New Development in Therapeutics for Metastatic Breast Cancer

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UCDAVIS
COMPREHENSIVE
CANCER CENTER

Objectives

1. HER2-positive
2. Hormone receptor positive
3. Triple negative
4. Germline *BRCA* mutations

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Original Article

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

Javier Cortés, M.D., Ph.D., Sung-Bae Kim, M.D., Ph.D., Wei-Pang Chung, M.D., Seock-Ah Im, M.D., Ph.D., Yeon Hee Park, M.D., Ph.D., Roberto Hegg, M.D., Ph.D., Min Hwan Kim, M.D., Ph.D., Ling-Ming Tseng, M.D., Vanessa Petry, M.D., Chi-Feng Chung, M.D., Hiroji Iwata, M.D., Ph.D., Erika Hamilton, M.D., Giuseppe Curigliano, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Chiun-Sheng Huang, M.D., Ph.D., M.P.H., Jee Hyun Kim, M.D., Ph.D., Joanne W.Y. Chiu, M.B., B.S., Jose Luiz Pedrini, M.D., Ph.D., Caleb Lee, M.D., Ph.D., Yali Liu, Ph.D., Jillian Cathcart, Ph.D., Emarjola Bako, M.D., Sunil Verma, M.D., Sara A. Hurvitz, M.D., for the DESTINY-Breast03 Trial Investigators

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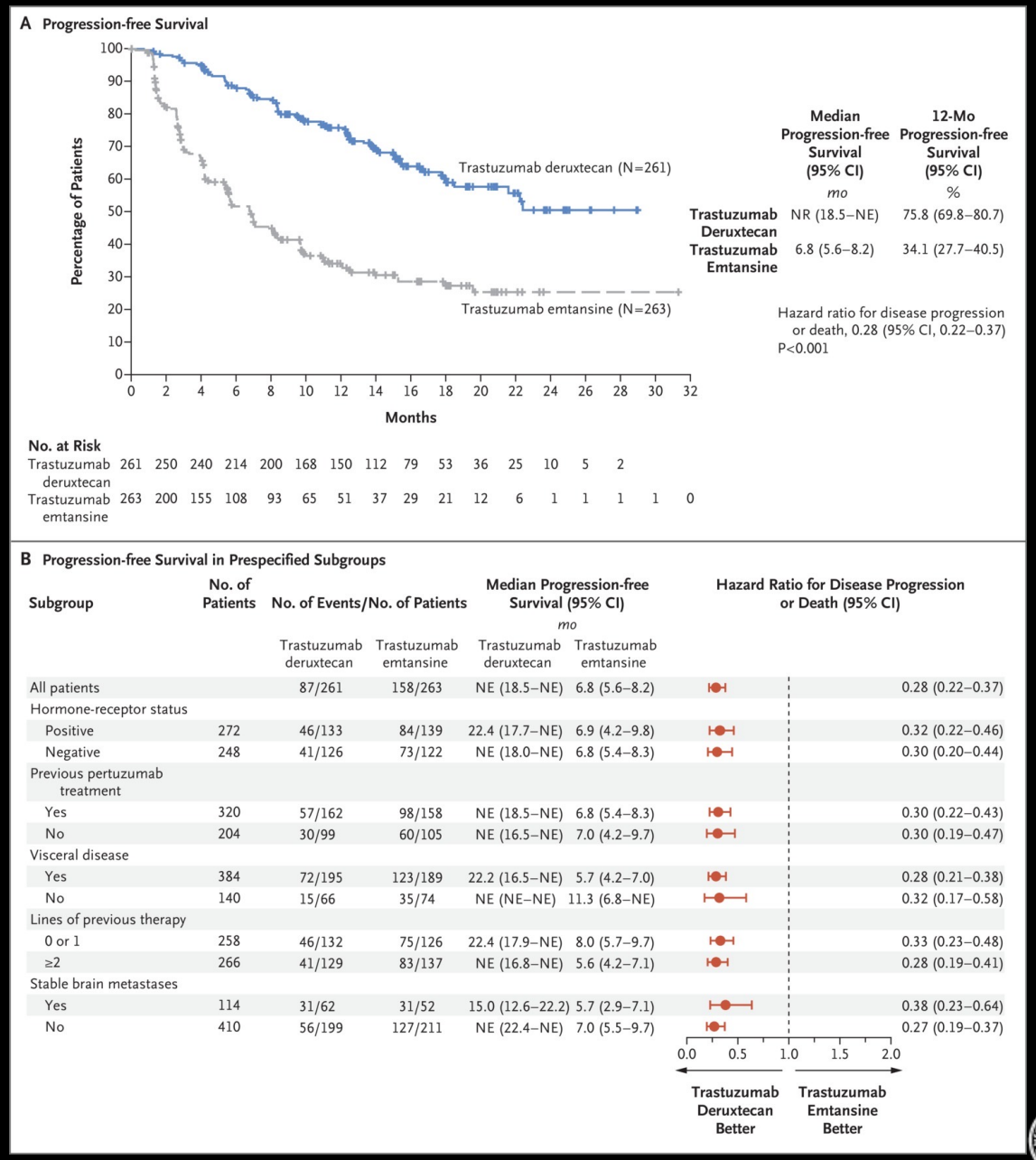
The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Analysis and Subgroup Analysis of Progression-free Survival.

- MBC prior taxane and trastuzumab
- Controlled brain metastases allowed
- No interstitial lung dz



Cortés J et al. N Engl J Med 2022;386:1143-1154

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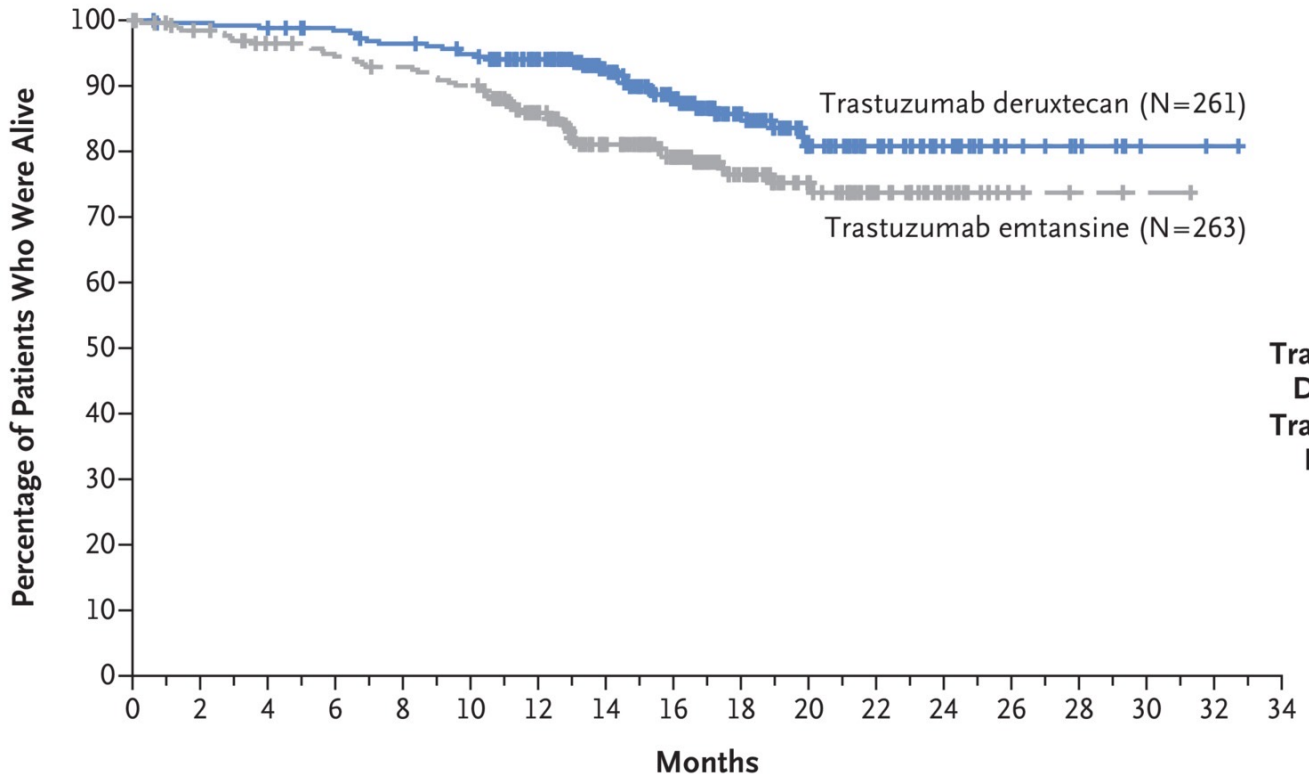
First Interim Analysis of Overall Survival.



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55 (95% CI, 0.36–0.86)
P=0.007

No. at Risk

Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

Cortés J et al. N Engl J Med 2022;386:1143-1154

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Most Common Drug-Related Adverse Events and Adjudicated Drug-Related Interstitial Lung Disease or Pneumonitis.

Table 2. Most Common Drug-Related Adverse Events and Adjudicated Drug-Related Interstitial Lung Disease or Pneumonitis.

Event	Trastuzumab Deruxtecan (N=257)		Trastuzumab Emtansine (N=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

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HER2-positive MBC

Setting	Regimen	Trial
1st-line	Taxane + trastuzumab and pertuzumab	CLEOPATRA
2nd-line	Trastuzumab deruxtecan	DESTINY 03
3rd-line	Tucatinib, trastuzumab + capecitabine	HER2CLIMB
	Trastuzumab emtansine	EMILIA
4th line and beyond	Trastuzumab + chemotherapy	
	Lapatinib + capecitabine	
	Trastuzumab + lapatinib	
	Neratinib + capecitabine	NALA
	Margetuximab + chemotherapy	SOPHIA

Objectives

1. HER2-positive
2. Hormone receptor positive
3. Triple negative
4. Germline *BRCA* mutations

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Hormone receptor positive MBC

Study	PALOMA 2 (palbociclib)	MONALEESA 2 (ribociclib)	MONALEESA 7 (ribociclib)	MONARCH 3 (abemaciclib)
Population	postmenopausal	postmenopausal	Pre/perimenopausal	postmenopausal
N	666	668	672	493
Prior chemotherapy for ABC?	No	No	≤ 1	No
Median PFS (mos)	24.8 vs 14.5	25.3 vs 16	23.8 vs 13	28.2 vs 14.7
OS (mos)	53.9 vs 51.2	63.9 vs 51.4	58.7 vs 48	67.1 vs 54.5
References	Finn, et al, NEJM 2016; Finn, et al, ASCO 2022	Hortobagyi, et al, NEJM 2016; Ann Onc 2018; Hortobagyi, et al, NEJM 2022	Tripathy, et al, Lancet Onc 2018; Lu, et al, Clin Can Res 2022	Sledge, et al JCO 2017; Goetz, et a, ESMO 2022

Hormone receptor positive MBC

Setting	Regimen	Trial	If endocrine resistant
1st line	AI + CDK 4/6 inhibitor		Taxane, capecitabine, other sequential therapies
2nd line	Fulvestrant		
-if *PIK3CA* alteration	Fulvestrant + alpelisib	SOLAR-1	
3rd line	Exemestane + everolimus	BOLERO-2	
	tamoxifen		
	SERD?		

UC DAVIS COMPREHENSIVE CANCER CENTER

Original Article

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

Shanu Modi, M.D., William Jacot, M.D., Ph.D., Toshinari Yamashita, M.D., Ph.D., Joohyuk Sohn, M.D., Maria Vidal, M.D., Ph.D., Eriko Tokunaga, M.D., Ph.D., Junji Tsurutani, M.D., Ph.D., Naoto T. Ueno, M.D., Ph.D., Aleix Prat, M.D., Ph.D., Yee Soo Chae, M.D., Ph.D., Keun Seok Lee, M.D., Ph.D., Naoki Niikura, M.D., Ph.D., Yeon Hee Park, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Xiaojia Wang, M.D., Ph.D., Miguel Gil-Gil, M.D., Ph.D., Wei Li, M.D., Ph.D., Jean-Yves Pierga, M.D., Ph.D., Seock-Ah Im, M.D., Ph.D., Halle C.F. Moore, M.D., Hope S. Rugo, M.D., Rinat Yerushalmi, M.D., Flora Zagouri, M.D., Ph.D., Andrea Gombos, M.D., Sung-Bae Kim, M.D., Ph.D., Qiang Liu, M.D., Ph.D., Ting Luo, M.D., Cristina Saura, M.D., Ph.D., Peter Schmid, M.D., Ph.D., Tao Sun, M.D., Dhiraj Gambhire, M.D., M.P.H., Lotus Yung, Pharm.D., Yibin Wang, Ph.D., Jasmeet Singh, M.D., M.P.H.A., Patrik Vitazka, M.D., Ph.D., Gerold Meinhardt, M.D., Nadia Harbeck, M.D., Ph.D., David A. Cameron, M.D., for the DESTINY-Breast04 Trial Investigators

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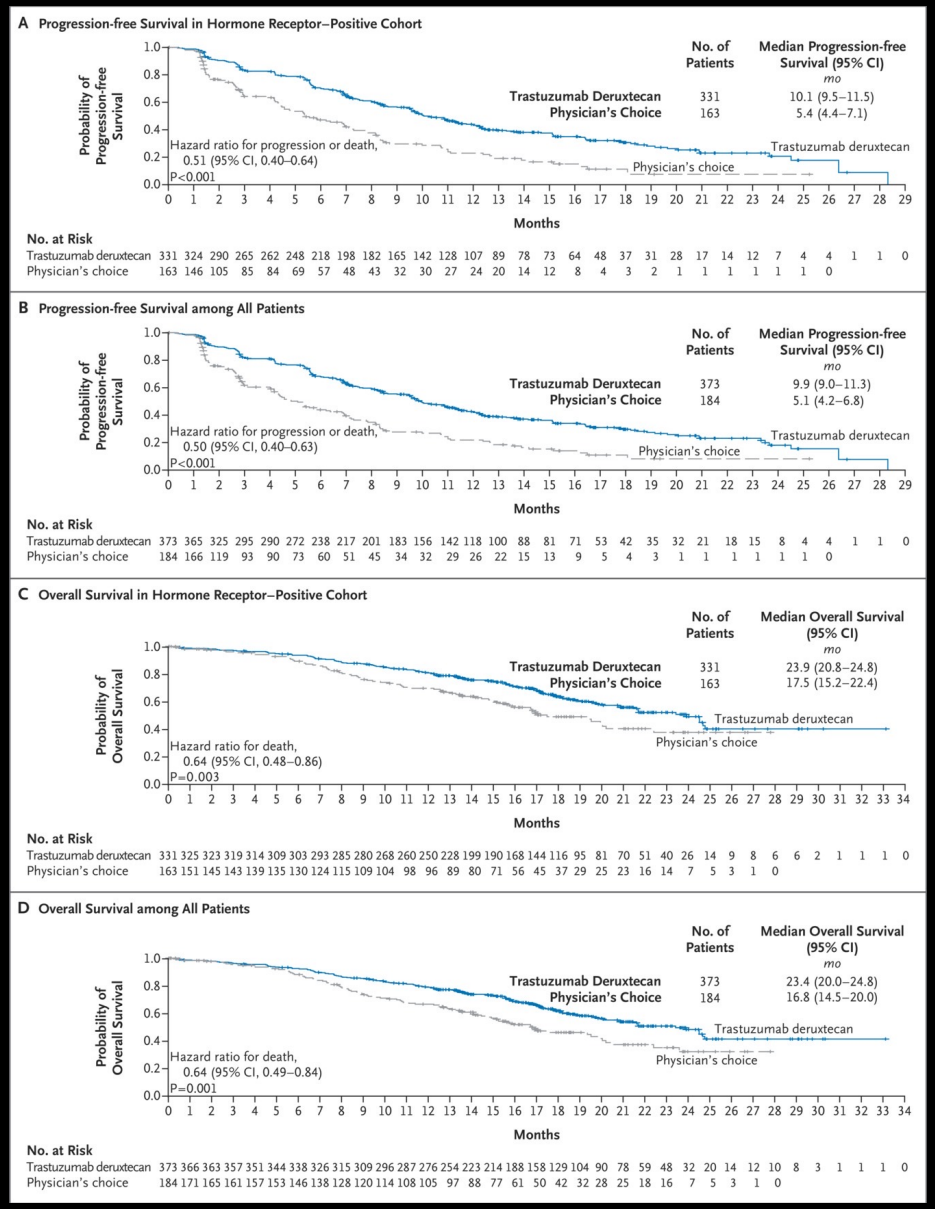
Kaplan–Meier Analysis of Progression-free Survival and Overall Survival in the Hormone Receptor–Positive Cohort and among All Patients.

- HR+ (89%) with HER2 1+ or 2+ by IHC
- 1 or 2 prior lines chemotherapy
- Controlled brain metastases allowed
- No interstitial lung dz

- Randomized 2:1 to trastuzumab deruxtecan or physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel/nab-paclitaxel)



Modi S et al. N Engl J Med2022;387:9-20

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Demographic and Clinical Characteristics of the Hormone Receptor–Positive Cohort and All Patients at Baseline.

Table 1. Demographic and Clinical Characteristics of the Hormone Receptor–Positive Cohort and All Patients at Baseline.*

Characteristic	Hormone Receptor–Positive Cohort		All Patients	
	Trastuzumab Deruxtecan (N=331)	Physician's Choice of Chemotherapy (N=163)	Trastuzumab Deruxtecan (N=373)	Physician's Choice of Chemotherapy (N=184)
Median age (range) — yr	56.8 (31.5–80.2)	55.7 (28.4–80.0)	57.5 (31.5–80.2)	55.9 (28.4–80.5)
Female sex — no. (%)	329 (99.4)	163 (100)	371 (99.5)	184 (100)
Region — no. (%)				
Europe or Israel	149 (45.0)	73 (44.8)	166 (44.5)	85 (46.2)
Asia	128 (38.7)	60 (36.8)	147 (39.4)	66 (35.9)
North America	54 (16.3)	30 (18.4)	60 (16.1)	33 (17.9)
Race — no. (%)†				
White	156 (47.1)	78 (47.9)	176 (47.2)	91 (49.5)
Black	7 (2.1)	2 (1.2)	7 (1.9)	3 (1.6)
Asian	131 (39.6)	66 (40.5)	151 (40.5)	72 (39.1)
Other	37 (11.2)	16 (9.8)	39 (10.5)	17 (9.2)
Missing data	0	1 (0.6)	0	1 (0.5)
Ethnic group — no. (%)†				
Hispanic or Latino	14 (4.2)	5 (3.1)	14 (3.8)	7 (3.8)
Non-Hispanic or Non-Latino	267 (80.7)	137 (84.0)	308 (82.6)	153 (83.2)
Unknown	9 (2.7)	4 (2.5)	9 (2.4)	7 (3.8)
Not applicable	41 (12.4)	17 (10.4)	42 (11.3)	17 (9.2)
HER2-low status — no. (%)‡				
IHC 1+	193 (58.3)	95 (58.3)	215 (57.6)	106 (57.6)
IHC 2+ and ISH-negative	138 (41.7)	68 (41.7)	158 (42.4)	78 (42.4)
ECOG performance-status score — no. (%)§				
0	187 (56.5)	95 (58.3)	200 (53.6)	105 (57.1)
1	144 (43.5)	68 (41.7)	173 (46.4)	79 (42.9)
Hormone receptor–positive — no. (%)¶	328 (99.1)	162 (99.4)	333 (89.3)	166 (90.2)
Metastasis — no. (%)				
Brain	18 (5.4)	7 (4.3)	24 (6.4)	8 (4.3)
Liver	247 (74.6)	116 (71.2)	266 (71.3)	123 (66.8)
Lung	98 (29.6)	58 (35.6)	120 (32.2)	63 (34.2)
Previous cancer therapy — no. (%)				
Targeted therapy	259 (78.2)	132 (81.0)	279 (74.8)	140 (76.1)
CDK4/6 inhibitor	233 (70.4)	115 (70.6)	239 (64.1)	119 (64.7)
Immunotherapy	10 (3.0)	8 (4.9)	20 (5.4)	12 (6.5)
Other	128 (38.7)	70 (42.9)	140 (37.5)	76 (41.3)
Endocrine therapy	330 (99.7)	160 (98.2)	347 (93.0)	165 (89.7)
Chemotherapy	331 (100)	162 (99.4)	373 (100)	183 (99.5)
Lines of therapy for metastatic disease				
Median no. of lines (range)	3 (1–9)	3 (1–8)	3 (1–9)	3 (1–8)
No. of lines — no. of patients (%)				
1	23 (6.9)	14 (8.6)	39 (10.5)	19 (10.3)
2	85 (25.7)	41 (25.2)	100 (26.8)	53 (28.8)
≥3	223 (67.4)	108 (66.3)	234 (62.7)	112 (60.9)

Modi S et al. N Engl J Med2022;387:9-20

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Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set.

Table 3. Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set.*

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)	39 (22.7)	14 (8.1)
General disorders: fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0	56 (32.6)	0

Interstitial pneumonitis 12.1% vs 0.6%, including 2 deaths in trastuzumab deruxtecan arm

Modi S et al. N Engl J Med2022;387:9-20

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Hormone receptor positive MBC

- FDA approved trastuzumab deruxtecan for HER2 1+, 2+ and ISH negative on August 5, 2022.

- The phase II DAISY trial has looked at heavily-pretreated patients with HER2 immunohistochemistry 0 to 3+ with promising results.

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer

NCT03901339

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

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- 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

Endpoints

Primary
- PFS by BICR

Secondary
- 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 ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; (Neo)adjuvant, neoadjuvant or adjuvant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

PRESENTED BY: Hope S. Rugo, MD

Demographics and Baseline Characteristics

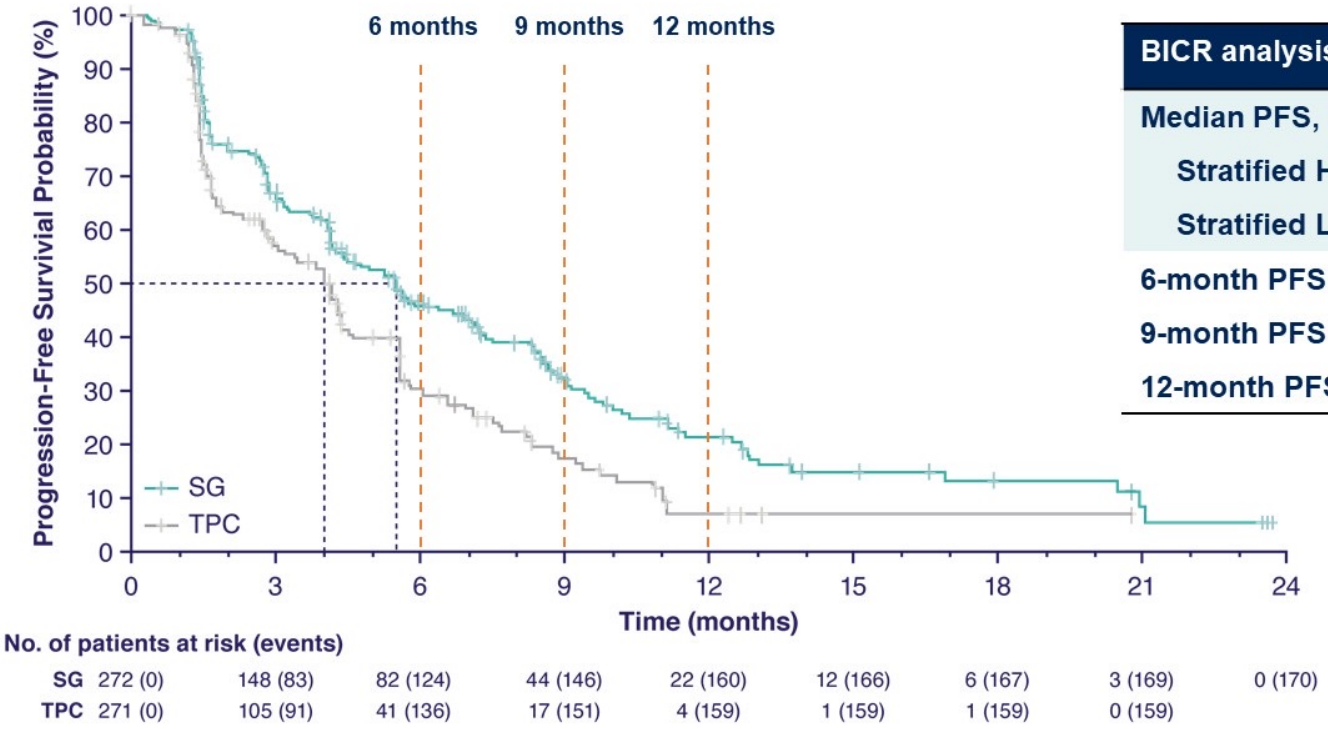
	SG (n=272)	TPC (n=271)
Female, n (%)	270 (99)	268 (99)
Median age, y (range)	57 (29-86)	55 (27-78)
<65 y, n (%)	199 (73)	204 (75)
≥65 y, n (%)	73 (27)	67 (25)
Race or ethnic group, n (%)		
White	184 (68)	178 (66)
Black	8 (3)	13 (5)
Asian	11 (4)	5 (2)
Other[a] / Not reported[b]	69 (25)	75 (28)
ECOG PS, n (%)		
0	116 (43)	126 (46)
1	156 (57)	145 (54)
Visceral metastases at baseline, n (%)	259 (95)	258 (95)
Liver metastases,[c] n (%)	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 randomization, 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 RECIST1.1 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.
CDK4/6, cyclin-dependent kinase 4/6; ECOG PS Eastern Cooperative Oncology Group performance status, ER estrogen receptor, (neo)adjuvant, neoadjuvant or adjuvant; PR progesterone receptor; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Primary Endpoint: BICR-Assessed PFS per RECIST v1.1 in the ITT Population

SG demonstrated a statistically significant improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death; a higher proportion of patients were alive and progression-free at all landmark timepoints



BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	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)

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

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Response Rates

BICR analysis	SG (n=272)	TPC (n=271)
ORR, n (%)	57 (21)	38 (14)
Odds ratio, nominal *P* value[a]	1.63, *P*=0.03	
Best overall response, n (%)		
CR	2 (1)	0
PR	55 (20)	38 (14)
SD	142 (52)	106 (39)
SD ≥6 mo	35 (13)	21 (8)
PD	58 (21)	76 (28)
NE	15 (6)	51 (19)
CBR,[b] n (%)	92 (34)	59 (22)
Odds ratio, nominal *P* value[a]	1.84, *P*=0.002	
Median DOR, mo (95% CI)	7.4 (6.5-8.6)	5.6 (3.8-7.9)

ORR (21% vs 14%) and CBR (34% vs 22%) were higher with SG vs TPC

[a]Not formally tested because OS at IA1 was not statistically significant.
[b]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; CR, complete response; DOR, duration of response; IA1, interim analysis 1; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Safety Summary

n (%)	SG (n=268)	TPC (n=249)
Grade ≥3 TEAE	198 (74)	149 (60)
TEAEs leading to treatment discontinuation	17 (6)	11 (4)
TEAEs leading to dose delay	178 (66)	109 (44)
TEAEs leading to dose reductions	89 (33)	82 (33)
TE SAEs	74 (28)	47 (19)
TEAEs leading to death[a]	6 (2)	0
Treatment-related	1 (<1)	0

- The most common TE SAEs (≥2% incidence) in this study were
  - SG: diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), and neutropenic colitis (2%)
  - TPC: febrile neutropenia (4%), pneumonia (2%), nausea (2%), and dyspnea (2%)

Overall, the safety profile of SG in this study was consistent with that observed in previous studies of SG

[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; TE, treatment-emergent; TEAE, treatment-emergent adverse event; SAE, serious adverse event; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

2022 ASCO® ANNUAL MEETING

A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer: MAINTAIN Trial

Kevin Kalinsky, Melissa K Accordino, Cody Chiuzan, Prabhjot Mundi, Meghna S Trivedi, Yelena Novik, Amy Tiersten, Amelia Zelnak, George Raptis, Lea Baer, Sun Y Oh, Erica Stringer-Reasor, Sonya Reid, Eleni Andreopoulou, William Gradishar, Kari B Wisinski, Anne O'Dea, Ruth O'Regan, Katherine D Crew, Dawn L Hershman

PRESENTED BY:
Kevin Kalinsky, MD, MS

Schema

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1

N=120

Arm 1
Ribociclib + Switch Endocrine Therapy*

Arm 2
Placebo + Switch Endocrine Therapy*

Primary Endpoint

- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

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Patient Characteristics and Prior Treatment

	Placebo (n=59)	Ribociclib (n=60)
Female - no. (%)	58 (99%)	60 (100%)
Median age – years (IQR)	59 (52-65)	55 (48-67)
Race or ethnic group – no. (%)		
White	42 (71%)	46 (77%)
Black	8 (14%)	5 (8%)
Asian	2 (3%)	5 (8%)
Other or not specified	7 (12%)	4 (7%)
ECOG PS – no. (%)		
0	38 (64%)	40 (67%)
1	21 (36%)	20 (33%)
De Novo Metastasis at Dx - no. (%)* **	32 (54%)	21 (35%)
Visceral Metastasis – no. (%)	35 (59%)	36 (60%)
Bone-Only Disease – no. (%)	9 (15%)	13 (22%)
≥ 2 prior ET for MBC – no. (%)	11 (19%)	11 (18%)
Chemotherapy for MBC – no. (%)	7 (12%)	4 (7%)

	Placebo (n=59)	Ribociclib (n=60)
Prior CDK 4/6 inhibitor – no. (%)		
Palbociclib*	51 (86%)	52 (87%)
Ribociclib**	8 (14%)	6 (10%)
Abemaciclib	0 (0%)	2 (3%)
Median duration of prior CDK 4/6 inhibitor - months (IQR)	17 (11-23.5)	15.5 (12-21)
Prior CDK 4/6 inhibitor duration– no. (%)**		
≤ 12 months	21 (36%)	18 (30%)
> 12 months	38 (64%)	42 (70%)
Prior CDK 4/6 inhibitor in metastatic setting - no. (%)	59 (100%)	60 (100%)
Intervening treatment after progression on prior CDK 4/6 inhibitor - no. (%)	6 (10%)	1 (2%)

* Includes 1 pt who did not tolerate prior abemaciclib and 2 pts with insurance issues with ribociclib; ** Includes 1 pt who did not tolerate prior palbociclib;
p=0.035; * 10 pts (17%) in placebo arm and 7 pts (12%) pts in ribociclib arm on prior CDK4/6 inhibitor ≤ 6 months; IQR = interquartile range

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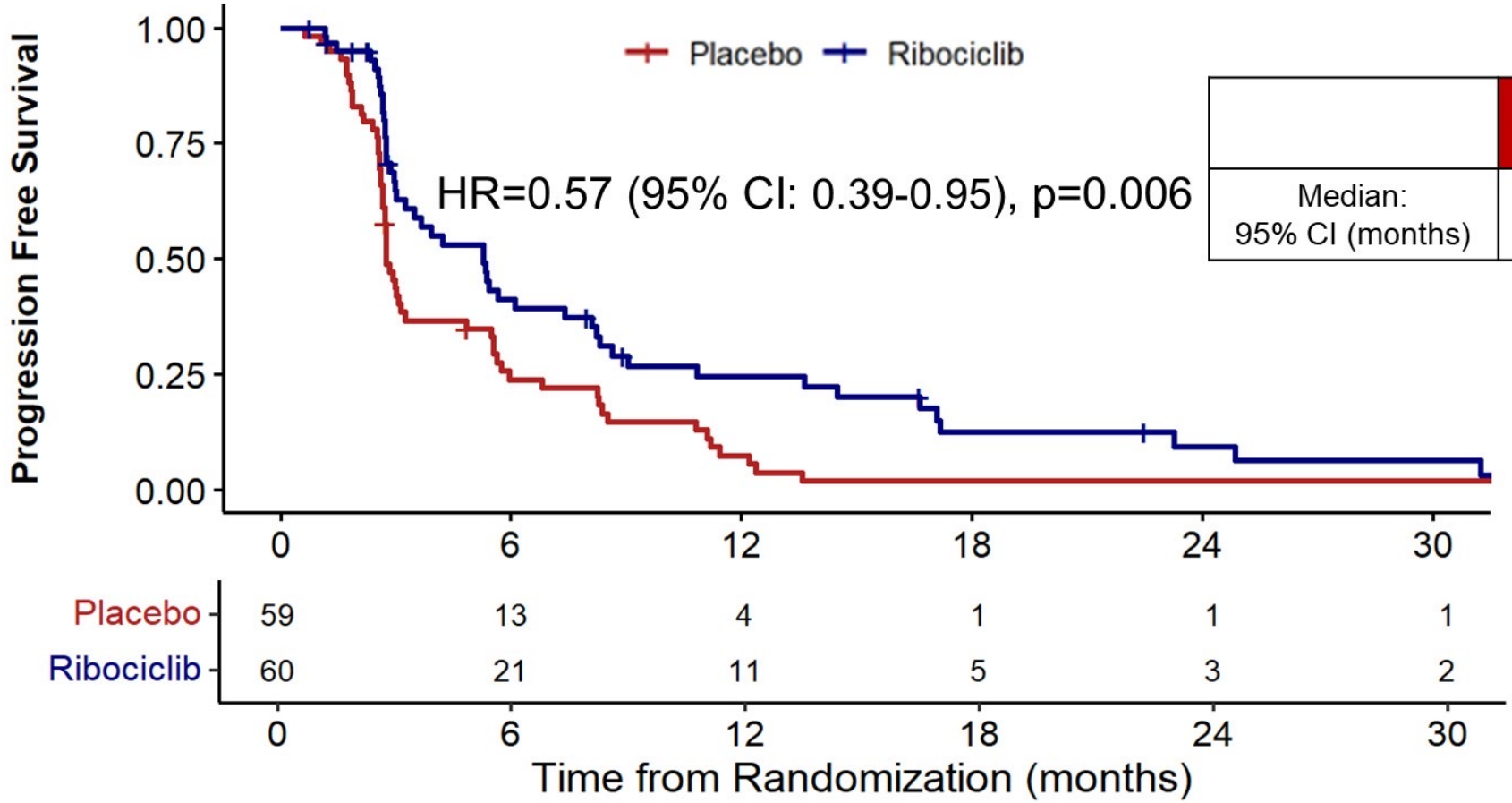
Primary Endpoint: Progression Free Survival (PFS)



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

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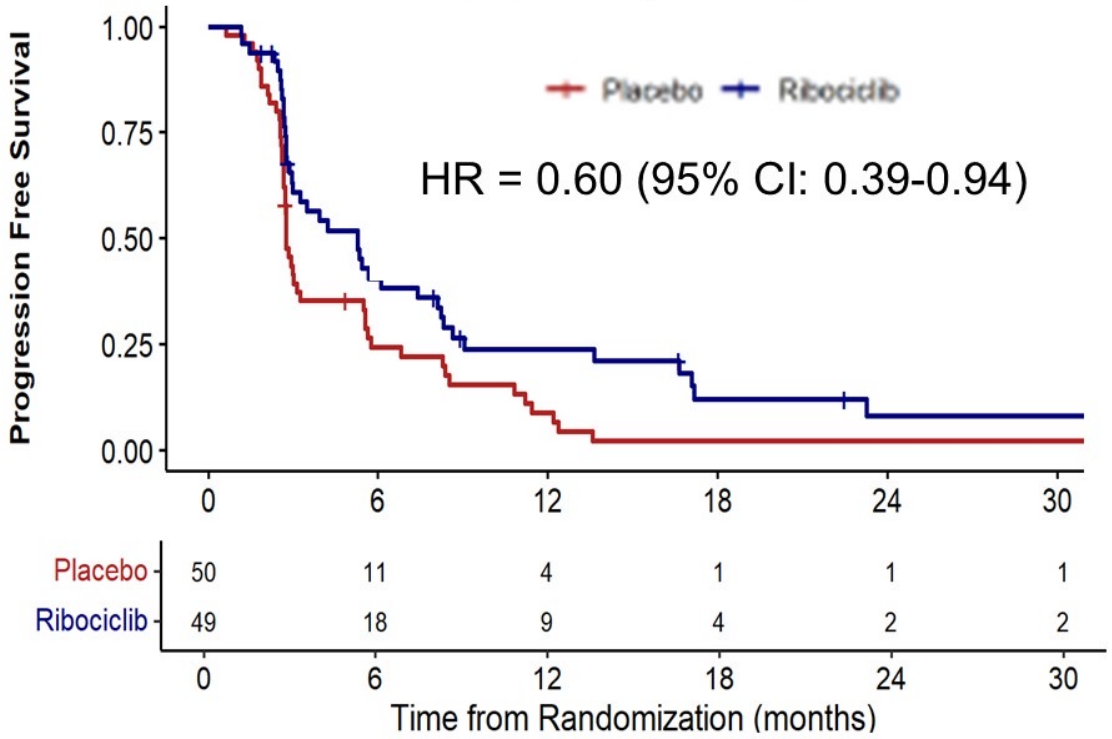
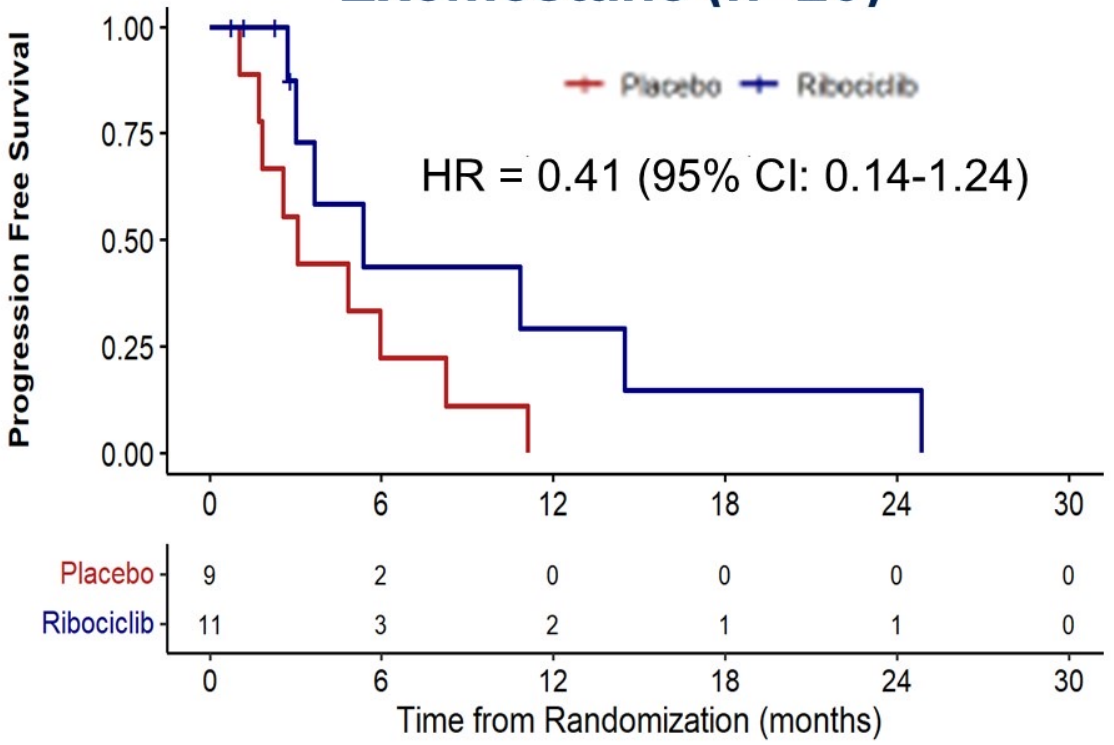
Exploratory Analysis
PFS in Fulvestrant or Exemestane Subgroups

Fulvestrant (n=99)



	Placebo (n=50)	Ribociclib (n=49)
Median (95% CI) (mos)	**2.76** (2.66-3.25)	**5.29** (2.96-8.12)

Exemestane (n=20)



	Placebo (n=9)	Ribociclib (n=11)
Median (95% CI) (mos)	**3.06** (1.84-5.95)	**5.36** (3.02-14.50)

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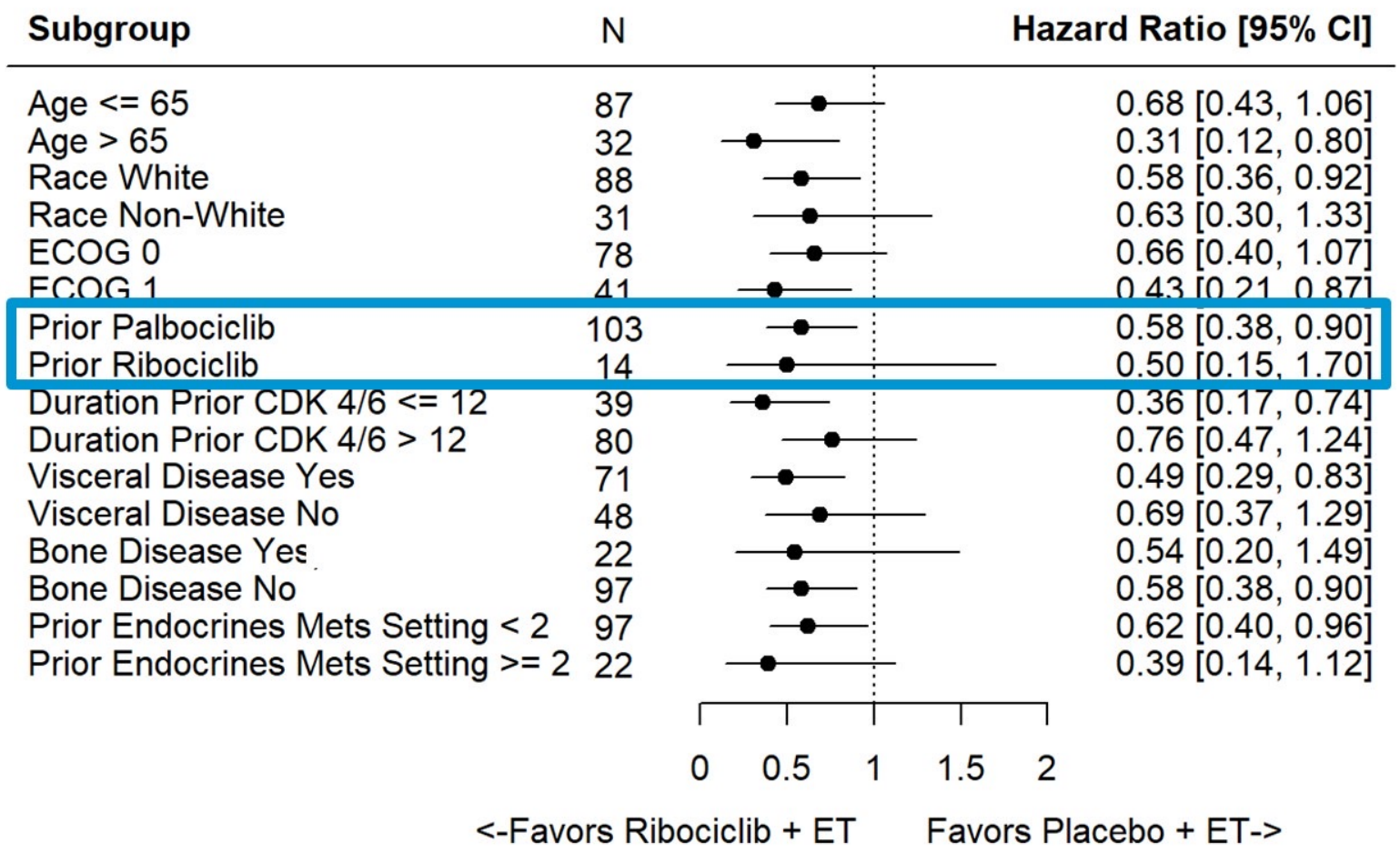
Progression Free Survival by Subgroup



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Treatment-Related Adverse Events

	Placebo + ET (n=59)			Ribociclib + ET (n=60)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic						
Neutropenia*	9 (15%)	0 (0%)	1 (2%)	43 (72%)	23 (38%)	1 (2%)
Anemia	13 (22%)	1 (2%)	0 (0%)	14 (23%)	1 (2%)	0 (0%)
Thrombocytopenia	3 (5%)	0 (0%)	0 (0%)	15 (25%)	0 (0%)	0 (0%)
Non-Hematologic						
ALT increased	12 (20%)	1 (2%)	0 (0%)	10 (17%)	0 (0%)	0 (0%)
AST increased	17 (29%)	4 (7%)	0 (0%)	15 (25%)	1 (2%)	0 (0%)
Vomiting	3 (5%)	0 (0%)	0 (0%)	9 (15%)	0 (0%)	0 (0%)
Fatigue	19 (32%)	0 (0%)	0 (0%)	20 (33%)	1 (2%)	0 (0%)
Headache	6 (10%)	0 (0%)	0 (0%)	5 (8%)	0 (0%)	0 (0%)
Diarrhea	6 (10%)	0 (0%)	0 (0%)	9 (15%)	0 (0%)	0 (0%)
Pneumonitis	0 (0%)	0 (0%)	0 (0%)	2 (3%)	1 (2%)	0 (0%)
Infection	3 (5%)	0 (0%)	0 (0%)	6 (10%)	3 (5%)	0 (0%)

- Febrile Neutropenia: 2 pts (3%) in ribociclib arm and 0 pt (0%) in placebo arm
- Post-baseline QTcF >480 ms, based on ECG data: 1 pt (2%) in ribociclib arm and 1 pt (2%) in the placebo arm
- Treatment-related deaths (n=3): 1 pt with sepsis, neutropenia, and disease progression in ribociclib arm. 1 pt with pneumonia without fever or neutropenia in each arm

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Hormone receptor positive MBC

Setting	Regimen	Trial	If endocrine resistant	Trial
1st line	AI + CDK 4/6 inhibitor		Taxane, capecitabine	
2nd line	Fulvestrant +/- ribociclib?	MAINTAIN	Trastuzumab deruxtecan if HER2 1+ or 2+ and ISH negative	DESTINY 04
-if PIK3CA alteration	Fulvestrant + alpelisib	SOLAR-1	Sacituzumab govitecan?	TROPiCS 02
3rd line	Exemestane + everolimus	BOLERO-2	Other sequential therapies	
	tamoxifen			
	SERD?			

Objectives

1. HER2-positive
2. Hormone receptor positive
3. Triple negative
4. Germline *BRCA* mutations

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Triple negative MBC

Setting	Regimen	Trial
1st line, if PDL-1 CPS ≥10	Pembrolizumab + chemotherapy (nab-paclitaxel, paclitaxel, gemcitabine/carboplatin)	KEYNOTE-355
1st line if PDL-1 <10	Taxane or taxane combination	
2nd line	Trastuzumab deruxtecan if HER2 1+ or 2+ and ISH negative	DESTINY 04
3rd	Sacituzumab govitecan	ASCENT
4th line	Other sequential therapies	

Objectives

1. HER2-positive
2. Hormone receptor positive
3. Triple negative
4. Germline *BRCA* mutations

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gBRCA-mutated MBC (HER2 negative)

PARP inhibitor	Prior lines of chemotherapy for MBC	Comparator	PFS (mos)	Trial
Olaparib	≤ 2	Capecitabine Eribulin Vinorelbine	7.0 vs 4.2	OlympiAD
Talazoparib	≤ 3	Capecitabine Eribulin Gemcitabine Vinorelbine	8.6 vs 5.6	EMBRACA

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Thank you.

Questions?

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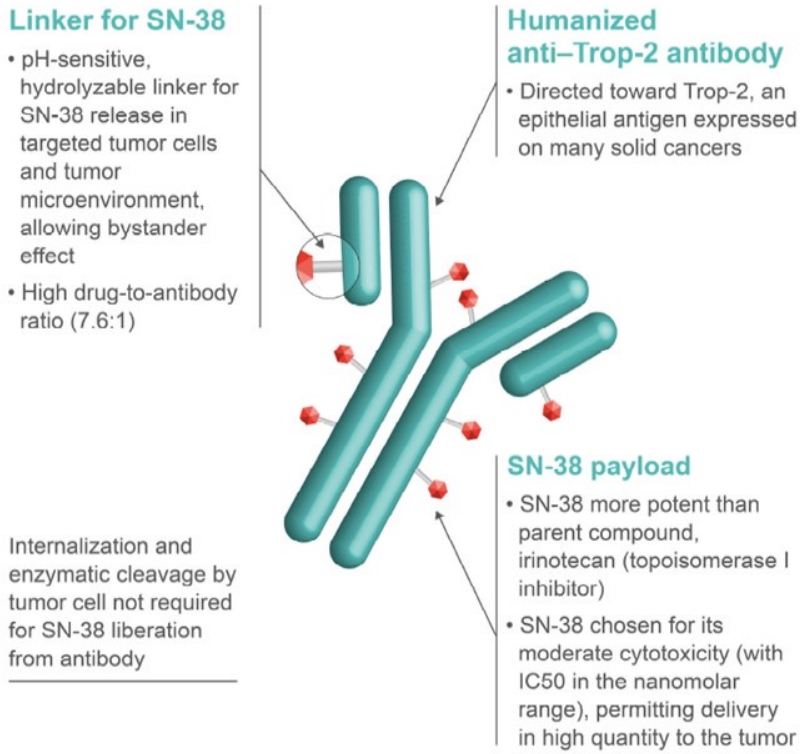
Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed Antibody-Drug Conjugate (ADC)[1-5]

- Trop-2, a transmembrane calcium signal transducer linked to tumor progression and poor prognosis, is highly expressed in approximately 80% of breast cancers regardless of subtype[6,7]
- SG is approved for patients with mTNBC with ≥2 prior therapies (≥1 in the metastatic setting)[8,9]
- In the IMMU-132-01 phase 1/2 study, SG showed encouraging clinical activity in patients with previously treated metastatic HR+/HER2- breast cancer (N=54)[10]
  - ORR by investigator assessment: 31.5% (prior CDK4/6i use subgroup, 25%)
  - Median PFS by investigator assessment: 5.5 months (95% CI, 3.6-7.6)
  - Median OS: 12 months (95% CI, 9.0-18.2)
  - A manageable safety profile consistent with that in other studies of SG[11]



ADC, antibody-drug conjugate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; ORR, objective response rate; mTNBC, metastatic triple-negative breast cancer; OS, overall survival, PFS, progression-free survival.

1. Goldenberg DM, et al. *Expert Opin Biol Ther.* 2020;20:871-885. 2. Nagayama A, et al. *Ther Adv Med Oncol.* 2020;12:1758835920915980.3. Goldenberg DM, et al. *Oncotarget.* 2015;6:22496-224512. 4. Cardillo TM, et al. *Bioconjugate Chem.* 2015;26:919-931. 5. Govindan SV, et al. *Mol Cancer Ther.* 2013;12:968-978. 6. Ambrogi F, et al. *PLoS One.* 2014;9:e96993. 7. Trerotola M, et al. *Oncogene.* 2013;32(2):222-233. 8. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Gilead Sciences, Inc.; April 2021. 9. European Medicines Agency:Trodelvy, INN-sacituzumab govitecan, https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf, March 2022. 10. Kalinsky K, et al. *Ann Oncol. 2020*;31:1709-1718. 11. Bardia A, et al. *N Engl J Med.* 2021;384:1529-1541.

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