Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Breast Cancer Updates: Antibody Drug Conjugates

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Disclosures

- **Consulting Fees:** AbbVie, Astra Zeneca, Blueprint Medicines, Biotheranostics, BMS, Genentech, Jounce Therapeutics, Lilly Pharmaceuticals, Novartis, Pfizer, Seattle Genetics, SunPharma Pvt Ltd, Taiho Oncology

- **Contracted Research (paid to the Institution)**:ADC Therapeutics, Astra Zeneca, Clovis Oncology, Debio Pharmaceuticals, Genentech, Immunomedics, Novartis, Lilly Pharmaceuticals, Merck/VelosBio, Novartis, Novita Pharmaceuticals, Pfizer, Puma Biotechnology, Zymeworks

- I will be discussing non-FDA approved indications during my presentation.

A brief history of antibody therapeutics in cancer

"Wir müssen chemisch zielen lernen"

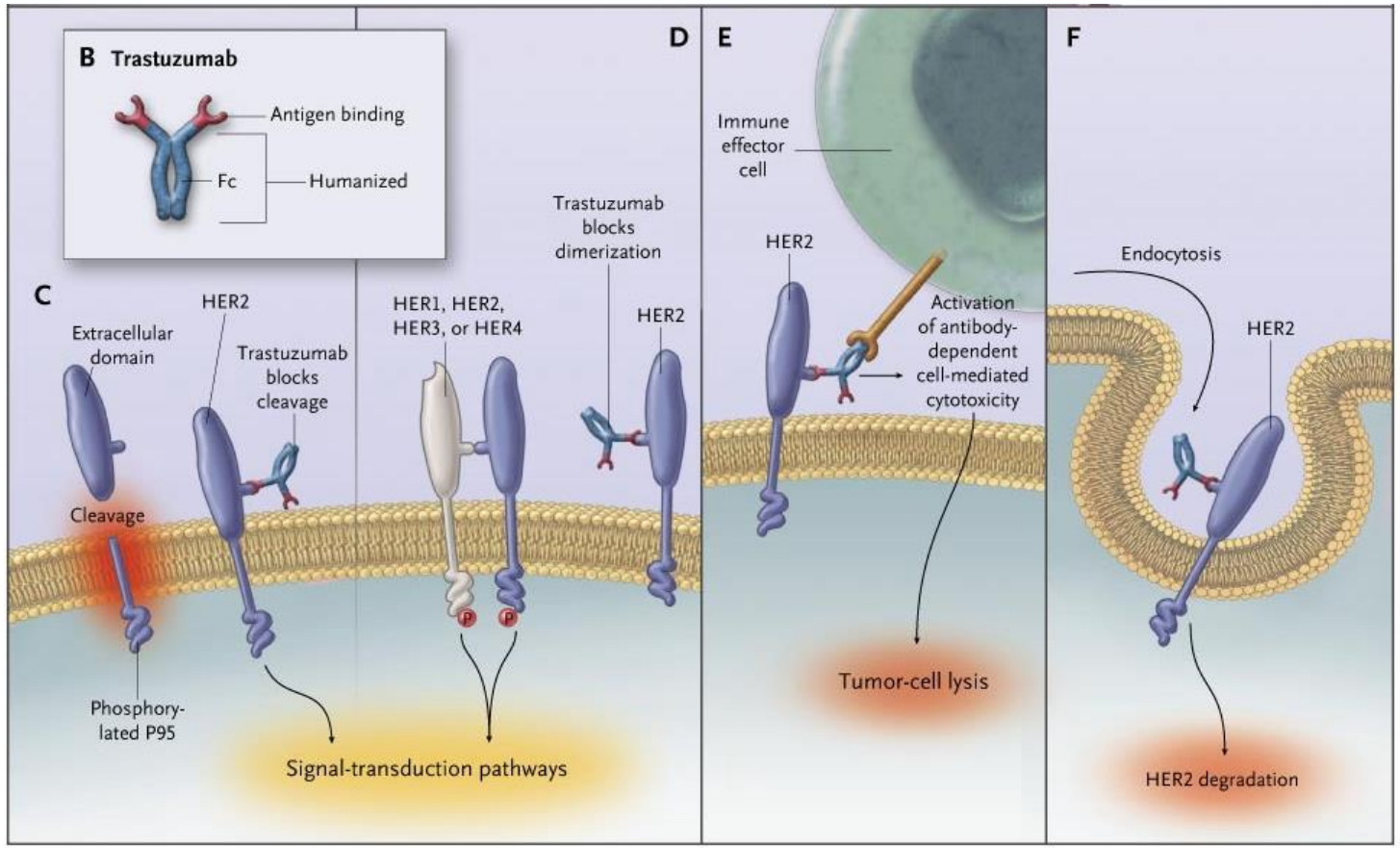
"We have to learn how to aim chemically"

-Paul Ehrlich, circa 1900

Nature Reviews | Cancer

Strebhardt et al. Nat Rev. Can. 2008

Trastuzumab: A canonical anti-cancer antibody



- Trastuzumab monotherapy has an ORR of ~15% in HER2+ MBC
- When combined with chemotherapy, ORR improves to ~50%
- Therapeutic resistance, and systemic toxicity of chemotherapy remain

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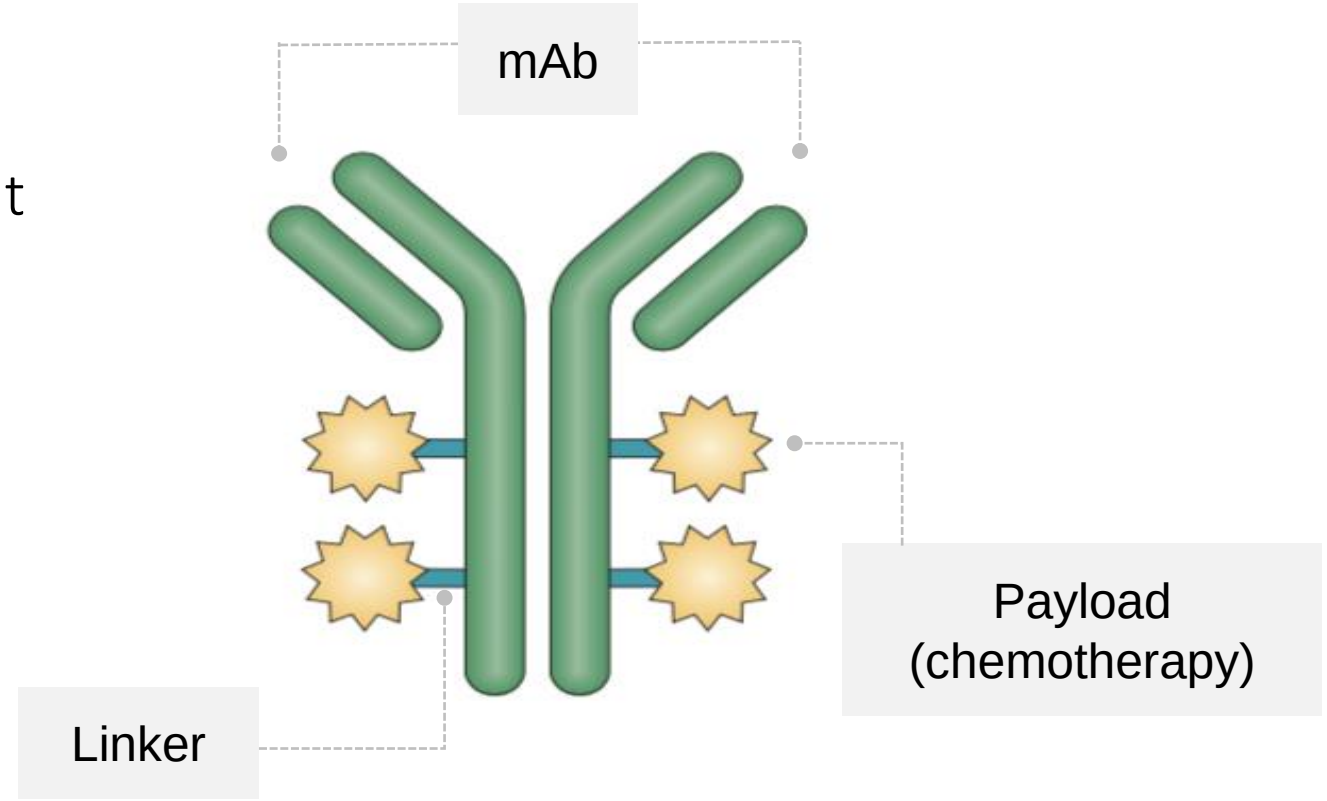
Hudis C. NEJM 2007; Slamon et al NEJM 2001

Antibody Drug Conjugates (ADCs)

- ADCs are a class of cancer therapies that combine antigen specificity and potent cytotoxicity in a single molecule
- Offer increased therapeutic index of anticancer agents



Structure of ADC

Drago JZ, Modi S, Chandarlapaty S. Nature Reviews Clinical Oncology 2021; Nakada T, et al. Chem Pharm Bull. 2019

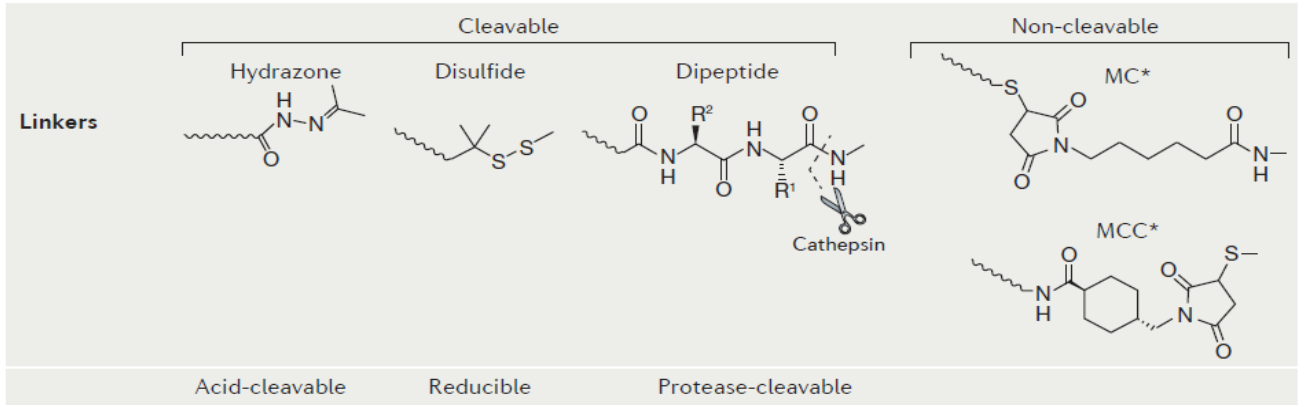
ADC design and construction

mAb

Linker

Payload (chemotherapy)

Antibodies	IgG1	IgG2	IgG3	IgG4
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate



Payloads	Auristatins	Maytansinoids	Calicheamicins	Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition
Examples:	MMAE MMAF	DM1 DM4	Ozogamicin	DXd SN-38

Drago, Modi, and Chandarlapaty; Nat Rev. Clin Onc. 2021

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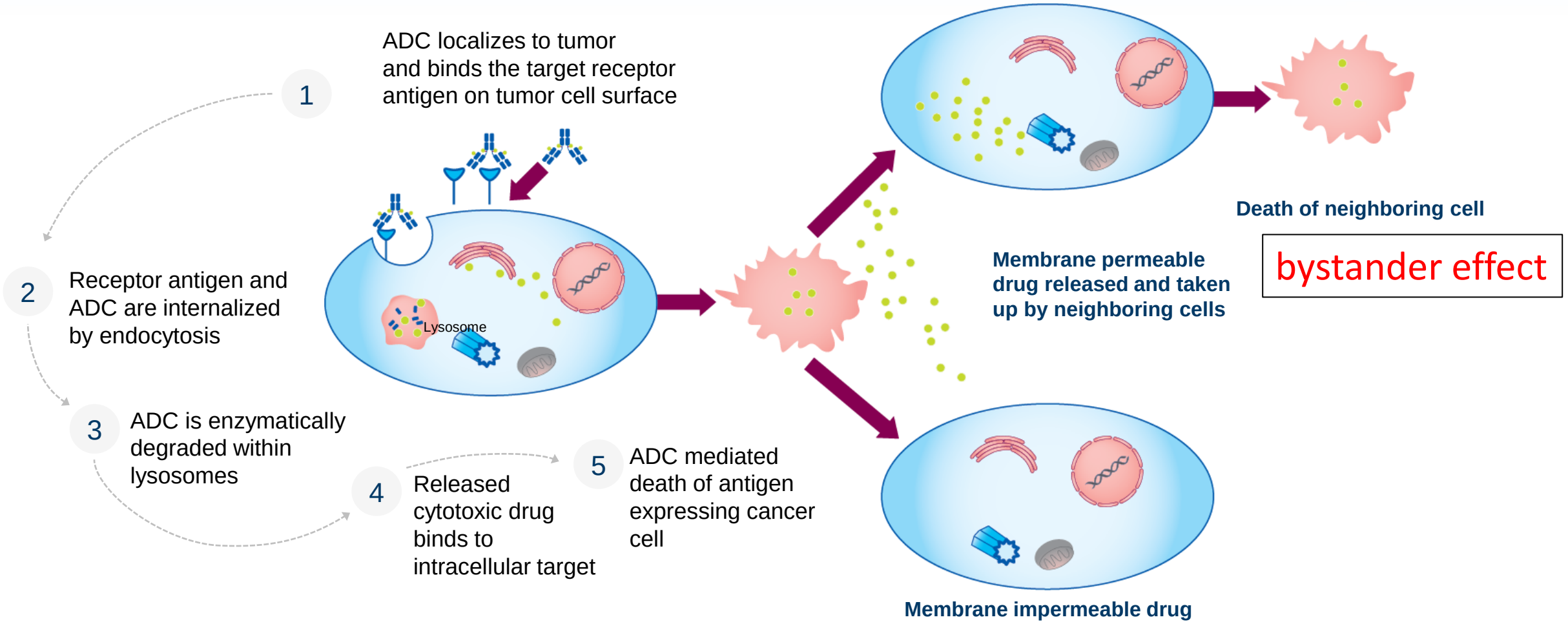
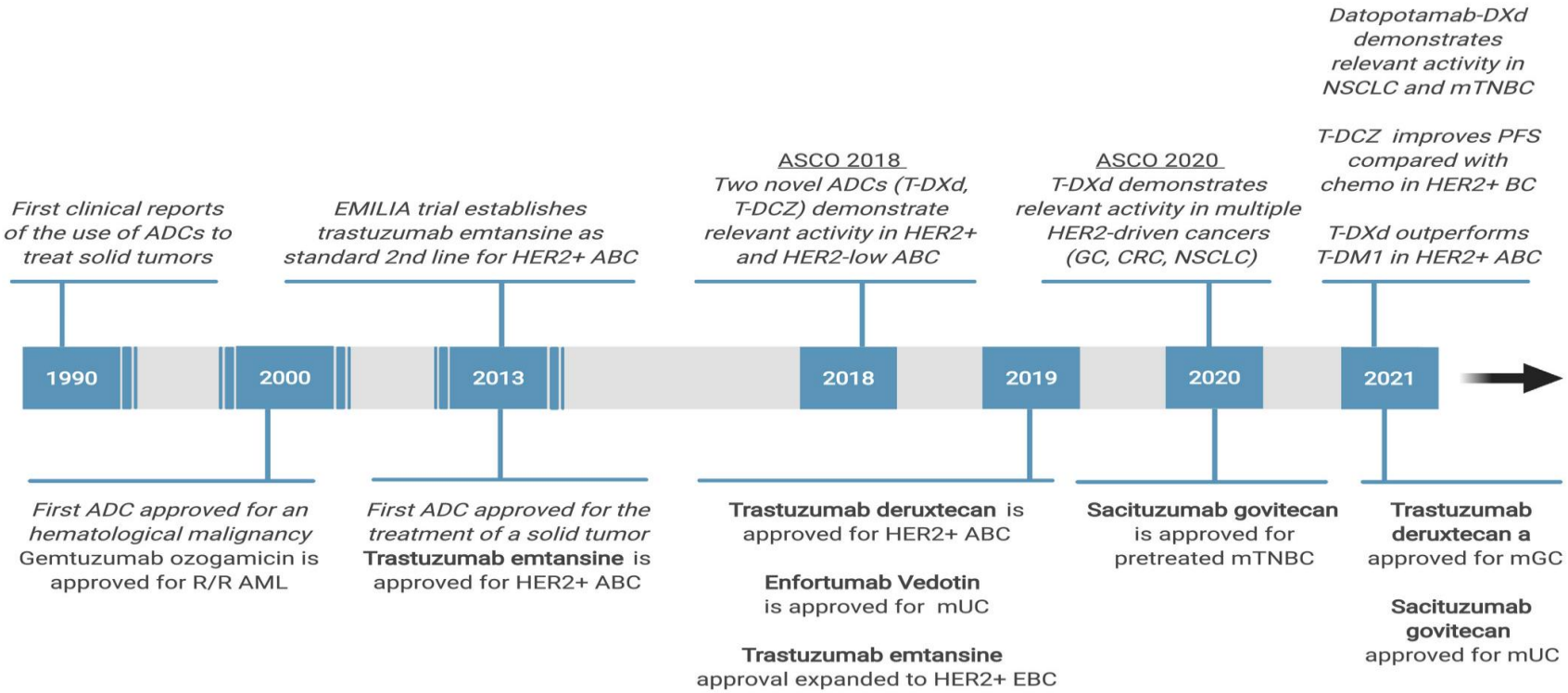
ADCs provide selective delivery of the toxic payload



Trail PA, et al. Pharmacol Ther. 2018;181:126-142

Milestones in the development of ADCs for the treatment of solid tumors



FDA APPROVALS

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Tarantino et al CA A Cancer J Clinicians, First published: 12 November 2021

Overview of ADCs in development for breast cancer

ADC	Target	Antibody	Payload	DAR	Clinical programme	Company
Trastuzumab emtansine (T-DM1, KADCYLA)	HER2	Trastuzumab	DM1	3.5	Approved in mBC with prior therapy, multiple trials in mBC	Roche Holding AG
Trastuzumab deruxtecan (T-DXd, DS-8201, ENHERTU)	HER2	Trastuzumab	DXd	8	Approved in mBC with two prior therapies, multiple trials in mBC	AstraZeneca and Daiichi Sankyo
(vic-)trastuzumab duocarmazine (SYD985)	HER2	Trastuzumab	Seco-DUBA	2.8	Phase 1 BC, Phase 3 mBC	Synthon Biopharmaceuticals BV
Sacitzumab govitecan (TRODELVY)	TROP2	RS7	SN-38	7.6	Approved in TNBC with two prior therapies, multiple trials in mTNBC, mBC	Gilead Sciences, Inc.
Datopotamab deruxtecan (Dato-DXd, DS-1062)	TROP2	Datopotamab	DXd	4	Phase 1 TNBC and HR+/HER2-	AstraZeneca and Daiichi Sankyo
Ladiratuzumab vedotin (SGN-LIV1A)	LIV1	hLIV22	Vc-MMAE	4	Phase 1 mBC, Phase 1/2 mTNBC	Seagen
RC48-ADC	HER2	Hertuzumab	MMAE	4	Phase 1 BC	RemeGen Co
Patritumab deruxtecan (U3-1402)	HER3	Patritumab	DXd	8	Phase 1/2 mBC	Daiichi Sankyo
A166	HER2	Trastuzumab	ND	ND	Phase 1/2 BC	Klus Pharma, Inc.
ALT-P7 (HM2-MMAE)	HER2	HM2	MMAE	ND	Phase 1 mBC	Alteogen, Inc.
ARX788	HER2	ND	Amberstatin269	1.9	Phase 1 mBC	Ambrx Biopharma
DHES0815A (anti-HER2/PBC-MA)	HER2	ND	PBD-MA	ND	Phase 1 mBC	Genentech and Roche Holding AG
MEDI4276	HER2	Trastuzumab scFv	AZI13599185	4	Phase 1 BC	MedImmune, LLC
XMT-1522 (TAK-522)	HER2	HT-18	AF-HPA	12	Phase 1 BC	Mersana Therapeutics, Inc.
AVID100	EGFR	MAB100	DM1	ND	Phase 1/2 TNBC	Formation Biologics, Inc.
CAB-ROR2-ADC	Ror2	CAB	ND	ND	Phase 1/2 TNBC	BioAtla
Anti-CA6-DM4 immunoconjugate (SAR566658)	CA6	DS6	SPDB-DM4	1	Phase 2 TNBC	Sanofi

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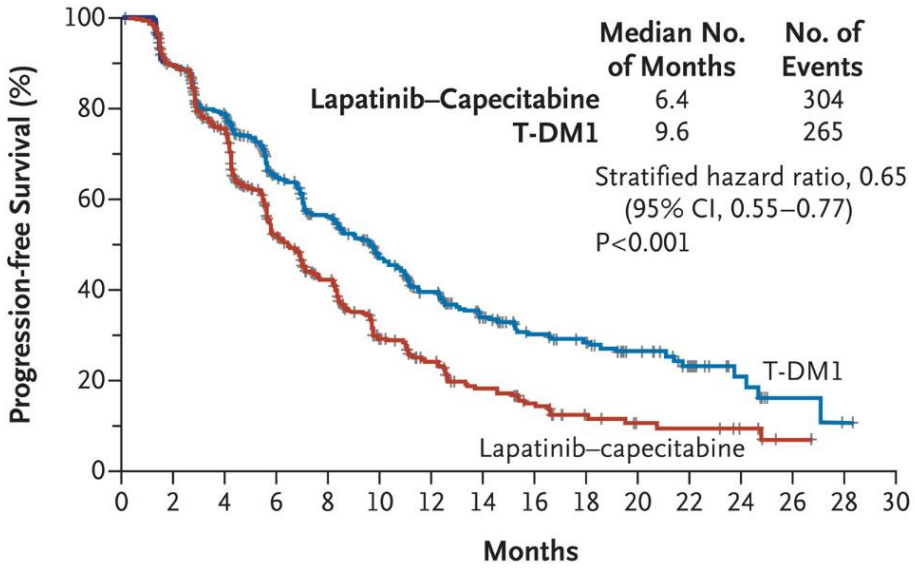
ADC=antibody-drug conjugate; AF-HPA=auristatin F-hydroxypropylamide; DM1=mertansine; DXd=trastuzumab deruxtecan; mBC=metastatic breast cancer; HER2/3=human epidermal growth factor receptor 2/3; MMAE=monomethyl auristatin E; ND=no defined; PBD-MA=pyrrolo benzodiazepine monoamide; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan; (m)TNBC=(metastatic) triple-negative breast cancer; TROP-2=trophoblast cell surface antigen 2.

1. Nagayama A, et al. Ther Adv Med Oncol. 2020; 2. Rinnerthaler G, et al. Int J Mol Sci. 2019 slide coutesy Hope Rugo

EMILIA: led to approval of first-generation ADC, T-DM1, and established its use in 2L HER2-positive mBC

T-DM1 improved OS in patients with previously treated HER2-positive mBC even with crossover treatment

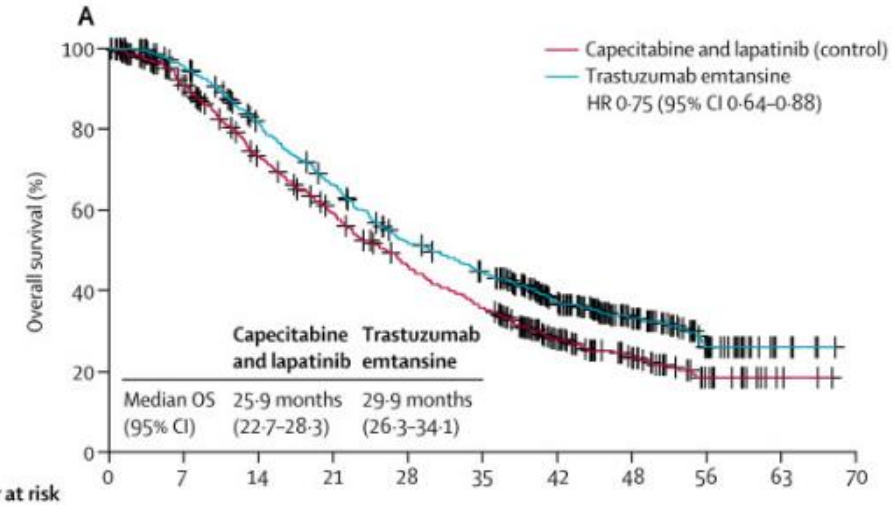
PFS in the ITT population



No. at Risk

Lapatinib–capecitabine	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

OS in the ITT population



Number at risk (number censored)

Capecitabine and lapatinib	496 (0)	418 (35)	326 (47)	258 (53)	195 (58)	153 (58)	82 (99)	48 (122)	19 (144)	3 (160)	0 (163)
Trastuzumab emtansine	495 (0)	451 (21)	374 (34)	302 (36)	231 (42)	194 (47)	127 (85)	68 (133)	23 (169)	5 (187)	0 (191)

2L=second-line; ADC=antibody-drug conjugate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AE=adverse event; CI=confidence interval; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; ITT=intention-to-treat; mBC=metastatic breast cancer; (m)OS=(median) overall survival; mPFS=median progression-free survival; ORR=objective response rate; T-DM1=trastuzumab emtansine.

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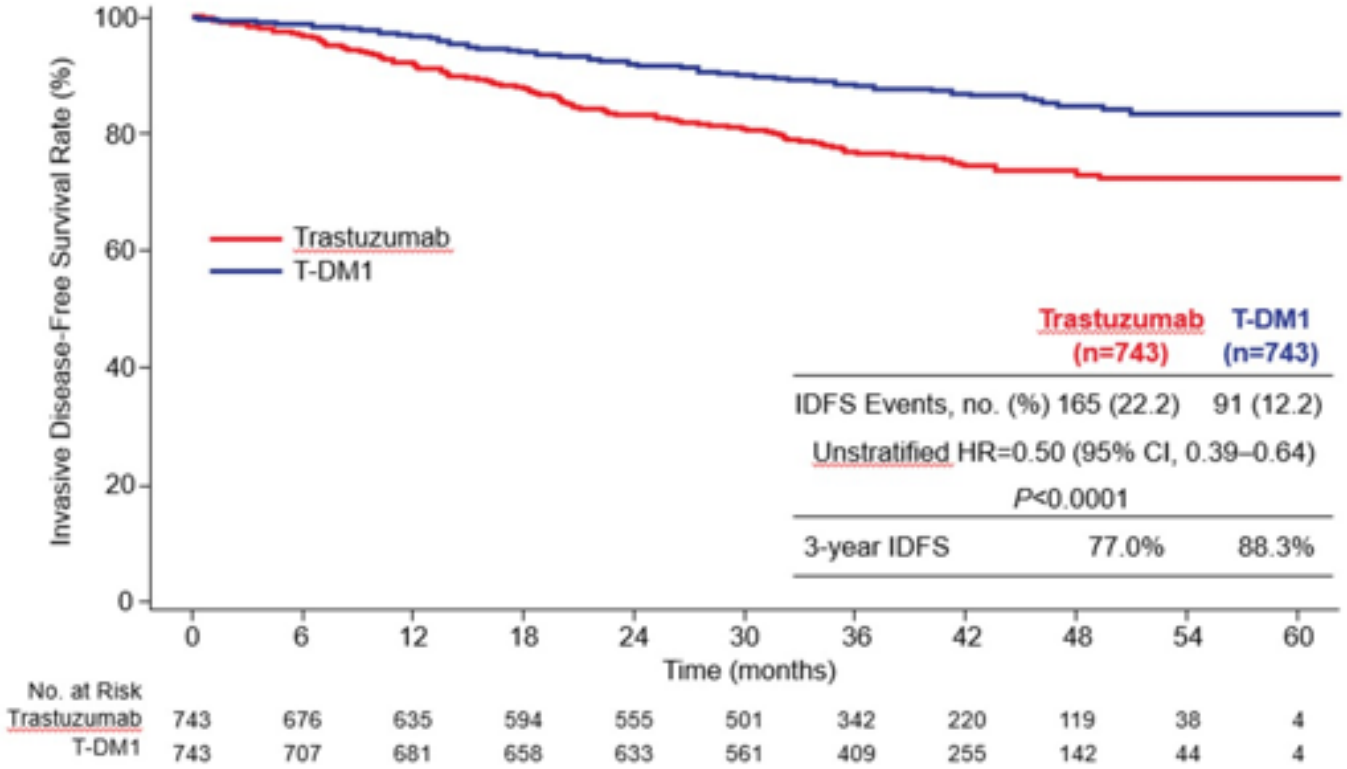
Dieras V, et al. Lancet Oncol. 2017;18(6):732–742; Verma S, et al. N Engl J Med. 2012;367(19):1783–1791.

KATHERINE (NCT01772472): IDFS improvement with T-DM1 compared to Trastuzumab in HER2+ Early Breast Cancer



This led to the approval of adjuvant T-DM1 for HER2+ breast cancer in those patients with residual disease after neoadjuvant taxane based chemotherapy with trastuzumab

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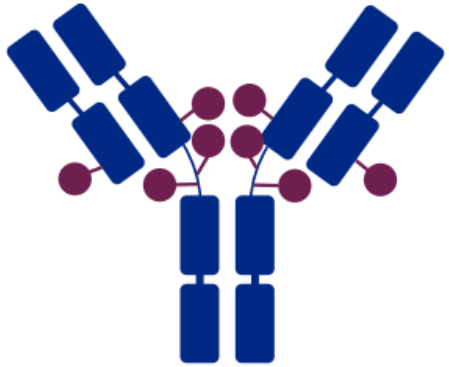
von Minckwitz et al NEJM 2019

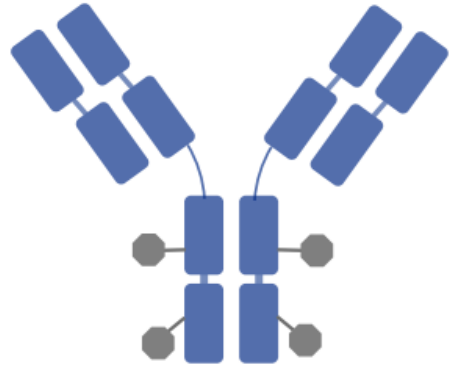
ADC characteristic differences between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



[a]The clinical relevance of these features is under investigation.

ADC, antibody-drug conjugate; MoA, mechanism of action.

1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67:173-185. 2. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-5108. 3. Trail PA, et al. Pharmacol Ther. 2018;181:126-142. 4. Ogitani Y, et al. Cancer Sci. 2016;107:1039-1046. 5. LoRusso PM, et al. Clin Cancer Res. 2011;17:6437-6447.

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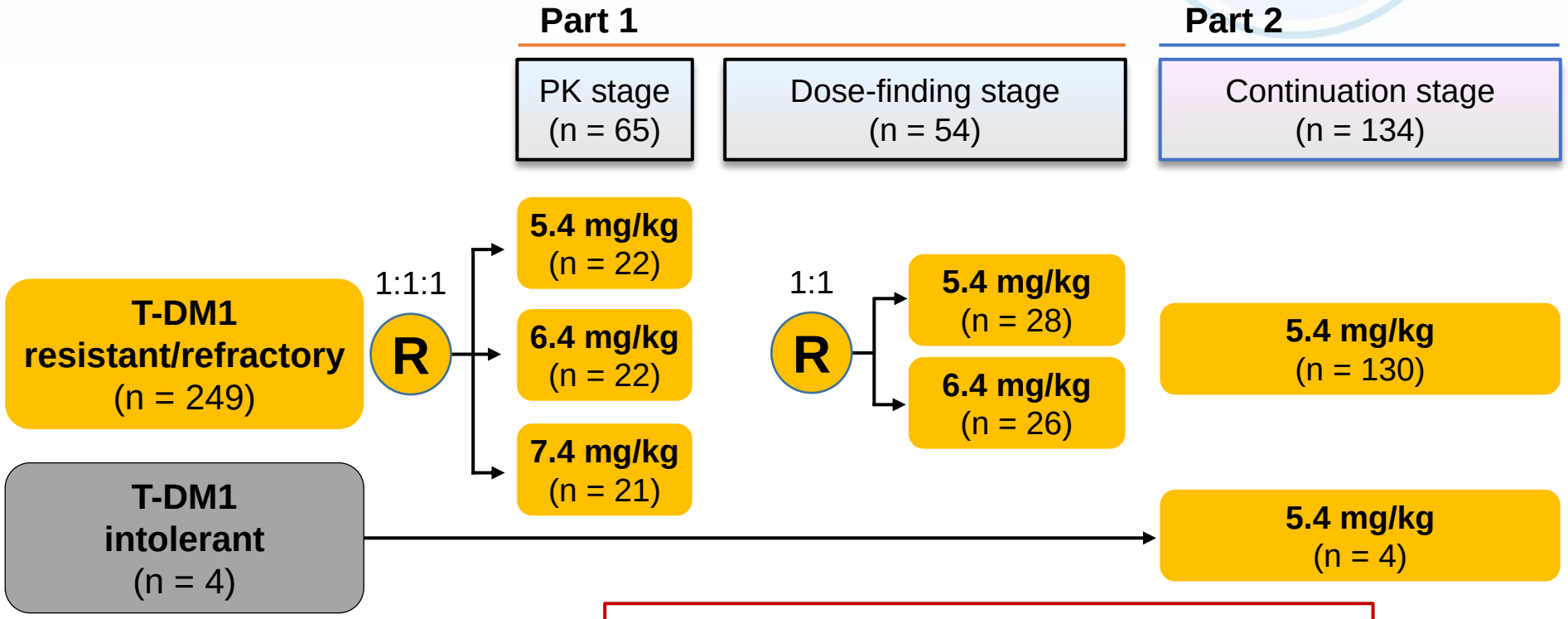
DESTINY-Breast01: Phase 2 Study of T-DXd in *HER2*-Positive MBC

- ≥18 years of age
- Unresectable and/or metastatic BC
- ***HER2* positive** (centrally confirmed on archival tissue)
- **Prior T-DM1**
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed



- **Primary endpoints:** confirmed ORR by independent central imaging facility review per RECIST v1.1

Median lines of therapy = 6 (range: 2-27)

- 100% received prior trastuzumab
- 100% received prior T-DM1
- 66% received prior pertuzumab
- 54% received other HER2 therapies

184 patients

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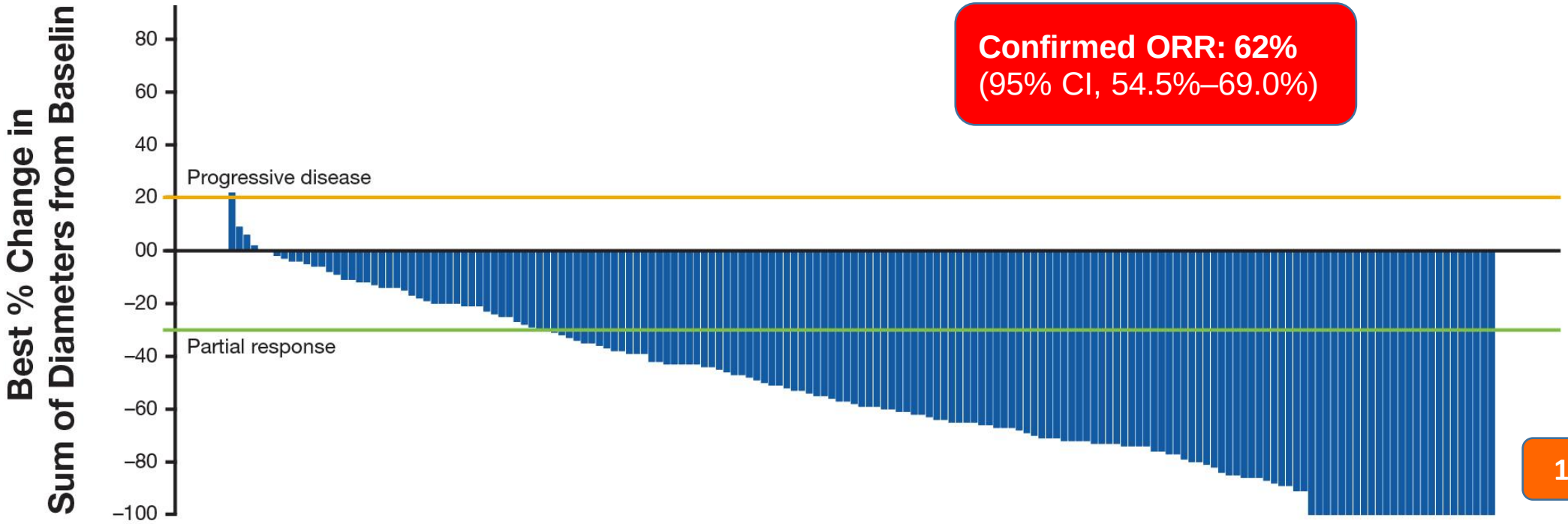
Modi S et al. N Engl J Med. 2020;382:610-621

DESTINY-Breast01: Phase 2 Study of T-DXd in HER2+ MBC (Updated Results With 26.5 mo Follow-Up)

N = 169, median 6 lines of therapy



Confirmed ORR: 62%
(95% CI, 54.5%–69.0%)

13/168 CRs: 7%

Median PFS was 19.4 months (95% CI, 14.1-25.0 months)
Median OS was 29.1 months (95% CI, 24.6-36.1 months)

By independent central review. A total of 169 patients from the enrolled analysis set (N=184) had both baseline and postbaseline target lesion assessments by independent central review and are included in this analysis.

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Saura C, et al. ESMO 2021; Modi S et al, NEJM 2020

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

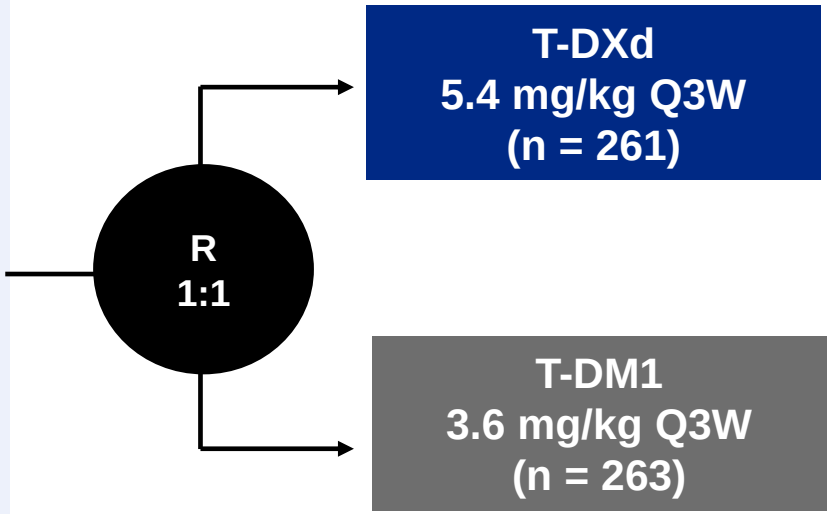
An open-label, multicenter study (NCT03529110)

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



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

Secondary endpoints

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

Prior therapy for MBC:

- 100% received prior trastuzumab
- 60% received prior pertuzumab
- 16% received HER2 TKI

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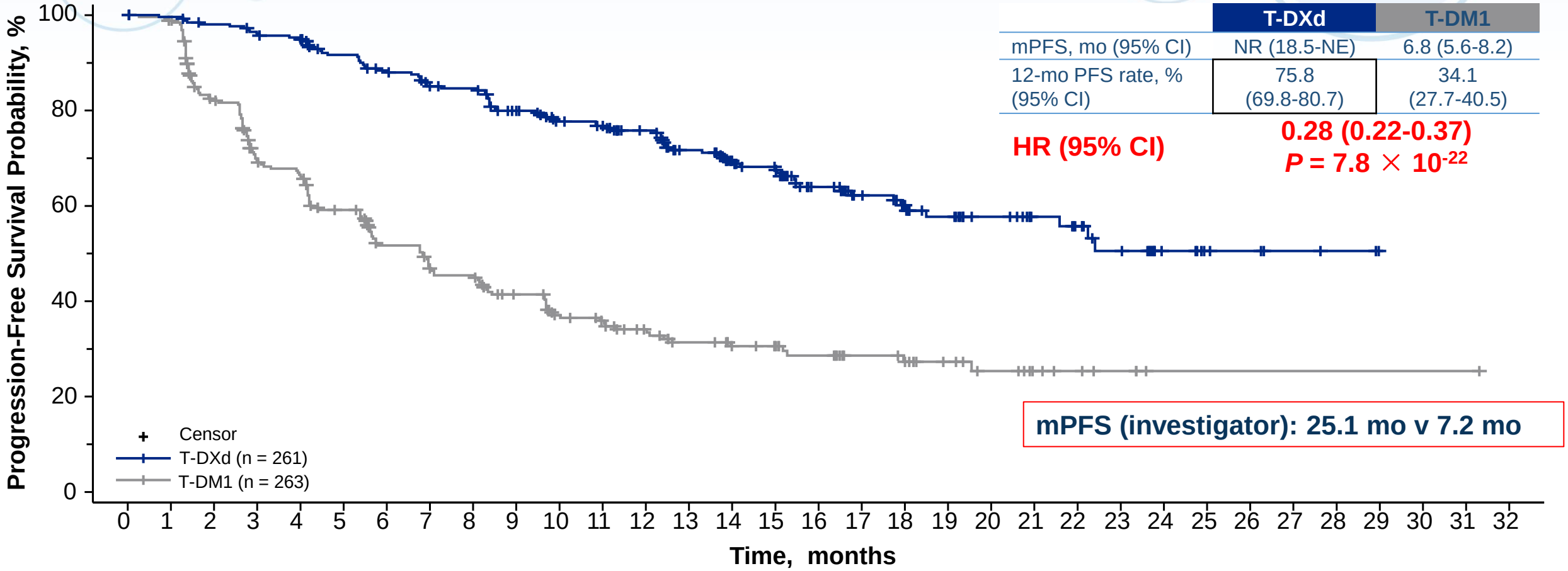
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Cortes, J et al. ESMO 2021

DB03: 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 × 10^{-22}**

mPFS (investigator): 25.1 mo v 7.2 mo

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

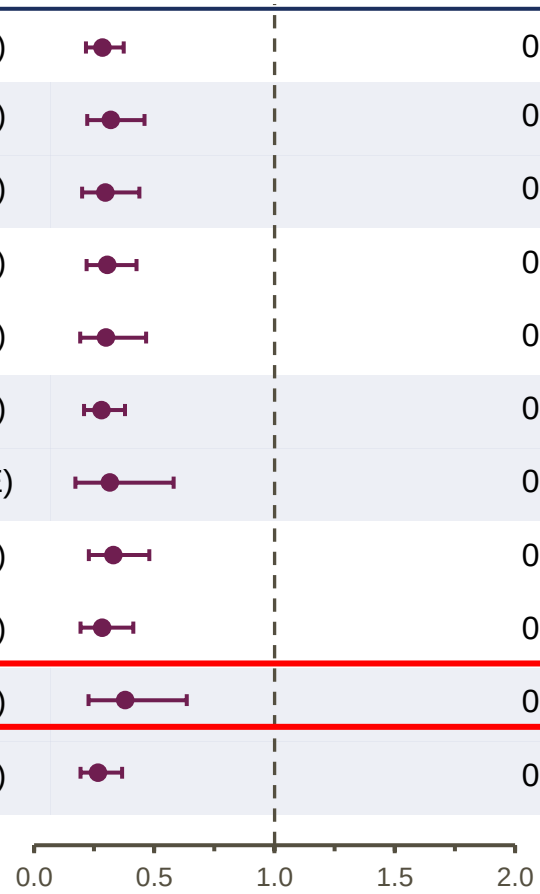
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
HR, hazard ratio; INV, investigator; mo, month; NE, not estimable; NR, not reached.

Cortes, J et al. ESMO 2021

DB03: Primary Endpoint: PFS by BICR

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)

[a]Rapid progressors on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.



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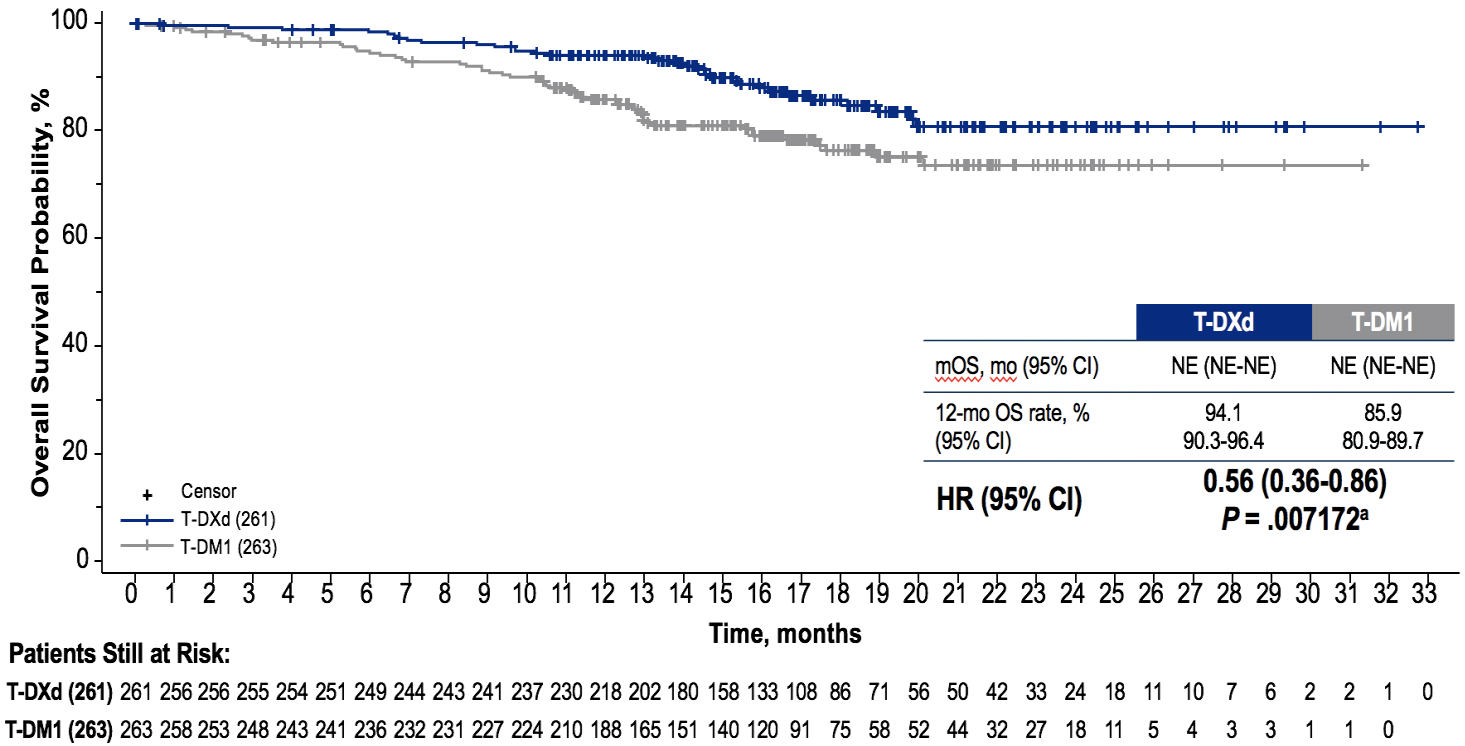
Cortes, J et al. ESMO 2021

DB03 Secondary Endpoints: Overall Survival and Response Rate



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	**0.56 (0.36-0.86)** ***P* = .007172**[a]	

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

CLEOPATRA, ORR= 80% CR= 5.5%

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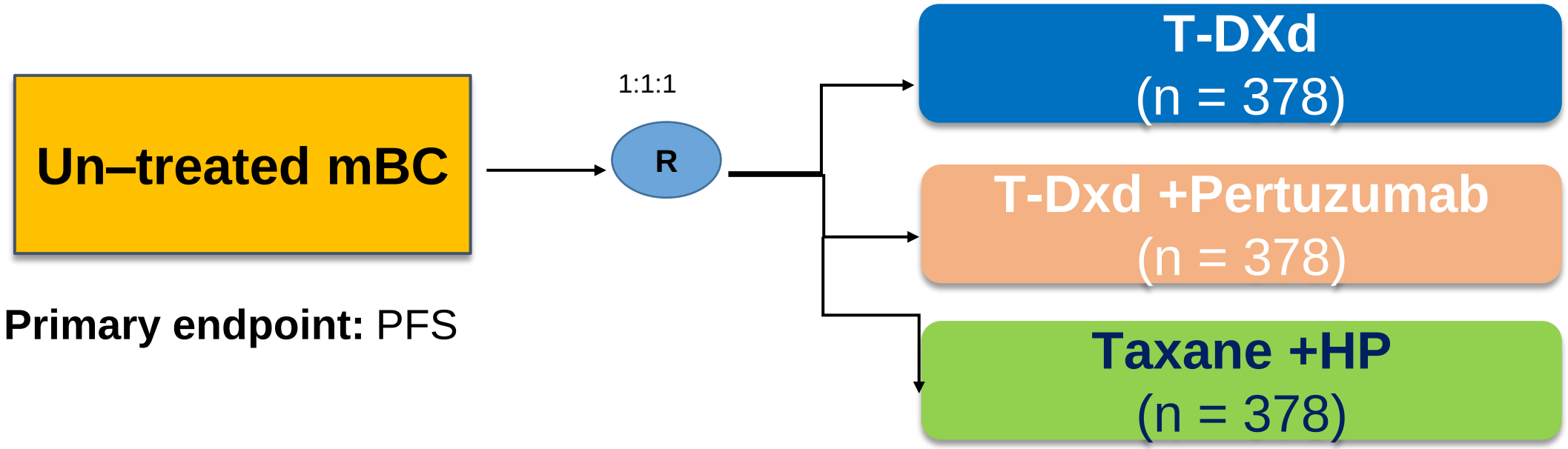
Cortes, J et al. ESMO 2021; Baselga J et al, NEJM 2012

Next Steps with TD-Xd

Destiny Breast-09 (NCT04784715): 1st Line Trial in HER2+ MBC



Primary endpoint: PFS

DESTINY Breast05: TD-Xd vs T-DM1 (NCT03742102)

TUXEDO-1 Phase 2 Trial of T-DXd for HER2+ BCBM

HER2+ MBC with newly diagnosed or progressive brain metastases N=15

→ **Trastuzumab Deruxtecan 5.4mg/kg IV q3wk**

Primary endpoint: CNS Response Rate

- Simon 2 Stage Design
- Stage 1: Intracranial Response in 5/6 patients **(ICRR: 83.3%)**
- Stage 2 is fully enrolled

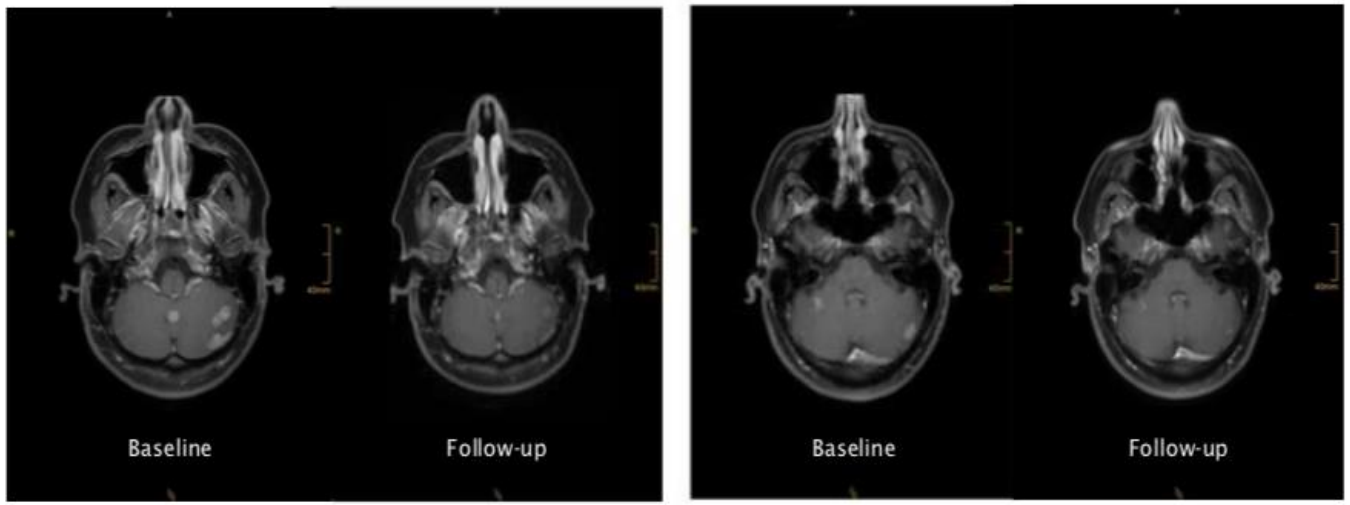


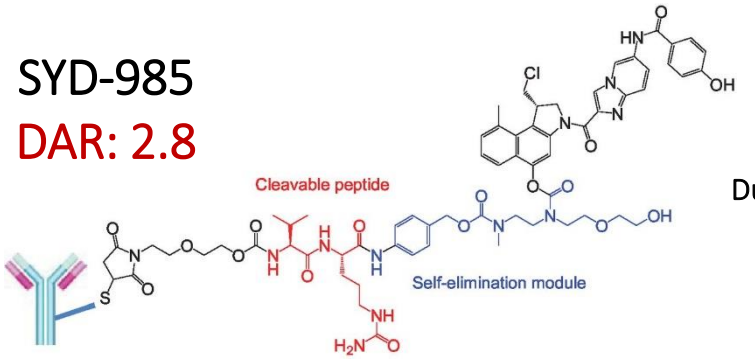
Figure 2 – Intracerebral response on cerebral MRI

A 37-year-old woman with bilateral cerebellar breast cancer brain metastases. T1-weighted contrast enhanced cerebral magnetic resonance images (MRI) at baseline (left) and follow-up (right) after 10 applications of therapy with T-DXd showing an ongoing partial response according to RANO criteria.

Bartsch R et al, ESMO 2021

TULIP (NCT03262935) compared the ≥3L-treatment of trastuzumab duocarmazine with physician's choice in patients with HER2-positive BC

SYD-985
DAR: 2.8



Randomised, two-arm, Phase III, open-label multicentre study

Inclusion criteria
- HER2-positive status
- Unresectable, locally advanced and/or mBC
- Progression during or after at least two HER2-targeting treatment regimens for *or* after T-DM1
- ECOG PS 0–2

R 2:1 (N=436)

Trastuzumab duocarmazine (IV Q3W)

Physician's choice: Lapatinib/capecitabine, trastuzumab/capecitabine, trastuzumab/vinorelbine, or trastuzumab/eribulin

Until PD, toxicity, or withdrawal

Primary endpoint
- PFS (BICR per RECIST 1.1)

Secondary endpoints
- OS
- ORR (BICR per RECIST 1.1)
- PFS (INV)
- PROs for HRQoL
- Safety and tolerability

- 3L=third line; BICR=blinded independent central review; ECOG=Eastern Cooperative Oncology Group; HER2=human epidermal growth factor receptor 2; HRQoL=health-related quality of life; INV=investigator assessment; IV=intravenous; mBC=metastatic breast cancer; ORR=objective response rate; OS=overall survival; PD, progressive disease; PFS=progression free survival; PRO=patient reported outcome; PS=performance status; Q3W=every 3 weeks; R=randomisation; RECIST, response evaluation in solid tumours. T-DM1=trastuzumab emtansine.

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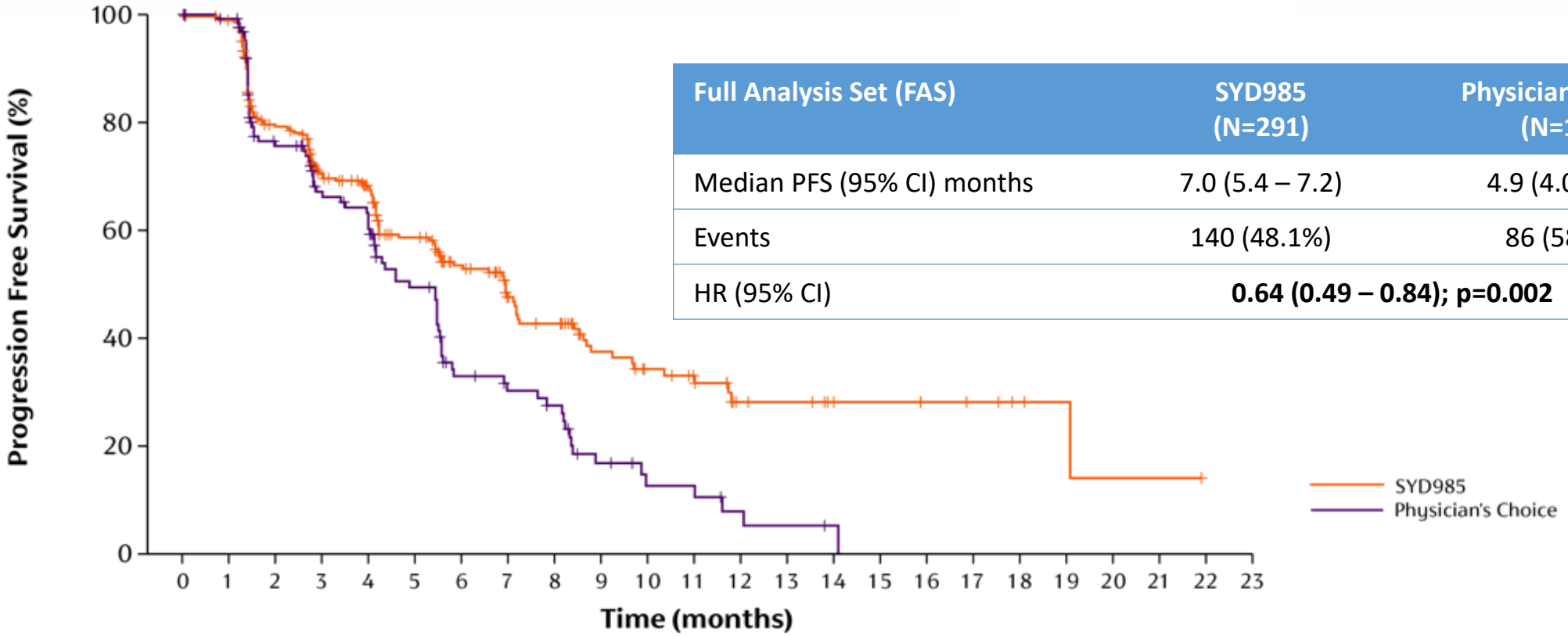
Dokter W, et al. *Mol Cancer Ther.* 2014;13(11):2618–2629

TULIP – Centrally Reviewed PFS



Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	**0.64 (0.49 – 0.84); p=0.002**	

No. Patients at Risk

SYD985	291	278	208	167	150	109	83	59	51	35	28	24	13	12	9	8	6	5	3	2	1	1	0
Physician's Choice	146	125	86	69	64	44	26	22	19	10	6	6	3	2	1	0							

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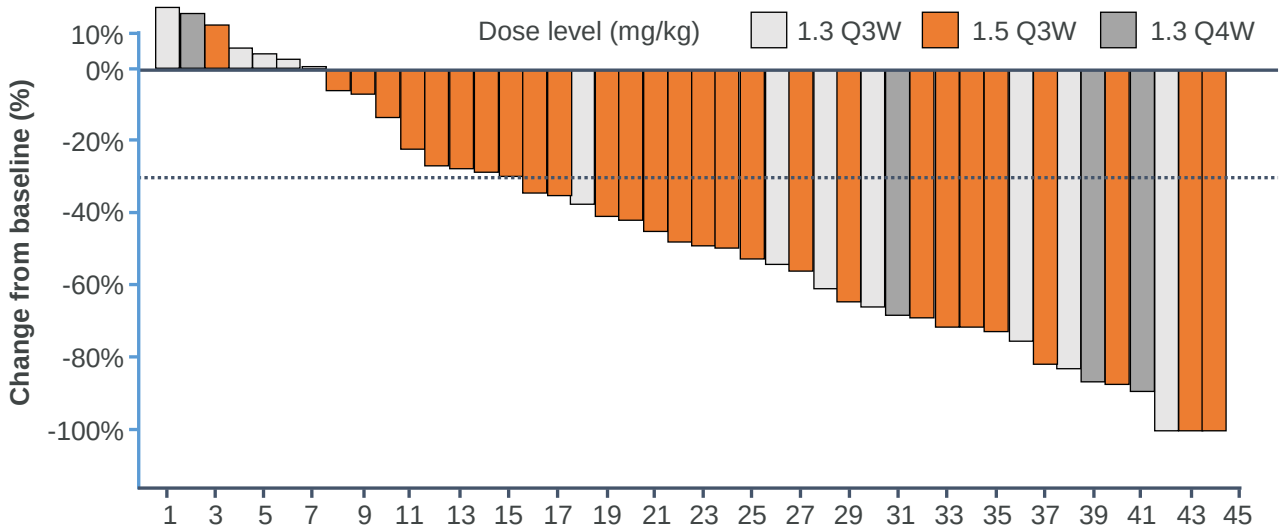
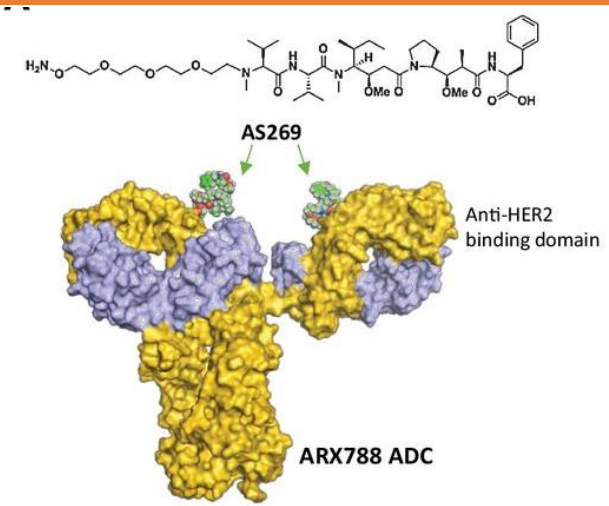
Saura et al, ESMO 2021

Other Novel ADC: ARX788

Phase I: ACE-Breast-01
ARX788

Dose-dependent antitumour activity of ARX788 in HER2-positive solid tumours





ARX788
DAR: 1.9

	ACE-Breast-01 1.5 mg/kg (N=19)	ACE-PanTumour-01 1.5 mg/kg (N=3)
Lines of therapy, median	6	–
ORR, %	74	67
DCR, %	100	100
mDoR / mPFS	NR	

ADC=antibody-drug conjugate; AE=adverse event; DCR=disease control rate; HER2=human epidermal growth factor receptor 2; mDoR=median duration of response; mPFS=median progression-free survival; NR=not reached; ORR=objective response rate; PK=pharmacokinetic; Q3W=every 3 weeks; Q4W=every 4 weeks; SAE=serious adverse event; T-DM1=trastuzumab emtansine; WBC=white blood cell.

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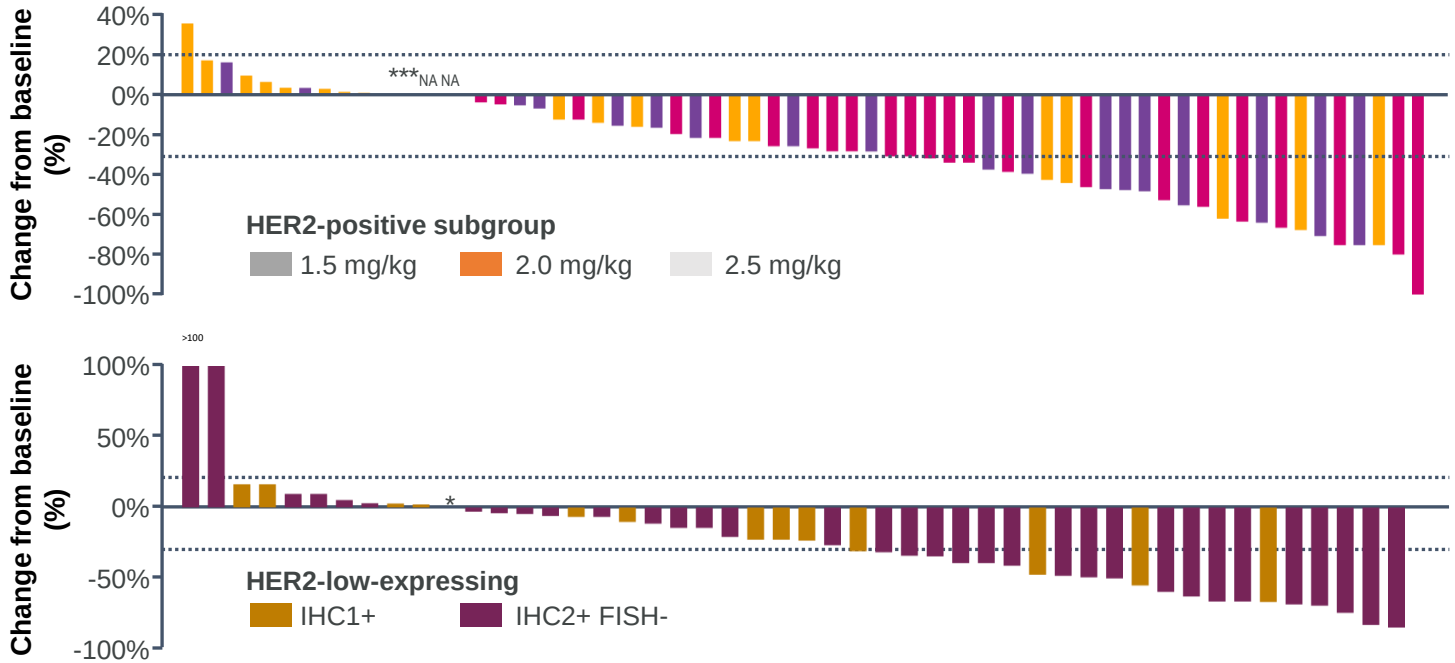
Skidmore et al Mol Cancer Therapeutics 2020; Hurvitz S, et al. Presented at ASCO 2021. Abstract #1038

Other Novel ADC: RC48

Phase Ib: NCT03052634
RC48-ADC

Best percentage change from baseline of target lesion



RC-48
Antibody: Hertuzumab
Payload: MMAE
DAR: 4

Clinical activity in 2.0 mg/kg cohorts	HER2-positive BC (2.0 mg/kg) (N=70)	HER2-low BC (2.0 mg/kg) (N=48)
ORR, n (%)	23 (32.9)	19 (39.6)
DCR, n (%)	60 (85.7)	43 (89.6)
mPFS, months (95% CI)	5.5 (4.6–6.5)	5.7 (4.1–8.3)

- *percent change from baseline of target lesion is 0%
- ADC=antibody-drug conjugate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BC=breast cancer; CI=confidence interval; DCR=disease control rate; γ–GT=gamma-glutamyl transferase; HER2=human epidermal growth factor receptor 2; mPFS=median progression-free surviva; ORR=objective response rate; T-DM1=trastuzumab emtansine; TRAE=treatment-related adverse event.

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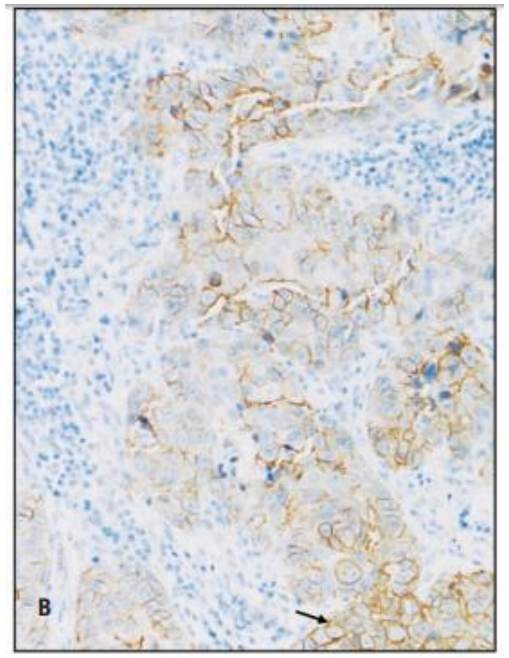
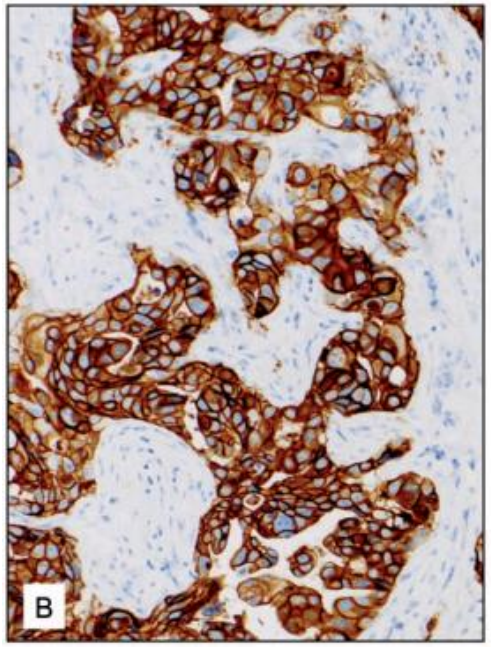
Wang J et al. Presented at ASCO 2021, Chicago US. Abstract #1022

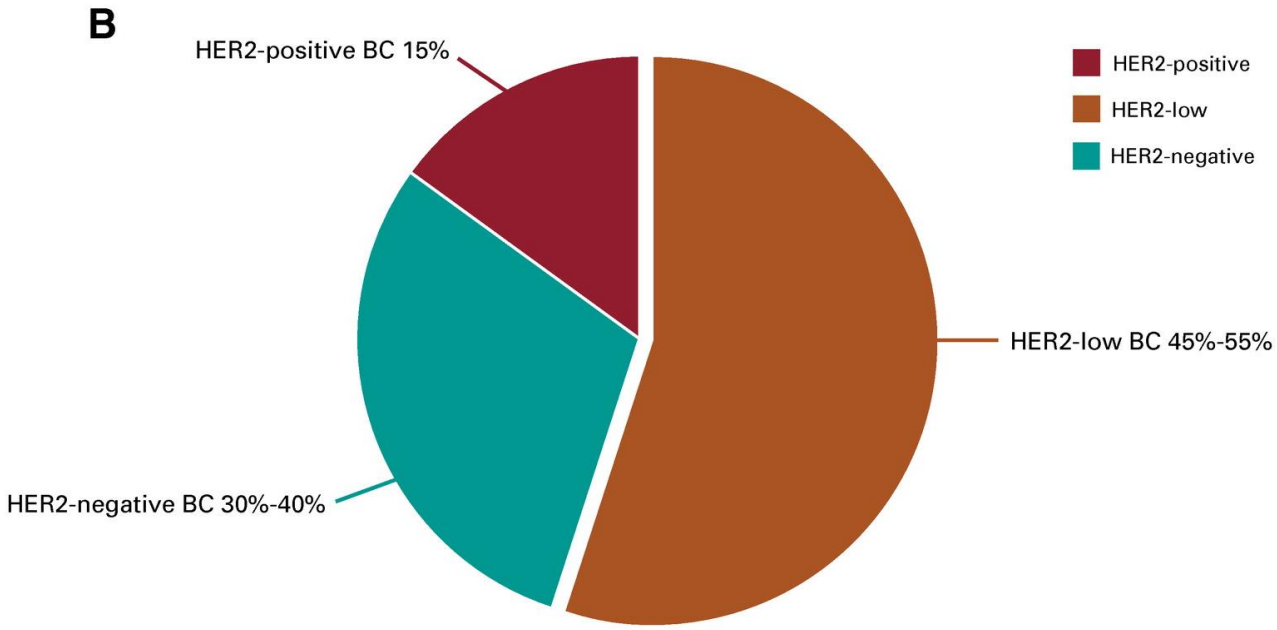
HER2-Low and HER2-Positive Breast Cancer

HER2 2+ by IHC



HER2 3+ by IHC



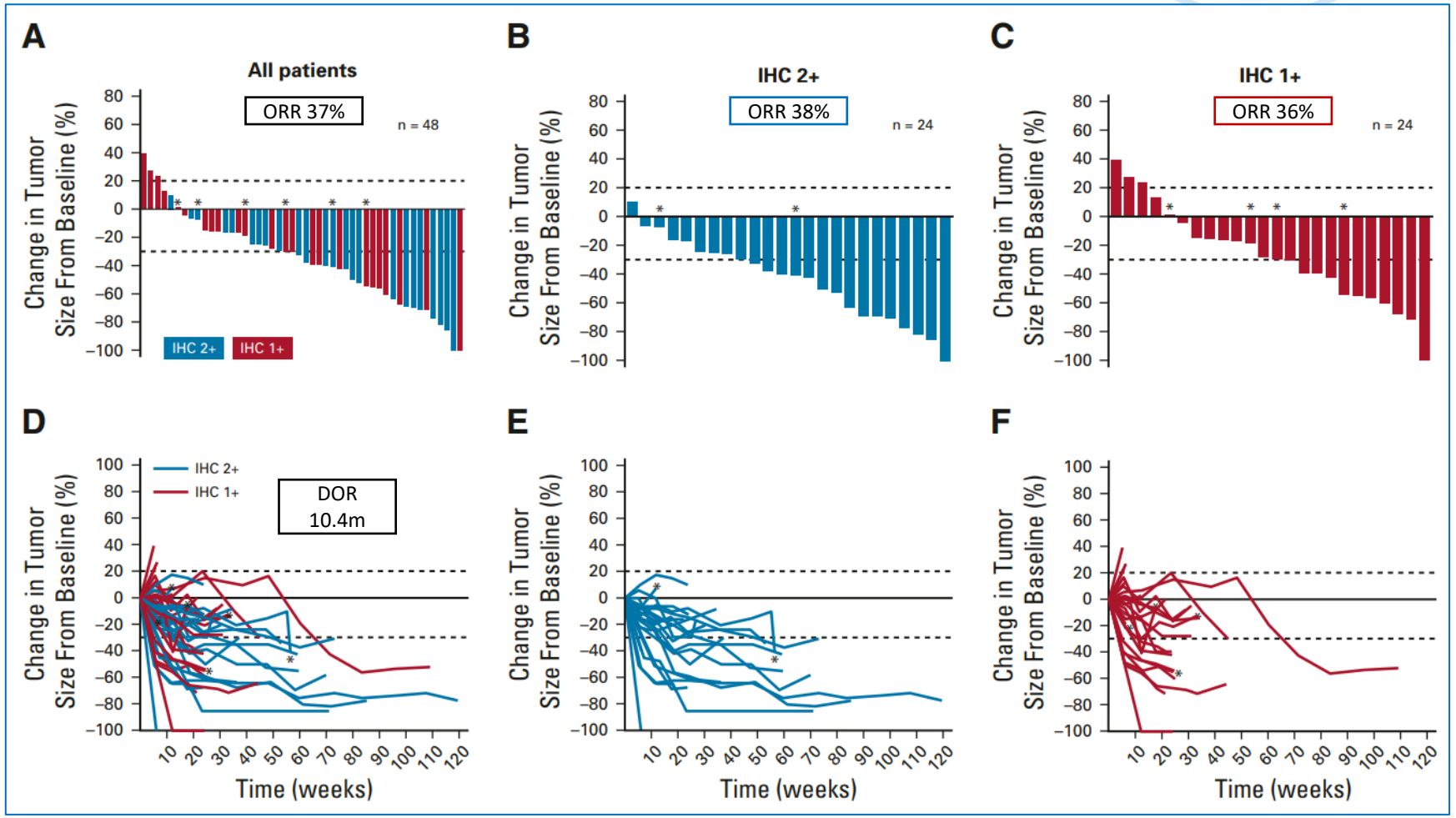


Hicks D, Schiffhauser L. Lab Med. 2011; Tarantino P et al. J Clin Oncol 2020

Trastuzumab Deruxtecan (T-DXd): Activity in HER2 low Breast Cancer

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	HER2-Low Breast Cancer N = 54
Median age (range), years	56.6 (33-75)
Country	
Japan	27 (50.0)
United States	27 (50.0)
ECOG performance status	
0	36 (66.7)
1	18 (33.3)
Median time from initial diagnosis (range), months[a]	105.0 (13.0-290.3)
Median No. of prior cancer regimens (range)	7.5 (2-16)
≥ 5 prior cancer regimens	45 (83.3)
CDK4/6 inhibitor	16 (29.6)
HER2-targeted therapy	10 (18.5)
Trastuzumab	10 (18.5)
Pertuzumab	7 (13.0)
T-DM1	5 (9.3)
Other	1 (1.9)
Previous cancer surgery	48 (88.9)
HER2 expression (IHC) by local assessment[b]	
2+ (ISH−)	26 (48.1)
1+	28 (51.9)
0	0
Hormone receptor status	
Positive	47 (87.0)
Negative	7 (13.0)
Sites of metastases at study entry	
Bone	34 (63.0)
Liver	29 (53.7)
Lung	14 (25.9)
Brain	5 (9.3)
Time from archival tissue collection to study enrollment, months[c]	
Mean ± SD	44.8 ± 44.3
Median (min, max)	23.2 (0.0, 157.7)



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Modi S, et al - J Clin Oncol. 2020

Ongoing trials with Trastuzumab Deruxtecan in HR+/HER2- breast cancer

- DESTINY-Breast04 (NCT03734029):
  -Trastuzumab Deruxtecan vs TPC in HER2-low MBC

- DESTINY-Breast06 (NCT04494425):
  -Trastuzumab Deruxtecan vs TPC in ER+/HER2-low MBC after CDK4/6i (chemo-naïve for MBC)

- DESTINY-Breast08 (NCT04556773):
  -Phase 1 combinations with endocrine therapy (anastrozole, fulvestrant), targeted therapies, immunotherapy and chemotherapy

- Neoadjuvant phase 2 study (NCT04553770):
  -Trastuzumab Deruxtecan + Anastrozole in HR+/HER2-low early breast cancer

Phase 2 DAISY Study: Trastuzumab Deruxtecan (T-DXd) in HER2 Over-expressing, Low-expressing, and Non-expressing Breast Cancer

Sponsor	UNICANCER and Daiichi Sankyo Europe
Study Objective	To evaluate antitumor activity of monotherapy T-DXd in HER2 over-expressing, low-expressing, and non-expressing breast cancer
Study Design	Phase 2, multicenter, open-label, single-arm, multicohort
Study Completion	Sept 2021 (primary completion); March 2025 (study completion)

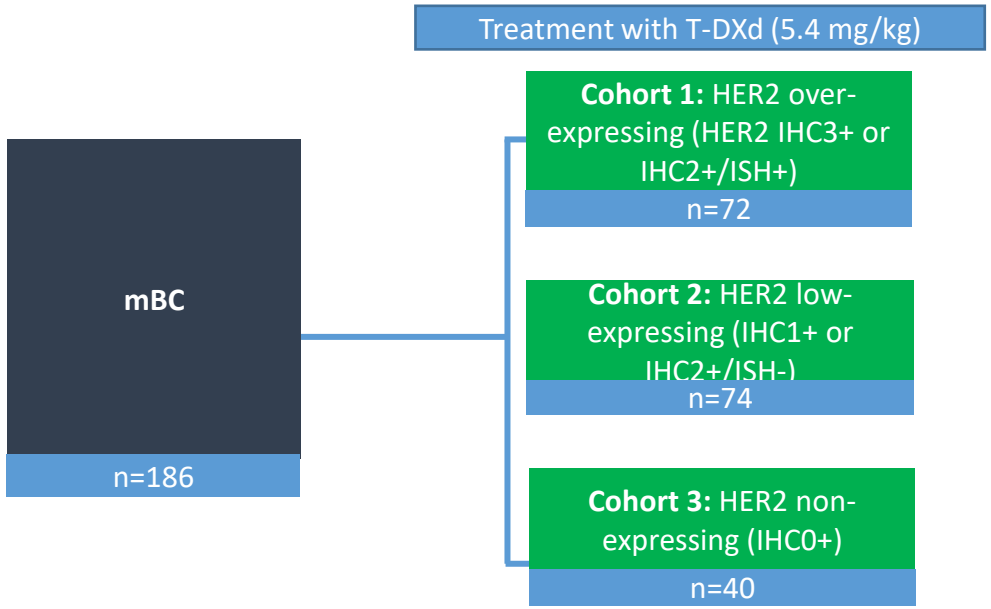
DAISY Trial[1,2]

Key Inclusion Criteria

- HER2 over-expressing (IHC3+/ISH+, IHC2+/ISH+), low-expressing (IHC2+/ISH-, IHC1+) or non-expressing (IHC0+)
- Not amenable to other therapy after ≥1L CT
- Prior treatment with anthracyclines & taxanes
- [HER2 over-expressing]: treated with trastuzumab and/or TDM-1
- [HER2-/HR+]: resistant to ET and CDK4/6is; treated with capecitabine

Key Exclusion Criteria

- Prior treatment with topoisomerase 1 inhibitor



Endpoints

- **Primary**: confirmed best objective response (BOR) in each cohort

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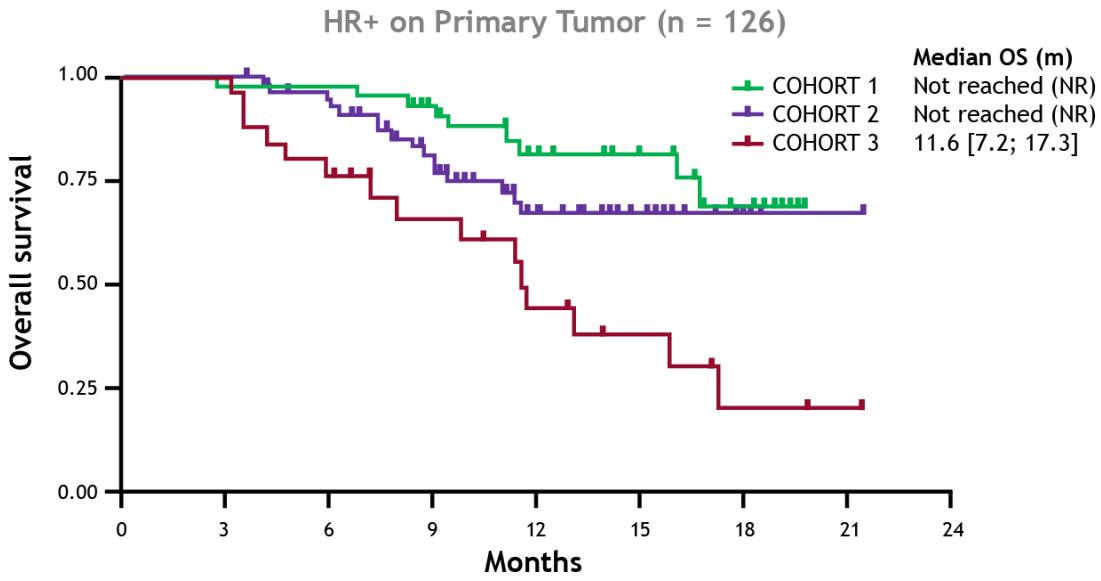
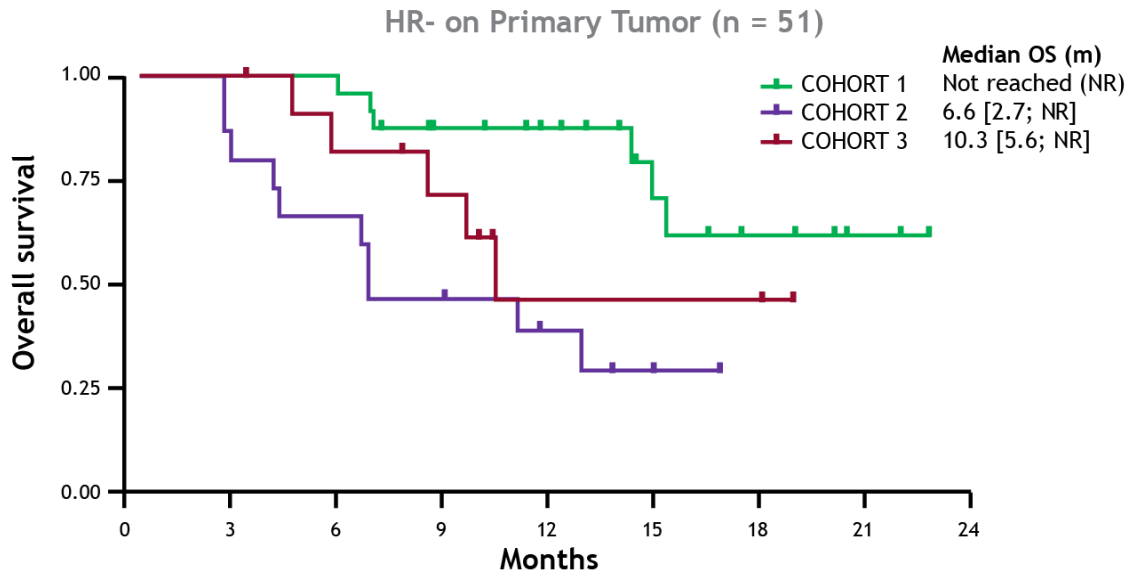
DAISY: Activity of T-DXd per Level of HR or HER2 Expression

Overall Survival





- T-DXd showed comparable efficacy in both HER2-low and HER2- Phase 2 DAISY cohorts

	Cohort 1 (HER2 over-expressing)	Cohort 2 (HER2 low-expressing)	Cohort 3 (HER2 non-detected)
BOR confirmed, %	71	38	30
Median DoR, mo	9.7	7.6	6.8
Median PFS, mo	11.1	6.7	4.2

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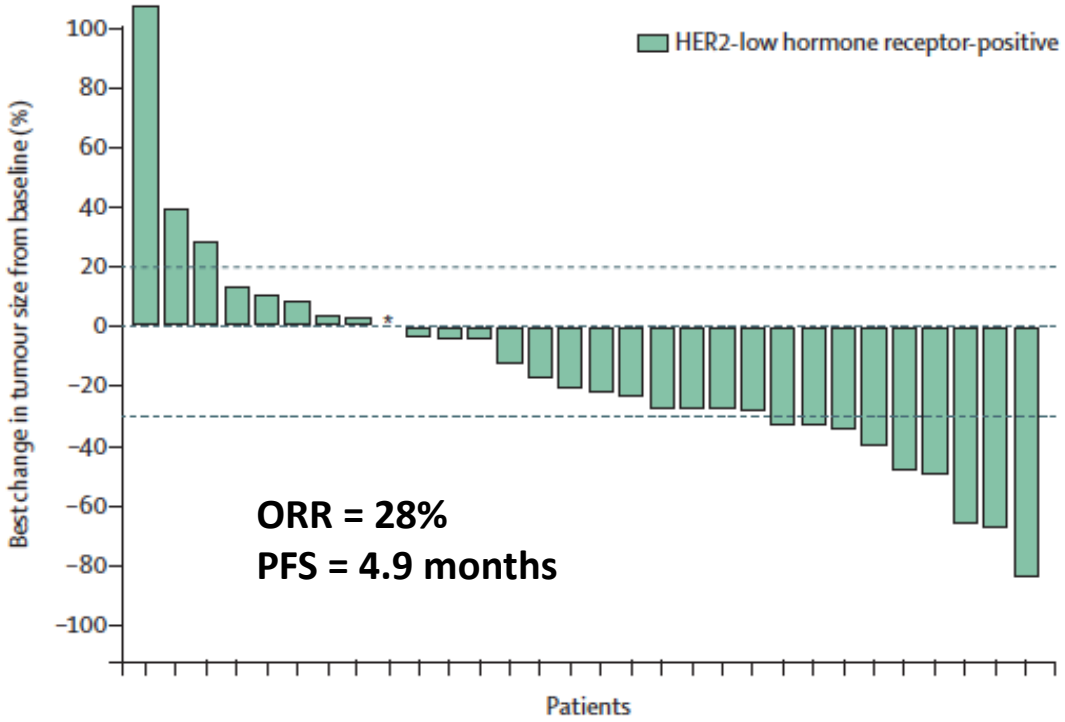
1. https://clinicaltrials.gov/ct2/show/NCT04132960. 2. Dieras V, et al. Presented at SABCS 2021. PD8-02.

Other agents targeting low HER2 expression in HR+/HER2- MBC

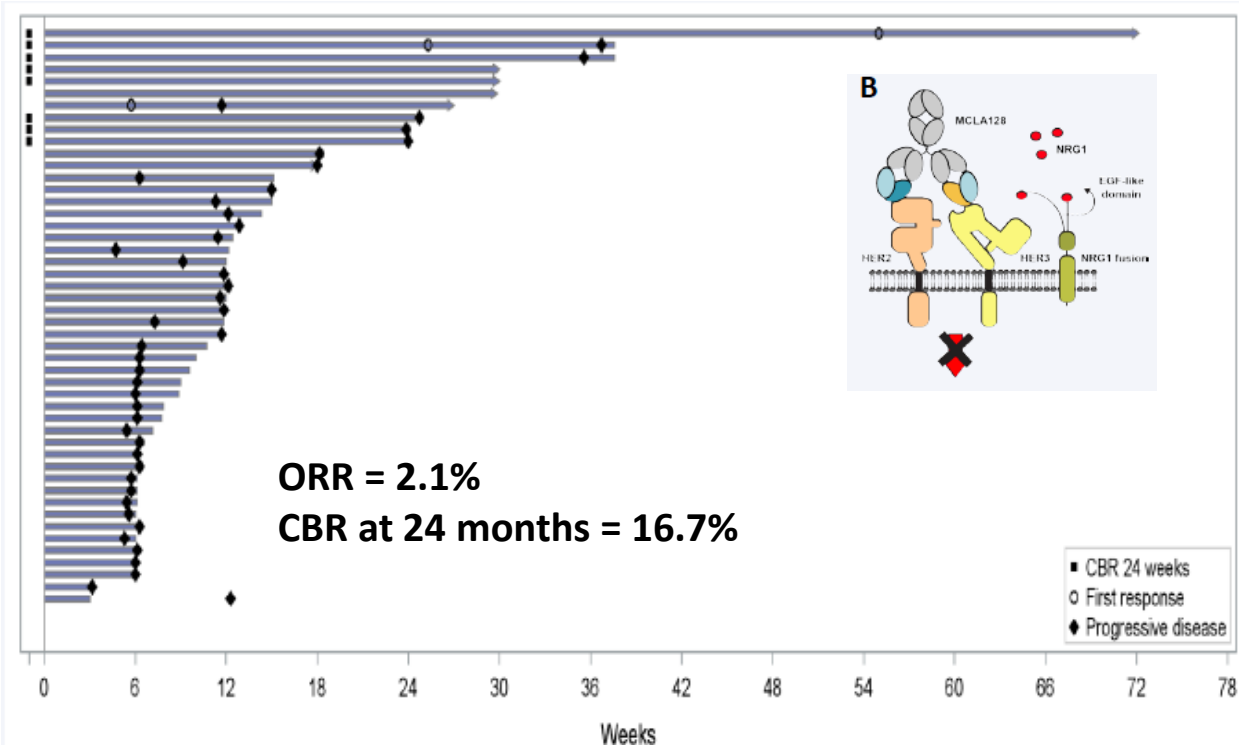
Trastuzumab Duocarmazine (SYD985)

(HER2 ADC)



Zenocotuzumab (MCLA-128) +ET

(HER2/HER3 bispecific antibody)



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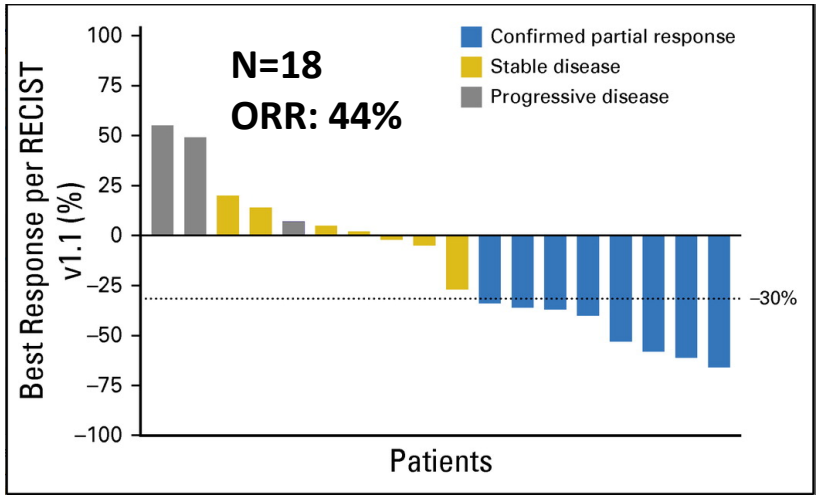
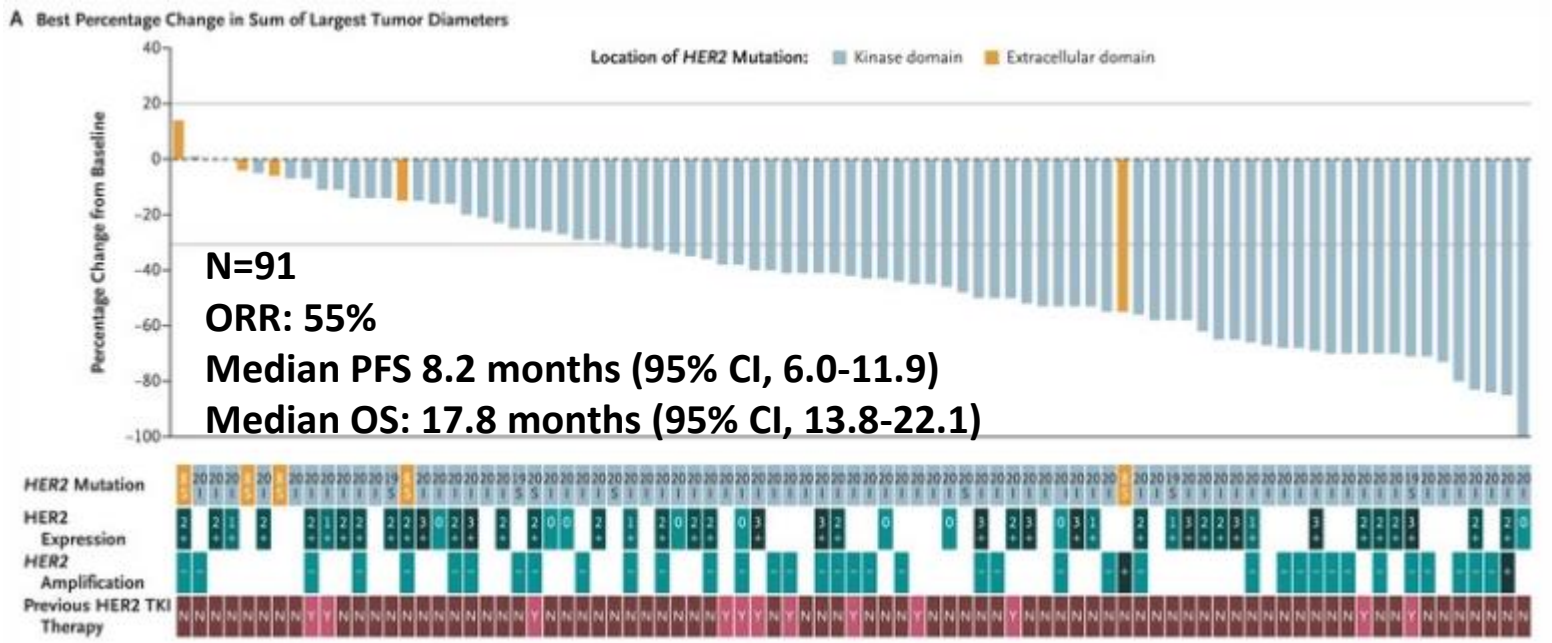
Banerji U et al. Lancet Oncol 2019; Pistilli B et al. SABCS 2020

HER2 ADCs in *ERBB2* mutant tumors

T-DM1 in *HER2* mutant Lung cancer



TD-Xd in *HER2* mutant Lung cancer



TD-Xd is being evaluated in *ERBB2* mutant solid tumors (DESTINY-PanTumor01; NCT04639219)

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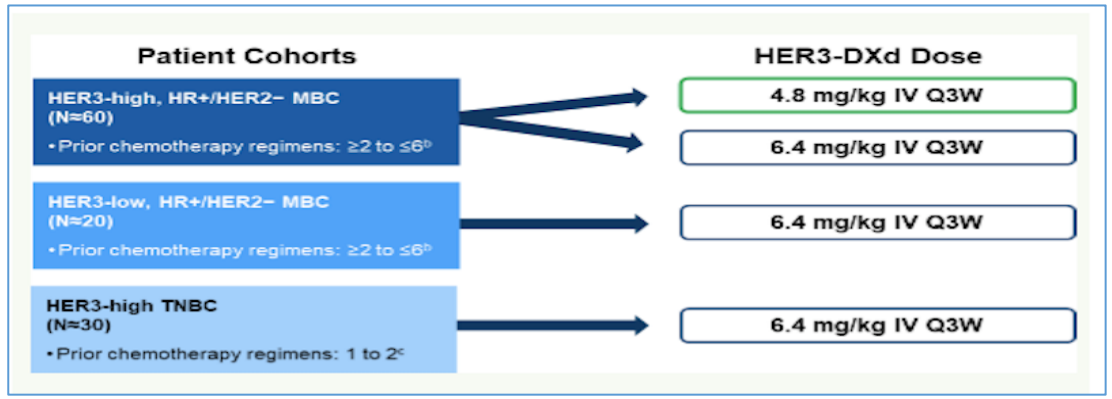
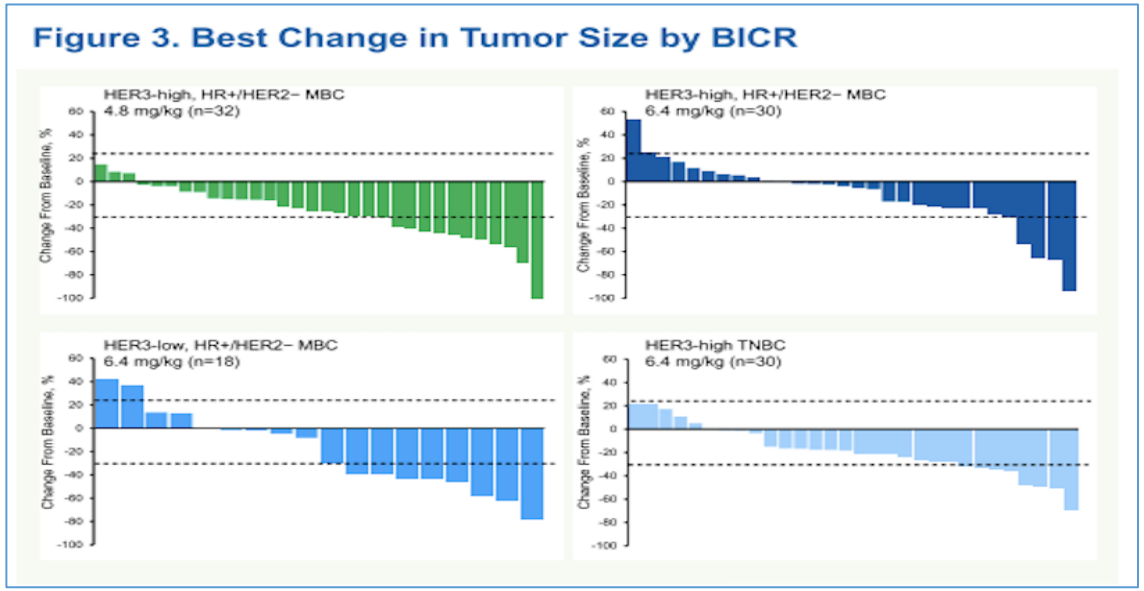
Li et al JCO 2018; Li BT et al. NEJM 2022

Patritumab Deruxtecan (U3-1402): HER3-targeting ADC

HER3 is overexpressed 30% of MBC and associated with worse prognosis



HER3 high: >75% expression,
HER3 low 25-75% expression



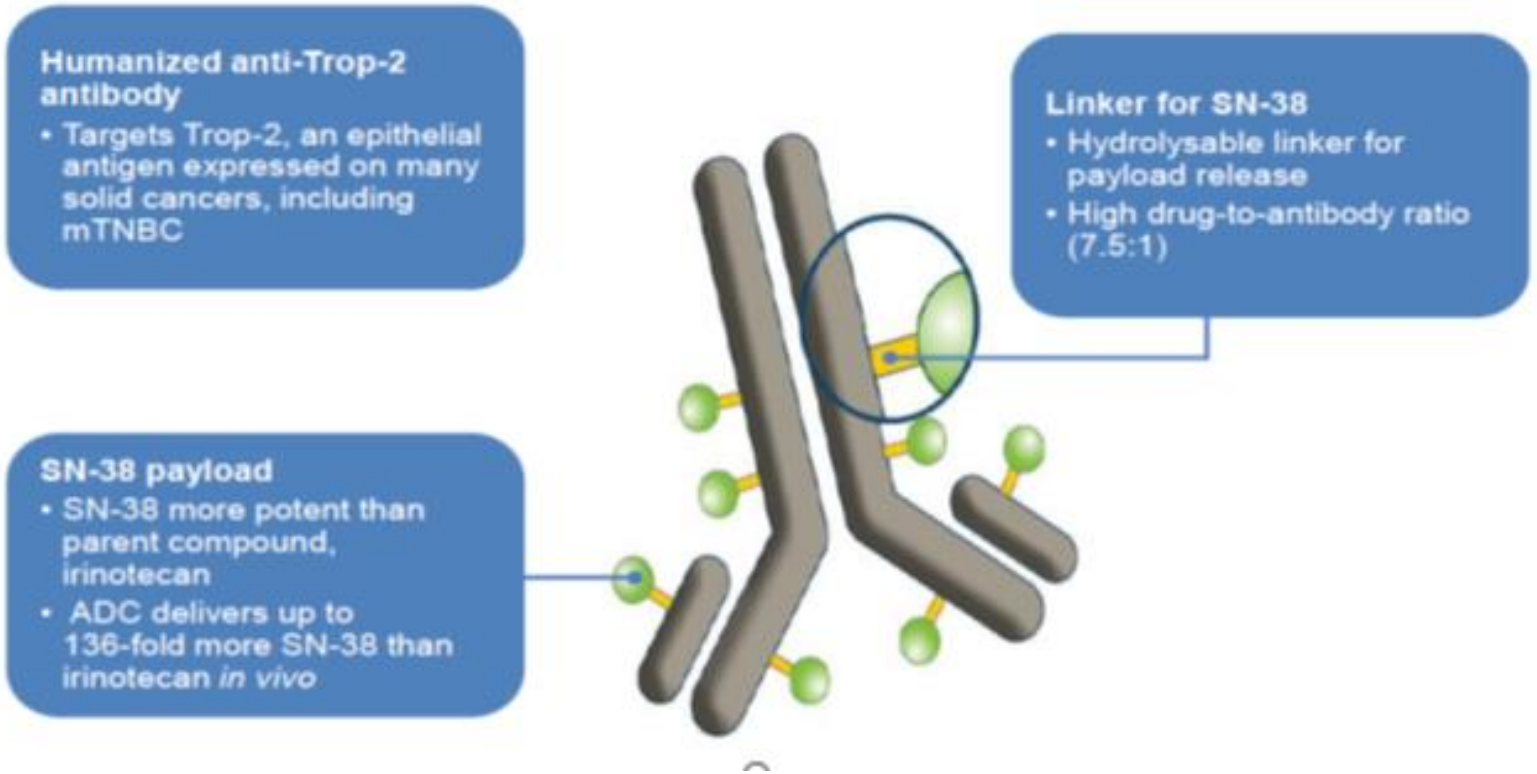
- Median of 6 prior lines of therapy
- 50% had prior CDK 4/6 inhibitors
- 85 patients evaluable for efficacy
- ORR = 10-33% across different doses levels

Krop I et al, SABCS 2020

Sacituzumab Govitecan: Anti-Trop2 ADC

TROP2

- Target for IMMU-132
- Glycoprotein that is overexpressed many epithelial cancers
- Overexpression correlates to poor prognosis in several cancers



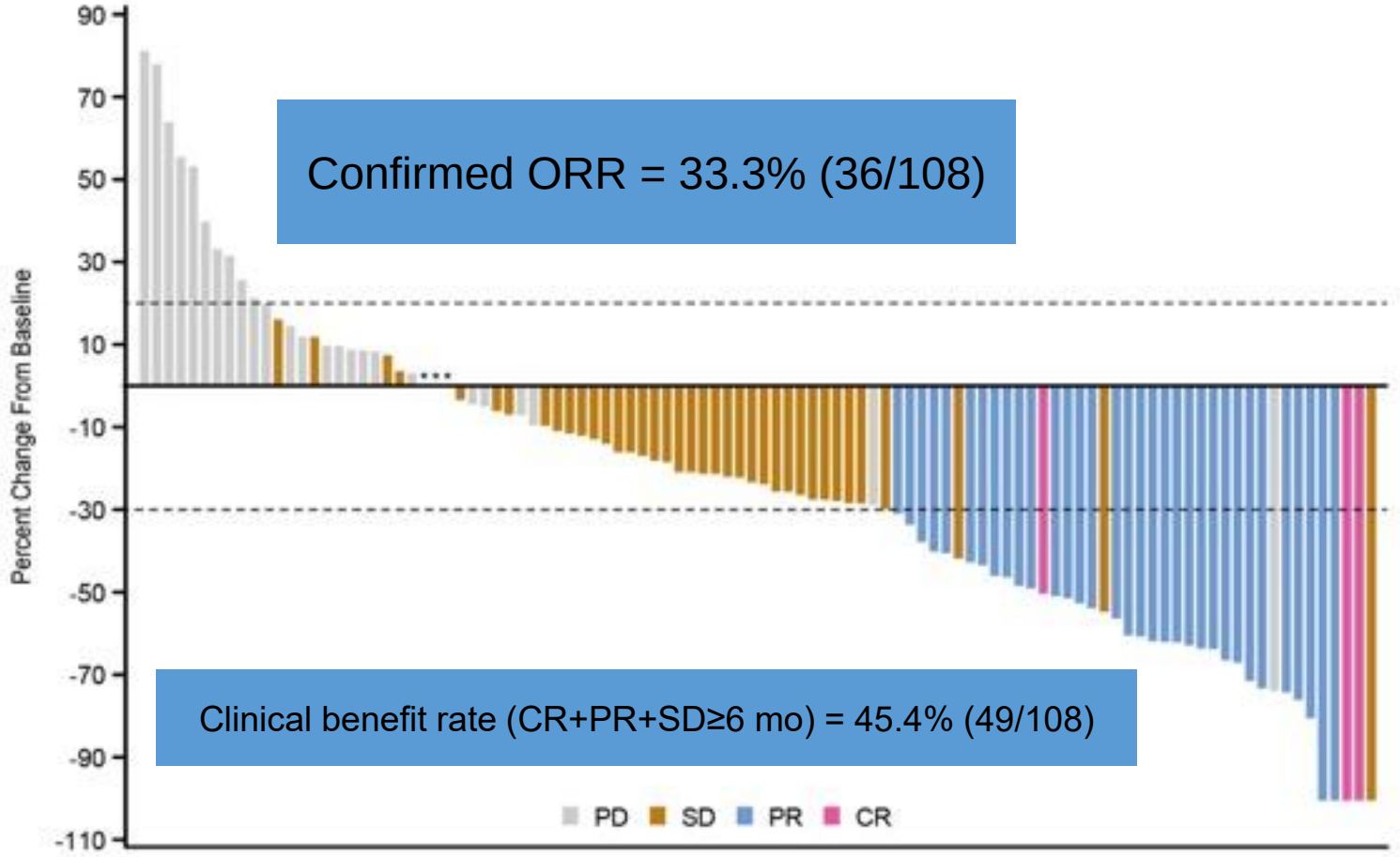
High DAR: (7.6:1)

Bardia A, et al. JCO. 2017

Sacituzumab Govitecan: Phase I/II Trial in mTNBC

108 patients with refractory mTNBC

Median of 3 prior lines of therapy (range 2-10) in the advanced setting



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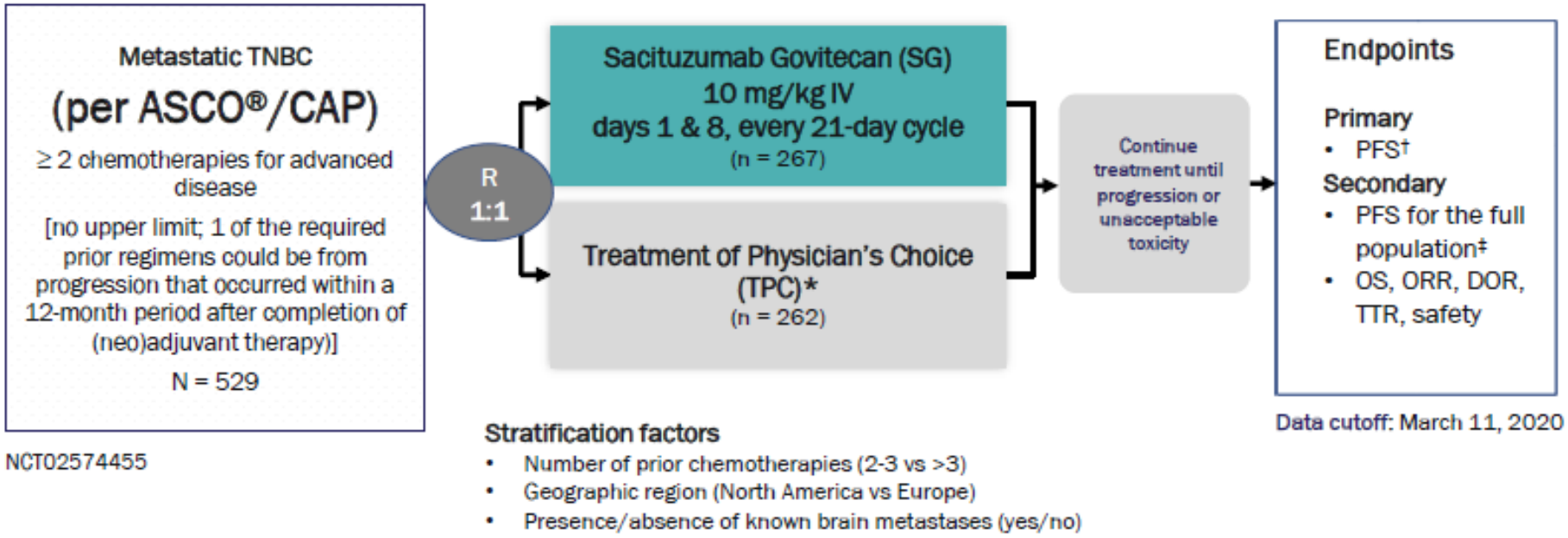
Bardia et al. NEJM. 2019

ASCENT Phase 3 trial of Sacituzumab Govitecan



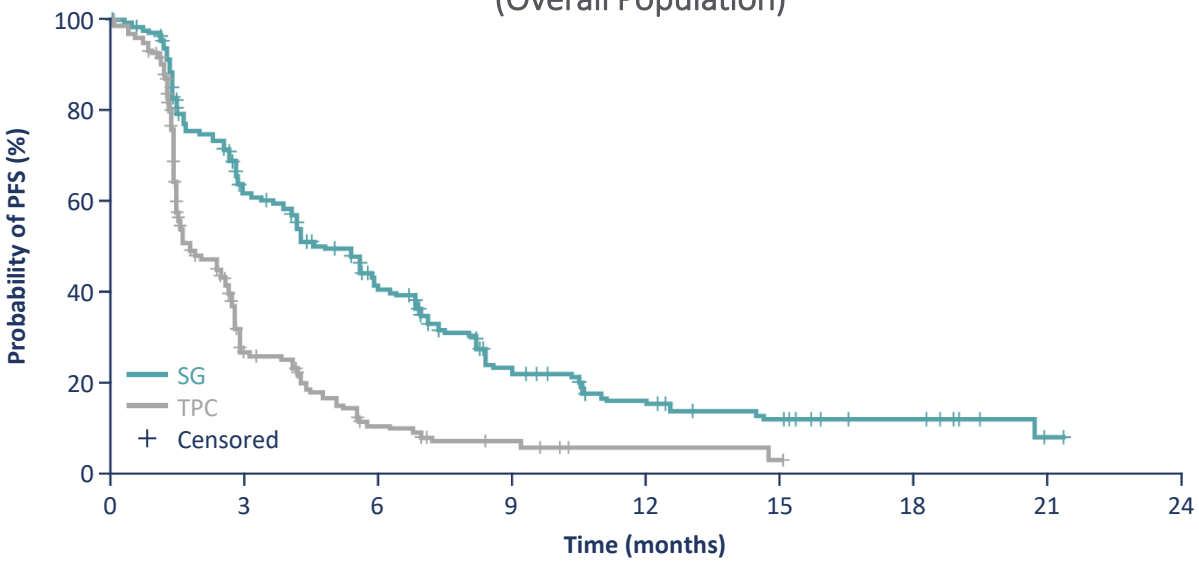
ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO®, American Society of Clinical Oncology; CAP, College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; MRI, magnetic resonance imaging; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

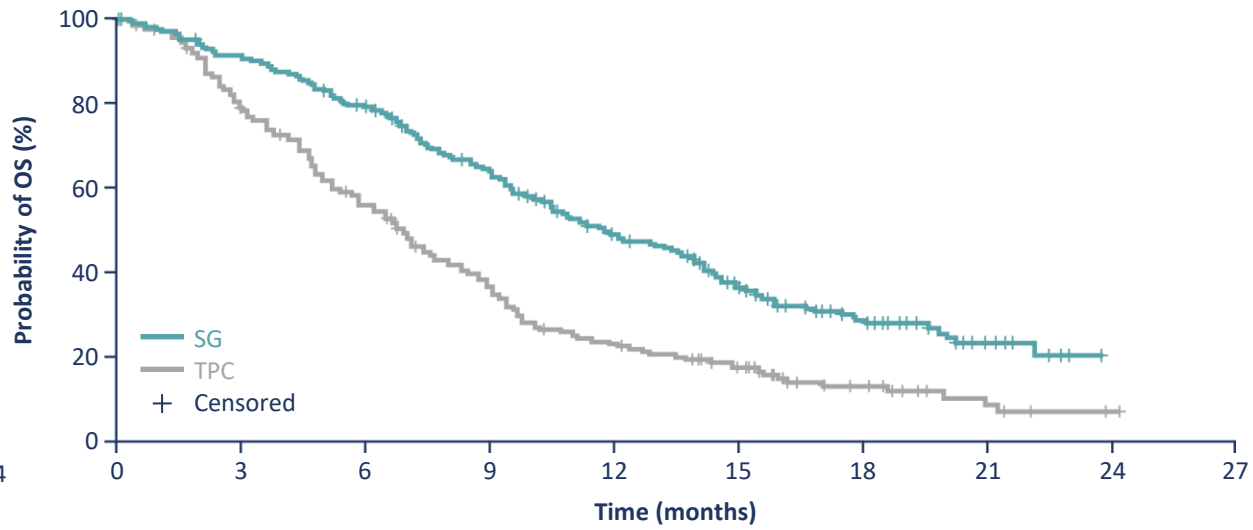
Bardia et al NEJM 2021

ASCENT: PFS and OS in the ITT Population

Progression-free Survival
(Overall Population)



Overall Survival
(Overall Population)



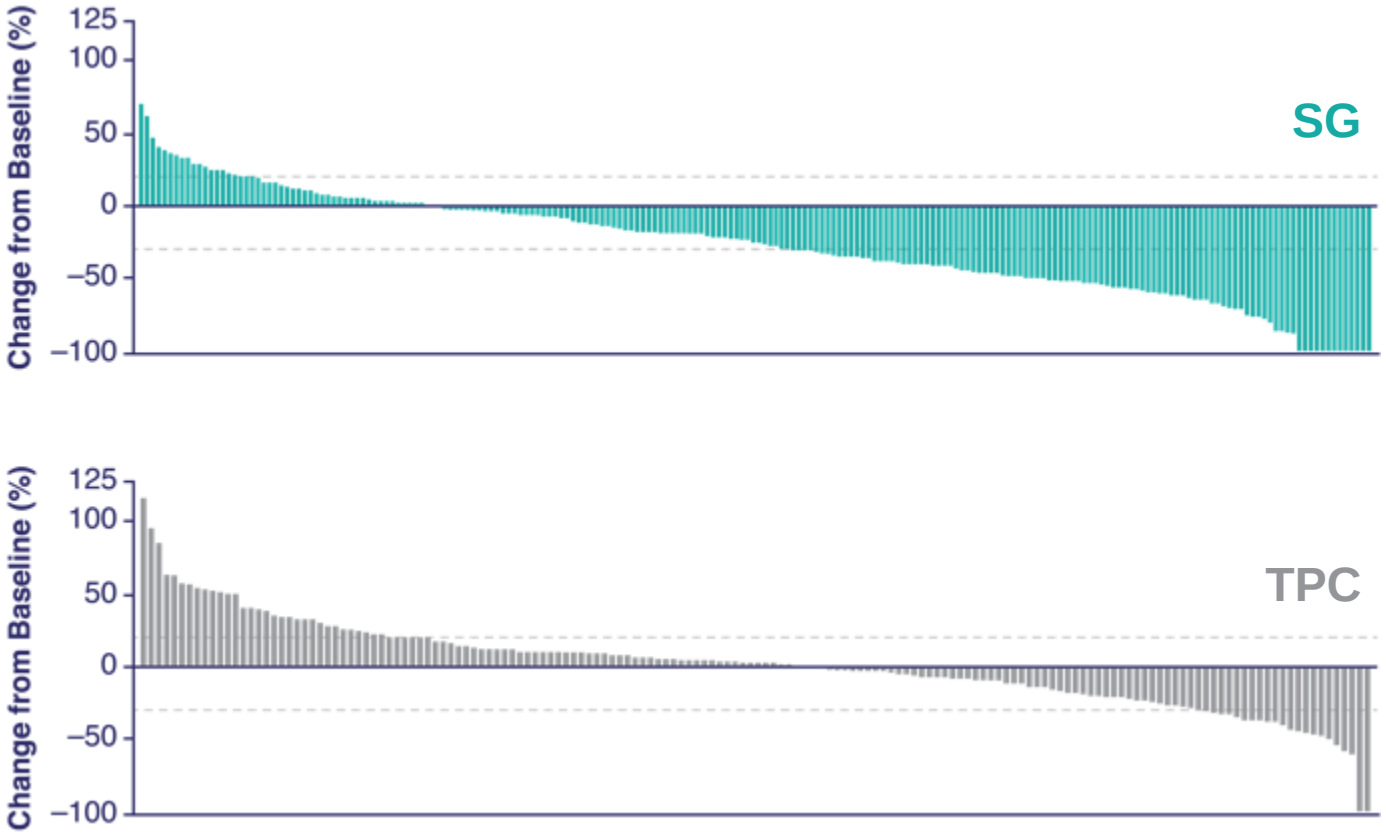
	SG (n=267)	TPC (n=262)
Median PFS, mo (95% CI)	4.8 (4.1-5.8)	1.7 (1.5-2.5)
HR (95% CI), *P* value	0.43 (0.35-0.54), *P*<0.0001	

	SG (n=267)	TPC (n=262)
Median OS, mo (95% CI)	11.8 (10.5-13.8)	6.9 (5.9-7.7)
HR (95% CI), *P* value	0.51 (0.41-0.62), *P*<0.0001	

HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice. Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541.

Bardia A, et al. N Engl J Med. 2021

Overall Response and Best Percent Change from baseline in tumor size

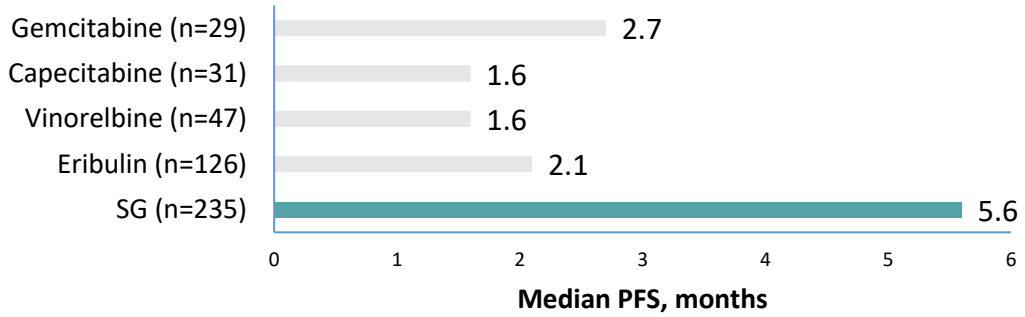


	SG (n=235)	TPC (n=233)
ORR—no. (%)	82 (35)	11 (5)
P-value	<0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	105 (45)	20 (9)
P-value	<0.0001	
Median DOR —mo (95%CI)	6.3 (5.5−9.0)	3.6 (2.8−NE)
P-value	0.057	

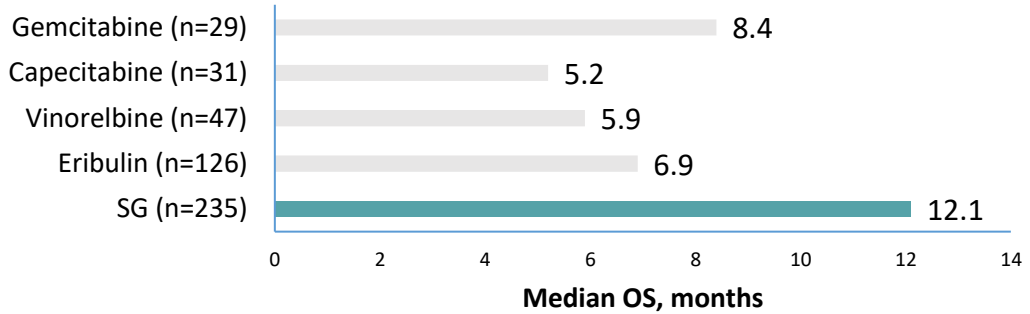
Bardia et al. NEJM 2021

ASCENT: Assessment of SG vs TPC, by Agent

PFS in ASCENT



OS in ASCENT



	Sacituzumab Govitecan (n=235)	TPC (n=233)			
		Eribulin (n=126)	Vinorelbine (n=47)	Gemcitabine (n=29)	Capecitabine (n=31)
ORR	**35%**	**5%**	**4%**	**3%**	**6%**
CBR	**45%**	**8%**	**6%**	**14%**	**10%**

The efficacy benefit observed with SG was retained when evaluating each TPC chemotherapy agent individually

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CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

O'Shaughnessy J, et al. ASCO 2021 (Poster 1077)

ASCENT: Exploratory analysis of TROP2 and gBRCA

- Trop-2 expression assessed by IHC
  - H-score <100 (including H-score 0): Trop-2 Low
  - H-score 100-200: Trop-2 Medium
  - H-score 200-300: Trop-2 High
- Clinical benefit with SG versus TPC in previously treated mTNBC is irrespective of level of Trop-2 expression

	SG (n=235)	TPC (n=233)
BRCA1/2 mutational status—no. (%)	149 (63)	143 (61)
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Trop-2 expression—no. (%)	151 (64)	139 (60)
(High) H-score 200-300	85 (56)	72 (52)
(Medium) H-score 100-200	39 (26)	35 (25)
(Low) H-score <100	27 (18)	32 (23)

	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)

	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 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)

	Trop-2 High H-score: 200-300 (n=157)		Trop-2 Medium H-score: 100-200 (n=74)		Trop-2 Low H-score: <100 (n=59)	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
ORR—% (no.)	44% (37)	1% (1)	38% (15)	11% (4)	22% (6)	6% (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

Hurvitz et al, SABCS 2020

Sacituzumab Govitecan: Activity in HR+ HER2- MBC

Metastatic Breast Cancer
ER+/HER2neg
(at last biopsy)

→ Sacituzumab Govitecan
10 mg/kg
Days 1 and 8, every 21 days
(Restaging scans every 8 weeks)

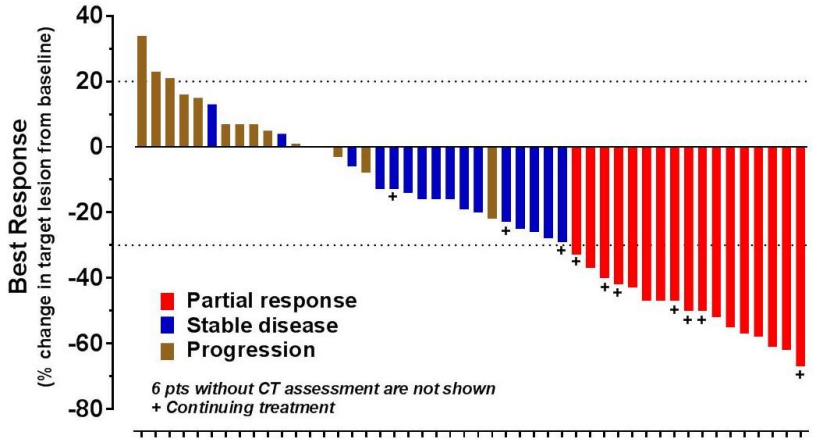
→ Until progression or unacceptable toxicity

Key Eligibility Criteria

- Adults, ≥18 years of age
- ECOG 0-1
- ≥1 prior therapies in metastatic setting
- Measurable disease

Evaluations

- Response evaluation by investigators according to RECIST 1.1
- Other evaluations: safety



Median number of metastatic chemo lines: 2
Median number of prior metastatic lines: 5

Efficacy	ITT	CDK4/6i Pretreated	CDK4/6i naive
ORR	31.5%	25%	41%
Median PFS	5.5 months	3.8 months	7.6 months
Median OS	12.7 months	11 months	21.7 months

Phase 3 (TROPICS02): Sacituzumab vs POC Chemo- ClinicalTrials.gov Identifier: NCT03901339

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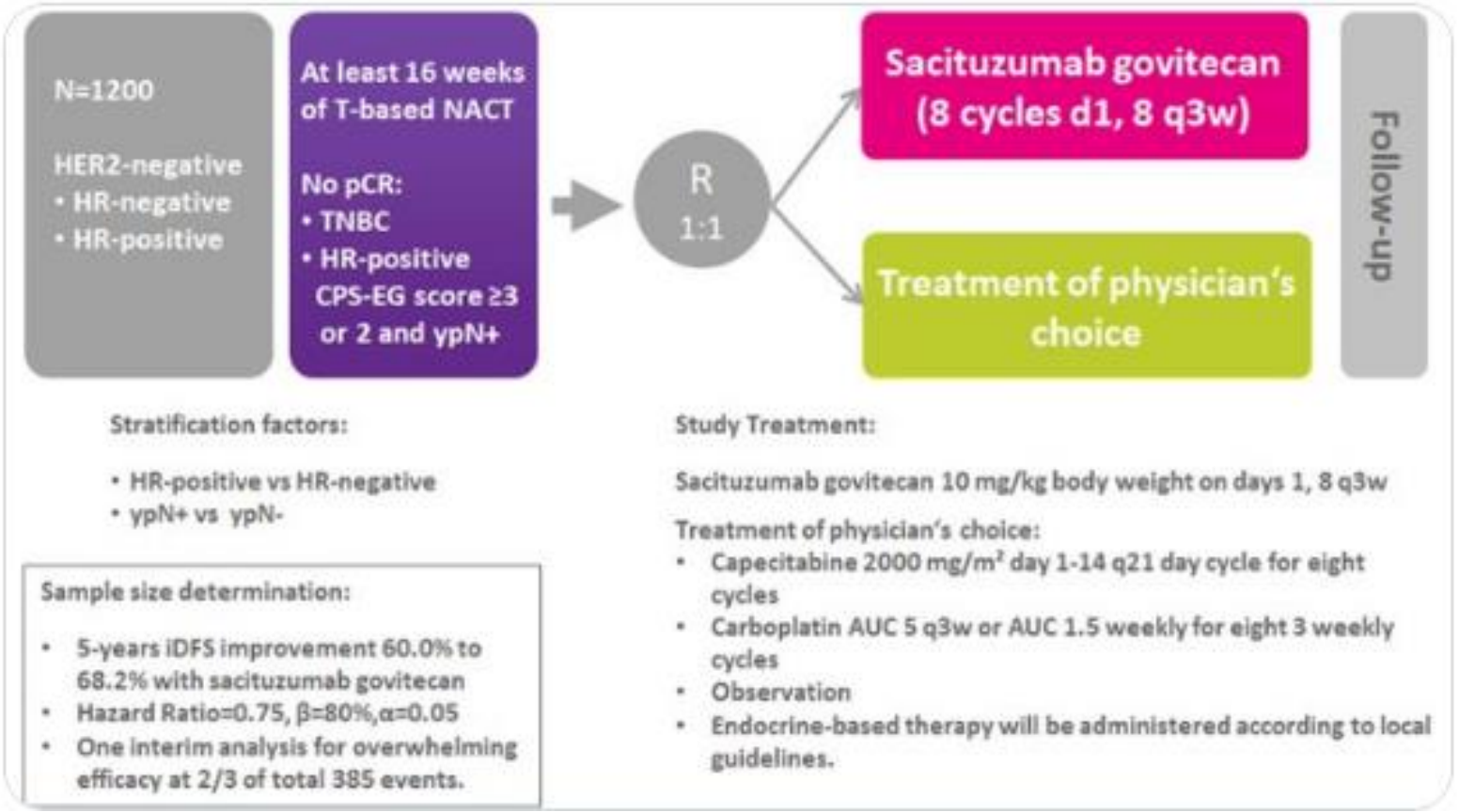
Bardia A, et al - ASCO Annual Meeting 2018 – Abst #1004; Kalinsky et al Annals of Oncology 2020

SASCIA (GBG 102): Sacituzumab Govitecan in primary HER2- breast cancer with residual disease after neoadjuvant therapy



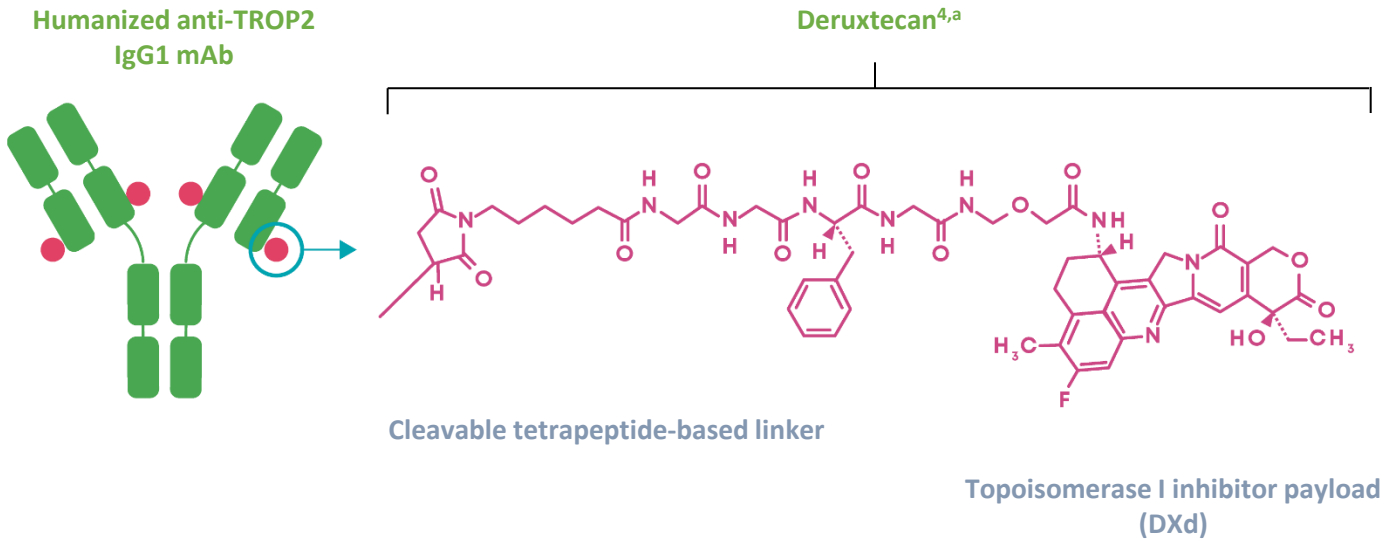
NCT04595565

Advances in Cancer Immunotherapy™

Datopotamab Deruxtecan (Dato-DXd)

Dato-DXd is an ADC with 3 components:

- A humanized anti-TROP2 IgG1[3] monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



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

[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.

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Krop I, et al. Presented at SABCS 2021. GS-1-05

Phase 1 TROPION–PanTumor01: Dato-DXd in mTNBC (updated results)

Sponsor	Daiichi-Sankyo and AstraZeneca
Study Objective	First in human study to investigate the safety and tolerability of DS-1062a (Dato-DXd) in TNBC, HR+/HER2- mBC (and other solid tumors)
Study Design	Phase 1, multicenter (Japan and US), open-label, single-group (no control)

TROPION-PanTumor01 Study Design (TNBC Cohort)[1,2]

2L+ study

Advanced Solid Tumor relapsed
- NSCLC
- TNBC
- HR+/HER2- BC
- SCLC
- HNSCC
- UC
- +10 other tumors

Key Inclusion Criteria

- Adults with unresectable or metastatic HER2- breast cancer ("refractory to or relapsed from standard treatment or for which no standard treatment is available")

Key Exclusion Criteria

- Prior TROP2 or deruxtecan treatment
- History of noninfectious ILD/pneumonitis that required steroids
- Clinically active brain mets

TNBC

n=24

Endpoints

- **Primary**: # of patients with dose-limiting toxicities, # of patients with AEs
- **Secondary**: PK endpoints, undefined efficacy endpoints are expected

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TROPION-PanTumor01 (TNBC Cohort): Baseline Characteristics

Patient Characteristics	TNBC (n=44)
Age, median (range), years	53 (32-82)
Country, n (%)	
US	31 (70)
Japan	13 (30)
ECOG PS, n (%)	
0	18 (41)
1	26 (59)
De novo metastatic disease, n (%)	
Yes	14 (32)
No	30 (68)

Patient Characteristics	TNBC (n=44)
Brain metastases, n (%)	5 (11)
Prior therapies in metastatic setting, median (range)	3 (1-10)
≥2 prior lines of therapy, n (%)[a]	30 (68)
Previous systemic treatment, n (%)	
Taxane	40 (91)
Platinum-based chemotherapy	23 (52)
Immunotherapy	19 (43)
PARPi	7 (16)
Topo I inhibitor-based ADC[b]	13 (30)

[a]Includes prior lines of therapy in the metastatic setting. [b]Sacituzumab govitecan, n=10; trastuzumab deruxtecan, n=2; patritumab deruxtecan, n=1.

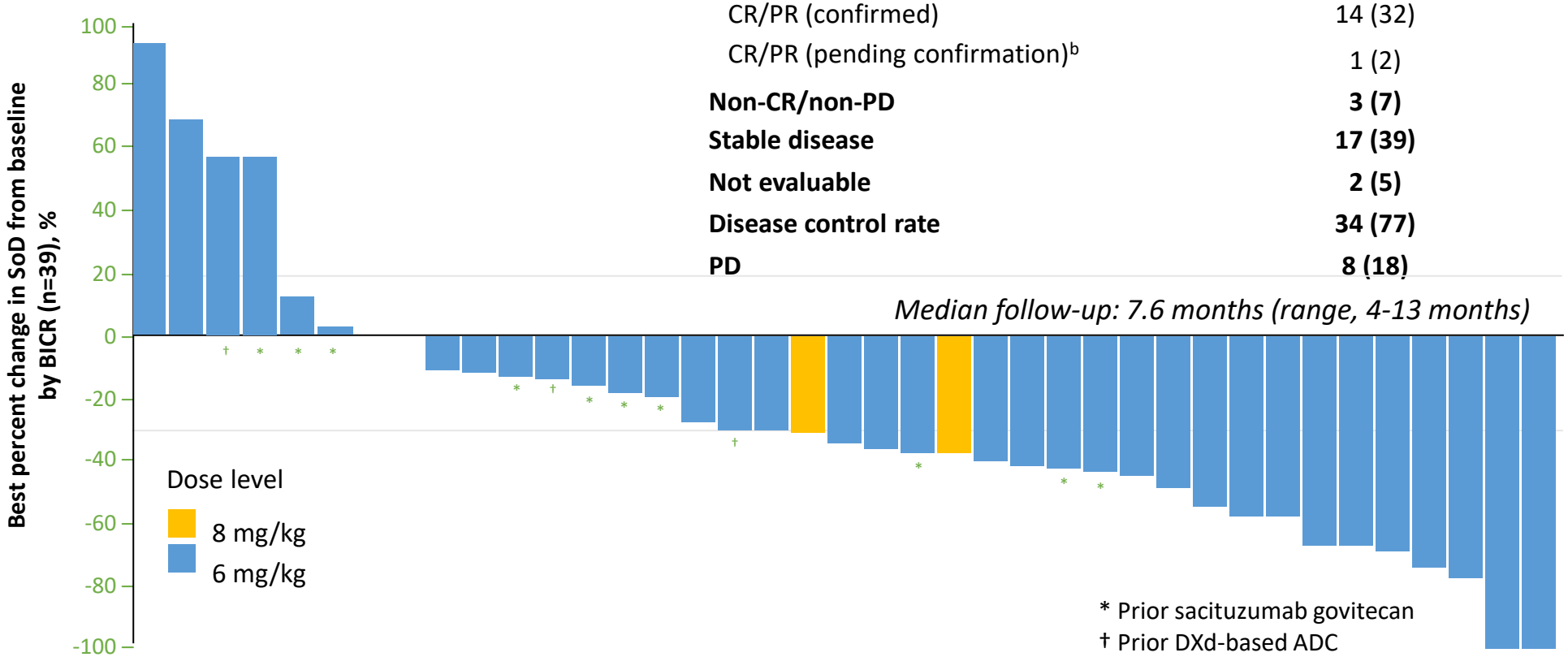
Krop I, et al. Presented at SABCS 2021. GS-1-05

Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

TROPION-PanTumor01 (TNBC Cohort): Responses by Blinded Independent Central Review (BICR)

Patients, n (%)[a]	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)**



[a]Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline assessments were not yet available for 2 patients. 3 patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD. [b]Includes patients with an unconfirmed response but are ongoing treatment.

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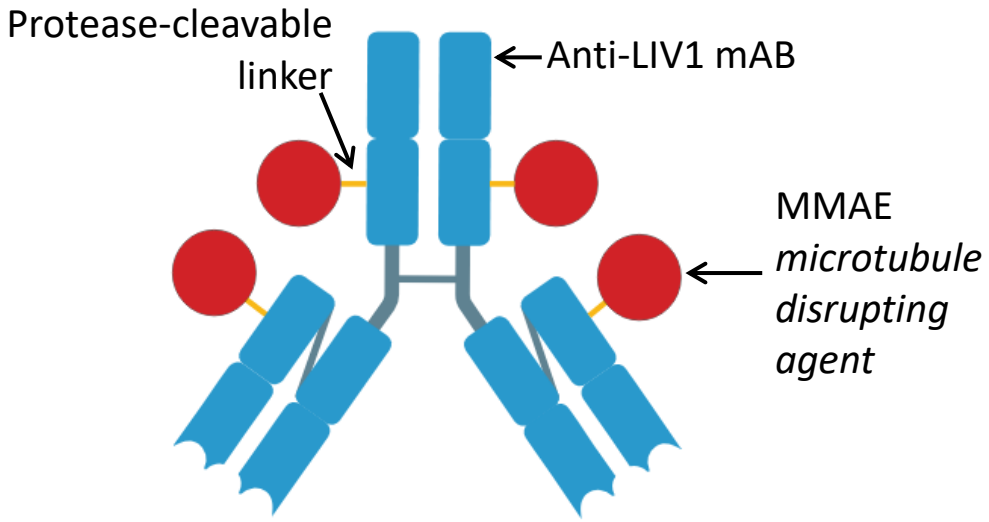
Krop I, et al. Presented at SABCS 2021. GS-1-05

Ladiratuzumab Vedotin: ADC Targeting LIV1



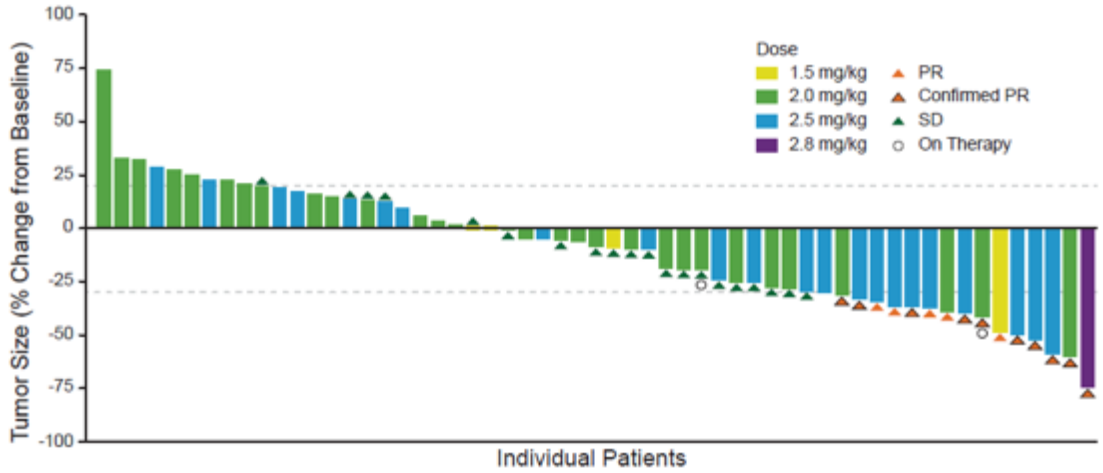
LIV1 is a transmembrane cell adhesion molecule highly expressed in metastatic breast cancer

Mech. of Action:

1. Binds to antigen
2. Complex internalized and trafficked to lysosome
3. Release of MMAE payload
4. Microtubule disruption
5. Cell cycle arrest/disruption

Phase I Study of Ladiratuzumab Vedotin

Confirmed ORR = 25% (15/60)



Next steps:
Weekly therapy to reduce toxicity

Modi S, et al. SABCS. 2017

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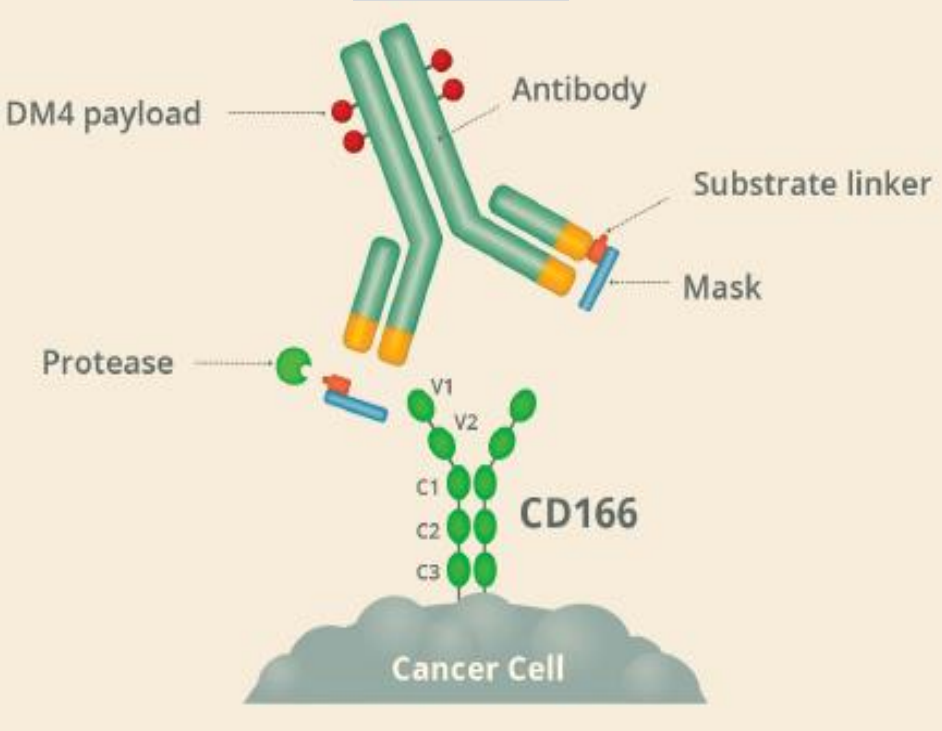
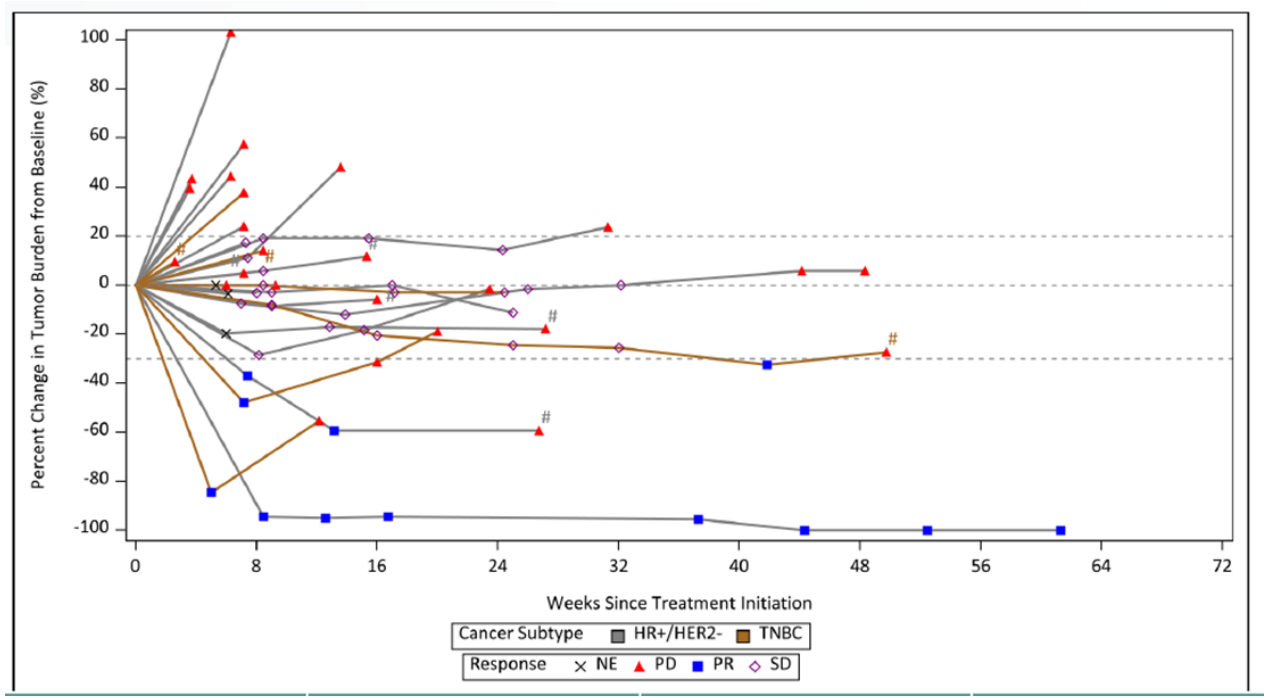
CX-2009 : Probody drug conjugate targeting CD166

CX-2009



- CD166 is a transmembrane protein that facilitates cell migration, differentiation and hematopoiesis
- CD166 is a broadly and highly expressed tumor antigen
- ~80% expression in HR+/HER2- BC and 50% in TNBC

Anti tumor activity (ph 1)



Boni et al ASCO 2020

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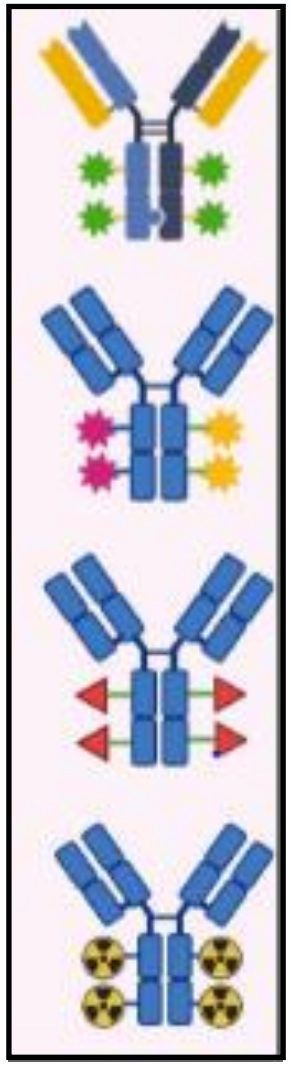
What's new on the horizon?

Bispecific ADCs
e.x. ZW-49 (NCT03821233)

Dual Payload ADCs
Overcome HER2 heterogeneity and resistance

ADCs with immune stimulating Payloads
e.x. TLR7/8 agonist- BDC-1001 (NCT04278144)

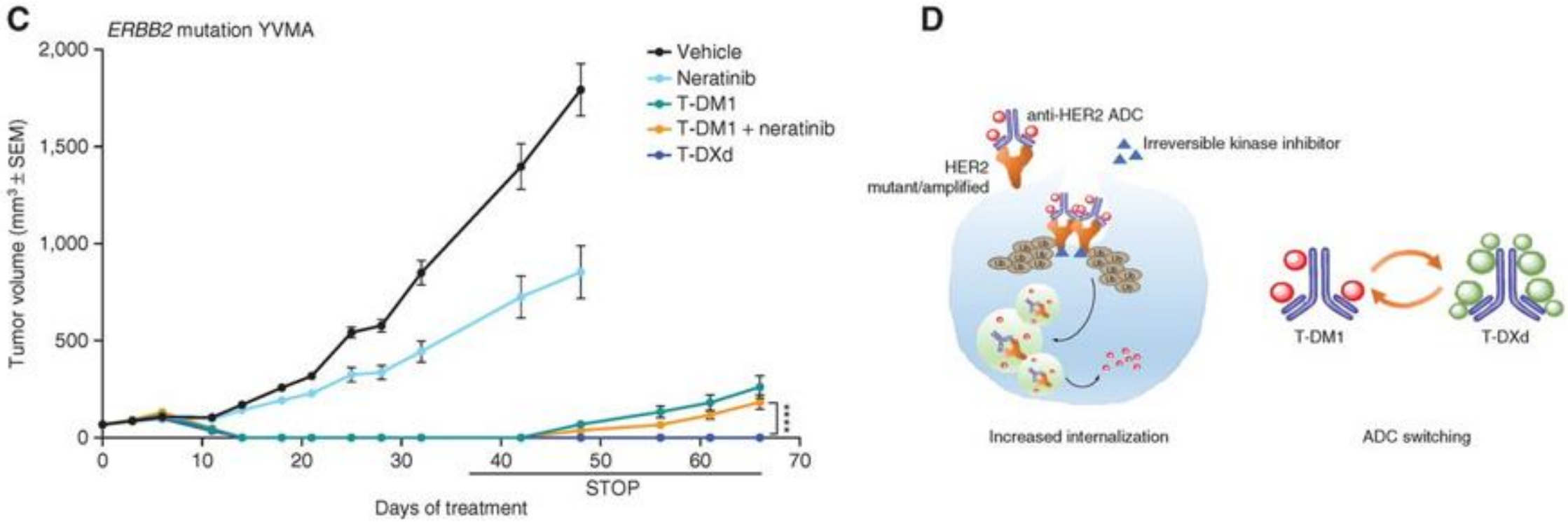
Radionuclide ADCs
e.x. Yttrium-90–conjugated, P-cadherin–targeting antibody, 90Y-FF-21101



Tarantino et al CA A Cancer J Clinicians, First published: 12 November 2021

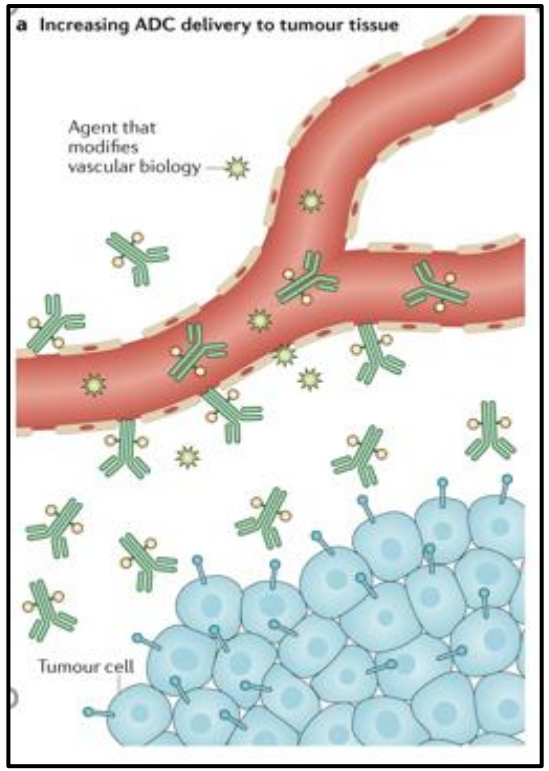
Future Directions: Strategies to enhance efficacy of ADCs

Role of ADC+ Neratinib

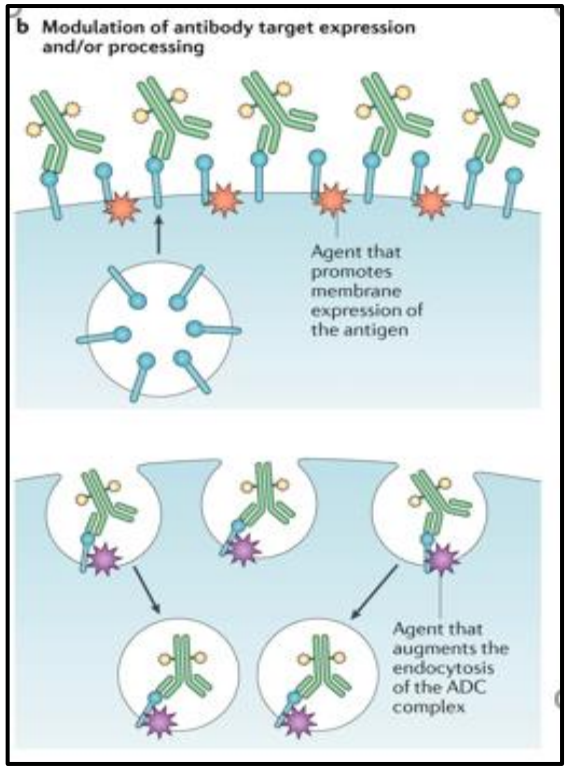


Li et al Cancer Discovery 2020

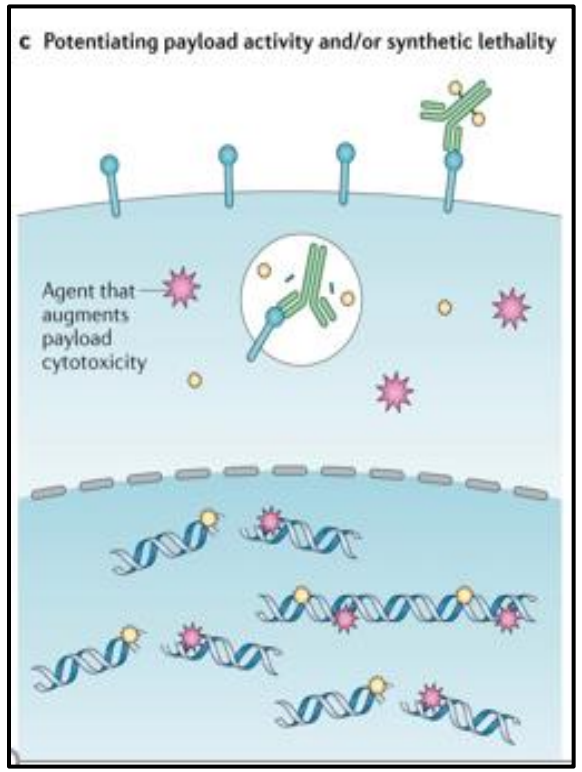
Future Directions: Strategies to enhance efficacy of ADCs



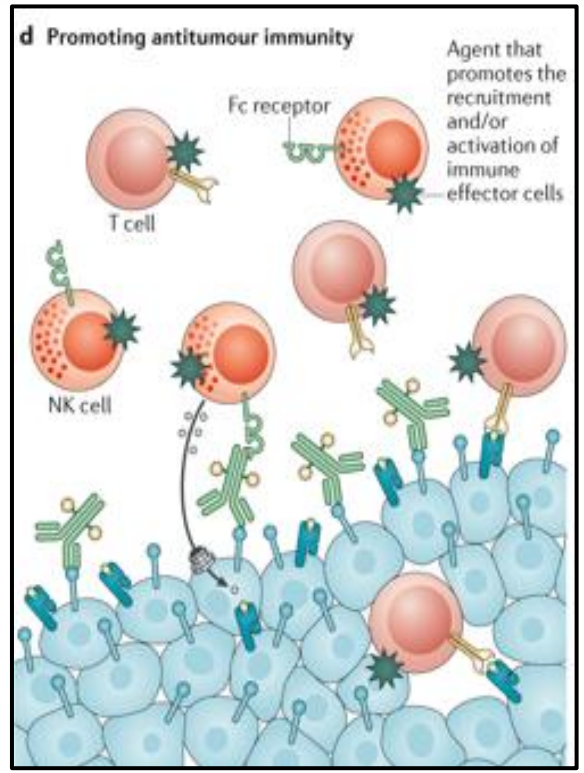
ADC + Bevacizumab (NCT02606305)



ADC + PI3K/Akt Inhibitors



TD-xD + PARPi (NCT04644068)



TDxD + IO (NCT03742102)

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Adapted from Drago, Modi, and Chandarlapaty; Nat Rev. Clin Onc. 2021

Key Takeaways
ADCs: The new wave

- **ADCs are an exciting and effective new therapy for mBC with evolving studies**

- **Established role in HER2+**
  - T-DXd is a new standard of care for mHER2+ BC
    - Ongoing Destiny Breast-04 in HER2 low disease
    - Multiple trials in mHER2+ disease, CNS mets, post-neoadjuvant in HER2+
  - New data with SYD985 for mHER2+ BC
  - Newer agents in development: ARX788, RC-48, ZW-49

- **Established role in TNBC**
  - SG is a new standard of care for mTNBC
    - Ongoing TROPiCS-02 trial in HR+ MBC
    - Post-neoadjuvant SASCIA trial
  - Dato-DXd is a new anti-TROP2 ADC
    - Phase III studies in HR+ and TNBC planned
- **Several Others are in development**

Key Takeaways
ADCs: Future Directions

- Need for Biomarkers
- Better understanding of target membrane dynamics, internalization and drug delivery
- Better understanding of mechanisms of resistance
- Strategies to augment ADC efficacy
  - IO, cytotoxics, targeted agents, agents that augment internalization
- Sequencing of ADCs to optimize outcomes

Acknowledgements

Patients and their families who inspire us everyday

Questions?