Neoadjuvant Immunotherapy for Triple Negative Breast Cancer

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A Cancer Center Designated by the National Cancer Institute

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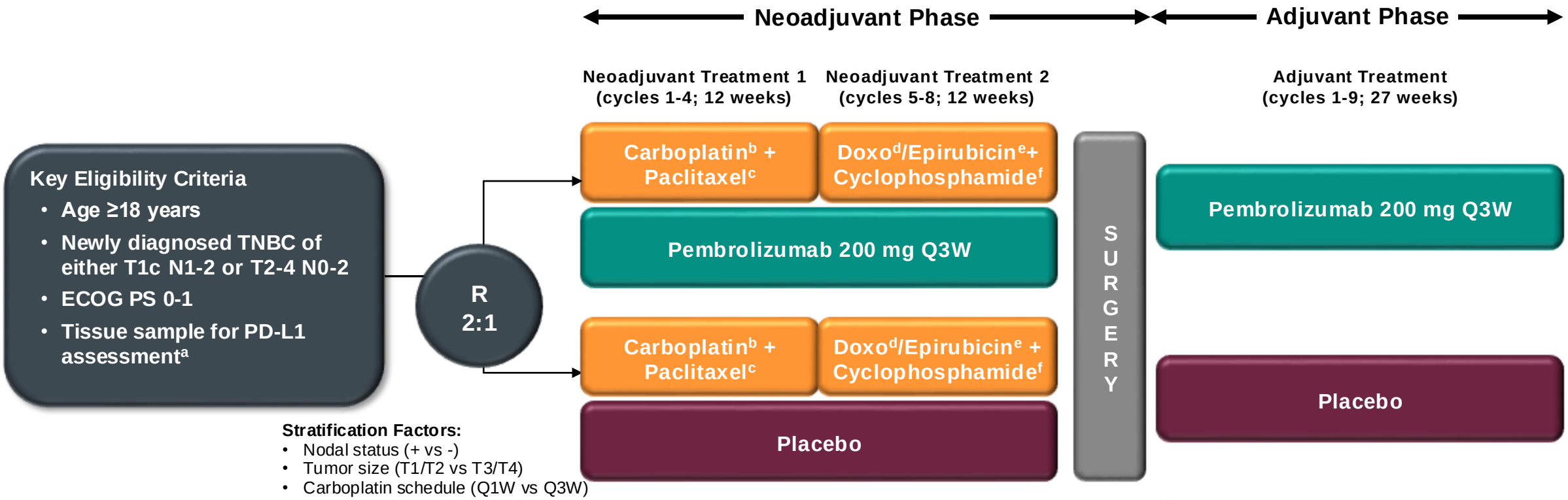
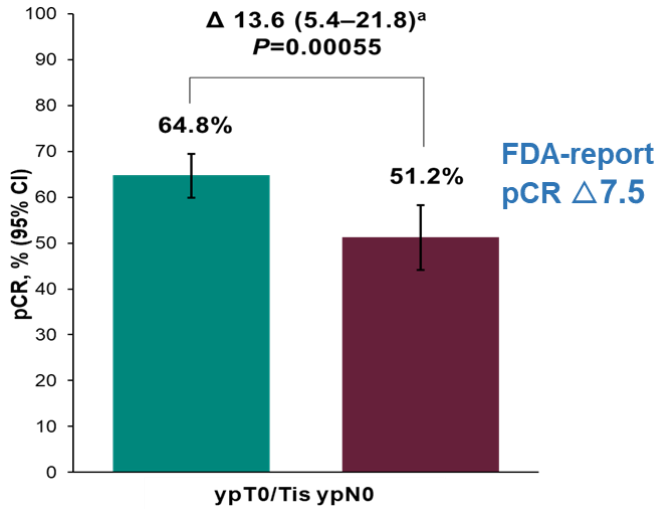
Neo-adjuvant immunotherapy in TNBC Overview and Key Take Aways

- Addition of immune check point inhibitor (Pembrolizumab) to anthracycline-taxane-platinum based NACT improves EFS/OS
  - Modest improvement in pCR leading to larger EFS/OS improvements
- Encouraging efficacy data with shorter duration taxane-platinum based chemoimmunotherapy (or ADC+IO)
  - In immune-enriched tumors these regimens leads to high (> 70%) pCR rates
- No clinically available individual patient selection biomarkers
  - Area of active translational research
- irAEs
  - Incidence in real world higher than noted in pivotal trial
  - Toxicity predictors not well understood
- Treatment optimization: Ongoing trials

KEYNOTE-522 Study Design (NCT03036488)



- Primary endpoints: pCR (ypT0/Tis ypN0) by local review, EFS by local review
- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE
- Exploratory endpoints: RCB, pCR by subgroups, EFS by pCR

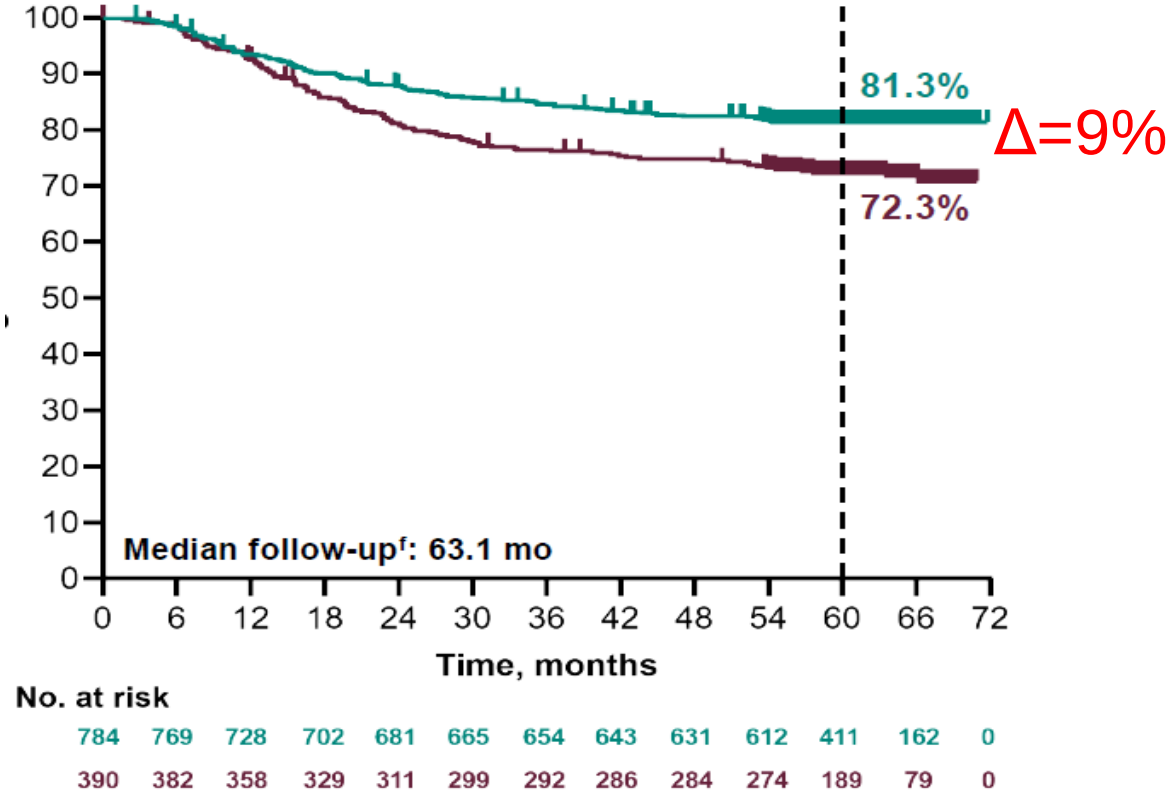


[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m^2 Q1W.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

KEYNOTE-522

EFS

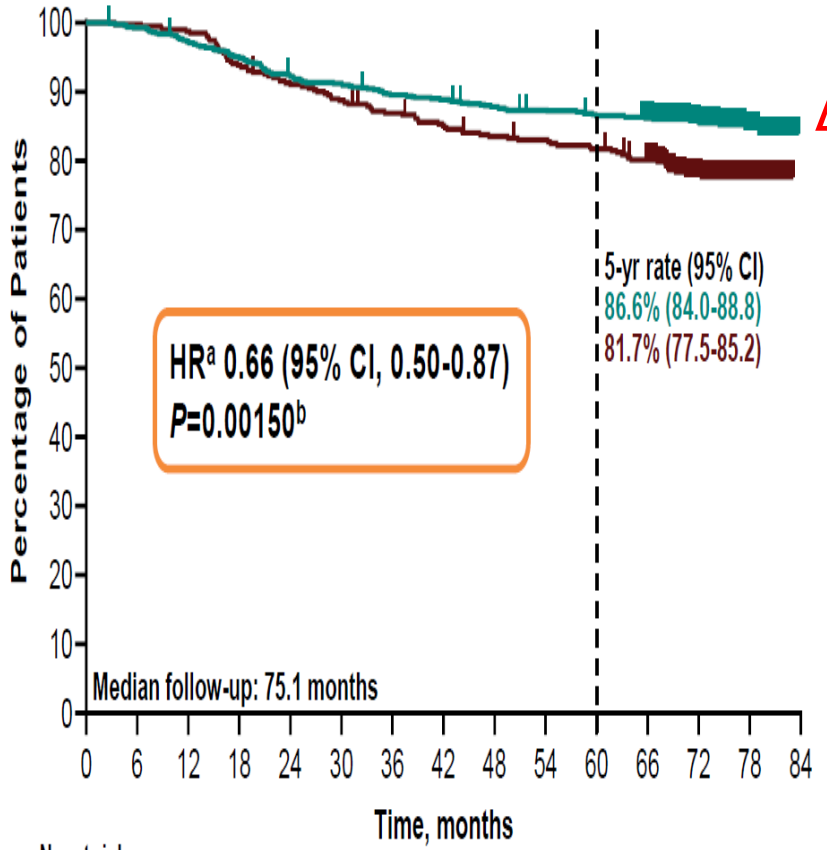
IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	



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

OS



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

No. at risk

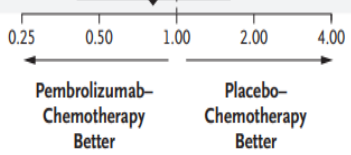
784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
390	389	385	366	354	345	336	328	321	318	313	300	199	82	0

Schmid P et al. *N Engl J Med*. 2020;382(9):810-821. Schmid P et al. *N Engl J Med*. 2022;386(6):556-567, Schmidt NEJM 2024 .

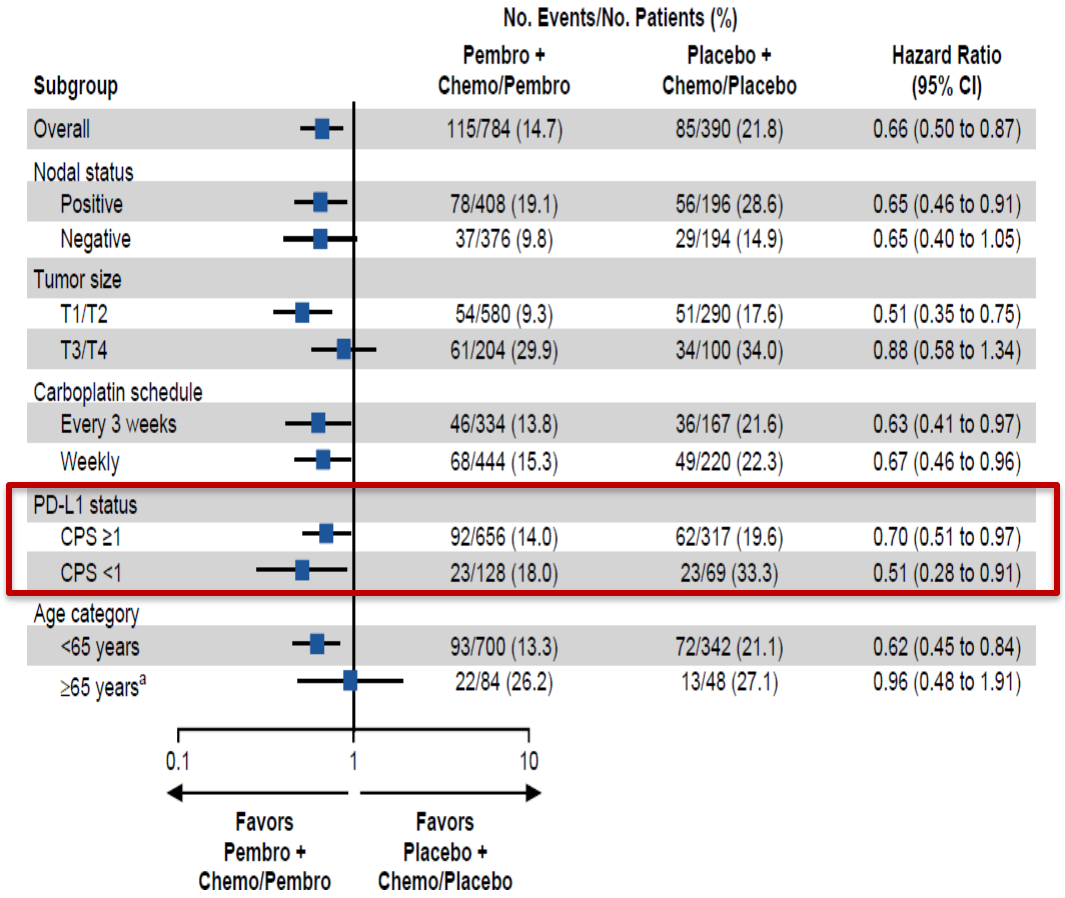
KEYNOTE-522

EFS

Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no. (%)		
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48–0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46–0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37–0.91)
Tumor size			
T1 to T2	64/581 (11.0)	59/290 (20.3)	0.51 (0.36–0.73)
T3 to T4	59/203 (29.1)	34/100 (34.0)	0.84 (0.55–1.28)
Carboplatin schedule			
Weekly	71/444 (16.0)	56/220 (25.5)	0.60 (0.42–0.86)
Every 3 wk	50/334 (15.0)	37/167 (22.2)	0.65 (0.42–0.99)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49–0.92)
Negative	25/128 (19.5)	25/69 (36)	0.48 (0.28–0.85)
Age			
<65 yr	103/700 (14.7)	79/342 (23.1)	0.61 (0.45–0.82)
≥65 yr	20/84 (24)	14/48 (29)	0.79 (0.40–1.56)
ECOG performance-status score			
0	101/678 (14.9)	80/341 (23.5)	0.60 (0.45–0.80)
1	22/106 (20.8)	13/49 (27)	0.81 (0.41–1.62)



OS



Higher event rate in PD-L1 negative, benefit of pembrolizumab noted regardless of PD-L1 status (83% PD-L1+)

Schmid P et al. *N Engl J Med*. 2020;382(9):810-821. Schmid P et al. *N Engl J Med*. 2022;386(6):556-567.

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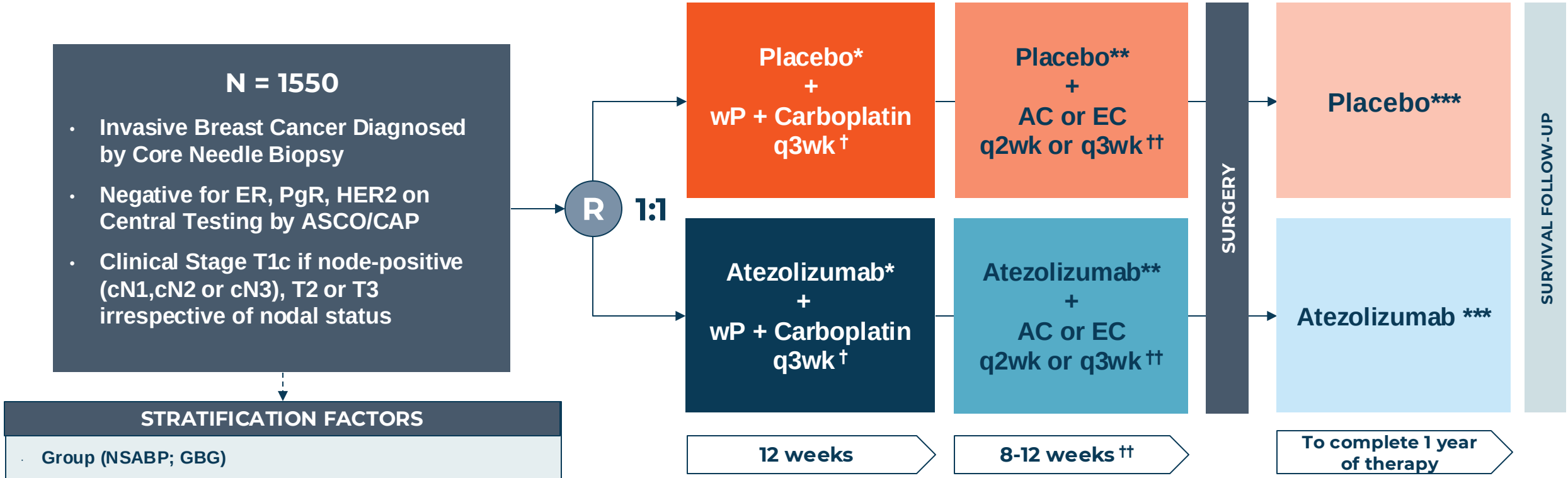
GeparDouze/NSABP B-59

Primary end point: EFS
Secondary end points: pCR, OS



STRATIFICATION FACTORS

- Group (NSABP; GBG)
- Clinical Size of Primary Tumor (1.1-3.0 cm; >3.0 cm)
- Clinical Nodal Status Documented by Imaging, FNA or Core Biopsy (negative; positive)
- PD-L1 status by VENTANA SP142 assay (positive ≥1% IC [proportion of tumor area occupied by PDL-1+ immune cells]; negative; indeterminate; not available#)
- AC/EC Schedule (q2wk; q3wk)

\# PD-L1 status was not available at randomization for 374 patients enrolled prior to amendments in July 2019.
* Atezolizumab (atezo) 1200 mg or placebo IV Day 1 every 3 wks for 4 doses.
† Paclitaxel 80 mg/m2 IV weekly x 12 doses (WP) + Carboplatin AUC of 5 IV Day 1 every 3 wks for 4 cycles.
** Atezo 1200 mg or placebo IV Day 1 every 3 wks for 3 to 4 doses depending on AC/EC schedule used.
†† Doxorubicin (A) 60 mg/m2 IV + cyclophosphamide (C) 600 mg/m2 IV Day 1 every 2 or 3 wks for 4 cycles. OR Epirubicin (E) 90 mg/m2 IV + cyclophosphamide (C) 600 mg/m2 IV Day 1 every 2 or 3 wks for 4 cycles.
*** Atezo 1200 mg or placebo IV Day 1 every 3 wks after surgery until 1 yr after the first dose. Adjuvant capecitabine was allowed for non-pCR as of February 2020 and olaparib as of December 2021.

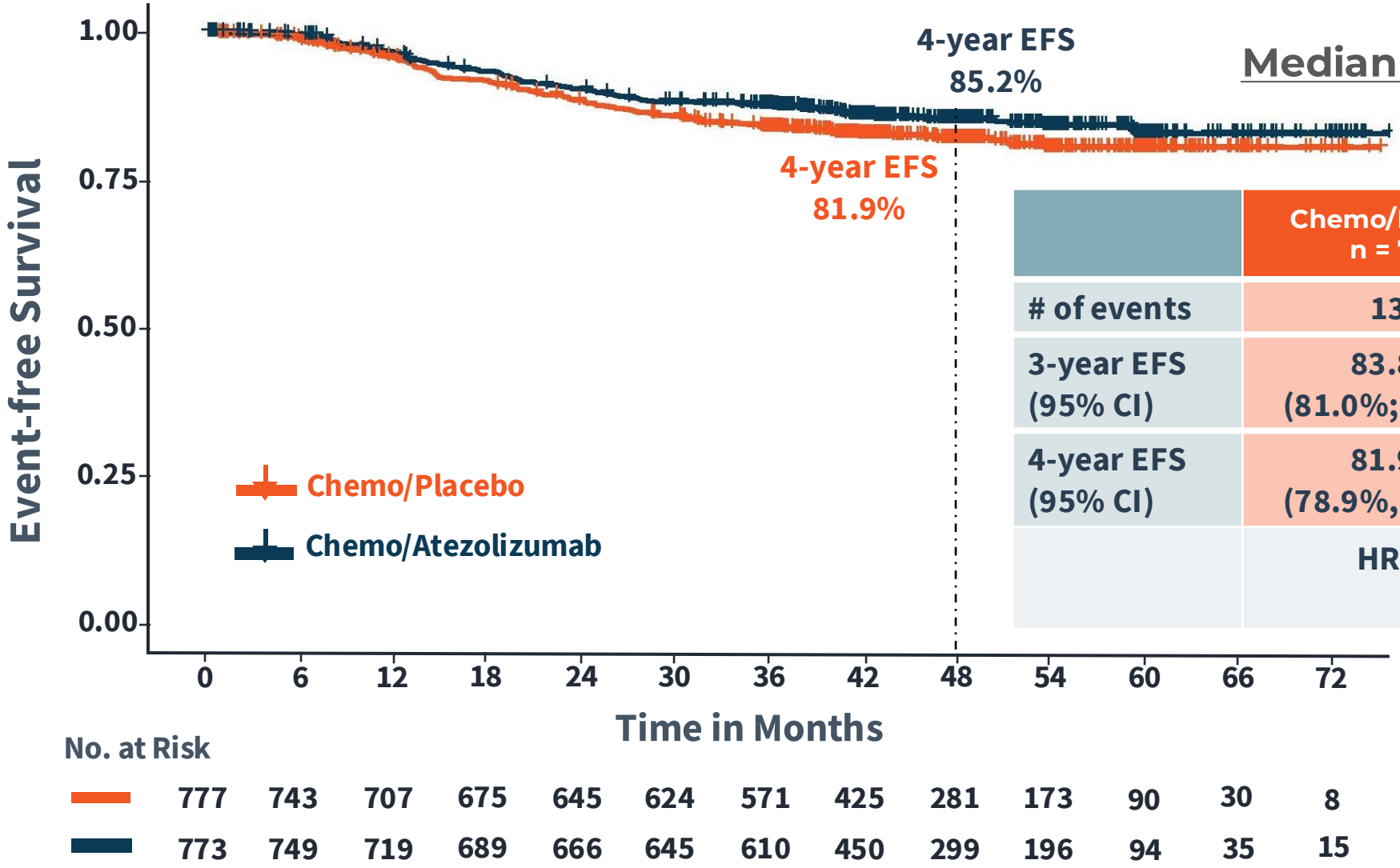
Geyer C et al, SABCS 2024

Patient Characteristics by Stratification Factors

Parameter	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773	Total N = 1550
Group			
GBG	490 (63.1%)	488 (63.1%)	978 (63.1%)
NSABP	287 (36.9%)	285 (36.9%)	572 (36.9%)
Nodal Status			
Negative	459 (59.1%)	452 (58.5%)	911 (58.8%)
Positive	318 (40.9%)	321 (41.5%)	639 (41.2%)
Clinical Size of the Primary Tumor			
1.1–3.0 cm	457 (58.8%)	453 (58.6%)	910 (58.7%)
>3 cm	320 (41.2%)	320 (41.4%)	640 (41.3%)
PDL1 Status			
Negative/Indeterminate/Not Available	496 (63.8%)	493 (63.8%)	989 (63.8%)
Positive	281 (36.2%)	280 (36.2%)	561 (36.2%)
AC/EC Schedule			
Every 2 weeks (q2w)	495 (63.7%)	489 (63.3%)	984 (63.5%)
Every 3 weeks (q3w)	282 (36.3%)	284 (36.7%)	566 (36.5%)
Stromal TILs Category on Baseline Specimen			
<30%	480 (61.8%)	480 (62.1%)	960 (61.9%)
≥30%	295 (38.0%)	288 (37.3%)	583 (37.6%)

Geyer C et al, SABCS 2024

GeparDouze: Event-free Survival



Median follow-up 46.9 months

	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	

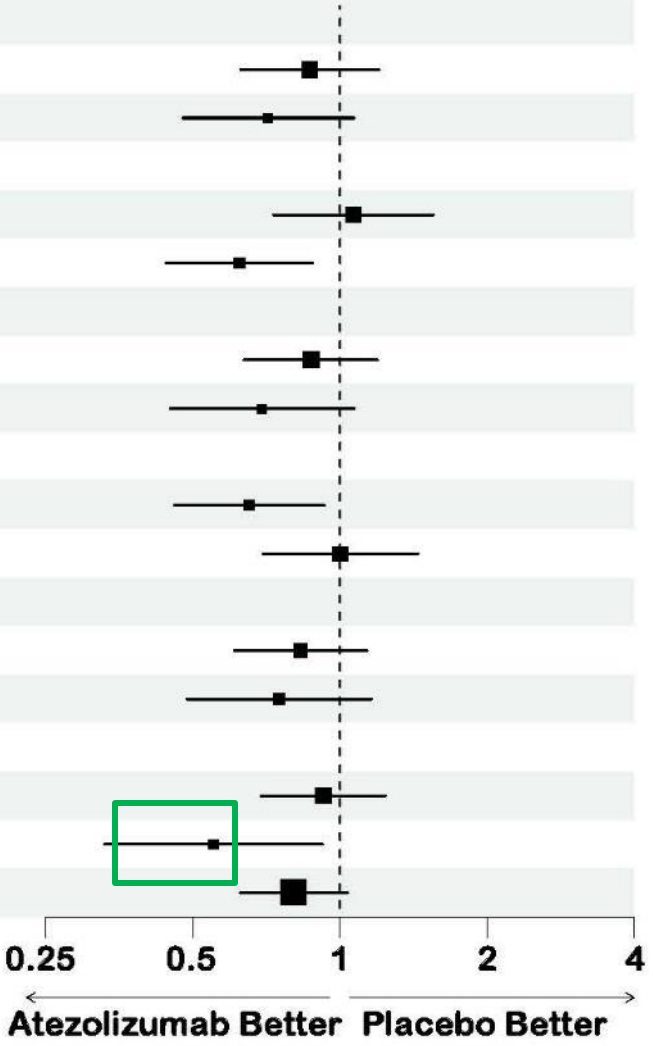
Numeric 3.3% difference in 4-year EFS

Geyer C et al, SABCS 2024

EFS Subgroup Analysis

Subgroup	N events/patients	HR (95% CI)	P	P for interaction
Group				0.457
GBG	146/978	0.868 (0.627, 1.202)	0.395	
NSABP	97/572	0.714 (0.478, 1.067)	0.100	
Clinical Nodal Status				0.039
Negative	109/901	1.066 (0.732, 1.552)	0.739	
Positive	134/649	0.623 (0.441, 0.879)	0.007	
AC/EC Schedule				0.401
Every 2 weeks	159/996	0.872 (0.638, 1.191)	0.389	
Every 3 weeks	84/554	0.694 (0.450, 1.069)	0.097	
Clinical Size of Primary Tumor				0.098
> 3.0 cm	128/647	0.653 (0.459, 0.929)	0.018	
1.1–3.0 cm	115/903	1.003 (0.696, 1.446)	0.986	
PD-L1 status				0.712
Negative/indeterminate/not available	160/853	0.831 (0.609, 1.135)	0.244	
Positive	83/697	0.752 (0.487, 1.160)	0.198	
TIL Category				0.086
<30%	180/960	0.925 (0.690, 1.239)	0.560	
>=30%	63/583	0.551 (0.330, 0.920)	0.023	
Overall	243/1550	0.805 (0.626, 1.037)	0.093	

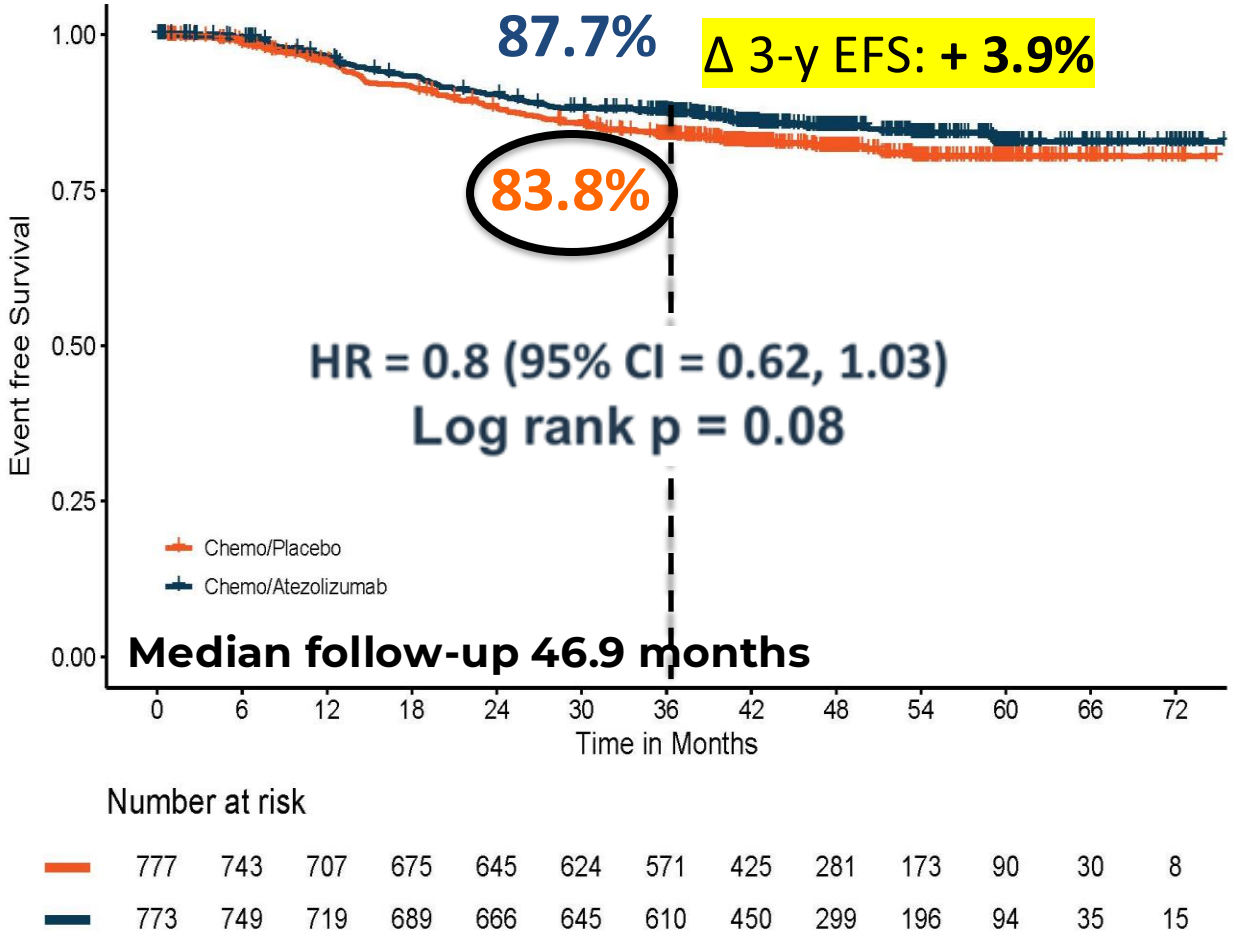
X-axis is under log scale.



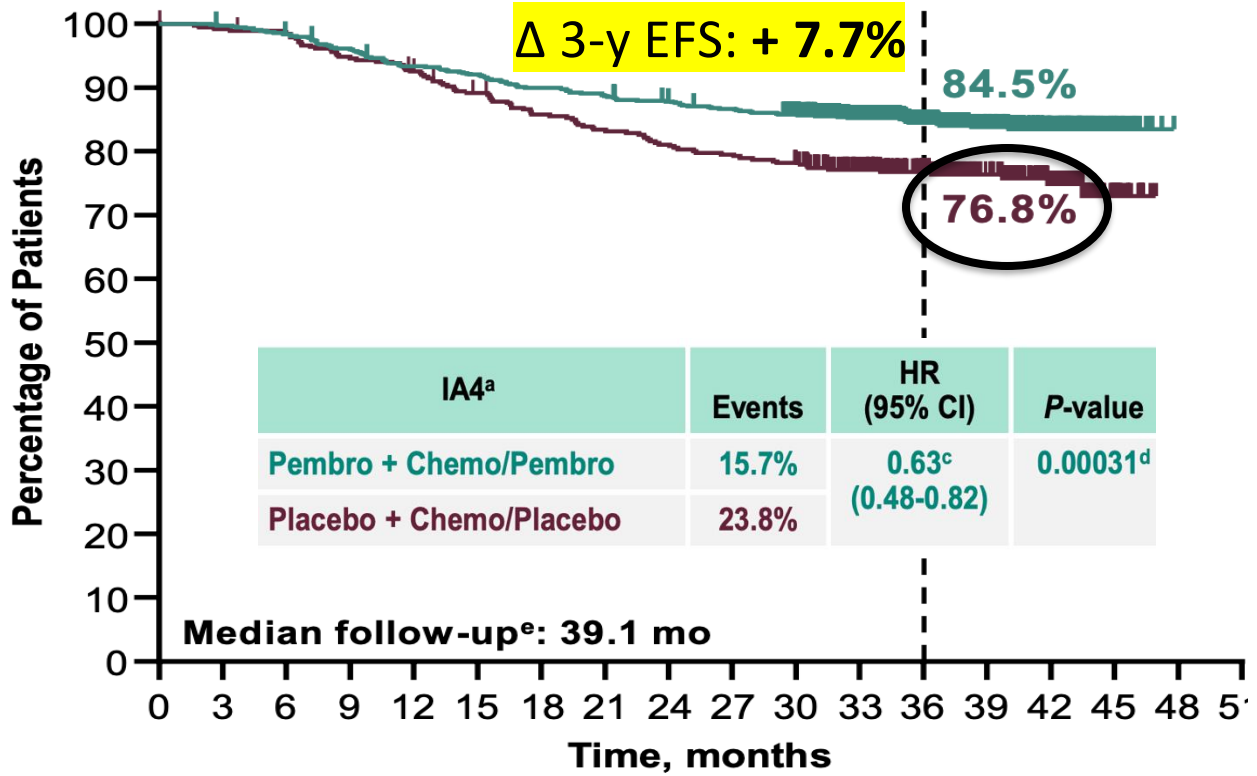
Geyer C et al, SABCS 2024

3-year Event-free Survival

NSABP B-59/GBG-96-GeparDouze



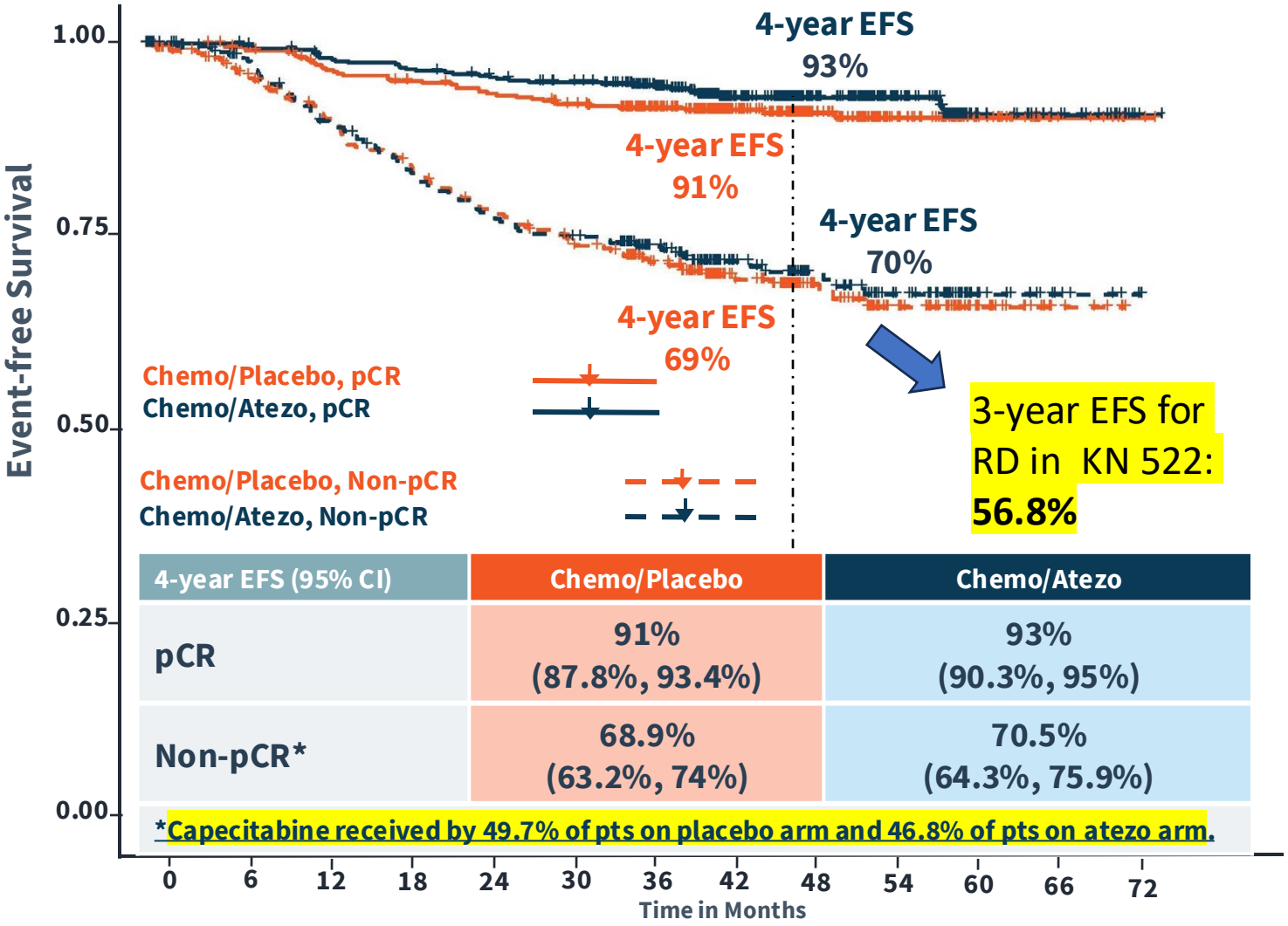
KEYNOTE-522



Geyer SABCS 2024; Schmid et al. NEJM 2020

Slide courtesy of Giampaolo Bianchini

GeparDouze pCR by Arm and EFS by pCR Status



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%)

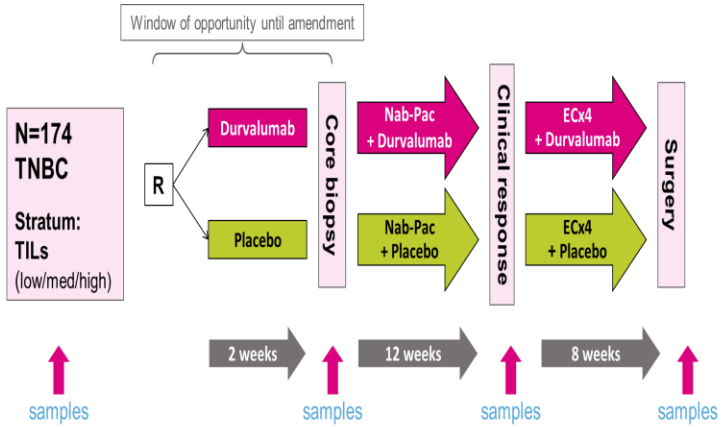
*Capecitabine received by 49.7% of pts on placebo arm and 46.8% of pts on atezo arm.

Geyer C et al, SABCS 2024

GeparDouze/B-59 vs KN522 results

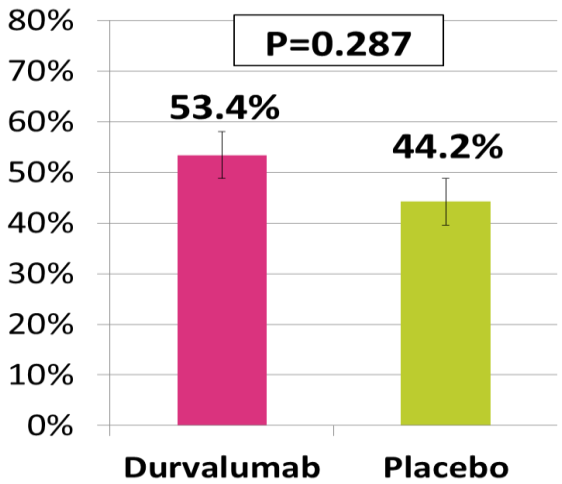
- GeparDouze/B-59 enrolled somewhat lower risk population compared to KN522
  - Suggestion of benefit in N+ subgroup in B-59
- Adjuvant capecitabine use
  - 50% of RD patients in B-59, not allowed in KN-522
- Chance
- PD-1 vs PDL-1 antibody
- Similar to findings in mTNBC
  - KN-355 vs IMpassion 130/131 (Atezolizumab plus taxane not statistically superior to taxane in PD-L1+ mTNBC)

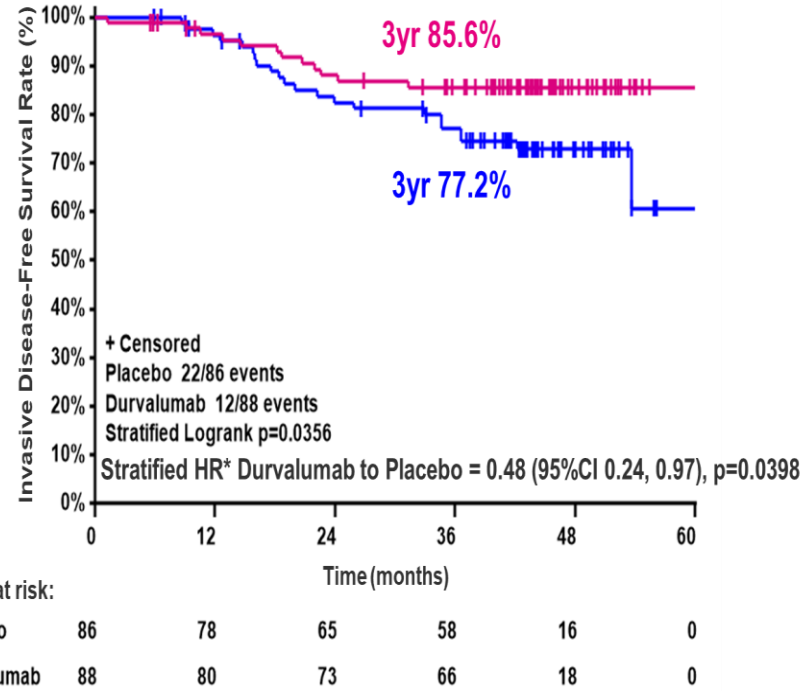
GeparNuevo: Addition of Durvalumab to Taxane/Anthracycline-containing Chemotherapy

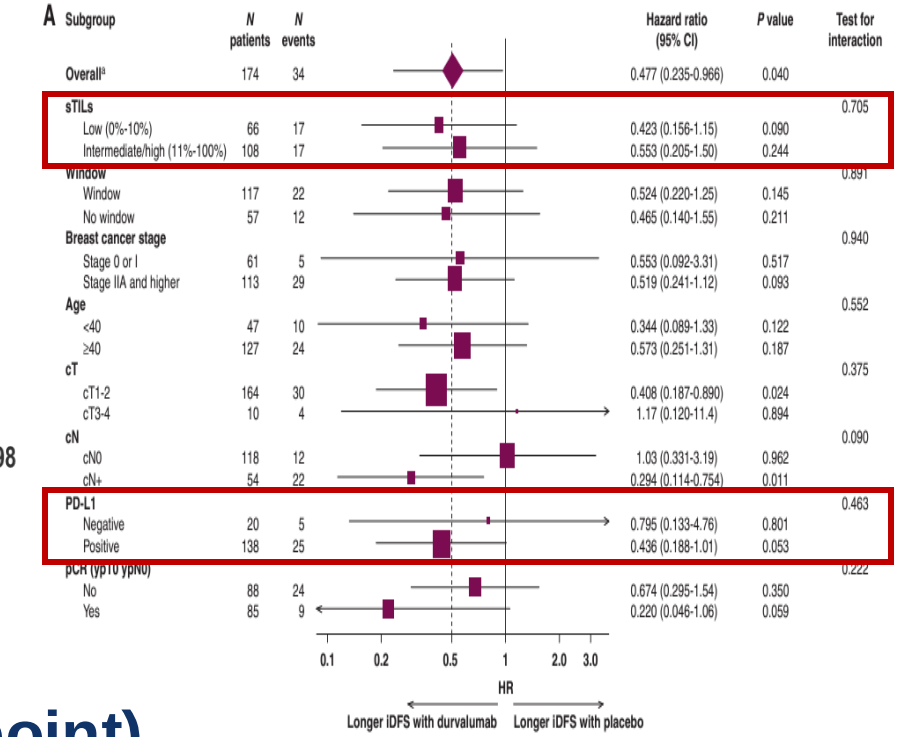


No adjuvant ICB

pCR: Primary endpoint







iDFS (secondary endpoint)

- More iDFS events in low-sTILs and PD-L1-negative groups
- Benefit of durva regardless of sTILs density and PD-L1 status

Loibl S et al. *Ann Oncol*. 2019;30(8):1279-1288. Loibl S et al. *Ann Oncol*. 2022;33(11):1149-1158.

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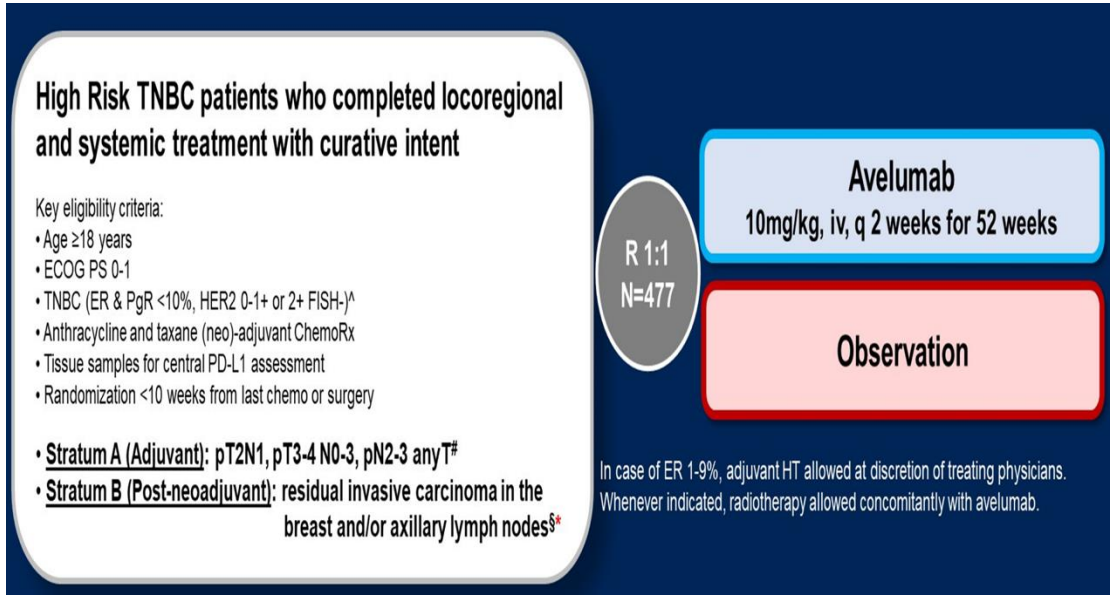
A-BRAVE Trial: Avelumab in Early-Stage TNBC With Residual Disease After NACT or High-Risk After Primary Surgery and Adjuvant Chemotherapy



N=477

Co-Primary end points

DFS in ITT and

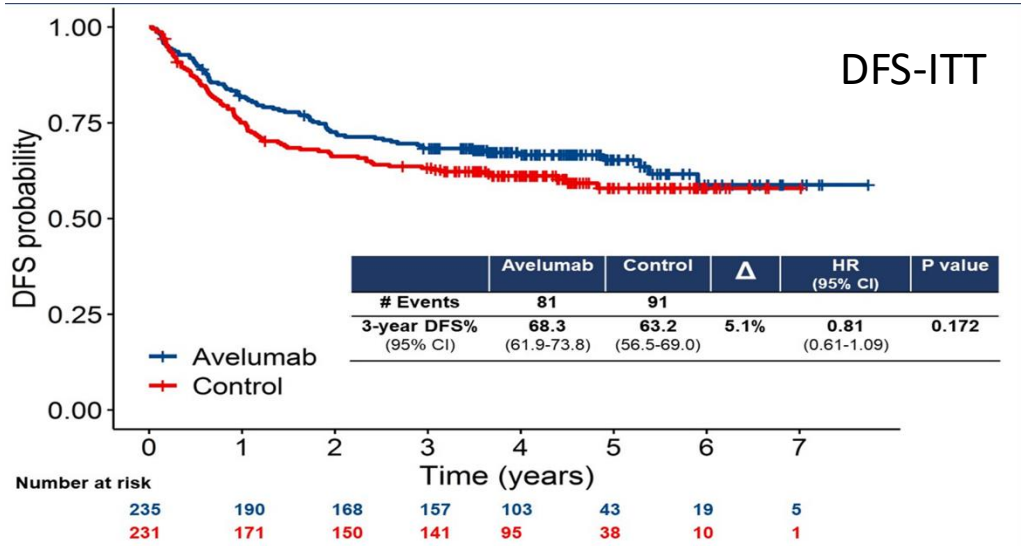
DFS in stratum B(post neoadjuvant)

S1418

Adjuvant pembrolizumab vs observation in patients with RD

Results awaited

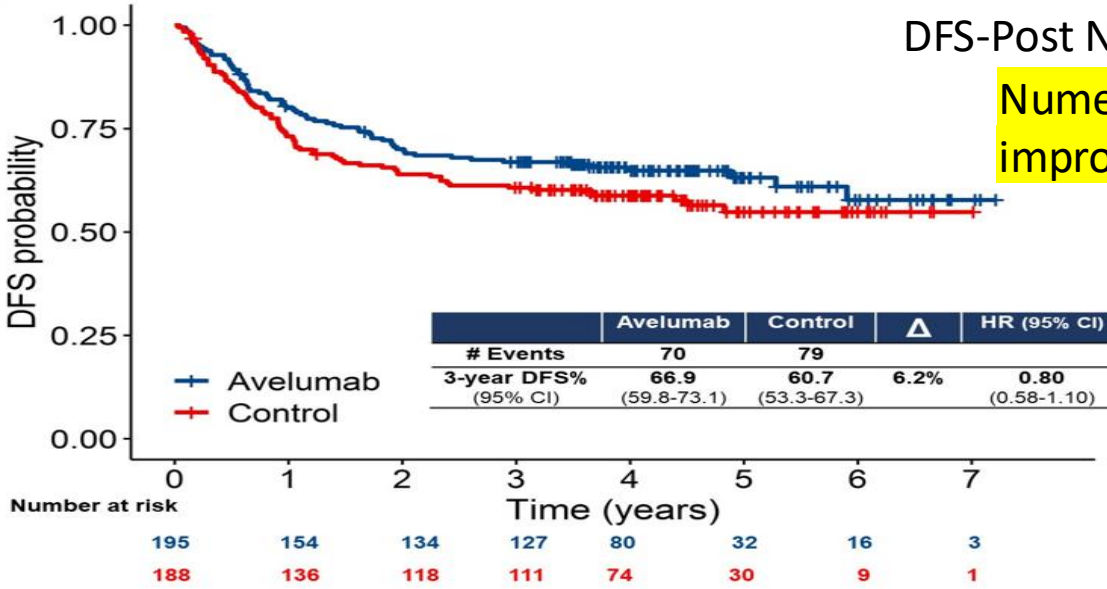
DFS-ITT



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	81	91			
3-year DFS% (95% CI)	68.3 (61.9-73.8)	63.2 (56.5-69.0)	5.1%	0.81 (0.61-1.09)	0.172

DFS-Post NA

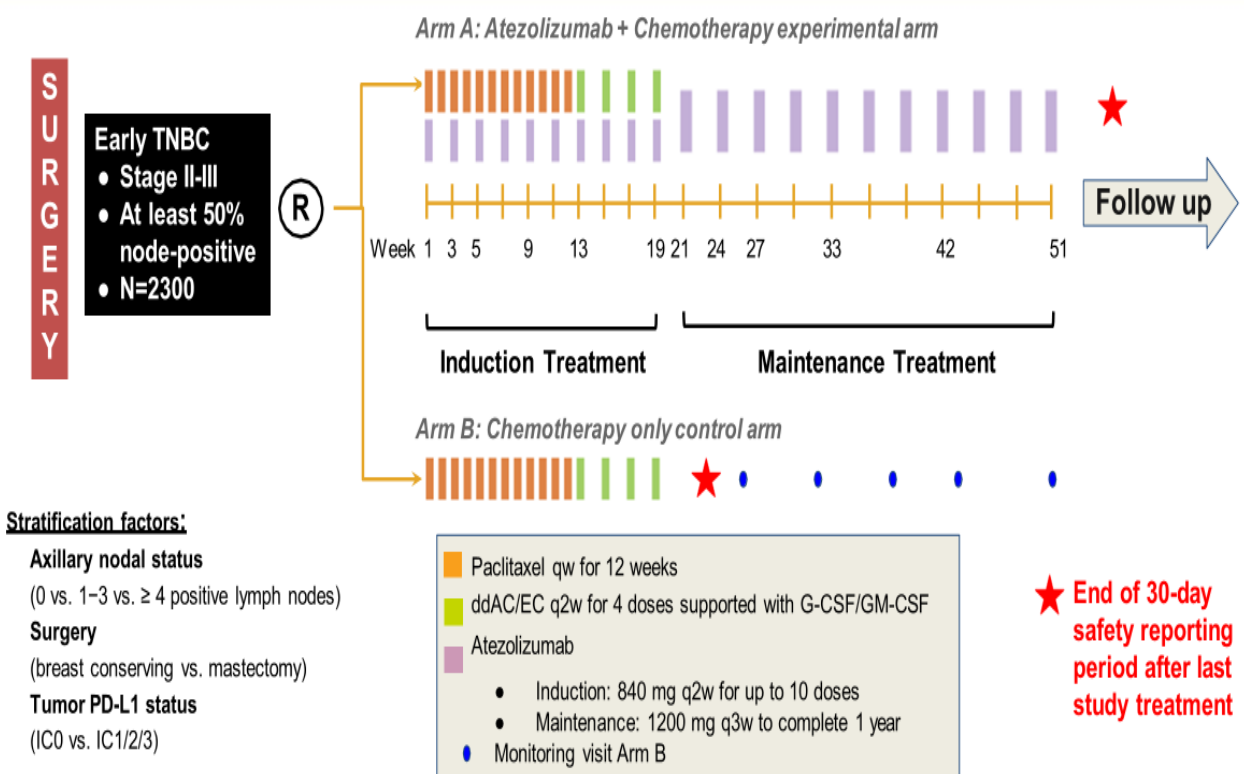
Numeric 6.2% improvement



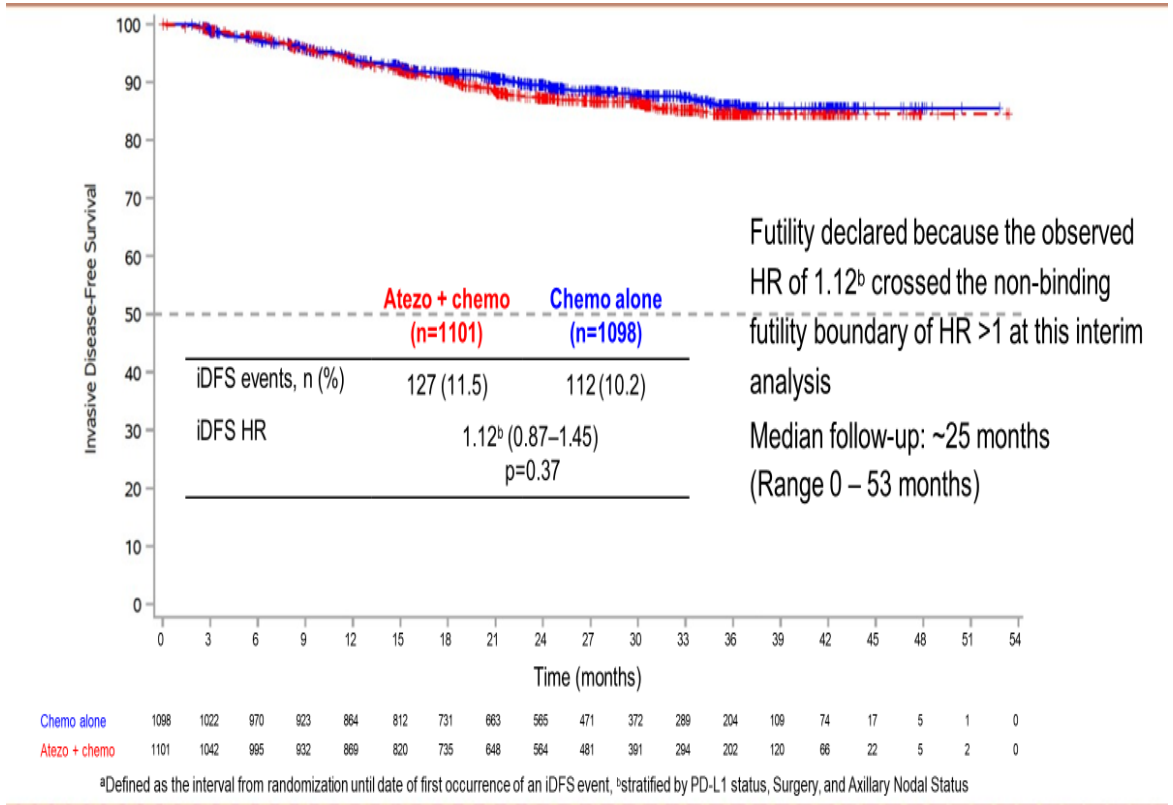
	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	70	79			
3-year DFS% (95% CI)	66.9 (59.8-73.1)	60.7 (53.3-67.3)	6.2%	0.80 (0.58-1.10)	0.170

Conte PF et al. 2024 ASCO Annual Meeting. Abstract LBA500.

ALEXANDRA/IMpassion030 Phase 3 trial



iDFS: Primary End Point



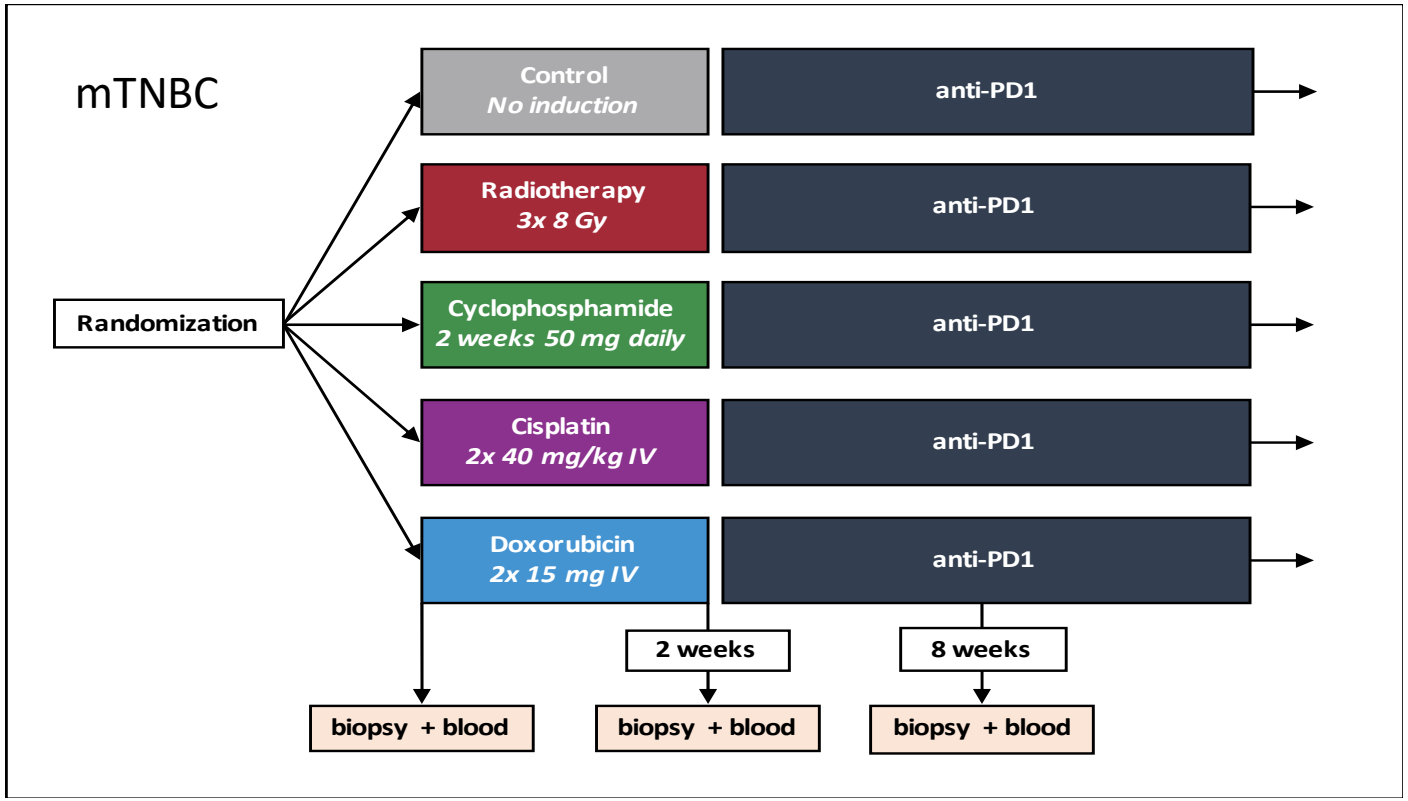
[a]Defined as the interval from randomization until date of first occurrence of an iDFS event, [b]stratified by PD-L1 status, Surgery, and Axillary Nodal Status

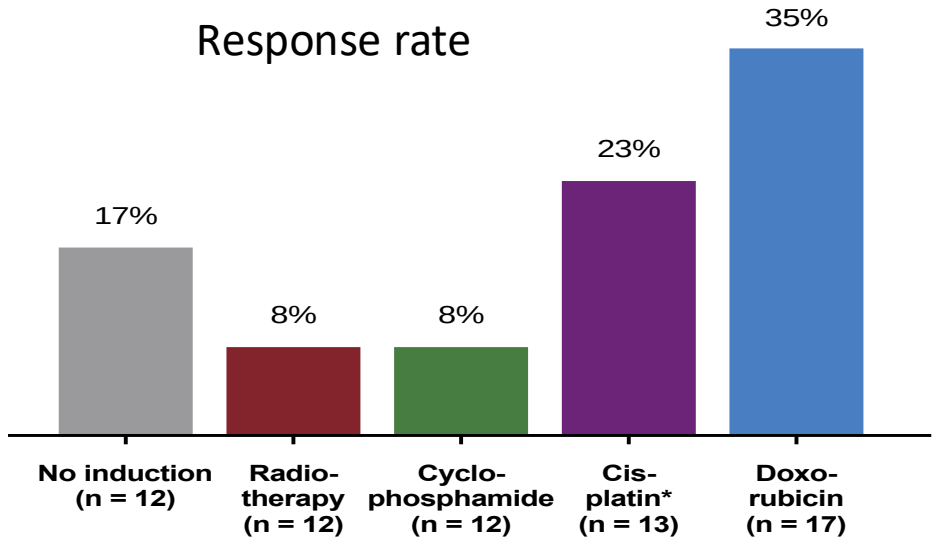
Timing of IO matters: Neoadjuvant IO more effective than adjuvant IO, ? Role in residual disease post NACT

Ignatiadis M et al. 2023 SABCS. Abstract GS01-03.

If using immunotherapy, can we de-escalate chemotherapy backbone?

Doxorubicin and Cisplatin induction sensitize to subsequent PD-1 Blockade: TONIC Trial

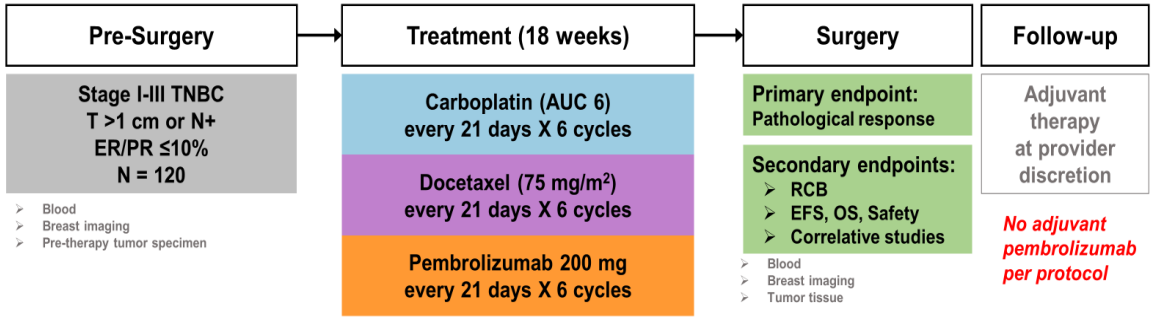


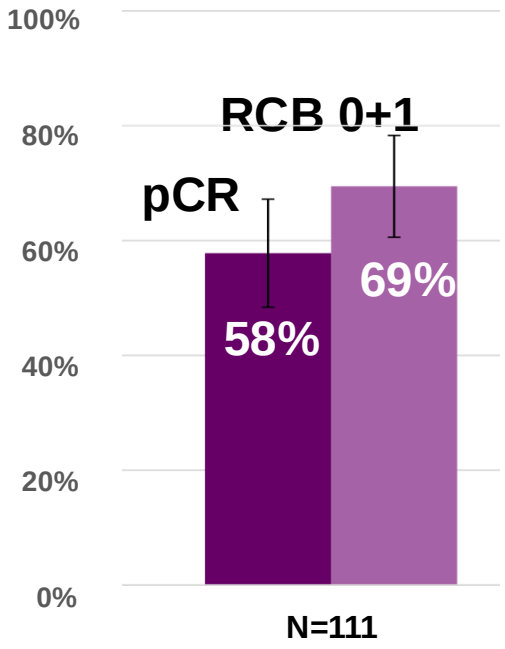


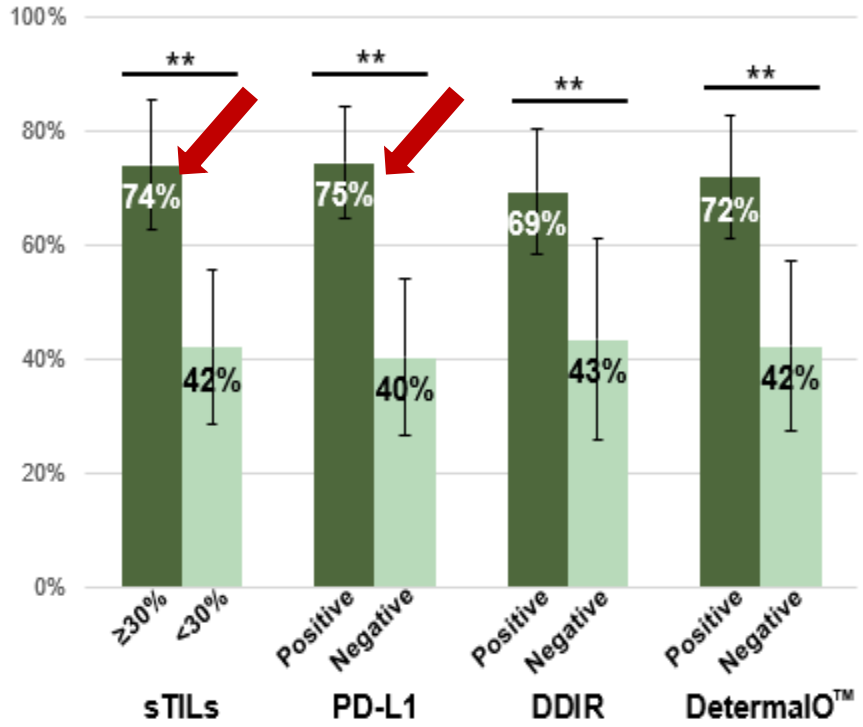
Short term doxorubicin and cisplatin induction led to a more favorable tumor microenvironment (upregulation of immune-related genes involved in PD-1-PD-L1 and T cell cytotoxicity pathways) and increase the likelihood of response to PD-1 blockade

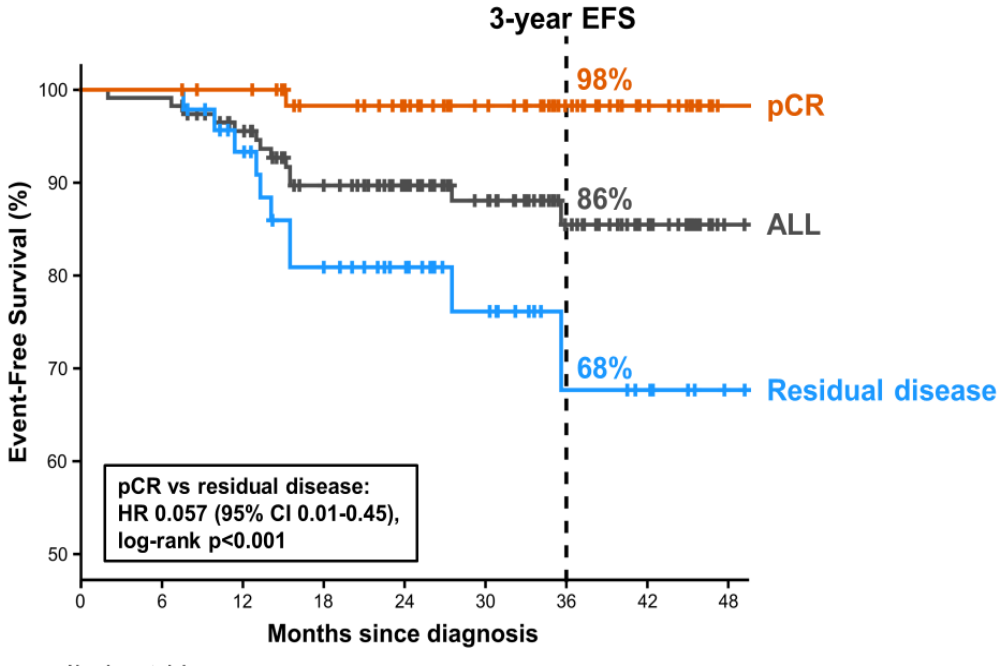
Voorwerk et al, Nature Medicine 2019

NeoPACT: Carboplatin + Docetaxel + Pembrolizumab





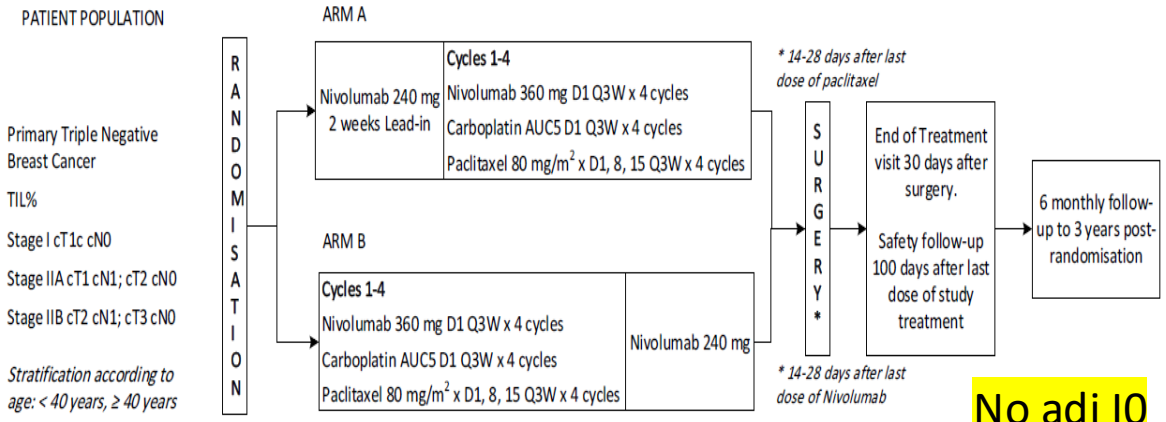




-Immune enrichment assessed by sTILs, PD-L1 or DetermaIO™ signature was noted in almost 50% of patients and was associated with high pCR rates exceeding 70%.
-pCR delta: 30-35% in immune high vs immune low

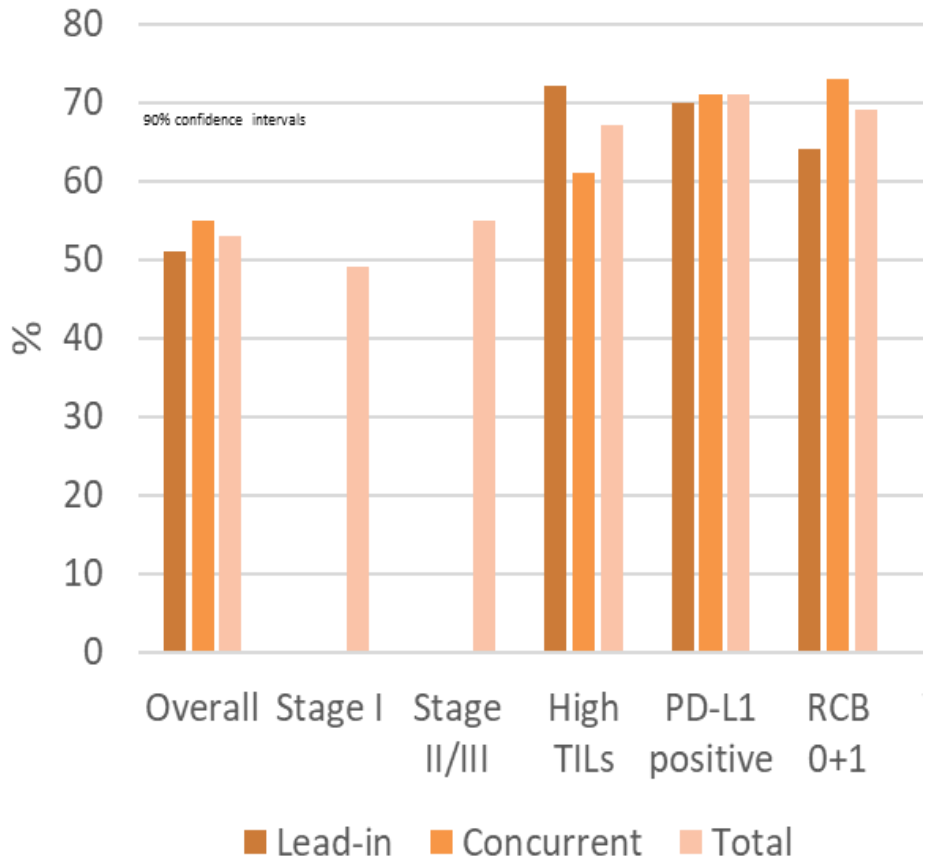
Sharma P et al. *JAMA Oncol*. 2024;10(2):227-235.

BCT1902/IBCSG 61-20 Neo-N: Randomized Phase II Study of Neoadjuvant Nivolumab (N) 2-Week Lead-in Followed by 12 Weeks of Concurrent N+carboplatin plus Paclitaxel (CbP) vs Concurrent N+CbP in TNBC



No adj I0

N=108, Stage I-II enrolled at 14 centers
35% stage I, 43-51% PDL1+ (≥ 1% SP-142)



- Overall pCR rate: 53% (90%CI 44-61%)
  - No evidence of pCR advantage with Lead-in nivo
  - Lead-in: 51% (90%CI 39-63%), Concurrent: 55% (90%CI 43-66%)
- Patients with immune enriched tumors, identified by high sTILs or PD-L1 positivity, had high pCR rates with 12 weeks of treatment;
  - pCR rate 71% in PD-L1 positive vs 33% in PD-L1 negative
  - pCR rate 67% in highs TILs group vs 47% low TIL group
- EFS pending

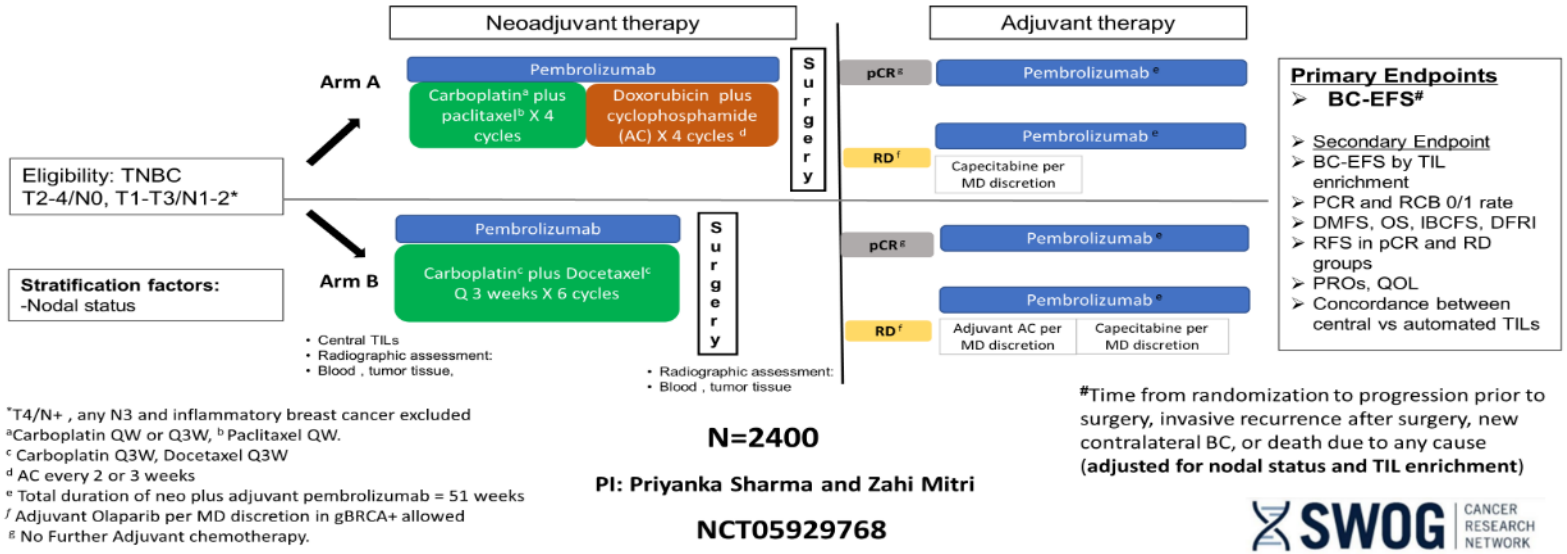
Loi S et al. 2023 SABCS. Abstract LBAO1-03.

Chemotherapy De-escalation in Early-Stage TNBC

S2212: Shorter Anthracycline-free Chemoimmunotherapy Adapted to pathological Response in Early TNBC (SCARLET)

Randomized non-inferiority trial

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



Primary Endpoints
- BC-EFS#

- Secondary Endpoint
- BC-EFS by TIL enrichment
- PCR and RCB 0/1 rate
- DMFS, OS, IBCFS, DFRI
- RFS in pCR and RD groups
- PROs, QOL
- Concordance between central vs automated TILs

*T4/N+ , any N3 and inflammatory breast cancer excluded
[a]Carboplatin QW or Q3W, [b] Paclitaxel QW.
[c] Carboplatin Q3W, Docetaxel Q3W
[d] AC every 2 or 3 weeks
[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks
[f] Adjuvant Olaparib per MD discretion in gBRCA+ allowed
[g] No Further Adjuvant chemotherapy.

N=2400

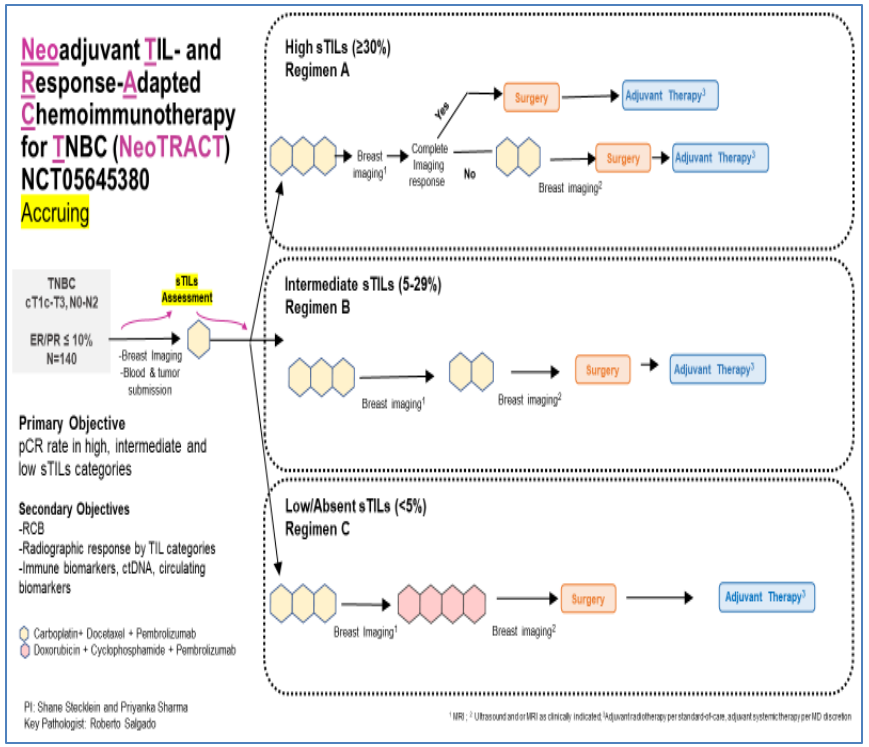
PI: Priyanka Sharma and Zahi Mitri

NCT05929768

#Time from randomization to progression prior to surgery, invasive recurrence after surgery, new contralateral BC, or death due to any cause **(adjusted for nodal status and TIL enrichment)**

SWOG CANCER RESEARCH NETWORK

sTILs are integral marker for primary and secondary end point analysis



De/escalation and adapting based on pretreatment TILs

Neoadjuvant Immunotherapy Response Biomarkers in TNBC

- PD-L1, TILs, immune signatures Prognostic but not predictive
  - Predict high response to neoadjuvant chemo or chemo-immunotherapy but NOT preferential response to addition of IO
  - Identify subgroups with excellent prognosis where de-escalation may be appropriate
- DETERMA IO score
  - Measures both tumor gene expression and the tumor immune microenvironment
  - Preferential benefit from chemo+atezo vs chemo in NeoTRIP and high pCR in NeoPACT
  - Planned analysis in S1418
- MHC-II expression on tumor cells
  - Predictive of pCR with durvalumab + NAC and pembrolizumab + NAC in cross-trial comparisons
  - Planned analysis in S1418
- CD8+TCF1+Ki67+
  - High CD8+TCF1+Ki67+ density linked to increased pCR and EFS with the addition of atezolizumab to chemotherapy in NeoTRIP
- ImSig Proliferation in immune-low tumors
  - NeoPACT-NeoSTOP, Validation in GeparNuevo and FLEX registry ongoing
- TNBC-DX

Sinn BV et al. *Clin Cancer Res*. 2021;27(9):2584-2591. Gonzalez-Ericsson PI, et al. *Clin Cancer Res*. 2021;27(19):5299-5306. Bianchini G et al. 2021 ESMO Annual Congress. Abstract LBA12. Sharma P et al. *JAMA Oncol*. 2024;10(2):227-235. Stecklein SR et al. 2023 ASCO Annual Meeting. Abstract 507. Gianni L et al. 2023 ESMO Annual Congress. Abstract LBA19.

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irAE: Post KN-522 data

Real World data

N=577 (17 sites), 18.2% Blacks

Adverse drug events(ADE) causing dose reduction	37.6%
ADE leading to early discontinuation	**39.5%**
irAE, all grades	71%
irAE ≥ 3 higher	**33.5%**

	Blacks	White	p
≥ 3 higher irAE	20.9%	33.8%	0.011
Hospitalization rate	39%	36%	0.5
pCR	**52.3%**	**55.9%**	0.6

Hofherr et al SABCS 2023

Knowledge Gaps

- Do all patients need 4-drug poly-chemotherapy when immunotherapy is part of NAST?
  - Can we de-escalate chemotherapy? S2212, NeoTRACT
  - I-SPY 2.2: novel agents/combinations to allow early de-escalation
- Role of adjuvant ICB
  - In setting of PCR (OptimICE-PCR)
  - In setting of Residual disease (SWOG 1418)
- Do all patients need chemotherapy plus immunotherapy?
  - Can we identify patients who do not need/unlikely to benefit from ICB?
- Patient perspective
  - Long term side effects of ICB in curative setting, toxicity predictors, impact on fertility
- Early identification of patients unlikely to achieve optimal response with neoadjuvant chemoimmunotherapy
  - Tissue, Imaging +/- Machine learning/AI, Circulating biomarkers (ctDNA)
  - Neoadjuvant testing of novel more effective therapies

Closing the gap

- Patient selection
- Optimizing IO duration and chemotherapy backbone
- Tailoring treatment de/escalation to response
- Risk-Benefit, QOL, Long term toxicity
- Predictive biomarkers of efficacy and toxicity
- Patient advocacy