Organizador:

Fundación Biomédica Miguel Servet

Mama diseminada

Iñaki Álvarez Busto
Servicio de Oncología Médica
Hospital Universitario Miguel Servet

Trastuzumab deruxtecan vs physician's choice of chemotherapy in patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–low or HER2-ultralow metastatic breast cancer with prior endocrine therapy: primary results from DESTINY-Breast06

Giuseppe Curigliano

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- Chemotherapy naïve in the mBC setting

Prior lines of therapy
- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors
- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

HER2-low = 713
HER2-ultralow = 153†

T-DXd
5.4 mg/kg Q3W
(n=436)

TPC
(n=430)

Options:
capecitabine 60%
nab-paclitaxel,
paclitaxel

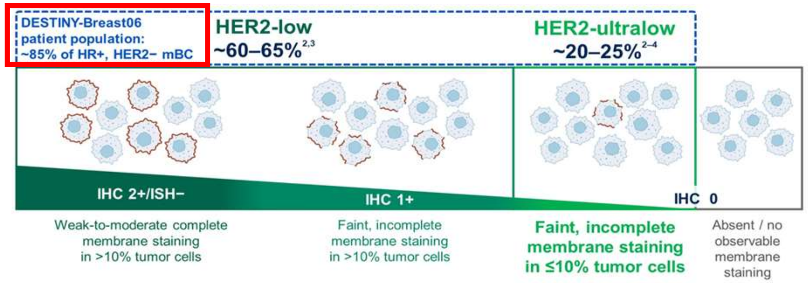
FU: 18.2m

ENDPOINTS

Primary
- PFS (BICR) in HER2-low

Key secondary
- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary
- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡



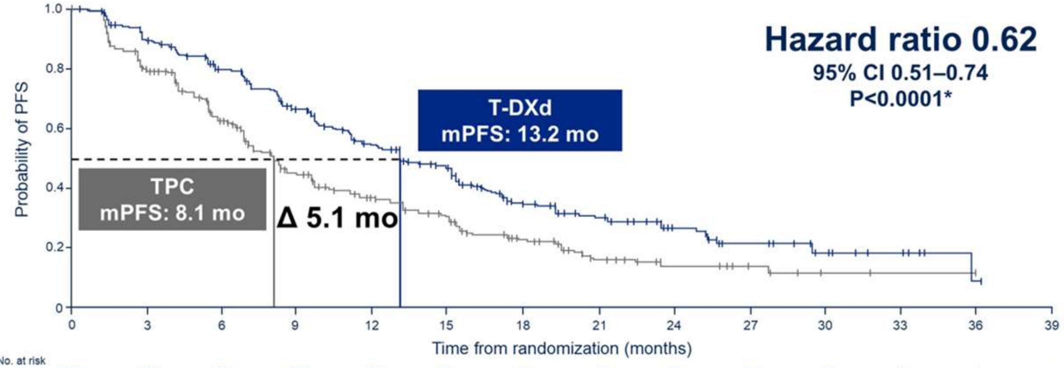
Patient demographics and key baseline characteristics

	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Age, median (range), years	58.0 (28–87)	57.0 (32–83)	58.0 (28–87)	57.0 (32–83)	58.0 (33–85)	57.5 (34–82)
Female, n (%)	359 (100)	353 (99.7)	436 (100)	429 (99.8)	76 (100)	76 (100)
ECOG PS at screening, n (%)†						
0	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)	44 (57.9)	39 (51.3)
1	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)	30 (39.5)	35 (46.1)
HER2 status, n (%)‡						
IHC 0 with membrane staining (HER2-ultralow)	–	–	76 (17.4)	76 (17.7)	76 (100)	76 (100)
IHC 1+ (HER2-low)	238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)	–	–
IHC 2+/ISH− (HER2-low)	117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)	–	–
ER/PR status, n (%)§						
ER+/PR+	206 (57.4)	193 (54.5)	253 (58.0)	237 (55.1)	46 (60.5)	44 (57.9)
ER+/PR−	141 (39.3)	152 (42.9)	167 (38.3)	181 (42.1)	26 (34.2)	29 (38.2)
ER−/PR+	3 (0.8)	2 (0.6)	3 (0.7)	2 (0.5)	–	–
Primary endocrine resistance¶	105 (29.2)	116 (32.8)	128 (29.4)	140 (32.6)	23 (30.3)	24 (31.6)
De-novo disease at diagnosis, n (%)	111 (30.9)	104 (29.4)	133 (30.5)	132 (30.7)	22 (28.9)	28 (36.8)
Bone-only disease at baseline, n (%)	11 (3.1)	10 (2.8)	13 (3.0)	13 (3.0)	2 (2.6)	3 (3.9)
Visceral disease at baseline, n (%)	309 (86.1)	299 (84.5)	376 (86.2)	364 (84.7)	66 (86.8)	65 (85.5)
Liver metastases at baseline, n (%)	243 (67.7)	232 (65.5)	296 (67.9)	283 (65.8)	52 (68.4)	51 (67.1)

Prior therapies

	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
ET in the metastatic setting						
Lines of ET						
Number of lines, median (range)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Number of lines, n (%)						
1	54 (15.1)	67 (19.0)	65 (14.9)	82 (19.2)	11 (14.5)	15 (19.7)
≤6 months on first-line ET + CDK4/6i	33 (9.2)	33 (9.4)	37 (8.5)	40 (9.3)	4 (5.3)	7 (9.2)
2	242 (67.6)	236 (67.0)	295 (67.8)	288 (67.3)	52 (68.4)	52 (68.4)
≥3	62 (17.3)	49 (13.9)	75 (17.2)	58 (13.6)	13 (17.1)	9 (11.8)
Prior therapies, n (%)						
ET monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
ET with CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
ET with other targeted therapy†	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)
Adjuvant/neoadjuvant setting‡						
Prior therapies, n (%)						
ET	227 (63.2)	218 (61.6)	275 (63.1)	256 (59.5)	48 (63.2)	38 (50.0)
Cytotoxic chemotherapy	192 (53.5)	196 (55.4)	228 (52.3)	234 (54.4)	36 (47.4)	38 (50.0)
Taxane	151 (42.1)	151 (42.7)	179 (41.1)	177 (41.2)	28 (36.8)	26 (34.2)
Anthracycline	167 (46.5)	173 (48.9)	197 (45.2)	206 (47.9)	30 (39.5)	33 (43.4)

PFS (BICR) in HER2-low: primary endpoint

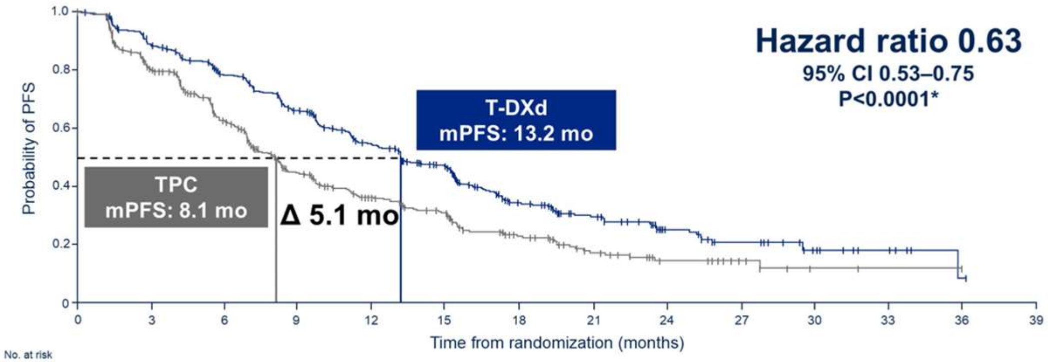


No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
T-DXd	359	310	265	213	163	131	72	49	28	17	10	6	1	0
TPC	354	254	192	118	85	65	37	19	10	6	2	1	1	0

T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

PFS (BICR) in ITT: key secondary endpoint



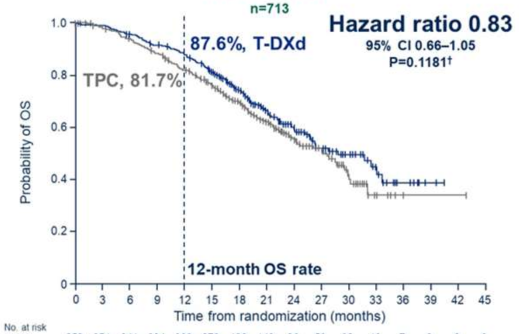
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
T-DXd	436	375	319	258	199	156	82	56	32	21	11	6	1	0
TPC	430	306	224	142	103	79	44	25	13	7	2	1	1	0

T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

*P-value of <0.015 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; ITT, intent-to-treat; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

OS in HER2-low and ITT: key secondary endpoints (~40% maturity)

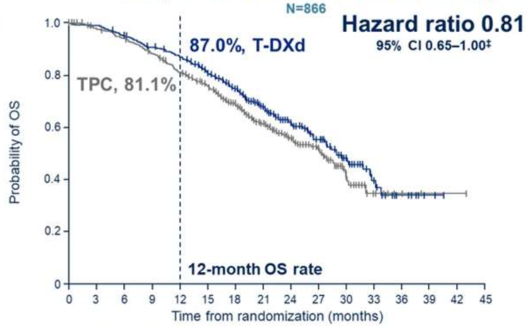
HER2-low*
n=713



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
T-DXd	359	354	341	324	309	279	198	140	96	53	32	16	7	2	0	0
TPC	354	333	319	298	273	247	185	126	86	53	23	6	2	1	1	0

20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

ITT (HER2-low + HER2-ultralow)
N=866



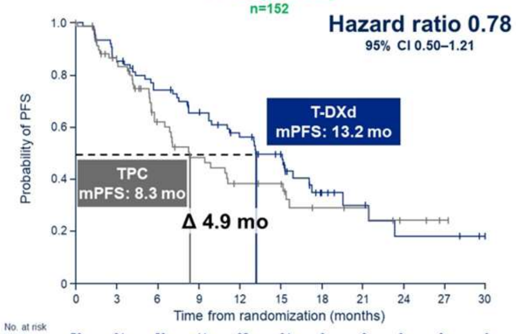
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
T-DXd	436	431	412	391	373	329	235	169	120	69	39	16	7	2	0	0
TPC	430	402	387	360	328	292	210	143	101	62	27	9	3	1	1	0

17.9% of patients in the TPC group received T-DXd post treatment discontinuation (ITT)

*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow up was 18.2 months (ITT)
CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

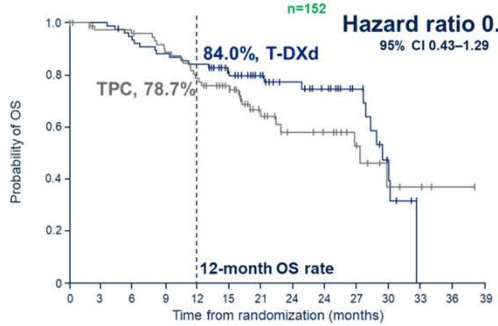
PFS and OS in HER2-ultralow: prespecified exploratory analyses

PFS (BICR)
n=152



No. at risk	0	3	6	9	12	15	18	21	24	27	30
T-DXd	76	64	53	44	35	24	9	6	3	3	0
TPC	76	52	32	24	18	14	7	6	3	1	0

OS*
n=152



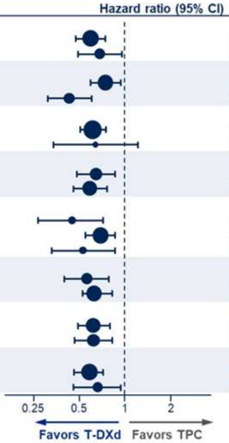
No. at risk	0	3	6	9	12	15	21	24	24	27	30	33	36	39
T-DXd	76	76	70	66	63	49	36	28	23	15	6	0	0	0
TPC	76	69	68	62	55	45	25	17	15	9	4	3	1	0

PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

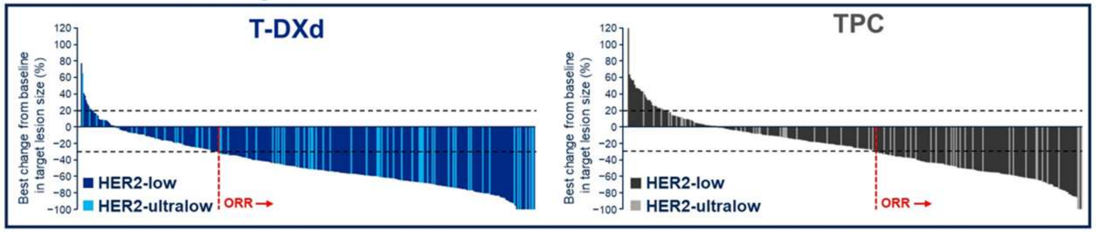
PFS (BICR) in HER2-low: subgroup analysis

	No. of events / no. of patients T-DXd	No. of events / no. of patients TPC	mPFS (95% CI), months T-DXd	mPFS (95% CI), months TPC	Hazard ratio (95% CI)
Age					
<65 years	158/252	157/244	13.2 (11.2–15.2)	7.8 (6.9–8.6)	0.59 (0.47–0.74)
≥65 years	67/107	75/110	13.2 (9.7–17.0)	8.5 (6.9–11.5)	0.68 (0.49–0.95)
HER2 status*					
IHC 1+	157/238	150/234	12.9 (11.0–15.2)	8.2 (7.1–9.8)	0.74 (0.59–0.93)
IHC 2+/ISH−	65/117	80/118	15.2 (12.2–21.4)	7.0 (6.2–8.4)	0.43 (0.31–0.60)
Prior CDK4/6i					
Yes	206/324	212/320	13.1 (11.2–15.2)	7.9 (6.9–8.6)	0.61 (0.51–0.74)
No	19/35	20/34	16.1 (9.7–NE)	11.1 (6.9–20.6)	0.64 (0.34–1.21)
Prior taxane use (adjuvant/neoadjuvant setting)					
Yes	94/151	101/151	12.9 (9.7–14.0)	7.4 (6.3–9.3)	0.64 (0.48–0.85)
No	131/208	131/203	15.0 (11.3–16.5)	8.3 (7.0–9.7)	0.59 (0.46–0.76)
Number of prior lines of ET (metastatic setting)					
1	27/54	45/67	15.2 (9.7–19.1)	8.0 (5.7–8.5)	0.45 (0.27–0.72)
2	158/242	153/236	13.1 (11.2–15.2)	8.3 (6.9–10.0)	0.69 (0.55–0.86)
≥3	39/62	33/49	12.3 (8.3–18.5)	8.1 (5.4–9.7)	0.53 (0.33–0.86)
Endocrine resistance					
Primary	66/105	83/116	13.1 (10.0–15.2)	6.8 (5.3–8.1)	0.56 (0.40–0.78)
Secondary	159/254	148/236	13.2 (11.3–15.5)	9.0 (7.5–11.1)	0.65 (0.52–0.82)
Choice of chemotherapy†					
Capecitabine	131/220	134/208	13.5 (11.4–15.4)	8.5 (7.0–11.4)	0.62 (0.49–0.79)
Taxanes (Nab-paclitaxel + paclitaxel)	94/139	98/146	12.9 (9.6–15.4)	7.3 (6.4–8.3)	0.62 (0.46–0.82)
Liver metastases					
Yes	163/243	166/232	11.4 (9.8–13.2)	7.0 (6.4–8.1)	0.58 (0.46–0.72)
No	62/116	66/122	17.0 (15.0–19.4)	11.3 (8.2–14.8)	0.66 (0.46–0.93)



Size of circle is proportional to the number of events
*Based on central laboratory data (ie the HER2 result from the most recent evaluable sample prior to randomization); †specified by the investigator prior to randomization
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ET, endocrine therapy;
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; (m)PFS, (median) progression-free survival;
NE, not evaluable; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Antitumor activity



	HER2-low* T-DXd (n=359)	HER2-low* TPC (n=354)	ITT T-DXd (n=436)	ITT TPC (n=430)	HER2-ultralow* T-DXd (n=76)	HER2-ultralow* TPC (n=76)
Confirmed ORR, n (%)	**203 (56.5)**	**114 (32.2)**	**250 (57.3)**	**134 (31.2)**	**47 (61.8)**	**20 (26.3)**
Best overall response, n (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Median duration of response, mo	14.1	8.6	14.3	8.6	14.3	14.1

Overall safety summary

	Safety analysis set* T-DXd (n=434)	Safety analysis set* TPC (n=417)
Total exposure, patient-years	438.5	263.5
Any TEAE, n (%)	429 (98.8)	397 (95.2)
Treatment-related TEAEs, n (%)	417 (96.1)	373 (89.4)
Grade ≥3	176 (40.6)	131 (31.4)
Serious TEAEs, n (%)	88 (20.3)	67 (16.1)
TEAEs associated with treatment discontinuation, n (%)	62 (14.3)	39 (9.4)
TEAEs associated with dose interruptions, n (%)	210 (48.4)	160 (38.4)
TEAEs associated with dose reductions, n (%)	107 (24.7)	161 (38.6)
TEAEs leading to death, n (%)	11 (2.5)	6 (1.4)
Treatment related (investigator assessed)‡	5 (1.2)	0

- **Median treatment duration:**
  - **T-DXd: 11.0 mo (range 0.4–39.6)**
  - **TPC: 5.6 mo (range 0.1–35.9)**
- Most common TEAE associated with treatment discontinuation:
  - T-DXd: 5.3%, pneumonitis†
  - TPC: 1.4%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction:
  - T-DXd: 4.4%, nausea
  - TPC: 16.5%, PPE

Adverse events of special interest

Adjudicated as drug-related interstitial lung disease / pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n=434)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)	49 (11.3)
TPC (n=417)	0	1 (0.2)	0	0	0	1 (0.2)

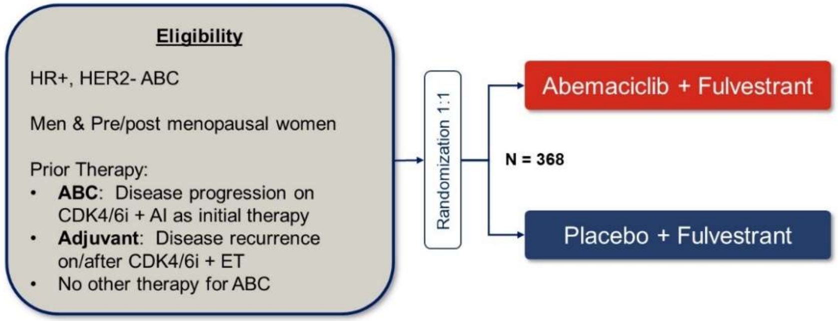
Left ventricular dysfunction†

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
T-DXd (n=434)	1 (0.2)	31 (7.1)	3 (0.7)	0	0	35 (8.1)
TPC (n=417)	0	11 (2.6)	1 (0.2)	0	0	12 (2.9)
Cardiac failure						
T-DXd (n=434)	0	0	0	0	0	0
TPC (n=417)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.7)

Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the Phase 3 postMONARCH trial

Kevin Kalinsky[1], Giampaolo Bianchini[2], Erika P. Hamilton[3], Stephanie L. Graff[4], Kyong Hwa Park[5], Rinath Jeselsohn[6], Umut Demirci[7], Miguel Martin[8], Rachel M. Layman[9], Sara Hurvitz[10], Sarah Sammons[11], Peter A. Kaufman[12], Montserrat Munoz[13],

postMONARCH Study Design



Primary Endpoint:
Investigator-Assessed PFS

Secondary Endpoints:
OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

Stratification Factors:
- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region

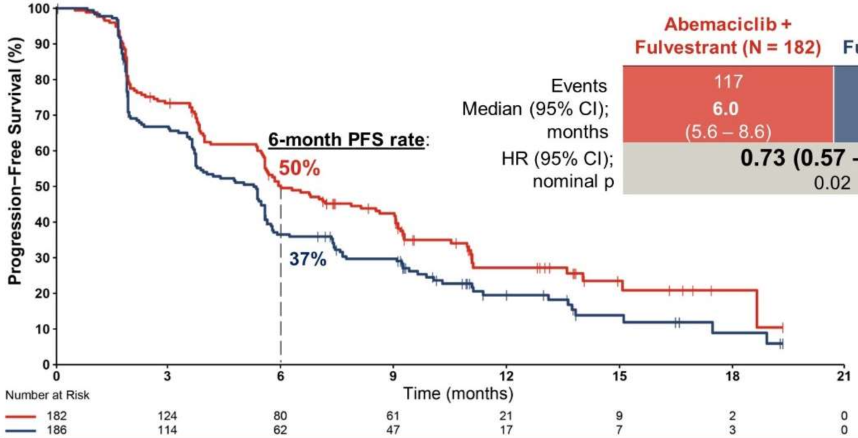
- Enrolled March 2022 to June 2023 across 96 centers in 16 countries
- Scans every 8 weeks for the first 12 months, then every 12 weeks
- Primary outcome targeted 251 events; interim analysis planned at ~70% of events
- Assuming a hazard ratio (HR) of 0.70, ~80% power to detect abemaciclib superiority, with a cumulative 2-sided type I error of 0.05
- Biomarker ctDNA analyzed by GuardantINFINITY assay

Balanced Baseline Patient & Disease Characteristics

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestrant N=186 (%)
Age	Median (range)	58 (27, 86)	61 (28, 85)
	< 65 years	69	63
	≥ 65 years	31	37
Gender	Female	99	100
ECOG	0	57	58
	1	43	43
Region	Other (includes EU)	73	72
	Asia	12	13
	USA	15	15
Race	White	82	82
	Asian	12	15
	Black/African American	4	2
Ethnicity	Not Hispanic/Latino	74	77
	Hispanic/Latino	15	15
HR Status	ER+	100	99
	PR+	79	81

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestrant N=186 (%)
Measurable Disease		72	68
Visceral metastasis		62	59
Site of Metastasis	Liver	37	38
	Bone-Only	18	23
Prior CDK4/6i Setting	ABC	100	98
	Adjuvant	0	2
Prior CDK4/6i	Palbociclib	59	59
	Ribociclib	34	33
	Abemaciclib	8	8
Prior CDK4/6i Duration	≥12 months*	71	77
	<12 months^	29	22
Median Prior CDK4/6i Duration (mo; range)#	All	19 (2, 110)	21 (3, 87)
	Palbociclib	19	23
	Ribociclib	15	18
	Abemaciclib	26	21

Primary Analysis: Abemaciclib Improved Investigator-Assessed PFS



	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	117	141
Median (95% CI); months	6.0 (5.6 – 8.6)	5.3 (3.7 – 5.6)
HR (95% CI); nominal p	0.73 (0.57 – 0.95) 0.02	

Abemaciclib led to 27% reduction in the risk of developing PFS event

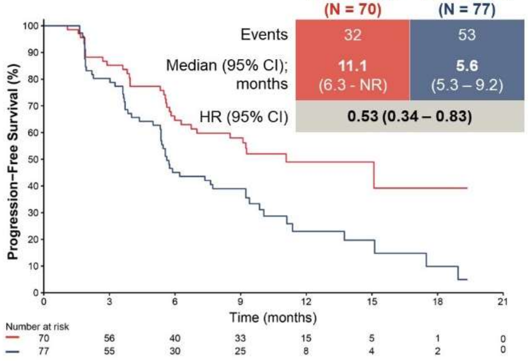
Secondary Analysis: Addition of Abemaciclib Improved ORR

	Abemaciclib + Fulvestrant N = 182	Placebo + Fulvestrant N = 186	Nominal p-value
Measurable disease population	131	127	
ORR by investigator, %	17	7	0.0145
ORR by BICR, %	23	8	0.0008

Subgroup Analysis: Investigator-Assessed PFS by Visceral Metastasis

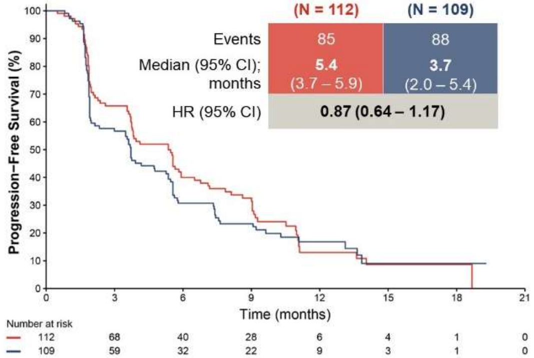
No visceral metastasis

	Abemaciclib + Fulvestrant (N = 70)	Placebo + Fulvestrant (N = 77)
Events	32	53
Median (95% CI); months	11.1 (6.3 - NR)	5.6 (5.3 – 9.2)
HR (95% CI)	0.53 (0.34 – 0.83)	



Visceral metastasis

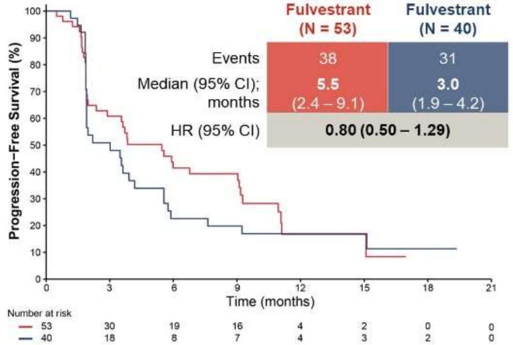
	Abemaciclib + Fulvestrant (N = 112)	Placebo + Fulvestrant (N = 109)
Events	85	88
Median (95% CI); months	5.4 (3.7 – 5.9)	3.7 (2.0 – 5.4)
HR (95% CI)	0.87 (0.64 – 1.17)	



Subgroup Analysis: Investigator-Assessed PFS by Prior CDK4/6i Duration

< 12 months^

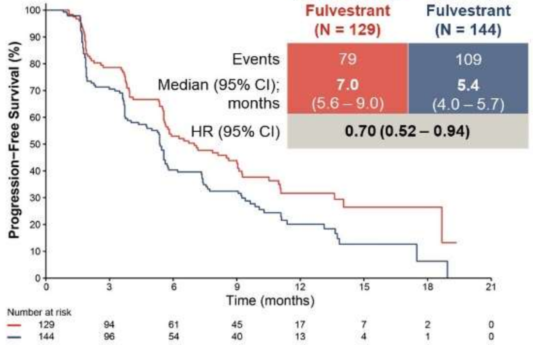
	Abemaciclib + Fulvestrant (N = 53)	Placebo + Fulvestrant (N = 40)
Events	38	31
Median (95% CI); months	5.5 (2.4 – 9.1)	3.0 (1.9 – 4.2)
HR (95% CI)	0.80 (0.50 – 1.29)	



^ < 12 months ABC or recurrence on EBC therapy

≥ 12 months*

	Abemaciclib + Fulvestrant (N = 129)	Placebo + Fulvestrant (N = 144)
Events	79	109
Median (95% CI); months	7.0 (5.6 – 9.0)	5.4 (4.0 – 5.7)
HR (95% CI)	0.70 (0.52 – 0.94)	

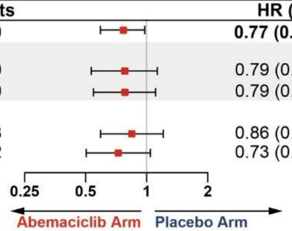


* ≥ 12 months ABC or recurrence after EBC therapy

Exploratory: Consistent Effect Across Biomarker Subgroups

		Abemaciclib + Fulvestrant N=182	Placebo + Fulvestrant N=186
ctDNA Evaluable Population		161 (88%)	159 (85%)
Biomarker Status	*ESR1* mutation	40%	51%
	PIK3CA or *PTEN* or *AKT1* alteration	46%	52%

Subgroup	n	events	HR (95% CI)	Interaction p-value
ctDNA Evaluable Population	**320**	**230**	**0.77 (0.59 to 1.00)**	
ESR1				0.98
Detected	145	110	0.79 (0.54 to 1.15)	
Not detected	175	120	0.79 (0.55 to 1.13)	
PIK3CA* or *AKT1* or *PTEN				0.55
Detected	156	118	0.86 (0.60 to 1.23)	
Not detected	164	112	0.73 (0.51 to 1.06)	



Safety Consistent with Known Abemaciclib Profile

	Abemaciclib + Fulvestrant N = 181	Placebo + Fulvestrant N = 185
Grade 5 TRAE+, n (%)	1 (0.6)	0
Dose reductions due to AE, n (%)	55 (30)	6 (3)
Discontinuations due to AE, n (%)	11 (6)	0

	Abemaciclib + Fulvestrant, N=181, %		Placebo + Fulvestrant, N=185, %	
TEAEs	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	**97**	**55**	**82**	**20**
Diarrhea	75	4	17	2
Neutropenia*	41	25^	3	0
Anemia*	35	11	15	4
Fatigue*	33	3	23	1
Nausea	33	3	18	0
Abdominal Pain*	24	2	16	0
Vomiting	20	2	6	0
Thrombocytopenia*	18	4	6	2
Decreased Appetite	18	1	7	0
Leukopenia*	18	8	3	0
AST Increased	15	6	11	2
ALT Increased	13	4	10	2
Arthralgia	12	1	12	1
Creatinine Increased	11	0	2	0
Cough	11	0	7	0
VTE*	5	2#	3	1
ILD*	3	1§	1	0

Post progression CDKi trials

	postMONARCH		MAINTAIN		PALMIRA		PACE	
ARM	ABEMA	PLAC	RIBO	PLAC	PALBO	CONT	PALBO	CONT
PFS	6.0 mos.	5.3 mos.	5.3 mos.	2.8 mos.	4.9 mos.	3.6 mos.	4.6 mos	4.8 mos.
▲	0.7 mos.		2.5 mos.		1.3 mos		-0.2 mos	
HR	0.73		0.57		0.84		1.11	
P value	0.02		0.006		0.149		0.06	

Control arm had longer PFS in postMONARCH likely indicating more ET-sensitive disease

Kalinsky et al ASCO 2024, Kalinsky et al J Clin Oncol 2023, Llombart-Cussac et al ASCO 2023, Mayer et al SABCS 2022

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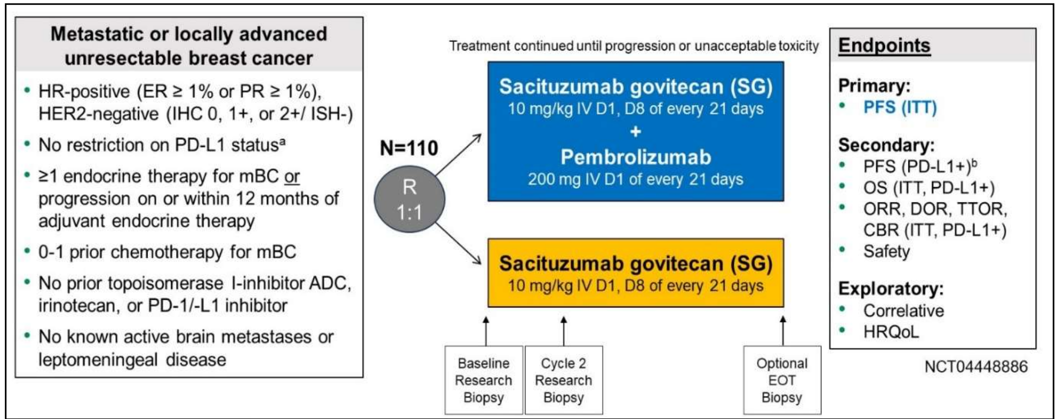
Take homes

- The addition of abemaciclib to fulvestrant significantly improved PFS in patients who previously received a CDKi in the first-line setting
- Patients who had received longer durations of CDKi in the first-line setting and those without visceral metastases had longer PFS
- Switching CDKi at progression is an option for patients in the second-line and greater setting, especially in the absence of a targetable mutation

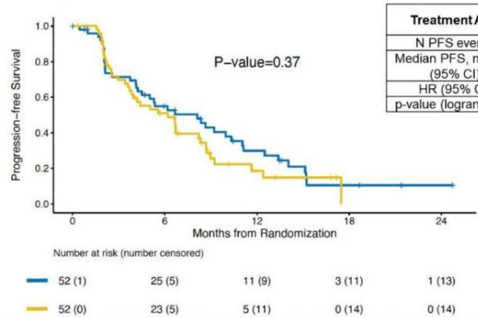
SACI-IO HR+: A randomized phase II trial of sacituzumab govitecan with or without pembrolizumab in patients with metastatic hormone receptor-positive/ HER2-negative breast cancer

Ana C. Garrido-Castro[1], Se Eun Kim[2], Jennifer Desrosiers[1], Rita Nanda[3], Yara Abdou[4], Amy S. Clark[5], Ruth Sacks[6], Thomas O'Connor[1], Natalie Sinclair[1], Steve Lo[7], Amy Thomas[1], Eileen Wrabel[1], Tess O'Meara[1], Nancy U. Lin[1], Harold J. Burstein[1], Mengni He[8], David Rimm[8], Elizabeth A. Mittendorf[1], Nabihah Tayob[2], Sara M. Tolaney[1]



- PDL1 CPS ≥ 1: 38.5% (PDL1 CPS ≥ 10: 6.7%)
- Tto previo con iCDK: 88%
- QT previa para M1: 49%

Progression-Free Survival



Treatment Arm	SG + Pembrolizumab (N=52)	SG (N=52)
N PFS events	38	38
Median PFS, months (95% CI)	**8.12** (4.51-11.12)	**6.22** (3.85-8.68)
HR (95% CI)	**0.81** (0.51-1.28)	
p-value (logrank test)	0.37	

The addition of pembrolizumab to SG showed a numerical improvement in median PFS (Δ = 1.9 months) compared to SG alone that did not reach statistical significance

Safety Summary

	SG + Pembrolizumab (N=52)	SG (N=52)
Any treatment-emergent AE (TEAE)	51 (98.1%)	50 (96.2%)
Any treatment-related AE (TRAE)	48 (92.3%)	49 (94.2%)
Any TEAE leading to dose discontinuation	3 (5.8%)	1 (1.9%)

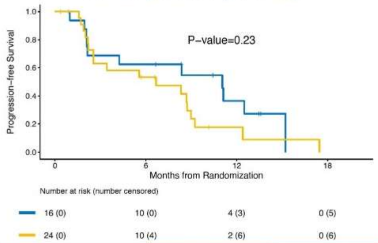
Treatment emergent AEs ≥15%	Grade ≥ 2	Grade 3-4	Grade ≥ 2	Grade 3-4
Neutrophil count decreased	36 (69.2%)	28 (53.8%)	31 (59.6%)	23 (44.2%)
Anemia	18 (34.6%)	3 (5.8%)	14 (26.9%)	5 (9.6%)
White blood cell decreased	14 (26.9%)	12 (23.1%)	8 (15.4%)	4 (7.7%)
Lymphocyte count decreased	8 (15.4%)	6 (11.5%)	3 (5.8%)	1 (1.9%)
Diarrhea	12 (23.1%)	3 (5.8%)	20 (38.5%)	4 (7.7%)
Nausea	15 (28.8%)	2 (3.8%)	17 (32.7%)	5 (9.6%)
Alopecia	22 (42.3%)	--	20 (38.5%)	--
Fatigue	20 (38.5%)	1 (1.9%)	18 (34.6%)	3 (5.8%)
Anorexia	6 (11.5%)	0 (0%)	9 (17.3%)	0 (0%)

The most common grade ≥ 3 TEAEs were neutropenia (54%), leukopenia (23%), lymphopenia (12%), febrile neutropenia (6%), anemia (6%), and diarrhea (6%) with **SG + Pembrolizumab**, and neutropenia (44%), anemia (10%), nausea (10%), diarrhea (8%), leukopenia (8%), fatigue (6%) and hypertension (6%) with **SG**

Progression-Free Survival by PD-L1 IHC status

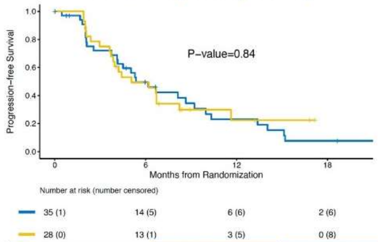
Señal en PDL1+

PD-L1-positive (CPS ≥1)



Treatment Arm	SG + Pembrolizumab (N=16)	SG (N=24)
N PFS events	11	18
Median PFS, mo (95% CI)	**11.05** (2.14-NA)	**6.68** (2.53-9.24)
HR (95% CI)	**0.62** (0.29-1.36)	
p-value (logrank test)	0.23	

PD-L1-negative (CPS <1)



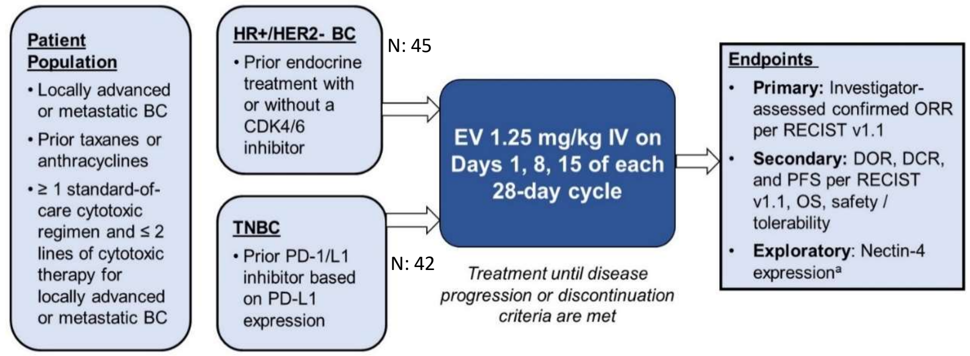
Treatment Arm	SG + Pembrolizumab (N=35)	SG (N=28)
N PFS events	27	20
Median PFS, mo (95% CI)	**5.36** (4.14-9.97)	**5.07** (3.85-NA)
HR (95% CI)	**1.06** (0.59-1.90)	
p-value (logrank test)	0.84	

Enfortumab Vedotin in the HR+/HER2− and Triple-Negative Breast Cancer Cohorts of EV-202

Antonio Giordano, MD, PhD;[1] Arif Ali Awan, MD;[2] Justine Yang Bruce, MD;[3] Hope S. Rugo, MD;[4] Jennifer R. Diamond, MD;[5] Yelena Novik, MD;[6] Joaquina Baranda, MD;[7] Kei Muro, MD, PhD;[8] Makiko Ono, MD;[9] Rita Nanda, MD;[10] Jason Kaplan, MD;[11] Seema Gorla, MD;[11] Shubin Liu, MSc;[11] Michele Wozniak, PhD;[11] Anthony Lee, PharmD;[12] Tiffany Traina, MD[13]

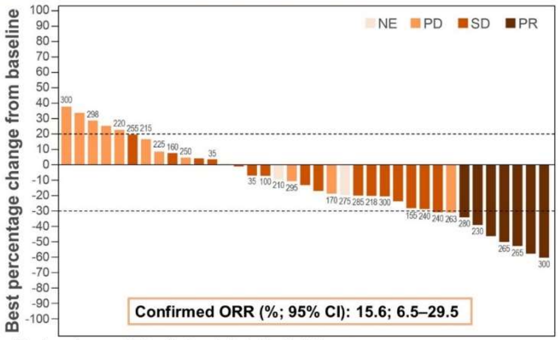
- Nectin-4 is a cell-adhesion molecule highly expressed in solid malignancies[1]
- Enfortumab vedotin (EV) is a Nectin-4–directed antibody–drug conjugate[2]
- EV is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma[3]

EV-202 Study Design: BC Cohorts



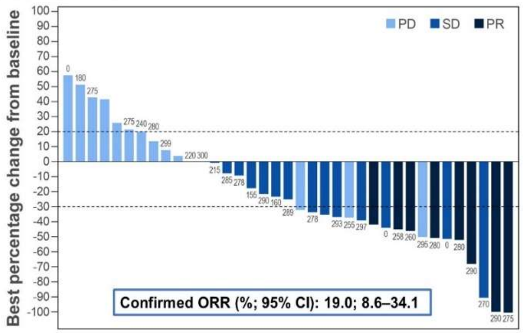
Note: The prespecified ORR efficacy thresholds were not met

Response Was Not Dependent on Nectin-4 Expression in Patients with HR+/HER2− Breast Cancer



Numbers above and below the bars indicate Nectin-4 H-scores.

Response Was Not Dependent on Nectin-4 Expression in Patients with TNBC



Numbers above and below the bars indicate Nectin-4 H-scores.

Treatment-Related Adverse Events (1/2)

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Parameter	HR+/HER2- Breast Cancer n=45		Triple-Negative Breast Cancer n=42	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TRAEs, overall, n (%)	45 (100.0)	20 (44.4)	41 (97.6)	12 (28.6)
TRAEs in ≥15% of participants for either cohort, n (%)				
Fatigue	20 (44.4)	0	12 (28.6)	0
Pruritis	19 (42.2)	3 (6.7)	14 (33.3)	1 (2.4)
Rash maculopapular	18 (40.0)	7 (15.6)	13 (31.0)	1 (2.4)
Nausea	17 (37.8)	1 (2.2)	16 (38.1)	1 (2.4)
Dysgeusia	10 (22.2)	0	13 (31.0)	0
Diarrhea	10 (22.2)	1 (2.2)	5 (11.9)	0
Dry skin	10 (22.2)	0	11 (26.2)	0
Alopecia	9 (20.0)	0	12 (28.6)	0
AST increased	8 (17.8)	3 (6.7)	10 (23.8)	2 (4.8)
ALT increased	8 (17.8)	1 (2.2)	9 (21.4)	1 (2.4)
Decreased appetite	7 (15.6)	0	10 (23.8)	0
Peripheral sensory neuropathy	7 (15.6)	1 (2.2)	9 (21.4)	0
Constipation	7 (15.6)	0	3 (7.1)	0
Anemia	4 (8.9)	0	7 (16.7)	0

Sacituzumab Tirumotecan (Sac-TMT, Also Known as SKB264/MK-2870) in Patients With Previously Treated Locally Recurrent or Metastatic Triple-Negative Breast Cancer (TNBC): Results From the Phase III OptiTROP-Breast01 Study

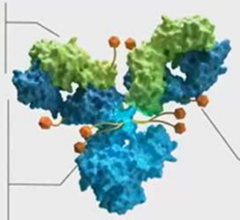
Binghe Xu,[1] Yongmei Yin,[2] Ying Fan,[1] Quchang Ouyang,[3] Lihua Song,[4] Xiaojia Wang,[5] Wei Li,[6] Man Li,[7] Xi Yan,[8] Shusen Wang,[9] Tao Sun,[10] Yue'e Teng,[11] Xianjun Tang,[12] Zhongsheng Tong,[13] Zhengkui Sun,[14] Xiaoping Jin,[15] Yina Diao,[15] Gesha Liu,[15] Junyou Ge[15]

Design of Sacituzumab Tirumotecan (sac-TMT)

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

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

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



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

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

OptiTROP-Breast01: Randomized, Controlled, Open-Label Phase III Study (NCT05347134)

Patients with locally recurrent or metastatic TNBC
- Relapsed or refractory to 2 or more prior chemotherapy regimens for unresectable, locally advanced or metastatic disease
  - For prior therapy, 1 could be in the (neo)adjuvant setting, provided progression occurred during treatment or within 12 months after treatment discontinuation
- Received taxane(s) in any setting

R 1:1

N: 263

Sac-TMT, 5 mg/kg IV, every 2 weeks

Physician's choice of chemotherapy: eribulin, capecitabine, gemcitabine, or vinorelbine

Treatment until disease progression, unacceptable toxicity or any other reason for discontinuation

Endpoints[a]
Primary
- PFS by BICR

Secondary
- OS
- PFS by investigator assessment
- ORR, DOR
- Safety

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

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

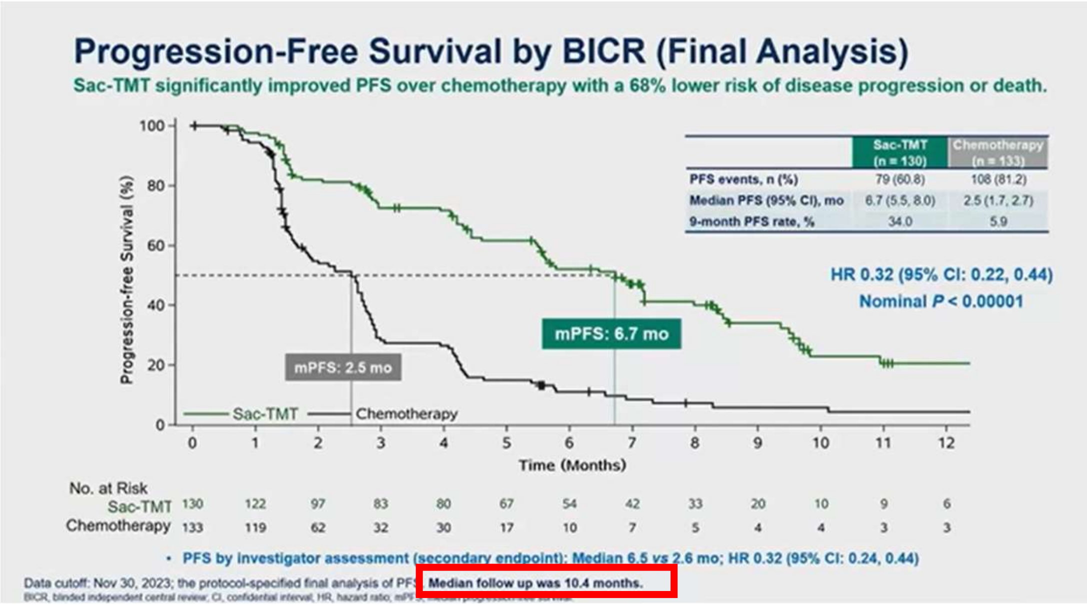
[a]Tumor response was assessed using RECIST version 1.1.
BICR, blinded independent central review; DOR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.

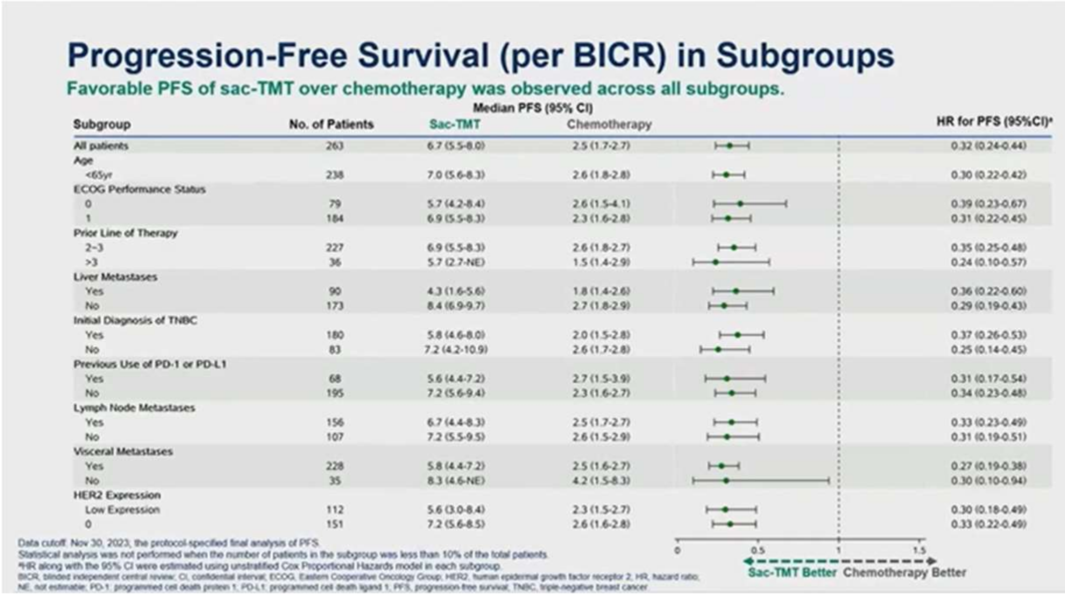
Patient Demographics and Baseline Characteristics

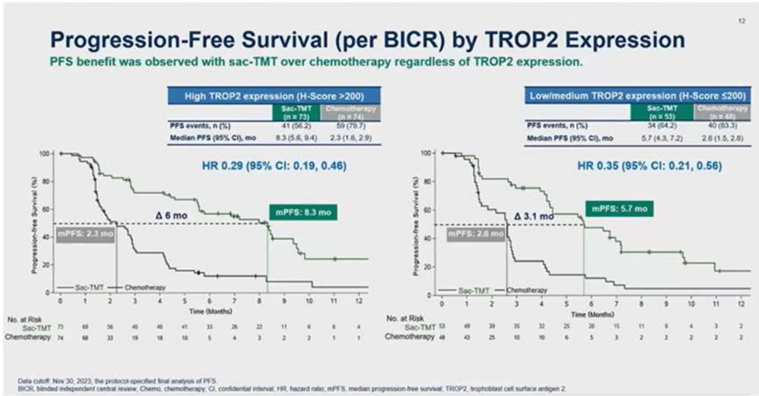
	Sac-TMT (n=130)	Chemotherapy (n=133)
Female, n (%)	130 (100)	133 (100)
Median age (range), yr	51 (19, 70)	51 (25, 72)
Age <65 years, n (%)	119 (91.5)	119 (89.5)
TNBC at initial diagnosis, n (%)	92 (70.8)	88 (66.2)
ECOG PS, n (%)		
0	40 (30.8)	39 (29.3)
1	90 (69.2)	94 (70.7)
Location of metastases, n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

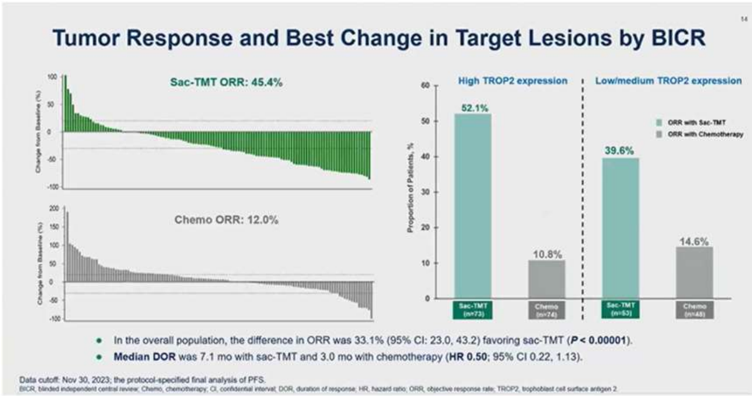
	Sac-TMT (n=130)	Chemotherapy (n=133)
Lines of prior therapy,[b] n (%)		
Median (range)	3.0 (2, 6)	2.0 (2, 6)
2	62 (47.7)	76 (57.1)
3	52 (40.0)	37 (27.8)
>3	16 (12.3)	20 (15.1)
Prior therapy, n (%)		
Taxane(s)	130 (100)	133 (100)
Anthracycline(s)	122 (93.8)	122 (91.7)
PD-1 or PD-L1 inhibitor(s)	32 (24.6)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

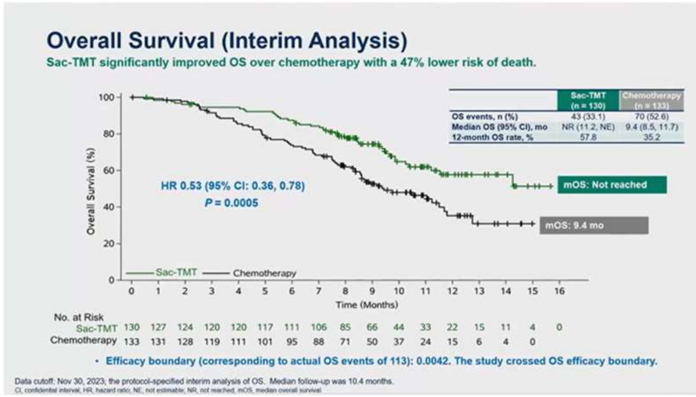
[a]Visceral metastases were defined as the presence of metastases from sites other than soft tissue, skin, lymph nodes, and chest wall.
[b]The prior lines included chemotherapy regimens in the (neo)adjuvant setting provided progression occurred during treatment or within 12 months after treatment discontinuation, and treatment regimens for patients with *BRCA* mutations who had previously received PARP inhibitors.
[c]TROP2 expression was assessed using immunohistochemistry (IHC) by MEDx (a company that specializes in companion diagnostics and provides complete solutions for precision medicine).
BRCA, breast cancer susceptibility gene; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; PARP, poly ADP-ribose polymerase; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2.


Progression-Free Survival by BICR (Final Analysis)
Sac-TMT significantly improved PFS over chemotherapy with a 68% lower risk of disease progression or death.
Sac-TMT (n = 130)
Chemotherapy (n = 133)
PFS events, n (%) 79 (60.8) 108 (81.2)
Median PFS (95% CI), mo 6.7 (5.5, 8.0) 2.5 (1.7, 2.7)
9-month PFS rate, % 34.0 5.9
HR 0.32 (95% CI: 0.22, 0.44)
Nominal P < 0.00001
mPFS: 6.7 mo
mPFS: 2.5 mo
Progression-free Survival (%)
Time (Months)
No. at Risk
Sac-TMT 130 122 97 83 80 67 54 42 33 20 10 9 6
Chemotherapy 133 119 62 32 30 17 10 7 5 4 4 3 3
• PFS by investigator assessment (secondary endpoint): Median 6.5 vs 2.6 mo; HR 0.32 (95% CI: 0.24, 0.44)
Data cutoff: Nov 30, 2023; the protocol-specified final analysis of PFS
Median follow up was 10.4 months.

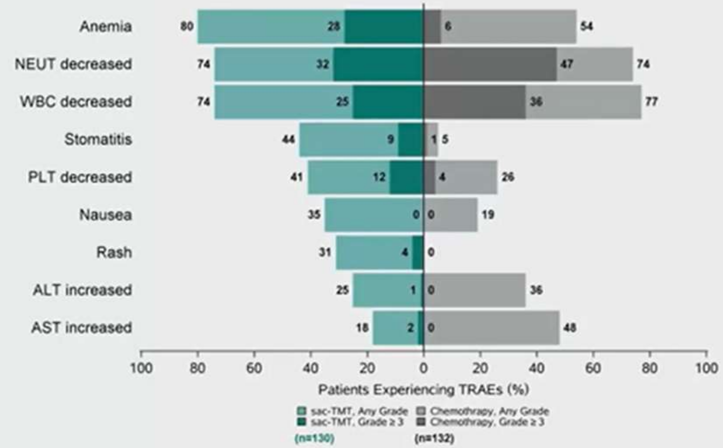

Progression-Free Survival (per BICR) in Subgroups
Favorable PFS of sac-TMT over chemotherapy was observed across all subgroups.
Subgroup | No. of Patients | Median PFS (95% CI) Sac-TMT | Chemotherapy | HR for PFS (95%CI)
All patients 263 6.7 (5.5-8.0) 2.5 (1.7-2.7) 0.32 (0.24-0.44)
Age <65yr 238 7.0 (5.6-8.3) 2.6 (1.8-2.8) 0.30 (0.22-0.42)
ECOG Performance Status 0 79 5.7 (4.2-8.4) 2.6 (1.5-4.1) 0.39 (0.23-0.67)
1 184 6.9 (5.5-8.3) 2.3 (1.6-2.8) 0.31 (0.22-0.45)
Prior Line of Therapy 2-3 227 6.9 (5.5-8.3) 2.6 (1.8-2.7) 0.35 (0.25-0.48)
>3 36 5.7 (2.7-NE) 1.5 (1.4-2.9) 0.24 (0.10-0.57)
Liver Metastases Yes 90 4.3 (1.6-5.6) 1.8 (1.4-2.6) 0.36 (0.22-0.60)
No 173 8.4 (6.9-9.7) 2.7 (1.8-2.9) 0.29 (0.19-0.43)
Initial Diagnosis of TNBC Yes 180 5.8 (4.6-8.0) 2.0 (1.5-2.8) 0.37 (0.26-0.53)
No 83 7.2 (4.2-10.9) 2.6 (1.7-2.8) 0.25 (0.14-0.45)
Previous Use of PD-1 or PD-L1 Yes 68 5.6 (4.4-7.2) 2.7 (1.5-3.9) 0.31 (0.17-0.54)
No 195 7.2 (5.6-9.4) 2.3 (1.6-2.7) 0.34 (0.23-0.48)
Lymph Node Metastases Yes 156 6.7 (4.4-8.3) 2.5 (1.7-2.7) 0.33 (0.23-0.49)
No 107 7.2 (5.5-9.5) 2.6 (1.5-2.9) 0.31 (0.19-0.51)
Visceral Metastases Yes 228 5.8 (4.4-7.2) 2.5 (1.6-2.7) 0.27 (0.19-0.38)
No 35 8.3 (4.6-NE) 4.2 (1.5-8.3) 0.30 (0.10-0.94)
HER2 Expression Low Expression 112 5.6 (3.0-8.4) 2.3 (1.5-2.7) 0.30 (0.18-0.49)
0 151 7.2 (5.6-8.5) 2.6 (1.6-2.8) 0.33 (0.22-0.49)
Sac-TMT Better Chemotherapy Better
Data cutoff: Nov 30, 2023; the protocol-specified final analysis of PFS.


Progression-Free Survival (per BICR) by TROP2 Expression
PFS benefit was observed with sac-TMT over chemotherapy regardless of TROP2 expression.
High TROP2 expression (H-Score >200)
HR 0.29 (95% CI: 0.19, 0.46)
Δ 6 mo
mPFS: 8.3 mo
mPFS: 2.3 mo
Low/medium TROP2 expression (H-Score ≤200)
HR 0.35 (95% CI: 0.21, 0.56)
Δ 3.1 mo
mPFS: 5.7 mo
mPFS: 2.6 mo


Tumor Response and Best Change in Target Lesions by BICR
Sac-TMT ORR: 45.4%
Chemo ORR: 12.0%
High TROP2 expression
Low/medium TROP2 expression
52.1%
10.8%
39.6%
14.6%
• In the overall population, the difference in ORR was 33.1% (95% CI: 23.0, 43.2) favoring sac-TMT (P < 0.00001).
• Median DOR was 7.1 mo with sac-TMT and 3.0 mo with chemotherapy (HR 0.50; 95% CI 0.22, 1.13).
Data cutoff: Nov 30, 2023; the protocol-specified final analysis of PFS.


Overall Survival (Interim Analysis)
Sac-TMT significantly improved OS over chemotherapy with a 47% lower risk of death.
Sac-TMT (n = 130) Chemotherapy (n = 133)
OS events, n (%) 43 (33.1) 70 (52.6)
Median OS (95% CI), mo NR (11.2, NE) 9.4 (8.5, 11.7)
12-month OS rate, % 57.8 35.2
HR 0.53 (95% CI: 0.36, 0.78)
P = 0.0005
mOS: Not reached
mOS: 9.4 mo
Time (Months)
No. at Risk
Sac-TMT 130 127 124 120 120 117 111 106 85 66 44 33 22 15 11 4 0
Chemotherapy 133 131 128 119 111 101 95 88 71 50 37 24 15 6 4 0
• Efficacy boundary (corresponding to actual OS events of 113): 0.0042. The study crossed OS efficacy boundary.
Data cutoff: Nov 30, 2023; the protocol-specified interim analysis of OS. Median follow-up was 10.4 months.

TRAEs in ≥ 30% of Patients



- The most common TRAEs for both sac-TMT and chemotherapy were hematologic toxicities.
- Two patients (1.5%) reported peripheral neuropathy (all were grade 1) and one patient (0.8%) reported grade 2 interstitial lung disease (recovered) with sac-TMT.
- Xerophthalmia (grade 2) and blurred vision (grade 1) occurred in one patient each (0.8%) with sac-TMT.

Data cutoff: Jun 21, 2023.
AEs were classified according to the MedDRA system of preferred terms and system organ class and according to severity by NCI CTCAE v5.0.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; NEUT, neutrophil count; PLT, platelet; TRAE, treatment-related adverse event; WBC, white blood cell.

Overall Safety Summary

	Sac-TMT (n=130) n (%)	Chemotherapy (n=132) n (%)
TRAEs	130 (100.0)	127 (96.2)
Grade ≥ 3 TRAEs	75 (57.7)	75 (56.8)
Serious TRAEs	27 (20.8)	17 (12.9)
TRAEs associated with treatment discontinuation	2 (1.5)	2 (1.5)
TRAEs associated with dose reduction	33 (25.4)	21 (15.9)
TRAEs associated with dose interruption	67 (51.5)	53 (40.2)
TRAEs associated with an outcome of death	1 (0.8)	0

- **Median duration of treatment**
  - **Sac-TMT: 15.4 weeks (range, 2.0–44.0)**
  - **Chemotherapy: 8.6 weeks (range, 1.0–40.7)**
- Most common TRAEs associated with dose reduction
  - Sac-TMT: anemia (13.8%) and stomatitis (5.4%)
  - Chemotherapy: NEUT decreased (11.4%) and WBC decreased (6.8%)
- Most common TRAEs associated with dose interruption
  - Sac-TMT *vs* chemotherapy: NEUT decreased (19.2% *vs* 28.0%) and WBC decreased (18.5% *vs* 25.0%)
- One death with sac-TMT was attributed to multiple causes, including COVID-19 infection as well as disease progression.

Data cutoff: Jun 21, 2023.
COVID-19, coronavirus disease 2019; NEUT, neutrophil count; TRAE, treatment-related adverse event; WBC, white blood cell.

Trastuzumab and pertuzumab in combination with eribulin mesylate or a taxane as first-line chemotherapeutic treatment for HER2-positive, locally advanced or metastatic breast cancer: results of a multicenter, randomized, non-inferiority phase 3 trial in Japan (JBCRG-M06/EMERALD)

Toshinari Yamashita MD, PhD, Kanagawa Cancer Center, Kanagawa, Japan

Study design

Patients with HER2+ LABC or MBC

- Age 20–70 years
- No prior use of chemotherapy (excluding T-DM1) for LABC/MBC
- Hormonal or anti-HER2 therapy alone, or their combination as treatment for recurrence, were allowed
- ECOG performance status score 0/1
- Left ventricular ejection fraction (LVEF) ≥50%
- Major organ function preserved
- At least 6 months since prior neoadjuvant or adjuvant cytotoxic chemotherapy

N: 446

R 1:1

Eribulin group (21-day cycle)
Eribulin 1.4 mg/m² days 1, 8
+
H + P[a] day 1

Taxane group (21-day cycle)
Docetaxel 75 mg/m² day 1 or Paclitaxel 80 mg/m² days 1, 8, 15
+
H + P[a] day 1

Primary endpoint :
- Progression-free survival (PFS), investigator-assessed

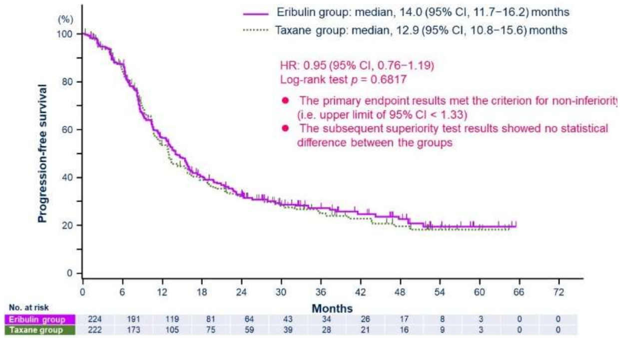
Secondary endpoints
- Objective response rate (ORR)
- Duration of response
- Overall survival (OS)
- Patient-reported outcomes (QoL and neuropathy)
- Safety and biomarker
- New metastases–free survival
- Duration of next treatment

Translational research
- Search for biomarker to improve individual precision therapy

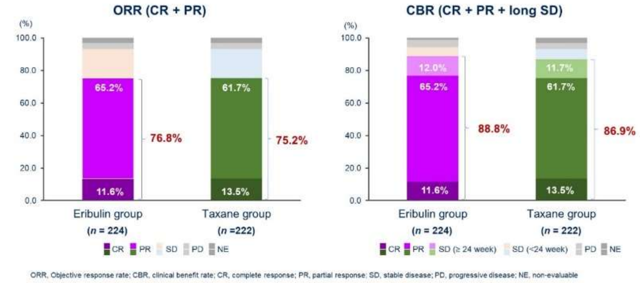
Stratification factors for randomization
- History of perioperative use of taxane
- Prior treatment with HER2-targeting antibody-drug conjugate after recurrence
- Presence of visceral metastases

[a]Trastuzumab (H) : 8 mg/kg loading dose, 6 mg/kg subsequent doses + pertuzumab (P): 840 mg/body loading dose, 420 mg/body subsequent doses
Treatment continued to disease progression or unmanageable toxicity

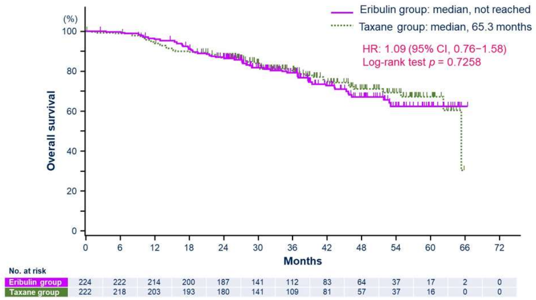
PFS (primary endpoint)



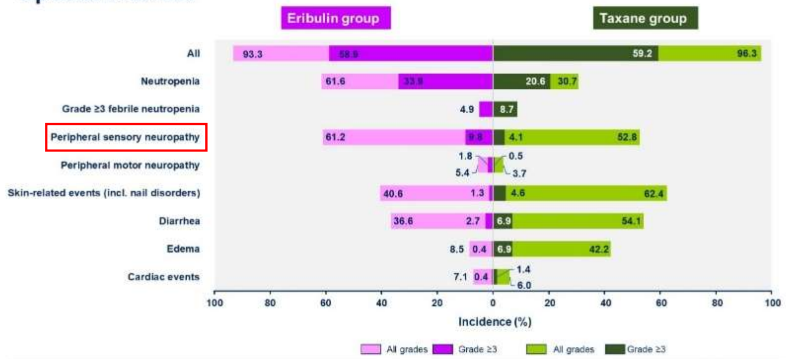
Response rate



OS



Drug-related treatment-emergent adverse events Special interest



	Duration of treatment (weeks)	
	Median	Mean
Eribulin	28.1	37.9
Docetaxel	18.1	20.7
Paclitaxel	20	24.7

Primary results from PATRICIA Cohort C (SOLTI-1303), a randomized phase II study evaluating palbociclib with trastuzumab and endocrine therapy in pretreated HER2-positive and PAM50 luminal advanced breast cancer.

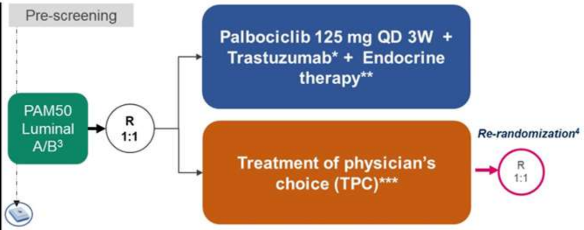
Eva Ciruelos, Tomás Pascual, Guillermo Villacampa, Sonia Pernas, Rodrigo Sanchez Bayona, José Ponce, Blanca Cantos, Santiago Escrivá-de-Romaní, Antonia Perelló, Alvaro Montaño, Eduardo Martínez, Ana Lopez, Mireia Mele, Juan de la Haba, Javier Cortés, Mafalda Oliveira, Lorea Villanueva, Xavier Gonzalez, Patricia Villagrasa and Aleix Prat

PATRICIA Cohort C: Study design

SOLTI

Open-label, multicenter, randomized phase II trial

- ✓ Male or Pre and postmenopausal women
- ✓ **HR+/HER2+ ABC**
- ✓ **PAM50 Luminal A or B subtype** by Prosigna® (research use only)
- ✓ **At least 1L for ABC**[1]
- ✓ **Baseline LVEF** ≥ 50%
- ✓ **Stable CNS metastasis allowed**[2]
- ✓ **No prior CDK4/6i**



Stratification factors:

- Number of previous regimens (1-2 vs ≥ 3)
- Visceral disease (yes vs no)

* Trastuzumab: loading dose of 8mg/kg followed by 6 mg/kg IV or 600 mg SC administration.
** Aromatase inhibitor, fulvestrant or tamoxifen +/- gonadal suppression
*** T-DM1, any endocrine therapy or chemotherapy (gemcitabine, vinorelbine, capecitabine, eribulin, paclitaxel or docetaxel) plus trastuzumab.

Primary endpoint

- Investigator-assessed PFS (RECIST 1.1)

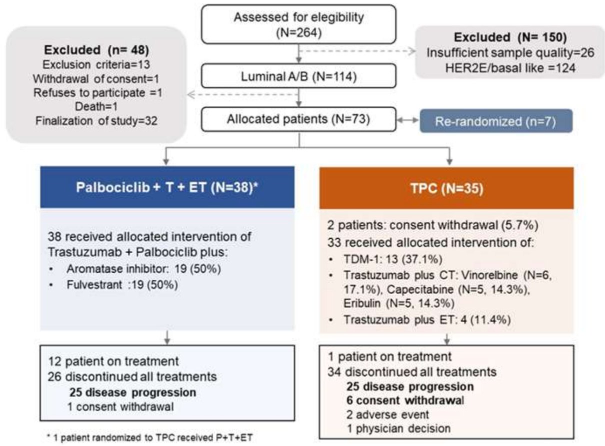
Secondary endpoints

- Overall response rate (ORR)
- Disease control rate (DCR)
- Duration of response
- Safety profile

The trial was **closed earlier** after 73 patients were randomized due to **low recruitment**. At data cut-off, 51 PFS events were observed. The study was **underpowered** based on the protocol assumptions (64% statistical power)

Patient´s disposition

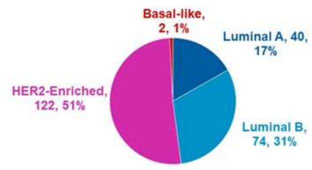
SOLTI



* 1 patient randomized to TPC received P+T+ET

PAM50 subtype distribution

Pre-screened tumors (N = 238)
Tissue type: primary tumor 54.8%; metastatic 45.2%



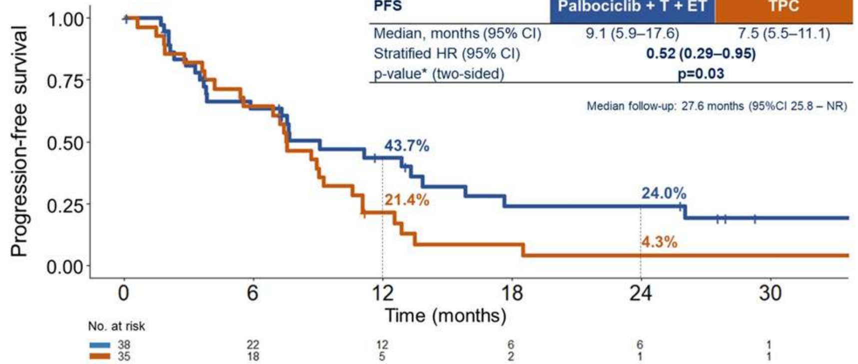
Molecular screening failure rate: 52.1%

Primary objective: Investigator-assessed PFS

SOLTI

PFS	Palbociclib + T + ET	TPC
Median, months (95% CI)	9.1 (5.9–17.6)	7.5 (5.5–11.1)
Stratified HR (95% CI)	**0.52 (0.29–0.95)**	
p-value* (two-sided)	**p=0.03**	

Median follow-up: 27.6 months (95%CI 25.8 – NR)



*p-value was estimated using a stratified mixed effect Cox model

DESTINY-Breast07: dose-expansion analysis of T-DXd monotherapy and T-DXd + pertuzumab in patients with previously untreated HER2+ mBC

Saturday, June 1, 2024

Fabrice André,[1] Erika Hamilton, Sherene Loi, Carey Anders, Peter Schmid, Daniil Stroyakovskiy,

DESTINY-Breast07: a Phase 1b/2, multicenter, open-label, two-part, modular study (NCT04538742)

PATIENT POPULATION

- Locally assessed HER2+ (IHC 3+, IHC 2+/ISH+) advanced/mBC, with measurable disease per RECIST 1.1
- Either no brain metastases or previously treated stable brain metastases
- ECOG PS of 0 or 1

Prior lines of therapy

- No prior therapy for mBC was allowed
- A disease-free interval of ≥12 months from adjuvant HER2-directed therapy or chemotherapy was required
- Prior taxane, trastuzumab, and pertuzumab exposure was allowed in the (neo)adjuvant setting

This is the first dataset of T-DXd monotherapy and T-DXd + pertuzumab as first-line treatment for HER2+ mBC

Randomized

- **Module 0: T-DXd monotherapy (n=75)** (T-DXd 5.4 mg/kg IV Q3W)*
- Module 1: T-DXd + durvalumab
- **Module 2: T-DXd + pertuzumab (n=50)** (T-DXd 5.4 mg/kg IV Q3W + pertuzumab 420 mg IV Q3W, with an 840-mg loading dose)†

Stratification factors

- HR status
- Disease status
- PD-L1 status

Endpoints for the Part 2 dose-expansion phase

Primary
Safety and tolerability, including AEs and SAEs

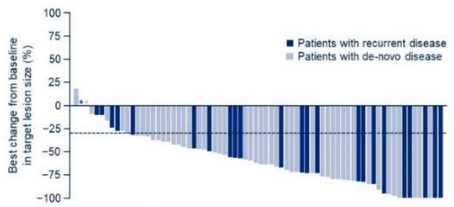
Key secondary
ORR, PFS (evaluated by investigator per RECIST 1.1), and DOR

DCO: December 22, 2023‡

Results reported here are from an interim analysis of the Part 2 dose-expansion phase for Modules 0 and 2 only; the Part 1 dose-finding phase of the study has been described previously[1]

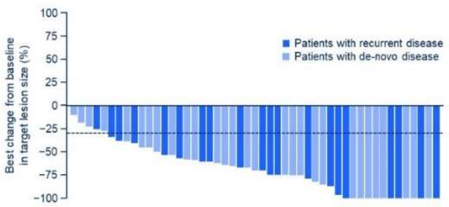
Response to treatment per RECIST 1.1 by investigator

T-DXd monotherapy (n=75)



Confirmed ORR, % (80% CI)	76.0 (68.5–82.4)
Complete response, n (%)	6 (8.0)
Partial response, n (%)	51 (68.0)
Median DOR, months (range)	NE (2.1–28.5)

T-DXd + pertuzumab (n=50)

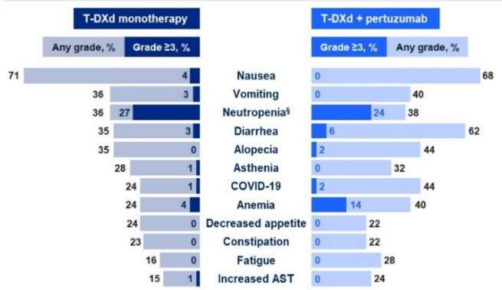


Confirmed ORR, % (80% CI)	84.0 (75.3–90.5)
Complete response, n (%)	10 (20.0)
Partial response, n (%)	32 (64.0)
Median DOR, months (range)	NE (4.5–28.3)

Safety overview

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median actual treatment duration, months (range)*		
T-DXd	16.3 (0.7–30.9)	17.8 (0.9–30.7)
Pertuzumab	N/A	17.6 (0.9–30.7)
Any AE, n (%)	75 (100)	50 (100)
Any AEs Grade ≥3, n (%)	39 (52.0)	31 (62.0)
AEs associated with drug interruptions of T-DXd, n (%)	44 (58.7)	32 (64.0)
AEs associated with dose reduction of T-DXd, n (%)	12 (16.0)	8 (16.0)
AEs associated with discontinuation of T-DXd, n (%)†	8 (10.7)	8 (16.0)
Any SAEs, n (%)	13 (17.3)	13 (26.0)
AEs leading to death, n (%)	1 (1.3)‡	0
AESIs, n (%)		
Pneumonitis (adjudicated as ILD related to T-DXd)	7 (9.3)	7 (14.0)
Grade 1	2 (2.7)	0
Grade 2	5 (6.7)	6 (12.0)
Grade 3	0	1 (2.0)
LV dysfunction (possibly related to T-DXd)	5 (6.7)	2 (4.0)

Any-grade AEs (>20% of patients in either module) with incidence of Grade ≥3 events



Grade 2 diarrhea events were reported in:
- **13.3%** of patients in the **T-DXd monotherapy** module
- **32.0%** of patients in the **T-DXd + pertuzumab** module

- The **safety profiles** of T-DXd and pertuzumab were **consistent** with their individual known profiles
  - The incidence of **ILD/pneumonitis events** was **9.3%** and **14.0%** in the T-DXd monotherapy and T-DXd + pertuzumab modules, respectively; there were **no ILD/pneumonitis-related deaths** in either module
- T-DXd monotherapy and T-DXd + pertuzumab are being evaluated versus THP, in patients with HER2+ mBC in the first-line setting, in the Phase 3 DESTINY-Breast09 clinical trial