulder, Lajos Pusztai, Christos Hatzis, and Gabriel N. Hortobagyi



Balko et al Nature Medicine 2012 doi:10.1038/nm.2795

CD8+ Tcell / FOXP3 (Treg) Ratio differentiates prognosis in post TNBC Residual Disease



Miyashita et al. Breast Cancer Research (2015) 17:124

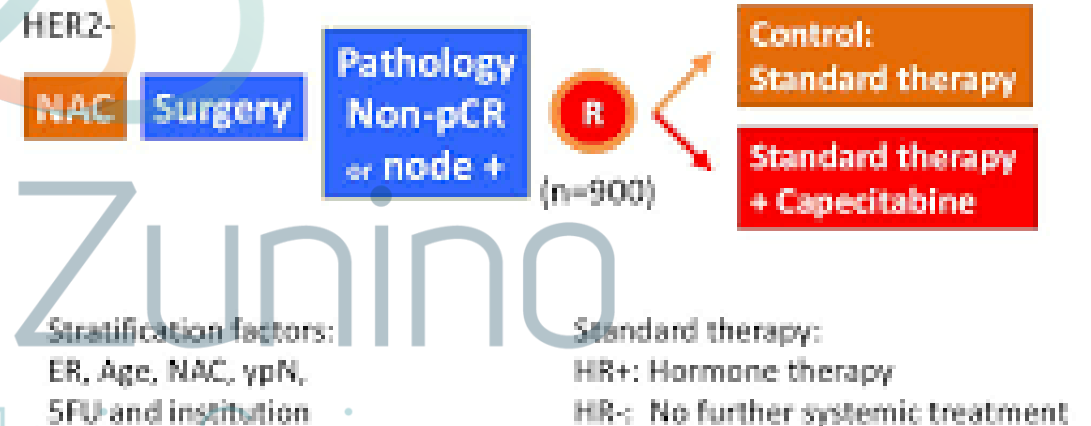
High TILs after neoadjuvant chemotherapy associated with better outcome for TNBC

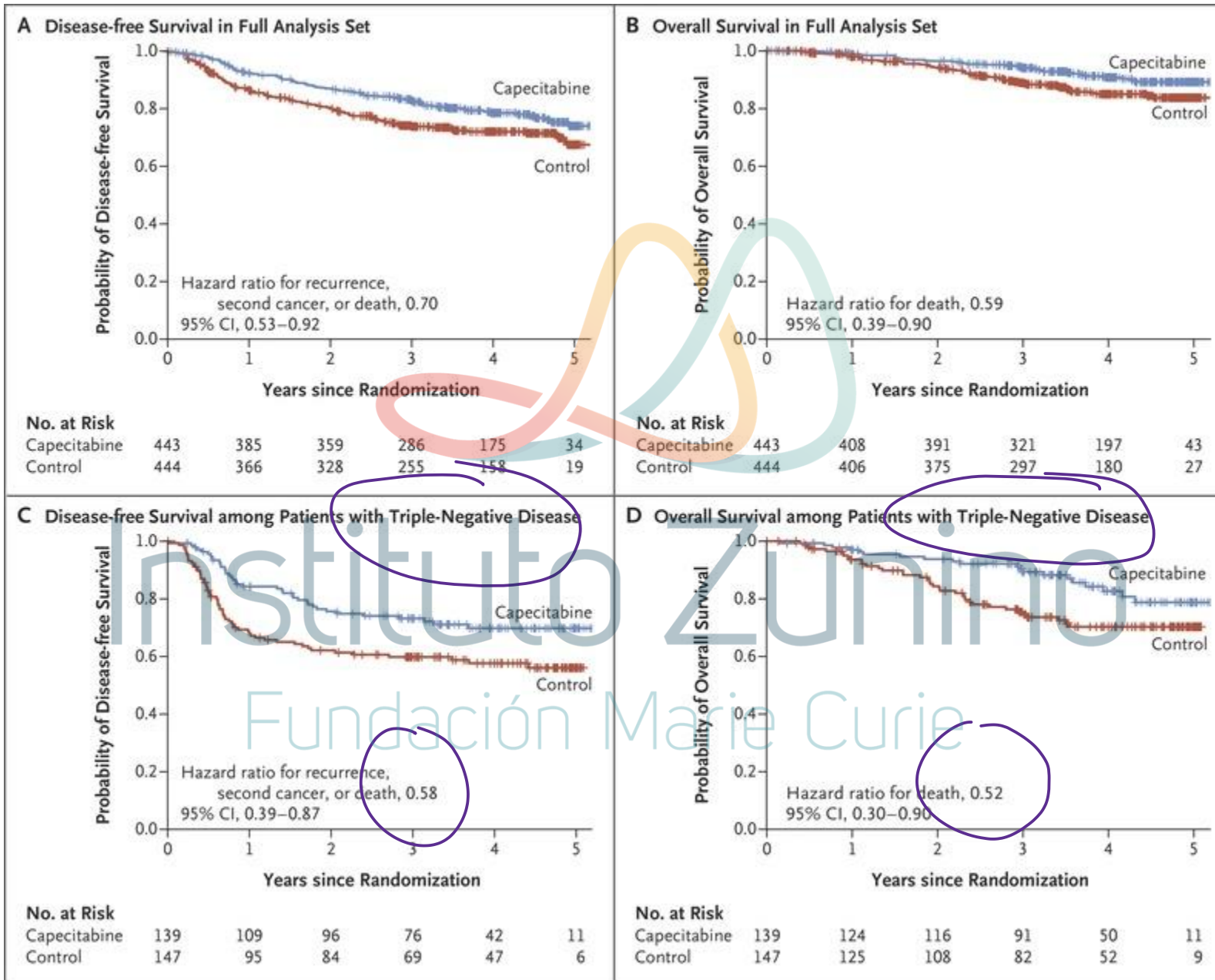
ORIGINAL ARTICLE

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

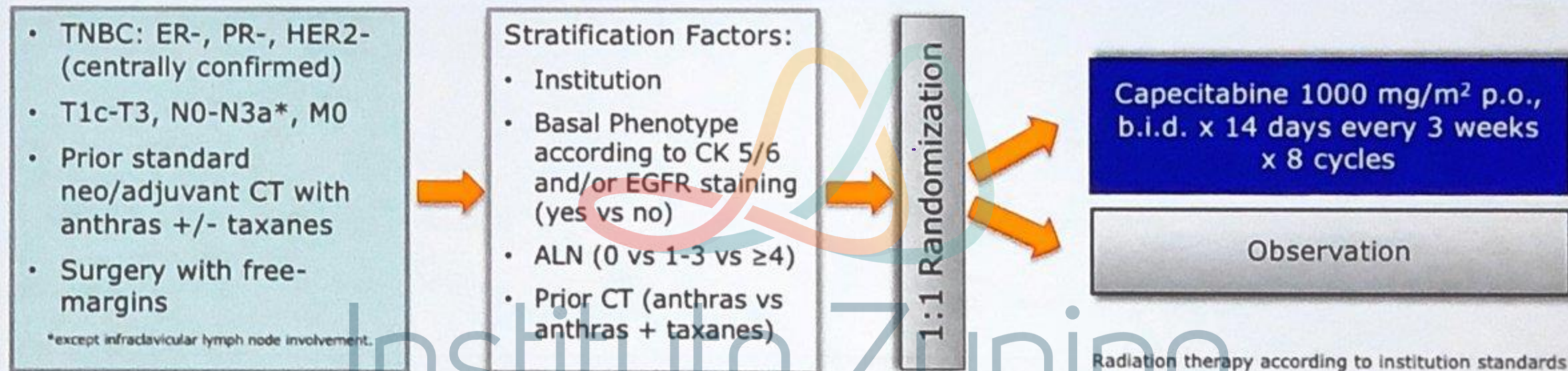
N. Masuda, S.-J. Lee, S. Ohtani, Y.-H. Im, E.-S. Lee, I. Yokota, K. Kuroi, S.-A. Im,
B.-W. Park, S.-B. Kim, Y. Yanagita, S. Ohno, S. Takao, K. Aogi, H. Iwata, J. Jeong,
A. Kim, K.-H. Park, H. Sasano, Y. Ohashi, and M. Toi

CREATE-X: Trial Design





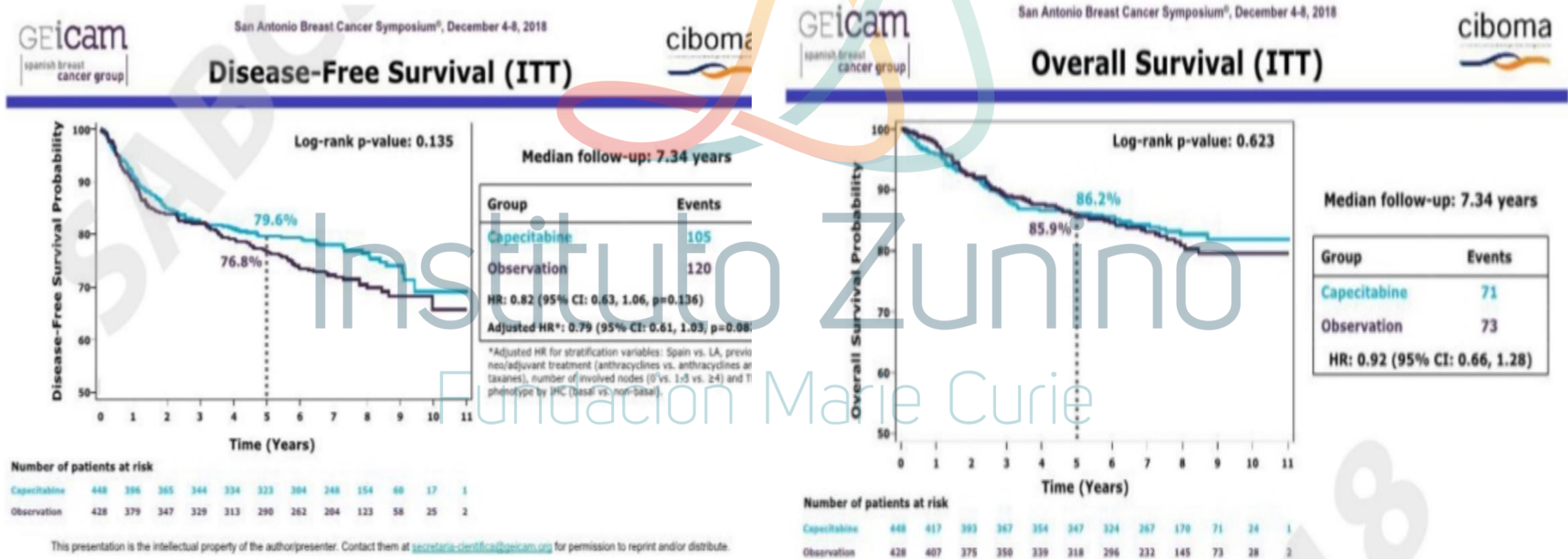
Study Design



- 6 cy. of standard CT mandatory except for N0 tumors (4 cy. of AC admitted).
- Primary endpoint: Disease-Free Survival (DFS).
- Secondary endpoints: Overall Survival (OS), subgroup analyses, safety, biomarkers.

Abbreviations: ER: Estrogen Receptor. PR: Progesterone Receptor. HER2: Epidermal Growth Factor Receptor 2. CT: Chemotherapy. Anthras: Anthracyclines. CK: Cytokeratins. EGFR: Epidermal Growth Factor Receptor. ALN: Axillary Lymph Nodes. Cy.: Cycles. AC: Doxorubicin + Cyclophosphamide.

GEICAM/CIBOMA Trial



ECOG-ACRIN 1131 (*Ingrid Mayer, Chair*)

TNBC stage II/III, received anthracycline-based NACT
 ≥ 1 cm residual disease at surgery
Basal subtype on PAM-50

Randomized

Capecitabine

Cisplatin or Carboplatin x 4
(Physician's discretion)

EFS and OS

Powered to detect a 33% improvement in EFS
Sample size: 558

3. Cuál es el mejor esquema de QT en Tumores TN Enfermedad Temprana ?



El tratamiento Standard debe incluir Antraciclina y Taxanos



Tratarlos a partir de Tamaño de 5 mm. (bajo umbral de tratamiento) excepto subtipos histológicos especiales



Frecuente utilización de densidad de Dosis

Triple negative breast cancer – adjuvant chemotherapy use and survival outcomes in Stage IA Disease

Ami Patel¹, Runhua Shi¹, Prakash Peddi¹ and Gary V. Burton¹

¹LSU Health Shreveport, Shreveport, LA

- Patients with National Cancer Database (2004-2012)
- 13065 breast cancer patients btwn the ages of 18-90 YO, Stage IA

Baseline characteristics

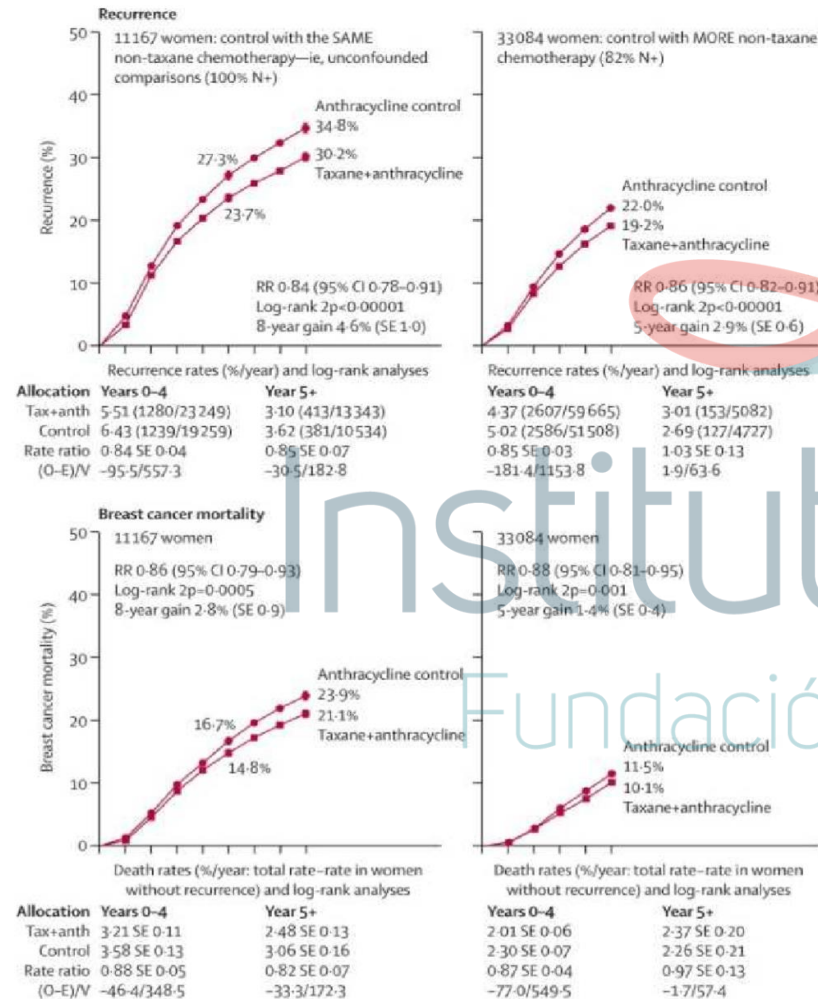
Factor	Level	n	%
Age (years)	18-49	2942	22.5
	50-64	5634	43.1
	65-74	2960	22.7
	75+	1529	11.7
Race	White	10349	79.2
	Black	2314	17.7
	Asian	402	3.1
Comorbidity index	0	10961	83.9
	1	1779	13.6
	2	325	2.5
	3	192	1.5
Treatment Started from Diagnosis (days)	0-11	1929	14.7
	12-23	3735	28.6
	24-39	4100	31.4
	40+	3081	23.6
Tumor Size (mm)	1-5	1275	9.7
	6-10	3197	24.5
	11-20	7729	59.2
Radiation	None Radiation	3305	25.3
	Radiation Only	869	6.6
	Radiation+Boost	4868	37.3
Chemotherapy	No	2316	17.7
	Yes	9253	71.0

4YR OS for TNBC with/without adjuvant CTx. use

Tumor size	No Chemotherapy	Chemotherapy	P value
T1a	93.78%	98.36%	0.146
T1b	91.91%	97.10%	< 0.0001
T1c	80.62%	94.41%	< 0.0001

SABCS 2016

Anthracycline-Taxane in EBC



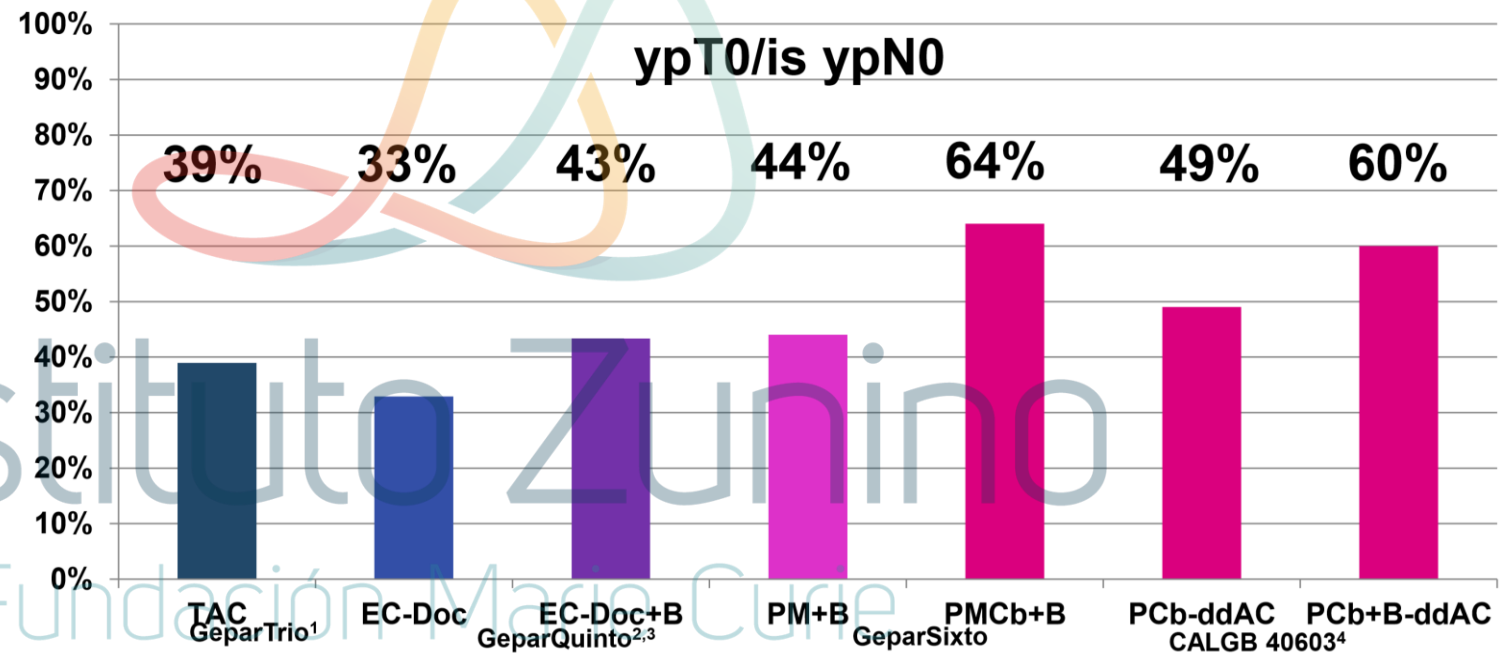
- A-T in EBC: Reduces recurrence, breast cancer mortality & overall mortality compared to anthracycline alone

How can we improve more?

*EBCTCG, Lancet 2012

3. Cual es el
mejor esquema
de QT en
Tumores TN Enf.
Temprana ?

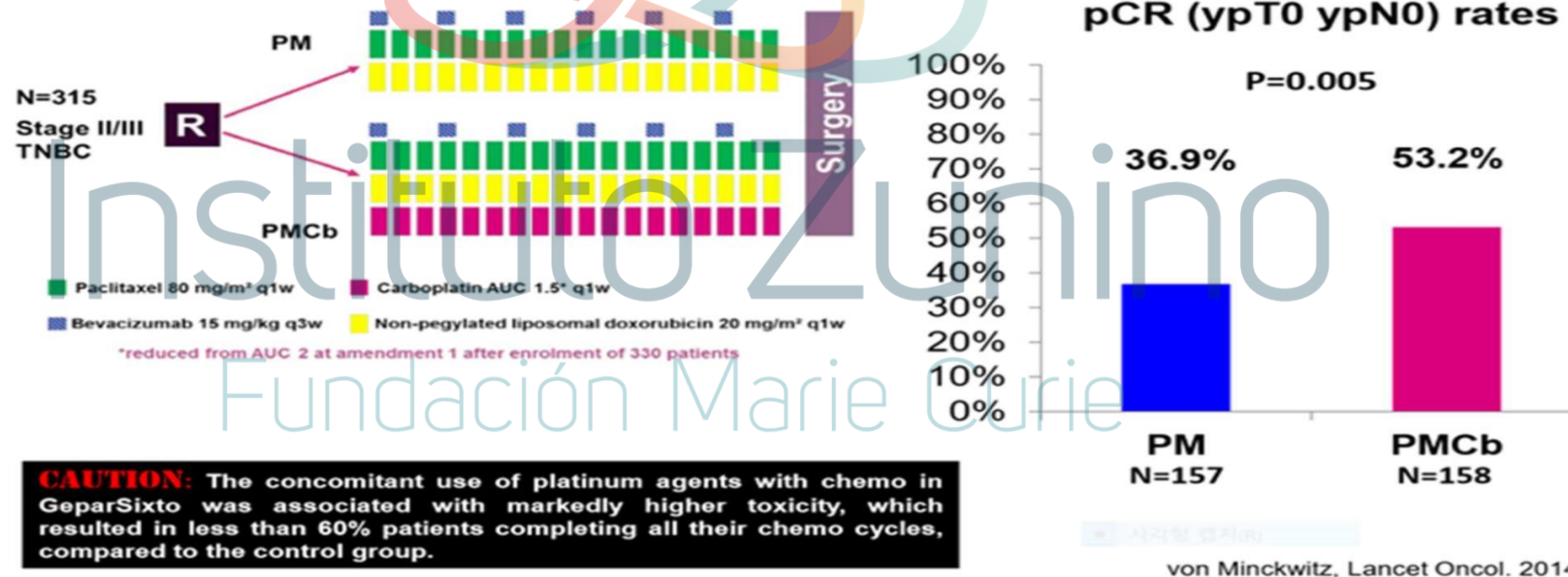
pCR has increased in TNBC with NACT evolution



¹ Huober BCRT 2010, ² von Minckwitz NEJM 2012, ³ Gerber, Annals Oncol ; Sikov⁴ SABCS2013

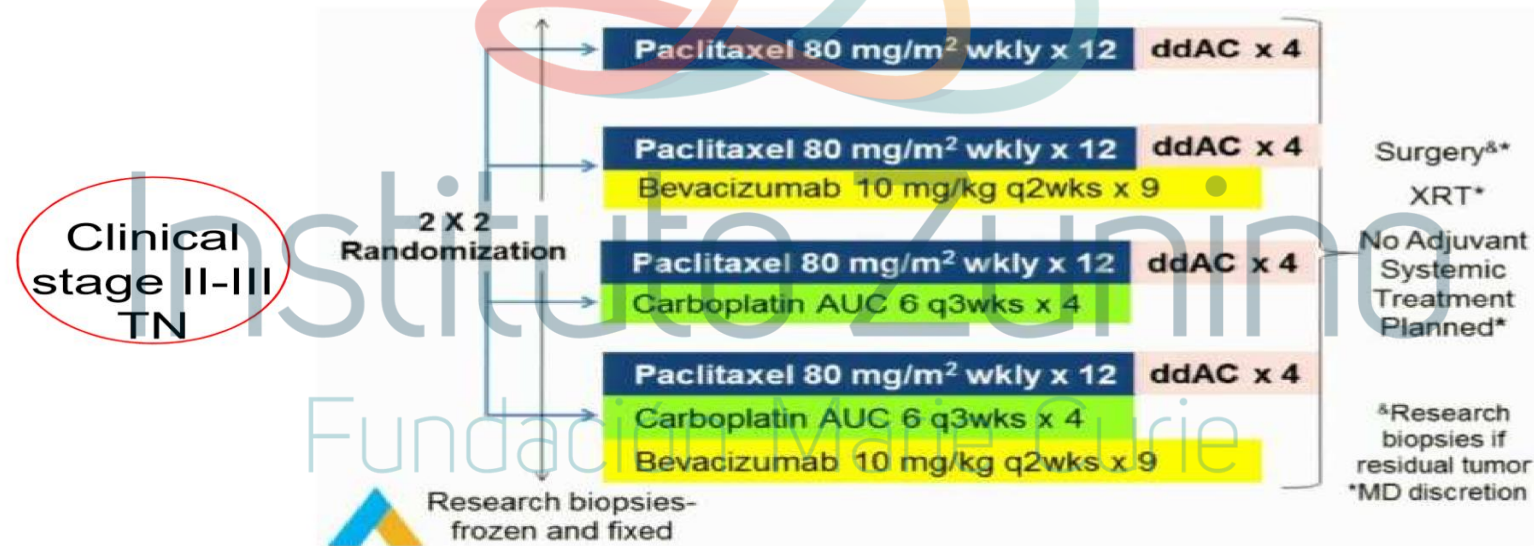
3. Cuál es el mejor esquema de QT en Tumores TN Enf. Temprana ?

GeparSixto



3. Cuál es el mejor esquema de QT en Tumores TN Enf. Temprana ?

CALGB 40603 – randomised phase II trial



Primary EP – pCR in breast (trial did not mandate surgery of axilla)

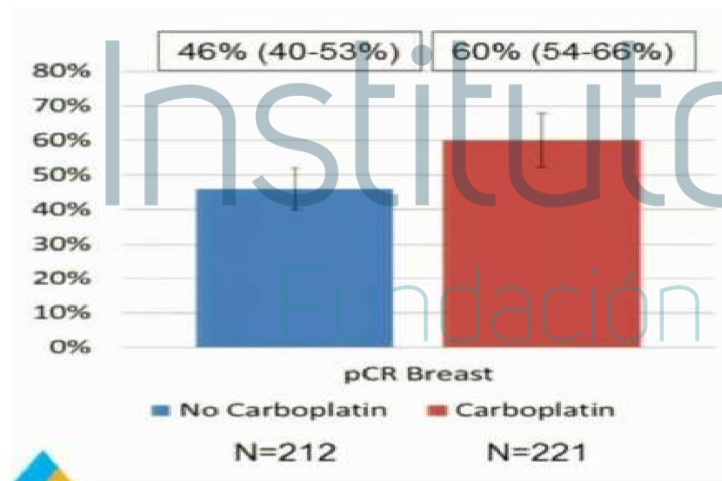
*Gcsf primary prophylaxis for ddAC cycles

Sikov et al, SABCS 2013

3. Cuál es el mejor esquema de QT en Tumores TN Enf. Temprana ?

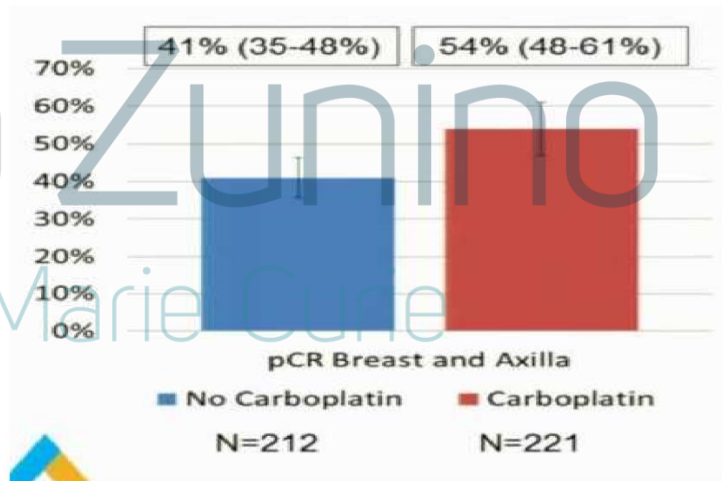
pCR (carboplatin)

pCR breast



OR 1.76 (p=0.0018)

pCR breast/axilla



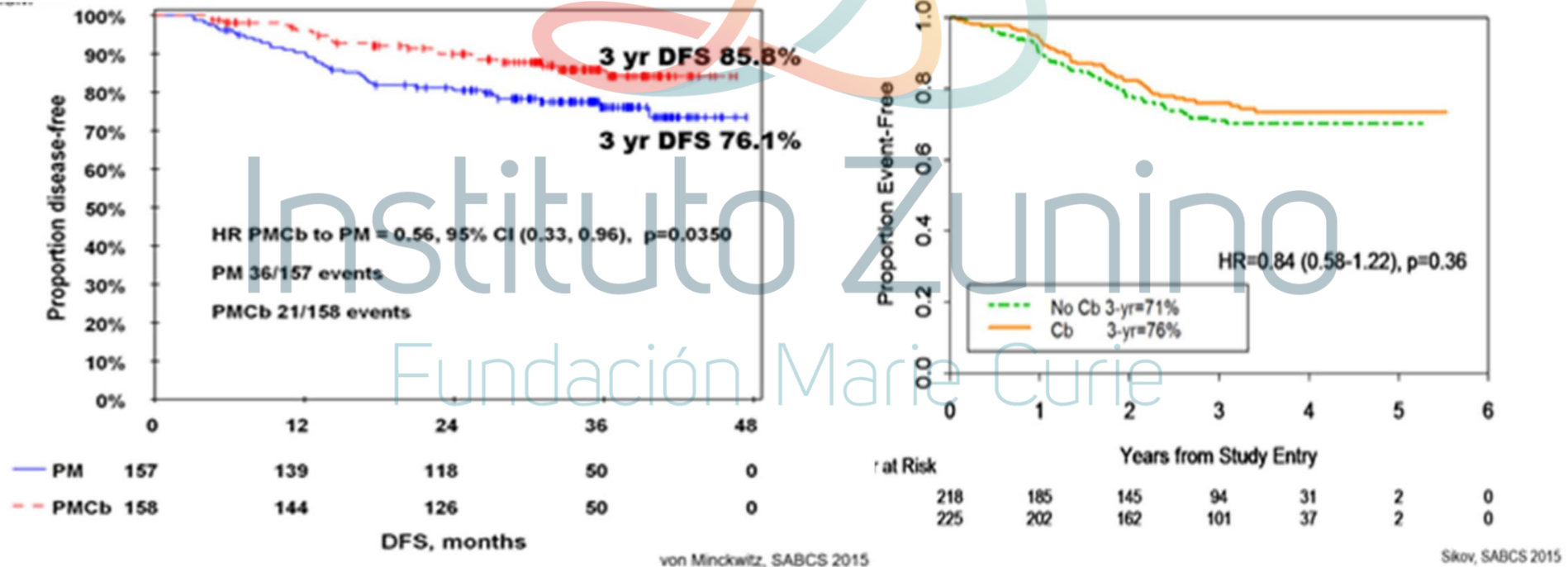
OR 1.71 (p=0.0029)

Sikov et al, SABCS 2013

3. Cuál es el mejor esquema de QT en Tumores TN Enf. Temprana ?

Disease Free Survival

GeparSixto (Med FU 35Mo) vs CALGB 40603 (Med FU 39Mo)



Cuando considerar tratamiento con *Cis/Carboplatino* en Neoadyuvancia ?

- Mutaciones de BRCA en línea germinal
- Pacientes de alto riesgo Estadío III/ jóvenes
- Rápido control locorregional de la enfermedad/ Incrementar la probabilidad de resecabilidad

CONTRA:

Mayor riesgo de toxicidad temprana y tardía

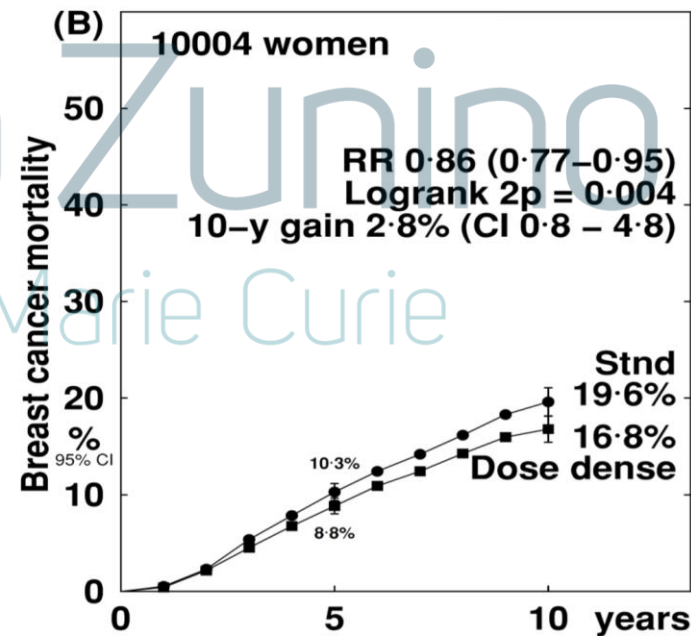
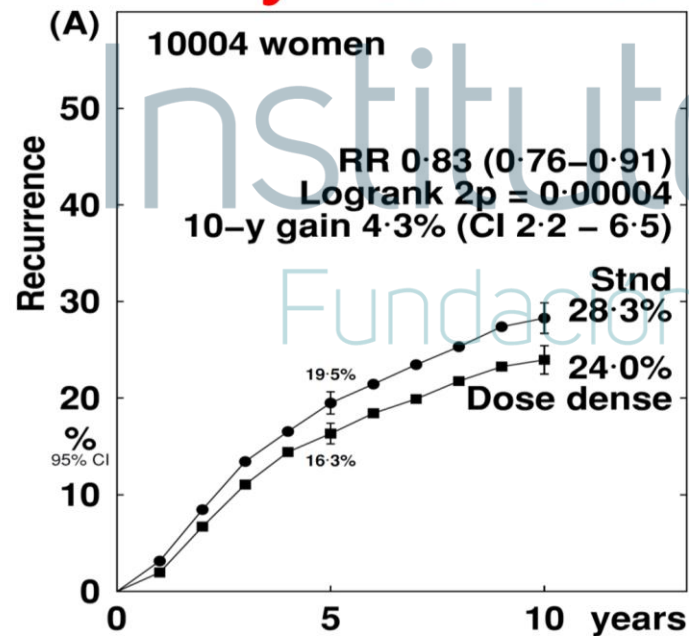
Esquemas con Densidad de Dosis de Antraciclinas

2-weekly (dose dense) vs the same chemotherapy given 3-weekly

EBCTCG SABCS 2017

Any Recurrence

Breast Cancer Mortality

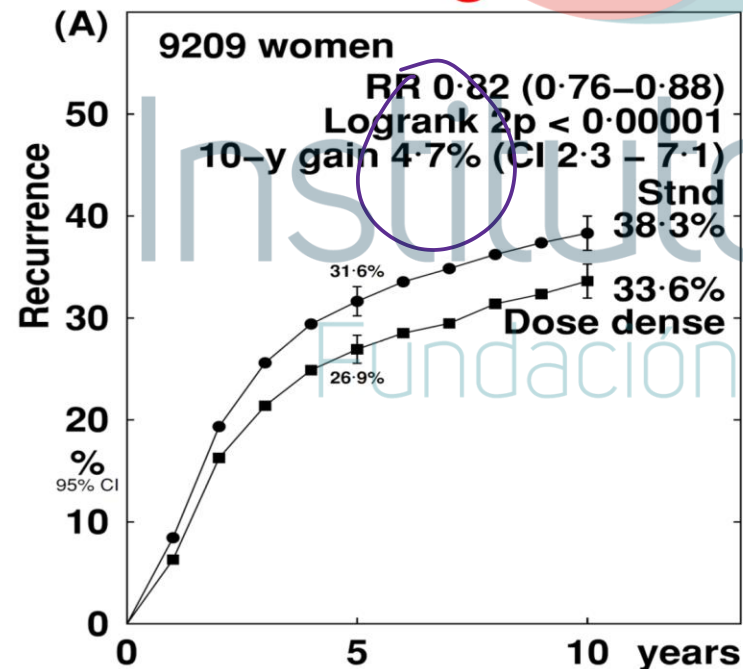


Esquemas con Densidad de Dosis de Antraciclinas

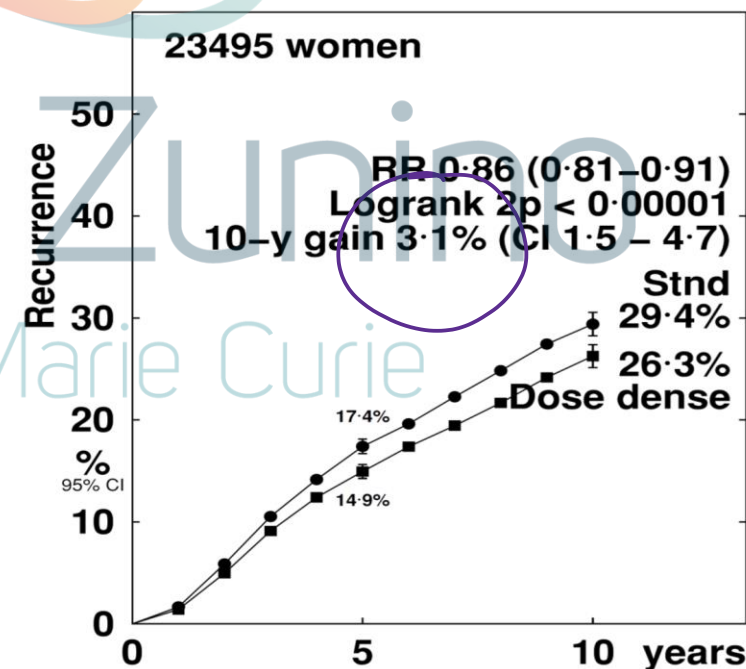
Pooled Analysis: recurrence by ER status

EBCTCG SABCS 2017

ER- Negative



ER - Positive



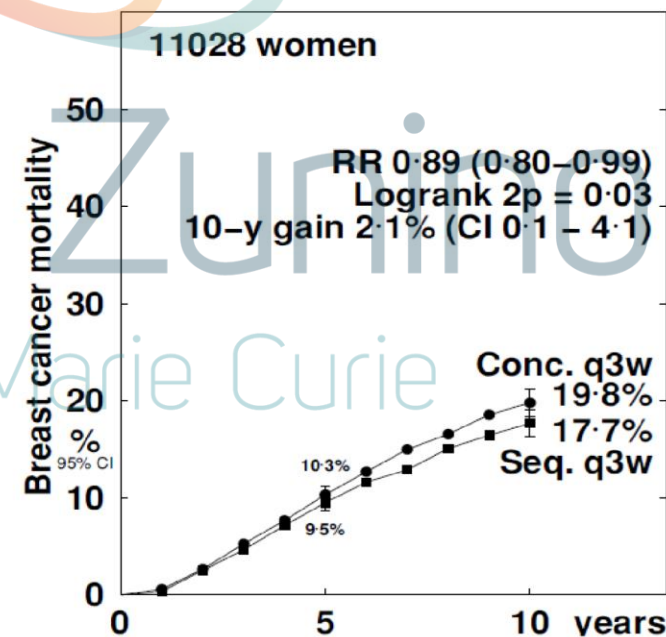
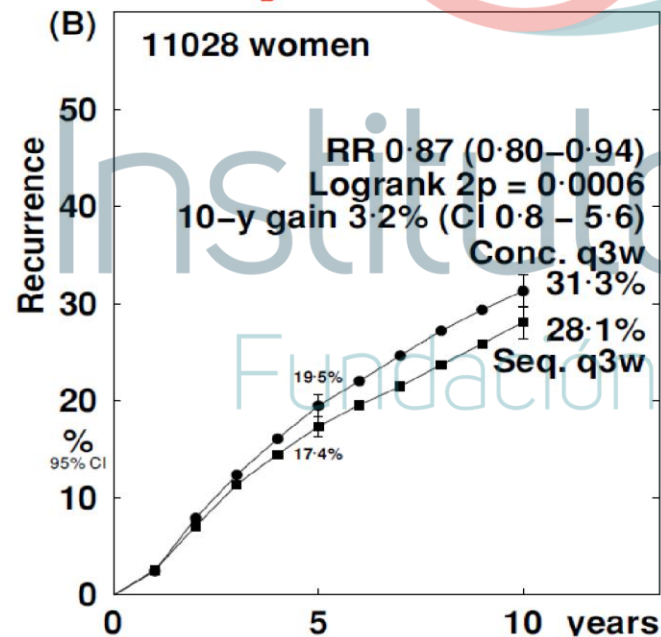
Esquemas Secuenciales vs. Concurrentes

EBCTCG SABCS 2017

Sequential (3-weekly) vs Concurrent (3-weekly) chemotherapy

Any Recurrence

Breast Cancer Mortality



Gold standard adjuvant regimen: EC q2wks x4→weekly paclitaxel x 12

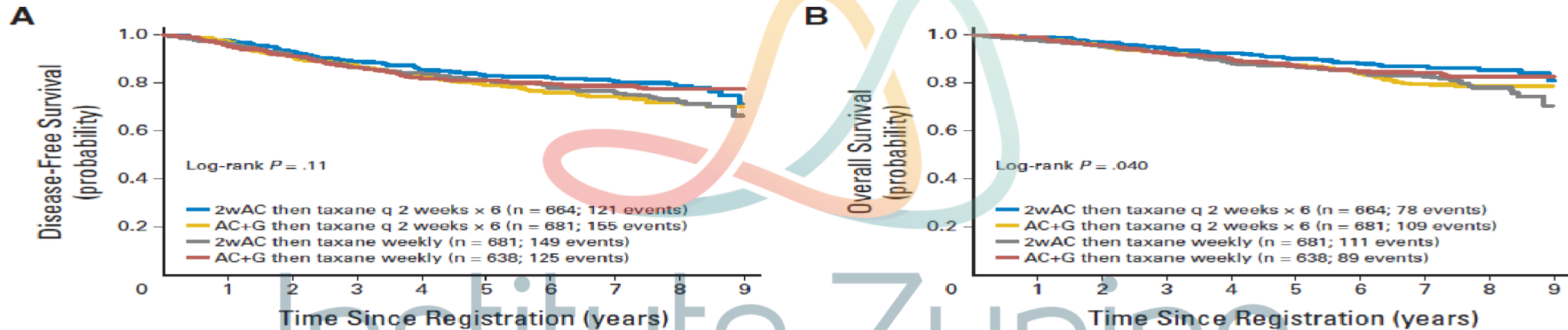


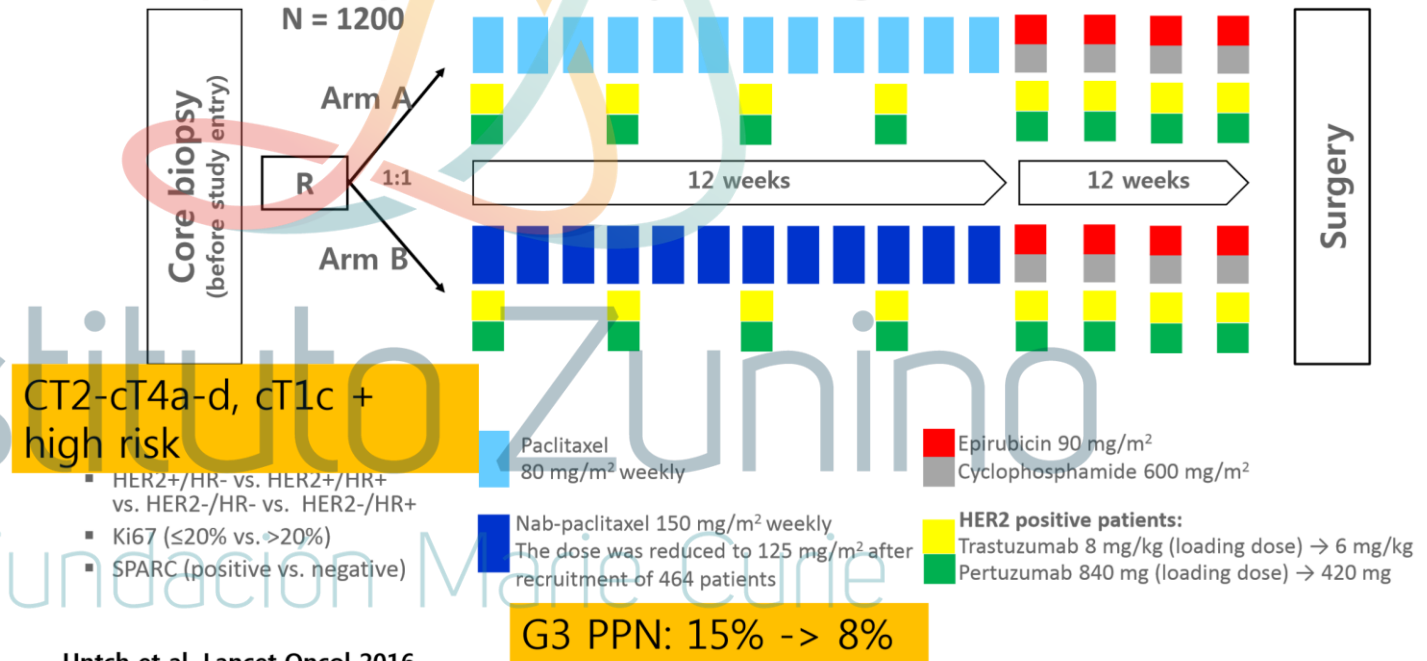
Table 3. Number of Patients with Type and Grade of Toxicity for Paclitaxel Once Every 2 Weeks Versus Once Per Week

Adverse Event	Grade for Paclitaxel Every 2 Weeks (n = 1,162)								Grade for Paclitaxel Once Per Week (n = 1,139)							
	≤ 2		3		4		5		≤ 2		3		4		5	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hemoglobin	1,135	97.7	25	2.2	2	0.2	0	0.0	1,123	98.6	16	1.4	0	0.0	0	0.0
Leukocytes	1,153	99.2	7	0.6	2	0.2	0	0.0	1,057	92.8	72	6.3	10	0.9	0	0.0
Neutrophils	1,140	98.1	17	1.5	5	0.4	0	0.0	1,000	87.8	105	9.2	34	3.0	0	0.0
Neurologic	961	82.7	193	16.6	8	0.7	0	0.0	1,020	89.6	115	10.1	4	0.4	0	0.0
Dermatologic/skin	1,132	97.4	30	2.6	0	0.0	0	0.0	1,117	98.1	22	1.9	0	0.0	0	0.0
Allergy	1,146	98.6	16	1.4	0	0.0	0	0.0	1,133	99.5	6	0.5	0	0.0	0	0.0
Febrile neutropenia	1,160	99.8	2	0.2	0	0.0	0	0.0	1,138	99.9	0	0.0	1	0.1	0	0.0
Musculoskeletal pain	1,035	89.1	124	10.7	3	0.3	0	0.0	1,106	97.1	33	2.9	0	0.0	0	0.0
Fatal event	1,161	99.9	0	0.0	0	0.0	4	0.3	1,139	100	0	0.0	0	0.0	3	0.3
All adverse events	750	64.5	384	33.0	24	2.1	4	0.3	727	63.8	363	31.9	48	4.2	3	0.3

Budd et al. JCO2015

Paclitaxel
semanal vs.
Nab-
Paclitaxel
semanal

GeparSepto Study Design

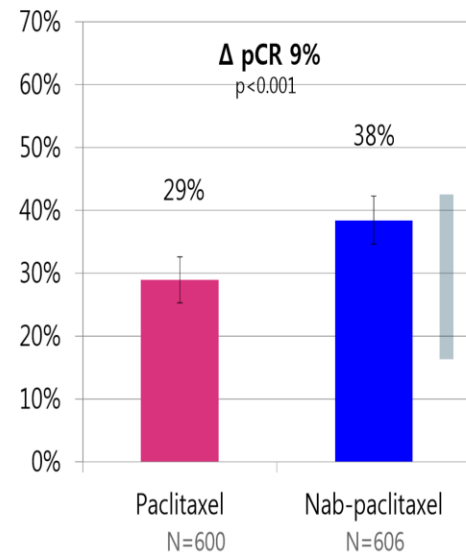


Untch et al. Lancet Oncol 2016

Loibl S. et al Lancet Oncol 2018

Paclitaxel semanal vs. Nab-Paclitaxel semanal

Primary Endpoint: pCR (ypT0 ypN0)



TNBC: 26% vs 48%, p=0.00027

HR+/HER2-: 12% vs 16%,

p=0.23

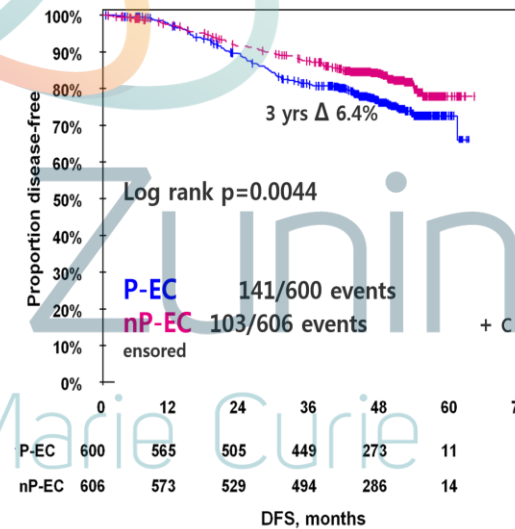
HR+/HER2+: 50% vs 56%,

P=0.30

HR-/HER2+: 67% vs 75%,

P=0.49

Disease-Free Survival



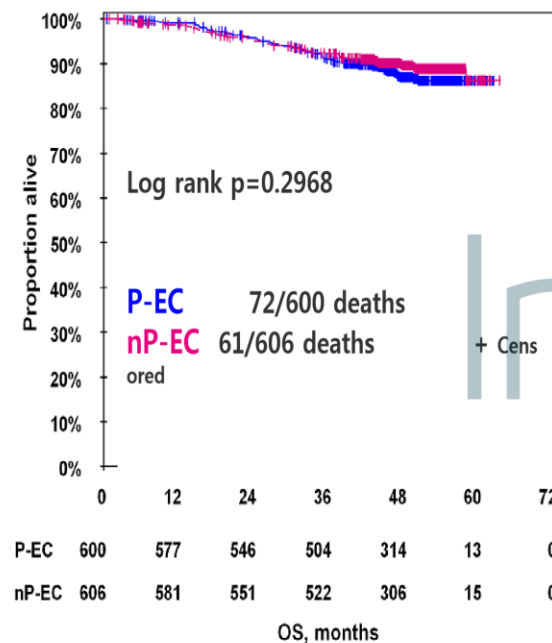
- Median FU of 49 months (IQR 44.6 - 52.9)
- HR (nP-EC vs. P-EC) = 0.69 (95% CI 0.54-0.89)
- Number needed to treat (NNT; 3yrs) = 16 pts

DFS rates (estimated):

Time	P-EC	95% CI, P-EC	nP-EC	95% CI, nP-EC
3 yrs	80.7%	(77.2-83.7)	87.1%	(84.1-89.6)
4 yrs	76.2%	(72.3-79.5)	83.5%	(80.2-86.4)

Paclitaxel semanal vs. Nab-Paclitaxel semanal

Overall Survival: Overall



OS rates (estimated):

Time	P-EC	95% CI, P-EC	nP-EC	95% CI, nP-EC
3 yrs	91.1%	(88.4-93.1)	92.3%	(89.8-94.2)
4 yrs	87.0%	(83.8-89.6)	89.6%	(86.8-91.9)

CONCLUSIONES:

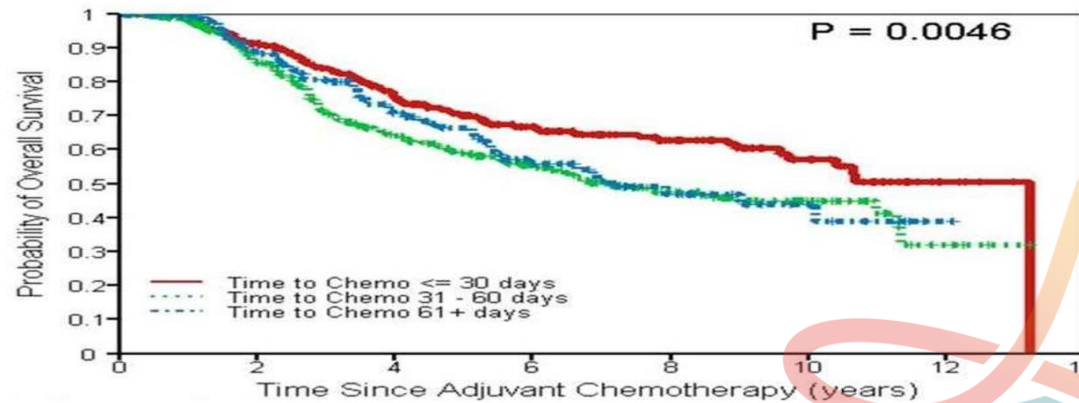
Debería utilizarse Nab-paclitaxel en neo/adyuvancia ?

Mayor tasa de RCp, modesto beneficio en SLE.

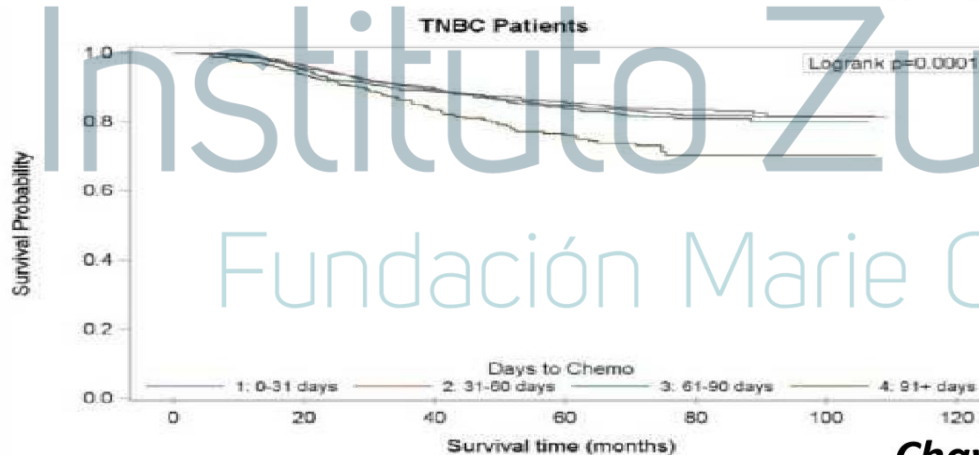
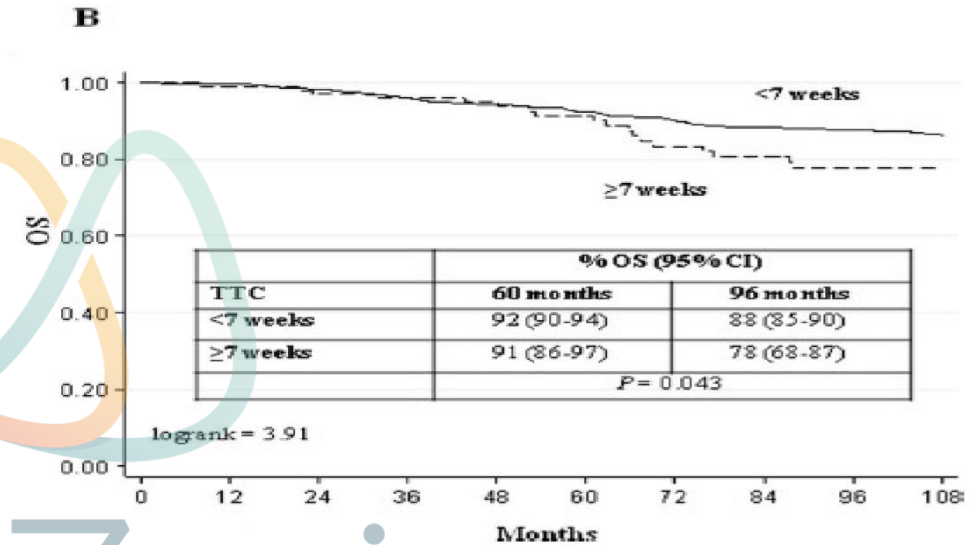
No ventaja en SG

Necesidad de ser validados en Estudios prospectivos grandes

Impact of delaying adjuvant CT in TNBC



Gagliato et al. JCO 2014



Farolfi et al. EJC 2015

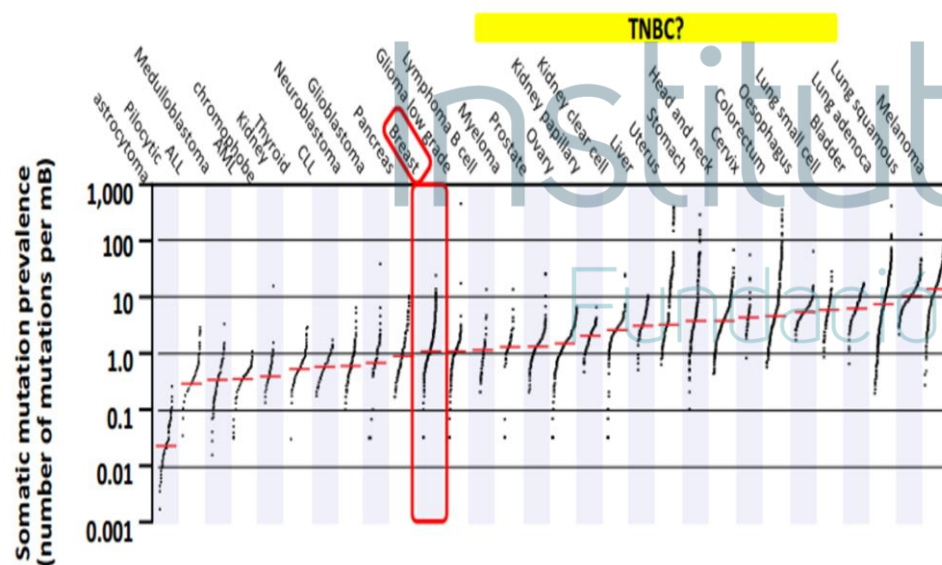
Breast cancer subtype
Hormone receptor-positive 1
ERBB2+ 1.04 (0.95-1.15)
TNBC 0.72 (0.63-0.81)
Unknown 1.02 (0.88-1.19)

Chavez-MacGregor et al. JAMA Oncol 2016

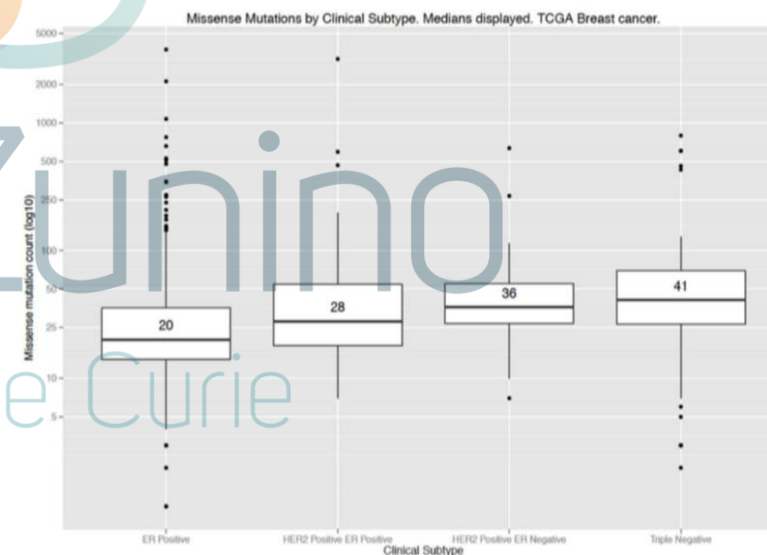
Futuro: Inmunoterapia en TN

Somatic mutations in cancers

Breast Cancer and mutations: Lower median rate detected compared to the most immune-sensitive cancers but wide range of mutations detected

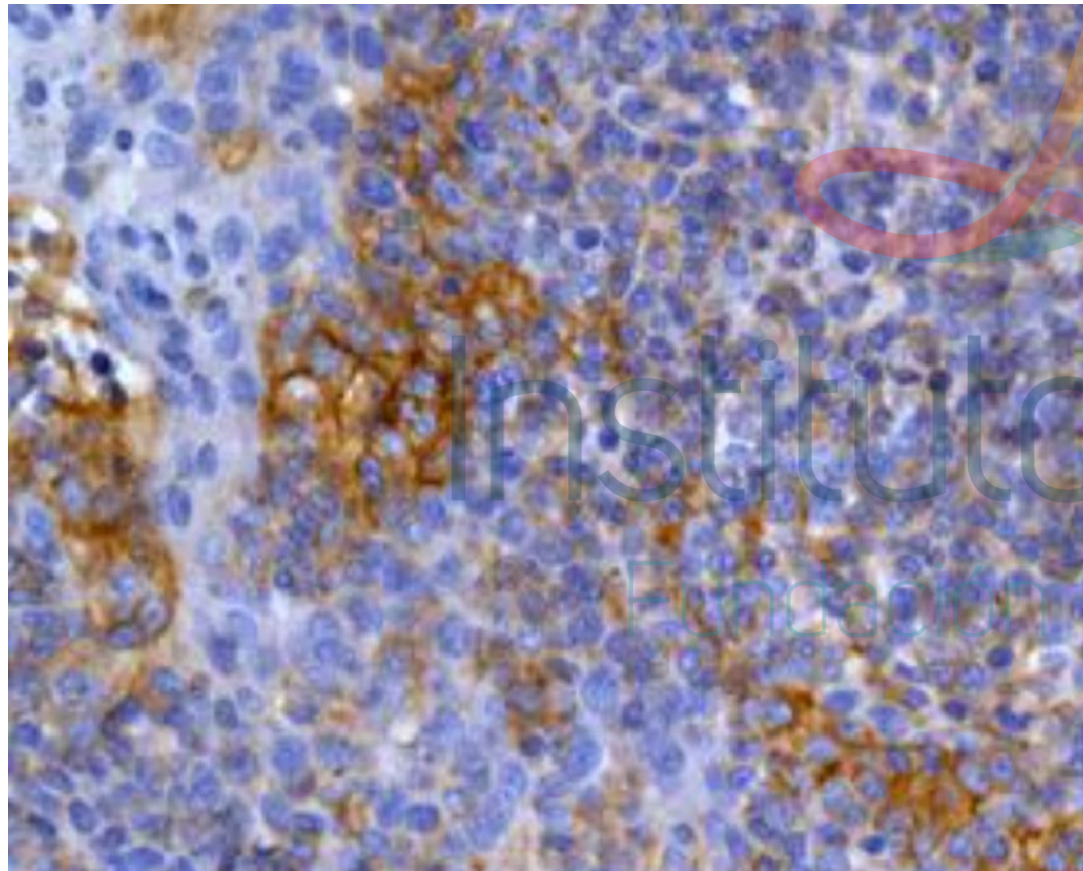


Breast cancer has fewer mutations

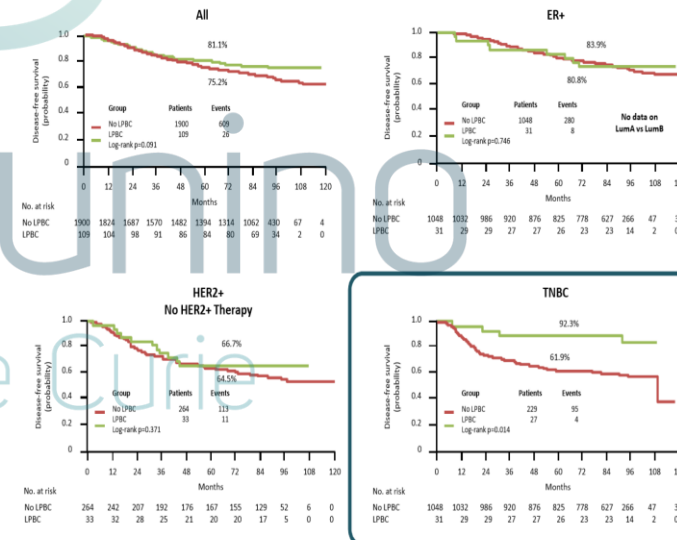


$p < 0.0001$

Futuro: Inmunoterapia en TN. Presencia de TILs



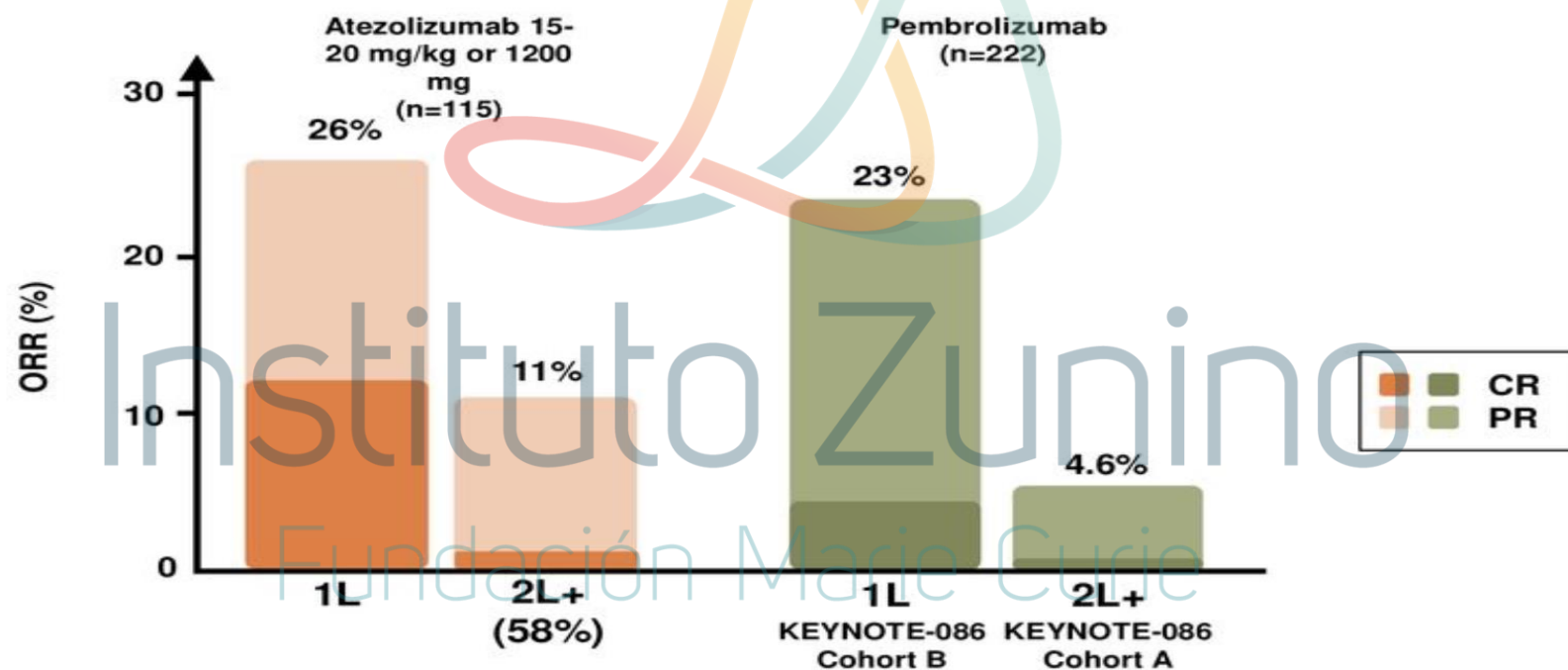
Tumour-infiltrating lymphocytes and outcome



Strongest link of TILs and outcome in TNBC

Loi, et al. J Clin Oncol 2013

Futuro: Inmunoterapia en TN.



1L, first line; 2L, second line; CR, complete response; ORR, objective response rate;
PD-1, programmed death -1; PD-L1, programmed death-ligand 1; PR, partial response

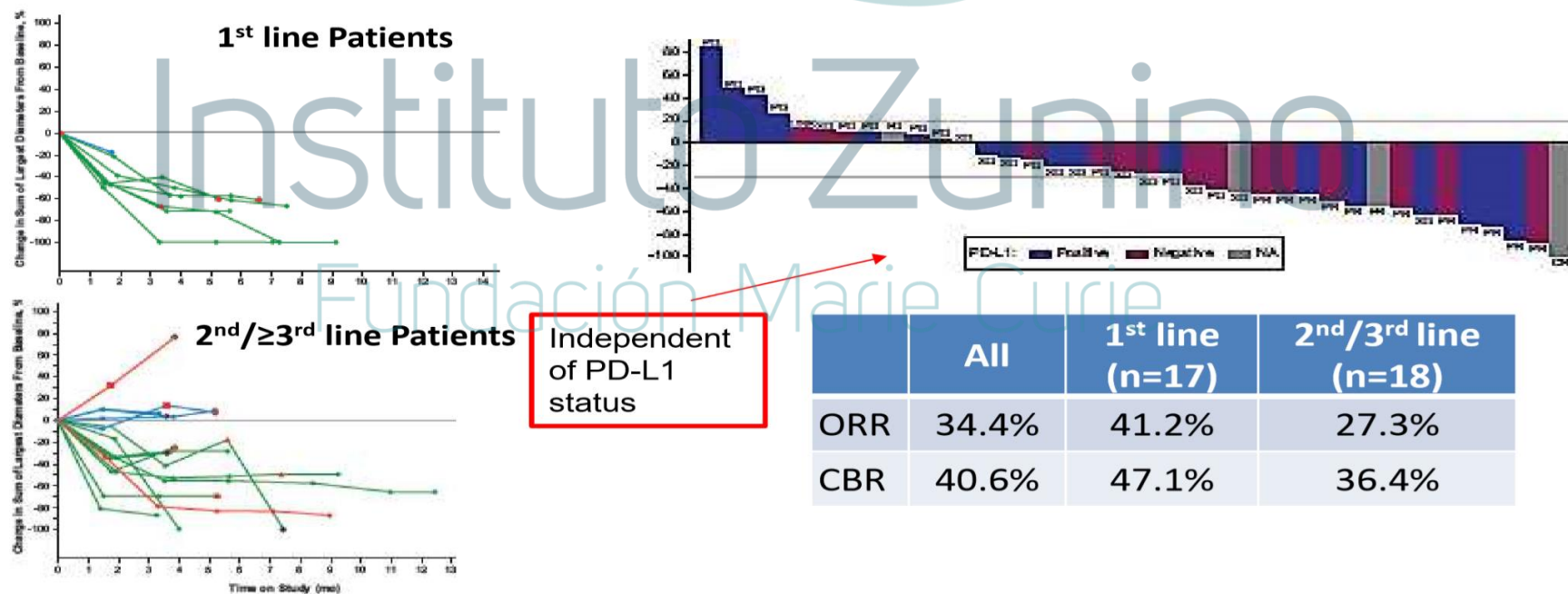
Schmid, et al. AACR 2017; Adams, et al ASCO 2017

Futuro: Inmunoterapia en TN

Combination of Immune- & Chemotherapy in mTNBC

Nab-Paclitaxel + anti-PD-L1 (Atezolizumab)

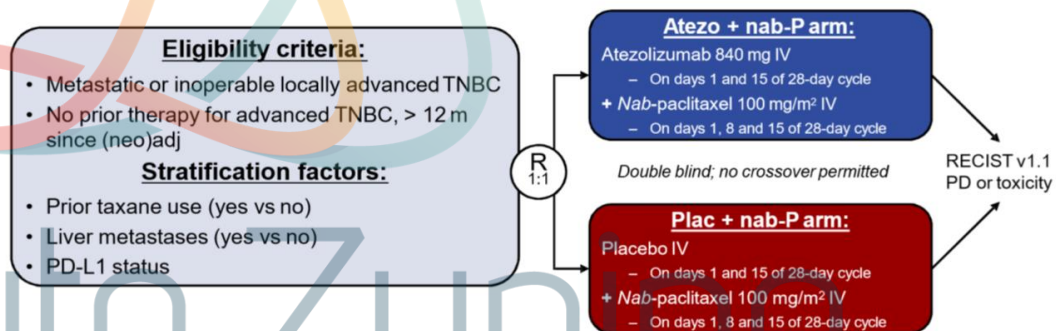
Eribulin + anti-PD-1 (Pembrolizumab)



Adapted from Adams S et al, SABCS 2015; Tolaney et al, SABCS 2016

Futuro:
Inmunoterapia
en TN

IMpassion130: PHASE III ATEZOLIZUMAB + NAB PACLITAXEL



Co-primary endpoints: PFS and OS in ITT and PD-L1+ populations

MUNICH 2018 ESMO congress

Schmid P et al, NEJM 2018

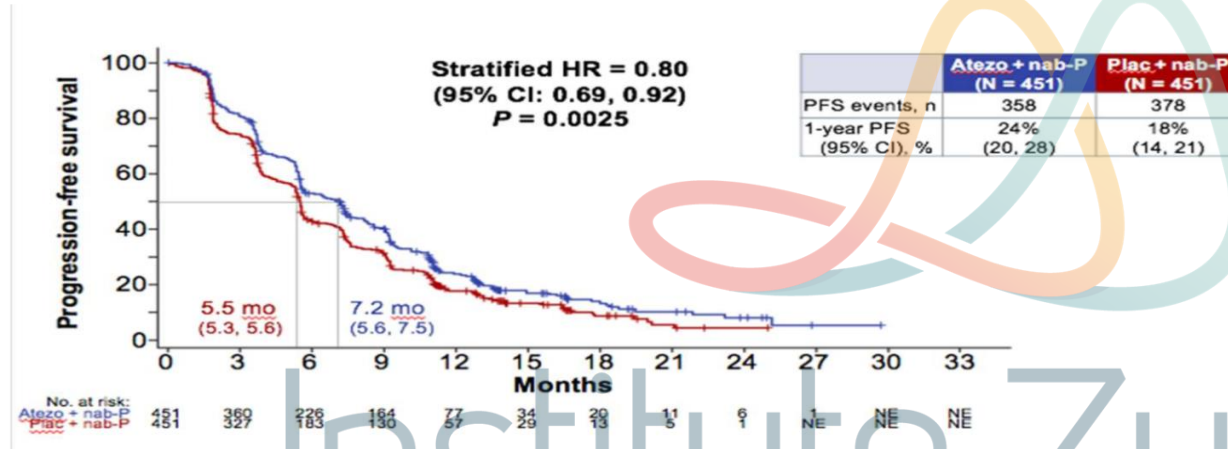
Futuro: Inmunoterapia en TN

IMpassion130 baseline characteristics

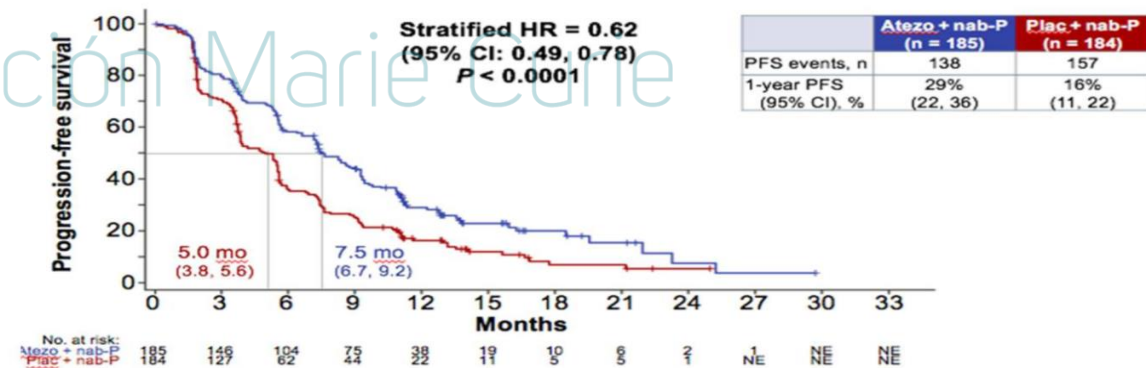
Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)	Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)	Metastatic disease, n (%)	404 (90%)	408 (91%)
Female, n (%)	448 (99%)	450 (100%)	No. of sites, n (%) ^d		
Race, n (%) ^a			0-3	332 (74%)	341 (76%)
White	308 (68%)	301 (67%)	≥ 4	118 (26%)	108 (24%)
Asian	85 (19%)	76 (17%)	Site of metastatic disease, n (%)		
Black/African American	26 (6%)	33 (7%)	Lung	226 (50%)	242 (54%)
Other/multiple	20 (4%)	26 (6%)	Bone	145 (32%)	141 (31%)
ECOG PS, n (%) ^{b,c}			Liver	126 (28%)	118 (26%)
0	256 (57%)	270 (60%)	Brain	30 (7%)	31 (7%)
1	193 (43%)	179 (40%)	Lymph node only ^d	33 (7%)	23 (5%)
Prior (neo)adjuvant treatment, n (%)			PD-L1+ (IC), n (%)	185 (41%)	184 (41%)
Prior taxane	231 (51%)	230 (51%)			
Prior anthracycline	243 (54%)	242 (54%)			

Data cutoff: 17 April 2018. ^a Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm. ^b Of n = 450 in each arm. ^c ECOG PS before start of treatment was 2 in 1 patient per arm. ^d Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm.

Futuro: Inmunoterapia en TN

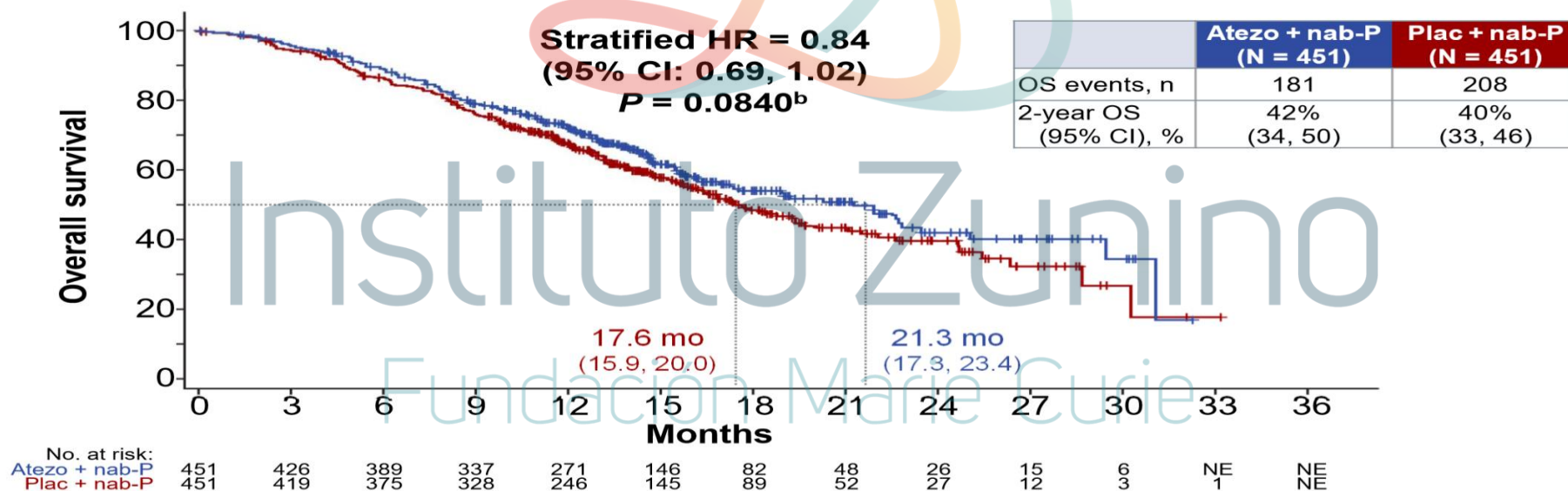


Primary PFS analysis: PD-L1+ population



Futuro: Inmunoterapia en TN

Interim OS analysis: ITT population^a



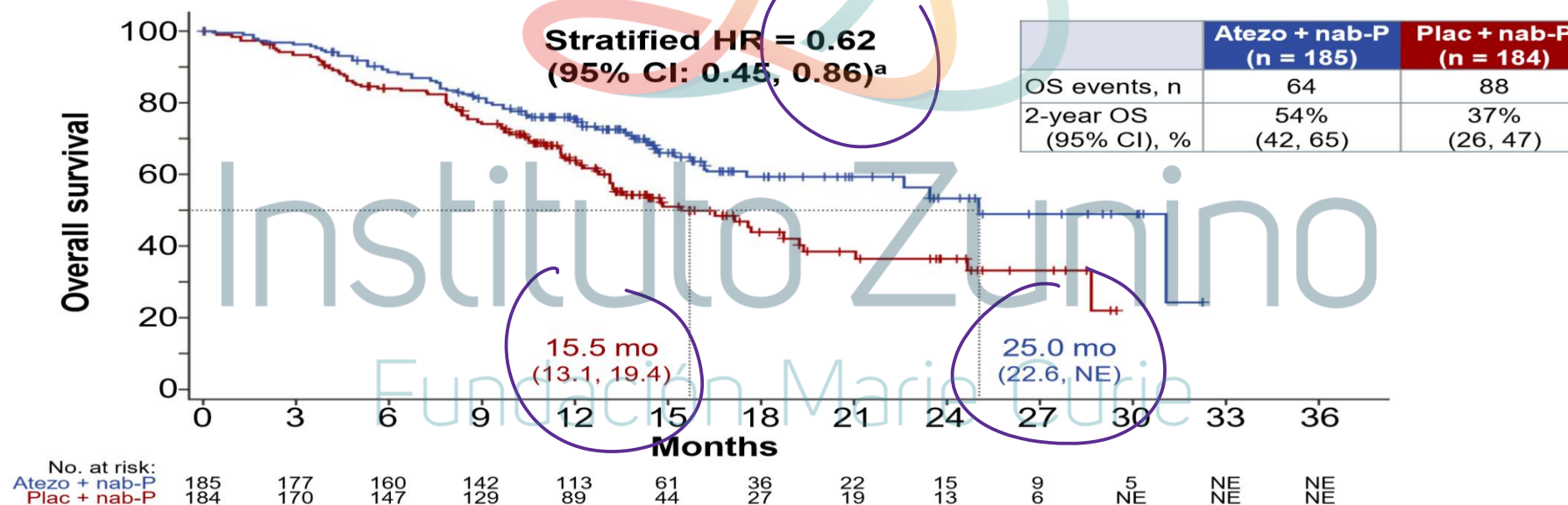
Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

^a For the interim OS analysis, 59% of death events had occurred. ^b Significance boundary was not crossed.

Schmid P, et al. IMpassion130.
ESMO 2018 (abstract 2056).

Futuro: Inmunoterapia en TN

Interim OS analysis: PD-L1+ population



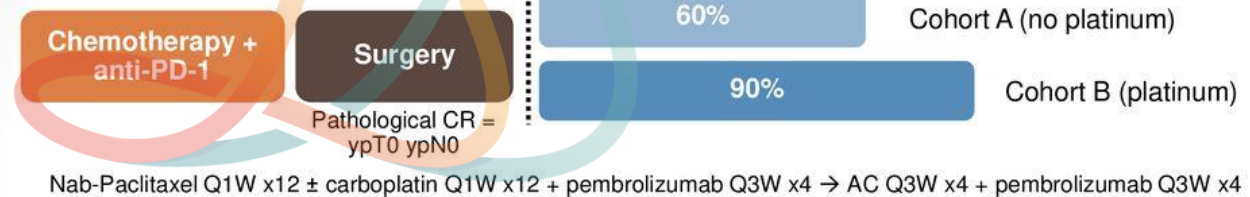
Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. ^a Not formally tested.

Schmid P, et al. IMpassion130. ESMO 2018 (abstract 2056).

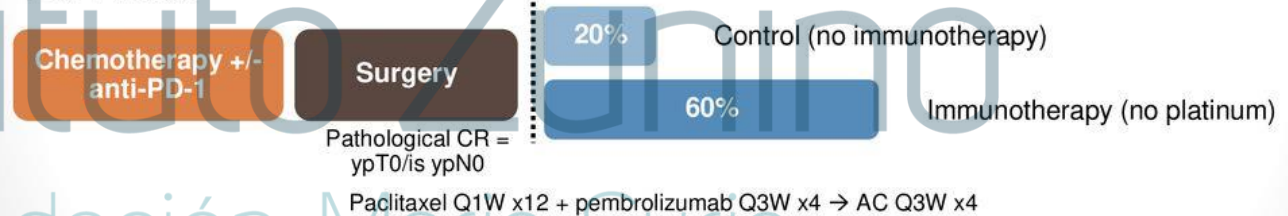
Futuro: Inmunoterapia en TN

Neoadjuvant chemotherapy + anti-PD-L1/anti-PD-1

KEYNOTE-173 phase 1/2 trial



I-SPY 2 trial



AC, doxorubicin + cyclophosphamide; CR, complete response; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; Q1W, every week; Q3W, every 3 weeks; ypT0/Tis ypN0, no invasive residual in breast or nodes - noninvasive breast residuals allowed; ypT0 ypN0, no invasive or noninvasive residual in breast or nodes

Schmid, et al. ASCO 2017;
Nanda, et al. ASCO 2017

Futuro:
Inmunoterapia en
TN

KEYNOTE-173: Pembrolizumab + Chemotherapy as Neoadjuvant Therapy for TNBC

- Multicohort, open-label phase Ib study

	Cycle 1		Cycle 5	Cycle 9
Cohort A	Pembro	Pembro + Nab-P 125 mg/m ²	Pembro + AC	
Cohort B	Pembro	Pembro + Nab-P 100 mg/m ² + Carboplatin AUC 6 D1	Pembro + AC	
Cohort C	Pembro	Pembro + Nab-P 125 mg/m ² + Carboplatin AUC 5 D1	Pembro + AC	
Cohort D	Pembro	Pembro + Nab-P 125 mg/m ² + Carboplatin AUC 2 D1, 8, 15	Pembro + AC	
Cohort E	Pembro	Pembro + Paclitaxel 80 mg/m ² + Carboplatin AUC 5 D1	Pembro + AC	
Cohort F	Pembro	Pembro + Paclitaxel 80 mg/m ² + Carboplatin AUC 2 D1, 8, 15	Pembro + AC	

All tx given IV. Cyclophosphamide: 600 mg/m² Q3W. Doxorubicin: 60 mg/m² Q3W. Nab-P, Pac: Days 1, 8, 15 Q3W. Pembro: 200 mg Day 1 in cycle 1, then Q3W. Definitive surgery per local standards and tissue collection for pCR 3-6 wks following completion of neoadjuvant therapy.

- Primary endpoint: safety/tolerability
- Secondary endpoints including: pCR rate, ORR, EFS, OS

Futuro: Inmunoterapia en TN

KEYNOTE-173: Efficacy

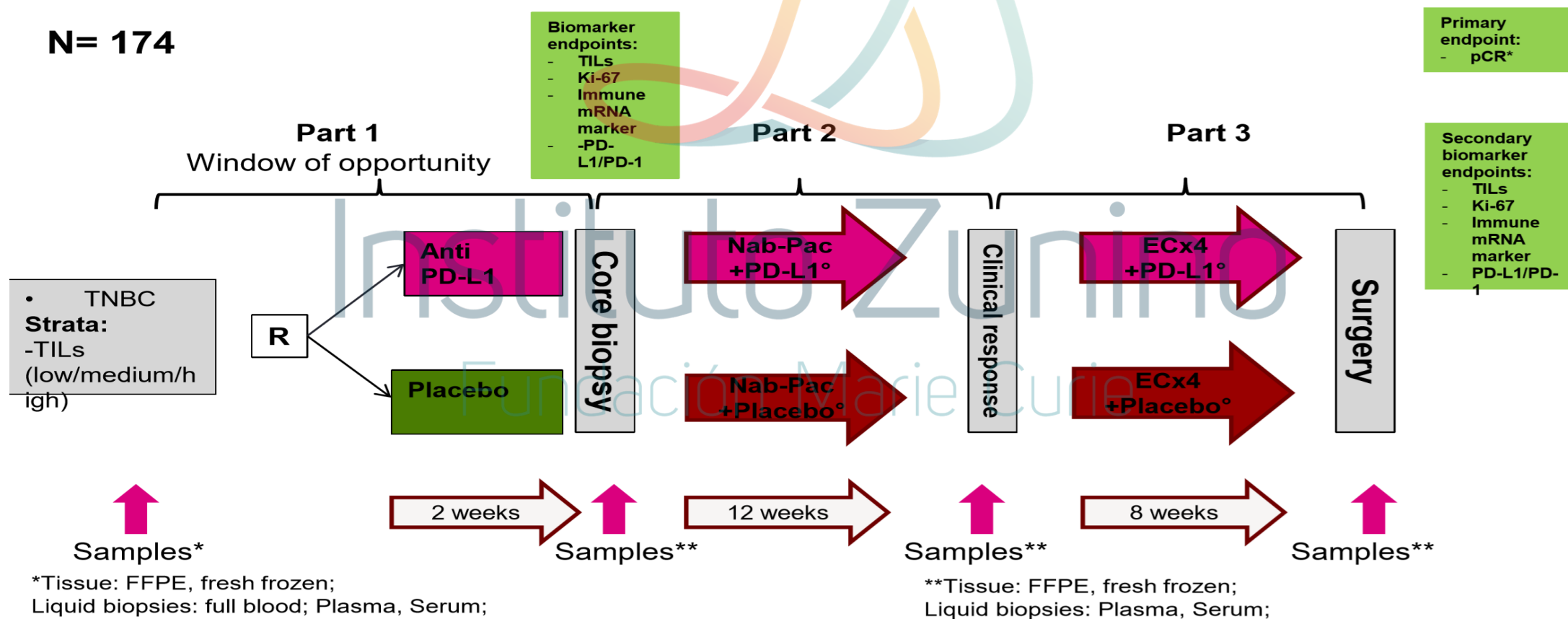
- Overall pCR rate at definitive surgery^[1]
 - ypT0/Tis ypN0: 60% (range: 30% to 80%)
 - ypT0 ypN0: 57% (range: 20% to 80%)
 - Highest rates observed in cohorts B-D (ie, patients receiving nab-paclitaxel and carboplatin in cycles 2-5)
- Patients achieving pCR showed better 12-mo and 24-mo EFS compared with those who did not^[1]
 - Better EFS (and OS) rates with vs without carboplatin
- Higher pretreatment sTILs and PD-L1 CPS and on-treatment sTILs were associated with higher pCR rates^[2]

Futuro: Inmunoterapia en TN



GeparNUEVO Durvulumab Study Design

N= 174



4. Ensayos clínicos con Inmunoterapia en TN Enf. Temprana

Phase	NCT ID & number	Defined condition of breast Cancer subtype	setting	stage	Experimental Drugs	Control	Primary endpoint
IO monotherapy							
III	SWOG1418 (NCT02954874)	Residual TNBC (ypT> 1cm or ypN+)	Adjuvant after NAC		Pembrolizumab for 1 year	Observation as per guideline	Invasive DFS (IDFS)
III	NCT02926196	High risk TNBC	Adjuvant or post-NAC		Avelumab for 1 year	Observation as per guideline	- Overall DFS - DFS in PD-L1(+) patients
IO-based combination							
II	I-SPY 2 (NCT01042379) * Neoadjuvant, personalized adaptive trial with novel agents	Locally advanced breast cancer including TNBC and HR+HER2- BC	Neoadjuvant	II, III	- Pembrolizumab+paclitaxel - Followed by doxorubicin + cyclophosphamide	Standard NAC	pCR : 62.4% vs 22.3%
IB	KEYNOTE-173 (NCT02622074)	Locally advanced TNBC	Neoadjuvant	II, III	(Arm A) : Pembrolizumab → Pembrolizumab + nabPaclitaxel (Arm B) : Arm A+ Carboplatin Followed by ddAC	NA	pCR (Arm A vs B) : 60% vs 90%
III	KEYNOTE-522 (NCT03036488)	TNBC	Neo/adjuvant		- Neoadjuvant : Pembrolizumab + wPaclitaxel + Carboplatin (4C)→ Pembrolizumab + AC (4C) - Adjuvant : Pembrolizumab (9C)	placebo rather than pembrolizumab	pCR, EFS
I/II	NCT02489448	TNBC	Neoadjuvant	I-III	- Durvalumab + nab-paclitaxel for 12 weeks	NA	pCR

Conclusiones



QUIMIOTERAPIA NEOADYUVANTE

AC/EC x 4 con densidad de dosis + G-CSF seguido de Paclitaxel semanal x 12

Comenzar el tratamiento rápidamente dentro de un grupo multidisciplinario

En caso de Enfermedad Residual considerar: 1. Capecitabine x 6-8 ciclos

2. Ensayo Clínico con

Inmunoterapia



Muchas Gracias por su Atención !!!
