Updates and Advances in Triple Negative Breast Cancer

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Disclosures

- Pfizer, Stemline – clinical trial funding
- Astra Zeneca – advisory board
- Gilead – speaker bureau
- Merck – speaker bureau

Triple Negative Breast Cancer ASCO Updates

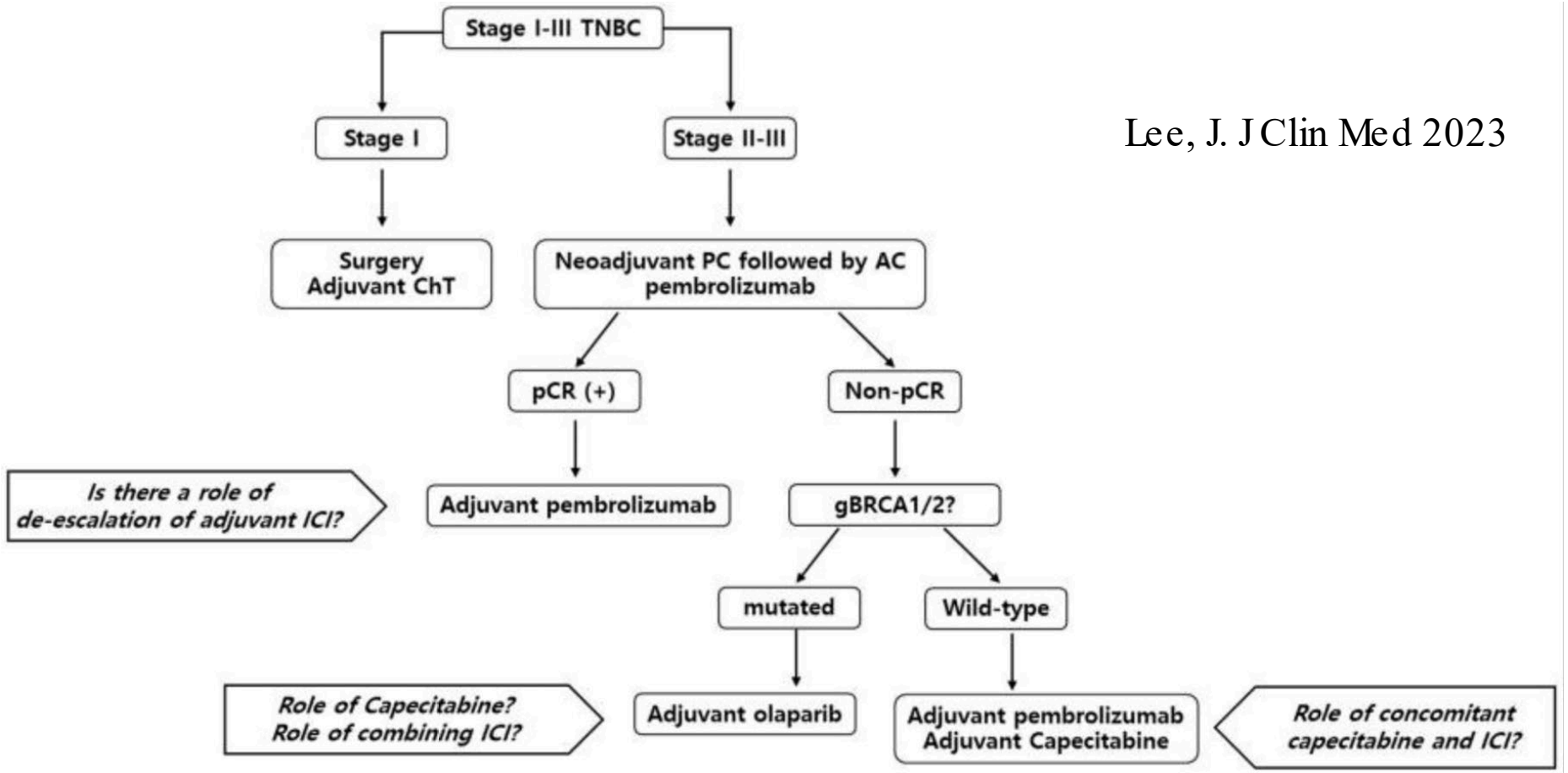
- Early Stage
  - ABCSG 45

- Metastatic
  - ASCENT 04
  - OptiTROP Breast 05

- Future directions

Early Stage

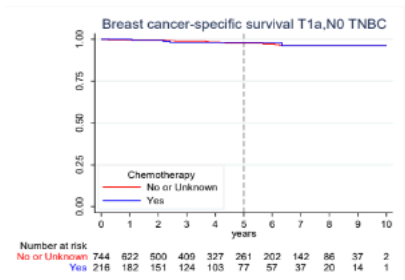
Landscape



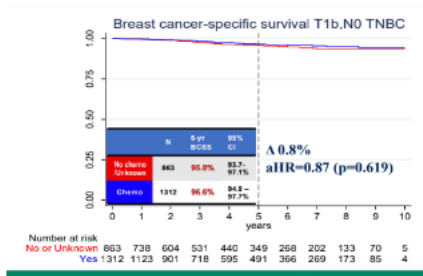
Lee, J. J Clin Med 2023

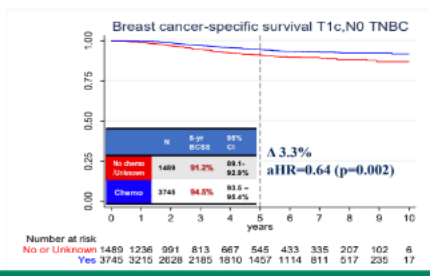
Stage I TNBC: SEER Registry 2010 – 2019

N=8,601



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





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

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

Chemotherapy significantly improved BCSS in patients with **T1c** TNBC
Event rates were low in stage Ia and Ib disease; changing patterns of chemotherapy use impact interpretation

Tarantino et al, ASCO 2023

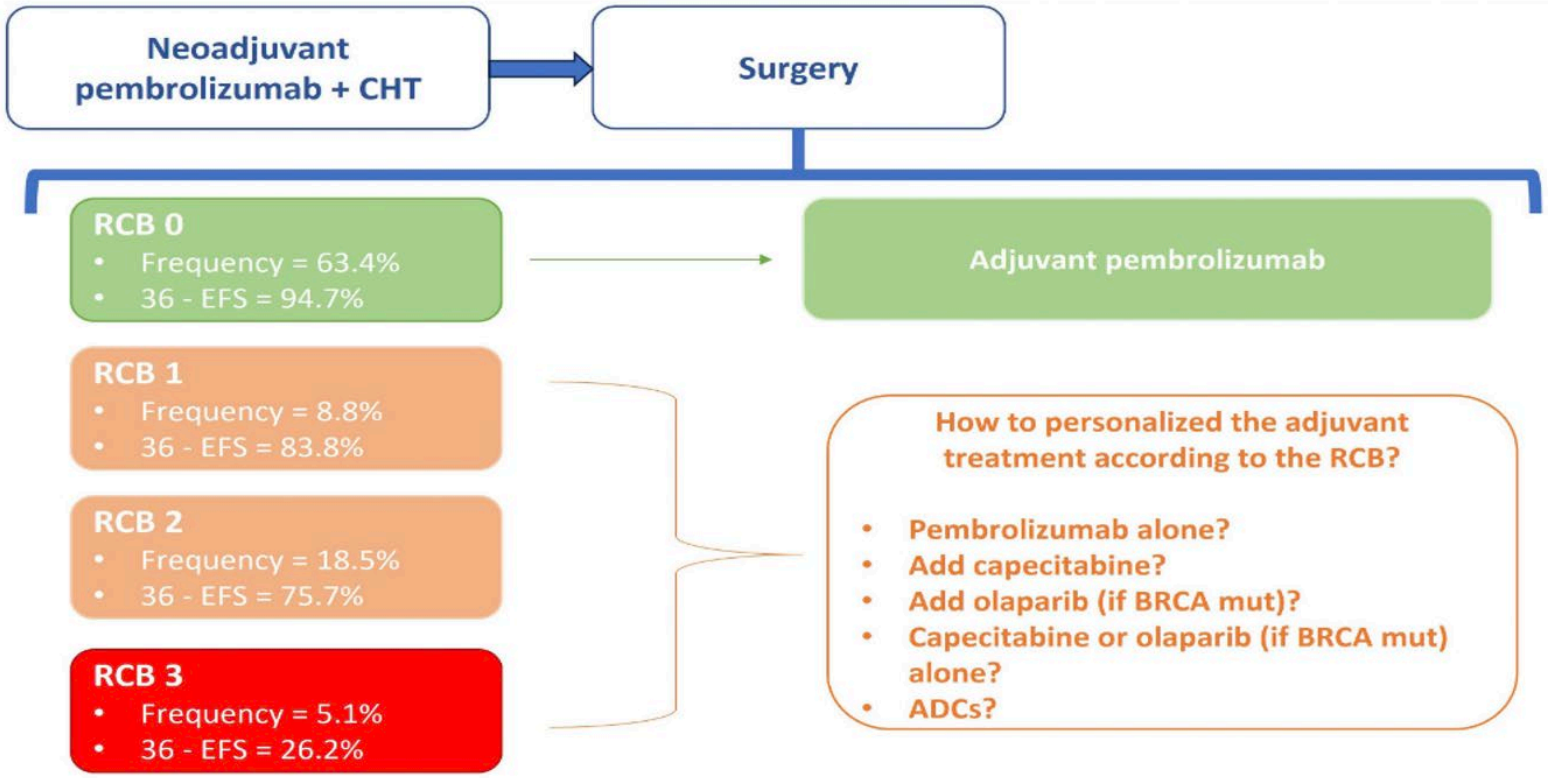
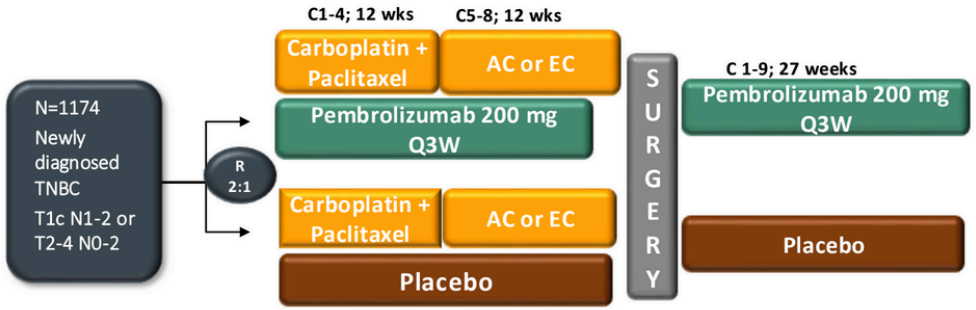


Figure 1. The unmet need for the optimal adjuvant treatment according to RCB [85]

De Santis et al. Expl Target Antitum Ther 2024
Pusztai LJCO 2022

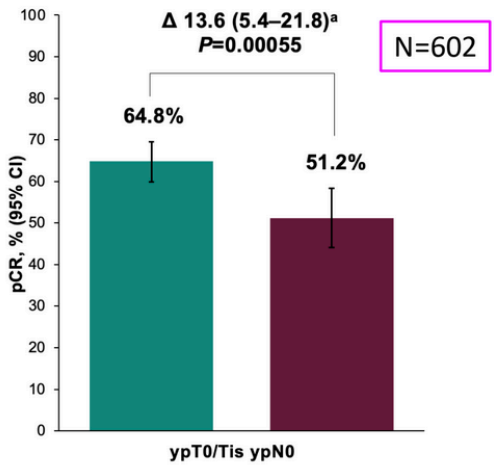
KN522: Neoadjuvant Immunotherapy

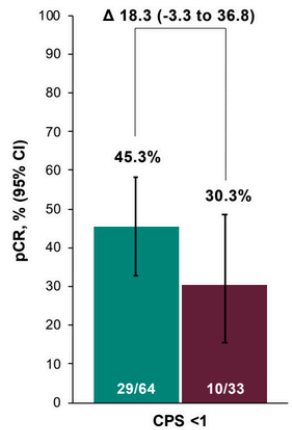


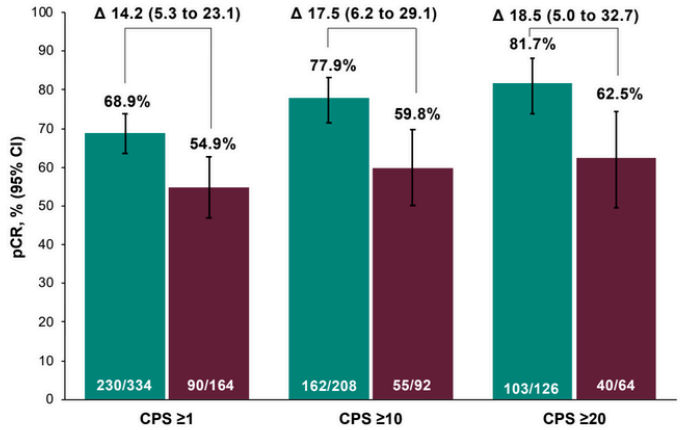
Patient population

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

PD-L1 is predictive of response to chemotherapy but benefit from immunotherapy is independent of PD-L1 status



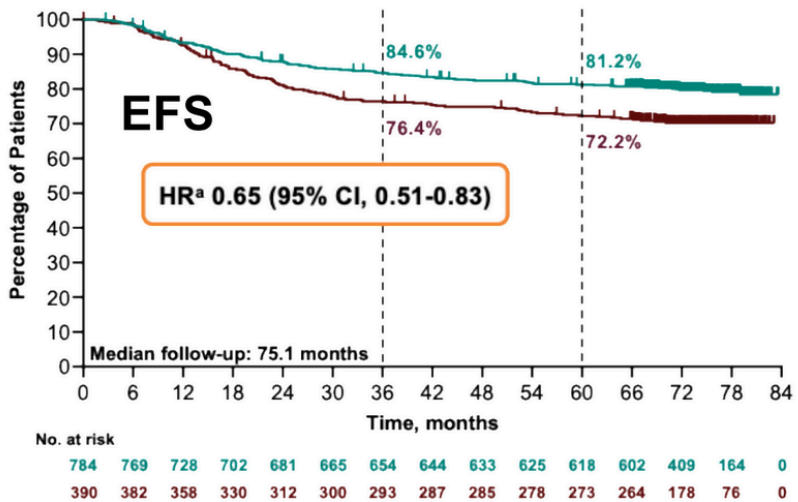




Schmid et al. N Engl J Med. 2020;382(9):810-821

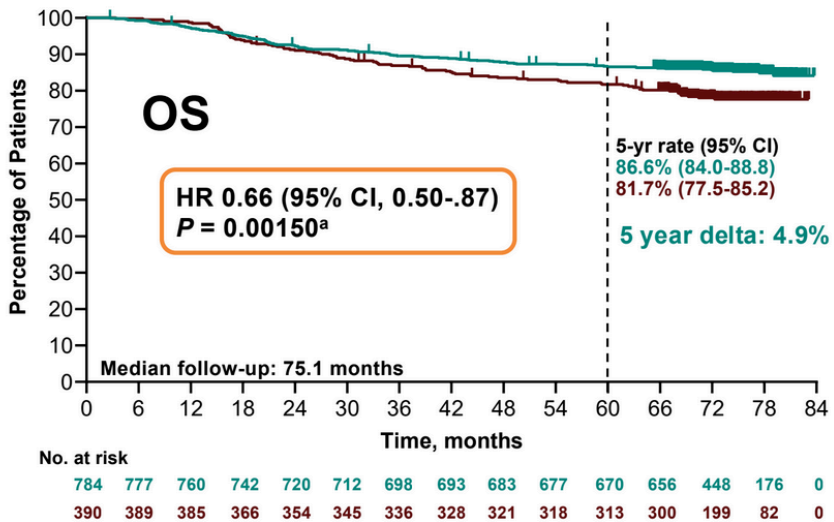
KEYNOTE 522: EFS and OS

	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%



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

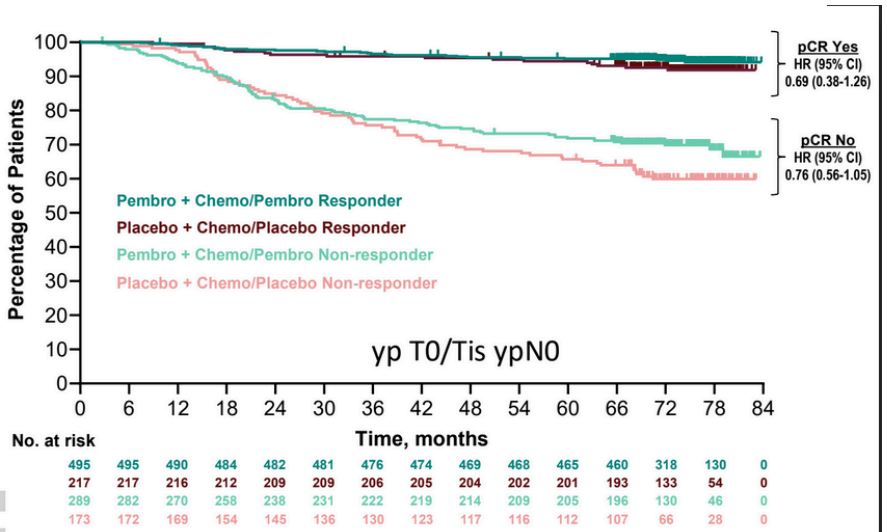
67.3% information fraction[a]



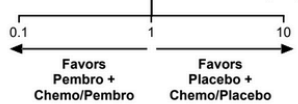
[a]With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis. Overall, 86/115 (74.8%) deaths in the pembro group and 62/85 (72.9%) deaths in the placebo group were due to disease progression or recurrence.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

Schmid et al, NEJM 2024

Overall Survival in Patient Subgroups and by pCR



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



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

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

2025 ASCO ANNUAL MEETING

ABCSG
AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

ABCSG 45: A prospective, open, randomized, phase II study of carboplatin/olaparib in the pre-operative treatment of patients with triple-negative primary breast cancer which exhibit the features of positive homologous recombination deficiency (HRD) status

Singer CS, Hlauschek D, Egle D, Bago-Horvath Z, Pfeiler G, Christine Brunner, Peters-Engl C, Petru E, Daniel Reimer, Pusch R, Seifert M, Pichler P, Suppan C, Anette Reimer, Greil R, Tan Y, Bartsch R, Katharina Knoll, Kermanidis AS, Gnant M, on behalf of the Austrian Breast & Colorectal Cancer Study Group

PRESENTED BY: Christian F Singer, Medical University of Vienna, Vienna, Austria

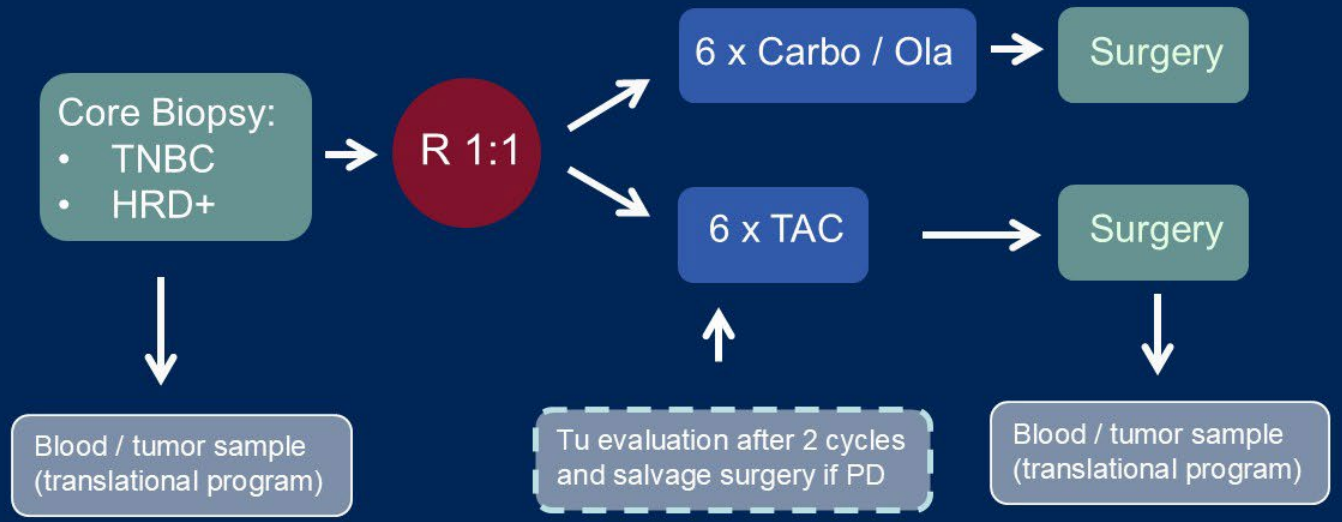
ABCSG 45 Background

- PARPi approved for the treatment of early and advanced BC in carriers of *gBRCA1/2* pathogenic variant (PV)
- PARPi also effective in HR-deficient (HRD+) advanced BC in patients without *gBRCA1/2* PV, with CBR > 50%[1,2]
- Patients with HRD+ TNBC achieve higher pCR rates in response to platinum-based NACT[3]
- Evidence from BRCA-deficient animal models suggests superior efficacy of olaparib + carboplatin combination[4]
- Role for neoadjuvant olaparib + carboplatin in early HRD+ TNBC ?

[1]Cortes A, *et al.* Breast 2024; [2]Gruber JJ *et al.* Nature Cancer 2022; [3]Chai Y et al. J Pers Med. 2022; [4]Rottberg et al, PNAS 2008

PRESENTED BY: Christian F Singer, Medical University of Vienna, Vienna, Austria

ABCSG 45 Study Design (I)



Phase II Study

- 90 patients randomized

Strata

- Tumor *BRCA1/2* status
- Menopausal status

Carbo/Ola: 6 x carboplatin AUC 5 q3w + olaparib ≥ 100 bid (days 4-19)

TAC: 6 x docetaxel 75 mg q3w + epirubicin 50 mg/m^2 q3w + cyclophosphamide 500 mg/m^2 q3w

PRESENTED BY: Christian F Singer, Medical University of Vienna, Vienna, Austria

ABCSG 45 Study Design (II)

2 Step Design

Step 1 (n=10):

- identification of optimal olaparib dose regimen

  100→200 →300 mg bid, days 4-19

Step 2 (n=36):

- 100 mg bid, days 4-19

Primary endpoint

- Residual Cancer Burden (RCB) 0/I

Secondary endpoints

- pCR
- safety and tolerability
- QoL

ABCSG 45 Study Design

Key Inclusion Criteria

- Early invasive TNBC
- HRD+ status (tumor *BRCA1/2* PV or Genomic Instability Score ≥ 42)
- ≥ T1c, any N allowed

Key Exclusion Criteria

- Contraindications against any of the trial drugs
- Locally advanced or inoperable tumor

ABCSG 45 Baseline Characteristics

	Carbo/Ola (n=46)	TAC (n=44)	Total (n=90)
Age, mean (SD)	50.2 (12.7)	51.6 (12.5)	**50.9** (12.5)
Menopausal status			
pre- and peri-menopausal	23 (50.0%)	23 (52.3%)	46 (51.1%)
postmenopausal	23 (50.0%)	21 (47.7%)	44 (**48.9%**)
Tumor *BRCA1/2* PV status			
negative	24 (52.2%)	24 (54.5%)	48 (53.3%)
positive	22 (47.8%)	20 (45.5%)	42 (**46.7%**)
Genomic Instability Status			
positive	42 (91.3%)	41 (93.2%)	83 (**92.2%**)
negative	1 (2.2%)	2 (4.5%)	3 (3.3%)
missing	3 (6.5%)	1 (2.3%)	4 (4.4%)
Genomic Instability Score mean (SD)	59.6 (11.7)	62.0 (12.1)	60.8 (11.9)
Germline *BRCA1/2* PV*			
negative	17 (37.0%)	19 (43.2%)	36 (40.0%)
positive	16 (34.8%)	16 (36.4%)	32 (35.6%)
missing	13 (28.3%)	9 (20.5%)	22 (24.4%)

	Carbo/Ola (n=46)	TAC (n=44)	Total (n=90)
T-stage			
T1	21 (45.7%)	15 (34.1%)	36 (**40.0%**)
T2	22 (47.8%)	28 (63.6%)	50 (55.6%)
T3	1 (2.2%)	0	1 (1.1%)
T4	2 (4.3%)	1 (2.3%)	3 (3.3%)
N-stage			
N0	28 (60.9%)	26 (59.1%)	54 (**60.0%**)
N1	14 (30.4%)	16 (36.4%)	30 (33.3%)
N2	2 (4.3%)	1 (2.3%)	3 (3.3%)
N3	1 (2.2%)	1 (2.3%)	2 (2.2%)
NX	1 (2.2%)	0	1 (1.1%)
Grading			
G2	2 (4.3%)	3 (6.8%)	5 (5.6%)
G3	44 (95.7%)	41 (93.2%)	85 (94.4%)
KI67 [%] mean (SD)	72.0 (17.4)	72.3 (18.2)	72.1 (17.6)

*) only assessed in a subset after randomization

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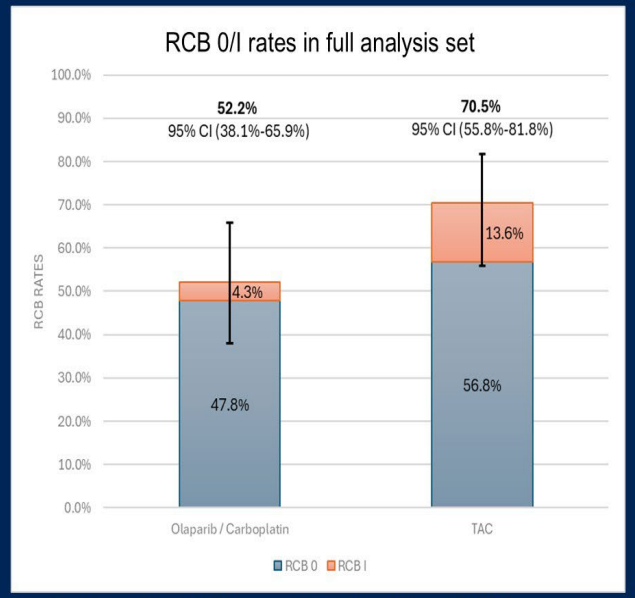
Primary Endpoint RCB 0/I



Cochran Mantel Haenszel Test p-value = 0.068

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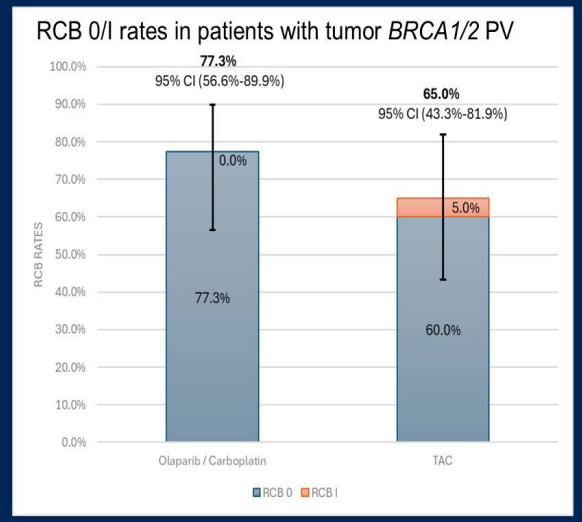
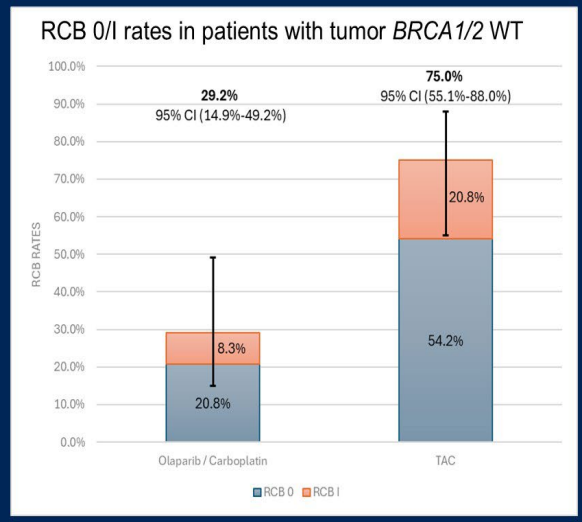
RCB 0/I and Tumor *BRCA1/2* Status





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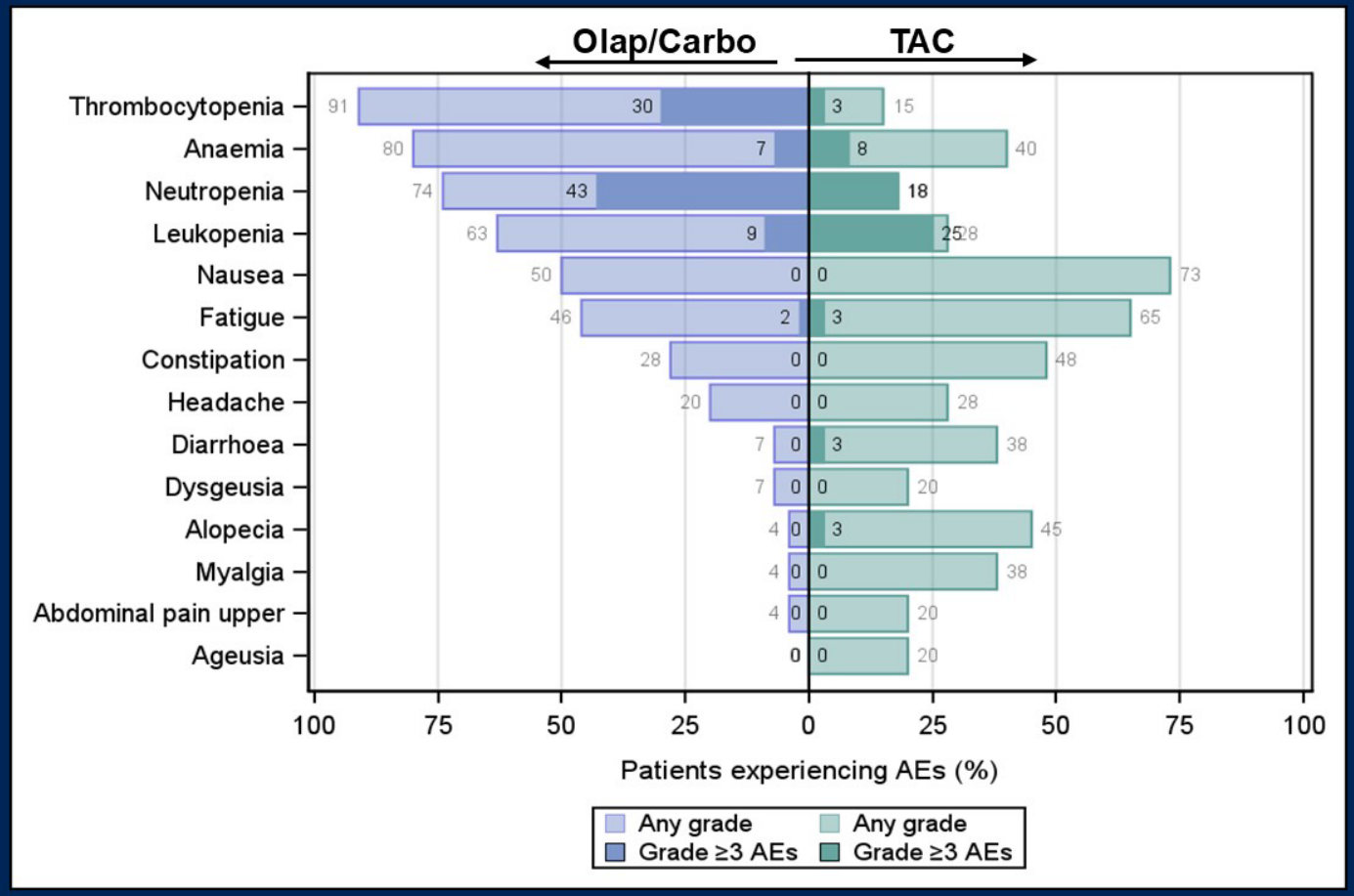
Adverse Events (>15%)



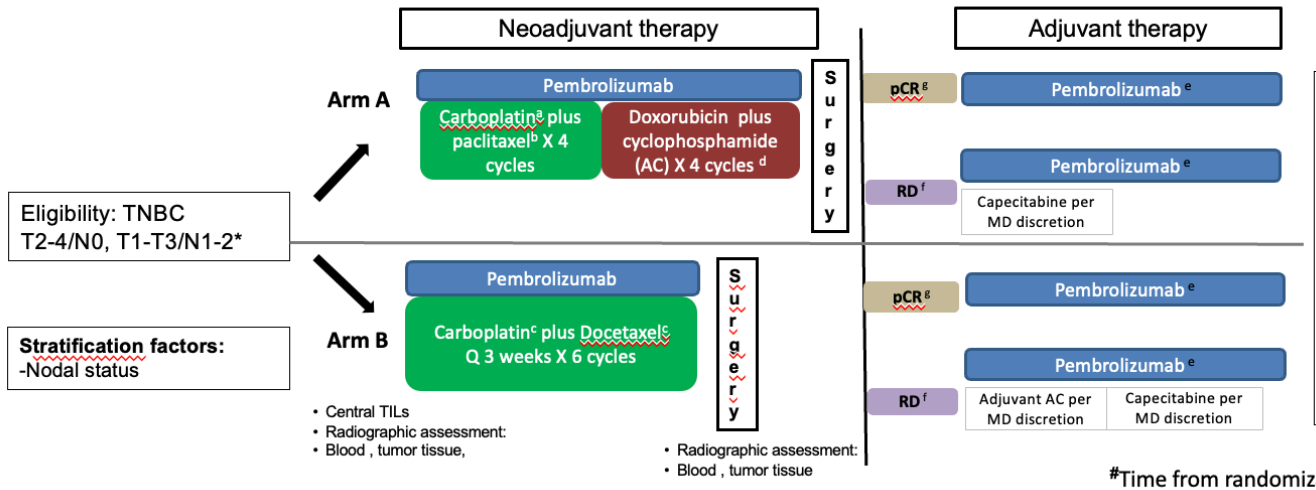
ABCSG 45 Conclusions

- HRD+ TNBC is highly sensitive to anthracycline/taxane-based NACT
- Patients with tumoral *BRCA1/2* PV achieve RCB0/I in > 77% in response to Carbo/Ola
- Main toxicities in Carbo/Ola arm are haematological (thrombocytopenia and neutropenia), in TAC arm additional non-hematological toxicities
- HRD and tumoral *BRCA1/2* status help to personalize treatment decisions in early TNBC

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

Randomized non-inferiority trial

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



Primary Endpoints

- **BC-EFS#**

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

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

N=2400

PI: Priyanka Sharma and Zahi Mitri

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

SWOG CANCER RESEARCH NETWORK

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

TROPION-Breast04

Key Eligibility Criteria

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

1:1

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

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

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

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

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

Stratification factors:

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

Dual primary endpoints:
pCR and EFS

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

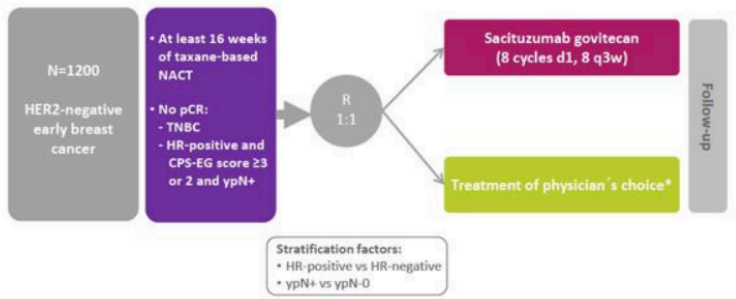
Exploratory endpoints include but are not limited to:
TROP2, PD-L1

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

PI: Heather McArthur
NCT06112379

GBG: SASCIA Post-Neoadjuvant Trial

NCT04595565

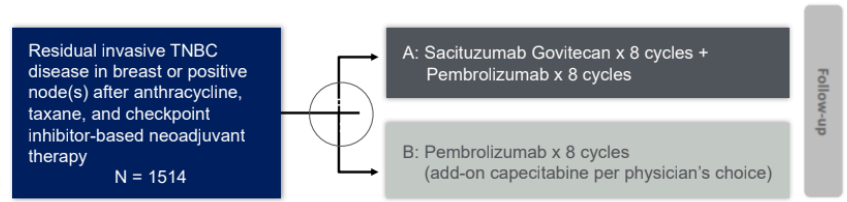


Challenge combining ER+ and TNBC pts

*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 Optimice-RD/ASCENT-05

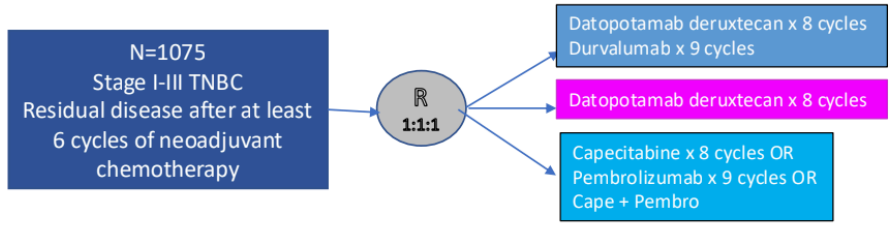
NCT05633654



PI: Sara Tolaney
Alliance Foundation Trial

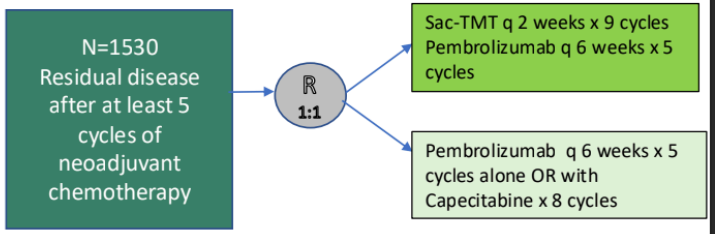
Phase III TROPION Breast03

NCT05629585



TROFUSE 012: Phase III Sac-TMT

NCT06393374



Metastatic

Advances for metastatic TNBC in the last decade

- ✔ PARP inhibitors olaparib and talazoparib improve PFS 2018
- ✔ Pembrolizumab and chemotherapy improves PFS & OS in PD-L1+ first line advanced TNBC 2020
- ✔ Sacituzumab govitecan improves PFS & OS in pre-treated advanced TNBC 2021
- ✔ Trastuzumab deruxtecan improves PFS & OS in pre-treated advanced HER2 low breast cancer, including TNBC 2022

Treatment landscape for mTNBC in 2025

First Line	Second Line	Third Line +
PD-L1+: Pembrolizumab + Chemotherapy (KN-355)	Sacituzumab Govitecan (ASCENT)	Biomarker positive: Targeted agents
PD-L1-: Taxane or Platinum	Trastuzumab Deruxtecan (DESTINY Breast-04)	
g*BRCA1/2*m: Olaparib or Talazoparib		
Systemic chemotherapy		

NCCN Guidelines. Breast Cancer. v4.2025.

PARP inhibitors in advanced breast cancer with a g*BRCA1/2* PV

Pivotal trials

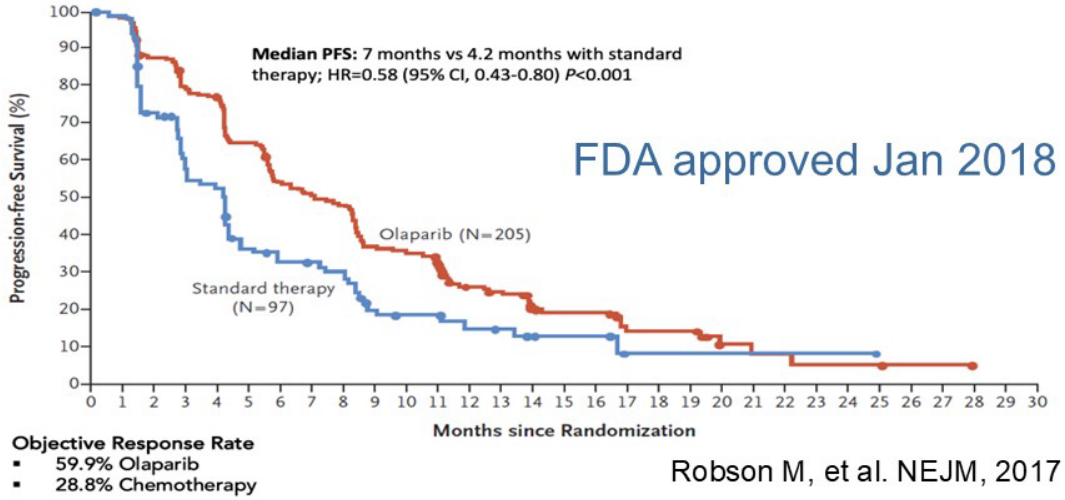
OlympiAD

*g**BRCA1/2***, HER2-negative, Metastatic Breast Cancer
≤2 previous chemotherapy regimens
HR+ disease had to progress on at least 1 prior endocrine therapy

RANDOMIZED 2:1
n=302

- **Olaparib 300 mg BID n=205**
- **MD Choice Chemotherapy* n=99**

*Capecitabine, eribulin, or vinorelbine



FDA approved Jan 2018

Robson M, et al. NEJM, 2017

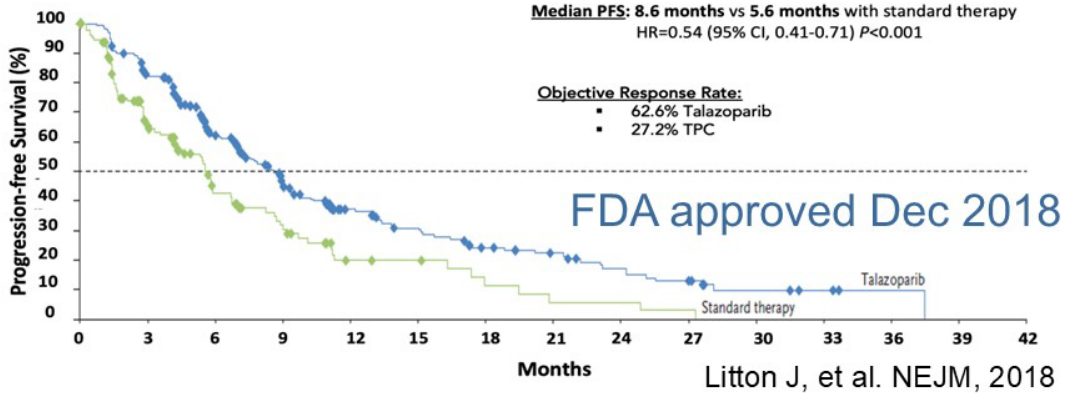
EMBRACA

*g**BRCA1/2***, HER2-negative, Locally Advanced or Metastatic breast cancer
≤3 previous chemotherapy regimens
No limit on number of prior endocrine therapies

RANDOMIZED 2:1
N=431

- **Talazoparib 1 mg daily n=287**
- **MD Choice Chemotherapy** n=144**

**Capecitabine, eribulin, vinorelbine, or gemcitabine



FDA approved Dec 2018

Litton J, et al. NEJM, 2018

Pembrolizumab added to 1st line chemotherapy in advanced TNBC
KEYNOTE-355

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- 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

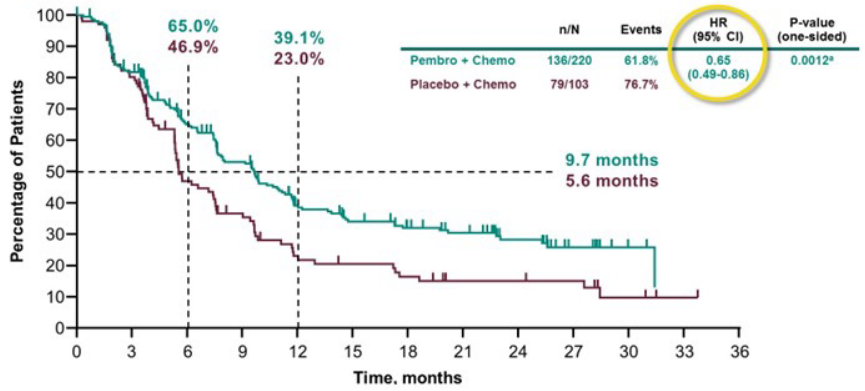
R 2:1

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

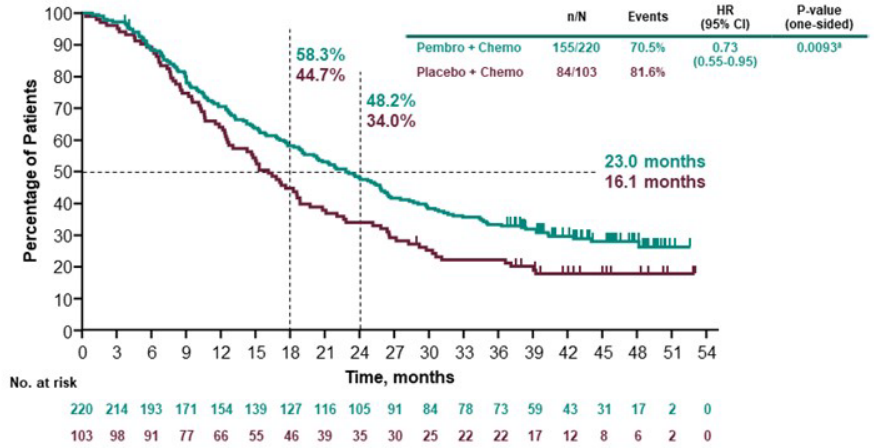
→ Progressive disease[d]/cessation of study therapy

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

Progression-Free Survival: PD-L1 CPS ≥10



Overall Survival: PD-L1 CPS ≥10



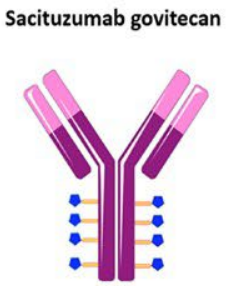
[a]Prespecified *P* value boundary of 0.0113 met.

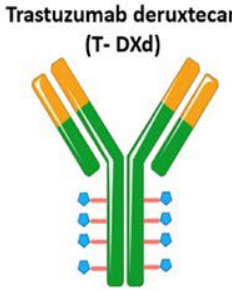
- November 2020: Granted accelerated FDA approval for PD-L1+ metastatic TNBC with CPS ≥ 10
- July 2021: Granted full FDA approval

Option for approximately 40% of patients

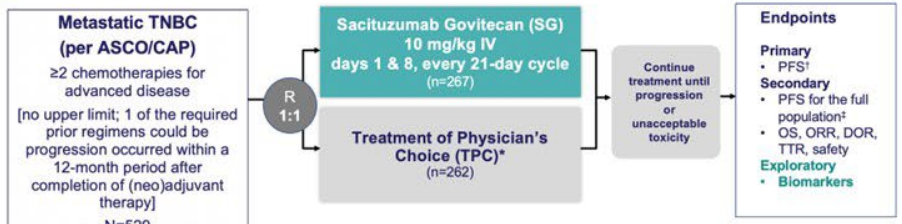
Cortes J, et al. Lancet. 2020;396(10265):1817-1828.
Cortes J, et al. N Engl J Med. 2022 Jul 21;387(3):217-226.

ADCs approved for triple-negative MBC



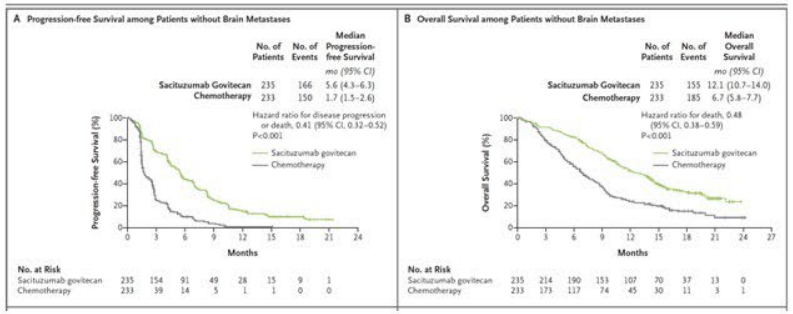


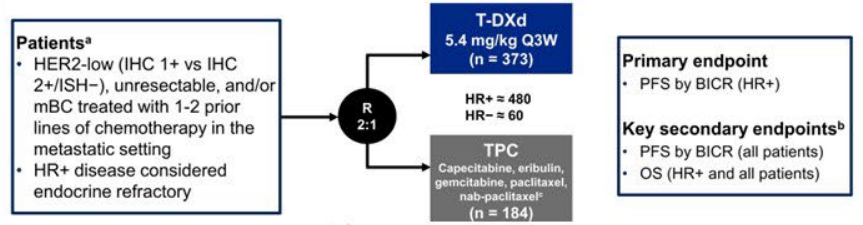
	Sacituzumab Govitecan (SG)	Trastuzumab Deruxtecan (T-DXd)
Target antigen	TROP2	HER2
Linker cleavage	pH and enzymatic	Enzymatic
Membrane-permeable payload	Yes	Yes
Payload MOA	SN-38/Topo 1 inhibitor	Topo 1 inhibitor
Drug-antibody ratio	7.6:1	8:1
Toxicities	↓ANC, diarrhea	↓plts, ↓LVEF, ILD



ASCENT Clinical Trial

FDA approved
April 2021

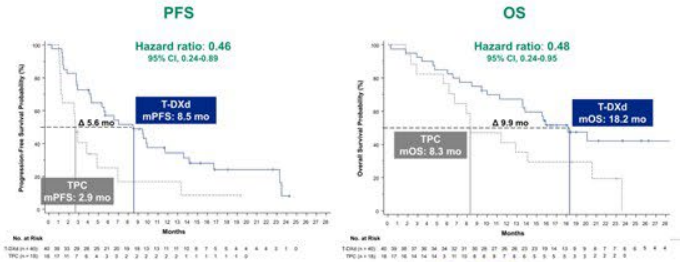




DESTINY-Breast04

FDA approved
August 2022

PFS and OS in HR− (Exploratory Endpoints)



2025 ASCO ANNUAL MEETING

Sacituzumab Govitecan Plus Pembrolizumab vs Chemotherapy Plus Pembrolizumab in Patients With Previously Untreated, PD-L1 Positive, Advanced or Metastatic Triple-Negative Breast Cancer: Primary Results From the Randomized, Phase 3 ASCENT-04/KEYNOTE-D19 Study

Sara M Tolaney[1], Evandro de Azambuja[2], Kevin Kalinsky[3], Sherene Loi[4], Sung-Bae Kim[5], Clinton Yam[6], Bernardo Rapoport[7,8], Seock-Ah Im[9], Barbara Pistilli[10], Wassim McHayleh[11], David W Cescon[12], Junichiro Watanabe[13], Manuel Alejandro Lara Banuelas[14], Ruffo Freitas-Junior[15], Javier Salvador Bofill[16], Maryam Afshari[17], Dianna Gary[17], Lu Wang[17], Catherine Lai[17], Peter Schmid[18]

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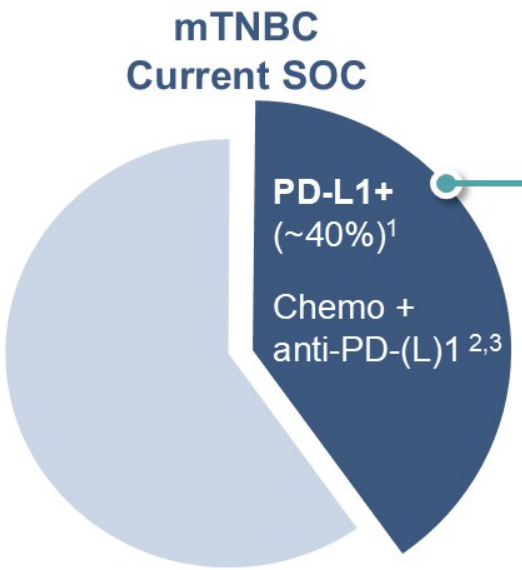
PRESENTED BY: Sara M Tolaney, MD, MPH

Unmet Need in Previously Untreated, PD-L1+, Locally Advanced Unresectable or Metastatic TNBC



Remaining unmet need

- Median PFS observed in prior studies of chemotherapy in combination with immune checkpoint inhibitors was 7.5-9.7 months[1, 4]; most patients still experience disease progression[5-7]
- About half of the patients treated for 1L mTNBC do not receive 2L treatment[5]

Rationale for this study

- SG is the only Trop-2–directed ADC with demonstrated OS benefit in multiple phase 3 studies; it is approved for 2L+ mTNBC and pre-treated HR+/HER2- mBC in multiple countries[8,9]
- Early studies have observed improved anti-tumor effects when immunotherapy is combined with ADCs[10]

We present the primary results from the global, randomized, phase 3 ASCENT-04/KEYNOTE-D19 study of SG + pembro vs chemo + pembro in previously untreated, PD-L1+, locally advanced unresectable or metastatic TNBC

1L, first line; 2L(+), second line (and further); ADC, antibody drug conjugate; chemo, chemotherapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; PFS, progression-free survival; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; SG, sacituzumab govitecan SOC, standard of care.

1. Cortes J, et al. *N Engl J Med*. 2022;387(3):217-226. 2. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V4.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed April 22, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 4. Schmid P, et al. *N Engl J Med*. 2018;379(22):2108-2121. 5. Punie K, et al. *Oncologist*. 2025;30(3).*ePublished*. 6. Skinner KE, et al. *Future Oncol*. 2021;18(8):931-941. 7. Geurts V, Kok M. *Curr Treat Options Oncol*. 2023;24(6):628-643. 8. TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; March 2025. 9. TRODELVY® (sacituzumab govitecan-hziy) [summary of product characteristics]. County Cork, Ireland: Gilead Sciences Ireland UC; August 2023. 10. Nicolo E, et al. *Cancer Treat Rev*. 2022;106:102395.

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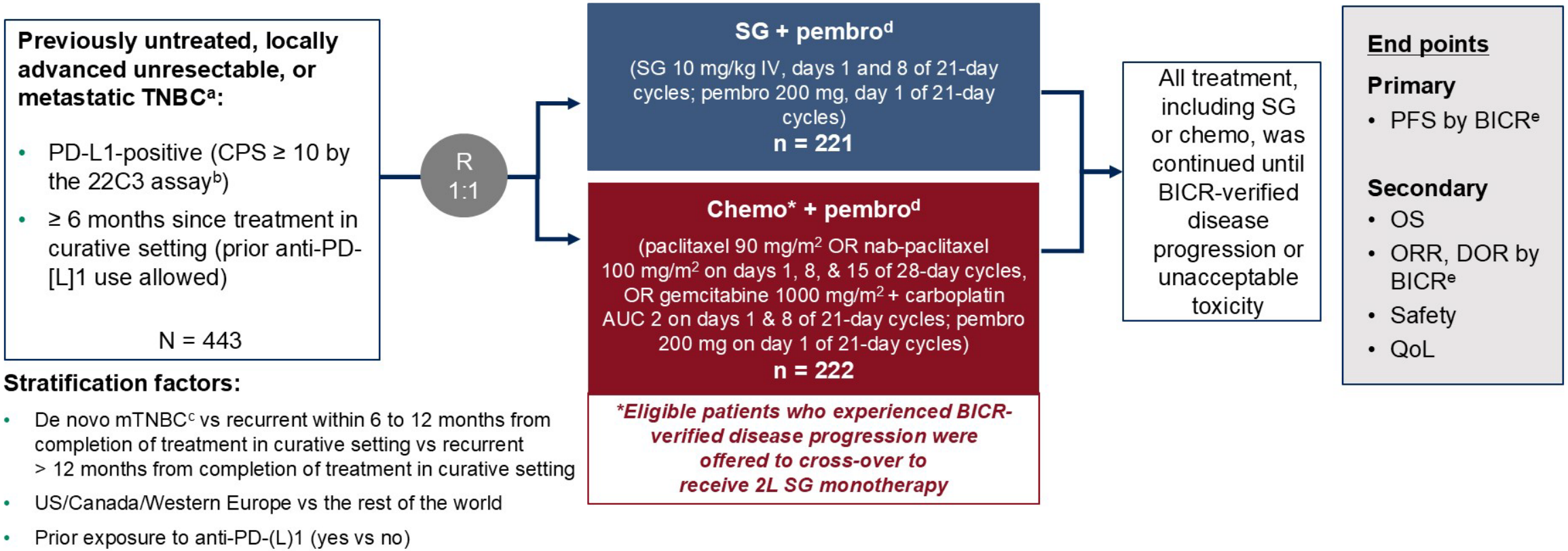
ASCENT-04/KEYNOTE-D19 Study Design



Stratification factors:

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

ClinicalTrials.gov identifier: NCT05382286.
[a]TNBC status determined according to standard American Society of Clinical Oncology-College of American Pathologists criteria. [b]Dako, Agilent Technologies. [c]Up to 35% de novo mTNBC. [d]Pembro was administered for a maximum of 35 cycles. [e]Per RECIST v1.1.
AUC, area under the curve; BICR, blinded independent central review; chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; QoL, quality of life; R, randomized; RECIST v1.1; Response Evaluation Criteria in Solid Tumors, version 1.1; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TTR, time-to-response.

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Demographics and Baseline Characteristics

ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Female sex, n (%)	221 (100)	222 (100)
Median age, (range) yr	54 (23-88)	55 (27-82)
≥ 65 yr, n (%)	58 (26)	57 (26)
Race or ethnic group,[a] n (%)		
White	139 (63)	118 (53)
Asian	43 (19)	63 (28)
Black	13 (6)	11 (5)
Other/not specified	26 (12)	30 (14)
Geographic region, n (%)		
US/Canada/Western Europe	85 (38)	85 (38)
Rest of the world[b]	136 (62)	137 (62)
ECOG PS at baseline,[c] n (%)		
0	156 (71)	154 (69)
1	65 (29)	67 (30)
Curative treatment-free interval, n (%)		
De novo	75 (34)	75 (34)
Recurrent within 6-12 mo	40 (18)	40 (18)
Recurrent > 12 mo	106 (48)	107 (48)

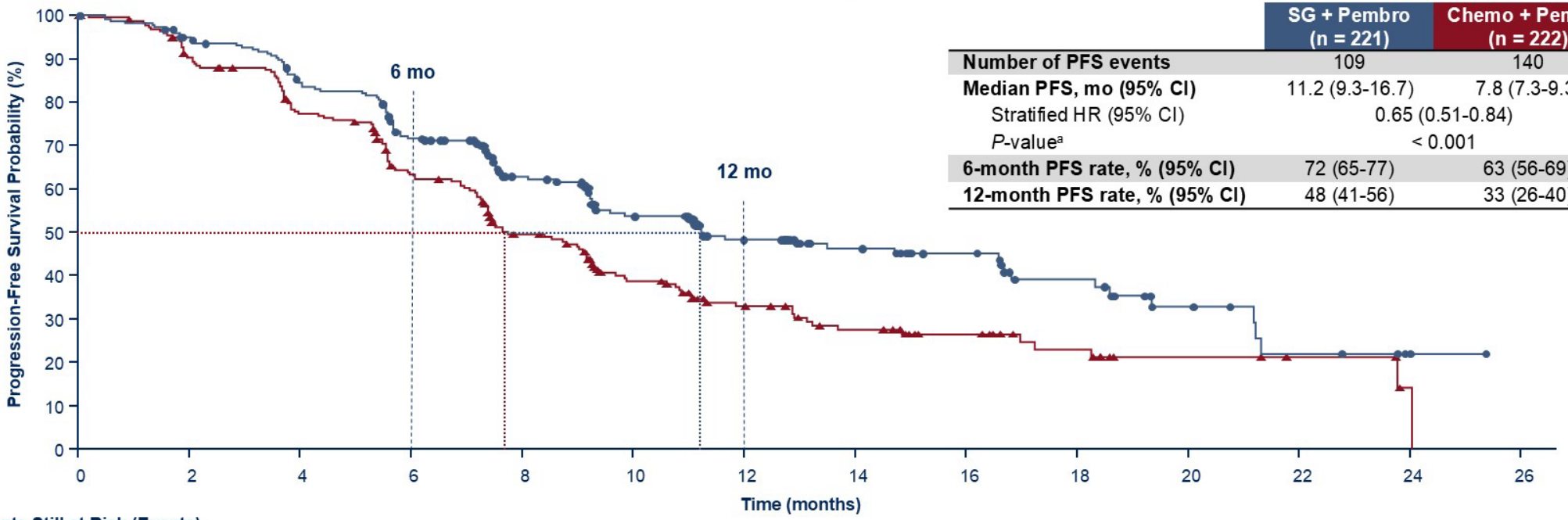
ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
PD-L1 CPS ≥ 10,[d] n (%)	221 (100)	222 (100)
Metastatic sites, n (%)		
Lymph node	159 (72)	154 (69)
Lung	111 (50)	95 (43)
Bone	61 (28)	45 (20)
Liver	55 (25)	57 (26)
Brain	8 (4)	6 (3)
Other[e]	81 (37)	71 (32)
Chemo selected prior to randomization,[f] n (%)		
Taxane	116 (52)	114 (51)
Gemcitabine/carboplatin	105 (48)	108 (49)
Prior anti-PD-(L)1 therapy,[g] n (%)	9 (4)	11 (5)

Data cutoff date: March 3, 2025.

[a]As reported by the patients; "other" includes American Indian or Alaska Native, other, and not permitted. [b]Rest of the world includes Argentina, Australia, Brazil, Chile, Czech Republic, Hong Kong, Hungary, Israel, Japan, Malaysia, Mexico, Poland, Singapore, South Africa, South Korea, Taiwan, and Turkey. [c]One patient in the chemo + pembro group had an ECOG PS ≥ 2. [d]PD-L1 status assessed using the PD-L1 IHC 22C3 assay (Dako, Agilent Technologies) at the time of enrollment. [e]Other metastatic sites includes pleura, pleural effusion, skin, soft tissue, chest wall, and muscle. [f]Actual chemo received was consistent with what was selected prior to randomization; however, two patients were randomized but did not receive treatment. [g]While 20 patients were included in the stratified subgroup of prior exposure to anti-PD-(L)1 therapy (yes) per the IRT system, only 6 patients received prior treatment with anti-PD-(L)1 agents per the clinical database.

Chemo, chemotherapy; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IRT, interactive response technology; ITT, intent-to-treat; PARPi, poly ADP-ribose polymerase inhibitor; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; SG, sacituzumab govitecan.

Progression-Free Survival by BICR



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

No. of Patients Still at Risk (Events)

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

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

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

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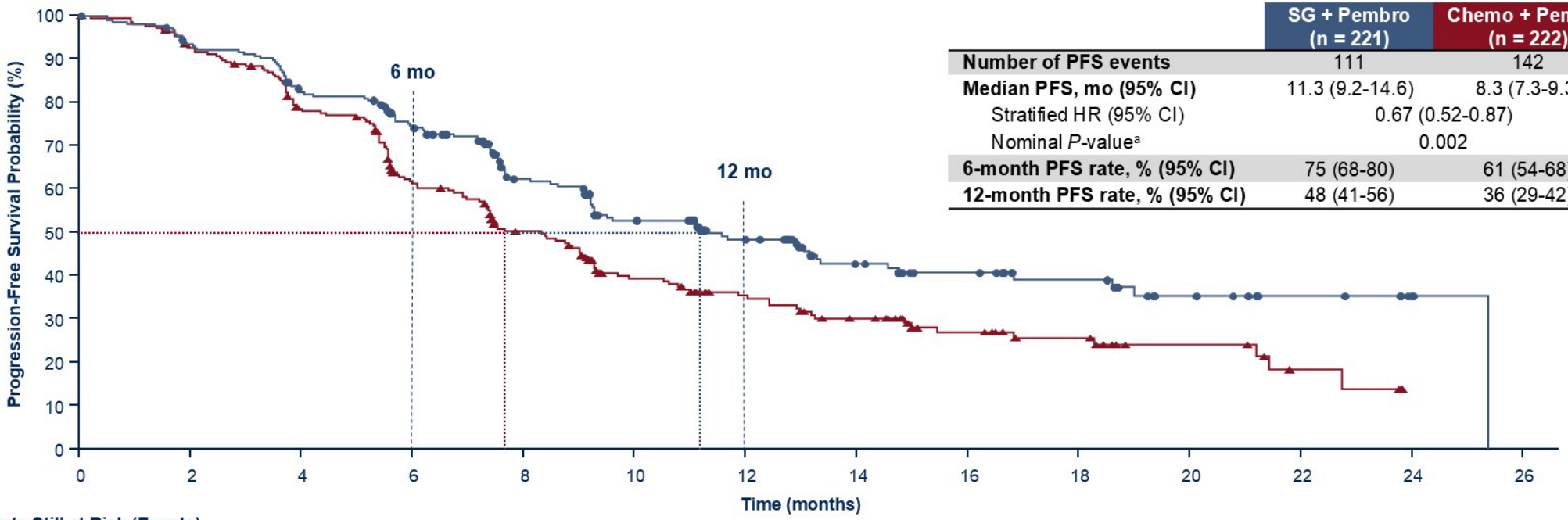
Progression-Free Survival by Investigator Assessment



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	111	142
Median PFS, mo (95% CI)	11.3 (9.2-14.6)	8.3 (7.3-9.3)
Stratified HR (95% CI)	0.67 (0.52-0.87)	
Nominal *P*-value[a]	0.002	
6-month PFS rate, % (95% CI)	75 (68-80)	61 (54-68)
12-month PFS rate, % (95% CI)	48 (41-56)	36 (29-42)

No. of Patients Still at Risk (Events)

SG + Pembro	221 (0)	202 (14)	174 (38)	152 (54)	108 (77)	81 (93)	63 (99)	43 (105)	33 (107)	24 (108)	13 (110)	7 (110)	2 (110)	0 (111)
Chemo + Pembro	222 (0)	199 (16)	164 (46)	120 (81)	91 (102)	63 (121)	47 (127)	36 (134)	24 (137)	18 (138)	10 (139)	4 (141)	0 (142)	

PFS by investigator assessment was consistent with the BICR analysis, demonstrating PFS benefit with SG + pembro vs chemo + pembro

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

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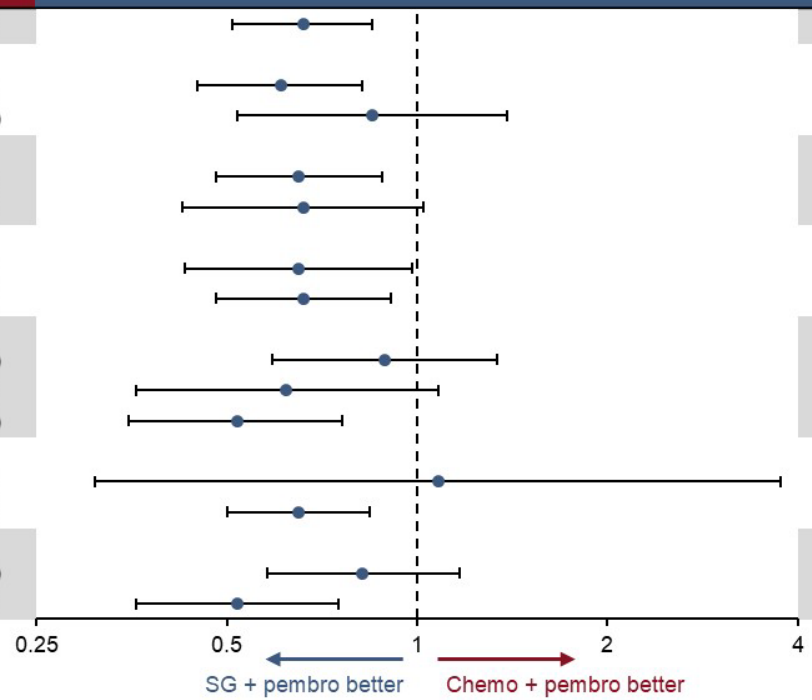
Subgroup Analysis of Progression-Free Survival by BICR

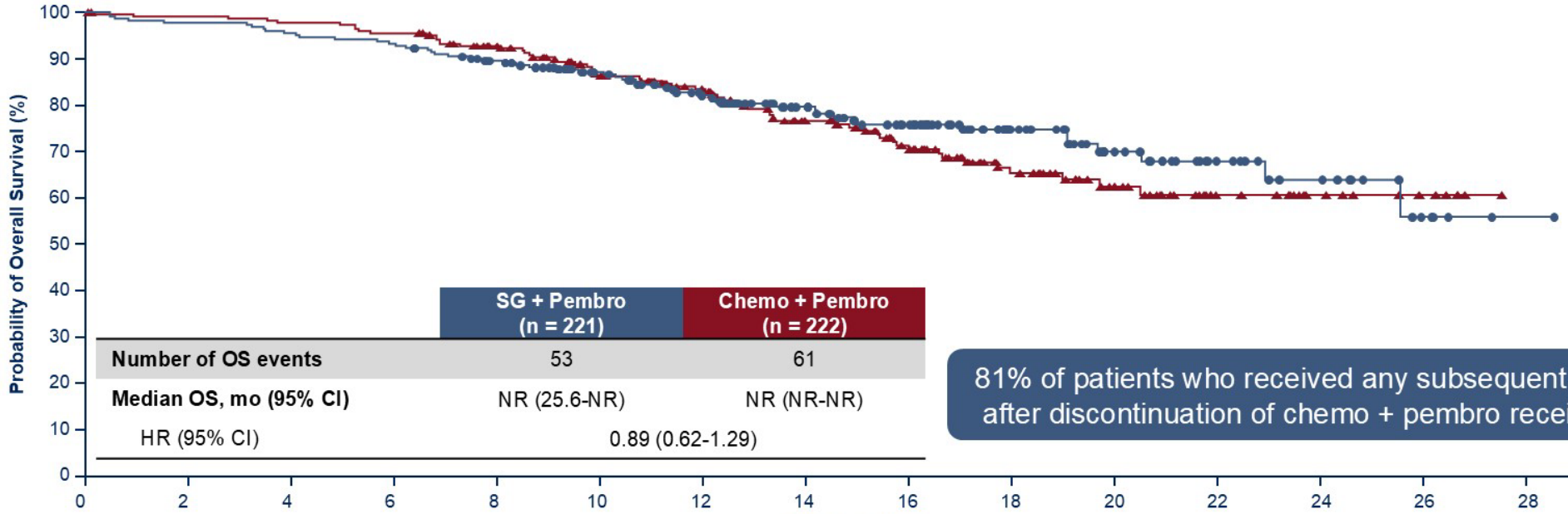
	SG + Pembro		Chemo + Pembro		Unstratified HR (95% CI)	Unstratified HR (95% CI)
	n	Median PFS, mo (95% CI)	n	Median PFS, mo (95% CI)		
ITT population	221	**11.2** (9.3-16.7)	222	**7.8** (7.3-9.3)		0.66 (0.51-0.85)
Age group						
< 65 yr	163	**11.3** (9.3-16.8)	165	**7.5** (7.0-9.2)		0.61 (0.45-0.82)
≥ 65 yr	58	**11.1** (7.5-NR)	57	**9.3** (7.3-13.2)		0.85 (0.52-1.39)
ECOG PS						
0	156	**12.9** (9.3-16.8)	154	**8.7** (7.3-9.9)		0.65 (0.48-0.88)
≥ 1	65	**9.2** (7.5-18.3)	67	**7.5** (5.6-9.3)		0.66 (0.43-1.03)
Geographic region						
US/Canada/Western Europe	85	**11.7** (7.5-19.4)	85	**7.4** (5.7-9.9)		0.65 (0.43-0.98)
Rest of the world	136	**11.2** (9.3-16.7)	137	**8.4** (7.4-9.3)		0.66 (0.48-0.91)
Curative treatment-free interval						
De novo	75	**8.1** (7.3-18.6)	75	**7.7** (6.1-11.9)		0.89 (0.59-1.34)
Recurrent 6-12 mo	40	**9.9** (5.7-16.8)	40	**7.2** (4.4-9.1)		0.62 (0.36-1.08)
Recurrent > 12 mo	106	**16.6** (11.0-NR)	107	**8.7** (7.3-10.8)		0.52 (0.35-0.76)
Prior (neo)adjuvant anti-PD-(L)1 therapy						
Yes	9	**7.5** (0.9-NR)	11	**6.6** (2.1-NR)		1.08 (0.31-3.75)
No	212	**11.7** (9.3-16.8)	211	**7.8** (7.4-9.3)		0.65 (0.50-0.84)
Chemo selected prior to randomization						
Taxane	116	**11.1** (8.6-16.7)	114	**9.2** (7.2-12.9)		0.82 (0.58-1.17)
Gemcitabine/Carboplatin	105	**11.3** (9.2-21.2)	108	**7.4** (6.9-9.0)		0.52 (0.36-0.75)



PFS benefit was observed for SG + pembro vs chemo + pembro across prespecified subgroups

Data cutoff date: March 3, 2025.
BICR, blinded independent central review; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, months; NR, not reached; PARPi, poly ADP-ribose polymerase inhibitor; PD-(L)1, programmed death (ligand) 1; pembro, pembrolizumab; PFS, progression-free survival; SG, sacituzumab govitecan.

Descriptive Overall Survival at Primary Analysis



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of OS events	53	61
Median OS, mo (95% CI)	NR (25.6-NR)	NR (NR-NR)
HR (95% CI)	0.89 (0.62-1.29)	

81% of patients who received any subsequent treatment after discontinuation of chemo + pembro received SG[a]

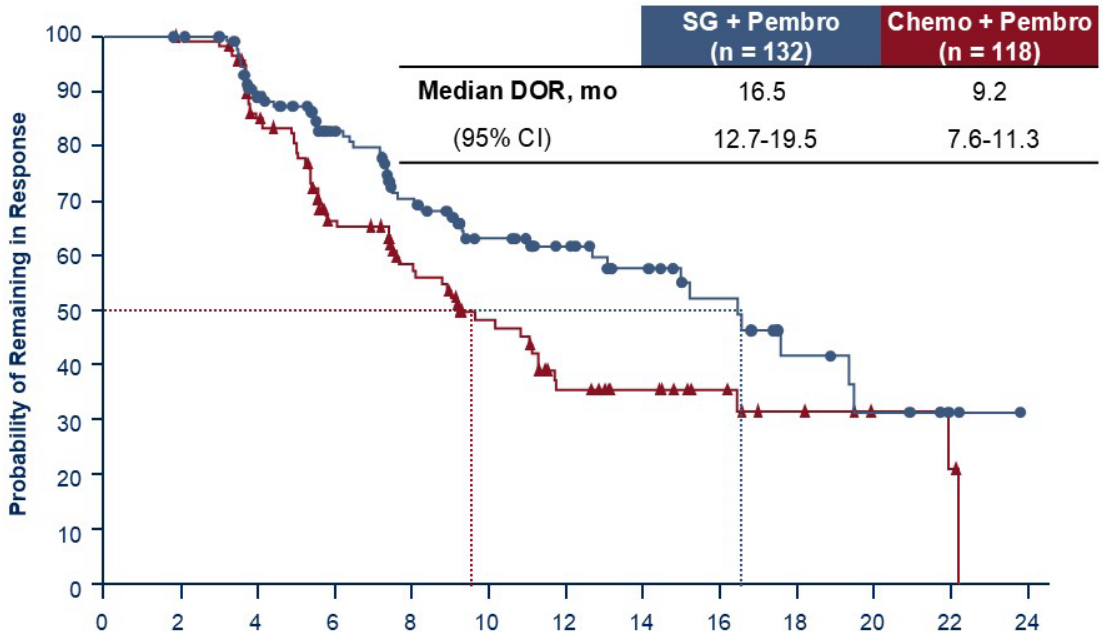
No. of Patients Still at Risk (Events)																
SG + Pembro	221 (0)	216 (5)	211 (10)	206 (15)	190 (23)	162 (28)	138 (37)	111 (41)	88 (46)	55 (47)	36 (50)	21 (51)	14 (52)	5 (53)	1 (53)	0 (53)
Chemo + Pembro	222 (0)	218 (2)	215 (5)	210 (10)	193 (16)	166 (29)	142 (34)	111 (45)	87 (53)	56 (58)	38 (60)	19 (61)	11 (61)	6 (61)	0 (61)	

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

Data cutoff date: March 3, 2025. Median follow-up was 14.0 months (range, 0.1-28.6).
[a]Of the 96 patients who received SG monotherapy as subsequent anticancer therapy, 77 received it as part of the protocol-specified crossover after meeting all crossover eligibility criteria, including BICR-verification of disease progression; the remaining 19 patients received subsequent SG monotherapy as commercial supply.
2L, second line; chemo, chemotherapy; HR, hazard ratio; pembro, pembrolizumab; NR, not reached; OS, overall survival; SG, sacituzumab govitecan.

Tumor Responses and Duration of Response by BICR

Variable	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Objective response rate[a] (95% CI), %	60 (52.9-66.3)	53 (46.4-59.9)
Stratified odds ratio (95% CI)	1.3 (0.9-1.9)	
Best overall response, n (%)		
Complete response	28 (13)	18 (8)
Partial response	104 (47)	100 (45)
Stable disease	70 (32)	70 (32)
Stable disease ≥ 6 months	23 (10)	29 (13)
Progressive disease	9 (4)	26 (12)
Not evaluable	10 (5)	8 (4)
Time to response,[b] median (range), months	1.9 (1.0-9.3)	1.9 (1.1-11.4)



A substantially longer duration of response and a higher overall response rate (including an increased complete response rate) was observed for SG + pembro vs chemo + pembro

Data cutoff date: March 3, 2025.
[a]Objective response rate is defined as the proportion of patients who achieved a best overall response of complete response/partial response; [b]Time to response (months) = (date of first documented complete or partial response - date of randomization + 1)/30.4375.
BICR, blinded independent central review; DOR, duration of response; mo, months; pembro, pembrolizumab; SG, sacituzumab govitecan.

Exposure and Safety Summary

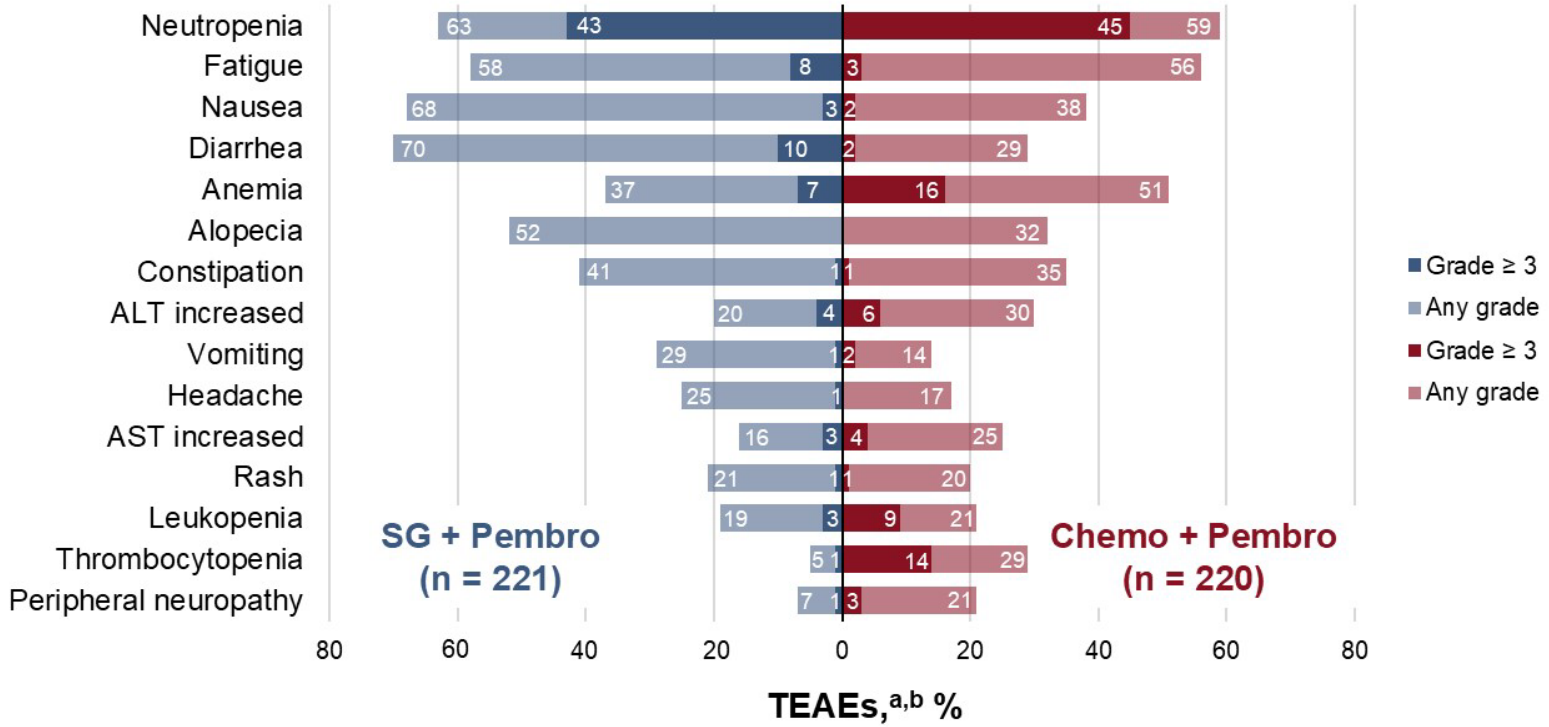
ITT population	SG + Pembro (n = 221)		Chemo + Pembro (n = 222)	
Treatment component	**SG**	**Pembro**	**Chemo**	**Pembro**
All treated patients, n	221	221	220	220
Median duration of treatment, mo (range)	8.9 (0.0-27.1)	8.5 (0.0-26.8)	6.2 (0.0-26.3)	6.4 (0.0-25.6)

n (%)	SG + Pembro (n = 221)	Chemo + Pembro (n = 220)
Any TEAE	220 (> 99)	219 (> 99)
Grade ≥ 3	158 (71)	154 (70)
Treatment-emergent SAE	84 (38)	68 (31)
Treatment-related	61 (28)	42 (19)
TEAEs leading to treatment discontinuation[a]	26 (12)	68 (31)
TEAEs leading to dose interruption	171 (77)	162 (74)
TEAEs leading to dose reduction[b]	78 (35)	96 (44)
TEAEs leading to death[c]	7 (3)	6 (3)
Treatment-related	3 (1)	1 (< 1)

Despite longer duration of treatment with SG + pembro, rates of grade ≥ 3 AEs were similar for both groups. TEAEs leading to dose reduction or treatment discontinuation were lower with SG + pembro

TEAEs were defined as any adverse events that began or worsened on or after the first dose date of study drug up to 30 days (or up to 90 days for SAEs) after the last dose date of study drug or the initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first. Data cutoff date: March 3, 2025.
[a]The most common any-grade TEAEs that led to treatment discontinuation were pneumonitis (1%) for the SG + pembro group and neuropathy peripheral (5%), pneumonitis (3%), and thrombocytopenia (3%) for the chemo + pembro group. [b]There was no dose reduction for pembrolizumab per the protocol. [c]TEAEs leading to death were pneumonia, sepsis, neutropenic sepsis, pulmonary embolism, and suicide (1 each), as well as 2 deaths of unknown cause in the SG + pembro group, and cardiac arrest, large intestine perforation, pneumonia, sepsis, post-procedural complication, and death of unknown cause (1 each) in the chemo + pembro group.
Chemo, chemotherapy; pembro, pembrolizumab; SAE, serious adverse event; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

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



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

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

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

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

Adverse Events of Special Interest

	AESI,[a] n (%)	SG + Pembro (n = 221)		Chemo + Pembro (n = 220)	
		Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
SG AESIs	Neutropenia[b]	143 (65)	104 (47)	132 (60)	100 (45)
	Hypersensitivity[b]	43 (19)	4 (2)	51 (23)	5 (2)
	Serious infections secondary to neutropenia[b]	6 (3)	5 (2)	3 (1)	3 (1)
	Diarrhea (Grade 3 or higher)	N/A	22 (10)	N/A	5 (2)
Pembro AESIs	Overall	30 (14)	9 (4)	56 (26)	16 (7)
	Infusion reactions (not immune-mediated)[a]	11 (5)	3 (1)	19 (9)	5 (2)
	Pneumonitis[b]	5 (2)	3 (1)	10 (5)	2 (1)
	Colitis[b]	4 (2)	1 (< 1)	1 (< 1)	1 (< 1)
	Hypothyroidism[b]	4 (2)	0	19 (9)	0
	Hypophysitis[b]	2 (1)	0	2 (1)	0
	Hyperthyroidism[b]	2 (1)	0	5 (2)	0
	Severe skin reactions,[b] including Stevens-Johnson syndrome and toxic epidermal necrolysis	2 (1)	2 (1)	2 (1)	2 (1)
	Hepatitis[b]	1 (< 1)	0	2 (1)	2 (1)
	Adrenal insufficiency[b]	1 (< 1)	0	2 (1)	1 (< 1)
	Pancreatitis[b]	0	0	2 (1)	2 (1)

AESIs were consistent with the known safety profiles of each agent; no new safety concerns were observed and no increased rates of AESIs were observed when combining SG with pembro

AESIs were adverse events determined based on a prespecified list of Medical Dictionary for Regulatory Activities (MedDRA) terms, which was updated with each new version of MedDRA. Immune-mediated adverse events were determined based on a prespecified list of Medical Dictionary for Regulatory Activities (MedDRA) terms, which was updated with each new version of MedDRA and specified as immune-mediated by the investigator. Data cutoff date: March 3, 2025.
[a]AESIs observed in ≥1% of patients in either group are presented; [b]Grouped term.
AESI, adverse event of special interest; chemo, chemotherapy; pembro, pembrolizumab; SG, sacituzumab govitecan.

Conclusions

- ASCENT-04/KEYNOTE-D19 is the first randomized, phase 3 study to evaluate the efficacy and safety of an ADC/checkpoint inhibitor combination for first-line treatment of patients with PD-L1+[a] mTNBC
- SG + pembro led to a statistically significant and clinically meaningful improvement in PFS vs chemo + pembro (median 11.2 vs 7.8 months; HR, 0.65; 95% CI, 0.51-0.84; $P < 0.001$)
  - PFS benefit was observed across prespecified subgroups
- OS data are immature, but an early trend in improvement was observed
- ORR was higher (including an increased complete response rate), and responses were more durable with SG + pembro vs chemo + pembro
- The safety profile of SG + pembro was consistent with the established profiles of either agent; no additive toxicity was observed

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

Data cutoff date: March 3, 2025
[a]CPS ≥ 10 per IHC 22C3 assay (Dako, Agilent Technologies).
ADC, antibody drug conjugate; chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; HR, hazard ratio; IHC, immunohistochemistry; mTNBC; metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer.

2025 ASCO ANNUAL MEETING

Sacituzumab Tirumotecan (Sac-TMT) as First-line Treatment for Unresectable Locally Advanced/Metastatic Triple-negative Breast Cancer (a/m TNBC): Initial Results From the Phase II OptiTROP-Breast05 Study

Yongmei Yin[1], Quchang Ouyang[2], Min Yan[3], Jian Zhang[4], Lihua Song[5], Wei Li[6], Yuanting Gu[7], Xiaoyu Liu[8], Jingfen Wang[9], Xiaojia Wang[10], Xi Yan[11], Jin Yang[12], Weipeng Zhao[13], Yuee Teng[14], Tingjing Yao[15], Zhengkui Sun[16], Xiaoping Jin[17], Yina Diao[17], Gesha Liu[17], Junyou Ge[17]

[1] Jiangsu Province Hospital, Nanjing, China; [2] Hunan Cancer Hospital, Changsha, China; [3] Henan Cancer Hospital, Zhengzhou, China; [4] Fudan University Cancer Hospital, Shanghai, China; [5] Shandong Cancer Hospital and Institute, Jinan, China; [6] The First Hospital of Jilin University, Changchun, China; [7] The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [8] Chongqing Cancer Hospital, Chongqing, China; [9] Linyi Cancer Hospital, Linyi, China; [10] Zhejiang Cancer Hospital, Hangzhou, China; [11] West China Hospital of Sichuan University, Chengdu, China; [12] The First Affiliated Hospital of Xi 'an Jiaotong University, Xi 'an, China; [13] Tianjin Cancer Hospital, Tianjin, China; [14] The First Hospital of China Medical University, Shenyang, China; [15] The First Affiliated Hospital of Bengbu Medical University, Bengbu, China; [16] Jiangxi Cancer Hospital, Nanchang, China;[17] Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., Chengdu, China

Background

Standard of care

- The 1L treatment for PD-L1 negative (CPS <10) TNBC is chemotherapy, but the ORR is only 35-45% and mPFS is 5–7 mo, representing a critical unmet need.[1-3]

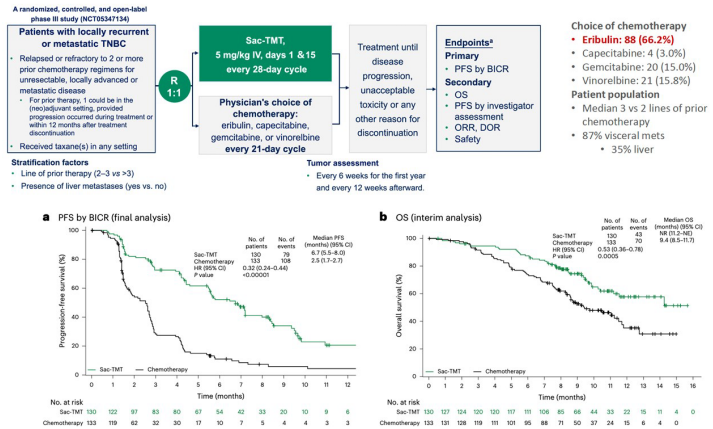
Rationale for development of sac-TMT in a/m TNBC

- TROP2 is overexpressed in approximately 88% of TNBC and is associated with poor survival.[4]
- Sac-TMT is a TROP2 ADC developed with a proprietary Kthiol linker conjugated to a novel topoisomerase I inhibitor, and was approved in China for patients with 2L+ TNBC.
  - Median PFS by BICR was 6.7 mo with sac-TMT and 2.5 mo with chemotherapy (HR 0.32; 95% CI: 0.24, 0.44).
  - Median OS was not reached with sac-TMT and 9.4 mo with chemotherapy (HR 0.53; 95% CI: 0.36, 0.78).[5]

ADC: antibody-drug conjugate; BICR: blinded independent central review; CPS: combined positive score; mPFS: median progression-free survival; ORR: objective response rate; OS: overall survival TROP2: trophoblast cell surface antigen 2.

1. Cortes J, et al. *N Engl J Med*. 2022. **2**. Schmid P, et al. *Lancet Oncol* , 2020. **3.** NCCN, Breast Cancer, 2024.2. **4**. Liao S, et al. *Drug Development Research*, 2021. **5**. Yin Y, et al. *Nat Med*, 2025.

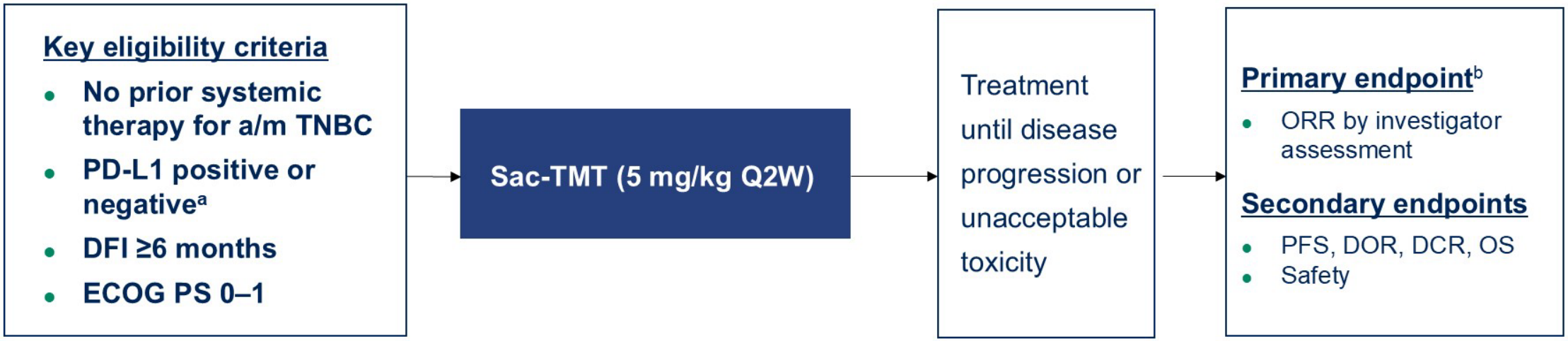
'ROP-Breast01 phase 3 data in pre-treated mTNBC



Xu B et al, ASCO 2024 & Yin Y et al. Nature Medicine 2025

OptiTROP-Breast05 Study Design

Multicenter, open-label phase II study (NCT05445908)



Tumor assessment

- Every 6 weeks for the first 18 months and every 12 weeks afterward.

[a]PD-L1 expression was assessed at a central lab with PD-L1 IHC 22C3 pharmDx.
[b]Tumor response was assessed using RECIST version 1.1.
DFI: disease-free interval; ECOG PS: Eastern Cooperative Oncology Group performance status; DCR: disease control rate; DOR: duration of response; RECIST: Response Evaluation Criteria in Solid Tumors.

Patient Demographics and Baseline Characteristics

Characteristic	Sac-TMT (N = 41)
Female, n (%)	41 (100)
Median age (range), yr	55 (34, 75)
≥65 years, n (%)	5 (12.2)
ECOG PS, n (%)	
0	23 (56.1)
1	18 (43.9)
Location of metastasis, n (%)	
Visceral sites[a]	25 (61.0)
Lung	19 (46.3)
Bone	8 (19.5)
Liver	6 (14.6)

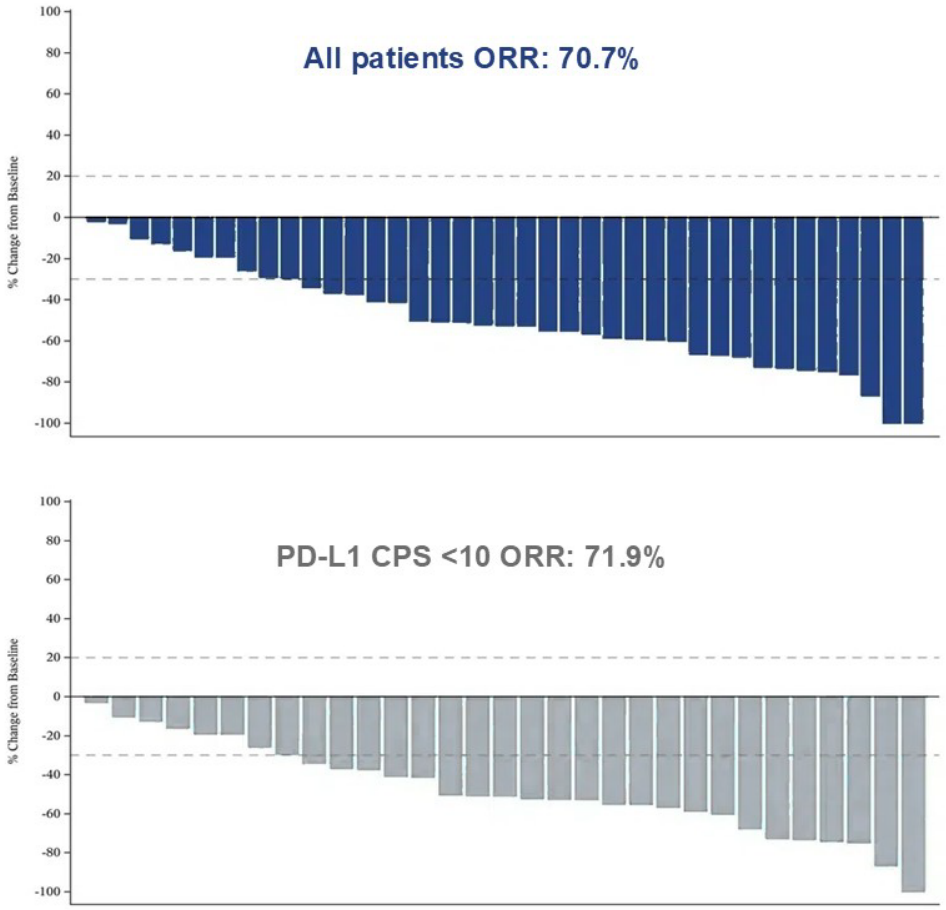
Characteristic	Sac-TMT (N = 41)
Disease-free interval, n (%)	
De novo metastasis	12 (29.3)
6-12 months	8 (19.5)
≥12 months	21 (51.2)
Prior treatments, n (%)	
Radiotherapy	15 (36.6)
Chemotherapy	27 (65.9)
Hormonal therapy	6 (14.6)
PD-L1 expression,[b] n (%)	
CPS <10	32 (78.0)
CPS ≥10	9 (22.0)

[a]Visceral metastases were defined as the presence of metastases from sites other than soft tissue, skin, lymph nodes, and chest wall.
[b]PD-L1 expression was assessed at a central lab with PD-L1 IHC 22C3 pharmDx.

Antitumor Responses

Antitumor Responses were observed regardless of PD-L1 expression.

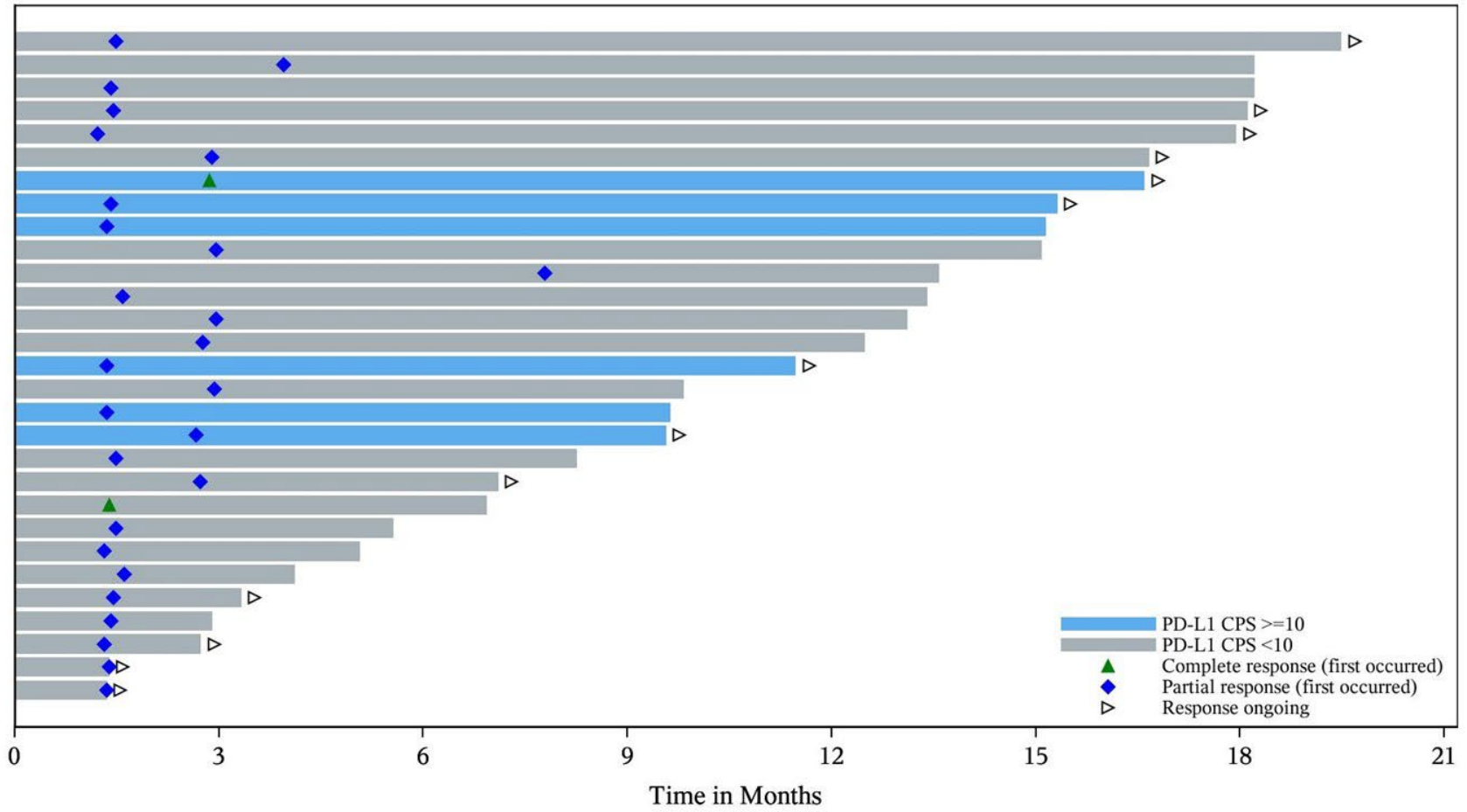
	All patients (N = 41)	PD-L1 CPS <10[c] (N = 32)
ORR[a], n (%) (95% CI)	29 (**70.7**) (54.5, 83.9)	23 (**71.9**) (53.3, 86.3)
CR[b], n (%)	2 (4.9)	1 (3.1)
PR, n (%)	27 (65.9)	22 (68.8)
Confirmed PR, n (%)	24 (58.5)	19 (59.4)
SD, n (%)	9 (22.0)	7 (21.9)
DCR, n (%) (95% CI)	38 (**92.7**) (80.1, 98.5)	30 (**93.8**) (79.2, 99.2)



Data cutoff: Nov 18, 2024. **Median follow-up was 18.6 months.**
[a] Including confirmed PR/CR or response pending confirmation.
[b] All CRs were confirmed by investigators.
[c] PD-L1 expression was assessed at a central lab with PD-L1 IHC 22C3 pharmDx.
CR: complete response; PR: partial response; SD: stable disease.

Duration of Response

Median DOR was 12.2 mo (range: 1.4+-18.0+) and 12-month DOR rate was 50.6% in all patients.

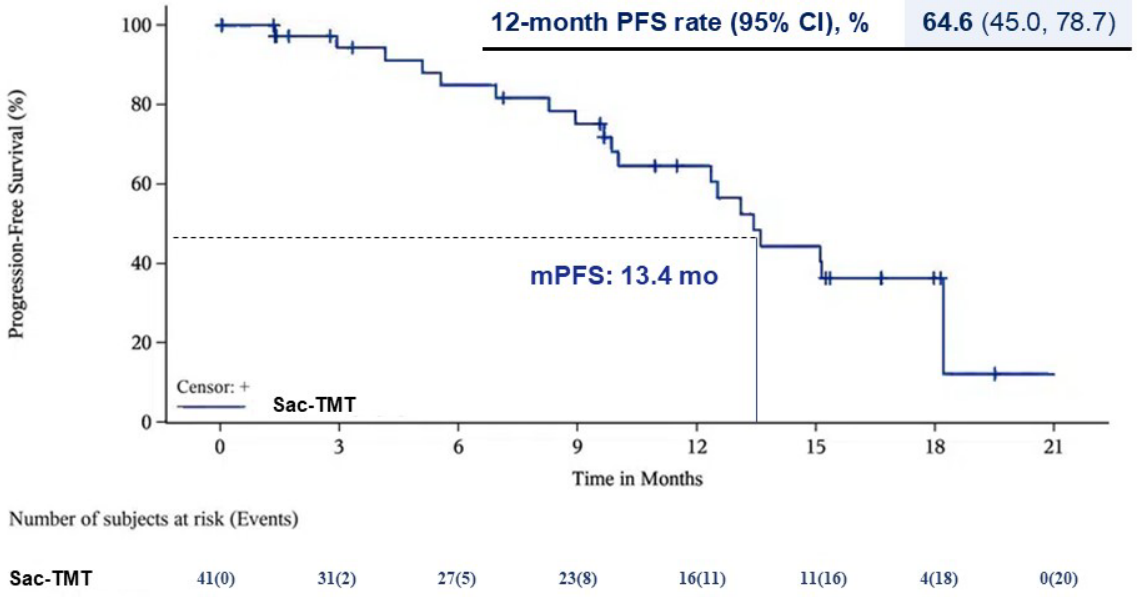


+ indicates there is no progressive disease by the time of last disease assessment.

Progression-Free Survival

PFS benefits were observed regardless of PD-L1 expression.

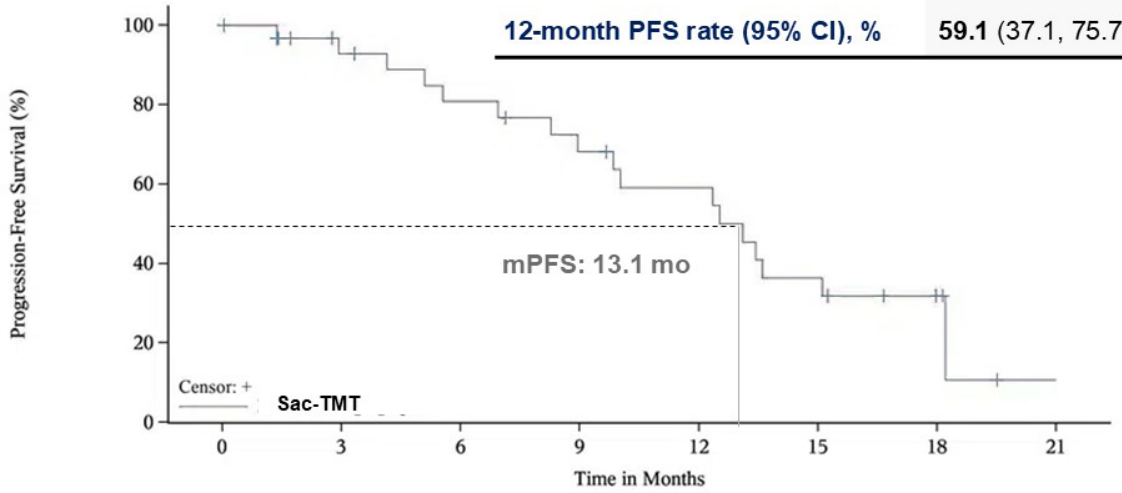
	All patients (N = 41)
PFS events, n (%)	20 (48.8)
Median PFS, months (95% CI)	**13.4** (9.9, 18.2)
12-month PFS rate (95% CI), %	**64.6** (45.0, 78.7)



Number of subjects at risk (Events)

Sac-TMT	41(0)	31(2)	27(5)	23(8)	16(11)	11(16)	4(18)	0(20)

	PD-L1 CPS <10 (N = 32)
PFS events, n (%)	18 (56.3)
Median PFS, months (95% CI)	**13.1** (8.9, 18.2)
12-month PFS rate (95% CI), %	**59.1** (37.1, 75.7)



Number of subjects at risk (Events)

Sac-TMT	32(0)	24(2)	20(5)	16(8)	13(10)	8(15)	4(16)	0(18)

Overall Safety Summary

	Sac-TMT (N = 41) n (%)
TRAEs[a]	41 (100)
Grade ≥3 TRAEs	26 (63.4)
Treatment-related SAEs	6 (14.6)
TRAEs leading to dose reduction	12 (29.3)
TRAEs leading to dose interruption	26 (63.4)
TRAEs leading to discontinuation	3 (7.3)
TRAEs leading to death	0

- **The most common grade ≥3 TRAEs (occurred in ≥5% of pts):**
  - Neutrophil count decreased (46.3%)
  - WBC count decreased (34.1%)
  - Anemia (12.2%)
  - Stomatitis (9.8%)
  - Lymphocyte count decreased (7.3%)
  - Fatigue (7.3%)
- Exophthalmia and blurred vision occurred in 1 patient each (3.1%).
- No reports of neuropathy or interstitial lung disease/pneumonitis.
- No treatment-related deaths were reported.

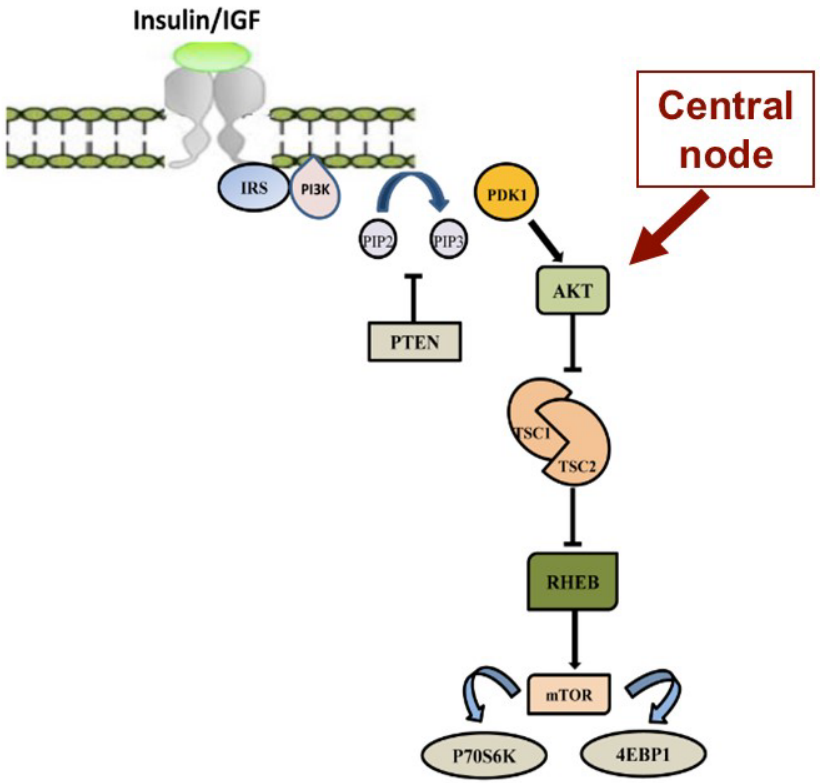
[a] TRAEs were determined as related to sac-TMT.
SAE: serious adverse event; TRAE: treatment-related adverse event; WBC: white blood cell.

Conclusions

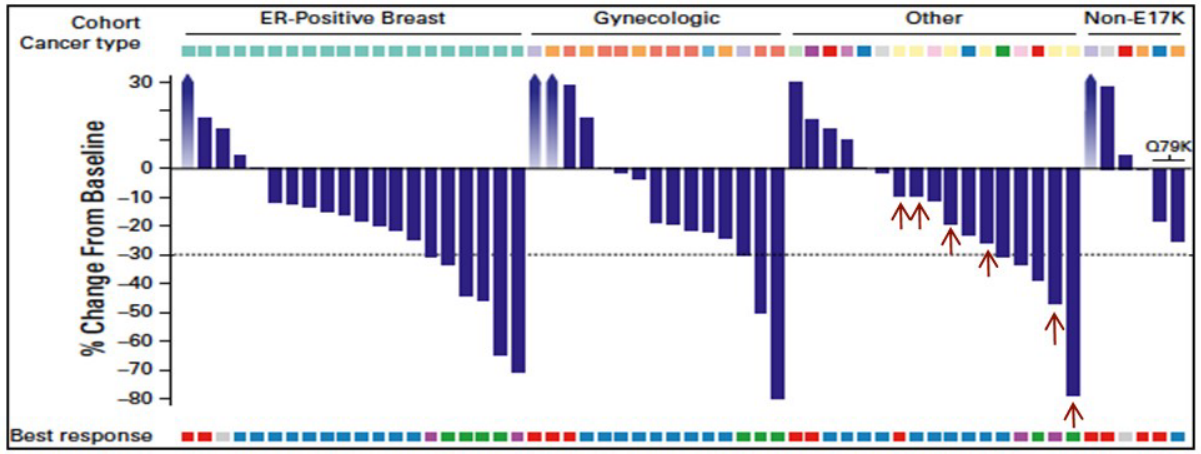
- **Sac-TMT demonstrated promising anti-tumor activity as 1L treatment for patients with a/m TNBC, regardless of the PD-L1 status.**
  - ORR was 70.7% and mDoR was 12.2 mo.
    - In PD-L1 CPS <10 subgroup, ORR was 71.9% and mDoR was 10.2 mo.
  - mPFS was 13.4 mo and the 12-mo PFS rate was 64.6%.
    - In PD-L1 CPS <10 subgroup, mPFS was 13.1 mo and the 12-mo PFS rate was 59.1%.
- **Sac-TMT showed a manageable safety profile, with no unexpected safety signals identified.**
  - Most frequent TRAEs were hematologic events and stomatitis.
  - TRAEs leading to treatment discontinuation occurred in 3 patients (7.3%).
  - No treatment-related deaths occurred.
- **Phase 3 studies of sac-TMT in 1L PD-L1-negative (CPS <10) a/m TNBC are underway:**
  - Sac-TMT vs. investigator's choice of chemotherapy in China (NCT06279364)
  - Global study of sac-TMT + pembroliumab vs. sac-TMT vs. chemotherapy (NCT06841354)

Emerging Therapies

Early Clinical Support for AKT Inhibition in TNBC



PI3K/AKT pathway is frequently activated in TNBC



- AZD5363 basket trial of multiple solid tumor types harboring AKT1 E17K mutations
- 6 patients with TNBC all with SD or PR to therapy

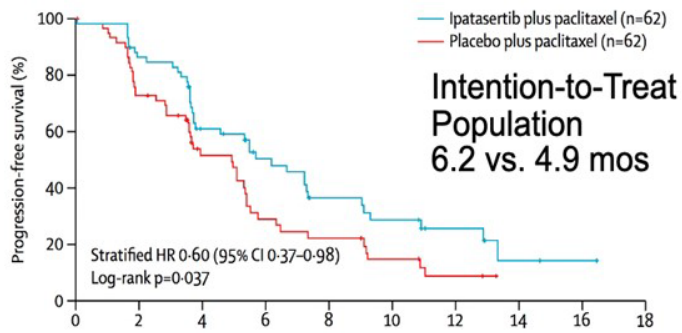
Massihnia D, et al. Oncotarget 2016
Hyman DM et al, J Clin Oncol, 2017

Phase 2 Data for AKT Inhibition in TNBC

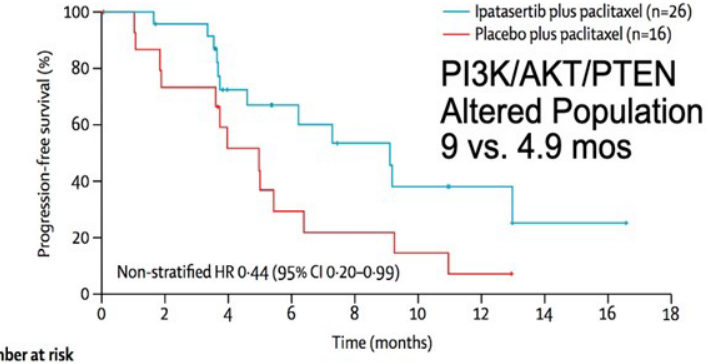
LOTUS

1st line mTNBC
Paclitaxel + Ipatasertib/Placebo

Kim S-B, et al. Lancet Oncol 2017



Number at risk (number censored)									
Ipatasertib plus paclitaxel	62	50 (4)	31 (9)	22 (13)	14 (15)	11 (15)	6 (19)	2 (21)	1 (22)	0 (23)
Placebo plus paclitaxel	62	43 (3)	23 (12)	13 (12)	10 (12)	6 (13)	3 (14)	0 (17)		

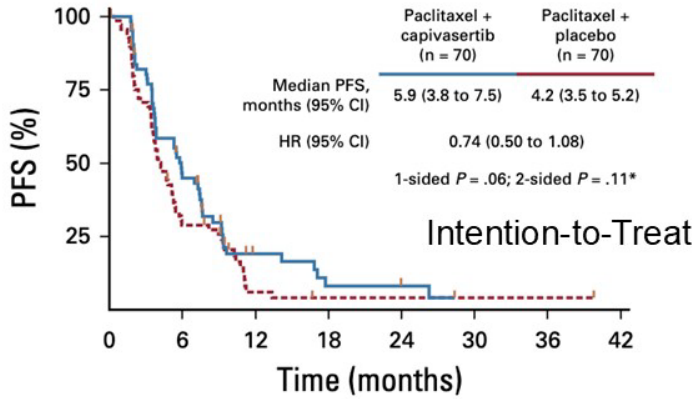


Number at risk (number censored)										
Ipatasertib plus paclitaxel	26	22 (3)	13 (7)	10 (9)	7 (10)	5 (10)	3 (12)	1 (13)	1 (13)	0 (14)
Placebo plus paclitaxel	16	11 (1)	7 (2)	4 (2)	3 (2)	2 (2)	1 (2)	0 (3)		

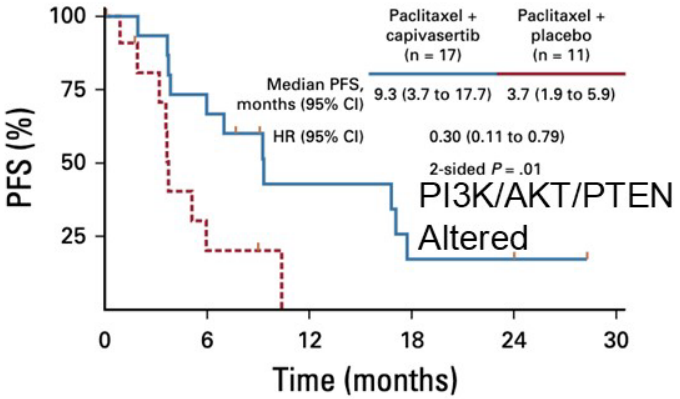
PAKT

1st line mTNBC
Paclitaxel + Capivasertib/Placebo

Schmid P, et al. J Clin Oncol 2020



No. at risk:								
Paclitaxel + capivasertib	70	26	7	3	2	0	0	0
Paclitaxel + placebo	70	19	3	1	1	1	1	0



No. at risk:						
Paclitaxel + capivasertib	17	10	5	2	1	0
Paclitaxel + placebo	11	2	0	0	0	0

Phase 3 Data for AKT Inhibition in TNBC Negative

IPATunity 130: Ipatasertib

- Measurable aTNBC
- *PIK3CA/AKT1/PTEN* alteration[a]
- No prior chemotherapy for aTNBC (≥12 months since last [neo]adjuvant chemotherapy)
- Candidate for taxane therapy
- ECOG performance status 0/1

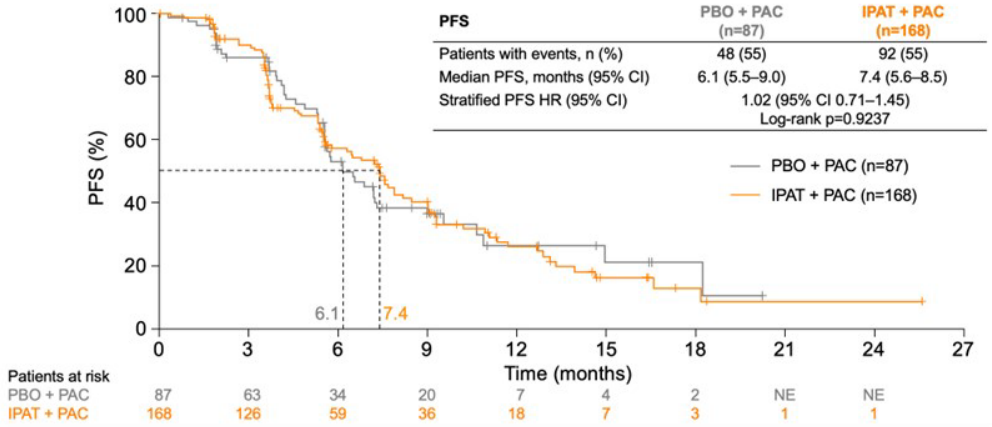
R 2:1

- PAC 80 mg/m² days 1, 8 & 15 + IPAT 400 mg qd days 1–21 q28d
- PAC 80 mg/m² days 1, 8, & 15 + PBO days 1–21 q28d

Treatment until disease progression, intolerable toxicity,[b] or elective withdrawal

Crossover from PBO to IPAT is not permitted

255 patients enrolled between Feb 6, 2018, and Apr 8, 2020



CAPItello-290: Capivasertib

Patients with locally advanced or mTNBC

- Men and pre-/post-menopausal women
- Eligible for taxane monotherapy
- No prior (neo)adjuvant chemotherapy within 6 months (12 months for taxanes)
- No prior systemic therapy for inoperable locally advanced or metastatic disease
- ECOG performance status 0 or 1
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumour sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 N=812

- Capivasertib–paclitaxel[a]
- Placebo–paclitaxel[a]

Stratification factors:
- Visceral vs non-visceral disease
- (Neo)adjuvant chemotherapy (yes/no)
- Region[b]

- First patient randomised: July 2019
- Last patient randomised: February 2022

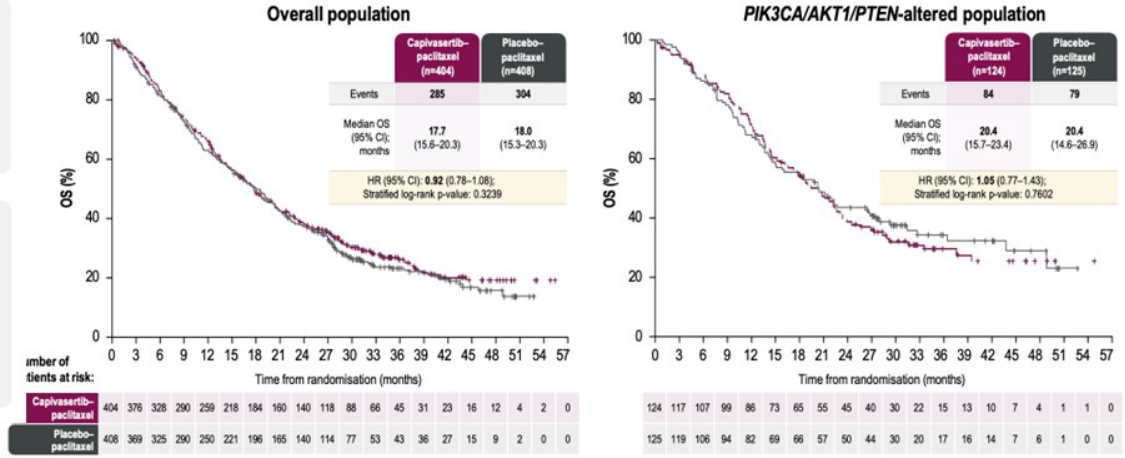
Dual primary endpoints

OS
- Overall population
- *PIK3CA/AKT1/PTEN*-altered population

Key secondary endpoints

PFS
- Overall population
- *PIK3CA/AKT1/PTEN*-altered population

Safety

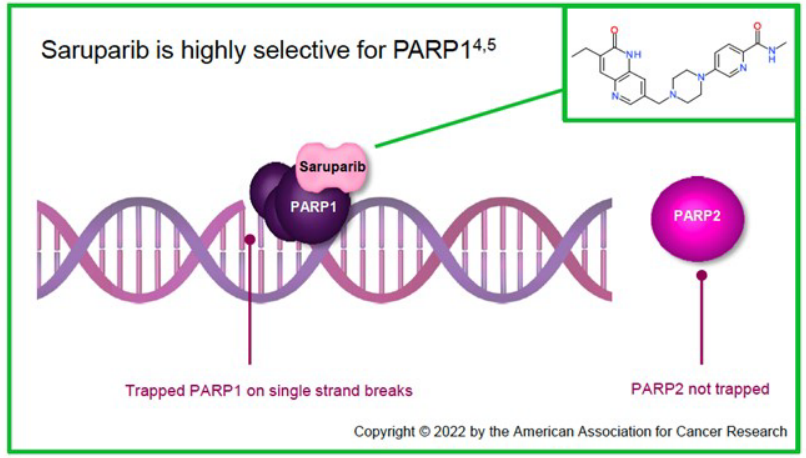


Dent RA, et al. SABCS 2020; McArthur H et al, ESMO 2024

PRESENTED BY: Melinda Telli, MD

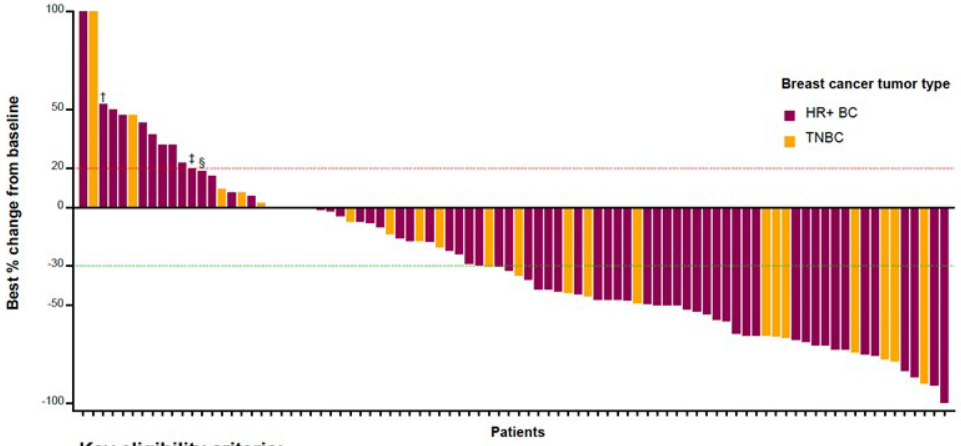
AACR American Association for Cancer Research
ANNUAL MEETING
2024 • SAN DIEGO
APRIL 5-10
#AACR24
AACR.ORG/AACR24

PETRA: First-in-human Phase 1/2a trial of the first-in-class new generation poly(ADP-ribose) polymerase-1 selective inhibitor (PARP1i) saruparib (AZD5305) in patients with advanced solid tumors with *BRCA1/2*, *PALB2* or *RAD51C/D* mutations



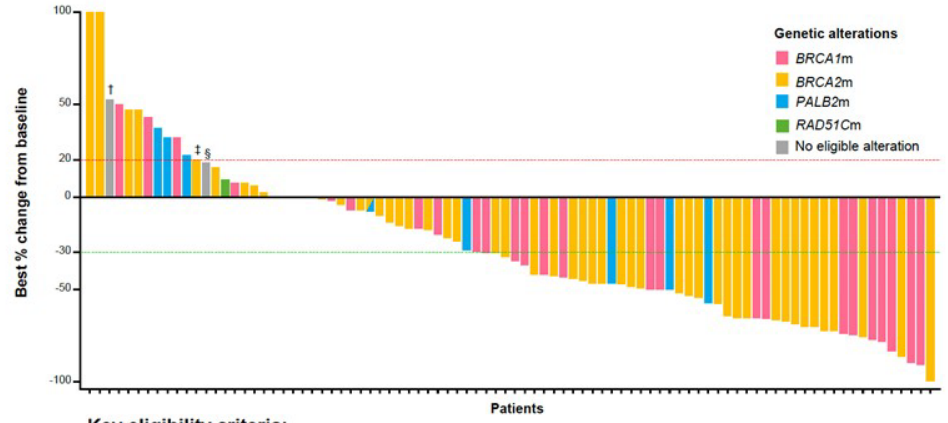
- PARP inhibitors (PARPi) are approved in multiple indications and are dual PARP1-PARP2 inhibitors and DNA trappers.[1,2]
- However, only PARP1 trapping is required for synthetic lethality in homologous recombination deficiency settings.[3]
- Saruparib (AZD5305) was developed through rational design to be **highly selective for PARP1**, **with increased potency** and **improved physicochemical properties** versus approved PARPi.

Tumor responses observed in both HR+ and triple-negative breast cancer (Part B1)*



Key eligibility criteria:
- No limit on prior chemotherapy lines
- *BRCA1/2*m, *PALB2*m, or *RADC51C/D*m

Tumor responses observed in mutation-defined subgroups in heavily pretreated HER2– breast cancer (Part B1)*

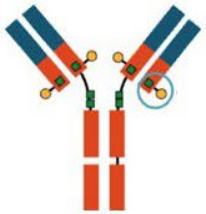


Key eligibility criteria:
- No limit on prior chemotherapy lines
- *BRCA1/2*m, *PALB2*m, or *RADC51C/D*m

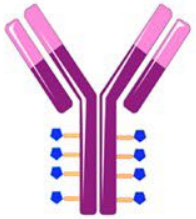
Yap T, et al. AACR Annual Meeting 2024

Antibody-drug conjugates under investigation in TNBC

Datopotamab deruxtecan (Dato-DXd)

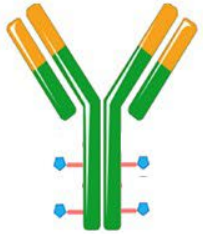


Sacituzumab tirumotecan (Sac-TMT)



Patritumab deruxtecan (HER3-DXd)

Disitimab vedotin (RC-48)



	Datopotamab Deruxtecan (Dato-DXd)	Sacituzumab Tirumotecan (Sac-TMT)	Patritumab deruxtecan (HER3-DXd)	Disitimab Vedotin (RC-48)
Target antigen	TROP2	TROP2	HER3	HER2
Linker cleavage	Yes	Yes	Yes	Yes
Membrane-permeable payload	Yes	Yes	Yes	Yes
Payload MOA	Topo 1 inhibitor	Topo 1 inhibitor	Topo 1 inhibitor	MMAE
Drug-antibody ratio	4:1	7.4:1	8:1	4:1

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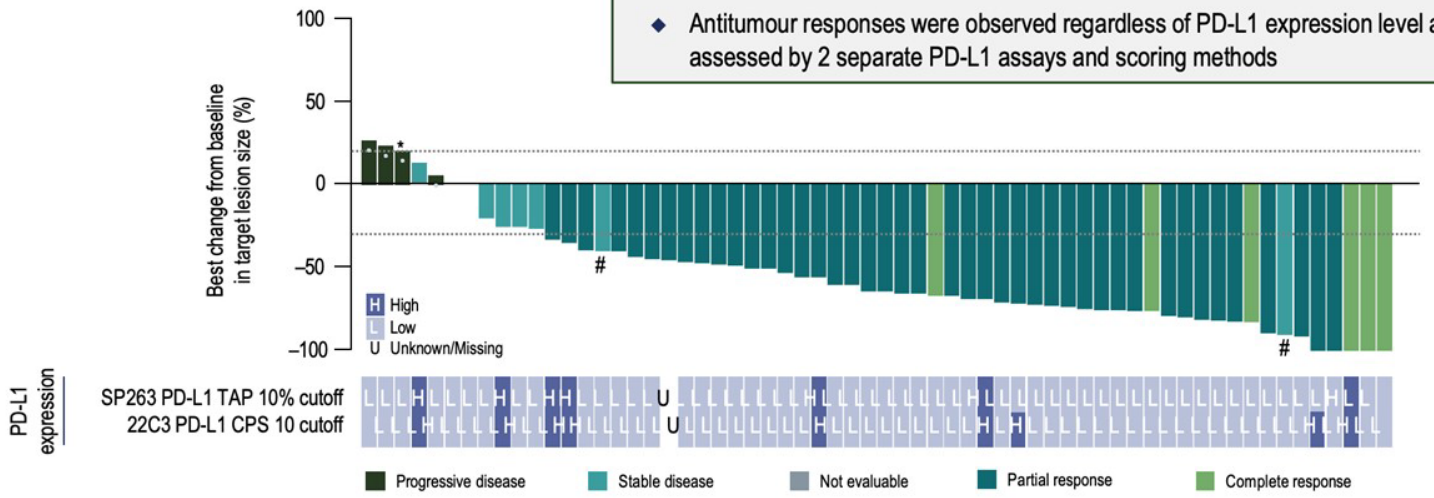
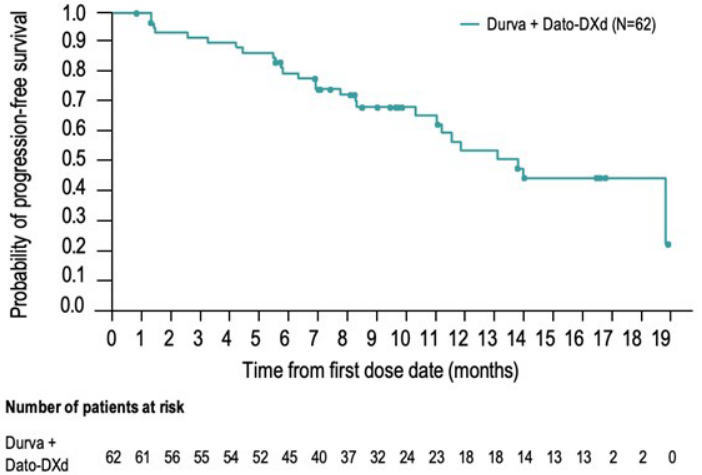
BEGONIA Arm 7: Phase Ib/II Dato-DXd + Durvalamab for 1st line metastatic TNBC

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



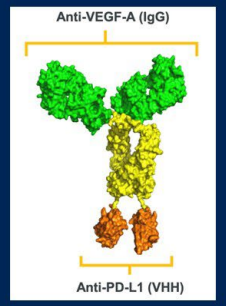
Median PFS was **13.8** months (95% CI, 11.0–NC)



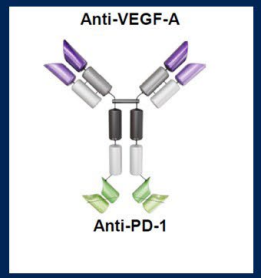
Schmid P, et al. ESMO Congress 2023

VEGF & PD-1/PD-L1 bispecific antibodies on a fast track

PM8002/BNT327



Ivonescimab



2025 ASCO ANNUAL MEETING #ASCO25

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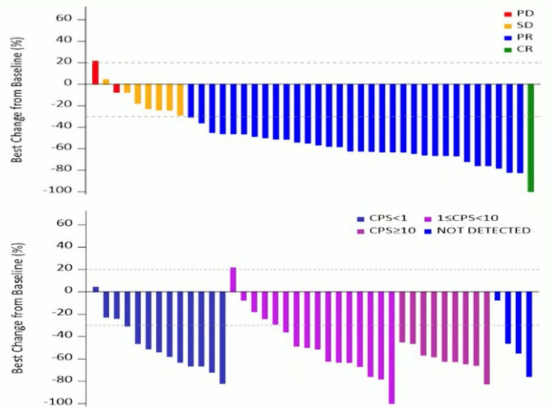
7 plus nab-paclitaxel for the 1st line treatment of C

	PD-L1 1≤CPS<10	PD-L1 CPS≥10	NOT DETECTED
	16	9	4
	1 (6.3)	0 (0.0)	0 (0.0)
	10 (62.5)	9 (100.0)	3 (75.0)
	4 (25.0)	0 (0.0)	0 (0.0)
	1 (6.3)	0 (0.0)	1 (25.0)
	68.8 (41.3, 89.0)	100.0 (66.4, 100.0)	75.0 (19.4, 99.4)
cORR % (95% CI)	73.8 (58.0, 86.1)	76.9 (46.2, 95.0)	56.3 (29.9, 80.3)	100.0 (66.4, 100.0)	75.0 (19.4, 99.4)
DCR % (95% CI)	95.2 (83.8, 99.4)	100.0 (75.3, 100.0)	93.8 (69.8, 99.8)	100.0 (66.4, 100.0)	75.0 (19.4, 99.4)
mPFS (Mo), (95%CI)	13.5 (9.4, --)	NR (5.7, --)	14.0 (7.2, --)	10.8 (5.5, 13.5)	14.0 (1.8, --)

- For the ITT population, mTTR was 1.9 mo and mDoR 11.7 mo; mOS was not reached



Meng Y, et al. ESMO Congress 2024

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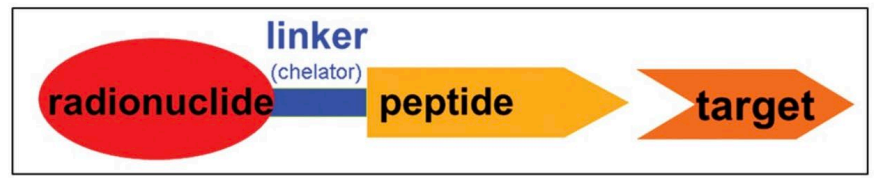
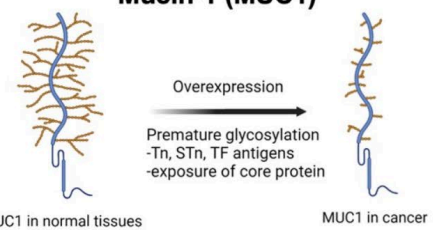
Theragnostics: Therapy + Diagnostics

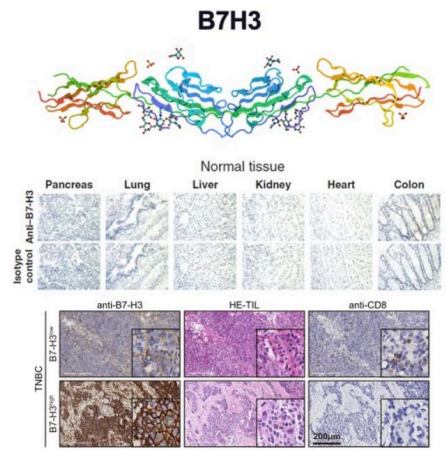


Mucin-1 (MUC1)



- Upregulation and premature glycosylation in cancer renders MUC1 distinguishable and targetable from normal tissue
- Overexpressed in 90% of breast cancer and 94% of the triple-negative subtype → more frequently over-expressed than SSTR's and PSMA
- ~80,000 receptors per cell and 20-120 tandem repeats per receptor → large number of binding sites available

B7H3



Hofman MS, et al. RadioGraphics 2015, 35, 500-516.
Mei J, et al. NPJ Breast Cancer 2024

Induced proximity therapeutics

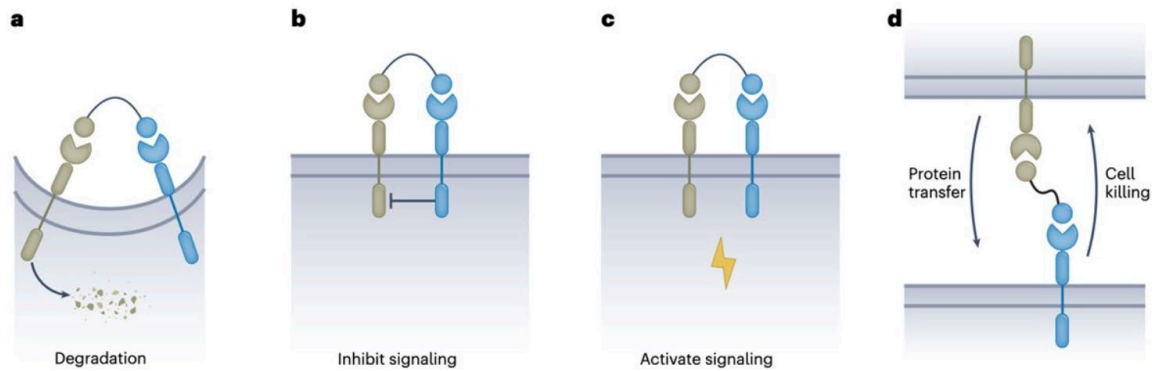


Fig. 1 | Bifunctional inducers of proximity can elicit diverse biological effects at the cell surface through multiple mechanisms of action. a, Degradation through lysosomal trafficking or E3 ligase-mediated ubiquitination. **b**, Receptor signaling inhibition. **c**, Activation of receptor signaling. **d**, By engaging multiple cells.

Induced proximity is a molecular engineering principle in which bifunctional molecules are designed to bring two protein targets into close contact, inducing a desired biological outcome

Till NA, Ramanathan M, Bertozzi CR. Nature Biotechnology 2025

Takeaways

- Progress is being made in the care of patients with triple negative breast cancer TNBC), but survival remains inferior to other subtypes
  - Five new therapies in the last decade
  - Median survival in mTNBC remains limited at 16-24 mos
- Nearly half of patients with mTNBC will only receive 1L of therapy
- TNBC remains an unmet need with limited targeted therapies


Thank You
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