Update on antibody-drug conjugates in solid cancers

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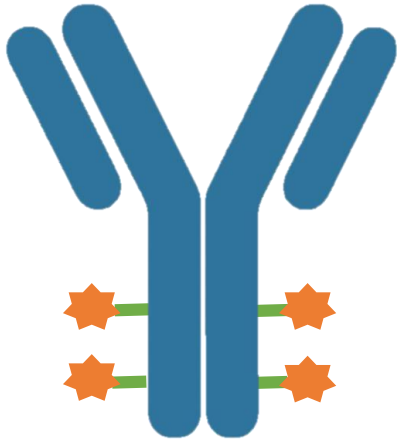
Disclosures

- Support for attending medical conferences: Roche, Bayer

Outline

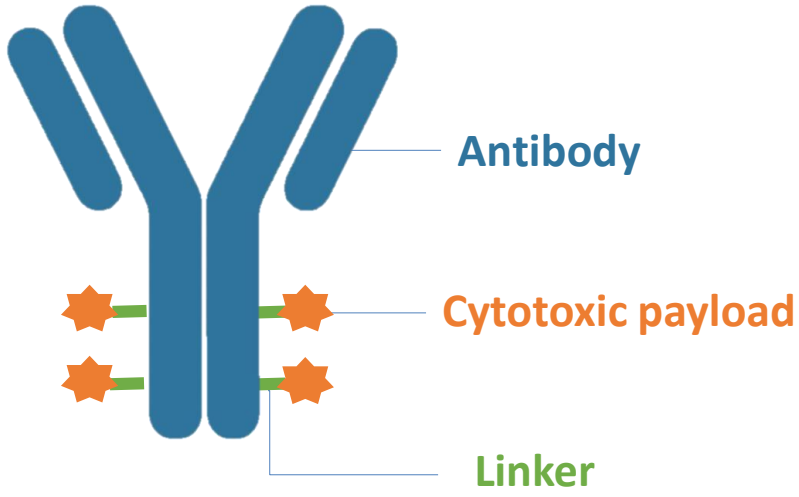
- ADCs structure and mechanisms of action
- Update on ADCs for the treatment of:
  - Breast cancer
  - Urothelial cancer
  - Lung cancer
  - Gastrointestinal cancer
- Perspectives and future directions

ADCs structure and mechanisms of action



What are antibody-drug conjugates (ADC)?

- ADCs are monoclonal antibodies conjugated by a linker with a cytotoxic payload
- Delivery of the payload to specific molecular targets in tumor cells
- Improved therapeutic index (↑ activity and ↓ toxicity)
- Overcome the limitations of mAb therapies and cytotoxic chemotherapy



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Subbiah et al. Current Problems in Cancer 2021

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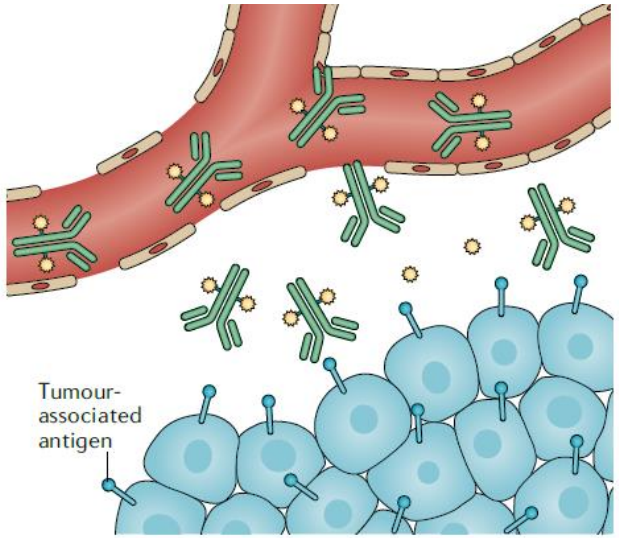
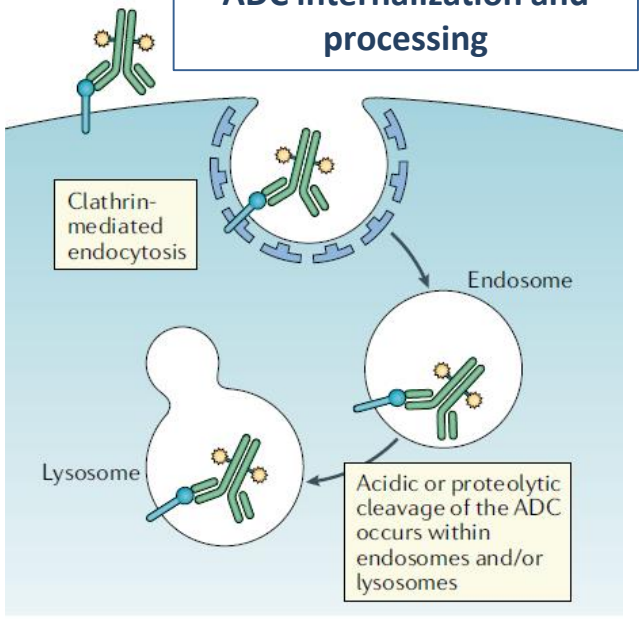
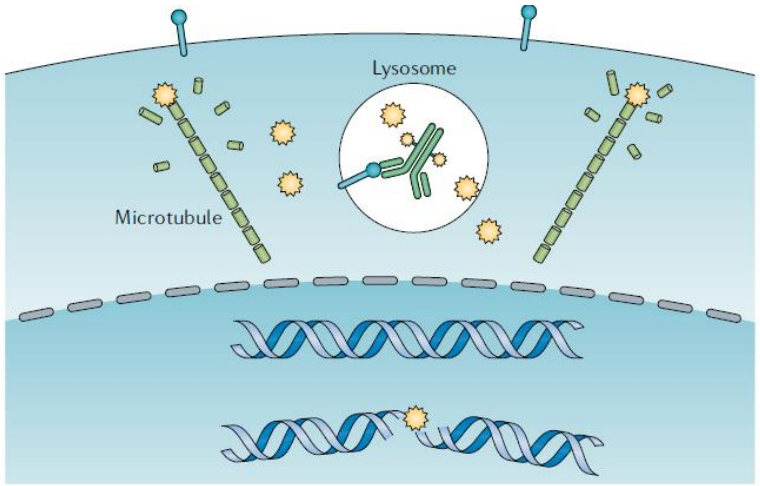
ADCs mechanisms of action



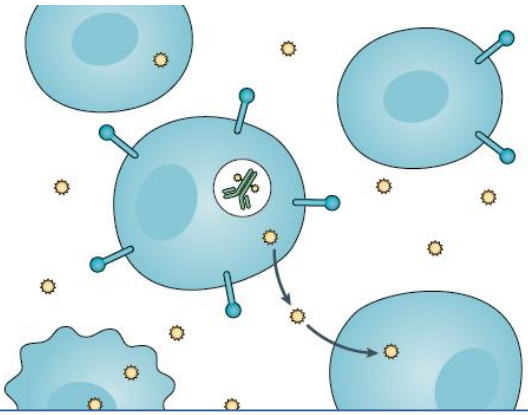
ADC internalization and processing



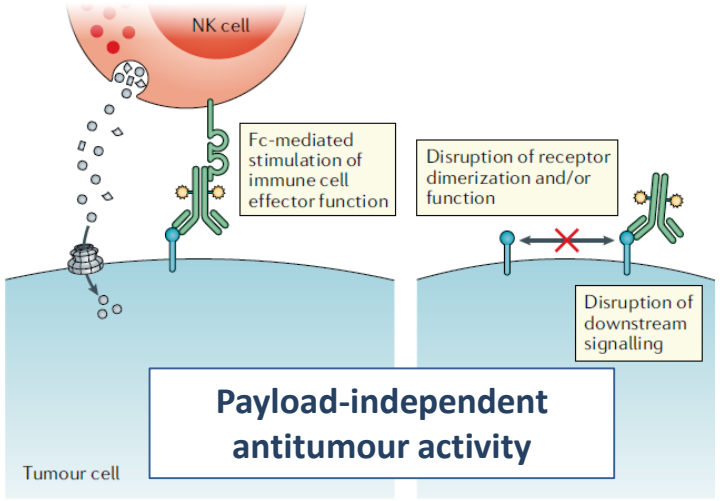
Intracelular payload release → cell death



Payload diffusion



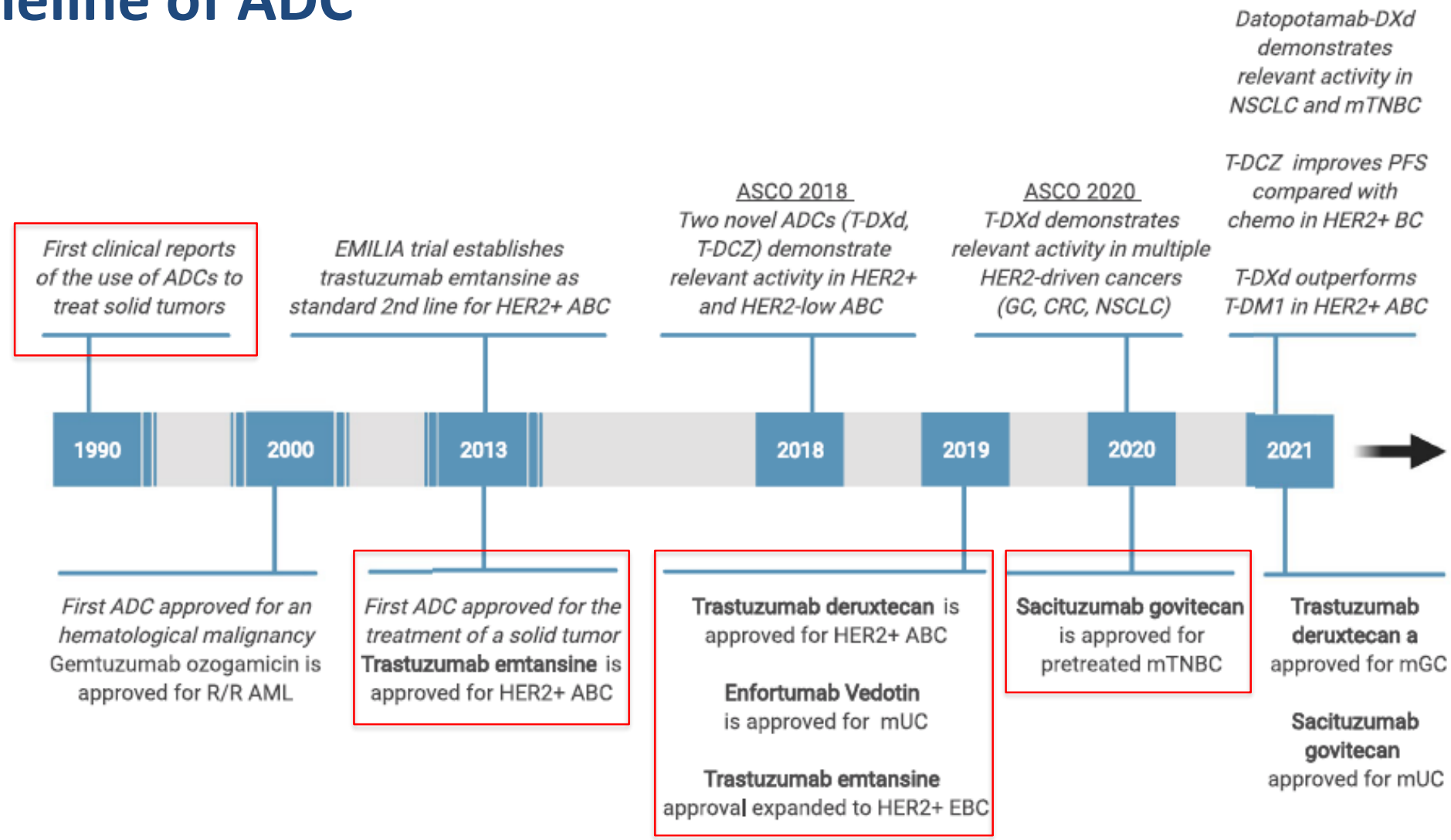
Cytotoxic activity against neighbouring cells ("bystander effect")



Payload-independent antitumour activity

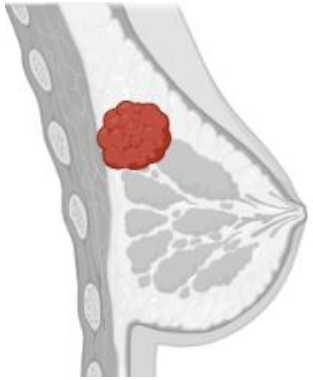
Adapted from: Drago et al. Nat Rev Clin Oncol 2021

Timeline of ADC



Tarantino et al. CA Cancer J Clin 2021

ADCs for the treatment of breast cancer



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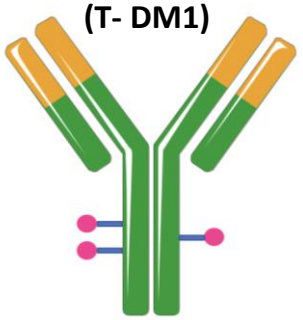
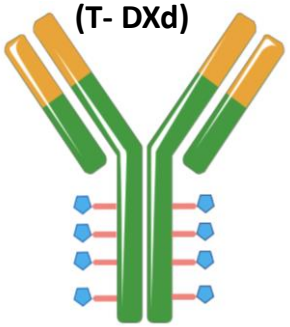
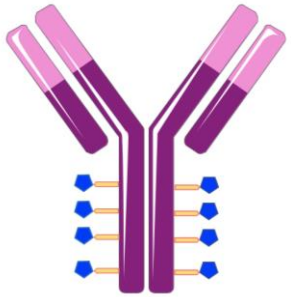
Currently approved ADCs for the treatment of breast cancer

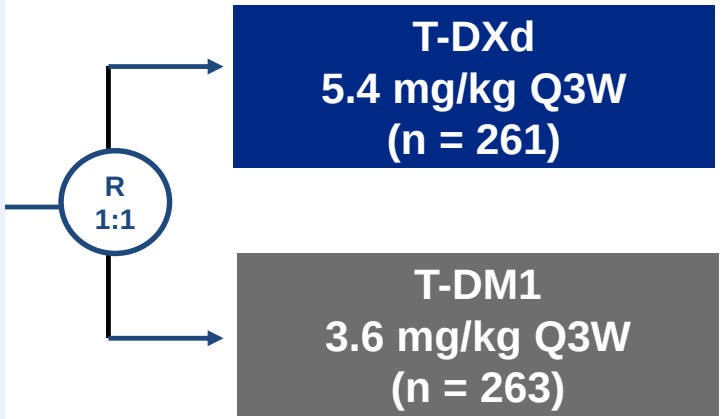
	Trastuzumab emtansine (T- DM1)	Trastuzumab deruxtecan (T- DXd)	Sacituzumab govitecan
			
Monoclonal antibody	Trastuzumab	Trastuzumab	Sacituzumab, hRS7
Type of monoclonal antibody	Humanized IgG1	Humanized IgG1	Humanized IgG1
Target antigen	HER2	HER2	Trop-2
Payload	Emtansine	Deruxtecan	SN-38
Payload class	Maytansinoid - Microtubule inhibitor	Camptothecin - Topoisomerase-I inhibitor	Camptothecin - Topoisomerase-I inhibitor
Payload membrane permeability	Low	High	High
Bystander effect	No	Yes	Yes
Linker subtype	Non-cleavable	Cleavable	Cleavable
Linker structure	Thioether linker (SMCC)	Tetrapeptide-based	Hydrolysable (CL2A)
Linker cleavage trigger	Lysosomal degradation	Lysosomal cathepsins	Low pH
Drug-to-antibody ratio	≈ 3.5 (mean)	≈ 8	≈ 7.6 (mean)
Conjugation	Stochastic Random Lysine	Site-specific Cysteine residues	Maleimide moiety
Endocytosis mechanism	Caveolae-endocytic pathway	Caveolae-endocytic pathway	Clatherin-mediated endocytosis
Half-life	≈ 4 days	≈ 7 days	≈ 15 hours (mean)
Excretion	Biliary	Biliary	Intestinal (enterohepatic circulation)

Nader-Marta G et al. (under review)

DESTINY-Breast03

Patients
- Unresectable or metastatic HER2+ breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting

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

Interim analysis for PFS (data cutoff: May 21, 2021)

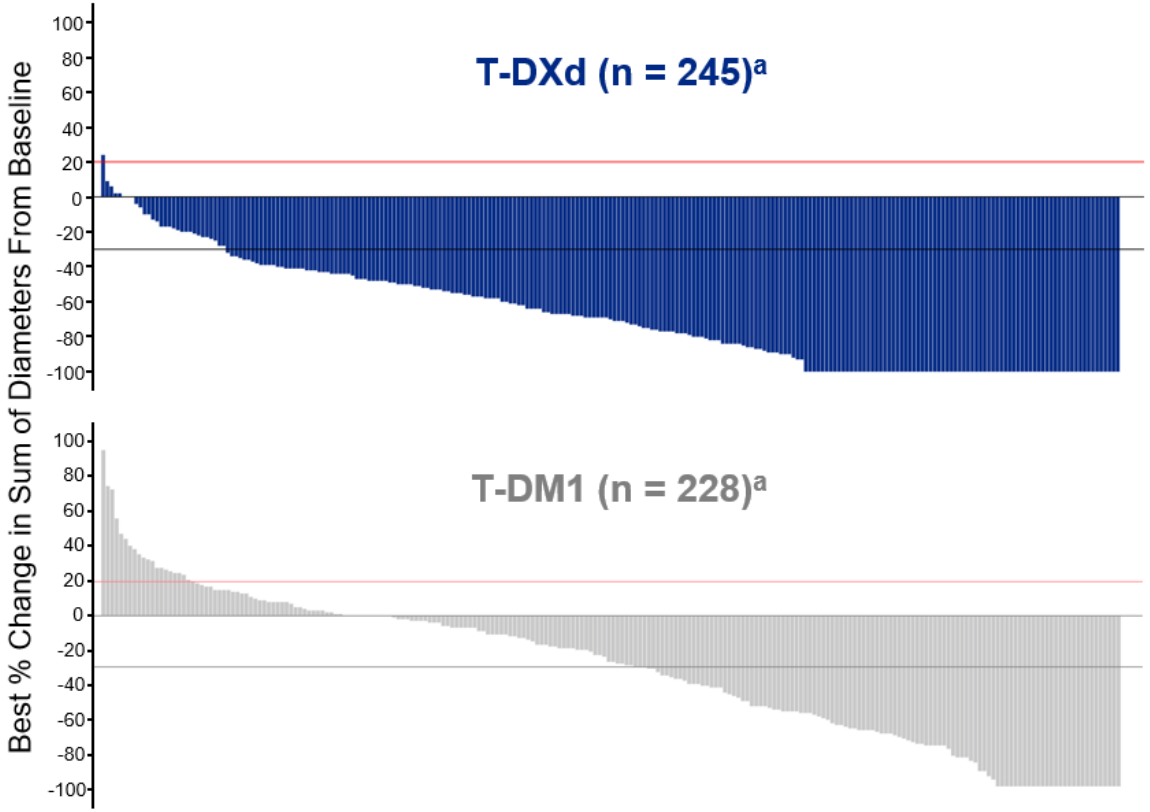
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC **recommendation** to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

Cortes J. ESMO 2021

DESTINY-Breast03

Confirmed ORR and Best Overall Response



	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)

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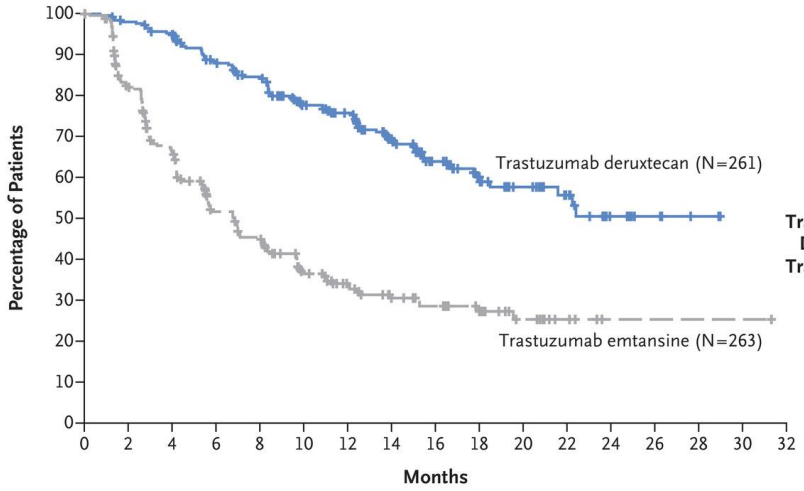
DESTINY-Breast03 – PFS and OS

Progression-free survival



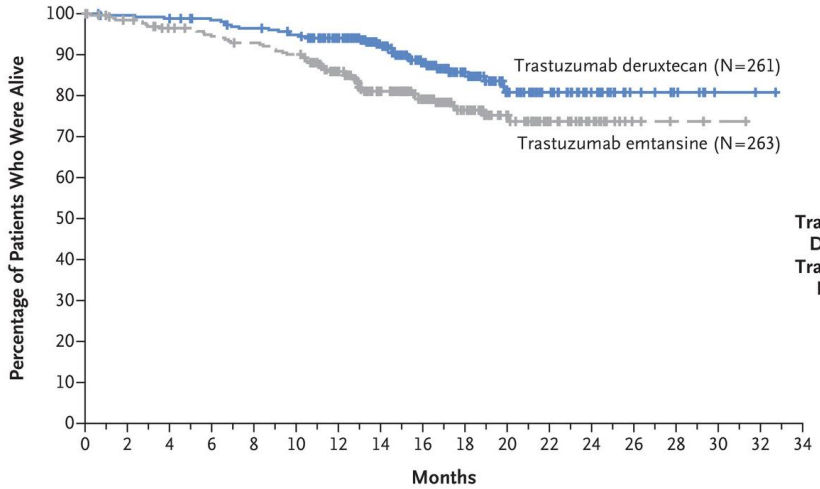
	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

HR 0.28

No. at Risk																
Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2	
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	0

Overall survival



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

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

No. at Risk																			
Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

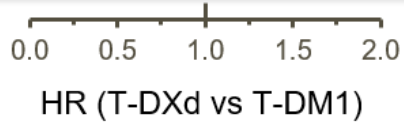
Early OS data with relatively few events
(33 in the T-DXd arm, 53 in the T-DM1 arm)
[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

T-DXd replaces T-DM1 as preferred second-line therapy for advanced HER2-positive breast cancer

DESTINY-Breast03

PFS in Key Subgroups

		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)



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DESTINY-Breast03 - Safety

n (%)	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE	252 (98.1)	226 (86.6)
Drug-related TEAE Grade ≥3	116 (45.1)	104 (39.8)
Serious drug-related TEAE	28 (10.9)	16 (6.1)
Drug-related TEAE associated with discontinuation	33 (12.8)	13 (5.0)
Drug-related TEAE associated with dose reduction	55 (21.4)	33 (12.6)
Drug-related TEAE associated with an outcome of death	0 (0.0)	0 (0.0)

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

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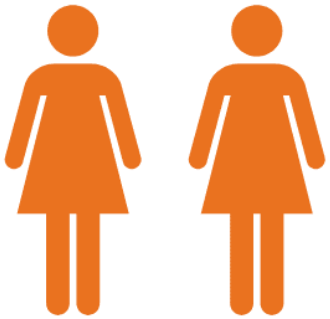
HER2-low breast cancer

HER2 EXPRESSION IN BC

~15% HER2-positive



~85% HER2-negative (IHC 0, IHC 1+, or IHC 2+/ISH–)

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Tarantino P et al. JCO 2020
Schettini F NPJ Breast Canc 2021

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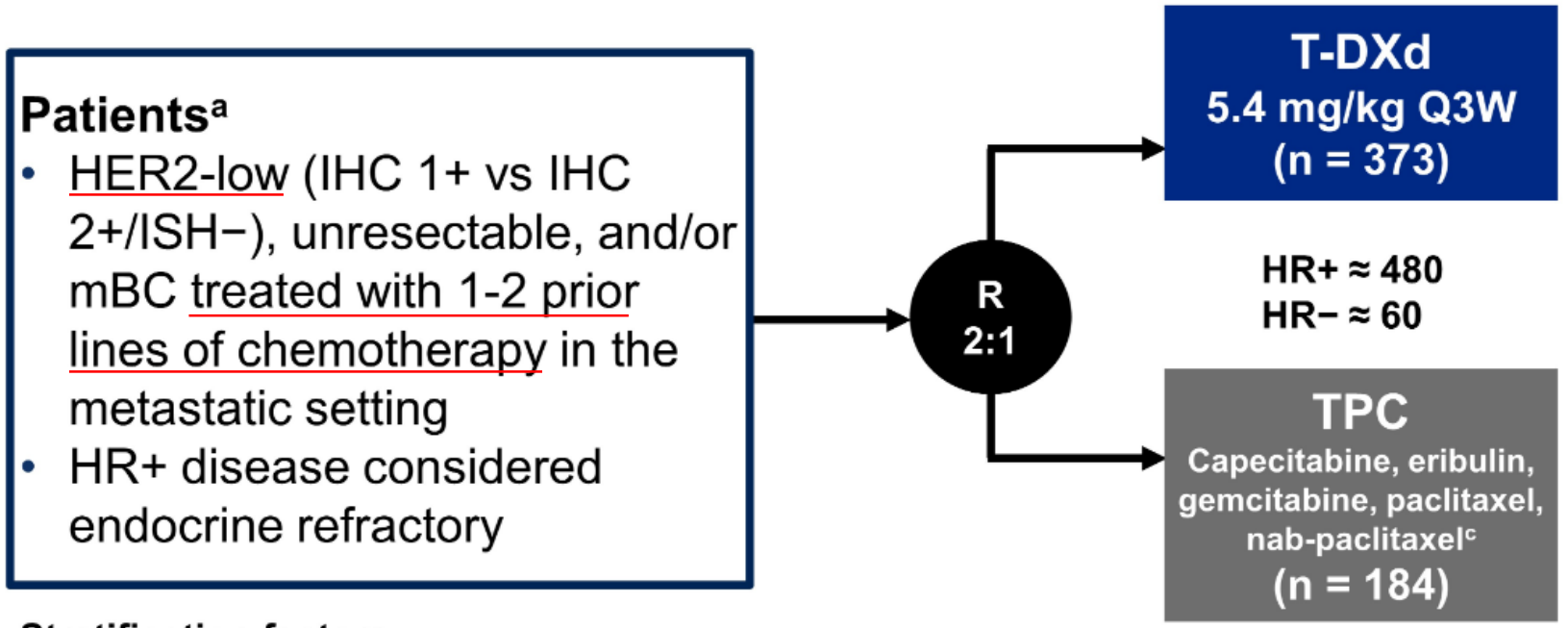
DESTINY-Breast04



Stratification factors

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

Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[b]

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

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DESTINY-Breast04

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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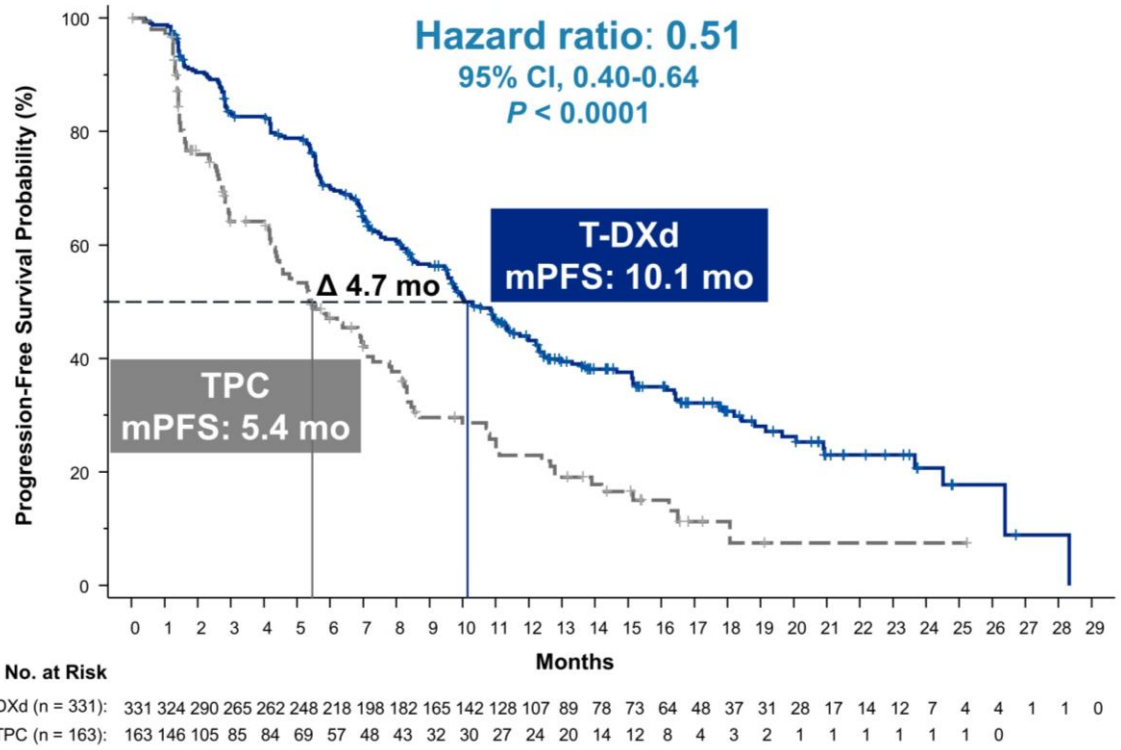
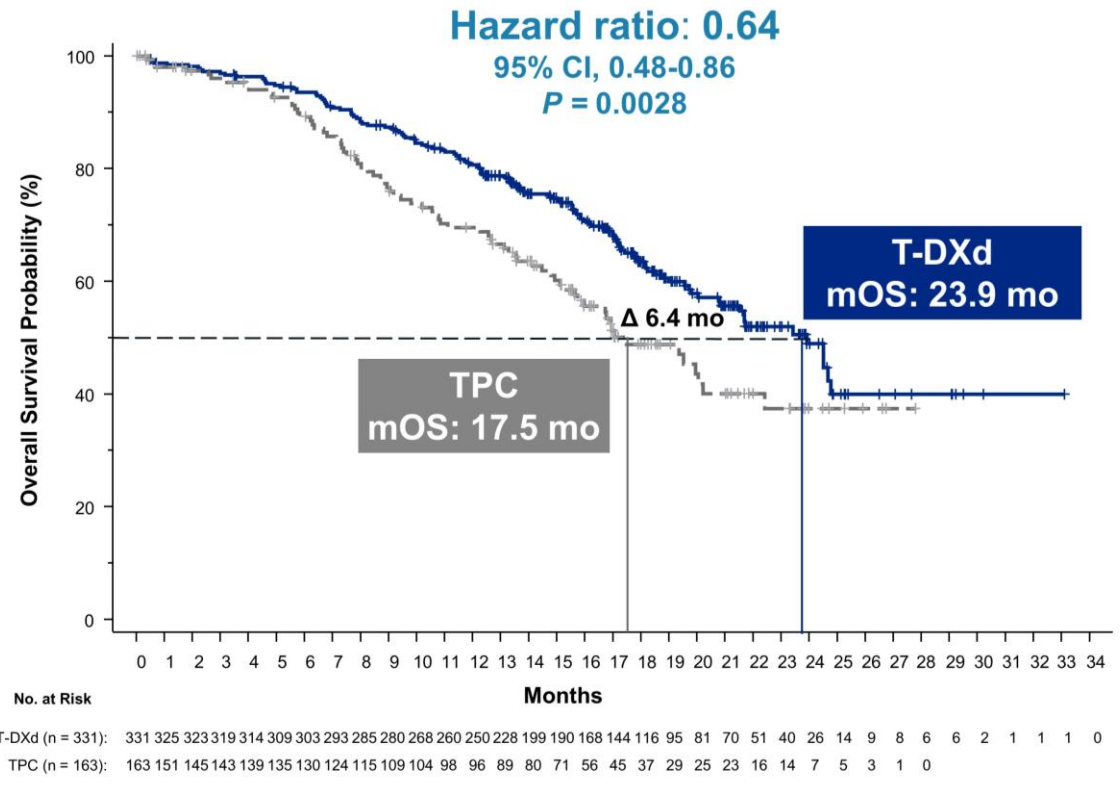
DESTINY-Breast04 – Hormone receptor-positive (N = 494)

Progression-free survival



Overall survival



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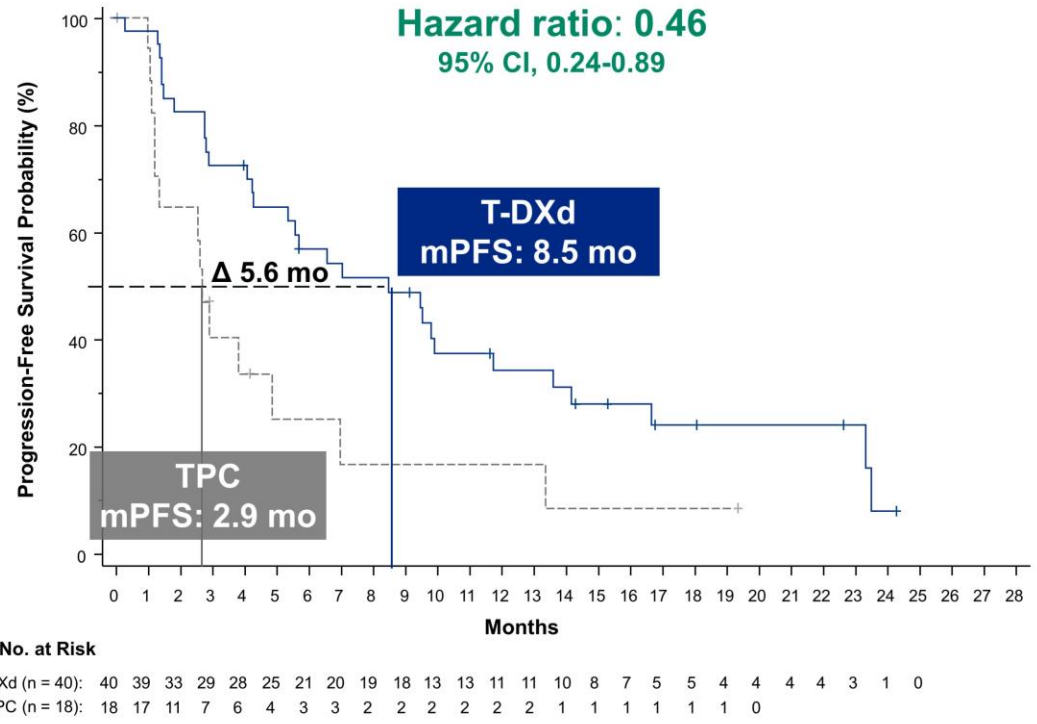
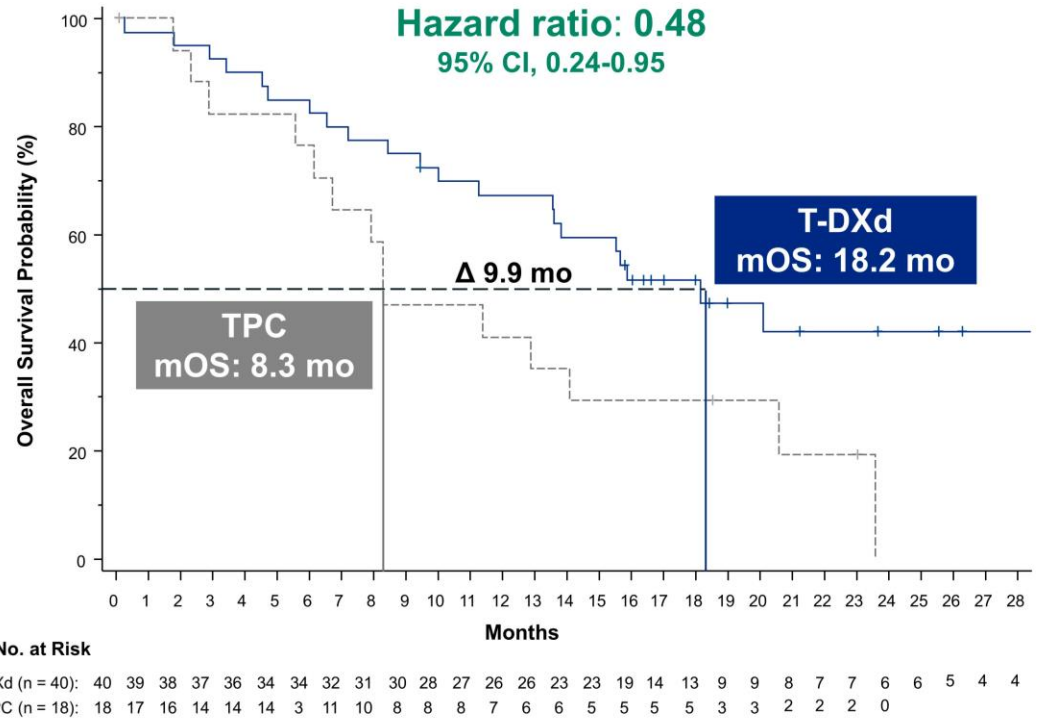
DESTINY-Breast04 – Hormone receptor-negative (N = 68)

Progression-free survival



Overall survival



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Sacituzumab Govitecan in TNBC

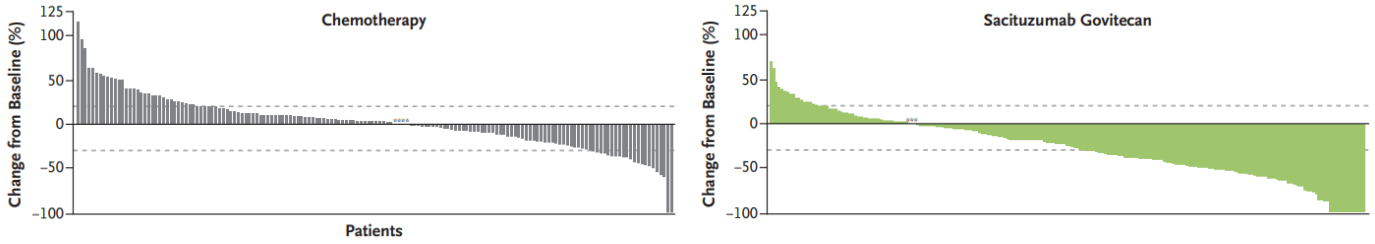
- ASCENT trial

- mTNBC (N = 468)
- ≥ 2 prior CT (prior taxane)
- ECOG PS 0-1

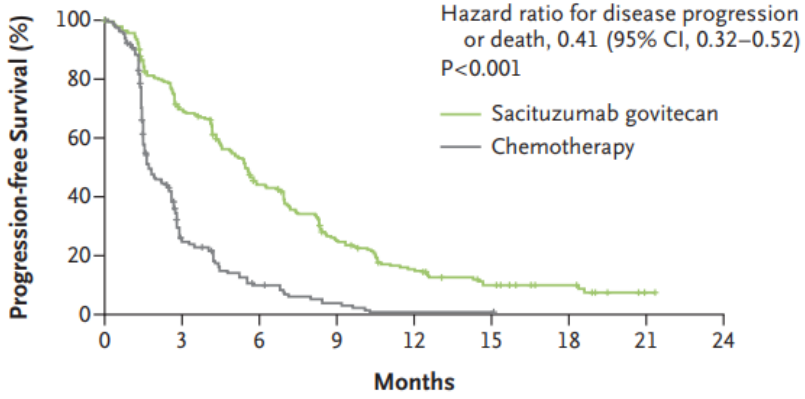
1:1

Sacituzumab govitecan
(10 mg/kg IV D1 and D8 q3w)

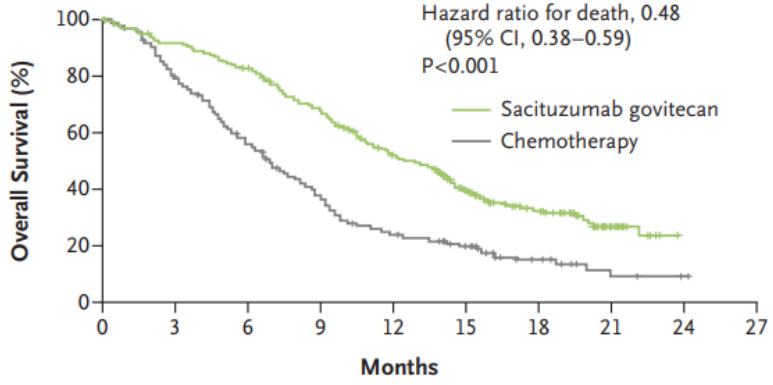
Single-agent chemotherapy
(eribulin, vinorelbine, capecitabine, or gemcitabine)



	No. of Patients	No. of Events	Median Progression-free Survival mo (95% CI)
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)



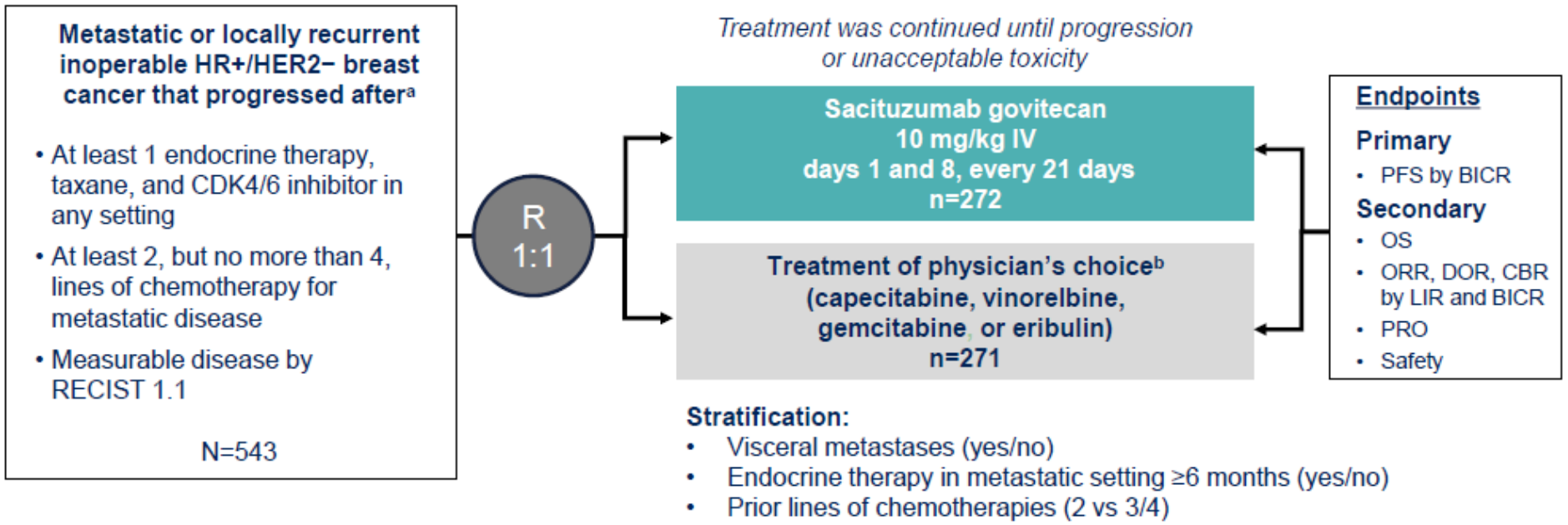
	No. of Patients	No. of Events	Median Overall Survival mo (95% CI)
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)



Bardia. NEJM 2021

Sacituzumab Govitecan in HR+ breast cancer

- TROPiCS-02 trial



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Rugo H et al. ESMO 2022

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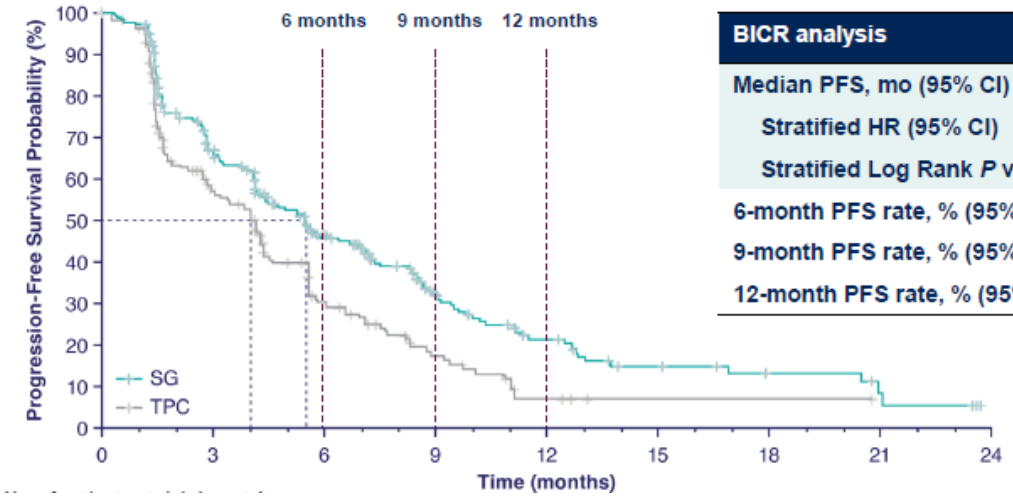
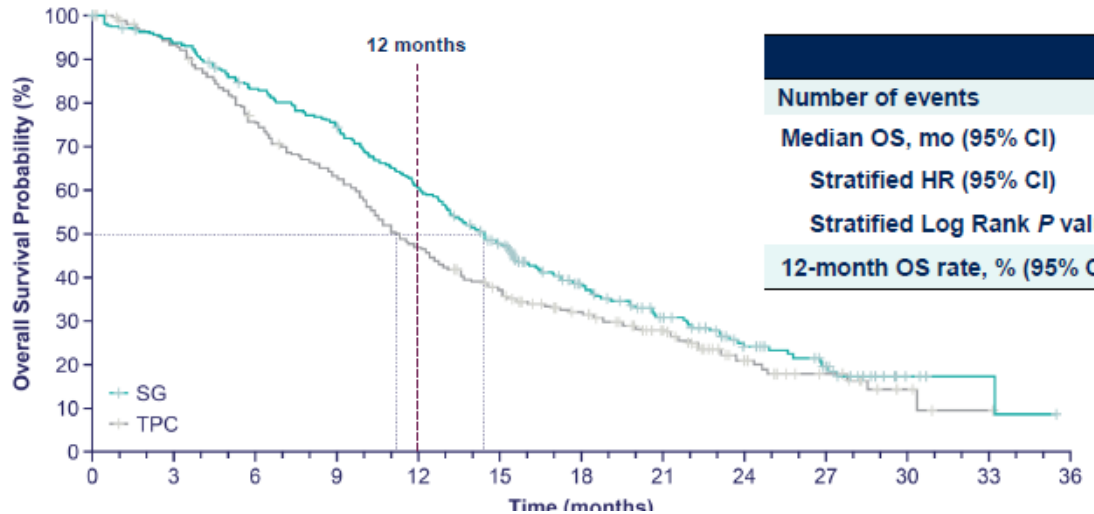
Sacituzumab Govitecan

- TROPiCS-02 trial



BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)



	SG (n=272)	TPC (n=271)
Number of events	191	199
Median OS, mo (95% CI)	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	*P*=0.020	
12-month OS rate, % (95% CI)	61 (55–66)	47 (41–53)

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Rugo H et al. ESMO 2022

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Treatment Algorithms for Metastatic Breast Cancer

Hormone receptor-positive / HER2-negative

ET (AI or fulvestrant) + CDK4/6 inhibitor

Cytotoxic chemotherapy (if visceral crisis)

▼

Fulvestrant + CDK4/6 inhibitor (if no prior use)

Fulvestrant-alpelisib (if PIK3CA mutated)

PARP inhibitor (if BRCA/PALB2 mutated)

Everolimus-exemestane

Trastuzumab deruxtecan (if HER2-Low*)

Sacituzumab govitecan

▼

Cytotoxic chemotherapy

Triple negative

ICI + Chemotherapy (if PD-L1+)

PARP inhibitor (if gBRCA mutation)

Chemotherapy (if PD-L1- and gBRCA wild type)

▼

Sacituzumab govitecan

Trastuzumab deruxtecan (if HER2-Low*)

▼

Cytotoxic chemotherapy

HER2-positive

Trastuzumab + Pertuzumab + Taxane**

▼

Trastuzumab deruxtecan

▼

Tucatinib + Trastuzumab + Capecitabine

▼

Trastuzumab emtansine

Trastuzumab-chemotherapy

Lapatinib-trastuzumab

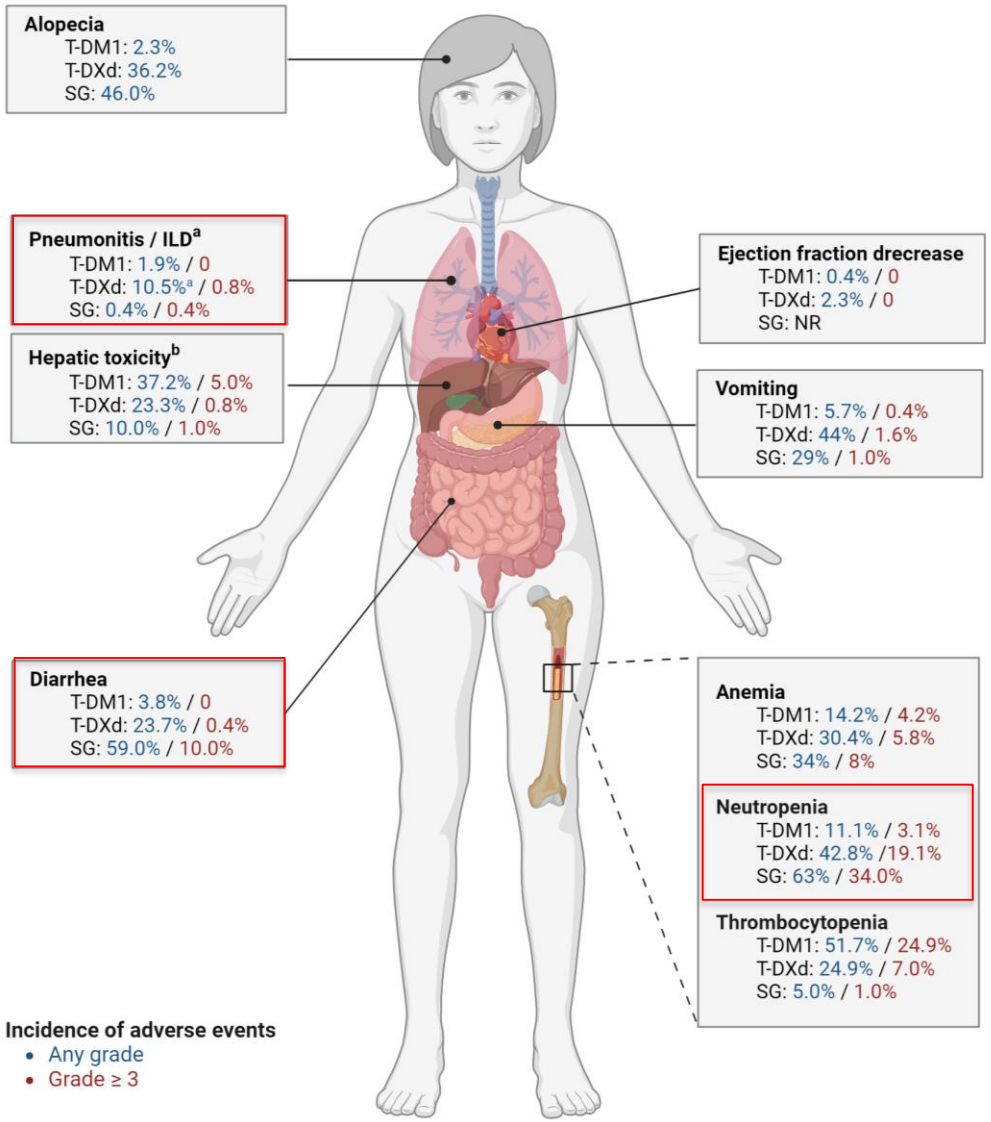
Margetuximab-chemotherapy

Neratinib-chemotherapy

ET + HER2-targeted agent

Nader-Marta G et al. (under review)

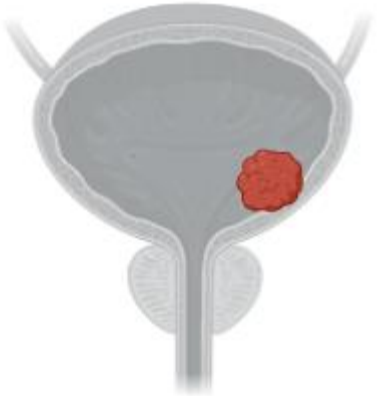
Toxicities of ADCs approved for BC treatment



Rates of adverse events retrieved from DESTINY-Breast03 and ASCENT trials

Nader-Marta G et al. (under review)

ADCs for the treatment of urothelial carcinoma



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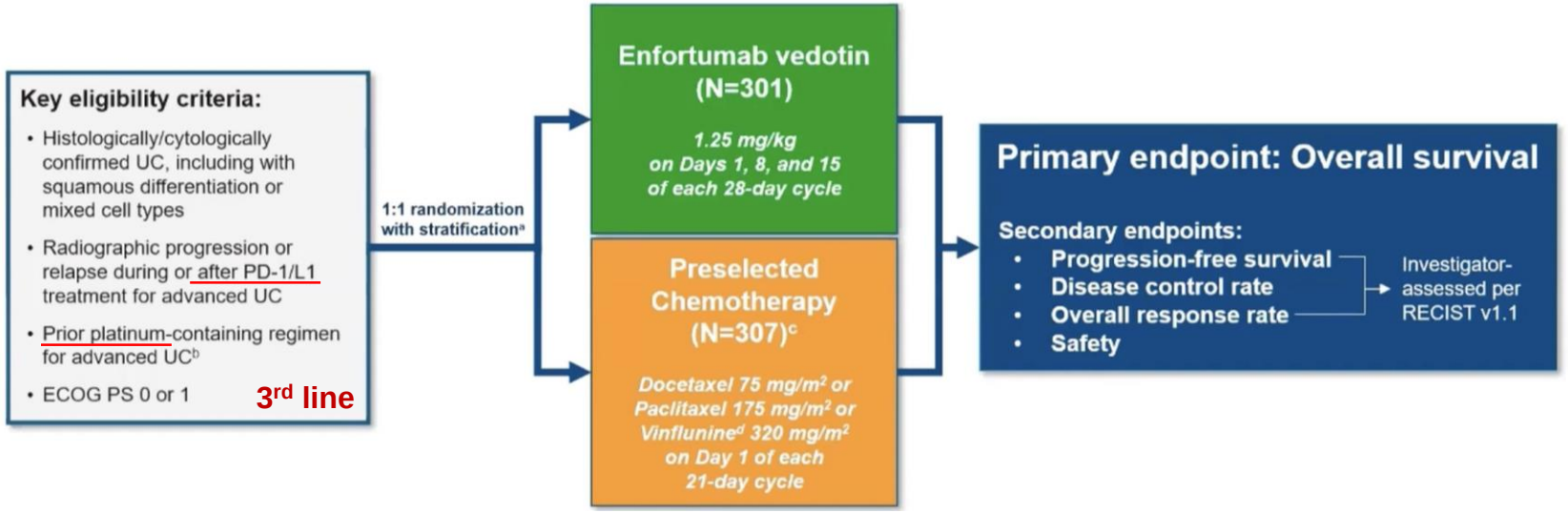
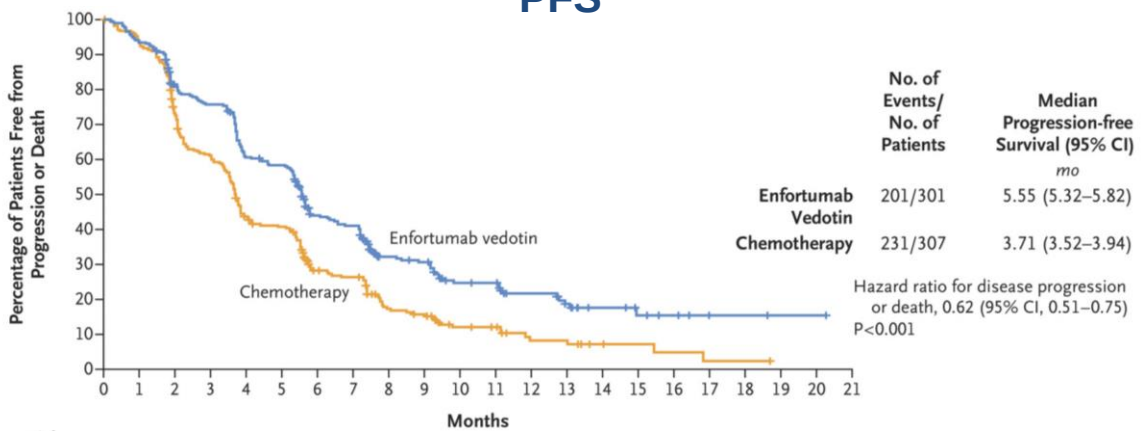
EV-301 - Enfortumab Vedotin in Urothelial Carcinoma

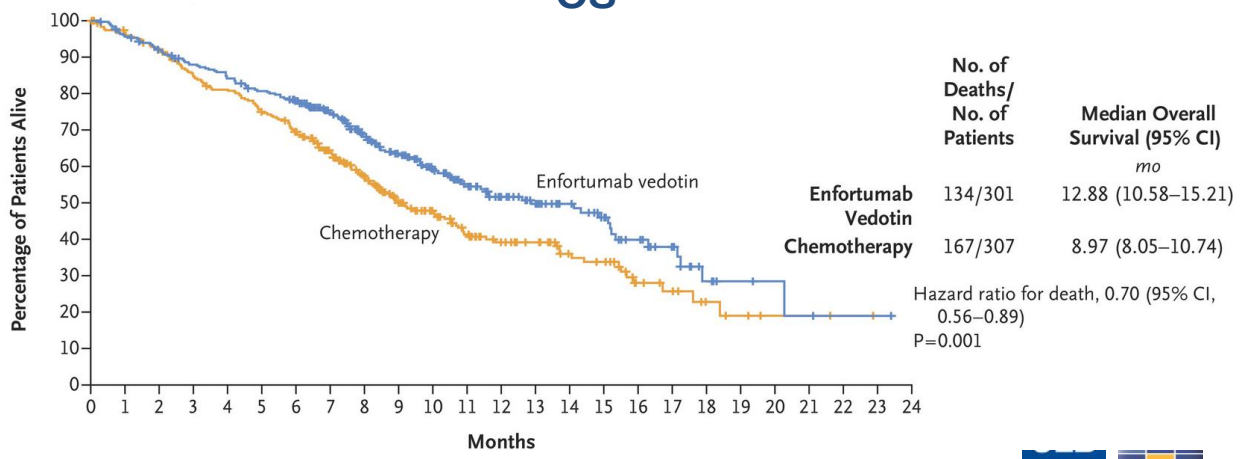
Enfortumab Vedotin
- Anti-Nectin-4 mAB
- Payload: microtubule inhibitor



PFS



OS

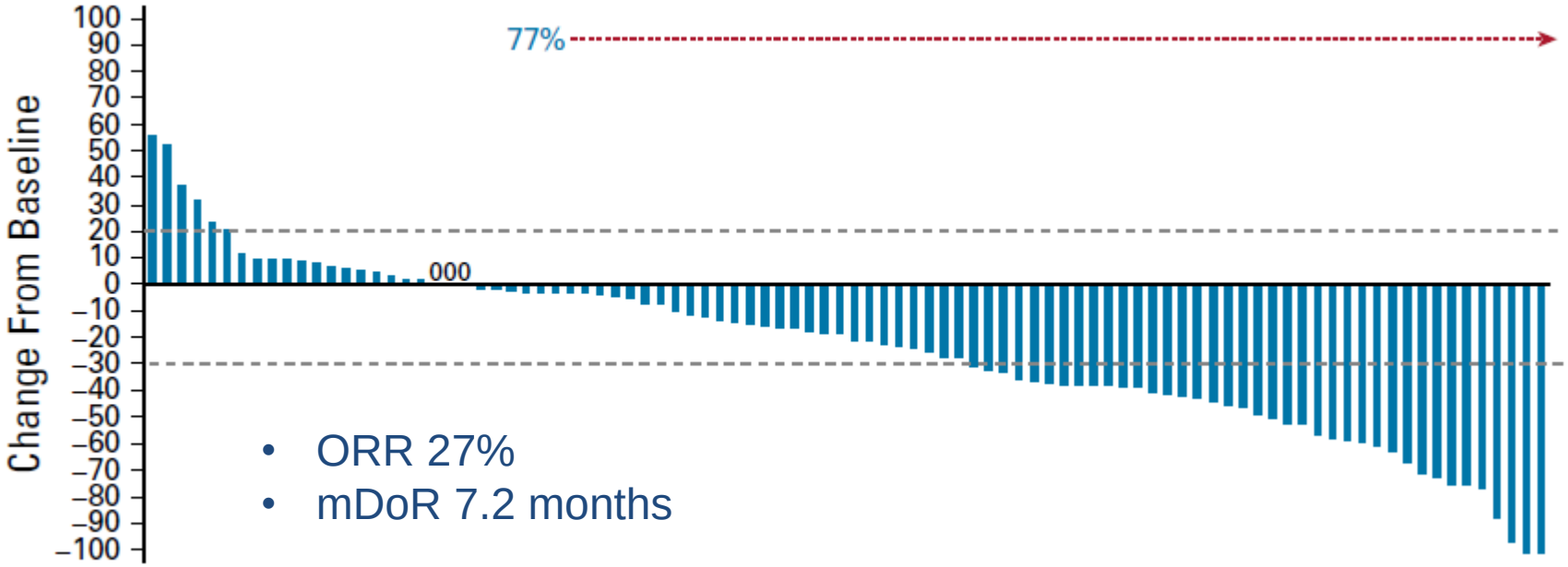


Powles et al. NEJM 2021

TROPHY-U-01 - Sacituzumab Govitecan in previously treated Urothelial Carcinoma

TROPHY-U-01 – Cohort 1

- Multicohort, open-label, phase II
- mUC after prior platinum and ICI
- N = 113



- ORR 27%
- mDoR 7.2 months

- mPFS 5.4 months
- mOS 11 months

Tagawa S et al. J Clin Oncol 2021

EV-Pembro vs EV - First-line mUC unfit for cisplatin

EV-103 Cohort K

- Open-label, multiple cohort
- Phase 1b/2 study

Cohort K

1:1 Randomization

enfortumab vedotin + pembrolizumab

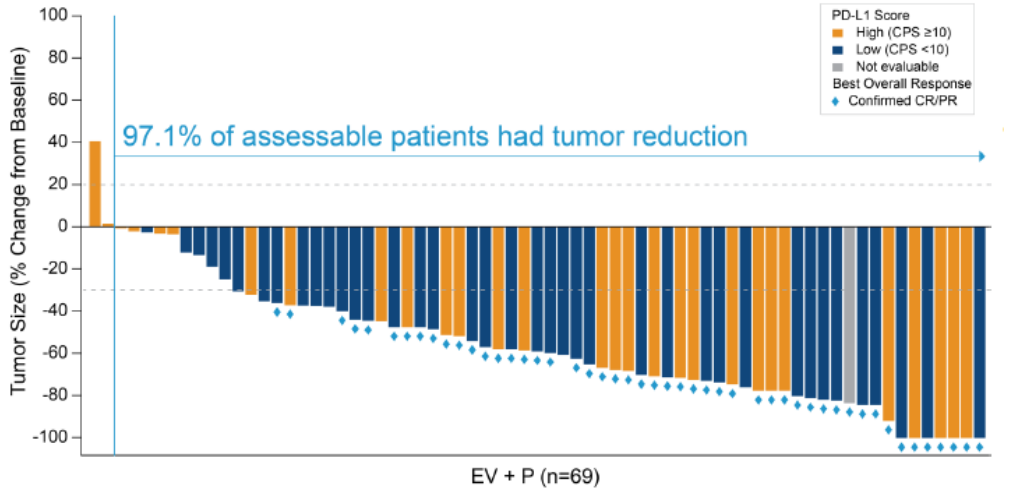
or

enfortumab vedotin

Cisplatin-ineligible 1L (N=151)

Primary endpoint: ORR by RECIST v1.1 per BICR

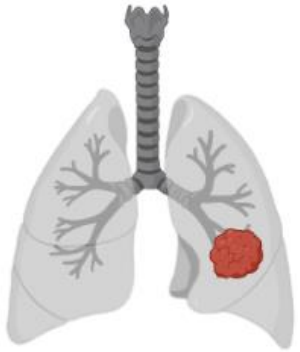
	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	**49 (64.5)** (52.7, 75.1)	**33 (45.2)** (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Duration of response, median (95% CI)	NR (10.25, -)	13.2 (6.14, 15.97)



BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response
PD-L1: Programmed Death-Ligand 1 PR: Partial Response

Rosenberg J ESMO 2022

ADCs for the treatment of NSCLC



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T-DXd in HER2-mutant NSCLC

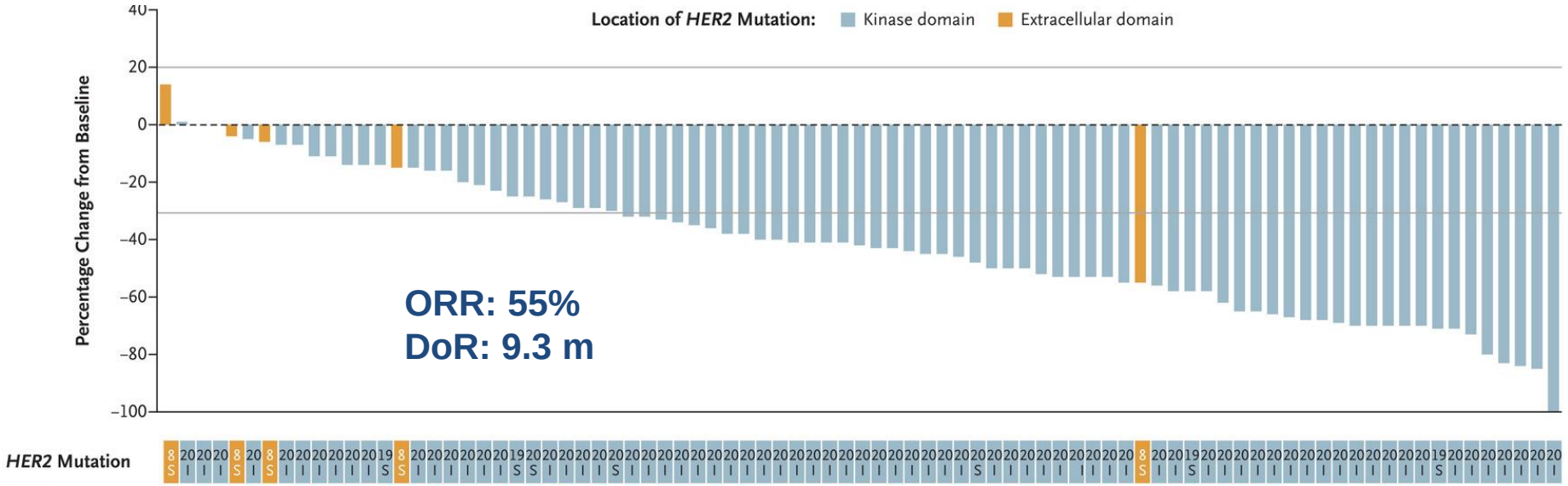
DESTINY-Lung01

- Phase II (N = 91)
- Metastatic HER2-mutant NSCLC (~ 3%)
  - 86% exon 20 insertions
- Refractory to standard treatment
- Primary endpoint: ORR

T-DM1 in HER2-mutant NSCLC

- Phase II Basket trial (N = 18)
- ORR: 44%
- mDOR: 4 m
- mPFS: 5 m

Li BT et al. JCO 2018

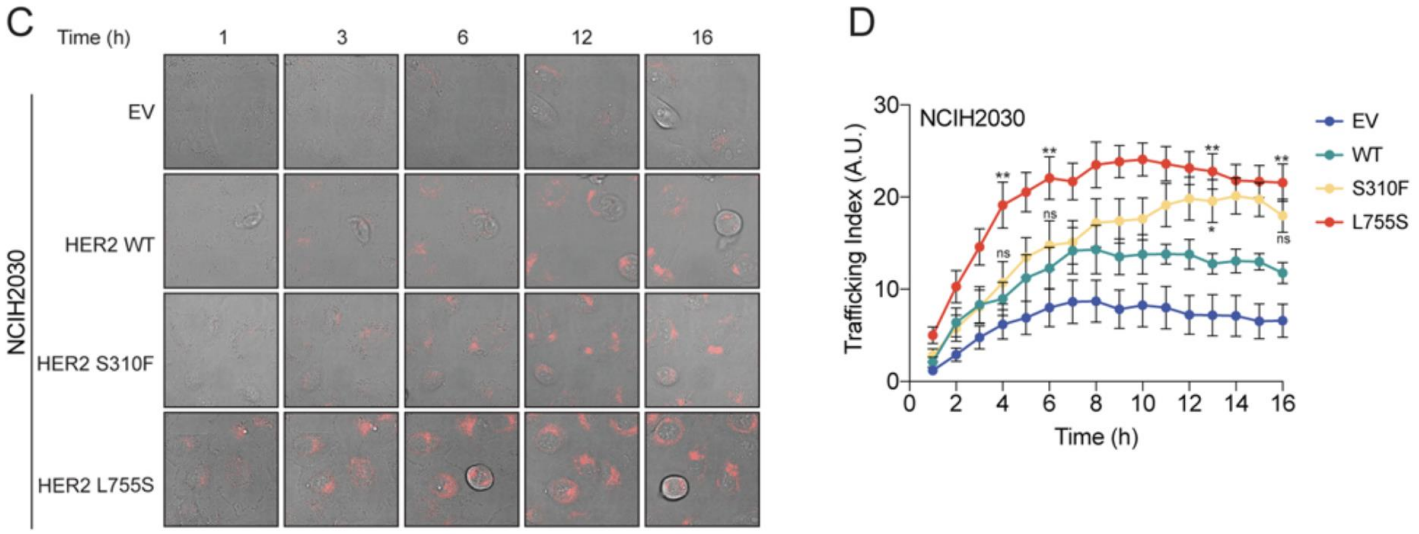


mPFS: 8.2m **mOS: 17.8m**

Li BT et al. NEJM 2022

ADCs activity in HER2-mutant tumors

Activating HER2 mutations increase receptor trafficking

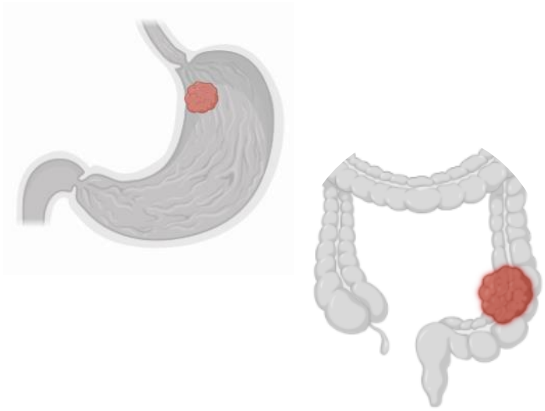


Increase the internalization rate of ADC–HER2 complexes

(regardless of the HER2 overexpression or intrinsic dependence on HER2 signalling for cell growth and/or survival)

Li BT et al. Cancer Discov 2020

ADCs for the treatment of gastrointestinal cancers



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T-DXd in HER2+ gastric cancer

DESTINY-Gastric01

HER2-positive gastric cancer (15-20%)

- Multicenter, open-label, randomized phase II study

Stratified by region (Japan vs Korea), ECOG PS (0 vs 1), HER2 status (IHC 3+ vs IHC 2+/ISH+)

Adult patients with HER2+* locally advanced or metastatic gastric or GEJ cancer that progressed on ≥ 2 prior regimens† (N = 188)

Randomized 2:1

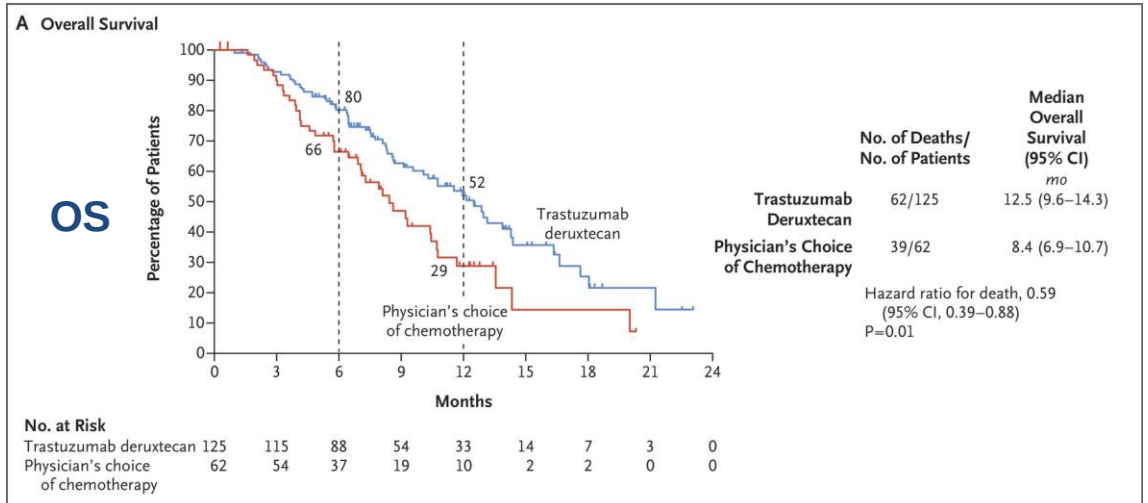
T-DXd 6.4 mg/kg, 3-week cycles (n = 126)

Physician's choice:
Irinotecan 150 mg/m² every 2 weeks or
Paclitaxel 80 mg/m² Days 1, 8, 15 every 4 weeks
(n = 62)

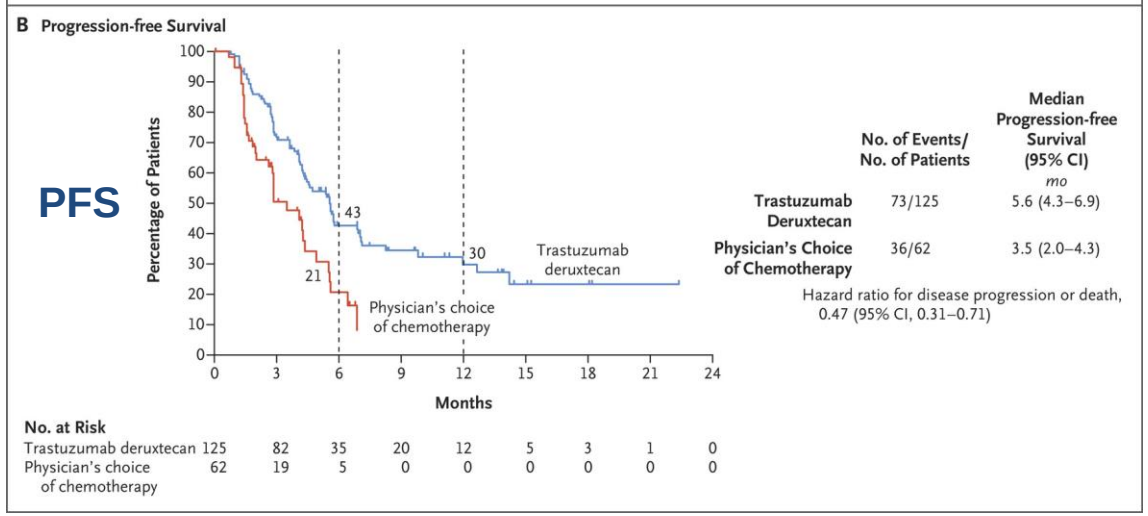
*HER2+ based on IHC 3+ or IHC 2+/ISH+ according to ASCO/CAP guidelines.
†Prior regimens included fluoropyrimidine, a platinum agent, and trastuzumab or approved biosimilar.

- Primary endpoint: ORR by ICR (RECIST v1.1)
- Secondary endpoints: OS (key), DoR, PFS, DCR, confirmed ORR, safety

OS



PFS



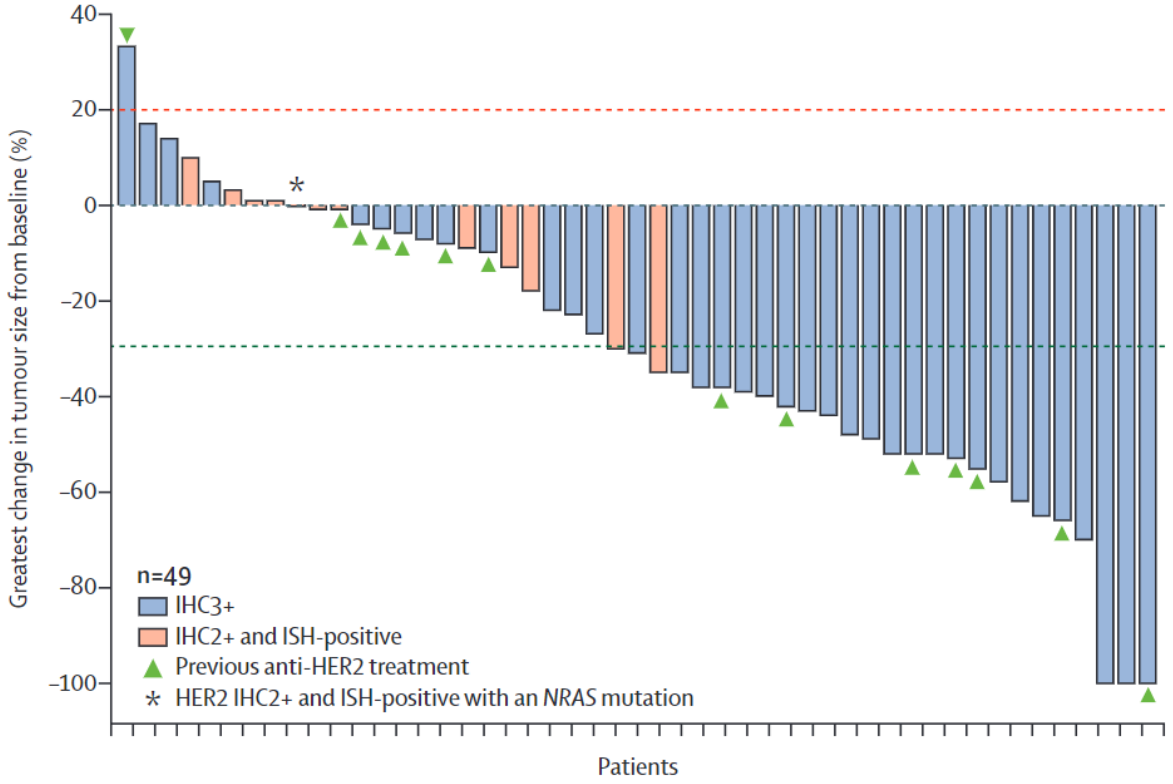
Shitara K et al. NEJM 2020

T-DXd in HER2+ Colorectal Cancer

DESTINY-CRC01 trial (N = 78)

- HER2-positive CRC (2-3%)
- Open-label, phase II
  - Cohort A: IHC 3+ or IHC 2+ and ISH+
  - Cohort B: IHC 2+ and ISH-neg
  - Cohort C: IHC 1+
- ≥ 2 prior lines (30% prior anti-HER2)

ORR in Cohort A (N = 49): 45.3%



mPFS: 7 m
mOS: 5.4 m

Siena S et al. Lancet Oncol 2021

Perspectives and future directions

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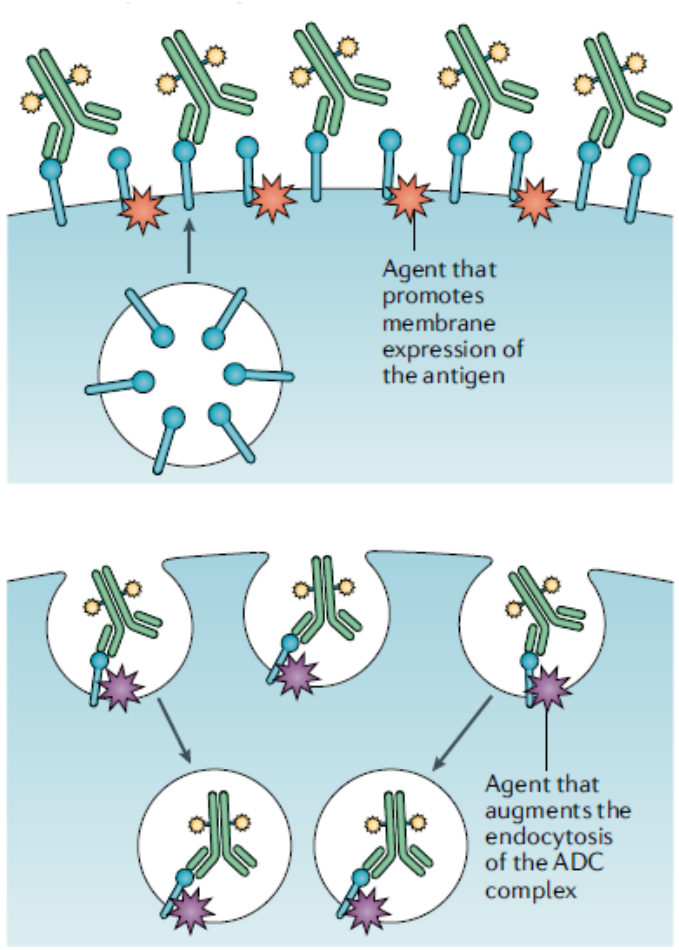
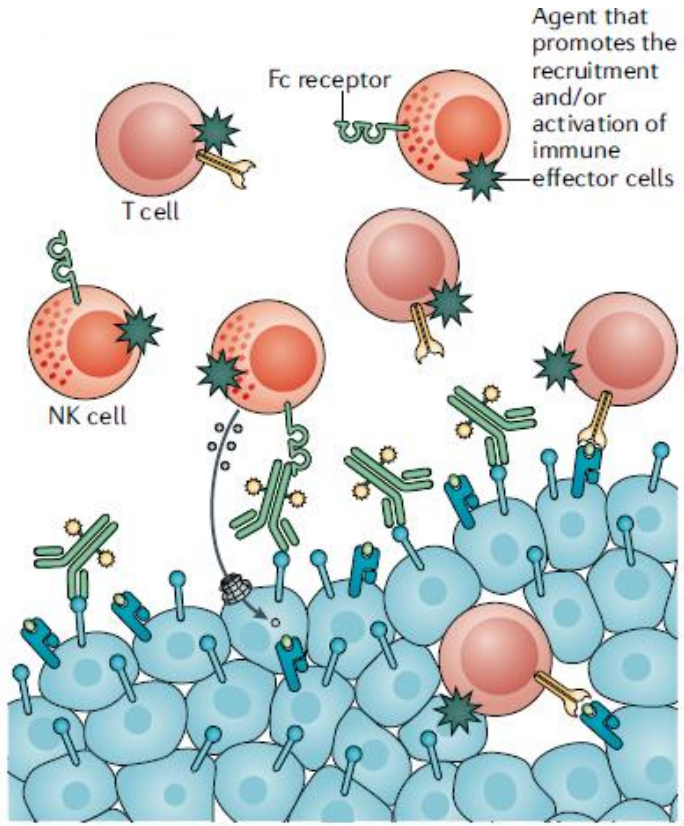
ADC-based combination strategies

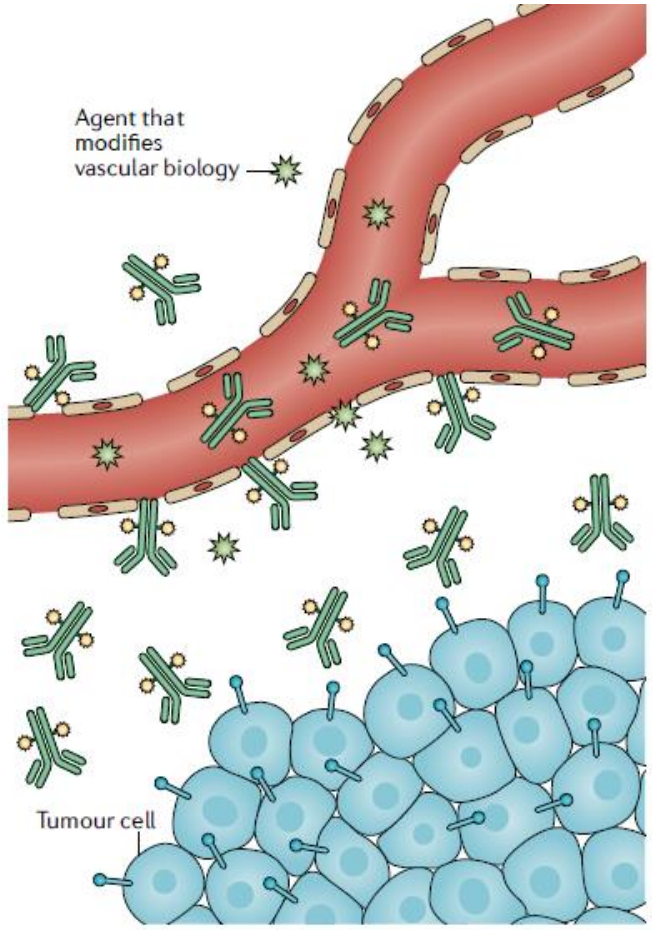
Modulation of target expression and/or processing



Promoting antitumour immunity



Increasing ADC delivery to tumour tissue



Adapted from: Drago et al. Nat Rev Clin Oncol 2021

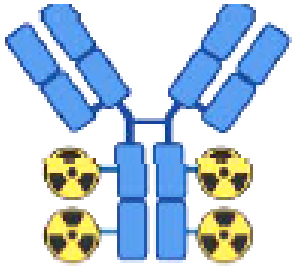
Novel Antibody–Drug Conjugates

Bispecific ADCs

Dual Payload ADCs

ADCs with immune-stimulating payloads (e.g. TLR8 agonist)

Radionuclide ADCs



Adapted from: Tarantino P et al. CA Cancer 2021

Novel targets for ADCs in solid tumors

Antibody–drug conjugate	Patload	Trial	Phase	Population	Treatment arm(S)	Biomarker
CEACAM5						
SAR408701	DM4 (tubulin inhibitor)	NCT02187848	I/II	Advanced solid tumors	SAR408701 monotherapy	No
		NCT04524689 (CARMEN-LC05)	II	Non-squamous mNSCLC (wild type for EGFR, ALK/ROS1, BRAF)	SAR408701 + pembrolizumab; pembrolizumab monotherapy	Yes
		NCT04394624 (CARMEN-LC04)	II	Non-squamous mNSCLC	SAR408701 + ramucirumab	yes
		NCT04154956 (CARMEN-LC04)	III	Non-squamous mNSCLC	SAR408701 monotherapy; docetaxel	Yes
c-MET						
Telisotuzumab vedotin (teliso-V)	MMAE (tubulin inhibitor)	NCT02099058	I	Advanced solid tumors (mNSCLC in dose expansion)	Teliso-V monotherapy Teliso-V + erlotinib (NSCLC) Teliso-V + nivolumab (NSCLC) Teliso-V + osimertinib (NSCLC)	Yes (dose expansion)
		NCT03539536	II	mNSCLC	Telisotuzumab vedotin monotherapy	Yes
TR1801-ADC	Pyrrolobenzodiazepine (DNA-crosslinking agent)	NCT03859752	I	Advanced solid tumors	TR1801-ADC monotherapy	Yes
SHR-A1403	Novel microtubule inhibitor	NCT03856541	I	Advanced solid tumors	SHR-A1403 monotherapy	No
FOLATE RECEPTOR ALPHA						
Mirvetuximab soravtansine (IMGN853)	DM4 (tubulin inhibitor)	NCT02606305	I/II	Advanced OC, fallopian tube, primary peritoneal cancer	IMGN853 + bevacizumab; IMGN853 + carboplatin; IMGN853 + pegylated liposomal doxorubicin; IMGN853 + pembrolizumab; IMGN853 + bevacizumab + carboplatin	Yes
		NCT03832361	II	mEC	IMGN853 monotherapy	Yes
		NCT02996825	I	Recurrent OC, primary peritoneal, fallopian tube, mEC, mTNBC	IMGN853 + gemcitabine	Yes
		NCT03552471	I	Advanced OC, fallopian tube, primary peritoneal cancer or mEC	IMGN853 + rucaparib	Yes
		NCT03835819	II	mEC	IMGN853 + pembrolizumab	Yes
		NCT04606914	II	Advance-stage OC, fallopian tube, primary peritoneal cancer (neoadjuvant setting)	IMGN853 + carboplatin	Yes
		NCT04274426 (MIROVA)	II	Recurrent OC, fallopian tube, primary peritoneal cancer	IMGN853 + carboplatin; Platinum-based chemotherapy	Yes

CEACAM5

c-MET

Folate Receptor Alpha

Antibody–drug conjugate	Patload	Trial	Phase	Population	Treatment arm(S)	Biomarker
		NCT04209855 (MIRASOL)	III	Advanced OC, fallopian tube, primary peritoneal cancer	IMGN853; Chemotherapy of investigator's choice (paclitaxel or topotecan or pegylated liposomal doxorubicin)	Yes
		NCT04296890 (SORAYA)	III	mOC, fallopian tube, primary peritoneal cancer	IMGN853 monotherapy	Yes
STRO-002	Herniasterlin (tubulin inhibitor)	NCT03748186	I	Advanced OC, fallopian tube, primary peritoneal cancer, mEC	STRO-002 monotherapy	No
MORAb-202	Eribulin (tubulin inhibitor)	NCT03386942	I	Advanced solid tumors	MORAb-202 monotherapy	Yes (only for selected subtypes)
		NCT04300556	I/II	mOC, fallopian tube, primary peritoneal cancer, mTNBC, mEC, NSCLC adenocarcinoma	MORAb-202 monotherapy	Yes (dose expansion)
HER3						
Patritumab deruxtecan (U3-1402)	Deruxtecan (TOP1 inhibitor)	NCT02980341	I/II	mBC	Patritumab deruxtecan monotherapy	Yes
		NCT03260491	I	mNSCLC	Patritumab deruxtecan monotherapy	No
		NCT04479436	II	mCRC	Patritumab deruxtecan monotherapy	2 cohorts (IHC 2+/3+; 1+/0)
		NCT04610528	Early phase I	HR+/HER2- eBC (treatment-naïve patients)	Patritumab deruxtecan monotherapy	4 cohorts
		NCT04619004 (HERTHENA-Lung01)	II	EGFR-mutated mNSCLC	Patritumab deruxtecan monotherapy	No
LIV-1						
Ladiratuzumab vedotin (SGN-LIV1A)	MMAE (tubulin inhibitor)	NCT01969643	I	mBC	SGN-LIV1A monotherapy; SGN-LIV1A + trastuzumab (part B)	No
		NCT03310957	Ib/II	mTNBC (first-line setting)	SGN-LIV1A + pembrolizumab	No
		NCT04032704	II	Advanced SCLC, NSCLC, HNSCC, ESCC, GC, GEJC, prostate cancer, melanoma	SGN-LIV1A monotherapy	No
		NCT03424005 (Morpheus-TNBC)*	I/II	mTNBC	SGN-LIV1A + atezolizumab	No
		NCT01042379 (I-SPY2)*	I	Triple-negative eBC (neoadjuvant setting)	SGN-LIV1A monotherapy	No
MESOTHELIN						
Anetumab ravtansine	DM4 (tubulin inhibitor)	NCT03126630	I/II	MPM	Anetumab ravtansine + pembrolizumab; Pembrolizumab monotherapy	Yes

HER3

LIV-1

Mesothelin

Antibody–drug conjugate	Patload	Trial	Phase	Population	Treatment arm(S)	Biomarker
		NCT03102320	I	Advanced solid tumors	Anetumab ravtansine monotherapy; Anetumab ravtansine + gemcitabine; Anetumab ravtansine + cisplatin	Yes
		NCT03587311	I/II	Advanced OC, fallopian tube, or primary peritoneal cancer	Anetumab ravtansine + bevacizumab; Paclitaxel + bevacizumab	Yes (only for part 2)
		NCT03816358	I/II	Pancreatic adenocarcinoma	Anetumab ravtansine + nivolumab; Anetumab ravtansine + nivolumab + ipilimumab; Anetumab ravtansine + nivolumab + gemcitabine	Yes
RC88	MMAE (tubulin inhibitor)	NCT04175847	I	Advanced solid tumors	RC88 monotherapy	Yes
BMS-986148	Tubulysin (tubulin inhibitor)	NCT02341625	I/II	MPM, NSCLC, OC, GC, pancreatic cancer	BMS-986148 monotherapy; BMS-986148 + nivolumab	Yes (dose expansion)
TISSUE FACTOR						
Tisotumab vedotin	MMAE (tubulin inhibitor)	NCT03485209 (InnovaTV 207)	II	mCRC, pancreatic cancer, squamous NSCLC, HNSCC	Tisotumab vedotin monotherapy	No
		NCT03438396	II	mCC	Tisotumab vedotin monotherapy	No
		NCT03657043 (InnovaTV 208)	II	Advanced OC, fallopian tube, peritoneal cancer	Tisotumab vedotin monotherapy	No
		NCT03786081	I/II	mCC	Tisotumab vedotin monotherapy Tisotumab vedotin + carboplatin Tisotumab vedotin + pembrolizumab Tisotumab vedotin + bevacizumab	No

Tissue factor

Criscitiello et al. J Hematol Oncol 2021

Take home messages

- ADCs are a class of potent anticancer agents characterized by a smart form of targeted drug delivery
- Unprecedented efficacy in the treatment of early and advanced cancer and across different cancer types
  - Potential for tumor-agnostic treatments
- New ADCs demonstrate efficacy in populations with low expression of target antigens
- Different toxicity profile ⚠️
- Future directions:
  - Explore synergistic interactions between ADCs and other agents
  - Understand resistance mechanisms → treatment sequencing

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Thank you for your attention

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