Inside the Issue: Integrating Antibody-Drug Conjugates into the Management of HR-Positive and Triple-Negative Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Wednesday, July 17, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Peter Schmid, FRCP, MD, PhD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Faculty

Professor Peter Schmid, FRCP, MD, PhD
Lead, Centre of Experimental Cancer Medicine
Barts Cancer Institute
London, United Kingdom

MODERATOR
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Research To Practice
Miami, Florida

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Chief, Division of Breast Oncology
Associate Director, Susan F Smith Center for Women's Cancers
Senior Physician
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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Survey Participant

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Dr Jhaveri — Disclosures
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Survey Participant

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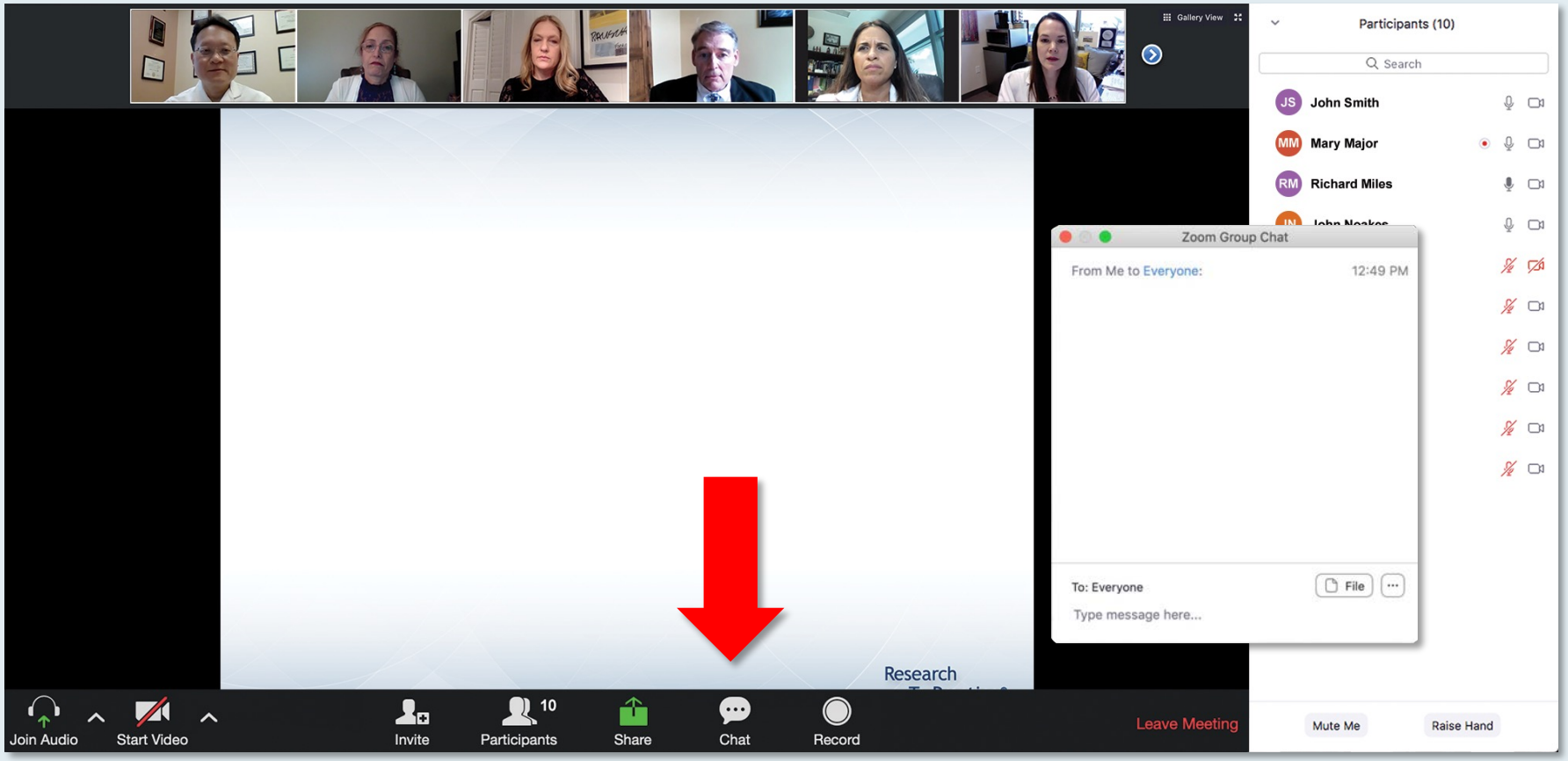

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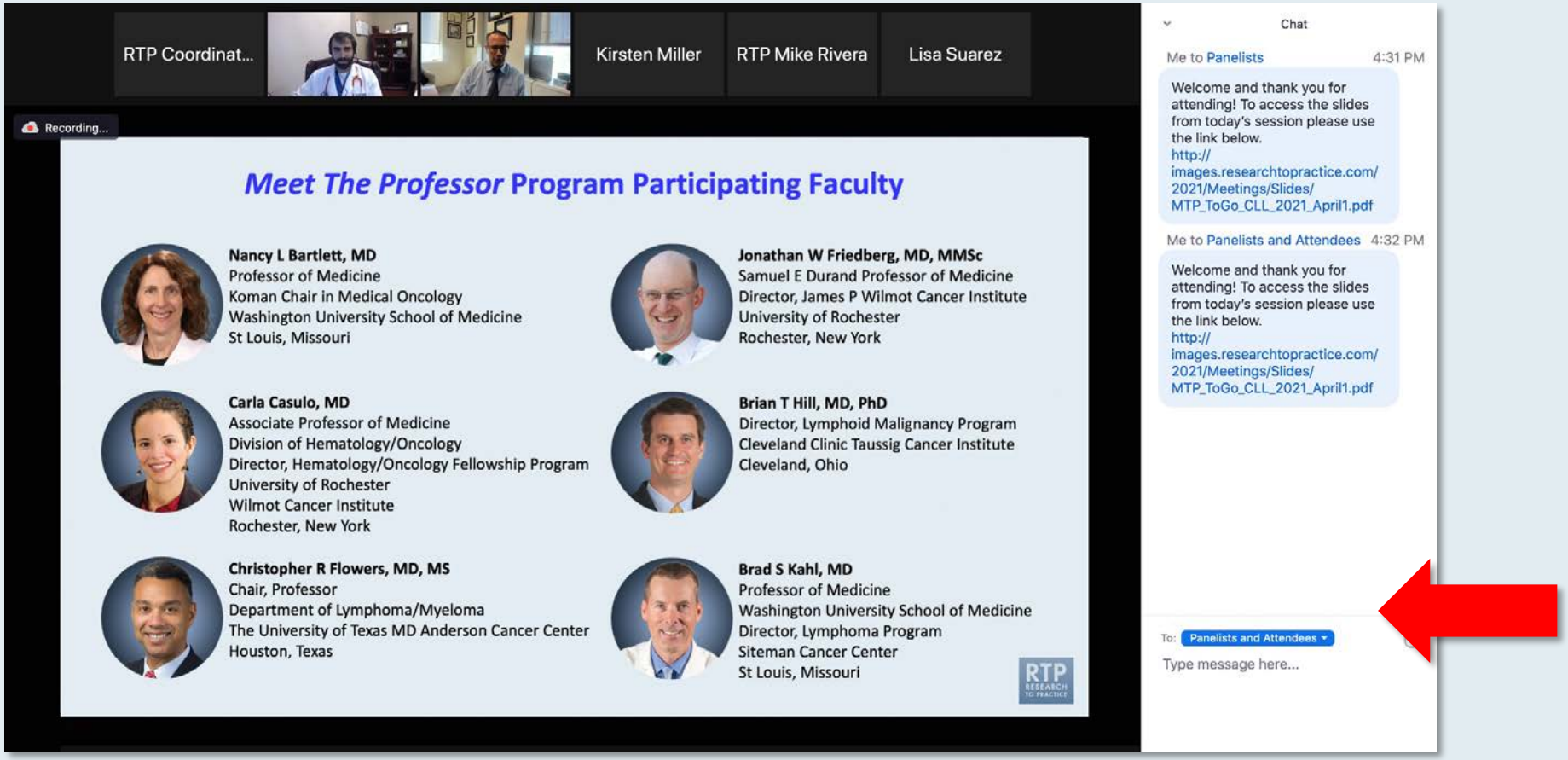

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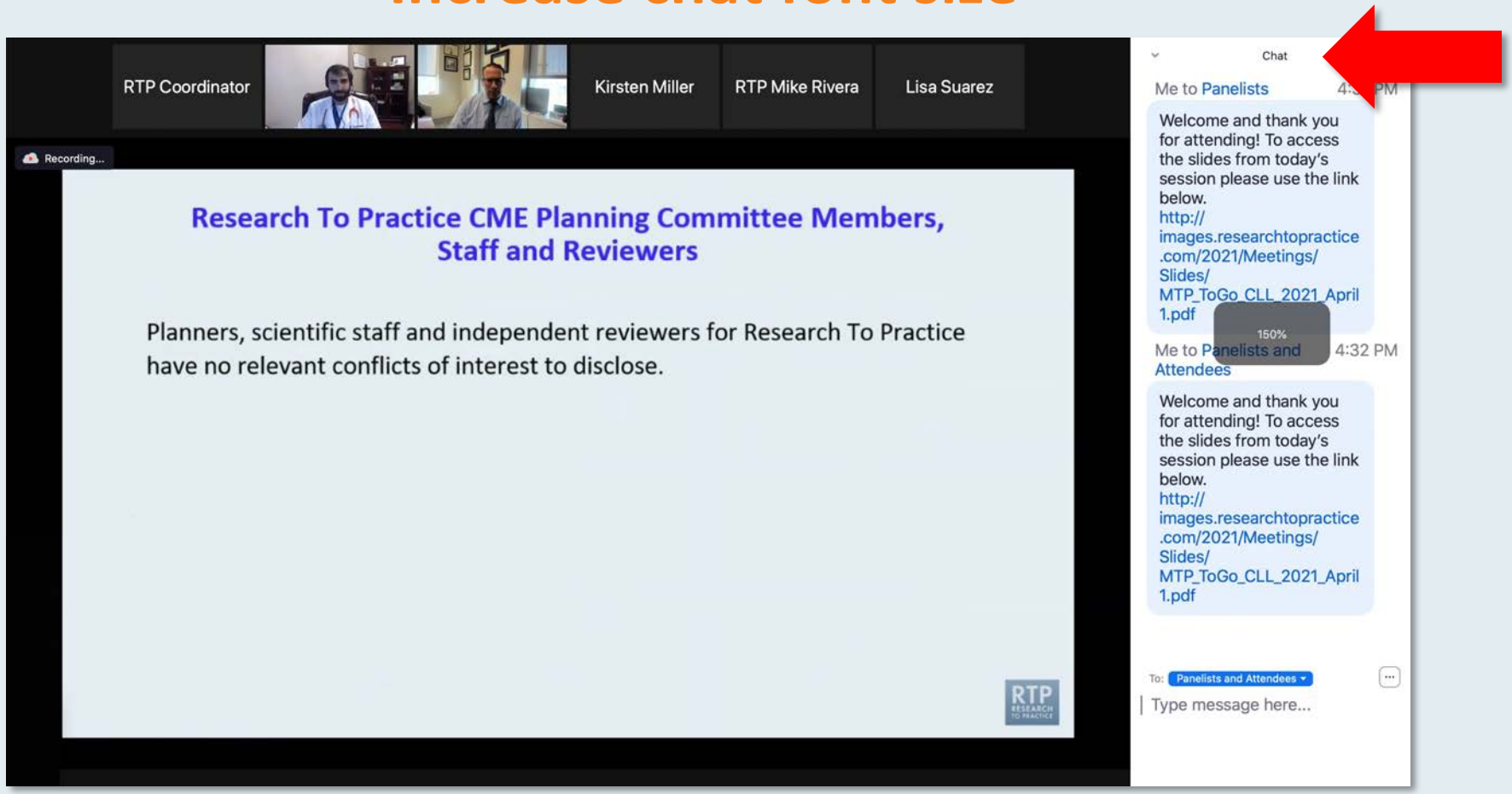

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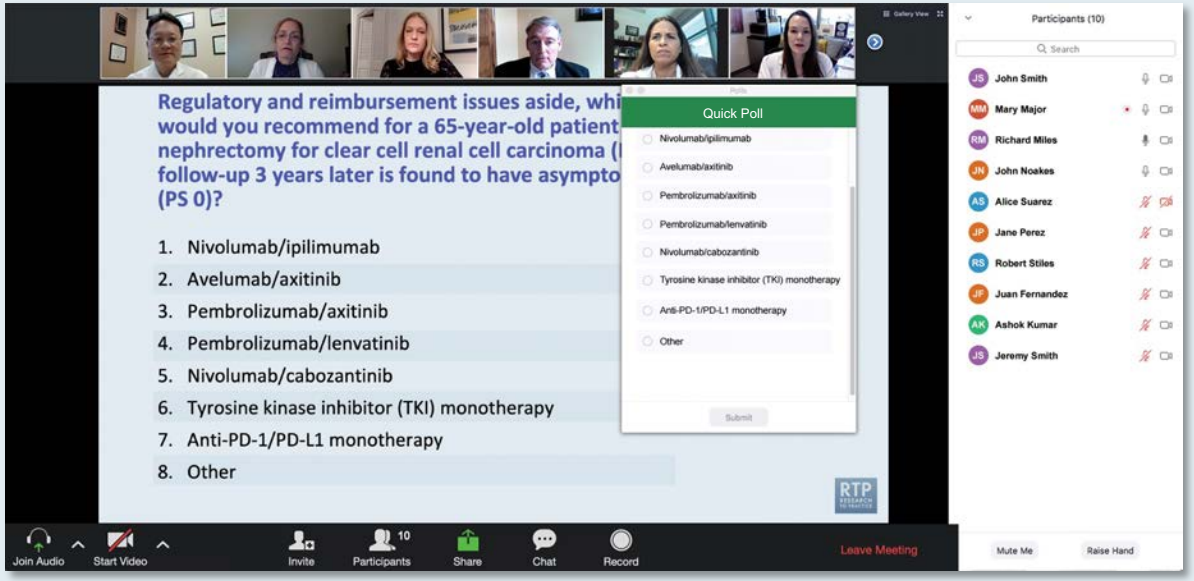

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What Clinicians Want to Know About the Management of Triple-Negative Breast Cancer

DR KEVIN KALINSKY
WINSHIP CANCER INSTITUTE OF EMORY UNIVERSITY

DR HEATHER MCARTHUR
UT SOUTHWESTERN MEDICAL CENTER

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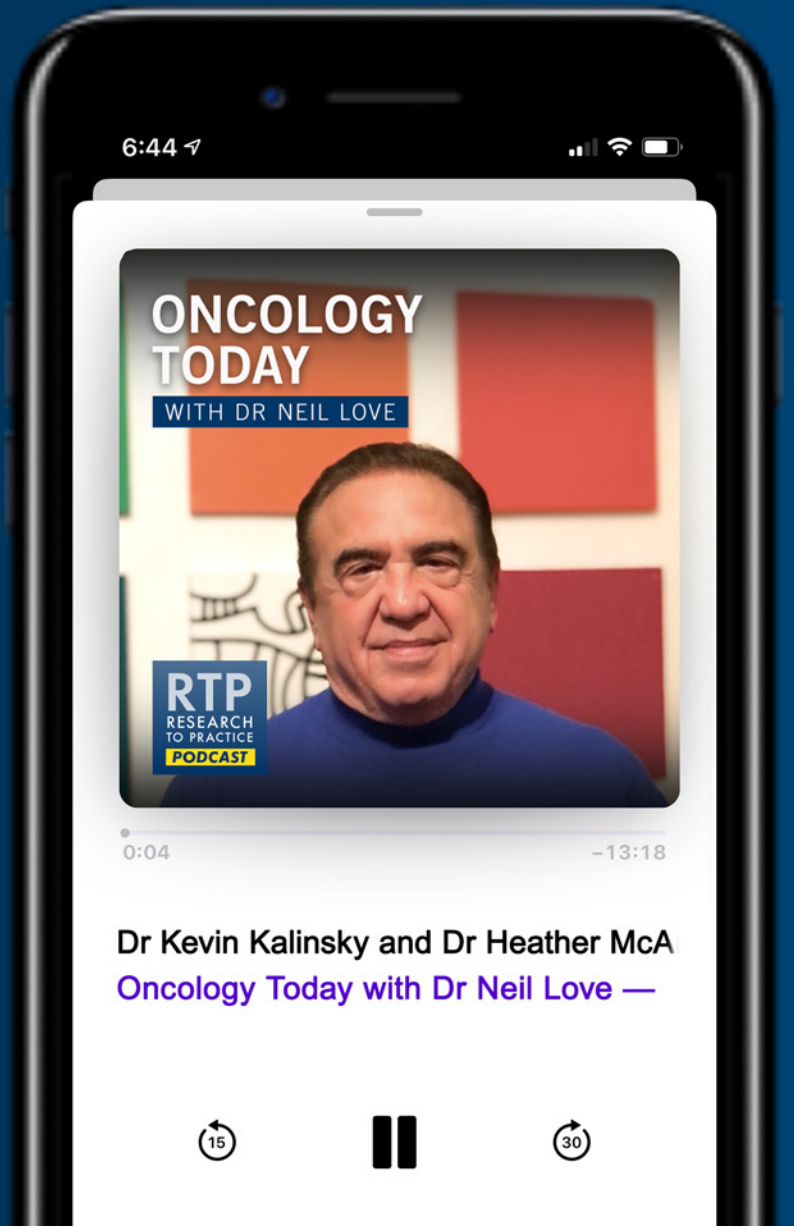

Inside the Issue: Integrating ALK-Targeted Therapy into the Management of Localized Non-Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar

Thursday, July 18, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Professor Ben Solomon, MBBS, PhD

Moderator

Neil Love, MD

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Inside the Issue: Integrating HER2-Targeted Strategies into the Management of Gastrointestinal Cancers

A CME/MOC-Accredited Live Webinar

Wednesday, August 21, 2024
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
John Strickler, MD

Moderator

Neil Love, MD

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Inside the Issue: Optimizing the Diagnosis and Treatment of Neuroendocrine Tumors

A CME/MOC-Accredited Live Webinar

Thursday, August 29, 2024
5:00 PM – 6:00 PM ET

Faculty

Pamela Kunz, MD
Simron Singh, MD, MPH

Moderator

Neil Love, MD

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Data + Perspectives: Clinical Investigators Discuss the Role of CAR T-Cell Therapy for Patients with Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Part 1 of a 2-Part CME Satellite Symposium Series During the Society of Hematologic Oncology 2024 Annual Meeting

Wednesday, September 4, 2024

11:46 AM – 12:46 PM CT

Faculty

Jason Westin, MD, MS

Additional faculty to be announced.

Moderator

Matthew Lunning, DO

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Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Diffuse Large B-Cell Lymphoma

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Grzegorz S Nowakowski, MD
Laurie H Sehn, MD, MPH

Moderator

Christopher R Flowers, MD, MS

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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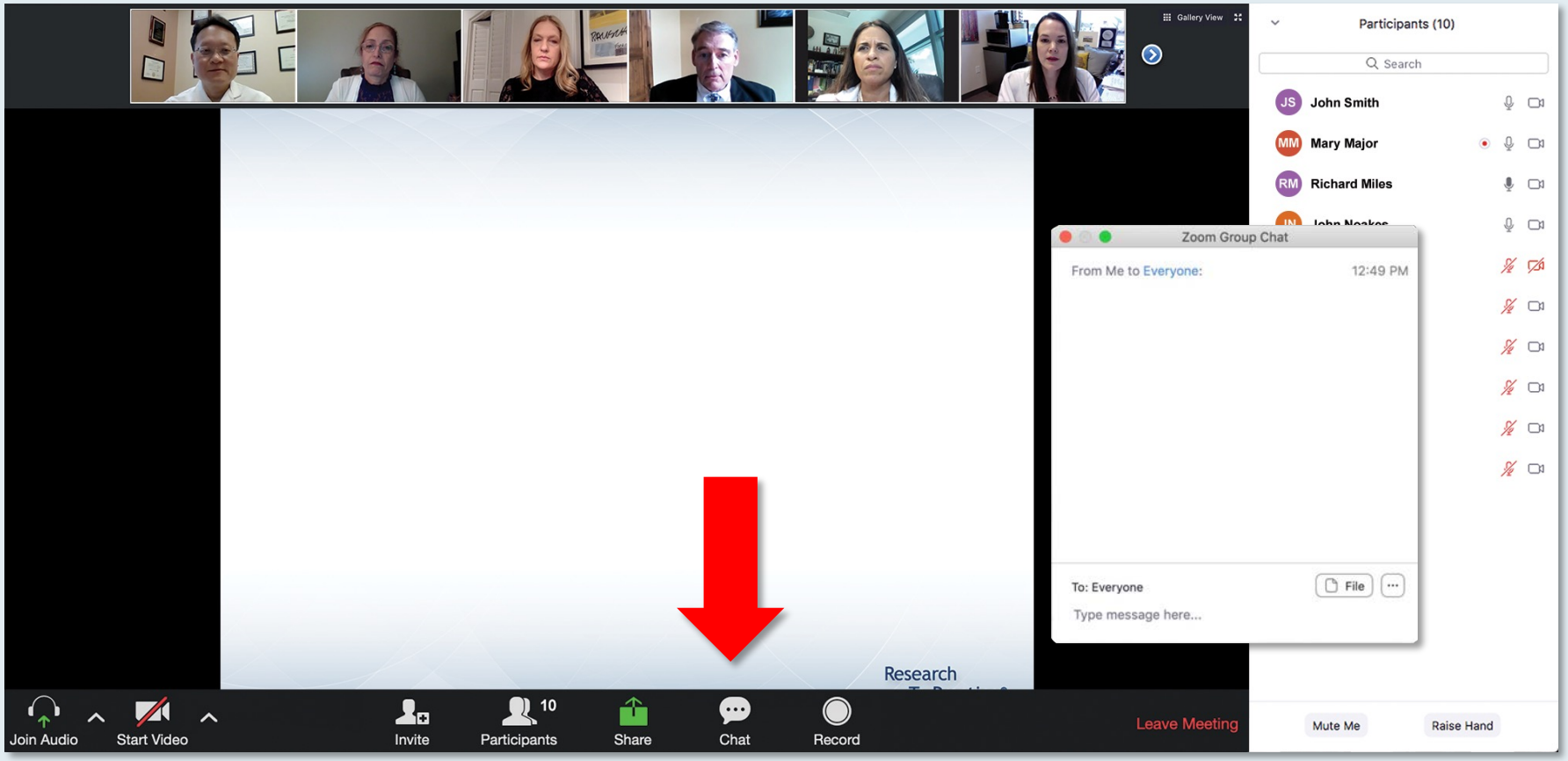

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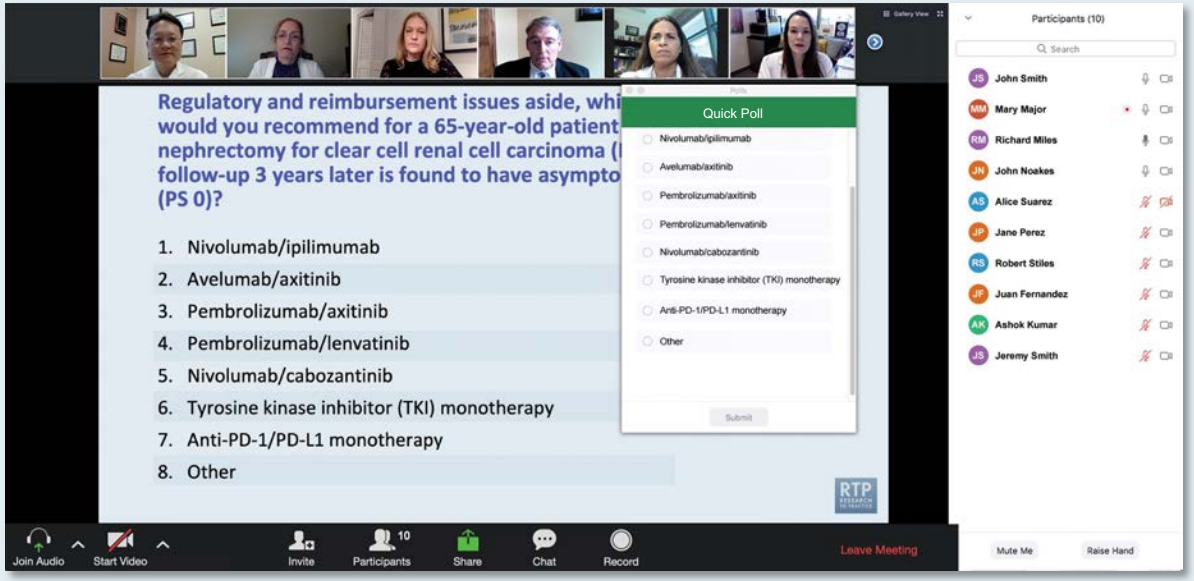

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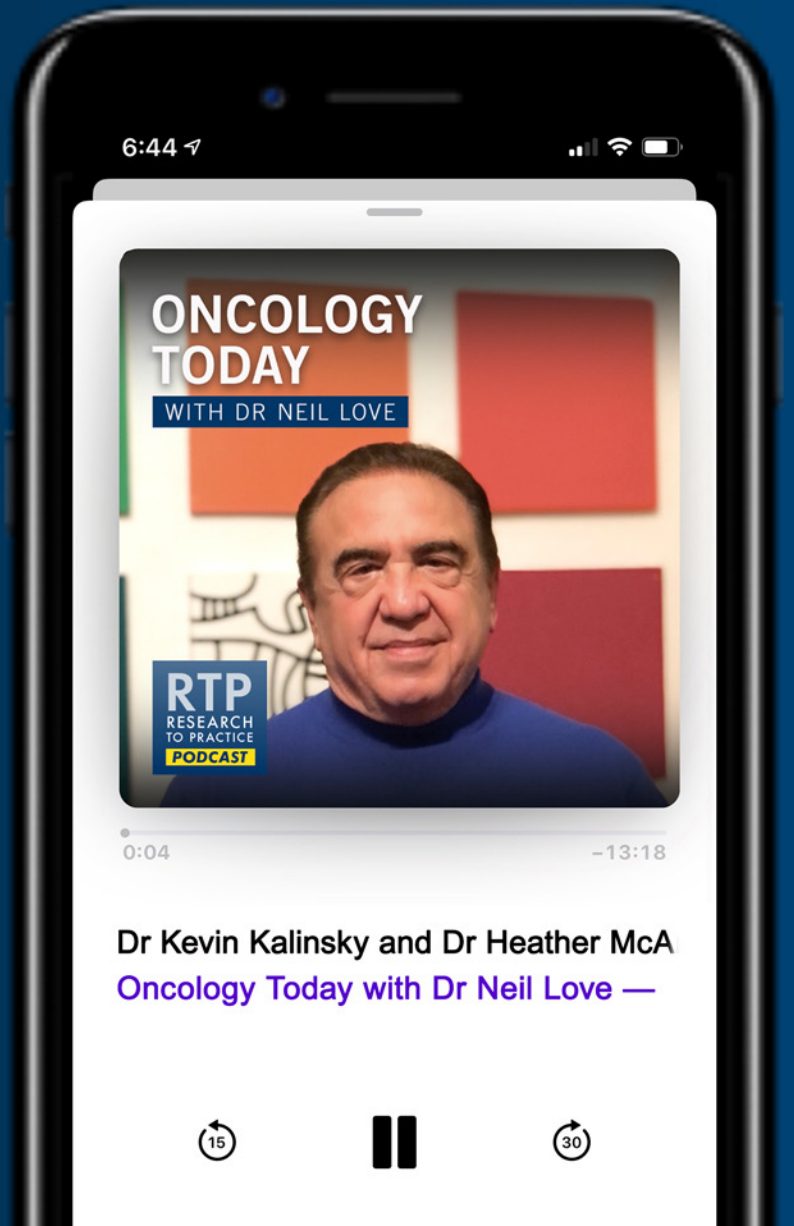

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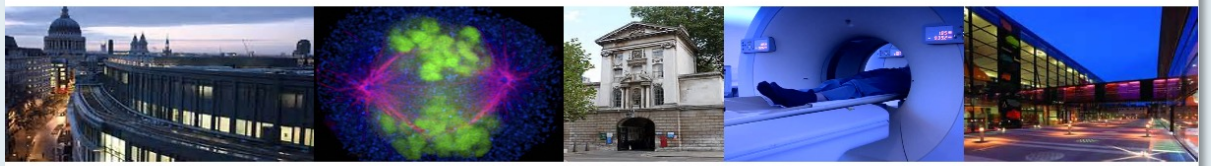
Expanding Role of TROP2-Directed Antibody-Drug Conjugates (ADCs) in Metastatic Breast Cancer (mBC) Management

Sara M Tolaney, MD, MPH
Chief, Division of Breast Oncology
Associate Director, Susan F Smith Center for Women's Cancers
Senior Physician
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Non-Trop-2 targeting ADCs in metastatic breast cancer

Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine
Barts Cancer Institute, St Bartholomew's Hospital
Queen Mary University of London



Agenda

Introduction: Pharmacology and Sequencing of Antibody-Drug Conjugates (ADCs) in Metastatic Breast Cancer (mBC)

Module 1: Expanding Role of TROP2-Directed ADCs in mBC Management — Dr Tolaney

Module 2: Other Targets for ADC Therapy in mBC — Prof Schmid

Agenda

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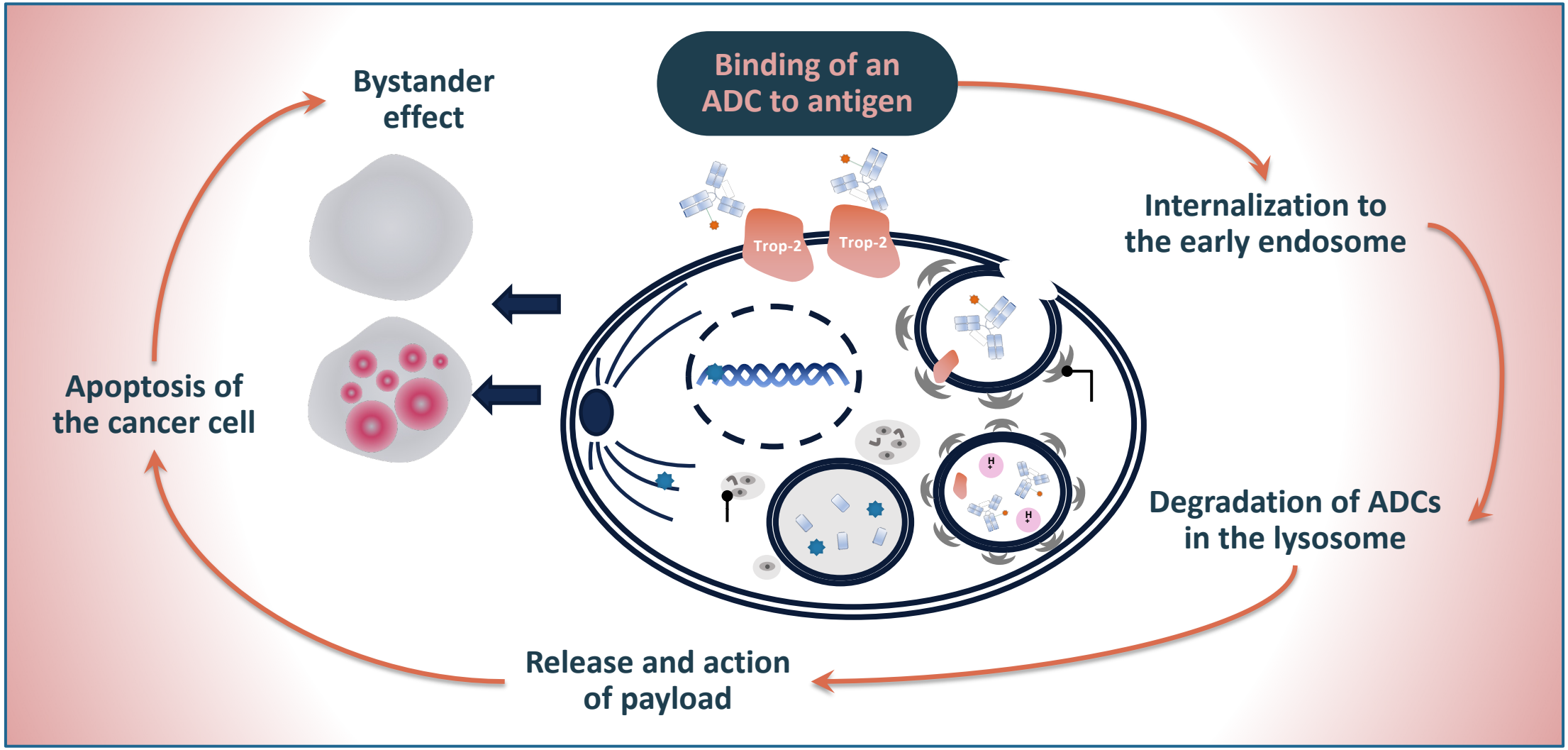
Module 2: Other Targets for ADC Therapy in mBC — Prof Schmid

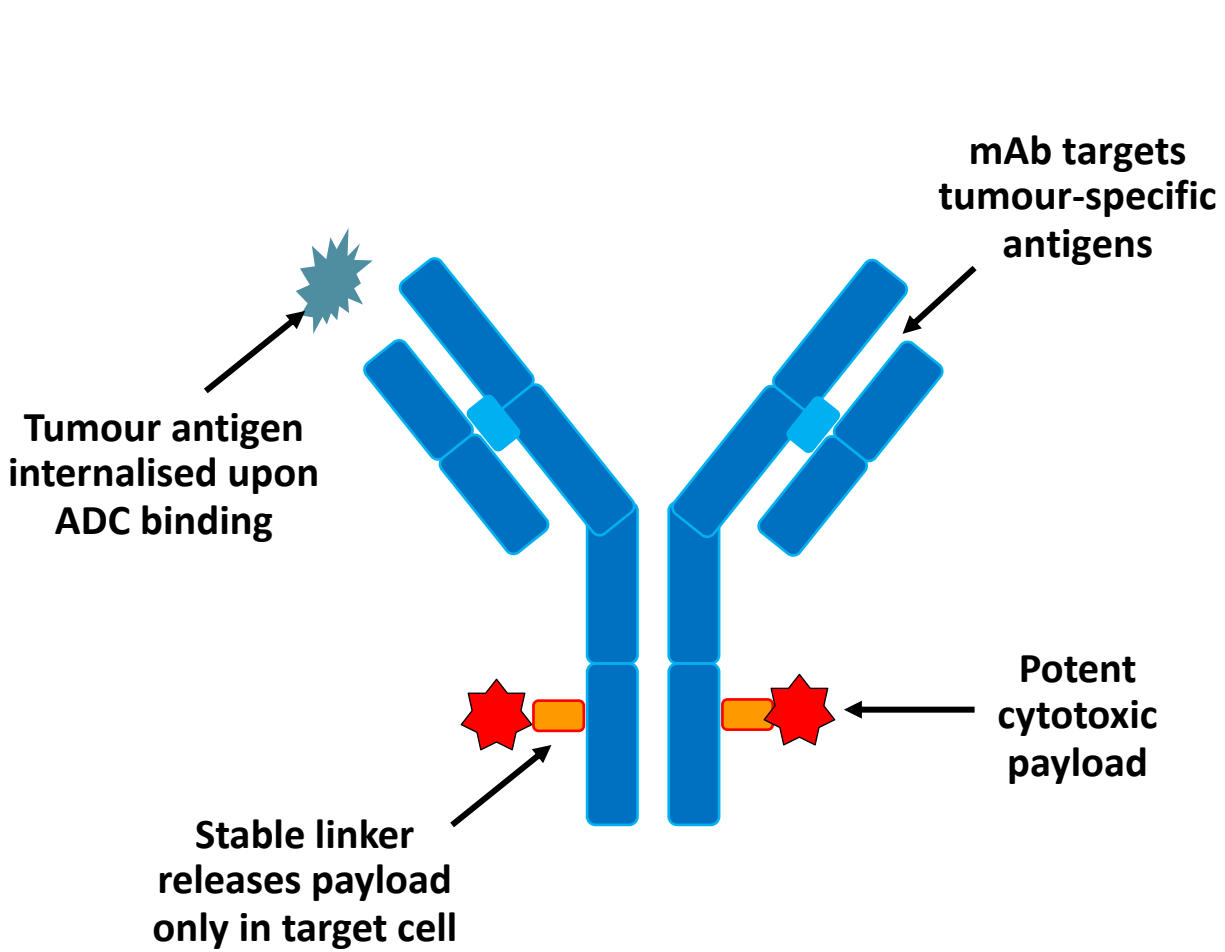
Antibody–Drug Conjugates (ADCs)

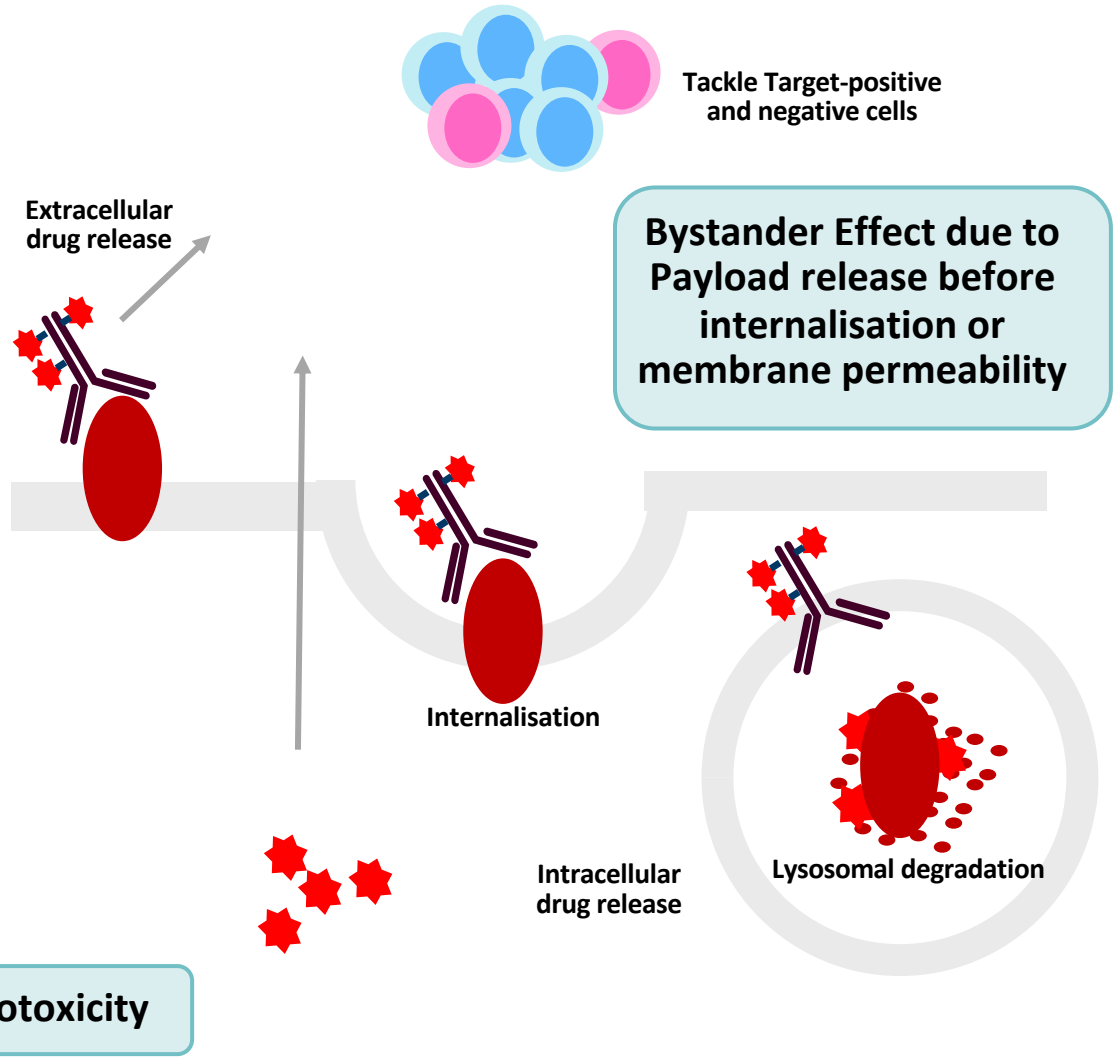
Selective Delivery of Toxic Payload



Courtesy of Sara M Tolaney, MD, MPH

New antibody–drug conjugates





Schmid P, Personal Communication

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

ADC, antibody–drug conjugates; DCR, disease control rate
Modi S, et al. Presented at SABCS 2017. Abstract PD3-07.

Development of Antibody–Drug Conjugates

1st Generation
Eg Gemtuzumab

- Mouse/chimeric MAB
- Low potency payload
- Random conjugation
- Non-cleavable Linker (unstable)
- Uncontrollable DAR

2nd Generation
T-DM1

- Humanised MABs (IgG1)
- Moderate potency payload
- Random conjugation
- Increased DAR
- Stable non-cleavable Linker

3rd Generation
Sacituzumab, T-DXd

- Better MABs, Fab-fragments
- More potent payloads
- Site-specific conjugation
- Consistent, high DAR
- Cleavable Linker
- Bystander Effect

Next Generation?

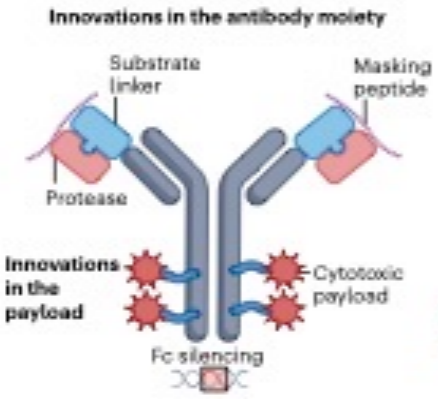
- Fab-fragments? Bispecifics?
- Fc silencing
- Probody-DCs: AG-masking
- Site-specific conjugation
- Different payload
- Combination of payloads

1980 1990 2000 2010 2015 2020

Pros/Contras
- Heterogeneity
- Low efficacy
- Narrow therapeutic index
- Off-target effects
- High immunogenicity

Pros/Contras
- Improved targeting
- More potent payload
- Lower immunogenicity
- Heterogeneity
- Fast clearance for high DARs
- Off-target effects (early release)
- Drug resistance

Pros/Contras
- Higher efficacy, even with lower antigen expression
- More potent payload
- Less off-target toxicity

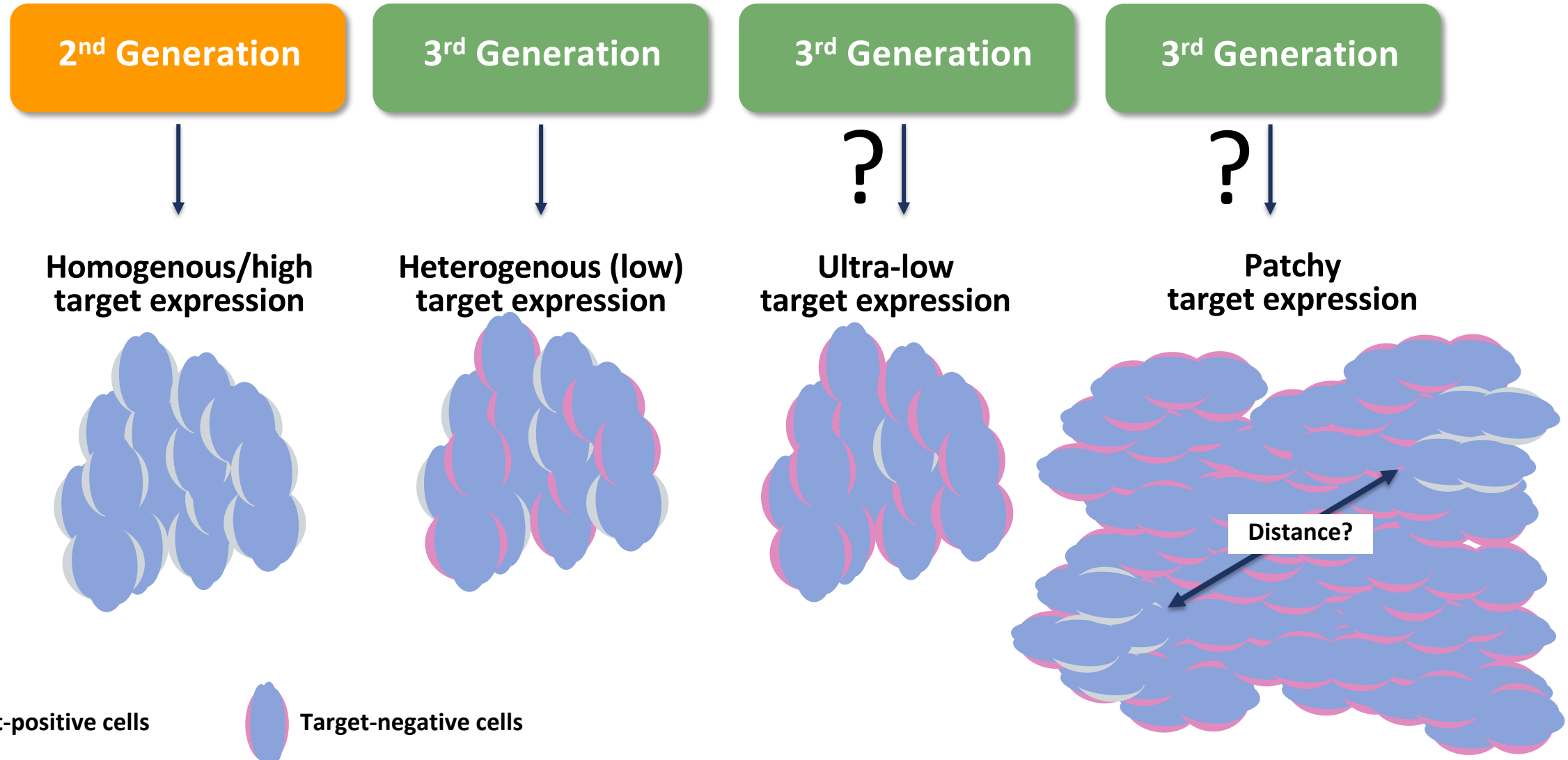


Schmid P, Personal Communication

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Chau, et al, Lancet 2019; Fu, et al, Signal Transduction Targeted Therapy 2022, Tarantino et al, Nat Rev Clin Oncol 2023

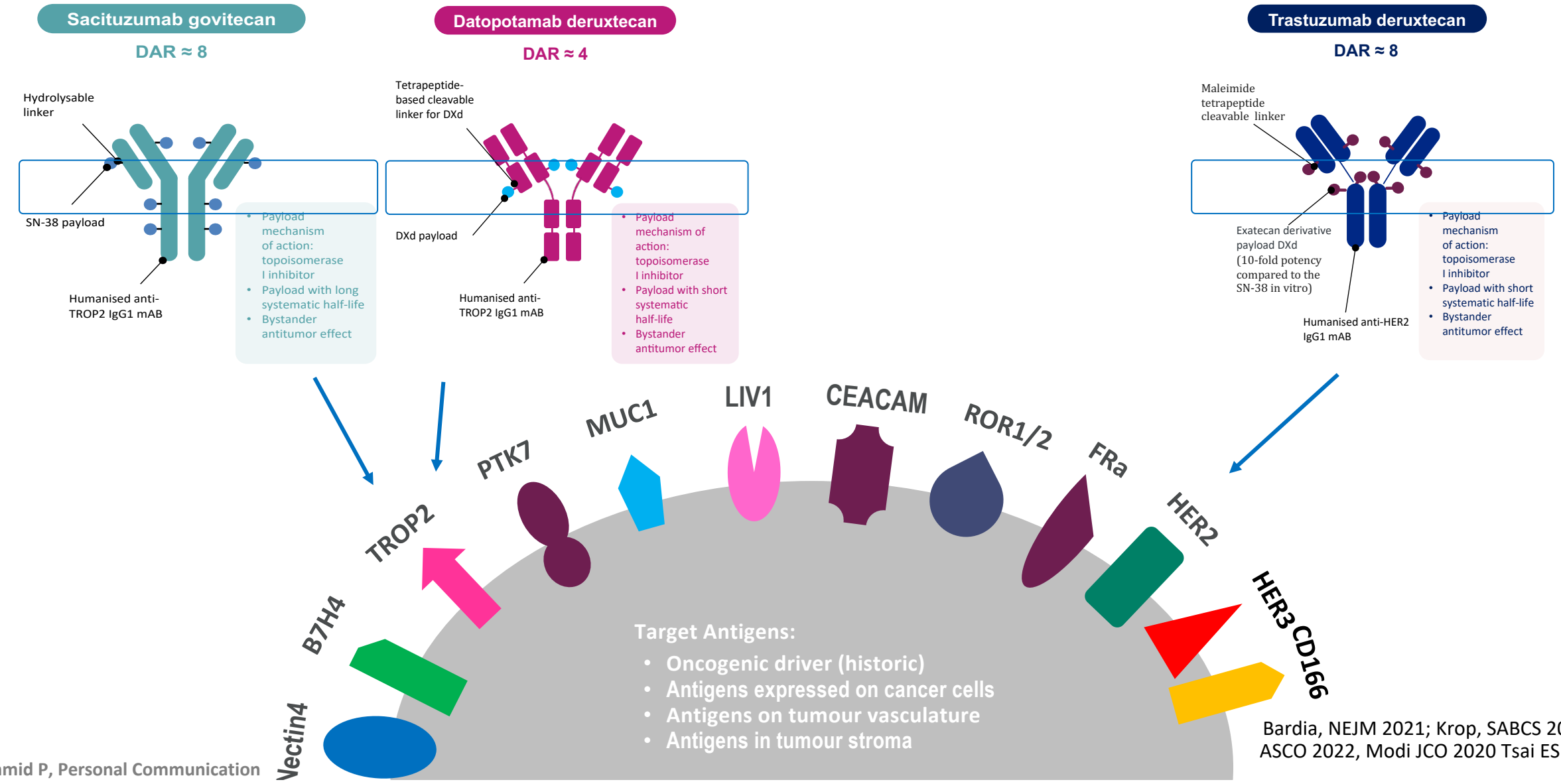
Target Expression and ADC activity



Schmid P, Personal Communication

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Targets for Antibody-Drug Conjugates in Breast Cancer



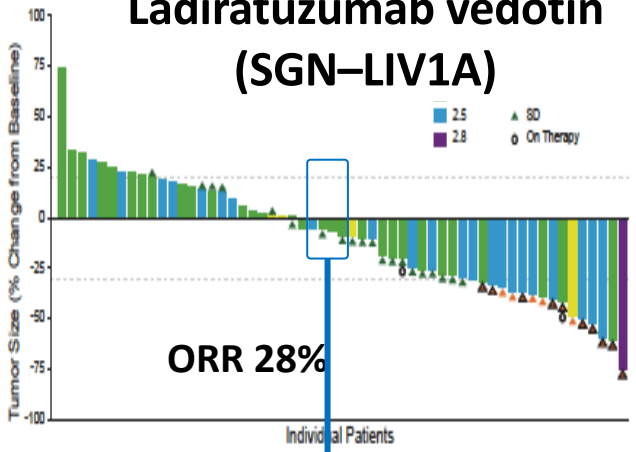
Schmid P, Personal Communication

Bardia, NEJM 2021; Krop, SABCS 2021, Krop ASCO 2022, Modi JCO 2020 Tsai ESMO 2021

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

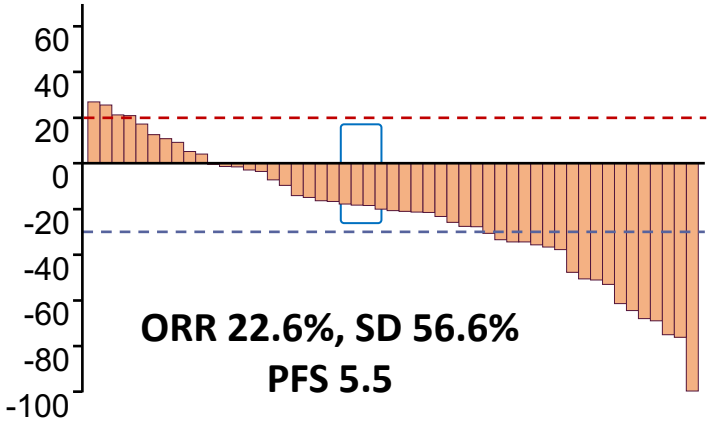
Targets for Antibody-Drug Conjugates in Breast Cancer

Ladiratuzumab vedotin (SGN–LIV1A)

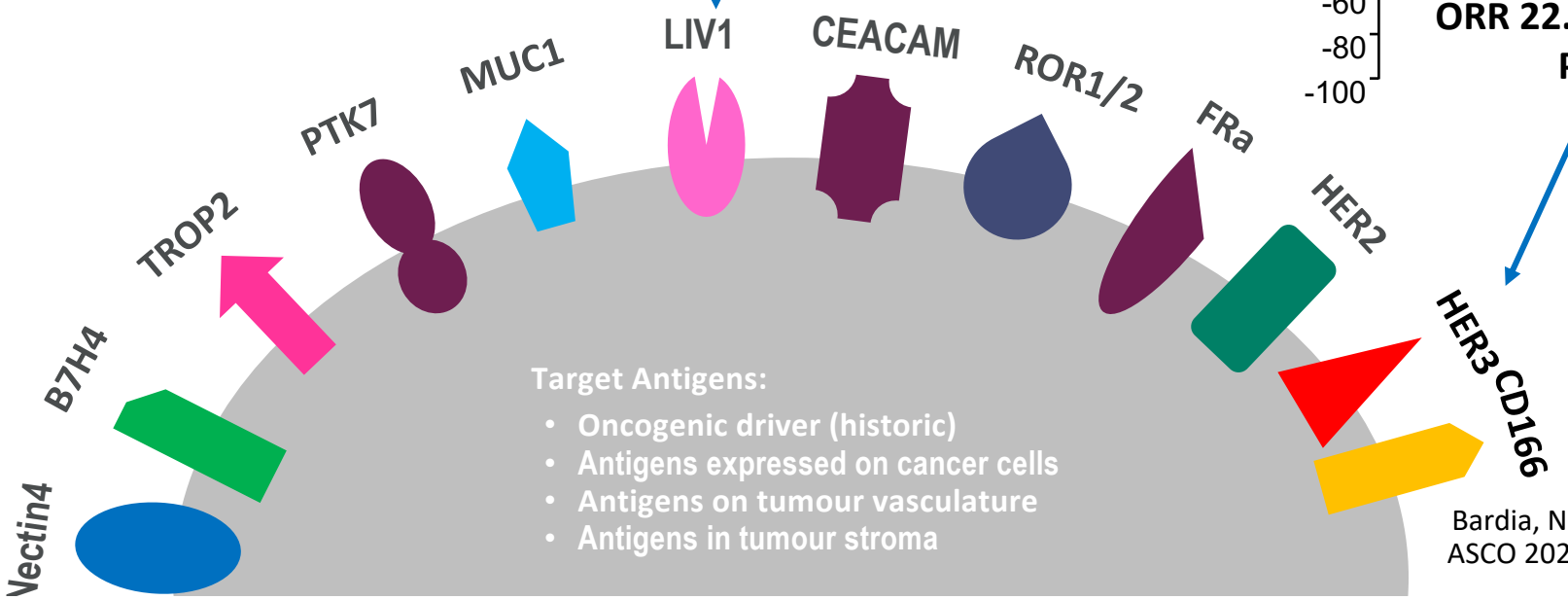


ORR 28%

Patritumab DXd



ORR 22.6%, SD 56.6%
PFS 5.5



Target Antigens:

- Oncogenic driver (historic)
- Antigens expressed on cancer cells
- Antigens on tumour vasculature
- Antigens in tumour stroma

Schmid P, Personal Communication

Bardia, NEJM 2021; Krop, SABCS 2021, Krop ASCO 2022, Modi JCO 2020 Tsai ESMO 2021

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Landscape of ADCs in HER2-negative MBC

	HR+/HER2- BC				TNBC	
ADC trials in MBC	**DESTINY-Breast06**	**DESTINY-Breast04**	**TROPION-Breast01**	**TROPiCS-02**	**DESTINY-Breast04**	**ASCENT**
Treatment arms	T-DXd (HER2) vs TPC	T-DXd (HER2) vs TPC	Dato-DXd (TROP2) vs TPC	SG (TROP2) vs TPC	T-DXd (HER2) vs. TPC	SG (TROP2) vs. TPC
HER2 status	>0 <1+, 1+, 2+/ISH-	1+, 2+/ISH-	0, 1+, 2+/ISH-	0, 1+, 2+/ISH-	1+, 2+/ISH-	0, 1+, 2+/ISH-
Prior chemotherapy for MBC	**0**	**1-2**	**1-2**	**2-4**	**1-2**	**≥1**
Median PFS HR (95% CI)	13.2 vs 8.1 mo. HR 0.63 (0.53-0.75)	9.6 vs 4.2 mo. HR 0.37 (0.30-0.56)	6.9 vs 4.9 mo. HR 0.63 (0.52-0.76)	5.5 vs 4.0 mo. HR 0.65 (0.53-0.81)	6.3 vs 2.9 mo. HR 0.29 (0.15-0.57)	5.6 vs 1.7 mo. HR: 0.41 (0.32-0.52)
Median OS HR (95% CI)	N/A HR 0.81 (0.65-1.00)	23.9 vs 17.6 mo. HR 0.69 (0.55-0.87)	N/A HR 0.84 (0.62–1.14)	14.5 vs 11.2 mo. HR 0.79 (0.65-0.95)	17.1 vs 8.3 mo. HR 0.58 (0.31-1.08)	12.1 vs 6.7 mo. 0.48 (0.38-0.59)
ORR	57.3% vs 31.2%	52.6% vs 16.3%	36.4% vs 22.9%	21% vs 14%	50.0% vs 16.7%	35% vs 5%

1. Is there a preferred initial ADC?

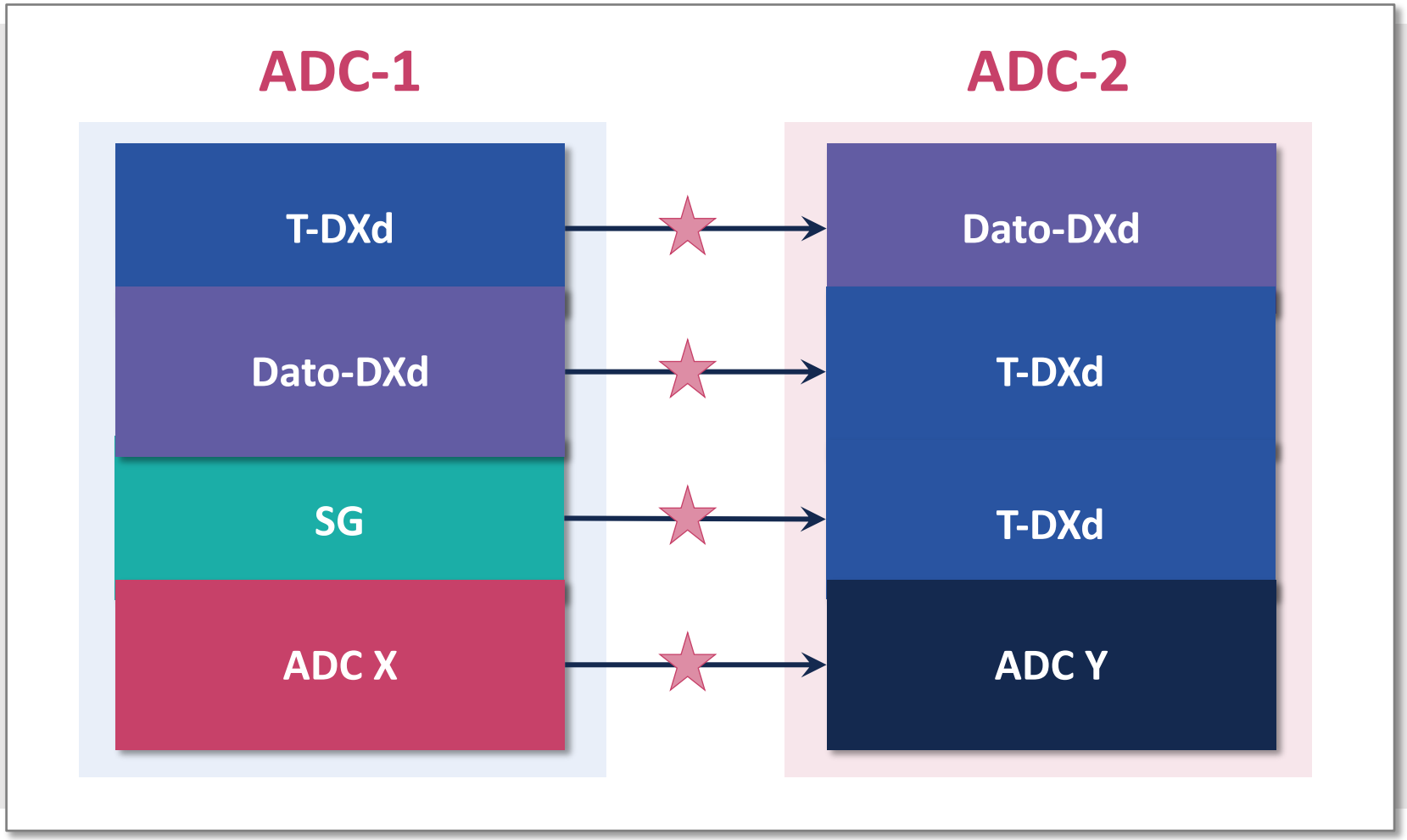
2. Is there a role for sequencing of ADCs?

Modified from Garrido-Castro AC. SABCS 2023; Curigliano G et al. ASCO 2024; Modi S et al. ESMO 2023; Bardia A et al. ESMO 2023; Tolaney S et al. ASCO 2023; Bardia A et al. N Engl J Med 2021;384:1529-41.

Courtesy of Sara M Tolaney, MD, MPH

Critical Question

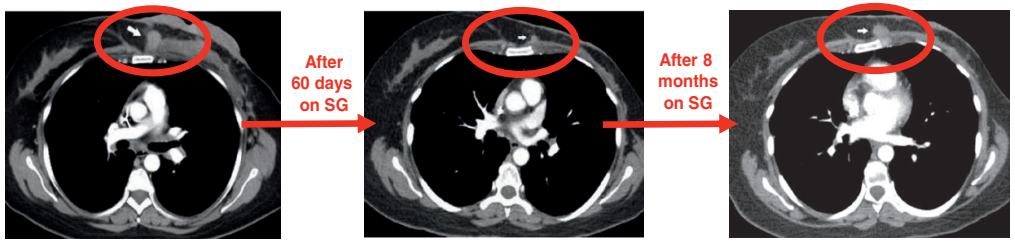
How will ADCs work in sequence?



Courtesy of Sara M Tolaney, MD, MPH

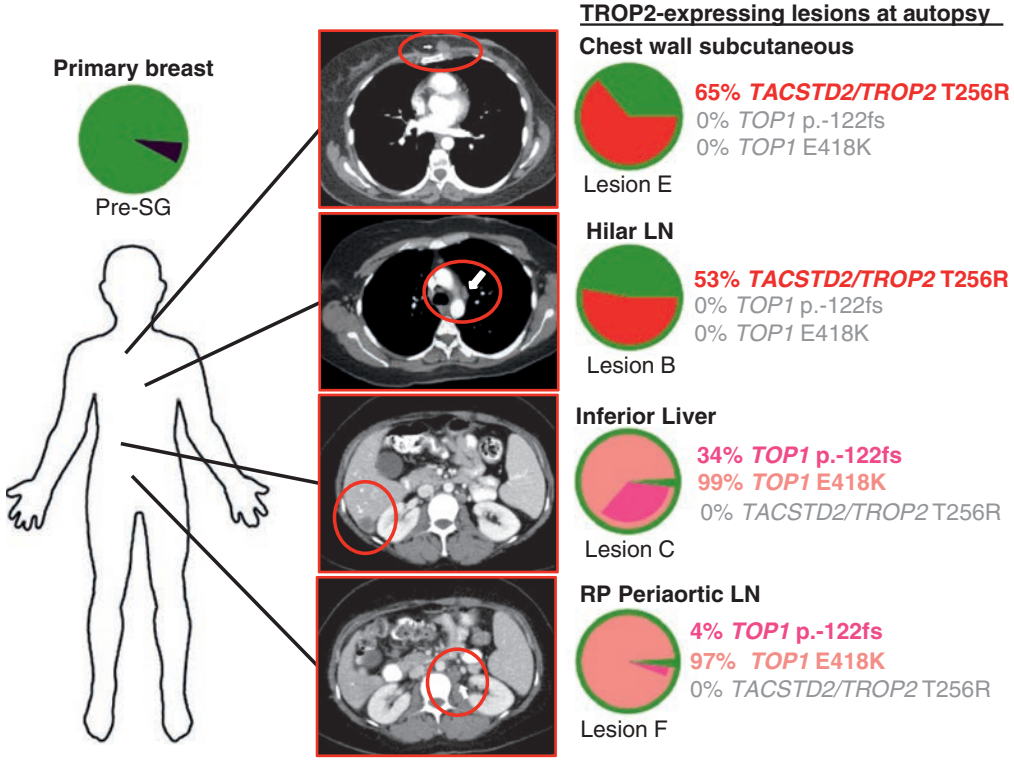
Resistance to ADCs

Serial biopsies of tumour lesions at progression on Sacituzumab



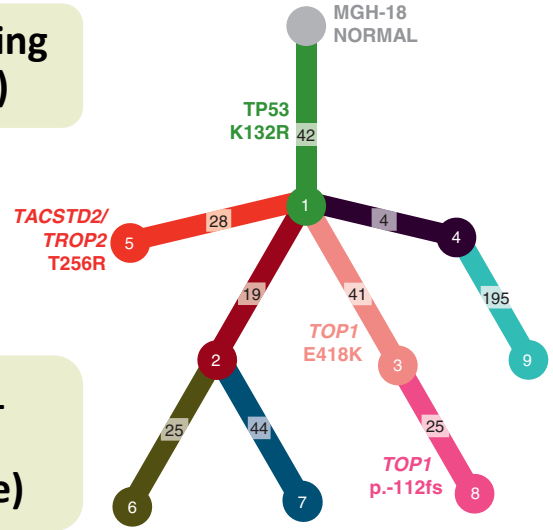
Resistance to Payload and/or Target:

- Resistance can be subclonal -> targeted Tx for Oligo-progression
- Rational sequences
- Combination of payloads and/or Targets
- Combination with immunotherapy



Altered TROP2 binding (Target resistance)

Failed SN38/TOP1 binding (Payload resistance)



Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Coates et al, Cancer Discovery 2021

Do you generally avoid administering 2 ADCs _____ after each other?

	Of any type	With the same target	With the same payload
 Prof Schmid	No	Yes	No
 Dr Tolaney	No	No	No
 Dr Brufsky	No	Yes	No
 Dr Burstein	No	No	Yes
 Dr Jhaveri	No	No	Yes
 Dr Spring	No	Yes	Yes

Regulatory and reimbursement issues aside, what would be your preferred next 2 lines of systemic therapy for a patient with ER-positive, HER2-negative (IHC = 0) mBC and disease progression on endocrine therapy then capecitabine?

	1st subsequent systemic treatment	2nd subsequent systemic treatment
 Prof Schmid	Sacituzumab govitecan	Paclitaxel
 Dr Tolaney	Sacituzumab govitecan	Paclitaxel
 Dr Brufsky	Sacituzumab govitecan	Eribulin
 Dr Burstein	Paclitaxel	—
 Dr Jhaveri	Datopotamab deruxtecan	Eribulin
 Dr Spring	Sacituzumab govitecan	Eribulin

Regulatory and reimbursement issues aside, what would be your preferred next 2 lines of systemic therapy for a patient with ER-positive, HER2-low mBC and disease progression on endocrine therapy then capecitabine?

	1st subsequent systemic treatment	2nd subsequent systemic treatment
 Prof Schmid	Trastuzumab deruxtecan	Sacituzumab govitecan
 Dr Tolaney	Trastuzumab deruxtecan	Paclitaxel or sacituzumab govitecan
 Dr Brufsky	Trastuzumab deruxtecan	Sacituzumab govitecan
 Dr Burstein	Trastuzumab deruxtecan	—
 Dr Jhaveri	Trastuzumab deruxtecan	Eribulin
 Dr Spring	Trastuzumab deruxtecan	Sacituzumab govitecan

Regulatory and reimbursement issues aside, what would be your preferred next 2 lines of systemic therapy for a patient with ER-negative, HER2-negative (IHC = 0) mBC and disease progression on anthracycline and taxane?

	1st subsequent systemic treatment	2nd subsequent systemic treatment
 Prof Schmid	Sacituzumab govitecan	Eribulin
 Dr Tolaney	Sacituzumab govitecan	Eribulin
 Dr Brufsky	Sacituzumab govitecan	Eribulin
 Dr Burstein	Sacituzumab govitecan	—
 Dr Jhaveri	Would depend on PD-L1 status, if treated with KN-522, TFI from pembrolizumab	Would depend on PD-L1 status, if treated with KN-522, TFI from pembrolizumab
 Dr Spring	Sacituzumab govitecan	Eribulin

TFI = treatment-free interval

Regulatory and reimbursement issues aside, what would be your preferred next 2 lines of systemic therapy for a patient with ER-negative, HER2-low mBC and disease progression on anthracycline and taxane?

	1st subsequent systemic treatment	2nd subsequent systemic treatment
 Prof Schmid	Sacituzumab govitecan	Trastuzumab deruxtecan
 Dr Tolaney	Sacituzumab govitecan	Trastuzumab deruxtecan
 Dr Brufsky	Sacituzumab govitecan	Trastuzumab deruxtecan
 Dr Burstein	Sacituzumab govitecan	—
 Dr Jhaveri	—	—
 Dr Spring	Sacituzumab govitecan	Trastuzumab deruxtecan

Agenda

Introduction: Pharmacology and Sequencing of Antibody-Drug Conjugates (ADCs) in Metastatic Breast Cancer (mBC)

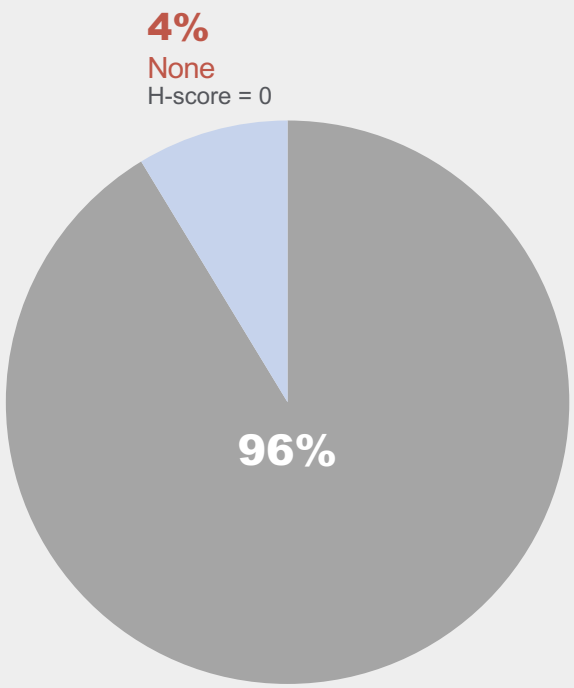
Module 1: Expanding Role of TROP2-Directed ADCs in mBC Management — Dr Tolaney

Module 2: Other Targets for ADC Therapy in mBC — Prof Schmid

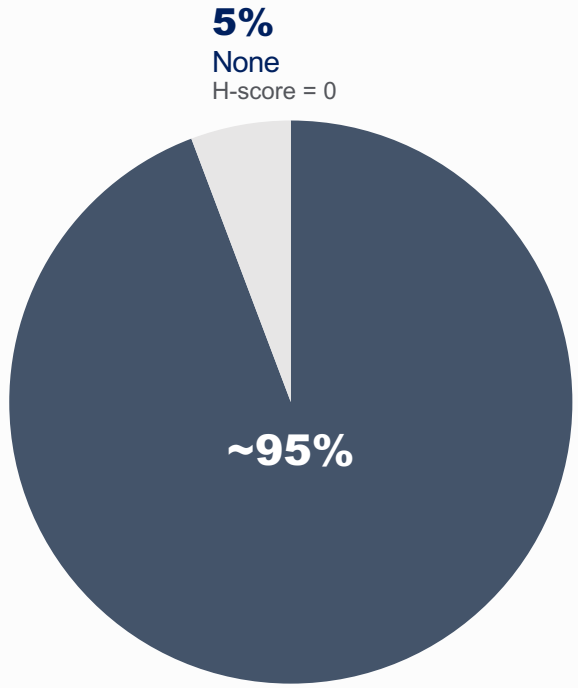
High Trop-2 Expression in mTNBC and HR+/HER2- mBC[1-3]

Trop-2 is expressed in **96% of patients with mTNBC[1-2]** and approximately **95% of patients with HR+/HER2- mBC[3]**

Trop-2 Expression in Patients with mTNBC (N=290)*,†[1-2]



Trop-2 Expression in Patients with HR+/HER2- mBC (N=238)‡ § [3]



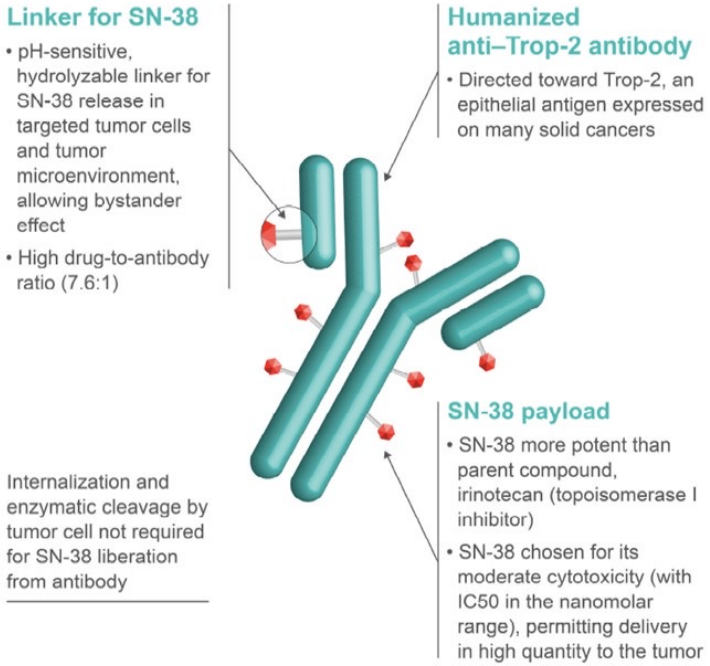
High Trop-2 expression rates suggest that **pre-therapy biomarker assessment is not required[1-3].**

*Trop-2 expression was determined on primary or metastatic archival tumour tissue; †Trop-2 expression was measured using a validated IHC assay in a central laboratory. ‡Trop-2 expression was determined on primary or metastatic archival tumour tissue; §membrane Trop-2 expression was assessed by a validated research IHC assay at a CAP/CLIA central laboratory. HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; H-score, histochemical score; IHC, immunohistochemistry; mBC, metastatic breast cancer; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen-2. 1. Hurvitz SA, et al. SABCS [virtual meeting]. 2020 (oral presentation GS3-06); 2. Bardia A, et al. *Ann Oncol*. 2021;32(9):1148–1156; 3. Rugo HS, et al. SABCS 2022. Oral presentation GS1-11.

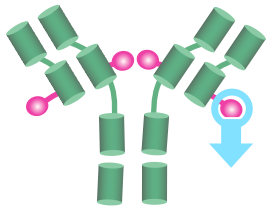
Courtesy of Sara M Tolaney, MD, MPH

ADCS ANTI-TROP2 IN MBC

Sacituzumab govitecan

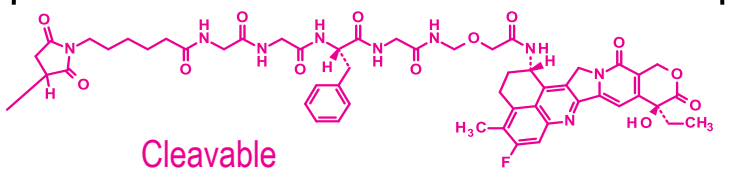


Datopotamab deruxtecan



- Payload mechanism of action: Topo-I inhibitor*
- High potency payload*
- Optimised drug to antibody ratio ≈4*†
- Payload with short systemic half-life*†
- Stable linker-payload*
- Tumour-selective cleavable linker*
- Bystander antitumour effect*

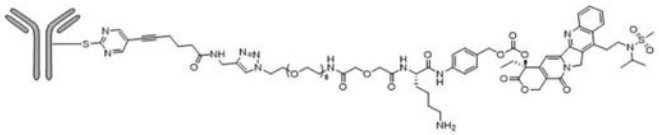
Deruxtecan



Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

Sacituzumab Tirumotecan (MK-2870)



- anti-TROP2 ADC
- Sulfonyl pyrimidine-CL2A-carbonate linker
- **Payload**: belotecan-derivative topoisomerase I inhibitor
- **DAR**: 7.4

Courtesy of Sara M Tolaney, MD, MPH

Curigliano G et al, ESMO Breast 2024

ASCENT:

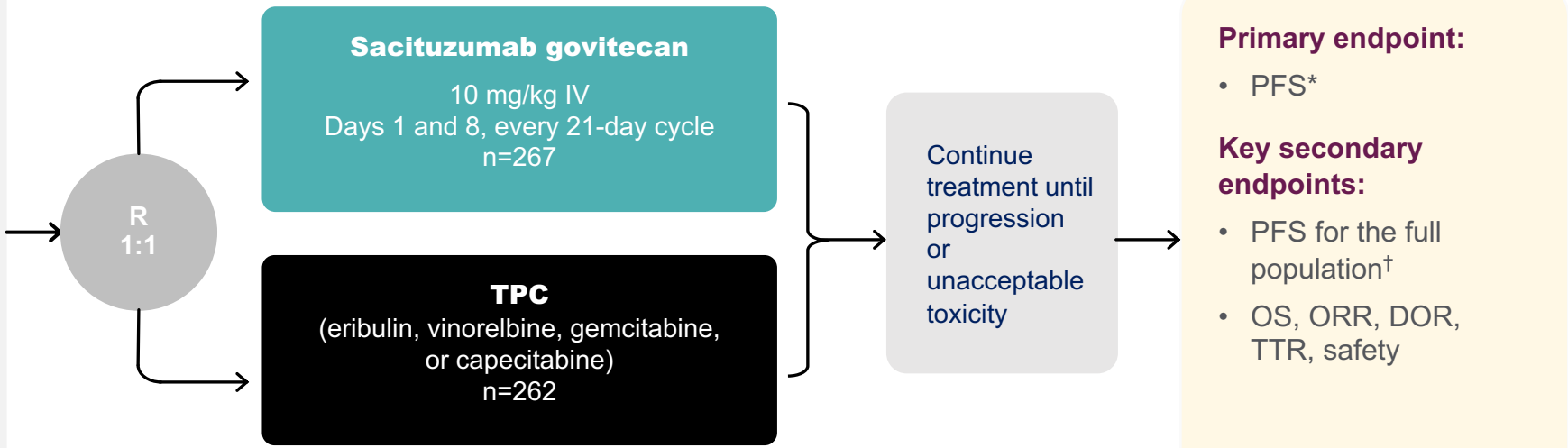
Phase 3 confirmatory study of sacituzumab govitecan vs TPC in 2L and later mTNBC[1,2]

NCT02574455

Metastatic TNBC
As per ASCO/CAP including HER2 IHC-0, IHC 1+ and IHC 2+ with ISH-

- ≥2 chemotherapies for advanced disease
- One of the required prior regimens could be from progression that occurred within a 12-month period after completion of neoadjuvant therapy
- Patients with stable brain metastases were allowed

N=529



Stratification factors
- Number of prior chemotherapies (2–3 vs >3)
- Geographic region (North America vs Europe)
- Known brain metastases (yes/no)

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

*PFS measured by an independent, centralised, and blinded group of radiology experts who assessed tumour response using RECIST 1.1 criteria in patients without brain metastasis. †The full population includes all randomised 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; CT, chemotherapy; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; ISH, *in-situ* hybridisation; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; TPC, treatment of physician's choice; TTR, time to response.

1. Adapted from Bardia A, et al. ESMO 2020. Abstract LBA17; 2. Adapted from Bardia A, et al. *N Engl J Med*. 2021;384(16):1529–1541.

Courtesy of Sara M Tolaney, MD, MPH

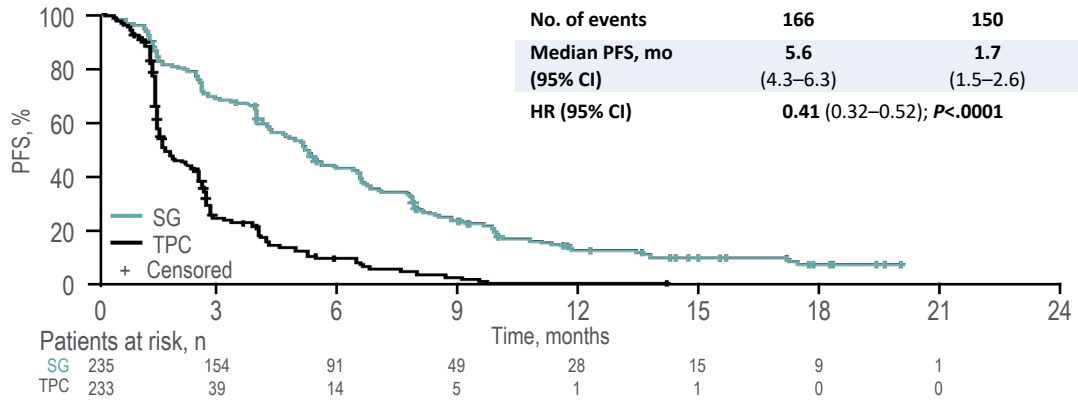
ASCENT

Sacituzumab govitecan demonstrated statistically significant and clinically meaningful improvement in PFS and OS that was consistent in the ITT and primary study population[1,2]

Primary study population[1,2]

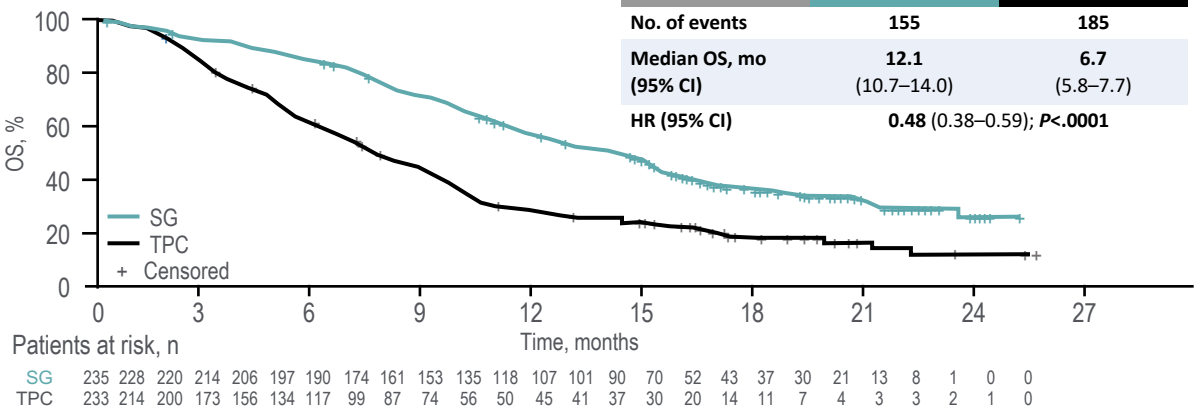
PFS

BICR analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS, mo (95% CI)	5.6 (4.3–6.3)	1.7 (1.5–2.6)
HR (95% CI)	0.41 (0.32–0.52); *P*<.0001	



OS

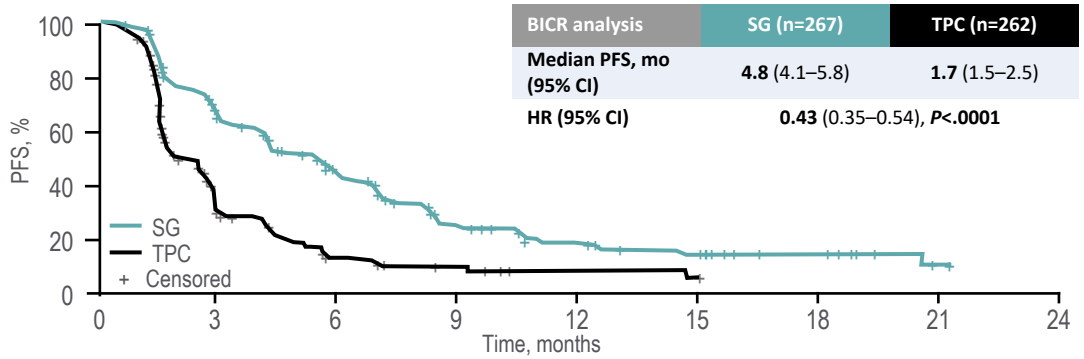
BICR analysis	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS, mo (95% CI)	12.1 (10.7–14.0)	6.7 (5.8–7.7)
HR (95% CI)	0.48 (0.38–0.59); *P*<.0001	



ITT (overall population)[1,2]

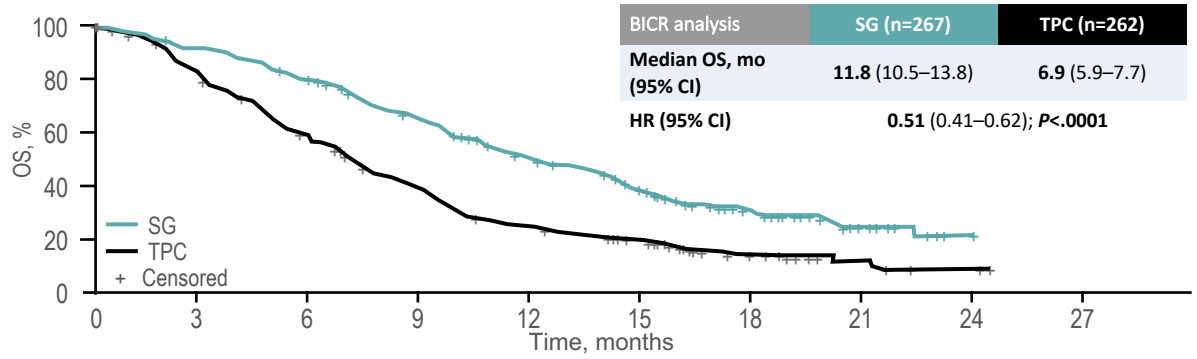
PFS

BICR analysis	SG (n=267)	TPC (n=262)
Median PFS, mo (95% CI)	4.8 (4.1–5.8)	1.7 (1.5–2.5)
HR (95% CI)	0.43 (0.35–0.54), *P*<.0001	



OS

BICR analysis	SG (n=267)	TPC (n=262)
Median OS, mo (95% CI)	11.8 (10.5–13.8)	6.9 (5.9–7.7)
HR (95% CI)	0.51 (0.41–0.62); *P*<.0001	



Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as predefined in the study protocol. Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35–0.54], P<.0001).

ADC, antibody–drug conjugate; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, month; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell-surface antigen 2. 1. Adapted from Bardia A, et al. *N Engl J Med*. 2021;384(16):1529–1541; 2. Adapted from Bardia A, et al. *N Engl J Med*. 2021;384(16):1529–1541 (Supplementary data, Figure S7).

Courtesy of Sara M Tolaney, MD, MPH

ASCENT

Sacituzumab govitecan demonstrated manageable safety profile: Neutropenia and diarrhoea were the most common treatment-related AEs[1]

TRAE*[1]		SG (n=258)			TPC (n=224)		
		All grade, %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	**Neutropenia†**	**63**	**34**	**17**	**43**	**20**	**13**
	Anaemia‡	34	8	0	24	5	0
	Leukopenia§	16	9	1	11	4	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhoea**	**59**	**10**	**0**	**12**	**<1**	**0**
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhoea (10% vs <1%), leukopenia (10% vs 5%), anaemia (8% vs 5%) and febrile neutropenia (6% vs 2%)

- **G-CSF usage was 49% in the SG arm vs 23% in the TPC arm – dose reductions due to TRAEs were similar (22% SG vs 26% TPC)**
- **No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG**
- **No treatment-related deaths with SG**; 1 treatment-related death (neutropenic sepsis) with TPC
- **AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%**

*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of "Neutropenia" and "Decreased neutrophil count." Due to overlapping reporting of events for these combined terms, all grades reported are not shown for the SG arm: Grade 1: 19%; Grade 2: 37%; Grade ≥3: 51%. ‡Combined preferred terms of "Anaemia" and "Decreased hemoglobin." §Combined preferred terms of "Leukopenia" and "Decreased white blood cell count."

AE, adverse event; G-CSF, granulocyte-colony stimulating factor; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE. 1. Adapted from Bardia A, et al. *N Engl J Med*. 2021;384(16):1529–1541.

Courtesy of Sara M Tolaney, MD, MPH

ASCENT-03: Sacituzumab govitecan vs TPC in 1L PD-L1– mTNBC NCT05382299

1L mTNBC PD-L1–

- Previously untreated, inoperable, locally advanced, or metastatic TNBC
- PD-L1– tumors (CPS <10, IHC 22C3 assay) OR PD-L1+ tumors (CPS ≥10, IHC 22C3 assay) if treated with anti-PD-(L)1 agent in the curative setting
- ≥6 months since treatment in curative setting
- Prior anti-PD-(L)1 agent allowed in the curative setting
- PD-L1 and TNBC status centrally confirmed

1:1

N=540
(≤25% *de novo*)

Sacituzumab govitecan
10 mg/kg IV on days 1 and 8 of 21-day cycles

TPC chemotherapy
Gem + carbo: gem 1000 mg/m^2 with carbo AUC 2 IV on days 1 and 8 of 21-day cycles
Paclitaxel: 90 mg/m^2 IV on days 1, 8, and 15 of 28-day cycles
Nab-paclitaxel: 100 mg/m^2 IV on days 1, 8, and 15 of 28-day cycles

Treated until BICR-confirmed progression or unacceptable toxicity

Crossover to SG allowed after BICR-verified disease progression

Long-term follow-up

Stratification Factors:

- *De novo* vs recurrent disease within 6-12 months of treatment in the curative setting vs recurrent disease >12 months after treatment in the curative setting
- Geographic region

BICR, blinded independent central review; CPS, combined positive score; IHC, immunohistochemistry; mTNBC, metastatic triple negative breast cancer; PD-L1, programmed death ligand 1; R, randomized; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. EU Clinical trial register: EudraCT: 2021-005743-79. https://www.clinicaltrialsregister.eu/ctr-search/search/ Accessed April 2022.

Courtesy of Sara M Tolaney, MD, MPH

TROPiCS-02:

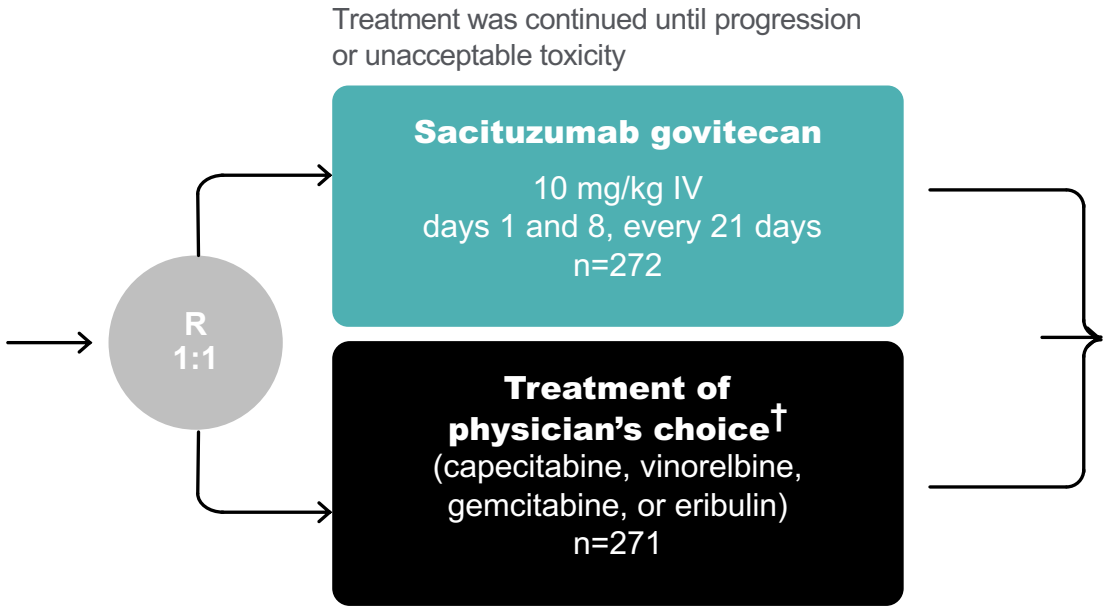
A Phase 3 Study of SG in pre-treated HR+/HER2- (IHC0, IHC1+, IHC2+/ISH-) locally recurrent inoperable or metastatic breast cancer[1,2]

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after*

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N=543

NCT03901339



Endpoints

Primary

- PFS by BICR

Secondary

- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

*Disease histology based on the ASCO/CAP criteria. †Single-agent standard-of-care treatment of physician's choice was specified prior to randomisation by the investigator.

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; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcome; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours.

1. Adapted from Rugo H, et al. ESMO 2022. Oral LBA76; 2. Rugo HS, et al. J Clin Oncol. 2022;40:3365–3376.

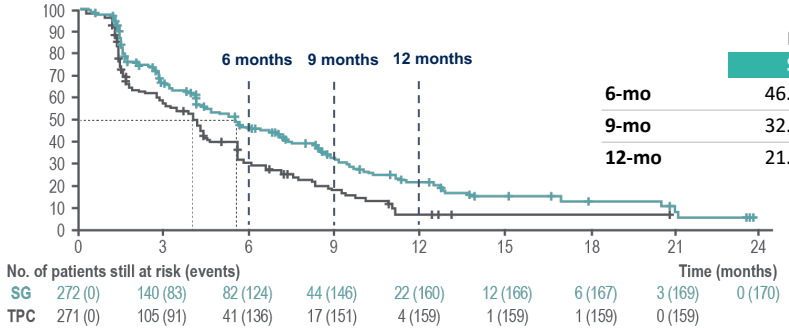
Courtesy of Sara M Tolaney, MD, MPH

TROPiCS-02:

Sacituzumab govitecan demonstrated a statistically significant and clinically meaningful improvement in PFS and OS vs chemotherapy, with continued improvement confirmed with longer follow-up[1–4]

PFS[1,2]

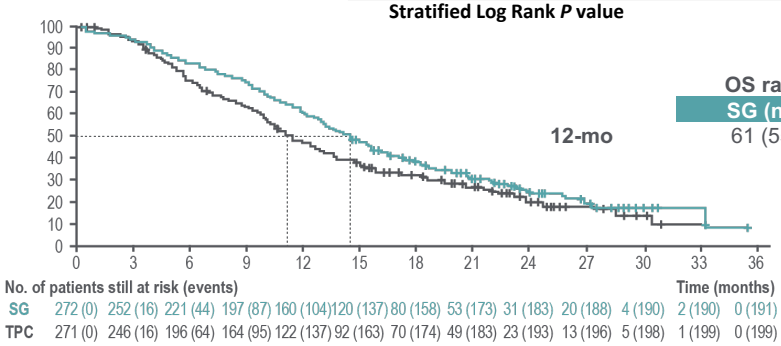
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

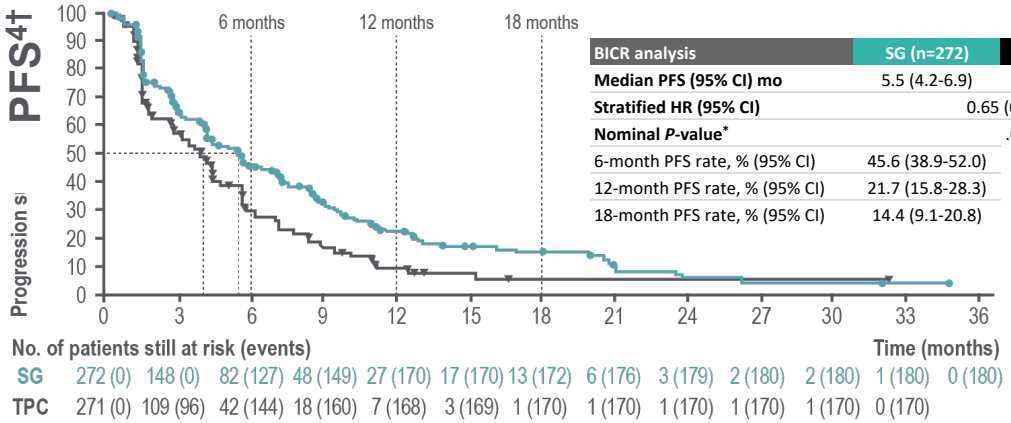
OS[3]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	.020	



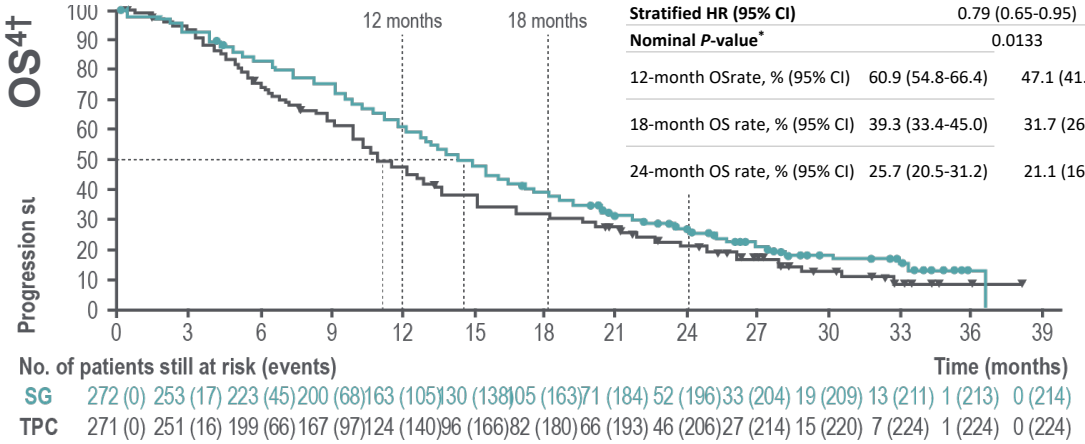
OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

PFS4†



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*	.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)

OS4†



BICR analysis	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*	0.0133	
12-month OSrate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-5302)
18-month OS rate, % (95% CI)	39.3 (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)

*Stratified log rank *P*-value. # Primary endpoint (PFS) assessed by blinded independent central review in the ITT study population, as predefined in the study protocol. Secondary endpoint (OS). † PFS and OS exploratory analysis with an extended follow-up of ~13 months. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice, ITT, intent-to-treat.

1. Adapted from Rugo HS, et al. *J Clin Oncol.* 2022;40:3365–3376; 2. Adapted from Rugo H, et al. ESMO 2022. Oral LBA76; 3. Adapted from Rugo H, et al. *Lancet.* 2023;S0140-6736(23)01245-X. 4. Tolaney S, et al. ASCO 2023. Abstract #1003.

Courtesy of Sara M Tolaney, MD, MPH

ASCENT-07 Ongoing

A Phase 3, Randomized, Open-label Study of SG vs TPC in Patients with HR+/HER2-negative (IHC 0, IHC 1+, IHC 2+/ISH Negative) Inoperable, Locally Advanced, or Metastatic BC and Have Received ET

Key Eligibility Criteria

- HR+/HER2-negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced or metastatic breast cancer
- No prior treatment with topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Patients must have one of the following
  - Disease progression on ≥2 previous lines of ET with or without a targeted therapy in the metastatic setting
    - Disease recurrence while on the first 24 months of starting adjuvant ET will be considered a line of therapy; these patients will only require 1 line of ET in the metastatic setting
  - Disease progression within 6 months of starting first-line ET with or without a CDK4/6i in the metastatic setting
  - Disease recurrence while on the first 24 months of starting adjuvant ET with CDK4/6i and if the patient is no longer a candidate for additional ET in the metastatic setting as determined by the investigator

R

N~654

Sacituzumab govitecan
10 mg/kg IV
Days 1 and 8, every 21 days

TPC
(capecitabine, paclitaxel, nab-paclitaxel)

Primary Endpoint

- PFS by BICR

Key Secondary Endpoints

- OS
- ORR by BICR
- Change from baseline in physical functioning and TTD of Global Health Status

Secondary Endpoints

- PFS by investigator
- ORR by investigator
- DoR
- Safety

NCT05840211—full participation criteria available at ClinicalTrials.gov

Stratification Factors

- Duration of prior CDK 4/6i in the metastatic setting (none vs ≤12 months vs >12 months)
- HER2 (HER2 IHC 0 vs HER2 IHC-low [IHC 1+; 2+/ISH negative])
- Geographic region (US/CAN/UK/EU vs ROW)

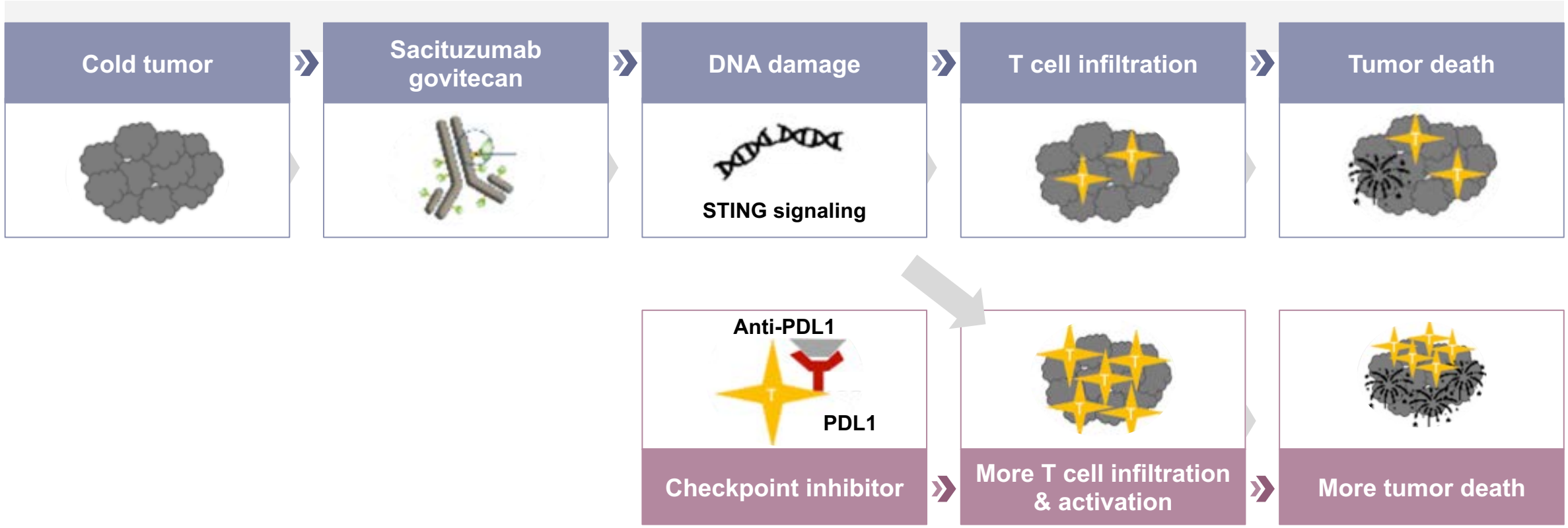
Courtesy of Sara M Tolaney, MD, MPH

Case Presentation – Dr Tolaney: A 55-year-old woman with previously treated HR-positive, HER2-negative mBC

- 55 yo female who was diagnosed with T2 N1 ER+ breast cancer; received ddACT followed by AI + palbociclib (on PALLAS trial)
- 3.5 yrs after diagnosis, developed transaminitis, and found to have liver metastases
- Liver Biopsy: ER+ PR- HER2 1+ ; NGS: high TMB (no PI3Km, no ESR1m)
- Started fulvestrant + abemaciclib; liver enzymes rose further
- Went onto capecitabine, with improvement in LFTs in just 2-3 wks, and remained on it for 13 months
- Developed disease progression with worsening bone and liver mets
- Enrolled onto a clinical trial (SACI IO HR+) and was randomized to sacituzumab govitecan monotherapy; had a response (-45% by RECIST); has been on study for 12 months and is developing slight progression in her liver (LFTs stable)

COMBINING SACITUZUMAB GOVITECAN WITH CHECKPOINT INHIBITION

Hypothesis: Sacituzumab govitecan induces DNA damage and results in STING activation, efficacy will be enhanced by checkpoint inhibition



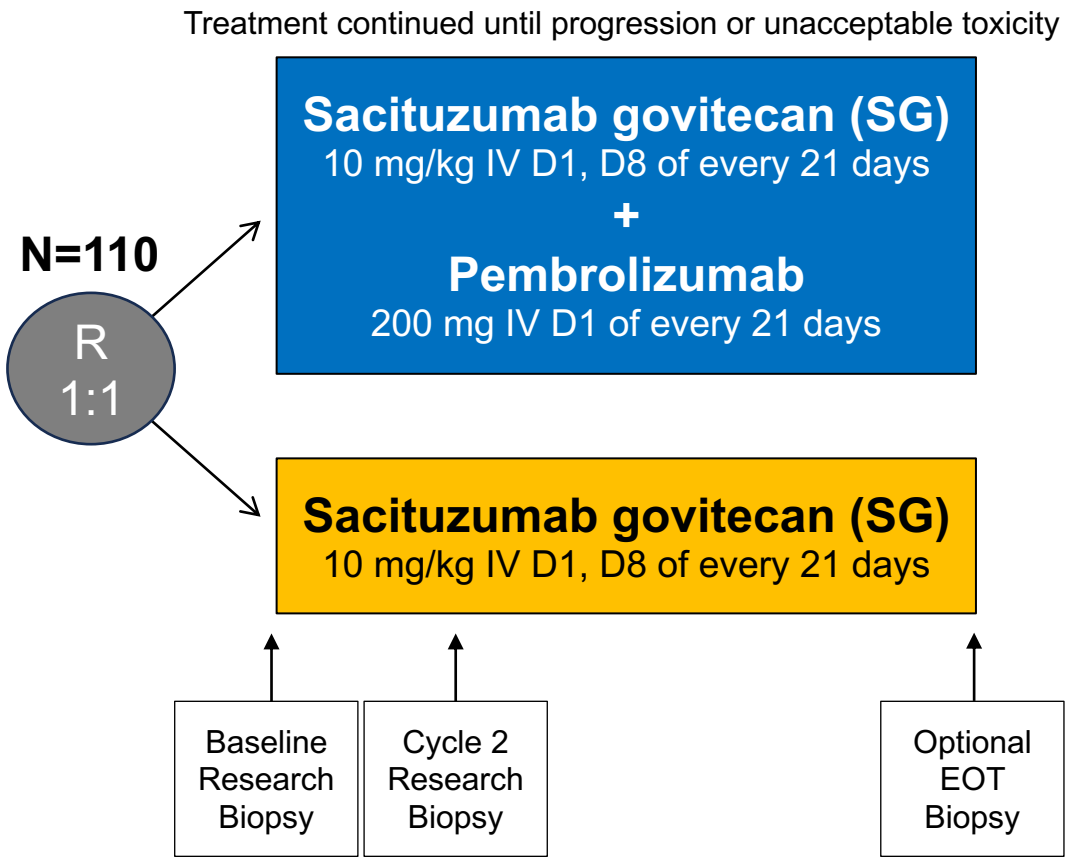
Sara M. Tolaney, MD, MPH

Courtesy of Sara M Tolaney, MD, MPH

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

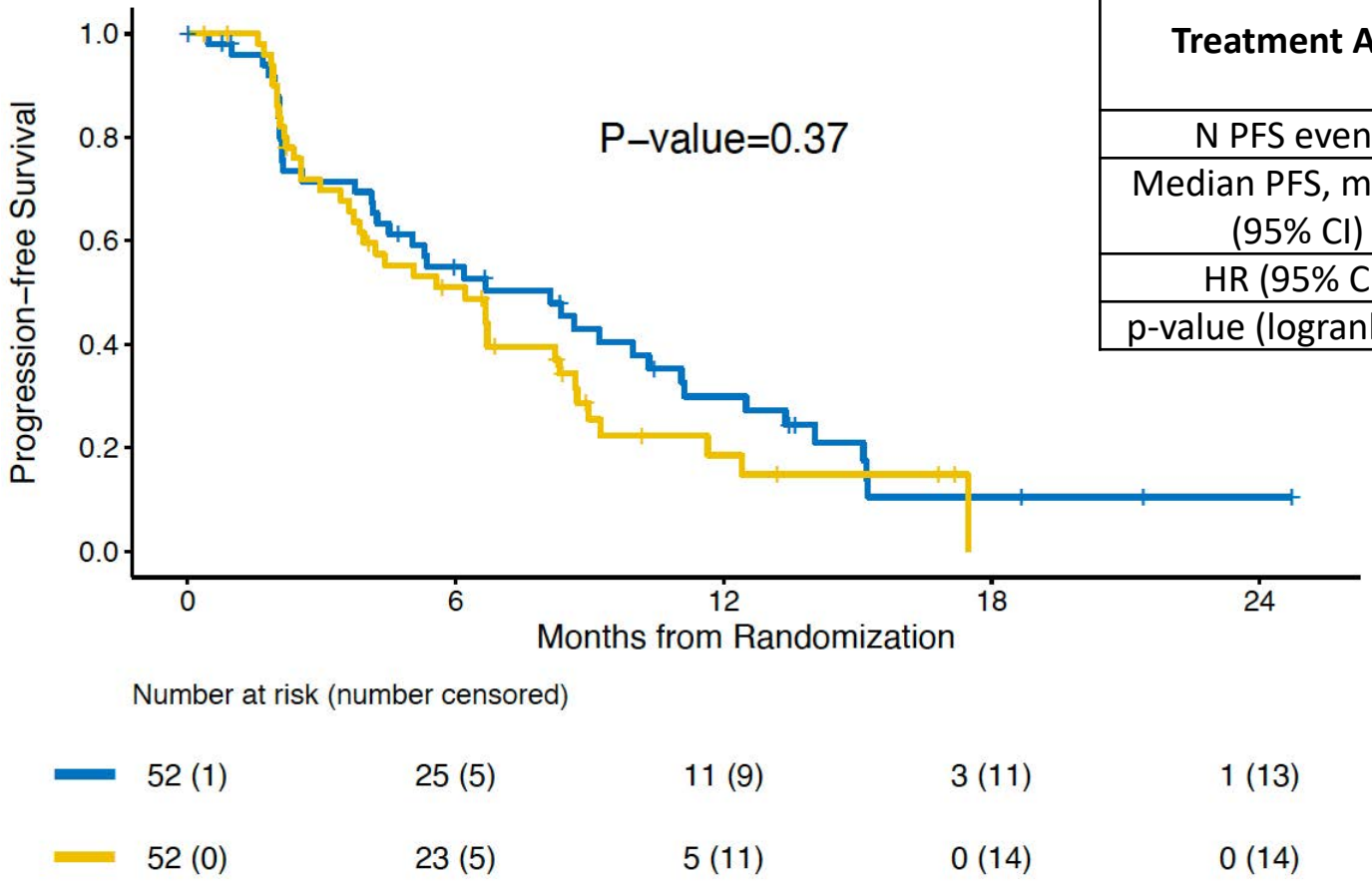
NCT04448886

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.

Ana C. Garrido-Castro, M.D. ASCO 2024;Abstract LBA1004.

Courtesy of Sara M Tolaney, MD, MPH

SACI-IO HR+: Progression-Free Survival



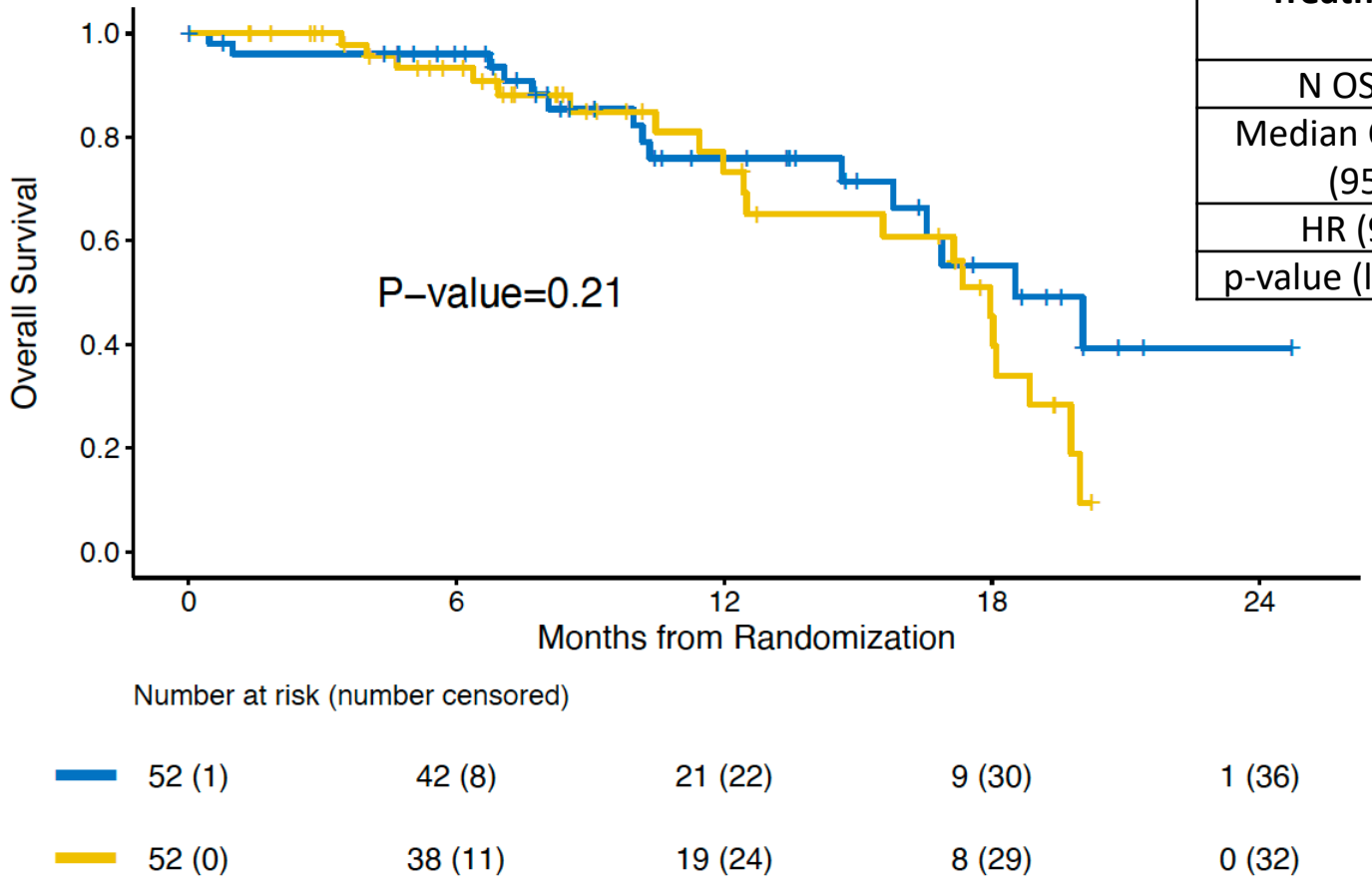
Treatment Arm	SG + Pembrolizumab (N=52)	SG (N=52)
N PFS events	38	38
Median PFS, months (95% CI)	**8.12** (4.51-11.12)	**6.22** (3.85-8.68)
HR (95% CI)	**0.81** (0.51-1.28)	
p-value (logrank test)	0.37	

The addition of pembrolizumab to SG showed a numerical improvement in median PFS (Δ = 1.9 months) compared to SG alone that did not reach statistical significance

Ana C. Garrido-Castro, M.D. ASCO 2024;Abstract LBA1004.

Courtesy of Sara M Tolaney, MD, MPH

SACI-IO HR+: Overall Survival



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	

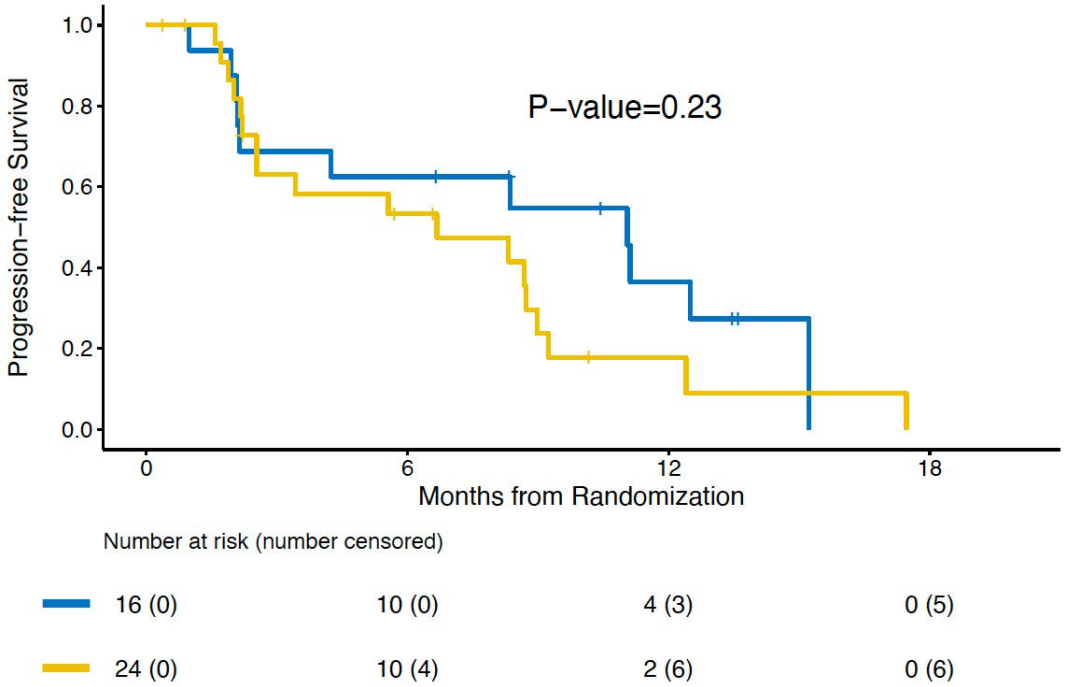
At a median follow-up of 12.5 months, no significant difference in OS was observed with SG plus pembrolizumab compared to SG alone

Ana C. Garrido-Castro, M.D. ASCO 2024;Abstract LBA1004.

Courtesy of Sara M Tolaney, MD, MPH

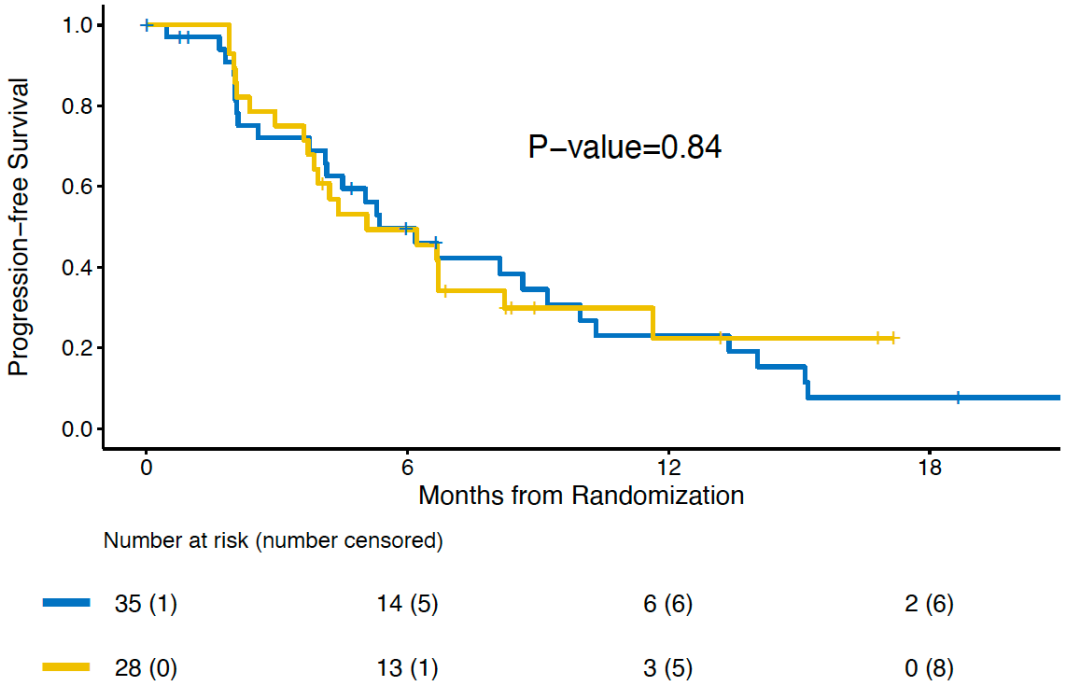
SACI-IO HR+: Progression-Free Survival by PD-L1 IHC status

PD-L1-positive (CPS ≥1)



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	

PD-L1-negative (CPS <1)



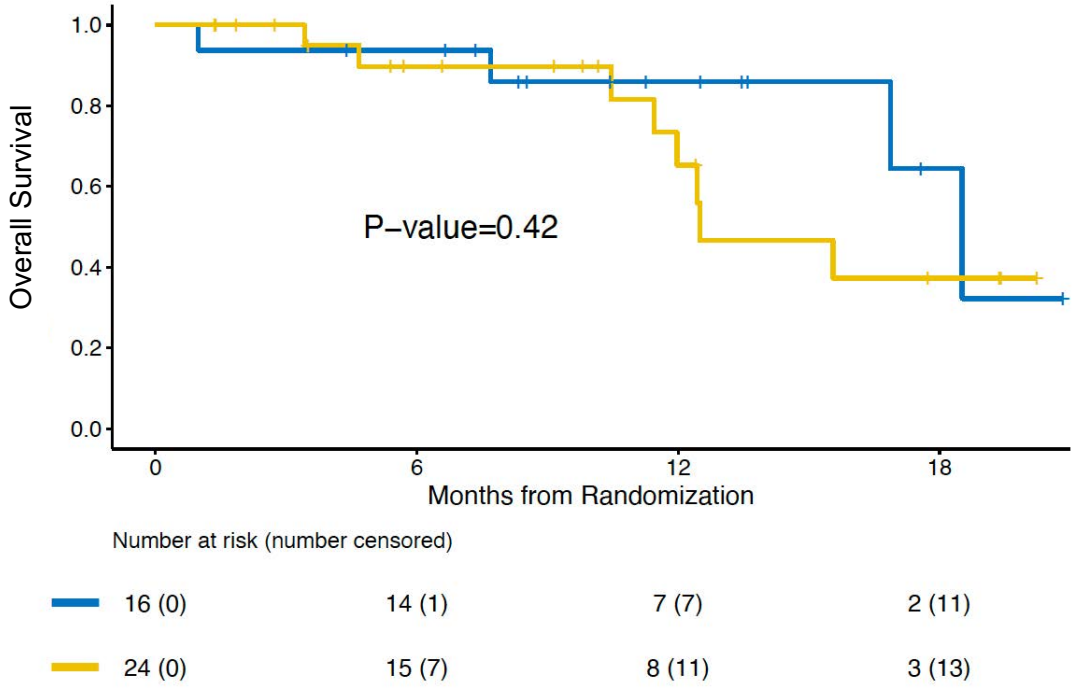
Treatment Arm	SG + Pembrolizumab (N=35)	SG (N=28)
N PFS events	27	20
Median PFS, mo (95% CI)	**5.36** (4.14-9.97)	**5.07** (3.85-NA)
HR (95% CI)	**1.06** (0.59-1.90)	
p-value (logrank test)	0.84	

Ana C. Garrido-Castro, M.D. ASCO 2024;Abstract LBA1004.

Courtesy of Sara M Tolaney, MD, MPH

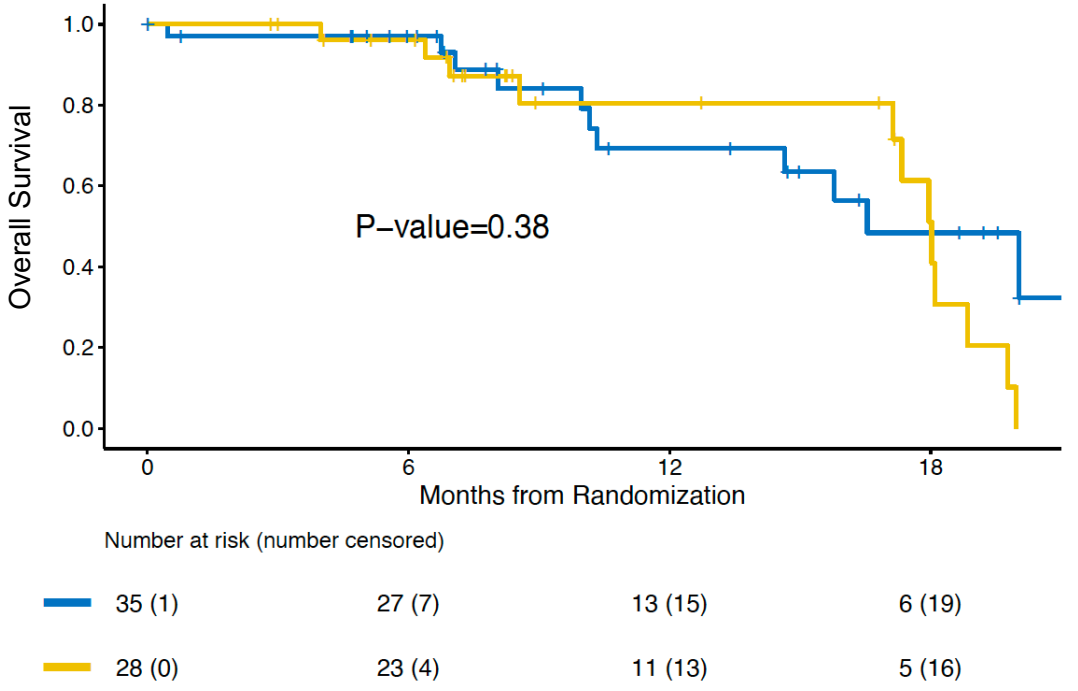
SACI-IO HR+: Overall Survival by PD-L1 IHC status

PD-L1-positive (CPS ≥1)



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	

PD-L1-negative (CPS <1)



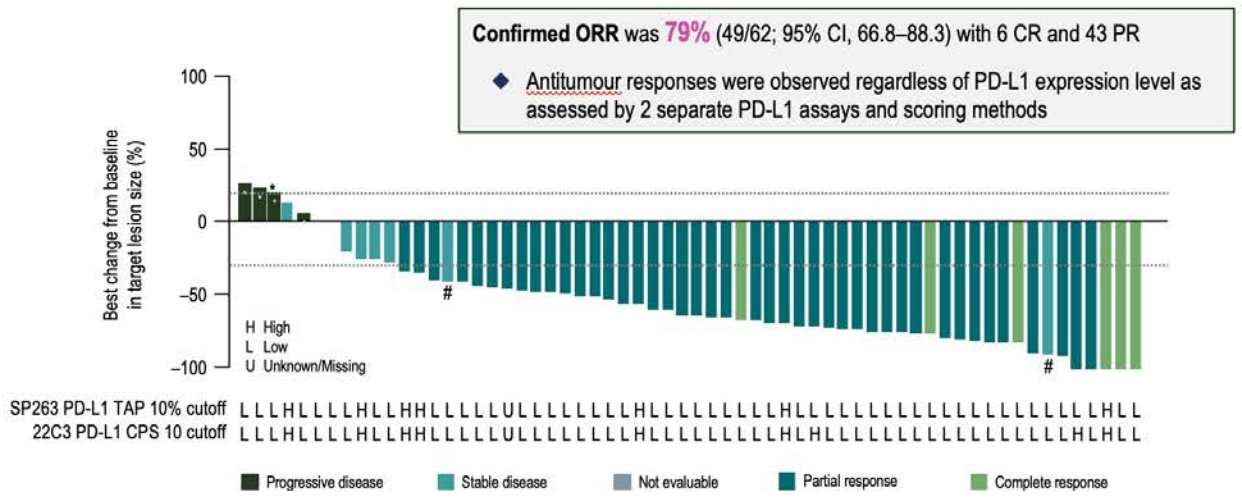
Treatment Arm	SG + Pembrolizumab (N=35)	SG (N=28)
N OS events	11	12
Median OS, mo (95% CI)	**16.55** (14.64-NA)	**18.03** (17.34-NA)
HR (95% CI)	**0.68** (0.29-1.59)	
p-value (logrank test)	0.38	

Ana C. Garrido-Castro, M.D. ASCO 2024;Abstract LBA1004.

Courtesy of Sara M Tolaney, MD, MPH

COULD AN ADC ALLOW CHECKPOINT INHIBITION TO HAVE BENEFIT IN METASTATIC TNBC THAT IS PD-L1-NEGATIVE?

BEGONIA:
Dato-DXd+ durvalumab



Schmid P et al, ESMO 2023

SACI-IO TNBC:
SG +/- pembro in PD-L1- 1L mTNBC

mTNBC:
No Prior Chemo
No Prior PD-1/L1

PD-L1 <1% by SP-142
ER ≤ 5%
PR ≤ 5%
HER2-

Exclude prior: PD-1/L1, SG, Irinotecan

R
1:1

N=110 pts

sacituzumab govitecan
10mg/kg IV d1,8 q21 days
+
pembrolizumab
200mg/kg Q3wks

sacituzumab govitecan
10mg/kg d1,8 q21 days

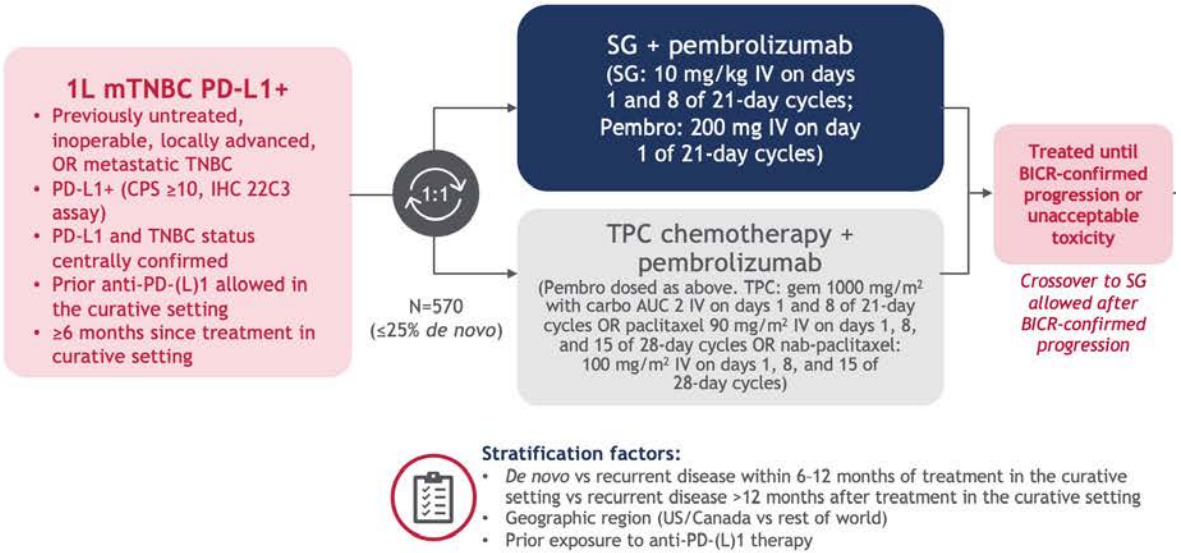
PI: Ana Garrido-Castro

Courtesy of Sara M Tolaney, MD, MPH

WILL ADC + IO BECOME THE NEW 1L SOC FOR mTNBC?

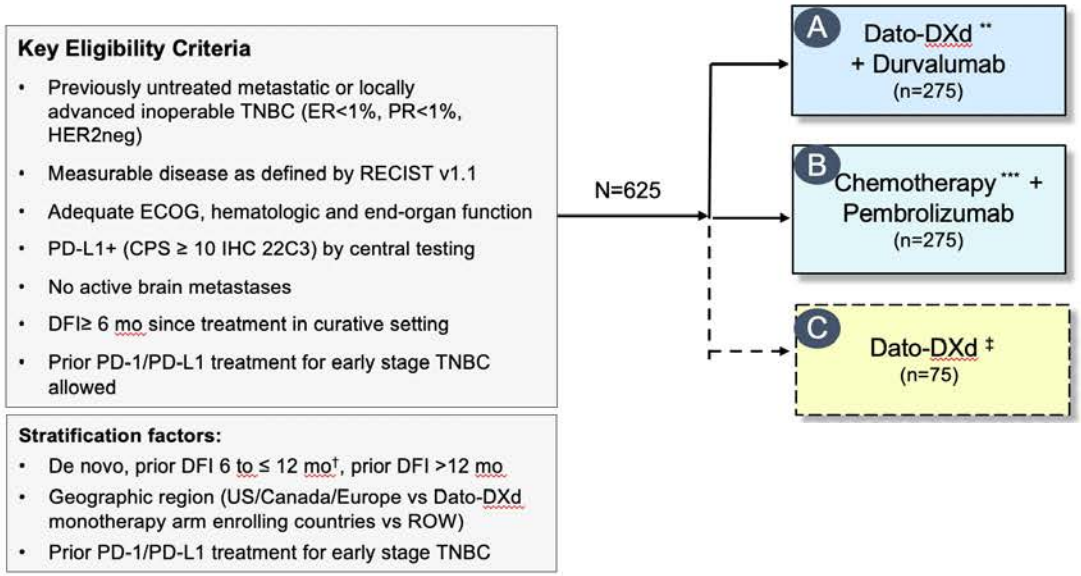
ASCENT-04

SG+ pembro vs TPC+ pembro in 1L PD-L1+ mTNBC



TROPION-Breast05

Dato-DXd +/- durva vs TPC + pembro in 1L PD-L1+ mTNBC



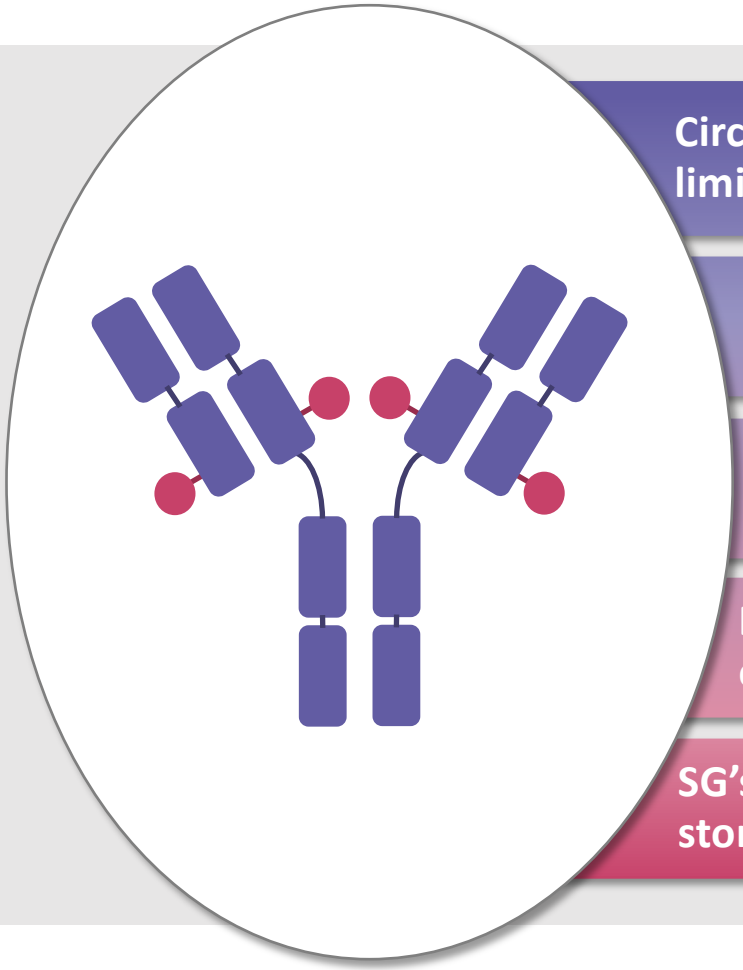
Sara M. Tolaney, MD, MPH

Courtesy of Sara M Tolaney, MD, MPH

Case Presentation – Dr Tolaney: A 51-year-old woman with previously treated triple-negative mBC

- 51 yo female who presented with a R-sided breast mass with an enlarged ipsilateral R axillary lymph node
- Biopsy of the breast and axillary lymph node were consistent with ER- PR- HER2 1+ breast cancer
- Staging scans revealed two suspicious pulmonary nodules, largest 2.5 cm
- Biopsy of one of the lung nodules was ER- PR- HER2 1+
- PD-L1 testing was sent off the breast biopsy and returned CPS 1 by 22C3
- NGS revealed no targetable alterations, germline testing without mutations
- Went onto a clinical trial SACI IO TNBC and was randomized to sacituzumab + pembrolizumab
- Achieved CR, and went onto pembrolizumab alone; after 35 cycles, stopped pembro, now NED off therapy

Datopotamab Deruxtecan (Dato-DXd)
TROP2 ADC in Development



- Circulating free payload is negligible due to high stability of the linker, thereby limiting systemic exposure or nontargeted delivery of the payload
- High-potency membrane-permeable payload (DXd) that requires TROP2-mediated internalization for release
- DS-1062 has a DAR of 4 for optimized therapeutic index
- DS-1062 has a substantially longer half-life than SG (≈ 5 days vs 11–14 hours), enabling a more optimal dosing regimen
- SG's DLT is neutropenia, while DS-1062's DLTs are maculopapular rash and stomatitis/mucosal inflammation

DLT, dose-limiting toxicity.

Courtesy of Sara M Tolaney, MD, MPH

Design of Sacituzumab Tirumotecan (sac-TMT)

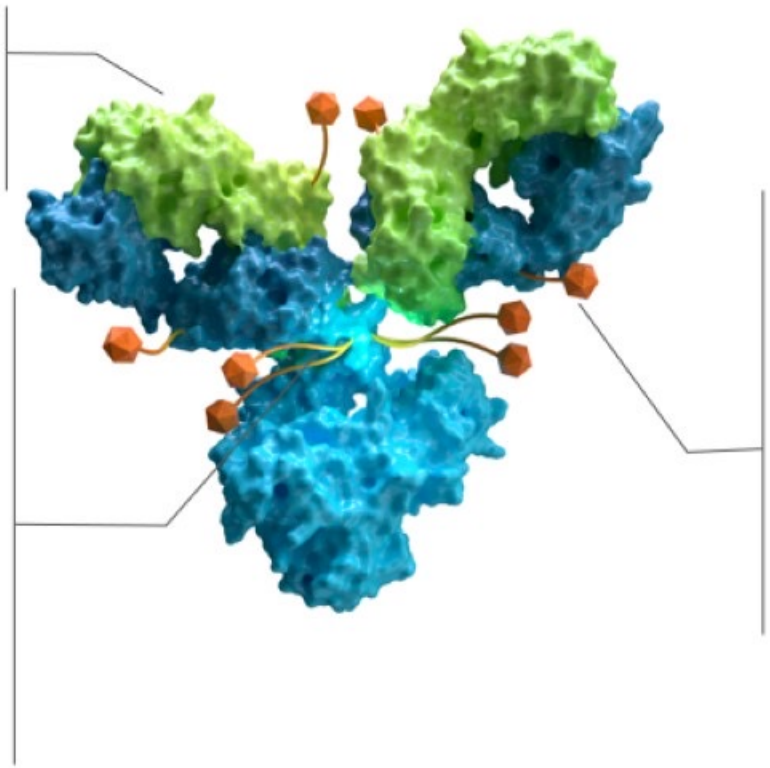
Sac-TMT is a TROP2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor at DAR 7.4. The features of sac-TMT lead to release of the payload both in the tumor microenvironment (TME) and inside tumor cells, achieving a balance between safety and efficacy.

Antibody

- hRS7, a recombinant humanized anti-TROP2 antibody with high affinity

Linker

- **Kthiol conjugation:** irreversible coupling to improve stability of ADC
- **Payload release:** intracellular cleavage and extracellular hydrolysis in TME
- **Balanced stability:** balance between efficacy and safety to expand therapeutic window



Payload

- **Novel topo I inhibitor** (a belotecan derivative), highly active
- Average **DAR: 7.4** (range: 7–8)
- **Bystander effect**
- Methylsulfonyl derivatization enhances linker stability and toxin permeability

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; TME, tumor microenvironment; TROP2, trophoblast cell surface antigen 2.

Courtesy of Sara M Tolaney, MD, MPH

Based on your personal clinical experience and knowledge of the available data, what is your estimate of the chance that a patient undergoing treatment with sacituzumab govitecan will require withholding or discontinuing administration because of treatment toxicity?

	Chance of withholding	Chance of discontinuation
 Prof Schmid	50%	<5%
 Dr Tolaney	50%	5%
 Dr Brufsky	15%	5%
 Dr Burstein	50%	10%
 Dr Jhaveri	25%	Low
 Dr Spring	25%	20%

Do you routinely employ G-CSF prophylaxis for all patients receiving sacituzumab govitecan or only for select patients?

 Prof Schmid	All patients
 Dr Tolaney	Patients with a history of neutropenia requiring growth factor
 Dr Brufsky	All patients
 Dr Burstein	Patients with low WBC at cycles 2 and beyond
 Dr Jhaveri	Patients with baseline neutropenia, those who have ANC <1,000 for day 8, those with neutropenia requiring G-CSF on prior chemotherapies
 Dr Spring	Select patients

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, how would you characterize the degree of alopecia observed with _____?

	Sacituzumab govitecan	Trastuzumab deruxtecan
 Prof Schmid	Complete alopecia as observed with anthracyclines	Complete alopecia as observed with anthracyclines
 Dr Tolaney	Complete alopecia as observed with anthracyclines	Moderate alopecia as observed with platinum agents
 Dr Brufsky	Moderate alopecia as observed with platinum agents	Less alopecia than that observed with platinum agents
 Dr Burstein	Moderate alopecia as observed with platinum agents	Moderate alopecia as observed with platinum agents
 Dr Jhaveri	Complete alopecia as observed with anthracyclines	Moderate alopecia as observed with platinum agents
 Dr Spring	Complete alopecia as observed with anthracyclines	Moderate alopecia as observed with platinum agents

Agenda

Introduction: Pharmacology and Sequencing of Antibody-Drug Conjugates (ADCs) in Metastatic Breast Cancer (mBC)

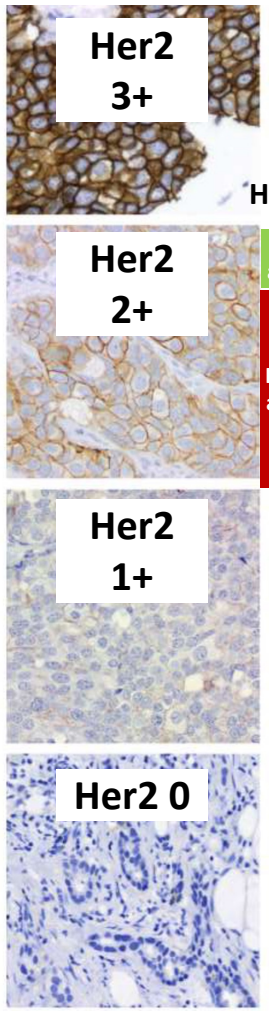
Module 1: Expanding Role of TROP2-Directed ADCs in mBC Management — Dr Tolaney

Module 2: Other Targets for ADC Therapy in mBC — Prof Schmid

HER2 low – new breast cancer subtype?

Her2 low subgroup:
- Therapeutic but not biological subtype as HER2 not oncogenic driver
- Benefit from new ADCs due to payload release before internalisation or membrane permeability
- Incidence: TNBC 34%, ER+ 63%
- HER2 low status variable over time

Her2 IHC



Her2 ISH

HER2 amplified

HER2 non amplified

HER2 'positive'

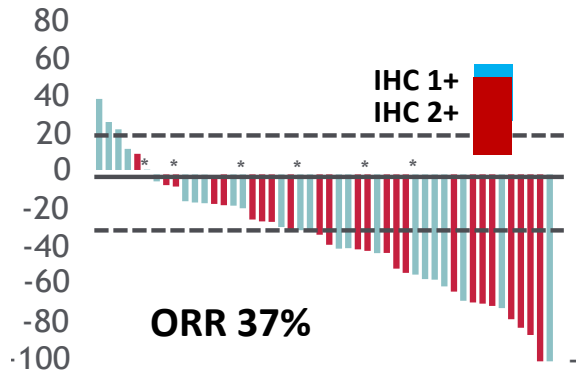
HER2 'negative'

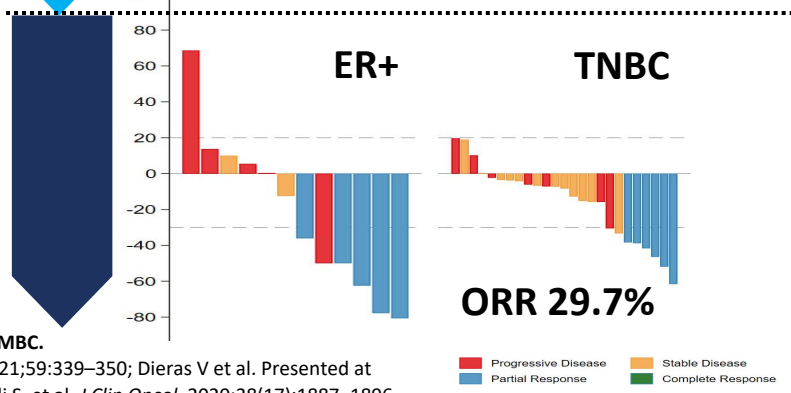
Benefit from Trastuzumab therapy

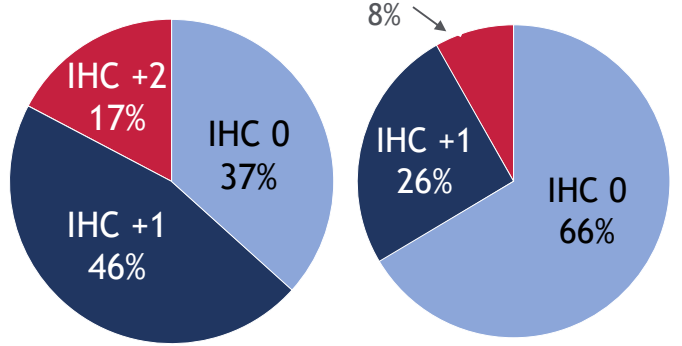
No Benefit from Trastuzumab therapy

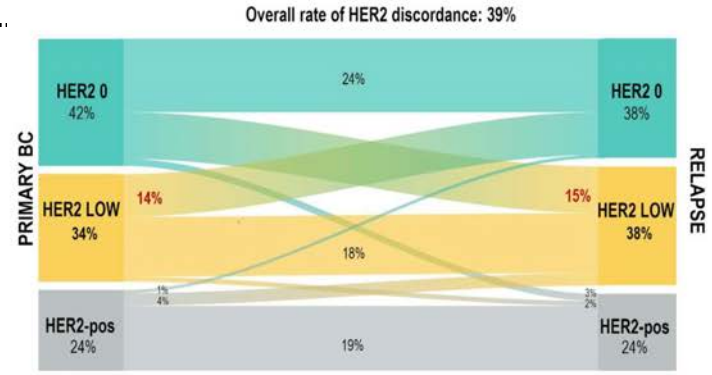
HER2 low

Benefit from T-DXd









Trastuzumab deruxtecan is not currently approved in the EU for use in patients with HER2-low MBC.

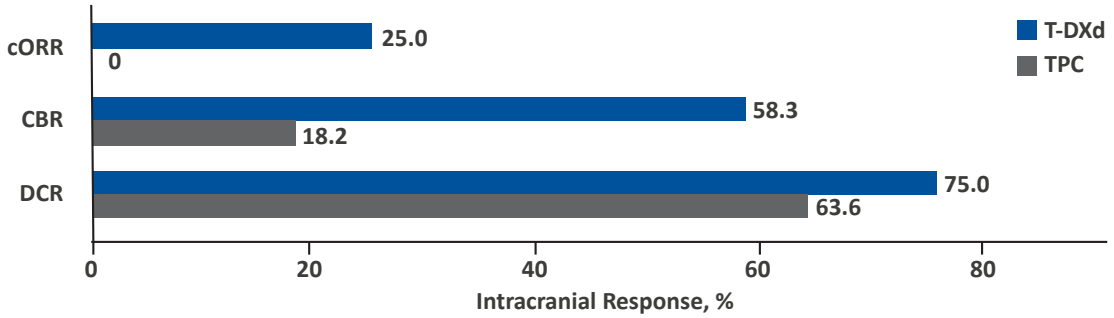
Marchio C, et al. *Seminars in Cancer Biol*. 2020;72:123–135; Schettini F and Prat A. *The Breast.* 2021;59:339–350; Dieras V et al. Presented at SABCS 2021; Schmid P, Personal Communication. Jacot W, et al. *Cancers*. 2021;13(23):6059; Modi S, et al. *J Clin Oncol*. 2020;38(17):1887–1896

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

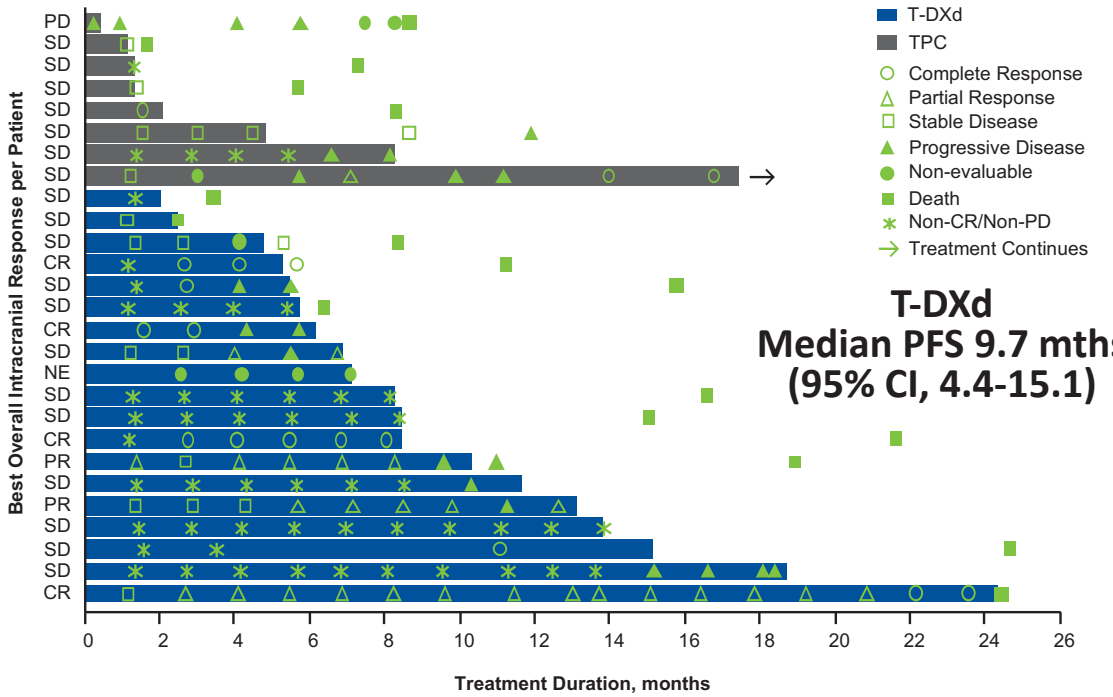
T-DXd in brain metastases in $HER2_{low}$

DESTINY-Breast04 Trial

35 patients with BICR-assessed, asymptomatic brain metastases at baseline (24 on T-DXd arm; 11 on TPC)



	Best Overall Intracranial Response	
n (%)	T-DXd (n = 24)	TPC (n = 11)
CR	4 (16.7)	0
PR	2 (8.3)	0
SD	12 (50.0)	7 (63.6)
PD	0	1 (9.1)
Not evaluable (NE)	1 (4.2)	0
Missing	5 (20.8)	3 (27.3)



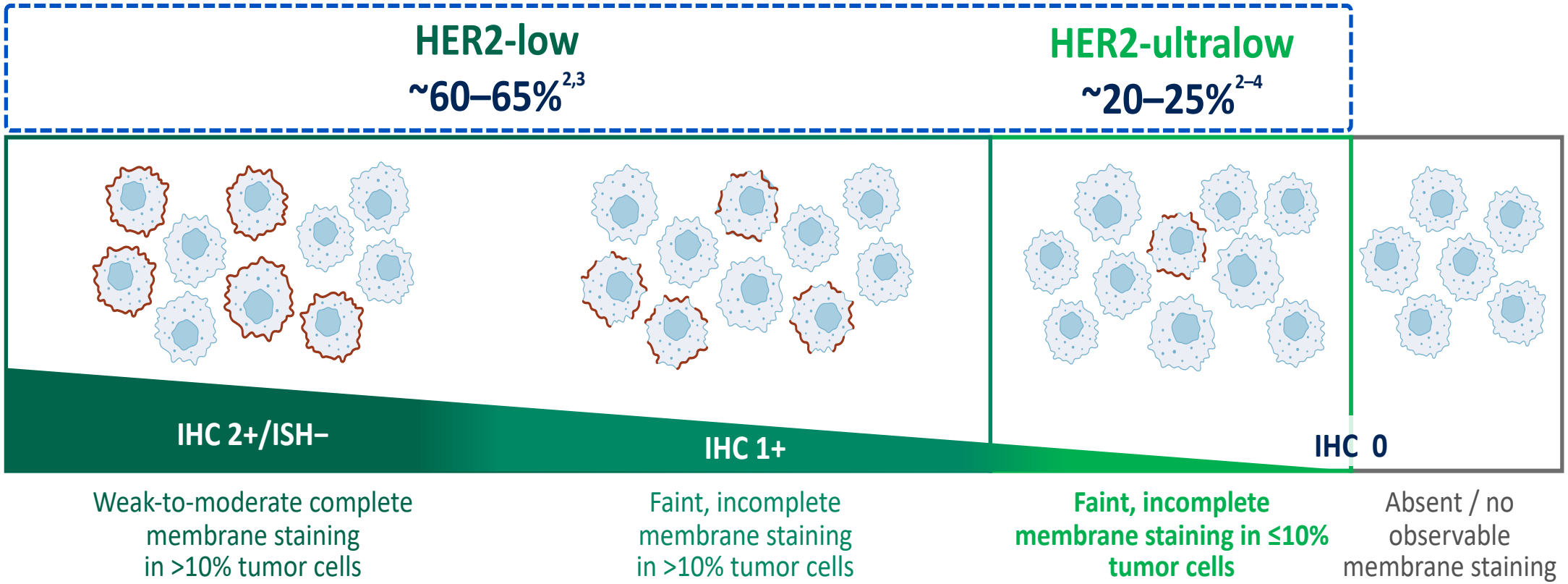
T-DXd
Median PFS 9.7 mths
(95% CI, 4.4-15.1)

- **Intracranial efficacy data suggest a benefit of T-DXd over TPC; this is consistent with the overall observed efficacy of T-DXd in patients with HER2-low mBC**
- **The observed efficacy of T-DXd in patients with HER2+ mBC with BM**

Tsurutani, et al. ESMO 2023

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Definition: HER2-low and HER2-ultralow

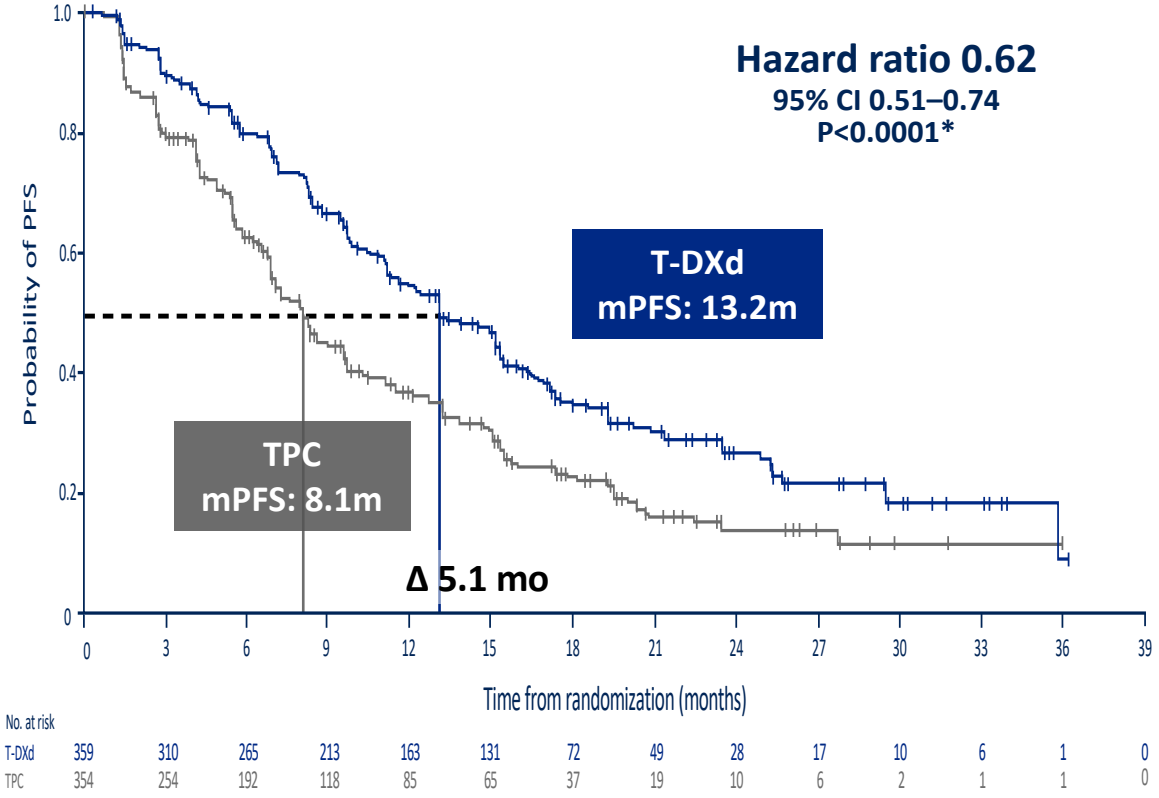


Courtesy of Professor Peter Schmid, FRCP, MD, PhD

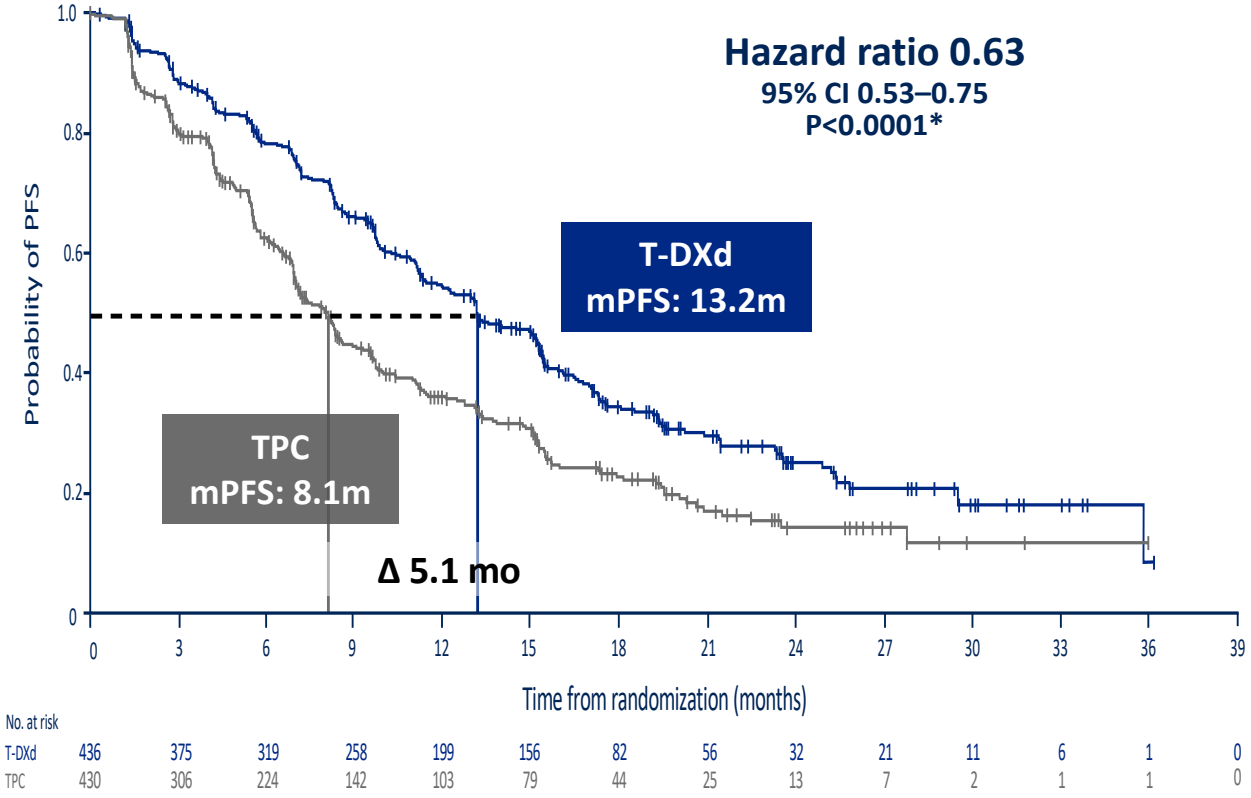
Curigliani G, et al. ASCO 2024

DESTINY-Breast06: PFS in HER2-low and ITT

PFS (BICR) in HER2-low
(Primary endpoint)



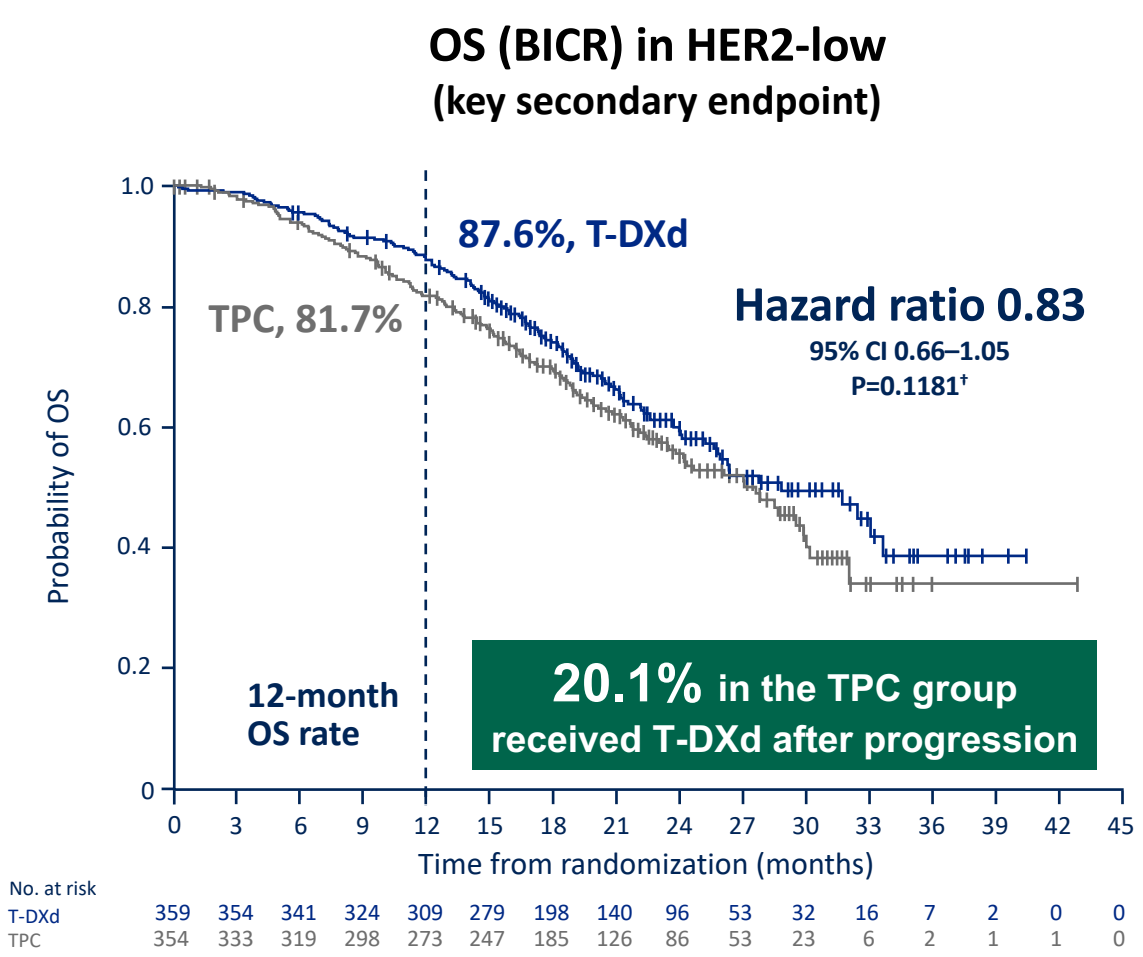
PFS (BICR) in ITT
(key secondary endpoint)

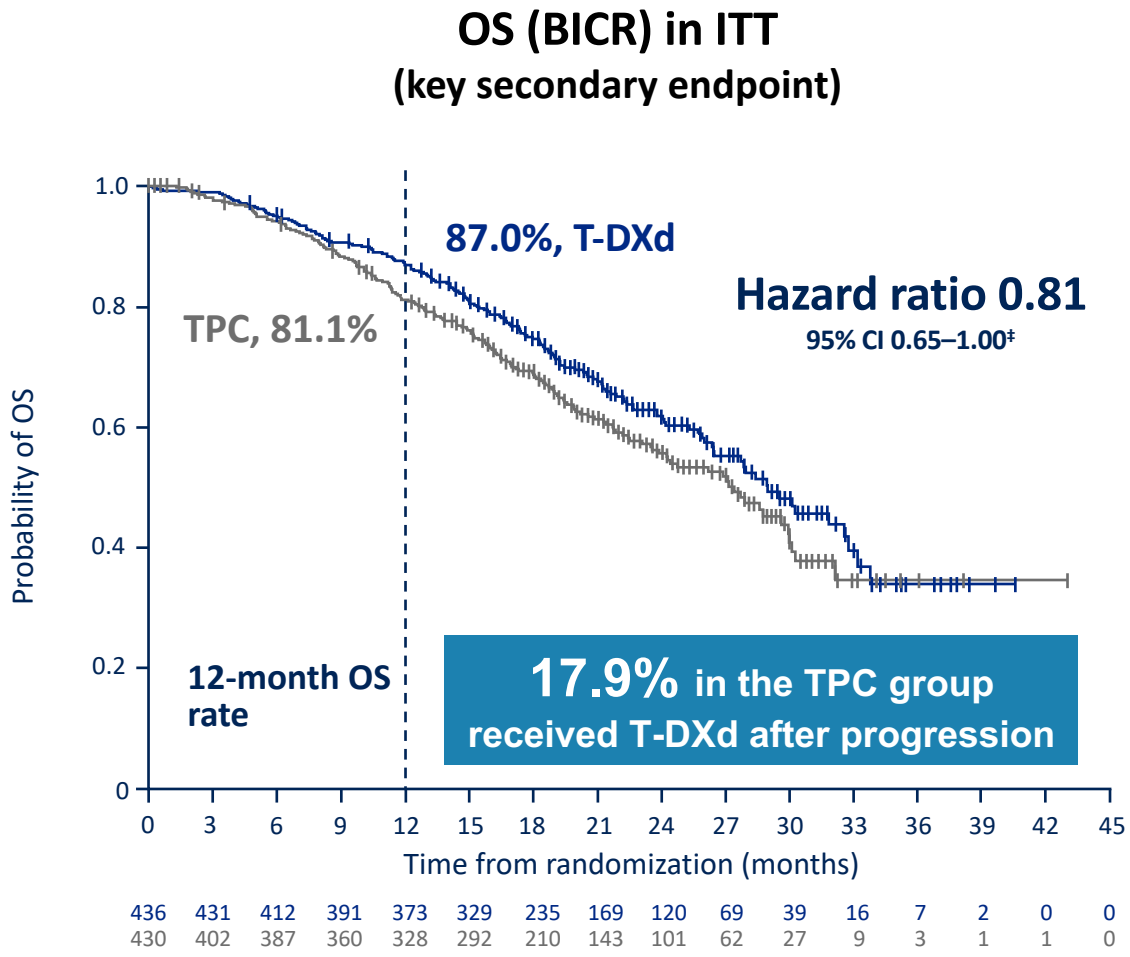


Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Curigliani G, et al. ASCO 2024

DESTINY-Breast06: OS in HER2-low and ITT





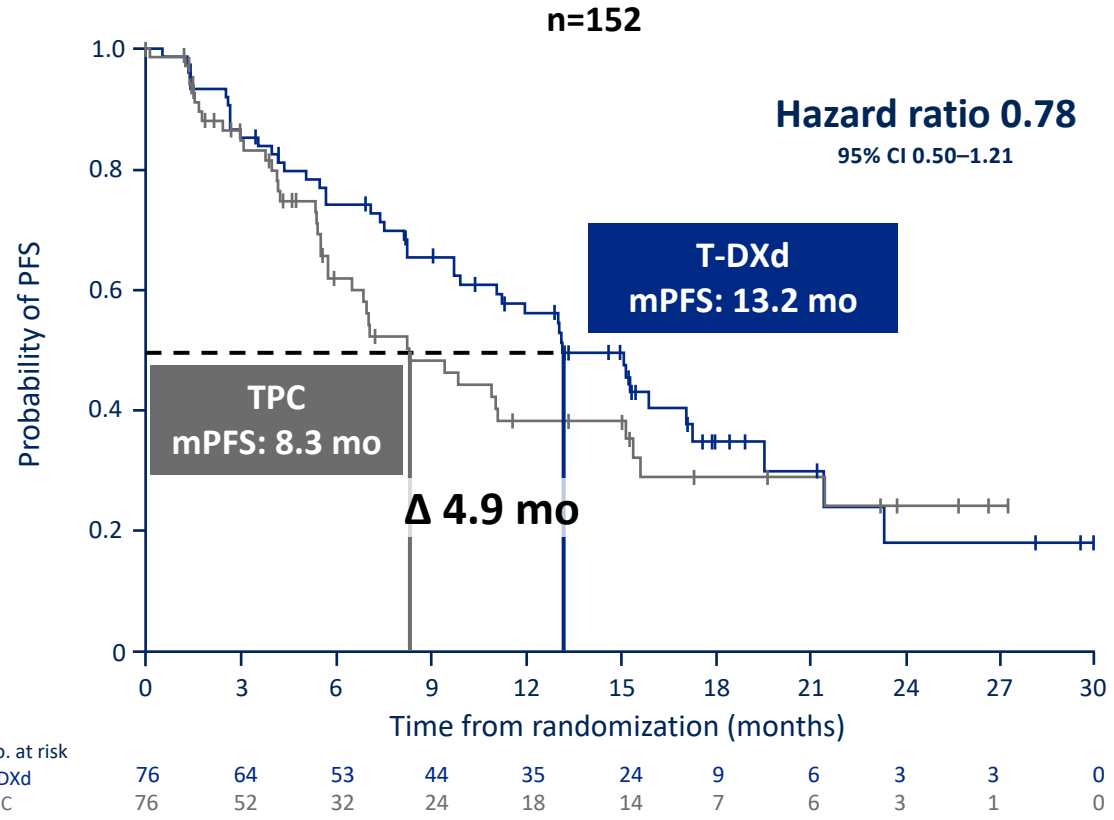
*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow up was 18.2 months (ITT)CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliani G, et al. ASCO 2024

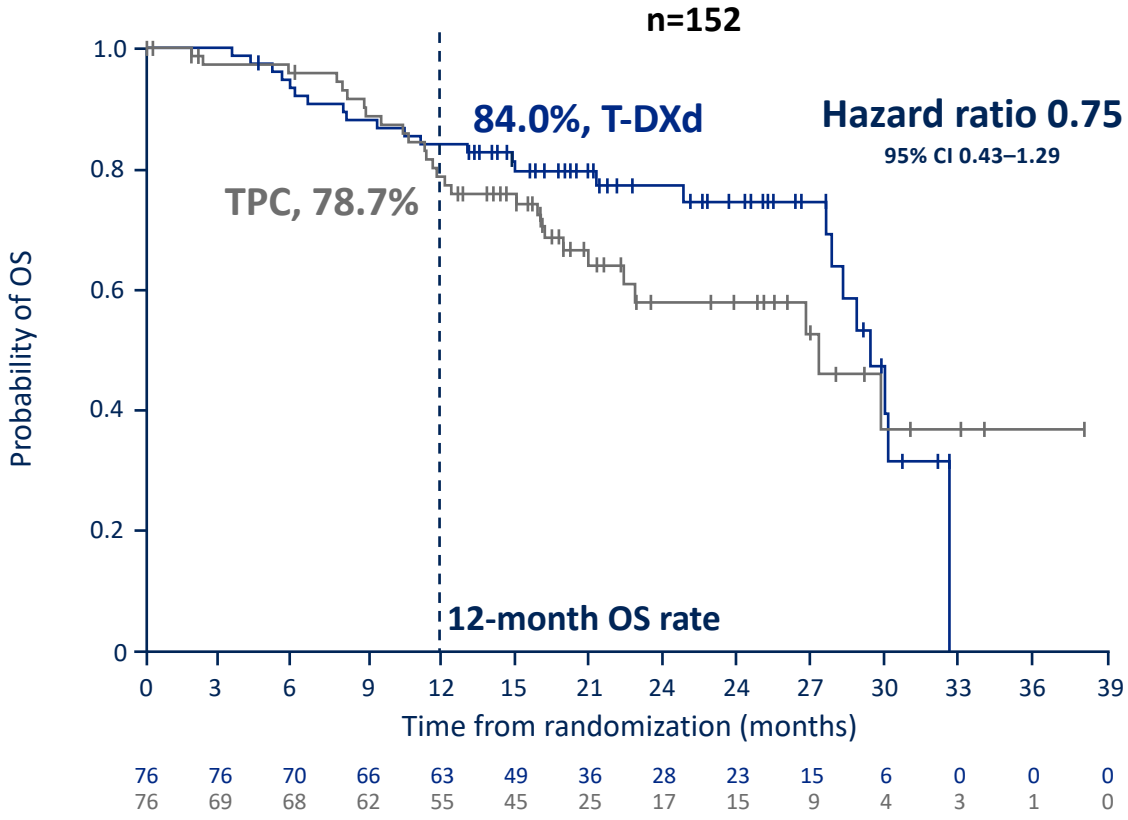
Courtesy of Professor Peter Schmid, FRCP, MD, PhD

DESTINY-Breast06: PFS and OS in HER2-ultralow

Progression-free Survival (BICR)



Overall Survival*



Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Curigliani G, et al. ASCO 2024

Case Presentation – Prof Schmid

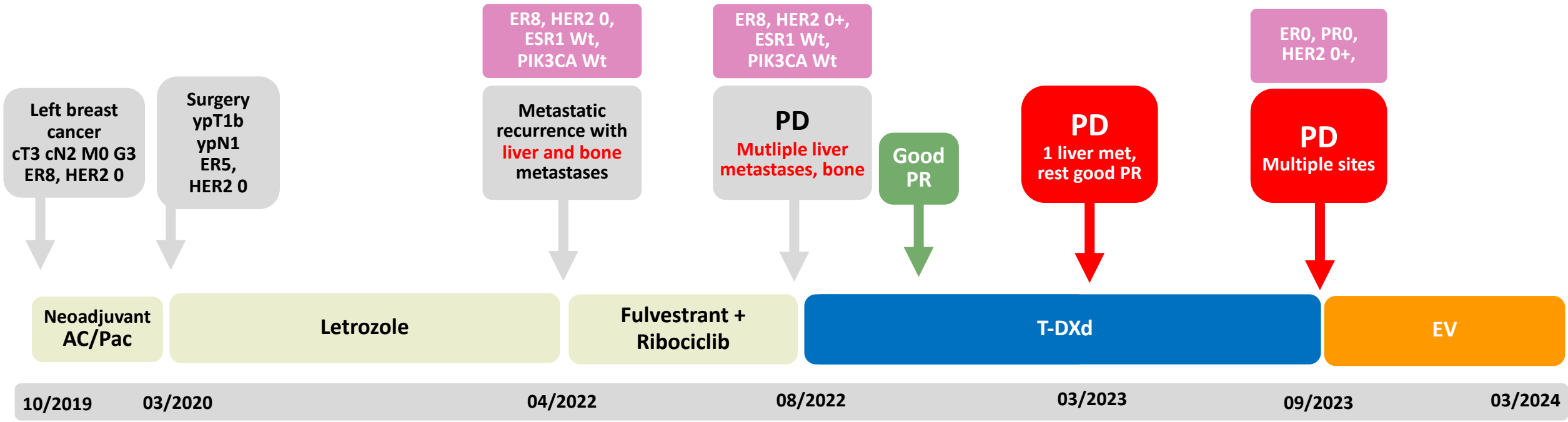
62 y/o woman
gBRCA/PALB2 wildtype

What would you do?
- Biopsy/Liquid biopsy
- ET
- Combination ET
- Capecitabine
- T-DXd

What to do?
- Further ET
- Capecitabine?
- Paclitaxel?
- T-DXd?

What would you do?
- Continue (no change)
- SRS/RFA, continue T-DXd
- Chemo
- Sacituzumab

What would you do?
- Continue (no change)
- Sacituzumab Govitecan
- Chemo
- Other ADC in trial



Side effects of ADCs

T-DM1

Fatigue 22-35%

Interstitial lung disease 0.5%

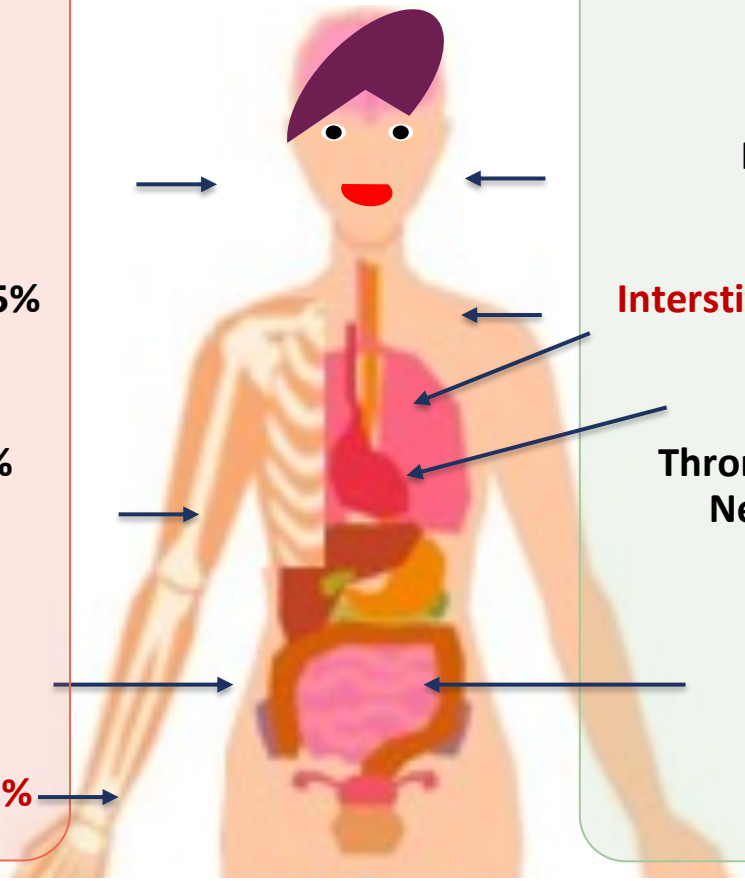
LVEF 2.2%

Thrombocytopenia 25%
Haemorrhage 35%

LFTs 24%

Diarrhoea 10-25%
Nausea 39-47%

Peripheral Neuropathy 32%



T-DXd

Fatigue 48%

Interstitial lung disease 12%

LVEF 4%

Thrombocytopenia 24%
Neutropenia 33%

LFTs 24%

Diarrhoea 22%
Nausea 73%

Determinants of ADC Toxicity

- Target (tissue distribution)
- Payload
- Linker
- Antibody-effects (on target or immune)
- Patient factors

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Modi, et al NEJM 2022. Hackshaw, BCRT 2022; Powell, ESMO open 2022; Abuhelwa, Drugs 2022;

T-DXd: Management of ILD

Routine Monitoring

1. Monitor for symptoms (cough, dyspnea, pyrexia)
2. Review every 4-6 weeks
3. Monitor SpO2 (examine if drop by 2-4% for 1-3d)
4. CT scans every 9-12 weeks

Diagnostic if ILD suspected

1. Lung function test
2. CT chest scan (ideally high-resolution CT)
3. Possibly Bronchoscopy
4. Bloods, blood and sputum cultures

	Grade 1	Grade 2	Grade 3/4
Description	Asymptomatic (diagnostic observations only)	Symptomatic; limiting instrument. ADL	Severe symptoms; limiting self-care ADL; oxygen (G3); Life-threatening (G4)
T-DXd	Hold (restart if resolved within 49 days, otherwise discontinue)	Discontinue	Discontinue
Dose reduction	Same dose if ≤28d, lower dose if > 28d	N/A	N/A
Steroids	0.5 mg/kg /day	≥1 mg/kg/day	Methylprednisolone i.v. 500-1000 mg/d for 3d, followed by ≥1 mg/kg/d prednisolone for 14d
Escalation	If worsens despite initiation of steroids, follow Grade 2 guidelines	if not better within 5d: Increase dose or switch to IV	if not better within 5d: Infliximab, IVIG or MMF
Duration	Until improvement, followed by gradual taper over ≥4 weeks	For at least 14d or until complete resolution of clinical and chest CT findings then gradually taper (for at least 4wks)	

Courtesy of Professor Peter Schmid, FRCP, MD, PhD

Regulatory and reimbursement issues aside, would you offer trastuzumab deruxtecan to a patient with _____?

	HER2 IHC 0 mBC with a HER2 mutation	mBC with a HER2 IHC score of 0 on repeated assessments
 Prof Schmid	Yes	Yes
 Dr Tolaney	Yes	Yes
 Dr Brufsky	No	No
 Dr Burstein	Yes	No
 Dr Jhaveri	Yes	No
 Dr Spring	Yes	Yes

Do you anticipate that ADCs will routinely be employed in the front-line setting for mBC in the future?

 Prof Schmid	Yes; alone in ER-positive disease, in combination with CIT in TNBC
 Dr Tolaney	Yes; for TNBC, likely ADC + IO in PD-L1+, or ADC alone if PD-L1-; in HR+ breast cancer, T-DXd is already moving as 1L chemo based on DB-06
 Dr Brufsky	Yes; alone
 Dr Burstein	Yes; alone
 Dr Jhaveri	Yes; alone
 Dr Spring	Yes; alone, most ADCs are very active as single agents

CIT = chemoimmunotherapy; TNBC = triple-negative breast cancer; IO = immunotherapy

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Based on your personal clinical experience and knowledge of the available data, what is your estimate of the chance that a patient undergoing treatment with trastuzumab deruxtecan will require withholding or discontinuing administration because of treatment toxicity?

	Chance of withholding	Chance of discontinuation
 Prof Schmid	30%	<5%
 Dr Tolaney	20%	15%
 Dr Brufsky	25%	10%
 Dr Burstein	50%	20%
 Dr Jhaveri	25%	Low
 Dr Spring	20%	15%

Based on your personal clinical experience and knowledge of the available data, what is your estimate of the chance that a patient undergoing treatment with datopotamab deruxtecan will require withholding or discontinuing administration because of treatment toxicity?

	Chance of withholding	Chance of discontinuation
 Prof Schmid	30%	<5%
 Dr Tolaney	25%	10%
 Dr Brufsky	20%	10%
 Dr Burstein	—	—
 Dr Jhaveri	25%	Low
 Dr Spring	15%	10%

Do you use chest imaging to monitor for interstitial lung disease in patients receiving trastuzumab deruxtecan who otherwise do not require chest imaging? How often do you order chest imaging? For how long do you continue to order chest imaging in patients who are experiencing an ongoing response?

	Chest imaging?	Frequency	Duration
 Prof Schmid	Yes	Every 9-12 weeks	As long as on treatment
 Dr Tolaney	Yes	Every 6-9 weeks	Every 6-9 weeks for first 12 months, then every 12 weeks
 Dr Brufsky	Yes	Every 12 weeks	Every 12 weeks
 Dr Burstein	No	N/A	N/A
 Dr Jhaveri	Yes	Every 9 weeks	Every 9 weeks for the first year, every 12 weeks after
 Dr Spring	Yes	After ~6 weeks, then 9 weeks, then every 12 weeks	Part of restaging but with time comfortable with every 3 months or so

Based on your personal clinical experience and knowledge of available data, how would you characterize the degree of mucositis observed with datopotamab deruxtecan? What preemptive strategies do you use to prevent mucositis in your patients receiving datopotamab deruxtecan, and how effective are these generally?

	Degree of mucositis observed	Preemptive strategies, effectiveness
 Prof Schmid	Typically Grade 1	Steroid mouthwash; Magic mouthwash
 Dr Tolaney	Typically Grade 1	Dexamethasone sw/sp QID
 Dr Brufsky	Typically Grade 2	Steroid mouthwash
 Dr Burstein	Typically Grade 1	Have not administered
 Dr Jhaveri	Typically Grade 2	Ice chips during infusion, dexamethasone mouthwash 3-4 times a day
 Dr Spring	Typically Grade 1	Prophylactic steroid mouthwash; effective

Inside the Issue: Integrating ALK-Targeted Therapy into the Management of Localized Non-Small Cell Lung Cancer

A CME/MOC-Accredited Live Webinar

Thursday, July 18, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Professor Ben Solomon, MBBS, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

CME and MOC credit information will be emailed to each participant within 5 business days.

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