

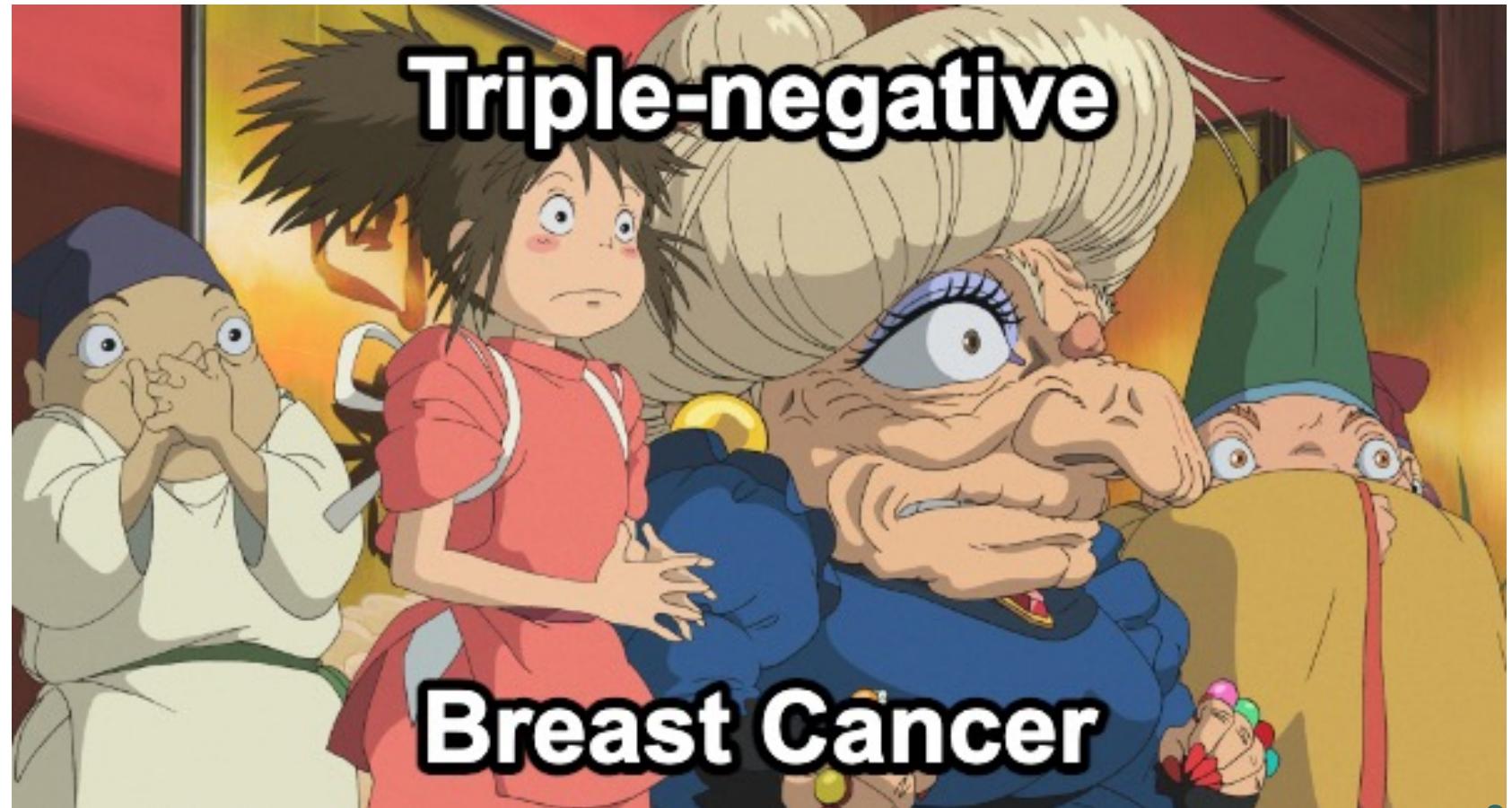
Treatment of Early Triple-Negative Breast Cancer

Beginning, End, and Everything in Between

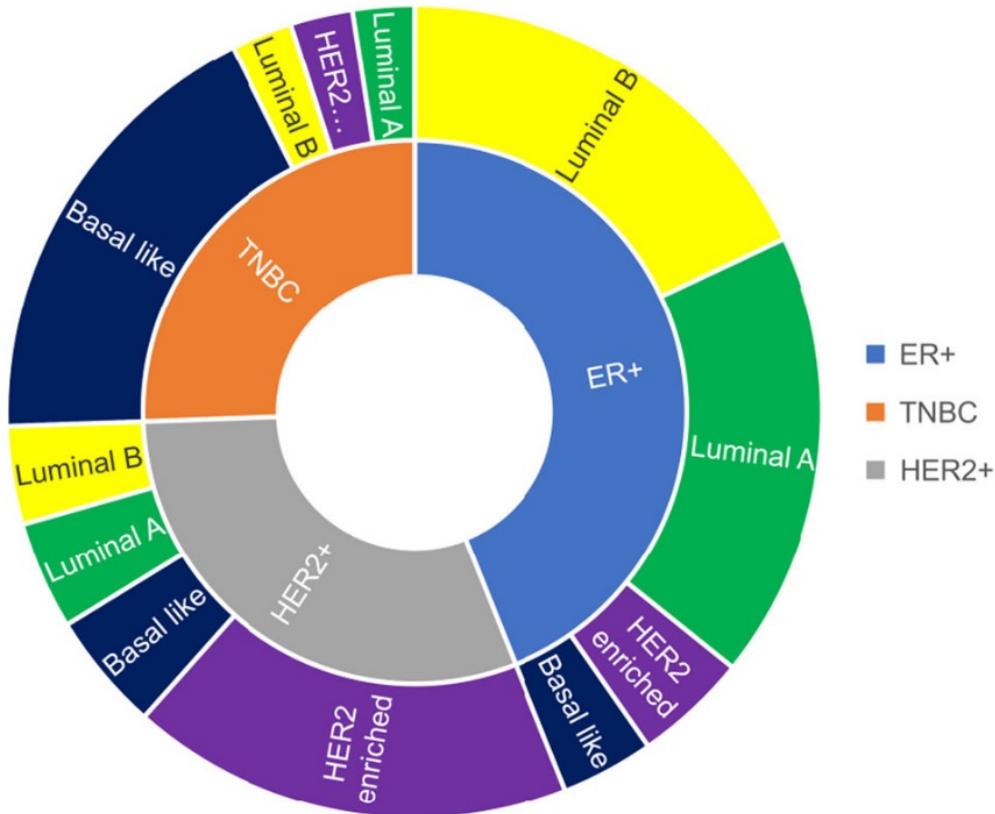
Fellow 1 林協霆
鍾奇峰醫師

INTRODUCTION

- early stage TNBC, remains the most challenging breast cancer subtype to treat
- limited targeted therapies
- higher rates of relapse and
- greater risk of mortality.



Intrinsic molecular subtypes of breast cancer



Molecular subtypes	Triple negative ER-, PR-, HER2-	HER2+ HER2+, ER-, PR-	Luminal B Luminal B+, ER-, PR-, HER2-	Luminal A Luminal A+, ER+, PR+, HER2-
% of breast cancers	15-20%	10-15%	20%	40%
Receptor expression		HER2		ER+/PR+
Histologic grade	High (grade III)			Low (grade I)
Level of cell differentiation				
Prognosis	Poor			Good
Correlates to histologic grade				
Response to medical therapy	Chemotherapy	Trastuzumab		Endocrine
	Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.			
	Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.			

Key Points on TNBC

- TNBC: 10%-15% of breast cancer
- The prevalence of TNBC is higher in:
 - young women (50 years and younger)
 - BRCA 1 mutation carriers
 - African American women
- adverse biological features
 - high grade,
 - high mitotic count
 - p53 positivity

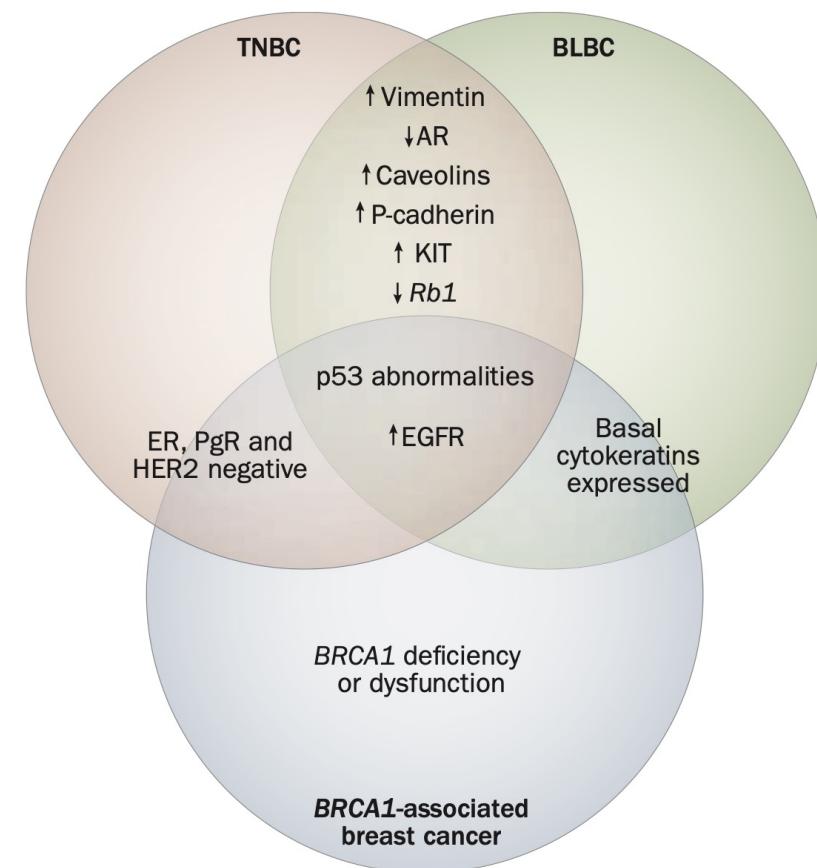


Figure 1 | Shared features of triple-negative, basal-like and *BRCA1*-associated breast cancers. Abbreviations: AR, androgen receptor, BLBC, basal-like breast cancer; ER, estrogen receptor; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

Breast Cancer staging: AJCC 8th

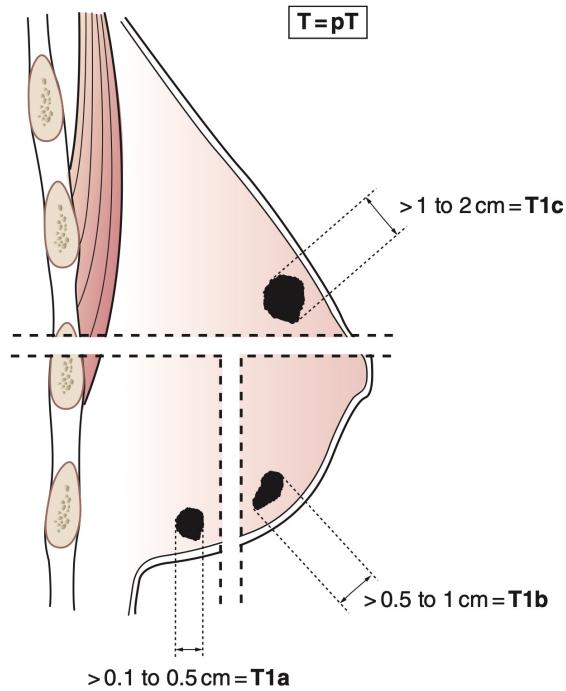


Fig. 320

>0.1 to 0.5 cm = T1a

>0.5 to 1 cm = T1b

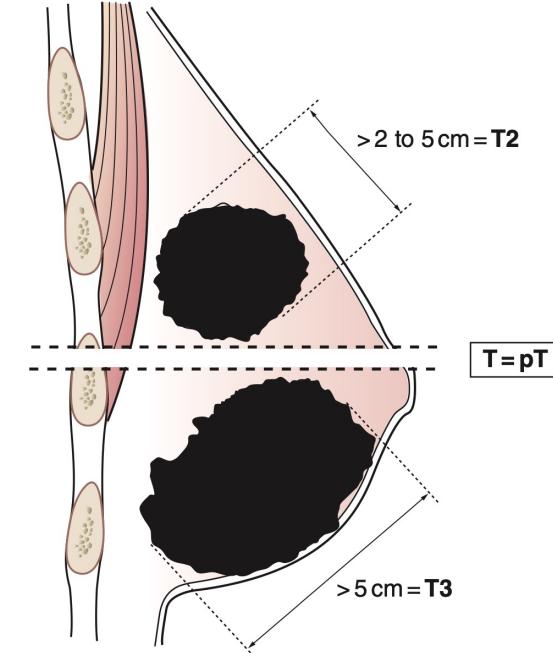


Fig. 321

>5 cm = T3

- pN1 – 1-3 axillary LN
- pN2 – 4-9 axillary LN, or + ipsilateral internal mammary LN

Breast carcinoma TNM anatomic stage group AJCC UICC 8th edition

When T is...	And N is...	And M is...	Then the stage group is...
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC

- N1: Stage II+
- T2: Stage II+
- T3N0: Stage II ✨
- N2: Stage III+
- T4: Stage III+



Risk profile and associated survival outcomes

Stage	Risk profile	N	Five-year DSS (%)	95% CI	Five-year OS (%)	95% CI
IIA	0	31	100		96.8	79.2-99.5
	1	634	99.4	97.5-99.8	97.1	94.7-98.4
	2	236	97.5	93.2-99.1	94.1	88.7-97
	3	98	91	81.8-95.7	88.2	78.5-93.8
IIB	0	11	100		100	
	1	309	96.9	92.6-98.8	94.6	89.6-97.2
	2	107	92.9	83.6-97.1	89.3	80.1-94.4
	3	40	91.5	75.6-97.2	91.5	75.6-97.2
IIIA	0	3	100		100	
	1	134	98.3	88.2-99.8	91.5	82.6-96
	2	50	92.2	77.2-97.5	90.3	75.7-96.3
	3	7	68.6	21.3-91.2	68.6	21.3-91.2
IIIC	0	0				
	1	39	92.2	72.1-98.0	84.4	63.7-93.9
	2	16	80.8	51.4-93.4	80.8	51.4-93.4
	3	10	33.3	6.3-64.6	33.3	6.3-64.6

1 points

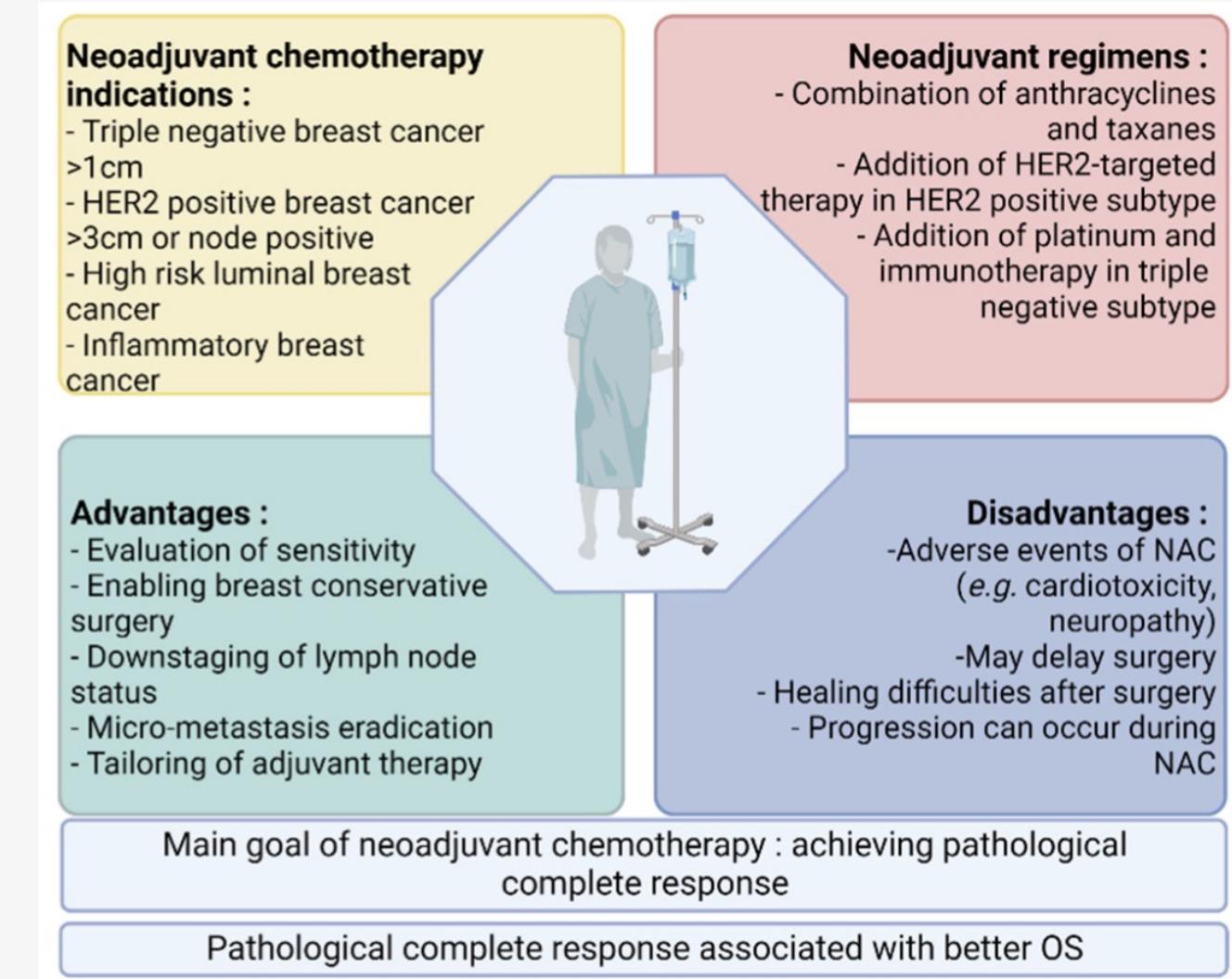
- Grade 3
- ER negative ⊖
- HER2 negative ⊖
- e.g. IIIC 3 points: 5yDSS:



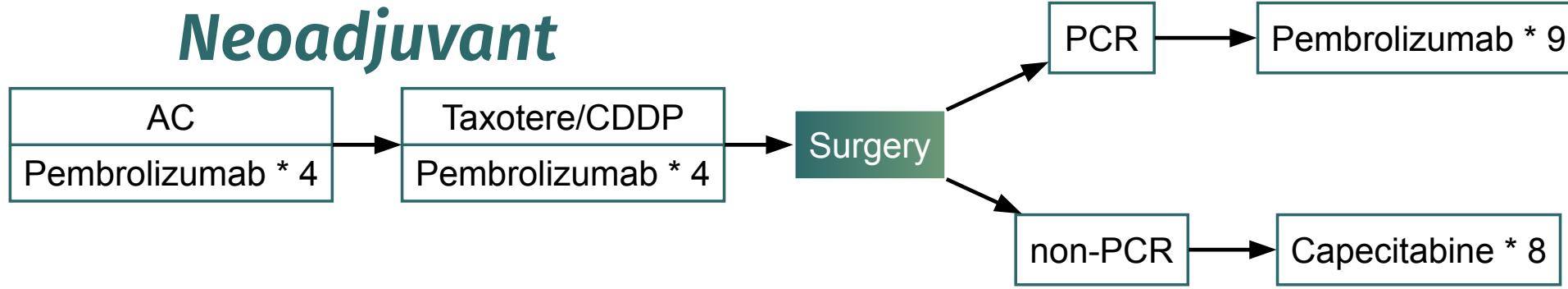
The role of neoadjuvant therapy (NAC) in early breast cancer

X

Figure 1. Overview of current indications, regimens, advantages and disadvantages of NAC.



KFSYSCC guide 2023 (for now)



- Stage IIA: T1N1M0, T2N0M0
- Stage IIB: T2N1M0
- Stage III T3N0M0

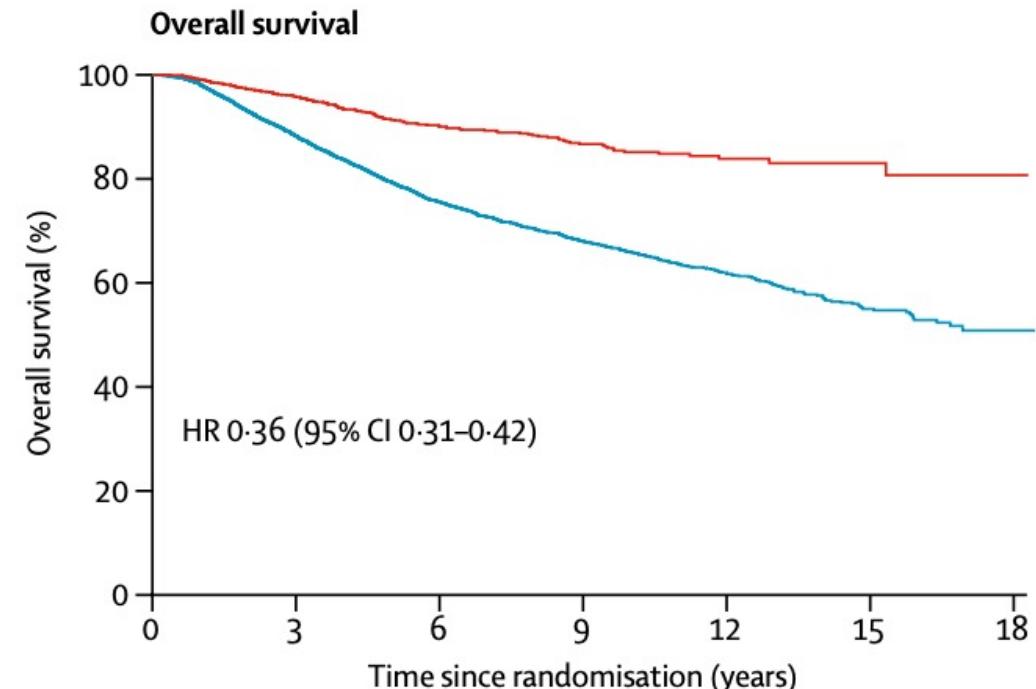
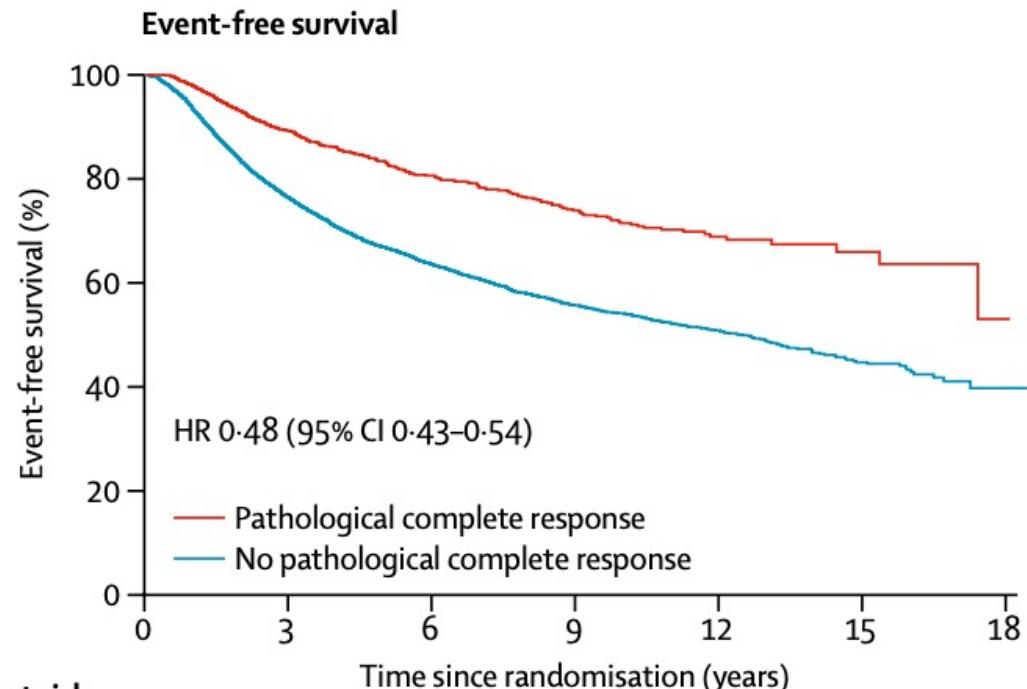
AC: doxorubicin and cyclophosphamide
TAXOTERE: docetaxel
CPPD: cisplatin
pCR: pathological complete response

Complete Pathologic Response

Why complete pathologic response matter?

Complete Pathologic Response (pCR): the goal of NAC

- **no invasive residual disease** in the **breast** or the **lymph nodes** after completing neoadjuvant therapy
 - ypT0 ypN0
 - ypT0/is ypN0
- The achievement of a pathologic complete response (pCR) after NAC
 - marker for systemic therapy sensitivity.
- pCR a/w improved long-term outcomes in TNBCs, **both EFS and OS**
 - HR:
 - EFS: 0.48, a.k.a. 降低 5 成 2 的復發機會
 - OS: 0.36, a.k.a. 降低 6 成 4 的死亡率



Number at risk							
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1

Figure 2: Associations between pathological complete response and event-free survival and overall survival

ypT0/is ypN0 definition of pathological complete response (ie, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ). HR=hazard ratio.

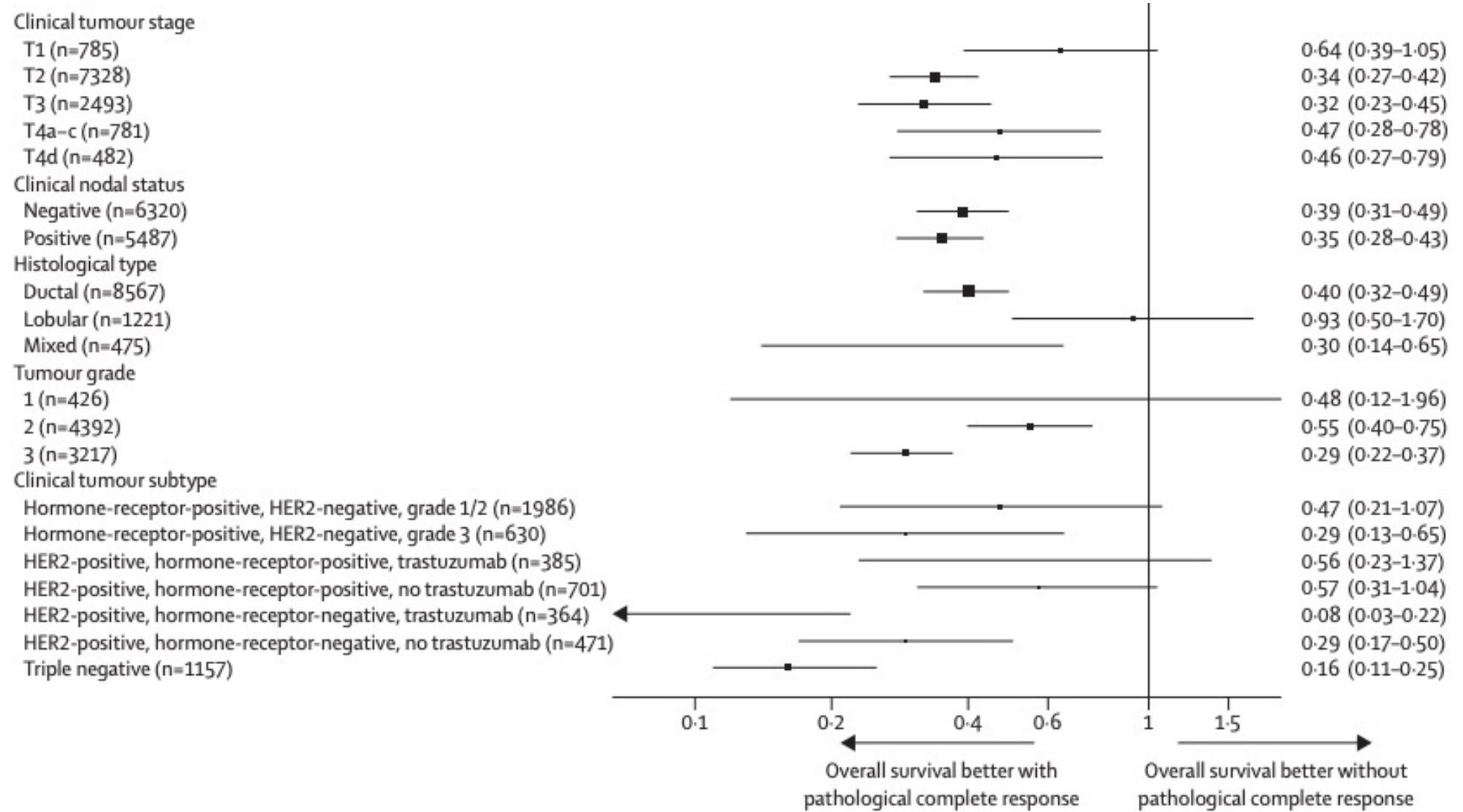


Figure 4: Percentage of patients achieving pathological complete response (A) and HRs for overall survival

The degree of response has been evaluated by residual cancer burden (RCB)

- (2) Primary Tumor Bed
 - Primary Tumor Bed Area:
 - Overall Cancer Cellularity(as percentage of area)
 - Percentage of Cancer That Is in situ Disease
- (2) Lymph Nodes
 - Number of Positive Lymph Nodes
 - Diameter of Largest Metastasis
 - Residual Cancer Burden
 - Residual Cancer Burden Class

Prognostic value of RCB score and RCB class in the overall pooled analysis cohort: EFS, Distance Relapse-free survival

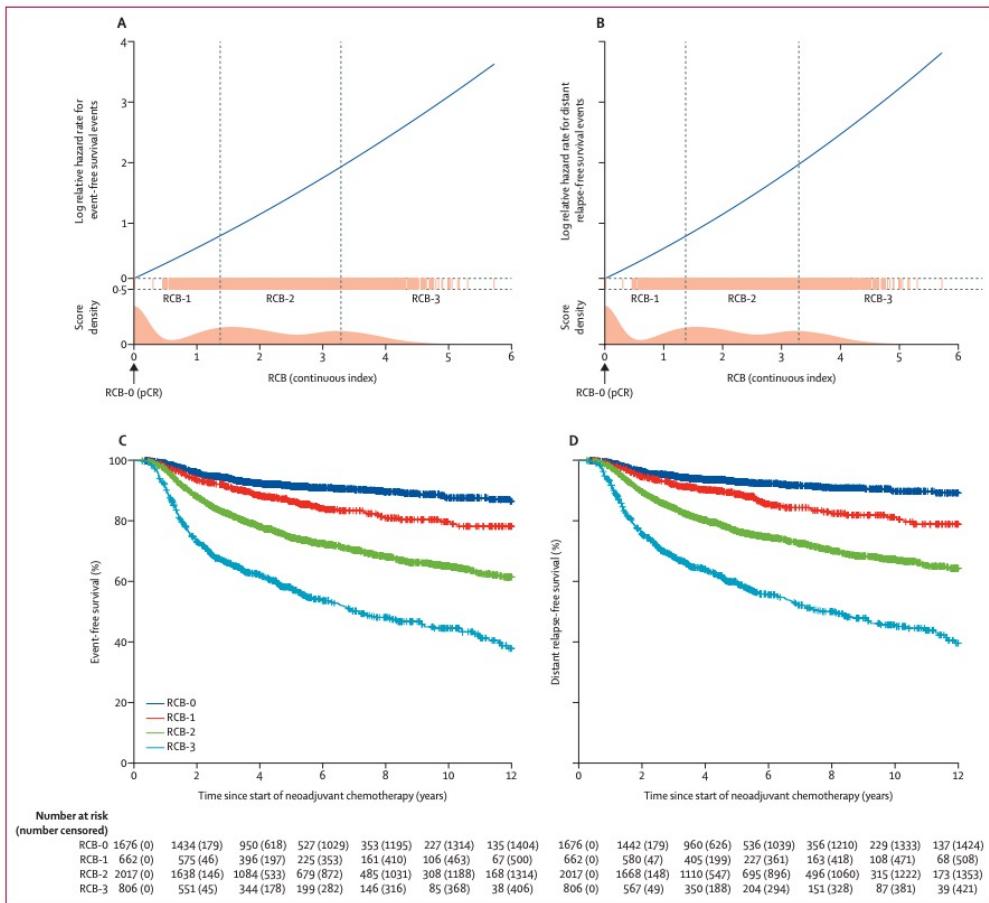
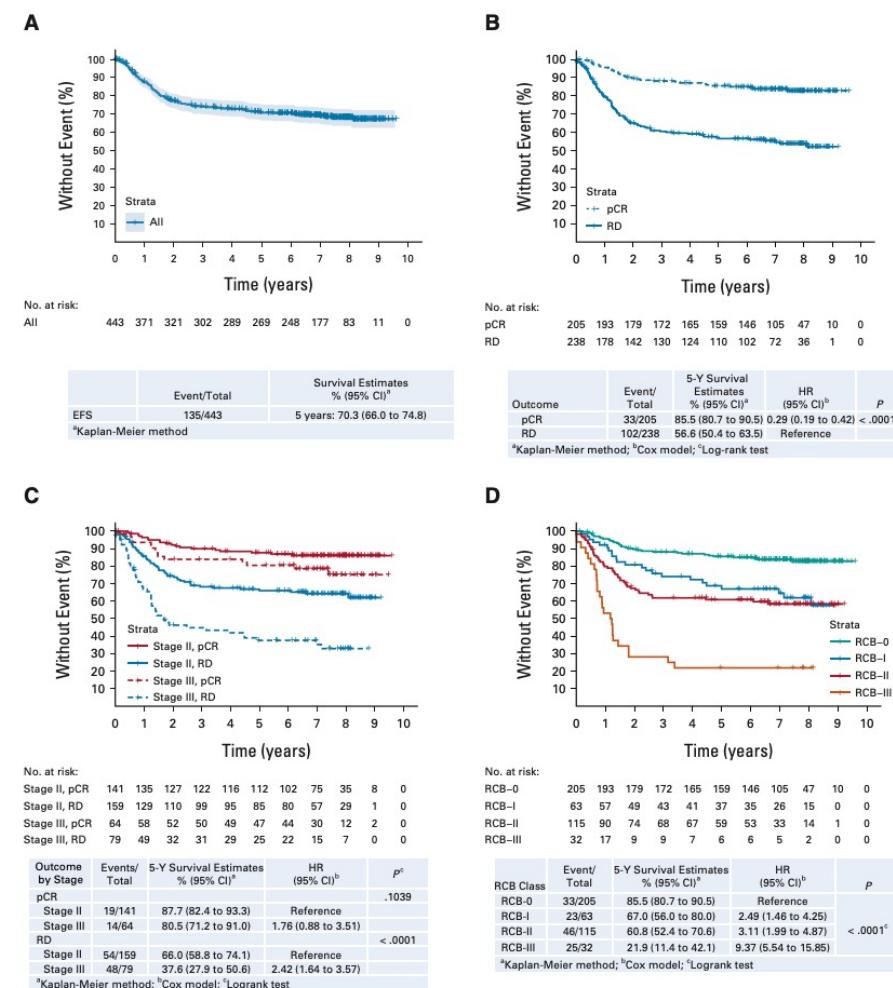
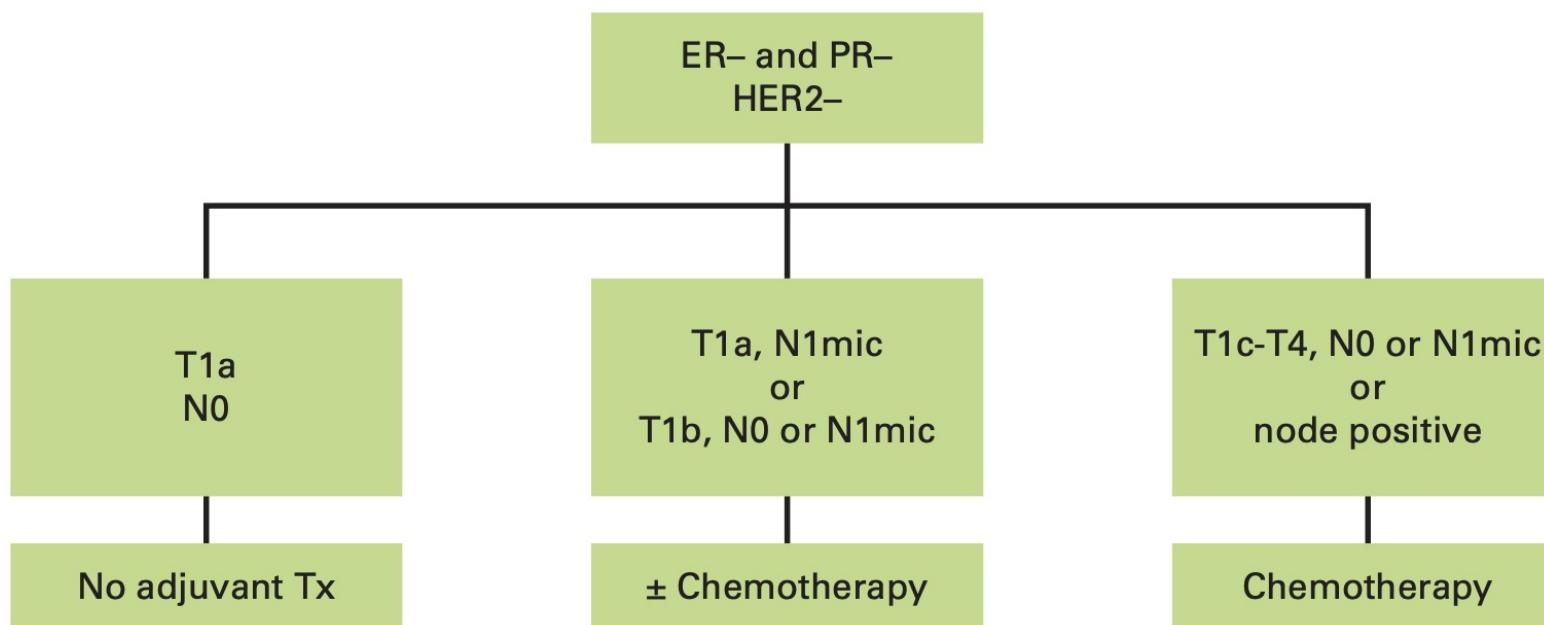


Figure 2: Prognostic value of RCB score and RCB class in the overall pooled analysis cohort

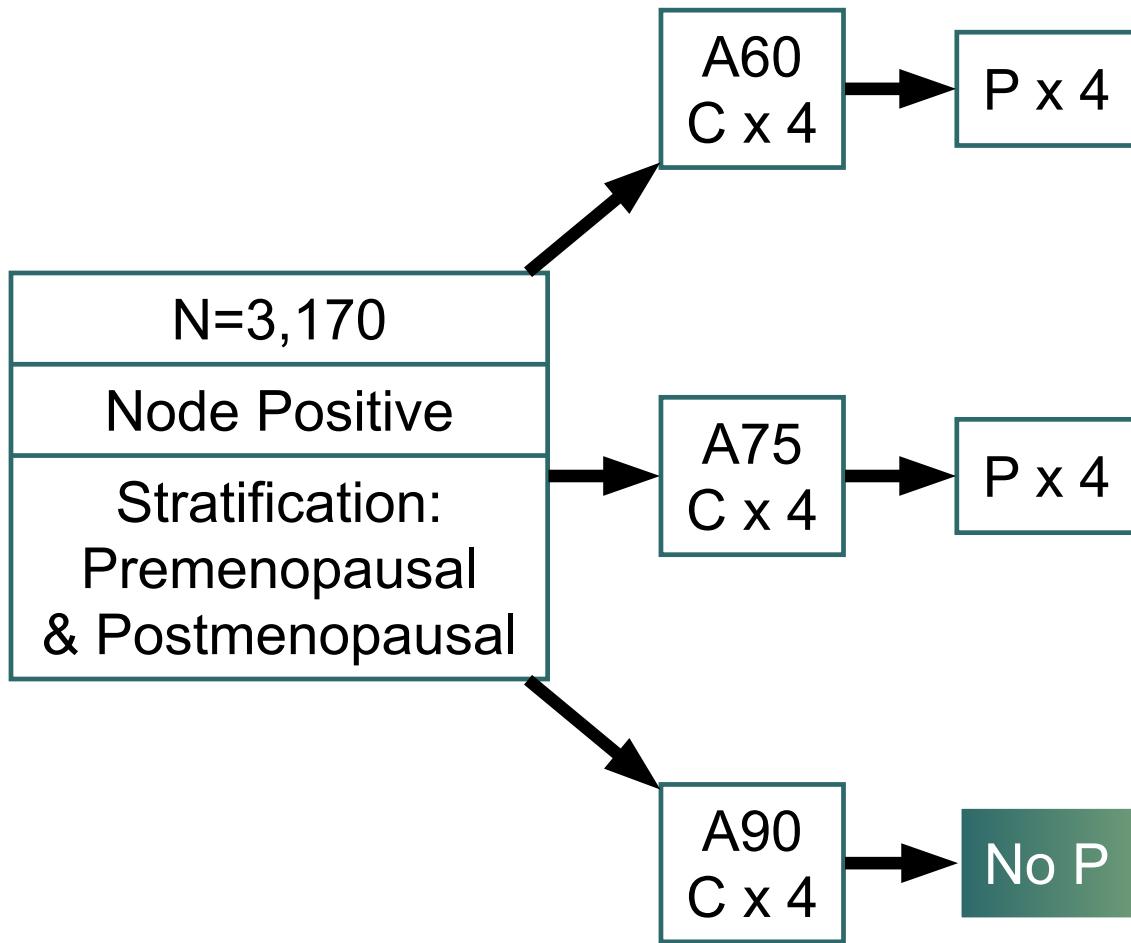
Plots of log relative hazard rate for event-free survival events (A) and distant relapse-free survival events (B) as a function of RCB score. Splines approximation of RCB with two degrees of freedom was used to allow for non-linear effect. A log linear increase in relative hazard rate implies that the hazard ratio associated with change in RCB remains constant over the range of RCB. Thresholds for corresponding RCB classes (RCB-0 to RCB-3) are shown for reference (vertical dashed lines). Vertical bars represent all RCB scores recorded on a continuous scale. Kaplan-Meier plots of event-free survival (C) and distant relapse-free survival (D) stratified by RCB class. Crosses denote patients censored. RCB=residual cancer burden. pCR=pathological complete response.



Neoadjuvant chemotherapy in TNBC



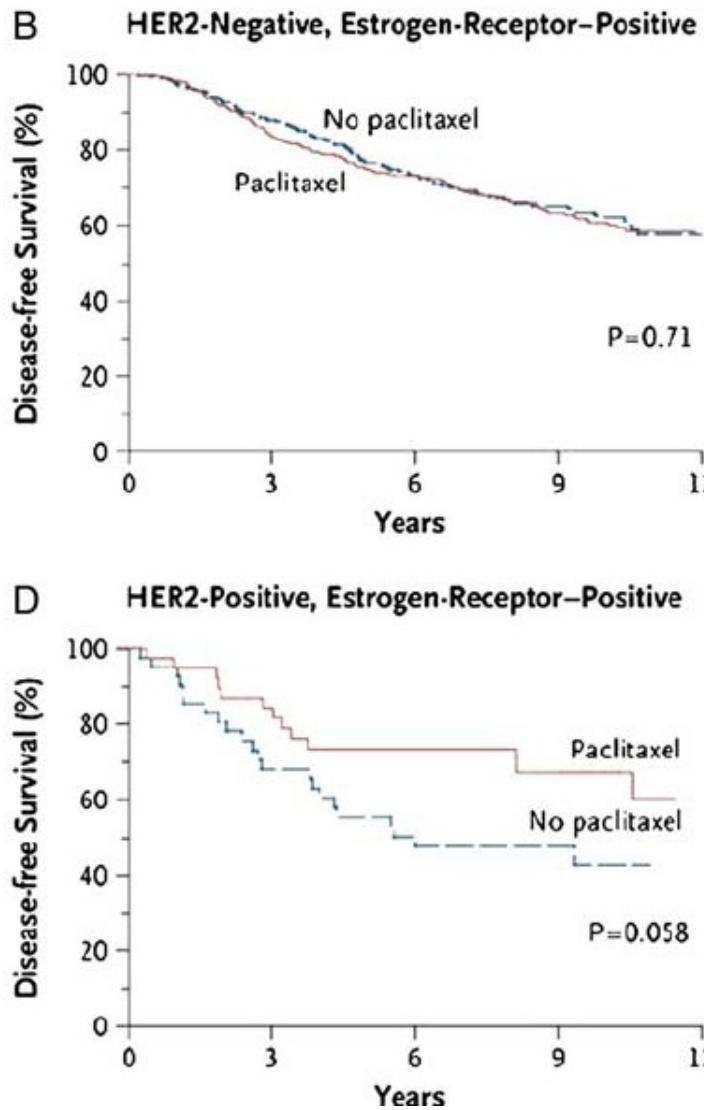
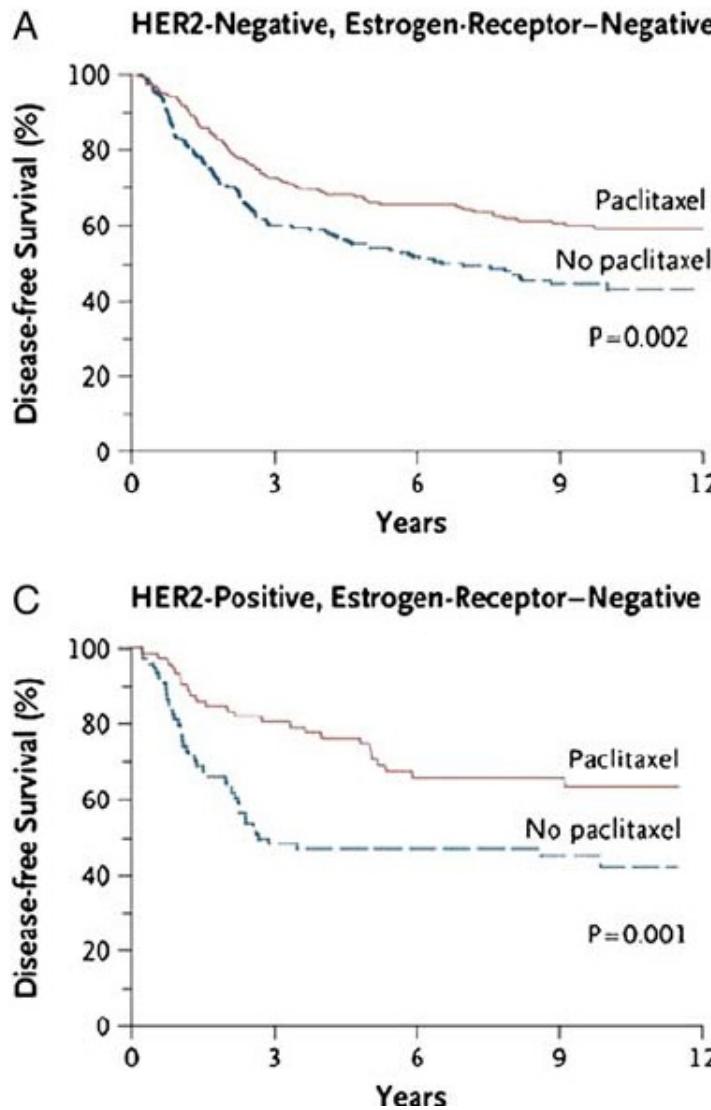
CALGB 9344/Intergroup 0148



randomized trial

- A = Doxorubicin (doses mg/m²)
- C = Cyclophosphamide (600 mg/m²)
- P = Paclitaxel (175 mg/m², 3 hour infusion)

Result



- ± Paclitaxel in Node-Positive Breast Cancer
- adjuvant paclitaxel: survival benefit LN positive BC
- except ER positive, HER2 negative group Fig. B

The Function of Platinum-Based Therapies in neoadjuvant

GeparSixto, randomized phase II study

- neoadjuvant **carboplatin** in stage II or III **TNBC and HER2-positive**
 - 18 weeks of paclitaxel 80 mg/m² IV once weekly and non-pegylated liposomal doxorubicin 20 mg/m² IV once weekly.
-
- Patients with TNBC received simultaneous bevacizumab 15 mg/kg IV once every 3 weeks.
 - Patients were randomly assigned to carboplatin AUC 1.5-2 mg/mL per min IV weekly (n = 296) versus no carboplatin (n = 299).
 - The pCR rate was **53.2% with carboplatin** versus **36.9% without carboplatin** (P = .005) in patients with TNBC

icarboplatin in TNBC

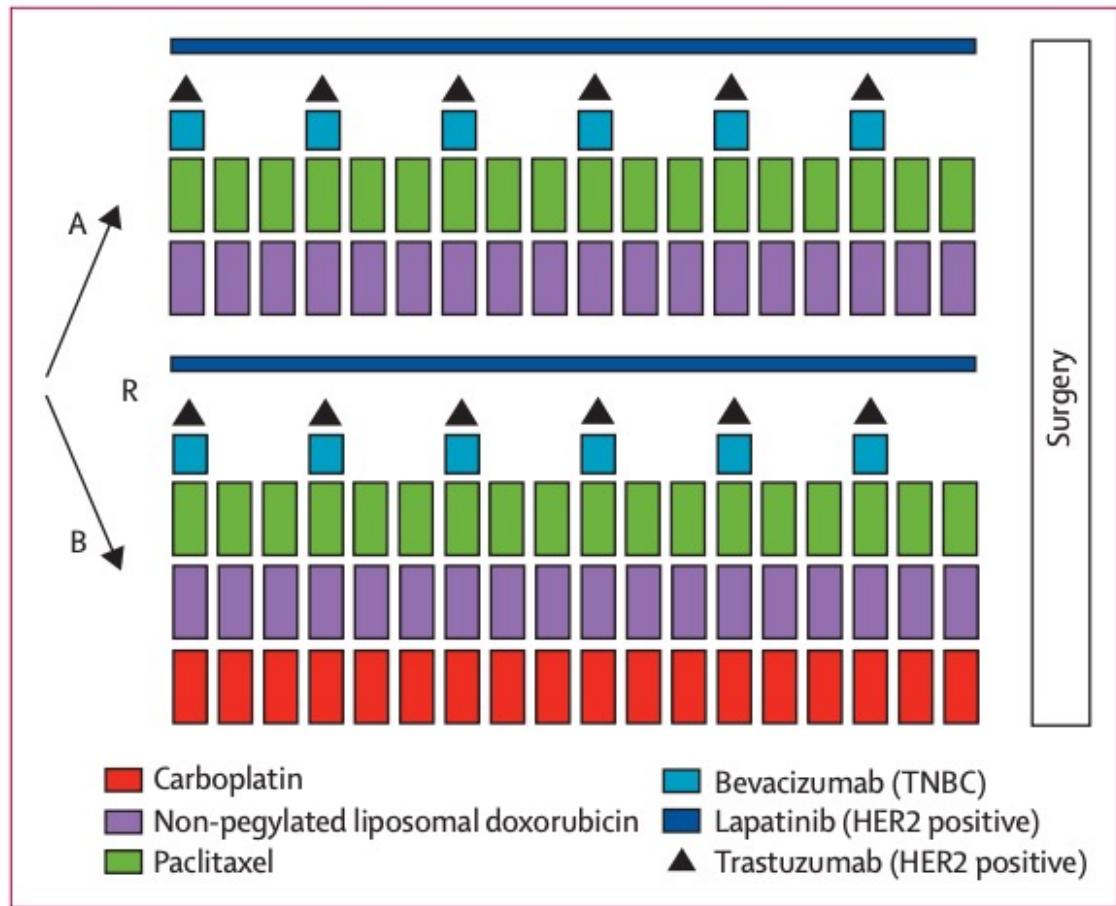
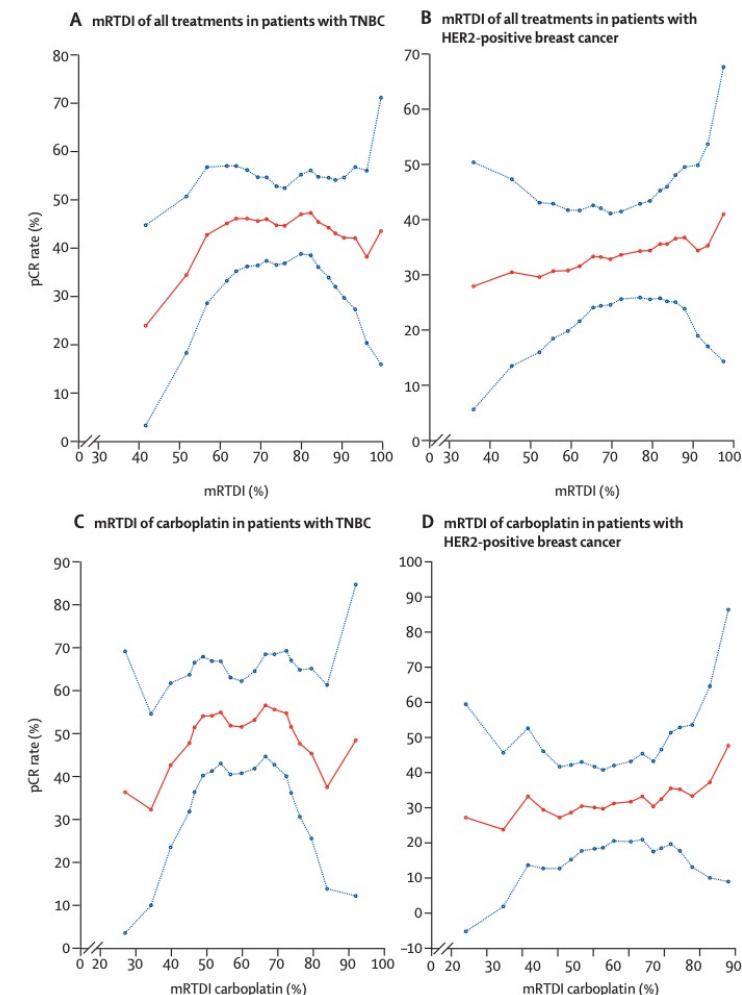


Figure 1: Trial design

Regimens were without (A) and with (B) carboplatin. TNBC=triple-negative breast cancer.

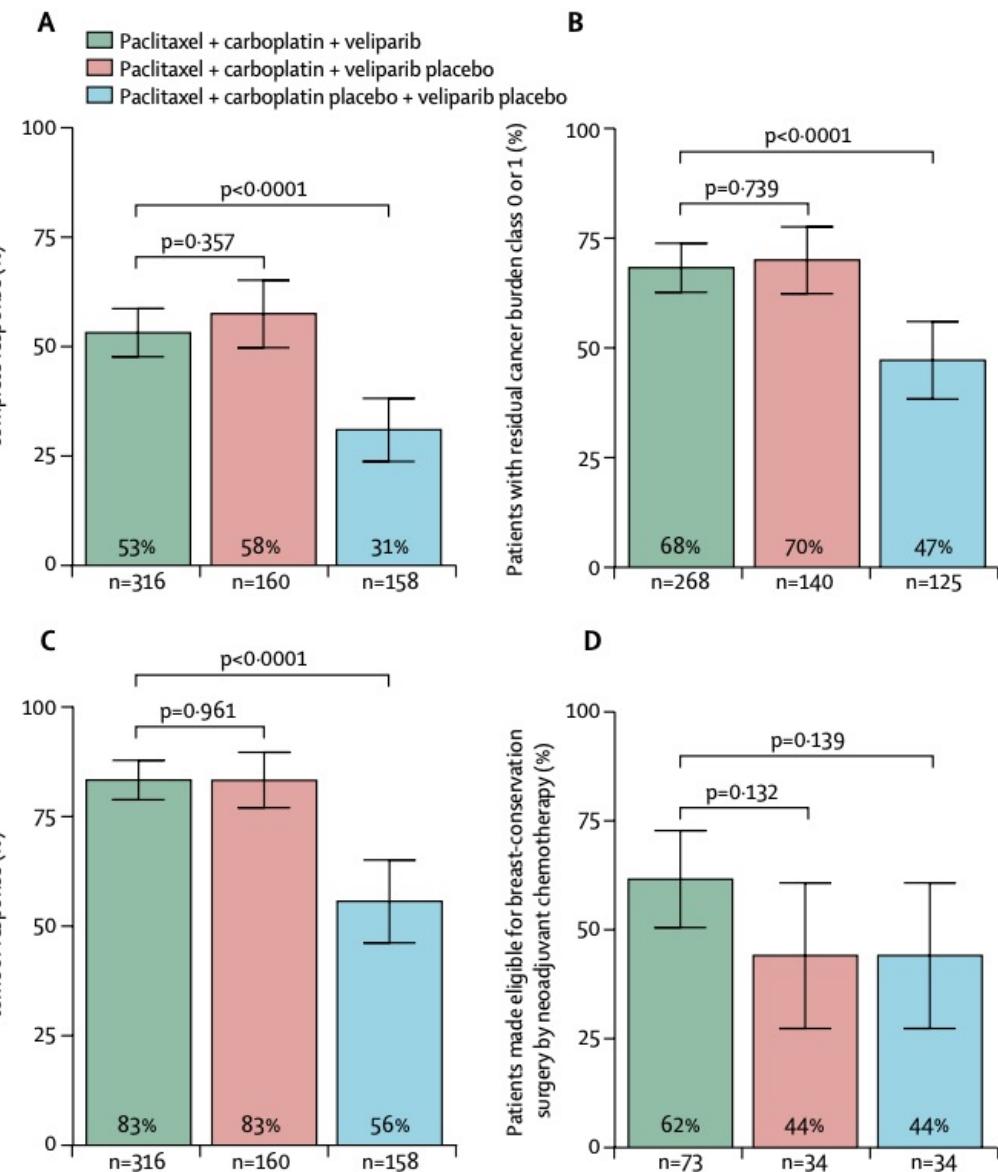


mRTDI=mean relative total dose intensity. TNBC=triple-negative breast cancer. pCR=pathological complete response
y-axis: pCR rate

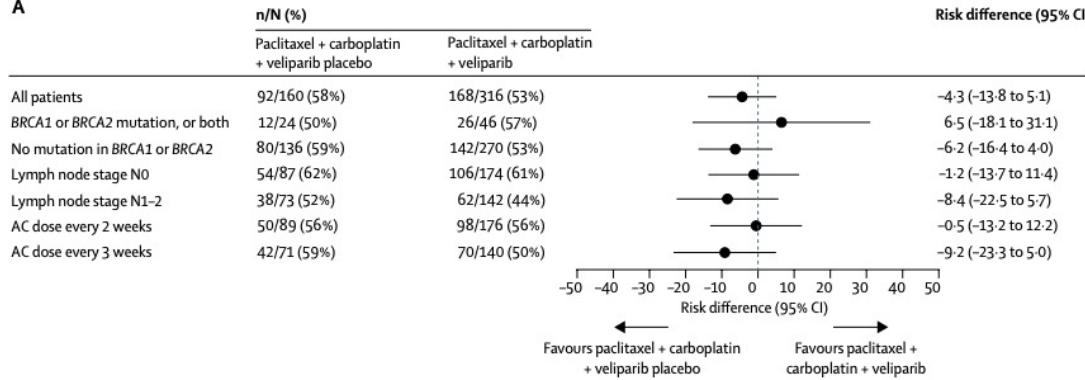
Similarly, the BrighTNess trial, a phase III randomized study

- Phase 3, randomized, double-blind, placebo-controlled trial
- Patients aged 18 years and older
- Previously untreated histologically or cytologically confirmed clinical stage II–III triple-negative breast cancer

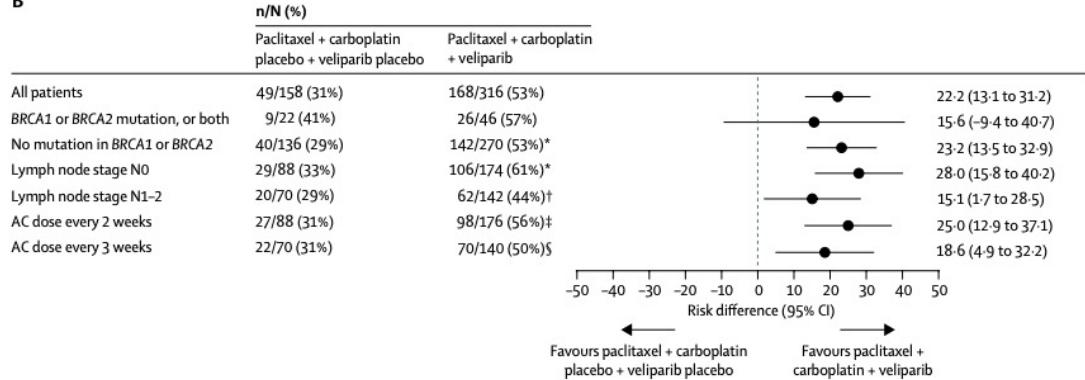
-
- Paclitaxel + carboplatin + veliparib
 - Paclitaxel + carboplatin
 - Paclitaxel
 - 4.5y, HR for EFS was 0.63



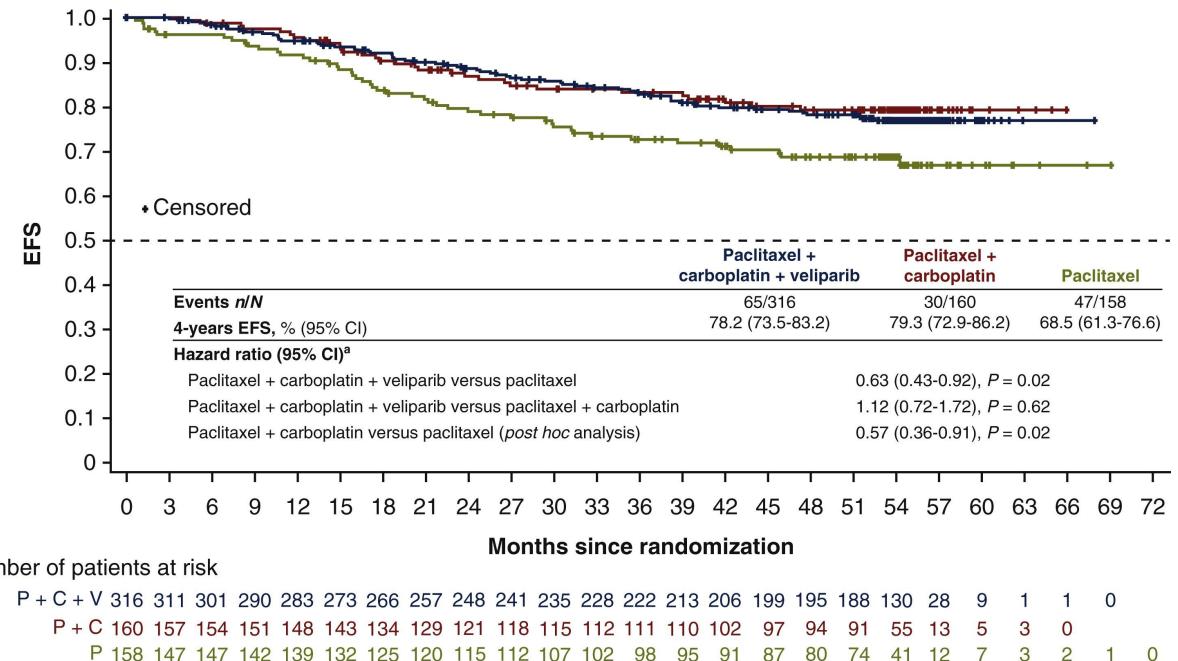
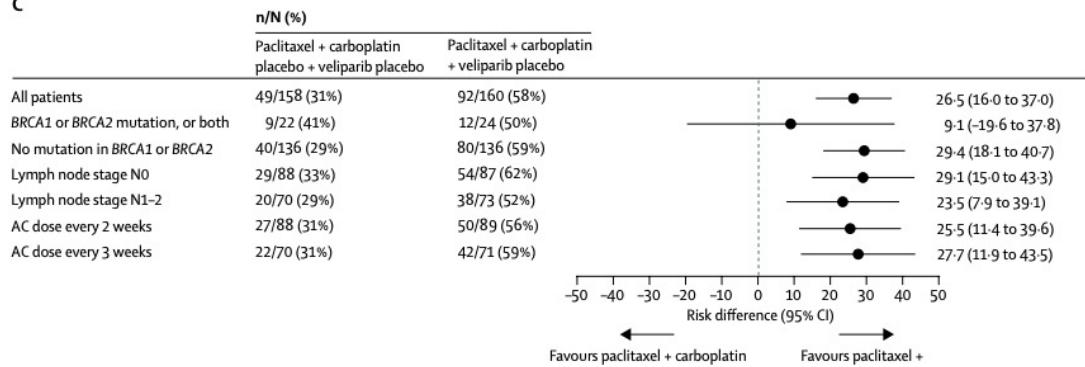
A



B



C



- A : 3 v 2 B : 3 v 1 C : 2 v 1
- carboplatin improve the pCR but veliparib not

Short Wrap up

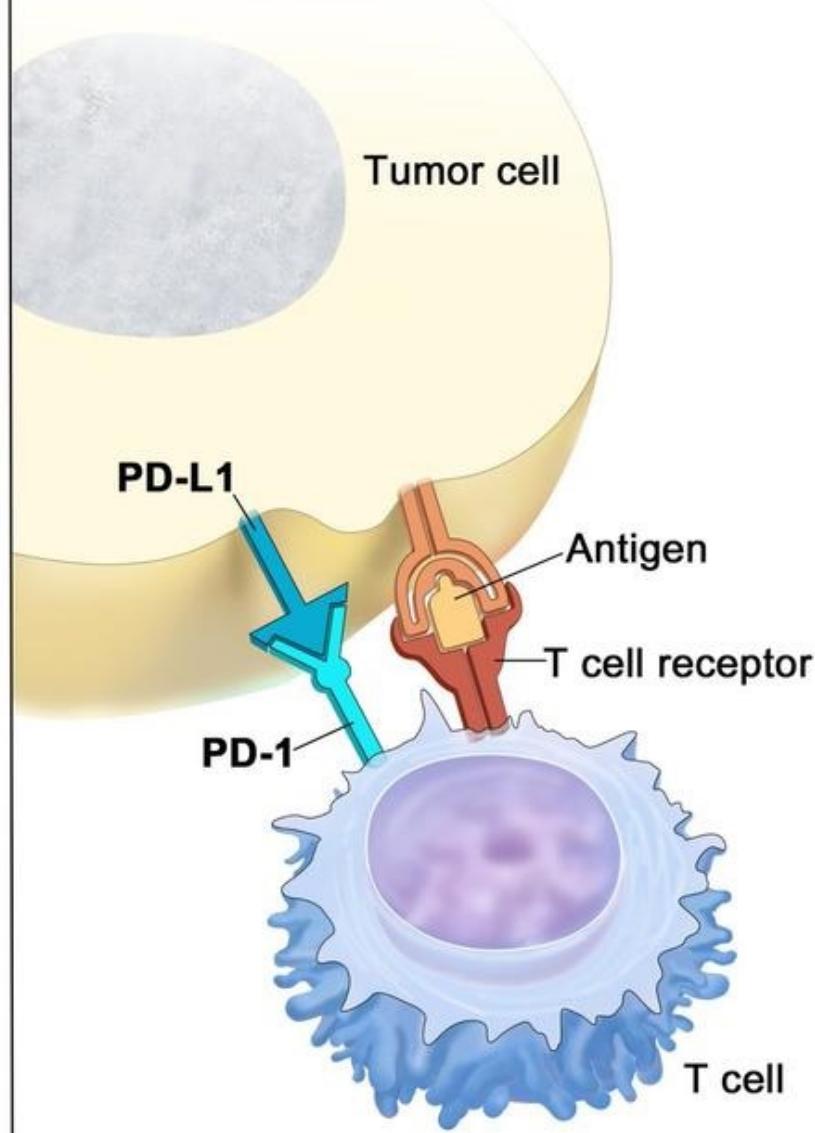
- Patients experiencing pathologic complete response had superior 5-year overall survival (OS)
- Carboplatin:
 - For patients who may not be eligible for ICI, a platinum-based regimens in the NAC setting have demonstrated robust responses **53% vs 31%**



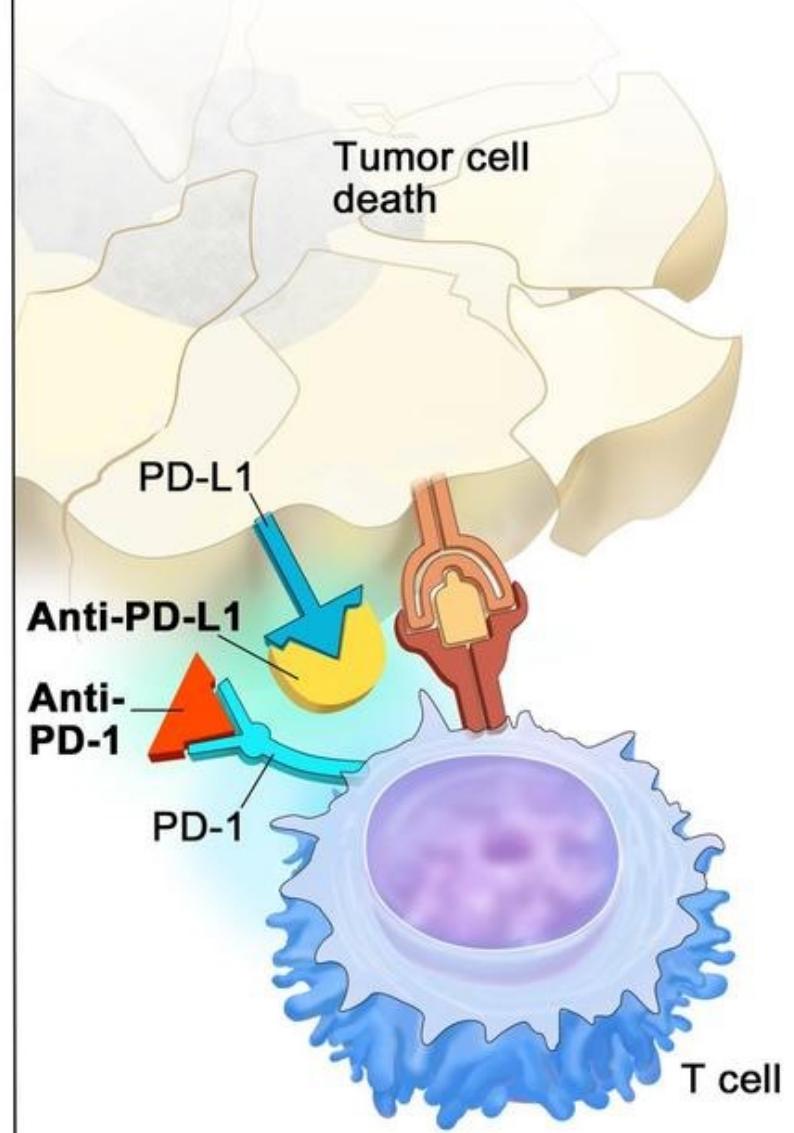
Chemoimmunotherapy in Stage II and III TNBC

A Paradigm Shift

PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell



Blocking PD-L1 or PD-1 allows T cell killing of tumor cell



Major FDA Approvals of PD-1 / PD-L1 Inhibitors

Drug	Commercial name	Owner	Target	First approval date
Pembrolizumab	Keytruda	MSD	PD-1	September 2014
Nivolumab	Opdivo	BMS	PD-1	December 2014
Atezolizumab	Tecentriq	Roche	PD-L1	May 2016
Avelumab	Bevancio	EMD and Pfizer	PD-L1	March 2017
Durmalumab	Imfinzi	AstraZeneca	PD-L1	May 2017

Source: Drugs.com



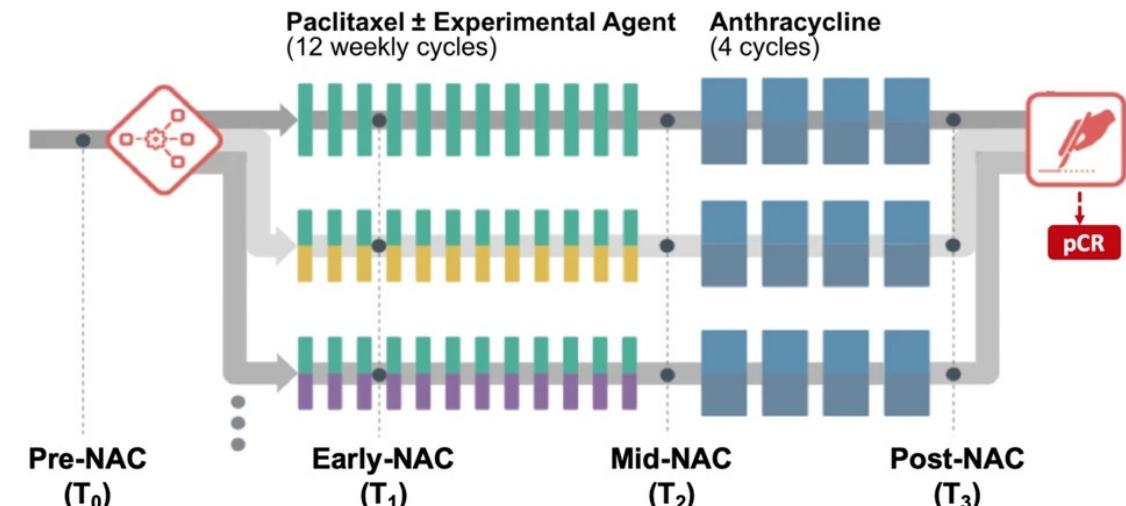
內專 107 以下治療"藥劑"與免疫或分子"標 靶"的配對，下列那些為真？

- (1). Afatinib 與 EGFR
- (2). Ipilimumab 與 PD-L1
- (3). Trastuzumab 與 HER-2
- (4). Rituximab 與 CD20
- (5). Pembrolizumab 與 PD-1

Phase II, I-SPY 2 trial improved outcomes with combination Pembrolizumab + NAC in ETNBC

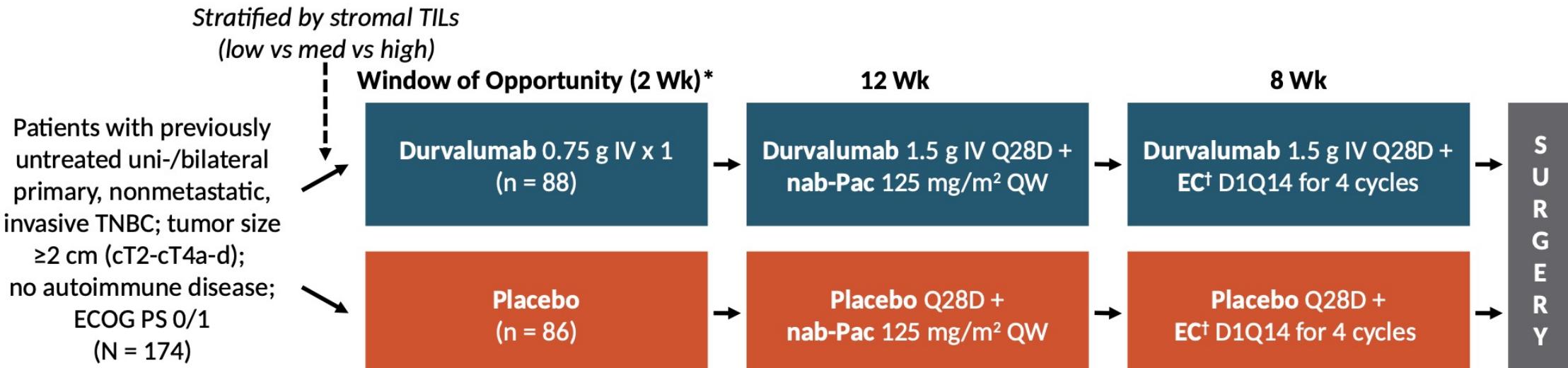
Estimated pCR Rate

Signature	Pembrolizumab + Standard Therapy	Standard Therapy Alone
TNBC	0.60 (0.43 – 0.78)	0.20 (0.06 – 0.33)
All HER2-	0.46 (0.34 – 0.58)	0.16 (0.06 – 0.27)
HR+/HER2-	0.34 (0.19 – 0.48)	0.13 (0.03 – 0.24)



- 990 patients

Neoadjuvant Durvalumab improves survival in early triple-negative breast cancer independent of pathological complete response



*Window of opportunity closed after n = 117 enrolled due to IDMC concerns about delay in patients starting CT in placebo arm. †Epirubicin 90 mg/m² + cyclophosphamide 600 mg/m².

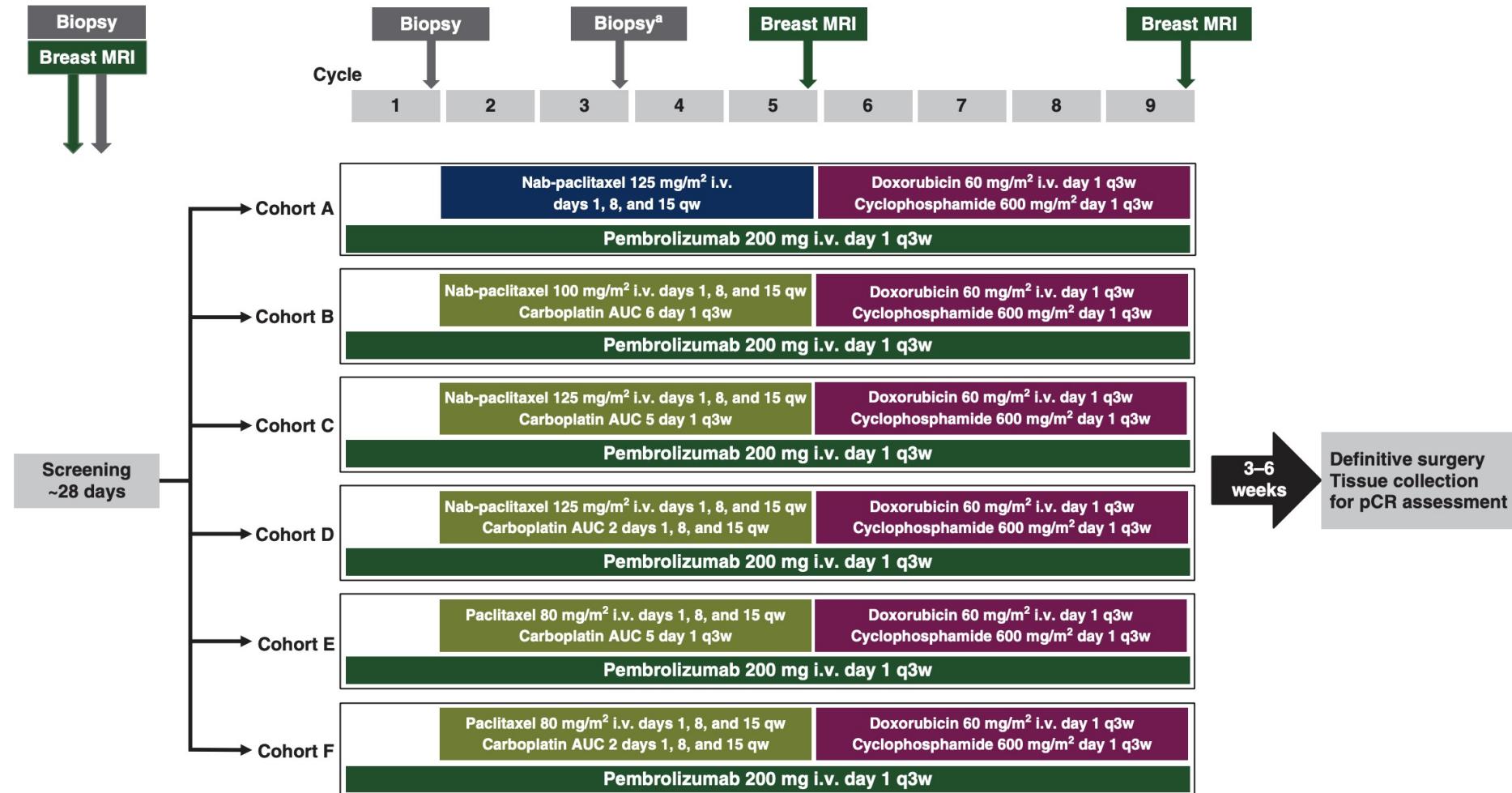
GeparNUEVO Survival Analysis: OS

iDFS Outcome	Durvalumab (n = 88)		Placebo (n = 86)	
Events, n	12		22	
3-yr iDFS, %	85.6		77.2	
Stratified HR* (95% CI)	0.48 (0.24-0.97; P = .0398)			
By pCR status	pCR (n = 47)	No pCR (n = 40)	pCR (n = 38)	No pCR (n = 48)
Events, n	2	9	7	15
3-yr iDFS, %	95.5	76.3	86.1	69.7
Log-rank P value	.0071			

pCR rate with durvalumab

- **53.4%** (95% CI 42.5% to 61.4%)
- versus placebo 44.2% (95% CI 33.5% to 55.3%)

Phase 1b open-label, multicohort KEYNOTE-173



Result

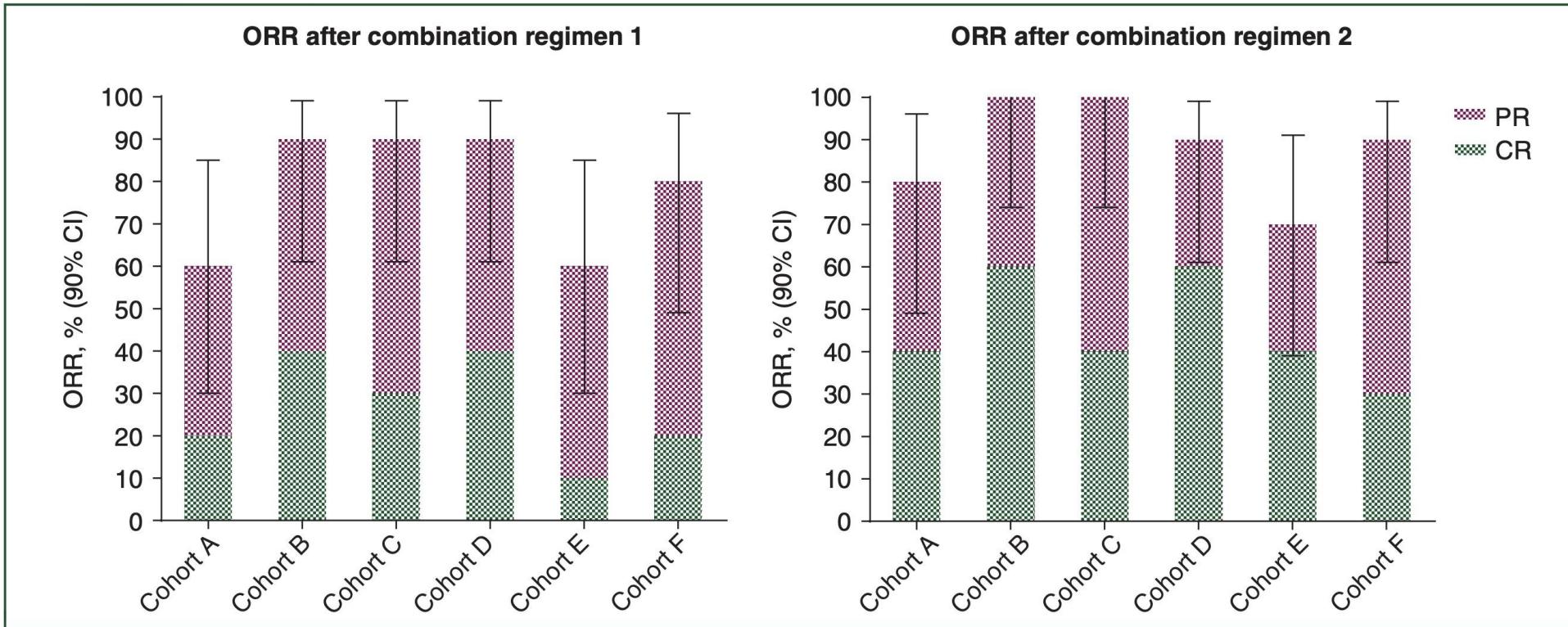


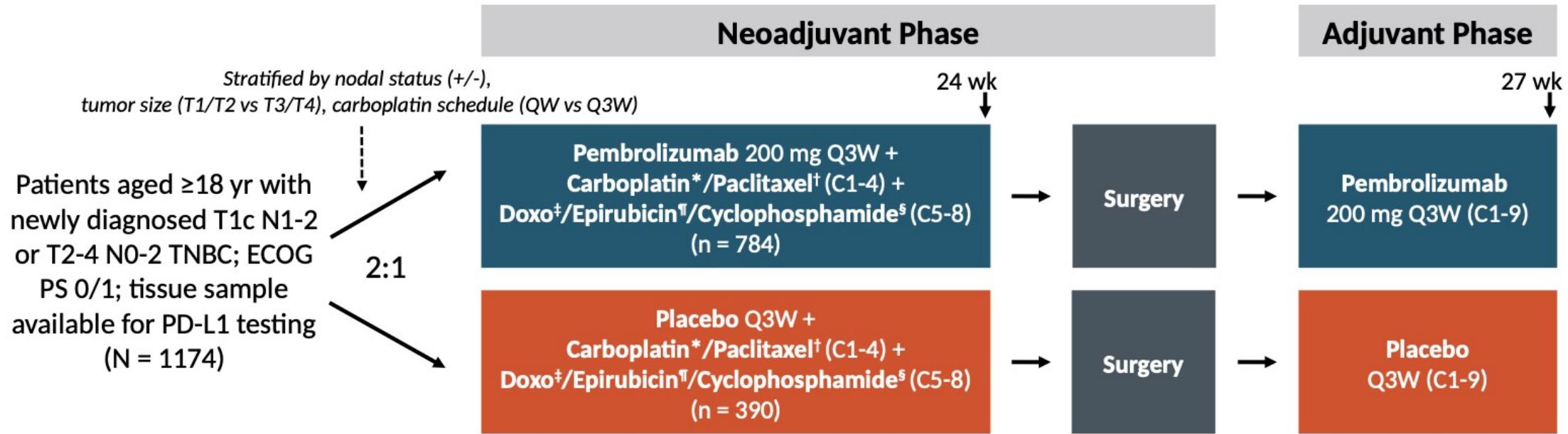
Figure 3. Response rates per RECIST, version 1.1, by investigator assessment.

Patients with missing outcome for objective response were considered non-responders.

CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response.

- (D) nab-paclitaxel 125 mg/m² qw; (E) paclitaxel 80 mg/m² qw + carboplatin AUC5 q3w.

KEYNOTE-522, Phase III randomized



- 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

Characteristics of the Patients at Baseline

- 784 patients:
 - the pembrolizumab–chemotherapy group
- 390 patients:
 - the placebo–chemotherapy group
- plus paclitaxel and carboplatin
- Stage II:
 - 590 (75.3) and 291 (74.6)

Table 1. Characteristics of the Patients at Baseline.*

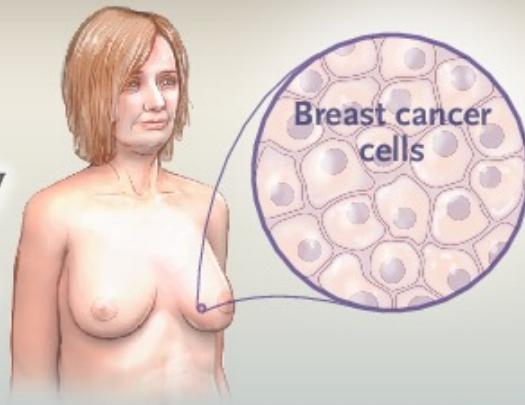
Characteristic	Pembrolizumab–Chemotherapy (N=784)	Placebo–Chemotherapy (N=390)
Age		
Median (range) — yr	49 (22–80)	48 (24–79)
<65 yr — no. (%)	701 (89.4)	342 (87.7)
Menopausal status — no. (%)		
Premenopausal	438 (55.9)	221 (56.7)
Postmenopausal	345 (44.0)	169 (43.3)
PD-L1 status — no. (%)†		
Positive	656 (83.7)	317 (81.3)
Negative	127 (16.2)	69 (17.7)
ECOG performance-status score — no. (%)‡		
0	678 (86.5)	341 (87.4)
1	106 (13.5)	49 (12.6)
Lactase dehydrogenase level — no. (%)		
≤ULN	631 (80.5)	309 (79.2)
>ULN	149 (19.0)	80 (20.5)
Administration of carboplatin — no. (%)		
Every 3 wk	335 (42.7)	167 (42.8)
Weekly	449 (57.3)	223 (57.2)
Primary tumor classification — no. (%)		
T1 to T2	580 (74.0)	290 (74.4)
T3 to T4	204 (26.0)	100 (25.6)
Nodal involvement — no. (%)		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)
Overall disease stage — no. (%)		
Stage II	590 (75.3)	291 (74.6)
Stage III	194 (24.7)	98 (25.1)
HER2 status score — no. (%)§		
0–1	595 (75.9)	286 (73.3)
2+	188 (24.0)	104 (26.7)

Pembrolizumab for Triple-Negative Breast Cancer

RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

**1174
Patients**

with previously
untreated
triple-negative
breast cancer



Neoadjuvant
Pembrolizumab
+ chemotherapy,
followed by surgery
and adjuvant pembrolizumab

(N=784)

Neoadjuvant
Placebo
+ chemotherapy,
followed by surgery
and adjuvant placebo

(N=390)

**Pathological complete
response at time of surgery**

64.8%

Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001

Event-free survival

91.3%

(95% CI, 88.8–93.3)

85.3%

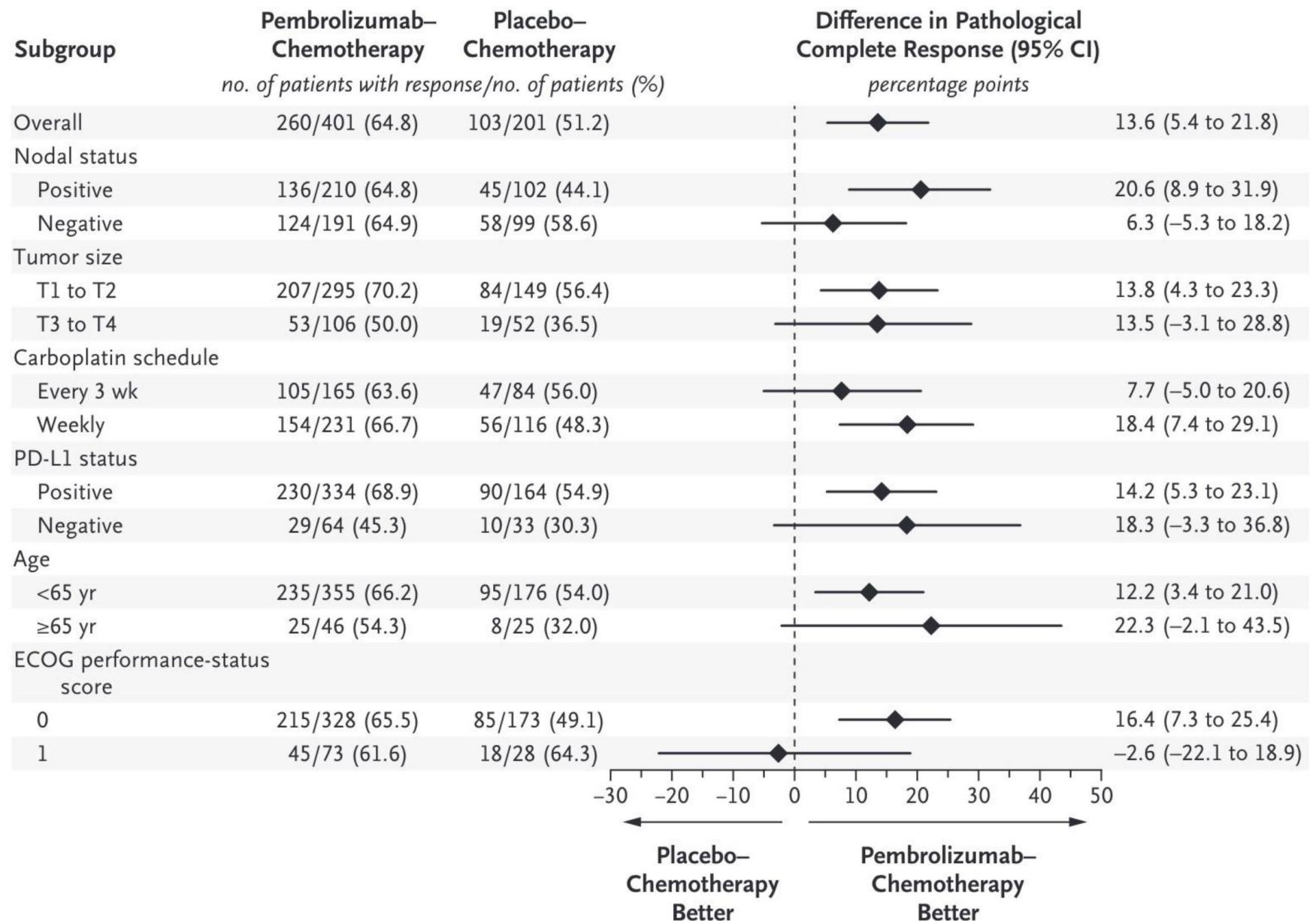
(95% CI, 80.3–89.1)

HR for an event or death, 0.63; 95% CI, 0.43–0.93

Grade ≥3 adverse events

76.8%

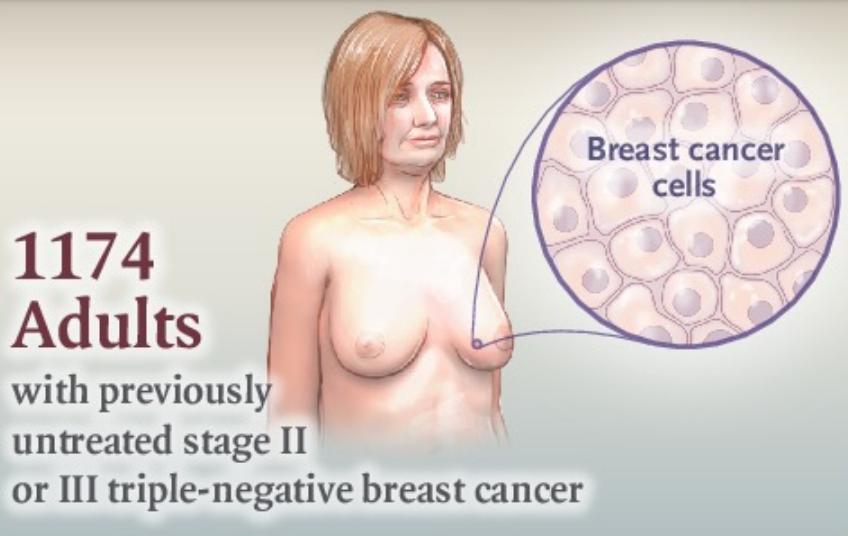
72.2%



- N0,
- T3/T4
- Q3W Carbo
- PD-L1 –
- 65+
- ECOG: 0

Pembrolizumab for Early Triple-Negative Breast Cancer

PHASE 3, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL



Neoadjuvant
Pembrolizumab
+ chemotherapy,
followed by surgery and
adjuvant pembrolizumab

(N=784)



Neoadjuvant
Placebo
+ chemotherapy,
followed by surgery and adjuvant placebo

(N=390)



Estimated event-free survival at 36 mo

84.5%

76.8%

HR for event or death, 0.63; 95% CI, 0.48–0.82; P<0.001

Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab after surgery significantly prolonged event-free survival.

Table 1. Summary of First Events in Analysis of Event-free Survival.

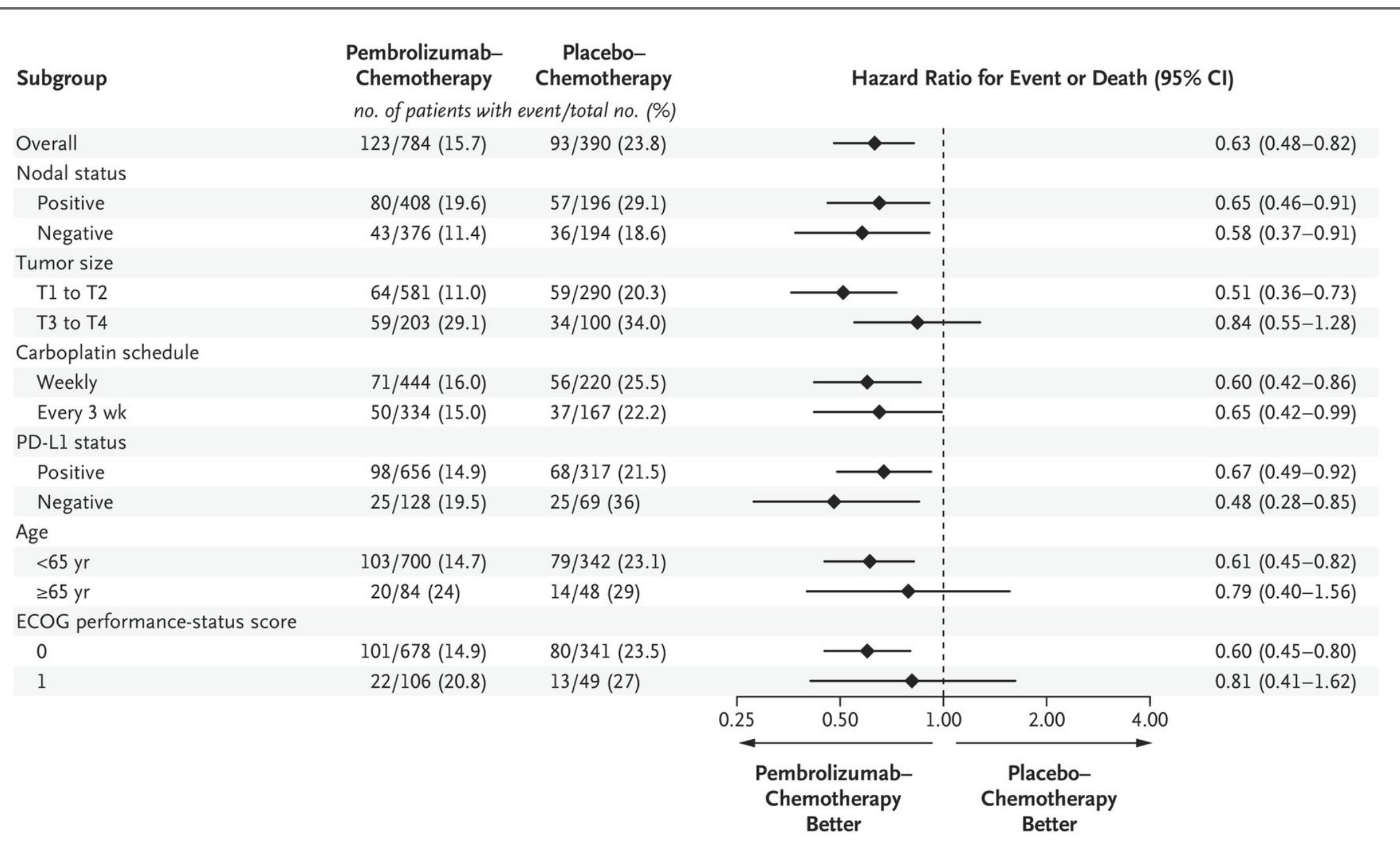
First Event	Pembrolizumab–Chemotherapy (N = 784)	Placebo–Chemotherapy (N = 390)
	<i>number (percent)</i>	
Any first event	123 (15.7)	93 (23.8)
Progression of disease that precluded definitive surgery	14 (1.8)	15 (3.8)
Local recurrence*	28 (3.6)	17 (4.4)
Distant recurrence	60 (7.7)	51 (13.1)
Second primary cancer†	6 (0.8)	4 (1.0)
Death	15 (1.9)	6 (1.5)

* A total of 13 patients in the pembrolizumab–chemotherapy group and 9 in the placebo–chemotherapy group with local recurrence had subsequent distant recurrence.

† Sites of second primary cancer included blood, bone marrow, chest wall, colon, endometrium, ovaries, stomach, and tongue.

15.7% VS 23.8%

HR: 0.66



Adverse Events in ICI

- Hypothyroidism
 - (15%)
- Severe skin reaction
 - (5.7%)
- Hyperthyroidism
 - (5.2%)
- Adrenal insufficiency
- Pneumonitis
- Thyroiditis
- Hypophysitis

Table 2. Adverse Events in the Combined Neoadjuvant and Adjuvant Phases (As-Treated Population).*

Event	Pembrolizumab–Chemotherapy (N=783)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of patients (percent)</i>			
Any adverse event	777 (99.2)	645 (82.4)	389 (100)	306 (78.7)
Treatment-related adverse event†	774 (98.9)	604 (77.1)	388 (99.7)	285 (73.3)
Nausea	495 (63.2)	27 (3.4)	245 (63.0)	6 (1.5)
Alopecia	471 (60.2)	0	220 (56.6)	0
Anemia	429 (54.8)	141 (18.0)	215 (55.3)	58 (14.9)
Neutropenia	367 (46.9)	270 (34.5)	185 (47.6)	130 (33.4)
Fatigue	330 (42.1)	28 (3.6)	151 (38.8)	6 (1.5)
Diarrhea	238 (30.4)	20 (2.6)	98 (25.2)	5 (1.3)
Alanine aminotransferase increased	204 (26.1)	43 (5.5)	98 (25.2)	9 (2.3)
Vomiting	200 (25.5)	19 (2.4)	86 (22.1)	6 (1.5)
Asthenia	198 (25.3)	28 (3.6)	102 (26.2)	9 (2.3)
Rash	196 (25.0)	12 (1.5)	66 (17.0)	1 (0.3)
Constipation	188 (24.0)	0	85 (21.9)	0
Neutrophil count decreased	185 (23.6)	146 (18.6)	112 (28.8)	90 (23.1)
Aspartate aminotransferase increased	157 (20.1)	20 (2.6)	63 (16.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	84 (21.6)	4 (1.0)
Immune-mediated adverse event‡	262 (33.5)	101 (12.9)	44 (11.3)	4 (1.0)
Hypothyroidism	118 (15.1)	4 (0.5)	22 (5.7)	0
Severe skin reaction	45 (5.7)	37 (4.7)	4 (1.0)	1 (0.3)
Hyperthyroidism	41 (5.2)	2 (0.3)	7 (1.8)	0
Adrenal insufficiency	20 (2.6)	8 (1.0)	0	0
Pneumonitis	17 (2.2)	7 (0.9)	6 (1.5)	2 (0.5)
Thyroiditis	16 (2.0)	2 (0.3)	5 (1.3)	0
Hypophysitis	15 (1.9)	10 (1.3)	1 (0.3)	0

Highlight of the KEYNOTE-522

- pt w/ pCR in both arms had improved 3-year EFS rates at
 - **94.4%** with pembrolizumab and
 - **92.5%** with placebo
- Conversely, the 3-year EFS rates for non-pCR patients were dismal in both arms, which were
 - **67.4%** with pembrolizumab
 - **56.8%** with placebo
- the addition of pembrolizumab to chemotherapy shifted more tumors to lower RCB scores of 0 or 1, conferring a better prognosis.
- Tumors with RCB scores of 2 or III had worse outcomes in both groups, which may be an even more specific prognostic indicator than pCR versus non-pCR

Phase III IMpassion031 study

- 333 pt 🧑‍🤝‍🧑 untreated stage II–III TNBC
 - 165 **atezolizumab**
 - 840 mg IV Q2W
 - 168 placebo
- with **nab-paclitaxel** 125 mg/m² QW x 12wks
- follow by **ddAC** for 8 wks
- increased pCR rates to
 - **58%** in the CIT arm versus **41%**

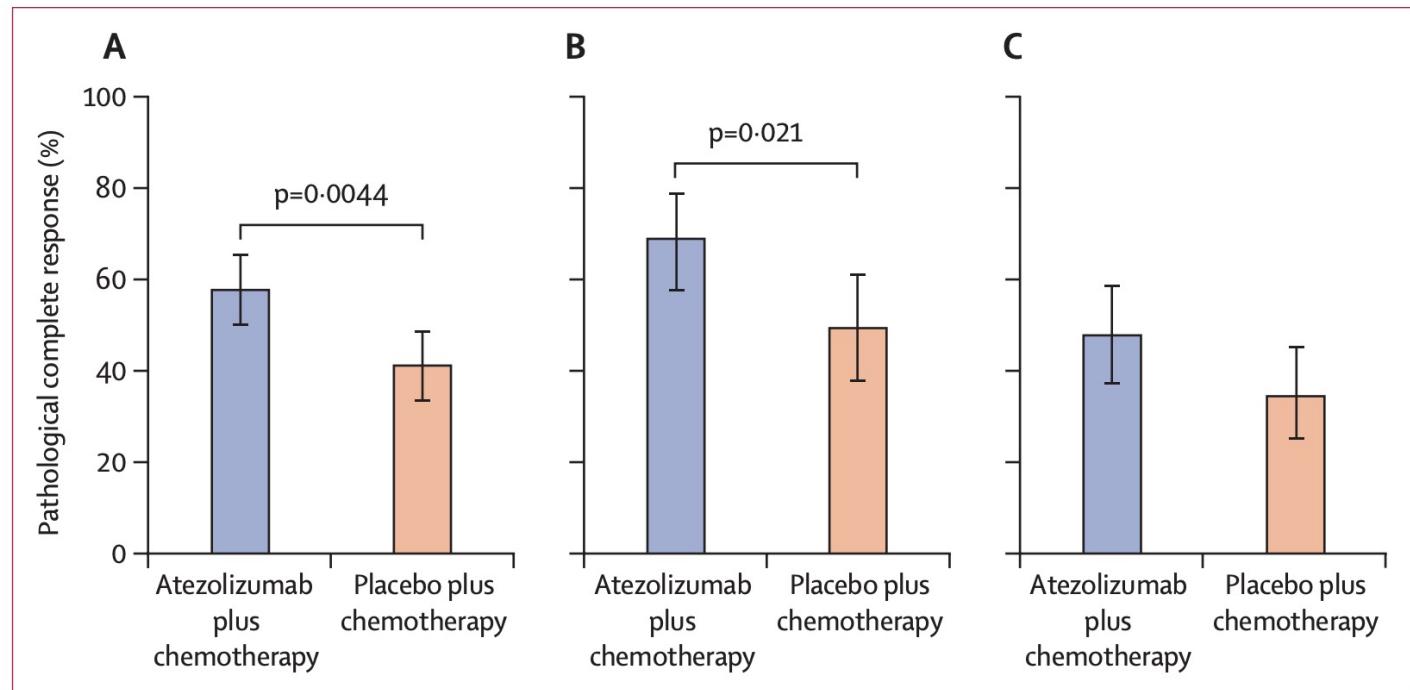
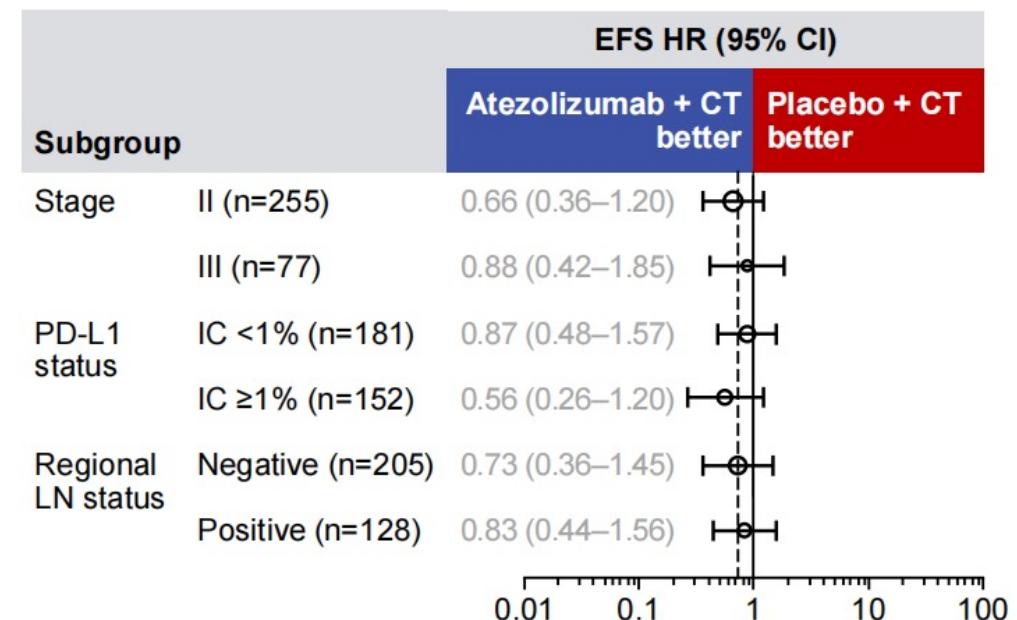
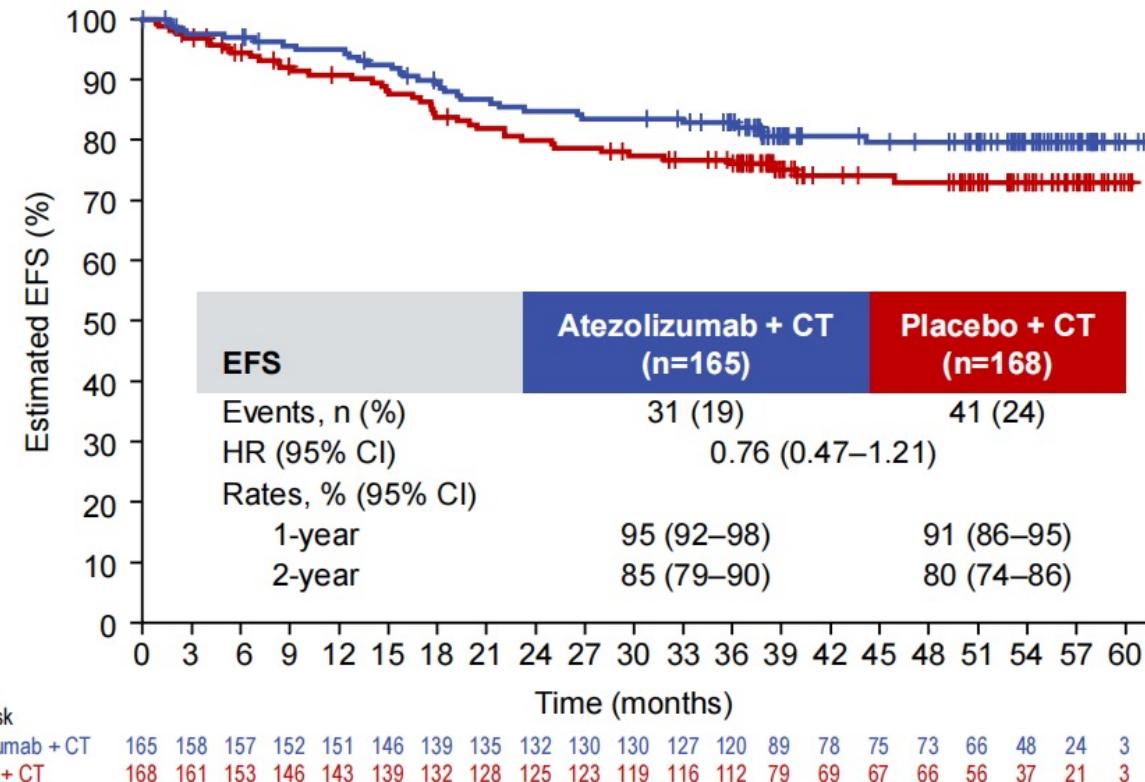


Figure 2: Pathological complete response co-primary endpoints in the all-randomised and PD-L1-positive populations, and pathological complete response in the PD-L1-negative population
(A) All-randomised population and PD-L1-positive populations. (B) PD-L1-positive population. (C) PD-L1-negative population (not formally tested). PD-L1=programmed cell death ligand 1.

EFS (ITT POPULATION AND SUBGROUPS)

Atezolizumab provides significant pC benefit and **numerically** improved EFS



pCR Rates in Randomized TNBC Neoadjuvant Studies

GeparNUEVO (N = 174) ¹	NeoTRIPaPDL1 (N = 280) ²	KEYNOTE-522 ^{3,4} (N = 1174)	IMpassion031 ⁵ (N = 333)
Nab-paclitaxel → EC Q2W ± durvalumab (no adj)	Nab-paclitaxel + carboplatin on Days 1,8 Q3W x 8 ± atezolizumab (no adj)	Paclitaxel + carboplatin → AC/EC Q3W ± pembrolizumab 1 yr	Nab-paclitaxel → ACT Q2W ± atezolizumab 1 yr
pCR: 53.4% vs 44.2% Δ 9.2% (P = .287)	pCR : 48.6% vs 44.4% Δ 4.2% (P = .48)	IA1 (n = 602): pCR: 64.8% vs 51.2% Δ 13.6% (P <.001) IA3 (N = 1174): pCR: 63% vs 55.6% Δ 7.5%	pCR: 58% vs 41% Δ 17% (P = .0044)

Adjuvant Treatment in ETNBC

pCR v.s. non-pCR

If non-pCR

CREATE-X: Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

CREATE-X

stage I-IIIB HER2- BC
aged 20-74 yrs of age
(non-pCR, N+) after neoadjuvant
ECOG PS 0/1
no previous oral fluoropyrimidines
(N = 910)



Intervention Arm

Capecitabine
2500 mg/m ² /day PO Days 1-14
Q3W 8 cycles

Hormonal therapy if ER/PgR+

Control Arm

Placebo
Hormonal therapy if ER/PgR+
No further therapy if ER/PgR-

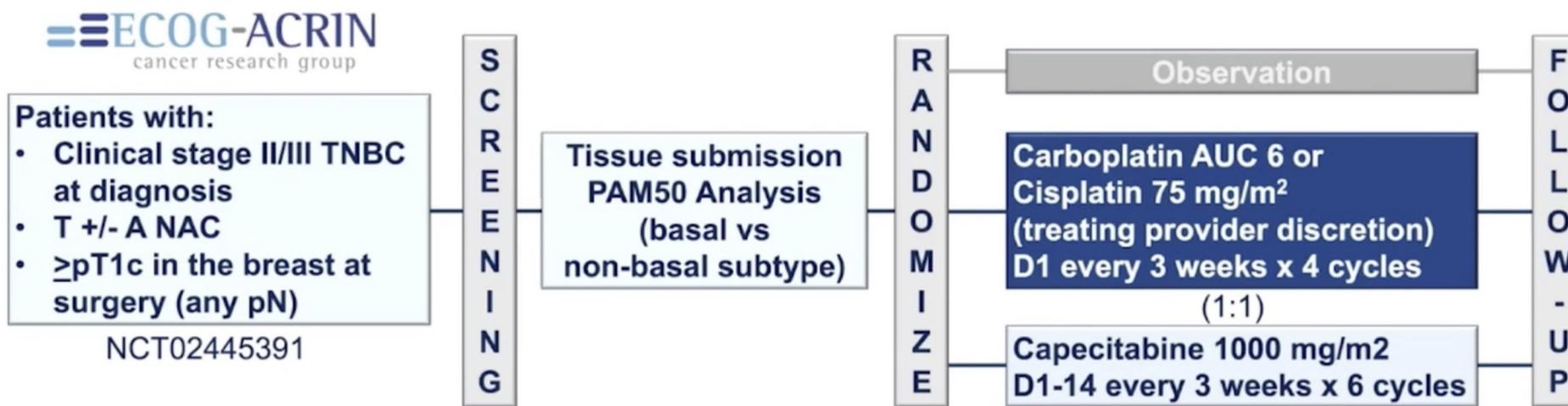


Stratification by
ER status, age, neoadjuvant,
chemotherapy,
use of 5-FU, institution, node status

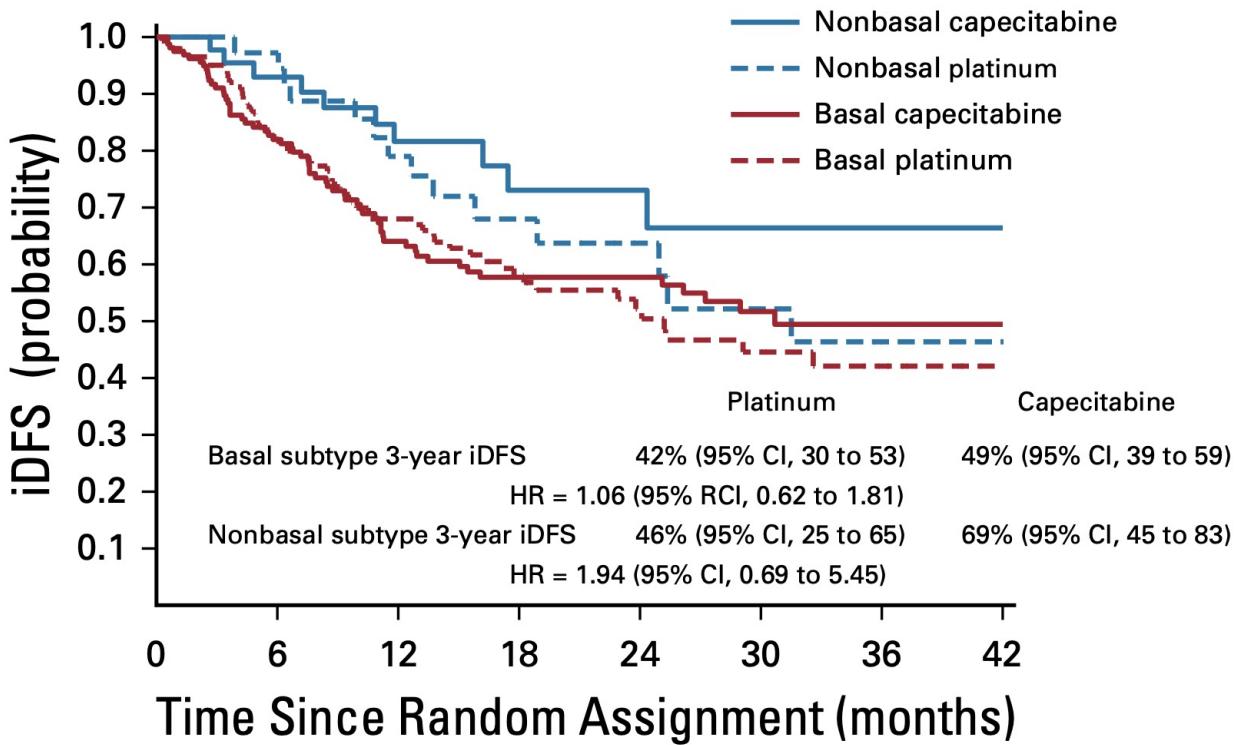
other chemotherapy, e.g. Platinum-Based Chemotherapy?

ECOG-ACRIN EA1131: Randomized Phase III Postoperative Trial of Platinum-Based Chemotherapy Versus Capecitabine

Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy



ECOG-ACRIN EA1131: Result



No. at risk:

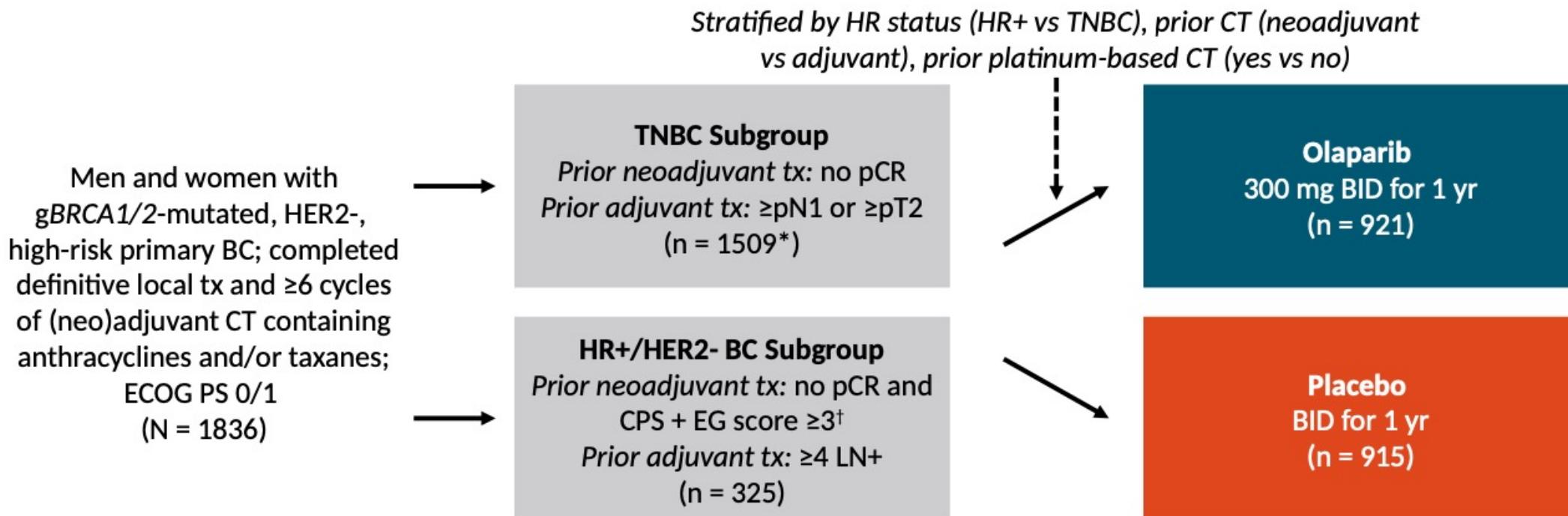
Nonbasal Capecitabine	46	37	26	16	11	6	3	2
Nonbasal Platinum	41	35	23	17	11	9	5	4
Basal Capecitabine	158	112	74	60	48	24	15	4
Basal Platinum	148	99	68	47	30	20	13	4

- 42% with platinum vs.
- 49% with capecitabine.

If non-pCR

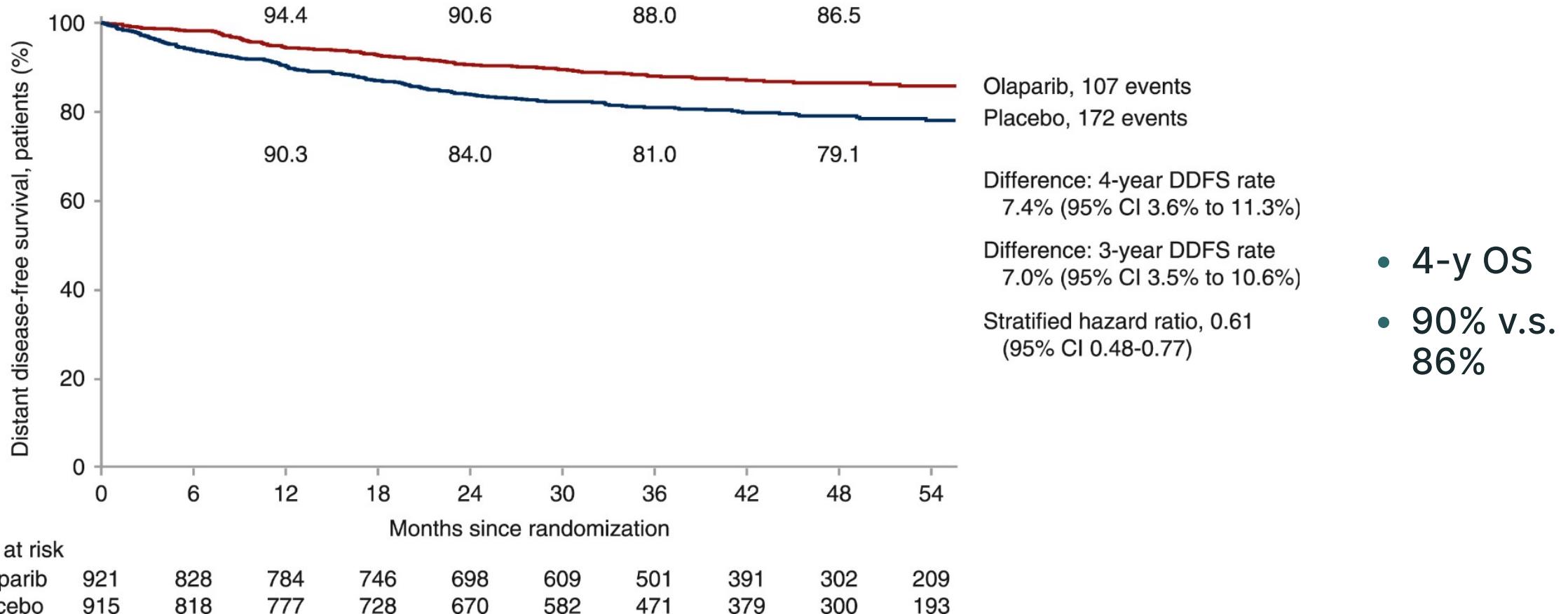
Germline BRCA mutations

Olympia: Adjuvant Olaparib with BRCA1 or BRCA2 mutated



OlympiA: Result

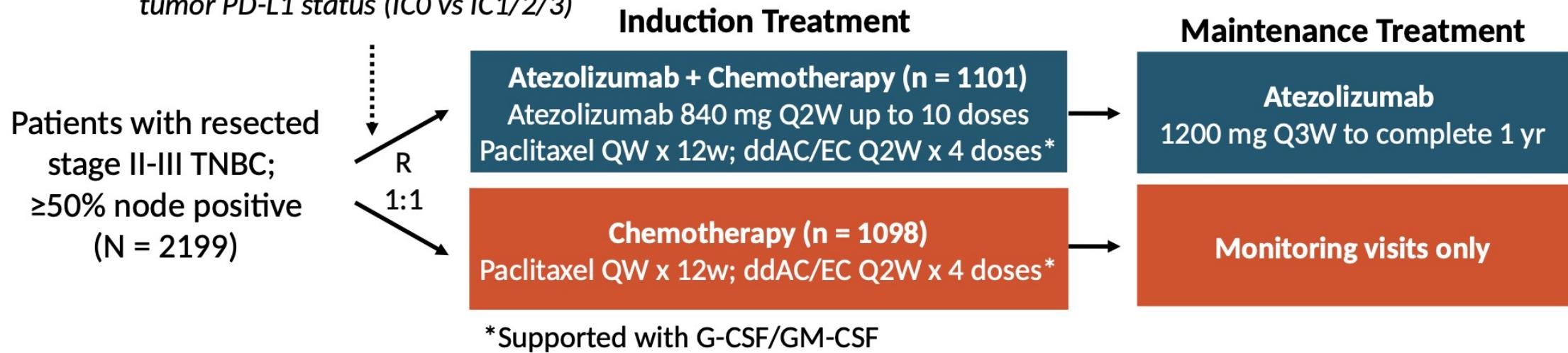
Adjvant olaparib versus placebo



ALEXANDRA/IMpassion030

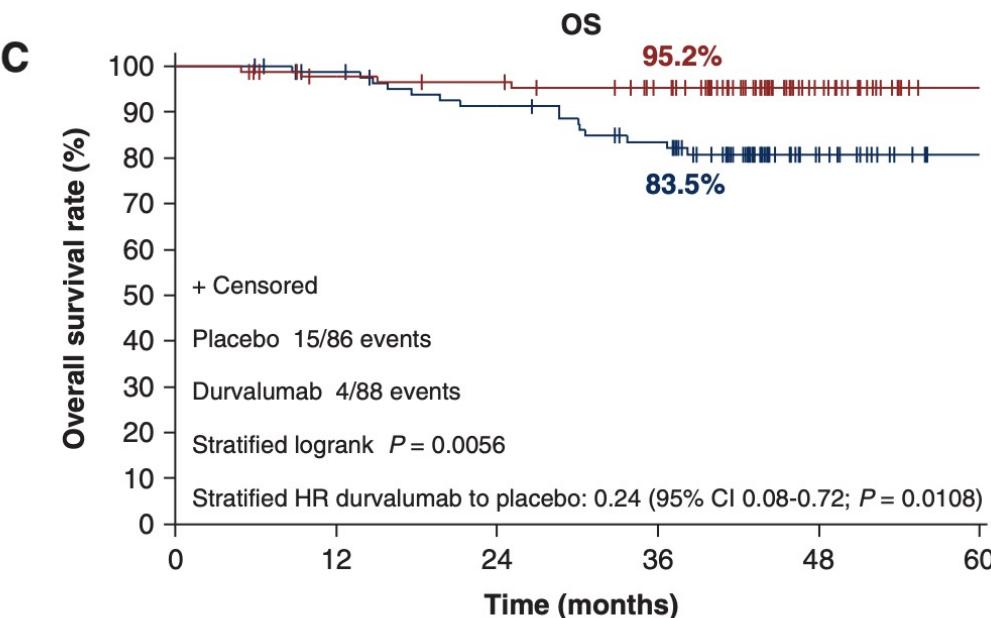
- atezolizumab to standard paclitaxel and ddAC (w/o carboplatin)

*Stratified by axillary nodal status (0 vs 1-3 vs ≥4 positive LN),
surgery (breast conserving vs mastectomy), and
tumor PD-L1 status (IC0 vs IC1/2/3)*



- Primary endpoint: iDFS in ITT population
- Secondary endpoints: iDFS in PD-L1-positive and node-positive subpopulations, iDFS including second primary nonbreast invasive cancer, OS, RFI, DRFI, DFS

Parameter	Atezo + Chemotherapy (n = 1101)	Chemotherapy (n = 1098)	HR (95% CI)	P Value
iDFS events, ITT, n (%)	127 (11.5)	112 (10.2)	1.12 (0.87-1.45)	.37
iDFS events, PD-L1+, n/N (%)	77/785 (9.8)	73/782 (9.3)	1.03 (0.75-1.42)	NR
OS events, ITT, n (%)	61 (5.5)	49 (4.5)	1.20 (0.82-1.75)	NR



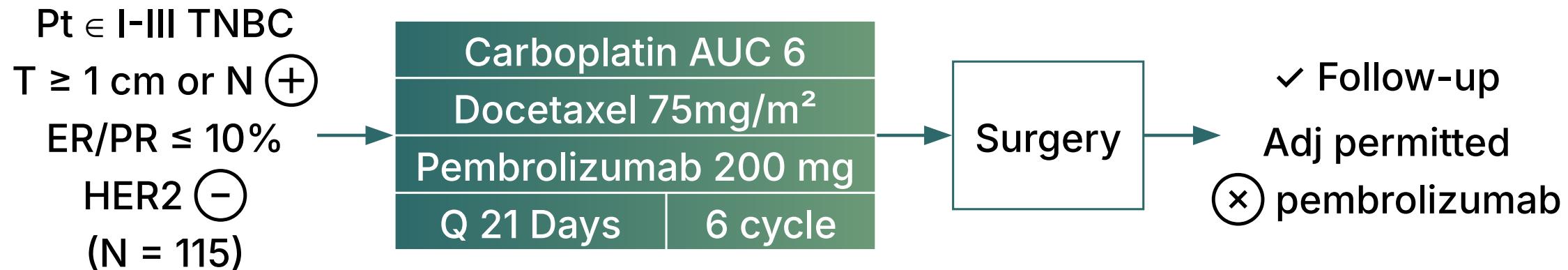
Patients at risk:

Placebo	86	80	72	63	16	0
Durvalumab	88	81	79	71	20	0

Clinical Questions That Remain for Early-Stage TNBC

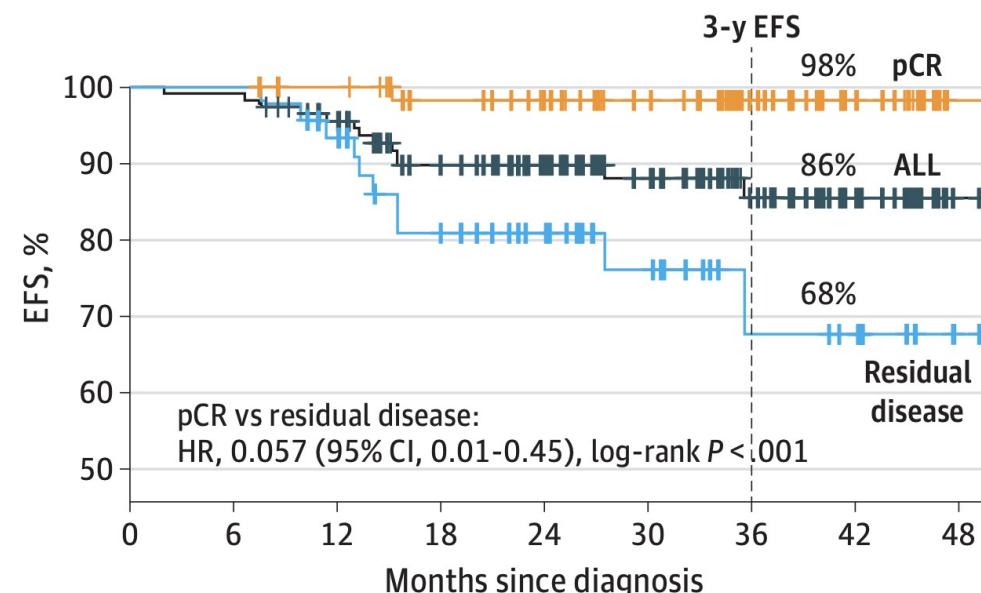
Neoadjuvant Immunotherapy	Adjuvant Immunotherapy	CT Backbone	ADCs	gBRCA1/2m
<ul style="list-style-type: none">▪ Does everyone benefit?▪ Biomarker selection▪ Balance risk and cost: who will benefit from CT alone?▪ Balance risk and toxicity: who can avoid immunotherapy?	<ul style="list-style-type: none">▪ Combining immunotherapy with capecitabine or PARP inhibitors?▪ Optimal duration of immunotherapy in patients who achieve pCR vs non-pCR▪ Impact of adjuvant immunotherapy?	<ul style="list-style-type: none">▪ Optimal CT backbone?▪ Platinum improves pCR (CALGB 40603, BrightTNess) and EFS (BrightTNess), but not OS; increase toxicity▪ Anthracyclines modulate tumor microenvironment?	<ul style="list-style-type: none">▪ Role for ADCs?▪ Sacituzumab govitecan▪ Trastuzumab deruxtecan▪ Datopotamab deruxtecan	<ul style="list-style-type: none">▪ Who can be treated with a PARP inhibitor alone?▪ How does PARPi monotherapy compare with CT?

Neoadjuvant Phase II Study of Pembrolizumab And Carboplatin Plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)



NeoPACT: Result: EFS

Figure 2. Event-Free Survival (EFS) of Patients in the Intent-to-Treat Group (N = 115)



No. at risk

ALL	115	114	103	87	71	53	32	17	1
pCR	64	64	62	55	46	37	24	11	0
Residual disease	47	47	40	31	25	16	8	6	1

HR indicates hazard ratio, and pCR, pathologic complete response.

- 111pt
- pCR: **64(57%)** → Adjuvant: 1 chemo, 1 pembro
- RD: 47 → Adjuvant: 38 chemo, 9 pembro
- c.f. KEYNOTE-522:
 - pCR: 64.8%, EFS 36 month 84.5%
 - in those without pCR, EFS rates
 - 67.4%
 - in those without pCR, EFS rates
 - 67.4%

Future directions

- AGO-B-041:
 - phase II trial,
 - NAC nab-paclitaxel(nP)/anthracycline + pembrolizumab
 - pCR: 66%.
- SWOG 2212 (SCARLET) will compare the
 - KEYNOTE-522 regimen with the NeoPACT regimen
 - with event-free survival as the primary endpoint.
- Alliance A012103 (OptimICE pCR; NCT05812807)
 - adjuvant pembrolizumab continuation vs discontinuation in stage II-III TNBC who achieved a pCR to neoadjuvant CT + CPI

- OptimICE-RD (ASCENT-05)
 - phase III study of 1,514 patients with residual TNBC (ClinicalTrials.gov identifier: NCT05633654),
 - safety and efficacy of the addition of **sacituzumab govitecan** or capecitabine to pembrolizumab.
- TROPION-Breast-03
 - **datopotamab deruxtecan** with or without **durvalumab** versus investigator's choice in patients with stage I-III TNBC without a pCR

Pt stage II, III TNBC s/p NAC pembrolizumab in **KFSYSCC**



Case: 06552566-劉 (51 years)

- Diagnosis: Left LABC
- Histological Type: IDC
- cTNM: cT(5cm)N2-3(f)MO
- ER/PR/HER2: 3/0/1+
- Ki-67: 60%
- NG: 3
- Neoadjuvant Therapy: Taxotere + Carboplatin x4 → ACx4 with Pembro x3
- NAC Date: 2023/01/25 - 2023/06/21
- Operation: WE+SLNB
- OP Date: 2023/07/12
- Post-op Staging: ypT0N0(sn0/1), pCR 

Case: 06706071-王 (33 years)

- Diagnosis: Left LABC
- Histological Type: IDC
- cTNM: cT3N1M0
- ER/PR/HER2: 0/0/0
- Ki-67: 40%
- NG: 3
- Neoadjuvant Therapy: ACx4 → Cisplatin/Taxotere x4 with Pembro x6
- NAC Date: 2023/03/20 - 2023/09/04
- Operation: WE+SLNB+ALND
- OP Date: 2023/10/13
- Post-op Staging: ypT0N0, pCR 

Case: 06715205-徐 (55 years)

- Diagnosis: Left LABC
- Histological Type: IDC
- cTNM: cT3(5.7cm)N3M1(neck L5)
- ER/PR/HER2: 0/0/1+
- Ki-67: 80%
- NG: 3
- Neoadjuvant Therapy: Taxol/Carbo x4 → ACx4 with Pembro x8
- NAC Date: 2023/04/19 - 2023/09/13
- Operation: MRM
- OP Date: 2023/10/11
- Post-op Staging: ypT0/Tis ypN0, pCR 🎉

Case: 05602289-藍 (51 years)

- Diagnosis: Right LABC
- Histological Type: IDC
- cTNM: cT3(6cm)N2(f)M0
- ER/PR/HER2: 0/0/0
- Ki-67: 74%
- NG: 3
- Neoadjuvant Therapy: Taxol/Carbo x4 → ACx4 with Pembro x8
- NAC Date: 2023/03/06 - 2023/08/14
- Operation: R't MRM
- OP Date: 2023/09/16
- Post-op Staging: ypT3(10.1cm)N3a(14/21)M0  

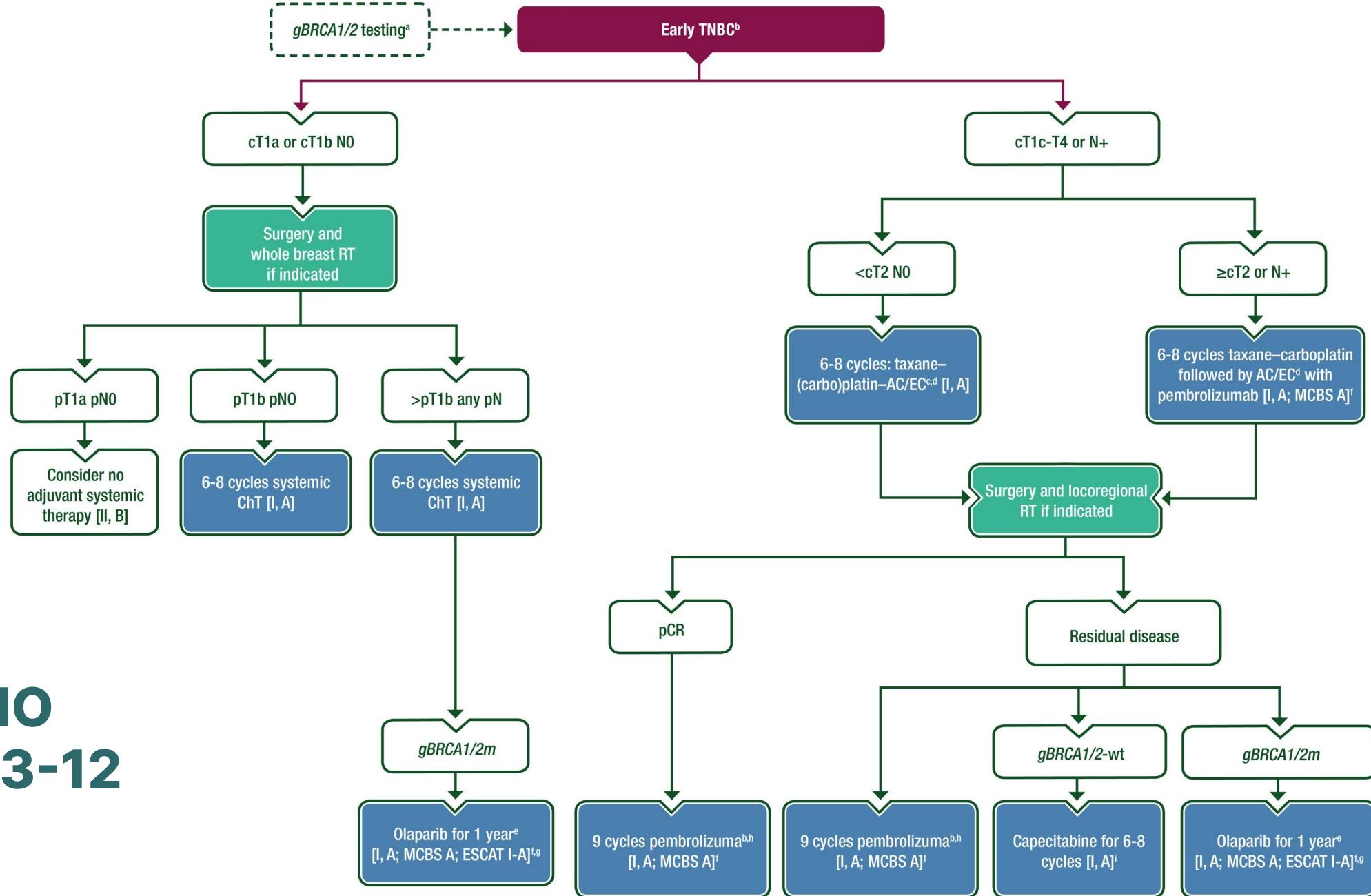
Case: 06538409-蔡 (43 years)

- Diagnosis: Right LABC
- Histological Type: IDC
- cTNM: cT3(4.5 cm)N0M0
- ER/PR/HER2: 0/0/0
- Ki-67: 60%
- NG: 3
- Neoadjuvant Therapy: AC x4 → Taxotere + Cisplatin x3 with Pembro x6
- NAC Date: 2022/12/13 - 2023/02/20
- Operation: Deceased 
- OP Date: NIL
- Post-op Staging: NIL

KFSYSCC Patient with TNBC s/p KEYNOTE-522 : Transposed

Case ID	06552566	06706071	06715205	05602289
姓	劉	王	徐	藍
Age	51	33	55	51
Diagnosis	Left LABC	Left LABC	Left LABC	Right LABC
Histological	IDC	IDC	IDC	IDC
cTNM	cT(5cm)N2-3(f)M0	cT3N1M0	cT3(5.7cm)N3M1(neck L5)	cT3(6cm)N2(f)M0
ER/PR/HER2	3/0/1+	0/0/0	0/0/1+	0/0/0
Ki-67	60%	40%	80%	74%
NG	3	3	3	3
Neoadjuvant Therapy	Taxotere + Carboplatin x4 -> ACx4 with Pembrolizumab x3	ACx4 -> Cisplatin/Taxotere x4 with Pembrolizumab x6	Taxol/Carbo x4 -> ACx4 with Pembrolizumab x8	Taxol/Carbo x4 -> ACx4 with Pembrolizumab x8
NAC Date	2023/01/25 - 2023/06/21	2023/03/20 - 2023/09/04	2023/04/19 - 2023/09/13	2023/03/06 - 2023/08/14
Operation	WE+SLNB	WE+SLNB+ALND	MRM	R't MRM
OP Date	2023/07/12	2023/10/13	2023/10/11	2023/09/16
Post-op Staging	ypT0N0(sn0/1), pCR	ypT0N0, pCR	ypT0/Tis ypN0	ypT3(10.1cm)N3a(14/1)M0, PD
Adjuvant Therapy	NIL	pending discussion	Xeloda	Xeloda

Summary

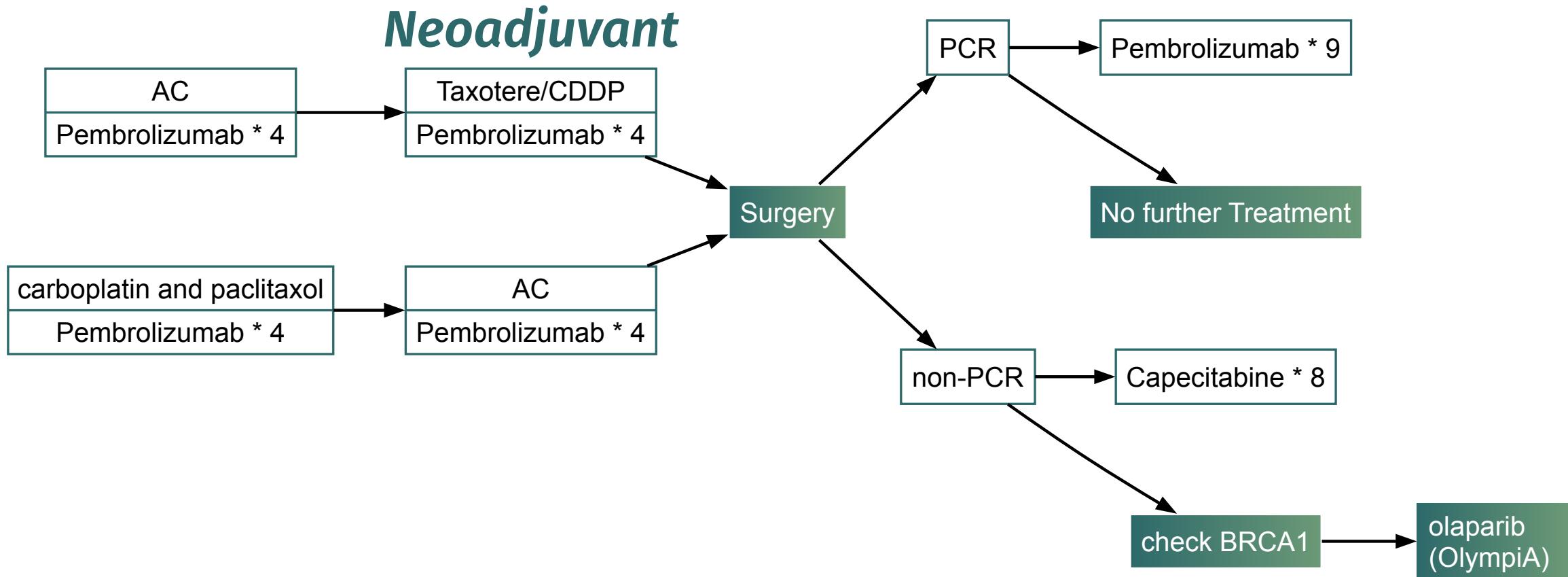


Highlight of ESMO 2023 ETNBC

- Pembrolizumab should be administered
 - every 3 weeks throughout the neoadjuvant phase [I, A] and
 - for nine 3-week cycles during the adjuvant phase,
 - regardless of pCR status [I, A; ESMO-MCBS v1.1 score: A].
- An ICI should not be given solely as adjuvant therapy without prior neoadjuvant ICI treatment
- For cT1c-4 N0, or any N-positive TNBC, neoadjuvant treatment is preferred
- The combination of olaparib and capecitabine in patients with gBRCAm should not be used

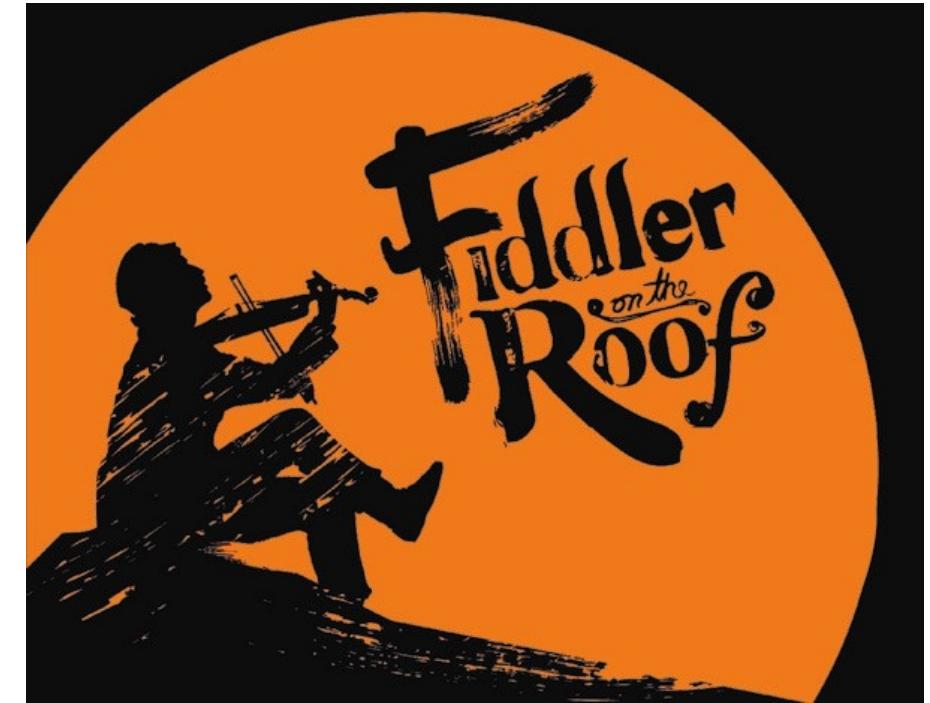
Back to our current TNBC guideline

KFSYSCC early TNBC treatment guideline 2024?



Take Home Messages

1. TNBC remains the worse outcomes compared with ER-positive and HER2-positive, largely attributed to limited treatment options.
2. Anthracycline and taxane-based chemotherapy regimens remain the standard of care for high-risk TNBC, with the addition of ICPis for stage II and III TNBC.
3. The KEYNOTE-522 regimen represents a ceiling treatment; it is very effective, but also very toxic
4. irAE is critical, avoiding severe life-threatening events.



 **Question: Who Should Be Treated With the KEYNOTE-522 Regimen?**

**Thank you
for your
time and
attention**

*Merry Christmas 🎄
and Happy New Year*



