First-line datopotamab deruxtecan (Dato-DXd) vs chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) for whom immunotherapy was not an option: Primary results from the randomised, phase 3 TROPION-Breast02 trial

Background

Advanced/metastatic TNBC is the most aggressive cancer subtype with the fewest treatment options
Metastatic TNBC 5-year OS: 14.9%[1]

~70% not candidates for 1L immunotherapy[2]

For these patients, there have been no new 1L drug approvals in over a decade; chemotherapy remains the mainstay of 1L care[4,5] and is associated with poor patient outcomes[6–8]

~50% do not receive treatment beyond 1L[2,3]

Many patients do not receive 2L treatment, highlighting the critical unmet need for more effective 1L options

TROPION-Breast02 was designed to determine whether 1L Dato-DXd can improve clinical outcomes in patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy is not an option

TROPION-Breast02: Study Design

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

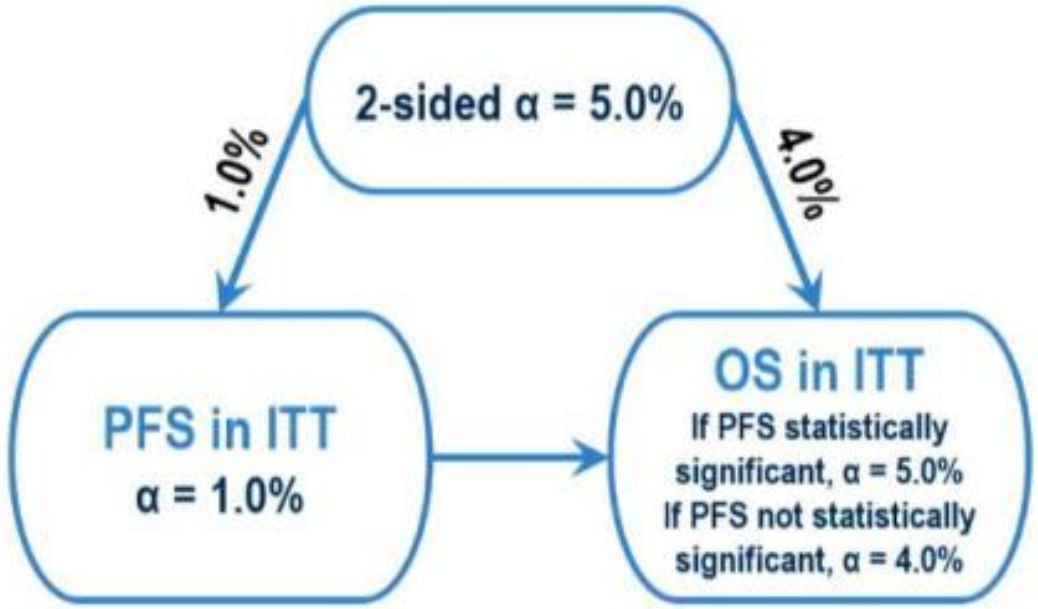
Randomisation stratified by:

- 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‖

TROPION-Breast02: Statistical Methods

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



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

- **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

Demographics and Baseline Characteristics

		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)

*Including not reported. †Based on central laboratory testing, using Agilent PD-L1 IHC 22C3 pharmDx Assay (Agilent Technologies, Santa Clara, CA). PD-L1 status missing/not applicable in 2 patients in the Dato-DXd arm and 1 patient in the ICC arm. ‡Prior (neo)adjuvant cancer therapy was received by 66% of patients, including nitrogen mustards (57%), taxanes (57%), anthracyclines (56%), pyrimidine analogues (27%), platinum compounds (16%), and PD-(L)1 inhibitors (5%). §Patients with asymptomatic, stable brain metastases were permitted in the study.

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	

Median PFS (95% CI)

10.8 mo (8.6–13.0)

5.6 mo (5.0–7.0)

Δ 5.3 mo*

Number at risk

Data-DXd	323	265	191	150	116	84	56	41	24	20	10	5	1	0
ICC	321	191	107	64	46	29	19	16	8	6	1	0	0	0

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

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)	

Median PFS (95% CI)

9.6 mo (7.4–11.2)

5.2 mo (4.2–5.6)

Δ 4.4 mo

Number at risk

Data-DXd	323	260	184	150	116	88	59	42	23	18	8	4	1	0
ICC	321	194	113	75	46	30	17	13	7	5	1	0	0	0

PFS by investigator assessment was consistent with PFS by BICR

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	

Median OS (95% CI)

23.7 mo (19.8–25.6)

18.7 mo (16.0–21.8)

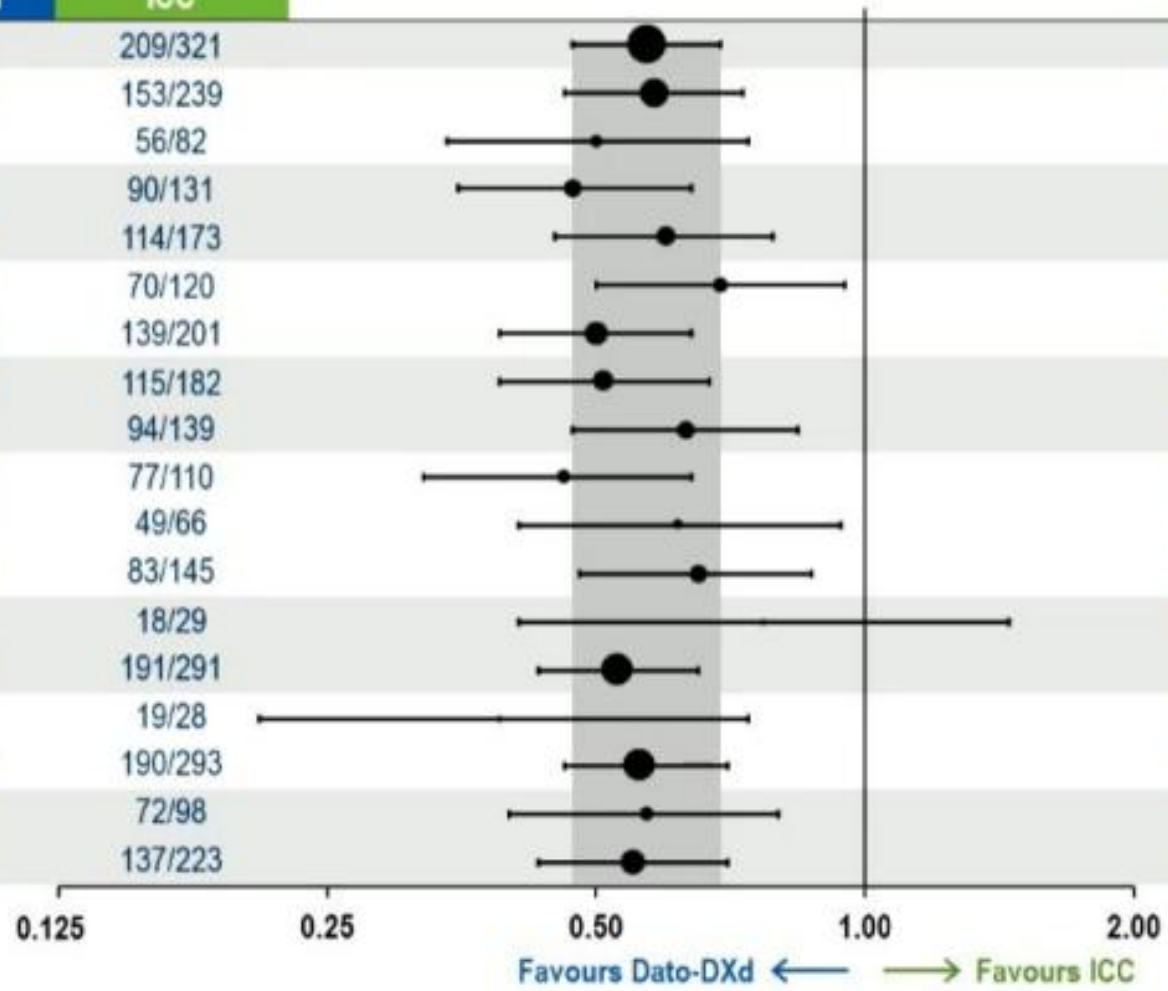
Δ 5.0 mo

Number at risk														
Data-DXd	323	311	291	272	235	201	157	122	86	64	37	14	3	0
ICC	321	290	268	231	199	158	122	93	70	48	27	12	4	0

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

PFS by BICR Subgroup Analysis

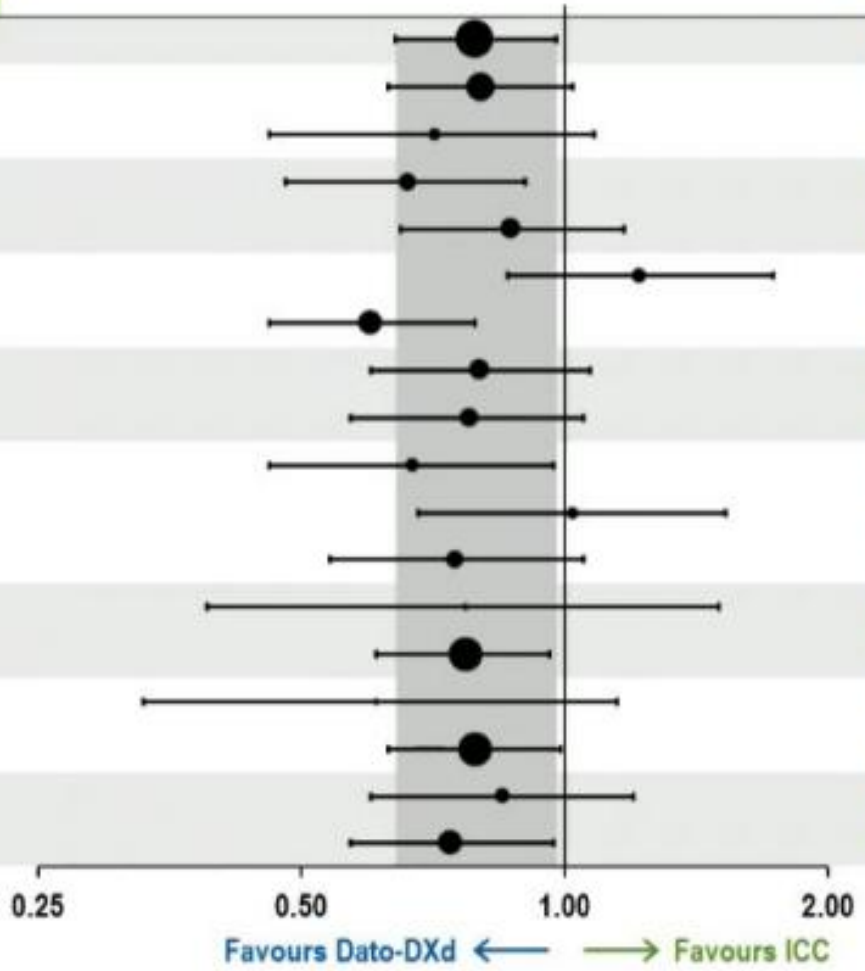
		Events/patients, n		Hazard ratio (95% CI)
		Dato-DXd	ICC	
All patients		199/323	209/321	**0.57** (0.47–0.69)
Age at randomisation	<65 years	153/245	153/239	**0.58** (0.46–0.73)
	≥65 years	46/78	56/82	**0.50** (0.34–0.74)
Race	Asian	91/151	90/131	**0.47** (0.35–0.64)
	Non-Asian	94/151	114/173	**0.60** (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)



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

OS Subgroup Analysis

		Events/patients, n		Hazard ratio (95% CI)
		Dato-DXd	ICC	
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)



*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.

Overall 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 the Dato-DXd arm only, ophthalmologic assessments were required every 3 cycles while on therapy; this was not required in the ICC arm. For all patients in both arms, ophthalmologic assessments were required at baseline, as clinically indicated, and at end of therapy. †Grouped term comprising preferred terms of neutropenia and neutrophil count decreased. ‡Grouped term comprising preferred terms of haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased. §Grouped term comprising preferred terms of white blood cell count decreased and leukopenia. ¶Grouped term comprising preferred terms of neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, paraesthesia, and peripheral sensory neuropathy. #Grouped term comprising preferred terms of fatigue, asthenia, and malaise. ‖Per Common Terminology Criteria for Adverse Events version 5.0, the maximum grade for alopecia is grade 2.

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

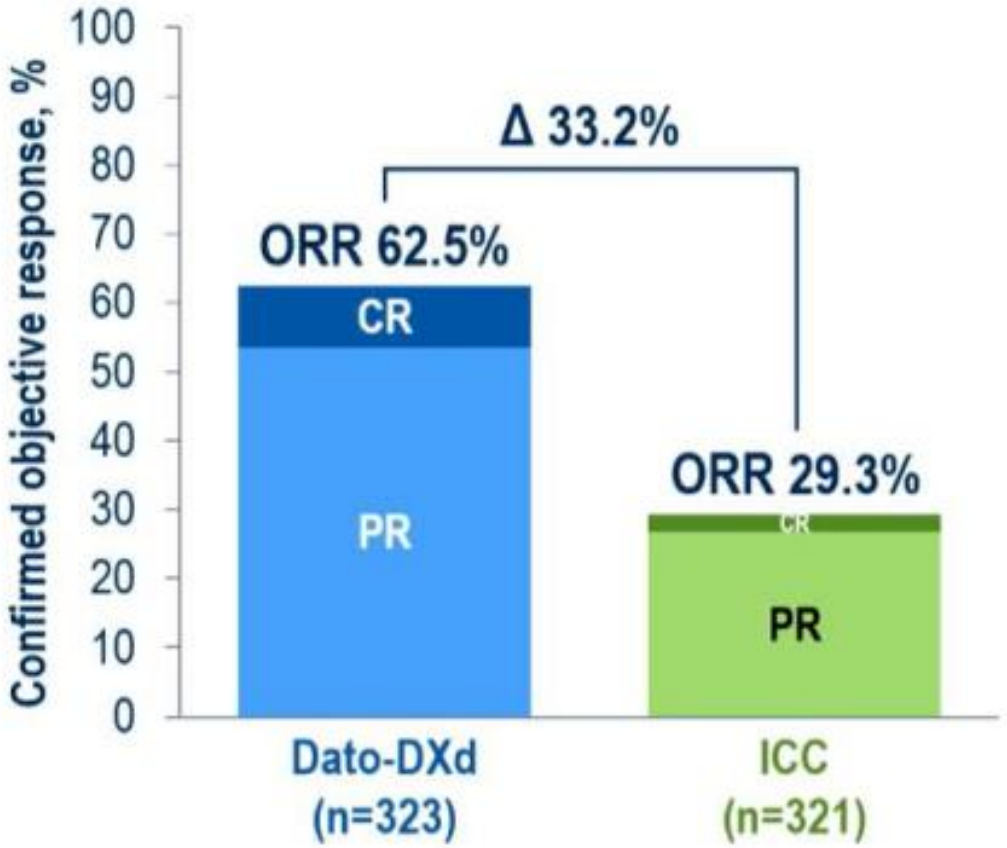
Treatment-related oral mucositis/stomatitis:

- 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

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

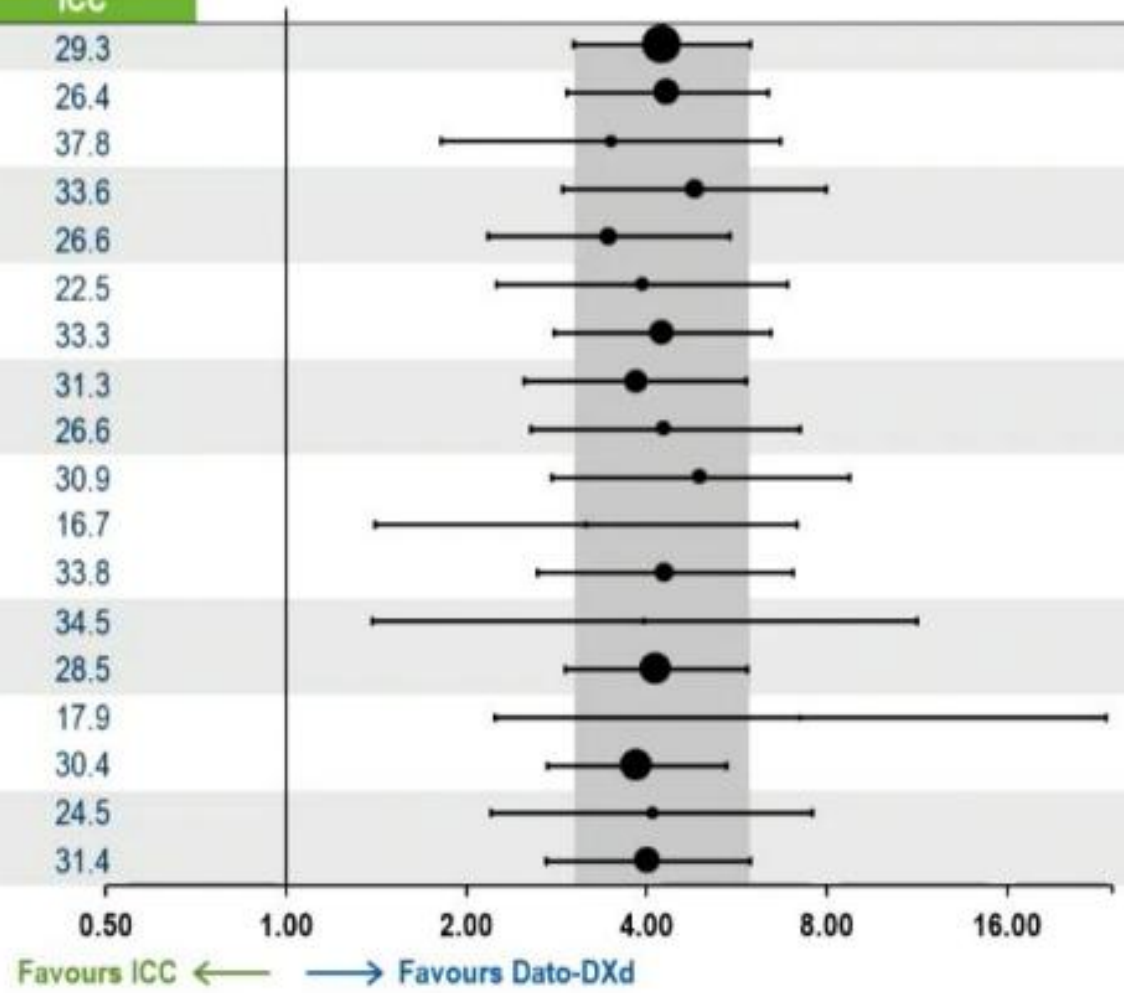
Duration of Response

	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

ORR by BICR Subgroup Analysis

		Confirmed objective response, %		Odds ratio (95% CI)
		Dato-DXd	ICC	
All patients		62.5	29.3	**4.24** (3.03–5.95)
Age at randomisation	<65 years	60.8	26.4	**4.34** (2.95–6.38)
	≥65 years	67.9	37.8	**3.49** (1.82–6.70)
Race	Asian	70.9	33.6	**4.81** (2.90–7.96)
	Non-Asian	55.6	26.6	**3.46** (2.17–5.51)
Geographic region	US, Canada, Europe	53.3	22.5	**3.94** (2.25–6.88)
	Other geographic regions	68.0	33.3	**4.25** (2.80–6.44)
ECOG PS	0	63.6	31.3	**3.83** (2.50–5.88)
	1	60.9	26.6	**4.30** (2.56–7.21)
DFI history	*De novo*	68.8	30.9	**4.93** (2.78–8.74)
	Prior DFI 0–12 months	38.8	16.7	**3.17** (1.41–7.15)
	Prior DFI >12 months	68.7	33.8	**4.30** (2.64–7.02)
PD-L1 status	High (CPS ≥10)	67.6	34.5	**3.97** (1.39–11.35)
	Low (CPS <10)	62.4	28.5	**4.15** (2.93–5.89)
Brain metastases*	Yes	61.1	17.9	**7.23** (2.23–23.44)
	No	62.7	30.4	**3.86** (2.73–5.45)
Liver metastases	Yes	57.0	24.5	**4.09** (2.20–7.57)
	No	64.8	31.4	**4.02** (2.72–5.95)



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

Conclusions

- TROPION-Breast02 **met both dual primary endpoints**: first-line Dato-DXd demonstrated statistically significant and clinically meaningful improvement in **OS and PFS** over ICC
  - OS HR 0.79 (95% CI 0.64–0.98); P=0.0291
  - PFS by BICR HR 0.57 (95% CI 0.47–0.69); P<0.0001
  - ≥5-month improvement in both median OS and PFS

TROPION-Breast02 enrolled patients who are **representative of the real-world** TNBC population, including those **often excluded from clinical trials** (e.g. 15% had DFI 0–6 months)

- The Dato-DXd **safety profile was manageable** and generally **consistent** with the known profile
  - Despite more than double the median duration of treatment, rates of grade ≥3 and serious TRAEs were similar, and discontinuations were lower, with Dato-DXd vs ICC

TROPION-Breast02 results support Dato-DXd as the new first-line standard of care for patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy is not an option

Acknowledgements

The authors would like to particularly thank:

- Patients
- Families and caregivers
- TROPION-Breast02 investigators and site personnel

TROPION-Breast02 (NCT05374512) is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialisation collaboration with AstraZeneca for Dato-DXd.