



UNIVERSITÀ DEL PIEMONTE ORIENTALE

LA TERAPIA PREOPERATORIA DEL CA MAMMARIO OPERABILE

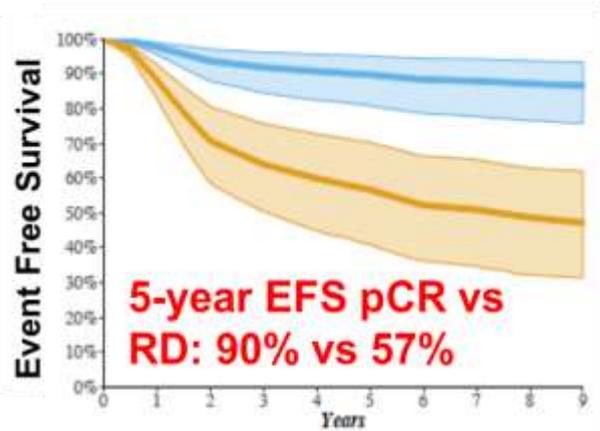
Alessandra Gennari, MD PhD
Dipartimento di Medicina Traslazionale
Università del Piemonte Orientale
SCDU Oncologia
AOU Maggiore della Carità
Novara

Goals of neoadjuvant therapy in breast cancer

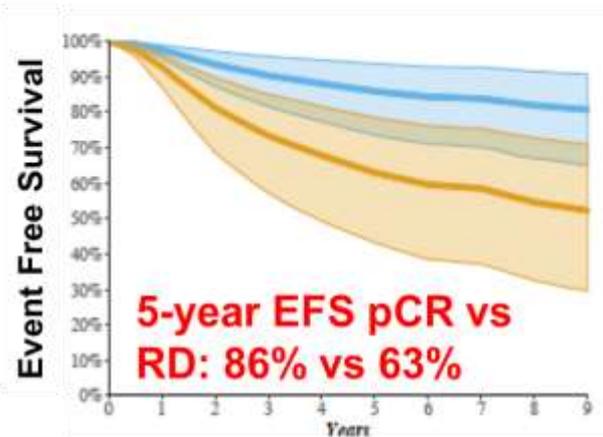
- Make tumours more operable, increase the rate of breast conserving surgeries
- Probably, to improve prognosis of certain disease subtypes (i.e. HER2+)
 - Allow patients to start treatment earlier
- Have a better idea of prognosis based on response to neoadjuvant treatment
- Reduce the extent of surgery required in breast and axilla
- Improve DFS and OS using pathological response rate for selection of subsequent treatment in individual patients

pCR as a surrogate endpoint for long-term outcomes

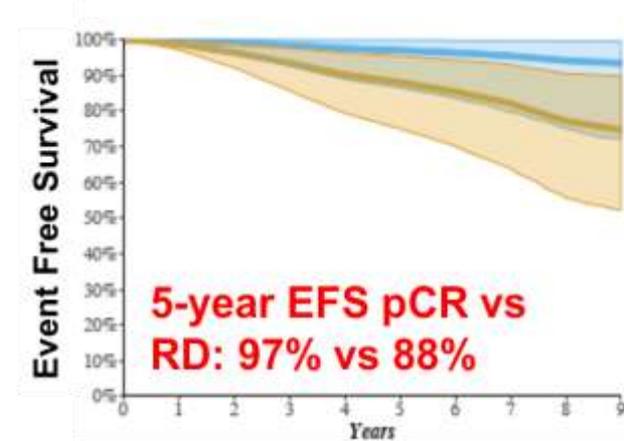
TNBC



HER2+



HR+/HER2-

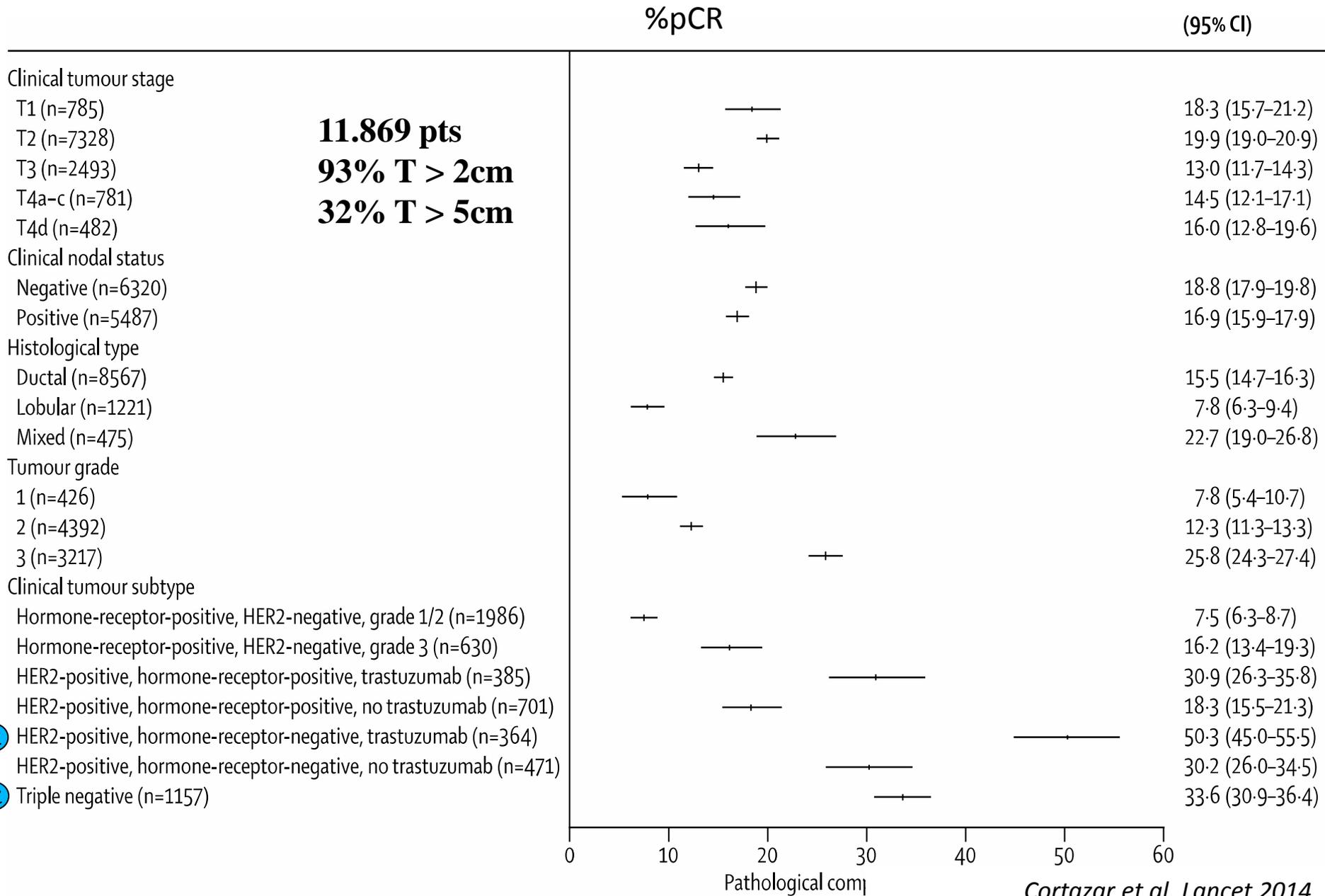


Blue: pCR group

Orange: Residual disease (RD) group

Similar results seen with OS

Neoadjuvant treatment The concept of pCR

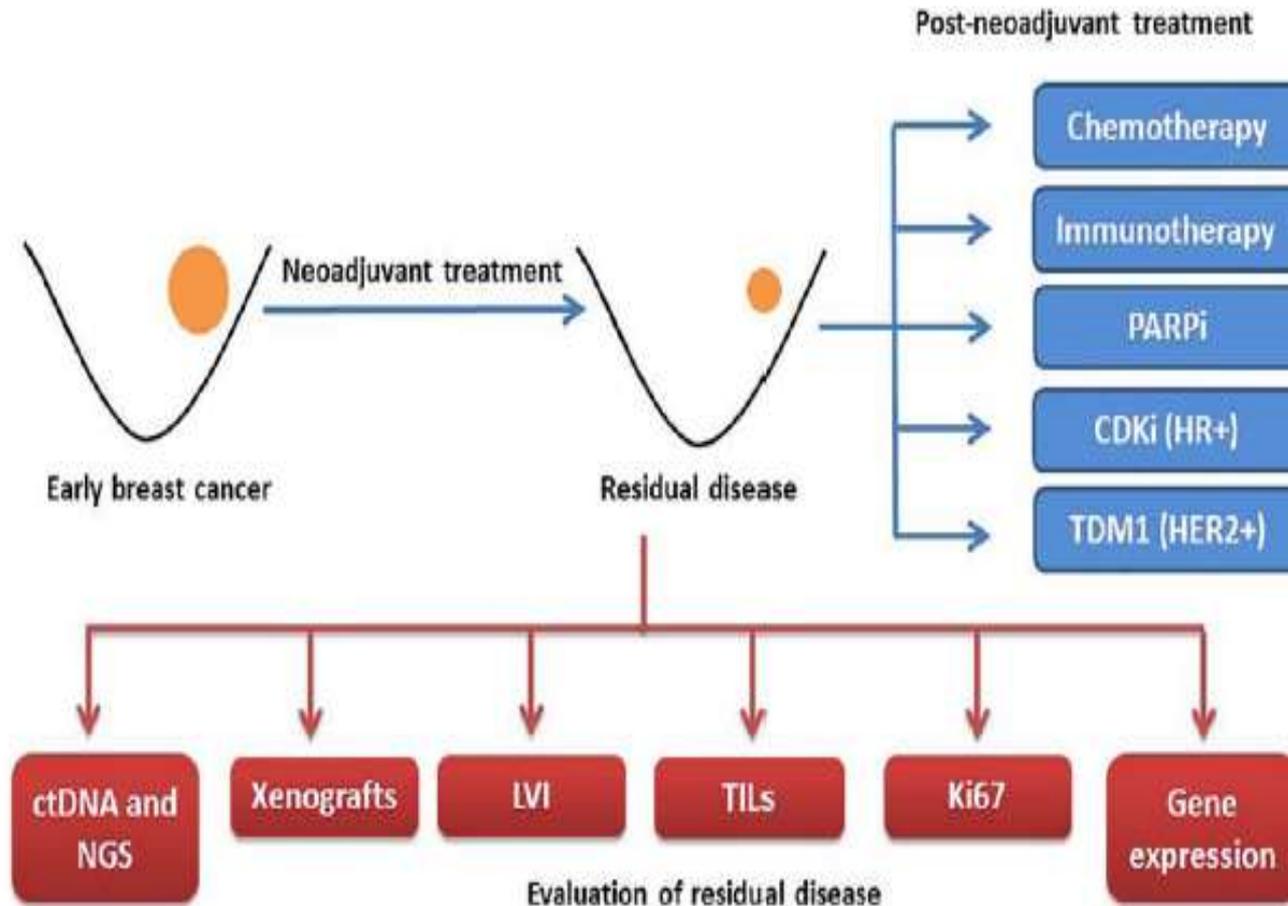


pCR by Molecular Subtype

pCR-rates acc. subtype	all	%	ypT0 ypN0	%	ypT0/ is ypN0	%
p-value				<0.001		<0.001
Luminal A	1,637	39.0	105	6.4	146	8.9
Lum B/ HER2 negative	357	8.5	40	11.2	55	15.4
Lum B/ HER2 pos w/ o trastuzumab	395	9.4	47	11.9	68	17.2
Lum B/ HER2 pos with trastuzumab	356	8.5	79	22.2	115	32.3
HER2 pos (nonlum.) w/ o trastuzumab	239	5.7	66	27.6	79	33.1
HER2 pos (nonlum.) with trastuzumab	298	7.1	98	32.9	152	51.0
Triple negative	911	21.7	282	31.0	326	35.8
Missing (ER/ PR/ HER2)	2,184	34.2				

von Minckwitz G et al. J Clin Oncol 2012;30:1796-1804.

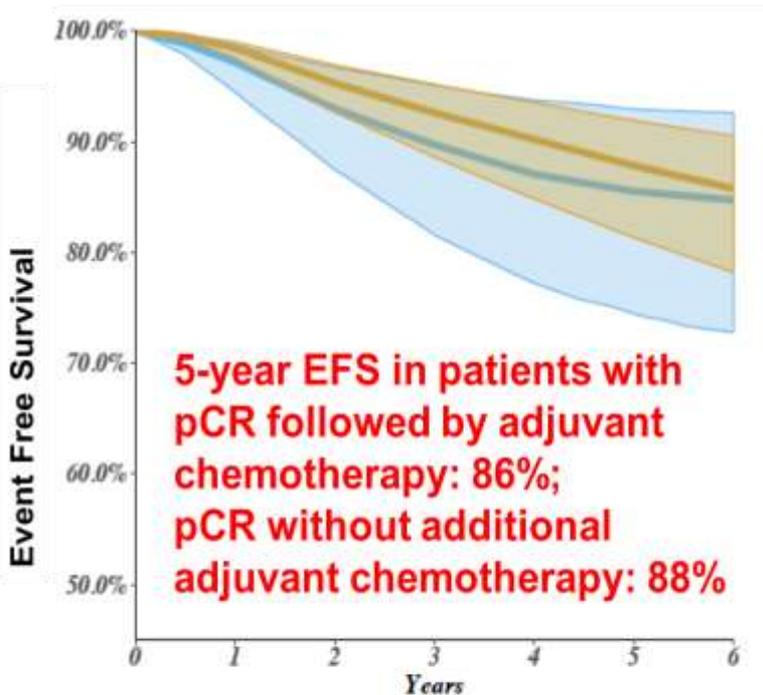
Post-neoadjuvant Treatment



Post-neoadjuvant treatment approach

- Convenient **for non-pCR** patients in high-risk subgroups
- The unbiased identification of **targetable molecular alterations in (residual)** breast cancers after neoadjuvant therapy may identify somatic alterations causally associated with drug resistance.
- These alterations could be **therapeutically targeted** as adjuvant treatment
- **No prior** “success stories”

Adjuvant chemotherapy after pCR



Blue: pCR without adjuvant chemotherapy
Orange: pCR with adjuvant chemotherapy

Adjuvant Chemotherapy	Hazard Ratio (pCR and EFS)	95% PI
Yes ¹	0.36	0.19-0.67
No ²	0.36	0.27-0.54

pCR was associated with significantly improved EFS in both groups, and there was no significant difference in Hazard Ratios between the two groups³.

¹ >90% of patients received adjuvant chemotherapy
² No more than 10% of patients received adjuvant chemotherapy
³ Paired T-test (difference in log-HR: 0.02, 95% PI: -0.75-0.73; p = 0.60)

Pathologic complete response rates with preoperative DNA-damaging agents in TNBC

Study	Design	N	pCR	
			Control	Platinum
GeparSixto	npIDox/Pac/Bev ± wCb (AUC1.5) x16 weeks	315	42.7%	53.2%
ALLIANCE 40603	wPac ± Cb (AUC6) ± bev → AC (2x2 design)	433	41%	54%
GEICAM/2006-03	EC → Doc ± Cb (AUC6)	94	30%	30%
ISPY2	wPac ± Cb / veliparib → AC	71	26% (est)	52% (est)
NCC-Japan	wPac ± Cb (AUC5) → CEF	75	26%	62%
University of Kansas	Cb (AUC6) / Doc x6 cycles vs AC x4 → T x4	92	42%	65%
BRIGHTNESS	wP ± Cb ± veliparib → AC x 4	634	31%	57% (53% with V)

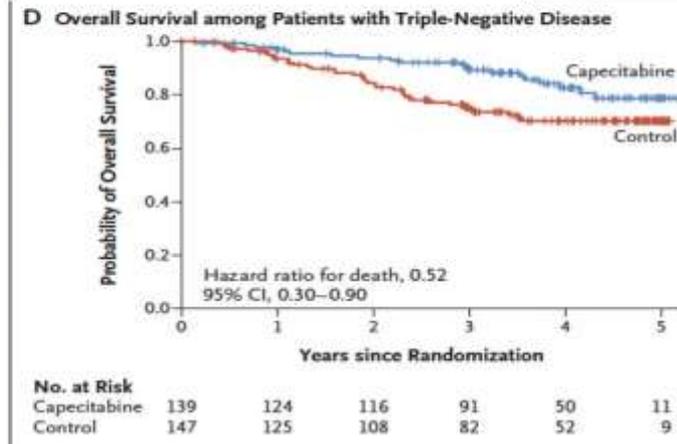
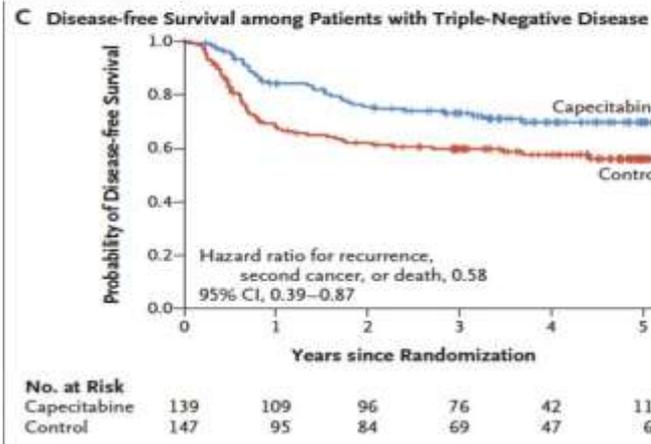
1. Von Minckwitz G et al. Lancet Oncol 2014; 2. Sikov WM et al., J Clin Oncol. 2019; 3. Rugo H et al. N Engl J Med. 2016; 4. Alba E et al. Breast Cancer Res Treat. 2012; 5. Tamura et al. ASCO 2014; 6. Sharma P et al. ASCO 2014; 7. Sharma P et al. AACR 2016; 8. Loibl S et al. Lancet Oncol. 2018; 9. Gluz O et al. J Natl Cancer Inst. 2018

CREATE-X: Trial Design



Stratification factors:
ER, Age, NAC, ypN,
5FU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment



Adjuvant capecitabine: CIBOMA study

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

*except infraclavicular lymph node involvement.

Stratification Factors:

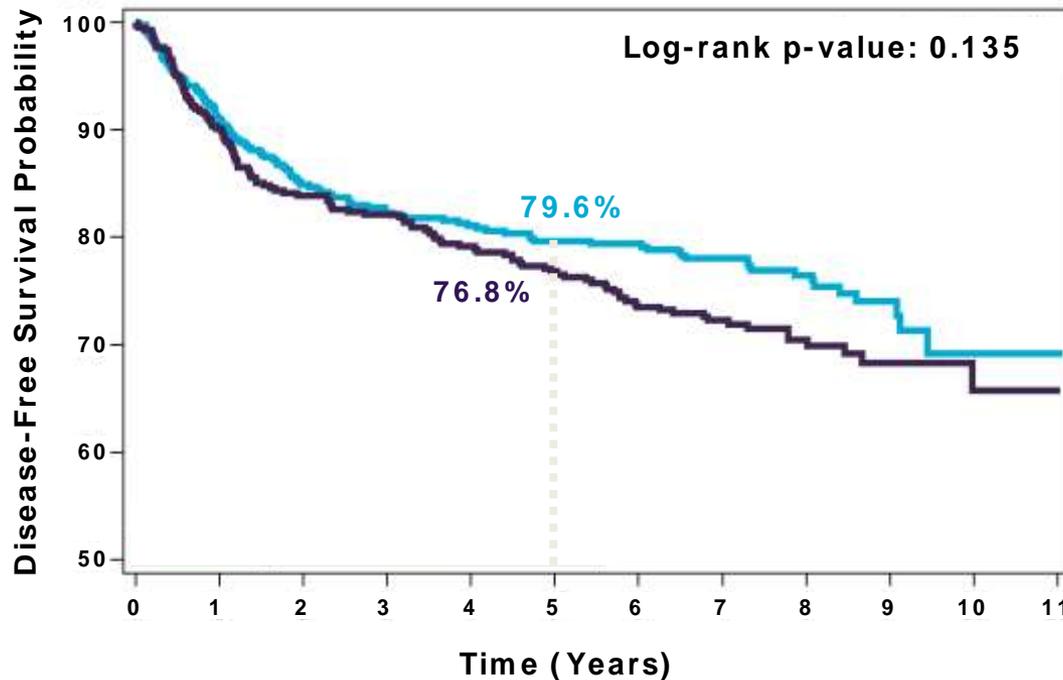
- Institution
- Basal Phenotype according to CK 5/6 and/or EGFR staining (yes vs no)
- ALN (0 vs 1-3 vs ≥ 4)
- Prior CT (anthras vs anthras + taxanes)

1:1 Randomization

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

Observation

Adjuvant capecitabine: CIBOMA study



Median follow-up: 7.34 years

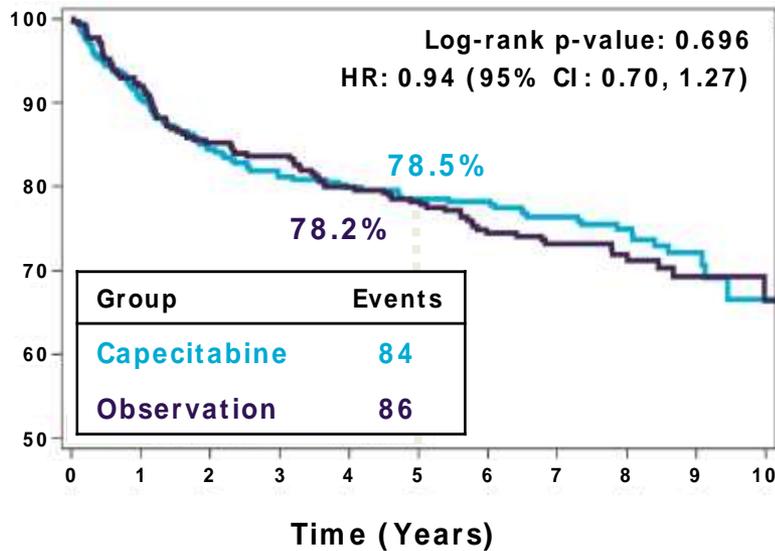
Group	Events
Capecitabine	105
Observation	120
HR: 0.82 (95% CI: 0.63, 1.06)	
Adjusted HR* : 0.79 (95% CI: 0.60, 1.02)	

*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), IHC phenotype by IHC (basal vs non-basal).

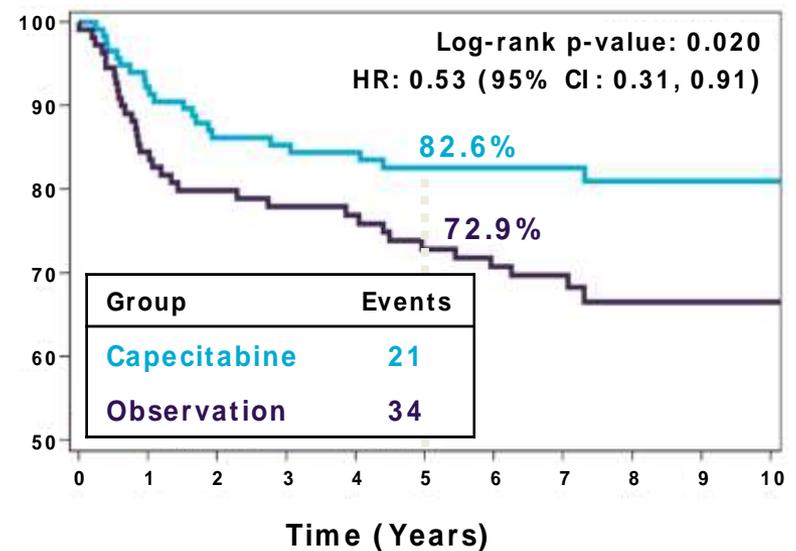
Number of patients at risk

Adjuvant capecitabine: CIBOMA study

Basal



Non-basal



Number of patients at risk

Cape.	329	290	266	274	241	232	223	186	126	52	14
Obs.	318	287	263	252	237	219	195	154	102	49	22

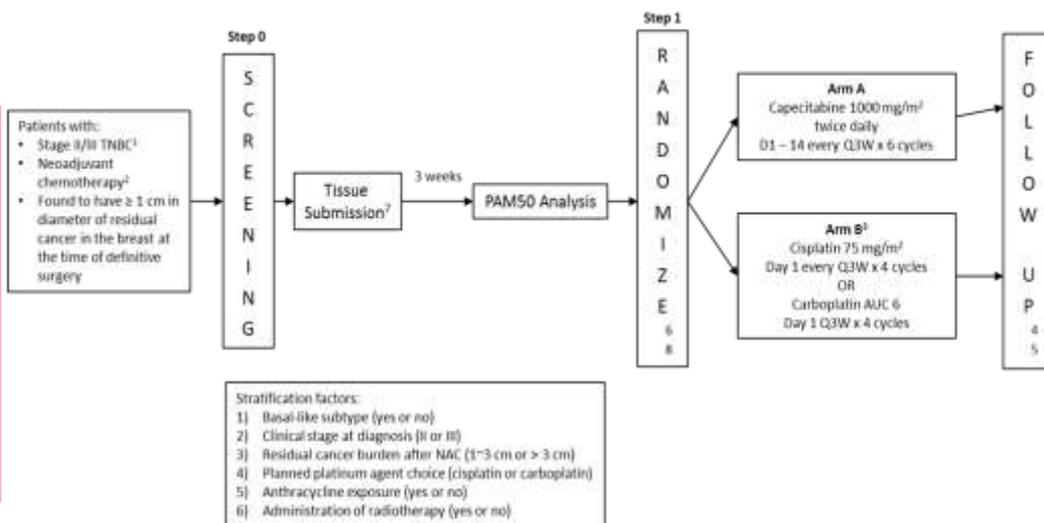
Number of patients at risk

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 interaction test: 0.0694

ECOG-ACRIN EA1131 Phase III Trial of Adjuvant Platinum vs. Observation in Patients with Basal-like Residual TNBC Following Neoadjuvant Chemotherapy

Hypothesis:
 In patients that have the highest risk of recurrence - basal-like TNBC with >1cm residual disease post neoadjuvant chemo - the addition of adjuvant platinum-based chemo will improve DFS



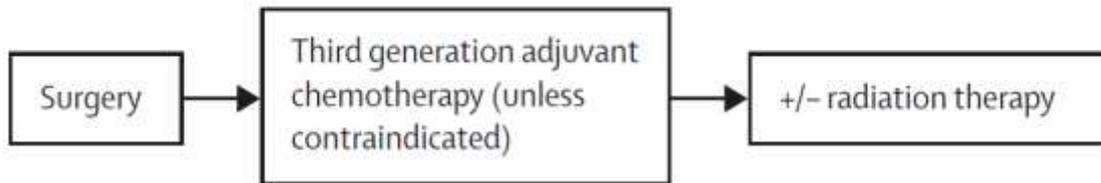
Accrual = 750
 1 cycle = 3 weeks

1. TNBC: ER/PR less than 10% positive staining with weak intensity score, or less than 1% positive staining with weak or intermediate intensity score; HER2 negative per ASCO guidelines.
2. Taxane ± anthracycline based; platinum agents or capecitabine not allowed.
3. Choice of platinum agent will be per treating physician discretion.
4. Primary endpoint: IDFS in patient with basal-like TNBC.
5. Secondary endpoints: IDFS in patient with non-basal-like TNBC, OS and RFS.
6. Patient must have completed adjuvant radiotherapy (if applicable) prior to randomization
7. Tumor tissue from the residual disease on the definitive surgical specimen must be submitted within 21 weeks post surgery for PAM50 analysis for determination of patient eligibility as outlined in Section 10.2. Patients cannot be randomized to treatment until institution receives confirmation of PAM50 analysis from the Molecular Diagnostics Laboratory performing the assessments.
8. Females of child-bearing potential must have a blood test or urine study within 2 weeks prior to treatment initiation to rule out pregnancy.

Treatment strategies

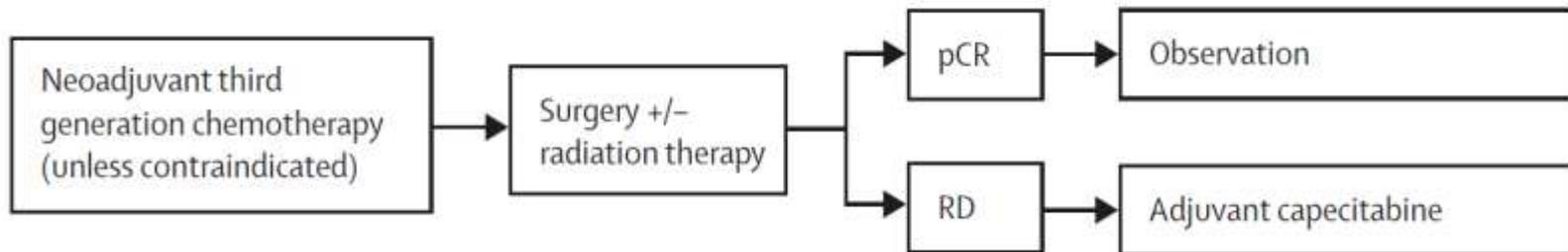
Prevailing practice

Clinical stage I and stage II TNBC

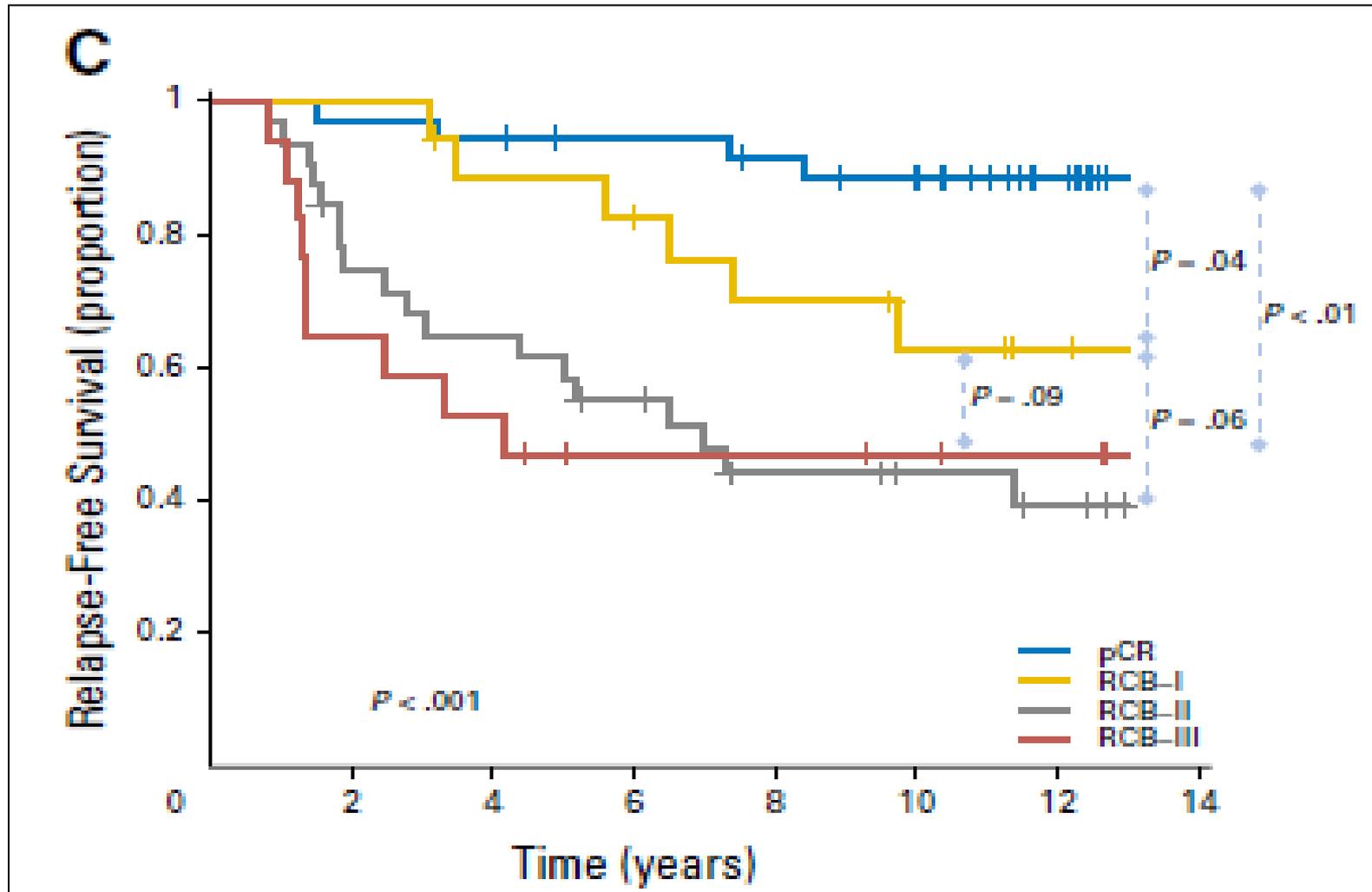


New framework

Clinical stage I and stage II TNBC



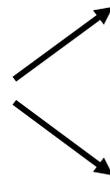
pCR as a prognostic marker in HER2+



KATHERINE: Trastuzumab Emtansine vs Trastuzumab as Adjuvant Therapy for HER2+ EBC

- International, randomized, open-label phase III study

Patients with HER2+ EBC (cT1-4/N0-3/M0) who had residual invasive disease in breast or nodes after neoadjuvant CT plus HER2-targeted therapy* at surgery (N = 1486)



**T-DM1[†] 3.6 mg/kg IV Q3W
x 14 cycles (n = 743)**

**Trastuzumab 6 mg/kg IV Q3W
x 14 cycles (n = 743)**

- Primary endpoint: IDFS
- Secondary endpoints including: distant recurrence-free survival, OS, safety

KATHERINE: Baseline Characteristics

Characteristic	T-DM1 (n = 743)	Trastuzumab (n = 743)
Median age, yrs (range)	49 (24-79)	49 (23-80)
▪ < 40 yrs, n (%)	143 (19.2)	153 (20.6)
▪ 40-64 yrs, n (%)	542 (72.9)	522 (70.3)
▪ ≥ 65 yrs, n (%)	58 (7.8)	68 (9.2)
Race, n (%)		
▪ White	551 (74.2)	531 (71.5)
▪ Asian	65 (8.7)	64 (8.6)
▪ American Indian*/Alaska native	36 (4.8)	50 (6.7)
▪ Black	21 (2.8)	19 (2.6)
▪ Other	70 (9.4)	79 (10.6)
Region, n (%)		
▪ North America	170 (22.9)	164 (22.1)
▪ Western Europe	403 (54.2)	403 (54.2)
▪ Rest of world	170 (22.9)	176 (23.7)
Prior anthracycline, n (%)	579 (77.9)	564 (75.9)

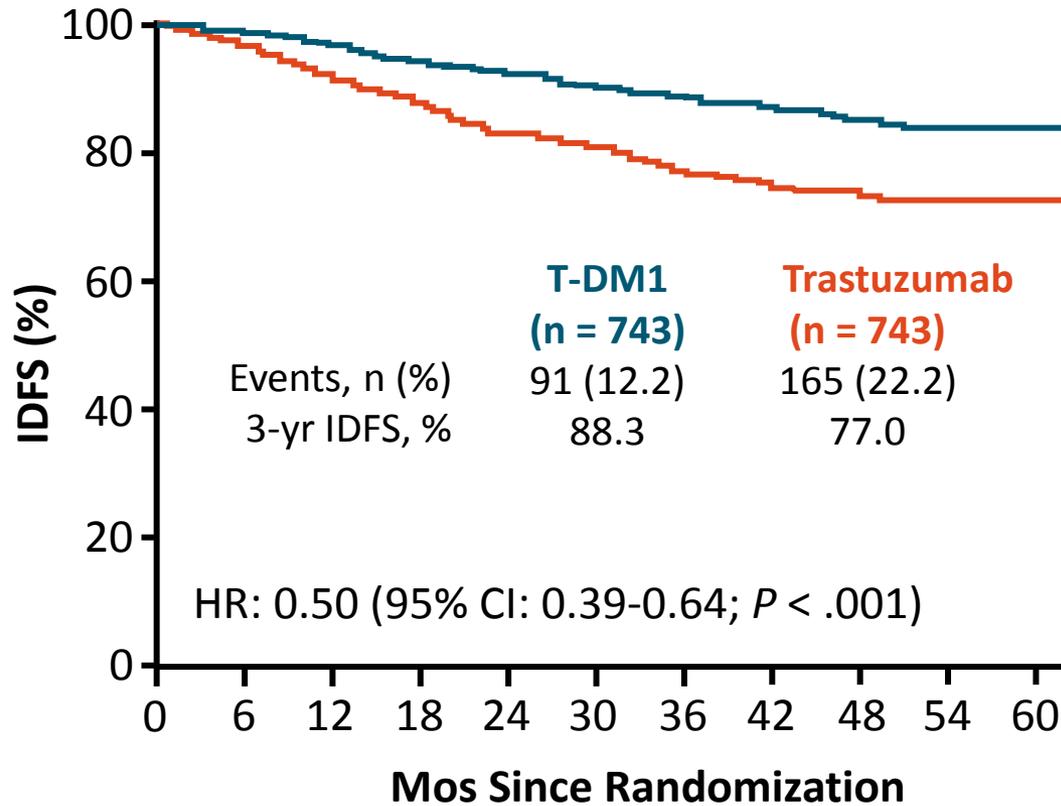
*Includes North, Central, and South American Indians.

Characteristic, n (%)	T-DM1 (n = 743)	Trastuzumab (n = 743)
Primary tumor stage ^{††}		
▪ ypT0, ypT1a, ypT1b, ypT1mic, ypTis	331 (44.5)	306 (41.2)
▪ ypT1/ypT1c	175 (23.6)	184 (24.8)
▪ ypT2	174 (23.4)	185 (24.9)
▪ ypT3, ypT4	63 (8.5)	67 (9.0)
Regional lymph node stage [†]		
▪ ypN0	344 (46.3)	335 (45.1)
▪ ypN1	220 (29.6)	213 (28.7)
▪ ypN2, ypN3	123 (16.6)	133 (17.9)
▪ ypNX	56 (7.5)	62 (8.3)
Residual invasive disease ≤ 1 cm AND negative axillary nodes (ypT1a, ypT1b, or ypT1mic and ypN0)	170 (22.9)	161 (21.7)

[†]At definitive surgery.

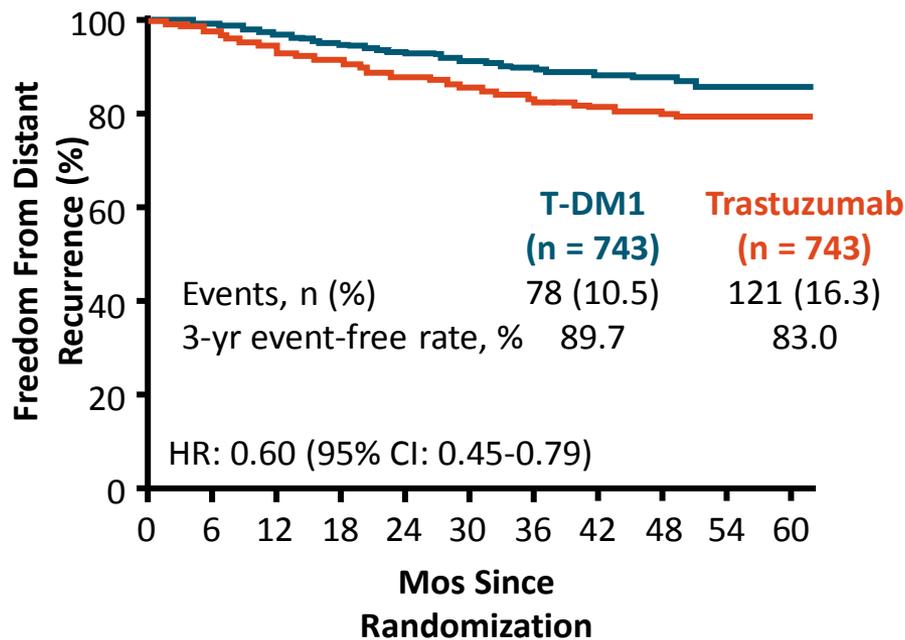
^{††}ypTX, n = 1 in trastuzumab arm; ypT1 without further subspecification, n = 5.

KATHERINE: IDFS

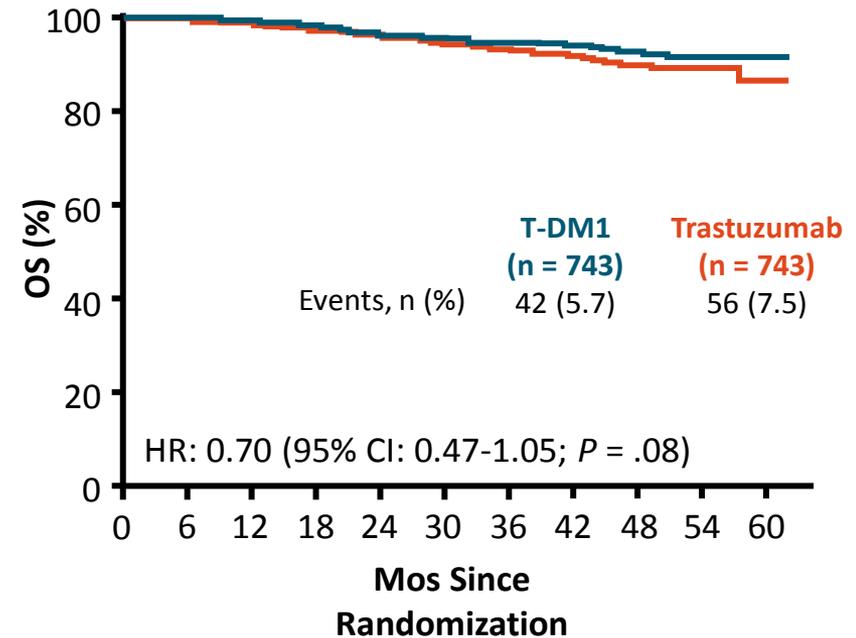


KATHERINE: Secondary Endpoints

Distant Recurrence



OS



KATHERINE: Conclusions

- In patients with HER2+ EBC who had residual invasive disease after neoadjuvant chemotherapy plus HER2-targeted therapy at surgery, T-DM1 significantly prolonged IDFS compared with trastuzumab
 - HR: 0.50 (95% CI: 0.39-0.64; $P < .001$)
 - Benefit with T-DM1 consistent across examined subgroups
- No unexpected safety signals
- Longer follow-up needed for OS
- Study investigators conclude that T-DM1 will likely represent a new standard of care in this population

A-BRAVE-TRIAL

**HIGH RISK PRIMARY TNBC PTS
WHO COMPLETED TREATMENT
WITH CURATIVE INTENT
INCLUDING SURGERY,
CHEMOTHERAPY AND
RADIOTHERAPY (if indicated)**

**Stratum A: Adjuvant
Stratum B: Post-neoadjuvant**

R

**Avelumab for 1
year**

Observation

Randomization 1:1 balanced for adjuvant and post-neoadjuvant patients.

- Co-primary endpoints:**
1. DFS in all-comers;
 2. DFS in PD-L1+ patients
- Secondary endpoints:** OS, Safety, Biomarkers

n=335 (for the 1st co-primary endpoint)