Antibody-Drug Conjugates (ADCs) in the treatment of breast cancer

Jane Lowe Meisel, MD

Miami Cancer Meeting

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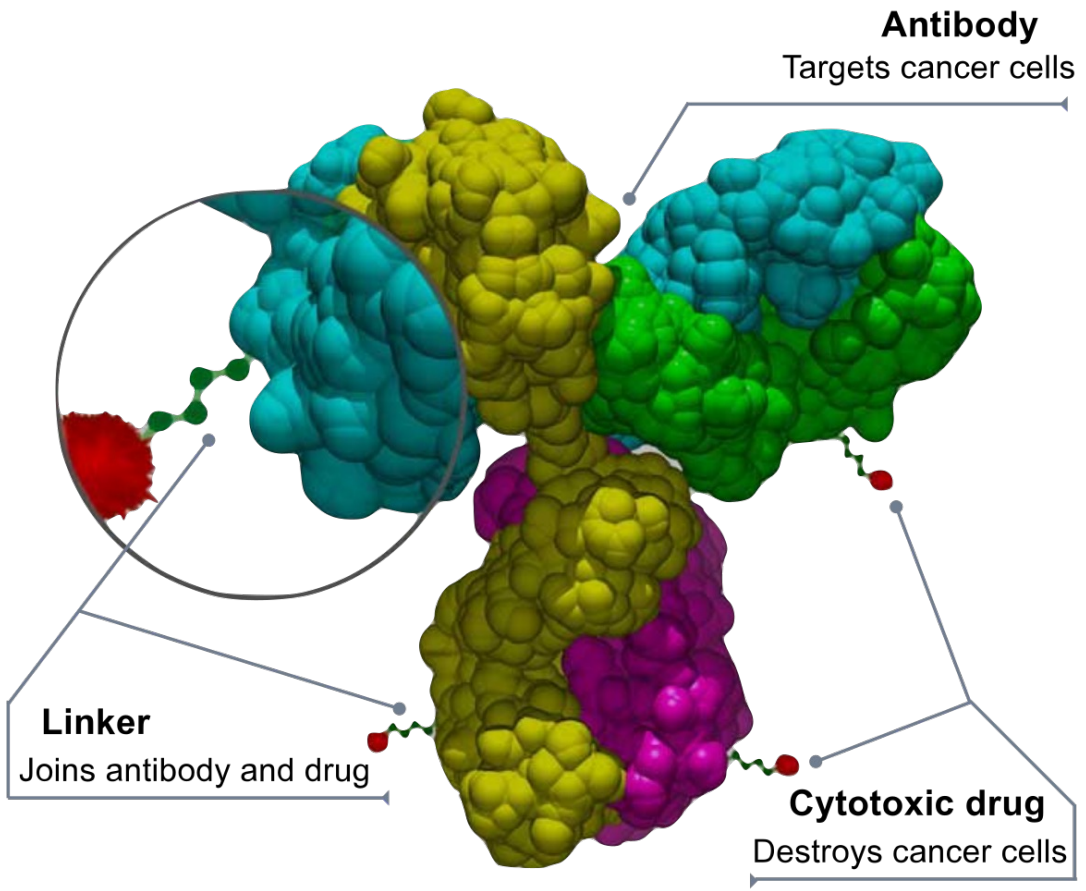
Antibody-Drug Conjugates (ADCs) 101

- Class of drugs intended to target and kill tumor cells while sparing healthy cells
- The antibody is linked to a cytotoxic drug (payload) that then destroys the cancer cells
- Combines the principles of the monoclonal antibody (targeting the antigen) with the cell-killing abilities of cytotoxics - - almost a more ‘targeted’ form of chemotherapy



Overview

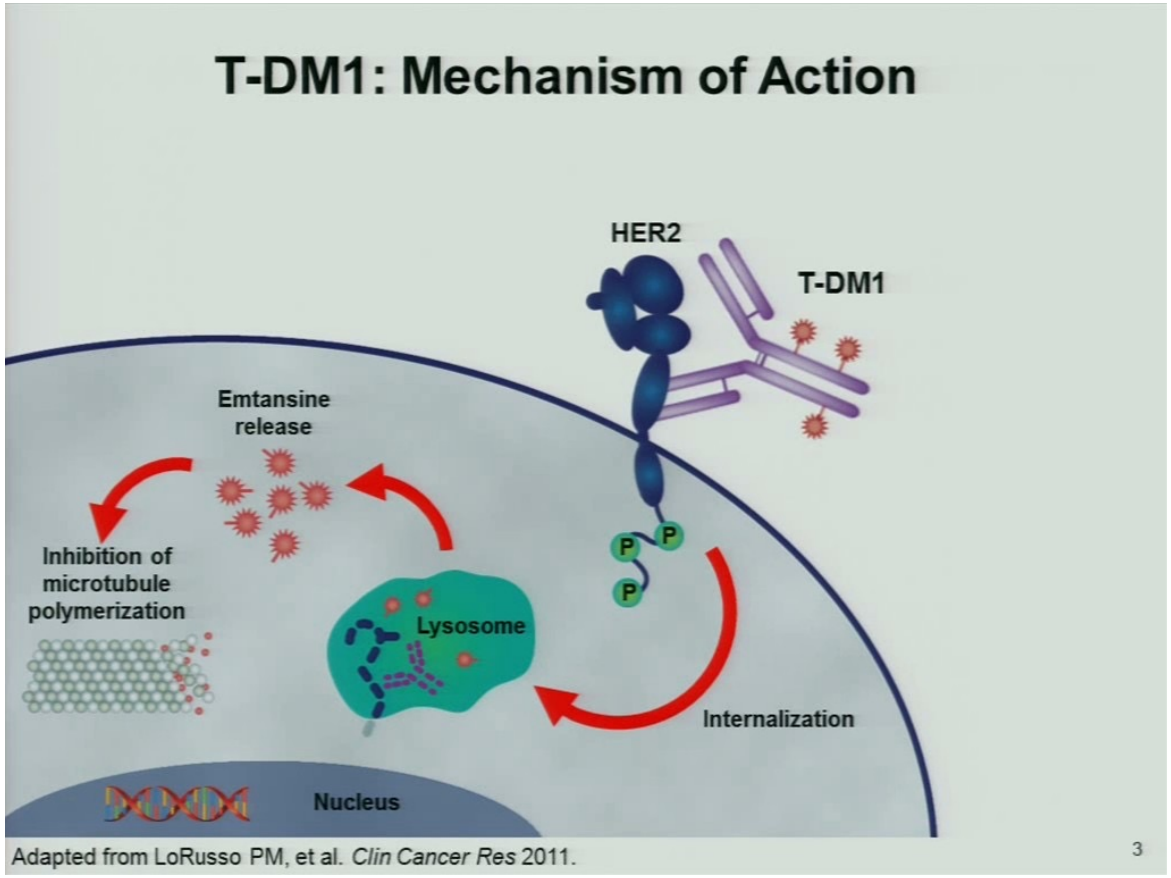
- Current ADCs available for use in breast cancer
  - Trastuzumab emtansine
    - HER2+ metastatic breast cancer, high-risk early stage HER2+ breast cancer
  - Trastuzumab deruxtecan
    - HER2+ metastatic breast cancer, HER2-low metastatic breast cancer
  - Sacituzumab govitecan
    - Metastatic TNBC, metastatic heavily pre-treated ER+ MBC

  ❖ Possible new directions for these agents, clinical scenarios

- New ADCs on the horizon

Trastuzumab emtansine

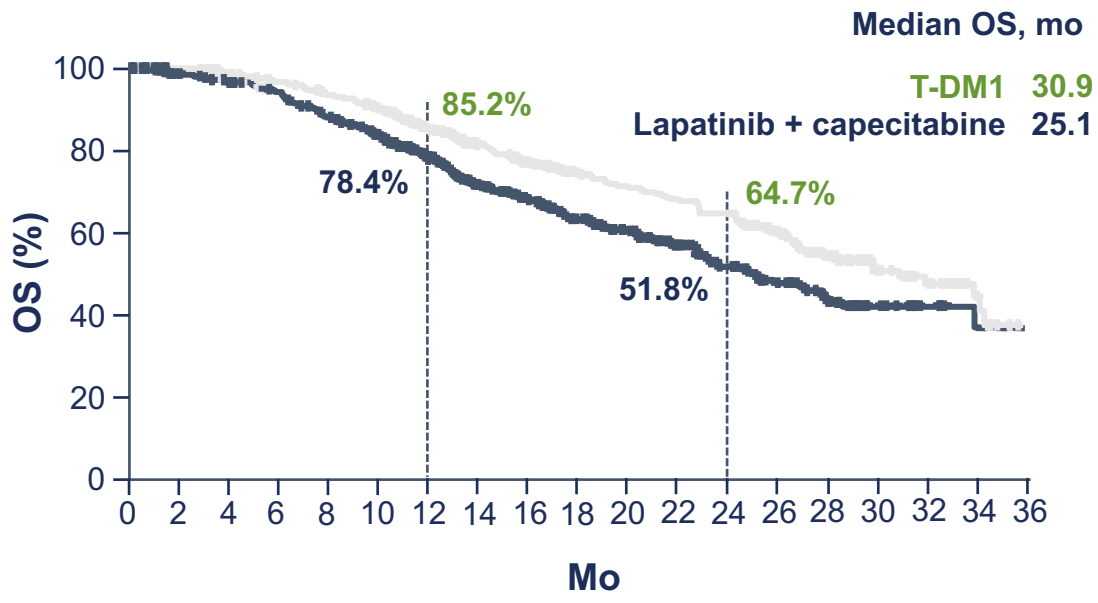
- The antibody: trastuzumab
- The cytotoxic payload: emtansine (or DM1)
- Drug-to-antibody ratio =3.5
- Adverse effects: fatigue, nausea, muscle pain, thrombocytopenia, increased LFTs



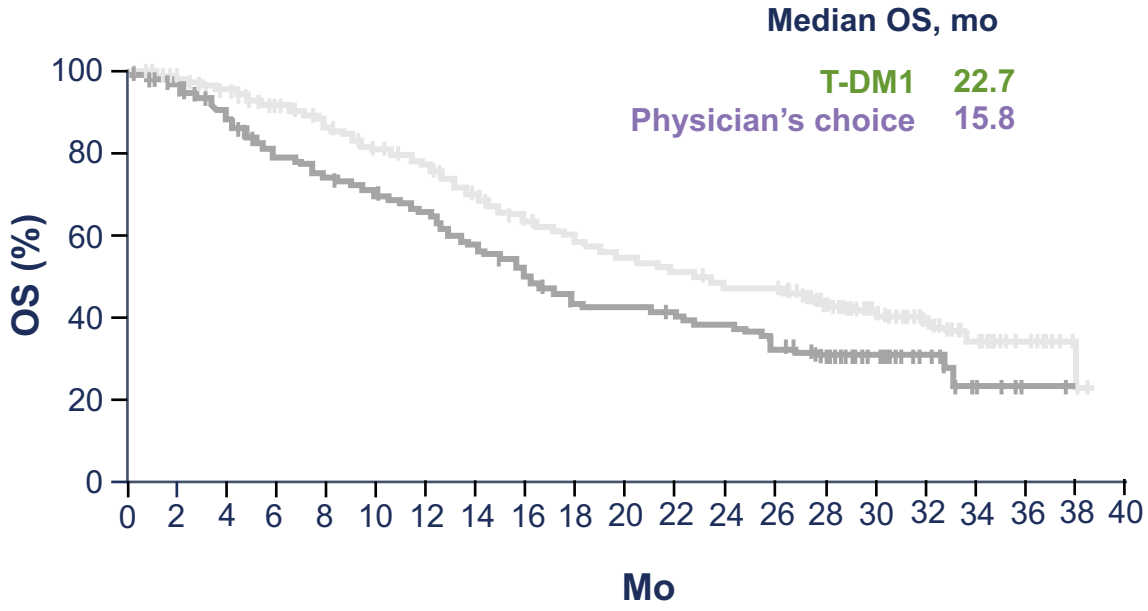
Lewis. Cancer Res. 2008;68:9280. LoRusso. Clin Cancer Res. 2011;17:6437.

EMILIA and TH3RESA: Standard Second-line Therapy for HER2+ MBC With T-DM1 After Progression on HER2-Targeted Agents

EMILIA: Randomized phase 3 study of T-DM1 vs lapatinib + capecitabine for HER2+ MBC with progression on trastuzumab + taxane (N = 991)



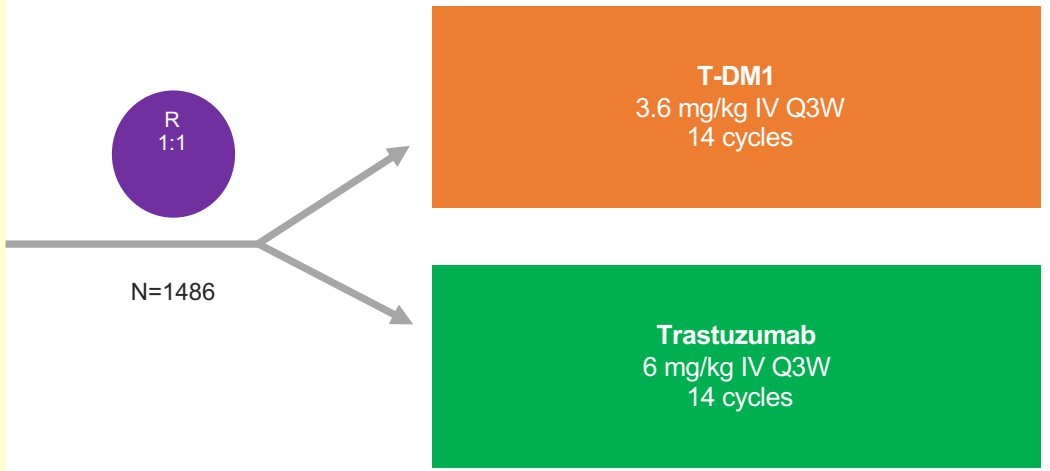
TH_3RESA: Randomized phase 3 study of T-DM1 vs physician's choice for HER2+ MBC with progression on taxane, lapatinib, and ≥2 HER2-targeted regimens including trastuzumab (N = 602)



Krop. Lancet Oncol. 2017;18:743. Verma. N Engl J Med. 2012;367:1783.

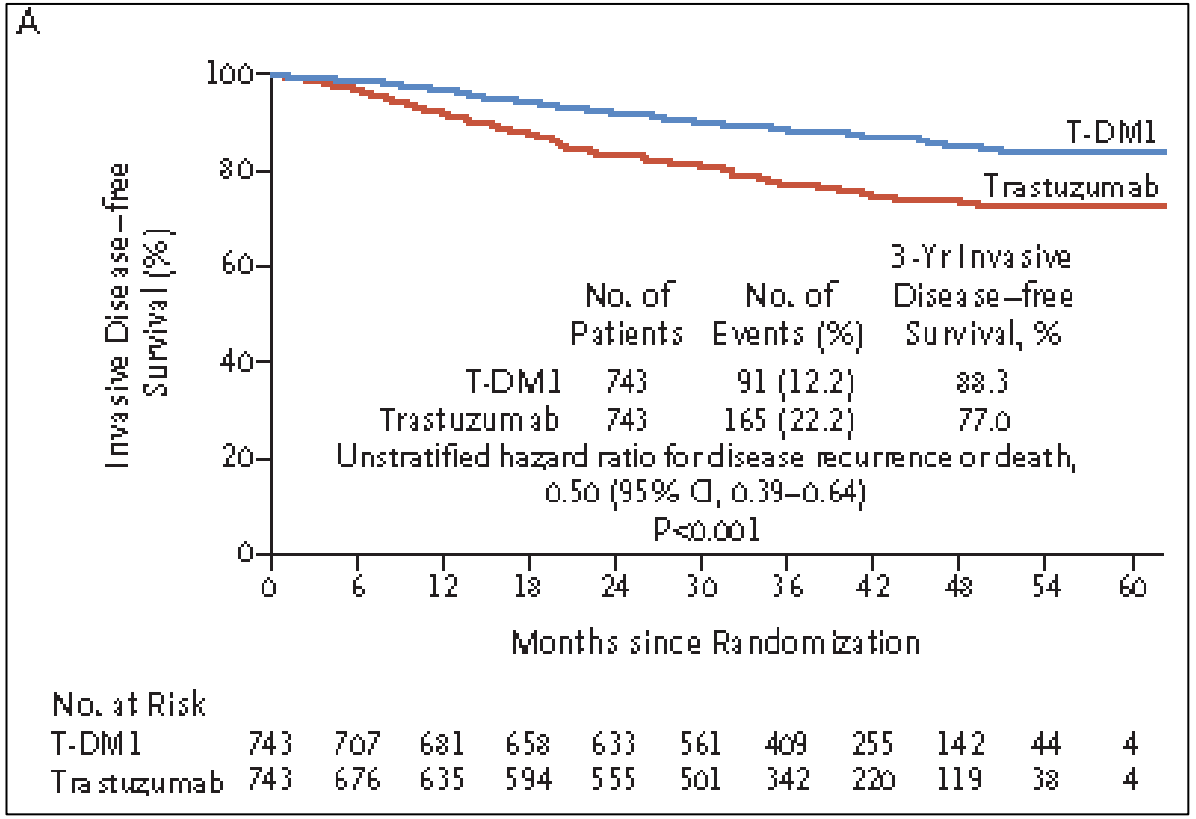
KATHERINE trial design

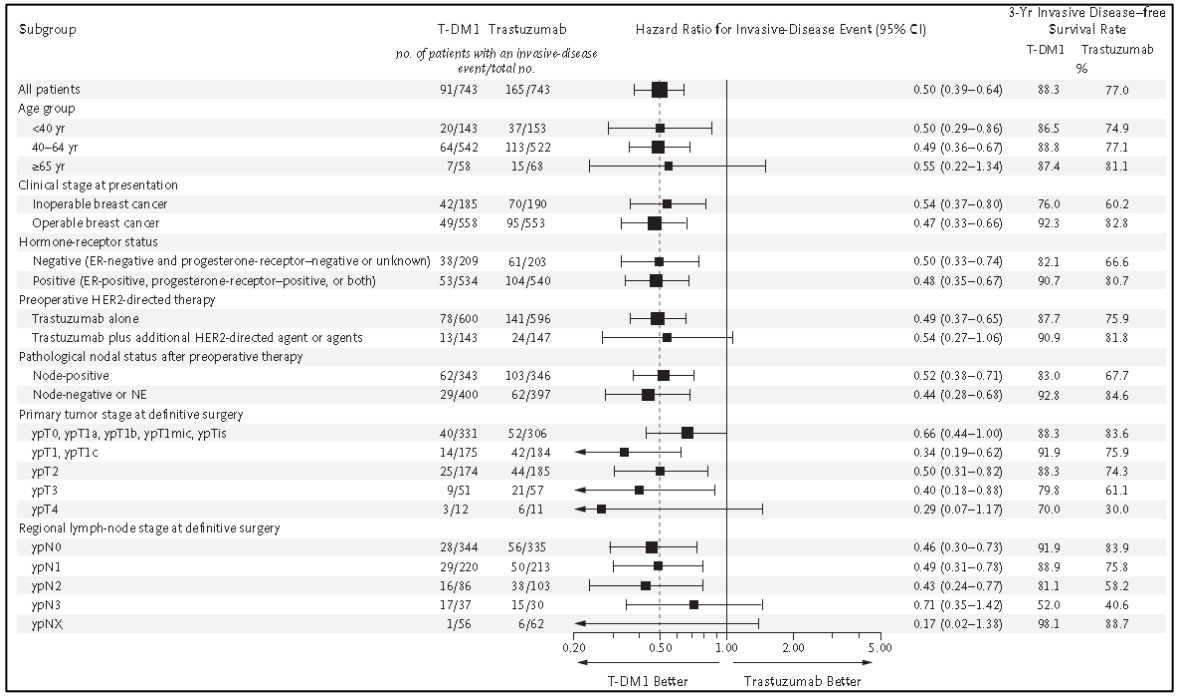
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have included:
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

KATHERINE trial results





N Engl J Med. Online Dec 5, 2018

Case example

47F with a newly diagnosed ER+PR+HER2 3+ IDC that is clinically T2N1.

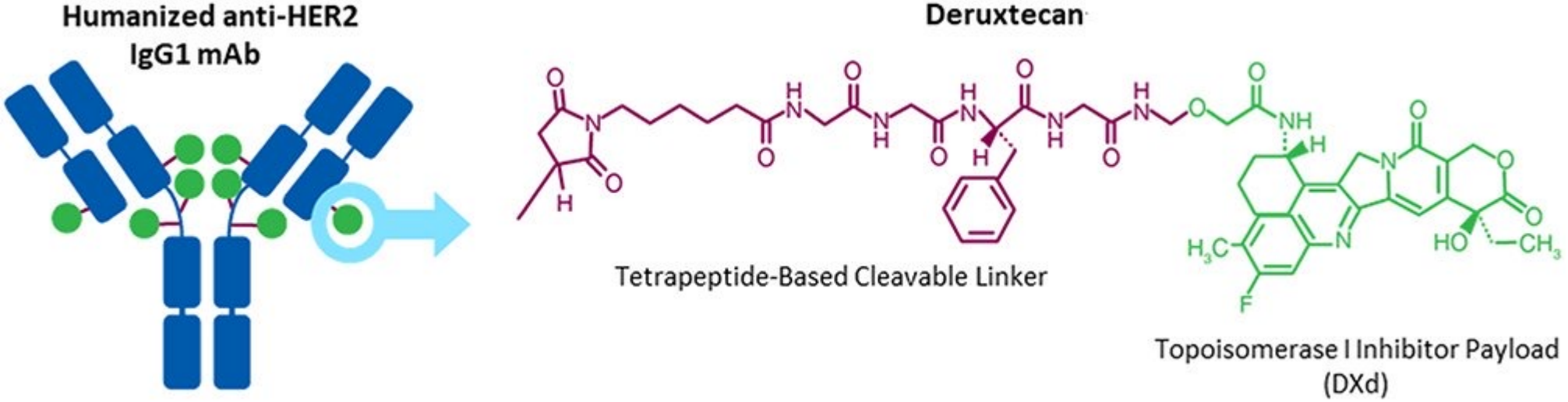
She undergoes neoadjuvant TCHP x 6 followed by lumpectomy and sentinel node biopsy.

Pathology reveals 1.8cm of residual with 40% cellularity, still ER+PR+ HER2 3+, and one node with 3mm of tumor; a second node with evidence of treatment effect.

First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral breast cancer	0.4	1.3
Death without prior event	0.3	0.4

von Minckwitz G, et al. *N Engl J Med.* 2019

Trastuzumab deruxtecan



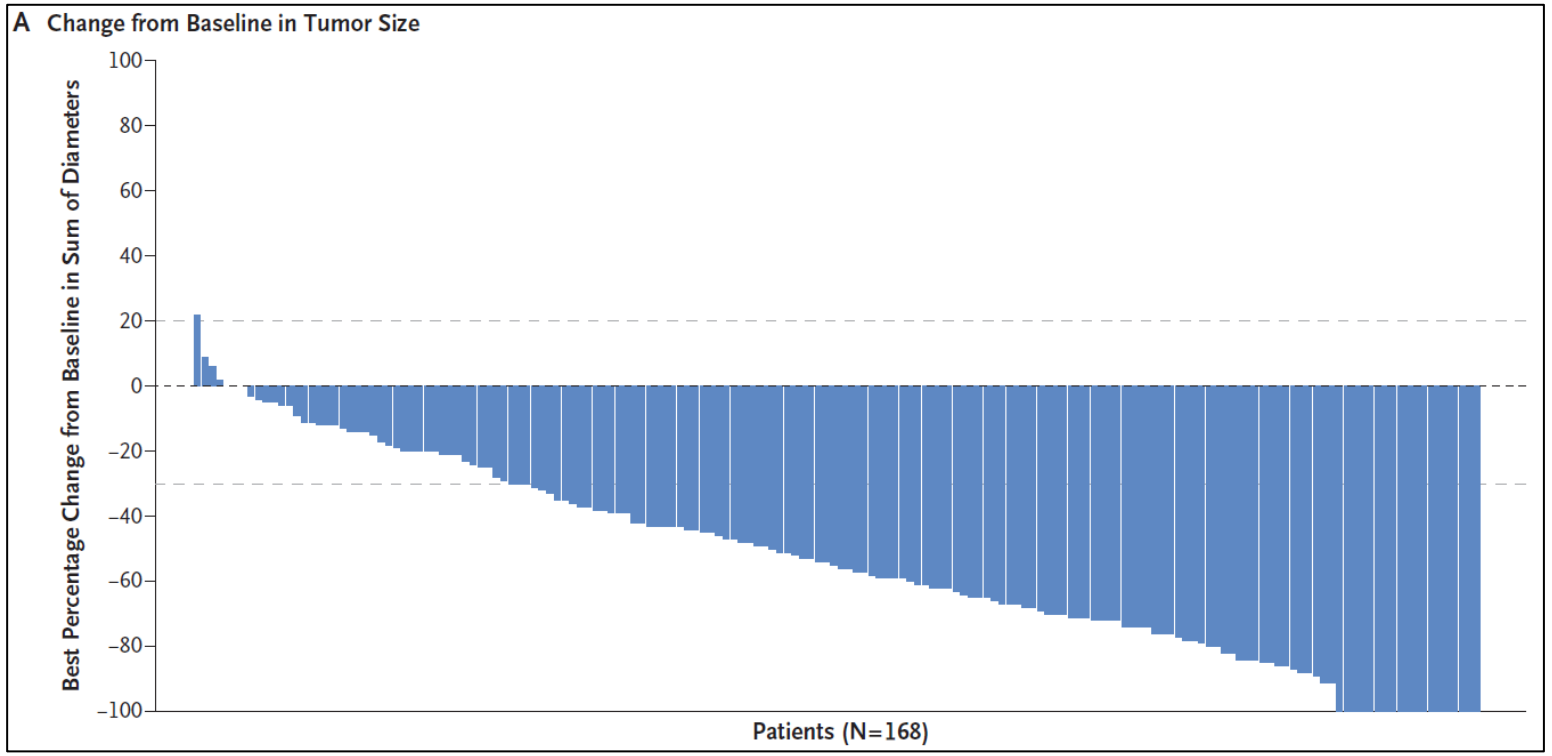
Unique features:

-High potency payload
-High drug to antibody ratio (~8)
-Payload with short systemic half-life
-Tumor selective cleavable linker
-Membrane permeable payload

Chem Pharm Bull (Tokyo). 2019; 67 (3): 173-185. Clin Cancer Res 2016; 22 (20): 5097-5108. Pharmacol Ther. 2018; 181:126-142. Cancer Sci 2016; 107 (7): 1039-1046.

DESTINY-Breast01 (NCT03248492)

- Single-arm phase 2 study of trastuzumab deruxtecan for HER2+ metastatic breast cancer
- Median 6 prior lines of therapy
- ORR= 61% (58% in patients with brain metastases)
- Median PFS 16.4 months (18.1 months in patients with brain metastases



Modi S et al N Eng J Med. 2020; 382 (7): 610-21.

DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd

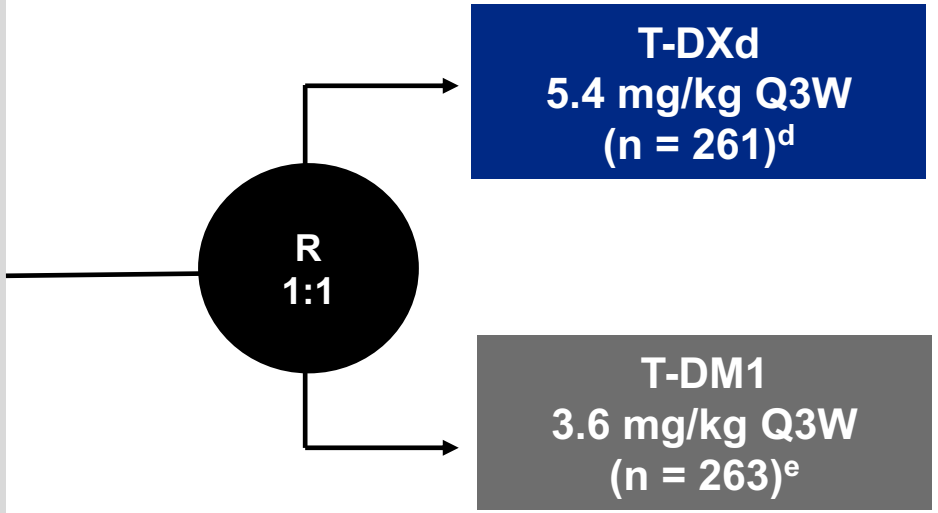
An open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer that has been previously treated with trastuzumab and a taxane[b]
- Could have clinically stable, treated brain metastases[c]
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

Secondary endpoints

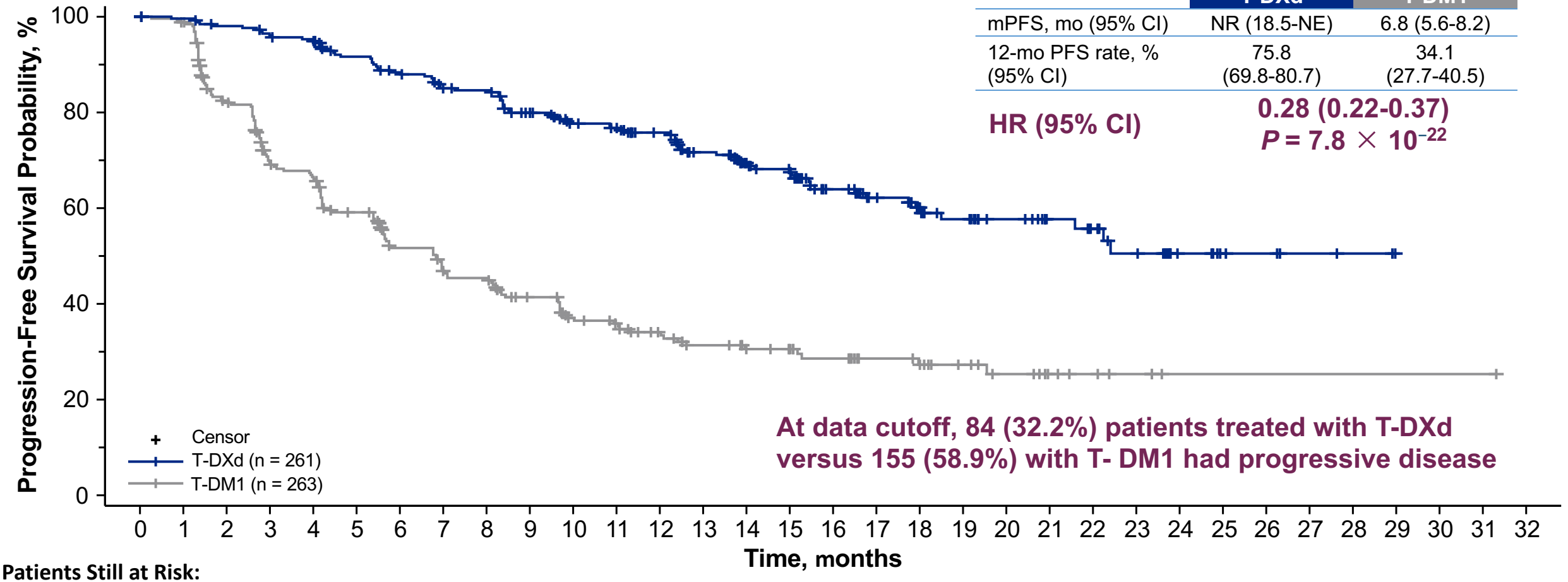
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

- At the time of data cutoff (May 21, 2021), 125 (48.6%) T-DXd patients and 214 (82.0%) T-DM1 patients had discontinued treatment
- Median follow up was 15.9 months
- BMs were measured at baseline by CT or MRI and lesions were monitored throughout the study

BICR, blinded independent central review; BM, brain metastasis; CT, computed tomography; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MRI, magnetic resonance imagining; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. [a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]Prior to protocol amendment, patients with stable, untreated BM were eligible. [d]4 patients were randomly assigned but not treated. [e]2patients were randomly assigned but not treated.

Primary Endpoint: PFS by BICR

	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	



At data cutoff, 84 (32.2%) patients treated with T-DXd versus 155 (58.9%) with T- DM1 had progressive disease

Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0			
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and was 13.9 months (range, 11.8-15.1) for T-DM1.

Cortés et al. *Ann Oncol*. 2021; 32(suppl_5):S1283-S1346. 10.1016/annonc/annonc741

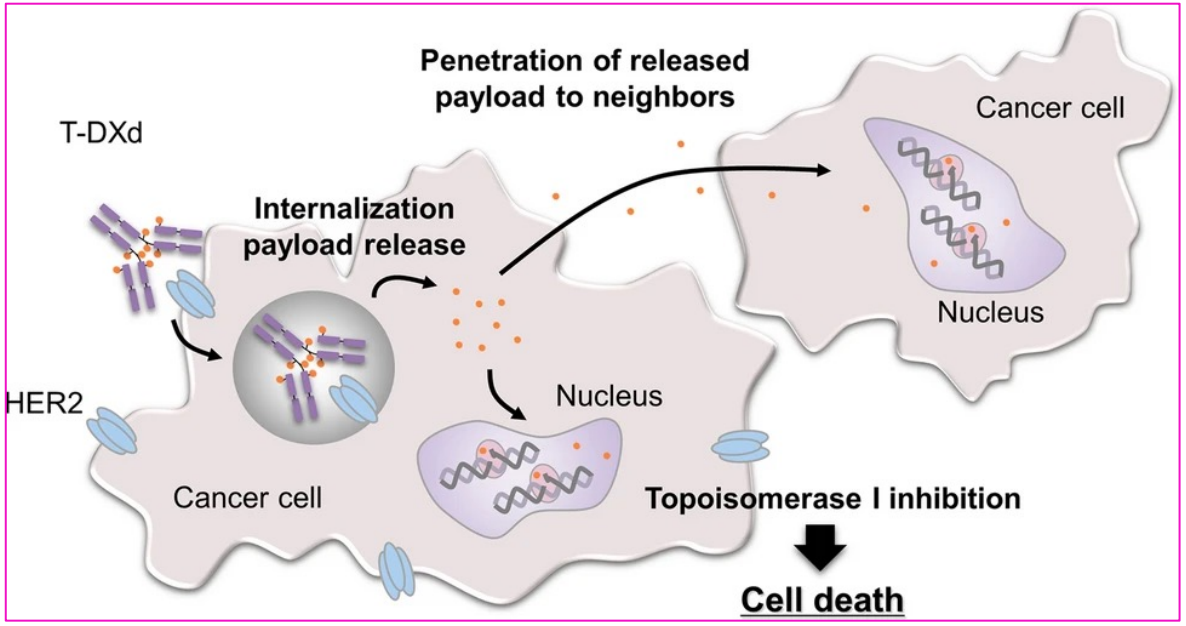
Trastuzumab deruxtecan

- After DESTINY-Breast 03, rapidly became a second-line standard of care
- Important to prepare patients for side effect profile that is different than T-DM1
  - Nausea, cytopenias, fatigue, alopecia
  - Have a low threshold to suspect ILD if symptoms develop
- In real-world practice, dose reductions and spacing out dosing can make the drug much more tolerable
- The every-three-week dosing and extremely short time to response make it a wonderful option for our patients

What about T-Dxd for HER2-low mBC?

- Drug biology:
  - Highly potent topoisomerase-1 inhibitor payload
  - 8:1 drug-antibody ratio
  - Bystander effect

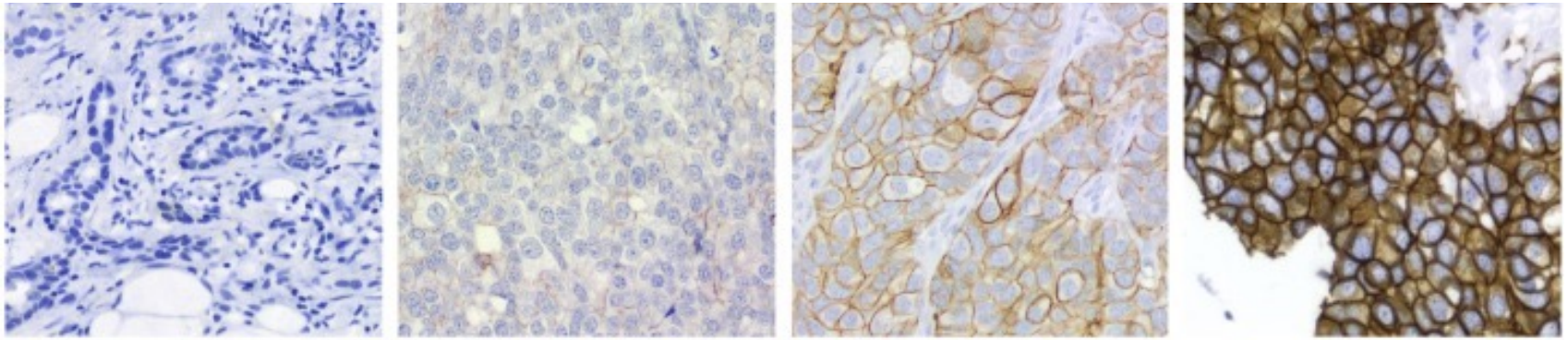
- Results from a phase 1b study reported efficacy in Her2-low MBC with a median PFS of 11.1 months and ORR 37%



J Clin Oncol 2020 Jun 10;38(17):1887-1896. Gastric Cancer 24 (2021): 780–789.

HER2-low advanced breast cancer

- Defined as cancer with HER2 IHC scores of 1+/2+ but ISH negative
  - Heterogeneous, lots of HR co-expression
- Until recently, HER2-low was treated as HER2 negative
- **DESTINY-Breast 04**: the first study to look at a medication specifically in a HER2-low population (trastuzumab deruxtecan)

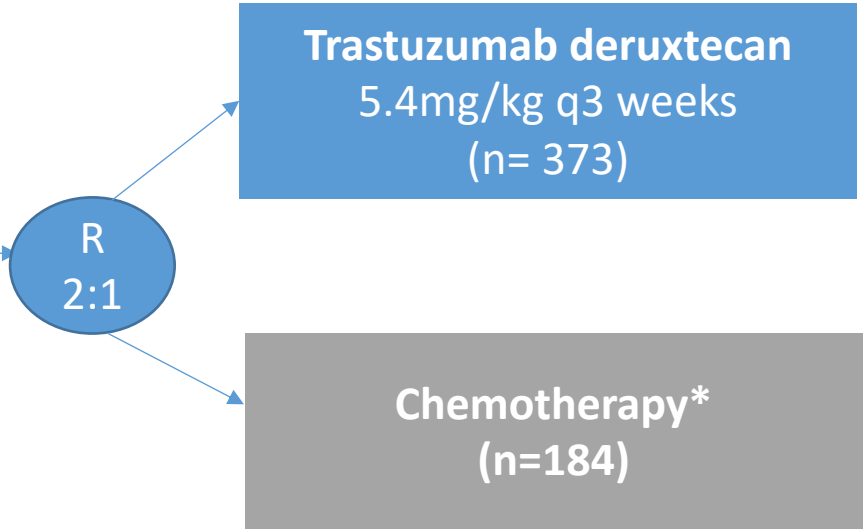


Seminars in Cancer Biology: 72 (2021), 123-135.

DESTINY-Breast04: First Randomized Phase 3 Study of T-Dxd for HER2-low MBC

- International, randomized, open-label phase III study

Eligibility:
-HER2-low (IHC 1+ or IHC 2+/ISH negative) unresectable or metastatic breast cancer
-If HR+, must have progressed on endocrine therapy and 1-2 prior lines of chemotherapy
-If HR+, must have disease considered endocrine refractory



Primary Endpoint:
-PFS by BICR (HR+)

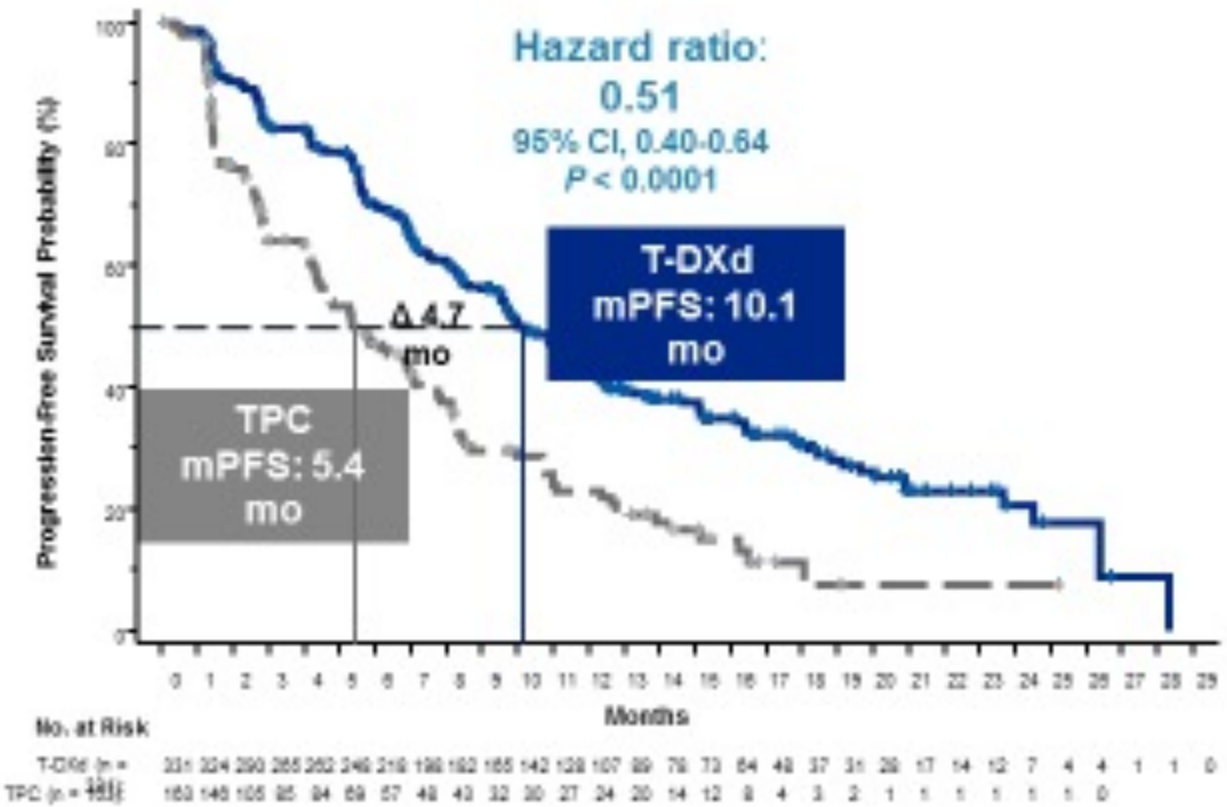
Key Secondary Endpoints:
-PFS by BICR (all patients)
-OS (HR+ and all patients)

*Investigator's choice of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

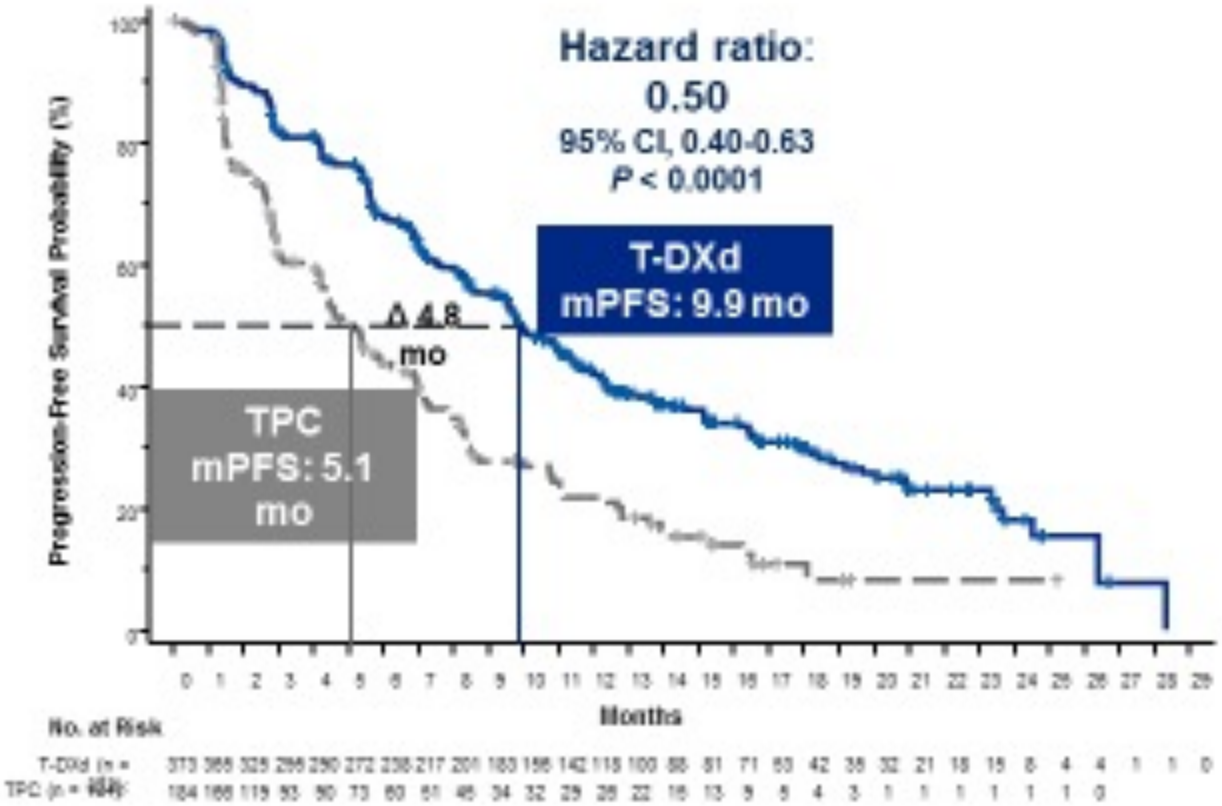
- Primary endpoints: PFS per BICR
- Secondary endpoints: OS, DoR, ORR, PFS per investigator

PFS in HR+ and All Patients

Hormone receptor–positive



All patients

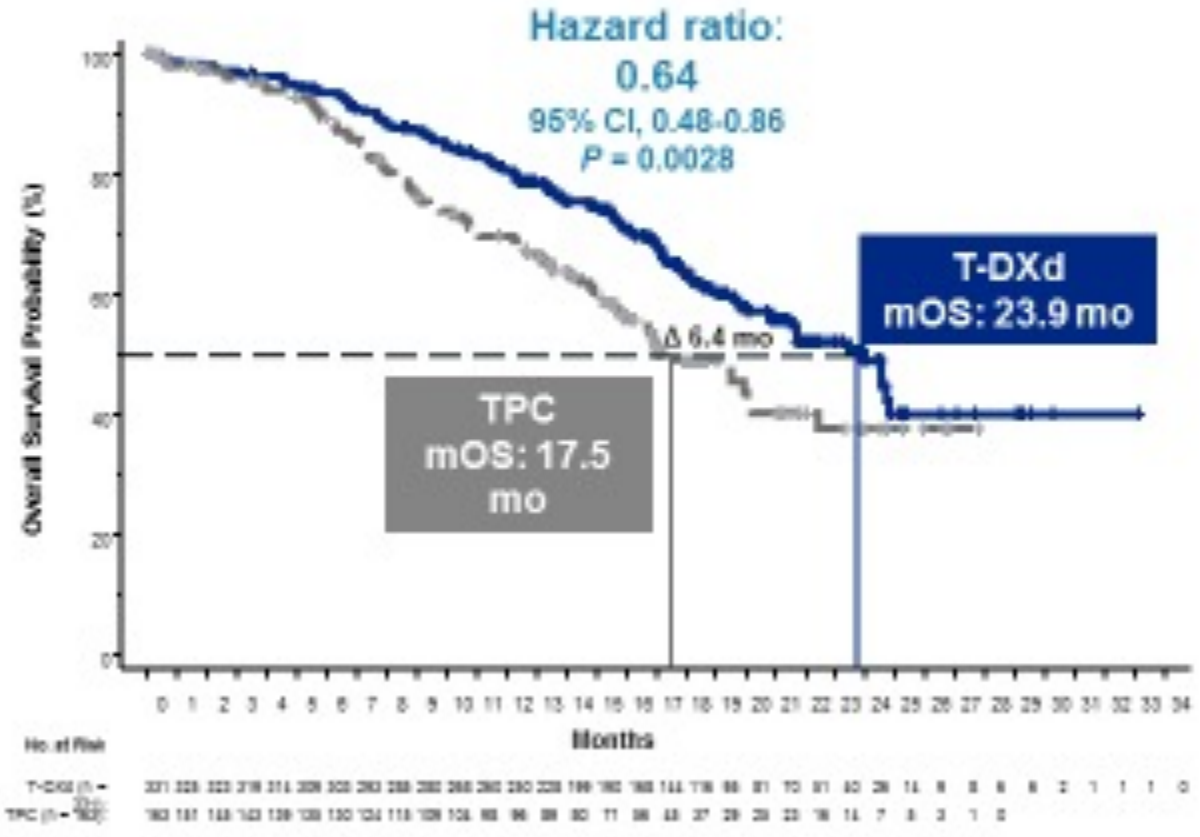


PFS by blinded independent central review.

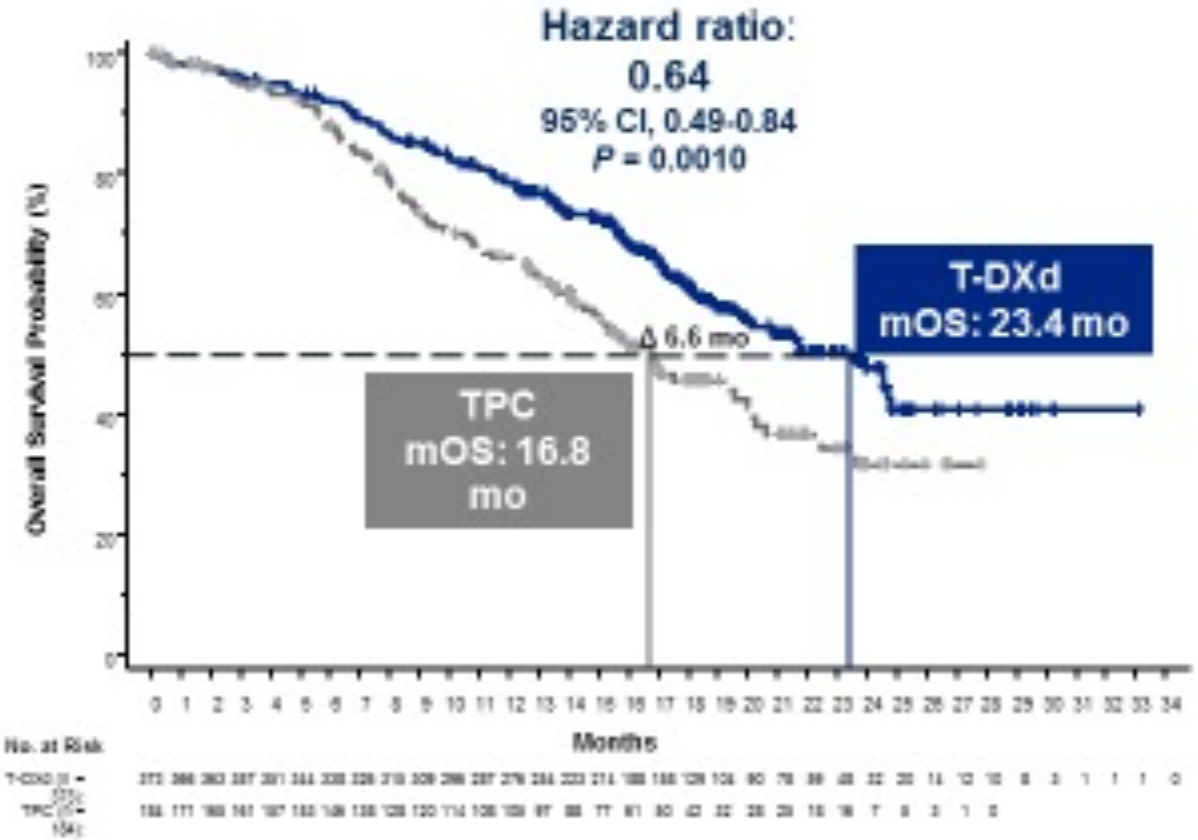
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



All patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.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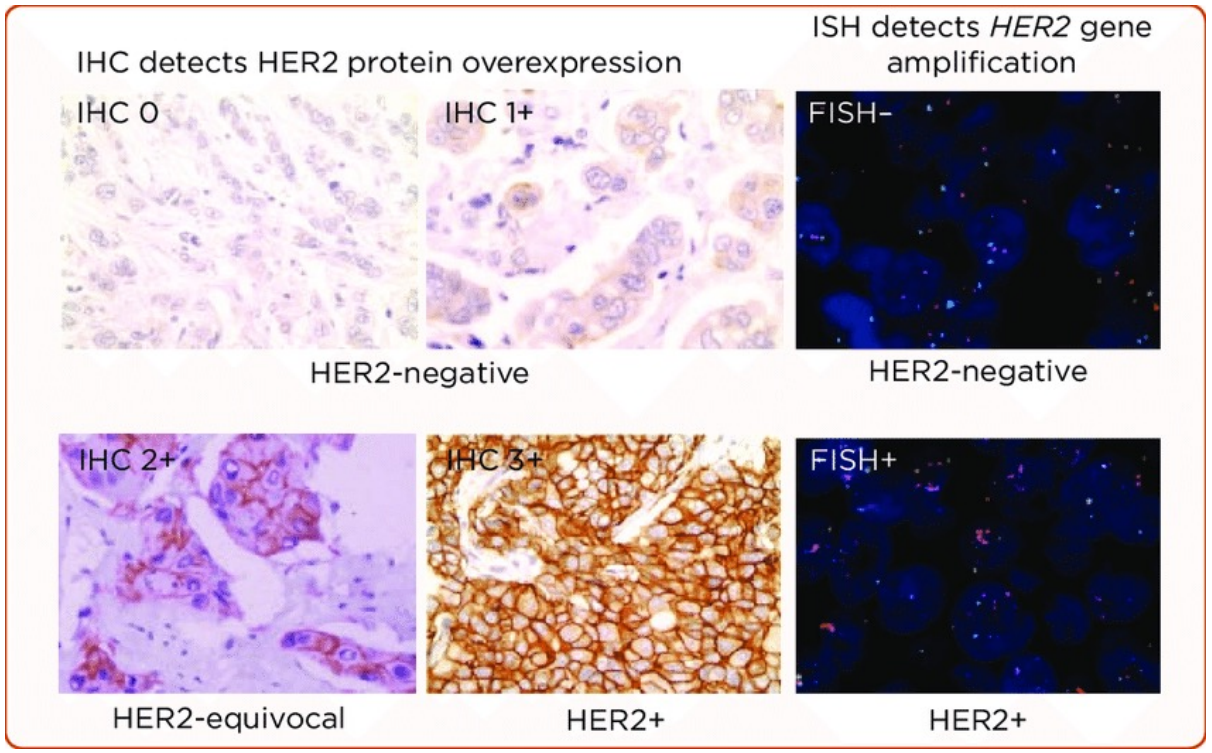
Clinical implications



- DESTINY Breast-04 changed the standard of care immediately
- Practically, all currently “HER2 negative” metastatic patients will need to be reclassified as either HER2 0 or HER2-low (1+ or 2+)
- Accurate methods for IHC testing now become particularly important
  - Studies suggest up to 20% of HER2 IHC testing performed in the real world may be inaccurate[1, 2]

[1]J Natl Cancer Inst 94::852,2002-854. [2]J Natl Cancer Inst 94::855,2002-857

A Clinical Example

- 75F whose history includes:
  - Early stage ER+PR+HER2- breast cancer in the late 1990s; s/p surgery, FAC x 6, tamoxifen x 7 years

  - Late 2018: develops metastatic ER+PR+HER2- metastatic breast cancer to bone, lung, mediastinal nodes
  - Palbociclib + letrozole: 25 months
  - Fulvestrant: 3 months
  - Capecitabine: 16 months
  - Exemestane/everolimus: 5 months

  - Then: progression with multiple new, enlarging liver lesions as well as progression elsewhere

A Clinical Example, cont.

- What is the next best option for this patient (s/p 3 lines endocrine therapy, one line of chemo for metastatic disease)?

Pre-June 2022	Post-June 2022
Chemotherapy options or clinical trial	Look back at HER2 status and decide

- 6/18/2018: ER 100% 3+ PR 99% 3+ HER2 1+ Ki67 37% 3+
  - (also would not have been unreasonable to test again)

- She started trastuzumab deruxtecan in 7/2022 (started at 4.4mg/kg, titrated up to 5.4mg/kg with cycle 3); LFTs and tumor markers declined and normalized; in 1/2023 had her first NED scan

Future directions for T-Dxd

- DESTINY-Breast 05: comparison of TDxd vs TDM1 in patients with residual disease after neoadjuvant chemotherapy for HER2+ breast cancer
- Trastuzumab deruxtecan +/- anastrozole as neoadjuvant therapy in early-stage ER+ HER2-low breast cancer (NCT04553770)
- DESTINY-Breast 06: HER2-low, HR+ advanced breast cancer who have had disease progression on more than 2 lines of endocrine therapy
- Trastuzumab deruxtecan in combination with other drugs in metastatic HER2-low breast cancer (NCT04556773)
  - Durvalumab, paclitaxel, capivasertib, AI, fulvestrant, capecitabine

Sacituzumab govitecan

- Antibody: Humanized monoclonal antibody to Trop2
- Payload: SN-38, a metabolite of irinotecan
- Drug-antibody ratio = 7.6

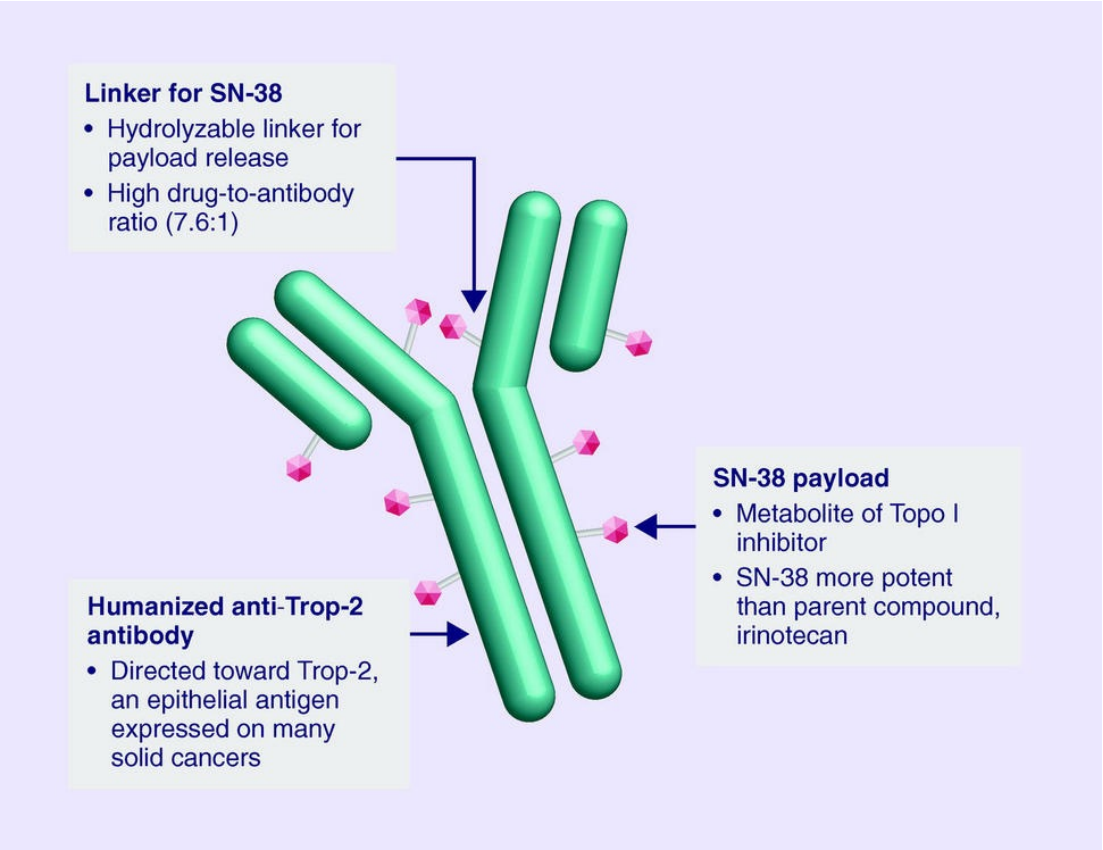
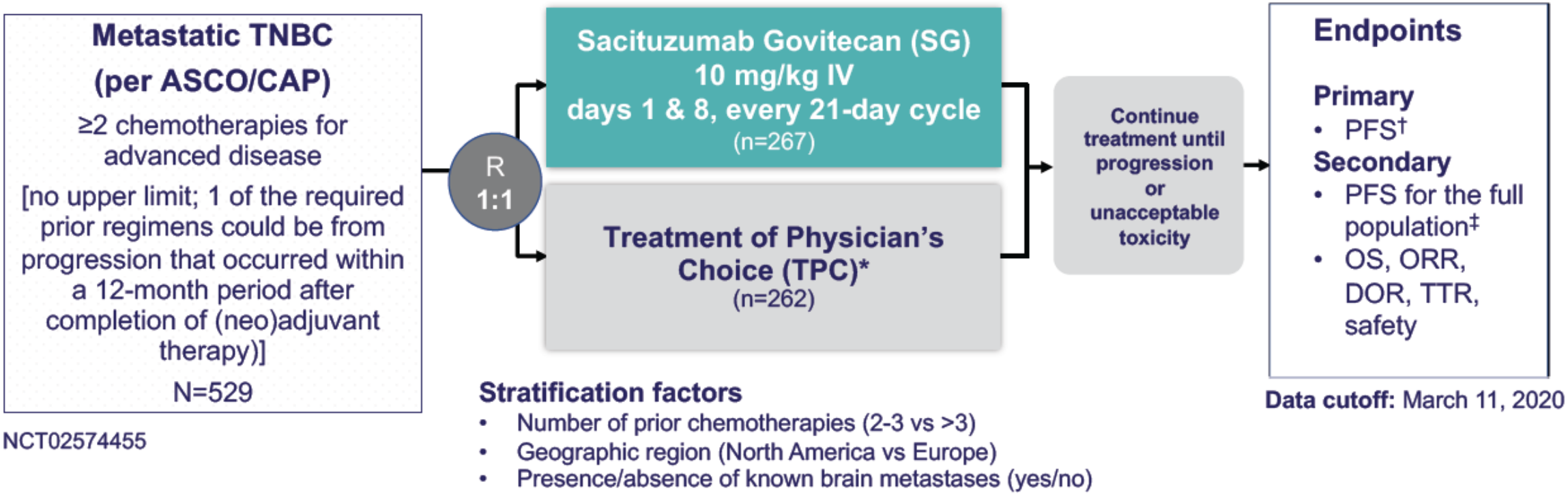


Photo courtesy of Future Medicine. 2020 Mar. doi:10.2217/fon-2020-0163

ASCENT: Randomized Phase III Sacituzumab vs. TPC



* TPC options: capecitabine, eribulin, gemcitabine, vinorelbine

Bardia et al ESMO 2020 LBA17

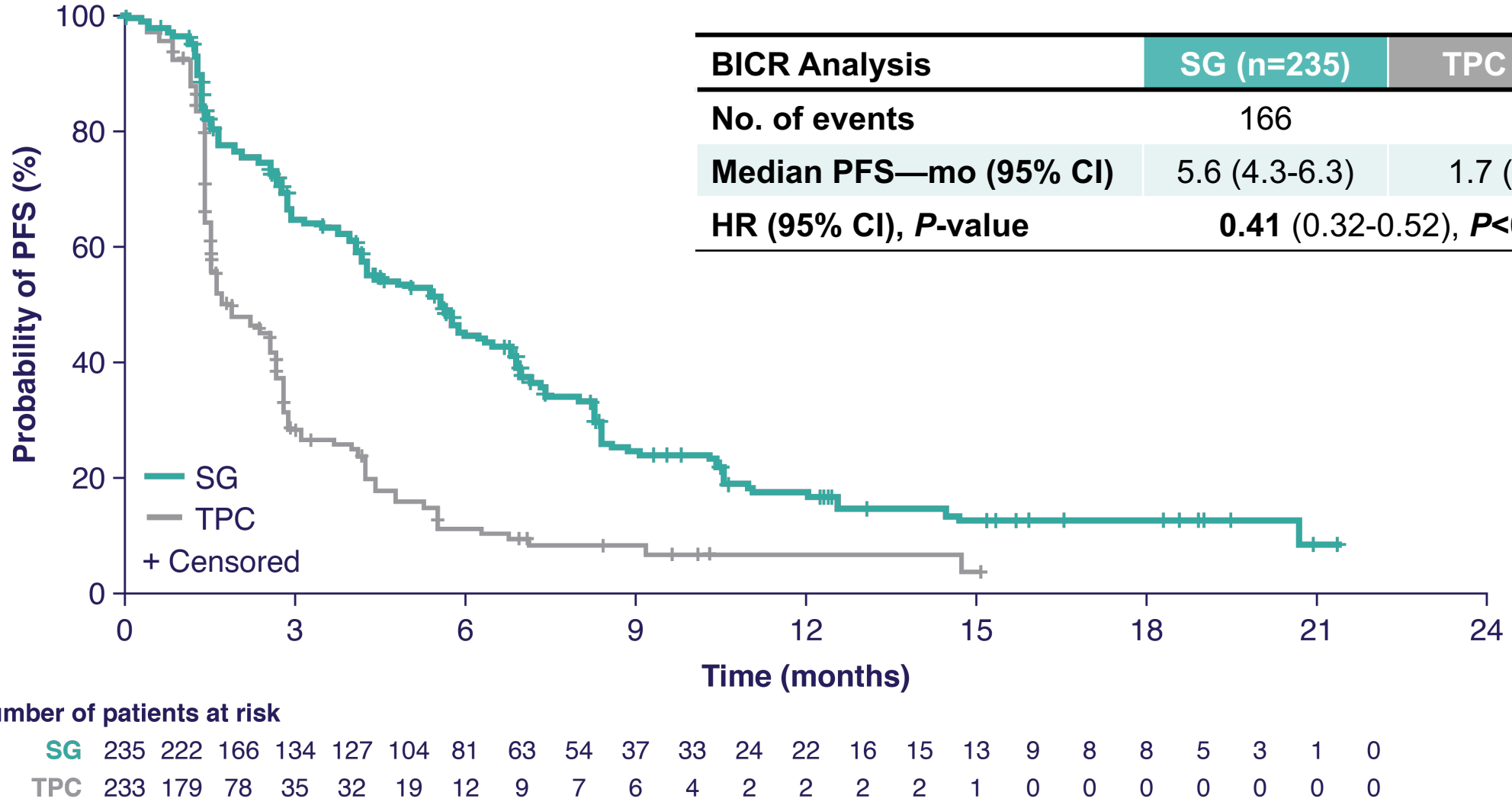
Patient characteristics

	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
***BRCA 1/2* mutational status—no. (%)**		
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Unknown	86 (37)	90 (39)
TNBC at initial diagnosis*		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)

	SG (n=235)	TPC (n=233)
Previous anticancer regimens† —median no. (range)	4 (2-17)	4 (2-14)
Most common previous chemotherapy—no. (%)		
Taxane‡	235 (100)	233 (100)
Anthracycline§	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous PARP inhibitor—no. (%)	17 (7)	18 (8)
Previous use of checkpoint inhibitors—no. (%)	67 (29)	60 (26)
Most common sites of disease‖—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

Bardia et al, ESMO 2020

Sacituzumab prolongs PFS by 60%

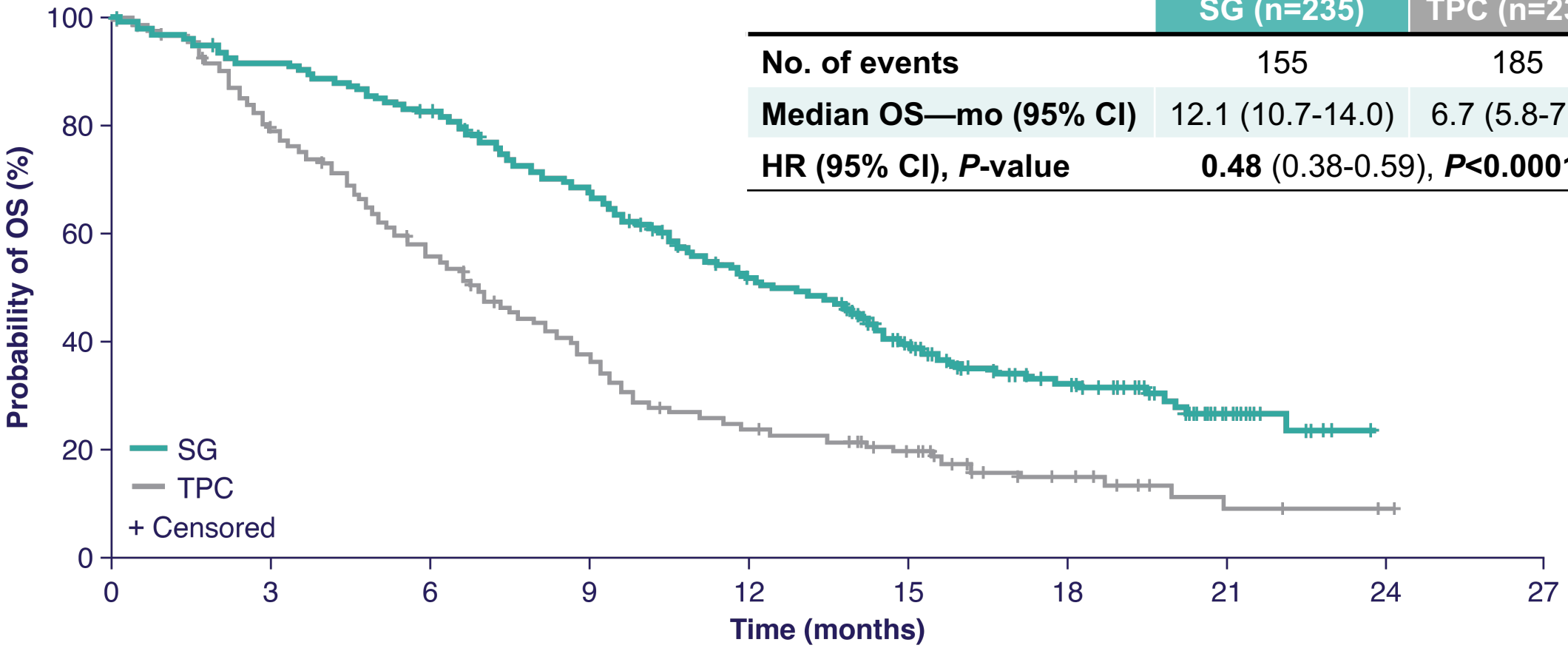


BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Bardia et al, ESMO 2020

Sacituzumab associated with 52% increase in OS!

	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	



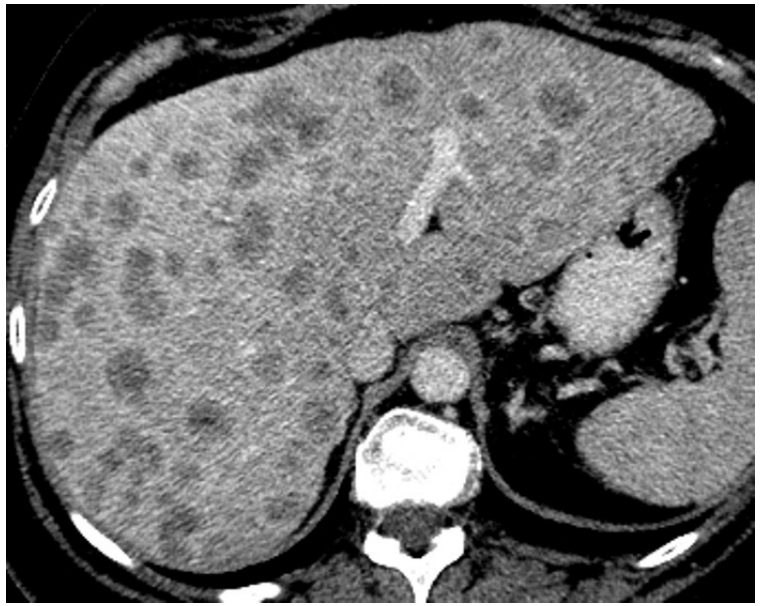
Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Bardia et al, ESMO 2020

Clinical case

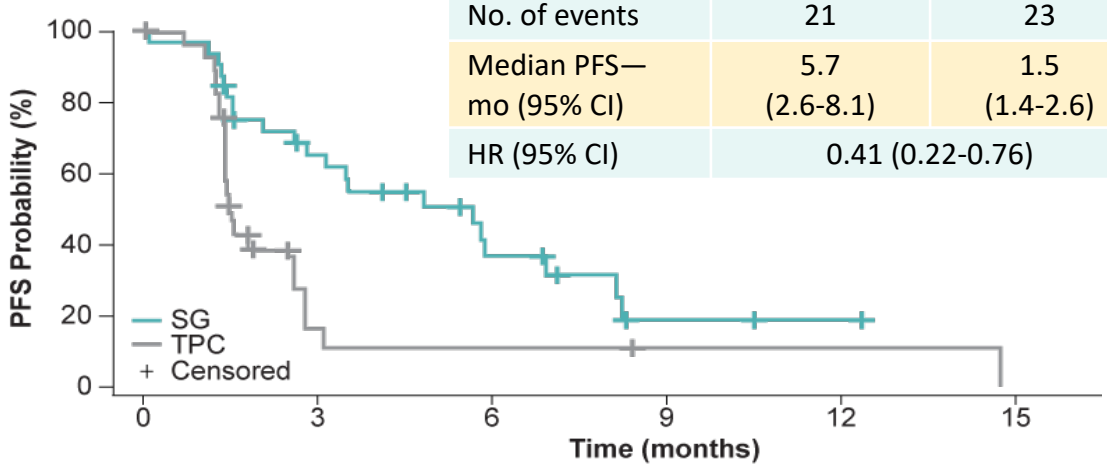
- 39F with PDL1+ BRCA- TNBC that recurs 10 months after completion of ddAC-T, in the liver and lungs at the time of this recurrence.
- She responds for 13 months to gem/carbo/pembrolizumab and then progresses with worsening liver/lung involvement and adenopathy.



ASCENT: PFS and OS in the Second-Line Setting for Metastatic TNBC

PFS

PFS BICR	SG (n=33)	TPC (n=32)
No. of events	21	23
Median PFS—mo (95% CI)	5.7 (2.6-8.1)	1.5 (1.4-2.6)
HR (95% CI)	0.41 (0.22-0.76)	

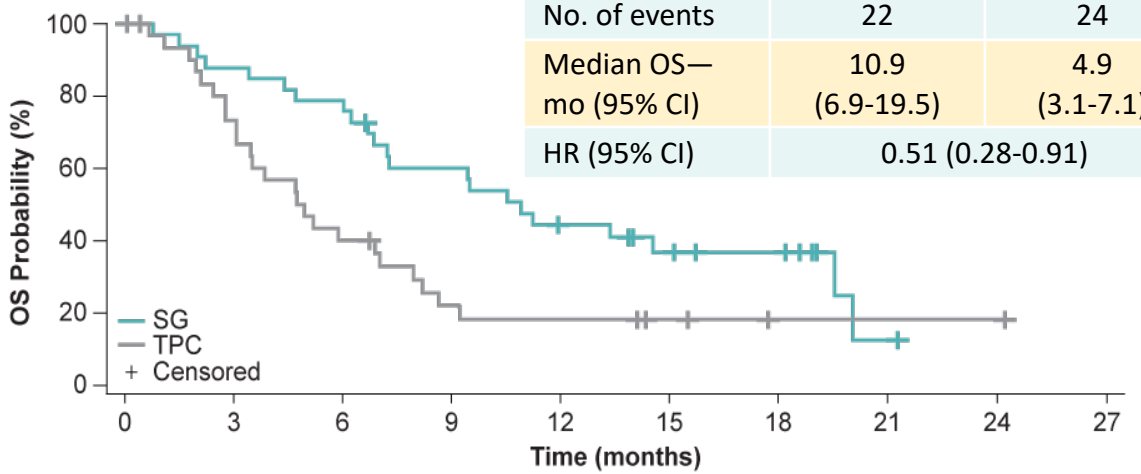


No. of Patients Still at Risk

SG	33	32	23	19	16	12	8	6	5	2	2	1	1	0	0	0
TPC	32	28	8	3	2	2	2	2	2	1	1	1	1	1	1	0

OS

OS	SG (n=33)	TPC (n=32)
No. of events	22	24
Median OS—mo (95% CI)	10.9 (6.9-19.5)	4.9 (3.1-7.1)
HR (95% CI)	0.51 (0.28-0.91)	



No. of Patients Still at Risk

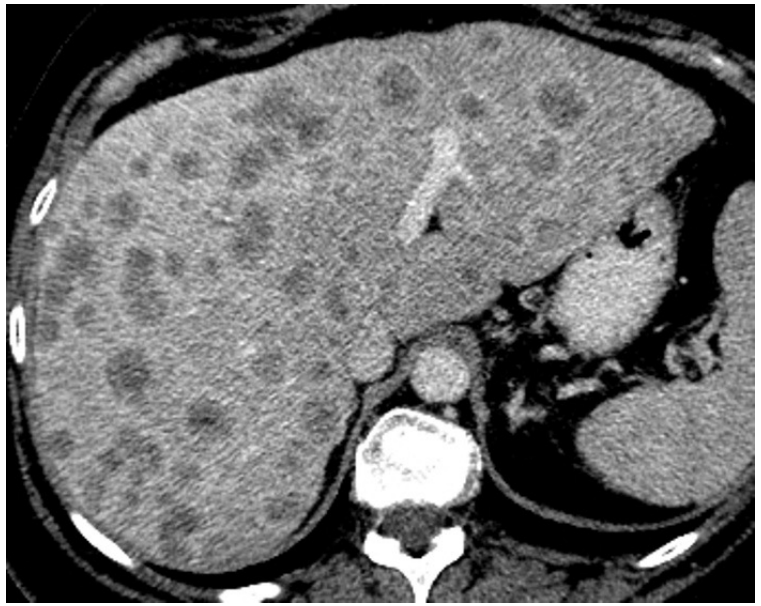
SG	33	32	31	29	28	26	26	21	19	19	17	15	13	13	11	9	7	7	7	4	2	1	0	0	0	0
TPC	32	29	27	22	17	14	12	10	8	6	5	5	5	5	5	3	2	2	1	1	1	1	1	1	1	0

- **Patients with recurrence ≤1 year after (neo)adjuvant chemotherapy and received only 1 line of therapy in the metastatic setting were eligible for ASCENT**
- **Patients who received SG as 2L therapy had a clinical benefit comparable to the overall ASCENT study population**

- Assessed in the brain metastasis-negative population who recurred ≤12 months after (neo)adjuvant chemotherapy and received 1 line of therapy in the metastatic setting, prior to study enrollment.
- SG, sacituzumab govitecan; TPC, treatment of physician's choice.
- Carey LA, et al. ASCO 2021. Poster 1080.

Clinical case

- 39F with PDL1+ BRCA- TNBC that recurs 10 months after completion of ddAC-T, in the liver and lungs at the time of this recurrence.
- She responds for 13 months to gem/carbo/pembrolizumab and then progresses with worsening liver/lung involvement and adenopathy.
- In the absence of a trial, she is a perfect candidate for sacituzumab govitecan



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

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

Endpoints

Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

[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.

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)

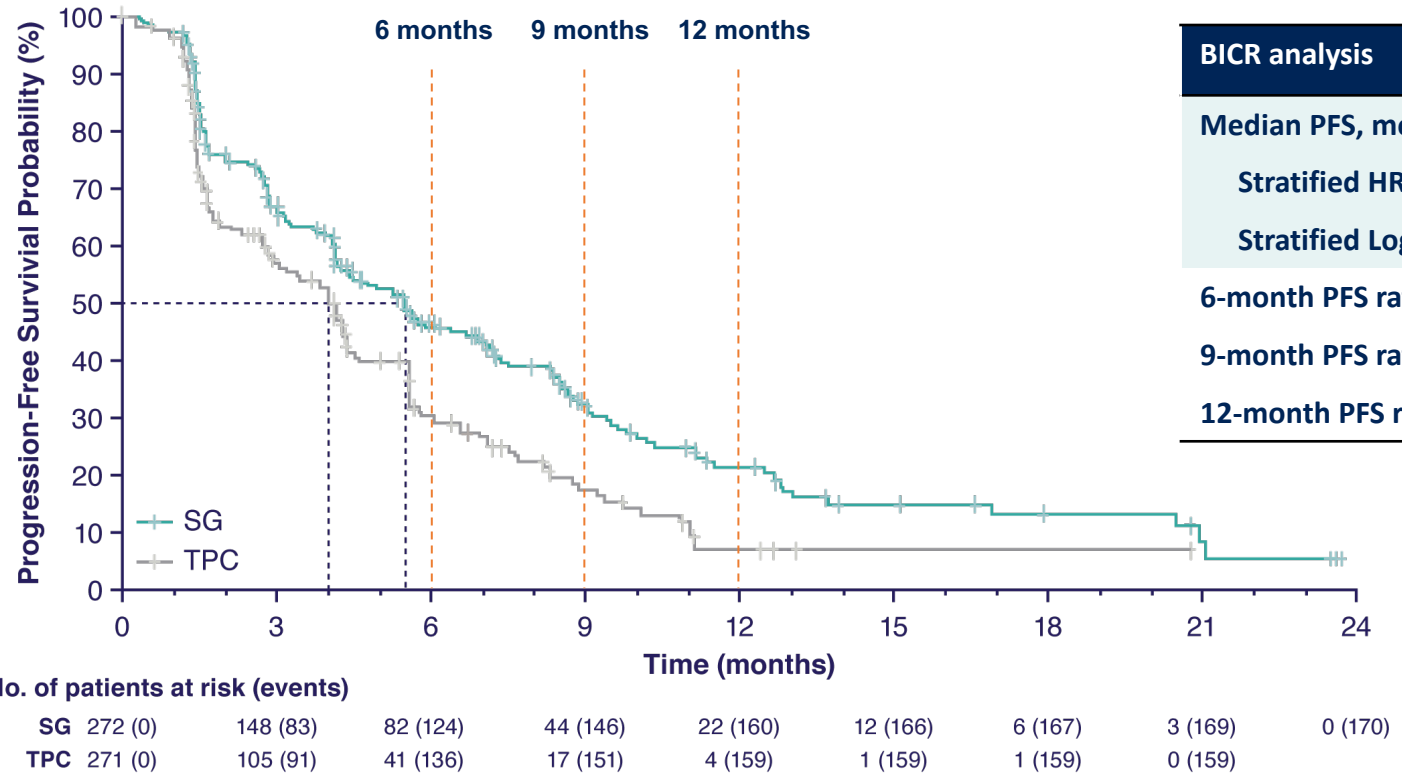
	SG (n=272)	TPC (n=271)
Median time from initial metastatic diagnosis to randomization, mo (range)	48.5 (1.2- 243.8)	46.6 (3.0- 248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)	173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 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.

Take-home points

ASCO 2022:

- Median PFS benefit may have been small, but given the heavily pretreated population, the landmark timepoints (6 mo, 12 mo) important to consider
- This is definitely a potential treatment option for patients with HR+ endocrine refractory metastatic breast cancer

ESMO 2022:

- Median OS reported: 14.4 months with sacituzumab vs 11.2 months for TPC (HR 0.79 (0.65-0.96), p=0.02).

LBA76, ESMO 2022.

Ongoing trials of sacituzumab

Metastatic breast cancer

- Sacituzumab + talazoparib for metastatic TNBC (NCT04039230)
- Sacituzumab +/- pembrolizumab in metastatic ER+ breast cancer (NCT04468061)

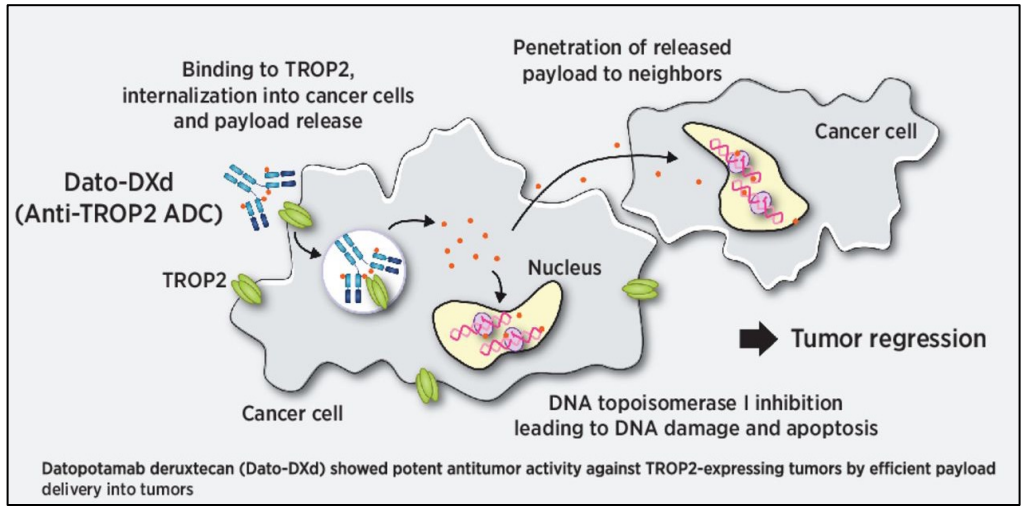
Early stage breast cancer

- Sacituzumab + pembrolizumab vs TPC in patients with TNBC who have residual disease after neoadjuvant chemotherapy (NCT05633654, ASCENT-05)

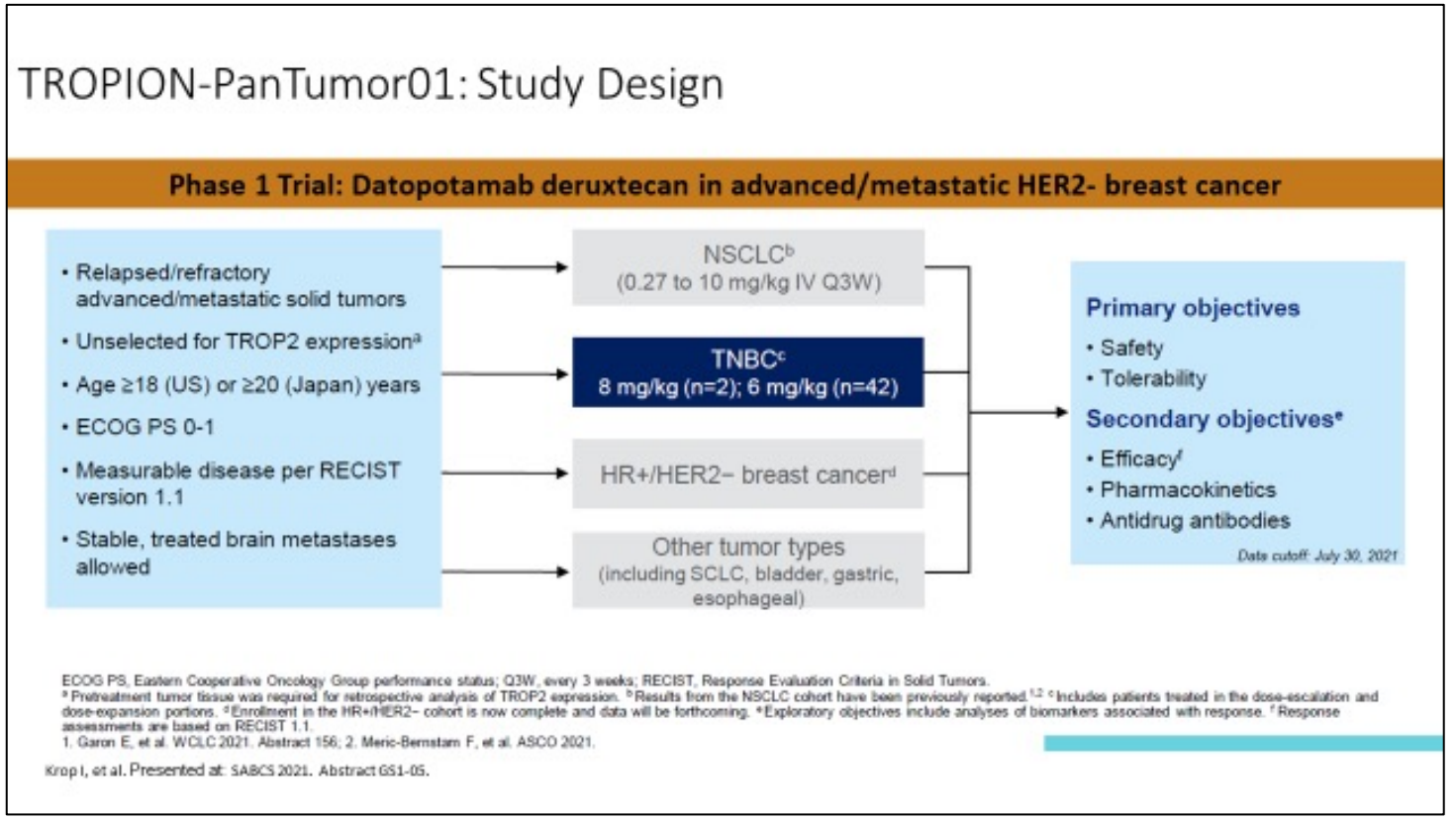
What about other ADCs?

- Datopotomab deruxtecan (anti-TROP2)
- Ladiratuzumab vedotin (anti-LIV1A)
- ARX788 (anti-HER2)
- Patritumab deruxtecan (anti-HER3)

Datopotamab deruxtecan (Dato-DXd, DS-1062a)



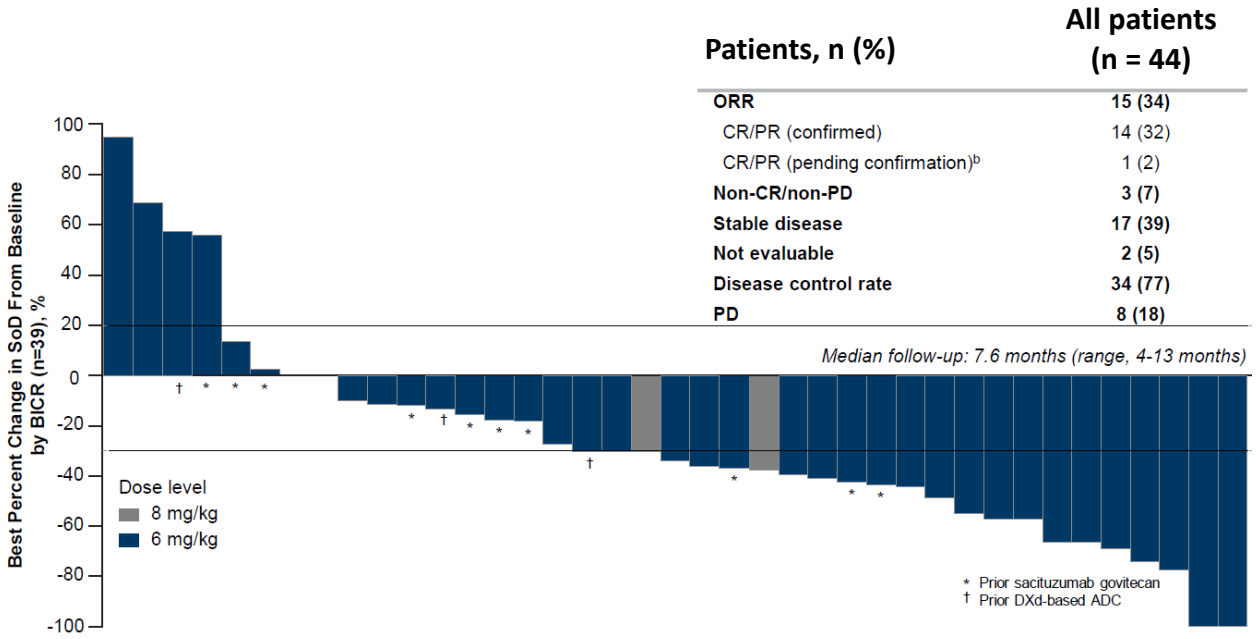
Datopotamab deruxtecan (Dato-DXd) showed potent antitumor activity against TROP2-expressing tumors by efficient payload delivery into tumors



Mol Cancer Ther (2021) 20 (12): 2329–2340.

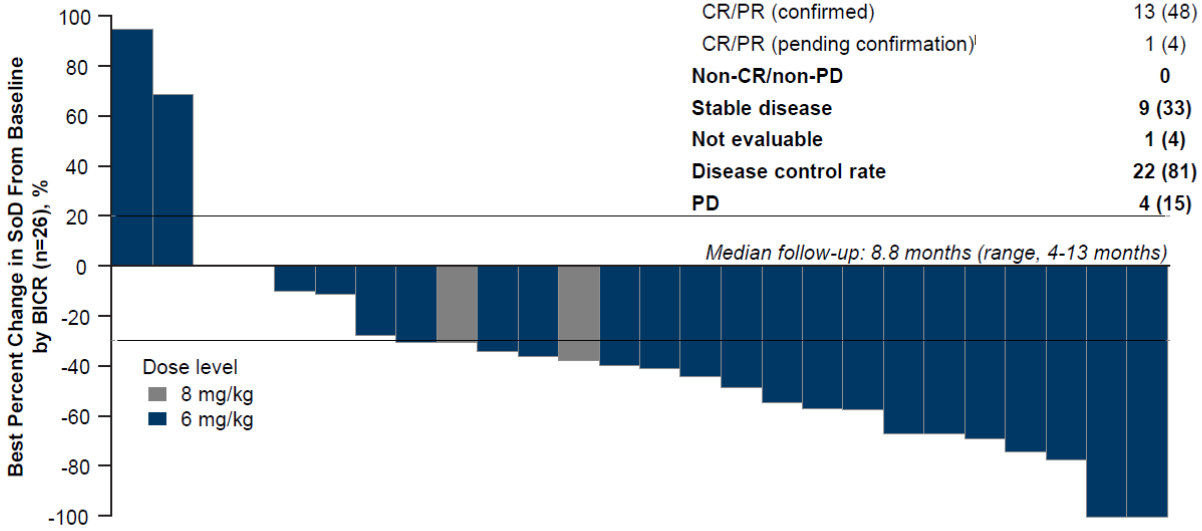
TROPION-PanTumor01: Antitumor Responses by BICR

All Patients With TNBC



Patients, n (%)	All patients (n = 44)
ORR	**15 (34)**
CR/PR (confirmed)	14 (32)
CR/PR (pending confirmation)[b]	1 (2)
Non-CR/non-PD	**3 (7)**
Stable disease	**17 (39)**
Not evaluable	**2 (5)**
Disease control rate	**34 (77)**
PD	**8 (18)**

Patients With TNBC Without Prior Topo I Inhibitor-Based ADC



Patients, n (%)	SG/DXd Naive Patients (n = 27)
ORR	**14 (52)**
CR/PR (confirmed)	13 (48)
CR/PR (pending confirmation)[l]	1 (4)
Non-CR/non-PD	**0**
Stable disease	**9 (33)**
Not evaluable	**1 (4)**
Disease control rate	**22 (81)**
PD	**4 (15)**

- Krop I, et al. Presented at: SABCS 2021. Abstract GS1-05.

Datopotamab: next steps

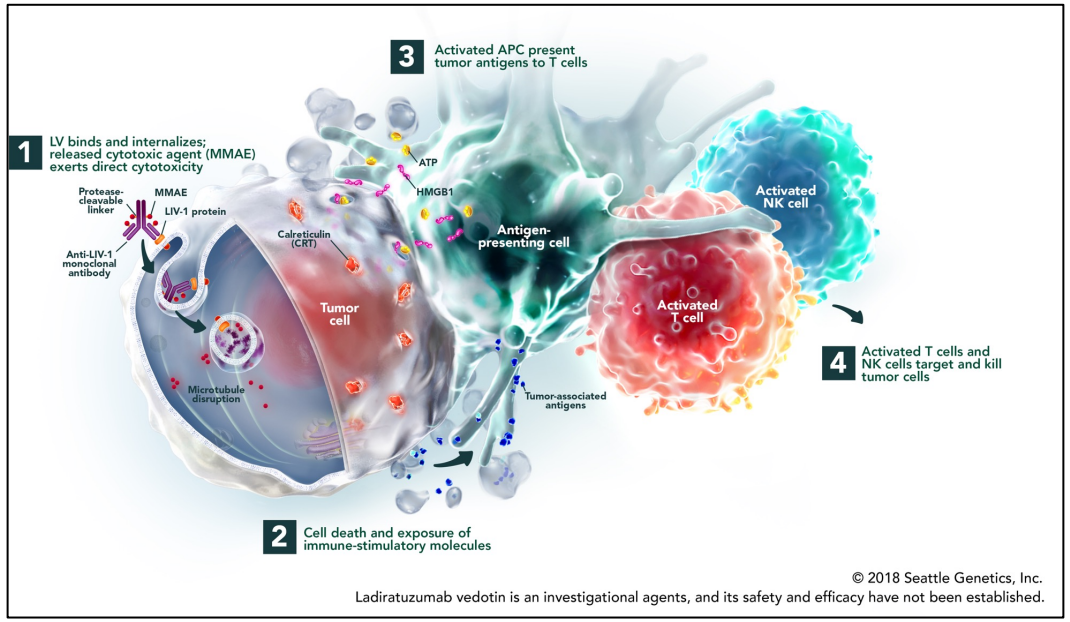
- Front-line therapy for mTNBC that is not PDL1+ (against physician's choice chemotherapy) (TROPION-Breast 02)
- In combination with durvalumab for patients with triple negative breast cancer as one arm of BEGONIA
- ER+ pretreated mBC (TROPION-Breast 01)

Ladiratuzumab vedotin (LV)

- LIV-1 is a transmembrane protein involved in the signaling pathway leading to epithelialmesenchymal transition (EMT) and expression has been linked with malignant progression to metastasis in breast cancer[1,3]

- LIV-1 is expressed in ≥90% of all clinical subtypes of metastatic breast cancer tumors with low expression in normal tissues[4]

- LV is an ADC directed against LIV-1, with MMAE as the payload



1. Lue H-W, et al. PLOS One. 2011;6(11):e27720.
2. Hogstrand C, et al. Biochem J. 2013;455:229-37.
3. Manning DL, et al. Eur J Cancer. 1994;30A(5):675-8.
4. Sussman D, et al. Mol Cancer Ther. 2014;13(12):2991-3000.

- Jane Meisel. Phase 1b/2 Study of Ladiratuzumab Vedotin (LV) in Combination with Pembrolizumab for First-Line Treatment of Triple-Negative Breast Cancer (SGNLVA-002, Trial in Progress)

Current Study Design

- SGNLVA-002 (NCT03310957) is an ongoing global single-arm, open-label, phase 1b/2 study of LV + pembrolizumab as 1L therapy for patients with unresectable locally advanced or mTNBC

- LV 1.5 mg/kg administered on Day 1 and Day 8 (off Day 15) of every 21-day cycle in combination with pembrolizumab administered on Day 1 of every cycle
  - Rationale for the combination: LV-induced immunogenic cell death elicits an inflammatory response, leading to enhanced antitumor immunity, antigen presentation, and tumor cell immune infiltration

- Eligible patients have metastatic TNBC, no prior cytotoxic treatment in the metastatic setting, tumor tissue PD-L1 CPS <10 using the PD-L1 IHC 22C3 clone, and at least 6 months since prior treatment with curative intent

Conclusion

- ADCs are revolutionizing the treatment of breast cancer
- Like many things that are successful in the metastatic setting, we may see these make their way into early stage disease as well
- Much research still remains to be done
  - How to optimally manage side effects
  - How to safely and effectively sequence ADCs

- Clinical trials continue to push the path forward, and we are grateful to all the patients who have made these new treatments a possibility for the women of today

Thank you!

Interstitial Lung Disease and T-Dxd

- Occurs in ~10% of patients
- Important to perform lung imaging frequently even in patients with stable or minimal disease involvement
- Grade 1 (asymptomatic, radiographic only): ok to hold treatment and if radiographic changes resolve, restart at lower dose
- Grade 2 or higher: discontinue and initiate steroids
- No known risk factors for ILD with T-Dxd, so at this time hard to predict who is likely to suffer from this – but important to note that T-Dxd was not studied in patients with pre-existing pneumonitis