



Multidisciplinary Approaches to Cancer Symposium

Triple Negative Breast Cancer: Which Antibody-drug Conjugates (ADC) and When?

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Disclosures

- Consultant for AstraZeneca & Novartis

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon must contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.



Objectives

- Triple negative breast cancer
- Antibody-drug conjugates (ADCs)
- ADCs in metastatic triple negative breast cancer (TNBC)
- Emerging ADCs in early-stage TNBC
- Cross resistance
- Summary

Background

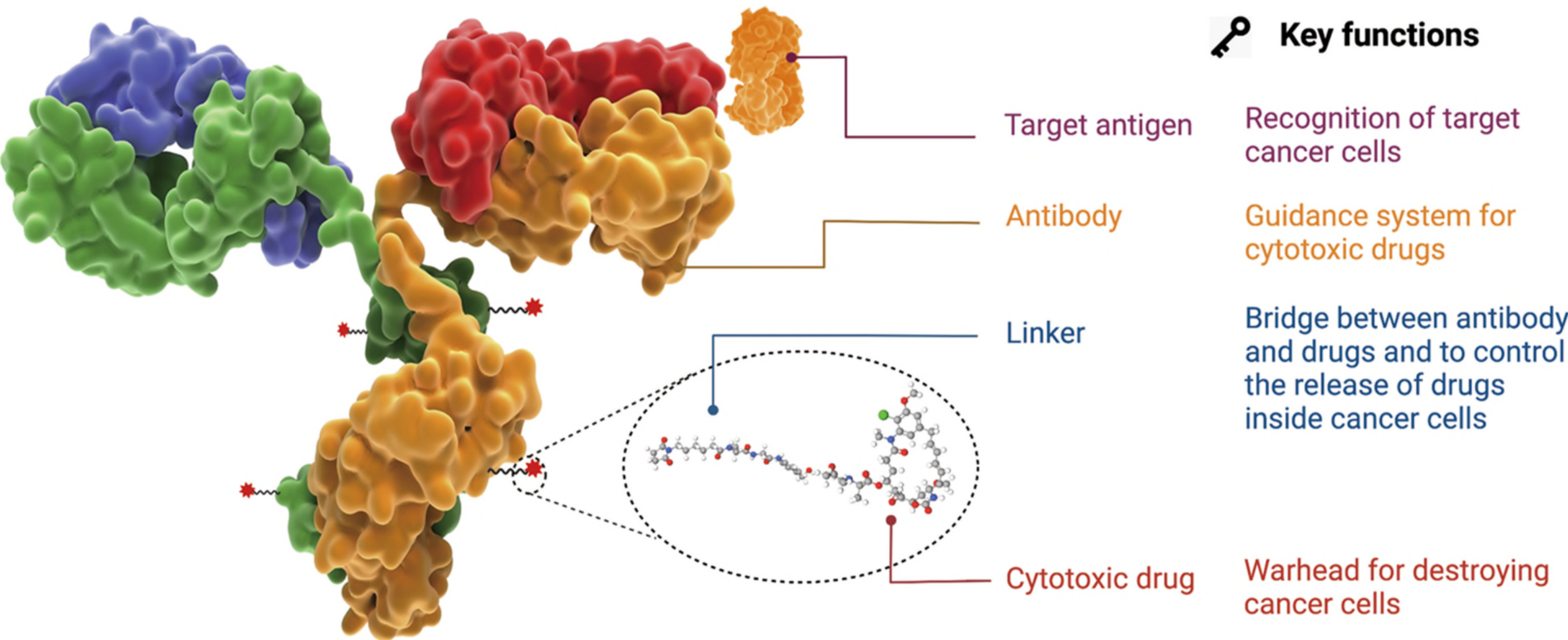
Triple negative breast cancer

- 15-20% of breast cancers
- Absence of ER, PR and HER2 amplification
- Associated with inferior outcomes compared to other breast cancer subtypes.
 - Early relapse
 - Mortality (median OS 11-15 months)
- Chemotherapy is mainstay treatment
 - Cytotoxic strategy
 - Poly(ADP-ribose) polymerase inhibitors (PARPi)
- Despite new developments, improvements in overall survival are limited.
- Antibody-drug conjugates have emerged as an important therapeutic class in metastatic triple negative breast cancer (mTNBC) and now being studied in early disease setting.

Antibody-drug conjugates

- Monoclonal antibody
 - Targets a specific tumor antigen and binds to tumor cell's surface
 - TROP2 is a transmembrane protein that is over expressed in TNBC.
- Cytotoxic payload
 - Internalized by tumor cell and released intracellularly leading to cell death.
- Clinical activity and safety
 - Target antigen
 - Linker stability
 - Payload class
 - Drug-to-antibody ratio
 - Bystander effect
 - Treatment setting

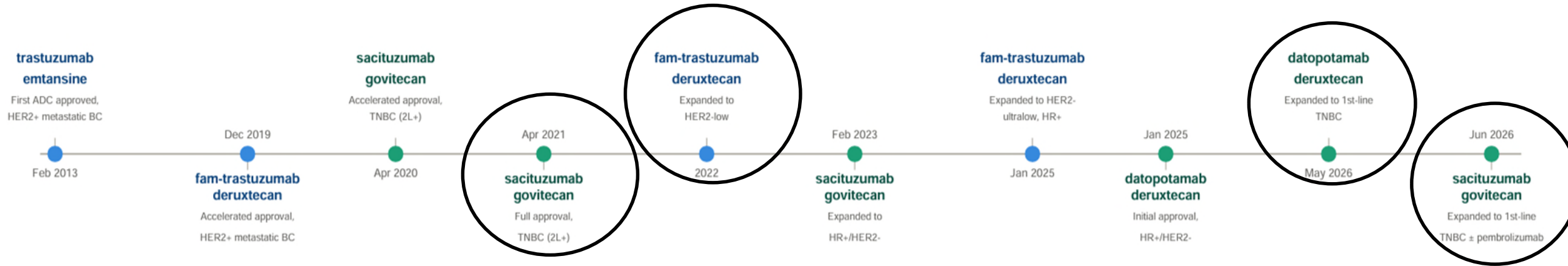




FDA-Approved Antibody-Drug Conjugates in Breast Cancer

Approvals and label expansions, 2013–2026

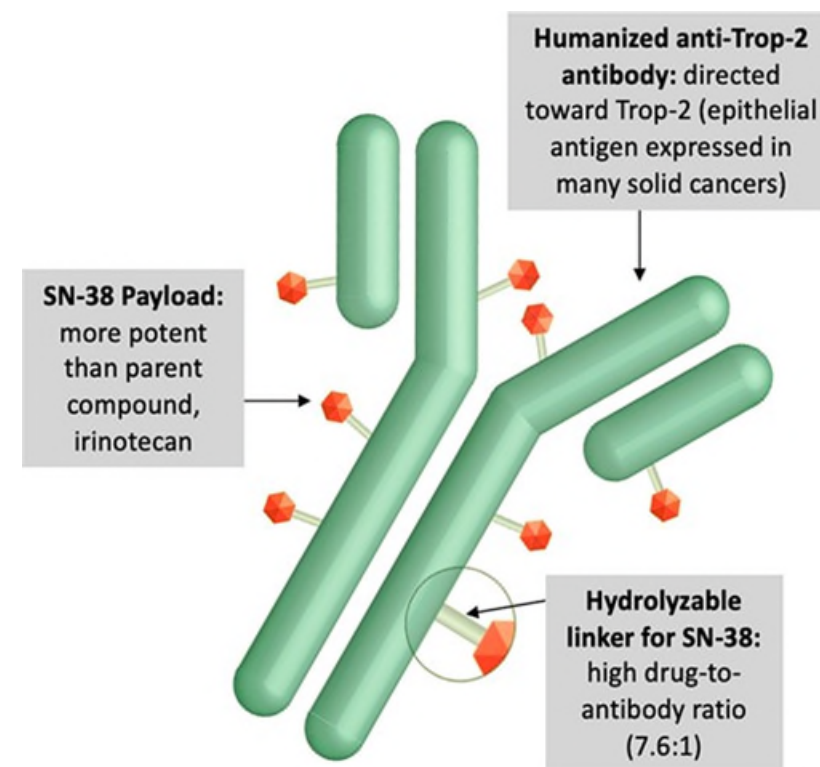
● HER2-directed ● TROP2-directed



ADCs: Metastatic triple negative breast cancer

Sacituzumab govitecan (SG)

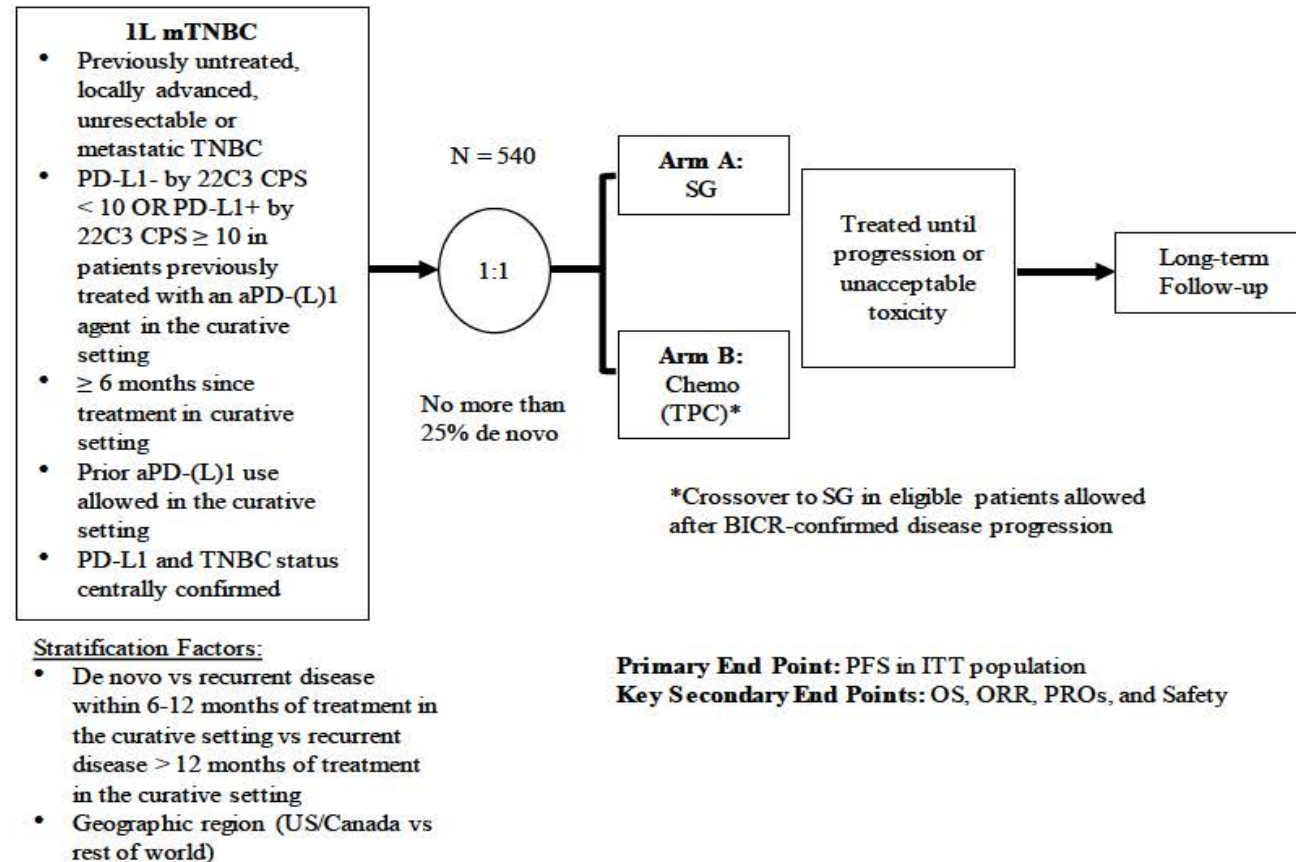
- Anti-TROP2 antibody linked to SN-38, an active metabolite of irinotecan, a topoisomerase I inhibitor.
- SN-38 is membrane permeable and elicit antitumor effects in adjacent tumor cells (bystander effect) before internalization of the ADC through hydrolysis of the linker.
- Drug to antibody ratio (DAR) is 8.
- Most common adverse effects include nausea, neutropenia, diarrhea, alopecia, fatigue, and anemia.



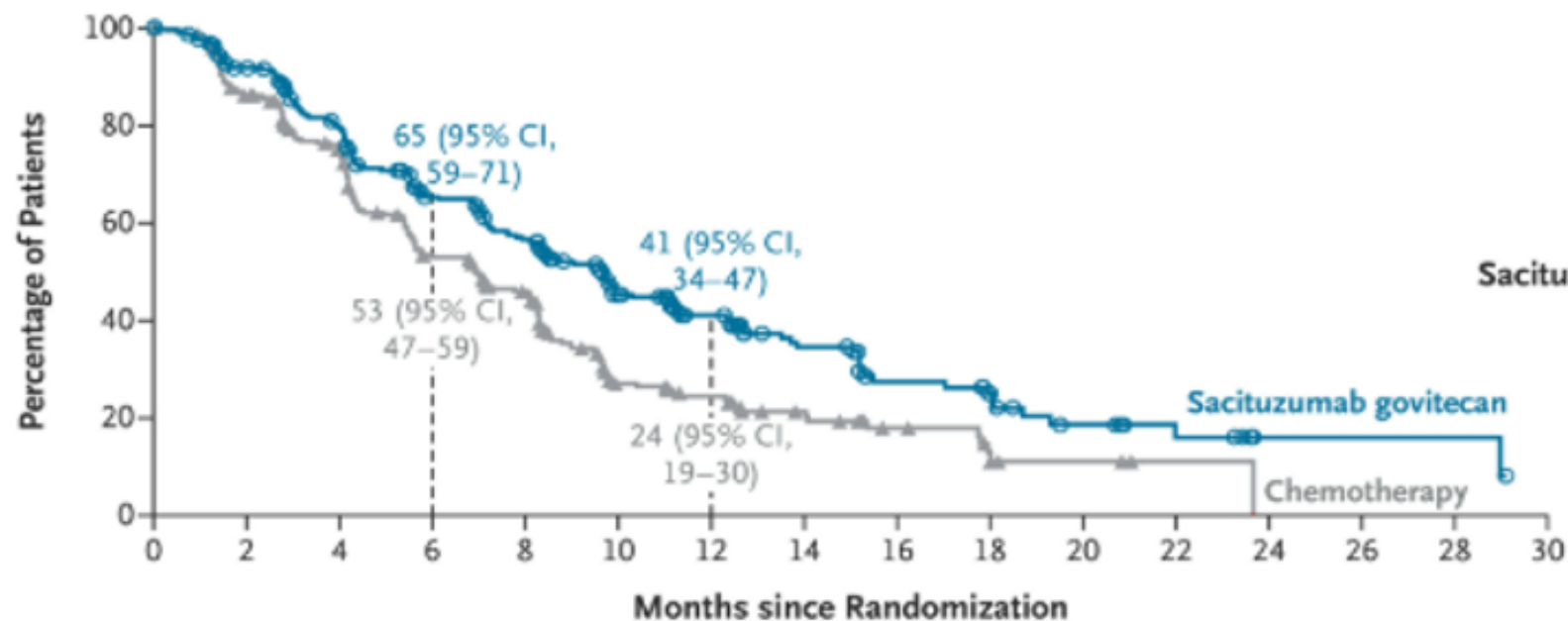
ASCENT-03

STUDY SCHEMA

Figure 1. Study Schema



A Progression-free Survival



Median Progression-free Survival (95% CI)

mo

Sacituzumab Govitecan 9.7 (8.1–11.1)

Chemotherapy 6.9 (5.6–8.2)

Stratified hazard ratio for disease progression or death, 0.62 (95% CI, 0.50–0.77)

$P < 0.001$

No. at Risk

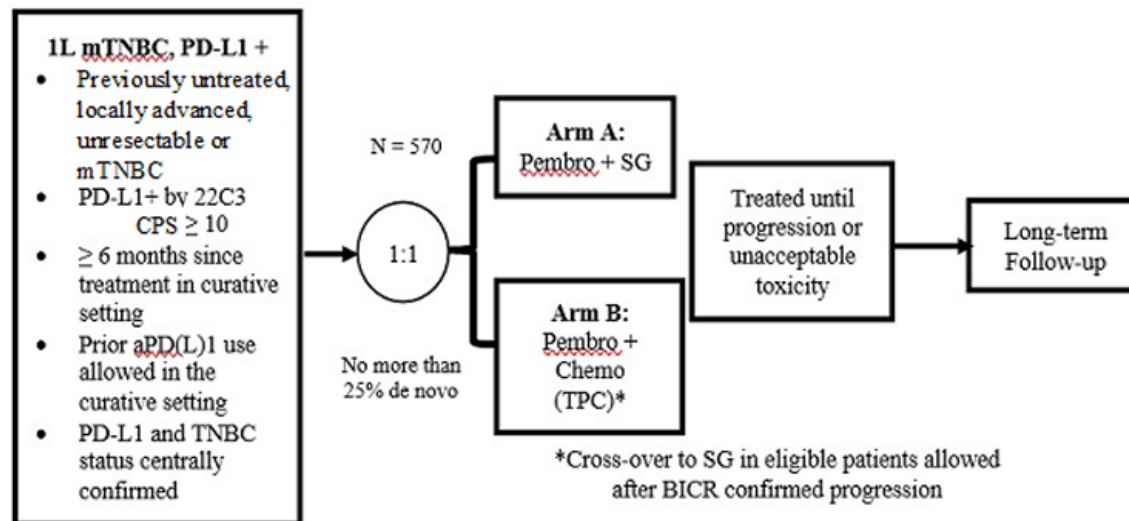
Sacituzumab govitecan	279	238	199	153	128	84	60	38	23	20	10	7	2	2	2	0
Chemotherapy	279	226	186	126	100	44	35	21	12	7	3	1	0			

No. of Events

Sacituzumab govitecan	0	22	53	88	108	131	138	146	153	154	159	159	160	160	160	161
Chemotherapy	0	37	65	118	135	172	176	180	183	186	187	187	188			

ASCENT-04

Figure 1. Study Schema

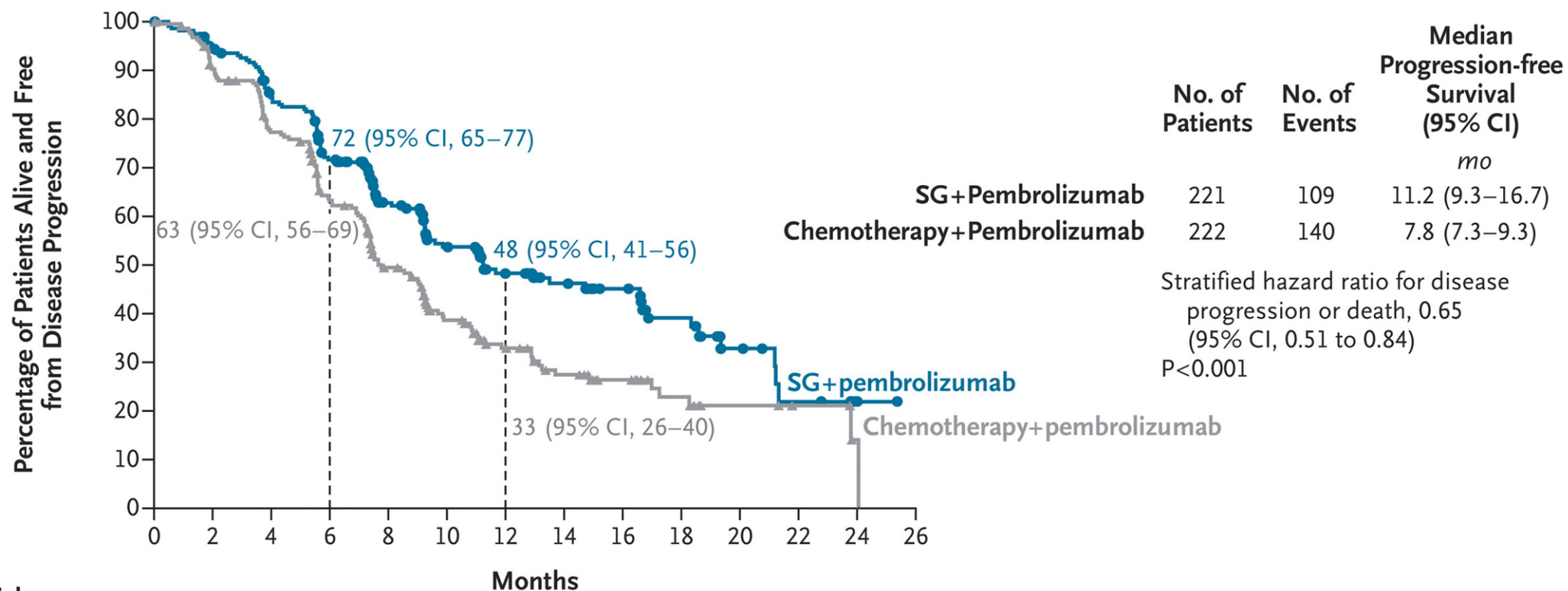


Stratification Factors:

- De novo versus within 6-12 months from completion of treatment in the curative setting versus > 12 months from completion of treatment in the curative setting**
- Geographic region (US/Canada/Western Europe versus Rest of World)
- Prior exposure to aPD-(L)1 (Yes/No)

Primary End point: PFS in ITT population

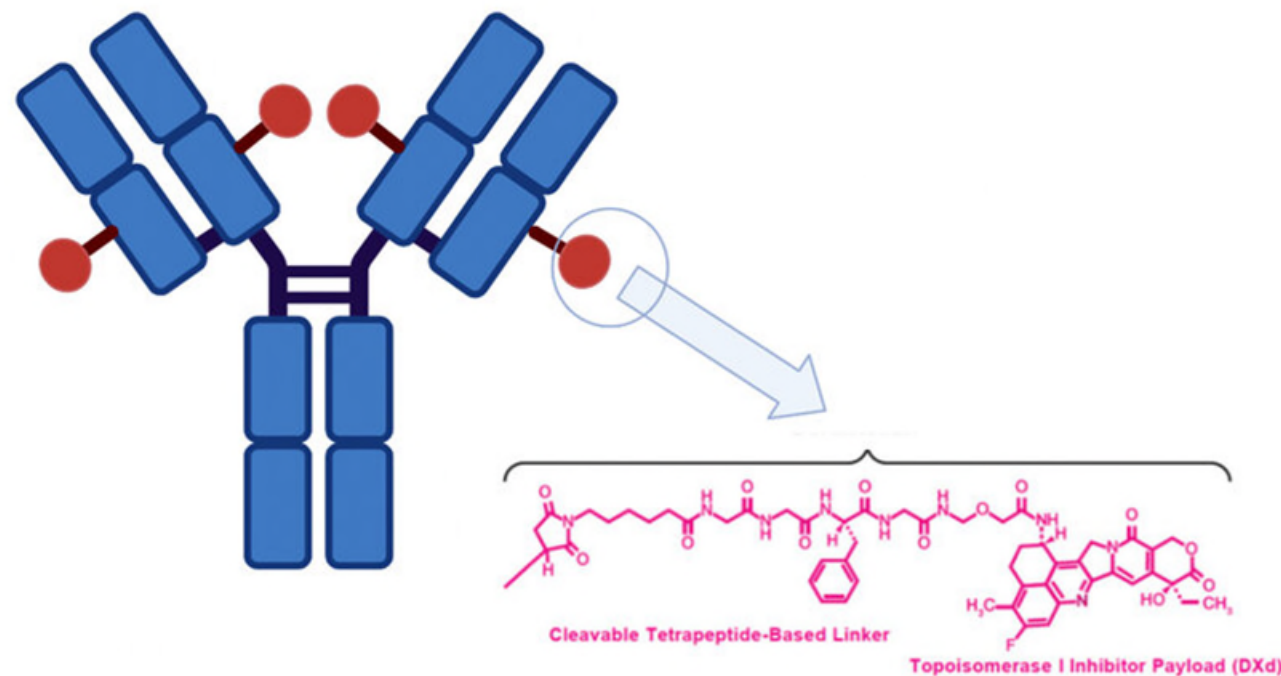
Key Secondary End points: OS, ORR, PROs and Safety



ADCs: Metastatic triple negative breast cancer

Datopotomab deruxtecan (Dato-Dxd)

- Anti-TROP2 antibody linked to exatecan-derived topoisomerase I inhibitor payload vi a tumor-selective cleavable linker.
- Same mechanism of action as SG.
- DAR is 4.
- Most common adverse effects include stomatitis, alopecia, nausea, vomiting, dry eye, constipation, anemia, neutropenia and ILD (~2%).



Tropion-Breast02

Key inclusion criteria:

- Patients with histologically or cytologically documented locally recurrent inoperable or metastatic TNBC*
- No prior chemotherapy or targeted systemic therapy in the locally recurrent inoperable or metastatic setting
- Immunotherapy not an option[†]
- ECOG PS 0 or 1
- No minimum DFI[‡]

1:1

Dato-DXd

6 mg/kg IV Day 1 Q3W
(n=323)

Investigator's choice of chemotherapy (ICC)[#]

Paclitaxel, nab-paclitaxel, capecitabine,
eribulin mesylate/eribulin, carboplatin
(n=321)

Endpoints

Dual primary:

- OS
- PFS by BICR per RECIST v1.1

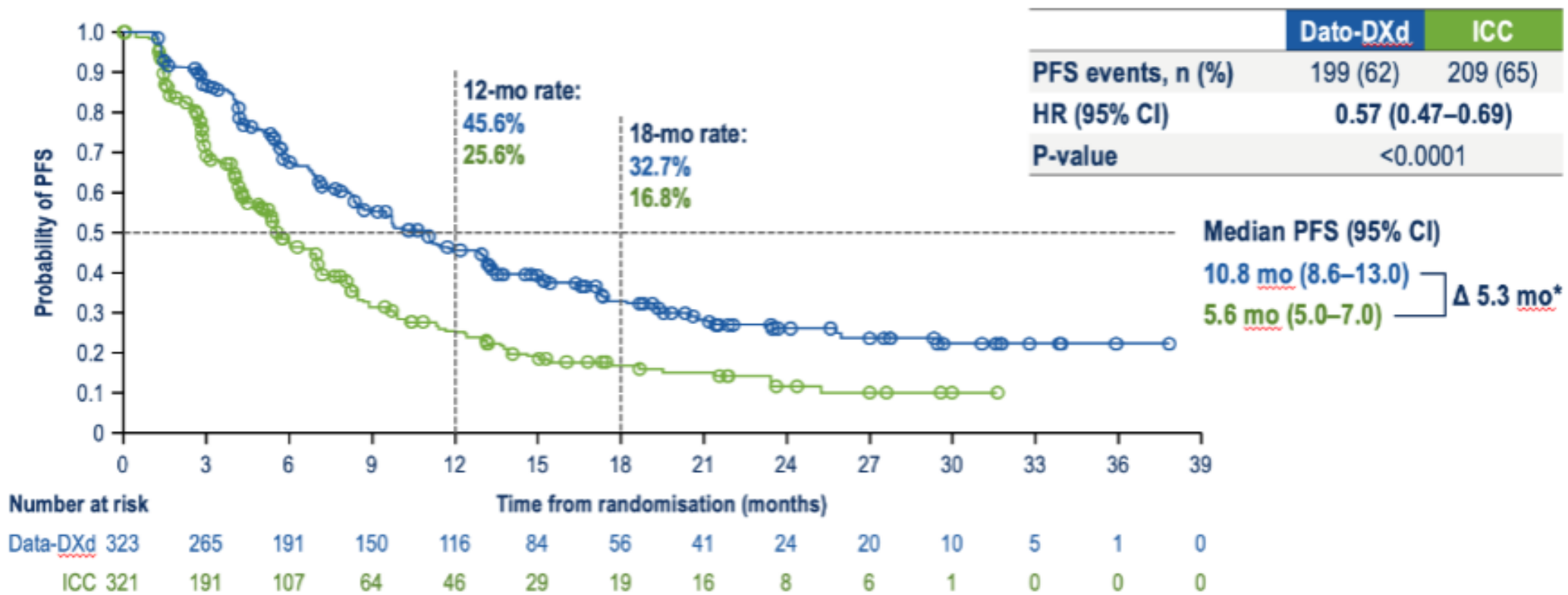
Secondary included:

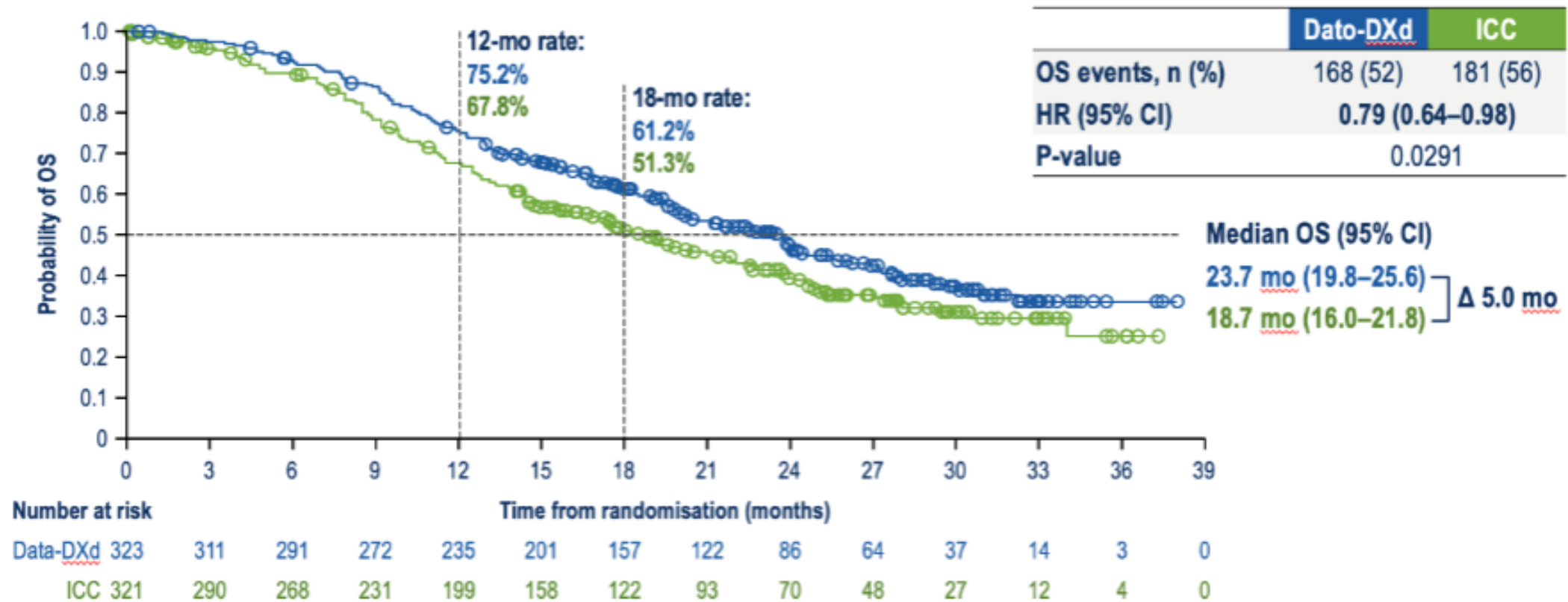
- PFS (investigator-assessed)
- ORR, DoR
- Safety

Randomisation stratified by:

- Geographic region (US/Canada/Europe vs other geographic regions)
- PD-L1 status (high [CPS ≥10] vs low [CPS <10])[§]
- DFI history (*de novo* vs prior DFI 0–12 months vs prior DFI >12 months)[†]

- Treatment continued until investigator-assessed RECIST v1.1 progressive disease, unacceptable toxicity, or another discontinuation criterion was met
- Following progression or discontinuation of study treatment, patients could receive subsequent therapies, including approved ADCs or chemotherapy, at the investigator's discretion^{||}



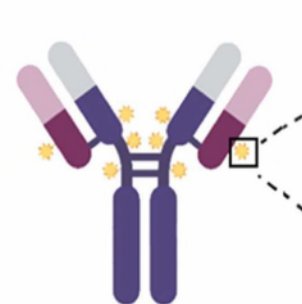


ADCs: Metastatic triple negative breast cancer

Trastuzumab deruxtecan

- Anti-HER2 antibody linked to a topoisomerase I inhibitor payload.
- Drug to antibody ratio of 8.
- Use is based on HER2-low expression in both HR+ and TNBC.
- Most common adverse effects include nausea, vomiting, fatigue, alopecia, myelosuppression, cardiotoxicity, ILD

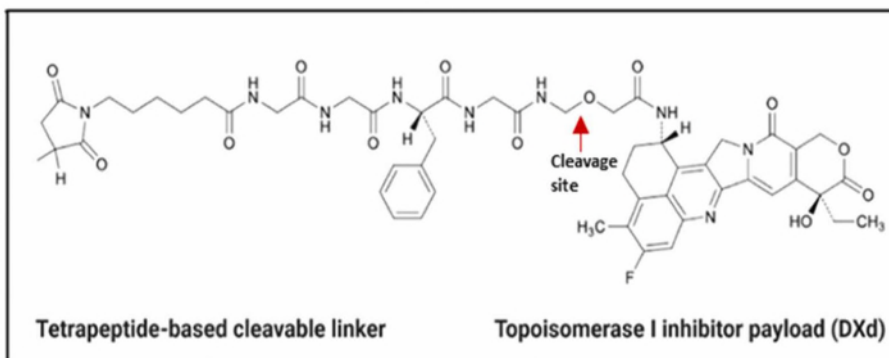
Trastuzumab deruxtecan (T-DXd)



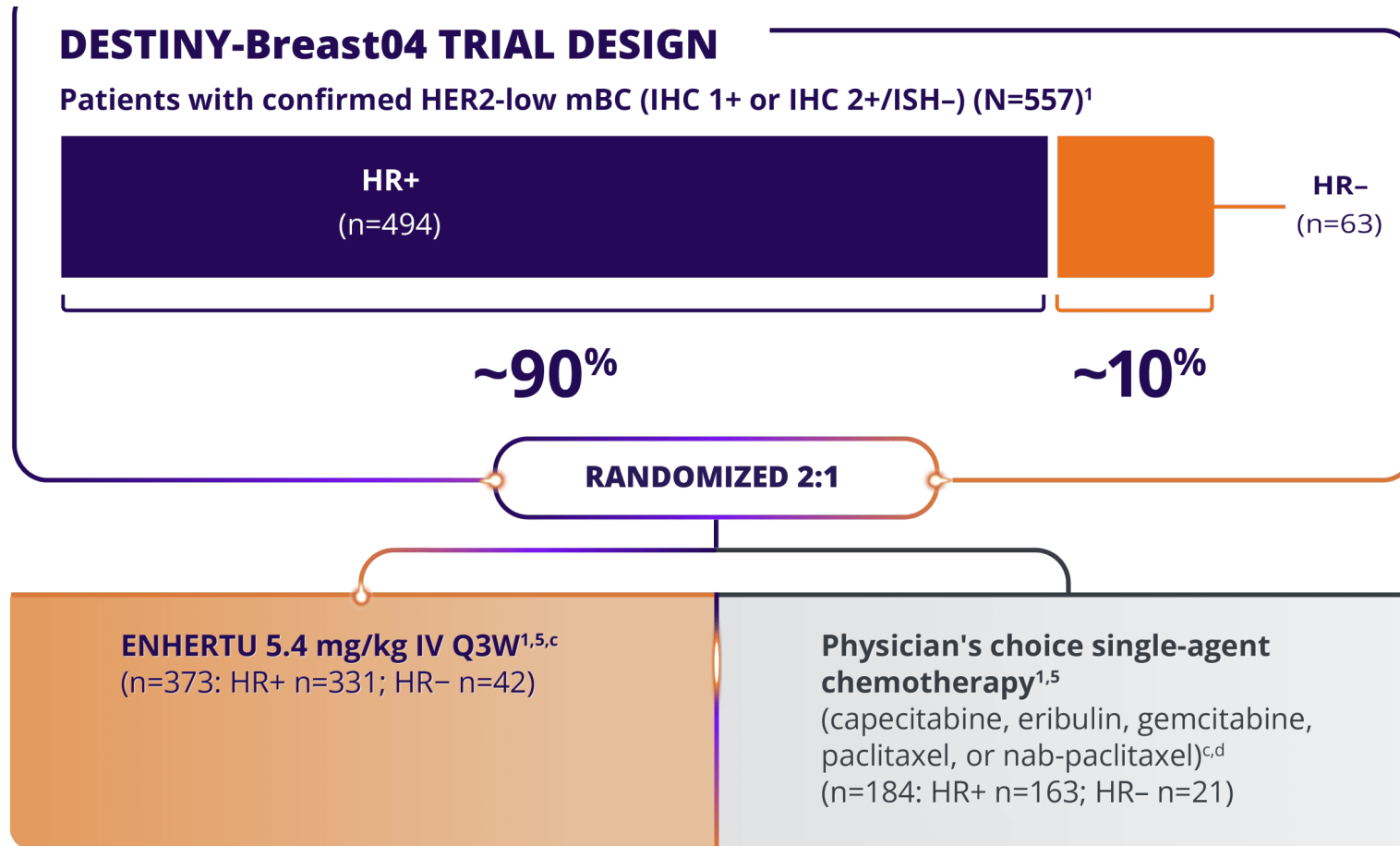
Humanized anti-HER2 IgG1 monoclonal antibody

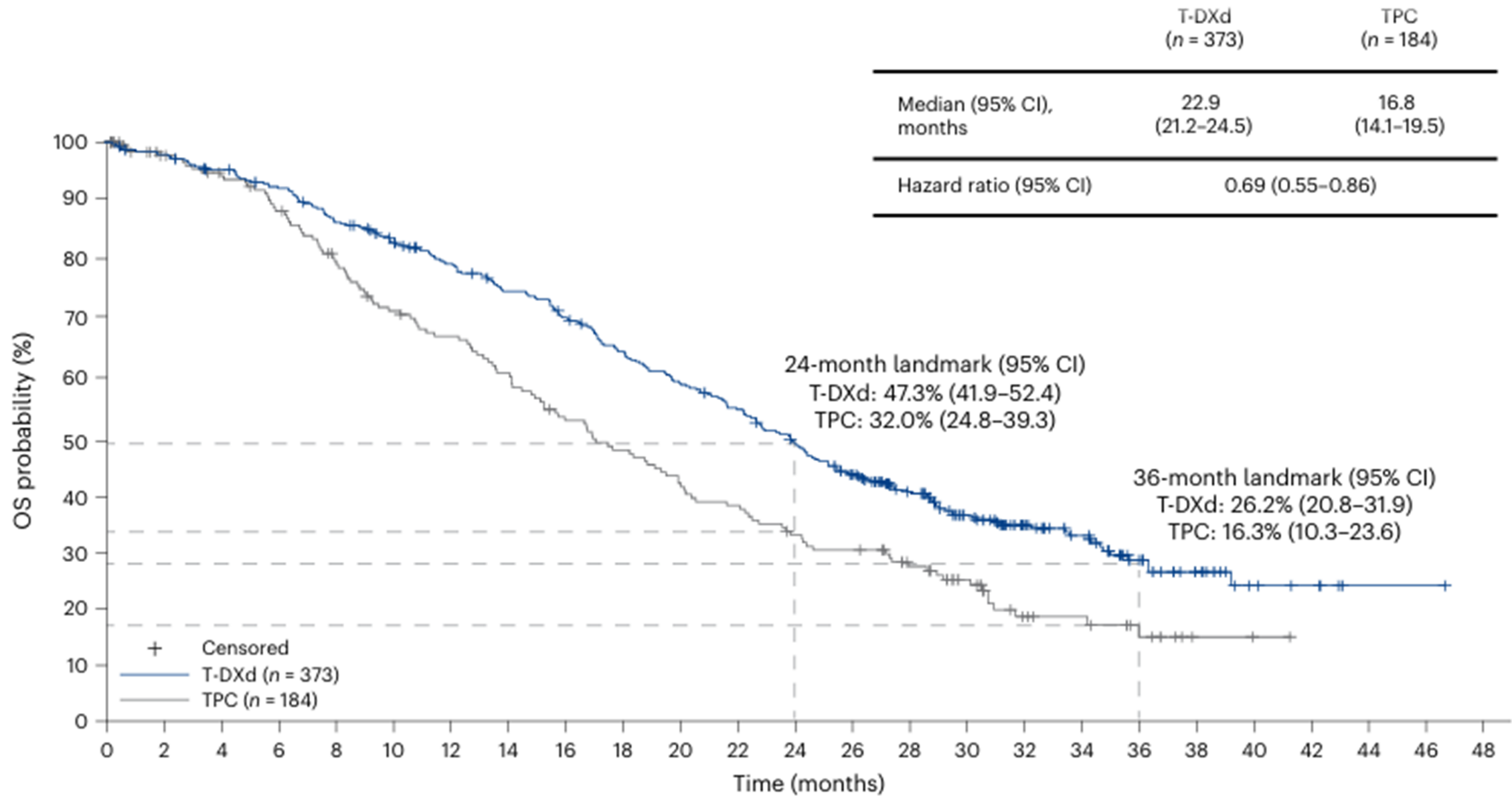
High drug to antibody ratio ~8

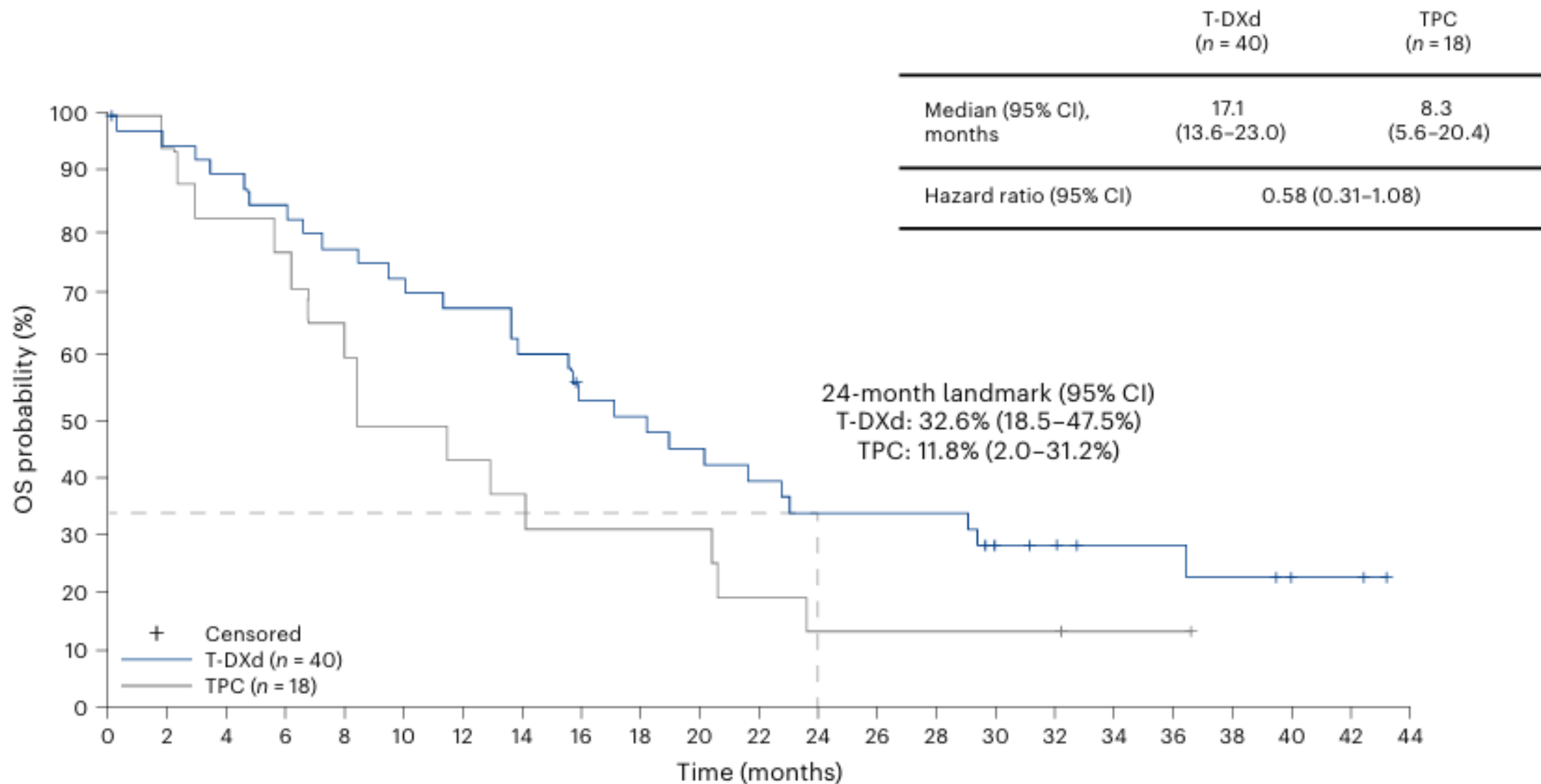
Deruxtecan



Destiny-Breast04







Emerging ADCs in Early-Stage TNBC

Trofuse-032 (NCT06966700)

- Sacituzumab tirometcan
 - Anti-TROP2 antibody conjugated to a belotecan-derived topoisomerase I inhibitor via a 2-methylsulfonyl pyrimidine linker (novel).
 - Stability in circulation and minimizes off-target toxicities
 - Has shown efficacy in HR+ and TNBC metastatic breast cancer. Approved in China for mTNBC.
 - Patients with are randomized to standard of care vs. anthracycline sparing regimen.
 - Primary objectives: % pCR, EFS.
 - Secondary outcomes: OS, % pCR-no DCIS, DPDRFS

ASCENT-05/Optimice-RD (NCT05633654)

Sacituzumab govitecan (SG)

- Patients with residual disease (in breast or lymph nodes) after neoadjuvant chemotherapy and surgery are randomized to SG vs TPC x 8 cycles.
- Primary outcomes: iDFS.
- Secondary outcomes: OS, TEAEs, dDFS, DOR, RFS, QoL.



Cross Resistance

- Sequential use of ADCs is of clinical importance due to potential cross resistance with agents having similar antibody targets.
- In the A3 study, PFS decreased by more than 50% with no target change. It was slightly better with target change. There was also a high rate of cross resistance when second ADC targeted the same antibody target.
- There is no single mechanism that explains diminished benefit of ADC2.
- Optimal sequence of ADCs is unknown, but should depend on target eligibility, CNS disease, toxicity, alternative options, access and patient goals.

Rachel Abelman et al. Sequential use of antibody-drug conjugate after antibody-drug conjugate for patients with metastatic breast cancer: ADC after ADC (A3) study. *J Clin Oncol* **41**, 1022-1022(2023).

Asare M, Okobi TO, Karass S, Okobi JT and Taiwo E (2026) The “ADC-after-ADC” paradigm: navigating cross-resistance and sequencing in breast cancer therapy. *Front. Oncol.* 16:1887974.



Summary

- Antibody-drug conjugates have moved from later line therapy into the first line metastatic triple negative setting.
 - Sacituzumab govitecan +/- pembrolizumab.
 - Datopotamab deruxtecan.
- Trastuzumab deruxtecan has some efficacy in mTNBC, after prior chemotherapy, if disease is HER2-low (IHC 1+ or IHC 2+).
- Treatment selection should be based on individualized factors such as PD-L1 status, prior ADC exposure, disease free interval (DFI), HER2 expression, toxicity profile, schedule of administration.
- Currently, ADCs do not have an approved indication in early-stage triple negative breast cancer, but multiple trials are ongoing.



Thank You!

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