Dana-Farber Cancer Institute

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Antibody Drug Conjugates to Enhance Anti-Tumor Immune Response

Ana C. Garrido-Castro, MD

Assistant Professor of Medicine, Harvard Medical School

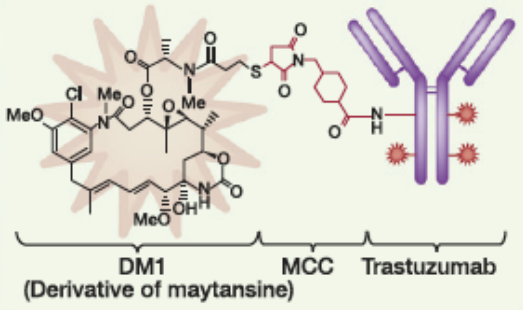
Breast Oncology Center, Dana-Farber Cancer Institute

MaTOS – March 29, 2025

Current Landscape of ADCs in Breast Cancer

Trastuzumab emtansine (T-DM1)

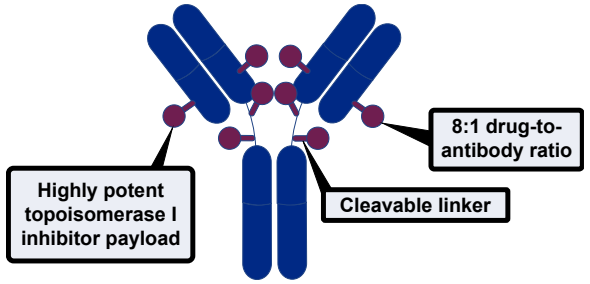
HER2-directed ADC



Previously treated metastatic or post-neoadjuvant early **HER2+** breast cancer

Trastuzumab deruxtecan (T-DXd)

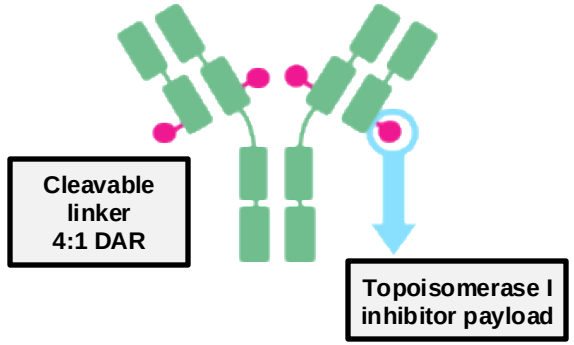
HER2-directed ADC



Previously treated unresectable or metastatic **HER2+** or **HER2-low/ultra-low** breast cancer

Datopotamab deruxtecan (Dato-DXd)

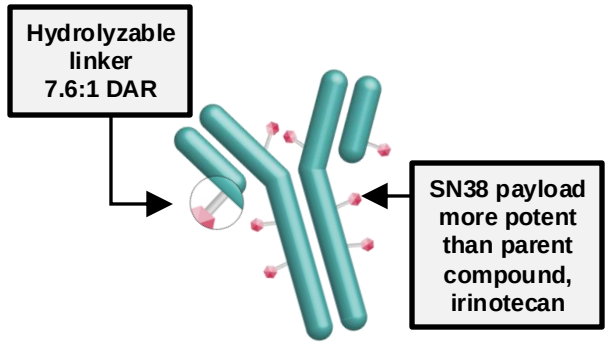
TROP2-directed ADC



Previously treated unresectable or metastatic **HR+/HER2-** breast cancer

Sacituzumab govitecan (SG)

TROP2-directed ADC



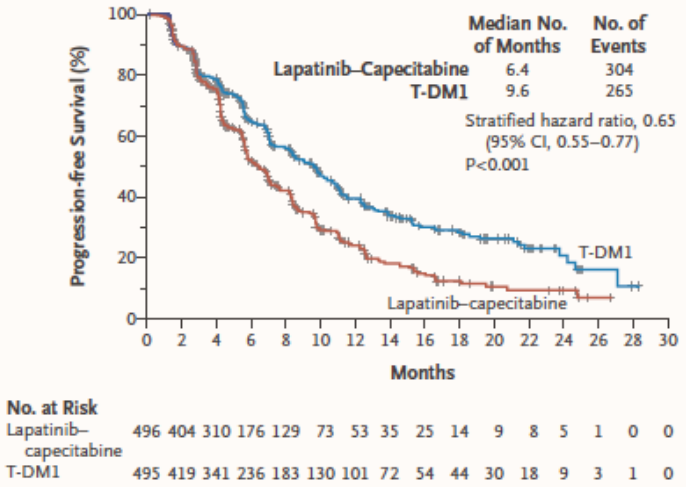
Previously treated unresectable or metastatic **TNBC** or **HR+/HER2-** breast cancer

Modified from: LoRusso P et al. Clin Cancer Res 2011;17(20):6437-47; Modi S et al. J Clin Oncol. 2022;40(17_suppl); Bardia A et al. Ann Oncol 2022;33(suppl_7):S88-S121; Bardia A et al. Ann Oncol 2020;31(suppl_4):S1142-S1215; Garrido-Castro AC. SABCS 2023.

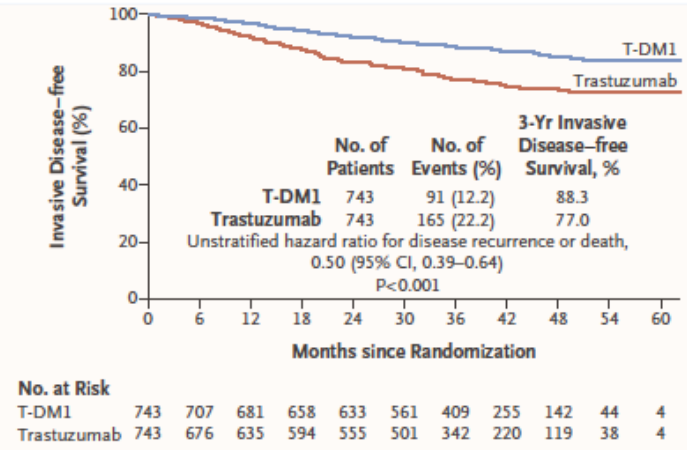
ADCs in HER2-positive Breast Cancer

T-DM1

EMILIA: mBC

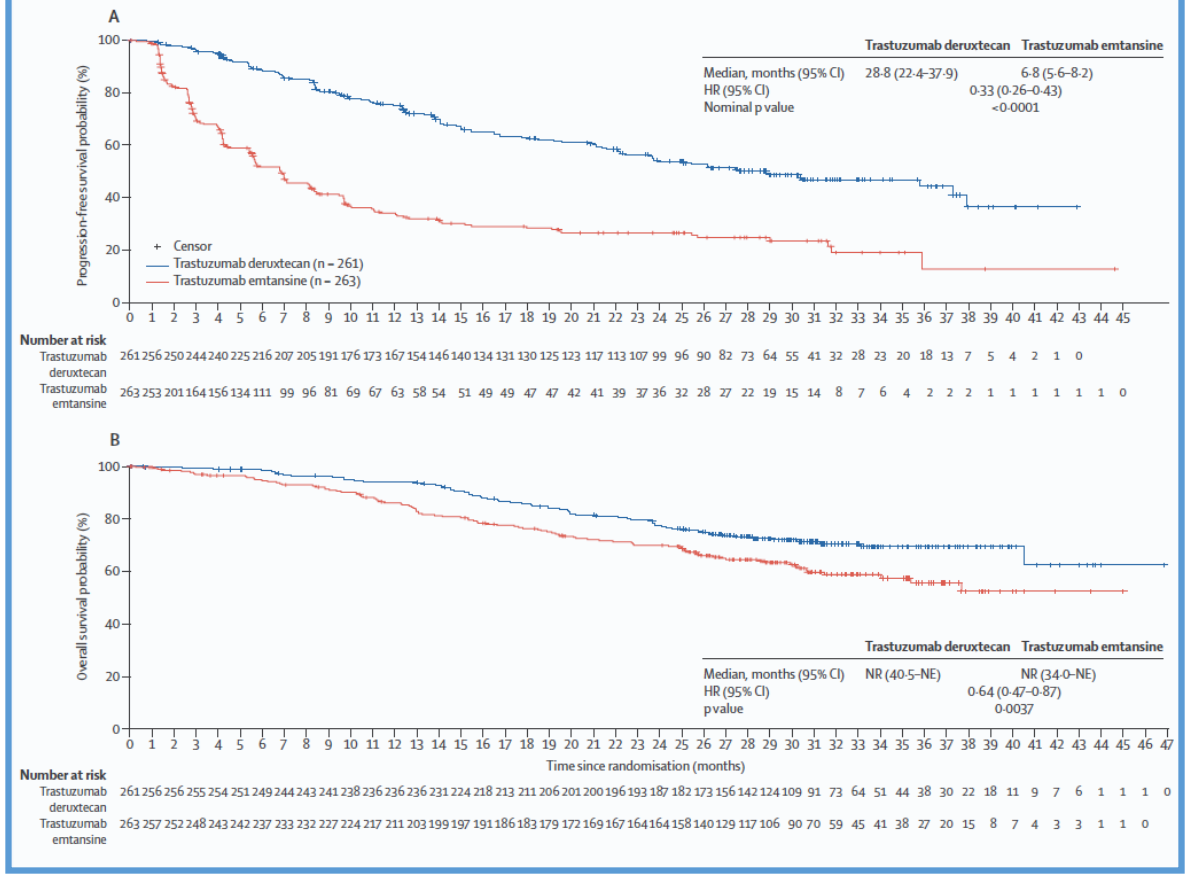


KATHERINE: eBC



T-DXd

DB03: mBC

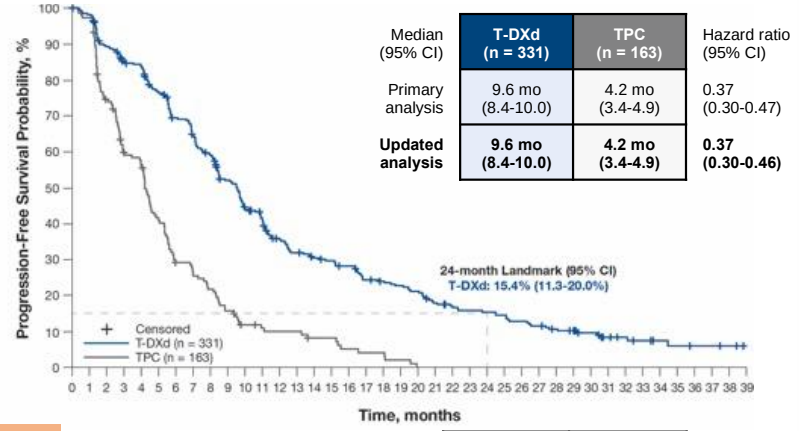


Verma S et al. N Engl J Med. 2012;367:1783-91; von Minckwitz G et al. N Engl J Med. 2019;380:617-28.; Hurvitz SA et al. Lancet. 2023;401 105-17.

DB04: T-DXd vs TPC for HER2-low MBC After Chemotherapy

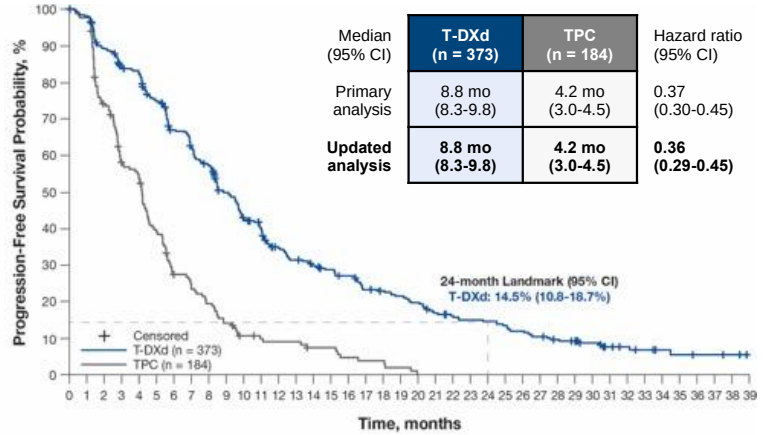
PFS

Hormone Receptor-positive (n=494)



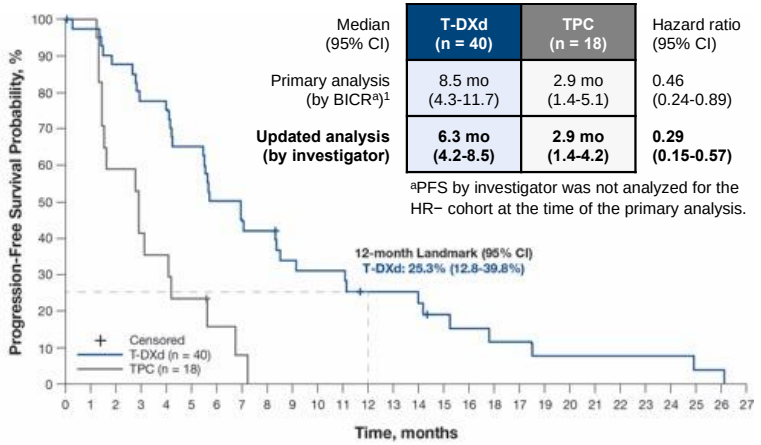
Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

ALL Patients (n=557)



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)**

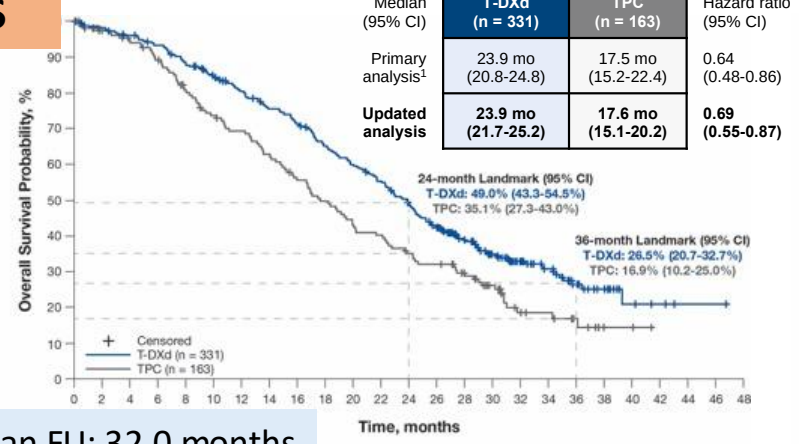
Hormone Receptor-negative (n=58)



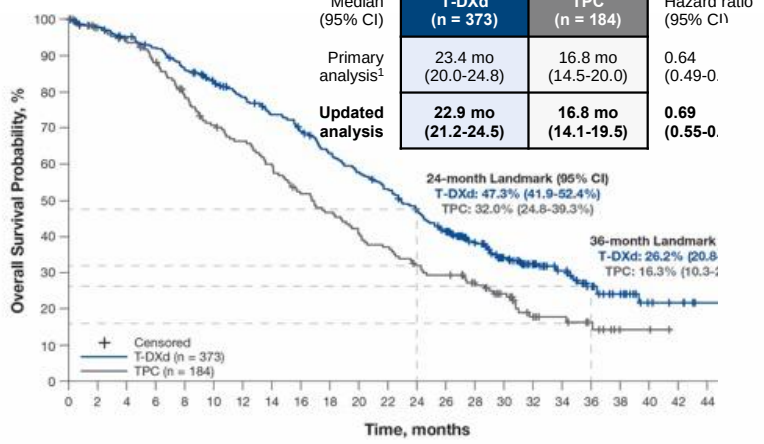
Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.

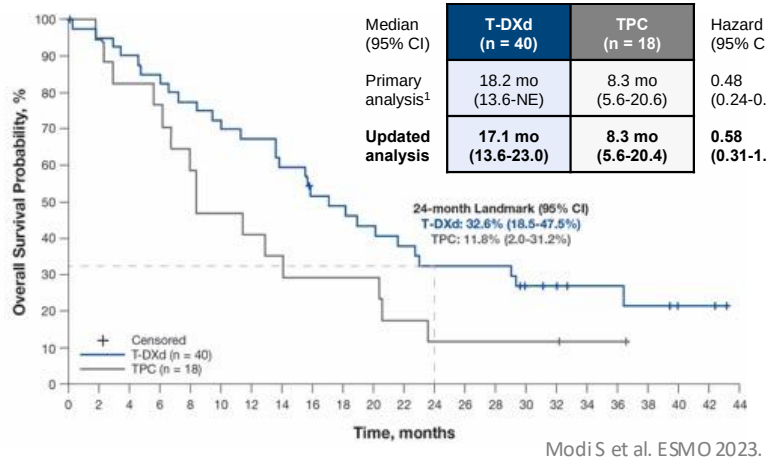
OS



Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



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.
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.**



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

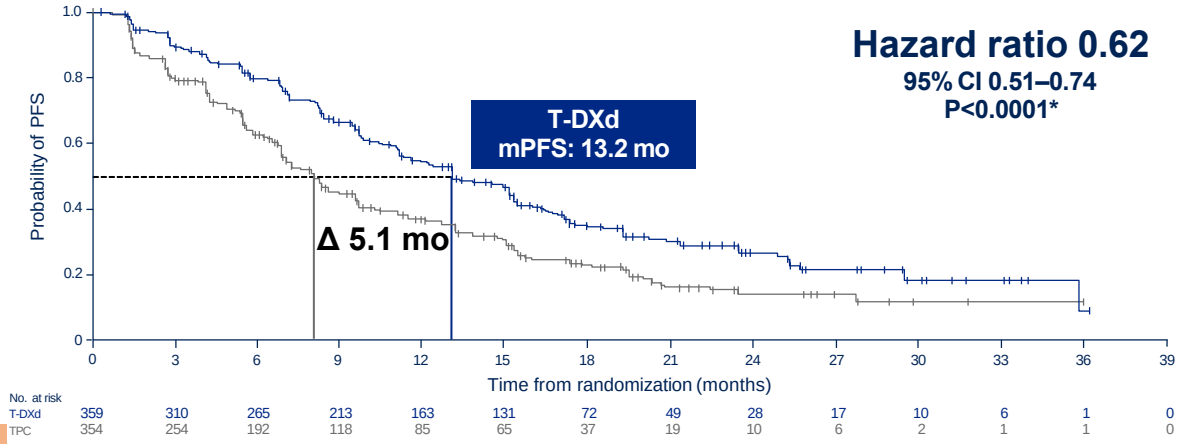
Median FU: 32.0 months

Modi S et al. ESMO 2023.

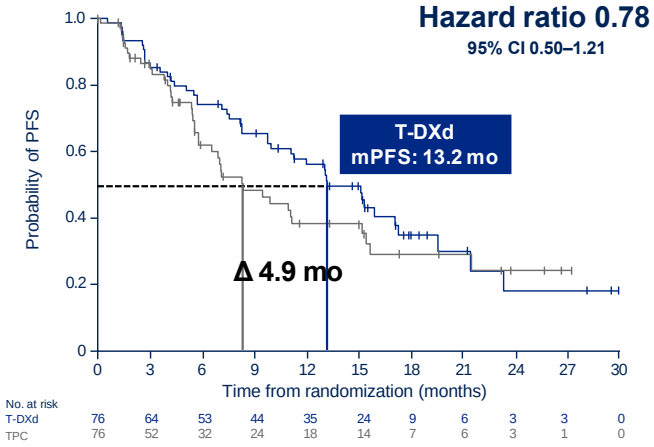
DB06: T-DXd for HER2-low/ultra-low Endocrine-Refractory MBC

PFS

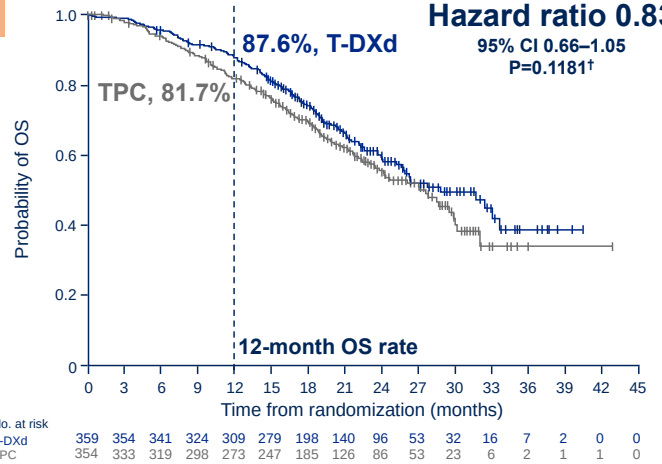
HER2-low (1+, 2+/ISH-) (n=713)



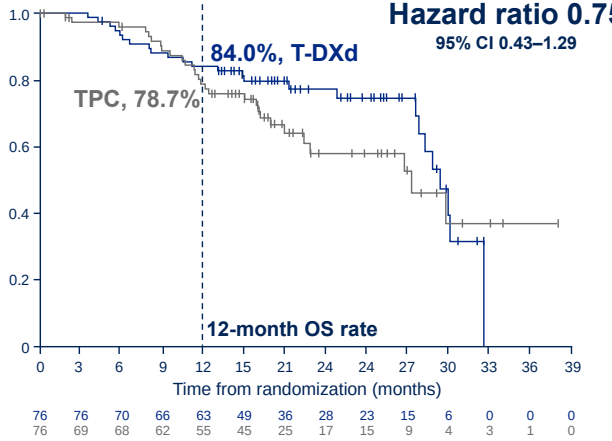
HER2 ultra-low (>0 <1+) (n=152)



OS



Median FU: 18.6 mo.



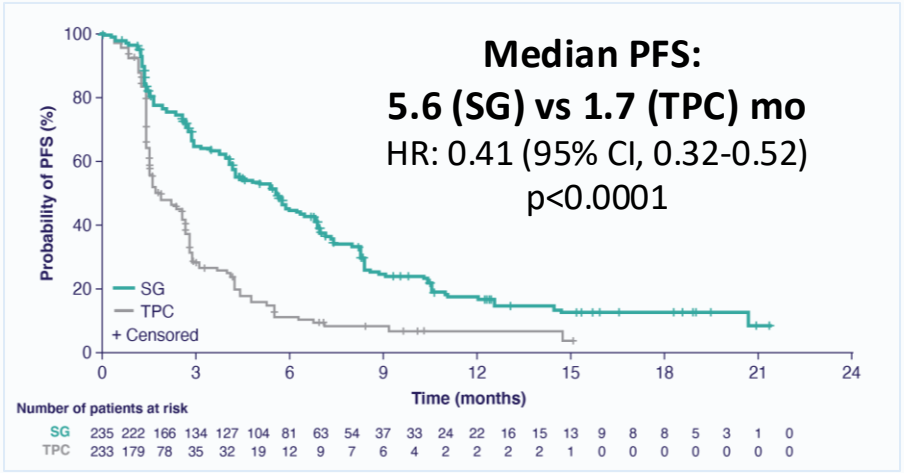
Median FU: 16.8 mo.

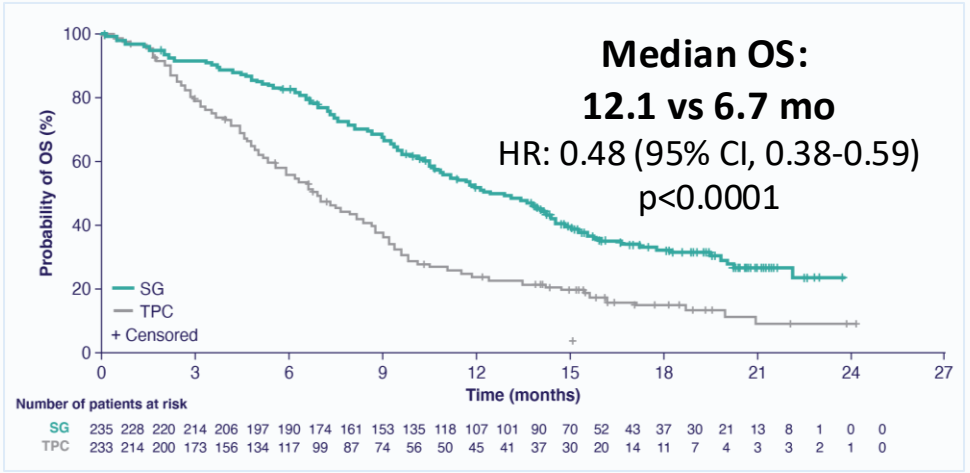
Curigliano G et al. ASCO 2024; Bardia A et al. N Engl J Med. 2024;391:2110-22.

Sacituzumab govitecan for HER2-negative MBC

ASCENT
TNBC
(n=468)

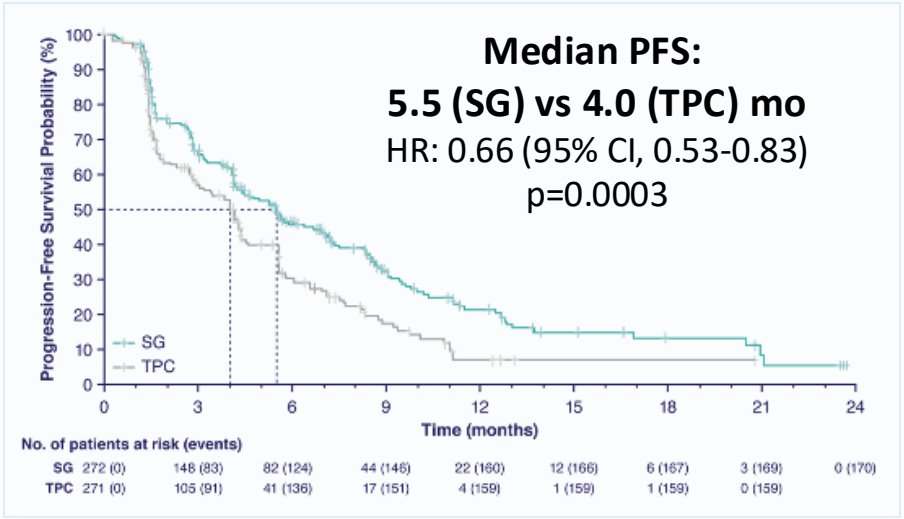
ORR: 35% vs. 5%
p<0.0001

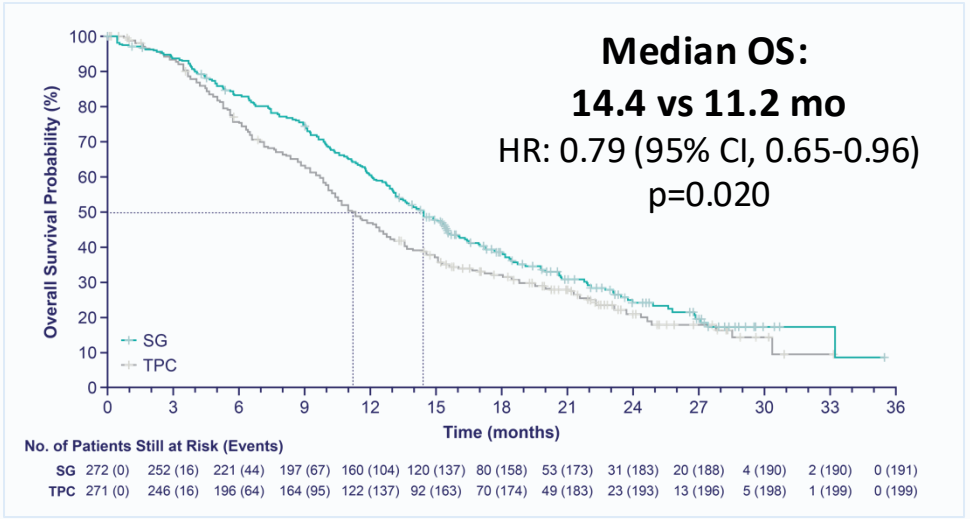




TROPiCS-02
HR+/HER2-
(n=543)

ORR: 21% vs. 14%
p=0.03

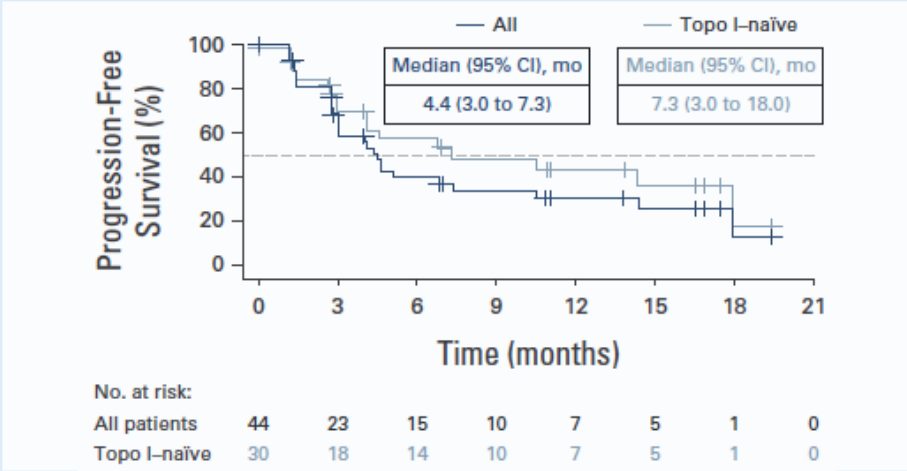


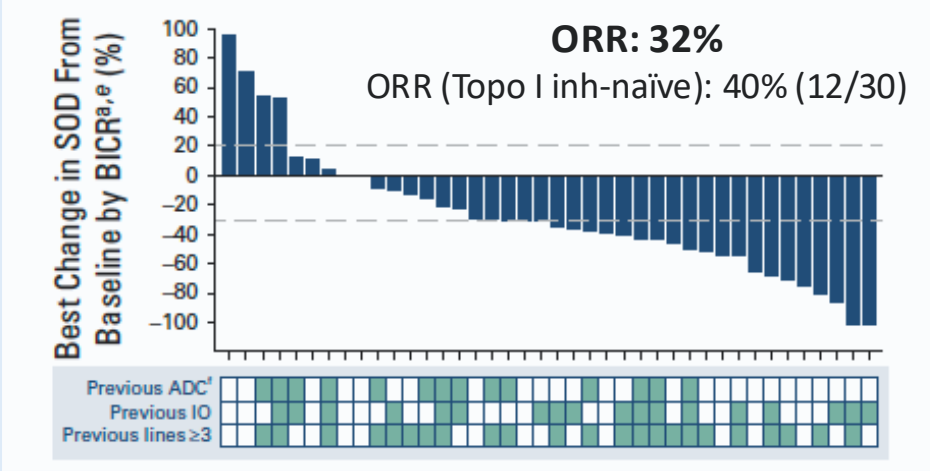


Bardia A et al. ESMO 2020; Rugo H et al. ASCO 2022; Rugo H et al. ESMO 2022.

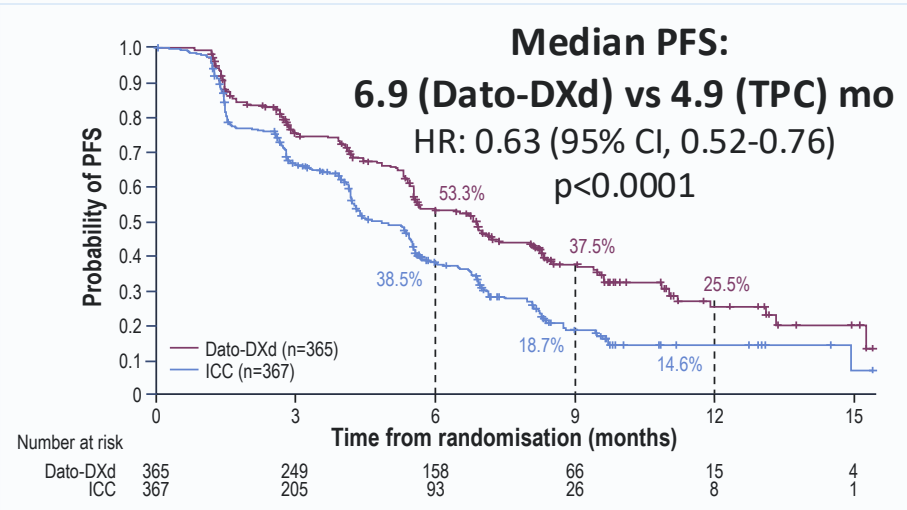
Datopotamab deruxtecan for HER2-negative MBC

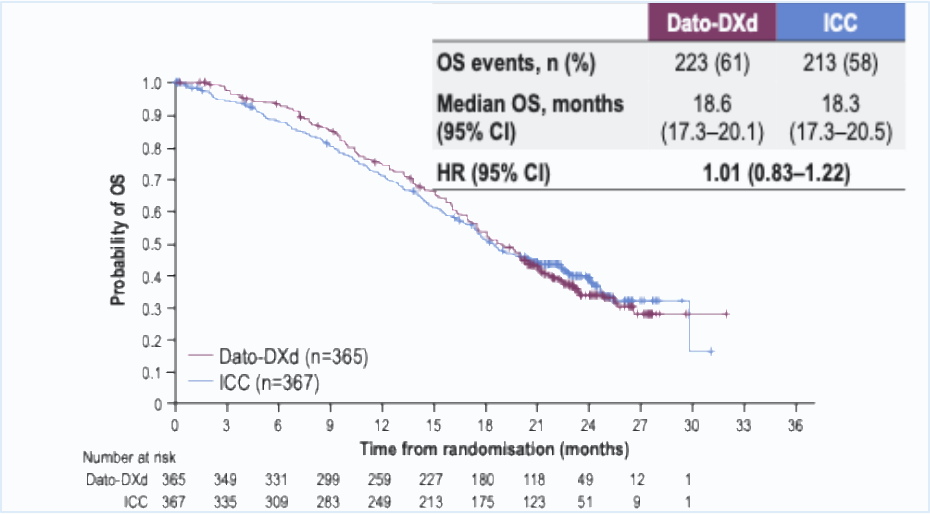
TROPION-PanTumor01
TNBC (n=44)





TB-01
HR+/HER2-
(n=732)



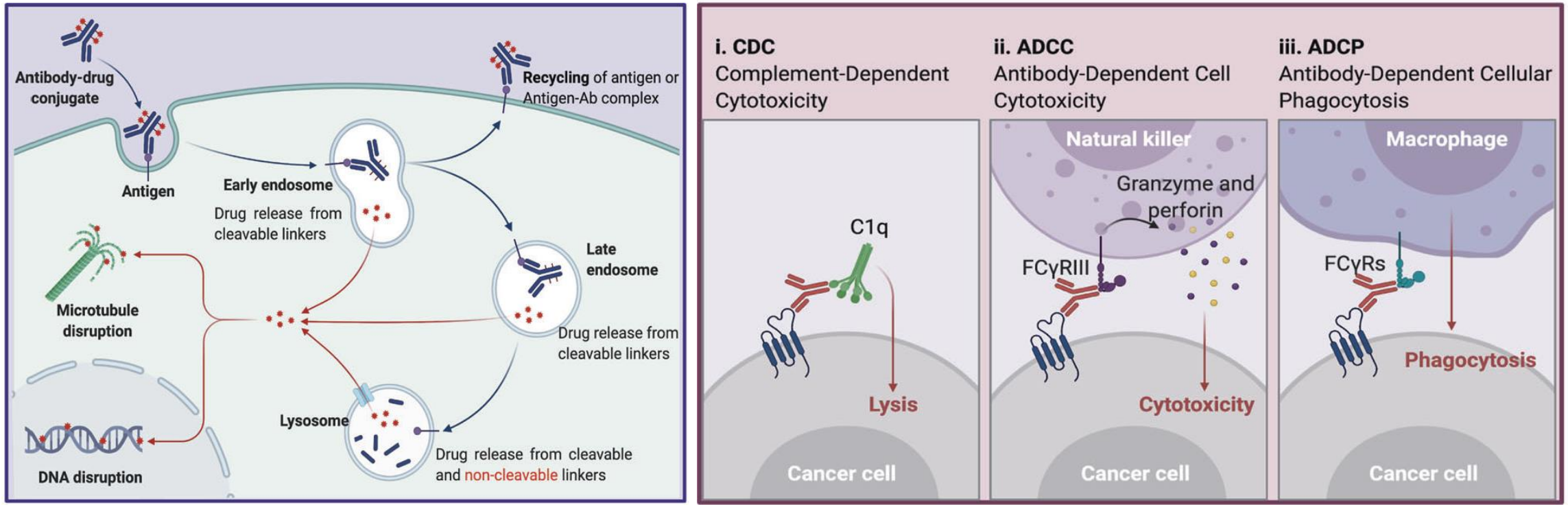


Bardia A et al. J Clin Oncol. 2024;42(19):2281-94; Bardia A et al. Ann Oncol. 2023;34(suppl_2):S1254-S1335; Bardia A et al. J Clin Oncol. 2024;43(3):285-96; Pistilli B et al. ESMO VP1-2025. doi:10.1016/j.annonc.2025.01.009.

ADCs in Breast Cancer

	Trastuzumab emtansine (T-DM1)	Trastuzumab deruxtecan (T-DXd)	Trastuzumab duocarmazine (SYD985)	Disitamab vedotin (RC48-ADC)	Sacituzumab govitecan (SG)	Datopotomab deruxtecan (Dato-DXd)	Sacituzumab tirumotecan (MK-2870)	Patritumab deruxtecan (U3-1402)	Enfortumab vedotin (EV)
Target	**HER2**	**HER2**	**HER2**	**HER2**	**TROP2**	**TROP2**	**TROP2**	**HER3**	**Nectin-4**
Payload	Microtubule inhibitor (DM1)	Topo I inhibitor (DXd)	DNA alkylation (duocarmazine)	Microtubule inhibitor (MMAE)	Topo I inhibitor (SN38)	Topo I inhibitor (DXd)	Topo I inhibitor (KL610023)	Topo I inhibitor (DXd)	Microtubule inhibitor (MMAE)
Linker cleavage	No	Enzymatic (peptidase)	Enzymatic (peptidase)	Enzymatic (peptidase)	Enzymatic and pH-dependent	Enzymatic (peptidase)	Enzymatic and pH-dependent	Enzymatic (peptidase)	Enzymatic (peptidase)
Bystander effect	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DAR	3.5	~8	~2.8	4	7.6	4	7.4	7.8	3.8
Dosing	D1 (Q3W)	D1 (Q3W)	D1 (Q3W)	D1 (Q2W)	D1, D8 (Q3W)	D1 (Q3W)	D1 (Q2W)	D1 (Q3W)	D1, D8, D15 (Q4W)

ADC Engagement with Immune Effector Cells to Elicit Antitumor Immunity

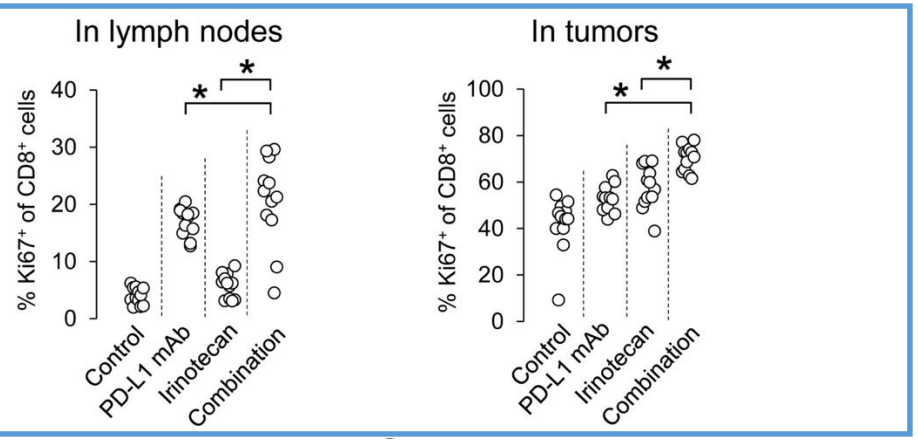


Fu Z et al. Sig Transduct Target Ther 2022:7(93). doi.org/10.1038/s41392-022-00947-7.

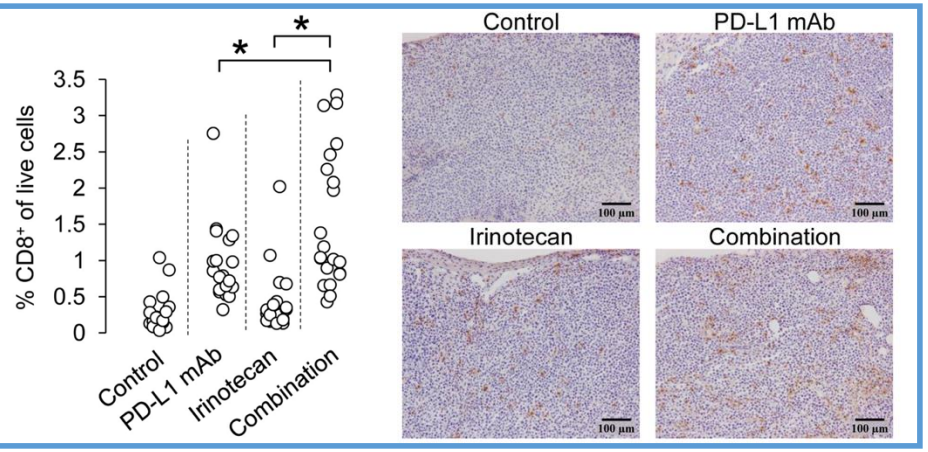
Topo-I Inhibition Depletes T-regs and Upregulates MHC class-I and PD-L1 Expression

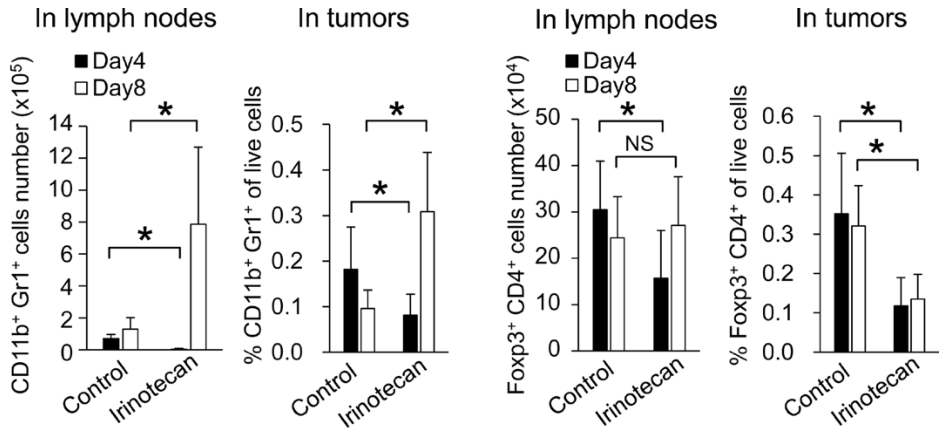
Increased CD8+ T-cell proliferation through depletion of T-regs

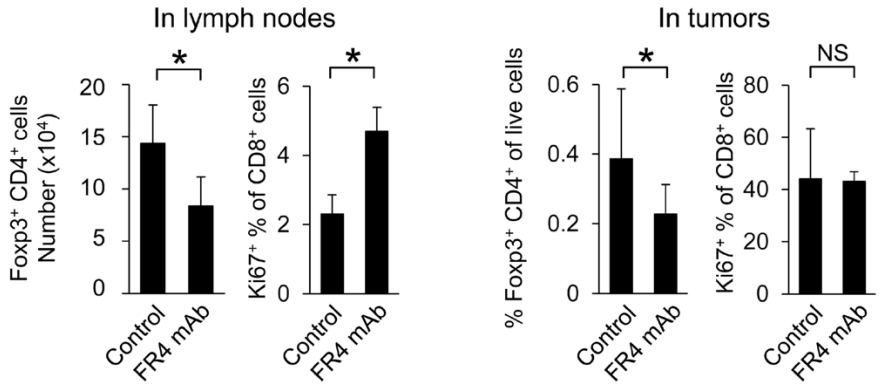
Day 8



Day 19







Iwai T et al. Oncotarget. 2018;9(59):31411-21 .

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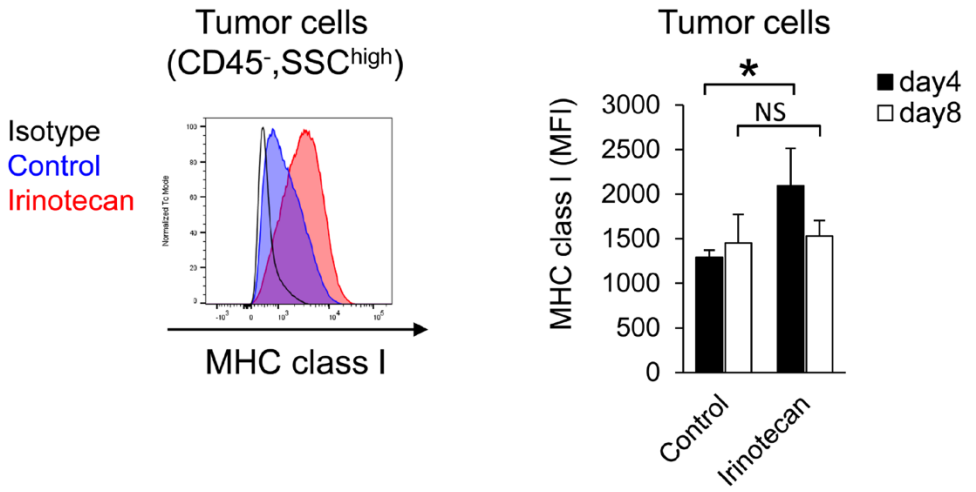
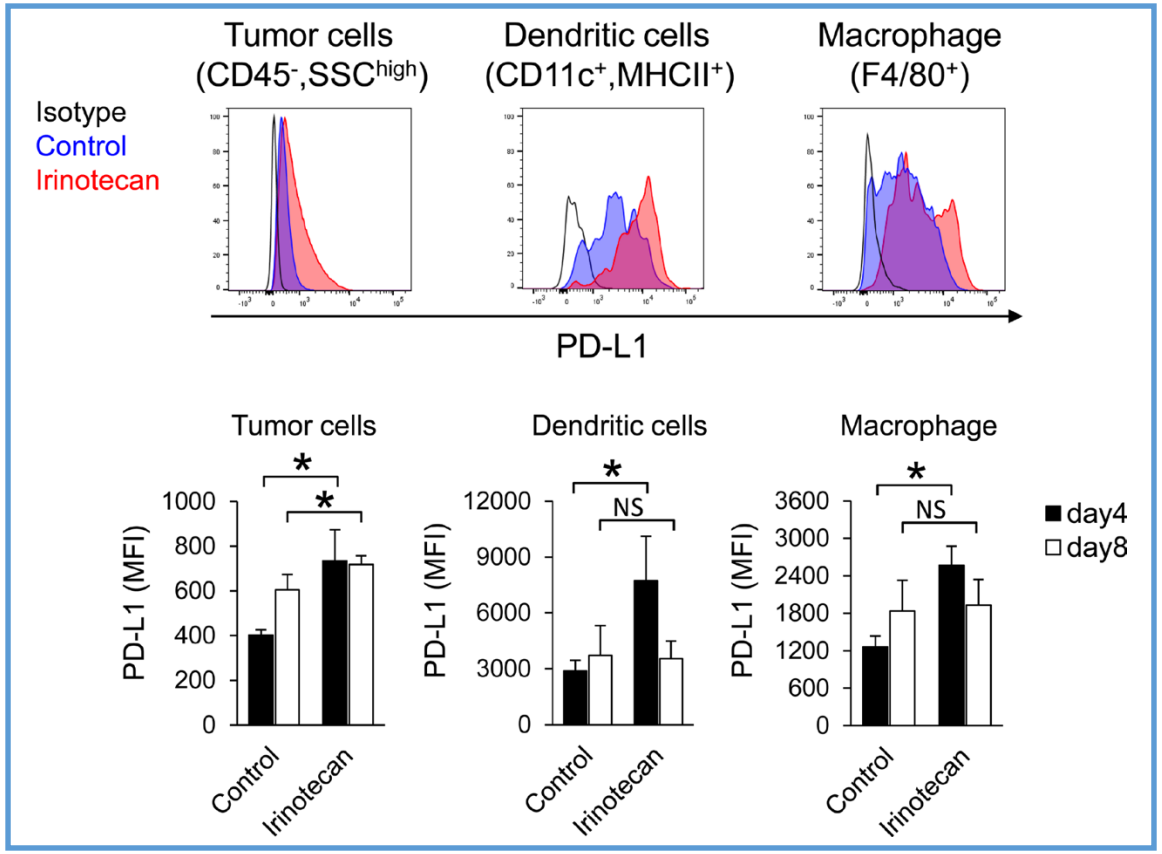
Topo-I Inhibition Depletes T-regs and Upregulates MHC class-I and PD-L1 Expression

Tumor MHC class-I



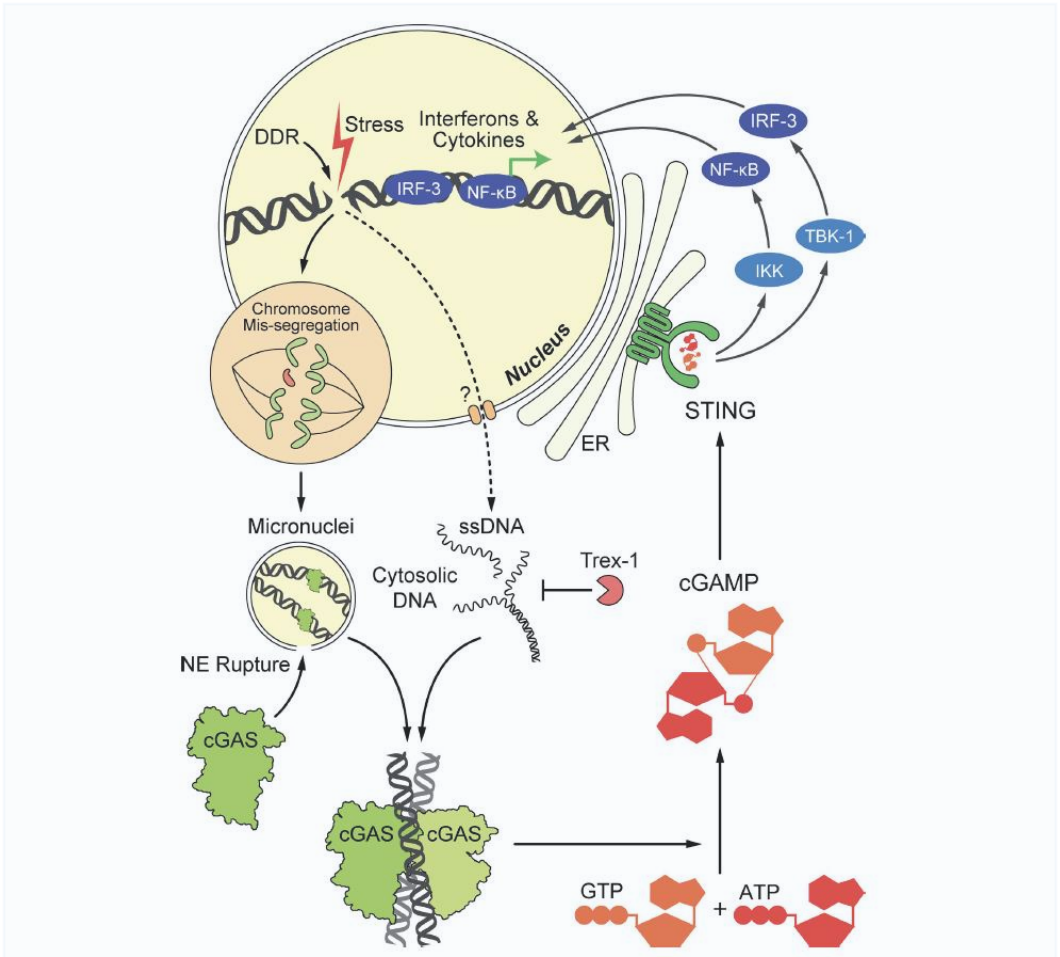
Tumor and Immune Cell PD-L1

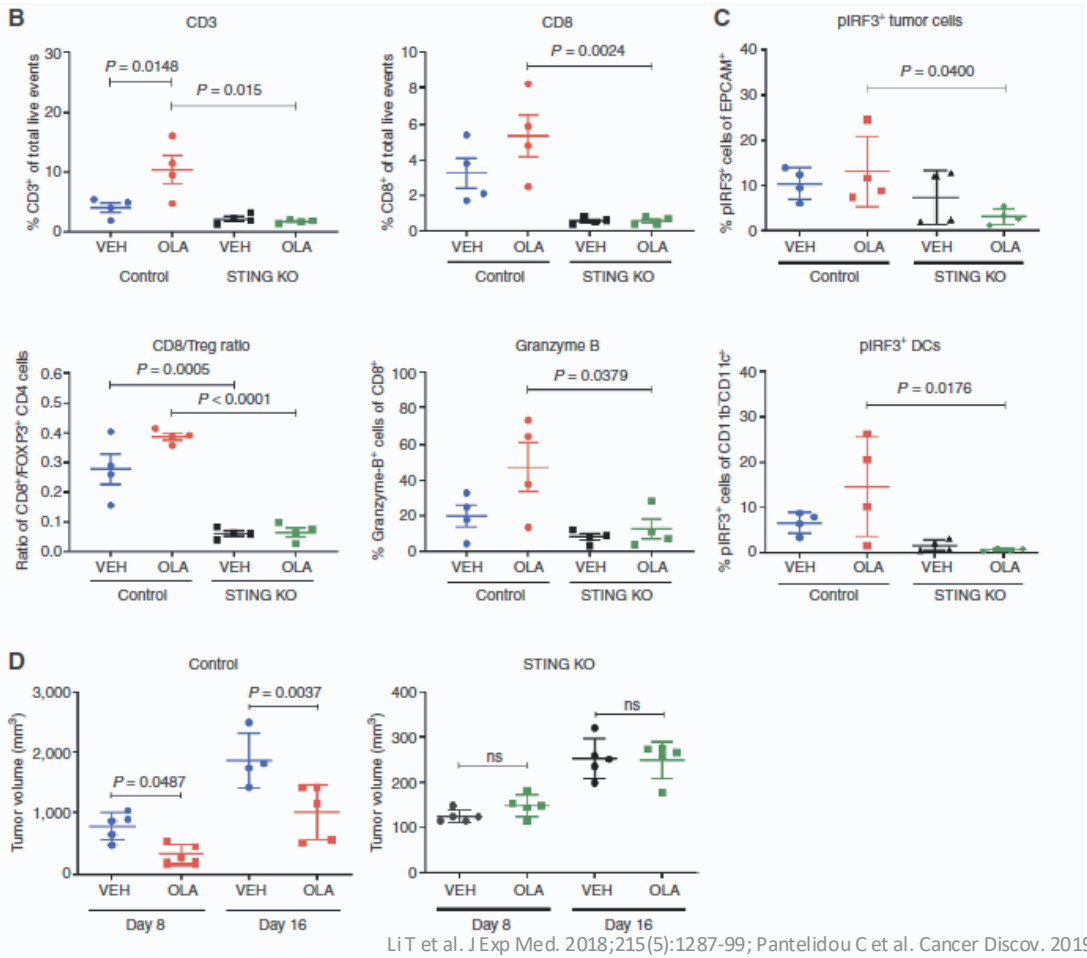


Iwai T et al. Oncotarget. 2018;9(59):31411-21 .

DNA Damage Induces cGAS-STING Pathway Activation

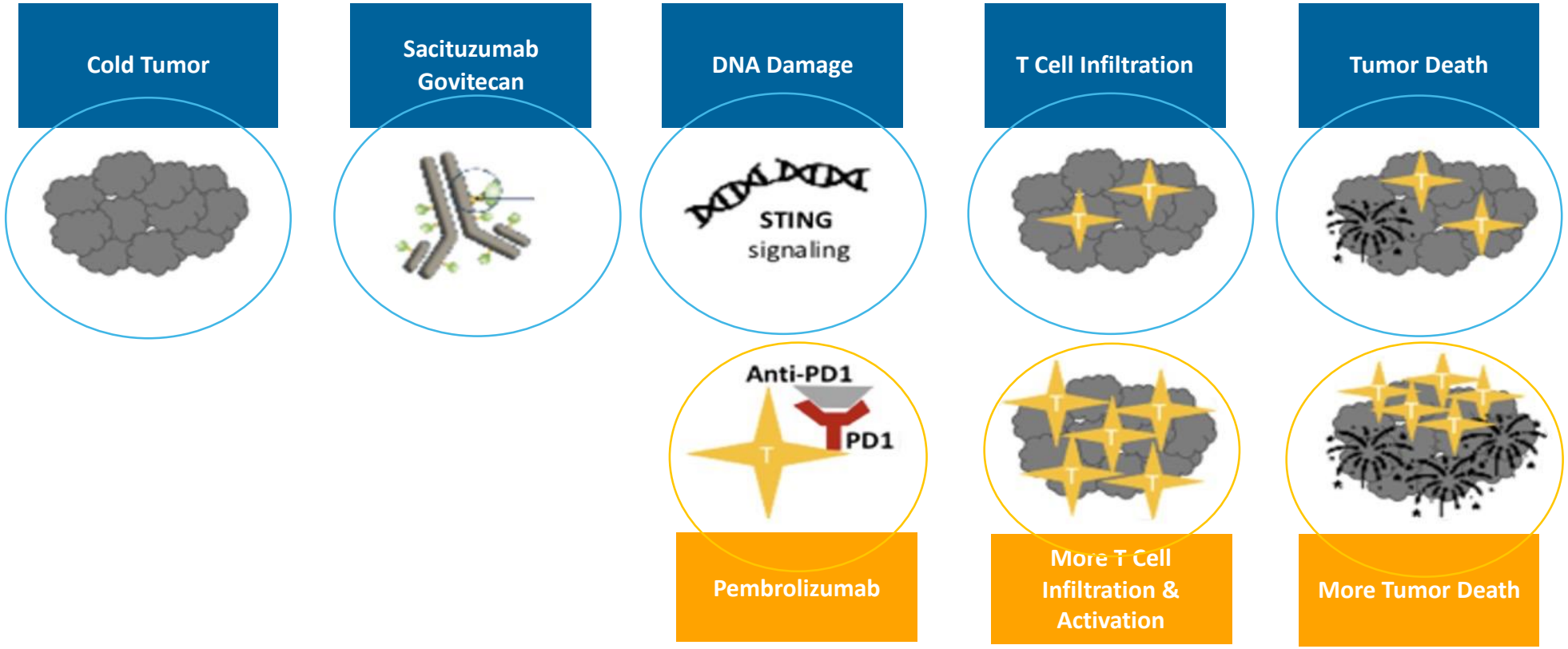
Intratumoral STING depletion abolishes PARPi-induced T-cell recruitment and antitumor efficacy





Li T et al. J Exp Med. 2018;215(5):1287-99; Pantelidou C et al. Cancer Discov. 2019;9(6):722-37.

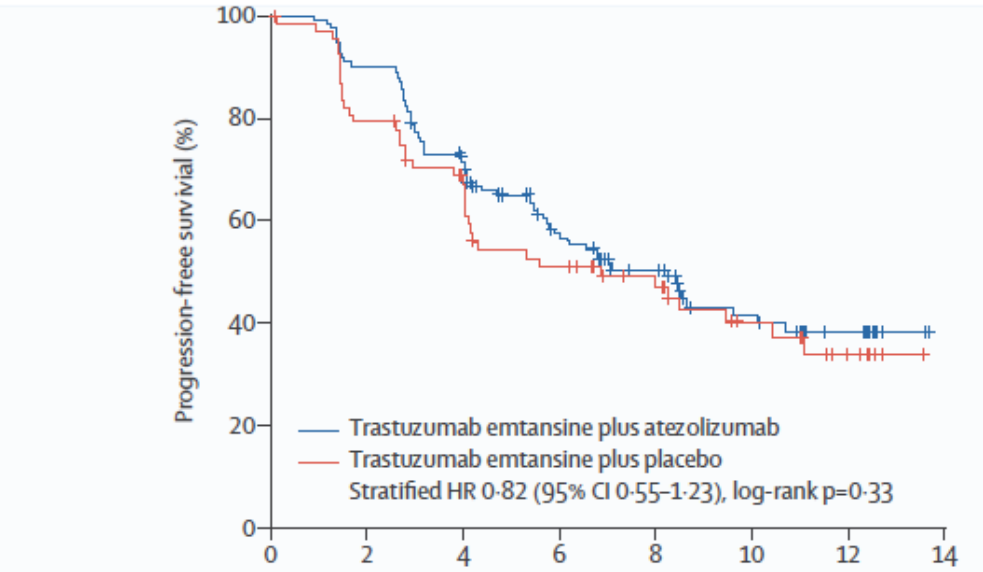
Hypothesis: TOPi ADC Synergize with ICI via DNA Damage-Induced T-cell Recruitment + Restoration of Effector Function



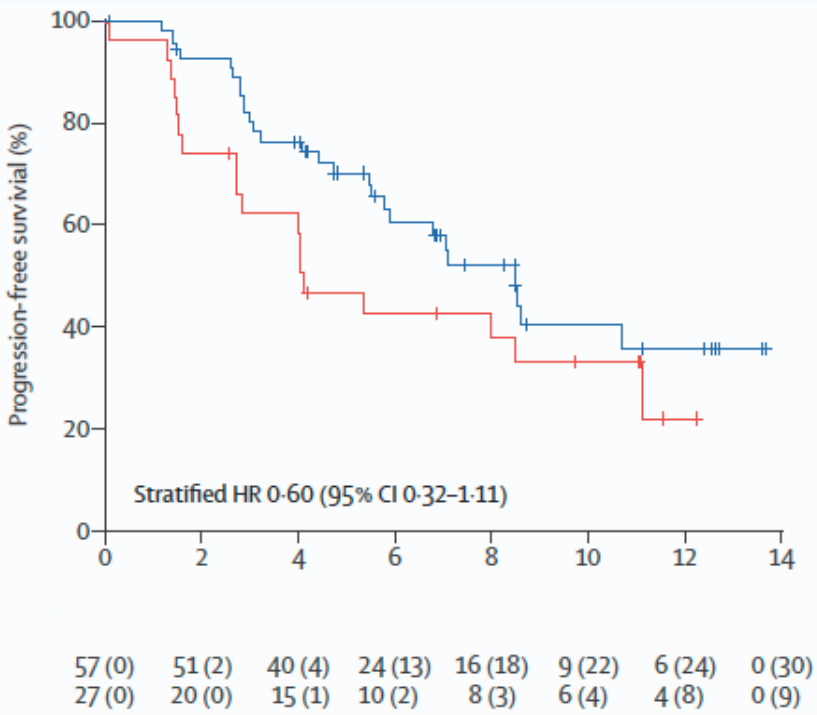
Slide courtesy of S. Tolaney

KATE-2: T-DM1 + Atezolizumab for HER2+ MBC

PFS in ITT



PFS in PD-L1+

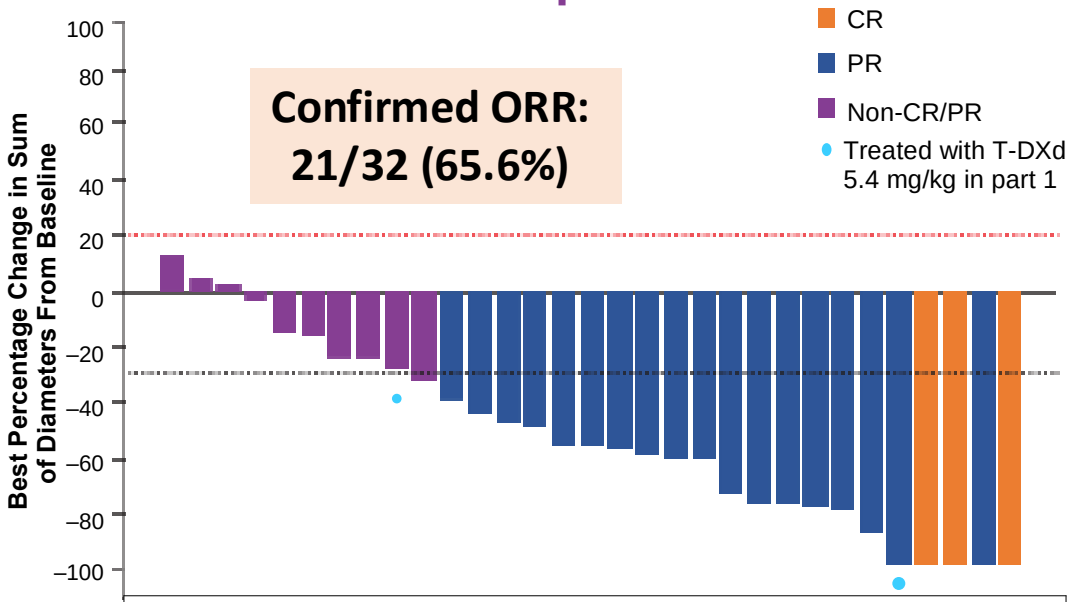


In the PD-L1+ subgroup, 1-year OS rate was numerically higher in T-DM1 + atezolizumab (94.3%) vs T-DM1 + placebo arm (87.9%); in PD-L1-, 85.1% vs. 89.7%

Emens L et al. ESMO 2019; Emens LA et al. Lancet Oncol. 2020;21:1283–95.

DS8201-A-U105: T-DXd + Nivolumab

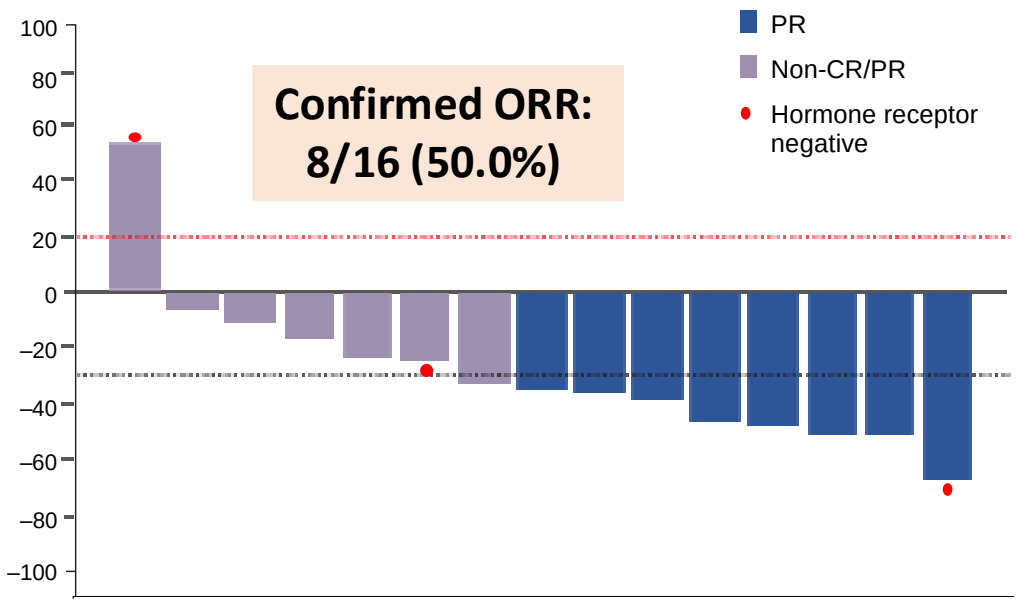
HER2-positive



Cohort 1 HER2-positive BC (n = 32)
Parts 1/2: T-DXd 5.4 mg/kg and Nivolumab 360 mg
Best (minimum) Percentage Change

n	Mean	SD	Median	Min	Max
31	–53.0	33.82	–57.0	–100	13

HER2-low



Cohort 2 HER2-low BC (n = 16)
Part 2: T-DXd 5.4 mg/kg and Nivolumab 360 mg
Best (minimum) Percentage Change

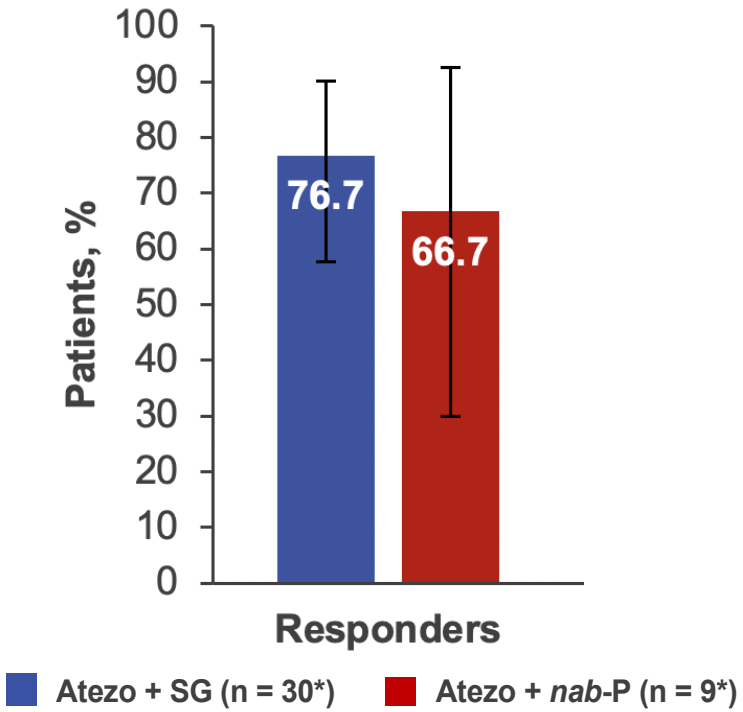
n	Mean	SD	Median	Min	Max
15	–29.2	28.56	–35.0	–68	54

Hamilton E. et al. ESMO Breast 2022.

MORPHEUS: Topo I-inhibitor ADC + ICI in 1L mTNBC

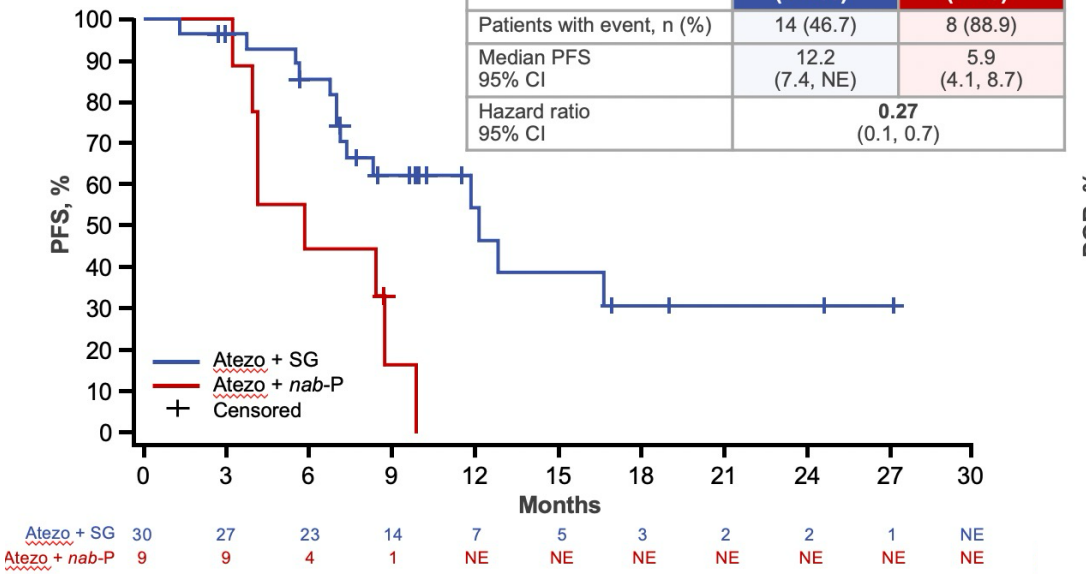
SG + Atezolizumab in 1L PD-L1+ mTNBC

Confirmed ORR = 76.7% (17% CR)



Median PFS: 12.2 mo

	Atezo + SG (n = 30)*	Atezo + *nab*-P (n = 9)*
Patients with event, n (%)	14 (46.7)	8 (88.9)
Median PFS 95% CI	12.2 (7.4, NE)	5.9 (4.1, 8.7)
Hazard ratio 95% CI	0.27 (0.1, 0.7)	



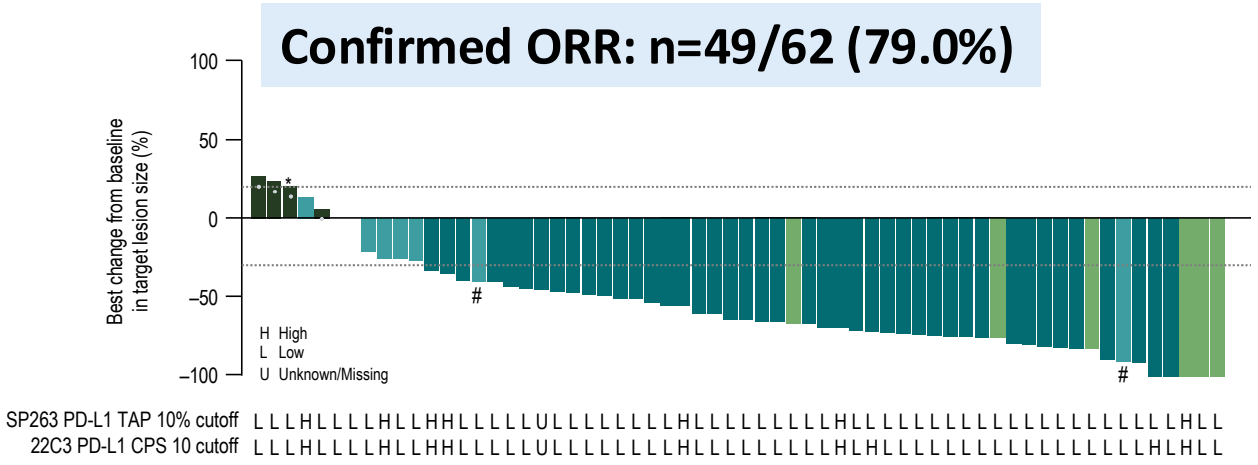
PFS data were immature at this analysis

Schmid P et al. ESMO Breast 2024.

BEGONIA: Topo I-inhibitor ADC + ICI in 1L mTNBC

Dato-DXd + Durvalumab in mTNBC

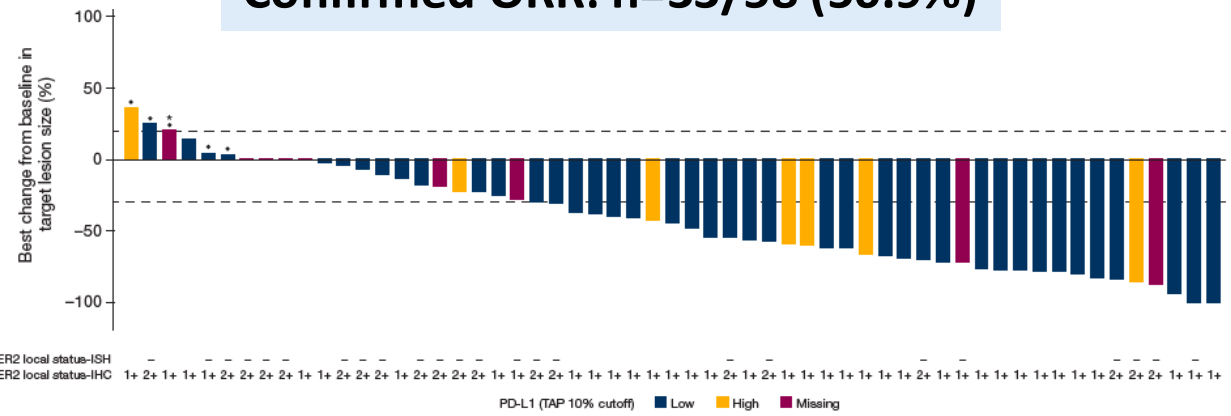
Confirmed ORR: n=49/62 (79.0%)



- Responses observed regardless of PD-L1
- No DLTs
- TRAE ILD/pneumonitis: G1, n=1; G2, n=2
- Stomatitis: most common AE leading to dose reduction (n=11)

T-DXd + Durvalumab in HER2-low mTNBC

Confirmed ORR: n=33/58 (56.9%)

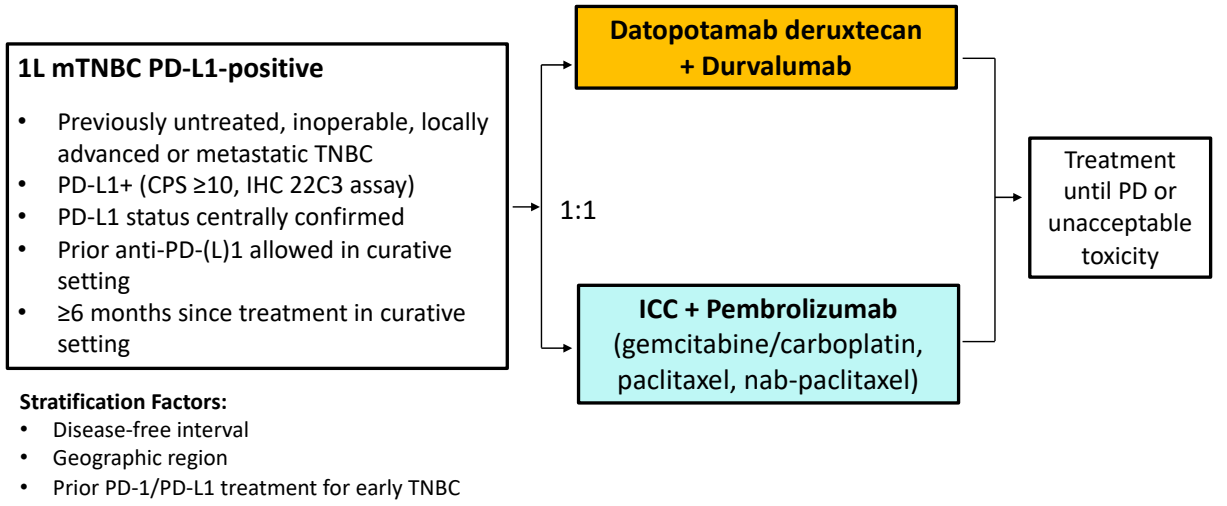


- Responses regardless of PD-L1 or HER2-low category
- No DLTs
- TRAE ILD/pneumonitis: G1, n=3; G2, n=3; G3, n=1, G5, n=1 (COVID-associated pneumonitis)

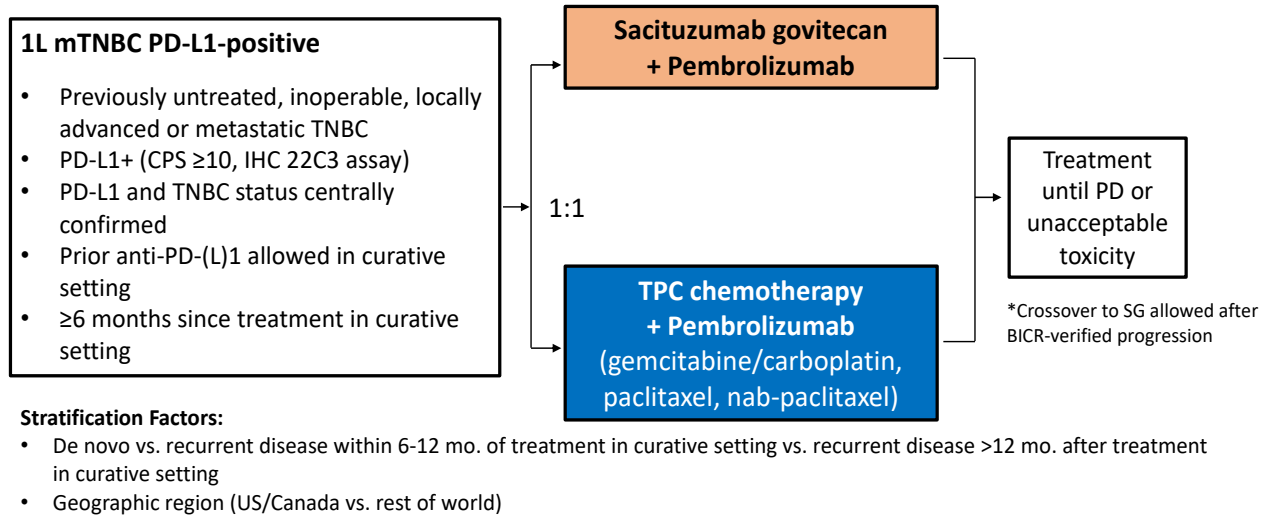
Schmid P et al. ESMO 2023; Schmid P et al. SABCS 2022.

TROP2-directed ADC + ICI in 1L PD-L1+ mTNBC

TROPION-Breast05: Dato-DXd + Durvalumab vs. TPC + Pembrolizumab in 1L PD-L1+ mTNBC



ASCENT-04: Sacituzumab govitecan + Pembrolizumab vs. TPC + Pembrolizumab in 1L PD-L1+ mTNBC



TROP2-directed ADC + PD-(L)1 Inhibitor for Residual Disease Post-Neoadjuvant Therapy

TROPION-Breast03: Dato-DXd +/- Durvalumab vs. TPC (pembrolizumab and/or capecitabine)

Key Eligibility Criteria

- Histologically confirmed invasive TNBC (ER<1%, PR<1%, HER2-negative)
- Completed at least 6 cycles of neoadjuvant therapy containing an anthracycline and/or a taxane with or without carboplatin, with or without pembrolizumab.
- Residual invasive disease after neoadjuvant therapy
- No evidence of locoregional or distant relapse
- Radiotherapy delivered before the start of study treatment
- No adjuvant systemic therapy
- ECOG PS 0 or 1
- Adequate bone marrow reserve and organ function
- No known germline BRCA1 or BRCA2 mutation

Stratification factors:

- Prior neoadjuvant pembrolizumab (Yes vs No)
- Residual disease (< 1 cm vs ≥ 1 cm)
- Prior neoadjuvant platinum chemotherapy (Yes vs No)

2:1:2

- Dato-DXd 6 mg/kg IV Q3W x 8 cycles + Durva 1120 mg IV Q3W x 9 cycles
- Dato-DXd 6 mg/kg IV Q3W x 8 cycles
- Investigator's Choice of Therapy (ICT)*

*capecitabine, pembrolizumab, or capecitabine + pembrolizumab

Primary endpoint
Dato+Durva vs ICT: iDFS

Secondary endpoints
Dato+Durva vs ICT: DDFS, OS
Dato vs ICT: iDFS, DDFS, OS
Dato+Durva vs Dato: iDFS, DDFS
PROs, PK, immunogenicity, safety

NCT05629585

ASCENT-05 (OptimICE-RD): SG plus pembrolizumab vs. TPC (pembrolizumab +/- capecitabine)

Residual invasive TNBC disease in breast or positive node(s) after neoadjuvant therapy
N = 1514

- A: Sacituzumab Govitecan x 8 cycles + Pembrolizumab x 8 cycles
- B: Pembrolizumab x 8 cycles (add-on capecitabine per physician's choice)

iDFS Follow Up

Stratification Factors:
- Geographic region
- Prior checkpoint inhibition
- Prior anthracycline
- Pathologic nodal status

Countries:
- United States
- Japan

Primary Endpoint:
Invasive Disease-Free Survival

Secondary Endpoints:
OS, dDFS, Safety, QoL

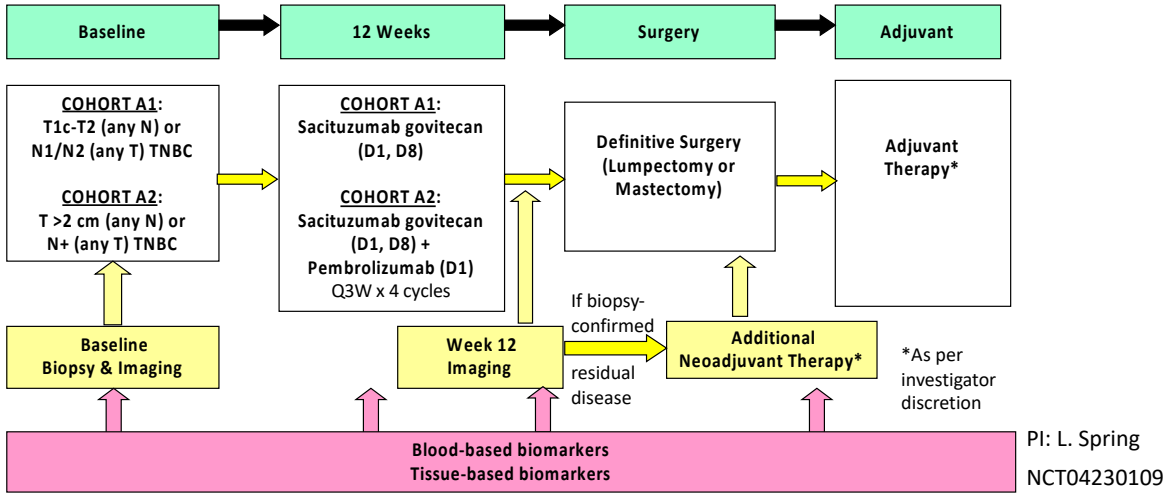
Biomarker Exploratory Endpoints:
ctDNA, Trop-2, PD-L1, TIL

PRO Exploratory Endpoint:
EQ-5D

NCT05633654

TROP2-directed ADC + PD-(L)1 Inhibitor as Neoadjuvant Therapy

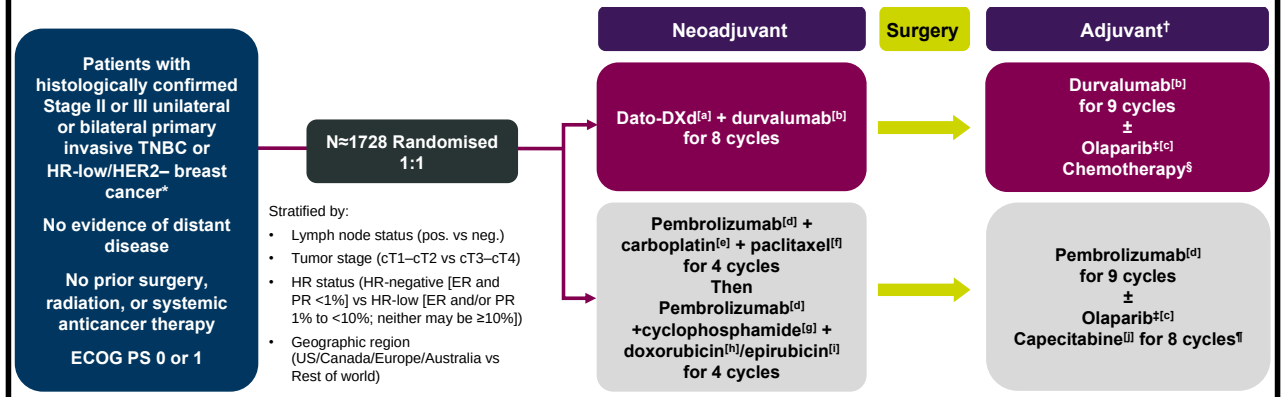
NeoSTAR: Sacituzumab govitecan +/- Pembrolizumab



PI: L. Spring

NCT04230109

TROPION-Breast04: Dato-DXd + Durvalumab vs. KN522 regimen for stage II-III TNBC



NeoSTAR	SG	SG + Pembro
TNBC eBC	**A1: pCR = 30%**	A2
HR+/HER2- eBC	B1	B2

I-SPY 2.2	Dato-DXd	Dato-DXd + Durva
TNBC eBC	Modeled pCR = 26%	Modeled pCR = 44%
HR+/HER2- eBC	Modeled pCR = 8%	Modeled pCR = 18%

McArthur HL et al. SABCS 2023; Spring L et al. ASCO 2022; Spring L et al. Ann Oncol 2024;5(3):293-301; Shatsky R et al. ASCO 2024; Meisel J et al. ASCO 2024.

TROP2-directed ADC + ICI in “Immune-cold” MBC

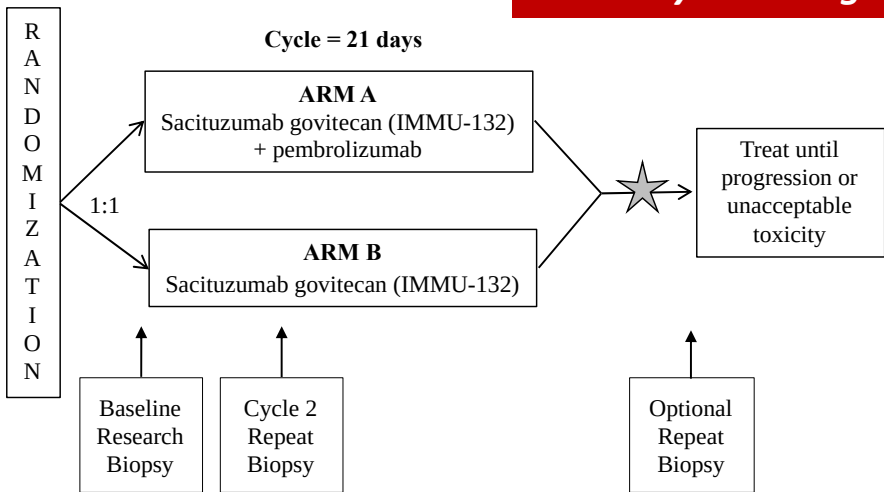
SACI-IO TNBC: Sacituzumab govitecan + Pembrolizumab vs. Sacituzumab govitecan in 1L PD-L1-negative mTNBC

Currently enrolling

N = 110 patients

Eligibility:

- Metastatic TNBC: ER ≤5%, PR ≤5%, HER2-negative per ASCO/CAP guidelines
- PD-L1 negative: IC < 1% by SP142 or CPS <10 by 22C3
- No prior therapy for metastatic disease & no prior PD-1/L1 inhibitor

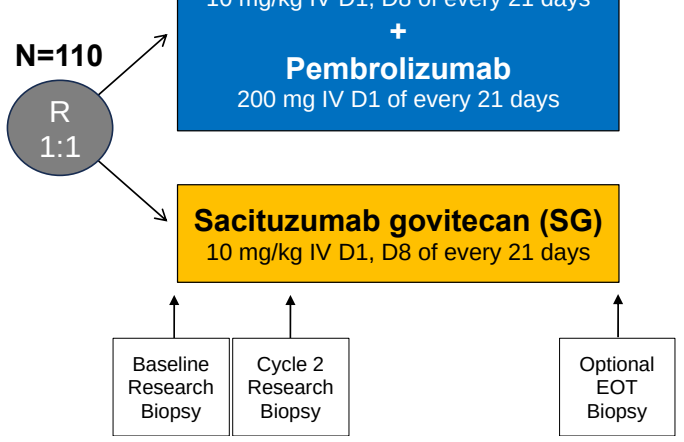


NCT04468061

SACI-IO HR+: Sacituzumab govitecan + Pembrolizumab vs. Sacituzumab govitecan in HR+/HER2- mBC (0-1 prior CT)

Metastatic or locally advanced unresectable breast cancer

- HR-positive (ER ≥ 1% or PR ≥ 1%), HER2-negative (IHC 0, 1+, or 2+/ ISH-)
- No restriction on PD-L1 status[a]
- ≥1 endocrine therapy for mBC or progression on or within 12 months of adjuvant endocrine therapy
- 0-1 prior chemotherapy for mBC
- No prior topoisomerase I-inhibitor ADC, irinotecan, or PD-1/-L1 inhibitor
- No known active brain metastases or leptomeningeal disease

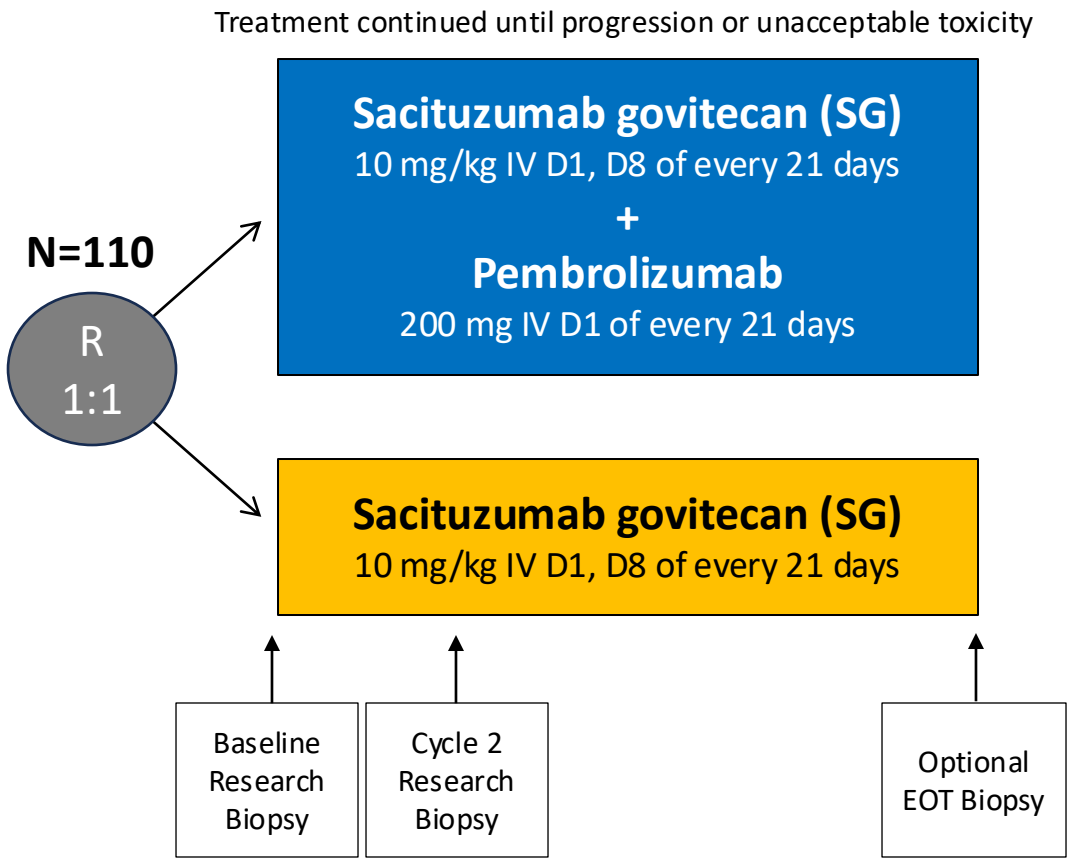


NCT04448886

SACI-IO HR+: Study Schema

Metastatic or locally advanced unresectable breast cancer

- HR-positive (ER ≥ 1% or PR ≥ 1%), HER2-negative (IHC 0, 1+, or 2+/ ISH-)
- No restriction on PD-L1 status[a]
- ≥1 endocrine therapy for mBC or progression on or within 12 months of adjuvant endocrine therapy
- 0-1 prior chemotherapy for mBC
- No prior topoisomerase I-inhibitor ADC, irinotecan, or PD-1/-L1 inhibitor
- No known active brain metastases or leptomeningeal disease



Endpoints

Primary:
- PFS (ITT)

Secondary:
- PFS (PD-L1+)[b]
- OS (ITT, PD-L1+)
- ORR, DOR, TTOR, CBR (ITT, PD-L1+)
- Safety

Exploratory:
- Correlative
- HRQoL

NCT04448886

Study activation date: 9/23/2020. Data cutoff for analysis: 3/9/2024.
[a] Protocol amendment activated in 1/2022 to allow participants with any PD-L1 status to enroll. [b] Central PD-L1 testing performed with PharmDx 22C3 assay. PD-L1-positive, combined positive score (CPS) ≥1. Note: There is no approved CDx with 22C3 for HR+/HER2- mBC.
Abbreviations: HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ADC, antibody drug conjugate; ITT, intent-to-treat; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DOR, duration of response; TTOR, time to objective response; CBR, clinical benefit rate; HRQoL, health-related quality of life.

Garrido-Castro AC et al. ASCO 2024.

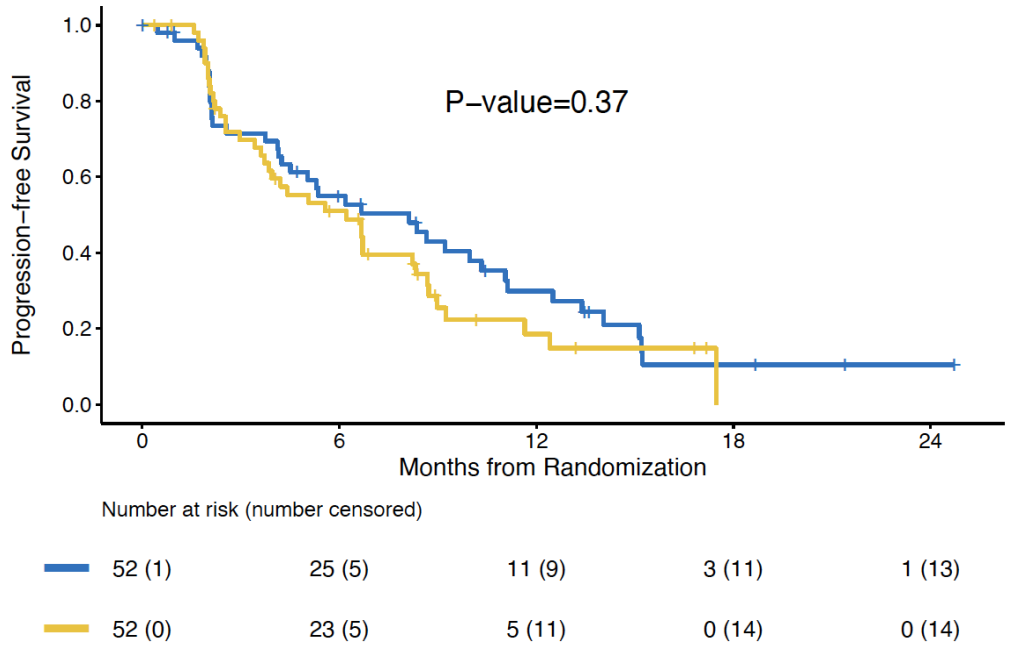
Baseline Characteristics

	SG + Pembrolizumab (N=52)	SG (N=52)	Total (N=104)
Age, median (range)	56.5 (31.0 - 81.0)	57.0 (27.0 - 80.0)	**57.0 (27.0 - 81.0)**
ER status[a]			
≥10%	49 (94.2%)	50 (96.2%)	**99 (95.2%)**
1-9%	2 (3.8%)	1 (1.9%)	**3 (2.9%)**
Unknown	1 (1.9%)	1 (1.9%)	**2 (1.9%)**
PD-L1 status[b]			
Negative	35 (67.3%)	28 (53.8%)	**63 (60.6%)**
CPS ≥1	16 (30.8%)	24 (46.2%)	**40 (38.5%)**
CPS 1-9	13 (25.0%)	20 (38.5%)	**33 (31.7%)**
CPS ≥10	3 (5.8%)	4 (7.7%)	**7 (6.7%)**
Not tested	1 (1.9%)	0 (0.0%)	**1 (1.0%)**
Presentation at mBC diagnosis			
De novo mBC	10 (19.2%)	13 (25.0%)	**23 (22.1%)**
Recurrent mBC	42 (80.8%)	39 (75.0%)	**81 (77.9%)**
Liver metastasis at baseline			
Yes	40 (76.9%)	41 (78.8%)	**81 (77.9%)**
No	12 (23.1%)	11 (21.2%)	**23 (22.1%)**
Prior neo-/adjuvant chemotherapy[c]			
Yes	28 (66.7%)	28 (71.8%)	**56 (69.1%)**
No	14 (33.3%)	11 (28.2%)	**25 (30.9%)**
Prior CDK4/6 inhibitor in any setting			
Yes	47 (90.4%)	45 (86.5%)	**92 (88.5%)**
No	5 (9.6%)	7 (13.5%)	**12 (11.5%)**
Prior chemotherapy regimens for mBC			
0	27 (51.9%)	26 (50.0%)	**53 (51.0%)**
1	25 (48.1%)	26 (50.0%)	**51 (49.0%)**

[a] Estrogen receptor (ER) in the most recent available tumor sample prior to study registration. ER positive (% unknown) in 2 patients. [b] Central PD-L1 testing performed on the baseline research biopsy (if a research biopsy was not performed, testing was performed on the most recent available archival tumor sample prior to study registration). Tissue was not available for testing in one patient. PD-L1-positive defined as combined positive score (CPS) ≥1. [c] Patients diagnosed with *de novo* stage IV breast cancer (SG + Pembrolizumab, n=10; SG, n=13) excluded from denominator.

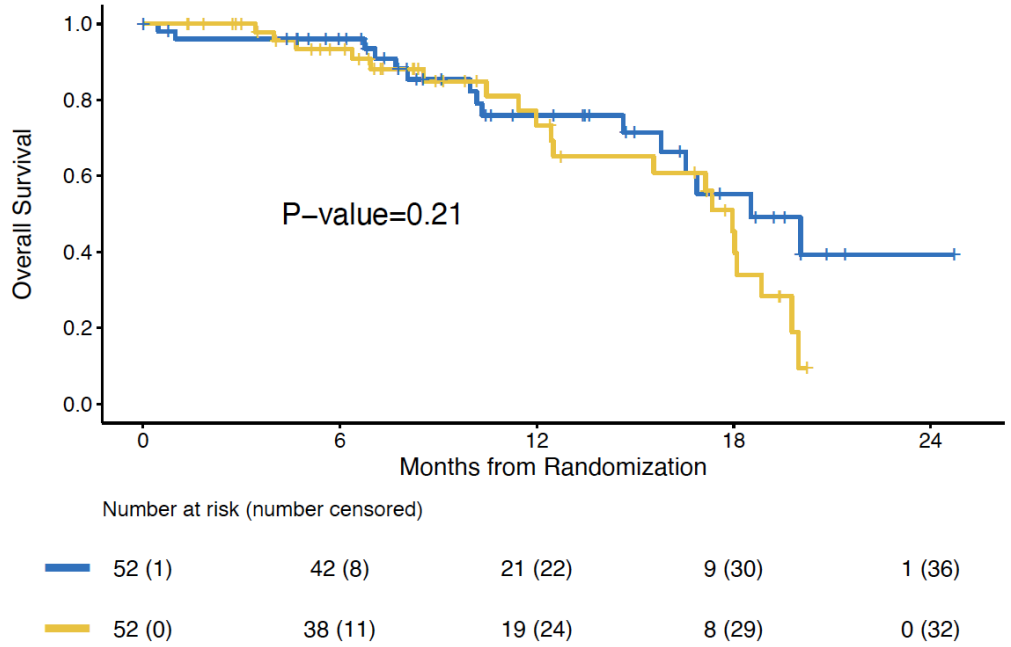
SACI-IO HR+: ITT

PFS



Treatment Arm	SG + Pembrolizumab (N=52)	SG (N=52)
N PFS events	38	38
Median PFS, months (95% CI)	**8.12** (4.51-11.12)	**6.22** (3.85-8.68)
HR (95% CI)	**0.81** (0.51-1.28)	
p-value (logrank test)	0.37	

OS



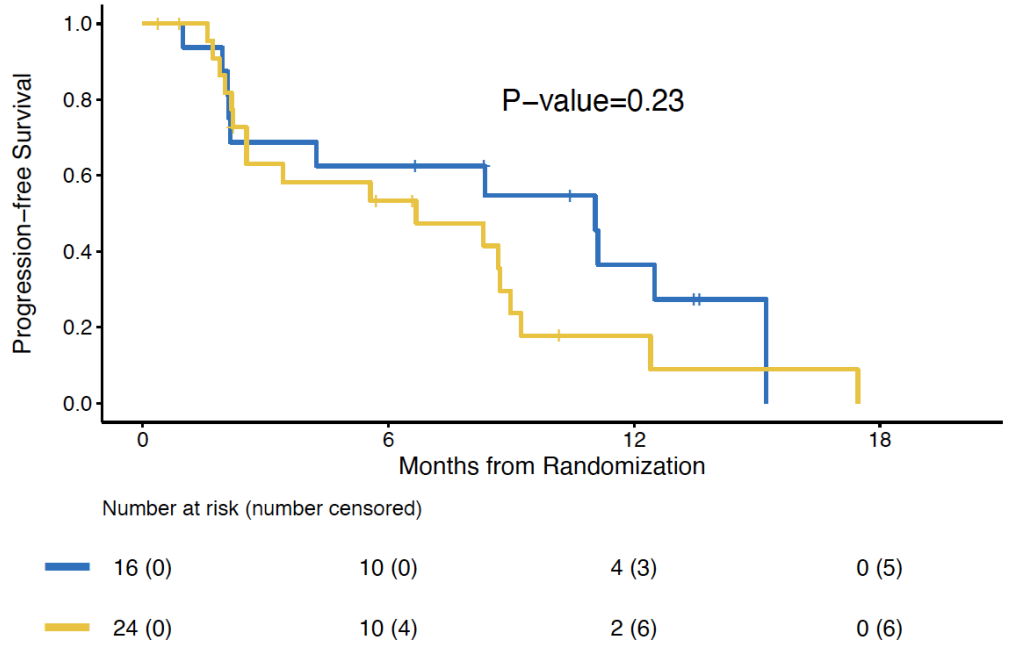
Treatment Arm	SG + Pembrolizumab (N=52)	SG (N=52)
N OS events	15	20
Median OS, months (95% CI)	**18.52** (16.55-NA)	**17.96** (12.50-NA)
HR (95% CI)	**0.65** (0.33-1.28)	
p-value (logrank test)	0.21	

Median follow-up: 12.5 months

Garrido-Castro AC et al. J Clin Oncol 2024;42(suppl 17; abstr LBA1004).

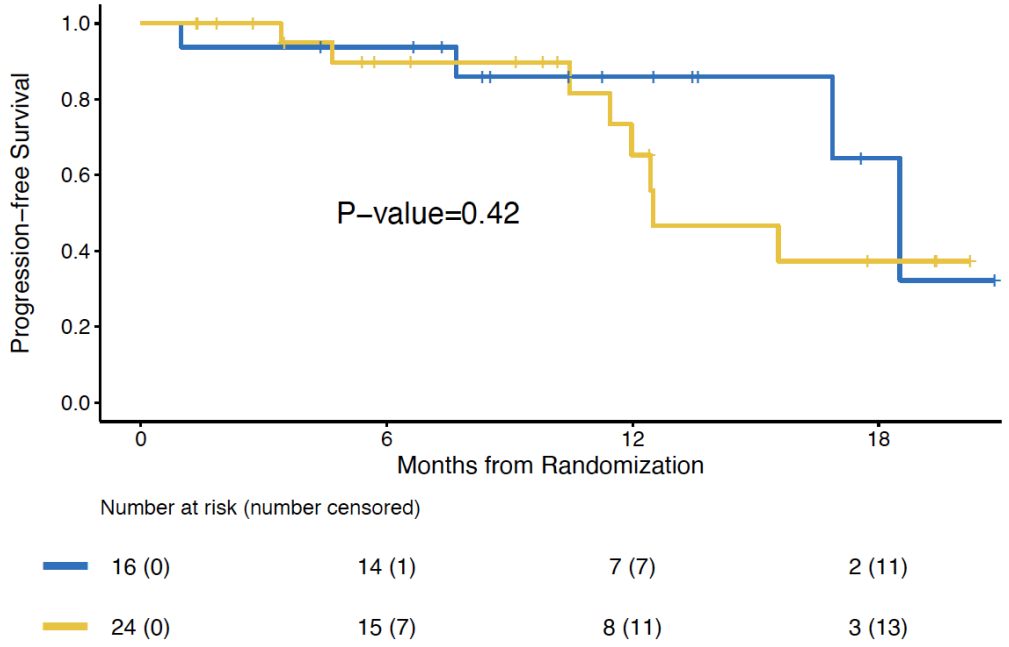
SACI-IO HR+: PD-L1+ (CPS≥1)

PFS



Treatment Arm	SG + Pembrolizumab (N=16)	SG (N=24)
N PFS events	11	18
Median PFS, mo (95% CI)	**11.05** (2.14-NA)	**6.68** (2.53-9.24)
HR (95% CI)	**0.62** (0.29-1.36)	
p-value (logrank test)	0.23	

OS

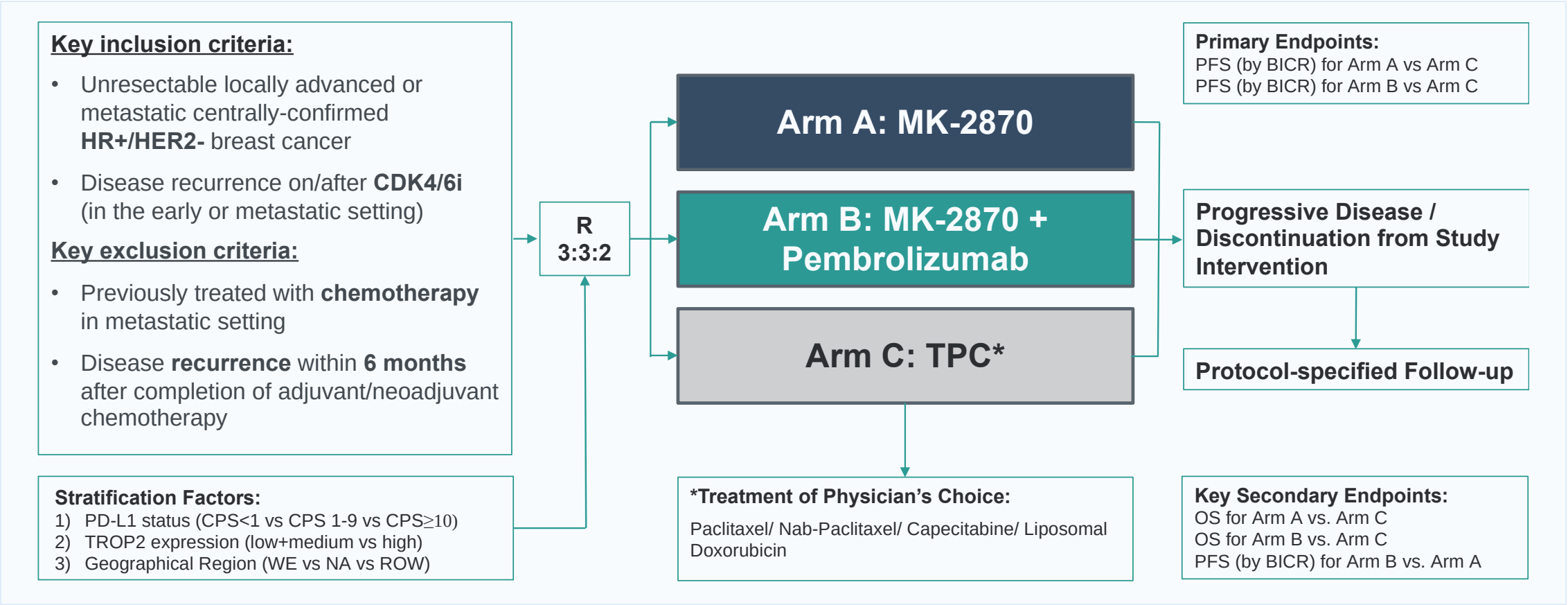


Treatment Arm	SG + Pembrolizumab (N=16)	SG (N=24)
N OS events	4	8
Median OS, mo (95% CI)	**18.52** (16.88-NA)	**12.50** (11.97-NA)
HR (95% CI)	**0.61** (0.18-2.04)	
p-value (logrank test)	0.42	

Median follow-up: 12.5 months

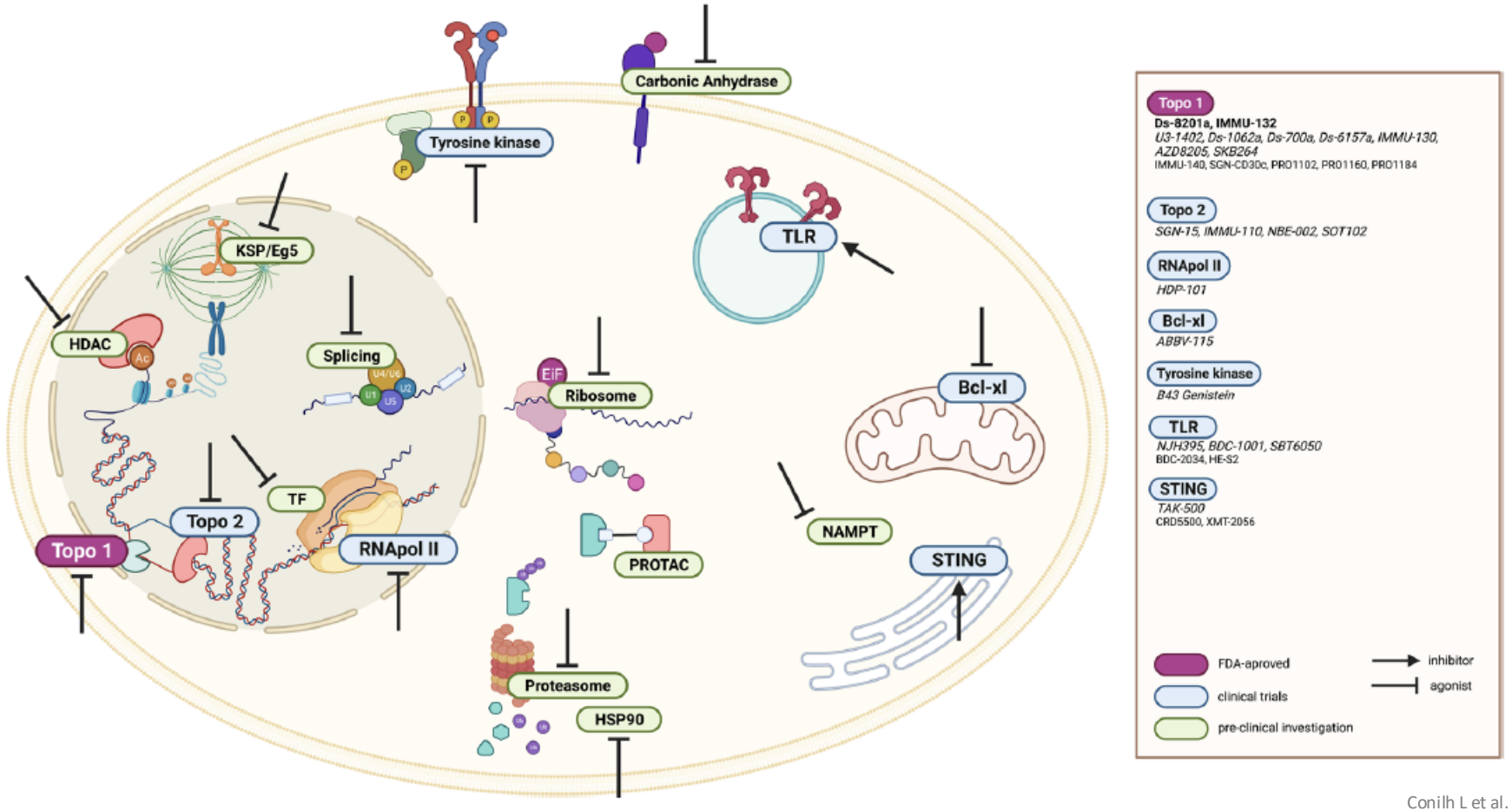
Garrido-Castro AC et al. J Clin Oncol 2024;42(suppl 17; abstr LBA1004).

TroFuse-010: Sac-TMT ± Pembrolizumab vs TPC in HR+/HER2- mBC after ET



Slide courtesy of S. Tolaney; https://www.clinicaltrials.gov/study/NCT06312176?term=NCT06312176&rank=1.

Landscape of ADC Payloads Beyond Microtubule and DNA-Intercalating Agents

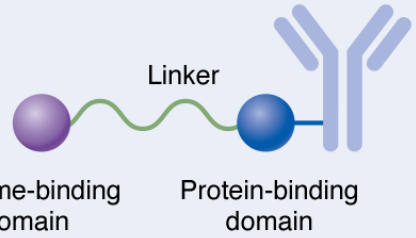


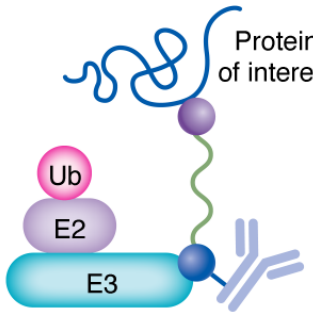
Conilh L et al. J Hematol Oncol 2023;16(1):3.

Novel ADC Payloads

Proteolytic targeting chimeras

PROTAC ADC

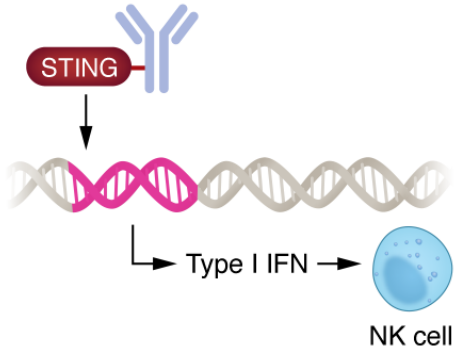




The PROTAC brings E3 ligase and target protein of interest (POI) in close proximity for ubiquitination

Immune stimulator

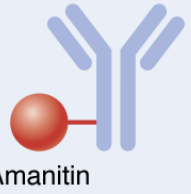
STING ADC

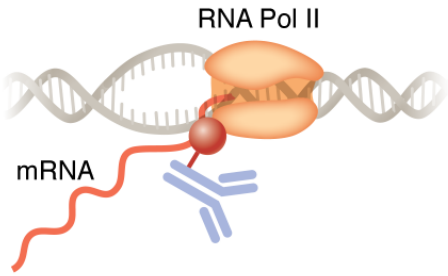


STING molecule activates kinases that upregulate type I IFN and ultimately stimulate immune cells

Transcription inhibition

RNA polymerase II inhibitor ADC

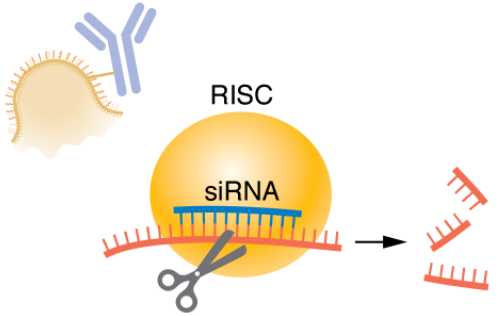




RNA polymerase inhibitor II blocks the synthesis of mRNA

Genetic material

Antibody-siRNA conjugate



siRNA binds to the cytoplasmic RISC complex to cleave target mRNA and ultimately reduce expression of the target gene

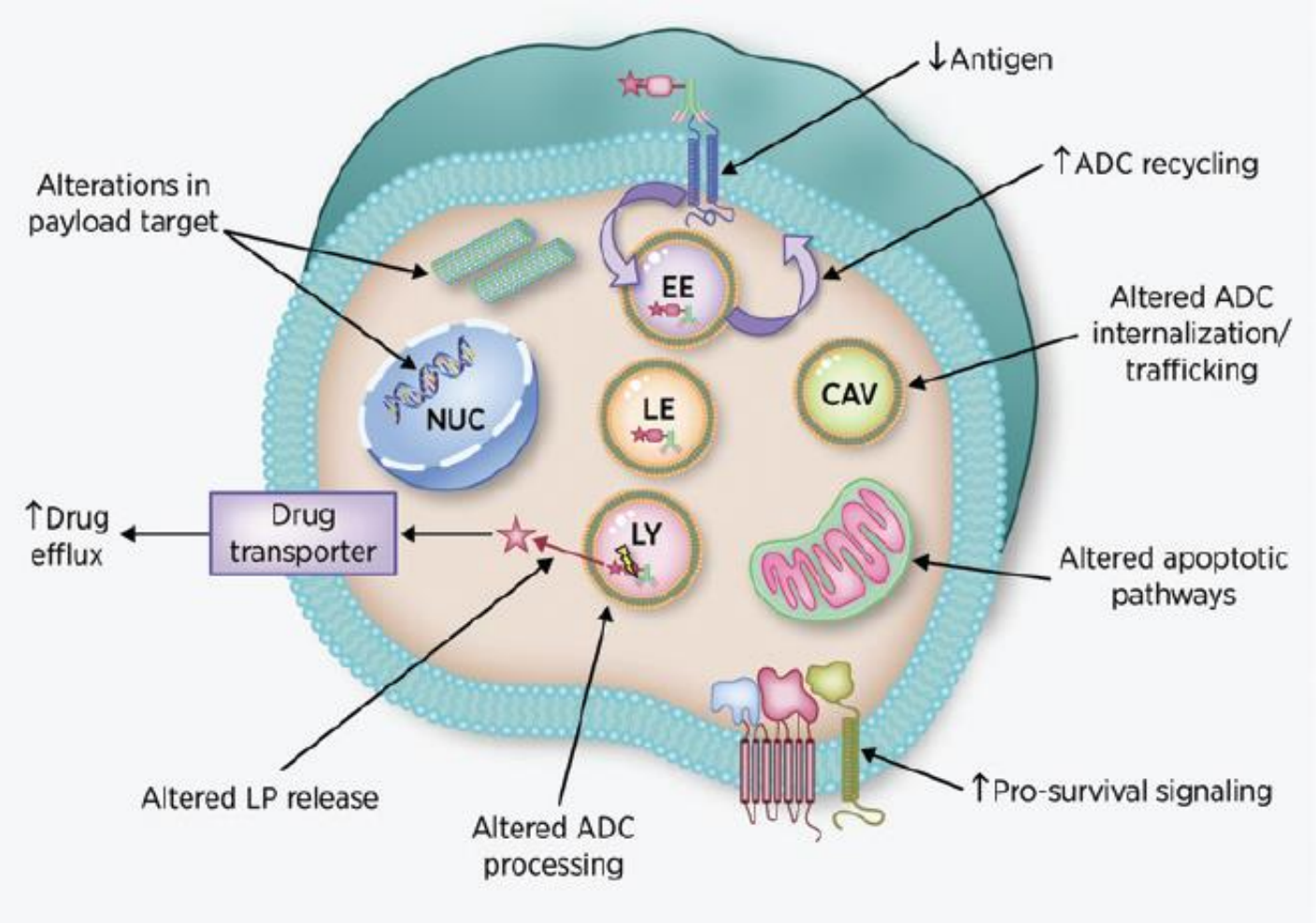
Chang HL et al. J Clin Invest. 2023;133(18):e172156.

Immune-Stimulating ADCs (ISACs)

Agent	Target	Payload	Latest trial phase	Setting	Trial number
TAK500	CCR2	STINGa	Phase Ia/b	Advanced solid tumors	NCT05070247
XMT-2056	HER2	STINGa	Phase I	Advanced solid tumors	NCT05514717
HE-S2	PDL1	TLR7-8a	Preclinical	Advanced solid tumors	Preclinical
PERTUZUMAB ZUVOLIMOD | SBT-6050	HER2	TLRa	Discontinued	Advanced solid tumors	NA
BDC-1001	HER2	TLR7-8a	Discontinued	Advanced solid tumors	NA
NJH395	HER2	TLR7a	Discontinued	Advanced solid tumors	NA
TAC 001	CD22	TLR9a	Phase II	Advanced solid tumors	NCT05399654

Izzo D et al. Ther Adv Med Oncol. 2025;17: 1-16.

ADC Resistance: Beyond Target and Payload



Loganzo F et al. Mol Cancer Ther. 2016;15(12):2825-34.

Key Takeaways

- Potential of ADCs to enhance antitumor immune response:
  - Antibody-dependent cell-mediated cytotoxicity and cellular phagocytosis, complement-dependent cytotoxicity
  - Tumor cell death-mediated activation of DCs
  - Depletion of regulatory T-cells, upregulation of MHC class-I and PD-L1 expression
  - Activation of cGAS-STING pathway → immune cell recruitment to tumor
- Novel ADCs and targeted therapy approaches in development:
  - New ADC targets (e.g., non-tumor cells in microenvironment) and payloads (e.g., immunomodulatory, radionuclide)
  - Bispecific ADCs (BsADCs)
  - Novel combinations (e.g., ICI, PARPi)
- Understanding mechanisms that drive response and resistance to therapies is key to help inform treatment strategies: combinations, sequencing, duration of therapy

Thank you