Antibody Drug Conjugate (ADC) nel carcinoma mammario: Target, risultati e prospettive future

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Disclosures

Honoraria as a consultant, advisor or speaker: Roche and Menarini/Stemline.

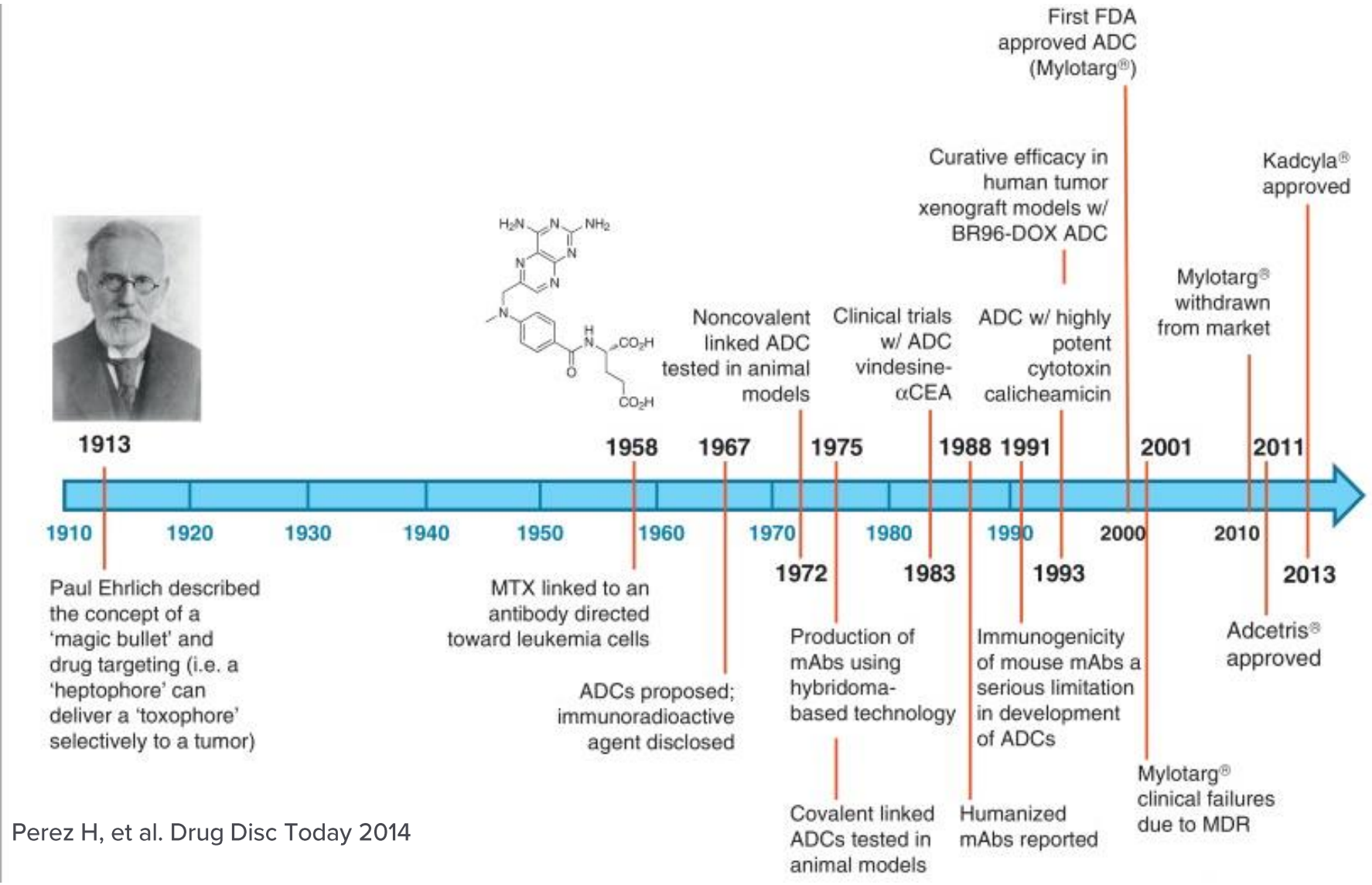
Travel and accommodation support: AstraZeneca.

Grant/Funding: ESMO José Baselga Fellowship for Clinician Scientists supported by AstraZeneca

Outline

- **ADC drug development in breast cancer**
- **ADCs targets with clinical approval**
  - HER2
  - TROP2
- **Challenges and opportunities**

Magic bullets for treating cancer



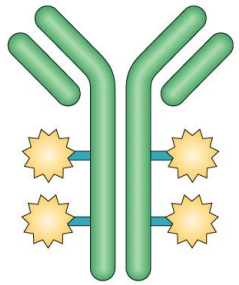
Perez H, et al. Drug Disc Today 2014

In **1913**, Paul Ehrlich described the concept of a **"magic bullet"** that could selectively deliver toxic molecules to tumor cells

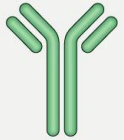
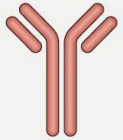
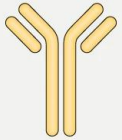
100 years later (**2013**), the **first antibody-drug conjugate** was approved for the treatment of a solid tumor (T-DM1)

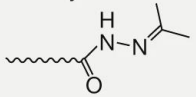
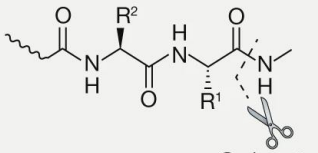
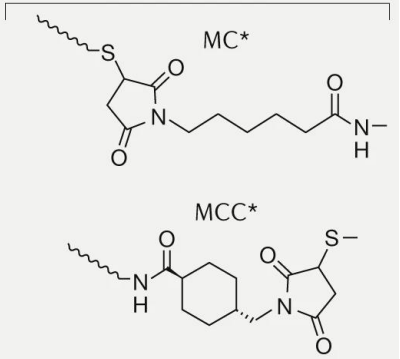
Antibody–drug conjugate (ADC) as modular component

a



b

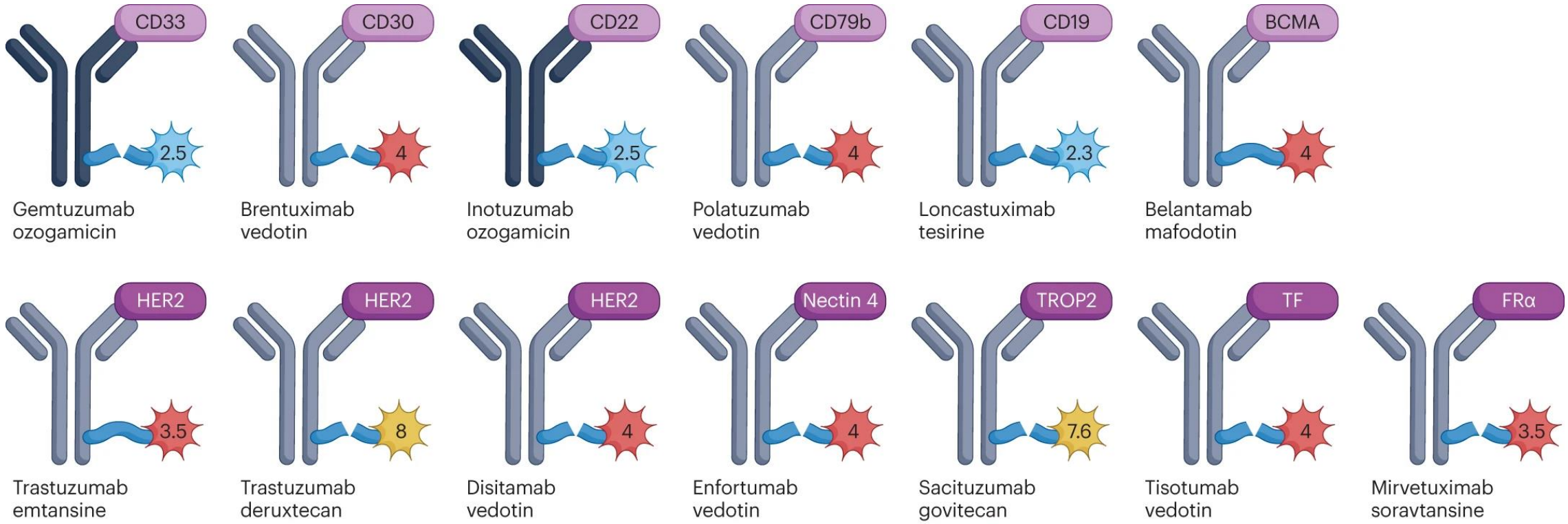
	IgG1	IgG2	IgG3	IgG4
Antibodies				
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

	Cleavable			Non-cleavable
Linkers	Hydrazone 	Disulfide 	Dipeptide 	
	Acid cleavable	Reducible	Protease cleavable	

Payloads	 Auristatins	 Maytansinoids	 Calicheamicins	 Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition

Drago J, et al. Nat Rev Clin Oncol 2021

Main characteristics of approved ADCs

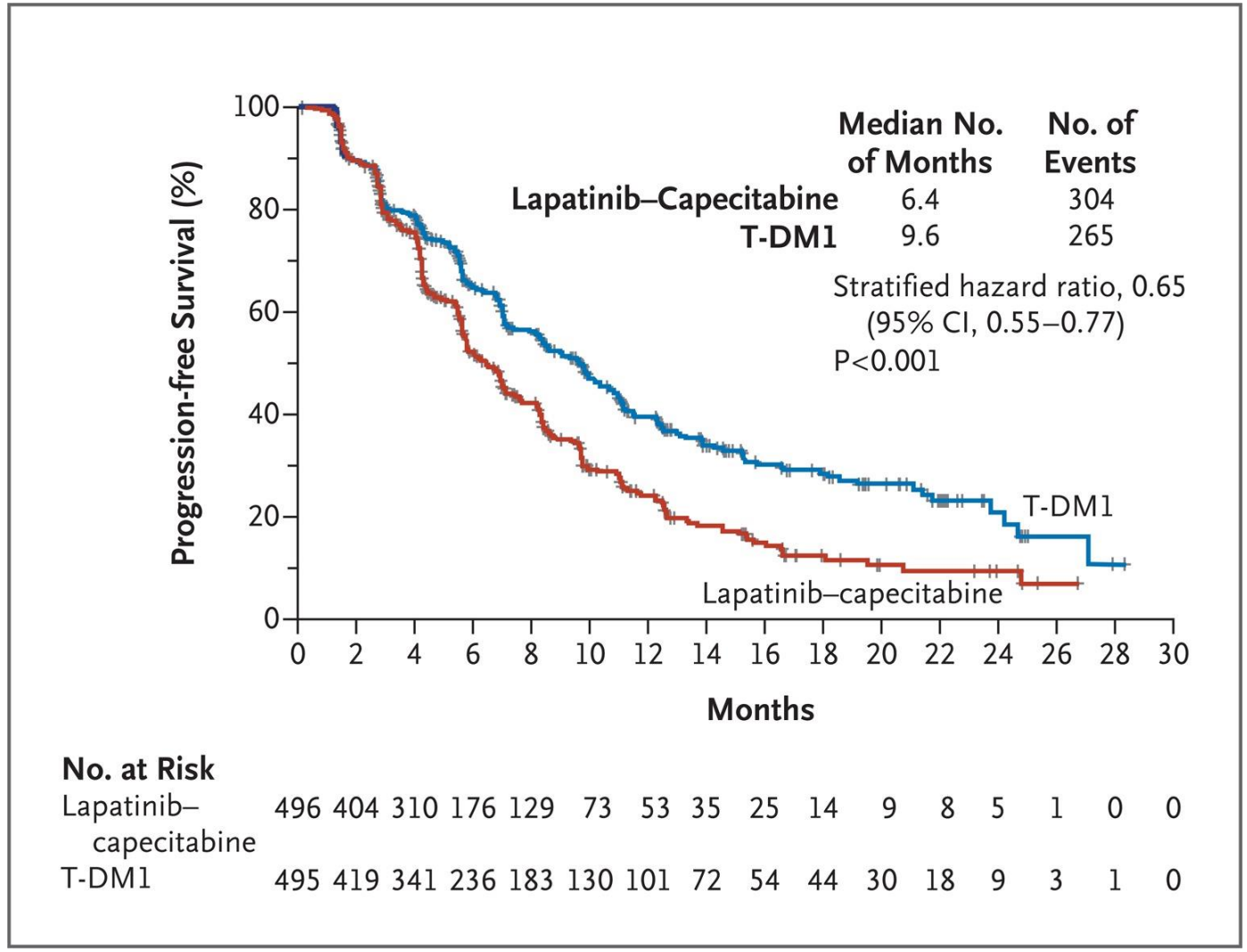


Dumontet C, et al. Nat Rev Drug Discov 2023

T-DM1

EMILIA TRIAL

It was granted approval by the FDA in 2013, after showing to improve PFS and OS in **HER2+** breast cancer in the **EMILIA trial**



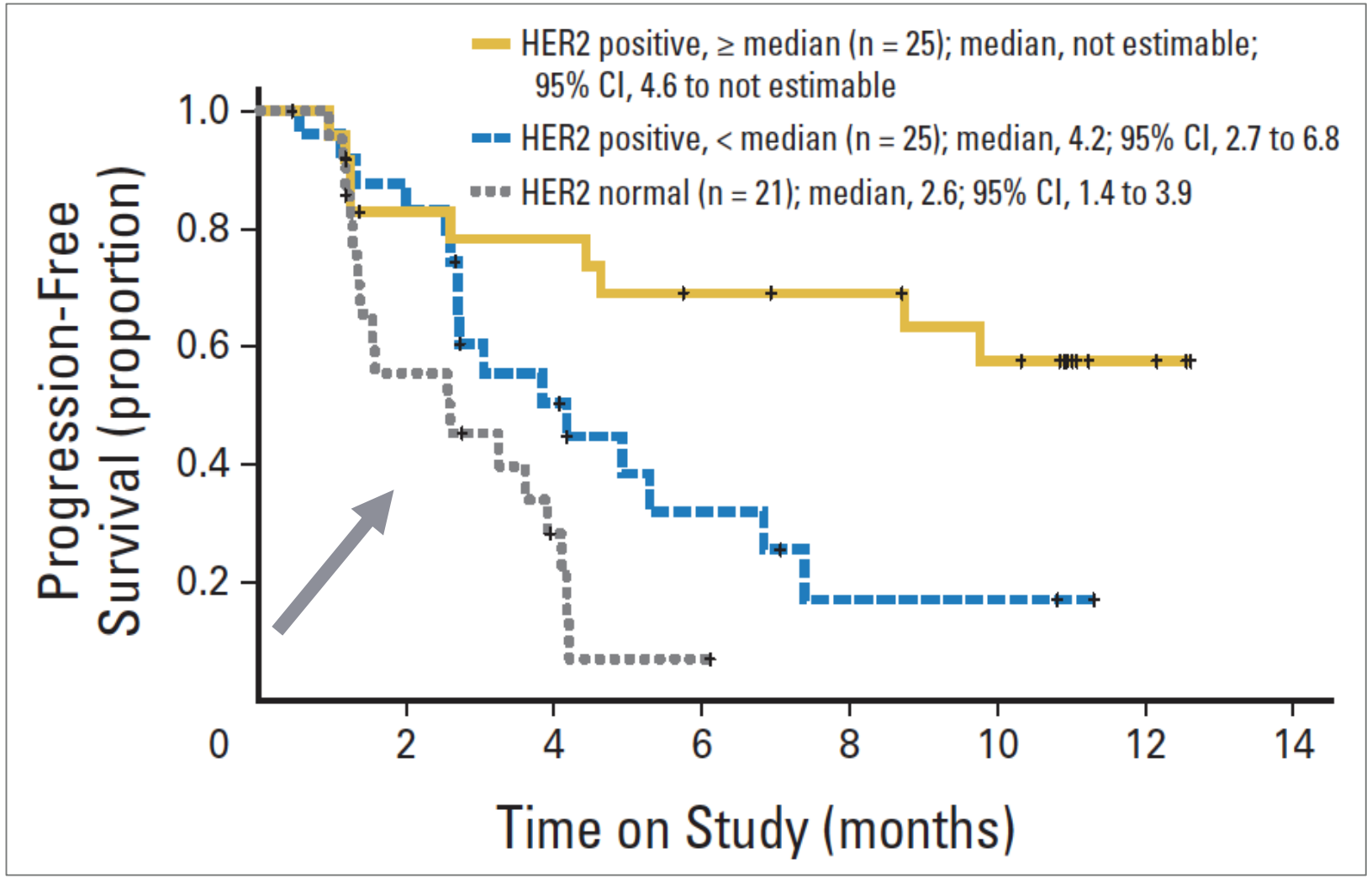
Verma S, et al. NEJM 2012

T-DM1

ACTIVITY IN HER2-NEGATIVE BREAST CANCER

The activity of T-DM1 in **HER2-negative** breast cancer is however poor

Among 21 HER2-negative MBC patients receiving T-DM1, only 1 achieved a response (**ORR 4.8%**) and the **median PFS was 2.6 months**



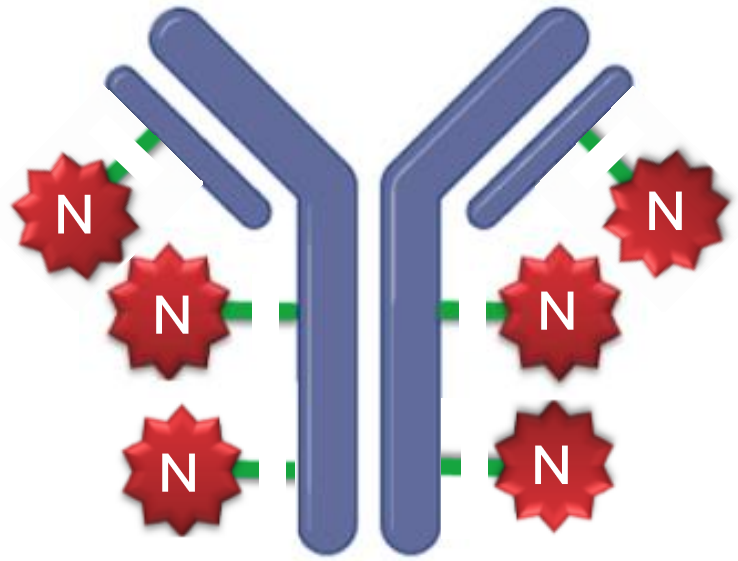
Burris HA, et al. J Clin Oncol. 2011

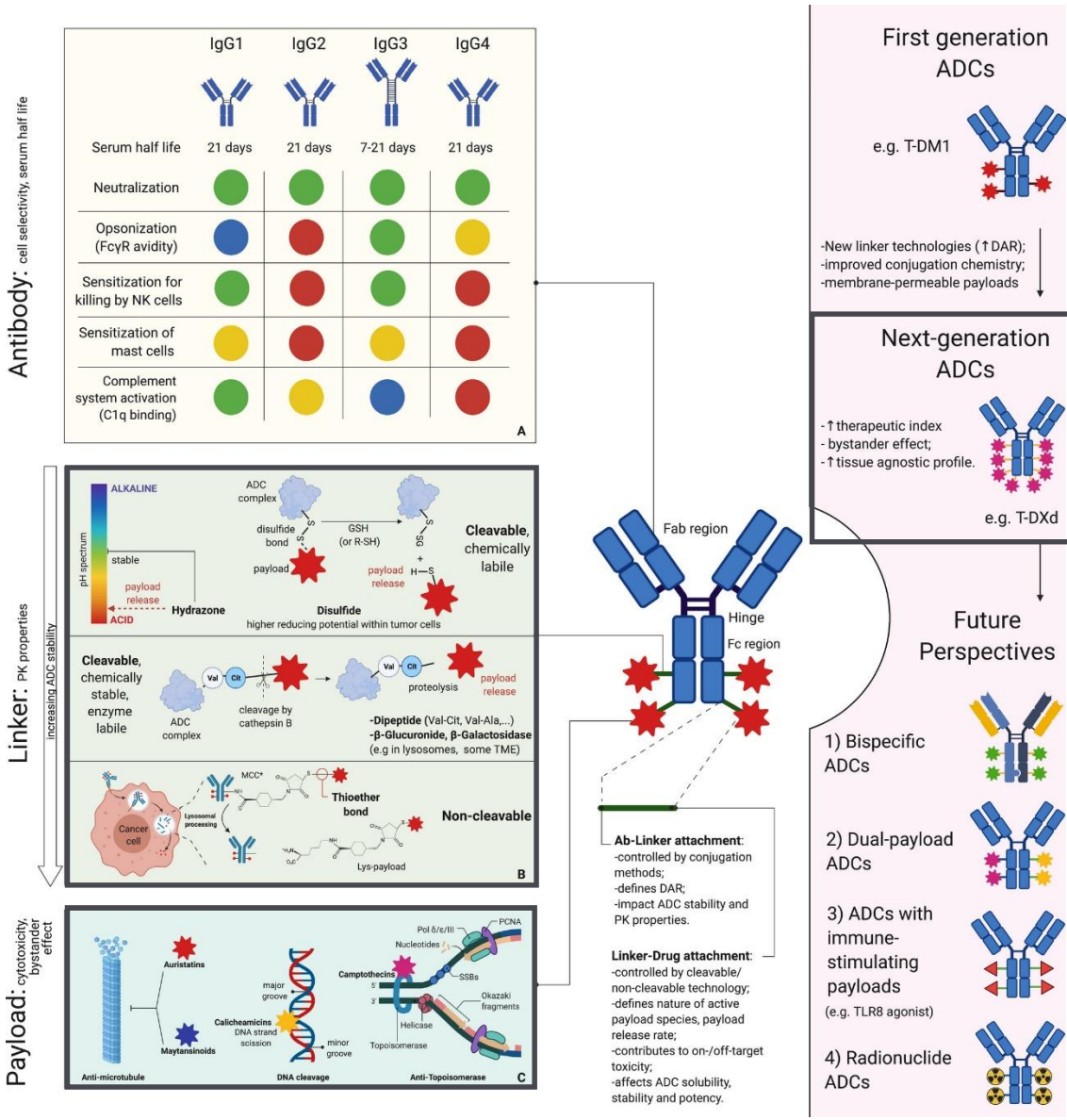
Novel conjugates

Higher DAR

Cleavable Linker

Novel payloads





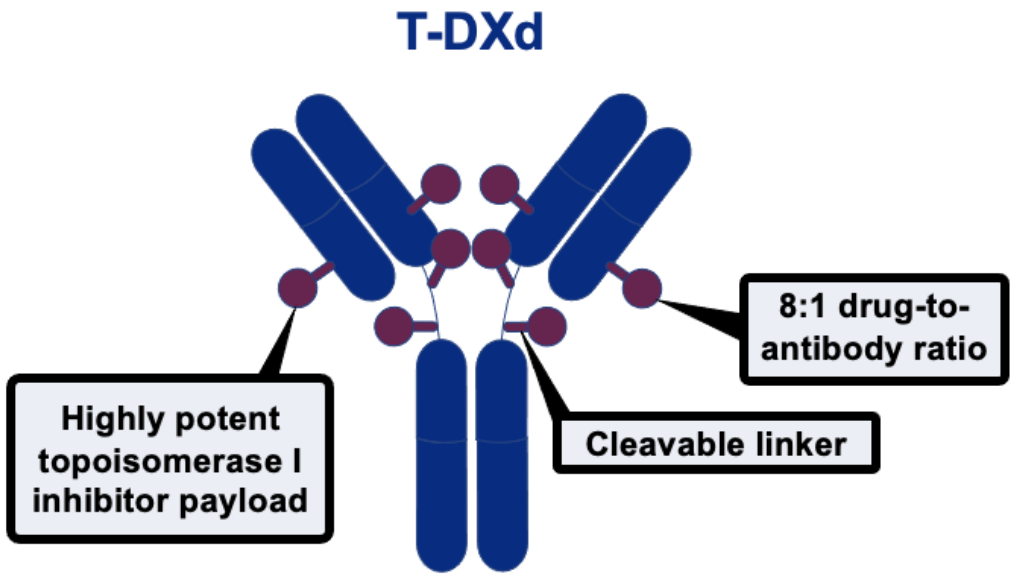
Tarantino P, et al. CA Cancer J Clinicians 2021

Summary of Phase III clinical trials of novel ADCs in MBC

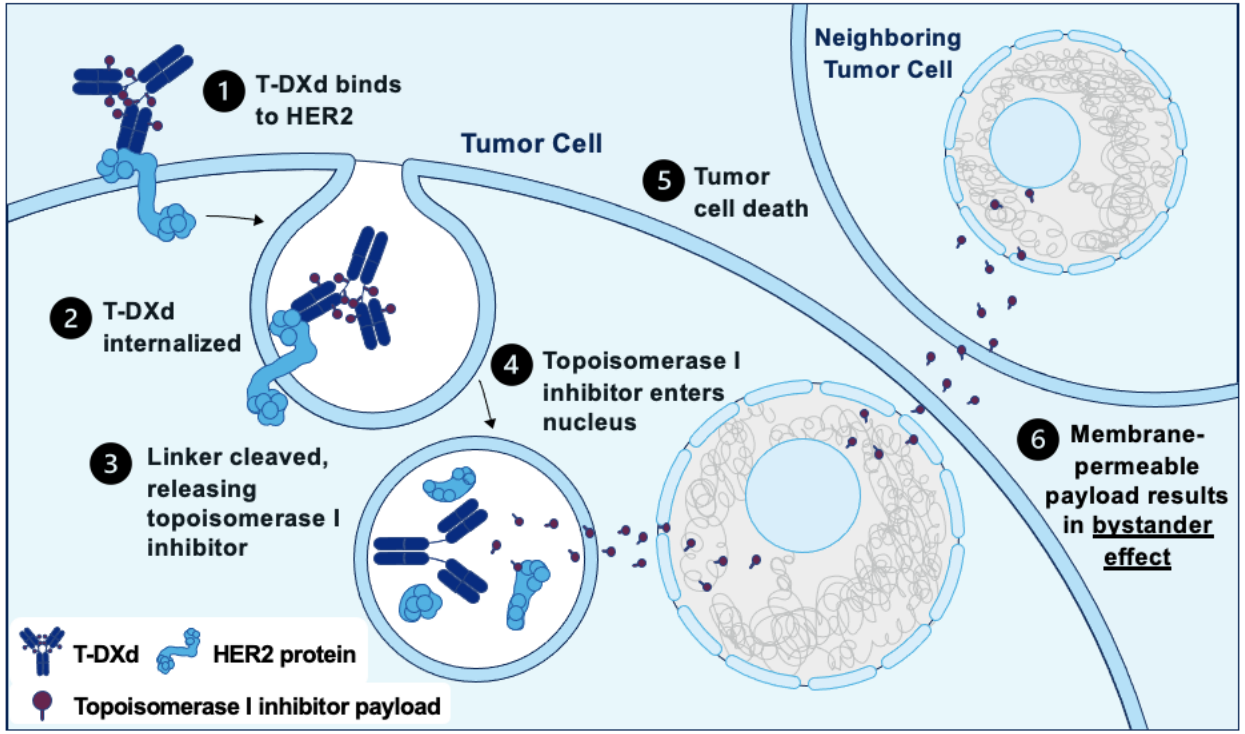
	T-DXd			**Sacituzumab-govitecan**		**Dato-DXd**
Target/Payload	HER2/ TOPO-1-inh			TROP2/ TOPO-1-inh		TROP2/ TOPO-1-inh
FDA Approved	Yes	Yes	Yes	Yes	Yes	No
EMA Approved	Yes	Yes	Yes	Yes	Yes	No
Study(s)	DB-03	DB-02	DB-04	ASCENT	TROPiCS-02	TROPION-Breast01
Subtype	HER2+	HER2+	HER2-low	TNBC	HR+/HER2-	HR+/HER2-
Setting	2° line	3° line	2-3° line	2-3° line	>=3° line	2-3° line
Control Arm	T-DM1	TPC	TPC	TPC	TPC	TPC
PFS (mo)	28.8 vs. 6.8	17.8 vs. 6.9	9.9 vs. 5.1	5.6 vs. 1.7	5.5 vs. 4.0	6.9 vs. 4.9
HR (95% CI)	0.33 (0.26-0.43)	0.36 (0.28-0.45)	0.50 (0.40-0.63)	0.41 (0.32-0.52)	0.66 (0.53-0.83)	0.63 (0.52-0.76)
P	<0.0001	<0.0001	<0.001	<0.001	0.0003	<0.0001
OS (mo)	Not reached	39.2 vs. 26.5	23.4 vs. 16.8	12.1 vs. 6.7	14.4 vs. 11.2	Not mature
HR (95% CI)	0.64 (0.47-0.87)	0.66 (0.50-0.86)	0.64 (0.49-0.84)	0.48 (0.38-0.59)	0.79 (0.65-0.96)	
P	0.0037	0.0021	0.001	p<0.001	0.02	

T-DXd

STRUCTURE AND MECHANISM OF ACTION



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect

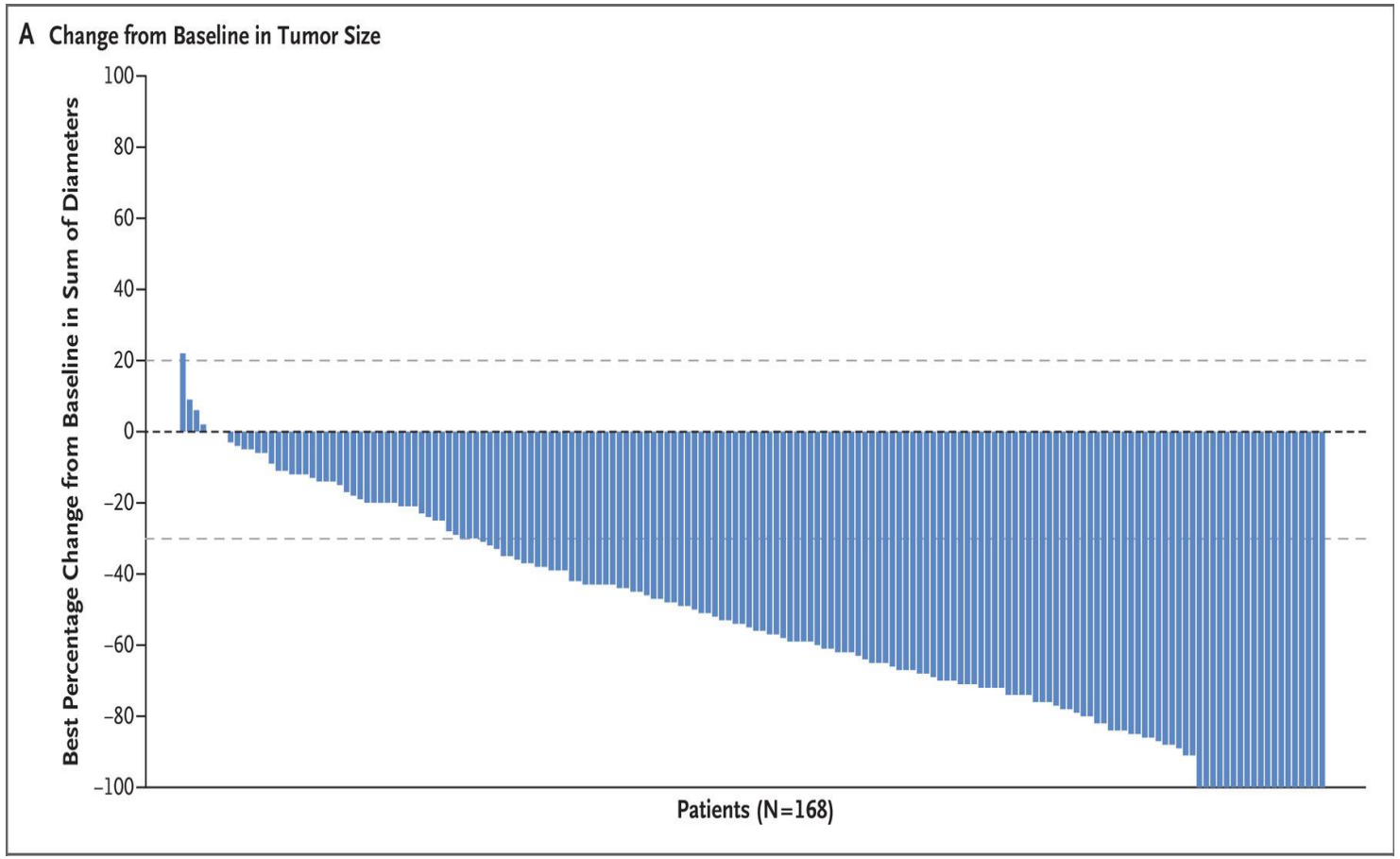


Modi S, et al. ASCO 2022

T-DXd (DESTINY Breast 01)

ACTIVITY IN HER2+ BREAST CANCER – LATE LINES

Approved by the FDA in 2019 for the treatment of **HER2**+ MBC based on the unprecedented activity observed in the DESTINY-Breast01 phase 2 trial

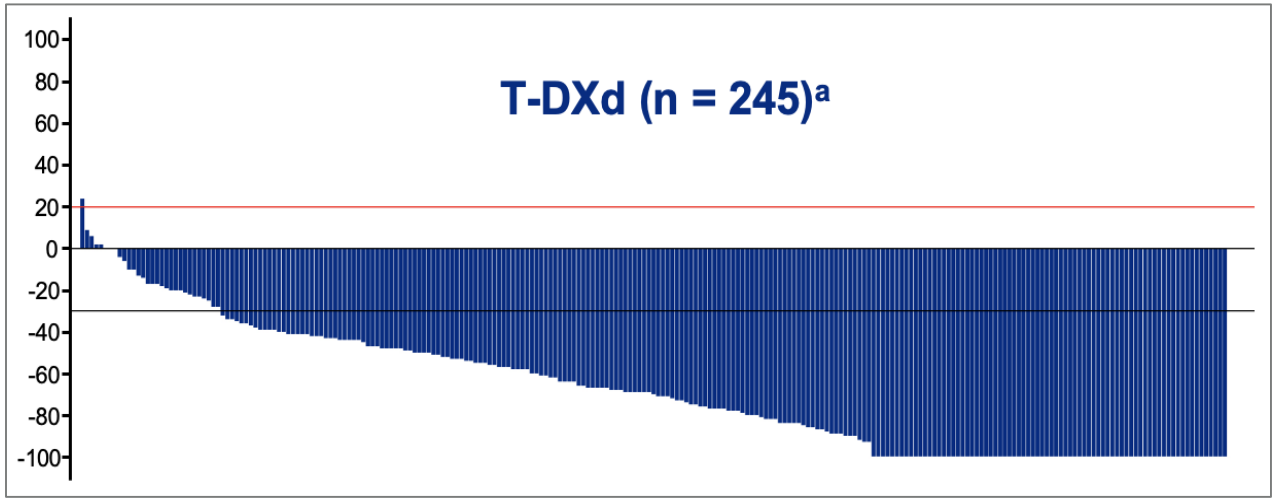


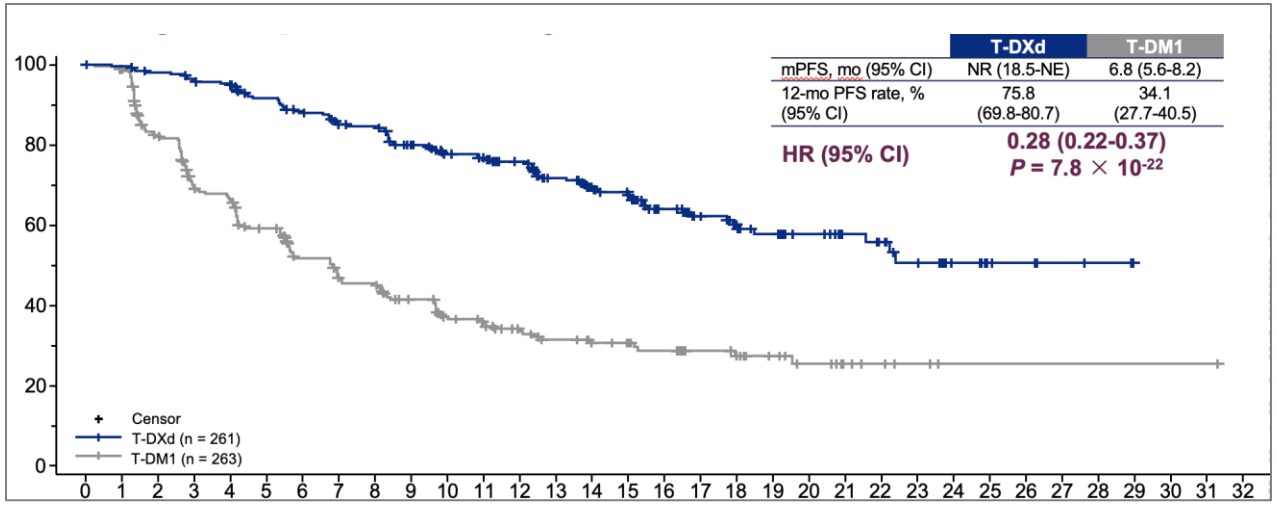
Modi S, et al. NEJM 2020

T-DXd (DESTINY Breast 03)

ACTIVITY IN HER2+ BREAST CANCER – SECOND LINE

Subsequently approved for the **second line** treatment of **HER2+** metastatic breast cancer, after showing to outperform T-DM1 in DESTINY-Breast03 phase 3 trial





Cortes J., et al. NEJM 2022

T-DXd (J101)

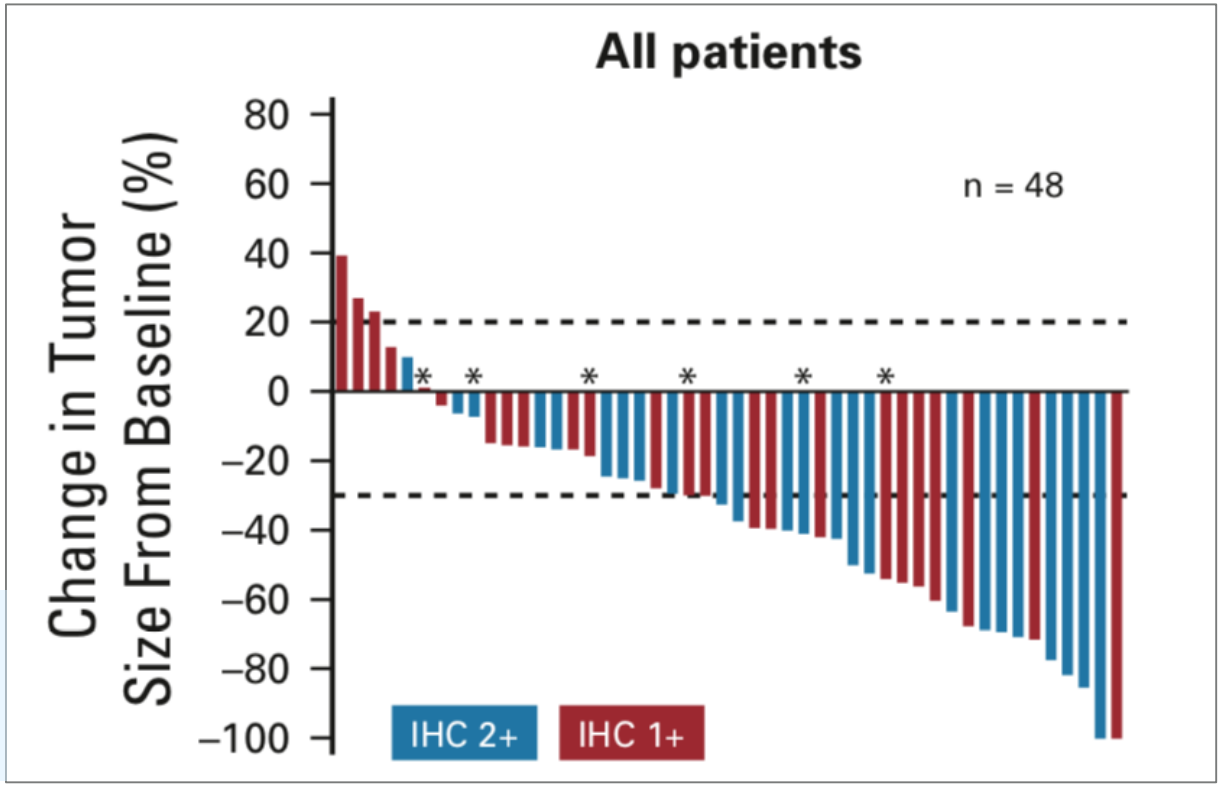
ACTIVITY IN HER2-LOW MBC

First presented at ASCO 2018, results from a Phase 1b study of trastuzumab deruxtecan (T-DXd) suggested activity in **HER2-low MBC**

Among 54 highly pre-treated (median 7.5) mBC patients with HER2 **IHC 1+ or 2+/FISH-**:

- ORR 37%
- mPFS 11 months

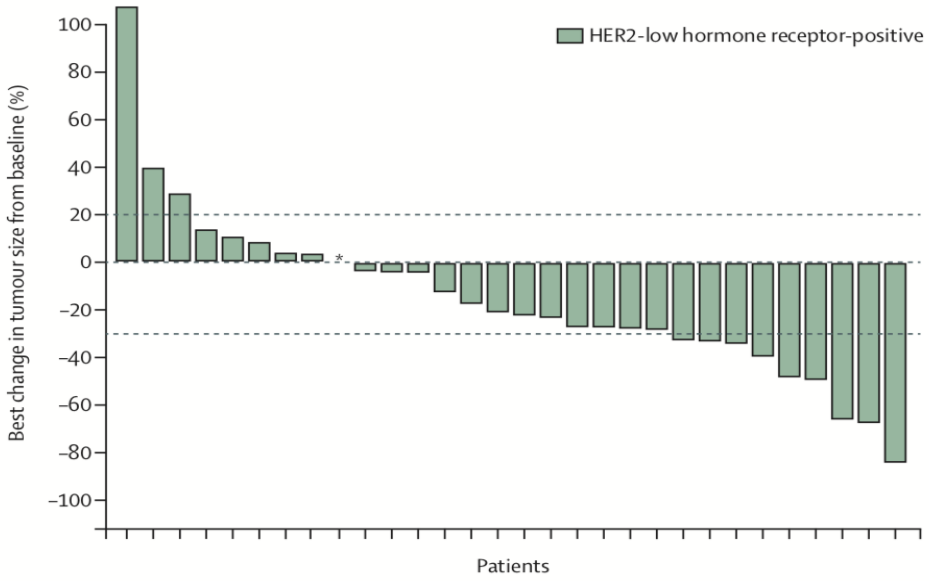
Common Grade ≥3 TEAEs included decreases in neutrophil, platelet, and WBC counts; anaemia; hypokalaemia; AST increase; decreased appetite; and diarrhoea



Modi S., et al. JCO 2020

Other active ADCs in HER2-low

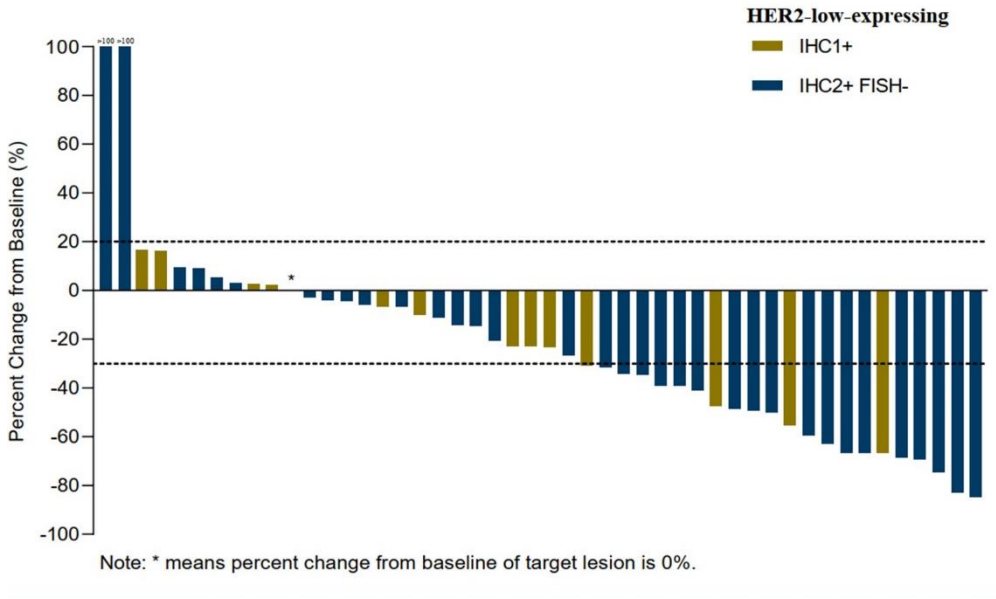
Trastuzumab duocarmazine (SYD985)[1]



49 HER2-low mBC patients: ORR 32%, mPFS 4 mo

Grade 1–4 TRAEs were fatigue (33%), conjunctivitis (31%), and dry eye (31%). Most patients (71%) had at least one ocular AE, with Grade 3 events reported in 7% of patients

Disitamab Vedotin (RC48-ADC)[2]



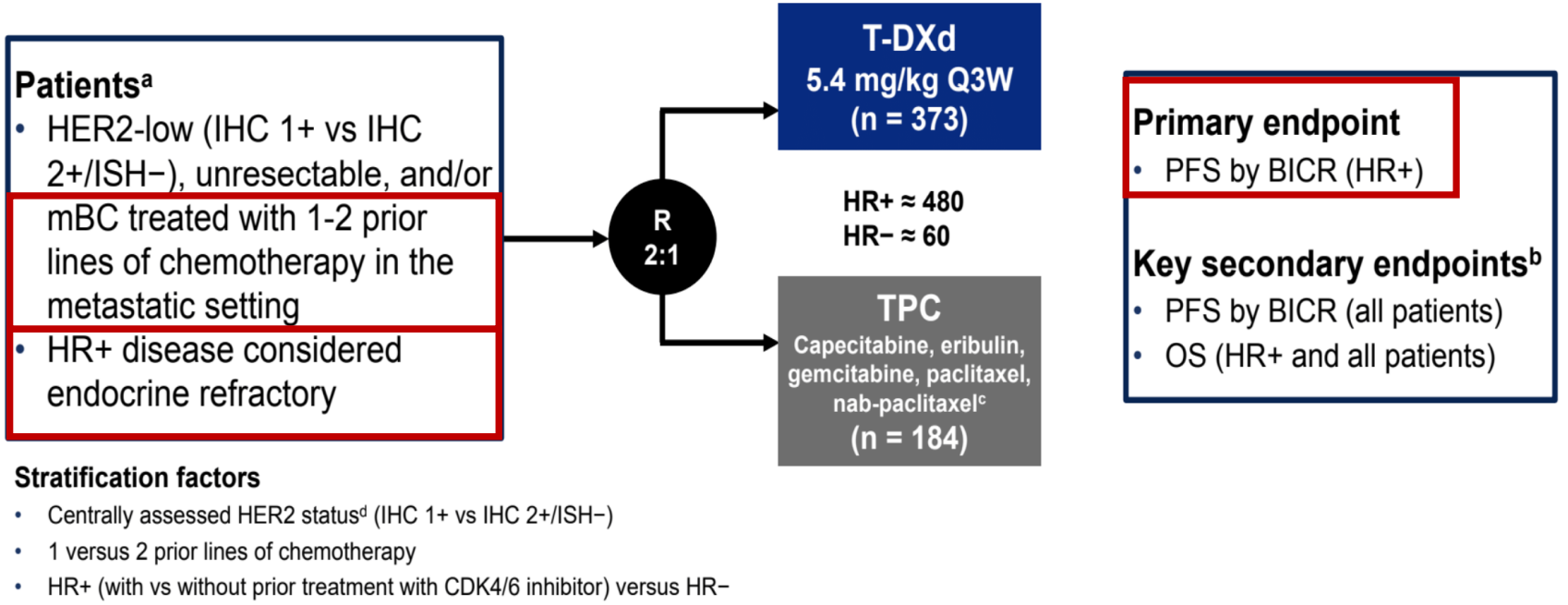
48 HER2-low mBC patients: ORR 40%, mPFS 5.7 mo

Grade ≥3 TRAEs occurred in 45.8% of patients.
The most common Grade ≥3 TRAEs were neutrophil count decrease (16.9%) and γ-GT increase (12.7%)

1. Banerji U, et al. Lancet Oncol. 2019; 2. Wang J, et al. ASCO 2021

DESTINY Breast 04

DESTINY-Breast04 Phase 3 trial initiated to confirm the benefit of targeting HER2-low expression in mBC



Modi S., et al. ASCO 2022; NEJM 2022

DESTINY Breast 04 - Population

60% HER2 1+, 40% HER2 2+ /ISH-

90% HR+ (n=499), 10% TNBC (n=58)

Median of 2 prior lines of ET and 1 chemo

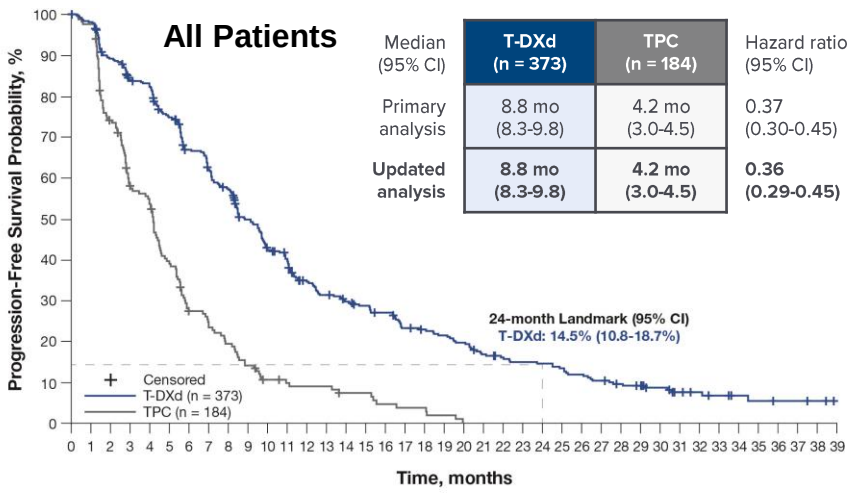
70% of HR+ received prior CDK4/6 inh

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

Modi S., et al. ASCO 2022; NEJM 2022

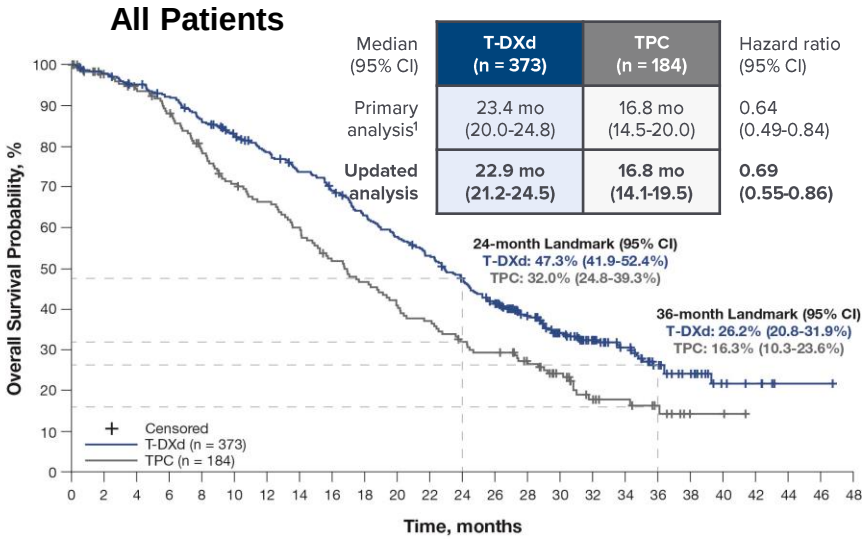
DESTINY Breast 04 – PFS and OS (ESMO 2023 Update)

Progression-Free Survival



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)**

Overall Survival

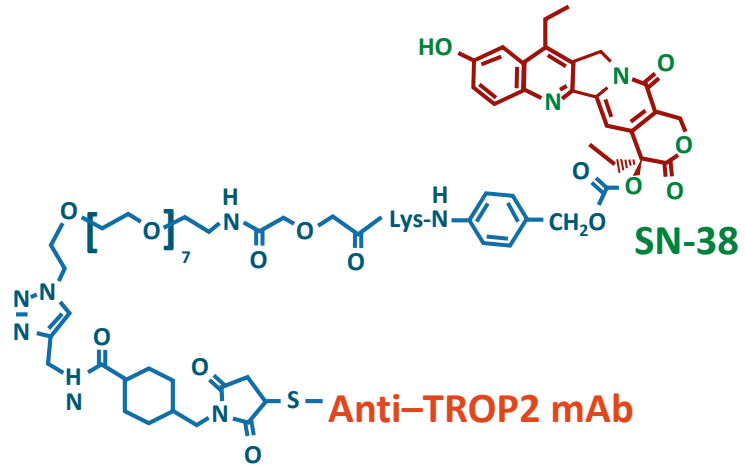


Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**

Results from the 32-month median follow-up for DESTINY-Breast04 confirm the sustained clinically meaningful improvement for T-DXd vs TPC previously demonstrated in HER2-low (IHC 1+, IHC 2+/ISH−) mBC, regardless of HR status

Modi S., et al. ASCO 2022; NEJM 2022; ESMO 2023

Sacituzumab Govitecan

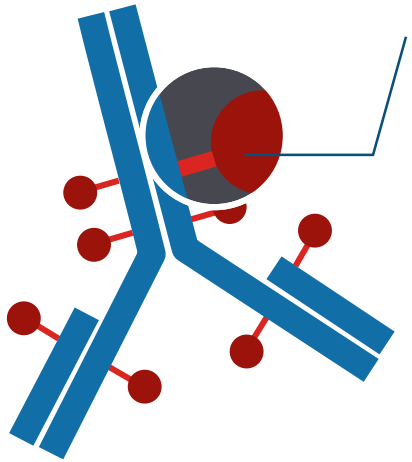


Humanized Anti-TROP2 Antibody

- Targets TROP2, an antigen expressed in many epithelial cancers
- Antibody type: hRS7 IgG1κ

SN-38 Payload Payload (Topoisomerase I Inhibitor)

- Delivers up to 136-fold more SN-38 to tumors than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor



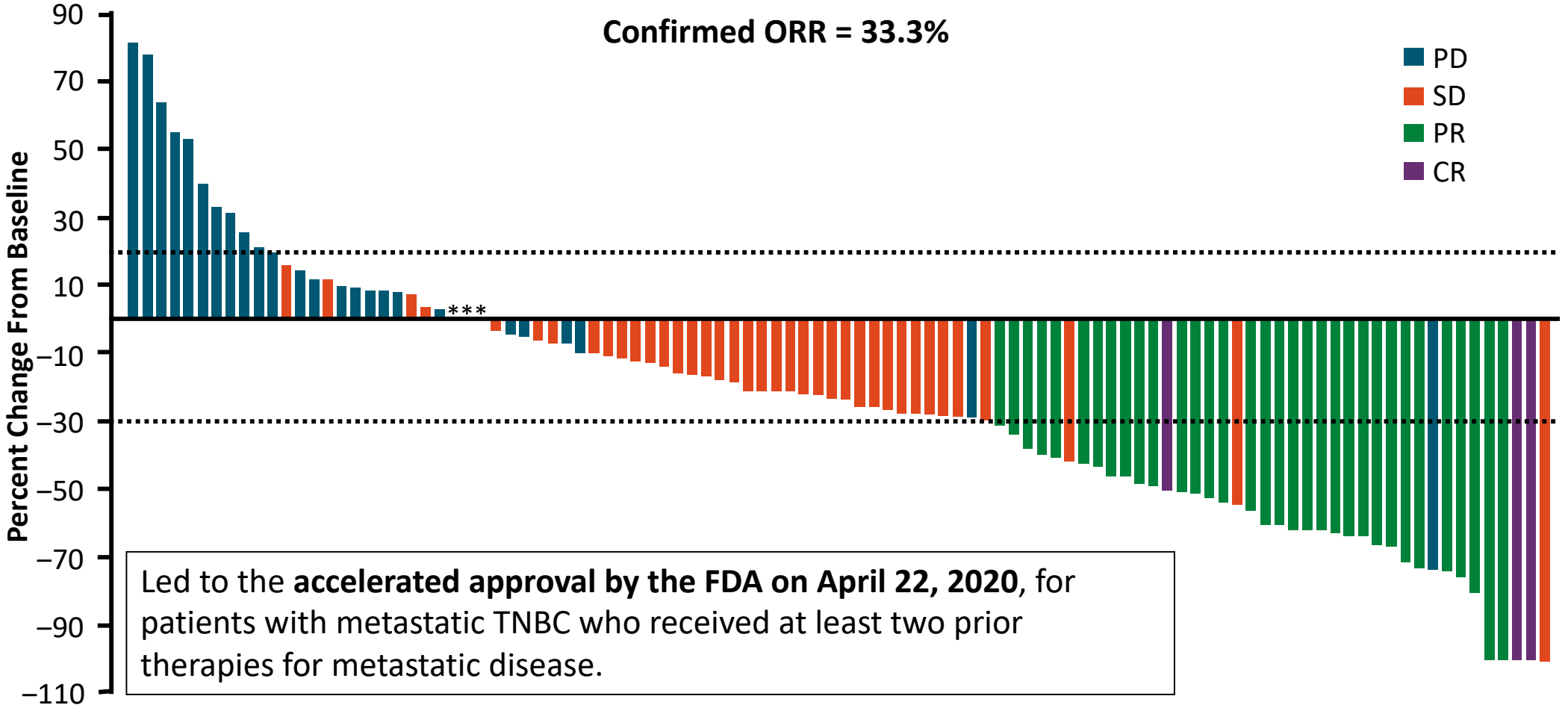
Linker for SN-38

- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

Goldenberg. Oncotarget. 2015;6:22496. Khoury. ASCO 2019. Abstr e14651. Ambrogi. PLoS One. 2014;9:e96993. Vidula. ASCO 2017. Abstr 1075. Sacituzumab govitecan PI. Tagawa. ASCO 2019. Abstr TPS3153. Bardia. JCO. 2017;35:2141. Goldenberg. MAbs. 2019;11:987. Sharkey. Clin Cancer Res. 2015;21:5131.

Bystander effect: In acidic tumor microenvironment, SN-38 is released from anti-TROP2 antibody, diffuses into neighboring cells

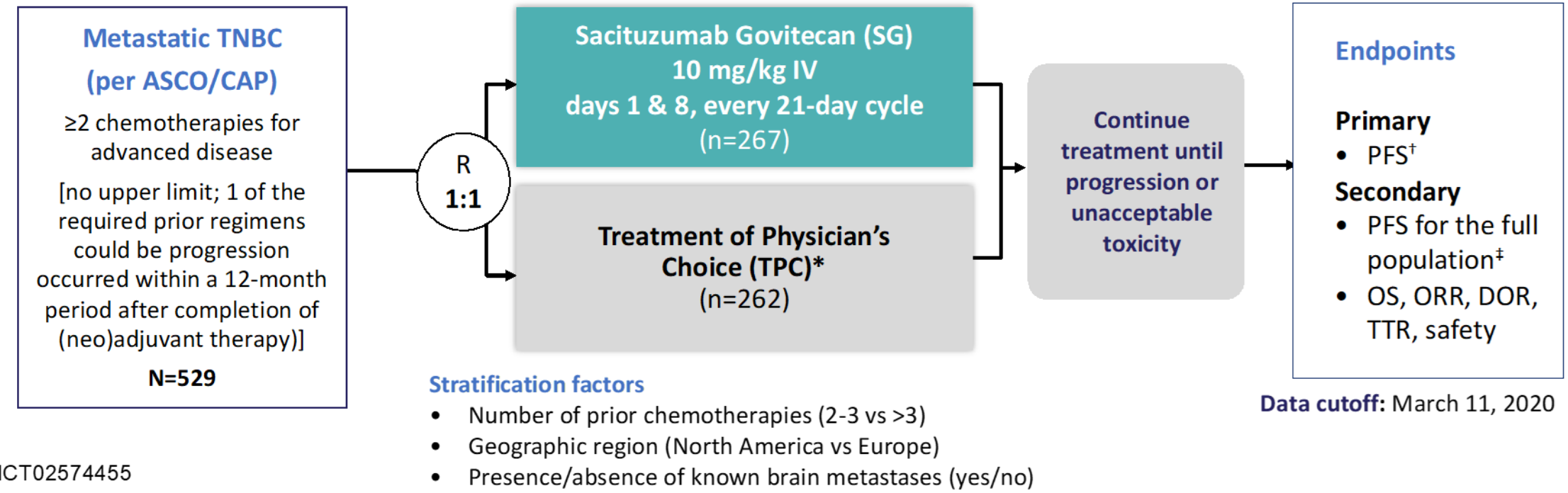
Phase I/II IMMU-132-01 Trial of Sacituzumab Govitecan in TNBC



Led to the **accelerated approval by the FDA on April 22, 2020**, for patients with metastatic TNBC who received at least two prior therapies for metastatic disease.

Bardia. NEJM. 2019;380:741.

Phase III ASCENT:
Sacituzumab Govitecan vs CT in Relapsed/Refractory Metastatic TNBC



Stratification factors

- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

NCT02574455

Demographics:

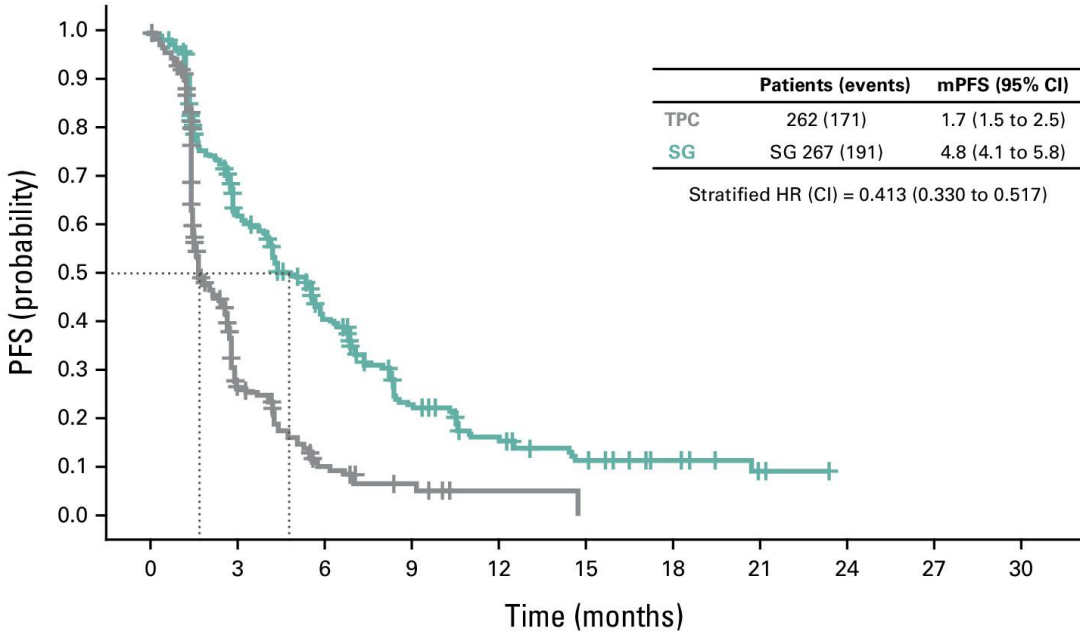
TPC: 53% eribulin, 20% vinorelbine, 15% gemcitabine, 13% capecitabine; 70% TN at initial diagnosis

Median prior regimens 4 (2-17); ~88% with visceral disease

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

ASCENT:
PFS and OS Among Patients w/o Brain Metastases (Final Analysis)

PFS

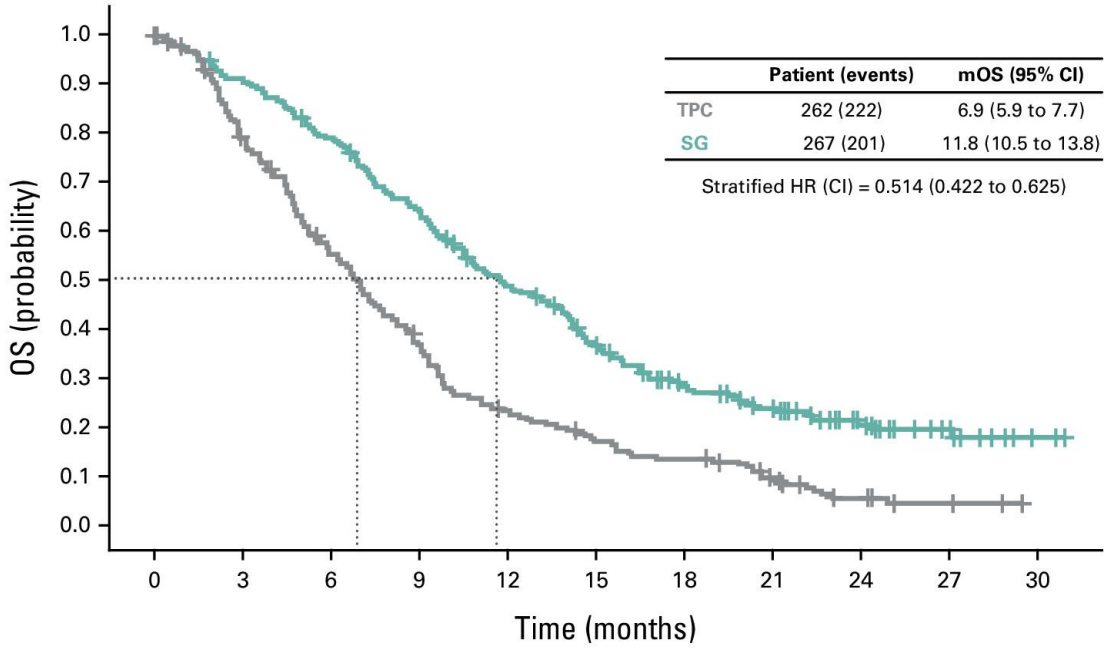


	Patients (events)	mPFS (95% CI)
TPC	262 (171)	1.7 (1.5 to 2.5)
SG	SG 267 (191)	4.8 (4.1 to 5.8)

Stratified HR (CI) = 0.413 (0.330 to 0.517)

No. at risk:									
TPC	262	40	12	5	1	0	0	0	0
SG	267	145	82	38	23	14	8	3	0

OS



	Patient (events)	mOS (95% CI)
TPC	262 (222)	6.9 (5.9 to 7.7)
SG	267 (201)	11.8 (10.5 to 13.8)

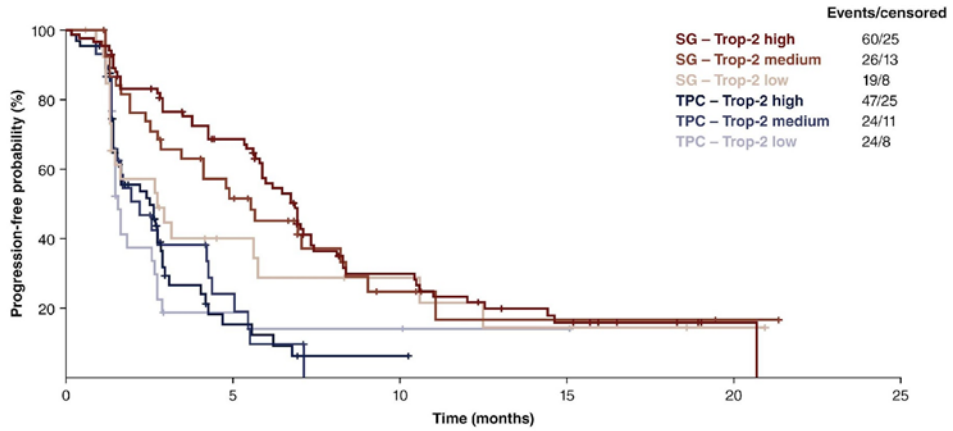
Stratified HR (CI) = 0.514 (0.422 to 0.625)

No. at risk:											
TPC	262	192	132	87	54	39	31	16	7	3	0
SG	267	242	209	169	125	92	62	42	25	11	2

Bardia A., et al. NEJM 2021; J Clin Oncol 2024

Is TROP2 Expression Associated With Outcomes? An Analysis From ASCENT Study of Sacituzumab Govitecan

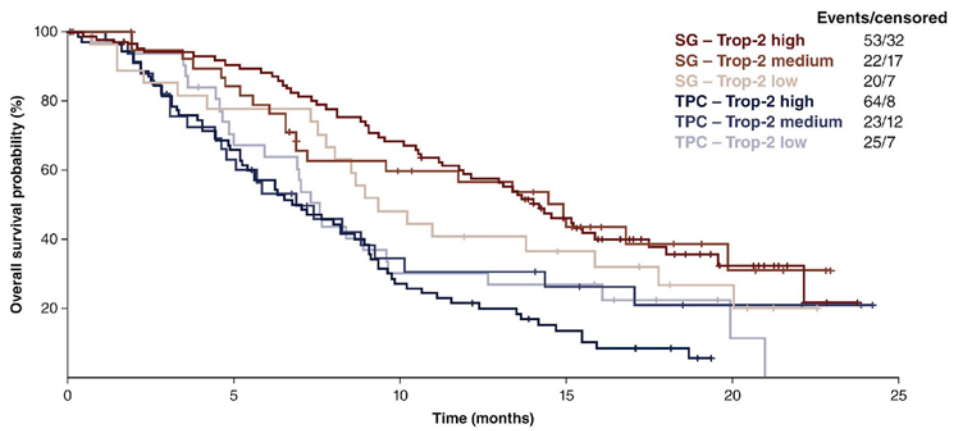
PFS



Number at risk						
SG – Trop-2 high	85	50	18	8	1	0
SG – Trop-2 medium	39	18	5	2	1	0
SG – Trop-2 low	27	7	4	2	1	0
TPC – Trop-2 high	72	5	1	0	0	0
TPC – Trop-2 medium	35	5	0	0	0	0
TPC – Trop-2 low	32	4	2	1	0	0

	Trop-2 high H-score: >200-300		Trop-2 medium H-score: 100-200		Trop-2 low H-score: 0 to <100	
	SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
Median PFS, months (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)

OS



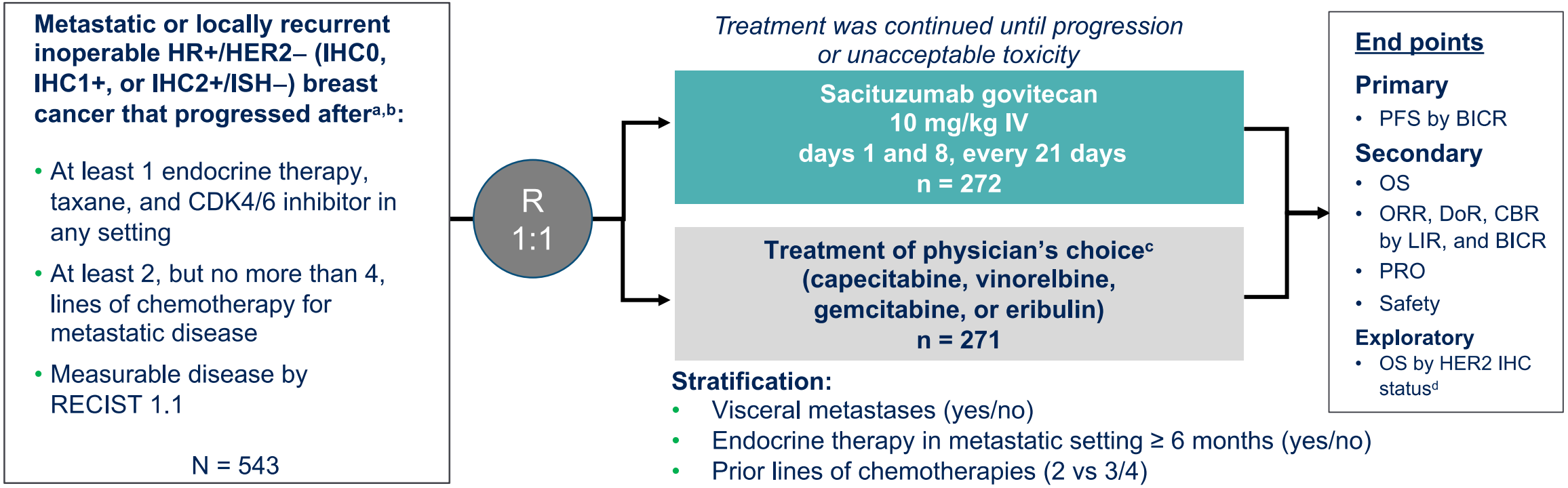
Number at risk						
SG – Trop-2 high	85	77	58	32	9	0
SG – Trop-2 medium	39	32	20	14	4	0
SG – Trop-2 low	27	21	13	8	4	0
TPC – Trop-2 high	72	46	19	8	0	0
TPC – Trop-2 medium	35	20	9	6	3	0
TPC – Trop-2 low	32	20	9	7	1	0

	Trop-2 high H-score: >200-300		Trop-2 medium H-score: 100-200		Trop-2 low H-score: 0 to <100	
	SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
Median OS, months (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)

No predictive role for Trop-2 expression
(too few patients in the Trop-2 low group to make a definitive conclusion)

Bardia A., et al. Ann Oncol 2021

TROPiCS-02 trial: Expanding the benefit of Sacituzumab Govitecan to the HR+ disease



ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]ClinicalTrials.gov. NCT03901339. [b]Disease histology based on the ASCO/CAP criteria. [c]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. [d]HER2-low was defined as IHC score of 1+, or score of 2+ with negative ISH result; HER2 IHC0 was defined as IHC score of 0.

1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376.

TROPiCS02 - Population

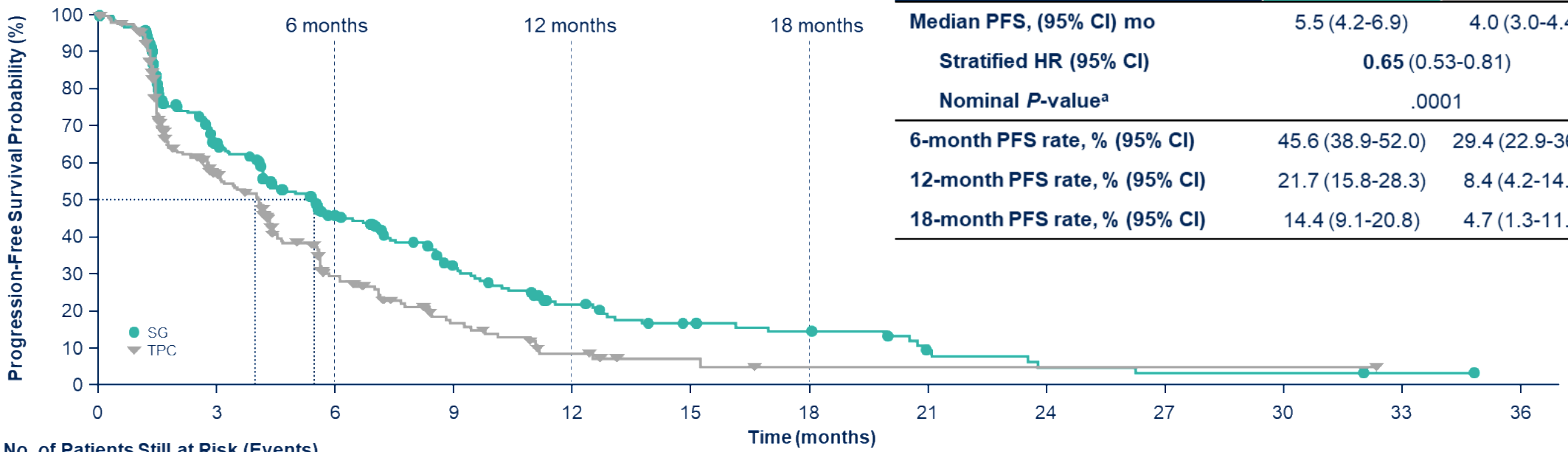
	SG (n=272)	TPC (n=271)
Female, n (%)	270 (99)	268 (99)
Median age, y (range)	57 (29-86)	55 (27-78)
<65 y, n (%)	199 (73)	204 (75)
≥65 y, n (%)	73 (27)	67 (25)
Race or ethnic group, n (%)		
White	184 (68)	178 (66)
Black	8 (3)	13 (5)
Asian	11 (4)	5 (2)
Other[a] / Not reported[b]	69 (25)	75 (28)
ECOG PS, n (%)		
0	116 (43)	126 (46)
1	156 (57)	145 (54)
Visceral metastases at baseline, n (%)	259 (95)	258 (95)
Liver metastases,[c] n (%)	229 (84)	237 (87)
De novo metastatic breast cancer, n (%)	78 (29)	60 (22)

	SG (n=272)	TPC (n=271)
Median time from initial metastatic diagnosis to randomization, mo (range)	48.5 (1.2- 243.8)	46.6 (3.0- 248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)	173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 inhibitor use, n (%)		
≤12 months	161 (59)	166 (61)
>12 months	106 (39)	102 (38)
Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting, n (range)[d]	3 (0-8)	3 (1-5)

All patients had prior CDK4/6 inhibitors and a median of 3 prior chemotherapies

Tolaney S. M. et al. *ASCO Annual Meeting 2023*

TROPiCS02 - PFS



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65** (0.53-0.81)	
Nominal *P*-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

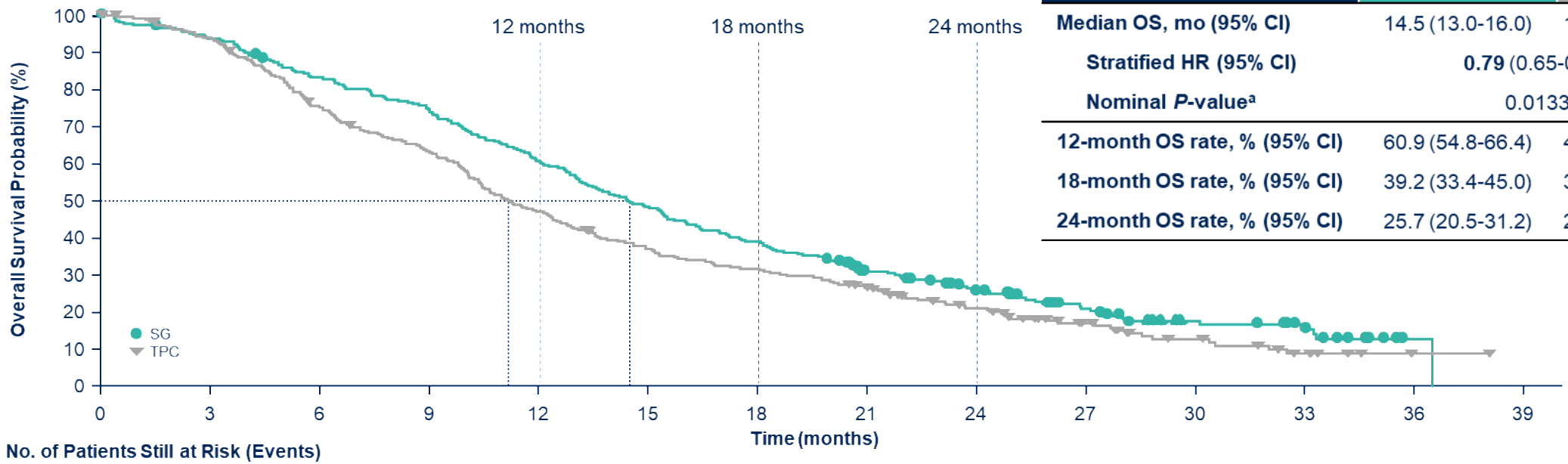
No. of Patients Still at Risk (Events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

Tolaney S. M. et al. *ASCO Annual Meeting 2023*

TROPiCS02 - OS



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65-0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

No. of Patients Still at Risk (Events)

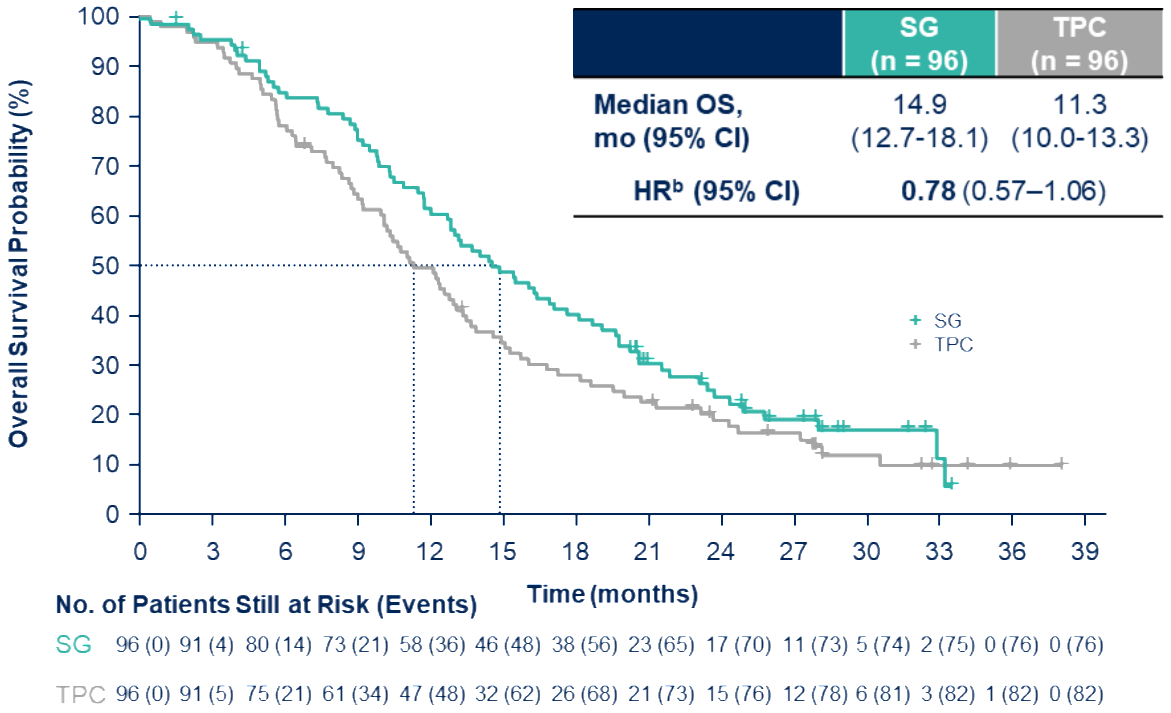
SG	272 (0)	253 (17)	223 (45)	200 (68)	163 (105)	130 (138)	105 (163)	71 (184)	52 (196)	33 (204)	19 (209)	13 (211)	1 (213)	0 (214)
TPC	271 (0)	251 (16)	199 (66)	167 (97)	124 (140)	96 (166)	82 (180)	66 (193)	46 (206)	27 (214)	15 (220)	7 (224)	1 (224)	0 (224)

SG continued to demonstrate improvement in OS vs TPC at longer follow-up, with 21% reduction in risk of death and a higher proportion of patients remaining alive at each landmark

Tolaney S. M. et al. *ASCO Annual Meeting 2023*

TROPiCS02 – OS by Trop2 expression

H-score < 100[a]

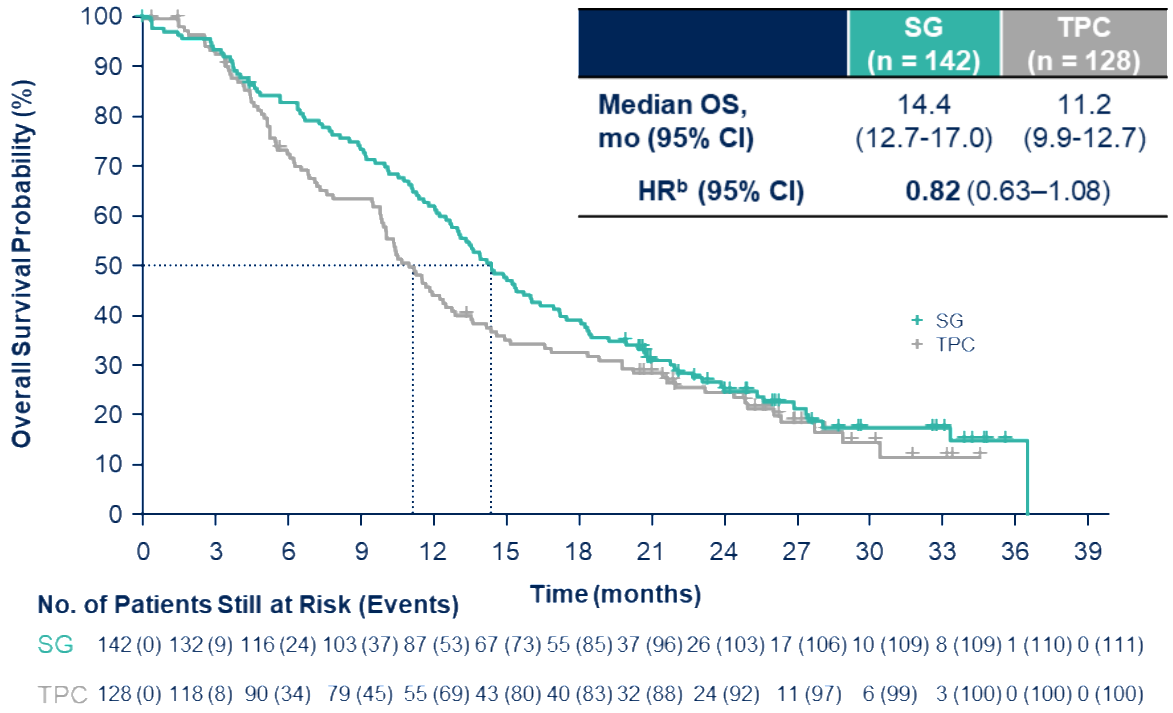


	SG (n = 96)	TPC (n = 96)
Median OS, mo (95% CI)	14.9 (12.7-18.1)	11.3 (10.0-13.3)
HR[b] (95% CI)	**0.78** (0.57–1.06)	

No. of Patients Still at Risk (Events)

SG	96 (0)	91 (4)	80 (14)	73 (21)	58 (36)	46 (48)	38 (56)	23 (65)	17 (70)	11 (73)	5 (74)	2 (75)	0 (76)	0 (76)
TPC	96 (0)	91 (5)	75 (21)	61 (34)	47 (48)	32 (62)	26 (68)	21 (73)	15 (76)	12 (78)	6 (81)	3 (82)	1 (82)	0 (82)

H-score ≥ 100[a]



	SG (n = 142)	TPC (n = 128)
Median OS, mo (95% CI)	14.4 (12.7-17.0)	11.2 (9.9-12.7)
HR[b] (95% CI)	**0.82** (0.63–1.08)	

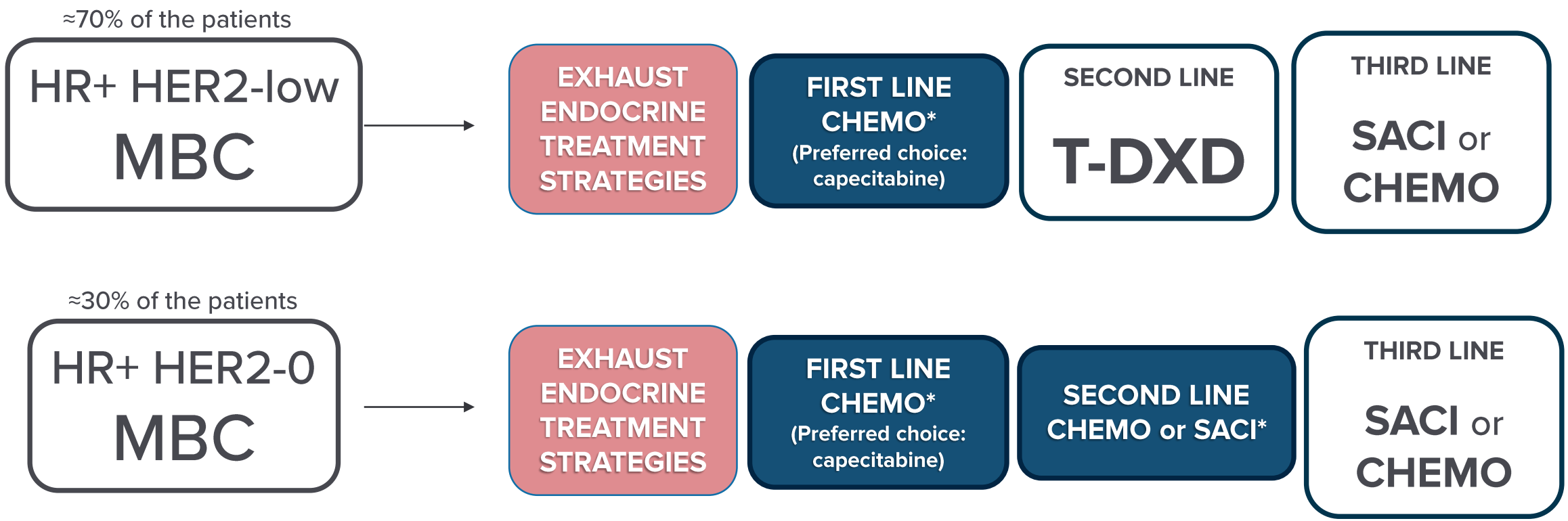
No. of Patients Still at Risk (Events)

SG	142 (0)	132 (9)	116 (24)	103 (37)	87 (53)	67 (73)	55 (85)	37 (96)	26 (103)	17 (106)	10 (109)	8 (109)	1 (110)	0 (111)
TPC	128 (0)	118 (8)	90 (34)	79 (45)	55 (69)	43 (80)	40 (83)	32 (88)	24 (92)	11 (97)	6 (99)	3 (100)	0 (100)	0 (100)

OS benefit was observed with SG over TPC in the H-score < 100 and the H-score ≥ 100 groups with longer follow-up, consistent with a previous analysis[1]

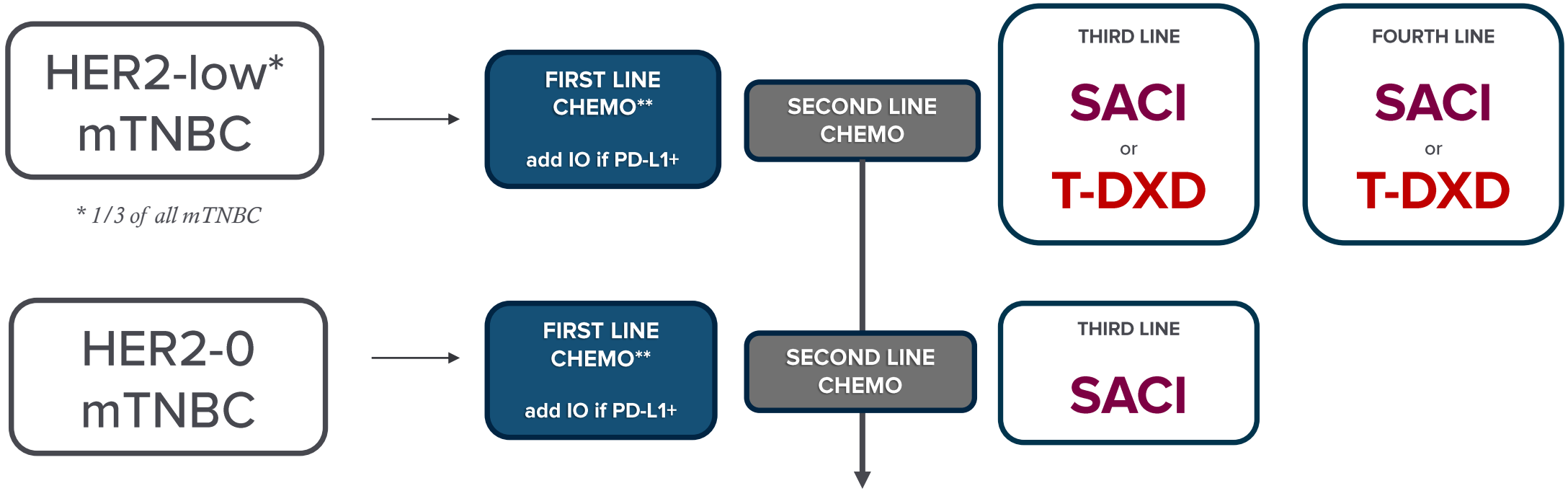
Tolaney S. M. et al. *ASCO Annual Meeting 2023*

Treatment of HR+ MBC with ADCs



*PARP inhibitors can be considered in the first through third line setting for BRCAm patients

Treatment of mTNBC with ADCs



AIFA restriction:

At least 2 lines of systemic therapy

If DFI<12 months after completion of (neo)adjuvant therapy, Sacituzumab can be prescribed as 2nd line

**PARP inhibitors can be considered in the first through third line setting for BRCAm patients

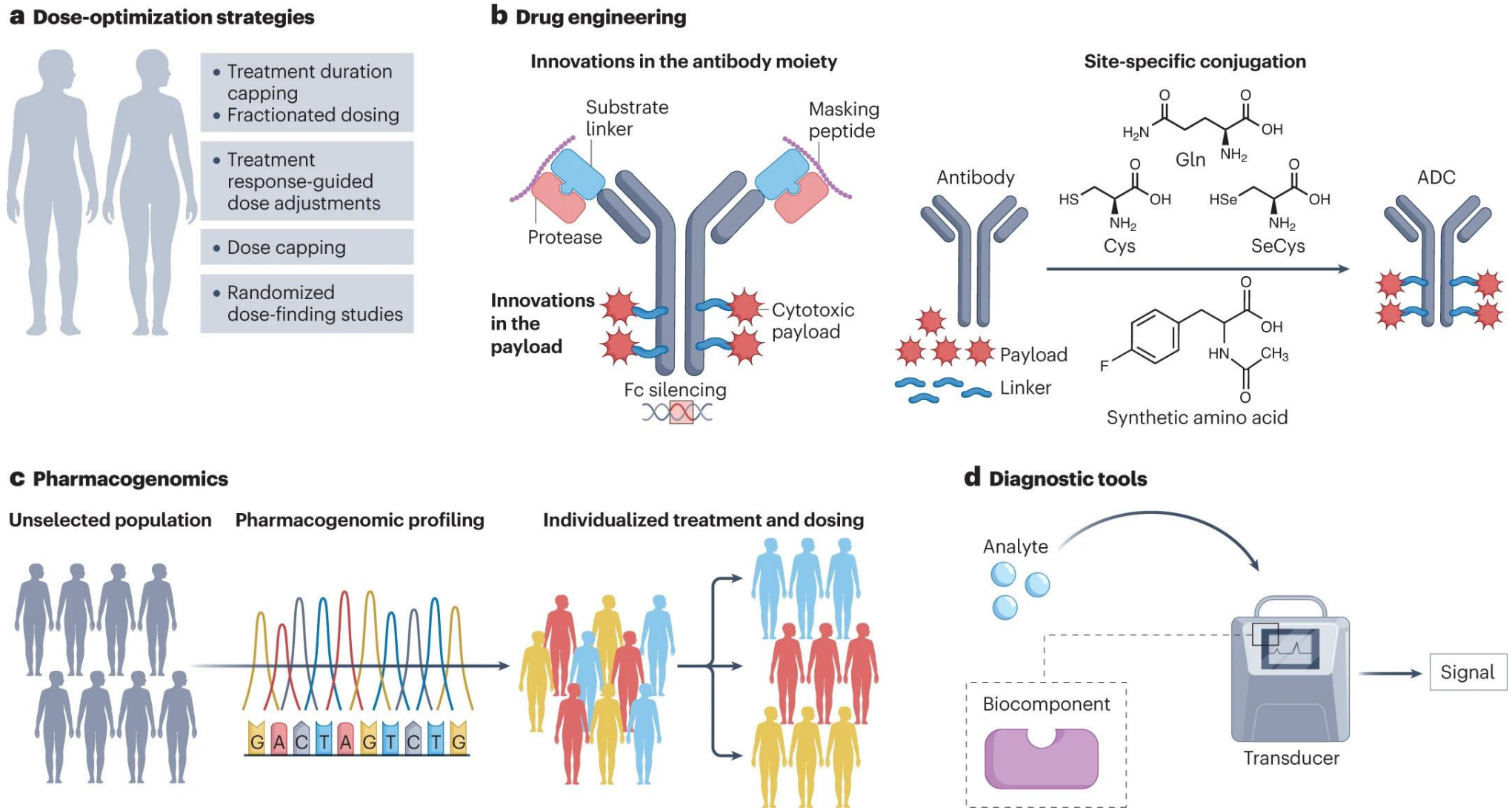
Remaining challenges and opportunities

1) Improving the toxicity profile of ADCs

2) Sequencing challenges

3) Exploring new ADC targets and designs

Optimizing the toxicity profile of ADCs



Tarantino P. et al. *Nature Rev Clin Onc 2023*

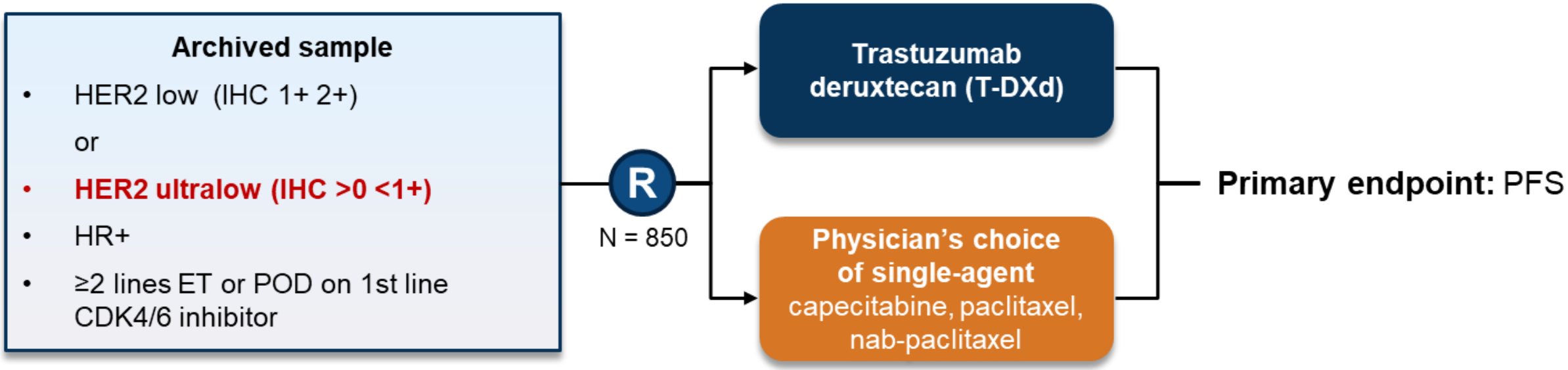
Remaining challenges and opportunities

1) Improving the toxicity profile of ADCs

2) Sequencing challenges

3) Exploring new ADC targets and designs

DESTINY-Breast06 may take T-DXd to the 1L and expand its use to some HER2-0 patients



- **Key differences with DESTINY-Breast04:** includes IHC 0+ ("ultralow"), larger (N = 850), restricted to HR+ disease, and includes chemo-naïve patients

Assuming DB06 reads out positive

HR+ mBC

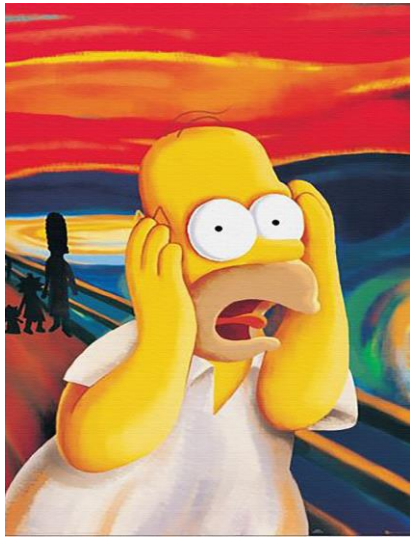
(except few “HER2-null”)

→ **EXHAUST ENDOCRINE TREATMENT STRATEGIES**

→ **T-DXD** (DB06)

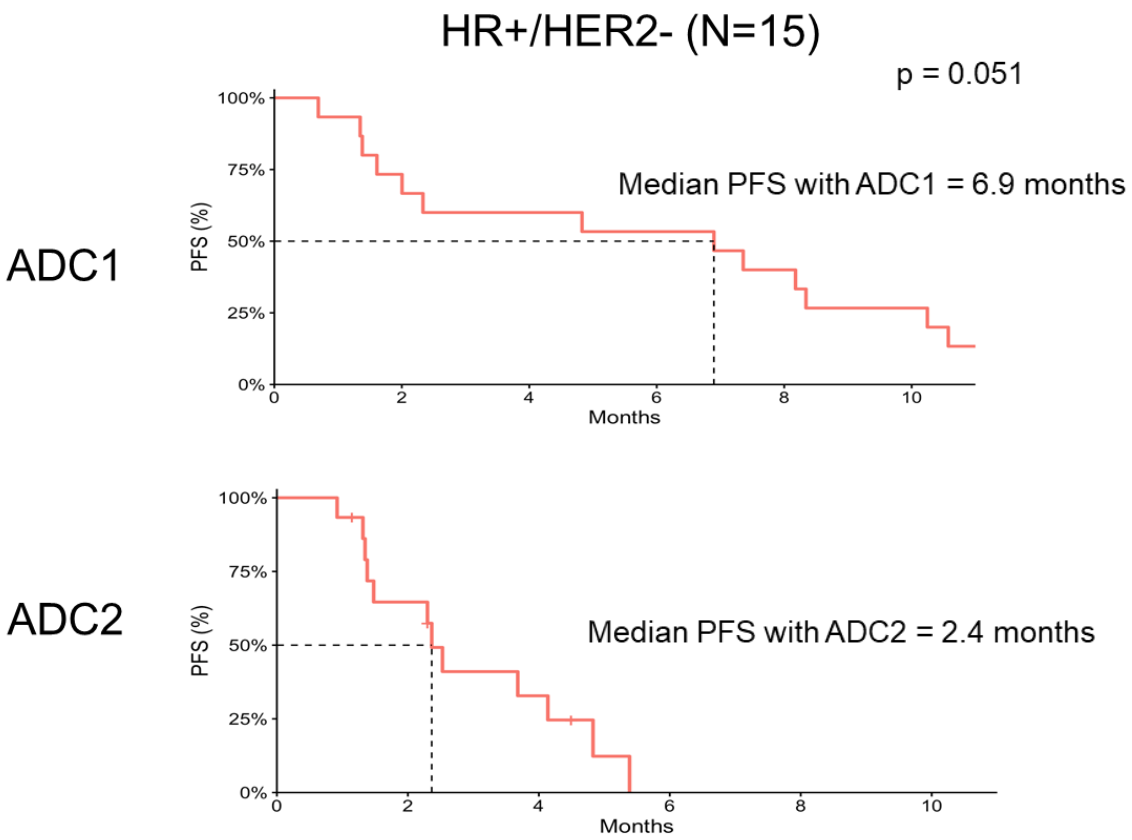
→ **Dato-DXd** (TB01) → **SG** (TROPiCS02)

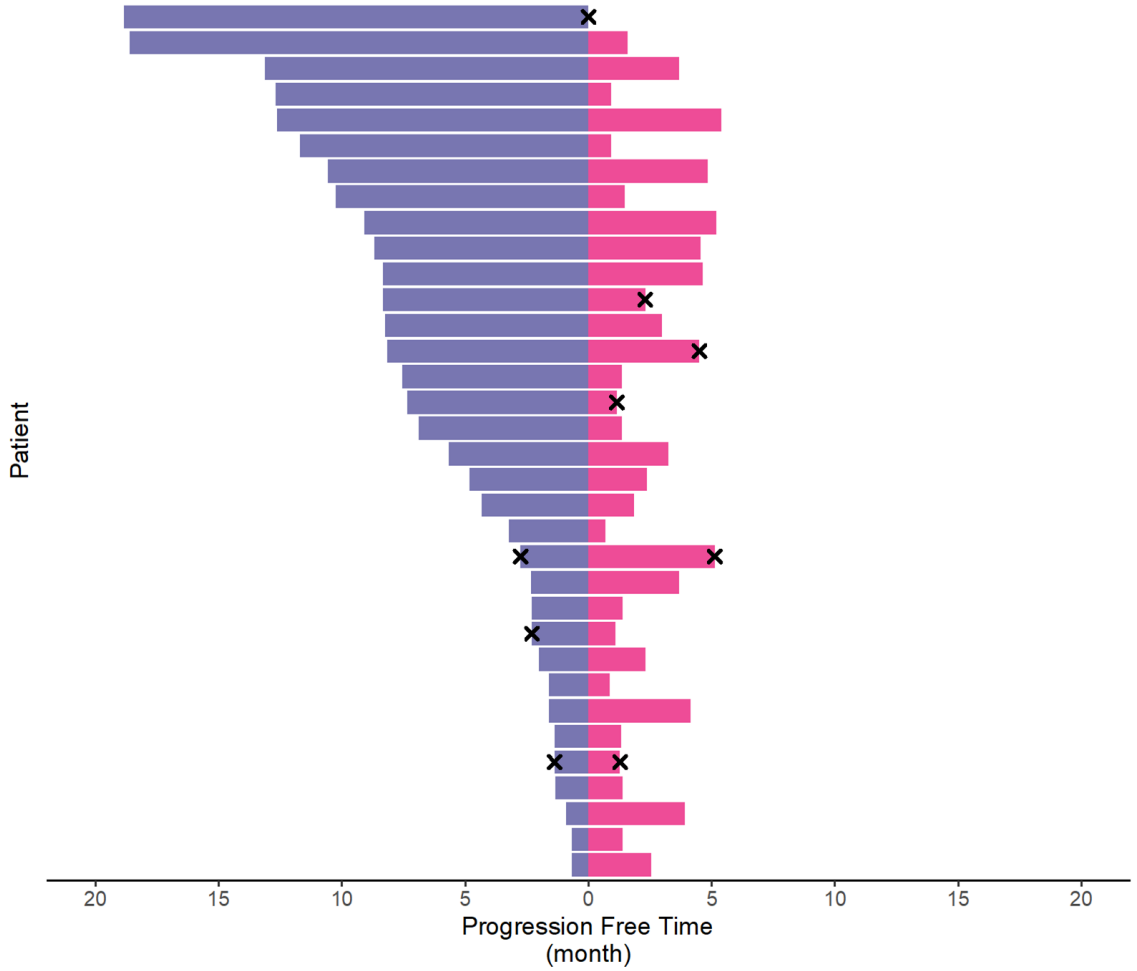
→ **SG** (TROPiCS02) → **Dato-DXd** (TB01)



TOPO1 ADC sequencing dilemma

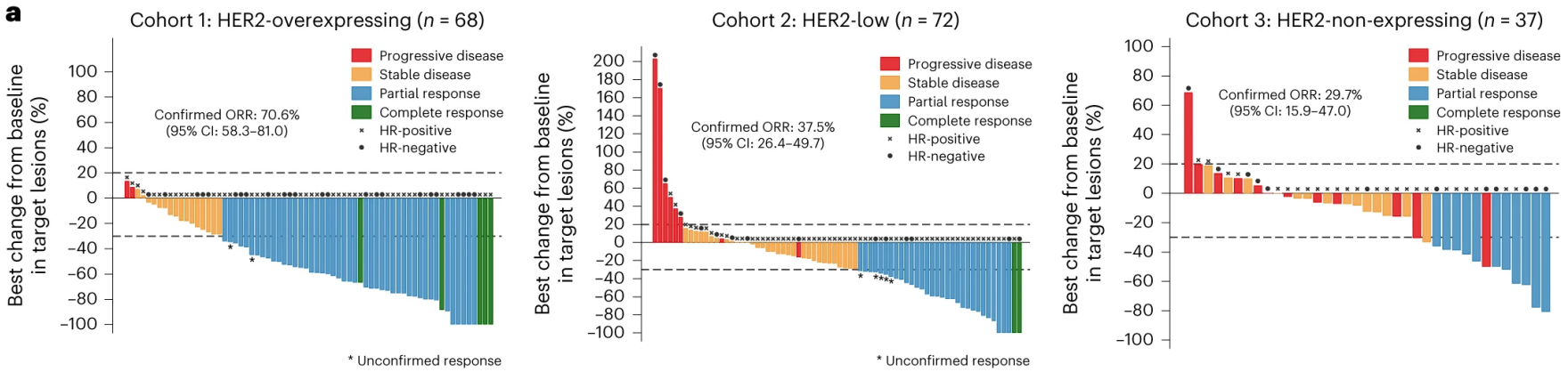
Real world experience from MGH, including 15 patients with HR+ MBC receiving multiple ADCs



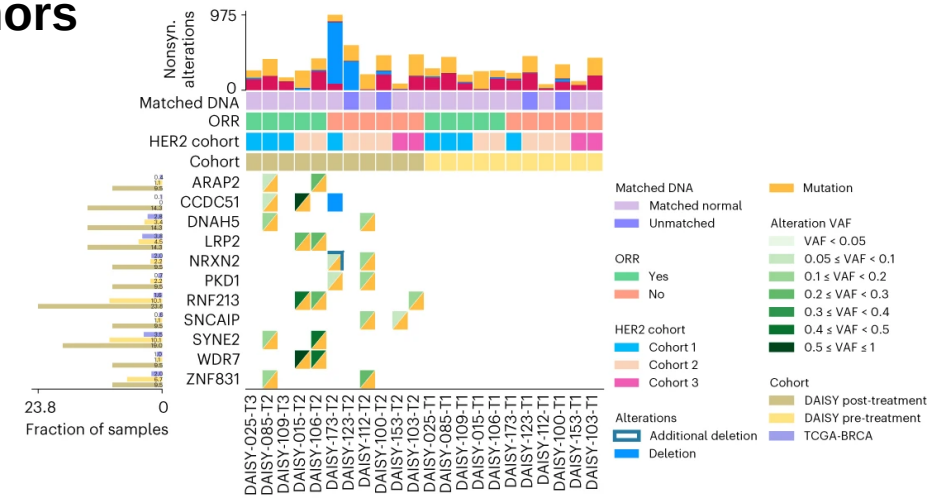


Abelman R et al. *ASCO 2023*

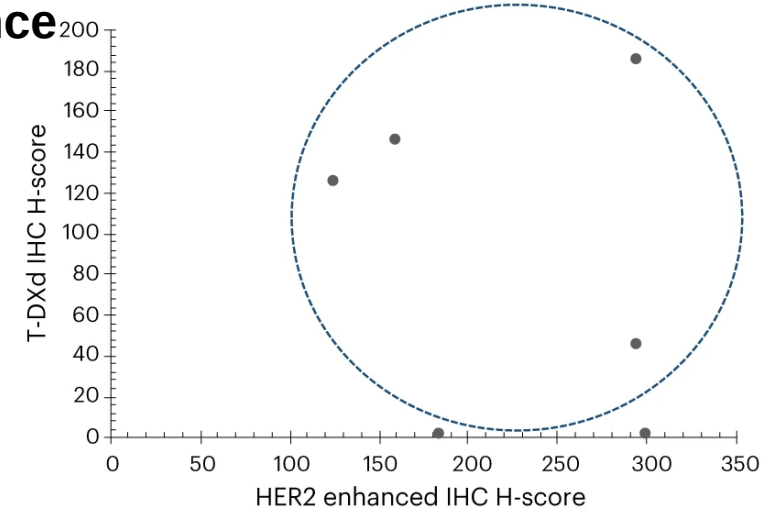
DAISY trial: translational science like this needed to inform effective ADC development



Acquired genomic alterations in T-DXd-resistant tumors



65% → decreased HER2 tumor expression after resistance



Mosele F., et al. Nat Med 2023

Remaining challenges and opportunities

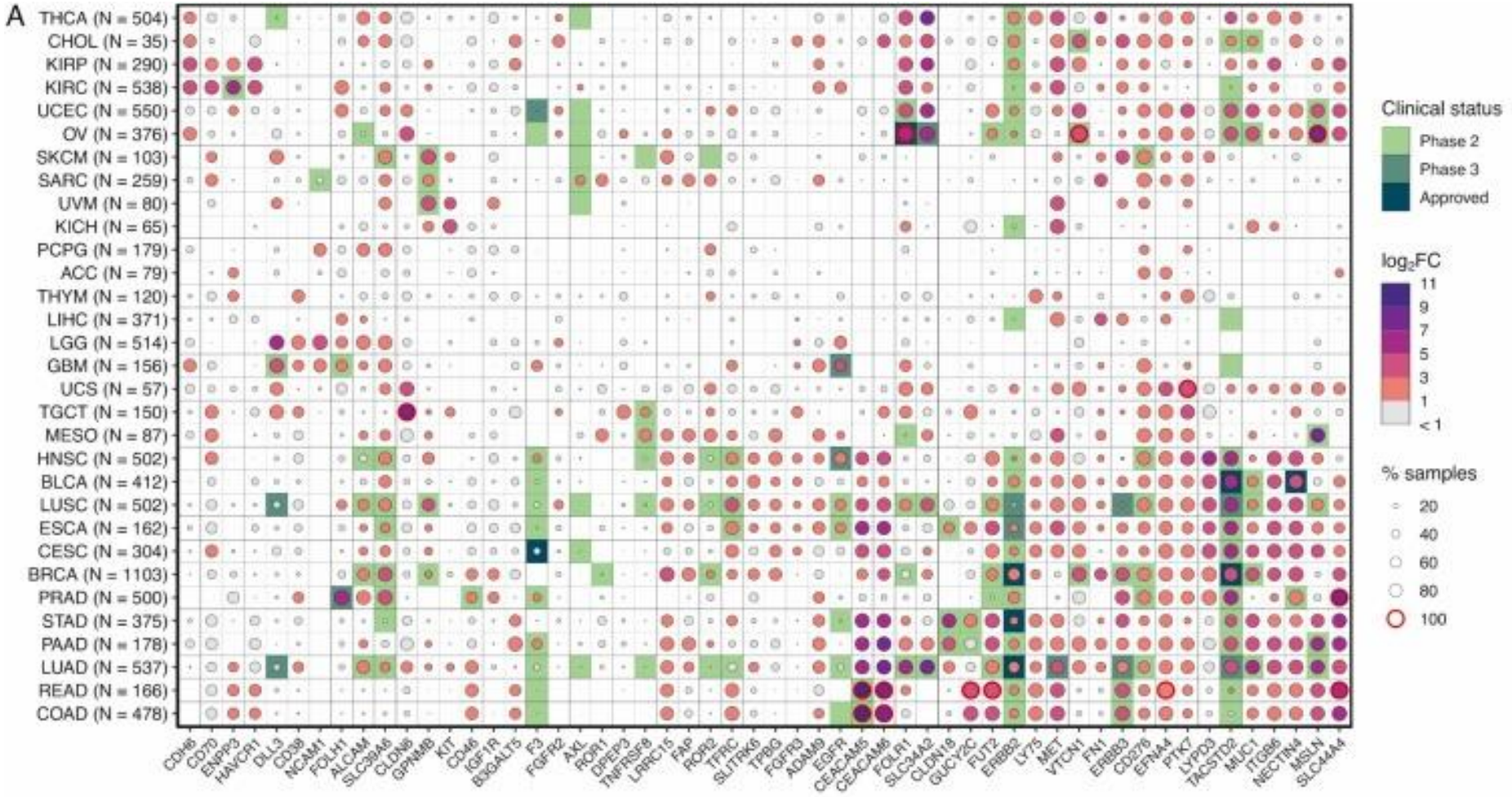
1) Improving the toxicity profile of ADCs

2) Sequencing challenges

3) Exploring new ADC targets and designs

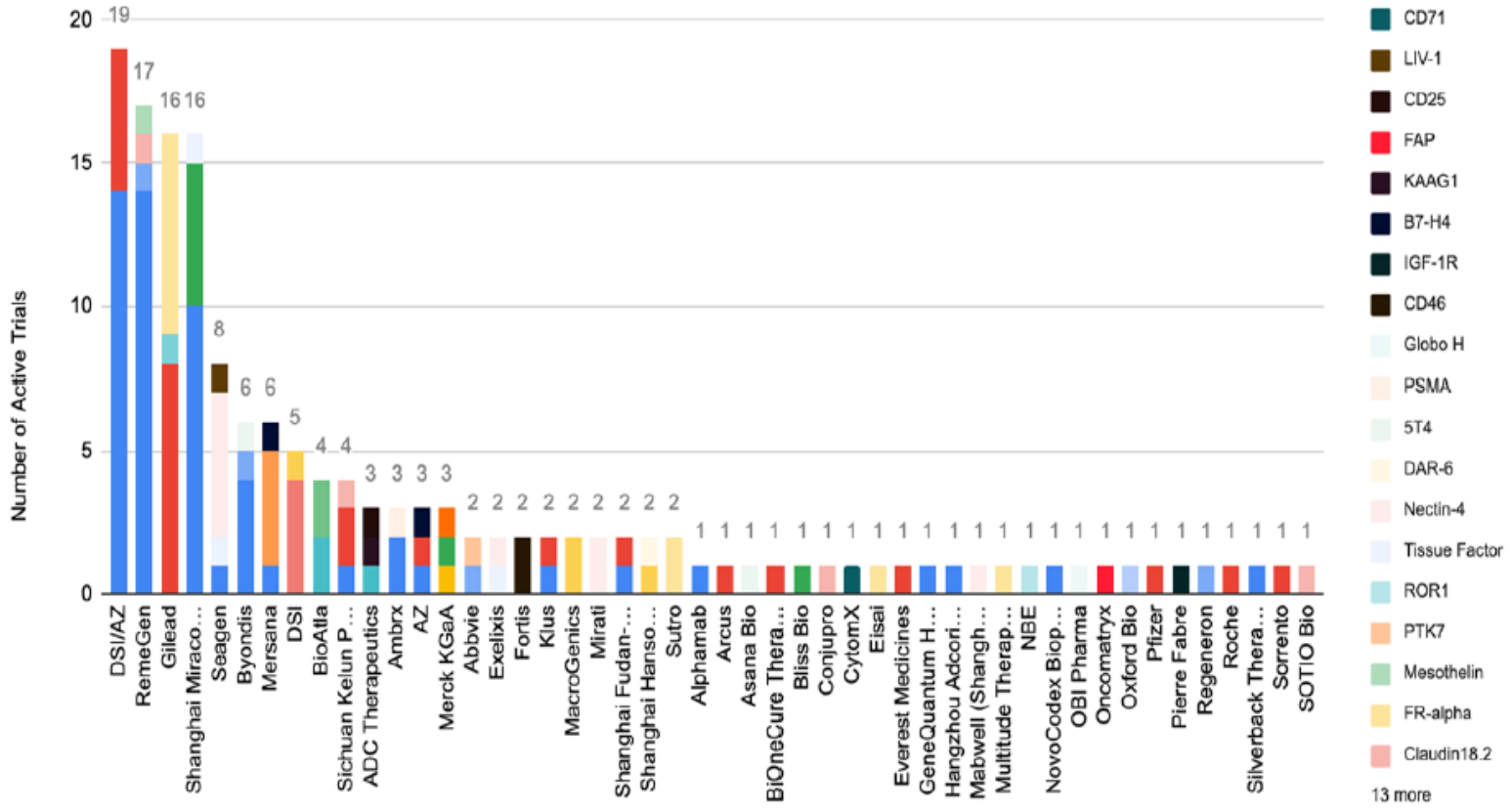

HER3
NECTIN4
FRα
MESOTHELIN
MUC1
LIV1
B7H4
CEACAM
CD166
CD71
What other target on the horizon?

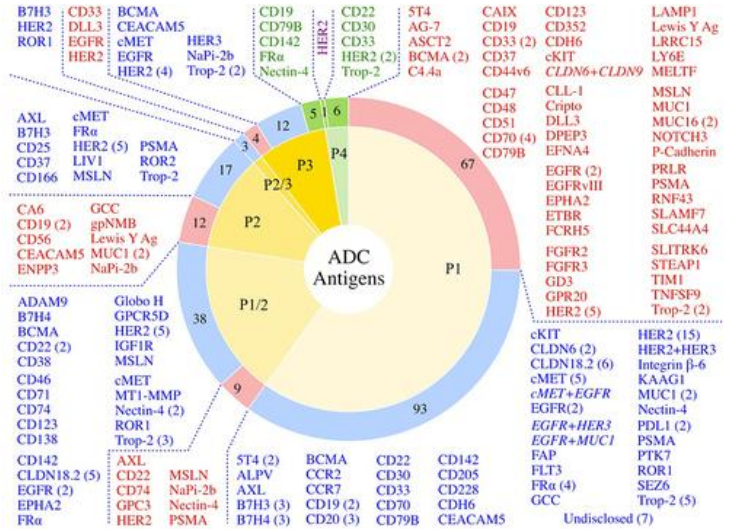
Antibody-drug conjugate (ADC) targets across solid tumors

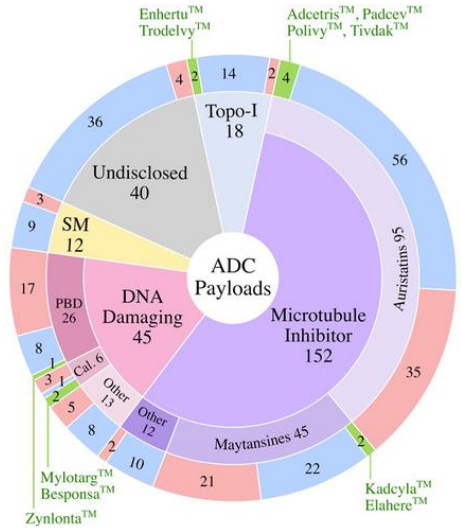


Bosi C, et al. Eur J Cancer 2023

Biomarkers needed because of future innovation: an avalanche of ADCs is coming

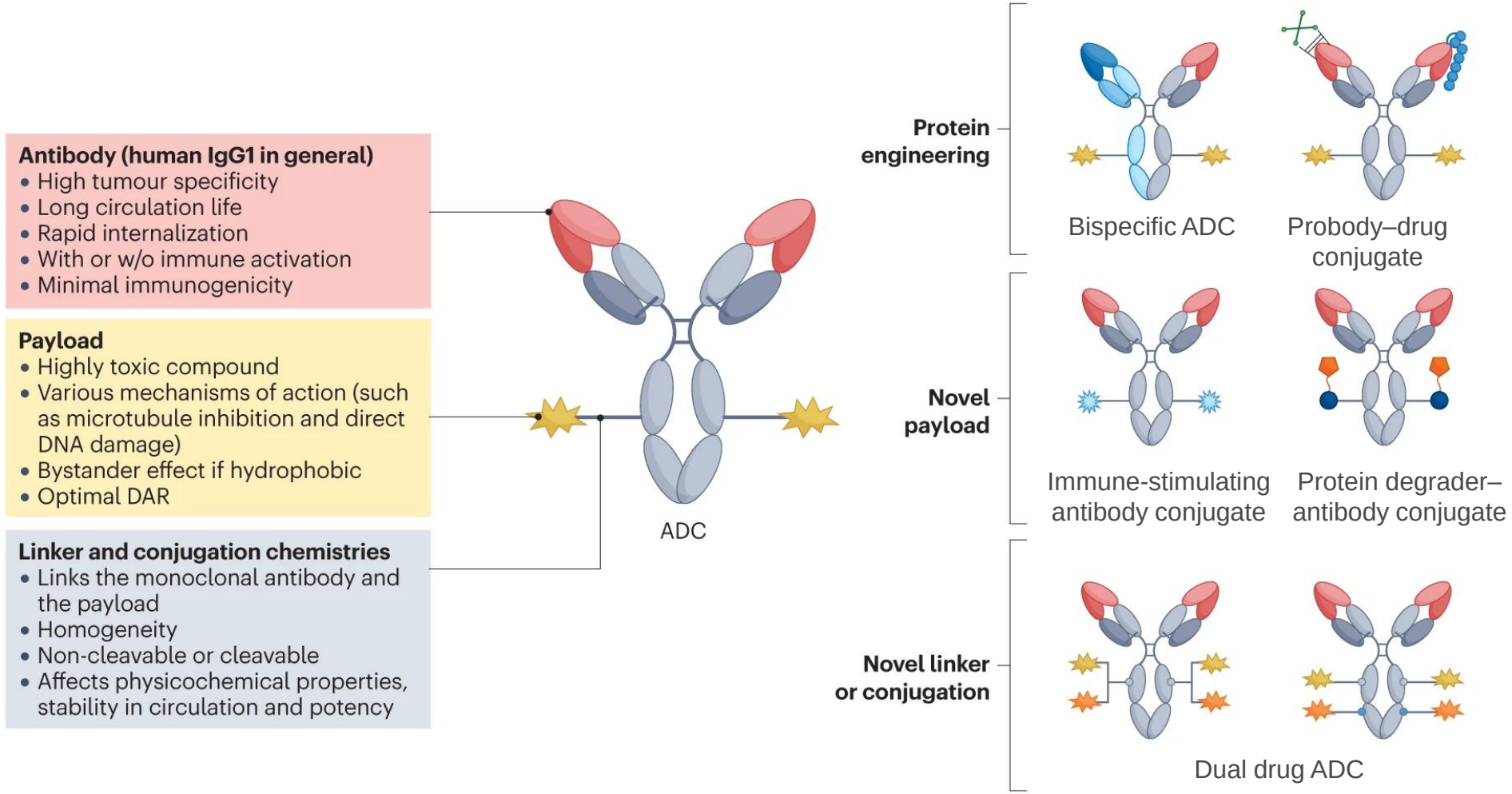






Maecker H, et al. mAbs 2023; Chandarlapaty, ESMO 2023

Exploring the next generation of antibody–drug conjugates



Tsuchikama Y., et al. Nat Rev Clin Oncol 2024

Take-Home Messages

- After revolutionizing the treatment of HER2+, ADCs have reached TNBC and HR+ disease, with **2 ADCs now included in treatment guidelines**
- Novel ADCs are clearly **more active than traditional chemotherapy**, although **the toxicity profile is not always improved**
- The demonstration that ADCs > chemo may have huge repercussions for the **treatment of early-stage breast cancer (many trials ongoing)**
- **A broad array of promising ADCs is on the horizon**, including innovative constructs based on bispecific antibodies, or ADCs delivering dual payloads, immunotherapy payloads and radionuclides
- Together with the development of novel ADCs, we **desperately need to identify biomarkers** to predict their efficacy and inform treatment sequencing