Antibody-drug conjugates in Metastatic Breast Cancer

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Disclosures

None

Agenda

- Sample case presentation

- Overview of ADCs

- TROPICS-02 : Sacituzumab govitecan vs Physician's Choice of Chemotherapy for previously treated HR+/HER2- (low or negative) Advanced Breast Cancer

- DESTINY-Breast04: Trastuzumab Deruxtecan vs Physician's Choice of Chemotherapy for Previously Treated HER2-Low Advanced Breast Cancer

Case Presentation

73-year-old woman who presented with a palpable breast mass in 2017, was found to have de novo metastatic disease with right femoral and isolated hepatic metastasis.

Breast biopsy showed infiltrating lobular carcinoma , Grade 3. Tumor was 95% ER positive and 2% PR positive. Ki-67 was 25%, HER2 was negative by FISH

In March of 2017 she began systemic therapy with Palbociclib and Letrozole and received monthly Denosumab (34 months)

Disease progression in the bones in January 2020, received Fulvestrant till May 2020 (3 months)

Disease progression in the liver, bones and pericaval lymph nodes and received Everolimus and Exemestane from June 2020- March 2021 (9 months)

Case Presentation

Developed new disease in the left axillary nodes, biopsied, ER 15%, PR neg, Her 2 1+, started Capecitabine March 2021 (8 months)

Additional molecular testing showed PIK C3A mutation and she was switched to

Fulvestrant and Alpelisib in November 2021 –May 2022 (7 months)

Disease progression in the liver in May 2022, biopsy repeated , adenocarcinoma, ER 90%, PR neg, Her 2 2+, FISH negative.

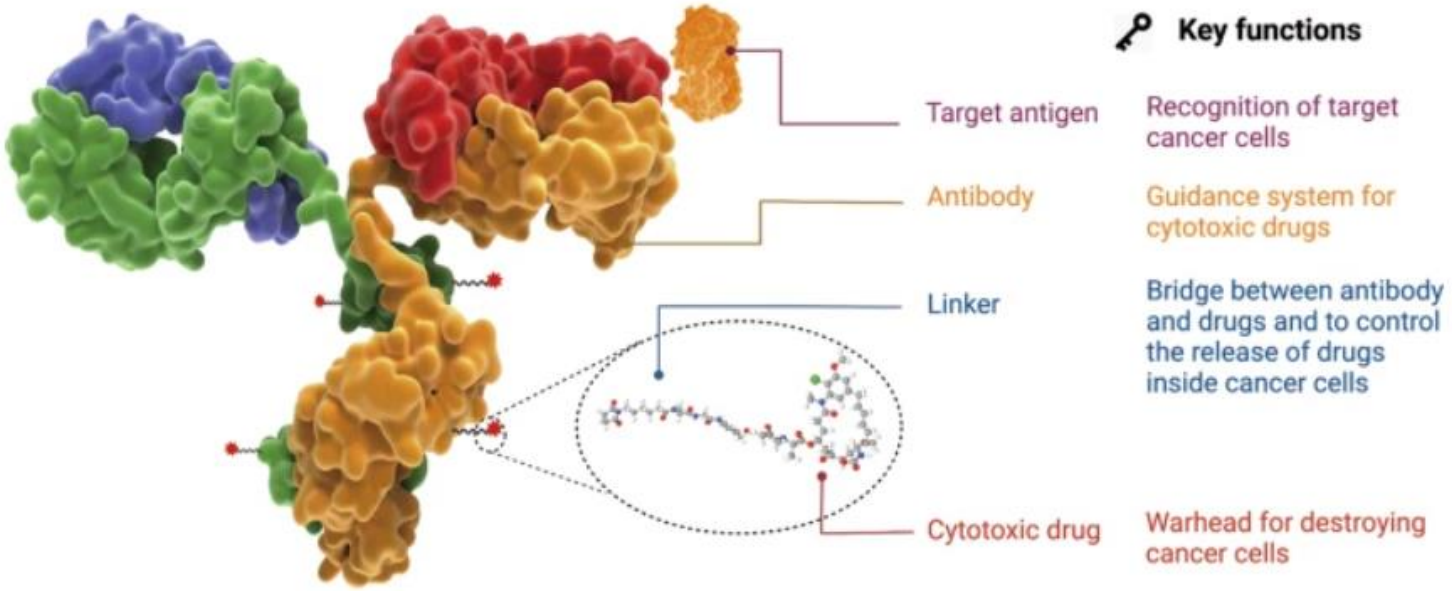
Traztuzumb Deruxtecan,TDxd started June 2022.

Total lines of therapy prior to initiation of TDxd: 3 endocrine , CDK4/6 inhibitor, mTOR I, 1 chemo, 1 targeted

The trials that we are about to discuss today will highlight some of the challenges presented by this patient population and how the standard of care has changed.

Antibody-drug conjugates

Fig. 2: The structure and characteristic of an ADC drug.



The core components including target antigen, antibody, linker, cytotoxic drug along with their key functions are demonstrated.

Fu, Z., Li, S., Han, S. *et al.* Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Sig Transduct Target Ther* **7**, 93 (2022). https://doi.org/10.1038/s41392-022-00947-7

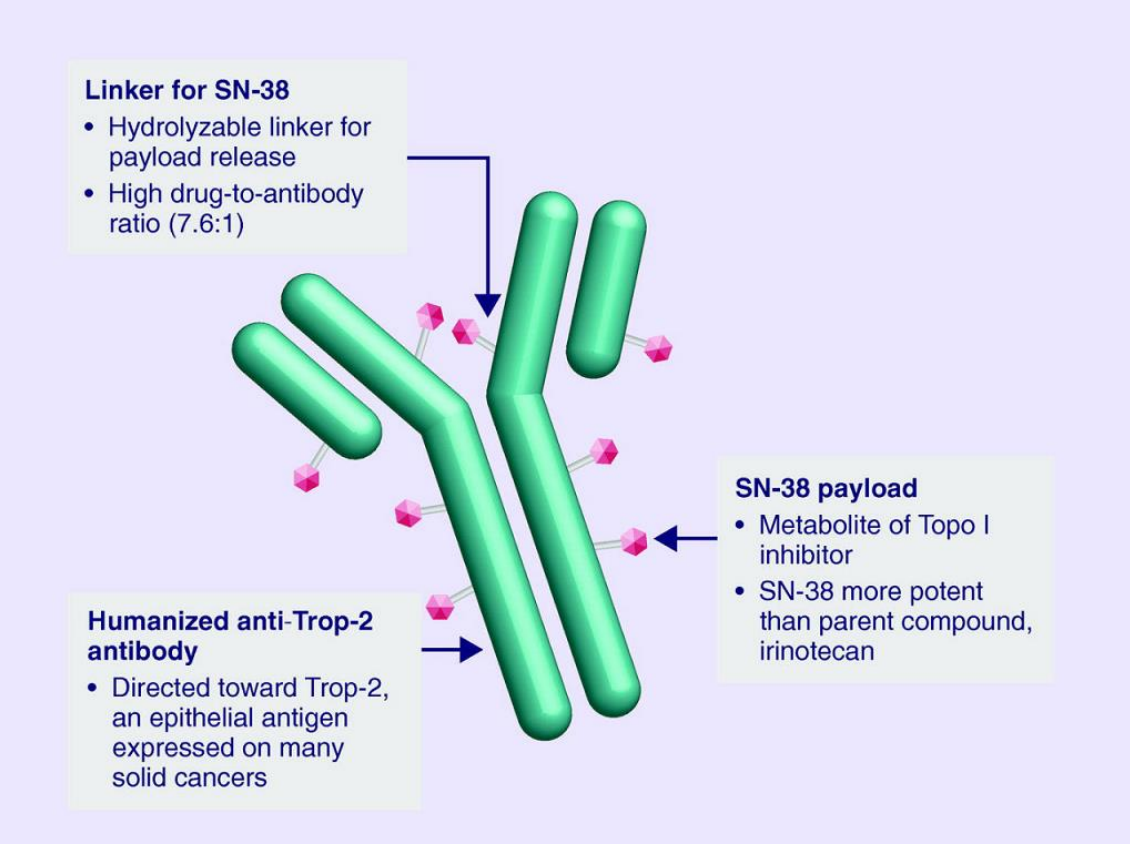
Table 1 FDA-approved ADCs for the treatment of solid tumors

From: Antibody–drug conjugates in solid tumors: a look into novel targets

	Target	Payload	Linker	DAR	Indications
Trastuzumab emtansine (T-DM1)	HER2	Maytansine (microtubule inhibitor)	Non-cleavable thioether linker	3.5	HER2-positive mBC pretreated with trastuzumab and a taxane; HER2-positive early BC with residual disease after neoadjuvant trastuzumab and taxanes
Trastuzumab deruxtecan (T-DXd)	HER2	Deruxtecan (topoisomerase inhibitor)	Protease-cleavable linker	8	HER2-positive mBC progressing to two or more prior anti-HER2-based regimens in the metastatic setting
Enfortumab vedotin (EV)	Nectin-4	Monomethyl auristatin E (microtubule inhibitor)	Protease-cleavable linker	3.8	Locally advanced/metastatic UC previously treated with a PD-(L)1 and a platinum-based chemotherapy in the (neo)adjuvant or metastatic setting
Sacituzumab govitecan (SG)	Trop-2	SN-38 (topoisomerase inhibitor)	Hydrolysable linker	7.5	Triple-negative mBC (who have received at least two prior therapies for metastatic disease)

Criscitiello, C., Morganti, S. & Curigliano, G. Antibody–drug conjugates in solid tumors: a look into novel targets. *J Hematol Oncol* **14**, 20 (2021). https://doi.org/10.1186/s13045-021-01035-z

Sacituzumab-Govitecan(SG)



Credit: Future Medicine. 2020 Mar. doi:10.2217/fon-2020-0163

TROPICS-02 Background

Trop-2

- Transmembrane calcium signal transducer associated with cancer progression and poor prognosis
- Highly expressed in approximately 80% of breast cancers

Sacituzumab govitecan: Trop-2–directed ADC

Phase III TROPiCS-2 study[8,9]

TROPICS-02 : Sacituzumab govitecan vs Physician's Choice of Chemotherapy for previously treated HR+/HER2- (low or negative) Advanced Breast Cancer

1.Ambrogi. PLoS One. 2014;9:e96993. 2. Trerotola. Cancer Res. 2013;73:3155. 3. Goldenberg. Expert Opin Biol Ther. 2020;20:871. 4. Nagayama. Ther Adv Med Oncol. 2020;12:1758835920915980. 5. Goldenberg. Oncotarget. 2015;6:22496. 6. Cardillo. Bioconjug Chem. 2015;26:919. 7. Govindan. Mol Cancer Ther. 2013;12:968. 8. Rugo. J Clin Oncol. 2022;[Epub]. 9. Bardia. NEJM. 2021;384:1529. 10. Rugo. ESMO 2022. Abstr LBA76. 11. Marmé. ESMO 2022. Abstr 214MO.

TROPiCS-02: Study Design

-Patients had metastatic or locally recurrent inoperable HR +/HER 2- breast cancer

- Disease progression after greater than one ET, taxane, and CDK 4/6 inhibitor;

-2-4 previous lines of CT for metastatic disease

-Measurable disease by RECIST

Primary endpoint: PFS
Secondary endpoints: OS, ORR,DoR, Clinical benefit ratio, Patient reported outcome

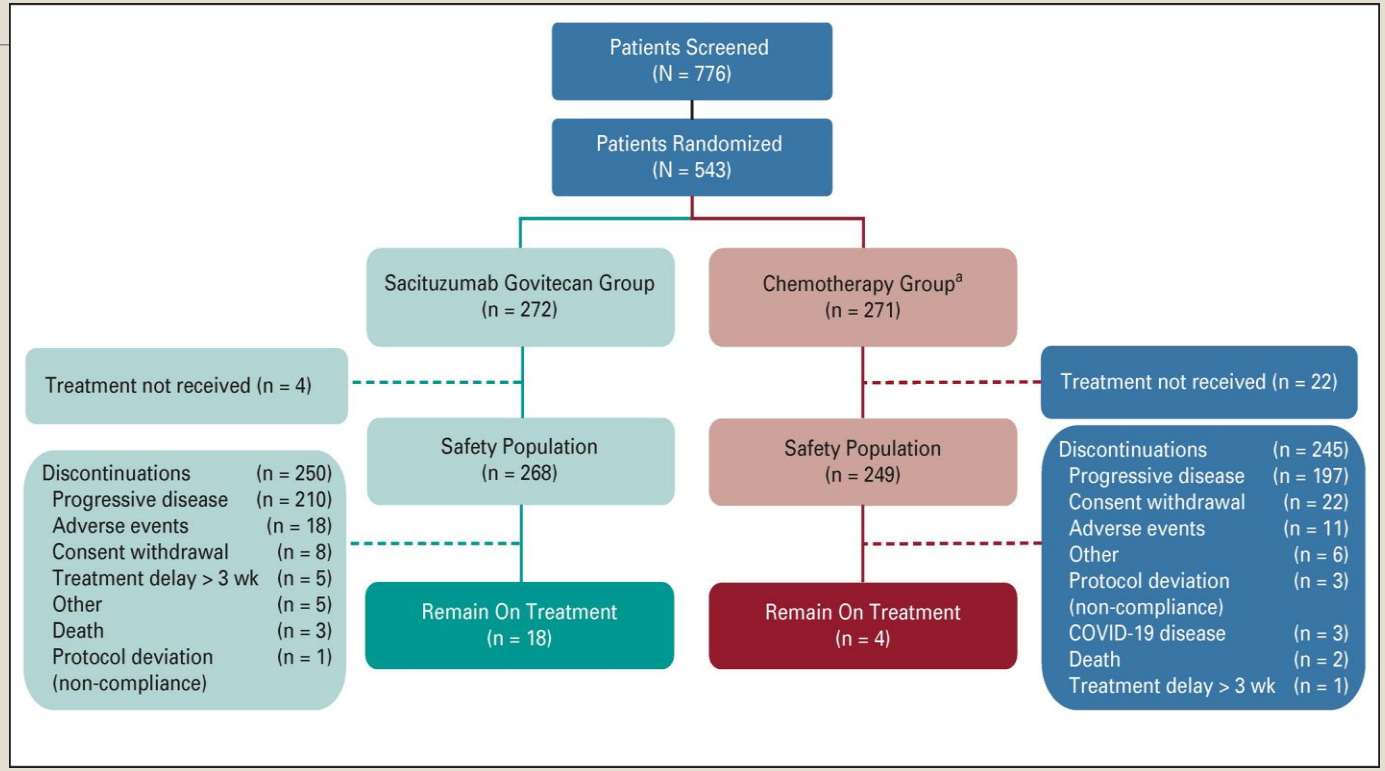


FIG 1. CONSORT diagram. Patients in the chemotherapy group were randomly assigned to eribulin (n = 130), vinorelbine (n = 63), gemcitabine (n = 56), or capecitabine (n = 22). AE, adverse event; SG, sacituzumab govitecan.

Published in: Hope S. Rugo; Aditya Bardia; Frederik Marmé; Javier Cortes; Peter Schmid; Delphine Loirat; Olivier Trédan; Eva Ciruelos; Florence Dalenc; Patricia Gómez Pardo; Komal L. Jhaveri; Rosemary Delaney; Olivia Fu; Lanjia Lin; Wendy Verret; Sara M. Tolaney; *Journal of Clinical Oncology* 2022 403365-3376.DOI: 10.1200/JCO.22.01002

TROPiCS-02: 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)

BL characteristics comparable among HER2-low, HER2 IHC0, and ITT populations

Published in: Hope S. Rugo; Aditya Bardia; Frederik Marmé; Javier Cortes; Peter Schmid; Delphine Loirat; Olivier Trédan; Eva Ciruelos; Florence Dalenc; Patricia Gómez Pardo; Komal L. Jhaveri; Rosemary Delaney; Olivia Fu; Lanjia Lin; Wendy Verret; Sara M. Tolaney; *Journal of Clinical Oncology* 2022 403365-3376.DOI: 10.1200/JCO.22.01002

TROPiCS-02: PFS by BICR

BICR Analysis	Sacituzumab Govitecan (n=272)		Physician's choice (n= 271)
Median PFS, mo (95%CI) Stratified hazard ratio 95% CI Stratified log rank P value	5.5 (4.2-7.0)	0.66 (0.53-0.83) .0003	4.0 (3.1-4.4)
6- mo PFS %(95 % CI)	46.1 (39.4-52.6)		30.3 (23.6-37.3)
9-mo PFS %(95% CI)	32.5 (25.9-39.2)		17.3 (11.5-24.2)
12-m0 PFS % (95% CI)	21.3 (15.2-28.1)		7.1 (2.8-13.9)

Statistically significant improvement in PFS with sacituzumab govitecan vs physician's choice
34% reduction in risk of disease progression/death
Higher proportion of patients alive and progression free at all landmark timepoints

TROPiCS-02: OS in ITT Population

Median follow up 12.5 months

OS in ITT population First planned interim analysis	Sacituzumab Govitecan (n=272)		Physician's choice (n= 271)
Median PFS, mo (95%CI) Stratified hazard ratio 95% CI Stratified log rank P value	14.4 (13.0-15.7)	0.79 (0.65-0.96) .020	11.2 (10.1-12.7)
12-m0 PFS % (95% CI)	61 (55-66)		47 (41-53)
Events, n	191		199

Statistically significant improvement in OS with sacituzumab govitecan vs physician's choice

- 21% reduction in risk of death
- 3.2 mo longer OS for patients who received sacituzumab govitecan vs physician's choice

PFS and OS in ITT population

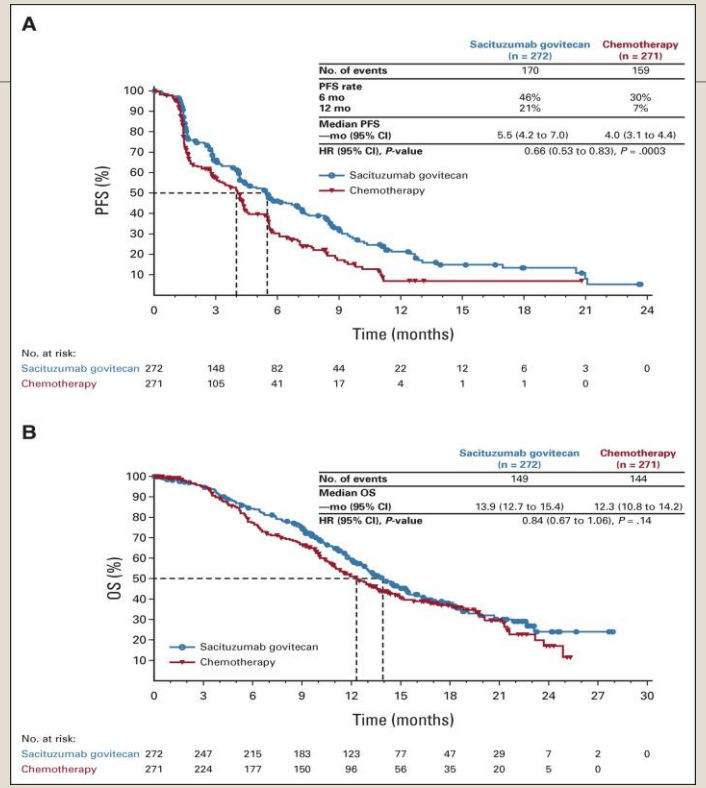


FIG 2. Efficacy outcomes in the intent-to-treat population. (A and B) PFS (final analysis) and OS (first planned interim analysis), respectively, in the intent-to-treat population (all randomly assigned patients). PFS was determined by blinded independent central review according to RECIST, version 1.1. HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

Published in: Hope S. Rugo; Aditya Bardia; Frederik Marmé; Javier Cortes; Peter Schmid; Delphine Loirat; Olivier Trédan; Eva Ciruelos; Florence Dalenc; Patricia Gómez Pardo; Komal L. Jhaveri; Rosemary Delaney; Olivia Fu; Lanjia Lin; Wendy Verret; Sara M. Tolaney; *Journal of Clinical Oncology* 2022 403365-3376.
DOI: 10.1200/JCO.22.01002

TROPiCS-02: Response

BICR Analysis	Sacituzumab Govitecan (n=272)		Physician's choice (n= 271)
ORR n (%) OR (95% CI)	57 (21)	 1.63 (1.03-2.56) P=.035	38 (14)
Best Overall response n (%) CR PR SD SD >6 m PD NE	 2 (1) 55 (20) 142(52) 35 (13) 58(21) 15 (6)		 0 38(14) 106 (39) 22 (8) 76 (28) 51 (19)
CBR n (%) OR 95% CI Median DOR, mo (95%CI)	92 (34) 8.1 (6.7-9.1)	 1.80(123-2.63);P=.003	60 (22) 5.6 (3.8-7.9)

Rugo. ESMO 2022. Abstr LBA76

TROPICS-02 Retrospective analysis of response by HER 2 status

BICR Analysis	HER2 Low*		HER2 IHC0	
	Sacituzumab Govitecan (n = 149)	Physician's Choice (n = 134)	Sacituzumab Govitecan (n = 101)	Physician's Choice (n = 116)
Median PFS, mo	6.4	4.2	5.0	3.4
▪ Hazard ratio (95% CI)	0.58 (0.42-0.79)		0.72 (0.51-1.00)	
▪ *P* value	<.001		.05	

TROPiCS-02: OS Subgroup Analysis

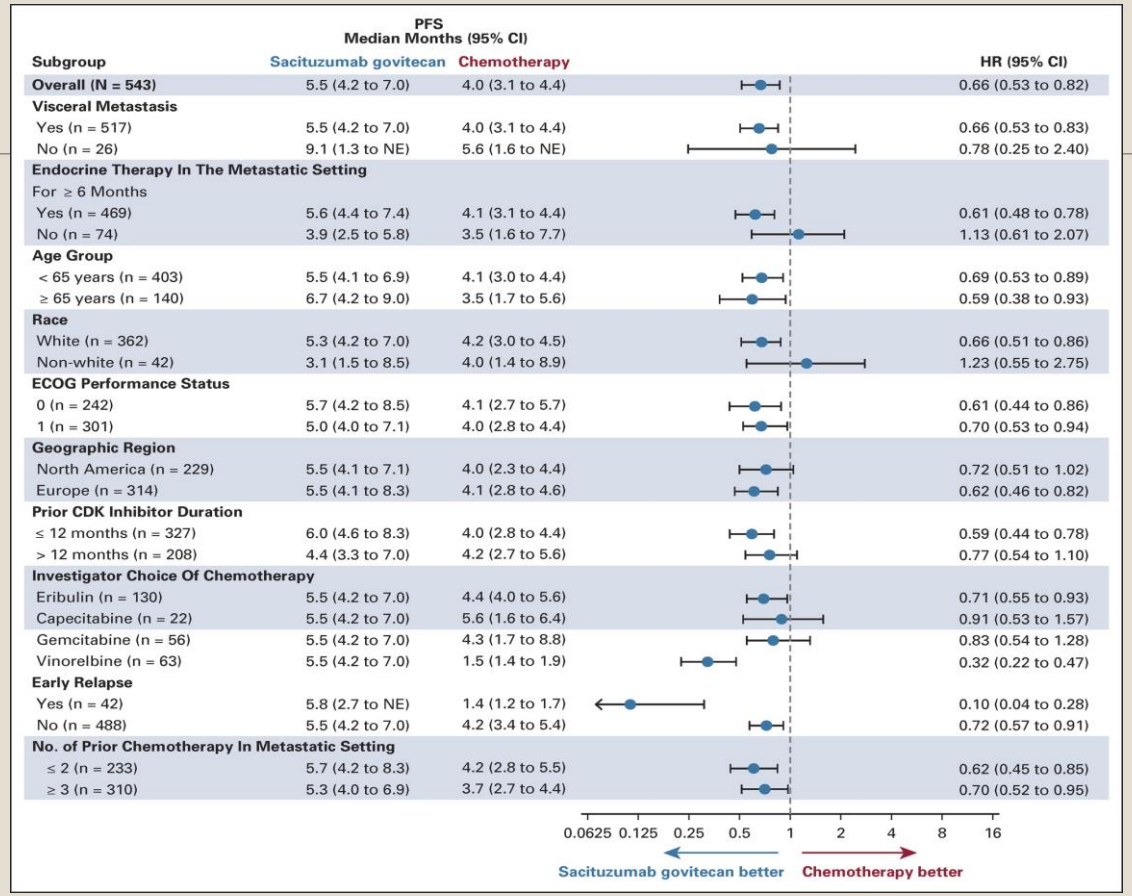


FIG 3. Subgroup analysis of PFS. Early relapse is defined as relapse to metastatic disease within 1 year of the end of (neo)adjuvant chemotherapy. Patients without chemotherapy in the (neo)adjuvant setting are not considered as early relapse. CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NE, not evaluable; PFS, progression-free survival; SG, sacituzumab govitecan.

Published in: Hope S. Rugo; Aditya Bardia; Frederik Marmé; Javier Cortes; Peter Schmid; Delphine Loirat; Olivier Trédan; Eva Ciruelos; Florence Dalenc; Patricia Gómez Pardo; Komal L. Jhaveri; Rosemary Delaney; Olivia Fu; Lanjia Lin; Wendy Verret; Sara M. Tolaney; *Journal of Clinical Oncology* 2022 403365-3376.DOI: 10.1200/JCO.22.01002

Treatment related AEs

TABLE 3. Summary of Treatment-Related AEs of Any Grade (≥ 10%) and Worst Grade 2 or Grade ≥ 3 (≥ 5%) in the Safety Population (all patients who received ≥ 1 dose of study treatment)

	SG (n = 268)			Chemotherapy (n = 249)		
Treatment-Related AE[a]	**All Grade**	**Grade 2**	**Grade ≥ 3**	**All Grade**	**Grade 2**	**Grade ≥ 3**
Hematologic, No. (%)						
Neutropenia[b]	188 (70)	45 (17)	136 (51)	134 (54)	29 (12)	94 (38)
Anemia[c]	91 (34)	44 (16)	17 (6)	62 (25)	31 (12)	8 (3)
Leukopenia[d]	37 (14)	7 (3)	23 (9)	23 (9)	8 (3)	13 (5)
Lymphopenia[e]	31 (12)	11 (4)	10 (4)	25 (10)	7 (3)	8 (3)
Febrile neutropenia	14 (5)	0	14 (5)	11 (4)	0	11 (4)
GI, No. (%)						
Diarrhea	152 (57)	56 (21)	25 (9)	41 (16)	12 (5)	3 (1)
Nausea	148 (55)	56 (21)	3 (1)	77 (31)	23 (9)	7 (3)
Vomiting	50 (19)	12 (4)	1 (< 1)	30 (12)	8 (3)	4 (2)
Constipation	49 (18)	8 (3)	0	36 (14)	8 (3)	0
Abdominal pain	34 (13)	12 (4)	2 (1)	17 (7)	4 (2)	0
Others, No. (%)						
Alopecia	123 (46)	105 (39)	0	41 (16)	18 (7)	0
Fatigue	100 (37)	37 (14)	15 (6)	73 (29)	31 (12)	6 (2)
Asthenia	53 (20)	26 (10)	5 (2)	37 (15)	19 (8)	2 (1)
Decreased appetite	41 (15)	9 (3)	1 (< 1)	34 (14)	13 (5)	1 (< 1)
Neuropathy[f]	23 (9)	8 (3)	3 (1)	38 (15)	16 (6)	6 (2)

Published in: Hope S. Rugo; Aditya Bardia; Frederik Marmé; Javier Cortes; Peter Schmid; Delphine Loirat; Olivier Trédan; Eva Ciruelos; Florence Dalenc; Patricia Gómez Pardo; Komal L. Jhaveri; Rosemary Delaney; Olivia Fu; Lanjia Lin; Wendy Verret; Sara M. Tolaney; *Journal of Clinical Oncology* 2022 403365-3376.DOI: 10.1200/JCO.22.01002

TROPiCS-02: Investigators' Conclusions

-In patients with heavily pretreated HR + /HER 2 negative advanced breast cancer who have received prior endocrine therapy , including prior CDK 4/6 therapy and at least two prior chemotherapy regimens for metastatic disease, SG demonstrated a statistically significant PFS benefit over TPC

-The primary endpoint of PFS was met with a 34% reduction in risk of disease progression or death HR 0.66, P less than 0.001

-A higher proportion of patients were alive and progression free at all landmarks time points with three times as many patients' progression free at one year mark 21% for SG, 7% for TPC

-Median 3.2-mo OS improvement (hazard ratio: 0.79; 95% CI: 0.65-0.96; *P* = .02)

-Delayed worsening of fatigue and global health status

-Safety of sacituzumab govitecan manageable and consistent with previous data

-Investigators concluded that given statistically and clinically meaningful benefit, sacituzumab govitecan should be considered as a potential treatment option in previously treated patients with HR+/HER2- MBC

1. Rugo. ESMO 2022. Abstr LBA76. 2. Bardia. 2021;32:1148. 3. Bardia. NEJM. 2021;384:1529.
4. Kalinsky. Ann Oncol. 2020;31:1709. 5. Marmé. ESMO 2022. Abstr 214MO.

DESTINY-Breast04: Background

Approximately 60% of metastatic breast cancers deemed HER2- do express low levels of HER2[1]

HER2 low defined as a score of 1+ by IHC or 2+ with negative FISH[1,2]

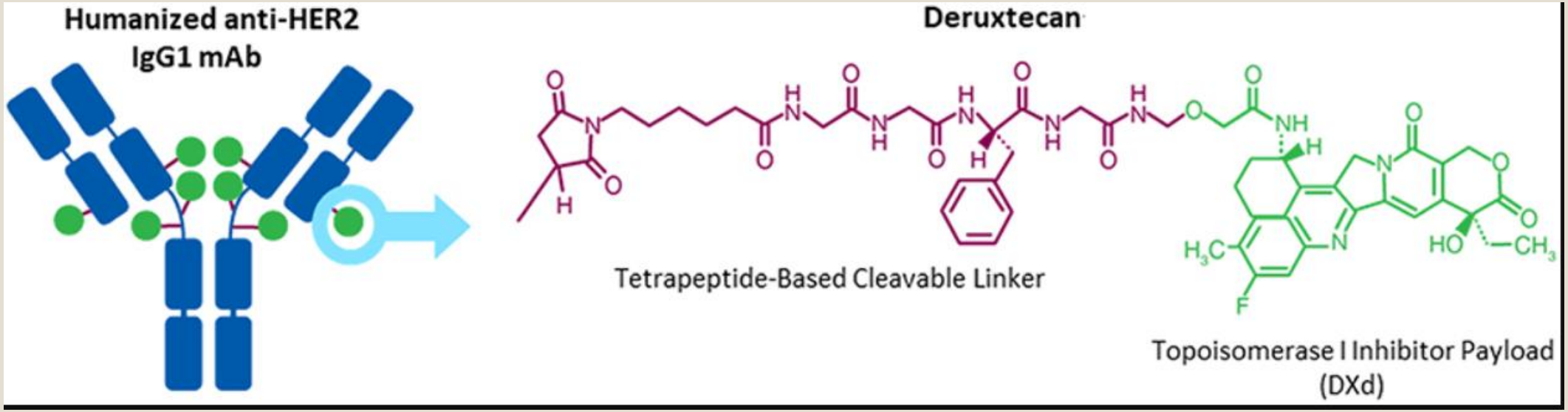
Trastuzumab deruxtecan is an anti-HER2 antibody–drug conjugate approved by the FDA for HER2+ metastatic breast cancer

- Preliminary reports showed activity against HER2-low–expressing tumor cells[1]

DESTINY- Breast04 compared efficacy and safety of trastuzumab deruxtecan vs physician's choice of chemotherapy in patients with pretreated HER2 low metastatic breast cancer[1,2]

1. Modi. NEJM. 2022;[Epub]. 2. Modi. ASCO 2022. Abstr LBA3. 3. Fehrenbacher. JCO. 2020;38:444

Structure of Trastuzumab Deruxtecan



DESTINY-Breast04: Phase III Study of T-DXd vs CT for HER2-Low MBC

Multicenter, randomized, open-label, phase III trial

Patients with HER2-low (IHC1+ or IHC2+/ISH-) unresectable or metastatic BC; 1-2 lines of CT in the metastatic setting or recurrence ≤6 mo after adjuvant CT; ≥1 ET if HR+; treated, stable brain metastases eligible
(N = 557)

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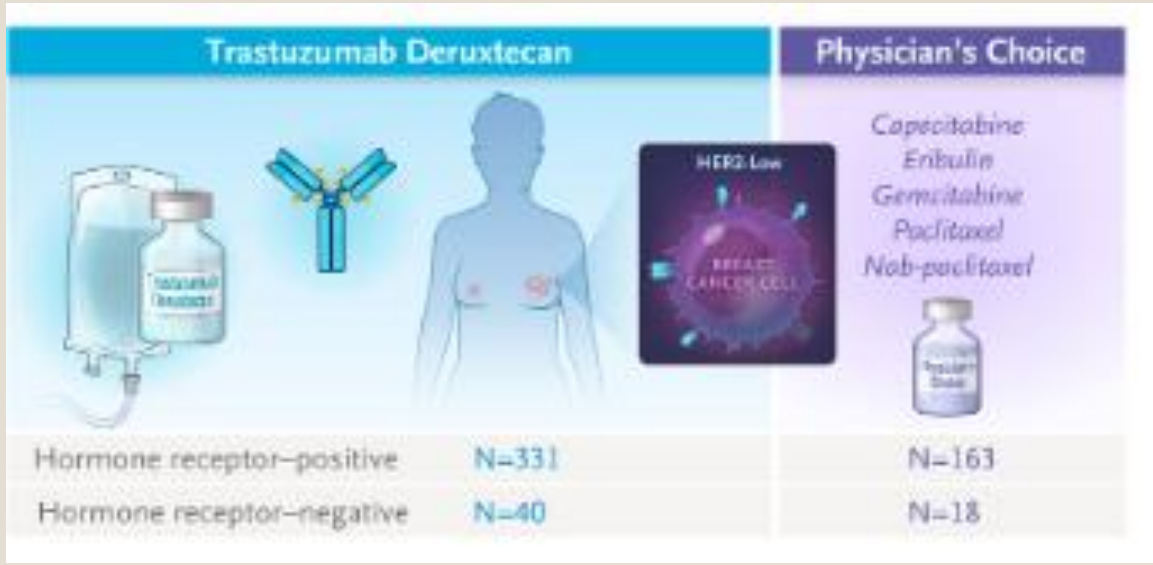


- Primary Endpoint : PFS in HR+ patient population by BICR
- Secondary endpoints: PFS in all patients, OS in HR+ and in all patients, ORR,DoR, efficacy in HR-patient population

DESTINY-Breast04: Baseline Characteristics

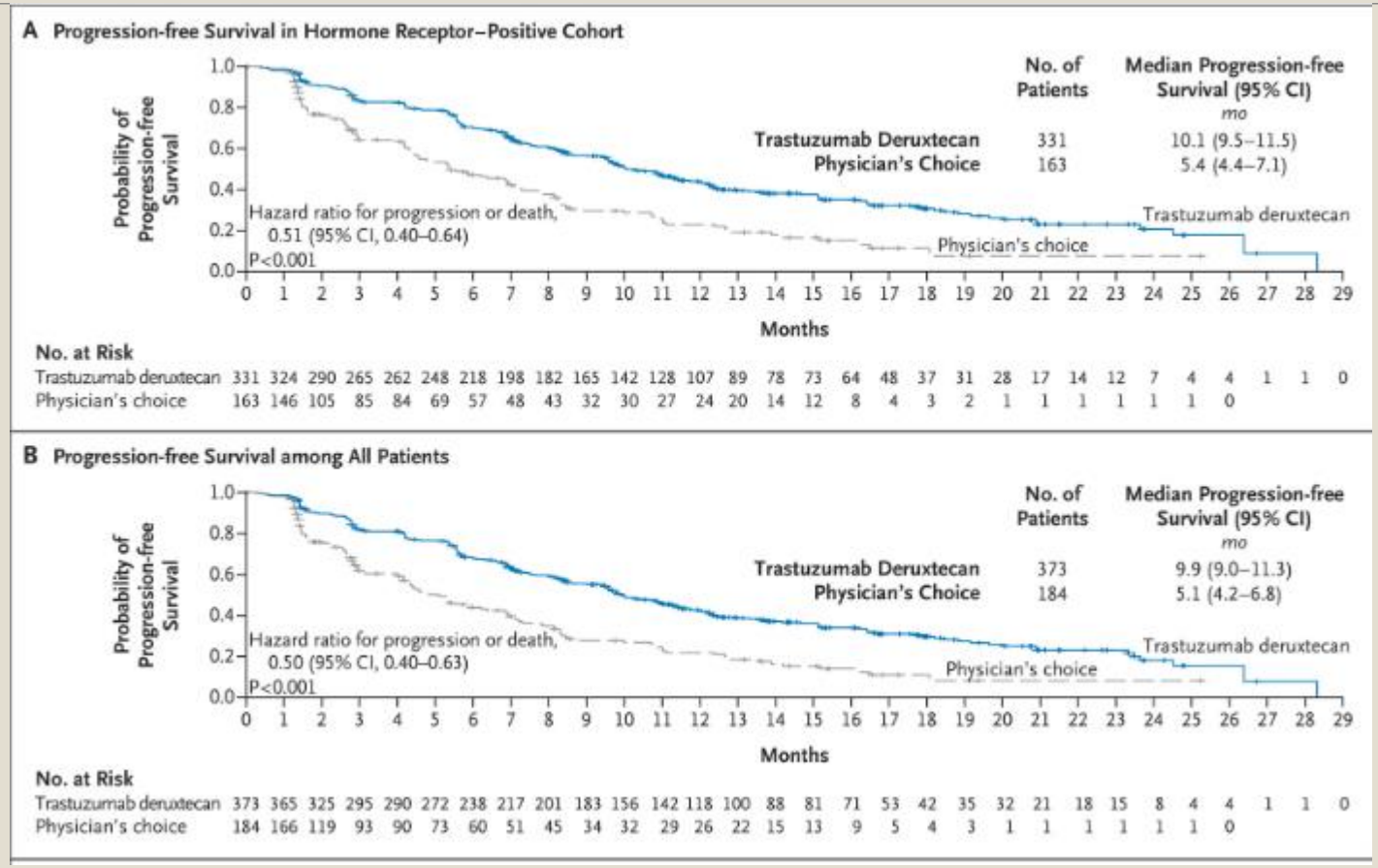
Characteristic	HR+ Patients		All Patients	
	T-DXd (n = 331)	CT (n = 163)	T-DXd (n = 373)	CT (n = 184)
Median age, yr (range)	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
▪ Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
▪ Asia	128 (39)	60 (37)	147 (39)	66 (36)
▪ North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
▪ 1+	193 (58)	95 (58)	215 (58)	106 (58)
▪ 2+/ISH-	138 (42)	68 (42)	158 (42)	78 (42)
ECOG PS, n (%)				
▪ 0	187 (57)	95 (58)	200 (54)	105 (57)
▪ 1	144 (44)	68 (42)	173 (46)	79 (43)
HR, n (%)				
▪ Positive	328 (99)	162 (99)	333 (89)	166 (90)
▪ Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

Modi;N Engl J Med 2022; 387:9-20

DESTINY-Breast04: Prior Therapies

Prior Therapy	HR+ Patients		All Patients	
	T-DXd (n = 331)	CT (n = 163)	T-DXd (n = 373)	CT (n = 184)
Median lines of systemic therapy,* n (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
No. of prior lines of systemic therapy*, n (%)				
▪ 1	23 (7)	14 (9)	39 (10)	19 (10)
▪ 2	85 (26)	41 (25)	100 (27)	53 (29)
▪ ≥3	223 (67)	108 (66)	234 (63)	112 (61)
Median lines of chemotherapy,* n (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
No. of prior lines of chemotherapy*, n (%)				
▪ 0	1 (0.3)	1 (0.6)	1 (0-3)	1 (0.5)
▪ 1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
▪ 2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
▪ ≥3	3 (0.9)	0	6 (1.6)	0
Median lines of ET,* n (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
No. of prior lines of ET,* n (%)				
▪ 0	28 (8)	17 (10)	60 (16)	34 (18)
▪ 1	105 (32)	49 (30)	108 (29)	51 (28)
▪ 2	110 (33)	53 (33)	115 (31)	54 (29)
▪ ≥3	88 (37)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)	259 (78)	132 (81)	279 (75)	140 (76)
▪ CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

DESTINY-Breast04: PFS



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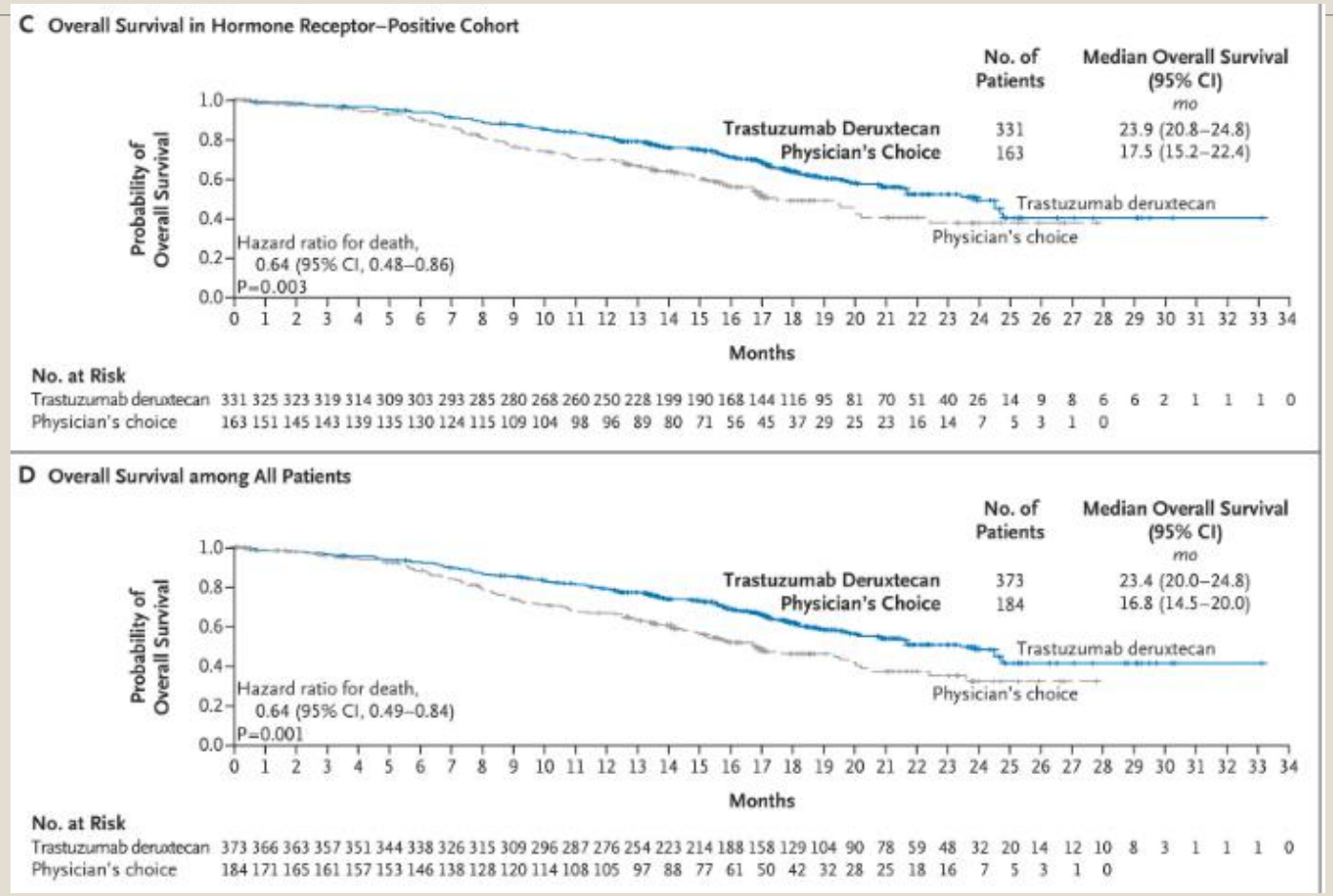
DESTINY-Breast04: Response

Response, n (%)	HR+ Patients		All Patients		HR- Patients	
	T-DXd (n = 333)	CT (n = 166)	T-DXd (n = 373)	CT (n = 184)	T-DXd (n = 40)	CT (n = 18)
Confirmed ORR, % (95% CI)	52.6 (47.0-58.0)	16.3 (11.0-22.8)	52.3 (47.1-57.4)	16.3 (11.3-22.5)	50.0 (33.8-66.2)	16.7 (3.6-41.4)
Best overall response, n (%)						
▪ CR	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)	1 (2.5)	1 (5.6)
▪ PR	164 (49.2)	26 (15.7)	183 (49.1)	28 (15.2)	19 (47.5)	2 (11.1)
▪ SD	117 (35.1)	83 (50.0)	129 (34.6)	91 (49.5)	12 (30.0)	8 (44.4)
▪ PD	26 (7.8)	35 (21.1)	31 (8.3)	41 (22.3)	5 (12.5)	6 (33.3)
▪ Not evaluable	14 (4.2)	21 (12.7)	17 (4.6)	22 (12.0)	3 (7.5)	1 (5.6)
DCR, n (%)	293 (88.0)	110 (66.3)	325 (87.1)	121 (65.8)	32 (80.0)	11 (61.1)
CBR, n (%)	237 (71.2)	57 (34.3)	262 (70.2)	62 (33.7)	25 (62.5)	5 (27.8)
Median DoR, mo	10.7	6.8	10.7	6.8	8.6	4.9
Median TTR, mo	2.76	2.73	2.73	2.22	1.51	1.41

DESTINY-Breast04: OS



DESTINY-Breast04: Safety

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

Modi;N Engl J Med 2022; 387:9-20

DESTINY-Breast 04 establishes T-Dxd as the new standard of care in HER2low, HR+/HR- mBC

- In this heavily pretreated population, T-Dxd is the first HER 2 targeted therapy to show statistically significantly improved PFS and OS vs physician's choice of chemotherapy
- Benefit observed across all patient subgroups, including across HER2 IHC scores and regardless of CDK4/6 inhibitor use
- Safety profile of trastuzumab deruxtecan was consistent with previous data
- Investigators concluded that results support use of trastuzumab deruxtecan as standard of care for HER2-low metastatic breast cancer

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022;[Epub].

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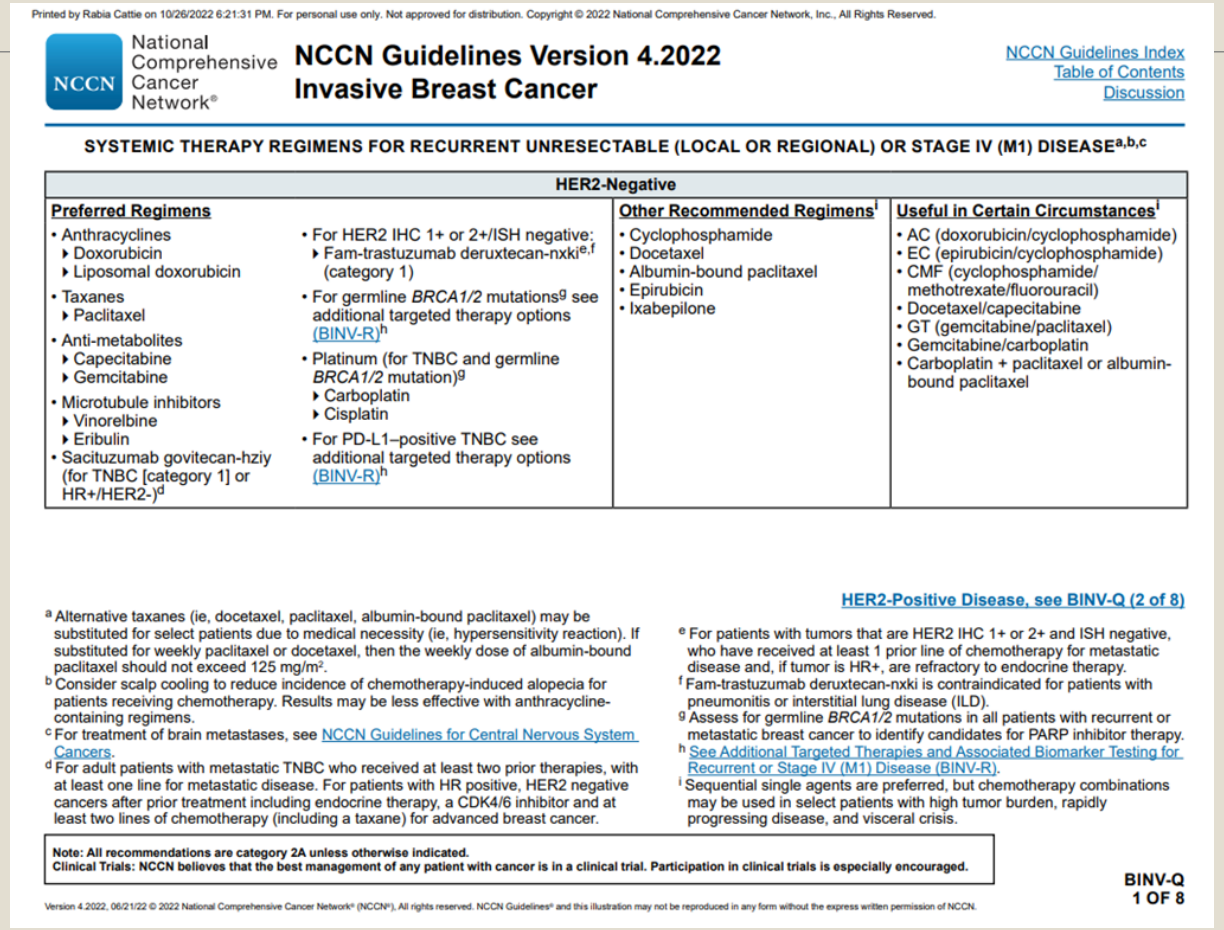

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative

Preferred Regimens		Other Recommended Regimens[i]	Useful in Certain Circumstances[i]
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • Sacituzumab govitecan-hziy (for TNBC [category 1] or HR+/HER2-)[d]	• For HER2 IHC 1+ or 2+/ISH negative: ▸ Fam-trastuzumab deruxtecan-nxki[e,f] (category 1) • For germline *BRCA1/2* mutations[g] see additional targeted therapy options (BINV-R)[h] • Platinum (for TNBC and germline *BRCA1/2* mutation)[g] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[h]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

HER2-Positive Disease, see BINV-Q (2 of 8)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.
[b] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.
[c] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[d] For adult patients with metastatic TNBC who received at least two prior therapies, with at least one line for metastatic disease. For patients with HR positive, HER2 negative cancers after prior treatment including endocrine therapy, a CDK4/6 inhibitor and at least two lines of chemotherapy (including a taxane) for advanced breast cancer.
[e] For patients with tumors that are HER2 IHC 1+ or 2+ and ISH negative, who have received at least 1 prior line of chemotherapy for metastatic disease and, if tumor is HR+, are refractory to endocrine therapy.
[f] Fam-trastuzumab deruxtecan-nxki is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).
[g] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.
[h] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).
[i] Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

DESTINY-Breast04 and TROPICS: Clinical Implications

All patients, especially HR positive, should be reclassified as HER 2 negative or HER 2 low.

Many patients will benefit from TDxd and in earlier lines of therapy.

In DESTINY-Breast04, there was a small TNBC population(ER/PR neg, HER 2 low) OS was 18 m and PFS was 8.5 m. TDxd should be option for TNBC patients after progression on Sacituzumab.

Sacituzumab govotecan should be an option for HR+ patients who are HER 2 negative (not low) and for HR+ HER 2 low patients after progression on TDxd with the potential of using it in earlier lines of therapy.

Earlier intervention could have benefitted the sample patient we discussed earlier

Next Steps

Sequencing these novel agents remains a challenge and learning opportunity.

We are looking forward to research combining Adcs with other endocrine and chemotherapy agents to further improve patient outcomes

Thank you