

foro debate oncología

Zaragoza 26-29 septiembre 2023



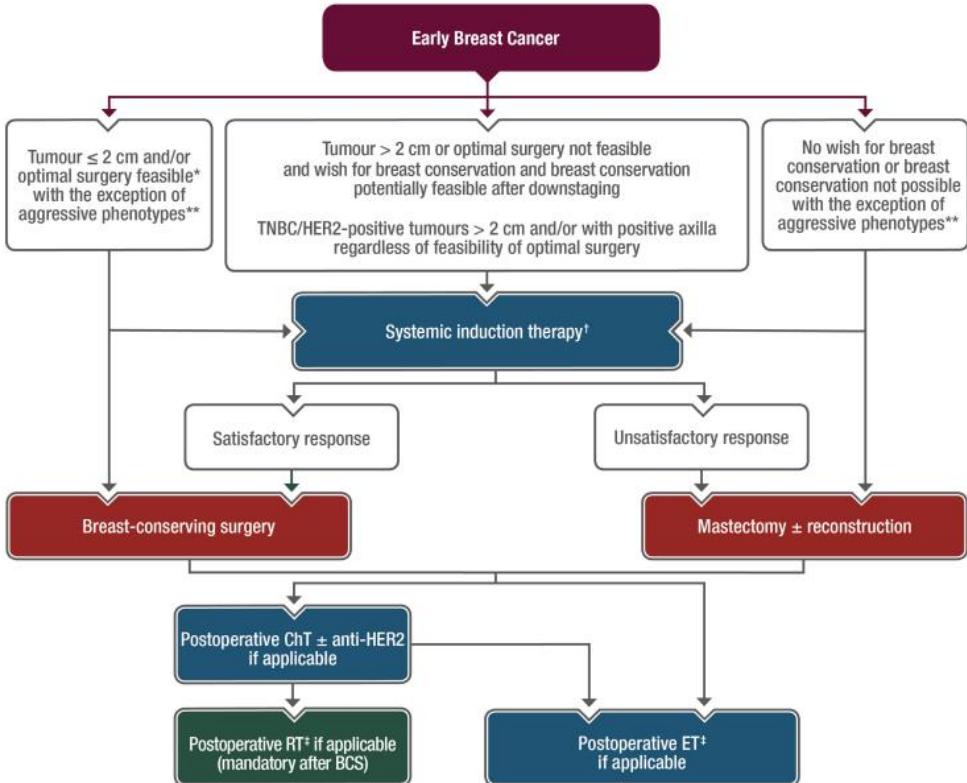
Cáncer de mama triple negativo. Novedades en el tratamiento de la enfermedad temprana

Dra. Raquel Andrés, Hospital Clínico Universitario Lozano Blesa, Zaragoza



CLINICAL PRACTICE GUIDELINES

Treatment



* Biology that requires ChT (TNBC, HER2-positive, luminal B-like), to assess response and prognosis and eventually decide on postoperative therapies, should preferentially receive preoperative ChT

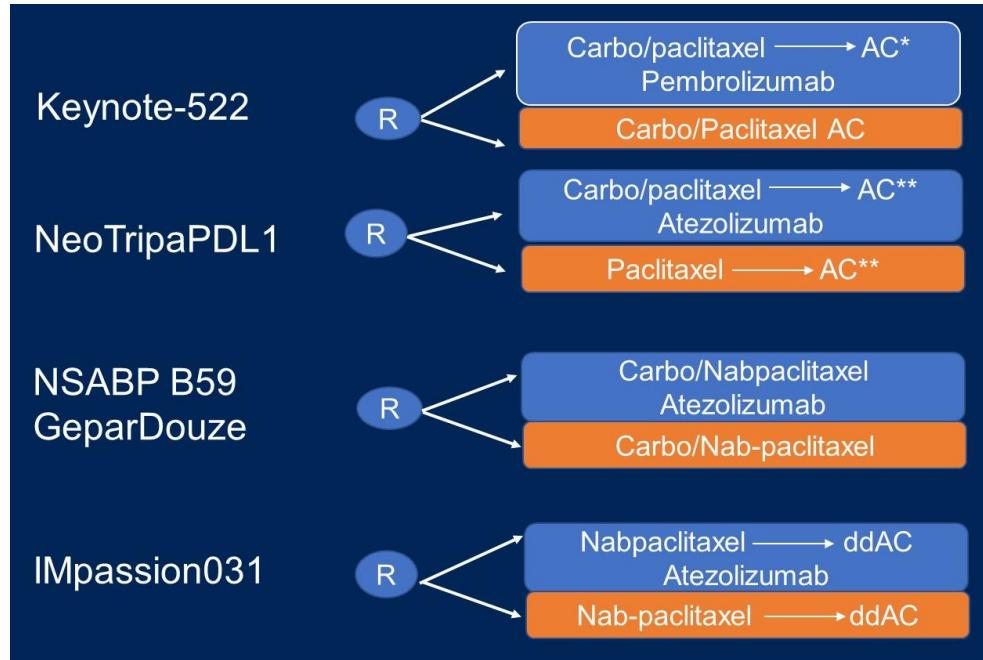
** Aggressive phenotypes: TNBC or HER2-positive breast cancer

† If ChT is planned, it should all be given as neoadjuvant

‡ Concomitant postoperative RT, postoperative ET and anti-HER2 therapy

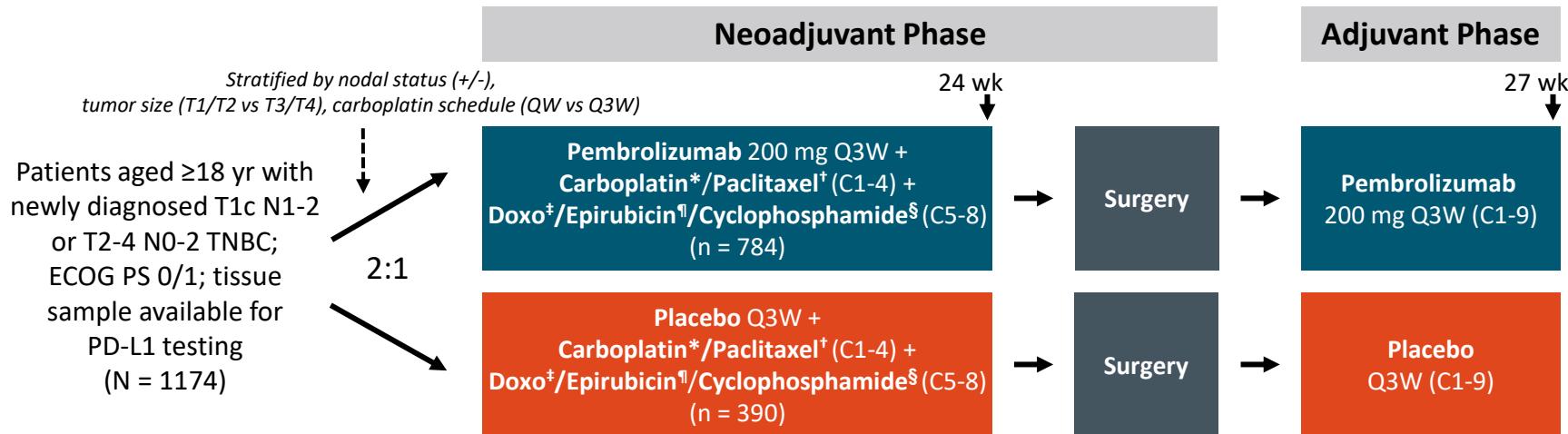


Evaluate the Role of Immunotherapy in Early Stage TNBC Neoadjuvant Phase III Trial



KEYNOTE-522: Pembrolizumab + Chemotherapy for Newly Diagnosed Early-Stage TNBC

- Randomized, placebo-controlled phase III trial
 - Median f/u: 39.1 mo (range: 30.0-48.0); data cutoff: March 23, 2021



- **Primary endpoints:** pCR (ypT0/Tis ypN0) by local review, EFS by local review
- **Secondary endpoints:** pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS (PD-L1+), safety, QoL
- **Exploratory endpoints:** RCB, pCR by subgroups, EFS by pCR

*AUC 5 Q3W or AUC 1.5 Q1W.

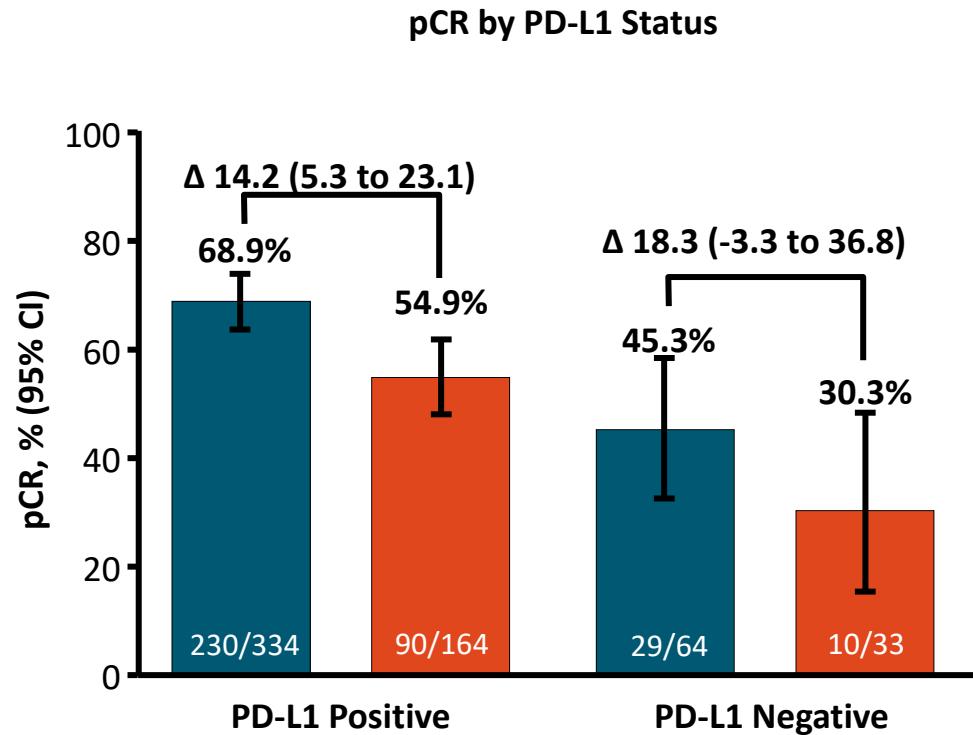
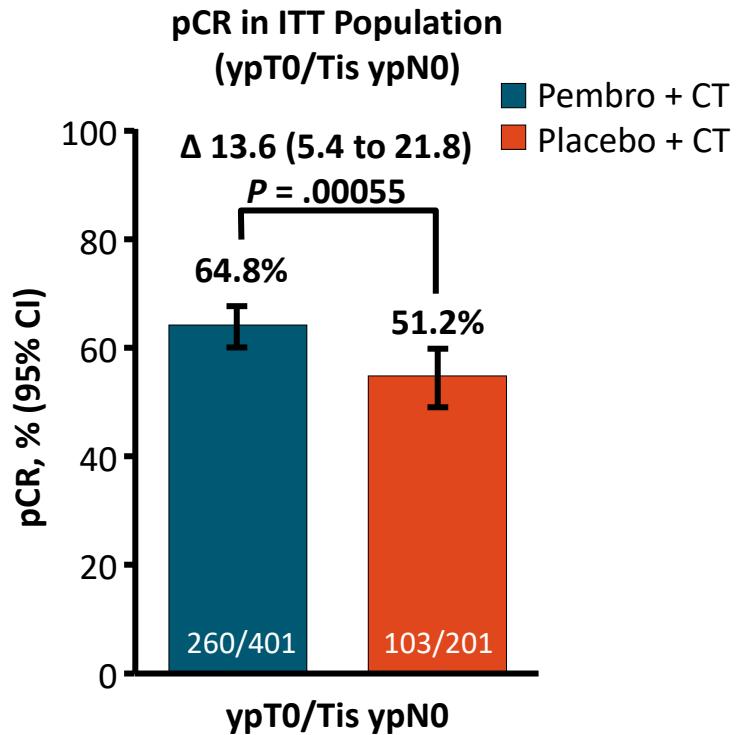
†80 mg/m² Q1W.

‡60 mg/m² Q3W.

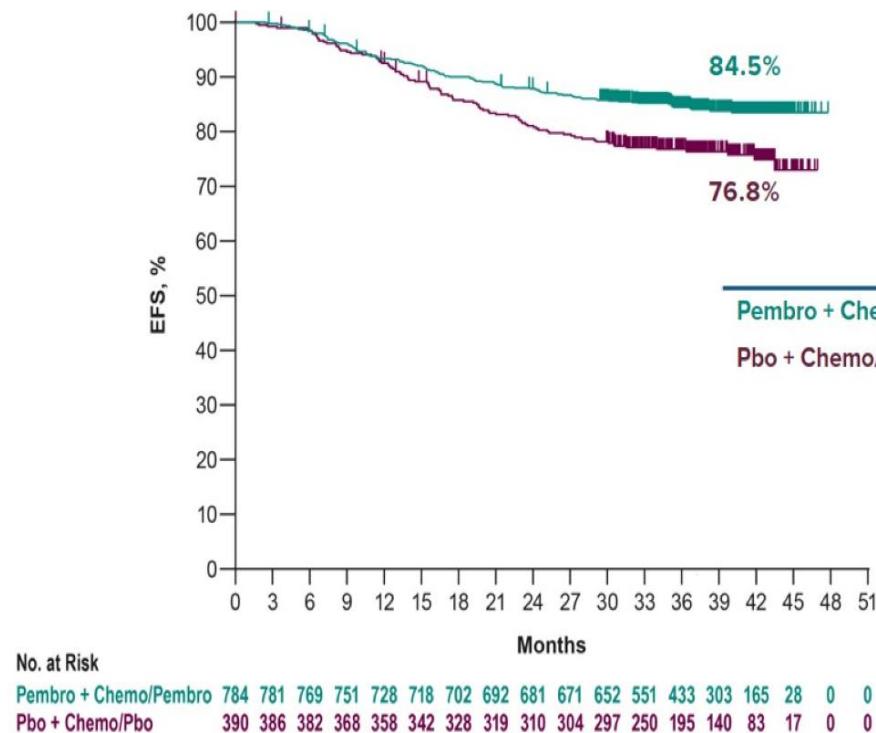
¶90 mg/m² Q3W.

§600 mg/m² Q3W.

KEYNOTE-522: PD-L1 Did Not Predict Benefit From Pembrolizumab



KEYNOTE-522: EFS UPDATE AT IA4 (39.1 m)



	Events	HR (95% CI)	P-value
Pembro + Chemo/Pembro	15.7%	0.63	.00031
Pbo + Chemo/Pbo	23.8%		

EFS Events	Pembro + CT (784)	Placebo + CT (390)
PD precluding surgery	14 (1.8%)	15 (3.8%)
Local recurrence	28 (3.6%)	17 (4.4%)
Distant recurrence	60 (7.7%)	51 (13.1%)
Second primary	6 (0.8%)	4 (1.0%)
Death	15 (1.9%)	6 (1.5%)



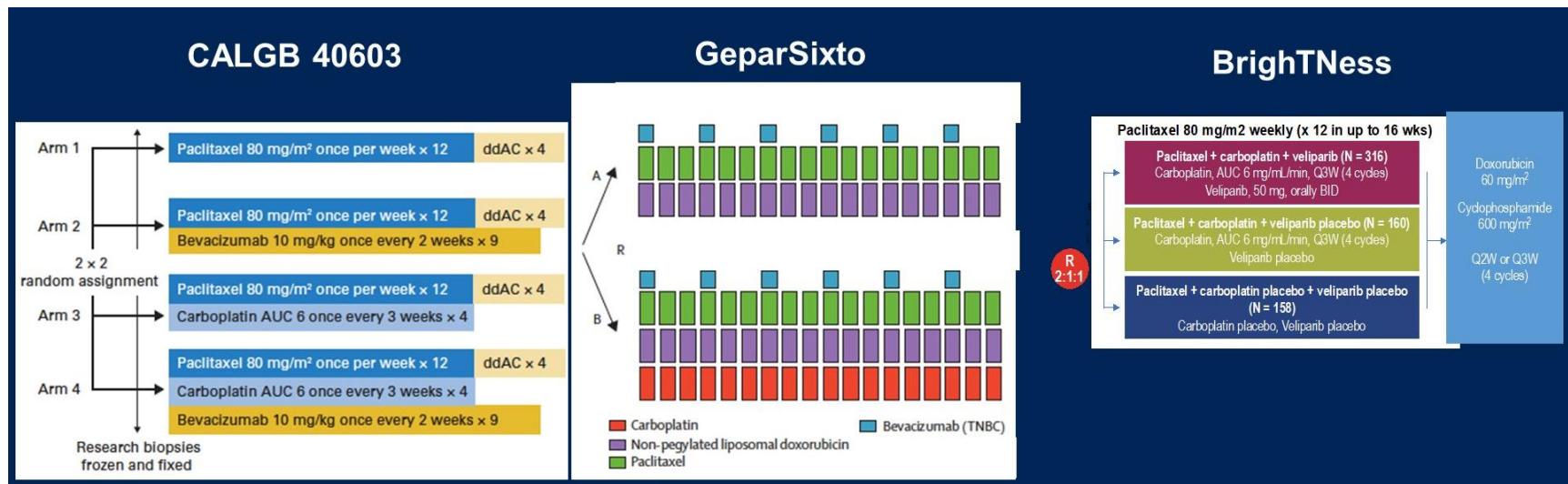
Neoadjuvant randomized trials with ICI and anthracycline-based regimens in early-stage TNBC

	KN522	I-SPY2	I-SPY2	I-SPY2	NeoTRIP	GeparNuevo	IMpassion031
N (exp/con)	1174 (784/390)	114 (29/85)	395 [70/325]	412(62/350)	280 (138/142)	174 (88/86)	333 (165/168)
°1 Endpoint	pCR; EFS	pCR	pCR	pCR	5-yr EFS	pCR	pCR (ITT; PD-L1+)
NAC	Carbo + T → AC/EC	wT → AC	wT → AC	wT → AC	Carbo + nabP	nabP → ddEC	nabP → ddAC
IO agent (duration)	Pembro vs Pbo (1 yr)	± Pembro (neoadj T only)	± Cemi/REGN3767 (neoadj T only)	± Cemi (neoadj T only)	± Atezo (neoadj only)	Durva. Pbo (neoadj only)	Atezo vs Pbo (1 yr)
IO target	PD-1	PD-1	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Stage	II-III (II: 75%)	II-III	II-III	II-III	II-III (II: 51%)	I-III (I: 35%)	II-III (II: 77%)
T min. size	cT1c	cT2	cT2	cT2	cT1c	cT1b	cT2
pCR (ITT)	65% vs 51% (IA1) (p=0.0006) 63% vs 56% (IA3)	60% vs 22% (grad)	53% vs 29%	31% vs 21%	44% vs 41% (p=0.66)	53% vs 44% (p=0.287)	58% vs 41% (p=0.0044)



Evaluating Platinum Therapy in Pre-operative Regimens

Addition of neoadjuvant carboplatin



von Minckwitz G, SABCS 2015. von Minckwitz G, *Lancet Oncol.* 2014, Castrellon AB, *Oncol Rev* 2017, Sikov JCO 2015, Sikov SABCS 2015, Loibl, S, et al. *Lancet Oncol.* 2018



pCR Rates without Platinum around 35%

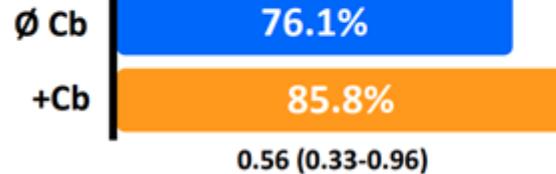
Carboplatin increases pCR rate to >50% with/without improvement in EFS and OS

GeparSixto



Paclitaxel 80 mg/m² q1w x18 + NPLD 20 mg/m² q1w x18 + Carboplatin AUC 1.5 q1w

3a-DFS

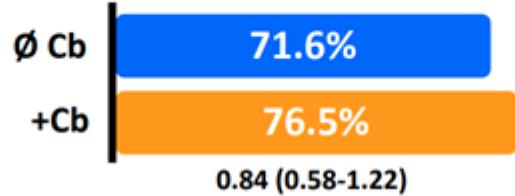


CALGB 40603

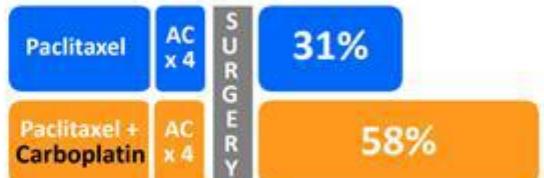


Paclitaxel 80 mg/m² q1w x 12 + Carboplatin AUC 6 q3w x 4

3a-EFS

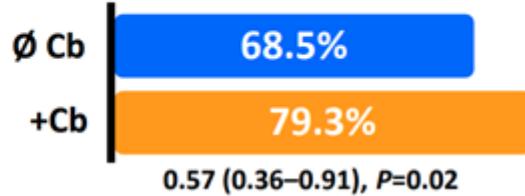


BrightTNess



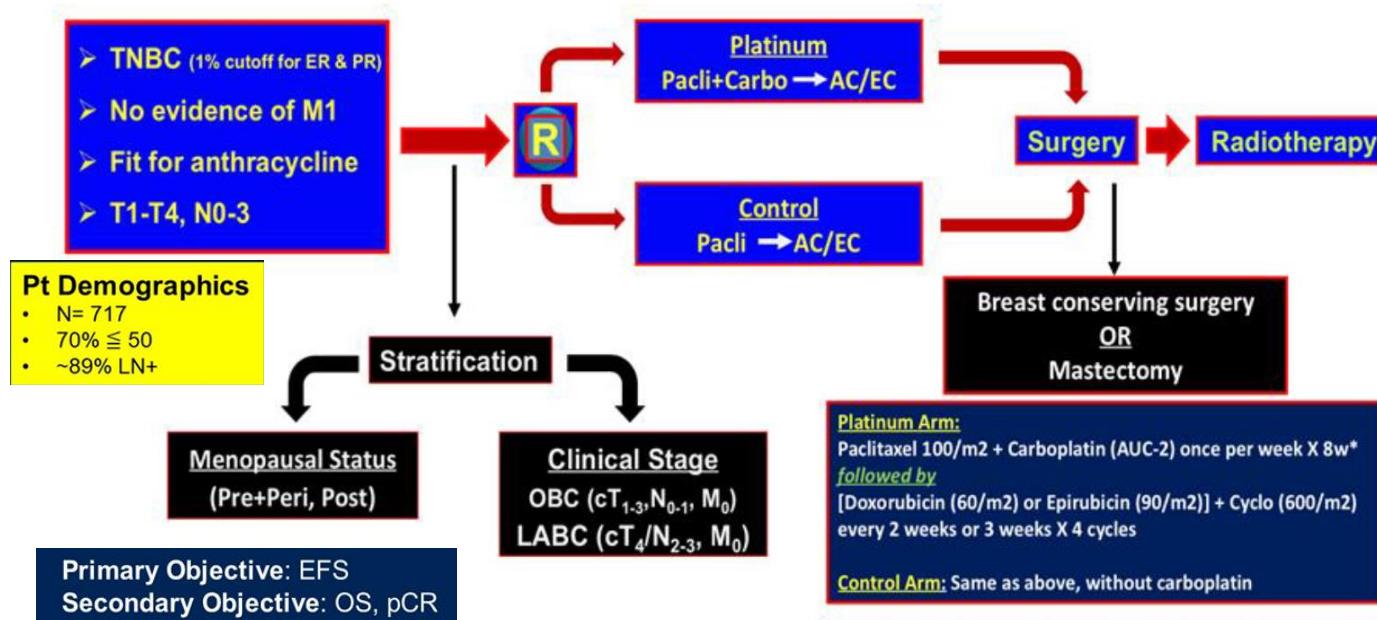
Paclitaxel 80 mg/m² q1w x 12 + Carboplatin AUC 6 q3w x 4

4a-EFS





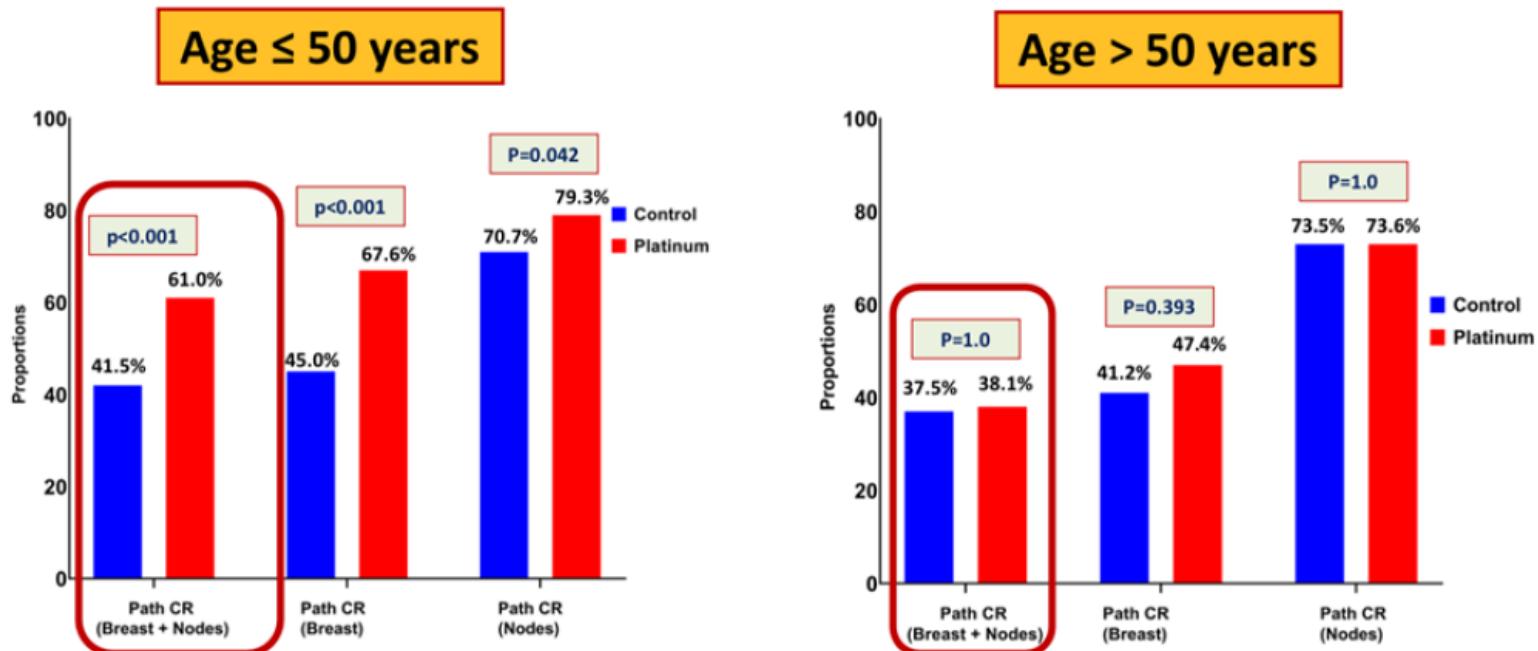
Phase III Neoadjuvant Platinum TNBC Study Tata Memorial Centre Hospital, Mumbai, India



*Gupta S, et al. Single agent weekly paclitaxel as neoadjuvant chemotherapy in locally advanced breast cancer: a feasibility study. Clin Oncol (R Coll Radiol). 2012 Nov;24(9):604-9.



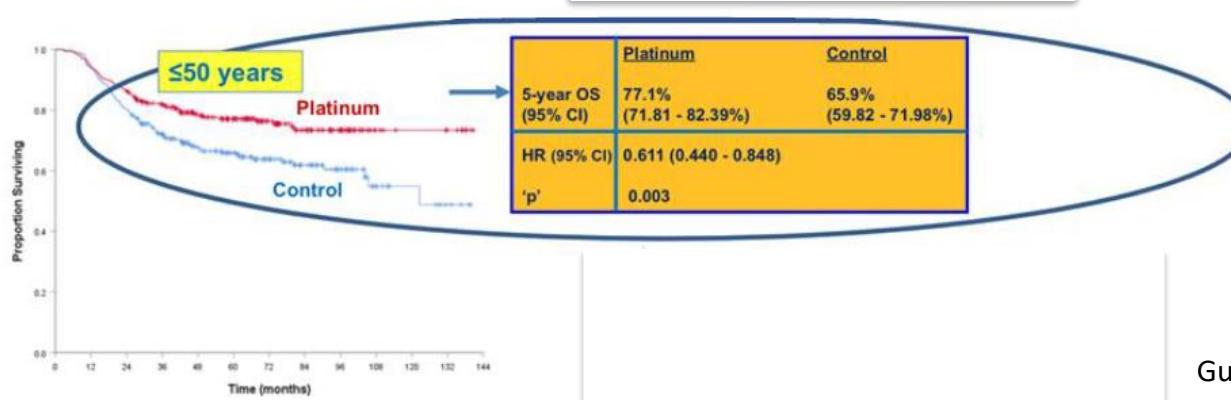
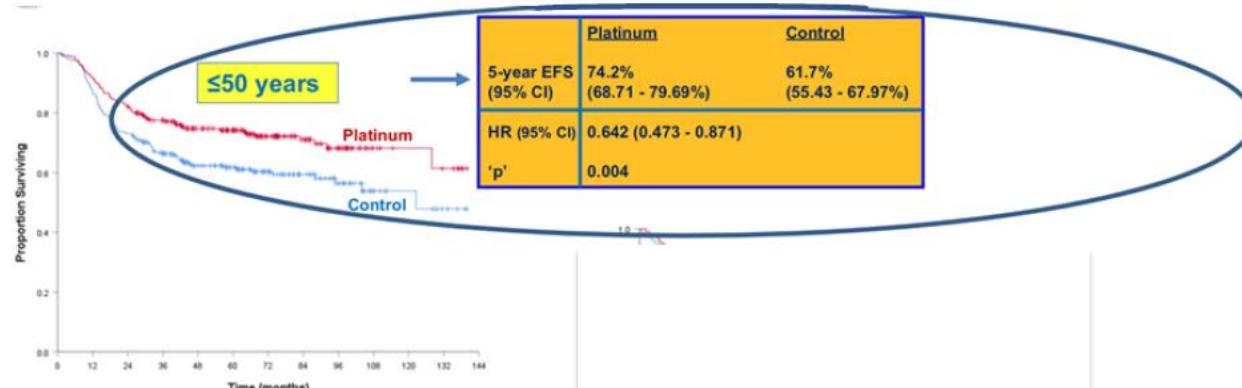
Pathological Response to NACT by Age & Rx-Arm



Multivariable (binary logistic) analysis for factors affecting pCR: Rx-Arm X Age interaction significant in a model including Rx-Arm, Age, cT size, cN status, Family History



EFS and OS IN < OR = 50 YEARS

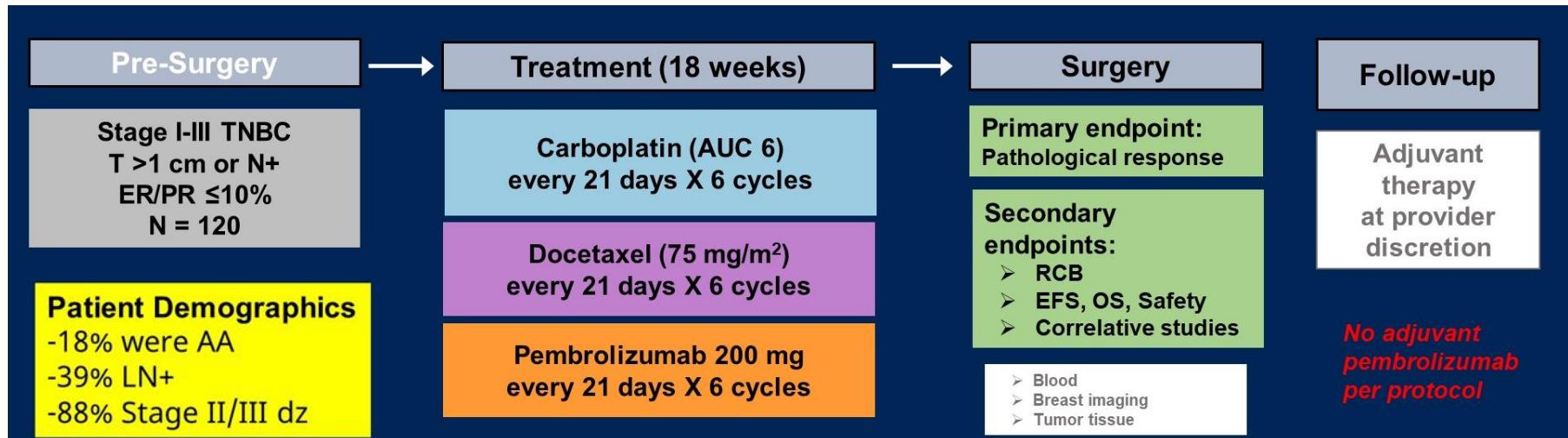


Gupta s et al, GS5-01, SABCS 2022



Can we reduce the Use of Anthracyclines?

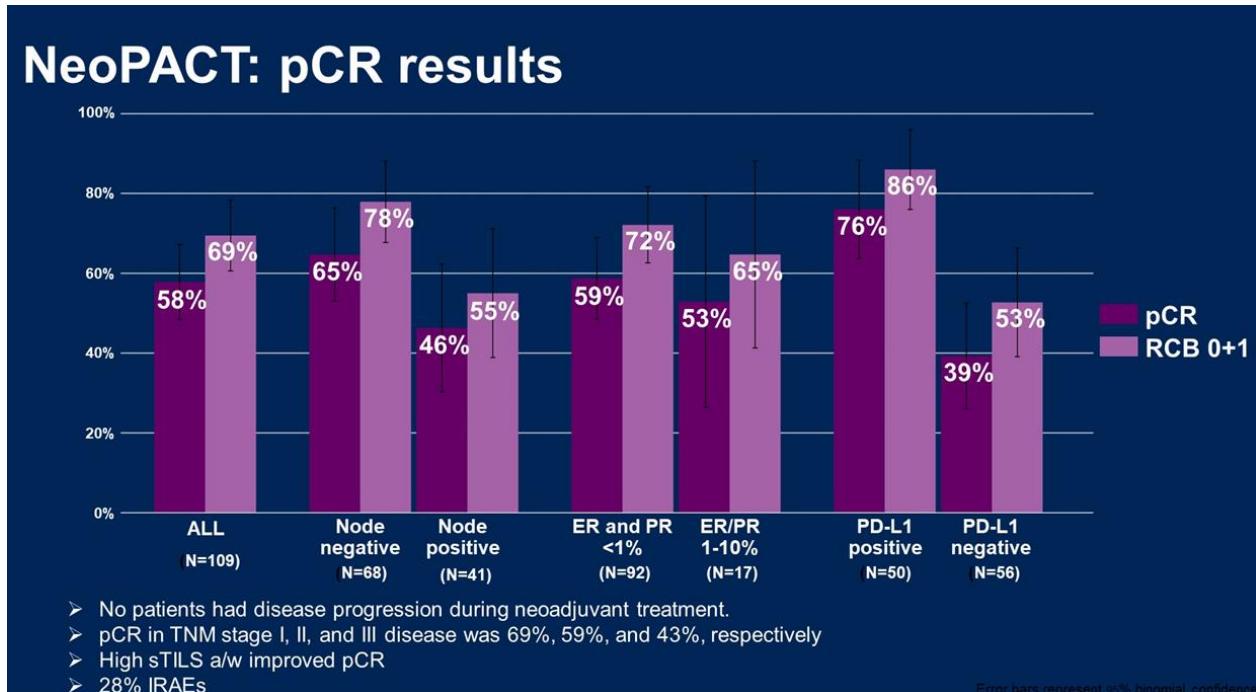
NeoPACT: Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in TNBC



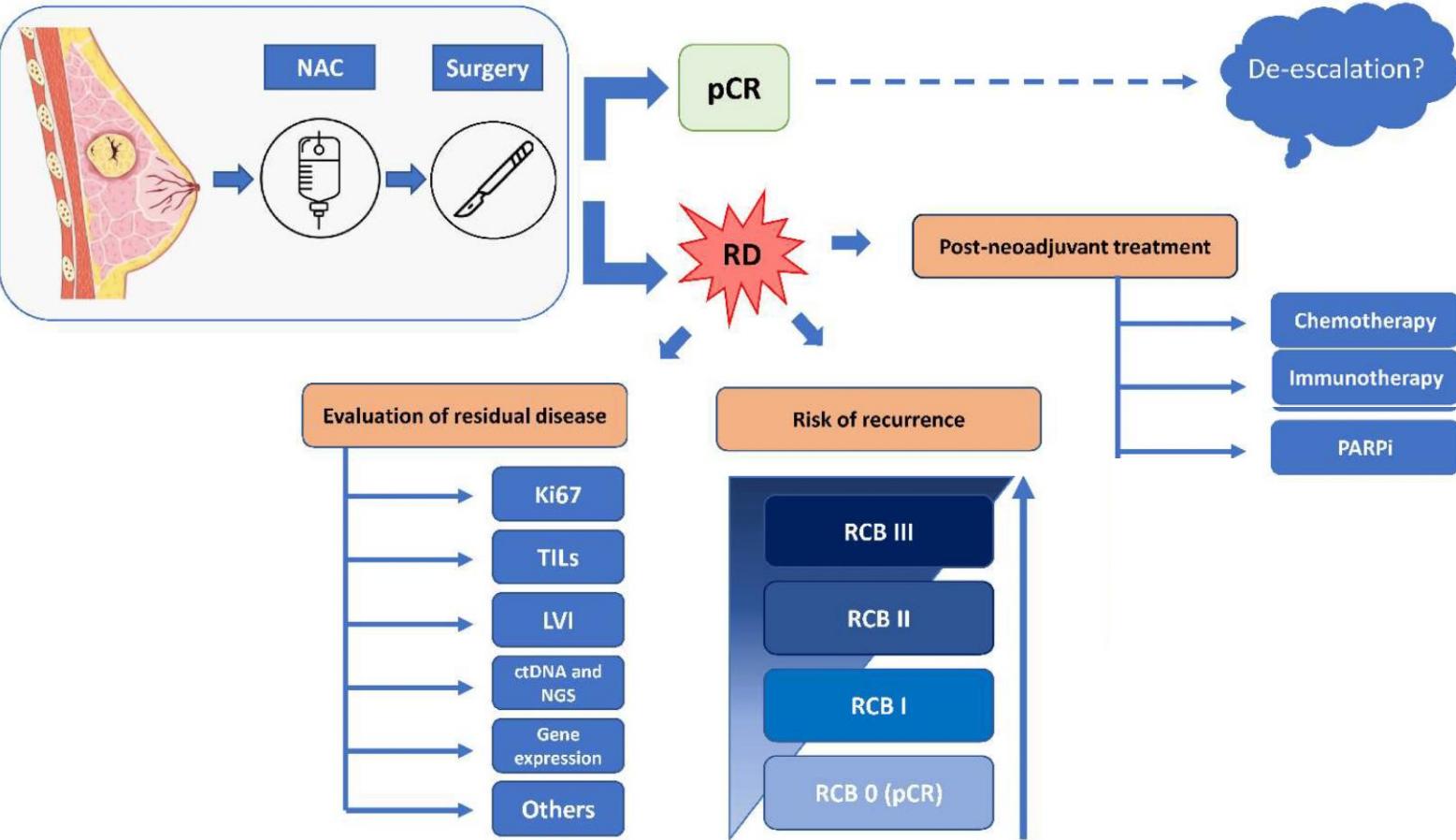


Can we reduce the Use of Anthracyclines?

NeoPACT: Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in TNBC



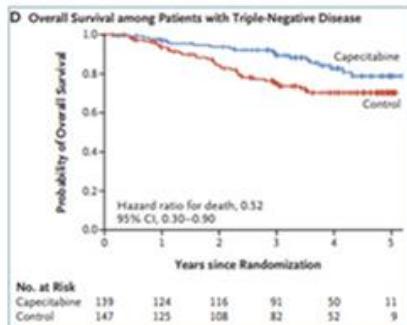
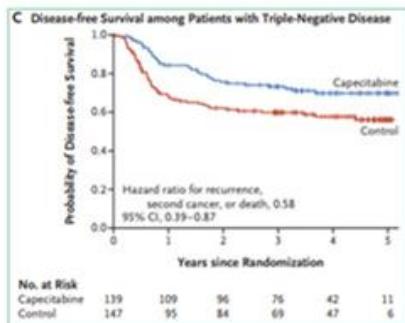
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CREATE-X Adjuvant Capecitabine in TNBC

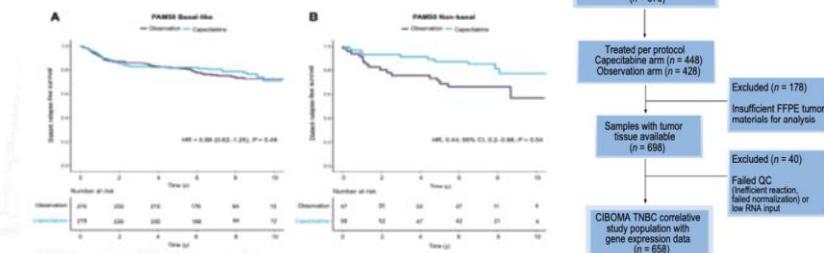
- Capecitabine 1250 mg/m² bid x 6-8 cycles vs control (N=910)
- 32% TNBC (N=286)
- 95% received anthracycline and taxane neoadjuvant therapy
- Preselected for poor prognosis



Masuda N et al. NEJM 376:22 2017

Triple-Negative PAM50 Non-Basal Breast Cancer Subtype Predicts Benefit from Extended Adjuvant Capecitabine

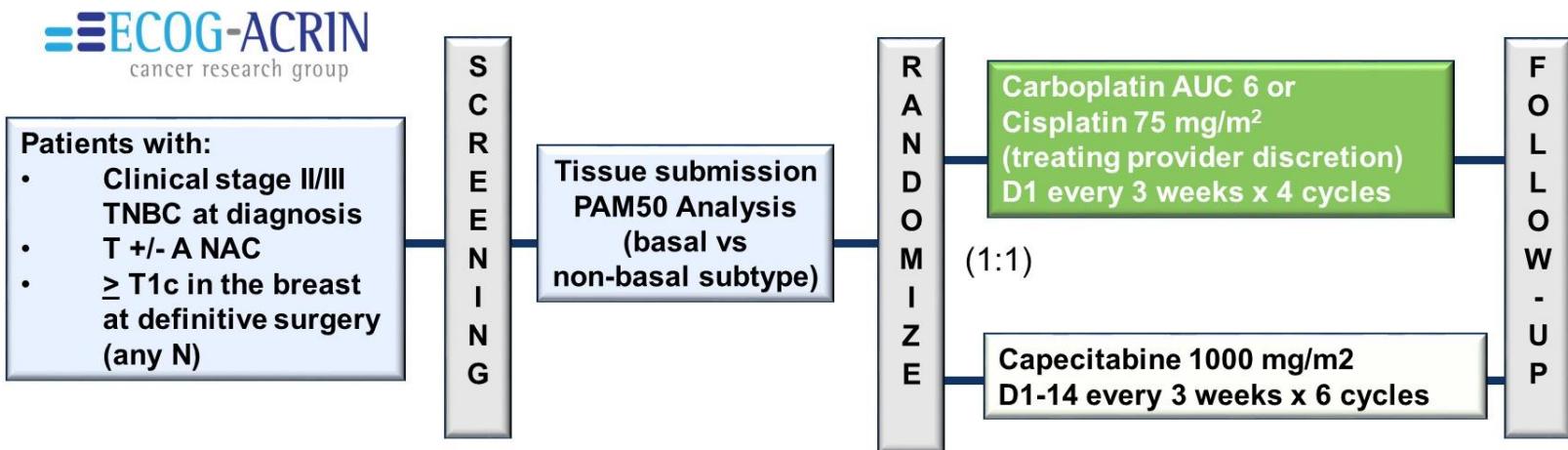
Karama Asleh^{1,2}, Ana Lluch^{1,4,5}, Angela Goytai¹, Carlos Barrios^{6,7}, Xue Q. Wang¹, Laura Torrecillas^{7,8}, Dongxia Gao¹, Manuel Ruiz-Borrego^{3,9}, Samuel Leung¹, José Bines^{2,10}, Ángel Guererro-Zotano^{3,11}, José Ángel García-Sáenz^{3,12}, Juan Miguel Cejalvo^{3,4,5}, Jesús Herranz³, Roberto Torres^{7,13}, Juan de la Haba-Rodríguez^{3,14,15}, Francisco Ayala^{3,16}, Henry Gómez^{7,17,18}, Federico Rojo^{3,19,20}, Torsten O. Nielsen¹, and Miguel Martín^{1,20,21}



Asleh K et al, Clin Cancer Res 2022



EA 1131 ECOG-ACRIN Adjuvant Capecitabine



N=410 (planned 775)

Primary endpoint- iDFS in pts with basal subtype TNBC



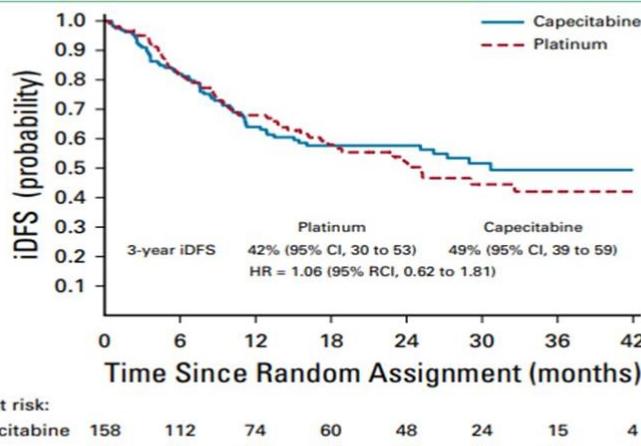
EA 1131 ECOG-ACRIN Adjuvant Capecitabine

5th interim analysis

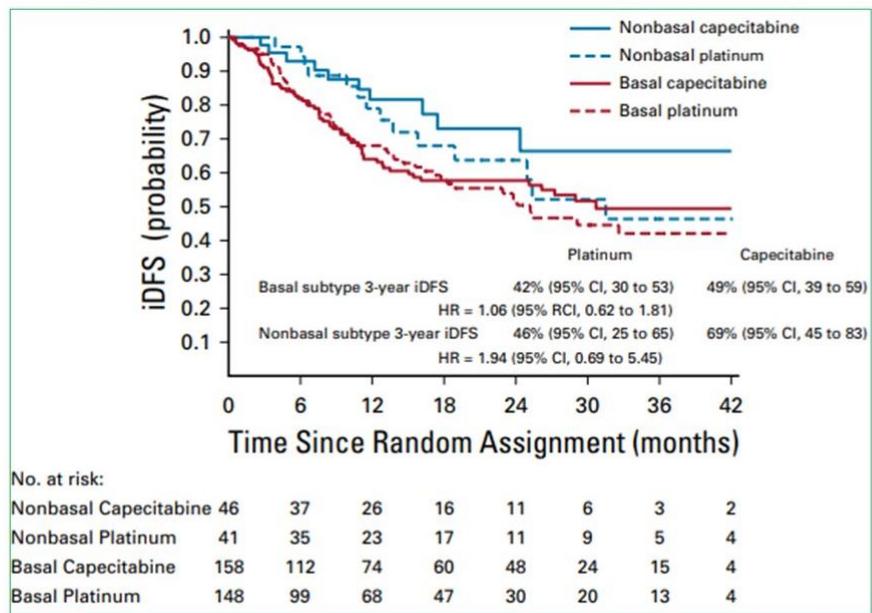
HR for platinum/capecitabine 1.09 (0.62-1.90)

The study was stopped on 3/25/2021

3-year iDFS-Basal subtype

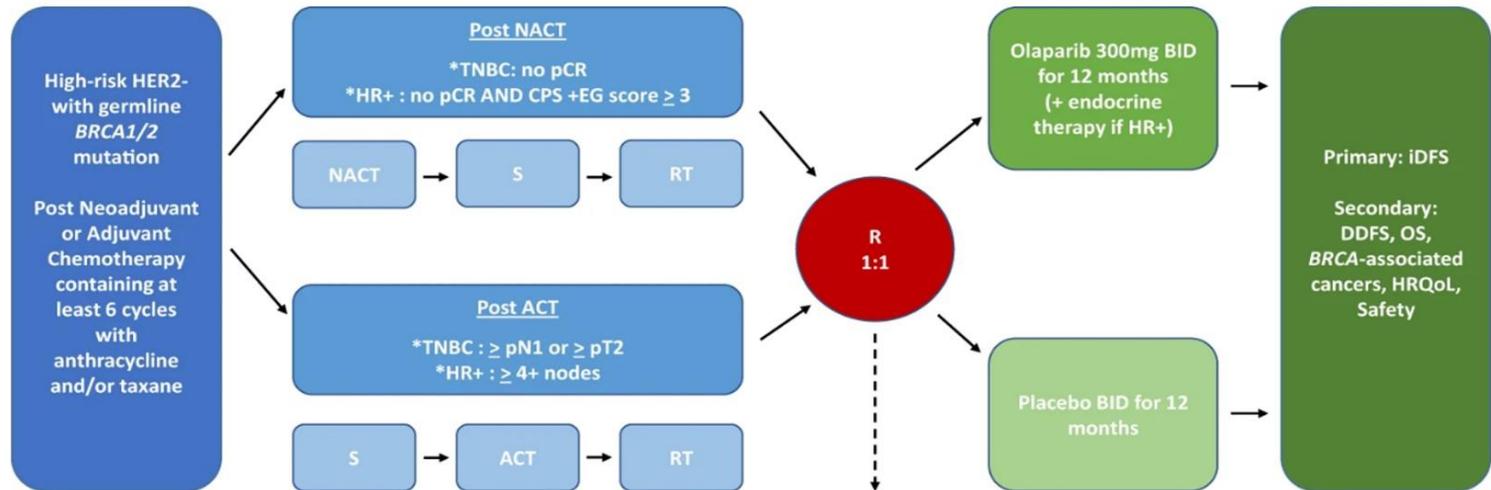


3-year iDFS by Treatment and Intrinsic Subtype





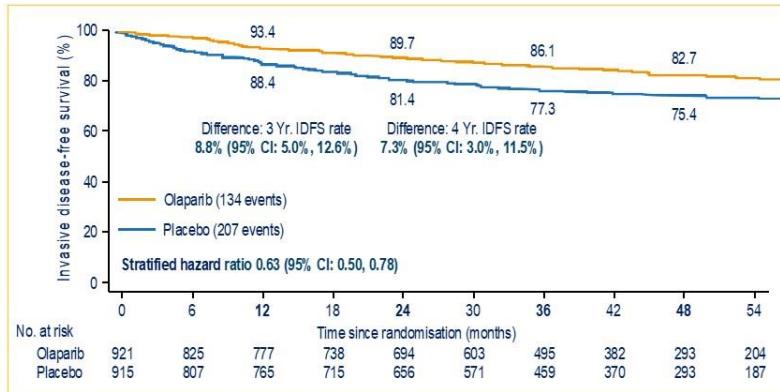
OlympiA: Adjuvant Olaparib for gBRCA1/2



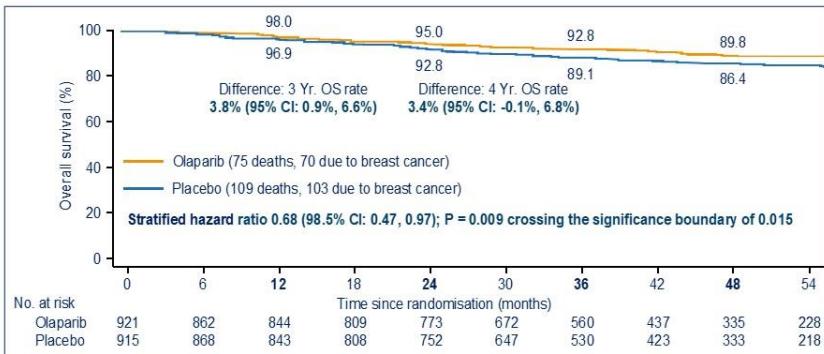
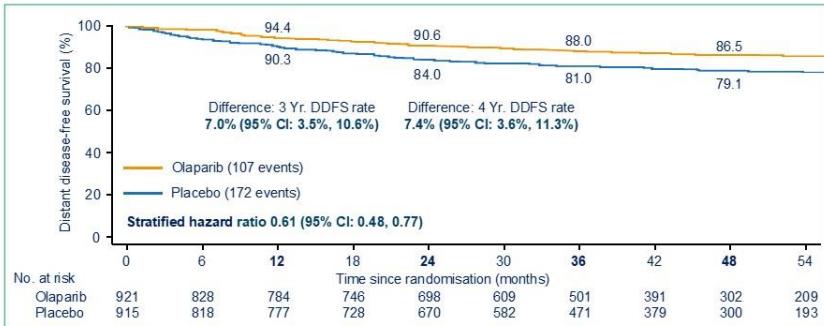
- 72% BRCA1, 82% TNBC
- 50% post NACT



OlympiA 3.5 years of median follow-up



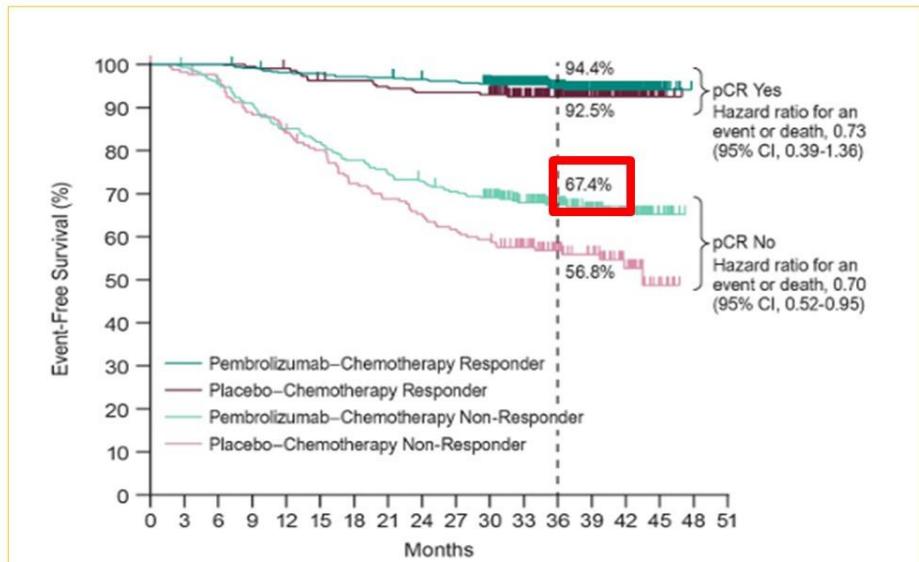
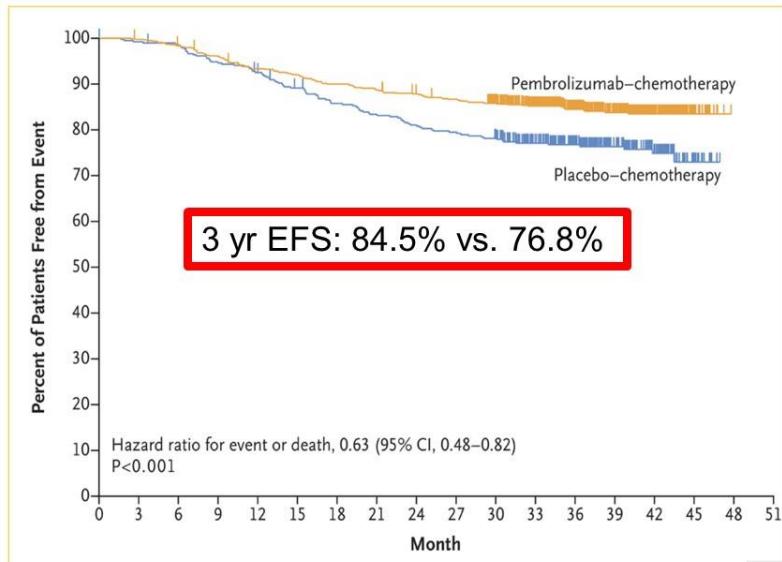
- No increase in MDS/AML compared to placebo
- Most toxicity grade 1/2; nausea most common
- Grade 3: Anemia 9%, fatigue 2%, neutropenia 5%





KEYNOTE-522

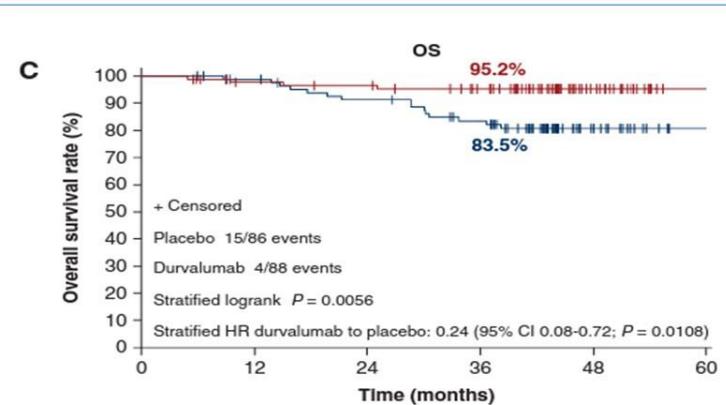
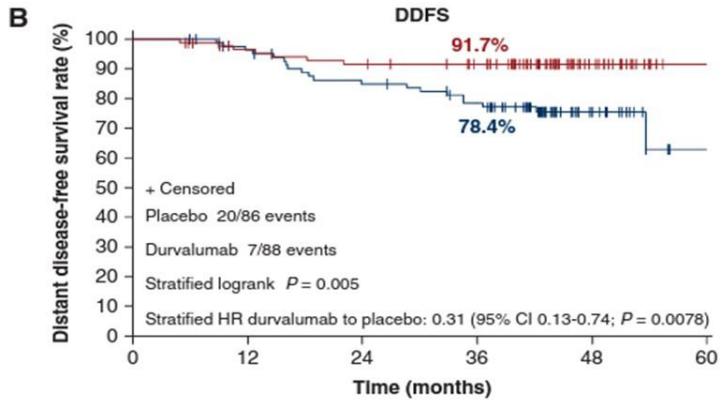
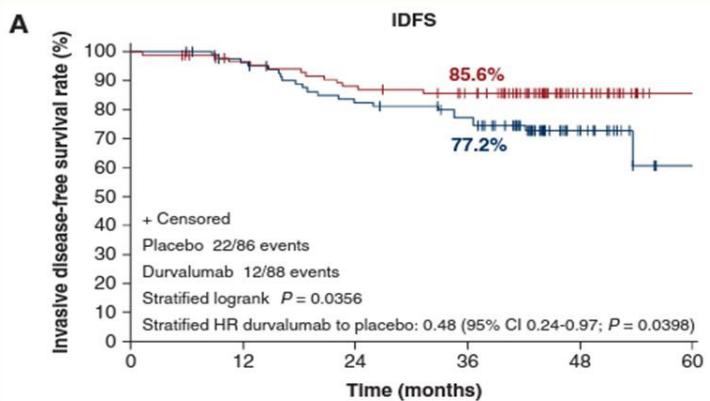
N=1174, Stage II-III TNBC
Neoadjuvant Carboplatin/taxol-AC/EC
Neoadjuvant and Adjuvant Pembrolizumab
vs. Placebo
Adjuvant Capecitabine not allowed





GeparNuevo

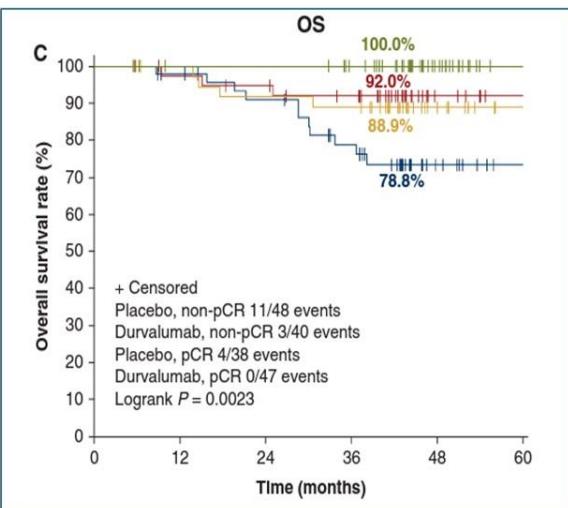
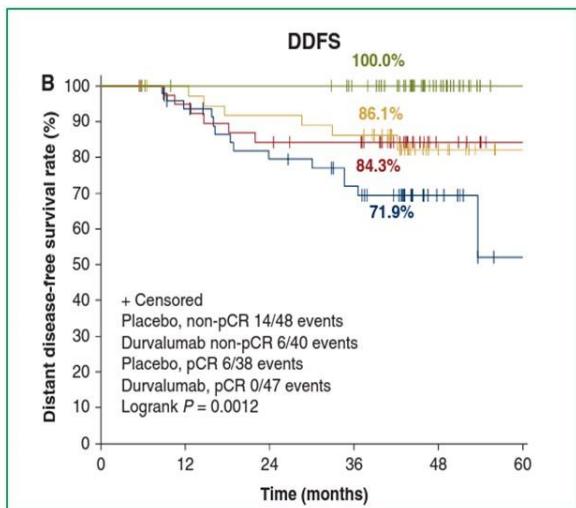
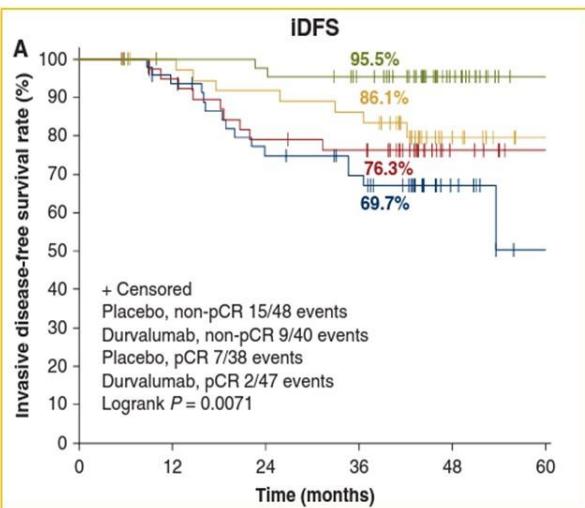
N=174, randomized Phase II
 Nab-paclitaxel-EC +Durvalumab/Placebo
 (Neoadjuvant only)
 Primary Endpoint: pCR
 pCR 53.4% vs 44.2% (Durva vs placebo)





GeparNuevo

- pCR Durvalumab
- pCR Placebo
- Non-pCR Durvalumab
- Non-pCR Placebo





Safety data of combination with immunotherapy

Open access

Original research



Phase II study of pembrolizumab and capecitabine for triple negative and hormone receptor-positive, HER2-negative endocrine-refractory metastatic breast cancer

Ami N Shah ,¹ Lisa Flaum,¹ Irene Helenowski,¹ Cesar A Santa-Maria,² Sanika Jain,¹ Alfred Rademaker,¹ Valerie Nelson,¹ Dean Tsarwhas,¹ Massimo Cristofanilli,¹ William Gralishar¹

Cancer Cell

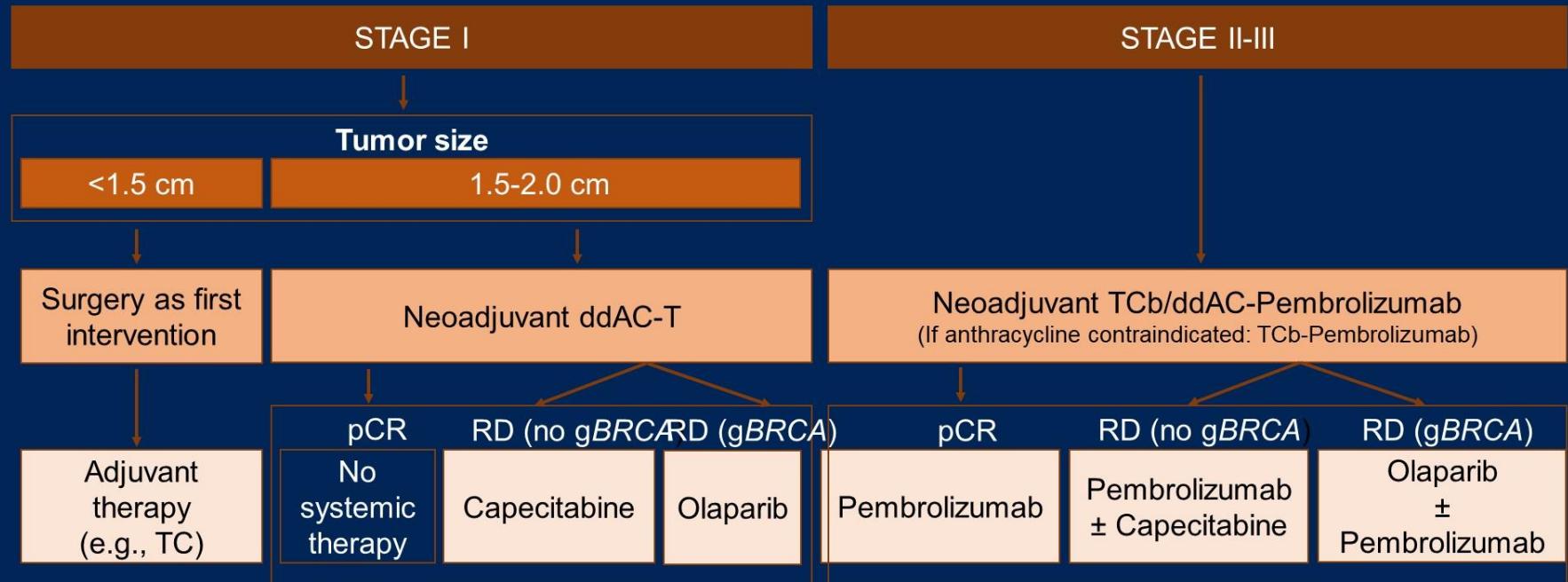
CellPress

Article

Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: Results from the adaptively randomized I-SPY2 trial

Lajos Pusztai,^{1,23,*} Christina Yau,² Denise M. Wolf,³ Hyo S. Han,⁴ Lili Du,⁵ Anne M. Wallace,⁶ Erica String-Reasor,⁷ Judy C. Boughey,⁸ A. Jo Chien,² Anthony D. Elias,⁹ Heather Beckwith,¹⁰ Rita Nanda,¹¹ Kathy S. Albain,¹² Amy S. Clark,¹³ Kathleen Kemmer,¹⁴ Kevin Kalinsky,¹⁵ Claudine Isaacs,¹⁶ Alexandra Thomas,¹⁷ Rebecca Shatsky,¹⁸ Theresa L. Helsten,¹⁸ Andres Forero-Torres,⁷ Minetta C. Liu,¹⁹ Lamorna Brown-Swigart,³ Emmanuel F. Petricoin,¹⁹ Julia D. Wulfkuhle,¹⁹ Smita M. Asare,²⁰ Amy Wilson,²⁰ Ruby Singhrao,²¹ Laura Sit,² Gillian L. Hirst,² Scott Berry,²¹ Ashish Sanil,²¹ Adam L. Asare,²⁰ Jeffrey B. Matthews,⁷ Jane Perlmutter,²² Michelle Melisko,² Hope S. Rugo,² Richard B. Schwab,¹⁸ W. Fraser Symmans,⁵ Doug Yee,¹⁰ Laura J. van't Veer,² Nola M. Hylton,² Angela M. DeMichele,¹³ Donald A. Berry,²¹ and Laura J. Esserman²

Treatment Algorithm for Early-Stage TNBC

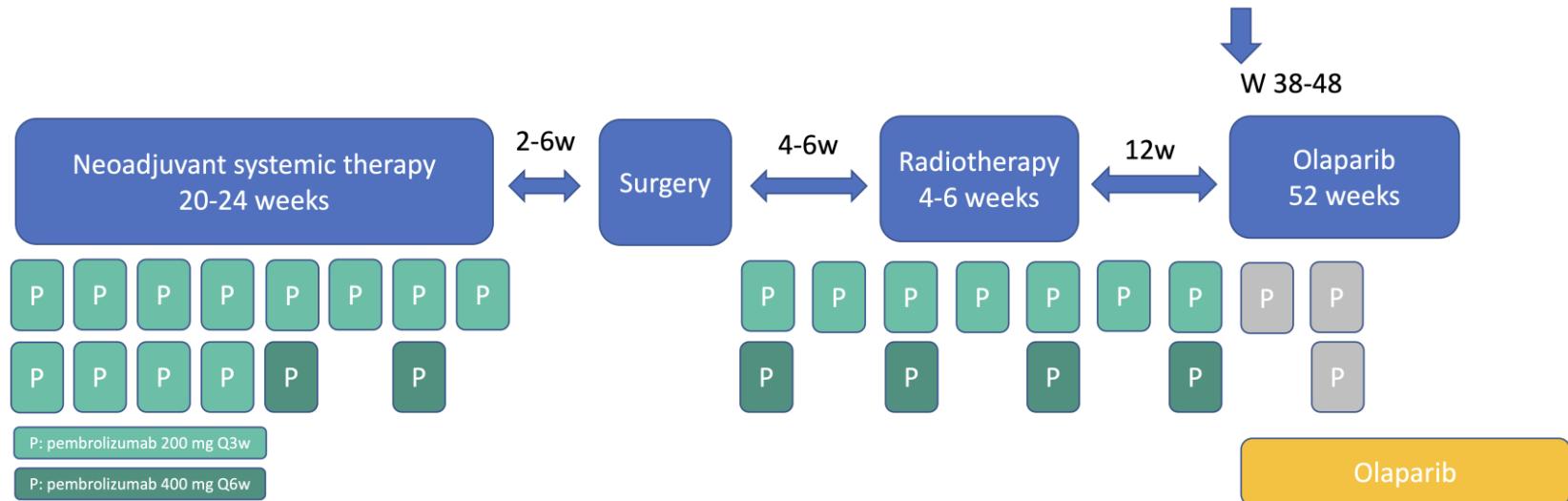




OVERLAPPING INDICATIONS IN THE ADJUVANT SETTING

Olaparib and Pembrolizumab: Option for sequential approach?

- In Olympia, olaparib could be initiated up to 12 weeks after the last local treatment

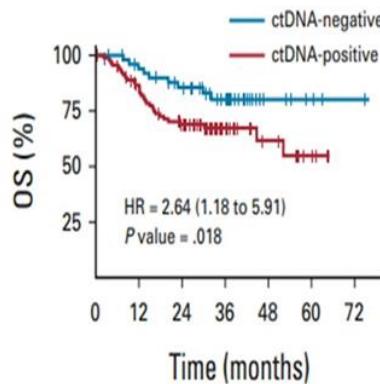
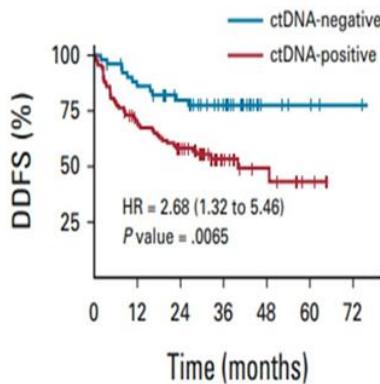
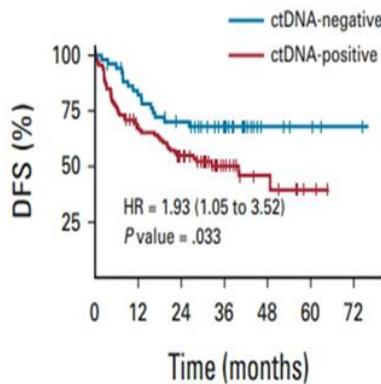




BRE12-158: A Postneoadjuvant, Randomized Phase II Trial of Personalized Therapy Versus Treatment of Physician's Choice for Patients With Residual TNBC

Biomarker ctDNA : BRE 12-158

Phase 2 randomized trial of genetically directed therapy after preop chemotherapy for TNBC patients



No. at risk:

Negative	53	41	33	23	6	4	1
Positive	93	59	44	18	7	2	0

No. at risk:

Negative	53	43	35	25	6	4	1
Positive	93	61	47	19	8	3	0

No. at risk:

Negative	53	46	39	26	7	4	1
Positive	93	74	54	23	10	4	0



Take Home Messages

- Neoadjuvant chemotherapy with carboplatin, taxane, and anthracycline-based regimens with pembrolizumab is currently considered SOC for patients with stage II-III TNBC (kN522).
 - In patients with contraindications to anthracycline chemotherapy, neoadjuvant therapy with carboplatin, taxane and pembrolizumab may be considered (NeoPACT)
-
- It's recommended to continue pembrolizumab in adjuvant setting for six months per KEYNOTE522 for both PCR and non PCR patient.
 - Combination therapy with pembrolizumab and capecitabine or olaparib can be considered for high-risk patients (non pCR), despite lack of randomized trial data.



FUTURE DIRECTIONS

Optimizing therapy – Escalation / De-escalation based on prognostic biomarkers.

Improved biomarkers needed beyond pCR particularly in the era of neoadjuvant therapy including checkpoint inhibitor:

- Tissue biomarkers
- Liquid biopsy: ctDNA to detect MRD (minimal residual disease)

New therapy – Antibody-Drug Conjugates (ADCs), Targeted therapies, Combinig agents with immune checkpoint inhibitors.

Her 2 low subtype.



GRACIAS

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