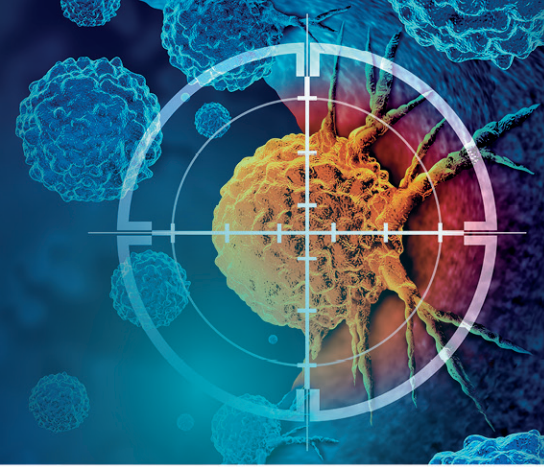
XVIII SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER



Cáncer de mama triple negativo: inmunoterapia y ADCs bailando juntos y por separado

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SaludMadrid Hospital General Universitario Gregorio Marañón

II G-M

GEICAM investigación en cáncer de mama

Declaración de conflictos de interés

Sara López-Tarruella, MD, PhD

EMPLEO

Hospital General Universitario Gregorio Marañón y Universidad Complutense (Madrid)

CONSULTORÍA / ASESORÍA

Astra Zeneca, Novartis, Roche, Pfizer, Celgene, Pierre-Fabre, Lilly, Seagen, Daiichi-Sankyo, Pharmalex, Gilead y MSD

PONENCIAS

Novartis, Roche, Pfizer, Daiichi-Sankyo y Lilly

CARGOS EN JUNTAS O SOCIEDADES (NO REMUNERADOS)

Miembro de la Junta Directiva y Comité Ejecutivo de GEICAM

FINANCIACIÓN DE INVESTIGACIÓN (PARTICIPACIÓN EN ENSAYOS COMO IP)

Novartis, Roche, Amgen, Genentech, Seagen, Gilead y Daiichi-Sankyo



TNBC: immunotherapy and ADCs dancing together and separately

01 Clinical context: where we stand

02 Biology behind: why ADCs and IO can dance together

03 Dancing together: ADC + IO in first-line PD-L1+ disease

04 Dancing separately: ADCs when IO is not an option, and toxicity

05 New therapeutic scenarios and clinical challenges: CNS Disease and Later-Lines

06 The dance moves earlier: high-risk early disease

07 Open questions @2026

08 Take-home messages

01

Clinical context; where we stand

Why first line is, for many patients, the only real opportunity

Advanced TNBC: room for improvement

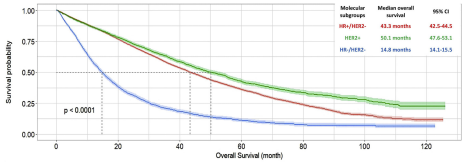
ESMÉ Registry (2008-17)

Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

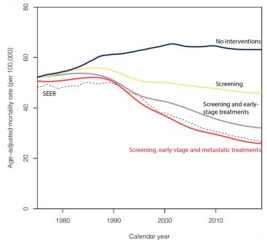
- N=23698 (14.3% TNBC)

Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	14.0 (12.3 - 15.9)
2011	14.2 (12.0 - 16.1)
2013	15.1 (12.9 - 17.6)
2016	14.2 (12.1 - 16.5)

- 30.1% de novo MBC (28.3% TNBC subtype)

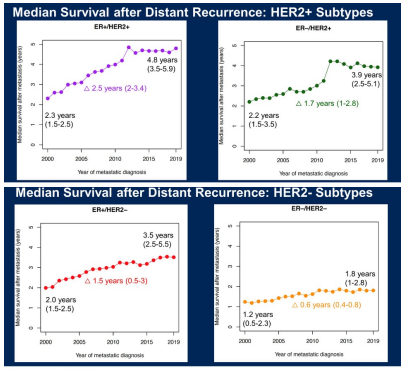


Contributions of screening, early-stage and metastatic treatment to BC mortality reduction by molecular subtype US (2000-2017)

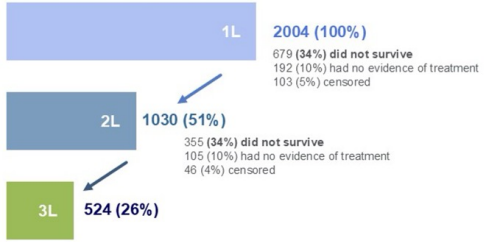


Overall mortality reduction in 2019
ALL 58% vs ER+/HER2+ 71% vs **TNBC 40%**

ABC treatments improved population-level survival in ALL subtypes since 2000



***FLATIRON_US (2011-22)**



Percentages for 2L and 3L patients are expressed as a proportion of the total patient population (2L: 1030/2004 (51%); 3L: 524/2004 (26%))

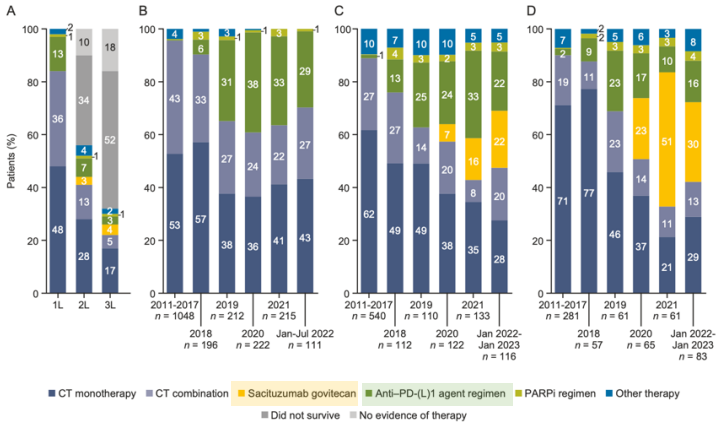
*This retrospective observational study used Flatiron Health de-identified electronic health record data from the USA. Punie K, et al.[1]



of patients who receive 1L treatment will subsequently get treated with 2L treatment…

…**do not survive** to receive a next line of therapy, **confirming the unmet need** for more efficacious treatment options **for previously untreated patients with mTNBC**[1,2]

Treatment patterns by line of treatment



- **ESME (2008-16, N=2963 pts):** mOS 14.8 mo
- **Flatiron (2011-22, N=2004 pts)*:** mOS 11.3 mo & 12mo-OS 48%
- **Flatiron (2018-23, N=1044 pts):** mOS 18.6 mo (PD-L1+) & 12.7 mo (PD_L1-)
- **Patient360 (2010-19, N=214):** mOS 14.5 mo & 12mo-OS 56%

Deluche et al EJC 2020; Grinda et al ESMO Breast 2022; Caswell-Jin et al ASCO 2022; Xiao et al Cancer Manag Res 2018; Punie et al Oncologist 2025; DeClue et al Future Oncol 2023; Trania et al SABCS 2024

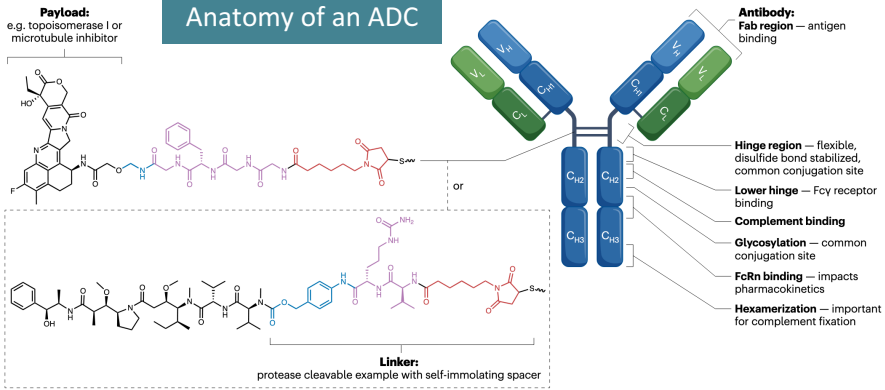
02

Biology behind: why ADCs and IO can dance together

What supports ADC + IO, and what is still a hypothesis

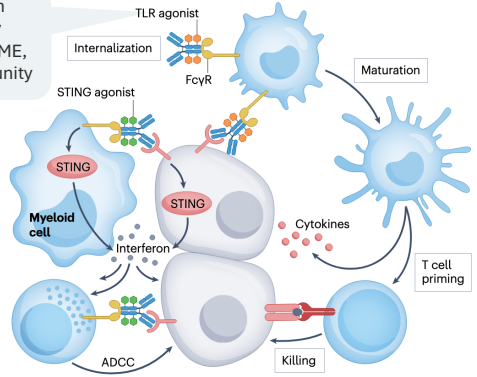
ADCs from cytotoxicity to immune priming

Anatomy of an ADC

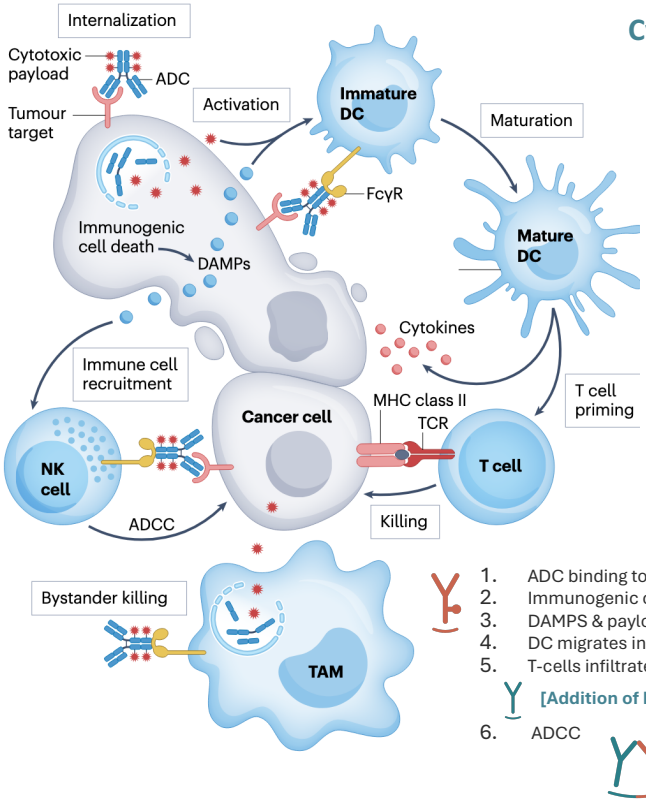


[Immune-stimulating antibody conjugates (ISACs)]

*ISACs are armed with PRR (pattern recognition receptor such as TLR) agonists that specifically activate innate immune responses within the TME, helping support robust and durable T cell immunity



Immune interactions of ADCs in TME



1. ADC binding to cancer cell
2. Immunogenic cell death
3. DAMPS & payload in TME activate immature DC
4. DC migrates in lymph node activating T-cell
5. T-cells infiltrate TME, attacking tumor cells

[Addition of ICIs overcome T-cell inhibition]

6. ADCC

Zippelius et al Nat Rev Cancer 2025; Nicolò et al Cancer Treat Rev 2022

*Damage-associated molecular patterns (DAMPs) i.e. calreticulin, ATP and high-mobility group box 1 (HMGB1)

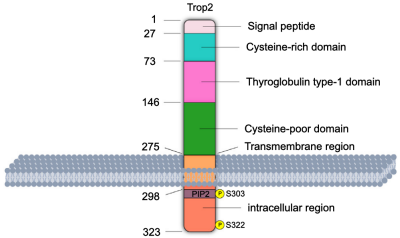
Payloads: cytotoxic and immunomodulatory effects

Payload class	Payload	Cytotoxic mode of action	Preclinical evidence of immune interactions	Evidence of synergy with immune checkpoint inhibition
Microtubule-targeting agents	Dolastatins (dolastatin 1, dolastatin 2, dolastatin 10)	Inhibition of tubulin polymerization by binding to the vinca domain of tubulin	ICD induction, direct DC activation	TBD
	Auristatins (MMAE, MMAF)		ICD induction, direct DC activation	Clinical
	Tubulysins		ICD induction	Preclinical
	Maytansinoids (DM1, DM4, ansamitocin P3)	Inhibition of tubulin polymerization by binding to β-tubulin on sites distinct from the vinca domain	ICD induction, direct DC activation	Preclinical
DNA damaging agents	Calicheamicins	Induces DNA double-strand breaks	Suppressive immune cell death	TBD
	Duocarmycins	DNA alkylation, which disrupts DNA replication and transcription	TBD	TBD
	PBD	DNA cross-linking, which induces DNA damage	ICD induction	Preclinical
	Anthracyclines (PNU)	DNA intercalation and inhibition of topoisomerase II, which impairs DNA replication	ICD induction	Preclinical
Topoisomerase I inhibitors	SN-38	Stabilization of topoisomerase I–DNA complexes, preventing DNA re-ligation, which results in DNA damage	TBD	TBD
	DXd		Direct DC activation	Preclinical
	KL610023		TBD	TBD
PRR agonists	TLR agonists	NA	DC activation, pro-inflammatory cytokine production	Preclinical evidence for free TLR agonists
	STING agonists		DC activation, pro-inflammatory cytokine production	Preclinical

Zippelius et al Nat Rev Cancer 2025

Anti-TROP2 TOP1i ADCs: one target, three different designs

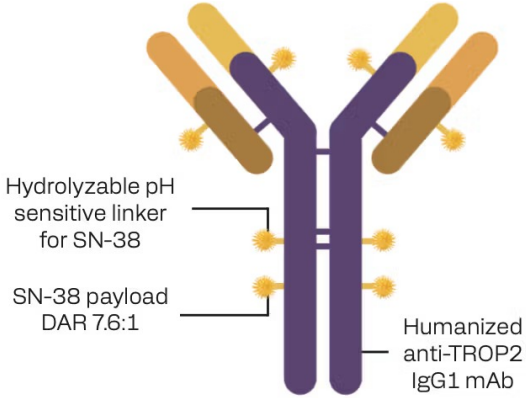
[Trophoblast cell-surface antigen 2]



TROP2 cell surface antigen overexpressed ≃ 93% TNBC (low expression in most normal tissues)

TROP2-mediated IC/EC **signaling pathways**:

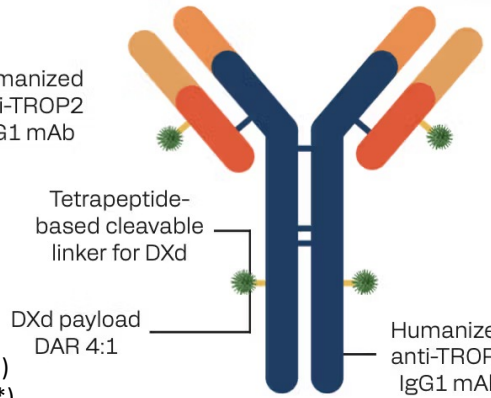
- Calcium signaling mediates effect of Trop2 on cell proliferation through intramembrane hydrolysis
- Promotes tumor cell invasion via the integrin β1-RACK1-FAK-Src signaling axis
- Regulates the expression of downstream target proteins/genes. Signaling pathways downstream of Trop2 (MAPK, JAK2/STAT, JnK, PI3K/Akt; ErbB3, IGF-1R)



Sacituzumab govitecan
D1,8 q21

[ASCENT] *2L+ aTNBC*

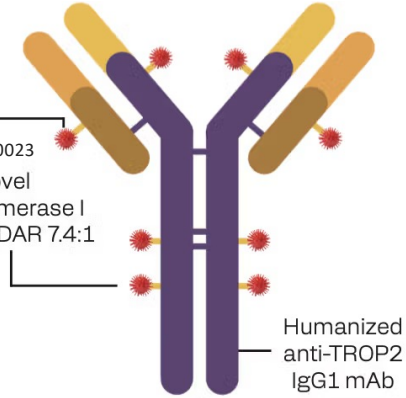
- mPFS 5.6 mo (HR 0.41*)
- mOS 12.1 mo (HR 0.48*)
- ORR 35%



Datopotamab deruxtecan
D1 q21

[TROPION PanTumor01] *2L+ aTNBC*

- mPFS 4.7 mo (7.3 mo topo I_Naïve) & ORR 32% (40% topo I Naïve)



Sacituzumab tirumotecan
D1 q14

[OptiTROP-Breast01] *2L+ aTNBC*

- mPFS 6.7 mo (HR 0.32*)
- mOS NR (HR 0.53*)
- ORR 45%

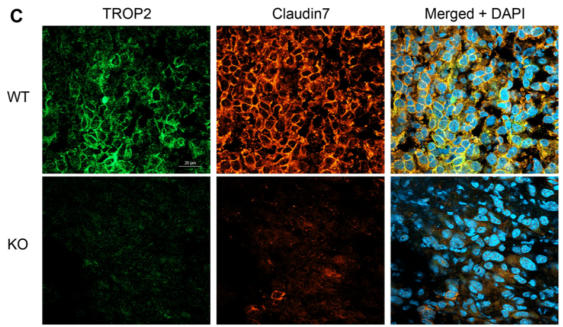
https://www.cancernetwork.com/view/3-things-you-should-know-about-trop2-as-a-therapeutic-target-in-triple-negative-breast-cancer; Liu et al Pharmacol Ther 2022; Bardia et al NEJM 2021; Yin et al Nat Med 2025; Bardia et al JCO 2024

Anti-TROP2 ADCs plus ICIs: mechanistic rationale for combination

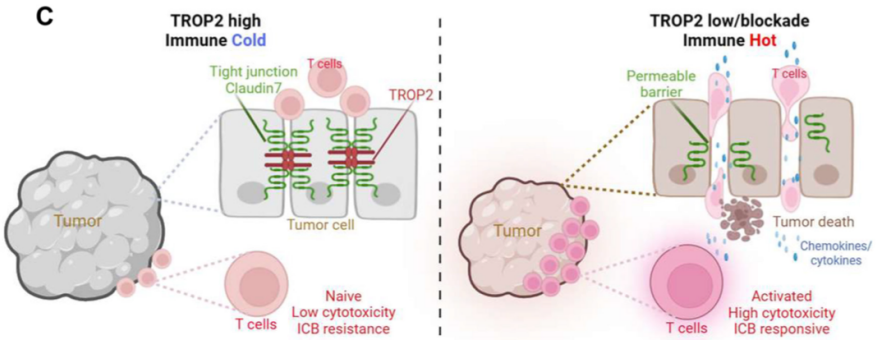
- **Barrier-mediated immune exclusion** is emerging as a **mechanism of immune evasion** in cancer (i.e in TNBC), but its molecular underpinnings remain poorly understood. TROP2 is a surface glycoprotein targeted by ADCs, yet its functional role beyond drug delivery has been unclear

◉ ***TROP2 could be a functional driver of immune evasion and provide a mechanistic rationale for combining TROP2-targeting therapies with immune checkpoint inhibitors to overcome resistance in immune-excluded tumors***

1. Spatial transcriptomics identifies tumor cell-specific programs associated with TNBC immune phenotypes immunogenic cell death.
2. TROP2 promotes mammary tumor growth in immunocompetent hosts.
3. TROP2 promotes mammary tumor immune exclusion.
4. TROP2 (key regulator) **promotes a tight junction-mediated barrie**r and **inhibits a pro-inflammatory TME***
5. TROP2 intracellular domain is dispensable for its tight junction and immune barrier function (**independent of its intracellular signaling function**).



TROP2 promotes immune-cold TME by enforcing mechanical barriers that limit T-cell infiltration



6. **TROP2 targeting via the anti-TROP2 antibody component of SG promotes anti-PD-1 efficacy.**
7. **High TROP2 associates with poor response to ICIs in human BC.**

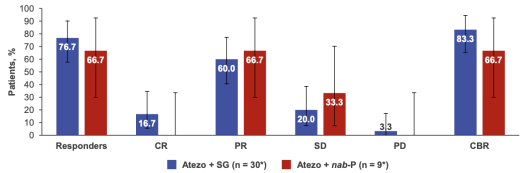
Anti-TROP2 ADCs plus immunotherapy: early-phase signals of activity

[MORPHEUS-pan BC]

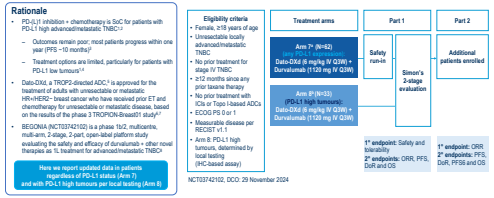


Primary efficacy endpoint: ORR

Best confirmed overall response rates by investigator, per RECIST v1.1

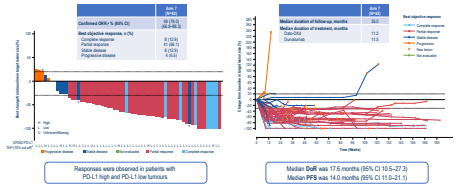


[BEGONIA]



Overall Response and Duration of Response (Arm 7)

Overall, 11.3% patients had PD-L1 high tumours and 87.1% had PD-L1 low tumours

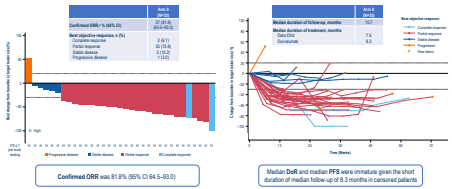


Responses were observed in patients with PD-L1 high and PD-L1 low tumours

Median DoR was 17.6 months (95% CI 10.5–27.3)
Median PFS was 14.0 months (95% CI 11.0–21.1)

Overall Response and Duration of Response (Arm 8)

PD-L1 high tumours



Confirmed ORR was 81.8% (95% CI 64.5–93.0)

Median DoR and median PFS were immature given the short duration of median follow-up of 8.3 months in censored patients

Trial	Phase · setting	Regimen	n	Key efficacy	Safety
BEGONIA arm 7	Ib/II · 1L mTNBC, PD-L1 all-comers	Dato-DXd + durvalumab	62	**cORR 79% · mPFS 14.0 mo · mDoR 17.6 mo · mOS NR (FU 35 mo)**	G≥3 TEAEs 59.7%
BEGONIA arm 8	Ib/II · 1L mTNBC, PD-L1-high	Dato-DXd + durvalumab	33	**cORR 82% (FU 10.7 mo,** 8.3 mo censored pts**)**	G≥3 TEAEs 36.4%
MORPHEUS-pan BC	Ib/II rand. · 1L mTNBC, PD-L1+ (SP142)	SG + atezolizumab vs atezo + nab-P	31 vs 11	**ORR 77% vs 67% · mPFS 12.2 vs 5.9 mo (HR 0.27)**	G3–4 70% vs 44% · irAEs 80% vs 56%
I-SPY2.2	II SMART · neoadj. stage II–III HER2−	Dato-DXd + durvalumab (block A)	106	**Immune+ subtype: pCR 43% after block A alone (79% all blocks)**	No new toxicities
NeoSTAR A2	II · neoadj. stage II–III TNBC	SG + pembrolizumab × 4 cycles	50	**pCR 32% "CT-free" (50% stage I) · 2-yr EFS 95% (ALL)** & 100%/ 92% (pCR/RD)	No new signals

Schmid et al ESMO Open 2024; Lv et al Clin Exp Med 2025; Schmid et al Nature Cancer 2026 & Ann Oncol 2026; Shatsky et al Nature Medicine 2024

03

Dancing together: first-line PD-L1+

ADC + pembrolizumab versus chemotherapy + pembrolizumab in CPS ≥10



ASCENT-04/KEYNOTE-D19: Changing the cytotoxic backbone

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

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

N = 443

R 1:1

SG + pembro[d]
(SG 10 mg/kg IV, days 1 and 8 of 21-day cycles; pembro 200 mg, day 1 of 21-day cycles)
n = 221

Chemo* + pembro[d]
(paclitaxel 90 mg/m² OR nab-paclitaxel 100 mg/m² on days 1, 8, & 15 of 28-day cycles, OR gemcitabine 1000 mg/m² + carboplatin AUC 2 on days 1 & 8 of 21-day cycles; pembro 200 mg on day 1 of 21-day cycles)
n = 222

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

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

End points

Primary
- PFS by BICR[e]

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

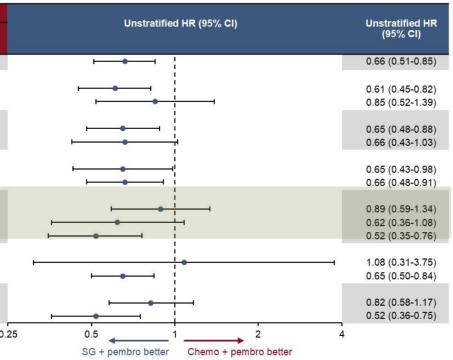
Stratification factors:
- De novo mTNBC[c] vs recurrent within 6 to 12 months from completion of treatment in curative setting vs recurrent > 12 months from completion of treatment in curative setting
- US/Canada/Western Europe vs the rest of the world
- Prior exposure to anti-PD-(L)1 (yes vs no)

Data cutoff date for Primary PFS: March 3, 2025
- There were 249 observed PFS events by BICR
- Median follow-up was 14.0 months (range, 0.1-28.6)
- At the data cutoff date, 95 patients (43%) in the SG + pembro group and 52 patients (23%) in the chemo + pembro group continued to receive study treatment

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)

	SG + Pembro n	SG + Pembro Median PFS, mo (95% CI)	Chemo + Pembro n	Chemo + Pembro Median PFS, mo (95% CI)	Unstratified HR (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)

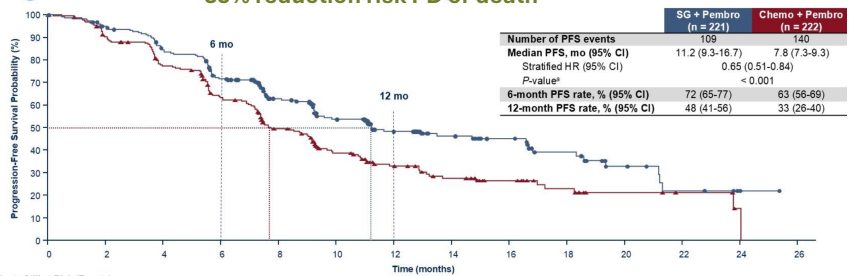


PFS benefit was observed for SG + pembro vs chemo + pembro across prespecified subgroups

Consistent with primary analysis mPFS is longer across all key pts subgroups with SG+pembro (all Trop-2 expression quartiles; both tBRCAwt and mut status and HER2 IHC0 and low expression subgroups)

Progression-Free Survival by BICR

Δ 3.4 mo mPFS (11.2 mo SG)
35% reduction risk PD or death



	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)

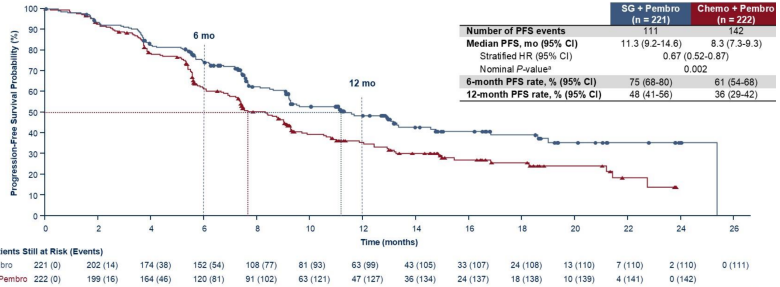
No. of Patients Still at Risk (Events)													
SG + Pembro	221 (0)	202 (11)	174 (33)	142 (59)	105 (75)	78 (89)	58 (96)	42 (98)	34 (99)	22 (103)	11 (106)	6 (109)	2 (109)	0 (109)
Chemo + Pembro	222 (0)	191 (21)	159 (48)	123 (76)	88 (102)	59 (120)	40 (128)	29 (134)	21 (135)	13 (137)	7 (138)	4 (138)	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

Tolaney et al. NEJM 2026, Tolaney et al. ASCO 2025 & 2026

ASCENT-04/KEYNOTE-D19: Secondary efficacy endpoints

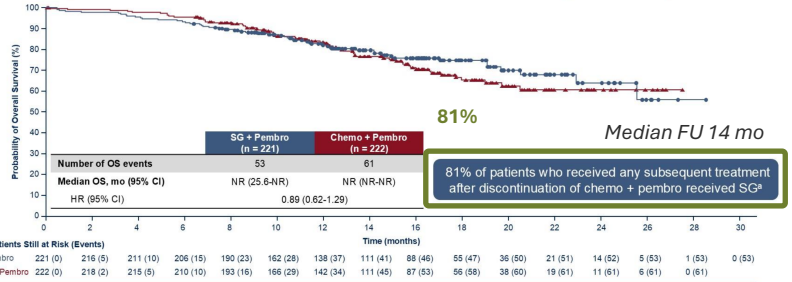
Progression-Free Survival by Investigator Assessment



	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)

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

Descriptive Overall Survival at Primary Analysis



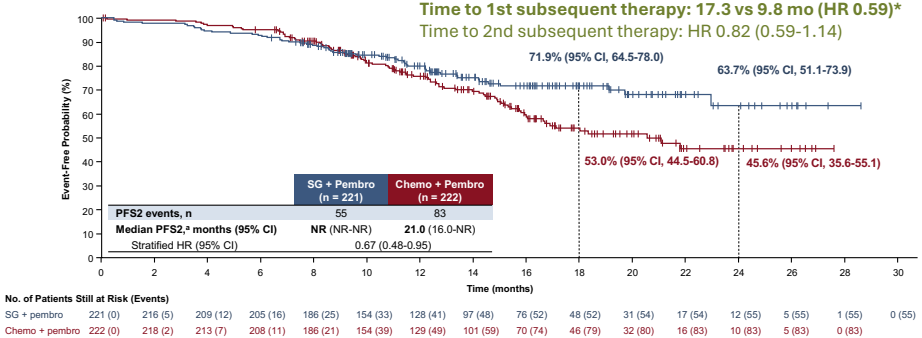
	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of OS events	53	61
Median OS, mo (95% CI)	NR (25.6-NR)	NR (NR-NR)
HR (95% CI)	0.89 (0.62-1.29)	

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

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

PFS After Next Line of Treatment (PFS2)

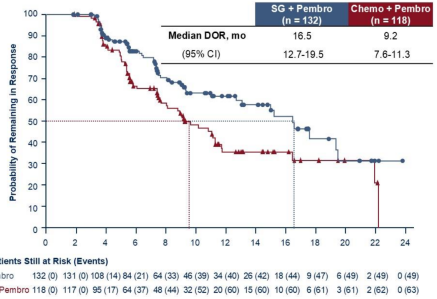
Time to 1st subsequent therapy: 17.3 vs 9.8 mo (HR 0.59)*
Time to 2nd subsequent therapy: HR 0.82 (0.59-1.14)



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
PFS2 events, n	55	83
Median PFS2,[a] months (95% CI)	NR (NR-NR)	21.0 (16.0-NR)
Stratified HR (95% CI)	0.67 (0.48-0.95)	

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)



	SG + Pembro (n = 132)	Chemo + Pembro (n = 118)
Median DOR, mo	16.5	9.2
(95% CI)	12.7-19.5	7.6-11.3

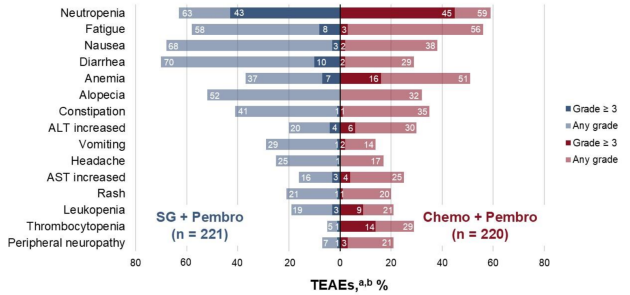
A substantially longer duration of response and a higher overall response rate (including an increased complete response rate) was observed for SG + pembro vs chemo + pembro

ASCENT-04/KEYNOTE-D19: QoL and toxicity profile

Safety Summary

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)

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



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

- Baseline QOL was generally maintained with SG + pembro, with benefits seen in several domains
- TTD in physical functioning was comparable between the groups, with **emotional functioning and pain** favoring SG + pembro vs chemo + pembro
- The sensitivity analyses to evaluate substantial and sustained changes showed that SG + pembro may delay the onset of decline in physical functioning, indicating a benefit in maintaining patients' ability to perform daily activities
- Mean changes from baseline favored SG + pembro for **physical, role, and emotional functioning,** as well as **pain and insomnia**
- There was worsening of symptoms such as **nausea/vomiting and diarrhea,** which are consistent with the safety profile of the SG + pembro group in the study, and can be managed by following established guidelines

SG + pembro maintained overall QOL, patients reported reduced symptom burden and improved functioning in multiple domains; these data complement the clinically meaningful improvement in PFS and support this treatment regimen as a potential new standard of care for patients with PD-L1+ mTNBC

Adverse Events of Special Interest

	AESI,[a] n (%)	SG + Pembro (n = 221) Any Grade	SG + Pembro (n = 221) Grade ≥ 3	Chemo + Pembro (n = 220) Any Grade	Chemo + Pembro (n = 220) 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

Tolaney et al. NEJM 2026, Tolaney et al. ASCO 2025 & 2026; Azambuja et al ESMO 2025

TROPION-Breast 05: Changing the cytotoxic backbone (and ICI)

Patients with previously untreated locally recurrent inoperable or metastatic PD-L1+ (CPS ≥10) TNBC

Key eligibility:

- **Measurable disease per RECIST 1.1**
- **No active brain metastases**
- **DFI ≥6 months since treatment in the curative setting**
- **ECOG PS 0 or 1**

*Approx 1950 pts screened to enroll 625 pts

N≈625 Randomised

Stratified by:

- DFI history (de novo vs prior DFI 6–12 months* vs prior DFI >12 months)
- Geographic location (US/Canada/Europe vs Dato-DXd monotherapy enrolling countries vs other geographic regions)
- Prior PD-1/PD-L1 treatment for early-stage TNBC (Yes vs No)

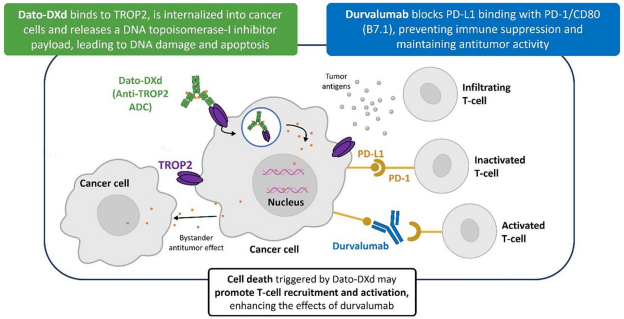
Arm 1
Dato-DXd
6 mg/kg IV Q3W
+
Durvalumab
1120 mg IV Q3W
(n=275)

Arm 2
Investigator's Choice of Chemotherapy†
+
Pembrolizumab
200 mg IV Q3W
(n=275)

Arm 3
Dato-DXd
6 mg/kg IV Q3W
(n=75)‡

***EC** Neoplastic spinal cord compression or active brain metastases, leptomeningeal carcinomatosis, or history of leptomeningeal carcinomatosis

***IC** PD-L1-high TNBC based on results from a validated PD-L1 (22C3) assay (CPS ⩾ 10) from a sponsor-designated central laboratory



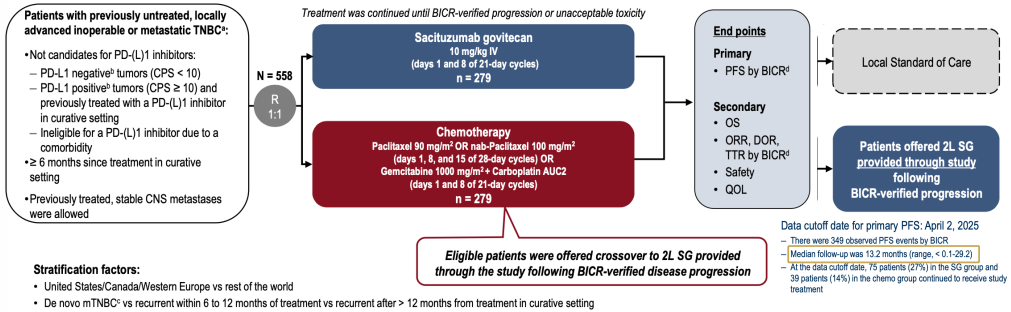
04

Dancing separately: IO-ineligible disease

Anti-TROP2 ADC monotherapy: PD-L1−, IO not indicated, early relapse

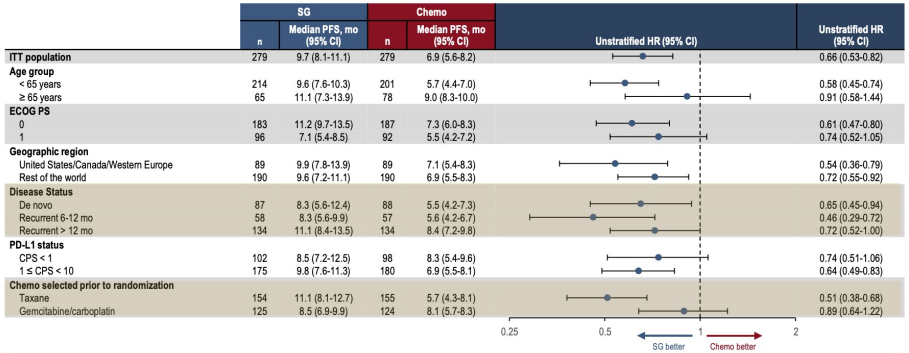


ASCENT-03 : 1L ADC vs CT when IO is not an option



ITT Population	SG (n = 279)	Chemo (n = 279)
Female sex, n (%)	278 (> 99)	277 (99)
Median age, (range) yr	56 (28-84)	54 (23-86)
≥ 65 yr, n (%)	65 (23)	78 (28)
Race or ethnic group,[a] n (%)		
White	178 (64)	178 (64)
Asian	66 (24)	65 (23)
Black	10 (4)	7 (3)
Other/not specified	25 (9)	29 (10)
Geographic region, n (%)		
United States/Canada/Western Europe	89 (32)	89 (32)
Rest of the world[b]	190 (68)	190 (68)
ECOG PS, n (%)		
0	183 (66)	187 (67)
1	96 (34)	92 (33)
Curative treatment-free interval, n (%)		
De novo	87 (31)	88 (32)
Recurrent within 6-12 mo	58 (21)	57 (20)
Recurrent > 12 mo	134 (48)	134 (48)

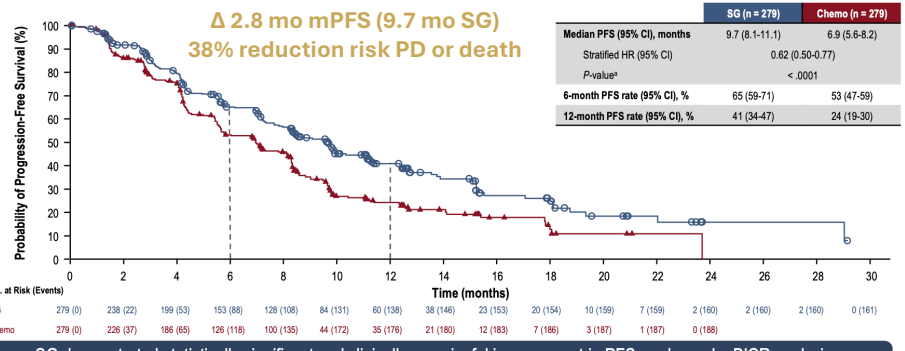
ITT Population	SG (n = 279)	Chemo (n = 279)
PD-L1 status,[c] n (%)		
Negative	277 (99)	278 (> 99)
Positive	1 (< 1)	1 (< 1)
Metastatic sites, n (%)		
Lung	166 (59)	170 (61)
Liver	81 (29)	72 (26)
Brain*	15 (5)	14 (5)
Chemo selected prior to randomization,[d] n (%)		
Taxane	154 (55)	155 (56)
Gemcitabine/carboplatin 2xCT	125 (45)	124 (44)
Prior (neo)adjuvant therapies, n (%)	185 (66)	191 (68)
Taxanes	162 (58)	162 (58)
Capecitabine	50 (18)	57 (20)
Platinum agents	51 (18)	49 (18)
PD-(L)1 inhibitors	13 (5)	11 (4)



PFS benefit of SG over chemo was observed across key prespecified subgroups

Consistent with the results of the primary analysis median PFS longer across all key biomarker subgroups with SG (all Trop-2 expression quartiles; both tBRCAwt and mut status and HER2 IHC0 and low expression subgroups)

Progression-Free Survival by BICR

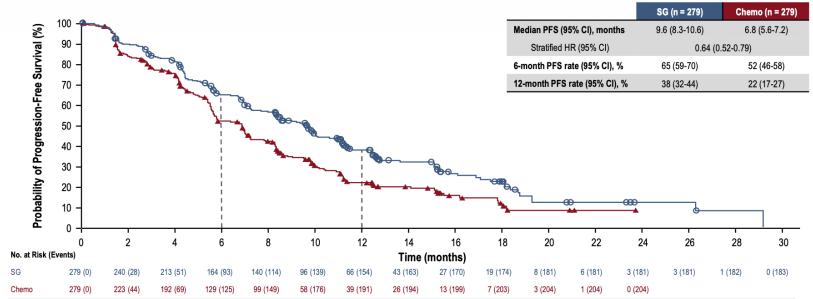


	SG (n = 279)	Chemo (n = 279)
Median PFS (95% CI), months	9.7 (8.1-11.1)	6.9 (5.6-8.2)
Stratified HR (95% CI)	0.62 (0.50-0.77)	
P-value[a]	< .0001	
6-month PFS rate (95% CI), %	65 (59-71)	53 (47-59)
12-month PFS rate (95% CI), %	41 (34-47)	24 (19-30)

SG demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo by BICR analysis, with a 38% reduction in risk of disease progression or death

ASCENT-03 : Secondary efficacy endpoints

Progression-Free Survival by Investigator Assessment[a]



	SG (n = 279)	Chemo (n = 279)
Median PFS (95% CI), months	9.6 (8.3-10.6)	6.8 (5.6-7.2)
Stratified HR (95% CI)	0.64 (0.52-0.79)	
6-month PFS rate (95% CI), %	65 (59-70)	52 (46-58)
12-month PFS rate (95% CI), %	38 (32-44)	22 (17-27)

SG demonstrated improved PFS vs chemo by investigator assessment, consistent with the BICR analysis

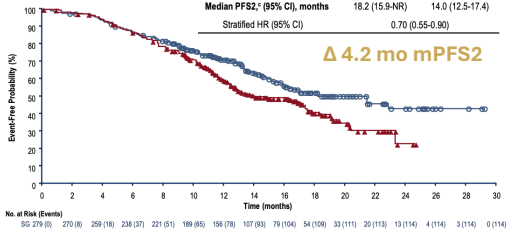
Descriptive Overall Survival and PFS2

Median FU 13.2 mo

- **Overall survival not yet mature[a]** **82%**
- Study continues to first formal OS analysis
- Of 179 patients who initiated subsequent treatment after chemo, 147 (82%) received SG

Overall survival	SG (n = 279)	Chemo (n = 279)
Number of events, %	103 (37)	103 (37)
Median (95% CI) , months	21.5 (17.7-NR)	20.2 (18.2-NR)
Stratified HR (95% CI)	0.98 (0.75-1.30)	
OS rate (95% CI), %		
12-month	75 (70-80)	73 (67-78)
24-month	46 (36-56)	42 (29-54)

Progression-Free Survival 2[b]

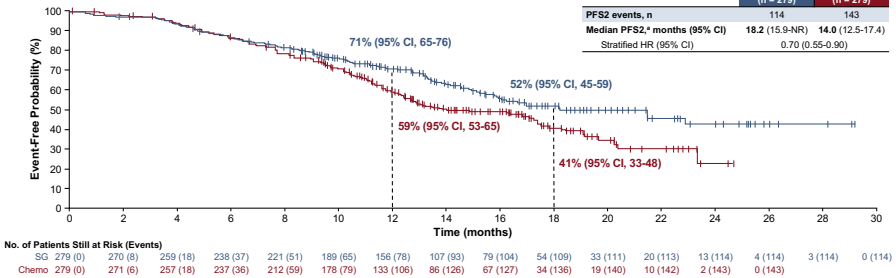


	SG (n = 279)	Chemo (n = 279)
Median PFS2,[c] (95% CI), months	18.2 (15.9-NR)	14.0 (12.5-17.4)
Stratified HR (95% CI)	0.70 (0.55-0.90)	

At the time of primary analysis, overall survival was immature and PFS2 was longer with SG vs chemo by investigator assessment

PFS After Next Line of Treatment (PFS2)

Time to 1st subsequent therapy: 11.2 vs 7.9 mo, HR 0.61 (9.50-0.75)
Time to 2nd subsequent therapy: 17.3 vs 16.6 mo, HR 0.82 (0.64-1.05)

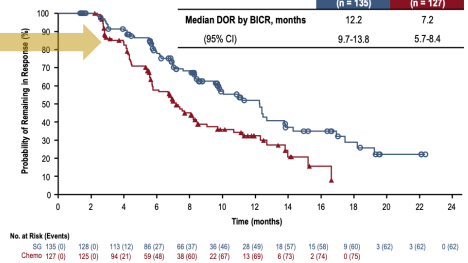


	SG (n = 279)	Chemo (n = 279)
PFS2 events, n	114	143
Median PFS2,[a] months (95% CI)	18.2 (15.9-NR)	14.0 (12.5-17.4)
Stratified HR (95% CI)	0.70 (0.55-0.90)	

Tumor Response

Variable	SG (n = 279)	Chemo (n = 279)
Objective response rate by BICR[a] (95% CI), %	48 (42-54)	46 (40-52)
Stratified odds ratio (95% CI)	1.1 (0.8-1.6)	
Best overall response by BICR, n (%)		
Complete response	20 (7)	15 (5)
Partial response	115 (41)	112 (40)
Stable disease	113 (41)	101 (36)
Stable disease ≥ 6 months	37 (13)	32 (11)
Progressive disease	14 (5)	36 (13)
Not evaluable	17 (6)	15 (5)
Time to response by BICR,[b] median (range), months	1.6 (0.7-16.7)	1.6 (0.9-6.8)

Duration of Response



	SG (n = 135)	Chemo (n = 127)
Median DOR by BICR, months	12.2	7.2
(95% CI)	9.7-13.8	5.7-8.4

Objective response rates were similar in both treatment groups; however, duration of response was substantially longer with SG vs chemo

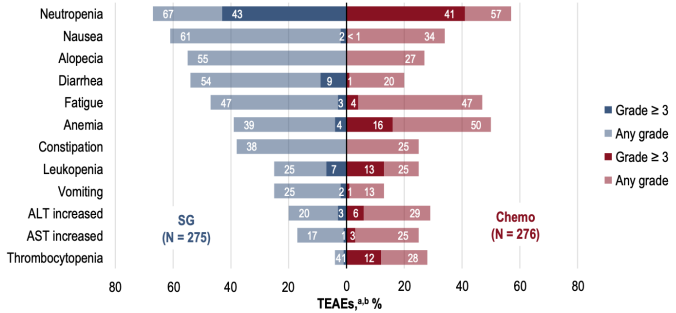
Cortes et al ESMO 2025 & NEJM 2025; Gyawali et al Lancet Oncol 2025; Barrios et al ASCO 2026

ASCENT-03 : QoL and toxicity profile

Safety Summary

TEAEs, n (%)	SG (n = 275)	Chemo (n = 276)
Any TEAE	273 (99)	269 (97)
Grade ≥ 3 TEAEs	181 (66)	171 (62)
Treatment-related	167 (61)	147 (53)
Treatment-emergent SAE	71 (26)	67 (24)
Treatment-related	46 (17)	37 (13)
TEAEs leading to treatment discontinuation	10 (4)	33 (12)
TEAEs leading to dose interruption	181 (66)	171 (62)
TEAEs leading to dose reduction	101 (37)	124 (45)
TEAEs leading to death *	7 (3)	1 (< 1)
Treatment-related	6 (2)	1 (< 1)

Safety Summary: Most Common Adverse Events



The AEs observed are consistent with the known safety profile of SG

In ASCENT-03, SG provided meaningful and sustained benefits in QOL vs chemotherapy; increased GI side effects with SG vs chemotherapy did not impact overall QOL. These data complement the clinically meaningful PFS to support SG as a potential new standard of care for patients with previously untreated advanced TNBC who are not candidates for PD-(L)1 inhibitors

- For key secondary end points, mean change from baseline in physical functioning favored SG vs chemotherapy; time to first deterioration in fatigue was similar between treatment groups

Physical Functioning: Scores were maintained in the SG group and deteriorated in the chemo group

- Exploratory analyses favored SG across multiple domains, including:
  - Change from baseline in global health status/QOL, role functioning, fatigue, pain, and dyspnea
  - TTD in dyspnea
  - TTI in physical, role, and social functioning, as well as fatigue and insomnia

Other Domains: Change from baseline and TTI in multiple domains favored SG

- Change from baseline and TTD in diarrhea and nausea/vomiting favored chemotherapy
- The gastrointestinal side effects of SG were consistent with the known safety profile of SG and can be managed by following established guidelines

GI Side Effects: Symptoms of diarrhea and nausea/vomiting were worse with SG vs chemo

- Safety of SG consistent with its known profile; use of **prophylactic G-CSF is advised** as appropriate (ALL G5 TRAEs related to infection and 5/6 cases related to neutropenia)
- Rates of treatment discontinuations due to TEAEs (4% vs 12%) were lower with SG vs CT

able 3. Management of Neutropenia

Neutropenia, n (%)	SG (n = 275)		Chemo (n = 276)	
Primary G-CSF prophylaxis	**Yes (n = 54)**	**No (n = 221)**	**Yes (n = 28)**	**No (n = 248)**
Any grade	28 (52)	159 (72)	21 (75)	137 (55)
Grade ≥ 3	15 (28)	109 (49)	14 (50)	99 (40)
Secondary G-CSF prophylaxis[a]	**Yes (n = 81)**	**No (n = 75)**	**Yes (n = 51)**	**No (n = 85)**
Any grade	46 (57)	52 (69)	38 (75)	50 (59)
Grade ≥ 3	30 (37)	20 (27)	29 (57)	39 (46)

[a]Excludes participants who received primary G-CSF prophylaxis. Chemo, chemotherapy; G-CSF, granulocyte-colony stimulating factor; SG, sacituzumab govitecan.

TROPION-Breast02: 1L ADC vs CT when IO is not an option

Randomised, phase 3, open-label, global study (NCT05374512)

Key inclusion criteria:
- Patients with histologically or cytologically documented locally recurrent inoperable or metastatic TNBC*
- No prior chemotherapy or targeted systemic therapy in the locally recurrent inoperable or metastatic setting
- Immunotherapy not an option†
- ECOG PS 0 or 1
- No minimum DFI‡

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=323)

Investigator's choice of chemotherapy (ICC)#
Paclitaxel, nab-paclitaxel, capecitabine, eribulin mesylate/eribulin, carboplatin
(n=321)

Endpoints
Dual primary:
- OS
- PFS by BICR per RECIST v1.1

Secondary included:
- PFS (investigator-assessed)
- ORR, DoR
- Safety

Randomisation stratified by:
- Geographic region (US/Canada/Europe vs other geographic regions)
- PD-L1 status (high [CPS ≥10] vs low [CPS <10])§
- DFI history (*de novo* vs prior DFI 0–12 months vs prior DFI >12 months)¶

- Treatment continued until investigator-assessed RECIST v1.1 progressive disease, unacceptable toxicity, or another discontinuation criterion was met
- Following progression or discontinuation of study treatment, patients could receive subsequent therapies, including approved ADCs or chemotherapy, at the investigator's discretion‖

†Including pts with PD-L1-low tumours, or pts with PD-L1-high BC (a) disease relapse after prior PD-(L)1 inh therapy for eBC, (b) comorbidities precluding PD-(L)1 inh, or (c) no regulatory access to PD-(L)1 inh

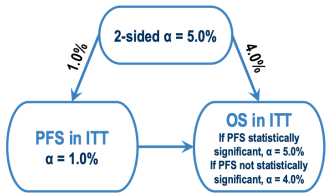
		Dato-DXd (n=323)	ICC (n=321)
Median age (range), years		56 (27–85)	57 (23–83)
Female, n (%)		323 (100)	319 (99)
Race, n (%)	Black or African American	13 (4)	14 (4)
	Asian	151 (47)	131 (41)
	White	131 (41)	153 (48)
	Other*	28 (9)	23 (7)
Geographic region, n (%)	US, Canada, Europe	120 (37)	120 (37)
	Other geographic regions	203 (63)	201 (63)
ECOG PS, n (%)	0	195 (60)	182 (57)
	1	128 (40)	139 (43)
DFI history, n (%)	*De novo*	109 (34)	110 (34)
	Prior DFI 0–12 months‡	67 (21)	66 (21)
	Prior DFI 0–6 months	***47 (15)***	***51 (16)***
	Prior DFI >12 months‡	147 (46)	145 (45)

		Dato-DXd (n=323)	ICC (n=321)
PD-L1 status,† n (%)	Low (CPS <10)	287 (89)	291 (91)
	High (CPS ≥10)	34 (11)	29 (9)
Metastases, n (%)	Visceral	253 (78)	233 (73)
	Liver	93 (29)	98 (31)
	Brain§	36 (11)	28 (9)
Number of metastatic sites, n (%)	<3	207 (64)	215 (67)
	≥3	116 (36)	106 (33)
Pre-selected choice of chemotherapy, n (%)	Nab-paclitaxel	180 (56)	172 (54)
	Paclitaxel	82 (25)	92 (29)
	Eribulin mesylate/eribulin	43 (13)	35 (11)
	Carboplatin	11 (3)	14 (4)
	Capecitabine	7 (2)	8 (2)

*prior (neo) adj: PD-L1 inh 5%; cape 27%; platinum 16%

- **Data cutoff for primary PFS and final OS analysis: August 25, 2025**
  - 408 observed PFS events by BICR (63% maturity)
  - 349 observed OS events (54% maturity)
  - Median study follow-up: 27.5 months (range 13.3–38.7)
  - 45 patients (14%) in the Dato-DXd group and 8 patients (3%) in the ICC group remained on study treatment

Multiple testing procedure with alpha-exhaustive recycling strategy for dual primary endpoints



- Study considered positive if PFS and/or OS analysis were statistically significant

Subsequent ADC therapy

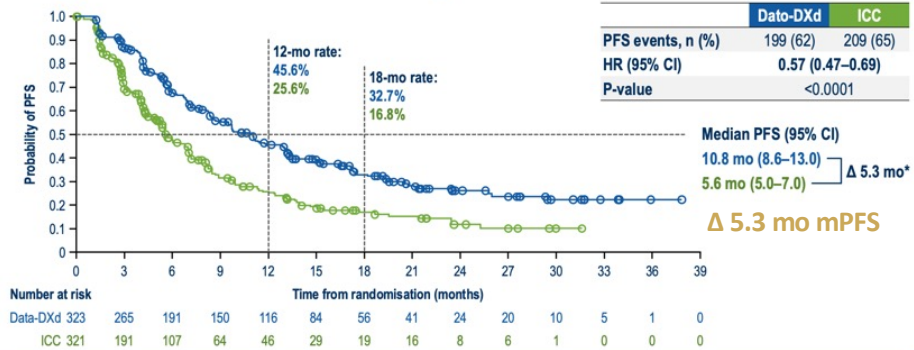
Subsequent therapy (in any treatment line), n (%)	Patients off study treatment at data cutoff: Dato-DXd n=278	ICC n=313
Any subsequent therapy*	210 (76)	232 (74)
Any ADC†	44 (21)	95 (41)
Sacituzumab govitecan	33 (16)	76 (33)
Sacituzumab tirumotecan	0	1 (<1)
Trastuzumab deruxtecan	16 (8)	34 (15)

Most patients in both arms received subsequent therapy, including approved ADCs; the most commonly used ADC was sacituzumab govitecan, followed by trastuzumab deruxtecan

*Percentages are calculated out of the number of patients off study treatment at data cutoff in each treatment group. 100 patients in the Dato-DXd arm and 112 patients in the ICC arm received a second subsequent therapy. †Percentages are calculated out of the number of patients who received any subsequent therapy in each treatment group. Includes sacituzumab govitecan, sacituzumab tirumotecan or trastuzumab deruxtecan only. Two patients in the Dato-DXd arm received disitamab vedotin. Patients could have received more than one ADC and are counted in each row for the ADC they received.
2L, second-line; SoC, standard of care.

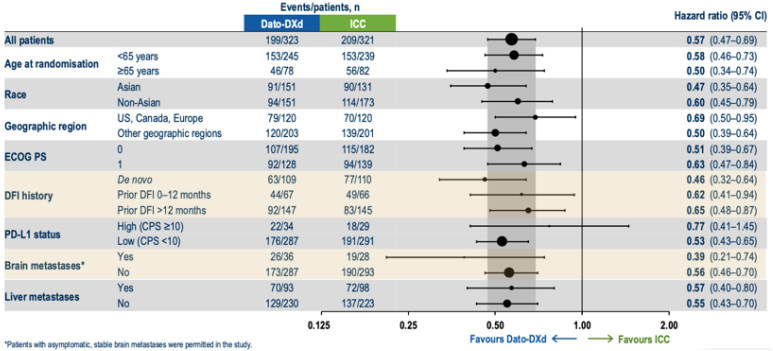
TROPION-Breast02: Dual primary efficacy endpoints

Progression-Free Survival by BICR



	Dato-DXd	ICC
PFS events, n (%)	199 (62)	209 (65)
HR (95% CI)	0.57 (0.47–0.69)	
P-value	<0.0001	

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with ICC, reducing the risk of progression or death by 43%

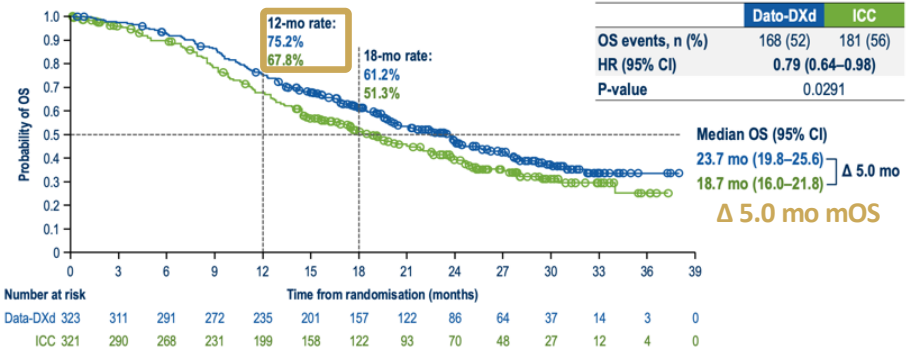


		Dato-DXd	ICC	Hazard ratio (95% CI)
All patients		199/323	209/321	0.57 (0.47–0.69)
Age at randomisation	<65 years	153/245	153/239	0.58 (0.46–0.73)
	≥65 years	46/78	56/82	0.50 (0.34–0.74)
Race	Asian	91/151	90/131	0.47 (0.35–0.64)
	Non-Asian	94/151	114/173	0.60 (0.45–0.79)
Geographic region	US, Canada, Europe	79/120	70/120	0.69 (0.50–0.95)
	Other geographic regions	120/203	139/201	0.50 (0.39–0.64)
ECOG PS	0	107/195	115/182	0.51 (0.39–0.67)
	1	92/128	94/139	0.63 (0.47–0.84)
DFI history	*De novo*	63/109	77/110	0.46 (0.32–0.64)
	Prior DFI 0–12 months	44/67	49/66	0.62 (0.41–0.94)
	Prior DFI >12 months	92/147	83/145	0.65 (0.48–0.87)
PD-L1 status	High (CPS ≥10)	22/34	18/29	0.77 (0.41–1.45)
	Low (CPS <10)	176/287	191/291	0.53 (0.43–0.65)
Brain metastases*	Yes	26/36	19/28	0.39 (0.21–0.74)
	No	173/287	190/293	0.56 (0.46–0.70)
Liver metastases	Yes	70/93	72/98	0.57 (0.40–0.80)
	No	129/230	137/223	0.55 (0.43–0.70)

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Favours Dato-DXd ← → Favours ICC

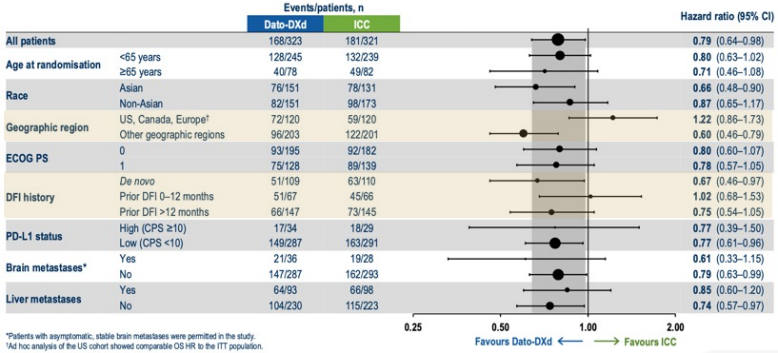
*Patients with asymptomatic, stable brain metastases were permitted in the study.

Overall Survival



	Dato-DXd	ICC
OS events, n (%)	168 (52)	181 (56)
HR (95% CI)	0.79 (0.64–0.98)	
P-value	0.0291	

Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with ICC, reducing the risk of death by 21%



		Dato-DXd	ICC	Hazard ratio (95% CI)
All patients		168/323	181/321	0.79 (0.64–0.98)
Age at randomisation	<65 years	128/245	132/239	0.80 (0.63–1.02)
	≥65 years	40/78	49/82	0.71 (0.46–1.08)
Race	Asian	76/151	78/131	0.66 (0.48–0.90)
	Non-Asian	82/151	98/173	0.87 (0.65–1.17)
Geographic region	US, Canada, Europe†	72/120	59/120	1.22 (0.86–1.73)
	Other geographic regions	96/203	122/201	0.60 (0.46–0.79)
ECOG PS	0	93/195	92/182	0.80 (0.60–1.07)
	1	75/128	89/139	0.78 (0.57–1.05)
DFI history	*De novo*	51/109	63/110	0.67 (0.46–0.97)
	Prior DFI 0–12 months	51/67	45/66	1.02 (0.68–1.53)
	Prior DFI >12 months	66/147	73/145	0.75 (0.54–1.05)
PD-L1 status	High (CPS ≥10)	17/34	18/29	0.77 (0.39–1.50)
	Low (CPS <10)	149/287	163/291	0.77 (0.61–0.96)
Brain metastases*	Yes	21/36	19/28	0.61 (0.33–1.15)
	No	147/287	162/293	0.79 (0.63–0.99)
Liver metastases	Yes	64/93	66/98	0.85 (0.60–1.20)
	No	104/230	115/223	0.74 (0.57–0.97)

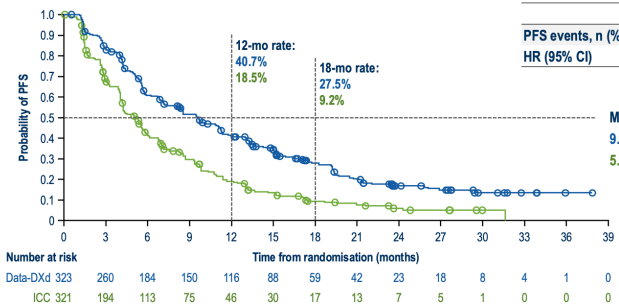
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Favours Dato-DXd ← → Favours ICC

*Patients with asymptomatic, stable brain metastases were permitted in the study.
†Ad hoc analysis of the US cohort showed comparable OS HR to the ITT population.

Dent et al ESMO 2025 & Ann Oncol 2026

TROPION-Breast02: Secondary efficacy endpoints

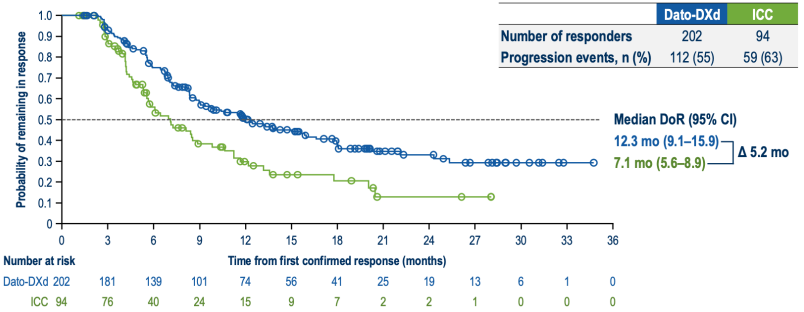
Progression-Free Survival by Investigator Assessment



	Dato-DXd	ICC
PFS events, n (%)	241 (75)	258 (80)
HR (95% CI)	0.56 (0.47–0.67)	

PFS by investigator assessment was consistent with PFS by BICR

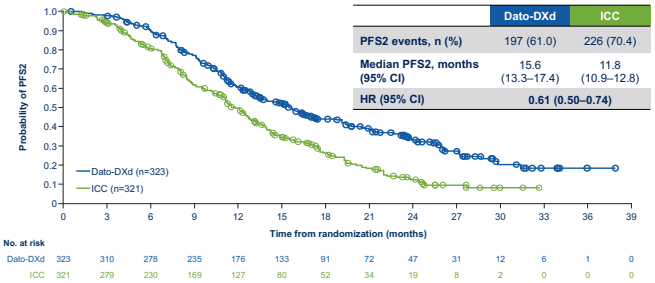
Duration of Response



	Dato-DXd	ICC
Number of responders	202	94
Progression events, n (%)	112 (55)	59 (63)

With Dato-DXd, median duration of response was >1 year

Time to second progression or death (PFS2)

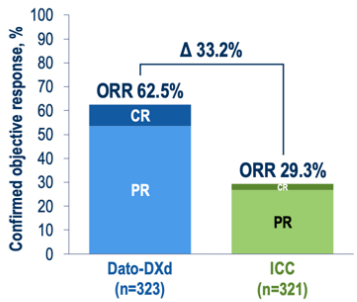


	Dato-DXd	ICC
PFS2 events, n (%)	197 (61.0)	226 (70.4)
Median PFS2, months (95% CI)	15.6 (13.3–17.4)	11.8 (10.9–12.8)
HR (95% CI)	0.61 (0.50–0.74)	

Efficacy benefits were sustained through PFS2, consistent with OS results

Time to 1st subsequent therapy/death: 10.9 vs 5.6 mo HR 0.49 (0.41-0.59)
Time to 2nd subsequent therapy/death: 16.7 vs 12.6 mo HR 0.67 (0.55-0.81)

Response by BICR



	Dato-DXd (n=323)	ICC (n=321)
Confirmed objective response, n (%)	202 (62.5)	94 (29.3)
Odds ratio (95% CI)	4.24 (3.03–5.95)	
Best confirmed objective response, n (%)		
Complete response	29 (9.0)	8 (2.5)
Partial response	173 (53.6)	86 (26.8)
Stable disease	87 (26.9)	151 (47.0)
Progressive disease	27 (8.4)	52 (16.2)
Not evaluable	7 (2.2)	24 (7.5)

With Dato-DXd, confirmed ORR was more than double that with ICC, and confirmed complete response rate was more than three times that with ICC

TROPION-Breast02: QoL and toxicity profile

Safety Summary

- **Median total treatment duration:**
  - Dato-DXd: 8.5 months (range 0.7–38.0)
  - ICC: 4.1 months (range 0.1–32.0)
- **Patients with total exposure >12 months:**
  - Dato-DXd: 35.1%
  - ICC: 9.4%

Treatment-related AEs, n (%)	Dato-DXd (n=319)	ICC (n=309)
Any grade	296 (93)	257 (83)
Grade ≥3	105 (33)	89 (29)
Serious TRAEs	29 (9)	26 (8)
Associated with dose interruption	76 (24)	60 (19)
Associated with dose reduction	85 (27)	56 (18)
Associated with discontinuation	14 (4)	23 (7)
Associated with death	0	0

Despite more than double the median duration of treatment in the Dato-DXd arm, rates of grade ≥3 and serious treatment-related AEs were similar, and discontinuations were lower, with Dato-DXd vs ICC

Most Common Treatment-Related AEs (≥15% of Patients)

Treatment-related AEs, n (%)	Dato-DXd (n=319)		ICC (n=309)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Dry eye*	76 (24)	4 (1)	9 (3)	0
Stomatitis	182 (57)	27 (8)	27 (9)	0
Nausea	142 (45)	2 (<1)	53 (17)	2 (<1)
Constipation	72 (23)	1 (<1)	31 (10)	0
Vomiting	65 (20)	4 (1)	23 (7)	1 (<1)
Decreased appetite	49 (15)	1 (<1)	20 (6)	1 (<1)
Neutropenia†	39 (12)	10 (3)	90 (29)	40 (13)
Anaemia‡	48 (15)	6 (2)	64 (21)	10 (3)
Leukopenia§	27 (8)	3 (<1)	55 (18)	13 (4)
Peripheral neuropathy¶	14 (4)	0	75 (24)	5 (2)
Alopecia	130 (41)	0	96 (31)	1 (<1)‖
Fatigue#	101 (32)	8 (3)	86 (28)	9 (3)

In TROPION-Breast02, the improved efficacy observed with Dato-DXd compared with ICC was complemented by **meaningful and sustained improvements in QoL outcomes**

- The impact of Dato-DXd on patients' symptoms, functioning and GHS/QoL was favourable compared with ICC, even though patients received Dato-DXd for longer
- TTD in GHS/QoL, physical functioning, pain, and breast and arm symptoms was delayed with Dato-DXd versus ICC, and mean change from baseline numerically favoured the Dato-DXd arm
- TTD was delayed in the Dato-DXd arm for the majority of other functioning and symptom scales
- Patient-reported symptomatic AEs were generally consistent with clinician-reported safety data, with limited interference affecting patients' daily activities

These PRO data further support Dato-DXd as a new first-line standard of care in patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy is not an option

Treatment-Related AESIs for Dato-DXd

AESI category, n (%) Preferred term*	Dato-DXd (n=319)			ICC (n=309)		
	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis†	78 (24)	87 (27)	27 (8)	22 (7)	8 (3)	0
Stomatitis	72 (23)	83 (26)	27 (8)	19 (6)	8 (3)	0
Ocular surface events‡§	76 (24)	50 (16)	23 (7)	9 (3)	5 (2)	1 (<1)
Dry eye	51 (16)	21 (7)	4 (1)	6 (2)	3 (1)	0
Keratitis	21 (7)	14 (4)	7 (2)	1 (<1)	0	0
Conjunctivitis	7 (2)	13 (4)	1 (<1)	0	0	0
Adjudicated drug-related ILD/pneumonitis¶	1 (<1)	7 (2)	1 (<1)#	1 (<1)	1 (<1)	0

Treatment-related oral mucositis/stomatitis:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 11 (3%), 36 (11%), and 0 patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 103/114 patients (90%) at data cutoff

Treatment-related ocular surface events:

- In the Dato-DXd arm, events led to dose interruption, reduction, and discontinuation in 18 (6%), 14 (4%), and 3 (<1%) patients, respectively
- Grade ≥2 events resolved to grade ≤1 in 49/73 patients (67%) at data cutoff

Choosing the 1L ADC in aTNBC: “personalized” selection

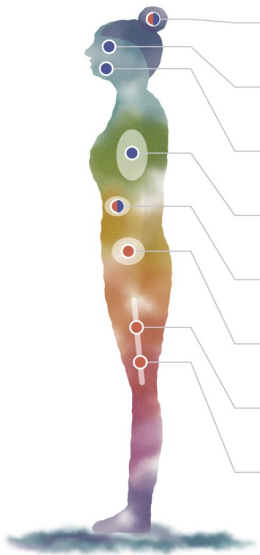
When efficacy is comparable, the toxicity profile, comorbidities and schedule guide the choice

Dato-DXd 6 mg/kg q21d

Main burden: mucosal and ocular (stomatitis, dry eye/keratitis); lo grade haematological toxicity
Management: prophylactic steroid mouthwash, preservativ free eye drops, ophthalmology follow-up
Consider: pre-existing ocular o mucosal disease; ILD monitorin

SG 10 mg/kg D1,8 q21d

Main burden: haematological and gastrointestinal (neutropenia, diarrhoea, alopecia)
Management: G-CSF prophylaxis as appropriate; early loperamide plan
Consider: UGT1A1*28 homozygosity (?), limited marrow reserve



Any grade · Grade ≥3

	Sacituzumab govitecan (ASCENT-03 · n=275)	Datopotamab deruxtecan (TROPION-Breast02 · n=319)
Alopecia (Hair)	55%	41%
Keratitis (Eye · dry eye 24%, G≥3 1% (Dato))	—	13% · G≥3 2%
Stomatitis (Oral mucosa)	—	57% · G≥3 8%
ILD / pneumonitis (Lung · adjudicated; 1 fatal (0.3%))	—	~3% · G≥3 <1%
Nausea (Upper GI)	61% · G≥3 2%	48% · G≥3 <1%
Diarrhea (Lower GI)	54% · G≥3 9%	—
Neutropenia (Bone marrow)	67% · G≥3 43%	12% · G≥3 3%
Anemia (Blood)	39% · G≥3 4%	15% · G≥3 2%
Dose reductions · discontinuation	37% · 4% Prevent: G-CSF primary prophylaxis if FN risk · early loperamide	27% · 4% Prevent: steroid mouthwash · eye drops + eye exams · ILD vigilance

Cross-trial comparison, not head-to-head: both enrolled patients not candidates for PD-(L)1 inh with different eligibility details and control arms. AEs rates from label tables;. — : not among AEs≥10%. Not shown: asymptomatic amylase ↑ with Dato-DXd (any 54%, G3–4 38%, lab)

Cortés et al. NEJM 2025 & ESMO 205; Dent et al Ann Oncol 2026 & ESMO 2025; Cardoso et al. Breast 2026; ; TRODELVY® and DATROWAY® US Prescribing Information.

05

New therapeutic scenarios & Clinical challenges

CNS disease and later lines treatment



New ADCs (Sac-TMT) in 1L aTNBC with alternative selection strategies

OptiTROP-Breast05

Open-label phase II trial (NCT05445908)
PD(L)-1 unselected

Key eligibility criteria
- No prior systemic therapy for a/m TNBC
- PD-L1 positive or negative[a]
- DFI ≥6 months
- ECOG PS 0–1

→ **Sac-TMT (5 mg/kg Q2W)** → Treatment until disease progression or unacceptable toxicity

Primary endpoint[b]
- ORR by investigator assessment

Secondary endpoints
- PFS, DOR, DCR, OS
- Safety

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

Antitumor Responses

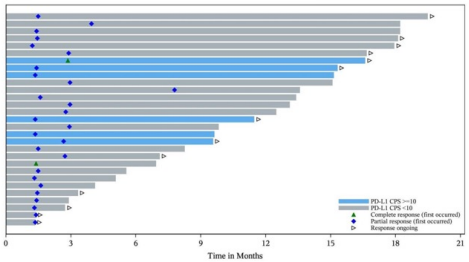
Antitumor Responses were observed regardless of PD-L1 expression. 78% (N=32) PD-L1 <10 and 22% (N=9) PD-L1 ≥10

	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.



- **ALL pts: mPFS 13.4 mo (12 mo PFS rate 64.6%)**
- PD-L1 CPS <10 : mPFS 13.1 mo (12mo PFS rate 59.1%)
- TRAEs G≥3 63.4% of pts (↓neutrophil count (46.3%), ↓WBC count (34.1%), anemia (12.2%), stomatitis (9.8%), ↓lymphocyte count (7.3%) and fatigue (7.3%))

TRoFuse-011

Randomized open-label phase III trial (NCT06841354)
PD-L1 negative ADC+ICI combo

Key eligibility criteria
- Previously untreated locally recurrent or metastatic TNBC with PD-L1 CPS <10
- Participants previously treated for early-stage breast cancer:
  - Must have completed treatment with curative intent ≥6 mo before first recurrence
  - Must have received (neo)adjuvant anthracycline and/or taxane (unless contraindicated)
  - May have received prior (neo)adjuvant ICI
- Participants with de novo metastatic TNBC are eligible if, in the investigator's opinion, the study intervention is in the best interest of the participant
- Must be a candidate for pembrolizumab and for 1 of the TPC options
- No active CNS metastases
- Measurable disease per RECIST version 1.1
- ECOG PS 0 or 1

Stratification factors
- TROP2 expression per IHC (low vs medium vs high)
- Disease status (de novo metastatic vs DFI ≥6 mo and <12 mo vs DFI ≥12 mo)
- Tumor PD-L1 expression (CPS <1 vs CPS 1–9)

→ **R (2:1:2) N ~ 1000**

- **Arm A**: Sac-TMT 4 mg/kg IV Q2W[a]
- **Arm B**: Sac-TMT 4 mg/kg IV Q2W[a] + Pembrolizumab 400 mg IV Q6W[b]
- **Arm C**: TPC[c]

Primary endpoints
- PFS per RECIST version 1.1 by BICR (arm A vs C and arm B vs C)
- OS (arm A vs C)

Secondary endpoints
- OS (arm B vs C and arm A vs B)
- PFS per RECIST version 1.1 by BICR (arm A vs B)
- ORR per RECIST version 1.1 by BICR (arm A vs C and arm B vs C)
- DOR
- HRQoL using EORTC QLQ-C30 (arm A vs C and arm B vs C)
- Safety

Yin et al ASCO 2025; Rugo et al Future Oncol 2026

(1) Pretreated aTNBC: new ADCs 2L+ (still Anti-TROP2/TOP1i)

OptiTROP-Breast01

Randomized phase III_ADC vs CT (NCT05347134)

Key Eligibility Criteria
- ECOG PS 0 or 1
- Histologically confirmed unresectable locally advanced or metastatic TNBC
- ≥2 prior systemic therapies, including ≥1 for metastatic disease
- Prior taxane therapy

R 1:1, N = 263

- **Sac-TMT** 5 mg/kg IV, Q2W (n = 130)
- **Physician's choice of chemotherapy:** eribulin, capecitabine, gemcitabine, or vinorelbine (n = 133)

Primary endpoint
- PFS assessed by BICR

Secondary endpoints
- OS (key secondary endpoint)
- Investigator-assessed PFS
- ORR, DCR, DOR
- Safety

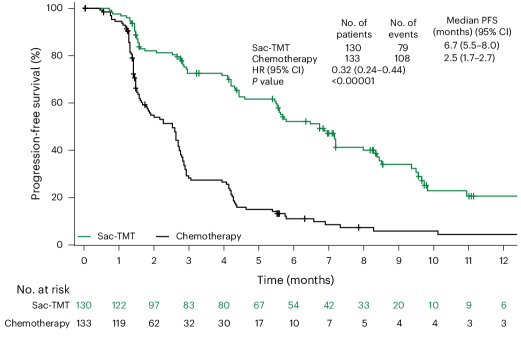
Stratification factors
- Number of prior lines of therapy (2–3 vs >3)
- Presence of liver metastases (yes vs no)

Patients received sac-TMT or chemotherapy until disease progression, unacceptable toxicity or any other reason for discontinuation

Characteristic	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)

Characteristic	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)

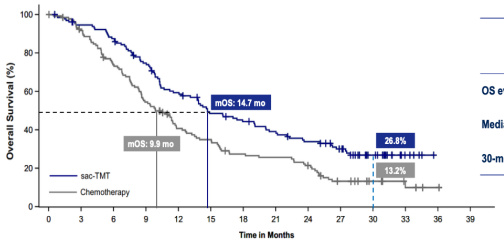
a PFS by BICR (final analysis)



Safety-related variables	Sac-TMT (n = 130) n (%)		Chemo (n = 132) n (%)	
TRAEs	130 (100)		127 (96.2)	
Grade ≥3 TRAEs	84 (64.6)		76 (57.6)	
Serious TRAEs	28 (21.5)		18 (13.6)	
TRAEs leading to discontinuation	2 (1.5)		2 (1.5)	
TRAEs leading to death	1 (0.8)[*]		0	
Selected common TRAEs[†]	All grade	Grade ≥3	All grade	Grade ≥3
Anemia	108 (83.1)	38 (29.2)	72 (54.5)	8 (6.1)
NEUT count decreased	102 (78.5)	47 (36.2)	98 (74.2)	62 (47.0)
WBC count decreased	100 (76.9)	38 (29.2)	101 (76.5)	48 (36.4)
Stomatitis	65 (50.0)	13 (10.0)	6 (4.5)	1 (0.8)
PLT count decreased	54 (41.5)	17 (13.1)	34 (25.8)	5 (3.8)
Nausea	52 (40.0)	0	26 (19.7)	0
Vomiting	46 (35.4)	0	18 (13.6)	0
Rash	44 (33.8)	5 (3.8)	1 (0.8)	0
ALT increased	37 (28.5)	1 (0.8)	47 (35.6)	0
AST increased	32 (24.6)	3 (2.3)	63 (47.7)	1 (0.8)

Overall Survival

Sac-TMT demonstrated a sustained OS benefit over chemotherapy, with a 40% reduction in the risk of death.



	Sac-TMT (n = 130)	Chemo (n = 133)
OS events, n (%)	88 (67.7)	109 (82.0)
Median OS, mo (95% CI)	14.7 (12.1, 20.1)	9.9 (8.6, 11.8)
30-mo OS rate, % (95% CI)	26.8 (19.0, 35.2)	13.2 (7.8, 20.0)

HR 0.60 (95% CI: 0.45–0.80)
Nominal *P* = 0.0004

Median follow-up: 29.4 months. Final OS analyses were descriptive. OS met the prespecified significance criterion at the interim analysis.

Data cutoff: 17 September 2025. CI, confidence interval; mo, month.

↑crossover

	Sac-TMT (n = 130)	Chemo (n = 133)
Subsequent anticancer therapy, n (%)	88 (67.7)	98 (73.7)
Chemotherapy	75 (57.7)	82 (61.7)
Targeted therapy	55 (42.3)	65 (48.9)
ADC	24 (18.5)	37 (27.8)
TROP2-directed ADCs	6 (4.6)	29 (21.8)
SG/Dato-DXd/others	3 (2.3) / 0 / 3 (2.3)	17 (12.8) / 5 (3.8) / 7 (5.3)
HER2-directed ADCs	16 (12.3)	11 (8.3)
T-DXd/others	15 (11.5) / 2 (1.5)	8 (6.0) / 3 (2.3)
ADCs with other targets	5 (3.8)	4 (3.0)
Immunotherapy	18 (13.8)	20 (15.0)

Final OS



HR 0.60 (95% CI 0.45–0.80); Nominal *P* = 0.0004

RPSFT-adjusted OS



HR 0.55 (95% CI 0.39–0.73)

Yin et al Nat Medicine 2025; Cu et al ESMO 2026

(1) Pretreated aTNBC: new ADCs 2L+ (TOP1i but Bispecific)

PANKU-Breast02

Open-label phase III_ADC vs CT in 2L+ (NCT06382142)

A multicenter, randomized, open-label, phase III study conducted at 81 study centers across China.

Key eligibility criteria:

- Unresectable locally advanced or metastatic TNBC
- Progressed after 1–2 prior lines of systemic therapy for advanced disease—including prior taxanes
- Measurable lesion per RECIST v1.1
- ECOG PS 0-1

Treatment until
Disease progression per RECIST v1.1 or intolerable toxicity

R 1:1
N=406

Iza-bren
2.5 mg/kg D1D8 Q3W

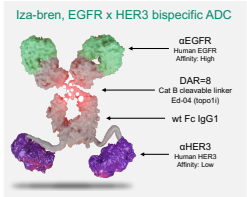
Chemotherapy
- Eribulin, D1D8 Q3W
- Capecitabine, BID, Q3W
- Gemcitabine, D1D8 Q3W
- Vinorelbine, D1D8 Q3W

Stratified by
- Previous lines of chemotherapy (1 line vs 2 lines)
- Prior anti-PD(L)-1 (yes vs no)
- HER2 expression (IHC 0 vs IHC 1+/2+ ISH-)

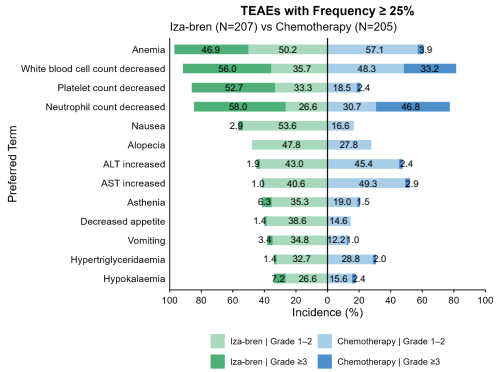
Dual primary endpoints
PFS (BICR) & OS
H_{PFS} α=0.025 → H_{OS} α=0

Secondary endpoints
ORR (BICR)
PFS (INV)
DCR, DoR, Safety, PK, Immunogenicity

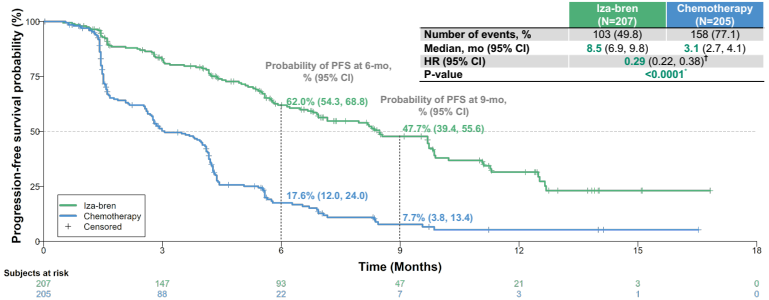
Note: The planned enrollment was 406 subjects. Iza-bren was dosed with 10% compensation per protocol; eribulin 1.4 mg/m² on days 1 and 8 Q3W; capecitabine 1000-1250 mg/m², BID from days 1 to 14 Q3W; gemcitabine 1000 mg/m² on days 1 and 8 Q3W; vinorelbine 25 mg/m² on days 1 and 8 Q3W.



- 69-70% 1L prior and 29-30% 2L prior
- 23-24% Anti-PD (L)1 prior
- 78-79% prior (neo)adjuvant Tx
- 31-36% liver and 36-38% bone mets
- 53-54% HER2 (IHC0)



PFS (BICR): Dual Primary Endpoint

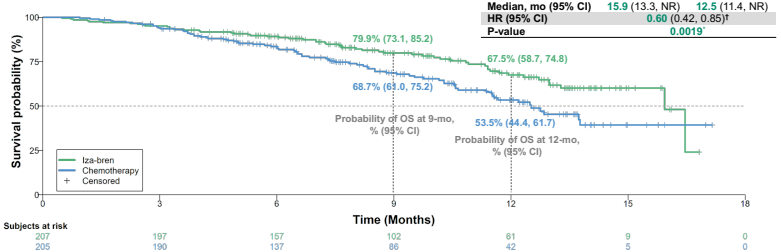


	Iza-bren (N=207)	Chemotherapy (N=205)
Number of events, %	103 (49.8)	158 (77.1)
Median, mo (95% CI)	8.5 (6.9, 9.8)	3.1 (2.7, 4.1)
HR (95% CI)	0.29 (0.22, 0.38)†	
P-value	<0.0001*	

Iza-bren showed statistically significant and clinically meaningful improvement in PFS vs chemotherapy (median Δ 5.4 mo).

PFS (BICR) was evaluated in the mITT population. The median duration of follow-up for PFS was 8.5 months.
Similar results were observed for PFS (BICR) in the ITT population, with 103 events in the iza-bren arm and 158 events in the chemotherapy arm. The hazard ratio (95% CI) was 0.29 (0.22,0.38).
†Based on a stratified Cox regression model. *One-sided, based on a stratified log-rank test.

OS: Dual Primary Endpoint



	Iza-bren (N=207)	Chemotherapy (N=205)
Number of events, %	56 (27.1)	77 (37.6)
Median, mo (95% CI)	15.9 (13.3, NR)	12.5 (11.4, NR)
HR (95% CI)	0.60 (0.42, 0.85)†	
P-value	0.0019*	

Iza-bren showed statistically significant and clinically meaningful improvement in OS vs chemotherapy (median Δ 3.4 mo) at pre-specified interim analysis.

OS was evaluated in the mITT population, with a median follow-up duration of 11.0 months. The pre-specified interim analysis was planned upon the observation of 255 BICR-confirmed PFS event, with approximately 175 OS events (70% information fraction) expected at the same time. At the analysis, the actual information fraction was 53.2%. **A P-value of 0.0021 was required for interim analysis superiority.**
Similar results were observed for OS in the ITT population, with 56 events in the iza-bren arm and 77 events in the chemotherapy arm. The hazard ratio (95% CI) was 0.60 (0.42, 0.85).
†Based on a stratified Cox regression model. *One-sided, based on a stratified log-rank test.

IZABRIGHT-Breast01: Pts with previously untx, metastatic TNBC or ER-low, HER2-negative breast cancer ineligible for anti-PD-(L)1 and endocrine therapies

(1) Pretreated aTNBC: new ADCs (new targets & new payloads)

Emiltatug Ledadotin
(Emi-Le; XMT-1660)
B7-H4-directed ADC



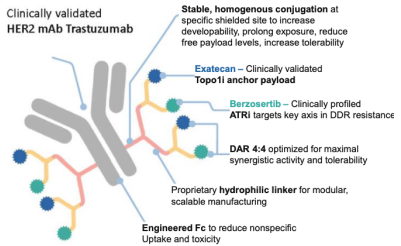
- B7-H4-directed ADC with proprietary auristatin F-HPA microtubule inhibitor payload
- Target-optimized DAR 6
- Designed with controlled bystander effect (different from MMAE, MMAF and topo-1)
- FDA fast track designation in breast

	TNBC (N=63)	HR+/HER2- MBC (N=37)	Total (N=141)
Median age	48	62	55
ECOG PS, n(%)			
0	30 (47.6%)	13 (35.1%)	66 (46.8%)
1	33 (52.4%)	24 (64.9%)	75 (53.2%)
Median prior lines of therapy (range)	5 (2-9)	7 (2-15)	4 (0-15)
Prior Topo-1 ADCs received, n (%)			
Prior trastuzumab deruxtecan	21 (33.3%)	15 (40.5%)	36 (25.5%)
Prior sacituzumab govitecan	54 (85.7%)	15 (40.5%)	70 (49.6%)
Prior both	17 (27.0%)	10 (27.0%)	27 (19.1%)
Prior either	58 (92.1%)	20 (54.1%)	79 (56.0%)
B7-H4 Expression[1], n (%)			
TPS Known	53 (84.1%)	31 (83.8%)	116 (82.3%)
High (TPS ≥70)	24 (45.3%)	8 (25.8%)	48 (41.4%)
Low (TPS <70)	29 (54.8%)	23 (74.2%)	68 (58.6%)
TPS Unknown	10 (15.9%)	6 (16.2%)	25 (17.7%)

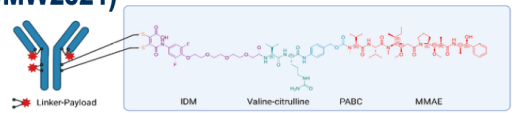
- **93% of TNBC previously tx with a topo-1 ADC**
- ~41% had high B7-H4, based on a TPS cutoff of ≥70%

CLIO-8221
Dual Payload ADC : HER2 x Topo1i + ATRi

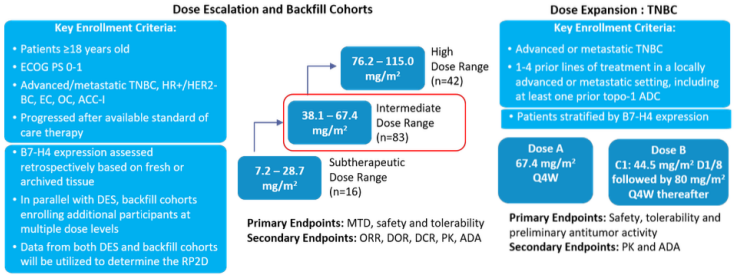
- Demonstrates activity in T-DXd insensitive or resistant settings (CDX) and patient derived xenograpft models (PDX)



Bulumtatug Fuvedotin (BFv, 9MW2821)

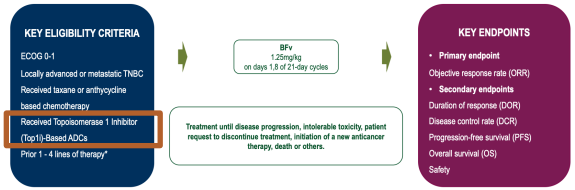


Emi-Le Phase 1 dose escalation/expansion study in MBC



Emi-Le had encouraging clinical activity (**ORR 23%**) in and tolerability in heavily pre-tx TNBC (median of 4 prior lines of therapy) with high B7-H4 expression and **previously treated with topo-1 ADC**

- Across all tumor types, in evaluable patients treated in the intermediate dose range (38.1-67.4 mg/m2) the **ORR was 31%**



1.25 mg/kg, D1,D8,Q3W (N= 60)	
ORR (95% CI)	30.0 (18.85,43.21)
DCR (95% CI)	80.0 (67.67, 89.22)

		1.25 mg/kg, D1,D8,Q3W (n=60)
Age Median (range)		50.5 (32,73)
ECOG PS n(%)	0	11 (18)
	1	49 (82)
Metastatic sites n(%)	Visceral metastasis	39 (65)
	Liver metastasis	20 (33)
	Brain metastasis	4 (7)
Nectin-4 expression	Positive (TPS ≥1%)	39 (65)
	Negative (TPS <1%)	13 (22)
	unknown	8 (13)

		1.25 mg/kg, D1,D8,Q3W (n=60)
Prior lines of therapy n(%)	1 line	10 (17)
	2 lines	25 (42)
	3 lines	22 (37)
	4 lines	3 (5)
Prior treatment n(%)	Taxane	60 (100)
	Anthracycline	46 (77)
	Platinum	21 (35)
	Checkpoint in hibitor	21 (35)
	HER-2 ADC*	20 (33)
	TROP2 ADC*	29 (48)
	Other ADC	12 (20)

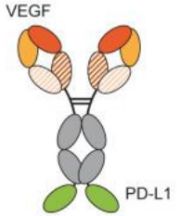
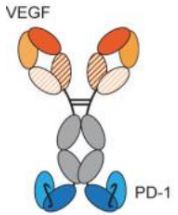
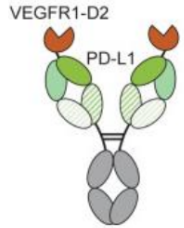
1.25 mg/kg, D1,D8,Q3W (N= 60)	
Number of events,n (%)	5
MedianDOR, months (95% CI)	8.8 (8.51, NR)
6-month DOR rate, % (95% CI)	81.5 (61.14, 100.00)

1.25 mg/kg, D1,D8,Q3W (N= 60)	
Number of events,n (%)	47
MedianPFS, months (95% CI)	3.7 (2.96, 4.40)
6-month PFS rate, % (95% CI)	30.2 (20.00, 45.49)

Hamilton E @ESMO 2026; Hamilton et al ASCO 2025; Yap T ASCO 2026; Zhang et al ESMO 2026

(1) Pretreated aTNBC: new combined IO approaches (new targets)

PD-(L)1 X VEGF Bispecific

	Pumitamig / BNT327	Ivonescimab / AK112 / SMT112	HB0025
			
Checkpoint X VEGF Target	**PD-L1 x VEGF-A**	**PD-1 x VEGF-A**	**PD-L1 x VEGF trap**

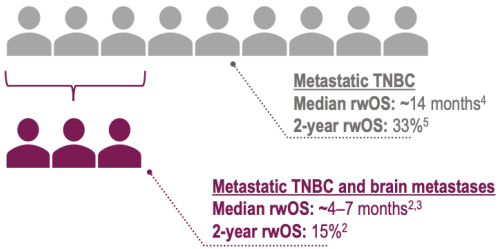
Key Breast Data	**PM8002-B004C-TNBC-R** (NCT05918133)[1]
	• Phase 1b/2, **1L TNBC**
	• BNT327 + nab-pac vs nab-pac
	• N=42
	  • **ORR: 78.6%** | mPFS: 13.5 months
	
	ROSETTA Breast-01 (NCT07173751)
	• Phase 3, 1L PD-L1–neg TNBC
	• BNT327+ chemo vs placebo
	• N=558
	  • PFS & OS
	
	PM8002-C013C-TNBC-R (NCT06419621)
	• Phase 3, 1L TNBC
	• BNT327 + nab-pac vs placebo
	• N~83
	  • PFS & OS
		AK117-203 (NCT05227664)[2,3]
		• Phase 2, **1L mTNBC**
		• Ivonescimab+ pac vs placebo + nab-pac
		• N~36, China
		  • **ORR: 80.0%** |DCR: 100%
		  • mPFS: 15.2 mo | 12-mo PFS:56.3%
		
		HARMONi-BC1 (NCT06767527)
		• Phase 3, 1L mTNBC
		• Ivonescimab+ nab-pac vs placebo + nab-pac
		• N~416, China
		  • PFS & OS
			HB0025-C-0201 (NCT07376629)[4]
			• Phase 2, **1L mTNBC**
			• N~ 66
			• HB0025+ nab-pac; escalation/expansion

1. WU J et al. ESMO 2024 Abstr 384MO
2. Shao X et al. *Nature Medicine* 202
3. Ouyang et al., ESMO IO 2025 129
4. Meng et al., ESMO Breast 2026 493
Alvarez-Vallina L & Sanz L. *Front Immunol*, 202

@ErikaHamilton9

(2) Brain metastases: TROPION-Breast02 exploratory analysis

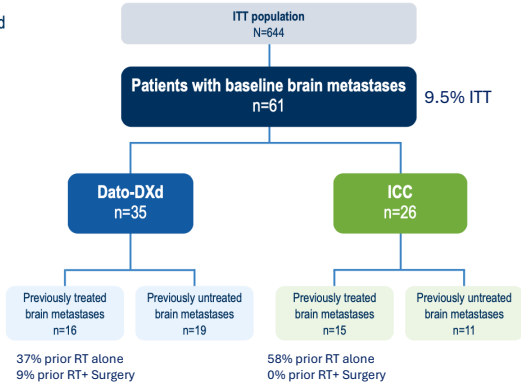
~1/3 of patients with metastatic TNBC will develop brain metastases during their disease, and have particularly poor prognosis[1–3]



Key inclusion criteria:

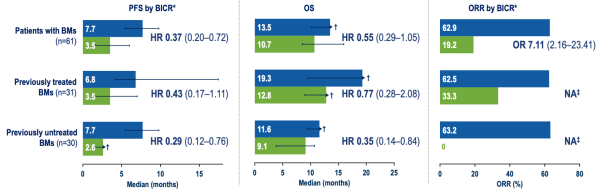
- Patients with previously untreated locally recurrent inoperable or metastatic TNBC
- Immunotherapy not an option
- No minimum DFI
- **Patients with asymptomatic treated or untreated brain metastases at baseline were eligible**

- For patients with brain metastases documented at baseline, brain MRI or CT was mandated at baseline, Q6W for 48 weeks, then Q9W until RECIST v1.1 progression
  - Patients with no baseline brain metastases did not require additional brain scans after screening unless clinically indicated
- Systemic responses were assessed per RECIST v1.1
- Intracranial responses were assessed per CNS-modified RECIST v1.1



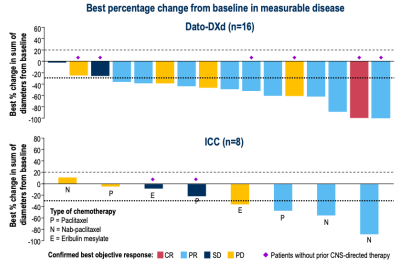
Systemic Efficacy in Patients With Brain Metastases

In patients with or without prior CNS-directed therapy



Intracranial Response in Patients with Measurable Disease

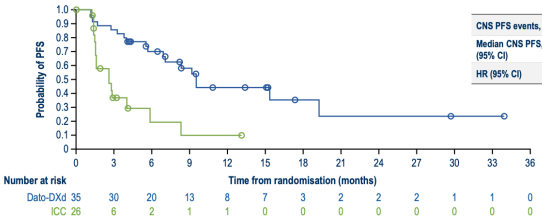
	Measurable disease*	
	Dato-DXd (n=16)	ICC (n=8)
Intracranial confirmed ORR,† %	62.5	37.5
Intracranial DCR at 12 weeks, %	75.0	50.0



In patients with measurable disease, Dato-DXd demonstrated a confirmed intracranial ORR of 62.5% vs 37.5% with ICC

*Measurable disease defined as patients with TLs at baseline. TLs defined as: contrast enhancing, suitable for accurate repeated measurements, and ≥10 mm in ≥1 dimension with CT or MRI or no less than double the slide thickness, whichever was largest. Intracranial disease that did not qualify as a TL or any surplus in TLs was classified as intracranial NTLs. †Intracranial confirmed ORR defined as the percentage of patients with ≥2 visits with a CNS response of PR or CR by CNS BICR per CNS-modified RECIST v1.1. Dashed lines represent thresholds for PR (-30%) and PD (20%).

CNS PFS in Patients with Brain Metastases



	Dato-DXd n=35*	ICC n=26*
CNS PFS events, n (%)†	18 (51.4)	16 (61.5)
Median CNS PFS, months (95% CI)	9.5 (6.9–19.3)	2.6 (1.5–5.8)
HR (95% CI)	0.27 (0.13–0.56)	

Dato-DXd demonstrated CNS PFS benefit compared with ICC, with an HR of 0.27

*Analysis included patients with any brain scan at baseline; †CNS PFS was defined as the time from randomisation to intracranial progression (determined by CNS BICR per CNS-modified RECIST v1.1) or death. Patients without an event were censored at their last evaluable CNS-modified RECIST assessment; events occurring after ≥2 consecutive missed assessments were censored at the last evaluable assessment before the event. CNS PFS events listed only include events that occurred within 2 assessments of the last evaluable assessment (CNS-modified RECIST progression: Dato-DXd: n=15 [42.9%], ICC: n=15 [57.7%] and death in the absence of progression: Dato-DXd: n=3 [8.6%], ICC n=1 [3.8%]).

(2) Brain metastases: Dato_DXd in aTNBC with active BMs: TUXEDO-2

Phase II Study of Dato-DXd in Triple-negative Breast Cancer Patients With Newly Diagnosed or Progressing Brain Metastases (TUXEDO-2)

Active, not recruiting
No longer looking for participants

ClinicalTrials.gov ID NCT05866432

Sponsor Medical University of Vienna

- Histologically confirmed triple-negative breast cancer
- Radiologically documented metastatic disease
- Newly diagnosed brain metastases or brain metastases progressing after prior local therapy
- Measurable disease (RANO-BM criteria)
- No indication for immediate local treatment
- Leptomeningeal disease allowed
- KPS ≥70%, ECOG ≤2
- Indication for systemic therapy
- Minimum of one prior line of chemotherapy for early or advanced disease
- Prior treatment with IOs, PARPi and/or TROP-2 directed compounds allowed
- Life expectancy of at least 3 months
- Age >18 years
- LVEF ≥50%

→ Datopotamab-deruxtecan (6.0 mg/kg i.v. once every three weeks)

→ Treatment until progression, unacceptable toxicity or withdrawal for any reason

→ Futher treatment according to local standard

Safety FU four weeks after EOT

Survival FU at 6, 12, and 18 months

Dato-DXd in pts. with TNBC active BM
Single-arm phase II
Primary endpoint: ORR (RANO-BM)
Simon Optimal Two Stage Design

Results Stage I
- **ITT ORR 37.5% (3/8)**
- **PP ORR 42.9% (3/7)**
- **PP without prior SG ORR 60% (3/5)**

Bartsch et al ESMO Breast 2024; https://clinicaltrials.gov/study/NCT05866432?cond=breast%20cancer&term=tuxedo-2&viewType=Card&rank=1

(2) Brain metastases: ASCENT-03 subgroup analysis

Patients with previously untreated, locally advanced inoperable or metastatic TNBC[a]:

- Not candidates for PD-(L)1 inhibitors:
  - PD-L1 negative[b] tumors (CPS < 10)
  - PD-L1 positive[b] tumors (CPS ≥ 10) and previously treated with a PD-(L)1 inhibitor in curative setting
  - Ineligible for a PD-(L)1 inhibitor due to a comorbidity
- ≥ 6 months since treatment in curative setting
- Previously treated, stable CNS metastases were allowed

Characteristics	ITT Population		Brain Metastases			
			Yes		No	
	SG (n = 279)	Chemo (n = 279)	SG (n = 15)	Chemo (n = 14)	SG (n = 264)	Chemo (n = 265)
Median age (range), years	56 (28-84)	54 (23-86)	55 (38-74)	56 (36-77)	56 (28-84)	54 (23-86)
≥ 65 years, n (%)	65 (23)	78 (28)	2 (13)	2 (14)	63 (24)	76 (29)
Race or ethnic group,[a] n (%)						
White	178 (64)	178 (64)	9 (60)	8 (57)	169 (64)	170 (64)
Asian	66 (24)	65 (23)	6 (40)	4 (29)	60 (23)	61 (23)
Black	10 (4)	7 (3)	0	0	10 (4)	7 (3)
Other or not specified	25 (9)	29 (10)	0	2 (14)	25 (9)	27 (10)
Geographic region, n (%)						
Canada/United States/Western Europe	89 (32)	89 (32)	1 (7)	1 (7)	88 (33)	88 (33)
Rest of the world[b]	190 (68)	190 (68)	14 (93)	13 (93)	176 (67)	177 (67)
ECOG PS, n (%)						
0	183 (66)	187 (67)	4 (27)	8 (57)	179 (68)	179 (68)
1	96 (34)	92 (33)	11 (73)	6 (43)	85 (32)	86 (32)
Disease stratification, n (%)						
De novo	87 (31)	88 (32)	2 (13)	2 (14)	85 (32)	86 (32)
Recurrent within 6-12 months	58 (21)	57 (20)	3 (20)	4 (29)	55 (21)	53 (20)
Recurrent > 12 months	134 (48)	134 (48)	10 (67)	8 (57)	124 (47)	126 (48)
Metastatic sites, n (%)						
Lung	166 (59)	170 (61)	10 (67)	13 (93)	156 (59)	157 (59)
Liver	81 (29)	72 (26)	6 (40)	5 (36)	75 (28)	67 (25)
Brain	15 (5)	14 (5)	15 (100)	14 (100)	0	0
Chemo selected prior to randomization, n (%)						
Taxane	154 (55)	155 (56)	9 (60)	7 (50)	145 (55)	148 (56)
Gemcitabine plus carboplatin	125 (45)	124 (44)	6 (40)	7 (50)	119 (45)	117 (44)

PFS by BICR across subgroups

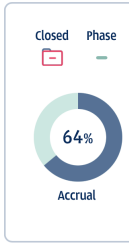
Subgroup	SG n	SG Median PFS (95% CI), mo	Chemotherapy n	Chemotherapy Median PFS (95% CI), mo	Unstratified HR (95% CI)
ITT population	279	9.7 (8.1-11.1)	279	6.9 (5.6-8.2)	0.66 (0.53-0.82)
Preselected chemo					
Taxane	154	11.1 (8.1-12.7)	155	5.7 (4.3-8.1)	0.51 (0.38-0.68)
Gem/carbo	125	8.5 (6.9-9.9)	124	8.1 (5.7-8.3)	0.89 (0.64-1.22)
Disease stratification					
De novo metastatic	87	8.3 (5.6-12.4)	88	5.5 (4.2-7.3)	0.65 (0.45-0.94)
Recurrent (6-12 mo)	58	8.3 (5.6-9.9)	57	5.6 (4.2-6.7)	0.46 (0.29-0.72)
Recurrent (> 12 mo)	134	11.1 (8.4-13.5)	134	8.4 (7.2-9.8)	0.72 (0.52-1.00)
Brain metastases					
Yes	15	8.4 (4.0-9.7)	14	4.4 (1.5-8.1)	0.38 (0.15-1.01)
No	264	9.7 (8.0-11.4)	265	7.0 (5.6-8.3)	0.66 (0.53-0.82)
Visceral metastases					
Yes	215	8.5 (7.3-9.9)	210	5.7 (4.5-7.8)	0.66 (0.52-0.84)
No	64	13.7 (7.2-NR)	69	8.3 (6.8-9.8)	0.68 (0.42-1.12)



Data cutoff date: April 2, 2025. BICR, blinded independent central review; chemo, chemotherapy; gem/carbo, gemcitabine + carboplatin; HR, hazard ratio; ITT, intent-to-treat; mo, months; NR, not reached; PFS, progression-free survival; SG, sacituzumab govitecan.

S2007 SWOG clinical trial number

A Phase II Trial of Sacituzumab Govitecan (IMMU-132) (NSC #820016) for Patients with HER2-Negative Breast Cancer and Brain Metastases



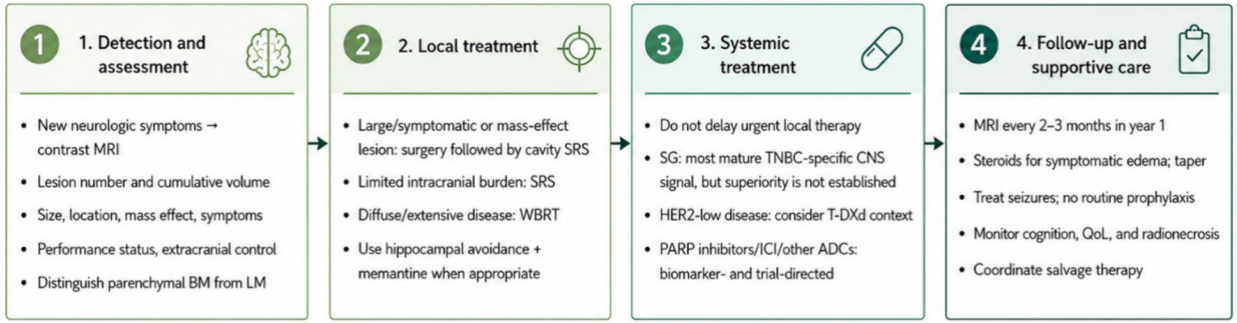
Abbreviated Title	Sacituzumab Govitecan for HER2-Neg Breast Cancer and Brain Metastases
Status Notes	Status Notes: Permanently Closed to Accrual 04/07/2025, 2:00 pm CT
Activated	12/15/2020
Closed	04/07/2025
Participants	ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS LISTED ON TITLE PAGE

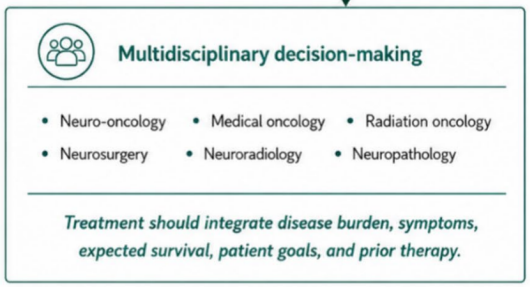
*IC

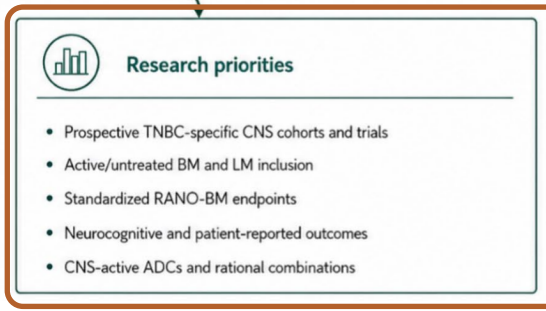
- Pts must have an MRI of the brain within 28d prior to registration and must have CNS mets with at least 1 measurable BM >= 1.0 cm in size (per RANO-BM) that has not been irradiated, or progressed despite prior RT
- Pts may have measurable or non-measurable extracranial disease
- Pts must have had CNS progression after previous CNS-directed therapy (radiation therapy, surgery, or any combination of therapy)

Punie et al ESMO 2026; https://www.swog.org/clinical-trials/s2007

(2) Brain metastases in TNBC and overview beyond ADCs

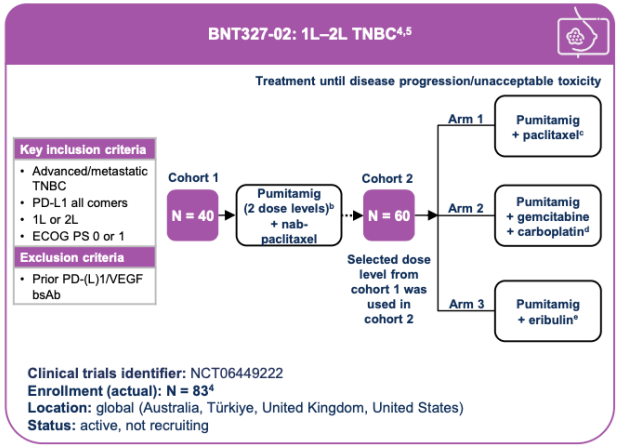


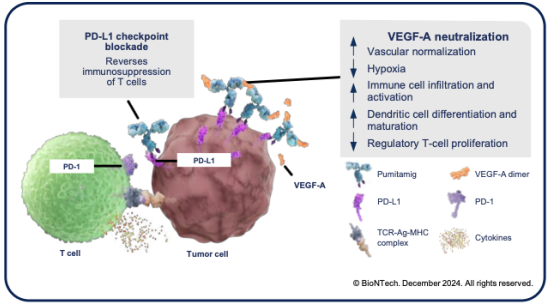




Strategy	Evidence source	Reported CNS outcomes	Conclusion	Key limitations
Sacituzumab govitecan	ASCENT stable-BM subgroup; TNBC real-world cohorts [32, 36, 44]	BM PFS 2.8 vs. 1.6 months; CNS response 35% vs. 5%; real-world icDCR 42% and icPFS 2.7 months	Most repeatedly reported TNBC-specific CNS signal	Stable-BM subgroup, retrospective cohorts, no CNS-powered head-to-head trial
Talazoparib	EMBRACA germline BRCA1/2 BM subgroup [45]	Intracranial response 18.2% vs. 20.0% with chemotherapy; OS 12.9 vs. 13.4 months	No demonstrated intracranial advantage over chemotherapy	Small subgroup; not CNS-powered
Atezolizumab + nab-paclitaxel	IMpassion130 BM subgroup [46]	No significant PFS or OS improvement	CNS benefit remains uncertain	Small heterogeneous subgroup; not CNS-powered
Trastuzumab deruxtecan	Dannehl et al. mixed HER2-positive/HER2-low real-world cohort [44]	icDCR 88%; median icPFS 11.2 months	Clinically relevant contextual evidence for HER2-positive/HER2-low disease	TNBC-specific outcomes not separately reported
Datopotamab deruxtecan	TUXEDO-2 ongoing phase II trial (NCT05866432)	Preliminary intracranial responses in 3 of 7 patients	Promising investigational TNBC-specific strategy	Very small preliminary sample; mature outcomes unavailable

(2) Brain metastases: Pumitamig + CT in SCLC or aTNBC with BM



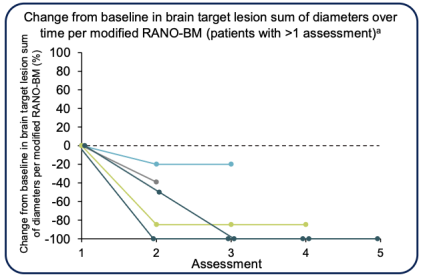


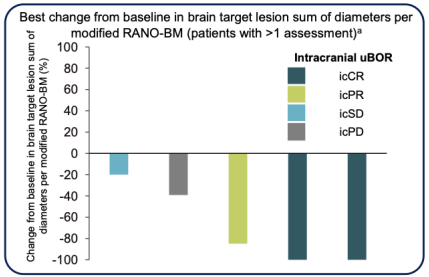
- Pumitamig is hypothesized to bind cooperatively to PD-L1 in a complex with VEGF-A, thereby localizing and concentrating dual blockade within the TME

	TNBC N = 81	
	Brain metastases n = 7	No brain metastases n = 74
Treatment setting	1L/2L	
Median age, years (range)	53.5 (36–64)	56.9 (32–85)
Female, n (%)	7 (100)	74 (100)
ECOG PS,[b] n (%)		
0	6 (85.7)	43 (58.1)
1	1 (14.3)	29 (39.2)
Smoker,[c] n (%)		
Never	1 (14.3)	48 (64.9)
Former	5 (71.4)	21 (28.4)
Current	1 (14.3)	4 (5.4)
Number of disease sites, n (%)		
0	0	1 (1.4)
1	0	15 (20.3)
2	0	20 (27.0)
3	2 (28.6)	26 (35.1)
≥4	5 (71.4)	12 (16.2)
Metastases, n (%)		
Brain/CNS	7 (100)	0
Liver	3 (42.9)	19 (25.7)

Patients with brain metastases derived similar systemic clinical benefit from pumitamig to patients without brain metastases

TNBC 1L/2L (+ nab-paclitaxel/paclitaxel/ gemcitabine + carboplatin/eribulin)		
Brain metastases n = 7	No brain metastases n = 74	
7	68	Response evaluable, n
4 (57.1)	39 (57.4)	cORR, n (%)
6 (85.7)	62 (91.2)	DCR, n (%)
NR (3.7–NR)	9.3 (NR–NR)	Median DOR, months (95% CI)
7.2 (1.8–NR)	11.0 (7.2–NR)	Median PFS, months (95% CI)
57.1	67.5	6-month rate, %





Intracranial response	Unconfirmed icORR	Confirmed icORR	Confirmed icCR	Missing/NE
All response evaluable patients (N = 7)	42.9%	42.9%	14.3%	28.6%

Encouraging intracranial responses were observed in patients with TNBC

Franks et al ESMO 2026_1951RO

06

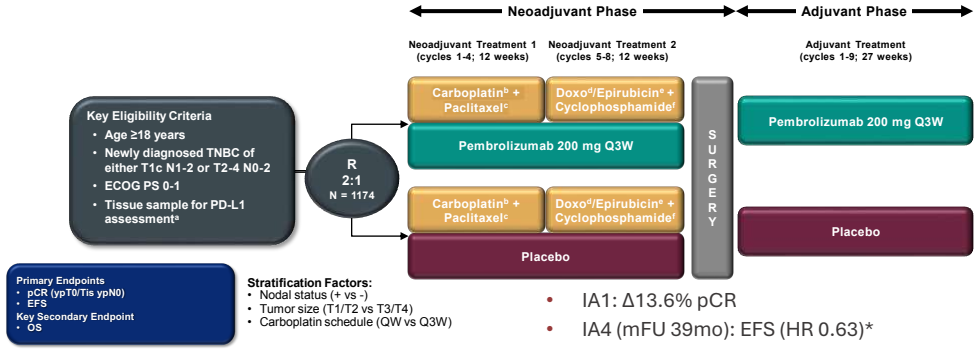
The dance moves earlier

High-risk early disease: IO already prolongs life, ADCs await their turn



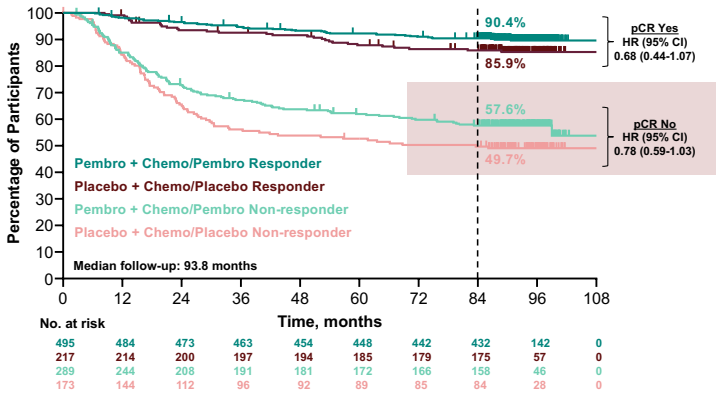
Perioperative Pembro in eTNBC: SOC consolidated @7 years

[KEYNOTE-522 trial]

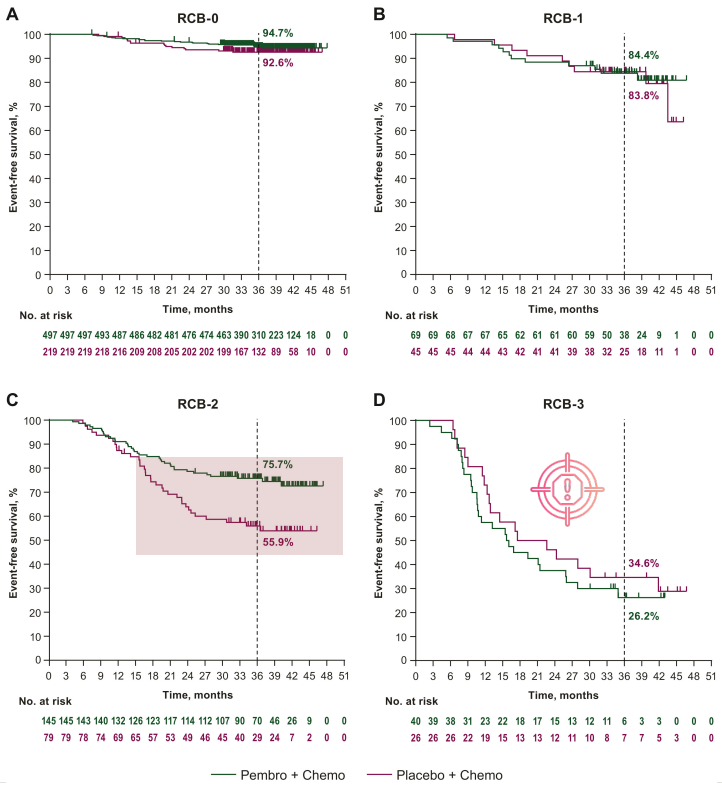


- IA1: Δ13.6% pCR
- IA4 (mFU 39mo): EFS (HR 0.63)*
- IA7 (mFU 75mo): OS (HR 0.66)*

EFS by pCR (ypT0/Tis ypN0) @FA



EFS by RCB class @IA4

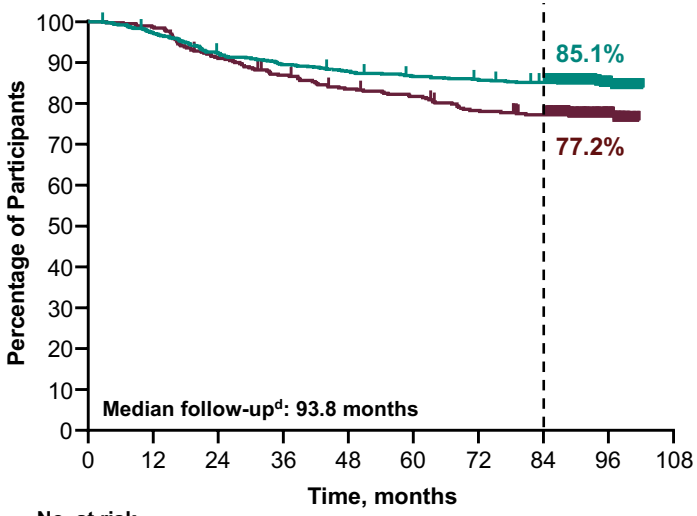


Schmid et al NEJM 2020 & SABCS 2019 & ESMO VP7 2021 & NEJM 2022 & SABCS 2023 & ESMO 2023; Puzstai et la An Oncol 2024; Schmid et al ASCO 2026

Perioperative Pembro in eTNBC: OS gain, non-pCR still challenging

[KEYNOTE-522 trial]

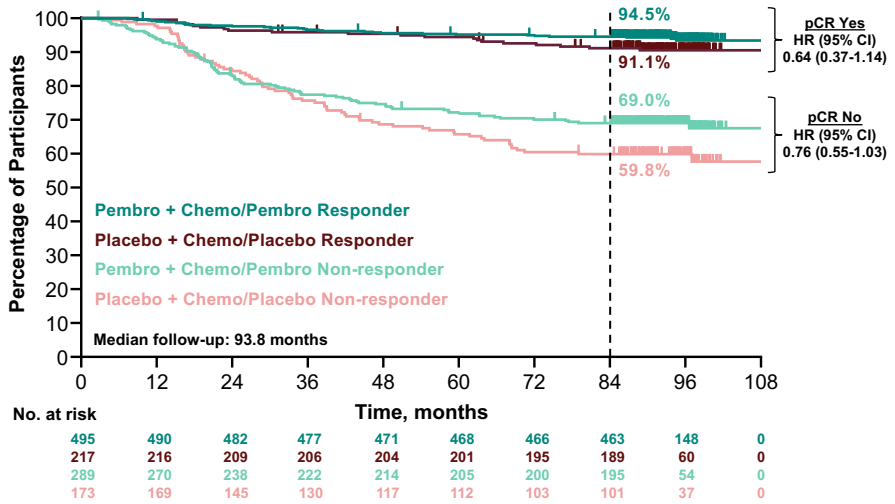
FA	Events	HR (95% CI)
Pembro + Chemo/Pembro	15.3%	0.64[a] (0.49-0.85)
Placebo + Chemo/Placebo	23.1%	



No. at risk

784	760	720	699	685	673	666	658	202	0
390	385	354	336	321	313	298	290	97	0

OS by pCR (ypT0/Tis ypN0) @FA



No. at risk

495	490	482	477	471	468	466	463	148	0
217	216	209	206	204	201	195	189	60	0
289	270	238	222	214	205	200	195	54	0
173	169	145	130	117	112	103	101	37	0

Group	n	7-year OS	Deaths at 7 years (est.)	HR (95% CI)
pCR · Pembro + chemo / pembro	495	94.5%	≈27 (5.5%)	0.64 (0.37–1.14)
pCR · Placebo + chemo / placebo	217	91.1%	≈19 (8.9%)	
No pCR · Pembro + chemo / pembro	289	69.0%	≈90 (31.0%)	0.76 (0.55–1.03)
No pCR · Placebo + chemo / placebo	173	59.8%	≈70 (40.2%)	

No pCR
≈9 fewer deaths per 100 patients at 7 years with pembrolizumab (NNT ≈11)

pCR
Excellent OS in both arms (>90%); absolute gain ≈3 per 100

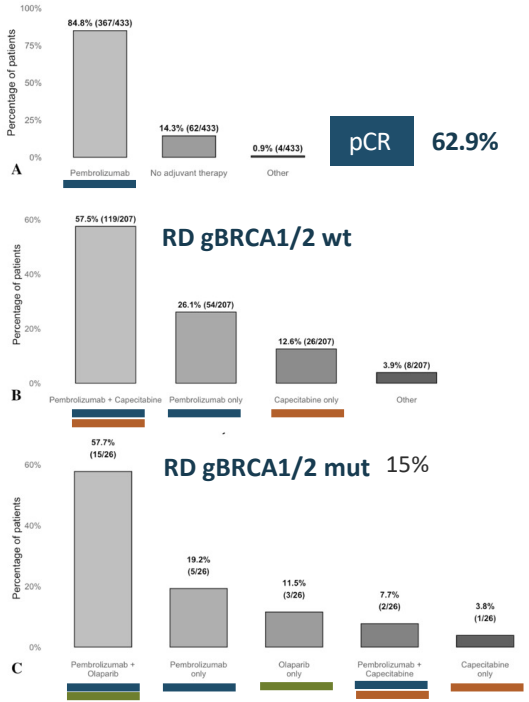
Schmid et al NEJM 2020 & SABCS 2019 & ESMO VP7 2021 & NEJM 2022 & SABCS 2023 & ESMO 2023; Puzstai et la An Oncol 2024; Schmid et al ASCO 2026

Relapse after NACT+IO: patterns and biology, the next barrier

ICIs and CT/PARPi combo in adjuvant post-NA setting in the *KN522 era*

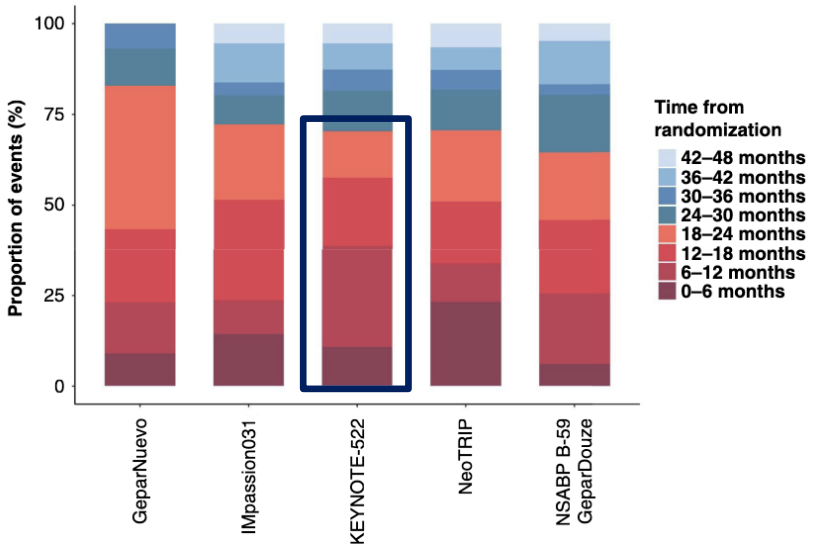
[Neo-Real/GBECAM 0123 RW_study]

- N= 726 pts Brazil/Argentina (71.2% stage II) and NACT+pembro



Time-dependent distribution of recurrences after NACT+IO

(from KN522, GeparNuevo, IM_031, GeparDouze & NeoTRIP)

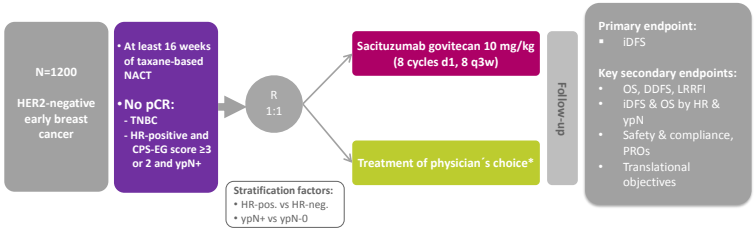


65-80% events within 24 mo

Licata et al CCR 2025; Aftimos et al Cancer Discov 2021; Allison et al JCO 2020; Derakhshan et al Ann Rev Pathol Mech Dis 2022

Residual disease after KN-522: is there room for ADCs?

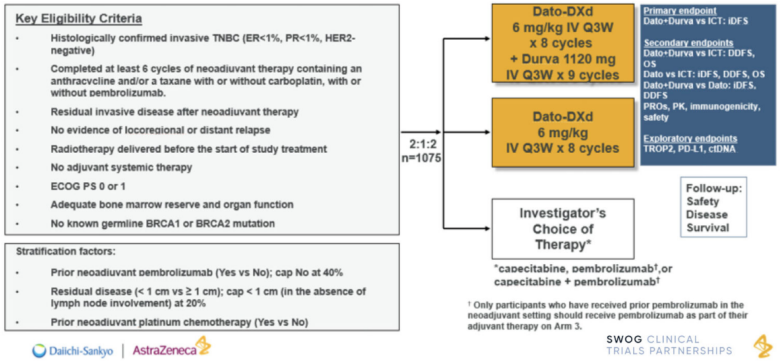
[SASCIA trial] (NCT04595565) pre-KN522 "era"



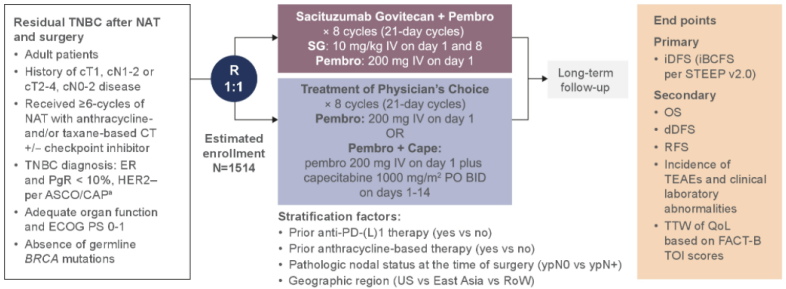
* **Capecitabine** (Cape, 2000 mg/m²/d, days 1-14, q21d for up to 8 cycles) or **platinum-based** chemotherapy (8 cycles) or **observation**.
Background therapy: in patients with HR-positive breast cancer, **endocrine-based therapy** will be administered according to local guidelines.

- Pts in SG arm more haematologic and non-haem. toxicities
- More dose delays in SG vs TPC (Cape)
- Dose reductions occured equally in both arms, mostly due to haematologic toxicities in SG and non-haemat. in TPC (Cape)

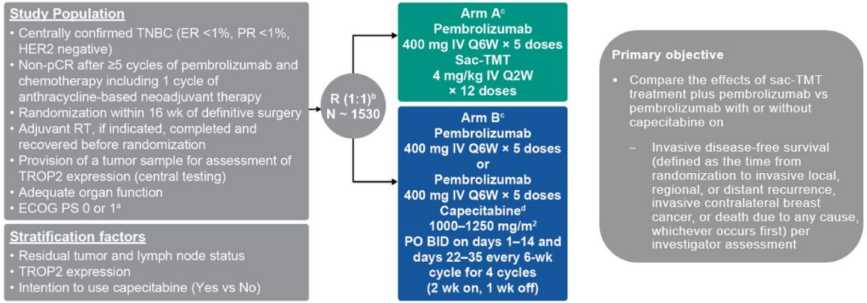
[TROPION-Breast03] (NCT05629585)



[ASCENT-05/OptimICE-RD] (AFT-65) (NCT05633654)



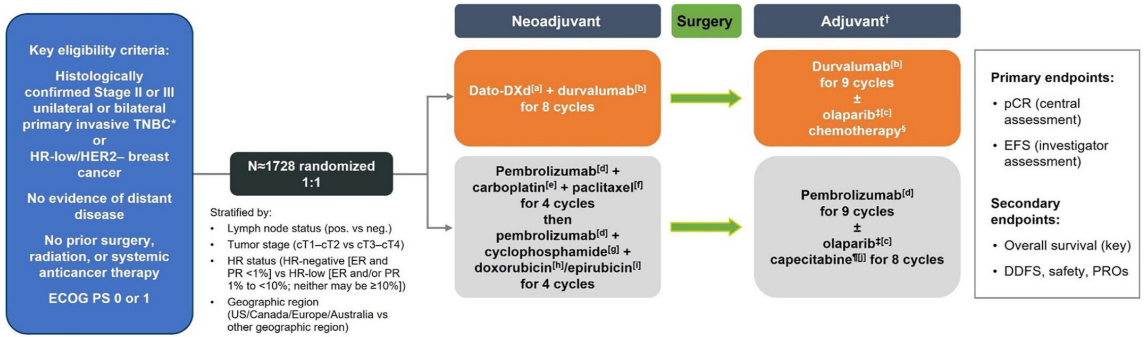
[TROFUSE-012] (NCT06393374)



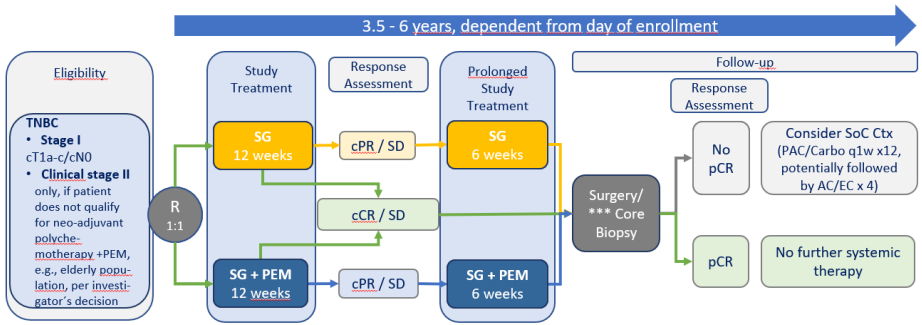
Marme et al ESMO Breast 2022; Tolaney et al ASCO 2023; https://www.swogctp.org/blog/general/swog-ctp-partners-with-astrazeneca-on-tropion-breast03-trial/; McArthur et al ASCO 2025

Neoadjuvant ADCs: can they improve on KN-522?

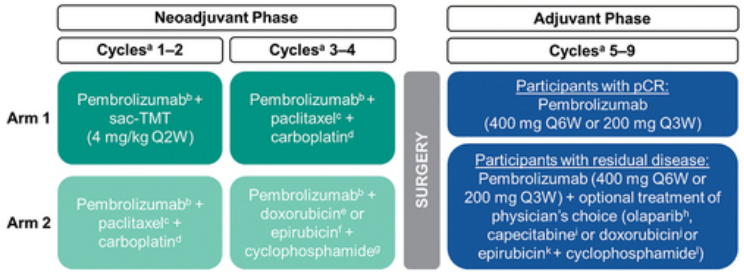
[TROPION-Breast04] (NCT06112379)



[ADAPT-TN-IV] (NCT07178730)



[TROFUSE-032] (NCT06966700)



[a]Cycle length = 6 weeks; [b]200 mg Q3W; [c]80 mg/m² QW; [d]AUC 1.5 QW; [e]60 mg/m² Q3W; [f]90 mg/m² Q3W; [g]600 mg/m² Q3W; [h]300 mg BID; [i]1000–1250 mg/m² BID 2 weeks on, 1 week off; [j]60 mg/m² Q2W or Q3W (arm 1 only); [k]90 mg/m² Q2W or Q3W (arm 1 only); [l]600 mg/m² Q2W or Q3W (arm 1 only).

McArthur et al TAMO 2025; https://wsg-online.com/studien/; Schmid et al Future Oncol 2026

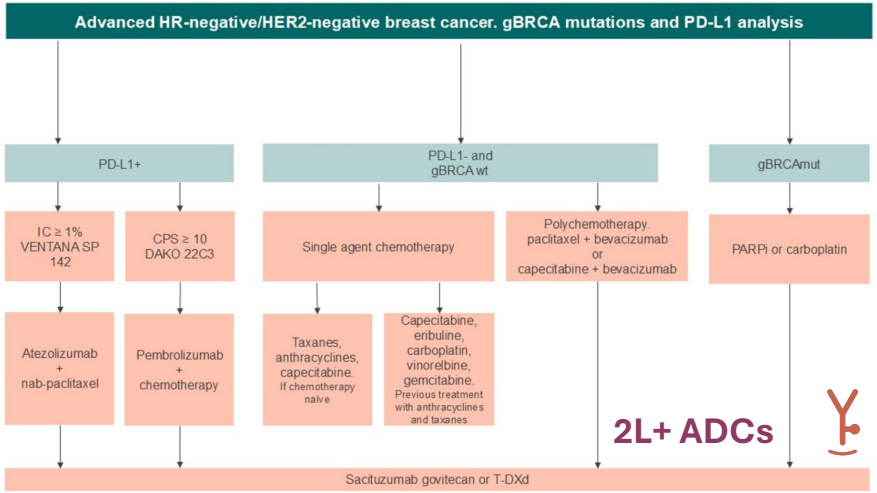
07

Open questions

What ESMO 2026 and ABC8 leave open

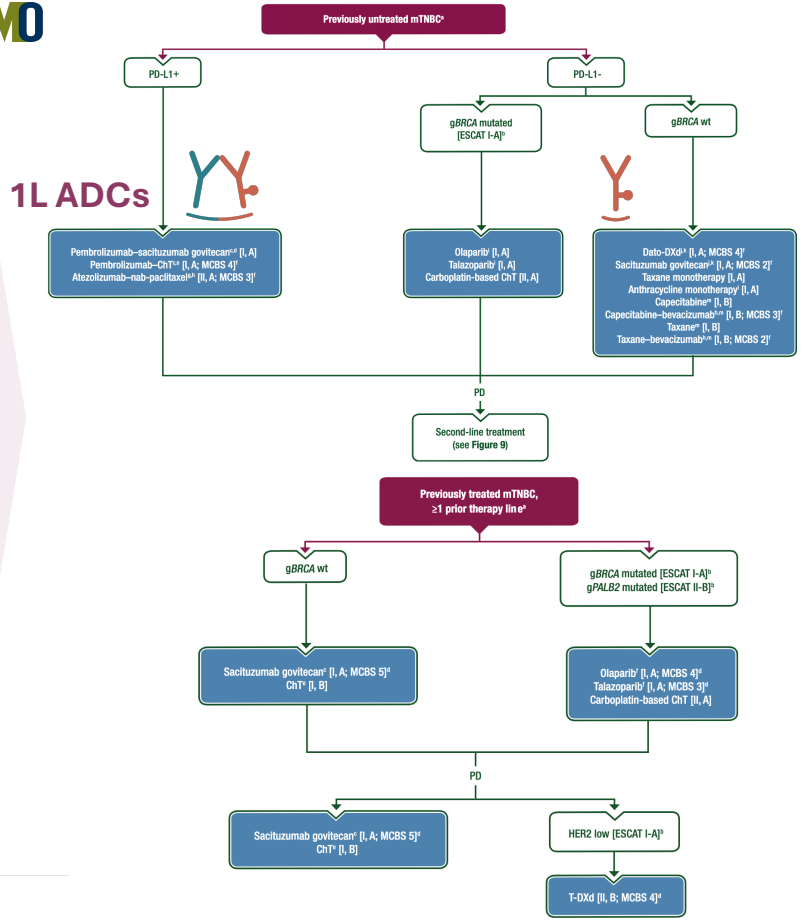
From SEOM to ABC8: the 2026 guideline landscape for advanced TNBC

SEOM



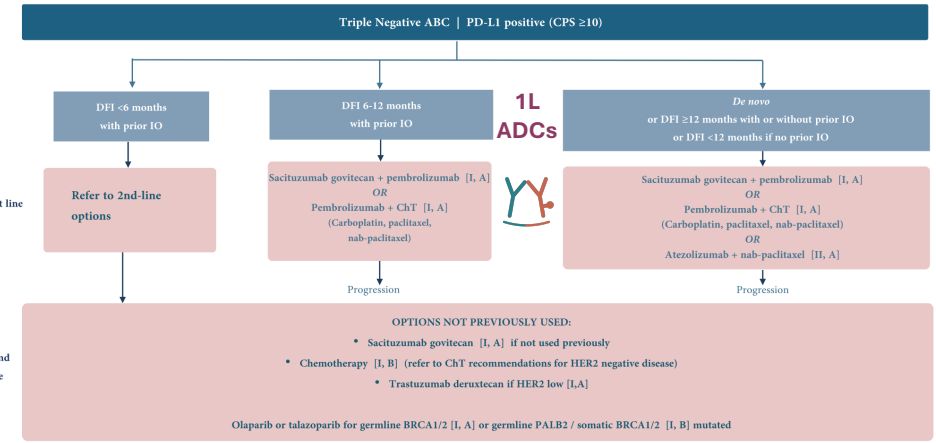
ESMO

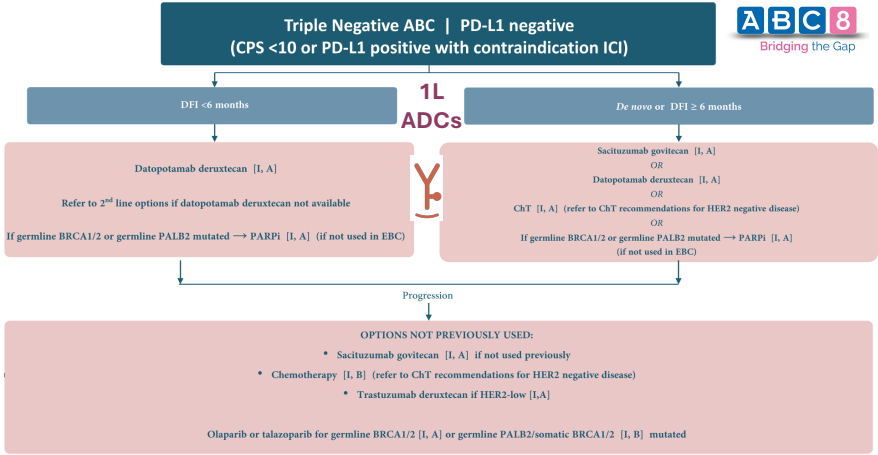
1L ADCs



Cardoso F, et al. Breast 2026, de Azambuja E, et al. Ann Oncol 2026; García-Saenz et al Clin Trans Oncol 2026

From SEOM to ABC8: the 2026 guideline landscape for advanced TNBC







PD-L1 CPS ≥10 · DFI ≥6 mo

SG + pembrolizumab

or CT + pembrolizumab

PD-L1– or IO-ineligible · gBRCA-wt

Dato-DXd or SG

Relapse <6 mo after curative therapy

Dato-DXd preferred

PD-L1– · gBRCA1/2-mutated

PARP inhibitor or platinum ?

Limited evidence after (neo)adjuvant IO

Second line and beyond

SG if not used before · T-DXd if HER2-low · chemotherapy (capecitabine, eribulin, vinorelbine, platinum) · clinical trial

ADC after ADC: no prospective evidence (ABC8: not recommended routinely)

Cardoso F, et al. Breast 2026, de Azambuja E, et al. Ann Oncol 2026; García-Saenz et al Clin Trans Oncol 2026

A few open questions after @NOV 2026

1

Relapse after KN-522: prior IO in only 4–5% of first-line trial patients

2

SG vs Dato-DXd: no head-to-head comparison in PD-L1– disease

3

Contribution of IO on top of the ADC not isolated

4

Biomarkers beyond PD-L1: quantitative TROP2, TILs, ctDNA

5

Sequencing after a 1L ADC: no prospective data

6

Challenging clinical scenarios: Active BM, leptomeningeal disease, ECOG 2–3, older patients

7

Safety of DXd + IO: ILD 20.7% with T-DXd + durvalumab (BEGONIA)

8

PARP inhibitor vs IO in gBRCAm; re-exposure after adjuvant olaparib

Cardoso F, et al. Breast 2026, de Azambuja E, et al. Ann Oncol 2026; García-Saenz et al Clin Trans Oncol 2026; Schmid et al Nat Medicine 2026

Take-home messages: TNBC_Immunotherapy and ADCs dancing together & separately

First-line is the opportunity: half of patients never reach second line, and payload-driven resistance leaves ADC-after-ADC sequencing "unanswered".



Together: in PD-L1+ disease (CPS ≥10), SG + pembrolizumab improves PFS and PFS2 versus chemotherapy + pembrolizumab)OS is immature and the contribution of IO on top of the ADC remains unclear)



Separately: when IO is not an option, Dato-DXd is the only first-line ADC with an OS benefit and with randomised data in relapse <6 months and in BM & SG improves PFS with flat OS under 82% crossover



Early disease: IO already prolongs survival (KEYNOTE-522 7-year OS HR 0.64). ADCs ± IO await their readout in residual disease and in the neoadjuvant setting

Next steps: Biomarkers (TILs, quantitative TROP2, ctDNA/TOP1) and trials that include post-KN-522 patients, active BM and early relapses.

Acknowledgements

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