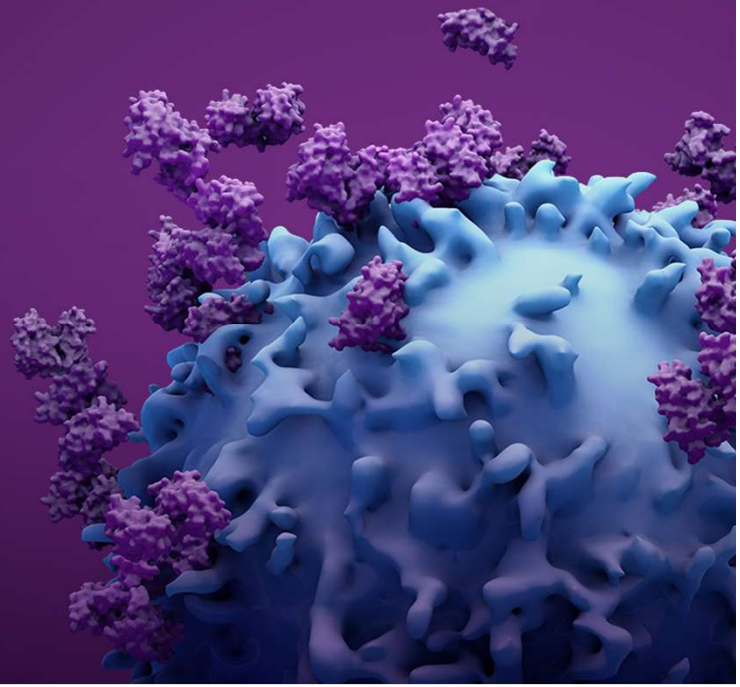
PrimO
Practical Recommendations in Immuno & Molecular Oncology
ADC Summit

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

Clinical Applications of ADCs

February 2, 2021



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Sponsors

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

Learning Objectives

Identify current thinking and rationale around patient selection and sequencing of ADCs in breast cancer

- Discuss current guidelines and recommendations
- Review patient cases to understand the clinical applications of FDA approved ADCs

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

Agenda

TIME (EST)	TOPIC	SPEAKERS
6:00 – 6:05 PM	Welcome and Objectives	Sanjiv
6:05 – 6:25 PM	Introduction to ADCs Where do we stand and where are we going?	Daver
6:25 – 7:15 PM 6:25 – 6:40 PM 6:40 – 6:50 PM 6:50 – 7:05 7:05 – 7:15	Practical Considerations of ADC's ADCs in Triple Negative Breast Cancer Patient Case #1 ADCs in HER2+ Breast Cancer Patient Case #2 & 3	 Hurvitz Hurvitz + Gradishar Gradishar Hurvitz + Gradishar
7:15 – 7:30 PM	Live Q&A	Hurvitz + Gradishar

Faculty Members

Naval G. Daver, MD
Associate Professor
Leukemia Department
MD Anderson Cancer Center
Houston, TX

Sara A. Hurvitz, MD, FACP
Professor of Medicine
Director, Breast Cancer Clinical Trials Program, Division of Hematology-Oncology
David Geffen School of Medicine, UCLA
Medical Director, Clinical Research Unit, Jonsson Comprehensive Cancer Center
Los Angeles, CA

William J. Gradishar, MD, FASCO, FACP
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
Northwestern University Feinberg School of Medicine
Chicago, IL

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Naval G. Daver, MD

Associate Professor
Leukemia Department
MD Anderson Cancer Center
Houston, TX

Disclosures

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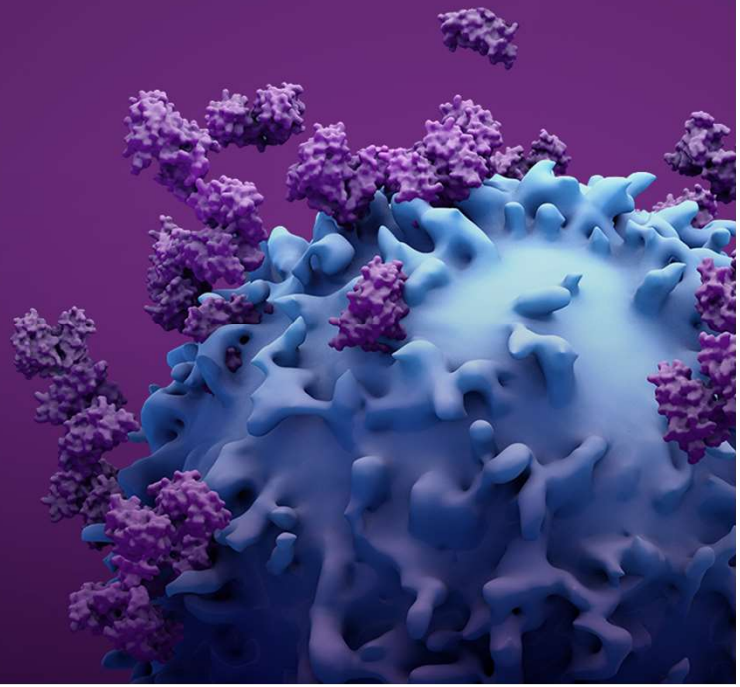
Intro to Antibody–Drug Conjugates (ADCs)

Where do we stand, and where are we going?

Naval G. Daver, MD
Associate Professor
Leukemia Department
MD Anderson Cancer Center
Houston, TX



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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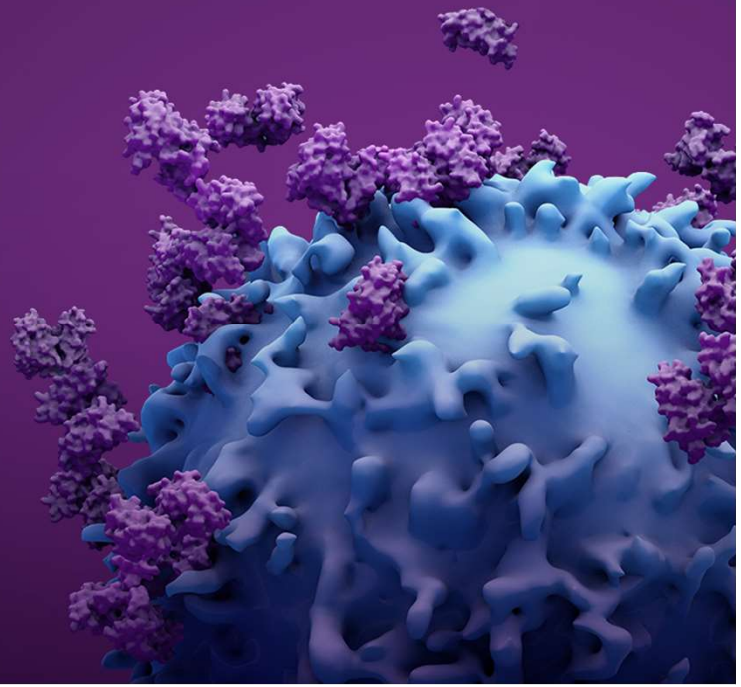
ADC Design and Structure



ADCs Are Built on Antibody Technology

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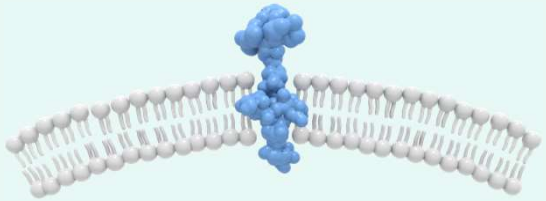
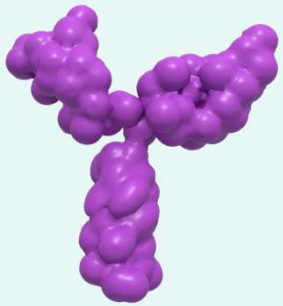
Target Antigen



- 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

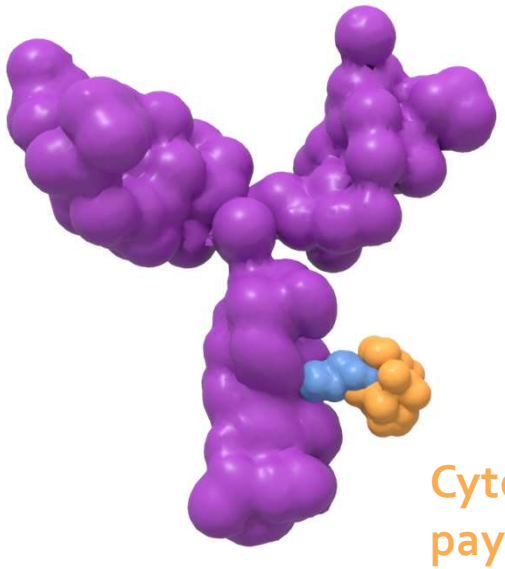
- Homogeneous target antigen expression in liquid tumors makes ADCs an attractive treatment option
- Heterogeneous target antigen expression in solid tumors may rely on bystander killing

- 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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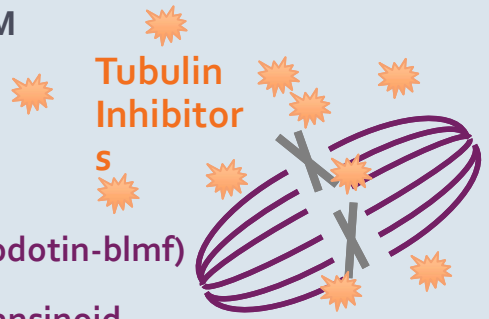
DNA damage

- 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

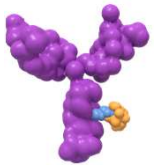
- Inhibit microtubule polymerization, causing G2/M phase cell-cycle arrest[2]
- MMAE
  (eg, brentuximab vedotin)
- MMAF (eg, belantamab mafodotin-blmf)
- DM1 is a highly potent maytansinoid
  (eg, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki)



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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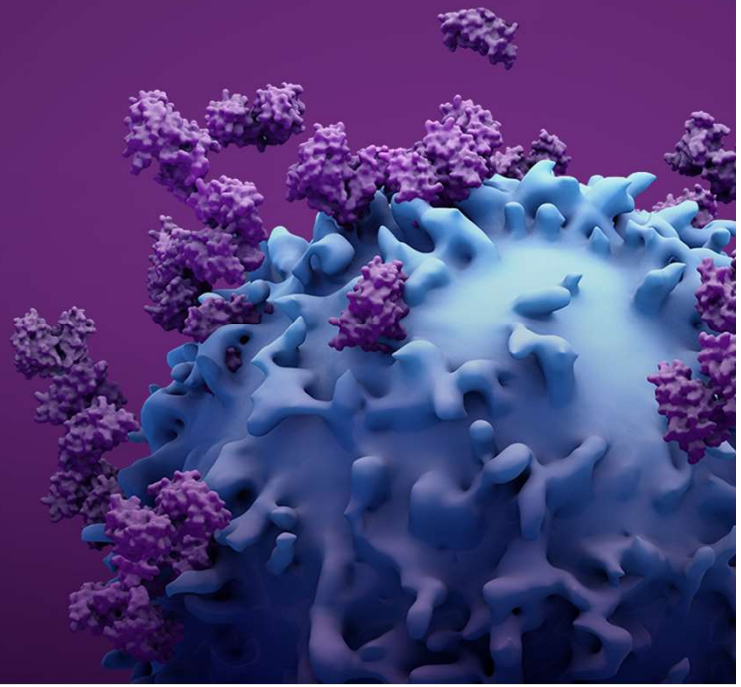
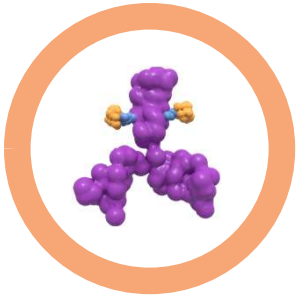
ADC Mechanism of Action



ADC Mechanism of Action[1,2]

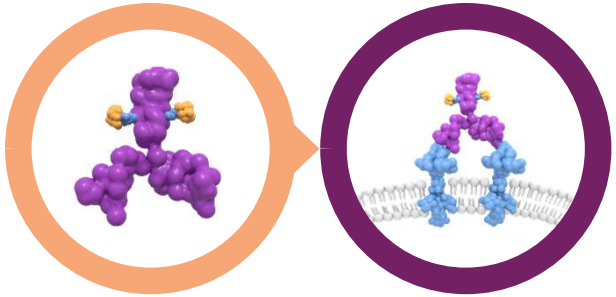


Circulation

- 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

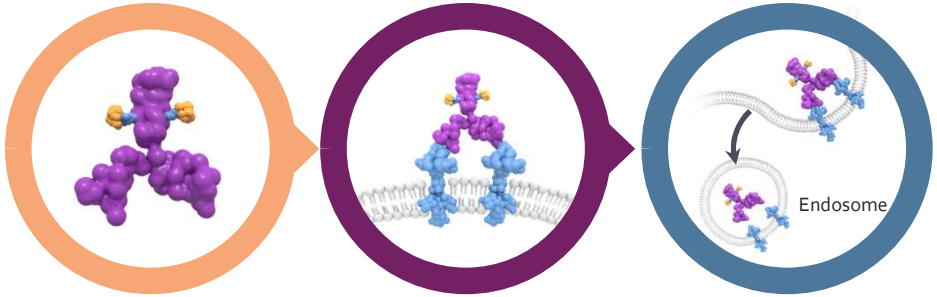
- ADC solution is prepared and released into the bloodstream

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

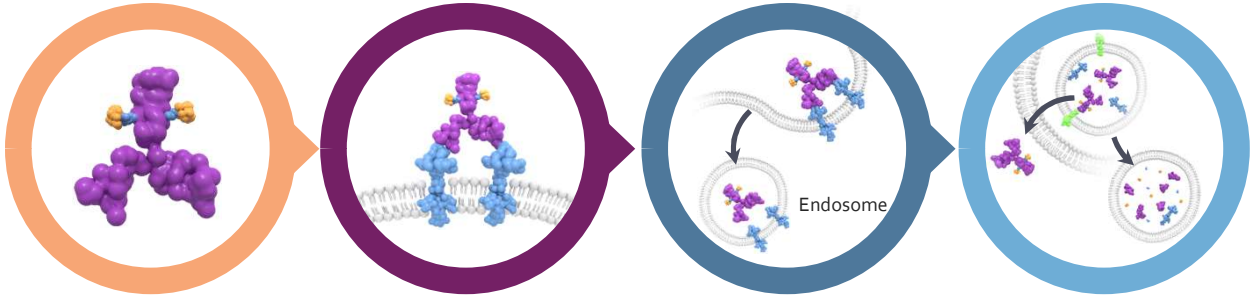
- mAb component of ADC binds to tumor antigen

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.

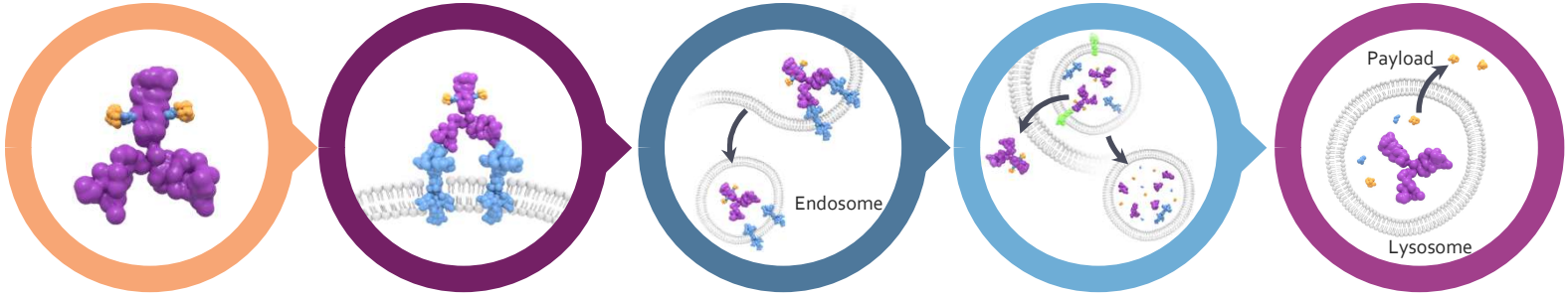
ADC Mechanism of Action[1,2]



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.

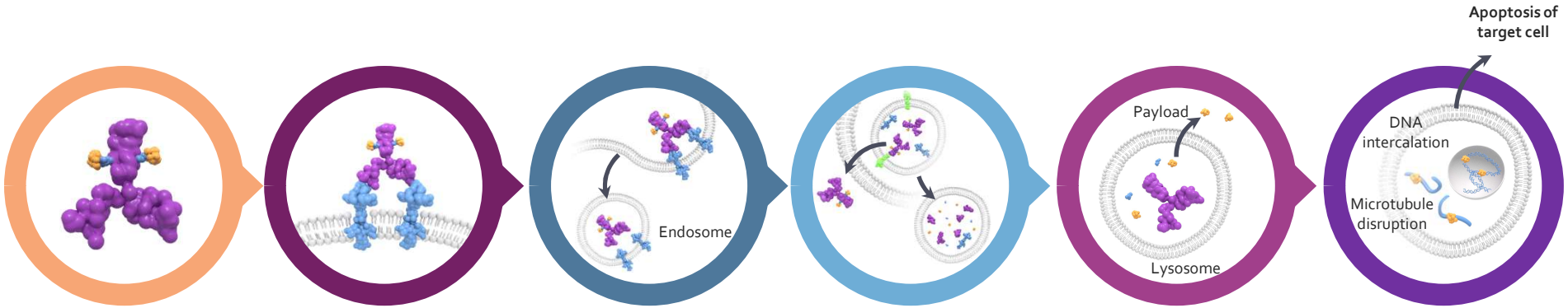
ADC Mechanism of Action[1,2]



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

- 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

Degradation & Recycling

- 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

Release of payload

- 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

Drug Action

- 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

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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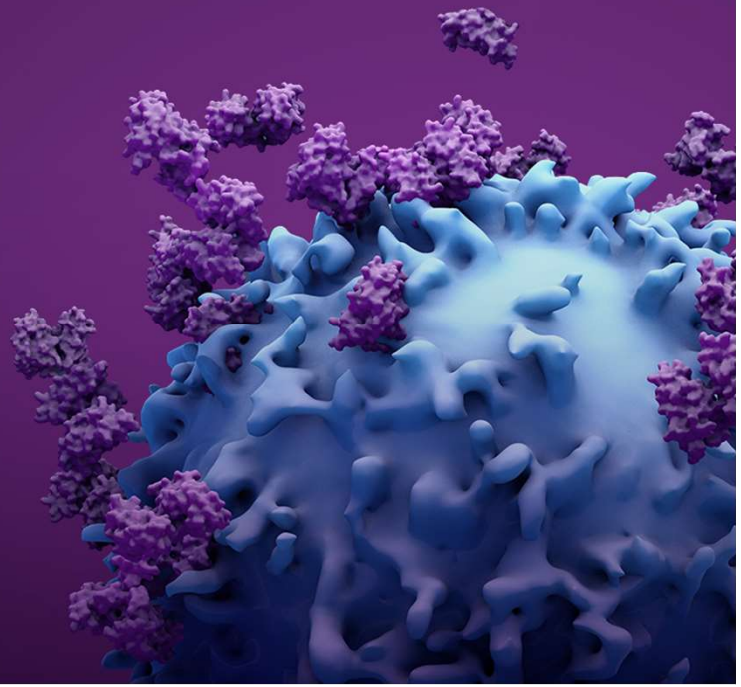
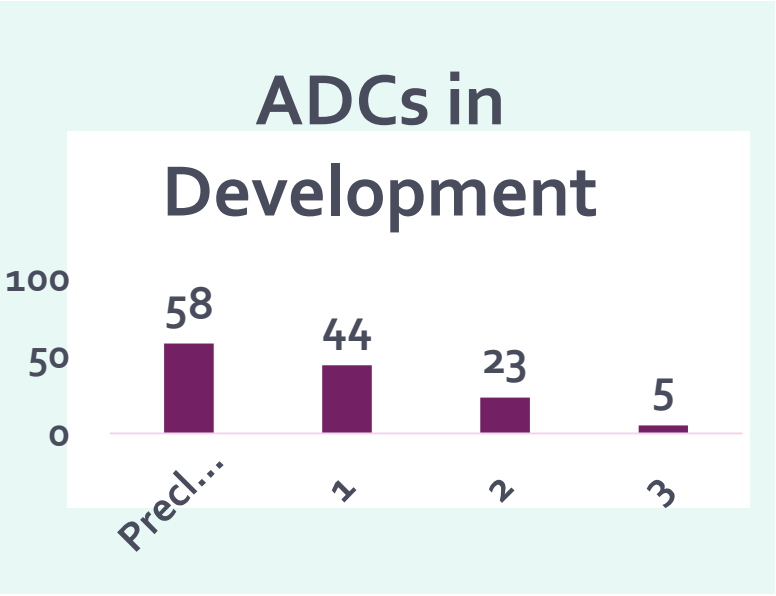
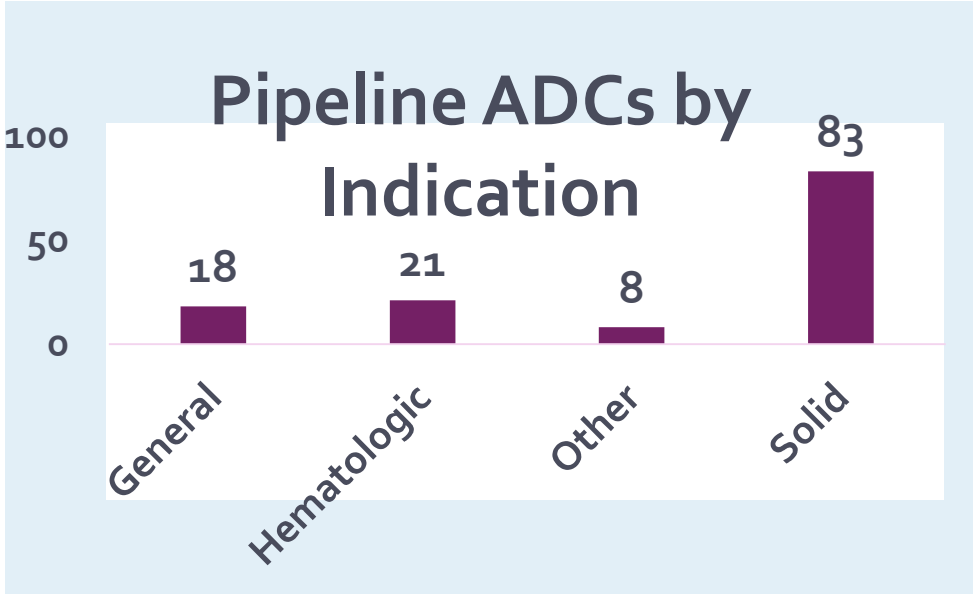
ADCs in Clinical Development



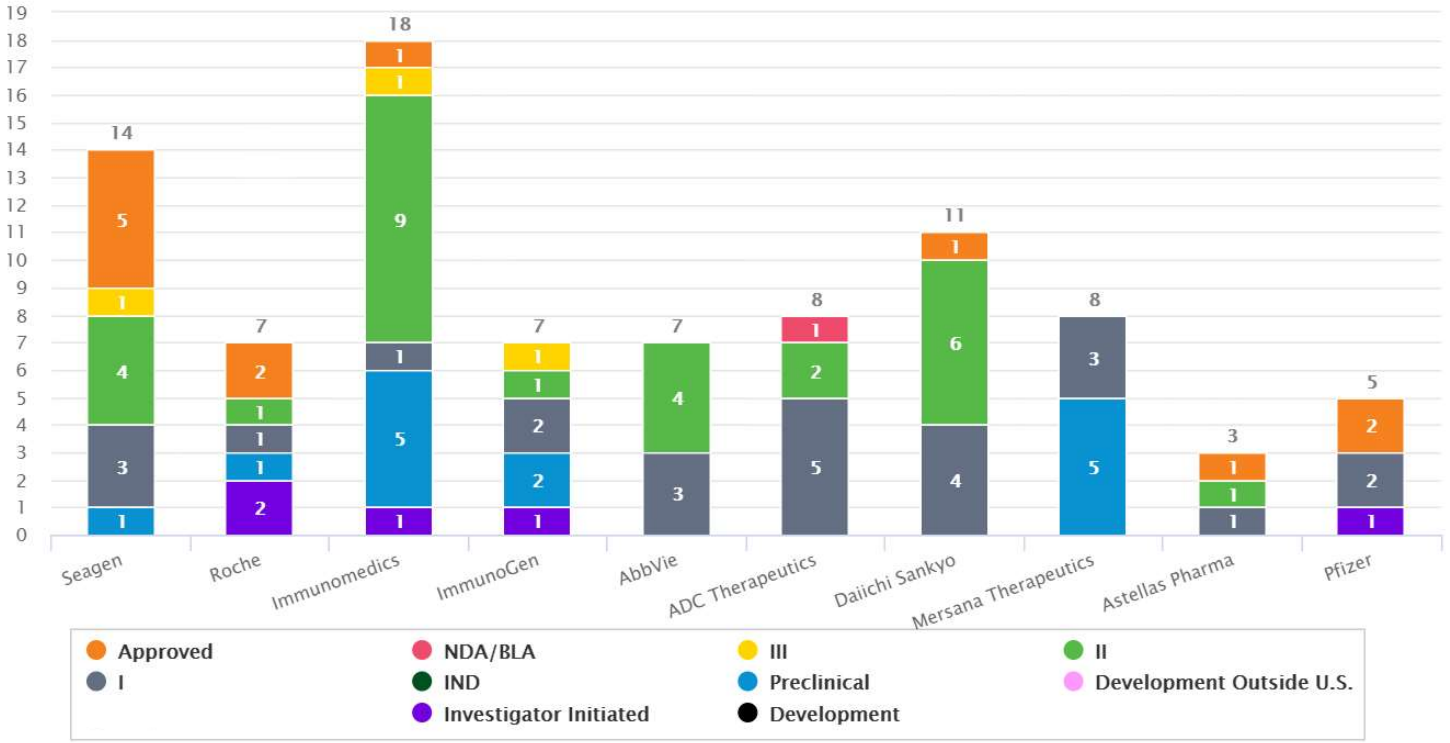
ADCs in Solid Tumors: More to Come





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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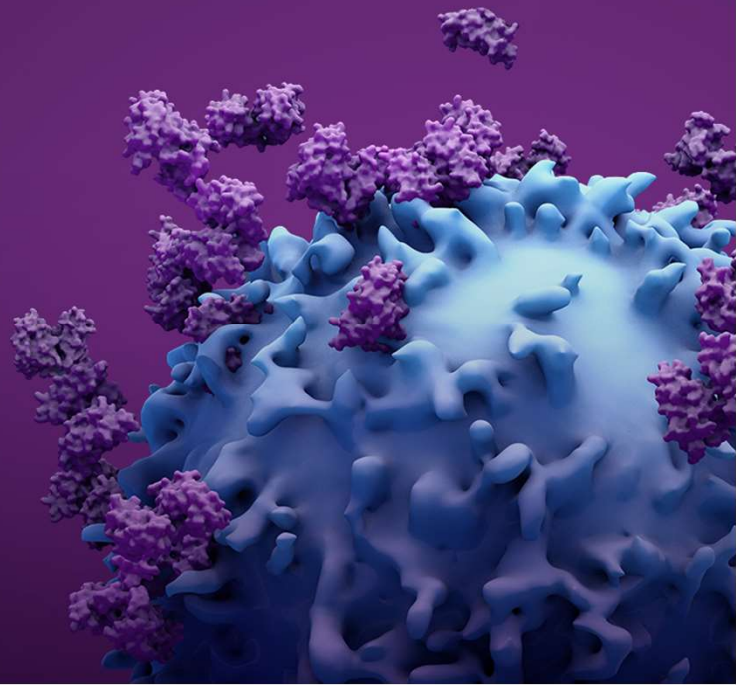
Thank You!



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Sara A. Hurvitz, MD, FACP

Professor of Medicine
Director, Breast Cancer Clinical Trials Program, Division of Hematology-Oncology
David Geffen School of Medicine, UCLA
Medical Director, Clinical Research Unit, Jonsson Comprehensive Cancer Center
Los Angeles, CA

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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William J. Gradishar, MD, FASCO, FACP

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
Northwestern University Feinberg School of Medicine
Chicago, IL

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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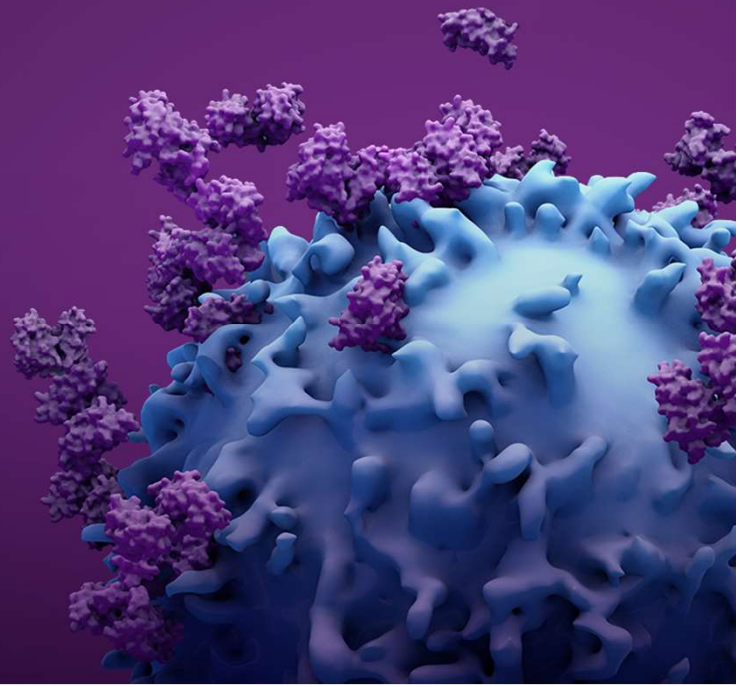
Antibody–Drug Conjugates: Practical Considerations and Applications in Clinical Use

Sara A. Hurvitz, MD, FACP
Professor of Medicine
David Geffen School of Medicine, UCLA
Los Angeles, CA

William J. Gradishar, MD, FASCO, FACP
Betsy Bramsen Professor of Breast Oncology & Professor of Medicine
Northwestern University Feinberg School of Medicine
Chicago, IL



Learning Objectives

Identify current thinking and rationale around patient selection and sequencing of ADCs in breast cancer

Breast Cancer Subtypes Guide Treatment Decisions

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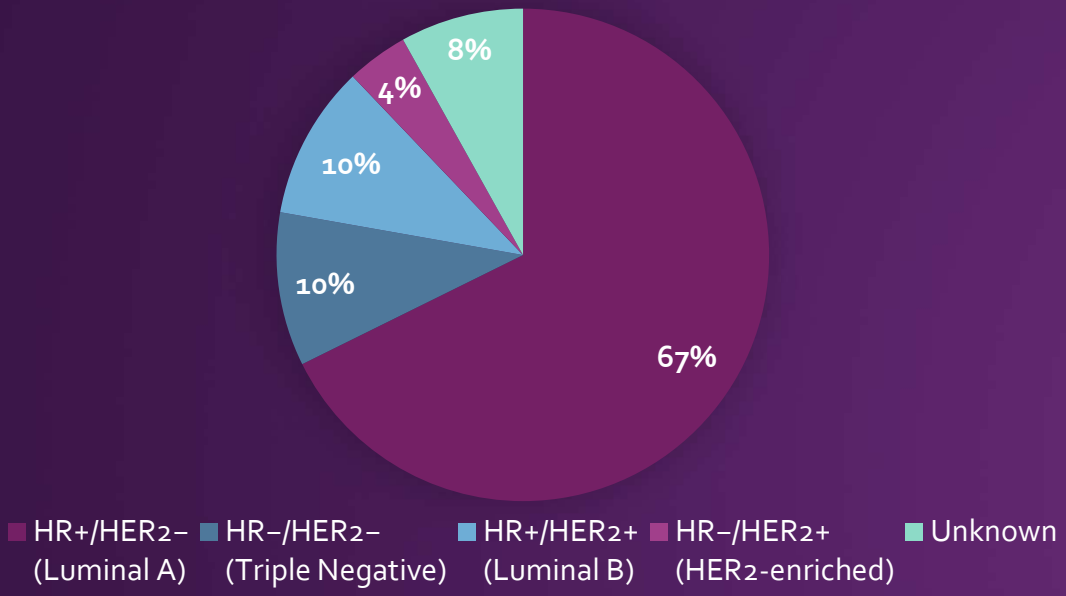
Female Breast Cancer Cases by Subtype (%) SEER 21 2012-2016



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.

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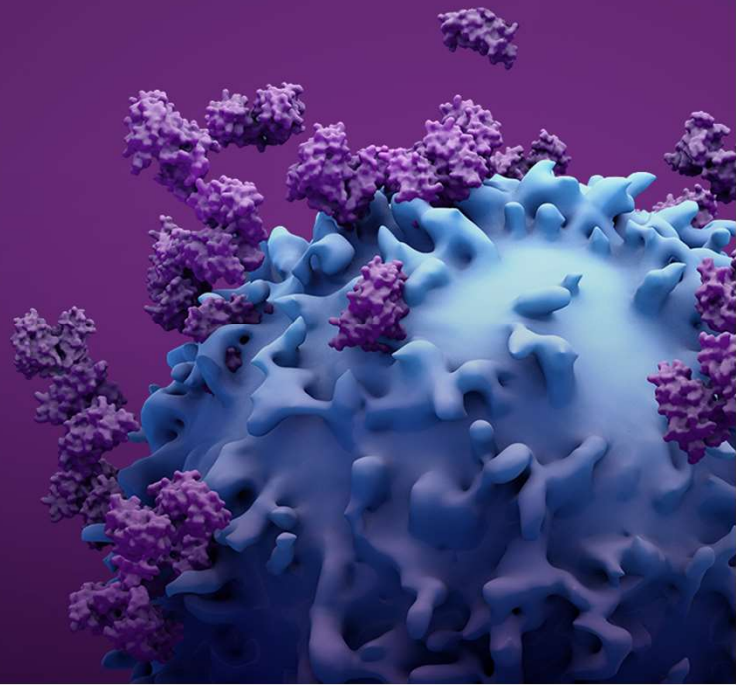
ADCs in TNBC



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.

Patient Case - 50 Y/O BRCA negative woman

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- Diagnosed with 3.3-cm high-grade TNBC left breast cancer cN0; received 6 cycles neoadjuvant TC with pCR
- 4 years later diagnosed with lung and bone metastases, ER/PR 0, HER2 FISH neg. Pt wishes to avoid alopecia
- Received 1L capecitabine (4 mos),2L line clinical trial of PI3Ki plus cisplatin (7 mos, intolerable AEs), 3L line clinical trial of atezolizumab/entinostat (2 mos, PD)
- She has an ECOG PS 1

Patient Case - 50 Y/O Woman

What would you recommend for her as 4L therapy? (She had 2 lines of chemotherapy in the metastatic setting but is relatively chemotherapy naïve)

Patient Case - 50 Y/O BRCA negative woman: UPDATE

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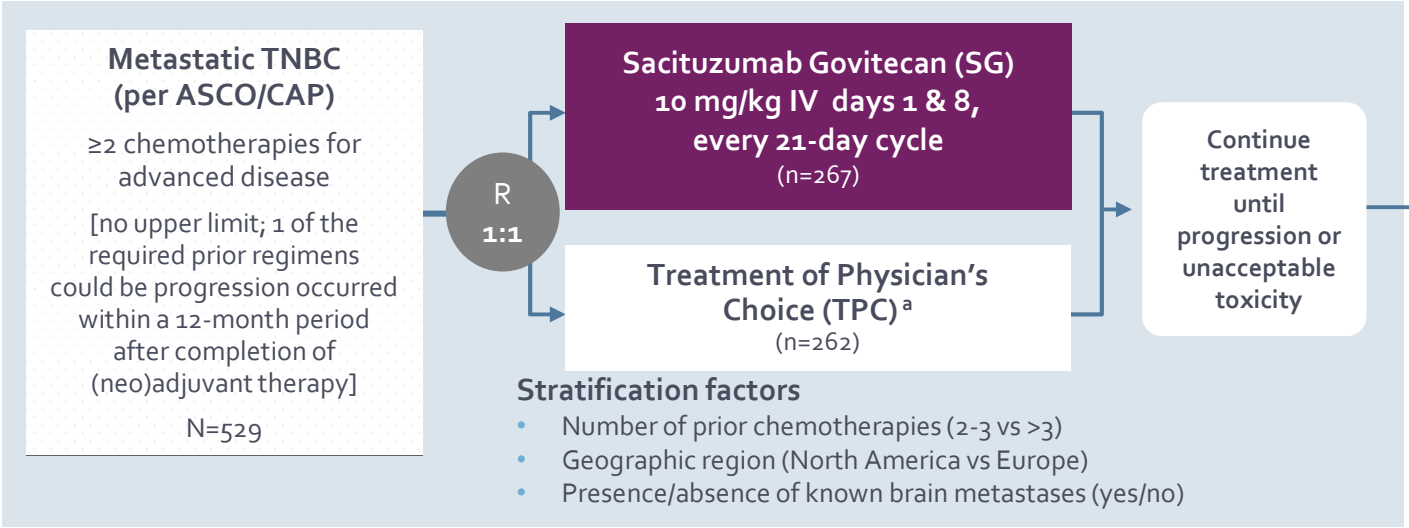
- Diagnosed with 3.3-cm high-grade TNBC left breast cancer cNo; received 6 cycles neoadjuvant TC with pCR
- 4 years later diagnosed with lung and bone metastases, ER/PR 0, HER2 FISH neg. Pt wishes to avoid alopecia
- Received 1L capecitabine (4 mos), 2L clinical trial of PI3Ki plus cisplatin (7 mos, intolerable AEs), 3L clinical trial of atezolizumab/ entinostat (2 mos, PD)
- *She enters ASCENT trial and receives sacituzumab govitecan. She develops grade 3 neutropenia after cycle 1*

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.

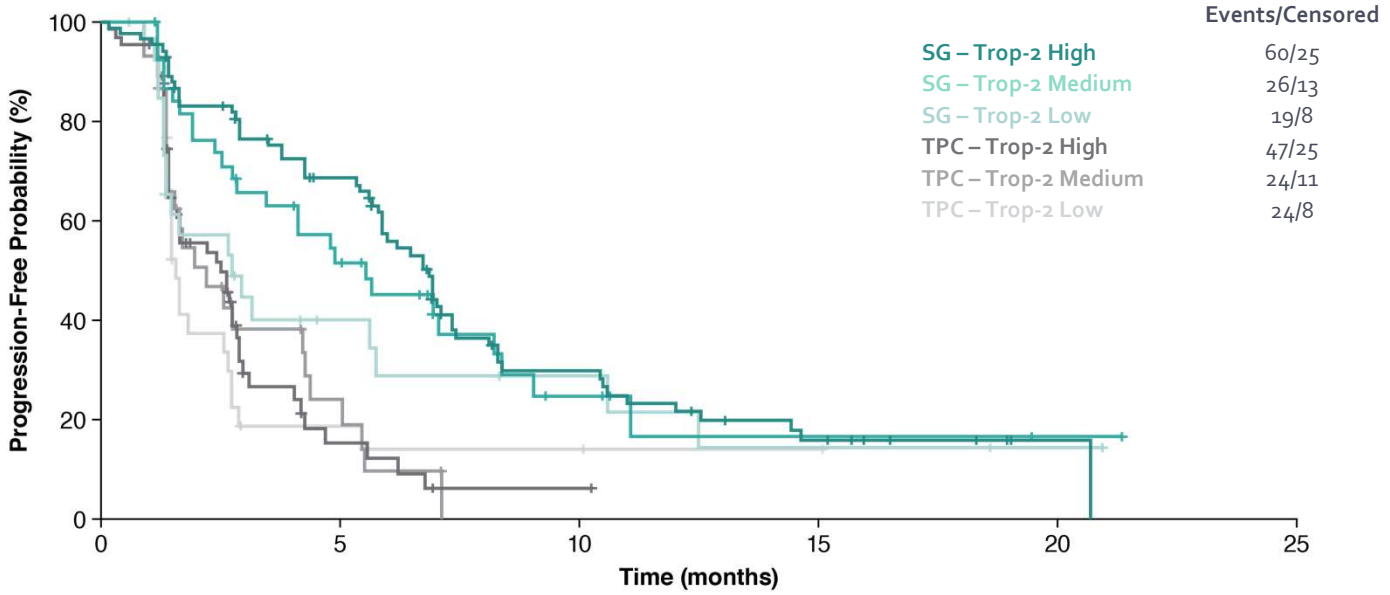
Demographics (Brain Mets-Negative)

	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;

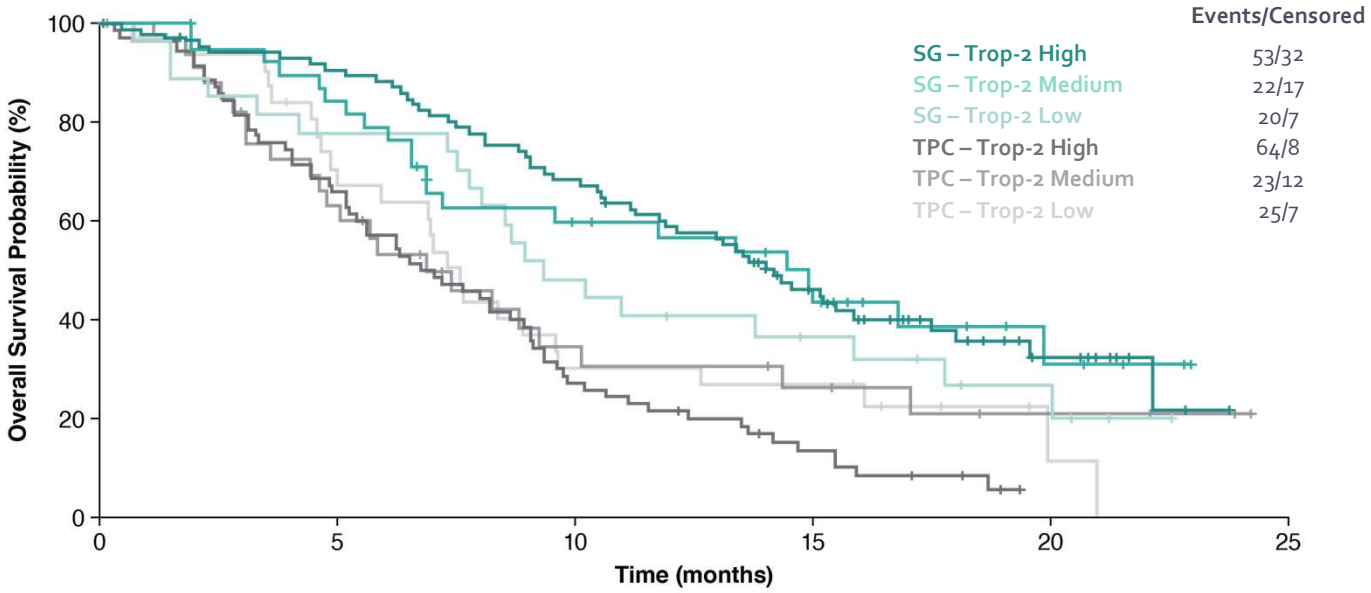
Progression-Free Survival by TROP-2 Expression



	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.

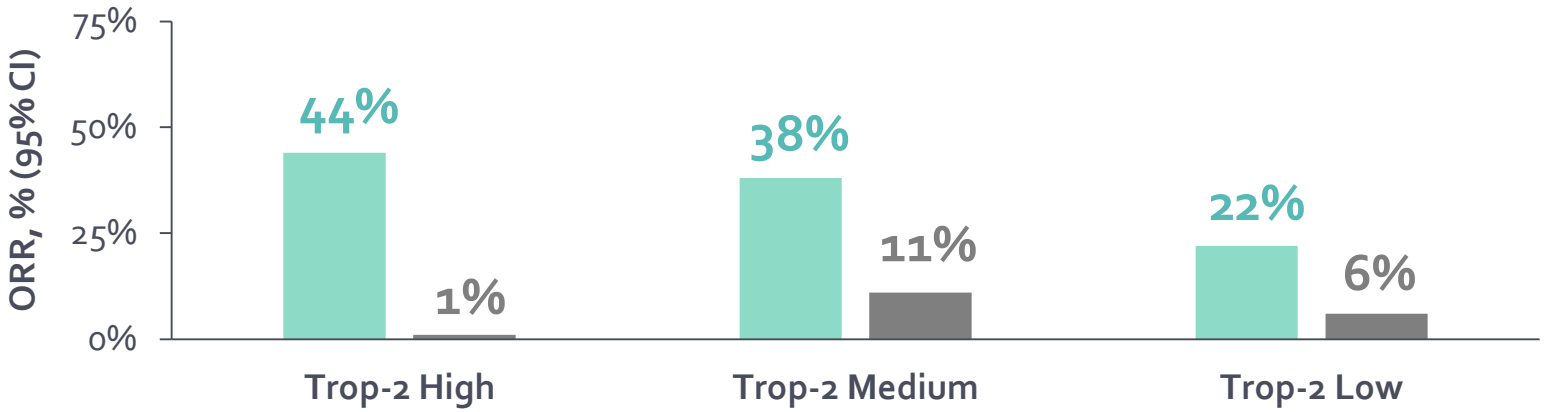
Overall Survival by TROP-2 Expression



	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

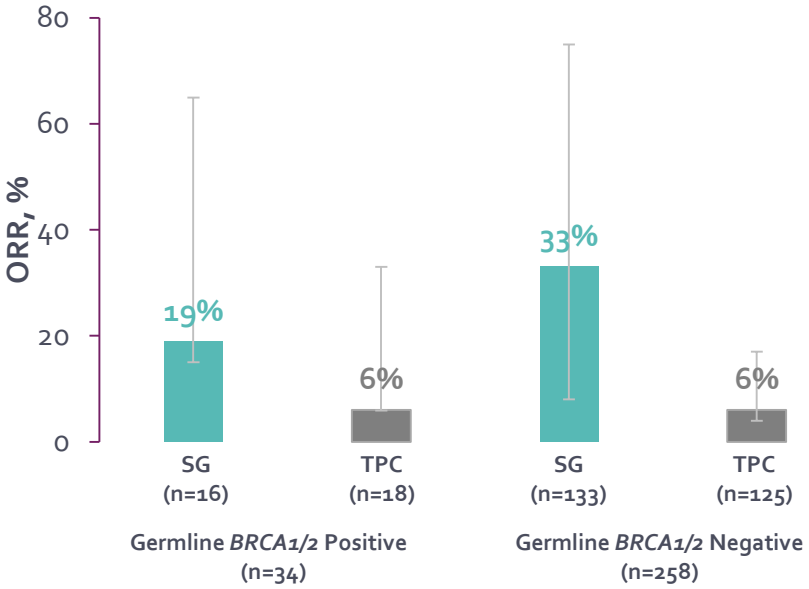


	Trop-2 High H-score: 200-300 (n=157)		Trop-2 Medium H-score: 100-200 (n=74)		Trop-2 Low H-score: <100 (n=59)	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
ORR—% (no.)	44% (37)	1% (1)	38% (15)	11% (4)	22% (6)	6% (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

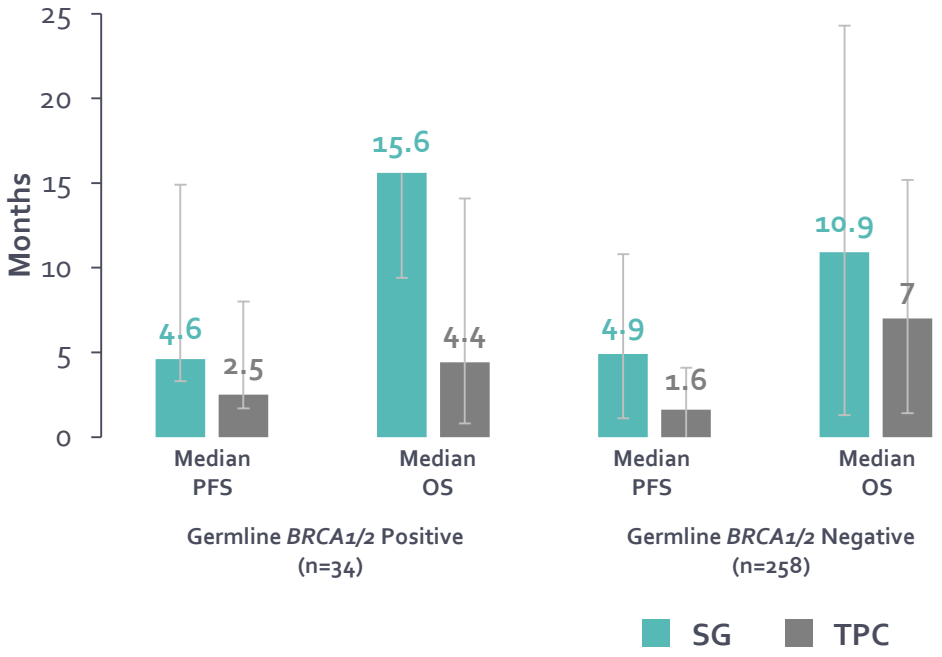
Assessed in the brain metastases-negative population. ORR and PFS are assessed by BICR. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
BICR, blind independent central review.

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.

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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.

Patient Case - 50 Y/O Woman

How do you manage the neutropenia associated with sacituzumab govitecan? Do you use growth factors up front or only after neutropenic event?

Patient Case - 50 Y/O Woman

How do you time GCSF given d1/8 dosing? Are there other toxicities that are particularly important to discuss with patients prior to starting therapy?

Patient Case - 50 Y/O Woman

She has a partial response lasting 14 months before PD in the lungs.

What therapy would you recommend next? Would you recommend next generation sequencing of the tumor?

Patient Case - 50 Y/O BRCA negative woman: UPDATE2

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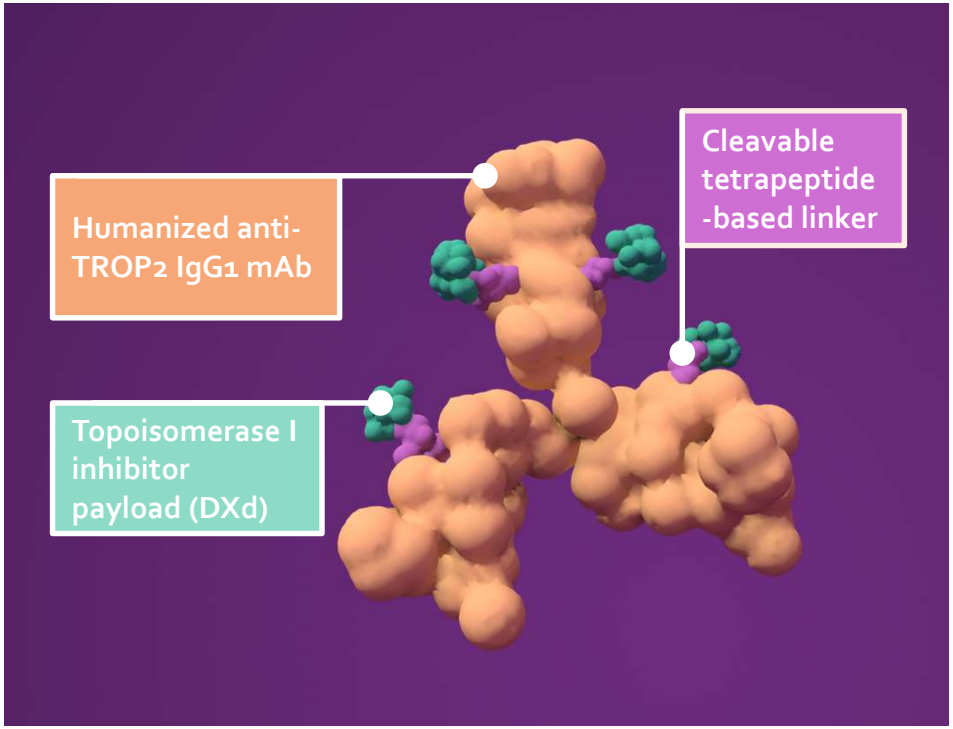
- T2Nohigh-grade TNBC left breast cancer, 6 cy TC→pCR
- 4 years later, lung and bone metastases, ER/PR 0, HER2 FISH neg
- Received 1L capecitabine (4 mos), 2L clinical trial of PI3Ki plus cisplatin (7 mos, intolerable AEs), 3L clinical trial of atezolizumab/entinostat (2 mos, PD)
- 4L Sacituzumab (14 mos PR)
- NGS: copy number loss of BRCA1. Enters study of niraparib/temozolomide. 5 mo SD
- Trial of CDK2/4/6 inhibitor: SD 2 mos
- Trial of DS1062a (anti-TROP2 ADC, deruxtecan payload). PR achieved after 2 cycles



- TROP2-targeting IgG1 ADC
- Cleavable tetrapeptide-based linker
- Topoisomerase I inhibitor payload (DXd)
- Drug-to-antibody ratio of 4
- DS-1062 selectively binds to the TROP2 receptor on the surface of a tumor cell
- After linker cleavage, DS-1062 induces tumor cells to undergo apoptosis through DNA damage via released DXd

Datopotamab Deruxtecan (Dato-DXd; DS-1062)

IgG1, immunoglobulin G1;TROP-2, trophoblast cell-surface antigen 2.

Spira A, *et al.* Datopotamab Deruxtecan (Dato-DXd; DS-1062), a TROP2 ADC, in Patients With Advanced NSCLC: Updated Results of TROPION-PanTumor01 Phase 1 Study. Oral Presentation at: World Conference on Lung Cancer Singapore; January, 2021

First-in-human Study of DS-1062a for Advanced Solid Tumors

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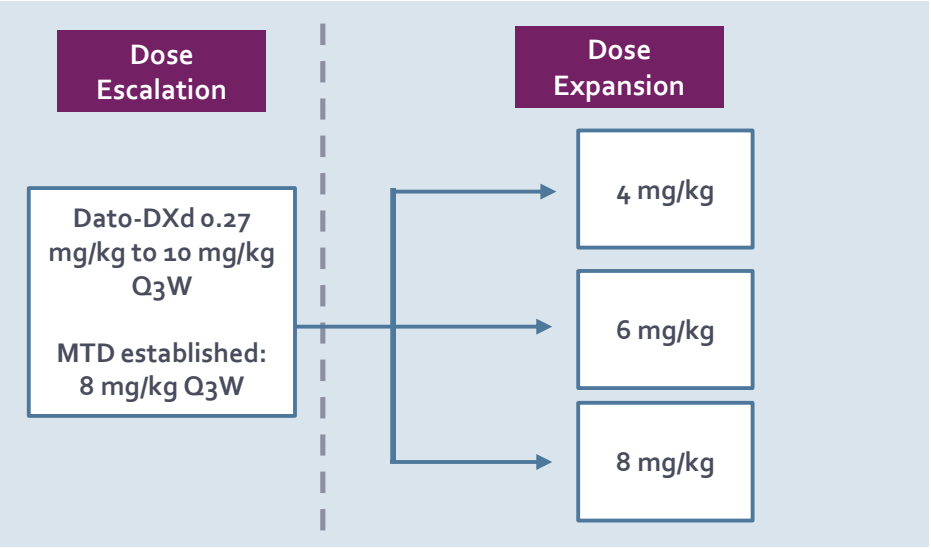
PATIENTS

- Relapsed/refractory advanced/metastatic TNBC
- Unselected for TROP2 expression
- Aged ≥ 18 (US) or ≥ 20 (Japan) years
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Stable, treated brain metastases allowed

STUDY DESIGN



TNBC cohort 6 mg/kg Q3w is enrolling

ENDPOINTS

1°

- Establish MTD
- Safety
- Tolerability

Select 2°

- Cmax
- Tmax
- AUC of DS-1062
- Ctrough

AUC, area under curve; Cmax, maximum concentration; Tmax, time to maximum.
Spira A, *et al.* WCLC 2020.

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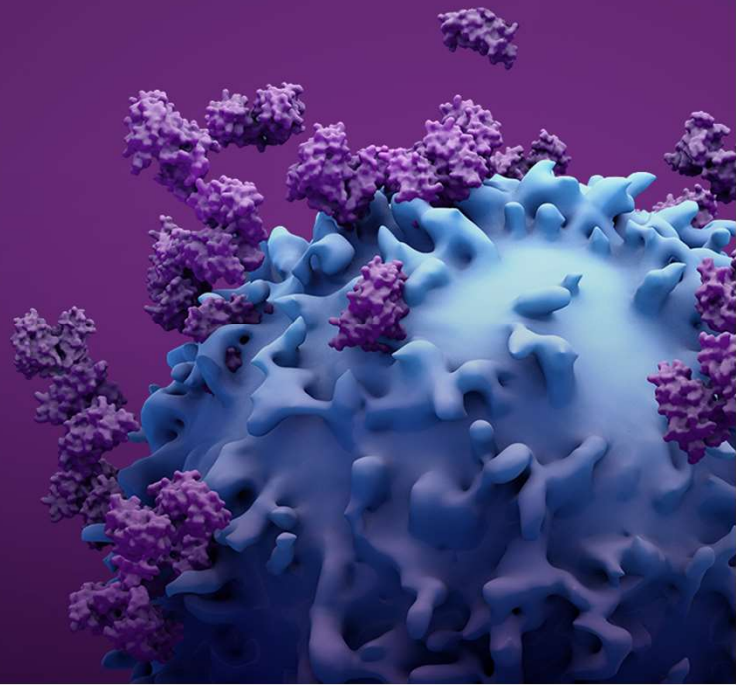
ADCs in HER2+ BC



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. 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.
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, trophoblast cell-surface antigen 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)

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.

Efficacy Outcomes in Patients With Advanced/Metastatic HER2+ BC

	N + CAPE[1,a] NALA	DS-8201[2] DESTINY-Breast01	T-DM1[3,a] EMILIA	Tucatinib + H + CAPE[4,b] HER2CLIMB
Study type	Ph 3	Ph 2	Ph 3	Ph 2
Total population (E vs C)	621 (307 vs 314)	184	991 (495 vs 496)	612 (410 vs 202)
ORR (% [95% CI]); E vs C	**33** vs **27** *P* = 0.1201	**60.9** [53.4-68.0]	**43.6** [38.6-48.6] vs **30.8** [26.3-35.7] *P* < 0.001	**40.6** [35.3-46.0] vs **22.8** [16.7-29.8] *P* < 0.001
CBR (% [95% CI]); E vs C	**45** vs **36** *P* = 0.0328	**76.1** [69.3-82.1]	--	--
mPFS (mo [95% CI]); E vs C	**8.8** vs **6.6**[c] *P* = 0.0003	**16.4** [12.7-NR]	**9.6** vs **6.4** HR 0.65 [0.55-0.77], *P* < 0.001	**7.8** [7.5-9.6] vs **5.6** [4.2-7.1][d] HR 0.54 [0.42-0.71], *P* < 0.001
mOS (mo [95% CI]); E vs C	**24.0** vs **22.2** HR 0.88 [0.72-1.07], *P* = 0.2086	NR	**30.9** vs **25.1** HR 0.68 [0.55-0.85], *P* < 0.001	**21.9** [18.3-31.0] vs **17.4** [13.6-19.9] HR 0.66 [0.50-0.88], *P* = 0.005
mDOR (mo [95% CI]); E vs C	**8.5** vs **5.6** HR 0.50 [0.33-0.74], *P* = 0.0004	**14.8** [13.8-16.9]	**12.6** [8.4-20.8] vs **6.5** [5.5-7.2]	--

C, control; CAPE, capecitabine; CBR, clinical benefit rate; E, experimental; H, trastuzumab; mDOR, median duration of response; mo, month; mOS, median overall survival; mPFS, median progression-free survival; N, neratinib; NR, not reached; ORR, objective response rate; P, phase.

Note: Direct cross-study comparisons must be interpreted with caution.

[a]Control arm: lapatinib + CAPE.
[b]Control arm: H + CAPE.
[c]Prespecified restricted means analysis.
[d]mPFS in the primary endpoint population (n=480).

1. Saura C, et al. *J Clin Oncol*. 2020;38(27):3138-3149. 2. Modi S, et al. *N Engl J Med*. 2019. 3. Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791. 4. Murthy RK, et al. *N Engl J Med*. 2019.

Efficacy Outcomes in Patients With HER2+ BC With Brain Metastases

	N + CAPE[1,a] TBCRC 022	N + CAPE[2] NALA		DS-8201[3] DESTINY-Breast01	T-DM1[4]	T-DM1[5] EMILIA	Tucatinib + H + CAPE[6] HER2CLIMB	
		N + CAPE	L + CAPE				Tuc + H + CAPE	H + CAPE
Study type	P2	P3		P2	Retrospective	Retrospective	P2	
Patients with BM	37	19	13	24	87	45	198	93
Brain/CNS ORR (%) [95% CI]	49 [32-66]	26.3	15.4	--	24.5	--	47	20
mPFS (mo) [95% CI]	5.5	--	--	18.1 [6.7-18.1]	7.0 [5.4-8.6]	5.9	9.9[b]	4.2
mOS (mo)	13.3	--	--	--	--	26.8	--	--
CNS incidence (%)	--	22.8[7,c]	29.2[7,c]	--	--	2[d]; 22.2[e]	--	--

BM, brain metastases; CNS, central nervous system; H, trastuzumab; L, lapatinib; mets, metastases; N, neratinib; Tuc, tucatinib.

Note: Direct cross-study comparisons must be interpreted with caution.

[a]Efficacy from cohort 3A (lapatinib naïve).
[b]HR=0.32 [95% CI, 0.22-0.48]; *P* < 0.0001.
[c]Patient population N + CAPE (N=307) and L + CAPE (N=314); statistically significant reduction (*P* = 0.043).
[d]In patients with no CNS mets at baseline (N=450).
[e]In patients with stable CNS mets at baseline.

1. Freedman RA, et al. *J Clin Oncol*. 2019;37(13):1081-1089. 2. Awada A, et al. Poster presented at: San Antonio Breast Cancer Symposium. December 10-14, 2019; San Antonio, TX. Poster P2-20-01. 3. Modi S, et al. *N Engl J Med*. 2019. 4. Fabi A, et al. Breast. 2018;41:137-143. 5. Krop IE, et al. *Ann Oncol*. 2015;26(1):113-119. 6. Presented at: ASCO 2020. 7. Saura C, et al. *J Clin Oncol*. 2019;37(15_suppl):1002-1002.

Safety Results With HER2-Targeting ADCs

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T-DXd[1]

The most common gr 3 or 4 TEAEs included **decreased neutrophil count, nausea, and anemia**

Patients who received T-DXd (N = 184)

TEAE (≥ 15%), n (%)	All Grades	Grade 3	Grade 4
Patients with any TEAE	183 (99.5)	89 (48.4)	7 (3.8)
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Neutropenia	**64 (34.8)**	**36 (19.6)**	**2 (1.1)**
Decreased appetite	57 (31.0)	3 (1.6)	0
Anemia	**55 (29.9)**	**15 (8.2)**	**1 (0.5)**
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased WBC count	**39 (21.2)**	**11 (6.0)**	**1 (0.5)**
Thrombocytopenia	**39 (21.2)**	**7 (3.8)**	**1 (0.5)**
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain	31 (16.8)	2 (1.1)	0

T-DM1[2]

The most commonly reported gr 3 or 4 events were **thrombocytopenia (12.9%)** and **elevated serum concentrations of AST (4.3%)** and **ALT (2.9%)**

Patients who received T-DM1 (N = 490)

TEAE (≥ 2%), n (%)	All Grades	Grade ≥3
Patients with any TEAE	470 (95.9)	200 (40.8)
Diarrhea	114 (23.3)	8 (1.6)
Palmar-plantar erythrodysesthesia	6 (1.2)	0
Vomiting	93 (19.0)	4 (0.8)
Neutropenia	29 (5.9)	10 (2.0)
Hypokalemia	42 (8.6)	11 (2.2)
Fatigue	172 (35.1)	12 (2.4)
Nausea	192 (39.2)	4 (0.8)
Mucosal inflammation	33 (6.7)	1 (0.2)
Anemia	51 (10.4)	13 (2.7)
Elevated ALT	**83 (16.9)**	14 (2.9)
Elevated AST	**110 (22.4)**	**21 (4.3)**
Thrombocytopenia	**137 (28.0)**	**63 (12.9)**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-related adverse events; WBC, white blood cell.

1. Modi S, et al. *N Engl J Med*. 2019;382(7):610-621; 2. Verma S et al. *N Engl J Med*. 2012. 367:1783-1791.

AEs of Interest With T-DXd: ILD[1-3]

- Identified across clinical development programs with T-DXd
- Protocol recommendation: monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade/total
DESTINY-Breast01	184	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)
DESTINY-CRC01	78	0	2 (2.6)	1 (1.3)	0	2 (2.6)	5 (6.4)
DESTINY-Lung01	42	0	5 (11.9)	0	0	0	5 (11.9)

1. Modi S. Poster presented at the San Antonio Breast Cancer Symposium; December 4-7, 2018; San Antonio, TX [poster P6-17-02]; 2. 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; 3. Siena S et al. A phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01. Presented at: American Society of Clinical Oncology 2020 Virtual Scientific Sessions; May 29 – 31. Accessed November 6, 2020. https://meetinglibrary.asco.org/record/185482/abstract;

Patient Case - 59 Y/O female presents with progressive HER2+ MBC

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- Dx with Stage II, ER+/HER+ Left-sided IDC 6 years earlier
- After lumpectomy and SLN (1.5 cm primary and 2 positive axillary nodes) adjuvant therapy with TCH x 6 followed by completion of 1 year of trastuzumab
- RT completed and an aromatase inhibitor was initiated
- Just after completing 5 years of AI therapy, she presented with bone pain and some respiratory sx. Evaluation revealed bone, liver and lung metastases and liver biopsy confirmed HER2+, but now ER poor
- Treatment with THP (paclitaxel) was started, and after 6 cycles there was almost complete resolution of lung mets and marked decrease liver mets; bone was stable. HP was continued for another 9 months at which time there was a slight increase in liver mets

Patient Case - 59 Y/O Woman

- Would you :
  - Add paclitaxel back to HP
  - D/c HP and start TDM-1
  - D/c HP and start T-DXd
  - D/c HP and start tucatinib, capecitabine, trastuzumab
- Would you also recommend endocrine therapy?

Patient Case - 59 Y/O Woman

Would you image the brain in the absence of symptoms? Would the presence of brain mets change your rec?

Patient Case - 42 Y/O premenopausal woman with a 3.5 cm self-detected right breast mass

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- PE confirms the mass, and an axillary lymph node is detected. A biopsy of both the mass and node confirm HER2 +/ER-/PR- disease
- The patient starts on TCHP preoperatively with an excellent clinical and imaging response
- Lumpectomy reveals 8 mm residual disease and no positive nodes. Residual disease remains HER2-positive
- TDM-1 was initiated, and the full course was completed
- *1.5 years after completion of all therapy new symptoms develop and liver transaminases noted to be slightly above normal. CT confirms several 1 cm liver mets. Biopsy c/w HER2 + recurrent BC*

Patient Case - 42 Y/O Woman

- What would your next treatment would be:
  - THP
  - T-DXd
  - Tucatinib, capecitabine, trastuzumab
  - Lapatinib /capecitabine

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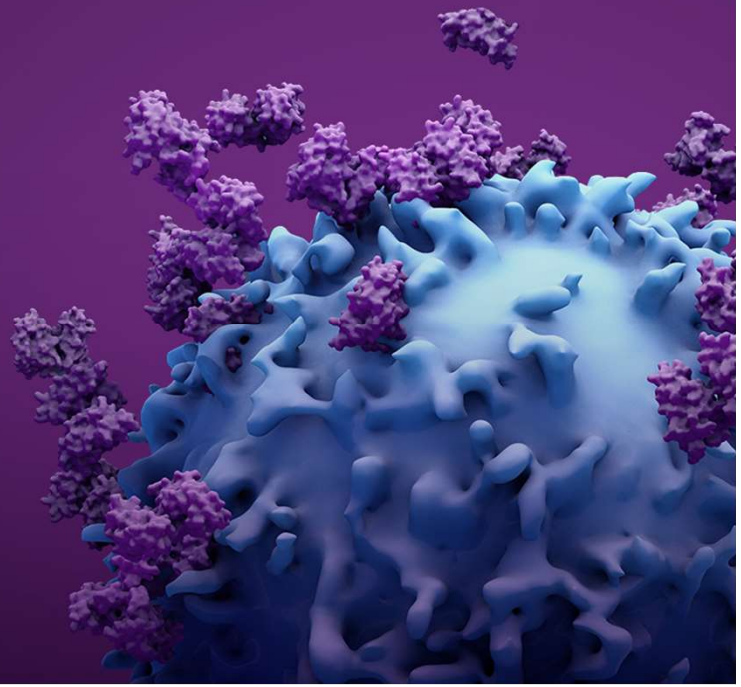
Thank You



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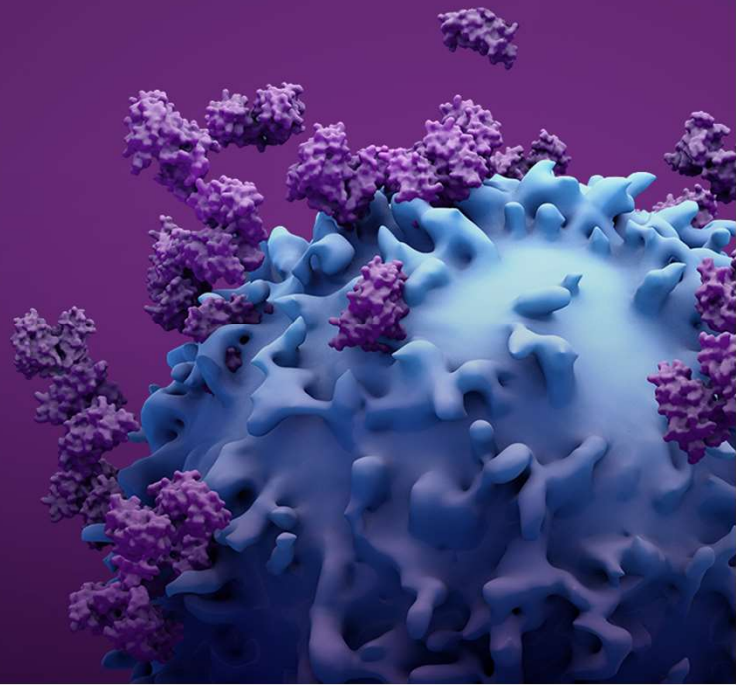
Live Q&A



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- Spiro: Slides 1-4
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- Daver: Slides 9-36
- Hurvitz: Slides 39-60, 69-75
- Gradishar: Slides 45-47, 55-58, 61-75