Antibody drug conjugates- ADC's for Breast Cancer

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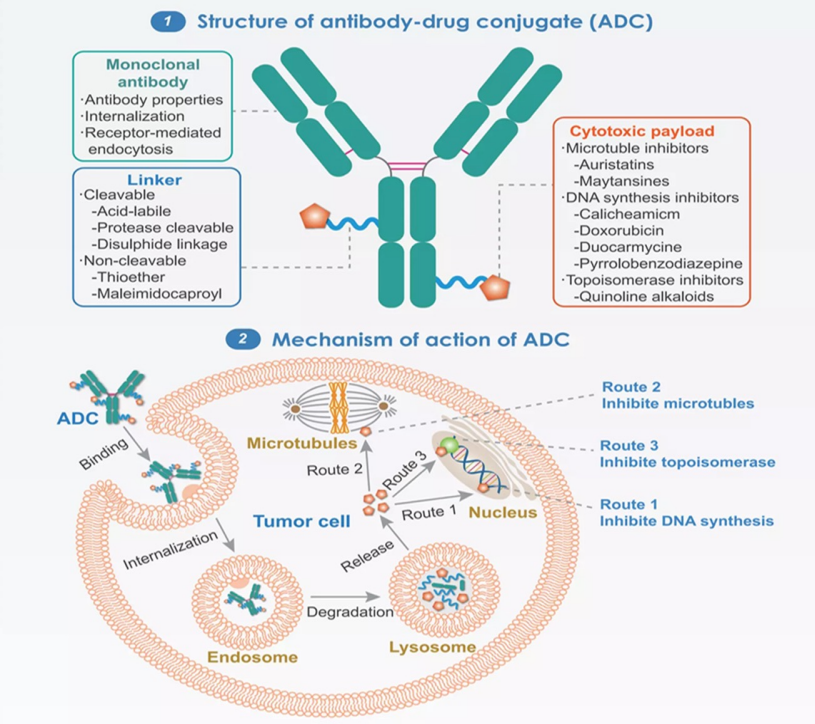
Program Overview

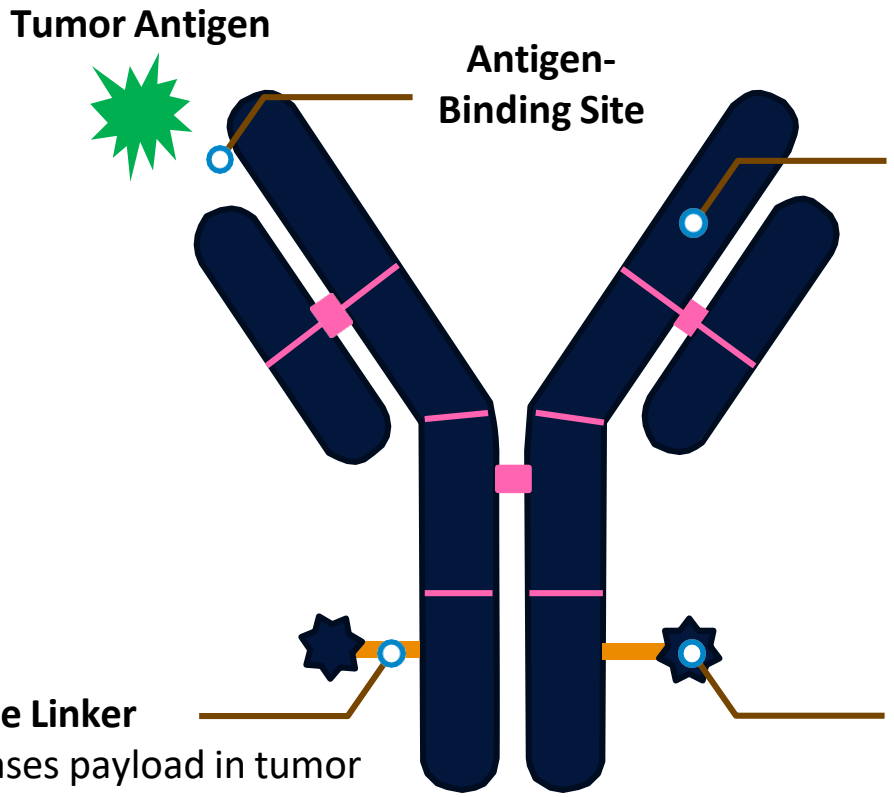
- ADC structure and MOA
- Available Agents
- Her-2 + breast cancer
- HR+ MBC
- TNBC MBC
- New agents and future directions

Structure of an antibody drug conjugate (ADC)

Antibody drug conjugates:

- Monoclonal Antidody (Different targets, HER-2, TROP-2 etc..)
- Linker (Cleavable or non Cleavable)
- Cytotoxic Payload(Topo-1 Inhibitor in breast SN-38, Deruxtecan etc..)
- Designed to deliver cytotoxic payload directly to targeted cancer cell
- Higher therapeutic index than each component alone



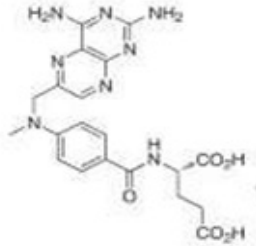


mAb
Targets tumor-specific or tumor-associated antigens

Potent Cytotoxic Payload
Amount of payload varies among ADCs

Stable Linker
Releases payload in tumor cell ± surrounding microenvironment

Timeline of ADC: Path toward targeted chemotherapy



1913 — Paul Ehrlich described the concept of a 'magic bullet' and drug targeting (i.e. a 'heptophore' can deliver a 'toxophore' selectively to a tumor)

1958 — MTX linked to an antibody directed toward leukemia cells

1967 — ADCs proposed; immunoradioactive agent disclosed

1972 — Noncovalent linked ADC tested in animal models

1975 — Production of mAbs using hybridoma-based technology

1975 — Covalent linked ADCs tested in animal models

1983 — Clinical trials w/ ADC vindesine-αCEA

1988 — Humanized mAbs reported

1991 — ADC w/ highly potent cytotoxin calicheamicin

1991 — Immunogenicity of mouse mAbs a serious limitation in development of ADCs

1993 — Curative efficacy in human tumor xenograft models w/ BR96-DOX ADC

2000 — First FDA approved ADC Gen-Ozogam

2001 — Gen-Ozogam clinical failures due to MDR

2010 — Gen-Ozogam withdrawn from market

2011 — Brentux-Vedotin approved

2013 — TDM1 approved

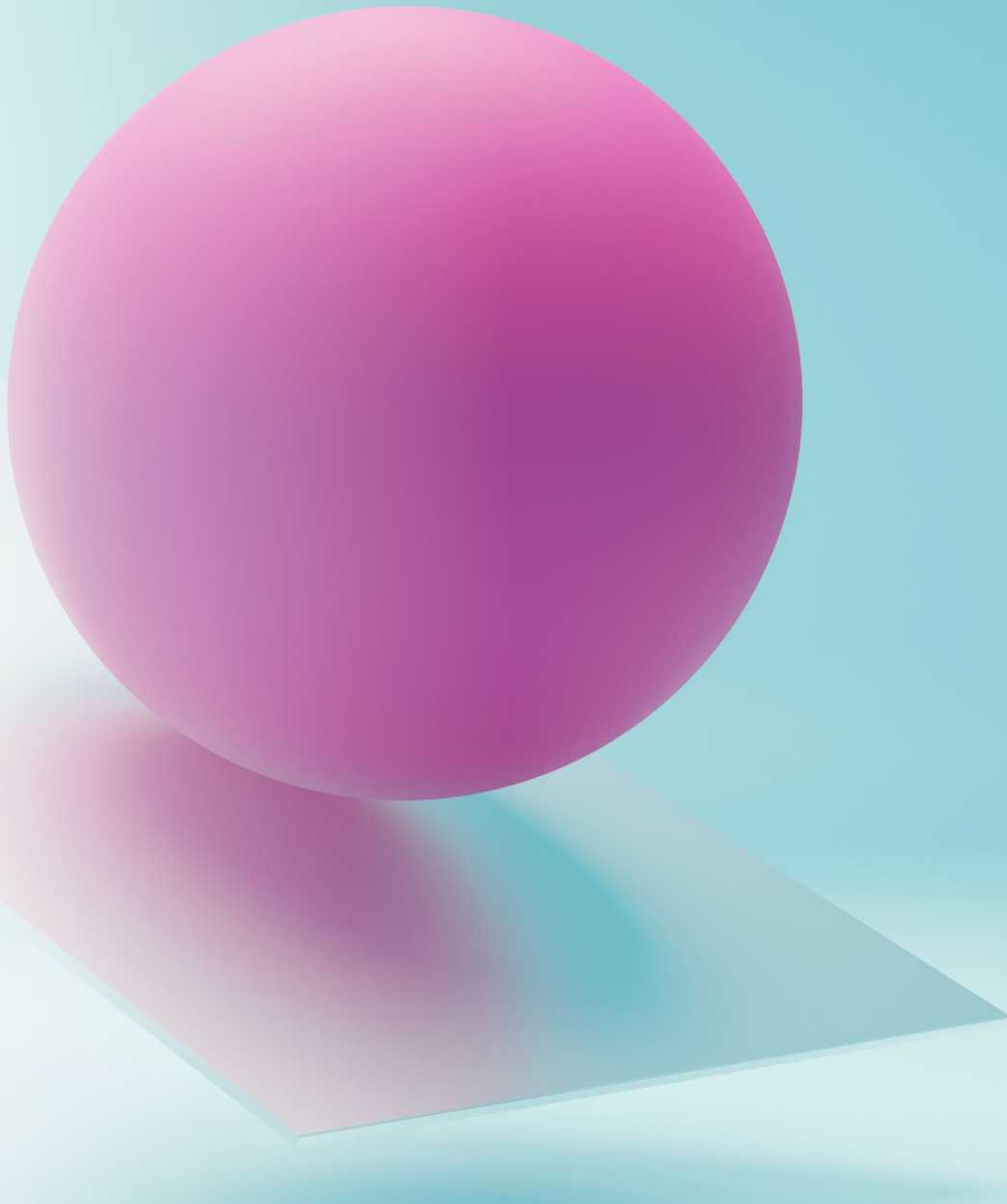
1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010

Trastuzumab emtansine

Trastuzumab deruxtecan

Sacituzumab govitecan

Overview of current treatment with ADCs for HER2+ Breast Cancer



T-DM1: 1st ADC to receive FDA approval for MBC HER2+(2013)

EMILIA trial: TDM-1 vs Cape/Lapatinib (prior Taxane/Trastuzumab)
PFS : 9.6 vs 6.4 months
OS: 30.9 vs 25.1 months

TH3RESA trial: TDM-1 vs TPC (> 2 lines of anti-HER2+)
PFS: 6.2 vs 3.3 months
OS: NR vs 14.9 months

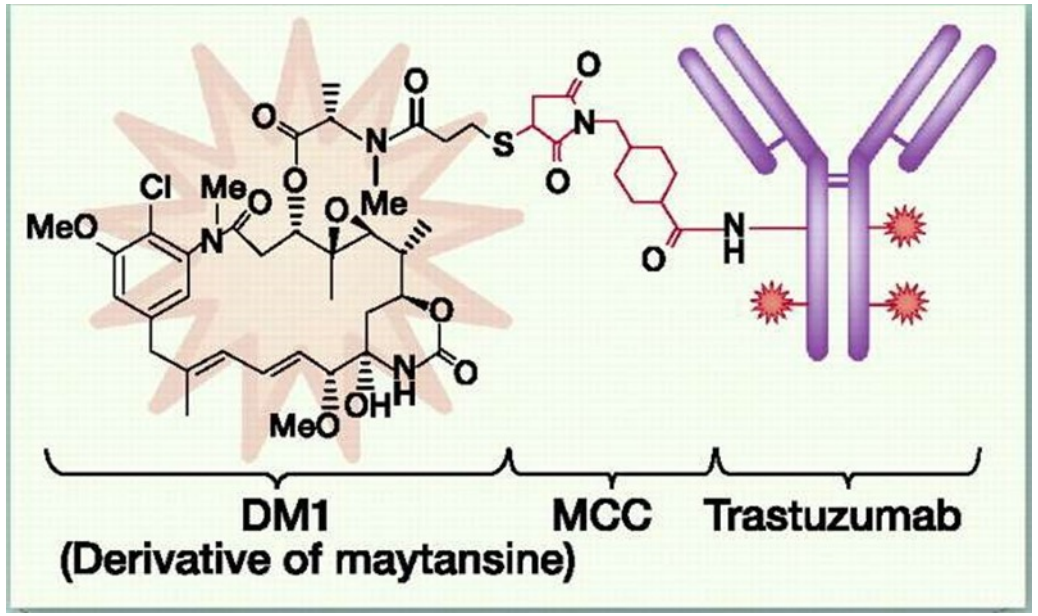


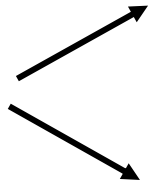
Figure from: Lo Russo PM et al. Clin Cancer Res 2011

This led to the approval for HER2+ MBC after prior treatment with Trastuzumab and Taxane

KATHERINE: Trastuzumab Emtansine vs Trastuzumab as Adjuvant Therapy for HER2+ EBC

International, randomized, open-label phase III study

Patients with HER2+ EBC (cT1-4/N0-3/M0) who had residual invasive disease in breast or axillary nodes after neoadjuvant chemotherapy plus HER2-targeted therapy* at surgery
(N = 1486)



T-DM1† 3.6 mg/kg IV Q3W x 14 cycles
(n = 743)

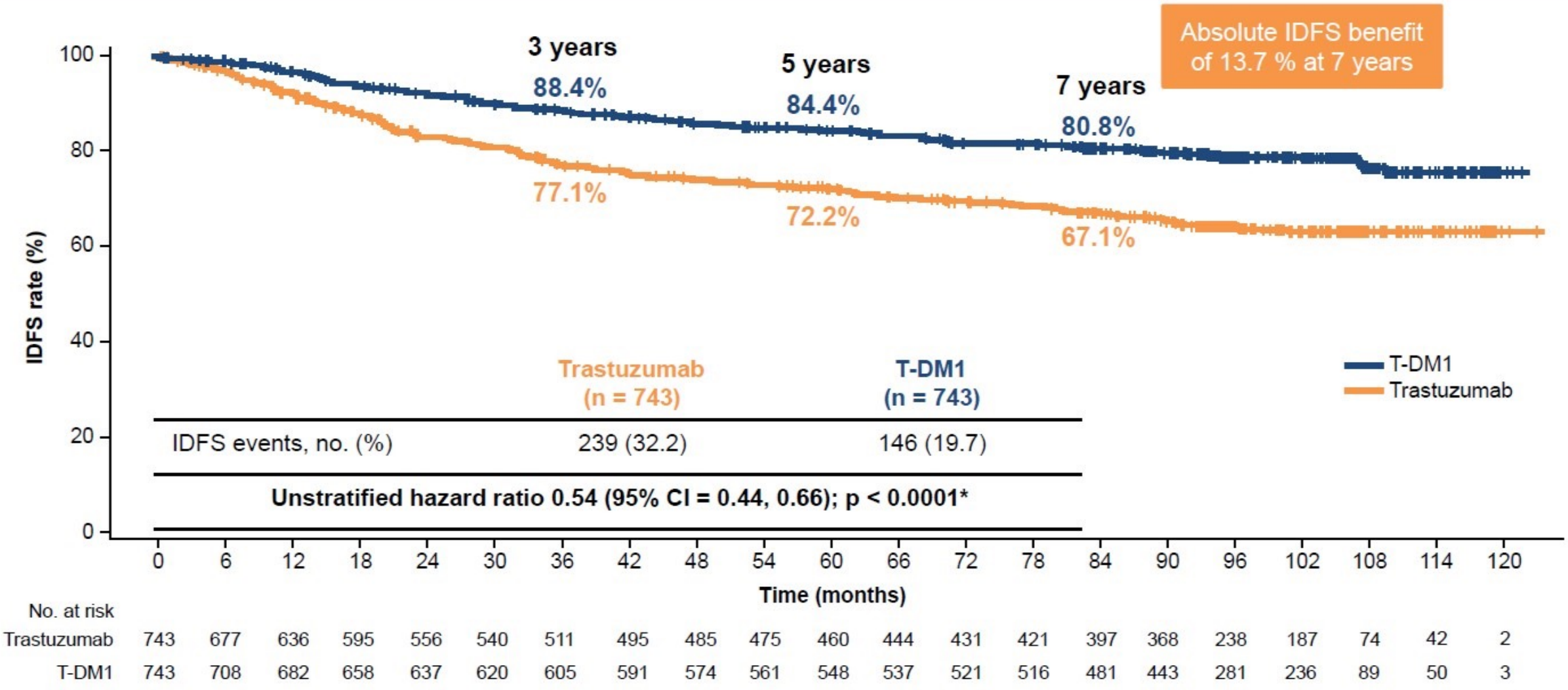
Trastuzumab 6 mg/kg IV Q3W x 14 cycles
(n = 743)

Randomization occurred within 12 wks of surgery; radiotherapy and/or endocrine therapy given per local standards. *Minimum of 9 wks taxane and trastuzumab. †Patients who d/c T-DM1 for toxicity allowed switch to trastuzumab to complete 14 cycles.

- Primary endpoint: IDFS
- Secondary endpoints including: distant recurrence-free survival, OS, safety

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz. NEJM. 2019;380:617.

KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)

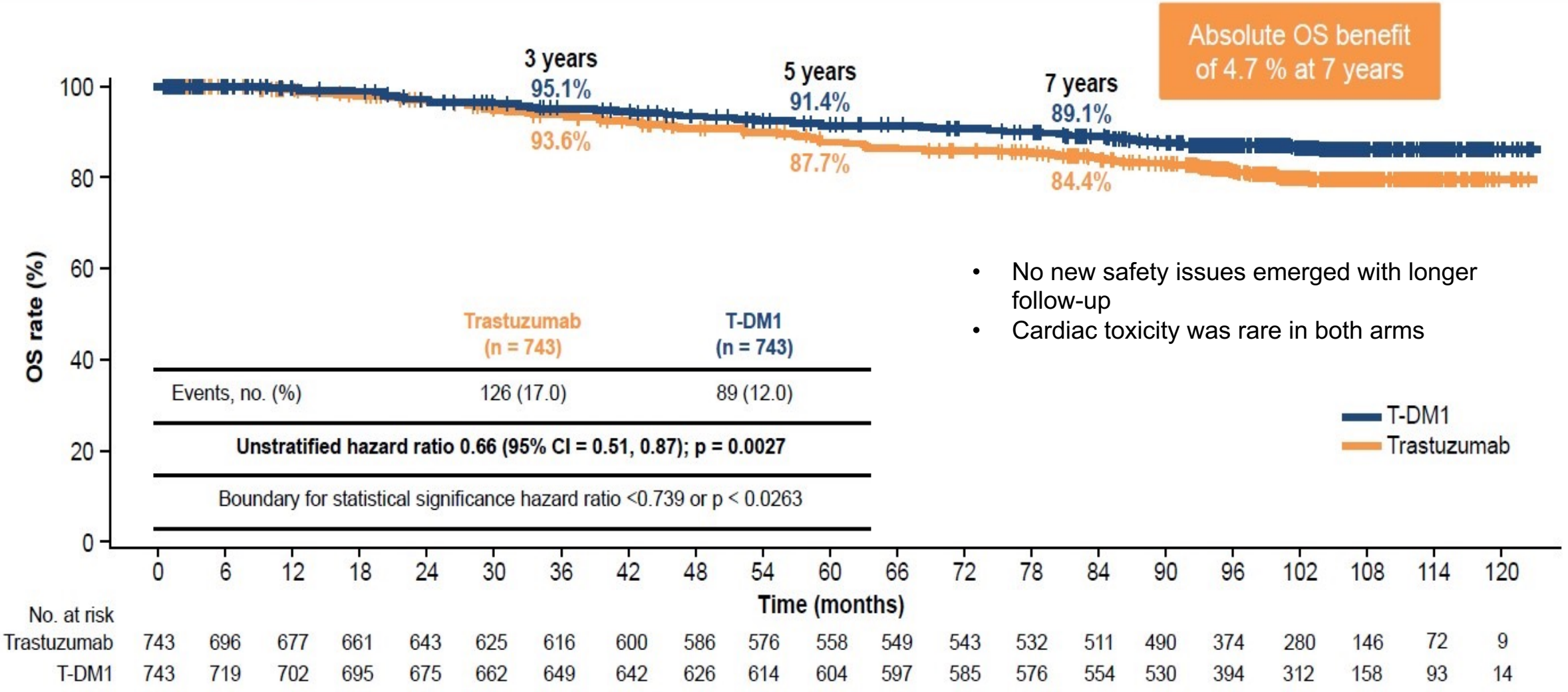


No. at risk

Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

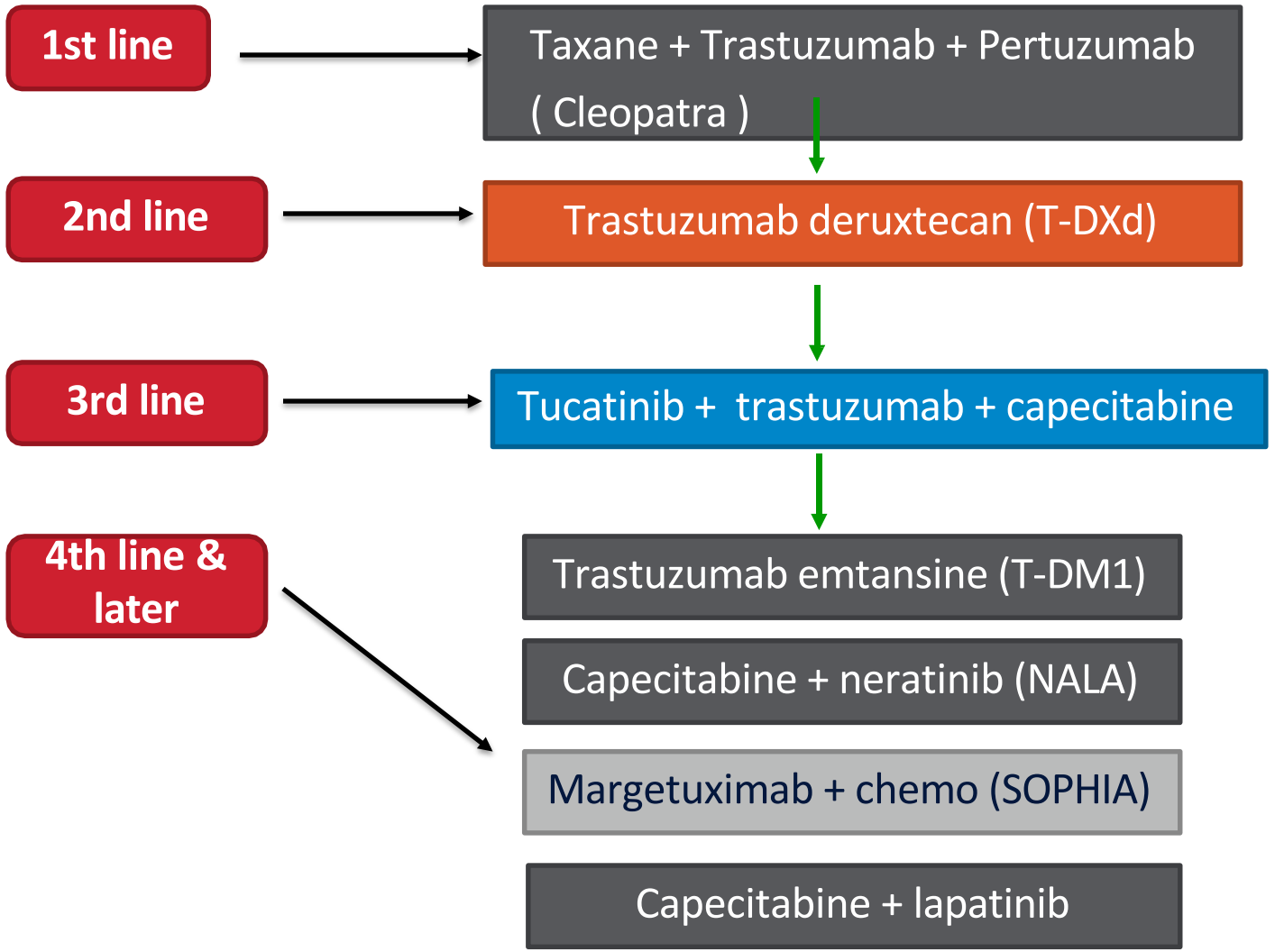
KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



- No new safety issues emerged with longer follow-up
- Cardiac toxicity was rare in both arms

Significant reduction in risk of death by 34% with T-DM1

Current treatment algorithm for HER2+ MBC



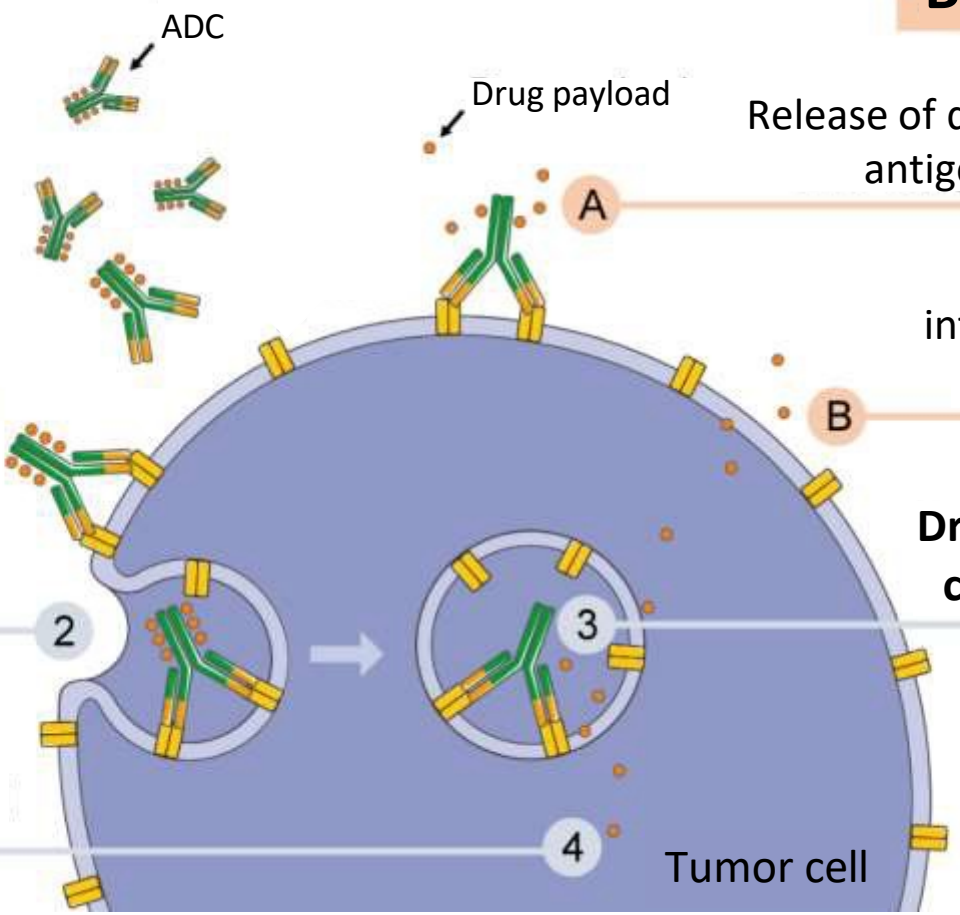
New/potent ADCs with bystander killing effect

Classical ADC Mode of Action

ADC binding to receptor (1)

Internalization by endocytosis (2)

Cytotoxic effect induced by drug payload (4)



Bystander Killing Effect

Release of drug payload from antibody after antigen binding, before internalization (A)

Release of drug payload into intercellular space because of high drug membrane permeability (B)

Drug payload release after linker cleavage by lysosomal enzymes (3)

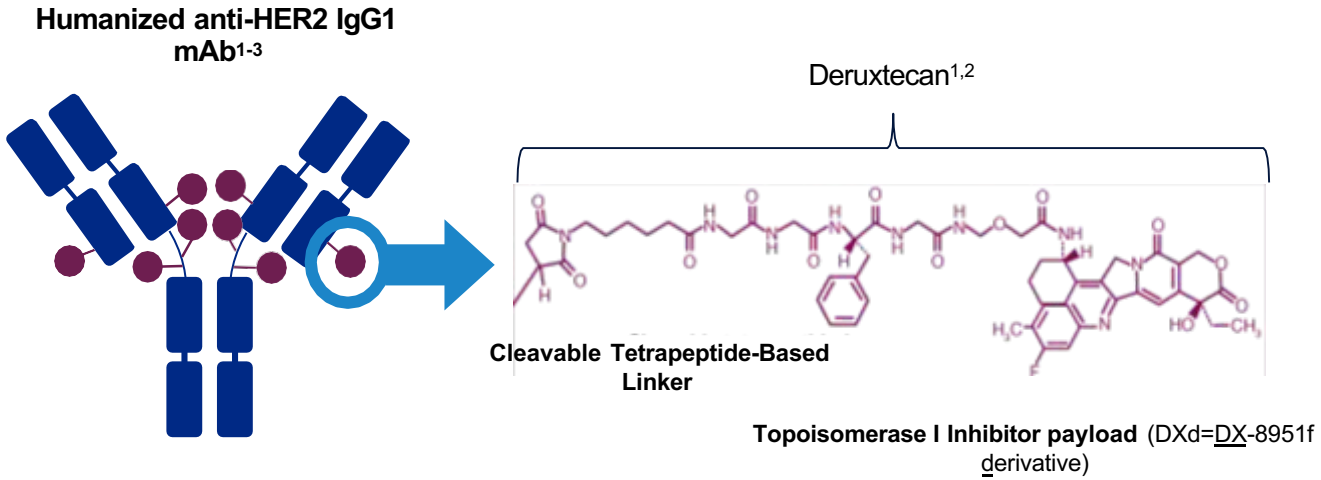
A high drug-to-antibody ratio increases antitumoral efficacy despite low antigen density on tumor cells

Rinnerthaler G et al. Int J Mol Sci. 2019;20:1115

Tratuzumab deruxtecan (T-DXd): novel HER2 ADC

T-DXd is an ADC composed of 3 components[1,2]:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



- Payload mechanism of action: topoisomerase I inhibitor[a,1,2]
- High potency of payload[a,1,2]
- High drug-to-antibody ratio ≈ 8[a,1,2]
- Payload with short systemic half-life[a,1,2]
- Stable linker-payload[a,1,2]
- Tumor-selective cleavable linker[a,1,2]
- Bystander antitumor effect[a,1,4]

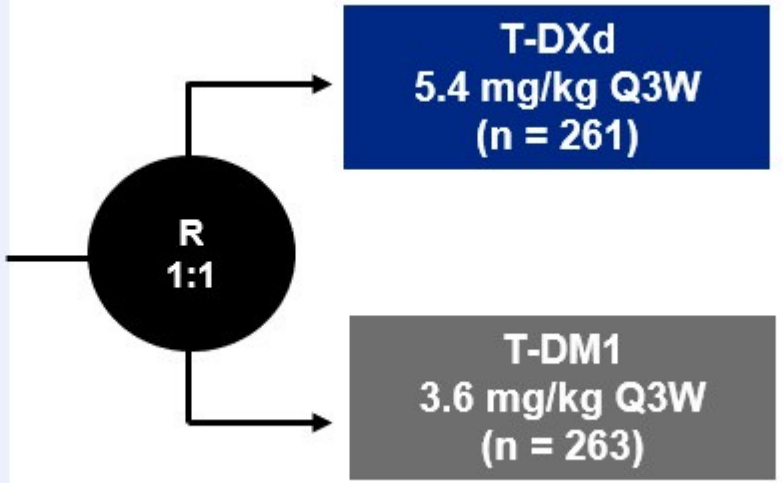
[a]The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate; IgG1, immunoglobulin G1; mAB, monoclonal antibody.

1. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046.

DESTINY Breast03: Ph 3 trial of T-DXd vs T-DM1 in 2L HER2+ MBC

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

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



Stratification by HR status, prior treatment with pertuzumab, history of visceral disease

Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

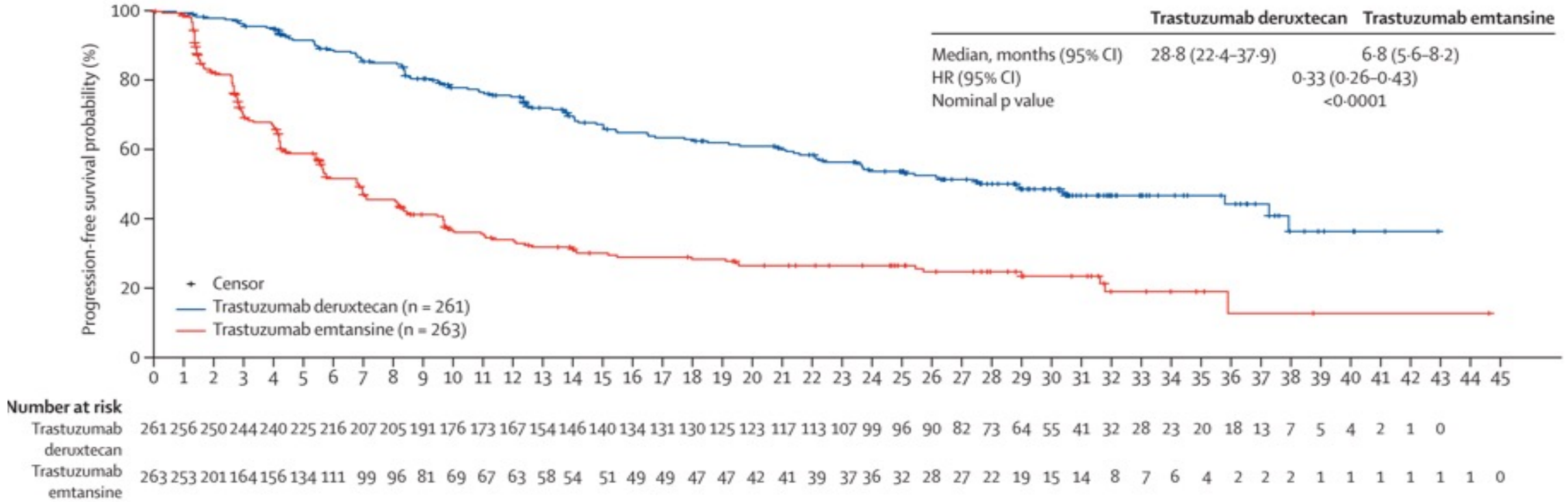
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

- **Primary endpoint:** PFS by BICR
- **Secondary endpoints:** OS (key), ORR (BICR and investigator), DoR (BICR), PFS (investigator), safety

Cortés. ESMO 2021. Abstr LBA1. Cortés. NEJM. 2022;386:1143

DESTINY Breast03: Significant improvement in PFS with T-DXd vs T-DM1

	T-DXd (n = 261)	T-DM1 (n = 263)
ORR	82.1%	36.7%
12-mo PFS, % (95% CI)	53.7 (46.8-60.1)	26.4 (20.5-32.6)

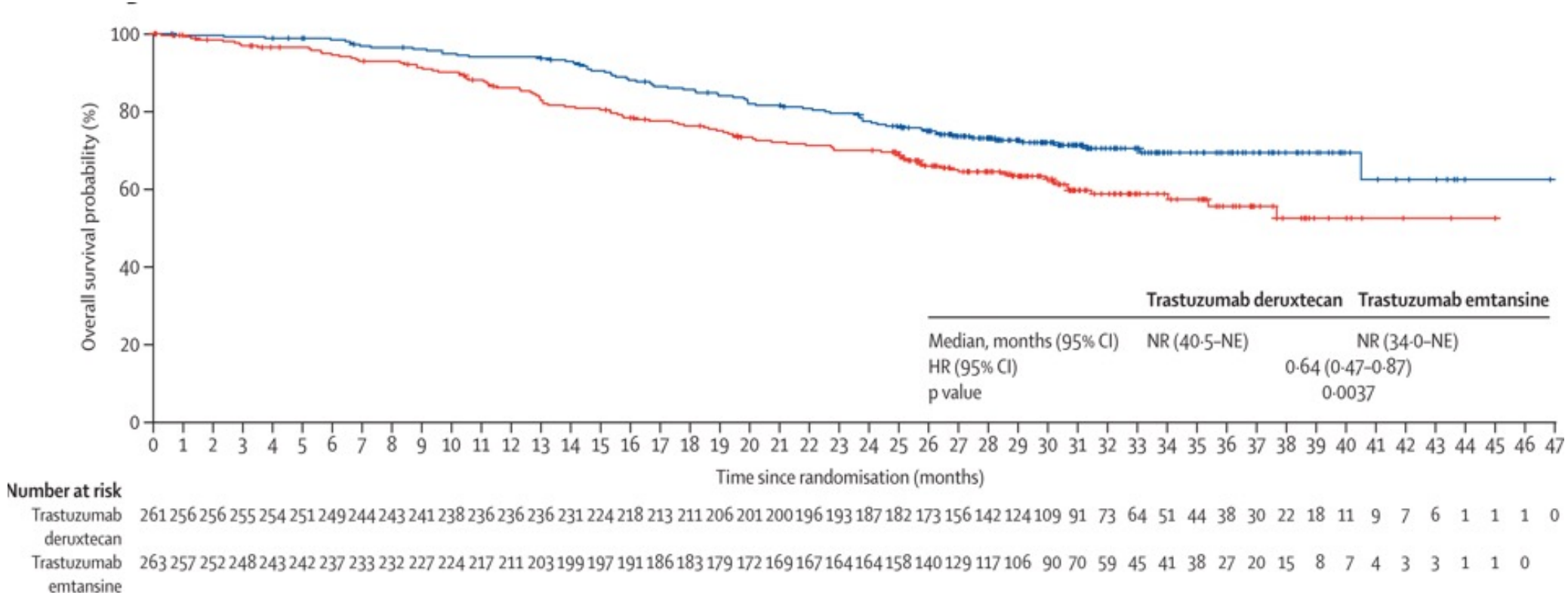


Trastuzumab deruxtecan (T-DXd) was approved by FDA on May 6, 2022 for treatment of HER2+ MBC after 1 prior anti-HER2 regimen for MBC or relapse ≤6 months from (neo)adjuvant anti-HER2 treatment

Hurvitz. *Ann Oncol*.2022;33: S464-S465

DESTINY-Breast03: Overall Survival (Secondary Endpoint)

	T-DXd (n = 261)	T-DM1 (n = 263)
OS, mo (95% CI)	NR(40.5-NE)	NR(34.0-NE)
24-mo OS, % (95% CI)	77.4 (71.7-82.1)	69.9 (63.7-75.2)



Hurvitz. *Ann Oncol*.2022;33: S464-S465

DESTINY-Breast03: Safety Summary and Adverse Events of Special Interest

Safety Outcome	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE, n (%)	252 (98.1)	226 (86.6)
▪ Grade ≥3	116 (45.1)	104 (39.8)
▪ Serious	28 (10.9)	16 (6.1)
Drug-related TEAE associated with, n (%)		
▪ Discontinuation	33 (12.8)	13 (5.0)
▪ Dose reduction	55 (21.4)	33 (12.6)
▪ Outcome of death	0	0
Median treatment duration, mo (range)	14.3 (0.7-29.8)	6.9 (0.7-25.1)

AE of Special Interest, n (%)	T-DXd (n = 257)	T-DM1 (n = 261)
Drug-related ILD/pneumonitis	27 (10.5)	5 (1.9)
▪ Grade 1	7 (2.7)	4 (1.5)
▪ Grade 2	18 (7.0)	1 (0.4)
▪ Grade 3	2 (0.8)	0
LVEF decrease*	6 (2.3)	1 (0.4)

*All grade 2; 1 case of grade 1 left ventricular dysfunction in the T-DXd arm.

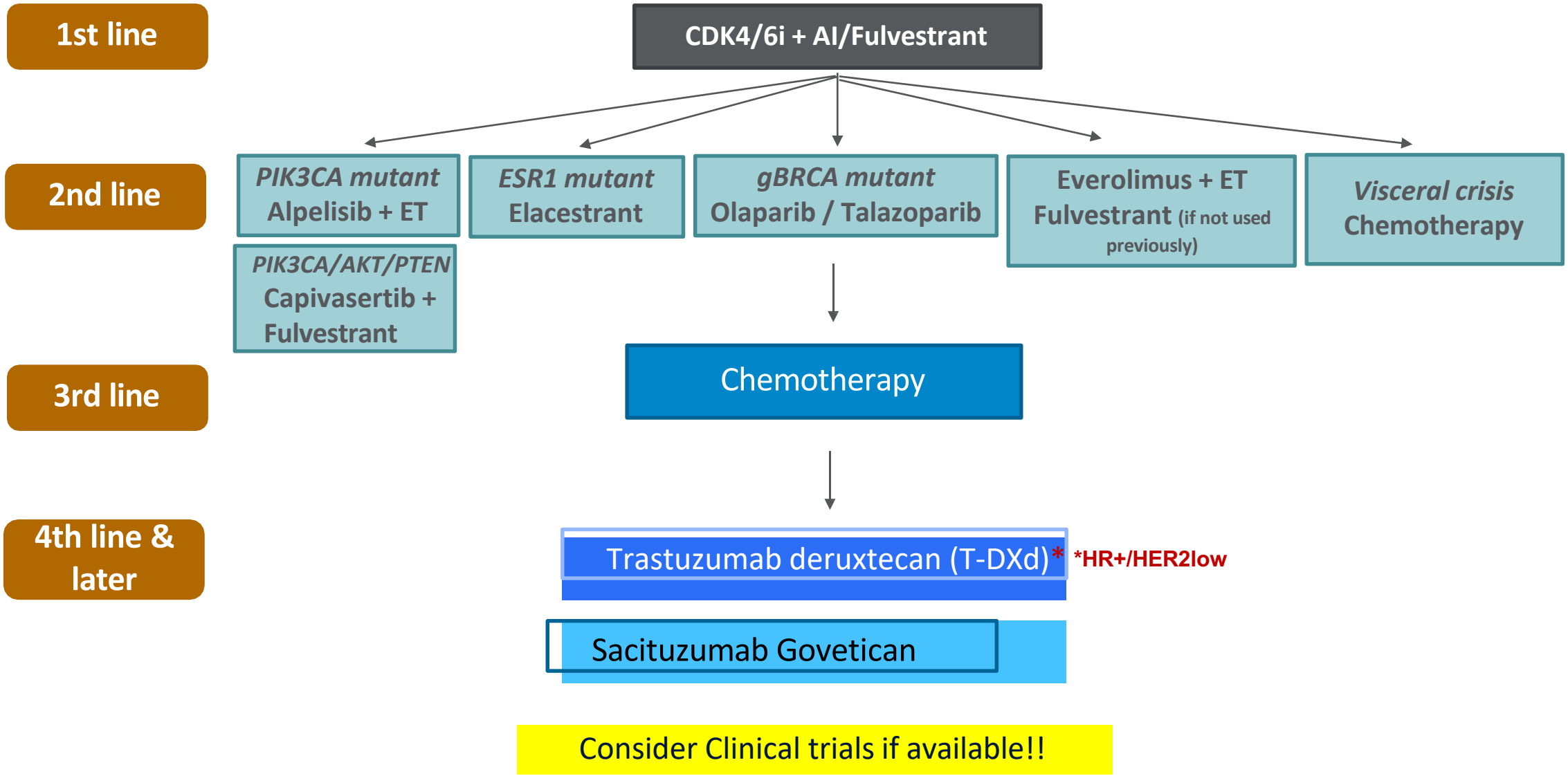
- Most common TEAEs associated with treatment discontinuation
  - T-DXd: ILD/pneumonitis (8.2%)
  - T-DM1: thrombocytopenia (2.7%)
- Most common TEAEs associated with dose reduction
  - T-DXd: nausea (6.2%) and neutropenia (3.5%)
  - T-DM1: thrombocytopenia (4.2%) and ALT and AST increased (2.7% each)

- No grade 4/5 events of drug-related ILD/pneumonitis or LVEF decrease
- In T-DXd arm, all LVEF decrease events were asymptomatic; no cases of cardiac failure occurred

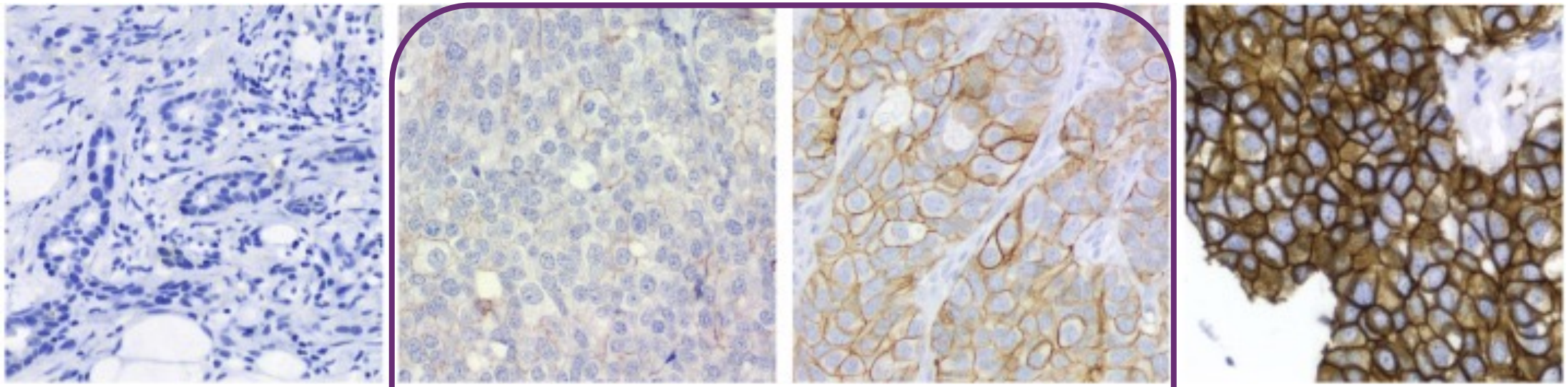
Cortés. ESMO 2021. Abstr LBA1. Cortés. NEJM. 2022;386:1143.

Overview of current treatment with ADCs for HR+ MBC

Current treatment algorithm for HR+/HER2- MBC



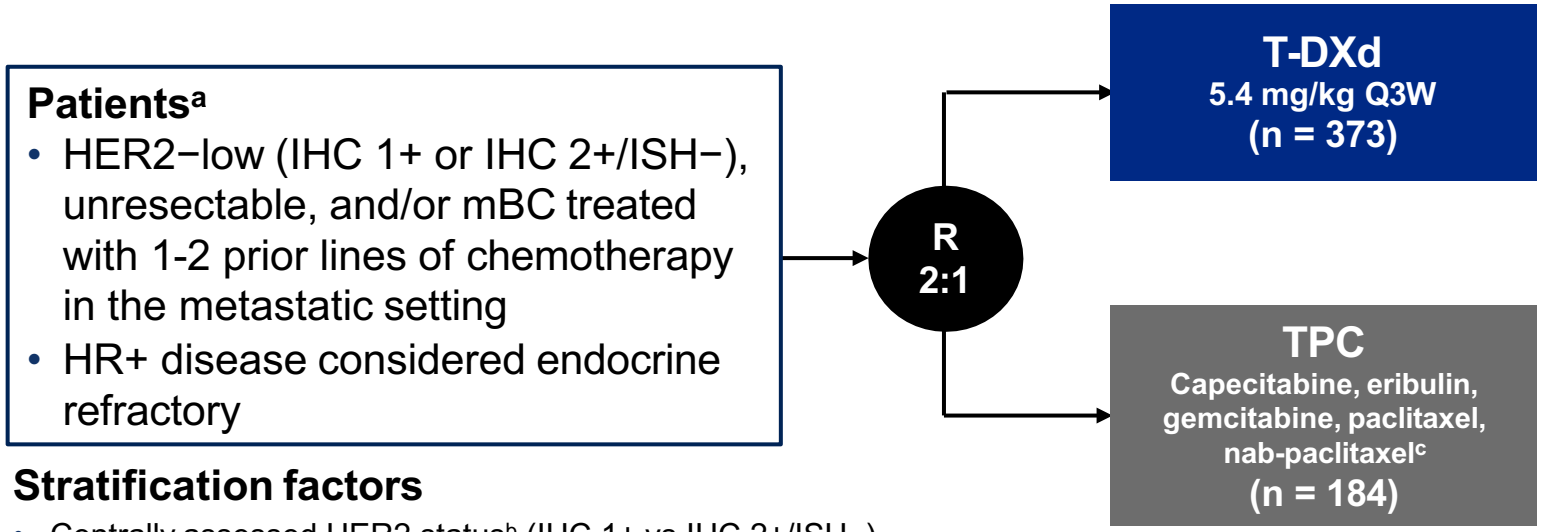
Historical Binary Classification of HER2 in Breast Cancer



Adapted from: Marchiò. Semin Cancer Biol. 2021:72:123.

DESTINY-Breast04: Study Design

An open-label, multicenter study (NCT03734029)[1-3]



Stratification factors

- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- One vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[d]

- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]

- **PFS by investigator**
- ORR by BICR and investigator
- DoR by BICR
- **Safety**
- PROs (HR+)[e]

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI: 31.0-32.8 months)

[a] If patients had HR+ mBC, prior endocrine therapy was required. [b] Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only (IUO) assay system, at the time of study. [c] TPC was administered according to the label. [d] Efficacy in the HR− cohort was an exploratory endpoint. [e] The PROs analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

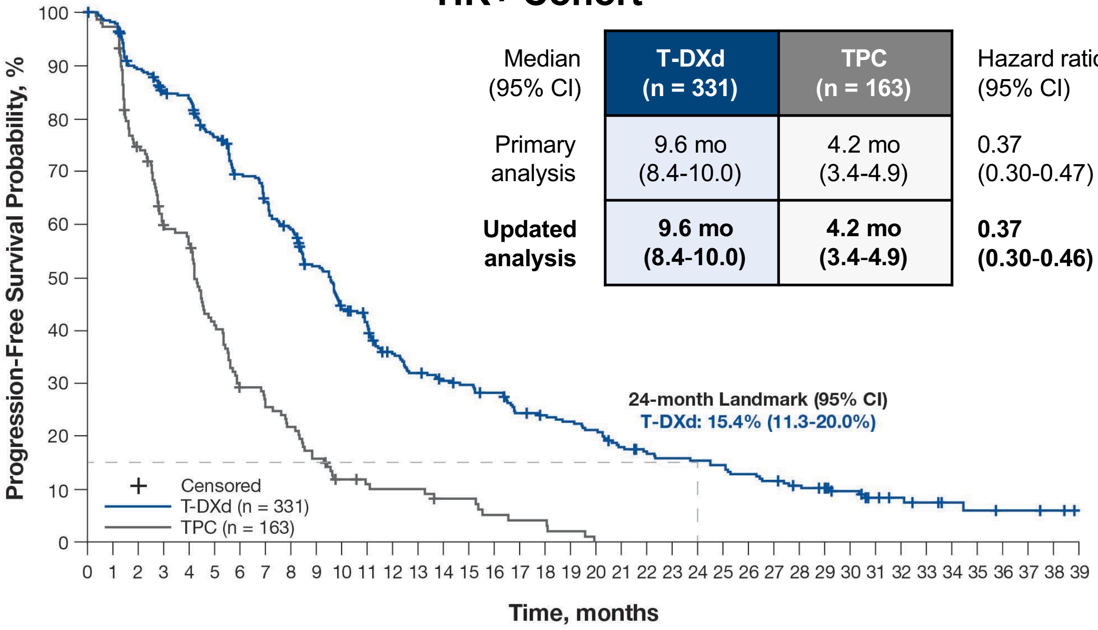
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; CI, confidence interval; DoR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; R, randomization; T-DXd, fam-trastuzumab deruxtecan-nxki; TPC, treatment of physician's choice.

1. Modi S, et al. *N Engl J Med*. 2022;387:9-20. 2. Harbeck N, et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A, et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Modi S, et al. ESMO 2023. Oral 376O.

DESTINY-Breast04 Updated OS: PFS (by Investigator[a])

HR+ Cohort

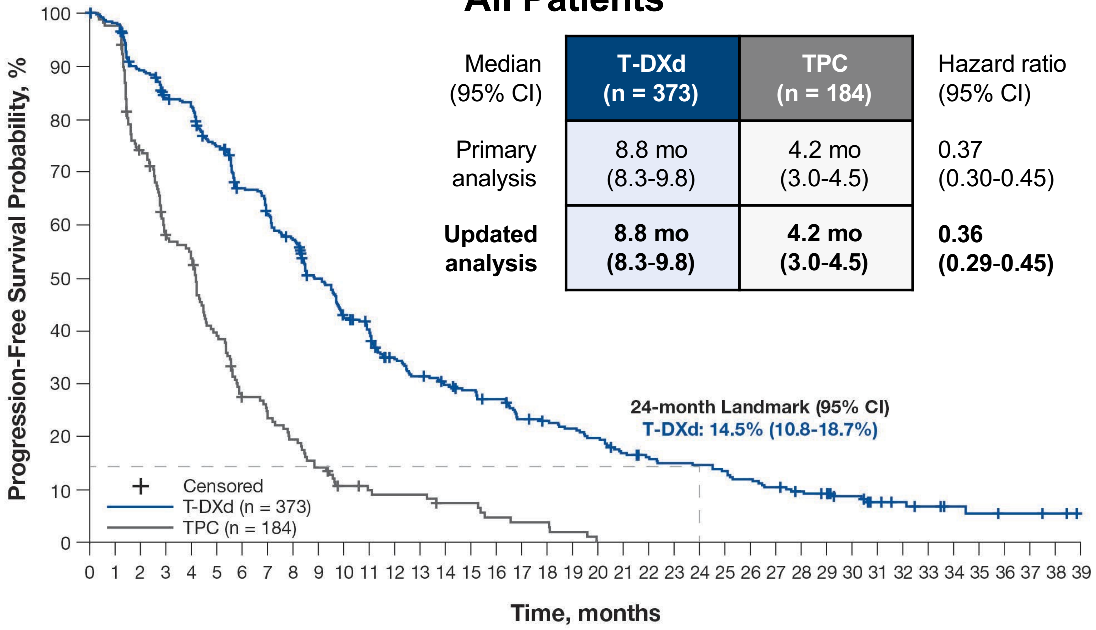


Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

Patients still at risk:

T-DXd (n = 331)	331	323	290	272	267	241	215	198	181	154	129	119	98	88	82	79	74	63	60	57	53	44	40	37	36	34	30	27	23	21	16	11	9	7	5	4	3	3	2	0
TPC (n = 163)	163	143	107	83	78	56	39	34	29	21	14	12	11	11	8	8	5	4	4	2	0																			

All Patients



Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**

Patients still at risk:

T-DXd (n = 373)	373	364	327	304	297	267	234	216	198	166	140	130	107	97	90	85	79	67	64	60	55	46	42	39	38	35	31	27	23	21	16	11	9	7	5	4	3	3	2	0
TPC (n = 184)	184	163	121	92	85	61	41	35	29	21	14	12	11	11	8	8	5	4	4	2	0																			

- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

[a] PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

BICR, blinded independent central review; CI, confidence interval; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, fam-trastuzumab deruxtecan-nxki; TPC, treatment of physician's choice.

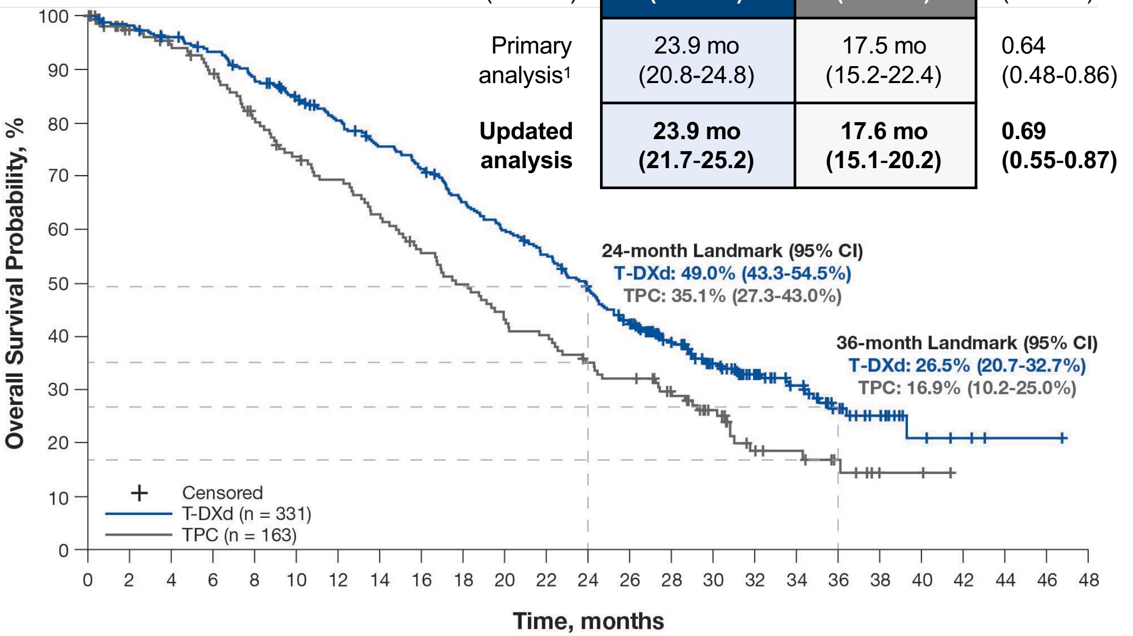
1. Modi S, et al. *N Engl J Med*. 2022;387:9-20.

Modi S, et al. ESMO 2023. Oral 376O.

DESTINY-Breast04 Updated OS: Overall Survival

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**

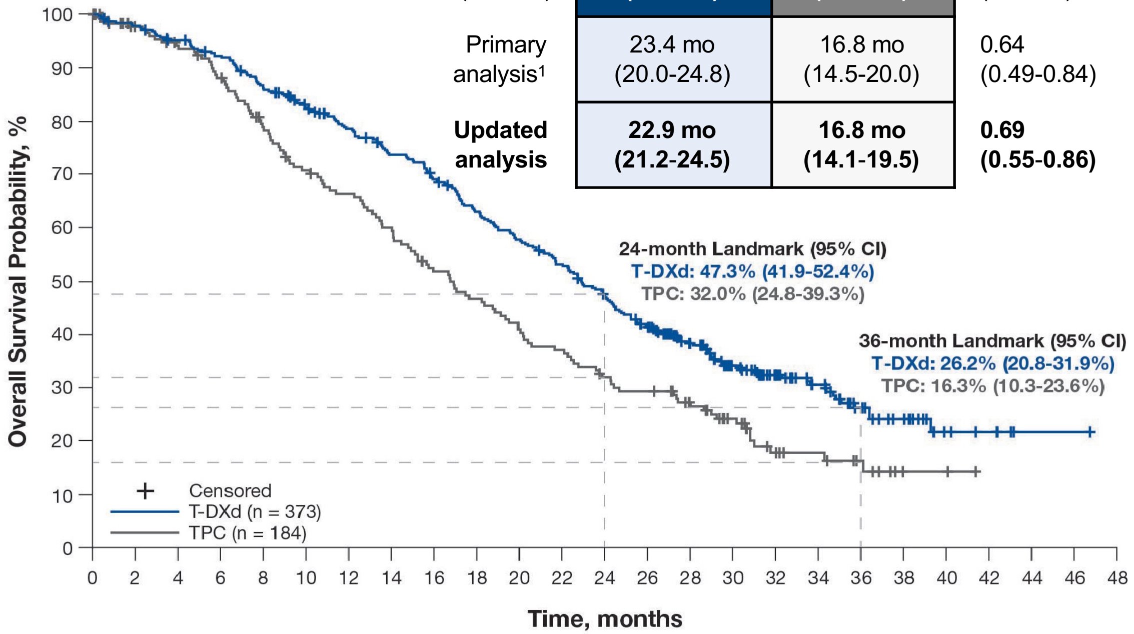


Patients still at risk:

T-DXd (n = 331)	331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0
TPC (n = 163)	163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373)	373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0
TPC (n = 184)	184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

CI, confidence interval; HR, hormone receptor; mo, month; OS, overall survival; T-DXd, fam-trastuzumab deruxtecan-nxki; TPC, treatment of physician's choice.

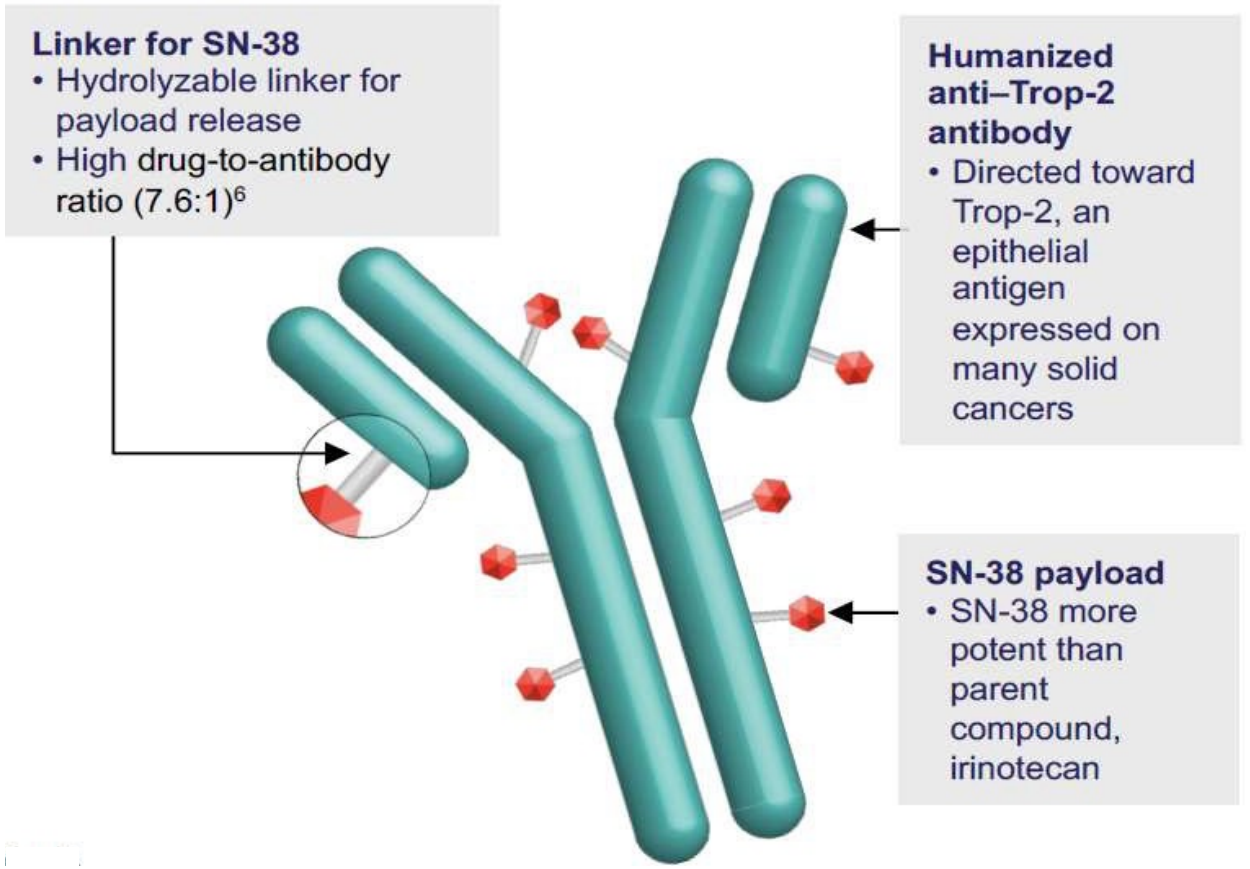
1. Modi S, et al. *N Engl J Med*. 2022;387:9-20.

Modi S, et al. ESMO 2023. Oral 376O.

T-DXd approved by the FDA for treatment of MBC for the newly defined "HER2-low" subtype on August 5, 2022

Sacituzumab govitecan (SG)

First-in-class TROP2 directed ADC



Approved for treatment of metastatic TNBC 2020 and HR+/HER2- MBC 2/2023

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Advanced Inoperable or Metastatic Breast Cancer[1,2]

Sacituzumab govitecan was studied in this randomized, open-label, active-controlled trial vs single-agent chemotherapy (NCT03901339)

Metastatic or locally advanced inoperable HR+/HER2- breast cancer that progressed after[1-3,a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting[1,2]
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease[1,2]
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST v1.1[3]

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity[2,b]

Sacituzumab govitecan[1,b]
10 mg/kg IV
Days 1 and 8 of a 21-day cycle
n=272

Single-agent chemotherapy[2,c]
eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22)
n=271

Stratification Factors[1,2]:

- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapy for metastatic disease (2 vs 3 or 4)

Endpoints

Primary[1-3]

- PFS by BICR based on RECIST v1.1 criteria

Secondary

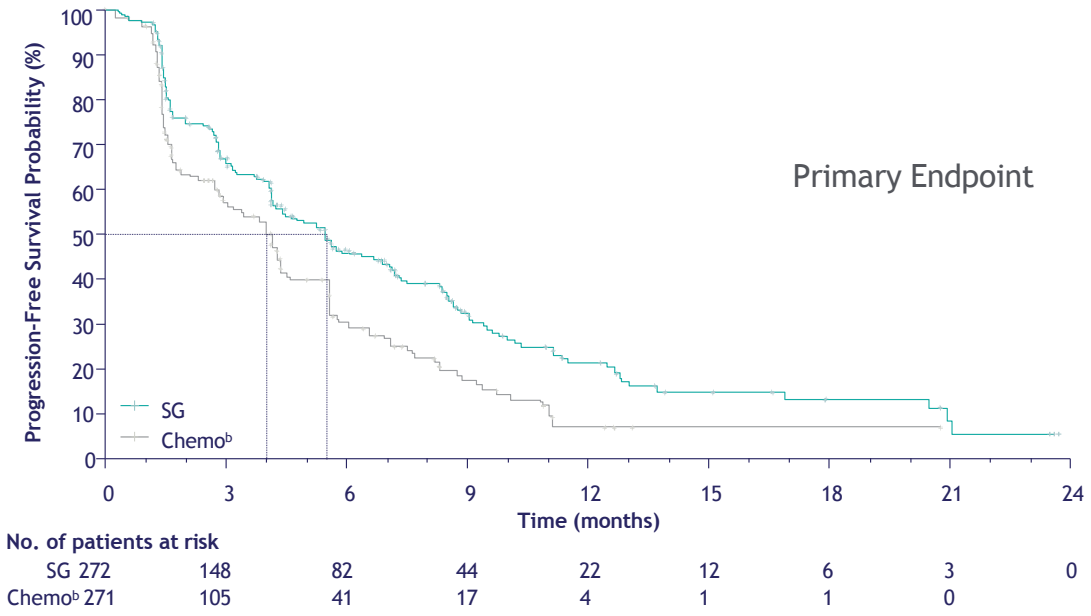
- OS[1,2]
- ORR and DOR, both by BICR[1,2]
- PROs[1,2]
- Safety[1,2]

[a]Disease histology based on the ASCO/CAP criteria.[3] [b]Administration of SG was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit.[2] [c]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.[3]

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IV, intravenously; (neo)adjuvant, neoadjuvant or adjuvant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcome; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376. 2. TRODELVY® [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2023. 3. Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376 [supplement].

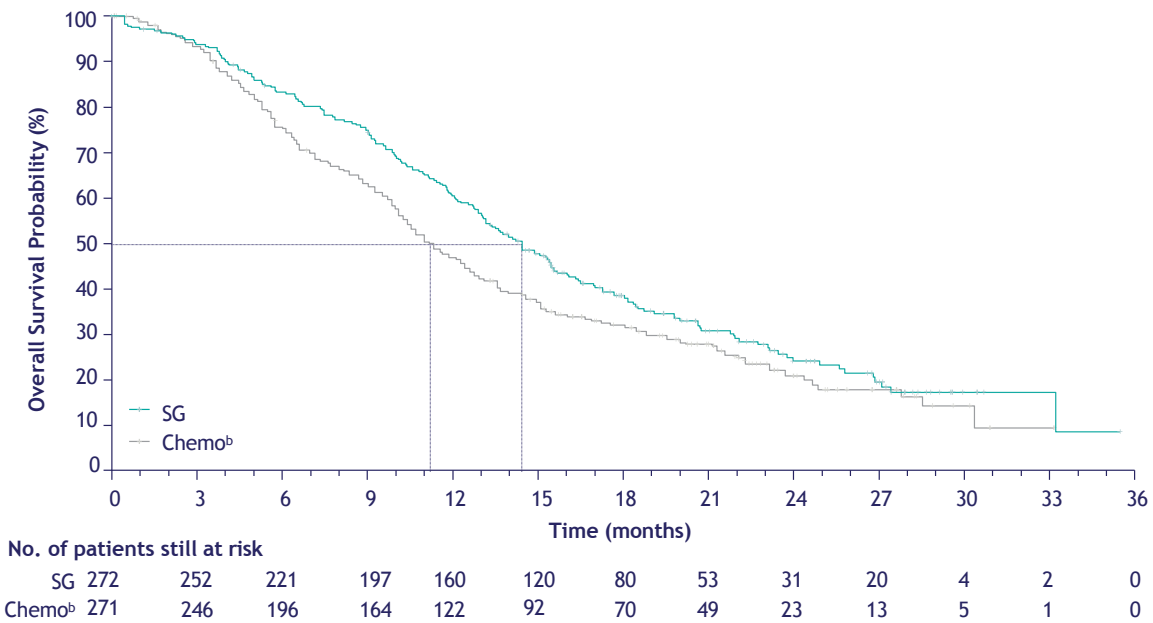
SG Demonstrated a Statistically Significant Improvement in PFS and OS[1-3,a]



Primary Endpoint

No. of patients at risk

SG	272	148	82	44	22	12	6	3	0
Chemo[b]	271	105	41	17	4	1	1	0	



No. of patients still at risk

SG	272	252	221	197	160	120	80	53	31	20	4	2	0
Chemo[b]	271	246	196	164	122	92	70	49	23	13	5	1	0

BICR Analysis per RECIST v1.1	SG (n=272)	Chemo[b] (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	

	SG (n=272)	Chemo[b] (n=271)
Number of events[2,3]	191	199
Median OS, mo (95% CI)[2,3]	14.4 (13.0-15.7)	11.2 (10.1-12.7)
Stratified HR (95% CI)	0.79 (0.65-0.96)	
Stratified log-rank *P* value	0.020	

Median follow-up was 10.2 months for PFS and 12.5 months for OS.[2]

[a]Intent-to-treat population.[1,2] [b]Single-agent chemotherapy.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376. 2. Rugo HS, et al. Presented at: European Society for Medical Oncology Congress; September 9-13, 2022; Paris, France. Presentation LBA76. 3. TRODELVY® [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2023.

Adverse Reactions and Lab Abnormalities Reported in Patients in the TROPiCS-02 Study

Adverse Reactions Reported in ≥10% of Patients With HR+/HER2- mBC in TROPiCS-02

	SG (n=268)		Single-Agent Chemotherapy[a] (n=249)	
Adverse reaction	All grades, %	Grade 3-4, %	All grades, %	Grade, 3-4 %
Gastrointestinal disorders				
Diarrhea	62	10	23	1
Nausea	59	1	35	3
Constipation	34	1	25	0
Vomiting	23	1	16	2
Abdominal pain	20	0	14	0
Dyspepsia[b]	11	0	6	0
General disorders and administration-site conditions				
Fatigue[c]	60	8	51	4
Metabolism and nutrition disorders				
Decreased appetite	21	2	21	0
Hypokalemia	10	2	4	0
Musculoskeletal and connective tissue disorders				
Arthralgia	15	0	12	0
Nervous system disorders				
Headache	16	1	15	1
Respiratory, thoracic, and mediastinal disorders				
Dyspnea[d]	20	0	17	0
Cough	12	0	7	0
Skin and subcutaneous tissue disorders				
Alopecia	48	0	19	0
Pruritus	12	0	2	0

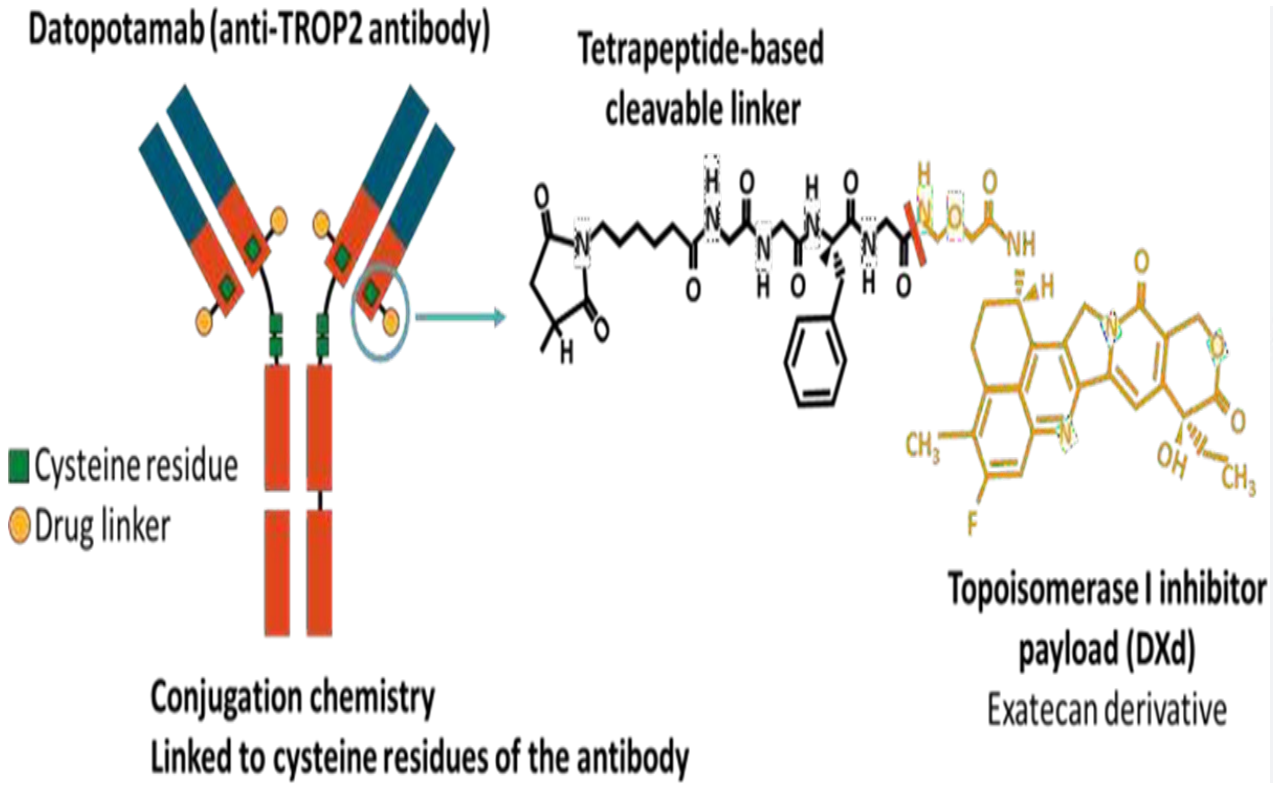
- The most common lab abnormalities occurring in ≥25% of patients treated with SG were decreased leukocyte count (88% for SG vs 73% for single-agent chemotherapy), decreased neutrophil count (83% for SG vs 67% for single-agent chemotherapy), decreased hemoglobin (73% for SG vs 59% for single-agent chemotherapy), decreased lymphocyte count (65% for SG vs 47% for single-agent chemotherapy), increased glucose (37% for SG vs 31% for single-agent chemotherapy), and decreased albumin (32% for SG vs 27% for single-agent chemotherapy)

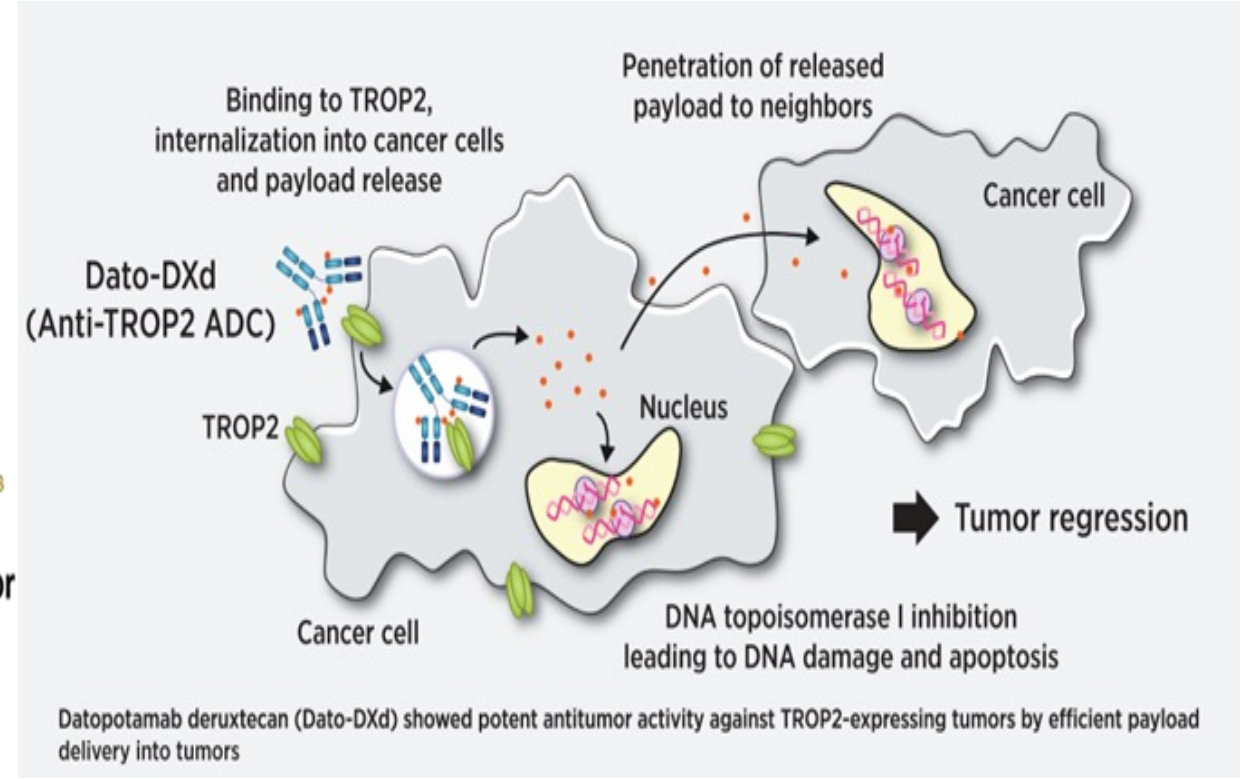
Graded per NCI CTCAE v.5.0. [a]Single-agent chemotherapy included one of the following single agents: eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22). [b]Including dyspepsia, gastroesophageal reflux disease. [c]Including fatigue, asthenia. [d]Including dyspnea; exertional dyspnea.

CTCAE, Common Terminology Criteria for Adverse Events; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; NCI, National Cancer Institute; SG, sacituzumab govitecan.

TRODELVY® [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2023.

Datopotomab Deruxtecan





Mol Cancer Ther. 2021;20(12):2329-2340. doi:10.1158/1535-7163.MCT-21-0206

TROPION-Breast01: Study Design[1]

Randomized, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria

Patients with HR+/HER2– BC[a] (HER2–defined as IHC 0/1+/2+; ISH–negative)

Previously treated with 1-2 lines of chemotherapy (inoperable/metastatic setting)

Experienced progression on ET and for whom ET was unsuitable

ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n = 365)

ICC
as per protocol directions[b]
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1-14 Q3W)
(n = 367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Randomization stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

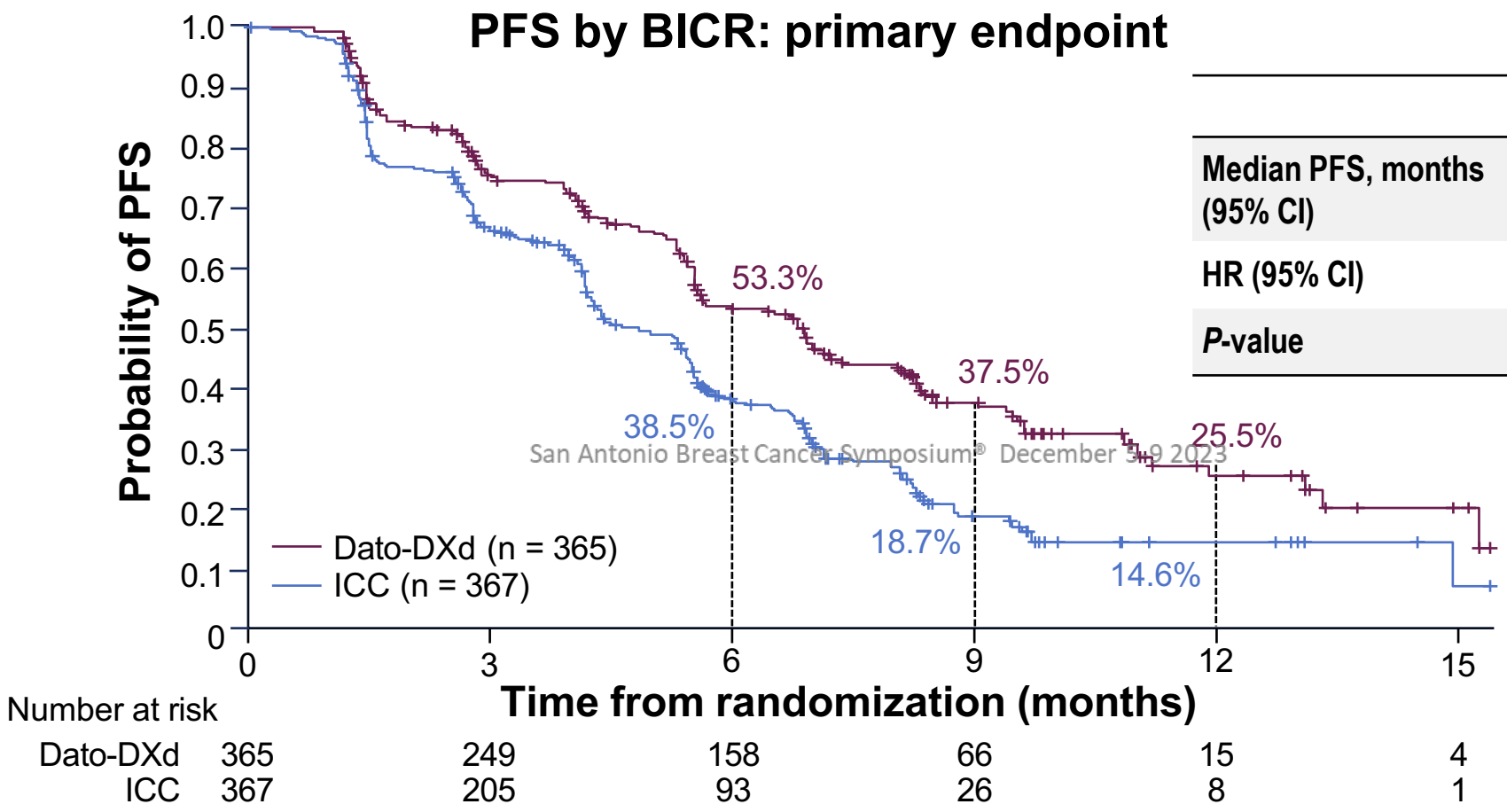
Detailed description of the statistical methods published previously.[1] [a] Per ASCO/CAP guidelines. [b] ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W.

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BC, breast cancer; BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; D, day; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ICC, investigator's choice of chemotherapy; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; US, United States.

1. Bardia A, et al. *Future Oncol* 2023;doi:10.2217/fon-2023-0188.

Bardia A, et al. ESMO 2023. Presidential Oral LBA11.

TROPION-Breast01: PFS



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7-7.4)	4.9 (4.2-5.5)
HR (95% CI)	**0.63 (0.52-0.76)**	
***P*-value**	< 0.0001	

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI: 0.53-0.76)

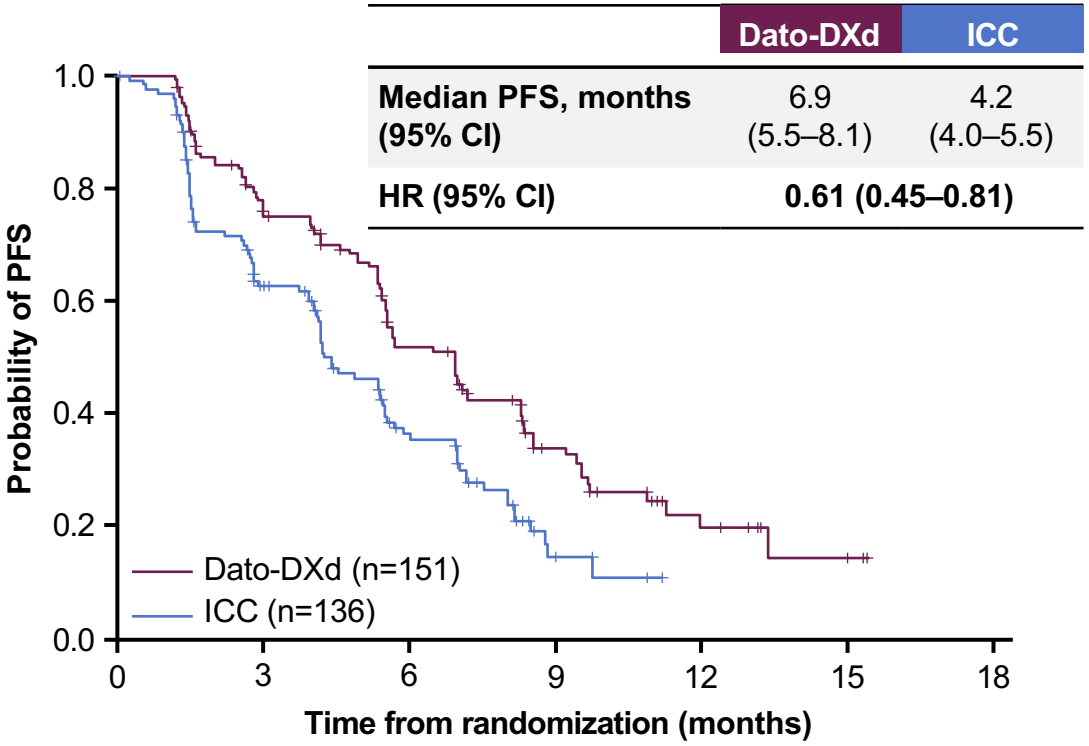
BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DCO, data cut-off; HR, hazard ratio; ICC, investigator's choice of chemotherapy; PFS, progression-free survival.
Bardia A, et al. ESMO 2023. Presidential Oral LBA11.

DCO: July 17, 2023.

PFS by BICR in Subgroups

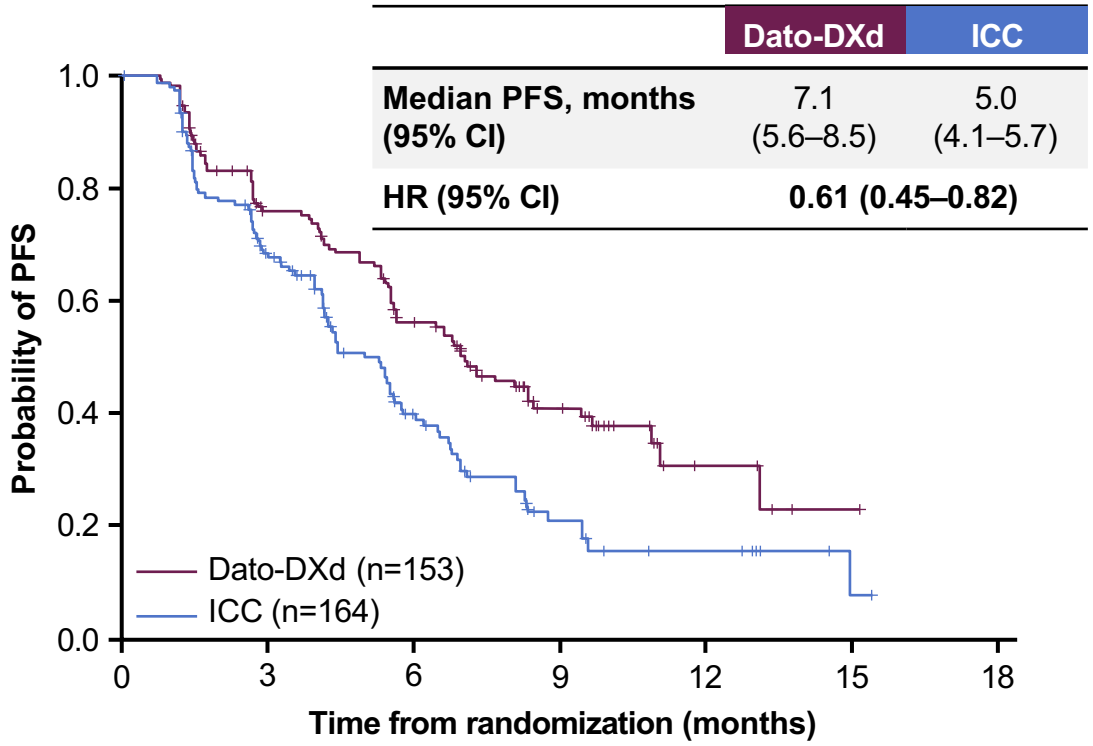
Prior CDK4/6 Inhibitor

Prior duration of CDK4/6 inhibitor: ≤12 months



No. at risk							
Dato-DXd	151	106	63	26	8	2	0
ICC	136	74	35	7	0	0	0

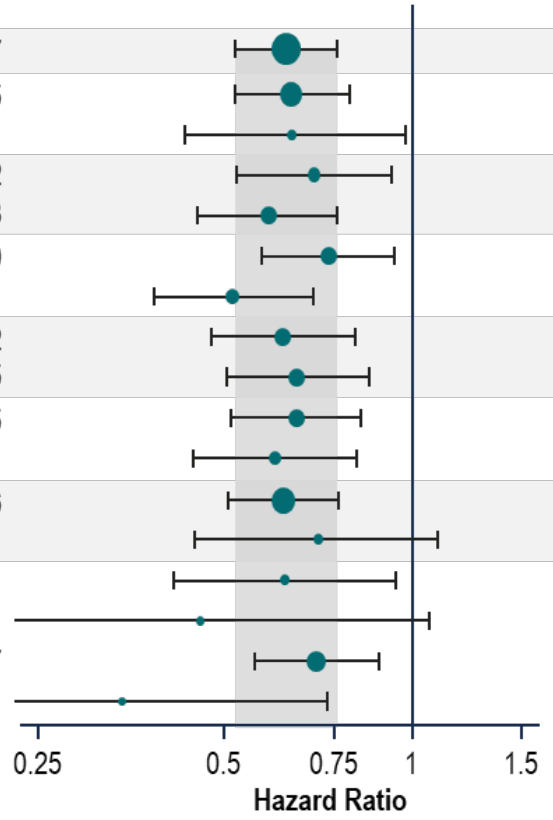
Prior duration of CDK4/6 inhibitor: >12 months



No. at risk							
Dato-DXd	153	102	70	28	6	1	0
ICC	164	90	40	13	7	1	0

TROPION-Breast01: PFS by BICR Across Subgroups

		Events/n Dato-DXd	Events/n ICC	Hazard ratio
All patients		212/365	235/367	0.63
Age at randomisation	<65 years	163/274	190/295	0.64
	≥65 years	49/91	45/72	0.65
Race	Asian	88/146	101/152	0.70
	Non-Asian	109/187	119/183	0.59
ECOG performance status	0	119/197	136/220	0.73
	1	91/165	98/145	0.52
Geographic region	US, Canada, Europe	110/186	112/182	0.62
	Rest of World[a]	102/179	123/185	0.66
Number of previous lines of chemotherapy	1	128/229	145/225	0.65
	2	84/135	90/141	0.60
Prior use of CDK4/6 inhibitor	Yes	177/299	190/286	0.62
	No	35/66	45/81	0.70
Prior use of taxane and/or anthracycline	Taxane alone	48/80	47/71	0.62
	Anthracycline alone	9/14	16/21	0.46
	Both taxane and anthracycline	141/236	155/247	0.70
	Neither taxane nor anthracycline	14/35	17/28	0.34



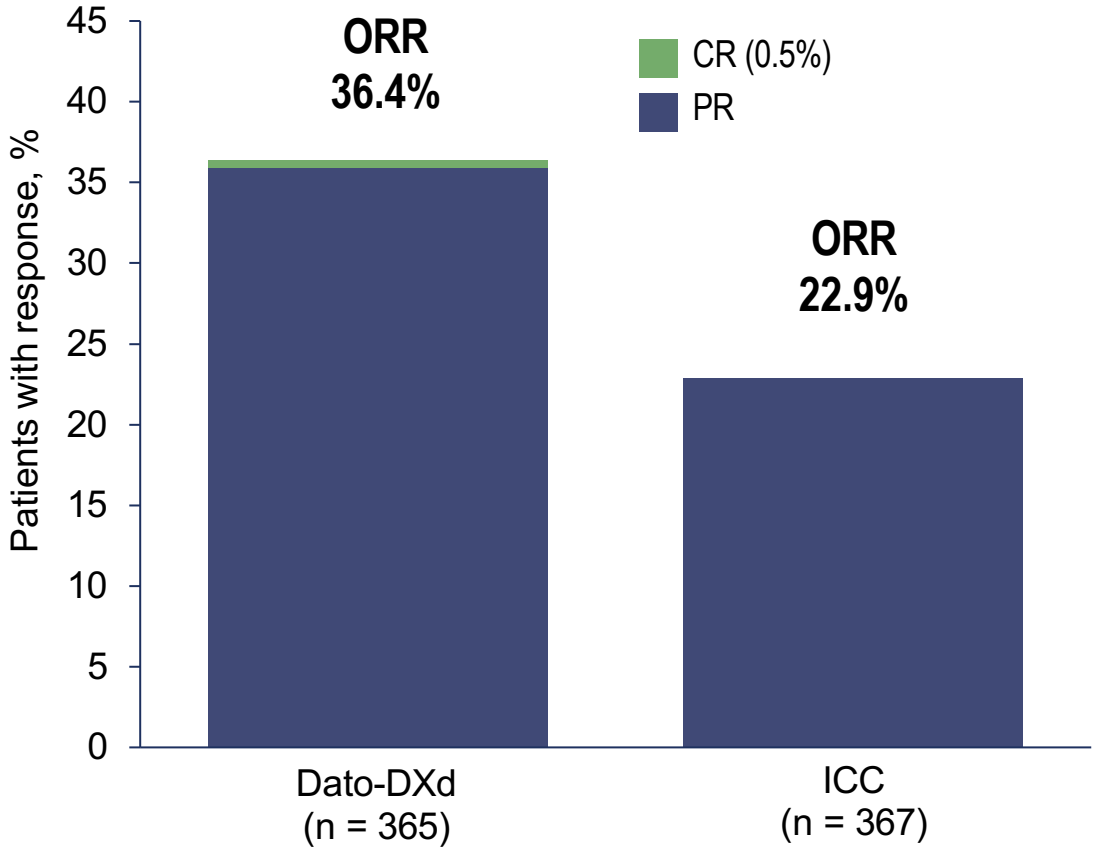
Consistent PFS benefit was seen across subgroups

Data cutoff: July 17, 2023.
Size of circle is proportional to the number of events across both treatment groups.
[a] Three patients from Canada were incorrectly stratified to Rest of World.
BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; Dato-DXd, datopotamab deruxtecan; ECOG, Eastern Cooperative Oncology Group; ICC, investigator's choice of chemotherapy; PFS, progression free survival.

Bardia A, et al. Presented at: ESMO Annual Meeting; October 20-24, 2023; Madrid, Spain. Abstract LBA11.

TROPION-Breast01: Response and Interim OS

Response rate



OS: Dual Primary Endpoint

- OS data were not mature[a]:
  - Median follow-up 9.7 months
- A trend favoring Dato-DXd was observed:
  - HR 0.84 (95% CI: 0.62–1.14)
- The study is continuing to the next planned analysis for OS

[a] Information fraction: 39%.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ICC, investigator's choice of chemotherapy; ORR, objective response rate; OS, overall survival.
Bardia A, et al. ESMO 2023. Presidential Oral LBA11.

DCO: July 17, 2023.

TROPION-Breast01: TRAEs Occurring in ≥ 15% of Patients and AESIs

System Organ Class Preferred term, n (%)	Dato-DXd (n = 360)		ICC (n = 351)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Blood and lymphatic system				
Anemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia[a]	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

- Most TRAEs were grade 1-2 and manageable

AESIs

- Oral mucositis/stomatitis:[b] led to treatment discontinuation in 1 patient in the Dato-DXd group
- Ocular events:[c] most were dry eye; one patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD:[d] rate was low; mainly grade 1/2

Adjudicated drug-related ILD	Dato-DXd	ICC
All grades, n (%)	9 (3)	0
Grade ≥ 3, n (%)	2 (1)[e]	0

[a] Neutropenia includes the PTs neutropenia and neutrophil count decreased. [b] Oral stomatitis/mucositis events included PTs of aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis, tongue ulceration; all grade: 59% with Dato-DXd, 17% with ICC; grade 3: 7% with Dato-DXd, 3% with ICC. [c] Ophthalmologic assessments were required at screening, and then every 3 cycles from C1D1 and at end of therapy; ocular events included selected PTs from Corneal Disorder SMQ and select relevant PTs from Eye Disorder SOC; all grade: 49% with Dato-DXd, 23% with ICC; grade 3: 1% with Dato-DXd (one patient with dry eye, one patient with punctate keratitis, and one patient with dry eye and ulcerative keratitis), 0% with ICC. [d] ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or ICC (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). [e] One adjudicated drug-related grade 5 ILD event: attributed to disease progression by investigator.

AESI, adverse event of special interest; C, cycle; D, day; Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice of chemotherapy; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, standard MedDRA queries; SOC, System Organ Class; TRAE, treatment-related adverse event.

Bardia A, et al. ESMO 2023. Presidential Oral LBA11.

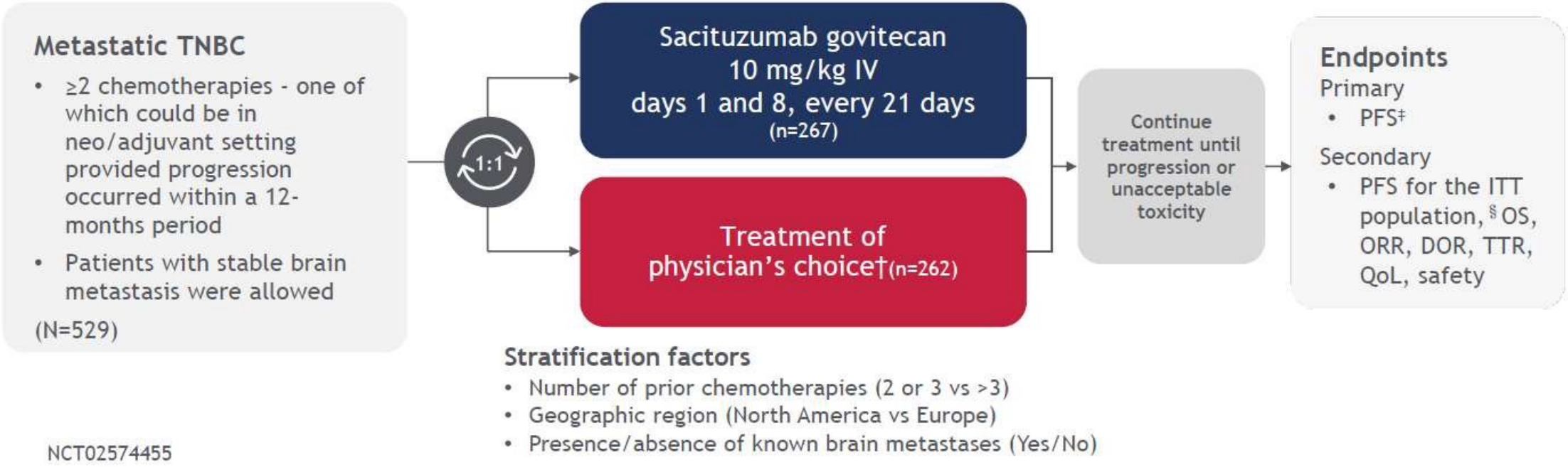
DCO: July 17, 2023.

Overview of current treatment with ADCs for mTNBC

ASCENT : Phase 3 confirmatory trial

Sacituzumab govitecan received accelerated approval from FDA (April 2020) for pts with metastatic TNBC treated with at least 2 prior therapies for MBC. Approval was based on a single arm trial of mTNBC (n=108)

ASCENT- phase 3 trial study design



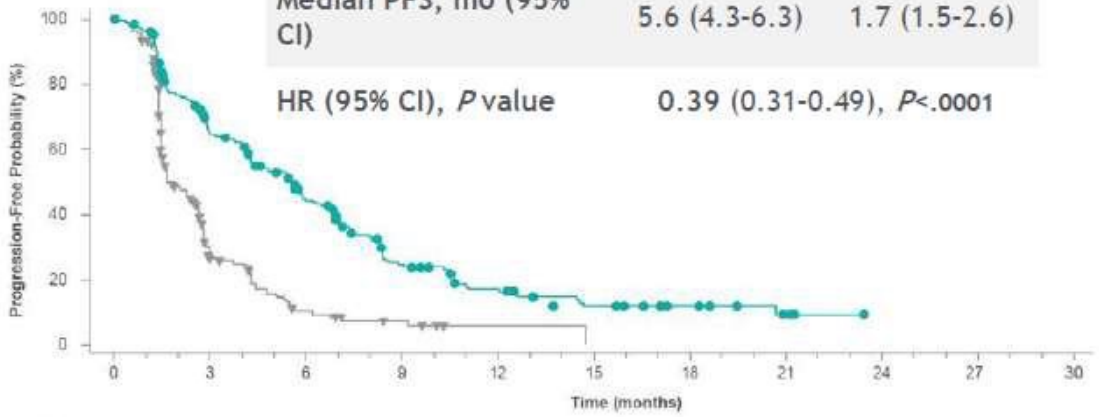
Bardia A et al. ESMO 2021; NEJM 2021

ASCENT : PFS & OS

Trial demonstrated statistically significant & clinically meaningful improvement in PFS and OS over single-agent chemotherapy

Progression-free survival (BICR Analysis)

BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	167	150
Median PFS, mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<.0001	

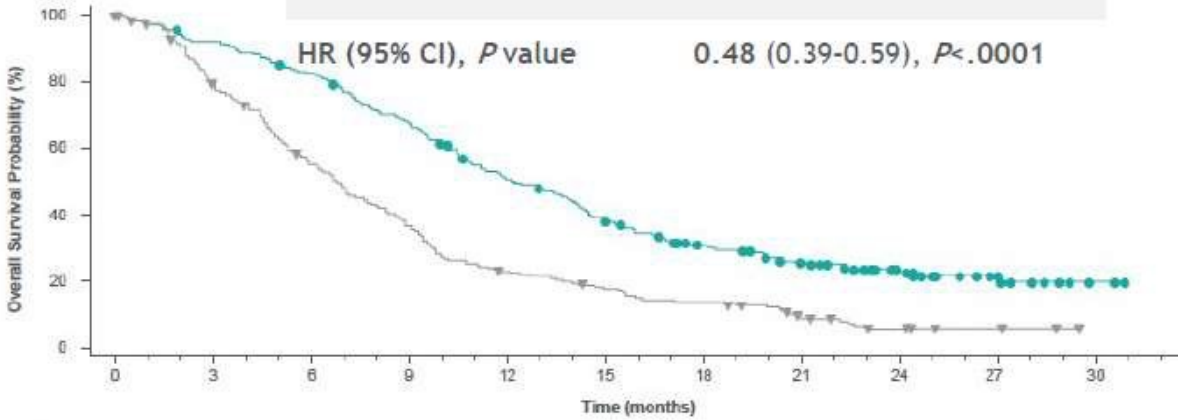


No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
IMMU-132	235	222	199	134	127	104	81	63	54	32	33	24	22	17	16	13	11	10	8	0	5	3	1	1	0
SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0		
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0		

Overall survival

	SG (n=235)	TPC (n=233)
No. of events	173	199
Median OS, mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	0.48 (0.39-0.59), *P*<.0001	



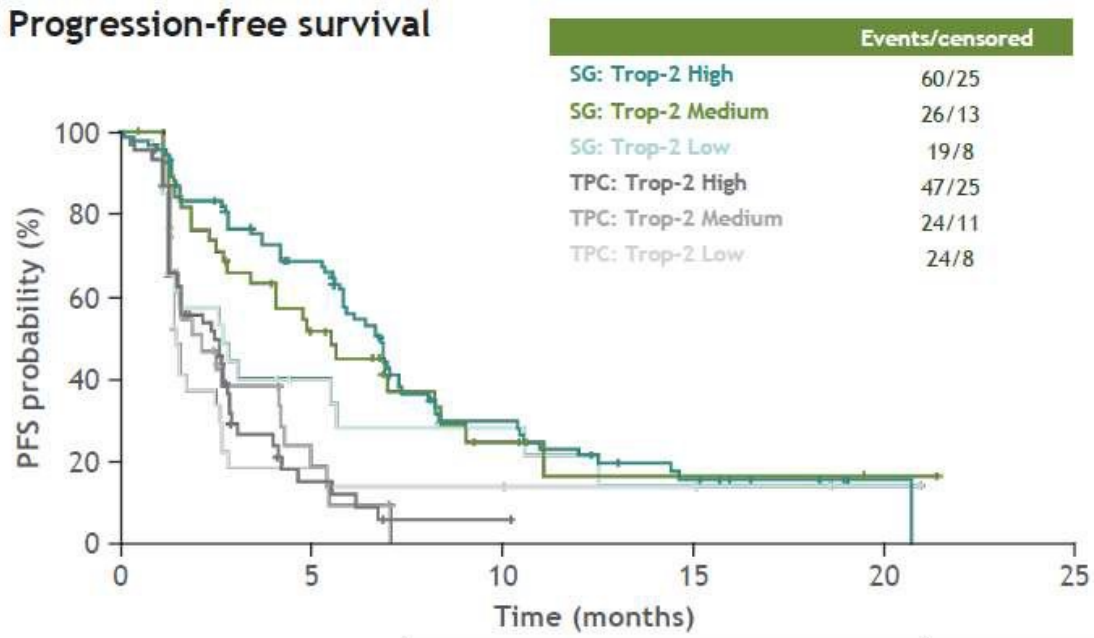
No. of Patients Still at Risk

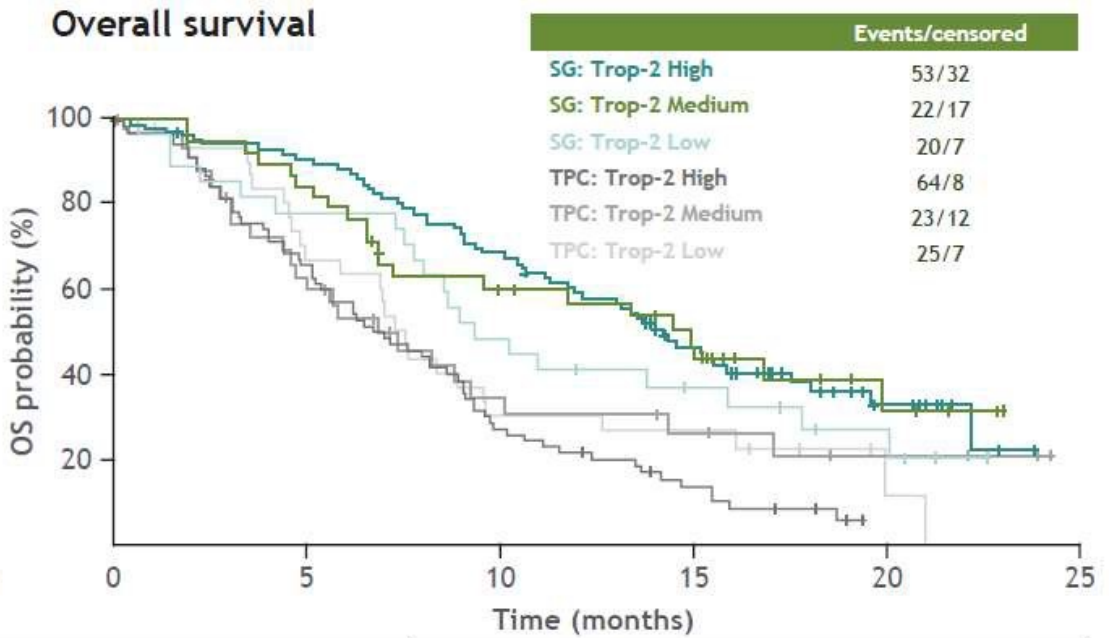
Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
IMMU-132	235	228	220	214	206	197	191	177	164	156	140	122	113	105	97	85	74	65	59	56	46	40	35	30	25	17	14	11	7	4	2
TPC	233	214	200	173	156	134	117	101	90	77	58	53	47	44	40	35	30	28	27	24	22	13	11	7	6	4	3	3	2	1	0

In April 2021, the FDA granted regular approval to Sacituzumab govitecan for pts with mTNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease

Bardia A et al. ASCO 2022

ASCENT : Clinical benefit irrespective of Trop-2 expression



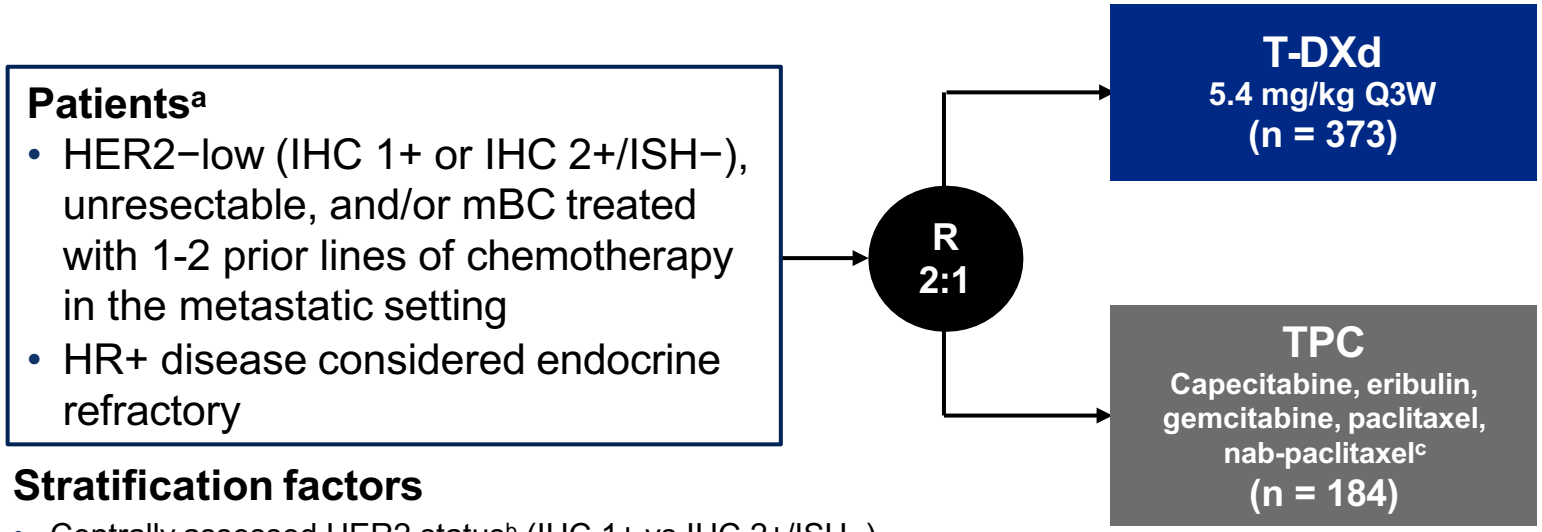


	Trop-2 High; H-score: 200-300		Trop-2 Medium; H-score: 100-200		Trop-2 Low; H-score: <100	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
Median PFS, mo (95% CI)	6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)
Median OS, mo (95% CI)	14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

Bardia A et al. ASCO 2022

DESTINY-Breast04: Study Design

An open-label, multicenter study (NCT03734029)[1-3]



Stratification factors

- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- One vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[d]

- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]

- **PFS by investigator**
- ORR by BICR and investigator
- DoR by BICR
- **Safety**
- PROs (HR+)[e]

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI: 31.0-32.8 months)

[a] If patients had HR+ mBC, prior endocrine therapy was required. [b] Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only (IUO) assay system, at the time of study. [c] TPC was administered according to the label. [d] Efficacy in the HR− cohort was an exploratory endpoint. [e] The PROs analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

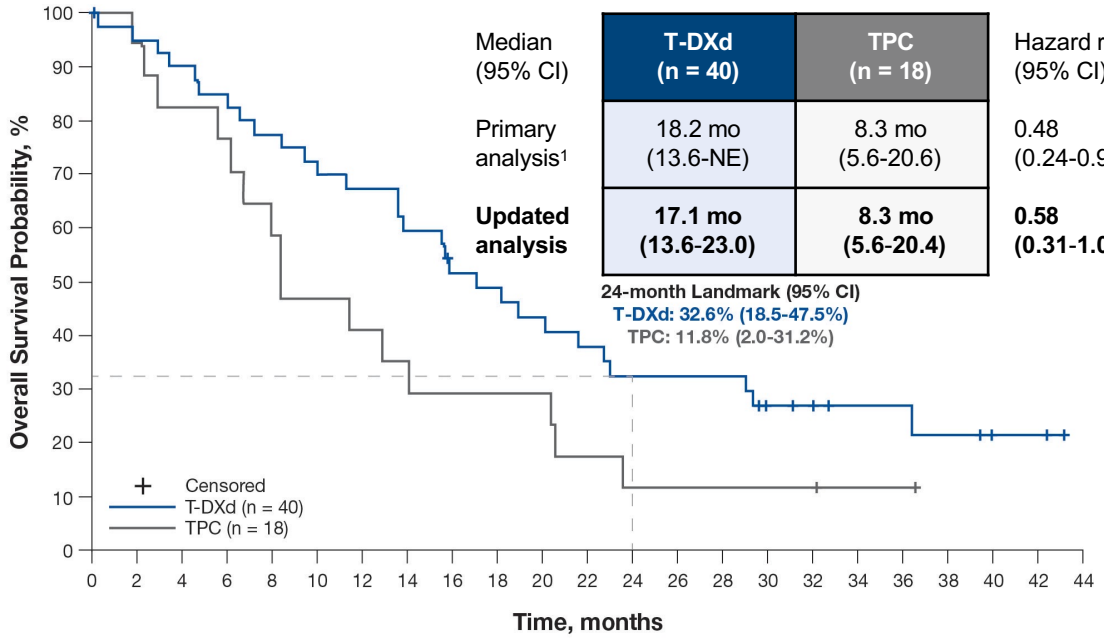
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; CI, confidence interval; DoR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; R, randomization; T-DXd, fam-trastuzumab deruxtecan-nxki; TPC, treatment of physician's choice.

1. Modi S, et al. *N Engl J Med*. 2022;387:9-20. 2. Harbeck N, et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A, et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Modi S, et al. ESMO 2023. Oral 376O.

DESTINY-Breast04 Updated OS: Efficacy in the HR− Cohort (Exploratory Analyses)

OS

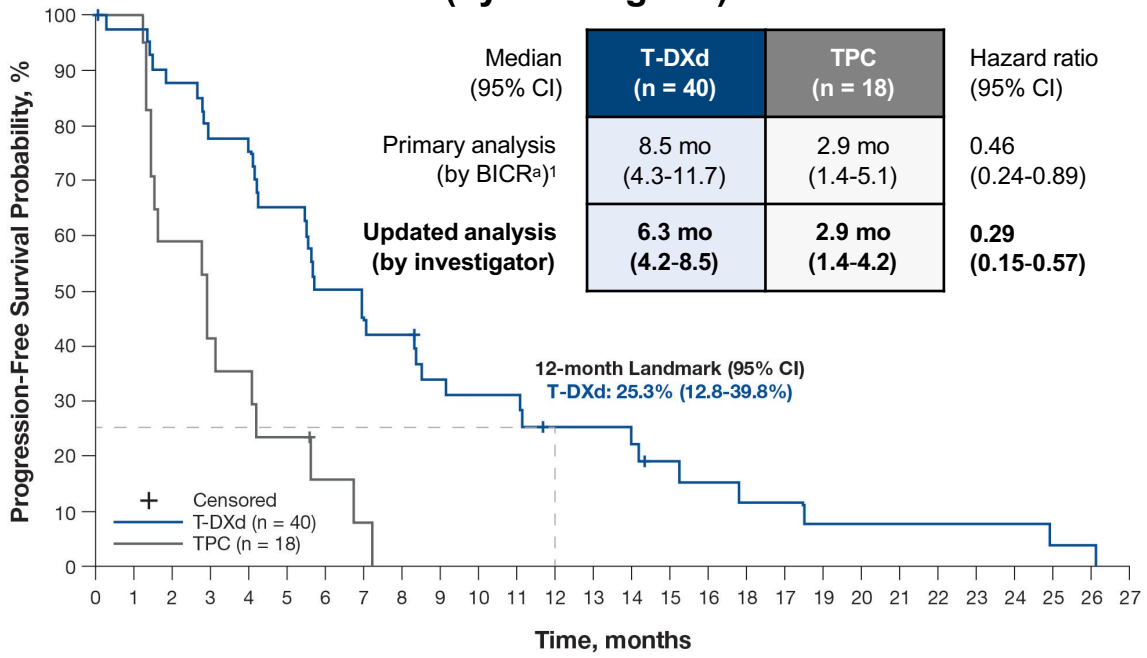


Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

PFS (by Investigator)



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

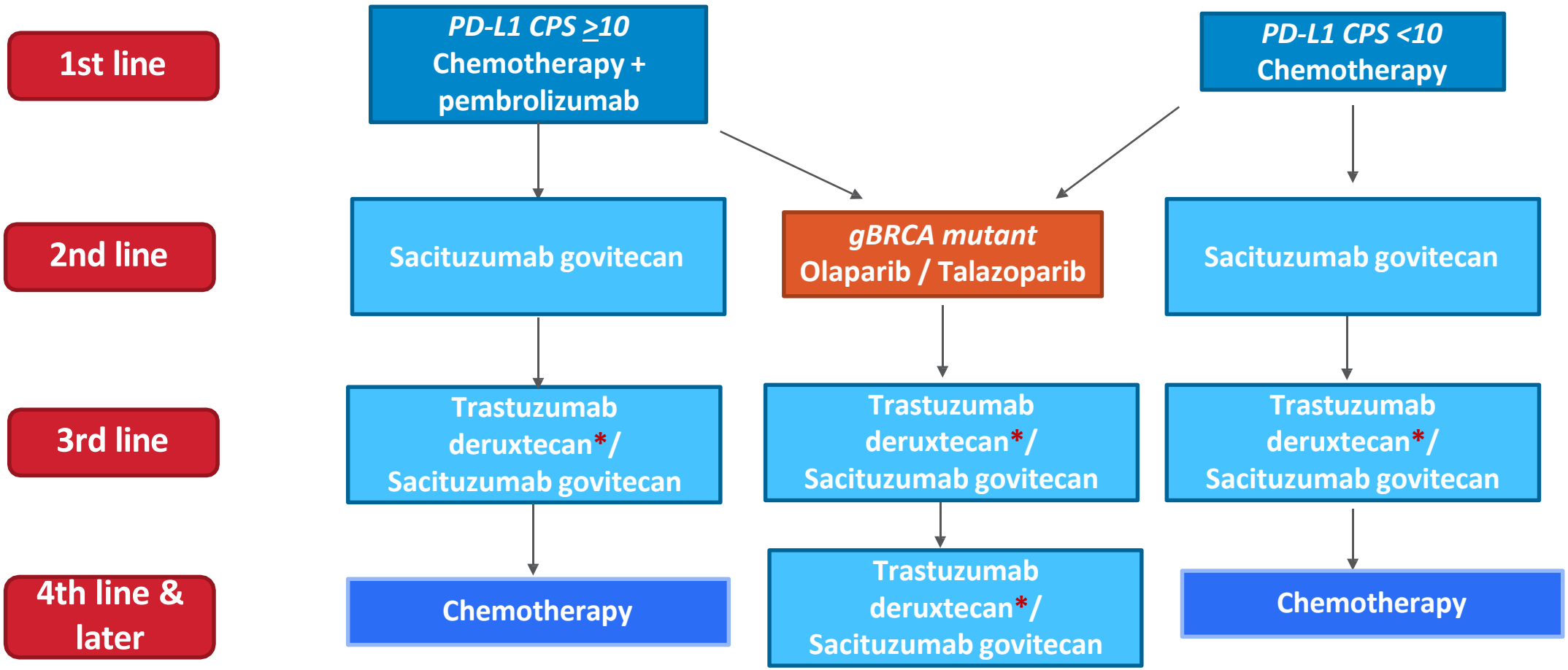
- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

[a] PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.
BICR, blinded independent central review; CI, confidence interval; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; PFS, progression-free survival; T-DXd, fam-trastuzumab deruxtecan-nxki; TPC, treatment of physician's choice.

1. Modi S, et al. *N Engl J Med*. 2022;387:9-20.

Modi S, et al. ESMO 2023. Oral 376O.

Current treatment algorithm for mTNBC



*HR+/HER2low

Consider Clinical trials if available!!

Management of ILD with T-DXd

1 Screen	2 Scan	3 Synergy	4 Suspend Treatment	5 Steroids
				
Careful patient selection during screening to optimize monitoring strategies Continue monitoring during treatment to exclude signs/symptoms of ILD	Monitor using high resolution chest CT Baseline scan recommended, with repeat scans every 6-12 weeks	Minimizing risk of ILD involves teamwork - educating patients and the care team is essential Multidisciplinary management is required once ILD is suspected	T-DXd should be interrupted if ILD is suspected T-DXd can be restarted only in case of asymptomatic ILD that has fully resolved	Corticosteroids are the mainstay of treatment and the dose should be tailored to toxicity grade

Tarantino P & Tolaney SM JCO Onc Prac 2023

Ongoing trials with ADCs for MBC

Moving T-DXd to 1st line MBC

DESTINY Breast09 (NCT04784715)

POPULATION

- HER2-positive mBC
- DFI >6 months from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- No prior systemic treatment for mBC except for endocrine therapy

Stratification factors:

- *De novo* vs recurrent (cap at 50% *de novo*)
- HR-positive vs negative
- *PIK3CA*m (detected vs not detected)

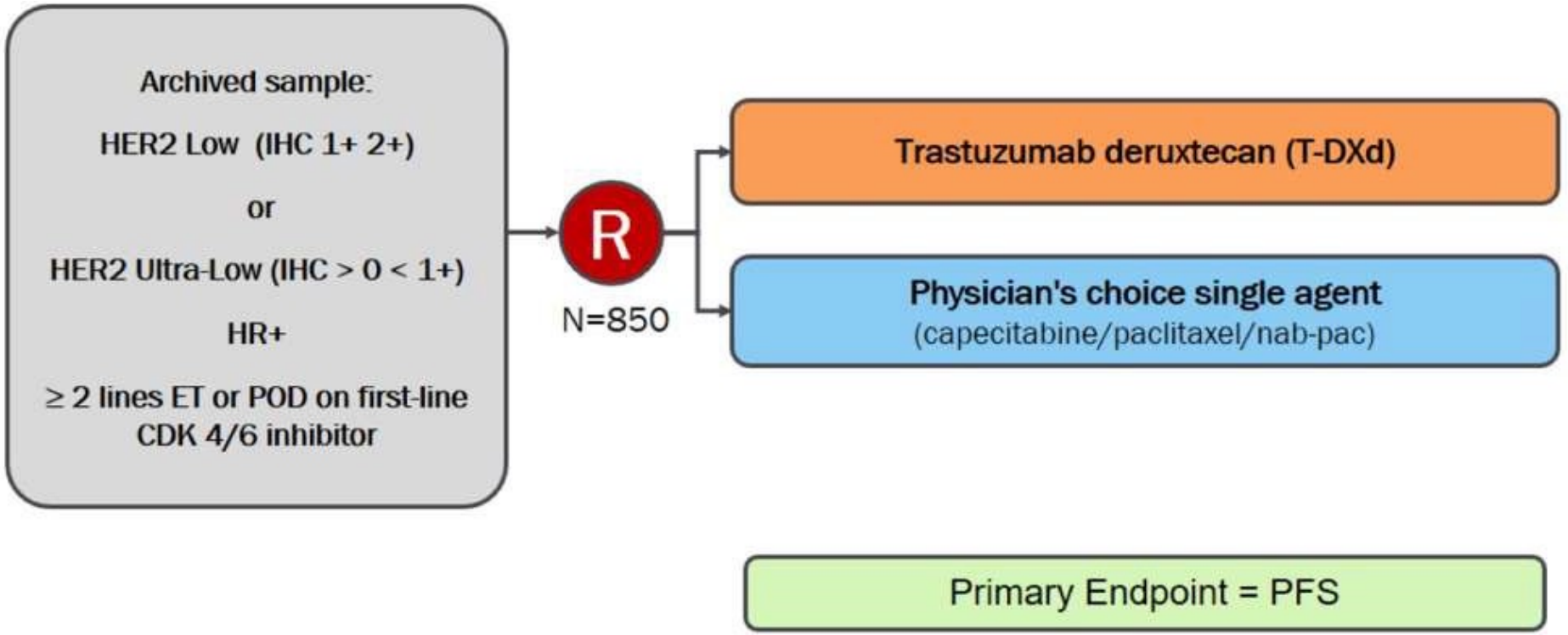
STUDY DESIGN

DESTINY Breast07 (NCT04538742) ***Enrollment closed***
T-DXd combinations with chemotherapy, immunotherapy and endocrine therapy in 1-2L setting in HER2+ MBC

DESTINY Breast06: T-DXd for HER2 low and ultra low MBC

NCT04494425

Enrollment closed – results anticipated in Q4 2023 /Q1 2024



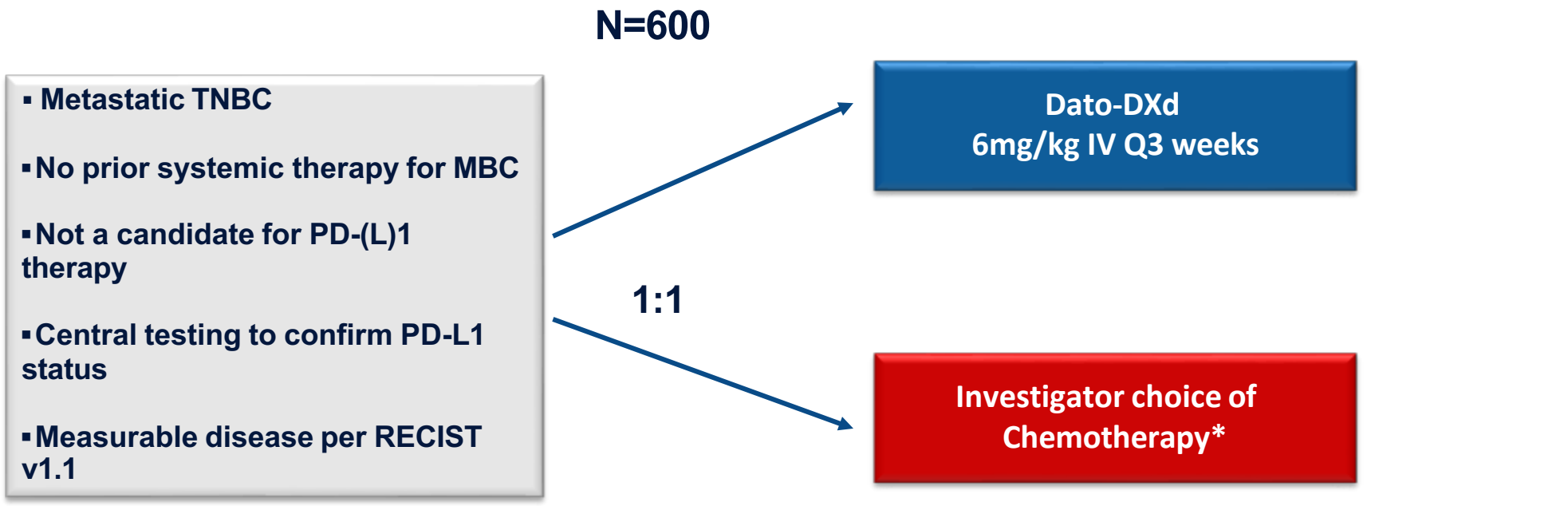
DESTINY Breast08 (NCT04556773) ***Enrollment closed***

T-DXd combinations with chemotherapy, immunotherapy and endocrine therapy in 1-2L HER2-low MBC

TROPION Breast02: Dato-DXd for 1L mTNBC

NCT05374512

- **Datopotamab DXd (Dato-DXd) is a TROP2 targeting ADC**
- **Trop 2 is highly expressed in breast cancer and its expression is associated with poor prognosis**

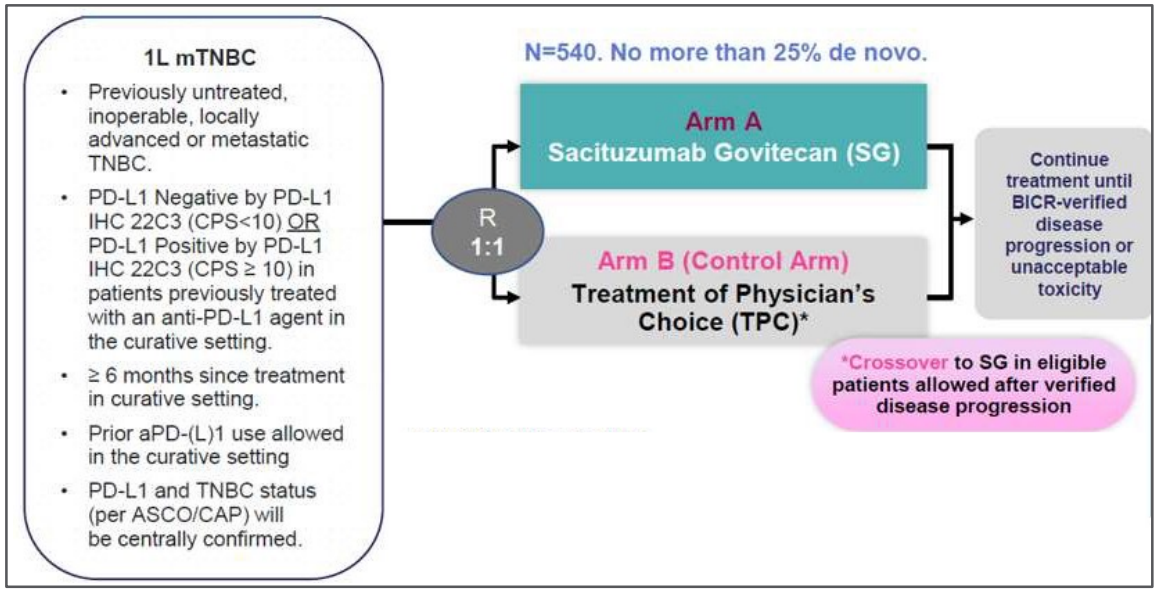


*If no prior taxane or DFI >12 months: paclitaxel or nab-paclitaxel
If prior taxane or DFI ≤12 months: Eribulin, Capecitabine, Carboplatin

ASCENT-03 and -04: Sacituzumab govitecan for 1L mTNBC

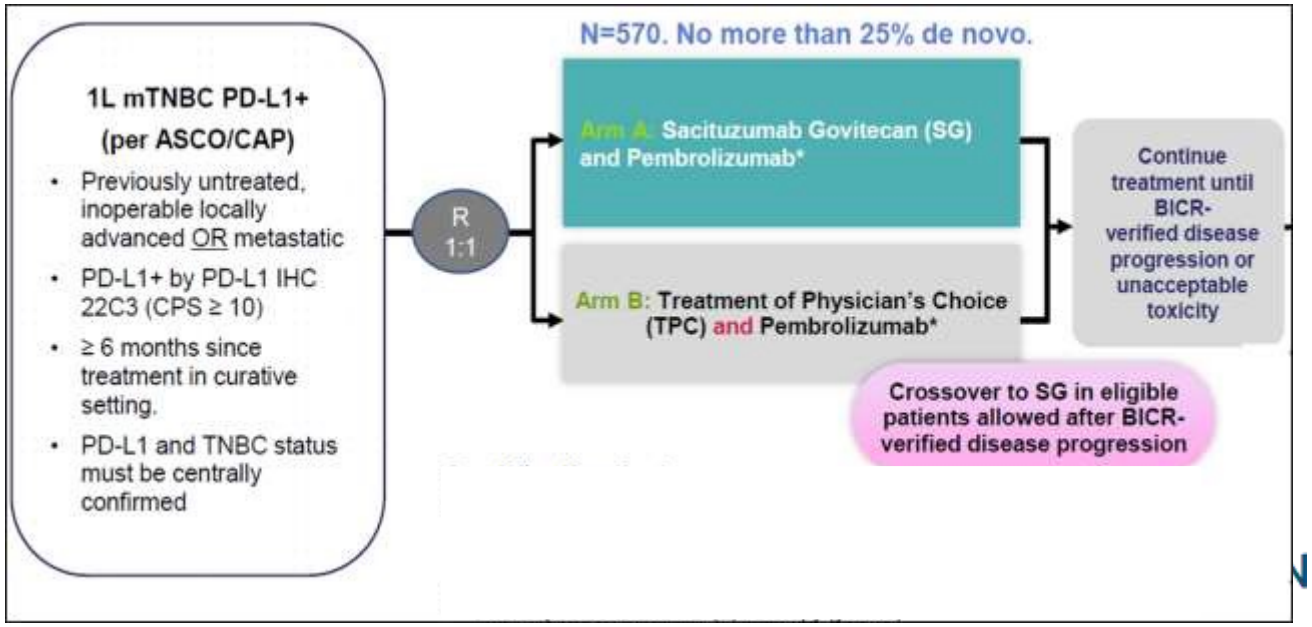
- **Sacituzumab Govitecan (SG) is a TROP2 targeting ADC**

ASCENT-03: PD-L1 neg or PD-L1+ and rcvd CPI for EBC



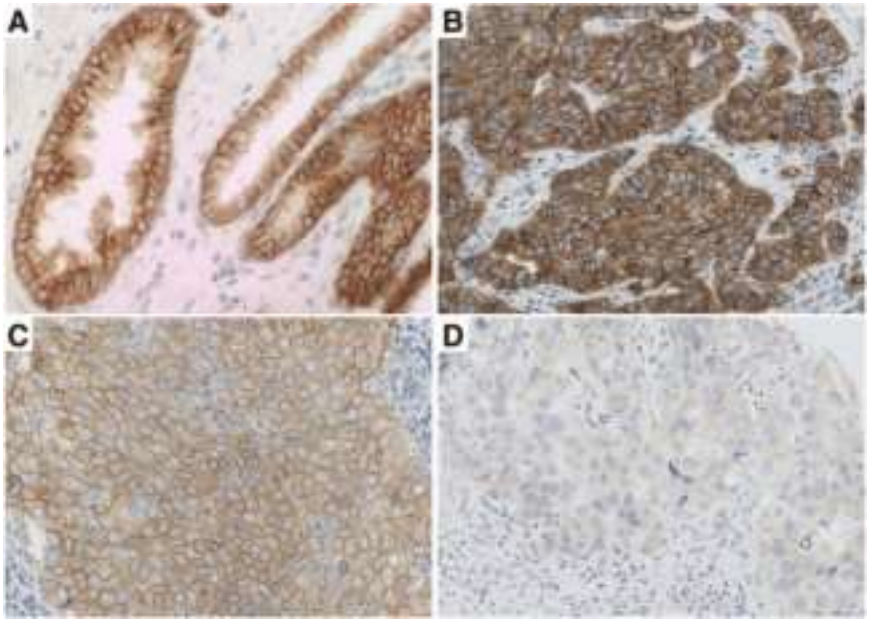
CPI: checkpoint inhibitor

ASCENT-04: PD-L1+ tumor



New Targets- HER-3

HER3 in breast cancer

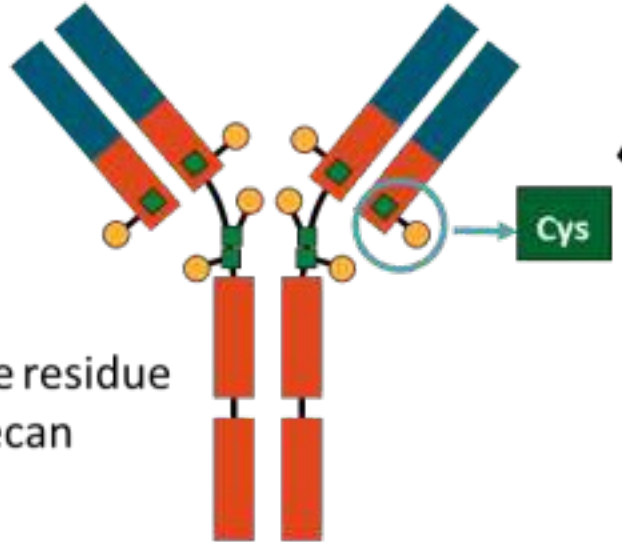


HER3 is expressed in >95% of breast cancers, with half showing a strong overexspression

Luthala S. et al. BMC Cancer 2018

HER3-DXd(Patritumab)

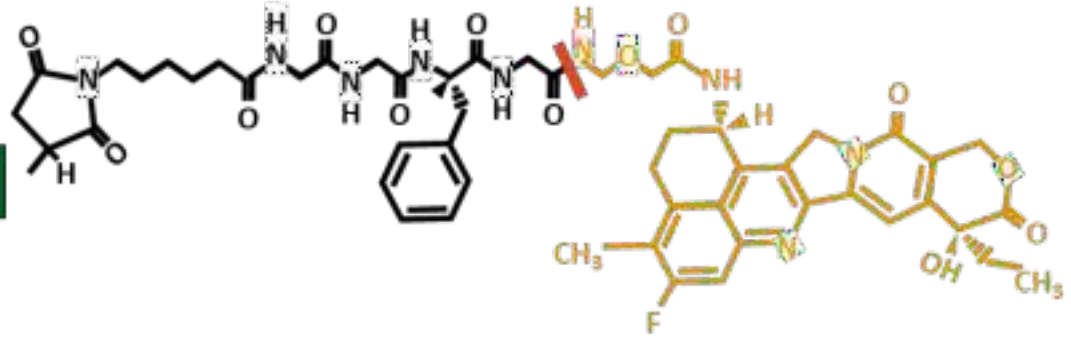
Human anti-HER3 IgG1 mAb



Cysteine residue
Deruxtecan

Conjugation chemistry:
Drug-linker conjugated to cysteine residues of mAb

Tetrapeptide-based cleavable Linker

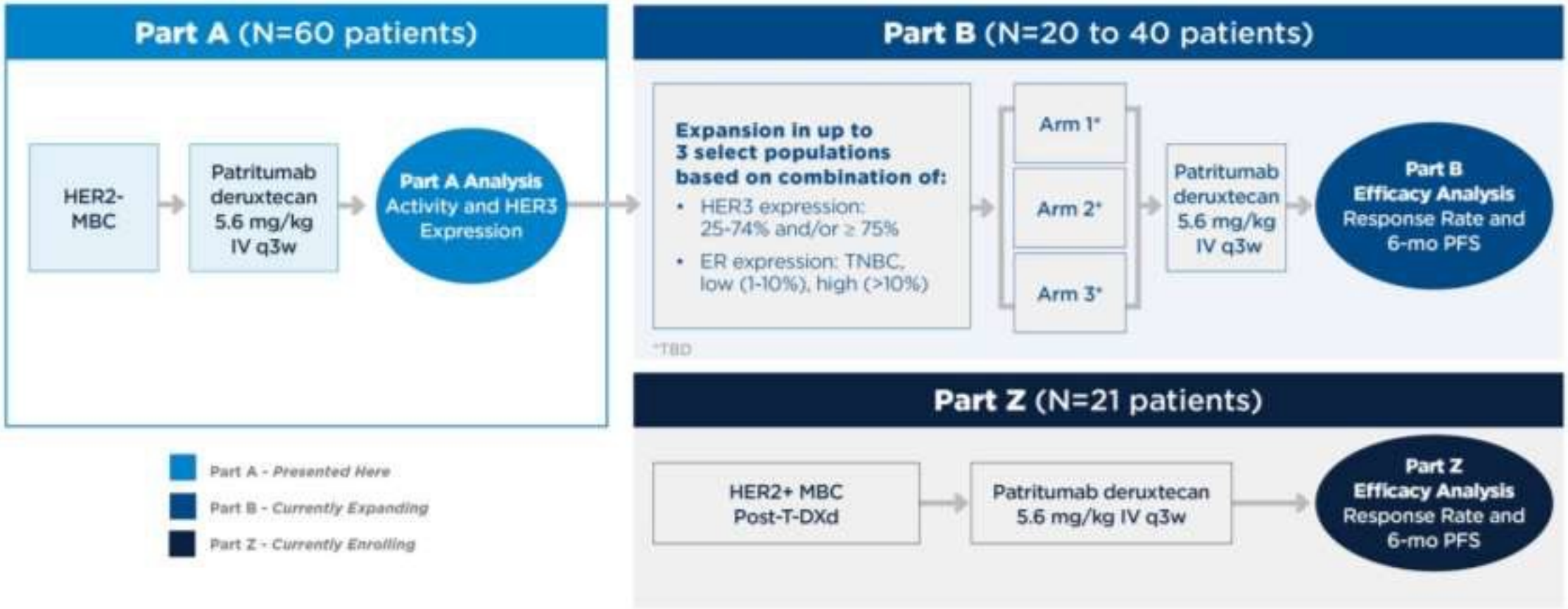


Topoisomerase I inhibitor payload (DXd)
Exatecan derivative

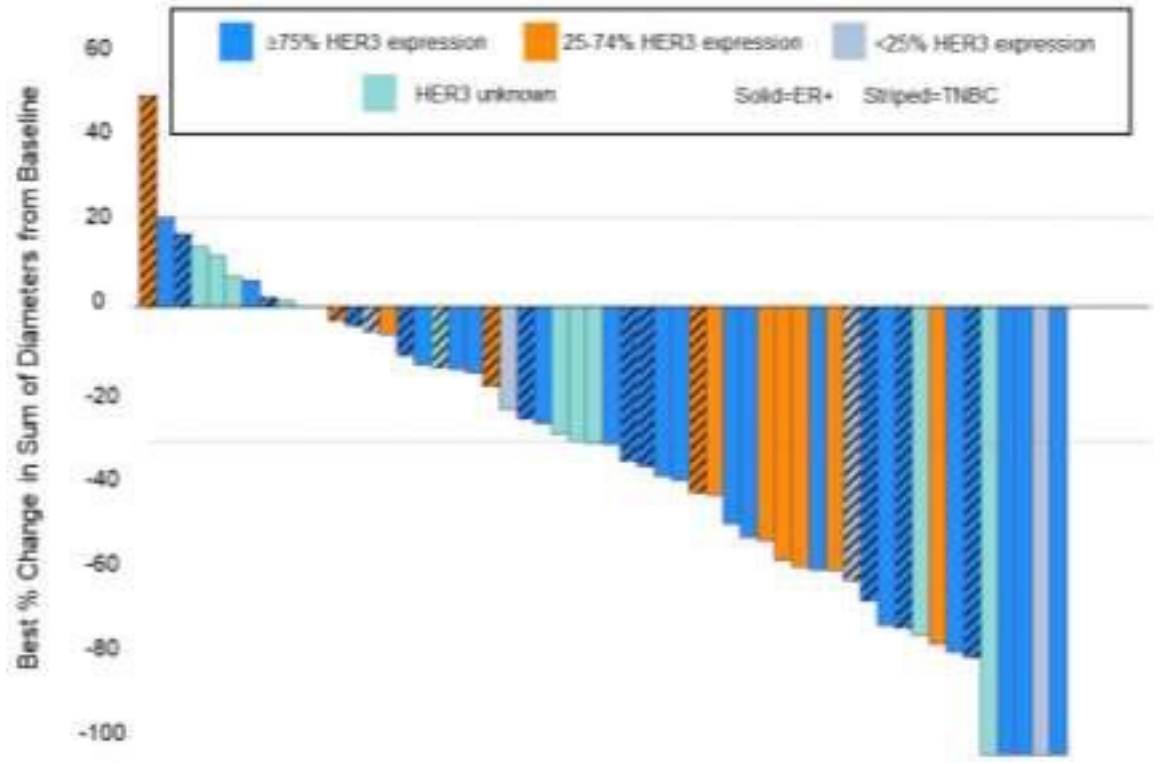
- High potency, membrane-permeable payload with short systemic half-life
- High drug:antibody ratio: ~8:1
- Stable linker-payload
- Tumor-selectable cleavable linker
- Bystander killing effect

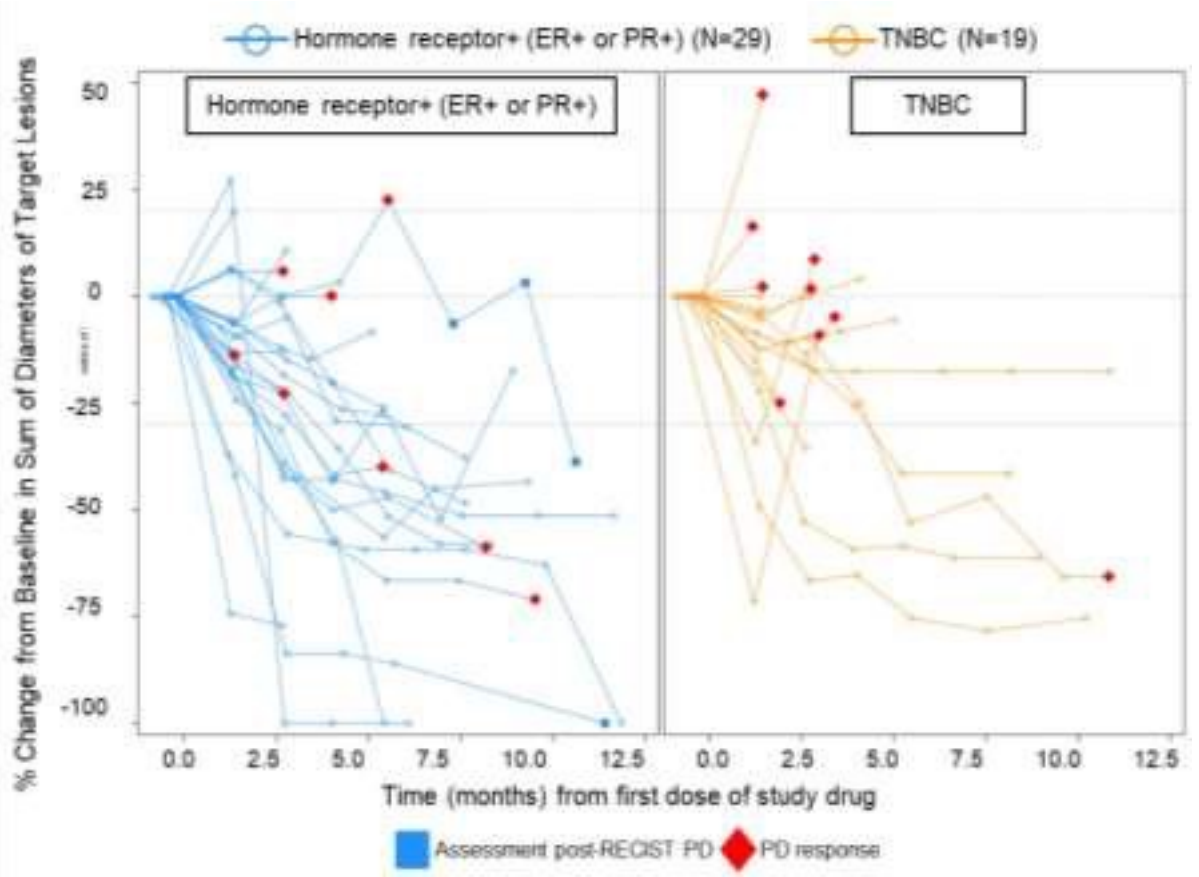
Yu. WCLC 2020. Abstr OA03.04. Hashimoto. Clin Cancer Res. 2019;25:7151.

Phase 2 trial of HER3-DXd for patients with HER2- MBC



Phase 2 trial of HER3-DXd for patients with HER2- MBC






Thank You