UCSF Helen Diller Family Comprehensive Cancer Center

Latest Treatments for Triple-Negative Breast Cancer

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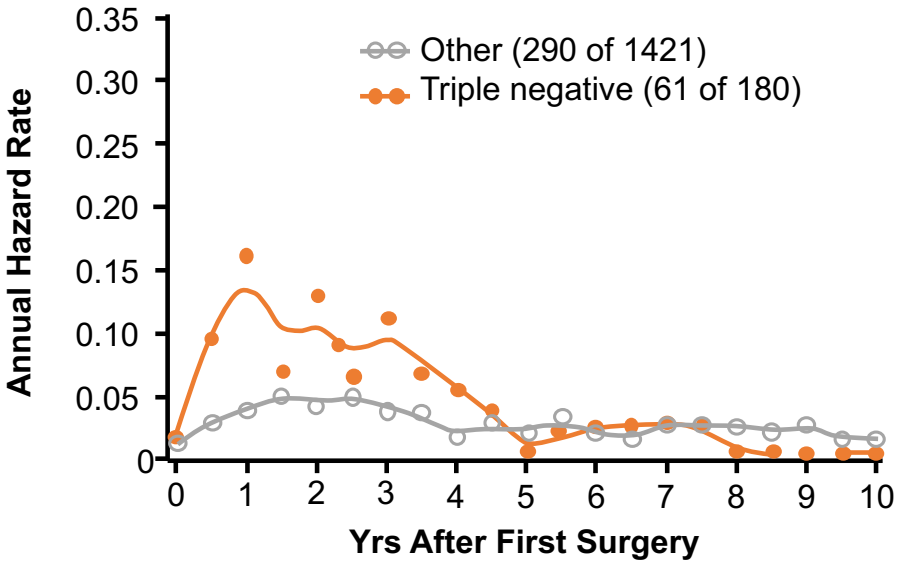
Triple Negative Breast Cancer

- General concepts
  - Heterogeneous disease
    - Highly 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 indolent subtypes, generally in older women



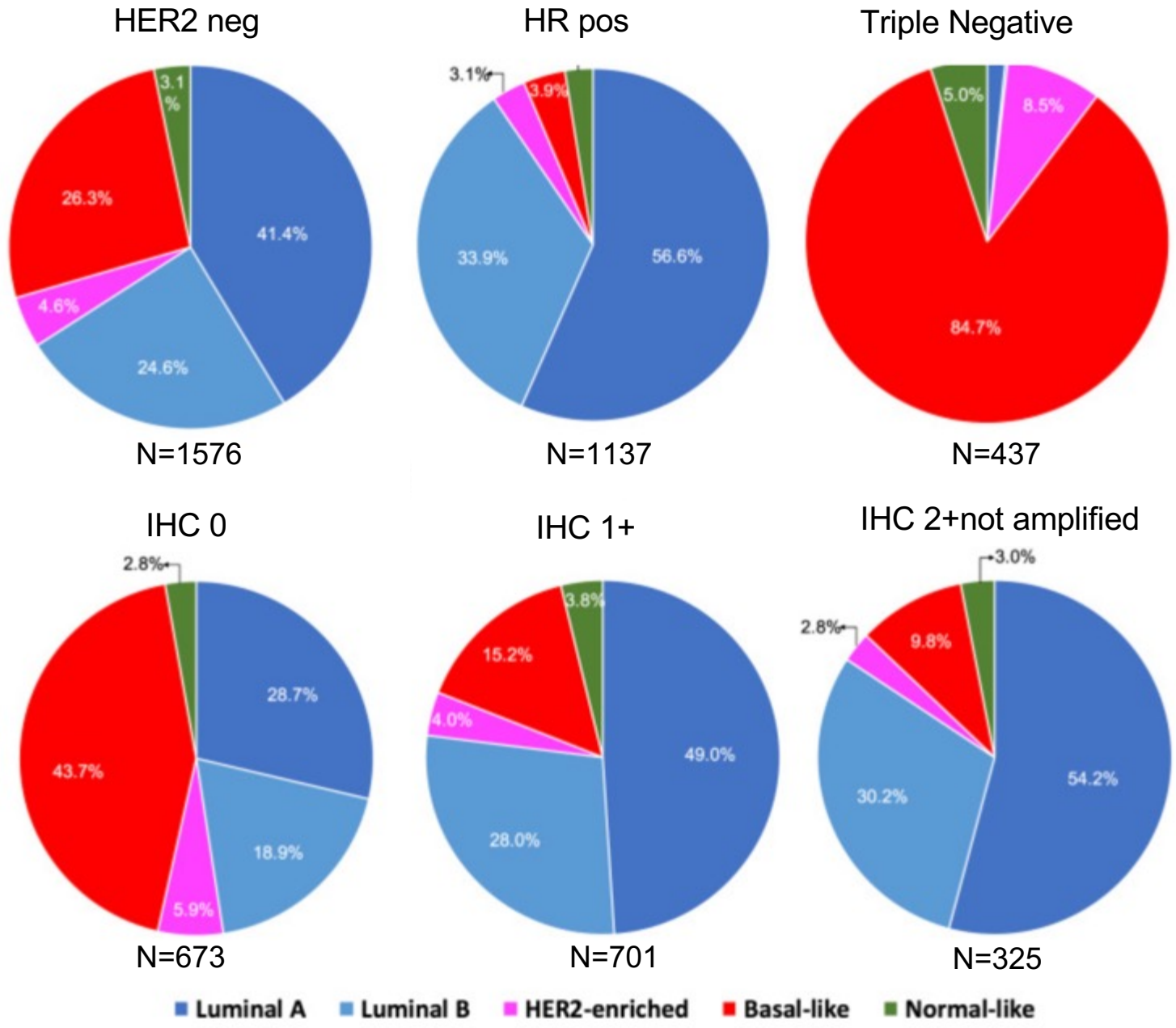
Lin NU, et al. Cancer. 2008;113:2638-2645. Liedtke C, et al. J Clin Oncol. 2008;26:1275-1281. Dent R, et al. Clin Cancer Res. 2007;13:4429-4434.

TNBC: Heterogeneity by Intrinsic Subtype

Current sequencing of therapy is dependent on:

- PD-L1 status
- Germline and somatic BRCA mutations
- Pathology – low proliferative subtypes, AR expression
- DFI and prior therapy
- **NGS is rarely useful**

- Despite advances in therapeutic options, we have made little progress in best sequencing
  - First: IO or not?
  - Second: mutation status?
  - Third: best order for chemo/ADC?



Schettini et al, NPJ Breast Cancer 2021

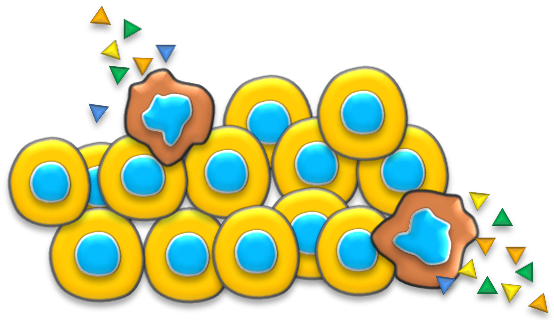
Targeting Treatment to Biology

- **Metastatic Disease**
  - Immunotherapy
    - Can we amplify the immune response?
  - PARP inhibitors: can we expand use?
  - Antibody drug conjugates
    - Sacituzumab govitecan
    - Trastuzumab deruxtecan
    - Datopotamab deruxtecan

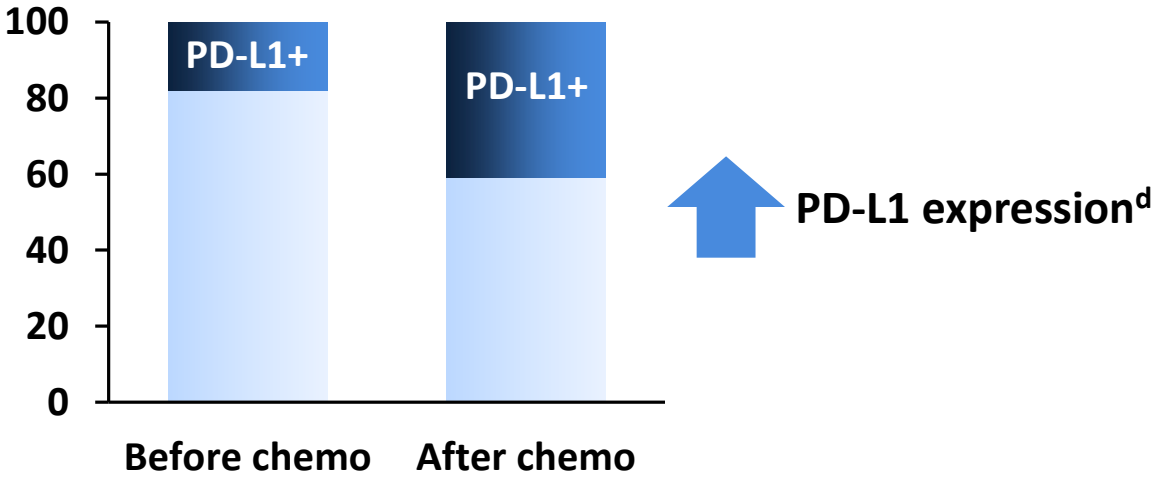
- **Early Stage Disease**
  - Optimal chemotherapy backbone
  - Immunotherapy
  - Post-neoadjuvant strategies

RATIONALE FOR COMBINING CHECKPOINT INHIBITION WITH CHEMOTHERAPY

- Chemotherapy results in:

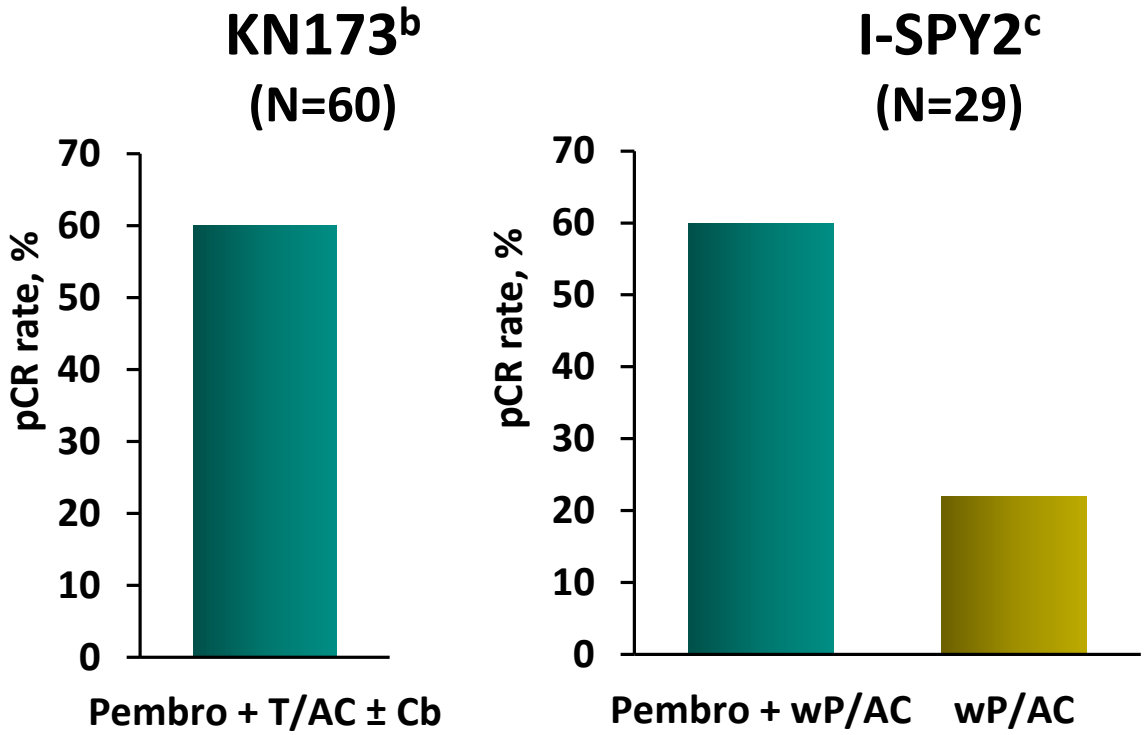


Tumor lysis and antigen shedding[a]



PD-L1 expression[d]

- Pembrolizumab plus standard neoadjuvant chemotherapy in TNBC

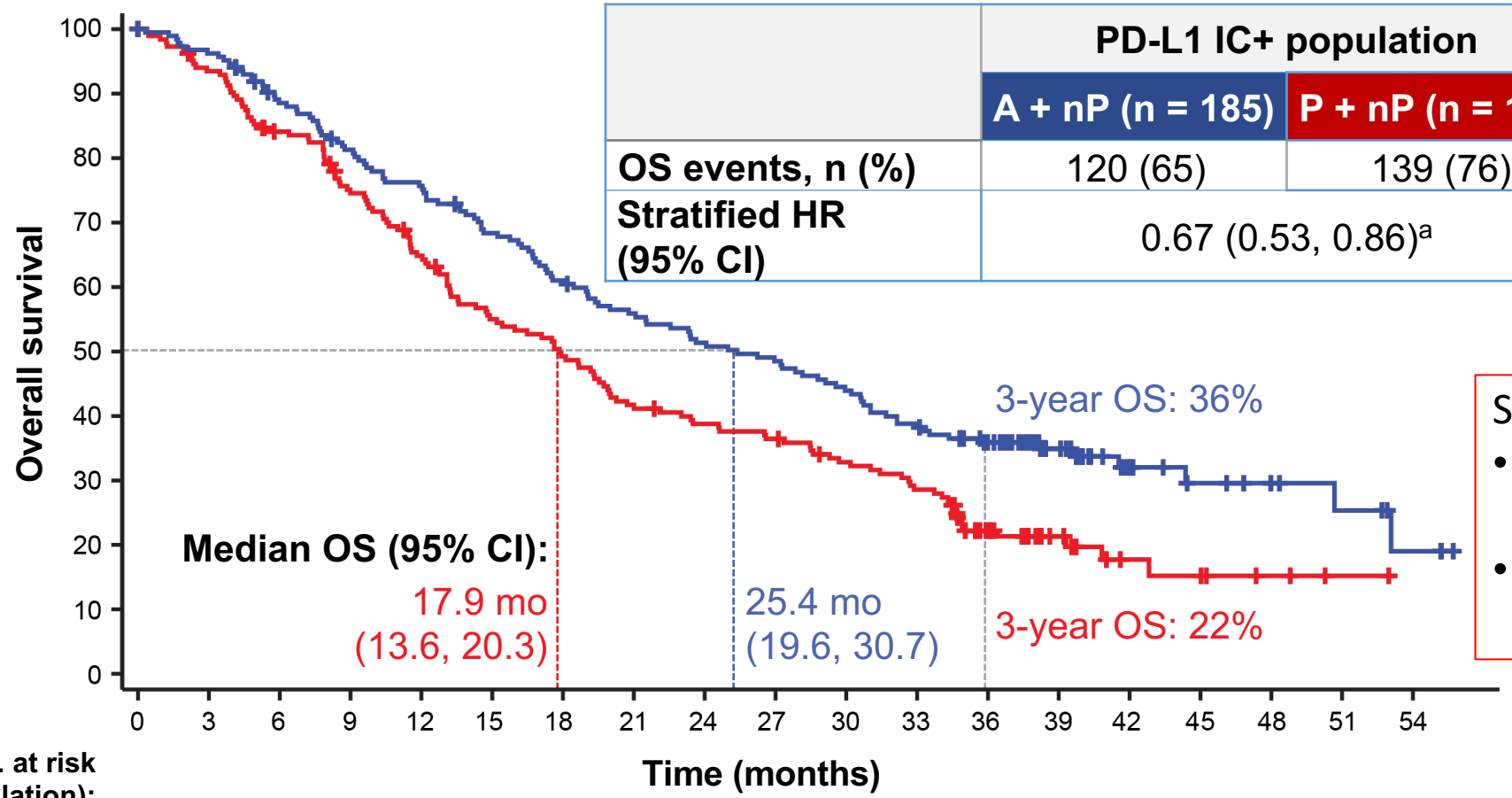


pCR=pathologic complete response as defined as ypT0/Tis ypN0; TNBC=triple-negative breast cancer; PAC=paclitaxel, doxorubicin, cyclophosphamide.

[a] Economopoulou P, et al. *Ann Oncol*. 2016;27:1675-1685; [b] Schmid P, et al. *Ann Oncol*. 2020;31:569-581; [c] Nanda R, et al. *JAMA Oncol*. 2020;6(5):1-9. Epub ahead of print;
[d] Bailly C, et al. *NAR Cancer*. March 2020;2(1).

IMpassion 130: Final OS in the PD-L1 IC+ population

	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	



No. at risk (PD-L1+ population):																			
A + nP	185	177	160	145	135	121	108	98	90	86	77	67	56	32	17	11	9	6	3
P + nP	184	170	150	132	113	95	85	72	66	62	54	47	28	14	7	6	3	1	NE

Subset Analysis for OS (HR)
- Prior taxane:
  - 0.83 (0.59-1.15)
- No prior taxane:
  - 0.55 (0.38-0.80)

Data cutoff, 14 April 2020. NE, not estimable.

[a] *P* value not displayed since OS in the PD-L1+ population was not formally tested due to the hierarchical study design.

Emens et al: Ann Oncol 2021
IMpassion130 Final OS.

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

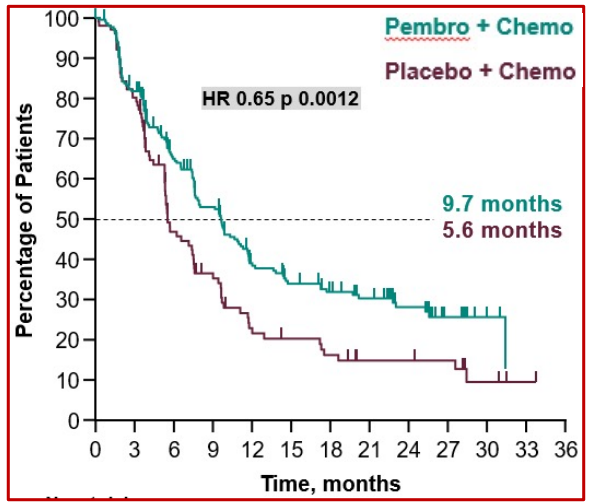
R 2:1

- 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)

PFS: PD-L1 CPS ≥10

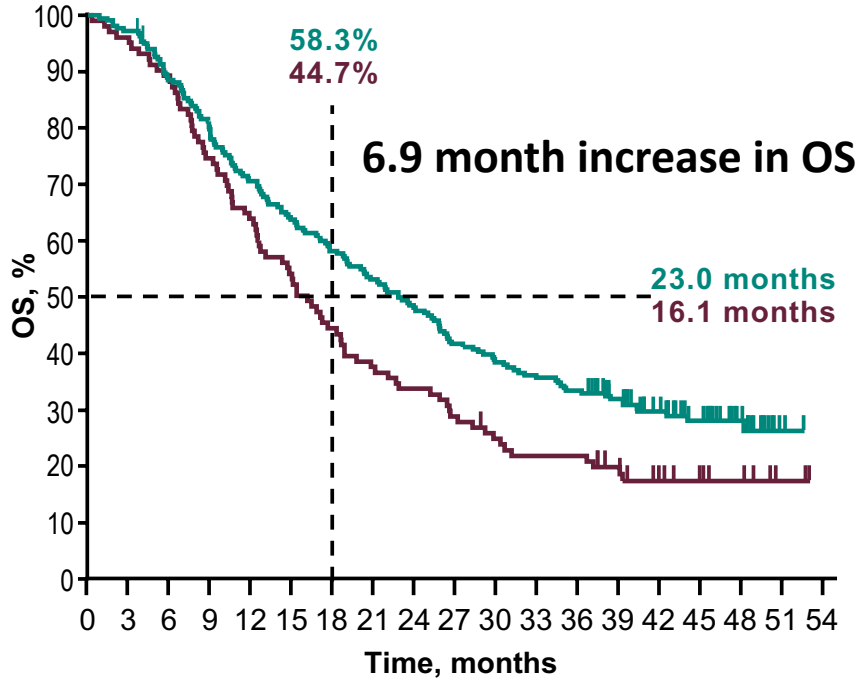


Prespecified *P* value boundary of 0.00411 met

38% of pts

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

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

Immunotherapy: First-Line Rx for mTNBC

	IMPASSION 131	IMPASSION 130	KEYNOTE 355
N (PD-L1+)	943 (292, 45%) ≥1%	902 (369, 41%) ≥1%	847 (332, 38%) CPS≥10
Randomization and Treatment	2:1 Paclitaxel 90 mg/m2 Atezolizumab	1:1 nab-Paclitaxel 100 mg/m2 Atezolizumab	2:1 Pac/nab/gem+carbo Pembrolizumab
de novo	28-30%	~37% (no chemo)	30%
Prior taxane	51-53%	51%	45%
PFS in PD-L1+	5.7 → 6 mo; HR 0.82 P=0.2	5 → 7.5 mo; HR 0.62 P<0.0001	5.6 → 9.7 mo; HR 0.65 P=0.0012 FDA approved 7/21
OS benefit	No	YES	YES

Miles et al, Ann Oncol 2021; Schmid et al, NEJM 2018 & Emens et al, Ann Oncol 2021; Cortes et al, Lancet 2020 & NEJM 2022

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

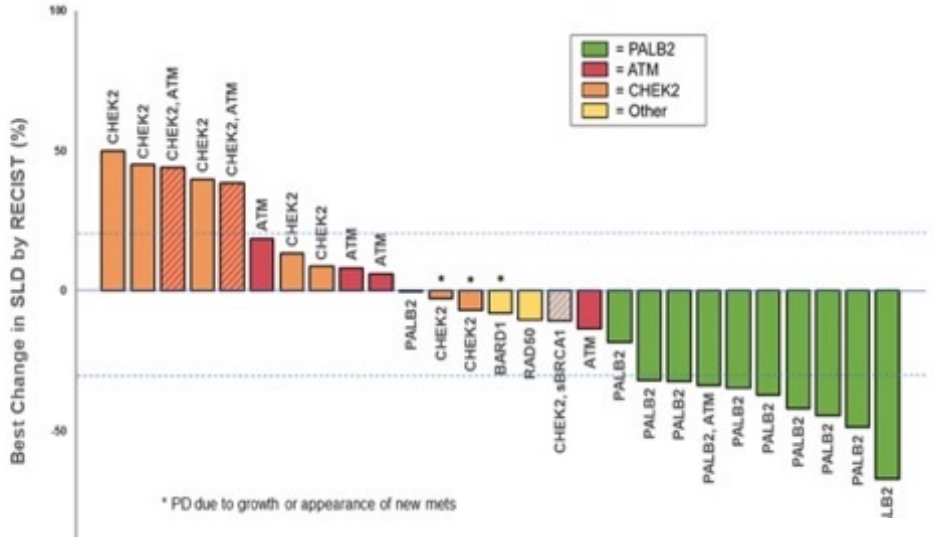
BROCADE3 trial (carbo/pac +/- veliparib): role of PARPi maintenance[5]?

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

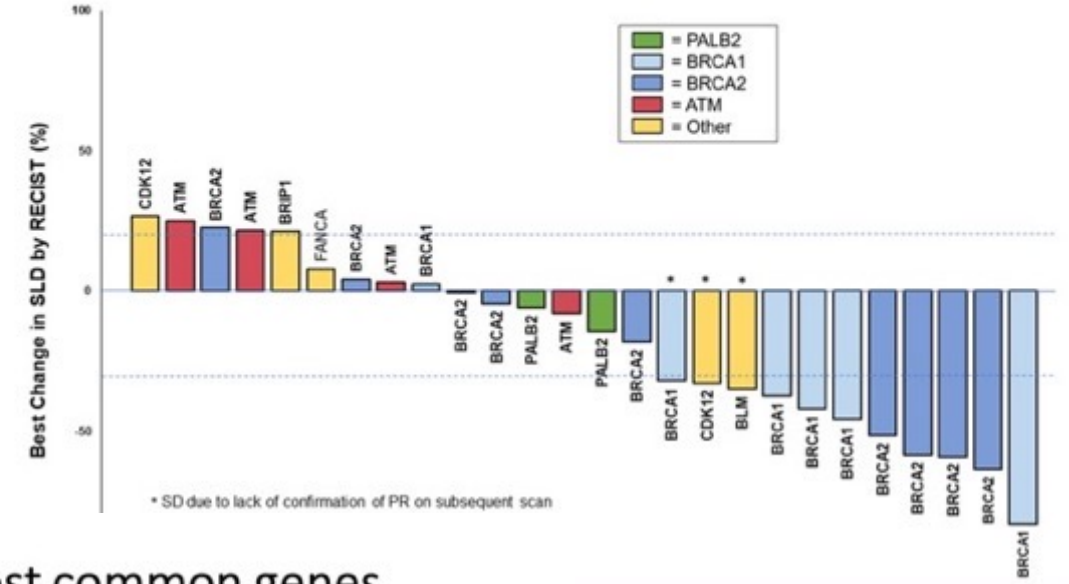
1. Senkus et al., Poster PB-002, presented at EBCC 2018; 2. AZ data on file (2019); 3. Eiermann W. et al., Poster 1070, presented at ASCO 2018; 4. Tutt A et al. *Nature Med*. 2018, 24(5):628-637 5. Dieras et al, Lancet Oncol 2020

Expanding the use of PARP inhibitors

Best Overall Responses: Cohort 1 (Germline)



Best Overall Responses: Cohort 2 (Somatic)*



Responses for 5 most common genes (somatic and germline mutations)

PALB2 N=13	*sBRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr **Somatic: 0/2 – both SD* (limited assessments)**	**8/16 PR (50%)**	**0/13 germline** **0/4 somatic**

15 patients remain on study

* 1 sPALB2- lost to follow-up after 1st tumor assessment with skin and tumor marker response
^ includes patient from Cohort 1 with sBRCA1 and gCHEK2
** Not included: patient with both gCHEK2 & sBRCA1; patient with gATM and gPALB2

Datacut May 4, 2020

*Somatic mutations much more frequent in lobular cancer

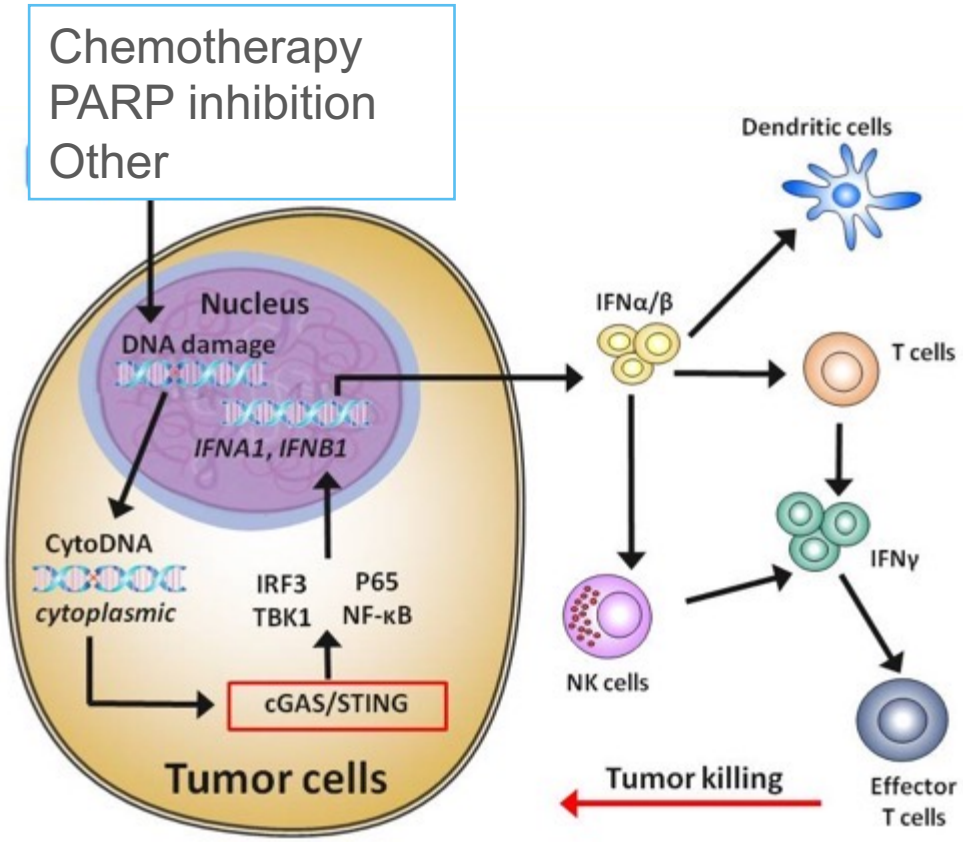
Tung et al, JCO 2020

Combining PARPi and Immune CPI: Making Cold Tumors Hot?

Unrepaired DNA damage from PARPi leads to presence of cytoplasmic DNA which activates the STING (Stimulator of Interferon Genes) pathway

Activation of STING

- ↑ expression and release of type 1 IFNs
- ↑ infiltration of effector T cells

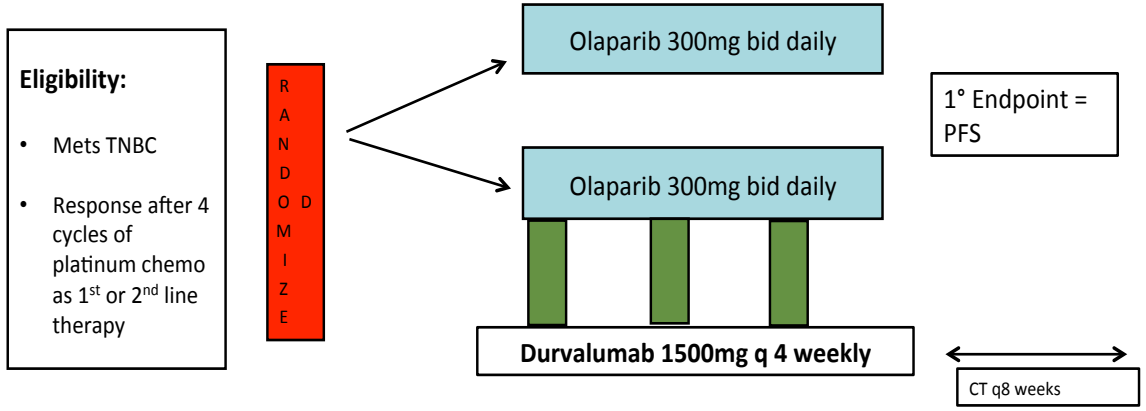


Huang J, et al. *Biochem Biophys Res Commun.* 2015;423:551–556;
Jiao S, et al. *Clin Cancer Res.* 2017;23:3711–3720; Sato H, et al. *Nat Commun.* 2017;8:1751;
Vinayak S, et al. *J Clin Oncol* 2018;36(suppl_15):abst 1011

PARPi + checkpoint inhibition as maintenance?

DORA study[1]

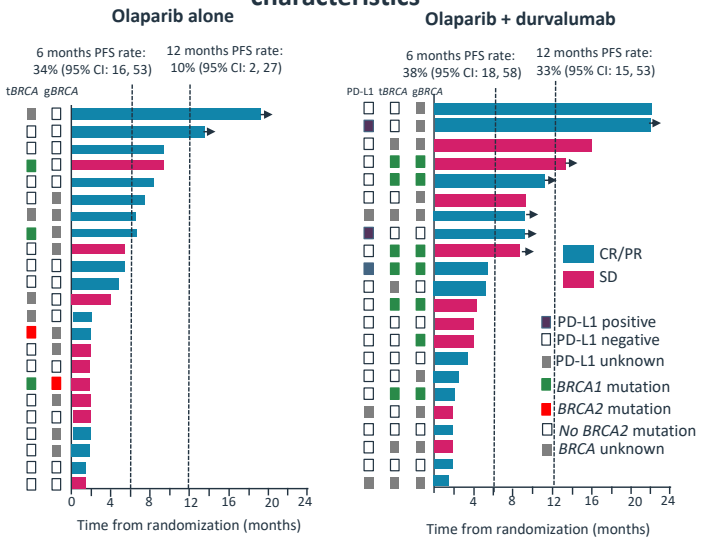
Phase II maintenance study of PARPi + anti-PD-L1 vs PARPi



Primary and subgroup PFS analysis

Median PFS (95% CI)	Olaparib alone (n=23)	Olaparib + durvalumab (n=22)
All patients	4.0 (2.6, 6.1)	6.1 (3.7, 10.1)
X^2 P value vs historical control	0.0023	<0.0001
Subgroups according to prior platinum sensitivity		
CR/PR to prior platinum	5.4 (3.0, 9.7)	7.6 (3.8, 15.1)
SD to prior platinum	2.2 (1.2, 4.3)	4.4 (2.1, 9.3)

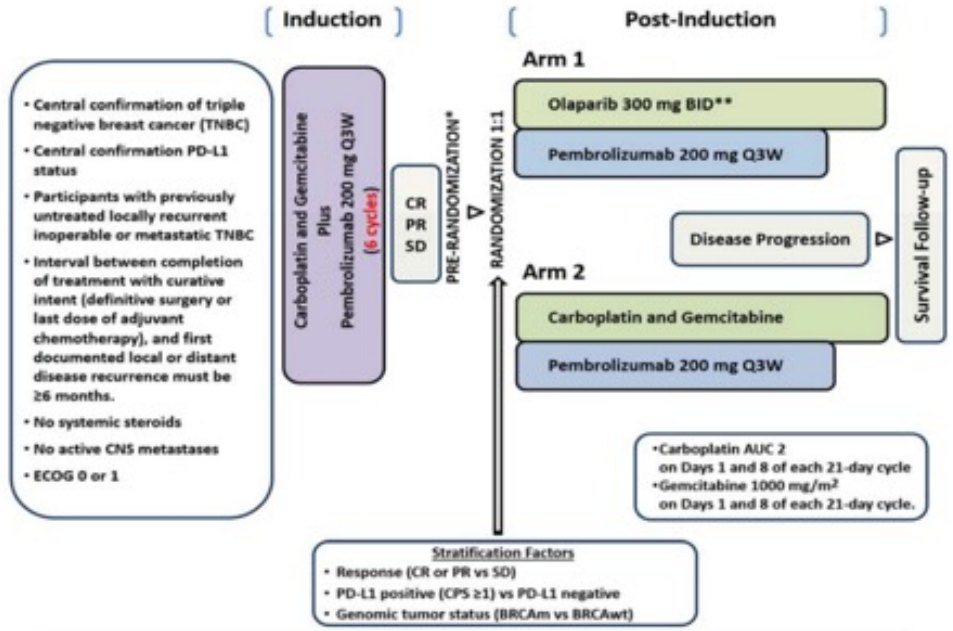
Treatment exposure/response according to tumor characteristics



CR, complete response; PR, partial response; SD, stable disease
Sammons SL, et al. SABCS 2022. Abstract PD11-12

KEYLYNK-009[2]

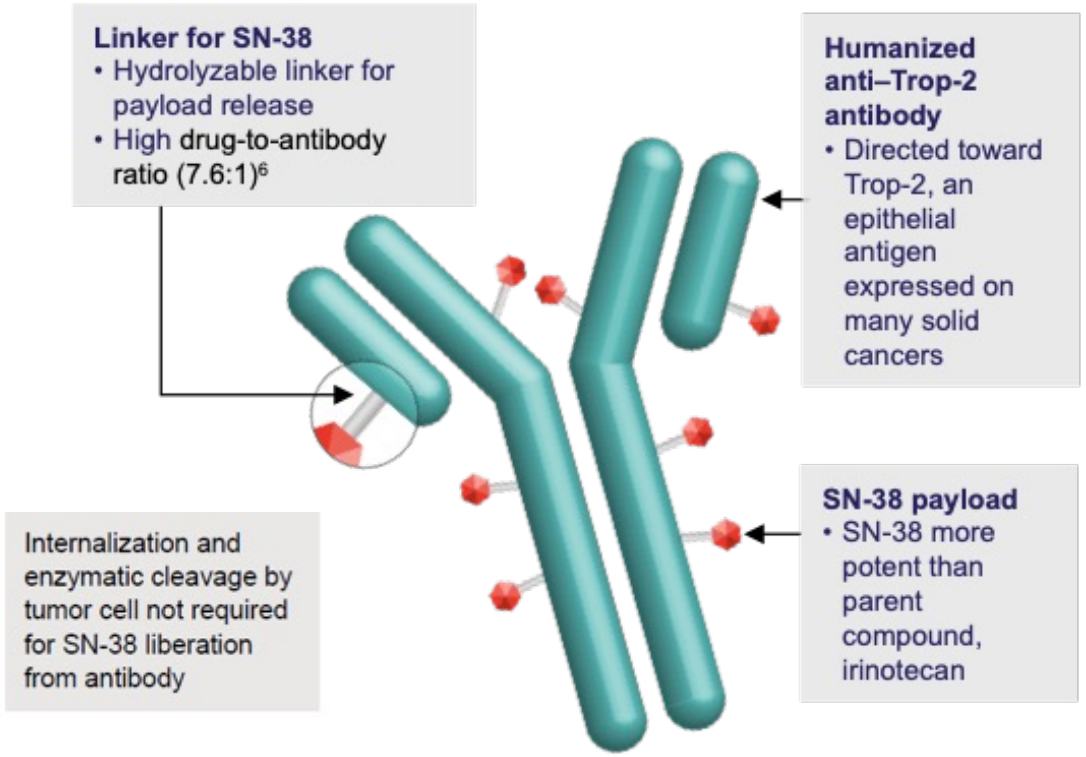
Phase II study of post-induction pembrolizumab + PARPi



Sammons et al, SABCS 2022, PD11-12

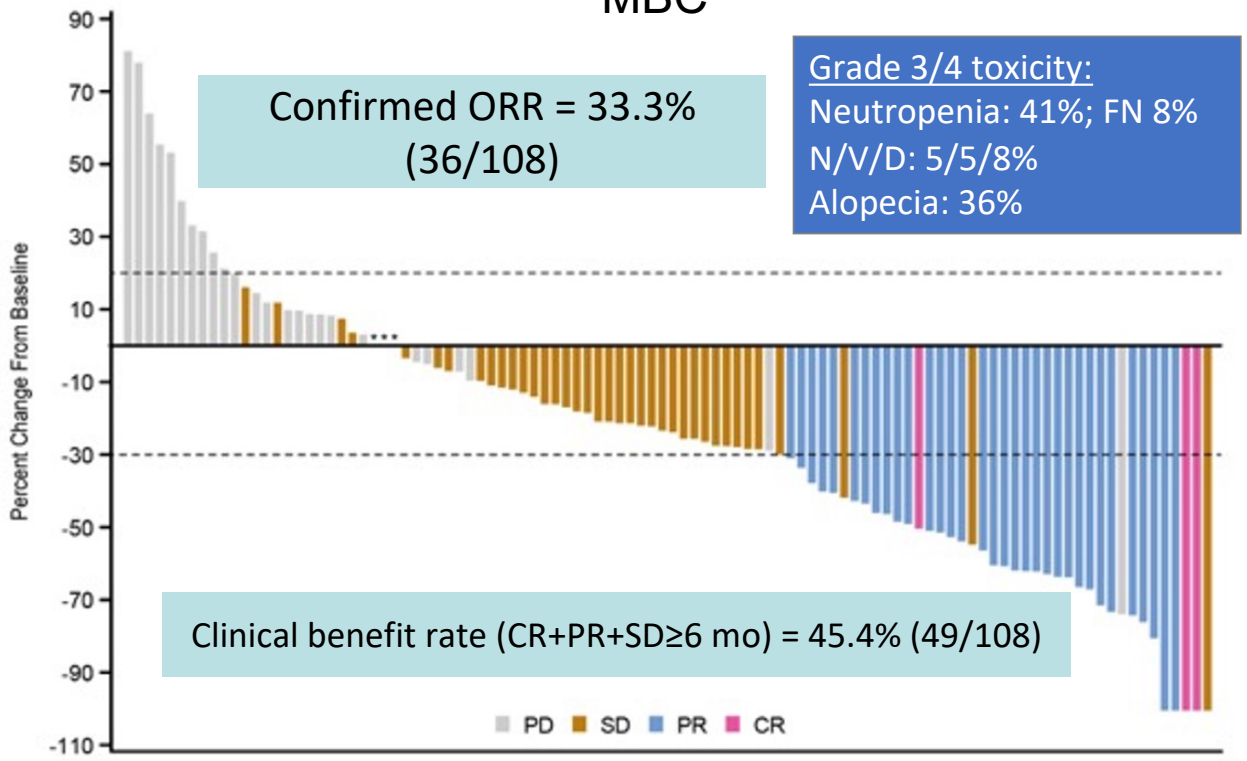
*1. Dent R, et al. Cancer Research. 2018; 78(4); 2. Rugo H, et al. JCO. 2020; 38 (suppl 15); 2. Rugo H, et al. Presented at SABCS 2020. Abstract #OT-30-31

Sacituzumab Govitecan (SG): First-in-Class Trop-2–Directed ADC



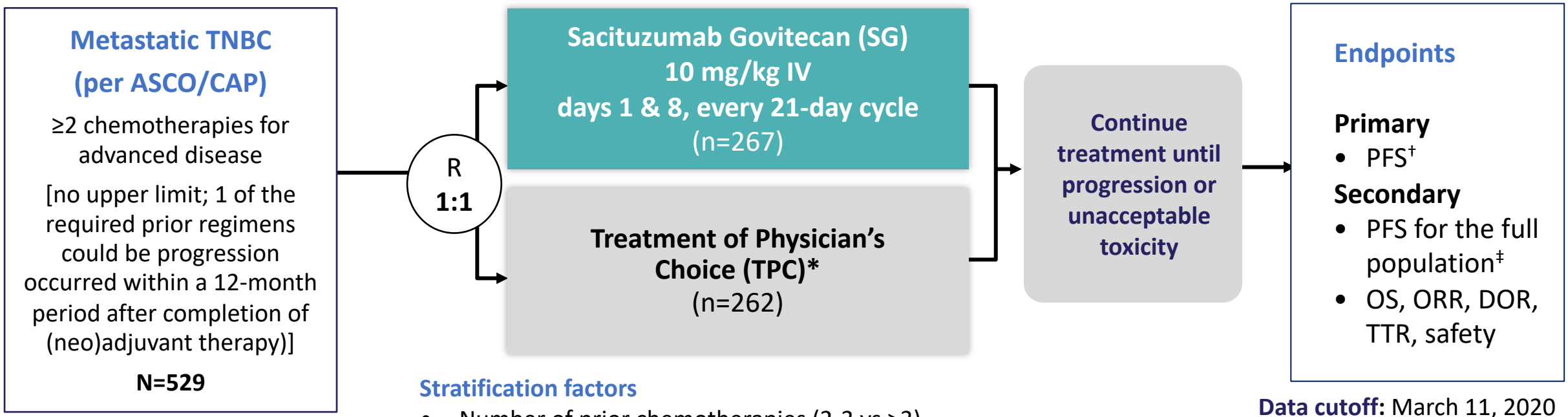
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- Full approval for the treatment of mTNBC and accelerated approval for advanced urothelial cancer

Phase I/II study in 108 patients with refractory mTNBC
Median of 3 prior lines of therapy (range 2-10) for MBC



Bardia et al. *NEJM*. 2019.

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



Stratification factors

- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

NCT02574455

Demographics:

TPC: 53% eribulin, 20% vinorelbine, 15% gemcitabine, 13% capecitabine; 70% TN at initial diagnosis

Median prior regimens 4 (2-17); ~88% with visceral disease

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

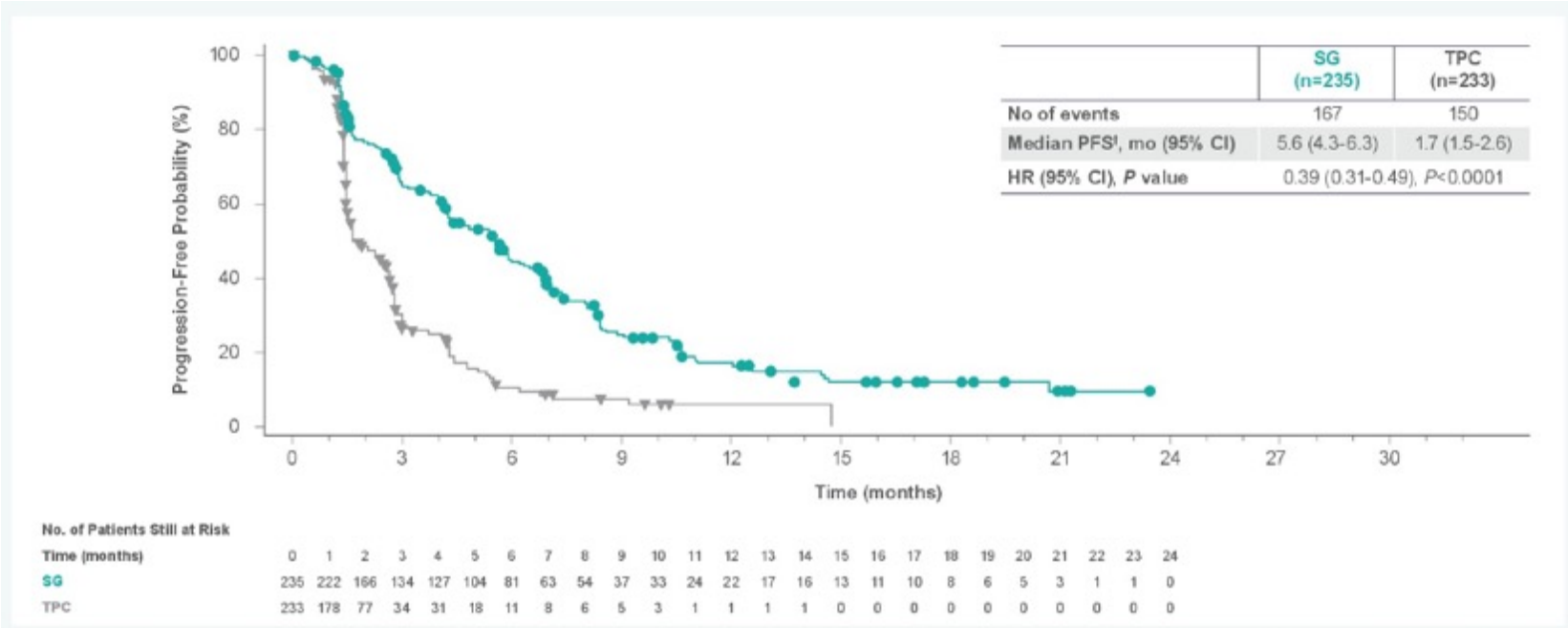
Bardia et al, NEJM 2021

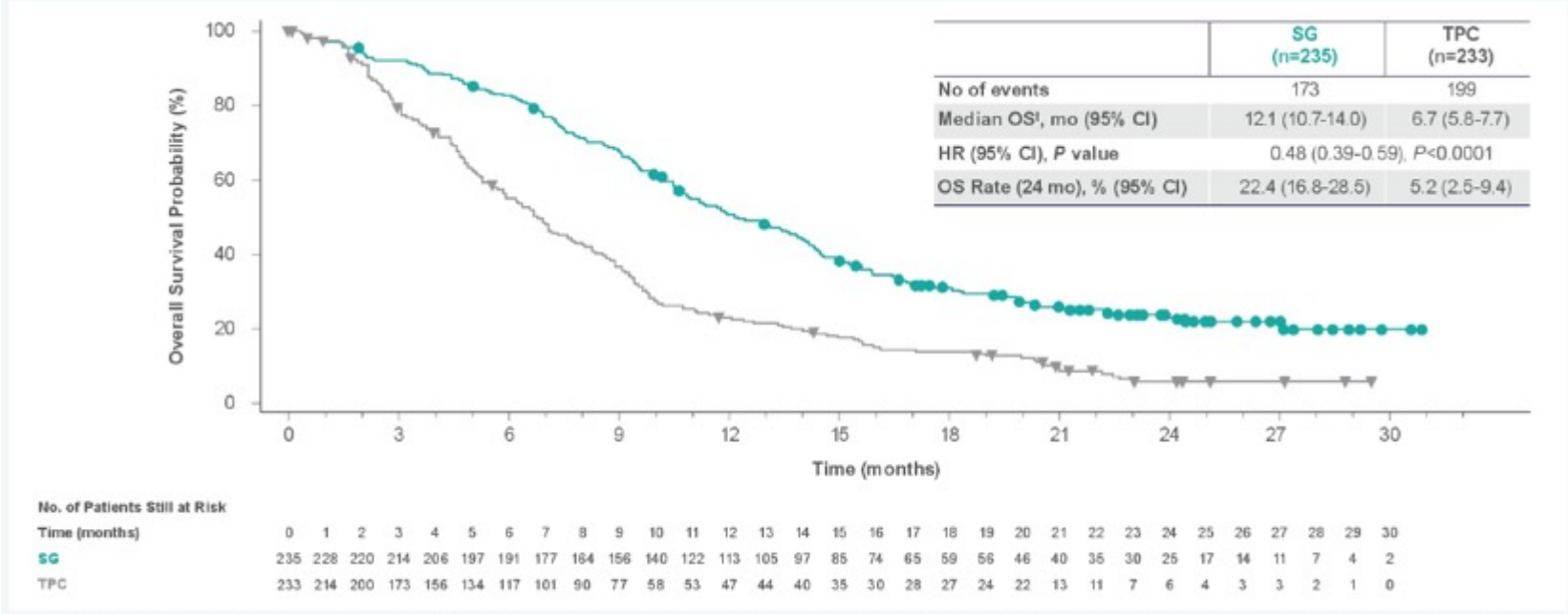
ASCENT

Final PFS and OS in the BMneg Population

Efficacy in ITT population consistent with the BMNeg population

- Median PFS of 4.8 vs 1.7 mo (HR 0.41, p<0.0001)
- Median OS of 11.8 vs 6.9 mo (HR 0.51, P<0.0001)





Bardia A, et al. N Engl J Med. 2021 and ASCO 2022

ASCENT Study: ORR, Additional Analyses, and Safety

	Patients without Brain Metastases	
	SG (N=235)	TPC (N=233)
Objective response — n (%)§	**82 (35)**	**11 (5)**
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
Clinical benefit — n (%)¶	105 (45)	20 (9)
SD — n (%)	81 (34)	62 (27)
SD for ≥6 mo	23 (10)	9 (4)
PD — n (%)	54 (23)	89 (38)
Response NE — n (%)‖	18 (8)	71 (30)
Median TTR (95% CI) — mo	1.5 (0.7–10.6)	1.5 (1.3–4.2)
Median DOR (95% CI) — mo	6.3 (5.5–9.0)	3.6 (2.8–NE)
HR (95% CI)	0.39 (0.14–1.07)	

Additional Analyses

- Activity consistent across medium and high TROP2 expression (too few with low/no expression) and regardless of BRCA mutation status
- 14% treated in the first-line setting (≤12 mo from adj/neoadj rx)
  - PFS 5.7 vs 1.5 months (HR 0.41; 95% CI, 0.22-0.76)
  - OS 10.9 vs 4.9 months (HR 0.51; 95% CI, 0.28-0.91)

Most common toxicities

- Neutropenia, diarrhea, nausea, alopecia, fatigue
- 63 vs 40% grade 3 NTP; 59 vs 12% all grade diarrhea (10% grade 3)
- G-CSF: 49% (SC) and 23% (TPC)
- AEs leading to discontinuation: 4.7% vs 5.4 % TPC, dose reductions due to TRAE similar (22 vs 26%)

Assessed by independent central review in brain met-neg population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo).
Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541; Bardia et al. Ann Oncol 2021; Carey et al NPJ BC 2022; Rugo et al, publication pending.

ASCENT-03 (NCT05382299): PD-L1 negative
N=540

First-line therapy
- PD-L1 neg TNBC
- TNBC Rxd with IO in early stage

→ Sacituzumab govitecan

→ TPC: paclitaxel, nab-paclitaxel, gem/carbo

ASCENT-04 (NCT05382286): PD-L1 positive
N=570

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

1:1

N=570
(≤25% *de novo*)

→ SG + pembrolizumab
(SG: 10 mg/kg IV on days 1 and 8 of 21-day cycles; Pembro: 200 mg IV on day 1 of 21-day cycles)

→ TPC chemotherapy + pembrolizumab
(Pembro dosed as above. TPC: gem 1000 mg/m² with carbo AUC 2 IV on days 1 and 8 of 21-day cycles OR paclitaxel 90 mg/m² IV on days 1, 8, and 15 of 28-day cycles OR nab-paclitaxel: 100 mg/m² IV on days 1, 8, and 15 of 28-day cycles)

SACI-IO TNBC: SG +/- pembrolizumab in 1st line PD-L1- TNBC

mTNBC:
No Prior Chemo
No Prior PD-1/L1

PD-L1 <1% by SP-142
ER ≤ 5%
PR ≤ 5%
HER2-

Stable brain mets
Strata: Neo/adjuvant progression <12m

Exclude prior: PD-1/L1, SG, Irinotecan

R
1:1

N=110 pts

→ **sacituzumab govitecan 10mg/kg IV d1,8 q21 days + pembrolizumab 200mg/kg Q3wks**

→ **sacituzumab govitecan 10mg/kg d1,8 q21 days**

Primary Endpoint
- PFS

Secondary Endpoint
- OS, ORR
- DOR, CBR

80% power to detect PFS improvement from 5.5 months (Arm B) to 8.5 months (Arm A)

PI: Sara Tolaney/Ana Garrido-Castro

Ascent-07:
First-line Chemotherapy in HR+

Key eligibility criteria:
- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)

N = 654
2:1 randomization

→ **Sacituzumab govitecan 10 mg/kg IV Days 1 and 8, every 21 days**

→ **Treatment of physician's choice (capecitabine, paclitaxel, nab-paclitaxel)**

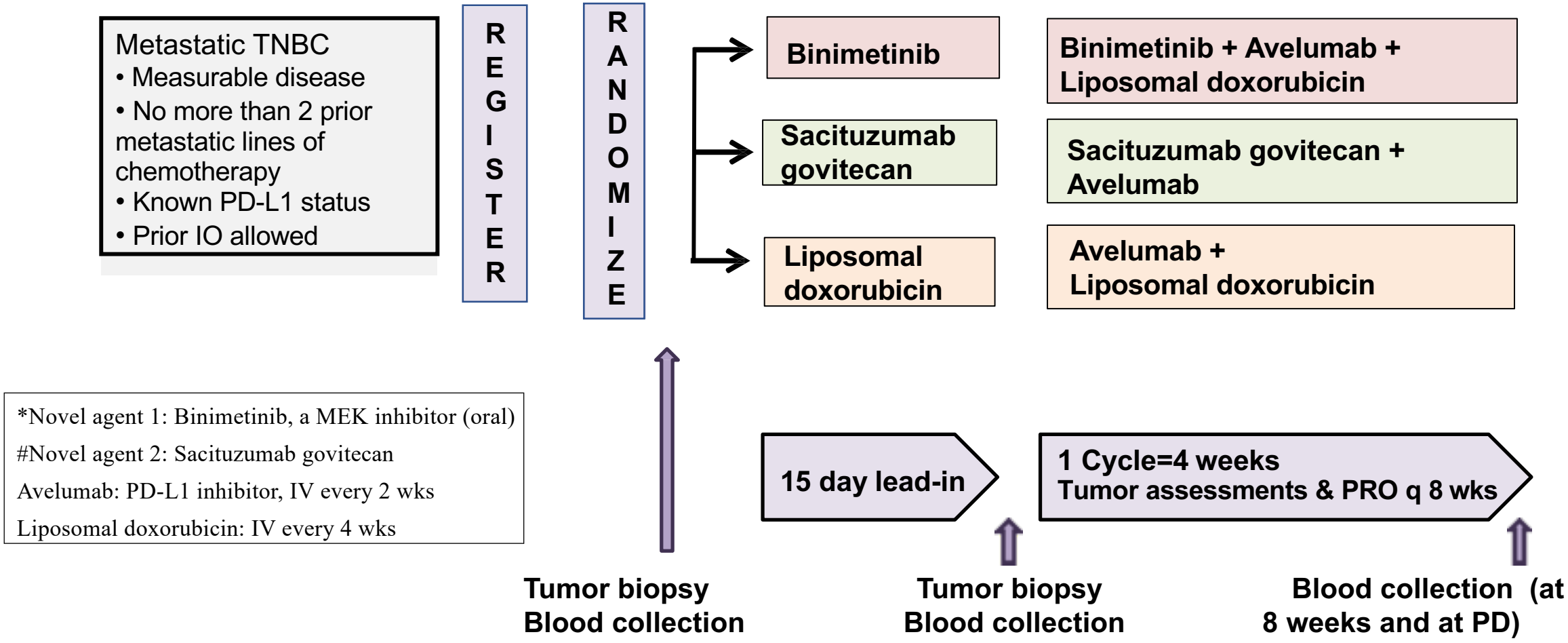
Stratification:
- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint
- PFS by BICR

Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints
- PFS by investigator
- ORR by investigator
- DOR
- Safety

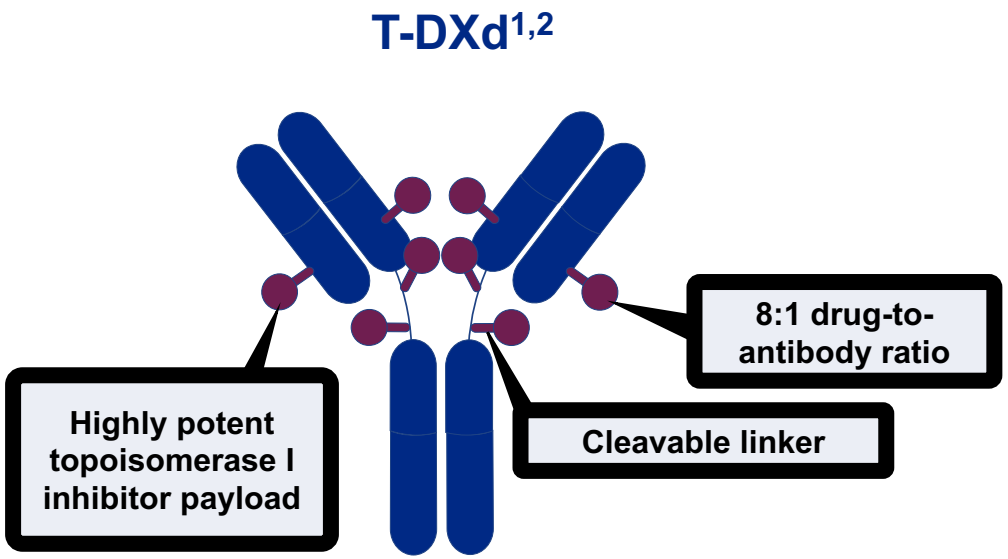
TBCRC 047: InCITe Trial Design



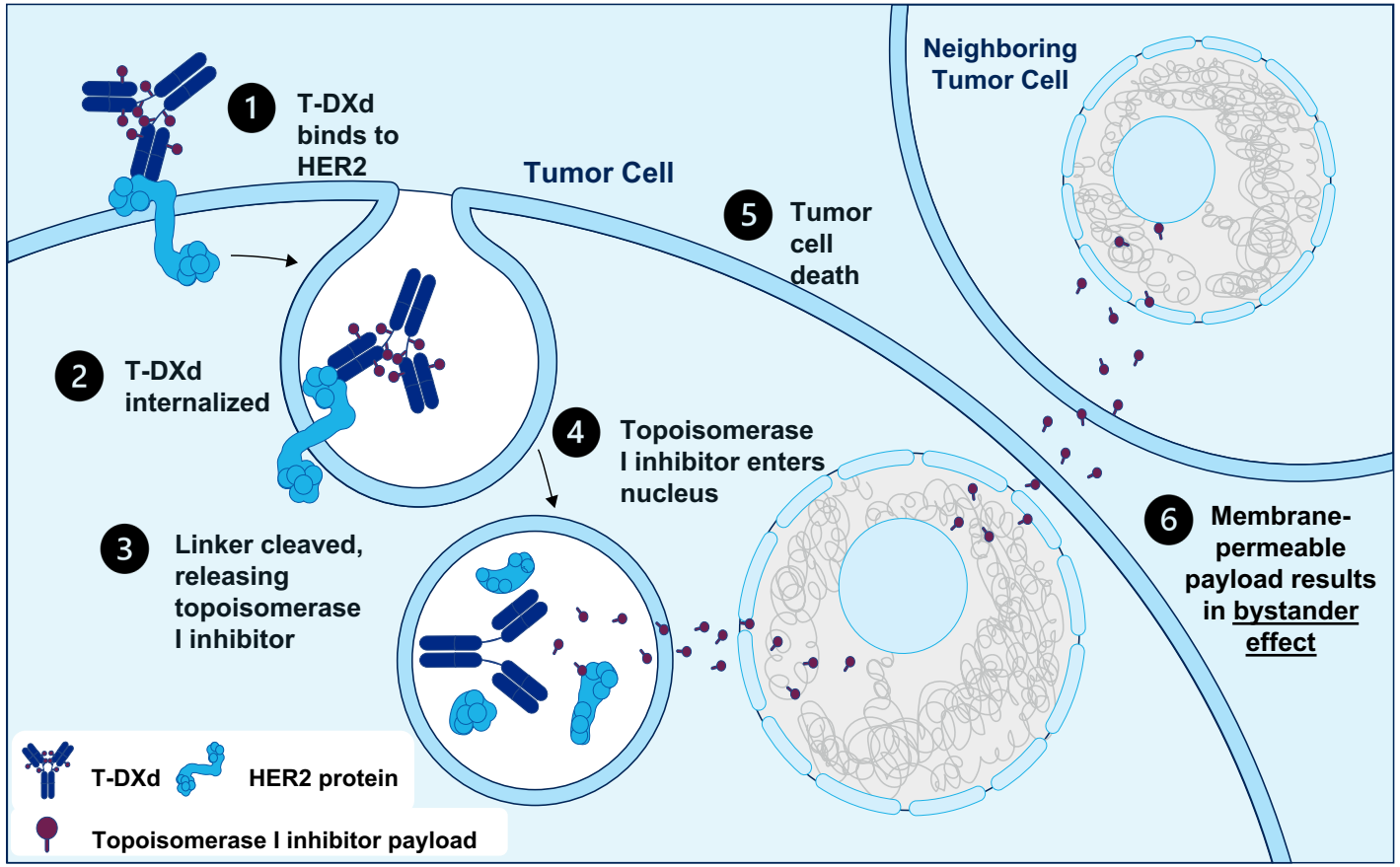
*Safety combination data from MiLO trial
#Safety combination data from several ongoing trials

PI: Hope S. Rugo

T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

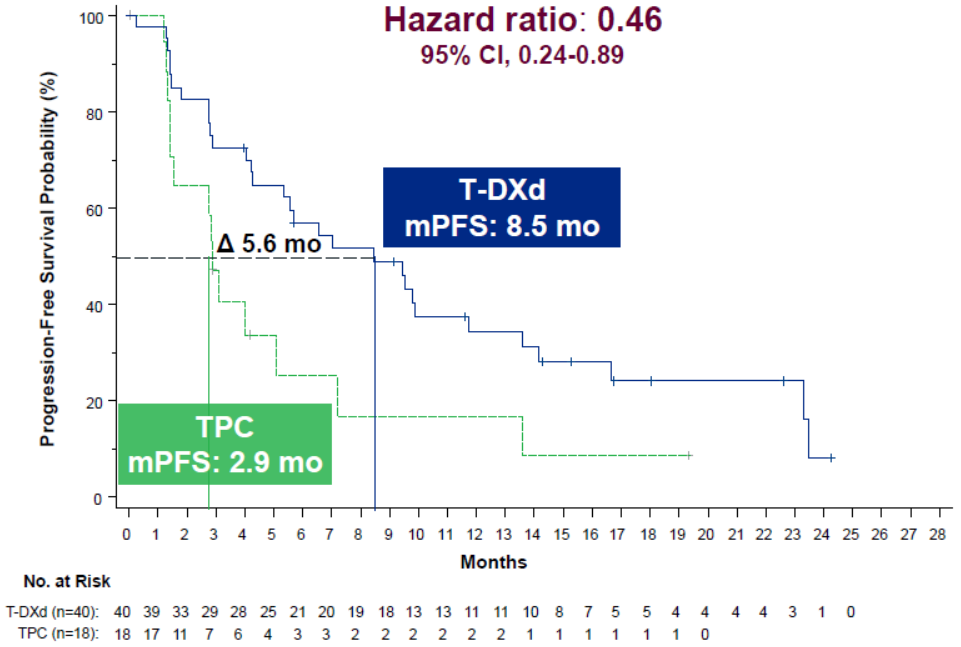
- **Results from a phase 1b study reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896.

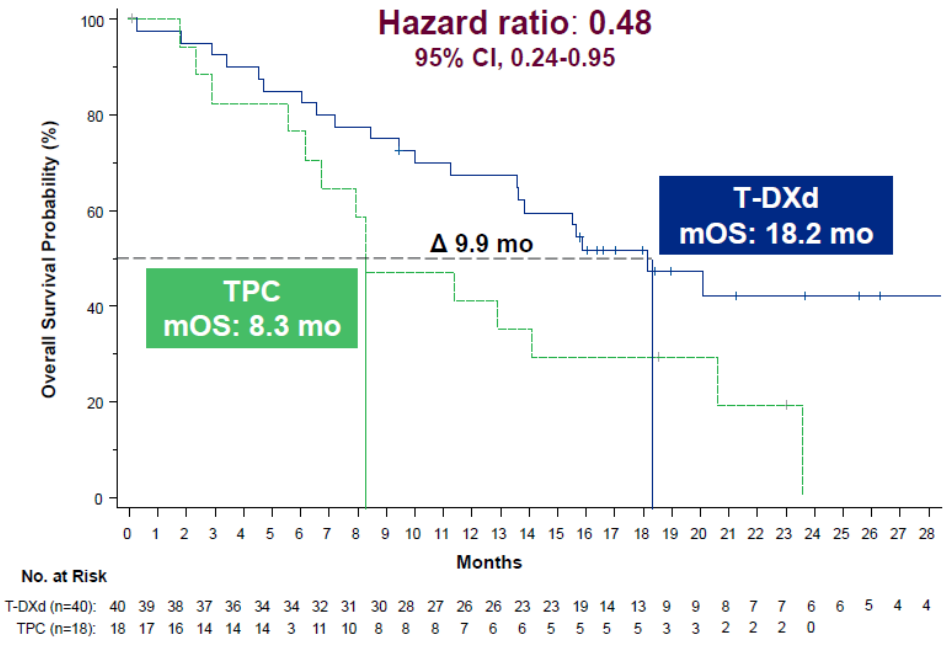
Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Efficacy in HRneg

PFS in HR-



PFS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median PFS, months	8.5	2.9
HR (95% CI)	0.46 (0.24-0.89)	

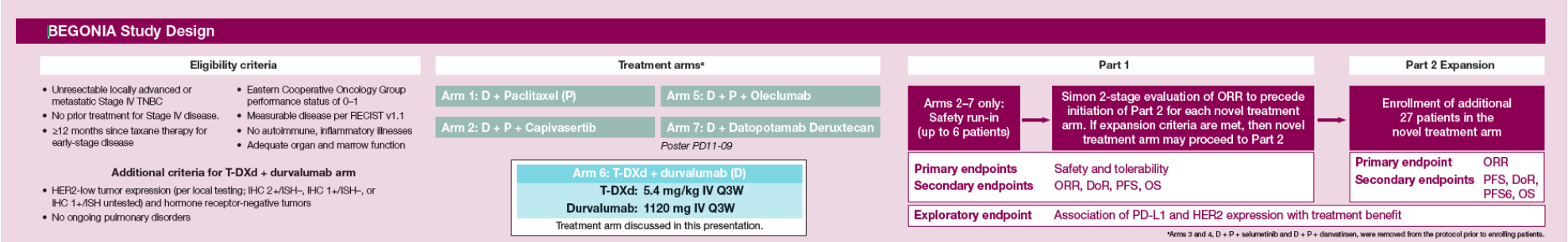
OS in HR-



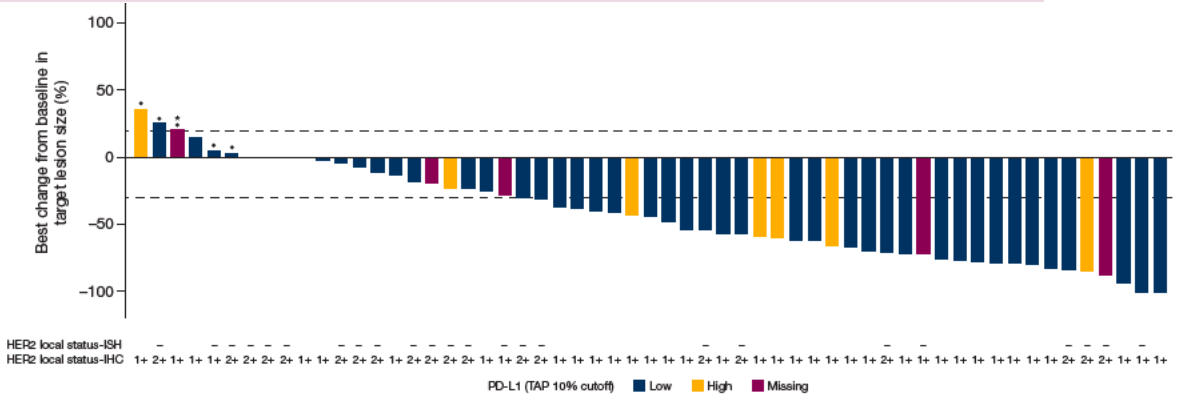
OS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median OS, months	18.2	8.3
HR (95% CI)	0.48 (0.24-0.95)	

Modi S, et al. ASCO 2022. Abstract LBA3, NEJM 2022

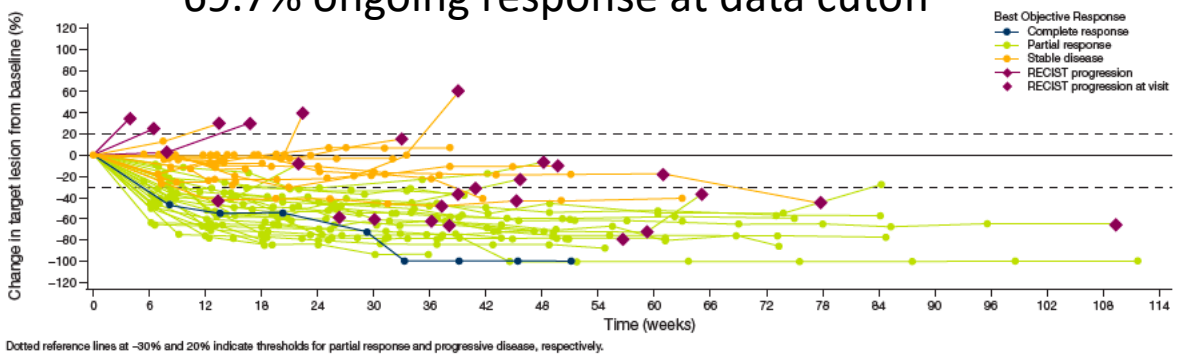
T-DXd + Durvalumab: The Begonia Trial



- First-line basket trial for HER2-low mTNBC
  - Arm 6 (n=58)
    - PD-L1 testing using SP263
    - ORR 56.9% (n=33)
    - PFS 12.6 mo (8.3-NC)
  - Safety
    - 8 cases of adjudicated ILD, 2 more pending review
      - Grade 1 (3), grade 2 (2), grade 3 (1), grade 5 (1, Covid related)
      - 17% stopped rx due to AEs



69.7% ongoing response at data cutoff

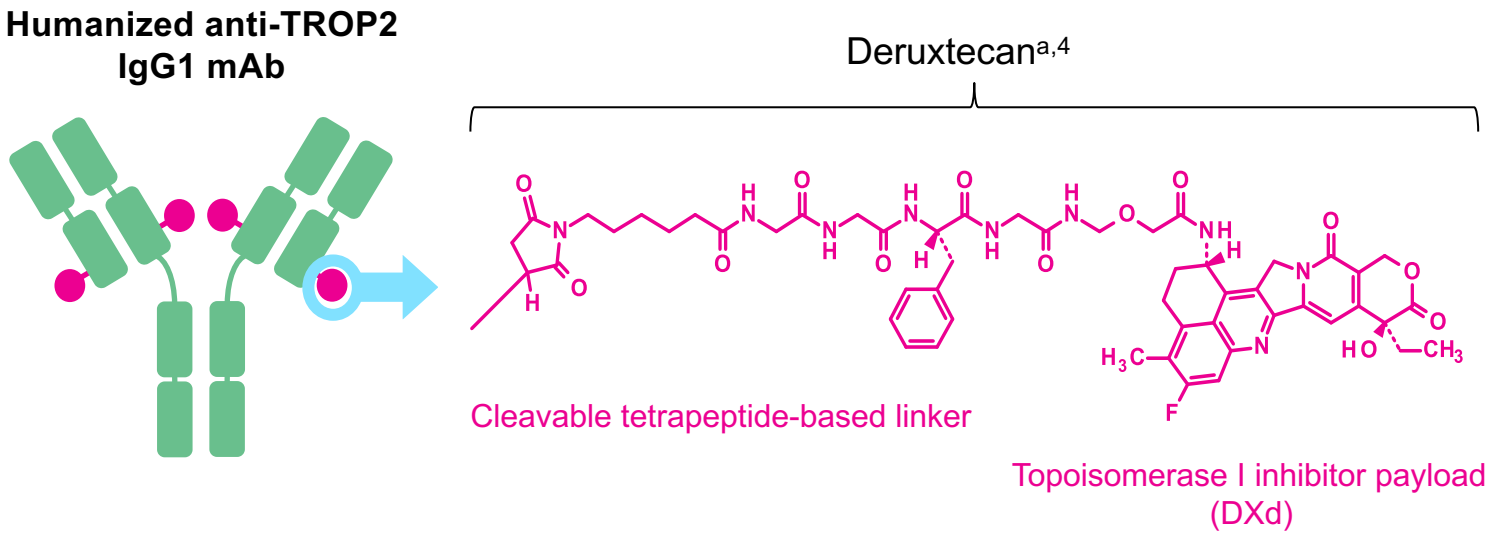


Schmid et al, SABCS 2022; PD11-08

Datopotamab Deruxtecan (Dato-DXd)

Dato-DXd is an ADC with 3 components[1,2]:

- A humanized anti-TROP2 IgG1[3] monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor [b,1]
High potency of payload [b,2]
Optimized drug to antibody ratio ≈4 [b,c,1]
Payload with short systemic half-life [b,c,2]
Stable linker-payload [b,2]
Tumor-selective cleavable linker [b,2]
Bystander antitumor effect [b,2,5]

[a] Image is for illustrative purposes only; actual drug positions may vary. [b] The clinical relevance of these features is under investigation. [c] Based on animal data.

1. Okajima D, et al. AACR-NCI-EORTC 2019; [abstract C026]; 2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173-185; 3. Daiichi Sankyo Co. Ltd. DS-1062. Daiichi Sankyo.com. Accessed October 6, 2020. https://www.daiichisankyo.com/media_investors/investor_relations/ir_calendar/files/005438/DS-1062%20Seminar%20Slides_EN.pdf; 4. Krop I, et al. SABCS 2019; [abstract GS1-03]; 5. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

TROPION-PanTumor01 Study: Dato-DXd Efficacy in TNBC

- Unresectable or metastatic HR+/HER2− (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Progressed on ≥1 endocrine therapy; previously treated with 1-3 prior lines of chemotherapy in the advanced setting
- Unselected for TROP2 expression[a]
- Age ≥18 years (US) or ≥20 years (Japan)
- ECOG PS 0-1
- Measurable disease per RECIST 1.1
- Stable, treated brain metastases allowed

→

NSCLC[b]
(0.27 to 10 mg/kg IV Q3W)

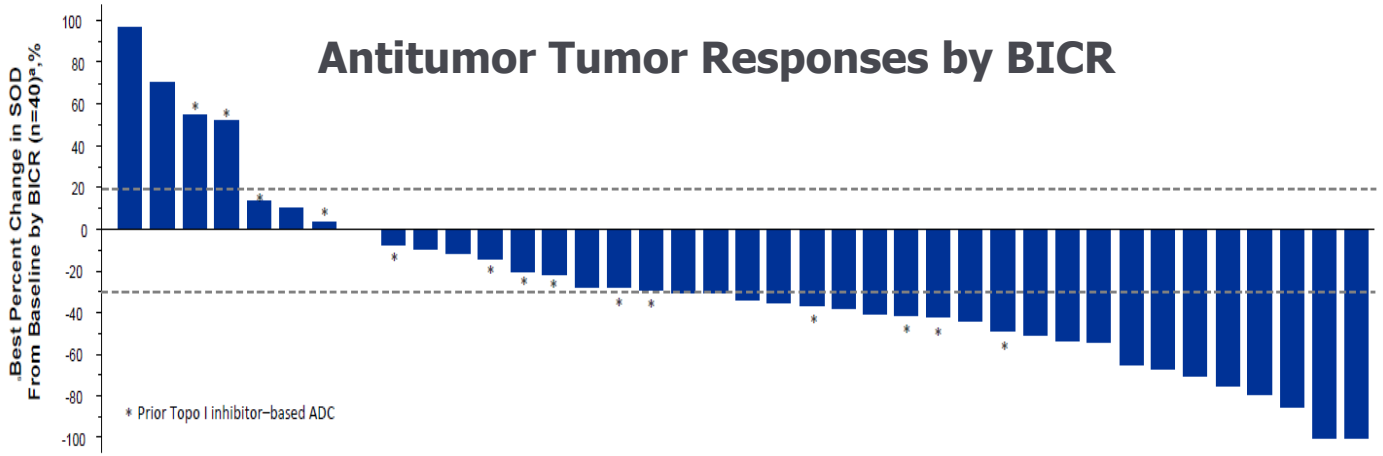
TNBC[c]
8 mg/kg IV Q3W (n=2);
6 mg/kg IV Q3W (n=42)

HR+/HER2− breast cancer
6 mg/kg IV Q3W (n=41)

Other tumor types
(SCLC, bladder, gastric, esophageal, CRPC, pancreas)

Primary objectives
- Safety
- Tolerability

Secondary objectives[d]
- Efficacy[e]
- Pharmacokinetics
- Antidrug antibodies



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%)

Bardia A, et al. SABCS 2022. Poster Presentation P6-10-03.

BEGONIA Trial: Dato-DXd + Durvalumab

- 1st line TNBC

TROPION-Breast02

NCT05374512

- 1st line therapy for TNBC
- PD-L2 negative

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 / PD-L1 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)

1:1

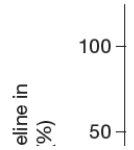
- **Dato-DXd**
- **Investigator's choice of chemotherapy**

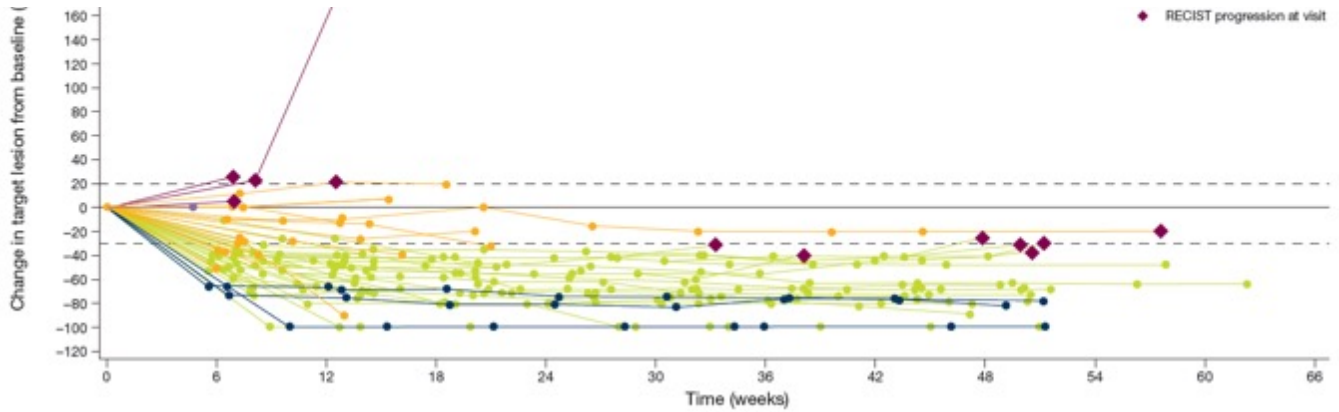
Dual primary endpoint:
PFS (BICR) and OS

Secondary endpoints:
PFS (inv), ORR, DoR, safety

- Stomatitis 55.7% no grade given
- Alopecia 45.9%
- Nausea 57.4%
- ILD/pneumonitis in 3.3% (2)

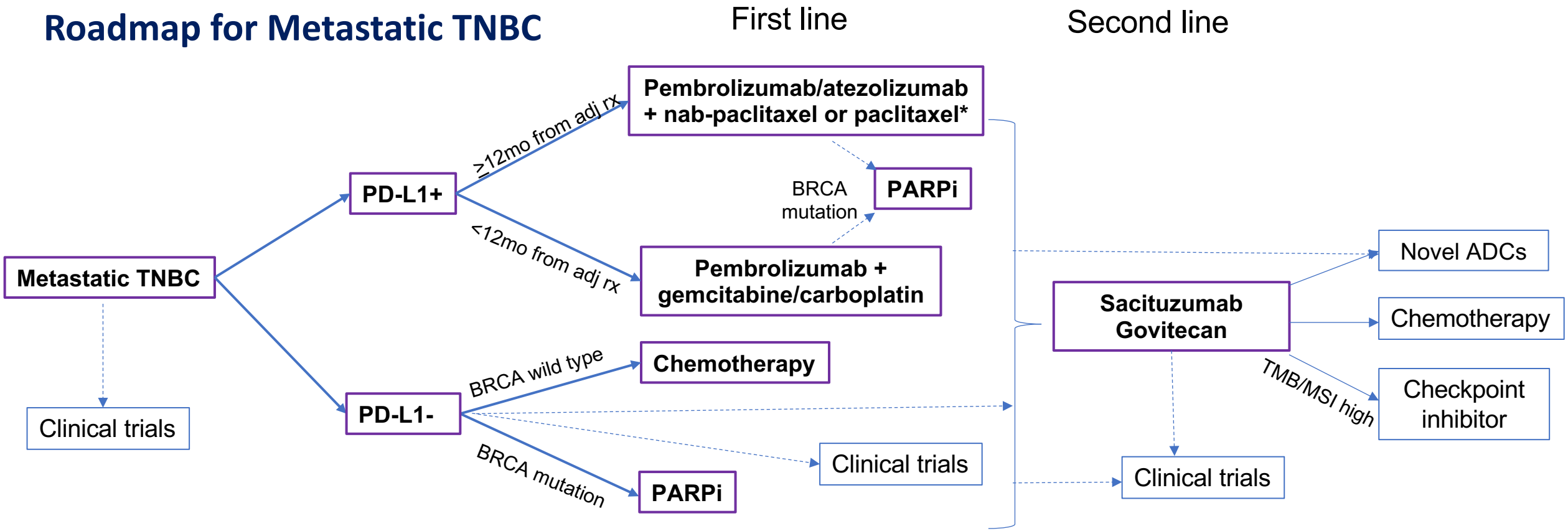
Best Change from Baseline of Target Lesion Size





Schmid et al, SABCS 2022; PD11-09

Roadmap for Metastatic TNBC



Pembrolizumab (CPS) *or atezolizumab ex US (SP142), nab-paclitaxel only*)

PARPi: PARP inhibitor (olaparib, talazoparib)

Role of AR targeting to be defined – LAR low proliferative subtypes?

Always consider clinical trials at each decision point

Early Stage Disease

TMC Neoadjuvant Platinum TNBC Study

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

- TNBC (1% cutoff for ER & PR)
- No evidence of M1
- Fit for anthracycline
- T1-T4, N0-3

R

Platinum
Pacli+Carbo → AC/EC

Control
Pacli → AC/EC

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

Surgery → Radiotherapy

No cape or CPI

Breast conserving surgery
OR
Mastectomy

Stratification

Menopausal Status
(Pre+Peri, Post)

Clinical Stage
OBC (cT_{1-3},N_{0-1}, M_0)
LABC (cT_4/N_{2-3}, M_0)

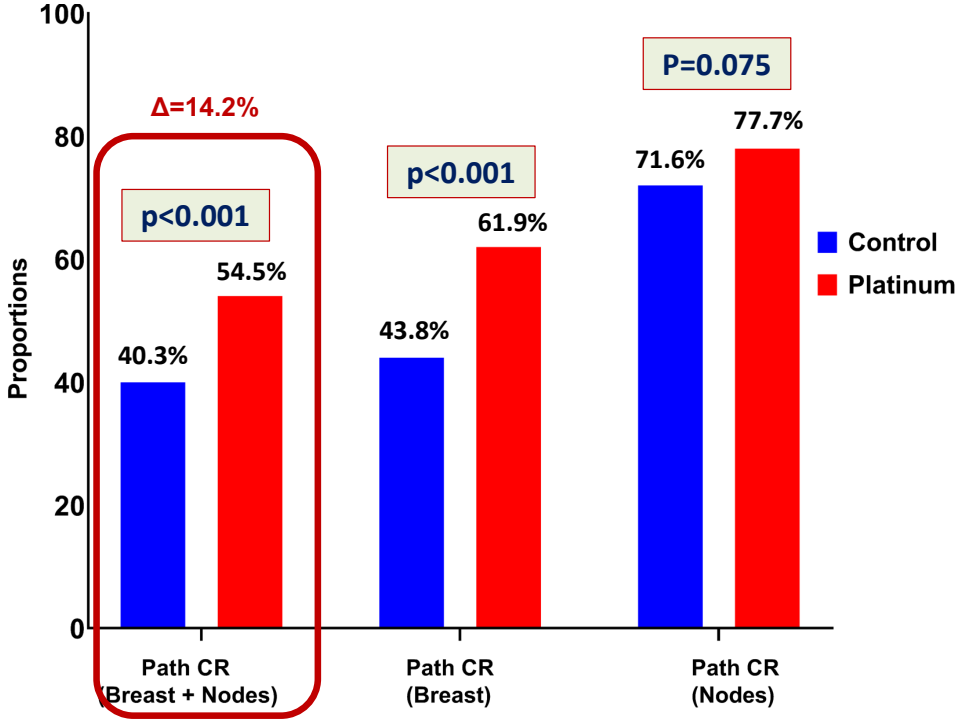
Platinum Arm:
Paclitaxel 100/m2 + Carboplatin (AUC-2) once per week X 8w*
followed by
[Doxorubicin (60/m2) or Epirubicin (90/m2)] + Cyclo (600/m2) every 2 weeks or 3 weeks X 4 cycles

Control Arm: Same as above, without carboplatin

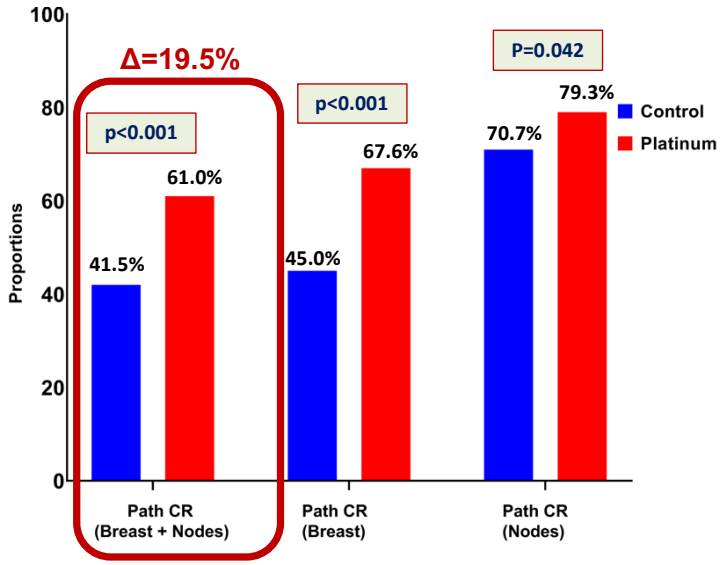
Gupta et al, SABCS 2022

*Gupta S, et al. Single agent weekly paclitaxel as neoadjuvant chemotherapy in locally advanced breast cancer: a feasibility study. Clin Oncol (R Coll Radiol). 2012 Nov;24(9):604-9

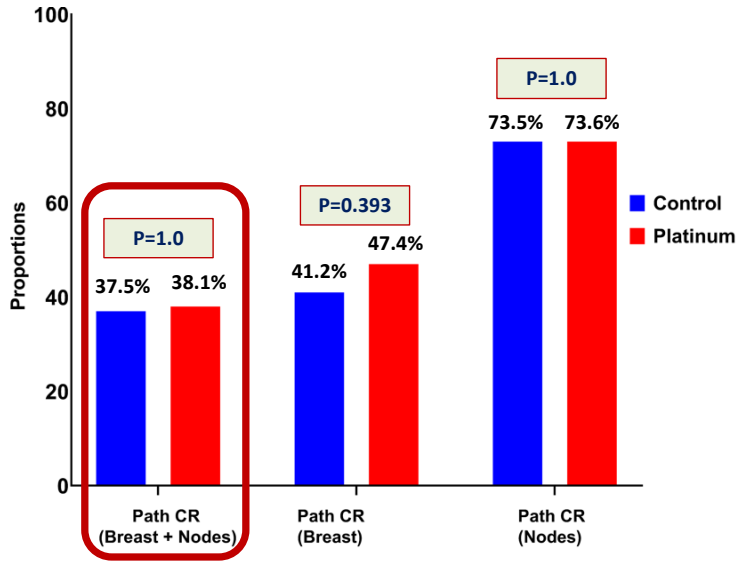
Pathologic Complete Response: Overall and by Age



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

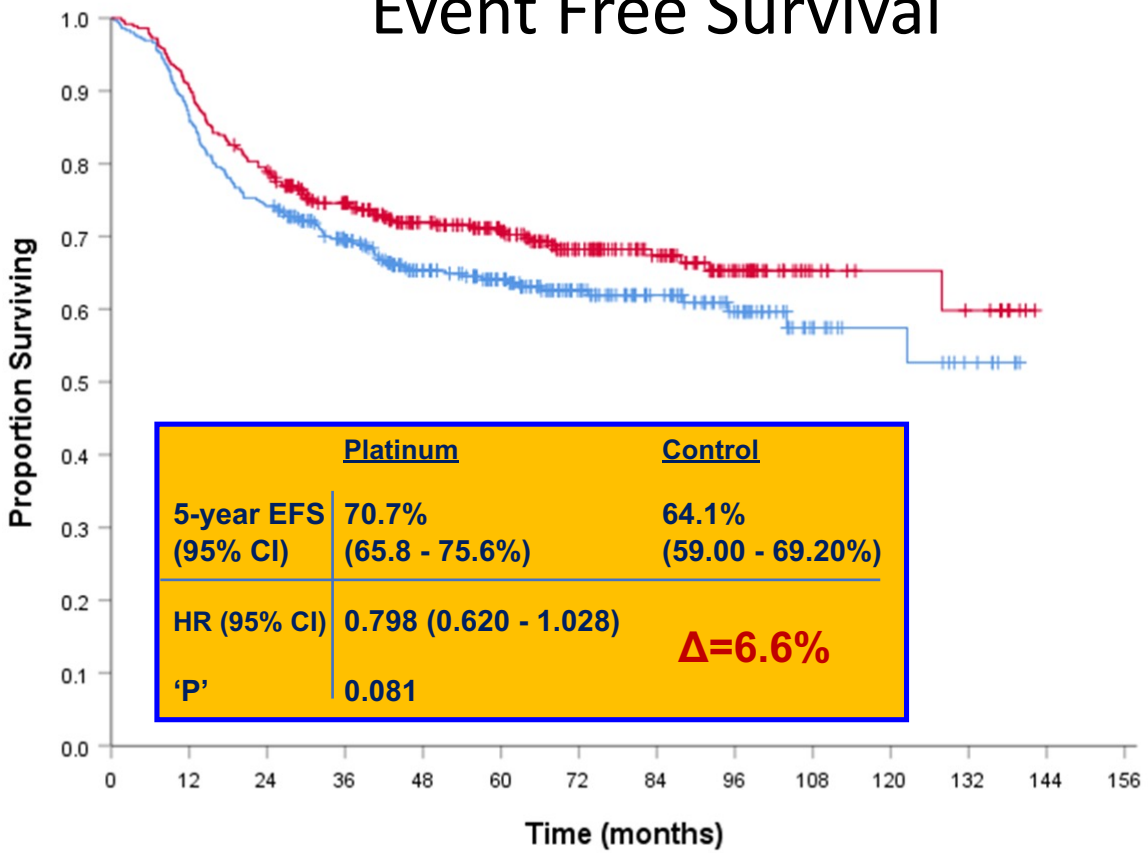
pCR highly prognostic for EFS regardless of age

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

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

Efficacy (n=717)

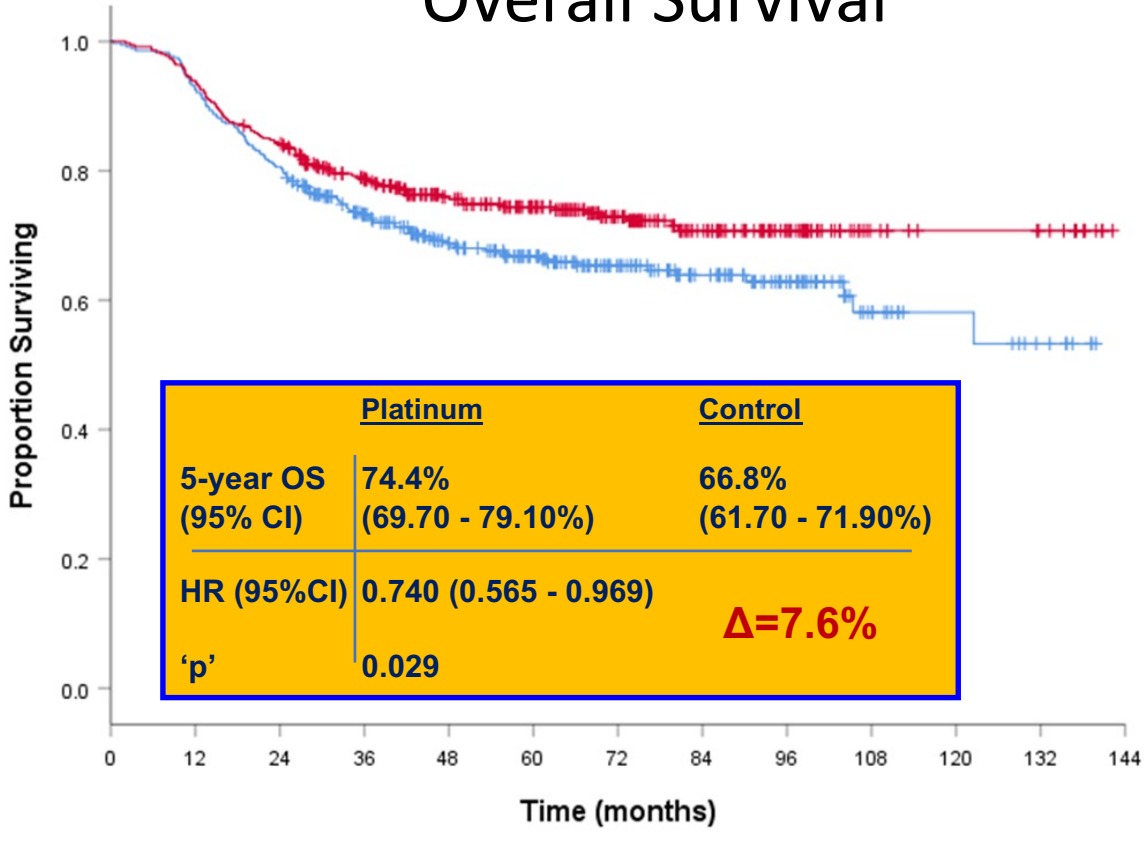
Event Free Survival



	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

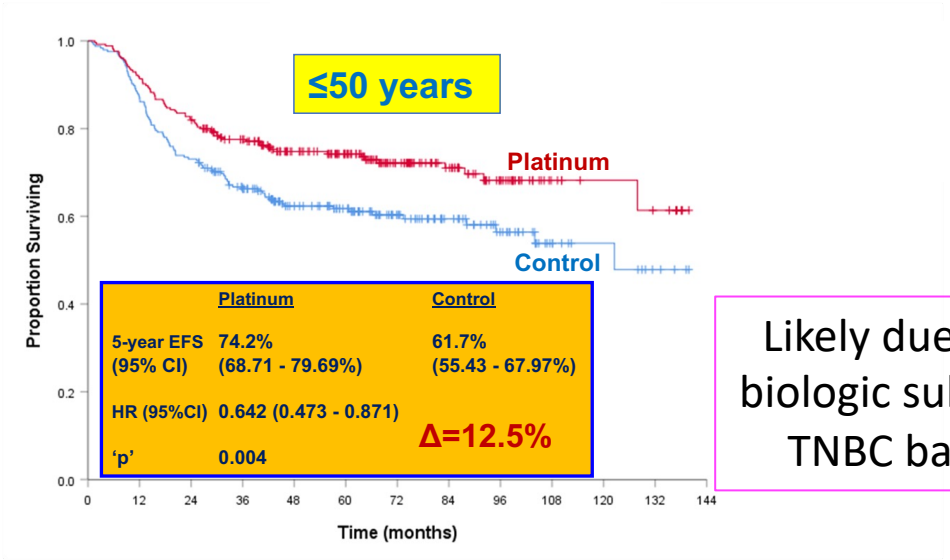
Overall Survival



	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	

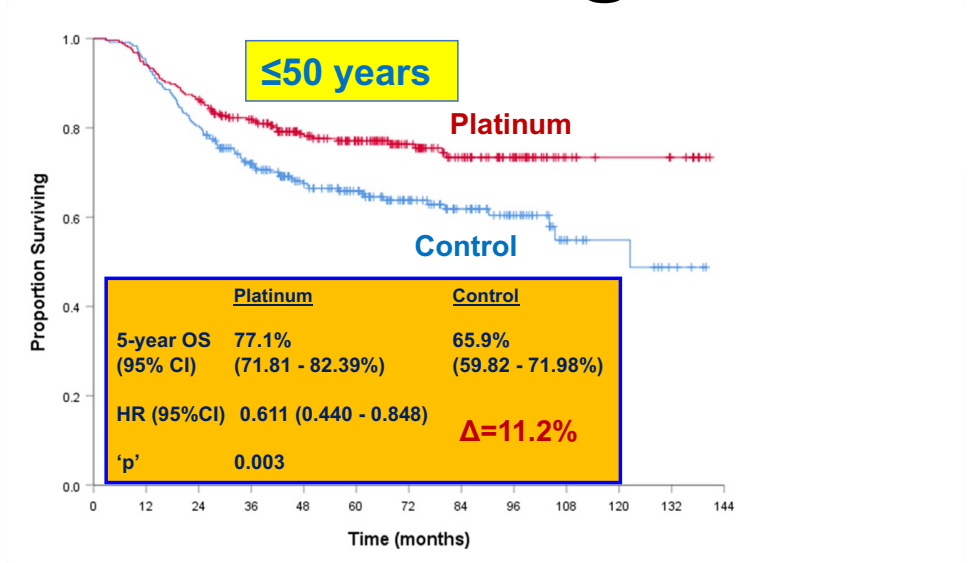
Control	356	330	287	229	179	147	106	74	48	20	12	7
Platinum	361	339	303	252	201	168	122	83	51	19	14	12

Differential Benefit Based on Age?

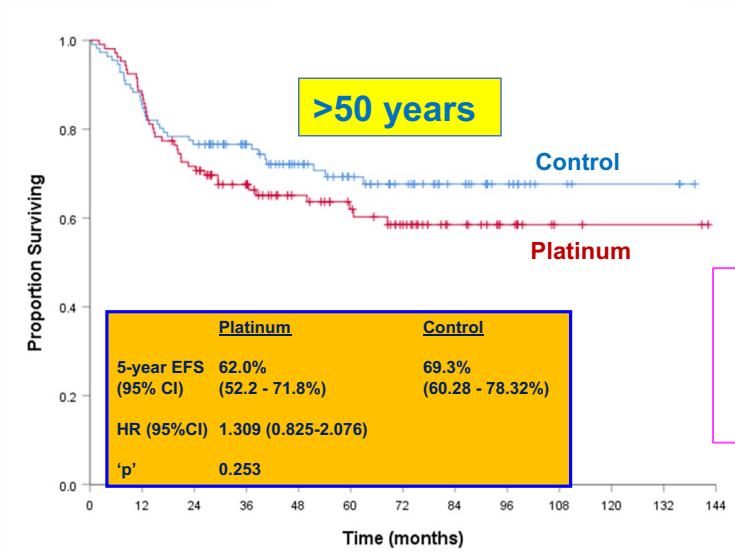


Control	245	213	179	149	115	98	69	49	32	14	9	4
Platinum	255	233	209	180	145	122	85	62	37	14	10	8

Likely due to different biologic subtypes within TNBC based on age

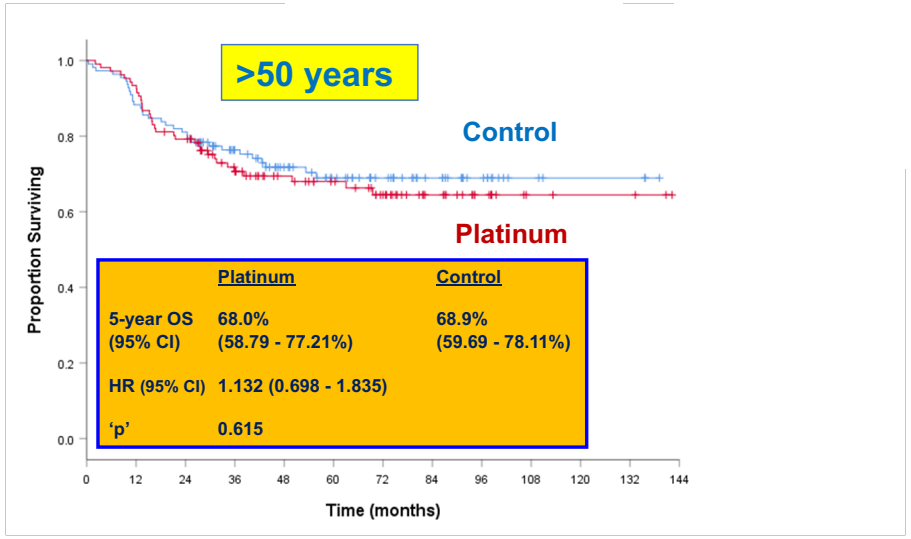


Control	245	232	197	160	125	104	74	53	35	15	9	4
Platinum	255	240	220	190	153	127	91	64	40	15	11	9



Control	111	95	85	69	54	43	32	21	13	5	3	3
Platinum	106	93	75	59	45	37	27	17	10	3	2	2

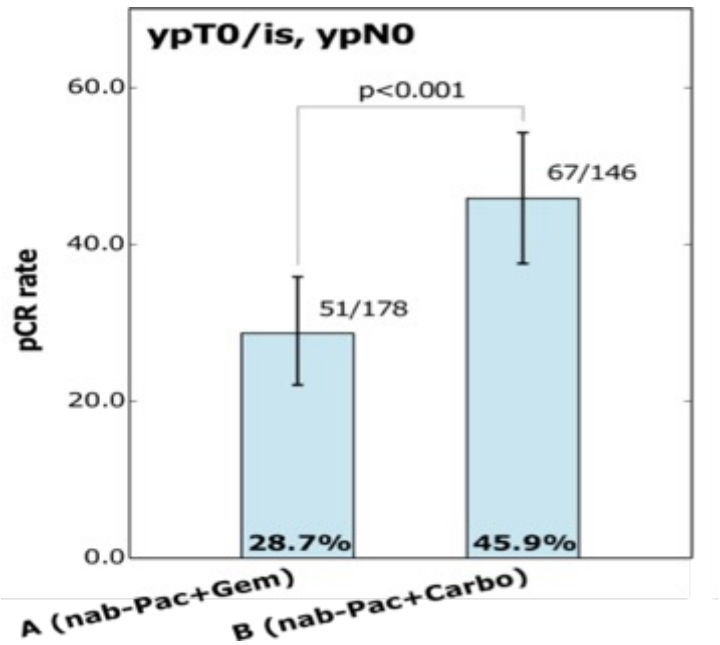
~80% completed all prescribed Rx, with no difference based on age



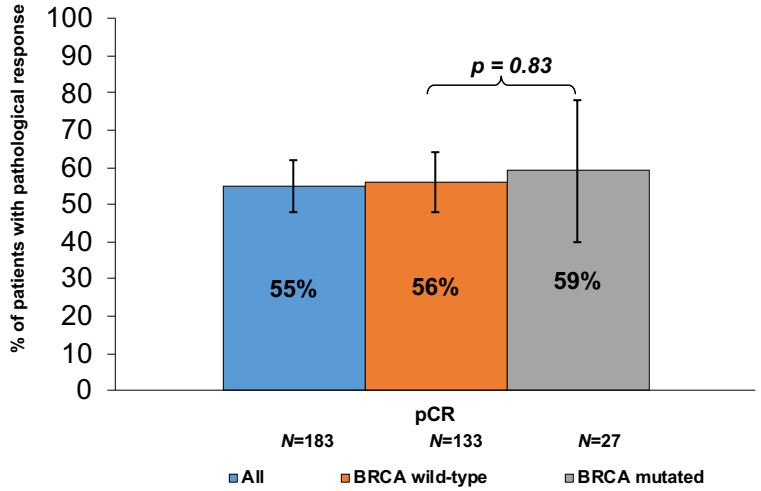
Control	111	98	90	69	54	43	32	21	13	5	3	3
Platinum	106	99	83	62	48	41	31	19	11	4	3	3

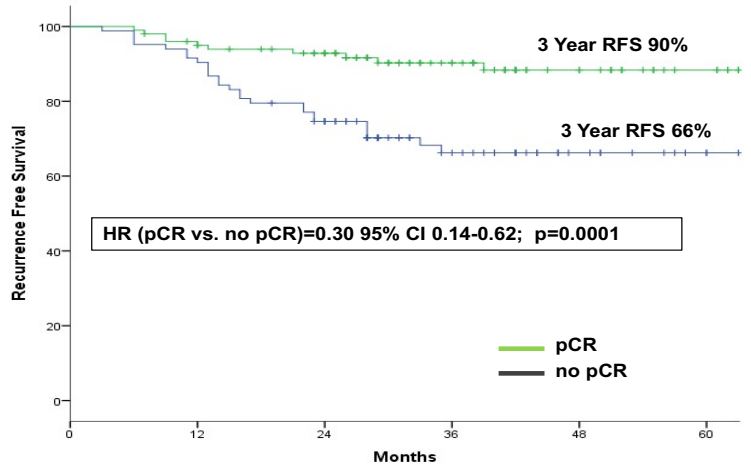
Can we Eliminate Anthracyclines?

ADAPT-TN; N=336



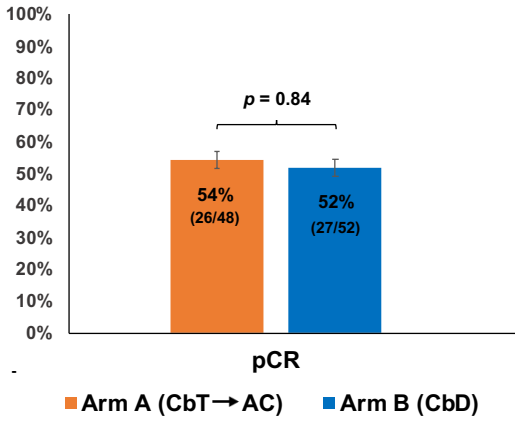
Pooled Analysis of 6 Cycles of Neoadjuvant Carboplatin plus Docetaxel (CbD) in TNBC

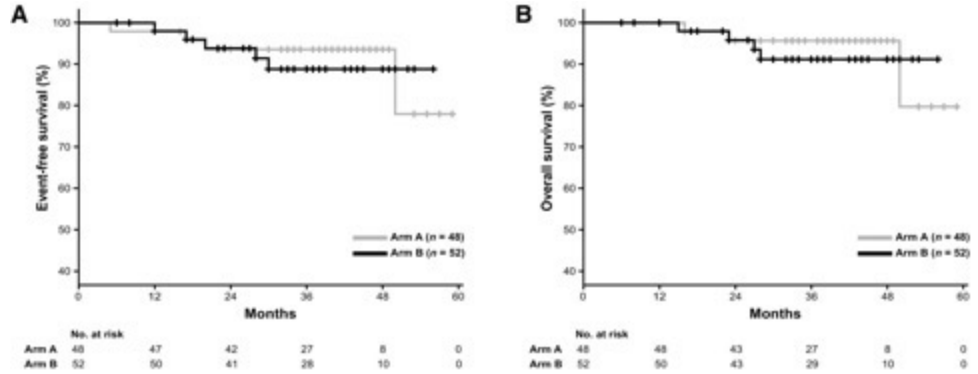




NeoStop Trial
TCa/AC vs Tca x 6
N=100

pCR and RCB

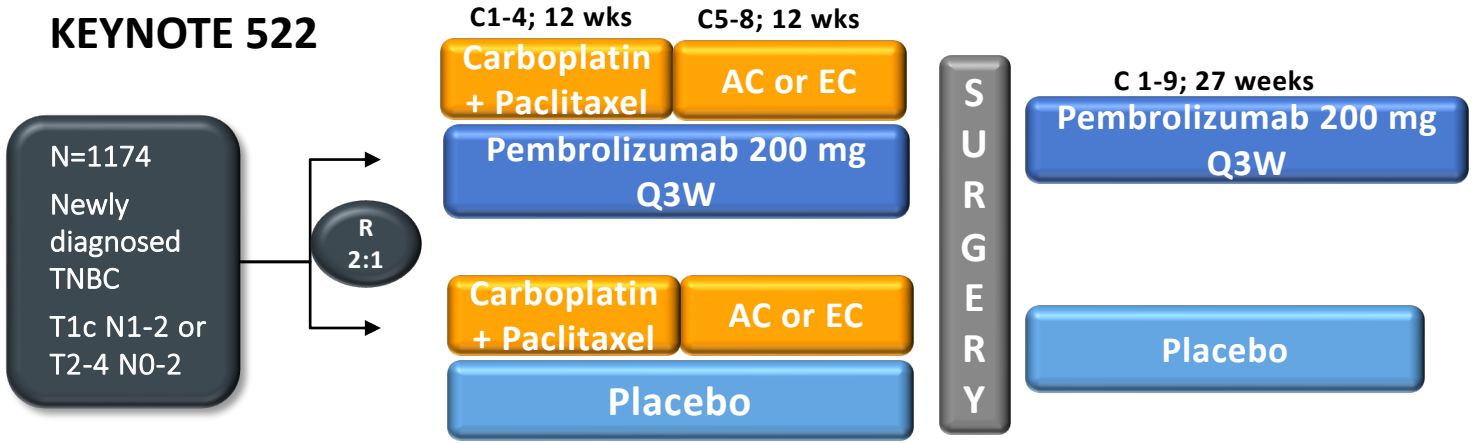




Gluz et al JNCI 2017; Sharma et al CCR 2016; Sharma et al CCR 2018; Sharma et al, CCR 2021.

Phase III Neoadjuvant Immunotherapy Trials

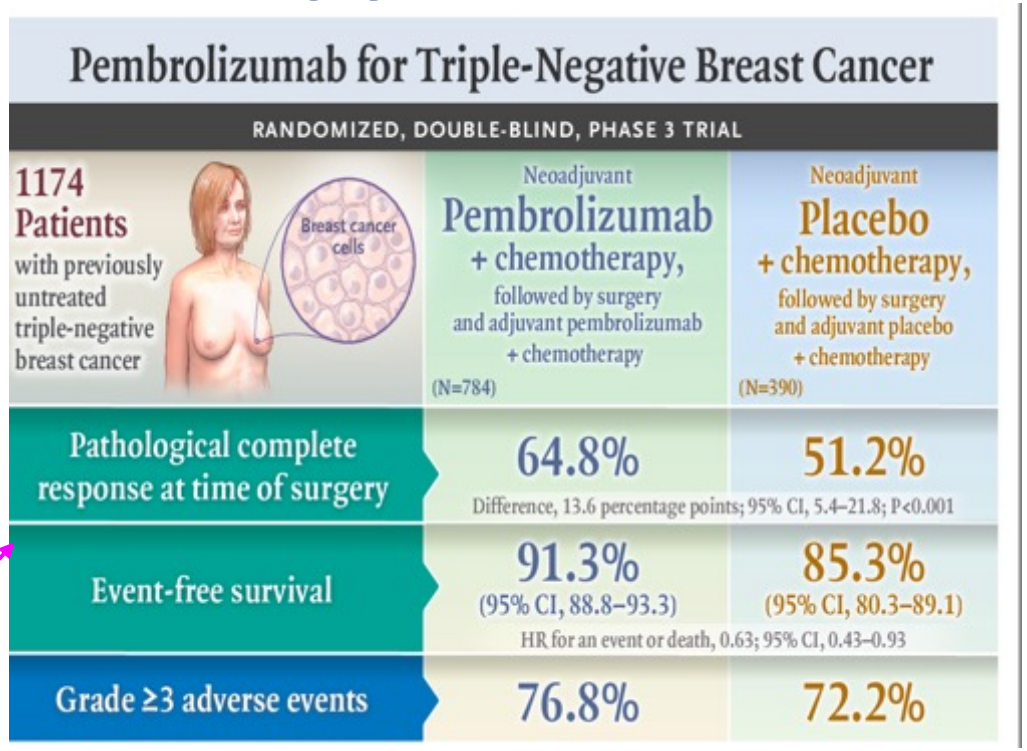
KEYNOTE 522



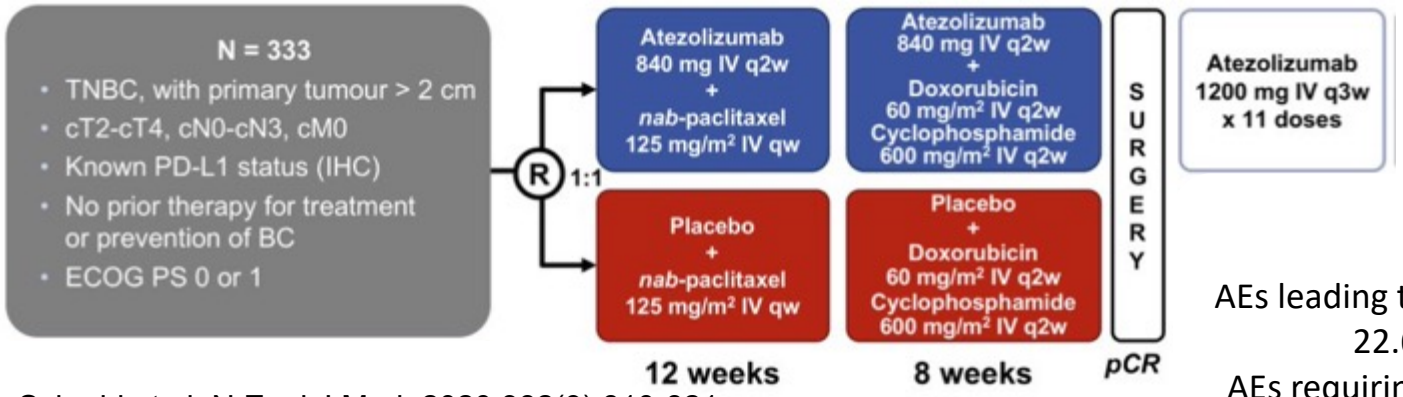
Patient population

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

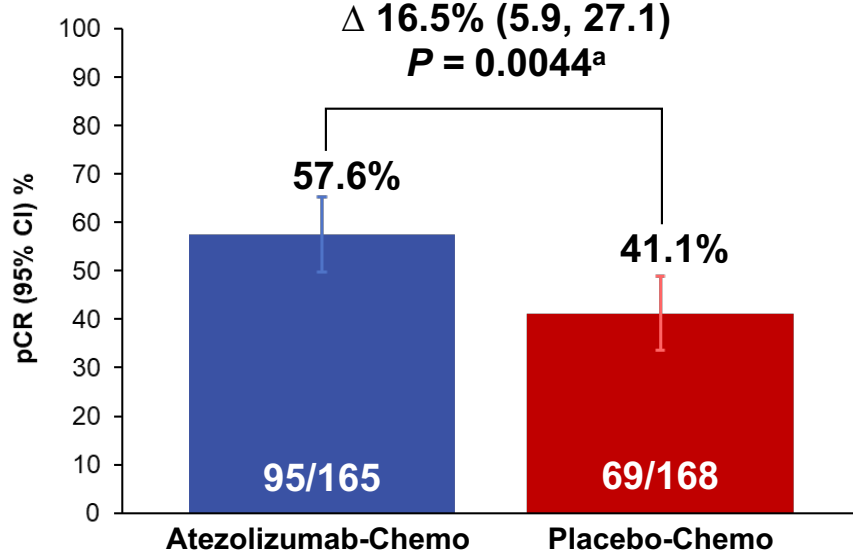
N=602



IMpassion 031



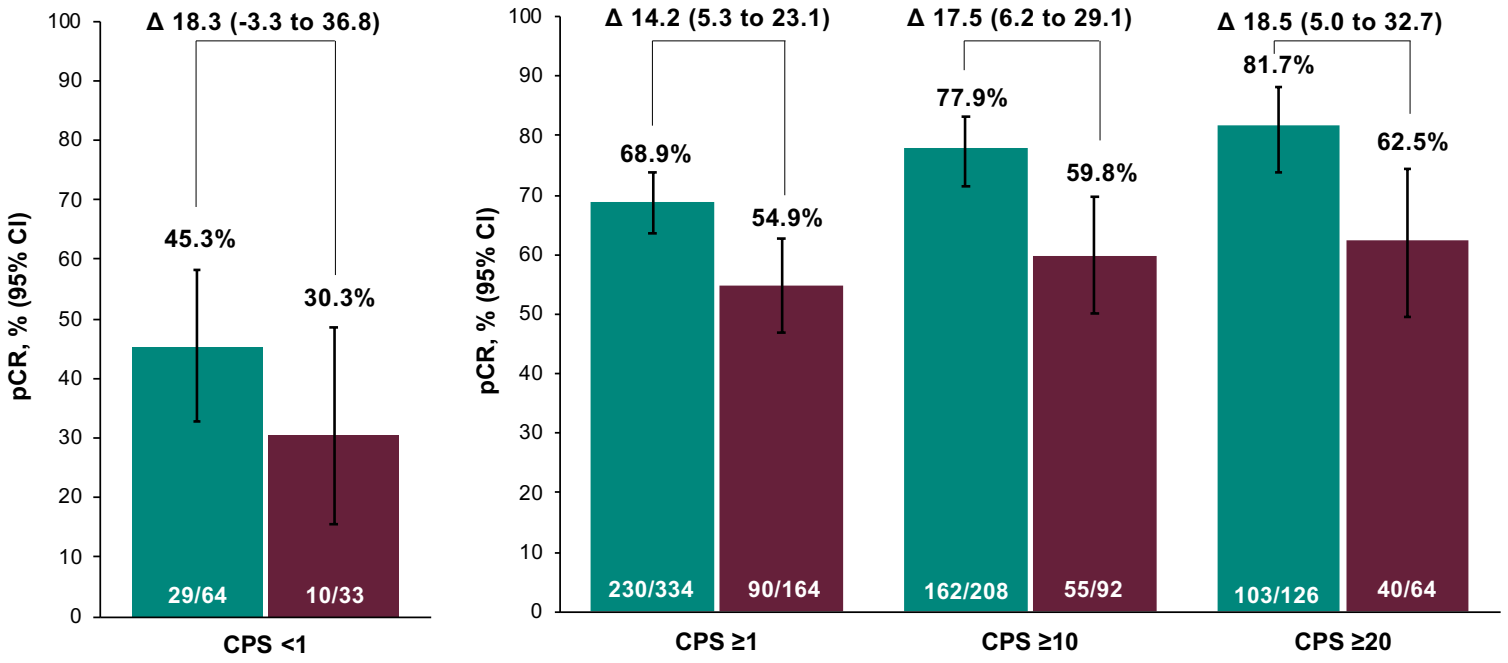
AEs leading to D/C of any drug:
22.6 v 19.8%
AEs requiring corticosteroids:
12.8 v 9.6%

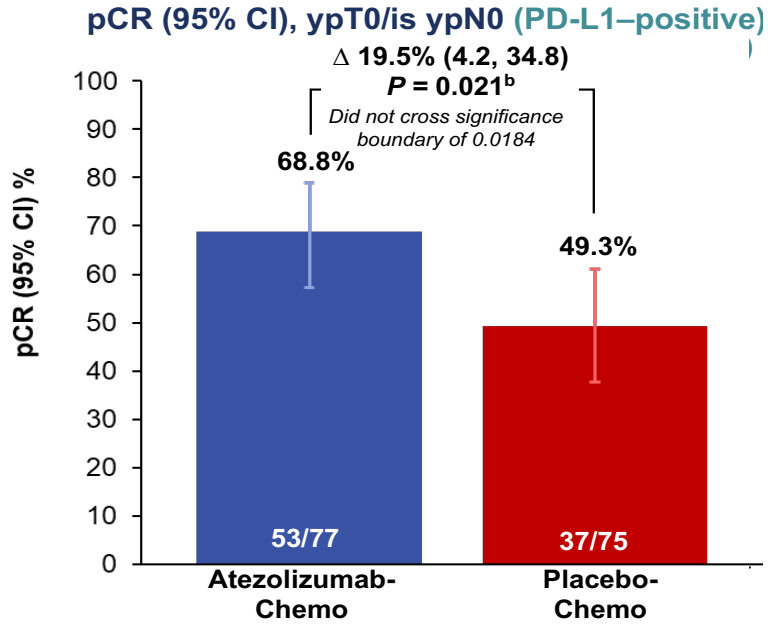


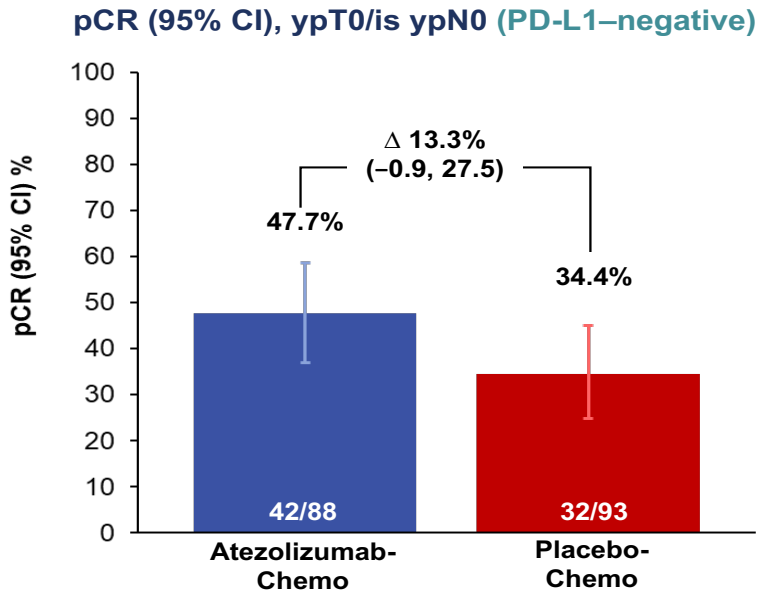
Schmid et al. N Engl J Med. 2020;382(9):810-821;
Mittendorf et al. Lancet 2020;396(10257):1090-1100.

Benefit from Immunotherapy is Independent of PD-L1 status

Is PD-L1 Predictive of Response to Chemotherapy?



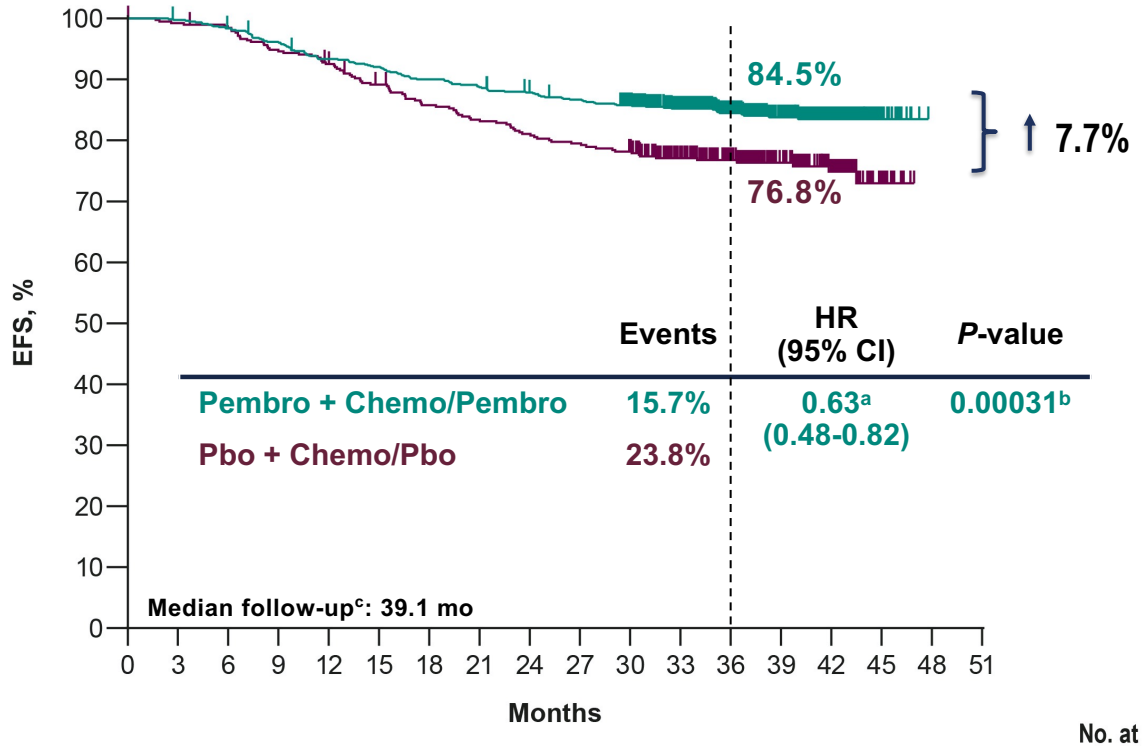




Schmid et al. SABCS 2019, Abstr. GS3-03;
Mittendorf et al. Lancet 2020;396(10257):1090-1100.

EFS and DRFS: Statistically Significant at IA4

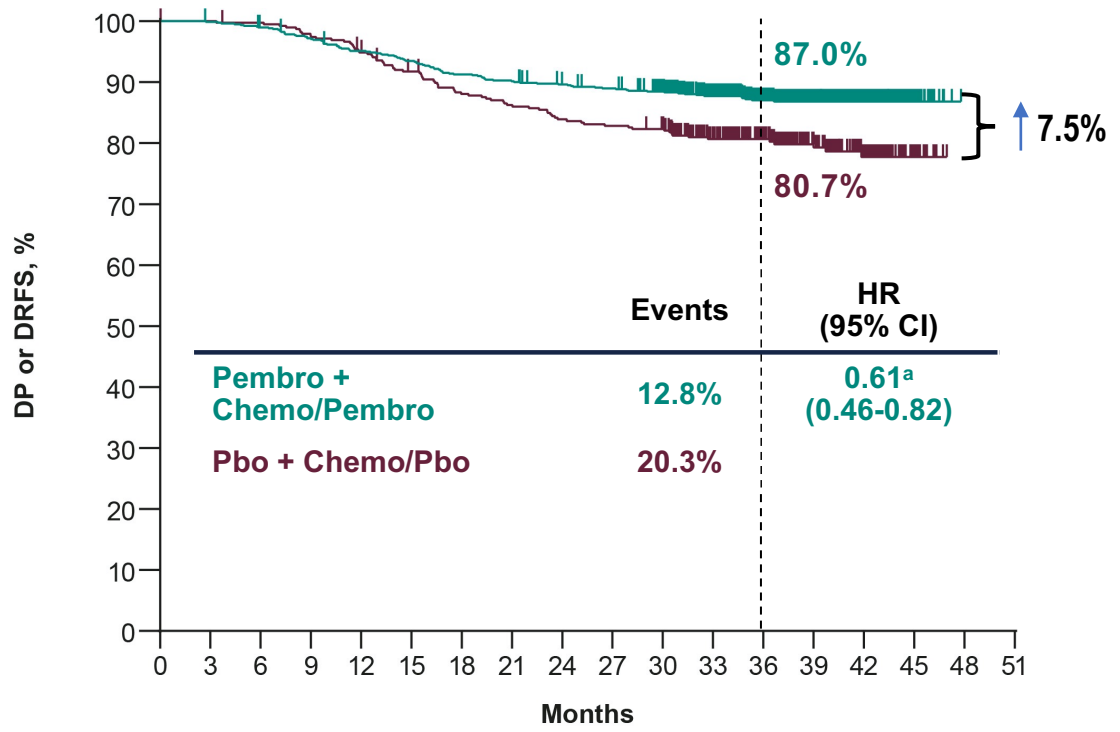
EFS



No. at Risk

Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

DRFS



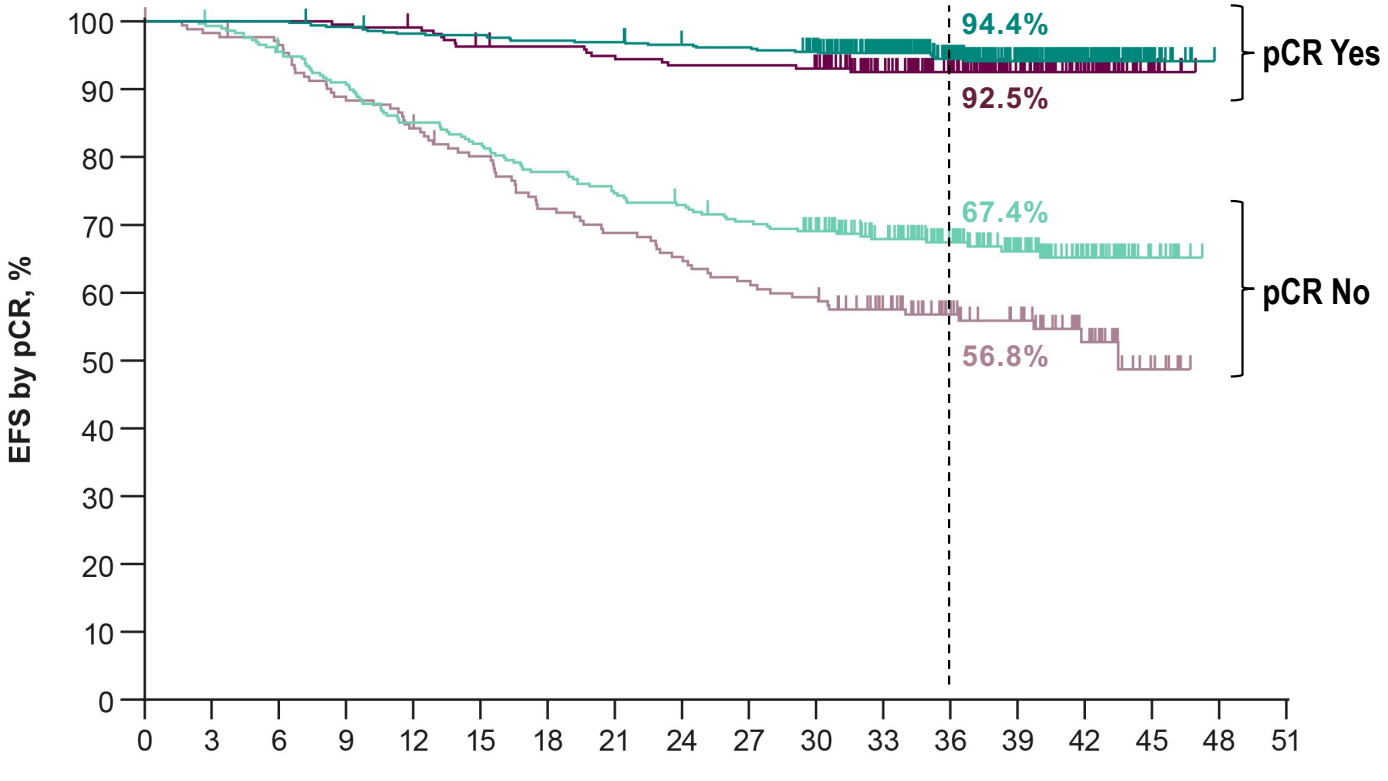
No. at Risk

Pembro + Chemo/Pembro	784	782	773	758	741	728	711	702	692	685	663	561	439	308	167	29	0	0
Pbo + Chemo/Pbo	390	389	387	379	367	352	337	330	321	317	312	259	202	143	84	17	0	0

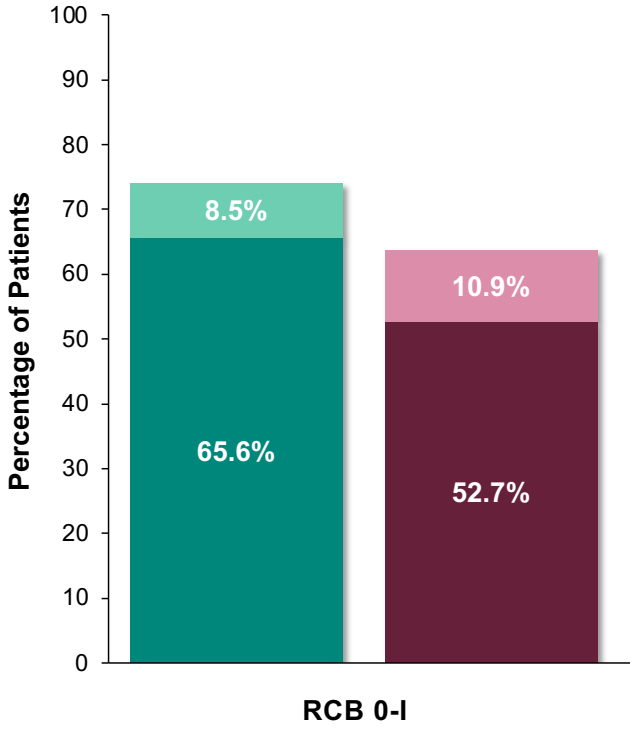
Schmid et al, ESMO virtual plenary 2021.

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]**Prespecified *P*-value boundary of 0.00517 reached at this analysis.**
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

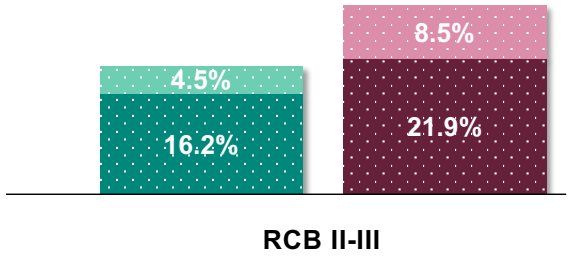
EFS by pCR (ypT0/Tis ypN0)



No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

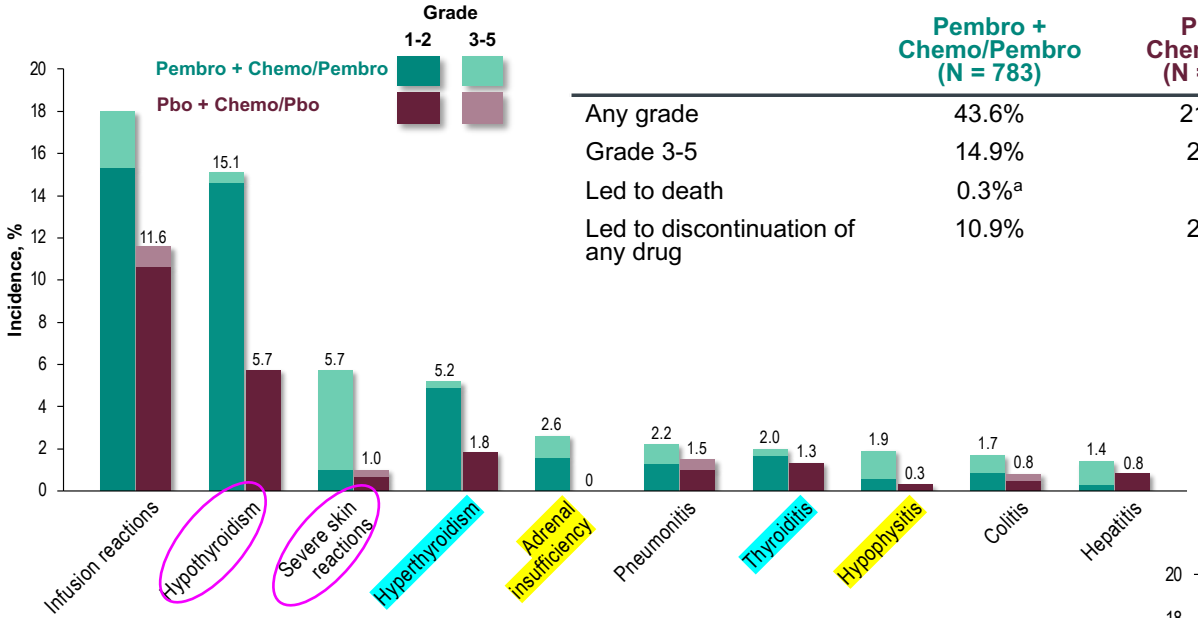


RCB Frame Shift with Pembrolizumab at IA1



Schmid et al. SABCS 2019. Abstract GS3-03; Data cutoff date: April 24, 2019

What is the Patient Cost of Therapy: Toxicity

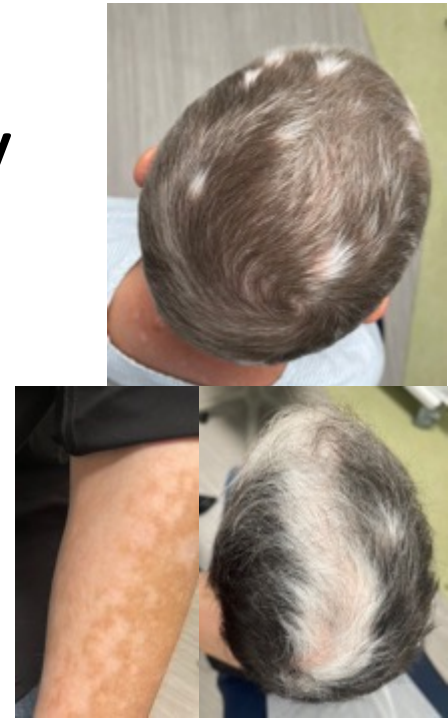


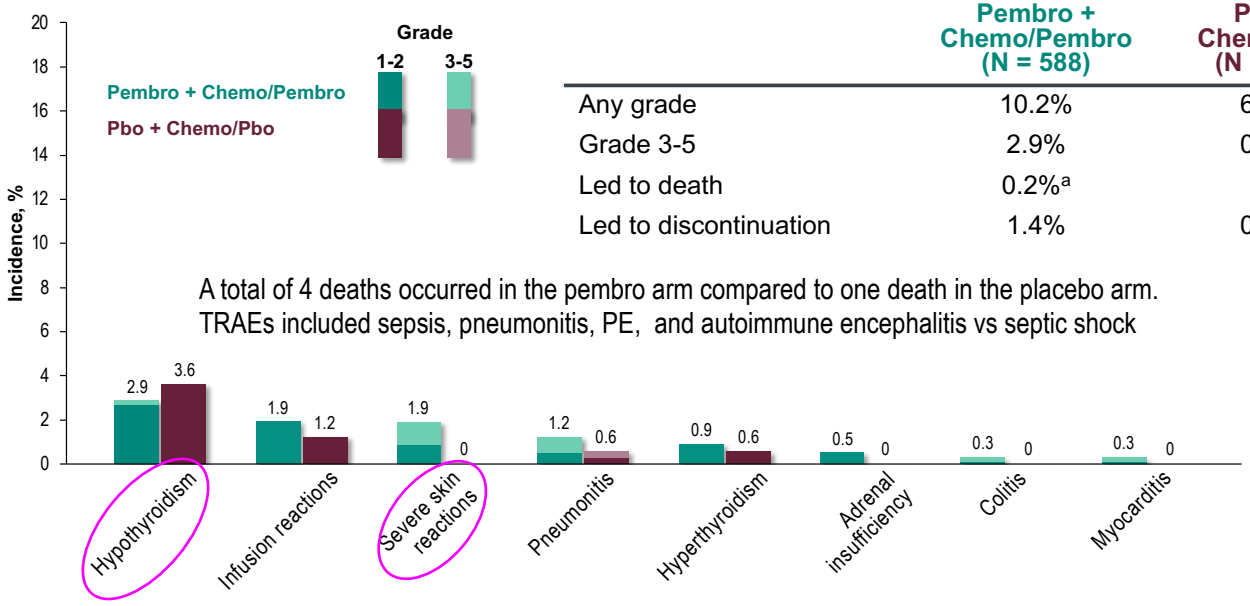
	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

Neoadjuvant + chemo

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

Checkpoint Inhibitors in Early TNBC

Variable	I-SPY	KEYNOTE-522	IMPASSION 031	NeoTRIP	GeparNUEVO
Total patients	69/180	**1174 (602)**	**333**	**280**	**174**
Type of CPi	PD1 **Pembro x 4**	**PD1** **Pembro x 1 year**	**PD-L1** **Atezo x 1 year**	**PD-L1** **Atezo x 8**	**PD-L1** **Durva x 8**
Stage	**Stage II/III**	**Stage II/III**	**Stage II/III**	**+ N3 disease**	**35% stage I**
Anthracycline pre-op	**yes**	**yes**	**yes**	**No***	**yes**
Included carboplatin	**no**	**yes**	**No (nab-pac)**	**Yes (nab-pac)** **2 wks on, 1 wk off x 8**	**no**
Improved pCR	**Yes**	**Yes** **51.2 v 64.8%** **P=0.00055**	**Yes** **41.1 v 57.6%** **P=0.0044**	**No**	**Numeric improvement** **(44 v 53%, p=0.18)**
Improved EFS	**NR:** **pCR>nonpCR**	**Yes**	**NR**	**NR**	**Yes** **EFS, DDFS and OS**

Nanda et al, JAMA Onc 2020; Schmid et al, NEJM 2020 & ESMO Plenary 2021; Mittendorf et al, Lancet 2020; Gianni et al, SABCS 2019; Loibl et al, Ann Oncol 2019 & ASCO 2021

*Callari et al, PD10-09:, SABCS 2021: role of anthracyclines in the modulation of the immune microenvironment

Ongoing Phase III Trials with IO in TNBC

Neoadjuvant/adjuvant

- Atezolizumab
  - NSABP B59/GeparDouze (n=1520)
    - Pac/carbo → AC/EC
  - EFS NeoTRIPaPDL1 (n=272)
  - EFS Impassion 031 (n=333)
- Pembrolizumab
  - NeoPACT (n=100)
    - Docetaxel/carbo/pembro x 6

Adjuvant

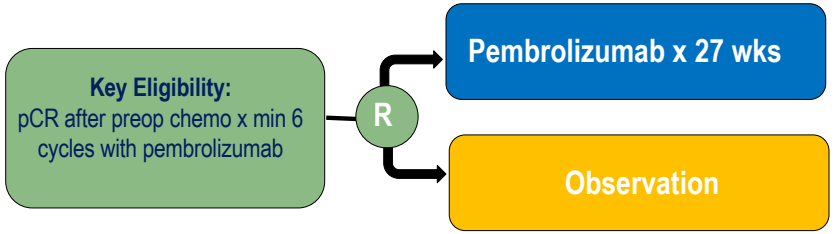
- Atezolizumab
  - Impassion 30 (n=2300)
    - Pac → AC/EC
- Avelumab
  - A-Brave (n=335)
    - Adjuvant and post NAC high risk: avelumab alone
- Pembrolizumab
  - SWOG S1418/NRG BR006 (n=1155)
    - Post NAC: Pembro vs Obs x 1 yr

- Completed
- Closed early, results pending

TNBC: Immunotherapy for Early-Stage Disease
What are the unanswered questions?

- Who needs checkpoint inhibitors
  - Balancing risk and cost: Can we identify a group of patients who will do well with chemotherapy alone?
  - Balancing risk and toxicity: are there patients who should not receive IO?
- Optimal chemotherapy backbone
  - Role of platinum salts: improved PCR and EFS but not OS; balance toxicity against impact on EFS
  - Anthracyclines may have an important role
- Optimal duration of CPI if pCR achieved?
    - Balancing risk and toxicity
- Optimal post-neoadjuvant therapy
    - Should we combine or sequence pembrolizumab with other post-neoadjuvant therapies?

OptimICE-pCR

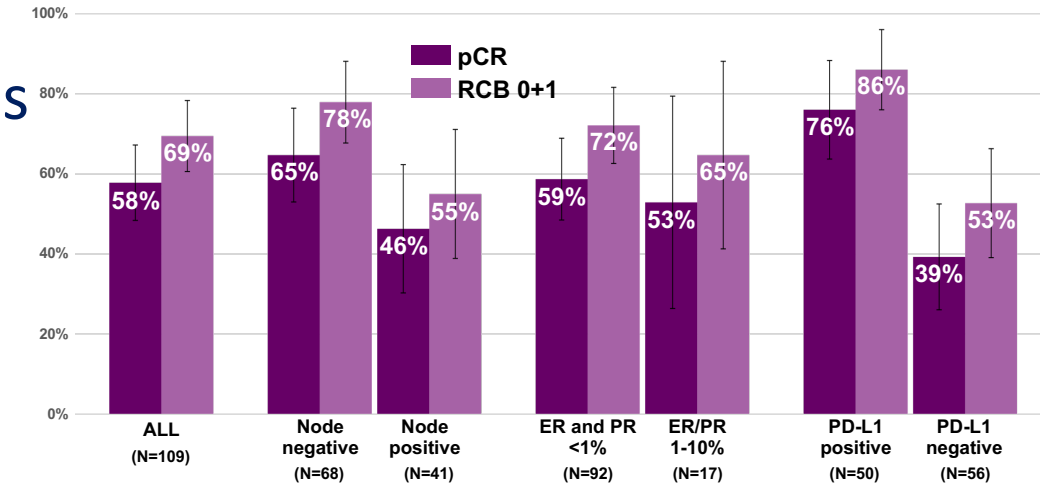


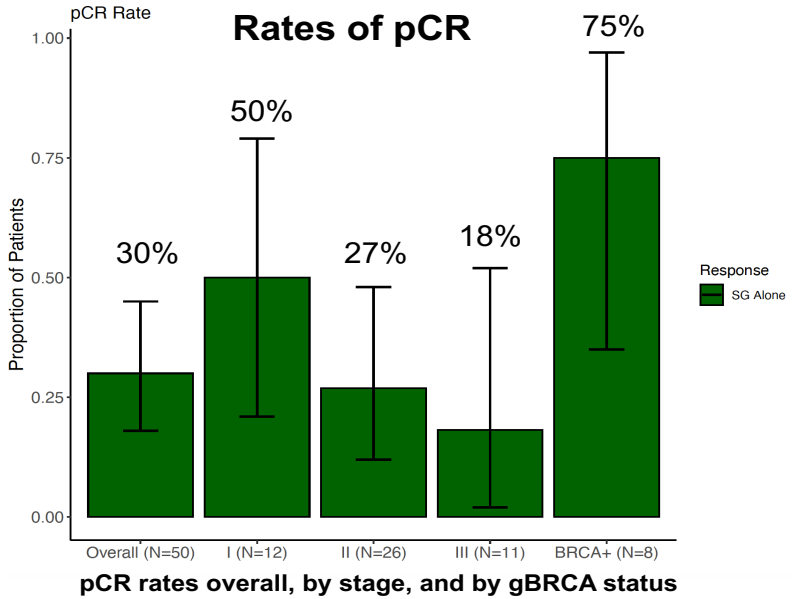
Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

PI: Tolaney
Alliance Trial

Alternative NeoAdjuvant Regimens for TNBC

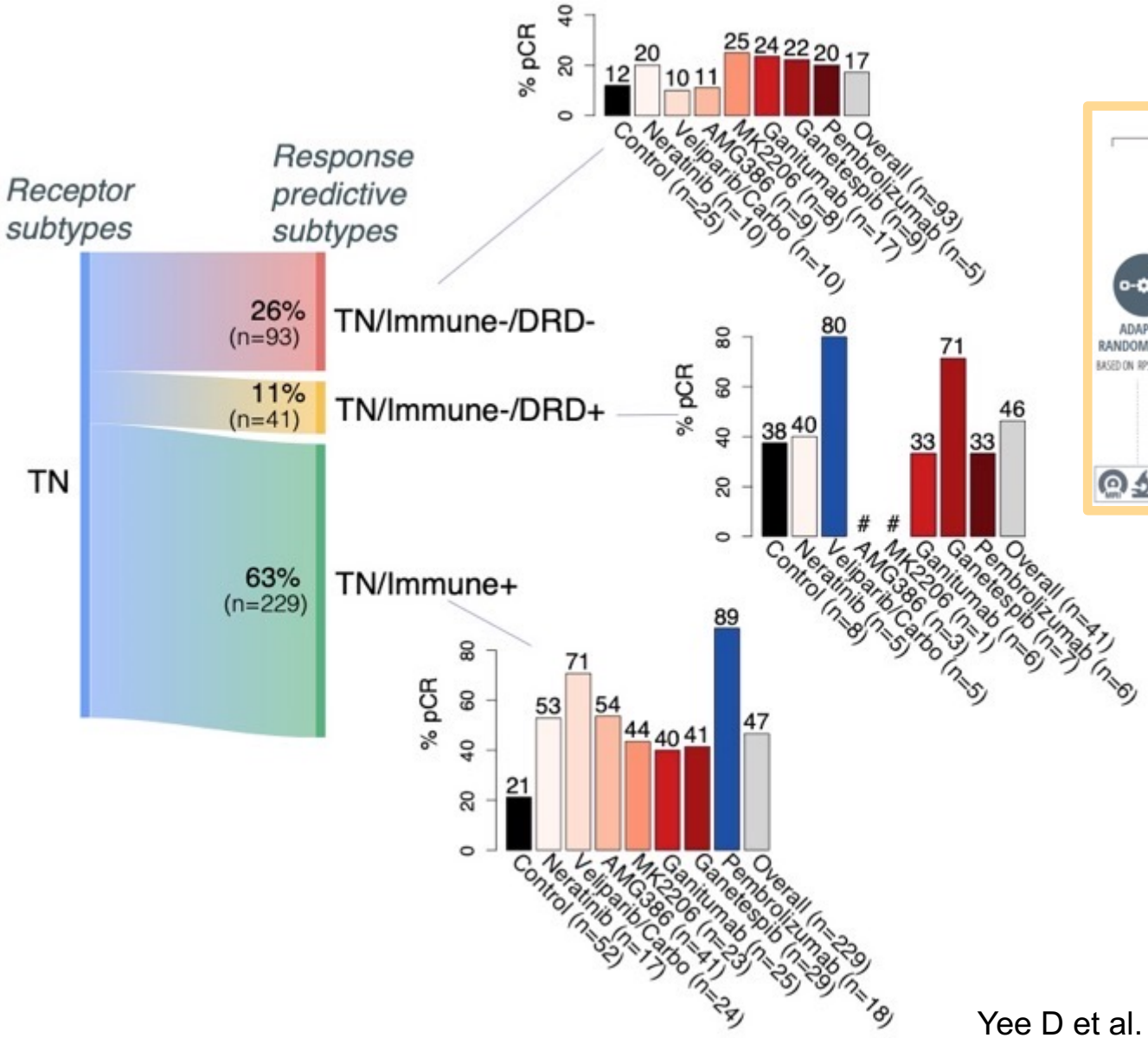
- NeoPACT:
  - Pembrolizumab/docetaxel/carboplatin x 6 cycles
  - 109 evaluable, 88% stage 2-3
  - pCR in TNM stage I, II, and III disease was 69%, 59%, and 43%, respectively.
  - Stage II-III, ER & PR IHC <1%
    - pCR and RCB 0+1 59% and 69%
  - 2-year EFS with pCR: 98%
- NeoSTAR: Sacituzumab govitecan 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

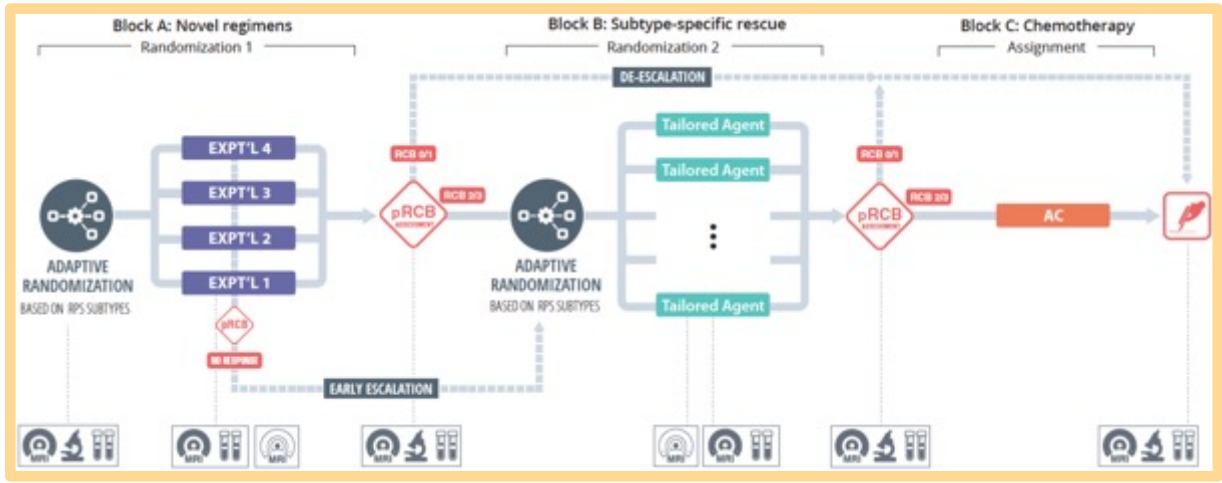




Sharma et al. ASCO 2022. Abstract 513; Spring et al. ASCO 2022. Abstract 512.

TNBC pCR and Response Predictive Subtypes in ISPY2: The Next Step in Personalized Medicine – ISPY2.2 and Others!



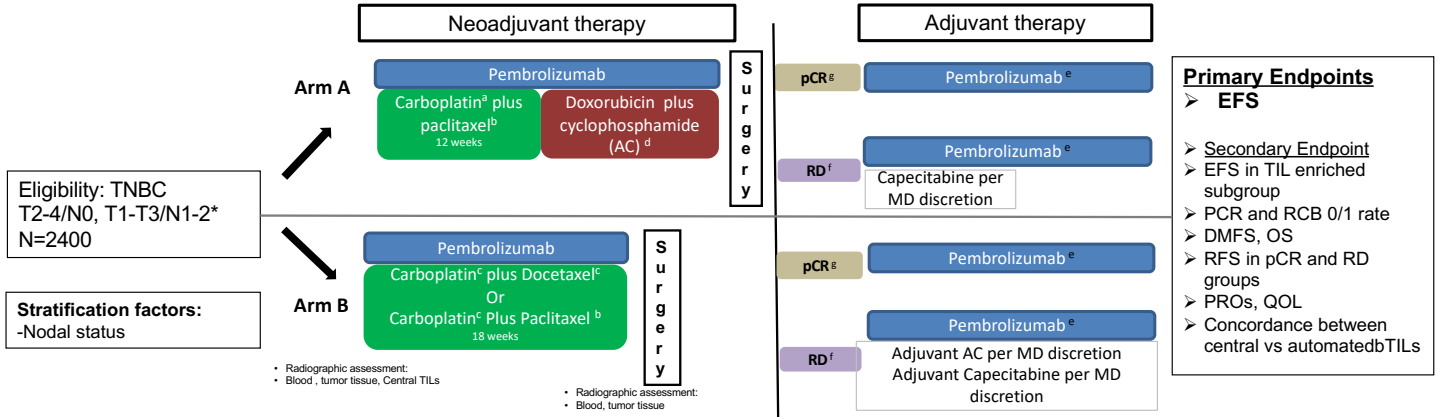


Yee D et al. 2022 ASCO Annual Meeting. Abstract 591; Wolf, Yao et al, CCR 2022.

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

- **EFS**
- Secondary Endpoint
- EFS in TIL enriched subgroup
- PCR and RCB 0/1 rate
- DMFS, OS
- RFS in pCR and RD groups
- PROs, QOL
- Concordance between central vs automatedbTILs

*T4/N+ , any N3 and inflammatory breast cancer excluded

[a]Carboplatin QW or Q 3W

[b] Paclitaxel QW.

[c] Carboplatin Q3W, Docetaxel Q 3W

[d] AC every 3 weeks

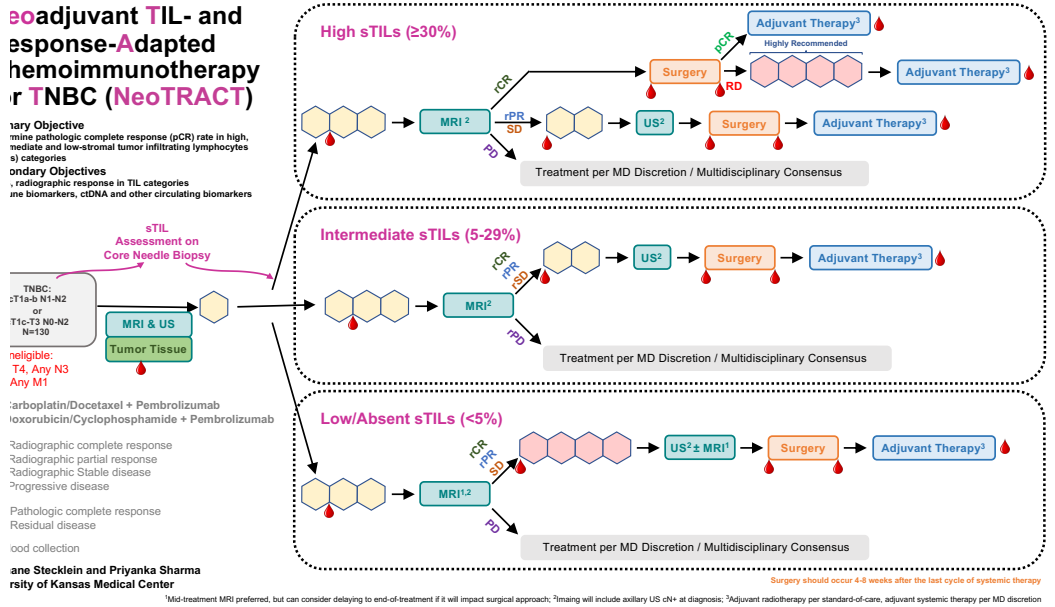
[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks (17 q 3 week doses)

[f] Co-enrollment in adjuvant NCTN escalation trials will be allowed after discussion with CTEP/study teams

[g] No Further Adjuvant chemotherapy. Co-enrollment in adjuvant NCTN de-escalation trials will be allowed after discussion with CTEP/study teams

PI: Priyanka Sharma, Zahi Mitri

SWOG CANCER RESEARCH NETWORK



Post-Neoadjuvant Therapy

Post-Neoadjuvant or Adjuvant Capecitabine

CREATE-X

Pts 20-74 yrs of age

stage I-IIIB HER2- BC and residual disease

(non-pCR or pN+) after neoadjuvant chemotherapy* and surgery;

ECOG PS 0 or 1;

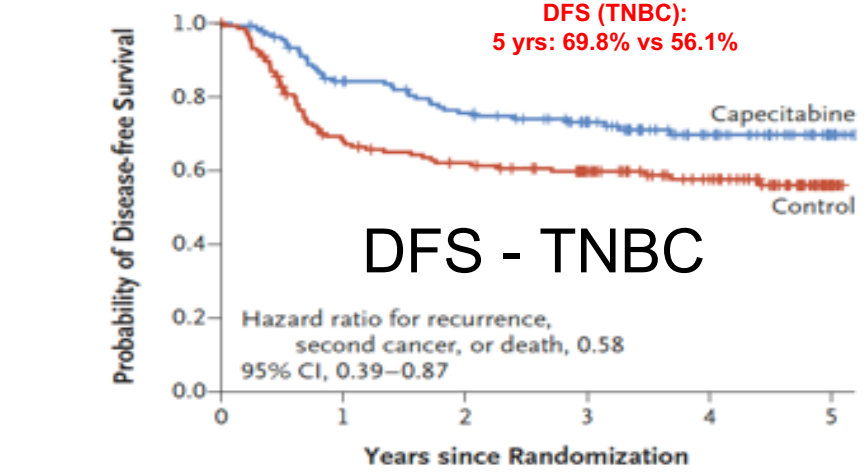
no previous oral fluoropyrimidines

(N = 910)†

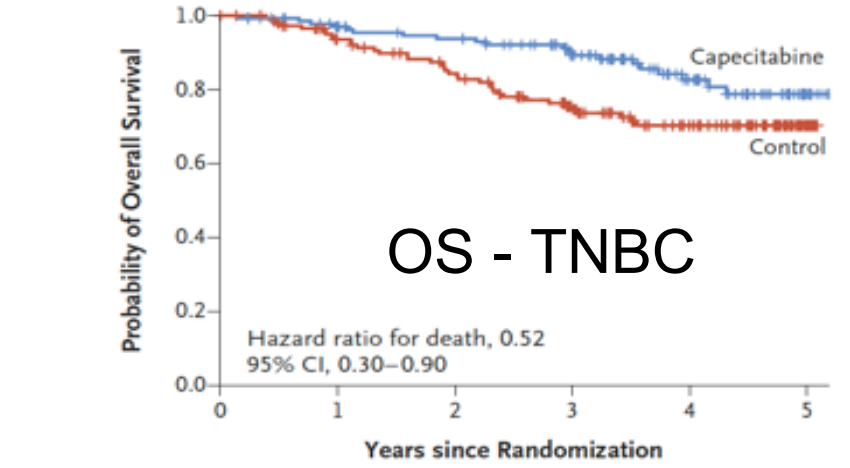
→ Capecitabine
2500 mg/m²/day PO Days 1-14
Q3W for 8 cycles‡
Hormonal therapy if ER/PgR+
(n = 455)†

→ Hormonal therapy if ER/PgR+
No further therapy if ER/PgR-
(n = 455)†

DFS (TNBC):
5 yrs: 69.8% vs 56.1%



No. at Risk						
Capecitabine	139	109	96	76	42	11
Control	147	95	84	69	47	6



No. at Risk						
Capecitabine	139	124	116	91	50	11
Control	147	125	108	82	52	9

Masuda N et al. N Engl J Med. 2017;376(22):2147-2159.

ECOG 1131

ECOG-ACRIN cancer research group

Patients with:
- **Clinical stage II/III TNBC at diagnosis**
- **T +/- A NAC**
- **≥ T1c in the breast at definitive surgery (any N)**

SCREENING

Tissue submission PAM50 Analysis (basal vs non-basal subtype)

RANDOMIZE

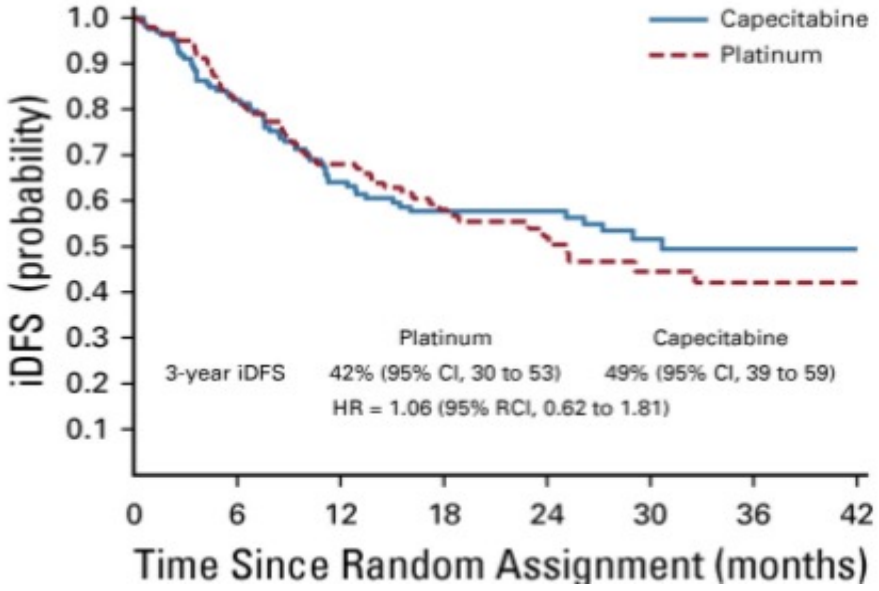
(1:1)

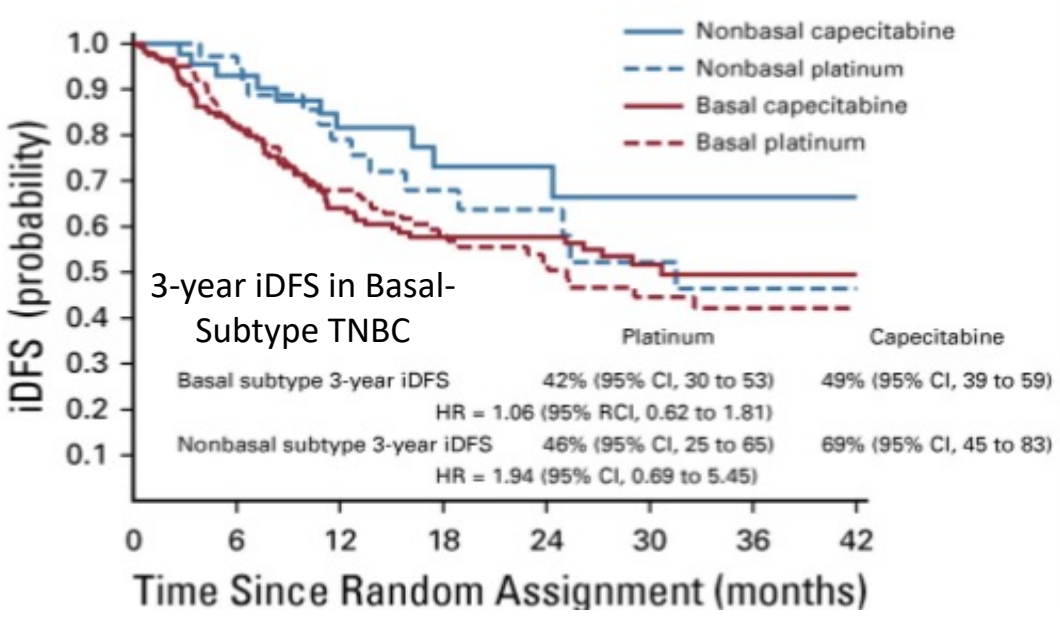
Carboplatin AUC 6 or Cisplatin 75 mg/m² (treating provider discretion) D1 every 3 weeks x 4 cycles

Capecitabine 1000 mg/m2 D1-14 every 3 weeks x 6 cycles

FOLLOW-UP

- ~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



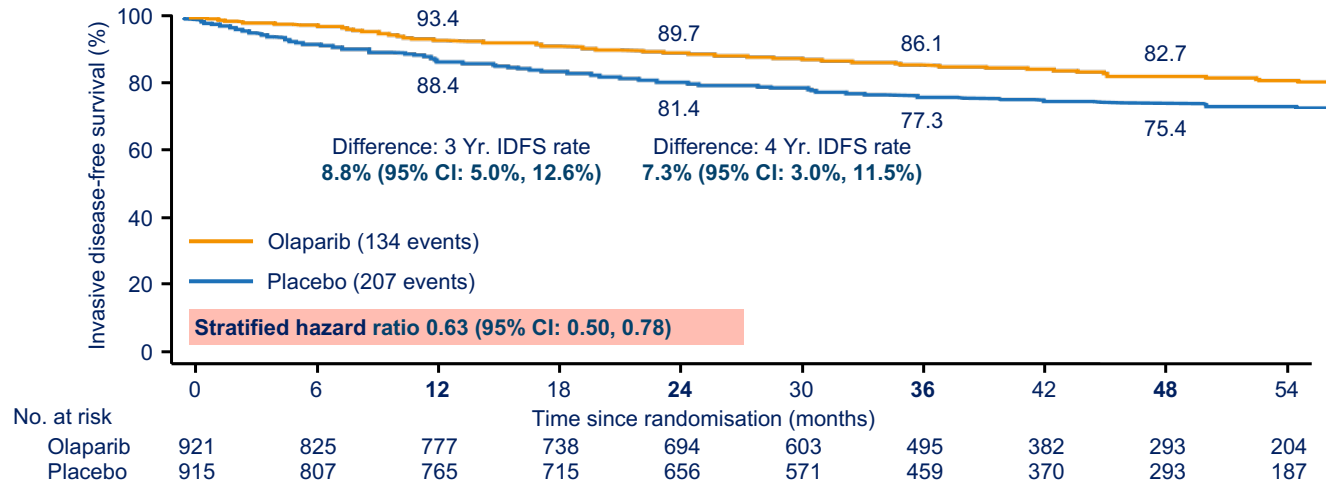


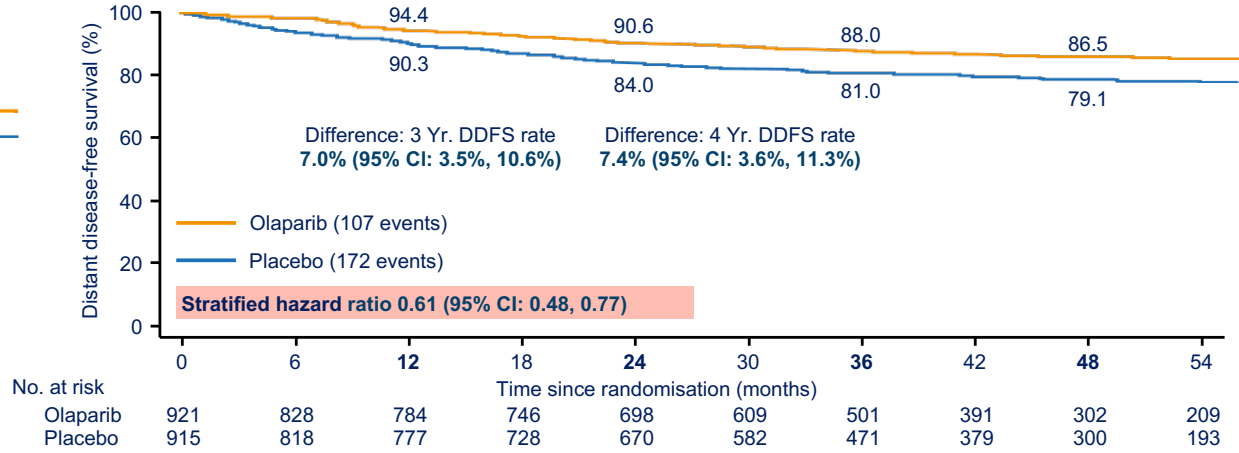
Mayer et al. J Clin Oncol. 2021;39(23):2539-2551.

Olympia: Updated Endpoints
Median FU 3.5 years, 2nd IA

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

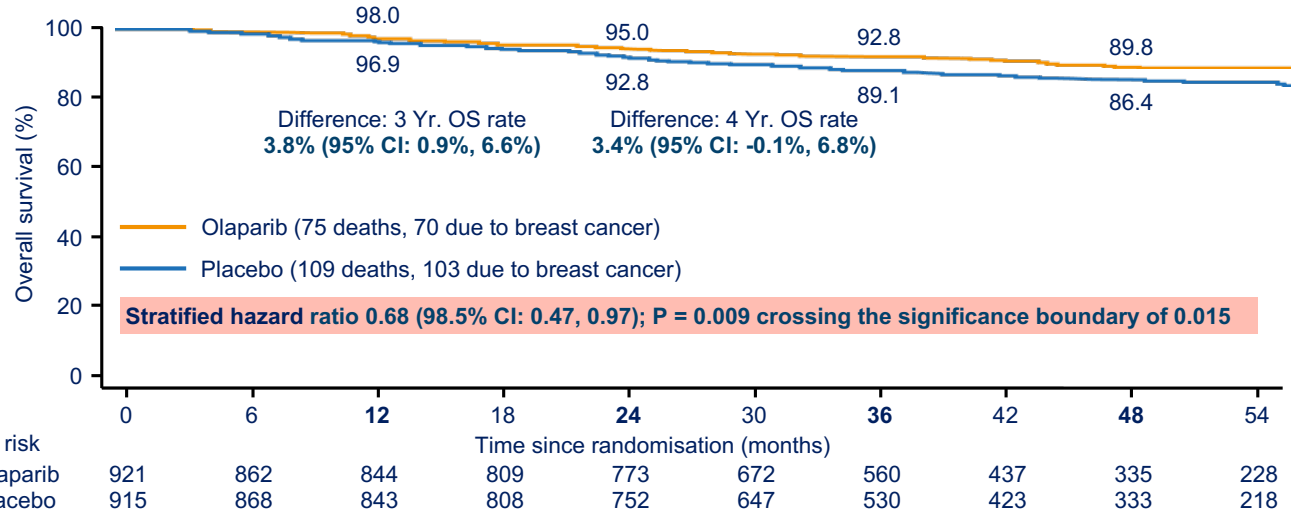
Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes





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

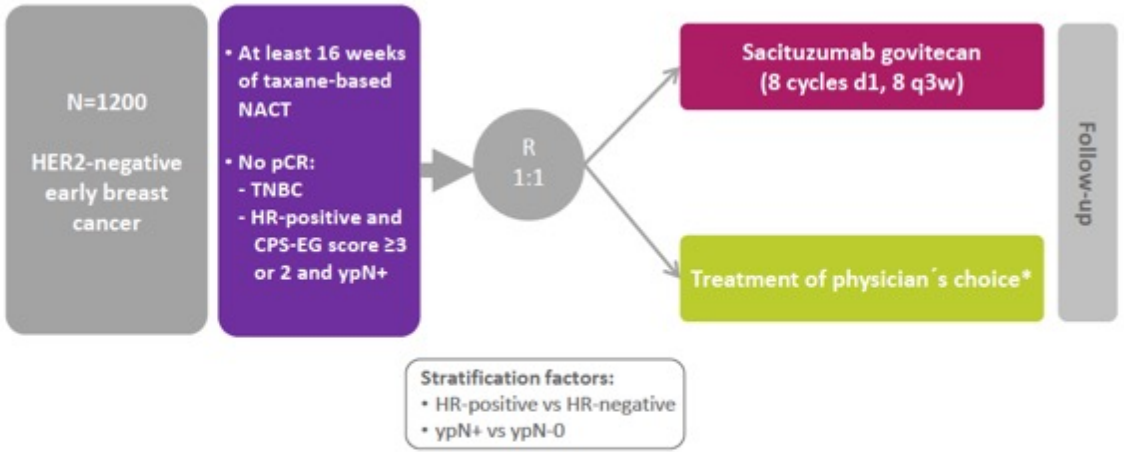
- No increase in MDS/AML compared to placebo
- Most toxicity grade 1/2; nausea most common
- Grade 3
  - Anemia 9%, fatigue 2%, neutropenia 5%



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

GBG: SASCIA Post-Neoadjuvant Trial

NCT04595565

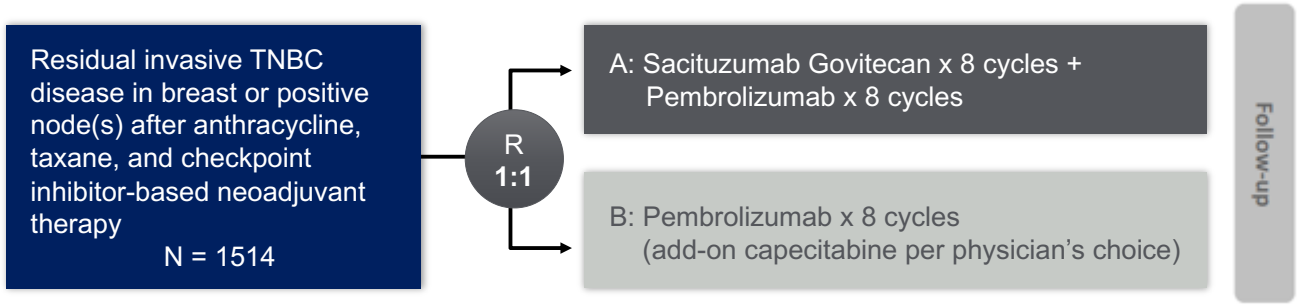


Challenge combining ER+ and TNBC pts

*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 Trial: Optimice-RD/ASCENT-05

Residual disease in TNBC



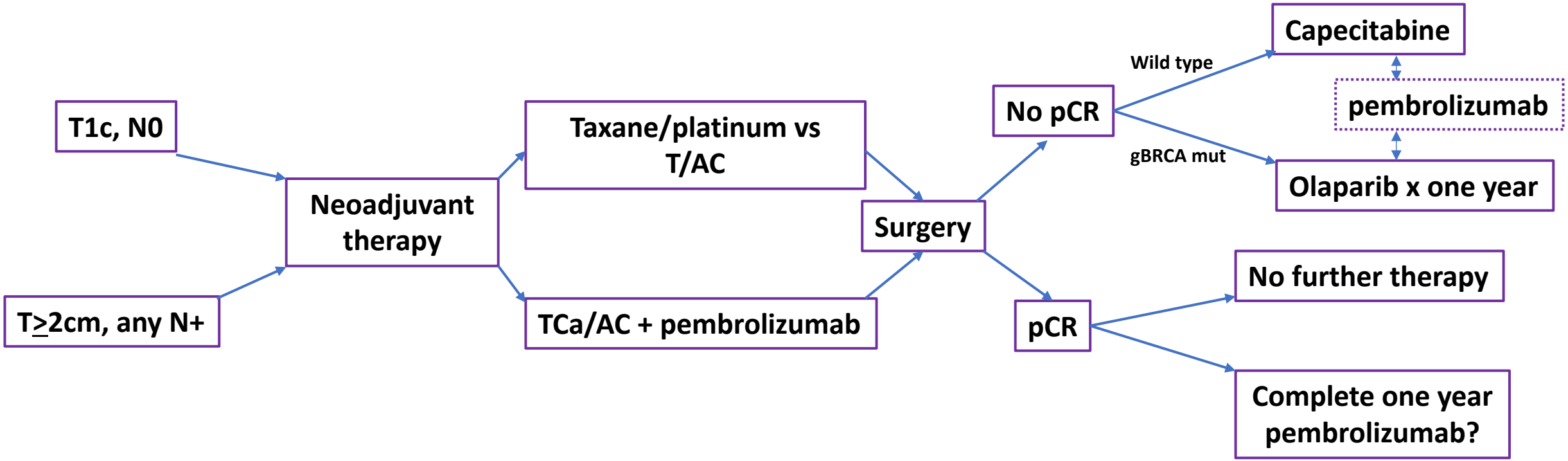
PI: Sara Tolaney

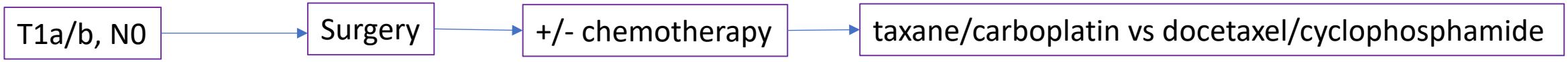
Alliance Foundation Trial

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
- The next step: therapy directed to biologic subsets

Roadmap for Early TNBC





Ongoing Trials: Tailoring neoadjuvant therapy to response; optimizing post-neoadjuvant therapy – ADCs, checkpoint inhibitor?

AC: anthracycline/cyclophosphamide; Ca: carboplatin

gBRCA mutation: neoadjuvant PARP inhibitors?

Thank you!