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THE HEART OF MEDICAL EDUCATION

EXPERT VIDEO WITH INTEGRATED ANIMATION

ADC IN HR+/HER2- mBC: OPTIMISING TREATMENT STRATEGIES AND AE MANAGEMENT

APRIL 2025

ADC, antibody drug conjugates; AE, adverse event; HR+, hormone receptor positive; mBC, metastatic breast cancer

DEVELOPED BY BREAST CANCER CONNECT

This programme is developed by BREAST CANCER CONNECT, an international group of experts in the field of breast cancer.

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Acknowledgement and disclosures

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EDUCATIONAL OBJECTIVES

1. Recognise the **efficacy and safety** profiles of **TROP2-directed ADCs** for patients with advanced or metastatic HR+/HER2- BC, and **their place in the treatment landscape**

2. Implement **optimisation of treatment selection**, and make the appropriate **sequencing decisions**

3. Be able to **monitor and manage adverse events** associated with ADC therapy

ADC, antibody-drug conjugate; BC, breast cancer; HR+, hormone receptor positive

CLINICAL TAKEAWAYS

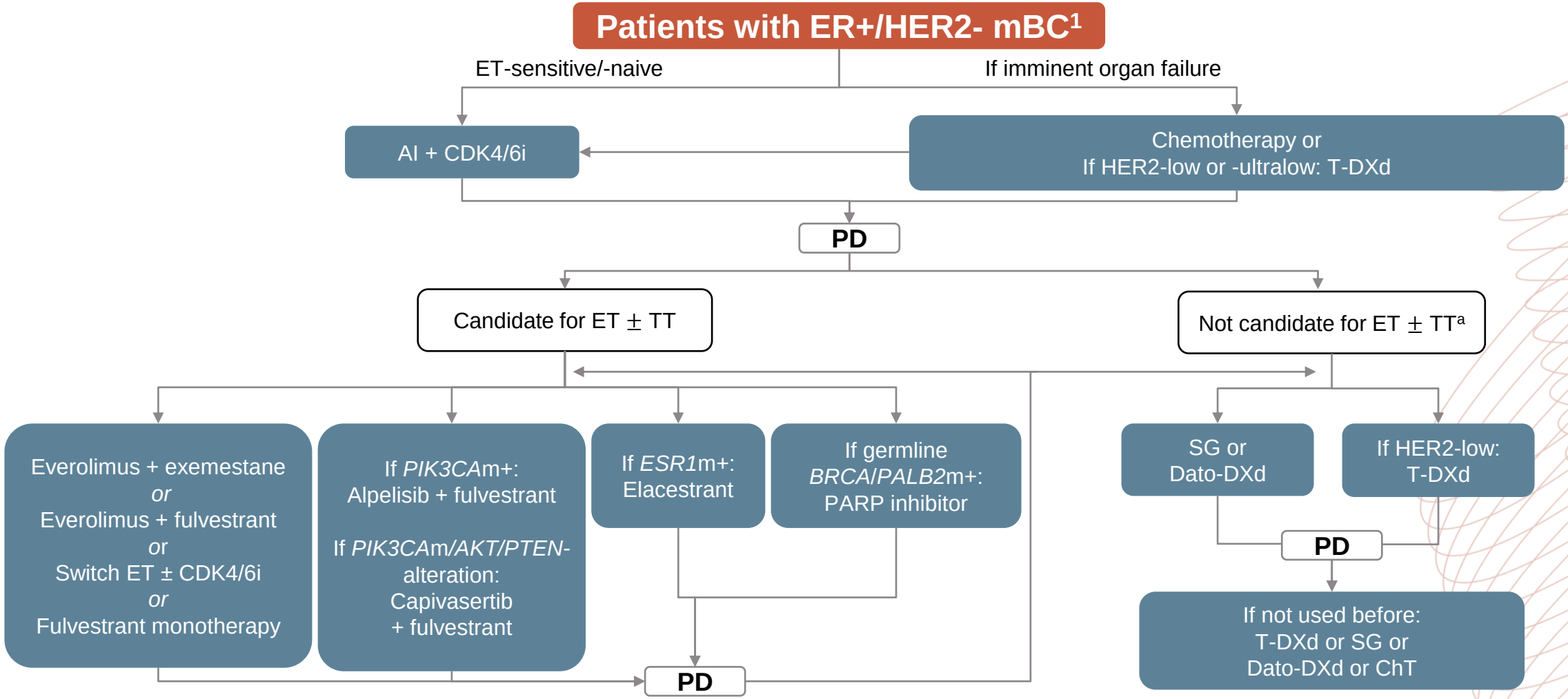
- **Endocrine-resistant** HR+/HER2− mBC remains a significant unmet need, and **ADCs** offer a more **effective and tolerable later-line alternative** to conventional chemotherapy
- **Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS** versus chemotherapy, with **continued benefits across secondary efficacy, safety and PRO endpoints**, despite OS not reaching statistical significance—potentially influenced by post-progression ADC use
- **Sacituzumab govitecan** remains a valuable treatment option for **heavily pretreated patients** with HR+/HER2− breast cancer, demonstrating **clinically meaningful improvements in PFS, OS, and PRO**, with a **manageable safety profile** when supported by appropriate care.
- To support treatment adherence and maintain QoL with ADCs, **effective management of AEs is crucial**—whether through prophylaxis, supportive medications, interventions, and/or dose modifications.
- In the absence of predictive biomarkers, **selection of ADCs for HR+/HER2− (IHC0) mBC** should be guided by prior treatments, clinical characteristics, toxicity profiles, and patient preferences.

ADC, antibody-drug conjugate; AE, adverse event; Dato-DXd, datopotamab deruxtecan; GI, gastrointestinal; HR+, hormone receptor positive; IHC; immunohistochemistry; mBC, metastatic breast cancer; PFS, progression free survival; PRO, patient-reported outcome; OS, overall survival

TREATMENT LANDSCAPE IN ER+/HER2- mBC IN PATIENTS WITH

ER+, estrogen receptor positive; mBC, metastatic breast cancer

TREATMENTS SELECTION FOR PATIENTS WITH ER+/HER2- mBC IS INFLUENCED BY ET-SENSITIVITY[1]



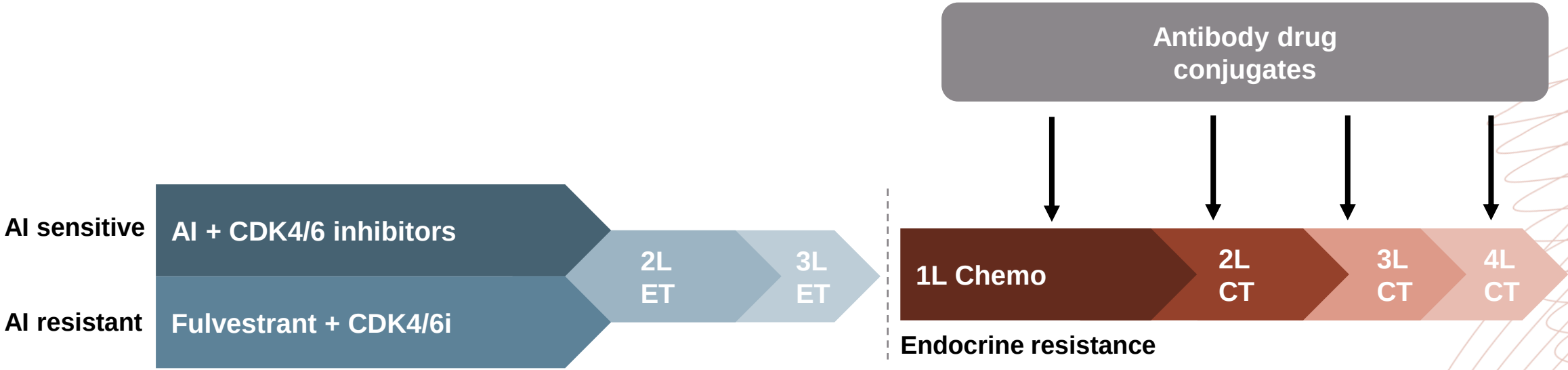
Adapted from: Gennari A, et al. *Ann Oncol.* 2021[1]

[a]If the patient has not received ChT in mBC setting, they can be treated either with ChT or, if the tumour is HER2-low/-ultralow, with T-DXd.

ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER+, estrogen receptor positive; ESR1m+, ESR1 mutant positive; ET, endocrine therapy; mBC, metastatic breast cancer; PD, disease progression; PFS, progression-free survival; SG, Sacituzumab govitican; T-DXd, trastuzumab deruxtecan; TT, targeted therapy

Adapted from: 1. Gennari A, et al. *Ann Oncol.* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed April 2025);

ADC INTRODUCED FOR PRETREATED PATIENTS WITH HR+ mBC AND RESISTANCE TO ADDITIONAL ET ± TARGETED THERAPIES[1]



This diagram is for illustrative purposes; treatment may vary based on individual patient needs

Primary endocrine resistance[2]

PD ≤6 months of 1st line ET-based therapy, while on ET (regardless of CDK4/6i use)

Secondary endocrine resistance[2]

PD after ≥6 months of 1st line ET
or PD after any duration of 2L+ ET-based therapy

1L, first line; 2L, second line; 3L, third line; 4L, fourth line; ADC, antibody-drug conjugate; AI, aromatase inhibitor; CT, chemotherapy; ET, endocrine therapy; HR+, hormone receptor positive; mBC, metastatic breast cancer; PD, disease progression

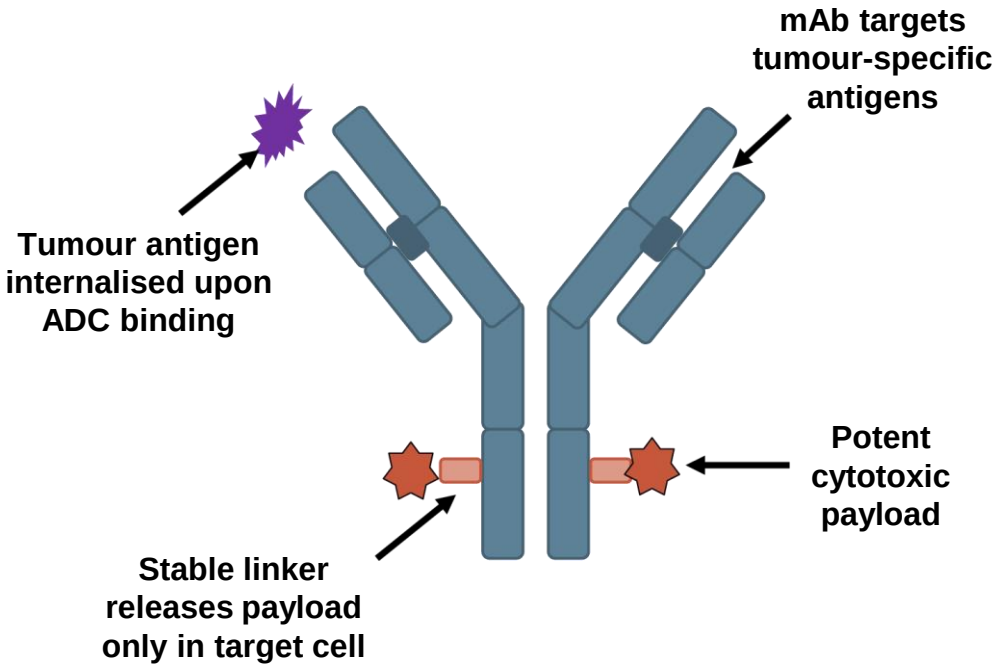
1. Schmid P. Presented at ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. Available here (accessed April 25, 2025); 2. Cardoso F, et al. Breast. 2024:76:103756

ADC IN HR+ mBC

ADC, antibody drug conjugates; HR+, hormone receptor positive; mBC, metastatic breast cancer

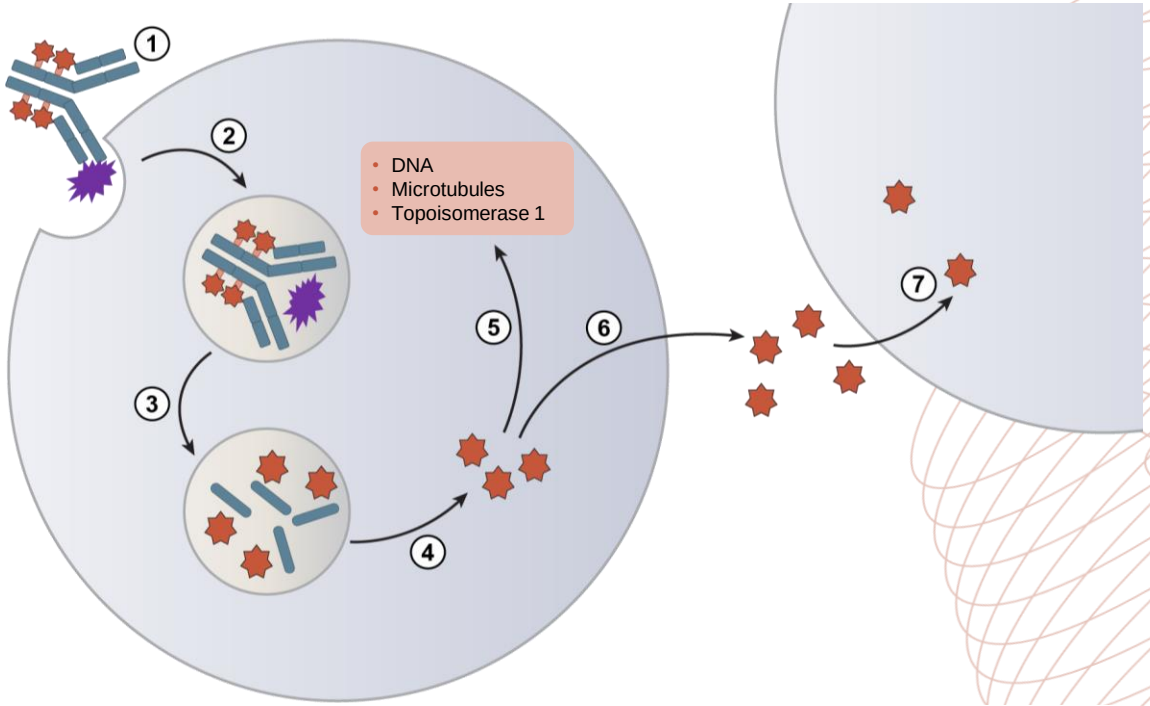
ADC STRUCTURE AND MECHANISM OF ACTION

Structure[1]



Mechanism of action[2]

(1) binding to antigen **(2)** internalisation of the ADC–antigen complex **(3)** lysosomal degradation of the antibody portion **(4)** release of payload within the cytoplasm **(5)** interaction with target (DNA, Microtubules, Topoisomerase 1)

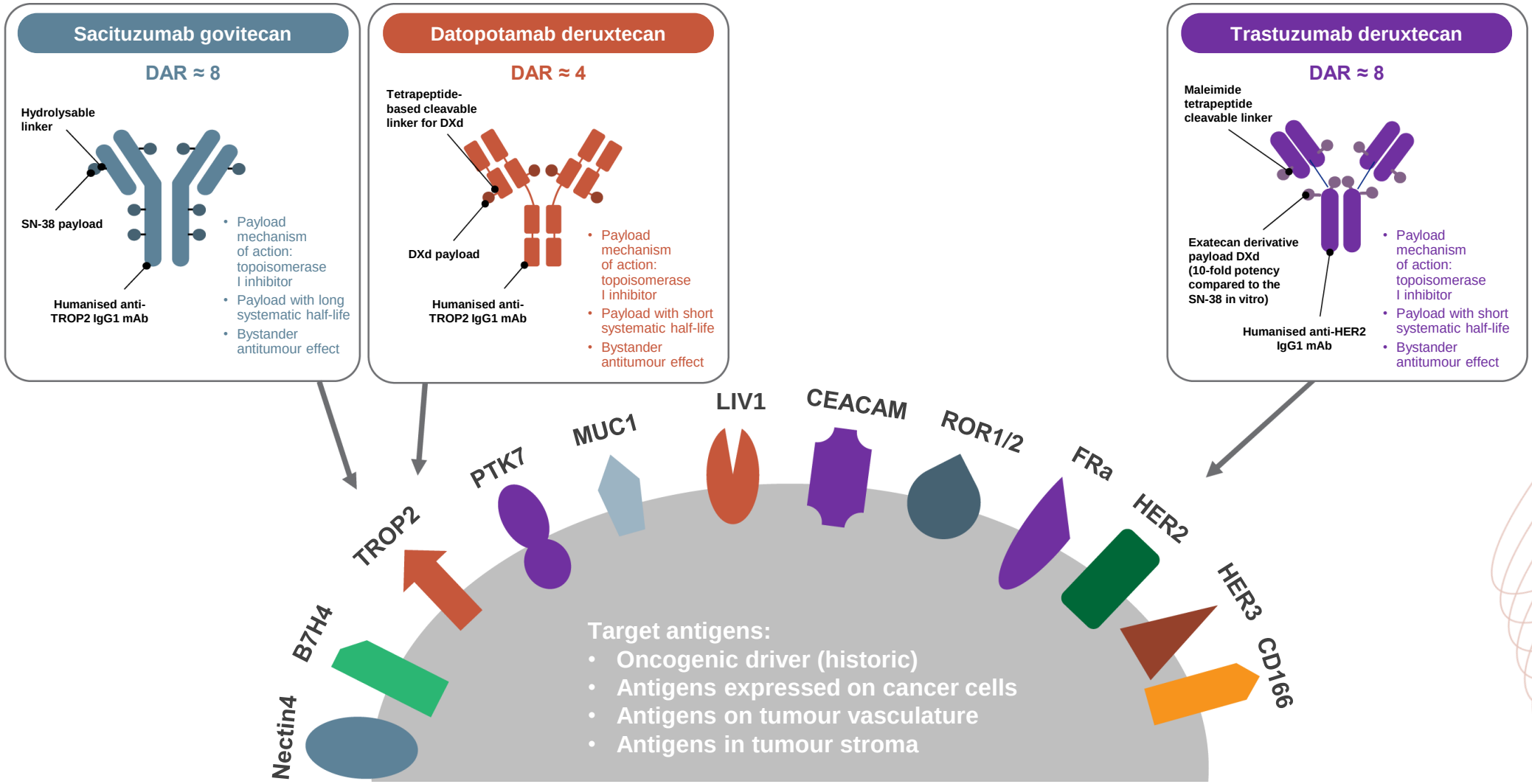


A fraction of the payload may be released in the extracellular environment **(6)** where it can be taken up by neighbour cells **(7)** a process known as the **bystander effect**

ADC, antibody-drug conjugate; mAb, monoclonal antibody

1. Modi S, et al. SABCS 2017. Abstract PD3-07; 2. von Amsberg G. Presented at ESMO Advanced Course on ADC Development, Therapeutic Applications and Research: Thoracic and Genitourinary Cancers 2024; November 25, 2024; Zurich, Switzerland. Available here (accessed April 25, 2025)

TARGETS FOR ADCs IN HR+ BREAST CANCER[1-5]



ADC, antibody-drug conjugate

1. Bardia A, et al. N Engl J Med. 2021;384:1529-1541; 2. Krop IE, et al. SABCS 2021. Abstract GS1-05; 3. Krop IE, et al. J Clin Oncol. 2022;40(number 16 suppl):1002. Presented at ASCO 2022. Abstract 1002; 4. Modi S, et al. J Clin Oncol. 2023;41(suppl 16):1020; 5. Tsai M, et al. Ann Oncol. 2021;32(suppl_5): S457-S515. Presented at ESMO 2021 (ePoster 335TiP)

SUMMARY OF ADCs AVAILABLE IN HR+ mBC

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

	DESTINY-Breast04[1]	DESTINY-Breast06[2]	TROPION-Breast01[3,4,5]	TROPiCS-02[6,7]
Target/population	**HER2 low** At least 1 line CT max 2	**HER2-low/-ultralow** 1st line	**TROP2** At least 1 line CT max 2	**TROP2** At least 2 lines CT max 4
Design	T-DXd vs ICC	T-DXd vs ICC	Dato-DXd vs ICC	SG vs ICC
Median PFS, months HR 95% CI	**10.1 vs 5.4** 0.51 0.40-0.64	**13.2 vs 8.1** 0.62 0.52-0.75	**6.9 vs 4.9** 0.63 0.52-0.76	**5.5 vs 4.0** 0.66 (0.53-0.83)
Median OS, months HR 95% CI	**23.9 vs 17.5** 0.64 0.48-0.86	Not mature	**18.6 vs 18.3** 1.01 0.83-1.22	**14.4 vs 11.2** 0.79 0.65-0.96
ORR, %	52.6 vs 16.3	57.3 vs 31.2	36.4 vs 22.9	21 vs 14
« crossover ADC », %	NR	20	24	NR

ADC, antibody-drug conjugate; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; HR+, hormone receptor positive; ICC, investigator's choice of chemotherapy; mBC, metastatic breast cancer; NR, not reported; PFS; progression free survival; OS, overall survival; ORR, objective response rate; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan

1. Modi S, et al. N Engl J Med. 2022;387:9-20; 2. Bardiya A, et al. N Engl J Med. 2024;391:2110-2122; 3. Bardia A, et al. Future Oncol. 2024;20(8):423-36; 4. Bardia A, et al. J Clin Oncol. 2025. 20;43:285-296; 5. Pistilli B, et al. Presented at ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025); 6. Rugo HS, et al. Lancet. 2023;402(10411):1423-1433; 7. Rugo HS, et al. J Clin Oncol. 2022;40:3365-3376

PATIENT CASE

PATIENT CASE

Patient
Marie T.
Age: 60 y.o.

What are the next available therapy options for patients like Marie T.?

Diagnosis [2015]

HR+/HER2- (IHC 0) IDC,
Stage IIA (T2N1M0)

Treatment (eBC) [2015-2022]

- Breast conserving surgery
- Paclitaxel chemotherapy
- Letrozole (7 years)

Progression [2022]

- Sites: bone (pelvis & vertebrae)
- Biopsy: Confirms HR+/HER2- (IHC 0) status and no detected mutations

Treatment (mBC) [2022-2025]

1L: Ribociclib + fulvestrant
(18 months stable → then PD)

2L: Everolimus + exemestane
(8 months, stable --> then PD)

3L: Weekly paclitaxel
(6 months, partial response → then PD)

1L, first-line; 2L, second line; 3L, third line; eBC, early breast cancer; HR+, hormone receptor positive; IDC, in situ ductal carcinoma; IHC, immunohistochemistry; M, metastatic stage; mBC, metastatic breast cancer; N, nodal stage; PD, disease progression; T, tumour stage

ADC IN HR+/HER2- (IHC0) METASTATIC BREAST CANCER

ADC, antibody drug conjugates; HR+, hormone receptor positive; IHC, immunohistochemistry

ADC AVAILABLE IN HR+/HER2- (IHC0)[a] mBC[1]

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

	DESTINY-Breast04[1]	DESTINY-Breast06[2]	TROPION-Breast01[3,4,5]	TROPiCS-02[6,7]
Target/population	**HER2 low** At least 1 line CT max 2	**HER2-low/-ultralow** 1st line	**TROP2** At least 1 line CT max 2	**TROP2** At least 2 lines CT max 4
Design	T-DXd vs ICC	T-DXd vs ICC	Dato-DXd vs ICC	SG vs ICC
Median PFS, months HR 95% CI	**10.1 vs 5.4** 0.51 0.40-0.64	**13.2 vs 8.1** 0.62 0.52-0.75	**6.9 vs 4.9** 0.63 0.52-0.76	**5.5 vs 4.0** 0.66 (0.53-0.83)
Median OS, months HR 95% CI	**23.9 vs 17.5** 0.64 0.48-0.86	Not mature	**18.6 vs 18.3** 1.01 0.83-1.22	**14.4 vs 11.2** 0.79 0.65-0.96
ORR, %	52.6 vs 16.3	57.3 vs 31.2	36.4 vs 22.9	21 vs 14
« crossover ADC », %	NR	20	24	NR

[a]No membrane staining.

ADC, antibody-drug conjugate; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; HR+, hormone receptor positive; ICC, investigator's choice of chemotherapy; mBC, metastatic breast cancer; NR, not reported; PFS; progression free survival; OS, overall survival; ORR, objective response rate; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan

1. Modi S, et al. N Engl J Med. 2022;387:9-20; 2. Bardiya A, et al. N Engl J Med. 2024;391:2110-2122; 3. Bardia A, et al. Future Oncol. 2024;20(8):423-36; 4. Bardia A, et al. J Clin Oncol. 2025. 20;43:285-296; 5. Pistilli B, et al. Presented at ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025); 6. Rugo HS, et al. Lancet. 2023;402(10411):1423-1433; 7. Rugo HS, et al. J Clin Oncol. 2022;40:3365-3376

TROPION-BREAST01 STUDY DESIGN

RANDOMISED, PHASE 3, OPEN-LABEL, GLOBAL STUDY (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2- breast cancer[a] (HER2- defined as IHC 0/1+/2+; FISH negative)
- Previously treated with 1-2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

R 1:1

Dato-DXd
6 mg/kg IV D1 Q3W
n=365

Investigator's choice of chemotherapy
as per protocol directions[b]
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1, 8 Q3W; capecitabine D1-14 Q3W)
(n=367)

Dual primary endpoints:

- PFS by BICR per RECIST v1.1, and OS

Secondary endpoints:

- PFS (investigator assessed) PFS2, TFST, TSST, ORR, DCR at 12 weeks, DoR, PROs, and safety

Randomisation stratified by:

- **Lines of chemotherapy** in inoperable/metastatic setting (1 vs 2)
- **Geographic location** (USA/Canada/Europe vs other geographic regions)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Statistical considerations: Study deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant

Detailed description of the statistical methods published previously[1]

[a] Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines

[b] ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W

BICR, blinded independent central review; D, day; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; FISH, fluorescent in-situ hybridisation; HR+, hormone receptor positive; IHC, immunohistochemistry; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; PFS2, time to second progression or death; PRO, patient-reported outcome; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

1. Bardia A, et al. Future Oncol. 2024;20:423-436; 2. Pistilli B, et al Presented at: ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025)

DEMOGRAPHICS AND BASELINE CHARACTERISTICS[1]

			Dato-DXd (N=365)	ICC (N=367)
Median age (range), years			56 (29–86)	54 (28–86)
Female, n (%)			360 (99)	363 (99)
Race, n (%)	Black or African American / Asian / White / Other[a]		4 (1) / 146 (40) / 180 (49) / 35 (10)	7 (2) / 152 (41) / 170 (46) / 38 (10)
Ethnicity, n (%)	Hispanic or Latino / Not Hispanic or Latino[b]		40 (11) / 322 (88)	43 (12) / 318 (87)
Prior lines of chemotherapy, n (%)[c]		1 / 2	229 (63) / 135 (37)	225 (61) / 141 (38)
Prior CDK4/6 inhibitor, n (%)		Yes / No	304 (83) / 61 (17)	300 (82) / 67 (18)
Prior taxanes and anthracyclines, n (%)		Taxane / Anthracycline	295 (81) / 228 (62)	296 (81) / 239 (65)
HER2 status at baseline by local testing, n (%)[d]		HER2 IHC 0	113 (31)	101 (28)
		HER2 IHC 1+, 2+ & FISH–	153 (42)	150 (41)

[a] Including not reported. [b] Ethnicity missing: 3 patients in Dato-DXd group; 6 patients in ICC group. [c] In the inoperable/metastatic setting; one patient in the Dato-DXd group had 3 prior lines of chemotherapy; one patient in the ICC group had 4 prior lines. [d] Latest known HER2 status (determined at diagnosis or at metastasis). All patients were required to have HER2-negative disease per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, and qualitative results (i.e. negative HER2) could be reported. Quantitative HER2 value was missing in 99 patients (27%) in the Dato-DXd group and 116 patients (32%) in the ICC group

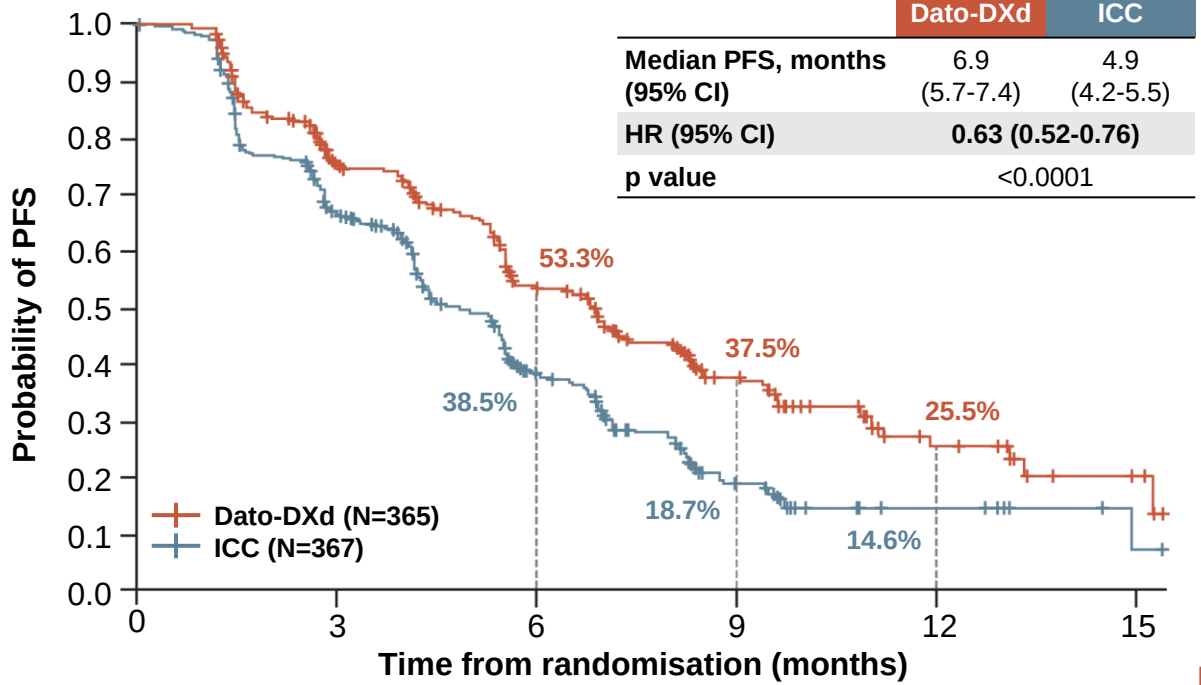
Dato-DXd, datopotamab deruxtecan; FISH, fluorescent in-situ hybridisation; ICC, investigator's choice of chemotherapy; IHC, immunohistochemistry

1. Bardia A, et al. Future Oncol. 2024;20:423-436; 2. Pistilli B, et al Presented at: ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025)

DATO-DXd SHOWED SIGNIFICANT IMPROVEMENT IN PFS BY BICR BUT OS RESULTS WERE NOT STATISTICALLY SIGNIFICANT

PFS by BICR[1,2]

	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7-7.4)	4.9 (4.2-5.5)
HR (95% CI)	**0.63 (0.52-0.76)**	
p value	<0.0001	

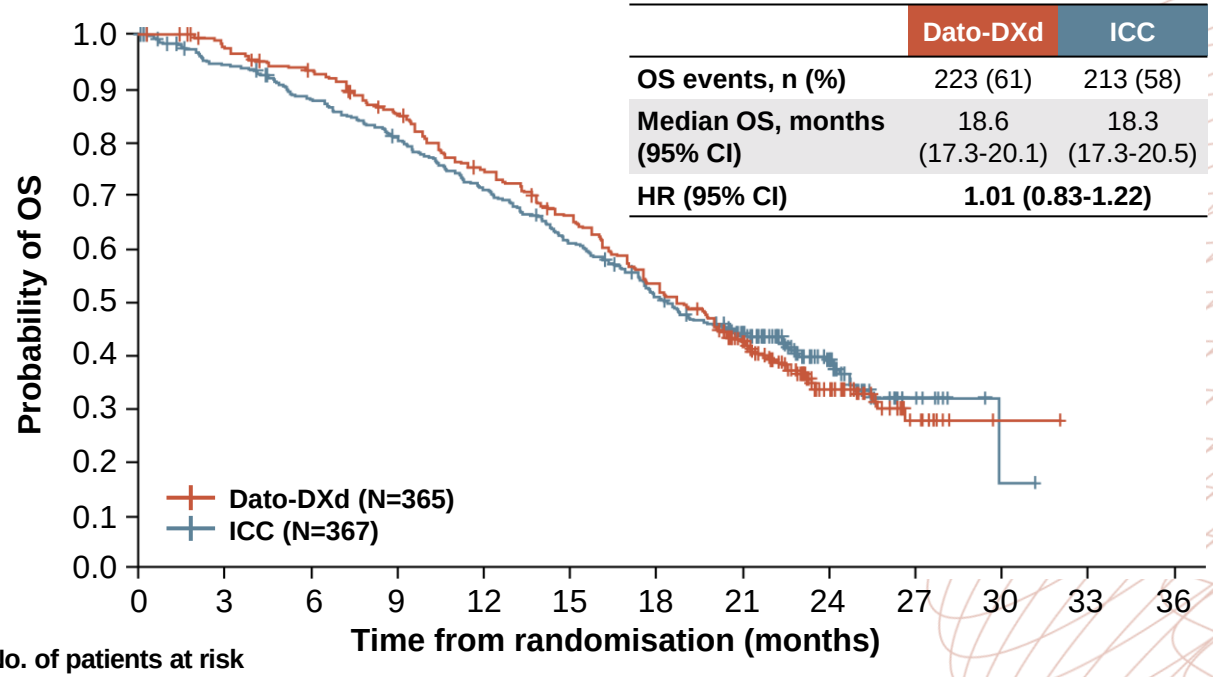


No. of patients at risk

Dato-DXd	365	249	158	66	15	4
ICC	367	205	93	26	8	1

OS[3,a]

	Dato-DXd	ICC
OS events, n (%)	223 (61)	213 (58)
Median OS, months (95% CI)	18.6 (17.3-20.1)	18.3 (17.3-20.5)
HR (95% CI)	**1.01 (0.83-1.22)**	



No. of patients at risk

Dato-DXd	365	349	331	299	259	227	180	118	49	12	1
ICC	367	335	309	283	249	213	175	123	51	9	1

- Maturity: 59.6%; Median follow-up: 22.8 months
- Protocol prespecified OS sensitivity analysis based on the stratification factors according to the eCRF[b]: **HR 0.99 (95% CI: 0.82-1.20)**

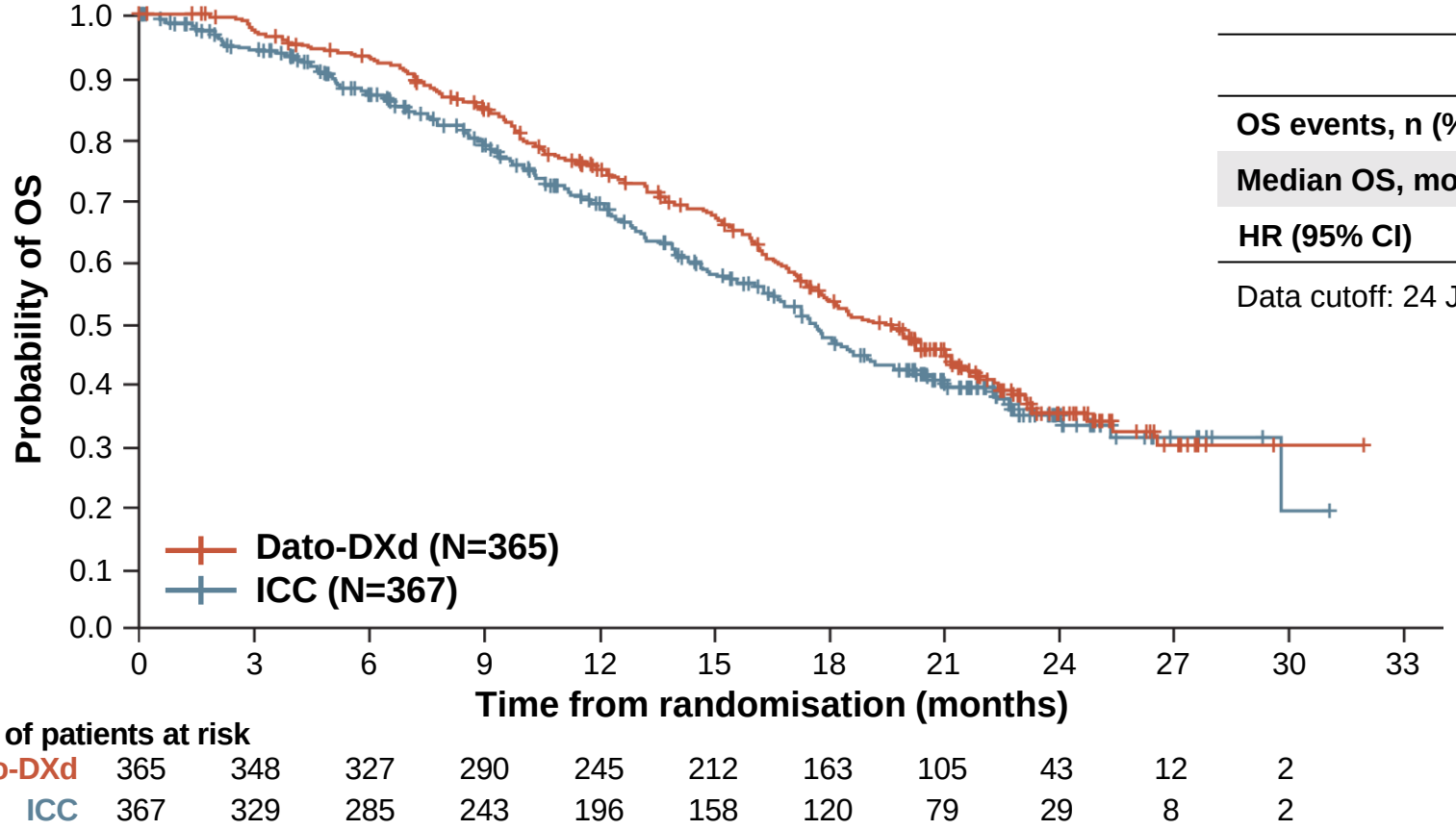
[a] Data cutoff: 24 July 2024. Pre-specified p-value boundary for OS analysis: α=0.0427, [b]Mis-stratification between interactive response technology and eCRF <5%.

BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; eCRF, electronic case report form; HR; hazard ratio; ICC, investigator's choice of chemotherapy; OS, overall survival; PFS, progression free survival.

1. Bardia A, et al. Future Oncol. 2024;20:423-436; 2. Bardia A, et al. J Clin Oncol. 2024;43;285-296; 3. Pistilli B, et al Presented at ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025).

SUBSEQUENT ADC TREATMENT MAY HAVE AFFECTED SURVIVAL RESULTS: OS ADJUSTED FOR SUBSEQUENT ADC[1]

POST-HOC SENSITIVITY ANALYSIS USING IPCW METHOD[2-4]



	Dato-DXd	ICC
OS events, n (%)	195 (53)	177 (48)
Median OS, months	19.1	17.5
HR (95% CI)	0.86 (0.70-1.06)	

Data cutoff: 24 July 2024

No. of patients at risk

Dato-DXd	365	348	327	290	245	212	163	105	43	12	2
ICC	367	329	285	243	196	158	120	79	29	8	2

ADC, antibody-drug conjugate; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ICC, investigator's choice of chemotherapy; IPCW, Inverse Probability Censoring Weighting; OS, overall survival

1. Pistilli B, et al Presented at: ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025); 2. Robins JM. In: 1993 Proceedings of the Biopharmaceutical Section, Alexandria, Virginia: American Statistical Association. pp. 24–33; 3. Robins JM, Finkelstein DM. Biometrics 2000;56:779-788; 4. Sherry AD, et al. BMJ Oncol. 2024;3:e000322

SECONDARY ENDPOINTS: EFFICACY CONTINUE TO FAVOUR DATO-DXd[1]

FINAL ANALYSIS

Median (95% CI), months	Dato-DXd (N=365)	ICC (N=367)	HR (95% CI)
PFS (investigator assessed)	6.9 (5.9-7.2)	4.5 (4.2-5.5)	**0.64 (0.55-0.76)**
PFS2	11.7 (10.8-13.1)	10.4 (9.6-11.5)	**0.76 (0.63-0.93)**
TFST	8.0 (7.2-8.8)	5.2 (4.6-5.8)	**0.58 (0.50-0.68)**
TSST	13.7 (12.4-15.0)	12.3 (10.8-13.7)	**0.83 (0.70-0.98)**

		Dato-DXd (N=365)	ICC (N=367)
Response (investigator assessed)	Confirmed overall response, n (%)	134 (**36.7**)	81 (**22.1**)
	CR	3 (0.8)	0
	PR	131 (35.9)	81 (22.1)
	DCR at 12 weeks, %	**80.8**	**66.8**
	Median DoR (95% CI), months	**7.2** (5.7-8.6)	**6.0** (4.7-7.7)

Data cutoff: 24 July 2024

CI, confidence interval; CR, complete response; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; ICC, investigator's choice of chemotherapy; PFS, progression-free survival; PFS2, time to second progression or death; PR, partial response; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

1. Pistilli B, et al Presented at: ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025)

SECONDARY ENDPOINTS: PRO RESULTS CONTINUE TO FAVOUR DATO-DXd[1]

FINAL ANALYSIS[a]

PRO	Median TTD[b], months (first instance[c])		HR (95% CI)	Median TTD, months (confirmed[d])		HR (95% CI)
	Dato-DXd	ICC		Dato-DXd	ICC	
GHS/QoL	3.4	2.1	0.83 (0.67-1.04)	9.7	4.8	0.76 (0.59-0.99)
Pain	3.5	2.8	0.84 (0.67-1.06)	10.0	5.5	0.72 (0.55-0.95)
Physical functioning	5.6	3.5	0.79 (0.62-1.01)	14.0	6.3	0.79 (0.60-1.03)

Data cutoff: 24 July 2024

[a] Data on patient-reported outcomes from the first interim analysis were presented previously at the 2024 ASCO Annual Meeting[1]; [b] TTD in GHS/QoL, pain, and physical functioning are secondary endpoints and were measured using the European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ-C30). Deterioration was defined as a change from baseline that reached a clinically meaningful deterioration threshold of 16.6 (for GHS/QoL and pain) or 13.3 (for physical functioning); [c] Time to first deterioration (primary analysis) was defined as the time from date of randomisation to date of first deterioration; [d] Time to confirmed deterioration (sensitivity analysis) required deterioration to be confirmed at a subsequent timepoint

Dato-DXd, datopotamab deruxtecan; CI, confidence interval; GHS/QoL, global health status/quality of life; HR, hazard ratio; ICC, investigator's choice of chemotherapy; PRO, patient-reported outcome; TTD, time to deterioration

1. Pernas S, et al. J Clin Oncol. 2024;42(number 16_suppl):1006. Presented at ASCO 2024; 2. Pistilli B, et al Presented at: ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025)

OVERALL SAFETY PROFILE OF DATO-DXd REMAINED FAVOURABLE COMPARED WITH ICC

TRAEs, n (%)	Dato-DXd (N=360)	ICC (N=351)
All grades	341 (95)	303 (86)
Grade ≥3	80 (22)	160 (46)
Associated with dose reduction	87 (24)	106 (30)
Associated with dose interruption	57 (16)	85 (24)
Associated with discontinuation	12 (3)	9 (3)
Associated with death	0	1 (0.3)[a]
Serious TRAEs	22 (6)	32 (9)

Data cutoff: 24 July 2024
The safety analysis population included all patients who received at least 1 dose of study drug

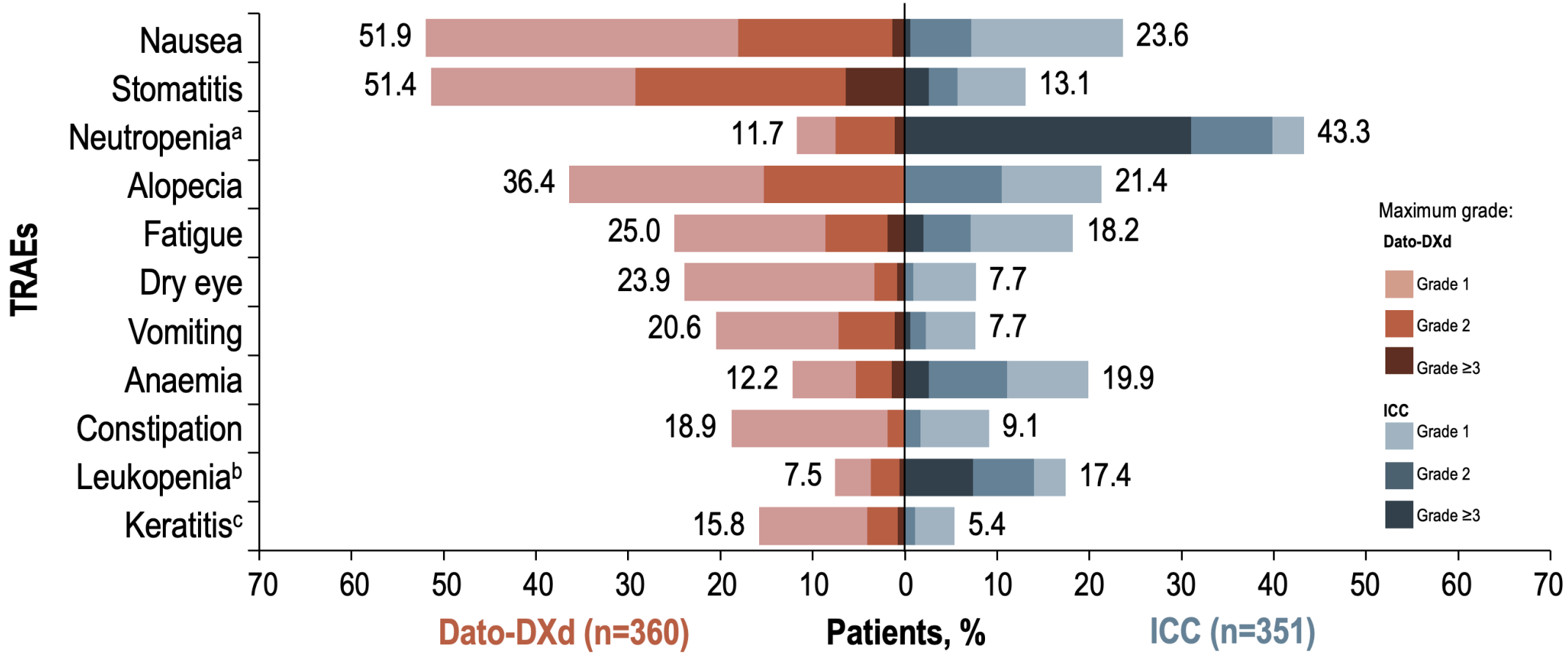
- Compared with the primary PFS data cutoff, with an additional ~12 months follow-up:
  - Overall safety profile was consistent
  - No late-onset toxicities were observed
- **Rate of grade ≥3 TRAEs in the Dato-DXd group was less than half that in the ICC group**
- Fewer TRAEs leading to dose reductions or interruptions with Dato-DXd compared with ICC; rates of TRAEs leading to discontinuation were similar between arms

[a] Investigator-reported cause of death: febrile neutropenia

Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice of chemotherapy; PFS, progression-free survival; TRAE, treatment-related adverse event

1. Pistilli B, et al Presented at ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025)

TRAEs OCCURRING IN ≥15% OF PATIENTS



Data cutoff: 24 July 2024. Data are ordered according to frequency in either the Dato-DXd or ICC arms

[a] Grouped term comprising neutropenia and neutrophil count decreased; [b] Grouped term comprising white blood cell count decreased and leukopenia; [c] Grouped term comprising keratitis, punctate keratitis, ulcerative keratitis

AE, adverse event; Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice of chemotherapy; TRAE, treatment related AE

1. Pistilli B, et al Presented at: ESMO Virtual Plenary: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial; February 12, 2025; Virtual meeting. VP1-2025. Available here (accessed April 25, 2025)

TROPICS-02: A PHASE 3 STUDY OF SG IN HR+/HER2- LOCALLY RECURRENT INOPERABLE OR METASTATIC BREAST CANCER[1]

Metastatic or locally recurrent inoperable HR+/HER2- breast cancer that progressed after[a]

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan 10 mg/kg IV days 1 and 8, every 21 days n=272

Treatment of physician's choice[b] (capecitabine, vinorelbine, gemcitabine, or eribulin) n=271

Primary endpoint:

- PFS by BICR

Secondary endpoints:

- OS
- ORR, DoR, CBR by LIR and BICR
- PRO
- Safety

Stratification:

- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

[a] Disease histology based on the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) criteria; [b] Single-agent standard-of-care treatment of physician's choice was specified prior to randomisation by the investigator

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HR+, hormone receptor positive; IV, intravenous; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; SG, sacituzumab govitecan

1. Rugo H et al. J Clin Oncol. 2022;40:3365-3376; 2. Rugo H, et al. Ann Oncol. 2022;33(supplement 7):S1386. Presented at ESMO 2022. Abstract LBA76. Available here (accessed April 25, 2025)

DEMOGRAPHICS AND BASELINE CHARACTERISTICS[1]

	SG (N=272)	TPC (N=271)
Female, n (%)	270 (99)	268 (99)
Median age, y (range)	57 (29-86)	55 (27-78)
<65 y, n (%)	199 (73)	204 (75)
≥65 y, n (%)	73 (27)	67 (25)
Race or ethnic group, n (%)		
White	184 (68)	178 (66)
Black	8 (3)	13 (5)
Asian	11 (4)	5 (2)
Other[a] / Not reported[b]	69 (25)	75 (28)
ECOG PS, n (%)		
0	116 (43)	126 (46)
1	156 (57)	145 (54)
Visceral metastases at baseline, n (%)	259 (95)	258 (95)
Liver metastases, n (%)[c]	229 (84)	237 (87)
***De novo* metastatic breast cancer, n (%)**	78 (29)	60 (22)

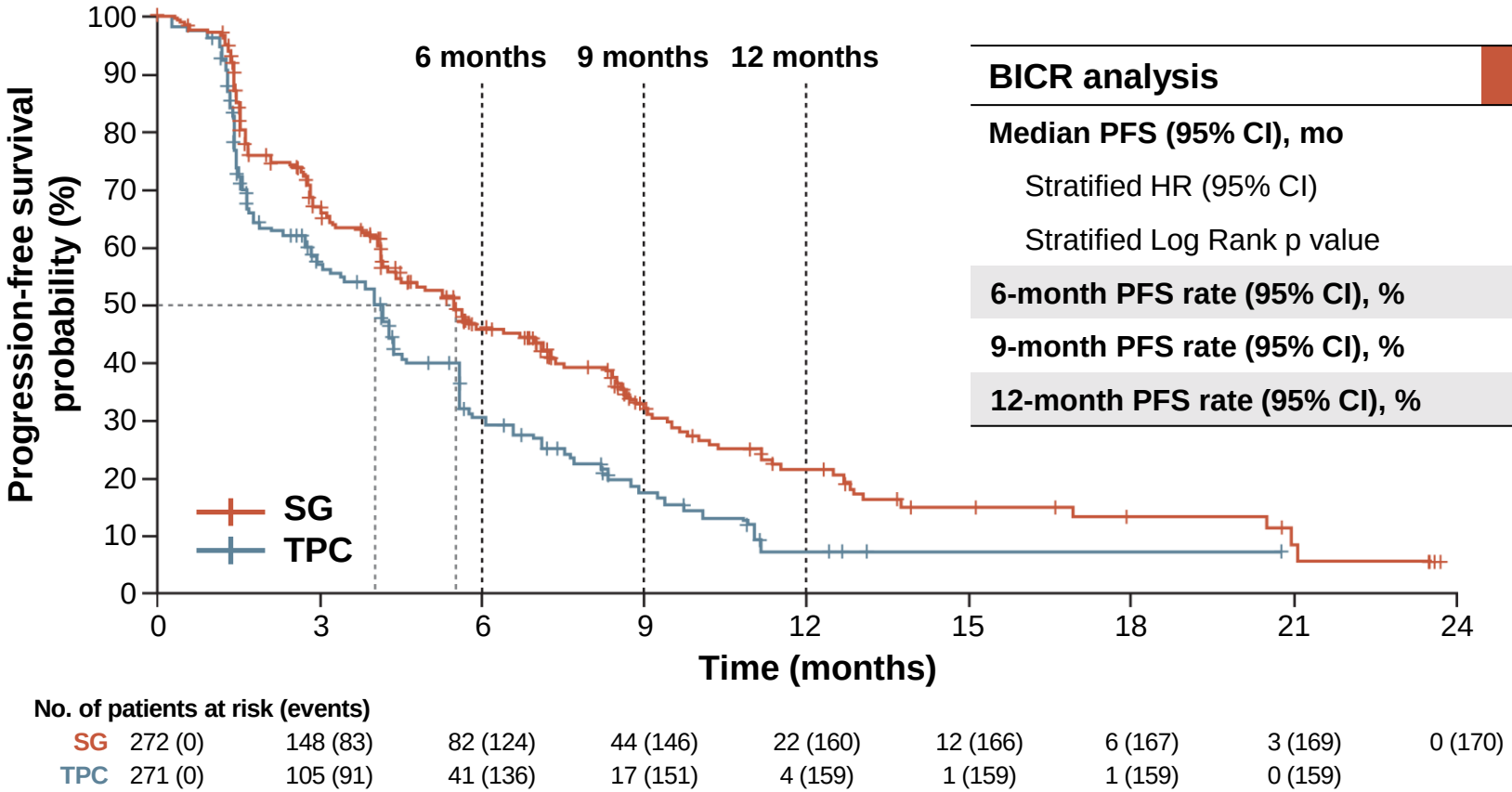
	SG (N=272)	TPC (N=271)
Median time from initial metastatic diagnosis to randomisation, mo (range)	48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)	173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 inhibitor use, n (%)		
≤12 months	161 (59)	166 (61)
>12 months	106 (39)	102 (38)
Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting, n (range)[d]	3 (0-8)	3 (1-5)

[a] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander; [b] Not reported indicates local regulators did not allow collection of race or ethnicity information; [c] Presence of baseline target/non-target liver metastases per RECIST 1.1 by local investigator review; [d] The reported number of prior therapies were miscounted at screening for some patients; 9 patients received prior chemotherapy regimens in the metastatic setting outside the per protocol range for inclusion criteria and were included in the intent-to-treat population

ECOG PS, Eastern Cooperative Oncology Group performance status; mo, months; RECIST, Response Evaluation Criteria in Solid Tumours; SG, sacituzumab govitecan; TPC, treatment of physician's choice; y, years

1. Rugo HS, et al. J Clin Oncol. 2022;40:3365-3376; 2. Rugo H, et al. Ann Oncol. 2022;33(supplement 7):S1386. Presented at ESMO 2022. Abstract LBA76. Available here (accessed April 25, 2025)

PFS IN ITT: SG SHOWED SIGNIFICANT BENEFIT IN PFS VS TPC WITH A 34% REDUCTION IN RISK OF PD/DEATH[1]



BICR analysis	SG (N=272)	TPC (N=271)
Median PFS (95% CI), mo	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	0.66 (0.53-0.83)	
Stratified Log Rank p value	0.0003	
6-month PFS rate (95% CI), %	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-month PFS rate (95% CI), %	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-month PFS rate (95% CI), %	21.3 (15.2-28.1)	7.1 (2.8-13.9)

No. of patients at risk (events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

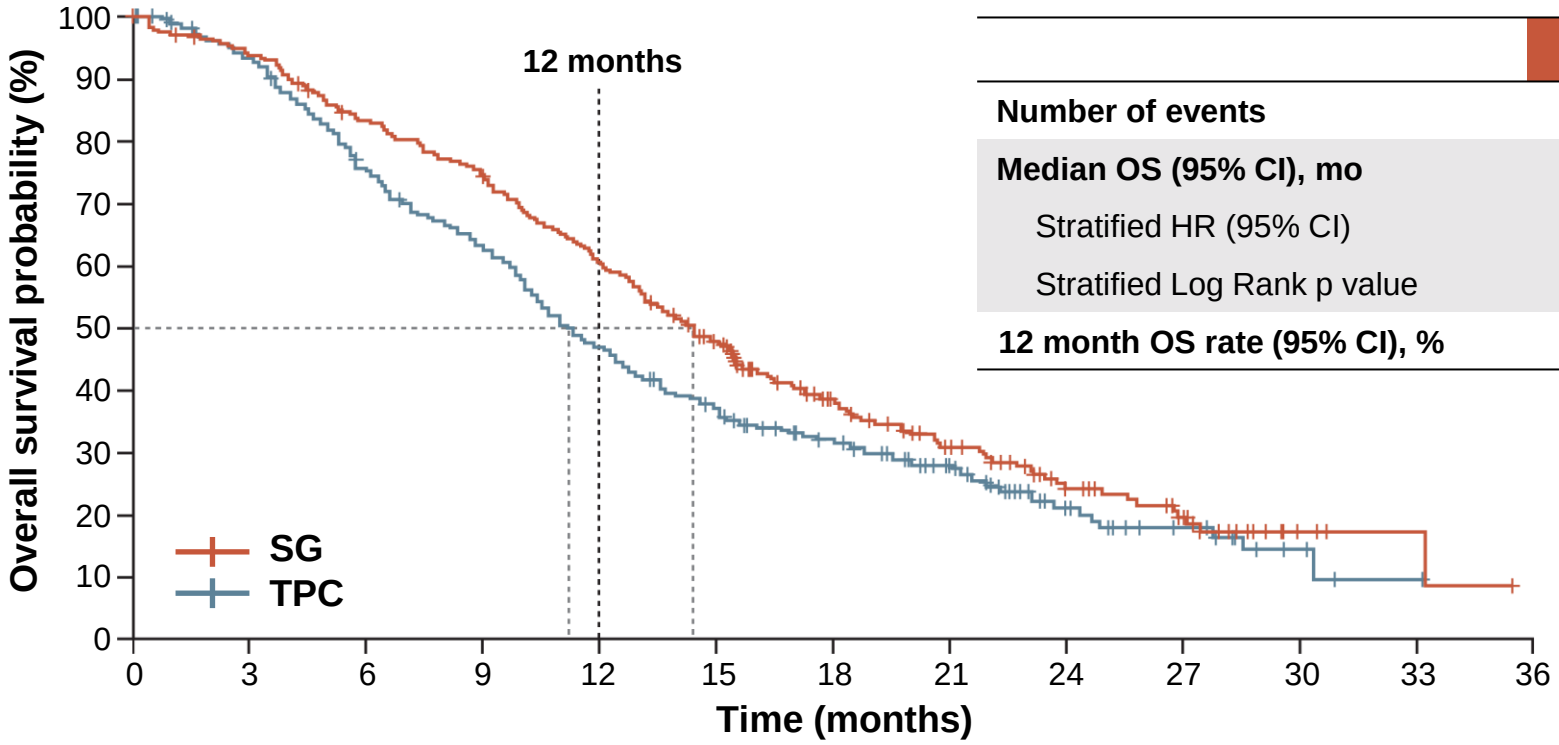
Median follow-up was 10.2 months

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; PD, disease progression; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice

1. Rugo HS, et al. J Clin Oncol. 2022;40:3365-3376; 2. Rugo H, et al. Ann Oncol. 2022;33(supplement 7):S1386. Presented at ESMO 2022. Abstract LBA76. Available here (accessed April 25, 2025)

OVERALL SURVIVAL: SG SHOWED A STATISTICALLY SIGNIFICANT BENEFIT IN OS VS TPC WITH 21% REDUCTION IN THE RISK OF DEATH[1]

2ND INTERIM ANALYSIS



	SG (N=272)	TPC (N=271)
Number of events	191	199
Median OS (95% CI), mo	14.4 (13.0-15.7)	11.2 (10.1-12.7)
Stratified HR (95% CI)	0.79 (0.65-0.96)	
Stratified Log Rank p value	0.020	
12 month OS rate (95% CI), %	61 (55-66)	47 (41-53)

No. of patients still at risk (events)

SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)
TPC	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)

Median follow-up was 12.5 months

CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice

1. Rugo HS, et al. Lancet. 2023;;402(10411):1423-1433; 2. Rugo H, et al. Ann Oncol. 2022;33(supplement 7):S1386. Presented at ESMO 2022. Abstract LBA76. Available here (accessed April 25, 2025)

RESPONSES: SG SIGNIFICANTLY IMPROVED ORR COMPARED WITH TPC, WITH PROLONGED DOR[1]

BICR analysis	SG (N=272)	TPC (N=271)
ORR, n (%)	57 (21)	38 (14)
Odds ratio (95% CI)	1.63 (1.03-2.56), p=0.035	
Best overall response, n (%)		
CR	2 (1)	0
PR	55 (20)	38 (14)
SD	142 (52)	106 (39)
SD ≥6 mo	35 (13)	22 (8)
PD	58 (21)	76 (28)
NE	15 (6)	51 (19)
CBR, n (%)[a]	92 (34)	60 (22)
Odds ratio (95% CI)	1.80 (1.23-2.63), p=0.003	
Median DoR (95% CI), mo	8.1 (6.7-9.1)	5.6 (3.8-7.9)

[a] CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR, and SD ≥6 months

BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of response; mo, months; NE, not evaluable; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice

1. Rugo HS, et al. Lancet. 2023;;402(10411):1423-1433; 2. Rugo H, et al. Ann Oncol. 2022;33(supplement 7):S1386. Presented at ESMO 2022. Abstract LBA76. Available here (accessed April 25, 2025)

PRO RESULTS: SG TREATMENT PROVIDED A SIGNIFICANT BENEFIT IN HRQoL & FATIGUE VS TPC[1]

EORTC QLQ-C30 time to deterioration endpoints

TTD	Patients SG/TPC, n/n	SG median TTD (95% CI), mo	TPC median TTD (95% CI), mo	Stratified HR (95% CI)	Stratified Log Rank p value
Global Health Status/QoL	234/207	4.3 (3.1-5.7)	3.0 (2.2-3.9)	0.75 (0.61-0.92)	0.006
Fatigue	234/205	2.2 (1.6-2.8)	1.4 (1.1-1.9)	0.73 (0.60-0.89)	0.002
Pain	229/202	3.8 (2.8-5.0)	3.5 (2.8-5.0)	0.92 (0.75-1.13)	0.415

Assessed in all patients in the intent-to-treat population who had an evaluable assessment of HRQoL at baseline and at least one evaluable assessment at post-baseline visits

CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HR, hazard ratio; HRQoL, health-related quality of life; mo, months; PRO, patient-reported outcomes; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTD, time to deterioration

1.Rugo H, et al. Ann Oncol. 2022;33(supplement 7):S1386. Presented at ESMO 2022. Abstract LBA76. Available here (accessed April 25, 2025)

SUMMARY OF COMMON TRAE OF ANY GRADE (≥10%) AND BY WORST GRADE ≥3 (≥5%) IN ANY TREATMENT ARM[1]

Treatment-related adverse events, n (%)[a]		Sacituzumab govitecan (N=268)		Chemotherapy (N=249)	
		All grade	Grade ≥3	All grade	Grade ≥3
Hematologic	Neutropenia[b]	188 (70)	136 (51)	134 (54)	95 (38)
	Anaemia[c]	91 (34)	17 (6)	62 (25)	8 (3)
	Leukopenia[d]	37 (14)	23 (9)	23 (9)	13 (5)
	Lymphopenia[e]	31 (12)	10 (4)	25 (10)	8 (3)
	Thrombocytopenia[f]	17 (6)	1 (<1)	41 (17)	9 (4)
	Febrile neutropenia	14 (5)	14 (5)	11 (4)	11 (4)
Gastrointestinal	Diarrhoea	152 (57)	25 (9)	42 (17)	3 (1)
	Nausea	148 (55)	3 (1)	77 (31)	7 (3)
	Vomiting	51 (19)	1 (<1)	30 (12)	4 (2)
	Constipation	50 (19)	0	36 (15)	0
	Abdominal pain	34 (13)	2 (1)	17 (7)	0
Investigations	AST increased	11 (4)	0	28 (11)	3 (1)
	ALT increased	12 (5)	0	24 (10)	6 (2)
Other	Alopecia	123 (46)	0	41 (17)	0
	Fatigue	101 (38)	15 (6)	73 (29)	7 (3)
	Asthenia	53 (20)	5 (2)	37 (15)	2 (1)
	Decreased appetite	42 (16)	1 (<1)	34 (14)	1 (<1)
	Neuropathy[g]	24 (9)	3 (1)	39 (16)	6 (2)

[a] Patients may report more than one event per preferred term. Adverse events were coded using MedDRA v25.0, and adverse event severity was graded per NCI CTCAE v5.0. [b] Combined preferred terms of 'neutropenia' and 'neutrophil count decreased.' [c] Combined preferred terms of 'anaemia,' 'haemoglobin decreased,' and 'red blood cell count decreased.' [d] Combined preferred terms of 'leukopenia' and 'white blood cell count decreased.' [e] Combined preferred terms of 'lymphopenia' and 'lymphocyte count decreased.' [f] Combined preferred terms of 'thrombocytopenia' and 'platelet count decreased.' [g] Combined preferred terms of 'gait disturbance,' 'hypoesthesia,' 'muscular weakness,' 'neuropathy peripheral,' 'paraesthesia', and 'peripheral sensory neuropathy.'

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TRAE, treatment-related adverse event

1.Rugo HS, et al. Lancet. 2023;;402(10411):1423-1433 (supplement)

SAFETY RESULTS ANALYSIS WAS CONSISTENT WITH THAT OF PREVIOUS STUDIES OF SG[1-4]

n (%)	SG (N=268)	TPC (N=249)
Grade ≥3 TEAE	198 (74)	150 (60)
TEAEs leading to treatment discontinuation	17 (6)	11 (4)
TEAEs leading to dose delay	178 (66)	109 (44)
TEAEs leading to dose reductions	90 (34)	82 (33)
TE SAEs	74 (28)	48 (19)
TEAEs leading to death[a]	6 (2)	0
Treatment-related	1 (<1)	0

[a] Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment-related (septic shock due to neutropenic colitis). The other 5 were: COVID-19 pneumonia, pulmonary embolism, pneumonia, nervous system disorder, and arrhythmia. Upon detailed review of the TEAEs leading to death, there were no patterns identified

TEAEs defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug

AE, adverse event; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; SAE, serious adverse event; SG, sacituzumab govitecan; TE, treatment-emergent; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice

1. Bardia A, et al. N Engl J Med. 2021;384:1529-1541. 2. Kalinsky K, et al. Ann Oncol. 2020;31:1709-1718. 3. Rugo HS, et al. J Clin Oncol. 2022;40:3365-3376; 4. Rugo H, et al. Ann Oncol. 2022;33(supplement 7):S1386. Presented at ESMO 2022. Abstract LBA76. Available here (accessed April 25, 2025)

ADVERSE EVENTS MANAGEMENT

SG/DATO-DXd: NAUSEA/VOMITING MANAGEMENT

SG and Dato-DXd are parenteral anticancer agent with *high emetic risk* (>90% frequency of emesis)[1,a]

	Nausea and vomiting grade scales[2]	
	Nausea	**Vomiting**
G1	Loss of appetite without alteration in eating habits	Intervention not indicated
G2	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Outpatient IV hydration; medical intervention indicated
G3	Inadequate oral caloric or fluid intake; tube feeding, TPN or hospitalization indicated	Tube feeding, TPN, or hospitalization indicated
G4	-	Life-threatening consequences
G5	-	Death

Prophylaxis treatment options[1]	
DAY 1 (Select A, B or C):	**DAYS 2, 3, 4:**
Treatment option A (preferred)[a] • Olanzapine[b] + NK1 RA + 5-HT_3 RA[c,d,] + Dexamethasone[e,f]	**Treatment option A:** • Olanzapine on days 2,3,4[b] • Aprepitant on days 2, 3 • If aprepitant PO is used on day 1 • ± Dexamethasone[e,f] on days 2, 3, 4
Treatment option B • Olanzapine[b] + Palonosetron + Dexamethasone[e,f]	**Treatment option B:** • Olanzapine on days 2, 3, 4[b]
Treatment option C: • NK1 RA+ 5-HT_3 RA[c,d,] + Dexamethasone[e,f]	**Treatment option C:** • Aprepitant on days 2,3 • If aprepitant PO is used on day 1 • Dexamethasone[e,f] on days 2, 3, 4

• Doses of SG should be withheld for G3 nausea or G3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolution to ≤ G1 is achieved[2]

[a] If not used previously, consider escalating to a 4-drug regimen (option A) if emesis occurred during a previous cycle of anticancer therapy with a 3-drug regimen (olanzapine-containing regimen B or E or NK1 RA-containing regimen C). Olanzapine-containing regimens may be useful for patients with severe nausea; [b]Data suggest that a 2.5-mg dose of olanzapine is efficacious. Consider this dose especially for patients who are older or who are over sedated; [c] If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product is used, no further 5-HT_3 RA is required; [d]When used in combination with an NK1 RA, there is no preferred 5-HT_3 RA; [e] Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on day 1 or subsequent days (for delayed nausea and emesis prevention) may be acceptable based on patient characteristics. If dexamethasone is eliminated on day 1 or subsequent days, consider the use of an antiemetic combination containing a 5-HT3 RA, NK1 RA, and olanzapine on day 1, and olanzapine for delayed CINV. See Discussion. Radhakrishnan V, et al. JCO Glob Oncol 2024;10:e2300301; [f] Use of corticosteroid premedication should be avoided with cellular therapies. Clinicians may wish to consider a dexamethasone-sparing approach with ICI therapy as well.

Dato-DXd, datopotamab deruxtecan; Dexa, Dexamethasone; IV, intravenous; PO, per os; SG, Sacituzumab govitegan; RA, receptor antagonist; TPN, total parenteral nutrition

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.1.2025 (Accessed April 2025); 2. Sacituzumab govitecan. Potential Management Strategies for Select Side Effects. 2023 available at: https://www.trodelvyhcp.com/-/media/project/trodelvy/trodelvyhcp/hcp/nurse-station/pdf/trodelvy_one-pan-breast-side-effects-quick-sheet-now-approved-removal_digital_us-trop-0998.pdf (accessed April 2025).

SG: NEUTROPENIA TOXICITY MANAGEMENT[1]

Neutropenia grade scale	
G0	ANC ≥ 2000/mm^3
G1	ANC ≥ 1500 to < 2000/mm^3
G2	ANC ≥ 1000 to < 1500/mm^3
G3	ANC ≥ 500 to < 1000/mm^3
G4	ANC <500/mm^3
Febrile neutropenia grade scale	
G1/2	-
G3	ANC <1000/mm^3 with a single temperature of >38.3 ℃ or sustained temperature of ≥ 38℃ for >1h
G4	Life-threatening consequence; urgent intervention indicated
G5	Death

Dose modification
Withold SG if ANC is below 1500/mm^3 on day 1 of any cycle, the neutrophil count is below 1000/mm^3 on day 8 of any cycle, or the patient develops neutropenic fever

Prophylaxis
If patients experience neutropenia: G-CSF prophylaxis

Note
Do not re-escalate SG dose after a dose reduction for adverse reactions has been made

Adverse reaction	Dose modification for severe neutropenia	
• G3/4 neutropenia that last ≥ 7 days OR • G3 febrile neutropenia OR • At time of scheduled treatment, G3/4 neutropenia which delays dosing by 2/3 weeks for recovery to ≤ G1	First	**25% dose reduction** from the original dose and administer G-CSF
	Second	**50% dose reduction** from the original dose and administer G-CSF
	Third	**Discontinue treatment** and administer G-CSF
• At time of scheduled treatment, G3/4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ G1	First	**Discontinue treatment** and administer G-CSF

ANC, absolute neutrophil count; G, grade; G-CSF, granulocyte-colony stimulating factor; SG, Sacituzumab govitecan

1. Sacituzumab govitecan. Potential Management Strategies for Select Side Effects. 2023 available at: https://www.trodelvyhcp.com/-/media/project/trodelvy/trodelvyhcp/hcp/nurse-station/pdf/trodelvy_one-pan-breast-side-effects-quick-sheet-now-approved-removal_digital_us-trop-0998.pdf (accessed April 2025).

SG: DIARRHOEA MANAGEMENT[1]

Diarrhoea grade scale	
G1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
G2	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living
G3	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living
G4	Life-threatening consequences; urgent intervention indicated
G5	Death

Premedication

Patients who exhibit an excessive cholinergic response to treatment with SG can receive appropriate premedication (eg, atropine) for subsequent treatments.

Ongoing supportive care

- Should diarrhoea occur, evaluate for infections causes. If no infectious cause is found, initiate 4 mg of loperamide followed by 2 mg with each episode of diarrhoea (up to 16 mg/day)
- Discontinue loperamide 12h after diarrhoea resolves. Additional supportive measures such as fluid and electrolyte support may be added as needed

Dose modification

- Doses of SG can be withheld or modified to help manage adverse reactions
- For patients who experience G3-4 diarrhoea at the time of scheduled treatment, withhold the dose of SG, resume when ≤ G1 diarrhea is achieved and reduce subsequent doses

Note

Do not re-escalate SG dose after a dose reduction for adverse reactions has been made

Adverse reaction	Dose modification for severe diarrhoea	
• G3/4 not controlled with antidiarrhoeal agents • At time of scheduled treatment, G3/4 delaying dose by 2/3 weeks for recovery to G1	First	**25% dose reduction** from the original dose
	Second	**50% dose reduction** from the original dose
	Third	**Discontinue treatment**
• G3/4 which does not recover to G1 (≤3 wks)	First	**Discontinue treatment**

G, grade; h, hours; SG, Sacituzumab govitecan; wks, weeks

1. Sacituzumab govitecan. Potential Management Strategies for Select Side Effects. 2023 available at: https://www.trodelvyhcp.com/-/media/project/trodelvy/trodelvyhcp/hcp/nurse-station/pdf/trodelvy_one-pan-breast-side-effects-quick-sheet-now-approved-removal_digital_us-trop-0998.pdf (accessed April 2025).

DATO-DXd: MUCOSITIS MANAGEMENT[1]

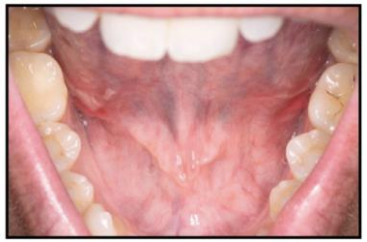
Step 1: Prophylaxis

Initiate daily OCP prior to administration of first Dato-DX dose:

- Gently brushing teeth after meals and at bedtime using a soft toothbrush and a bland fluoride-containing toothpaste
- Daily flossing, unless it causes pain or bleeding
- Daily use of steroid-containing mouthwash[a] (4x per day, swish for 1-2 minutes then spit out)
- In the absence of steroid-containing mouthwash, daily use of inert, bland mouthwash[b]
- Education on the importance of oral hygiene, hydration, and lubrication of the oral mucosa and adherence to OCP

Step 2: Confirm

Example of stomatitis after one week of Dato-DXd dose delay and treatment



Step 3: Manage

Supportive Care

- Increase the frequence of bland mouthwashes to up to every hour, if necessary
- Provide pain management
- As soon as oral pain, inflammation, and/or ulceration develops, strongly consider using a steroid-containing mouthwash e if not already in use
- Cryotherapy (iced chips or iced water held in the mouth throughout the infusion) should be considered
- Consider referral to a dentist, oral surgeon, or dermatologist for severe or persistent events

Optimise prophylactic and supportive medications for any oral mucositis/stomatitis even, regardless of grade

Dato-DXd dose recommendations[e]:

- G1: Maintain dose
- G2: Consider a dose delay or reduction if clinically indicated
- G3:
  - If prophylactic/supportive medications have not yet been optimised, delay dose until event has been resolved to ≤G1/baseline, optimise medication, then maintain dose
  - If prophylactic/supportive medications have been optimised, delay dose until resolved to ≤G1/baseline then reduce dose by 1 level
- G4: Discontinue Dato-DXd

[a]Dexamethasone 0.1 mg/mL oral solution (10 mL, four times per day, swish for 1–2 min then spit out), or local alternative. Similar mouthwash regimens using an alternative steroid can be used as advocated by institutional/local guidelines. Oral nystatin suspension or other topical antifungal agents can be used ≥ 15 min after the steroid-containing mouthwash as advocated by institutional/local guidelines; [b] Non-alcoholic and/or bicarbonate-containing mouthwash (four to six times per day); [c] Dato-DXd dose was delayed at the end of Cycle 2 and the patient was treated with clobetasol gel and magic mouthwash (mixture of sucralfate, suspension of aluminum hydroxide, and diphenhydramine); [d] Doxepin 0.5 %, viscous lidocaine 2 %; [e]Do not re-escalate Dato-DXd dose after a dose reduction for adverse reactions has been made.

Dato-DXd, datopotamab deruxtecan; G, grade OCP, oral care plan.

1. Heist RS, et al. *Cancer Treat Rev*. 2024:125:102720.

CLINICAL TAKEAWAYS

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- **Endocrine-resistant** HR+/HER2− mBC remains a significant unmet need, and **ADCs** offer a more **effective and tolerable later-line alternative** to conventional chemotherapy
- **Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS** versus chemotherapy, with **continued benefits across secondary efficacy, safety and PRO endpoints**, despite OS not reaching statistical significance—potentially influenced by post-progression ADC use
- **Sacituzumab govitecan** remains a valuable treatment option for **heavily pretreated patients** with HR+/HER2− breast cancer, demonstrating **clinically meaningful improvements in PFS, OS, and PRO**, with a **manageable safety profile** when supported by appropriate care.
- To support treatment adherence and maintain QoL with ADCs, **effective management of AEs is crucial**—whether through prophylaxis, supportive medications, interventions, and/or dose modifications.
- In the absence of predictive biomarkers, **selection of ADCs for HR+/HER2− (IHC0) mBC** should be guided by prior treatments, clinical characteristics, toxicity profiles, and patient preferences.

ADC, antibody-drug conjugate; AE, adverse event; Dato-DXd, datopotamab deruxtecan; GI, gastrointestinal; HR+, hormone receptor positive; IHC; immunohistochemistry; mBC, metastatic breast cancer; PFS, progression free survival; PRO, patient-reported outcome; OS, overall survival

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