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Dr. **Martin** has disclosed conculting fees for Roche, Novartis, Lilly, Astra Zeneca and Amgen and contracted research with Novartis. These relationships do not impact his ability to present an unbiased presentation.

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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.

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Disclosure

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Background

- Early TNBC is very sensitive to neo/adjuvant chemotherapy.
- However, a proportion of operable patients eventually relapses in spite of conventional adjuvant polychemotherapy[1]:
  - stage I: 7-10%
  - stage II:15-20%
  - stage III: 25-50%
- New adjuvant approaches are needed for these patients.

[1]Li X et al. Breast Cancer Res Treat 161:279-287, 2017.

Abbreviations: TNBC: Triple Negative Breast Cancer.

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Capecitabine

- Oral fluoropyrimidine approved for the treatment of metastatic breast cancer.
- This drug is partially non cross-resistant with anthracyclines and taxanes.
- Capecitabine has been incorporated into adjuvant chemotherapy regimens in randomized trials, mostly with negative results[1,2].
- A single trial (Create-X) has found a benefit on PFS and OS by adding maintenance capecitabine to those patients with persistent residual disease after conventional neoadjuvant chemotherapy[3].
- TNBC patients obtained the maximum benefit with capecitabine in the Create-X study.

[1]Joensuu H et al. J Clin Oncol 30:11-18, 2011.
[2]Martin M et al, J Clin Oncol 33:3788-3795, 2015.
[3]Masuda N et al. N Engl J Med 376:2147-2159, 2017.

Abbreviations: PFS: Progression Free Survival. OS: Overall Survival. HR: Hormone Receptor.

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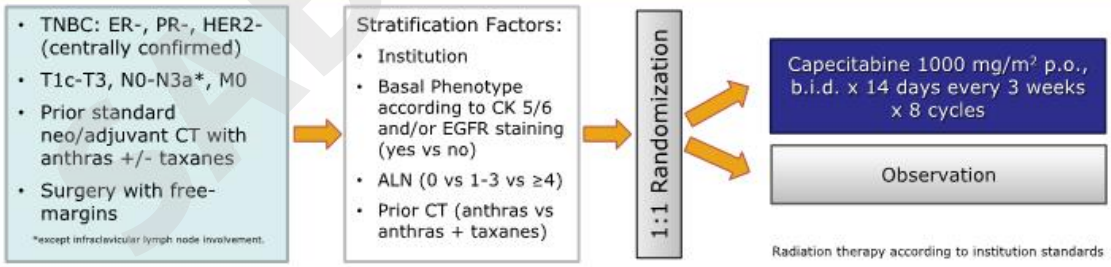
Study Design



- 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.

Statistical Plan

- Primary analysis: DFS for ITT population.
- According to GEICAM "El Alamo" registry, the expected 5-year DFS for a similar population is 64.7%[1].
- Study hypothesis: capecitabine will increase 5-year DFS to 73.7% (Δ 9%, 80% power to detect a HR of 0.701).
- 834 eligible patients needed, assuming a drop-out rate of 5%, a total of 876 patients were to be enrolled (438 in each arm).
- 255 DFS events projected.
- Stratified Log-rank test and Cox proportional-hazards model by stratification factors.

[1]Project "The Alamo III". ISBN: 84-938762-5-9. Legal deposit: M-36626-2013.

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Recruitment per Country

Phase 3, international, open-label study randomized 876 patients in 8 countries and 80 sites.

Recruitment period:
from 26th-Oct-2006 to 12nd-Sep-2011

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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)

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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.

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Patient and Tumor Characteristics (3)

	Capecitabine (n=448)	Observation (n=428)
Breast surgery, n (%)		
• Conservative	237 (52.9)	242 (56.5)
• Mastectomy	205 (45.8)	185 (43.2)
• Not available	6 (1.3)	1 (0.2)
Axillary surgery, n (%)		
• Axillary lymph node dissection (ALND)+/- (SLNB)	349 (78.0)	306 (71.5)
• Sentinel lymph node biopsy (SLNB)	99 (22.1)	122 (28.5)
Radiation therapy, n (%)		
• Yes	352 (78.6)	346 (80.8)
• No	91 (20.3)	81 (18.9)
• Unknown	5 (1.1)	1 (0.2)

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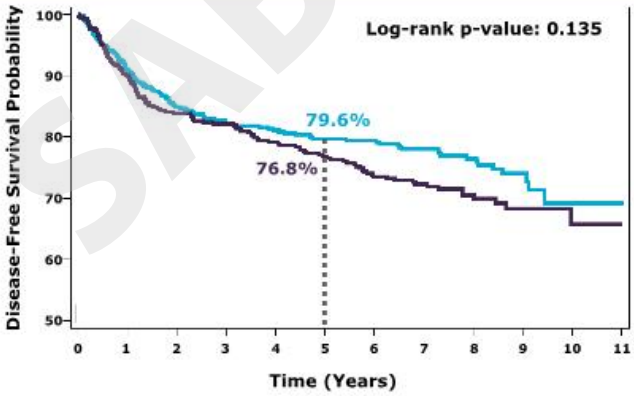
Disease-Free Survival (ITT)



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

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).

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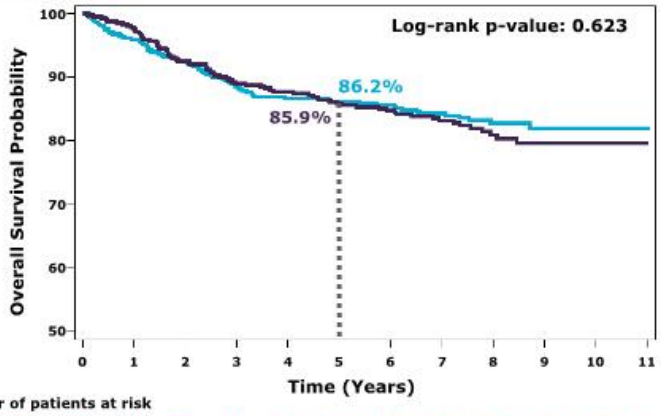
Overall Survival (ITT)



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

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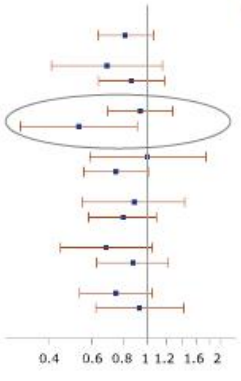
Subgroup Analysis of DFS (ITT)

Subgroup	Subgroup	Capecit.	Observ.	HR (95% CI)
Overall	**n=876 (100%)**	**105**	**120**	**0.819 (0.630-1.065)**
Menopausal Status				
Premenopausal	276 (32)	24	35	0.686 (0.408-1.153)
Postmenopausal	600 (68)	81	85	0.867 (0.639-1.176)
Phenotype				
Basal	628 (72)	84	86	0.942 (0.697-1.272)
Non-basal	248 (28)	21	34	0.530 (0.307-0.913)
Chemotherapy				
Neoadjuvant	164 (19)	29	24	1.006 (0.586-1.727)
Adjuvant	705 (80)	74	96	0.747 (0.552-1.012)
Type of CT				
Taxanes	285 (33)	33	36	0.884 (0.551-1.418)
No taxanes	591 (67)	72	84	0.798 (0.583-1.093)
N0 vs. N+				
N0	444 (51)	34	52	0.685 (0.445-1.057)
N+	420 (49)	70	67	0.878 (0.628-1.228)
Region				
Spain	532 (61)	60	75	0.750 (0.534-1.053)
Latin America	344 (39)	45	45	0.934 (0.618-1.413)



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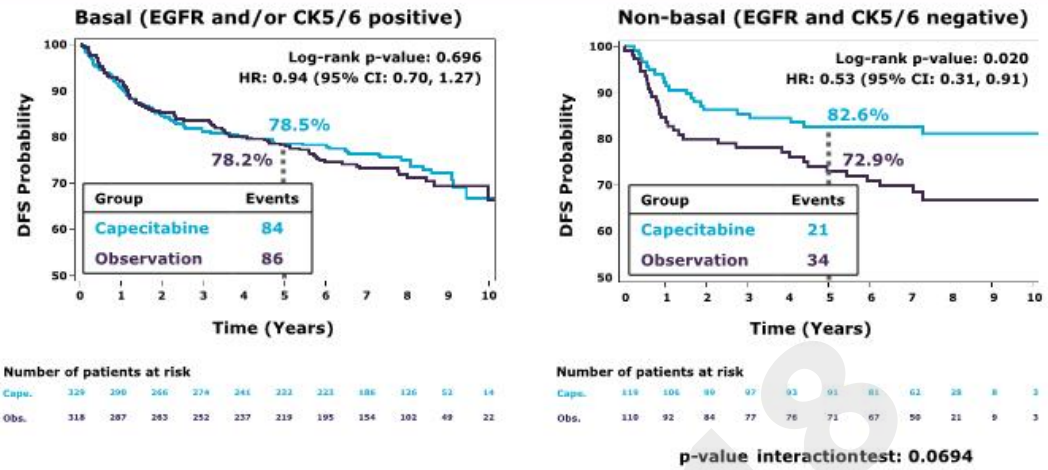
Subgroup Analysis of DFS (ITT)



Number of patients at risk

Cape.	329	290	266	274	241	222	223	186	126	52	14	
Obs.	318	287	263	252	237	219	195	154	102	49	22	

Number of patients at risk

Cape.	119	106	99	97	93	91	81	62	28	8	3	
Obs.	110	92	84	77	76	71	67	50	21	9	3	

p-value interactiontest: 0.0694

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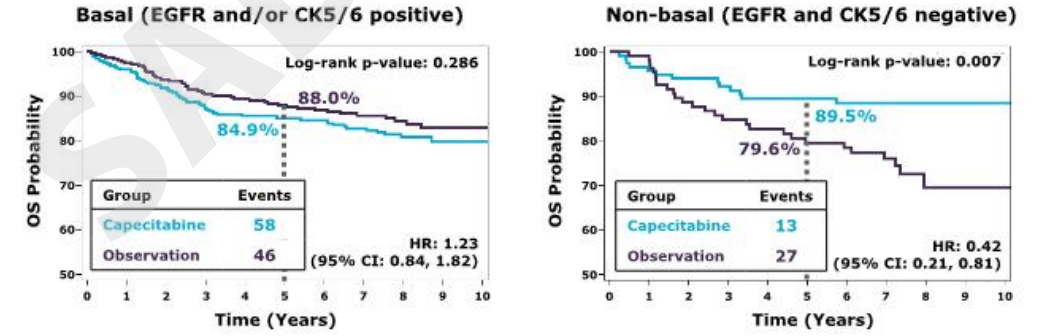
Subgroup Analysis of OS (ITT)



Number of patients at risk

Cape.	329	307	286	283	256	249	238	200	139	63	21	
Obs.	318	301	284	268	259	242	223	179	123	64	25	

Number of patients at risk

Cape.	119	110	107	104	98	98	88	67	31	8	3	
Obs.	110	106	91	82	80	76	73	53	22	9	3	

p-value interaction test: 0.0052

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DFS Events: Overall and Non-basal Populations

	OVERALL POPULATION		NON-BASAL POPULATION	
	Capecitabine (n=448)	Observation (n=428)	Capecitabine (n=119)	Observation (n=110)
Any DFS event,n (%)	**105 (23.4)**	**120 (28.0)**	**21 (17.6)**	**34 (30.9)**
Death without known recurrence, n (%)	14 (3.1)	10 (2.3)	2 (1.7)	3 (2.7)
Locoregional recurrence (after mastectomy), n (%)	0	4 (1.0)	0	2 (1.8)
Ipsilateral breast cancer recurrence, n (%)	5 (1.1)	12 (2.8)	2 (1.7)	3 (2.7)
Contralateral invasive breast cancer, n (%)	12 (2.7)	14 (3.3)	3 (2.5)	2 (1.8)
Distant recurrence (any)n (%)	**64 (14.3)**	**66 (15.4)**	**13 (10.9)**	**18 (16.4)**
• Lung	31 (6.9)	29 (6.8)	7 (5.9)	6 (5.5)
• Bone	19 (4.2)	19 (4.4)	4 (3.4)	5 (4.5)
• Lymph nodes	16 (3.6)	18 (4.2)	1 (0.8)	4 (3.6)
• Liver	13 (2.9)	20 (4.7)	2 (1.7)	6 (5.5)
• CNS	15 (3.3)	16 (3.7)	3 (2.5)	6 (5.5)
• Other	11 (2.4)	12 (2.8)	2 (1.7)	3 (2.7)

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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)**

Safety (Adverse Events ≥5%)

Adverse Events (AEs)	Capecitabine (n=436), n (%)			Observation (n=425), n (%)		
NCI-CTCAE v3.0	**Grade 1-4**	**Grade 3**	**Grade 4**	**Grade 1-4**	**Grade 3**	**Grade 4**
Hand and foot syndrome	306 (70.2)	82 (18.8)	-	3 (0.7)	-	-
Diarrhea	154 (35.3)	14 (3.2)	1 (0.2)	6 (1.4)	-	-
Nausea	103 (23.6)	4 (0.9)	-	6 (1.4)	-	-
Vomiting	45 (10.3)	3 (0.7)	-	2 (0.4)	-	-
Abdominal pain, general	27 (6.2)	1 (0.2)	-	1 (0.2)	-	-
Any cardiac event, general	5 (1.2)	2 (0.5)	-	4 (0.9)	1 (0.2)	-
Fatigue	172 (39.5)	13 (3.0)	-	48 (11.3)	-	-
Irregular menses	69 (15.8)	57 (13.1)	-	67 (15.7)	55 (12.9)	-

Abbreviations: NCI-CTCAE v3.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Two toxic deaths reported in capecitabine arm: septic shock (without neutropenia), liver toxicity.

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Safety (Laboratory AEs ≥5%)

Adverse Events (AEs)	Capecitabine (n=436), n (%)			Observation (n=425), n (%)		
NCI-CTCAE v3.0	**Grade 1-4**	**Grade 3**	**Grade 4**	**Grade 1-4**	**Grade 3**	**Grade 4**
Hemoglobin	107 (24.5)	1 (0.2)	-	27 (6.4)	-	-
Leucocytes (total WBC)	136 (31.2)	1 (0.2)	-	58 (13.6)	-	-
Lymphopenia	63 (14.4)	3 (0.7)	1 (0.2)	33 (7.7)	1 (0.2)	-
Neutrophils/ Granulocytes	125 (28.7)	8 (1.8)	-	46 (10.8)	-	-
Thrombocytopenia	22 (5.0)	1 (0.2)	-	8 (1.8)	-	-
ALT, SGPT	85 (19.5)	1 (0.2)	-	18 (6.6)	-	-
AST, SGOT	83 (19.0)	-	1 (0.2)	23 (5.4)	-	-
Hyperbilirubinemia	52 (11.9)	2 (0.5)	1 (0.2)	2 (0.5)	-	-

Abbreviations: NCI-CTCAE v3.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. WBC: white blood cells. SGPT: serum glutamic pyruvic transaminase. SGOT: serum glutamic oxaloacetic transaminase.

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Conclusions

- This study failed to show a statistically significant increase in DFS by adding capecitabine to standard neo/adjuvant chemotherapy in early TNBC:
  - 5-year DFS with capecitabine vs observation: 79.6% vs 76.8% (Δ 2.8%, HR: 0.82, p=0.14, adjusted HR: 0.79, p=0.082).
- In a prospective subset analysis, TNBC patients with non-basal like phenotype (IHC) had a statistically significant increase in DFS and OS with extended adjuvant capecitabine:
  - 5-year DFS with capecitabine vs observation: 82.6% vs 72.9% (HR 0.53, p=0.02, Δ9.7%).
  - 5-year OS with capecitabine vs observation: 89.5% vs 79.6% (HR 0.42, p=0.007, Δ9.9%).
- Tolerance of extended adjuvant capecitabine was as expected, with a median dose intensity of 86.3% and 75.2% of patients completing the planned 8 cycles.

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H. Universitario de Guadalajara, Spain
Instituto Oncológico de Barcelona, Spain

Staff members of:

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