Updates in Triple Negative Breast Cancer

Shipra Gandhi, MD

Assistant Professor of Oncology

Roswell Park Comprehensive Cancer Center

Empire State Hematology and Oncology Review of San Antonio Breast Cancer Symposium

Disclosures

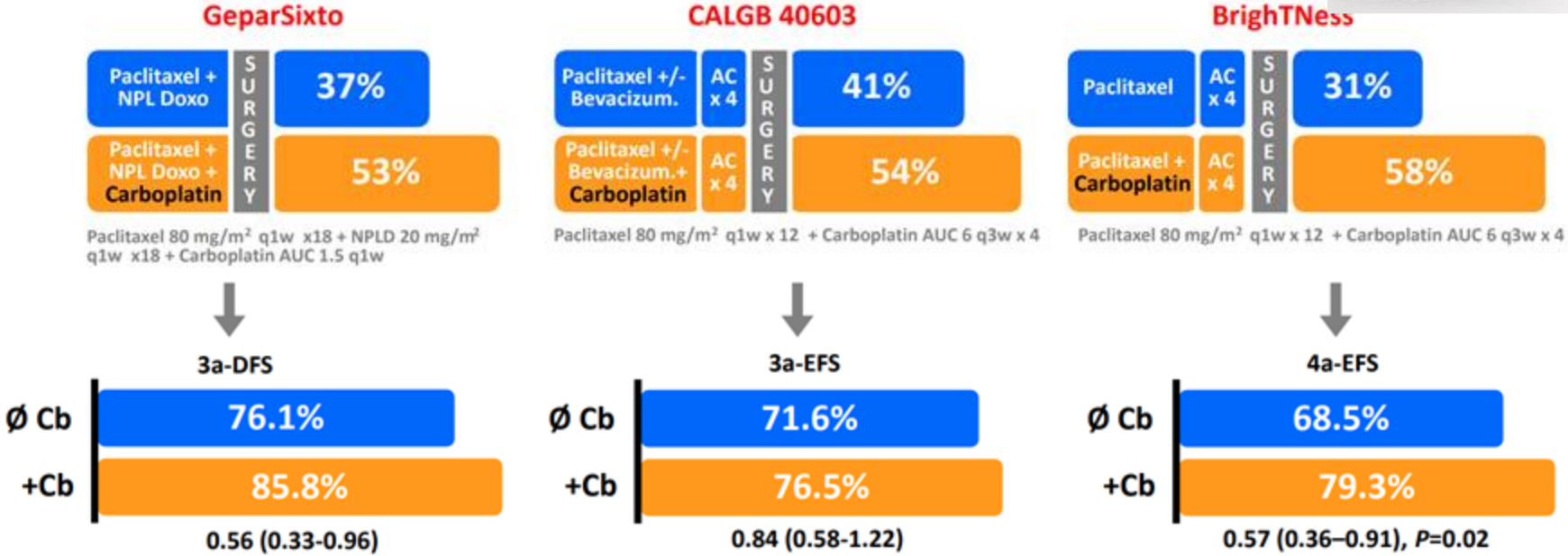
- Consulting - Astrazeneca

EARLY - STAGE

Role of platinum in TNBC

pCR Rates without Platinum around 35%

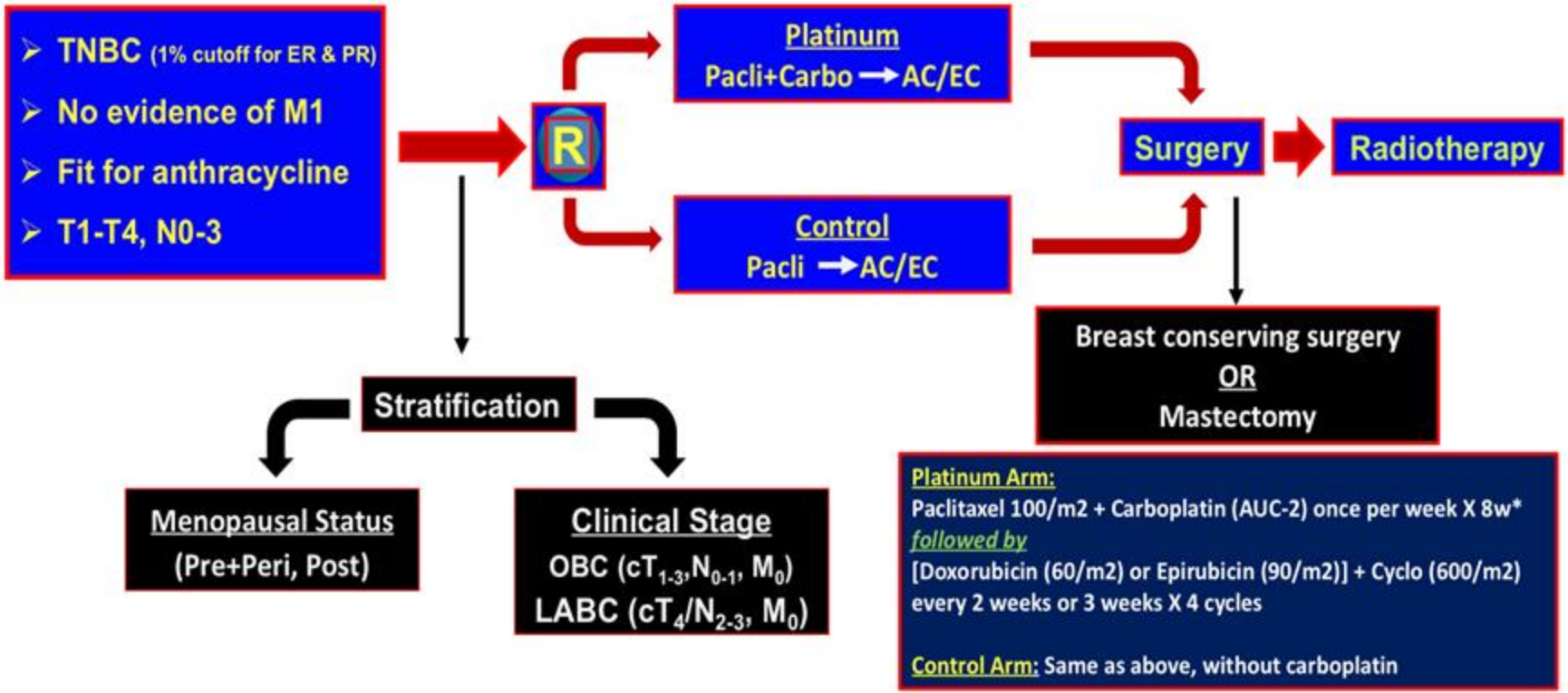
Carboplatin increases pCR rate to >50% with/without improvement in EFS and OS



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

Addition of platinum to sequential taxane-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: A phase III randomized controlled trial

Gupta S et al. SABCS 2022



*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

Gupta S et al. SABCS 2022

Study Design and Statistical Consideration

Primary endpoint: Event-free survival (EFS) defined by disease progression, relapse, second cancer or death due to any cause whichever was earliest.

Secondary endpoints: Overall survival (OS) and pathological complete response (pCR, ypT0 or Tis & ypN0) proportion.

Gupta S et al. SABCS 2022

Patient & Tumor Characteristics

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Age (years)			
Median (Range)			
≤ 50 years			
> 50 years			
Menopausal Status			
Pre- or Peri-menopausal			
Post-menopausal			
Family History of Any Cancer			
Yes			
No			

Patient & Tumor Characteristics

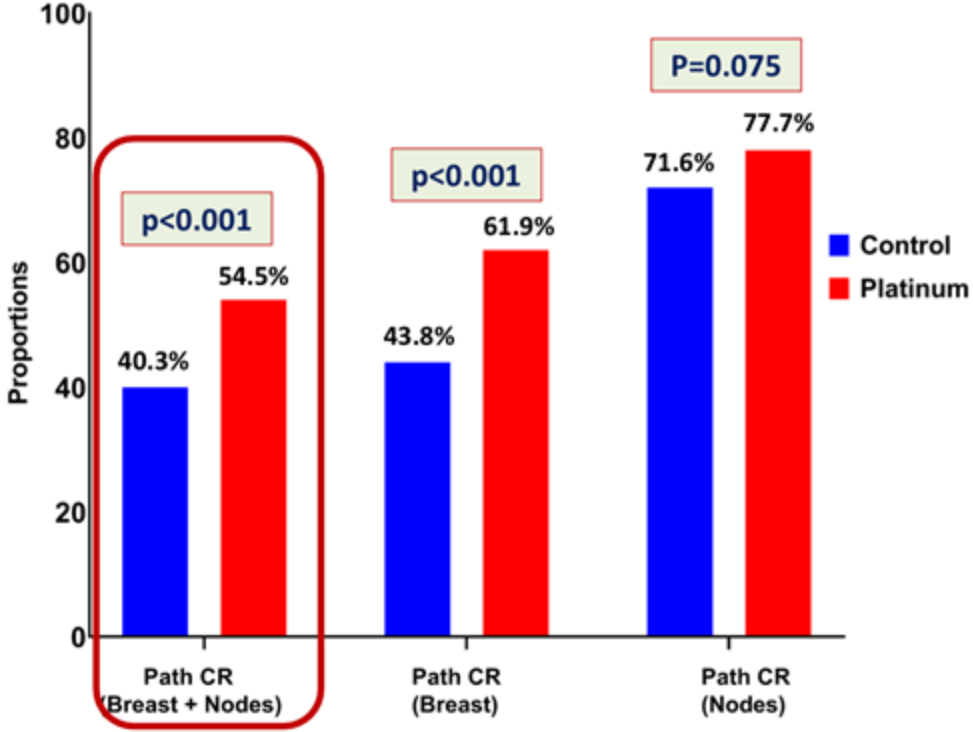
	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Receptor Status			
TNBC	356 (100%)	361 (100%)	717 (100%)
Other	0 (0%)	0 (0%)	0 (0%)
Pathological Subtype			
Invasive Duct Carcinoma	310 (87.1%)	331 (91.7%)	641 (89.4%)
Metaplastic	33 (9.3%)	22 (6.1%)	55 (7.7%)
Others	13 (3.7%)	8 (2.2%)	21 (2.9%)
Grade			
II	2 (0.6%)	3 (0.8%)	5 (0.7%)
III	354 (99.4%)	358 (99.2%)	712 (99.3%)

Patient & Tumor Characteristics

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Clinical Stage (pre-NACT)			
	9%)	143 (39.6%)	285 (39.7%)
	1%)	218 (60.4%)	432 (60.3%)
	%)	41 (11.4%)	80 (11.2%)
	0%)	320 (88.6%)	637 (88.8%)
	0.0)	6.0 (1.5-20.0)	6.0 (1.2-20.0)
	%)	81 (22.4%)	160 (22.3%)
	3%)	280 (77.6%)	557 (77.7%)

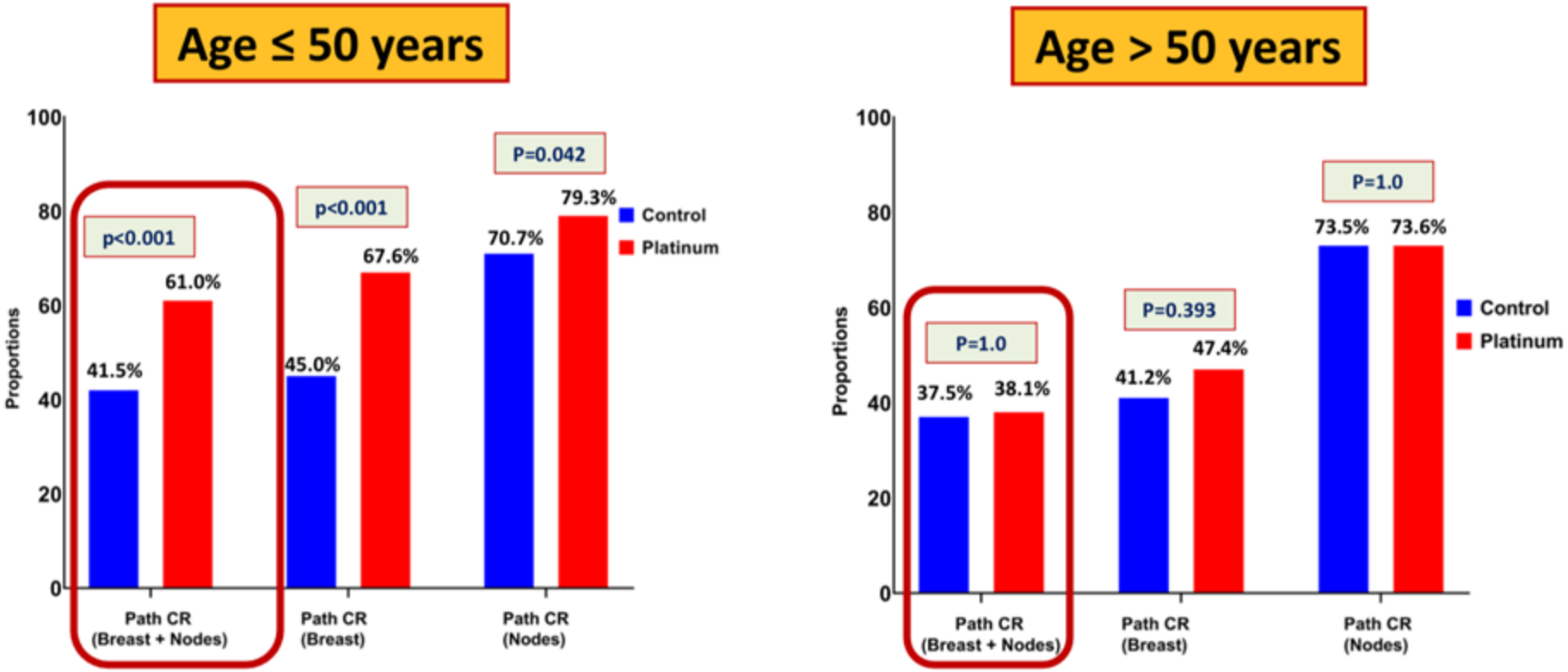
Gupta S et al. SABCS 2022

ITT: Pathological Response to NACT by Rx-Arm



Gupta S et al. SABCS 2022

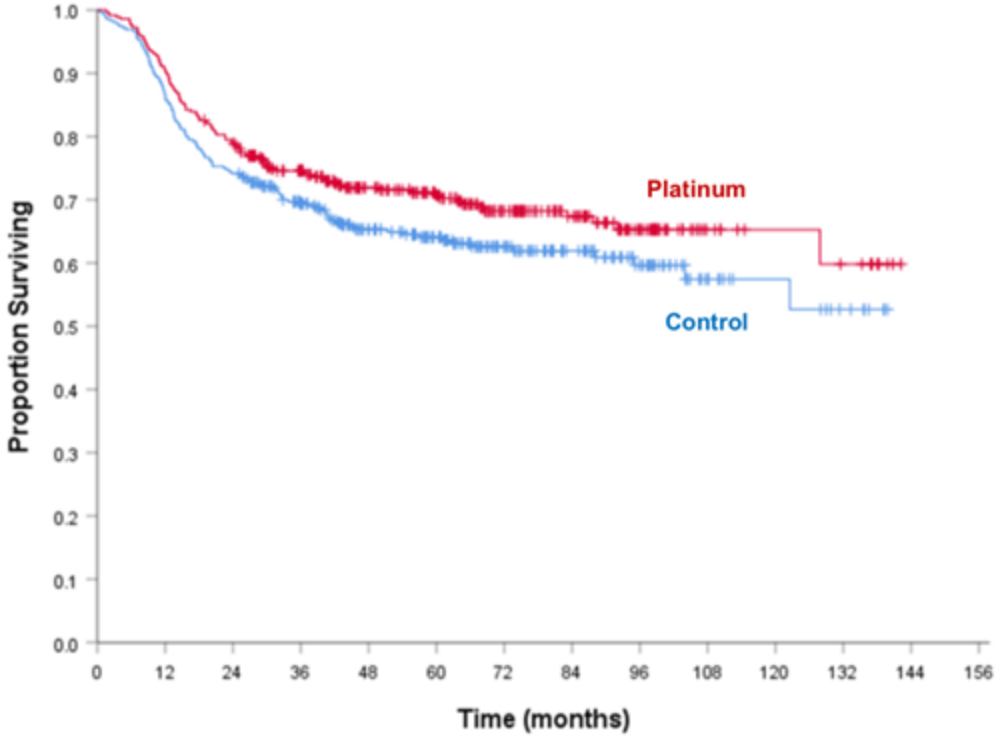
Pathological Response to NACT by Age & Rx-Arm



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

Gupta S et al. SABCS 2022

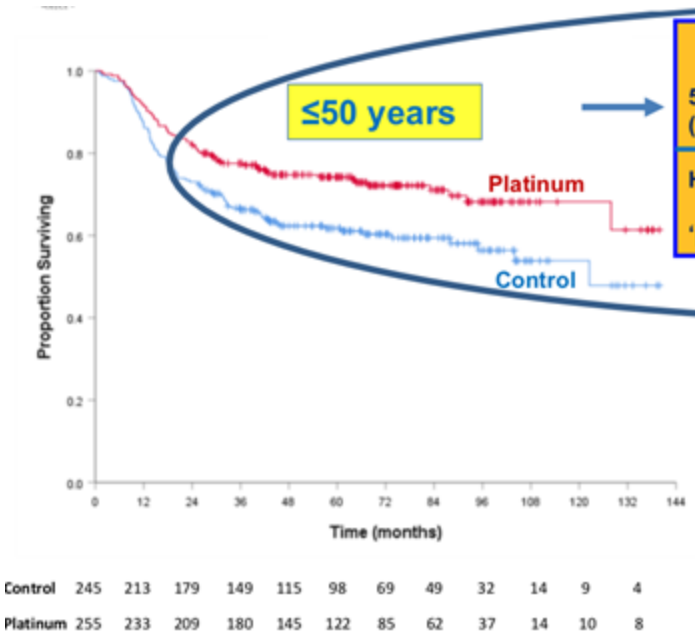
Event-free Survival in ITT (N=717)



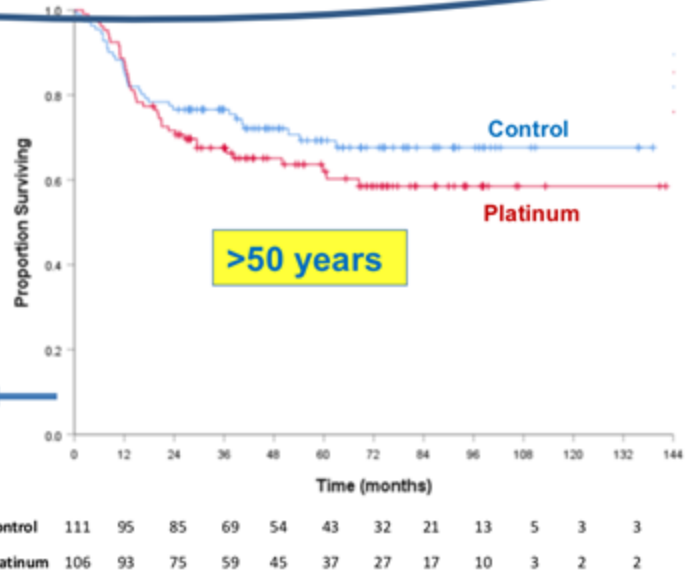
Control	356	308	264	218	169	141	101	70	45	19	12	7
Platinum	361	326	284	239	190	159	112	79	47	17	12	10

Gupta S et al. SABCS 2022

Event Free Survival in Younger and Older Patients



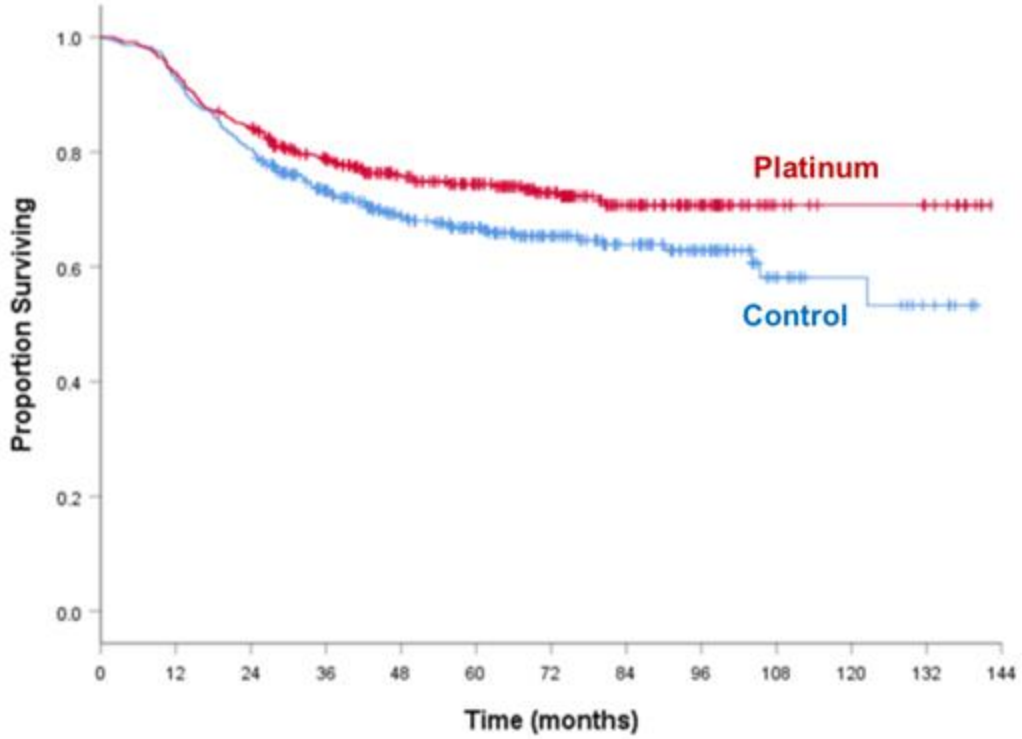
	Platinum	Control
5-year EFS (95% CI)	74.2% (68.71 - 79.69%)	61.7% (55.43 - 67.97%)
HR (95% CI)	0.642 (0.473 - 0.871)	
'p'	0.004	



	Platinum	Control
5-year EFS (95% CI)	62.0% (52.2 - 71.8%)	69.3% (60.28 - 78.32%)
HR (95% CI)	1.309 (0.825-2.076)	
'p'	0.253	

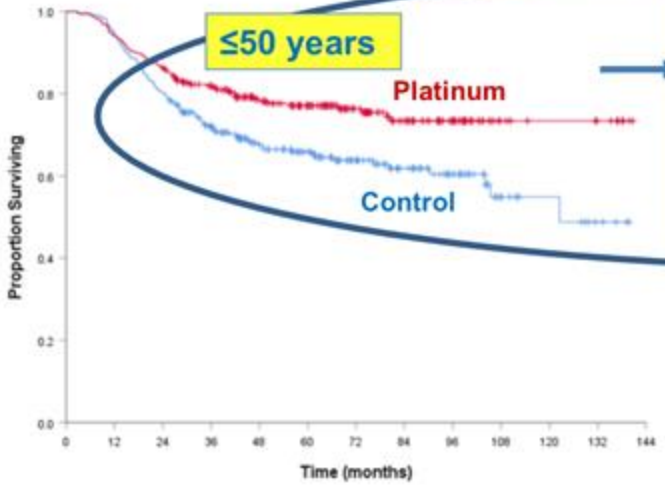
Gupta S et al. SABCS 2022

Overall Survival in ITT (N=717)



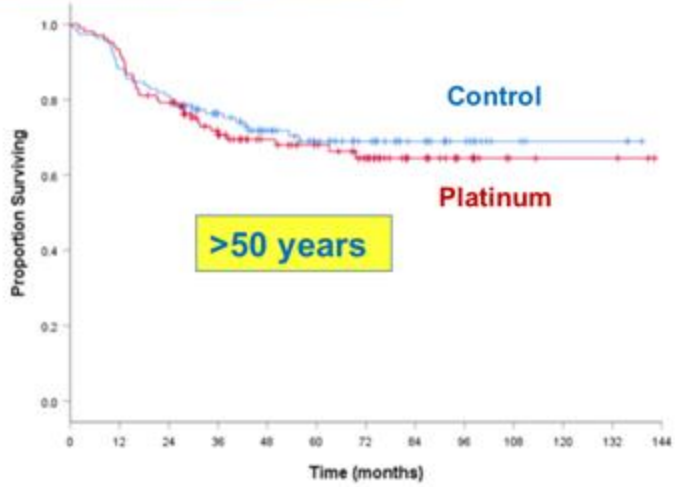
Control	356	330	287	229	179	147	106	74	48	20	12	7
Platinum	361	339	303	252	201	168	122	83	51	19	14	12

Gupta S et al. SABCS 2022



	Platinum	Control
5-year OS (95% CI)	77.1% (71.81 - 82.39%)	65.9% (59.82 - 71.98%)
HR (95% CI)	0.611 (0.440 - 0.848)	
'p'	0.003	

Control	245	232	197	160	125	104	74	53	35	15	9	4
Platinum	255	240	220	190	153	127	91	64	40	15	11	9

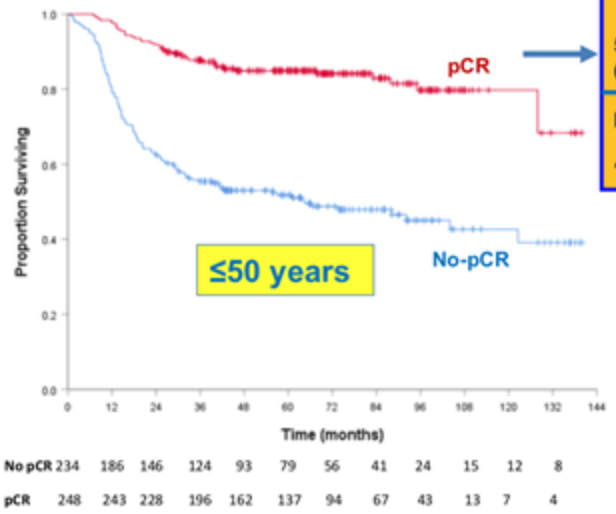


	Platinum	Control
5-year OS (95% CI)	68.0% (58.79 - 77.21%)	68.9% (59.69 - 78.11%)
HR (95% CI)	1.132 (0.698 - 1.835)	
'p'	0.615	

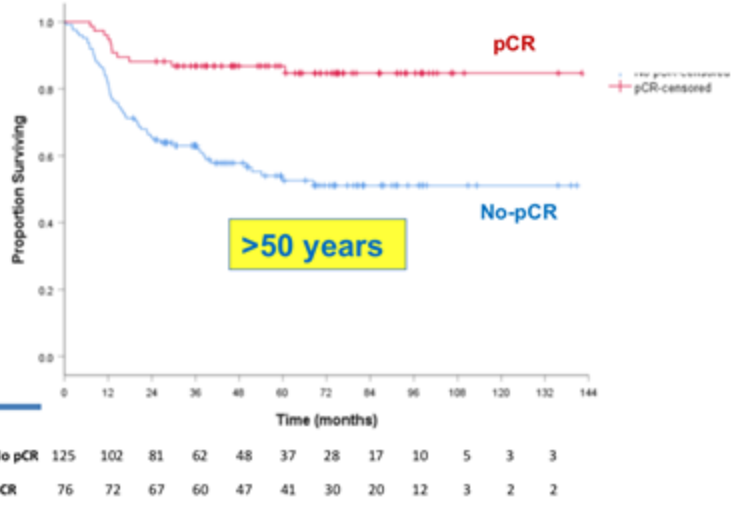
Control	111	98	90	69	54	43	32	21	13	5	3	3
Platinum	106	99	83	62	48	41	31	19	11	4	3	3

Gupta S et al. SABCS

Prognostic impact of pathological complete response in younger and older patients



	pCR (ypT0/is ypN0)	No-pCR
5-year EFS (95% CI)	84.9% (80.39 - 89.41%)	51.8% (45.33 - 58.27%)
HR (95% CI)	0.248 (0.174 - 0.353)	
'p'	<0.001	



	pCR (ypT0/is ypN0)	No-pCR
5-year EFS (95% CI)	86.8% (79.16 - 94.44%)	52.6% (43.19 - 62.01%)
HR (95% CI)	0.258 (0.135 - 0.493)	
'p'	<0.001	

Gupta S et al. SABCS

Compliance to Neoadjuvant Chemotherapy

	Platinum (N=361)	Control (N=356)
Completed 8 cycles of Weekly Paclitaxel or Weekly Paclitaxel-Carboplatin	341 (94.5%)	346 (97.2%)
Completed 12 cycles of NACT (8# weekly taxane +/- platinum followed by 4# AC/EC)	280 (77.6%)	285 (80.1%)

Treatment compliance and toxicity were not different in younger and older patients.

Gupta S et al. SABCS

CONCLUSIONS

- Addition of carboplatin to sequential taxane-anthracycline neoadjuvant chemotherapy significantly improves overall survival and tends to improve event-free survival among patients with operable and locally-advanced TNBC.
  - The benefit seems confined to younger or premenopausal patients in whom there is substantial and significant improvement in EFS and OS.
- Increased pCR with carboplatin is predictive of EFS and OS benefit in younger patients ***AND*** lack of improvement in pCR is predictive of lack of EFS and OS benefit in older patients.

Gupta S et al. SABCS

CONCLUSIONS

- The precise reasons for interaction between age/menopausal status and carboplatin are unclear.
- Our survival results are concordant with GeparSixto and BrighTNess studies but discordant with CALGB 40603.
  - We used weekly carboplatin in all patients in the platinum arm (like GeparSixto) which likely increased compliance and reduced toxicity.
  - We used the standard chemotherapy backbone of taxane, anthracycline and cyclophosphamide.
  - We did not use bevacizumab or PARP inhibitors.

Gupta S et al. SABCS 2022

CONCLUSIONS

Addition of carboplatin to taxa… …nthracycline neoadjuvant chemothera… …ould be the standard treatment in patient… …TNBC who are ≤50 years or who are pre-m… …ausal.

PRACTICE CHANGING !!!!

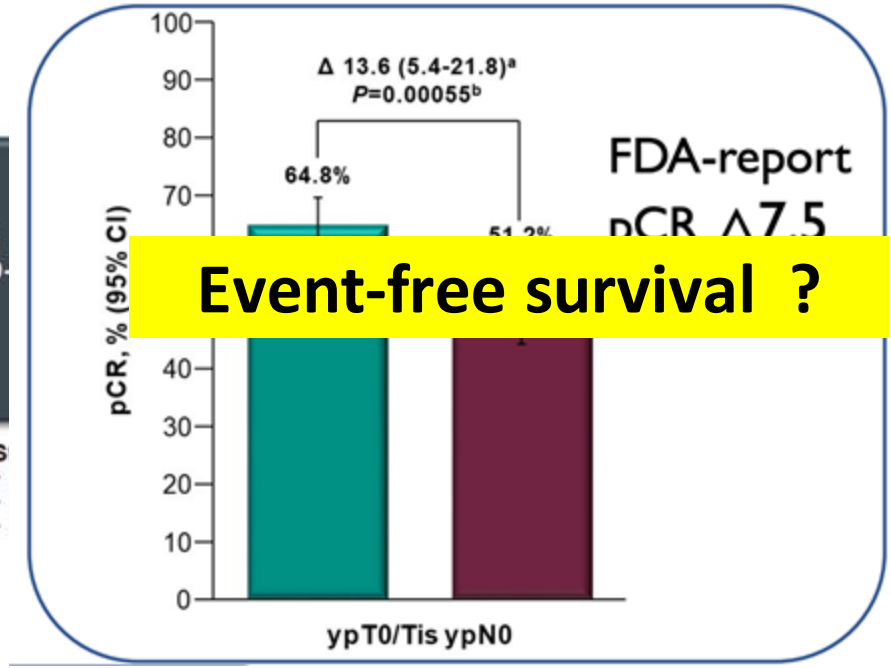
Gupta S et al. SABCS 2022

KEYNOTE-522

Neoadjuvant Phase → Adjuvant Phase

Key Eligibility Criteria

- Age ≥18 years
- Newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-
- ECOG PS 0-1
- Tissue sample for PD-L1 assessment[a]



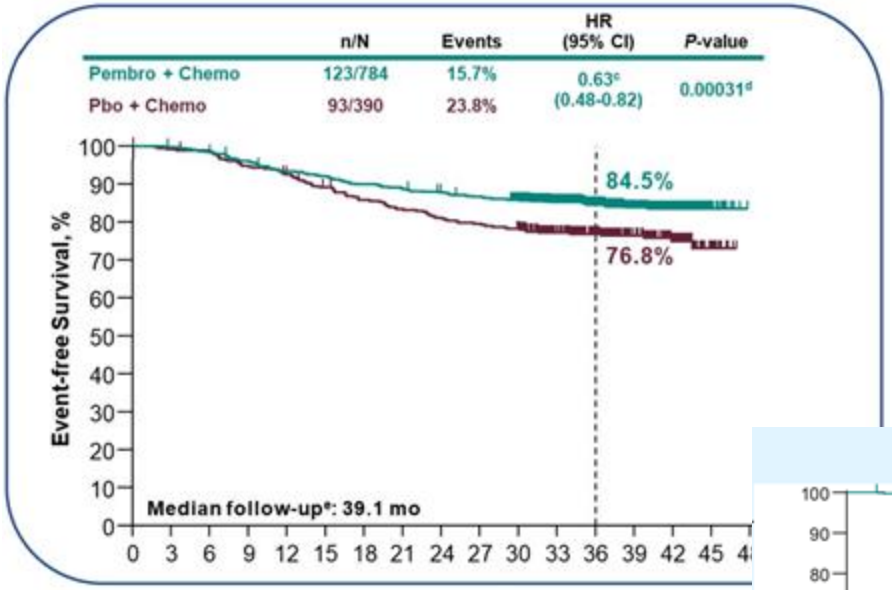
FDA-report
pCR Δ7.5

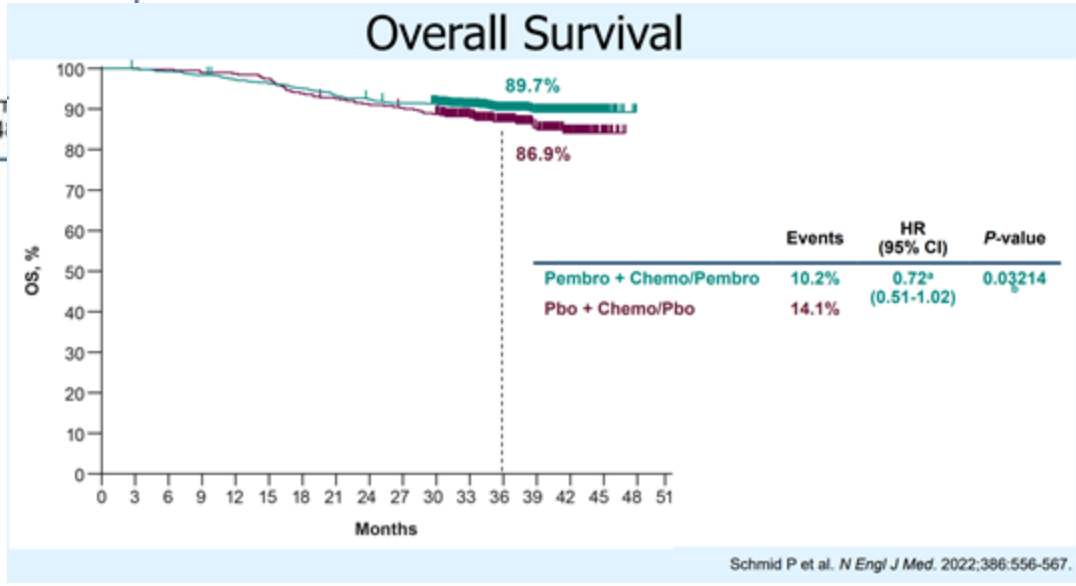
Event-free survival ?

Adjuvant Treatment
(cycles 1-9; 27 weeks)

- Pembrolizumab 200 mg Q3W
- Placebo

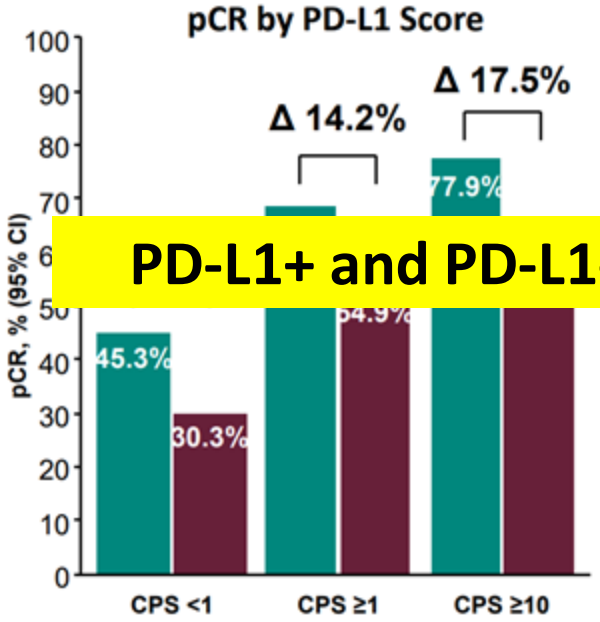
Schmid P et al. NEJM 2022



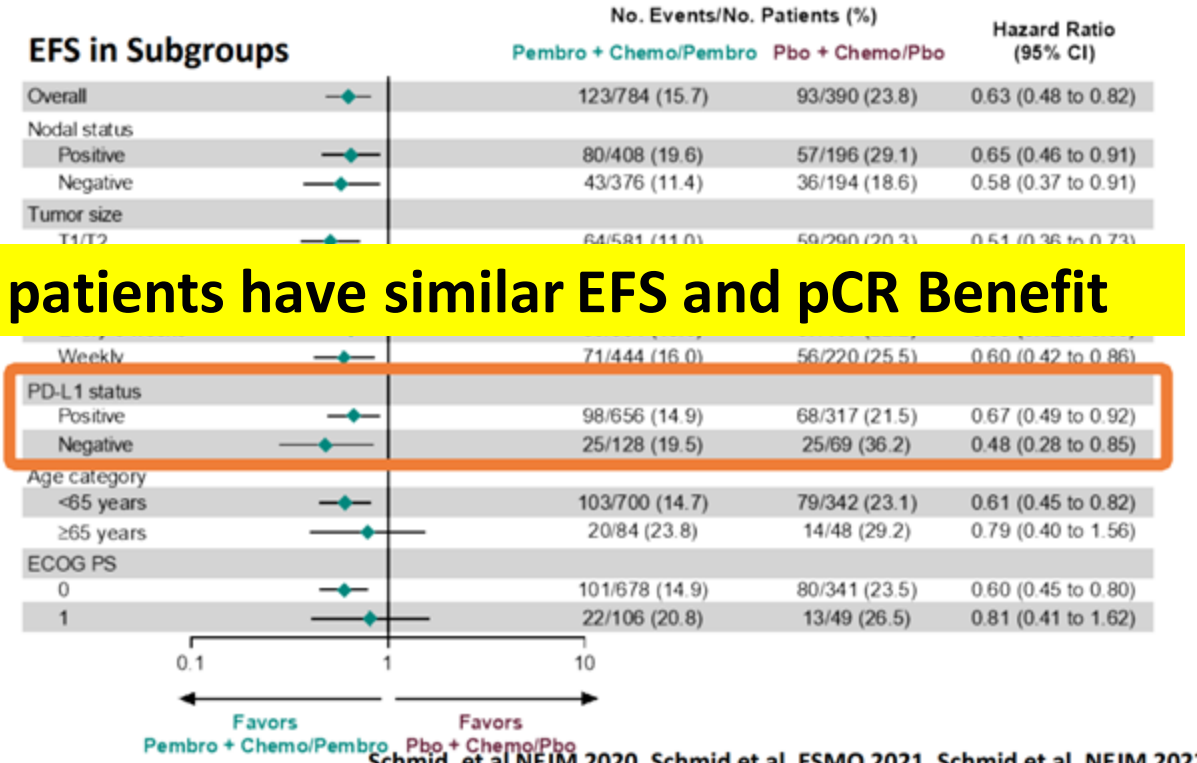


Schmid P et al. NEJM 2022

PD-L1 Status and Benefit from Immunotherapy



PD-L1+ and PD-L1- patients have similar EFS and pCR Benefit



Schmid, et al NEJM 2020, Schmid et al, ESMO 2021, Schmid et al, NEJM 2022

KEYNOTE 522

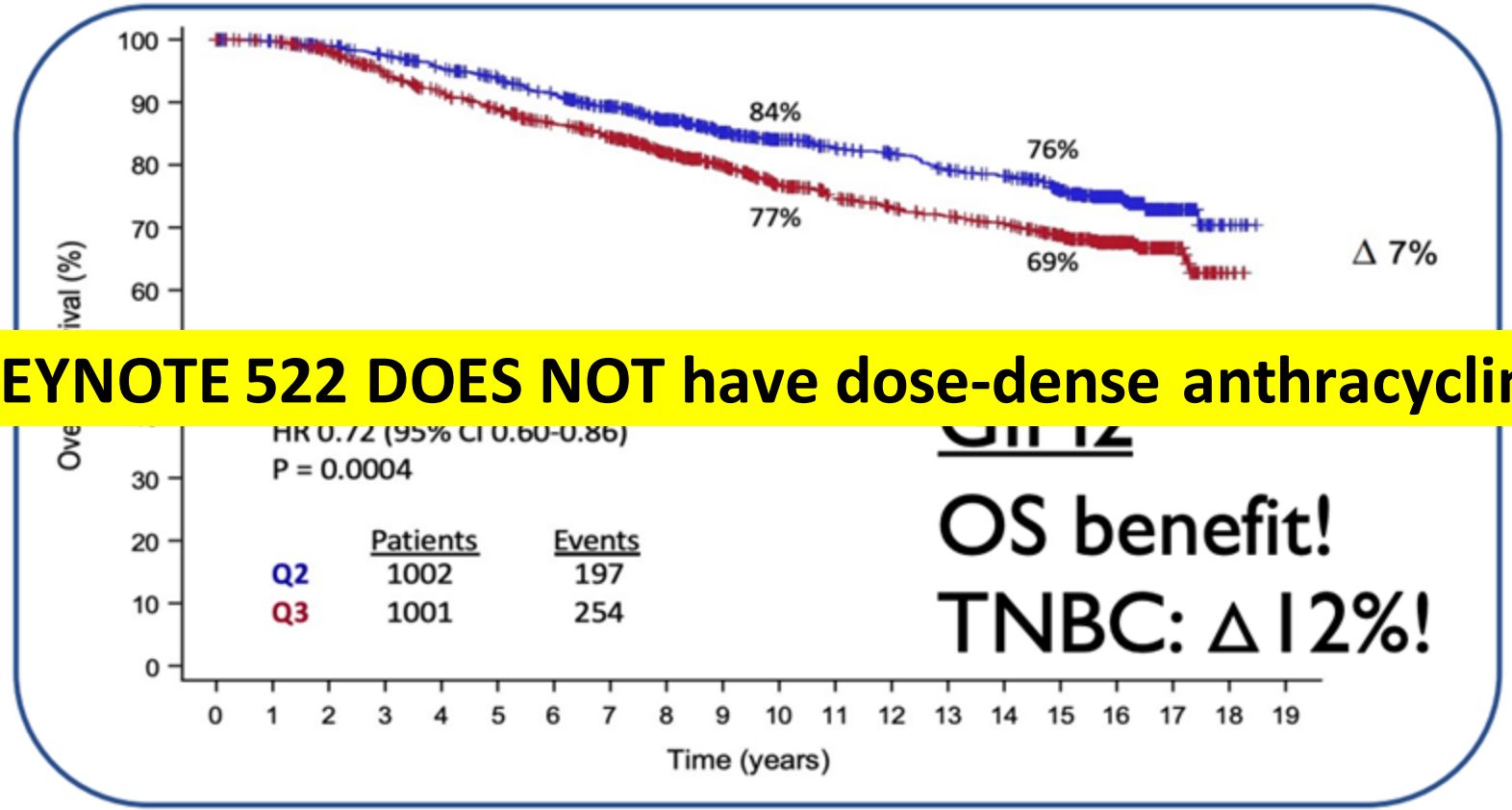
Every 3 weeks doxorubicin and cyclophosphamide

RESIDUAL DISEASE

No olaparib

No capecitabine

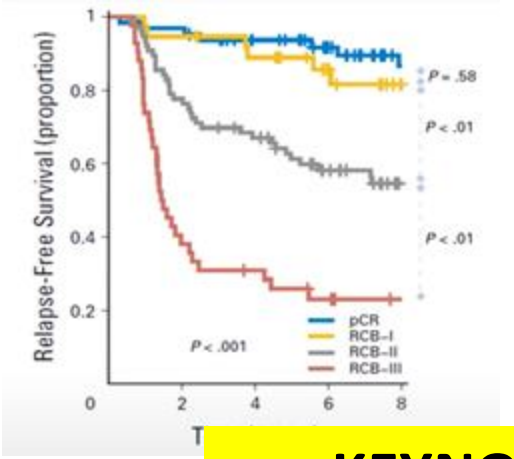
Personal communication from Gandhi S.

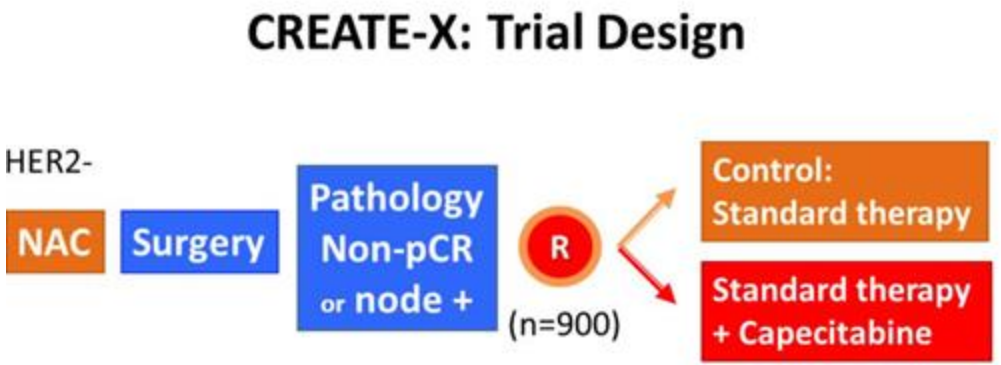


KEYNOTE 522 DOES NOT have dose-dense anthracyclines

De Mastro et al. Lancet Oncol 2022

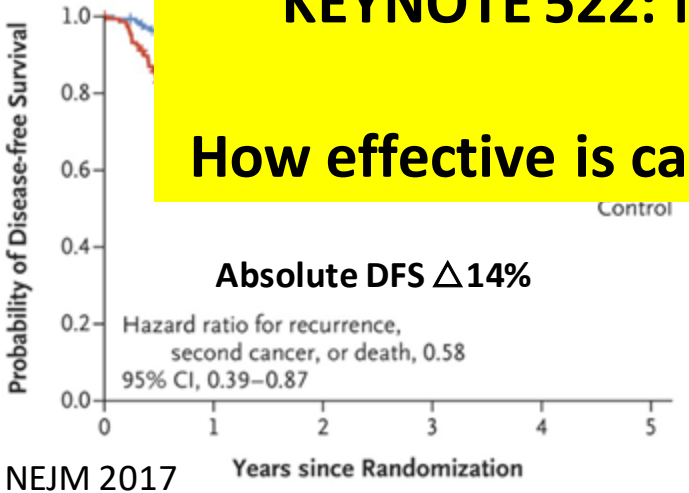
Adjuvant capecitabine improves outcomes in patients with residual TNBC



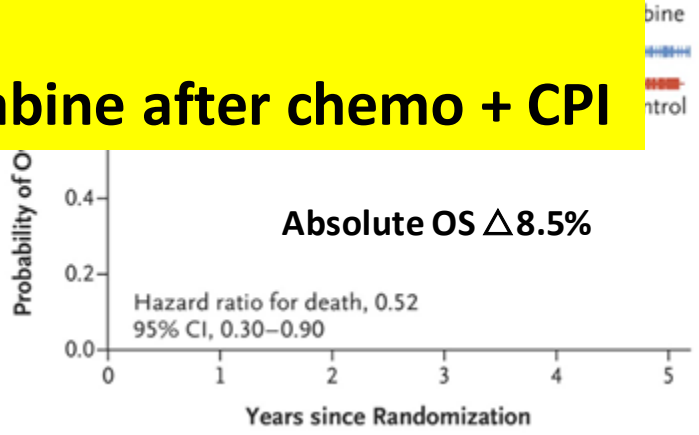


KEYNOTE 522: NO adjuvant capecitabine

How effective is capecitabine after chemo + CPI



?



Masuda et al. NEJM 2017

OlympiA: Phase III Study of Olaparib as Adjuvant Therapy for High-Risk, HER2-Negative Primary Breast Cancer with Germline BRCA1/2 Mutations

82% were TNBC

Enrollment (N = 1,500)

- TNBC
- Germline mutation in BRCA1 or BRCA2
- Completed neoadjuvant or adjuvant chemotherapy
- High risk of recurrence

R

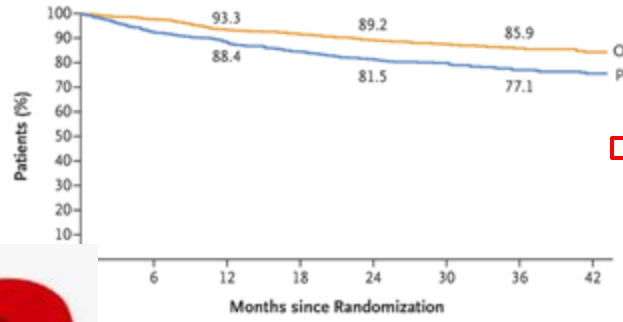
Olaparib 300 mg BID PO

Matched placebo

Primary endpo

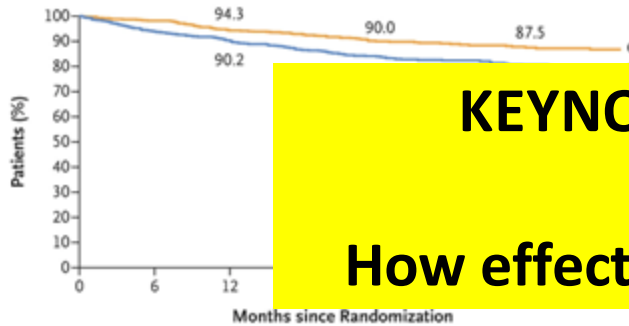
Clinically highly meaning … germline BRCA1/2-associated … (may be generaliz … 2, somatic BRCA1/2mt)

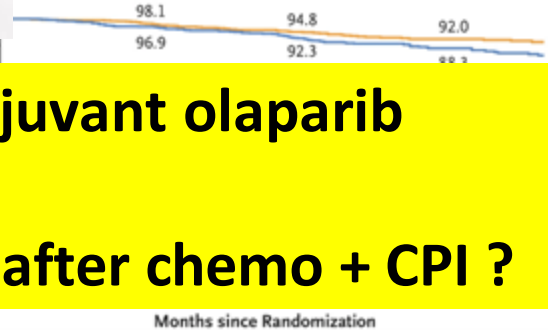
A Invasive Disease–free Survival



No. at Risk								
Olaparib	820	737	607	477	361	276	183	
Placebo								

B Distant Disease–free Survival





No. at Risk								
Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

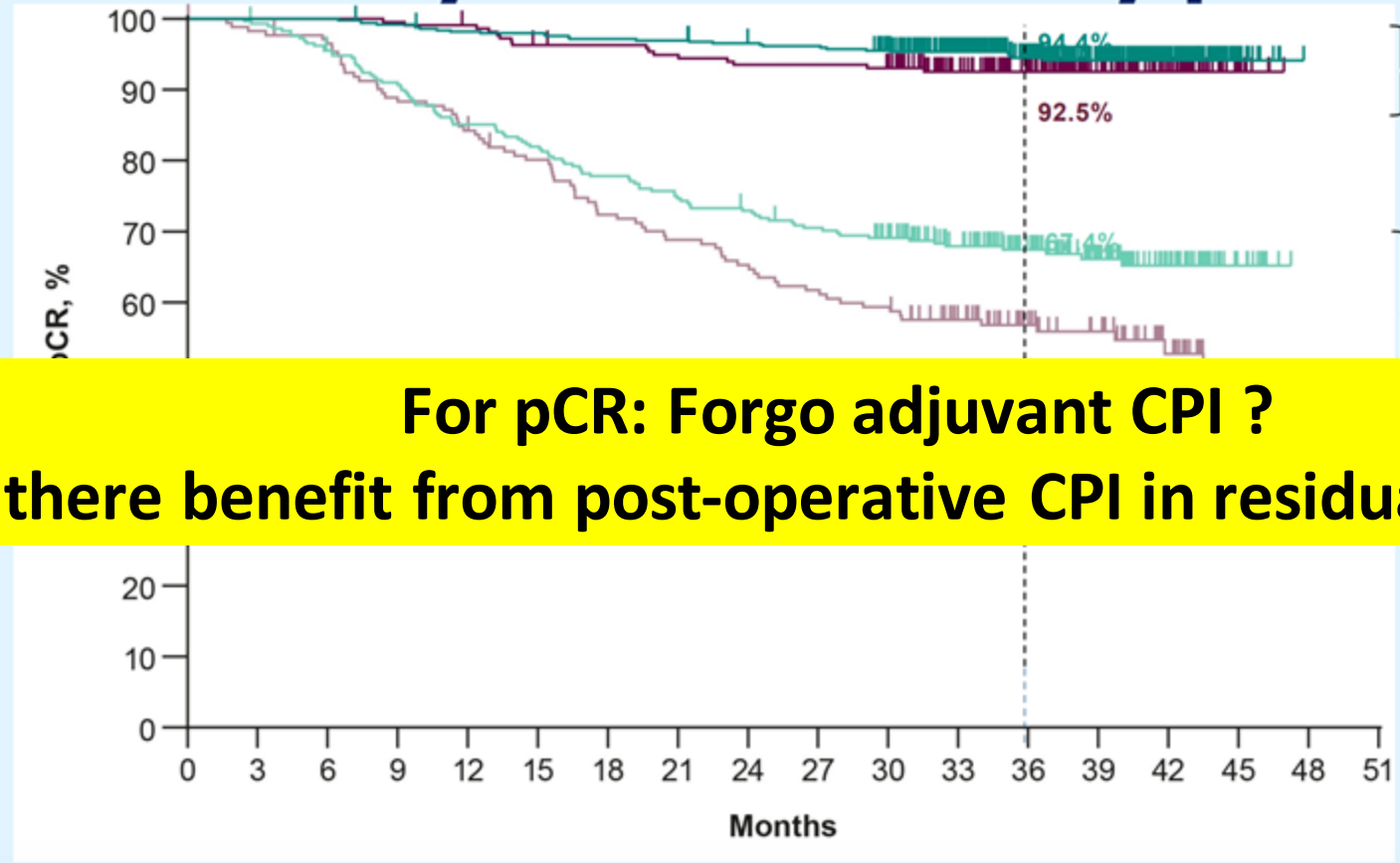
No. at Risk								
Olaparib	921	856	801	659	531	400	310	205
Placebo	915	865	801	659	516	397	292	199

KEYNOTE 522: NO adjuvant olaparib

How effective is olaparib after chemo + CPI ?

Tutt et al. NEJM 2021

Keynote 522 EFS by pCR



For pCR: Forgo adjuvant CPI ?

Is there benefit from post-operative CPI in residual disease ?

Schmid et al. NEJM 2022

GeparNUEVO Study Design

GBG GERMAN BREAST GROUP

Primary Endpoint - pathological complete response
pCR – ypT0, ypN0

Gepar Nuevo

PI

N=17
TNBC

Stratu
TILs
(low/me

Surgery

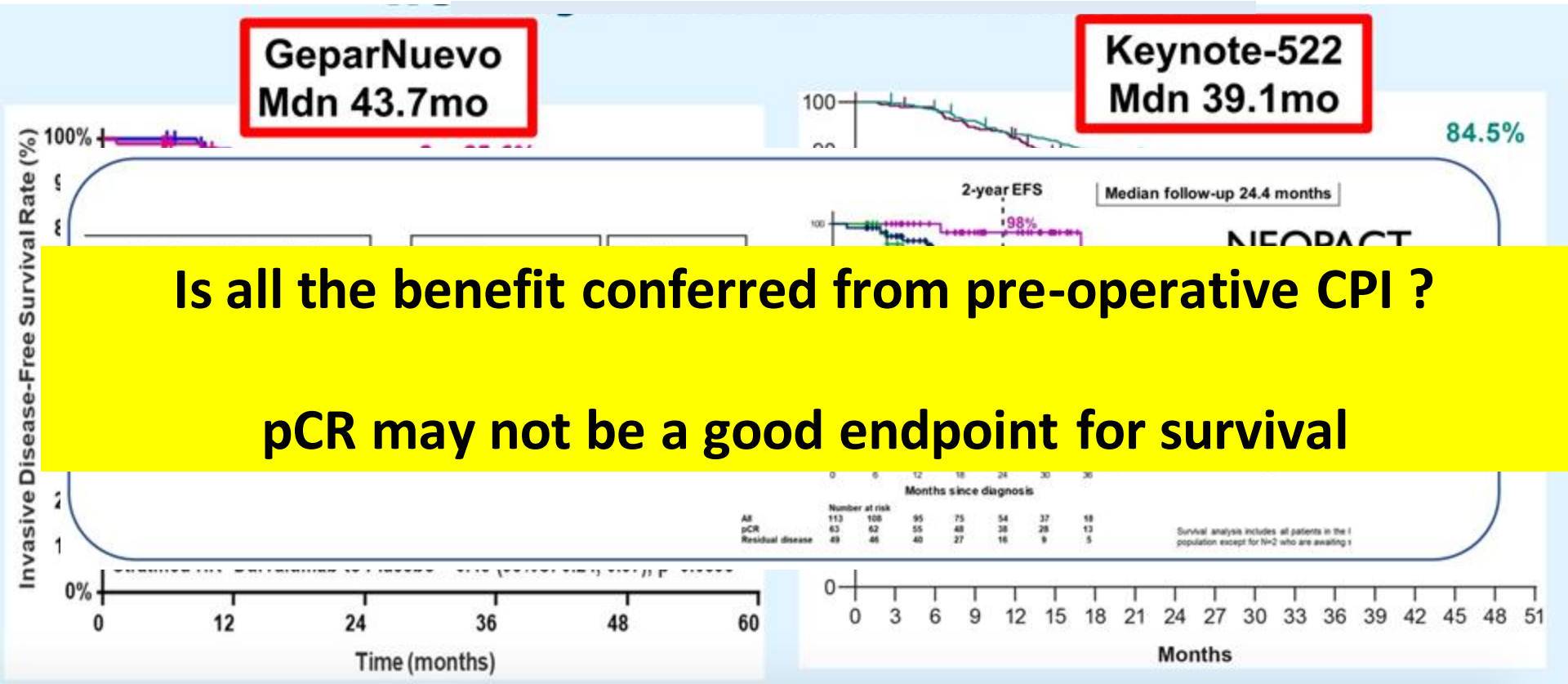
*Tissue: FFPE
Liquid biopsies: full blood; plasma, serum;

1.5g d1q28

* Continuous corrected χ^2 test
** For stratification factor (TIL groups)

Cyclophosphamide 600mg/m² d1q14

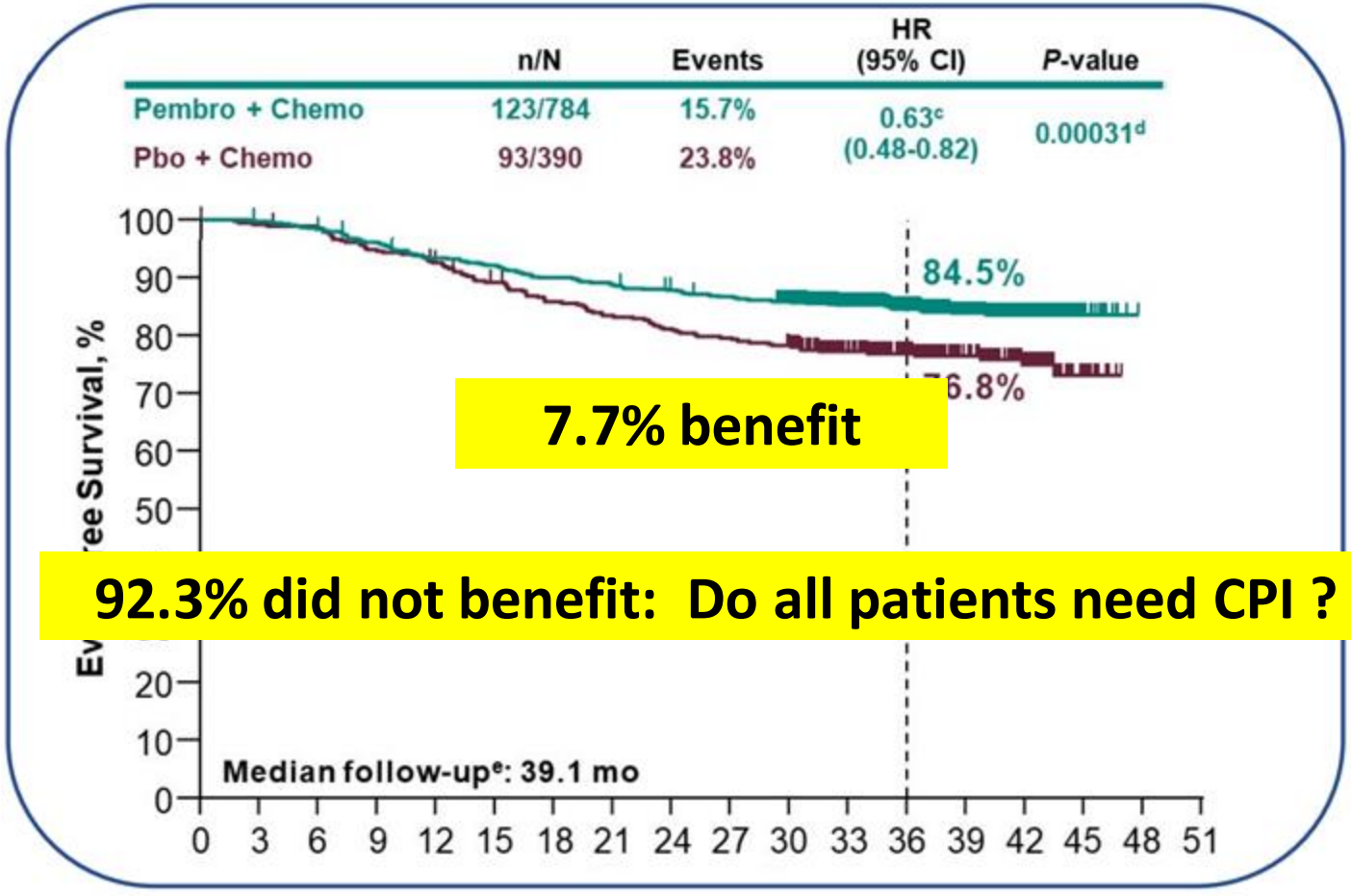
Loibl S et al. Annals of Oncology 2022



Is all the benefit conferred from pre-operative CPI ?

pCR may not be a good endpoint for survival

Loibl S, et al. Annals of Oncology 2022; Schmid P, NEJM 2022; Sharma P, ASCO 202



Schmid et al. NEJM 2022

Predictors of response to immune checkpoint inhibitors ?

DESPERATELY NEEDED !!!!

Comparison of an atezolizumab monotherapy window followed by atezolizumab and chemotherapy versus atezolizumab and chemotherapy alone in triple negative breast cancer (TNBC) – an interim analysis of the adaptive randomized neoadjuvant two-arm trial neoMono

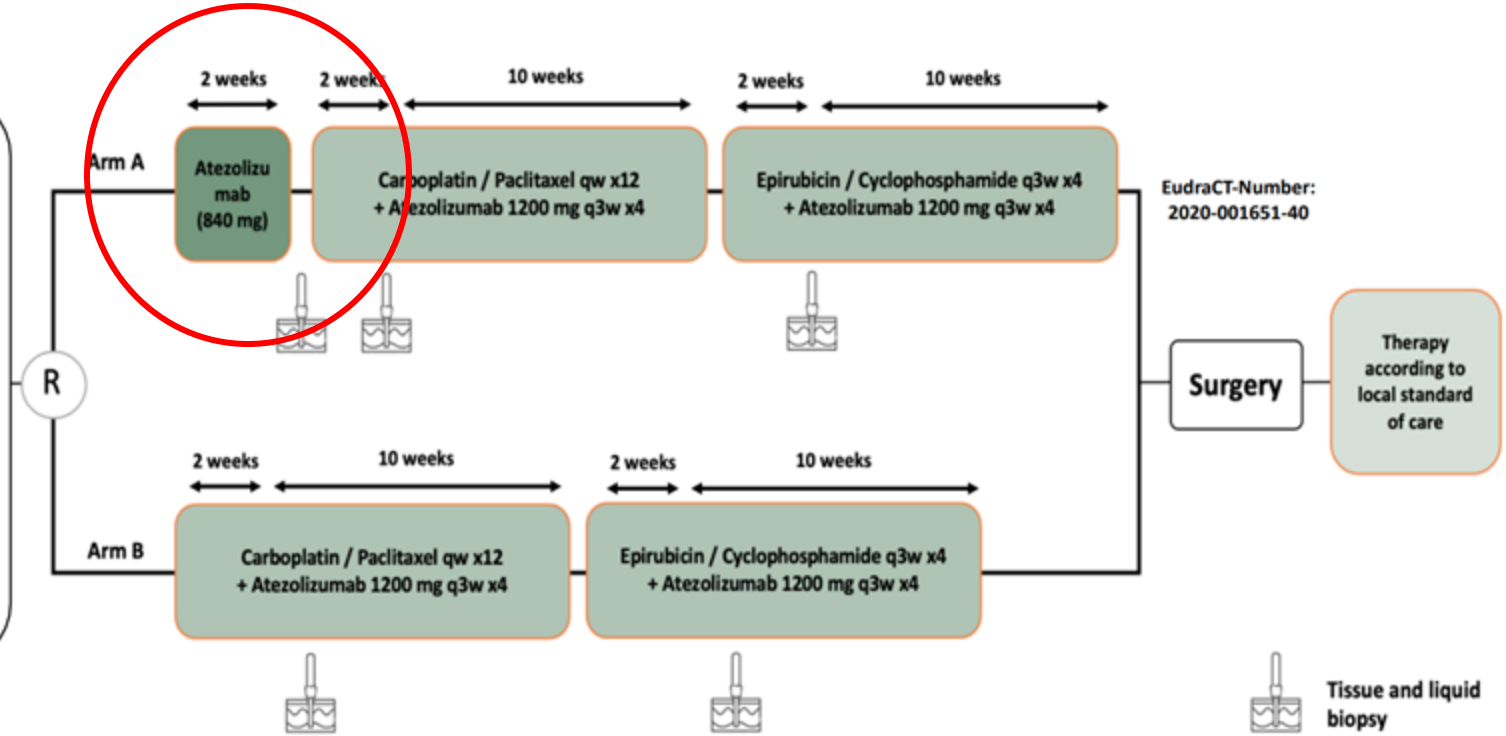
Hans-Christian Kolberg, Johannes Schumacher, Ramona Erber, Michael Braun, Bernhard Heinrich, Oliver Hoffmann, Peter A. Fasching, Georg Kunz, Michael P. Lux, Joachim Rom, Christian Schem, Eva-Maria Grischke, Mustafa Deryal, Kristina Lübbe, Arndt Hartmann, Sabine Kasimir-Bauer, Cornelia Kolberg-Liedtke

Marienhospital Bottrop; phaon scientific; palleos healthcare; Universitätsklinikum Erlangen; Rotkreuzklinikum München, Hämatologische-Onkologische Praxis Augsburg; University Hospital Essen; St. Johannes Hospital Dortmund; Klinikum Paderborn; Klinikum Frankfurt Höchst; Mammazentrum Hamburg am Krankenhaus Jerusalem; Universitätsklinikum Tübingen; CaritasKlinikum Saarbrücken; DIAKOVERE-Frauenklinik Henriettenstift

McArthur H, SABCS 2022

Phase-II-neoMono trial

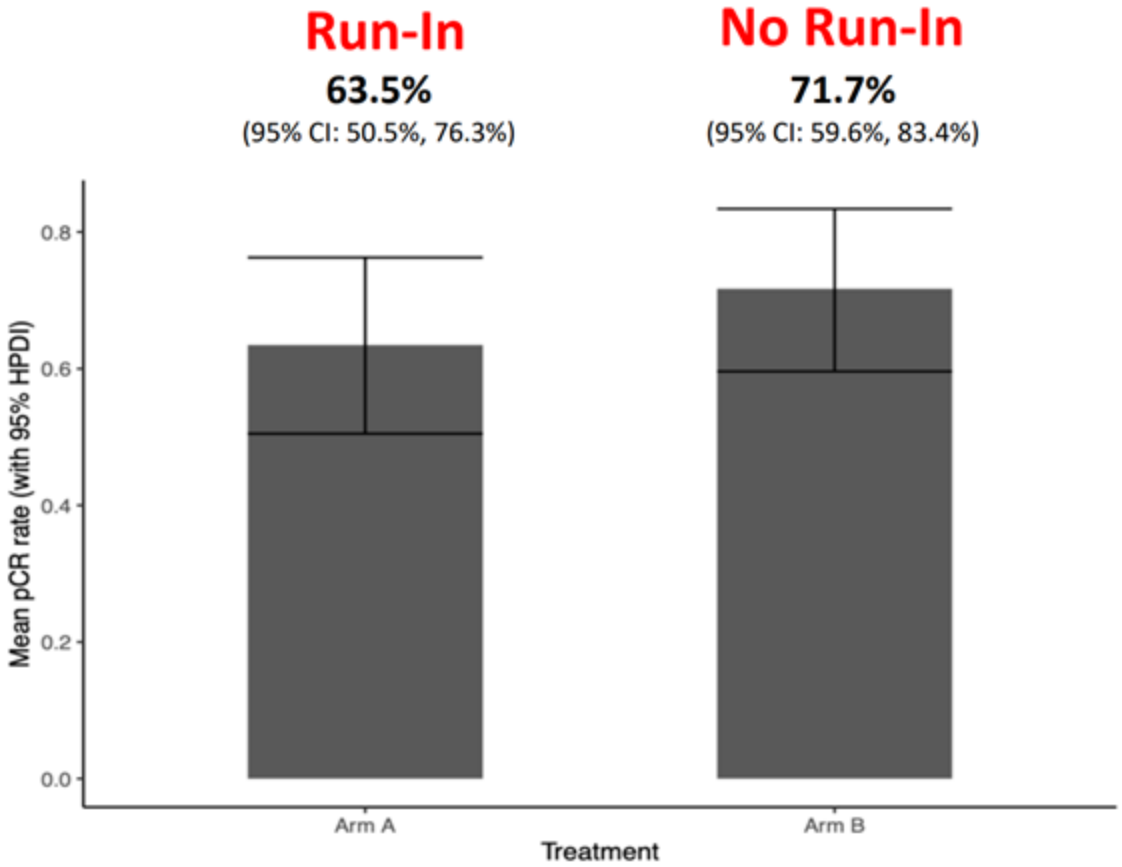
- 108 female and male patients
- TNBC (defined as ER/PR < 10% and HER2 negative)
- Stage cT1c – cT4d (irrespective of nodal status).



Kolberg-Liedtke et al., SABCS 2021
Kolberg et al., SABCS 2022

Results of neoMono interim analysis (ITT population)

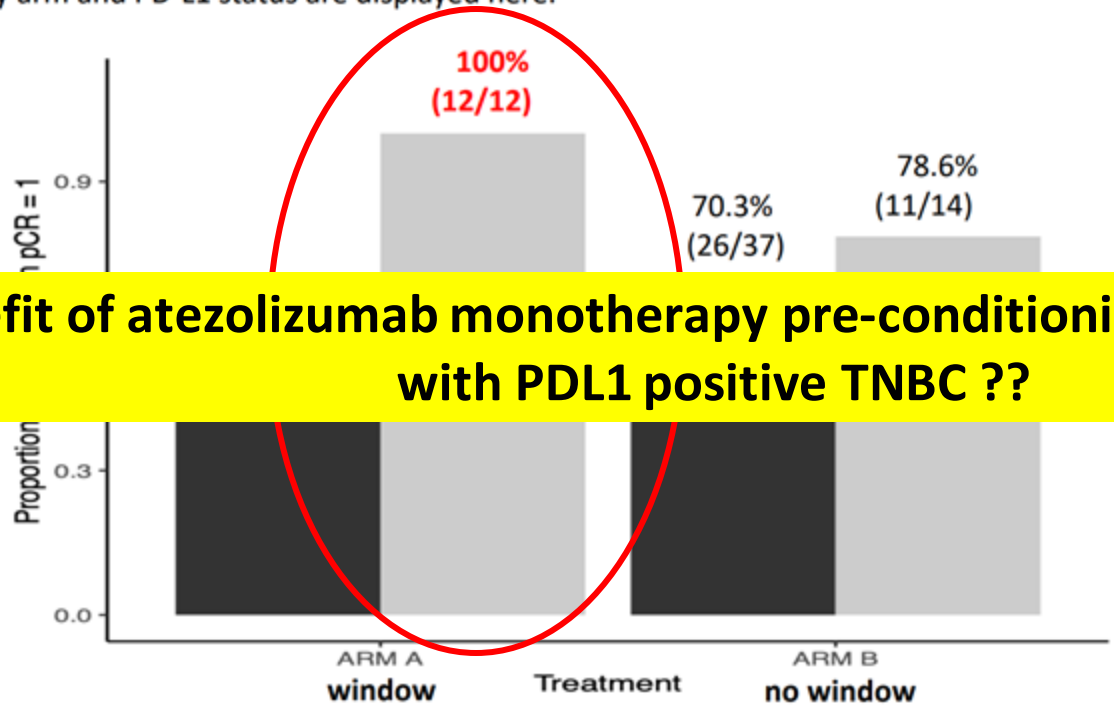
- All patients have hormone receptor status <1%
- 25.7% stage I
- 61.0% stage II
- 13.3 % stage III
- PD-L1 positive in 26.7%



Kolberg et al., SABCS 2022

Interim analysis: results after stratification for PD-L1 (IC) status

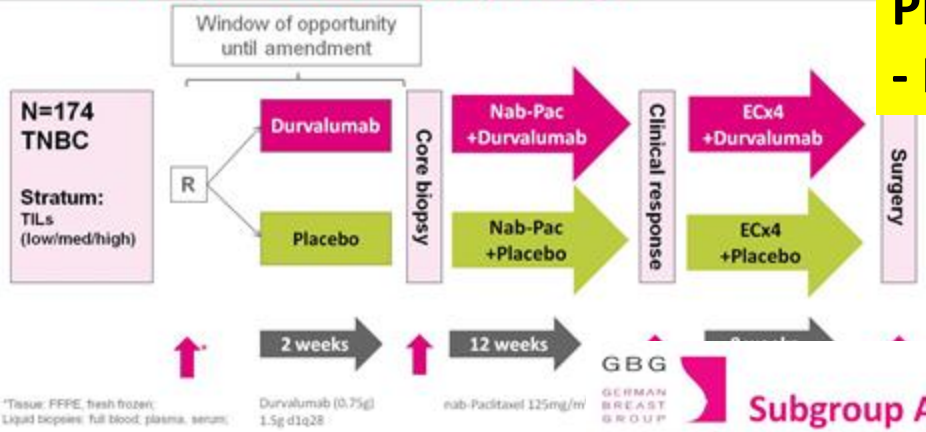
Due to an observed association between study arm and PD-L1 status regarding pCR in multivariable analysis, pCR results stratified according to study arm and PD-L1 status are displayed here.



Benefit of atezolizumab monotherapy pre-conditioning among patients with PDL1 positive TNBC ??

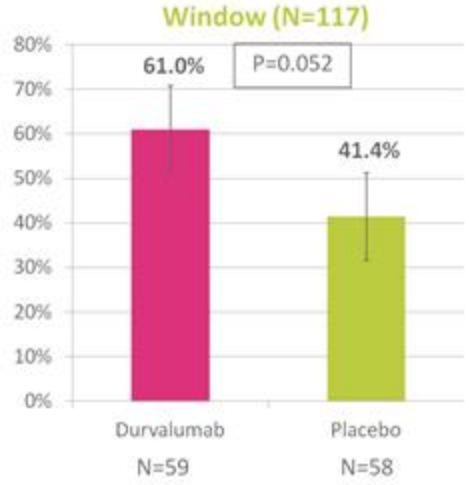
Kolberg et al., SABCS 2022

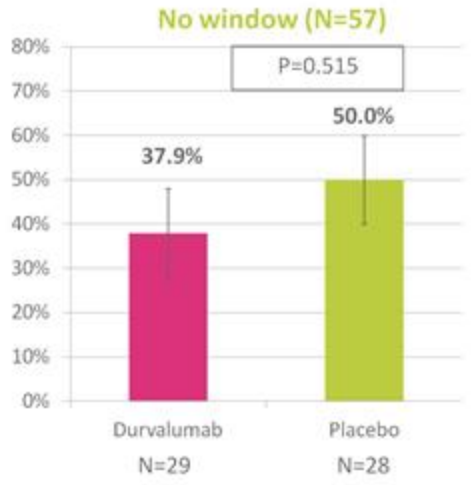
GeparNUEVO Study Design



Predictor of response ?
- Pre-conditioning with CPI monotherapy

Subgroup Analysis of the Window Cohort





Loibl S et al. Annals of Oncology 2022

THE UNIVERSITY OF KANSAS CANCER CENTER

San Antonio Breast Cancer Symposium® - December 6-10, 2022

NCI Comprehensive Cancer Center

Association of TNBC-DX scores with outcomes in triple-negative breast cancer (TNBC) treated with neoadjuvant pembrolizumab and chemotherapy: a correlative analysis from NeoPACT and NeoSTOP trials

Priyanka Sharma[1], Shane R Stecklein[2,3], Rachel Yoder[4], Joshua M Staley[4], Roberto Salgado[5,6], Laia Paré[7], Benedetta Conte[8], Fara Brasó-Maristany[8], Anne P O'Dea[1], Lauren E Nye[1], Manana Elia[9], Deepti Satelli[9], Gregory Crane[9], Richard McKittrick[9], Qamar J Khan[1], Andrew K Godwin[2-4], and Aleix Prat[7-11]

[1]University of Kansas Medical Center, Westwood, KS; [2]University of Kansas Medical Center, Kansas City, KS; [3]Kansas Institute for Precision Medicine, [4]The University of Kansas Cancer Center, Westwood, KS; [5]GZA-ZNA-Hospitals, Antwerp, Belgium; [6]Peter Mac Callum Cancer Centre, Melbourne, Australia; [7]Reveal Genomics, Barcelona, Spain; [8]IDIBAPS, Barcelona, Spain; [9]University of Kansas Medical Center, Lee's Summit, MO; [10]Hospital Clínico de Barcelona, Spain; [11]Universidad de Barcelona, Spain; [12]SOLTI Breast Cancer Research Group, Barcelona, Spain

PD11-07

Background

- Neoadjuvant chemoimmunotherapy is considered standard treatment for patients with stage II-III TNBC. Availability of biomarkers that can predict both pathological response and survival with chemoimmunotherapy can optimize this therapy.
- TNBC-DX risk score includes the 14-gene immunoglobulin (IGG) immune signature, tumor size, and nodal status and has shown prognostic value for survival in early-stage TNBC.[1]
- Currently unknown are the value of the TNBC-DX risk score and IGG immune signature in predicting outcomes in the context of neoadjuvant chemoimmunotherapy and predicting pathologic complete response (pCR) following neoadjuvant therapy.
- Here we asses IGG signature and TNBC-DX risk score in patients with TNBC treated with neoadjuvant chemoimmunotherapy (NeoPACT; NCT03639948)[2] or neoadjuvant chemotherapy without immunotherapy (NeoSTOP; NCT02413320)[3] on two trials.

Aim

- To investigate impact of TNBC-DX and IGG immune signature on outcomes in TNBC patients.

Methods

- NeoPACT and NeoSTOP trials with patients included in this analysis are described in Figure 1. Only Arm B of NeoSTOP was included in this correlative analysis as the chemotherapy regimen for Arm B was identical to that of NeoPACT.
- RNA isolated from pretreatment tumor tissue was subjected to next-generation sequencing.
- The 14-gene IGG immune signature and TNBC-DX risk score were calculated in silico as previously described.[1] Evaluation of stromal tumor-infiltrating lymphocytes (sTILs) was performed by one pathologist (RS) as previously described.[4]
- Markers were tested for prediction of pCR. Logistic regression analysis was used to examine effect of multiple variables. Event-free survival (EFS) curves were assessed by the Kaplan-Meier method and groups compared by log-rank test, followed by Cox regression analysis.

Results

- 14-gene IGG signature in NeoPACT: IGG signature was significantly associated with improved pCR (odds ratio [OR]=1.106, 95% CI 1.024-1.196, P=0.011 for every 0.2 increment). The pCR rates in IGG-high (above median) and IGG-low (below median) groups were 70% and 43%, respectively (OR=3.171, 95% CI 1.450-6.938, P=0.004) (Figure 2). sTILs and IGG signature were predictive (as modeled individually and jointly) for pCR in multivariable analyses adjusting for T stage and nodal status (Table 1). Neither sTILs (hazard ratio [HR] 0.613, 95% CI 0.179-2.097, P=0.436) nor the 14-gene IGG signature (HR=0.509, 95% CI 0.149-1.741, P=0.272) was prognostic for EFS in NeoPACT.
- TNBC-DX risk score in NeoPACT: In contrast, TNBC-DX risk score was strongly associated with EFS (HR=5.345, 95% CI 1.153-24.763, P=0.017), even after adjusting for sTILs and pCR status (HR=7.868, 95% CI 0.987-62.722, likelihood ratio test P=0.013). Estimated 3-year EFS in TNBC-DX high and low risk groups (above and below median, respectively) was 93% and 80%, respectively (P=0.017) (Figure 3).
- IGG signature and TNBC-DX risk score in NeoSTOP: No association of IGG signature with pCR (pCR 55% and 52% in IGG-high and IGG-low groups, respectively) (Figure 2) or TNBC-DX score with EFS (3-year EFS 88% and 91% in TNBC-DX high and low risk groups, respectively) was observed.
- A moderate correlation between IGG signature and sTILs was observed when both trial datasets were combined (r=0.642, P<0.001) (Figure 4).
- On CIBERSORTx leukocyte deconvolution analysis, IGG-high tumors exhibited significant enrichment of CD8+ T cells (P<0.001, q=0.004), plasma cells (P<0.001, q<0.001), CD4+ activated memory T cells (P<0.001, q<0.001), M1 macrophages (P<0.001, q<0.001), γδ T cells (P=0.01, q=0.03) and naïve B cells (P=0.03, q=0.08) and depletion of unpolarized M0 macrophages (P=0.008, q=0.03), immunosuppressive M2 macrophages (P=0.02, q=0.06) and resting mast cells (P=0.009, q<0.03) (Figure 5).

Figure 1. Patient population

NeoPACT (NCT03639948)
Enrollment period: 2018-2022
N=120
Carboplatin (AUC 6) + docetaxel (75 mg/m²) + pembrolizumab (200 mg) every 21 days x 6 cycles

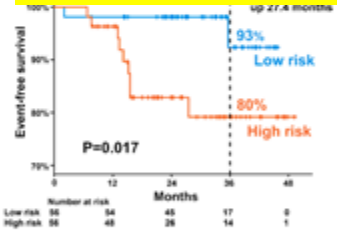
- N=112 (with available pretreatment tissue)
- Median age 50 years
- 17% Black, 3% Hispanic
- 7% with *gBRCA1/2* mutation
- 38% node-positive
- pCR = 58%

NeoSTOP (NCT02413320)
Enrollment period: 2015-2018
N=52 (Arm B)
Carboplatin (AUC 6) + docetaxel (75 mg/m²) every 21 days x 6 cycles

- N=43 (with available pretreatment tissue)
- Median age 54 years
- 19% Black, 2% Hispanic
- 16% with *gBRCA1/2* mutation
- 33% node-positive
- pCR = 53%

TNBC-DX score

s versus IGG



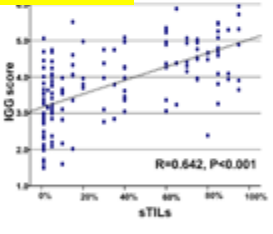


Figure 2. pCR by IGG category

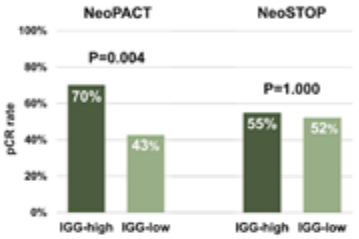


Figure 5. Immune cell composition according to IGG signature

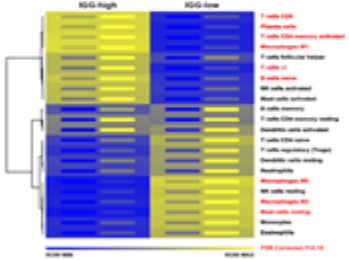


Table 1. Multivariable analysis: pCR in NeoPACT

Model	Variable	Odds ratio	95% CI	p	C-statistic
1	sTILs ≥ 30% vs < 30%	4.509	1.893-10.735	<0.001	0.713
2	IGG high vs low	3.648	1.590-8.369	0.002	0.695
3	sTILs ≥ 30% vs < 30%	3.127	1.189-8.224	<0.001	0.735
	IGG high vs low	2.184	0.854-5.585		

The p-value is a likelihood ratio test of the addition of the biomarker(s) to a model including T stage category and nodal status. The C-statistic is the area under the ROC, ranging from chance (0.5) to perfect (1.0).

Conclusions

- High expression of the 14-gene IGG immune signature in pretreatment tumor samples predicts for pCR following pembrolizumab-based neoadjuvant chemoimmunotherapy in early-stage TNBC.
- The combination of the IGG signature with tumor burden as assessed by TNBC-DX is prognostic for long-term outcomes in patients treated with neoadjuvant chemoimmunotherapy.
- Availability of biomarkers that can predict both pathologic response and survival with chemoimmunotherapy can optimize this therapy, and evaluation of this biomarker in larger studies is warranted.
- In patients treated with chemotherapy (on NeoSTOP), IGG signature was not associated with pCR, and TNBC-DX was also not prognostic for survival. This could be due to small sample size of this chemotherapy-treated population.
- IGG-high tumors exhibited enrichment of anti-tumor leukocytes and depletion of immunosuppressive leukocytes on CIBERSORTx leukocyte deconvolution analysis.
- The IGG signature moderately correlates with sTILs but may capture a distinct immune composition.

Funding: The University of Kansas Cancer Center (KUCC), the Cancer Center Support Grant to KUCC (P30 CA168524) (Biospecimen Repository Core Facility), the KUCC ACS-IRG Pilot award, University of Kansas Medical Center Research Institute (Lied Pilot award), National Institutes of Health KL2 award (KL2TR002367-05), Team Michelle, and by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, EVOMET, European Union's Marie Sklodowska-Curie Actions, PhD fellowship program under grant agreement 955951 to BC, Fundación Científica AECC Ayudas Investigador AECC 2021 INVES21943BRAS to FBM, Breast Cancer Research Foundation Award BCRF-22-198 to AP.

References: 1. Conte et al ESMO Breast 2021. 2. Sharma et al ASCO 2022. 3. Sharma et al Clin Cancer Res 2021. 4. Salgado et al Ann Oncol 2015

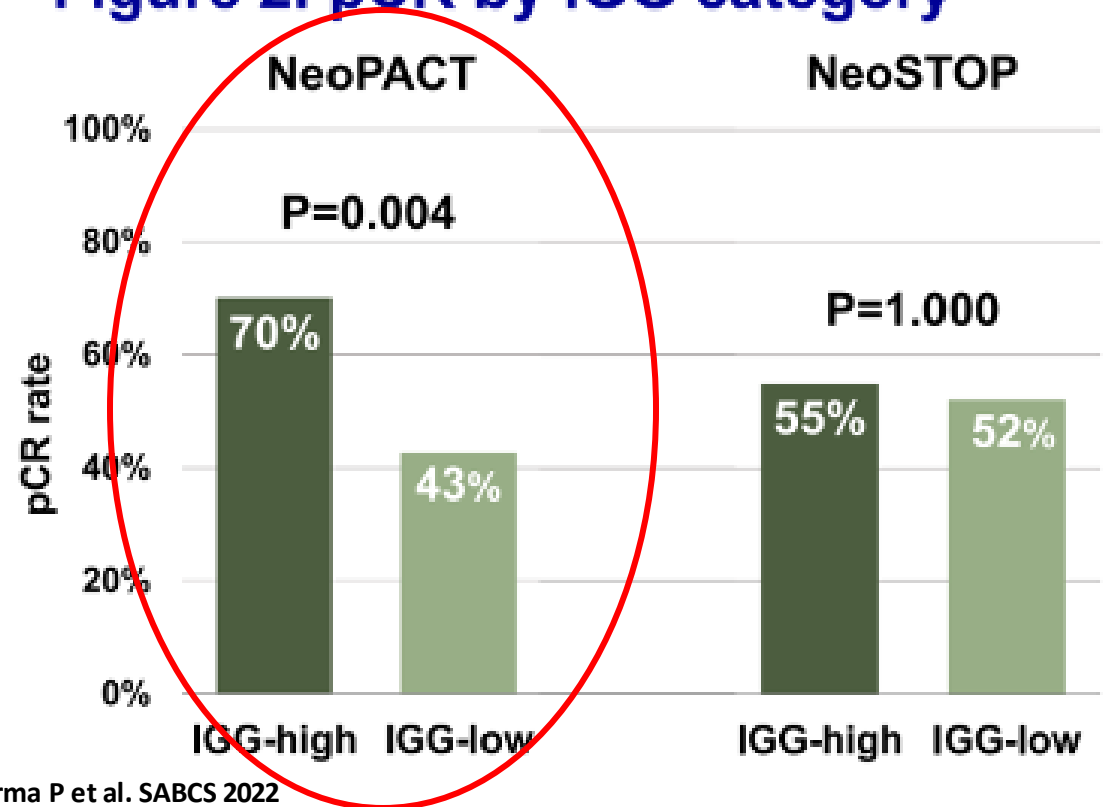
Figure 1. Patient population

NeoPACT (NCT03639948)
Enrollment period: 2018-2022
N=120
Carboplatin (AUC 6) + docetaxel (75 mg/m²) + pembrolizumab (200 mg)

NeoSTOP (NCT02413320)
Enrollment period: 2015-2018
N=52 (Arm B)
Carboplatin (AUC 6) + docetaxel (75 mg/m²)

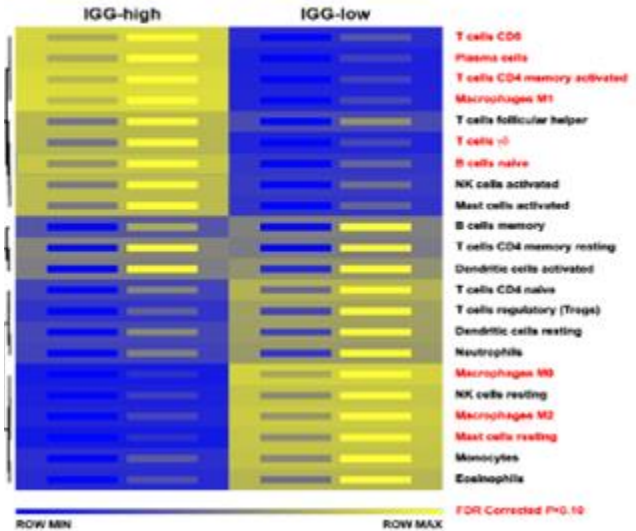
Predictor of CPI response ?
- IGG signature

Figure 2. pCR by IGG category



Sharma P et al. SABCS 2022

ıre 5. Immune cell composition ording to IGG signature

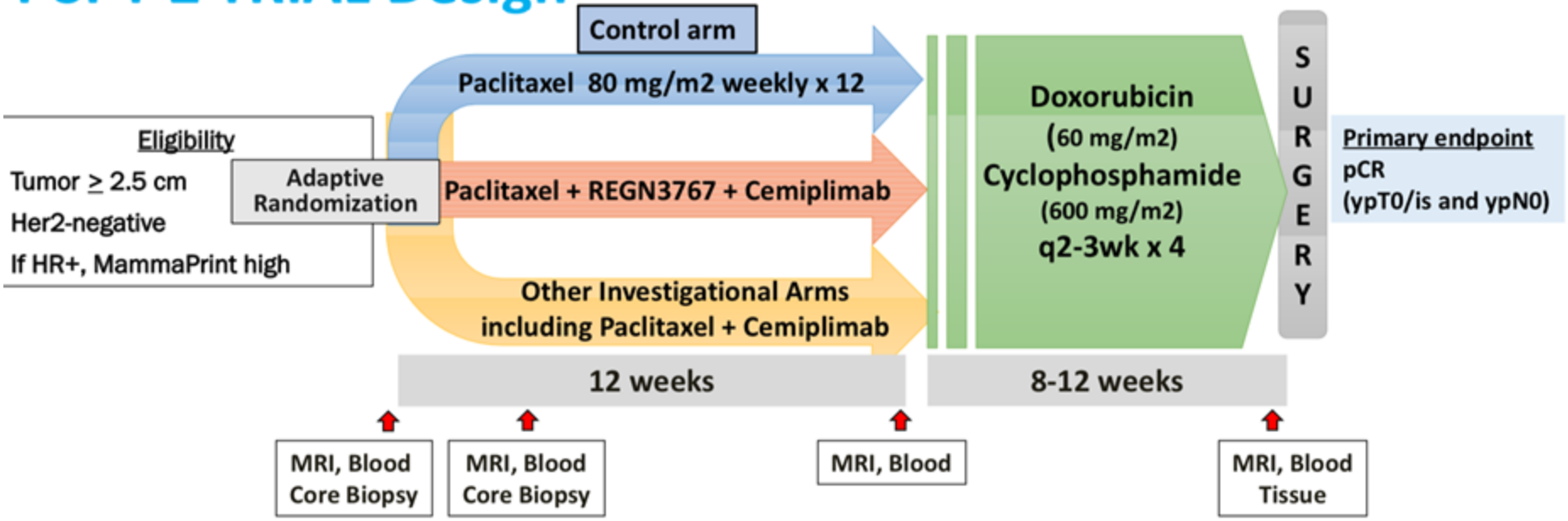


Preclinical data suggests synergistic interaction between anti-LAG3 and anti-PD1 therapy

Evaluation of anti-PD-1 Cemiplimab plus anti-LAG-3 REGN3767 in Combination with Paclitaxel in Early-Stage, High-Risk HER2-negative Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

Isaacs et al. SABCS 2022

I-SPY 2 TRIAL Design

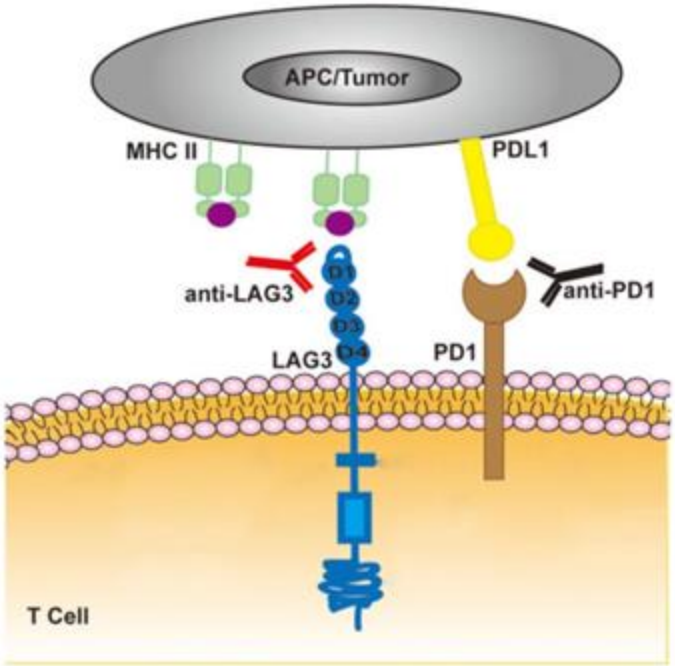


- REGN3767 + Cemiplimab was studied in **3 HER2-negative** biomarker signatures: **all HER2-; TNBC; HR+/HER2**
- Agent Graduation:
  - ≥85% predicted probability of success in a 300-patient phase 3 neoadjuvant trial
- Graduation is assessed for each pre-specified biomarker signature

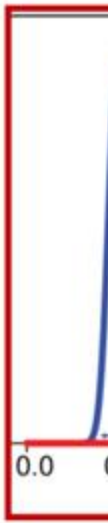
Isaacs et al. SABCS 2022

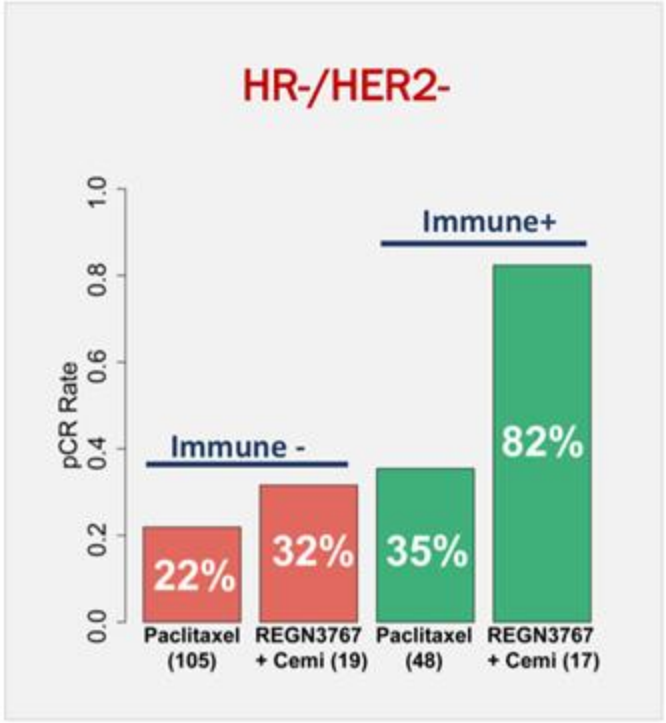
REGN3767: LAG-3 Antagonist

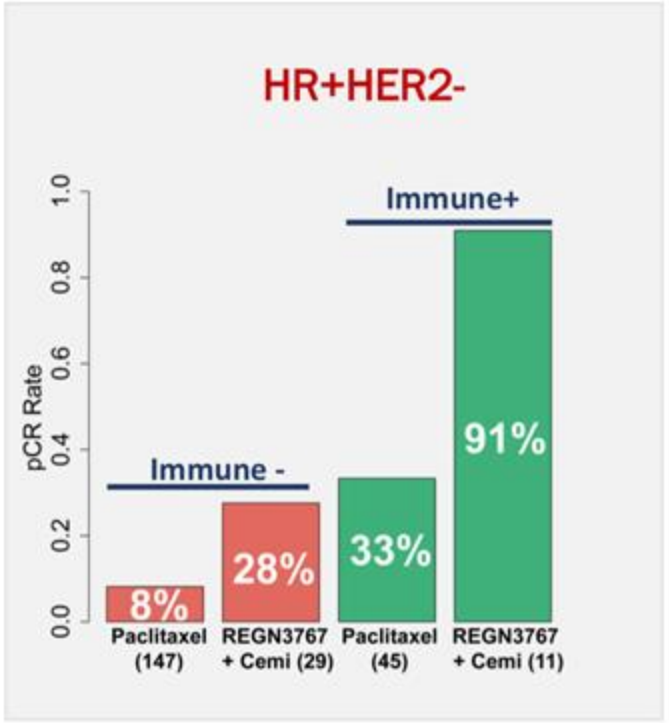
- REGN3767 (Fianlimab) is a fully humanized, high-affinity mAb that binds to and antagonizes lymphocyte activation gene 3 (LAG-3)[1]
- LAG-3
  - Cell surface molecule expressed on immune cells including T cells
  - Binds to MHC class II leading to inhibition of T-cell proliferation and activation[1]
  - REGN3767 blocks LAG-3/MHC class II-driven T cell inhibition[1]
  - Often co-expressed with PD-1
- Cemipimab is anti-PD-1[2] approved for treatment of NSCLC and cutaneous and squamous cell CA



Isaacs et al. SABCS 2022







Observed (not modeled) pCR rates are shown
345 control and 76 cemi+REGN3767 of primary efficacy analysis population have ImPrint data

Isaacs et al. SABCS 2022

Conclusions from the I-SPY 2 Trial

- Cemiplimab + REGN 3767 highly effective combination in both TNBC and HR+/HER2 negative breast cancer

- ImPrint signature identified greatest benefit from checkpoint inhibitor based therapy

Not ready for prime time

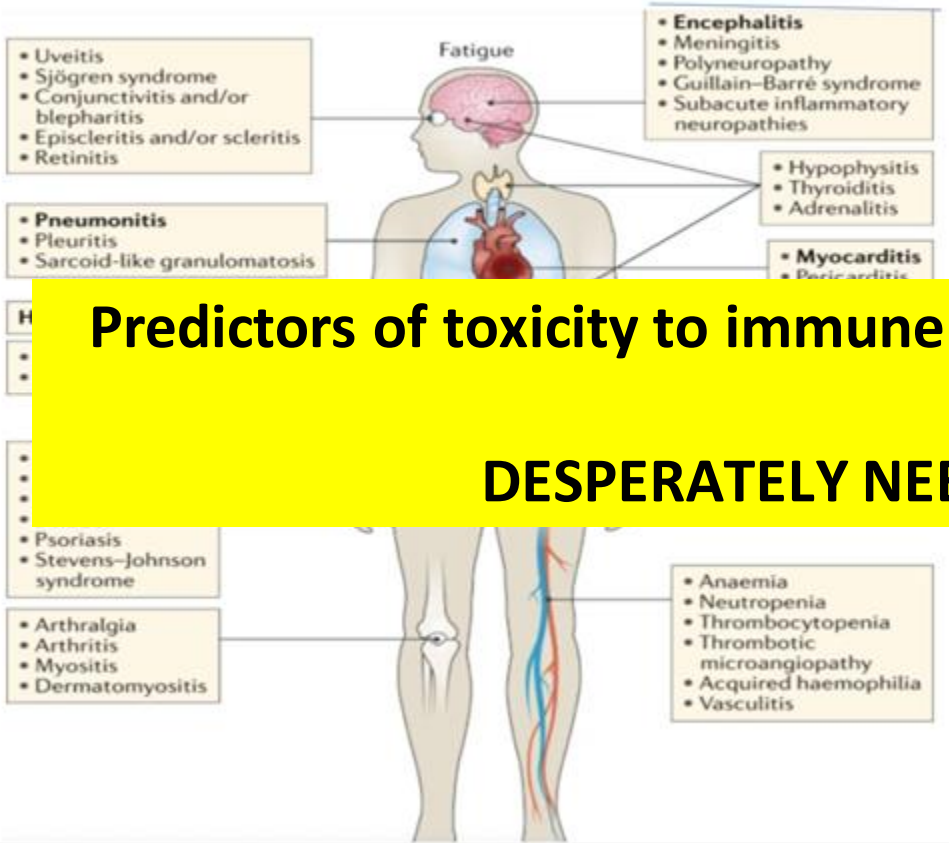
Predictor for CPI response ? ImPrint signature

well as 3 cases (5%) of Type 1 diabetes
  - This rate has not been observed in other patient populations
  - Small studies have suggested lower irAEs with lower doses of immunotherapy

- Given activity, evaluating safety profile of lower dose REGN3767 given in combination with cemiplimab + paclitaxel

Isaacs et al. SABCS 2022

Immune-related Adverse Events and Associated Symptoms



SYMPTOMS
Diarrhea
Fatigue
Dizziness
Shortness of breath
Rash
Vomiting
Neuropathy
Mouth/Throat sores
Joint pain
Abdominal pain
Cough
Constipation
Taste changes
Swelling
Blurry vision
Pain urination
Dry eyes

Predictors of toxicity to immune checkpoint inhibitors ?

DESPERATELY NEEDED !!!!

Martins et al, 2019, Nature Reviews Clinical Oncology

Basu A et al. SABCS 202

Identification of Symptoms Associated with irAEs in the I-SPY Trial

Need to identify predictors of irAE

- **Avoid immune checkpoint inhibition**
- **Intervene early to prevent irAEs**

Prese

[1]Basu A
M, [1]Jon
C, [5]DeMichele A, [6]Nanda R, [1]Kim M, [1]Wolf D, [7]Hershman D,
[1]Esserman L, [1]Rugo HS

[1]University of California, San Francisco, San Francisco, CA
[2]Quantum Leap Healthcare Collaborative, San Francisco
[3]University of California, San Diego, San Diego, CA
[4]Georgetown University, Washington DC
[5]University of Pennsylvania School of Medicine, Philadelphia, PA
[6]University of Chicago, Chicago, IL
[7]Columbia University, New York, NY

On behalf of the I-SPY2 Investigators

Basu A et al. SABCS 2022

Clinician-assessed adverse events (CTCAE v 5.0)

- Included all grade 1-4 AEs
- Collected weekly to every 2-3 weeks depending on chemotherapy schedule
- Follow-up: up to 1 year

Patient-reported Outcomes (PRO-CTCAE/PROMIS)

- Patients filled in in at least 2 timepoints including baseline
- Surveys were collected weekly for symptoms, and monthly for QOL
- Surveys collected through 24 months
- Reported using the Likert scale 1-5 (from none/mild to severe)

Basu A et al. SABCS 2022

Results: Co-occurring Symptoms up until 6 week timepoint

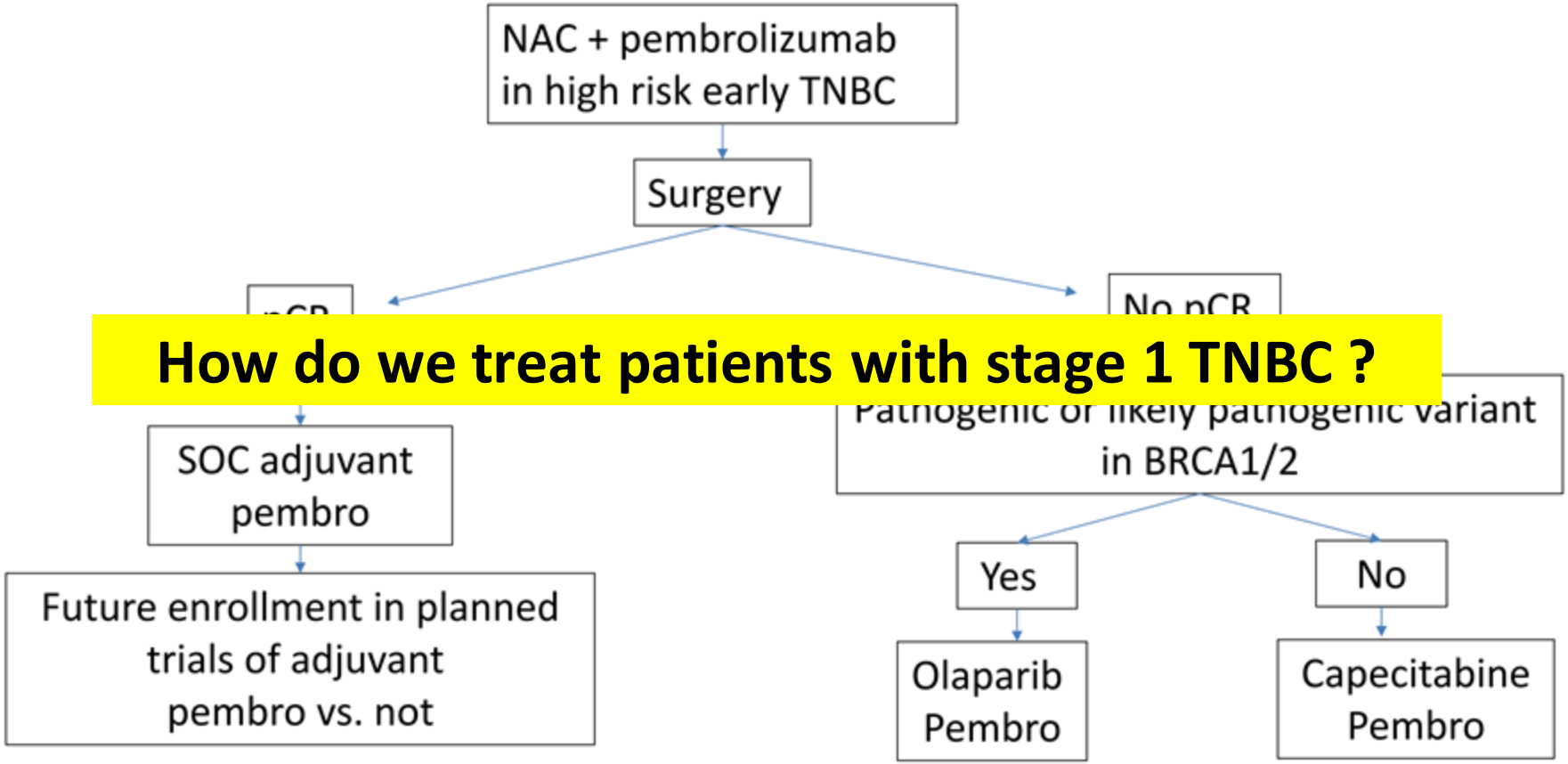
Incipient disease before laboratory abnormality

FUTURE:

Early identification of symptoms may guide close surveillance or potential treatment modification

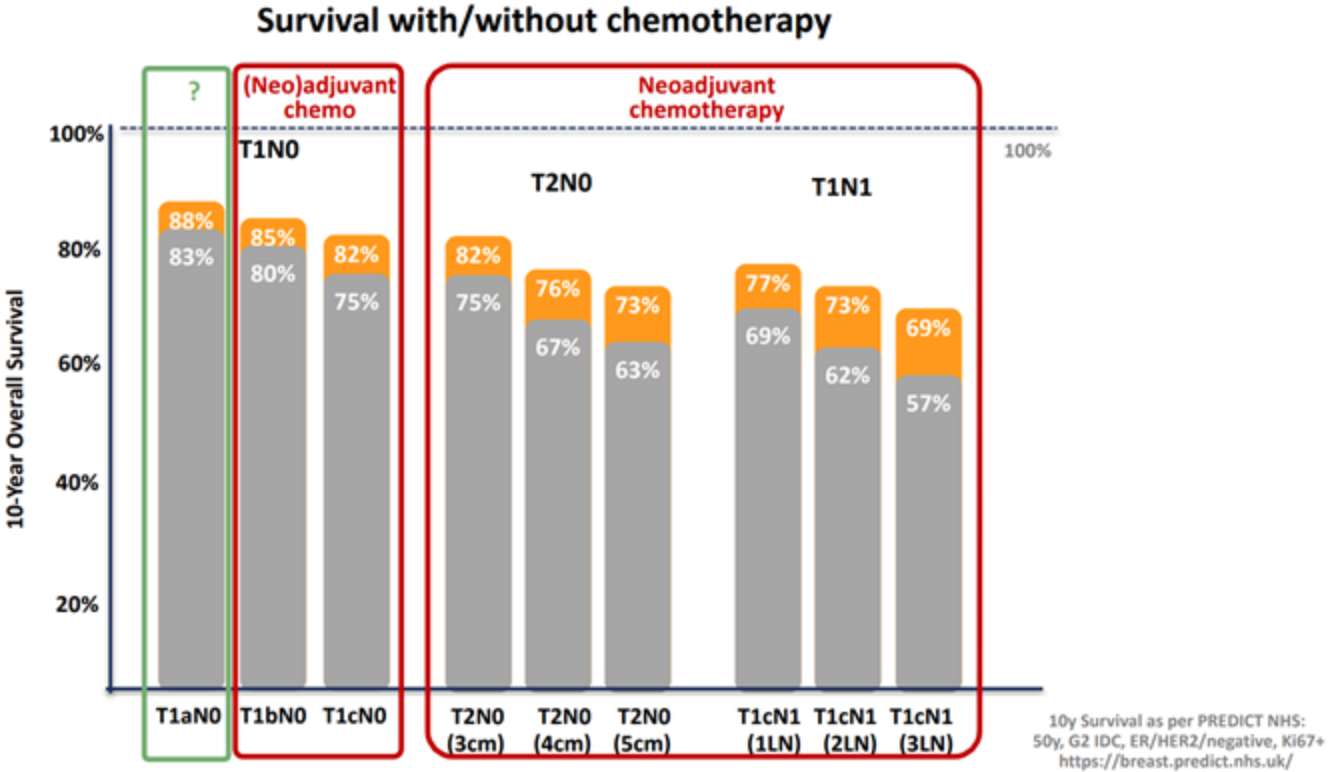
Basu A et al. SABCS 2022

Algorithm for management of high risk early TNBC



Personal communication from Gandhi S.

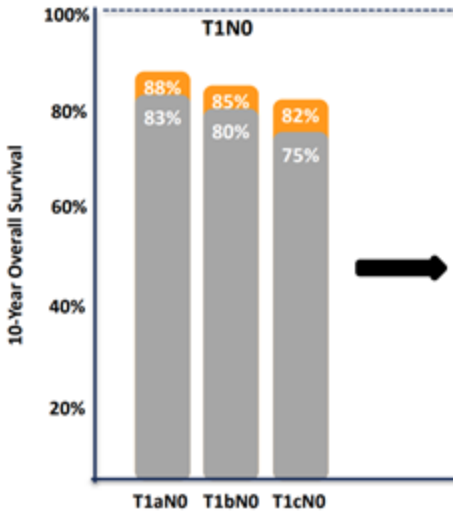
Do all patients with early stage TNBC need systemic treatment ?



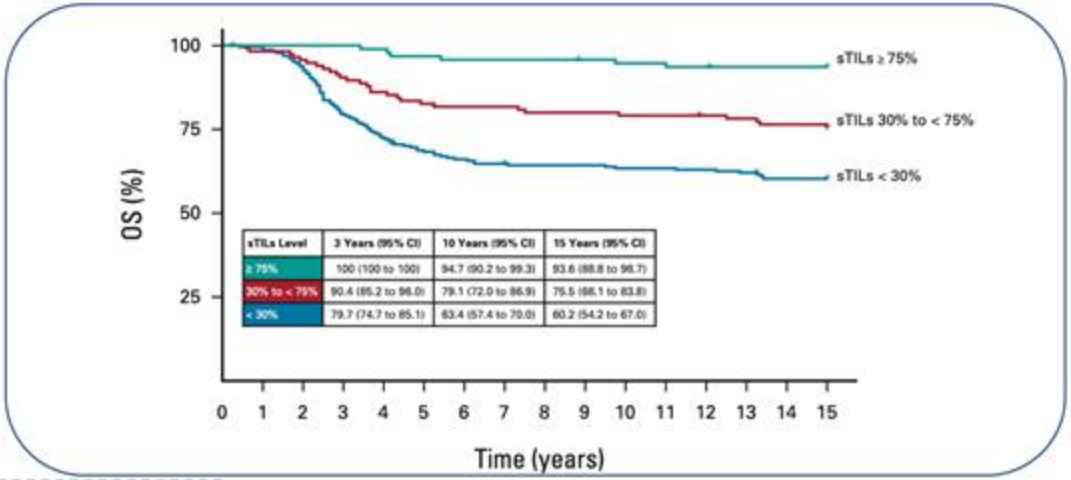
Schmid P, SABCS

Do all patients with early stage TNBC need systemic treatment ?

De-escalate therapy ?



<40yrs, no chemo, N0, TIL (tumor-infiltrating lymphocytes) >=75%:
only 2% distant mets @15yrs!



sTILs Level	3 Years (95% CI)	10 Years (95% CI)	15 Years (95% CI)
≥ 75%	100 (100 to 100)	94.7 (90.2 to 99.3)	93.6 (88.8 to 98.7)
30% to < 75%	90.4 (85.2 to 96.0)	79.1 (72.0 to 86.9)	75.5 (68.1 to 83.8)
< 30%	79.7 (74.7 to 85.1)	63.4 (57.4 to 70.0)	60.2 (54.2 to 67.0)

De Jong et al. JCO 2022

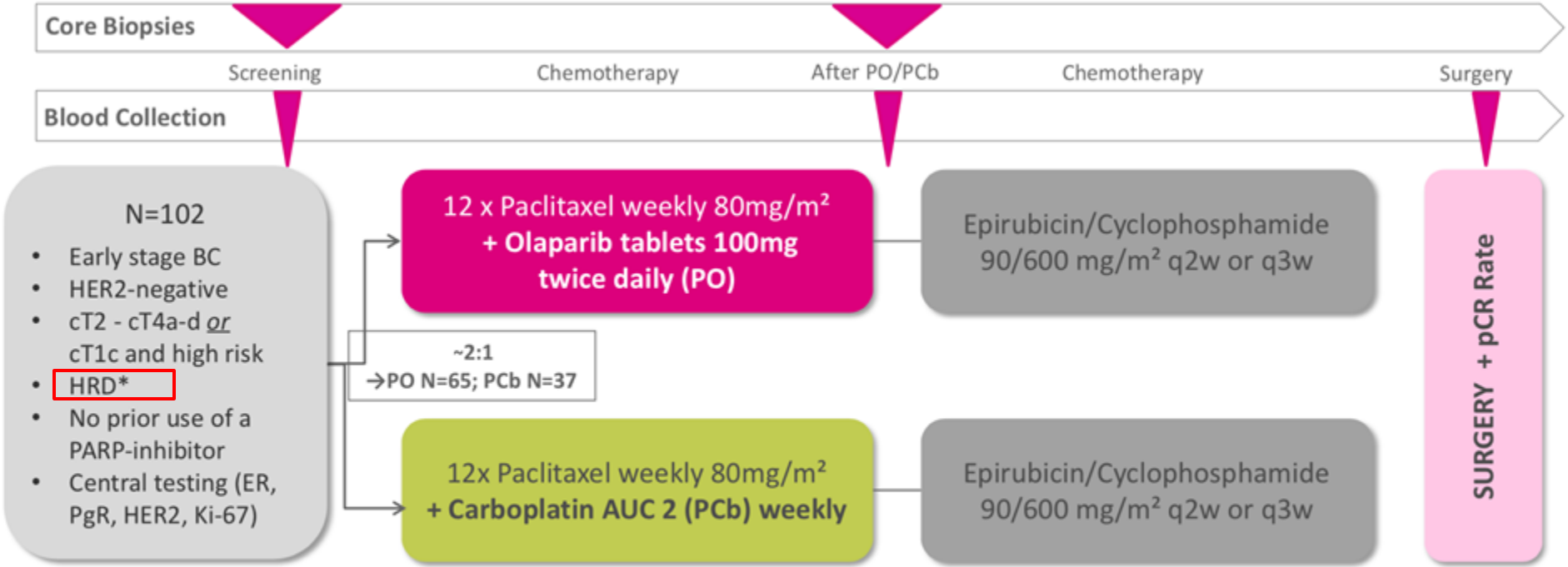
GeparOLA - GBG 90

Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative early breast cancer and homologous recombination deficiency – long-term survival of the GeparOLA study

Fasching et al. SABCS 2022

72.6% TNBC

GeparOLA Study Design



Stratification Factors:

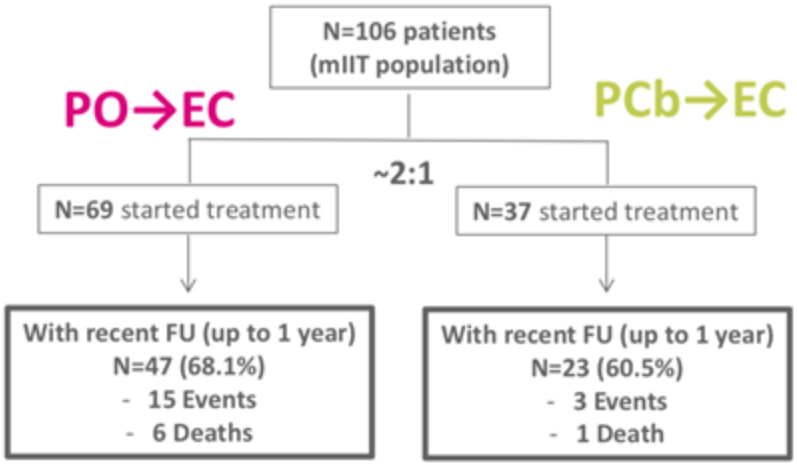
- Age (<40 years vs >= 40 years)
- Hormone Receptor Status (HR+ vs HR-)

* Patients with either a known somatic or germline *BRCA*1/2 mutation or HRD score[1] high (defined as a MyChoice™ Score of ≥42)

Fasching *et al.* Ann Oncol. 2020
[1]Timms et al. Breast Cancer Res 2014

Patient disposition and Patient Characteristics

Consort Diagram



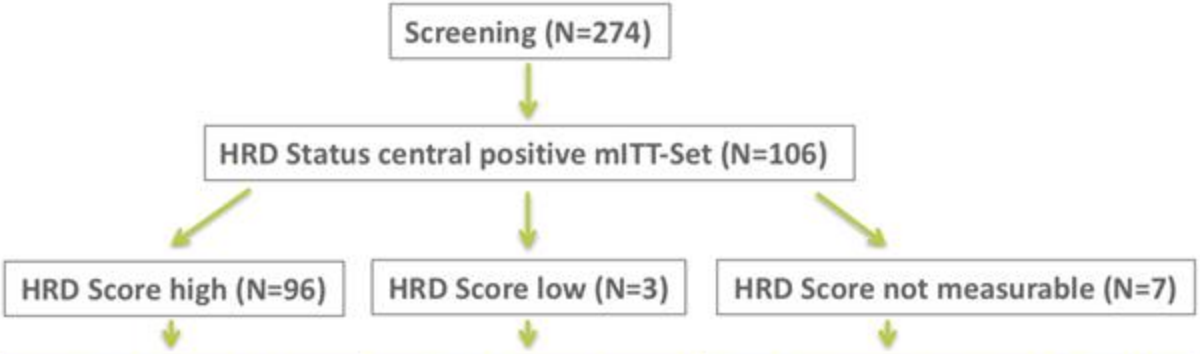
Main Baseline Characteristics

	PO→EC N=69 N (%) *	PCb→EC N=37 N (%) *	Overall N=106 N (%) *
Age (years), median (range)	48.0 (25.0, 71.0)	45.0 (26.0, 67.0)	47.0 (25.0, 71.0)
cT2	41 (60.3)	23 (62.2)	64 (61.0)
cN+	17 (24.5)	16 (45.7)	33 (31.8)
ER and/or PgR positive**	19 (27.5)	10 (27.0)	29 (27.4)
Ki-67 > 20%**	63 (91.3)	32 (86.5)	95 (89.6)
g/tBRCA-mutation	38 (55.9)	21 (56.8)	59 (56.2)

*valid percent
** central testing

Fasching et *al*. Ann Oncol. 2020

Screening for Patients: HRD status and g/t BRCA 1/2 mutations

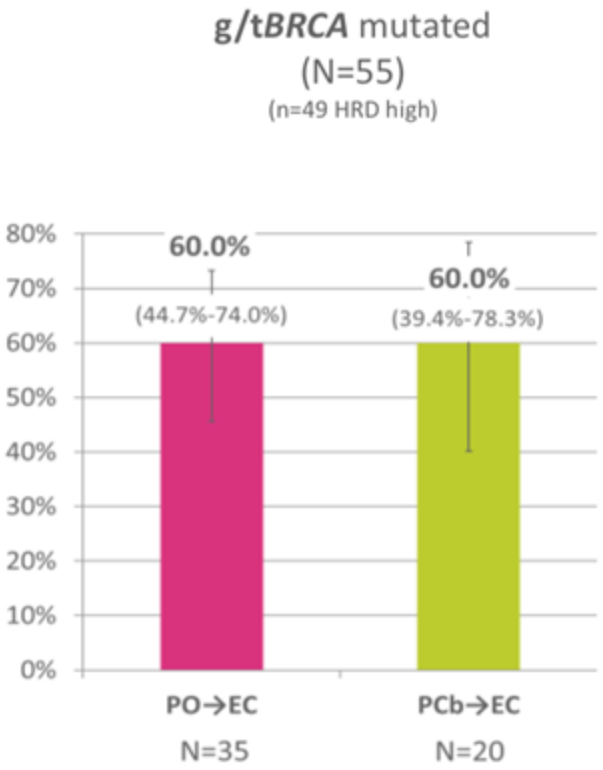


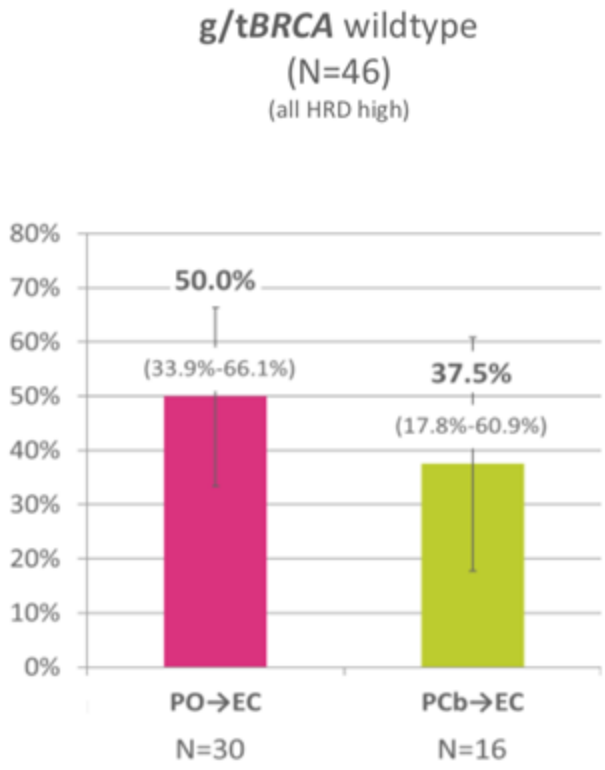
g/t*BRCA*	HRD Score high N (%)	HRD Score low N (%)	HRD Score not measurable* N (%)
Mutated (n=55)	49 (46.2)	3 (2.8)	3 (2.8)
Intact (n=46)	46 (43.4)	0 (0.0)	0 (0.0)
Not measurable*	1 (0.9)	0 (0.0)	4 (3.8)**

■ Eligible patients
* Insufficient quality or quantity of DNA
** Eligibility criteria: *gBRCA* local positive

Fasching et al. SABCS 2022

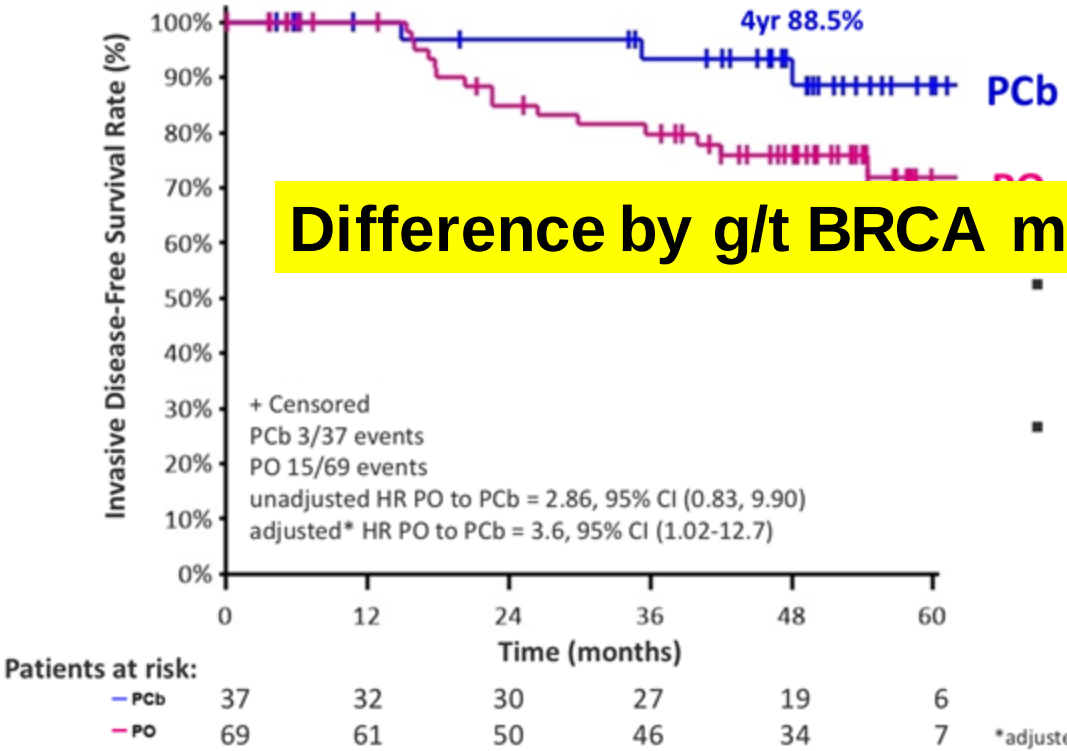
pCR rates in g/t BRCA Subgroups





Fasching et *al*. Ann Oncol. 2020

iDFS in the overall study population



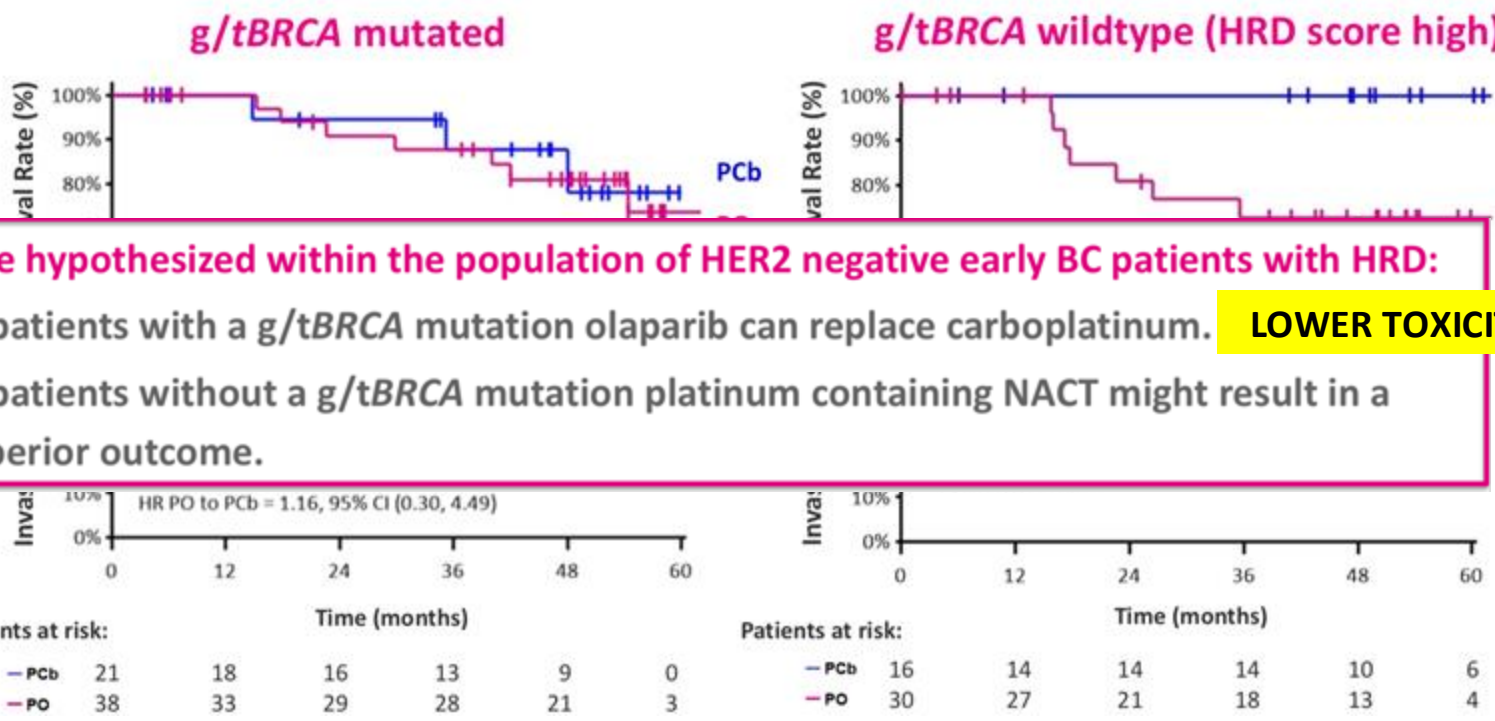
Difference by g/t BRCA mutation ??

- Median follow-up of 49.8 (range 0.1 – 69.1) months
- 4-year loco-regional recurrence rate after PO treatment was higher (10.3%) compared to PCb treatment (4.9%)

*adjusted for nodal status and gene mutation status

Fasching et al. SABCS 2022

iDFS by BRCA-1/2 mutation status

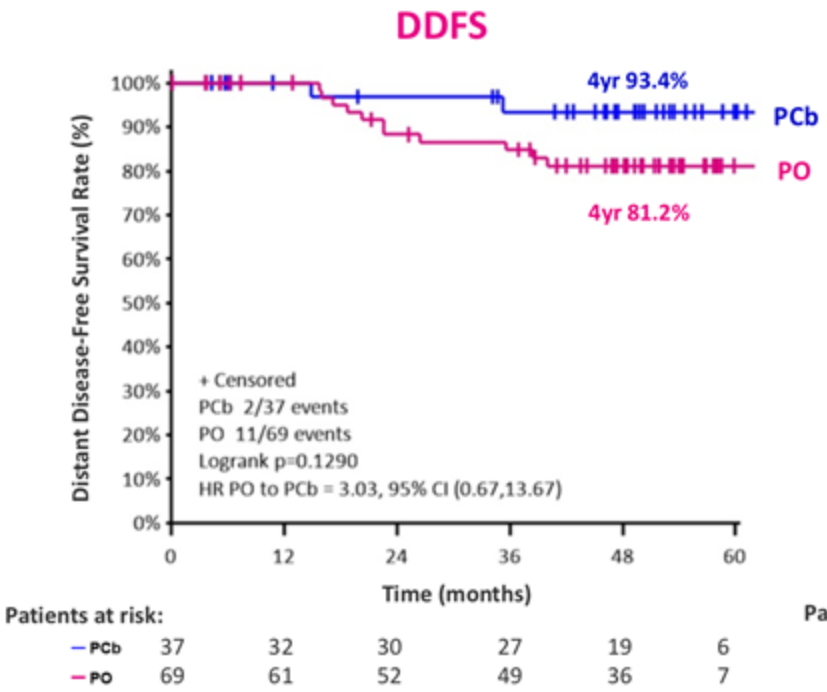


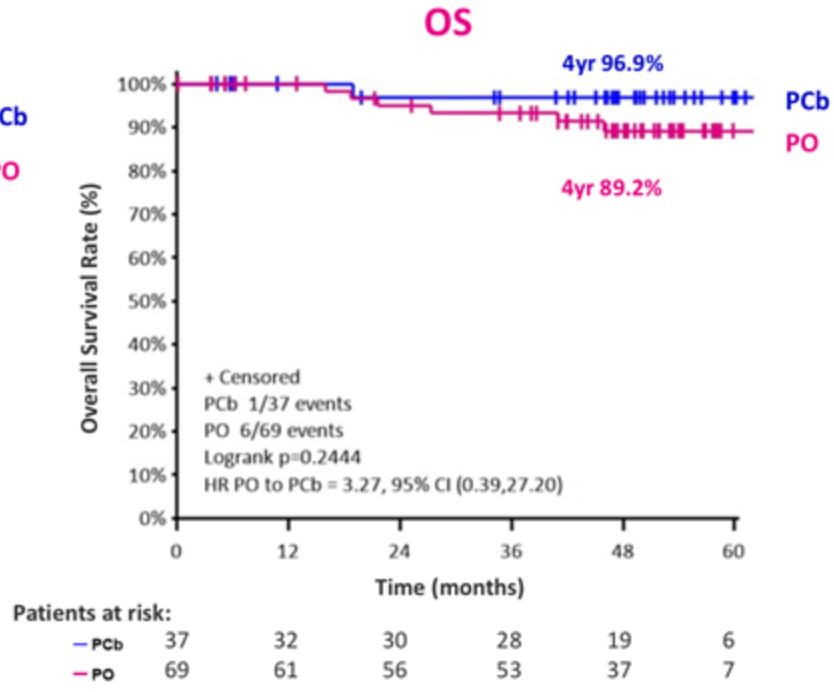
It can be hypothesized within the population of HER2 negative early BC patients with HRD:

- In patients with a g/t*BRCA* mutation olaparib can replace carboplatinum. **LOWER TOXICITY PROFILE**
- In patients without a g/t*BRCA* mutation platinum containing NACT might result in a superior outcome.

Fasching et al. SABCS 2022

DDFS and OS in the overall study population





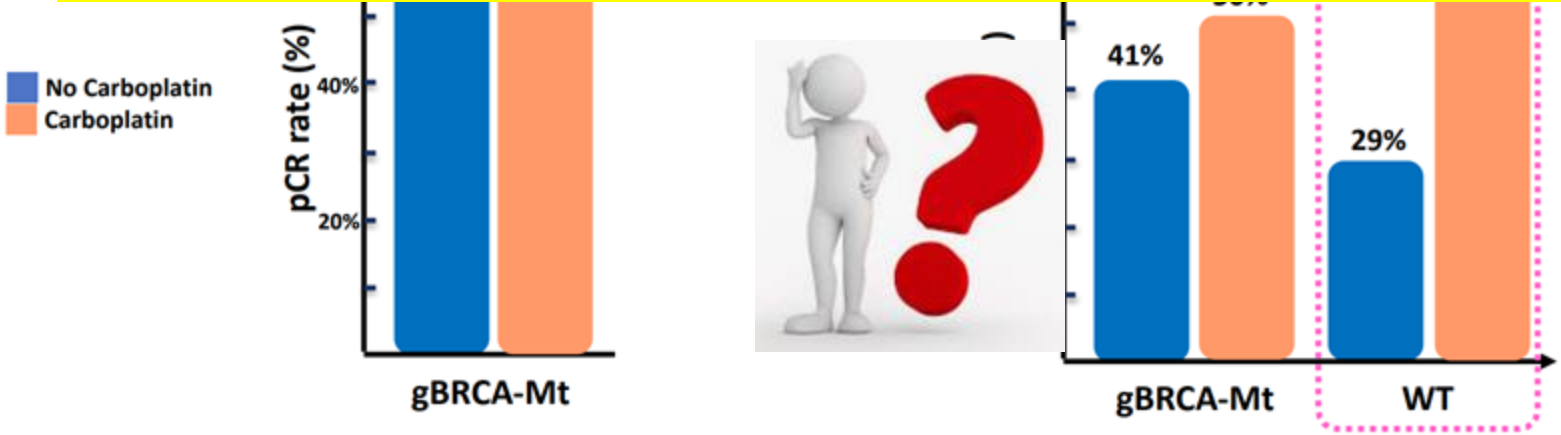
Fasching et al. SABCS 2022

gBRCA status is not predictive of benefit from Platinum

Platinum benefit seen in gBRCA1/2 wildtype patients

Carboplatin may not be needed for gBRCA mutant population ??

Does this change implications of using carboplatin in KEYNOTE 522 ??



Loibl et al, Lancet Oncol 2018; Hahnen et al, JAMA Oncol 2017

Conclusions: Management of Early stage TNBC

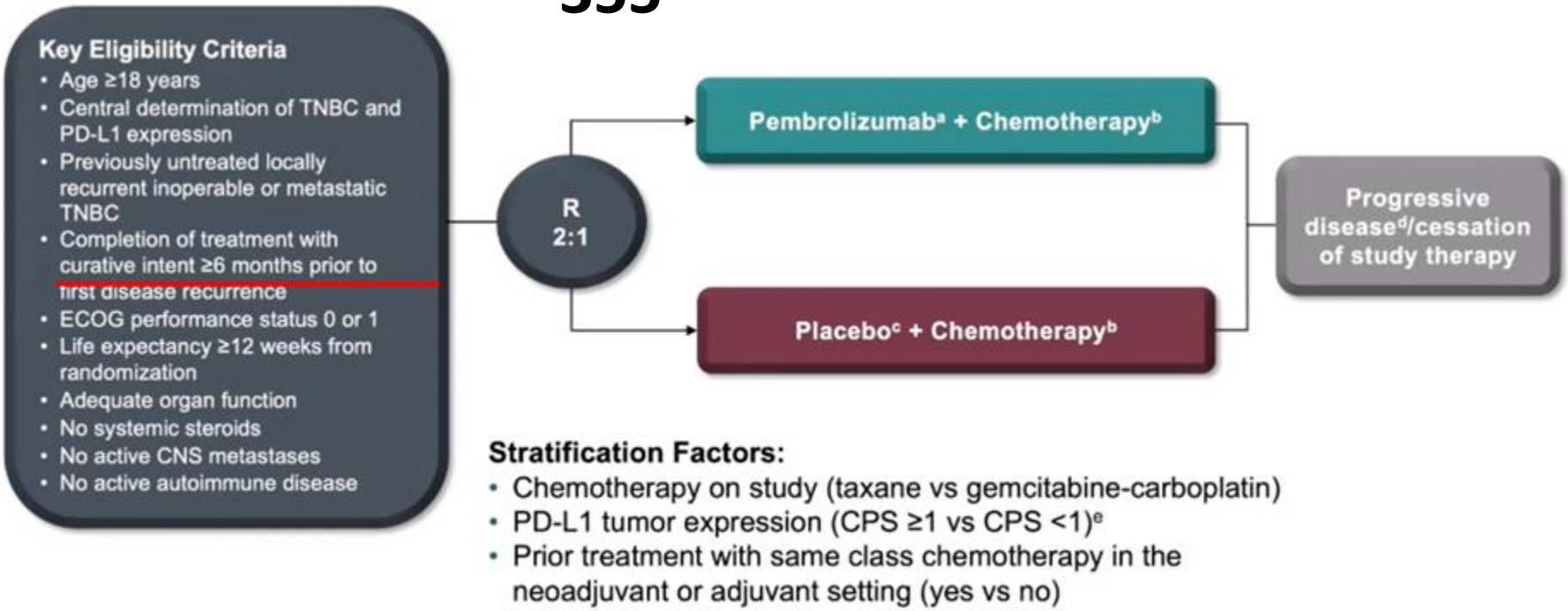
TNBC < 1 cm	upfront surgery -> followed by docetaxel and cyclophosphamide
TNBC 1-2 cm	upfront surgery/neoadjuvant ….. ??
TNBC >2 cm or LN positive	KEYNOTE 522 regimen
pCR post NACT and pembrolizumab	irAE/ toxicities – can discontinue pembrolizumab
Residual disease (gBRCA mutation)	Olaparib + pembrolizumab
Residual disease (gBRCA wild-type)	Capecitabine + pembrolizumab
Residual disease (gPALB2, sBRCA1/2)	Consider Olaparib vs. capecitabine + pembrolizumab

Weekly carboplatin should be used as part of KEYNOTE 522 regimen

Personal communication from Gandhi S.

ADVANCED STAGE

KEYNOTE 355

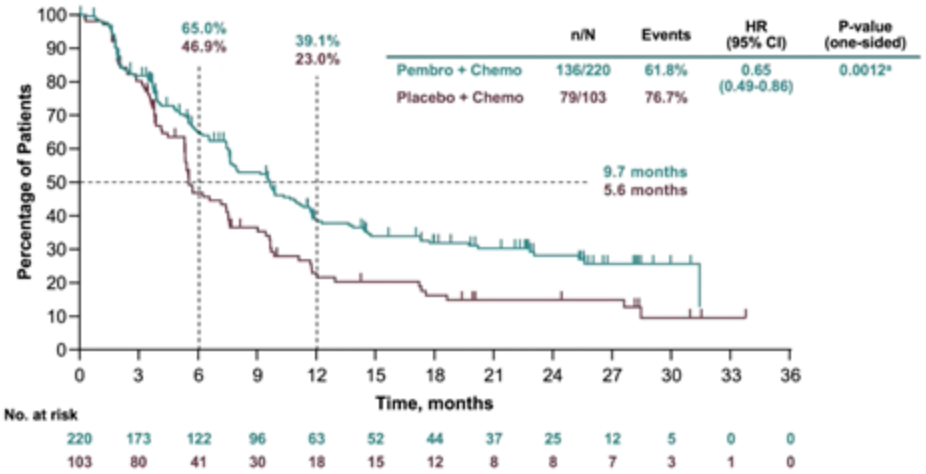


[a]Pembrolizumab 200 mg IV Q3W.
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days.
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days.
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days.

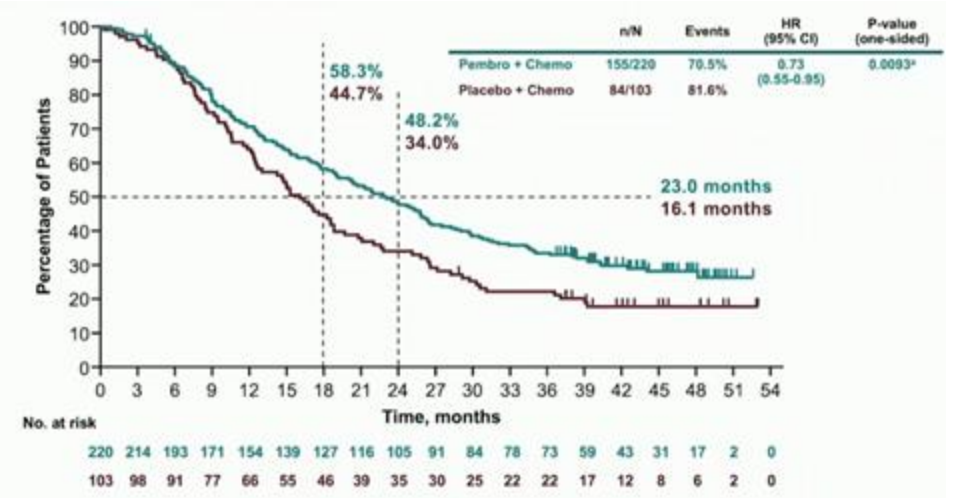
[c]Normal saline.
[d]Treatment may be continued until confirmation of progressive disease.
[e]PD-L1 CPS at cutoff 10 was not a stratification factor.

Rugo H. SABCS 2021

PDL1 CPS >= 10



Progression free survival



Overall survival

Only for 40% metastatic TNBC patients who are PD-L1 positive

Rugo H. SABCS 2021

BEGONIA (*NCT03742102*)

Key Eligibility
- Female ≥ 18 yo
- Metastatic or inoperable locally advanced TNBC
- 1L metastatic setting
- ≥ 12 months since prior taxane therapy
- No prior ICI or Topo1-based ADC
- ECOG 0-1
- No history of pneumonitis (Arm 6)

Endpoints
- **Primary:** safety and tolerability
- **Secondary**: ORR, PFS, DoR, OS

- Tumor response evaluated every 6 weeks for first 48 weeks then every 12 weeks
- PD-L1 expression measured SP263 (≥ 10% tumor area positivity)

Unresectable, HR-, HER2 low breast cancer
[IHC2+/ISH-, IHC 1+/ISH-, IHC 1+/ISH untested]

Durvalumab 1120mg q3 weeks

Trastuzumab deruxtecan 5.4mg/kg q3 weeks

Antibody-Drug Conjugate
HER2 antibody + Topo1 inhibitor payload

Unresectable, HR-, HER2- breast cancer

Durvalumab 1120mg q3 weeks

Datopotamab deruxetecan 6mg/kg q3 weeks

Antibody-Drug Conjugate
TROP-2 antibody + Topo1 inhibitor payload

Gatti-Mays M. SABCS 2022; Schmid et al. SABCS 2022

	T-DXd + Durvalumab *PD 11-08* *BEGONIA, Arm 6*	T-DXd *DESTINY- Breast04* *Modi et al. NEJM. 2022.*	Dato-DXd + Durvalumab *PD 11-09* *BEGONIA, Arm 7*	Dato-DXd *TROPION-PanTumor01* *Krop et al. SABCS 2021.*
Prior Tx*	***1L Metastatic*** ***27% no prior tx***	***Median of 3 prior tx*** ***62% had ≥ 3 prior***	***1L Metastatic*** ***41% no prior tx***	***Median of 3 prior tx*** ***68% had ≥ 2 prior***
ORR	**56.9%**	**50%**	**73.6%**	**34%** *52% in Trop2 ADC naïve*
mPFS	***12.6 months*** *(8.3 to not calculated)*	**8.5 months** *(4.3 to 11.7)*	---	---
Toxicity	*GI symptoms, fatigue, neutropenia, alopecia*		*GI symptoms, stomatitis, alopecia, fatigue*	

**BEGONIA study was for 1st line, metastatic TNBC, whereas both DESTINY-Breast04 and TROPION were in heavily treated patients*

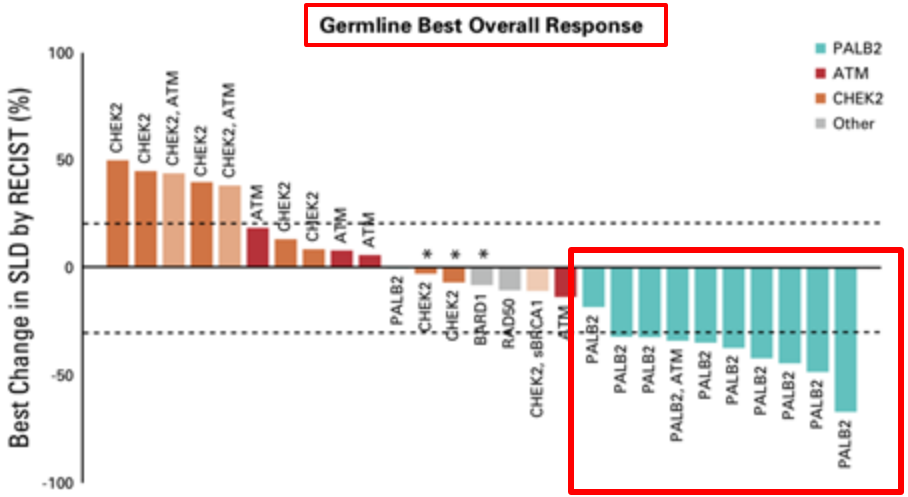
Gatti-Mays M. SABCS 2022; Schmid et al. SABCS 202

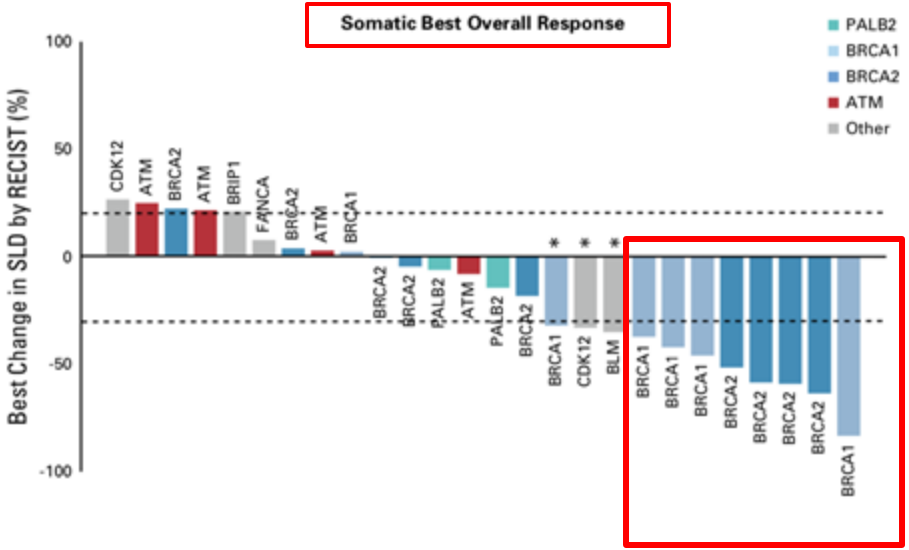
	KEYNOTE 355	T-DXd + Durvalumab	Dato-DXd + Durvalumab
ORR	ITT: 41% PDL1 CPS >=10 : 53.2%	56.9%	73.6%
mPFS	ITT: 7.5 months PDL1 CPS >= 10: 9.7 months	12.6 months	-----

Will PD-L1 status no longer be a good biomarker for immune response ?

Gatti-Mays M. SABCS 2022; Schmid et al. SABCS 2022
Personal communication from S. Gandhi

TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes





Tung NM et al. JCO 2020

PARP inhibitors in metastatic TNBC

Germline BRCA 1/2 mutations ☑

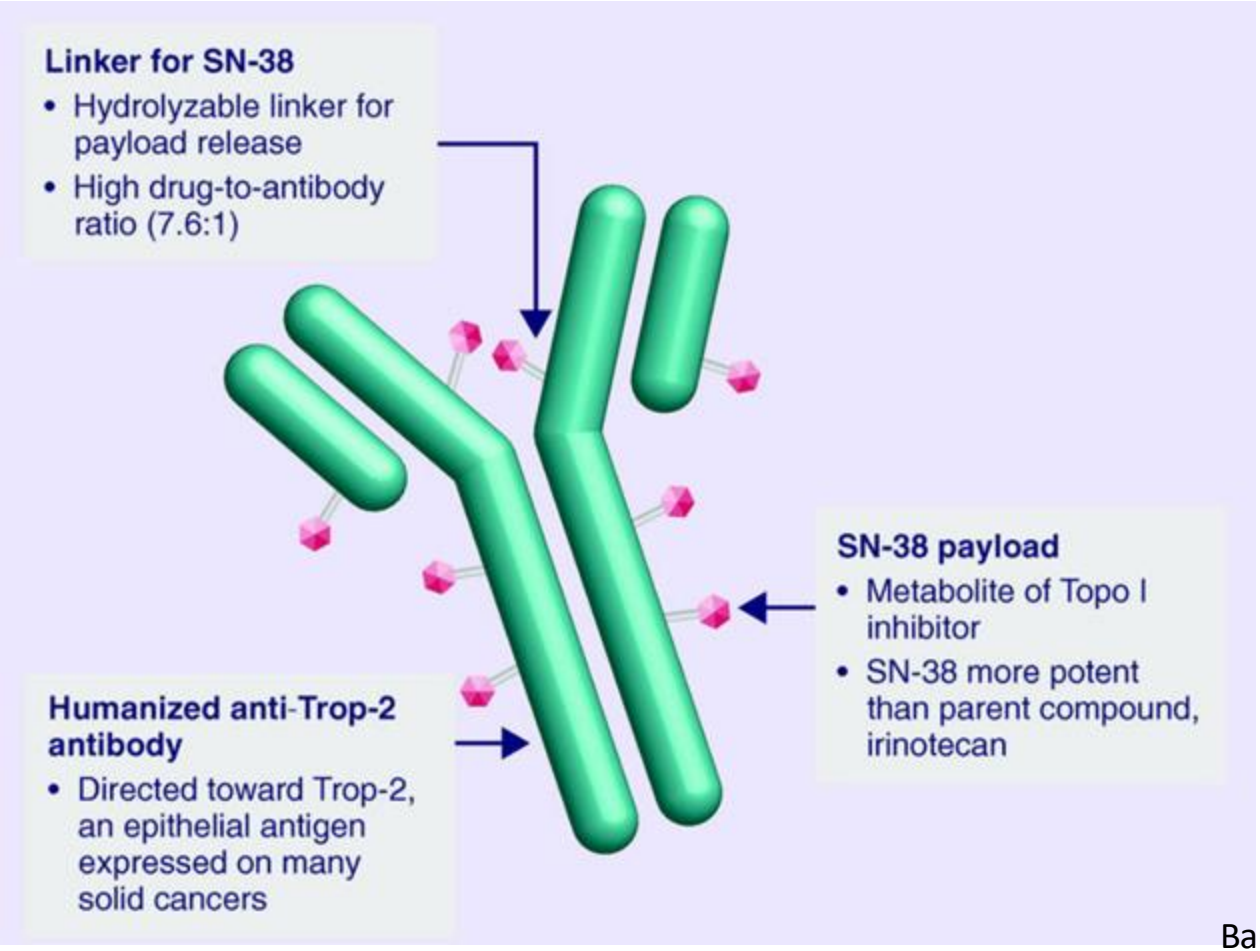
Somatic BRCA 1/2 mutations ☑

Germline PALB2 mutations ☑

PARP inhibitors in BRCA wildtype: NOT YET

Personal communication from Gandhi

Sacituzumab Govitecan



Bardia A et al. NEJM

Phase 3 ASCENT Trial: Sacituzumab Govitecan vs TPC in mTNBC

Metastatic TNB

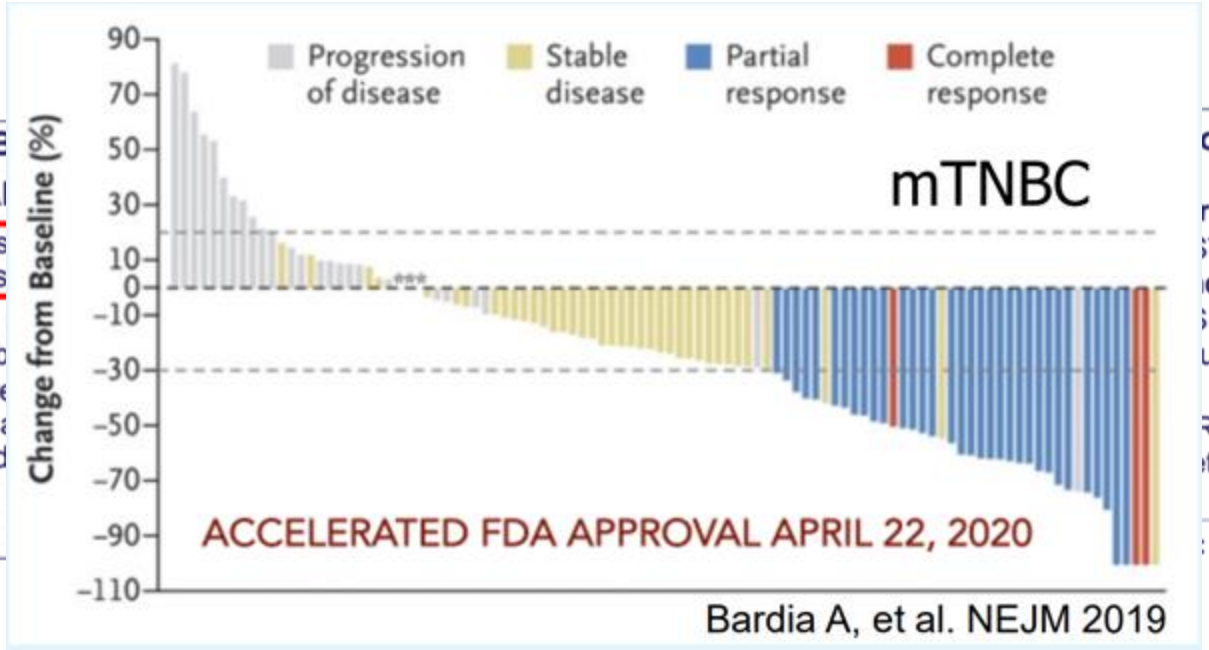
(per ASCO/CA

≥2 chemotherapies
advanced diseas

[no upper limit; 1 of the
prior regimens could b
progression that occurre
a 12-month period a
completion of (neo)ad
therapy)]

N=529

NCT02574455



oints

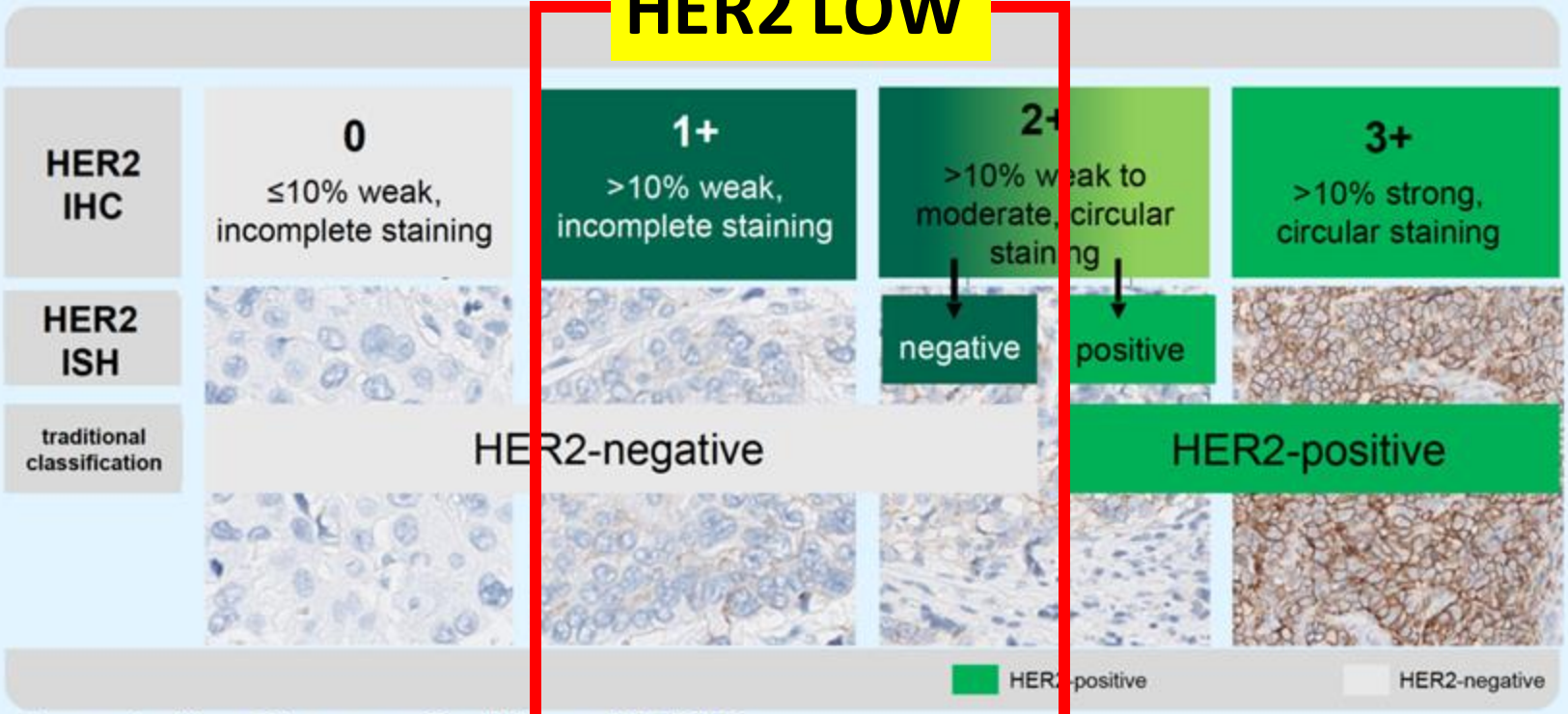
ry
†
dary
for the full
ulation‡
ORR,
R, TTR,
ty

March 11, 2020

* TPC options: capecitabine, eribulin, gemcitabine, vinorelbine

Bardia A et al. NEJM

HER2 Expression in Breast Cancer

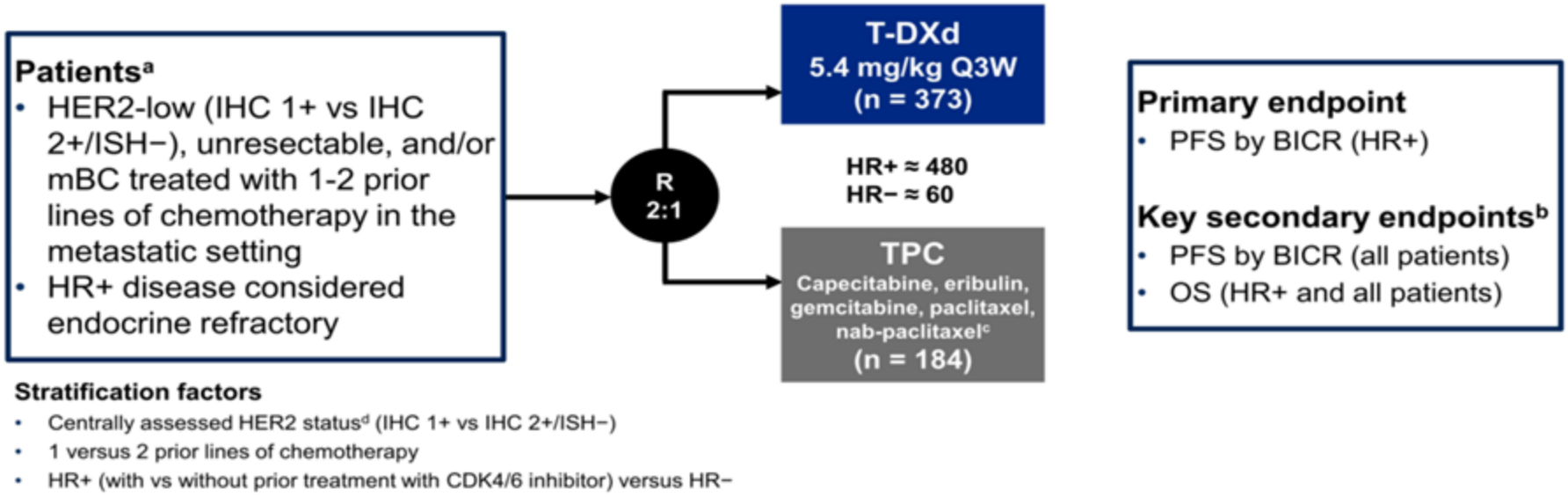


Presented by: Giuseppe Curigliano, MD PhD

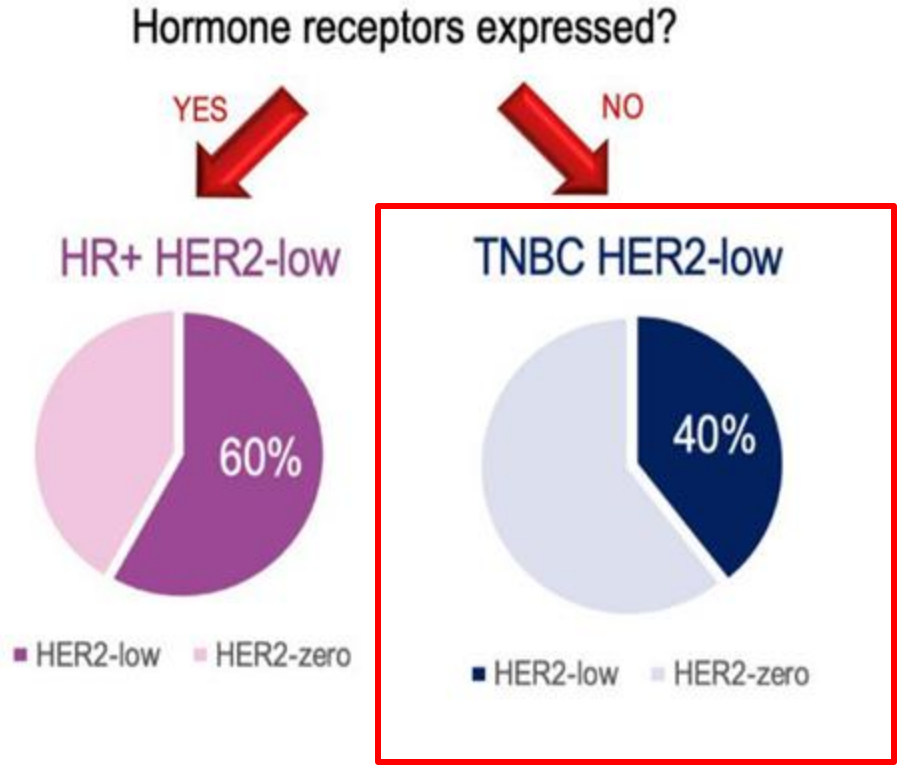
Denkert, Lebeau, Schildhaus, Jackisch, Rüschoff „Die Pathologie, 2022

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



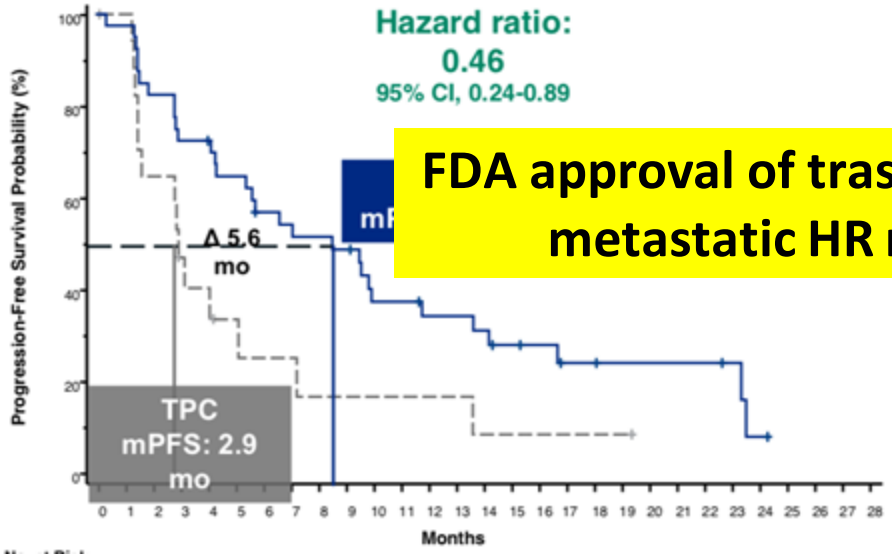
Modi S et al. NEJM 2022



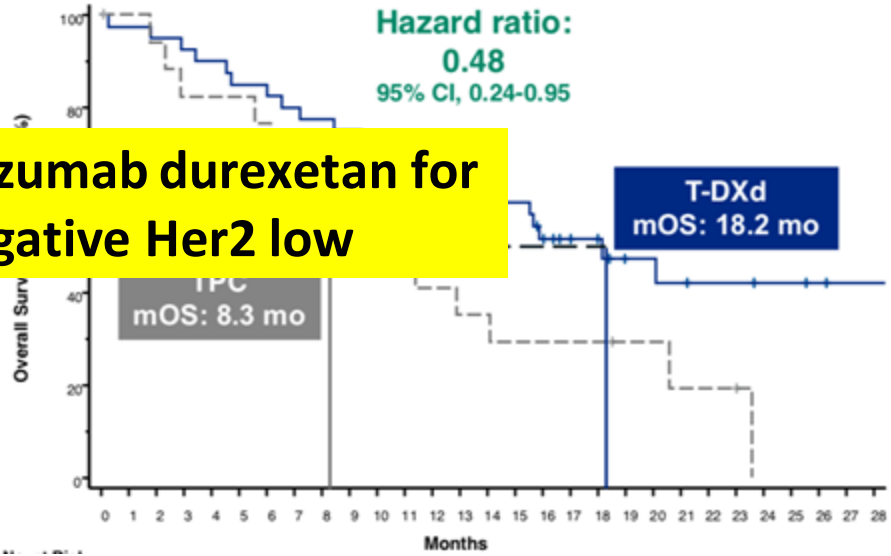
Modi S et al. NEJM 2022

PFS and OS in HR− (Exploratory Endpoints)

Hormone receptor-negative

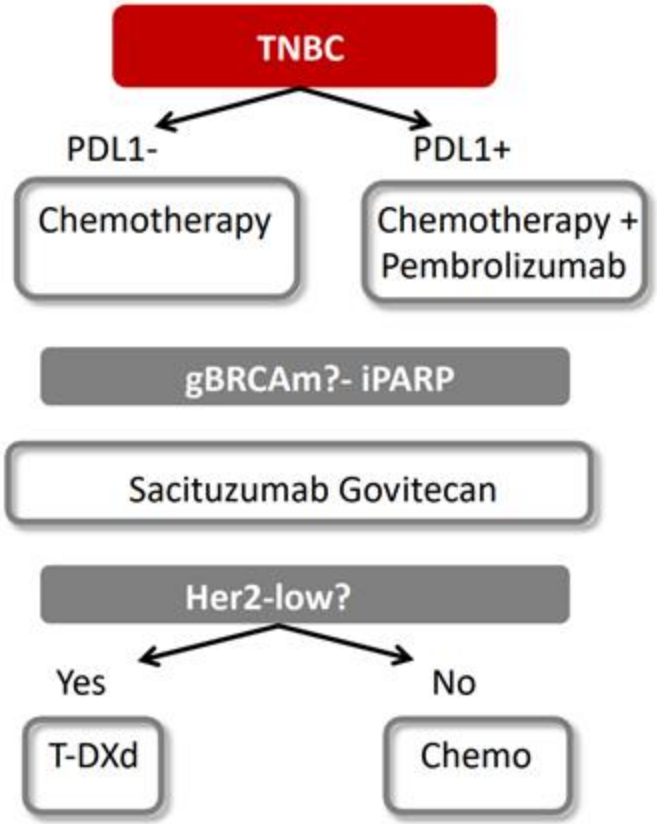


FDA approval of trastuzumab durexetan for metastatic HR negative Her2 low



Modi S et al. NEJM 2022

CONCLUSIONS : Therapy sequencing in metastatic TNBC



CLINICAL TRIALS !!

Chavez M, SABCS 2022

CLINICAL TRIALS AT ROSWELL PARK

- Metastatic triple negative and HER2 positive breast cancer with asymptomatic brain metastases : Dendritic cell vaccine + pembrolizumab
- Metastatic TNBC patients : Chemokine modulation therapy + pembrolizumab
- Biopsy accessible metastatic TNBC: Intratumoral dendritic cell vaccine + pembrolizumab

Personal communication from Gandhi

Thank you