Atlanta Breast Cancer CONFERENCE

How I Treat Triple Negative Breast Cancer

September 27, 2025

Partners for Advancing Clinical Education

Bio Ascend™

Atlanta Breast Cancer CONFERENCE

A-BRAVE and PEARLY trial reference and TBCRC 048
OptiTROP Breast 01 and Huppert sequencing

Tung N et al ASCO 2024
Huppert LA et al npj Breast Cancer 2025
Sohn J et al. ASCO 2024
Xu B et al. ASCO 2024

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Triple-Negative Breast Cancer Compared with Other Phenotypes in the California Cancer Registry Study

- **Population-based study**
  - 6370 with “triple-negative” disease (12%) vs. with 44,704 “other” cases

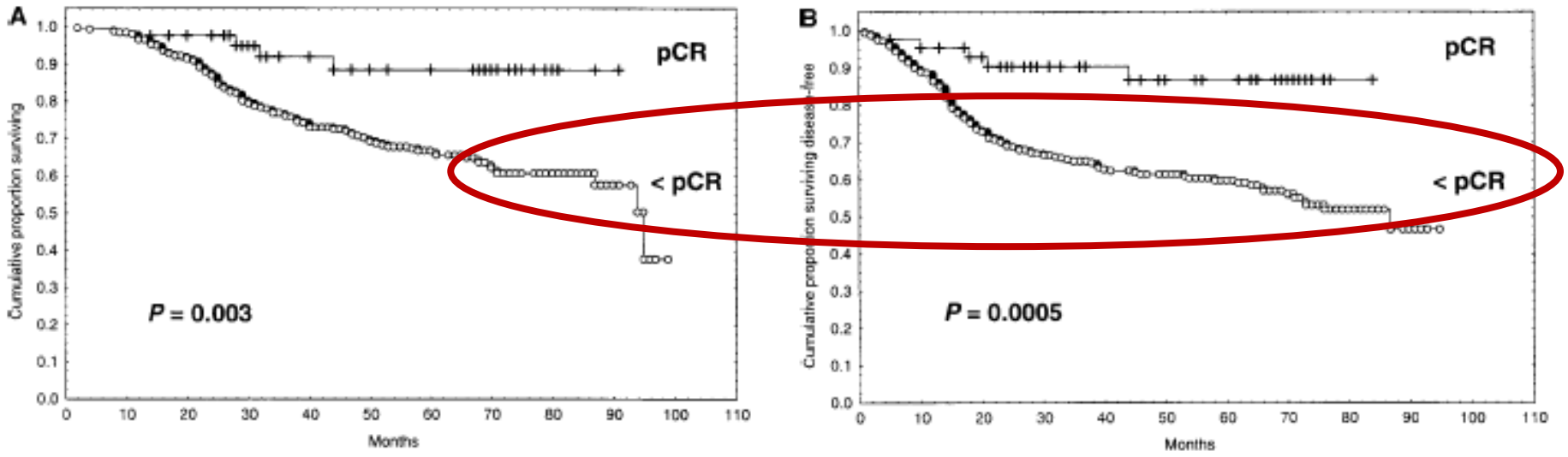
- **TNBC more likely to be associated with**
  - Younger age (<40): OR 1.53
  - Non-Hispanic black (OR 1.77) or Hispanic (OR 1.23)
  - Higher grade (72% grade 3)
  - More advanced stage (66% ≥ stage II vs. 50% ER+HER2-)
  - Poorer 5 year RFI irrespective of stage
    - TNBC: 76% (similar to 76% for HER2-Pos)
    - HR-Pos, HER2-Neg: 94%

Bauer KR et al. Cancer 2007 (PMID: 17387718); Parise CA et al. The Breast Journal 2009 (PMID: 19764994)

Benefits of neoadjuvant chemotherapy in TNBC

- pCR is a surrogate for both disease free and overall survival

Approach 1: **Change neoadjuvant therapy to increase pCR rate**



Overall Survival

Disease-free Survival

Approach 3: **Stop systemic therapy in patients achieving a pCR**

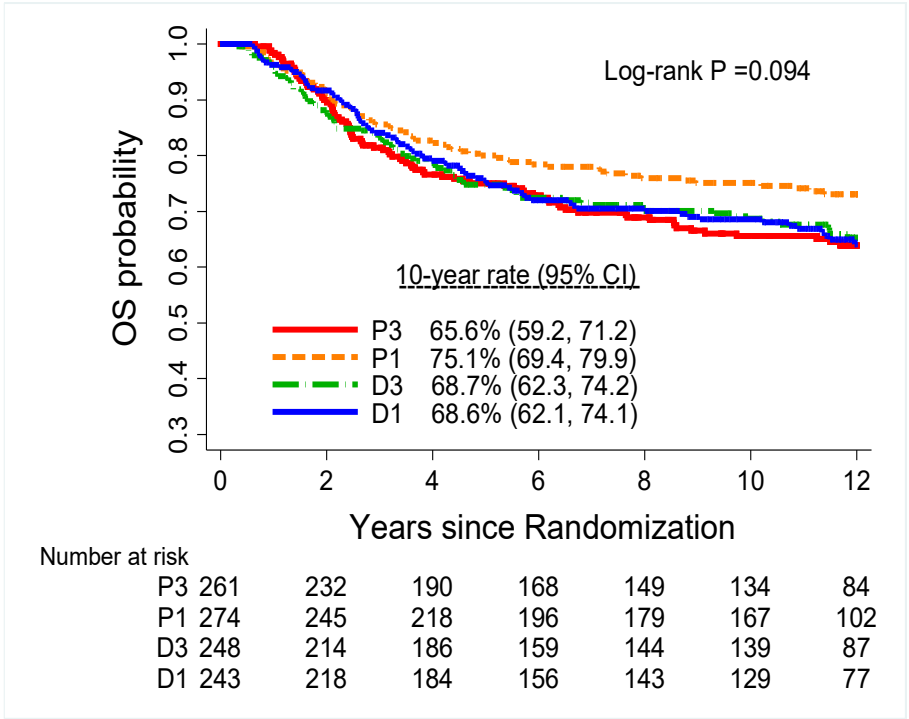
Approach 2: **Add adjuvant therapy to improve outcome for high-risk pts**

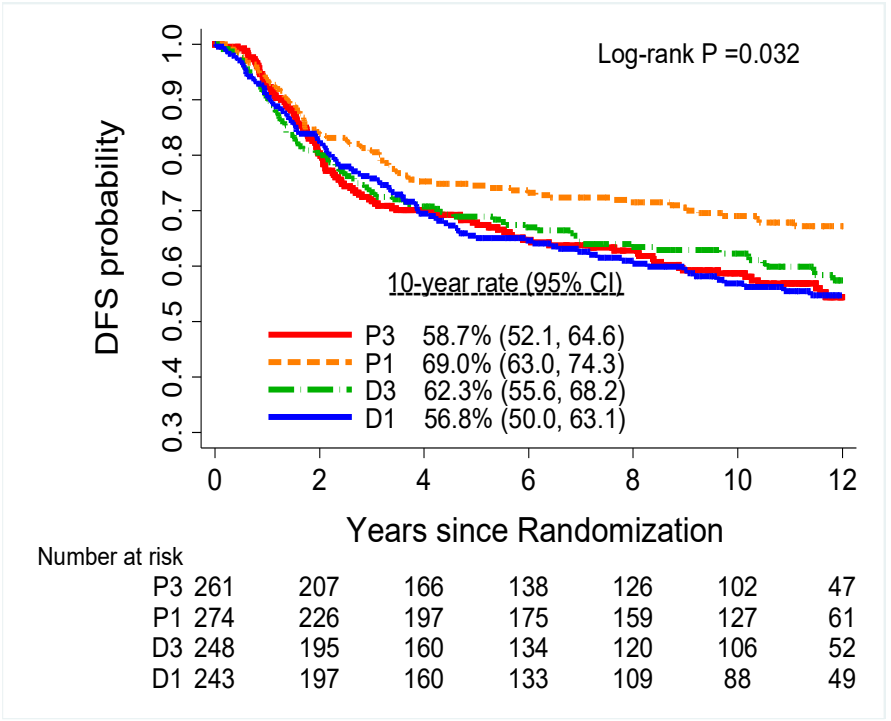
Retrospective analysis of 372 patients with LABC treated with neoadjuvant doxorubicin based chemotherapy (FAC). 16% (n = 60) had a complete pathologic response (pCR)

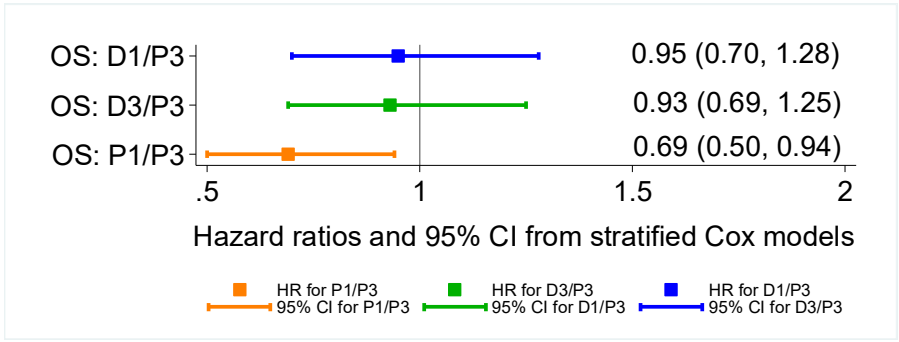
Kuerer HM et al. J Clin Oncol 17:460-9, 1999.

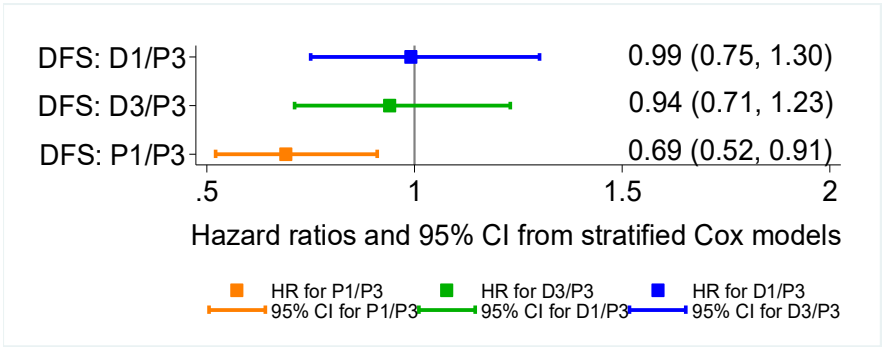
E1199: AC followed by Paclitaxel or Docetaxel (Weekly vs. Every 3 Weeks)

Exploratory Analysis in TNBC (N=1025) – Weekly Paclitaxel Associated with Improved DFS and OS









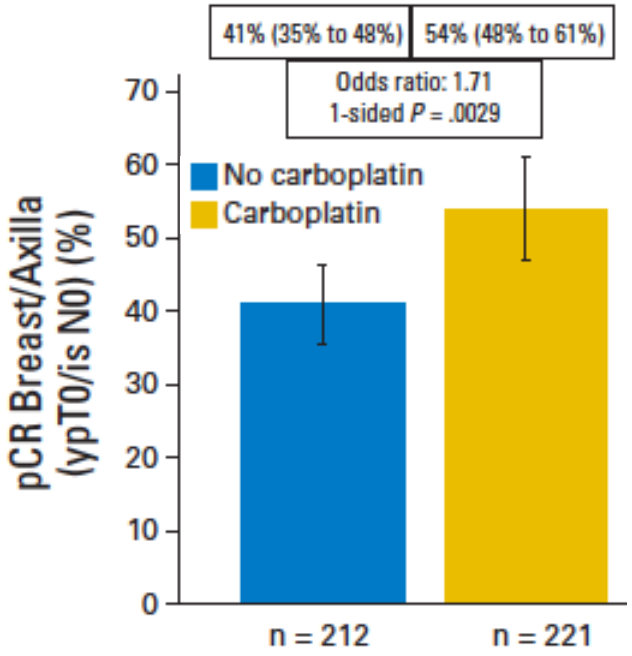
Sparano et al. N Engl J Med. 2008 (PMID: 18420499); Sparano et al. J Clin Oncol. 2015 (PMID: 26077235)

Does Carboplatin Improve Outcomes?

Addition of neoadjuvant carboplatin to taxanes/anthracycline regimens in TNBC

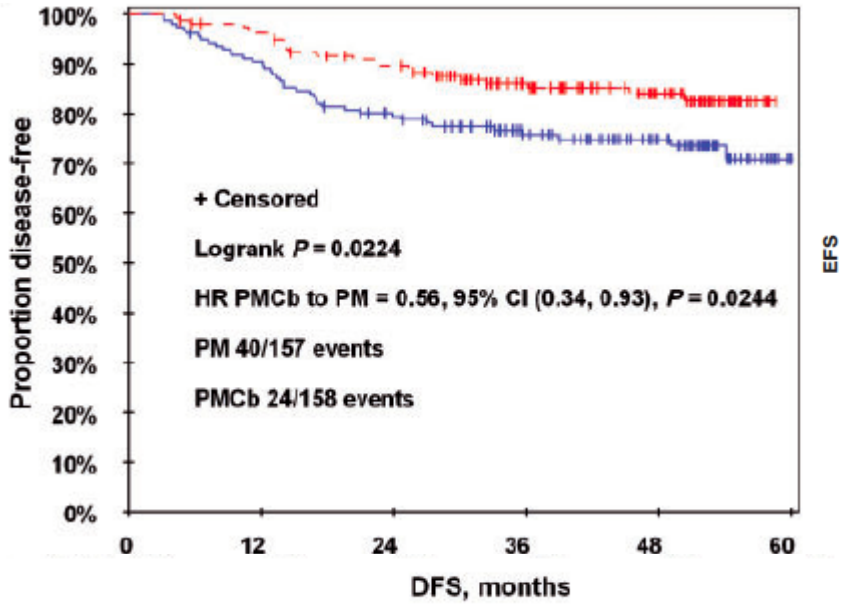
CALGB 40603

- 2x2 factorial randomized phase II (n=443)
- pCR increased: 41% to **54%** (p=0.003)
- Addition of Cb did ***not*** improve EFS: 5-yr EFS HR 0.99 (0.70-1.40)



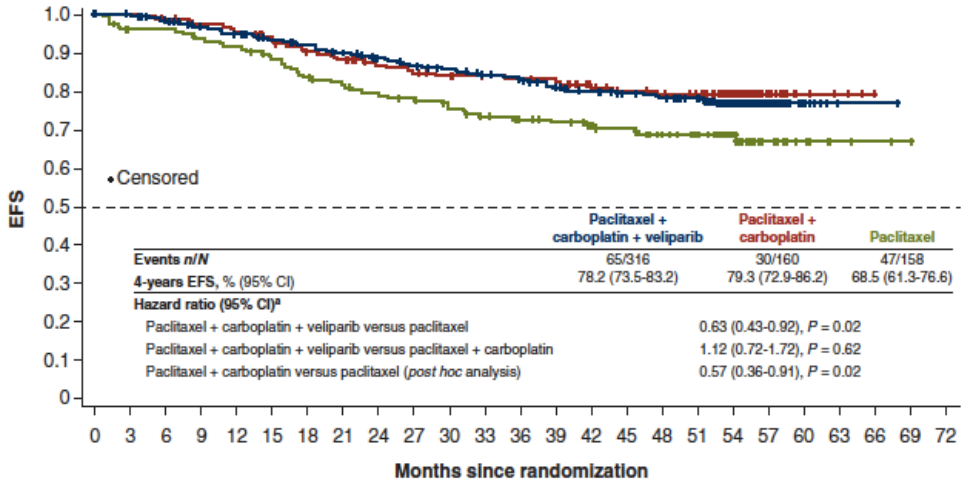
GeparSixto

- Randomized phase II (n=588)
- pCR: 43% to **53%** (p=0.015)
- Addition of Cb ***improved*** DFS (not OS): 3-yr DFS HR 0.56 (0.34-0.93): 76% to 86%



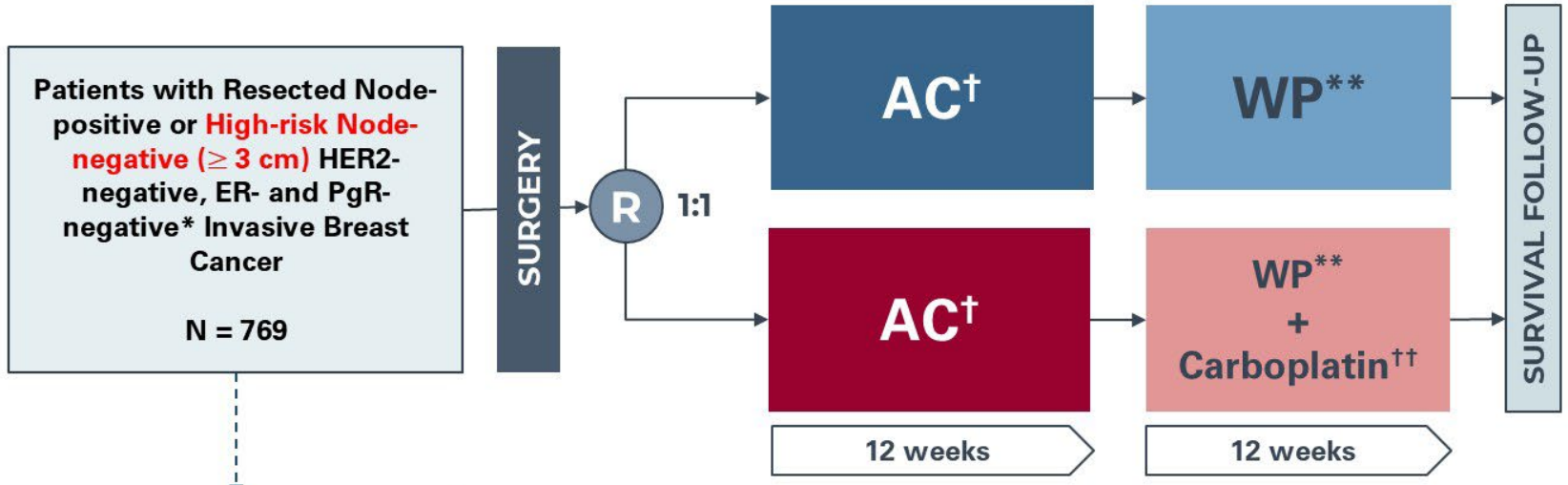
BrighTNess

- Randomized phase III (n=634)
- pCR increased: 49% (T), **58%** (TCb), 53% (TCbV)
- Addition of Cb ***improved*** EFS (not OS): 4-yr EFS
  - T vs. TCbV: HR 0.63 (0.43-0.92): 69% to 78%
  - T vs. TCb: HR 0.57 (0.36-0.91): 69% to 79%



Sikov W et al. J Clin Oncol. 2015; Sikov W et al. ASCO 2019; Modified from von Minckwitz G et al. Lancet Oncol. 2014; Loibl S et al. Ann Oncol. 2018; Loibl S et al. Lancet Oncol. 2018; Geyer CE et al. Ann Oncol. 2022

NRG-BR003 Study Design



STRATIFICATION FACTORS

- Number of positive nodes (0, 1–3, 4–9, 10+)
- *BRCA* mutation status (positive; negative or unknown)

* Patients are eligible if the tumor staining meets one of the following criteria:
  - ER-negative and PgR-negative by ASCO/CAP guidelines, OR
  - ER or PgR stains are positive in 1-9% of cells and neither is positive in ≥10% of cells

† Doxorubicin (A) 60 mg/m2 IV + cyclophosphamide (C) 600 mg/m2 IV every 2 weeks for 4 cycles (dose-dense schedule)

** Paclitaxel 80 mg/m2 IV weekly for 12 doses

†† Carboplatin AUC of 5 IV every 3 weeks for 4 cycles

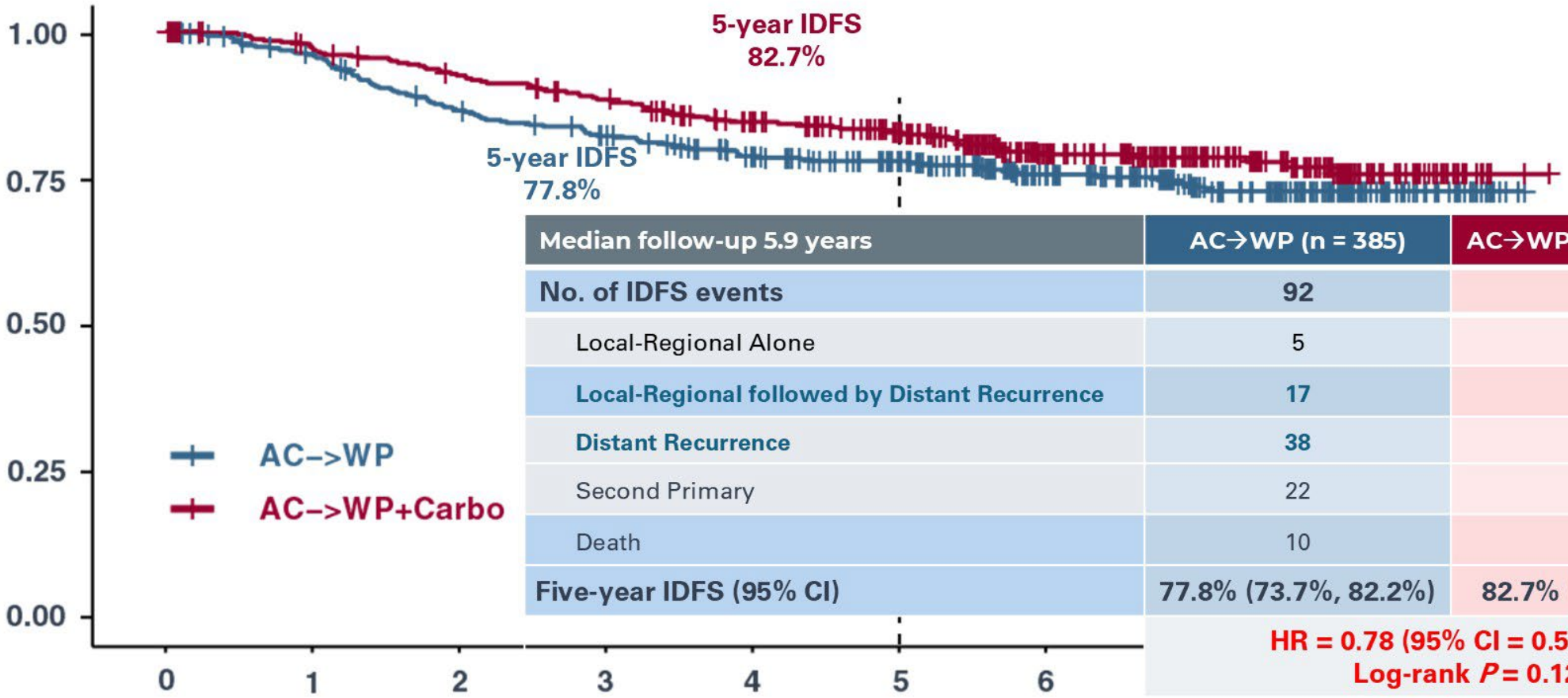
Primary Endpoint:

- **Invasive disease-free survival (IDFS)**

Secondary Endpoints:

- Overall survival (OS)
- Breast cancer-free survival (BCFS)
- Recurrence-free interval (RFI)
- Distant recurrence-free interval (DRFI)
- Frequencies of adverse events categorized using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0)

Invasive Disease-Free Survival

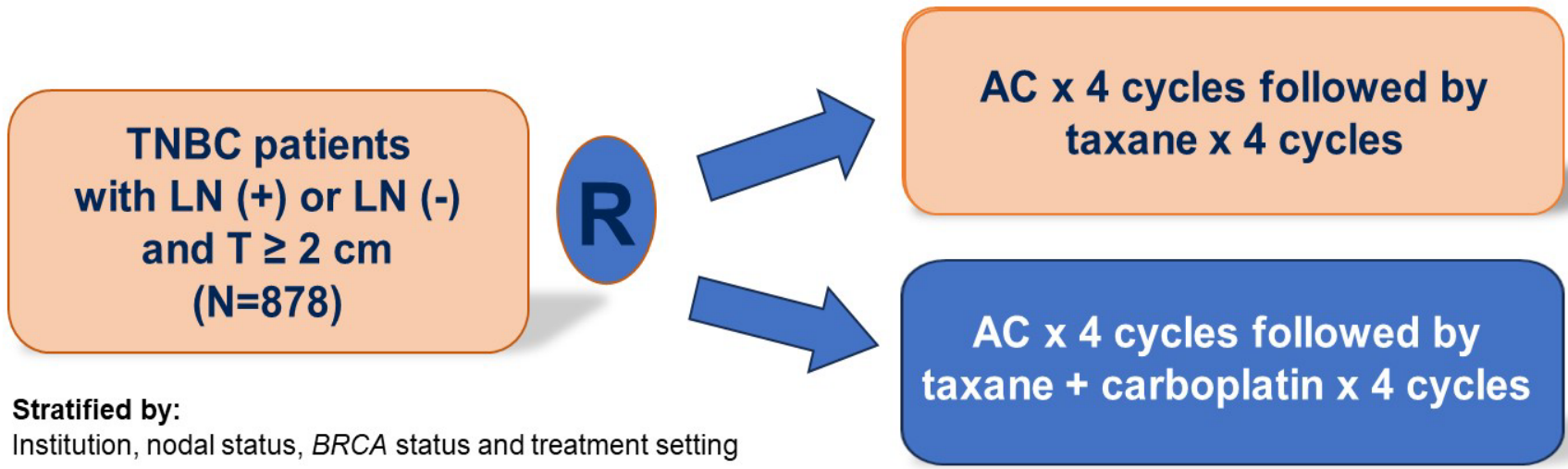


Median follow-up 5.9 years	AC→WP (n = 385)	AC→WP+Carbo (n = 384)
No. of IDFS events	92	77
Local-Regional Alone	5	5
Local-Regional followed by Distant Recurrence	17	8
Distant Recurrence	38	36
Second Primary	22	19
Death	10	9
Five-year IDFS (95% CI)	77.8% (73.7%, 82.2%)	82.7% (78.9%, 86.7%)
	HR = 0.78 (95% CI = 0.58, 1.06) Log-rank *P* = 0.12	

No. at risk

AC→WP	385	356	318	296	267	238	168	117	58	7	0
AC→WP+Carbo	384	362	342	323	292	256	174	121	57	4	0

PEARLY Study Design (NCT02441933)



Stratified by:
Institution, nodal status, *BRCA* status and treatment setting

AC: 60/600mg/m^2 q3 wks x 4
Taxane:
Paclitaxel 80mg/m^2 q1 wk x 12
or
Docetaxel 75mg/m^2 q3 wks x 4
Carboplatin: AUC 5 q3 wks x 4

AC, doxorubicin and cyclophosphamide

Primary Endpoint

– 5-year EFS (Event-Free Survival) rate

Disease progression or inoperable status for neoadjuvant group
Local or distant recurrence, second primary cancer, or death from any cause

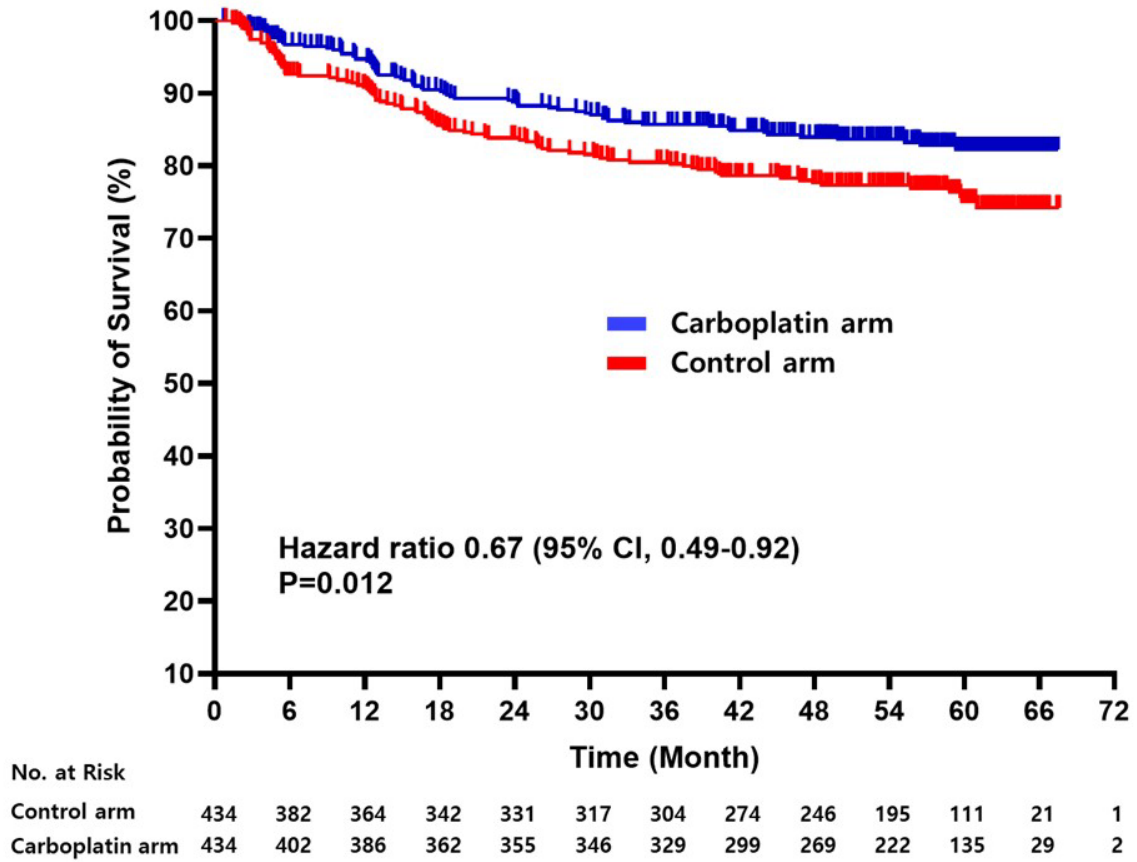
Secondary Efficacy Endpoints

Overall survival, OS
Distant recurrence-free survival, DRFS
Invasive disease-free survival, IDFS

Safety Endpoints

Safety and tolerability
QoL : EORTC-QLQ-CIPN20, EQ-5D

Primary Efficacy Endpoint: EFS



ITT analysis	Carbo arm (n=434)	Control arm (n=434)
5-year EFS rate	82.3%	75.1%
Stratified HR (95% CI)	0.67 (0.49-0.92)	
Stratified Log Rank *P value*	0.012	

Adjuvant Paclitaxel + Carboplatin in Early TNBC

N=647 1:1 randomization to (mg/m2)

- Weekly paclitaxel 80/carboplatin AUC 2 D1, 8, 15 q28d x 6 cycles
- CEF (500/100/500) x3 cycles then docetaxel 100 x 3 cycles

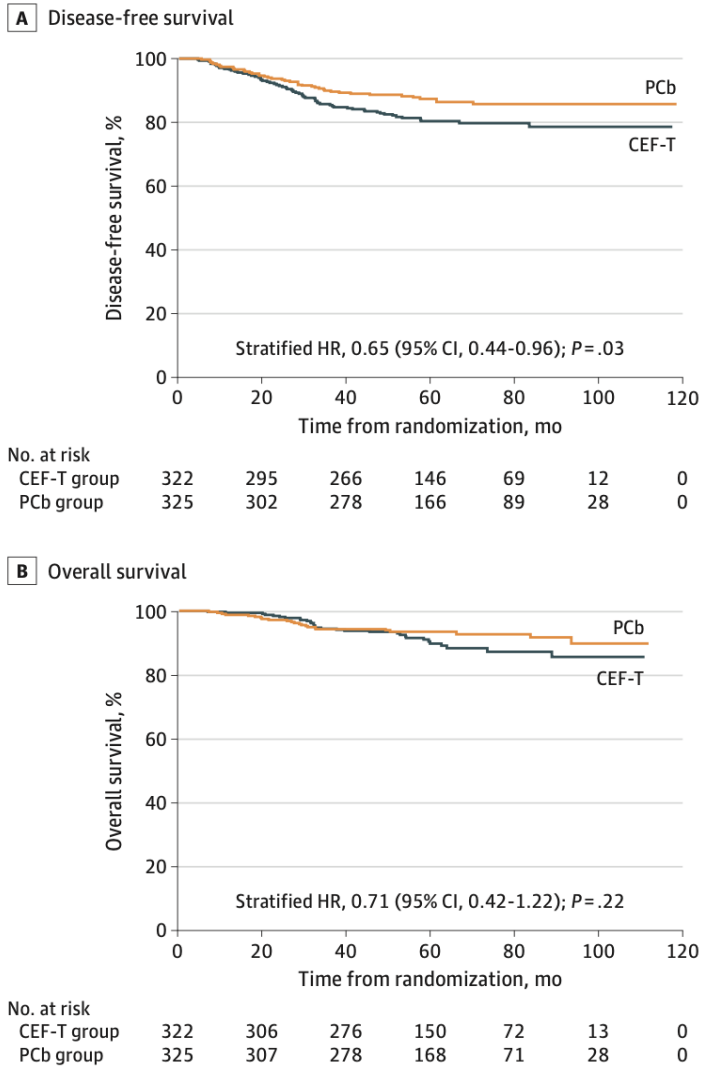
74% Node- & 26% Node+
54% T1 & 46% T2/T3
27% Grade 1/2 & 73% Grade 3

Table 2. First Disease-Free Survival Event by Treatment

	No. (%)	
Disease-free survival event	CEF-T (n = 322)	PCb (n = 325)
Local and regional recurrence	10 (3.1)	4 (1.2)
Contralateral breast tumor	8 (2.5)	9 (2.8)
Distant metastasis	33 (10.2)	20 (6.2)
Second primary malignancy	8 (2.5)	7 (2.2)
Death	3 (0.9)	2 (0.6)
Total	62 (19.3)	42 (12.9)

Yu et al. JAMA Oncol. 2020 (PMID: 32789480)

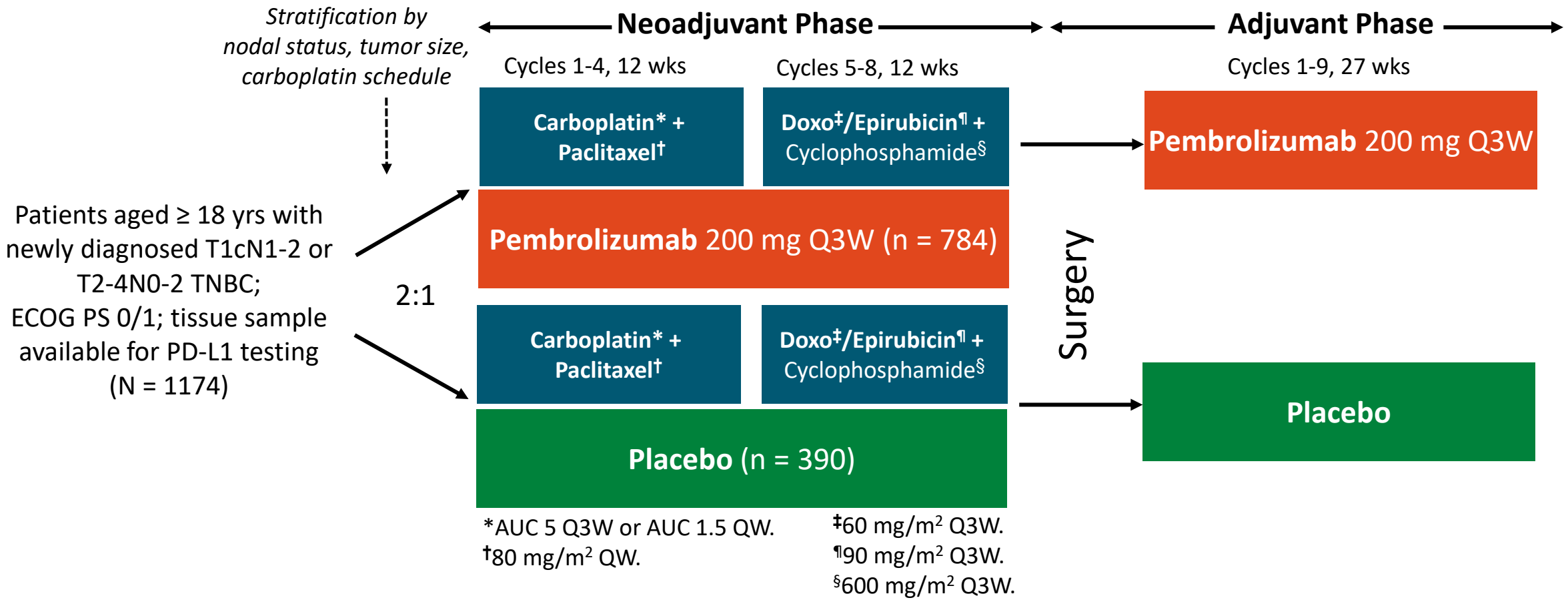
Figure 2. Disease-Free Survival and Overall Survival



Does Carboplatin Improve Outcomes?

Yes, likely improves IDFS by about 5% when added to AC/T

KEYNOTE-522: Study Design



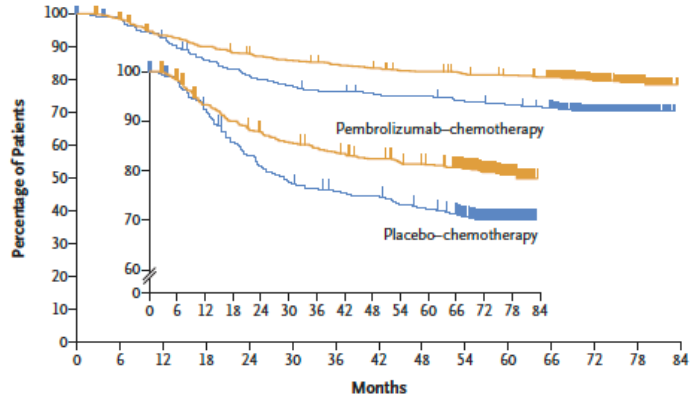
- **Primary endpoints: pCR (ypT0/Tis ypN0) by local review, EFS by local review**
- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE
- Exploratory endpoints: RCB, pCR by subgroups, EFS by pCR

Schmid. NEJM. 2020;382:810.

KEYNOTE-522 (Phase 3): FINAL EFS & OS

EFS

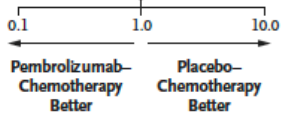
A Event-free Survival According to Treatment Group in the Intention-to-Treat Population



No. at Risk															
Pembrolizumab–chemotherapy	784	769	728	702	681	665	654	644	633	625	618	602	409	164	0
Placebo–chemotherapy	390	382	358	330	312	300	293	287	285	278	273	264	178	76	0

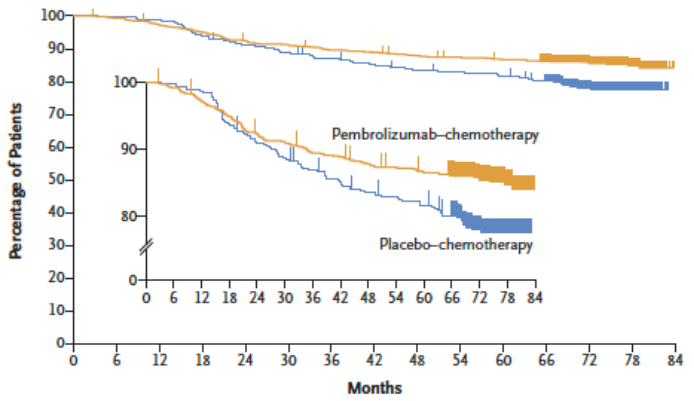
B Subgroup Analyses of Event-free Survival

Subgroup	Pembrolizumab–Chemotherapy *no. of patients with event/total no. (%)*	Placebo–Chemotherapy *no. of patients with event/total no. (%)*	Hazard Ratio for Event or Death (95% CI)
Overall	159/784 (20.3)	114/390 (29.2)	0.65 (0.51–0.83)
Nodal status			
Positive	102/408 (25.0)	65/196 (33.2)	0.72 (0.53–0.98)
Negative	57/376 (15.2)	49/194 (25.3)	0.56 (0.38–0.82)
Tumor size			
T1 to T2	91/580 (15.7)	76/290 (26.2)	0.55 (0.41–0.75)
T3 to T4	68/204 (33.3)	38/100 (38.0)	0.86 (0.58–1.28)
Carboplatin schedule			
Every 3 wk	65/334 (19.5)	45/167 (26.9)	0.68 (0.47–1.00)
Weekly	92/444 (20.7)	69/220 (31.4)	0.62 (0.46–0.85)
PD-L1 status			
CPS ≥1	128/656 (19.5)	86/317 (27.1)	0.68 (0.52–0.90)
CPS <1	31/128 (24.2)	28/69 (40.6)	0.53 (0.31–0.88)
Age			
<65 yr	130/700 (18.6)	98/342 (28.7)	0.61 (0.47–0.80)
≥65 yr	29/84 (34.5)	16/48 (33.3)	0.99 (0.54–1.82)



OS

A Overall Survival According to Treatment Group in the Intention-to-Treat Population



No. at Risk															
Pembrolizumab–chemotherapy	784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
Placebo–chemotherapy	390	389	385	366	354	345	336	328	321	318	313	300	199	82	0

B Subgroup Analyses of Overall Survival

Subgroup	Pembrolizumab–Chemotherapy *no. of patients who died/total no. (%)*	Placebo–Chemotherapy *no. of patients who died/total no. (%)*	Difference in 5-Year Overall Survival (95% CI) *percentage points*
Overall	115/784 (14.7)	85/390 (21.8)	4.9 (0.3 to 9.4)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	7.2 (0.0 to 14.3)
Negative	37/376 (9.8)	29/194 (14.9)	2.9 (–2.5 to 8.2)
Tumor size			
T1 to T2	54/580 (9.3)	51/290 (17.6)	5.1 (0.5 to 9.6)
T3 to T4	61/204 (29.9)	34/100 (34.0)	4.5 (–6.5 to 15.5)
Carboplatin schedule			
Every 3 wk	46/334 (13.8)	36/167 (21.6)	4.7 (–2.1 to 11.6)
Weekly	68/444 (15.3)	49/220 (22.3)	5.2 (–0.8 to 11.3)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	3.5 (–1.4 to 8.3)
CPS <1	23/128 (18.0)	23/69 (33.3)	11.9 (–0.4 to 24.2)
Age			
<65 yr	93/700 (13.3)	72/342 (21.1)	5.0 (0.3 to 9.7)
≥65 yr	22/84 (26.2)	13/48 (27.1)	2.4 (–12.8 to 17.6)

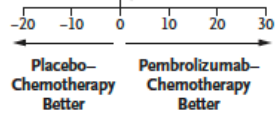
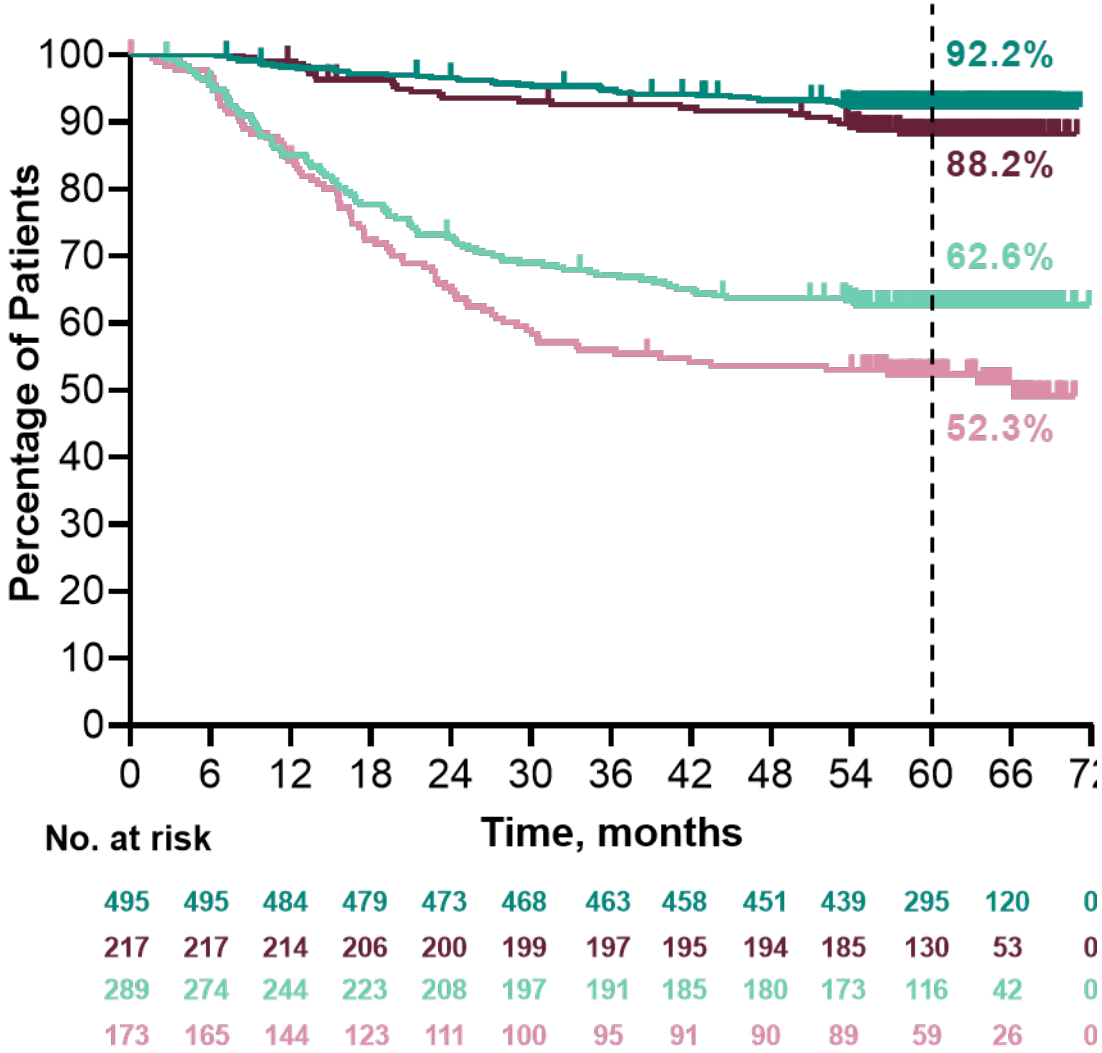


Table 1. Summary of First Events in Analysis of Event-Free Survival.

Event	Pembrolizumab–Chemotherapy (N=784)	Placebo–Chemotherapy (N=390)
	number (percent)	
Any event	159 (20.3)	114 (29.2)
Progression of disease that precluded definitive surgery	14 (1.8)	15 (3.8)
Local recurrence	33 (4.2)	20 (5.1)
Distant recurrence	77 (9.8)	56 (14.4)
Second primary cancer	16 (2.0)	10 (2.6)
Death	19 (2.4)	13 (3.3)

Schmid et al. NEJM 2024 (PMID PMID: 39282906)

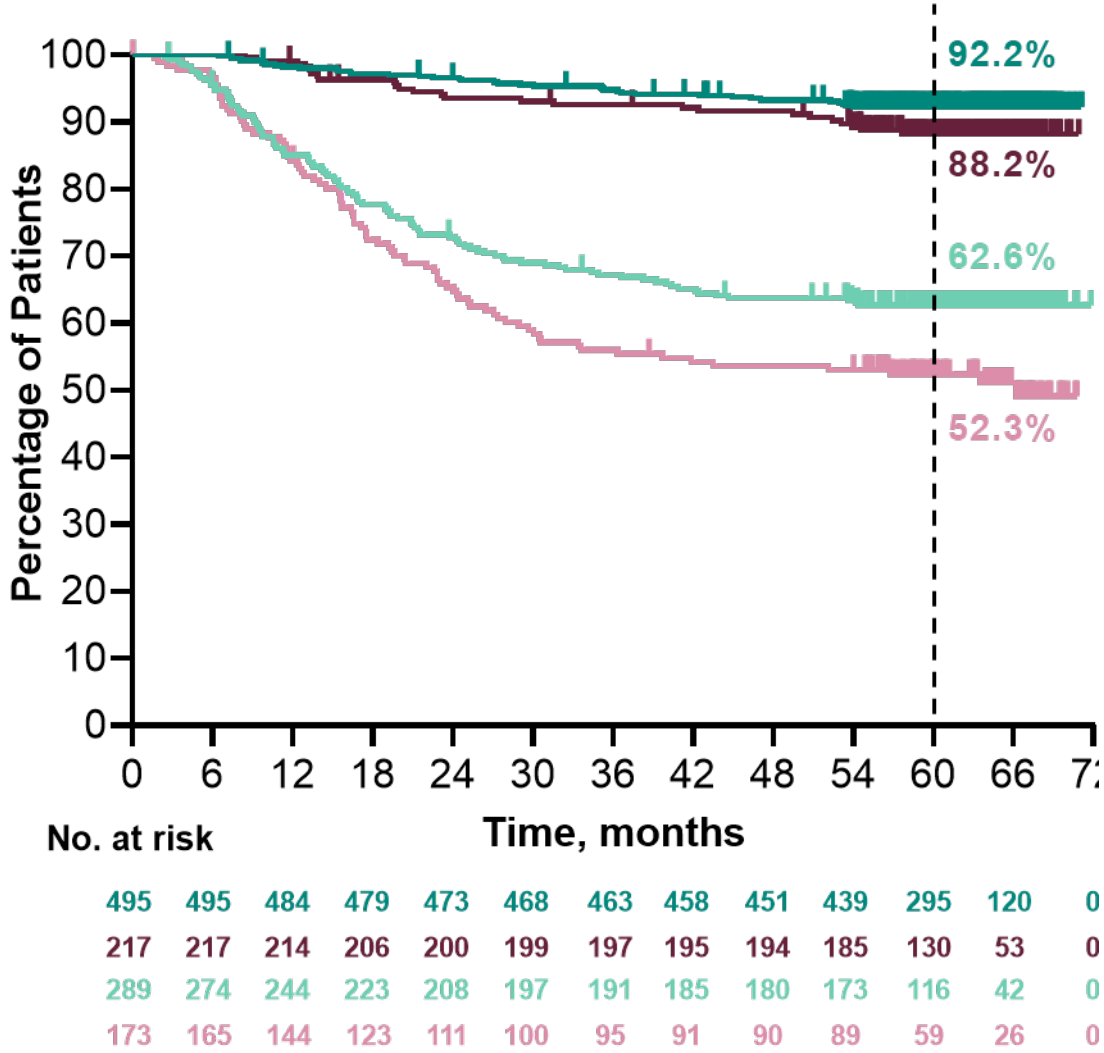
KEYNOTE-522: EFS by PCR



? Benefit from adjuvant ICB

38% event rate despite neo+adjuvant ICB

KEYNOTE-522: EFS by PCR



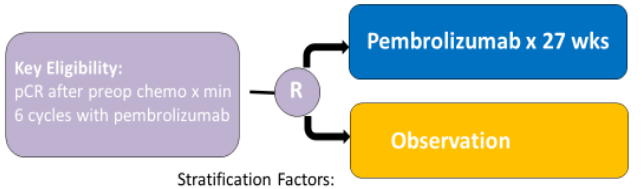
? Benefit from adjuvant ICB

38% event rate despite neo+adjuvant ICB

Preop Data-DXd + Durvalumab, Sac-TMT + Pembro and HER3-DXd + Pembro

OptimICE-pCR

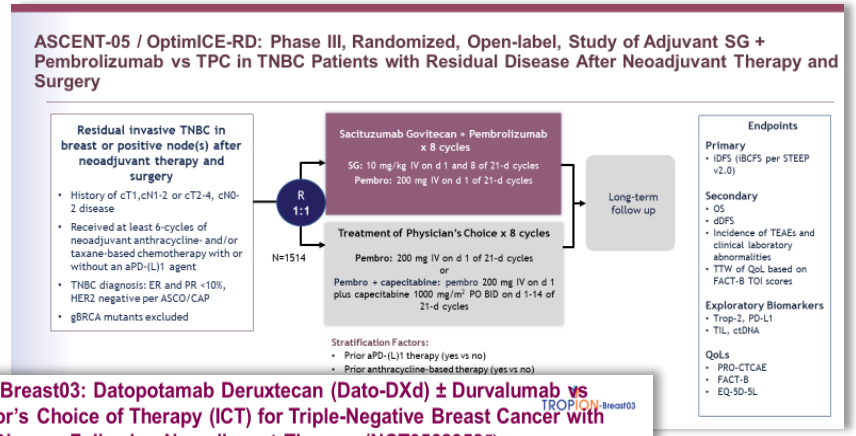
A Randomized, Open-label, Phase 3 Study of Adjuvant Pembrolizumab Versus Observation in Triple Negative Breast Cancer with pCR After Surgery and Neoadjuvant Chemotherapy and Checkpoint Inhibitor Therapy

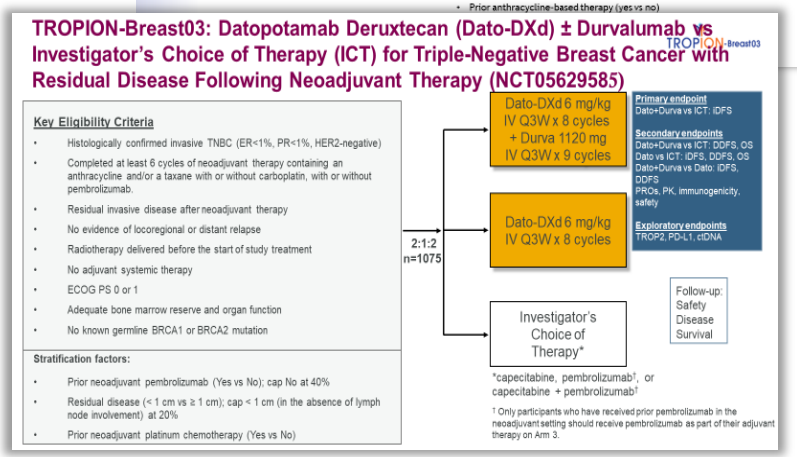


Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

- **Primary Objective:**

To evaluate whether observation results in a non-inferior RFS compared to adjuvant pembrolizumab in early-stage TNBC patients who achieve a pCR after neoadjuvant chemotherapy with ICI therapy

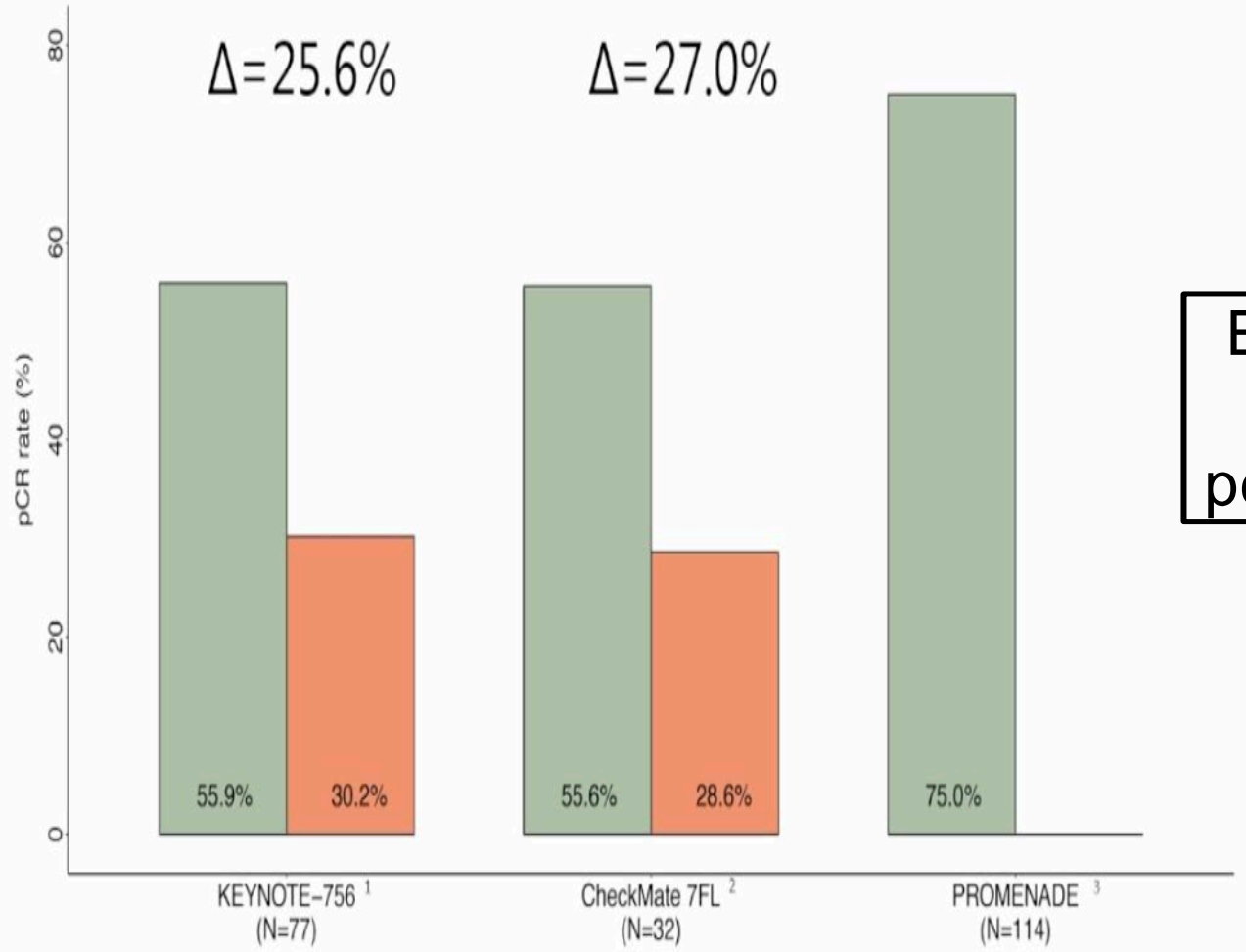




TroFuse Adjuvant Sac-TMT + Pembro

Do pts with ER low disease benefit from immunotherapy?

Patients with ER-Low Positive Breast Cancer Benefit from Preoperative Immunotherapy added to Chemotherapy



ER-Low Positive (1-10%) can be treated as TNBC per NCCN guidelines (plus ET)

[1] Cardoso et al. ESMO 2023; [2] Loi et al. SABCS 2023; [3] Cherifi et al. ESMO 2024

Phase II NeoPACT: Neoadjuvant Pembrolizumab + Carboplatin/Docetaxel without Anthracyclines (n=115)

Overall pCR 58%

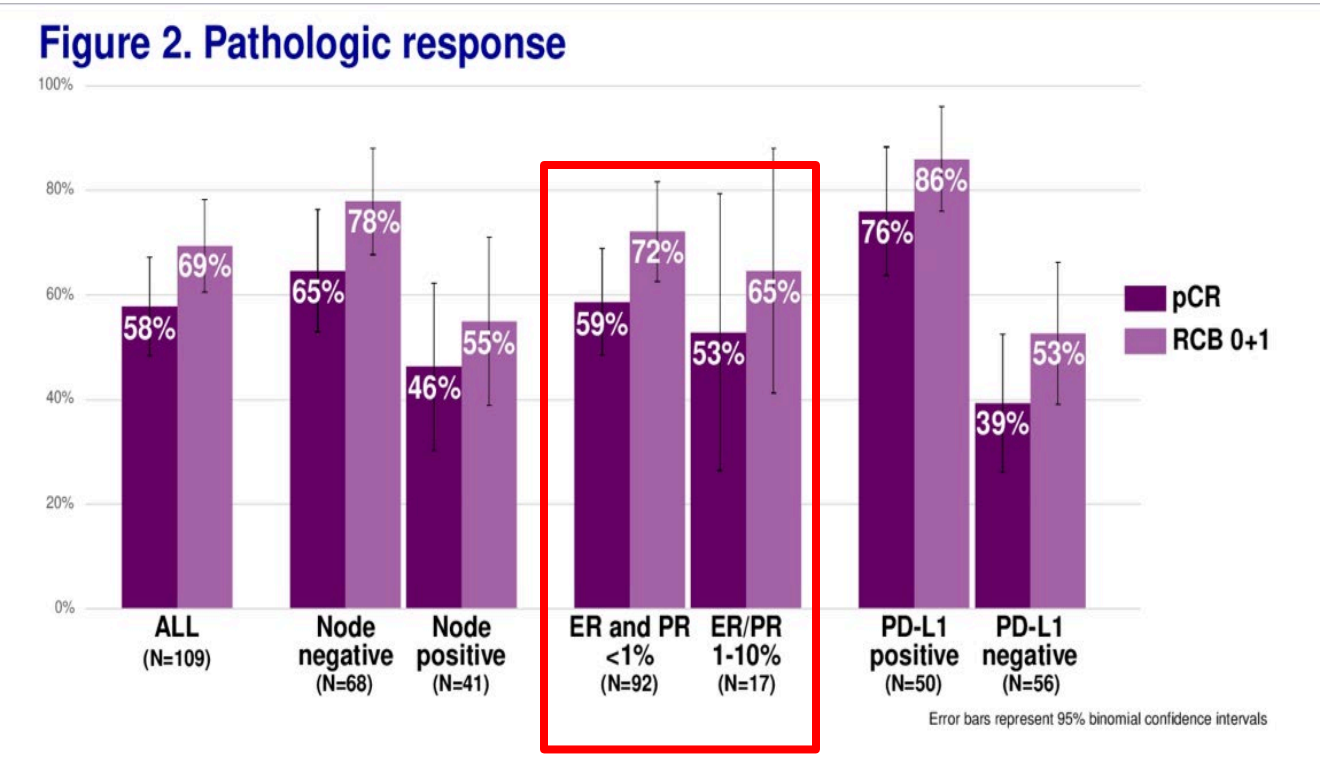
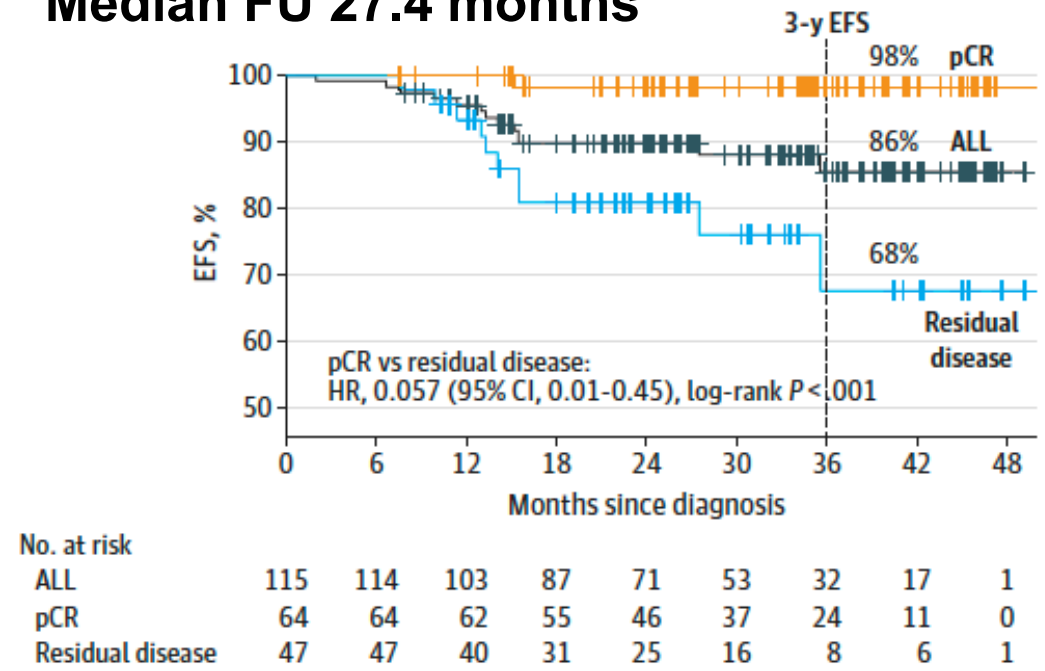


Figure 2. Event-Free Survival (EFS) of Patients in the Intent-to-Treat Group (N = 115)

Median FU 27.4 months



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

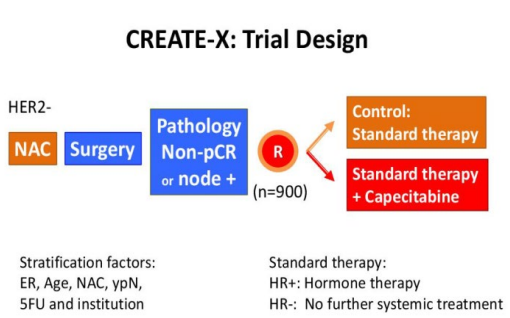
≥Grade 3 IRAEs 3.8%

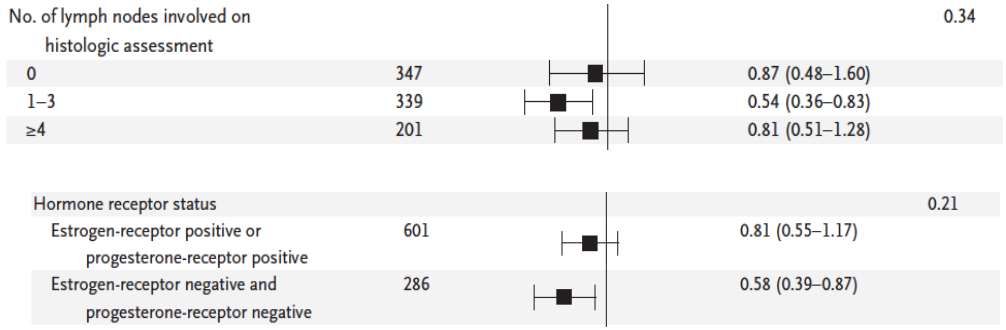
SCARLET Trial" NeoPACT vs KN522 in Stage II/III TNBC

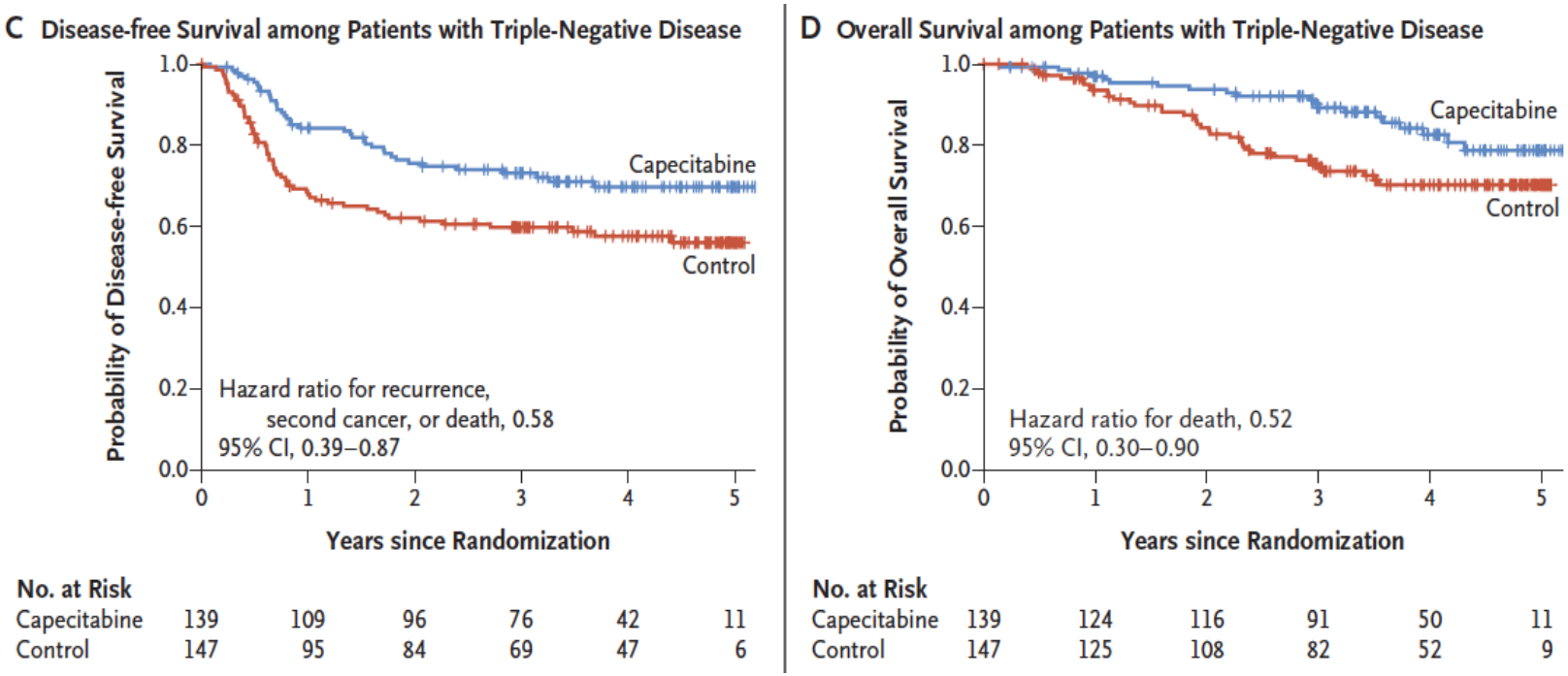
Sharma et al. JAMA Oncol 2024 (PMID: 37991778)

Which adjuvant therapies improve outcomes in pts with residual disease after preoperative therapy?

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

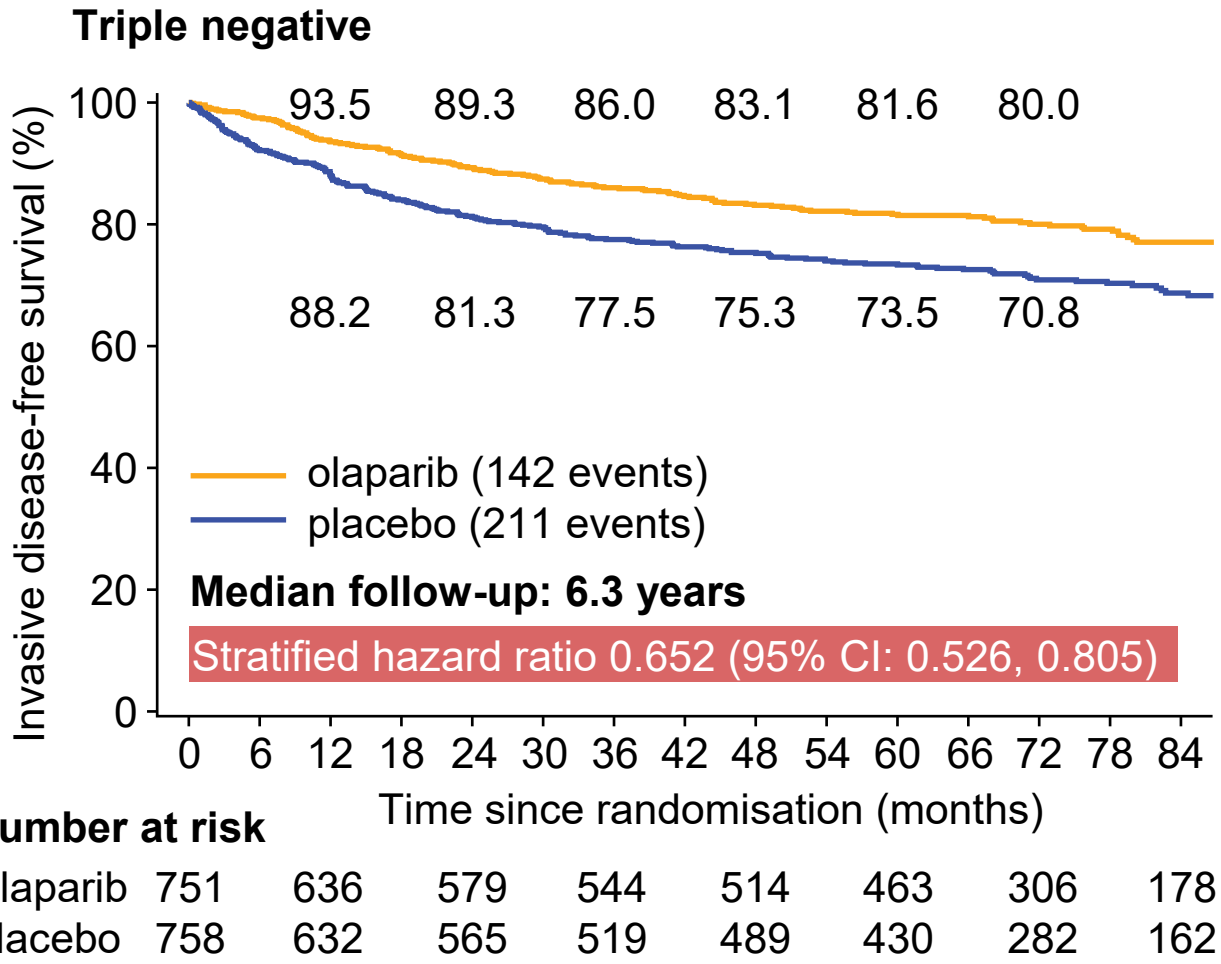


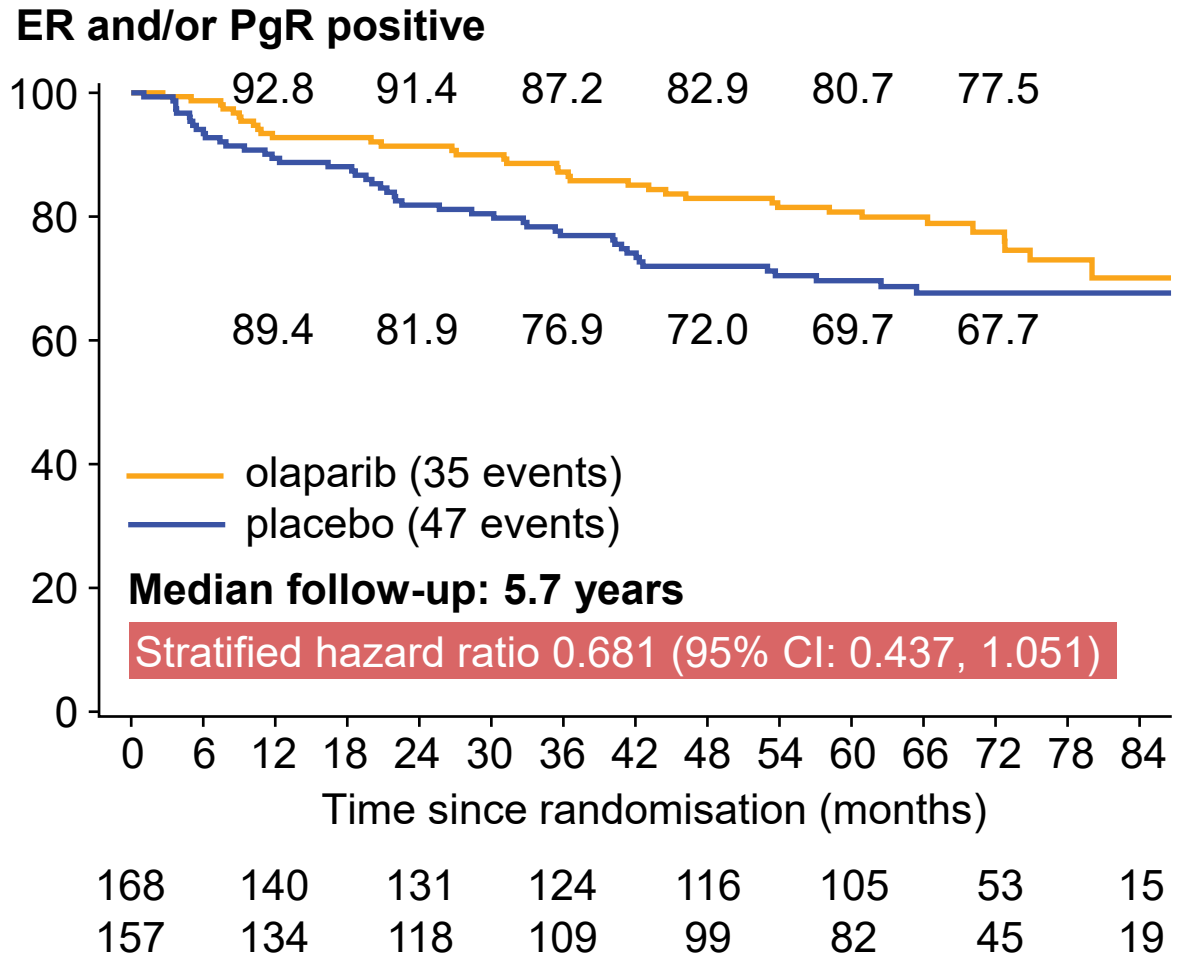




Masuda et al. N Engl J Med. 2017 (PMID: 28564564)

IDFS with Olaparib by HR Status in gBRCA1/2 high risk EBC pts in OlympiA Trial



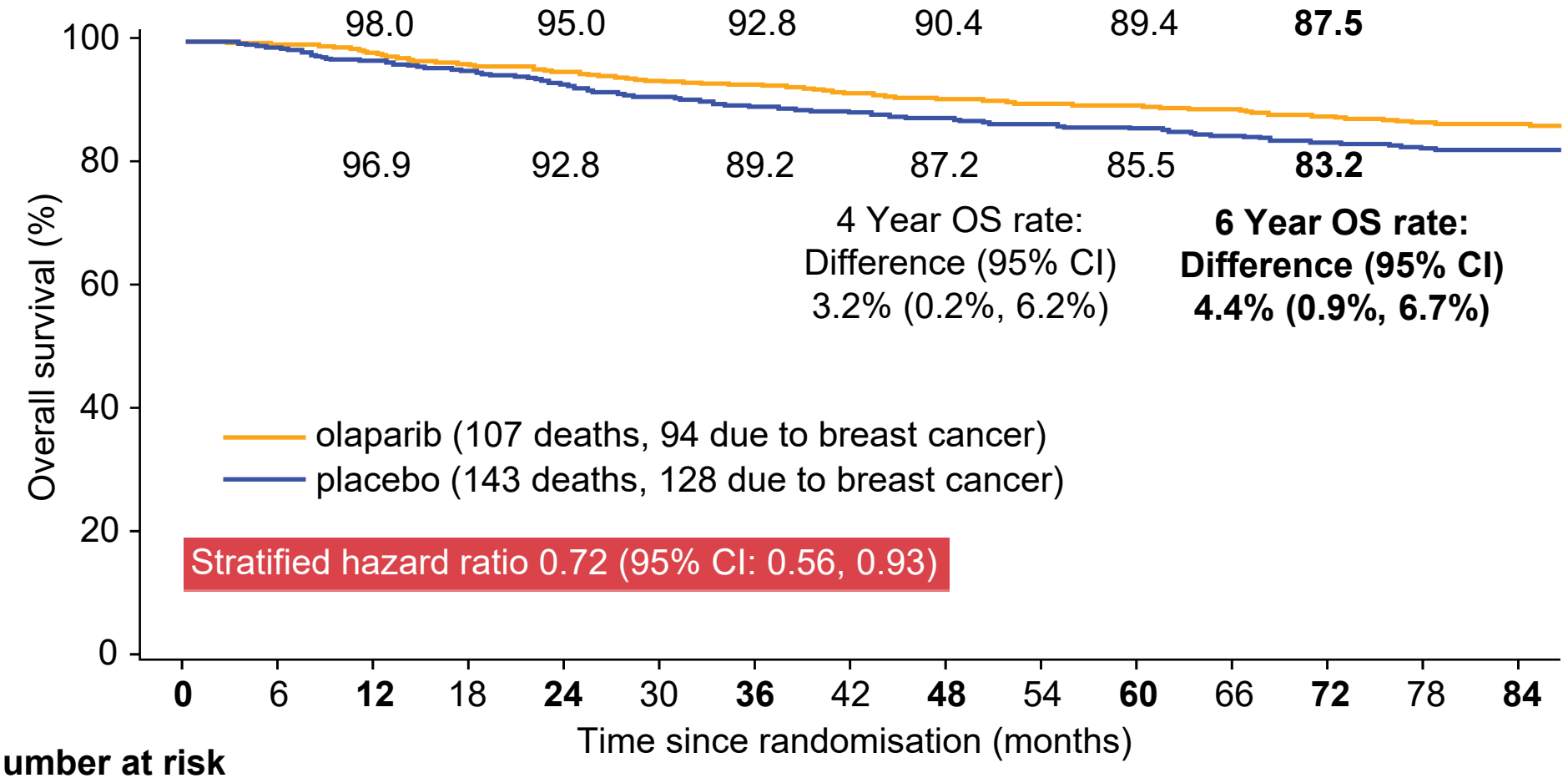


Number at risk

Olaparib	751	636	579	544	514	463	306	178
Placebo	758	632	565	519	489	430	282	162

Olaparib	168	140	131	124	116	105	53	15
Placebo	157	134	118	109	99	82	45	19

Analysis of OS (ITT) n OlympiA Trial



Number at risk

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

Does adjuvant pembro improve outcomes if pts did not receive preop chemo/pembro?

A-BRAVE Trial - Study Design

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 taxane (neo)-adjuvant ChemoRx
- Tissue samples for central PD-L1 assessment
- Randomization <10 weeks from last chemo or surgery

- **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=477

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

Observation

In case of ER 1-9%, adjuvant HT allowed at discretion of treating physicians.
Whenever indicated, radiotherapy allowed concomitantly with avelumab.

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

Primary efficacy objectives
- Disease-free survival (DFS)
- DFS in Stratum B (post-neoadjuvant)

Secondary efficacy objectives
- Overall survival (OS)
- DFS in PD-L1 positive patients*

Safety objectives
- Overall safety of avelumab

Investigator-driven study, sponsored by University of Padova.
Drug supply and Grant support by Merck KGaA.

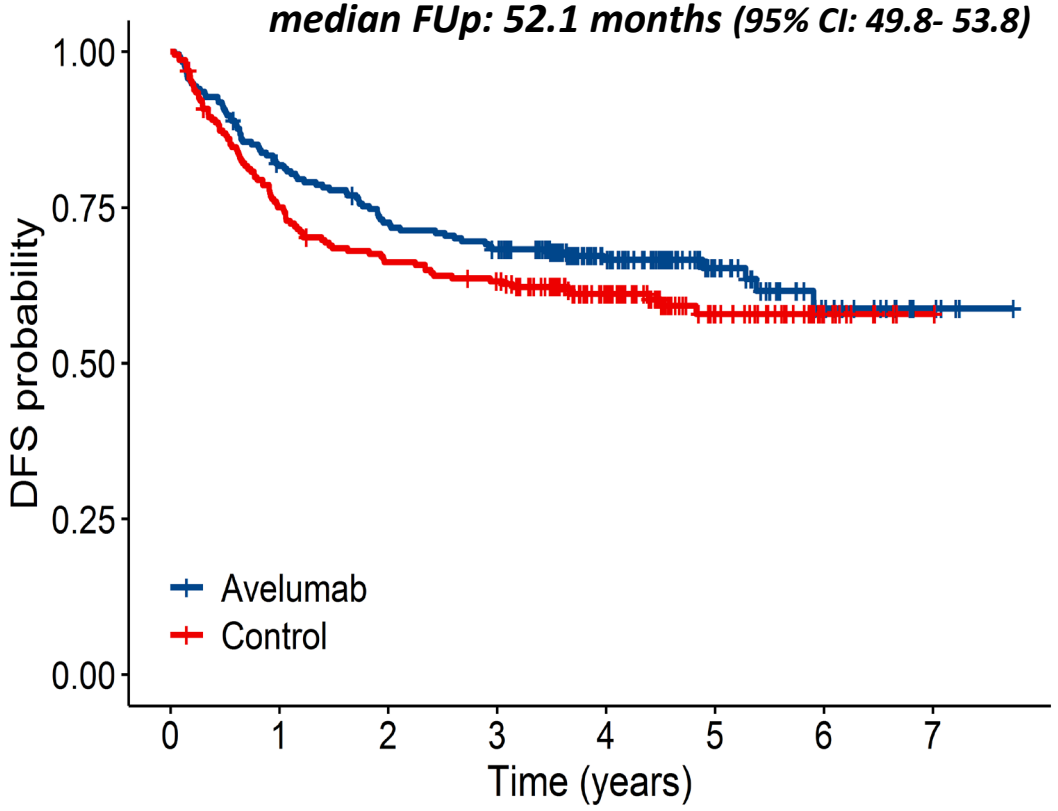
Conte PF et al. Ann Oncol 2025

A-BRAVE Trial – Disease-free Survival

Conte PF et al. ASCO 2024

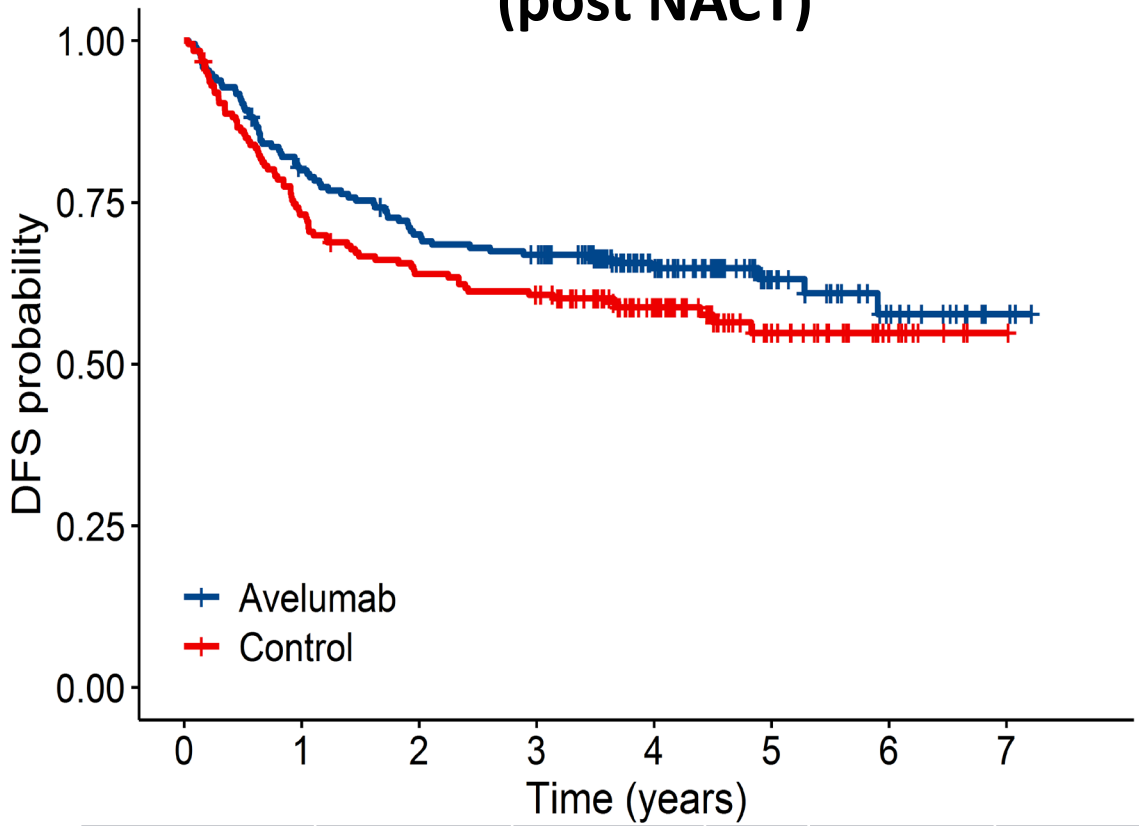
Disease-Free Survival, ITT

median FUp: 52.1 months (95% CI: 49.8- 53.8)



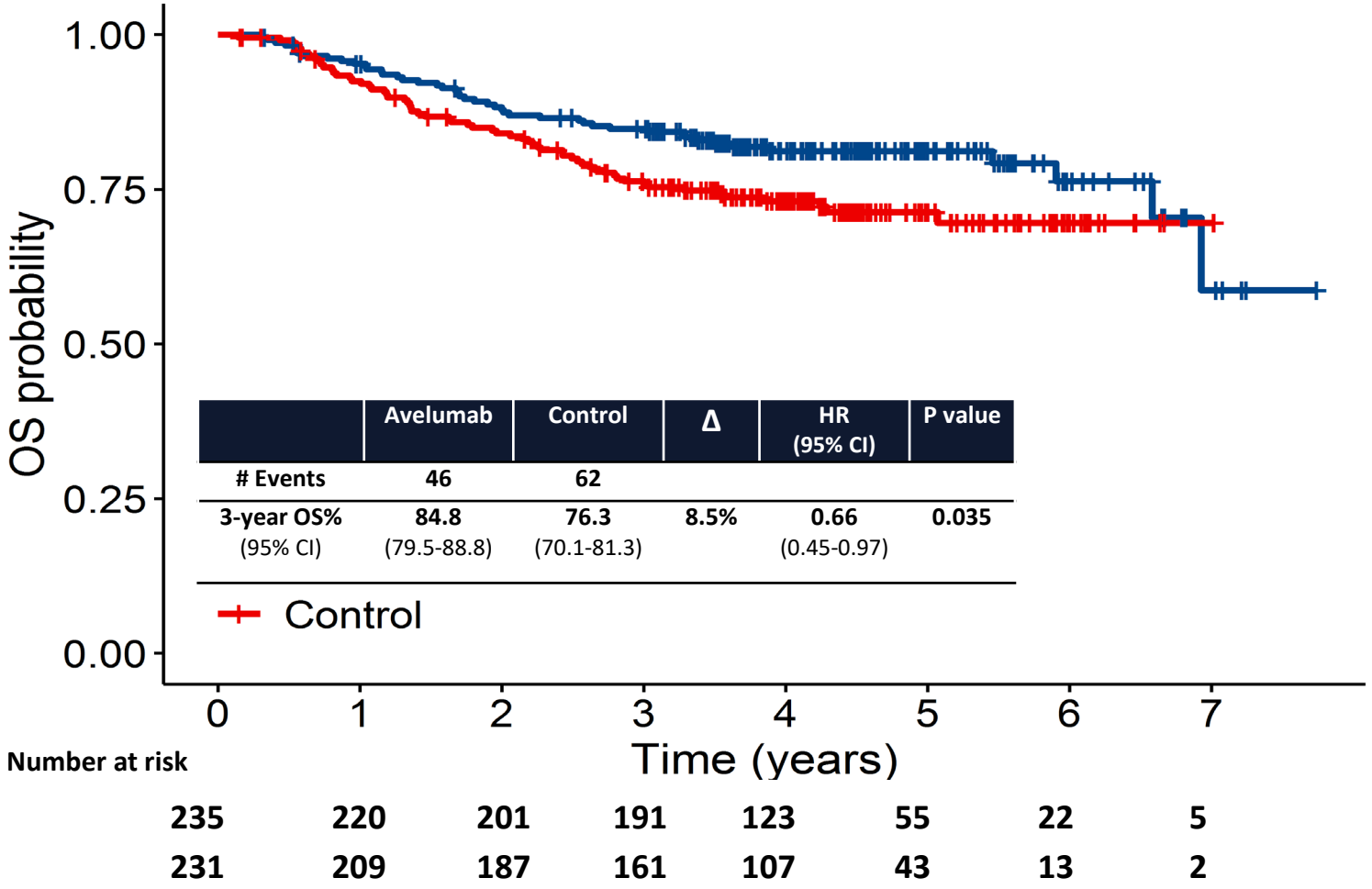
	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	**81**	**91**			
3-year DFS% (95% CI)	**68.3** (61.9-73.8)	**63.2** (56.5-69.0)	**5.1 %**	**0.81** (0.61-1.09)	**0.172**

Disease-Free Survival, Stratum B (post NACT)



	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**

A-BRAVE Trial – ITT Overall Survival



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	46	62			
3-year OS% (95% CI)	84.8 (79.5-88.8)	76.3 (70.1-81.3)	8.5%	0.66 (0.45-0.97)	0.035

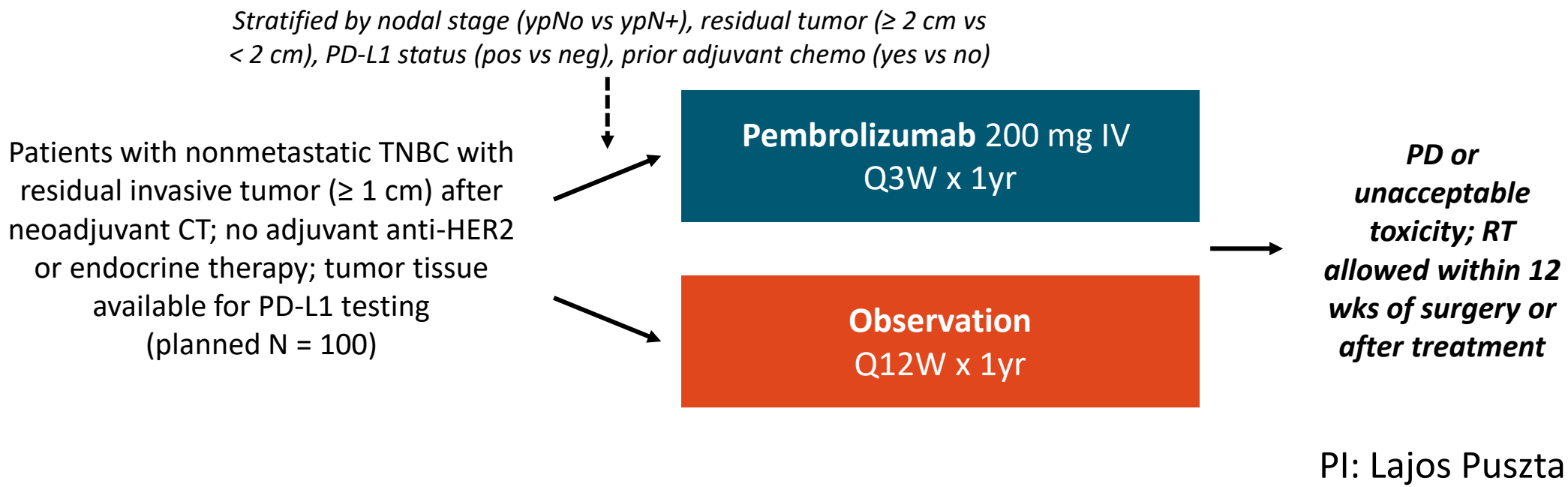
Number at risk

235	220	201	191	123	55	22	5
231	209	187	161	107	43	13	2

Conte PF et al. Ann Oncol 2025

Is adjuvant pembrolizumab effective in TNBC patients with RD after neoadjuvant chemotherapy?

- SWOG S1418/NRG BR-006 Randomized phase III trial

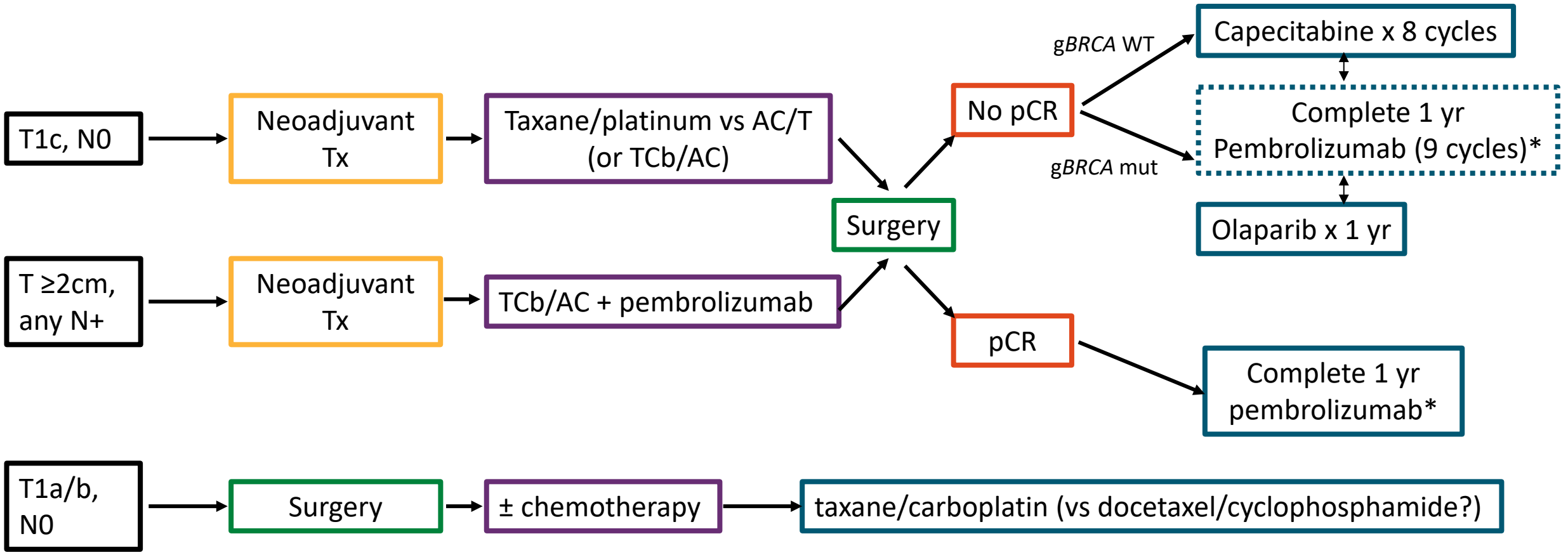


PI: Lajos Pusztai

- Primary endpoints: iDFS, severity of fatigue, physical function
- Secondary endpoints: OS, DRFS, safety, QoL

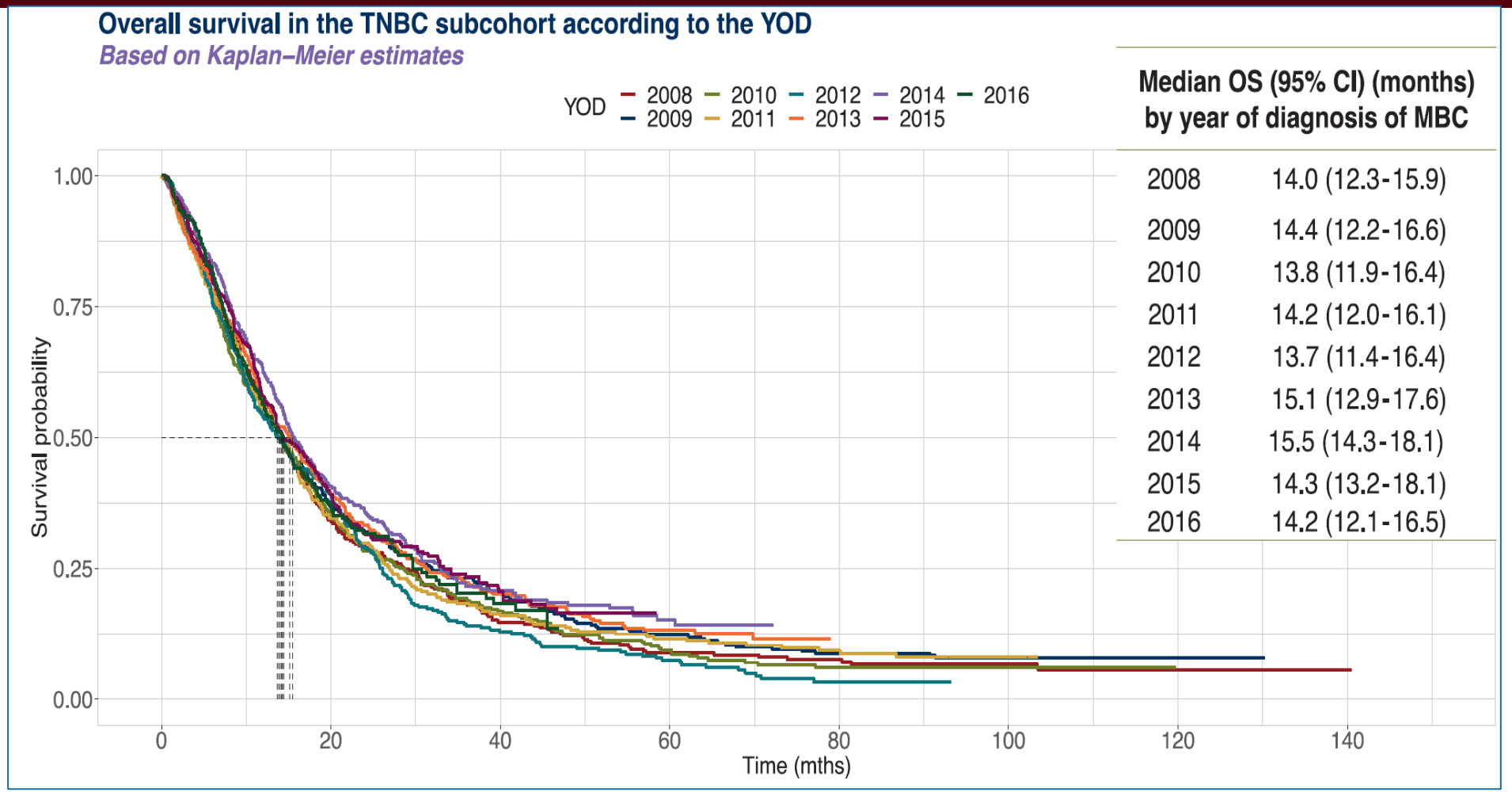
NCT02954874.

Strategy for Managing Patients With Stage I-III TNBC



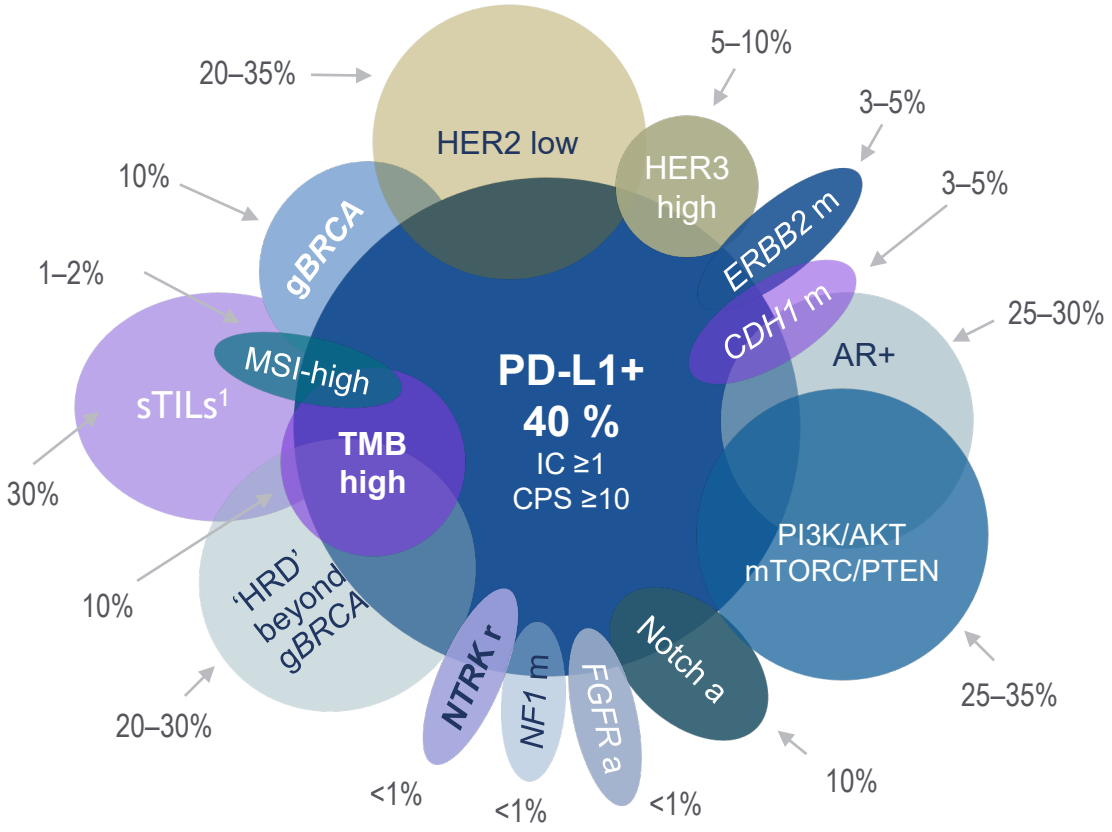
*For patients who received neoadjuvant chemotherapy plus pembrolizumab

Metastatic TNBC represents one of the biggest unmet needs in breast oncology



Median OS has remained <18 months for decades, with improvements seen only in the ~20–30% of PD-L1–positive patients eligible for chemo-immunotherapy (KN355, mOS: 23.0 vs 16.1 mos).

In TNBC, the clinical impact of biomarkers remains limited due to absence of consensus, robust predictive data and availability of registered drugs



Immune checkpoint inhibitors[2–5]	Antiandrogens[12,14]
Other I/O agents (bispecific ab)[6]	Notch inhibitors[11,12]
PARP inhibitors[7,11-13]	NTRK inhibitors[15]
Other DNA damaging agents[7]	ROS1 inhibitors[16]
HER2/HER3-directed ADCs[8,9]	FGFR inhibitors[17]
HER2-3 TKI[10]	MEK inhibitors[11]
PI3K/AKT/mTOR inhibitors[11,12]	BET inhibitors[13]
CDK4/6-inhibitors[11]	…

1. Brown LC, et al. *Cancer J.* 2021;01:27(1):25–31; 2. Emens L, et al. *J Natl Cancer Inst.* 2021;113(8):1005–1016; 3. Obeid E, et al. Presentation at SABCS 2017. Abstract PD6-03; 4. Winer E, et al. Presentation at ASCO Virtual Meeting 2020. Abstract 1013; 5. Kurata K, et al. *Cancer Res.* 2019;79(suppl 4):P1-06-11; 6. Sobhani N, et al. *Int J Mol Sci.* 2020;21:2011; 7. Hartman AR, et al. *Cancer.* 2012;118:2787–2795; 8. Schettini F, et al. *NPJ Breast Cancer.* 2021;7:1; 9. Tarantino P, et al. *J Clin Oncol.* 2020;38:17:1951–1962; 10. Schlam I, Swain SM. *NPJ Breast Cancer.* 2021;7:56; 11. Bareche Y, et al. *Ann Oncol.* 2018;29:895–902; 12. Giuli M, et al. *J Oncol.* 2019:8707053; 13. Aftimos P, et al. Presentation at SABCS 2020. Abstract PS11-10; 14. Gucalp A, et al. *Curr Probl Cancer.* 2016;40:141–150; 15. Rosen E, et al. *Cancer Res.* 2021;81(suppl 4):PS11–06; 16. Bajrami I, et al. *Cancer Discov.* 2018;8(4):498–515; 17. Chew C, et al. *Cell Commun Signal.* 2020;18;13.

KEYNOTE-355 Study Design (NCT02819518)

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression[a]
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

R 2:1

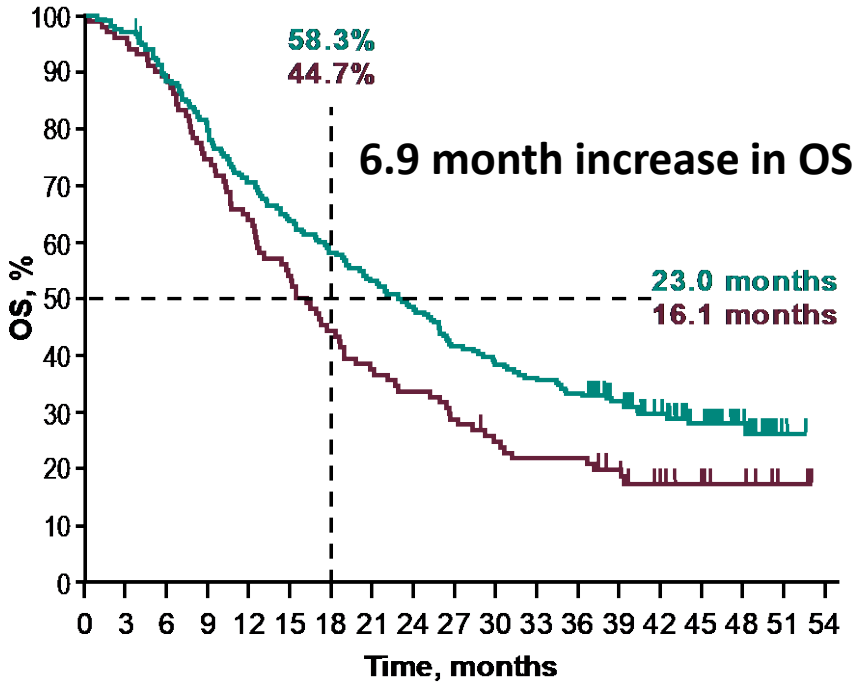
- Pembrolizumab[b] + Chemotherapy[c]
- Placebo[d] + Chemotherapy[c]

→ Progressive disease[e]/cessation of study therapy

Stratification Factors:
- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 or CPS <1)[f]
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

OS: PD-L1 CPS ≥10

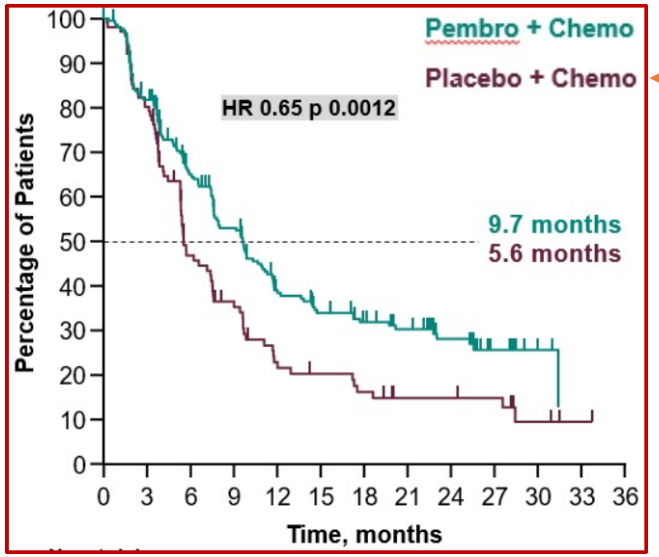
	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		



No. at risk

220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

PFS: PD-L1 CPS ≥10



Prespecified P value boundary of 0.00411 met

PD-L1 CPS≥10: only 38% of pts

Cortes et al, Lancet 2020; Rugo et al , ESMO 2021; Cortes et al, NEJM 2022

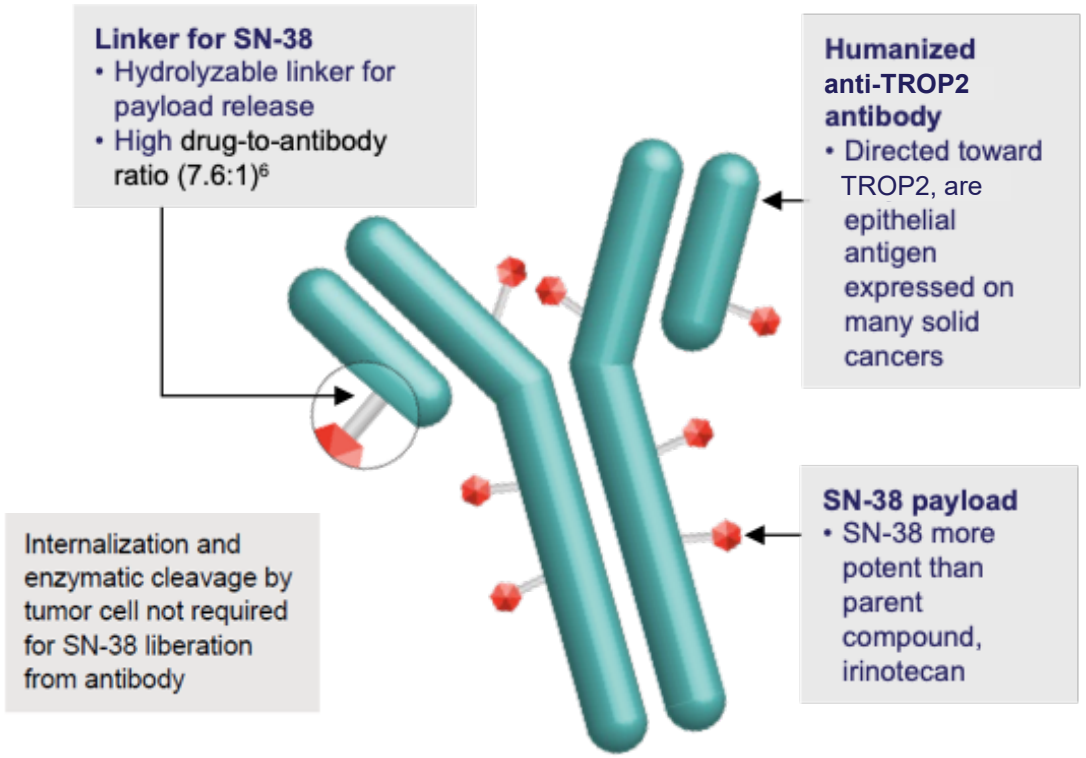
Will ADC +/- IO Become the New 1L SOC for mTNBC?

TROP2-directed ADCs

	Sacituzumab govitecan (IMMU-132)	Datopotamab deruxtecan (DS-1062a)	Sacituzumab tirumotecan (MK-2870)
Antibody	hRS7 Humanized IgG1 mAb	MAAP-9001a Humanized IgG1 mAb	hRS7 Humanized IgG1 mAb
Payload	SN38 (DNA Topoisomerase I inhibitor)	DXd (DNA Topoisomerase I inhibitor)	KL610023 (DNA Topoisomerase I inhibitor)
Linker Cleavage	Enzymatic and pH-dependent	Enzymatic	Enzymatic and pH-dependent
Bystander Effect	Yes	Yes	Yes
DAR	7.6	4	7.4
Half-life	11-14h	~5 days	57h
Dosing	D1, D8 of Q3W schedule	Q3W	Q2W

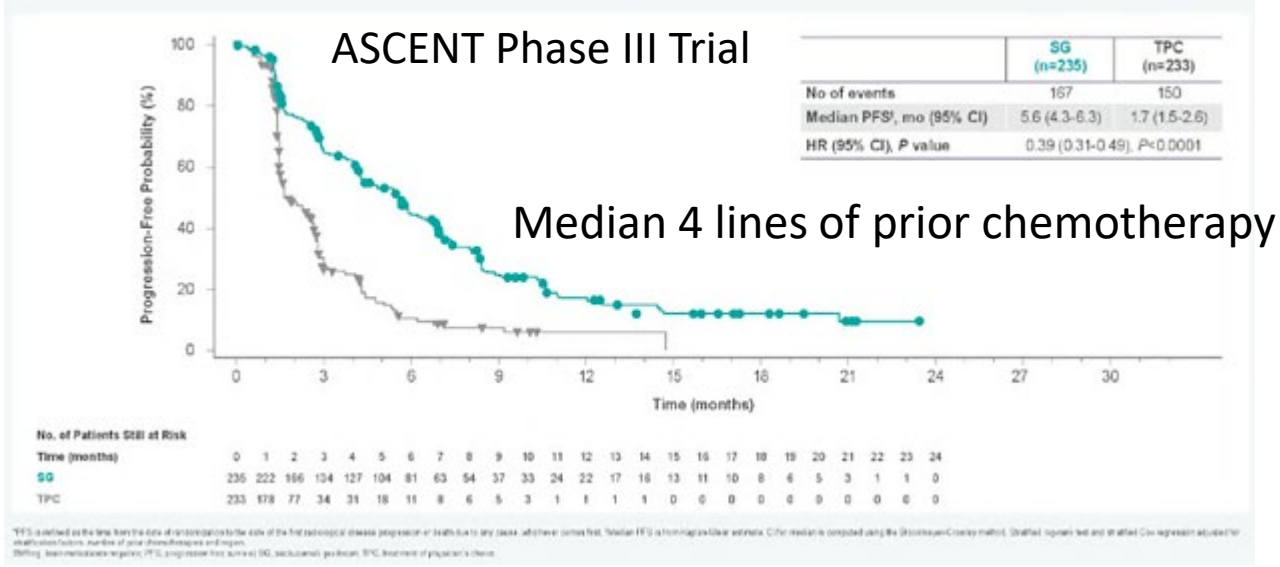
Sands J et al. ASCO 2018; Okajima D et al. ASCO 2018; Bardia A et al. ESMO Breast Cancer 2021; Cheng Y et al. Front Oncol 2022.

Sacituzumab Govitecan (SG): First-in-Class TROP2–Directed ADC



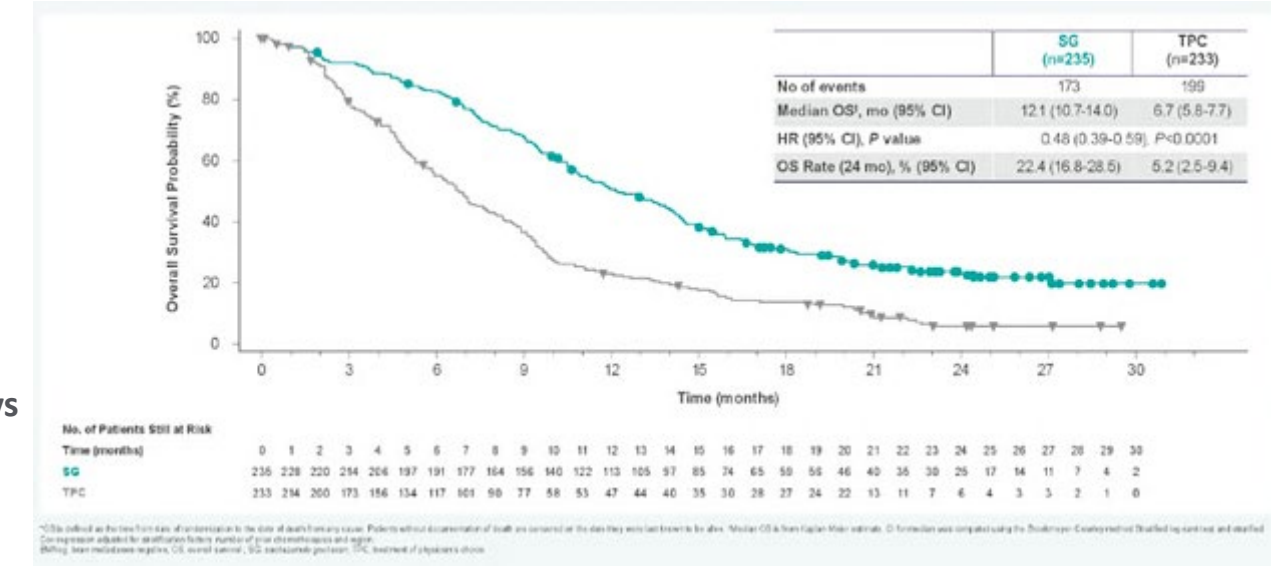
- TROP2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- **Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), FN (6% vs 2%)**
  - G-CSF: 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
  - No severe CV toxicity, no grade >2 neuropathy or grade >3 ILD with SG

ASCENT Phase III Trial



	SG (n=235)	TPC (n=233)
No of events	167	150
Median PFS[1], mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<0.0001	

Median 4 lines of prior chemotherapy



	SG (n=235)	TPC (n=233)
No of events	173	199
Median OS[1], mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	0.48 (0.39-0.59), *P*<0.0001	
OS Rate (24 mo), % (95% CI)	22.4 (16.8-28.5)	5.2 (2.5-9.4)

Bardia et al. *NEJM*, 2021.

ASCENT-04/KEYNOTE-D19 Study Design

Previously untreated, locally advanced unresectable, or metastatic TNBC[a]:

- PD-L1-positive (CPS ≥ 10 by the 22C3 assay[b])
- ≥ 6 months since treatment in curative setting (prior anti-PD-[L]1 use allowed)

N = 443

R 1:1

SG + pembro[d]

(SG 10 mg/kg IV, days 1 and 8 of 21-day cycles; pembro 200 mg, day 1 of 21-day cycles)

n = 221

Chemo* + pembro[d]

(paclitaxel 90 mg/m^2 OR nab-paclitaxel 100 mg/m^2 on days 1, 8, & 15 of 28-day cycles, OR gemcitabine 1000 mg/m^2 + carboplatin AUC 2 on days 1 & 8 of 21-day cycles; pembro 200 mg on day 1 of 21-day cycles)

n = 222

***Eligible patients who experienced BICR-verified disease progression were offered to cross-over to receive 2L SG monotherapy**

All treatment, including SG or chemo, was continued until BICR-verified disease progression or unacceptable toxicity

End points

Primary

- PFS by BICR[e]

Secondary

- OS
- ORR, DOR by BICR[e]
- Safety
- QoL

Stratification factors:

- De novo mTNBC[c] vs recurrent within 6 to 12 months from completion of treatment in curative setting vs recurrent > 12 months from completion of treatment in curative setting
- US/Canada/Western Europe vs the rest of the world
- Prior exposure to anti-PD-(L)1 (yes vs no)

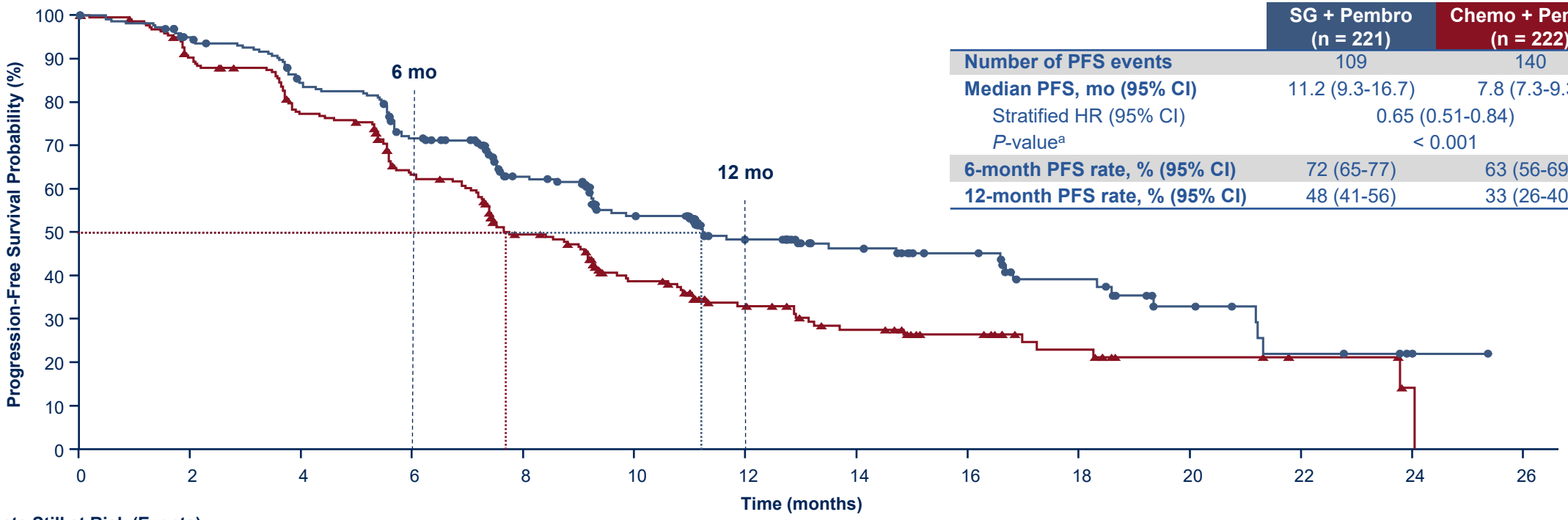
ClinicalTrials.gov identifier: NCT05382286.

[a]TNBC status determined according to standard American Society of Clinical Oncology-College of American Pathologists criteria. [b]Dako, Agilent Technologies. [c]Up to 35% de novo mTNBC. [d]Pembro was administered for a maximum of 35 cycles. [e]Per RECIST v1.1.

AUC, area under the curve; BICR, blinded independent central review; chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; QoL, quality of life; R, randomized; RECIST v1.1; Response Evaluation Criteria in Solid Tumors, version 1.1; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TTR, time-to-response.

Tolaney S et al. ASCO 2025

Progression-Free Survival by BICR



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	109	140
Median PFS, mo (95% CI)	11.2 (9.3-16.7)	7.8 (7.3-9.3)
Stratified HR (95% CI)	0.65 (0.51-0.84)	
P-value[a]	< 0.001	
6-month PFS rate, % (95% CI)	72 (65-77)	63 (56-69)
12-month PFS rate, % (95% CI)	48 (41-56)	33 (26-40)

No. of Patients Still at Risk (Events)

SG + Pembro	221 (0)	202 (11)	174 (33)	142 (59)	105 (75)	78 (89)	58 (96)	42 (98)	34 (99)	22 (103)	11 (106)	6 (109)	2 (109)	0 (109)
Chemo + Pembro	222 (0)	191 (21)	159 (48)	123 (76)	88 (102)	59 (120)	40 (128)	29 (134)	21 (135)	13 (137)	7 (138)	4 (138)	1 (139)	0 (140)

SG + pembro demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo + pembro by BICR analysis, with a 35% reduction in risk of disease progression or death

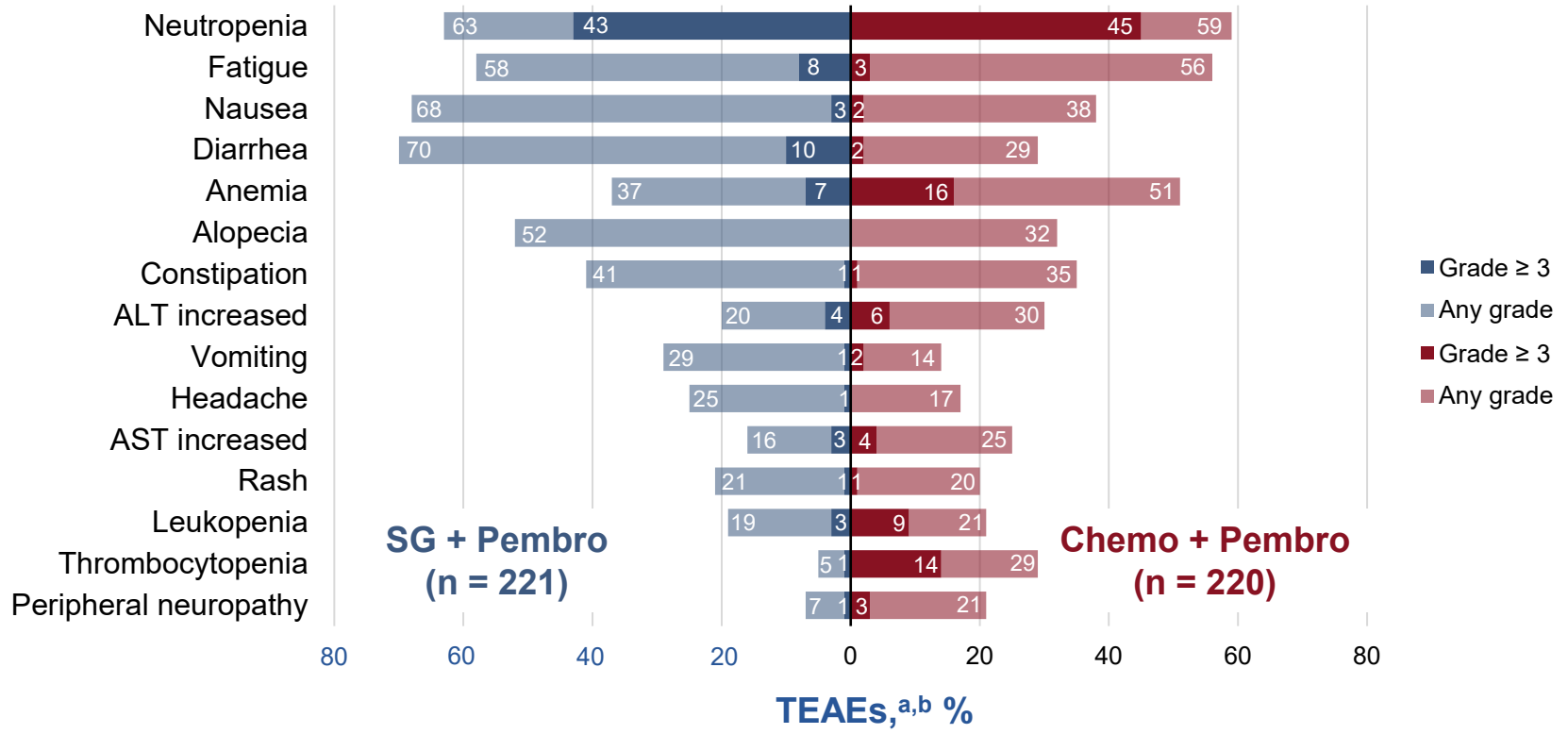
OS data were immature (maturity rate, 26%), however, a positive trend in improvement was observed for SG + pembro vs chemo + pembro

Tolaney S et al. ASCO 2025

Data cutoff date: March 3, 2025.
[a]Two-sided *P*-value from stratified log-rank test.
BICR, blinded independent central review; chemo, chemotherapy; HR, hazard ratio; PFS, progression-free survival; pembro, pembrolizumab; SG, sacituzumab govitecan.

Most Common Adverse Events (≥20% in any group)

The AEs observed are consistent with the known profiles of both SG and pembro



Results from ASCENT-04/KEYNOTE-D19 support the use of SG + pembro as a potential new standard of care for patients with previously untreated, PD-L1+, locally advanced unresectable or metastatic TNBC

TEAEs were defined as any adverse events that began or worsened on or after the first dose date of study drug up to 30 days (or up to 90 days for SAEs) after the last dose date of study drug or the initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first. Data cutoff date: March 3, 2025.

[a]TEAEs were included if they occurred in ≥ 20% of patients in either arm. [b]Combined preferred terms of Neutropenia includes neutrophil count decreased, Leukopenia includes white blood cell count decreased, Anemia includes hemoglobin decreased and red blood cell count decreased, Thrombocytopenia includes platelet count decreased, Fatigue includes asthenia.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; chemo, chemotherapy; pembro, pembrolizumab; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

Tolaney S et al. ASCO 2025

ASCENT-03:

MET PRIMARY PFS ENDPOINT

Sacituzumab govitecan vs TPC in 1L PD-L1– mTNBC

1L mTNBC PD-L1–

- Previously untreated, inoperable, locally advanced, or metastatic TNBC
- PD-L1− tumors (CPS <10, IHC 22C3 assay) OR PD-L1+ tumors (CPS ≥10, IHC 22C3 assay) if treated with anti-PD-(L)1 agent in the curative setting
- ≥6 months since treatment in curative setting
- Prior anti-PD-(L)1 agent allowed in the curative setting
- PD-L1 and TNBC status centrally confirmed

N=540
(≤25% *de novo*)

Stratification Factors:

- *De novo* vs recurrent disease within 6-12 months of treatment in the curative setting vs recurrent disease >12 months after treatment in the curative setting
- Geographic region

Sacituzumab govitecan
10 mg/kg IV on
days 1 and 8 of 21-day cycles

TPC Chemotherapy

- **Gem + carbo:** gem 1000 mg/m2 with carbo AUC 2 IV on days 1 and 8 of 21-day cycles
- **Paclitaxel:** 90 mg/m2 IV on days 1, 8, and 15 of 28-day cycles
- **Nab-paclitaxel:** 100 mg/m2 IV on days 1, 8, and 15 of 28-day cycles

Crossover to SG allowed after BICR-verified disease progression

BICR, blinded independent central review; CPS, combined positive score; IHC, immunohistochemistry; mTNBC, metastatic triple negative breast cancer; PD-L1, programmed death ligand 1; R, randomized; SG, sacituzumab govitecan; TPC, treatment of physician's choice. 1. EU Clinical trial register: EudraCT: 2021-005743-79. https://www.clinicaltrialsregister.eu/ctr-search/search/ Accessed April 2022.

TROPION-PanTumor01 Study: Dato-DXd *Efficacy*

ORR by BICR:
- All patients: **32%**
- Topo I inhibitor-naive patients: **44%**

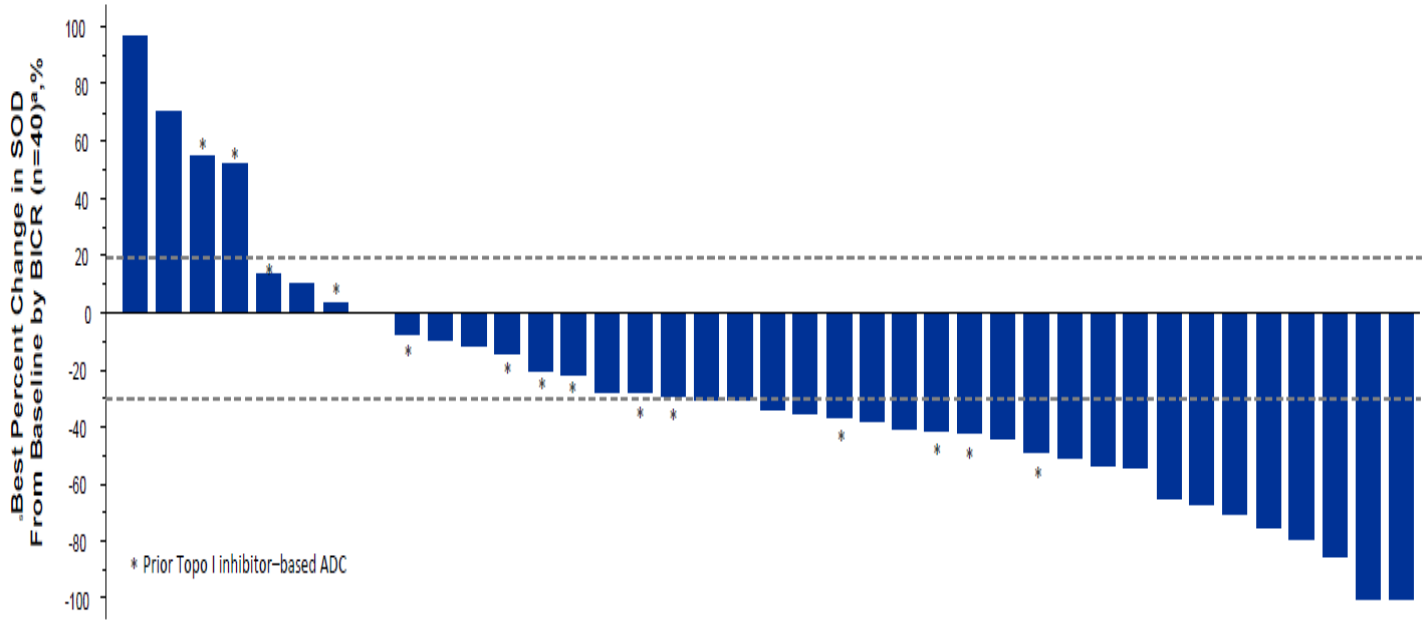
mDOR: 16.8 months in both groups

mPFS:
- All patients: 4.4 months
- Topo I inhibitor-naive patients: 7.3 months

mOS:
- All patients: 13.5 months
- Topo I inhibitor-naive patients: 14.3 months

AEs: Most common TEAEs: stomatitis (73%), nausea (66%), vomiting (39%)

Antitumor Tumor Responses by BICR



Bardia A, et al. *J Clin Oncol.* 2024 Apr 23;42(19):2281–2294.

Ongoing Phase 3 Clinical Trials with Dato-DXd in 1L

TROPION-Breast02[1]

Key Eligibility Criteria:

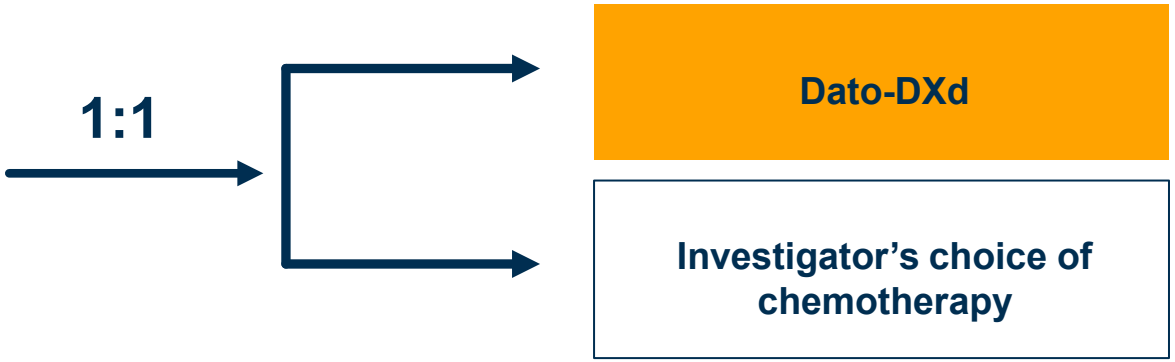
- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1/PDL1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification Factors:

- Geographic location
- DFI (de novo vs DFI ≤ 12 months vs DFI >12 months)

Dual Primary Endpoint:
PFS (BICR) and OS

Secondary Endpoints:
PFS (inv), ORR, DoR, Safety



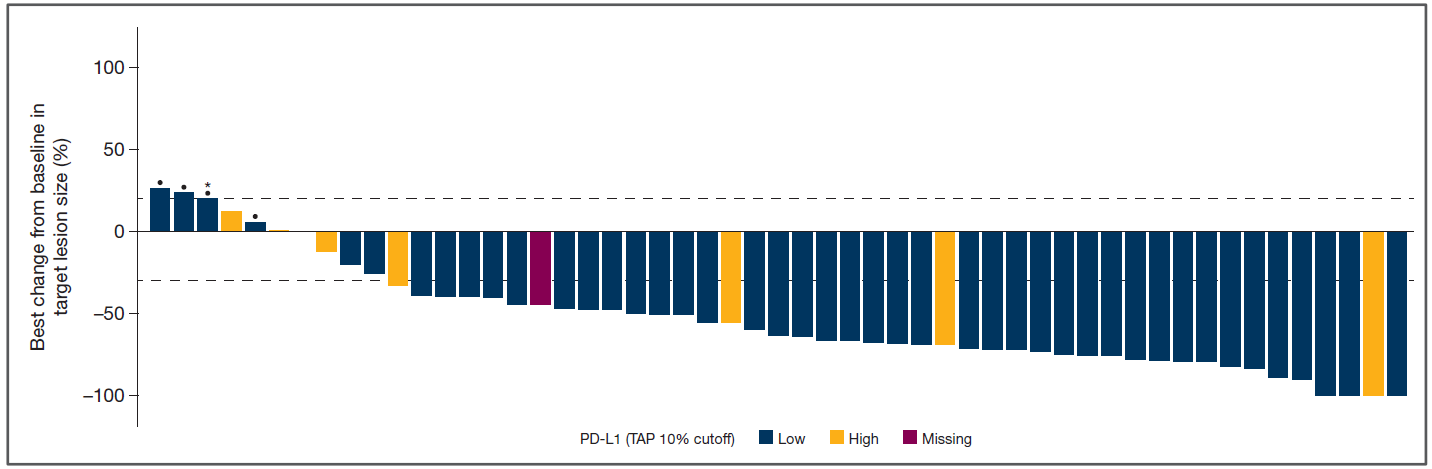
- **1st line therapy for TNBC**
- **PD-L1 negative**

1. https://clinicaltrials.gov/study/NCT05374512

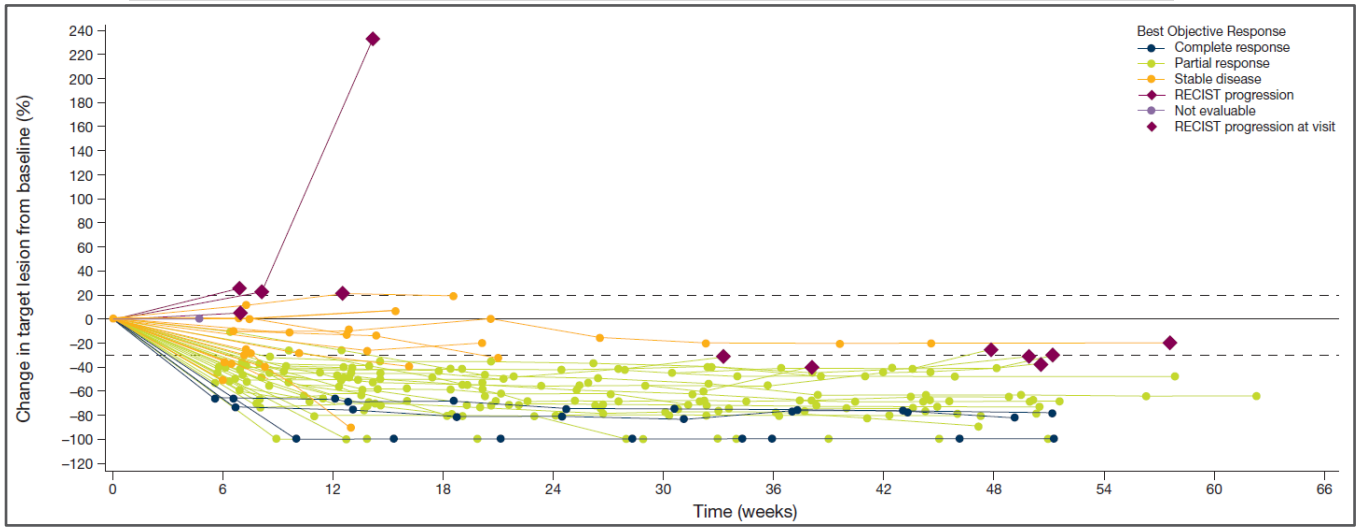
BEGONIA: Dato-DXd + durvalumab in 1L m TNBC

- **Confirmed ORR= 39 (73.6%)**
  - ✓ CR = 4
  - ✓ PR = 35

Best Change from Baseline of Target Lesion Size (n=53)



Change from baseline in sum of target lesions over time



Most responses were durable

✓ Responses in PD-L1 low and PD-L1 high tumors

Schmid P et al. SABCS 2022; PD 11-09.

TROPION-Breast05

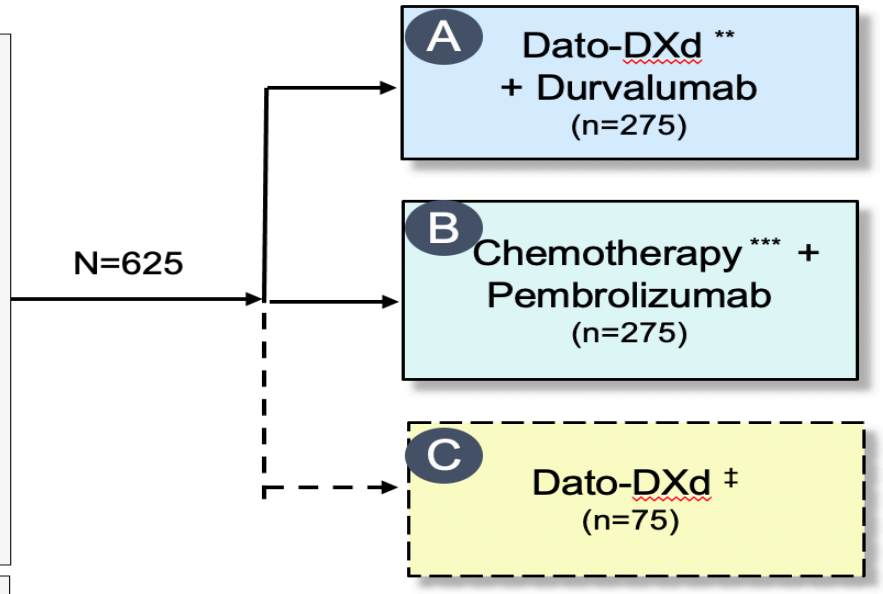
Dato-DXd +/- durva vs TPC + pembro in 1L PD-L1+ mTNBC

Key Eligibility Criteria

- Previously untreated metastatic or locally advanced inoperable TNBC (ER<1%, PR<1%, HER2neg)
- Measurable disease as defined by RECIST v1.1
- Adequate ECOG, hematologic and end-organ function
- PD-L1+ (CPS ≥ 10 IHC 22C3) by central testing
- No active brain metastases
- DFI≥ 6 mo since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

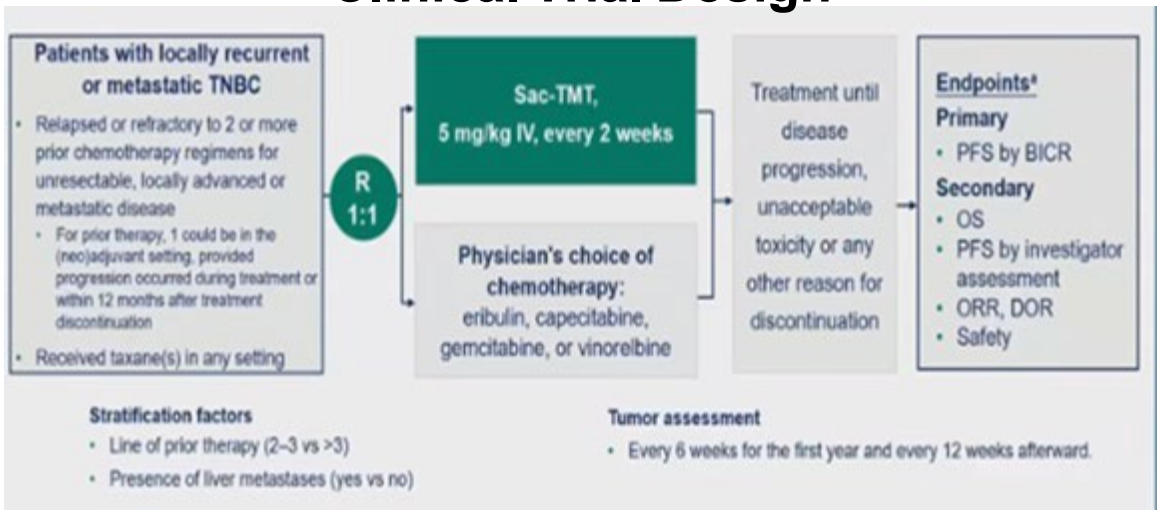
Stratification factors:

- De novo, prior DFI 6 to ≤ 12 mo†, prior DFI >12 mo
- Geographic region (US/Canada/Europe vs Dato-DXd monotherapy arm enrolling countries vs ROW)
- Prior PD-1/PD-L1 treatment for early stage TNBC

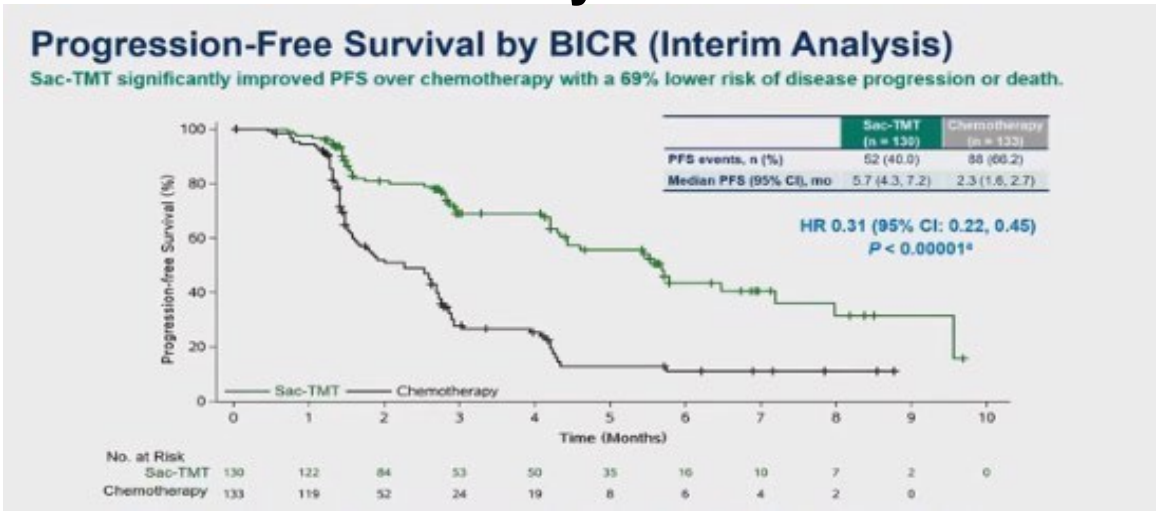


OptiTROP-Breast01: Phase 3 Study of Sacituzumab Tirumotecan in mTNBC

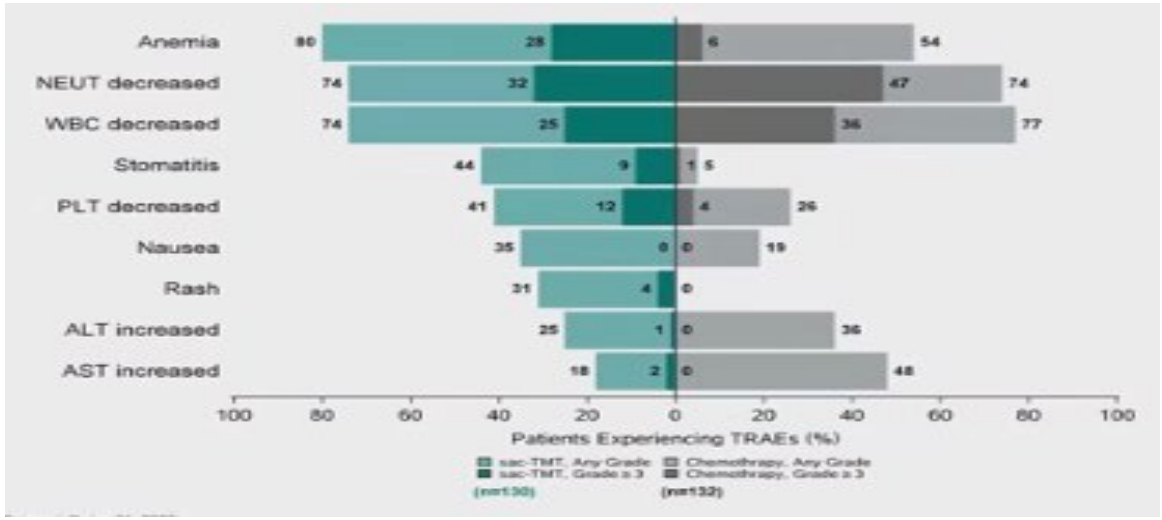
Clinical Trial Design



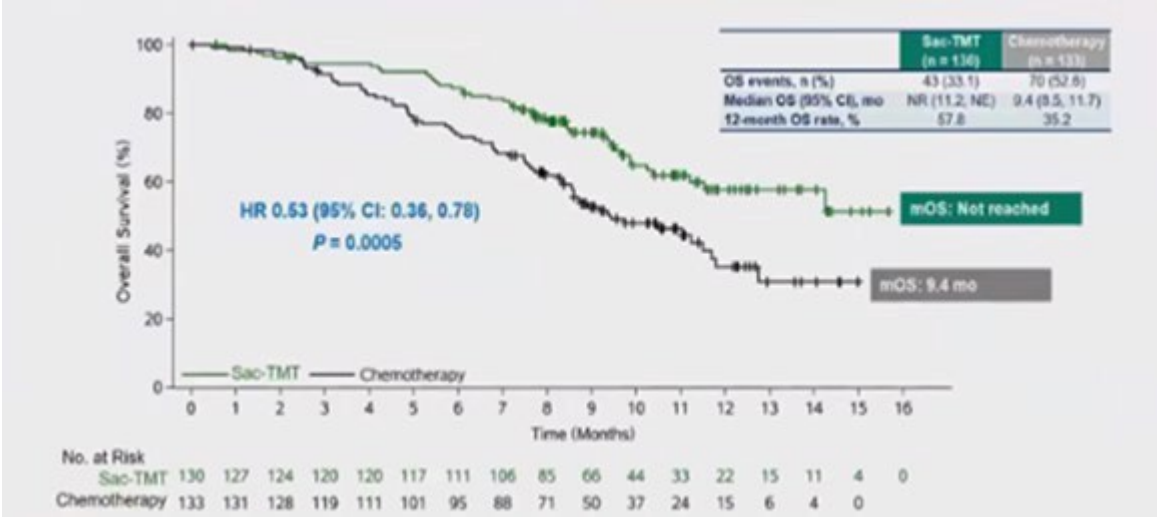
PFS by BICR



TRAEs in ≥30% of pts



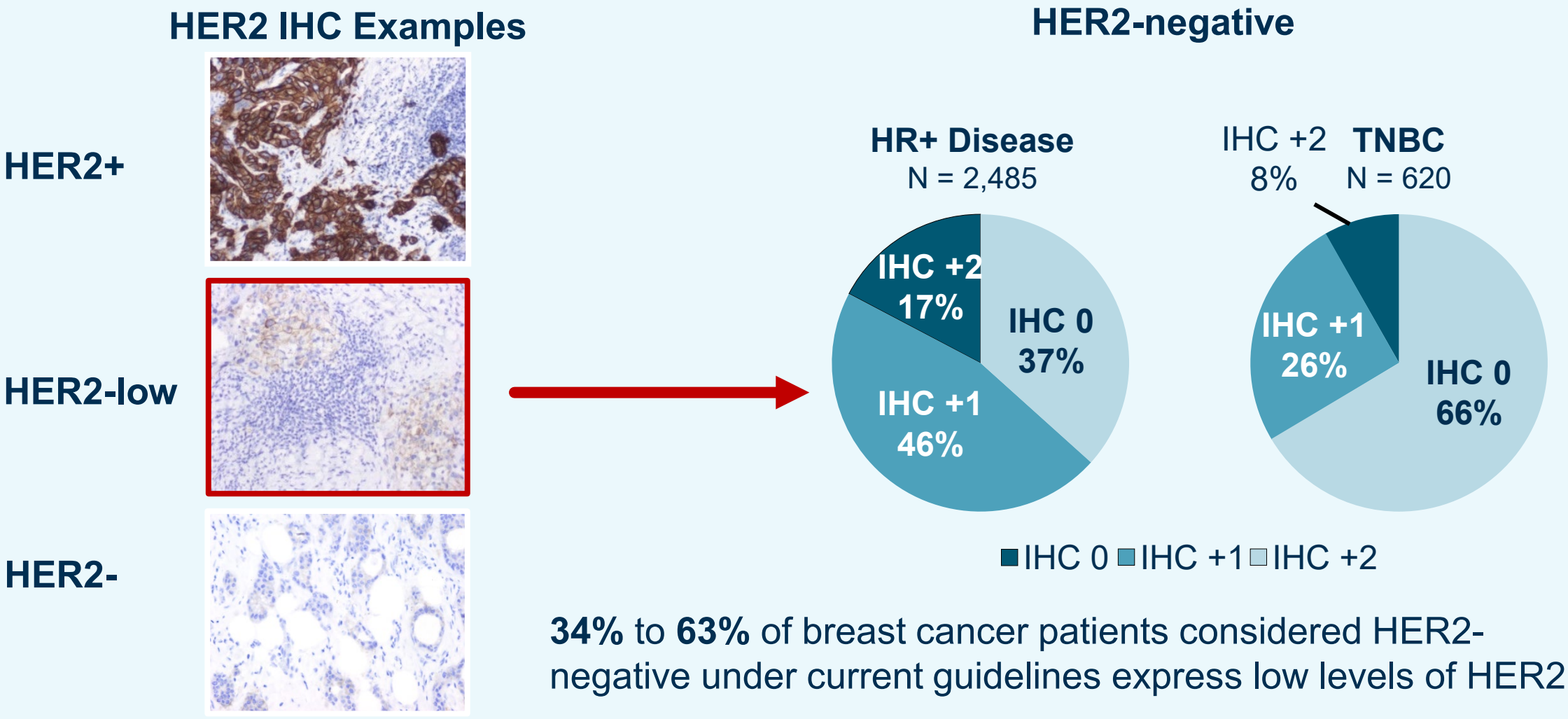
OS



Xu B et al. ASCO 2024. Abstract 104.

1L TroFuse-011 Trial mTNBC PD-L1 CPS < 10: Sac-TMT +/- Pembro vs TPC chemoRx

Prevalence of HER2-low by HR status



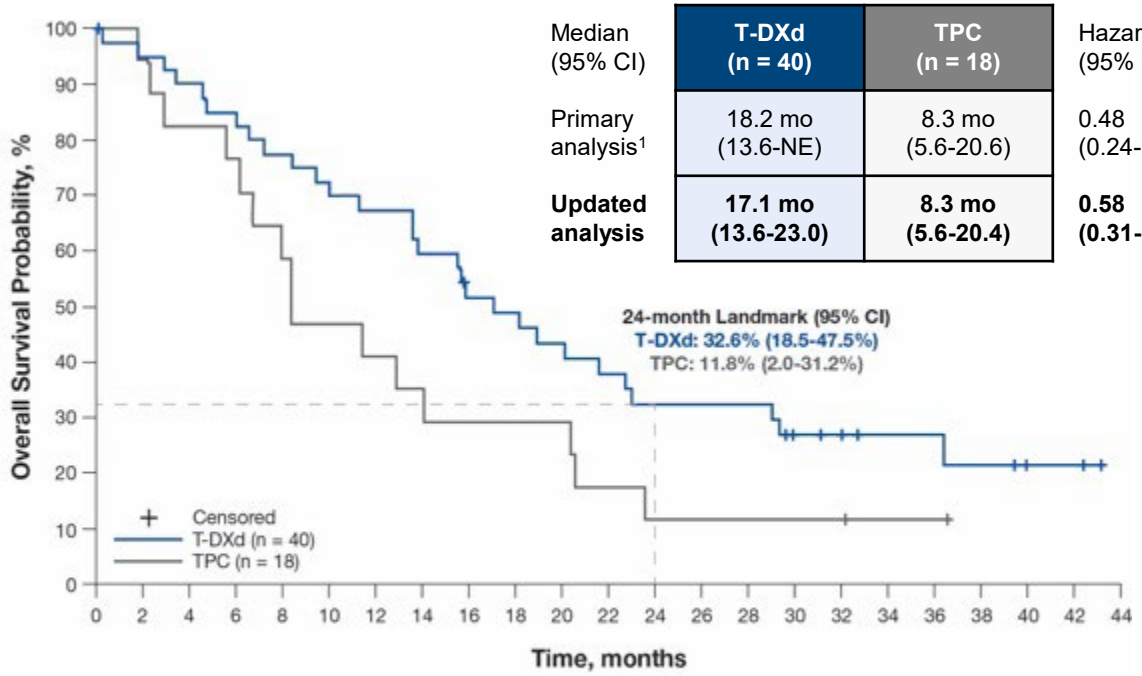
34% to **63%** of breast cancer patients considered HER2-negative under current guidelines express low levels of HER2

Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

DESTINY-Breast04: T-DXd vs TPC Efficacy in HR− HER2 Low MBC (Exploratory Analyses)

Overall Survival

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**



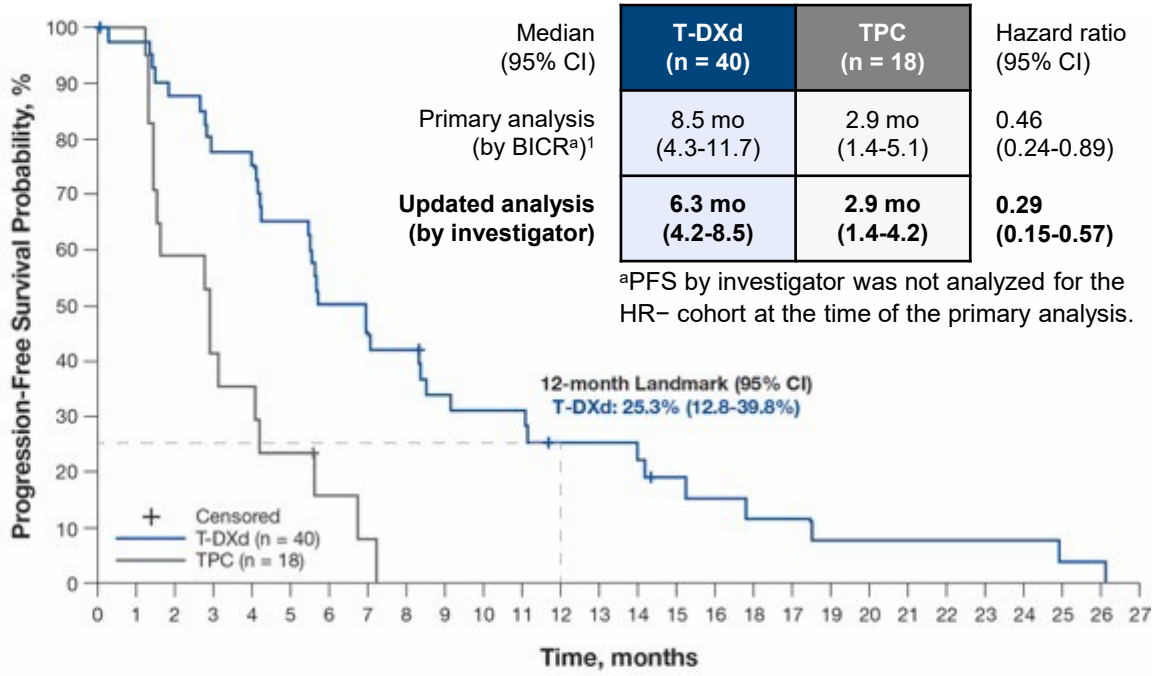
Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.



Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- Median FU now 32 months vs 18.4 at primary analysis
- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

BICR, blinded independent central review; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi et al, NEJM 2022; ESMO 2023

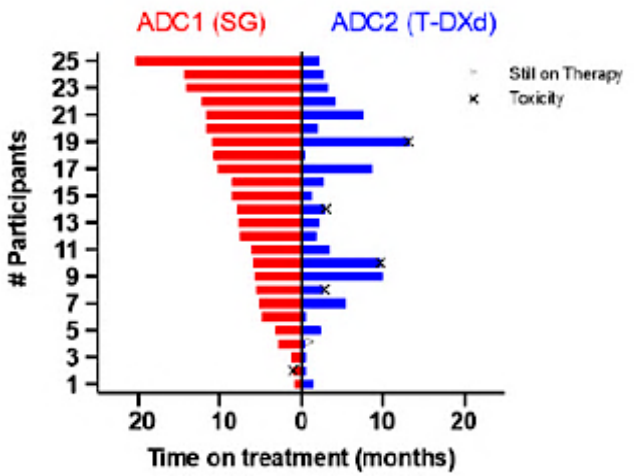
Can we Sequence ADCs in HR−/HER2-low MBC?

SG → T-DXd (n=25, 89.3%)

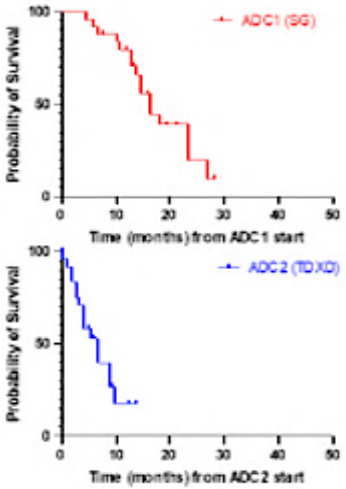
- Median lines of therapy for MBC prior to SG: 2.0 (range 0-5)
- Intervening therapies between ADCs: 40.0%

	ADC1 (SG)	ADC2 (T-DXd)
ORR (CR+PR) by investigator assessment, %	68.0%	35.0%
CBR (CR + PR + SD) by investigator assessment, %	80.0%	45.0%
Median rwPFS, months	7.8	2.8
Median rwOS from time of each ADC start, months	16.5	6.5

rwPFS



rwOS

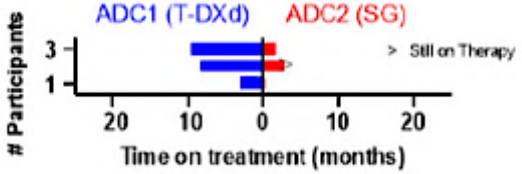


T-DXd → SG (n=3, 10.7%)

- Median lines of therapy for MBC prior to T-DXd: 3.0 (range 1-5)
- Intervening therapies between ADCs: 66.7%

	ADC1 (T-DXd)	ADC2 (SG)
ORR (CR+PR) by investigator assessment, %	33.3%	0.0%
CBR (CR + PR + SD) by investigator assessment, %	66.7%	50.0%
Median rwPFS, months	undetermined	
Median rwOS from time of each ADC start, months	undetermined	

rwPFS



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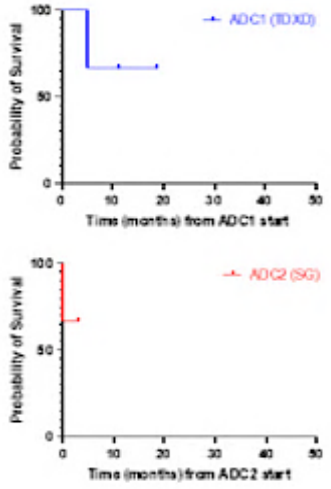


Multiple randomized trials sequencing ADCs in MBC are underway

Huppert LA, et al. npj Breast Cancer 2025

Poor Outcomes with Chemotherapy in 2L+ Metastatic TNBC

Drug	Phase	N	Population	Median PFS (mo)	Median OS (mo)
>1st-line treatment[a]					
Ixabepilone[1]	2 (pooled analysis)	60	Resistant to anthracycline, cyclophosphamide & taxane or taxane only	1.6 - 2.7	—
Capecitabine[1]	3 (pooled analysis)	208	Prior or resistant to anthracycline & taxane	1.7	—
Eribulin[2]	3 (pooled analysis)	199	≥1 prior chemo	2.8	12.4
Single-agent chemotherapy[3] (taxane, gemcitabine, capecitabine, or vinorelbine)	3 (subgroup analysis in TNBC)	47	Progressed on prior non-bevacizumab-containing 1L chemotherapy	2.7	12.6
Capecitabine[4]	3	38	Prior anthracycline and taxane; no more than 2 prior cytotoxic regimens for MBC	2.5	13.2
Pembrolizumab[5]	3	312	PD on last therapy; prior anthracycline or taxane; 1-2 prior systemic therapies	2.1	9.9
Single-agent chemotherapy[5] (capecitabine, eribulin, gemcitabine, or vinorelbine)		310		3.3	10.8

- [a]Includes breast cancer drugs with data from phase 2/3 studies.
- 1. Perez EA, et al. *Breast Cancer Res Treat*. 2010;121:261-271. 2. Pivot X, et al. *Ann Oncol*. 2016;27:1525-1531. 3. Brufsky A, et al. *Breast Cancer Res Treat*. 2012;133:1067-1075. 4. Park IH, et al. *Cancer Res Treat.* 2019;51:43-52. 5. Cortes J, et al. *Ann Oncol.* 2019;30:v859-v86. Abstract LBA21.

Efficacy of Single Agent Carboplatin and PARP Inhibitors in Patients with *gBRCA* Mutations and MBC

	OlympiAD[1,2] Olaparib vs. TPC	**EMBRACA**[3] Talazoparib vs. TPC	**TNT**[4] Carboplatin vs. docetaxel
PFS	**5.6 months** vs. 2.9 months **HR = 0.43** 95% CI (0.29, 0.63)	**5.8 months** vs. 2.9 months **HR= 0.60** 95% CI (0.41, 0.87)	**6.8 months** vs. 4.4 months
ORR	**51.8%** vs. 5.4% (n=83) (n=37) *Investigator assessment*	**61.8%** vs. 12.5% (n=102) (n=48) *Investigator assessment*	**68.0%** vs. 33.3% (n=25) (n=18)

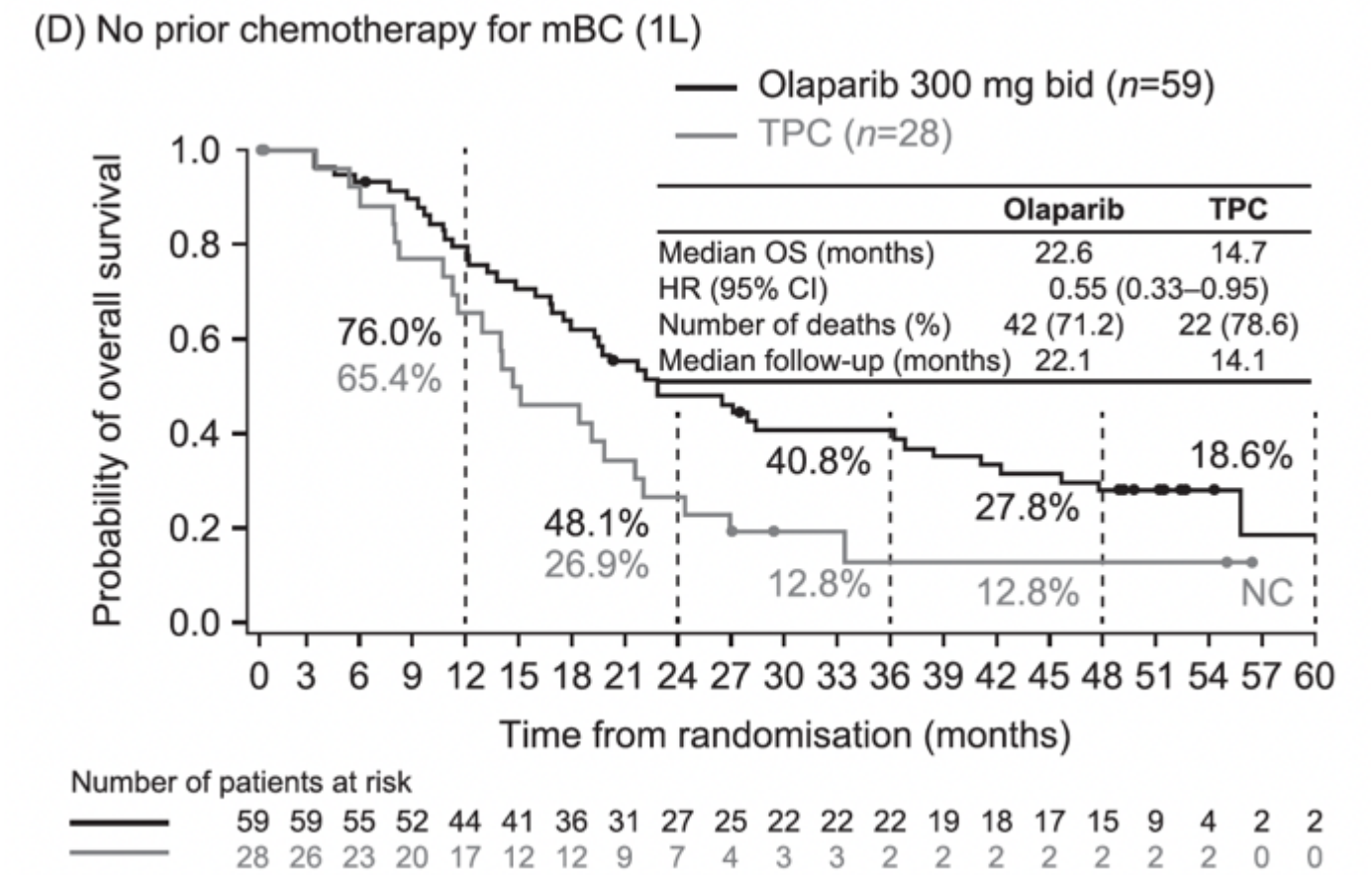
TNT: small numbers, more toxicity with carboplatin vs PARPi, and all 1st line

In the absence of head to head studies between olaparib and other PARPi no comparisons can be made.

1. Senkus et al., Poster PB-002, presented at EBCC 2018; 2. AZ data on file (2019); 3. Eiermann W. et al., Poster 1070, presented at ASCO 2018; 4. Tutt A et al. *Nature Med*. 2018, 24(5):628-637

OlympiAD: Improved OS with Olaparib in 1L MBC Pts

- No statistically significant differences in survival curves in:
  - Overall population and > 1 lines of chemotherapy in metastatic setting
  - hormone receptor subtype
  - Prior exposure to platinum
- No new safety signal – No AML/MDS



Robson M et al.
Eur J Cancer, 2023

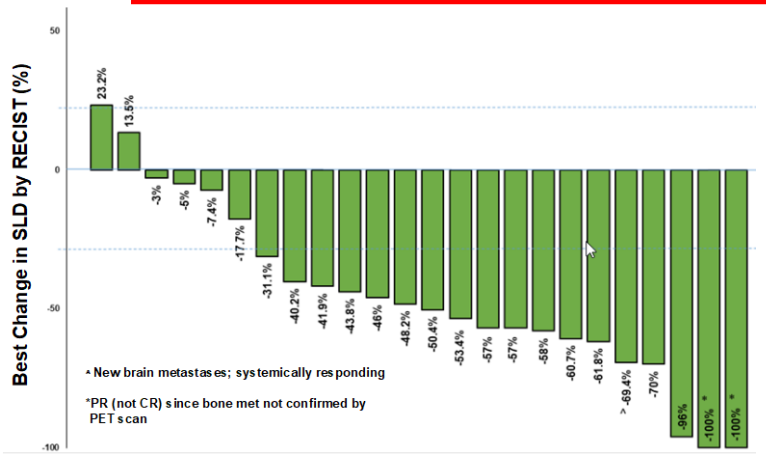
TBCRC 048 Olaparb Expanded

Responses for g*PALB2*

g*PALB2* N=24	
Best Response	**Responses (rate, %)**
Complete Response (CR)	1 (4%)
Partial Response (PR)	17 (71%)
Stable Disease (SD)	5 (21%)
Progressive Disease (PD)	1 (4%)
ORR = 75% (18/24, 80%-CI: 60%-86%)	
CBR (18 wks) = 83% (20/24, 90%-CI: 66%-94%)	

Datacut May 3, 2024

Median PFS= 9.6 months (90%-CI: 8.3- 12.4)
Median DOR= 7.1 months (90% CI: 5.5- 11.0)



Tumor subtype	Responses
TNBC	2/2
ER+/HER2-neg	13/19
HER2+	3/3

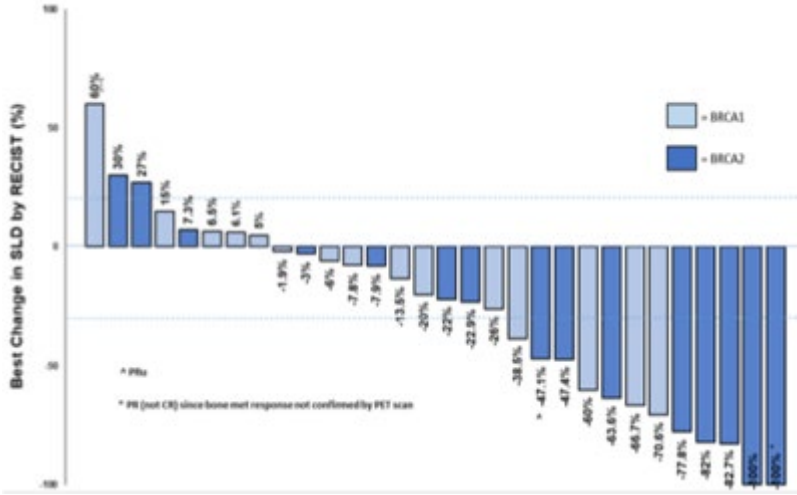
MUST TEST ALL TNBC Pts for germline mutations

Responses for s*BRCA1/2*

s*BRCA1/2* N=30	
Best Response	**Responses, (rate, %)**
Complete Response (CR)	1 (3%)
Partial Response (PR)^	10 (33%)
Stable Disease (SD)	13 (43%)
Progressive Disease (PD)	6 (20%)
ORR = 37% (11/30, 80%-CI: 25%-50%)	
CBR (18 wks) = 53% (16/30, 90%-CI: 37%-69%)	

^ 1 unconfirmed PR did not count for ORR or CBR

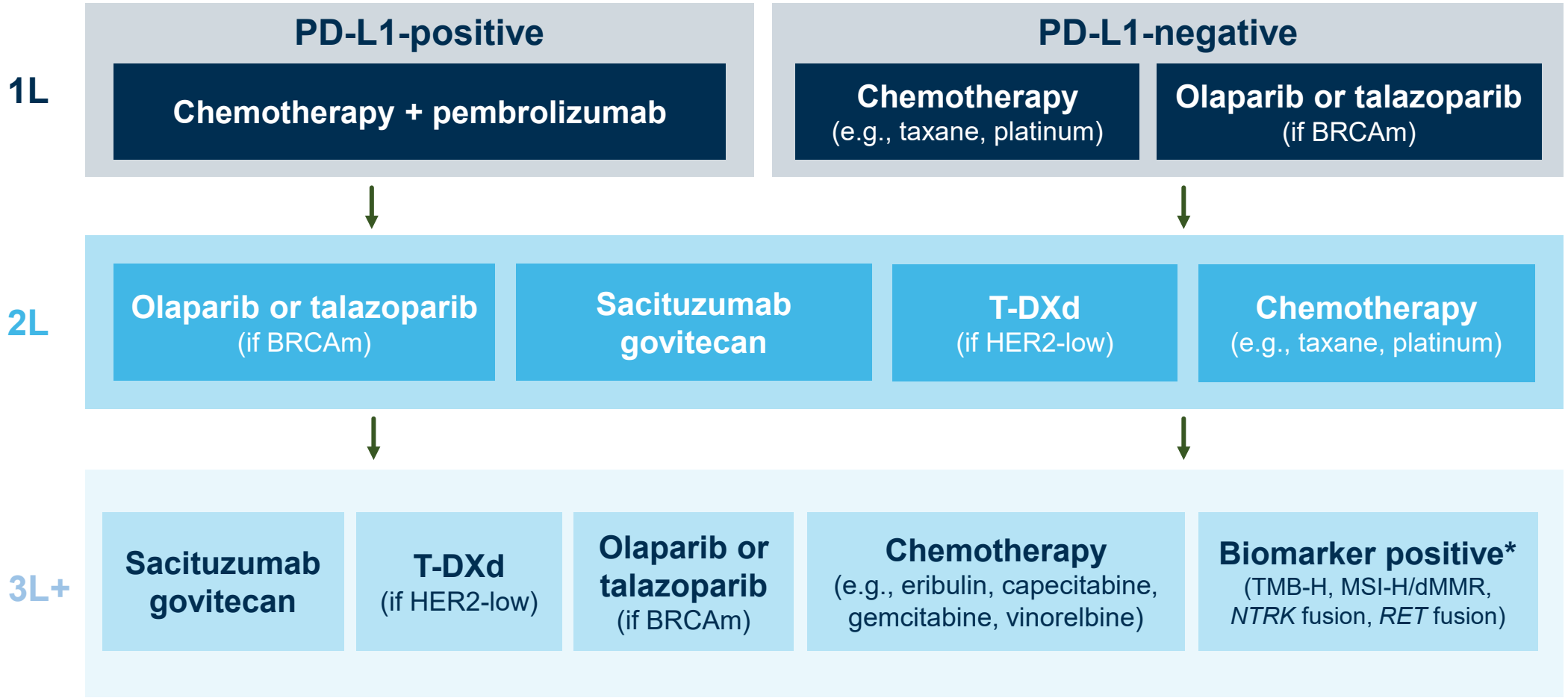
Median PFS= 7.2 months (90%-CI: 3.9- 13.6)
Median DOR= 12.4 months (90% CI: 4.3- NR)



Tung et al, ASCO 2024

Treatment Algorithm for Metastatic TNBC

1L Sacituzumab +/- pembrolizumab likely new SOC regimens



*TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; *NTRK* fusion: Larotrectinib, Entrectinib; *RET* fusion: Selpercatinib