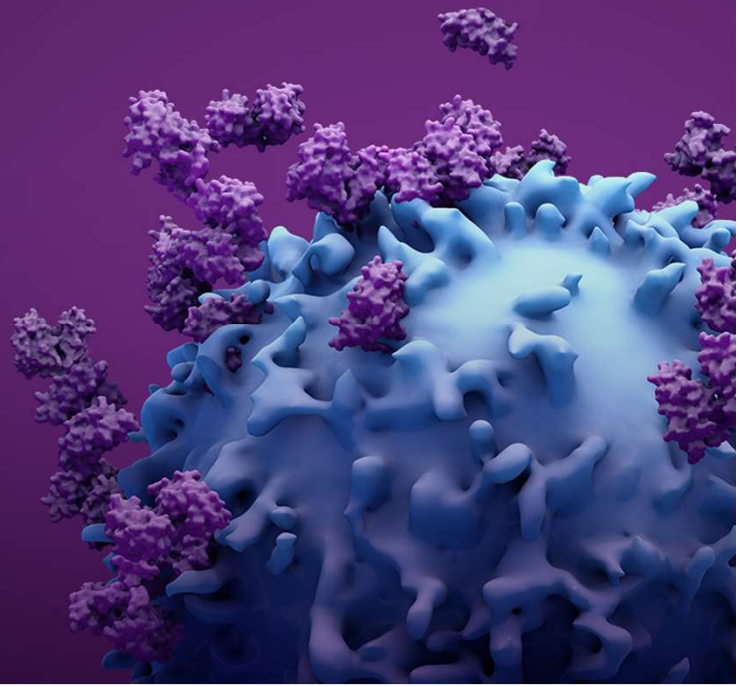
PrimO
Practical Recommendations in Immuno & Molecular Oncology
ADC Summit

Practical Recommendations in Immuno and Molecular Oncology (PRIMO) Antibody-Drug Conjugate (ADC) Summit

The Emerging Role of ADCs in Breast Cancer

January 27, 2021



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The PRIMO ADC Summit acknowledges support from educational grants provided by Daiichi Sankyo and Cancer Expert Now.

Learning Objectives

Review 3 FDA-approved ADCs and ADCs in clinical development for breast cancer

- Analyze the unmet need in patients with breast cancer
- Discuss their mechanisms of action
- Analyze available clinical data and discuss ongoing clinical trials

ADC, antibody–drug conjugate; BC, breast cancer; FDA, US Food and Drug Administration.

Agenda

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WEDNESDAY, JAN 27, 2021 6PM – 7:30 PM EST	TOPIC	SPEAKERS
6:00 - 6:25 PM	**Introduction to ADCs** Where do we stand and where are we going?	Daver
6:25 – 7:00 PM 6:25 – 6:35 PM 6:35 – 6:40 PM 6:40 – 6:45 PM 6:45 – 7:00 PM	**ADCs in Breast Cancer** FDA-Approved ADCs in Breast Cancer ADCs Targeting HER2 T-Dxd in HER2-Low ADCs in Triple Negative Breast Cancer	 Hurvitz Hurvitz Gradishar Gradishar
7:00 – 7:10	**Updates from SABCS**	Hurvitz
7:10 – 7:20 PM 7:10 – 7:15 PM 7:15 – 7:20 PM	**Treatment Considerations for ADCs in Breast Cancer** Clinical Applications of ADCs Combinations with Immunotherapy	 Hurvitz Gradishar
7:20 – 7:30 PM	**Live Q&A**	Hurvitz + Daver

Faculty Members

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Betsy Bramsen Professor of Breast Oncology & Professor of Medicine
Chief, Division of Hematology/Oncology
Director, Maggie Daley Center for Women's Cancer Care
Deputy Director, Clinical Network
Robert H. Lurie Comprehensive Cancer Center
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Disclosures

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Advisory/Consulting: Pfizer, Novartis, BMS, Otsuka, Celgene, Incyte, Jazz, Karyopharm, Sunesis, Immunogen, Abbvie, Astellas, Daiichi-Sankyo, Agios

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Intro to Antibody–Drug Conjugates (ADCs)

Where do we stand, and where are we going?

Naval G. Daver, MD
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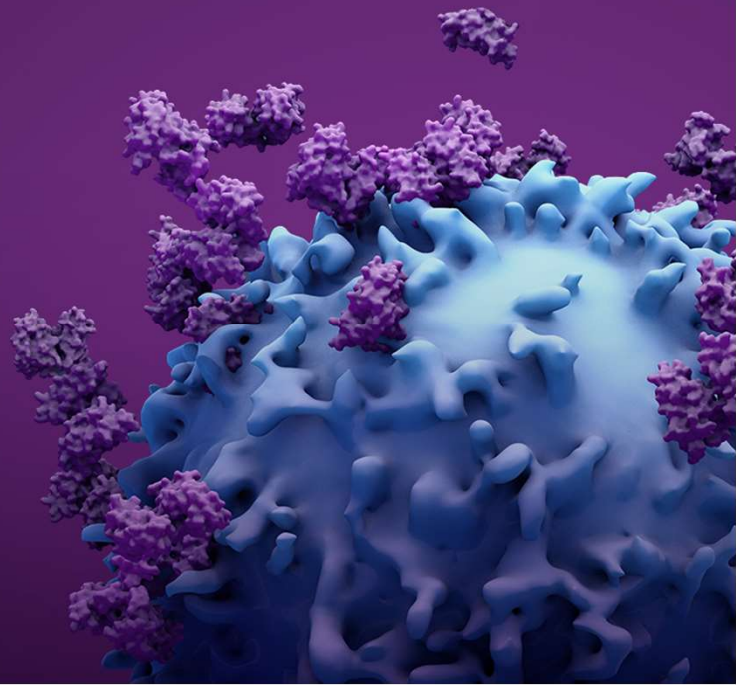

Learning Objectives

Discuss ADCs currently FDA approved and in development

- Review the development and structure of ADCs
- Overview common ADC mechanism of action
- Discuss ongoing clinical development of ADCs for solid tumors

FDA, US Food and Drug Administration.

History & Development of ADCs

Paul Ehrlich received the Nobel Prize for Physiology or Medicine[1]

- "Magic bullet concept": drugs go straight to their intended targets[2]
- Targeted medicine should efficaciously attack pathogens yet remain harmless in healthy

1908

1970

Antibodies were first armed with toxins to selectively kill target cells[3,4]

2000

MYLOTARG® (gemtuzumab ozogamicin)[4]

First marketed ADC; approved for the treatment of acute myeloid leukemia

2010

MYLOTARG withdrawn from market

Voluntarily withdrawn from the market due to lack of clinical benefit and excess mortality

2011

ADCETRIS® (brentuximab vedotin)

Commonly recognized as the first clinically validated ADC[4]

2013

KADCYLA® (ado-trastuzumab emtansine)[4]

First ADC approved for a solid tumor indication (HER2-positive metastatic breast cancer)

2017

MYLOTARG reapproved

HER2, human epidermal growth factor receptor 2.

1. The Nobel Prize in Physiology or Medicine 1908. NobelPrize.org. Nobel Media AB 2020. Wed. 7 Oct 2020. https://www.nobelprize.org/prizes/medicine/1908/summary/; 2. Strebhardt, K., et al. *Nature Reviews Cancer*. 2008; 8(6), 473-480;
3. Moolten F.L., et al. *Science*. 1970; 169, 68-70; 4. Carter P, et al. *Nat Rev Drug Disc*. 2017; 17(3), 197–223.

Issues of Early ADCs

- Early ADCs used drugs that have been approved for clinical use, such as vinblastine and doxorubicin, but the low clinical activity of these drugs resulted in **suboptimal ADC efficacy**
- Some cytotoxins were **too toxic** to be non-target agents in clinical application but appeared to be promising payloads for ADCs
- Currently, **most payloads are derivatives of the microtubule inhibitor family**, such as auristatin and maytansine

Tang H, et al. *Front Pharmacol.* 2019; 10: 373.

ADCs FDA Approved for Hematologic Malignancies

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Drug	Manufacturer	Condition	Approval (y)
MYLOTARG (gemtuzumab ozogamicin)[1]	Wyeth Pharmaceuticals Inc./Pfizer Inc.	Relapsed or refractory CD33-positive AML	2000, 2017
ADCETRIS (brentuximab vedotin)[2]	Seattle Genetics, Inc.	Relapsed HL and relapsed systemic ALCL	2011
BESPONSA® (inotuzumab ozogamicin)[3]	Pfizer Inc.	Relapsed or refractory CD22-positive B-cell precursor ALL	2017
LUMOXITI® (moxetumomab pasudotox-tdfk)[4]	AstraZeneca Pharmaceuticals LP	Adults with relapsed or refractory hairy cell leukemia	2018
POLIVY® (polatuzumab vedotin-piiq)[5]	Genentech, Inc.	Relapsed or refractory diffuse large B-cell lymphoma	2019
PADCEV® (enfortumab vedotin-ejfv)[6]	Agensys, Inc./Seattle Genetics, Inc./Astellas Pharma US, Inc.	Adult patients with locally advanced or metastatic urothelial cancer who have received a PD-1 or PD-L1 inhibitor and a Pt-containing therapy	2019
BLENREP® (belantamab mafodotin-blmf)[7]	GlaxoSmithKline Pharmaceuticals Ltd	Adult patients with relapsed or refractory MM	2020

ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; Pt, platinum; y, year.

1. Mylotarg. Package insert. Pfizer Inc; 2000; 2. Adcetris. Package insert. Seattle Genetics; 2011; 3. Besponsa. Package insert. Pfizer Inc; 2017; 4. Lumoxiti. Package insert. AstraZeneca; 2018; 5. Polivy. Package insert. Genentech Inc; 2019; 6. Padcev. Package insert. Astellas Pharma US Inc; 2019; 7. Blenrep. Package insert. GlaxoSmithKline; 2020.

ADCs FDA Approved for Solid Tumors (Breast Cancer)

Trade name	Company	Subtype	Condition	Approval Y
KADCYLA (ado-trastuzumab emtansine)[1]	Genentech, Inc.	HER2-positive	HER2-positive mBC following treatment with trastuzumab and a taxane	2013
ENHERTU® (fam-trastuzumab deruxtecan-nxki)[2]	Daiichi Sankyo, Inc.		Adult patients with unresectable or metastatic HER2-positive BC who have received ≥2 prior anti–HER2-based regimens	2019
TRODELVY® (sacituzumab govitecan-hziy)[3]	Immunomedics, Inc.	TNBC	Adult patients with metastatic TNBC who have received at least 2 prior therapies	2020

BC, breast cancer; mBC, metastatic breast cancer; TNBC; triple-negative breast cancer;.
1. Kadcyla. Package insert. Genentech Inc; 2013; 2. Enhertu. Package insert. Daiichi Sankyo, Inc; 2019; 3. Trodelvy. Package insert. Immunomedics, Inc; 2020.

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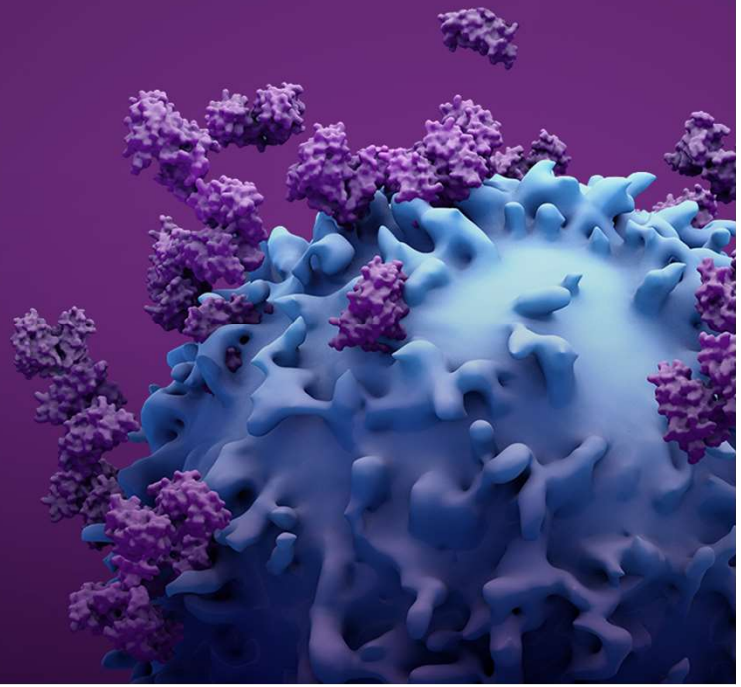
ADC Design and Structure



ADCs Are Built on Antibody Technology

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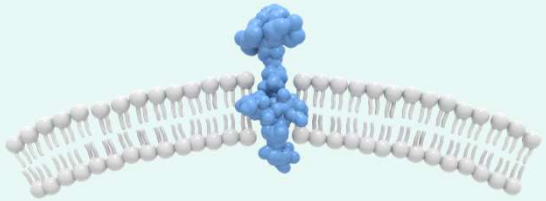
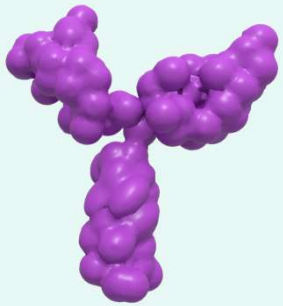
Target Antigen



- High relative level of expression
- Immunizing extracellular domain
- No shed into the circulation
- Internalization capability
- May intervene in cell growth and has expression that covers multiple types of malignancies

Conjugate Antibody



- High specificity
- High affinity
- Capable of inducing receptor-mediated internalization

Nejadmoghaddam MR, et al. *Avicenna J Med Biotech.* 2019;11(1): 3-23.

ADCs in Development Target a Wide Range of Antigens With Different Characteristics

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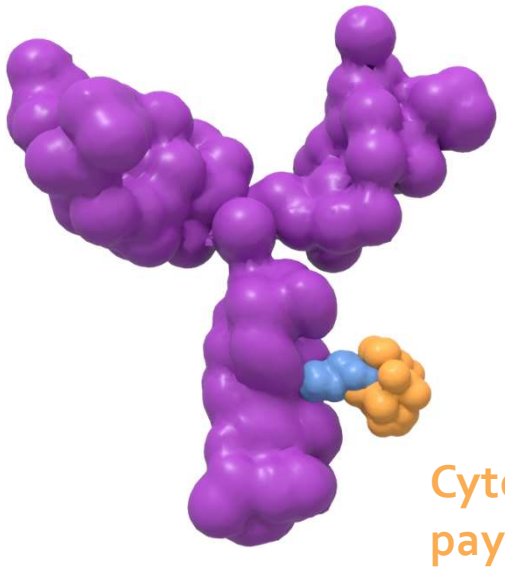
Indication	Target Antigen in Clinical and Preclinical Development
Hematologic malignancies	
NHL	CD19, CD20, CD21, CD22, CD37, CD70, CD72, CD79a/b, CD180
HL	CD30
AML/ALL	CD33, CD123, CLL1/CD19, CD22
MM	CD56, CD74, CD138, endothelin B receptor
Solid tumors	
Lung	CD56, CD326, CRIPTO, FAP, mesothelin, GD2, 5T4 and alpha v beta6, HER2, HER3, Trop2
CRC	CD74, CD174, CD227 (MUC-1), CD326 (Epcam), CRIPTO, FAP, ED-B
Pancreatic	CD74, CD227 (MUC-1), nectin-4 (ASG-22ME), alpha v beta6
Breast	CD174, GPNMB, CRIPTO, nectin-4 (ASG-22ME) and LIV1A, HER2, HER3, Trop2
Ovarian	MUC16 (CA125), TIM-1 (CDX-014), mesothelin
Melanoma	GD2, GPNMB, ED-B, PMEL 17, endothelin B receptor
Prostate	PSMA, STEAP-1, TENB2
Renal	CAIX, TIM-1 (CDX-014)
Mesothelioma	Mesothelin

- Homogeneous target antigen expression in liquid tumors makes ADCs an attractive treatment option
- Heterogeneous target antigen expression in solid tumors may rely on bystander killing

- Target antigens can be specific (eg, those targeted for hematologic malignancies)
- Others may be expressed across multiple tumor types (eg, those targeted across solid tumors)

CAIX, carbonic anhydrase IX; CRC, colorectal cancer; HER3, Human epidermal growth factor receptor 3; FAP, fibroblast activation protein; NHL, non-Hodgkin lymphoma; PSMA, prostate-specific membrane antigen; PMEL, premelanosome protein; STEAP-1; six transmembrane epithelial antigene of the prostate 1; TIM-1, T-cell immunoglobulin and mucin domain 1; Trop2; calcium signal transducer 2.
Perez HJ, et al. *Drug Discov Today*. 2014;19(7):869-881.

Cytotoxic Payload[1]



Cytotoxic payload

Highly potent, with IC50 values in the subnanomolar range

Targets:

- DNA (eg, duocarmycins, calicheamicins, PBDs, and SN-38 [the active metabolite of irinotecan])
- Tubulin (eg, maytansines and auristatins)

Payload Criteria:

- Amenability to conjugation
- Solubility
- Stability

IC50, half maximal inhibitory concentration; PBD, pyrrolobenzodiazepine.
Chau C, et al. *Lancet*. 2019;394(10200):793-804.

There Are 2 Key Cytotoxic Payload Mechanisms of Action

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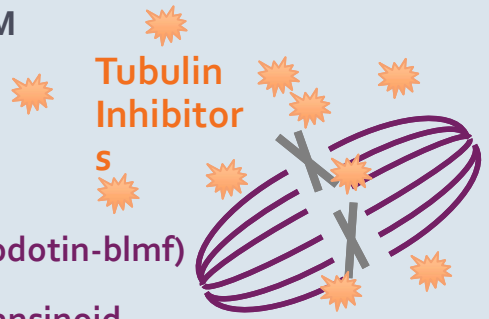
DNA damage

- Target DNA minor grooves and induce double-strand breaks (eg, calicheamicins), DNA alkylation by binding specifically at AT-rich regions (eg, duocarmycins), and guanine residues (eg, PDBs)[1]
- Calicheamicin-based ADCs:
  - gemtuzumab ozogamicin
  - inotuzumab ozogamicin

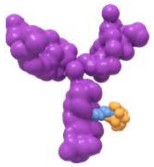
Tubulin inhibition

- Inhibit microtubule polymerization, causing G2/M phase cell-cycle arrest[2]
- MMAE
  (eg, brentuximab vedotin)
- MMAF (eg, belantamab mafodotin-blmf)
- DM1 is a highly potent maytansinoid
  (eg, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki)



DM1, derivative of maytansine 1; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F.
1. Chau C, et al. *Lancet*. 2019;394(10200):793-804; 2. Francisco JA, et al. *Blood*. 2003;102(4):1458-1465.

Linkers Connect the Payload to the mAb and Maintain Stability in Circulation[1-4]



Payload Release Mechanism

Cleavable

- Payload release from its carrier depends on the physiological environment[1,3]
  - Acid-sensitive (eg, gemtuzumab ozogamicin, inotuzumab ozogamicin)
  - Lysosomal protease-sensitive (eg, brentuximab vedotin)

Non-Cleavable

- Attached by a nonreducible bond to the mAb that is more stable in the bloodstream[1]
- Lysosomal degradation of the mAb is necessary for payload release (eg, ado-trastuzumab emtansine)
- Requires an efficient internalization process and optimal trafficking to lysosomes

mAB, monoclonal antibody.

1. Chau C, et al. *Lancet*. 2019;394(10200):793-804; 2. Francisco JA, et al. *Blood*. 2003;102(4):1458-1465; 3. Beck A, et al. *Nat Rev Drug Discov*. 2017;16(5):315-337; 4. Dan N, et al. *Pharmaceuticals (Basel)*. 2018; 9(11):32.

Drug to Antibody Ratio (DAR)[1,2]

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The number of drug molecules attached to an mAb

High DAR (>4):

- ↑ **Potency**
- ↑ **Off-target effects**
- ↑ **Drug clearance rates**
- ↓ **Tolerability**
- ↓ **Efficacy**

Drug	DAR (0 – 8)
Enhertu (fam-trastuzumab deruxtecan-nxki)	8
Trodelvy (sacituzumab govitecan-hziy)	7.6
Besponsa (inotuzumab ozogamicin)	6
Blenrep (belantamab mafodotin-blmf)	4
Adcetris (brentuximab vedotin)	4
Padcev (enfortumab vedotin)	3.8
Polivy (polatuzumab vedotin-piiq)	3.5
Kadcyla (Trastuzumab emtansine)	3.5
Mylotarg (gemtuzumab ozogamicin)	2-3
Lumoxiti (moxetumomab pasudotox-tdfk)	N/A

1. Chau C, et al. *Lancet*. 2019;394(10200):793-804; 2. Beck A, et al. *Nat Rev Drug Discov*. 2017;16(5):315-337.

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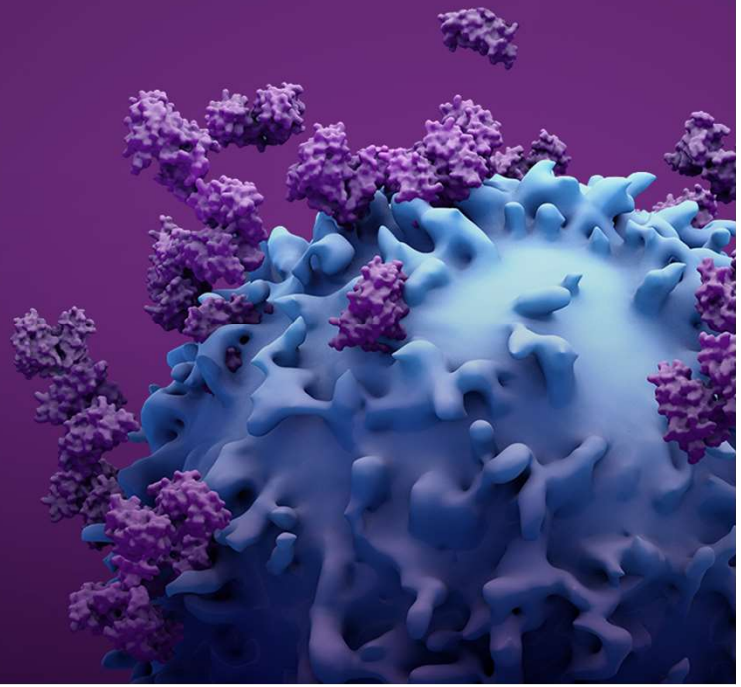
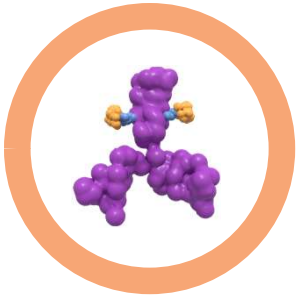
ADC Mechanism of Action



ADC Mechanism of Action[1,2]

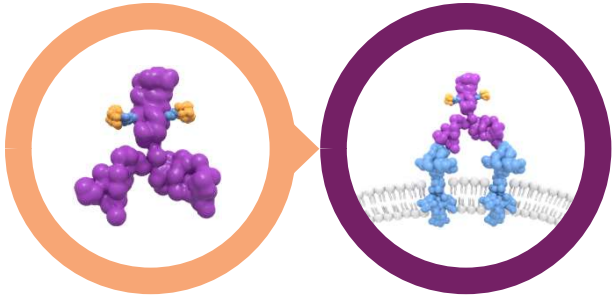


Circulation

- ADC solution is prepared and released into the bloodstream

1. Chau C et al. *Lancet*. 2019;394(10200):793-804; 2. Peters C et al. *Biosci Rep*. 2015;35(4):e00225.

ADC Mechanism of Action[1,2]



Circulation

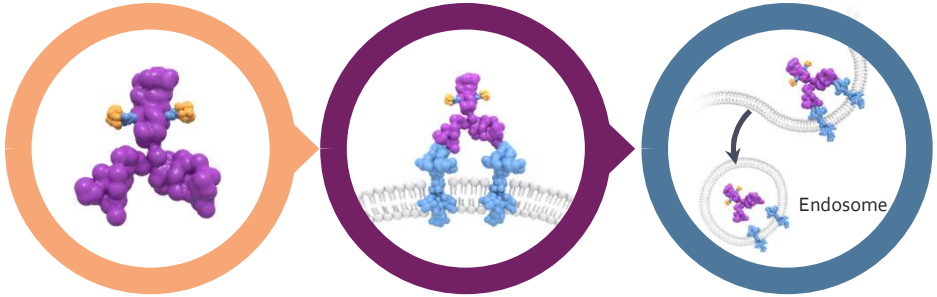
- ADC solution is prepared and released into the bloodstream

Binding

- mAb component of ADC binds to tumor antigen

1. Chau C et al. *Lancet*. 2019;394(10200):793-804; 2. Peters C et al. *Biosci Rep*. 2015;35(4):e00225.

ADC Mechanism of Action[1,2]



Circulation

- ADC solution is prepared and released into the bloodstream

Binding

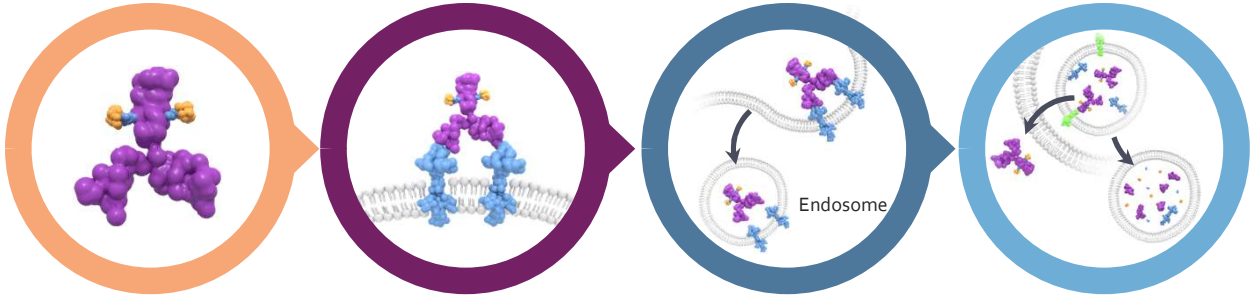
- mAb component of ADC binds to tumor antigen

Internalization

- ADC–antigen complex becomes internalized
- Forms an early endosome containing the ADC–antigen complex

1. Chau C et al. *Lancet*. 2019;394(10200):793-804; 2. Peters C et al. *Biosci Rep*. 2015;35(4):e00225.

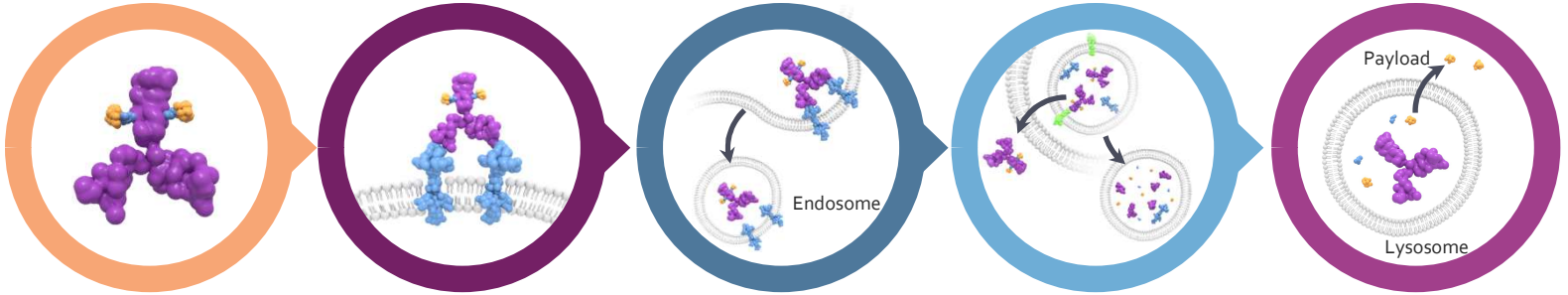
ADC Mechanism of Action[1,2]



Circulation	Binding	Internalization	Degradation & Recycling
ADC solution is prepared and released into the bloodstream	mAb component of ADC binds to tumor antigen	ADC–antigen complex becomes internalized Forms an early endosome containing the ADC–antigen complex	A fraction of ADCs bind to FcFn receptors in early endosomes and get transported back out of the cell Proton pumps on lysosomes create an acid labile environment that facilitates ADC degradation and proteolytic cleavage by proteases such as cathepsin-B and plasmin

1. Chau C et al. *Lancet*. 2019;394(10200):793-804; 2. Peters C et al. *Biosci Rep*. 2015;35(4):e00225.

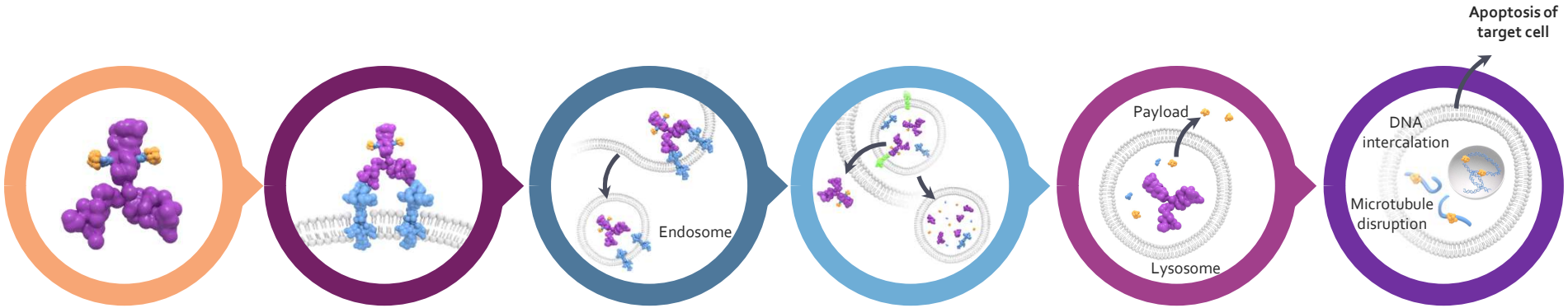
ADC Mechanism of Action[1,2]



Circulation	Binding	Internalization	Degradation & Recycling	Release of payload
ADC solution is prepared and released into the bloodstream	mAb component of ADC binds to tumor antigen	ADC–antigen complex becomes internalized Forms an early endosome containing the ADC–antigen complex	A fraction of ADCs bind to FcFn receptors in early endosomes and get transported back out of the cell Proton pumps on lysosomes create an acid labile environment that facilitates ADC degradation and proteolytic cleavage by proteases such as cathepsin-B and plasmin	Lysosomes fuse with late endosomes causing ADCs to undergo catabolism and release the toxic payload, which is then transported from the lysosome lumen to the cytosol

1. Chau C et al. *Lancet*. 2019;394(10200):793-804; 2. Peters C et al. *Biosci Rep*. 2015;35(4):e00225.

ADC Mechanism of Action[1,2]



Circulation	Binding	Internalization	Degradation & Recycling	Release of payload	Drug Action
ADC solution is prepared and released into the bloodstream	mAb component of ADC binds to tumor antigen	ADC–antigen complex becomes internalized Forms an early endosome containing the ADC–antigen complex	A fraction of ADCs bind to FcFn receptors in early endosomes and get transported back out of the cell Proton pumps on lysosomes create an acid labile environment that facilitates ADC degradation and proteolytic cleavage by proteases such as cathepsin-B and plasmin	Lysosomes fuse with late endosomes causing ADCs to undergo catabolism and release the toxic payload, which is then transported from the lysosome lumen to the cytosol	Cytotoxic payload causes cell death via DNA intercalation or by inhibiting microtubule polymerization

1. Chau C et al. *Lancet*. 2019;394(10200):793-804; 2. Peters C et al. *Biosci Rep*. 2015;35(4):e00225.

Mechanisms of ADC Resistance

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ADC binding to target antigen

- Target downregulation
- Loss of antigen expression
- Mutated antigen affects target recognition

Receptor-mediated ADC internalization

- Reduced cell-surface trafficking, causing insufficient ADC internalization
- Internalization and trafficking defects

Payload release to the cytosol

- Loss of lysosomal transporter expression
- Overexpression of drug efflux transporters

Apoptosis of the target cell

- Loss of the bystander effect

Chau C et al. *Lancet*. 2019;394(10200):793-804.

Considerations for Treatment With ADCs[1,2]

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Efficacy does not always correlate with dose

ADC efficacy may be affected by:

- Payload concentration threshold
- Antigen–antibody saturation (causing the ADC concentration to be higher in circulation than at the corresponding receptors)

Some antigens may shed from tumor cells and circulate, resulting in invalid antibody–antigen combinations

The relative lack of immunosuppressive side effects of many ADCs suggests that a potential clinical benefit of some ADCs may be the engagement of the immune system

1. Tang H, et al. *Front Pharmacol*. 2019;10:373; 2. de Goeij B, et al. *Curr Opin Immunol*. 2016;40:14-23.

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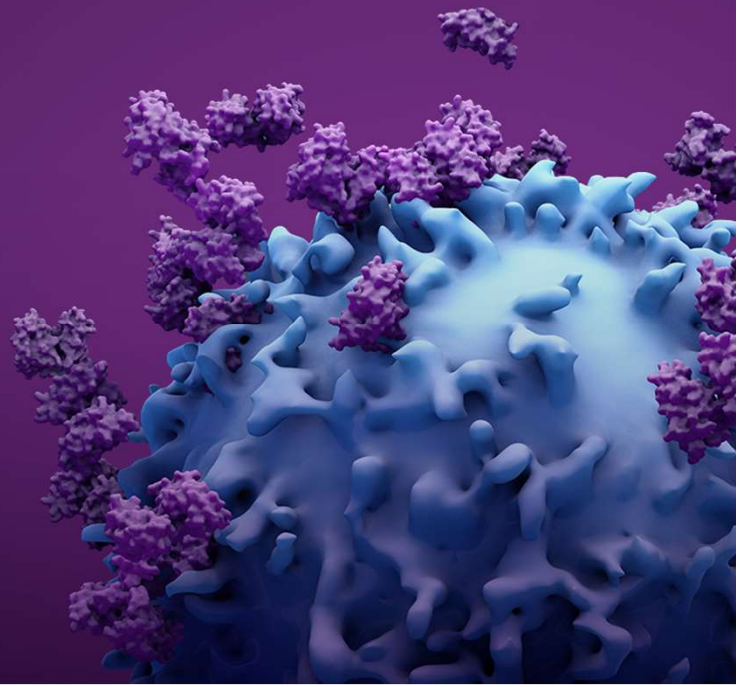
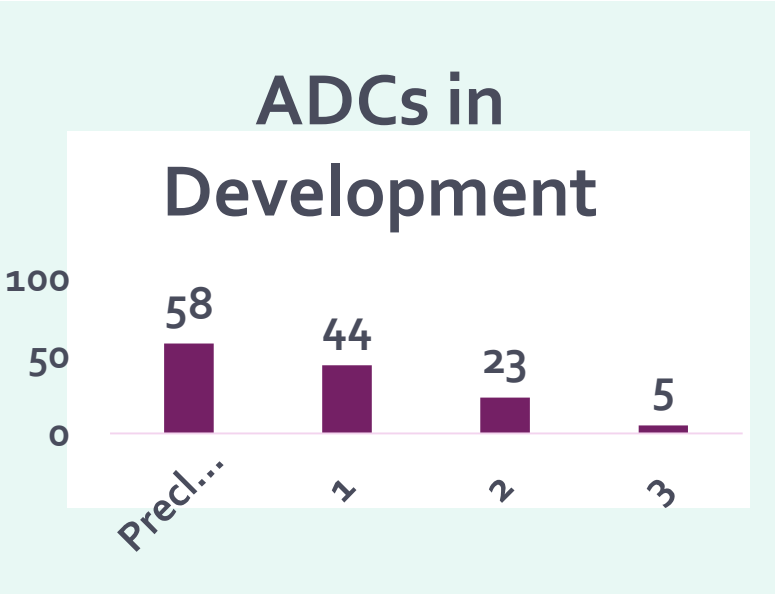
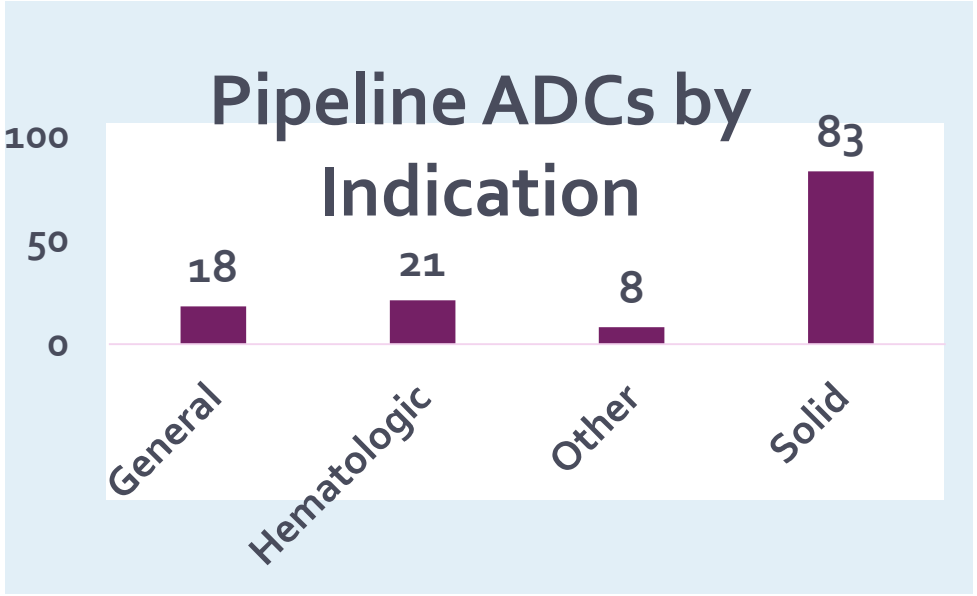
ADCs in Clinical Development



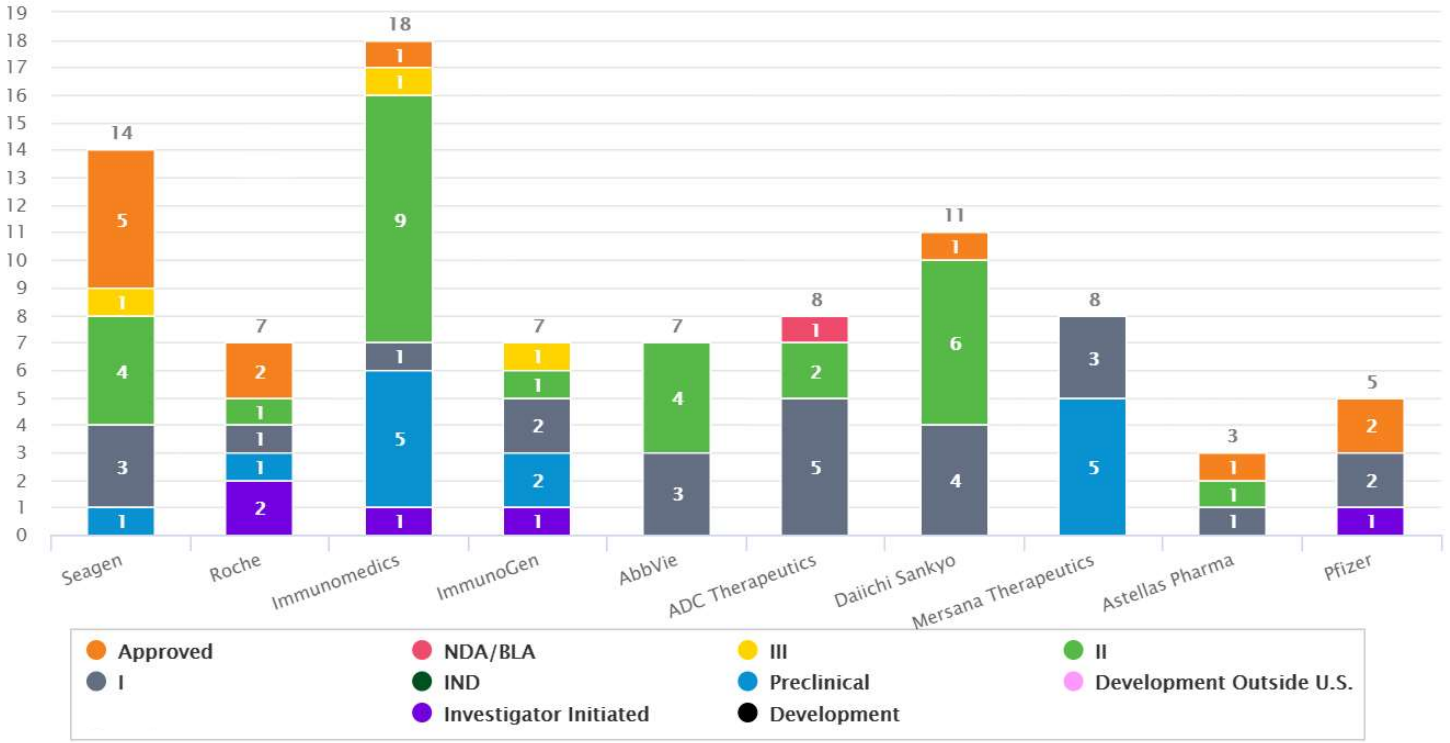
ADCs in Solid Tumors: More to Come





Informa Business Intelligence, Inc., 2020.

Number of ADCs Approved and in Development by Phase (Top 10 Companies)



Seagen; Seattle Genetics.
Informa Business Intelligence, Inc., 2020

HER2 ADC Competitive Landscape

Company	Project (Payload)	Potential Indication	Pre-Clinical	Ph 1	Pivotal
Daiichi Sankyo Cancer Enterprise	DS-8201	Breast, Gastric, NSCLC, CRC	Ph 3, Ph 2, Ph 1		
Synthon	SYD985	Breast, Gastric	Ph 3, Ph 1		
Bio-Thera	BA8001	Breast, Gastric	Ph 3		
Remegen, Ltd.	RC-48	Breast, Gastric, Bladder	Ph 2		
Takeda Mersana	XMT-1522	Breast, Gastric, NSCLC	Ph 1		
Ambrx	ARX-788	Breast, Gastric	Ph 1		
Pfizer	PF-06804103	Breast, Gastric, NSCLC, GEJ	Ph 1		
Roche Genentech	DHES-0815A	Breast	Ph 1		
Alteogen	ALT-P7	Breast	Ph 1		
Klus Pharma	A166	Solid Tumor	Ph 1/2		

GEJ, gastroesophageal junction.
Tsurutani, J, 2020. Adcs - Targeting HER Family.

Key Takeaways

- ADCs represent a novel drug class that delivers highly potent "**targeted chemotherapy**" to the tumor site
- Majority of ADCs are currently FDA approved for hematologic malignancies; 3 are FDA approved in solid tumors (ie, breast cancer)
- ADCs are composed of an antibody, a linker, and a payload
  - Characteristics of each component contribute to efficacy and safety
- **Many clinical studies with ADCs are ongoing, especially for solid tumors**

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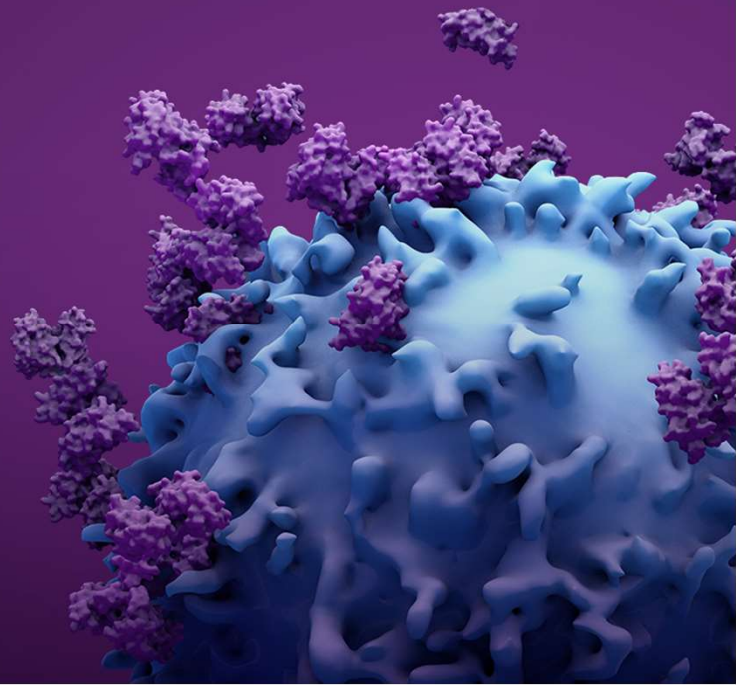
Thank You!



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Disclosures

Contracted Research: Ambrx, Amgen, Arvinas, Bayer, Daiichi-Sankyo, Dignitana, Genentech, GSK, Immunomedics, Lilly, Macrogenics, Novartis, OBI Pharma, Pfizer, Pieris, PUMA, Radius, Roche, Sanofi, Seattle Genetics

Travel: Eli Lilly and Company

Stock options: NKMaX

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Disclosures

Advisory Boards: AstraZeneca Pharmaceuticals LP; Eli Lilly and Company; Novartis Pharmaceuticals Corp.; Genentech, Inc.; Seattle Genetics, Inc.; MacroGenics, Inc.; Puma Biotechnology, Inc.; Merck & Co., Inc.

Data Safety Monitoring Board: Genentech, Inc.; Seattle Genetics, Inc.

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Antibody–Drug Conjugates in Development for Breast Cancer

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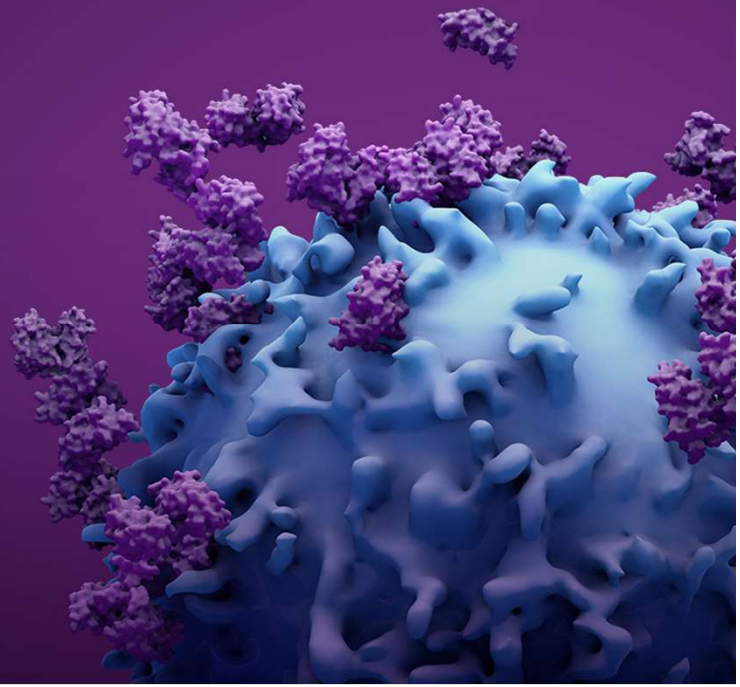

Learning Objectives

Review 3 FDA-approved ADCs and ADCs in clinical development for breast cancer

- Analyze the unmet need in patients with breast cancer
- Discuss their mechanisms of action
- Analyze available clinical data and discuss ongoing clinical trials

ADC, antibody–drug conjugate; BC, breast cancer; FDA, US Food and Drug Administration.

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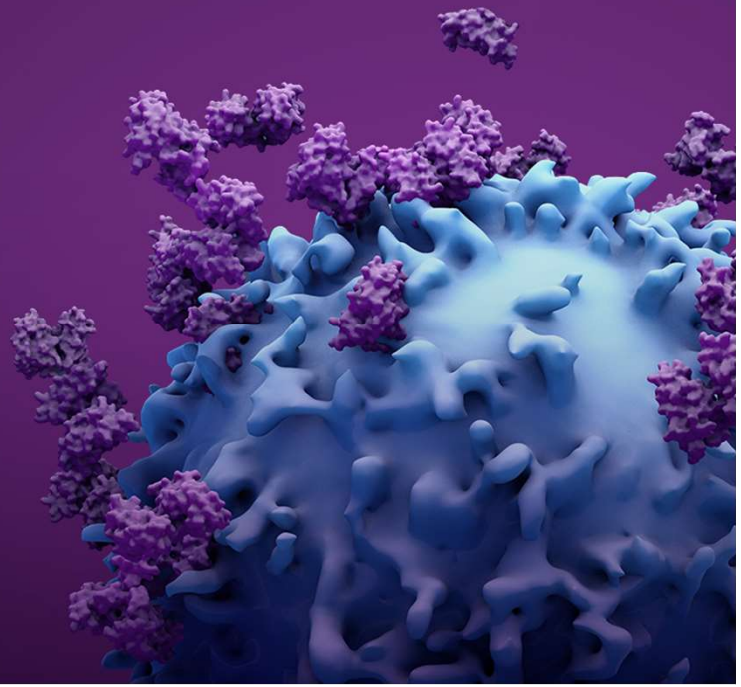
FDA-Approved ADCs in Breast Cancer



The Majority of Breast Cancer Cases Are Diagnosed in Early Stages, When the Disease Is Curable

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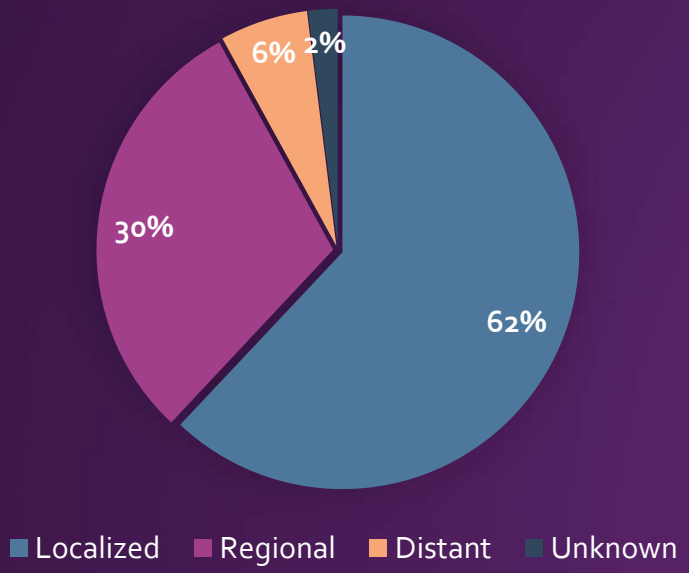

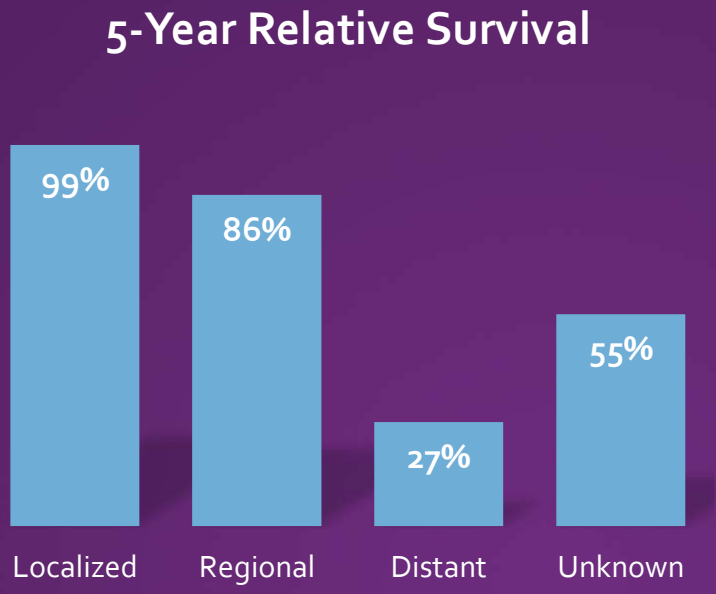

Breast Cancer Stage Distribution of SEER Incidence Cases, 2008-2017. URL: https://seer.cancer.gov/explorer/application.php?site=55&data_type=1&graph_type=4&compareBy=sex&chk_sex_3=3&chk_race_1=1&chk_age_range_1=1&advopt_precision=1&showDataFor=race_1_and_age_range_1. Accessed: November 8, 2020.

Breast Cancer Subtypes Guide Treatment Decisions

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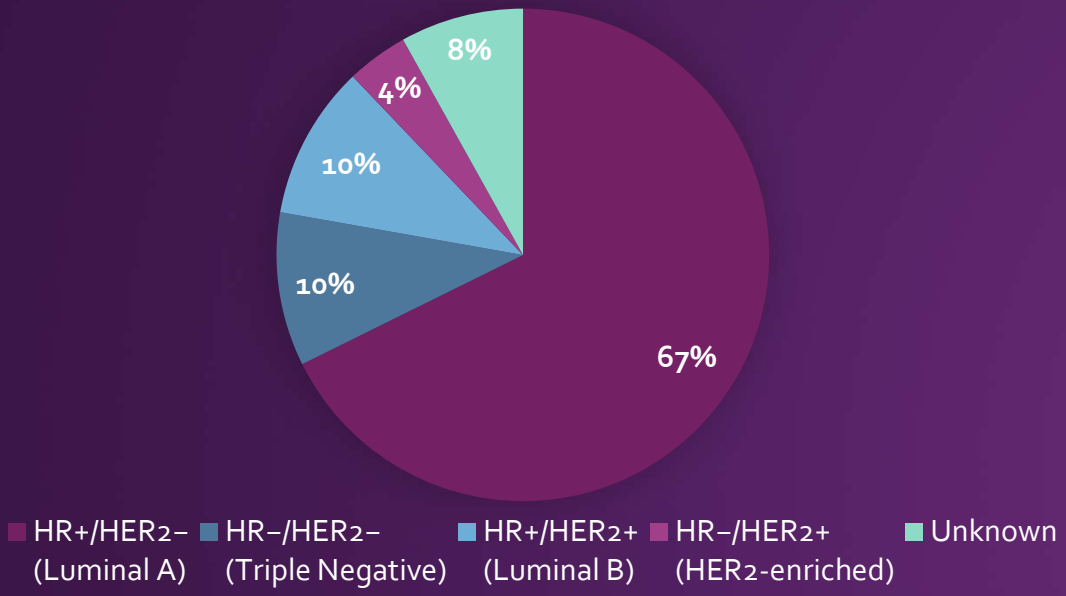
Female Breast Cancer Cases by Subtype (%) SEER 21 2012-2016



Rate of New Breast Cases per 100,000 Women, SEER 21 2012-2016

Subtype	New Cases
HR+/HER2−	85.8
HR−/HER2−	13.0
HR+/HER2+	12.9
HR−/HER2+	5.4
Unknown	10.4
Total	127.5

HER, human epidermal growth factor receptor; HR, hormone receptor.
Cancer Stat Facts: Female Breast Cancer Subtypes. URL: https://seer.cancer.gov/statfacts/html/breast-subtypes.html.

FDA-Approved ADCs in Breast Cancer (BC)

Drug name	Target	Indication	FDA Approval
KADCYLA® (trastuzumab emtansine)[1]	HER2	**Early Breast Cancer**: 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. **Metastatic Breast Cancer**: 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
ENHERTU ® (trastuzumab deruxtecan)[2]	HER2	Adults with unresectable or metastatic HER2+ breast cancer who have received ≥2 prior anti-HER2 based regimens	12/2019
TRODELVY ® (sacituzumab govitecan)[3]	TROP-2	Adult patients with metastatic triple-negative breast cancer (TNBC) who have received ≥ 2 prior therapies for metastatic disease	06/2020

1. KADCYLA (trastuzumab emtansine) [package insert]. San Francisco, CA: Genentech, Inc; 2019.
2. ENHERTU (trastuzumab deruxtecan) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2019.
3. TRODELVY (sacituzumab govitecan-hziy) [package insert]. Morris Plains, NJ: Immunomedics, Inc; 2020.

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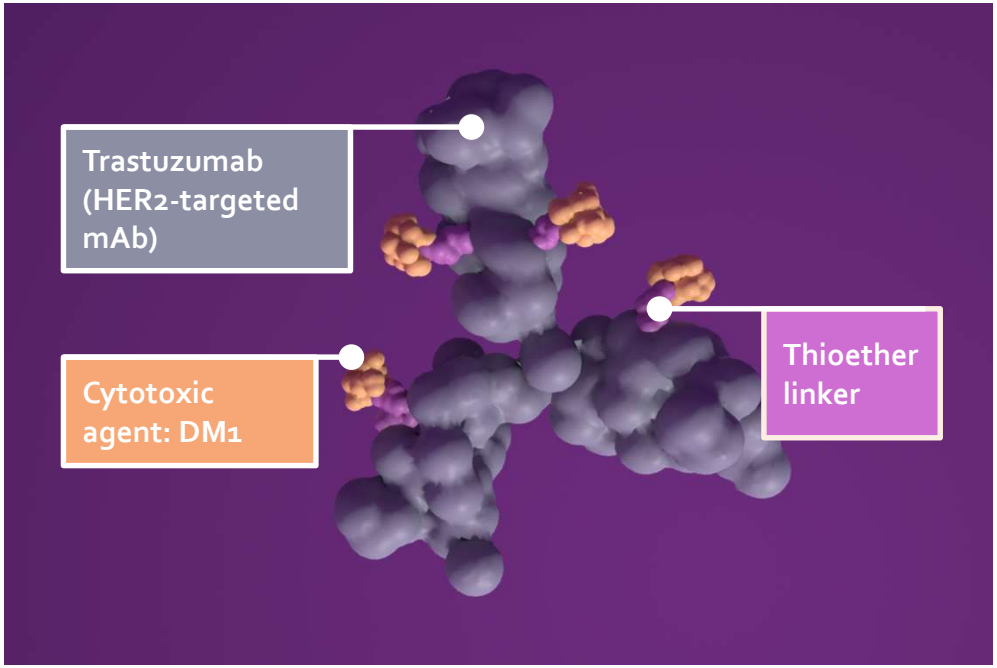

- HER2+ antitumor and DM1 cytotoxic activity[1]
- DM1 payload
- DM1, a maytansinoid, is approximately 20 to 200 times more potent than taxanes and vinca alkaloids[2,3]
- MCC linker was designed to provide a more stable bond between[1-3] trastuzumab and the active cytotoxic agent, with the goal of minimizing systemic exposure in circulation

DM1, myotonic dystrophy type 1; mAB, monoclonal antibody; MCC, N-succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate; T-DM1, trastuzumab emtansine.

1. KADCYLA Prescribing Information. Genentech, Inc. 2019; 2. Lewis Phillips GD, Li G, Dugger DL, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res. 2008;68(22):9280-9290; 3. Staudacher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? Br J Cancer. 2017;117(12):1736-1742; 4. Brufsky AM. HER2-Positive Metastatic Breast Cancer: Current Status and Promising Agents. https://www.clinicaloptions.com/sitecore/content/clinicaloptions/cco/oncology/programs/her2-positive-mbc-care/module/text-module/page-5#. Published April 13, 2020. Accessed October 22, 2020.

Breast Cancer | T-DXd

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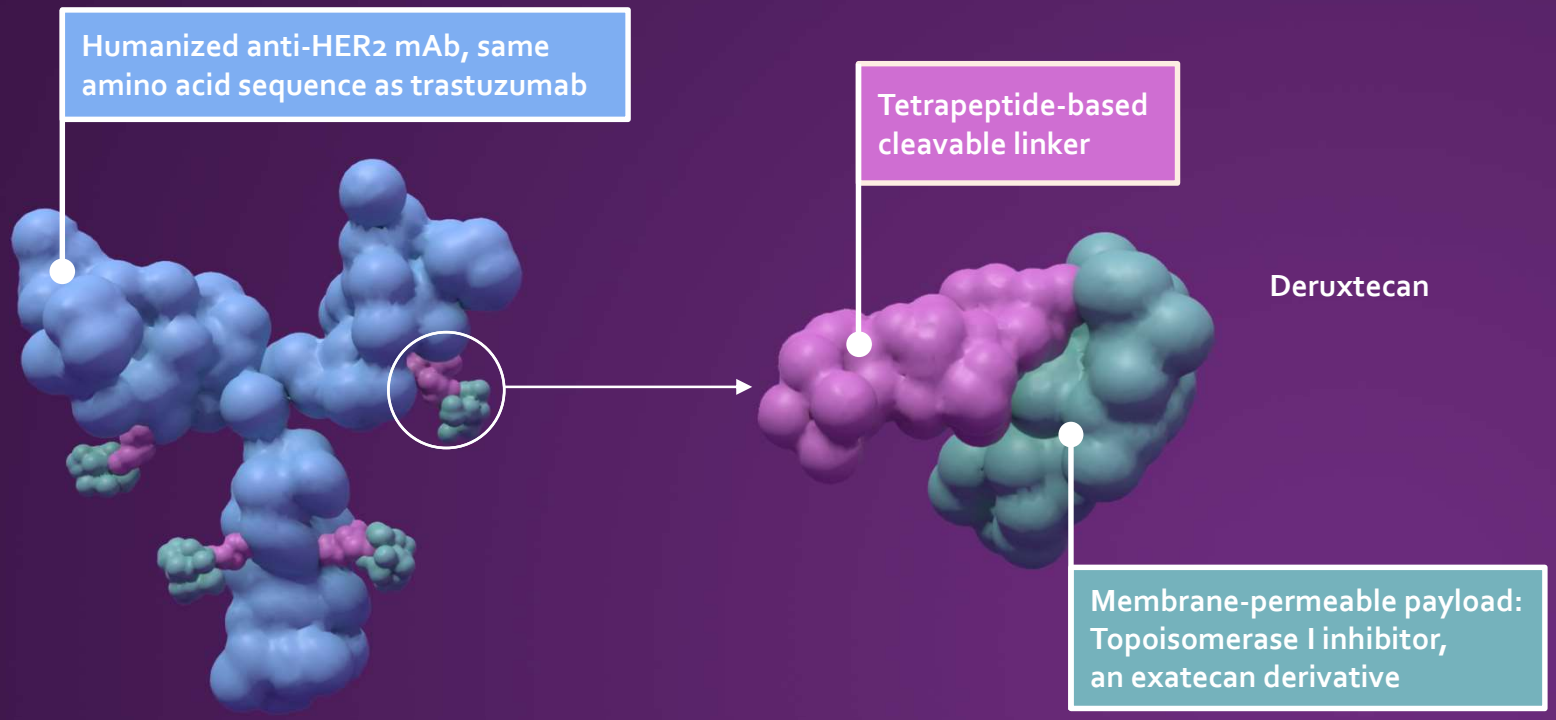
Trastuzumab Deruxtecan (T-DXd)



Smit EF et al. Trastuzumab Deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer: interim results of DESTINY-Lung01. Presented at: American Society for Clinical Oncology 2020 Virtual Scientific Program; May 29 – 31. Accessed November 6, 2020. https://meetinglibrary.asco.org/session/12667

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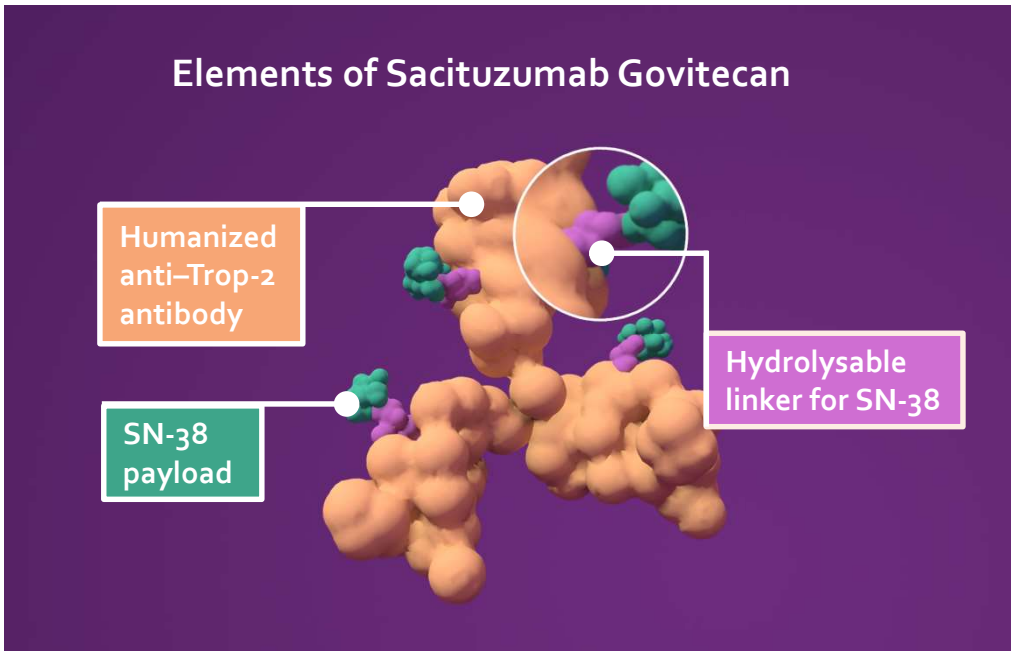

- SN-38 is the active metabolite of irinotecan, a topoisomerase I inhibitor that interferes with cell growth and spread[1]
- Sacituzumab govitecan delivers up to 136x more SN-38 than irinotecan[2]
- Inhibition of topoisomerase I by SN-38 leads to apoptosis[1]

Mechanism of Sacituzumab Govitecan (IMMU-132)

1. Bardia A et al. J Clin Oncol. 2017;35(19):2141-2148; 2. Goldenberg DM et al. Oncotarget. 2015;6(26):22496–22512.

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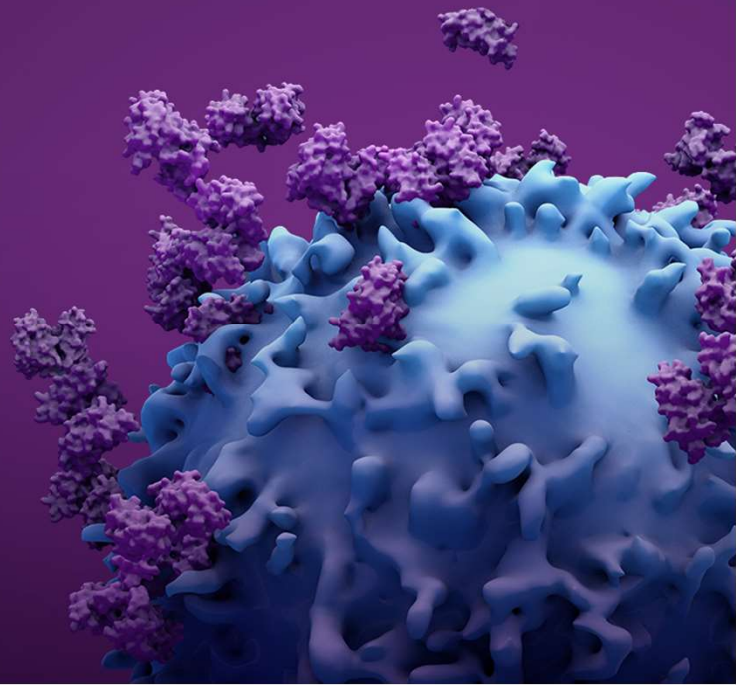
ADCs Targeting HER2



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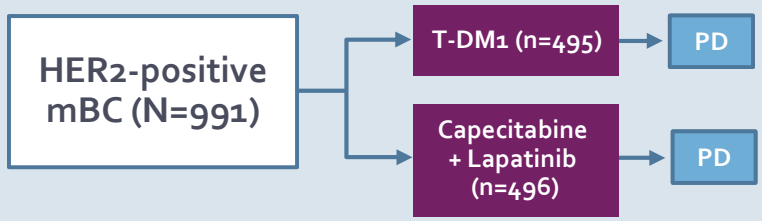
EMILIA: Improved OS With T-DM1 vs Capecitabine + Lapatinib in Pts With HER2+ Locally Advanced or mBC

PATIENTS

- HER2-positive locally advanced or mBC
- Previously treated with trastuzumab and taxane

STUDY DESIGN



ENDPOINTS

1°

- PFS
- OS
- Safety

Select 2°

- ORR
- DOR
- CBR
- TTF

CBR, clinical benefit rate; DOR, duration of response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Pts, patients; ORR, overall response rate; TTF, time to treatment failure.
U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT00829166. Accessed November 8, 2020. Last updated: October 31, 2016.

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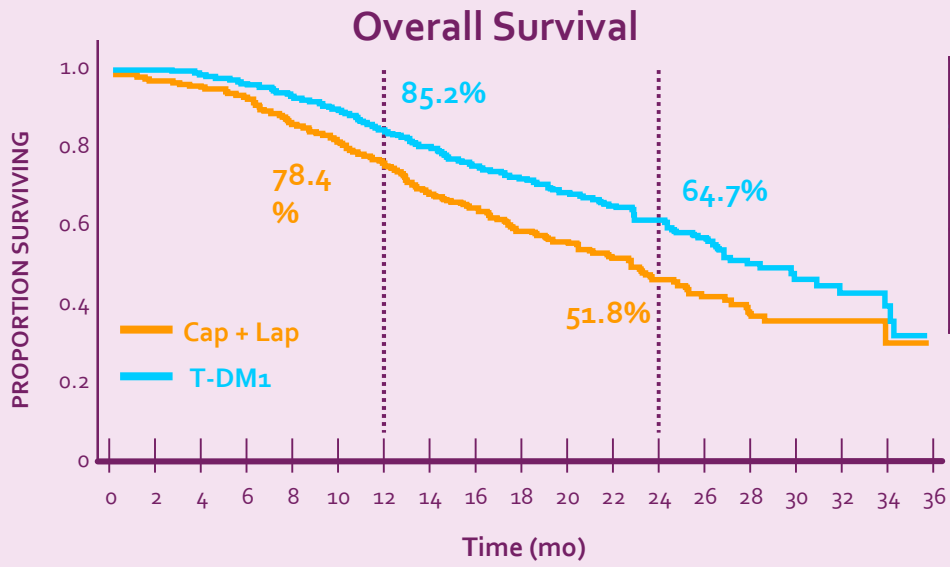
EMILIA Led to Kadcyla Approval in Patients With HER2+ Locally Advanced or mBC in Feb 2013[1,2]

ANTITUMOR ACTIVITY



	Median (mo)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55-0.85); *P* = 0.0006

Efficacy stopping boundary P = *0.0037 or HR=0.727*

Data cut-off July 31, 2012;
Unstratified HR=0.70 (*P* = 0.0012)

Cap, capecitabine; CI, confidence interval; HR, hazard ratio; Lap, lapatinib; mo, month.

1. CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 125427Orig1s000. fda.gov.URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000SumR.pdf. Published February 21, 2013. Accessed May 11, 2020; 2. Verma S et al. *N Engl J Med*. 2012;367:1783-1791.

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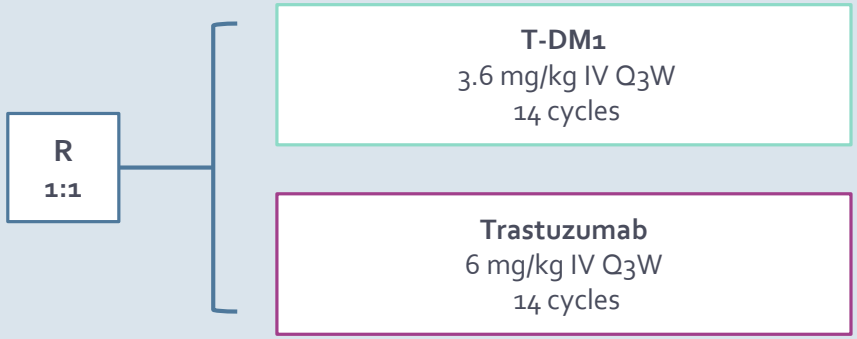
KATHERINE: Ph 3, Open-Label Study of Adjuvant T-DM1 vs Trastuzumab for Residual Invasive HER2-Positive BC

PATIENTS

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
  - Minimum of 9 weeks of taxane
  - Anthracyclines and alkylating agents allowed
  - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
  - Second HER2-targeted agent allowed
  - Residual invasive tumor in breast or axillary nodes
  - Randomization within 12 weeks of surgery

STUDY DESIGN



Radiation and endocrine therapy per protocol and local guidelines

ENDPOINTS

1°

- iDFS

Select 2°

- DFS
- OS
- Distant recurrence-free survival
- safety

Presented by Charles E. Geyer at the San Antonio Breast Cancer Symposium 2018 Dec 4-8
Von Minckwitz G et al. *N Engl J Med.* 2019;380(7):617-628.

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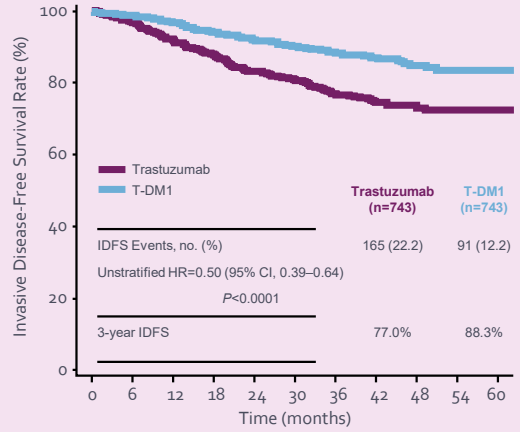
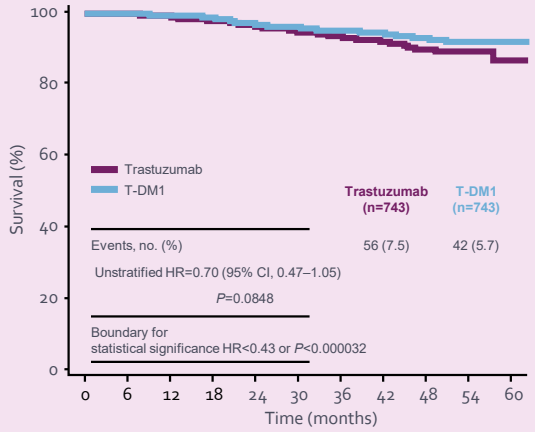
KATHERINE: iDFS and OS

ANTITUMOR ACTIVITY





SAFETY RESULTS

- The most common AEs of gr ≥3 with T-DM1: decreased platelet count (in 5.7% of pts) and hypertension (2.0%); with trasuzumab: hypertension (1.2%), radiation-related skin injury (1.0%)
- SAEs occurred in 94 patients who received T-DM1 (12.7%) and 58 patients who received trastuzumab (8.1%)
- AEs leading to discontinuation occurred in 133 patients in the T-DM1 group (18.0%) and 15 patients in the trastuzumab group (2.1%)
- 1 pt in the T-DM1 group with a decreased platelet count died from an intracranial hemorrhage that occurred after a fall. The % of patients with hemorrhage of gr ≥3 were similar in the T-DM1 group and the trastuzumab group (0.4% and 0.3%)

Presented by Charles E. Geyer at the San Antonio Breast Cancer Symposium 2018 Dec 4-8

T-DM1 Approved Based Upon Results From KATHERINE

As of May 6, 2019, the FDA has approved ado-trastuzumab emtansine (T-DM1; KADCYLA) for use as an adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease following neoadjuvant trastuzumab (Herceptin) and chemotherapy[1]

NCCN Guidelines Recommend T-DM1 for HER2-positive Breast Cancer Residual Disease :

- If HER2-positive with presence of residual disease[2]
- T-DM1 alone for 14 cycles (KATHERINE[3])

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Selected Ongoing Studies With T-DM1

Study	Ph	Patients	N	Arms	1° EP	Est Study Completion
ATOP TRIAL[1]	2	• ≥60 years of age • HER2-positive breast cancer • Standard chemotherapy/trastuzumab declined by pt or pt is not deemed an eligible candidate for therapy	82	Experimental: T-DM1	5-year iDFS rate	01/2022

Several clinical studies of combinations with T-DM1 are ongoing and not represented in this list.

EST, estimated; ET, endocrine therapy; EP< endpoint; iDFS, invasive disease-free survival; pCR, pathological compete response rate; ph, phase; pt, patient.

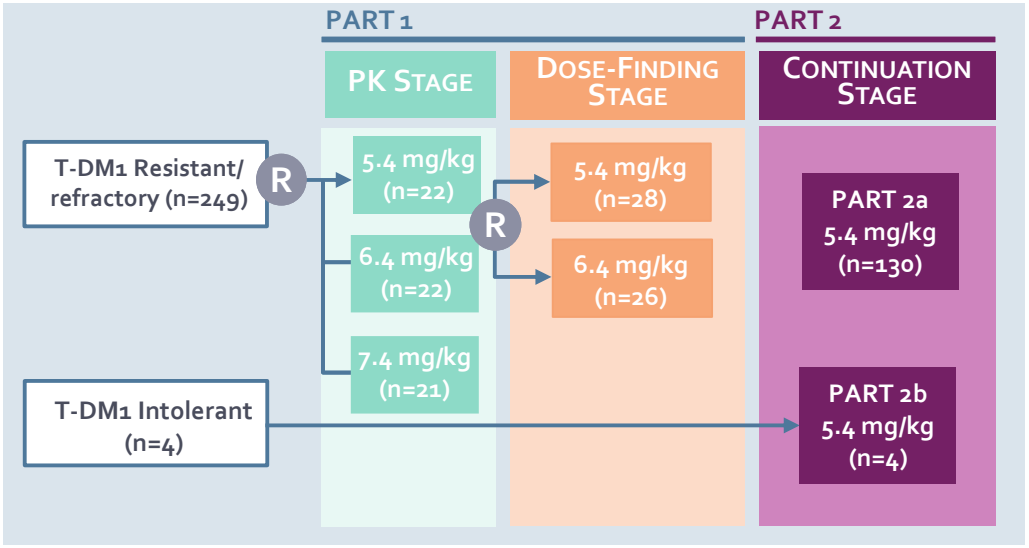
1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03587740. Published July 16, 2018. Accessed November 7, 2020. Last updated: October 5, 2020;
2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT01745965. Published December 10, 2012. Accessed November 7, 2020. Last updated: July 23, 2020.

DESTINY-BREAST01 Study Schema[1,2]

PATIENTS

- ≥18 years of age
- Unresectable and/or mBC
- HER2-positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed

STUDY DESIGN



ENDPOINTS

1°

Confirmed ORR

Select 2°

- Investigator-assessed ORR
- DCR
- DOR
- CBR
- PFS
- OS
- PK

DCR, disease control rate; ILD, interstitial lung disease, PK, pharmacokinetics.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03248492. Accessed November 7, 2020. Last updated: August 18, 2020;
2. Modi S et al. *N Engl J Med*. 2020;382(7):610-621.

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DESTINY-BREAST01 (NCT03248492), Phase 2, Showed Positive Outcomes in OS, PFS, ORR, and Change in Baseline Tumor Size, Leading to Accelerated Approval of Trastuzumab Deruxtecan in 2019[1,2]

ANTITUMOR ACTIVITY

Endpoint	Result (N = 184)
OS, % (95% CI) at 6 mo	93.9 (89.3, 96.6)
OS, % (95% CI) at 12 mo	86.2 (79.8, 90.7)
PFS, mo (95% CI) for all patients	16.4 (12.7, NR)
PFS, mo (95% CI) for patients with asymptomatic brain metastases	18.1 (6.7, 18.1)
CBR	76.1 (69.3, 82.1)
Confirmed ORR	60.9 (53.4, 68)

SAFETY RESULTS

- Most common AEs of gr ≥3 were decreased neutrophil count (20.7% of patients), anemia (8.7%), and nausea (7.6%)
- T-DXd was associated with ILD in 13.6% of patients (gr 1 or 2, 10.9%; gr 3 or 4, 0.5%; and gr 5, 2.2%)

AE, adverse event; gr, grade; NR, not reached.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03248492. Accessed November 7, 2020. Last updated: August 18, 2020;
2. Modi S et al. *N Engl J Med*. 2020;382(7):610-621.

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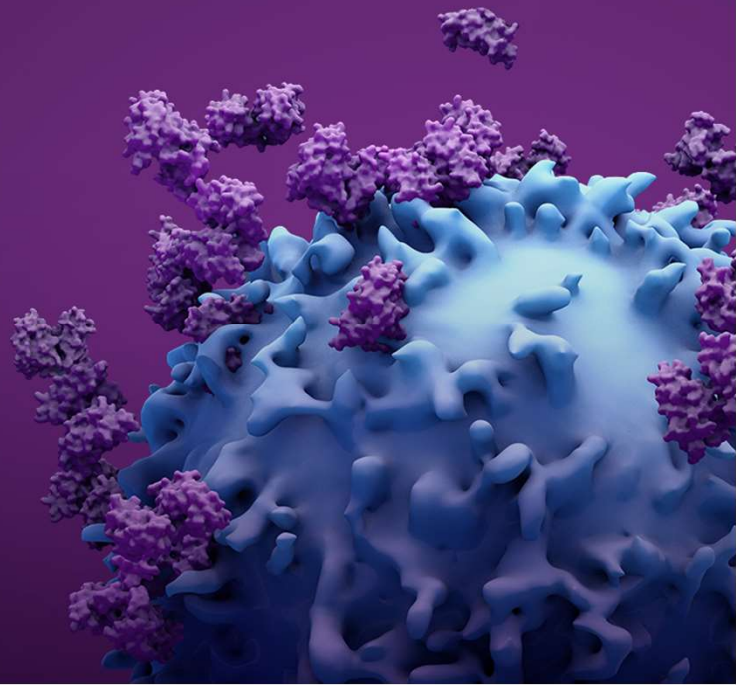
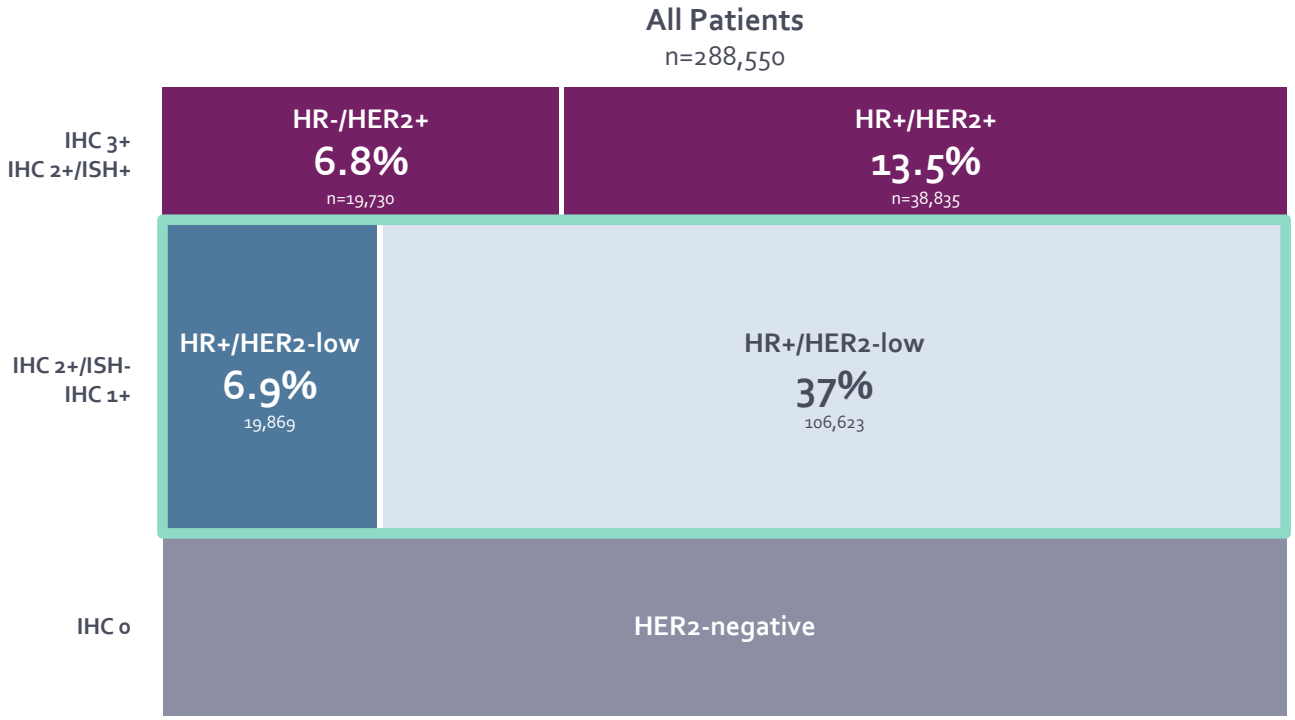
T-DXd in HER2-Low



Ongoing Clinical Trials Have Defined Tumors With HER2-Low Expression as IHC 1+ or IHC 2+ and in-Situ Hybridization (ISH)-Negative



*Source: Decision Resources, inclusive of US, Europe, and Japan (Breast Cancer, Last updated, December 2017, CAncerMPACT (2017))

NSABP B-47: HER2-Negative Patients Derived Similar Benefits From Trastuzumab as Demonstrated in HER2-Positive Patients

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STUDY DESIGN

NSABP B-47

- Randomized phase 3 study of 3,270 patients tested the hypothesis that trastuzumab can be effective in patients with node-positive or high-risk node-negative breast cancer who are "HER2-low" (1+ or 2+ by immunohistochemistry, not amplified by fluorescence in situ hybridization)
- **Patients were randomized to chemotherapy with or without trastuzumab for 1 year to determine if the addition of trastuzumab improves DFS**

ANTITUMOR ACTIVITY

- Study demonstrated feasibility of identifying and accruing these patients to trials
- The randomized trial showed no improvement in invasive disease–free survival, overall survival, or other endpoints when women received 1 year of trastuzumab in addition to standard chemotherapy vs chemotherapy alone

1. https://www.ascopost.com/issues/january-25-2018/nsabp-b-47-no-benefit-for-adjuvant-trastuzumab-in-her2-low-breast-cancer/; 2. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673-1684,2005; 3. Fehrenbacher L, Cecchini RS, Geyer CE, et al: NSABP B-47 (NRG Oncology): Phase III randomized controlled trial comparing adjuvant chemotherapy with adriamycin and cyclophosphamide followed by weekly paclitaxel, or docetaxel and cyclophosphamide with or without a year of trastuzumab in women with node-positive or high-risk node-negative invasive breast cancer expressing HER2 staining intensity of IHC 1+ or 2+ with negative FISH. 2017 San Antonio Breast Cancer Symposium. Abstract GS1-02. Presented December 6, 2017.

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J101 Ongoing Phase 1 Trial With T-DXd Demonstrated Positive Results in Patients With Heavily Pretreated, Advanced, HER2-Low BC

PATIENTS

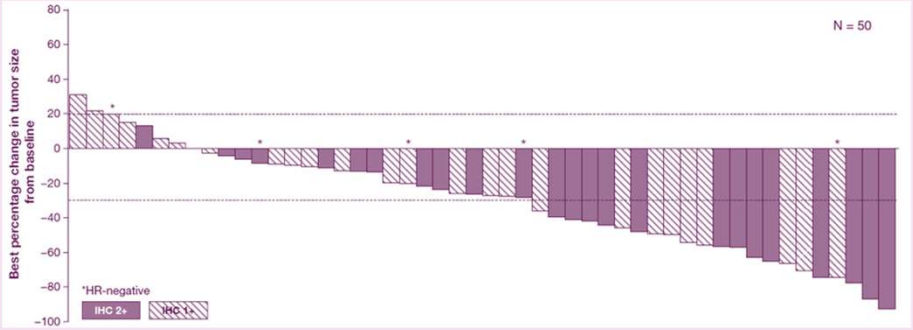
Patients with breast cancer or gastric/GEJ adenocarcinoma

mCRM with EWOC

Two-part dose escalation and dose expansion phase

ANTITUMOR ACTIVITY

T-DXd Demonstrated a 44.2% ORR (19/43) with a Manageable Safety Profile



SAFETY RESULTS

- 99.4% of patients experienced a TEAE regardless of causality
- 22.9% of patients experienced a serious TEAE
- 50.0% of patients experienced grade ≥3 TEAE
- 4 fatal cases of ILD/pneumonitis

N = 51	Confirmed ORR n/N (%)	Confirmed DCR n/N (%)	DOR Median (range), mo	PFS Median (95% CI), mo
HER2-low BC (IHC 2+ / ISH– or IHC 1+)	44.4%	83.3%	11 (4.5, 12.8)	8 (5.6, 13.9)

EWOC, escalation with overdose control; GEJ, gastroesophageal junction; IHC, immunohistochemistry; ISH, in situ hybridization; mCRM, modified Continuous Reassessment Method; TEAE, treatment-emergent adverse event.

Modi S et al. *J Clin Oncol*. 2020;38(17):1887-1896.

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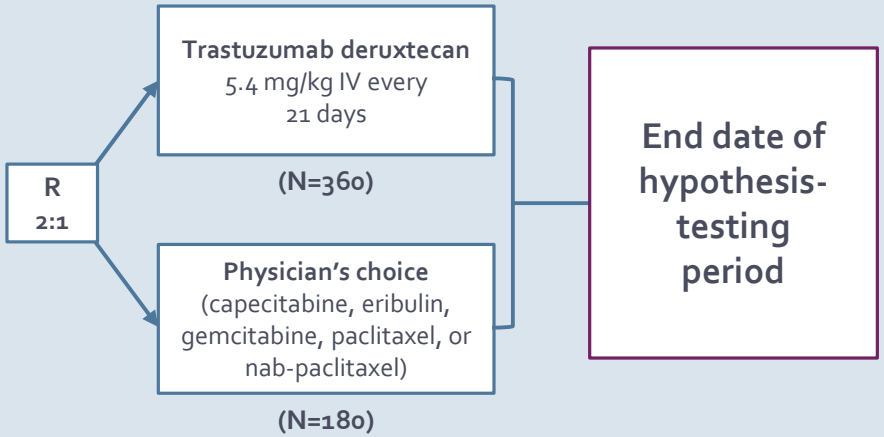
DESTINY-Breast04: Multicenter, Int'l, Randomized, Open-Label Phase 3 Study of T-DXd vs Investigators Choice in HER2-Low BC

PATIENTS

- Unresectable and/or metastatic HER2-low BC
- (IHC 2+/ISH- or IHC 1+)

STUDY DESIGN



ENDPOINTS

1°

PFS

Select 2°

- OS
- ORR
- Safety

Estimated study completion: January 2023

U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed November 7, 2020. Last updated: October 20, 2020.

PrimO Practical Recommendations in Immuno & Molecular Oncology ADC Summit

Ongoing Studies With T-DXd

Study	Ph	Patients	N	Arms	1° EP	'''''''''''''
DESTINY-Breast02 (NCT03523585)[1]	3	Previously treated unresectable and/or metastatic HER2-positive BC	600	• Experimental: T-DXd • Comparator: trastuzumab + capecitabine • Comparator: lapatinib + capecitabine	PFS based on BICR (2° EP: OS, ORR, DOR, PFS based on investigator's assessment)	09/2024
DESTINY-Breast03 (NCT03529110)[2]	3	Unresectable and/or metastatic HER2-positive BC previously treated with trastuzumab and taxane	500	• Experimental: T-DXd • Comparator: T-DM1	PFS based on BICR (2° EP: OS, ORR, DOR, PFS based on investigator's assessment)	04/2023
DESTINY-Breast04 (NCT03734029)[3]	3	Previously treated unresectable and/or metastatic HER2-low BC	540	• Experimental: T-DXd • Comparator: PC (capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel)	PFS based on BICR (2° EP: PFS based on investigator's assessment, OS, ORR, DOR)	01/2023
DESTINY-Breast05 (NCT04622319)	3	Patients with HER2-positive primary BC with residual invasive disease in breast or axillary lymph nodes with higher risk of recurrence	1600	• Head-to-head comparison of T-DXd vs T-DM1	iDFS (2° EP: OS, DFS)	09/2027
DESTINY-Breast06 (NCT04494425)[4]	3	HER2-Low, HR+ adv or metastatic BC who have had disease progression on ≥2 lines of ET	850	• Experimental: T-DXd • Comparator: SOC (capecitabine, paclitaxel, nab-paclitaxel)	PFS in HR+, HER2-low (2° EP: PFS in ITT, OS, ORR, DOR, PFS, safety, TTD, HRQoL)	12/2022

BICR, blinded independent central review ; HRQoL, health-related quality of life; ITT, intention-to-treat; PC, physician's choice SOC, standard of care.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03523585. Accessed November 7, 2020. Last updated: September 30, 2020; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03529110. Accessed November 7, 2020. Last updated: September 25, 2020; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03529110; 3. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed November 7, 2020. Last updated: October 20, 2020; 4. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04494425. Accessed: November 7, 2020. Last updated: November 5, 2020.

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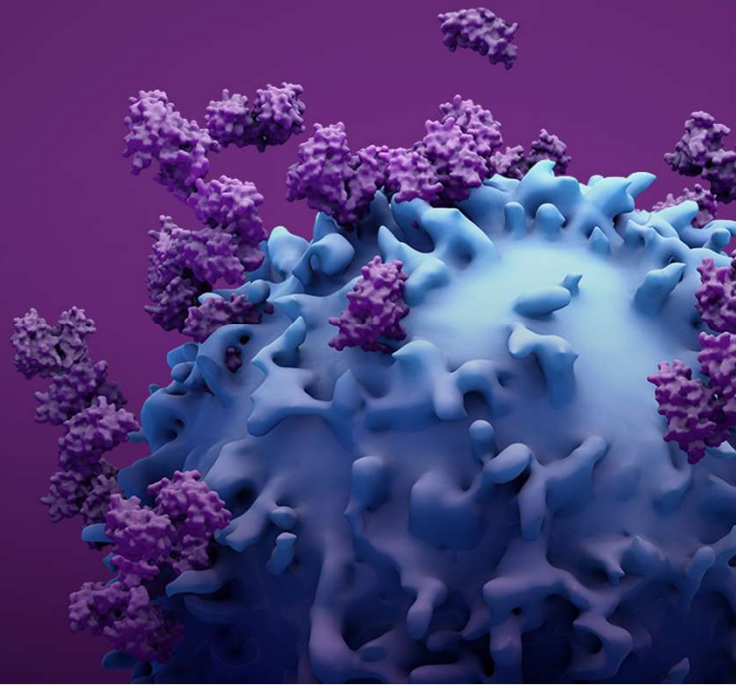
ADC Summit

ADCs IN TRIPLE-NEGATIVE BREAST CANCER (TNBC)



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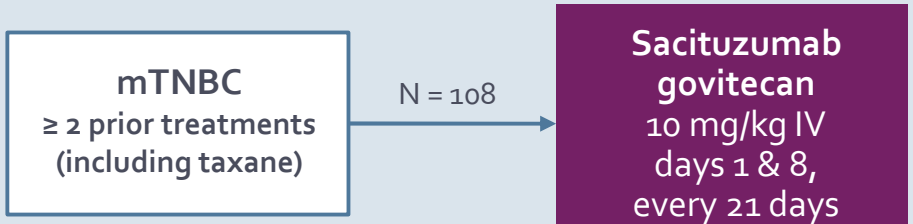
IMMU-132-01: Ph 1/2 Study of Sacituzumab Govitecan (IMMU-132) in Pts With Epithelial Cancers[1,2]

PATIENTS

- ≥18 years of age
- Stage IV mTNBC
- Refractory to or relapsed after 2 standard therapeutic regimens (for TNBC)

STUDY DESIGN



ENDPOINTS

1°

ORR

Select 2°

- Time to response
- DOR
- CBR
- PFS
- OS

TNBC, triple-negative breast cancer.

1. Bardia A et al. *N Engl J Med*. 2019; 380(8):741-751; 2. Goldenberg DM et al. Oncotarget. 2015;6(26):22496–22512; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT01631552. Accessed November 7, 2020. Last updated: September 9, 2020.

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Sacituzumab Govitecan Was Associated With Durable Objective Responses in Patients With Heavily Pretreated mTNBC

ANTITUMOR ACTIVITY

- **ORR = 33.3% (36/108)**
- CBR = 45.4% (49/108)

Endpoint	Result (N = 108)
Median PFS, mo (95% CI)	5.5 (4.1, 6.3)
Median OS, mo (95% CI)	13.0 (11.2, 13.7)
Median time to onset of response, mo (range)	2.0 (1.6, 13.5)
Median DOR, mo (95% CI)	7.7 (4.9, 10.8)

SAFETY RESULTS

- 4 deaths (3.7%) occurred during treatment
- 3 pts (2.8%) discontinued treatment because of AEs
- Gr 3 or 4 AEs occurred in ≥10% of pts, including anemia and neutropenia
  - Gr 3 or 4 neutropenia occurred in 45 pts (41.7%)
  - Gr 3 anemia occurred in 12 pts (11%)
- 10 pts (9.3%) had febrile neutropenia

Bardia A et al. *N Engl J Med*. 2019; 380(8):741-751.

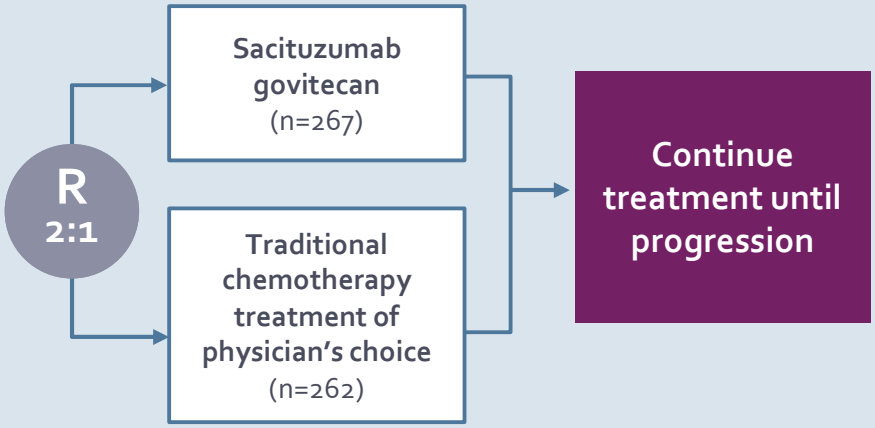
PrimO Practical Recommendations in Immuno & Molecular Oncology ADC Summit

ASCENT: Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Previously Treated TNBC[1,2]

PATIENTS

- ≥18 years of age
- mTNBC
- ≥2 prior treatments or >1 therapy for advanced disease

STUDY DESIGN



ENDPOINTS

1°

PFS

Select 2°

OS

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT02574455. Accessed November 7, 2020. Last updated: October 8, 2020;
2. Bardia A. ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Presented at: European Society for Medical Oncology Virtual 2020 Scientific Sessions. September 19, 2020. https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/ascent-a-randomized-phase-iii-study-of-sacituzumab-govitecan-sg-vs-treatment-of-physician-s-choice-tpc-in-patients-pts-with-previously-treat.

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ASCENT: Results Confirm Sacituzumab Govitecan Should Be Considered as a New SOC in Pts With Pretreated mTNBC

ANTITUMOR ACTIVITY

BCIR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
mPFS – mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	**0.41** (0.32-0.52) ***P* < 0.0001**	

OS	SG (n=235)	TPC (n=233)
No. of events	155	185
mOS – mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	**0.48** (0.38-0.59) ***P* < 0.0001**	

	SG (n=235)	TPC (n=233)
ORR – no. (%)	82 (35)	11 (%)
P value	< 0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)

SAFETY RESULTS

- Key gr ≥3 TRAEs (SG): neutropenia (51%), diarrhea (10%), leukopenia (10%) anemia (8%), and febrile neutropenia (6%)
- No severe cardiovascular toxicity, no gr >2 neuropathy or gr >3 ILD with SG
- No treatment-related deaths with SG
- AEs leading to treatment discontinuations were low for SG (4.7%)

mOS, median overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Bardia A. ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Presented at: European Society for Medical Oncology Virtual 2020 Scientific Sessions. September 19, 2020. https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/ascent-a-randomized-phase-iii-study-of-sacituzumab-govitecan-sg-vs-treatment-of-physician-s-choice-tpc-in-patients-pts-with-previously-treat.

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TROPiCS-02: Ph 3 Study of Sacituzumab Govitecan (IMMU-132) in Patients With HR+/HER2–Negative mBC

PATIENTS

- ≥18 years of age
- HR+/HER2– mBC
- ≥1 prior anticancer hormonal treatment
- ≥1 prior CDK4/6 inhibitor treatment in the metastatic setting

STUDY DESIGN

HR+/HER2– mBC

≥2 prior treatment failures
AND
<4 prior chemotherapy regimens
N=108

→ **Sacituzumab govitecan**
10 mg/kg IV
days 1 & 8, every 21 days

→ **Traditional chemotherapy treatment of PC**
(eribulin, gemcitabine, capecitabine & vinorelbine)

ENDPOINTS

1°

- PFS
- ORR

Select 2°

- OS
- DOR

Estimated study completion: May 2023

CDK4/6, cyclin-dependent kinase 4/6 inhibitor.

U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03901339. Accessed November 7, 2020. Last updated: September 29, 2020.

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Ongoing Studies With Sacituzumab Govitecan in Breast Cancer

Study	Ph	Patients	N	Arms	1° EP	Est Study Completion
NCT04230109 **(NeoSTAR)**[1]	2	Pts with localized TNBC	~50	Safety and efficacy of sacituzumab govitecan in localized TNBC	DFS, OS	August 31, 2023
NCT03992131 **(SEASTAR)**[2]	1b/2	Pts with TNBC and other cancers	329	Safety, tolerability, PK, and preliminary efficacy of sacituzumab govitecan + rucaparib in patients an advanced/metastatic solid malignancy	Safety, ORR	March 2024
NCT04039230[3]	1/2	Pts with mTNBC	65	Effects of sacituzumab govitecan + talazoparib	Safety	August 31, 2024

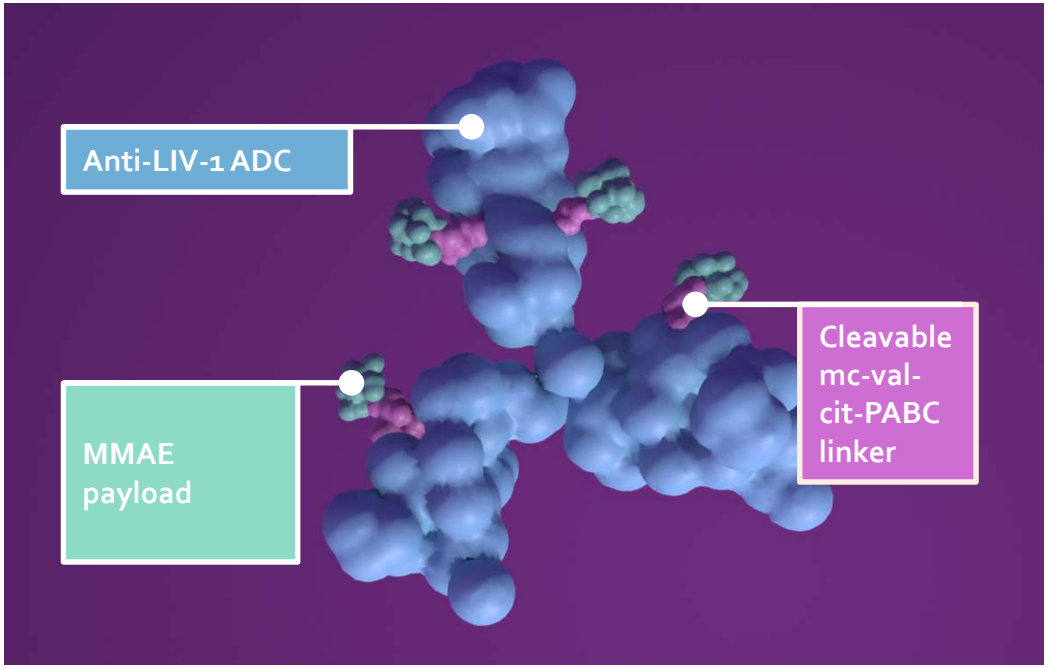
DFS, disease-free survival.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04230109. Accessed November 7, 2020. Last updated: July 16, 2020; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03992131. Accessed November 7, 2020. Last updated: August 26, 2019; 3. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://www.clinicaltrials.gov/ct2/show/NCT04039230. Accessed November 7, 2020. Last updated: May 5, 2020

Select Investigational ADCs in Breast Cancer

Trial	Drug name	Target	Ph	Brief Summary
NCT01969643[1]	Ladiratuzumab vedotin	Anti–LIV-1	1	Safety/tolerability in patients with mTNBC
NCT03262935[2]	Trastuzumab duocarmazine (SYD985)	HER2-targeting	3	Patients with HER2+ mBC pretreated with T-DM1
NCT02980341[2]	U3-1402	HER3-targeting	1/2	Trial in patients with HER3+ mBC

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT01969643. Accessed November 7, 2020. Last updated: October 22, 2020;
2. Rinnerthaler G et al. *Int J Mol Sci*. 2019;20(5):1115.



Ladiratuzumab vedotin (SGN-LIV1A)

- Ladiratuzumab vedotin delivers a potent microtubule-disrupting agent called MMAE via a protease-cleavable linker, to cancer cells expressing LIV-1[1,2]
- LIV1 is a transmembrane cell adhesion molecule highly expressed in metastatic breast cancer
- The disruption of microtubules leads to targeted tumor cell cycle arrest/disruption[2]

MMAE, monomethyl auristatin E; mc-val-cit-PABC, Maleimidocaproyl-L-valine-L-citrulline-p-aminobenzyl alcohol.

1. Goldenberg DM et al. Oncotarget. 2018;9(48):28989–29006; 2. Sussman DM et al. *Mol Cancer Ther.* 2014;13(12):2991-3000.

SGNLVA-001: A Phase 1 Safety Study of Ladiratuzumab Vedotin (SGN-LIV1A) in Patients With Heavily Pretreated mBC[1,2]

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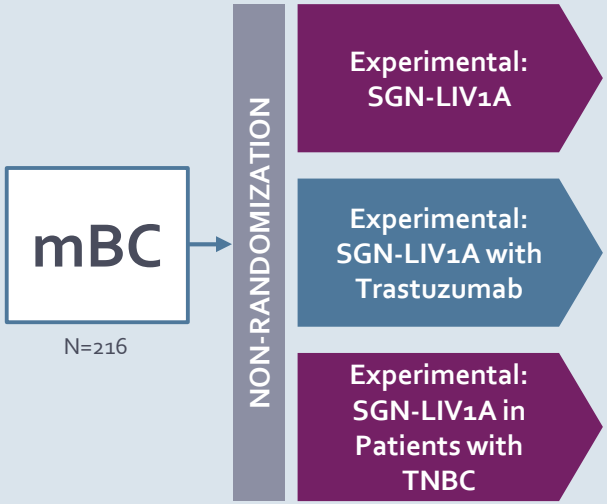
STUDY DESIGN



ANTITUMOR ACTIVITY

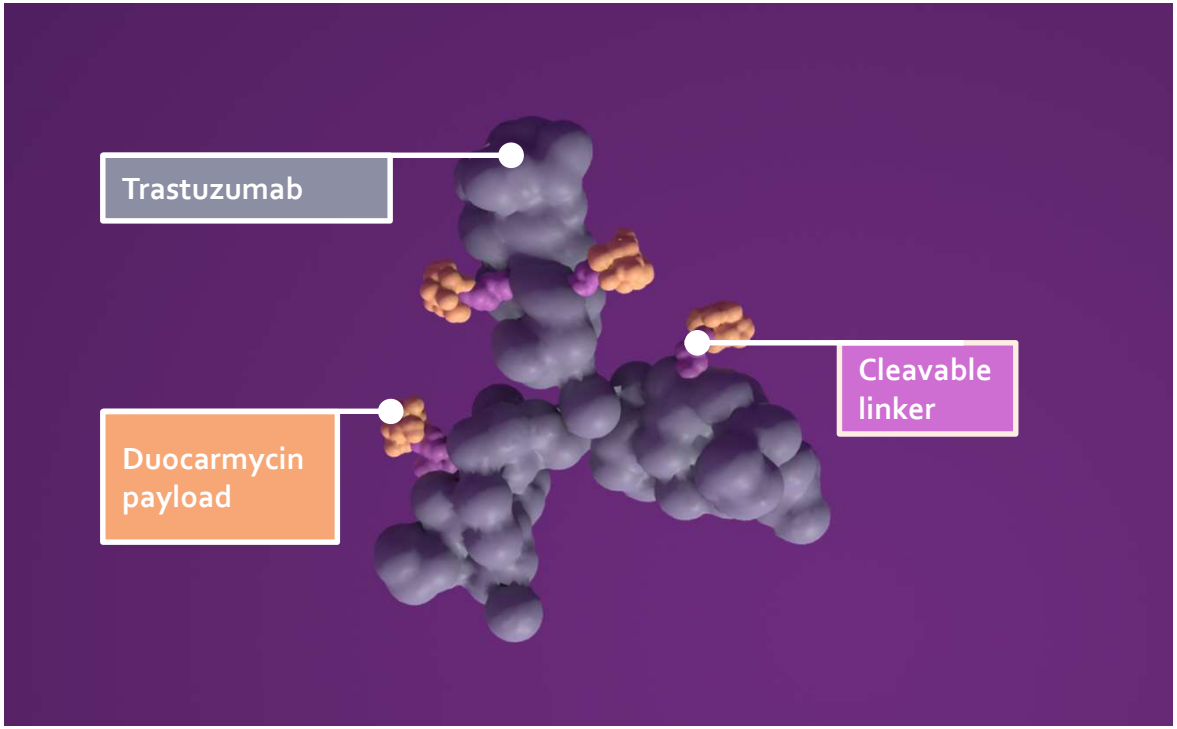
- All patients (n=60)
  - ORR = 25%
- RP2D of 2.5 mg/kg IV q3w (n = 26)
  - ORR = 34.6%
  - PFS = 2.9 months

SAFETY RESULTS

- At the recommended dose, ladiratuzumab vedotin was generally well tolerated, and most AEs were grade 1/2
- Toxicities: alopecia, nausea, neutropenia, transaminitis, neuropathy

q3w, every 3 weeks.

1. U.S. National Library of Medicine ClinicalTrials.gov. URL: https://www.clinicaltrials.gov/ct2/show/NCT01969643. Accessed November 8, 2020. Last updated: October 22, 2020; 2. Modi S, et al. Cancer Res.2018;78(4 Suppl): Abstract PD3-14.



Trastuzumab Duocarmazine (SYD985)[1,2]

- HER2-targeting ADC[1]
- Duocarmycins are DNA-alkylating agents composed of a DNA-alkylating and a DNA-binding moiety[2]

1. Banerji U et al. *Lancet Oncol*. 2019;20(8):1124-1135; 2. Rinnerthaler G et al. *Int J Mol Sci*. 2019;20(5):1115.

SYD985 Shows Promising Efficacy in Heavily Pretreated Patients With HER2-Positive Breast Cancer

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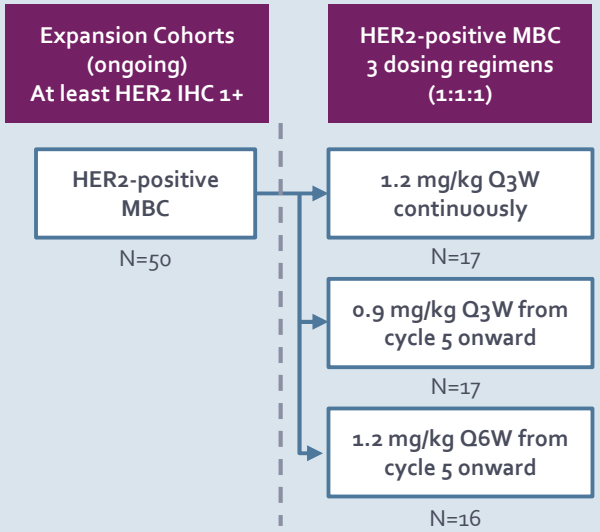
STUDY DESIGN

- Patients with any solid tumor and at least HER2 IHC 1+ status



ANTITUMOR ACTIVITY

Patients with BC	N	ORR (%)	Median PFS (95% CI)
HER2-positive T-DM1 pretreated	50 40	14 (29) 9 (24)	9.4 (4.5-12.4) 8.3 (4.1-15.0)
HR+/HER2-low	32	6 (20)	4.1 (2.4-5.4)
TNBC	17	4 (27)	4.4. (1.0-7.1)

SAFETY RESULTS

- Majority of ADRs were gr 1 or 2 in intensity, with 6% of all ADRs gr ≥3
- Ocular toxicity and fatigue were most commonly reported
- No treatment-related deaths

ADR, adverse drug reaction; Q6W; every 6 weeks.

Saura C et al. A phase I expansion cohorts study of SYD985 in heavily pretreated patients with HER2-positive or HER2-low metastatic breast cancer. Poster presented at: American Society of Clinical Oncology Annual Meeting. June 1-5, 2018

TULIP: Ph 3 Randomized, Active-Controlled, Superiority Study of SYD985 vs PC in Patients With HER2-Positive Locally Advanced or mBC

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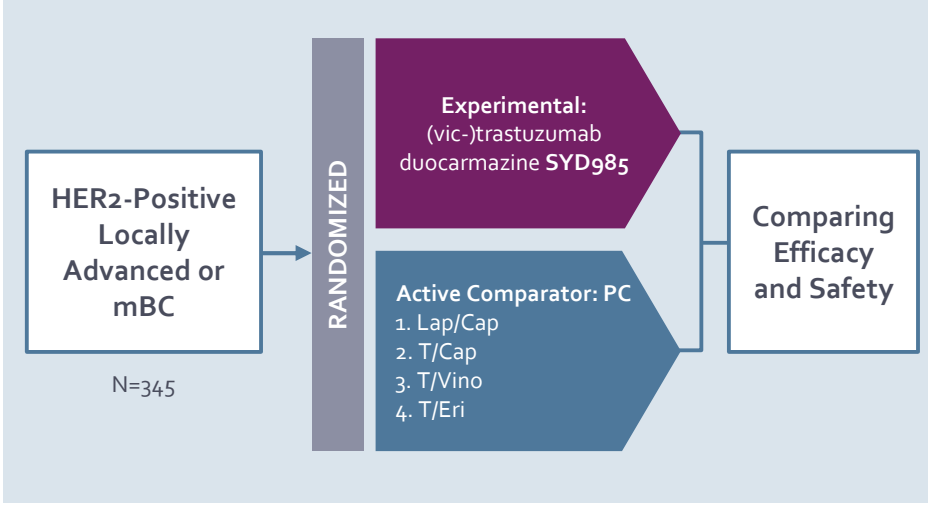
PATIENTS

- Female pts with unresectable HER2-positive locally advanced or mBC
- Progression during or after at least 2 HER2-targeting treatment regimens

STUDY DESIGN



ENDPOINTS

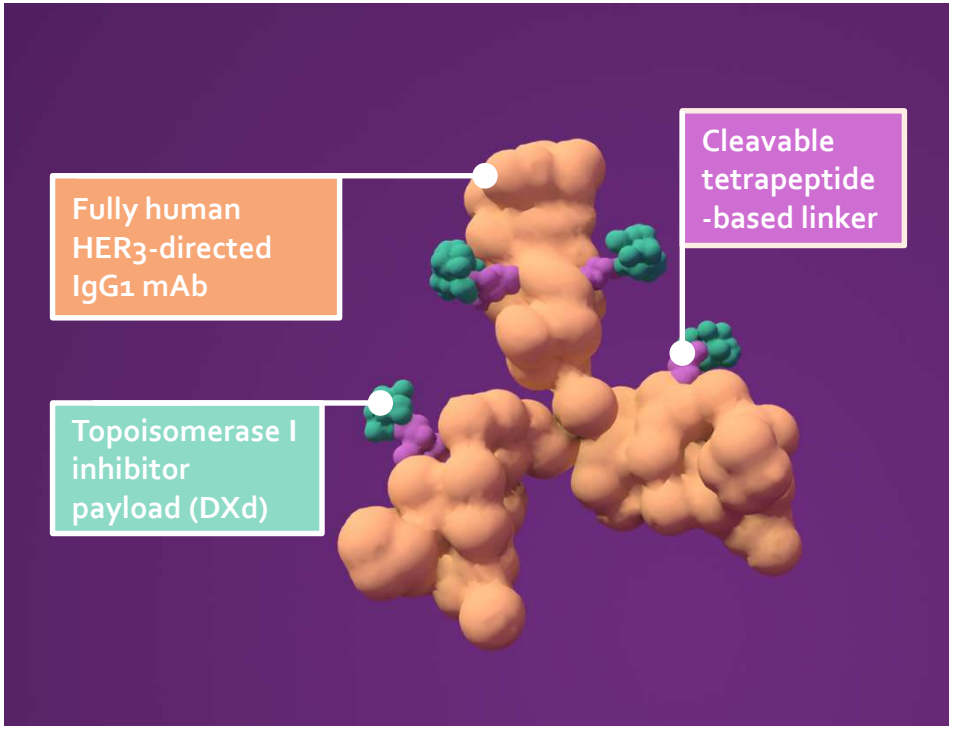
1°

PFS

Select 2°

- OS
- ORR
- Investigator-assessed PFS
- PROs for HRQoL

Eri, eribulin, Pc, physician's choice; PROS, patient-reported outcomes; T, trastuzumab; Vino, vinorelbine.
U.S. National Library of Medicine ClinicalTrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03262935. Accessed November 8, 2020. Last updated: October 5, 2020.



Patritumab Deruxtecan (U3-1402)

- HER3-targeting IgG1 ADC
- Cleavable tetrapeptide-based linker
- Topoisomerase I inhibitor payload (DXd)
- U3-1402 shows HER3-specific binding with highly efficient internalization into tumor cells
- After linker cleavage, U3-1402 induces tumor cells to undergo apoptosis through DNA damage via released DXd

IgG1, immunoglobulin G1.
Hashimoto et al. Clin Cancer Res. 2019;25(23):7151-7161.

Phase 1/2, Multicenter, Open-Label, Multiple-Dose Study of U3-1402, in Pts With HER3-Positive mBC

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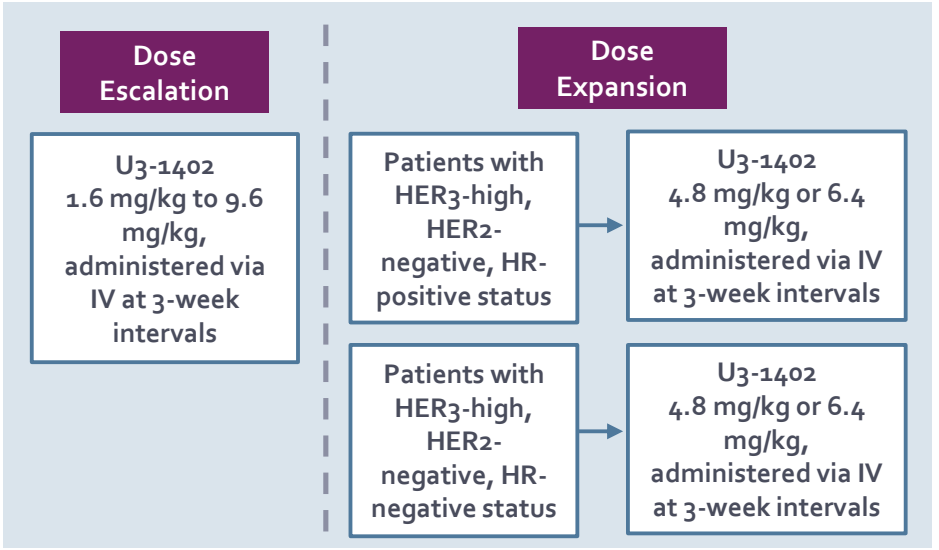
PATIENTS

- Advanced/unresectable or metastatic HER3-positive BC
- Disease refractory to intolerable with standard treatment
- Received 2-6 prior chemotherapy regimens for BC, of which ≥2 were administered for advanced/unresectable or metastatic disease

STUDY DESIGN



ENDPOINTS

1°

- Safety
- No. of patients with tumor response

Select 2°

- AUC of U3-1402
- Cmax
- Tmax

AUC, area under curve; Cmax, maximum concentration; Tmax, time to maximum.

U.S. National Library of Medicine ClinicalTrials.gov. URL:https://clinicaltrials.gov/ct2/show/NCT02980341. Accessed November 8, 2020. Last updated: April 6, 2020.

Key Learnings

- There are 2 ADCs FDA approved in HER2+ BC
- Sacituzumab govitecan gained FDA approval for adults with mTNBC who received ≥2 prior therapies for metastatic disease
- Clinical trials are ongoing for several agents for the treatment of patients with HER2-low, HER3-positive, and TNBC

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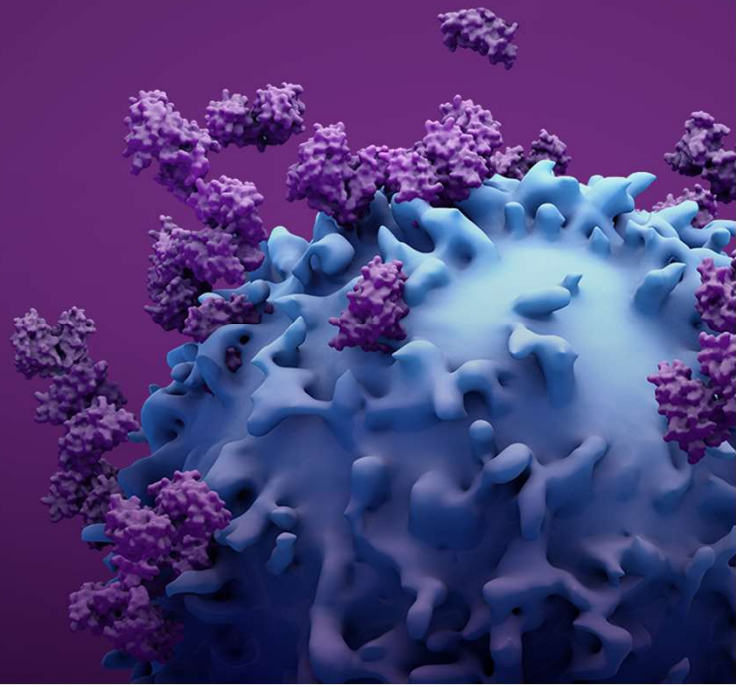
Thank You!



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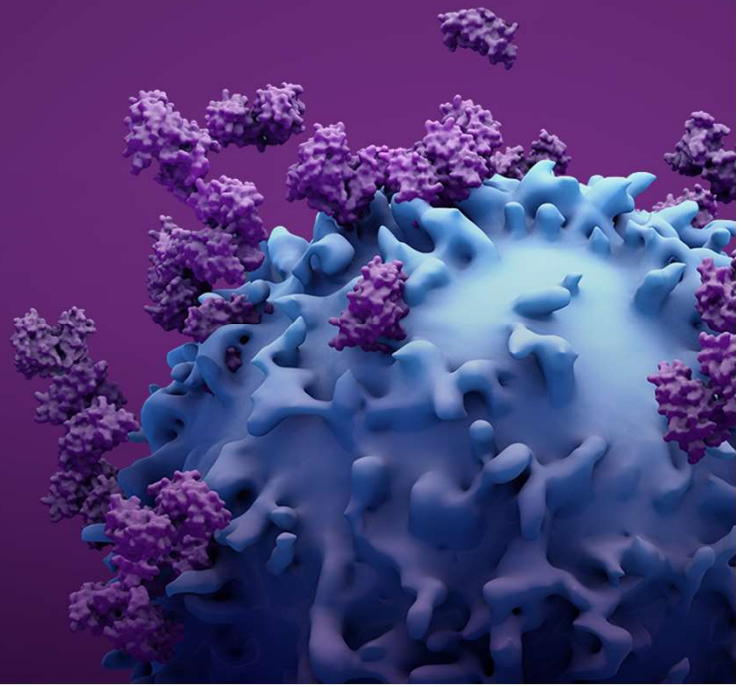
ADC Summit

Updates From San Antonio Breast Cancer Symposium 2020



Biomarker Evaluation in the Phase 3 ASCENT Study of Sacituzumab Govitecan Versus Chemotherapy in Patients With Metastatic Triple-Negative Breast Cancer

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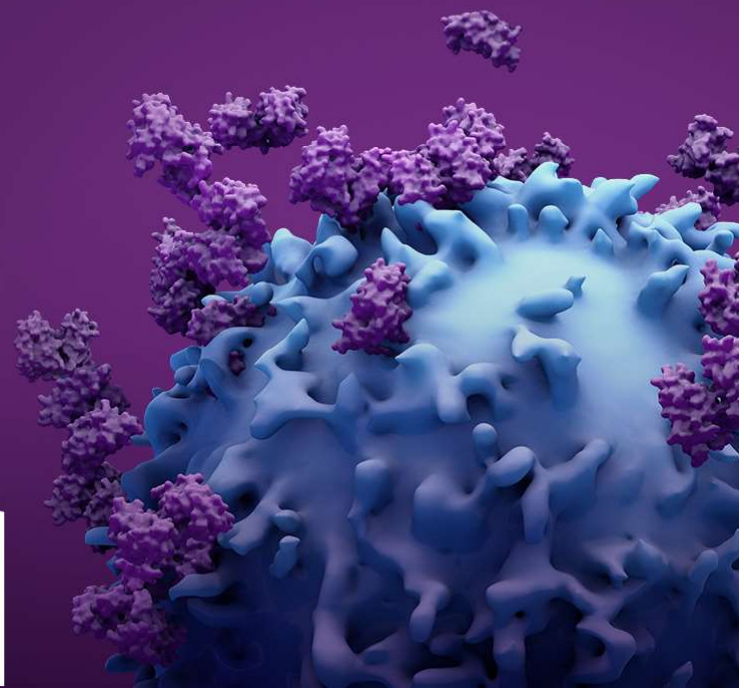
ASCENT Clinical Trial

Sara A. Hurvitz,[1] Sara M. Tolaney,[2] Kevin Punie,[3] Delphine Loirat,[4] Mafalda Oliveira,[5] Kevin Kalinsky,[6] Amelia Zelnak,[7] Philippe Aftimos,[8] Florence Dalenc,[9] Sagar Sardesai,[10] Erika Hamilton,[11] Priyanka Sharma,[12] Sabela Recalde,[13] Eva Ciruelos Gil,[14] Tiffany Traina,[15] Joyce O'Shaughnessy,[16] Javier Cortes,[17] Michaela Tsai,[18] Linda Vahdat,[19] Véronique Diéras,[20] Lisa Carey,[21] Hope S. Rugo,[22] David M. Goldenberg,[23] Quan Hong,[23] Martin Olivo,[23] Loretta M. Itri,[23] and Aditya Bardia[24]

[1]Medical Oncology, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; [4]Institut Curie, Paris, France; [5]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [6]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [7]Northside Hospital, Atlanta, GA, USA; [8]Institut Jules Bordet, Brussels, Belgium; [9]Institut Claudius Regaud, Toulouse, France; [10]The Ohio State University Wexner Medical Center, Columbus, OH, USA; [11]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [12]University of Kansas Cancer Center - The Richard and Annette Bloch Cancer Care Pavilion, Kansas City, KS, USA; [13]Institut Catala d'Oncologia Hospitalet, Barcelona, Spain; [14]Hospital Universitario 12 de Octubre, Madrid, Spain; [15]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [16]Texas Oncology - Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [17]IOB Institute of Oncology, Quiron Group, Madrid & Barcelona, Spain; [18]VPCI Oncology Research, Minneapolis, MN, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [20]Centre Eugène-Marquis, Rennes, France; [21]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [22]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [23]Immunomedics, Morris Plains, NJ, USA; and [24]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA



To obtain presentation, https://bit.ly/2020hurvitzgs3-06

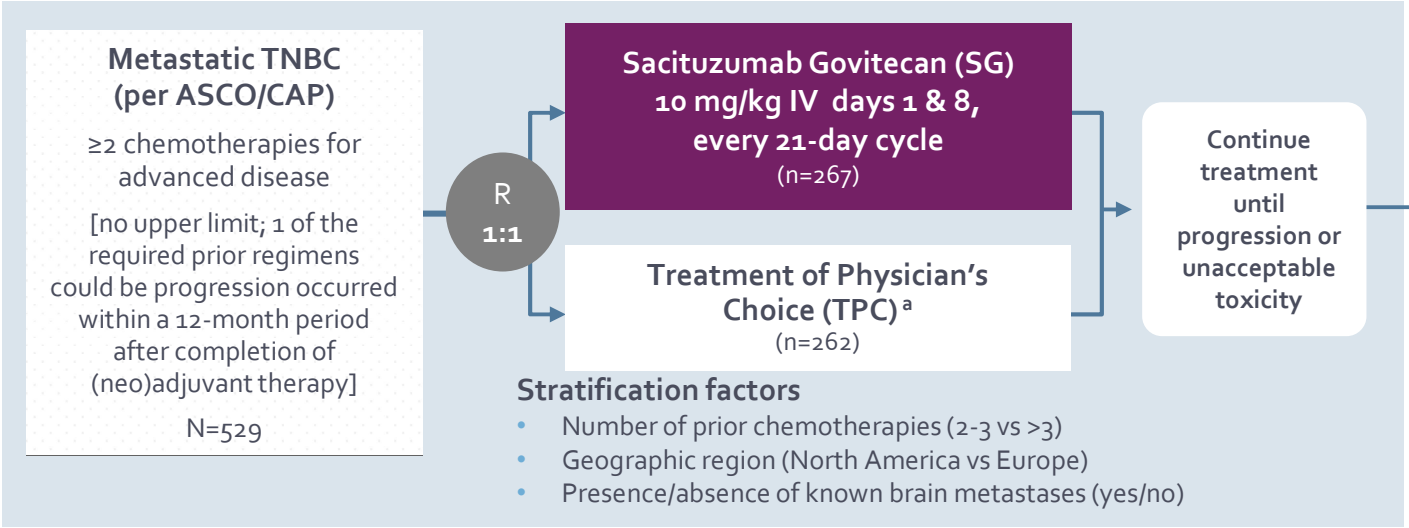
SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio AACR

ClinicalTrials.gov Number: NCT02574455

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

STUDY DESIGN



ENDPOINTS

Primary
- PFS [b]

Secondary
- PFS for the full population [c]
- OS, ORR, DOR, TTR, safety

Exploratory
- **Biomarkers**

Data cutoff:
March 11, 2020

NCT02574455

We report the exploratory biomarker analysis in the brain metastases-negative (Brain Mets-Negative) population

[a] TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. [b] 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. [c] 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.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Statistics: Subgroup Analysis

- Exploratory biomarker assessments included Trop-2 expression and germline *BRCA1/2* mutation status
- Primary or metastatic archival biopsy or surgical specimens were requested at study entry to determine Trop-2 expression
  - Known Trop-2 expression was not required to determine patient eligibility
  - Trop-2 expression was assessed using a validated immunohistochemistry assay and categorized based on an H-score, a numerical value (0 to 300) representing a weighted summation of percent staining
    - H-score <100 (including H-score 0): Trop-2 Low
    - H-score 100-200: Trop-2 Medium
    - H-score 200-300: Trop-2 High
- Status of germline *BRCA1/2* mutations was collected at baseline, if known
- The association between efficacy and biomarkers was investigated
- **We report the exploratory biomarker analysis in primary study population (Brain Mets-Negative)**
  - **Only patients with known Trop-2 or *BRCA1/2* results are included in the analysis**
- Data cutoff date for analysis is March 11, 2020

BRCA, breast cancer gene; H-score, histochemical score; Trop-2, trophoblast cell surface antigen 2.

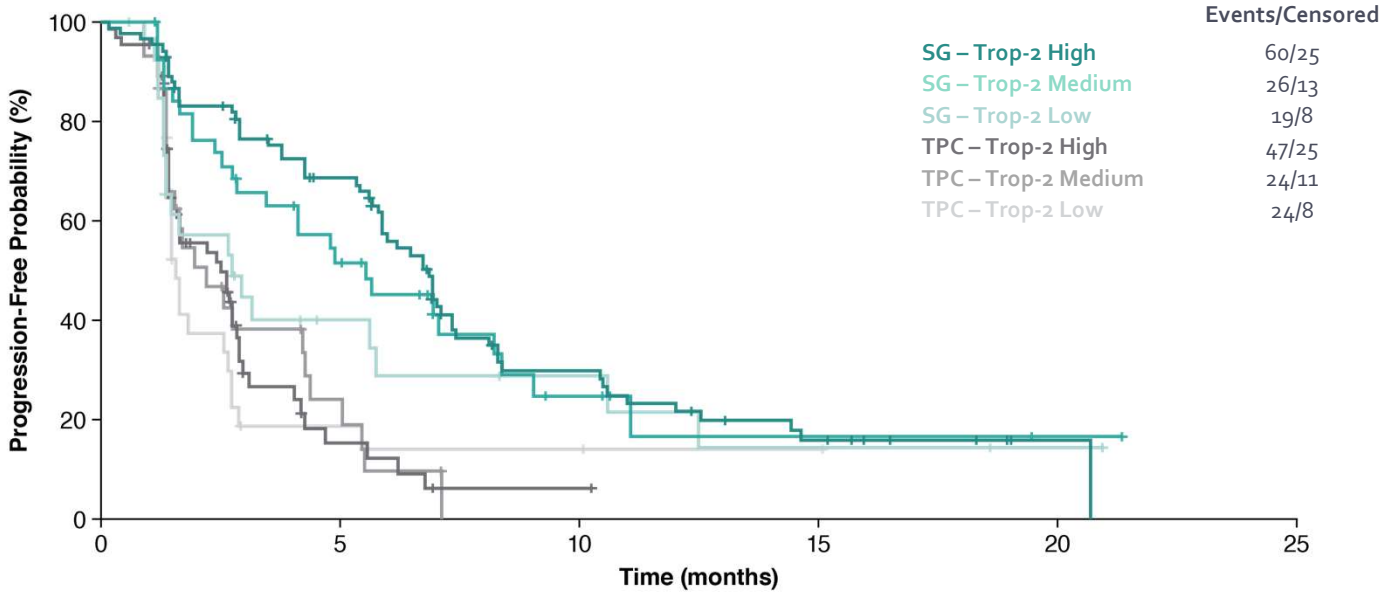
Demographics (Brain Mets-Negative)

	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
BRCA1/2 mutational status—no. (%)	149 (63)	143 (61)
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Trop-2 expression—no. (%)	151 (64)	139 (60)
(High) H-score 200-300	85 (56)	72 (52)
(Medium) H-score 100-200	39 (26)	35 (25)
(Low) H-score <100	27 (18)	32 (23)

	SG (n=235)	TPC (n=233)
Original diagnosis of TNBC [a]		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)
Previous anticancer regimens [b]— median (range)	4 (2-17)	4 (2-14)
Most common prior chemotherapy—no. (%)		
Taxane [c]	235 (100)	233 (100)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous PARP inhibitor—no. (%)	17 (7)	18 (8)
Previous use of checkpoint inhibitors—no. (%)	67 (29)	60 (26)
Most common sites of disease [d]—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

Assessed in the brain metastases-negative population. [a] Patients in study either had TNBC at initial diagnosis or had hormone receptor-positive disease that converted to hormone-negative at time of study entry. [b] Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting. [c] Includes paclitaxel, paclitaxel albumin, and docetaxel. [d] Based on independent central review of target and nontarget lesions at baseline.
ECOG PS, Eastern Cooperative Oncology Group performance status; PARP, poly-ADP ribose polymerase;

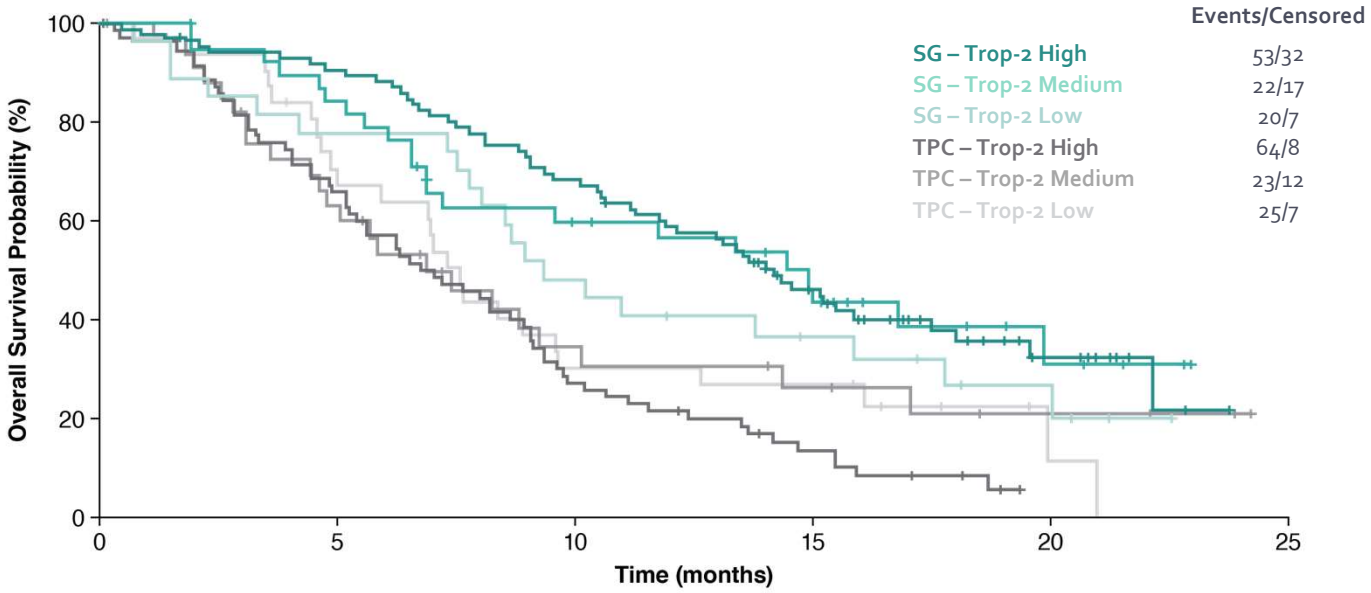
Progression-Free Survival by Trop-2 Expression



	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.

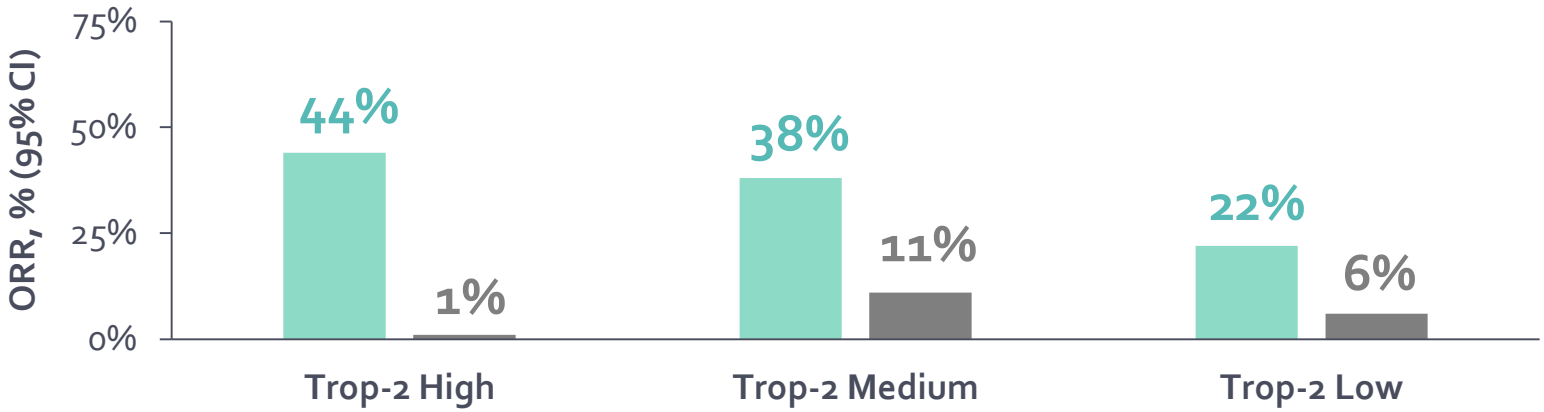
Overall Survival by Trop-2 Expression



	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 OS—mo (95% CI)	14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

Assessed in brain metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.

ORR by Trop-2 Expression

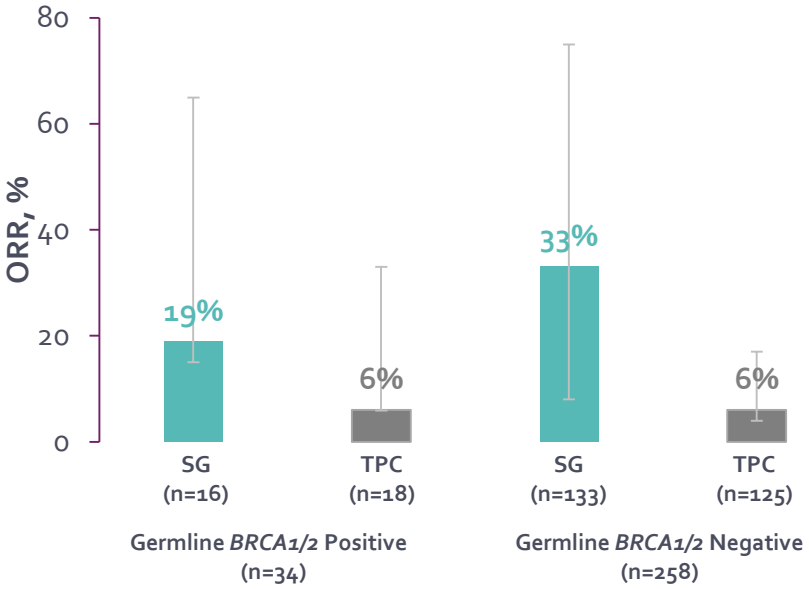


	Trop-2 High H-score: 200-300 (n=157)		Trop-2 Medium H-score: 100-200 (n=74)		Trop-2 Low H-score: <100 (n=59)	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
ORR—% (no.)	44% (37)	1% (1)	38% (15)	11% (4)	22% (6)	6% (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

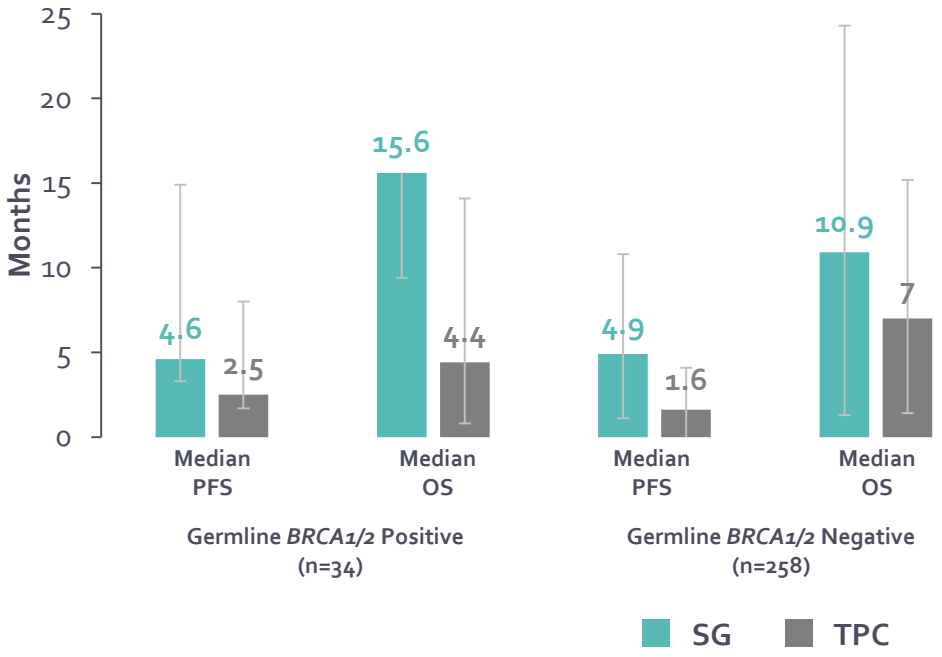
Assessed in the brain metastases-negative population. ORR and PFS are assessed by BICR. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
BICR, blind independent central review.

Efficacy Summary by Germline *BRCA1/2* Status

ORR by *BRCA1/2* Status



PFS and OS by *BRCA1/2* Status



Assessed in the brain metastases-negative population. ORR and PFS are assessed by BICR.

Conclusions

- Outcomes in these subgroups confirm that clinical benefit with SG versus TPC in previously treated mTNBC is irrespective of level of Trop-2 expression
  - Higher efficacy outcomes were observed in patients treated with SG who had a medium/high Trop-2 H-score (vs low Trop-2 H-score) versus those treated with TPC
- SG outperformed TPC regardless of germline *BRCA1/2* mutation status at study entry
- Caution should be exercised in data interpretation given the small sample sizes in the Trop-2 low subgroup and germline *BRCA1/2*-positive subgroup
- Trop-2 expression did not affect toxicity, and SG demonstrates a manageable safety profile consistent with that of the ASCENT overall study population and shown in previous reports[1]

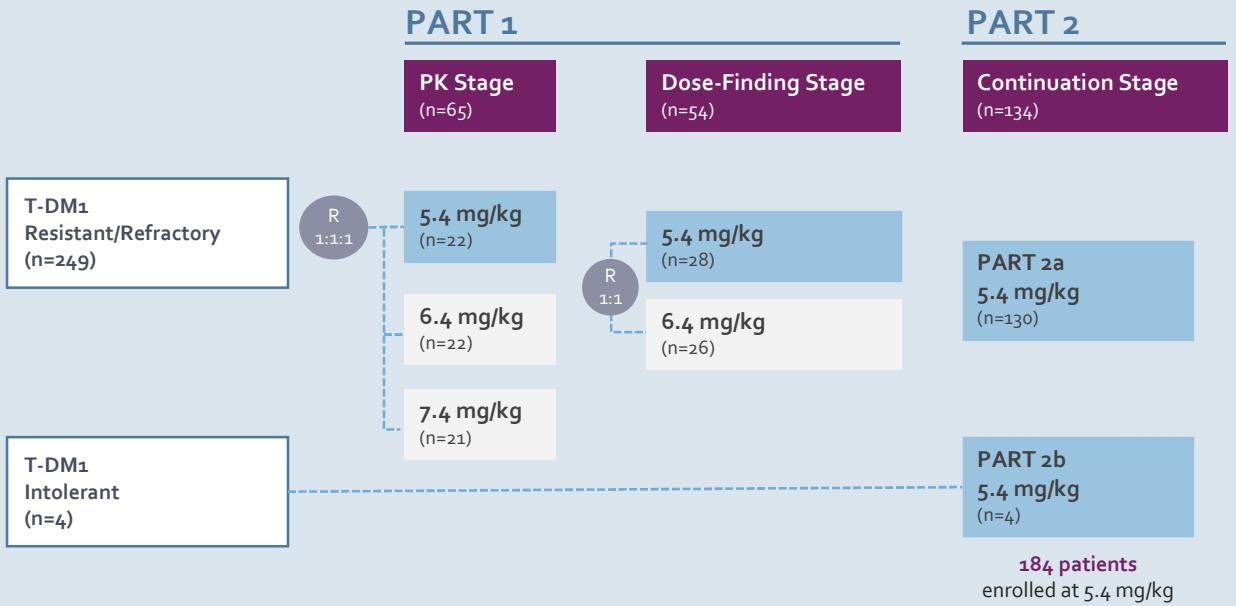
1. Bardia A, et al. ESMO 2020. Abstract LBA17.

DESTINY BREAST 01: Methods

POPULATION

- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2-positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Pretreated and stable brain metastases were allowed

STUDY DESIGN



BC, breast cancer; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; PK, pharmacokinetics; T-DM1, trastuzumab emtansine.
Modi et al

Results

EFFICACY

- Median follow-up was 20.5 months (range, 0.7-31.4 months), representing an additional 9.4 months from the prior analysis (as of 8 June 2020)
- Durable activity was demonstrated with a confirmed objective response rate of 61.4% (95% CI, 54.0%-68.5%) and a median duration of response of 20.8 months
- With increased maturity of the data, median progression-free survival (PFS) increased to 19.4 months (95% CI, 14.1-NE)
- Preliminary median OS was 24.6 months
  - mOS was estimated at 35% maturity, with 119 patients censored and only 17 patients at risk at 24 months; additional follow-up is required for more mature OS data
  - The estimated percent of patients alive at 12 and 18 months was 85% (95% CI, 79%-90%) and 74% (95% CI, 67%-80%), respectively
- Three new cases ILD, 1 grade 1, 1 grade 2, 1 grade 5 (total 5 cases grade 5 (2.7%) ILD)
- Most occurred during first 12 months

NE, not estimable.
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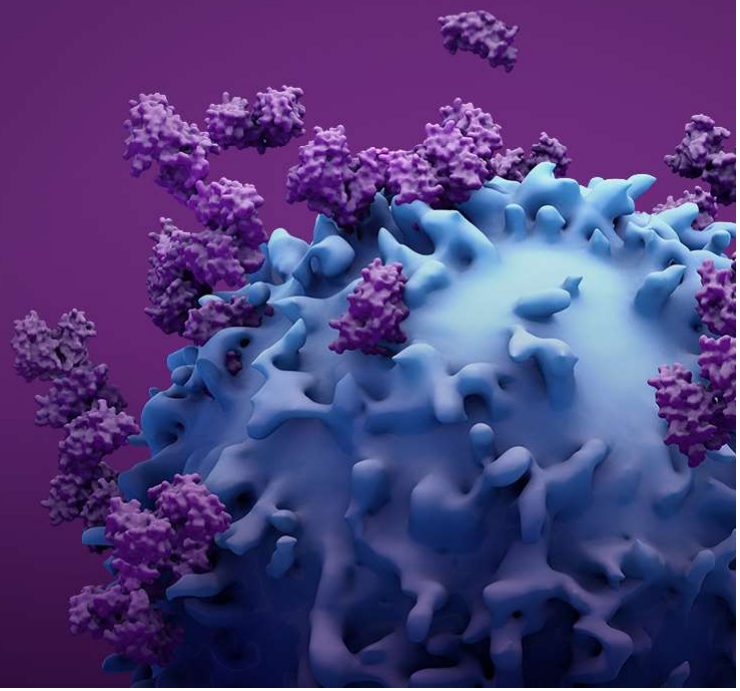
e-Poster Presentation
SABCS 2020

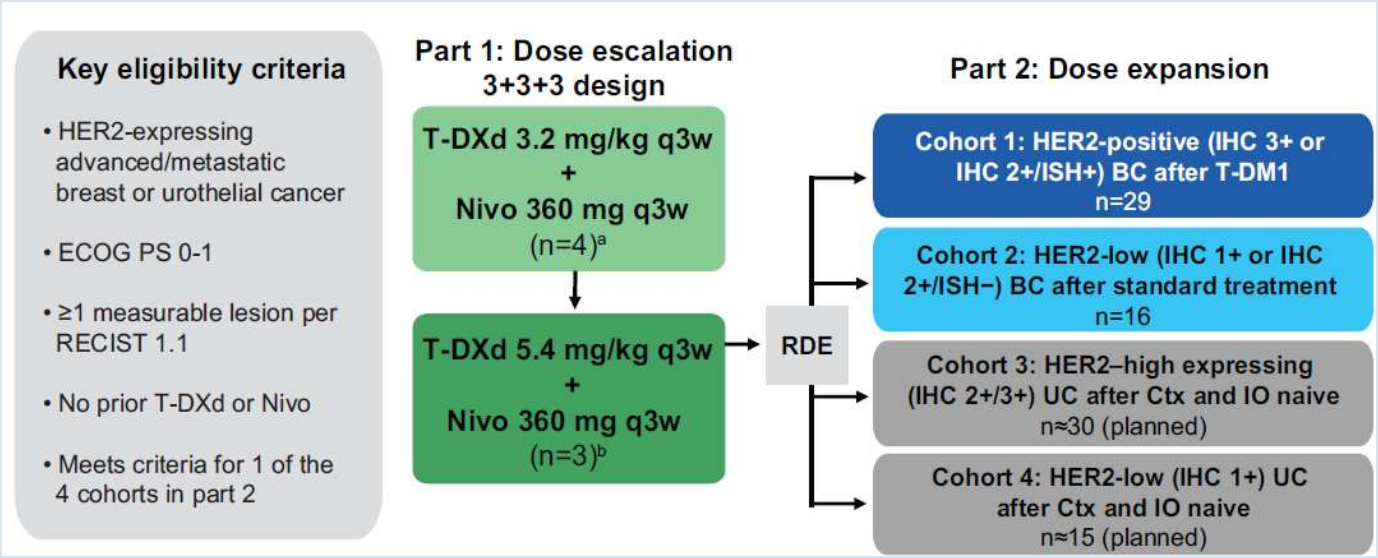
Trastuzumab deruxtecan (T-DXd; DS-8201) with nivolumab in patients with HER2-expressing advanced breast cancer: a 2-part, phase 1b, multicenter, open-label study

Erika Hamilton, Charles L. Shapiro, Daniel Petrylak, Valentina Boni, Miguel Martin, Gianluca Del Conte, Javier Cortes, Laila Agrawal, Hendrik-Tobias Arkenau, Antoinette R. Tan, Philip Debruyne, Anna Minchom, Annemie Rutten, Frances Valdes-Albini, Evan Y. Yu, Bincy Augustine, Anthony D'Amelio Jr, Daniel Barrios, Sara A. Hurvitz



Methods

STUDY DESIGN



[a] Three patients were HER2 positive; 1 was HER2 low. [b] All patients were HER2 positive.
BC, breast cancer; Ctx, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IO, immuno-oncologic; ISH, in situ hybridization; Nivo, nivolumab; q3w, every 3 weeks; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; UC, urothelial cancer.

Results

PATIENTS

Table 1. Demographic and baseline clinical characteristics

Characteristic	HER2 positive (n=32)	HER2 low (n=16)
Age, median (range), years[a]	55 (36-76)	47 (34-64)
Female, n (%)	32 (100)	16 (100)
Region, n (%) United States/Europe	20 (63)/12 (38)	7 (44)/9 (56)
ECOG PS, n (%)[b] 0/1	20 (63)/12 (38)	8 (50)/8 (50)
HER2 expression, n (%)[c] IHC 3+/IHC 2+, ISH+ IHC 1+/IHC 2+, ISH–	27 (84)/5 (16) –	– 6 (38)/10 (63)[d]
HR status, n (%) Positive/negative	20 (63)/12 (38)	13 (81)/3 (19)
Prior lines of systemic therapy for advanced/ metastatic disease, median (range) 1, n (%) 2, n (%) 3, n (%) ≥4, n (%)	 0 2 (6) 2 (6) 28 (88)	 1 (6) 2 (13) 1 (6) 12 (75)

Data for all patients who received ≥1 dose of T-DXd 5.4 mg/kg. Percentages may not total 100 because of rounding. [a] Median age at informed consent. [b] Performance status on the ECOG scale ranges from 0 to 5, with higher scores indicating greater disability. [c] HER2 expression was centrally confirmed prospectively by analysis of archival tissue (most recent tumor tissue preferred) according to the guidelines from the American Society of Clinical Oncology/College of American Pathologists. According to these guidelines, HER2 positivity was defined as HER2 IHC 3+ or IHC 2+/ISH+. d One patient was IHC 2+, ISH equivocal.
HR, hormone receptor.

Results

EFFICACY

Table 2. Summary of efficacy by ICR

	HER2 positive (n=32)	HER2 low (n=16)
Confirmed ORR by ICR [95% CI][a]	59% [41-76] (n=19)	38% [15-65] (n=6)
CR	3% (n=1)	0
PR	56% (n=18)	38% (n=6)
SD	31% (n=10)	38% (n=6)
PD	6% (n=2)	13% (n=2)
NE	3% (n=1)	13% (n=2)
DCR, median [95% CI][b]	91% [75-98] (n=29)	75% [48-93] (n=12)
DOR, median [95% CI], months[c]	NE [4.1-NE]	NE [2.8-NE]

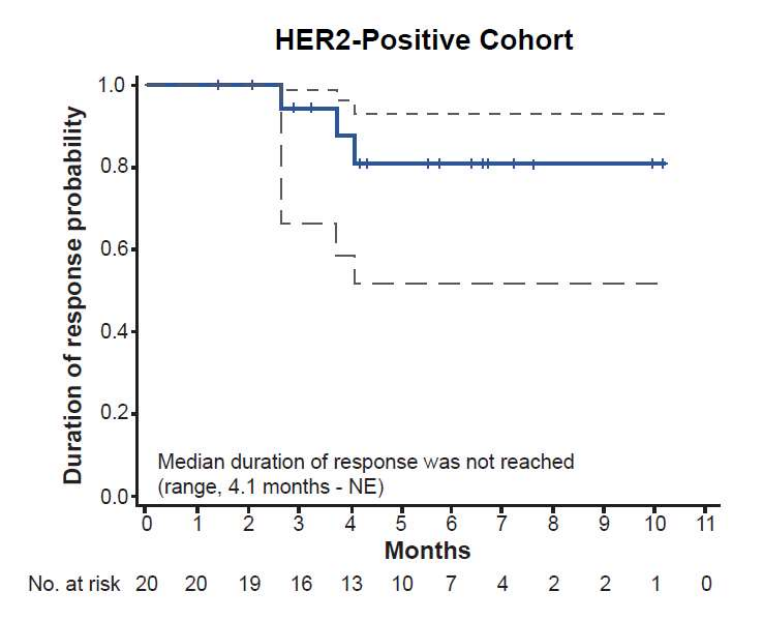
[a] Defined as a CR or PR that was confirmed on a follow-up scan performed ≥4 weeks after the initial CR/PR was noted. [b] Disease control was defined as a confirmed CR + PR + SD. [c] Among patients with confirmed CR or PR.

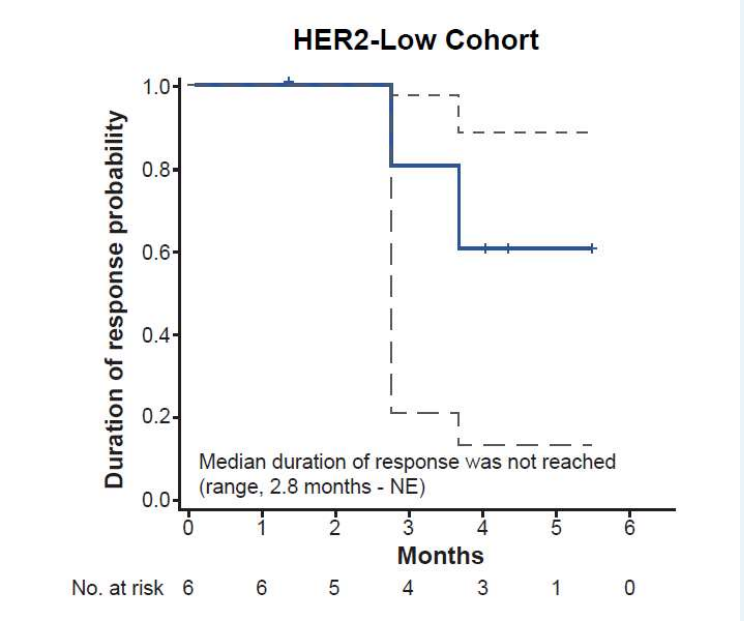
CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. Analyses all patients from parts 1 and 2 who received ≥1 dose of T-DXd 5.4 mg/kg and Nivo 360 mg and had measurable tumors as assessed by ICR at baseline. Percentages may not total 100 because of rounding.

Results

EFFICACY

Figure 3. Kaplan-Meier Analysis of Duration of Response by ICR

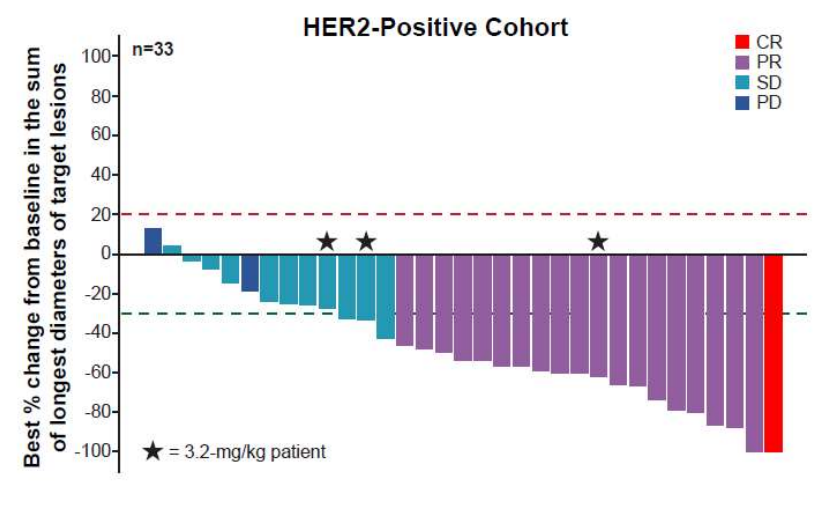


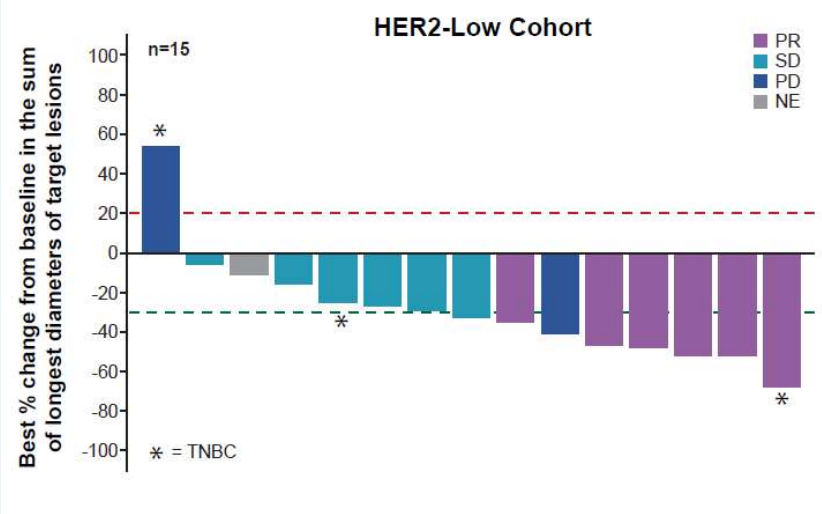


Results

EFFICACY

Figure 3. Best Percent Change From Baseline in Tumor Size for Individual Patients





Patients were required to have measurable disease per local assessment to be eligible for this study. Percentage changes shown here were by ICR. The line at 20% indicates PD, and the line at −30% indicates a PR. Shown here are patients in the full analysis set (received ≥1 dose of either study drug). Two patients in the HER2-positive cohort were not included due to no postbaseline assessment by ICR (n=1) and no baseline target lesions by ICR (n=1). In the HER2-low cohort, the 1 patient who received T-DXd 3.2 mg/kg is not shown due to no postbaseline assessment by ICR.

Results

SAFETY

- Overall, 43.8% of patients experienced a grade ≥3 treatment-emergent adverse event (TEAE) (**Table 3**)
- In all patients who received the RDE (n=48), the most common any-grade TEAEs were nausea (54.2%), fatigue (45.8%), and alopecia (41.7%) (**Table 4**)
  - TEAEs associated with death occurred in 5 patients (HER2 positive, n=3; HER2 low, n=2), 1 of which (interstitial lung disease [ILD]/pneumonitis) was related to study drug (HER2-positive cohort)
- In patients who received the RDE, 5 (10.4%; all HER2 positive) had adjudicated drug-related ILD/pneumonitis, including 1 fatal case (2.1%). The remaining 4 cases were grade 2. There was 1 additional case of drug-related ILD (grade 3) in the HER2-positive cohort at the 3.2-mg/kg dose level

Conclusions

- In this interim analysis of DS8201-A-U105, combination treatment with T-DXd and Nivo demonstrated antitumor activity and had a manageable safety profile in patients with either HER2-positive or HER2-low metastatic breast cancer
  - The initial results of this study suggest that T-DXd can be safely combined with immune checkpoint inhibitors in patients with breast cancer
- Patients in the HER2-positive and HER2-low cohorts who received the RDE (T-DXd 5.4 mg/kg IV q3w + Nivo 360 mg IV q3w) had a confirmed ORR by ICR of 59.4% (19/32) and 37.5% (6/16), respectively
- The safety profile of the T-DXd and Nivo combination was similar to that of single-agent T-DXd in HER2-positive patients. No new safety signals were observed; however, the rate of treatment discontinuation due to TEAEs was higher than previously reported for each agent when administered as monotherapy
  - ILD/pneumonitis, a known risk with T-DXd, was actively monitored and managed with dose modification or discontinuation, corticosteroids, and supportive care in accordance with the study protocol
- While the confirmed ORR for the T-DXd and Nivo combination was similar to that of T-DXd when administered as monotherapy, longer follow-up and additional studies are needed to determine whether addition of immunotherapy to T-DXd provides further clinical benefit than T-DXd treatment alone

IV, intravenous.

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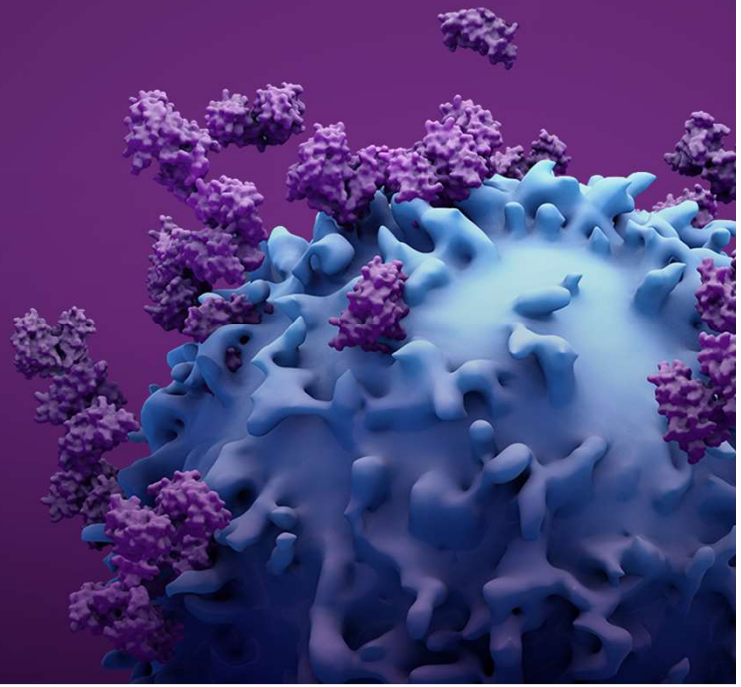
Clinical Applications of ADCs



2 ADCs Currently Approved for HER2+ BC[1,2]

Trastuzumab emtansine (T-DM1; Kadcyla)	indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within 6 months of completing adjuvant therapy.
Trastuzumab deruxtecan (DS8201a; T-DXd; Enhertu)	indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; TROP-2, tumor-associated calcium signal transducer 2.

1. KADCYLA (trastuzumab emtansine) [package insert]. San Francisco, CA: Genentech, Inc; 2019; 2. ENHERTU (trastuzumab deruxtecan) [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2019.

ADCs in HER2+ BC: NCCN Guidelines

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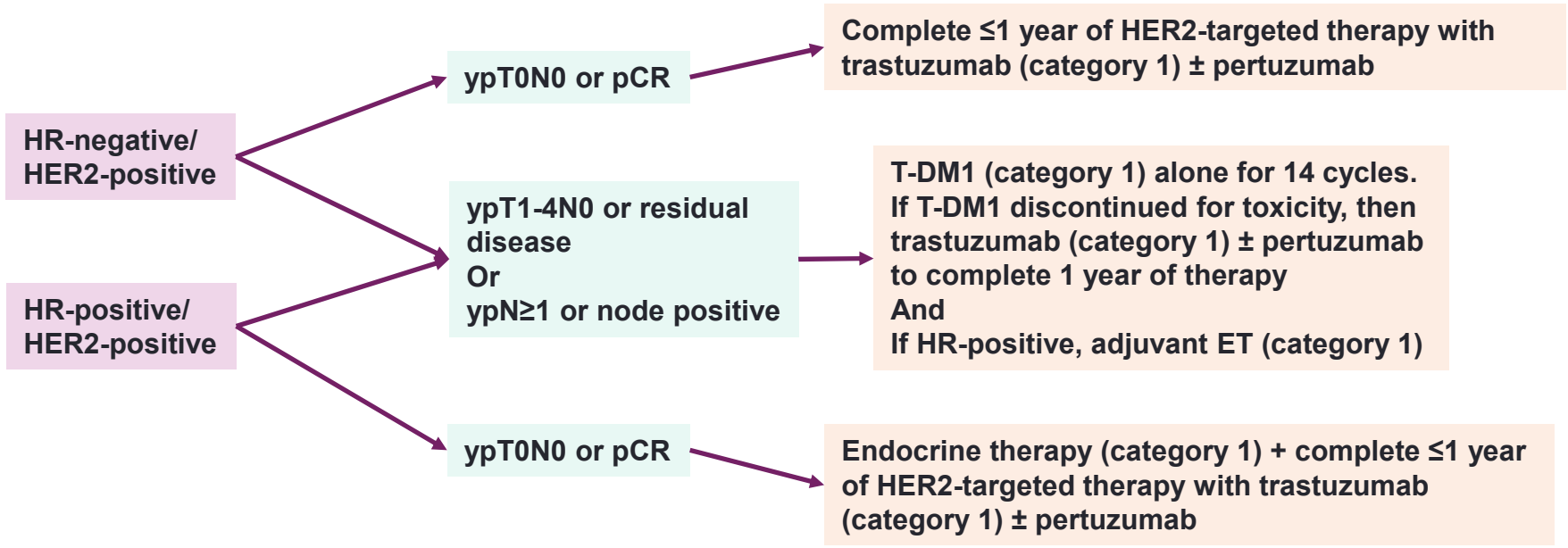
PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Positive
Preferred Regimens: • Paclitaxel + trastuzumab • TCH • TCHP • If no residual disease after preoperative therapy or no preoperative therapy: complete ≤ 1 year of HER2-targeted therapy with trastuzumab ± pertuzumab • If residual disease after preoperative therapy: T-DM1 (cat 1) alone. If T-DM1 is discontinued for toxicity, then trastuzumab (cat 1) ± pertuzumab to complete 1 year of therapy
Useful in Certain Circumstances: • Docetaxel + cyclophosphamide + trastuzumab • AC followed by T + trastuzumab AC followed by T + trastuzumab + pertuzumab
Other recommended Regimens: • AC followed by docetaxel + trastuzumab • AC followed by docetaxel + trastuzumab + pertuzumab

AC, doxorubicin/cyclophosphamide; TCH, docetaxel/carboplatin/trastuzumab; TCHP, docetaxel/carboplatin/trastuzumab/pertuzumab; T, paclitaxel.
NCCN, National Comprehensive Cancer Network.

ADCs in HER2+ BC: NCCN Guidelines (Continued)

ADJUVANT SYSTEMIC THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY



NCCN, National Comprehensive Cancer Network.

ADCs in HER2+ BC: NCCN Guidelines (Continued)

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE: ER- AND/OR PR-NEGATIVE; HER2-POSITIVE

Systemic therapy + HER2-targeted therapy with:

- **Pertuzumab + trastuzumab + taxane**
- **T-DM1**
- **T-DXd**
- **Trastuzumab + chemotherapy**
- **Other HER2-targeted therapies**

→ **Continue therapy until progression or unacceptable toxicity** → **Progression** → **Another line of systemic therapy + HER2-targeted therapy** → **Most patients will be candidates for multiple lines of systemic therapy to palliate advanced BC. At each reassessment, clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared-decision making process**

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE: ER- AND/OR PR-POSITIVE; HER2-POSITIVE

Systemic therapy + HER2-targeted therapy with:

- **Pertuzumab + trastuzumab + taxane**
- **T-DM1**
- **T-DXd**
- **Trastuzumab + chemotherapy**

- **Endocrine therapy +/- HER2-targeted therapy (if premenopausal, consider ovarian ablation or suppression)**
- **Other HER2-targeted therapies**

→ **Continue therapy until progression or unacceptable toxicity**

NCCN, National Comprehensive Cancer Network.

1 ADC Currently Approved for TNBC[1]

Sacituzumab govitecan (Trodelvy)

indicated for the treatment of adult patients with mTNBC who have received at least 2 prior therapies for metastatic disease. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1. TRODELVY (sacituzumab govitecan-hziy) [package insert]. Morris Plains, NJ: Immunomedics, Inc; 2020.

NCCN Guidelines—Systemic Therapy For Recurrent TNBC

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SYSTEMIC THERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE

HER2-Negative		
Preferred Regimens: • Anthracyclines: doxorubicine, liposomal doxorubicin • Taxanes: paclitaxel • Anti-metabolites: capecitabine, gemcitabine • Microtubule inhibitors: vinorelbine, eribulin • For germline BRCA1/2 mutations, see additional targeted therapy options • Platinum (for TNBC and germline BRCA1/2 mutation): carboplatin, cisplatin • For PD-1L-positive TNBC see additional targeted therapy options	**Other Recommended Regimens**: • Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicine • Ixabepilone • Sacituzumab govitecan-hziy (for TNBC)	**Useful in Certain Circumstances**: • AC (doxorubicin/cyclophosphamide) • ED (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/uorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Paclitaxel/becacizumab • Carboplatin + paclitaxel or albumin-bound paclitaxel

BRCA, BReast CAncer gene; PD-L1, programmed death-ligand 1.
NCCN, National Comprehensive Cancer Network.

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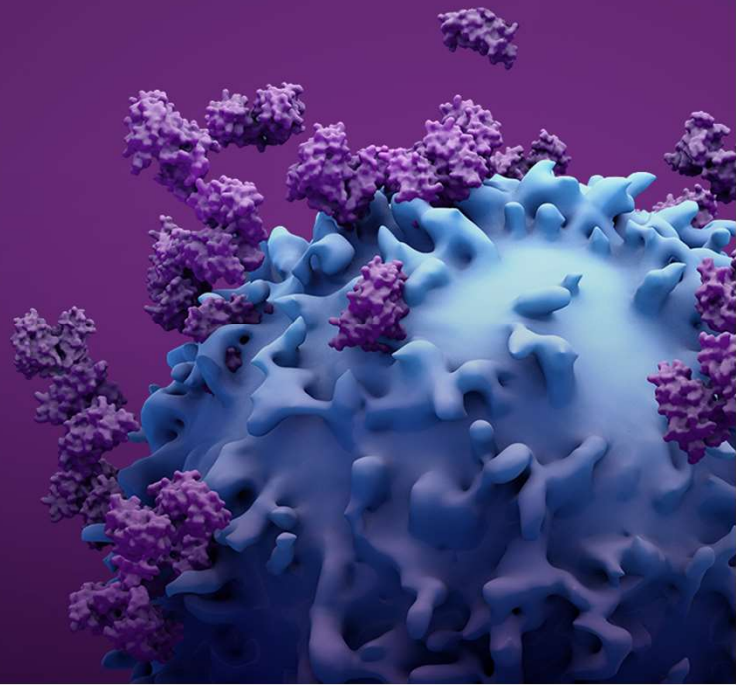
Combinations With Immunotherapy



ADC and Immunotherapy Combinations: Rationale[1,2]

- Preclinical data suggests ADCs result in TIL expansion and effector T cell activation, which may help overcome anti-CTLA4 and anti-PD-1 resistance[1]
- Proposed synergy: ADCs increase T-cell infiltration and immunotherapy revives exhausted T-cells[1]
- Sacituzumab govitecan: Response rate of 44% (8 of 18) among patients who had received previous checkpoint inhibitors[2]
  - Suggests a lack of cross-resistance with immune checkpoint inhibitors and the potential of combination therapy

1. Tray N et al. *Future Oncol*. 2018;14(25):2651-2661; 2. Bardia A et al. *N Engl J Med*. 2019:380;741-751.

ADCs and Immunotherapy Combinations

Trial	Regimen	Ph	N	Brief Summary	Study Completion
NCT04042701[1]	Trastuzumab deruxtecan + Pembrolizumab	1b	~115	1. Dose escalation to determine recommended dose of combination 2. Dose expansion to evaluate efficacy, safety, and tolerability of combination in patients with metastatic HER2+ or HER2-low BC	4/2022
NCT03424005 **(Morpheus-TNBC)**[6]	Ladiratuzumab vedotin/sacituzumab govitecan + Atezolizumab	1b/2	~280	Safety and efficacy of multiple immunotherapy-based combinations in metastatic or inoperable TNBC	6/2022
NCT03310957 **(KEYNOTE-721)**[5]	Ladiratuzumab vedotin + Pembrolizumab (1L)	1b/2	~122	Safety and efficacy of ADC + immunotherapy combination in locally-advanced or metastatic TNBC	3/2023
NCT03032107[2]	Trastuzumab emtansine + Pembrolizumab	1	~27	Tests safety of intervention in patients with metastatic HER2+ BC and attempts to define the appropriate dosage for future studies	7/2024

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04042701. Published August 2, 2019. Accessed April 21, 2020; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03032107. Published January 26, 2017. Accessed April 21, 2020; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02924883. Published October 5, 2016. Accessed April 24, 2020; 4. Emens LA, Esteva F, Beresford M, et al. In: Proceedings of the 2018 San Antonio Breast Cancer Symposium; 2018 Dec 4-8; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2019;79(4 Suppl):Abstract nr PD3-01. doi: 10.1158/1538-7445.SABCS18-PD3 01; 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03310957. Published October 16, 2017. Accessed April 21, 2020; 6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03424005. Published February 6, 2018. Accessed April 21, 2020.

KATE2: Randomized, Phase 2 Study of Atezolizumab + T-DM1 vs Placebo + T-DM1 In Previously Treated HER2+ aBC

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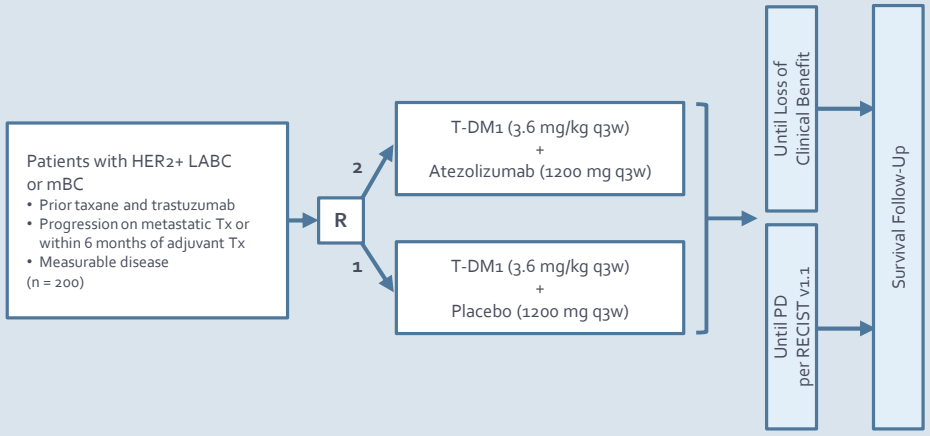
PATIENTS

Patients with HER2-positive, locally-advanced or mBC who had received prior tratuzumab and taxane-based therapy

STUDY DESIGN



ENDPOINTS

1°

PFS (ITT)

Select 2°

- OS (ITT)
- ORR (ITT)
- DOR (ITT)

Presented at: SABCS 2018.

KATE2 Did Not Demonstrate Meaningful PFS Benefit in the ITT Population

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ANTITUMOR ACTIVITY

Median PFS (95% CI):
T-DM1 + atezolizumab: 8.5 mo (5.7 to NE)
T-DM1 + placebo: 4.1 mo (2.7 to 11.1)
Stratified HR, 0.60 (95% CI: 0.32, 1.11)

Secondary EP: ORR in ITT Population		
	T-DM1 + Atezolizumab	T-DM1 + Placebo
ORR%	45.5	43.5
CR%	6.1	7.2
PR%	39.4	36.2
SD%	37.9	29.0
PD%	16.7	26.1

SAFETY RESULTS

Incidence, n (%)	T-DM1 + Atezo (N=132)	T-DM1 + Placebo (N=68)
Pts with ≥1 AE	131 (99.2)	65 (95.6)
Gr ≥3	58 (43.9)	28 (41.2)
Gr 5	1 (0.8)	0
Pts with ≥1 SAE	43 (32.6)	13 (19.1)
AE leading to atezolizumab/placebo discontinuation	33 (25.0)	10 (14.7)
AE leading to T-DM1 discontinuation	20 (15.2)	9 (13.2)
AE leading to T-DM1 dose reduction	22 (16.7)	6 (8.8)

Emens LA et al. Poster Presented at SABCS December 4-8, 2018
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30465-4/fulltext

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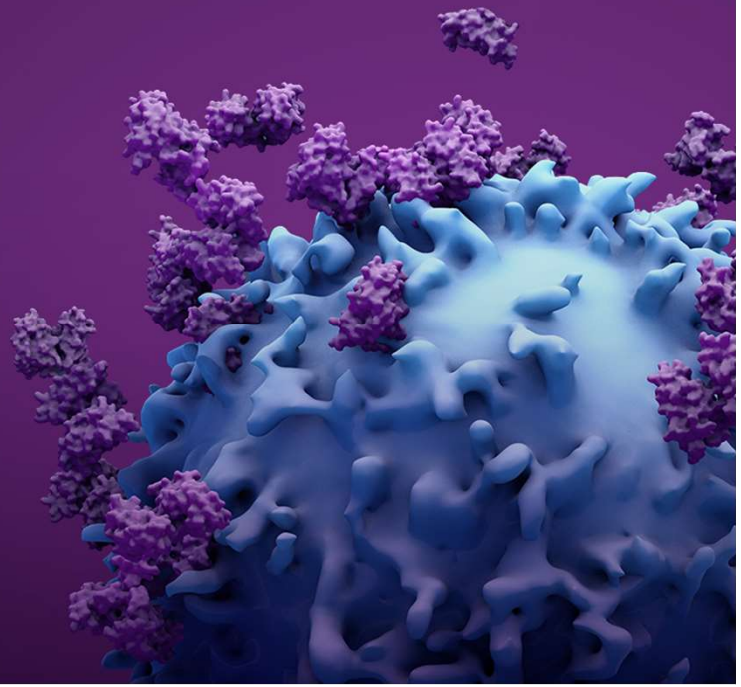
Thank You!



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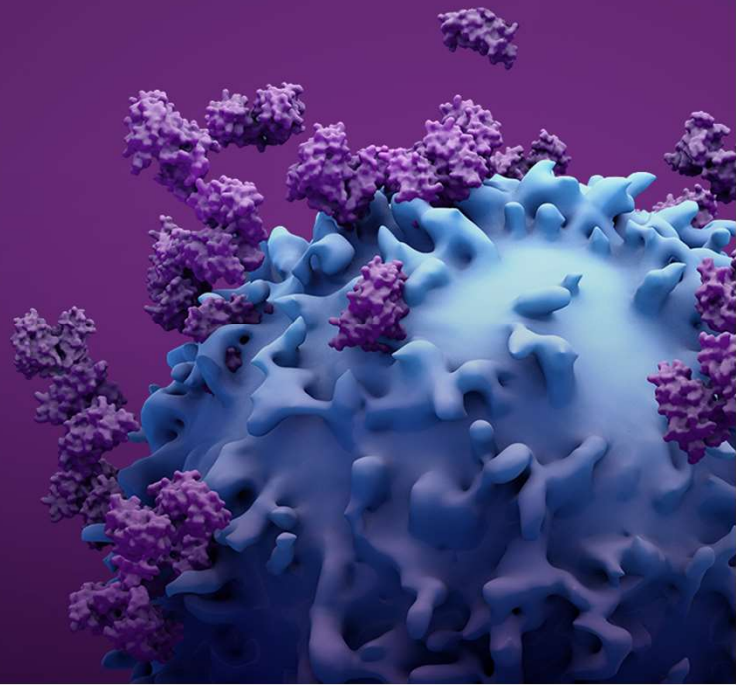
Live Q&A



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Join Us Again!

Clinical Applications of ADCs

Wednesday, Feb 3, 2021

6:00-7:30 PM EST

The Emerging Role of ADCs in Lung, Gastrointestinal, and Colorectal Cancers

Wednesday, Feb 17, 2021

6:00-7:30 PM EST

Follow us on social *@CancerExpertNow*

Presentation Breakdown

- Spiro: Slides 1-4
- Sanjiv: Slides 5-8, 37-38, 56, 113-114
- Daver: 9-36, 113
- Hurvitz: Slides 39-56, 80-106, 113
- Gradishar: Slides 57-79, 107-112