UCSF Helen Diller Family Comprehensive Cancer Center


# Latest Treatments for Triple-Negative Breast Cancer

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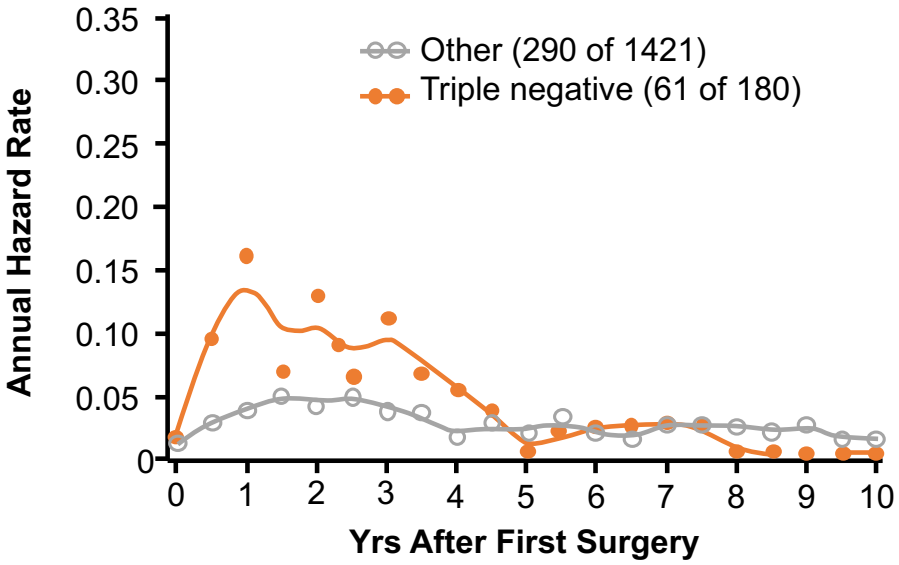
# Triple Negative Breast Cancer

- 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.

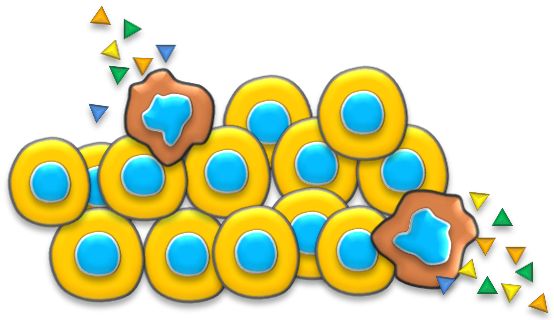
# Targeting Treatment to Biology

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

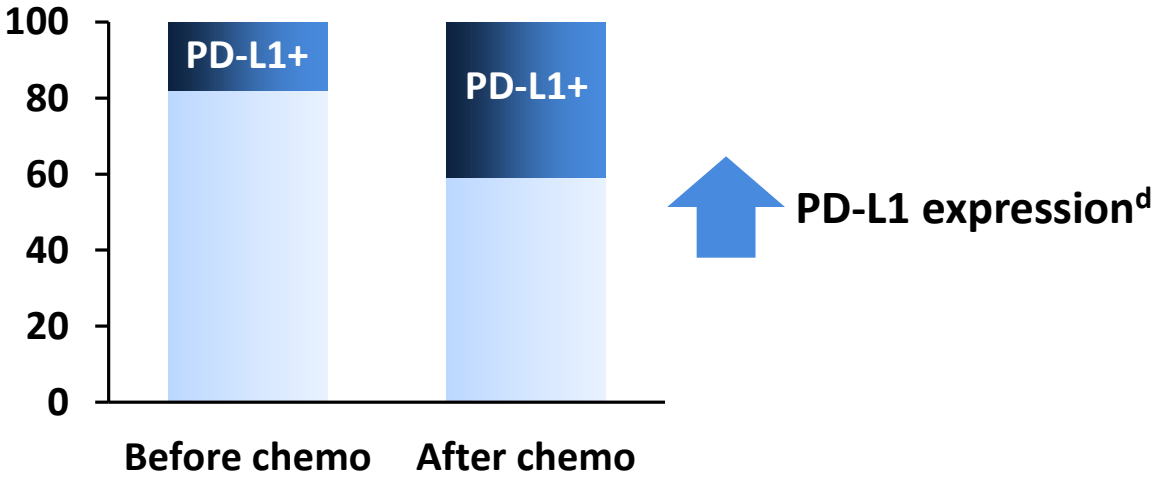
- **Early Stage Disease**
  - Optimal chemotherapy backbone
  - Immunotherapy
  - Post-neoadjuvant strategies

# RATIONALE FOR COMBINING CHECKPOINT INHIBITION WITH CHEMOTHERAPY

- Chemotherapy results in:

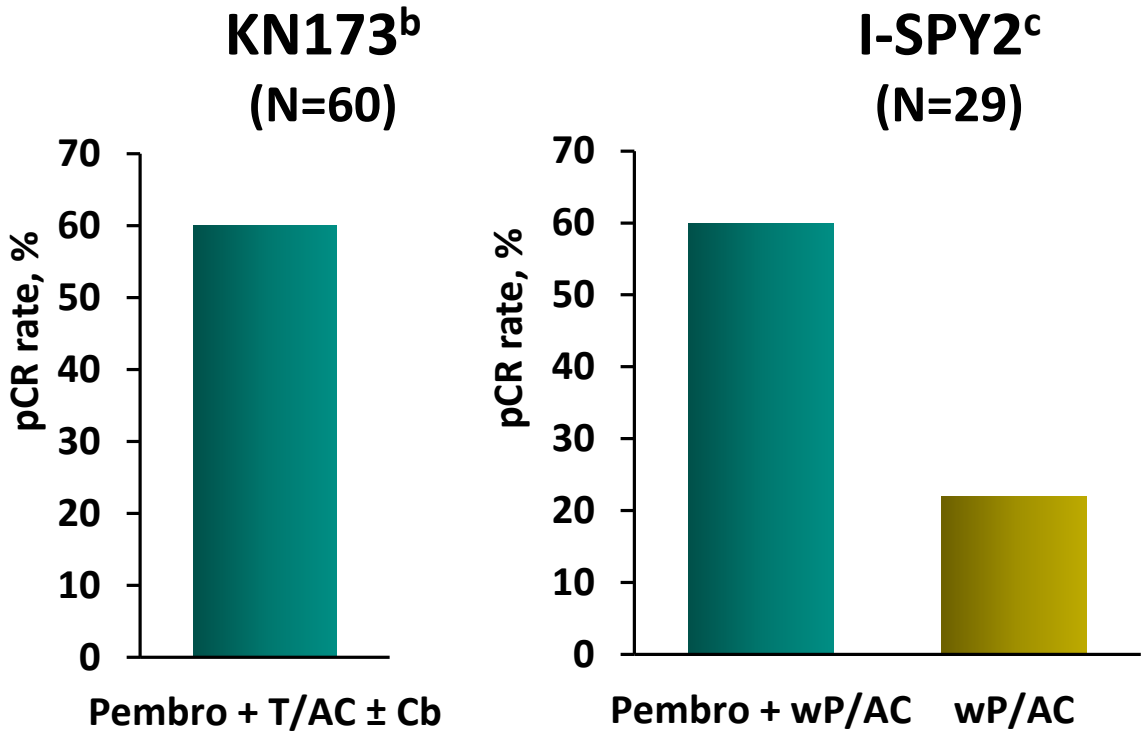


Tumor lysis and antigen shedding[a]




PD-L1 expression[d]

- Pembrolizumab plus standard neoadjuvant chemotherapy in TNBC

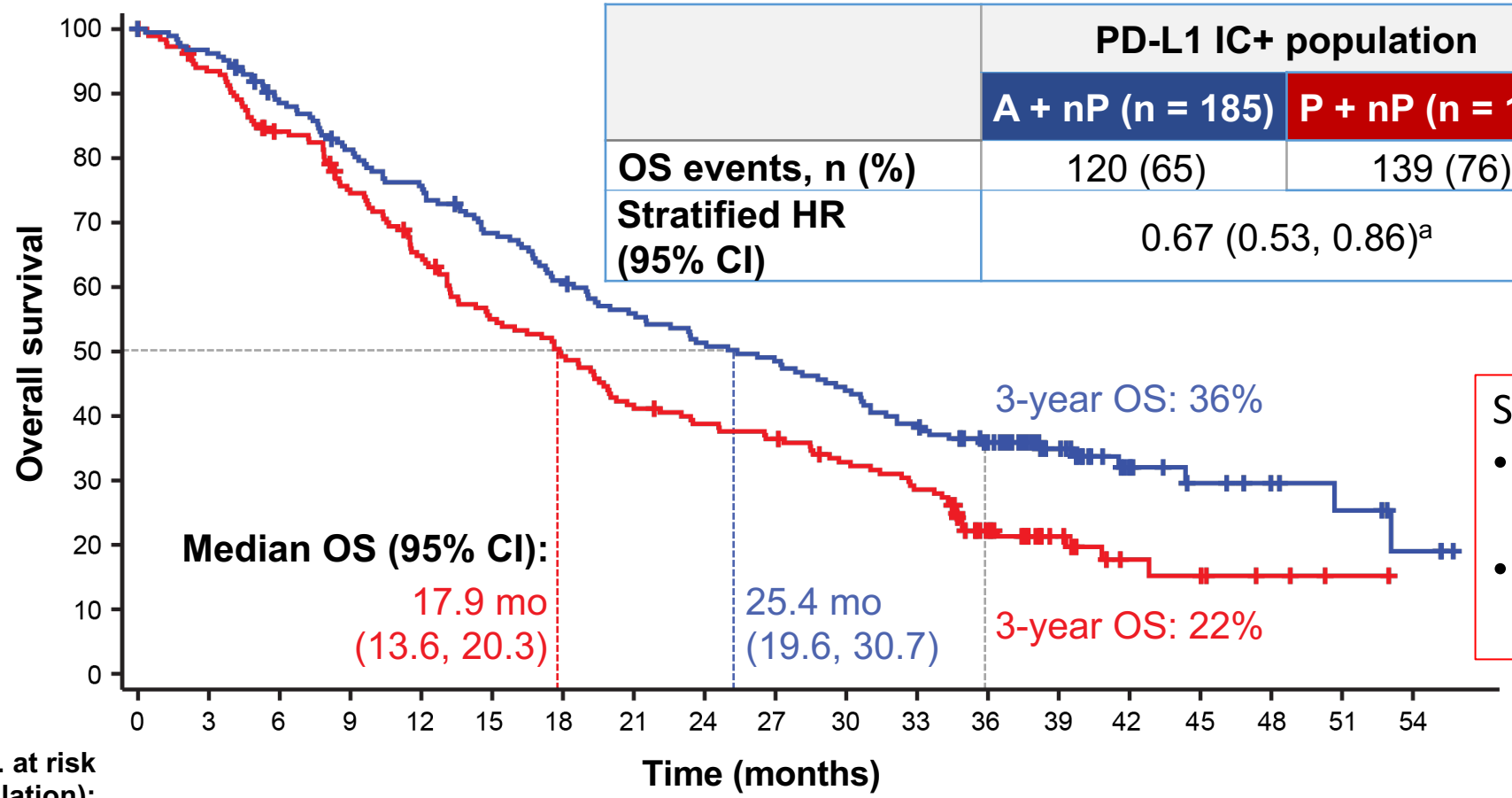



pCR=pathologic complete response as defined as ypT0/Tis ypN0; TNBC=triple-negative breast cancer; PAC=paclitaxel, doxorubicin, cyclophosphamide.

[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

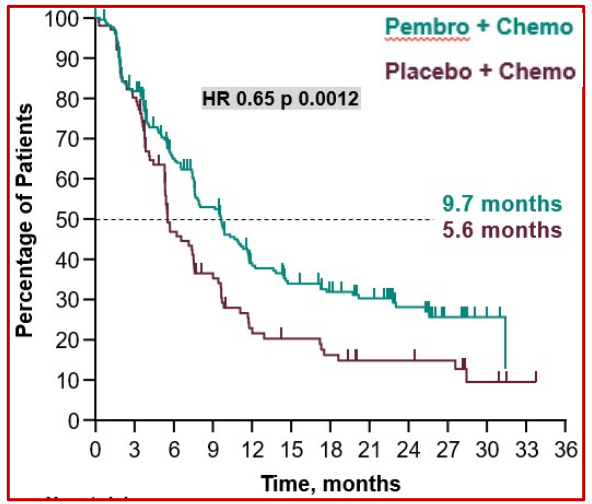
R 2:1

- 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

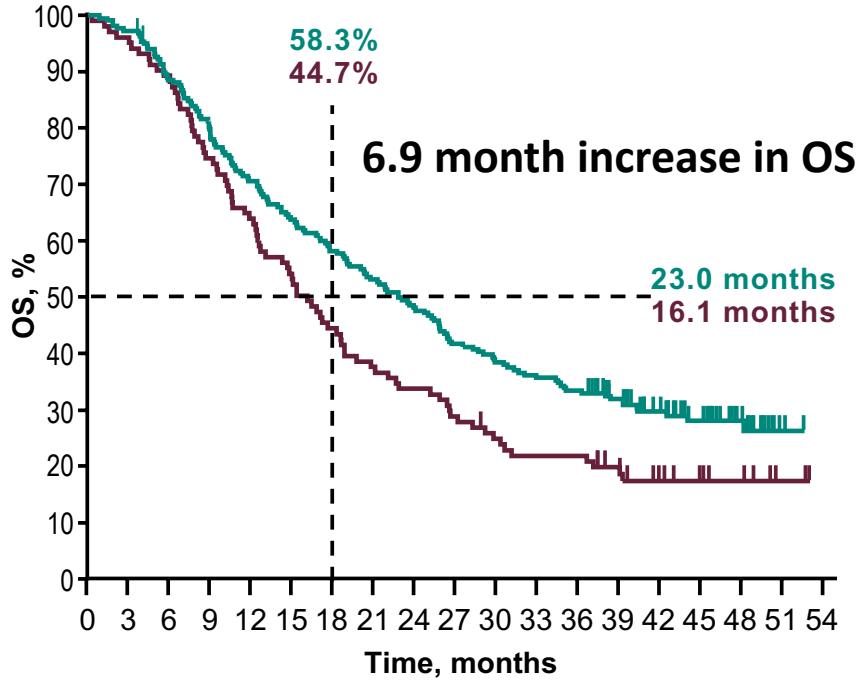



**Prespecified *P* value boundary of 0.00411 met**

**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%)<br>≥1% | 902 (369, 41%)<br>≥1% | 847 (332, 38%)<br>CPS≥10 |
| Randomization and Treatment | 2:1<br>Paclitaxel 90 mg/m2<br>Atezolizumab | 1:1<br>nab-Paclitaxel 100 mg/m2<br>Atezolizumab | 2:1<br>Pac/nab/gem+carbo<br>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<br>P=0.2 | 5 → 7.5 mo; HR 0.62<br>P<0.0001 | 5.6 → 9.7 mo; HR 0.65<br>P=0.0012<br>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]<br>Olaparib vs. TPC | **EMBRACA**[3]<br>Talazoparib vs. TPC | **TNT**[4]<br>Carboplatin vs. docetaxel |
|---|---|---|---|
| **PFS** | **5.6 months** vs. 2.9 months<br><br>**HR = 0.43**<br>95% CI (0.29, 0.63) | **5.8 months** vs. 2.9 months<br><br>**HR= 0.60**<br>95% CI (0.41, 0.87) | **6.8 months** vs. 4.4 months |
| **ORR** | **51.8%** vs. 5.4%<br>(n=83) (n=37)<br><br>*Investigator assessment* | **61.8%** vs. 12.5%<br>(n=102) (n=48)<br><br>*Investigator assessment* | **68.0%** vs. 33.3%<br>(n=25) (n=18) |

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

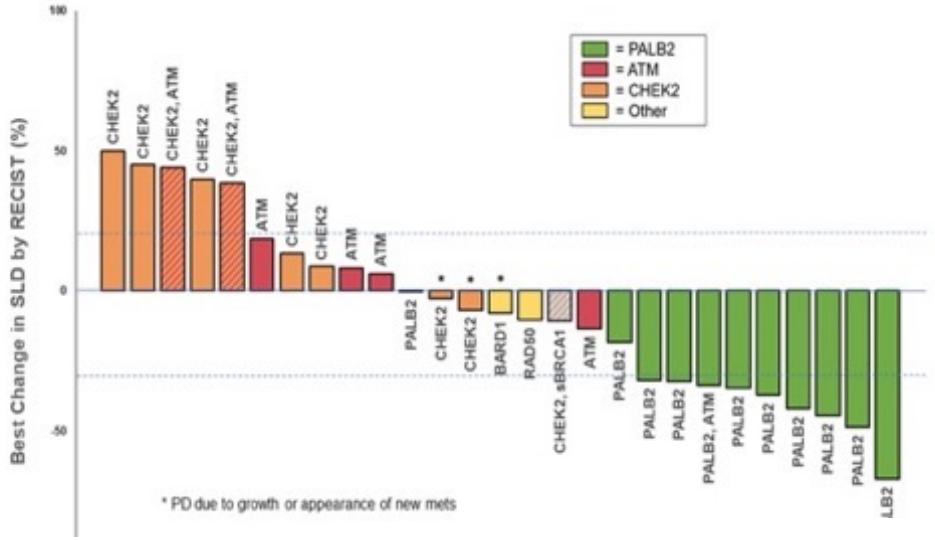
BROCADE3 trial (carbo/pac +/- veliparib): role of PARPi maintenance[5]?

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

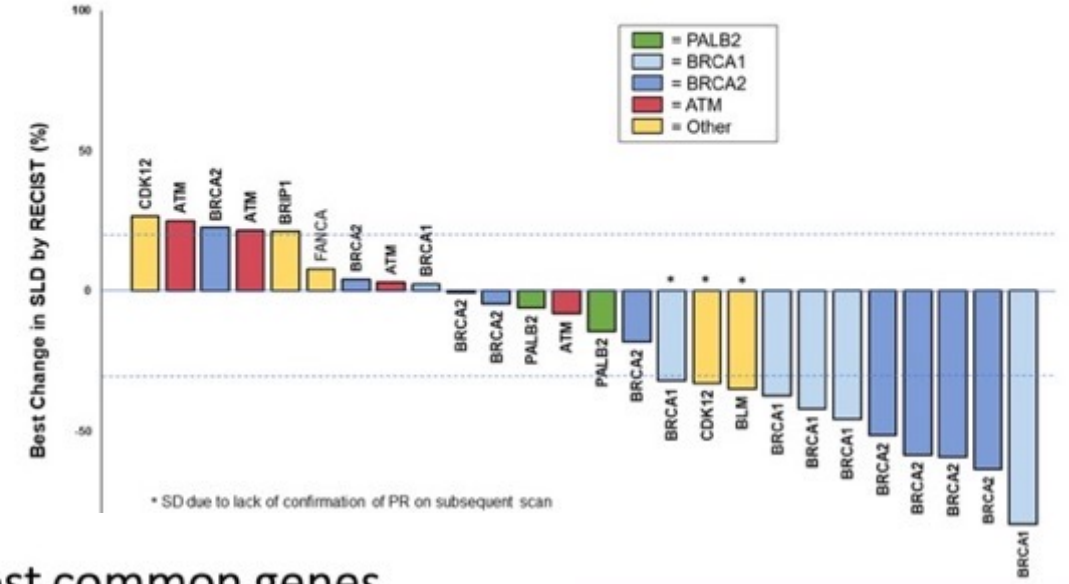
1. Senkus et al., Poster PB-002, presented at EBCC 2018; 2. AZ data on file (2019); 3. Eiermann W. et al., Poster 1070, presented at ASCO 2018; 4. Tutt A et al. *Nature Med*. 2018, 24(5):628-637 5. Dieras et al, Lancet Oncol 2020

# 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%)**<br>10/11 had tumor regression; 1 SD > 1 yr<br>**Somatic: 0/2 – both SD* (limited assessments)** | **8/16 PR (50%)** | **0/13 germline**<br>**0/4 somatic** |

**15 patients remain on study**

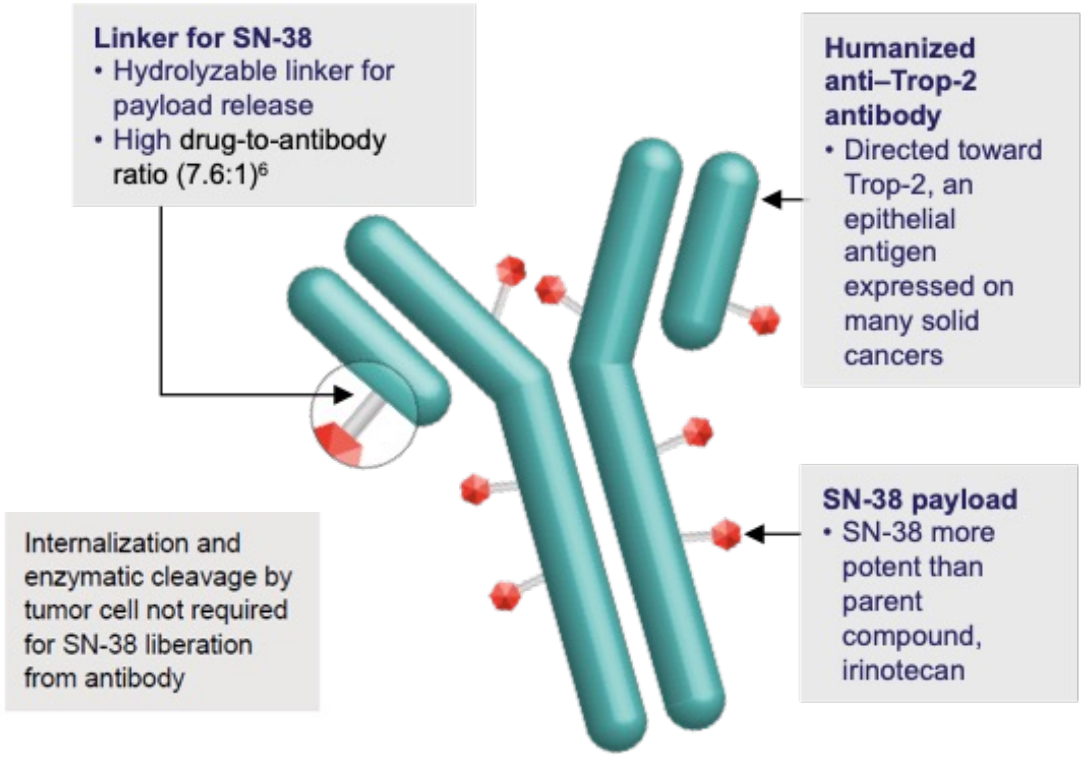
* 1 sPALB2- lost to follow-up after 1st tumor assessment with skin and tumor marker response
^ includes patient from Cohort 1 with sBRCA1 and gCHEK2
** Not included: patient with both gCHEK2 & sBRCA1; patient with gATM and gPALB2

Datacut May 4, 2020

*Somatic mutations much more frequent in lobular cancer

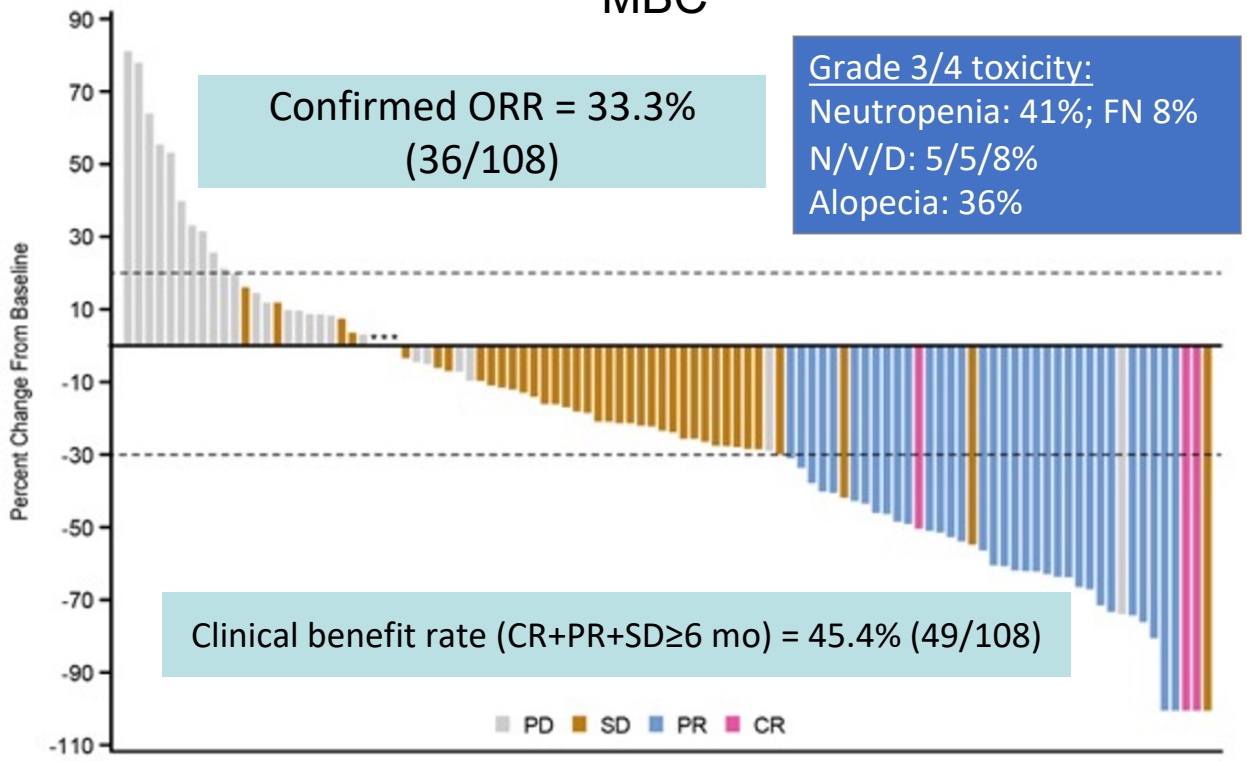
Tung et al, JCO 2020

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



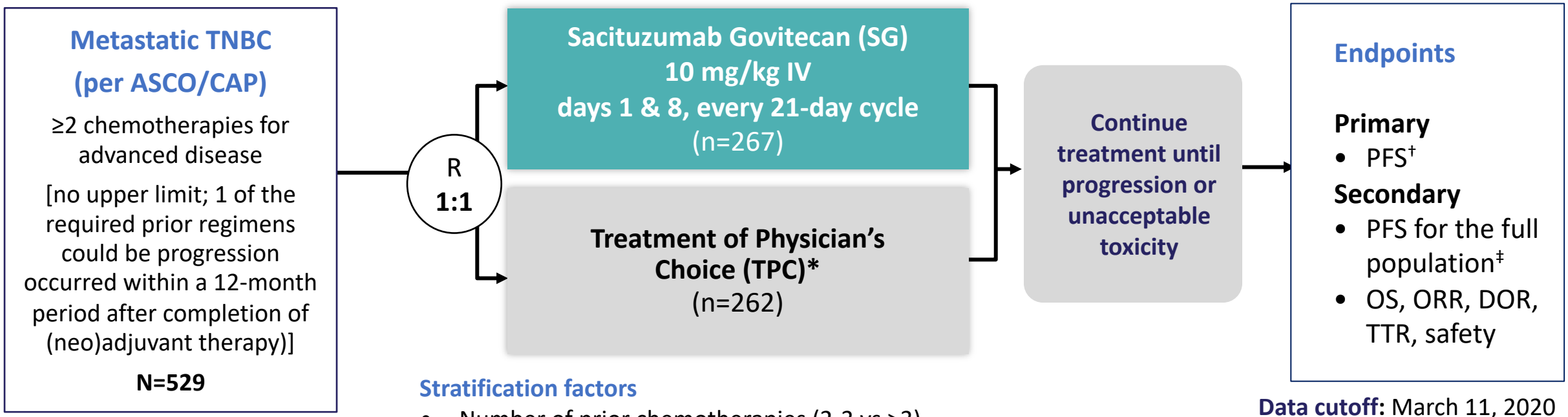

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- Full approval for the treatment of mTNBC and accelerated approval for advanced urothelial cancer

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.

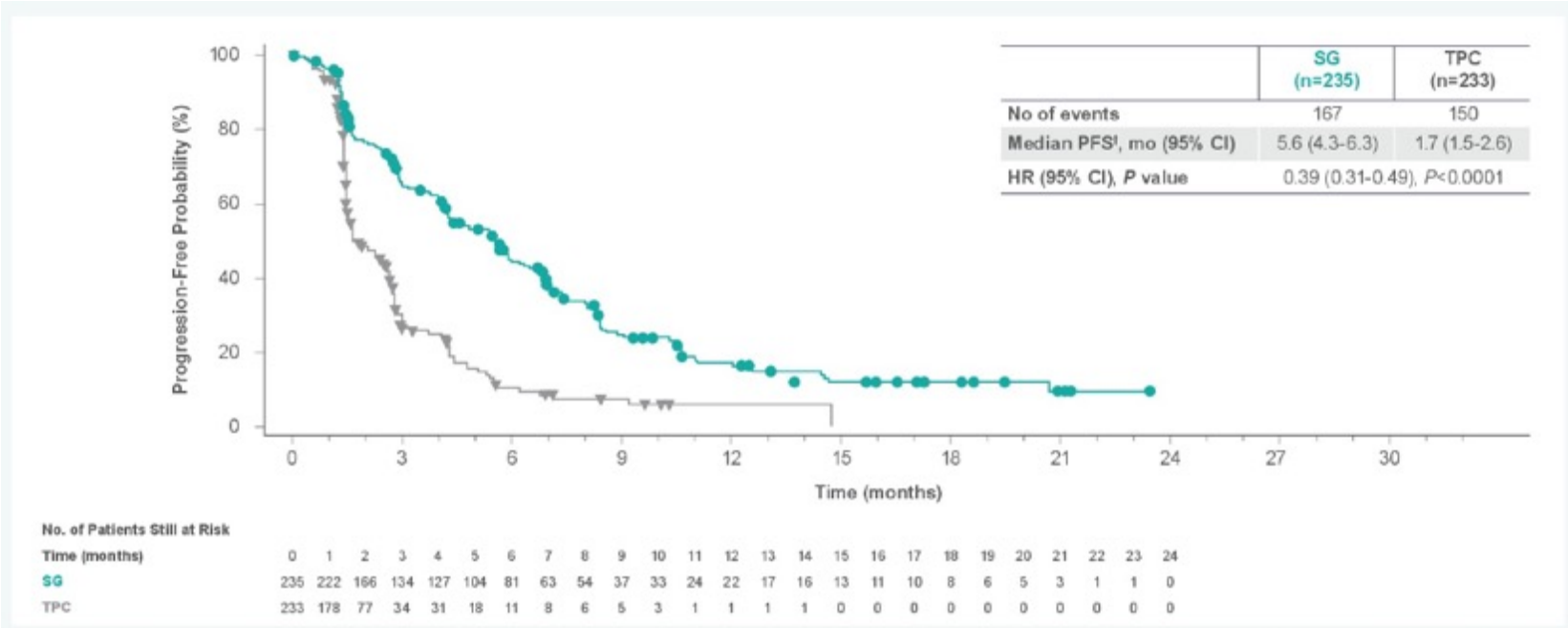
Bardia et al, NEJM 2021

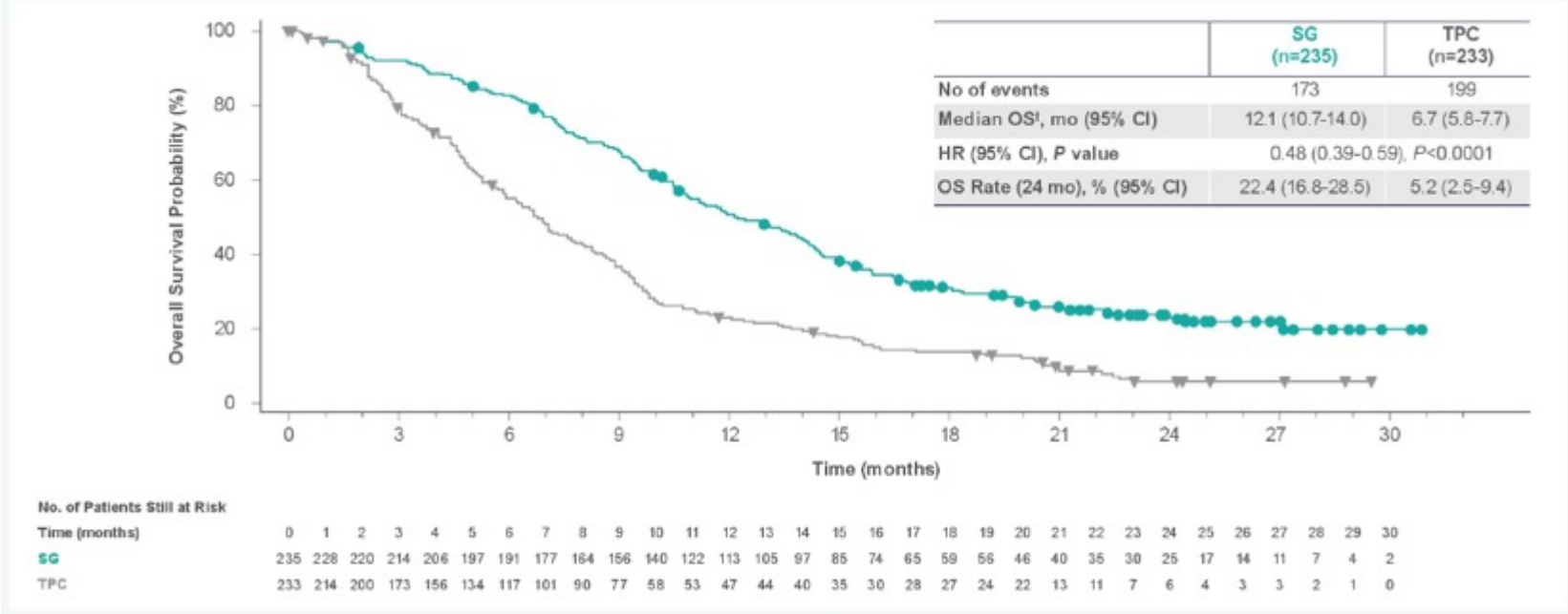
# ASCENT

# 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, NPJ Breast 2022

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

**Ascent-07:**
**First-line Chemotherapy in HR+**

# TBCRC 047: InCITe Trial Design

Metastatic TNBC
- Measurable disease
- No more than 2 prior metastatic lines of chemotherapy
- Known PD-L1 status
- Prior IO allowed

REGISTER

RANDOMIZE

- **Binimetinib** → **Binimetinib + Avelumab + Liposomal doxorubicin**
- **Sacituzumab govitecan** → **Sacituzumab govitecan + Avelumab**
- **Liposomal doxorubicin** → **Avelumab + Liposomal doxorubicin**

*Novel agent 1: Binimetinib, a MEK inhibitor (oral)
#Novel agent 2: Sacituzumab govitecan
Avelumab: PD-L1 inhibitor, IV every 2 wks
Liposomal doxorubicin: IV every 4 wks

**15 day lead-in** → **1 Cycle=4 weeks**
**Tumor assessments & PRO q 8 wks**

**Tumor biopsy**
**Blood collection**

**Tumor biopsy**
**Blood collection**

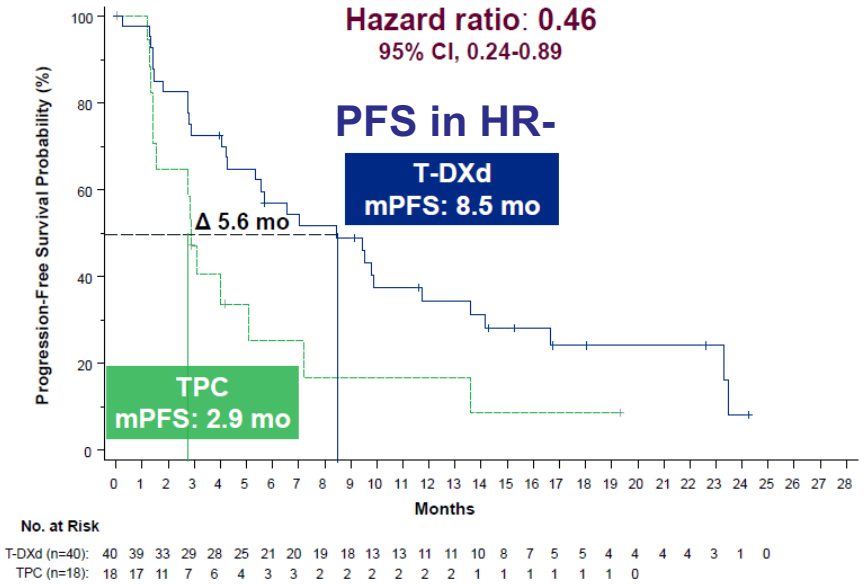
**Blood collection (at 8 weeks and at PD)**

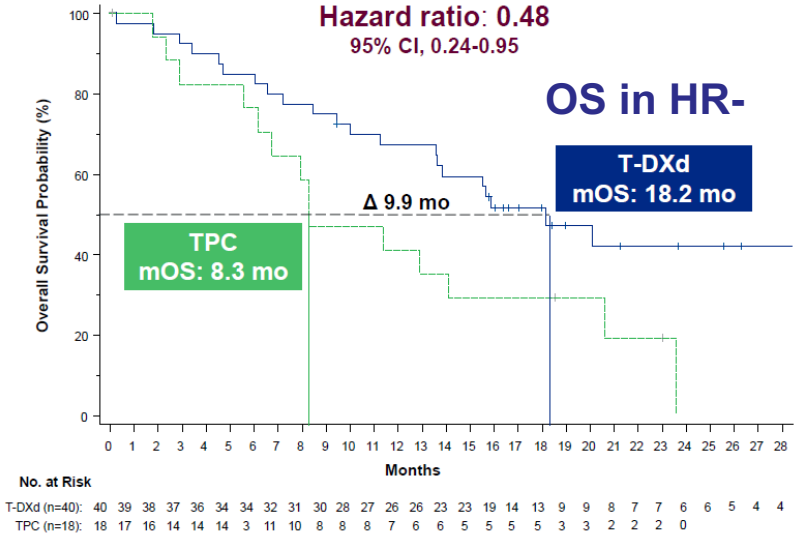
*Safety combination data from MiLO trial
#Safety combination data from several ongoing trials

PI: Hope S. Rugo

PI: Sara Tolaney; Alliance Foundation Trial

# DESTINY-Breast04: Exploratory Efficacy of TDXd in TN HER2-Low MBC

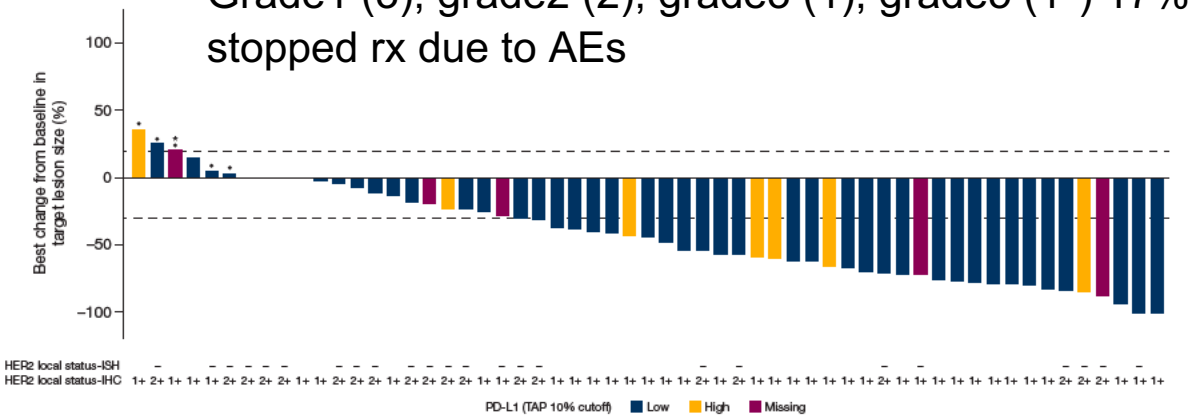


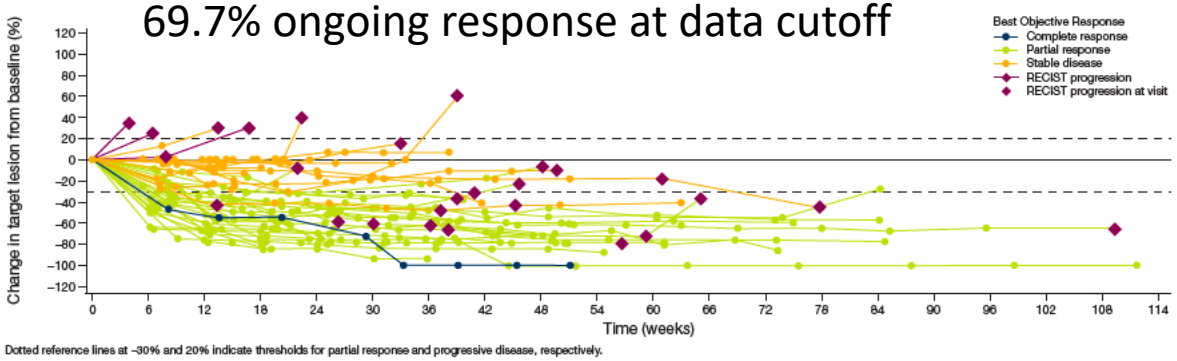




Modi S, et al. NEJM 2022

# 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
      - Grade1 (3), grade2 (2), grade3 (1), grade5 (1*) 17% stopped rx due to AEs



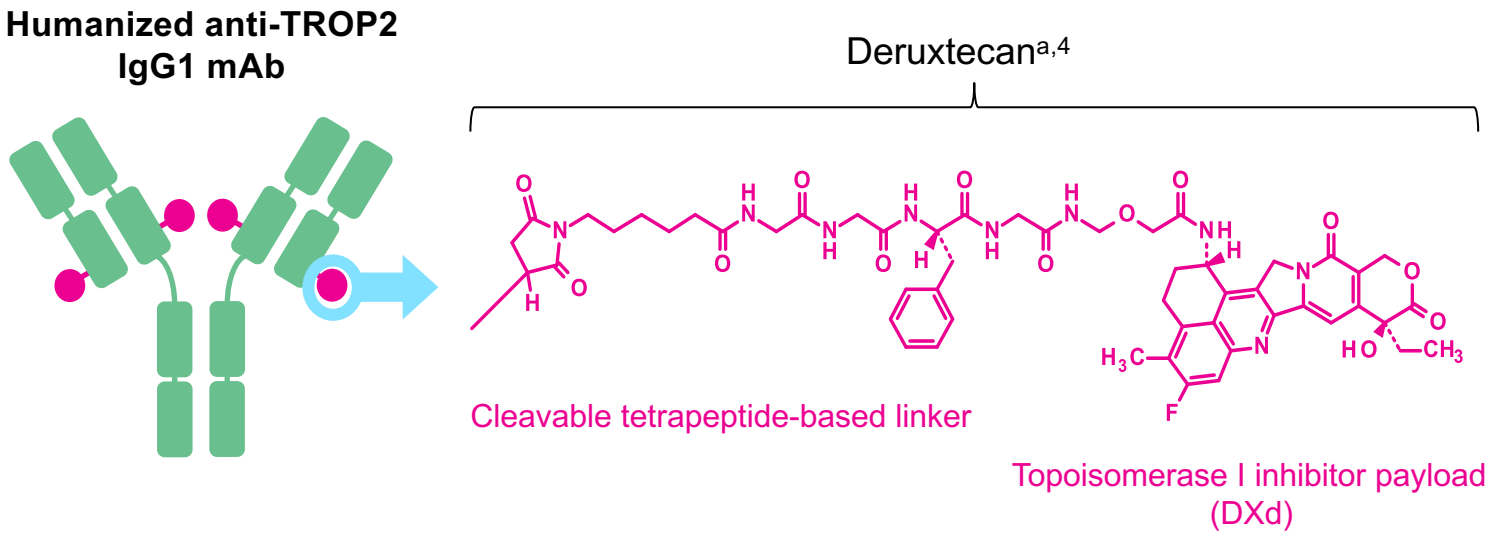

*Covid related

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-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**

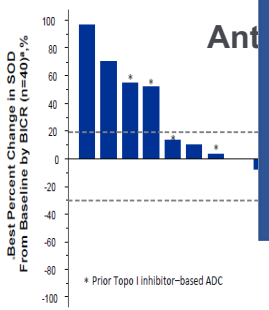
**Dual primary endpoint:**
PFS (BICR) and OS

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

**mOS:**

- All patie
- Topo I in

**AEs**: Most
nausea (66



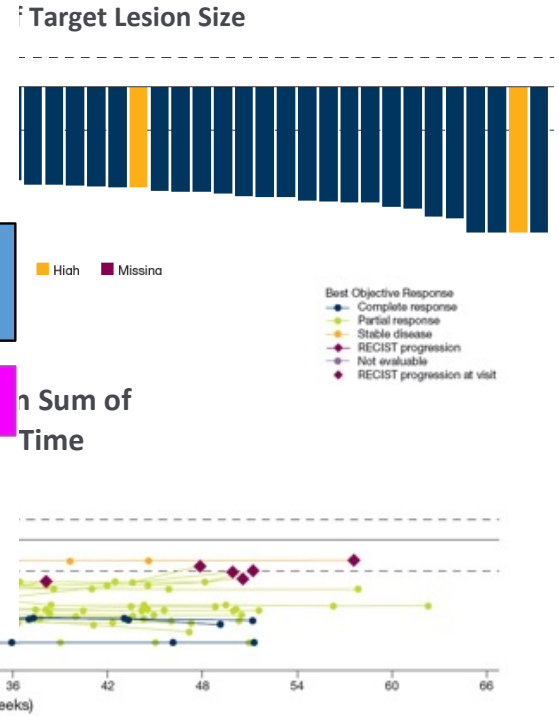

# Phase III TROPION Breast03

NCT05629585

N=1075
Stage I-III TNBC
Residual disease after at least 6 cycles of neoadjuvant chemotherapy

R
1:1:1

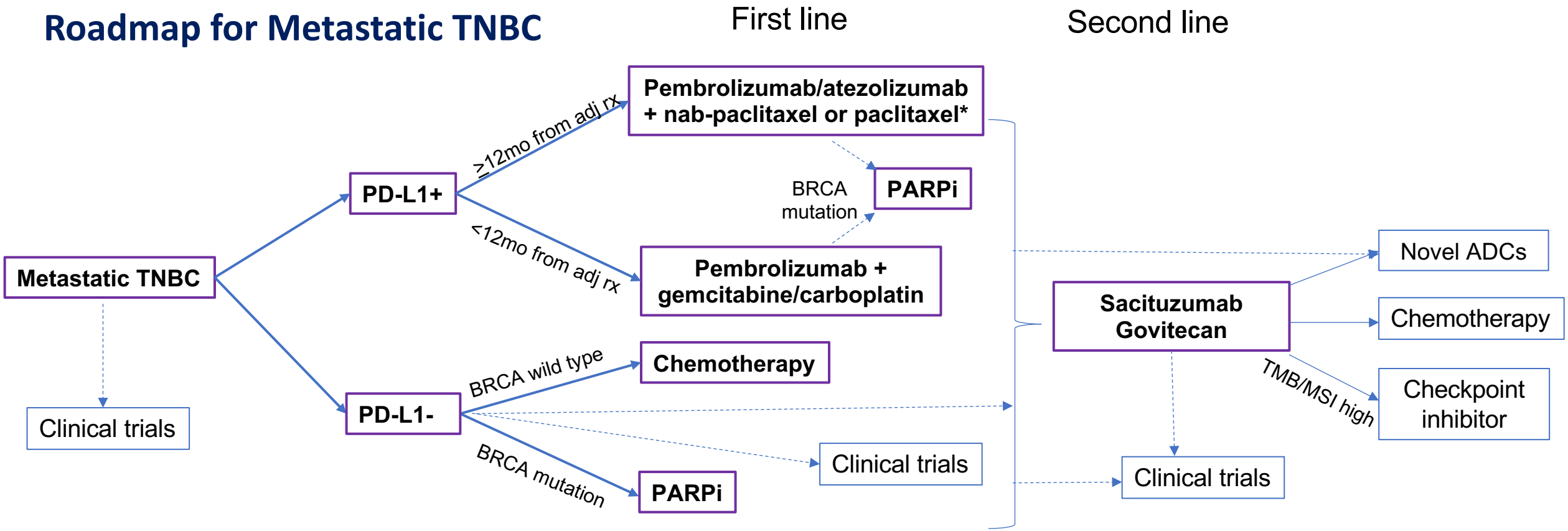
- Datopotamab deruxtecan x 8 cycles
  Durvalumab x 9 cycles
- Datopotamab deruxtecan x 8 cycles
- Capecitabine x 8 cycles OR
  Pembrolizumab x 9 cycles OR
  Cape + Pembro




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

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

Stratification

**Menopausal Status**
(Pre+Peri, Post)

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

Surgery → Radiotherapy

No cape or CPI

**Breast conserving surgery**
**OR**
**Mastectomy**

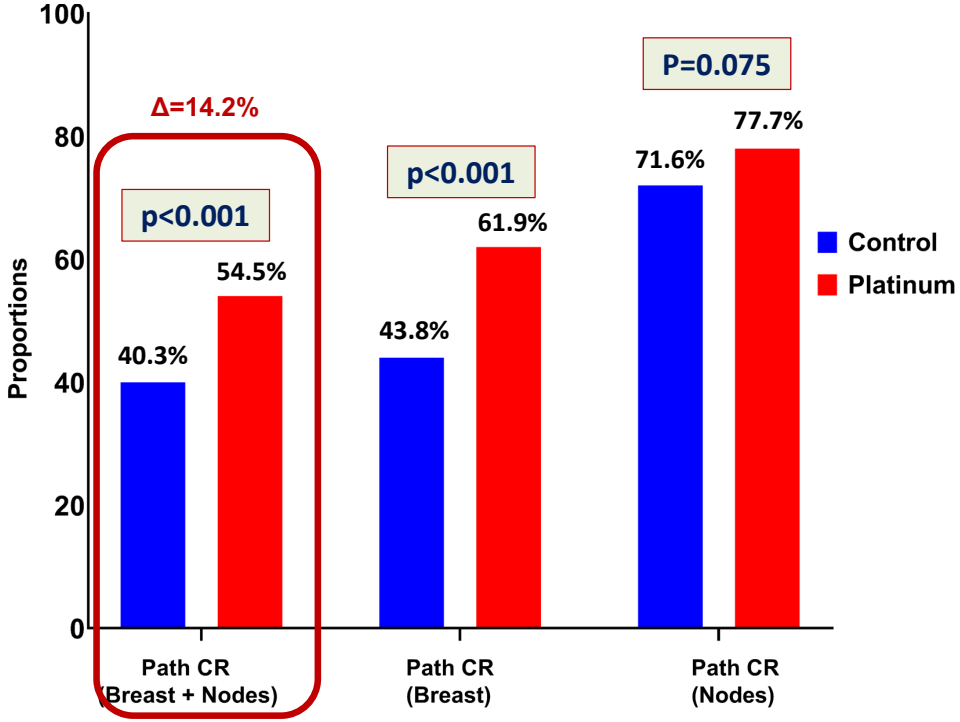
**Platinum Arm:**
Paclitaxel 100/m2 + Carboplatin (AUC-2) once per week X 8w*
*followed by*
[Doxorubicin (60/m2) or Epirubicin (90/m2)] + Cyclo (600/m2) every 2 weeks or 3 weeks X 4 cycles

**Control Arm:** Same as above, without carboplatin

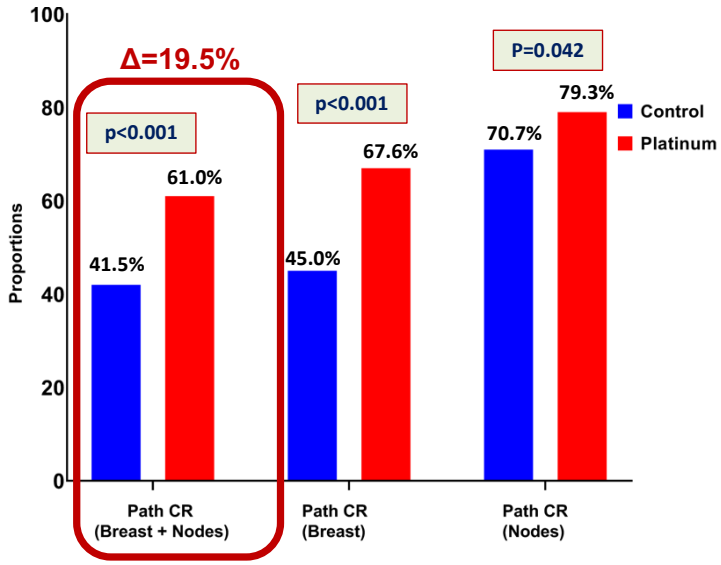
Gupta et al, SABCS 2022

*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

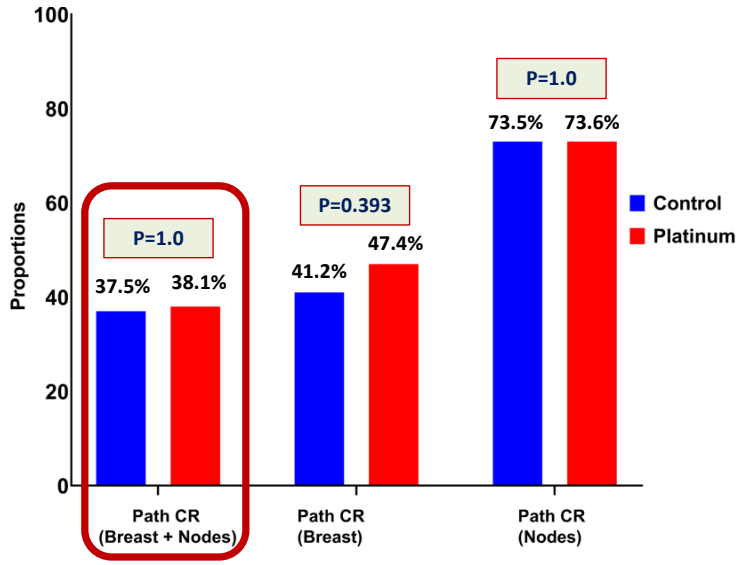
# Pathologic Complete Response: Overall and by Age




## 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

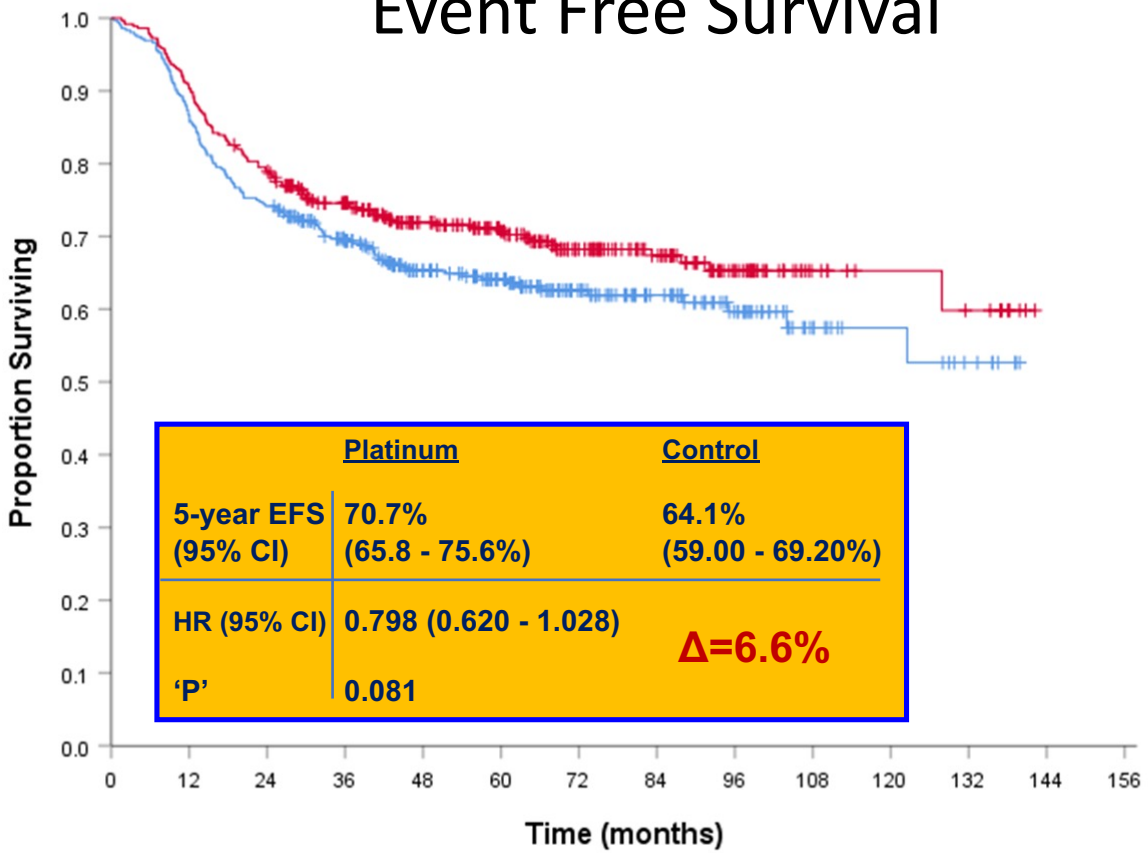
pCR highly prognostic for EFS regardless of age

| | 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)

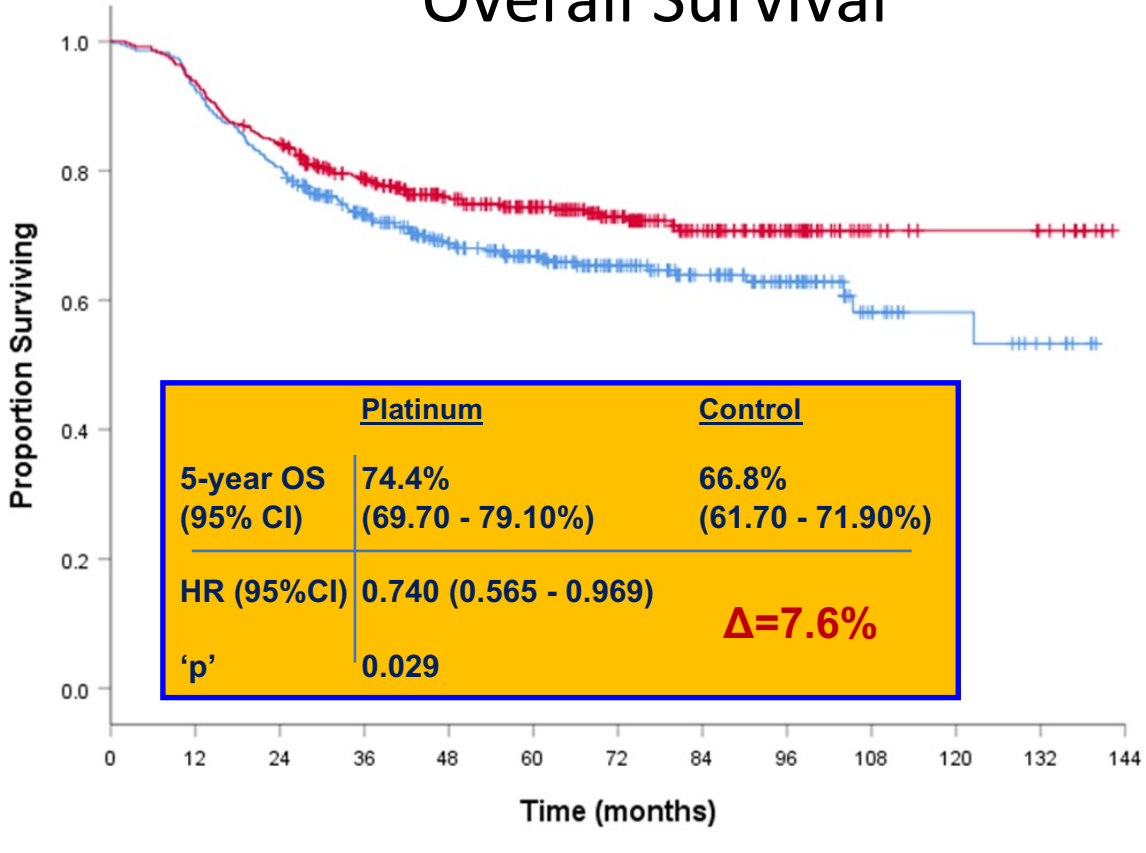
## Event Free Survival




| | 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

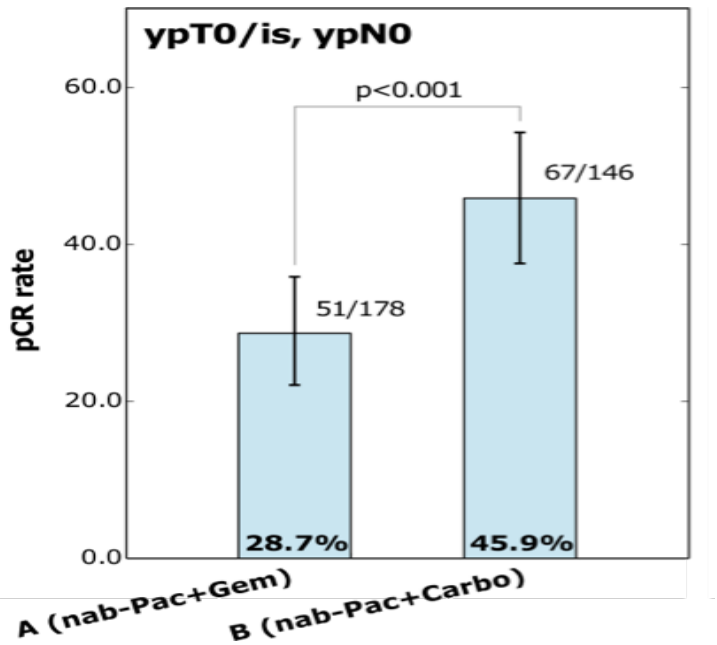



| | Platinum | Control |
|---|---|---|
| 5-year OS (95% CI) | 74.4% (69.70 - 79.10%) | 66.8% (61.70 - 71.90%) |
| HR (95%CI) | 0.740 (0.565 - 0.969) | Δ=7.6% |
| 'p' | 0.029 | |

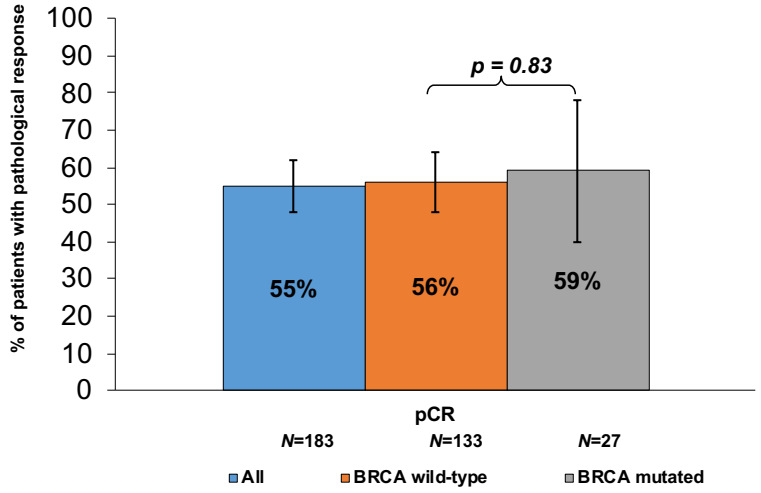
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 356 | 330 | 287 | 229 | 179 | 147 | 106 | 74 | 48 | 20 | 12 | 7 |
| Platinum | 361 | 339 | 303 | 252 | 201 | 168 | 122 | 83 | 51 | 19 | 14 | 12 |

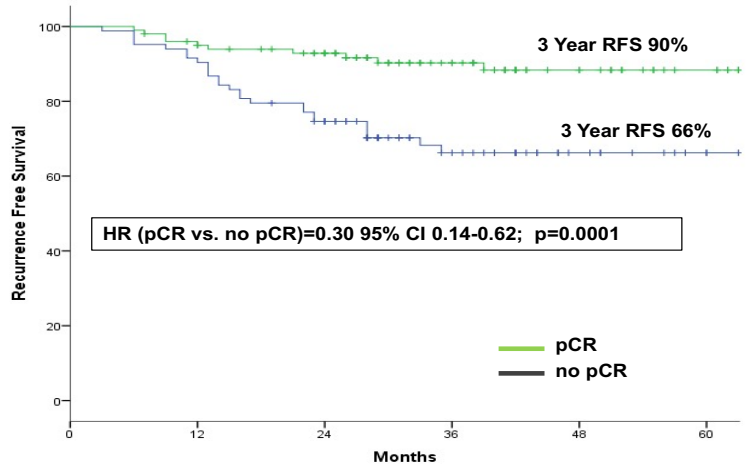
# Can we Eliminate Anthracyclines?

ADAPT-TN; N=336



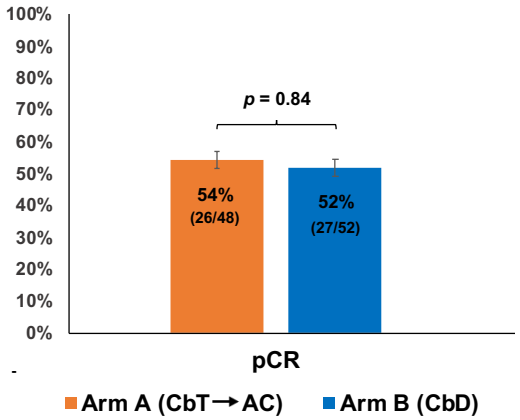

Pooled Analysis of 6 Cycles of Neoadjuvant Carboplatin plus Docetaxel (CbD) in TNBC

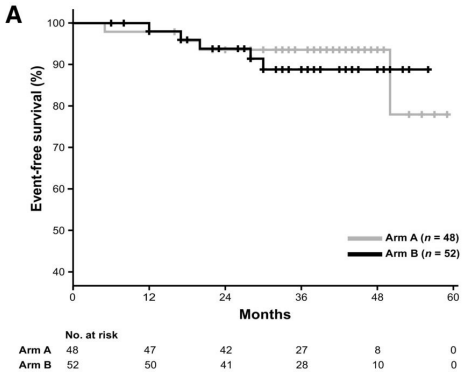


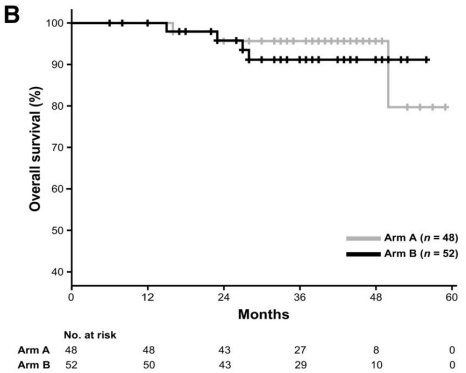




NeoStop Trial
TCa/AC vs Tca x 6
N=100

pCR and RCB



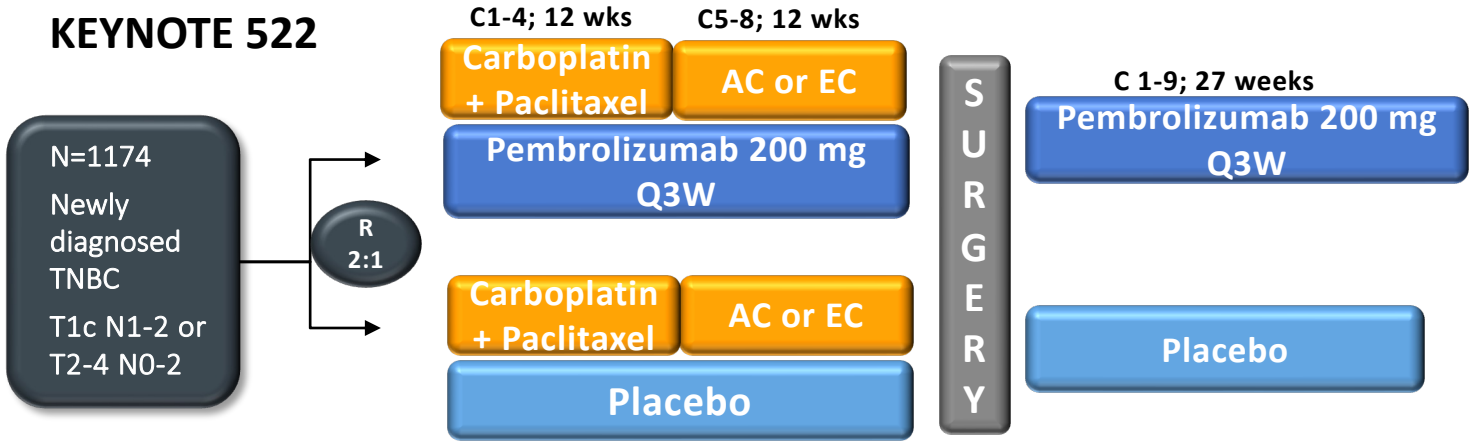




Gluz et al JNCI 2017; Sharma et al CCR 2016; Sharma et al CCR 2018; Sharma et al, CCR 2021.

# Phase III Neoadjuvant Immunotherapy Trials

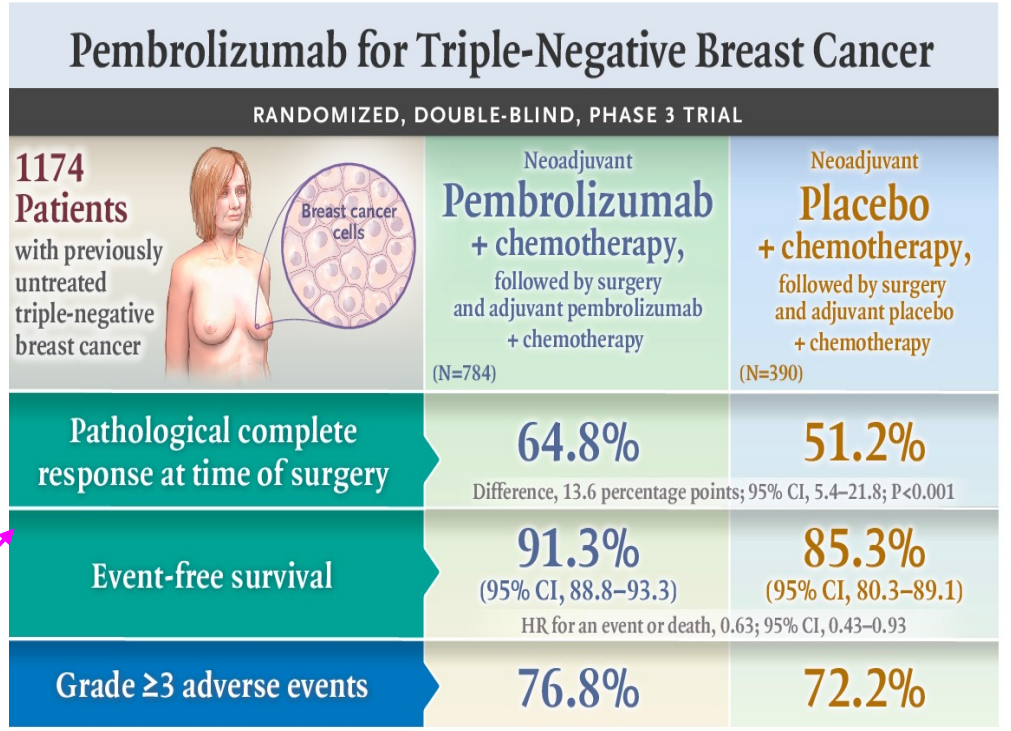
## KEYNOTE 522



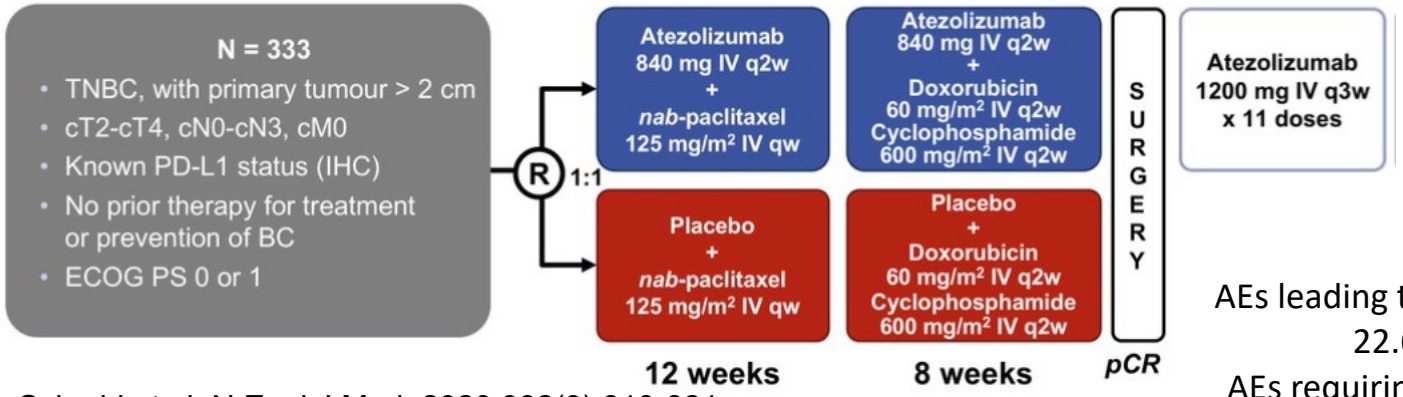

**Patient population**

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

N=602

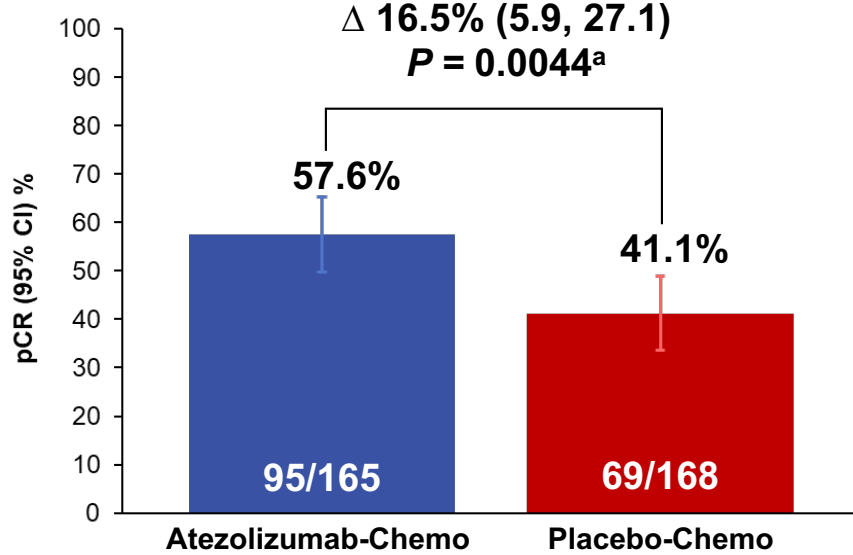



## IMpassion 031




AEs leading to D/C of any drug: 22.6 v 19.8%

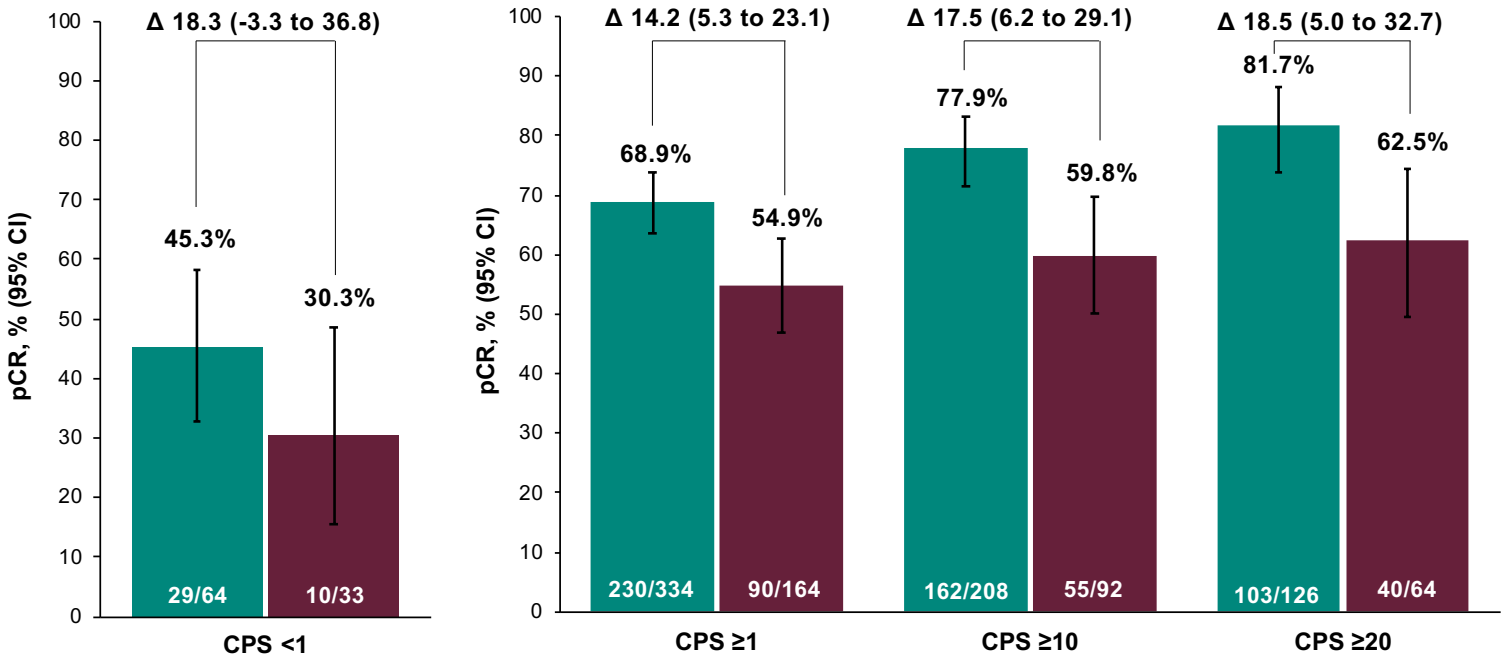
AEs requiring corticosteroids: 12.8 v 9.6%

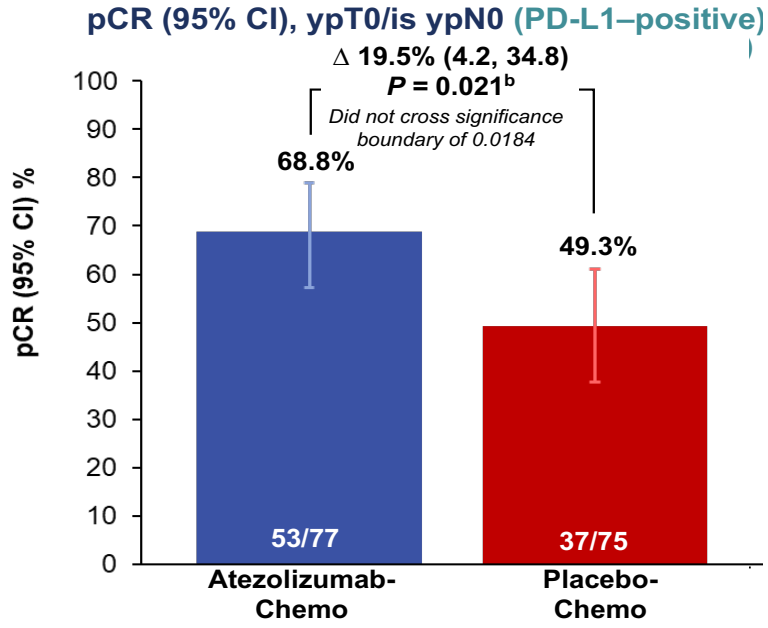


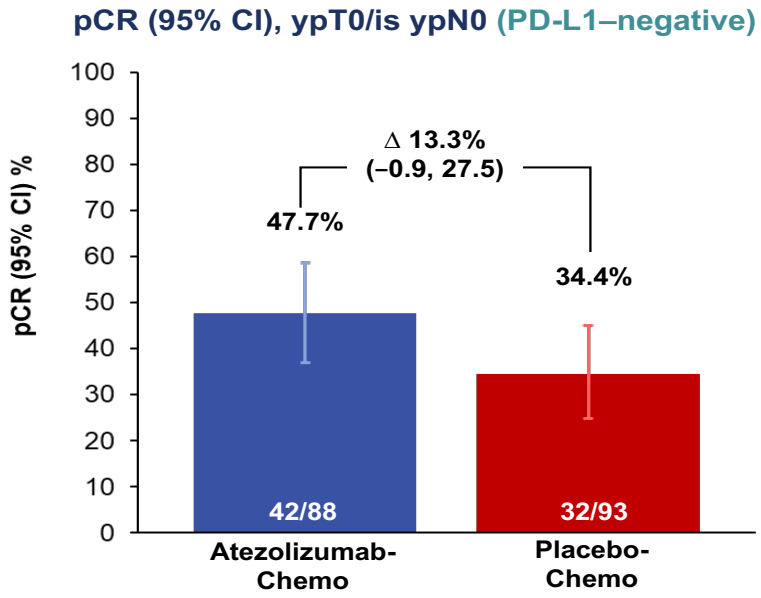

Schmid et al. N Engl J Med. 2020;382(9):810-821;
Mittendorf et al. Lancet 2020;396(10257):1090-1100.

# Benefit from Immunotherapy is Independent of PD-L1 status

## Is PD-L1 Predictive of Response to Chemotherapy?

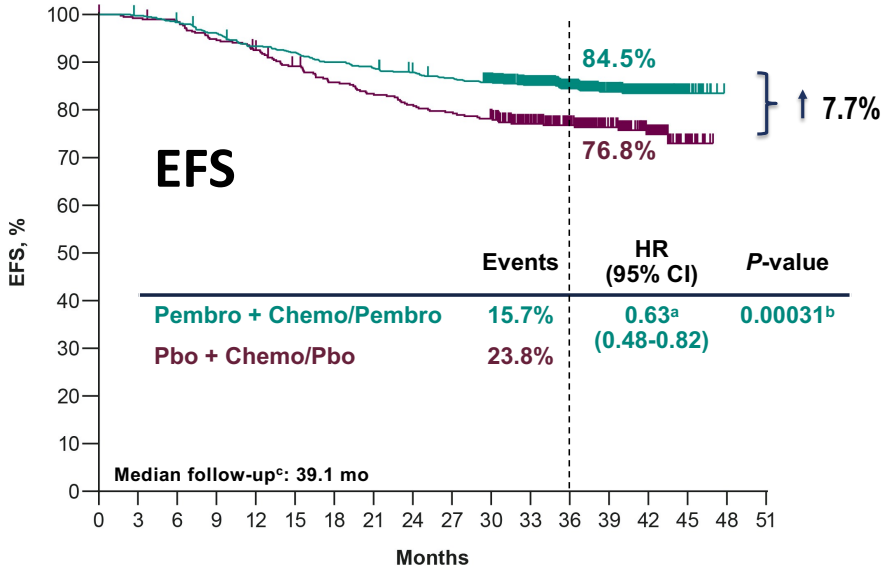


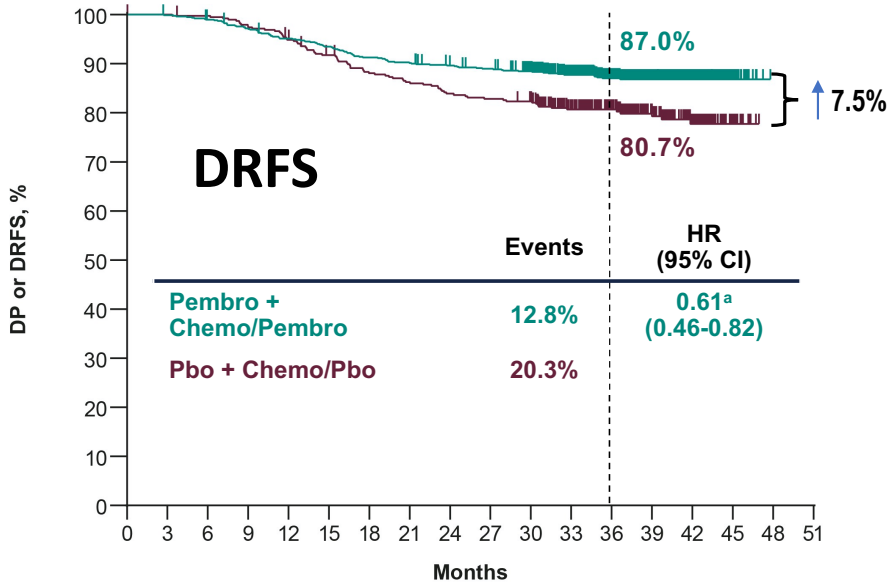

Schmid et al. SABCS 2019, Abstr. GS3-03;
Mittendorf et al. Lancet 2020;396(10257):1090-1100.

# Pembrolizumab Improves EFS and DRFS



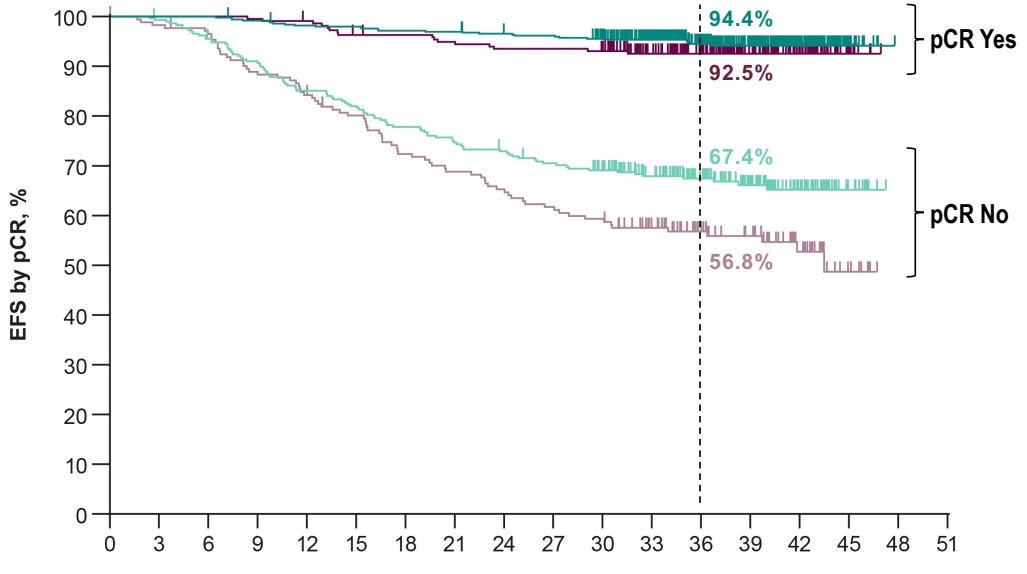

No. at Risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |




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 |



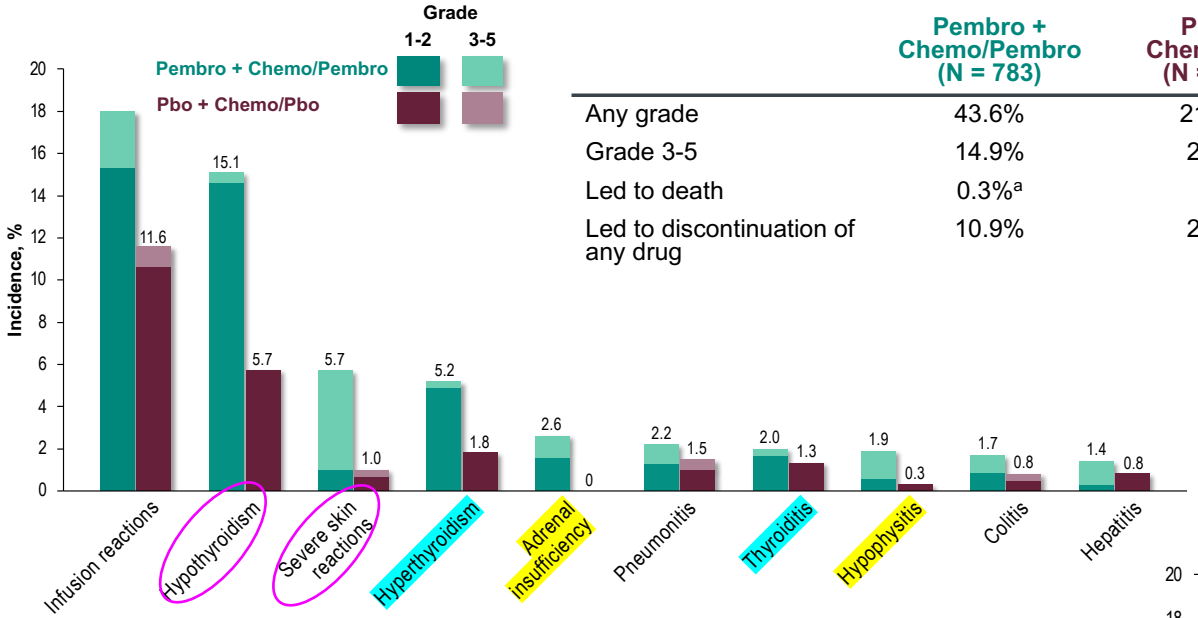

No. at Risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |

Schmid et al, NEJM 2022

[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.

# What is the Patient Cost of Therapy: Toxicity

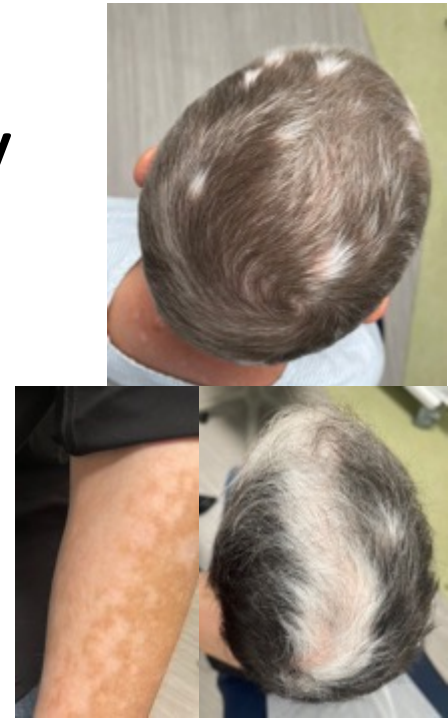


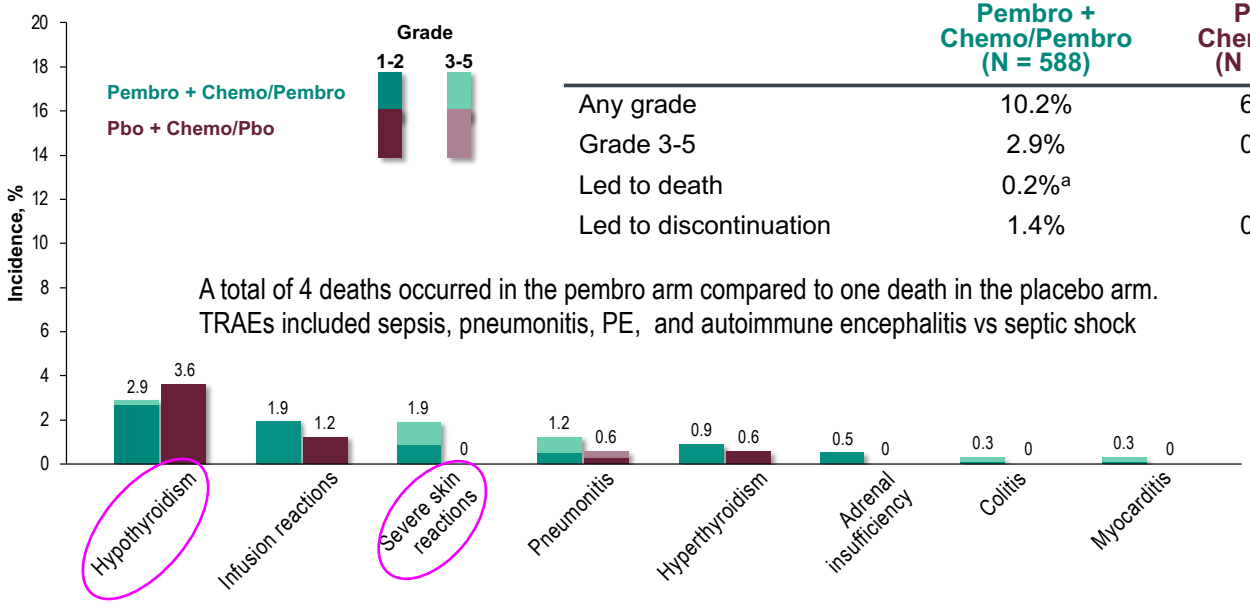

| | Pembro + Chemo/Pembro (N = 783) | Pbo + Chemo/Pbo (N = 389) |
|---|---|---|
| Any grade | 43.6% | 21.9% |
| Grade 3-5 | 14.9% | 2.1% |
| Led to death | 0.3%[a] | 0 |
| Led to discontinuation of any drug | 10.9% | 2.6% |

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<br>**Pembro x 4** | **PD1**<br>**Pembro x 1 year** | **PD-L1**<br>**Atezo x 1 year** | **PD-L1**<br>**Atezo x 8** | **PD-L1**<br>**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)**<br>**2 wks on, 1 wk off x 8** | **no** |
| | | | | | |
| Improved pCR | **Yes** | **Yes**<br>**51.2 v 64.8%**<br>**P=0.00055** | **Yes**<br>**41.1 v 57.6%**<br>**P=0.0044** | **No** | **Numeric improvement**<br>**(44 v 53%, p=0.18)** |
| Improved EFS | **NR:**<br>**pCR>nonpCR** | **Yes** | **NR** | **NR** | **Yes**<br>**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

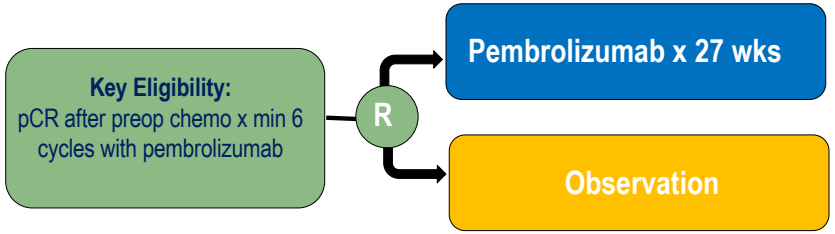
- Atezolizumab
  - Impassion 30 (n=2300)
    - Pac → AC/EC
- Avelumab
  - A-Brave (n=335)
    - Adjuvant and post NAC high risk: avelumab alone
- Pembrolizumab
  - SWOG S1418/NRG BR006 (n=1155)
    - Post NAC: Pembro vs Obs x 1 yr

- 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

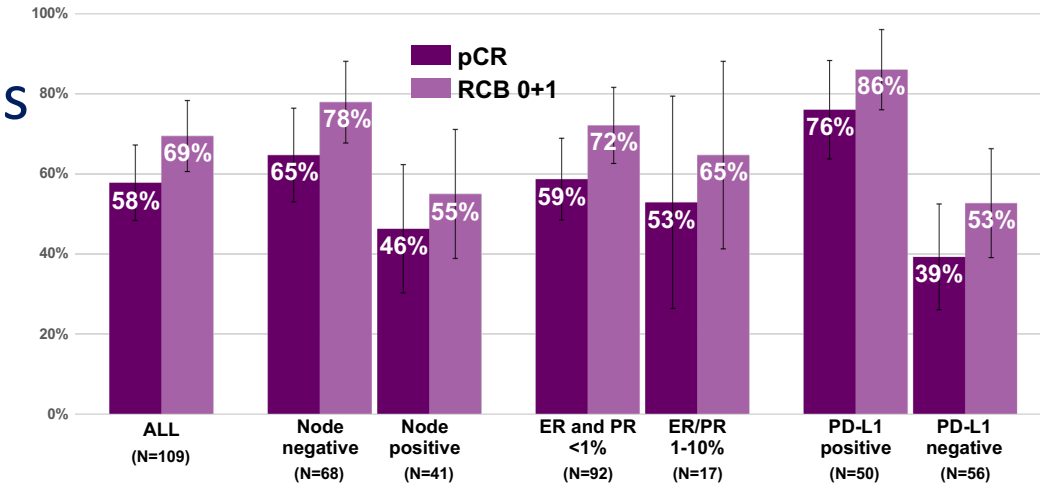


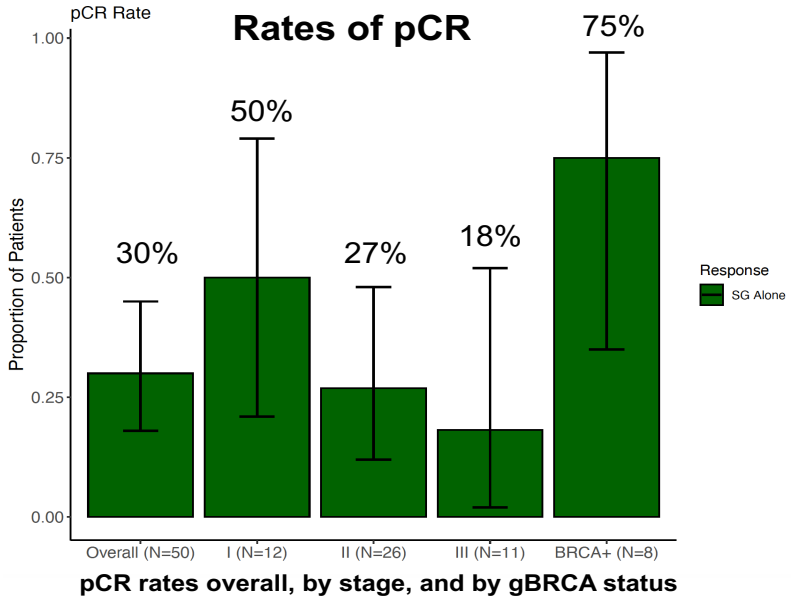

Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

PI: Tolaney
Alliance Trial

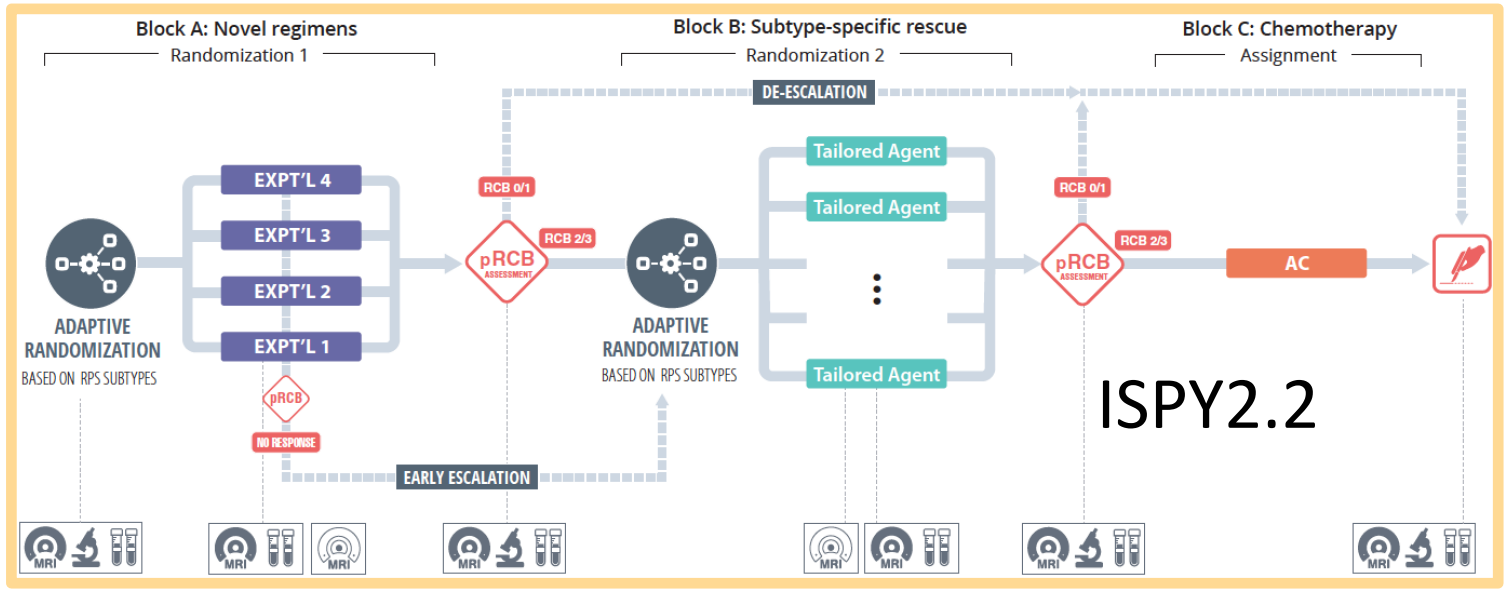
# Alternative NeoAdjuvant Regimens for TNBC

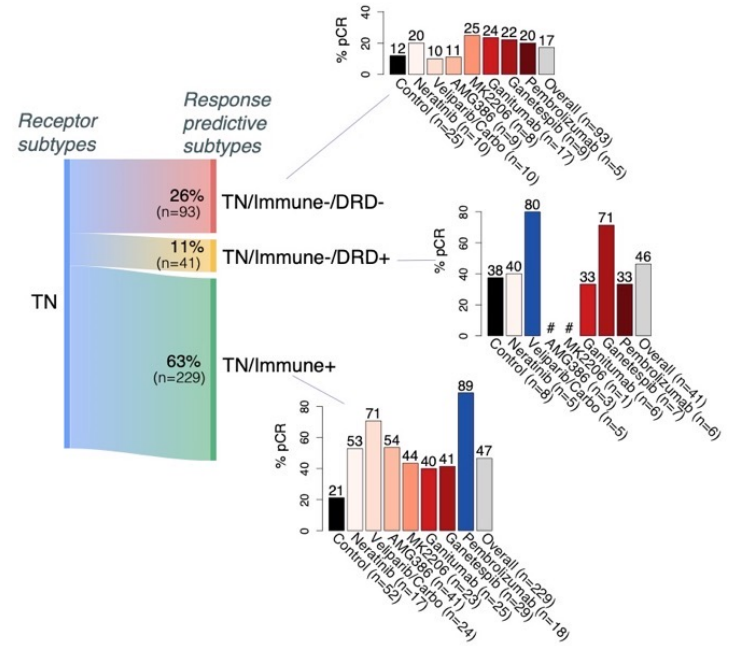
- NeoPACT:
  - Pembrolizumab/docetaxel/carboplatin x 6 cycles
  - 109 evaluable, 88% stage 2-3
  - pCR in TNM stage I, II, and III disease was 69%, 59%, and 43%, respectively.
  - Stage II-III, ER & PR IHC <1%
    - pCR and RCB 0+1 59% and 69%
  - 2-year EFS with pCR: 98%
- NeoSTAR: Sacituzumab govitecan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



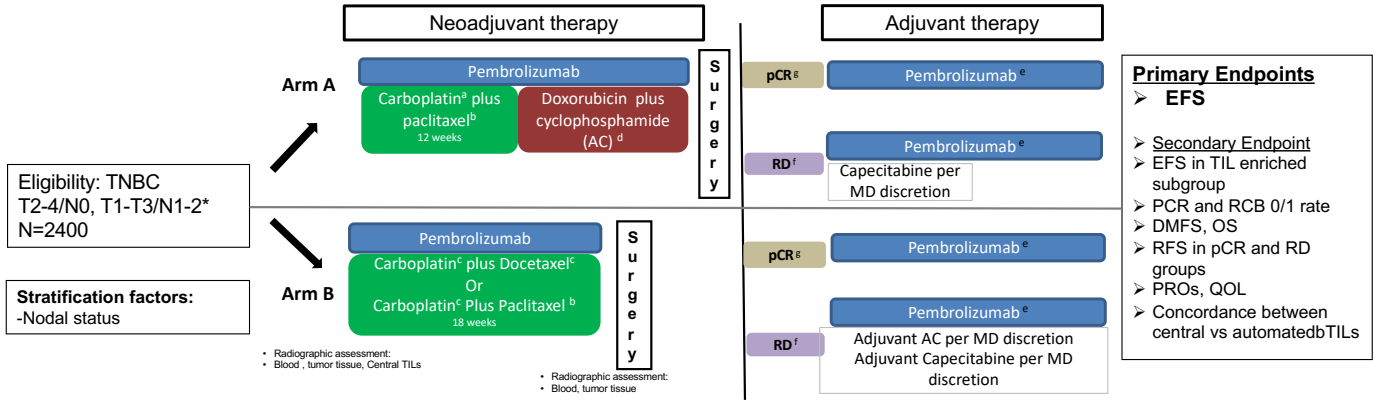




Yee D et al. 2022 ASCO Abstract 591; Wolf, Yao et al, CCR 2022.

## 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

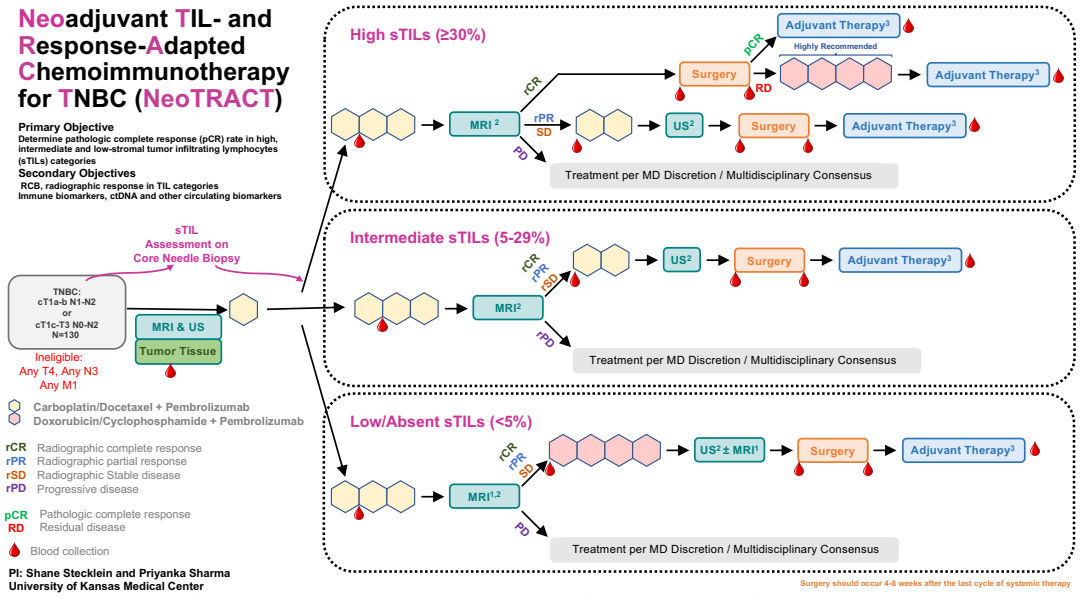
- Secondary Endpoint
- EFS in TIL enriched subgroup
- PCR and RCB 0/1 rate
- DMFS, OS
- RFS in pCR and RD groups
- PROs, QOL
- Concordance between central vs automatedbTILs

*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

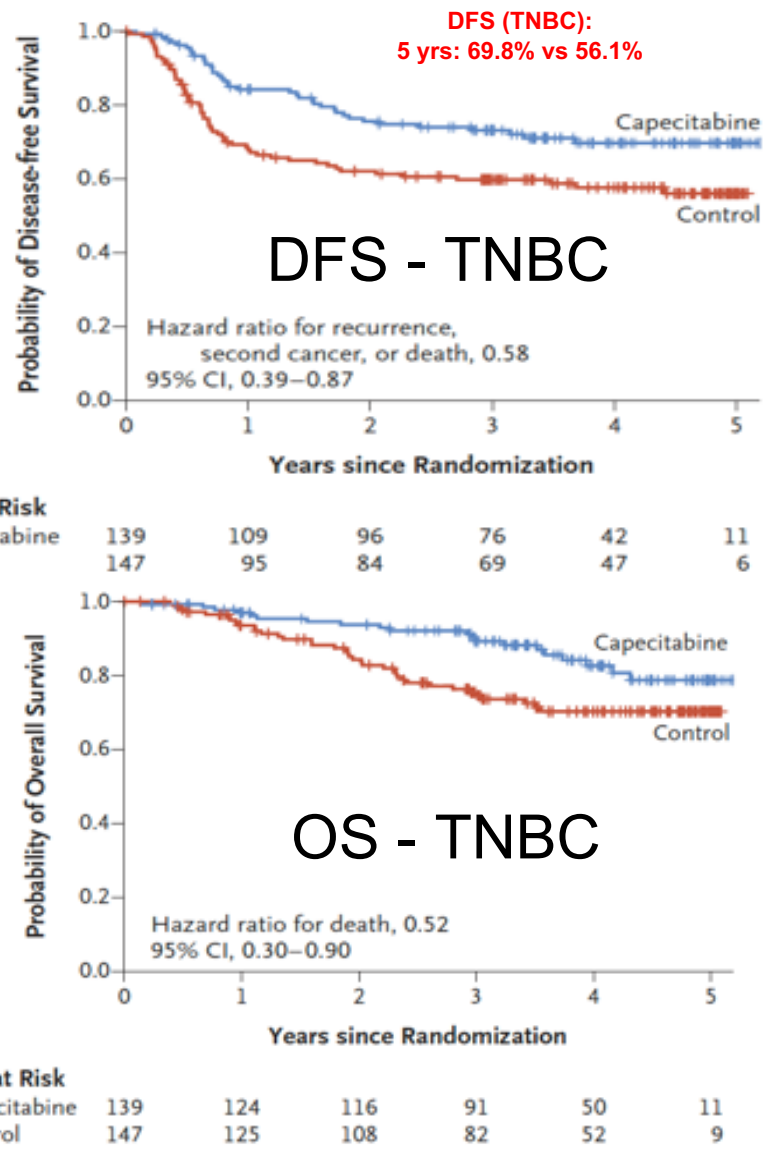
## Neoadjuvant TIL- and Response-Adapted Chemoimmunotherapy for TNBC (NeoTRACT)



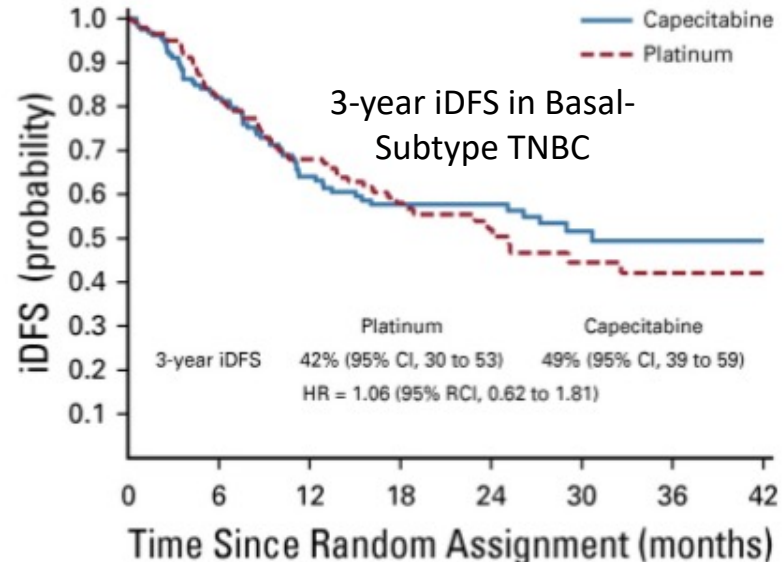
# Post-Neoadjuvant Therapy

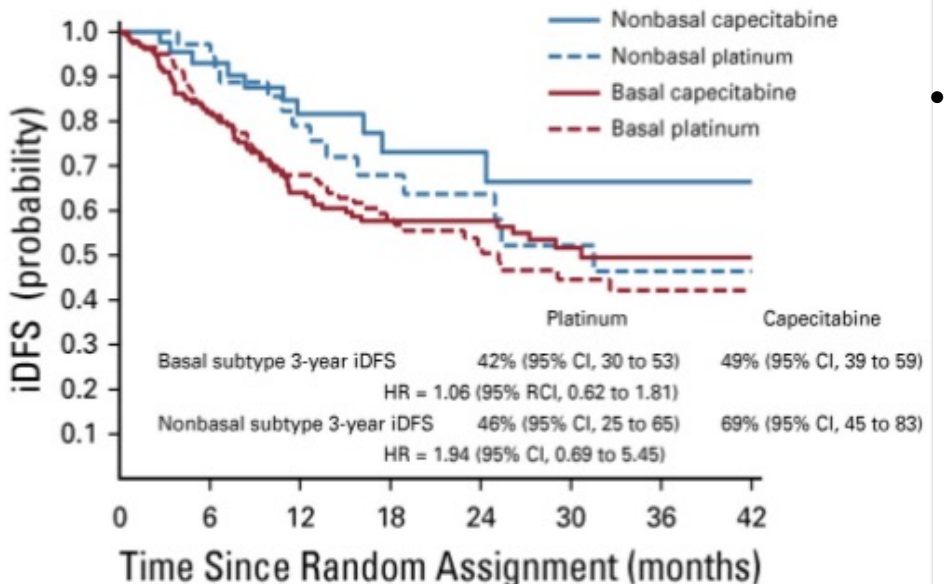
# Post-Neoadjuvant Capecitabine

## CREATE-X




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




## ECOG 1131

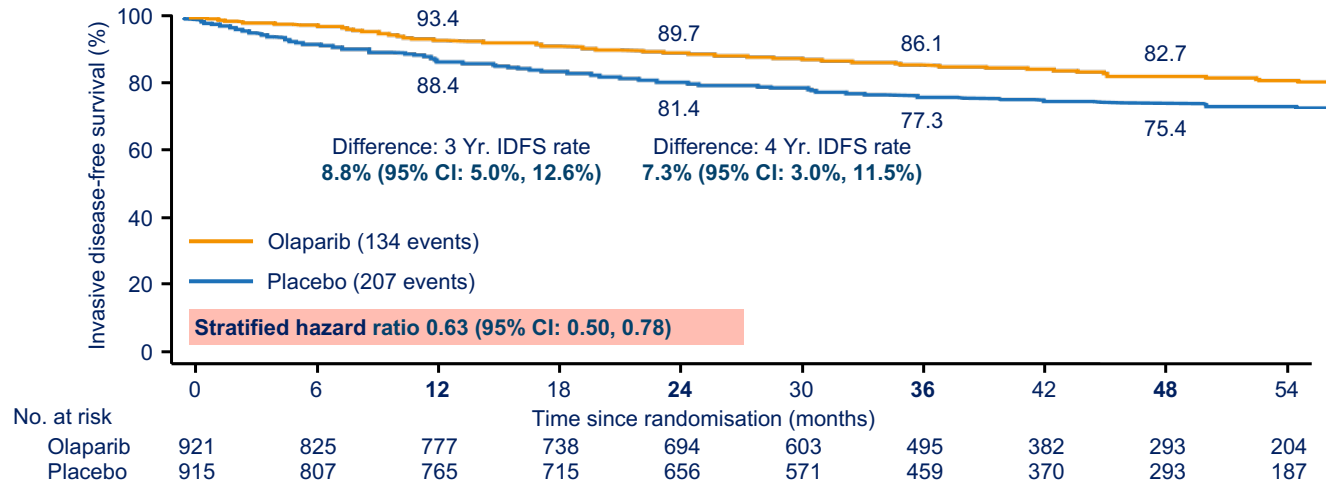
- ~80% of patients with residual TNBC after NAC have basal-subtype by PAM50 analysis
- Platinum agents were associated with more severe hematological toxicities
- Irrespective of treatment arm, a much higher than expected event rate was observed in this high-risk population

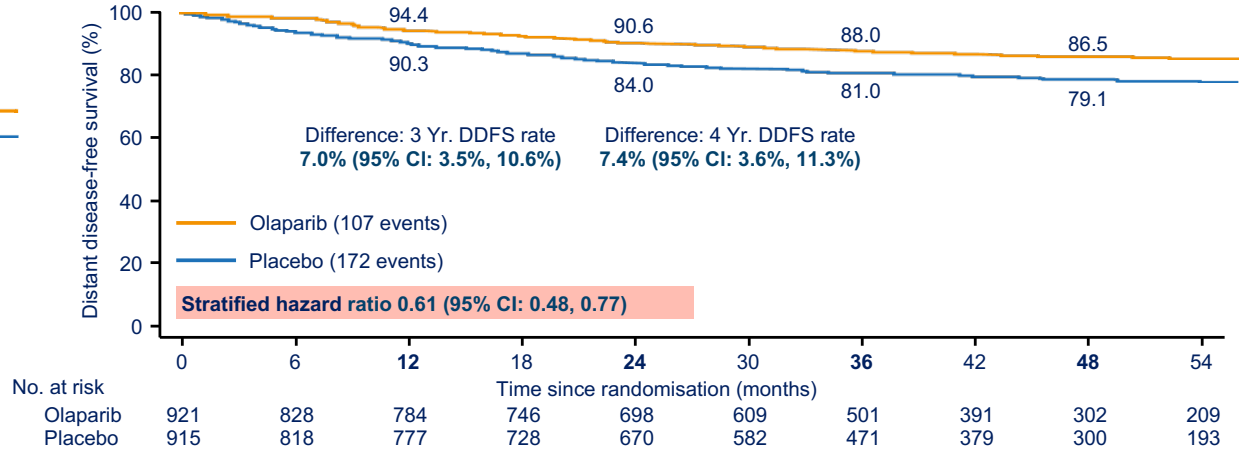
Mayer et al. J Clin Oncol. 2021

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

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

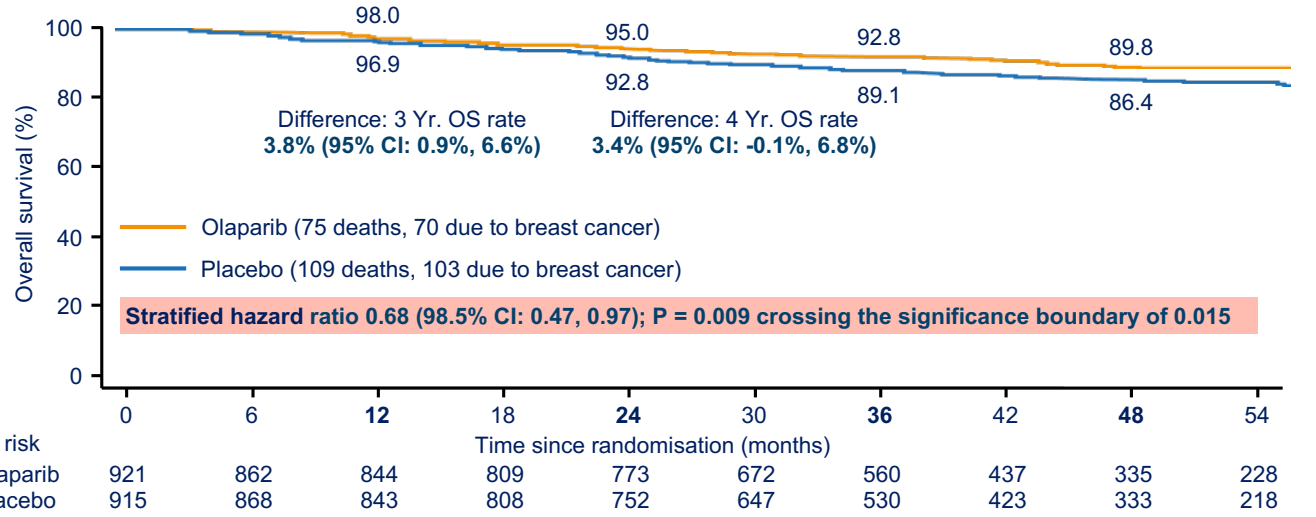
**Adjuvant Group**
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes




- 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%

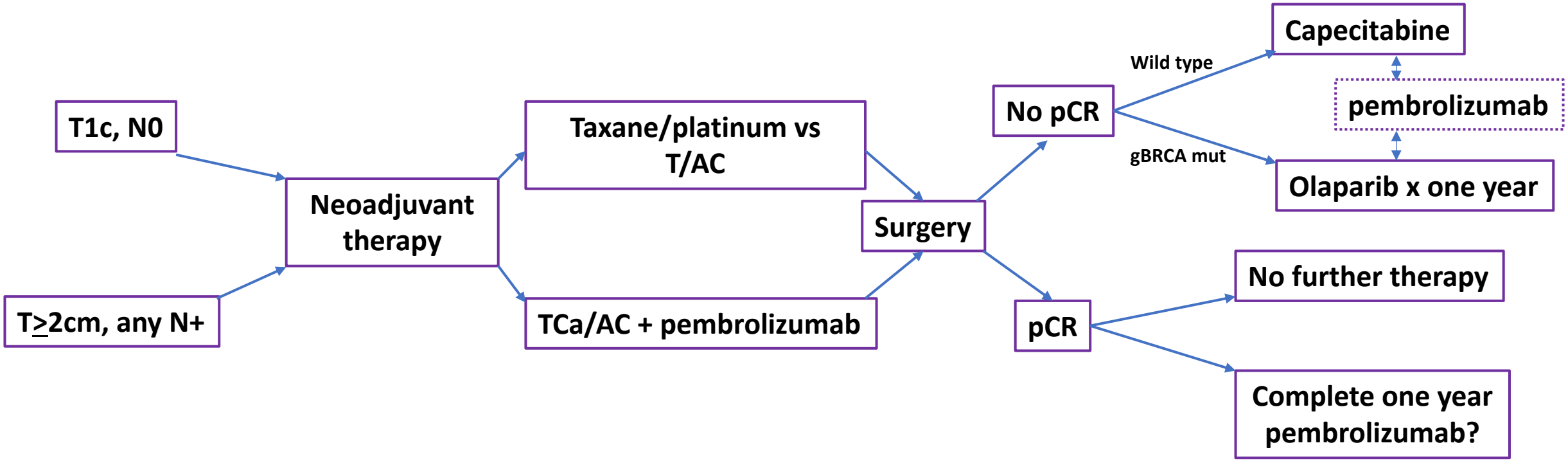


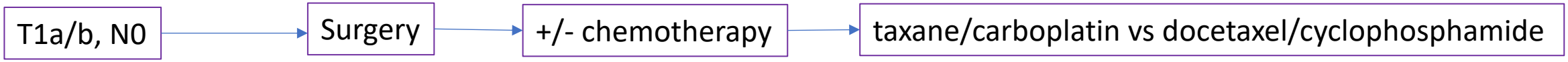

Tutt et al. N Engl J Med. 2021;384(25):2394-2405;
Tutt et al. ESMO Plenary 2022.

# 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
  - Improving post-neoadjuvant therapy

# 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!