Where Science Becomes Hope

OPTIMIZING ANTIBODY-DRUG CONJUGATES IN HER2-NEGATIVE BREAST CANCER

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July 25, 2024

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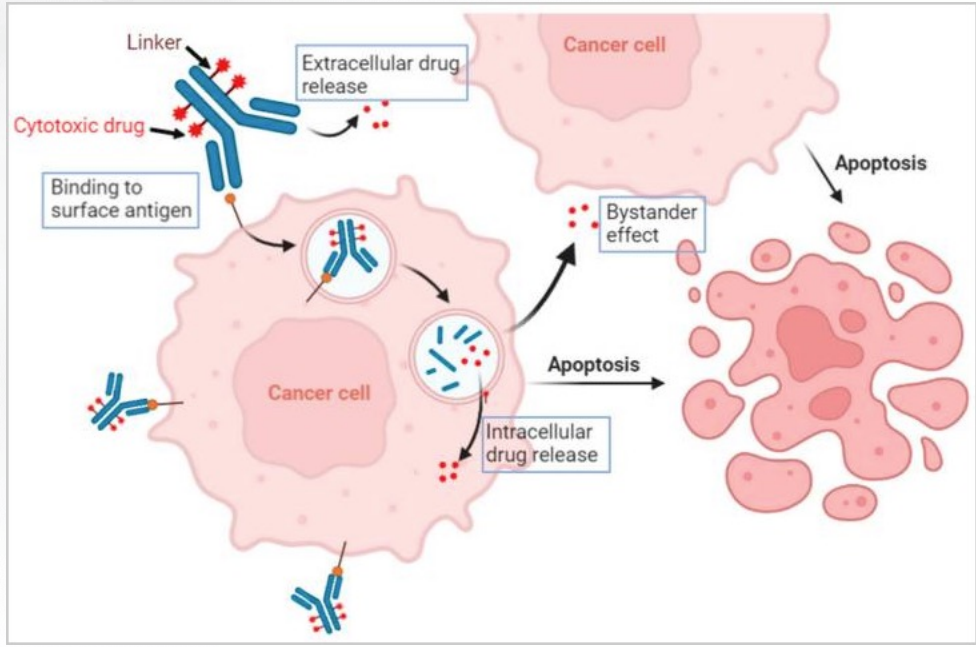
OUTLINE

1. Background
2. Trastuzumab deruxtecan (T-DXd)
3. Sacituzumab govitecan
4. Novel ADCs
5. Current approach

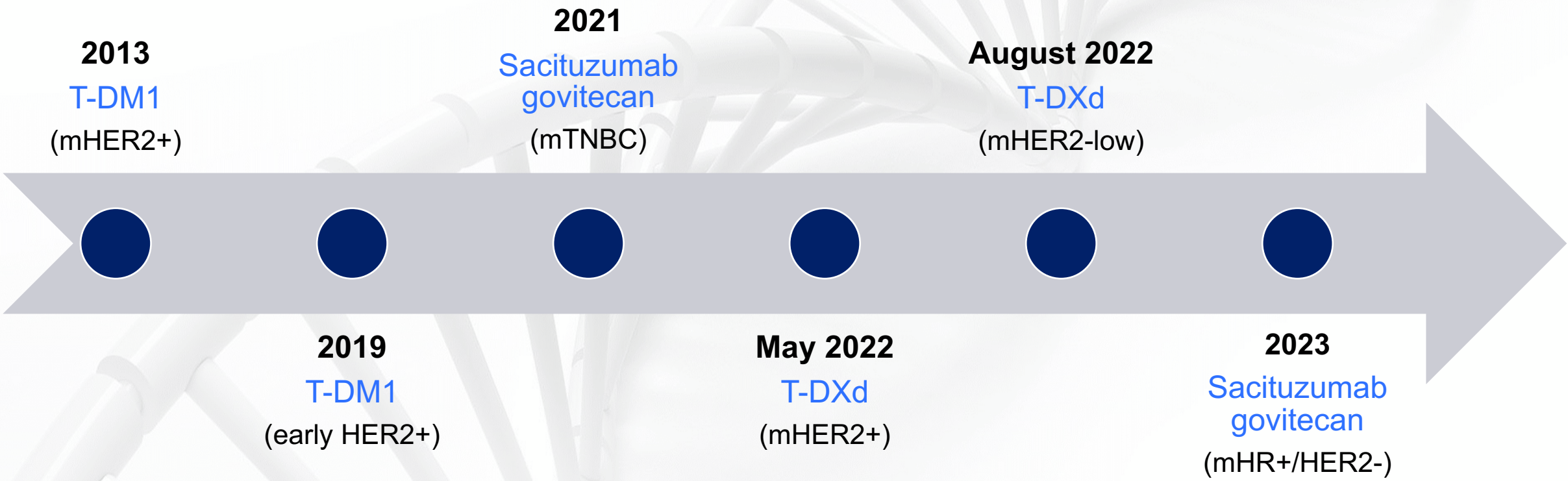
ANTIBODY-DRUG CONJUGATES (ADCS)

- Monoclonal antibody linked to cytotoxic payload
- Allows for more targeted delivery of potent drugs to cancer cells expressing specific antigens
  - Goal: increased efficacy + reduced toxicity vs conventional chemotherapy
- Neighboring antigen-negative tumor cells can be killed by the bystander effect
- Mechanisms of toxicity
  - Premature release of cytotoxic payload
  - Target antigen expressed on healthy cells
  - Bystander effect leads to killing of nearby healthy cells



Mark C, et al. Int J Mol Sci. 2023

FDA APPROVAL OF ADCS IN BREAST CANCER



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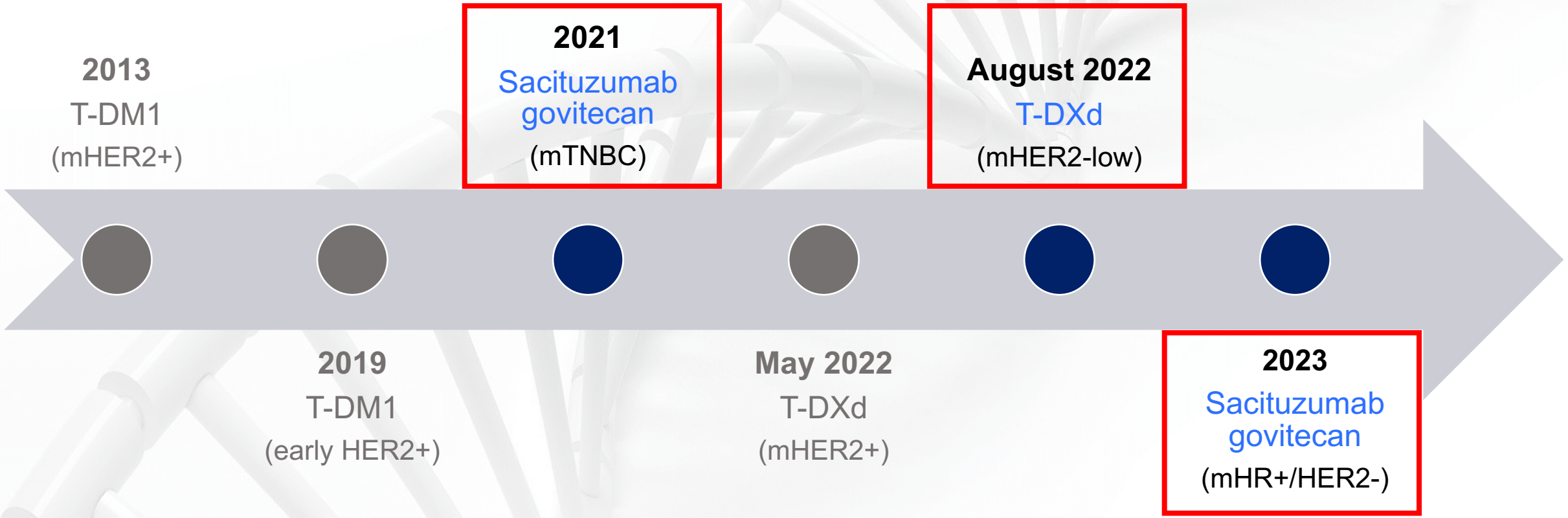
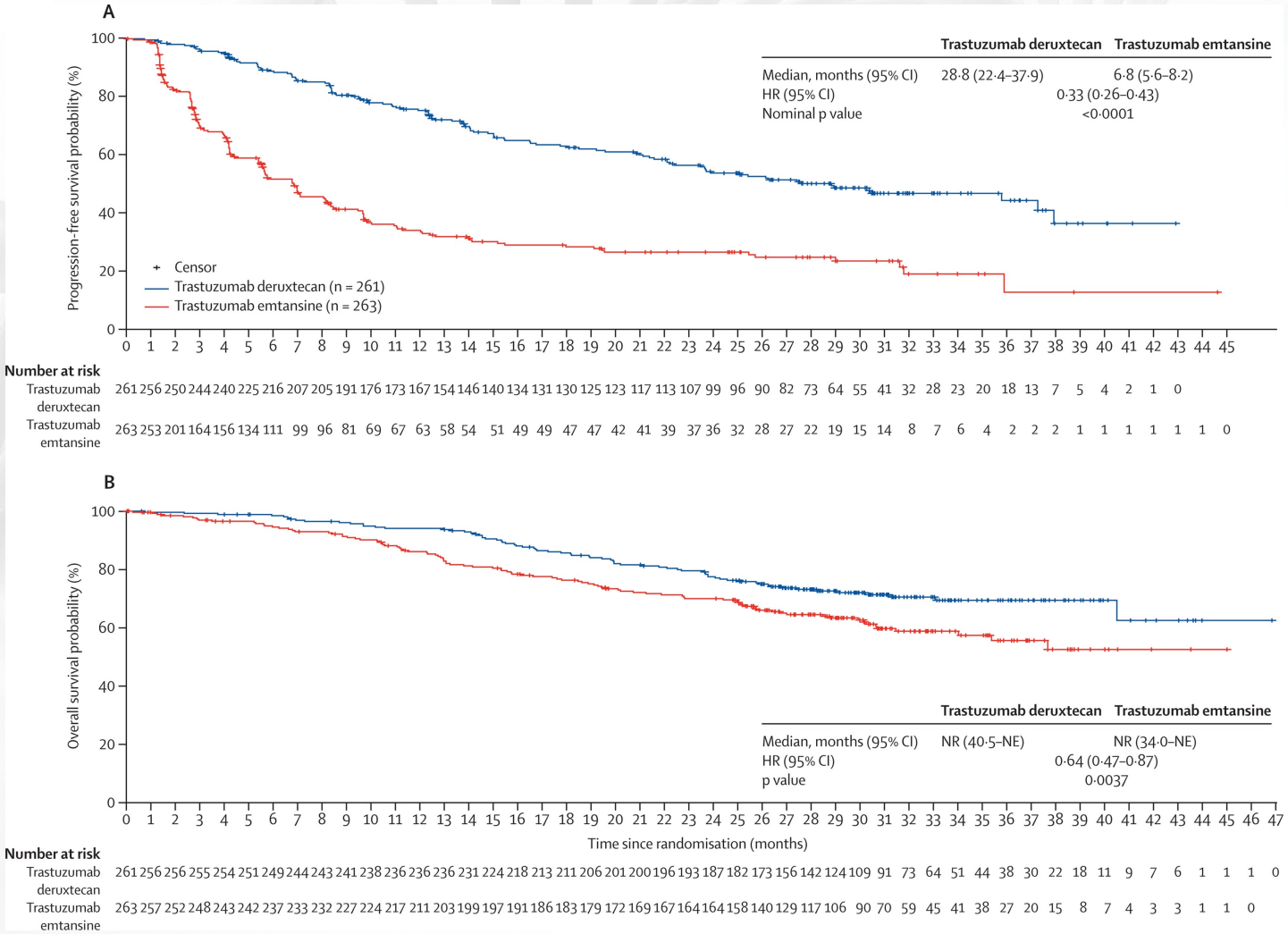


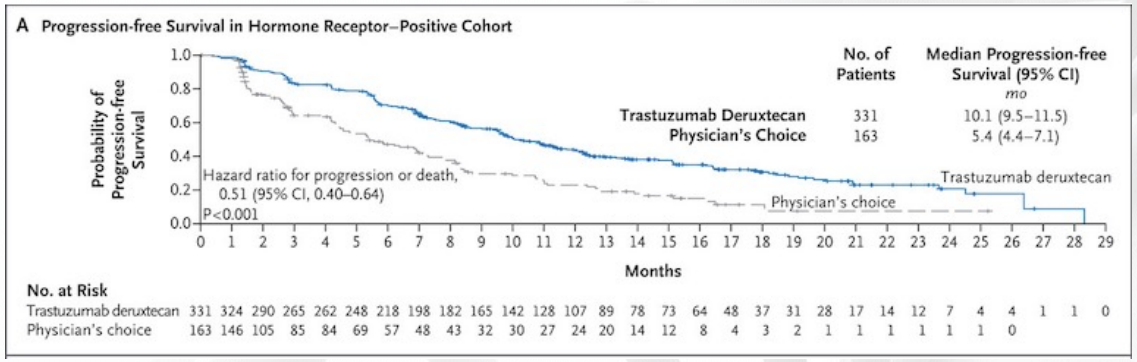
TRASTUZUMAB DERUXTECAN (T-DXD)

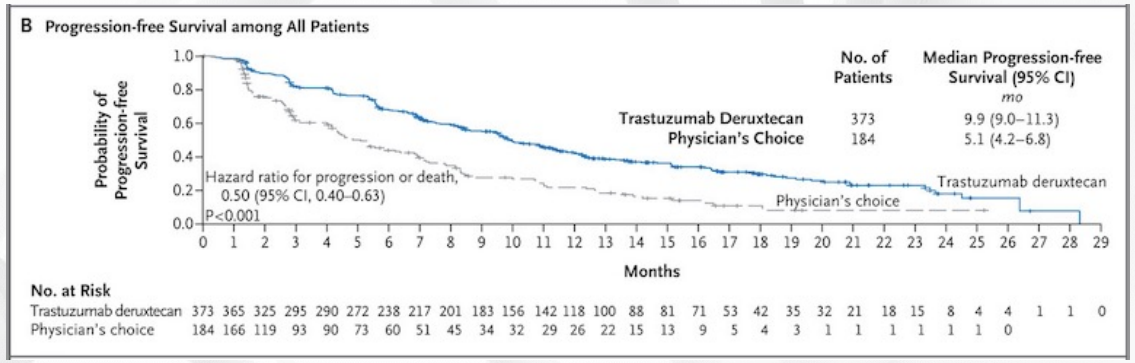
- Trastuzumab + topoisomerase I inhibitor
- Specialized cleavable linker allows limits premature release of deruxtecan → reduced toxicity
- Drug:antibody ratio ~8
- **DESTINY-Breast 03:** Improved PFS and OS vs T-DM1 in mHER2+ BC

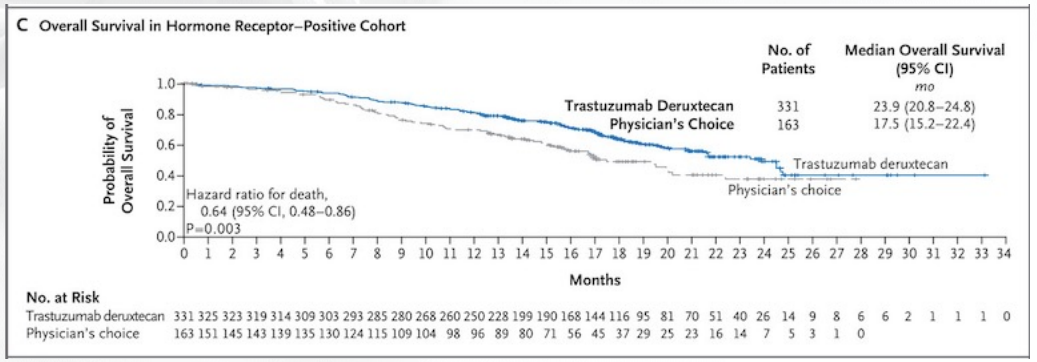


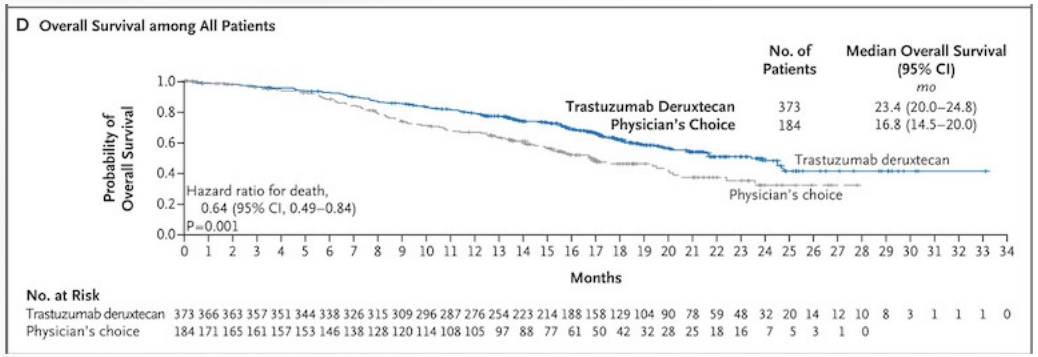
DESTINY-BREAST 04

- Phase III randomized trial of patients with HER2-low metastatic breast after 2 lines of prior chemotherapy
  - ➢ HER2-low = IHC 1+ OR IHC 2+ and FISH negative → 45-55% of all breast cancers
- Improved PFS and OS vs physician's choice chemotherapy









Hurvitz SA, Hegg R, Chung WP, et al. Lancet. 2023 Feb 18;401(10376):556

T-DXD ADVERSE EVENTS

- Serious AE rate vs chemotherapy 27.8% vs 25%; Grade 3 events 52.6% vs 67.4%
- Discontinuation rate 2/2 AEs 16.2% vs 8.1%
- ILD/pneumonitis occurred in 12.1% on T-DXd arm (1 death)
- LV dysfunction occurred in 4.6% on T-DXd arm

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)	39 (22.7)	14 (8.1)
General disorders: fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0	56 (32.6)	0

Hurvitz SA, Hegg R, Chung WP, et al. Lancet. 2023 Feb 18;401(10376):556

DESTINY-BREAST 06: HER2 ULTRA-LOW

- Patients with mHR+/HER2-low or ultralow BC after ≥ 1 line of endocrine therapy and no prior chemotherapy randomized to T-DXd or treatment of physician's choice (TPC)
  - HER2-ultralow = IHC 0 with membrane staining < 1+
- Interim analysis: T-DXd improved PFS vs TPC in HER2-low (13.2 vs 8.1mo) and HER2-ultralow (13.2 vs 8.3mo)
  - OS data immature

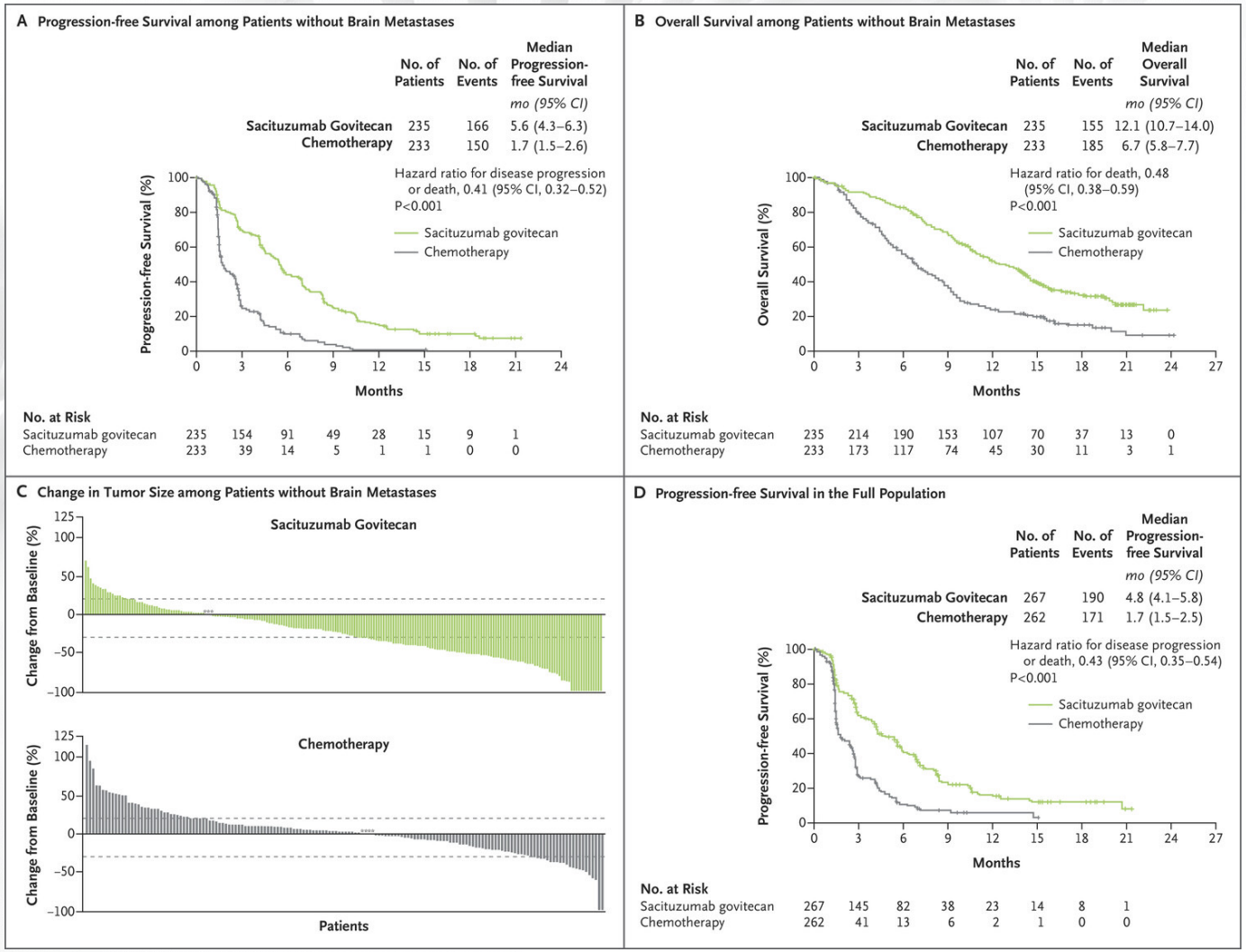
Curigliano, et al. JCO. 2024. doi: 10.1200/JCO.2024.42.17_suppl.LBA10

SACITUZUMAB GOVITECAN

- Humanized anti- **Trophoblast cell-surface antigen 2** (TROP-2) mAB + SN-38 (irinotecan metabolite, microtubule inhibitor)
  - Cell surface receptor involved in tumor cell growth and invasion
  - Expressed in ~80% of breast cancers
  - Expressed across breast cancer subtypes
  - Unfavorable prognostic indicator

ASCENT

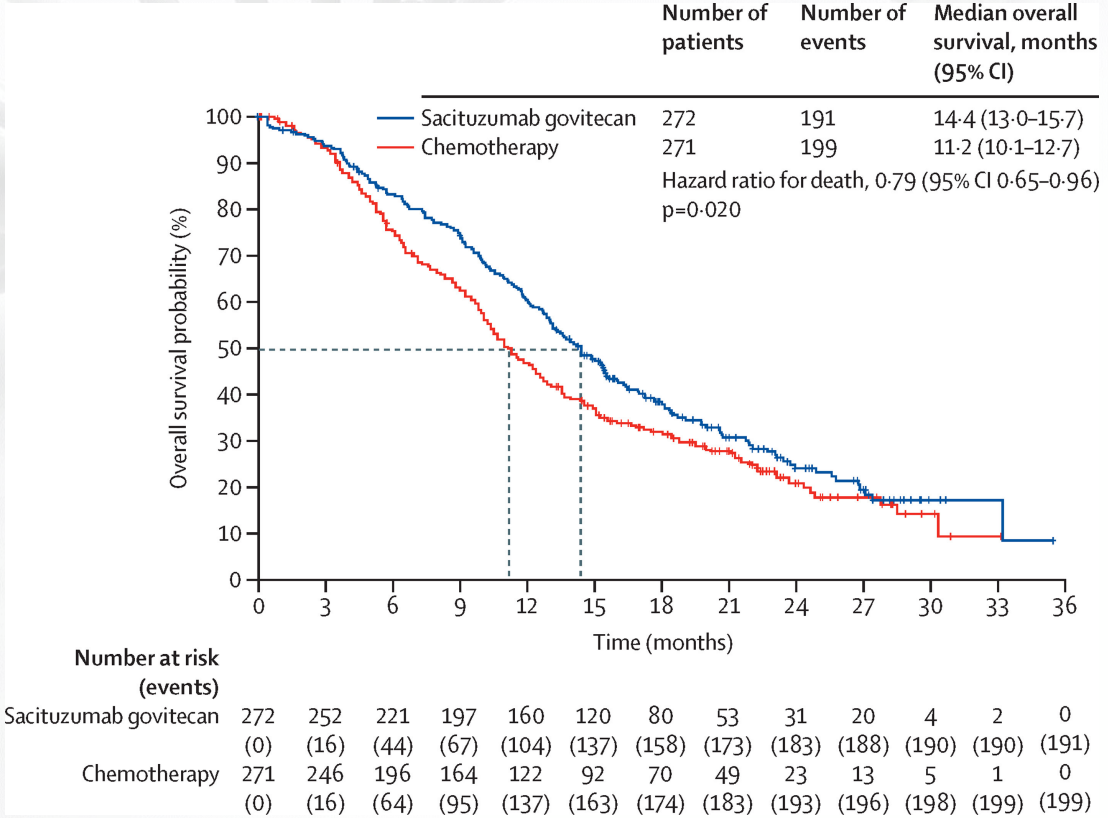
- Phase III randomized trial of patients with relapsed or refractory mTNBC
- Improved PFS (primary endpoint) and OS with sacituzumab vs single agent physician's choice chemotherapy



Bardia, et al. N Engl J Med 2021;384:1529-1541

TROPICS-02

- Phase III trial of patients with endocrine resistant, chemotherapy-treated mHR+/HER2- BC
- Patients had received at least one prior endocrine therapy, a taxane, and a CDK4/6i in any setting
- 2-4 prior chemotherapy regimens for metastatic disease
- Improved PFS vs chemotherapy (eribulin, vinorelbine, capecitabine, gemcitabine)



Rugo HS, et al. *Lancet*. 2023;402(10411):1423-1433. doi:10.1016/S0140-6736(23)01245-X

SACITUZUMAB ADVERSE EVENTS

- Grade ≥ 3 febrile neutropenia sacituzumab vs chemotherapy 5% vs 4%
- All-grade neuropathy 9% vs 16%
- No pneumonitis in sacituzumab group

	Sacituzumab govitecan (n=268)	Chemotherapy (n=249)
Grade 3 or higher	198 (74%)	150 (60%)
Leading to treatment discontinuation	17 (6%)	11 (4%)
Leading to dose delay	178 (66%)	109 (44%)
Leading to dose reduction	90 (34%)	82 (33%)
Serious events	74 (28%)	48 (19%)
Leading to death*	6 (2%)	0
Treatment-related death	1 (<1%)	0

Rugo HS, et al. *Lancet*. 2023;402(10411):1423-1433. doi:10.1016/S0140-6736(23)01245-X

DATOPOTAMAB DERUXTECAN (DATO-DXD)

- Humanized anti-TROP2 mAB + topoisomerase I inhibitor
- **TROPION-PanTumor 01:** Interim data of phase I trial showed antitumor activity and manageable safety profile in refractory mHR+/HER2- BC and mTNBC
- **TROPION-Breast01:** Phase III trial of 2-3L Dato-DXd vs investigator's choice chemotherapy in HR+/HER2- breast cancer
- **TROPION-Breast02:** Phase III trial of 1L Dato-DXd vs investigator's choice chemotherapy in mTNBC not eligible for PD-1/PD-L1 inhibitor therapy
- **BEGONIA:** Phase Ib/II trial of Dato-DXd + durvalumab in metastatic TNBC
- **TROPION-Breast03:** Phase III trial of neoadjuvant Dato-DXd +/- durvalumab vs SOC in stage I-III TNBC with residual invasive disease
- **I-SPY2.2:** Phase II sequential multiple assignment randomized trial- neoadjuvant Dato-DXd + durvalumab pCR rate 72%
- Adverse events: Oral mucositis/stomatitis, dry eye, ILD

Bardia A, et al. *J Clin Oncol*. 2024;42(19):2281-2294. doi:10.1200/JCO.23.01909
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Dent RA, et al. *Future Oncol*. 2023;19(35):2349-2359. doi:10.2217/fon-2023-0228

Bardia A, et al. *Ther Adv Med Oncol*. 2024;16:17588359241248336.
Schmid, et al. Ann Oncol. 2023. doi: 10.1016/j.annonc.2023.09.556
Shatsky, et al. J Clin Oncol. 2024.42.17_suppl.LBA50

OTHER NOVEL ADCS

- **HER2 targeted**
  - Disitamab vedotin (RC48)
  - ARX-788
- **HER3 targeted**
  - Patritumab deruxtecan (HER3-DXd)
- **LIV1 targeted**
  - Ladiratuzumab vedotin

FUTURE DIRECTIONS

- Use in early-stage breast cancer
- When to use what biomarkers
  - Tumor heterogeneity
- Determine optimal order of ADCs
  - Potential cross-resistance to antibody target and/or payload
- Combination therapy to overcome resistance
  - Immune checkpoint inhibitors
  - Targeted therapies
- Bispecific ADCs
  - Enhanced tumor cell specificity, reduced toxicity
  - Could overcome resistance
  - Limited targets in breast cancer
- Dual payloads

SUMMARY: CURRENT APPROACH TO ADCS IN HER2- BREAST CANCER

	T-DXd	Sacituzumab
mHR+/HER2 0	No	After endocrine therapy and ≥ 2 lines of chemotherapy
mHR+/HER2 low	After ≥ 1 line of chemotherapy	After endocrine therapy and ≥ 2 lines of chemotherapy
mHR-/HER2 0	No	After ≥ 1 line of chemotherapy
mHR-/HER2 low	After ≥ 1 line of chemotherapy	After ≥ 1 line of chemotherapy

- If HER2 0, consider repeat biopsy at progression if feasible and safe
- Monitor for toxicities
  - Neutropenia (sacituzumab)- consider GCSF, alternative dosing schedule
  - ILD/pneumonitis (T-DXd)- low threshold for imaging, pulmonology consult; permanently discontinue if ≥ Grade 2
  - Cardiotoxicity (T-DXd) - TTE at baseline and every 3 months