HER2 low Breast Cancer

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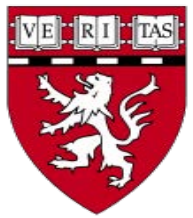

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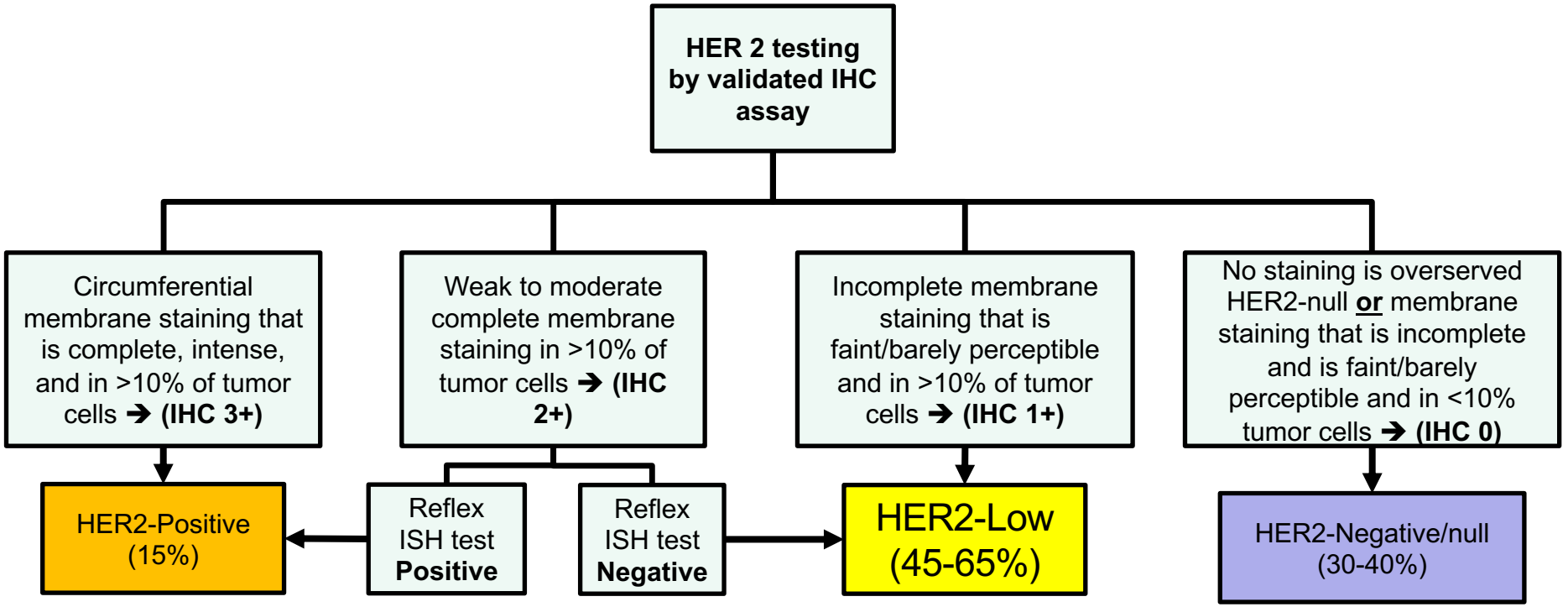
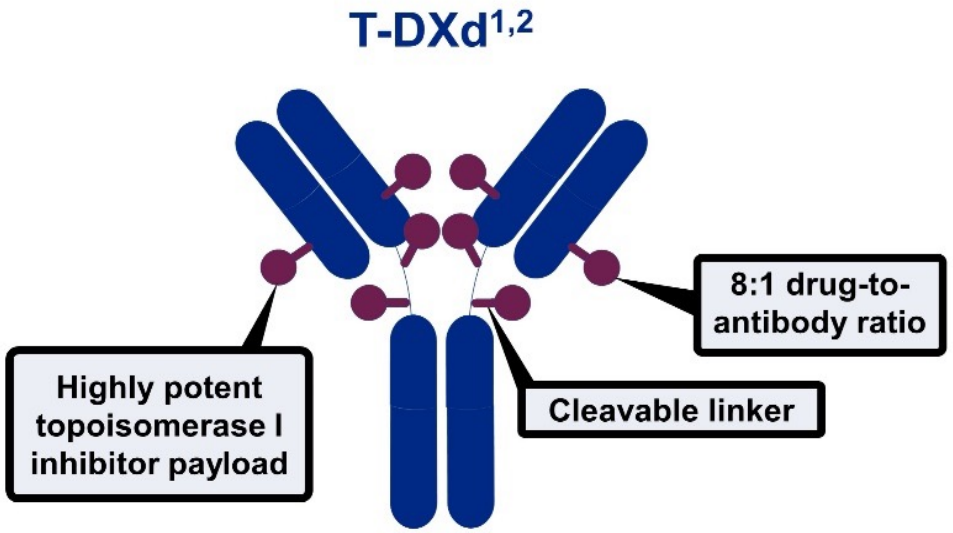
Objectives

- Understand rationale of ADCs for HER2 low breast cancer
- Gain knowledge related to HER2 ADC, trastuzumab deruxtecan, including efficacy and toxicity
- Review upcoming therapies for HER2 low breast cancer

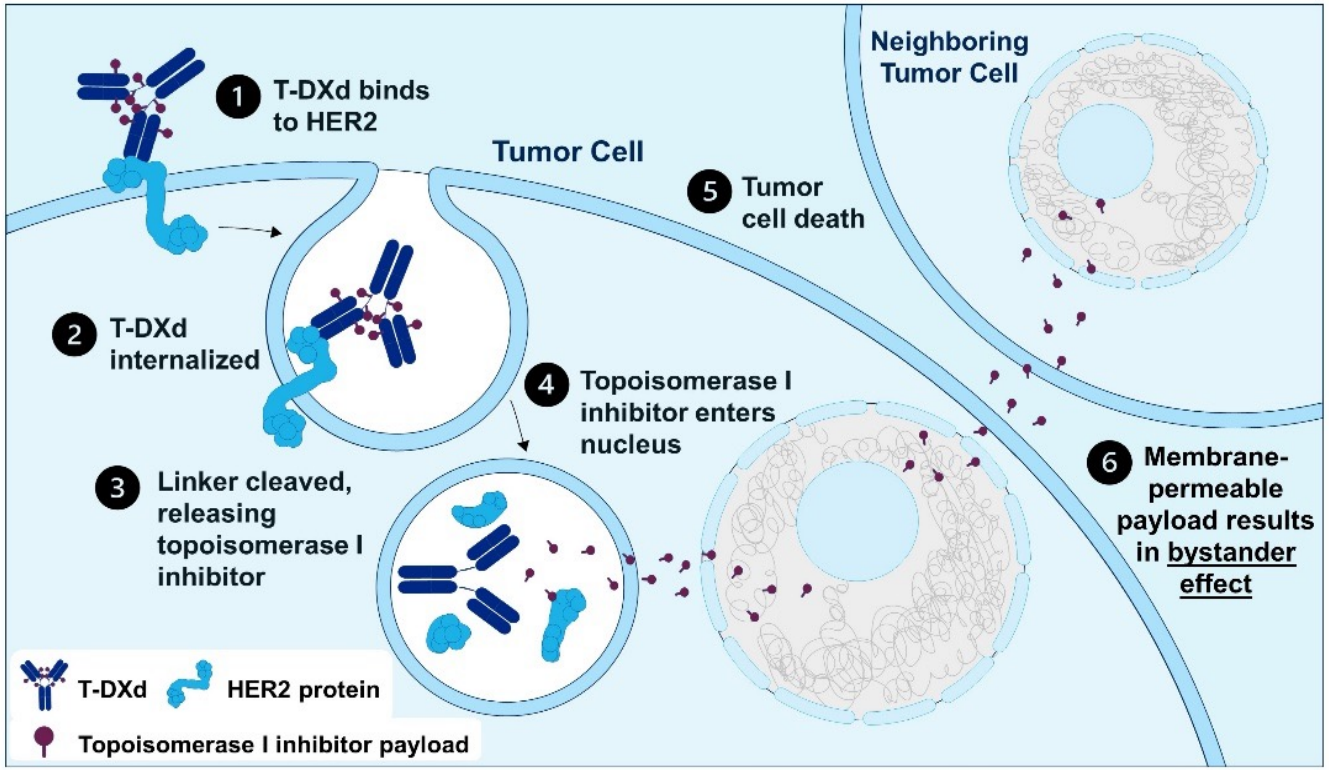
HER2-Low Breast Cancer: Current Definition



Trastuzumab Deruxtecan (T-DXd): Selective delivery of toxic payload



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[1,2]

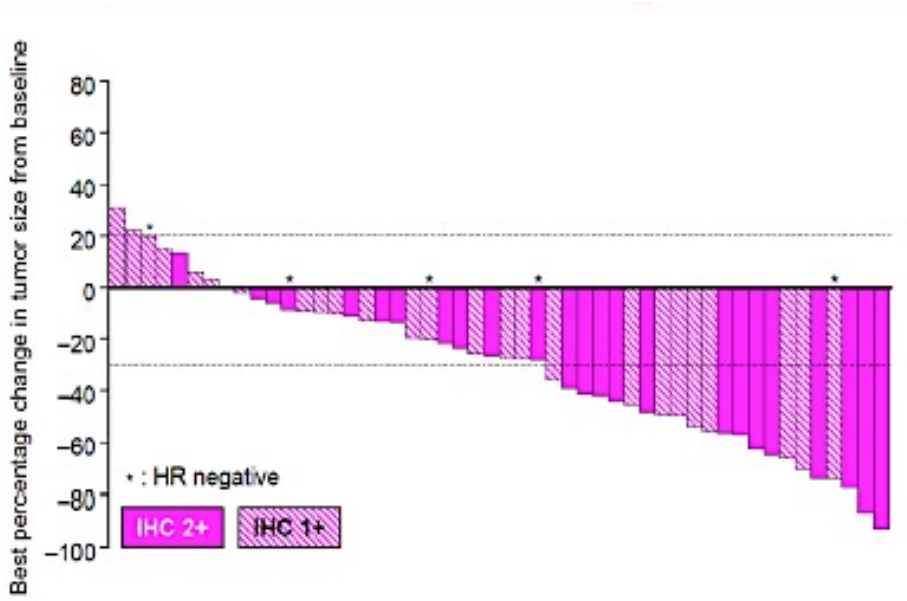


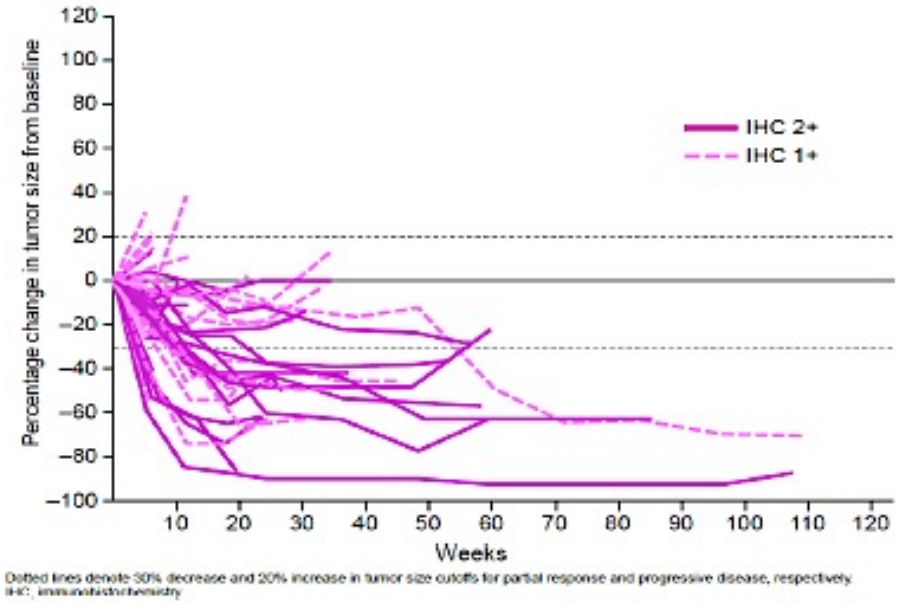
Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

Nagayama, A, et al. Target Oncol. 2017

Modi S, et al. ASCO 2022.

Trastuzumab Deruxtecan (T-DXd): HER2 Low Tumors





Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively.
IHC, immunohistochemistry.

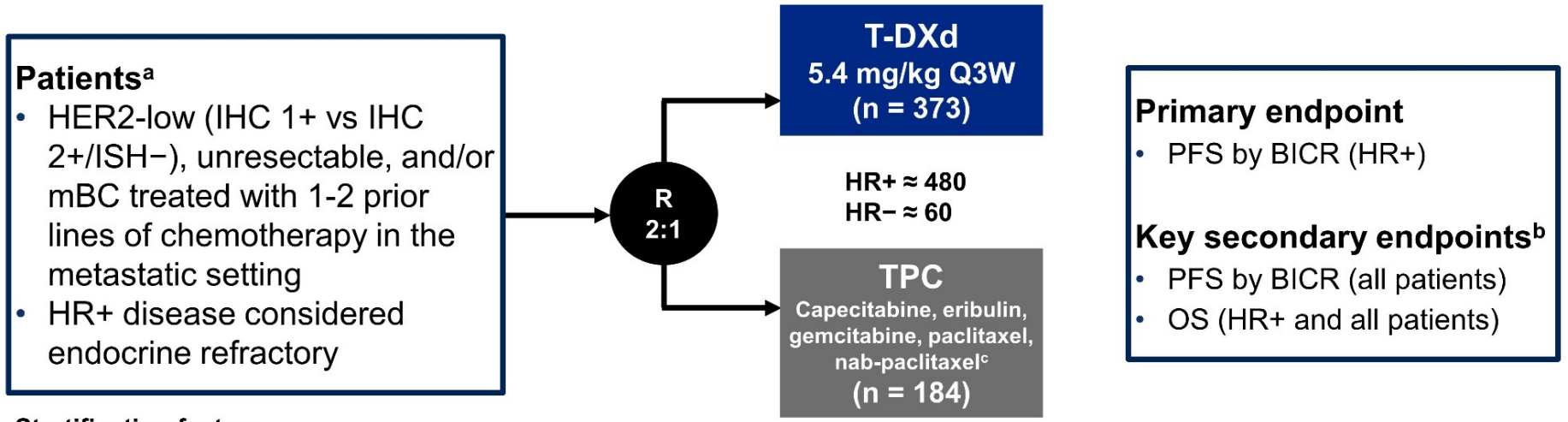
	Confirmed ORR	mDoR	mPFS
All (N = 51)	44.2% (N=43)	9.4m	7.6m
IHC 2+ (n = 24)	54.5% (N=22)	11.0m	13.6m
IHC 1+ (n = 27)	33.3% (N=21)	7.9m	5.7m
HR+ (n = 45)	47.4% (N=38)	11.0m	7.9m
Prior CDK4/6 inhibitor (n = 15)	33.3% (N=12)	NR	7.1m

Modi S et al. J Clin Oncol. 2020.

Trastuzumab Deruxtecan vs TPC: Study Design (DESTINY-B04)

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

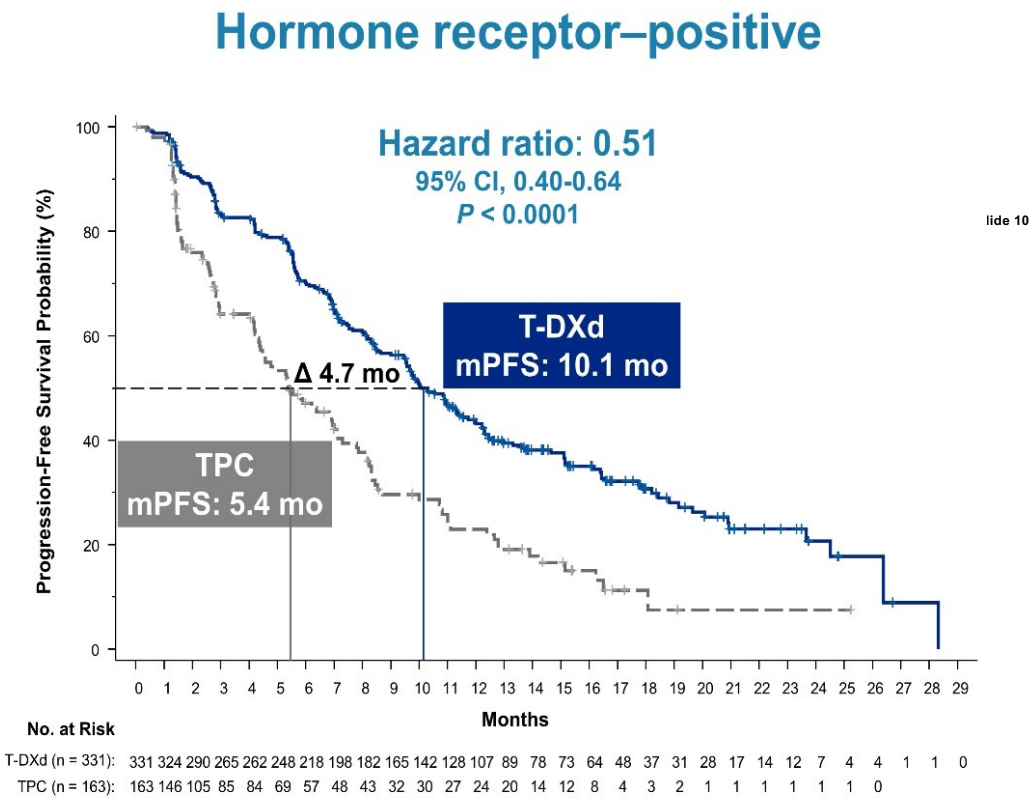
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

Trastuzumab Deruxtecan vs TPC: PFS (HR+/HER2 Low BC)

Progression-Free Survival



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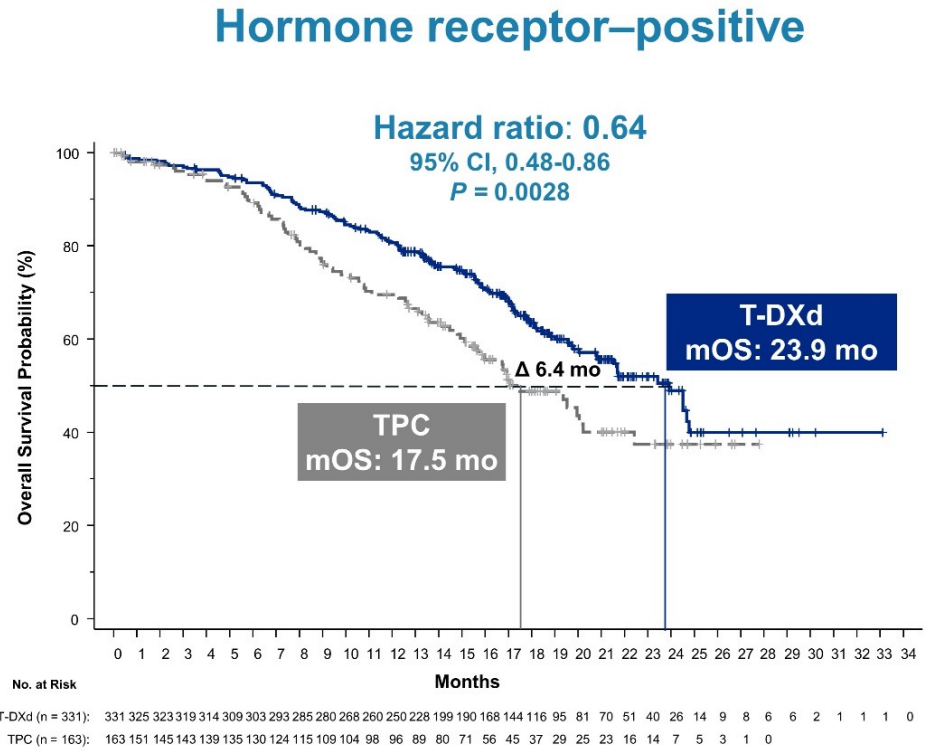
Overall Survival

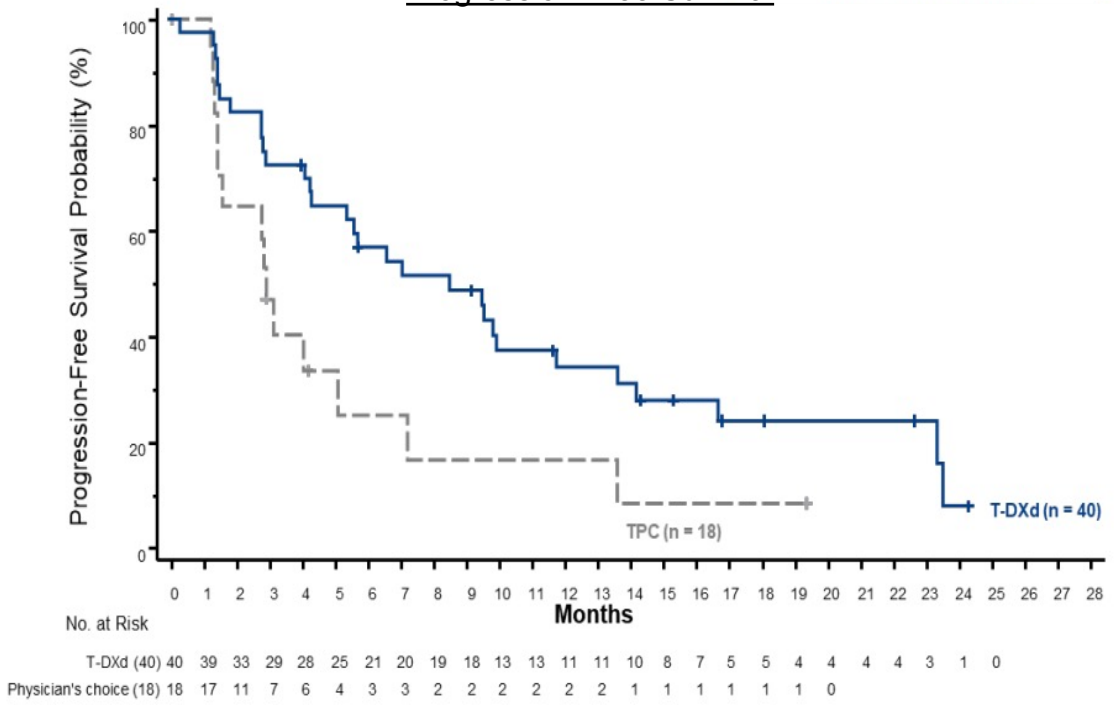


PFS by blinded independent central review.
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan;

Trastuzumab Deruxtecan: Efficacy in HER2-low mTNBC

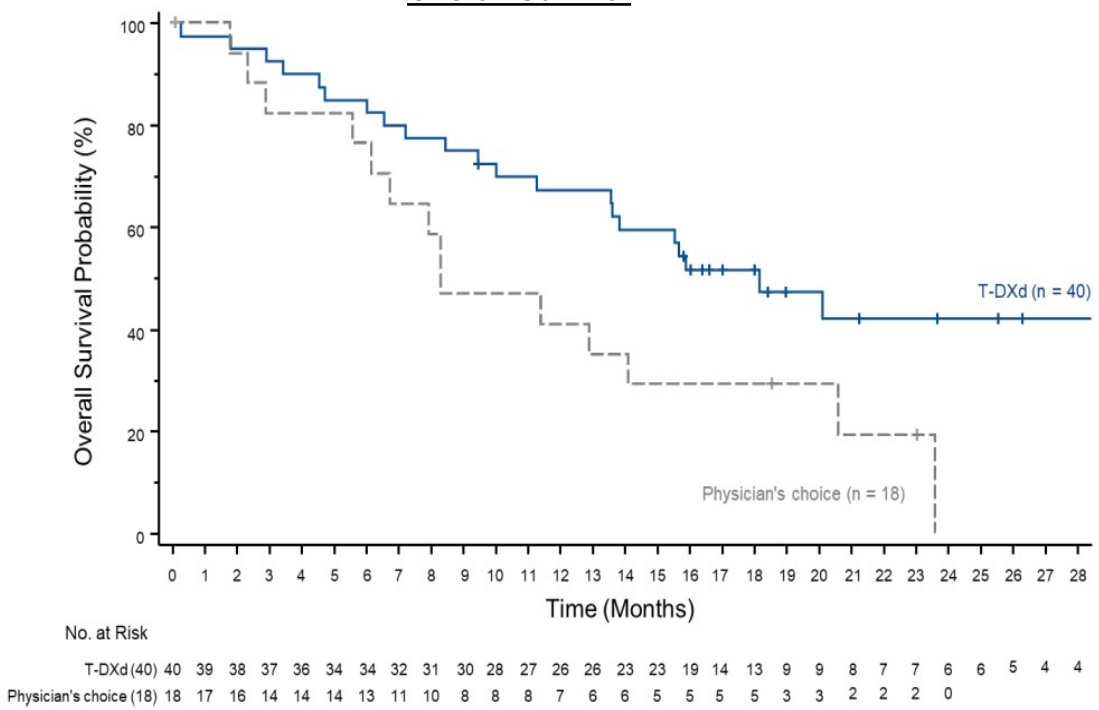
Exploratory Endpoint

Progression-Free Survival



	T-DXd (n=40)	TPC (n=18)
Median PFS (95% CI)	8.5 (4.3-11.7)	2.9 (1.4-5.1)
HR (95% CI), *P*-value	**0.46** (0.24-0.89)	

Overall Survival



	T-DXd (n=40)	TPC (n=18)
Median OS (95% CI)	18.2 (13.6-NE)	8.3 (5.6-20.6)
HR (95% CI), *P*-value	**0.48** (0.24-0.95)	

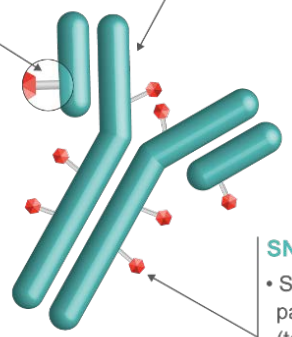
Modi S et al. *NEJM*. 2022.

What about activity of other ADCs for HER2 low MBC?

Trop2 ADC for HR+ MBC: Sacituzumab Govitecan

Humanized anti–Trop-2 antibody
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

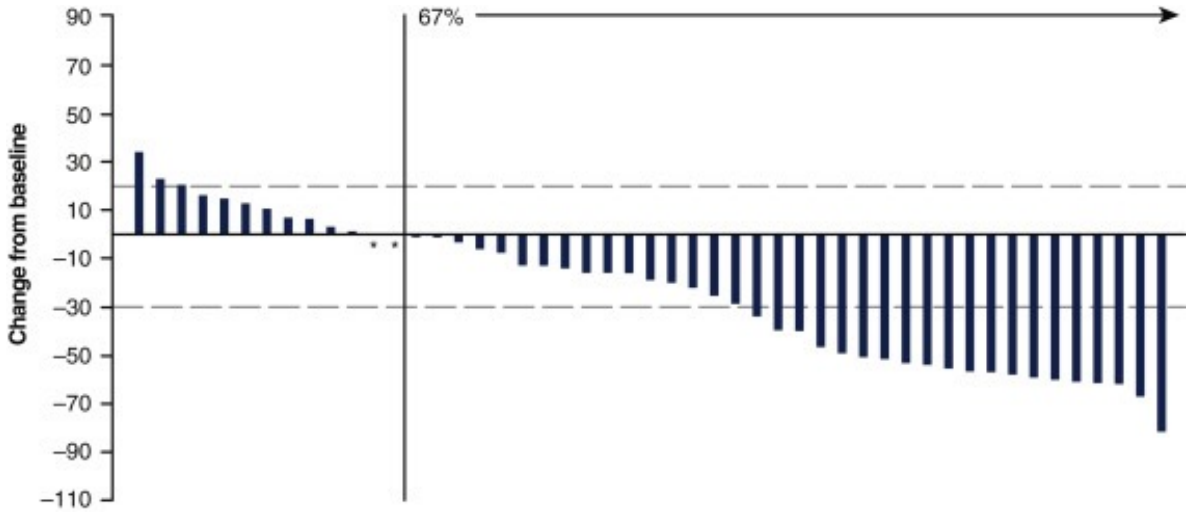
Linker for SN-38
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)



SN-38 payload
- SN-38 more potent than parent compound, irinotecan (topoisomerase I inhibitor)
- SN-38 chosen for its moderate cytotoxicity (with IC50 in the nanomolar range), permitting delivery in high quantity to the tumor

Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody

Confirmed ORR = 31.5%



Phase I/II Basket Trial

≥3rd Line HR+/HER2- MBC N=54[a]

Other Advanced Epithelial Cancers

- Adults, ≥18 y
- Patients with metastatic epithelial cancers who progressed ≥1 standard therapeutic regimen for their disease
- ECOG performance status 0/1
- Measurable disease by CT/MRI

Sacituzumab govitecan 10 mg/kg IV

Days 1 and 8 every 21 days (restaging scans every 8 weeks)

Until progression or unacceptable toxicity

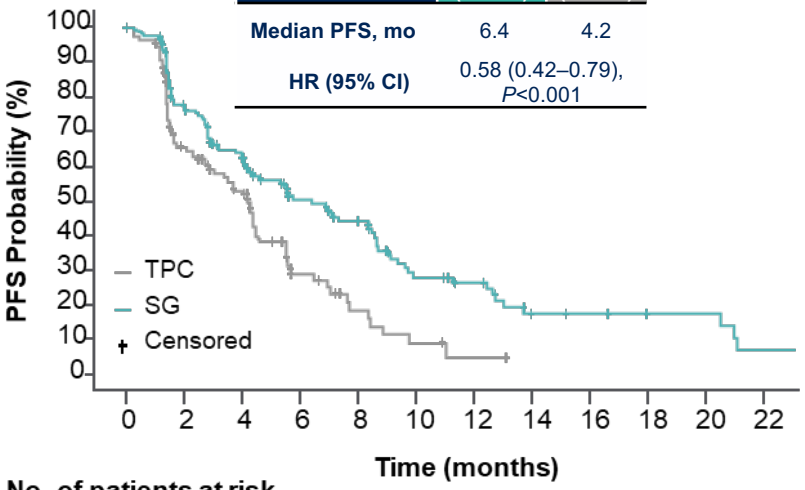
Endpoints:
- Response evaluation by investigators according to RECIST 1.1
- Duration of response
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety

Kalinsky K et al. Ann Oncol. 2020

Sacituzumab Govitecan vs TPC: Efficacy by HER2 status (TROPiCS-02)

HER2-Low[a]

	SG (n=149)	TPC (n=134)
Median PFS, mo	6.4	4.2
HR (95% CI)	0.58 (0.42–0.79), *P*<0.001	

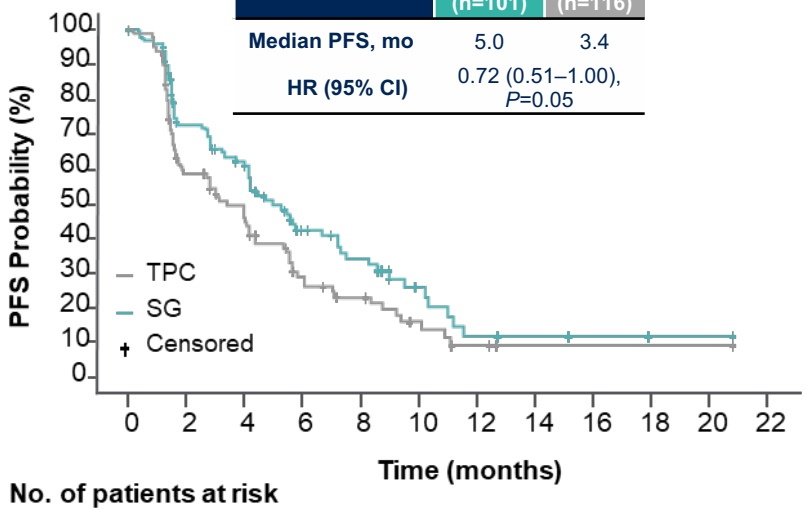


No. of patients at risk

TPC	134	65	43	16	8	4	1	0	0	0	0	0
SG	149	99	77	50	38	22	16	8	7	5	5	2

HER2 IHC0

	SG (n=101)	TPC (n=116)
Median PFS, mo	5.0	3.4
HR (95% CI)	0.72 (0.51–1.00), *P*=0.05	

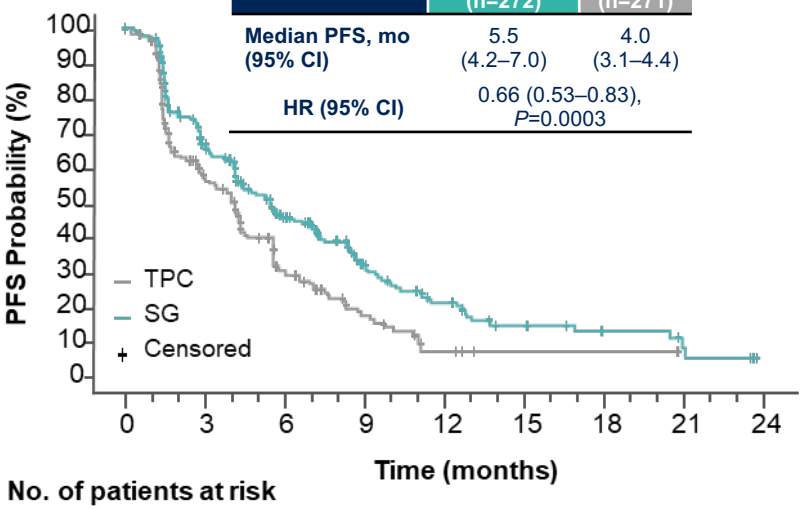


No. of patients at risk

TPC	116	53	39	20	14	7	3	1	1	1	1	0
SG	101	64	50	27	20	9	4	3	2	1	1	0

ITT[1]

	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
HR (95% CI)	0.66 (0.53–0.83), *P*=0.0003	



No. of patients at risk

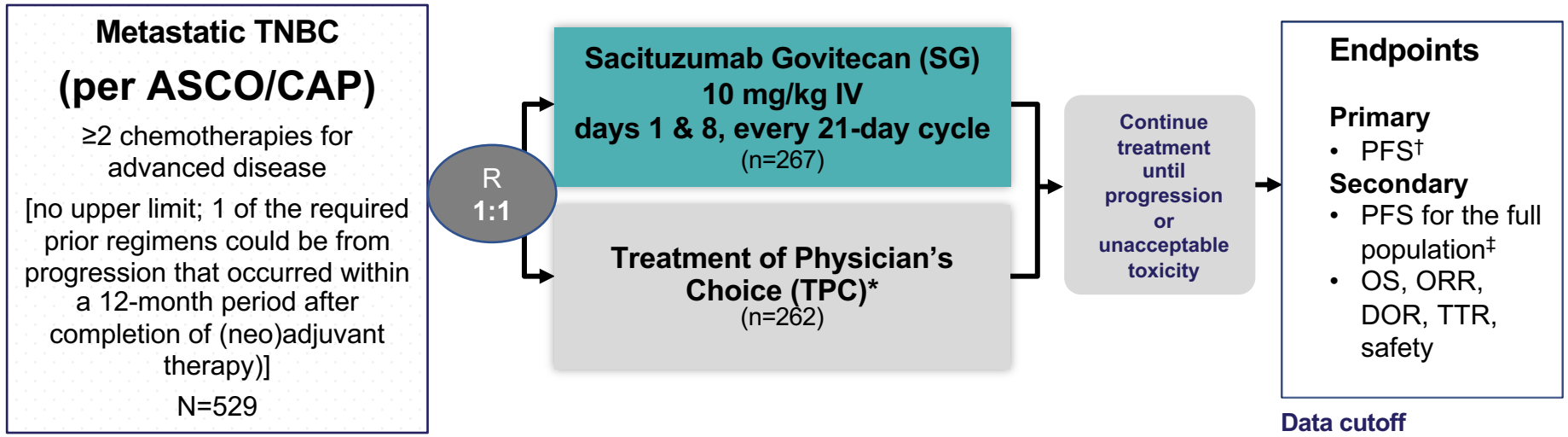
TPC	271	105	41	17	4	1	1	0	
SG	272	148	82	44	22	12	6	3	0

- Within the HER2-Low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- The hazard ratio for median PFS in a sensitivity analysis of the HER2-Low subgroup (excluding ISH-unverified[b]) was similar (HR, 0.53)

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.
[b]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-low, consistent with the trial eligibility criteria to enroll HER2-negative patients.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology.

Presented by: Dr. Frederik Marmé

Phase III Study of Sacituzumab Govitecan vs TPC: ASCENT



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.

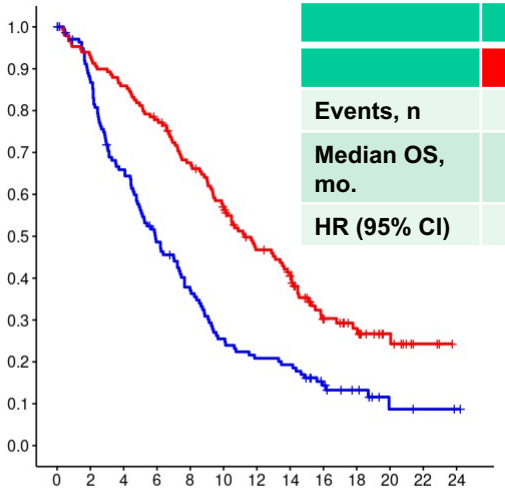
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Bardia A et al. *NEJM*. 2021

Sacituzumab Govitecan vs TPC: Efficacy in HER2 low mTNBC (ASCENT)

A

HER2 IHC0

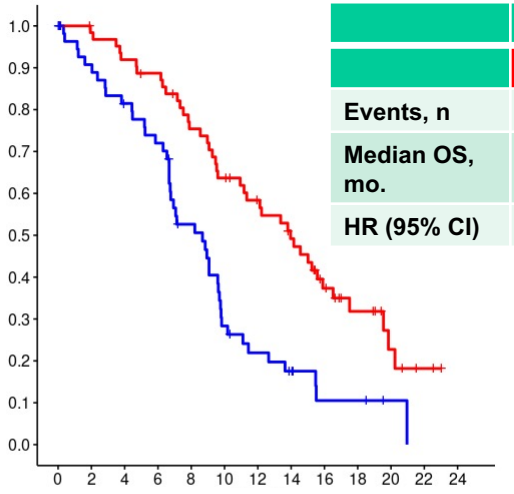


	HER2 IHC0	
	SG	TPC
Events, n	149	144
Median OS, mo.	11.3	5.9
HR (95% CI)	0.51 (0.39-0.66), *P*<0.001	

SG, HER2 IHC0	149	139	128	115	98	80	62	52	29	22	11	4	0
TPC, HER2 IHC0	144	118	88	64	48	33	27	25	15	9	3	2	1

B

HER-Low



	HER2-Low*	
	SG	TPC
Events, n	63	60
Median OS, mo.	14.0	8.7
HR (95% CI)	0.43 (0.28-0.67), *P*<0.001	

SG, HER2 IHC0	63	61	57	54	45	38	32	26	17	10	5	2	0
TPC, HER2 IHC0	60	49	43	38	26	14	10	7	3	3	1	0	0

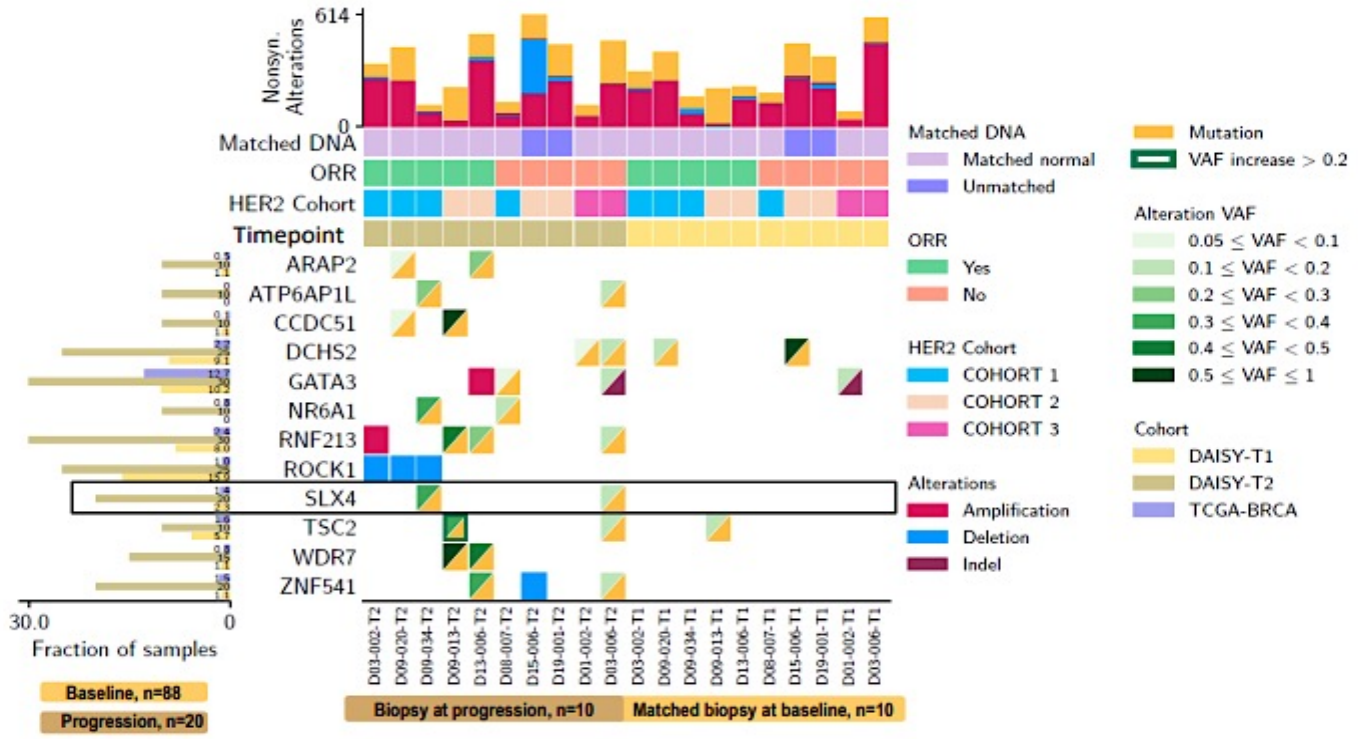
*HER2-Low defined as IHC1+ or ICH2+ and ISH-negative.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Hurvitz S et al. ESMO Breast. 2022

How to sequence the different ADCs?

Mechanism Governing Resistance: Trastuzumab Deruxtecan (DAISY)

- 20 frozen tumor biopsies at progression analyzed by WES
- 10 samples with matched biopsy at baseline

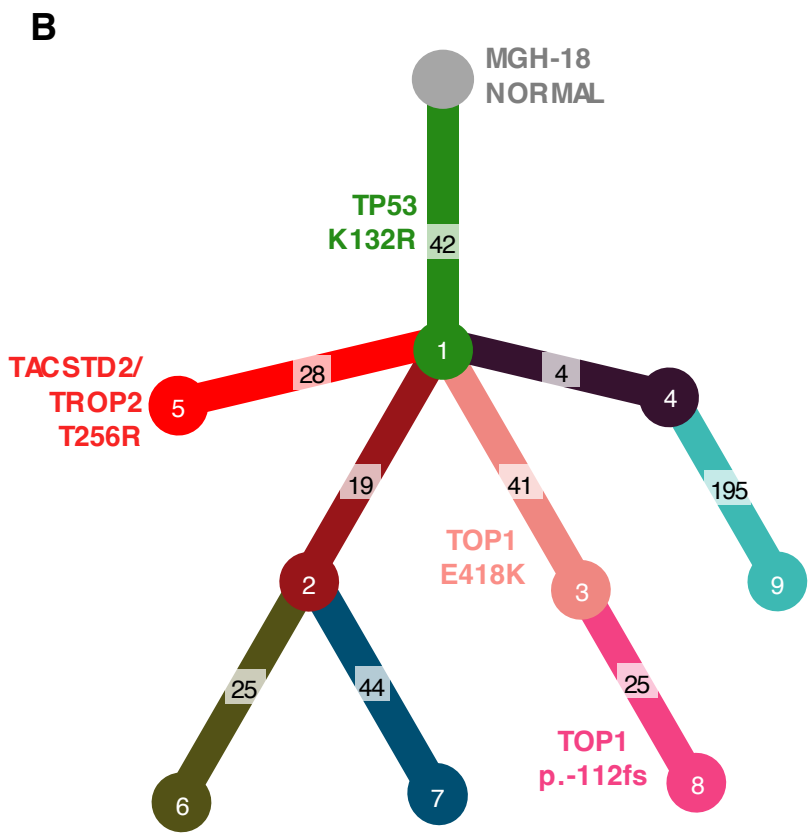


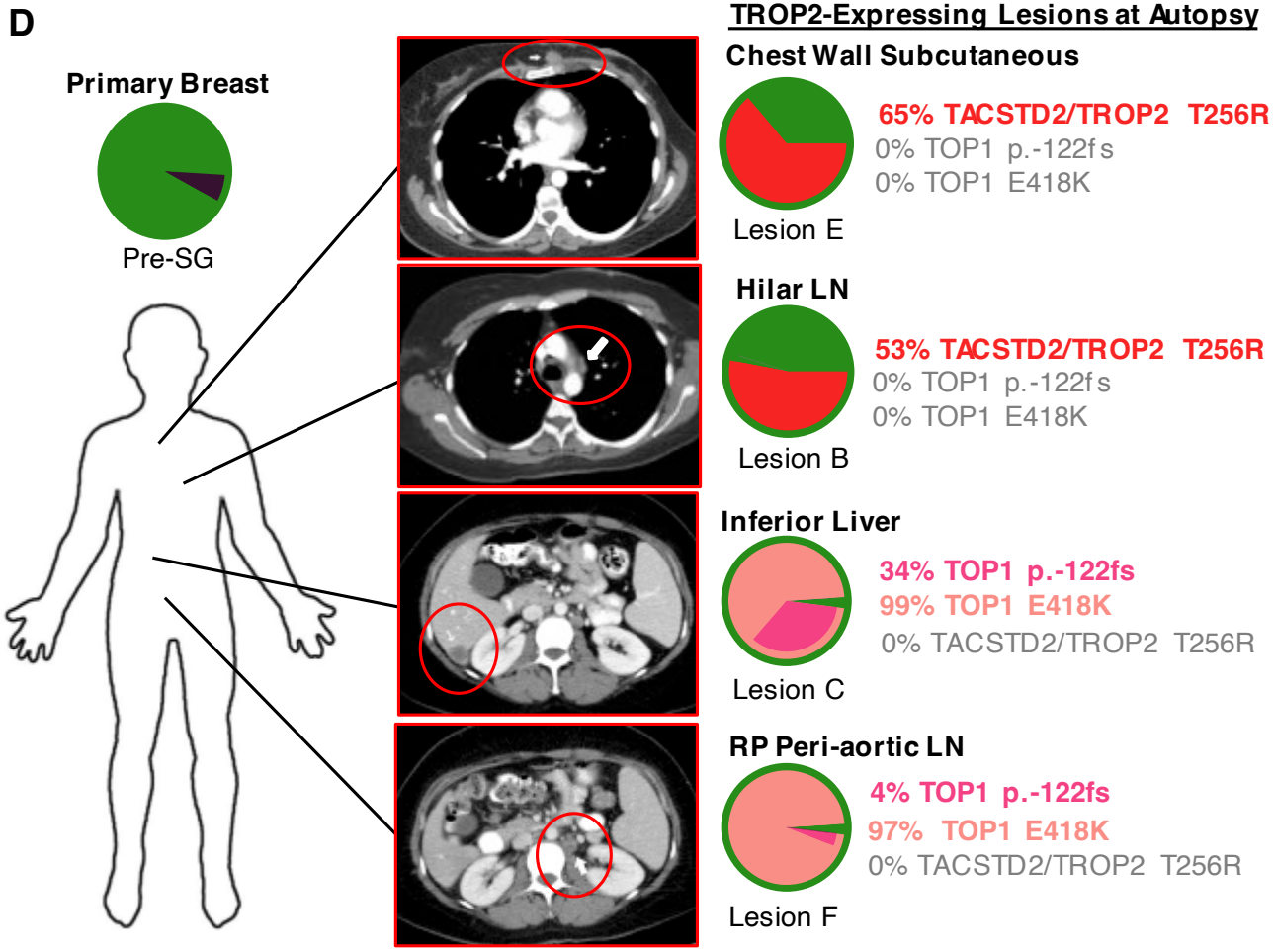
- *SLX4* encodes a DNA repair protein that regulates endonucleases, whose role in camptothecin resistance remains unclear
- 4/20 (20%) *SLX4* mutation biopsies at progression
- 2 *SLX4* mutations were not detectable in baseline samples
- 2 *SLX4* mutations there was no matched baseline sample

PARIS 2022 ESMO congress

M. F. Mosele, MD

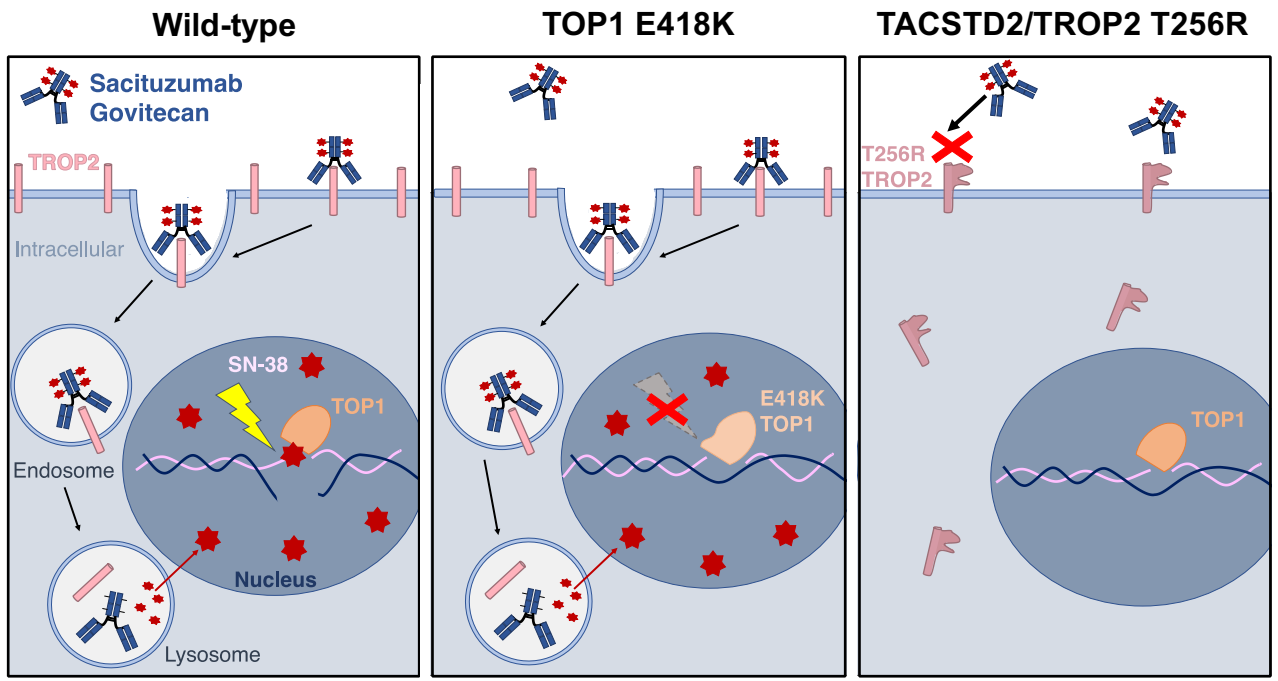
Mechanism Governing Resistance: Antibody vs Payload

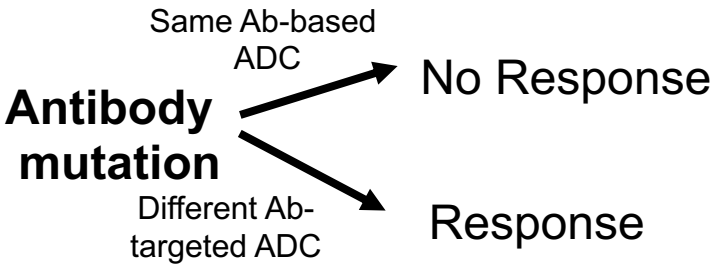


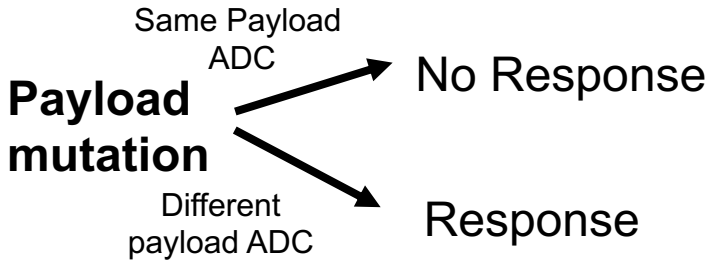


Coates, Sun et al Cancer Discovery 2021.

Implications of resistance mechanisms for ADC sequencing







Coates, Sun et al Cancer Discovery 2021.

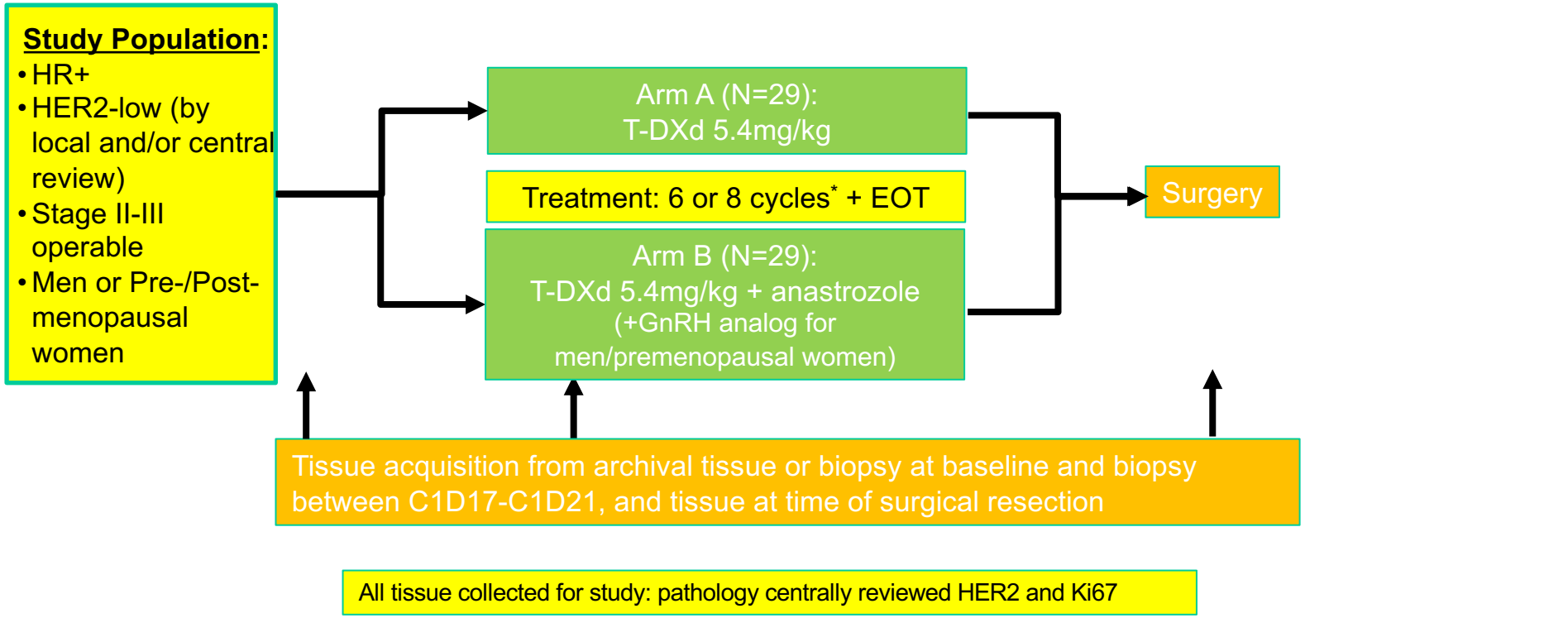
ADCs to target MBC: Multiple Agents in Development

Antibody Drug Conjugate	Target	Payload
Trastuzumab deruxtecan (DS-8201a)	HER2	Topo-1 inhibitor
Sacituzumab govitecan (IMMU-132)	Trop-2	Topo-1 inhibitor
Datopotamab deruxtecan (DS-1062)	Trop-2	Topo-1 inhibitor
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1	Microtubule inhibitor
Patritumab deruxtecan (U3-1402)	HER3	Topo-1 inhibitor
Trastuzumab duocarmazine	HER2	Alkylating agent
Disitamab vedotin	HER2	Microtubule inhibitor

Both target and payload important considerations for efficacy/toxicity profile and ADC sequencing

How about Early Breast Cancer?

TRIO-US B-12 (TALENT): Study Design



* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatment cycles from 6 to 8 for newly enrolled participants, or those who had not yet had surgery. EOT 21-28 days after last dose of T-DXd.

TRIO-US B-12 (TALENT): Results

Placeholder

Summary

- Trastuzumab deruxtecan has demonstrated impressive activity in HER2 low metastatic breast cancer, both HR+ and HR-, and approved in 2nd line (and plus) MBC setting.
- Sacituzumab govitecan approved for mTNBC, regardless of HER2 expression (not surprising). Activity also seen in HR+ metastatic breast cancer.
- There are multiple ADCs in development to target antigens overexpressed in MBC.
- Understanding mechanism of resistance, antibody vs payload, could help guide therapeutic sequencing of ADCs.
- Additional studies evaluating different ADCs targeting different antigens could redefine the current receptor-based classification of breast cancer.

Thank you for your attention

 @DrAdityaBardia

Appendix

Editorial Review

- Incidence and clinicopathologic characteristics of HER2-low breast cancer
  - Slide 4
- Historical management approach for HR-positive, HER2-low mBC; available data with established HER2-targeted agents (eg, trastuzumab, pertuzumab, T-DM1)
  - Slides (none) – non-CME objective related; can be covered verbally
  - Note to NL (11/30/22): Please advise how you would like to address
- Mechanism of action of trastuzumab deruxtecan (T-DXd); rationale for its activity in patients with HER2-low breast cancer
  - Slides 5-6, 16-18
- Key findings among patients with ER-positive disease from the DESTINY-Breast04 trial evaluating T-DXd versus chemotherapy for patients with previously treated HER2-low advanced breast cancer
  - Slides 7-9
- Early results (eg, TRIO-US B-12 TALENT) with T-DXd-containing neoadjuvant therapy for HR-positive, HER2-low localized breast cancer
  - Slides 21-22
    - Title and data placeholder slide (Hurvitz SA et al. GS3-02, Wednesday 12/7/22 at 10:30pm EST)
-
- ***Slides 11-14 are on sacituzumab govitecan but focus is on HER2-low subset, but may overlap with Dr Rugo's assignment (Delete?)***

Appendix Slides – None