JOURNAL CLUB UPDATES

TNBC fase metastatica

Maria Vittoria Dieci

Disclosure slide

- Consultancy/advisory role: Novartis, Eli lilly, Seagen, Exact Science, Pfizer, Daiichi Sankyo, Gilead, MSD, AstraZeneca
- Invited speaker: Exact sciences, Daiichi Sankyo, Novartis, Roche, Eli lilly, AstraZeneca
- Research grant: Roche (Institutional)
- Travel expenses: Eli Lilly, Roche, Gilead, Daiichi Sankyo
- Patent: listed as co-inventor on patent application of HER2-DX

Definition of TNBC

Abstract #1100: **Prognosis and tumor-infiltrating lymphocytes (TILs) in estrogen receptor (ER)-low metastatic breast cancer (MBC): analysis from a large multi-institutional cohort and the TONIC phase II trial with nivolumab**

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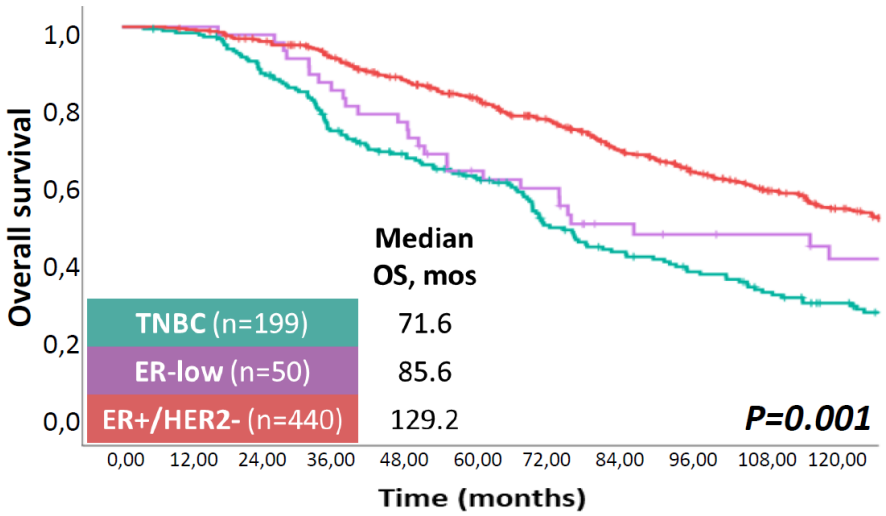
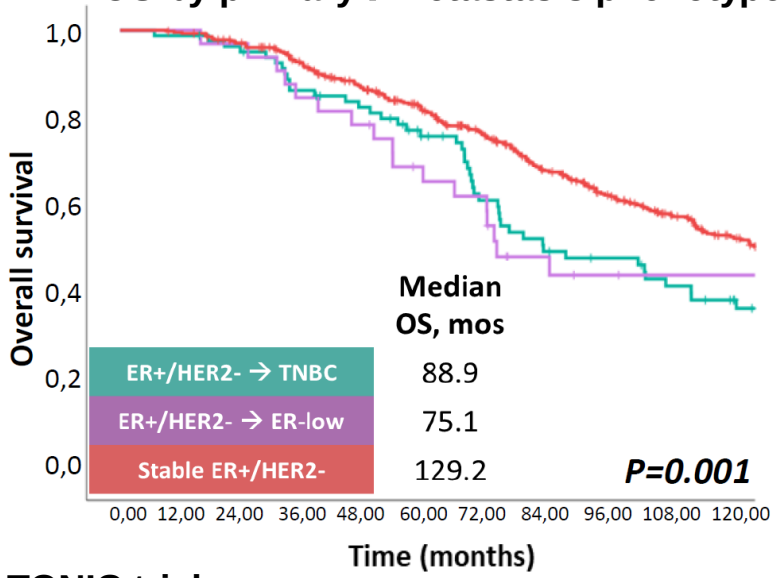
OS by metastasis phenotype



OS by primary→metastasis phenotype



Outcomes of patients in the TONIC trial

CBR

	TNBC (n=95)	ER-low (n=15)	P-value
Yes	21 (22.1%)	3 (20.0%)	1

PFS

	TNBC (n=95)	ER-low (n=15)	P-value
Median, mos	1.9	1.7	0.7

OS

	TNBC (n=95)	ER-low (n=15)	P-value
Median, mos	8.6	5.3	0.3

Early relapsers: still an unmet need

IMpassion132: OS in patients with PD-L1+ TNBC

Double-blind placebo-controlled randomised phase 3 trial

- Unresectable locally advanced/ metastatic TNBC
- Prior anthracycline and taxane for early TNBC
- Disease progression <12 months after last treatment with curative intent for early TNBC[a]
- No prior CT for advanced TNBC
- Known PD-L1 status (SP142)

R 1:1

- Carboplatin/gemcitabine or capecitabine[b] + atezolizumab 1200 mg q3w
- Carboplatin/gemcitabine or capecitabine[b] + placebo q3w

Treatment continued until disease progression or unacceptable toxicity

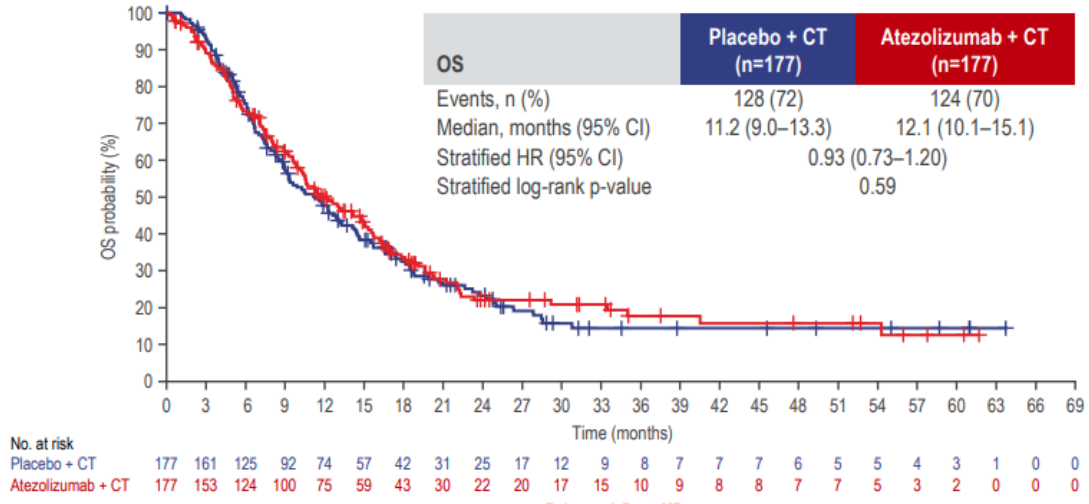
Stratification factors:

- Visceral (lung and/or liver) metastases
- CT backbone
- PD-L1 status (during all-comer enrolment)

Primary endpoint:

- OS (hierarchical testing: PD-L1- TNBC[c] then, if positive, modifie ITT population[d])

No significant improvement in OS with atezolizumab (median follow-up: 9.8 months)



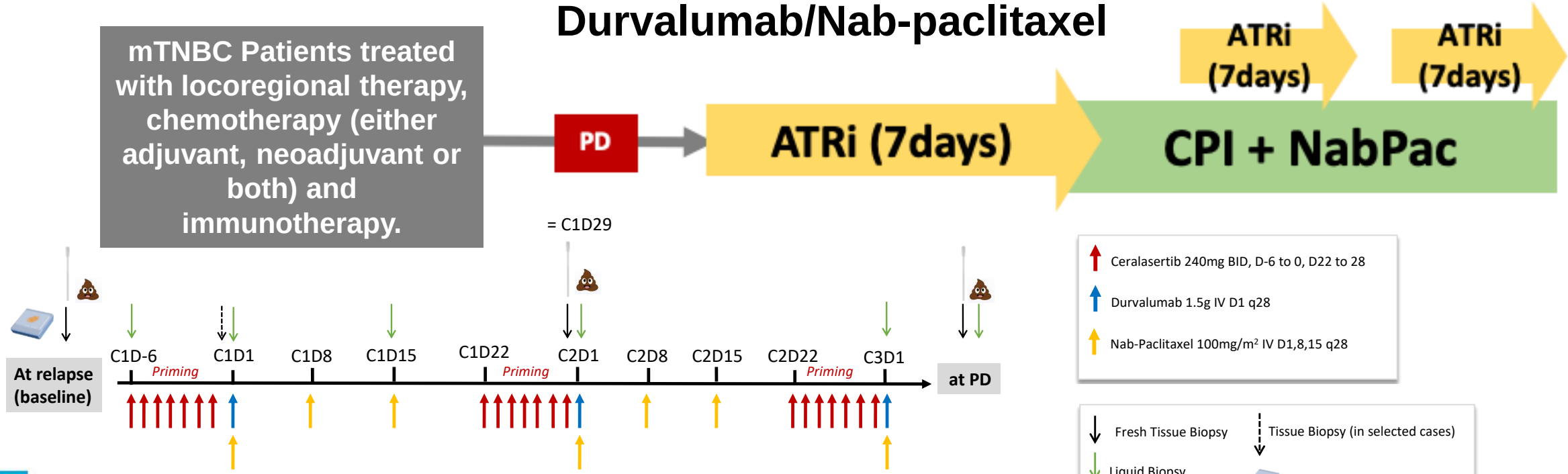
OS	Placebo + CT (n=177)	Atezolizumab + CT (n=177)
Events, n (%)	128 (72)	124 (70)
Median, months (95% CI)	11.2 (9.0–13.3)	12.1 (10.1–15.1)
Stratified HR (95% CI)	0.93 (0.73–1.20)	
Stratified log-rank p-value	0.59	

Dent R, et al. ESMO 2024 & Ann Oncol 2024

The ATRiBRAVE trial

Restoring Sensitivity To Immunotherapy in Advanced Triple Negative Breast Cancer Exploiting Ceralasertib Priming Followed By Combined Durvalumab/Nab-paclitaxel

mTNBC Patients treated with locoregional therapy, chemotherapy (either adjuvant, neoadjuvant or both) and immunotherapy.



Program ID 22759
PI: Stefano Piccolo

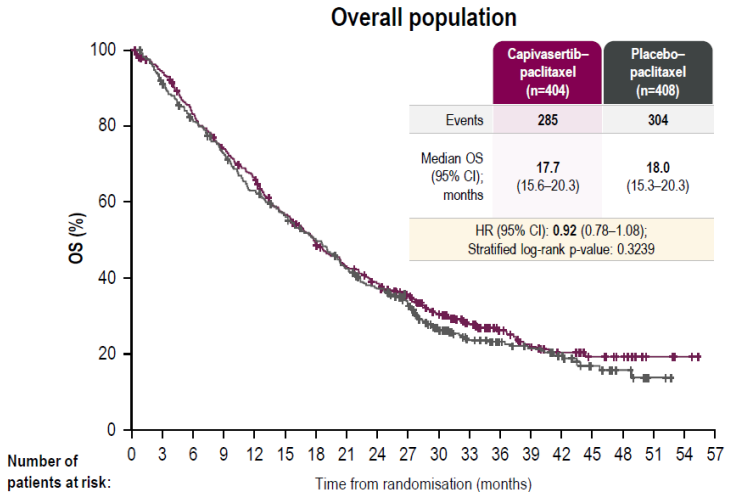
Trial sponsor

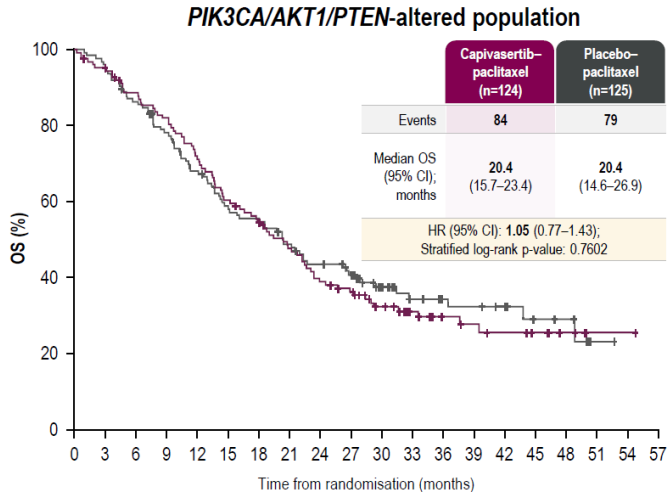
Coordinating center

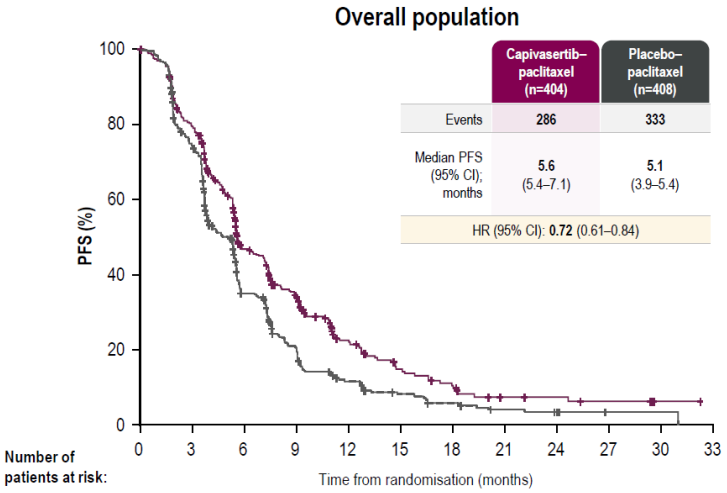
Clinical study chair:
Valentina Guarneri

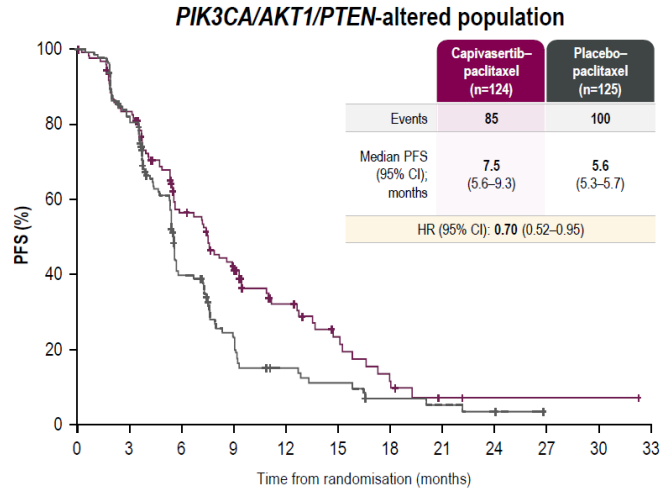
Currently enrolling patients

1st line paclitaxel + capivasertib: CAPItello-290 phase III









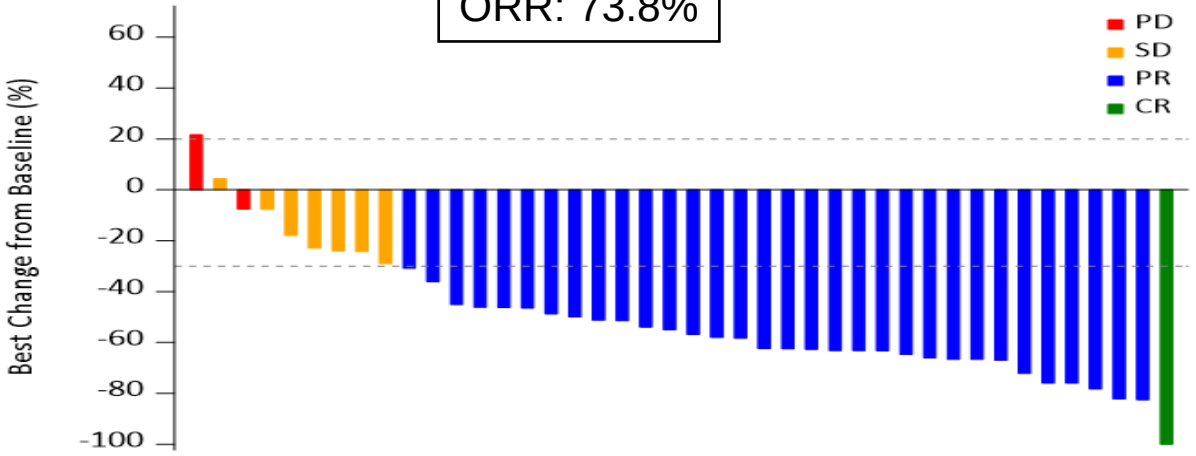
- Combination with CT leads to reduced exposure to single drugs
  - Slightly more capivasertib reductions/interruptions/discontinuations vs CAPItello 291
  - More paclitaxel reductions/interruptions/discontinuations in the experimental arm
- Biologic rationale
  - Lack of data on synergism with CT
  - IPATunity130 with Ipatasertib + Paclitaxel in PIK3CA/AKT/PTEN altered mTNBC: negative

Schmid P et al., ESMO 2024; Turner NC et al., NEJM 2023; Dent R et al., Clin Cancer Res 2024

1st line bi-specific Ab (VEGF & PD-L1)
Phase II trials: ORR

PM8002/BNT327 + Nab-Paclitaxel

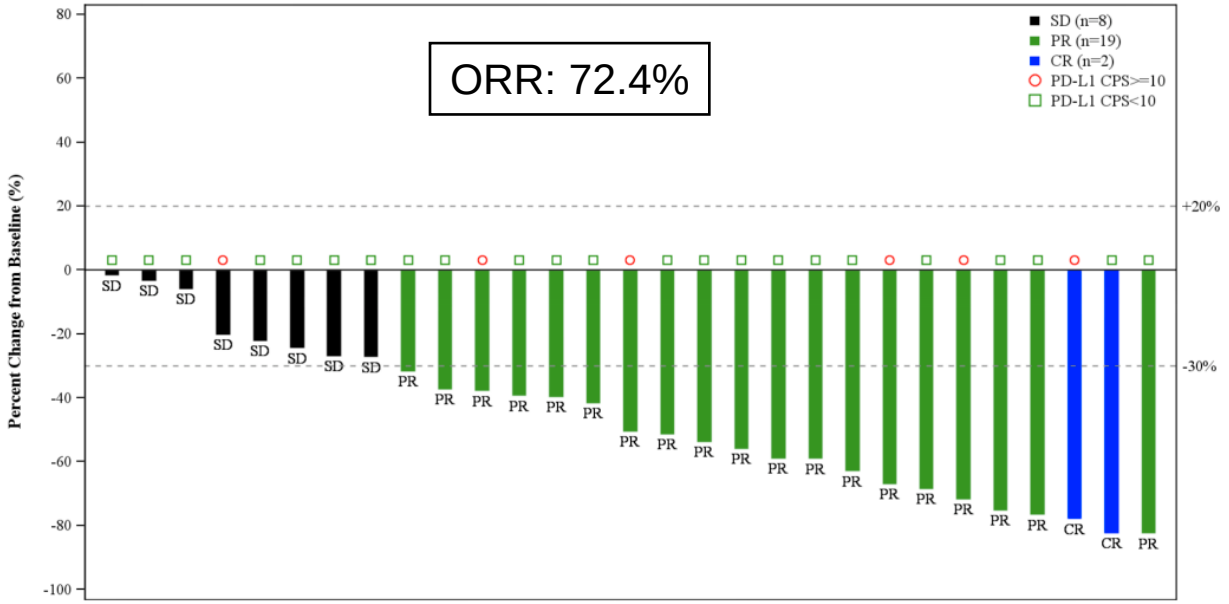
ORR: 73.8%



Meng Y. et al, ESMO 2024

Ivonescimab + Paclitaxel/Nab-paclitaxel

ORR: 72.4%

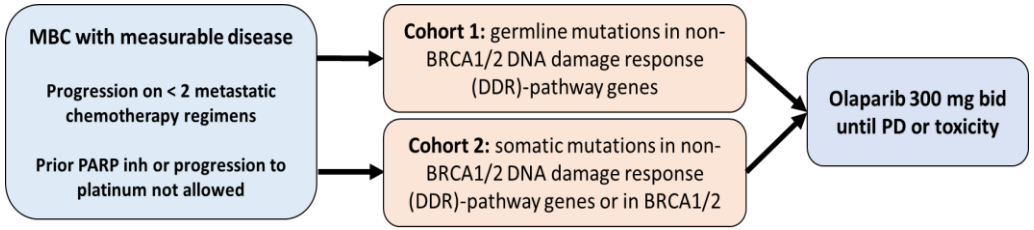


Wang X. et al, ESMO 2024

Efficacy independent from PD-L1 expression

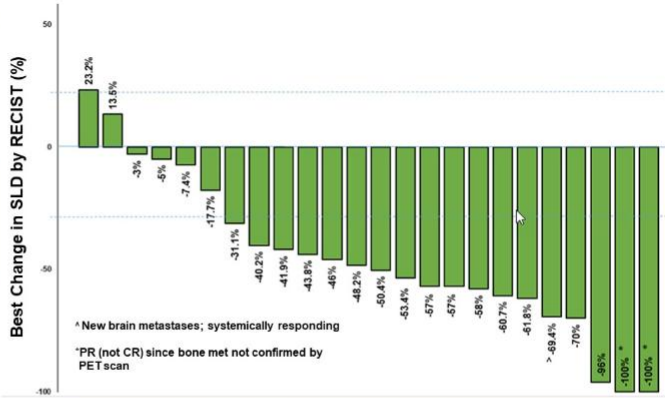
Olaparib: expanding options beyond gBRCAmut

TBCRC 048 expansion cohorts



gPALB2 N=24	
Best Response	Responses (rate, %)
Complete Response (CR)	1 (4%)
Partial Response (PR)	17 (71%)
Stable Disease (SD)	5 (21%)
Progressive Disease (PD)	1 (4%)
ORR = 75% (18/24, 80%-CI: 60%-86%)	
CBR (18 wks) = 83% (20/24, 90%-CI: 66%-94%)	

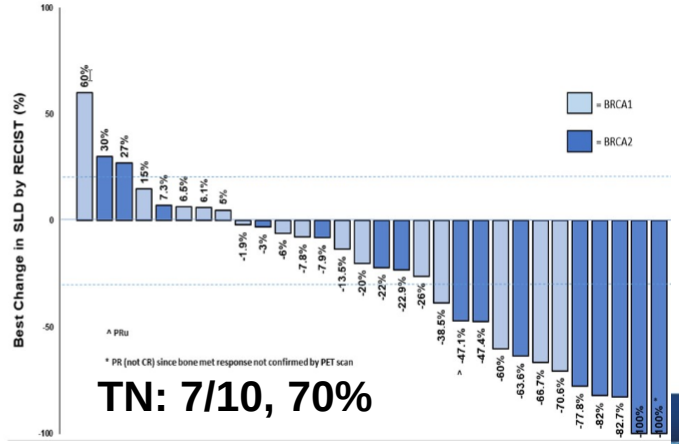
Datacut May 3, 2024



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

sBRCA1/2 N=30	
Best Response	Responses, (rate, %)
Complete Response (CR)	1 (3%)
Partial Response (PR)^	10 (33%)
Stable Disease (SD)	13 (43%)
Progressive Disease (PD)	6 (20%)
ORR = 37% (11/30, 80%-CI: 25%-50%)	
CBR (18 wks) = 53% (16/30, 90%-CI: 37%-69%)	

^ 1 unconfirmed PR did not count for ORR or CBR



TN: 7/10, 70%

Datacut May 3,, 2024

Tung NM, et al. ASCO 2024

ADCs for TNBC: available and in development

ADC	Target	Linker	Payload	DAR
Trastuzumab deruxtecan	HER2	cleavable	Topo 1	8
Sacituzumab govitecan	TROP2	cleavable	Topo 1	7.6
Sacituzumab tirumotecan	TROP2	cleavable	Topo 1	7.4
Datopotamab deruxtecan	TROP2	cleavable	Topo 1	4
Ladiratuzumab vedotin	LIV1	cleavable	MMAE	4
Patritumab deruxtecan	HER3	Stable tetrapeptide based-cleavable	Topo 1	7.8
Enfortumab vedotin	Nectin-4	cleavable	MMAE	4

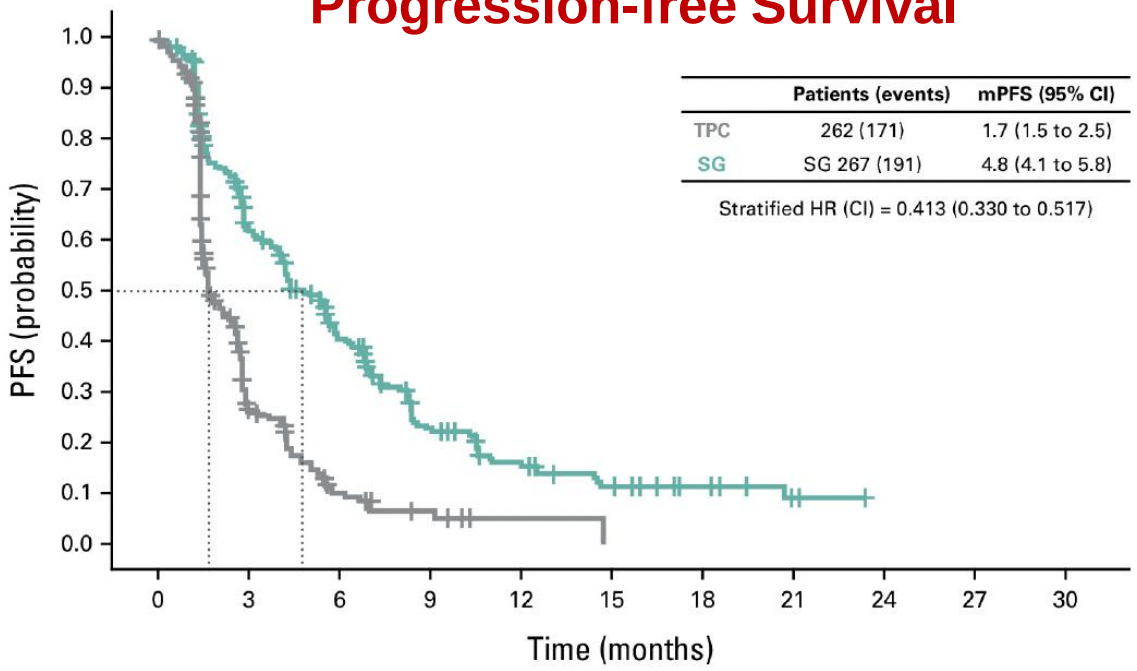
Both available for TNBC

Phase III data

Phase I data

ASCENT: final results

Progression-free Survival

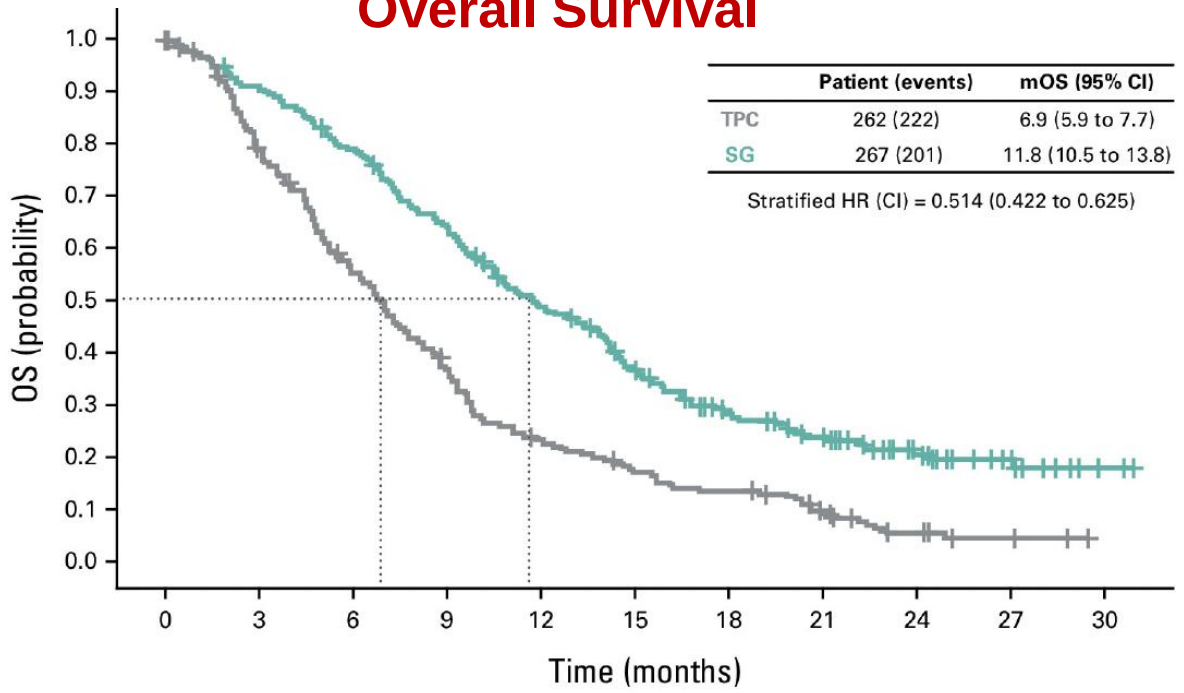


	Patients (events)	mPFS (95% CI)
TPC	262 (171)	1.7 (1.5 to 2.5)
SG	SG 267 (191)	4.8 (4.1 to 5.8)

Stratified HR (CI) = 0.413 (0.330 to 0.517)

No. at risk:									
TPC	262	40	12	5	1	0	0	0	0
SG	267	145	82	38	23	14	8	3	0

Overall Survival



	Patient (events)	mOS (95% CI)
TPC	262 (222)	6.9 (5.9 to 7.7)
SG	267 (201)	11.8 (10.5 to 13.8)

Stratified HR (CI) = 0.514 (0.422 to 0.625)

No. at risk:											
TPC	262	192	132	87	54	39	31	16	7	3	0
SG	267	242	209	169	125	92	62	42	25	11	2

G.U. 03/03/2025: «…pazienti adulti con cancro della mammella triplo negativo metastatico o non resecabile che abbiano ricevuto in precedenza almeno due terapie sistemiche, almeno una delle quali per la malattia avanzata.»

Bardia A, et al. JCO 2024

Design of Sacituzumab Tirumotecan (sac-TMT)

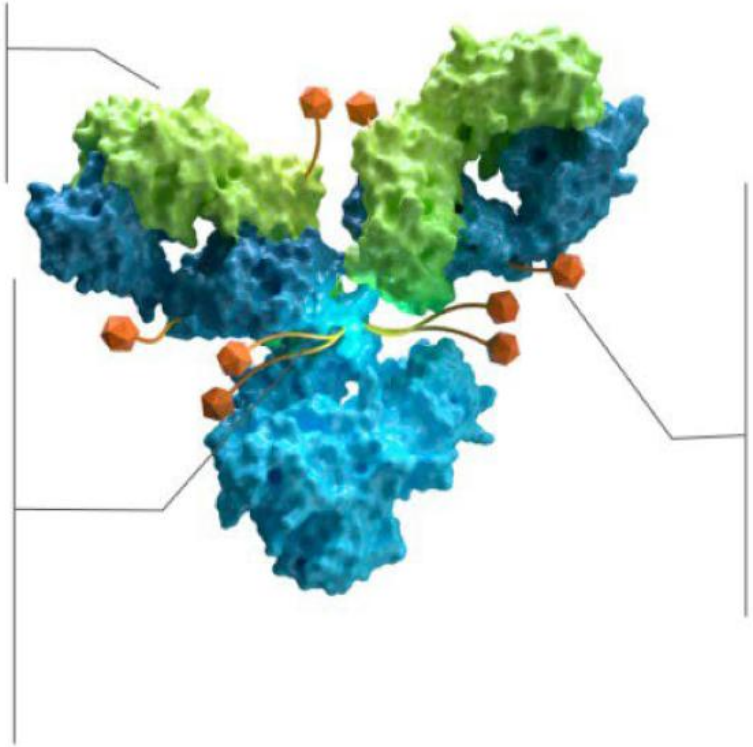
Sac-TMT is a TROP2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor at DAR 7.4. The features of sac-TMT lead to release of the payload both in the tumor microenvironment (TME) and inside tumor cells, achieving a balance between safety and efficacy.

Antibody

- hRS7, a recombinant humanized anti-TROP2 antibody with high affinity

Linker

- **Kthiol conjugation:** irreversible coupling to improve stability of ADC
- **Payload release:** intracellular cleavage and extracellular hydrolysis in TME
- **Balanced stability:** balance between efficacy and safety to expand therapeutic window



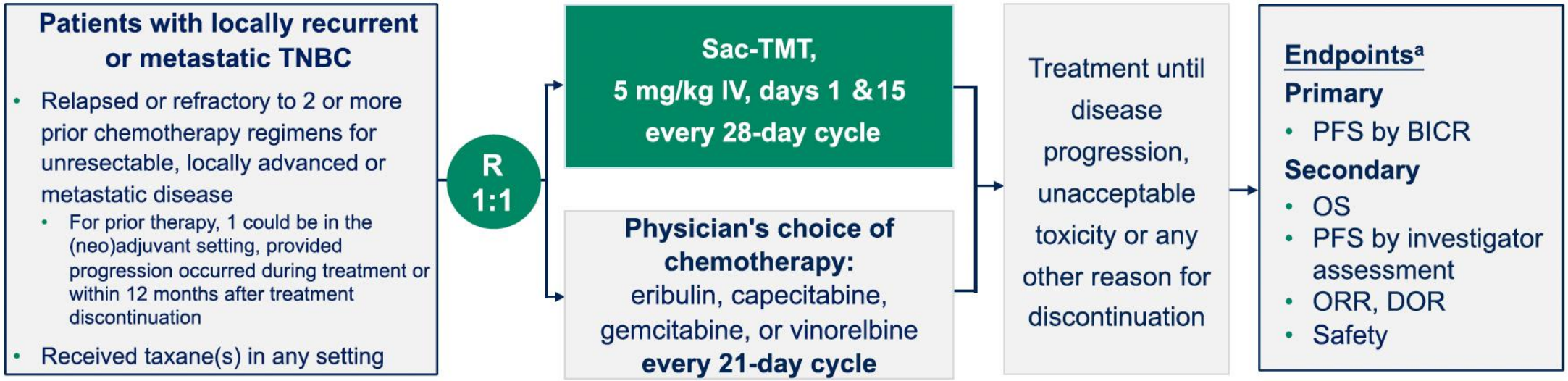
Payload

- **Novel topo I inhibitor** (a belotecan derivative), highly active
- Average **DAR: 7.4** (range: 7–8)
- **Bystander effect**
- Methylsulfonyl derivatization enhances linker stability and toxin permeability

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; TME, tumor microenvironment; TROP2, trophoblast cell surface antigen 2.

OptiTROP-Breast01 trial: Study design

- A randomized, controlled, and open-label phase III study (NCT05347134)



Stratification factors

- Line of prior therapy (2–3 *vs* >3)
- Presence of liver metastases (yes vs. no)

Choice of chemotherapy

- **Eribulin: 88 (66.2%)**
- Capecitabine: 4 (3.0%)
- Gemcitabine: 20 (15.0%)
- Vinorelbine: 21 (15.8%)

Tumor assessment

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

Binghe Xu et al. ASCO 2024

Patient Demographics and Baseline Characteristics

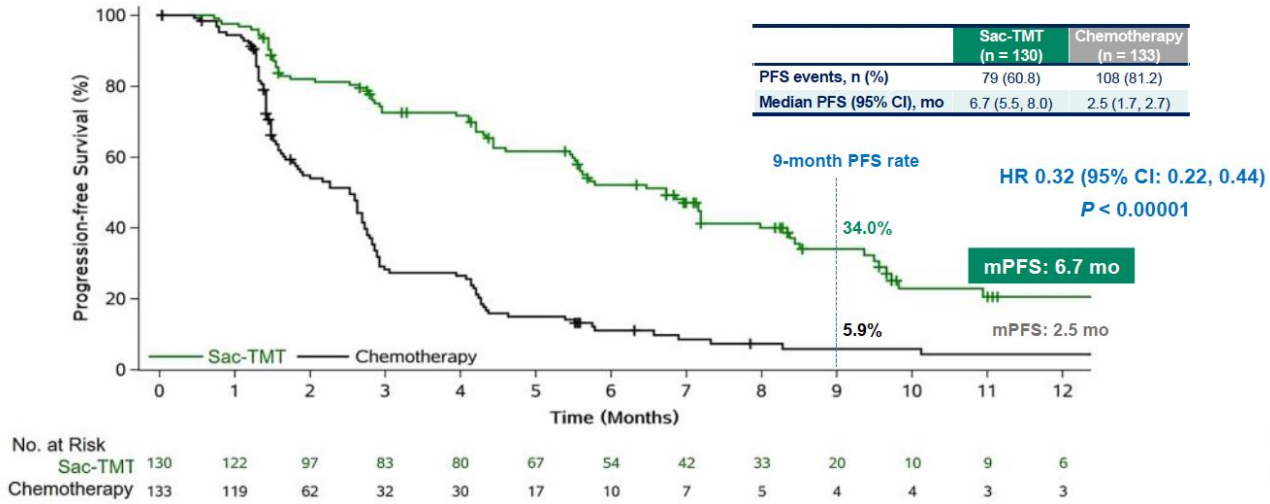
	Sac-TMT (n=130)	Chemotherapy (n=133)
Female, n (%)	130 (100)	133 (100)
Median age (range), yr	51 (19, 70)	51 (25, 72)
Age <65 years, n (%)	119 (91.5)	119 (89.5)
TNBC at initial diagnosis, n (%)	92 (70.8)	88 (66.2)
ECOG PS, n (%)		
0	40 (30.8)	39 (29.3)
1	90 (69.2)	94 (70.7)
Location of metastases, n (%)		
Visceral sites[a]	115 (88.5)	113 (85.0)
Lymph node	81 (62.3)	75 (56.4)
Lung	62 (47.7)	64 (48.1)
Liver	45 (34.6)	45 (33.8)

	Sac-TMT (n=130)	Chemotherapy (n=133)
Lines of prior therapy,[b] n (%)		
Median (range)	3.0 (2, 6)	2.0 (2, 6)
2	62 (47.7)	76 (57.1)
3	52 (40.0)	37 (27.8)
>3	16 (12.3)	20 (15.1)
Prior therapy, n (%)		
Taxane(s)	130 (100)	133 (100)
Anthracycline(s)	122 (93.8)	122 (91.7)
PD-1 or PD-L1 inhibitor(s)	32 (24.6)	36 (27.1)
(Neo)adjuvant	116 (89.2)	117 (88.0)
TROP2 expression,[c] n (%)		
High (H-Score >200)	73 (56.1)	74 (55.6)
Low/medium (H-Score ≤200)	53 (40.8)	48 (36.1)
Unknown	4 (3.1)	11 (8.3)

ASCENT: 31%

OptiTROP-Breast01 trial: Study Results

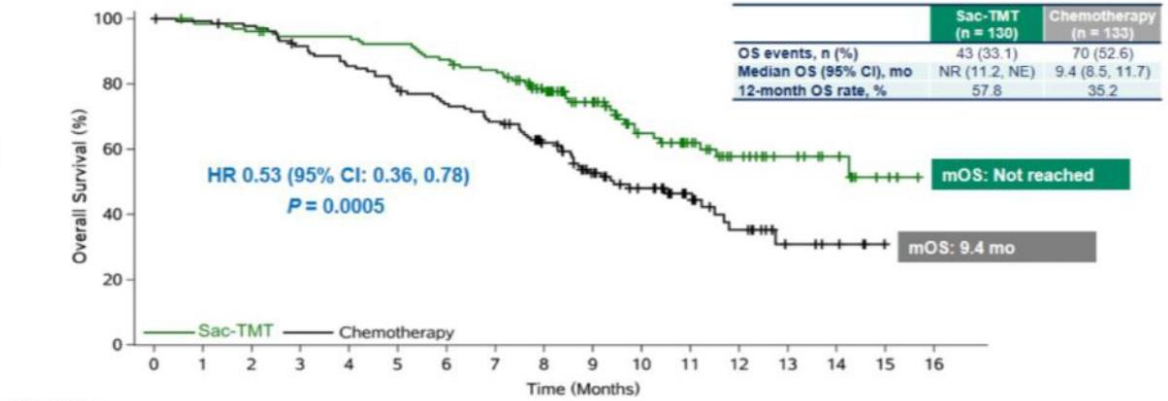
Final PFS by BICR



	Sac-TMT (n = 130)	Chemotherapy (n = 133)
PFS events, n (%)	79 (60.8)	108 (81.2)
Median PFS (95% CI), mo	6.7 (5.5, 8.0)	2.5 (1.7, 2.7)

- PFS by investigator assessment (secondary endpoint): Median 6.5 *vs* 2.6 mo; HR 0.32 (95% CI: 0.24, 0.44)

Interim OS

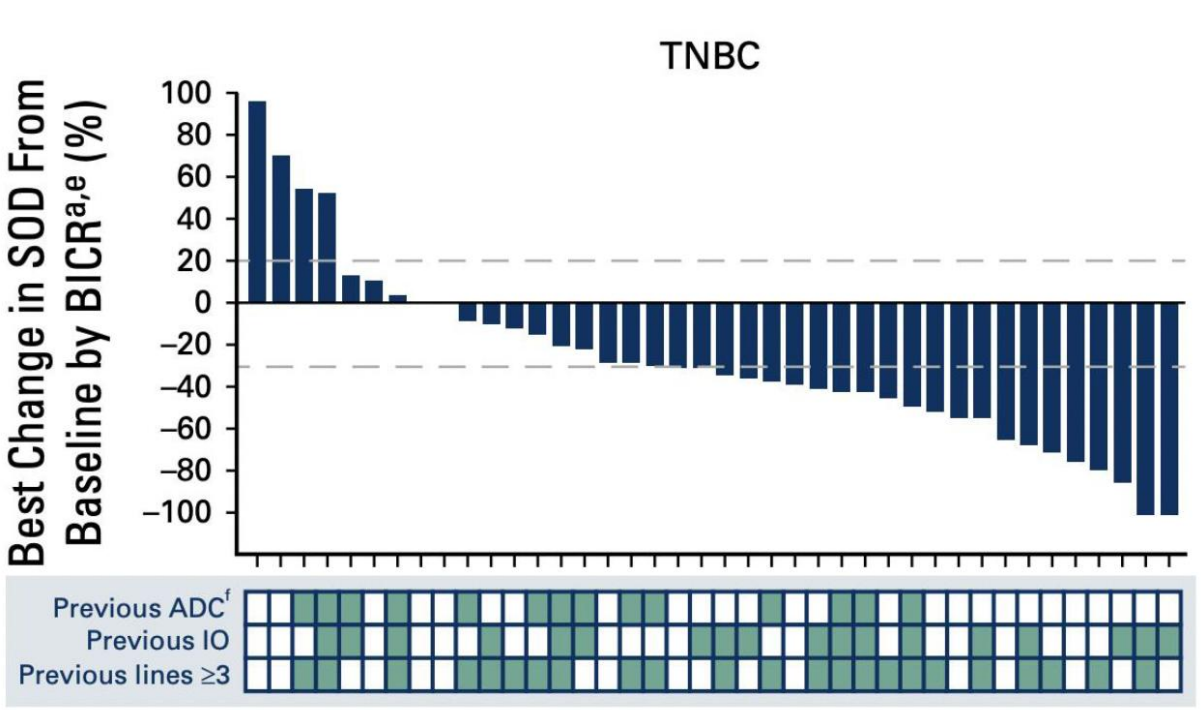


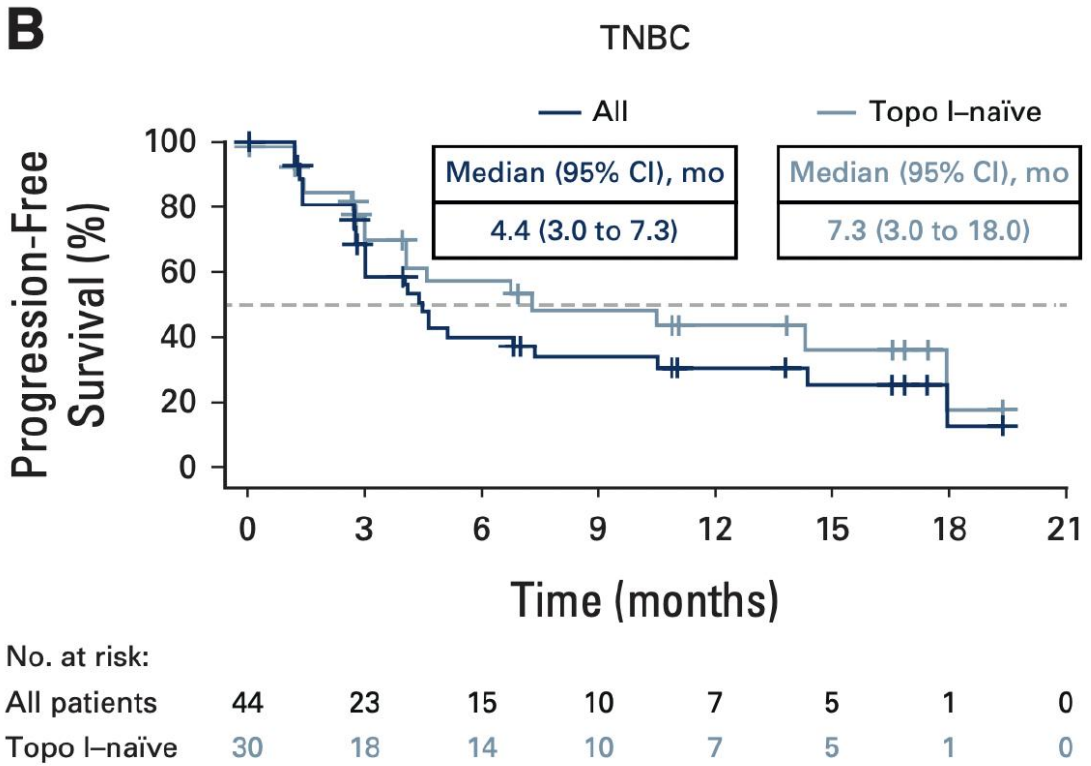
	Sac-TMT (n = 130)	Chemotherapy (n = 133)
OS events, n (%)	43 (33.1)	70 (52.6)
Median OS (95% CI), mo	NR (11.2, NE)	9.4 (8.5, 11.7)
12-month OS rate, %	57.8	35.2

- Efficacy boundary (corresponding to actual OS events of 113): 0.0042. The study crossed OS efficacy boundary.

Binghe Xu et al. ASCO 2024

Datopotamab-DXd: TROPION-Pan Tumor01

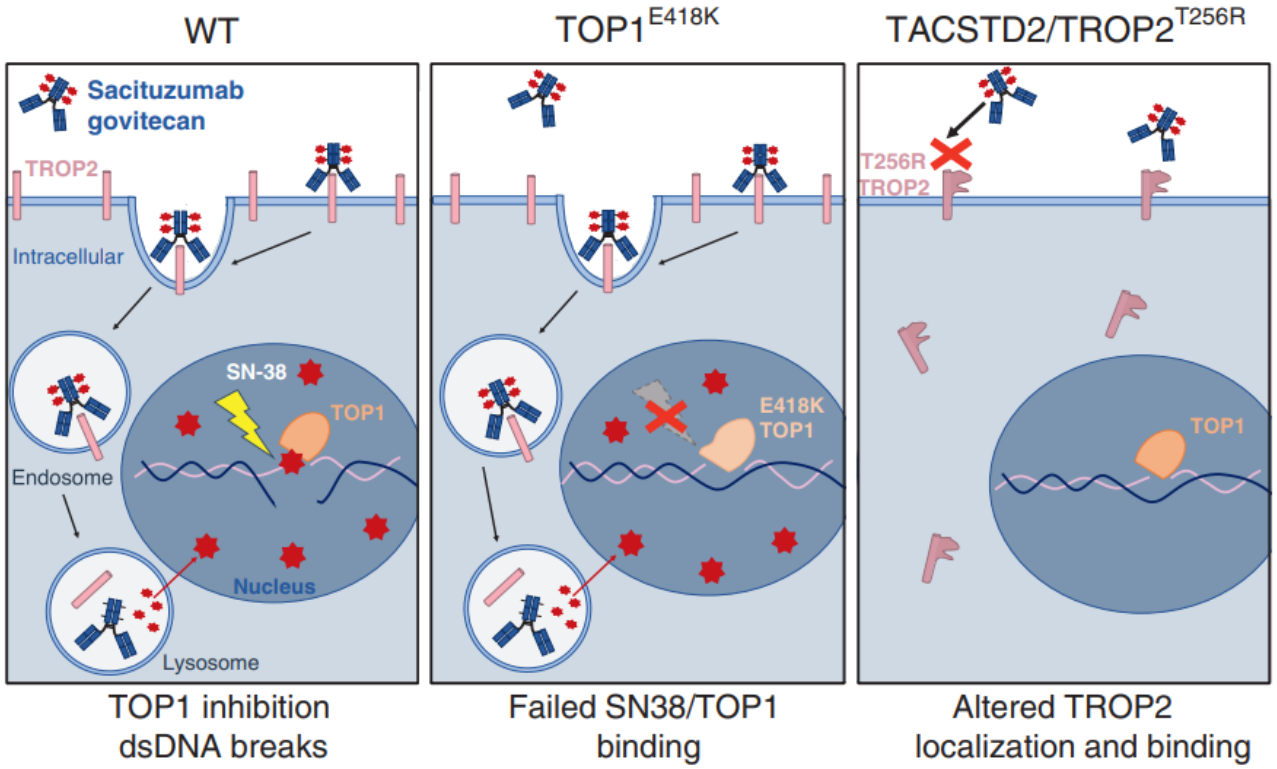




Bardia, JCO 2024

ADC sequencing

- ADC2 generally has lower efficacy vs ADC1
- Some patients derive greater benefit from ADC2 vs ADC1
- Is ADC2 better/equivalent vs standard CT?



Coates J et al., Cancer Discov 2021

Thank you!

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Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

Primary prophylaxis with GCSF and loperamide: PRIMED

KEY INCLUSION CRITERIA

- Male and female patients aged ≥18 years.
- Histologically confirmed triple-negative or HR+/HER2- breast cancer.
- Unresectable locally advanced or metastatic disease.
- Patients must have received at least one and up to two prior lines of chemotherapy for advanced disease.
- Previous therapy must have included a taxane in any setting.
- HR+/HER2- patients must have had disease progression to at least one prior endocrine therapy and a CDK4/6 inhibitor in the metastatic setting.
- Evaluable disease per RECIST v.1.1.
- ECOG Performance Status of 0 or 1.
- Adequate organ and bone marrow function.

Sacituzumab govitecan
10 mg/kg IV D1 and D8 every 21-day cycle
+
G-CSF
(First two cycles*)
300 µg SC QD two consecutive days 48 hours after administration of each infusion of sacituzumab govitecan
+
Loperamide
(First two cycles*)
2 mg PO BID or 4 mg QD during the first two cycles

21-day cycles until disease progression or unacceptable toxicity

N=25 → Interim analysis after 2 cycles → + N=25 (N=50)

Stage 1 → Stage 2

Baseline · C3D1 · EoS

ENDPOINTS

Primary endpoints
(First two cycles)
- Incidence of grade ≥ 3 neutropenia.
- Incidence of grade ≥ 2 diarrhea.

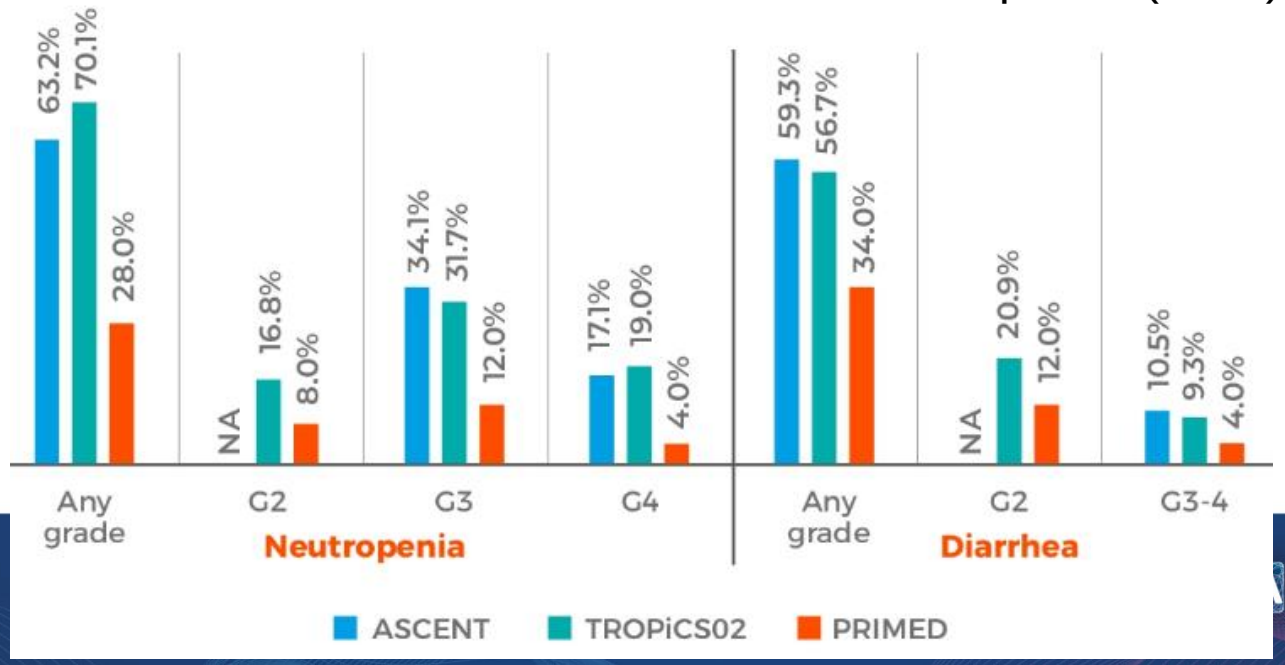
Secondary endpoints
- Incidence of febrile neutropenia and additional AEs as per NCI-CTCAE v.5.0.
- Discontinuation rate.
- Dose reduction rate.
- Health-related QoL from QLQ-C30 questionnaire.
- ORR, CBR, PFS, and other efficacy endpoints.

*Consider extending to the next cycle if necessary.

52% constipation (G1-2)

Current indication for GCSF prophylaxis: in case of prior complicated/severe neutropenia

Short- vs long-lasting



TBCRC 048: Phase II Study of Olaparib for MBC and Mutations in Homologous Recombination-Related Genes

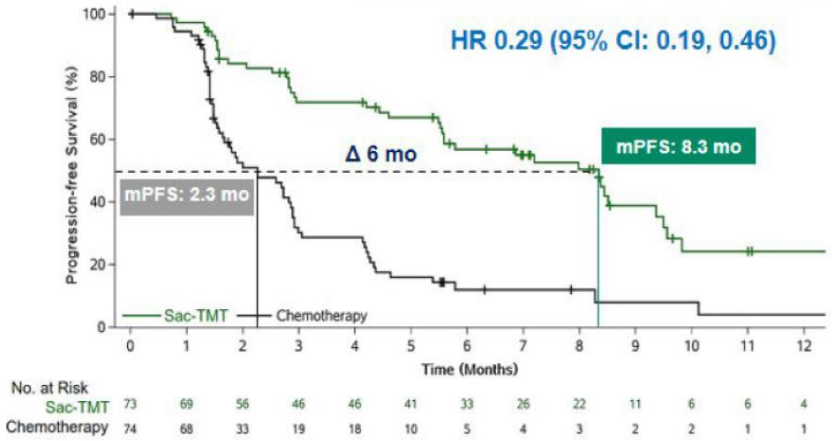
- PARP inhibitors (PARPi) approved for g*BRCA1 and* g*BRCA2* mutation (g*BRCA*m) carriers with metastatic or early stage high risk breast cancer
- TBCRC 048: phase 2 trial of olaparib in MBC pts with a **germline or somatic mutation in homologous recombination (HR)-pathway genes other than *BRCA1/2* or** in pts with **s*BRCA*m** (in absence of g*BRCA*m)
- Results:

Gene	ORR (90% CI)
g*PALB2* (n=11)	82% (48%-98%)
s*BRCA* (n=16)	50% (25%-75%)
ATM, *CHEK2* (n=18)	0%

Tung NM, et al. JCO 2020

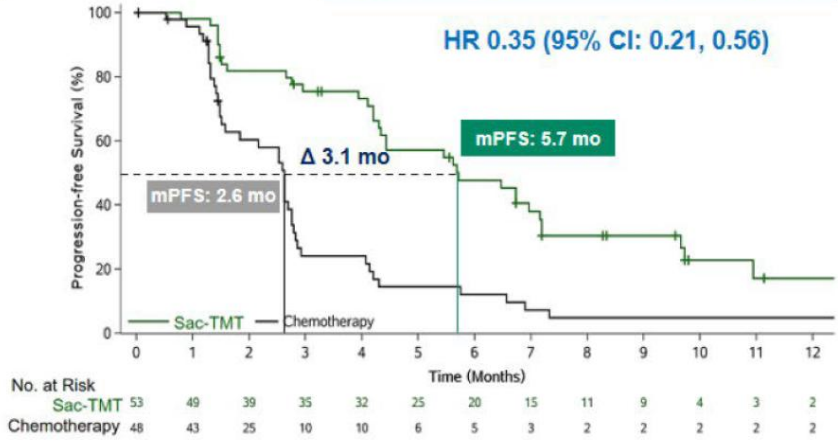
High TROP2 expression (H-Score >200)	Sac-TMT (n = 73)	Chemotherapy (n = 74)
PFS events, n (%)	41 (56.2)	59 (79.7)
Median PFS (95% CI), mo	8.3 (5.6, 9.4)	2.3 (1.6, 2.9)

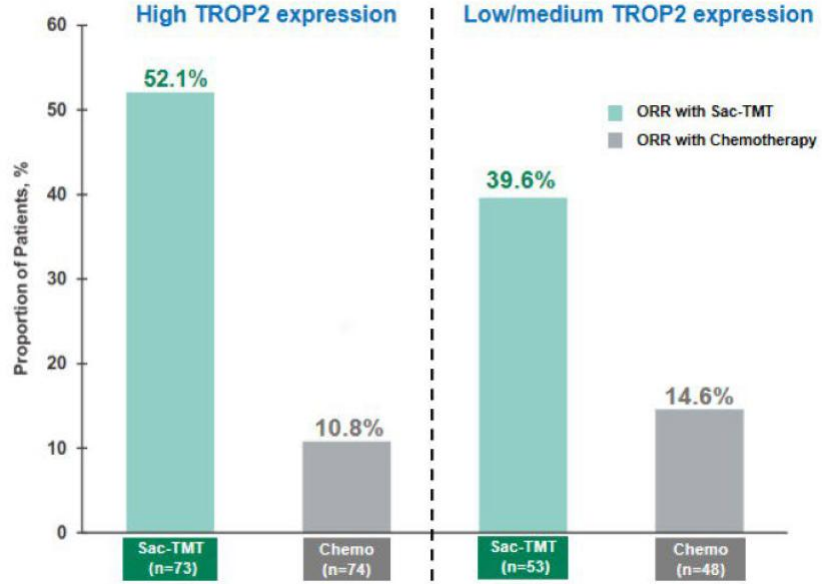
HR 0.29 (95% CI: 0.19, 0.46)



Low/medium TROP2 expression (H-Score ≤200)	Sac-TMT (n = 53)	Chemotherapy (n = 48)
PFS events, n (%)	34 (64.2)	40 (83.3)
Median PFS (95% CI), mo	5.7 (4.3, 7.2)	2.6 (1.5, 2.8)

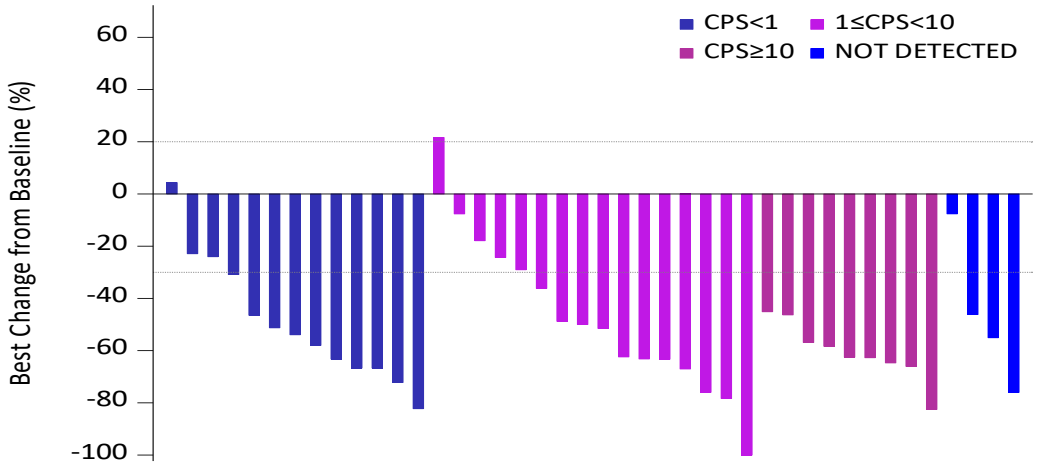
HR 0.35 (95% CI: 0.21, 0.56)





ORR according to PD-L1 expression and PFS

PM8002/BNT327 + Nab-Paclitaxel

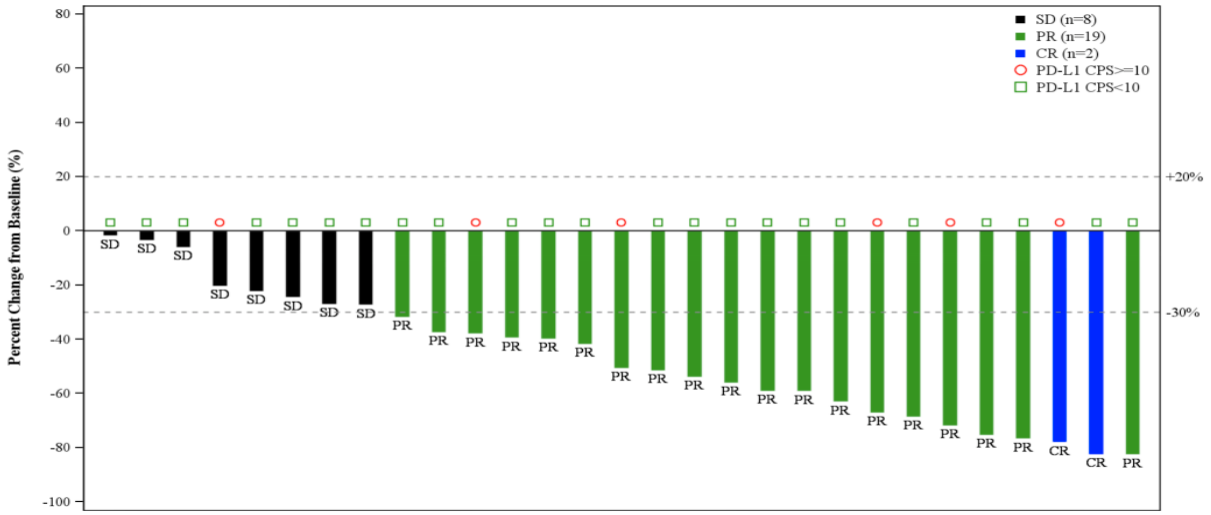


	CPS<1	1≤CPS<10	CPS≥10	ND
ORR	76.9%	68.8%	100.0%	75.0%

	ITT	1≤CPS<10	CPS≥10	ND
mPFS (95%CI), month	13.5 (9.4, --)	14.0 (7.2, --)	10.8 (5.5, 13.5)	14.0 (1.8, --)

Meng Y. et al, ESMO 2024

Ivonescimab + Paclitaxel/Nab-paclitaxel



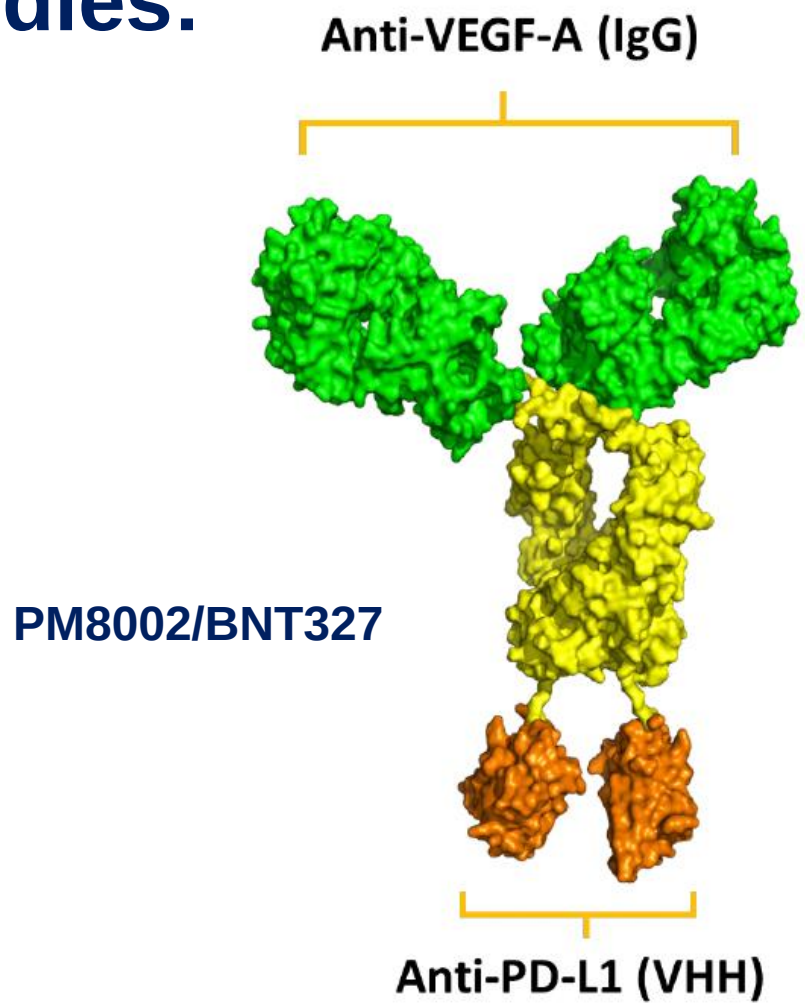
	CPS < 1	CPS < 10	CPS≥10
ORR	86.7%	69.6%	83.3%

	CPS < 1	< 10	CPS≥10
mPFS (95%CI), month	9.30 (5.26, --)	9.30 (5.55, --)	NR (5.36, --)

Wang X. et al, ESMO 2024

Bispecific Antibodies:

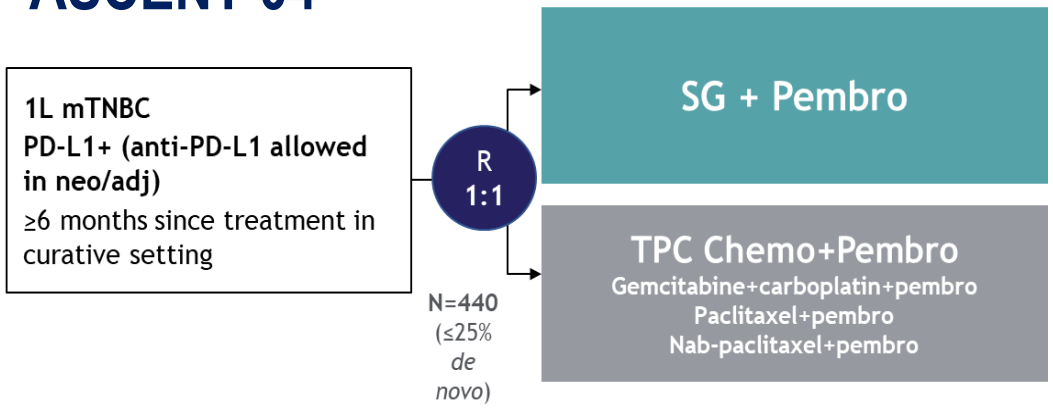
Targeting both PD-L1 and VEGF-A



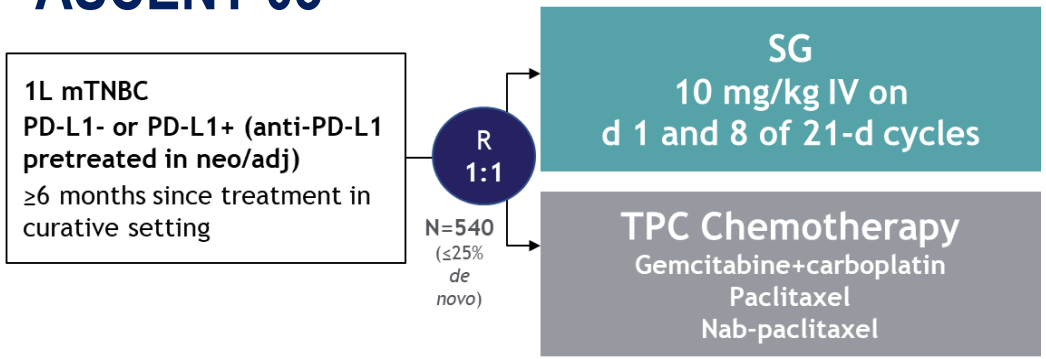
1. NCI. Anti-PD-L1/anti-VEGF-A antibody PM8002; 2. Lee J, et al. For Immunopathol Dis Therap 2015; 3. de Aguiar RB, et al. Front Immunol 2021; 4. Bourhis M, et al. Front Immunol 2021

Is combining better than sequencing? Moving best option first?

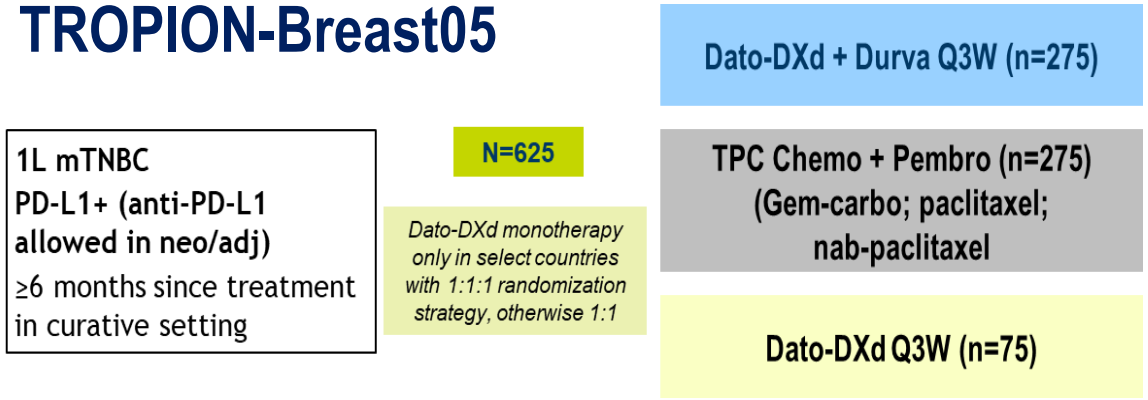
ASCENT-04



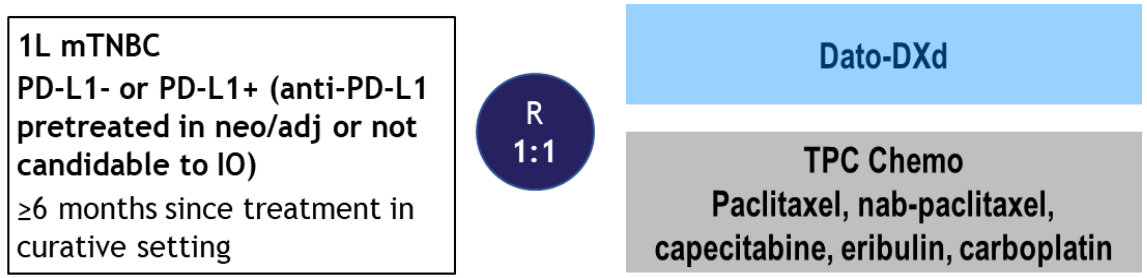
ASCENT-03



TROPION-Breast05



TROPION-Breast02



Combining the most active treatments upfront might be key to improve outcomes of mTNBC pts (especially in de-novo mBC)

CAPItello-290: Study overview

Phase 3, randomised, double-blind, placebo-controlled study (NCT03997123)

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

HER2-negative was defined as IHC 0 or 1+, or IHC 2+/ISH–. [a]Paclitaxel: 80 mg/m^2, Day 1 of Weeks 1–3 of each 4-week cycle, capivasertib: 400 mg twice daily, Days 2–5 of Weeks 1–3 of each 4-week cycle, placebo: twice daily, Days 2–5 of Weeks 1–3 of each 4-week cycle; [b]China, Asia-Pacific (excluding China), United States, Rest of the World.

ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HbA1c, glycosylated haemoglobin A1c; IHC, immunohistochemistry; ISH, *in situ* hybridisation; R, randomisation.