Clube da Mama
Pós-San Antonio Breast Cancer Symposium 2018

O QUE MUDA NA NOSSA PRÁTICA?

AUGUSTO R GABRIEL

FEVEREIRO/2019

Agradecimentos

- Audiência
- Orgnização do evento
- Prof Charles E Geyer, Prof Miguel Martin, Profa Zaida Morante

Phase III Study of Trastuzumab Emtansine (T-DM1) vs Trastuzumab as Adjuvant Therapy in Patients with HER2-Positive Early Breast Cancer with Residual Invasive Disease after Neoadjuvant Chemotherapy and HER2-Targeted Therapy Including Trastuzumab: Primary Results from KATHERINE (NSABP B-50-I, GBG 77 and Roche BO27938)

Charles E. Geyer, Jr., Chiun-Sheng Huang, Max S. Mano, Sibylle Loibl, Eleftherios P. Mamounas, Michael Untch, Norman Wolmark, Priya Rastogi, Andreas Schneeweiss, Andrés Redondo, Hans H. Fischer, William Jacot, Alison K. Conlin, Claudia Arce-Salinas, Irene L. Wapnir, Christian Jackisch, Michael P. DiGiovanna, Peter A. Fasching, John P. Crown, Pia Wülfing, Zhimin Shao, Elena Rota Caremoli, Haiyan Wu, Lisa H. Lam, David Tesarowski, Melanie Smitt, Hannah Douthwaite, Stina M. Singel, and Gunter von Minckwitz, on behalf of the KATHERINE investigators

GBG GERMAN BREAST GROUP

NSABP Foundation, Inc. Partners In Cancer Research

Roche Genentech

The NEW ENGLAND JOURNAL of MEDICINE

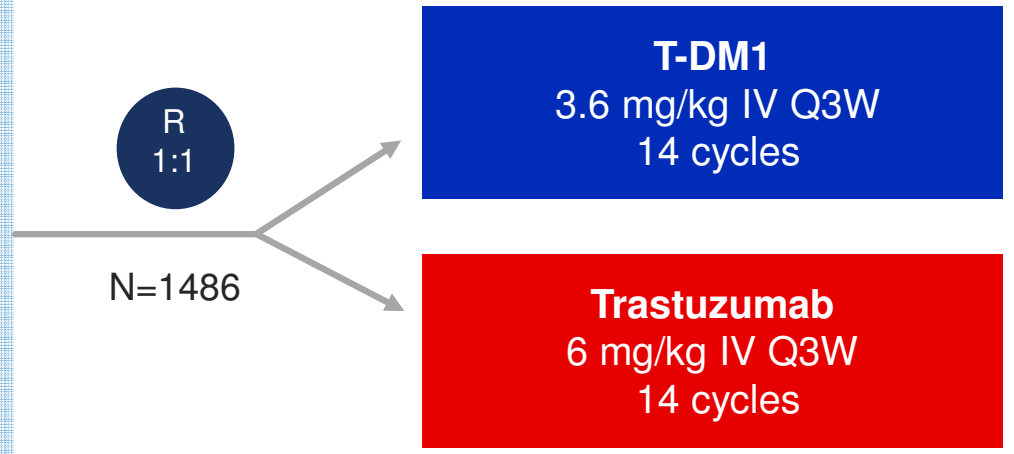
ORIGINAL ARTICLE

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

Gunter von Minckwitz, M.D., Chiun-Sheng Huang, M.D., Ph.D., Max S. Mano, M.D., Ph.D., Sibylle Loibl, M.D., Eleftherios P. Mamounas, M.D., Michael Untch, M.D., Ph.D., Norman Wolmark, M.D., Priya Rastogi, M.D., Andreas Schneeweiss, M.D., Andres Redondo, M.D., Ph.D., Hans H. Fischer, M.D., William Jacot, M.D., Ph.D., Alison K. Conlin, M.D., Claudia Arce-Salinas, M.D., Ph.D., Irene L. Wapnir, M.D., Christian Jackisch, M.D., Ph.D., Michael P. DiGiovanna, M.D., Ph.D., Peter A. Fasching, M.D., John P. Crown, M.D., Pia Wülfing, M.D., Zhimin Shao, M.D., Elena Rota Caremoli, M.D., Haiyan Wu, Ph.D., Lisa H. Lam, Pharm.D., David Tesarowski, Ph.D., Melanie Smitt, M.D., Hannah Douthwaite, M.Sc., Stina M. Singel, M.D., Ph.D., and Charles E. Geyer, Jr., M.D., for the KATHERINE Investigators*

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

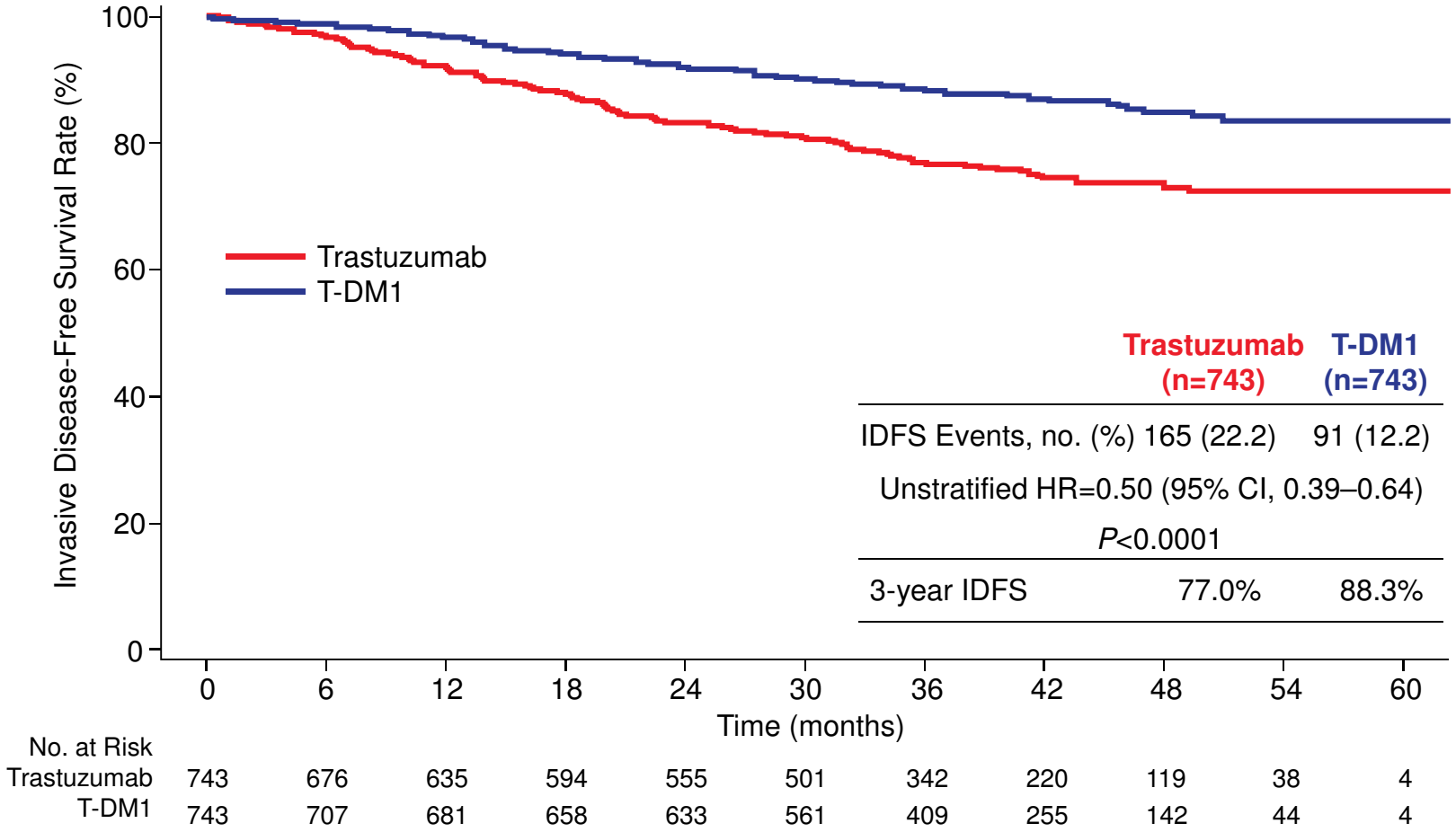


Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

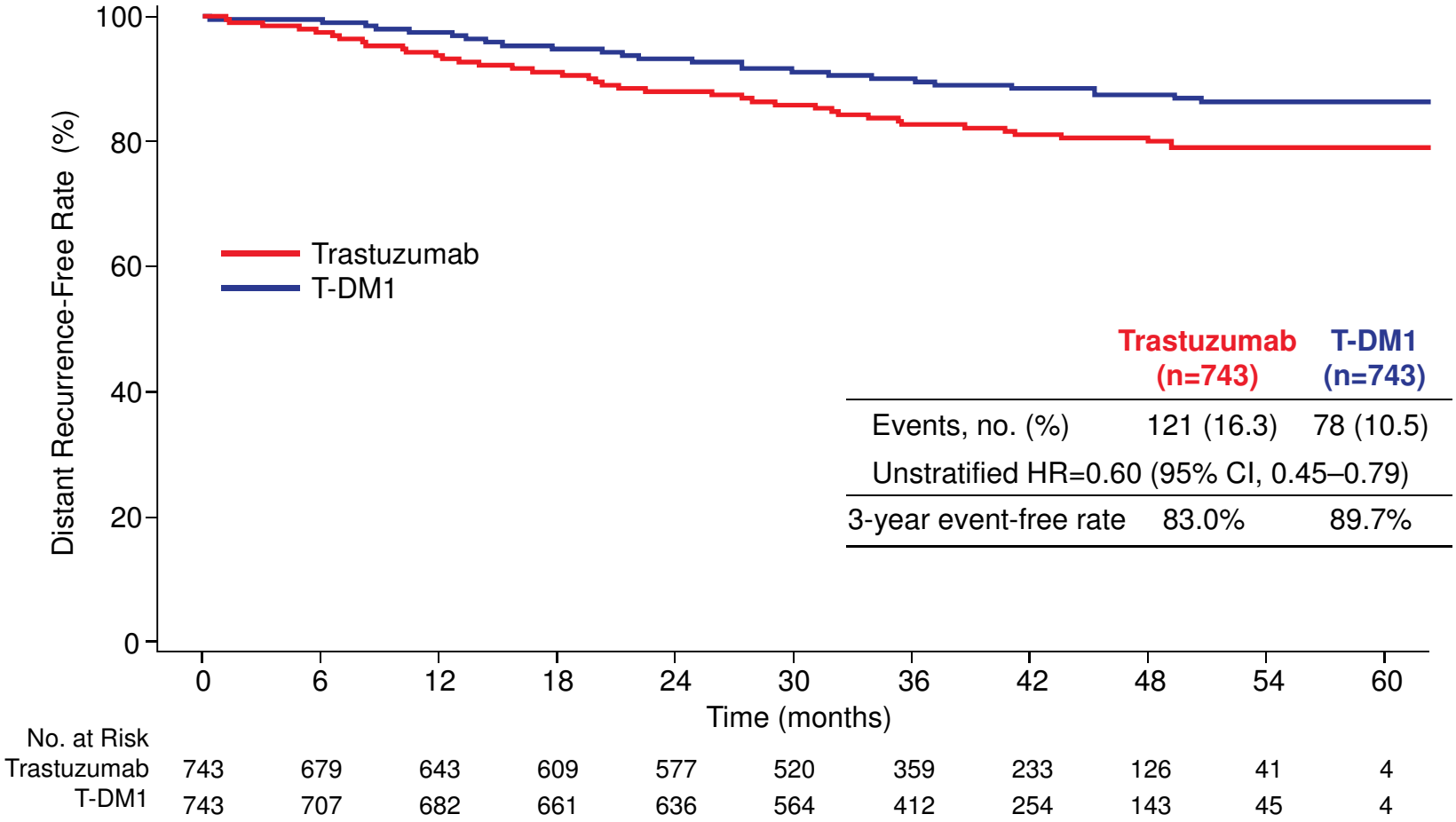
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Invasive Disease-Free Survival



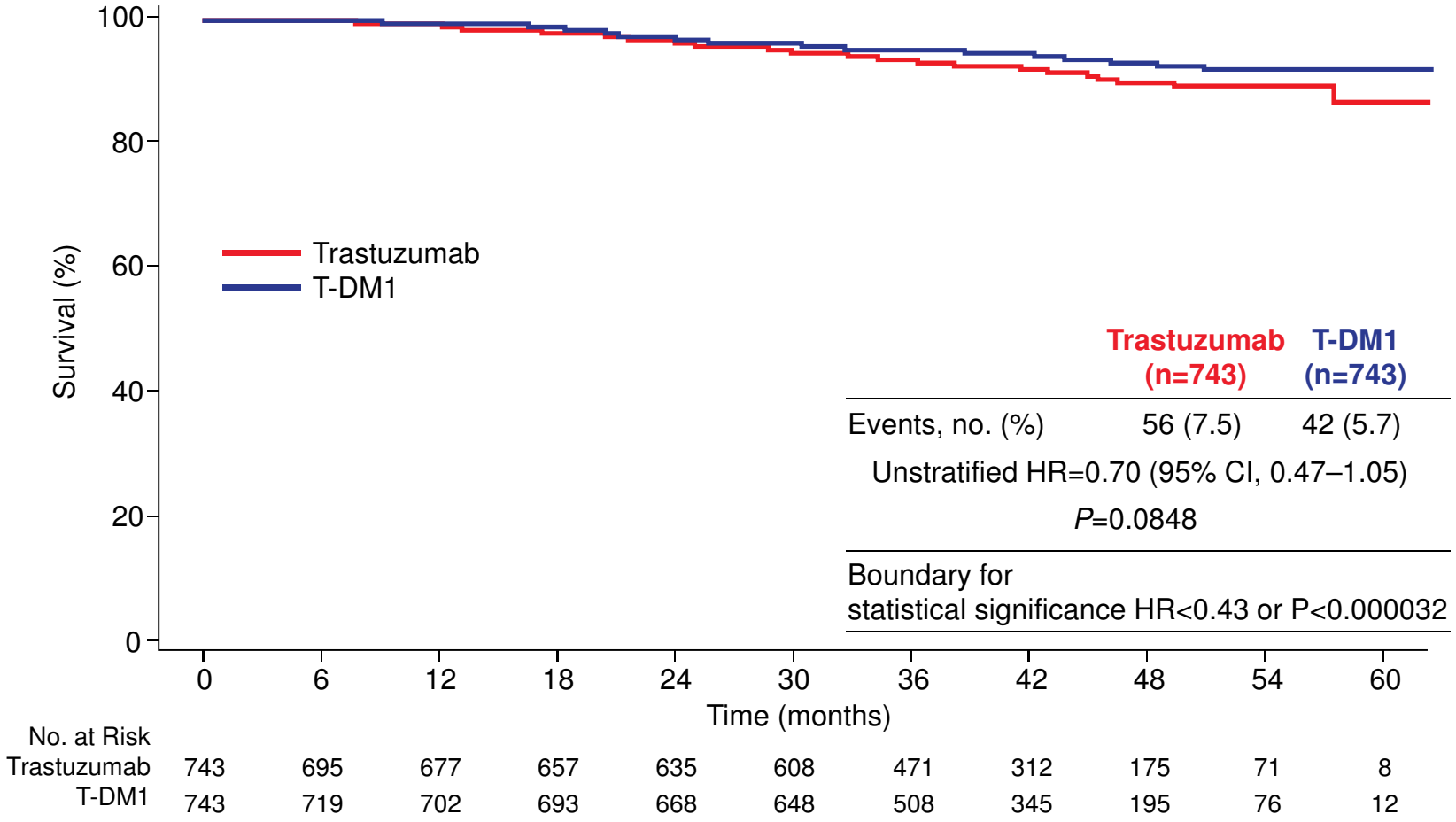
	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64)		
P<0.0001		
3-year IDFS	77.0%	88.3%

Distant Recurrence



	Trastuzumab (n=743)	T-DM1 (n=743)
Events, no. (%)	121 (16.3)	78 (10.5)
Unstratified HR=0.60 (95% CI, 0.45–0.79)		
3-year event-free rate	83.0%	89.7%

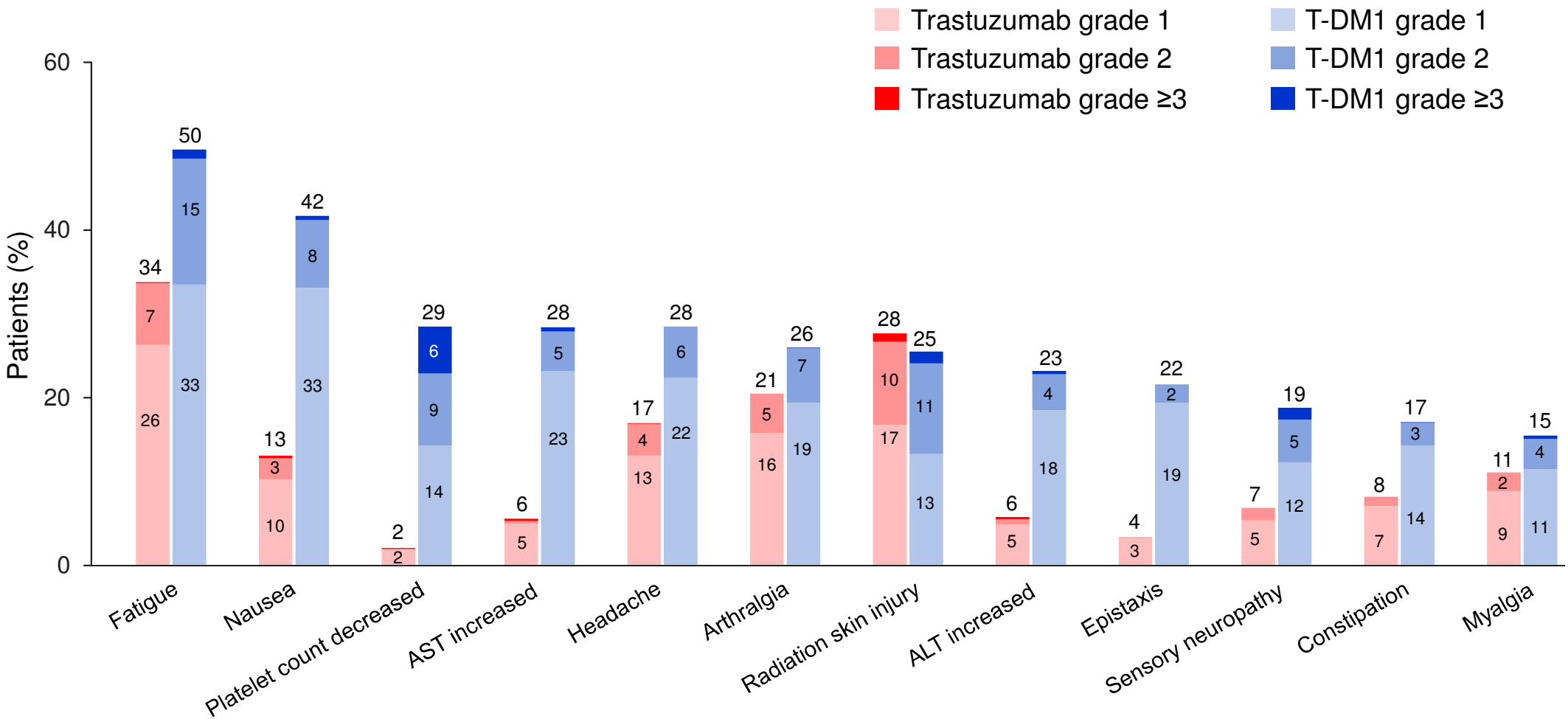
Overall Survival



Exposure to Study Treatment

	Trastuzumab (n=720)	T-DM1 (n=740)
Cycles of trastuzumab/T-DM1 completed, n (%)		
7 cycles	664 (92.2)	637 (86.1)
14 cycles	583 (81.0)	528 (71.4)
Patients with a dose reduction, n (%)		
No dose reduction	N/A	634 (85.7)
One dose level reduction (3.0 mg/kg)	N/A	77 (10.4)
Two dose level reductions (2.4 mg/kg)	N/A	29 (3.9)

All Grade AEs ≥15% Incidence in Either Arm



Katherine

- Análise de custo (paciente de 60 kg):
  - 14 ciclos de Trastuzumabe (T)– R$ 166000,00
  - 14 ciclos de T + Pertuzumabe – R$ 341000,00
  - 14 ciclos de TDM1- R$ 238000,00

TNBC

- CIBOMA/GEICAM
- Impassion 130
- É do Peru

San Antonio Breast Cancer Symposium®, December 4-8, 2018

Efficacy results from GEICAM/2003-11_CIBOMA/2004-01 study: a randomized phase III trial assessing adjuvant capecitabine after standard chemotherapy for patients with early triple negative breast cancer

Professor Miguel Martin

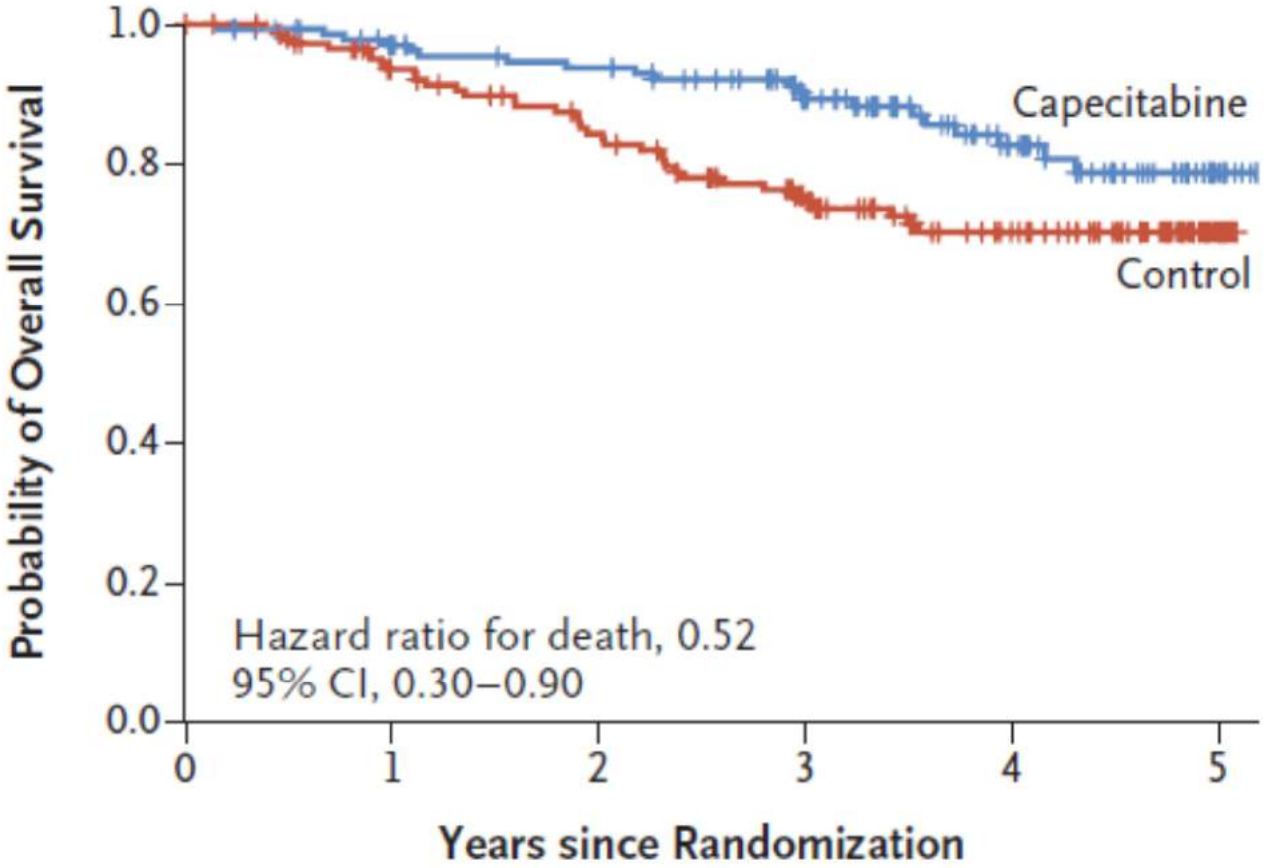
Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense, Madrid, Spain

Authors: Miguel Martín, Carlos H Barrios, Laura Torrecillas, Manuel Ruiz-Borrego, Jose Bines, Jose Segalla, Amparo Ruiz, Jose A García-Sáenz, Roberto Torres, Juan de la Haba, Elena García-Martínez, Henry L Gómez, Antonio Llombart, María Rodríguez de la Borbolla, José M Baena, Agustí Barnadas, Lourdes Calvo, Laura Pérez-Michel, Manuel Ramos, Javier Castellanos, Álvaro Rodríguez-Lescure, Jesús Cárdenas, Jeferson Vinholes, Eduardo Martínez de Dueñas, Maria J Godes, Miguel A Seguí, Antonio Antón, Pilar López-Álvarez, Jorge Moncayo, Gilberto Amorim, Esther Villar, Salvador Reyes, Carlos Sampaio, Bernardita Cardemil, Maria J Escudero, Susana Bezares, Eva Carrasco, Ana Lluch, on behalf of CIBOMA (Iberoamerican Coalition for Research in Breast Oncology), LACOG (Latin American Cooperative Oncology Group) and GEICAM Spanish Breast Cancer Group.

EudraCT number: 2005-002838-36. NCT: 00130533.

CREATE X

D Overall Survival among Patients with Triple-Negative Disease



No. at Risk						
Capecitabine	139	124	116	91	50	11
Control	147	125	108	82	52	9

Study Design

- TNBC: ER-, PR-, HER2- (centrally confirmed)
- T1c-T3, N0-N3a*, M0
- Prior standard neo/adjuvant CT with anthras +/- taxanes
- Surgery with free-margins

*except infraclavicular lymph node involvement.

Stratification Factors:

- Institution
- Basal Phenotype according to CK 5/6 and/or EGFR staining (yes vs no)
- ALN (0 vs 1-3 vs ≥4)
- Prior CT (anthras vs anthras + taxanes)

1:1 Randomization

- Capecitabine 1000 mg/m² p.o., b.i.d. x 14 days every 3 weeks x 8 cycles
- Observation

Radiation therapy according to institution standards

- 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.

Patient and Tumor Characteristics (1)

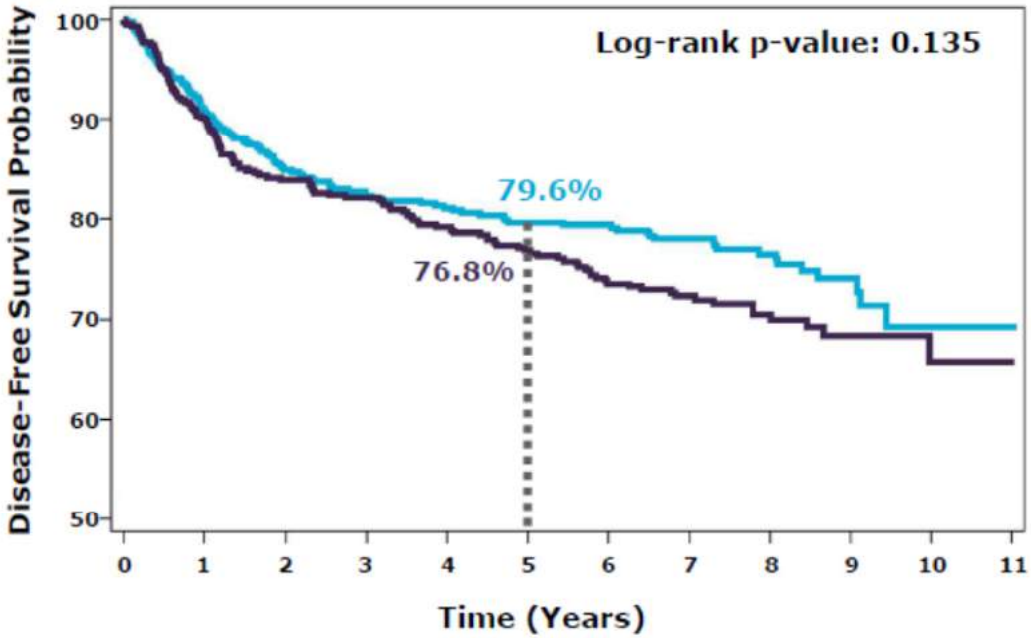
	Capecitabine (n=448)	Observation (n=428)
Median age, years (range)	50 (20-79)	49 (23-82)
Region, n (%)		
• Spain	272 (60.7)	260 (60.7)
• Latin America (LA)	176 (39.3)	168 (39.3)
Menopausal status at diagnosis, n (%)		
• Premenopausal	136 (30.4)	140 (32.7)
• Postmenopausal	312 (69.6)	288 (67.3)
Stage at diagnosis, n (%)		
• I	62 (13.8)	74 (17.3)
• II	270 (60.3)	271 (63.3)
• III	106 (23.7)	80 (18.7)
• Not available	10 (2.2)	3 (0.7)
Nodal status, n (%)		
• Negative	244 (54.5)	242 (56.5)
• 1–3 positive nodes	121 (27.0)	124 (29.0)
• ≥4 positive nodes	77 (17.2)	61 (14.3)
• Not available	6 (1.3)	1 (0.2)

Patient and Tumor Characteristics (2)

	Capecitabine (n=448)	Observation (n=428)
Type of CT, n (%)		
• Adjuvant (only)	353 (78.8)	352 (82.2)
• Neoadjuvant (+/- adjuvant)	89 (19.9)	75 (17.5)
• Missing data	6 (1.3)	1 (0.2)
pCR in patients with neoadjuvant CT*, n (%)	22 (24.7)	19 (25.3)
CT regimens, n (%)		
• Anthracyclines-based	147 (32.8)	138 (32.2)
• Anthracyclines and Taxanes-based	301 (67.2)	290 (67.8)

*Pathological complete response in breast and axilla after neoadjuvant chemotherapy.

Disease-Free Survival (ITT)



Median follow-up: 7.34 years

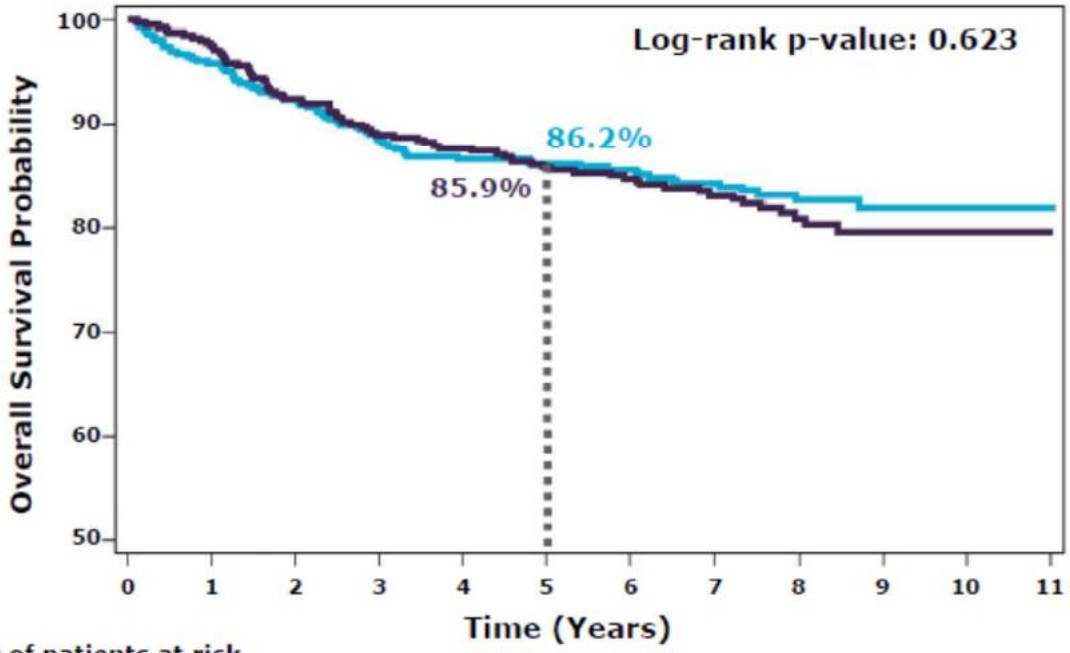
Group	Events
Capecitabine	105
Observation	120
HR: 0.82 (95% CI: 0.63, 1.06, p=0.136)	
Adjusted HR*: 0.79 (95% CI: 0.61, 1.03, p=0.082)	

*Adjusted HR for stratification variables: Spain vs. LA, previous neo/adjuvant treatment (anthracyclines vs. anthracyclines and taxanes), number of involved nodes (0 vs. 1-3 vs. ≥4) and TN phenotype by IHC (basal vs. non-basal).

Number of patients at risk

Capecitabine	448	396	365	344	334	323	304	248	154	60	17	1
Observation	428	379	347	329	313	290	262	204	123	58	25	2

Overall Survival (ITT)



Median follow-up: 7.34 years

Group	Events
Capecitabine	71
Observation	73
HR: 0.92 (95% CI: 0.66, 1.28)	

Number of patients at risk

Capecitabine	448	417	393	367	354	347	324	267	170	71	24	1
Observation	428	407	375	350	339	318	296	232	145	73	28	2

Capecitabine Administration

- Relative MEDIAN dose intensity: **86.3%**.
- Distribution by number of cycles administered:

Administered Cycles	
Number of cycles	**Capecitabine (N=448), n (%)**
0	12 (2.7)
1	18 (4.0)
2	22 (4.9)
3	11 (2.5)
4	13 (2.9)
5	16 (3.6)
6	9 (2.0)
7	10 (2.2)
8	**337 (75.2)**

Ciboma ≠ Create X

- TNBC
- QT adjuvante
- QT neoadjuvante
- Negativo

- HER2 negativos
  - (31% TN)
- QT neoadjuvante
- Ganho de SLD (TN)

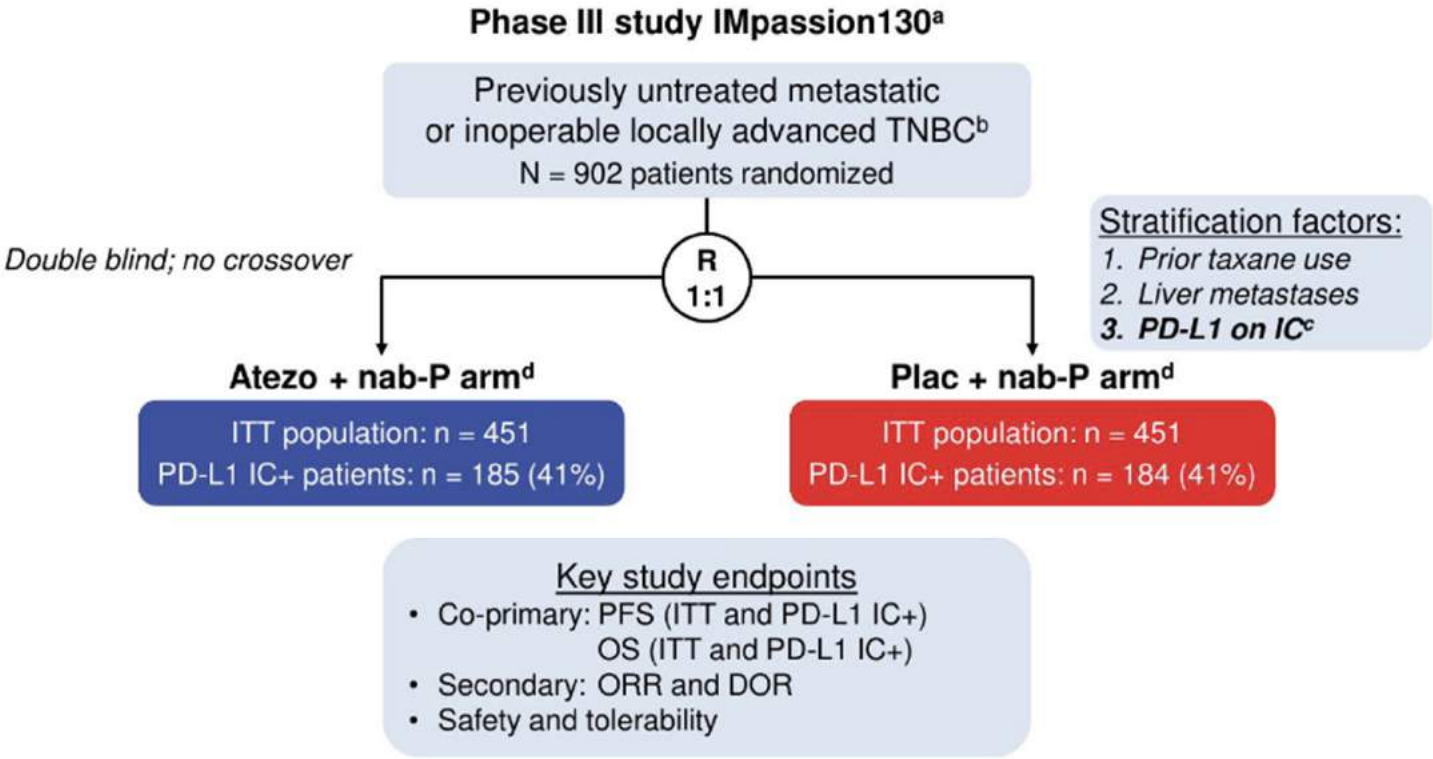
IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer

Leisha A. Emens,[1] Sherene Loi,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Véronique Diéras,[5] Hiroji Iwata,[6] Carlos H. Barrios,[7] Marina Nechaeva,[8] Luciana Molinero,[9] Anh Nguyen Duc,[10] Roel Funke,[9] Stephen Y Chui,[9] Amreen Husain,[10] Eric P. Winer,[11] Sylvia Adams,[12] Peter Schmid[13]

[1]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; [2]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [4]University Hospital Heidelberg, Heidelberg, Germany; [5]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [6]Aichi Cancer Center Hospital, Aichi, Japan; [7]Department of Medicine, PUCRS School of Medicine, Porto Alegre, Brazil; [8]Arkhangelsk Regional Clinical Oncology Dispensary, Arkhangelsk, Russia; [9]Genentech, Inc., South San Francisco, CA; [10]F. Hoffmann-La Roche AG, Basel, Switzerland; [11]Dana-Farber Cancer Institute, Boston, MA; [12]New York University Langone Medical Center, New York, NY; [13]Barts Cancer Institute, Queen Mary University of London, London, UK

Emens LA, et al. IMpassion130 biomarkers.
SABCS 2018 (program #GS1-04)

IMpassion130 study design: Prespecified analyses in the ITT and PD-L1 IC+ population

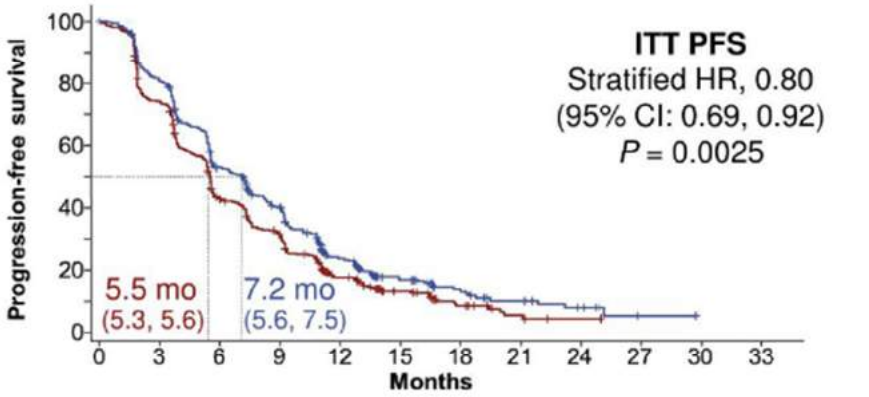


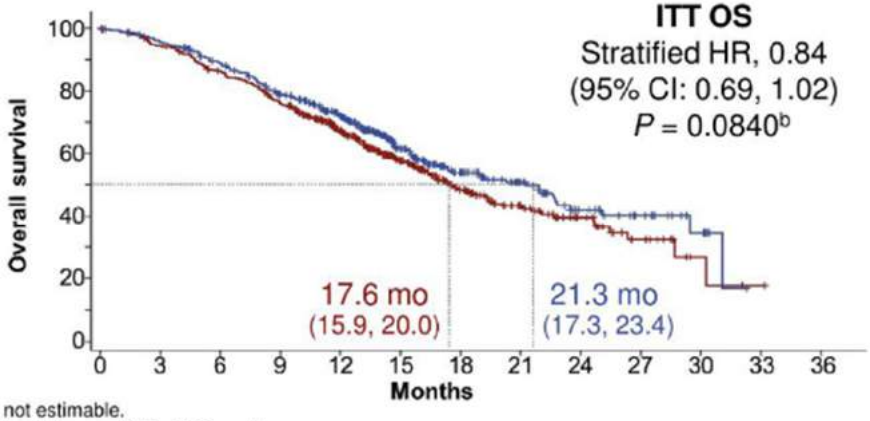
[a] NCT02425891. [b] Locally evaluated per ASCO-CAP guidelines. Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo.
[c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status, PD-L1+: PD-L1 on ≥ 1% of IC). [d] Atezolizumab or placebo 840 mg IV on days 1 and 15 + *nab*-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15 of 28-day cycle until RECIST v1.1 PD. 1. Schmid *N Engl J Med* 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

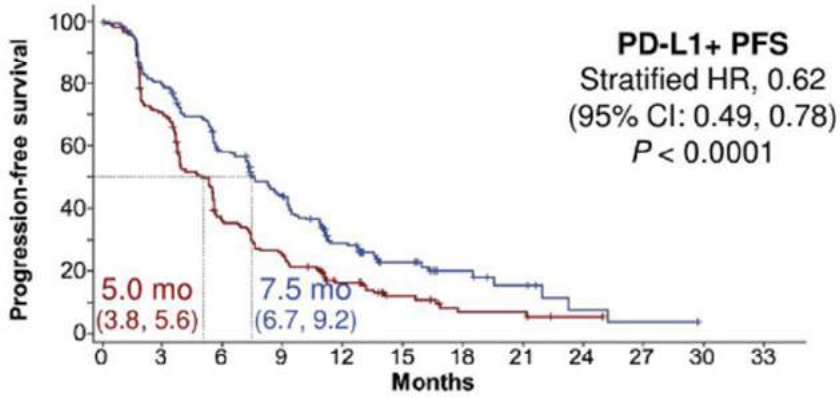
IMpassion130 primary analysis[1,2]: Clinically meaningful PFS and OS benefit in the PD-L1+ population

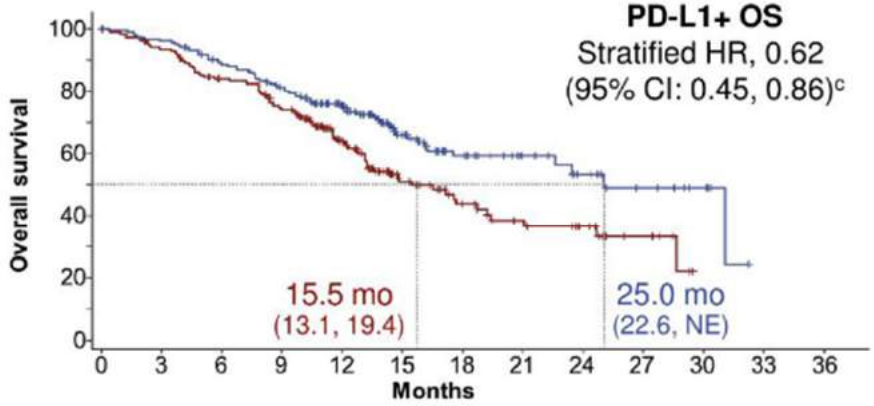
ITT population





PD-L1+ population[a]



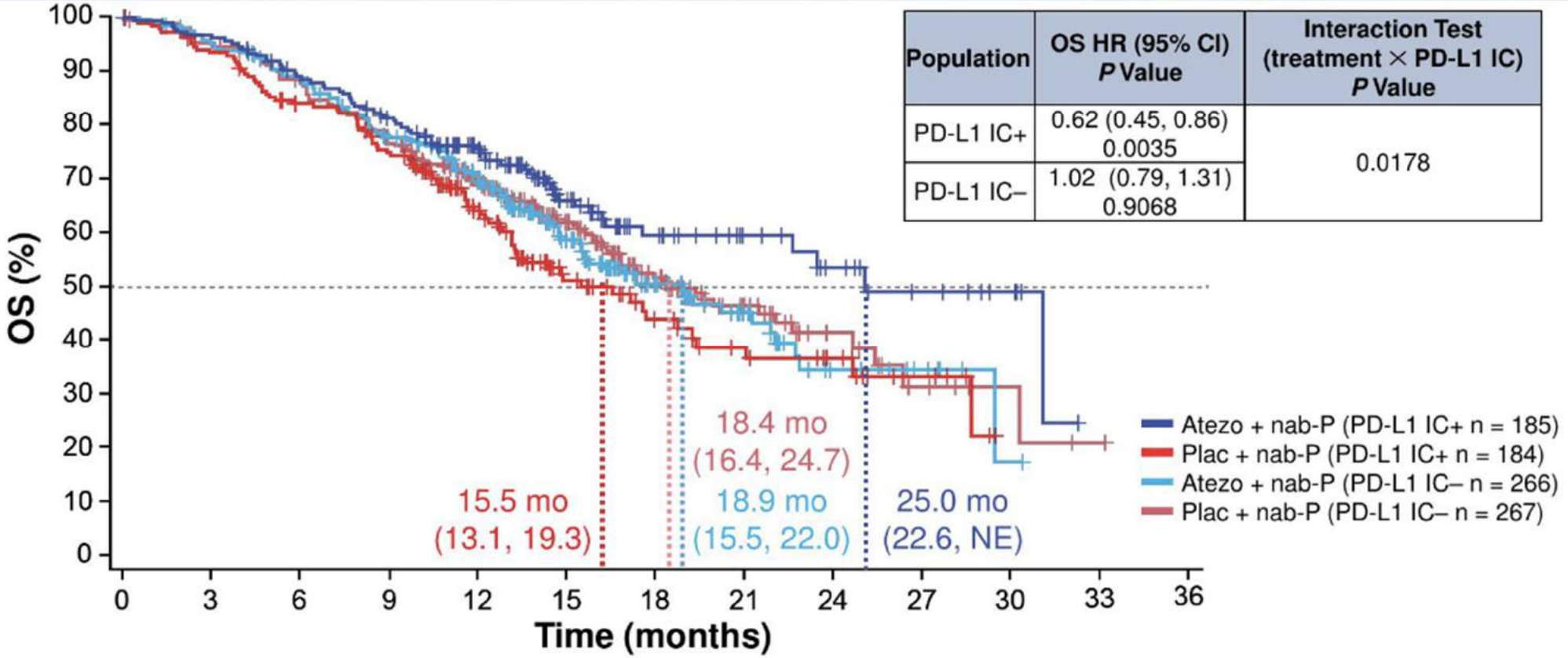


NE, not estimable.
Median follow-up (ITT): 12.9 months.
[a] PD-L1+: PD-L1 in ≥ 1% of IC. [b] Not significant. [c] Not formally tested per hierarchical study design.
1. Schmid *N Engl J Med* 2018. 2. Schmid ESMO 2018 [LBA1_PR].

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

PD-L1 IC status (positive vs negative) predicts OS benefit with atezolizumab + *nab*-paclitaxel

Population	OS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.45, 0.86) 0.0035	0.0178
PD-L1 IC–	1.02 (0.79, 1.31) 0.9068	

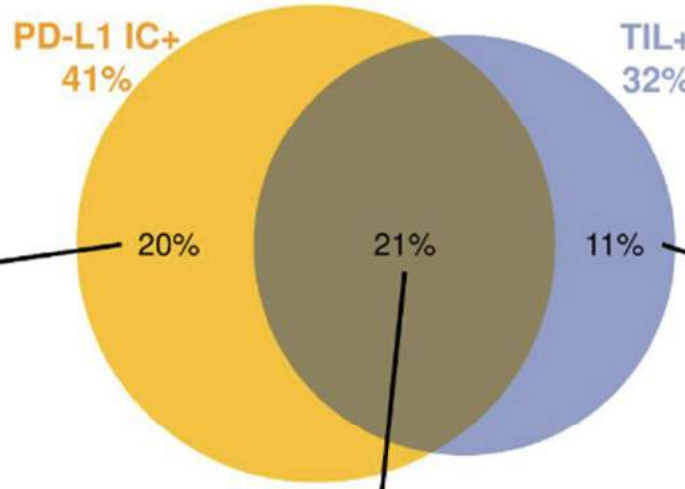


- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values are nominal. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

Stromal TILs has clinical benefit if co-occurring with PD-L1 IC+



TIL–/PD-L1 IC+ (n = 176)

	HR (95% CI)	*P* Value
PFS	0.74 (0.54, 1.03)	0.07
OS	0.65 (0.41, 1.02)	0.06

TIL+/PD-L1 IC+ (n = 190)

	HR (95% CI)	*P* Value
PFS	0.53 (0.38, 0.74)	≤ 0.005
OS	0.57 (0.35, 0.92)	0.02

TIL+/PD-L1 IC– (n = 94)

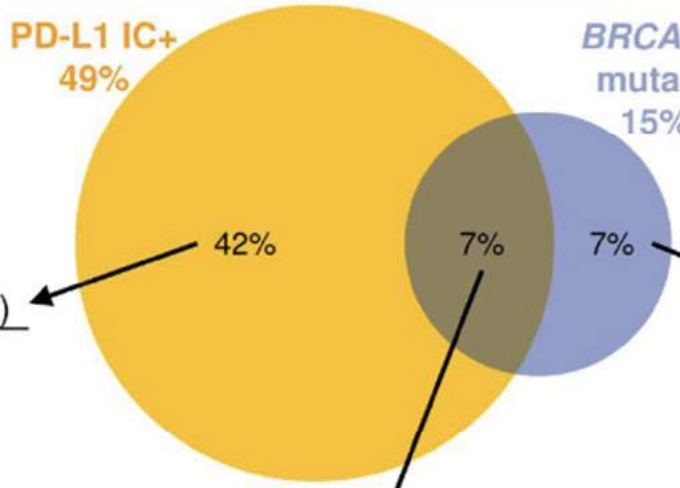
	HR (95% CI)	*P* Value
PFS	0.99 (0.62, 1.57)	0.97
OS	1.53 (0.76, 3.08)	0.24

- TIL+ were enriched for PD-L1 IC+ ($P < 0.0001$) but PD-L1 IC+ were not enriched for TIL+ (P = ns)[a]
- ***Patients with TIL+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

BEP (TILs): n = 893. Cutoff of 10% was used to distinguish low vs intermediate/high levels of TILs (Denkert *Lancet Oncol* 2018). All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

The clinical benefit derived by PD-L1 IC+ patients was independent of their *BRCA1/2* mutation status



***BRCA1/2* non-mut/PD-L1 IC+** (n = 257)

	HR (95% CI)	*P* Value
PFS	0.63 (0.48, 0.83)	≤ 0.005
OS	0.62 (0.43, 0.91)	0.01

***BRCA1/2* mut/PD-L1 IC+** (n = 45)

	HR (95% CI)	*P* Value
PFS	0.45 (0.21, 0.96)	0.04
OS	0.87 (0.26, 2.85)	0.82

***BRCA1/2* mut/PD-L1 IC–** (n = 44)

	HR (95% CI)	*P* Value
PFS	0.77 (0.37, 1.61)	0.49
OS	0.85 (0.29, 2.43)	0.76

- *BRCA1/2* mutants and PD-L1 IC+ are independent from each other (*P* = ns)[a]
- ***Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+[b]***

BEP (BRCA1/2): n = 612. Per FoundationOne *BRCA1/2* testing, *BRCA1/2* mutant: known and likely mutations. All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests. [b] Data interpretation limited by small number of *BRCA1/2*-mutant patients.

Avaliação Prospectiva Multi Institucional de diferentes Anticorpos para IHQ de avaliação de expressão de PD-L1 no tumor e infiltrado imune

Table 2. ICC for the Pathologist Scores and Concordance Statistics

	Antibody, ICC (95% CI)				
Cells[a]	22c3	28-8	SP142	E1L3N	Summary, Mean (SD)
Tumor cells	0.882 (0.873-0.891)	0.832 (0.820-0.844)	0.869 (0.859-0.879)	0.859 (0.849-0.869)	0.86 (0.02)
Immune cells	0.207 (0.190-0.226)	0.172 (0.156-0.189)	0.185 (0.169-0.203)	0.229 (0.211-0.248)	0.19 (0.03)

Abbreviation: ICC, intraclass correlation coefficient.

Rimm et al, JAMA Oncol 2017

É do Peru!

Impact of the delayed initiation of adjuvant chemotherapy in the outcomes of triple negative breast cancer

Zaida Morante, MD, Rossana Ruiz, MD, Gabriel de la Cruz – Ku, MD, Fernando Namuche, MD, Raul Mantilla, Maria Guadalupe Luján, MS, Hugo Fuentes, MD, Jesus Schwarz, MD, Alfredo Aguilar, MD, Silvia Neciosup, MD-PhD, Henry Gomez, MD-PhD

VOLUME 32 · NUMBER 8 · MARCH 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical Impact of Delaying Initiation of Adjuvant Chemotherapy in Patients With Breast Cancer

Debora de Melo Gagliato, Ana M. Gonzalez-Angulo, Xiudong Lei, Richard L. Theriault, Sharon H. Giordano, Vicente Valero, Gabriel N. Hortobagyi, and Mariana Chavez-MacGregor

Processed as a Rapid Communication manuscript. See accompanying editorial on page 717.
Listen to the podcast by Dr Marco Colleoni at www.jco.org/podcasts

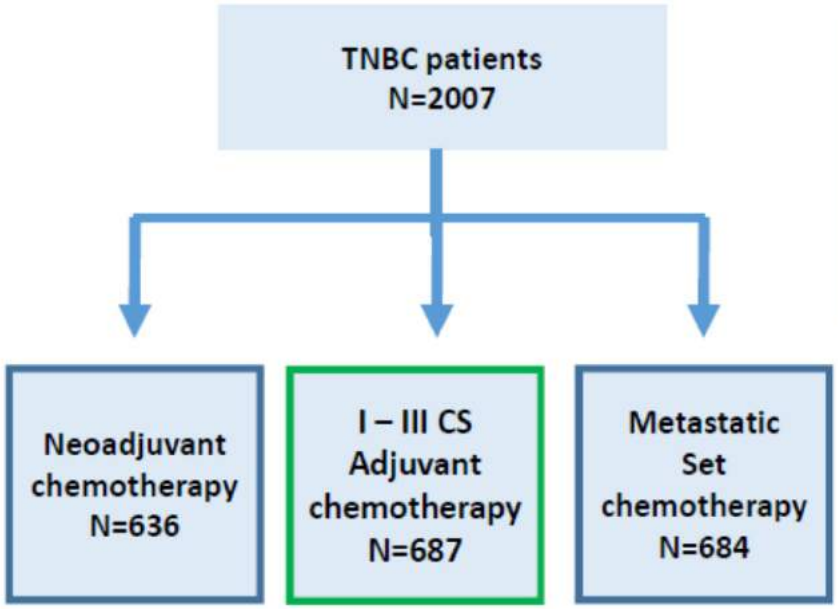
- 6, 827 women diagnosed with BC stages I to III.
- TTC 61 days after surgery was associated with adverse outcomes.
  - **Stage II** → DFRS (HR, 1.20; 95% CI: 1.02 to 1.43)
  - **Stage III** → OS (HR, 1.76; 95% CI: 1.26 to 2.46), RFS (HR, 1.34; 95% CI: 1.01 to 1.76) and DFRS (HR, 1.36; 95% CI: 1.02 to 1.80)
- TNBC/HER-2 patients who started chemotherapy 61 days after surgery had worse survival.
  - **TNBC** → (HR, 1.54; 95% CI, 1.09 to 2.18)
  - **HER-2** → (HR, 3.09; 95% CI, 1.49 to 6.39)

Gagliato D, et al. J Clin Oncol. 2014 Mar 10; 32(8): 735–744.

Objectives

We evaluated the influence of time to adjuvant chemotherapy (TTC) on the survival (OS – DFS - DRFS) of TNBC patients diagnosed at the Instituto Nacional de Enfermedades Neoplasicas (Lima, Peru) between 2000 to 2014.

Methods: study population (1)



Inclusion criteria

- ER (-), PR (-) and HER2 (-) tumors.
- CS I, II and III TNBC diagnosed and treated at INEN
- Upfront treatment: surgery
- Complete adjuvant chemotherapy
- Complete tumor and treatment information on clinical record

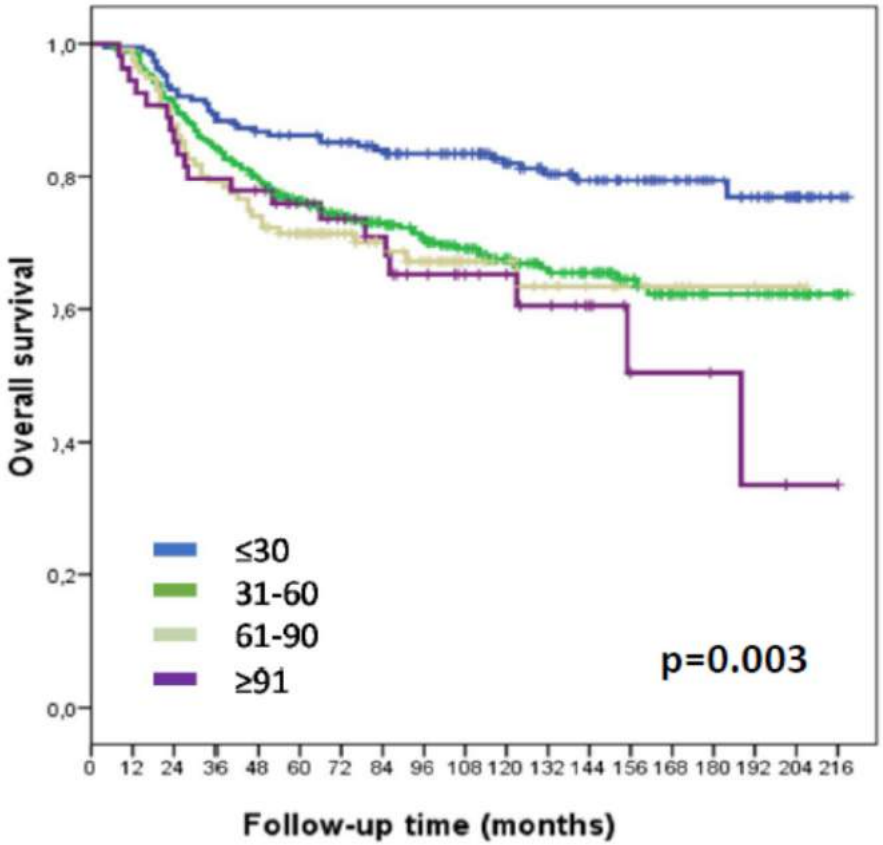
Exclusion criteria (N=1320)

- Inflammatory breast cancer
- Unknown tumor size or surgery type
- Incomplete or unknown chemotherapy or surgery dates
- Neoadjuvant chemotherapy

Methods: definition of time to chemotherapy (TTC) (2)

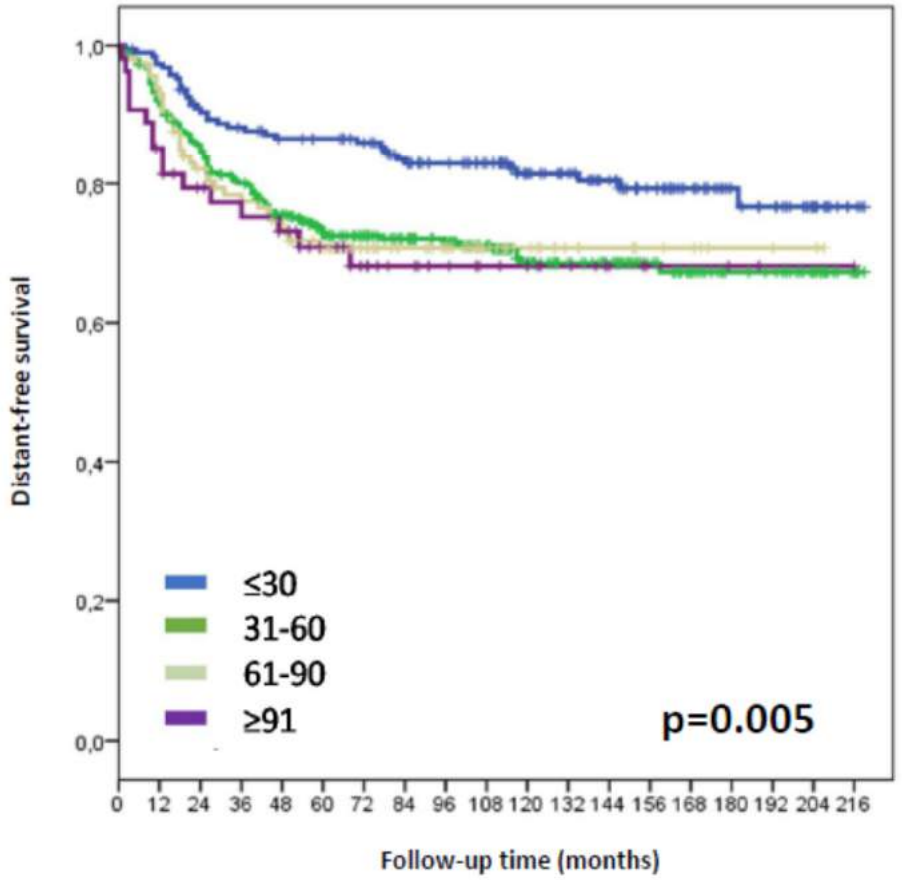
- TTC was defined as the number of days between surgery and the first dose of chemotherapy.
- Patients were categorized into 4 groups:
    - ≤30 days
    - 31-60 days
    - 61-90 days
    - ≥91 days

Overall survival estimated curves by TTC



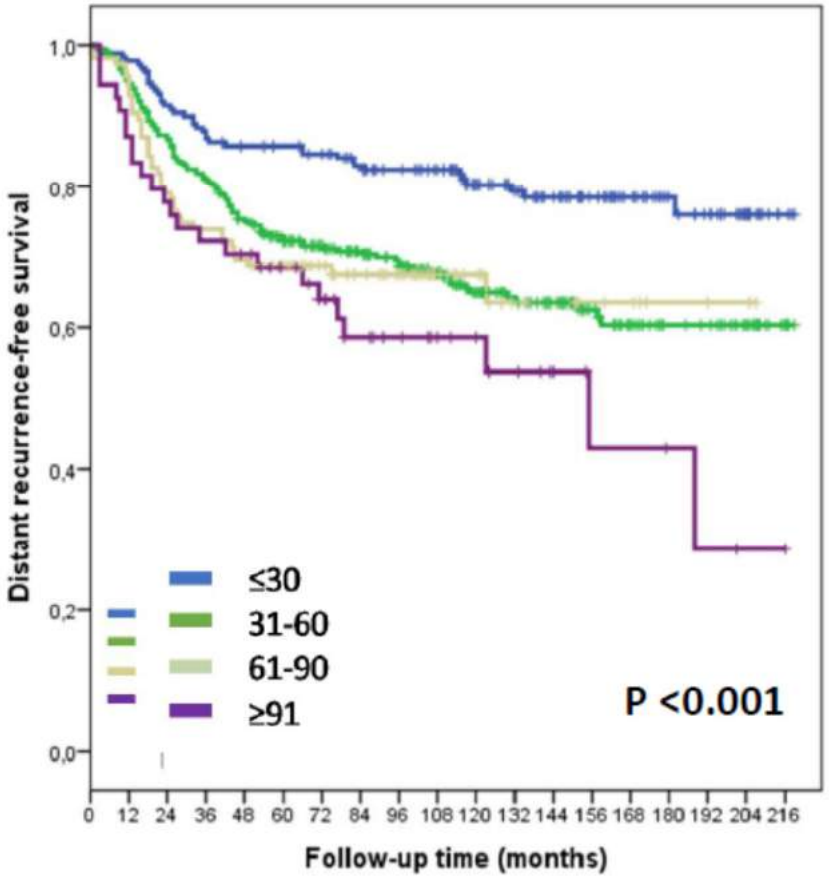
			Overall survival		
TTC (days)	Total	Events	12mo	60mo	**120mo**
≤30	189	37	99.5%	86.2%	**82%**
31-60	329	105	98.8%	76.2%	**67.4%**
61-90	115	37	97.4%	71.3%	**67.1%**
≥91	54	20	94.4%	75.8%	**65.1%**

Disease-free survival estimated curves by TTC



			Disease-free survival		
TTC (days)	Total	Events	12mo	60mo	**120mo**
≤30	189	36	97.3%	86.5%	**81.4%**
31-60	329	96	91.5%	72.9%	**68.6%**
61-90	115	33	92.9%	70.8%	**70.8%**
≥91	54	16	85.2%	70.9%	**68.1%**

Distant disease-free survival estimated curves by TTC



			Distant disease-free survival		
TTC (days)	Total	Events	12mo	60mo	**120mo**
≤30	189	39	97.9%	85.7%	**80.2%**
31-60	329	112	94.5%	72.2%	**64.9%**
61-90	115	38	93%	68.7%	**67.5%**
≥91	54	24	87%	68.4%	**58.6%**

TNBC

- Importância das células imunes na resposta à imunoterapia
- Adição de quimioterapia adjuvante para pacientes com resposta parcial à quimioterapia neoadjuvante
- Importância do tempo entre a cirurgia e o início da quimioterapia – favorece a quimioterapia neoadjuvante


Folks!