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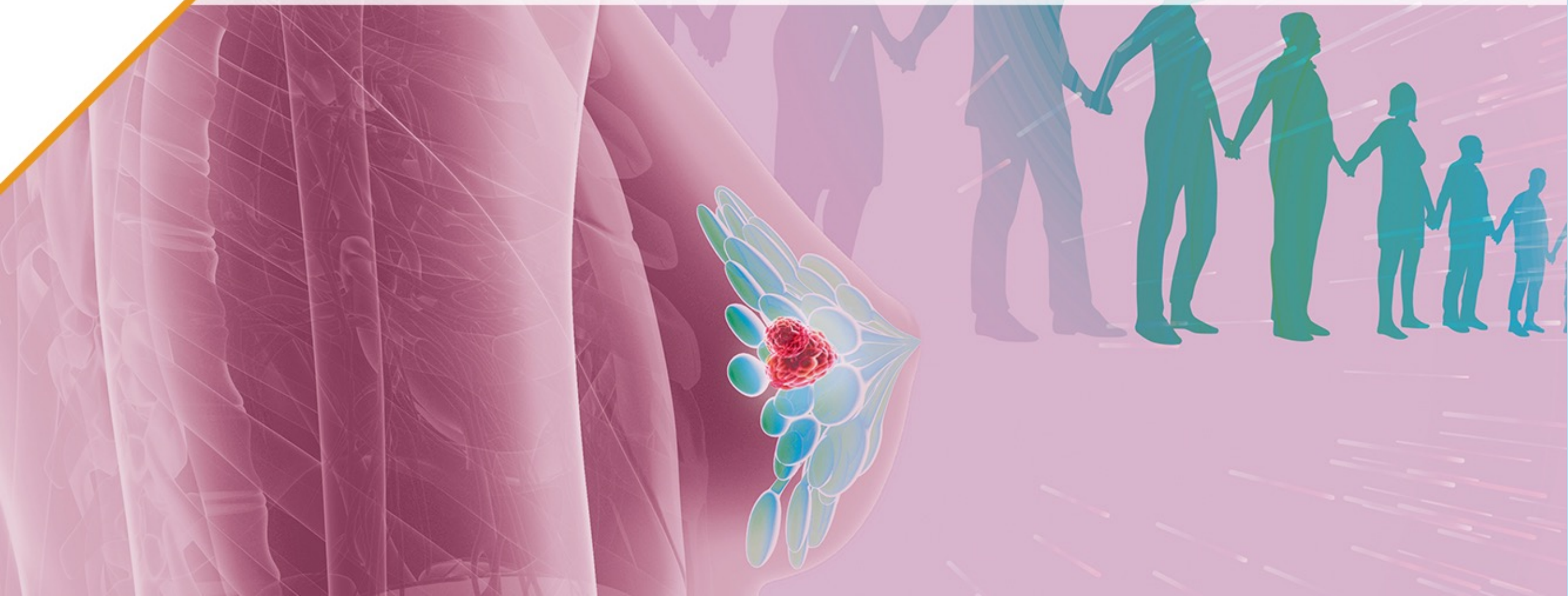
Advances in the Standard of Care in TNBC:

Addressing Health Disparities and Integrating ADCs Into Treatment



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Disclosure of Conflicts of Interest

- **Ricki Fairley**, reported a financial interest/relationship or affiliation in the form of *Grant*: Novartis Pharmaceuticals Corp; Genentech, Inc; Gilead; and Eisai Inc.

- **Sara Tolaney, MD, MPH**, reported a financial interest/relationship or affiliation in the form of *Advisory board*: AstraZeneca Pharmaceuticals LP; Lilly USA; Merck & Co, Inc; Nektar Pharmaceuticals Inc; Novartis Pharmaceuticals Corp; Pfizer, Inc; Genentech/Roche; Immunomedics, Inc; Bristol-Myers Squibb Co; Eisai Inc; Nanostring; PUMA Biotechnology; Sanofi; Celldex, Inc; and Paxman. *Consultant*: AstraZeneca Pharmaceuticals LP; Lilly USA; Merck & Co, Inc; Nektar Pharmaceuticals Inc; Novartis Pharmaceuticals Corp; Pfizer, Inc; Bristol-Myers Squibb Co; Eisai Inc; Nanostring; Paxman; and Odonate. *Research funding*: AstraZeneca Pharmaceuticals LP; Lilly USA; Merck & Co, Inc; Nektar Pharmaceuticals Inc; Novartis Pharmaceuticals Corp; Pfizer, Inc; Genentech/Roche; Immunomedics, Inc; Exelixis, Inc; Bristol-Myers Squibb Co; Eisai Inc; Nanostring; and Cyclacel. *Steering Committee*: Seattle Genetics, Inc.

- **Kristen Whitaker, MD, MS**, reported a financial interest/relationship or affiliation in the form of *Consultant*: Novartis Pharmaceuticals Corp.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Describe how health disparities contribute to inequalities in health outcomes in women with TNBC
- Discuss the importance of adequate screening, genetic testing, and diagnosis to facilitate early identification and treatment of TNBC among black women and other medically underserved minority populations in the United States
- Identify women with TNBC who may benefit from treatment with an antibody-drug conjugate or other novel therapy to help overcome disparities in care and promote health equity

Understanding Health Disparities and Inequities in TNBC

Black Breast Cancer

THE BLACK BREAST CANCER ALLIANCE

Overview

- The State of Breast Cancer in Black Women
- Key Factors Affecting Mortality
- What's the Perception of Clinical Trials?
- Black Data Matters Research
- What Will Change the Game?

Breast Cancer Is One of the Most FATAL Health Issues for Black Women!

- Black women are **41%** more likely to die of breast cancer than white women
- Black women under 35 get breast cancer at ***two times*** the rate of white women and die at ***three times*** **the rate**
- Black breast cancer survivors have a 39% higher risk for breast cancer recurrence compared to white women
- Black women with breast cancer have a 52% higher risk for death than white women

Breast Cancer Prevention Partners; American Cancer Society; *Oncology Times* 2019;41(1):24.
Richardson et al. *Weekly*. 2016;65(40):1093-1098. Sparano et al. *JAMA Oncol.* 2020;6(3):367-374.

Metastatic Breast Cancer

- The odds of advanced (stage III/IV) disease versus stage I disease among black women were almost four times those of white women
- Black women are 61% more likely to develop metastatic breast cancer than white women
- Black women are diagnosed with de novo metastatic breast cancer at a 58% higher rate than white women

Source: NIH, National Institutes of Health.

Triple-Negative Breast Cancer Is Wreaking Havoc

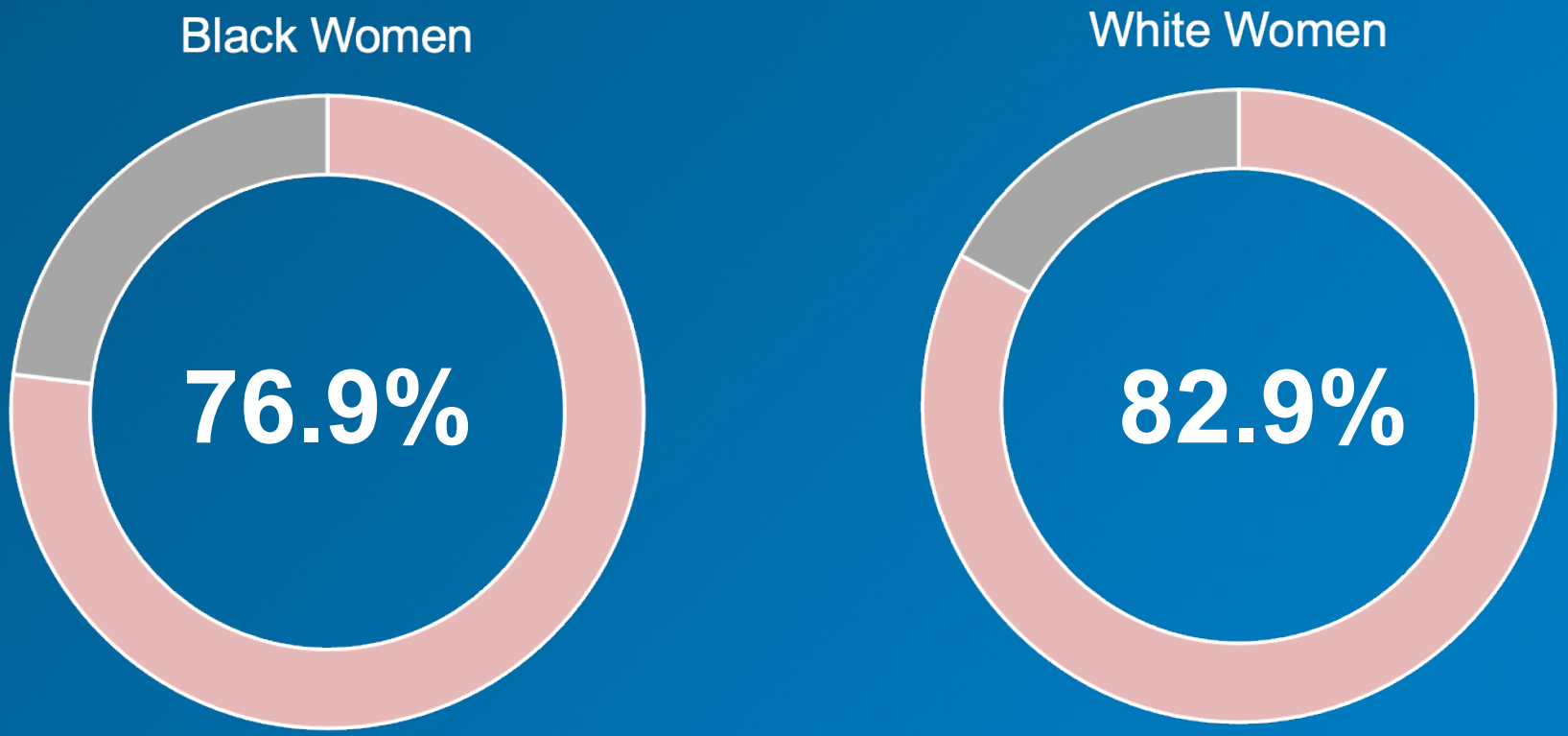
- The risk of developing TNBC is nearly 3-fold higher in black women vs non-black women, which may predict a worse prognosis
- 20% to 30% of breast cancers diagnosed in black women are triple negative
- Women under age 40 have a 2-fold higher risk of being diagnosed with TNBC than women age 50-64
- Women diagnosed with late-stage breast cancer are 69% more likely to have triple-negative disease than other breast cancer subtypes

TNBC, triple-negative breast cancer.

Penn Medicine. Siddharth and Sharma. *Cancers (Basel)* 2018;10(12):514. Stead et al. *Breast Cancer Res.*2009; 11(2):R18. Scott et al. *Cancer* 2019;125(19):3412-3417.

Black Women Are Less Likely to Survive 5 Years

Cumulative breast cancer–specific survival at 5 years



Cho et al. *JAMA Oncol*. 2021;7(7):1016-1023.

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Black Women Are at Higher Risk for Triple-Negative Breast Cancer Mortality

- A greater proportion of black women have (vs. white women):
  - Stage III tumors (20.3% vs 15.2%)
  - Tumors exceeding 5 cm in size (14.3% vs 9.6%)
  - Positive lymph nodes (39% vs 31.6%)
  - Poorly-differentiated or undifferentiated histology (81.5% vs 76%)

Black Women Have an 18% Higher Risk for Death Due To Non-Metastatic TNBC Than White Women

Cho et al. *JAMA Oncol*. 2021;7(7):1016-1023.

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Physiologic Factors Increase Incidence of Obesity in Black Women

- CDC age-adjusted prevalence of obesity among US adults (2017-2018): 42.4%
  - 41% for black men
  - 57% for black women
- Prevalence among non-Hispanic black women was higher than all other groups
- Researcher Barbara Gower, PhD investigating reasons for these differences
- Preliminary conclusions suggest that black women are more prone to obesity because:
  - They secrete more insulin and clear less of it
  - High amounts of insulin in bloodstream after meals signals body to store more fat
  - Factor in diets high in sugar that cause insulin levels to spike, and these women already prone to higher levels of circulating insulin will store more fat, compared to women with lower insulin secretion and higher insulin clearance

Hales et al. https://www.cdc.gov/nchs/products/databriefs/db360.htm. Gower et al. *Eur J Clin Nutr*. 2021;75(4):628-635.

Obesity Is a Breast Cancer Risk Factor for Black Women

- Black women have a significantly higher mean BMI (23%) compared with white women (32 kg/m^2 vs 26 kg/m^2)

- Having a BMI >30 kg/m^2 is associated with an increased risk (HR 2.77) for TNBC and an increased risk for ER+/PR+/HER2− breast cancer in postmenopausal women

BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TNBC, triple-negative breast cancer.

Friebel-Klingner et al. *Breast Cancer Res Treat.* 2021;189(3):827-835. McCarthy et al. *Cancer Med*. 2021;10(18):6456-6467.

Most Black Mothers Are Single Parents

- 67.9% of all black working women are single moms, making them the primary, if not sole, economic providers for their families
- Add breast cancer to those dynamics!
- What choice will a single mom make between missing work to receive treatment versus going to work to feed her kids?

Wilson V. 2017. https://www.epi.org/blog/african-american-women-stand-out-as-working-moms-play-a-larger-economic-role-in-families/

Black Women May Miss a Risk-Reducing Opportunity Because Breastfeeding May Not Be an Option

- 85% of white mothers say they breastfed versus 76% of black mothers

- Black moms are less likely to breastfeed because:
  - Hospital maternity wards that serve larger black populations are less likely to help black women initiate breastfeeding after giving birth or offer lactation support following delivery, according to the CDC study. Often, staff in these facilities instead offer black babies formula
  - Black women are more likely than others to need to return to work earlier than 12 weeks, and tend to be confronted with “inflexible work hours” that make consistent nursing and expression of milk difficult

- Parous women who breastfed for at least 1 year had a 31% lower risk for TNBC than women who had never breastfed

- Parous black women aged 20-44 years who breastfed for 6 months or longer had an 82% lower risk for TNBC than their counterparts who had never breastfed

Ma et al. *Breast Cancer Res*. 2017;19(1):6. CDC. 2021. https://www.cdc.gov/breastfeeding/data/facts.html.

By the Numbers

92% of black women agree breast health is important

25% of women have recently discussed breast health

17% have taken steps to better understand their risk

This Ad Council survey was conducted by Ipsos Public Affairs in February-April 2018. The nationally representative online survey included 810 black women ages 30-55.

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Screening Protocols Are Not Clear to Black Women

- 54% of all women ages 21 to 39 and 26% of women ages 40 to 60 say they don't know how often they should be screened for breast cancer
- 47% of black women of all ages say they don't know how often they should be screened for breast cancer
- 28% of all women have not scheduled any breast cancer screening during the COVID-19 pandemic
- That percentage drastically increases when looking specifically at black women

Prevent Cancer Foundation. 2021. https://www.preventcancer.org/2021/09/survey-says-women-are-skipping-cancer-screenings-during-pandemic-but-they-plan-to-get-back-on-the-books/

How Racial & Ethnic Disparities Contribute to Care Variations in TNBC

Black Women Experience Treatment Delays

- Black women are much more likely to delay following up with a doctor after an abnormal mammogram
- 20% wait more than 60 days to follow up compared with 12% of white women
- Only 69% of black women start treatment within 30 days of diagnosis compared with 83% of white women
- Young black women have the longest and most significant delays in care

Richardson et al. *Am J Public Health* 2010;199(9):1769-1778. Lund et al. *Breast Cancer Res Treat*. 2008;109(3):545-557.

The Hard Truth About Clinical Research

- The unique physiology of black women has not been factored into clinical trial research
- To address the skewed mortality statistics among black women, they must be included in current and future breast cancer research

"[Inadequate minority representation in drug trials means that] we aren't doing good science... If we aren't doing good science and releasing these drugs out into the public, then we are at best being inefficient, at worst being irresponsible."

– Dr. Johnathan Jackson
Founder of Community Access
Recruitment and Engagement Center
Massachusetts General Hospital

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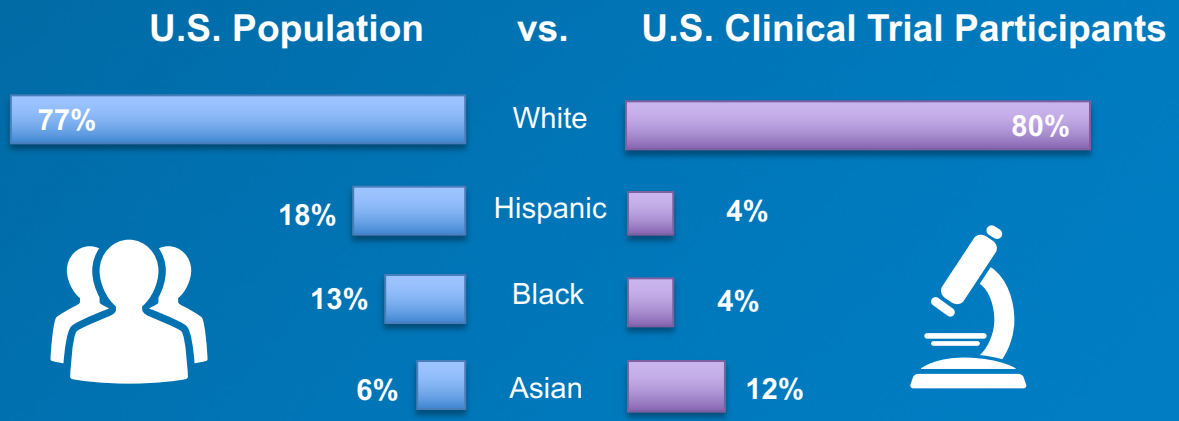
Blacks Are Significantly Underrepresented in Clinical Research

- Blacks represent 13.4% of the US population, but only 7% of clinical trial participants
- Since 2016, the FDA has approved four novel drugs for breast cancer. However, none of those clinical trials had more than 3% black participants



US Census Bureau. Camidge et al. *Future Oncol*. 2021;17(24):3271-3280.

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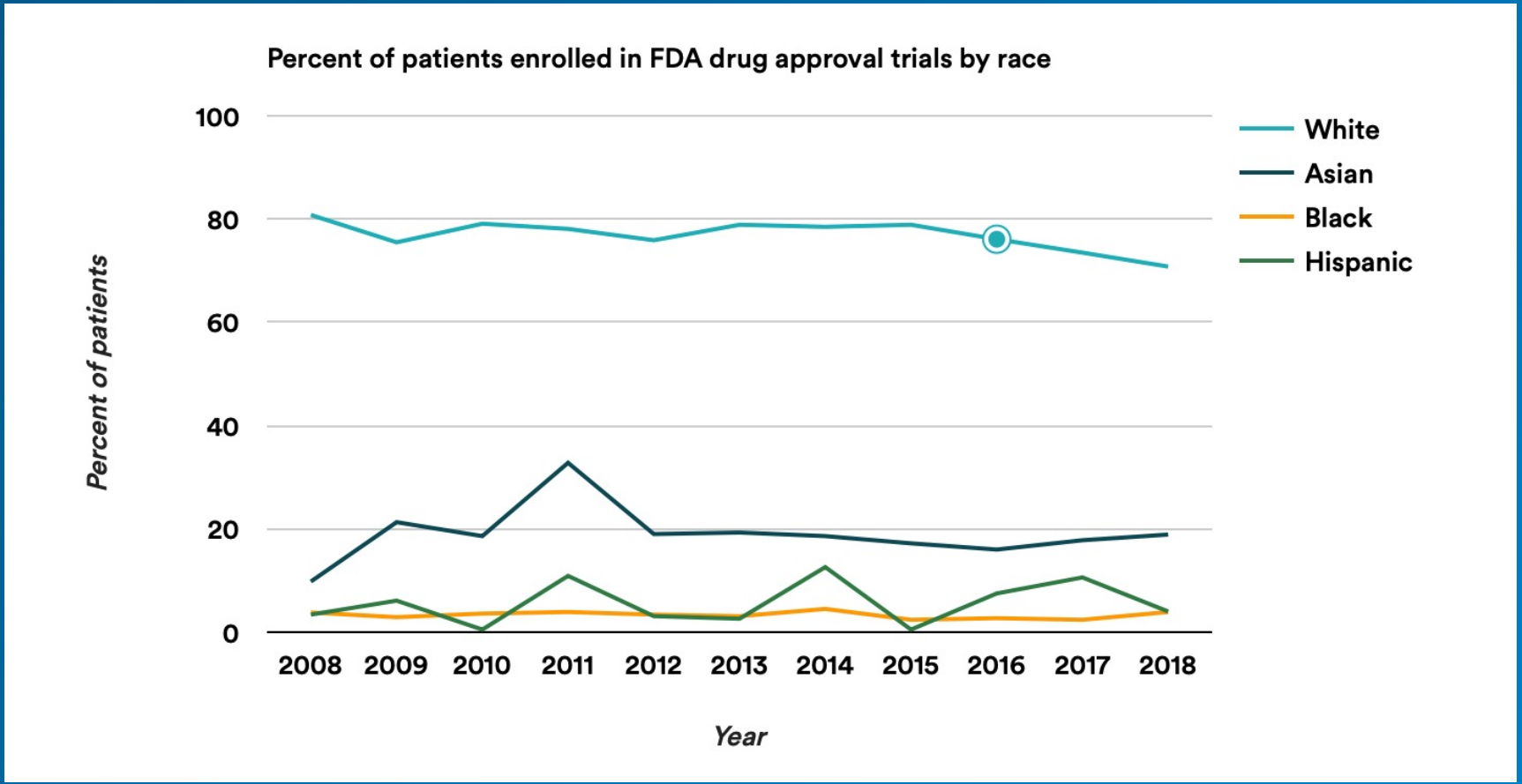
Disparity of Race Reporting and Representation in Clinical Trials Leading to Cancer Drug Approvals from 2008 to 2018



Loree et al. *JAMA Oncol*. 2019;5(10):e191870.

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Black Breast Cancer and Barriers to Clinical Research

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Black Data Matters

- The mission of Black Data Matters is to empower black patients to directly change a research and medical system that often fails them

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AXIS


MOREHOUSE
SCHOOL OF MEDICINE


touch
THE BLACK BREAST
CANCER ALLIANCE


BREASTCANCER.ORG


HI
Center for
Healthcare
Innovation


citizen


SUSAN G.
KOMEN.

Black Data Matters Goals

- Increase participation of black women in clinical trials to advance science and save lives
- Disrupt how the breast cancer ecosystem engages black women in clinical trial research
- Strive towards health equity for black women diagnosed with or at risk for breast cancer
- Help black women get the best breast cancer care

Our Research Aims To

- Confirm & validate tactical barriers to clinical trial participation
- Measure the impact of placebo myth
- Unpack the ramifications of medical mistrust
- Uncover & understand emotional barriers to clinical trial participation
- Understand the disconnect between current recruiting tactics/messaging and trial participation
- Prioritize the development of relevant and effective messaging to overcome barriers to participation

What Was Different About Our Qualitative Approach?

- Designed to explore the deeply rooted emotional barriers and cultural drivers affecting black women's resistance to clinical trials

- Intimate conversations were moderated by a black breast cancer survivor who is a patient advocate and respected member of the black breast cancer community

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Qualitative Methodology

- All digital
- 6 hour-long individual interviews
- 14 two-hour focus groups
- Participants (N = 48) included:
  - Black women with breast cancer who had never participated in a clinical trial, (n = 29)
  - Family members of black women with breast cancer (n = 10)
  - Black women at risk for breast cancer (n = 9)
- Participants ranged in age from 27-63 (mean age 42)
- Patient population included 19 patients with stage II and III breast cancer, and 10 patients with stage IV breast cancer

“Don’t do a clinical trial! You will get the sugar pill and die.”

- Metastatic Patient (Stage IV)

“I feel like a lot of the research is not with Black women. So if I had someone who went through it already, I trust their pain and their feedback.”

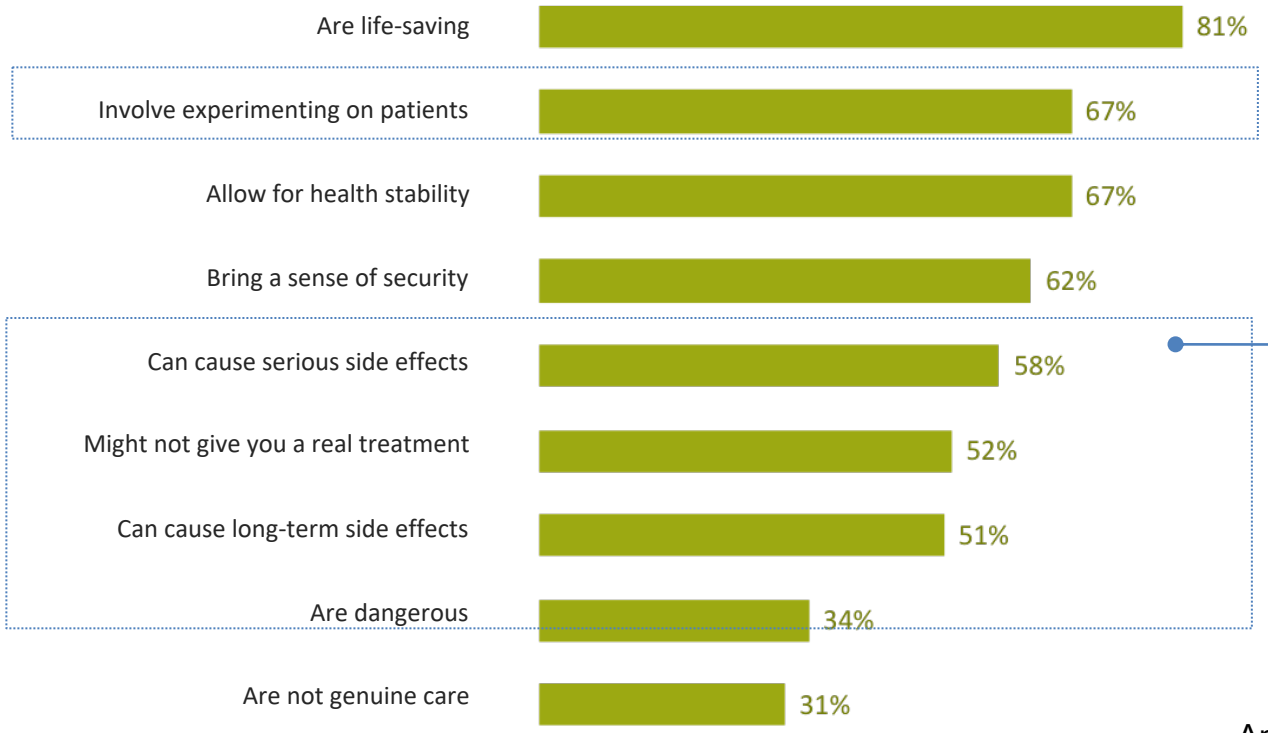
- Patient Stage II

“Whenever I would hear clinical trial, I would always think experiment because it was never really broken down to me, I never considered it, and I've never been approached personally to participate. But I know with my former oncologist, I wouldn't say that I trusted him too much… he didn't really answer a lot of my questions...”

- Patient Stage II/III

Although they see benefits, many view trial participation as risky due to clinical trials' experimental nature and belief that they can cause serious and long-term side effects

Clinical Trials Perceptions: Summary of Agree Somewhat / Agree Strongly

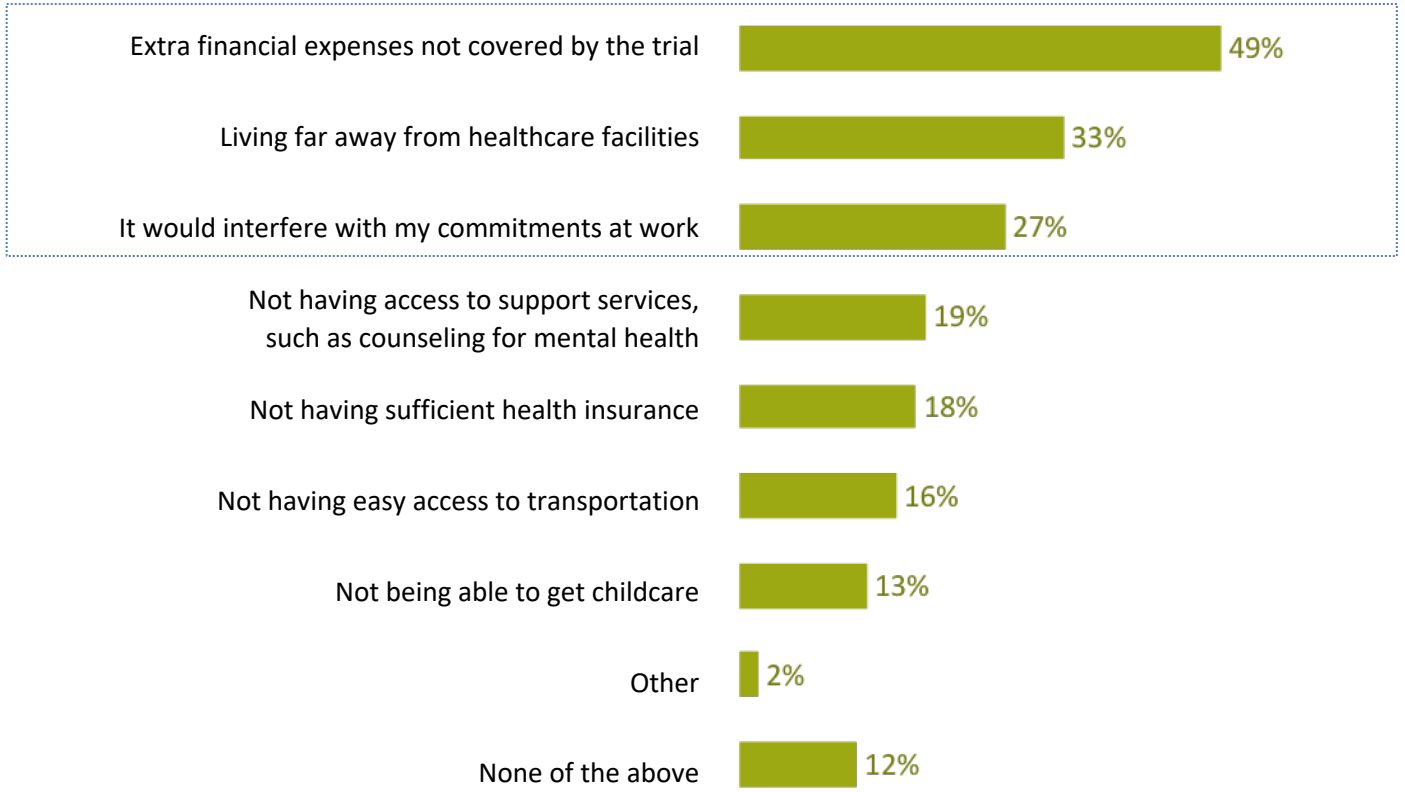


Includes 63% of **patients who are active in the breast cancer community** and 67% of **patients who have participated** in clinical trials

Among Patients Aware of Clinical Trials (n=245)

A3. How much do you agree or disagree with the following statements regarding clinical trials as a treatment for breast cancer?

Key logistical barriers to trial participation include financial expenses, living far away from healthcare facilities, and interference with work commitments

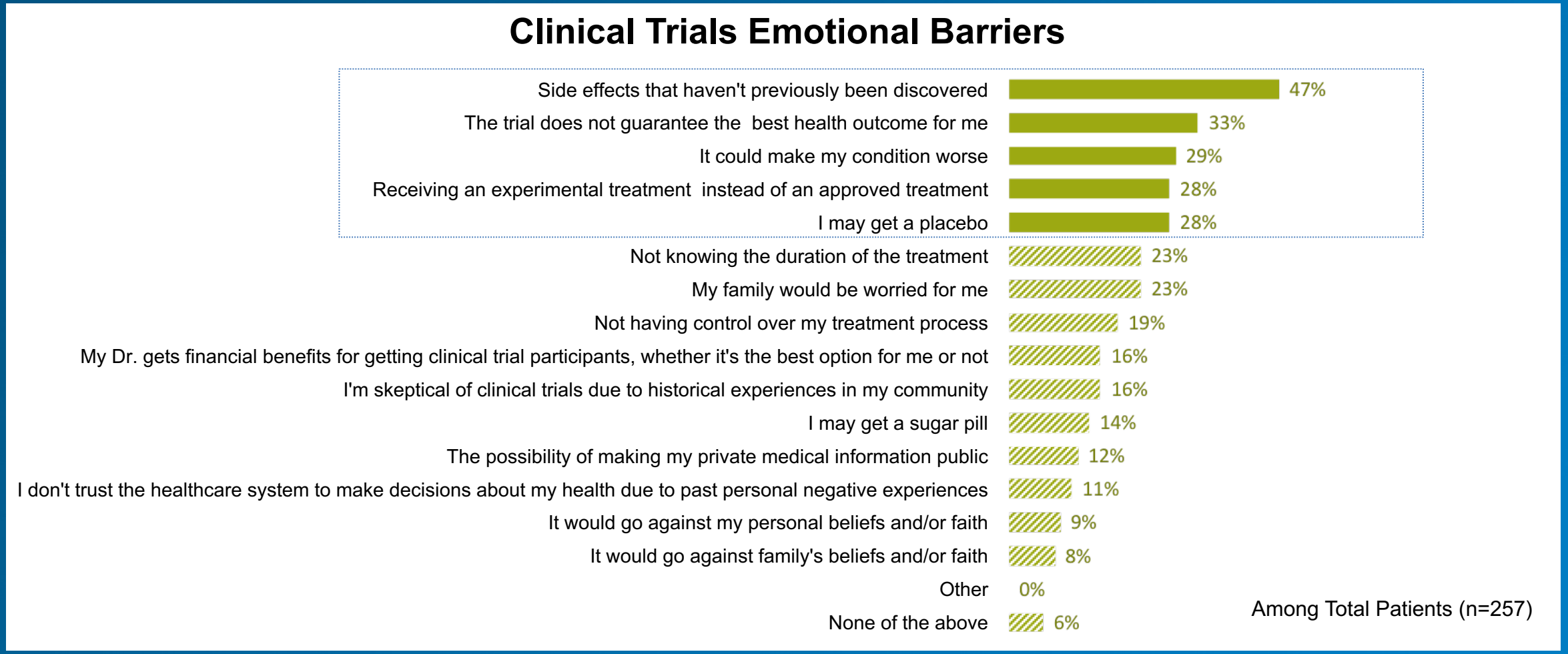


"Feels like you got to pack up and move somewhere and they watch you through a glass…too many movies. Everything is white and sterile."
– Patient Stage II-III

Among Total Patients (n=257)

A16. If you wanted to participate in a clinical trial for breast cancer and were selected as a participant, which of the following, if any, do you think would limit your ability to participate?

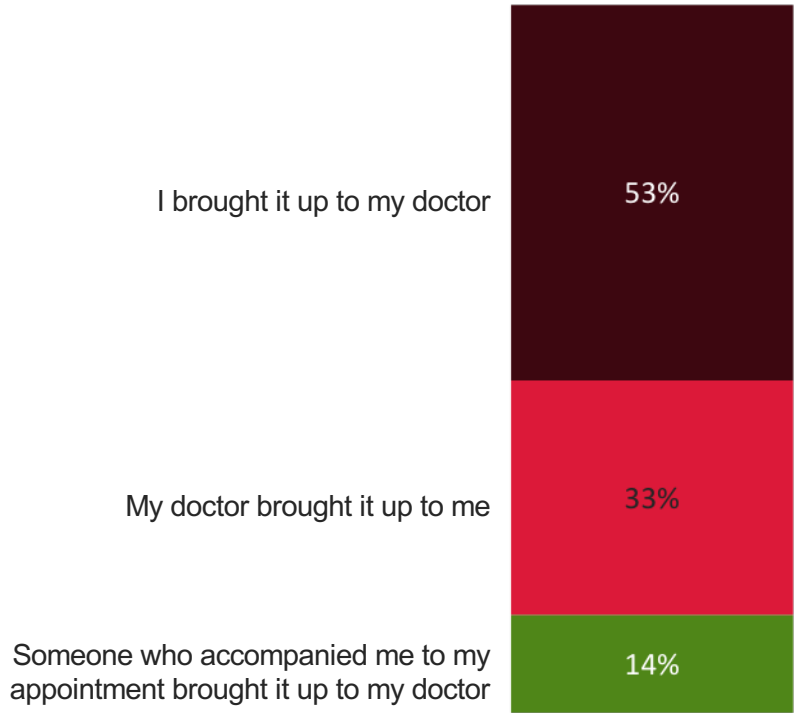
Uncertainty shapes patients' emotional barriers to trial participation



A17. Which of the following, if any, are concerns you have about participating in clinical trials for breast cancer?

Almost two-thirds of patients have discussed clinical trials with their doctor, but it's the patient who is more likely to initiate this conversation

Clinical Trial Discussions with Healthcare Providers



But Black women with breast cancer indicate clinical trials are left out of the conversation as a treatment option.

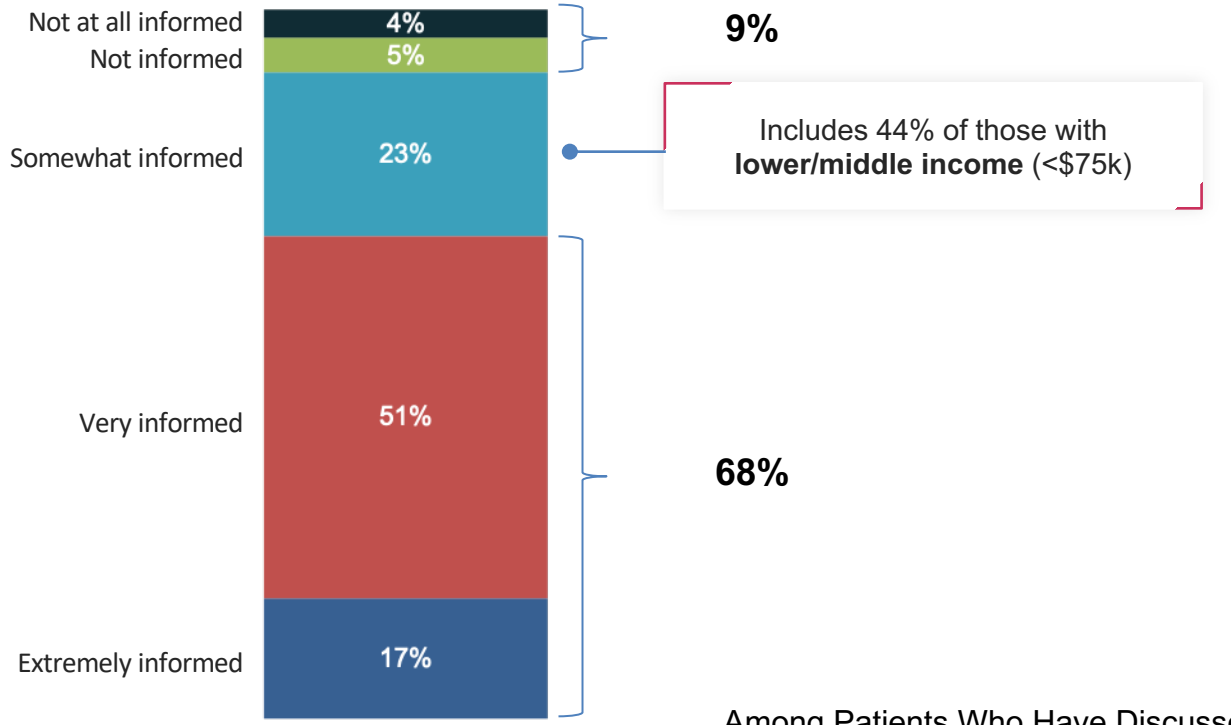
> *"Whenever I would hear clinical trial, I would always think experiment because it was never really broken down to me, I never considered it, and I've never been approached personally to participate. But I know with my former oncologist, I wouldn't say that I trusted him too much, but he didn't really answer a lot of my questions (…). I feel like it's the trust thing, I don't think a lot of times the relationship is built where you trust enough to say I'll participate."*
> **– Patient Stage II-III (4/15 7PM)**

Among Patients Who Have Discussed Clinical Trials (n=155)

A6. How many times have you talked to your doctor about possibly participating in a clinical trial for breast cancer?
A7. During the **first** time you talked to your doctor about possibly participating in a clinical trial for breast cancer, who brought it up?

Almost a third of patients who discussed clinical trials with their doctor felt somewhat or not informed after these conversations

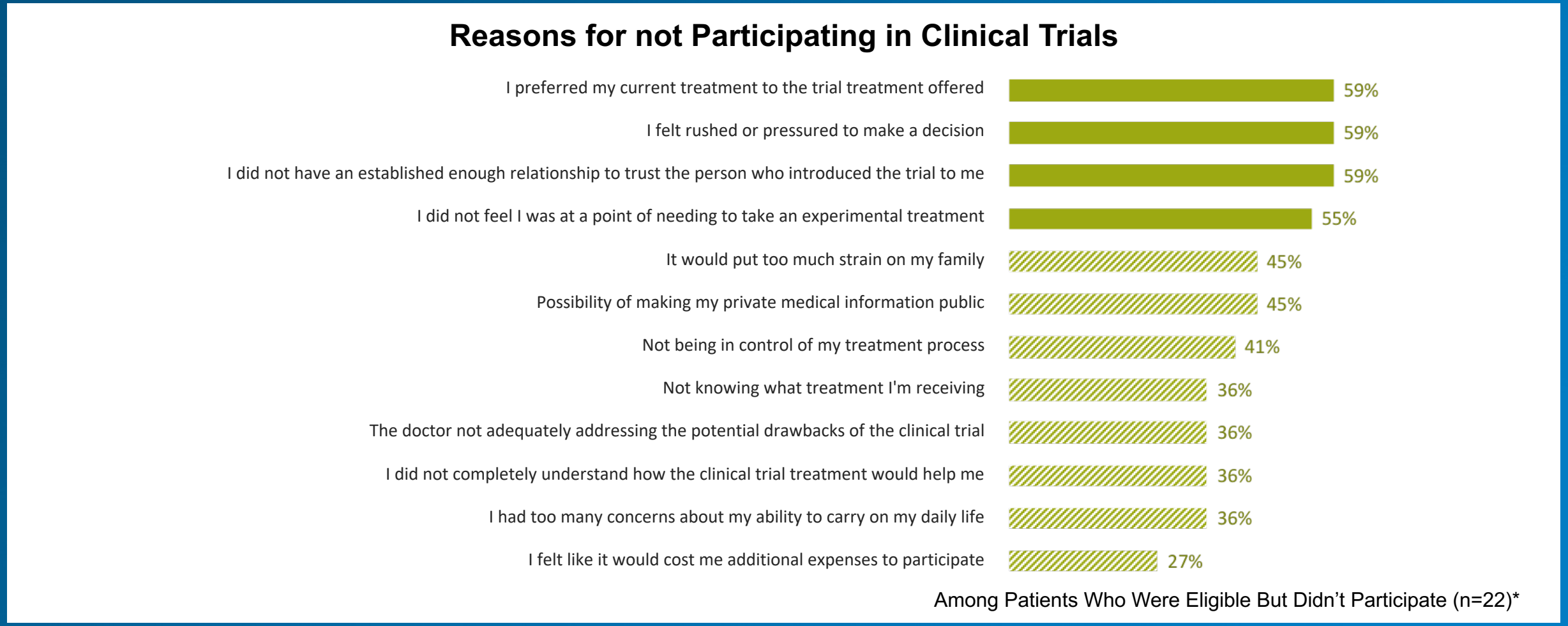
Informed about Clinical Trials after Discussion



Among Patients Who Have Discussed Clinical Trials (n=155)

A12. Overall, after all of the conversations you had with your doctor, how informed did you feel about the clinical trial?

Top reasons why eligible patients didn't participate include not having a well-established relationship with their HCP, feeling rushed, and a preference for their current treatment



*Small base size; directional finding only

A14. And how much did each of the following items influence your decision not to participate, after talking about it with your doctor?

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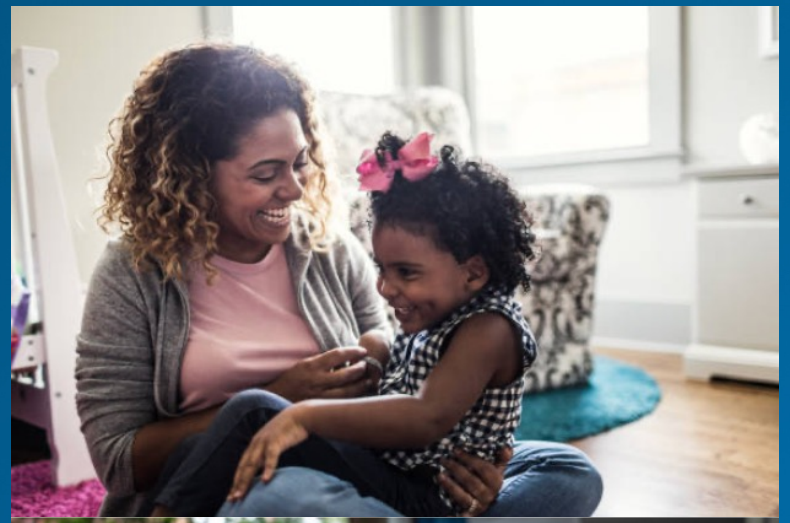
But There's Hope!

Culturally relevant, educational messaging delivered by a trusted member of the community is effective in driving a perception shift, with many respondents willing to reconsider their hesitation or skepticism

Messages That Changed Perceptions



- A clear, simple explanation of standard of care and how cancer trials work
- Think about community & family: Do it for your daughter!
- Every drug they take (ibuprofen, diphenhydramine) was once in a trial
- You get high quality of care & surveillance in a trial
- Even standard treatments are actually a trial for their body and their cancer

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Changing the Game

Rigorous research → **Changing the game**

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Movement Evolution

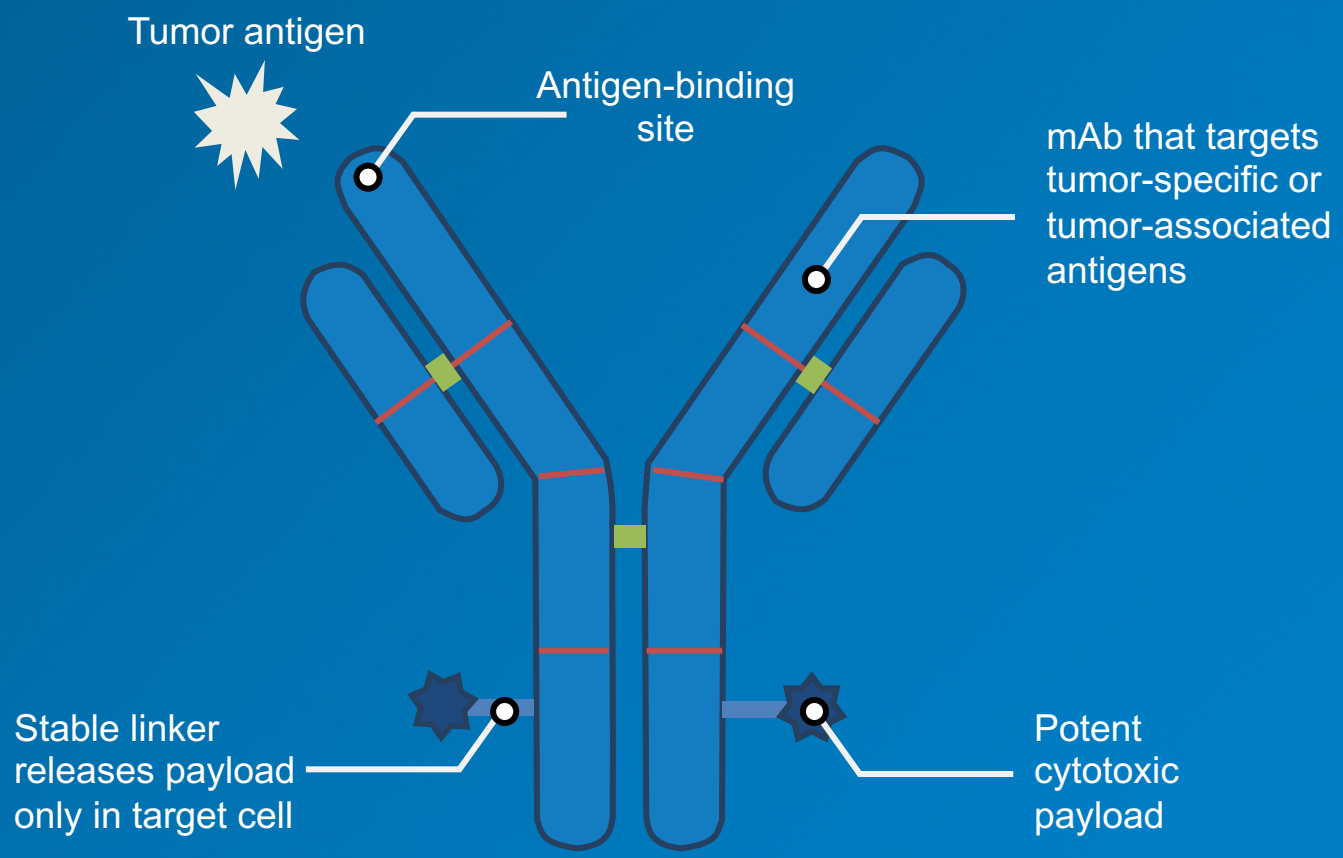
- A surround-sound, collaborative, community-based education movement
- Led by ‘Breastie Choir’
- The right information from the right voice delivered where black women live, work, pray and play

Advancing the Standard of Care With ADCs: Current and Emerging Treatment Regimens for TNBC

ADCs, antibody-drug conjugates; TNBC, triple-negative breast cancer.

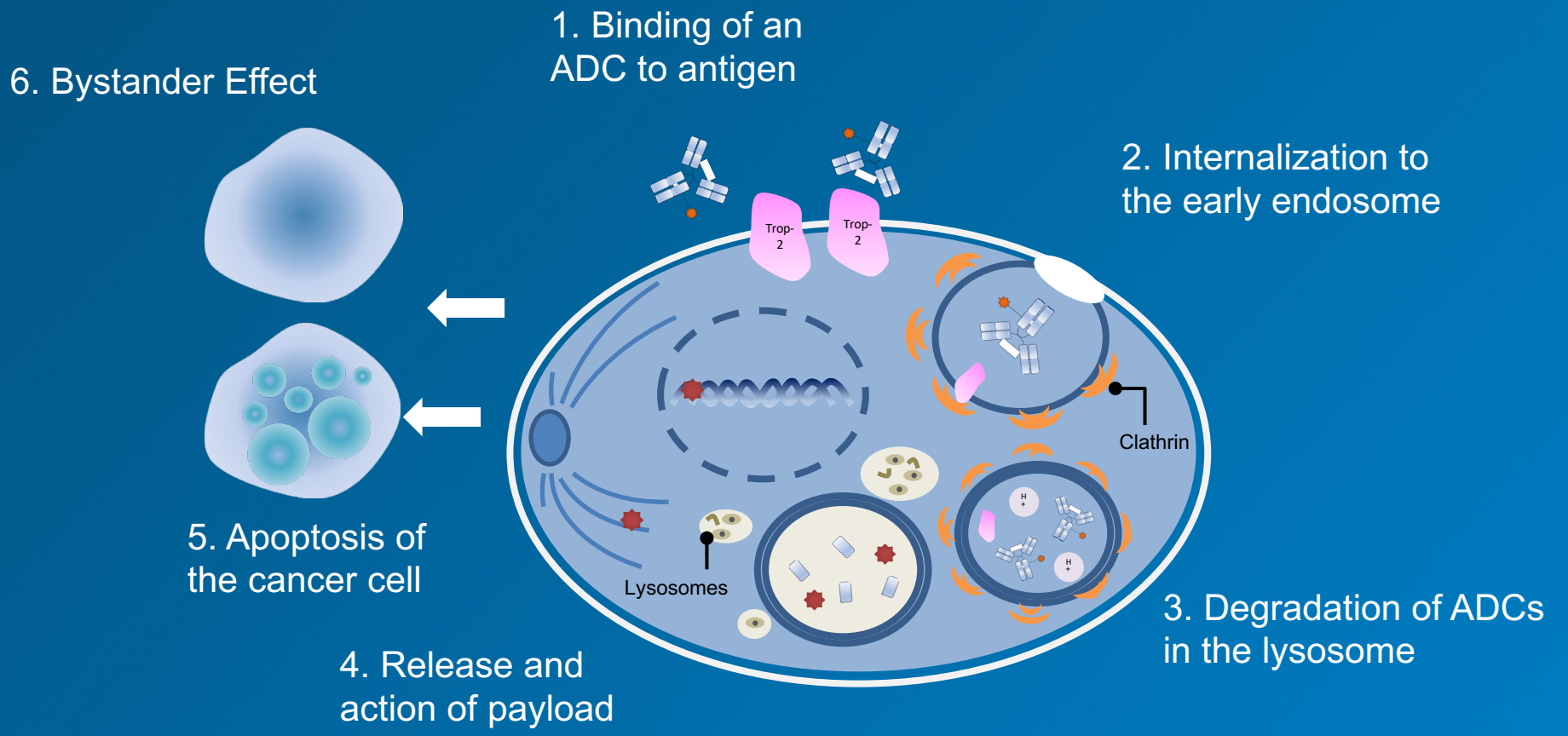
Structure of Antibody–Drug Conjugates

- **Tumor antigen:** Abundant in tumors, minimal in normal tissues; internalized upon ADC binding
- **Antibody:** High affinity and avidity for antigen; optimal pharmacokinetics; internalized
- **Linker:** Stable in plasma; efficient release of cytotoxic agent inside tumor cells
- **Payload:** Drug cytotoxic to targeted tumor cells; not hydrophobic; must be potent as limited number of molecules can be attached to antibody



ADC, antibody-drug conjugate; mAb, monoclonal antibody.
Thomas et al. *Lancet Oncol*. 2016;17:e254-e262.

Selective Delivery of Toxic Payload



ADC, antibody-drug conjugate.

Nagayama et al. *Target Oncol.* 2017;12(6):719-739.

FDA-Approved ADCs in Breast Cancer

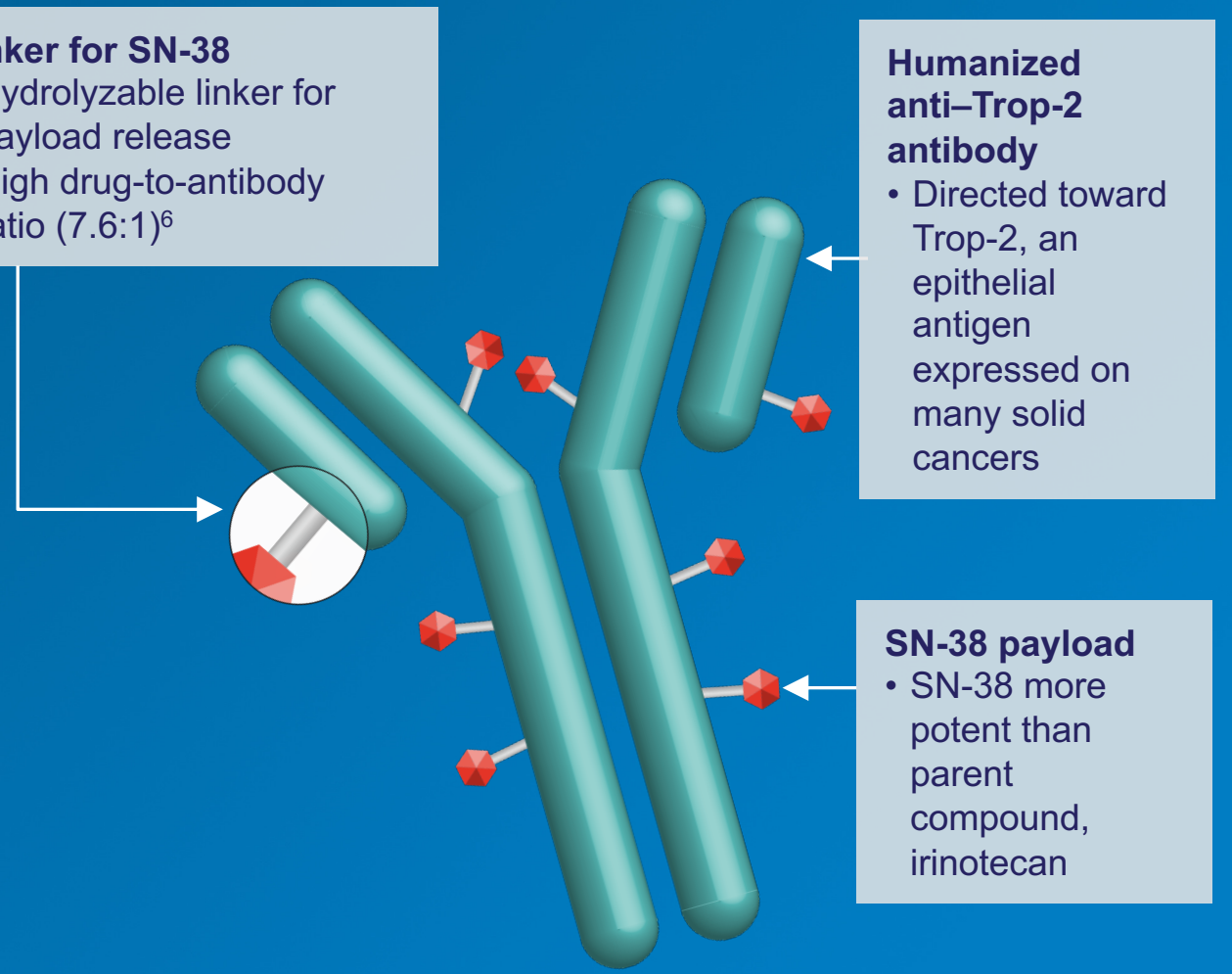
Drug Name	Target	Indication	FDA Approval
Trastuzumab emtansine	HER2	As a single agent, is indicated for the adjuvant treatment of patients with **HER2-positive early breast cancer** who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment	05/2019
		As a single agent, is indicated for the treatment of patients with **HER2-positive, metastatic breast cancer** who previously received trastuzumab and a taxane, separately or in combination	02/2013
Trastuzumab deruxtecan	HER2	Adults with unresectable or **metastatic HER2+ breast cancer** who have received ≥2 prior anti-HER2 based regimens	12/2019
Sacituzumab govitecan	TROP-2	Adult patients with unresectable, locally advanced or **metastatic TNBC** who have received ≥ 2 prior therapies (at least 1 in metastatic setting)	04/2020 (accelerated) 4/2021 (regular)

ADCs, antibody-drug conjugates; FDA, US Food & Drug Administration; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; TROP-2, trophoblast cell surface antigen 2.

FDA, 2013, 2019, 2020, 2021.

Sacituzumab Govitecan (SG)
A First-in-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for liberation of SN-38, a topoisomerase inhibitor, from antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and Fast Track designation in metastatic urothelial cancer[7]



ADC, antibody−drug conjugate; FDA, US Food & Drug Administration; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg et al. *Expert Opin Biol Ther*. 2020;20(8):871-885.
4. Nagayama et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo et al. *Bioconjugate Chem.* 2015;26:919-931. 6. Goldenberg et al. *Oncotarget.* 2015;6:22496-224512.
7. US Food & Drug Administration. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer.

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC

Metastatic TNBC
(per ASCO/CAP)

≥2 chemotherapies for advanced disease

[no upper limit; 1 of the required prior regimens could be from progression that occurred within a 12-month period after completion of (neo)adjuvant therapy)]

N = 529

NCT02574455

R
1:1

Sacituzumab Govitecan (SG)
10 mg/kg IV days 1 & 8, every 21-day cycle
(n = 267)

Treatment of Physician's Choice (TPC)*
(n = 262)

Continue treatment until progression or unacceptable toxicity

Primary Endpoint
- PFS†

Secondary Endpoints
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

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

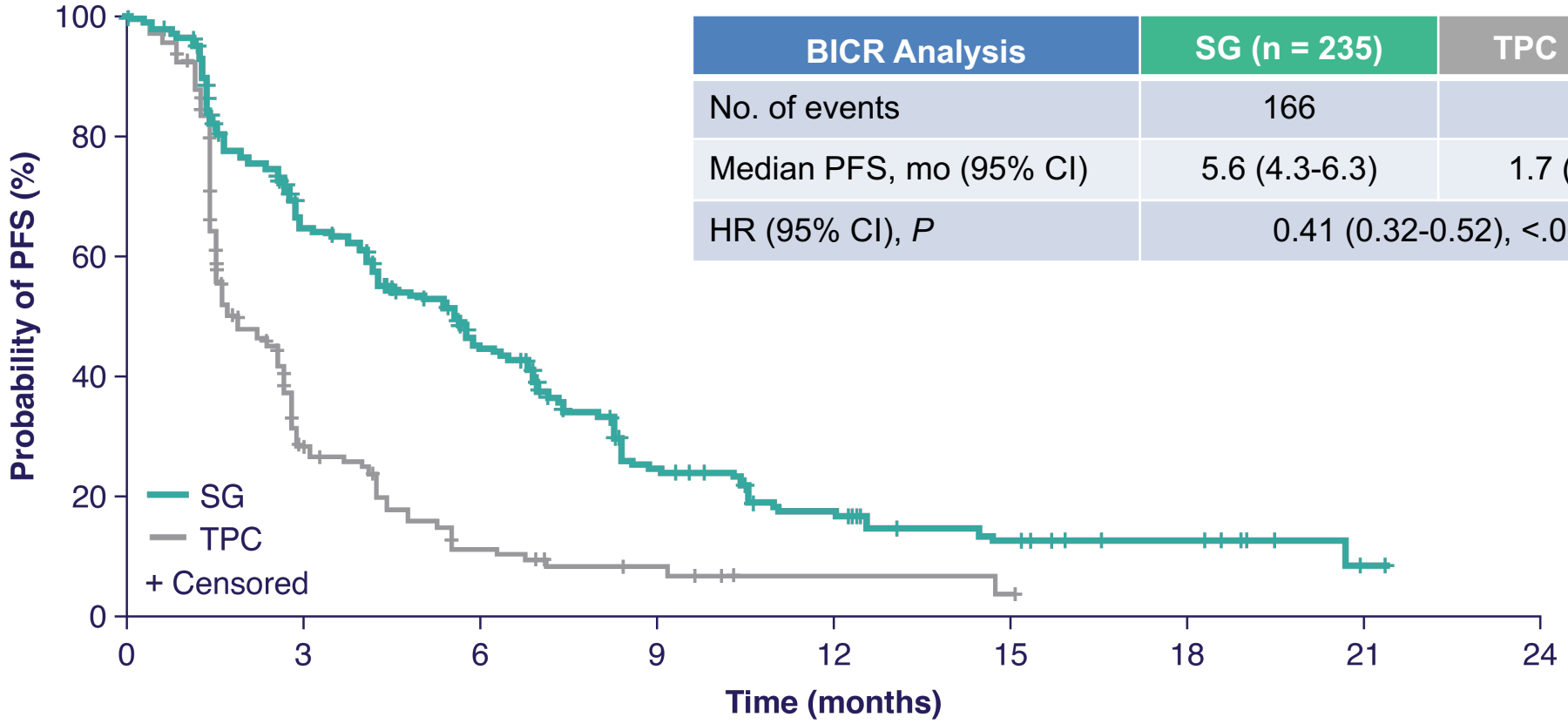
Data cutoff: March 11, 2020

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
Bardia A et al. *N Engl J Med* 2021; 384:1529-1541; National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

ASCENT: Progression-Free Survival (BICR Analysis) Brain Metastases-negative Population

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), *P*	0.41 (0.32-0.52), <.0001	



Number of patients at risk

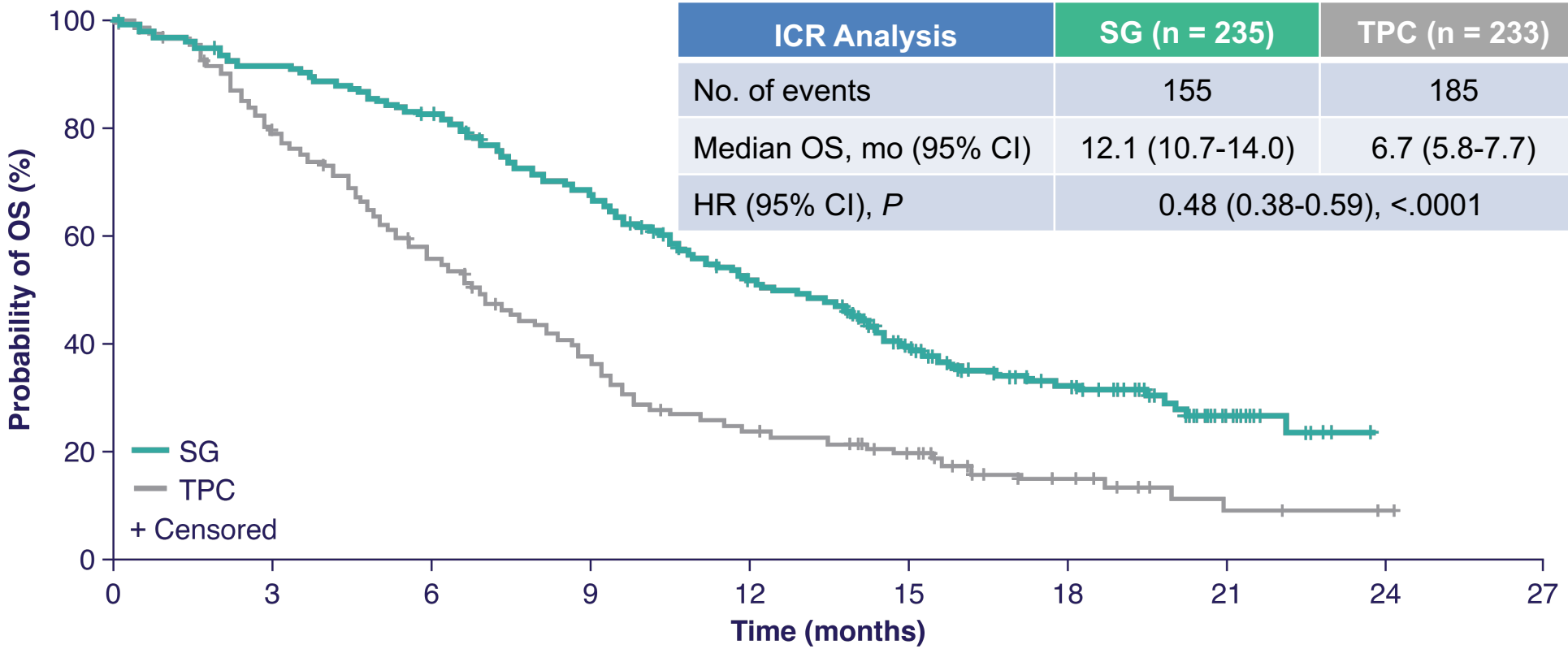
SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined 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], $P < .0001$).
BICR, blinded independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
Bardia et al. *Ann Oncol*. 2020;31(suppl 4):S1142-S1215; *N Engl J Med* 2021; 384:1529-1541.

AXIS Medical Education

ASCENT: Overall Survival

ICR 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), *P*	0.48 (0.38-0.59), <.0001	



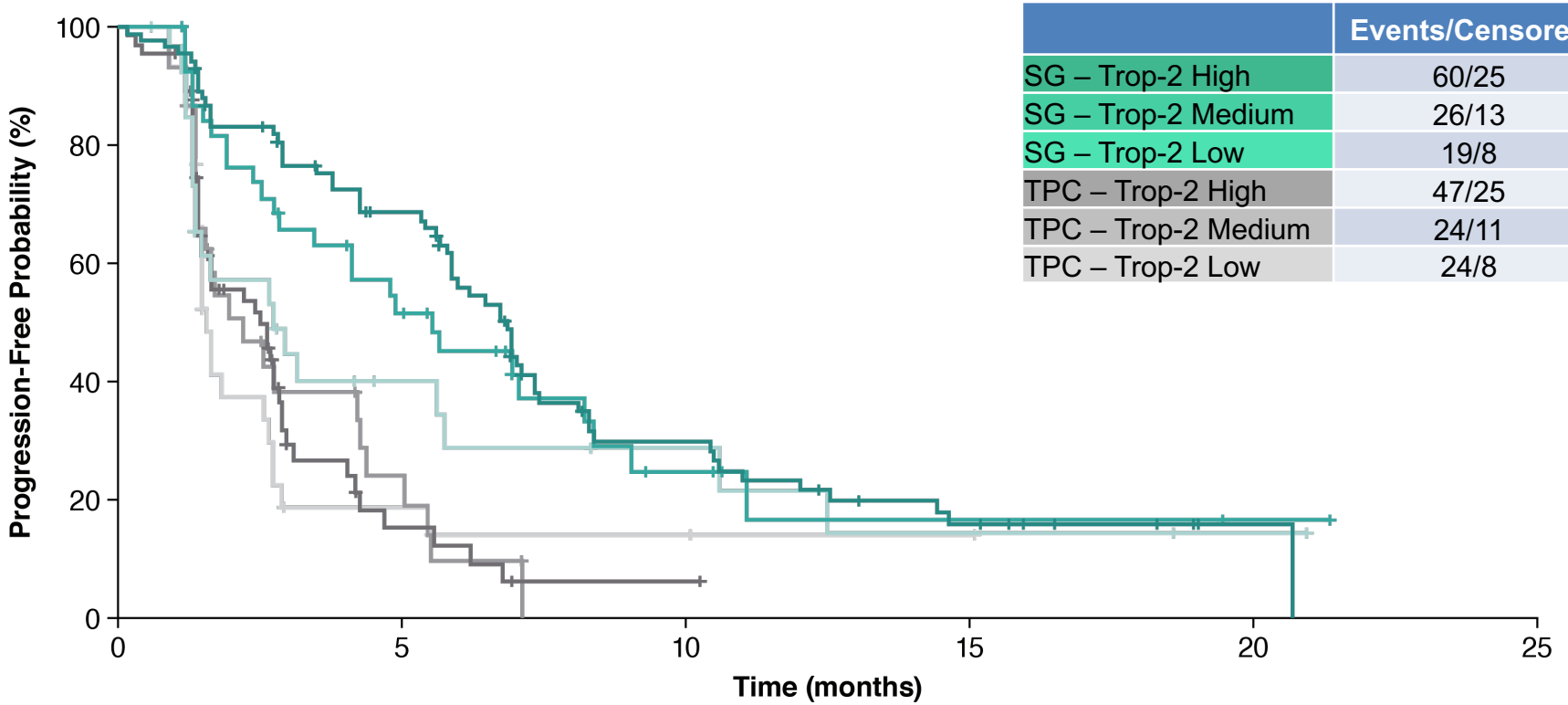
Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
Bardia et al. *Ann Oncol*. 2020;31(suppl 4):S1142-S1215; *N Engl J Med* 2021; 384:1529-1541.

AXIS Medical Education

ASCENT: Progression-Free Survival by Trop-2 Expression



	Events/Censored
SG – Trop-2 High	60/25
SG – Trop-2 Medium	26/13
SG – Trop-2 Low	19/8
TPC – Trop-2 High	47/25
TPC – Trop-2 Medium	24/11
TPC – Trop-2 Low	24/8

	Trop-2 High | H-score: 200-300		Trop-2 Medium | H-score: 100-200		Trop-2 Low | H-score: <100	
	SG (n = 85)	TPC (n = 72)	SG (n = 39)	TPC (n = 35)	SG (n = 27)	TPC (n = 32)
Median PFS, mo (95% CI)	6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)

Assessed in brain metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
H-score, histochemical score; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

Bardia et al. *Ann Oncol*. 2021;32(9):1148-1156.

ASCENT: TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

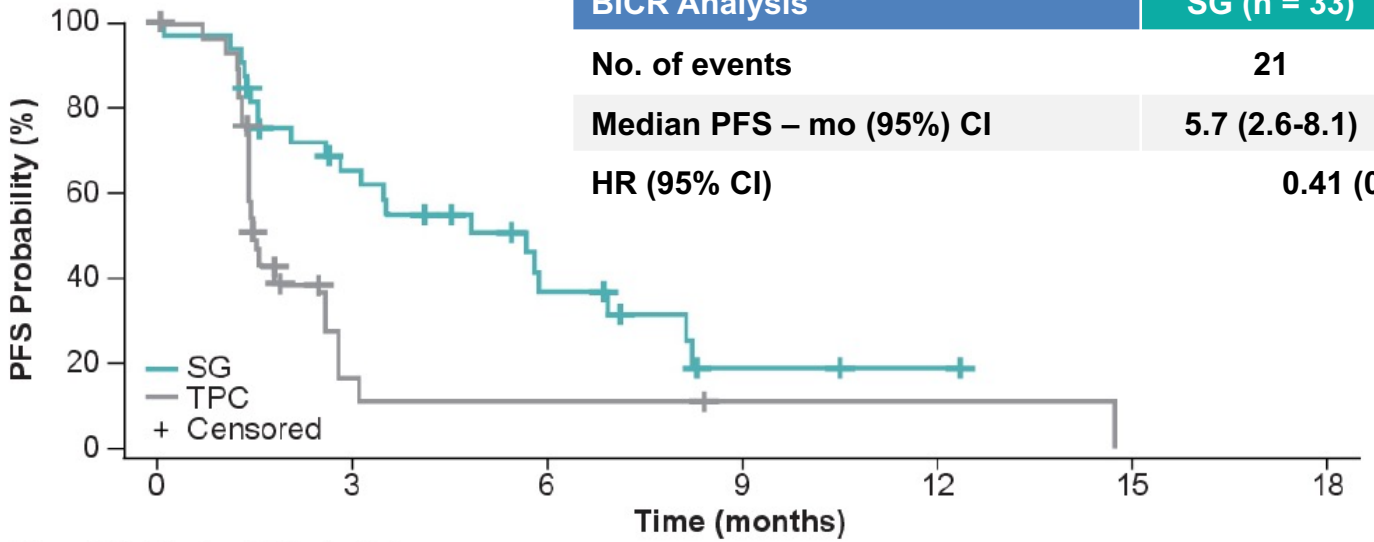
		SG (n = 258)			TPC (n = 224)		
TRAE*		All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	63	46	17	43	27	13
	Anemia‡	34	8	0	24	5	0
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	Diarrhea	59	10	0	12	<1	0
	Nausea	57	2	<1	26	<1	0
	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%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (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 received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months

*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'.
‡Combined preferred terms of 'anemia' and 'decreased hemoglobin'.
§Combined preferred terms of 'leukopenia' and 'decreased white blood cell count'.
G-CSF, granulocyte-colony stimulating factor; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAEs, treatment-related adverse events.
Bardia et al. *Ann Oncol*. 2021;32(9):1148-1156.

Assessment of Sacituzumab Govitecan in Patients with Prior Neoadjuvant/Adjuvant Chemotherapy in the Phase 3 ASCENT Study in Metastatic TNBC: Second-line Patients

Progression-Free Survival



BICR Analysis	SG (n = 33)	TPC (n = 32)
No. of events	21	23
Median PFS – mo (95%) CI	5.7 (2.6-8.1)	1.5 (1.4-2.6)
HR (95% CI)	0.41 (0.22-0.76)	

FDA approved for mTNBC patients with ≥2 systemic therapies, at least one of them for metastatic disease

Assessed by independent central review in the BM-negative population who recurred ≤12 months after (neo)adjuvant chemotherapy and received 1 line of therapy in the metastatic setting prior to study enrollment.
BICR, blinded independent central review; BM_{NEG}, brain metastases negative; CBR, clinical benefit rate; CI, confidence interval; HR, hazard ratio; mDOR, median duration of response; mOS, median overall survival; mPFS; median progression-free survival; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; R/R, relapsed/refractory; SG, sacituzumab govitecan; TNBC, triple negative breast cancer; TPC, treatment of physician's choice.
Carey et al. *J Clin Oncol*. 2021;39(15):1080.

AXIS Medical Education

Saci-IO TNBC Study:
SG +/- Pembrolizumab in First-line PD-L1- TNBC

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

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

Stable brain mets
Strata: Neo/adjuvant progression <12 mo

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

R
1:1

N = 110

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

sacituzumab govitecan 10 mg/kg d1,8 q21 days

Primary Endpoint
- PFS

Secondary Endpoint
- OS, ORR
- DOR, CBR

80% power to detect PFS improvement from 5.5 mo (Arm B) to 8.5 mo (Arm A)

NCT04468061. PI: Sara Tolaney/Ana Garrido-Castro.
CBR, clinical best response; Chemo, chemotherapy; DOR, duration of response; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; mets, metastases; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; PR, partial response; Q3wks, every 3 weeks; SG, sacituzumab govitecan.

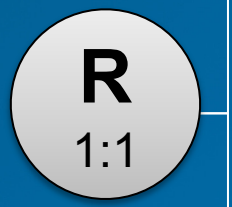
Saci-IO HR+ Study:
SG +/- Pembrolizumab in HR+ PD-L1+ MBC

HR+ HER2- mBC:
≥ 1 Hormonal
0-1 Prior Chemo

PD-L1 ≥ 10% by 22C3
ER ≥ 1%
PR ≥ 1%
HER2-negative

Stable brain mets

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



N = 110

sacituzumab govitecan
10 mg/kg IV d1,8 q21 days
+
pembrolizumab
200 mg Q3wk

sacituzumab govitecan
10 mg/kg IV d1,8 q21 days

Primary Endpoint
- PFS

Secondary Endpoint
- OS, ORR
- DOR, CBR

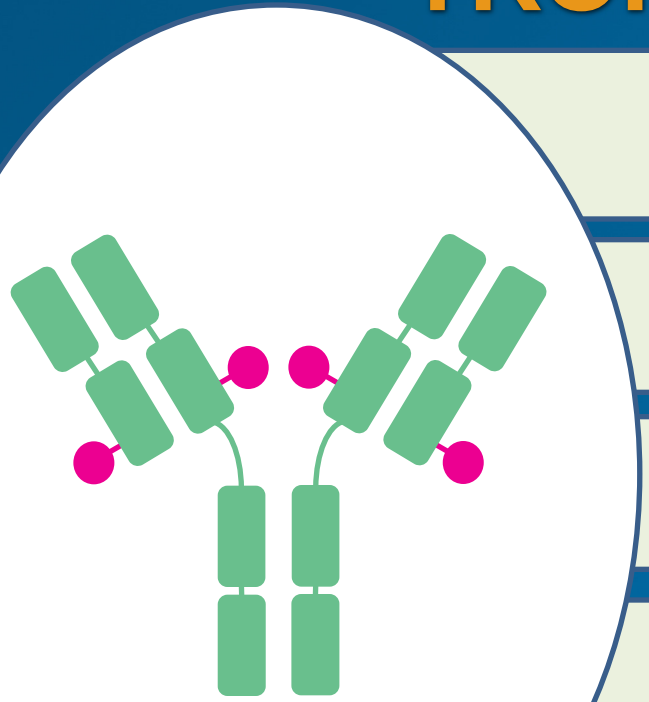
80% power to detect PFS improvement from 5.5 mo (Arm B) to 8.5 mo (Arm A)

NCT04448886. PI: Sara Tolaney/Ana Garrido-Castro.
CBR, clinical best response; Chemo, chemotherapy; DOR, duration of response; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mets, metastases; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; PR, partial response; Q3wk, every 3 weeks; SG, sacituzumab govitecan.

Combination Trials In TNBC

- MORPHEUS-TNBC, a phase 1b/2 study that includes a cohort of PD-L1-positive patients receiving sacituzumab govitecan combined with atezolizumab (NCT03424005)
- Combination of sacituzumab govitecan plus durvalumab (Syed, 2020)
- Phase 3 trial of sacituzumab govitecan plus pembrolizumab vs chemotherapy plus pembrolizumab as a first-line treatment for patients with locally advanced or metastatic TNBC

Datopotamab Deruxtecan (DS-1062): 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[1]
- High-potency membrane-permeable payload (DXd; topoisomerase inhibitor) that requires TROP2-mediated internalization for release[2]
- DS-1062 has a DAR of 4 for optimized therapeutic index[2]
- DS-1062 has a substantially **longer half-life** than SG (≈ 5 days vs 11-14 hours), enabling a more optimal dosing regimen[3]
- SG's DLT is neutropenia, while DS-1062's DLTs are maculopapular rash and stomatitis/mucosal inflammation[4-6]

1. Goldenberg et al. *Oncotarget* 2015;6:22496-22512.
2. Ogitani et al. *Clin Cancer Res* 2016;22(20):5097-5108.
3. Ocean et al. *Cancer.* 2017;123:3843-3854.
4. Bardia et al. *J Clin Oncol* 2017;35:2141-2148.
5. Lisberg et al. *J Clin Oncol* 2020;38(15):9619.
6. Heist et al. Oral presentation at: WCLC; September 7-10, 2019; Barcelona, Spain.

DAR, drug-to-antibody ratio; DLT, dose-limiting toxicity; SG, sacituzumab govitecan.

TROPION-PanTumor01: TNBC Cohort

Phase 1, First-in-human, Dose Escalation and Expansion Study

- Advanced/metastatic HR-/HER2-negative breast cancer (TNBC)[a]
- Relapsed/progressed on standard treatment
- Unselected for TROP2 expression[b]
- Measurable disease (per RECIST version 1.1)

→

Dato-DXd 6mg/kg IV Q3W

N ≈ 40

2 patients received 8 mg/kg prior to selection of the 6-mg/kg dose for dose expansion

→

Primary objectives include:

- Safety, Tolerability

Secondary objectives include:

- Efficacy, Pharmacokinetics

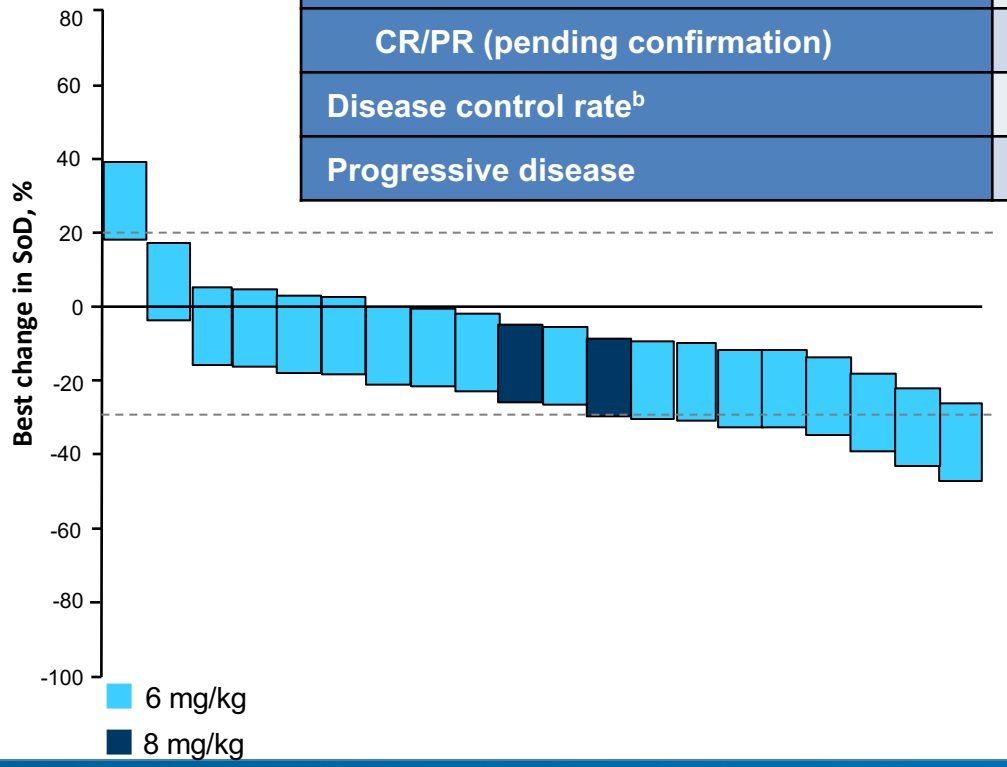
Data cutoff January 8, 2021

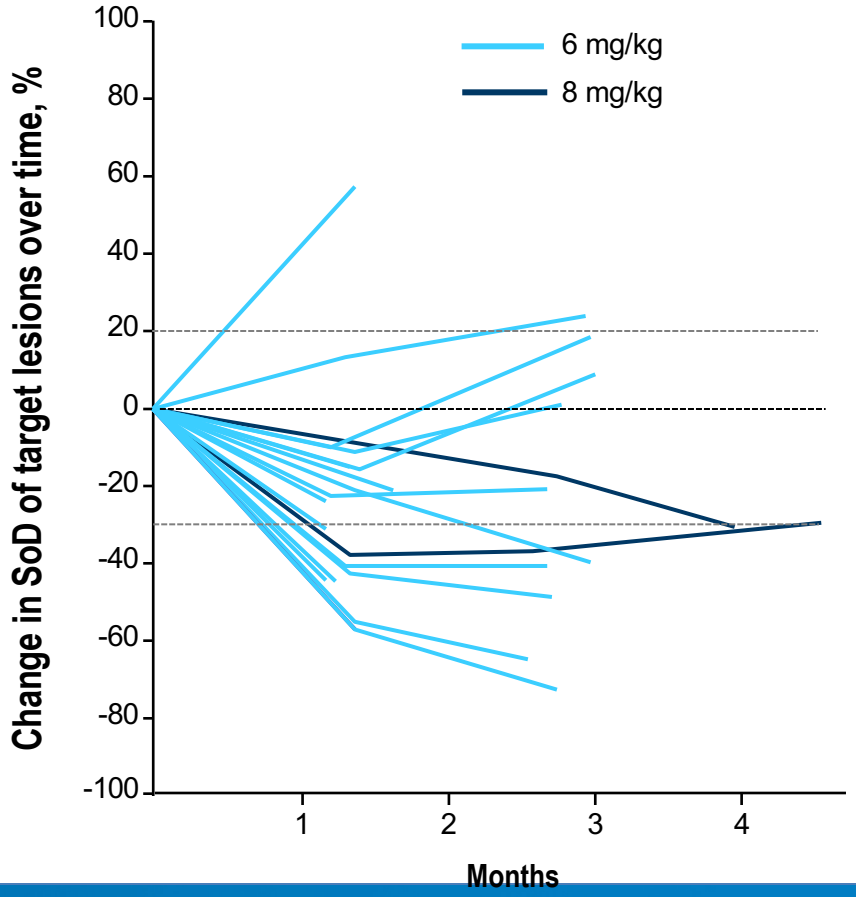
- Current analysis includes 24 patients treated at the 6-mg/kg dose (n = 22) and 8-mg/kg dose (n = 2)[c]
- Treatment ongoing in 18 patients (75%); 6 patients (25%) discontinued treatment, all due to disease progression[d]

[a] Estrogen receptor positivity <1%; [b] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression;
[c] An HR+ cohort is currently open for enrollment at 6 mg/kg; [d] Progression includes progressive disease per RECIST 1.1 and clinical progression. HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.
NCT03401385.

TROPION-PanTumor01: Dato-DXd TNBC Cohort Antitumor Activity (by BICR)

Patients, n (%)[a]	N = 21
Objective response rate	9 (43)
CR/PR (confirmed)	5 (24)
CR/PR (pending confirmation)	4 (19)
Disease control rate[b]	20 (95)
Progressive disease	1 (5)





Data cutoff: January 8, 2021

[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 3 patients at the data cutoff. One patient was not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD.

[b] Includes patients with a best overall response of CR, PR, stable disease, or non-CR/non-PD.

BICR, blinded independent central review; CR, complete response; PD, progressive disease; PR, partial response; SoD, sum of diameters; TNBC, triple-negative breast cancer.

Bardia et al. *Ann Oncol*. 2021;32(suppl_2):S60-S78. 10.1016/annonc/annonc508.

TROPION-PanTumor01: Dato-DXd TNBC Cohort Majority of Patients Were Heavily Pretreated

Patient Characteristics	N = 24
Age, median (range), y	57.0 (32-82)
Country, n (%)	
US	18 (75)
Japan	6 (25)
ECOG PS, n (%)	
0	8 (33)
1	16 (67)
De-novo metastatic disease, n (%)	
Yes	9 (38)
No	15 (63)

Patient Characteristics	N = 24
Brain metastases, n (%)	2 (8)
Prior therapies, median (range), n[a]	4 (1-9)
≥2 prior lines of therapy, n (%)[a]	21 (88)
Previous systemic treatment, n (%)[a]	
Taxanes	20 (83)
Platinum-based chemotherapy	12 (50)
Immunotherapy	8 (33)
Sacituzumab govitecan	2 (8)
PARPi	1 (4)

[a] Includes prior lines of therapy in the (neo)adjuvant and/or metastatic setting.
Data cutoff: January 8, 2021
ECOG PS, Eastern Cooperative Oncology Group performance status; PARPi, poly (ADP-ribose) polymerase inhibitor; TNBC, triple negative breast cancer.
Bardia et al. *Ann Oncol*. 2021;32(suppl_2):S60-S78. 10.1016/annonc/annonc508.

TROPION-PanTumor01: Dato-DXd TNBC Cohort
Dato-DXd Demonstrated a Manageable Safety Profile

Patients, n (%)	N = 24	
	Any grade	Grade ≥3
TEAEs	24 (100)	8 (33)
Treatment related	24 (100)	4 (17)
Serious TEAEs[a]	3 (13)	3 (13)
Treatment related	0	0
Fatal TEAEs	0	–
Treatment related	0	–

- Dose reductions due to AEs occurred in 6 patients (25%) and were most commonly due to stomatitis (3 patients [13%]) and mucosal inflammation (2 patients [8%])
- No patients discontinued treatment due to AEs

Data cutoff: January 8, 2021

[a] A serious TEAE was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect or is an important medical event.

AE, adverse event; TEAE, treatment-emergent adverse event; TNBC, triple-negative breast cancer.

Bardia et al. *Ann Oncol*. 2021;32(suppl_2):S60-S78. 10.1016/annonc/annonc508.

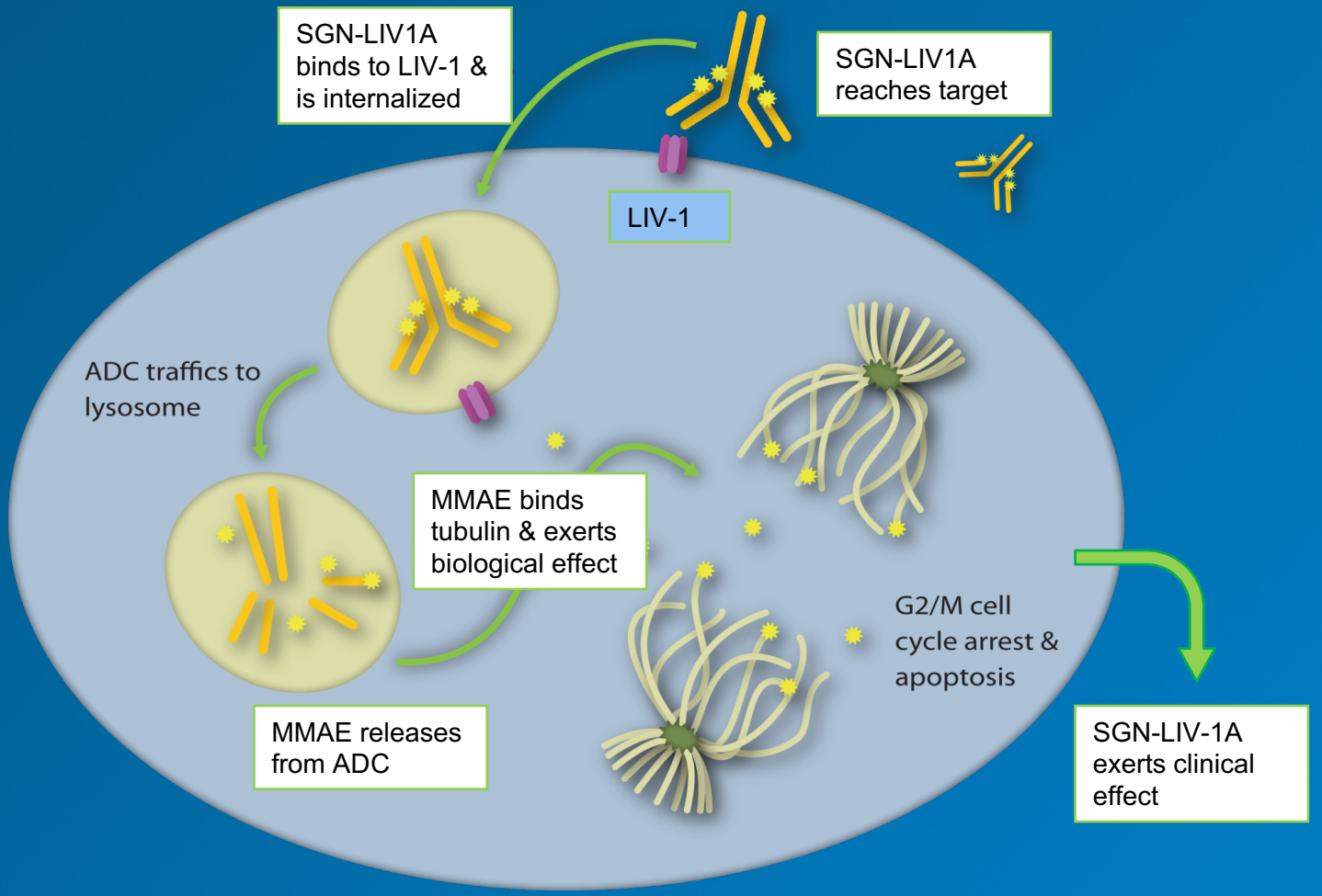
TROPION-PanTumor01: Dato-DXd TNBC Cohort Manageable, Predominantly Nonhematologic AEs

- Predominantly grade 1 or 2 (67%) and nonhematologic
- No cases of grade ≥3 diarrhea or neutropenia
- No cases adjudicated as drug-related ILD were observed

Preferred Term, n (%)[a]	N = 24	
	Any grade	Grade ≥3
TEAEs	24 (100)	8 (33)
Stomatitis	15 (63)	3 (13)
Nausea	15 (63)	0
Fatigue	10 (42)	1 (4)
Vomiting	10 (42)	0
Alopecia	6 (25)	–
Cough	5 (21)	0
Pruritus	5 (21)	0
Anemia	4 (17)	1 (4)
Headache	4 (17)	0
Constipation	4 (17)	0

[a] TEAEs observed in ≥15% of patients.
Data cutoff: January 8, 2021
AEs, adverse events; ILD, interstitial lung disease; TEAEs, treatment-emergent adverse events; TNBC, triple-negative breast cancer.
Bardia et al. *Ann Oncol*. 2021;32(suppl_2):S60-S78. 10.1016/annonc/annonc508.

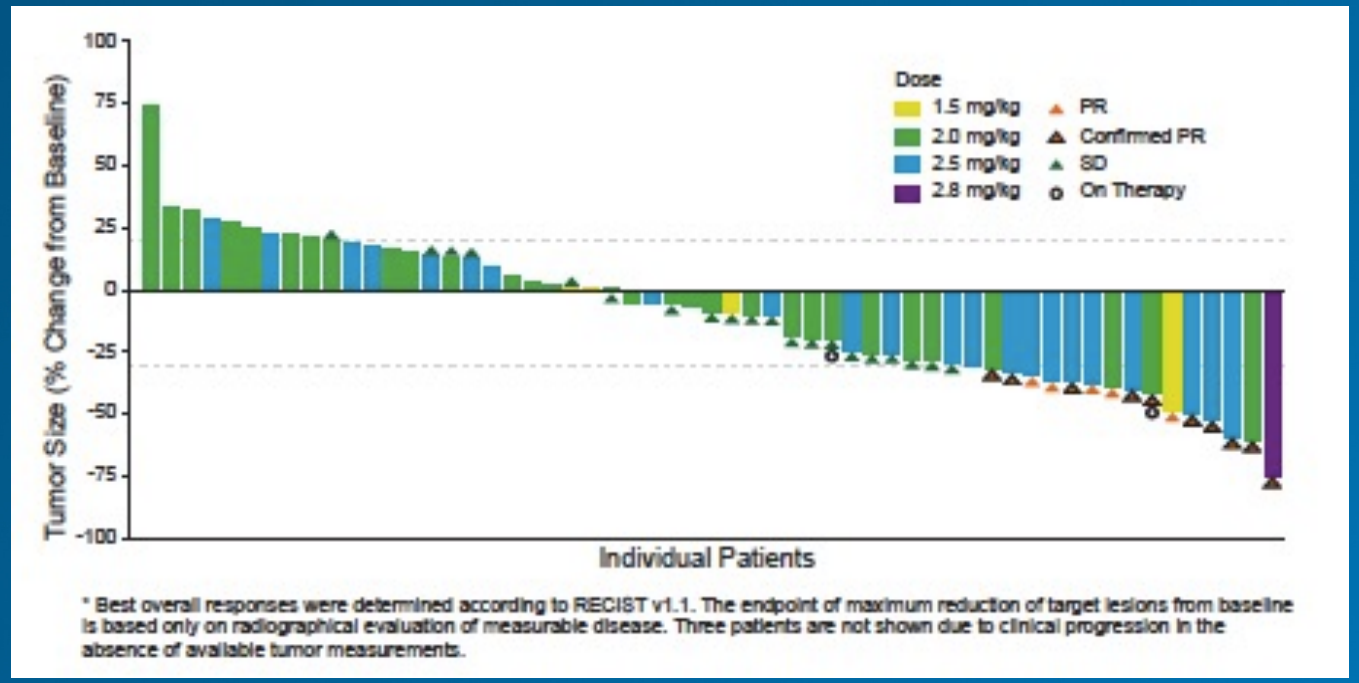
Ladiratuzumab Vedotin (SGN-LIV1A) Mechanism of Action



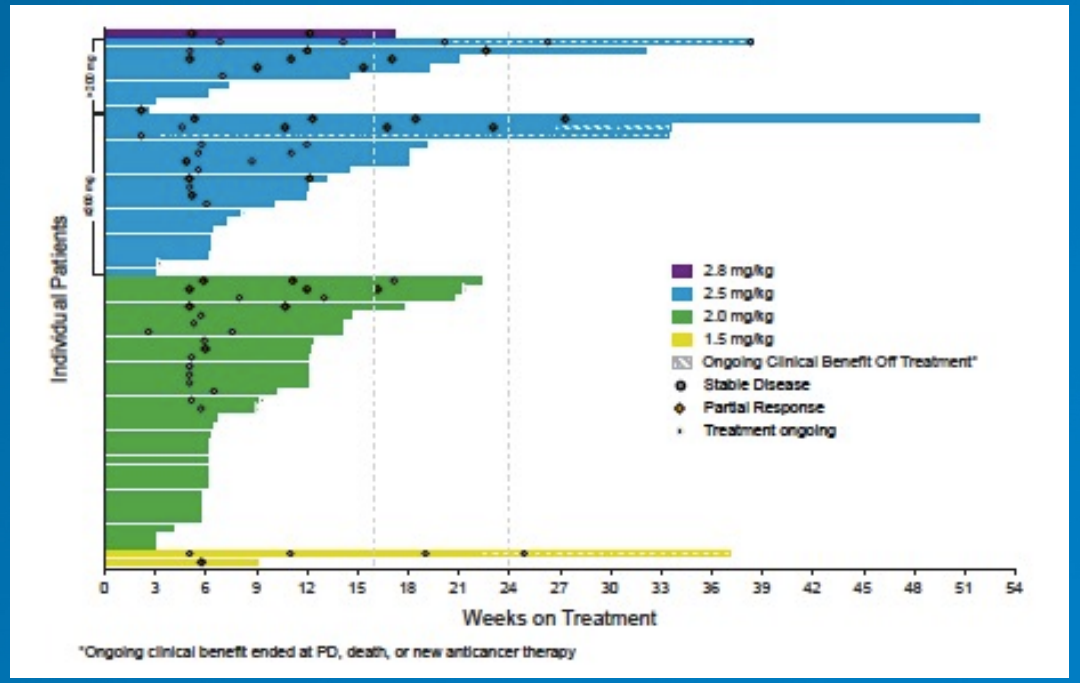
ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E.

Sussman et al. *Mol Cancer Ther*. 2014 Dec; 13(12):2991-3000.

Ladiratuzumab Vedotin (SGN-LIV1A)



Median 3 prior chemo for MBC
TNBC n = 63
ORR = 25%



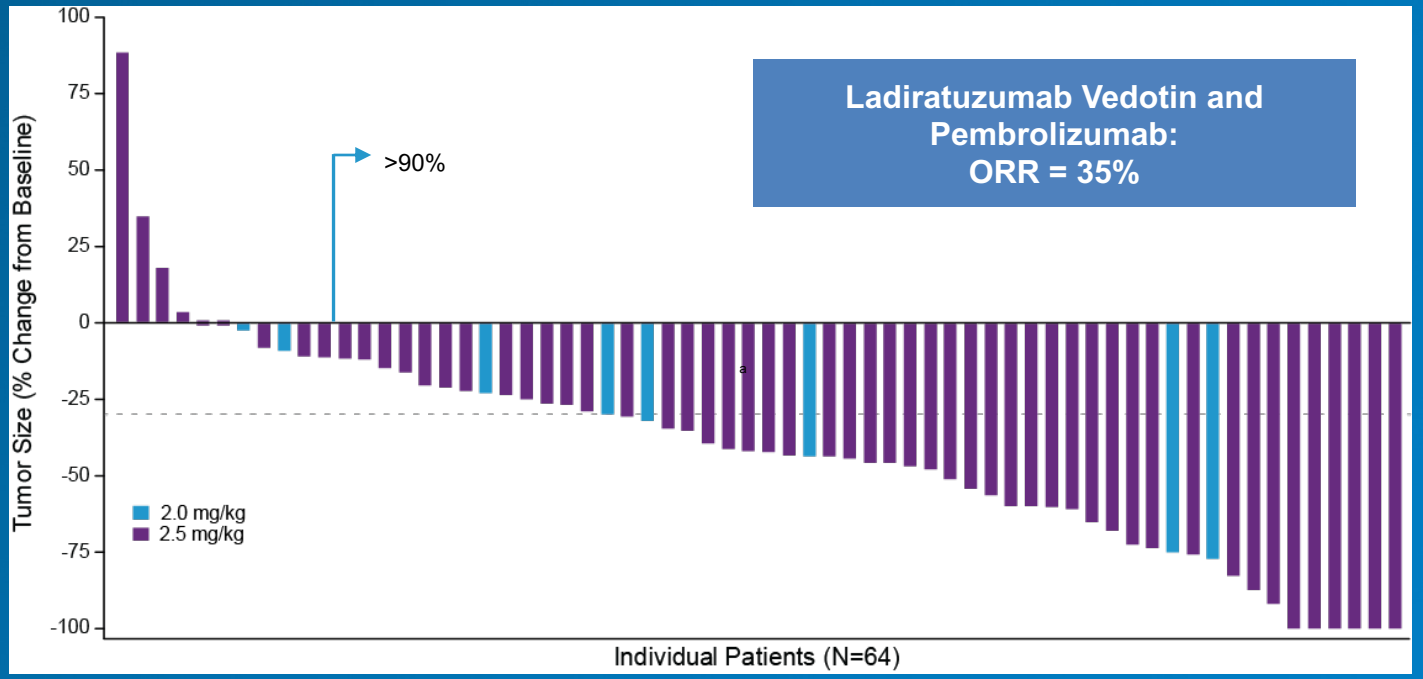
Median PFS = 11.6 weeks

MBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; TNBC, triple-negative breast cancer.
Modi et al. SABCS 2017. Abstract PD3-14.

AXIS Medical Education

Combination of Ladiratuzumab (ADC targeting LIV1 linked to MMAE) and Immunotherapy

- The efficacy evaluable population includes all treated subjects with at least one evaluable post-baseline assessment according to RECIST v1.1 or those off study (N = 69)
- Of the efficacy evaluable population, 5 subjects did not have evaluable response assessments before study discontinuation



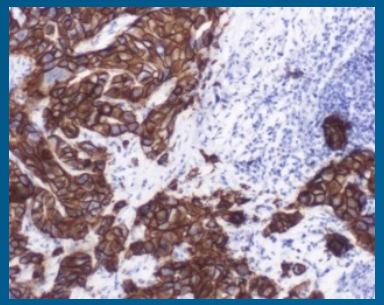
ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E; ORR, objective response rate.

Han et al. *J Clin Oncol*. 2019;37(15):TPS1110.

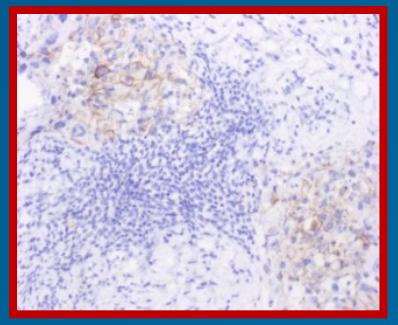
Prevalence of HER2-low by HR Status

HER2 IHC examples

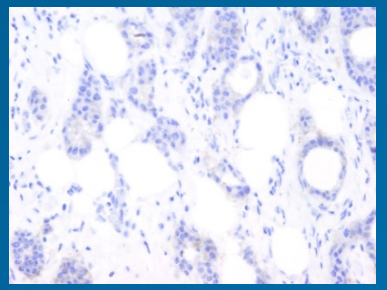
HER2+



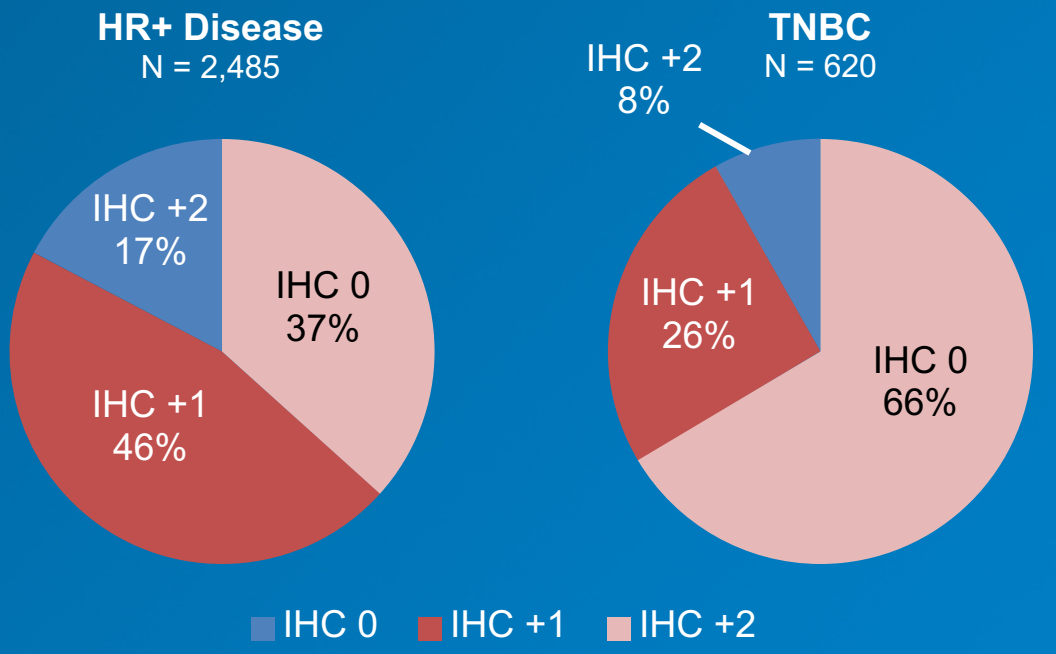
HER2-low



HER2-



HER2-negative



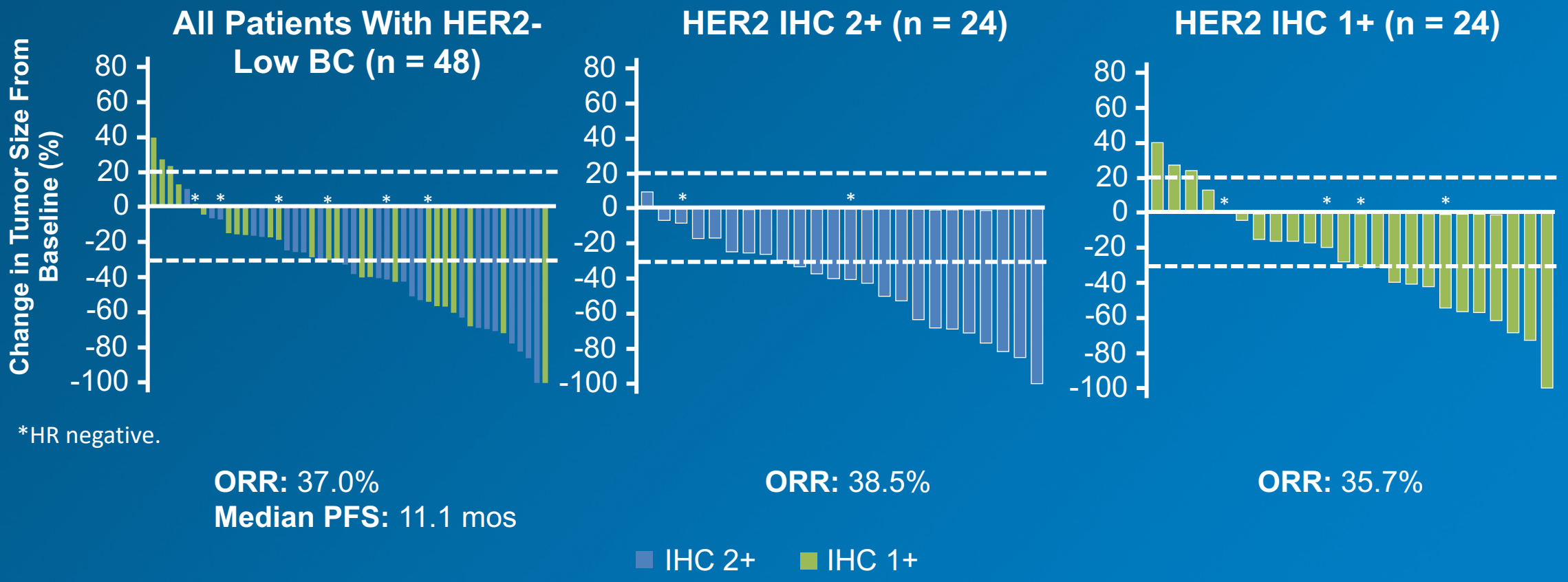
34% to 63% of breast cancer patients considered HER2-negative under current guidelines express low levels of HER2

HER2, human epidermal growth factor receptor 2, HR, hormone receptor; IHC, immunohistochemical staining; TNBC, triple negative breast cancer.

Schettini. *Ann Oncol*. 2020;31(suppl 2):S15-S41.

Slide courtesy of Aleix Prat.

Phase 1b Trial: Trastuzumab Deruxtecan for Heavily Pretreated HER2-Low Advanced Breast Cancer



BC, breast cancer; HER2, human epidermal growth factor receptor 2, HR, hormone receptor; IHC, immunohistochemical staining; ORR, objective response rate; PFS, progression-free survival.

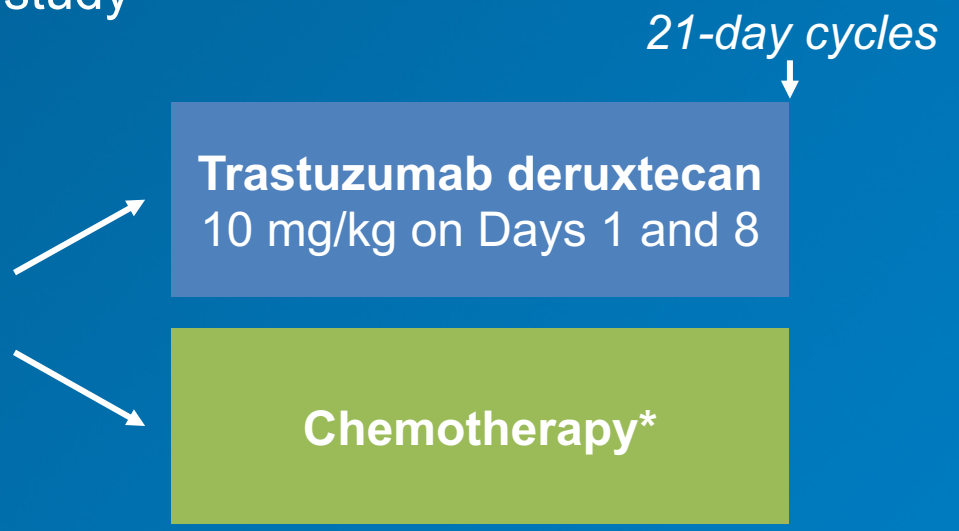
Modi et al. *J Clin Oncol*. 2020;38:1887.

DESTINY-Breast04: Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC

International, randomized, open-label phase 3 study

Women and men with unresectable and/or metastatic HER2-low breast cancer;
progression on endocrine therapy,
1-2 prior lines chemotherapy;
no prior HER2 positivity (IHC3+ or ISH+)

(planned N = 540)



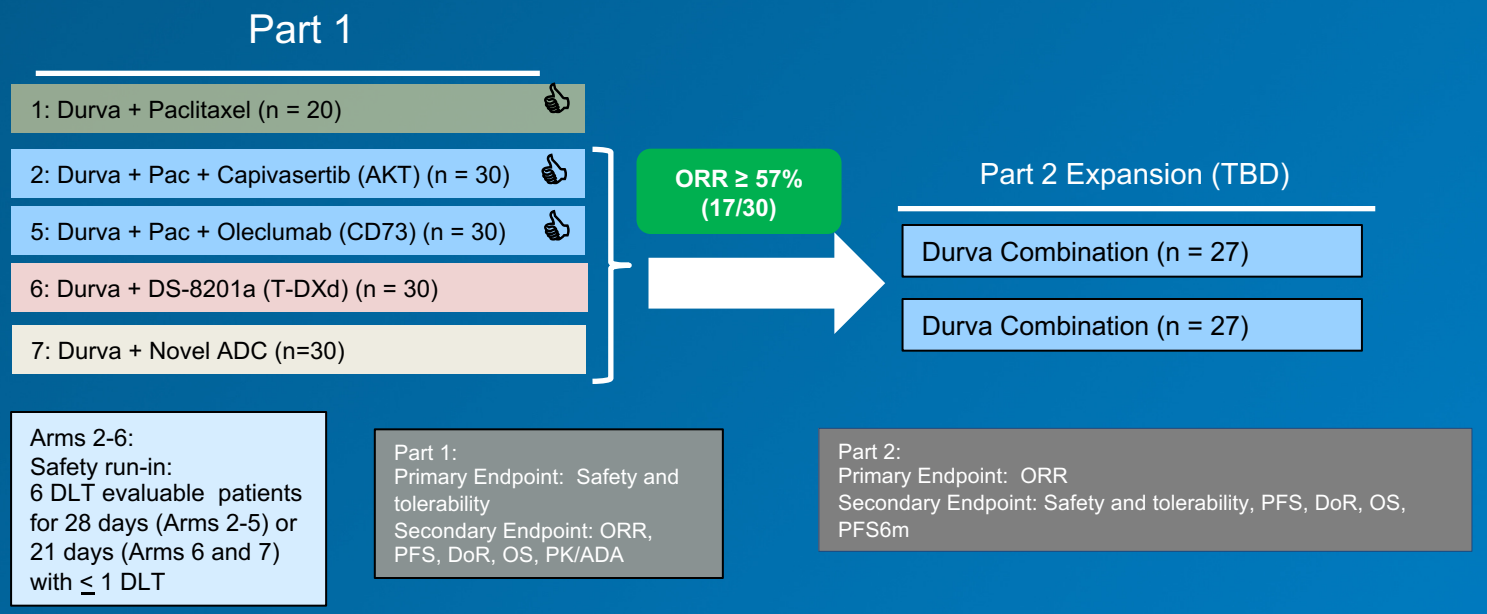
*Investigator's choice of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

- Primary endpoints: PFS per BICR
- Secondary endpoints: OS, DoR, ORR, PFS per investigator

BC, breast cancer; BICR, blinded independent central review; DoR, duration of response; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
NCT03734029.

BEGONIA Study Design: T-Dxd + Durvalumab for HER2 low TNBC

- Metastatic TNBC
- No prior treatment for stage IV disease
- ECOG PS 0 -1
- RECIST evaluable
- Patients may have relapsed from earlier stage disease but must be ≥ 12 months since prior taxane treatment
- **Arm 6: Locally confirmed HER2 IHC 1-2+ (ISH-)**



Note:
- Arms 3 (Durva + selumetinib + pac) and Arms 4 (Durva + danvatirsen + pac) were removed before patient enrollment
- Part 1 of this study is considered Stage 1 of the Simon 2-Stage design, and Part 2 of this study is considered Stage 2
- Amendment for a new arm (Arm 7) to include a novel combination of durvalumab + a novel ADC (will include HER2-0 patients)

= Enrollment complete; only Arm 6 is open at this time

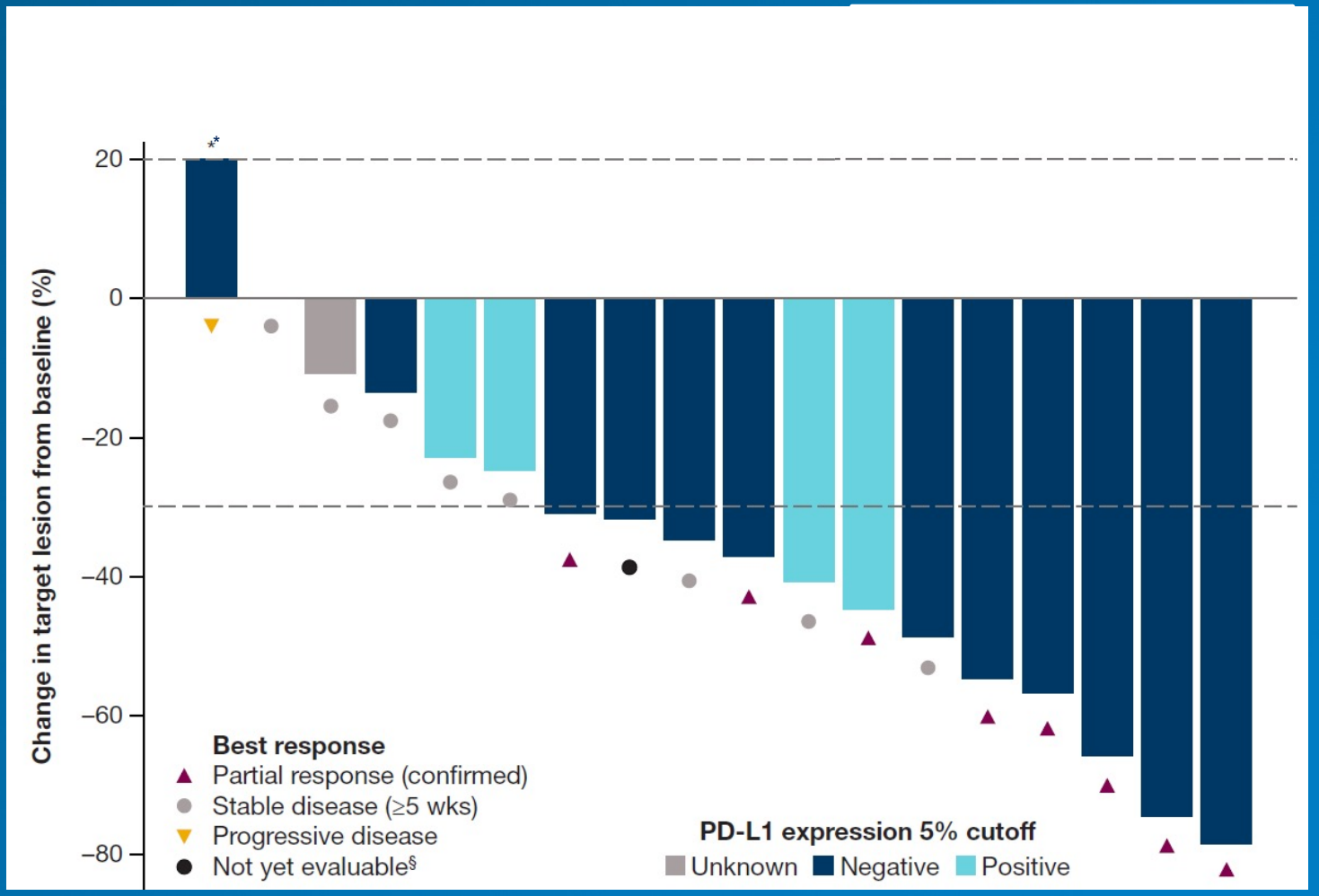
ADC, antibody-drug conjugate; DLT, dose-limiting toxicity; DoR, duration of response; Durva, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; Pac, paclitaxel; PFS, progression-free survival; TBD, to be determined; T-Dxd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer.

Schmid et al. *J Clin Oncol*. 2021;39(15):1023.

T-Dxd+ Durvalumab: Efficacy

Responses observed in both PD-L1–positive (confirmed ORR 1/1 [100%]) and PD-L1–negative (confirmed ORR 7/10 [70.0%]) groups

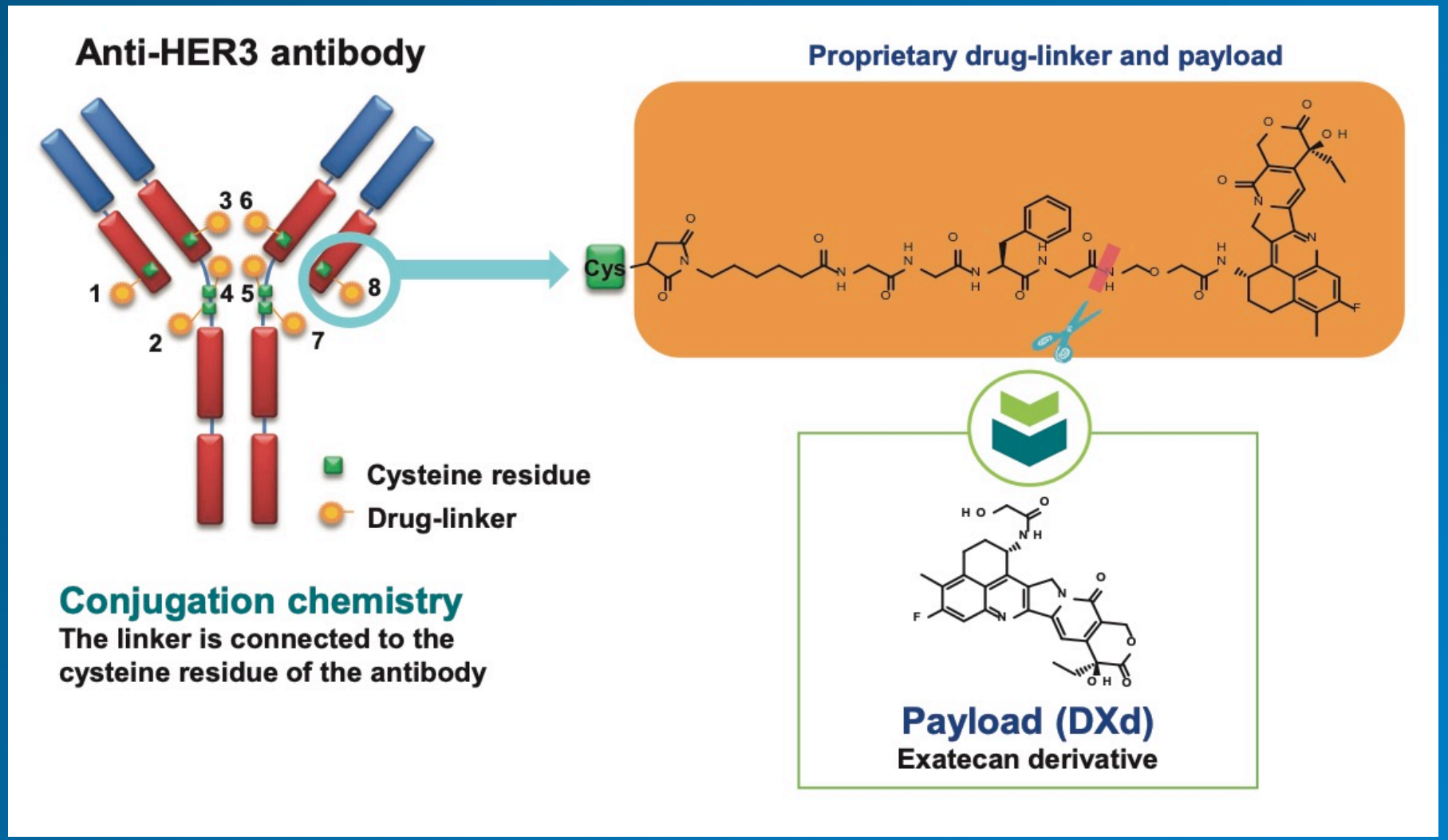
Parameter	D+T-DXd
Patients who completed at least 1 on-treatment assessment, n	18
Response evaluable analysis set, n	12
Confirmed ORR, n (%) 95% CI Complete response, n Partial response, n	8/12 (66.7) 41.0, 86.7 0 8
Stable disease, n	8
Progressive disease, n	1



Will there be a role for TDxd+ Durvalumab in 1L HER2-low TNBC?
And will activity be greater than TDxd alone even in PD-L1-negative patients?

D, durvalumab; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; PD-L1, programmed cell death protein ligand 1; T-Dxd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer.
Schmid et al. *J Clin Oncol*. 2021;39(15):1023.

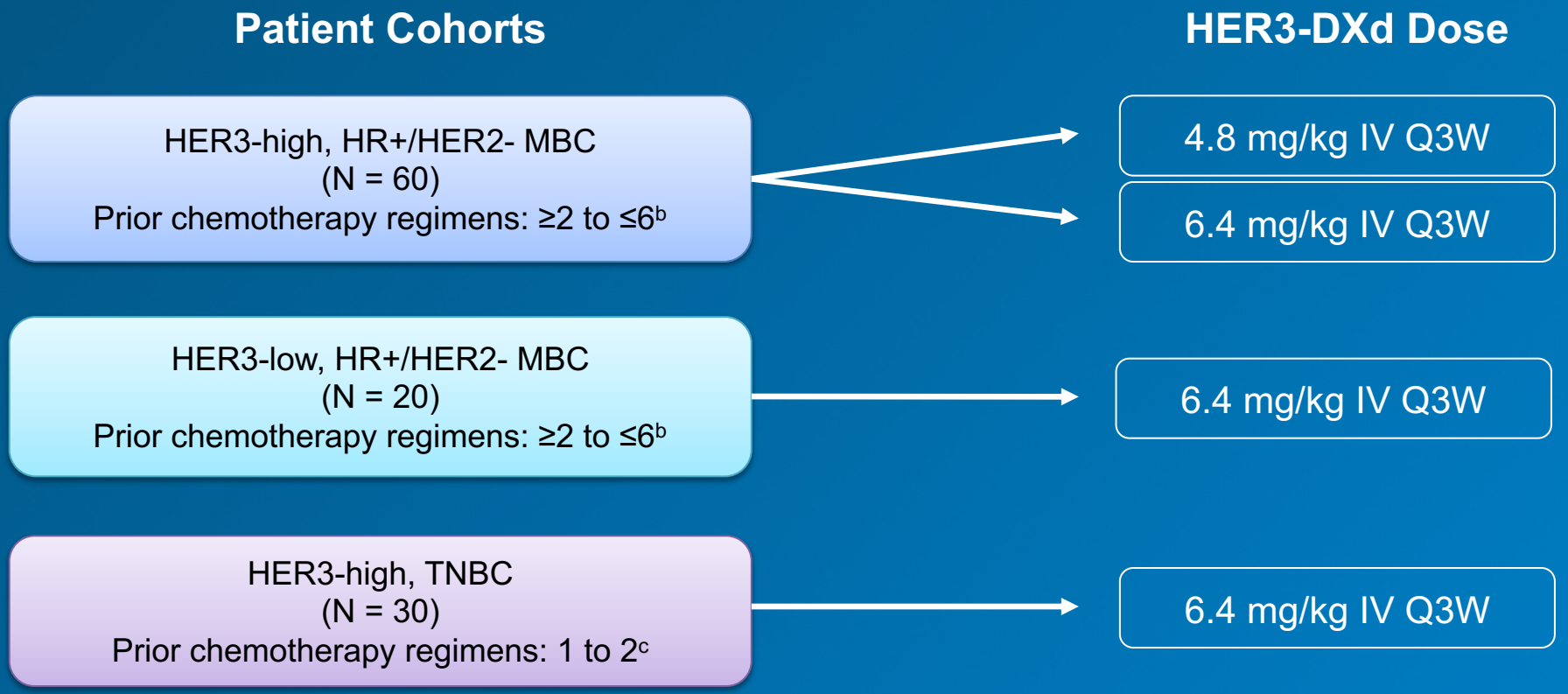
Patritumab Deruxtecan (U3-1402): HER3 ADC



ADC, antibody-drug conjugate; HER3, human epidermal growth factor receptor 3.
Krop et al. Publication no PD1-09. SABCS 2020.

AXIS Medical Education

U3-1402: Study Design



DXd, deruxtecan; HER3, human epidermal growth factor receptor 3; HR, hormone receptor; MBC, metastatic breast cancer; Q3W, every 3 weeks.
[a]HER3-DXd at doses of 1.3, 3.2, 4.8, 6.4, and 8.0 mg/kg Q3W was evaluated in the dose escalation and dose finding parts of the study. [b]≥2 lines in the locally advanced/metastatic setting.
[c]in the locally advanced/metastatic setting.
Krop et al. Publication no PD1-09. SABCS 2020.

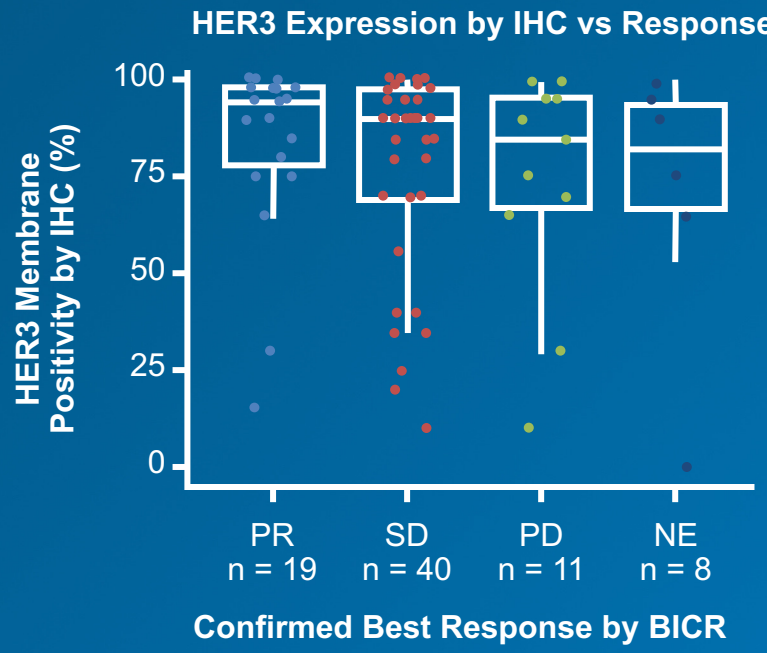
U3-1402: Results

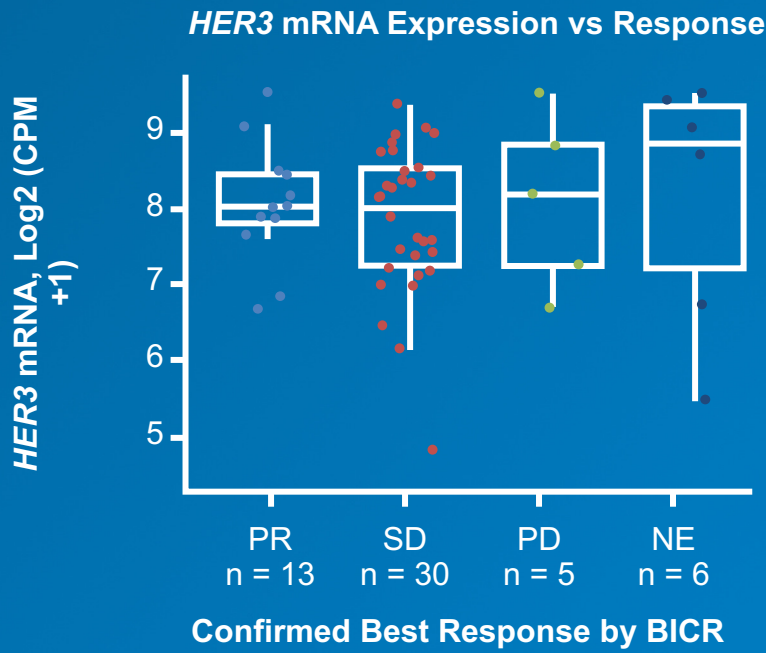
Efficacy by BICR	HER3-high, HR+/HER2- MBC		HER3 low, HR+/HER2- MBC	HER3-high TNBC
Dose	4.8 mg/kg (n=33)	6.4 mg/kg (n=31)	6.4 mg/kg (n=21)	6.4 mg/kg (n=31)
Follow-up, median, months	16.8	20.4	18.7	7.4
Confirmed ORR, %	30.3	12.9	33.3	16.1
PR	30.3	12.9	33.3	16.1
SD	60.6	61.3	33.3	67.7
PD	6.1	22.6	14.3	9.7
NE	3.0	3.2	19.0	6.5
DCR, %	90.9	74.2	66.7	83.9
Median DOR, months	5.0	7.2	5.3	NR
Median PFS, months	8.4	2.8	5.8	5.5
Median OS, months	14.3	9.7	9.2	NR

BICR, blinded independent central review; DCR, disease control rate; DOR duration of response; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS progression-free survival; PR, partial response; SD, stable disease.
Adapted from Krop et al. Publication no PD1-09. SABCS 2020.

Patritumab Deruxtecan: Association Between HER3 Expression and Response

- Among patients with HR+ MBC, there does not appear to be a clear relationship between pretreatment HER3 expression and response (membrane HER3 expression measured by IHC and *HER3* mRNA expression by RNAseq)



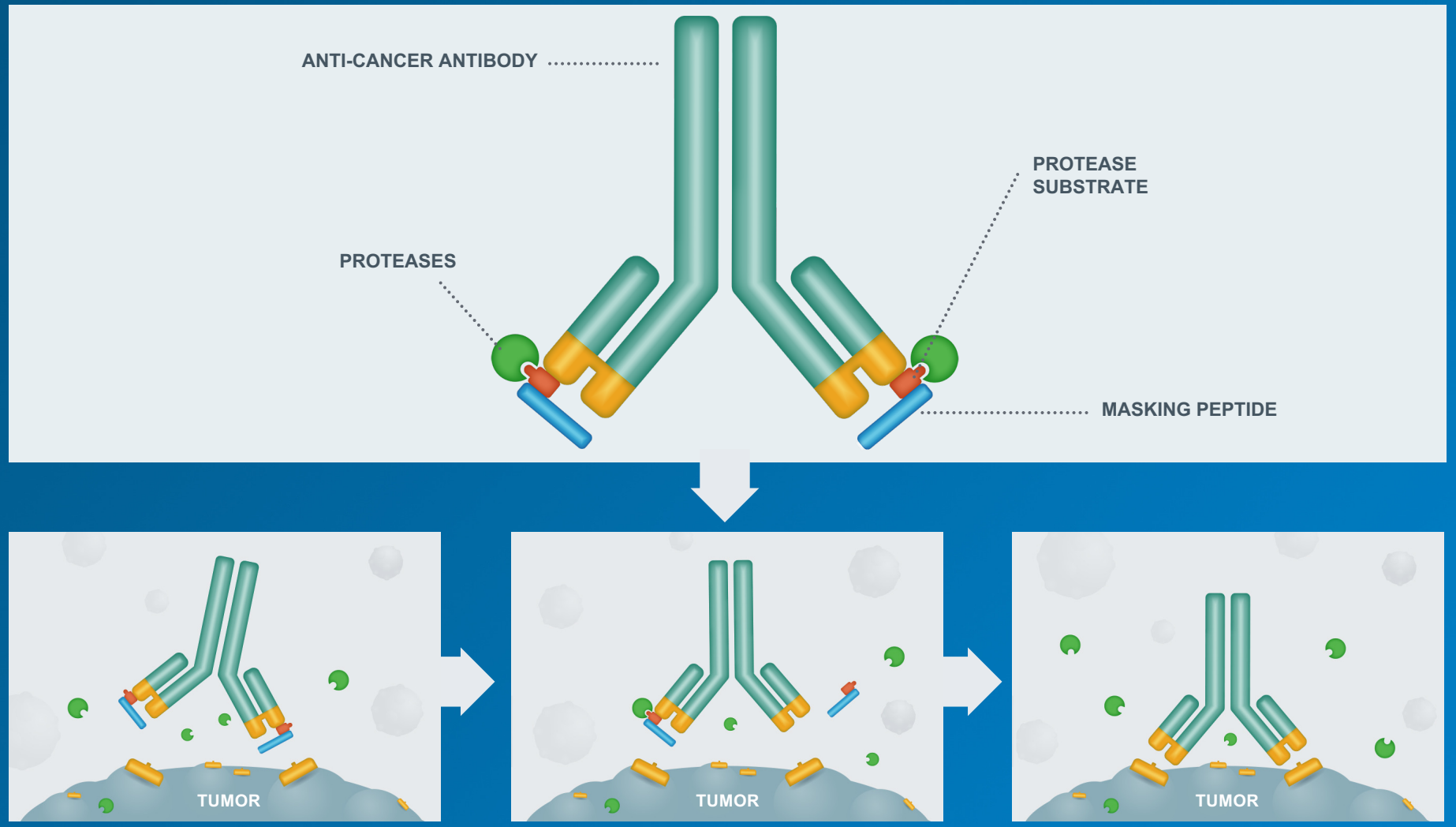


- Further analysis with additional clinical data will be performed in the future

BICR, blinded independent central review; HER3, human epidermal growth factor receptor 3; HR, hormone receptor; IHC, immunohistochemistry; MBC, metastatic breast cancer; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.
Krop et al. Publication no PD1-09. SABCS 2020.

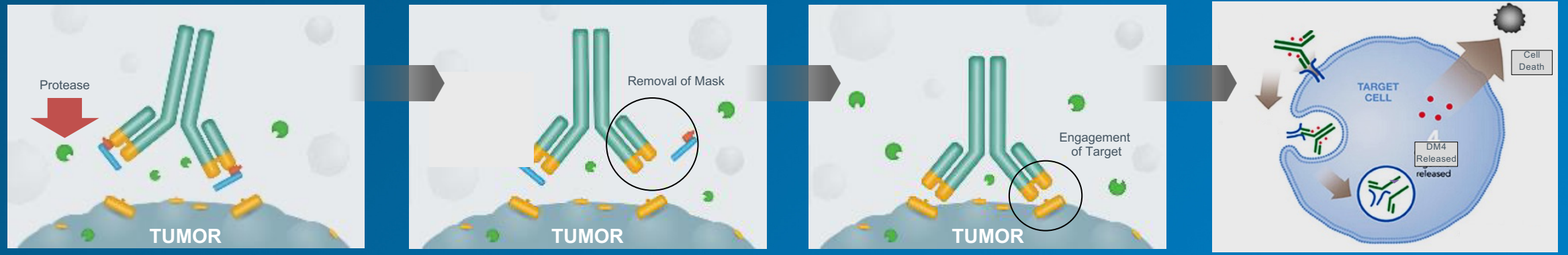
AXIS Medical Education

Probody Therapeutics Are Designed to be Activated in the Tumor Microenvironment



Autio et al. *Clin Cancer Res*. 2020 Mar 1;26(5):984-989.

Translational Program Designed to Provide Evidence of Probody Therapeutics MOA and Biologic Activity in Patients



POTENTIAL PREDICTIVE MARKERS

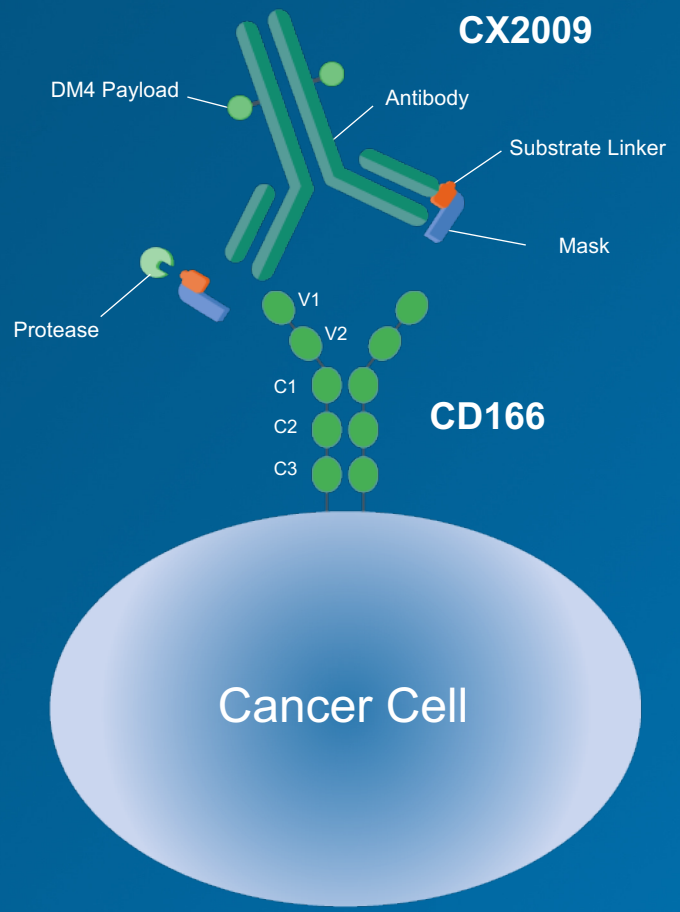
PROBODY TX ACTIVATION

PROBODY TX LOCALIZATION IN TUMOR

PAYLOAD DELIVERY

MOA, mechanism of action; TX, treatment.
Autio et al. *Clin Cancer Res*. 2020 Mar 1;26(5):984-989.

CX-2009: A Probody Drug Conjugate Targeting CD166 (ALCAM)

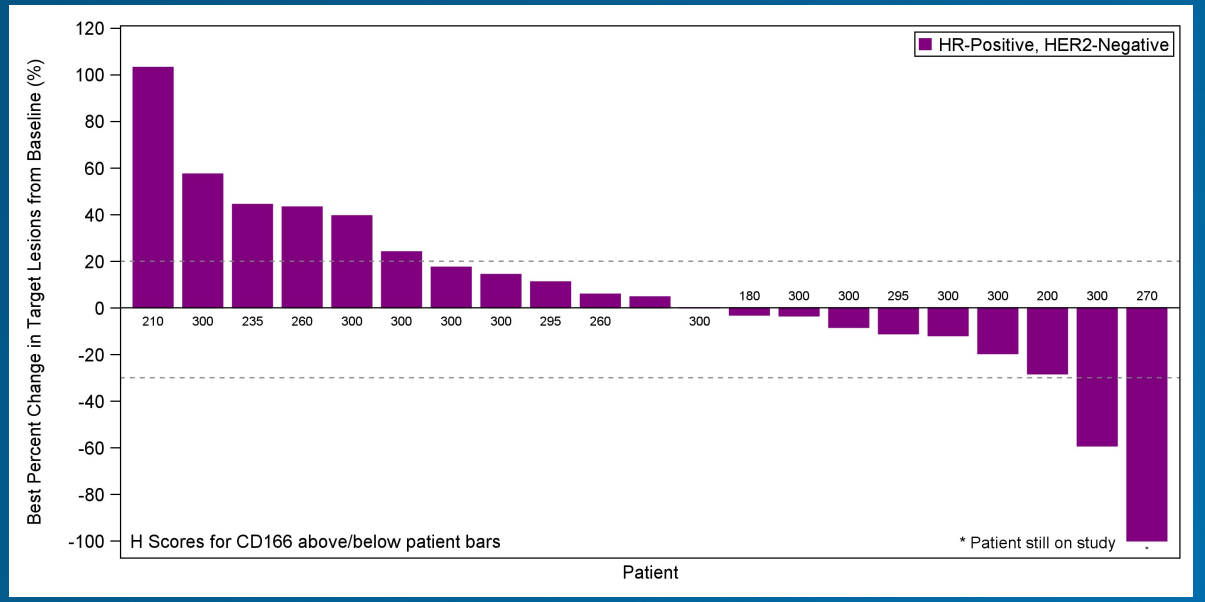


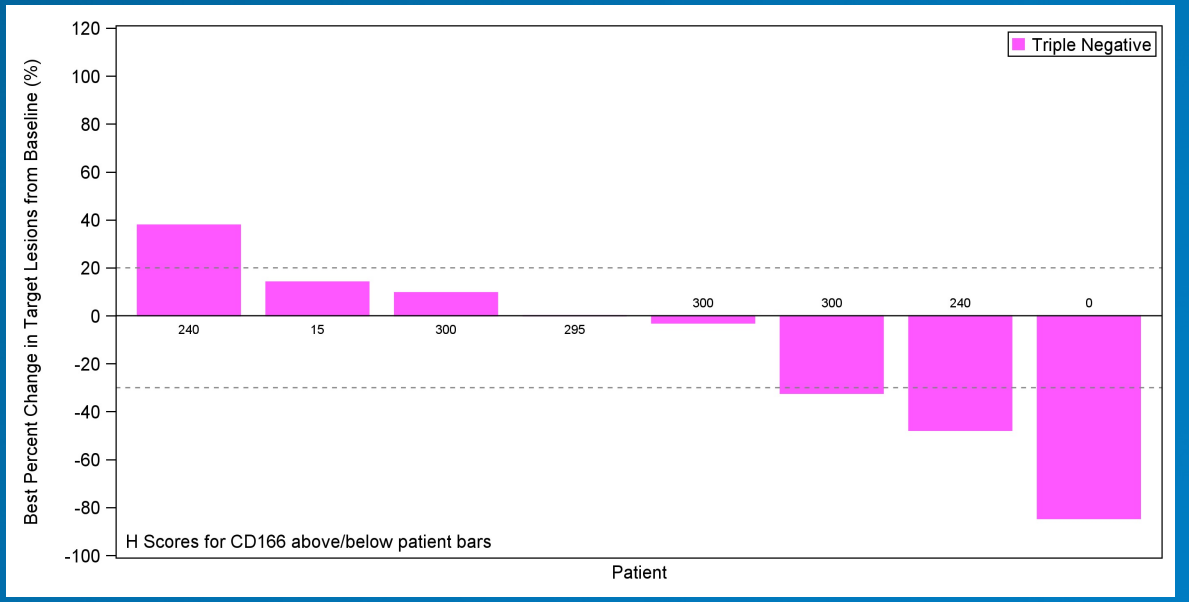
- CD166 (activated leukocyte cell adhesion molecule) is a transmembrane protein that functions as a junctional adhesion molecule, and facilitates cell migration, differentiation and hematopoiesis
- CD166 is a broadly and highly expressed tumor antigen
- CD166 is present on normal tissues (lung, GI, liver, pancreas)
- SPDB-DM4 linker-payload
  - Microtubule inhibition has activity in multiple tumor types
  - Ocular, neuropathic and hepatic toxicities are well characterized DM4-related toxicities

Boni et al. *J Clin Oncol*. 2020;38:526.

Observed Clinical Activity in Breast Cancer With CX-2009 (Doses ≥4 mg/kg Q3W)

Breast cancer patients with measurable disease who received ≥ 4 mg/kg CX-2009 and had a post-baseline assessment





Parameter	Evaluable* Breast Cancer Patients		
	Overall (n = 32)	HR+/HER2- (n = 22)	TNBC (n = 10)
CBR16	13 (41%)	9	4
CBR24	9 (28%)	5 (2 cPR)	4 (3 uPR)
*Includes those with non-measurable but evaluable (eg, bone-only) disease			

CBR16, clinical benefit rate at 16 weeks; CBR24, clinical benefit rate at 24 weeks; cPR, confirmed partial response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; uPR, unconfirmed partial response; TNBC, triple-negative breast cancer.

Liu et al. *Cancer Res* 2021;81(4 Suppl):Abstract nr PS11-07.

CX-2009 Breast Cancer Phase 2 Study Design

Monotherapy (7 mg/kg Q3W) and Combination with Pacmilimab (CX-072; anti-PD-L1) In Advanced, HER2 non-Amplified Breast Cancer

Key Eligibility

Ocular prophylaxis required
- Treated/stable brain metastases allowed
- No active corneal disease
- Measurable disease required

HR+/HER2 non-amplified
- 0 – 2 prior cytotoxics for advanced disease
- Prior CDK4/6i required

TNBC
- CD166 High
- ≥ 1 and ≤ 3 priors for advanced disease
- **Arm C exclusion criteria:**
  - PD-L1 negative/unknown
  - I/O refractory
  - History of or active autoimmune condition

Breast Cancer SubType

Arm A
HR+/HER2 non-amp (n~40)
CX-2009

Arm B
TNBC (n~40)
CX-2009

Arm C
TNBC (n~40)
CX-2009 + CX-072

Endpoints

Primary: Overall response rate by central review

Secondary: ORR (Inv), PFS, DCR, CBR24, DoR, OS, Safety, PK, ADA

Exploratory: Biomarker correlation with outcome

Readout: Initial data expected Q4 2021

DCR, disease control rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; TNBC, triple-negative breast cancer.
NCT04596150; Miller et al. *Cancer Res* 2021;81(4 Suppl):Abstract nr OT-03-08.

AXIS Medical Education

Summary: ADCs in Breast Cancer

- 3 FDA-approved ADCs in breast cancer
  - Trastuzumab emtansine: HER2+ early and metastatic breast cancer
  - Trastuzumab deruxtecan: HER2+ metastatic breast cancer
  - Sacituzumab govitecan: TNBC

- Many questions remain
  - Will HER2 ADCs become a standard in HER2-low breast cancer?
  - Will TROP2 ADCs work in HR+ breast cancer?
  - Will one ADC work after another if they have non-cross resistant payloads?
  - Will one ADC work after another if they have the same target and different payloads?
  - Will there be optimal combination therapies?

- Numerous ongoing trials with novel targets, novel ADC mechanisms, and novel combinations

ADCs, antibody-drug conjugates; FDA, US Food & Drug Administration; HER2, human epidermal growth factor receptor 2.

Case Study Example

Case: Presentation

- 56-year-old black woman reported feeling a mass in her right breast and enlarged axillary lymph nodes
  - No family history of breast or ovarian cancer
  - Core biopsy: 4 cm high-grade infiltrating ductal carcinoma
  - Immunohistochemistry: ER/PR/HER2 negative tumor
  - FNA axilla: positive
  - Staging scans with liver metastases→ biopsy confirms TNBC

- **What additional tests should be done on the tumor tissue?**
- **Should germline testing be offered?**

ER, estrogen receptor; FNA, fine needle aspiration; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TNBC, triple-negative breast cancer.

Case: Findings

- PD-L1 testing performed, 22C3 CPS>10, SP142 IC>1
- *BRCA* testing negative

- **What first-line therapy would you offer?**

PD-L1, programmed cell death protein ligand 1.

Case: First-Line Treatment

- Patient started on nab-paclitaxel + atezolizumab
  - At the time, this was an FDA-approved option
- Initial reduction in liver metastases and breast mass
- Disease progression after 10 months with increase in liver metastases
- **What would you offer second line?**

Case: Second-line Treatment

- Patient started treatment with sacituzumab govitecan

AXIS Medical Education

Advances in the Standard of Care in TNBC:

Addressing Health Disparities and Integrating ADCs Into Treatment