Immunoterapia vs capecitabina nei carcinomi mammari triplo negativi

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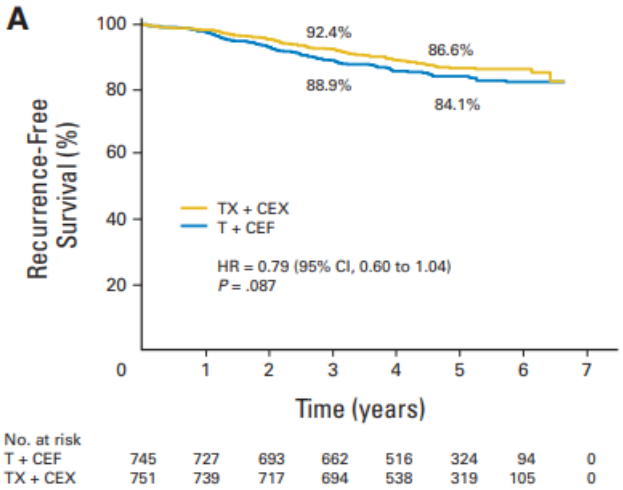
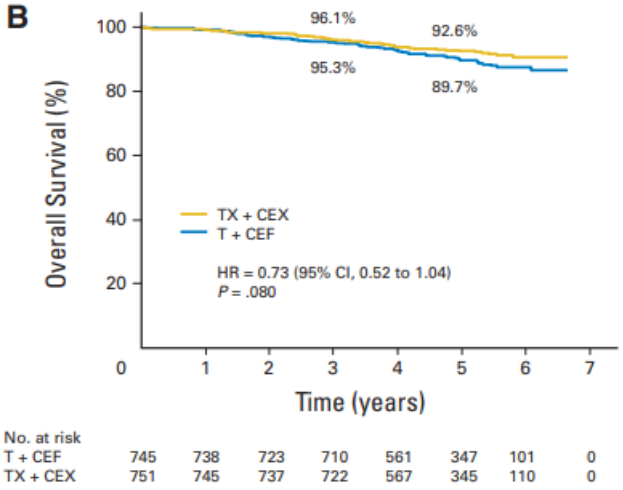
In which settings?

- **Capecitabine:**
  - Adjuvant setting
  - Neo-adjuvant setting
  - Adjuvant post-neoadjuvant setting
- **Immunotherapy:**
  - Neoadjuvant setting
  - Adjuvant post-neoadjuvant setting (*on-going*)

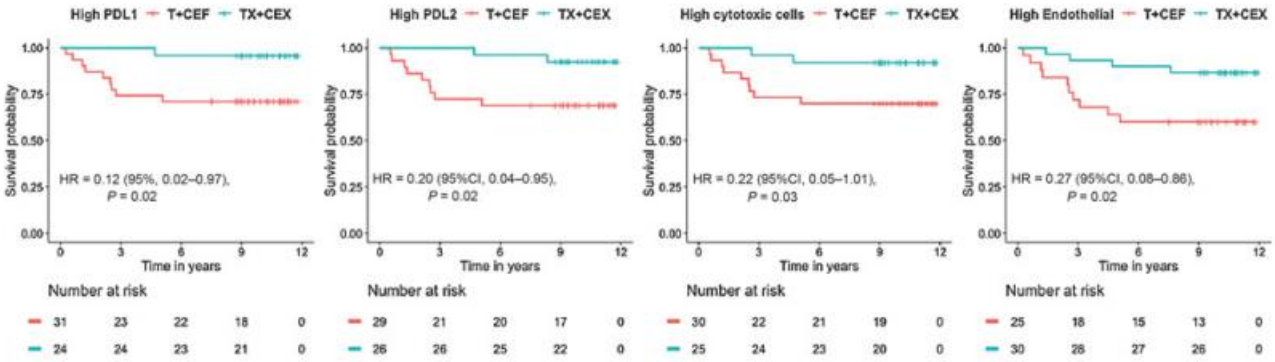
- ***Both in advanced settings: it's not today's topic***

Adjuvant Capecitabine, Docetaxel, Cyclophosphamide, and Epirubicin for Early Breast Cancer: Final Analysis of the Randomized FinXX Trial



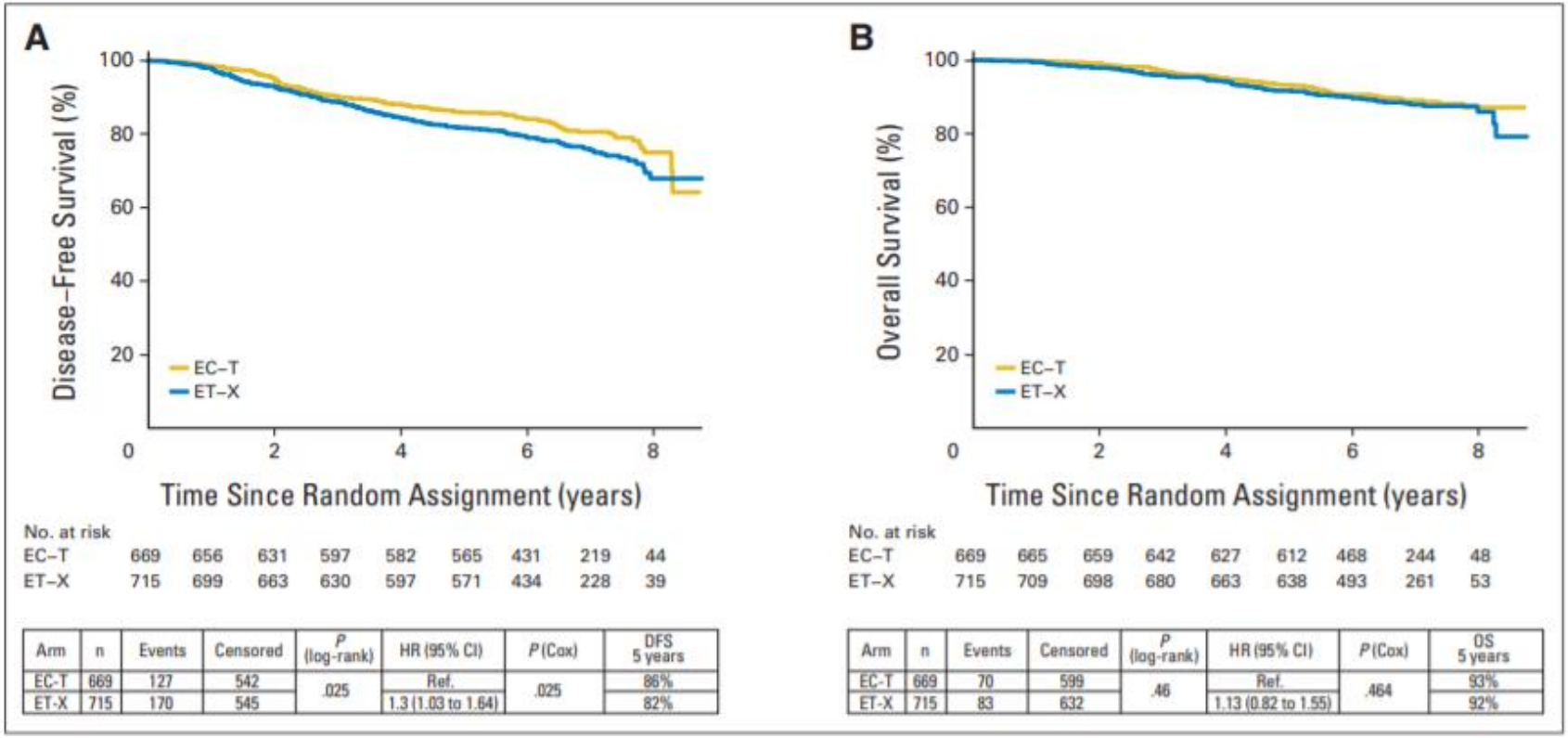


Predictive Biomarkers for Adjuvant Capecitabine Benefit in Early-Stage Triple-Negative Breast Cancer in the FinXX Clinical Trial



Joensuu et al, JCO 2012; Asleh et al, Clin Cancer Res 2020

Epirubicin Plus Cyclophosphamide Followed by Docetaxel Versus Epirubicin Plus Docetaxel Followed by Capecitabine As Adjuvant Therapy for Node-Positive Early Breast Cancer: Results From the GEICAM/2003-10 Study



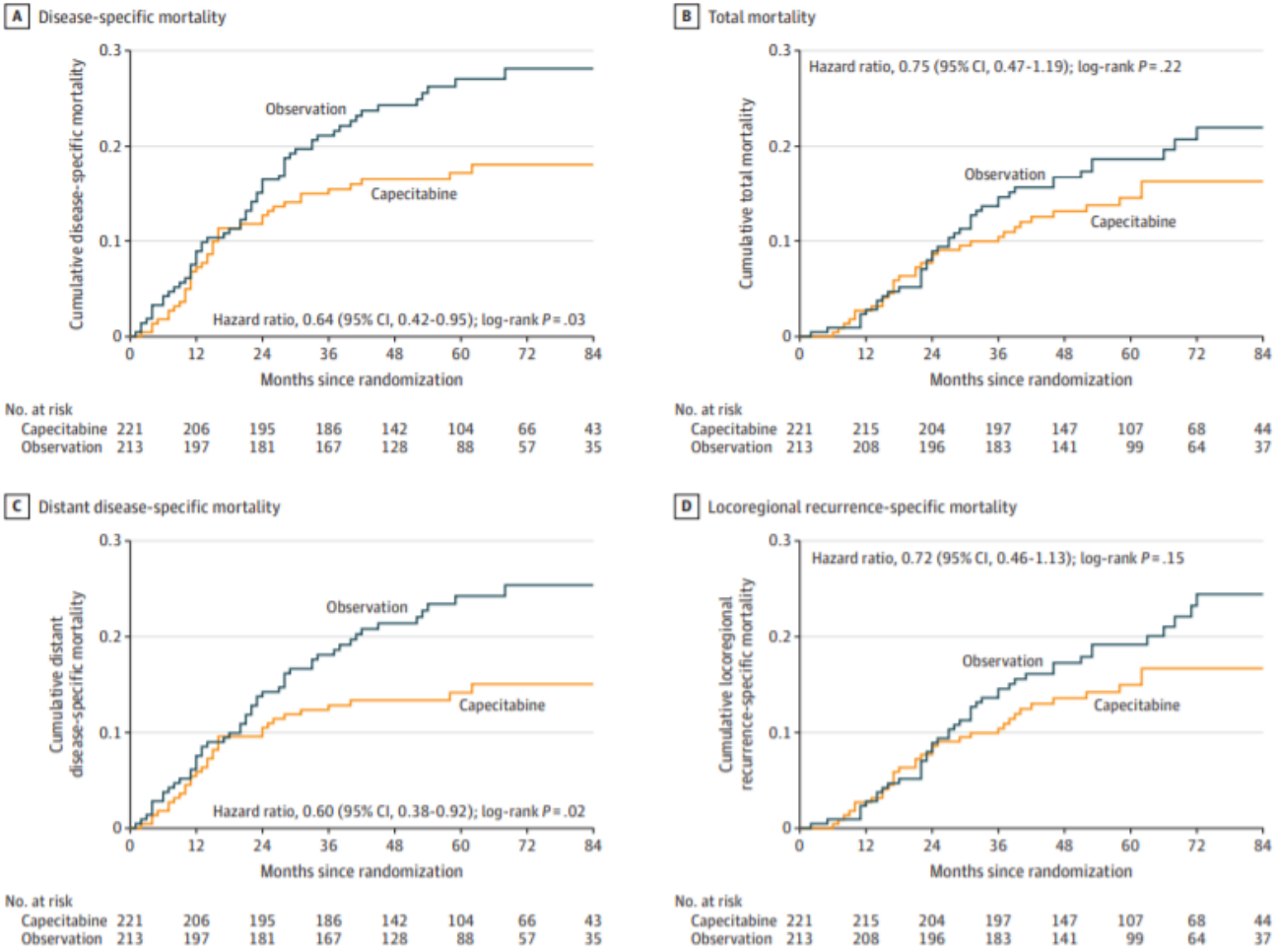
Arm	n	Events	Censored	*P* (log-rank)	HR (95% CI)	*P* (Cox)	DFS 5 years
EC-T	669	127	542	.025	Ref.	.025	86%
ET-X	715	170	545		1.3 (1.03 to 1.64)		82%

Arm	n	Events	Censored	*P* (log-rank)	HR (95% CI)	*P* (Cox)	OS 5 years
EC-T	669	70	599	.46	Ref.	.464	93%
ET-X	715	83	632		1.13 (0.82 to 1.55)		92%

Martin et al, JCO 2015

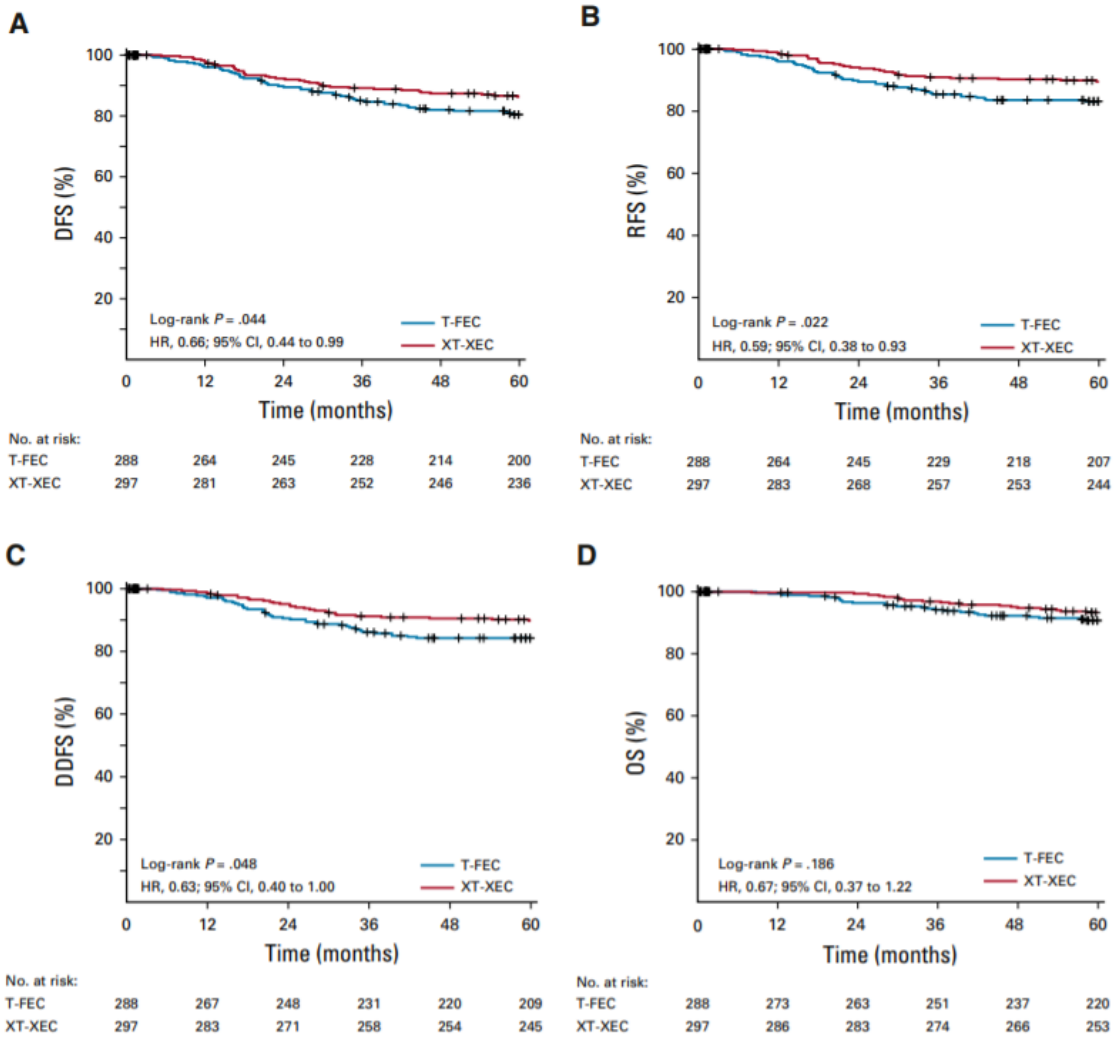
Effect of Capecitabine Maintenance Therapy Using Lower Dosage and Higher Frequency vs Observation on Disease-Free Survival Among Patients With Early-Stage Triple-Negative Breast Cancer Who Had Received Standard Treatment

The SYSUCC-001 Randomized Clinical Trial

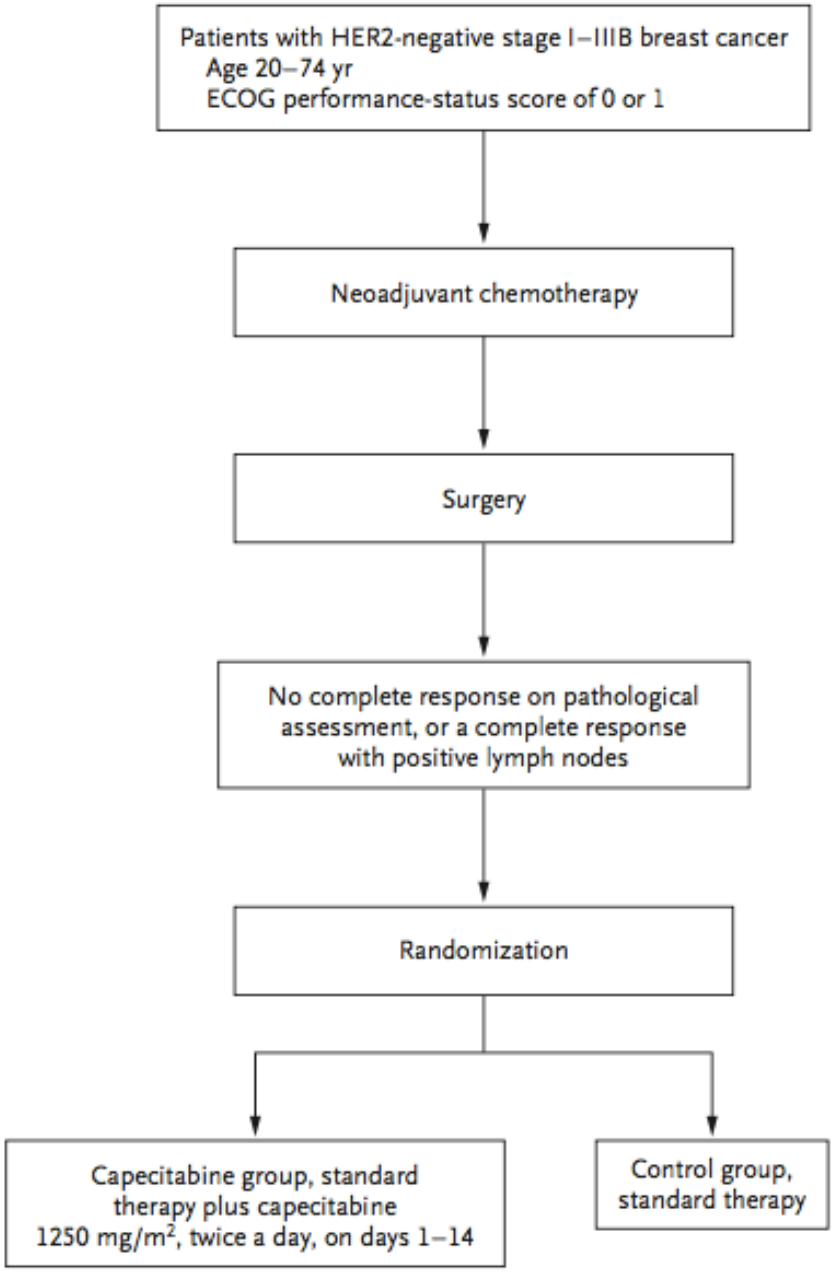


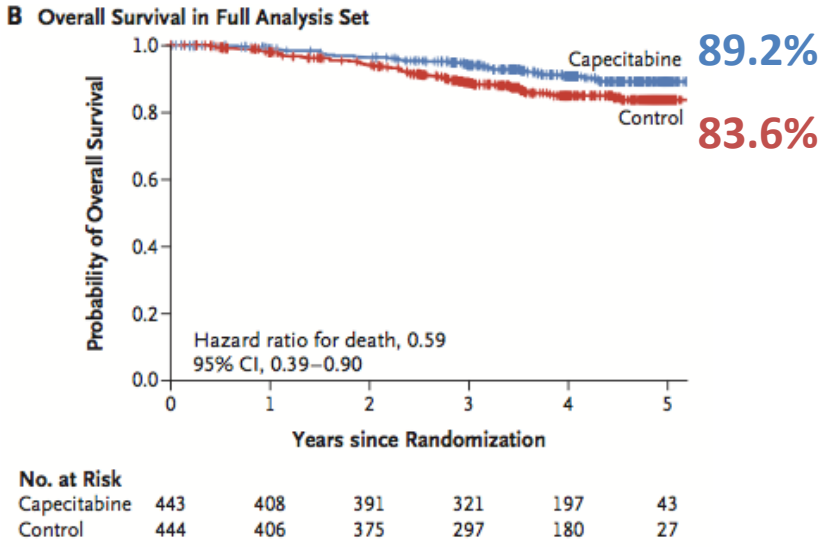
Wang et al, JAMA 2020

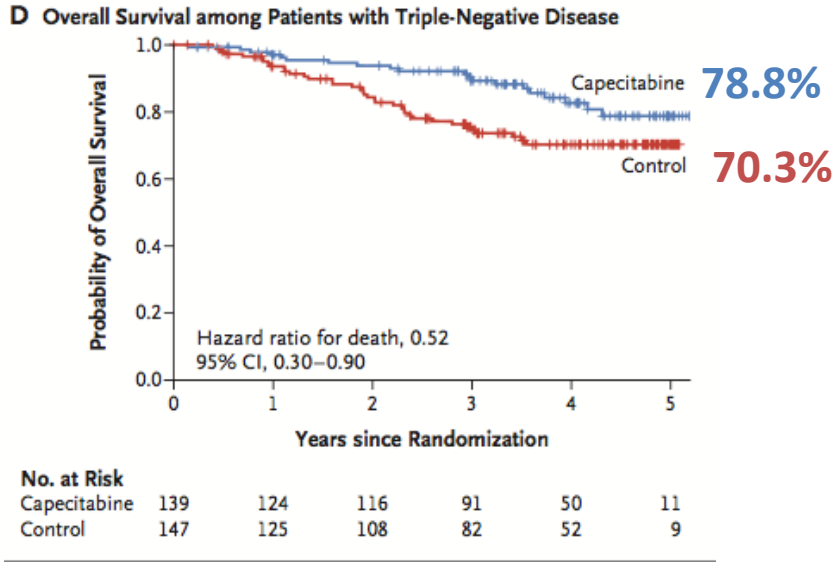
Adjuvant Capecitabine With Docetaxel and Cyclophosphamide Plus Epirubicin for Triple-Negative Breast Cancer (CBCSG010): An Open-Label, Randomized, Multicenter, Phase III Trial



Li et al, JCO 2020







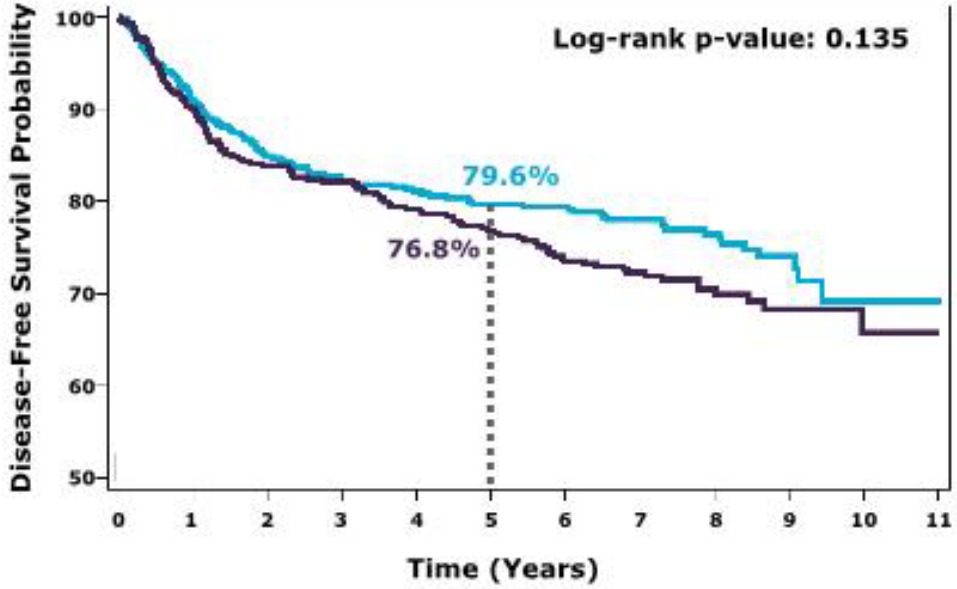
Masuda et al. NEJM 2017

GEICAM spanish breast cancer group

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

ciboma

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

Martin et al. SABCS 2018 & JCO 2019

The role of capecitabine-based neoadjuvant and adjuvant chemotherapy in early-stage triple-negative breast cancer: a systematic review and meta-analysis

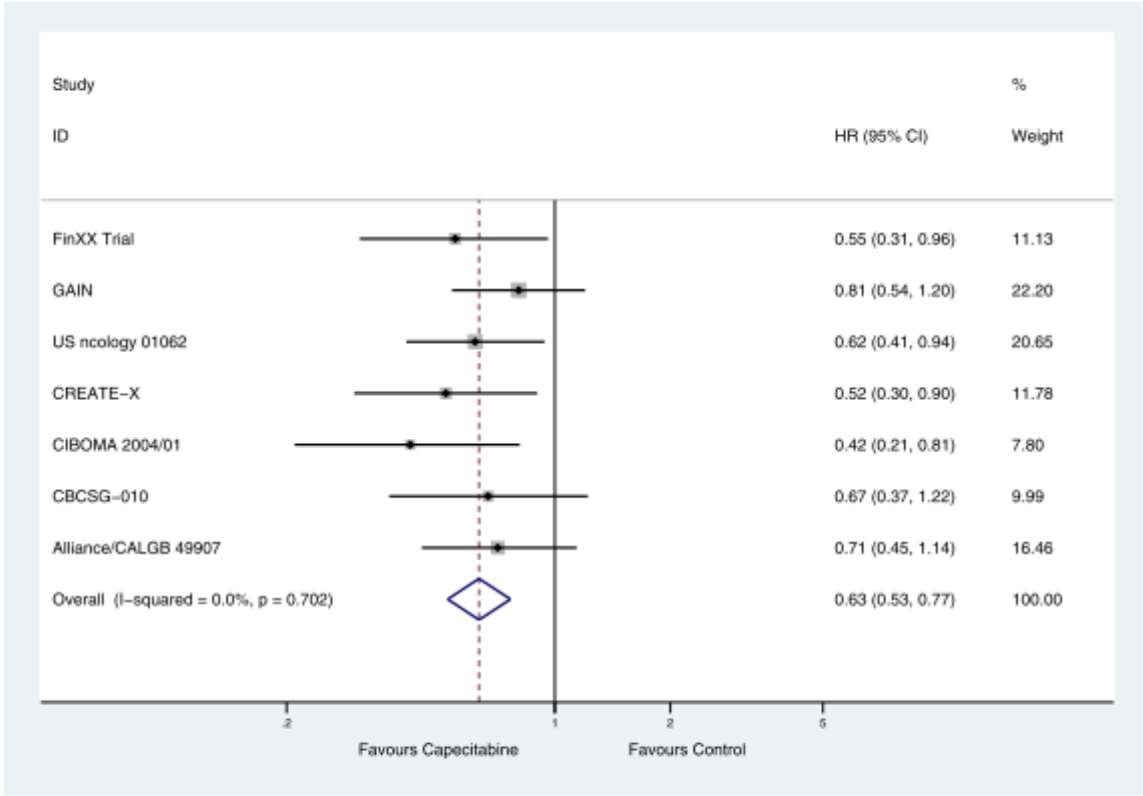


Fig. 2 Effects of combined capecitabine regimens in neoadjuvant and adjuvant chemotherapy on overall survival (OS)

Huo et al, BMC Cancer 2021

Residual disease: Standard of care escalation strategies

Capecitabine – absolute 5-yrs OS benefit of 8.5% (HR 0.52) – Create-X study

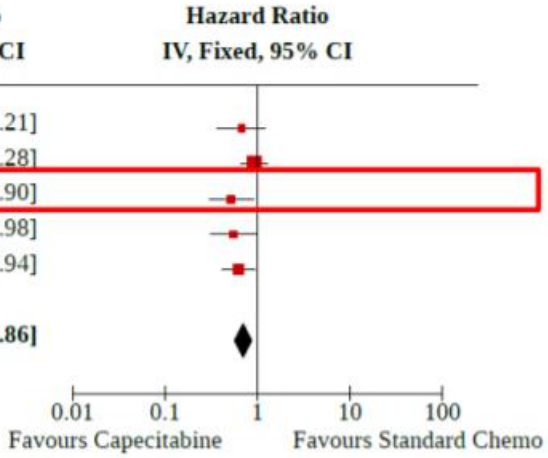
Analysis 5.4. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 4: OS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4005	0.303	273	288	11.8%	0.67 [0.37 , 1.21]
CIBOMA 2004-01	-0.0834	0.1695	448	428	37.6%	0.92 [0.66 , 1.28]
CREATE-X	-0.6539	0.2806	443	444	13.7%	0.52 [0.30 , 0.90]
FINXX	-0.5978	0.2925	93	109	12.6%	0.55 [0.31 , 0.98]
USON 01062	-0.478	0.211	396	384	24.3%	0.62 [0.41 , 0.94]
Total (95% CI)			**1653**	**1653**	**100.0%**	**0.70 [0.57 , 0.86]**

Heterogeneity: Chi² = 4.75, df = 4 (P = 0.31); I² = 16%

Test for overall effect: Z = 3.46 (P = 0.0005)

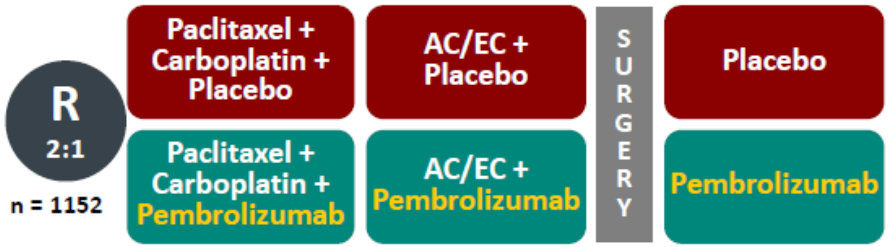
Test for subgroup differences: Not applicable



Hoon, Cochrane Database of Systematic Reviews 2021

Neoadjuvant IO plus CT:
A success story

Keynote 522

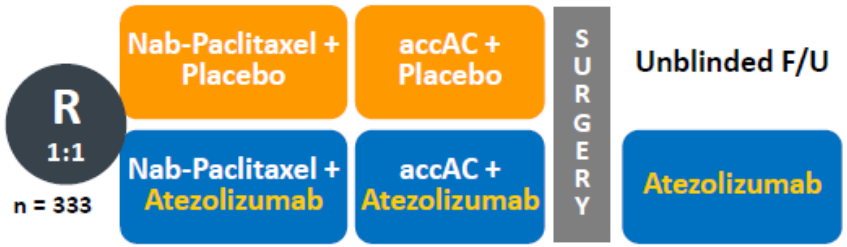


- PDL1+ (22C3 CPS1) 82%
- N+ 52%, T3/4 26%
- Carbo QW 41%

Co-primary endpoints:
- pCR (ypT0/Tis ypN0)
- Event-free Survival

Pembrolizumab: 200 mg given IV q3w
Paclitaxel: 80 mg/m^2 given IV qw for 12 weeks;Carboplatin: AUC5 q3w x 4 or AUC1.5 qw x 12
Doxorubicin: 60 mg/m^2 given IV q2w/Cyclophosphamide: 600 mg/m^2 given IV q2w

Impassion 031



- PDL1+ (SP142≥1%) 53%
- N+ 38% (34% Ate; 43% Pla)
- T3/4 28%

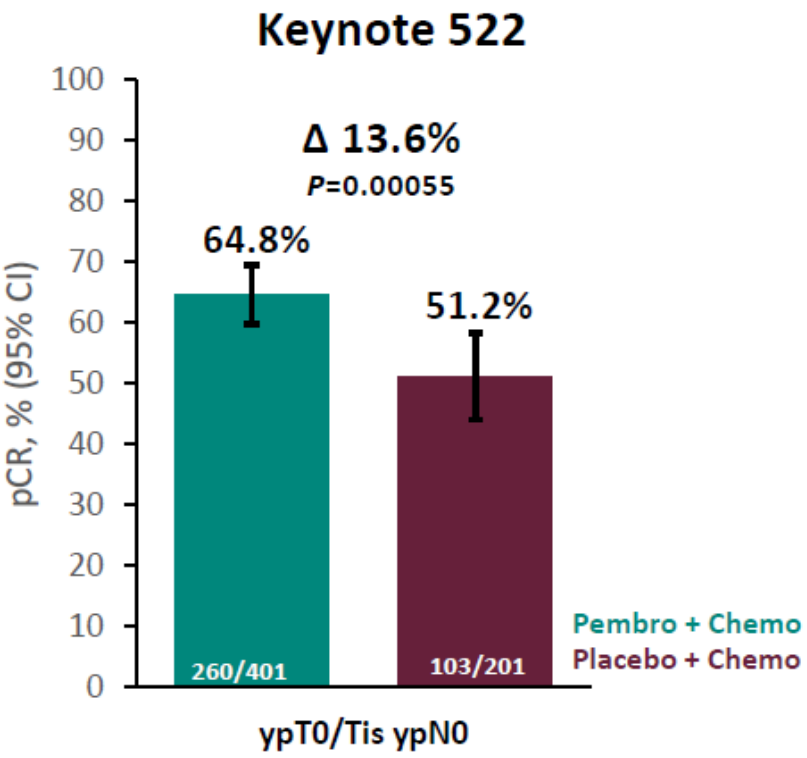
Primary endpoint:
- pCR (ypT0/Tis ypN0) in ITT & PD-L1+

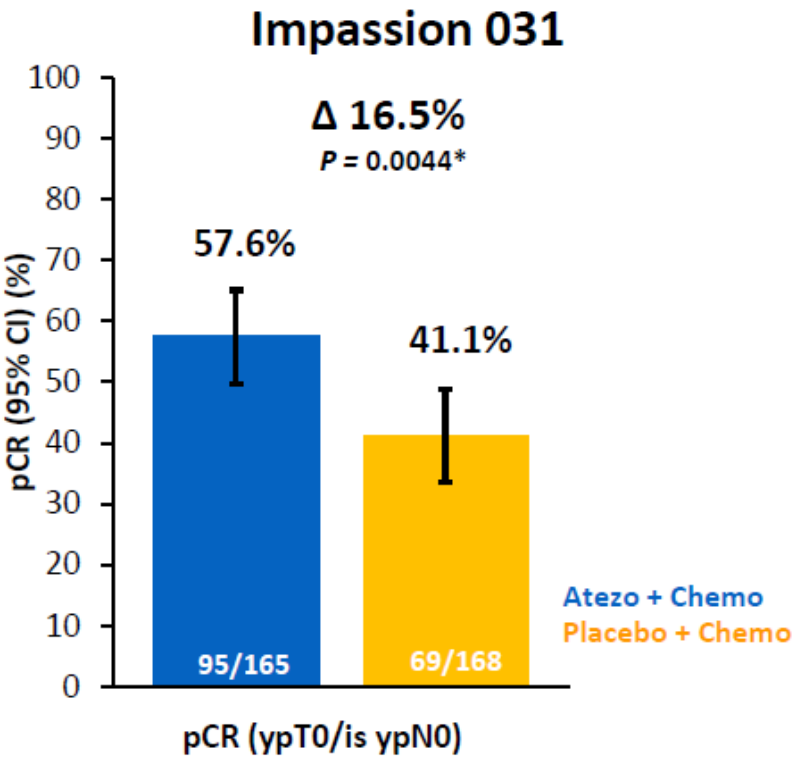
Atezolizumab: 840 mg given IV q2w (neoadjuvant); 1200 mg IV q3w x 11 (adjuvant)
Nab-paclitaxel: 125 mg/m^2 given IV qw for 12 weeks
Doxorubicin: 60 mg/m^2 given IV q2w/Cyclophosphamide: 600 mg/m^2 given IV q2w

Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Harbeck et al, ESMO 2020 Lancet 2020

Neoadjuvant CIT in TNBC: Pathological complete response

Addition of CIT significantly improves pCR in ITT Population



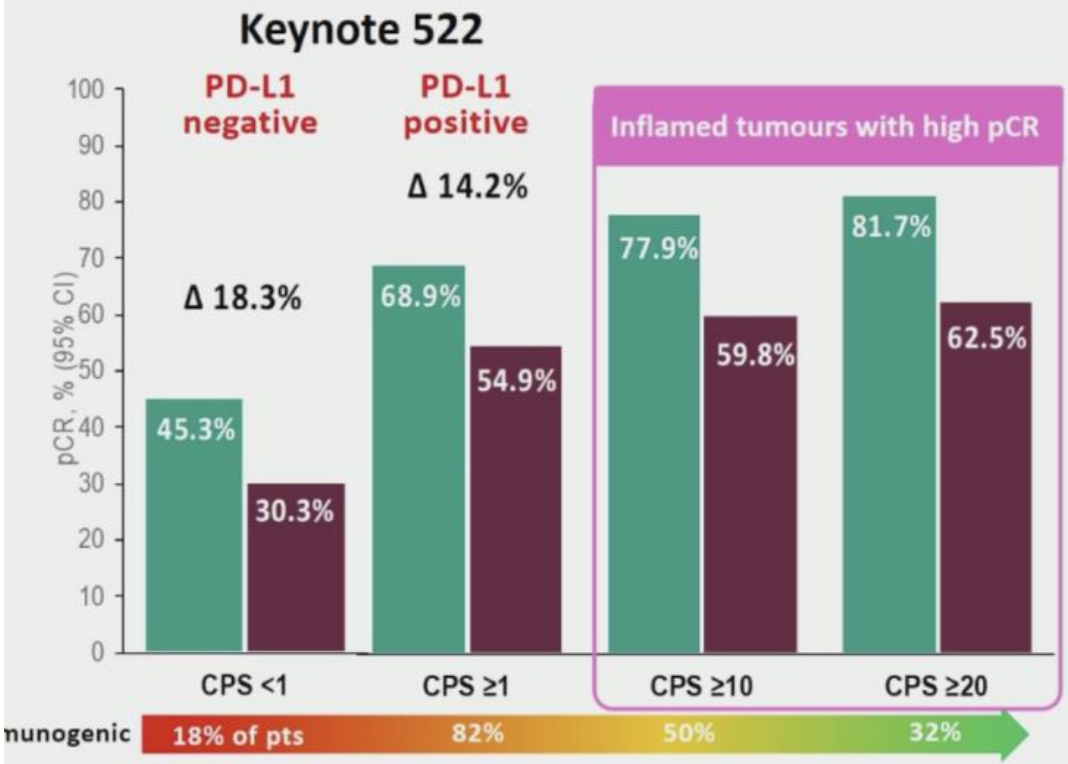


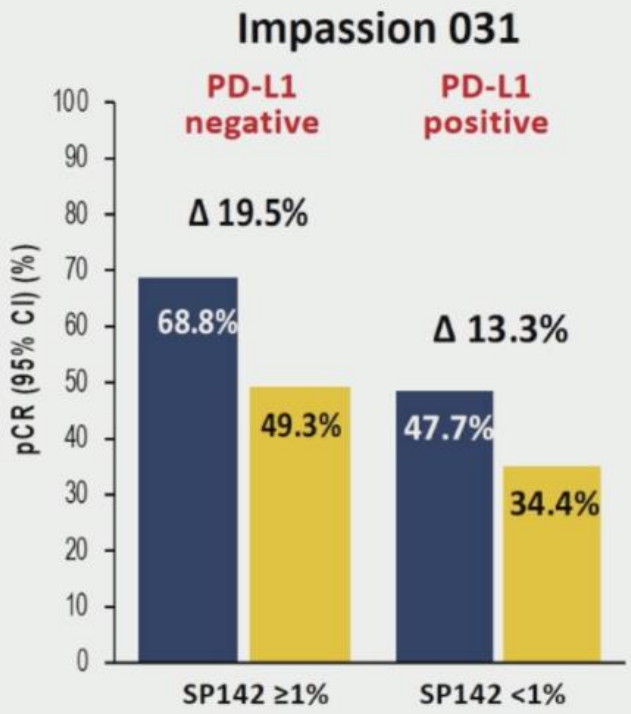
Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Harbeck et al, ESMO 2020

Lancet 2020

Neoadjuvant CIT in TNBC: pCR rates by PD-L1 expression

PDL1-positive and PDL1-negative patients benefit from CIT



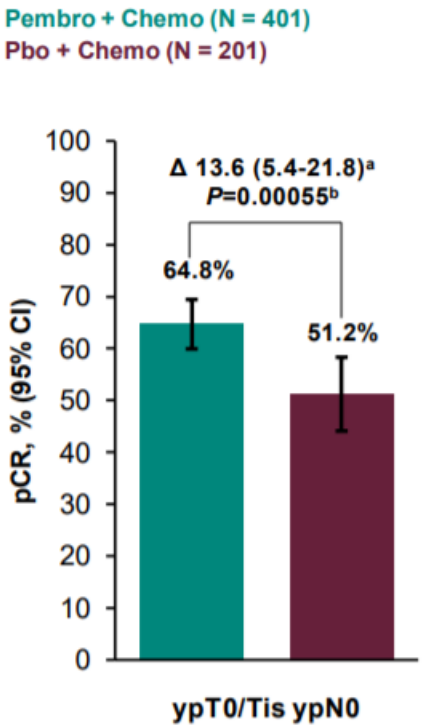


Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Harbeck et al, ESMO 2020

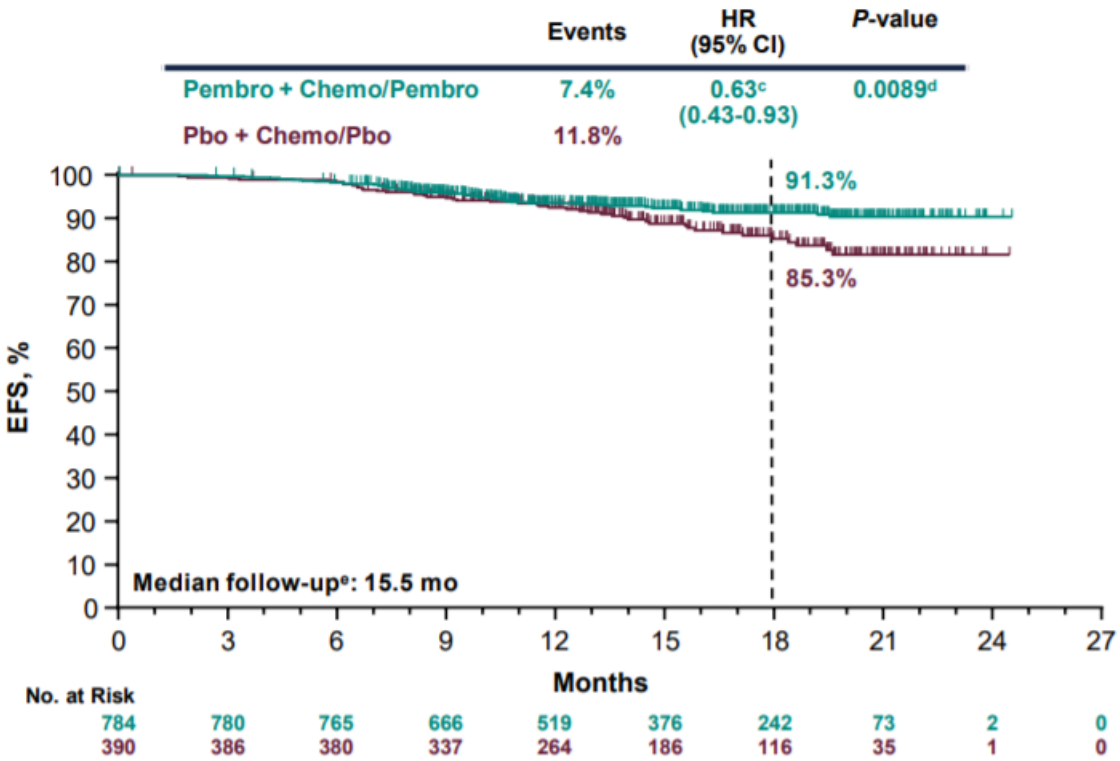
Lancet 2020

Prior Analyses of KEYNOTE-522

Primary pCR Endpoint at IA1[1]



First EFS Analysis at IA2[1]

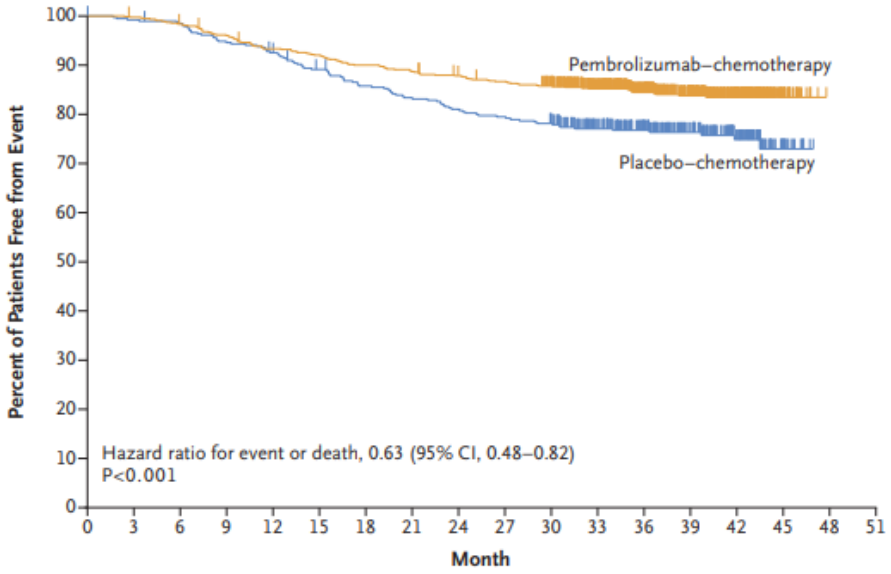


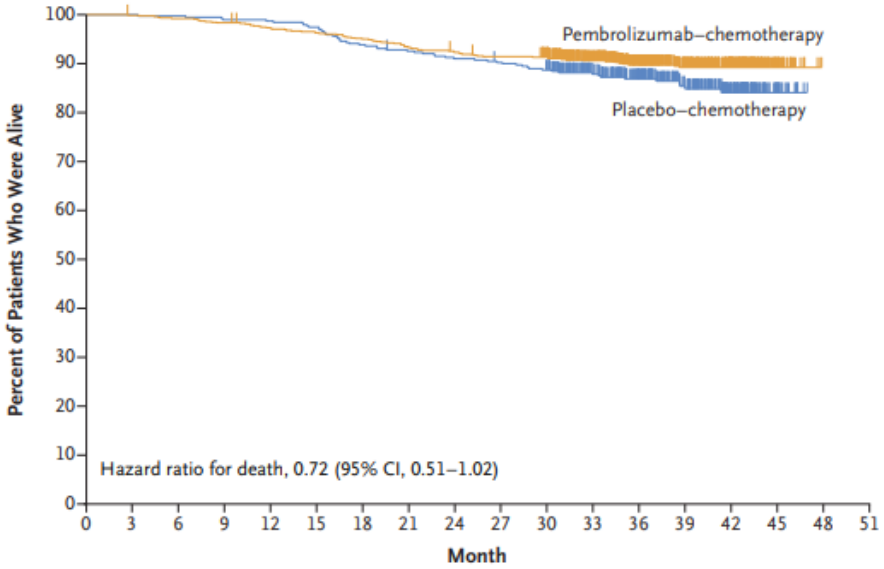
Schmid et al, NEJM 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer





FDA U.S. FOOD & DRUG ADMINISTRATION

On July 26, 2021, the FDA approved pembrolizumab (brand name Keytruda) for high-risk, early-stage, triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

Schmid et al, NEJM 2022

A-BRAVE-TRIAL

PHASE III RANDOMIZED STUDY OF ADJUVANT TREATMENT WITH THE ANTI-PD-L1 ANTIBODY AVELUMAB FOR HIGH-RISK TRIPLE NEGATIVE BREAST CANCER PATIENTS: THE A-BRAVE TRIAL.

Pierfranco Conte[1,2], Maria Vittoria Dieci[1,2], Giancarlo Bisagni[3], Michelino De Laurentiis[4], Carlo A. Tondini[5], Peter Schmid[6], Gian Luca De Salvo[7], Giacomo Moratello[7], Valentina Guarneri[1,2]

[1]DISCOG, University of Padova, Italy; [2]Medical Oncology 2, IOV-IRCCS, Padova, Italy; [3]Oncology Unit, Azienda USL-IRCCS, Reggio Emilia, Italy; [4]National Cancer Institute "Fondazione Giovanni Pascale", Napoli, Italy; [5]UOC Oncologia, ASST Papa Giovanni XXIII, Bergamo, Italy; [6]Barts Cancer Institute, London, UK; [7]Clinical Trials and Biostatistics Unit, IOV-IRCCS, Padova, Italy

Study design

HIGH RISK PRIMARY TNBC PTS WHO COMPLETED TREATMENT WITH CURATIVE INTENT INCLUDING SURGERY AND CHEMOTHERAPY

Stratum A: Adjuvant
Stratum B: Post-neoadjuvant

R

- Avelumab 10 mg/kg I.V. q2w for 1 year
- Observation

Randomization 1:1 balanced for adjuvant and post-neoadjuvant patients.
Radiotherapy allowed (if indicated) after randomization.

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

SWOG 1418

TNBC stage II/III, received anthracycline-based NACT
≥ 1 cm residual disease at surgery or any LN+

Randomized

- **Placebo**
- **Pembrolizumab 200 mg IV Q 3 wks x 1 year**

DFS

Powered to detect a 33% improvement in DFS (overall and PD-L1+)
Sample size: 1000

NCT02954874 (PI: Puztai)

Novel strategies under study

non-exhaustive list

Franzoi, Ann Oncol 2020; Foldi, Curr Treat Options in Oncol 2021

Study	population	Investigational agent(s)	Control agent(s)	NCT no
SASCIA/GBG-102	No pCR - HER2-	8 x sacituzumab-govitecan	Physician's choice	NCT04595565
ATOX-2018	No pCR - TNBC	capecitabine + atezolizumab	capecitabine	NCT03756298
BreastImmune03	No pCR - TNBC	Ipi + nivo + radiotherapy	capecitabine + radiotherapy	NCT03818685
NSABP-B59/GBG-96	Neoadj TNBC	Pcarbo – AC/EC + atezolizumab	Pcarbo – AC/EC + placebo	NCT03281954
SUBITO	Neoadj stage III HER2-, HRD-pos	4xdd AC - High-dose alkylating chemo + PSCT (2 x miniCTC)	ddAC – 4xPCarbo 1 year Olaparib (no pCR +capecitabine)	NCT02810743
NeoStar	Neoadj TNBC	4 x sacituzumab-govitecan ± pembrolizumab	N/A	NCT04230109
Bellini	Neoadj HER2-	Nivolumab ± ipilimumab	N/A	NCT03815890

Linn, ESMO 2021