UCSF Helen Diller Family Comprehensive Cancer Center

Optimal Treatment for Early Stage Triple Negative Breast Cancer

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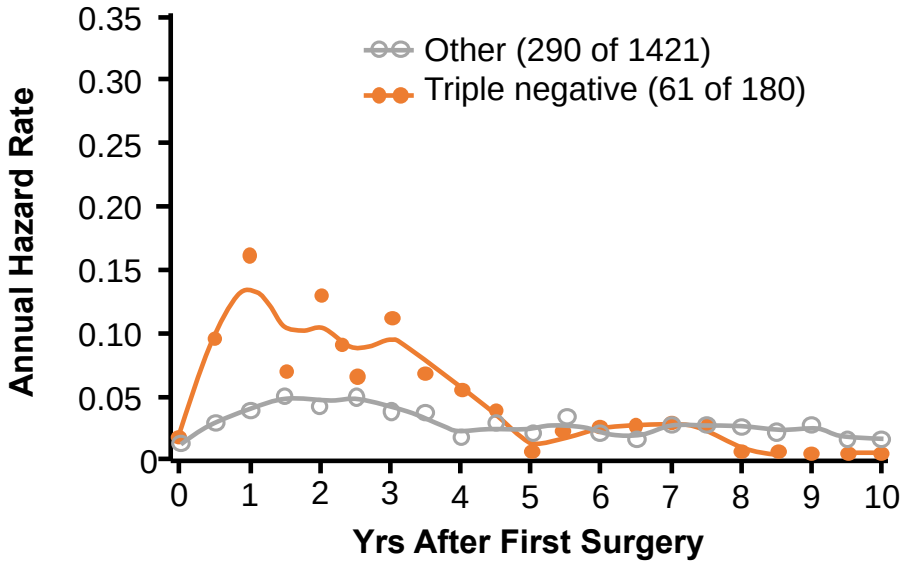
Triple Negative Breast Cancer

- General concepts
  - Heterogeneous disease
    - Proliferative, generally chemotherapy responsive
    - Rapid development of resistance
  - High risk of early recurrence
    - Visceral dominant disease, early/frequent brain metastases
    - Short median survival (<2yrs) after diagnosis of metastases
  - Rare subtypes
    - Indolent subtypes, generally in older women (adenoid cystic)



Lin NU, et al. Cancer. 2008;113:2638-2645. Liedtke C, et al. J Clin Oncol. 2008;26:1275-1281. Dent R, et al. Clin Cancer Res. 2007;13:4429-4434.

Progress!

General

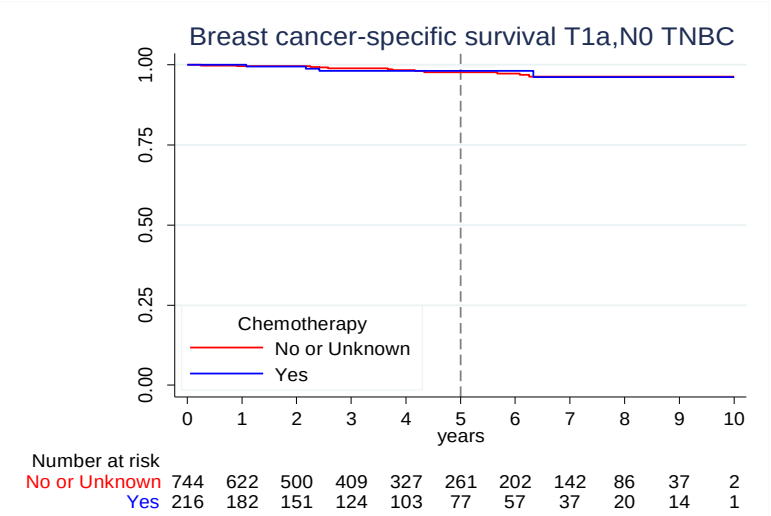
- **Neoadjuvant therapy preferred for all but the smallest tumors**
  - pCR (no invasive disease in breast or node) associated with a markedly improved outcome
  - Allows the potential to individualize therapy to response

Topics

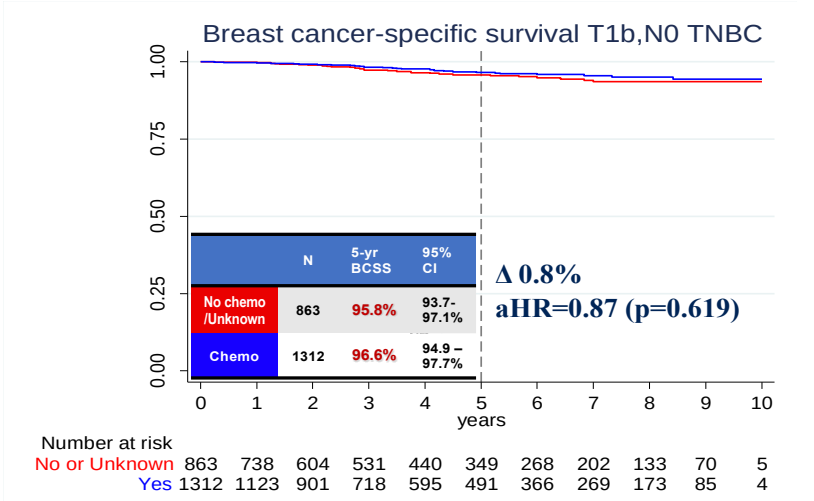
- Neoadjuvant platinum
- Immunotherapy: neoadjuvant vs adjuvant
- Alternative regimens
- Post-neoadjuvant therapy and PARP inhibitors

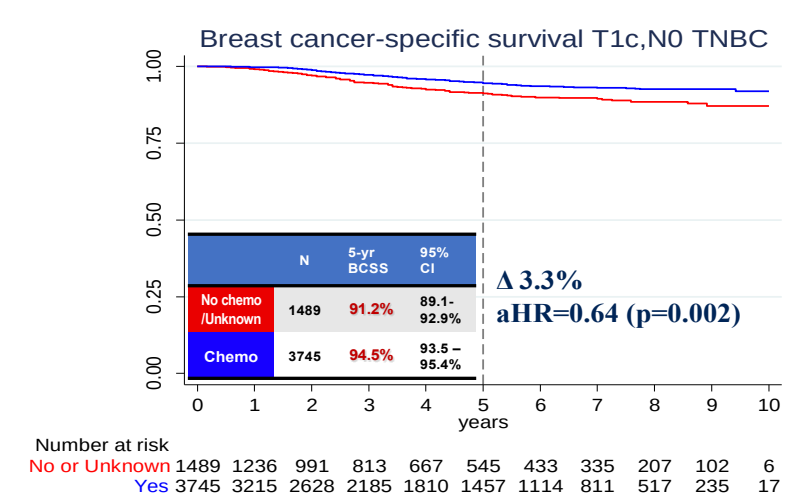
- Next steps?

Stage I TNBC: SEER Registry 2010 – 2019
N=8,601



No adjusted analysis could be performed due to low event rate.





Multivariable cox models adjusted for: age at diagnosis, race, tumor grade, histology, radiation, marital status, income, and rurality.

The **use of chemotherapy significantly increased over time** for patients diagnosed with **T1b** and **T1c** TNBC

Chemotherapy significantly improved BCSS in patients with **T1c** TNBC

Event rates were low in stage Ia and Ib disease; changing patterns of chemotherapy use impact interpretation

Tarantino et al, ASCO 2023

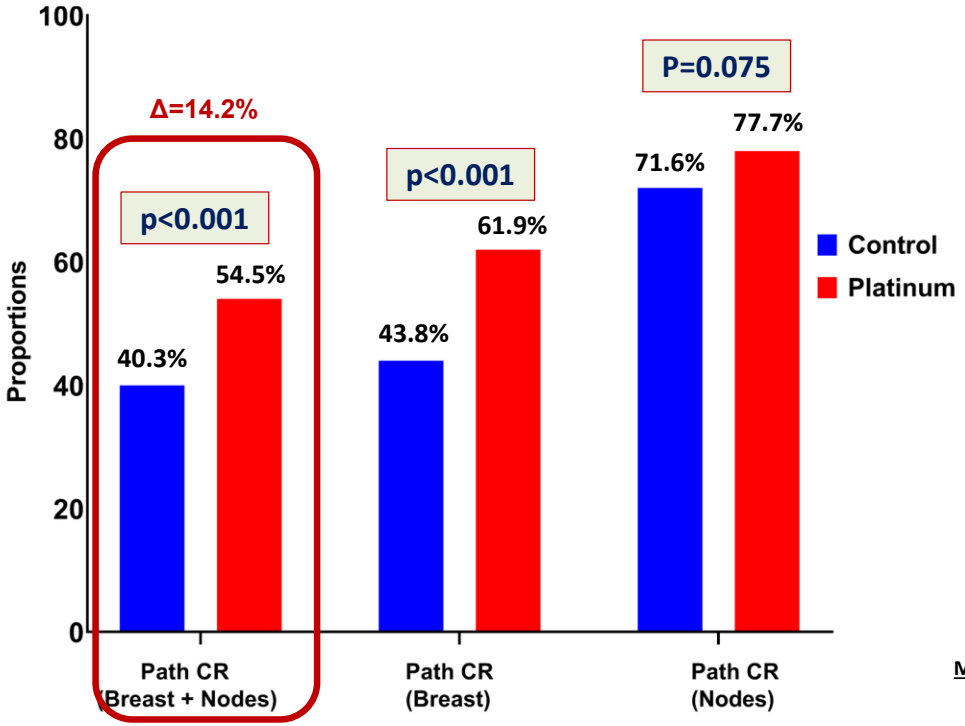
Platinum Added to Taxane/Anthracycline Chemotherapy in Early Stage TNBC

- Increases pCR (smaller benefit in gBRCA+)
  - Increase BCS, decreases extent of axillary surgery
- Increases toxicity when added to AC/T or T/AC regimen
- Improved EFS and OS
  - Age related effect?
- Possible alternative to anthracycline based chemotherapy

TMC Neoadjuvant Trial in TNBC:

Weekly Paclitaxel x 8 weeks +/- Weekly Carboplatin followed by AC/EC

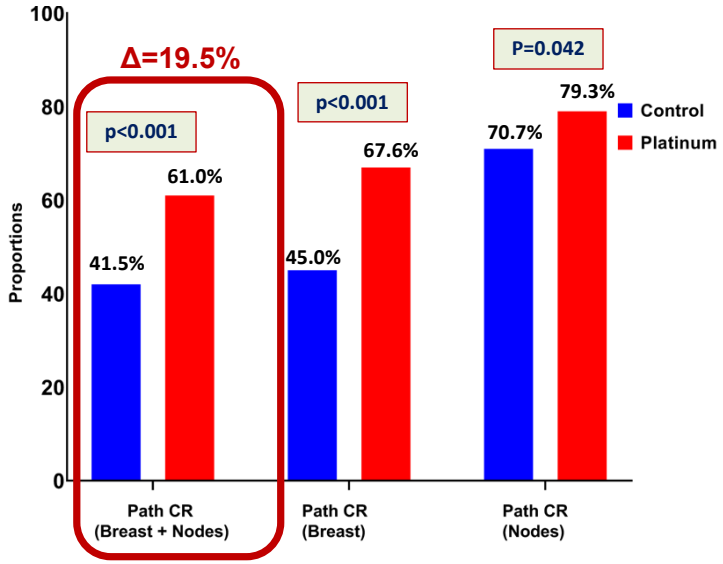
717 pts accrued over 10 years; Median FU 67.6 mo.



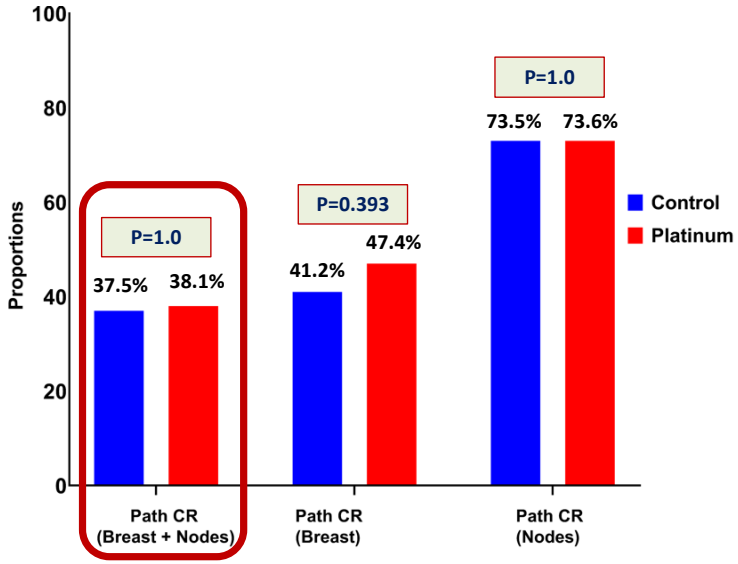
58% premenopausal
89% node positive
78% T> 5cm

pCR highly prognostic for EFS regardless of age

Age ≤ 50 years



Age > 50 years



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

Prognostic impact of pCR

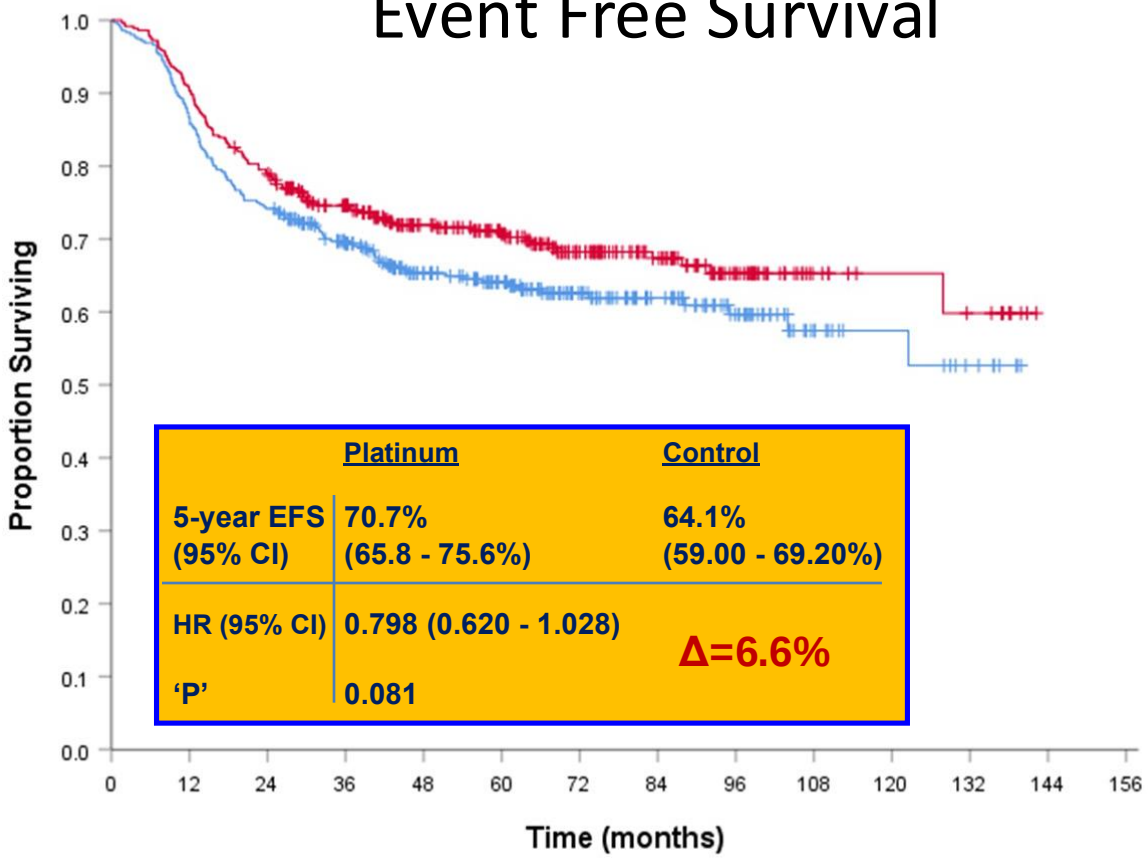
	pCR (ypT0/is ypN0)	No-pCR	
5-year EFS (95% CI)	84.9% (80.39 - 89.41%)	51.8% (45.33 - 58.27%)	Δ=33.1%
HR (95%CI)	0.248 (0.174 - 0.353)		
'p'	<0.001		

	pCR (ypT0/is ypN0)	No-pCR	
5-year EFS (95% CI)	86.8% (79.16 - 94.44%)	52.6% (43.19 - 62.01%)	Δ=34.2%
HR (95%CI)	0.258 (0.135 - 0.493)		
'p'	<0.001		

Gupta et al, SABCS 2022

Long Term Efficacy (n=717)

Event Free Survival

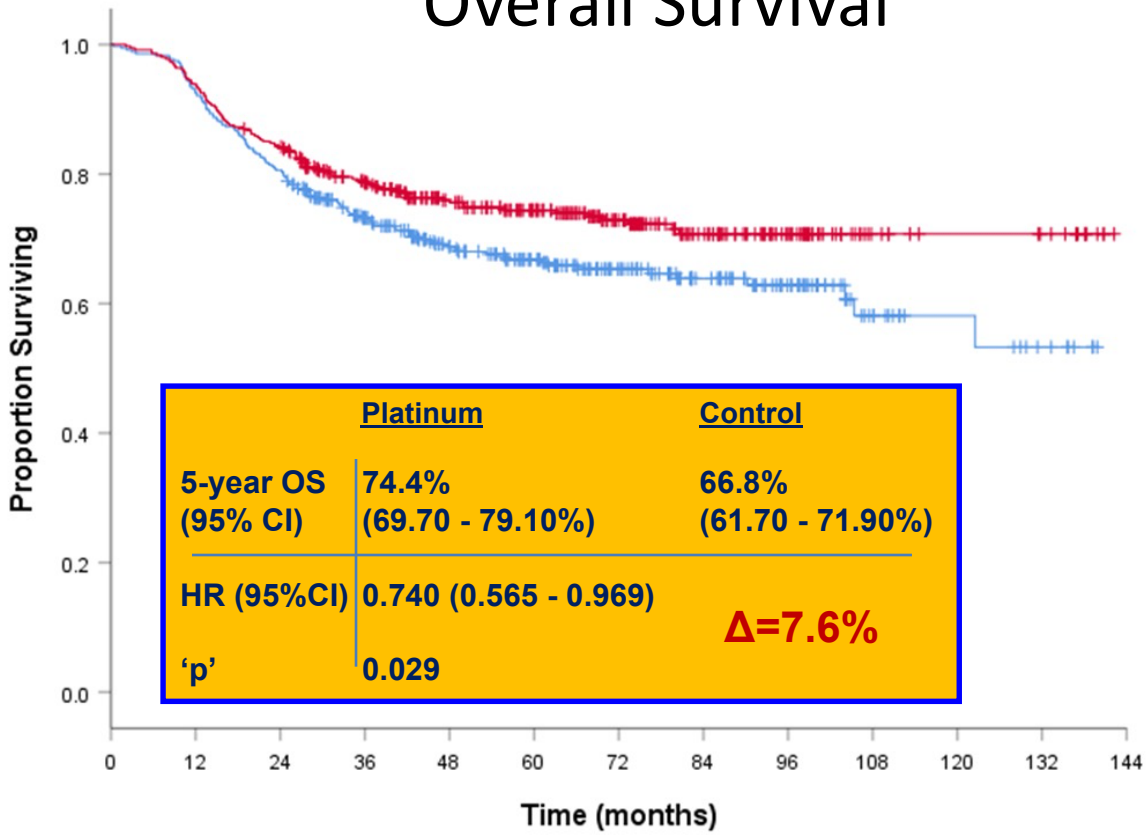


	Platinum	Control
5-year EFS (95% CI)	70.7% (65.8 - 75.6%)	64.1% (59.00 - 69.20%)
HR (95% CI)	0.798 (0.620 - 1.028)	Δ=6.6%
'P'	0.081	

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

Age ≤ or > 50yrs: 12.5% vs no difference

Overall Survival



	Platinum	Control
5-year OS (95% CI)	74.4% (69.70 - 79.10%)	66.8% (61.70 - 71.90%)
HR (95%CI)	0.740 (0.565 - 0.969)	Δ=7.6%
'p'	0.029	

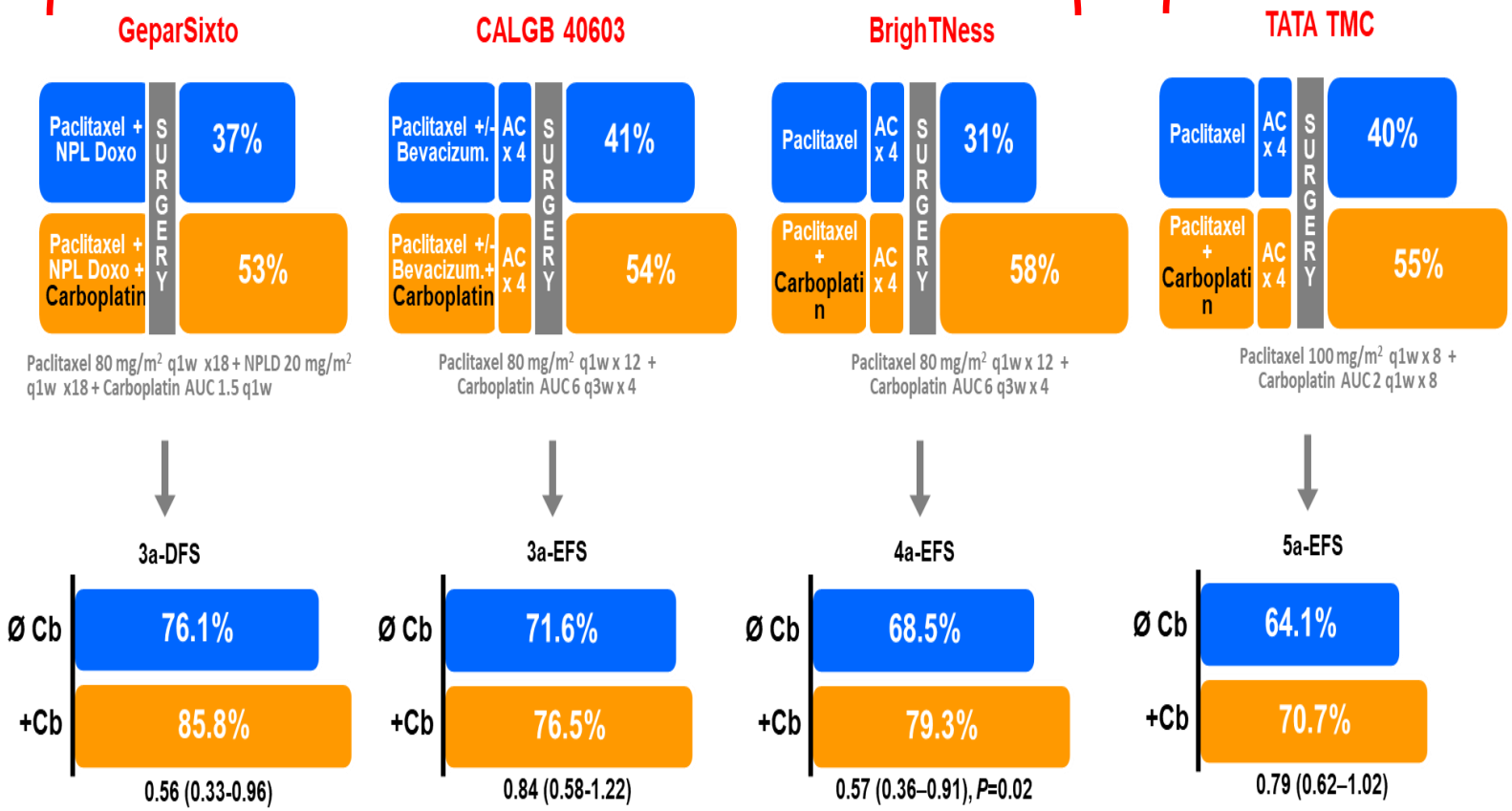
Control	356	330	287	229	179	147	106	74	48	20	12	7
Platinum	361	339	303	252	201	168	122	83	51	19	14	12

Age ≤ or > 50yrs: 11.2% vs no difference

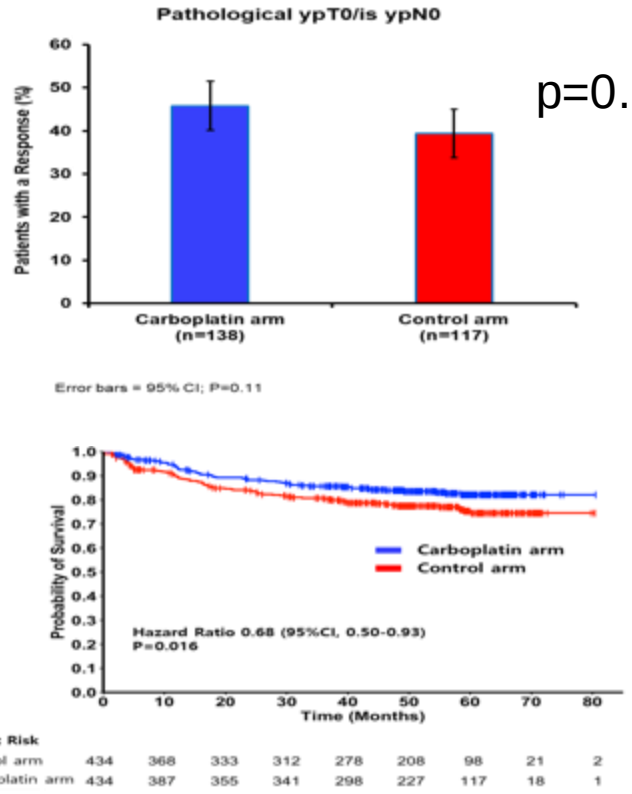
For Early Stage TNBC, the Addition of Platinum Improves Outcome

Primary endpoint : pCR

Primary endpoint : EFS



(Phase III- PEARLY trial)

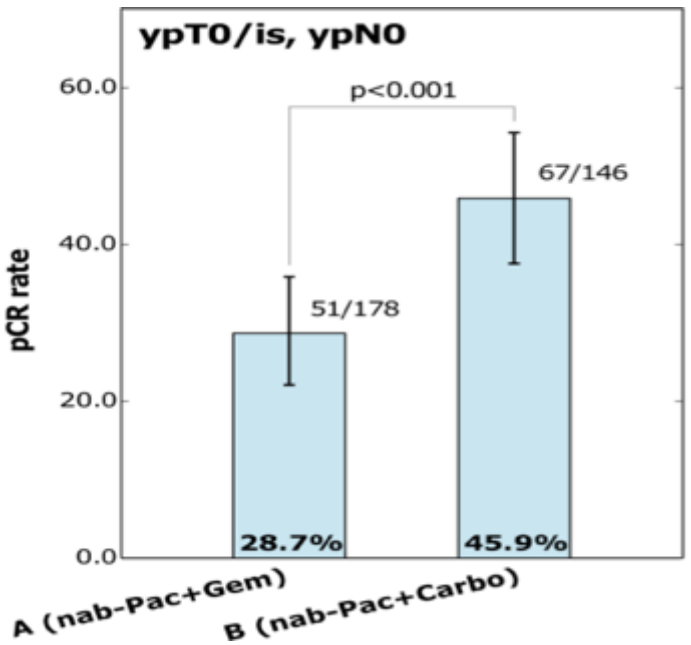


von Minckwitz G, SABCS 2015,; von Minckwitz G. *Lancet Oncol.* 2014; Sikov, *JCO* 2015, Sikov, SABCS 2015 S2-05; Loibl, S, et al. *Lancet Oncol.* 2018, Gupta, et al, SABCS 2022; Sohn J, et al. ASCO 2024

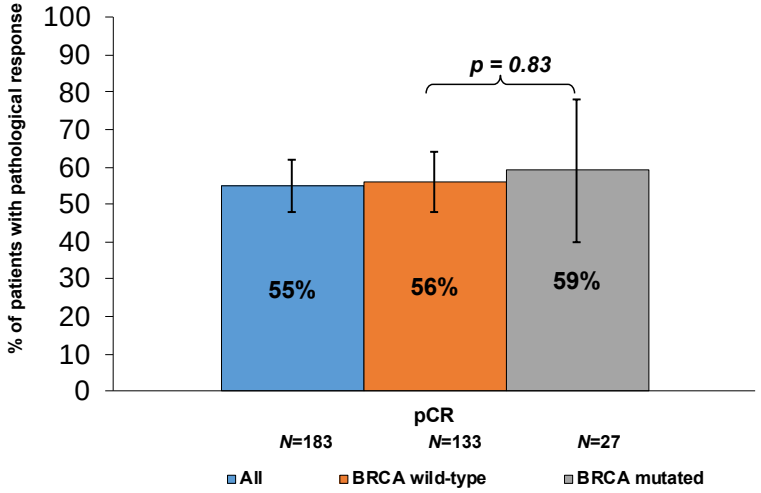
Courtesy of Cortes

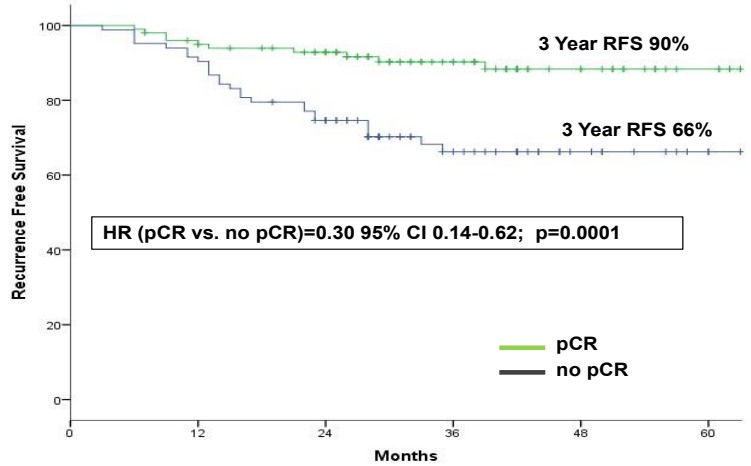
Can we Eliminate Anthracyclines?

ADAPT-TN; N=336



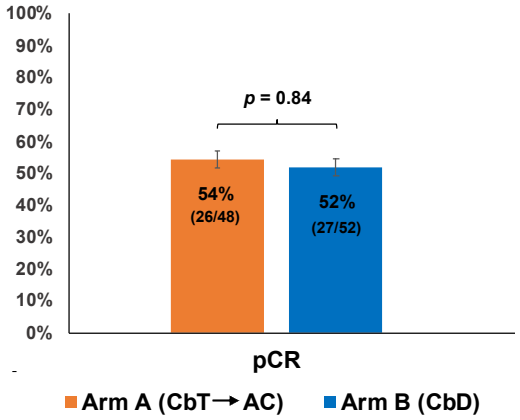
Pooled Analysis of 6 Cycles of Neoadjuvant Carboplatin plus Docetaxel (CbD) in TNBC

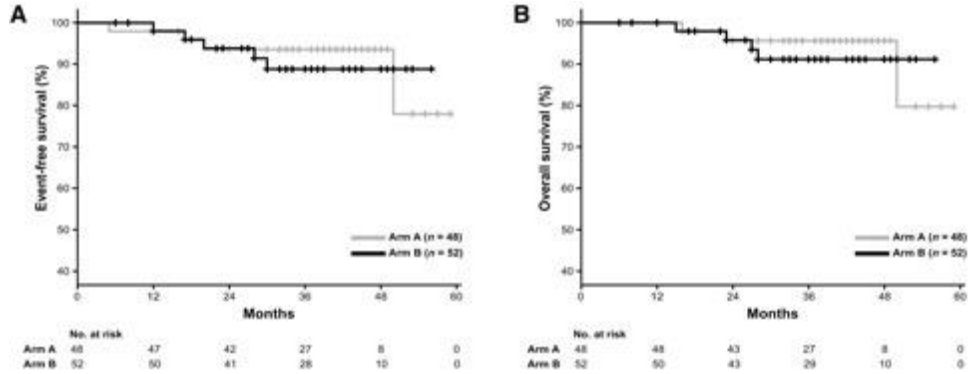




NeoStop Trial
TCa/AC vs Tca x 6
N=100

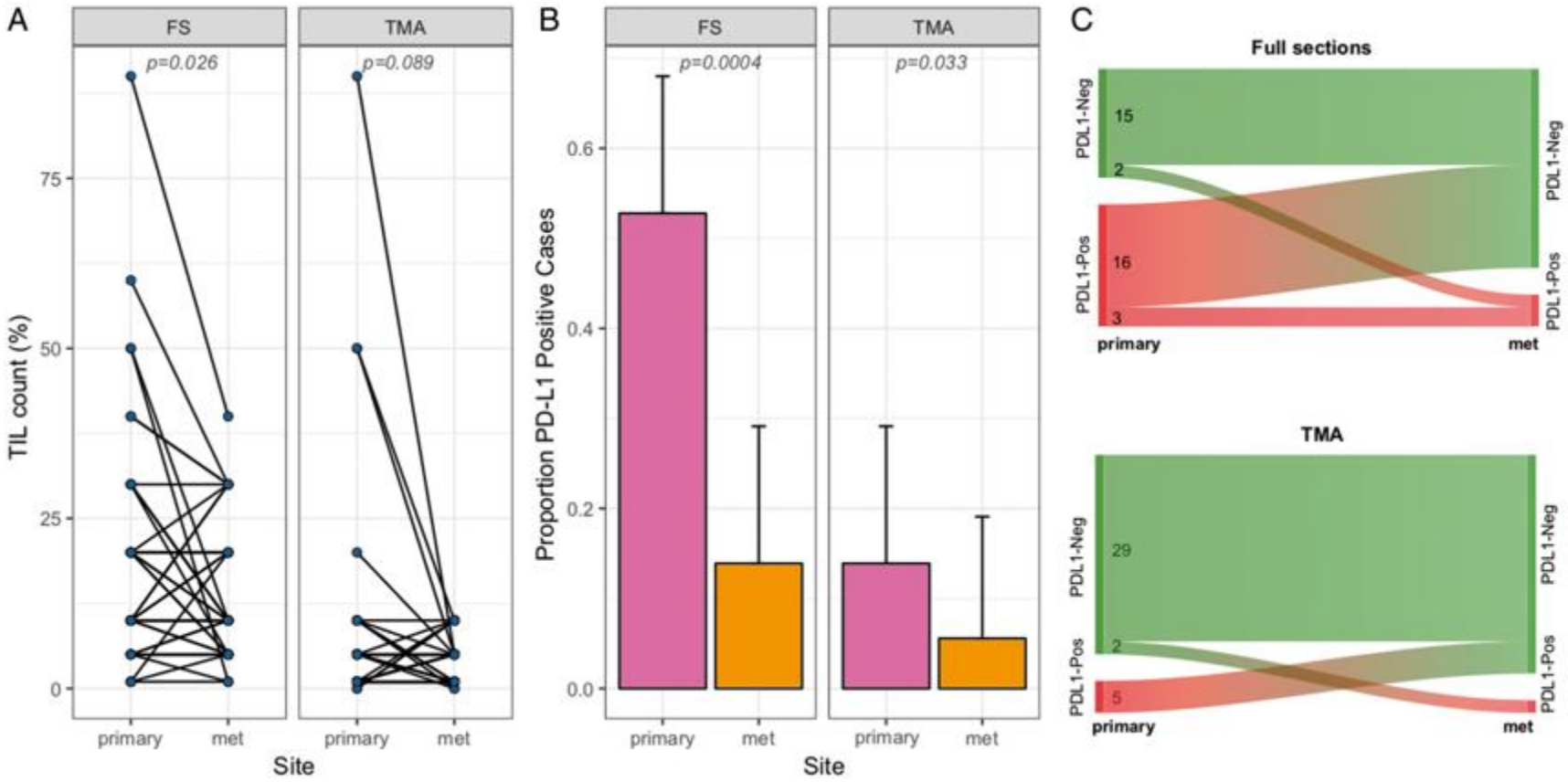
pCR and RCB





Gluz et al JNCI 2017; Sharma et al CCR 2016; Sharma et al CCR 2018; Sharma et al, CCR 2021.

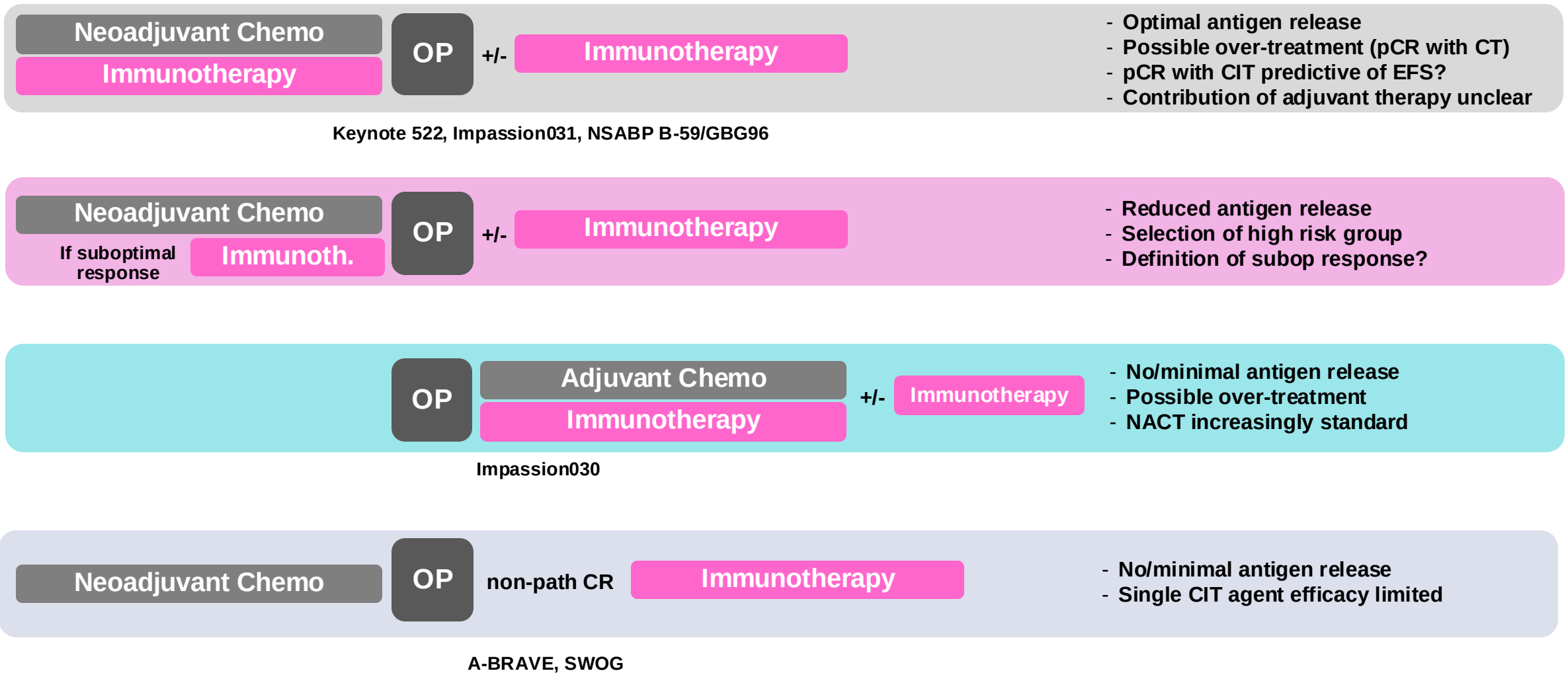
Immunologic Differences Between Primary and Metastatic Tumor Samples



Percent TIL counts in full sections and TMAs.

Szekely, et al (Pusztai), Ann Oncol 2018

Chemoimmunotherapy Trial Designs in Early Stage TNBC

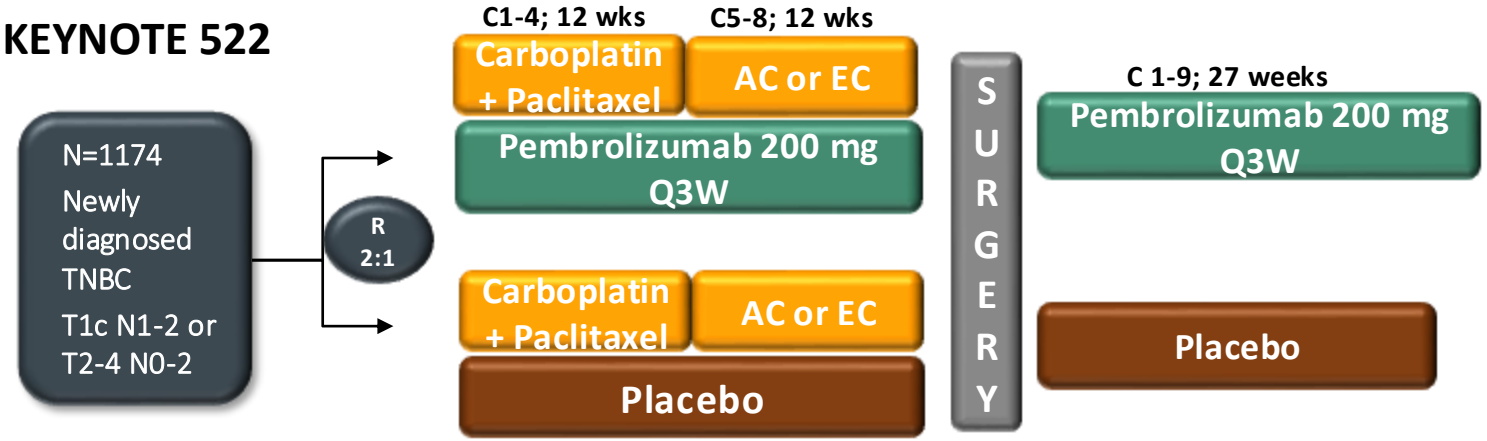


Chemo: Chemotherapy; CIT: Cancer immunotherapy; CR: Complete response; CT: Computed tomography; EFS: Event free survival; NACT: Neo-adjuvant chemotherapy; OP: Operation; pCR: Pathological complete response; Pembro: Pembrolizumab; RCB: Residual cancer burden; TNBC: Triple negative breast cancer

Courtesy of and revised from Schmid

Phase III Neoadjuvant Immunotherapy Trials

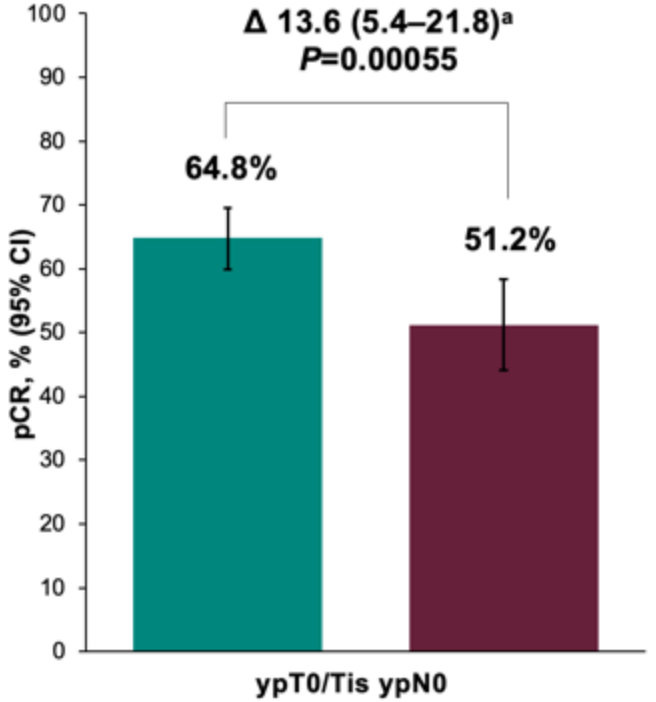
KEYNOTE 522



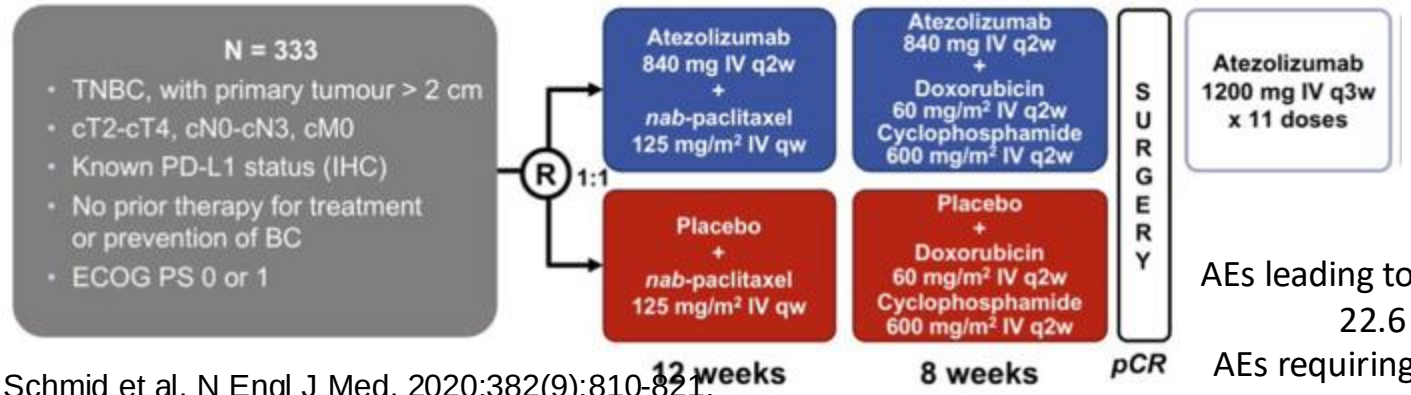
Patient population

- ~51% node positive
- 75% stage II/25% stage III
- ~56% premenopausal

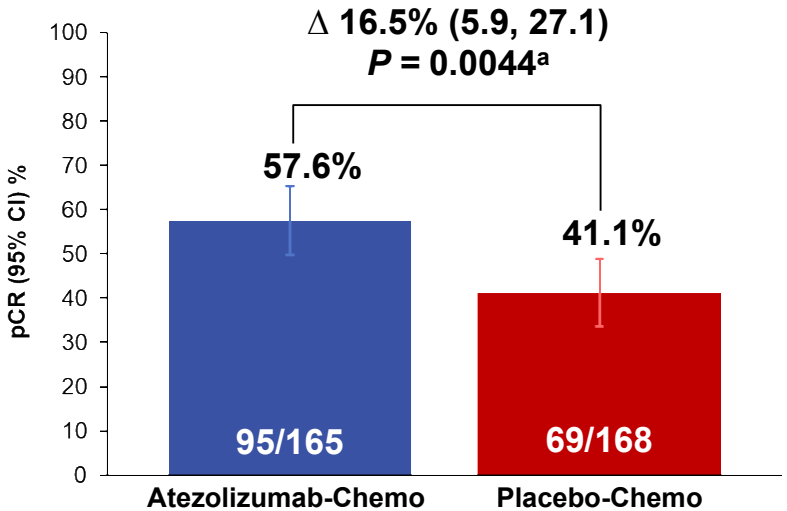
N=602



IMpassion 031



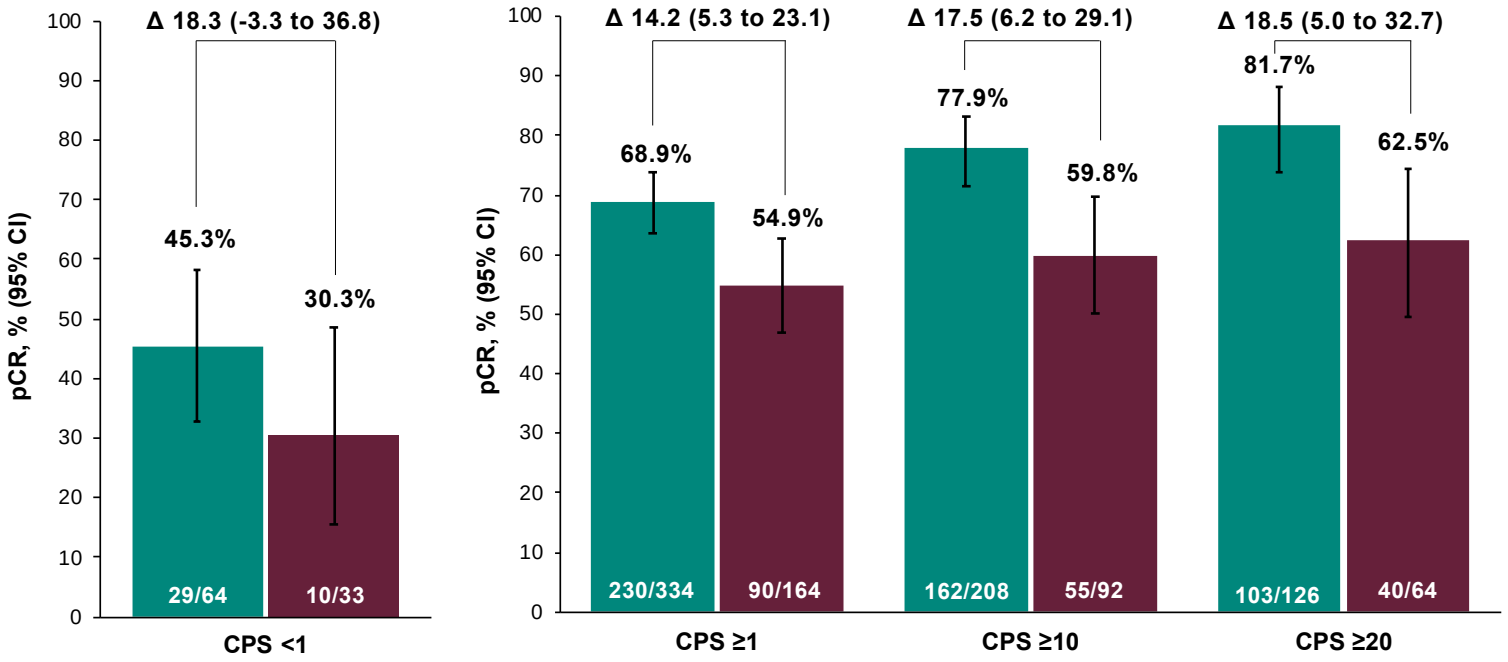
AEs leading to D/C of any drug:
22.6 v 19.8%
AEs requiring corticosteroids:
12.8 v 9.6%

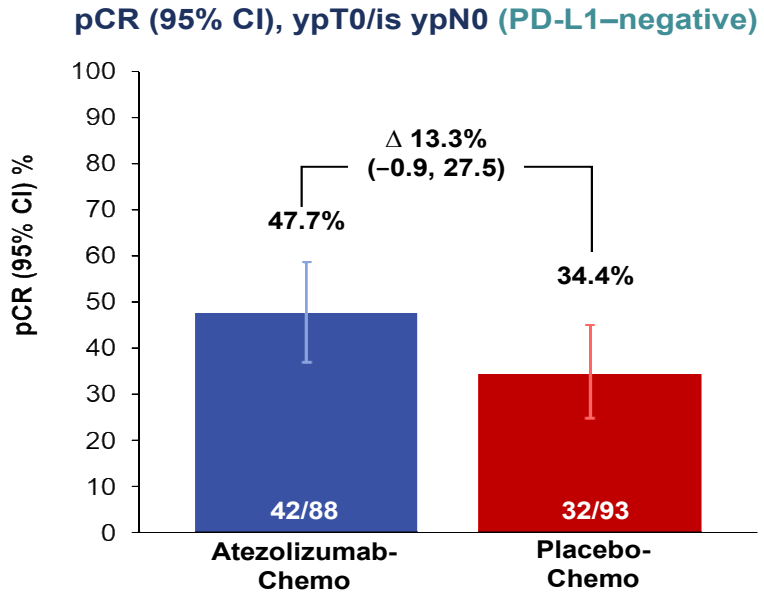


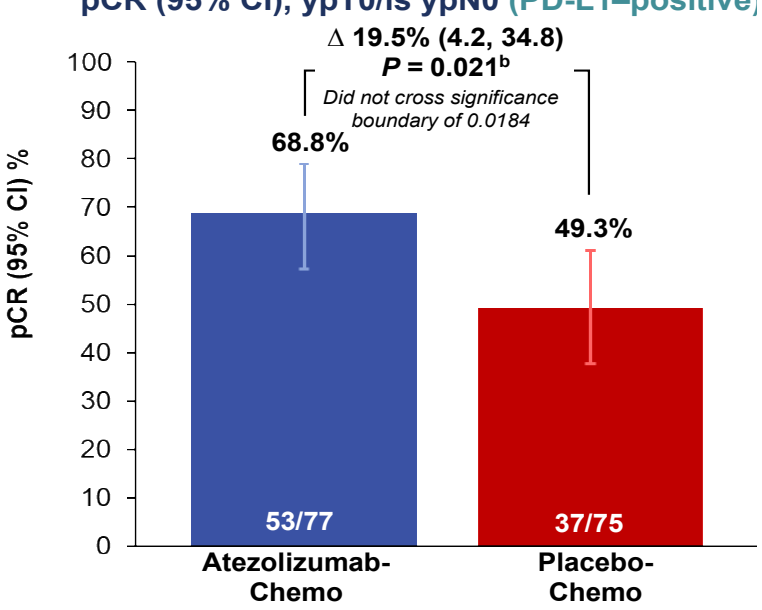
Schmid et al. N Engl J Med. 2020;382(9):810-821;
Mittendorf et al. Lancet 2020;396(10257):1090-1100.

Benefit from Immunotherapy is Independent of PD-L1 status

PD-L1 is Predictive of Response to Chemotherapy



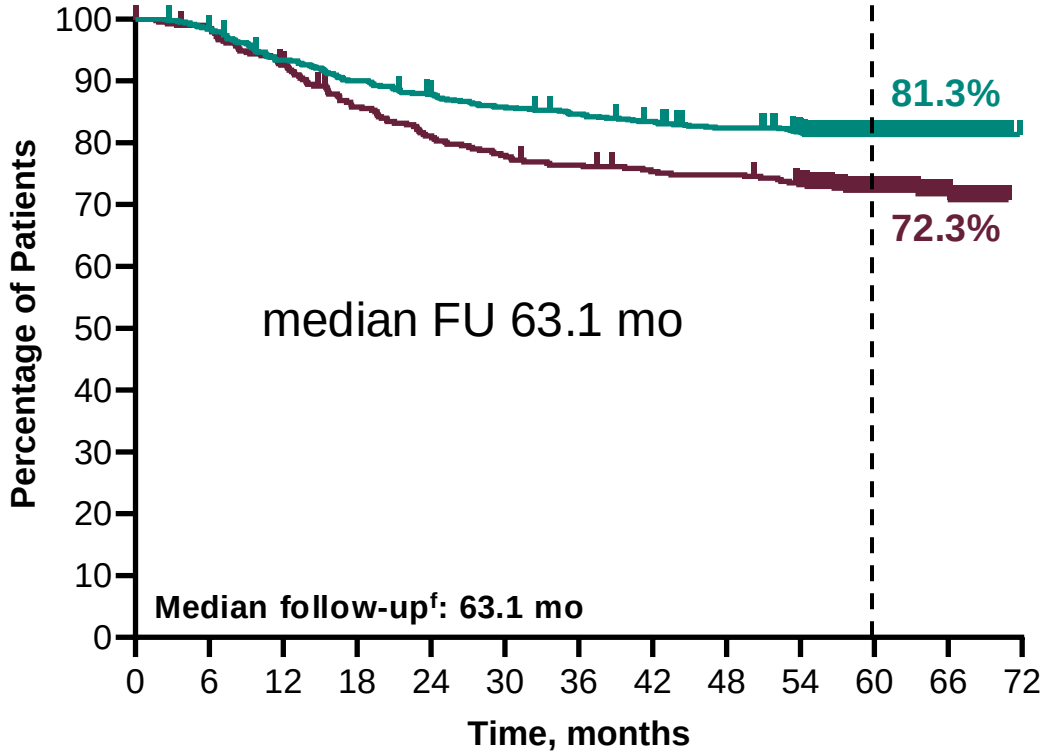




Schmid et al. SABCS 2019, Abstr. GS3-03;
Mittendorf et al. Lancet 2020;396(10257):1090-1100.

KEYNOTE 522: EFS and OS

IA6	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	

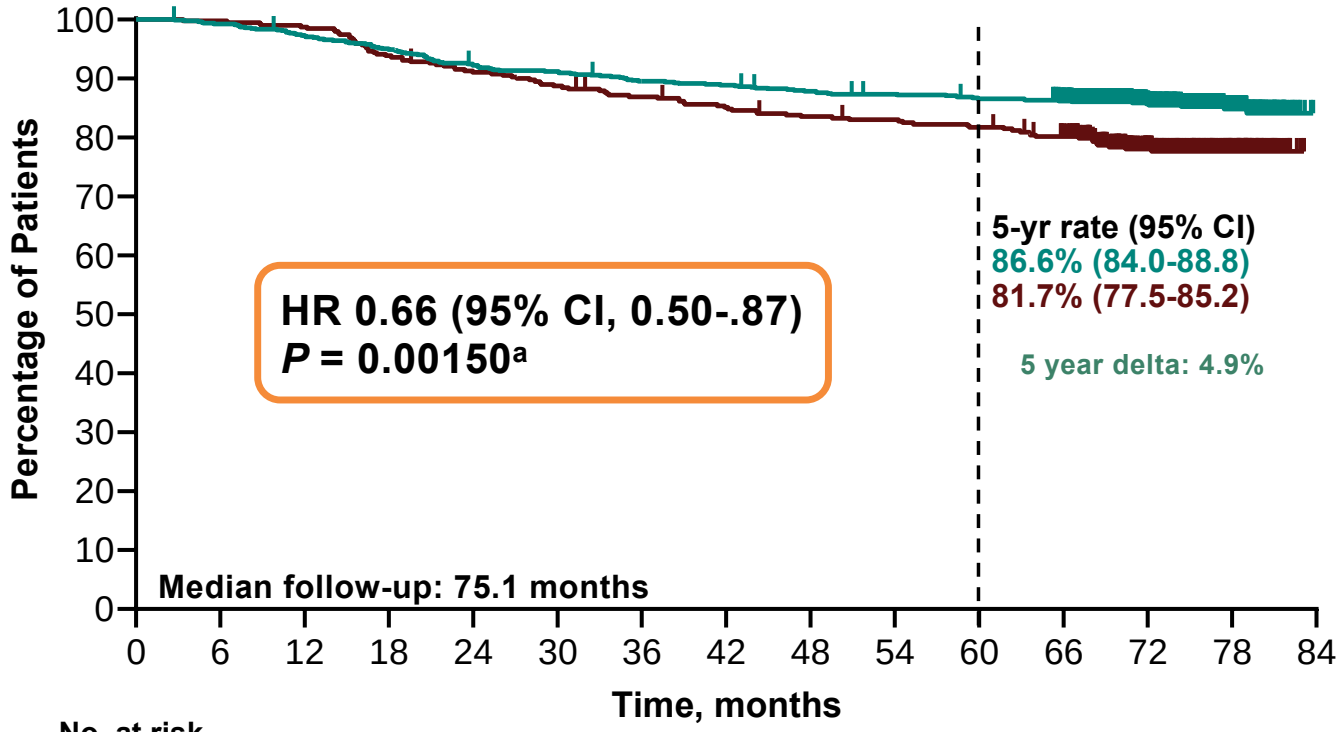


No. at risk

784	769	728	702	681	665	654	643	631	612	411	162	0
390	382	358	329	311	299	292	286	284	274	189	79	0

	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

67.3% information fraction[a]



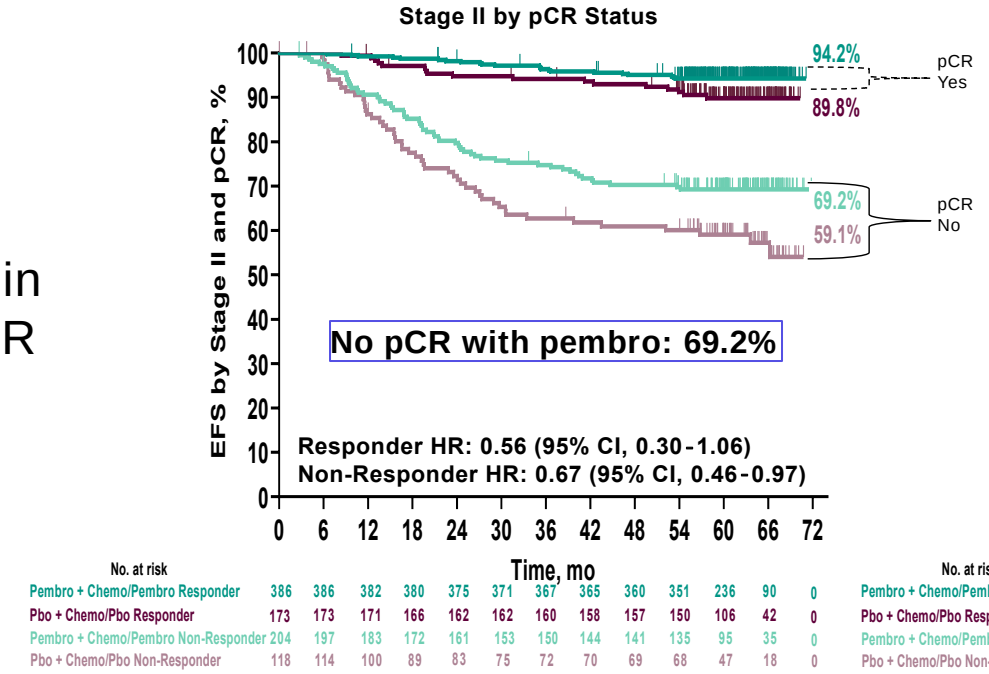
No. at risk

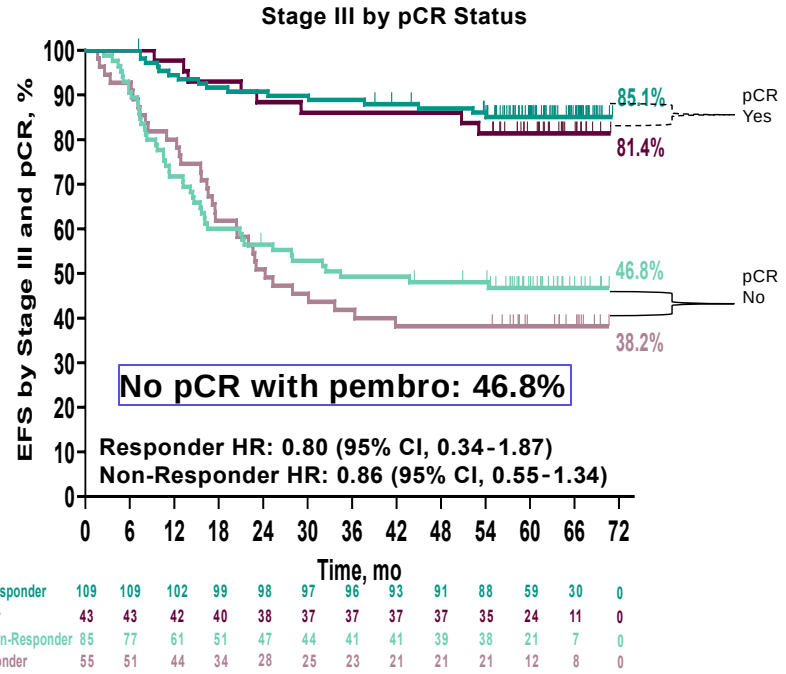
784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
390	389	385	366	354	345	336	328	321	318	313	300	199	82	0

[a]With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis. Overall, 86/115 (74.8%) deaths in the pembro group and 62/85 (72.9%) deaths in the placebo group were due to disease progression or recurrence. The unstratified piecewise HR was 0.87 before the 2-year follow-up and 0.51 afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. Data cutoff date: March 22, 2024.

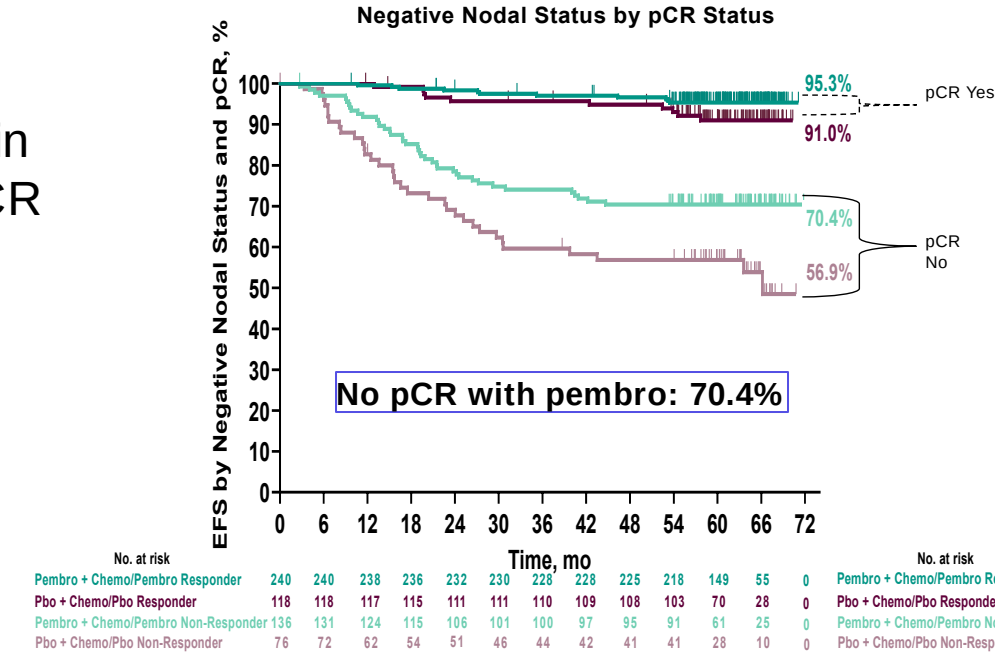
Schmid et al, NEJM 2024

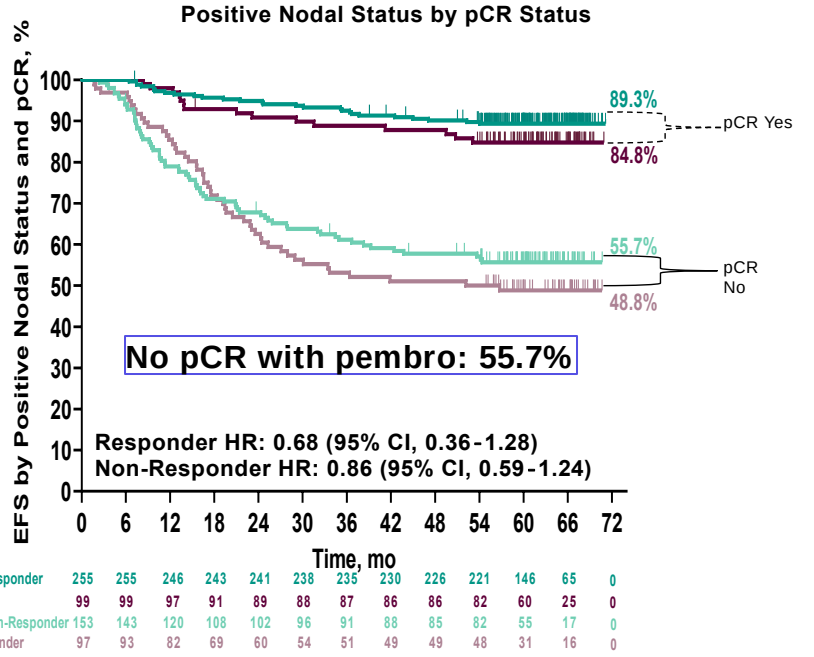
EFS at IA6 by Disease Stage in Patients With and Without pCR





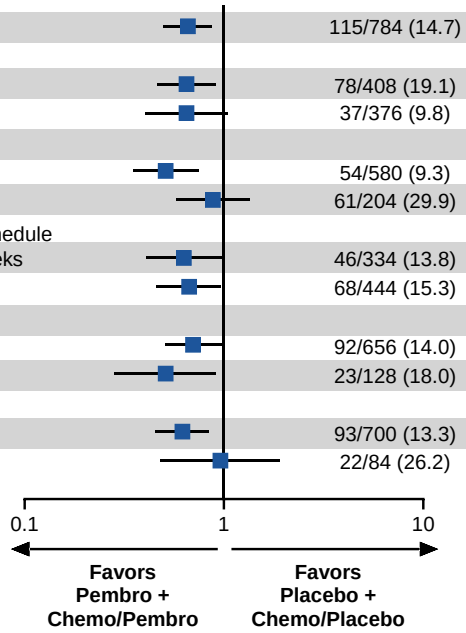
EFS at IA6 by Nodal Status in Patients With and Without pCR

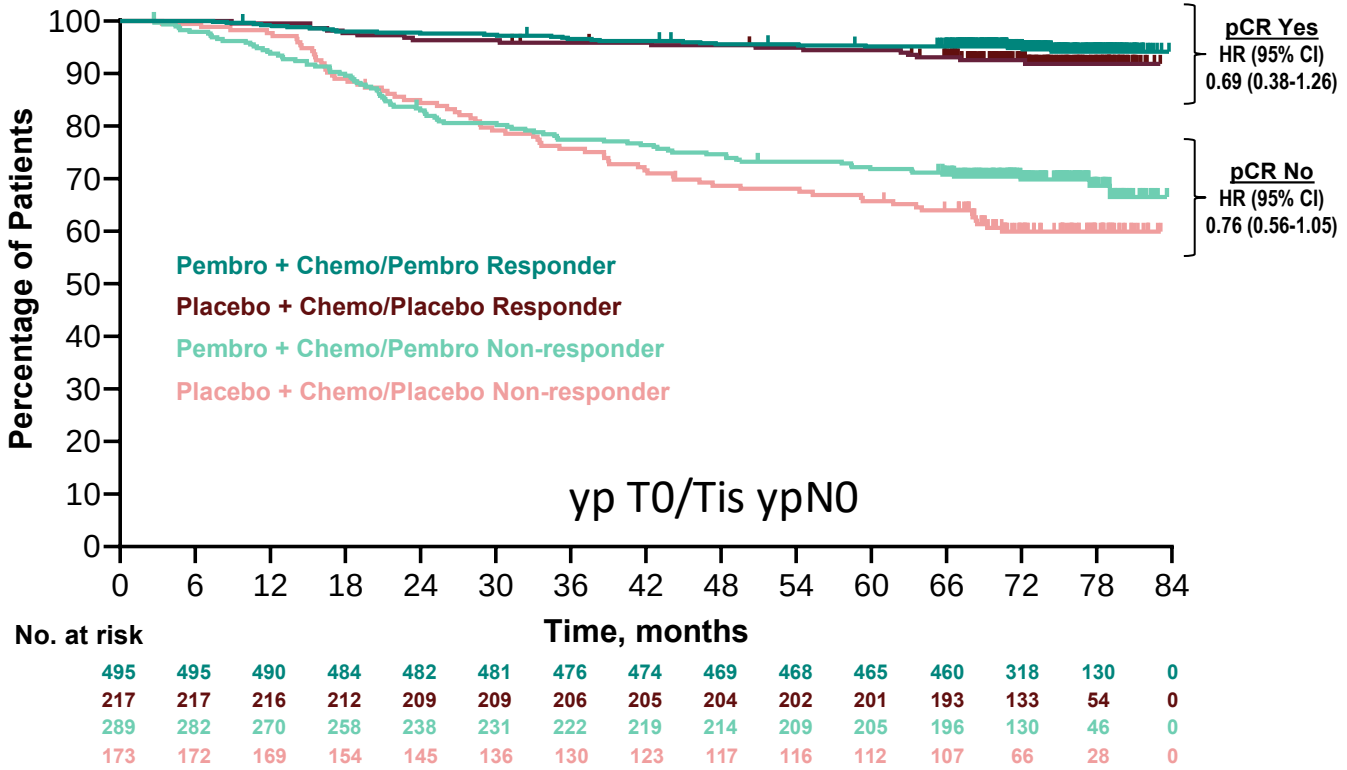




Overall Survival in Patient Subgroups

Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Hazard Ratio (95% CI)
Overall	115/784 (14.7)	85/390 (21.8)	0.66 (0.50 to 0.87)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	0.65 (0.46 to 0.91)
Negative	37/376 (9.8)	29/194 (14.9)	0.65 (0.40 to 1.05)
Tumor size			
T1/T2	54/580 (9.3)	51/290 (17.6)	0.51 (0.35 to 0.75)
T3/T4	61/204 (29.9)	34/100 (34.0)	0.88 (0.58 to 1.34)
Carboplatin schedule			
Every 3 weeks	46/334 (13.8)	36/167 (21.6)	0.63 (0.41 to 0.97)
Weekly	68/444 (15.3)	49/220 (22.3)	0.67 (0.46 to 0.96)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	0.70 (0.51 to 0.97)
CPS <1	23/128 (18.0)	23/69 (33.3)	0.51 (0.28 to 0.91)
Age category			
<65 years	93/700 (13.3)	72/342 (21.1)	0.62 (0.45 to 0.84)
≥65 years[a]	22/84 (26.2)	13/48 (27.1)	0.96 (0.48 to 1.91)

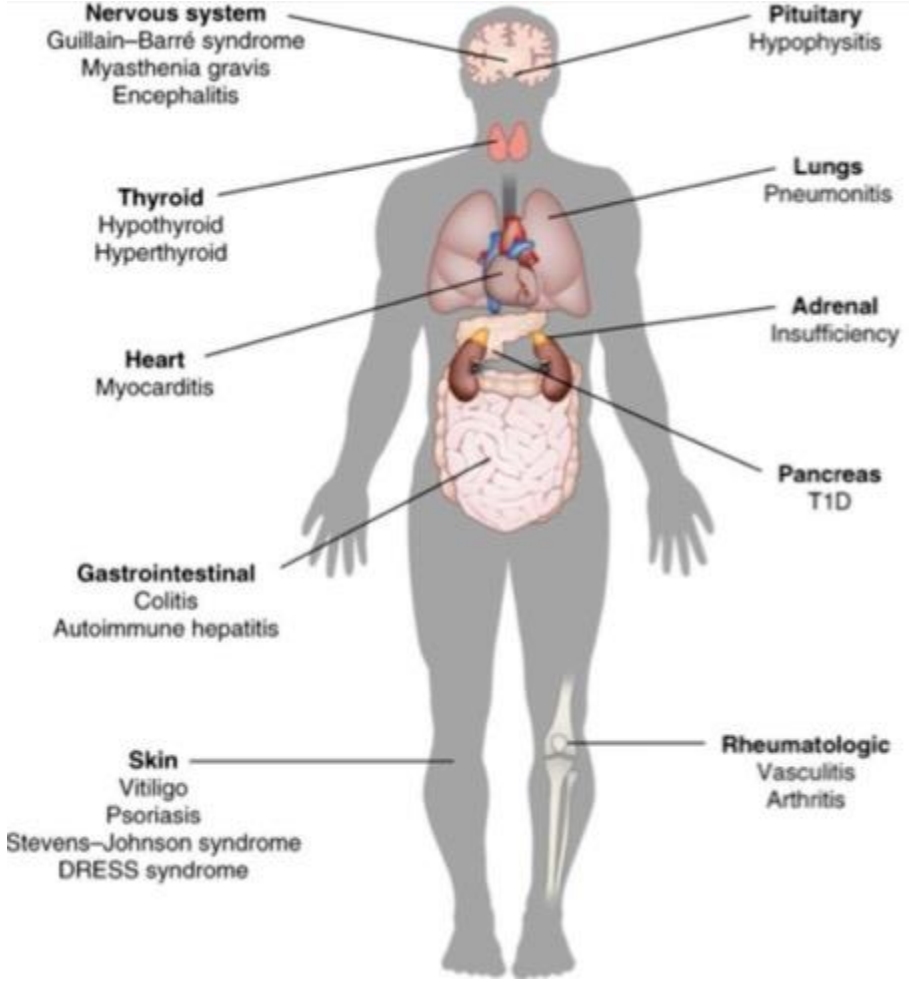




Benefit from pembrolizumab seen for both EFS and OS in non-PCR

It's impossible to separate out the benefi from neoadjuvant vs continued adjuvant pembro

Safety of neoadjuvant immune check point inhibitors in early stageTNBC

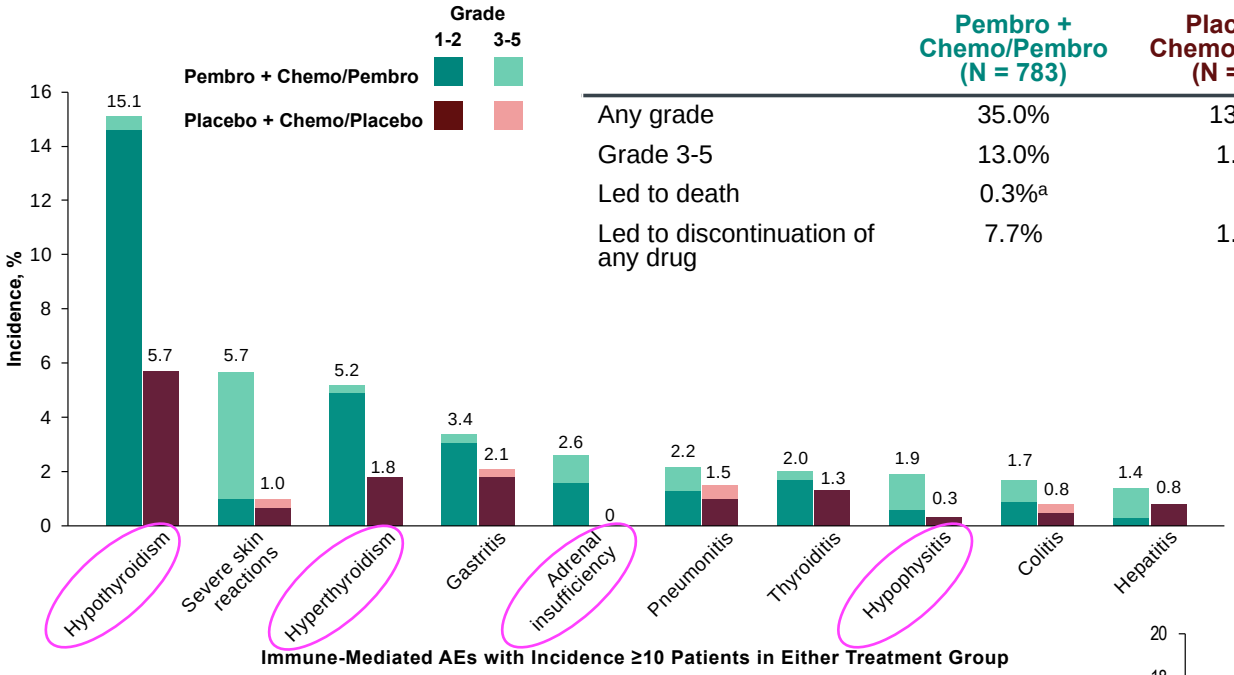


irAE incidence in eTNBC

- Any grade: 40-44%
- Grade 3-5: 14-15%
- Higher incidence in women!
- **Early recognition and prompt management is critical**
  - Delayed toxicity
    - Can occur months to years after Rx
- Management guidelines
  - ASCO/NCCN/SITC
  - Steroid refractory irAEs

D'Abreo and Adams. Nat Rev Clin Oncol 2019, Brahmer et al, J Clin Oncol 2018; Jacob et al, SABCS 2023

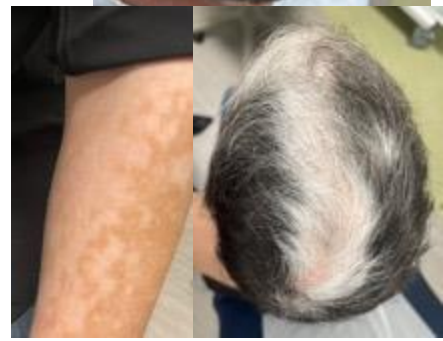
What is the Patient Cost of Therapy: irAEs in KN522

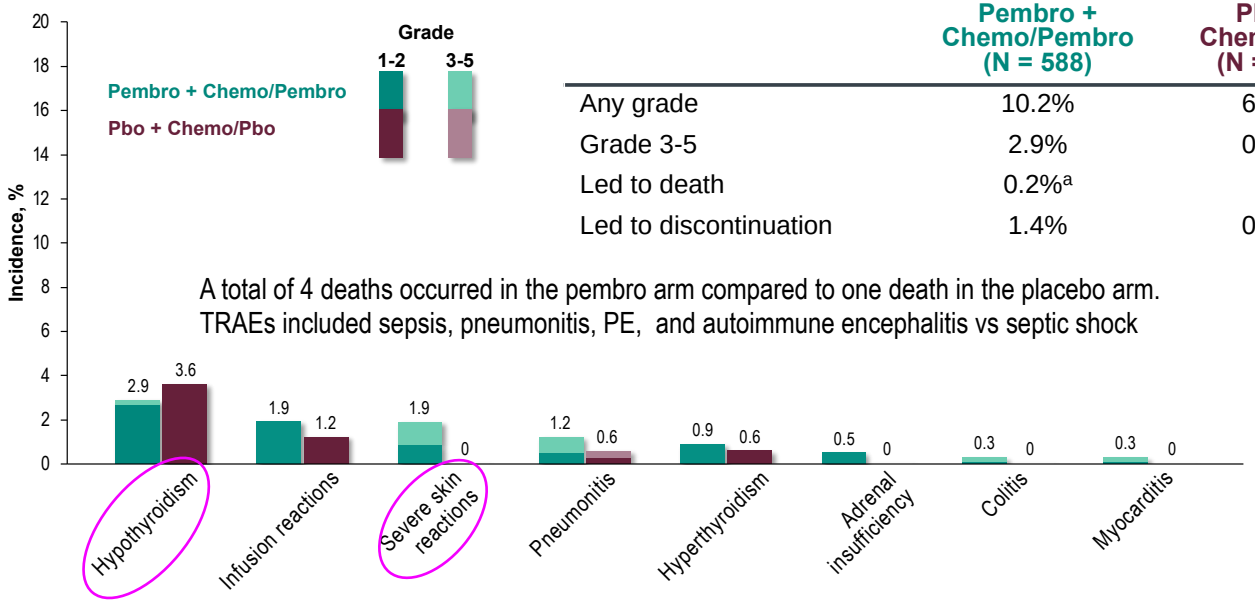


	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	35.0%	13.1%
Grade 3-5	13.0%	1.5%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	7.7%	1.0%

Neoadj + chemo/adj

Adjuvant



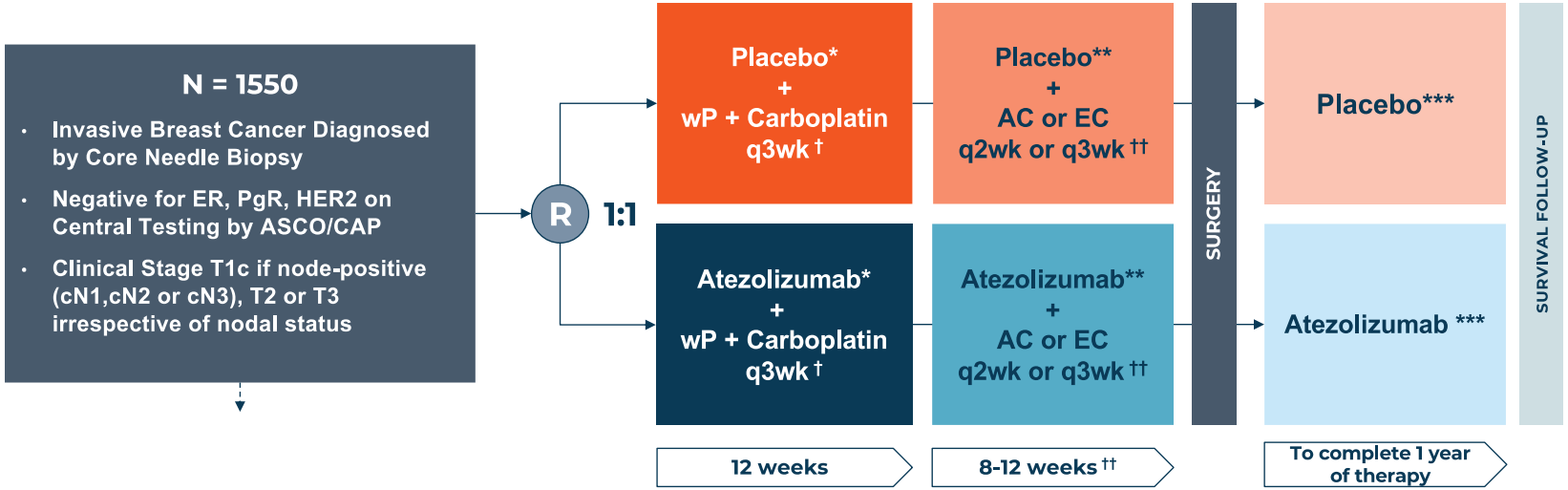


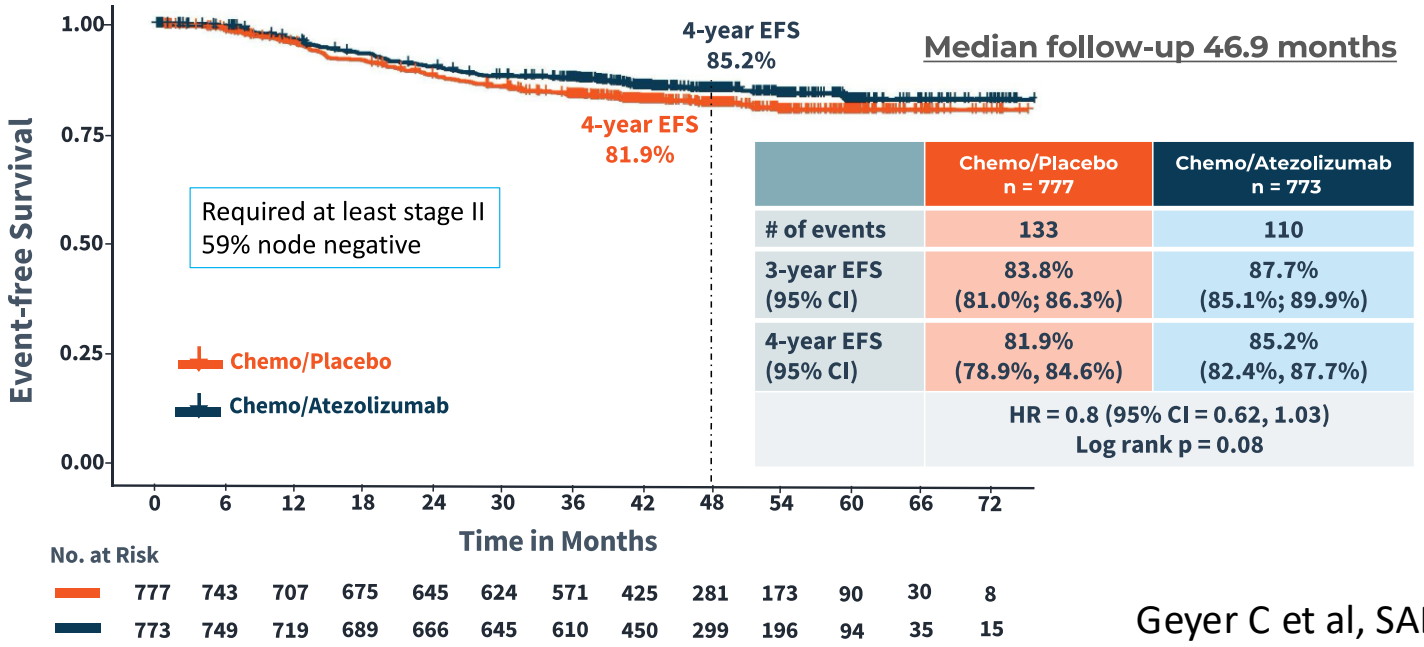
	Pembro + Chemo/Pembro (N = 588)	Pbo + Chemo/Pbo (N = 331)
Any grade	10.2%	6.0%
Grade 3-5	2.9%	0.3%
Led to death	0.2%[a]	0
Led to discontinuation	1.4%	0.3%

A total of 4 deaths occurred in the pembro arm compared to one death in the placebo arm.
TRAEs included sepsis, pneumonitis, PE, and autoimmune encephalitis vs septic shock

Schmid et al, ESMO 2024 and NEJM 2020

GeparDouze/NSABP B-59

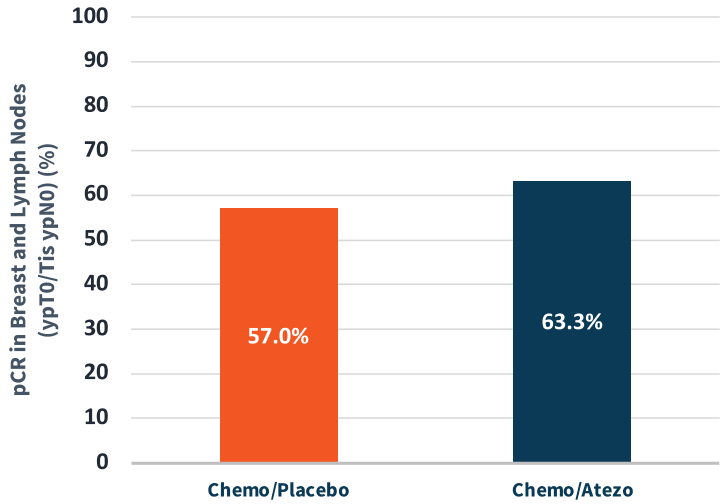




	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773
# of events	133	110
3-year EFS (95% CI)	83.8% (81.0%; 86.3%)	87.7% (85.1%; 89.9%)
4-year EFS (95% CI)	81.9% (78.9%, 84.6%)	85.2% (82.4%, 87.7%)
	HR = 0.8 (95% CI = 0.62, 1.03) Log rank p = 0.08	

Demographics

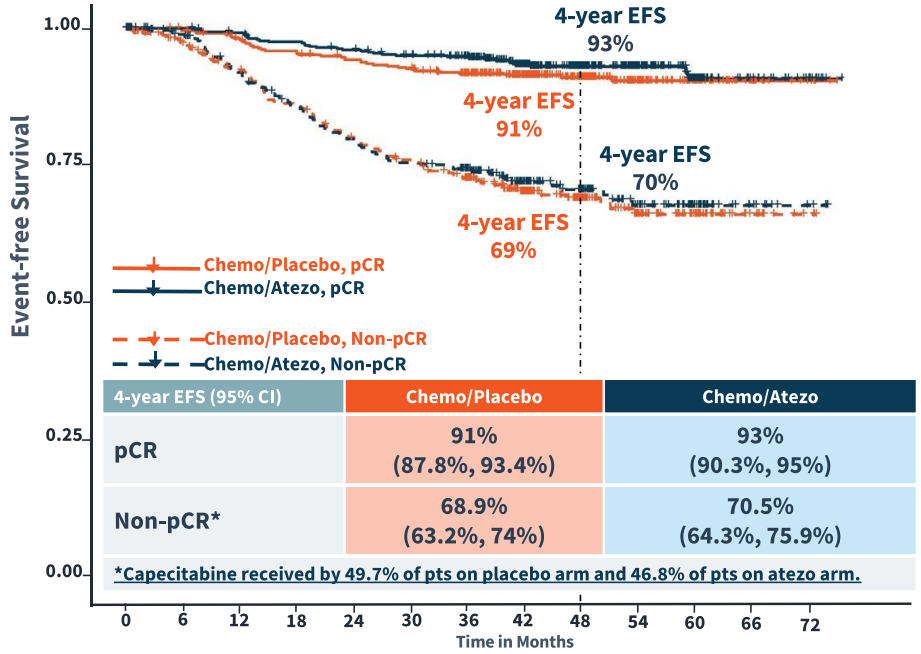
Required at least stage II
59% node negative



	Chemo/Placebo n = 777	Chemo/Atezo n = 773
% pCR [a] (95% CI)	57.0% (53.5%, 60.5%)	63.3% (59.9%, 66.7%)
Difference in % pCR (95% CI)	6.3% (1.4%, 11.1%) (p_{adj} = 0.0091) [b]	

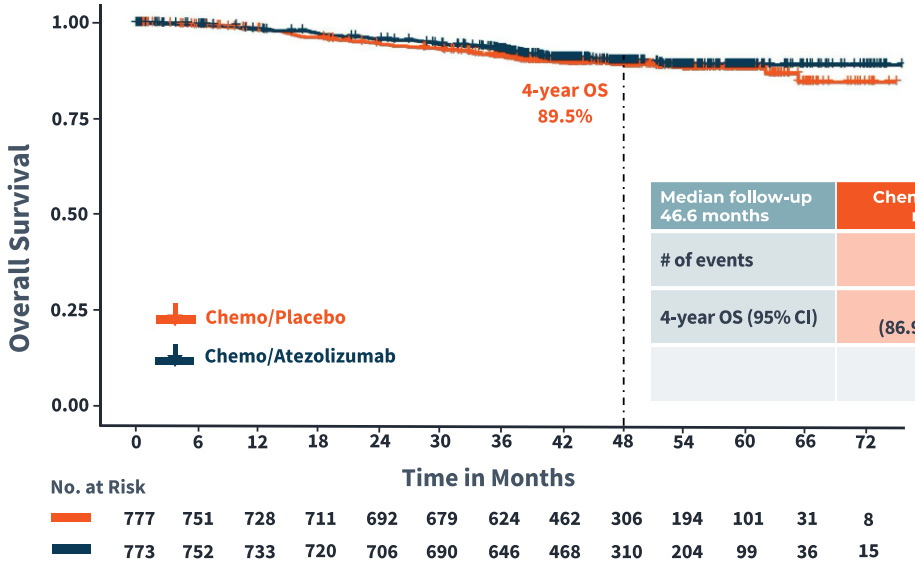
[a] Those with missing pCR status are considered as non-responders.
[b] 2-sided CMH test adjusted by stratification factors collapse of PD-L1 status.

Geyer C et al, SABCS 2024



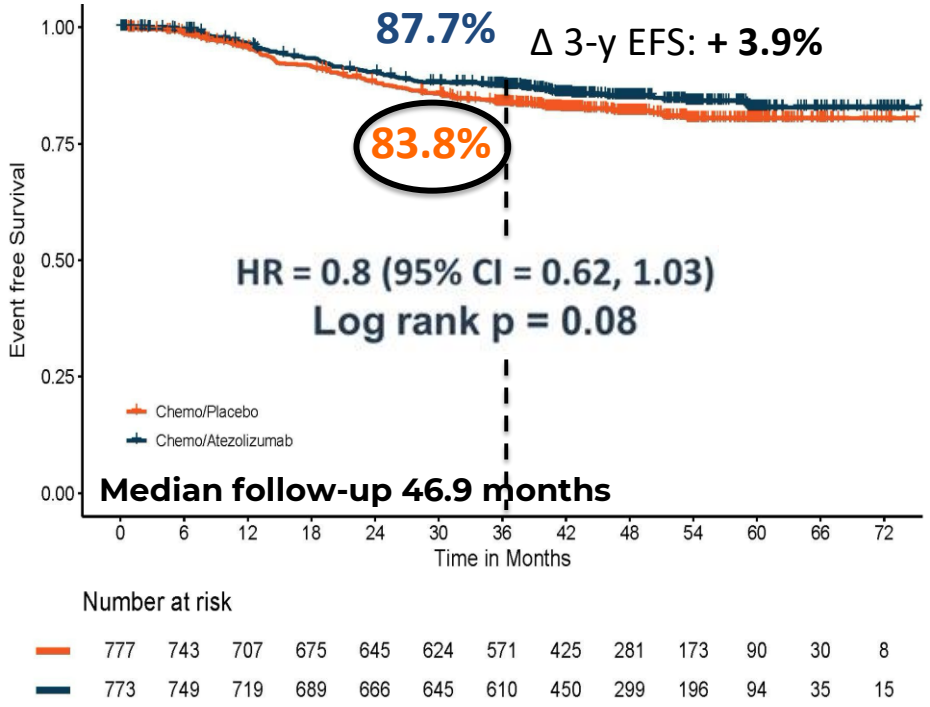
4-year EFS (95% CI)	Chemo/Placebo	Chemo/Atezo
pCR	91% (87.8%, 93.4%)	93% (90.3%, 95%)
Non-pCR*	68.9% (63.2%, 74%)	70.5% (64.3%, 75.9%)

*Capecitabine received by 49.7% of pts on placebo arm and 46.8% of pts on atezo arm.

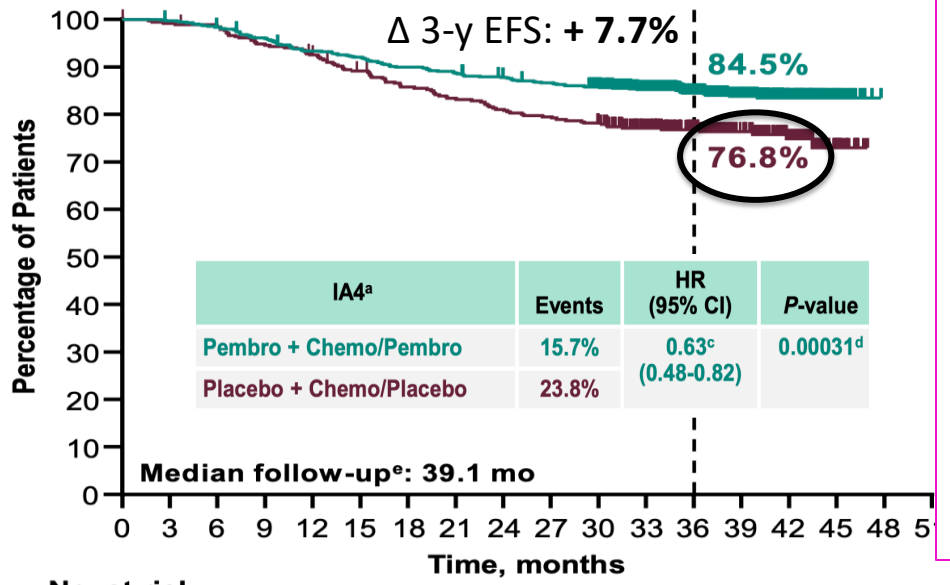


Median follow-up 46.6 months	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773
# of events	79	70
4-year OS (95% CI)	89.5% (86.9%, 91.5%)	90.2% (87.7%, 92.3%)
	HR = 0.86 (95% CI = 0.62, 1.19)	

NSABP B-59/GBG-96-GeparDouze



KEYNOTE-522

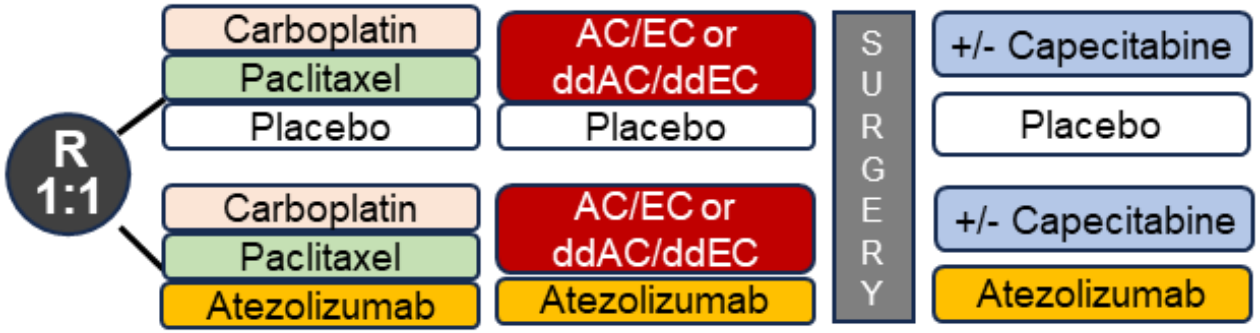


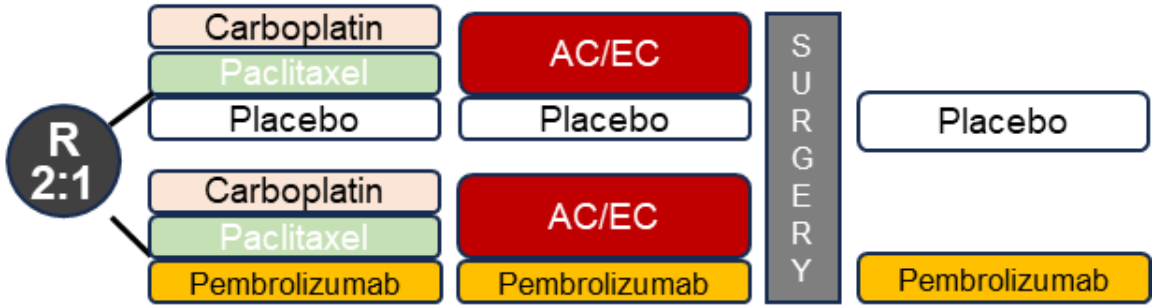
IA4[a]	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48-0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		

Reasons for lack of benefit with atezo and improved outcome in the control arm?

- Capecitabine use in almost 50%
- Higher percent node negative
- Use of dose dense AC/EC?

Anti-PD-L1 and anti-PD1 are not made equal





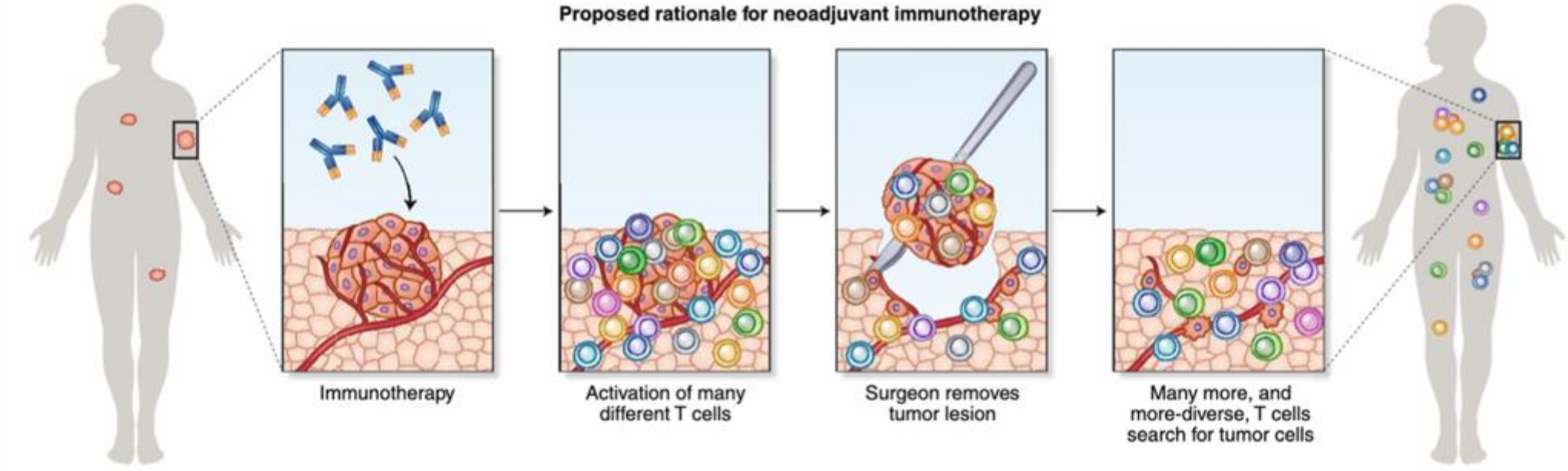
Atezolizumab
Anti-PD-L1

Pembrolizumab
Anti-PD1

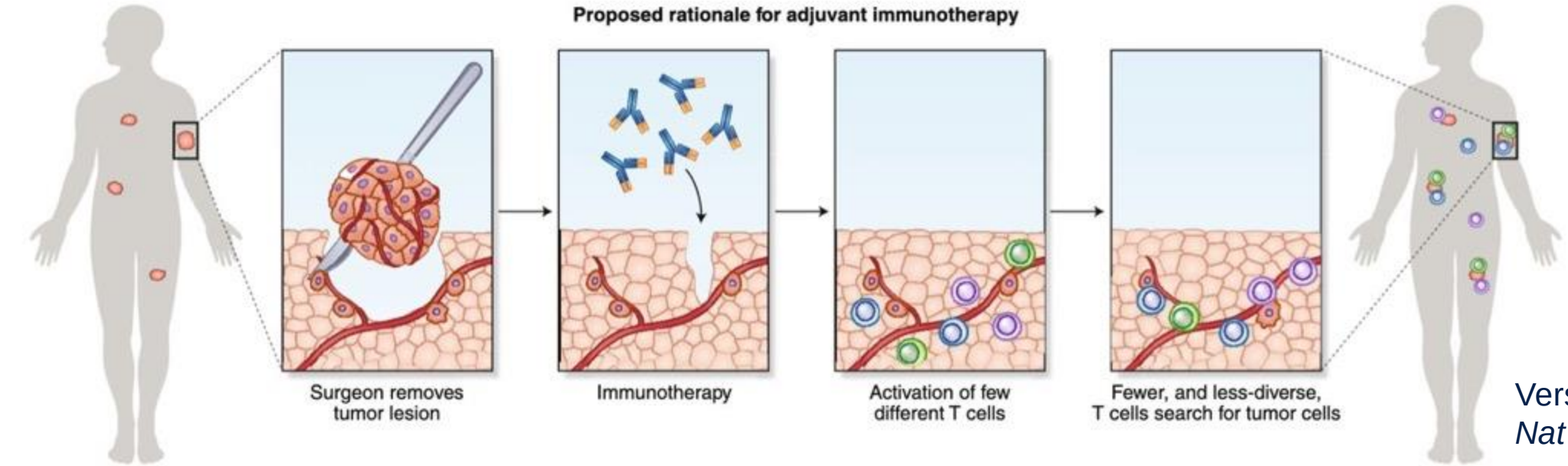
Slide courtesy of Giampoalo Bianchini

Proposed rationale for neoadjuvant vs. adjuvant immunotherapy

Neoadjuvant



Adjuvant

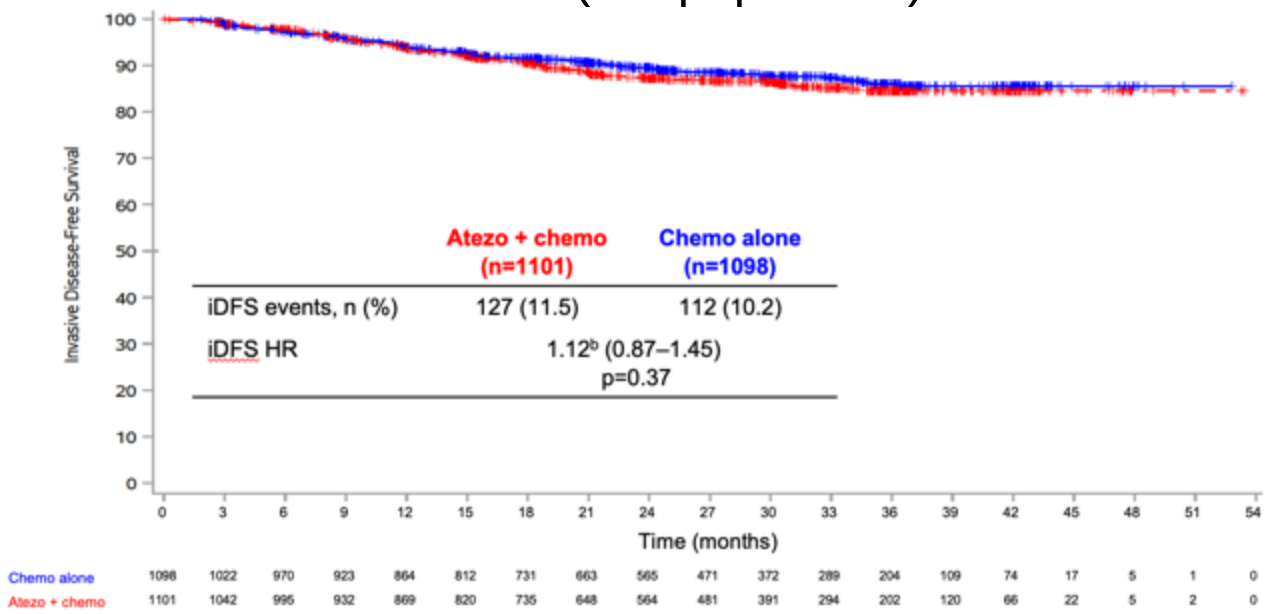


Versluis JM et. al.
Nat Med 2020

Adjuvant IO in IMpassion030: Treatment Setting Matters

Primary efficacy endpoint:

iDFS (ITT population)



Demographics: 52% node negative; 85% stage II; 71% PD-L1+

** Median f/u 25 months: Futility declared because the observed HR of 1.12 in the ITT population crossed the non-binding futility boundary of HR >1 at this interim analysis.

Secondary efficacy endpoints:

- iDFS in PD-L1+ subgroup – No difference
- OS (ITT population) – No difference

Conclusions:

- These data do not support the addition of adjuvant atezolizumab to chemotherapy in patients who have undergone primary surgery for early-stage TNBC
- *Why?*
  - Is the PDL1 inhibitor inferior to PD1 inhibitors for TNBC? (GeparDouze/B59 also negative)
- **Given these data, neoadjuvant IO administration is clearly preferred, followed by adjuvant IO as indicted.**
- **More definitive data regarding timing will come from the SWOG trial S1418 (adjuvant pembrolizumab for early-stage TNBC)**

Ignatiadis et. al. SABCS 2023

A-BRAVE Trial: Avelumab after Chemotherapy for Early Stage TNBC

High Risk TNBC patients who completed locoregional and systemic treatment with curative intent

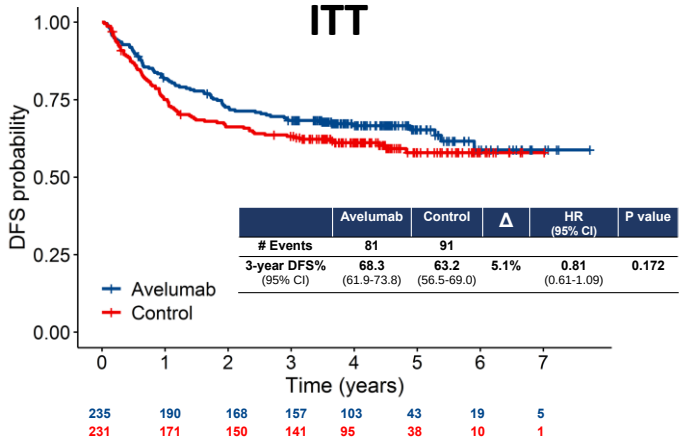
Key eligibility criteria:
- Age ≥18 years
- ECOG PS 0-1
- TNBC (ER & PgR <10%, HER2 0-1+ or 2+ FISH-)^
- Anthracycline and taxanes (neo)-adjuvant ChemoRx*
- Tissue samples for central PD-L1 assessment
- **Stratum A (Adjuvant): pT2N1, pT3-4 N0-3, pN2-3 anyT#**
- **Stratum B (Post-neoadjuvant): residual invasive carcinoma in the breast and/or axillary lymph nodes§**

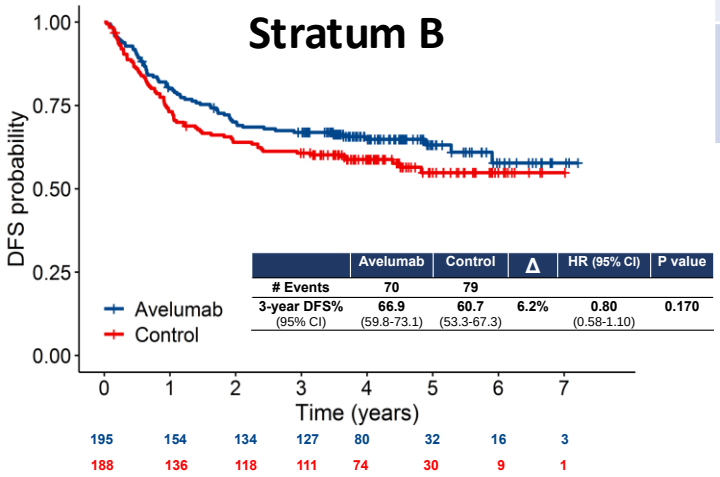
R 1:1
N=474

Avelumab
10mg/kg, iv, q 2 weeks for 52 weeks

Observation

^ for patients in the neoadjuvant stratum, TN status required in the preoperative and in the post-surgical specimen
*** After amendment of 06/2018, patients in stratum B were allowed to receive additional post-operative chemotherapy and were randomized at completion of treatment.**
§ excluding ypT1micN0, ypT1micN0i+, ypT0N0i+
 # trial initially limited to pN≥2; protocol amendment in 10/2017 to include patents with pT2N1 and pT3-4 N0-3 disease stage
Randomization balanced for Stratum A and Stratum B





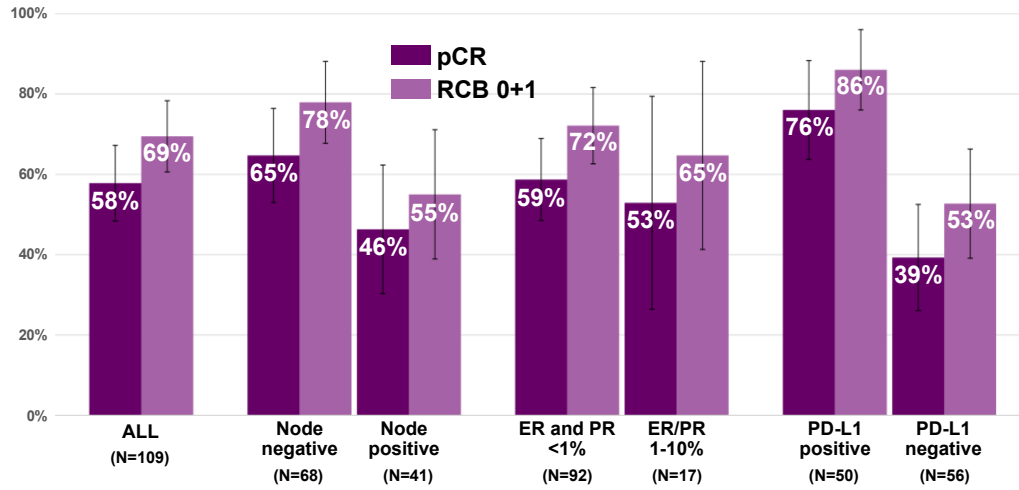
Endpoint and population			Δ 3-yr rate	HR (95% CI)
DFS	ITT	Co-primary	**+ 5.1%**	**0.81** (0.61-1.09)
	Post-neoadj	Co-primary	**+ 6.2%**	**0.80** (0.58-1.10)
OS	ITT	Secondary	**+ 8.5%**	**0.66** (0.45-0.97)
	Post-neoadj	Exploratory	**+ 8.6%**	**0.69** (0.46-1.03)
DDFS	ITT	Exploratory	**+ 7.5%**	**0.70** (0.50-0.96)

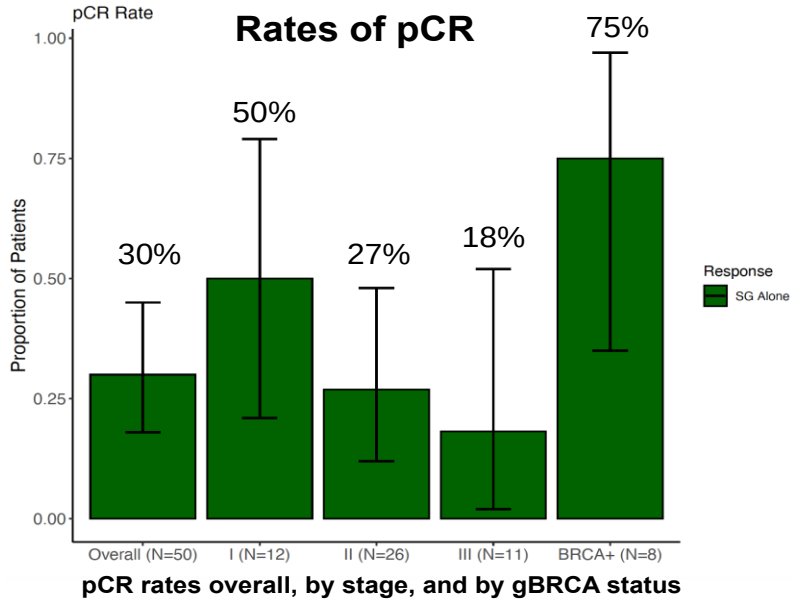
Hard to interpret data in this mixed population
- Should we consider IO in patients who have surgery first?
- Not enough data to change treatment practice
- IO in the neoadjuvant setting (KN522) remains the **standard of care**

Conte et al, ASCO 2024

Alternative NeoAdjuvant Regimens for TNBC

- NeoPACT:
  - Pembrolizumab/docetaxel/carboplatin x 6 cycles
  - 109 evaluable, 88% stage 2-3
  - Stage II-III, ER & PR IHC <1%
    - pCR and RCB 0+1 59% and 69%
    - ≥30% TILS and immune signature predict pCR
  - 2-year EFS with pCR: 98%
- NeoSTAR: Sacituzumab govitecan x 4
  - N=50 (12 stage I disease, 26 stage II, 11 stage III; 62% node neg; 9 pts gBRCA+).
  - pCR rate 30% (n= 15/50; (18%, 45%); RCB1, 3
  - Ongoing study plus pembrolizumab





pCR rates overall, by stage, and by gBRCA status

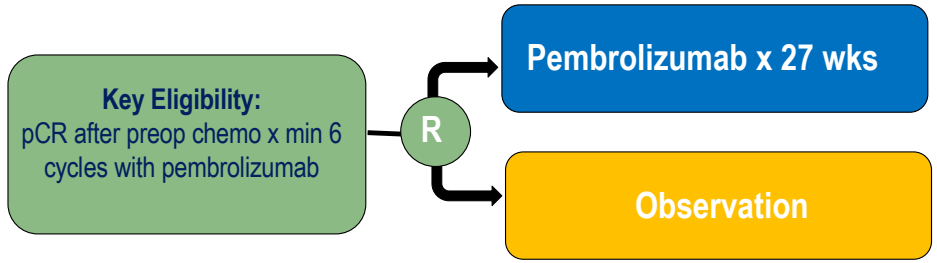
Sharma et al. ASCO 2022. Abstract 513; Spring et al. ASCO 2022. Abstract 512.

TNBC: Immunotherapy for Early-Stage Disease Questions

- Optimal duration of CPI if pCR achieved?
- Balancing risk
  - Can we identify a group of patients who will do well with chemotherapy alone?
- Optimal post-neoadjuvant therapy
    - Should we combine or sequence pembrolizumab with other post-neoadjuvant therapies?
- Optimal chemotherapy backbone
  - Role of platinum salts established
  - Alternate chemotherapy regimens?

OptimICE-pCR

PI: Tolaney
Alliance Trial



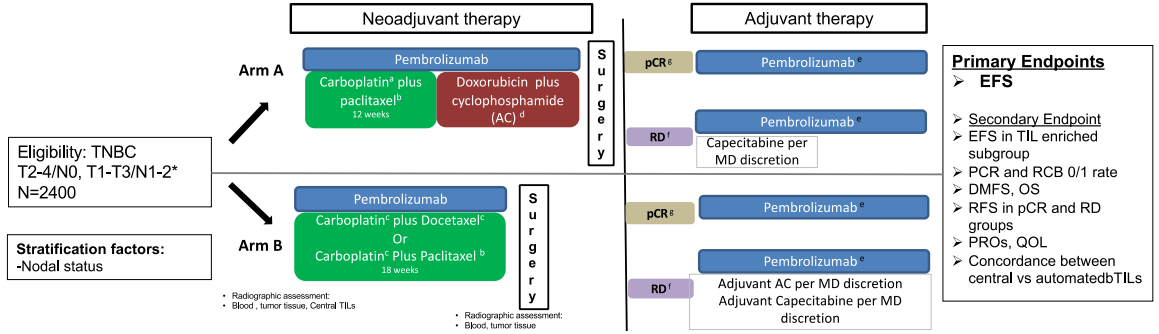
Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

Next Steps in the Neoadjuvant Setting

Non-anthracycline regimen

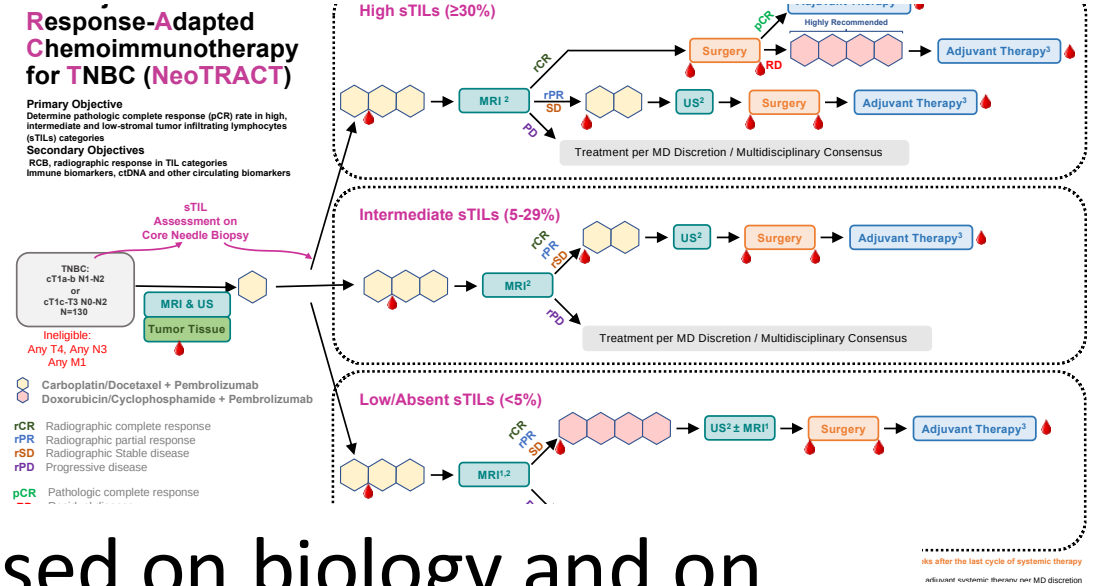
Randomized non-inferiority trial

Hypothesis: In patients with early stage TNBC, carboplatin-taxane chemoimmunotherapy is non-inferior to taxane-platinum-anthracycline-based chemoimmunotherapy

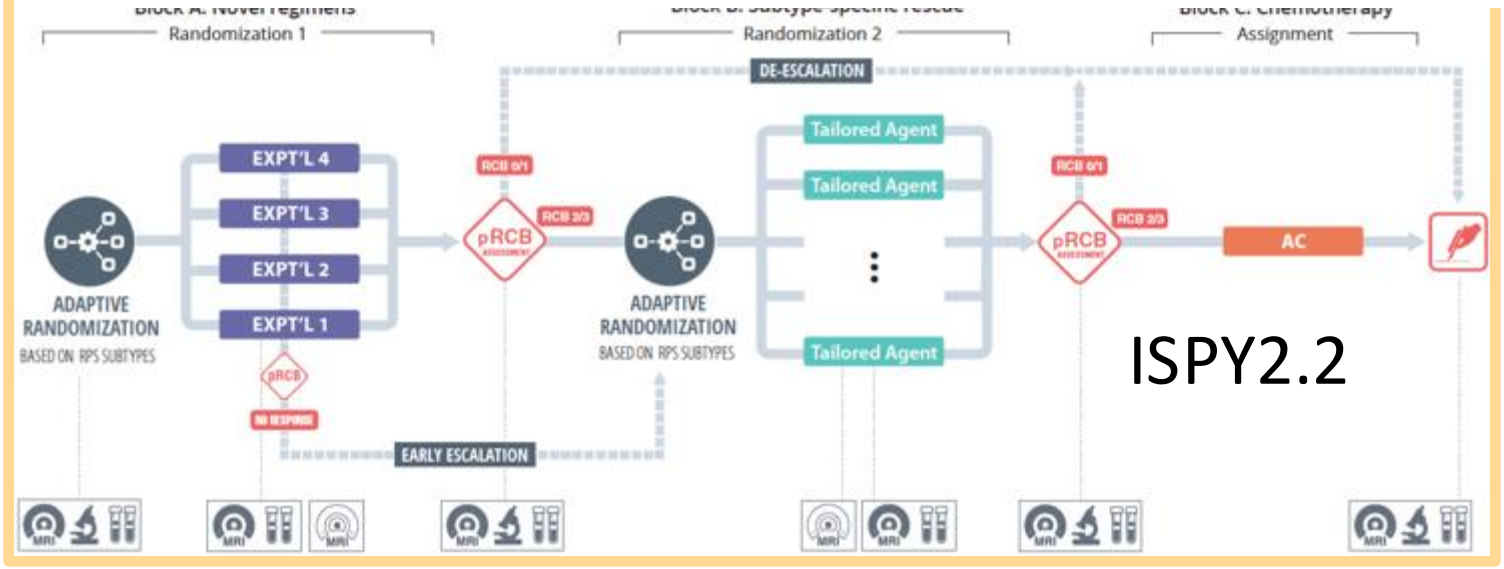


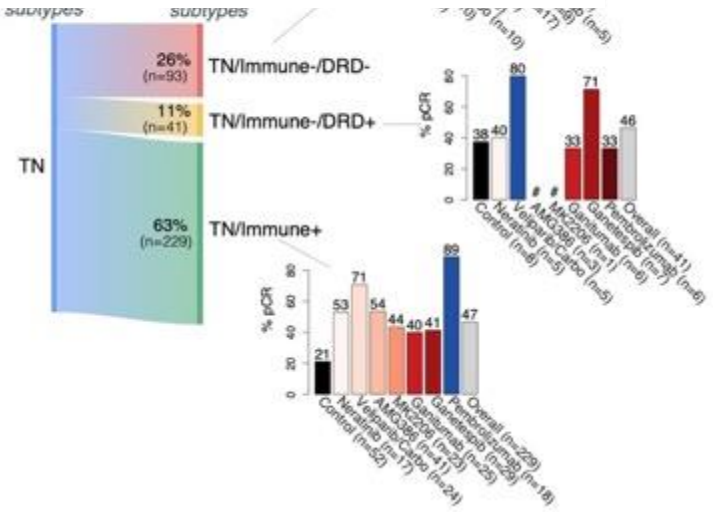
*T4/N+ , a
[a]Carboplat
[b] Paclitaxe
[c] Carbopla
[d] AC every
[e] Total dur
[f] Co-enroll
[g] No Furth

Stratify treatment based on TILS



ISPY2.2: Individualize therapy based on biology and on response in the neoadjuvant setting; test new agents first

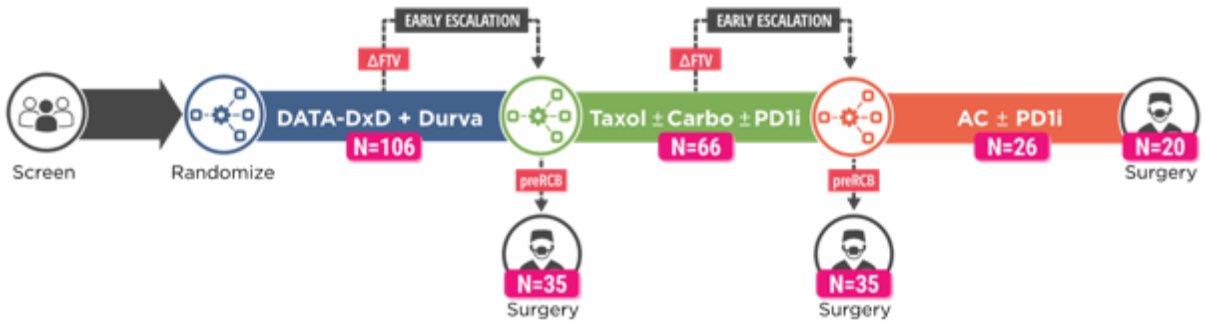




Yee D et al. 2022 ASCO Abstract 591; Wolf, Yao et al, CCR 2022.

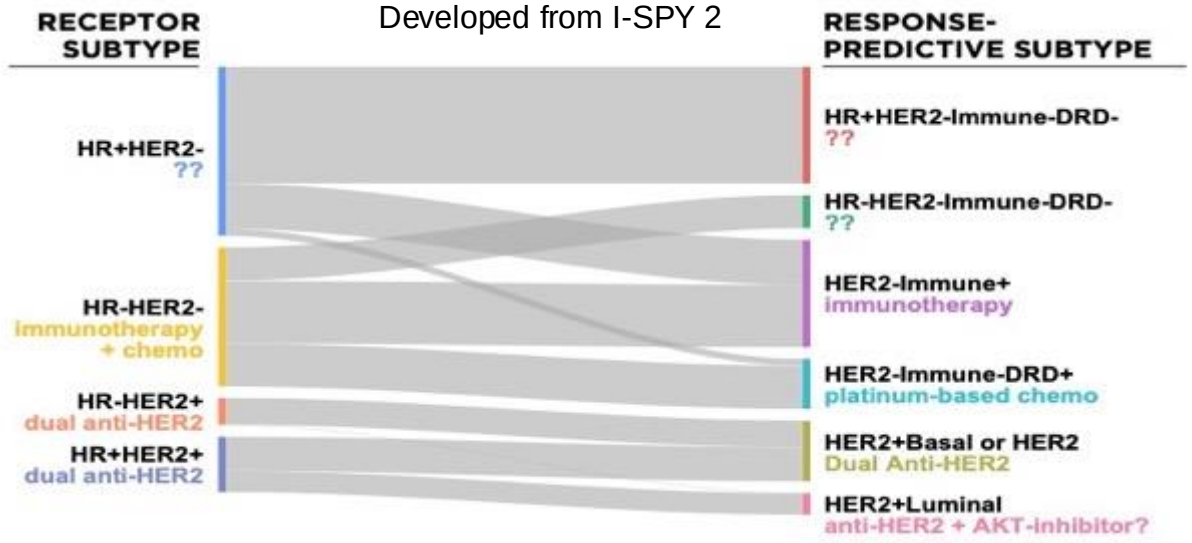
Can We Optimize Neoadjuvant Systemic Treatment?

Dato-DXd + Durva Schema



Primary Endpoint: pCR

Block B: Based on RPS (Response Predictive Subtypes)

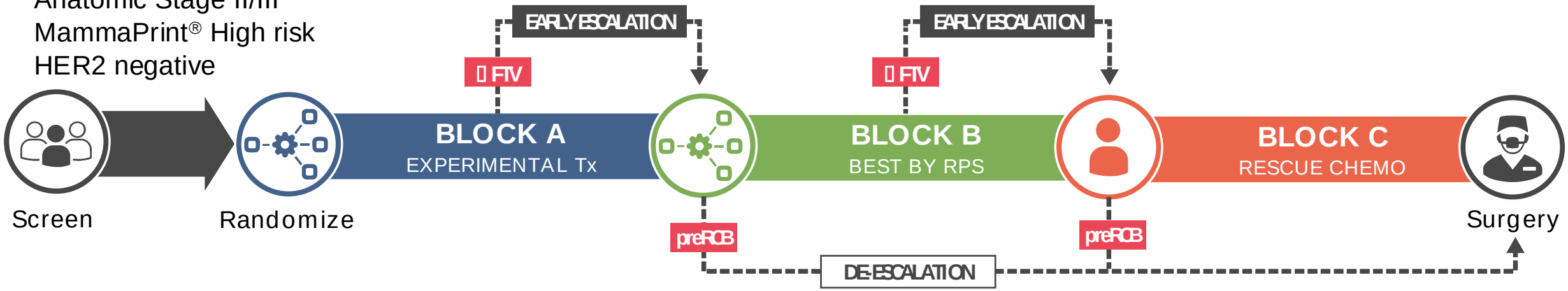


- RPS developed from ~990 I-SPY2 patients across 9 arms
- Reflects predicted sensitivity to immune, DNA damage repair deficiency, HER2-targeting agents
- Used to inform I-SPY 2.2 Block B agent drug assignments/ randomization
- In Dato+Durva arm (HER2-)
  - 38% of HR+ are immune+
  - 49% of HR- are immune+

Shatsky et al, ASCO 2024; Adapted from Cortes, ASCO 2024

I-SPY 2.2 Design Features: Multiple Sequential Regimens

Eligibility for Dato+Durva arm:
Anatomic Stage II/III
MammaPrint® High risk
HER2 negative



Treatment Assignments/Randomization based on Response Predictive Subtype (RPS)

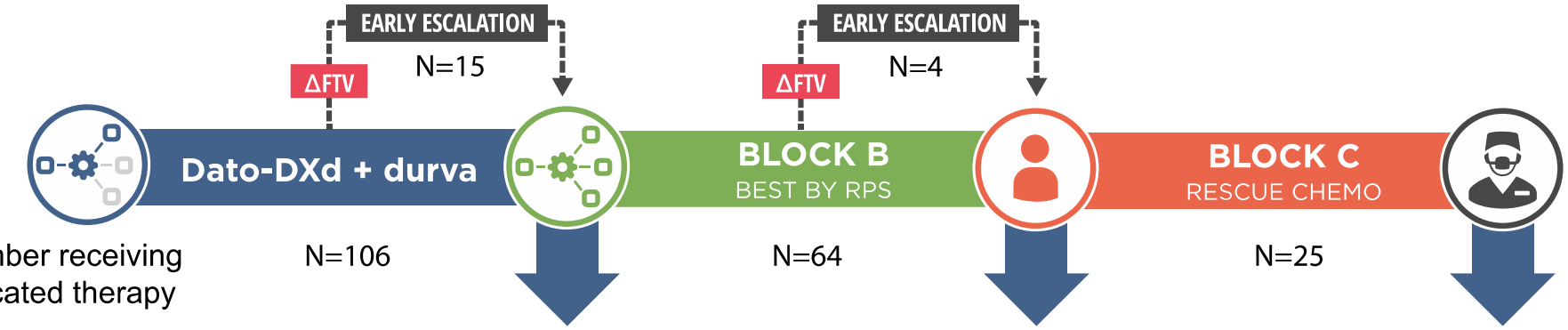
HR+ HER2- Immune- DRD-	Taxol	AC
HR- HER2- Immune- DRD-:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune+:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+:	Taxol + Carbo	AC + Pembro

Comparator arm: Dynamic control

Specific to each subtype identified from previously tested I-SPY2 agents between March 2010 and April 2022 (e.g. paclitaxel -> AC ; paclitaxel + pembrolizumab -> AC ; paclitaxel + veliparib + carboplatin -> AC)

Trivedi et al, ESMO 2024 and
Shatsky et al, Nat Med 2024

Timing of pCR in Immune+ and HR- subtypes



				Total
Num exiting block	42	39	25	**106**
Num pCR after block	25	22	6	**53**

	After Block A	After Block B	After Block C	Total
HER2-Immune+ (N=47)				
N achieving pCR	20	14	3	37
Cumulative % of total observed pCR	54%	92%	100%	
HR-HER2-* (N=64)				
N achieving pCR	21	15	3	39
Cumulative % of total observed pCR	54%	92%	100%	

BARCELONA 2024 ESMO congress

* Excludes 1 patient who did not receive pembrolizumab in Block B

ISPY2.2: Key Takeaways

The ISPY 2.2 Dato + Durva treatment strategy resulted in an overall pCR rate of 50%

- The highest pCR rate was seen in Immune+ (79%) followed by HR- (62%) subtypes
  - > 50% of pCRs achieved by Block A alone and >90% achieved by Block B
  - Many patients were able to avoid taxane and/or anthracycline treatment
- In HR-/Immune-/DRD-, the modeled pCR rate for the treatment strategy outperformed the dynamic control

TB04 Study Design: Ph3 Dato-DXd + Durva in Neoadjuvant/Adjuvant TNBC

TROPION-Breast04

Neoadjuvant | Surgery | Adjuvant

Key Eligibility Criteria

- Histologically confirmed Stage II or III unilateral or bilateral primary invasive breast cancer.
- TNBC (ER and PR < 1%) or hormone receptor-low breast cancer (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%), and HER2-negative.
- No evidence of distant disease.
- No prior surgery, radiation, or systemic anticancer therapy.
- ECOG PS 0 or 1.
- Adequate hematologic and organ function.

1:1

Experimental Arm

Dato-DXd + durvalumab
Q3W x 8 (24 weeks)

→ Durvalumab
x 9 cycles
+/- chemotherapy
a, b, c

Control Arm

Pembrolizumab + carboplatin + paclitaxel
Q3W x 4 (12 weeks)

→ Pembrolizumab + doxorubicin or epirubicin + cyclophosphamide
Q3W x 4 (12 weeks)

→ Pembrolizumab
x 9 cycles
+/- chemotherapy
a, c, d

Dual primary endpoints:
pCR and EFS

Secondary endpoints:
OS, DDFS, safety and tolerability, PROs, PK, immunogenicity

Exploratory endpoints include but are not limited to:
TROP2, PD-L1

Stratification factors:

- Lymph node status (positive versus negative)
- Tumour stage (cT1 to cT2 versus cT3 to cT4
- Hormone receptor status (hormone receptor-negative [ER and PR < 1%] versus hormone receptor-low (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%])
- Geographic region (US/Canada/Europe/Australia versus Rest of World).

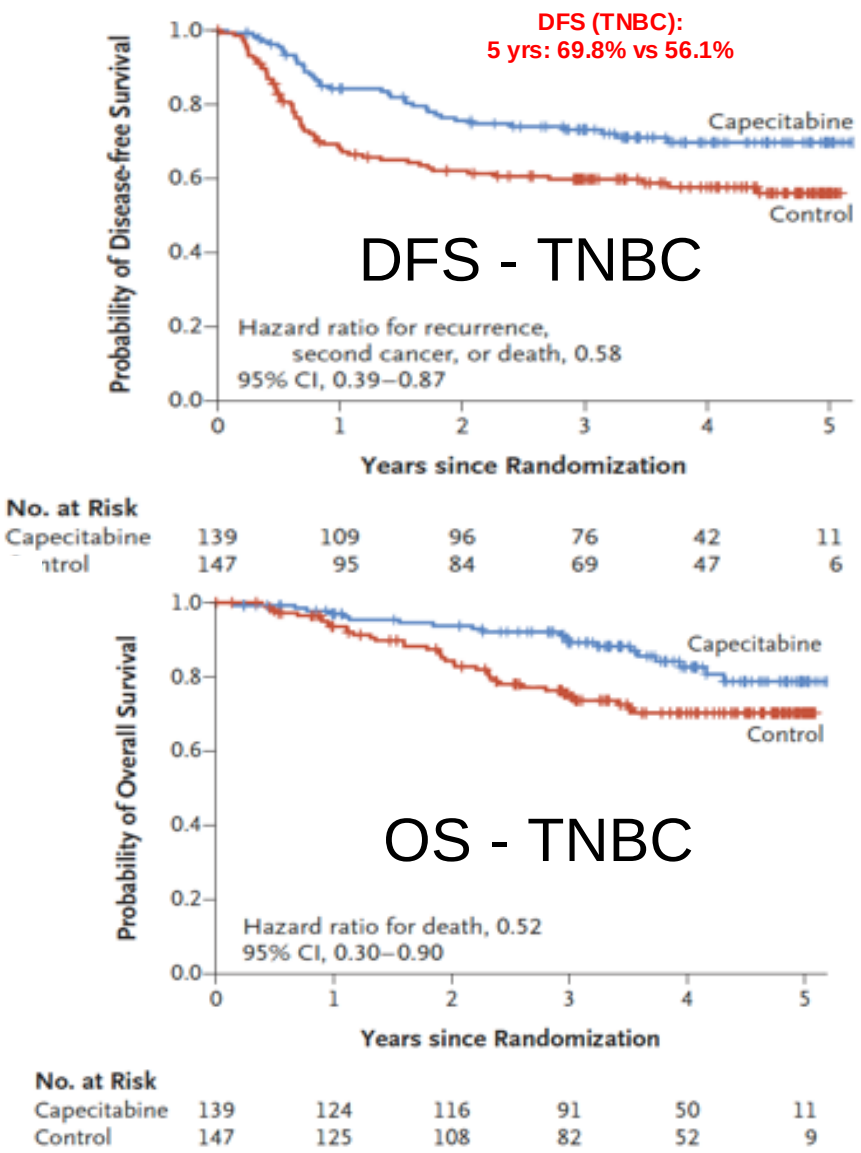
a. Endocrine therapy is permitted for participants with hormone receptor-low tumours. No adjuvant CDK4/6 inhibitor (eg, abemaciclib, ribociclib).
b. Adjuvant chemotherapy may be given in combination with durvalumab for participants with residual disease. Chemotherapy options at discretion of investigator, either: doxorubicin/epirubicin + cyclophosphamide, followed by paclitaxel + carboplatin; doxorubicin/epirubicin + cyclophosphamide followed by paclitaxel; carboplatin + paclitaxel; capecitabine.
c. Olaparib may be administered to participants who are g*BRCA*-positive with residual disease.
d. Adjuvant capecitabine may be given in combination with pembrolizumab for participants with residual disease, at the discretion of investigator.

PI: Heather McArthur
NCT06112379

Post-Neoadjuvant Therapy

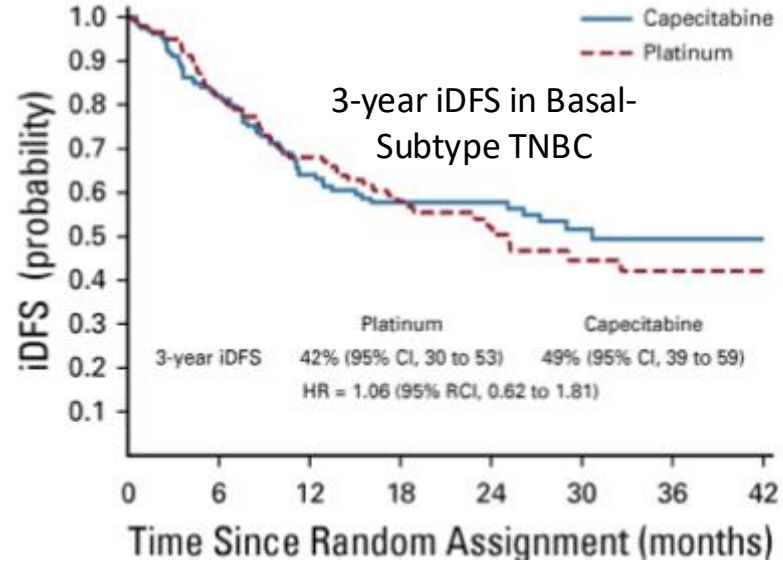
Post-Neoadjuvant Capecitabine

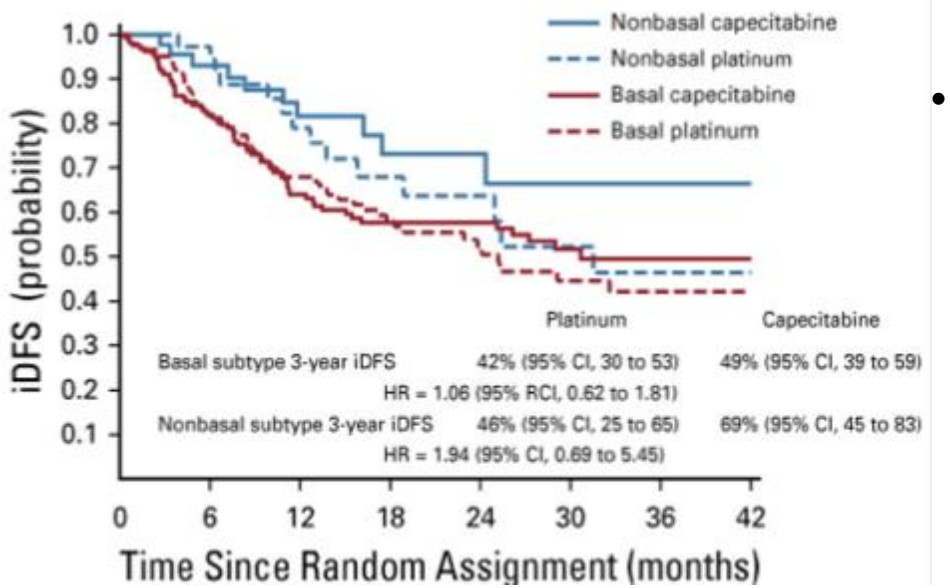
CREATE-X



Masuda N et al. N Engl J Med.2017.

ECOG 1131





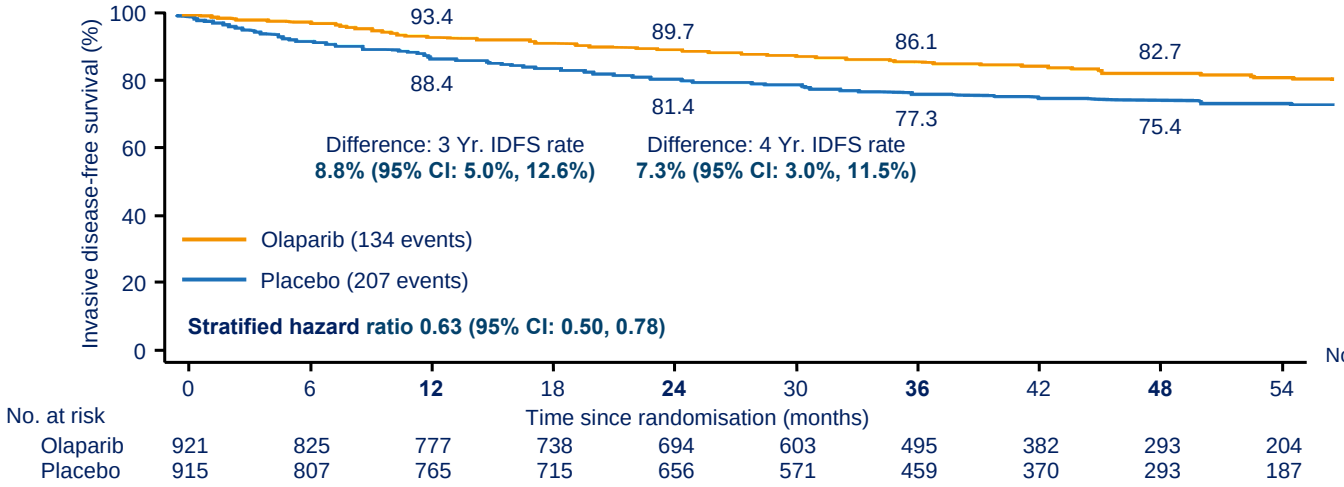
- ~80% of patients with residual TNBC after NAC have basal-subtype by PAM50 analysis
- Platinum agents were associated with more severe hematological toxicities
- Irrespective of treatment arm, a much higher than expected event rate was observed in this high-risk population

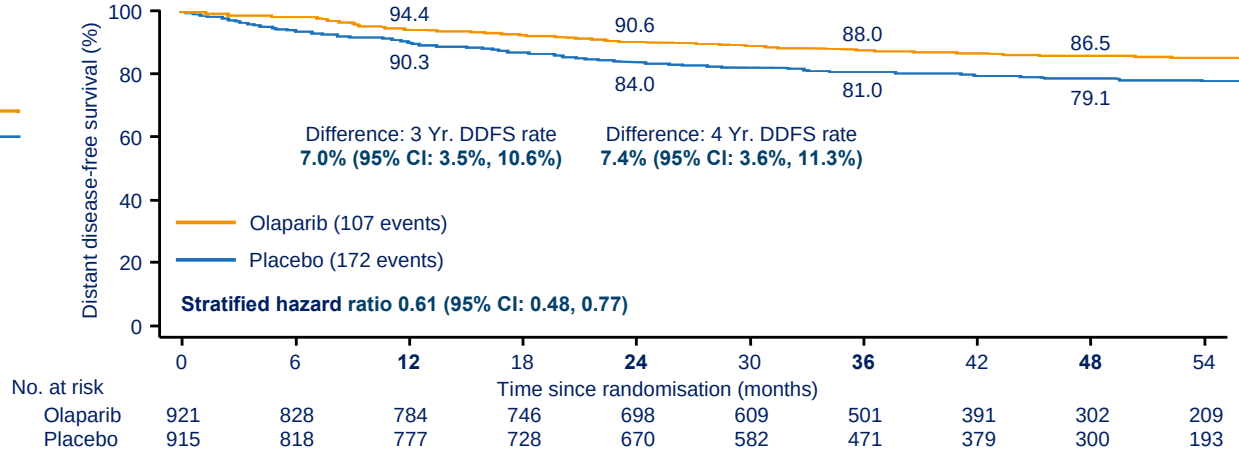
Mayer et al. J Clin Oncol. 2021

Olympia:
Median FU 3.5 years, 2nd IA

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

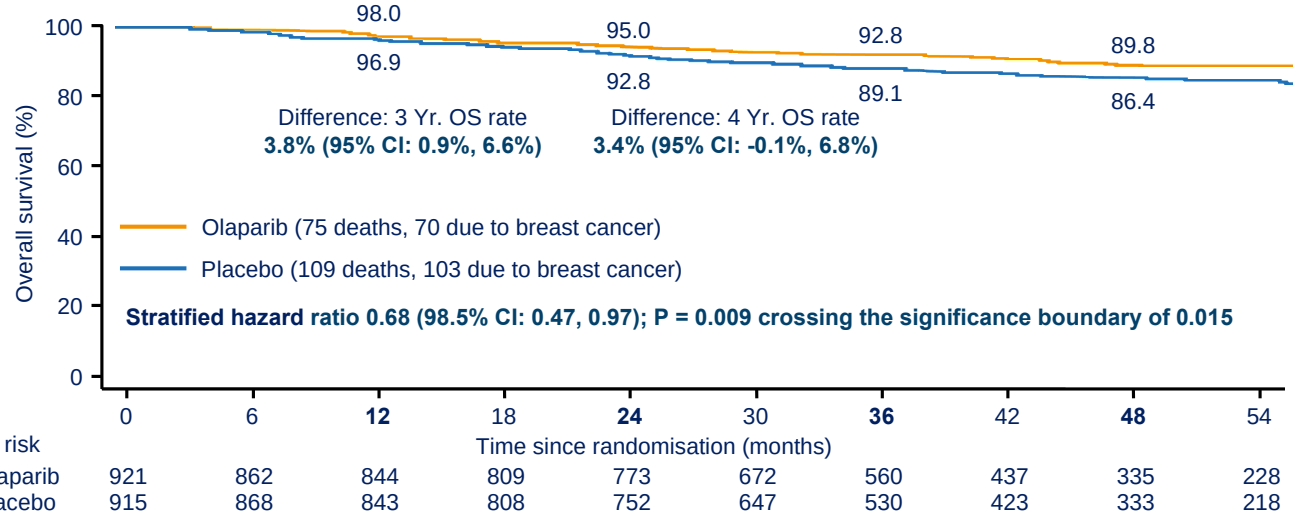
Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes





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

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



Tutt et al. N Engl J Med. 2021;384(25):2394-2405;
Tutt et al. ESMO Plenary 2022; Geyer et al, Ann Oncol 2022

10 Year FU from the Olympia Trial

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (ER and/or PgR positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *ER and/or PgR positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *ER and/or PgR positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles Adjuvant Chemotherapy** → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

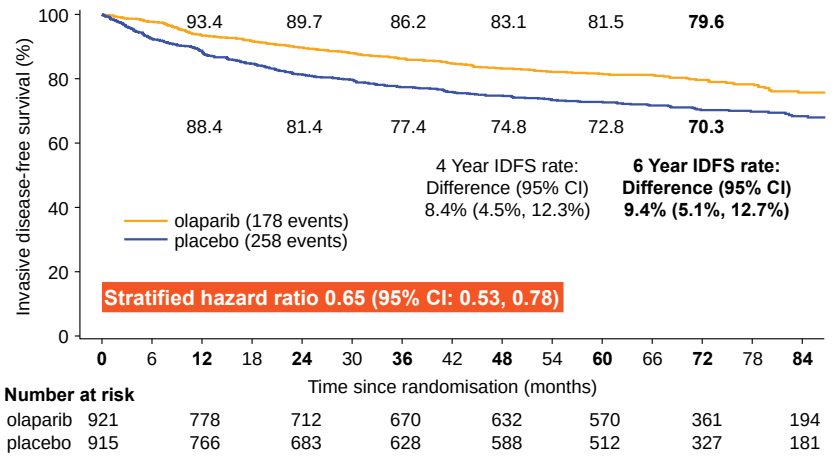
Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- ER and/or PgR positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherap

10

IDFS



Judy E. Garber, MD, MPH

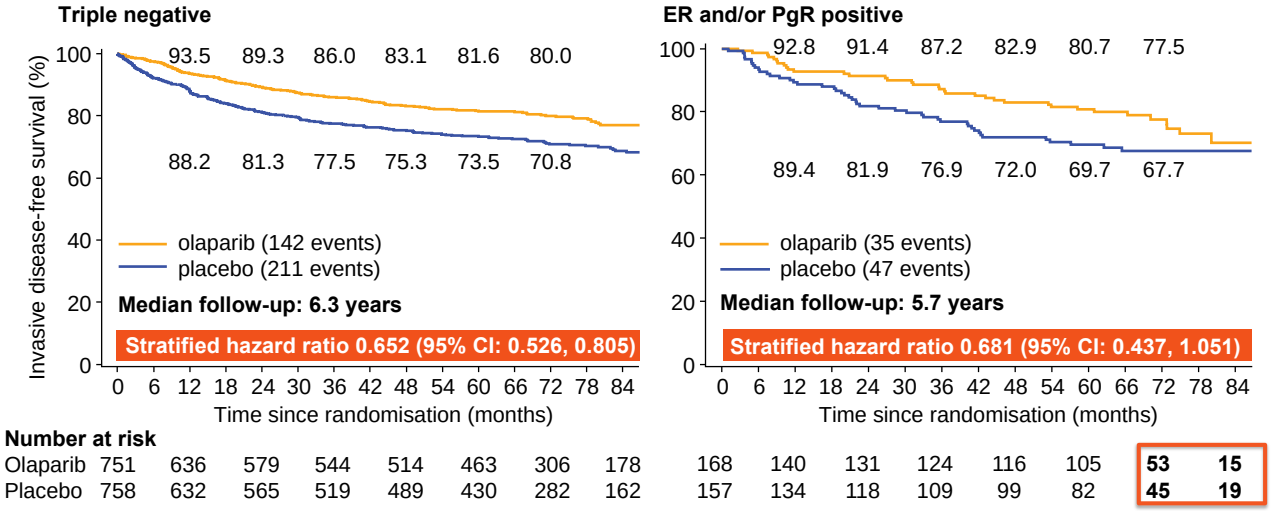
Demographics

Median age: 42.5
BRCA1: 72%
BRCA2: 27%

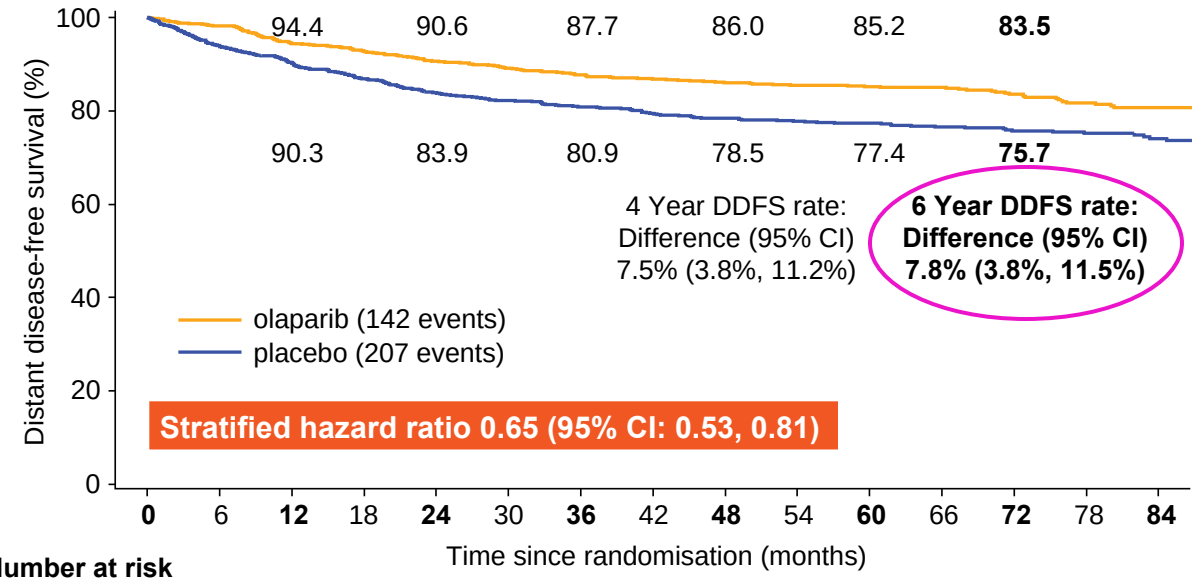
Premenopausal: 61%
TNBC: 82%
Neoadjuvant Rx: 50% (26% with platinum

New primary ovarian/fallopian tube CA: 5 vs 14
New CL invasive breast cancer: 34 vs 42

Garber et al, SABCS 2024



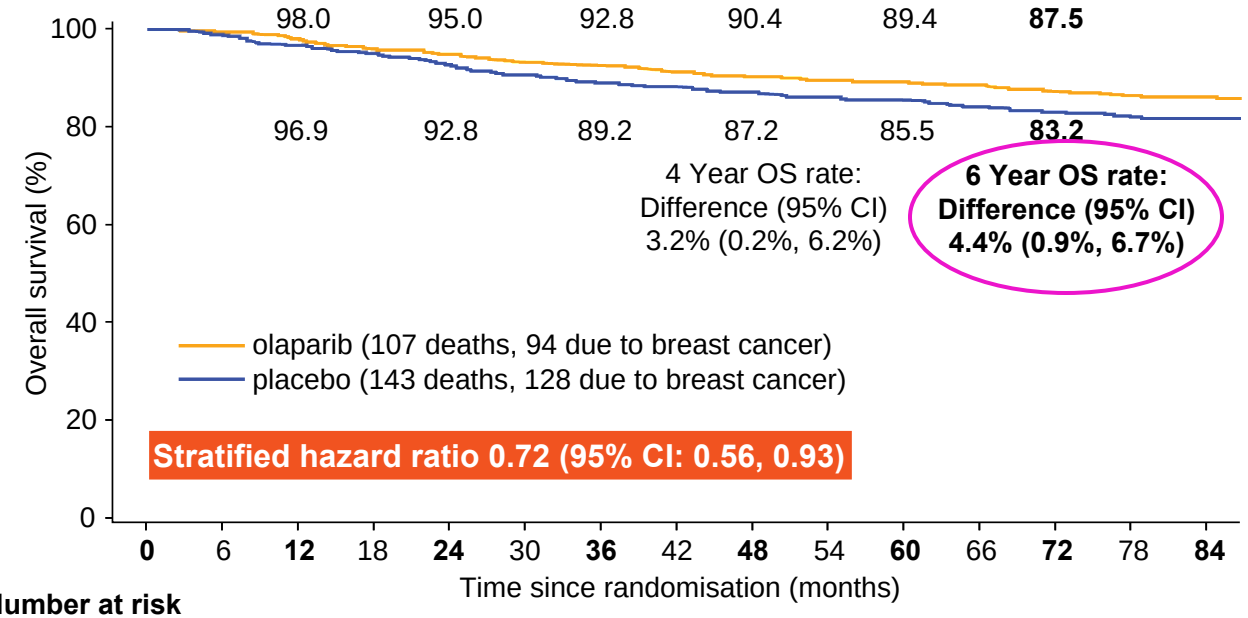
DDFS (ITT)



Number at risk

olaparib	921	785	718	679	649	588	373	200
placebo	915	778	698	649	604	534	340	189

OS (ITT)

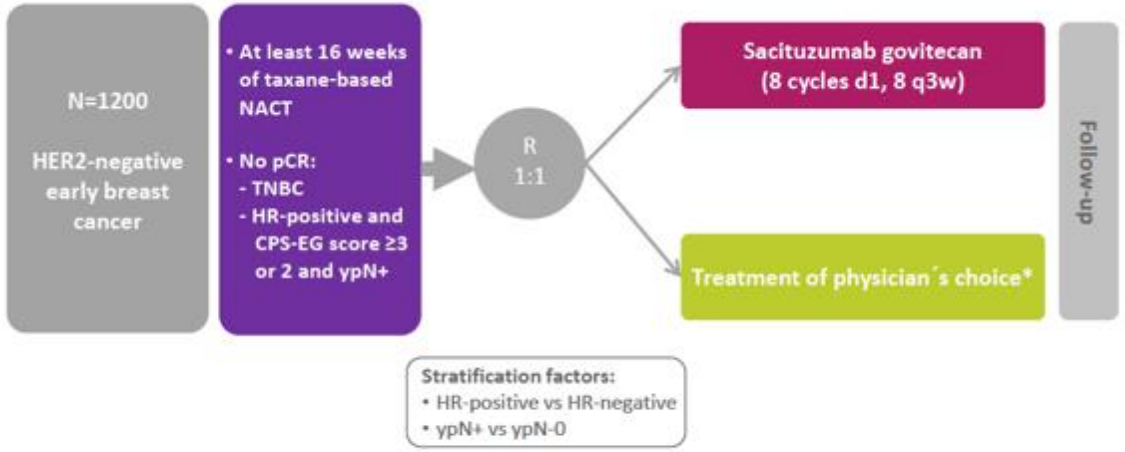


Number at risk

olaparib	921	846	795	765	728	660	420	224
placebo	915	843	788	739	698	616	390	221

GBG: SASCIA Post-Neoadjuvant Trial

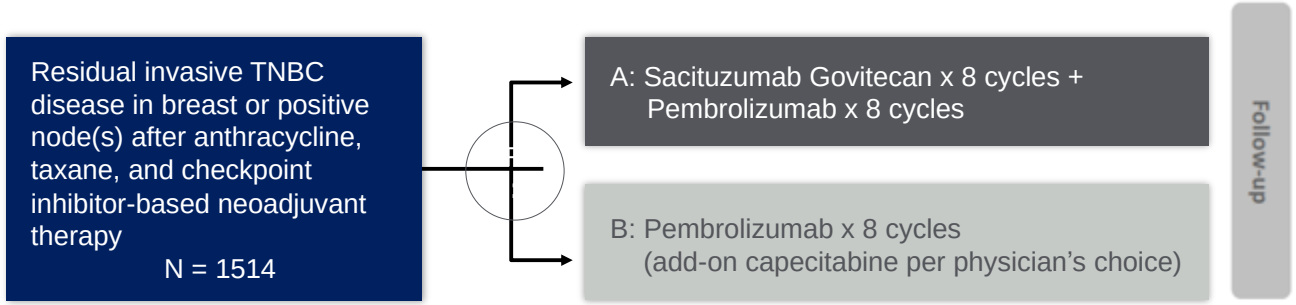
NCT04595565



*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation.
Background therapy: in patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

Phase III Optimice-RD/ASCENT-05

NCT05633654

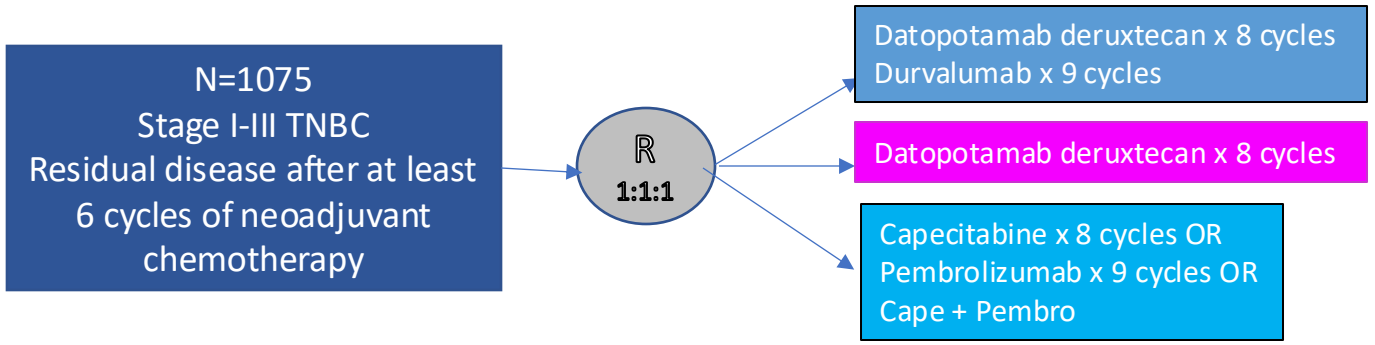


PI: Sara Tolaney
Alliance Foundation Trial

Challenge combining ER+ and TNBC pts

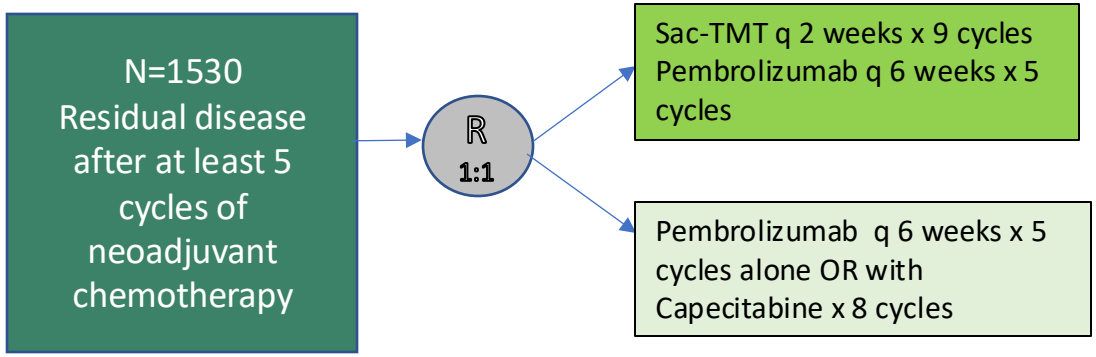
Phase III TROPION Breast03

NCT05629585

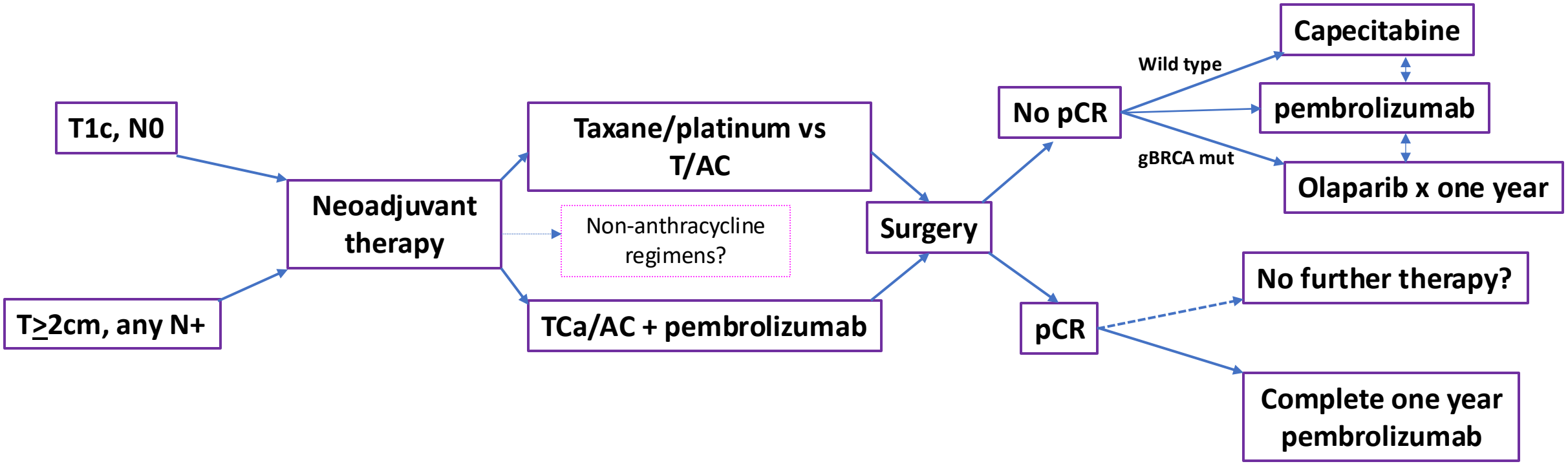


TROFUSE 012: Phase III Sac-TMT

NCT06393374



Todays Roadmap for Early TNBC



AC: anthracycline/cyclophosphamide; Ca: carboplatin

gBRCA mutation: neoadjuvant PARP inhibitors?

TNBC: Early-Stage Disease

- Significant progress!
- Neoadjuvant therapy preferred for all but the smallest tumors
  - pCR (no invasive disease in breast or node) associated with a markedly improved outcome
  - Allows individualization of therapy to response
- Immunotherapy approved for early-stage high risk TNBC
  - Understanding who needs immunotherapy and managing toxicity are critical issues
- Optimal post-neoadjuvant therapy
  - A work in progress
  - Escalation is clearly needed
- The next step: therapy directed to biologic subsets and tailoring therapy to response


Thank you!
UCSF Helen Diller Family Comprehensive Cancer Center