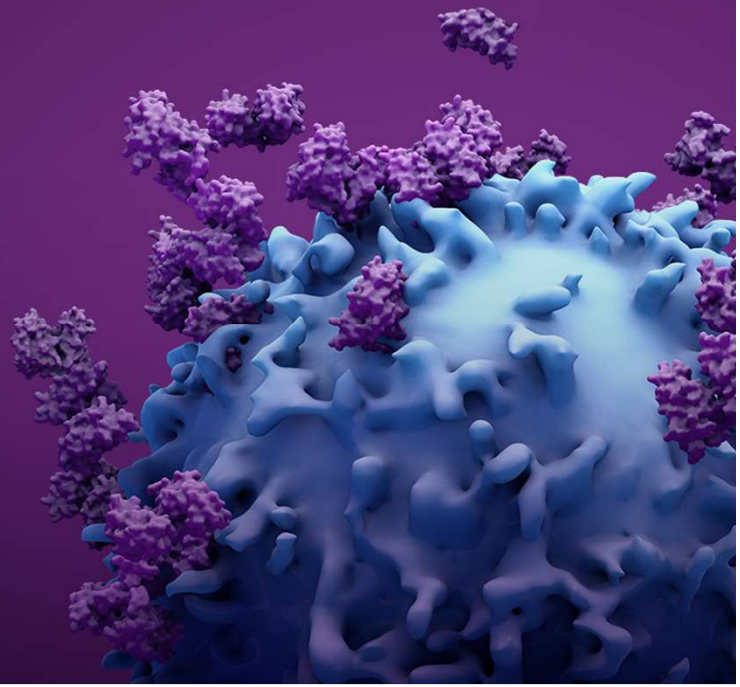
PrimO
Practical Recommendations in Immuno & Molecular Oncology
ADC Summit

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

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

February 17, 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 ADCs in development for NSCLC, GI cancers, and CRC

- Discuss ADCs currently FDA approved and in development
- Analyze the unmet need in patients with these NSCLC, GI cancers, and CRC
- Discuss their mechanisms of action
- Analyze available clinical data and discuss ongoing clinical trials

ADC, antibody–drug conjugate; CRC, colorectal cancer; GI, gastrointestinal; NSCLC, non-small cell lung cancer; FDA, US Food and Drug Administration.

Agenda

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TIME	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 – 6:50 PM 6:25 – 6:38 6:38 – 6:50	ADCs in NSCLC with updates from WCLC Trastuzumab Deruxtecan, SAR408701 Sacituzumab Govitecan, Patritumab Deruxtecan, Telisotuzumab Vedotin	West Ramalingam
6:50 – 7:15 PM	ADCs in Gastrointestinal Cancers with updates from ASCO GI	Shroff
7:15 – 7:30 PM	Live Q/A	West, Ramalingam (Lung); Shroff (GI/CRC)

Faculty Members

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Disclosures

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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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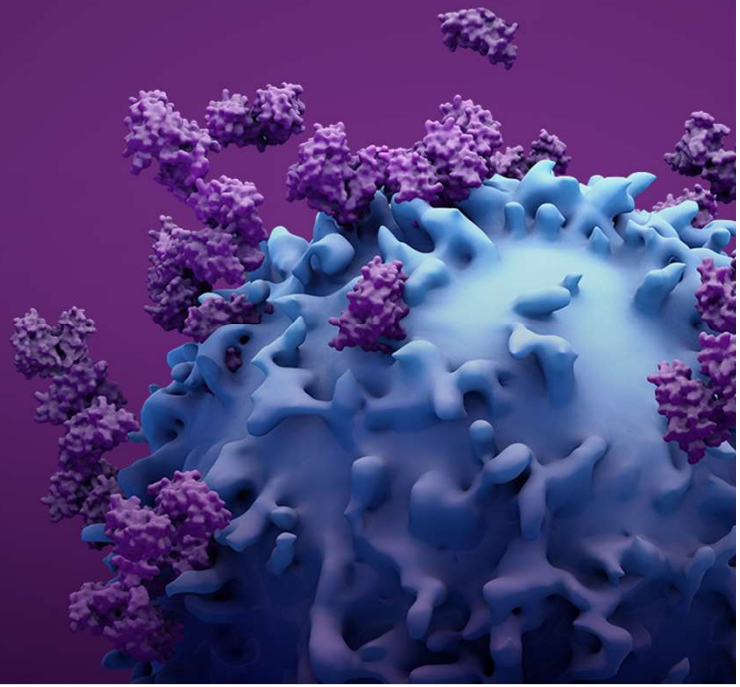

Learning Objectives

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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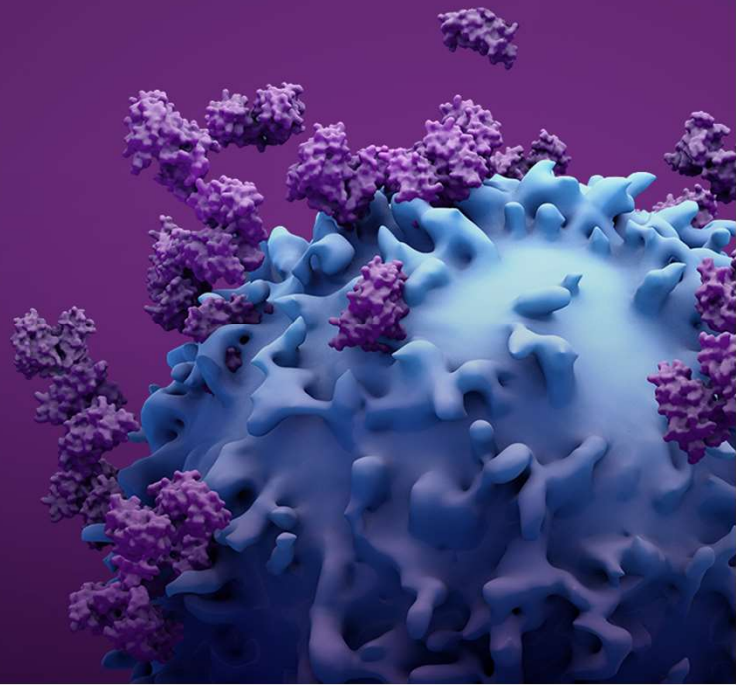
ADC Design and Structure



ADCs Are Built on Antibody Technology

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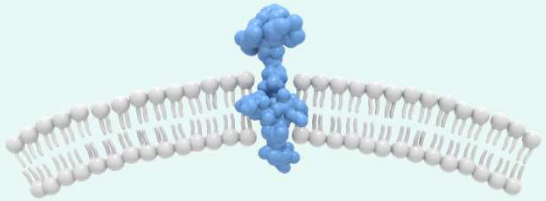
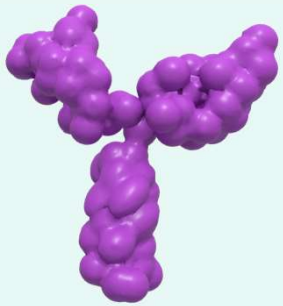
Target Antigen



- 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

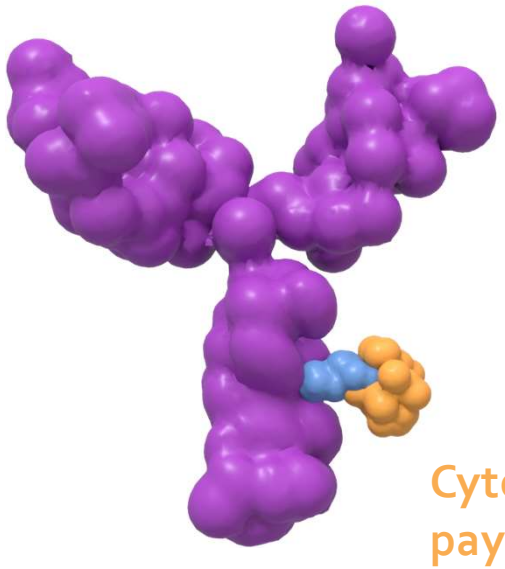
- Homogeneous target antigen expression in liquid tumors makes ADCs an attractive treatment option
- Heterogeneous target antigen expression in solid tumors may rely on bystander killing

- 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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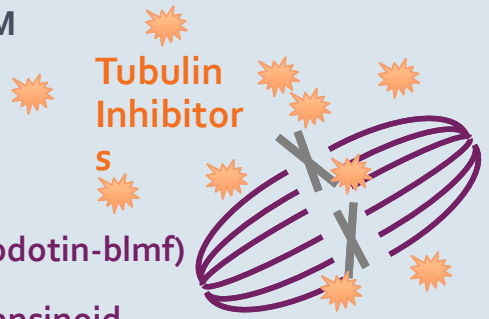
DNA damage

- 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

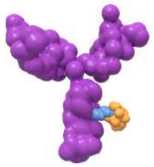
- Inhibit microtubule polymerization, causing G2/M phase cell-cycle arrest[2]
- MMAE
  (eg, brentuximab vedotin)
- MMAF (eg, belantamab mafodotin-blmf)
- DM1 is a highly potent maytansinoid
  (eg, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki)



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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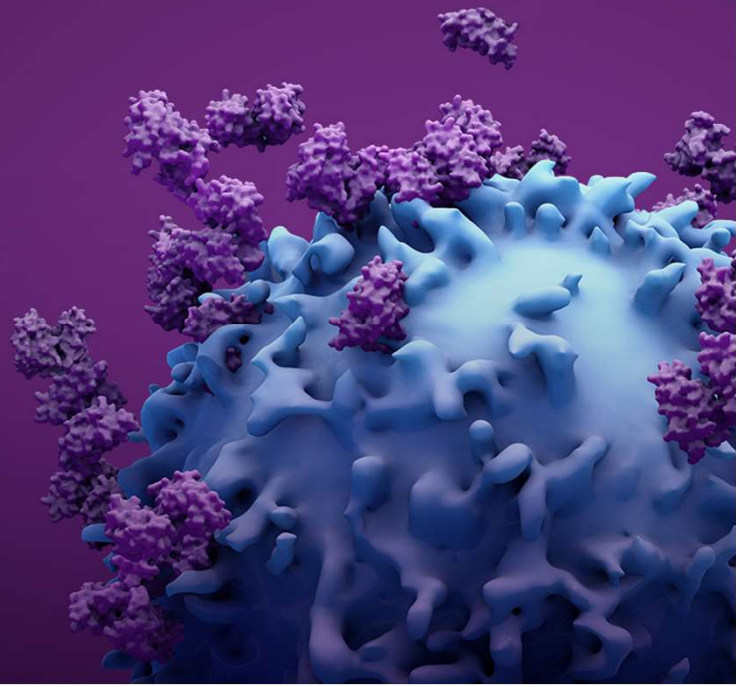
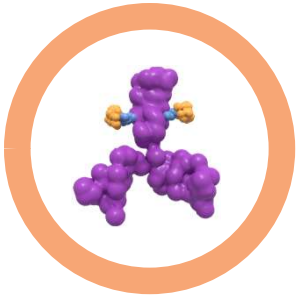
ADC Mechanism of Action



ADC Mechanism of Action[1,2]

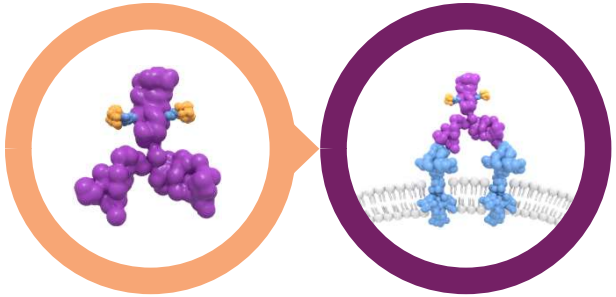


Circulation

- 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

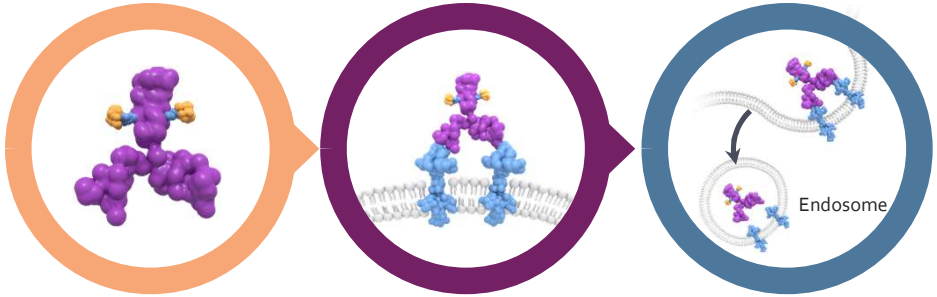
- ADC solution is prepared and released into the bloodstream

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

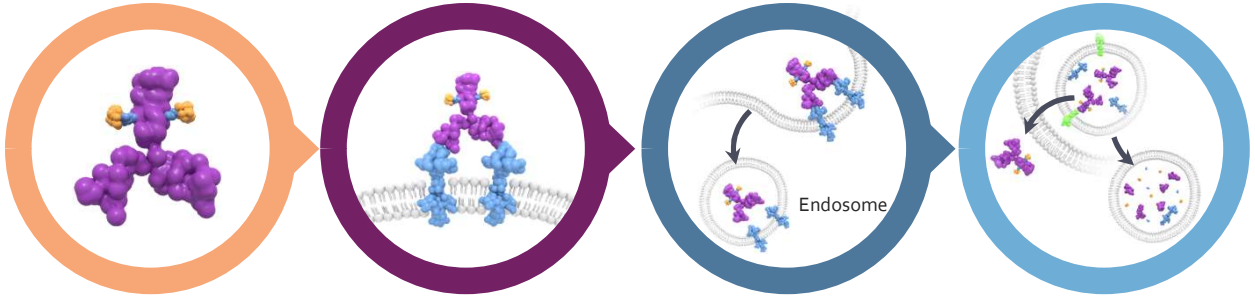
- mAb component of ADC binds to tumor antigen

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.

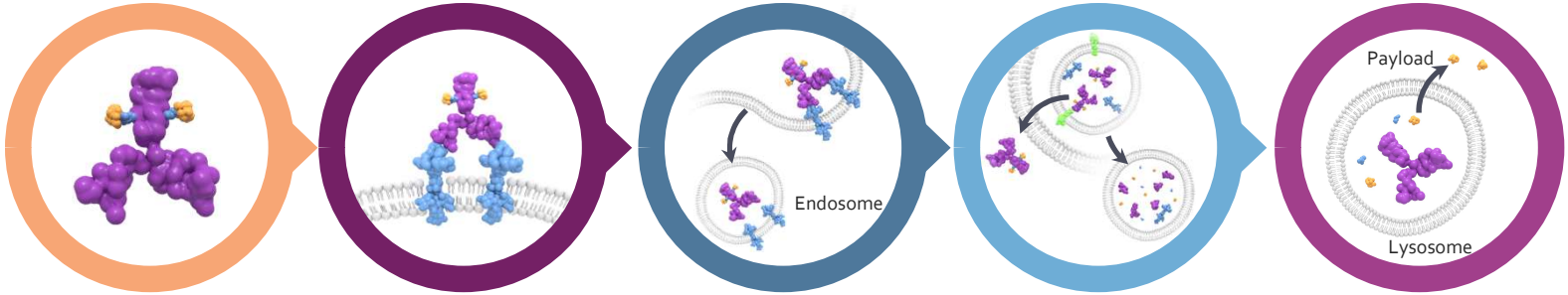
ADC Mechanism of Action[1,2]



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.

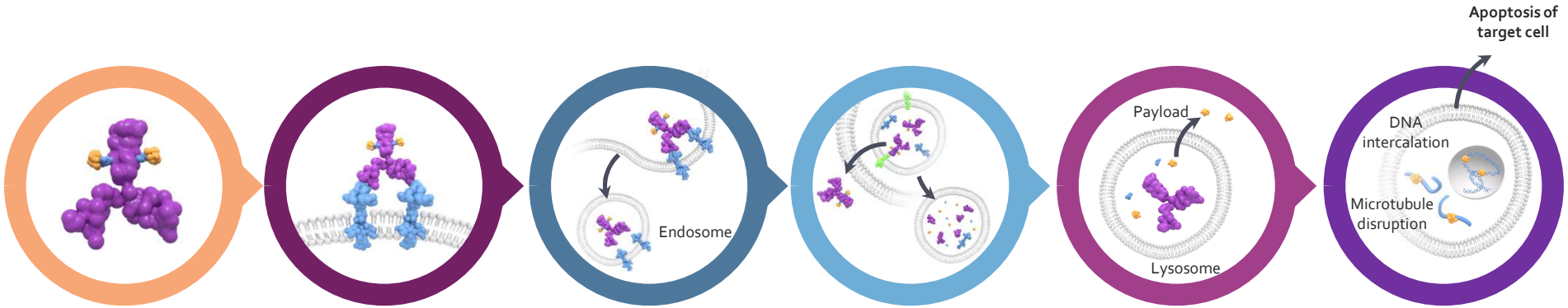
ADC Mechanism of Action[1,2]



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

- 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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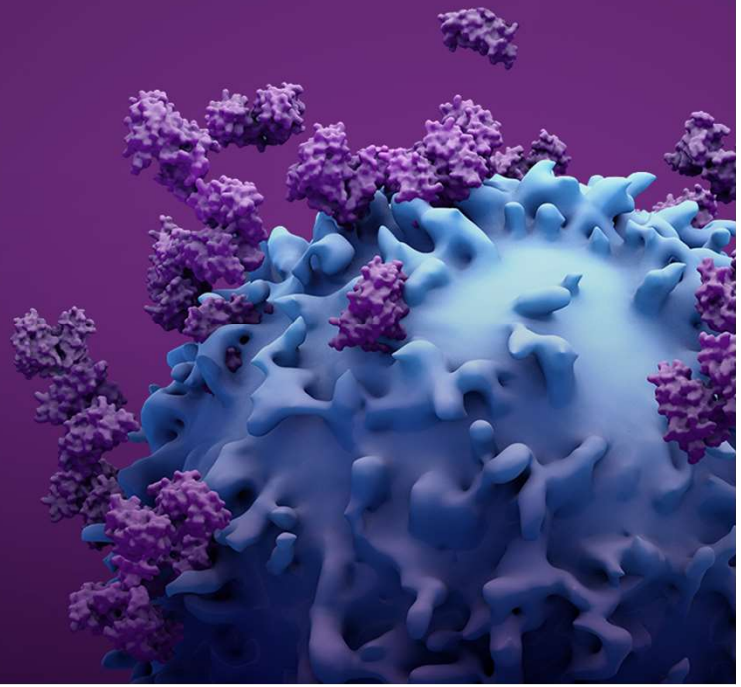
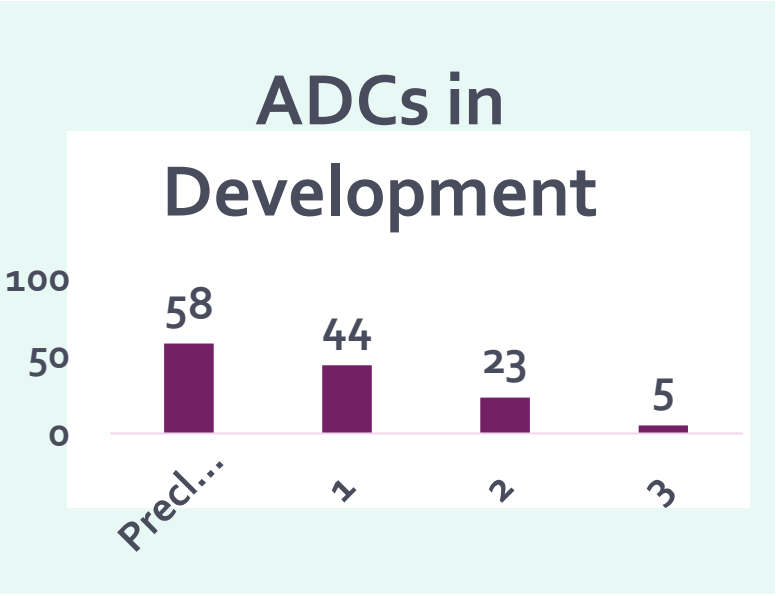
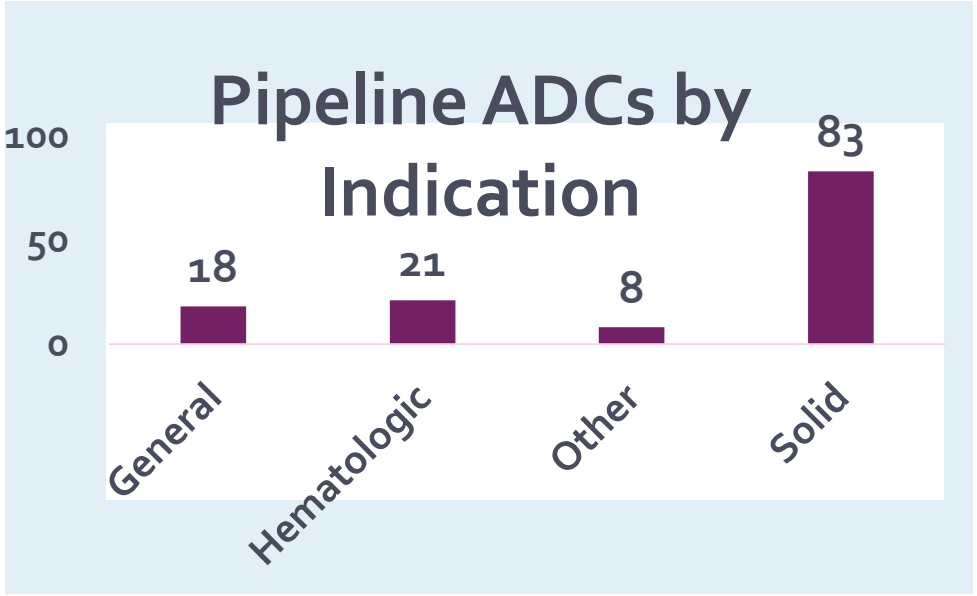
ADCs in Clinical Development



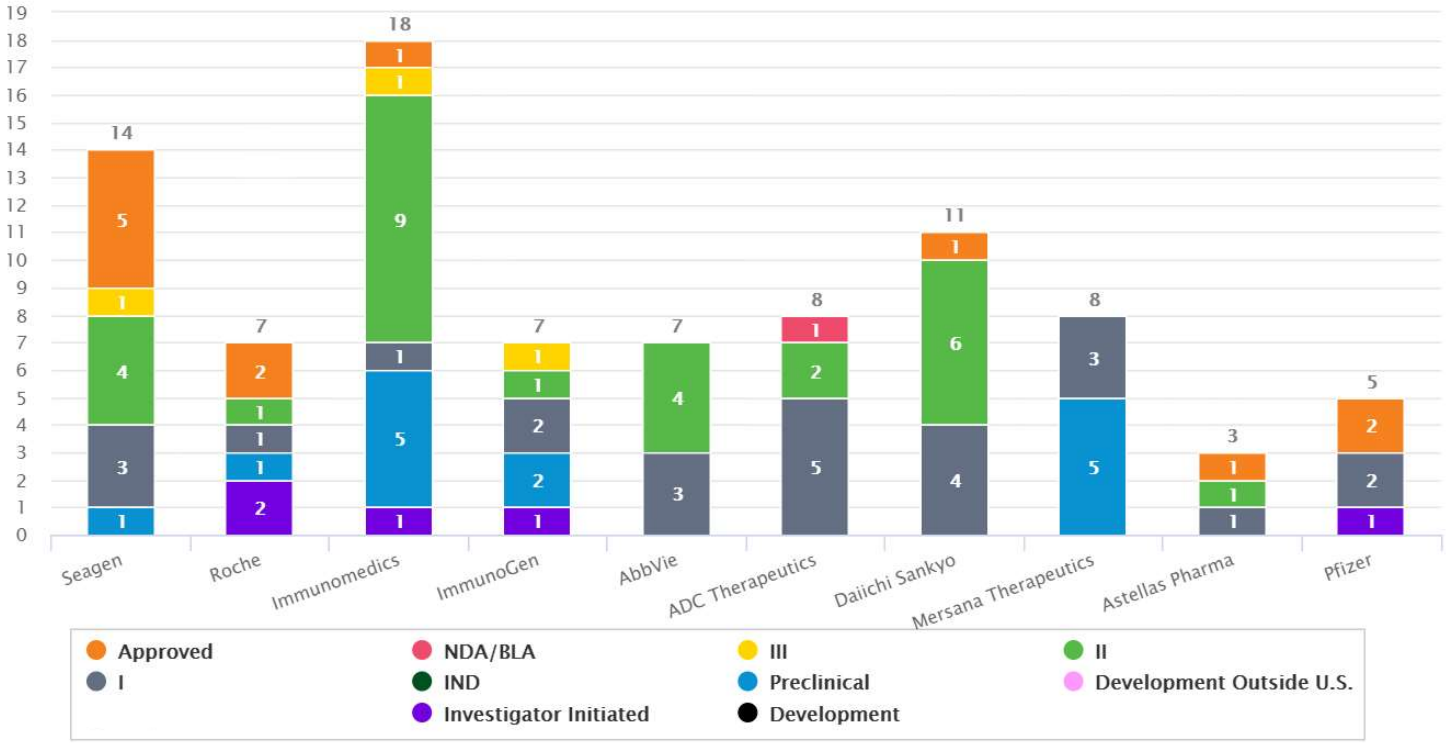
ADCs in Solid Tumors: More to Come





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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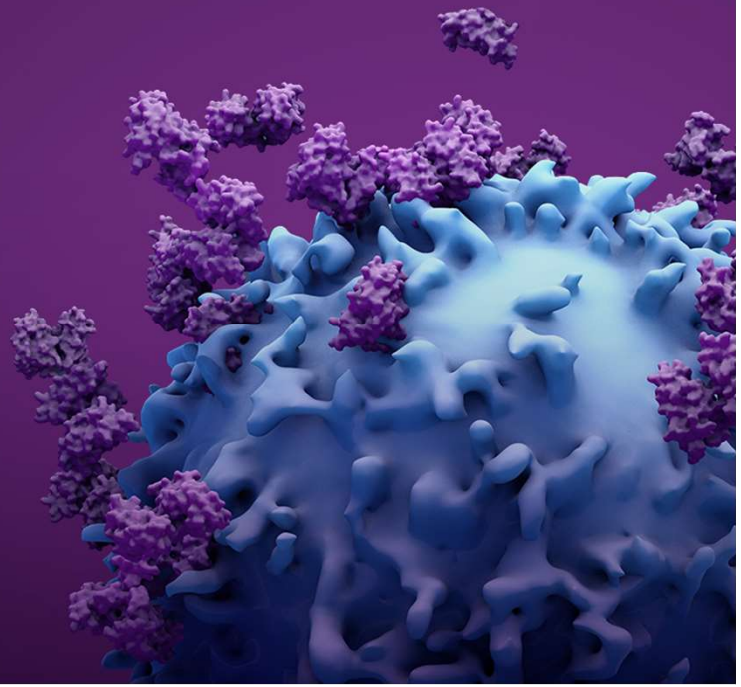
Thank You!



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Disclosures

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Disclosures

Consultant: Amgen; Abbvie; BMS; Genentech/Roche; Merck; AstraZeneca; Takeda; Eisai; Daichii Sankyo; Sanofi

Grant: Tesaro; Merck; AstraZeneca; Advaxis; BMS; Amgen; Takeda

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Disclosures

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Antibody–Drug Conjugates in Development for Non-small Cell Lung Cancer, Gastric Cancer, and Colorectal Cancer

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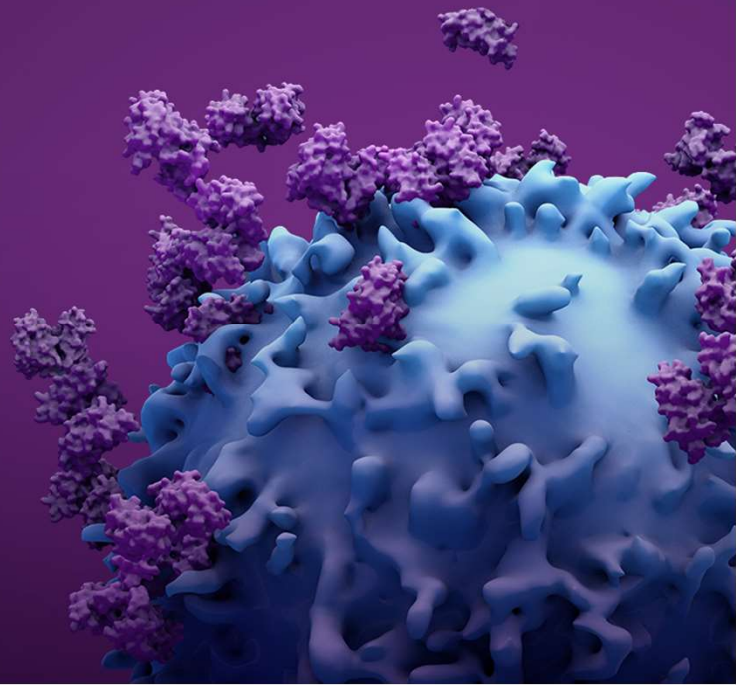

Learning Objectives

- Review ADCs in development for NSCLC, GI cancers, and CRC
  - Analyze the unmet need in patients with these NSCLC, GI cancers, and CRC
  - Discuss their mechanisms of action
  - Analyze available clinical data and discuss ongoing clinical trials

ADC, antibody–drug conjugate; CRC, colorectal cancer; GI, gastrointestinal; NSCLC, non-small cell lung cancer.

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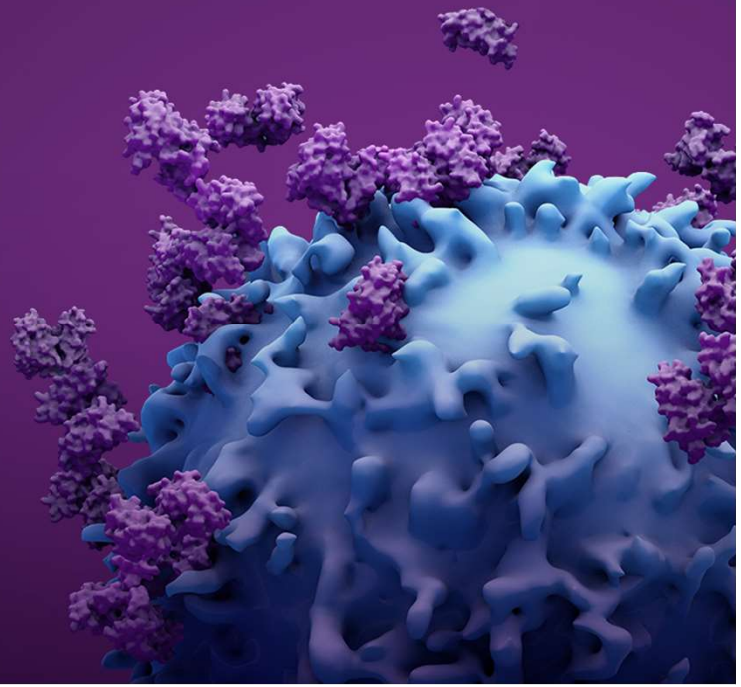
ADCs in NSCLC



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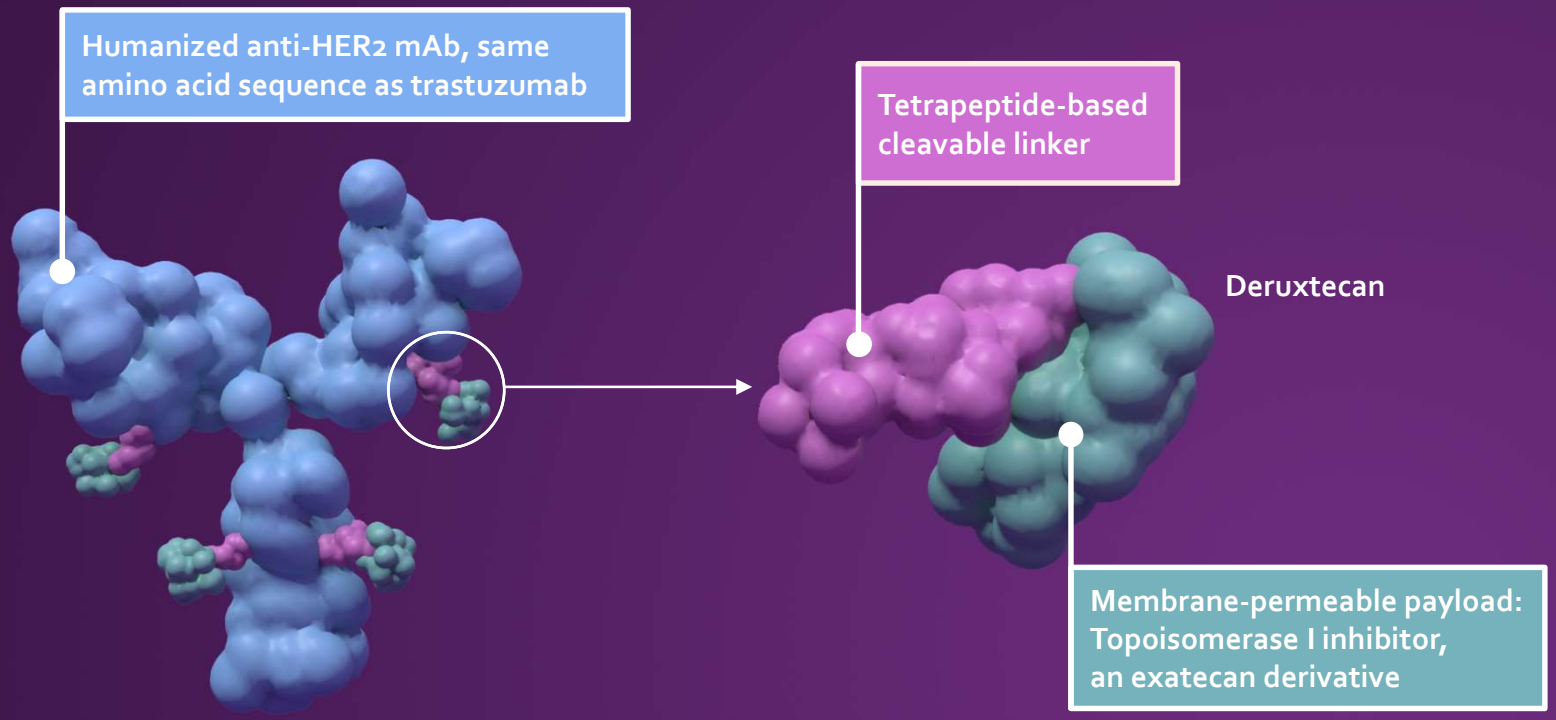
Trastuzumab Deruxtecan (T-DXd)



mAB, monoclonal antibody.

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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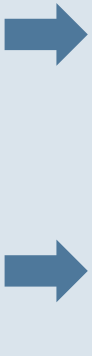
DESTINY-Lung01: Phase 2, Multicenter, Open-Label, 2-Cohort Non-Randomized Study of T-DXd for HER2-Overexpressing or HER2-Mutated NSCLC[1,2]

PATIENTS

- Unresectable and/or metastatic NSQ NSCLC
- Relapsed/refractory to standard treatment
- Measurable disease by RECIST v1.1
- ECOG PS of 0 or 1
- HER2-expressing or HER2-activating mutation
- No prior HER2-targeted therapy, except pan-HER TKIs

STUDY DESIGN



Cohort 1: (n = 49)
HER2-overexpressing
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg Q3W

Cohort 1a: (n = 41)
HER2-overexpressing
(IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg Q3W

Cohort 2: (n = 42)
HER2-mutated
T-DXd 6.4 mg/kg Q3W

Cohort 2: (n = 49)
HER2-mutated
T-DXd 6.4 mg/kg Q3W

ENDPOINTS

1°

ORR

Select 2°

- DOR
- PFS
- OS
- DCR
- Safety and tolerability

IHC, immunohistochemistry; NSQ, nonsquamous; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1;ECOG PS, Eastern Cooperative Oncology Group performance status.

1. 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, 2020. Accessed November 6, 2020. https://meetinglibrary.asco.org/session/12667. 2. US National Library of Medicine, Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03505710. Accessed November 8, 2020. 3. Nakagawa K, et al. Trastuzumab deruxtecan in HER2-overexpressing metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01. Presented at: World Conference on Lung Cancer Singapore; January 2021.

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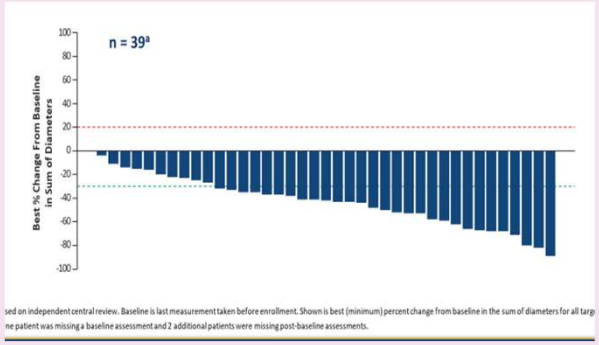
T-DXd Demonstrated a High ORR and a Durable Response in Patients With HER2-Mutated NSCLC

ANTITUMOR ACTIVITY

	Patients (n=42)
Confirmed ORR by ICR	**61.9% (n=26)** (95% CI, 45.6%-76.4%)
CR	2.4% (n=1)
PR	59.5% (n=25)
SD	28.6% (n=12)
PD	4.8% (n=2)
Not evaluable	4.8% (n=2)
DCR	90.5% (95% CI, 77.4%-97.3%)
DOR, medium	Not reached (95% CI, 5.3 months-NE)
PFS, median	14.0 mo (95% CI, 6.4-14.0 months)

Best Change in Tumor Size



SAFETY RESULTS

- The safety was consistent with the ph 1 trial and expansion in mTNBC
- Febrile neutropenia in 2 patients was the major gr 3 or 4 treatment-related SAE, but it was manageable
- A low frequency (7%) of grade ≥3 diarrhea was observed
- Discontinuation of treatment because of TRAEs occurred in 2 patients (4%)
- No treatment-related deaths occurred
- 49% of patients experienced a modest 25% dose reduction

CI, confidence interval; CR, complete response; DCR, disease control rate; gr, grade; ICR, Independent Central Review; mo, month; mTNBC, metastatic triple-negative breast cancer; PD, progression of disease; ph, phase; PR, partial response; SAE, serious adverse event; SD, standard deviation; TRAE, treatment-related adverse event;.

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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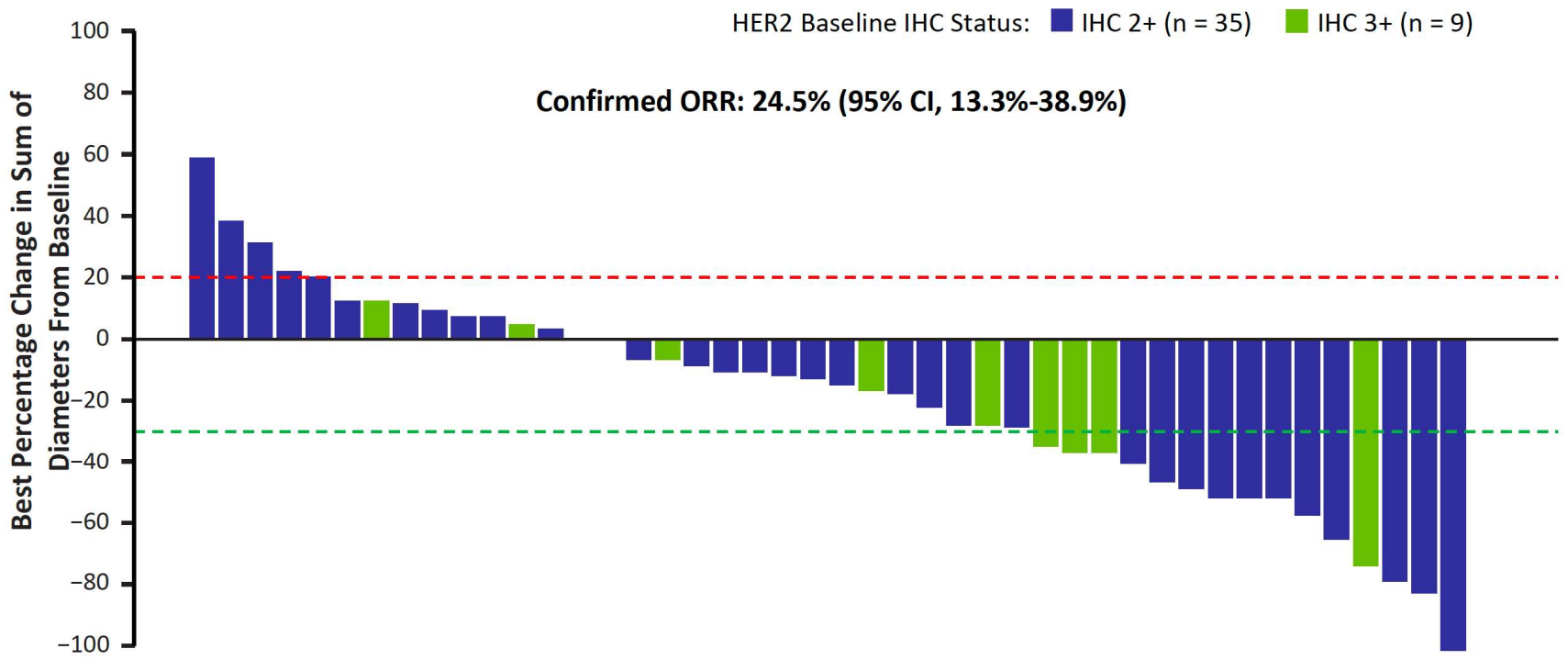
Efficacy in HER2–Overexpressing NSCLC



Nakagawa K, et al. Trastuzumab deruxtecan in HER2-overexpressing metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01. Presented at: World Conference on Lung Cancer Singapore; January 2021.

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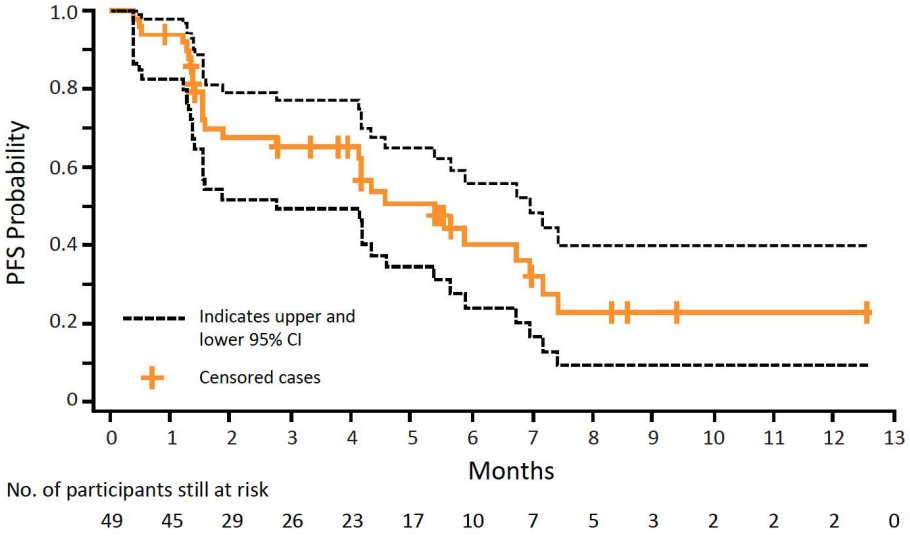
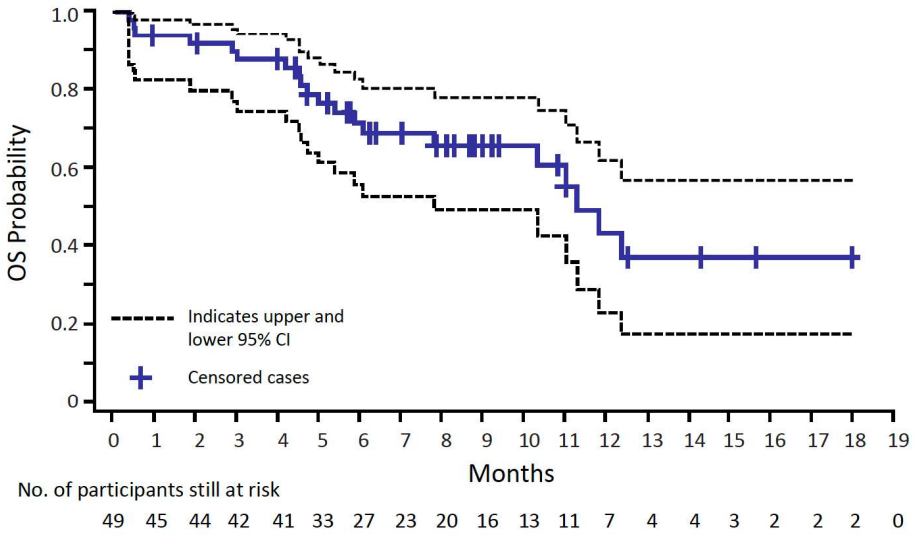
Efficacy in HER2–Overexpressing NSCLC (Continued)

PFS (N = 49)
Median: 5.4 months (95% CI, 2.8-7.0 months)



OS (N = 49)
Median: 11.3 months (95% CI, 7.8-NE)



Progressive disease was assessed by ICR using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). The median was based on Kaplan-Meier estimate; 95% CI for the median was computed using the Brookmeyer-Crowley method.

Median follow-up was 6.1 months (range, 0.4-18.0 months). Full analysis set data are shown.

Nakagawa K, et al. Trastuzumab deruxtecan in HER2-overexpressing metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01. Presented at: World Conference on Lung Cancer Singapore; January 2021.

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Notable T-DXd Toxicity: ILD

All Patients (N = 49)						
N (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/Total
Adjudicated drug-related ILD[a]	2 (4.1%)	3 (6.1%)	0	0	3 (6.1%)	8 (16.3%)

Adjudicated drug-related ILD[b]

- Median time to onset: 64.5 days (range, 2-126)
- All patients had drug withdrawn
- Steroid treatment was used in patients who had grade 2 (n = 3) and those who had grade 5 ILD (n = 3)
- 3 patients recovered (grade 1 [n = 1] and grade 2 [n = 2]) and 2 patients had not recovered by data cutoff (grade 1 [n = 1] and grade 2 [n = 1])
- 4 of 8 patients had immune checkpoint inhibitors included in their prior lines of therapy

Grade 5 ILD[c] events

- Medical history of the 3 patients included
  1. Pulmonary embolism, productive cough, dyspnea, pleural effusion, and lobectomy; 4 prior lines of therapy
  2. Cough, dyspnea, pleural effusion, and pulmonary embolism; 5 prior lines of therapy
  3. Dyspnea, SLE without lung involvement, and TTP; 1 prior line of therapy
- Steroid treatment was initiated within 5 days after the event was reported by the investigator[d]
- All had previously received immune checkpoint inhibitors
- Primary cause of death was PD in 2 patients and pneumonitis in 1 patient

SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura. [a]Drug-related ILD was determined by an independent ILD adjudication committee based on 44 preferred terms. [b]All potential cases of ILD that occurred before the data cutoff were adjudicated. [c]The 3 cases of grade 5 ILD were initially reported by the investigator as grade 4 pneumonitis and grade 4 respiratory failure (n = 1), grade 4 respiratory failure (n = 1), and grade 5 pneumonitis (n = 1). [d]Steroid treatment was initiated 2 days later for case 1, 5 days later for case 2, and on the same day for case 3. Safety analysis set data are shown.

Nakagawa K, et al. Trastuzumab deruxtecan in HER2-overexpressing metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01. Presented at: World Conference on Lung Cancer Singapore; January 2021.

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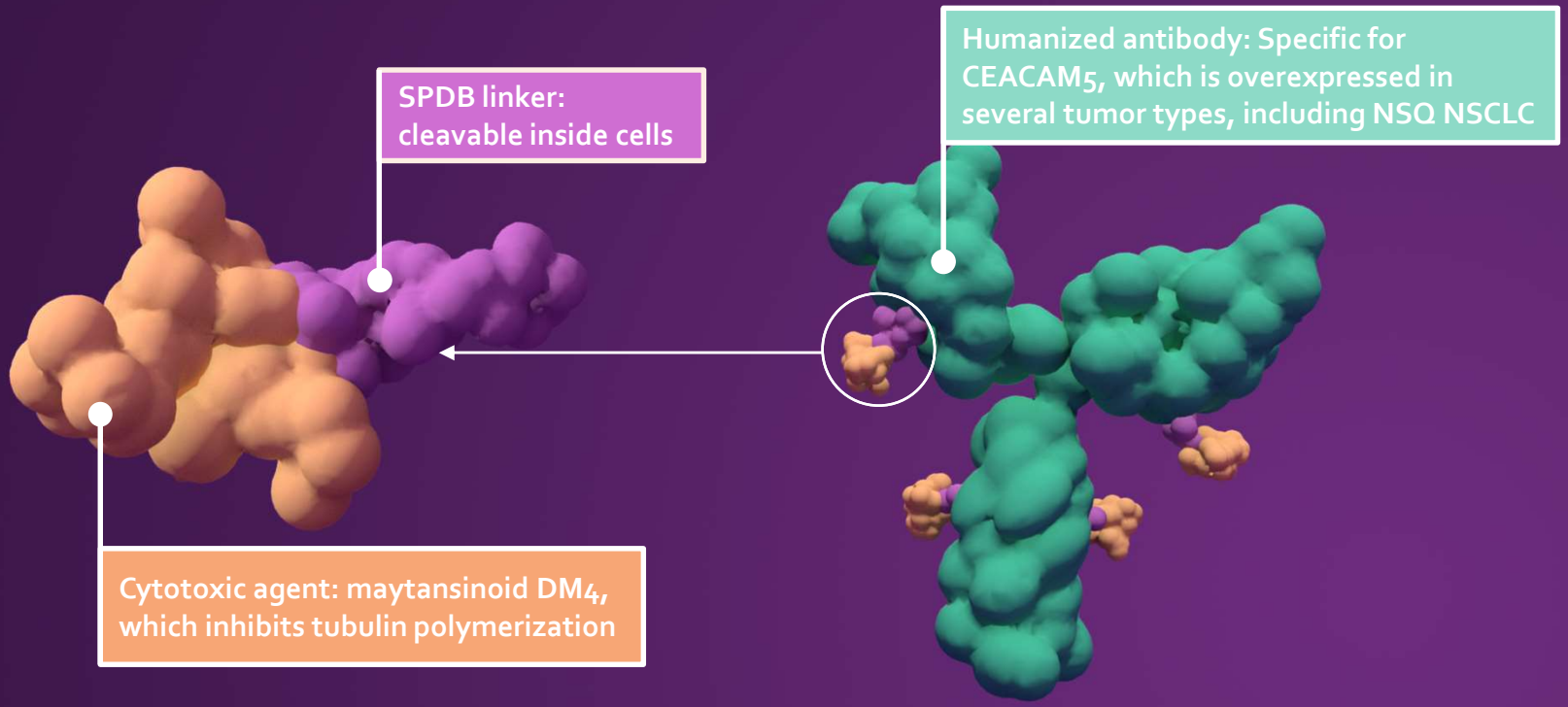
SAR408701



Gazzah A et al. Efficacy and safety of the antibody-drug conjugate (ADC) SAR408701 in patients (pts) with non-squamous non-small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). Presented at: American Society for Clinical Oncology 2020 Virtual Scientific Program; May 29 – 31. Accessed November 8, 2020. https://meetinglibrary.asco.org/record/187279/abstract.

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TED13751: Phase 1/2, Non-Randomized, Parallel Assignment Study Evaluation of SAR408701 in Patients With Advanced Solid Tumors[1,2]

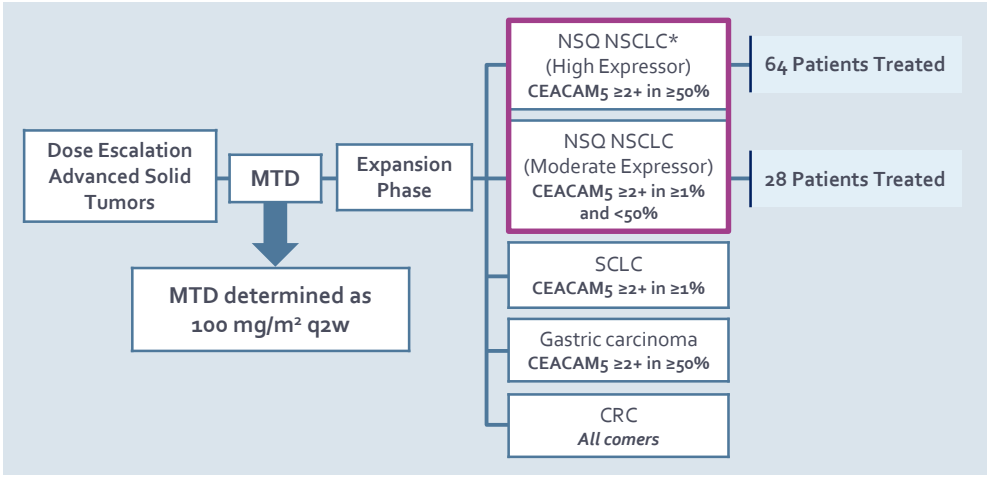
First-in-Human Study Evaluating the Safety, PK, and Antitumor Activity of SAR408701 in Pts With Advanced Solid Tumors

PATIENTS

Adults with locally advanced/metastatic solid malignant tumors for which no standard alternative therapy was available.

- **Dose Escalation Cohorts**: pts with tumors expressing/likely expressing CEACAM5 (eg, CRC, NSQ NSCLC, and gastric adenocarcinoma)
- **Expansion Phase cohorts**: pts with CRC or CEACAM5+ NSQ NSCLC, SCLC, or gastric carcinoma
  - High expression cohort: CEACAM5 ≥50% at ≥2+ intensity (20% of NSQ NSCLC)
  - Moderate expression cohort: CEACAM5 between ≥1% and <50% at ≥2+ intensity (24% of NSQ NSCLC)

STUDY DESIGN



ENDPOINTS

1°

- DLT (escalation phase)
- ORR (expansion phase)

Select 2°

- Safety
- DOR

MTD, maximum tolerated dose; PK, pharmacokinetics; pts, patients; Q2W, every 2 weeks; SCLC, small cell lung cancer.

1. Gazzah A et al. Efficacy and safety of the antibody-drug conjugate (ADC) SAR408701 in patients (pts) with non-squamous non-small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). Presented at: American Society for Clinical Oncology 2020 Virtual Scientific Program; May 29 – 31. Accessed November 8, 2020. https://meetinglibrary.asco.org/record/187279/abstract; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT02187848. Accessed: November 8, 2020. Last updated: April 30, 2020.

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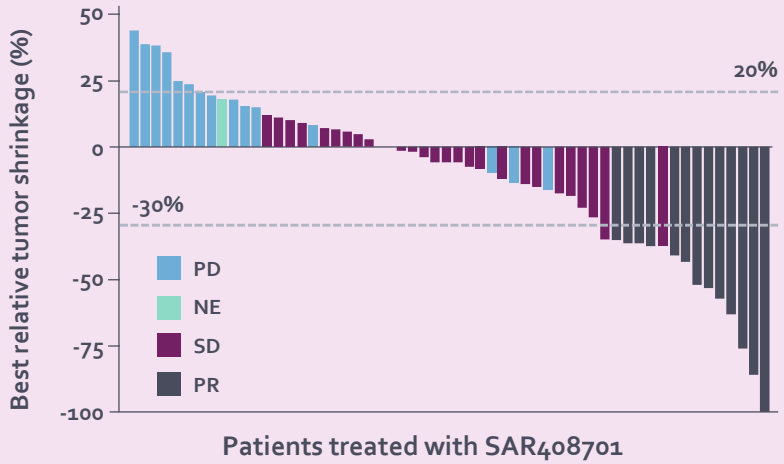
SAR408701 Was Well Tolerated, Showed Promising Antitumor Activity in Patients With Heavily Pretreated, Advanced NSQ NSCLC With High CEACAM5 Expression

ANTITUMOR ACTIVITY

Overall Population

Response, n (%)	High expression (n=64)
ORR	13 (20.3%) [12.27-31.71]
Confirmed PR	13 (20.3%)
SD	28 (43.8%)
DCR	41 (64.1%)
PD	21 (32.8%)

Best Relative Tumor Shrinkage – High Expressor Cohort



SAFETY RESULTS

- Most common TEAEs grade ≥3 were keratopathy/keratitis (10.9%) and dyspnea (10.9%)
- A total of 25 (27.2%) pts had corneal TEAEs leading to dose modification, and 1 pt discontinued treatment
- Ocular events are manageable with dose delay or reduction; primary prophylaxis was not effective

TEAE, treatment-emergent adverse event.

Gazzah A et al. Efficacy and safety of the antibody-drug conjugate (ADC) SAR408701 in patients (pts) with non-squamous non-small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). Presented at: American Society for Clinical Oncology 2020 Virtual Scientific Program; May 29 – 31. Accessed November 8, 2020. https://meetinglibrary.asco.org/record/187279/abstract.

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Ongoing Clinical Studies With SAR408701

	Ph	Patients	N	Arms	1° EP	Est Study Completion
CARMEN-LC04 (NCT04394624)[1]	**2**	• Metastatic NSQ NSCLC • CEACAM5 expression confirmed via IHC • After 1 prior line of chemo in a metastatic setting or metastatic disease during/within 6 mo of (neo)adjuvant treatment • After/during Pt-based chemo and 1 ICI	**36**	Single arm; IV SAR408701 + IV ramucirumab	DLT	03/2022
CARMEN-LC03 (NCT04154956)[2]	**3**	• Adults with histologically or cytologically proven metastatic NSQ NSCLC • Progression after Pt-based chemo and ICI • CEACAM5 expression confirmed via IHC	**554**	Randomized; SAR408701 vs docetaxel	PFS, OS	03/2024

Regulatory application for 2L or greater treatment of NSCLC is expected in 2022.

2L, second line; ICI, immune checkpoint inhibitor; IV, intravenous; Pt, platinum.

1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04394624. Accessed: November 8, 2020. Last updated: October 28, 2020;
2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04154956. Accessed: November 8, 2020. Last updated: October 28, 2020.

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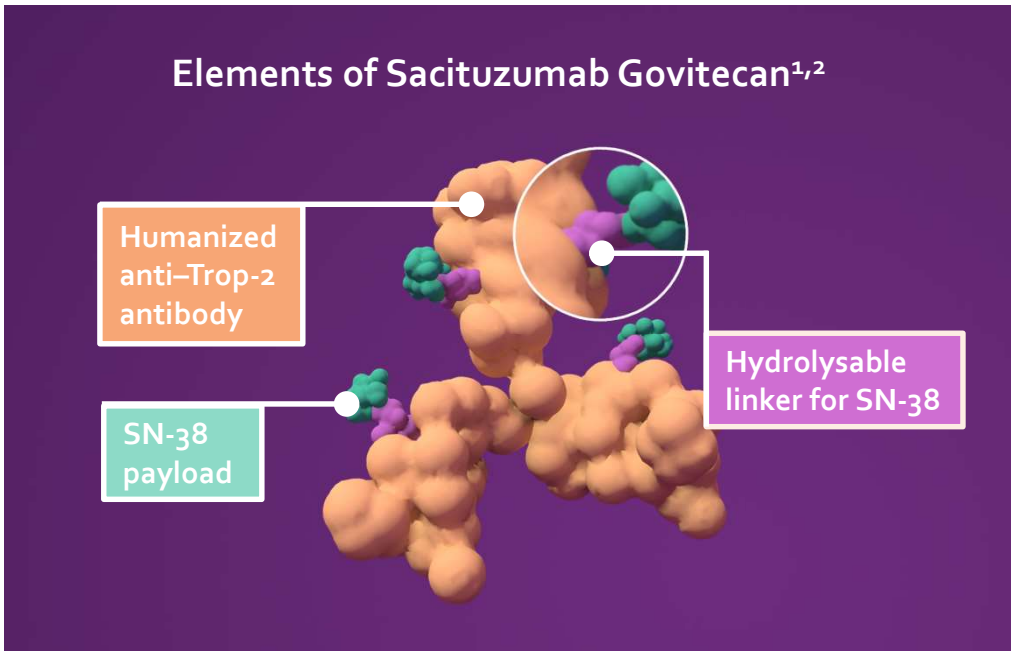

- SN-38 is the active metabolite of irinotecan, a topoisomerase I inhibitor that interferes with cell growth and spread[1]
- Sacituzumab govitecan delivers ≤136x more SN-38 than irinotecan[2]
- Inhibition of topoisomerase I by SN-38 leads to apoptosis[1]

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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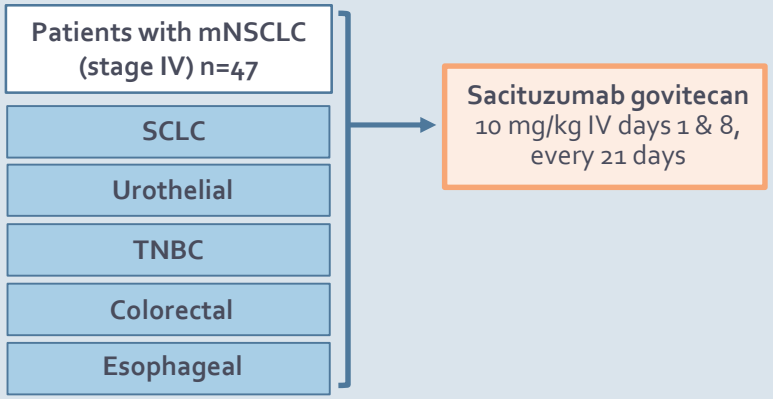
Phase 1/2 Open-Label, Basket-Design, Single-Arm, Multicenter Study of Sacituzumab Govitecan in Patients With Epithelial Cancers[1-3]

PATIENTS

Basket Trial
Patients with relapsed/refractory metastatic epithelial cancer who received ≥1 standard therapeutic regimen

STUDY DESIGN



ENDPOINTS

1°

- ORR

Select 2°

- DOR
- PFS
- OS

Anticipated Study Completion: 08/2020

mNSCLC, metastatic non-small cell lung cancer;

1. Heist RS et al. *J Clin Oncol*. 2017;35(24):2790-2797; 2. Goldenberg DM et al. *Oncotarget*. 2015;6(26):22496–22512; 3. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT01631552. Accessed: November 8, 2020. Last updated: September 9, 2020.

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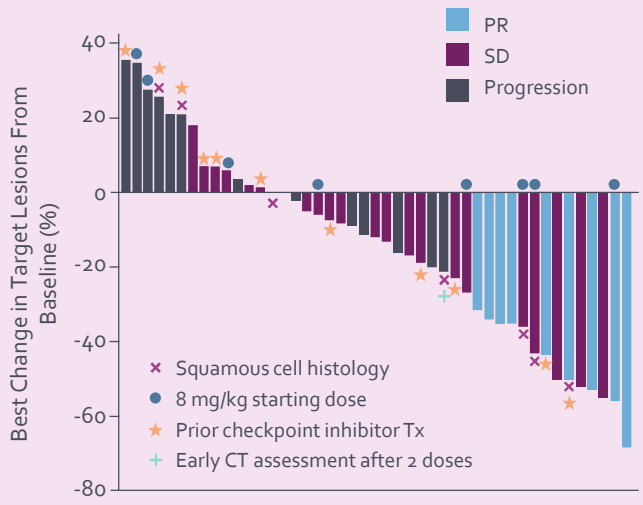
Sacituzumab Govitecan Is Therapeutically Active in Patients With Diverse Metastatic Epithelial Tumors, With Manageable Neutropenia as the Major Toxicity[1,2]

ANTITUMOR ACTIVITY



Response	No. (%)
All patients	
Best overall response (n=47)	
PR	9 (19)
SD	23 (49)
PD	15 (32)
Objective response duration, months	
Median (95% CI)	6.0 (4.8 to 8.3)
Clinical benefit (PR + SD ≥ 4 months)	20 (43)
PFS (n=54), months	
Median (95% CI)	5.2 (3.2 to 7.1)
OS (n=54), months	
Median (95% CI)	9.5 (5.9 to 16.7)

SAFETY RESULTS

- The safety was consistent with the ph 1 trial and expansion in mTNBC
- Febrile neutropenia in 2 patients was the major grade 3 or 4 treatment-related SAE, but it was manageable
- A low frequency (7%) of grade ≥3 diarrhea was observed
- Discontinuation of treatment because of TRAEs occurred in 2 patients (4%)
- No treatment-related deaths occurred
- 49% of patients experienced a modest 25% dose reduction

CT, computed tomography; Tx, treatment.

1. Heist RS et al. *J Clin Oncol*. 2017;35(24):2790-2797; 2. Goldenberg DM et al. *Oncotarget*. 2015;6(26):22496–22512.

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Ongoing Studies With Sacituzumab Govitecan

	Ph	Patients	N	Arms	1° EP	Est Study Completion
Morpheus Lung (NCT03337698)	**1/2**	• 1L cohort: pts who have not received any systemic therapy for their disease • 2L cohort consists of pts who progressed during/after Pt-containing regimen + ICI	**380**	• Randomized; multiple immunotherapy-based treatment combinations	ORR	04/2022

1L, first line.

U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03337698. Accessed: November 8, 2020. Last updated: September 2, 2020.

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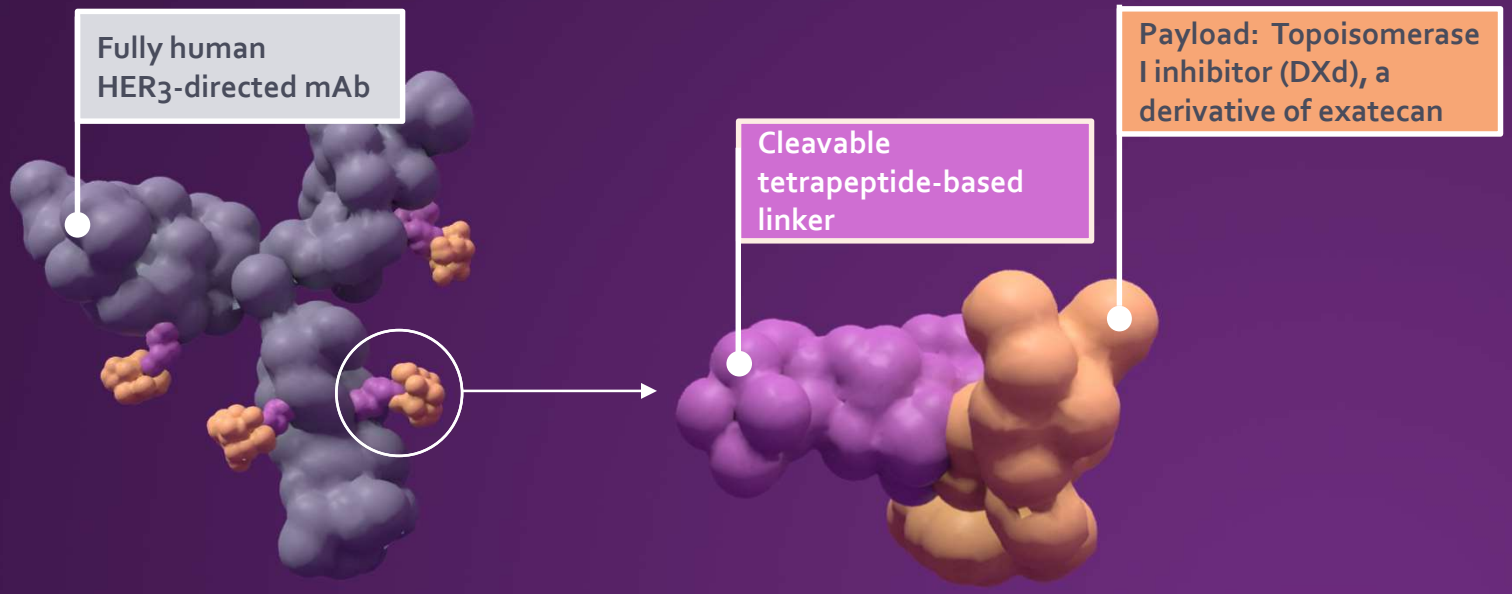
Patritumab Deruxtecan (U3-1402)[1,2]



57%–67% of EGFR-mutant NSCLCs show some level of HER3 expression[3,4]

Drug-to-antibody ratio: 8

EGFR, epidermal growth factor receptor.

1. Duma N et al. *Mayo Clin Proc*. 2019;94(8):1623-1640; 2. Tan CS et al. *Mol Cancer*. 2018;17:29; 3. Yi, et al. *Mod Pathol*. 1997;10:142-148; 4. Kawano, et al. J Surg Res. 2008;146:43-48.

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Phase 1: Preliminary Phase 1 Dose Expansion Data of Patritumab Deruxtecan in Patients With EGFR-Mutated NSCLC[1-5]

STUDY DESIGN

Dose Escalation

*Metastatic/unresectable **EGFR-mutated NSCLC** either after progression on osimertinib or T790M-negative after progression on erlotinib, gefitinib, or afatinib*

Patritumab deruxtecan 5.6 mg/kg Q3W
N = 12

Dose Expansion Cohort 1

Metastatic/unresectable **EGFR-mutated NSCLC** and treatment with ≥1 EGFR TKI and ≥ 1 prior platinum-based chemotherapy regimen

Patritumab deruxtecan 5.6 mg/kg Q3W
n = 45

Primary Objective: Antitumor activity of patritumab deruxtecan

Secondary Objectives: Safety and tolerability of patritumab deruxtecan

ANTITUMOR ACTIVITY

Summary or Results	
Efficacy Measure	Total Evaluable in Cohort 1 (n=56)
Confirmed ORR (%) (95% CI %)	25% (14.4-38.4)
CR	2%
PR	23%
SD	45%
PD	16%
NE	14%
DCR (%) (95% CI)	70% (55.9-81.2)
Median DOR (95% CI) (months)	6.9 months (3.0-7.0)

SAFETY RESULTS

- Most common gr >3 TEAEs were thrombocytopenia and neutropenia
- TEAEs associated with treatment discontinuation (9%) include fatigue, decreased appetite, ILD, pneumonia, and URTI
  - No discontinuations due to thrombocytopenia or neutropenia
- 3 ILD events were related to treatment
- No TEAEs associated with death

Phase 1 study completion expected 12/2023
Global phase 2 study evaluating patritumab deruxtecan in similar patient population is planned

gr, grade; ILD, interstitial lung disease; CR, confirmed response; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PR, partial response; Q3W, every 3 weeks; URTI, upper respiratory tract infection.

1. Daiichi-Sankyo Media press release. Accessed November 8, 2020. https://www.daiichisankyo.com/media/press_release/detail/index_4072.html. 2. Yu H, et al. Efficacy and safety of patritumab deruxtecan (U3-1402), a novel HER3 directed antibody drug conjugate, in patients (pts) with EGFR-mutated (EGFRm) NSCLC. Presented at: European Society for Medical Oncology 2020 Virtual Scientific Program; September 18, 2020. Accessed November 8, 2020. https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/efficacy-and-safety-of-patritumab-deruxtecan-u3-1402-a-novel-her3-directed-antibody-drug-conjugate-in-patients-pts-with-egfr-mutated-egfrm. 3. US National Library of Medicine, Clinicaltrials.gov. Accessed November 8, 2020. https://clinicaltrials.gov/ct2/show/NCT03260491?term=U3-1402&draw=2&rank=2. 4. Jänne P, et al. Dynamics of molecular markers in EGFR-mutated NSCLC patients treated with patritumab deruxtecan (HER3-DXd; U3-1402). Presented at: 2020 World Conference on Lung Cancer Singapore; January 2021. 5. Yu H, et al. Efficacy and safety of the novel HER3 directed antibody drug conjugate patritumab deruxtecan (HER3-DXd; U3-1402) in EGFR-mutated NSCLC. Presented at: 2020 World Conference on Lung Cancer Singapore; January 2021.

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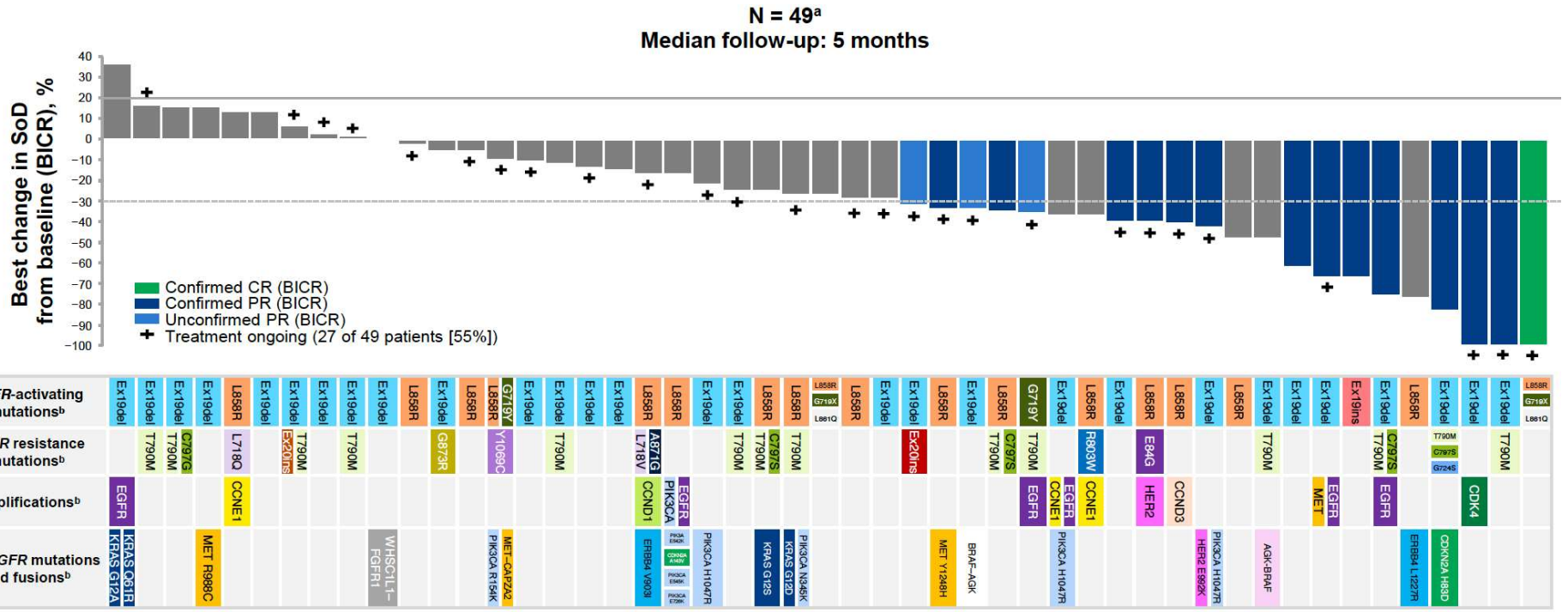
Efficacy in EGFR^{MT} NSCLC



BICR, blinded independent central review; cfDNA, circulating free DNA; SoD, sum of diameters.

[a]This analysis does not include 7 patients (out of 56) without postbaseline tumor assessments by the data cutoff date. [b]Performed centrally using Oncomine TM Comprehensive Assay v3 from pretreatment tumor tissue. Results from local testing are included for patients when tissue was unavailable for central analysis. Additional mutations detected using GuardantOMNI™ assay from cfDNA in blood collected prior to treatment with HER3-DXd are included. For cfDNA analysis, a minor allelic frequency of 0.5% was used as a threshold for inclusion of mutations. The copy number data from cfDNA are not shown.

Jänne P, et al. Dynamics of molecular markers in EGFR-mutated NSCLC patients treated with patritumab deruxtecan (HER3-DXd; U3-1402). Presented at: 2020 World Conference on Lung Cancer Singapore; January 2021.

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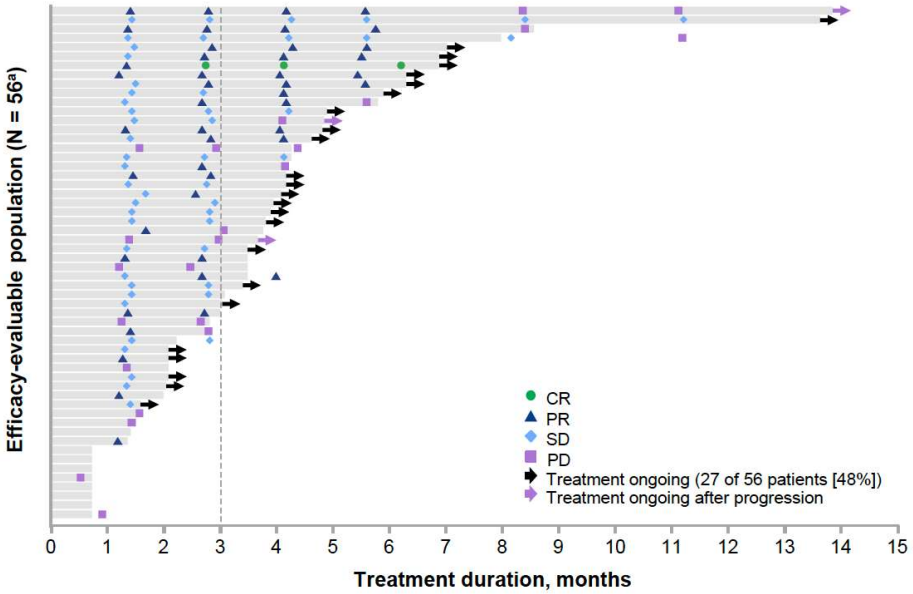
Response Characteristics



Activity according to BICR evaluation (efficacy-evaluable population) N = 56[a]	
Confirmed BOR, n/N (%)	
CR	1/56 (2%)
PR	13/56 (23%)
SD	25/56 (45%)
PD	9/56 (16%)
NE	8/56 (14%)
Confirmed ORR, % (n/N; 95% CI)	25% (14/56; 14.4-38.4)
DCR, % (n/N; 95% CI)	70% (39/56; 55.9-81.2)
Median TTR, months (range)	2.0 (1.2-2.8)
Median DOR, months (range)	6.9 (3.0-7.0)

BOR, Best Overall Response.

[a]Of 56 patients, 22 (39%) had best percentage decrease in sum of tumor diameters ≥ 30%.

Yu H, et al. Efficacy and safety of the novel HER3 directed antibody drug conjugate patritumab deruxtecan (HER3-DXd; U3-1402) in EGFR-mutated NSCLC. Presented at: 2020 World Conference on Lung Cancer Singapore; January 2021.

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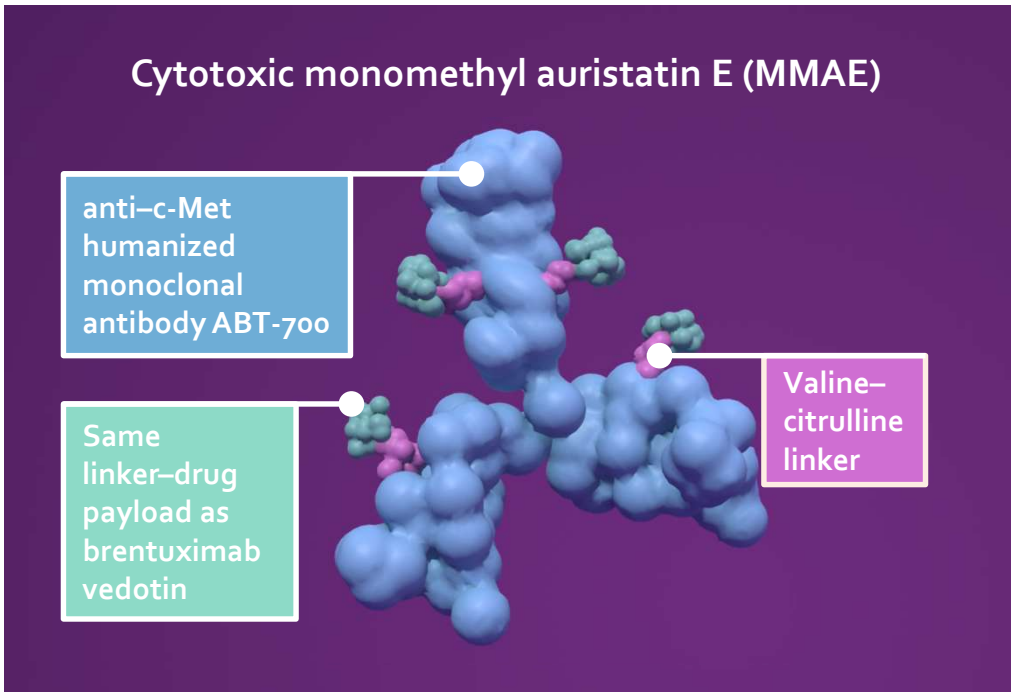
Patritumab Deruxtecan: Safety Profile

TEAEs in ≥ 20% of patients, n (%)	N = 57	
	All grades	Grade ≥3
Fatigue	33 (58)	5 (9)
Nausea	31 (54)	2 (4)
Thrombocytopenia[a]	30 (53)	16 (28)
Decreased appetite	20 (35)	1 (2)
Neutropenia[b]	19 (33)	11 (19)
Vomiting	17 (30)	1 (2)
Alopecia	12 (30)	NA
Anemia[c]	15 (26)	5 (9)
Constipation	14 (25)	0

[a]Thrombocytopenia includes platelet count decreased and thrombocytopenia. [b]Neutropenia includes neutrophil count decreased and neutropenia. [c]Anemia includes hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased.

Yu H, et al. Efficacy and safety of the novel HER3 directed antibody drug conjugate patritumab deruxtecan (HER3-DXd; U3-1402) in EGFR-mutated NSCLC. Presented at: 2020 World Conference on Lung Cancer Singapore; January 2021.



- **MET amplification** is a therapeutically actionable target generally occurring in < 1% to 5% of de novo cancers. **c-Met overexpression** is more common, occurring in ≤50% of many advanced solid tumors
- MMAE binds to tubulin, thereby inhibiting mitosis and causing tumor cell death
- c-Met is a receptor tyrosine kinase expressed on the surface of epithelial and endothelial cells
- c-Met signaling dysregulation is associated with oncogenic transformation and resistance to chemotherapy and radiotherapy and correlates with poor prognosis

Telisotuzumab Vedotin (ABBV-399) is an ADC Targeting cMet Under Investigation to Treat NSCLC

Strickler JH et al. *J Clin Oncol.* 2018;26(33):3298-3306.

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Phase 1 Open-Label, Dose-Escalation Study: Telisotuzumab Vedotin + Erlotinib Demonstrated Acceptable Safety and Promising Activity in Pts With *EGFR*m c-Met+ NSCLC Who Failed Frontline EGFR TKI[1,2]

STUDY DESIGN

Patients with *EGFR*m c-Met+ NSCLC Who Failed Frontline EGFR TKI

Experimental arm A: Telisotuzumab vedotin + erlotinib

ANTITUMOR ACTIVITY

	*EGFR*m (n=29)	*EGFR* non-m+ (n=7)
ORR, % (95% CI)	34.5 (17.9, 54.3)	28.6 (3.7, 71.0)
CR, n	1	0
mDOR, mo (95% CI)	NR	NR
	(2.8, NE)	(NR, NE)
mPFS, mo (95% CI)	NR	5.9
	(2.8, NE)	(1.2, NE)
Median follow-up, mo	4	6
6-mo PFS rate (95% CI)	0.51 (0.30, 0.69)	0.43 (0.10, 0.73)

SAFETY RESULTS

- All-grade (gr; ≥20%) AEs were
  - Dermatitis acneiform (38%)
  - Diarrhea (36%)
  - Peripheral motor/sensory neuropathy (52%; 7% gr 3)
  - Dyspnea, fatigue, hypoalbuminemia (31% each)
  - Decreased appetite, nausea (24% each)
  - Asthenia, vomiting (21% each)
- Gr ≥3 (≥10%) AE: pulmonary embolism (14%)

mDOR, median duration of response; mPFS, median progression-free survival; NE, not estimable; NR, not reached.

1. Camidge DR et al. *J Clin Oncol*. 2019; 37(15):Abstract 3011; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT02099058. Accessed: November 8, 2020. Last updated: October 12, 2020.

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Ongoing Studies With Telisotuzumab Vedotin

	Ph	Patients	N	Arms	1° EP	Est Study Completion
NCT03539536	2	• Locally advanced/metastatic c-Met+ (via IHC) NSQ NSCLC with known EGFR status • Progressed on prior therapy (eg, ICI as monotherapy or in combination with chemo) • ≤2 lines prior chemo in the metastatic setting	310	Single arm; telisotuzumab vedotin	ORR	08/2023

U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03539536. Accessed: November 8, 2020. Last updated: November 6, 2020.

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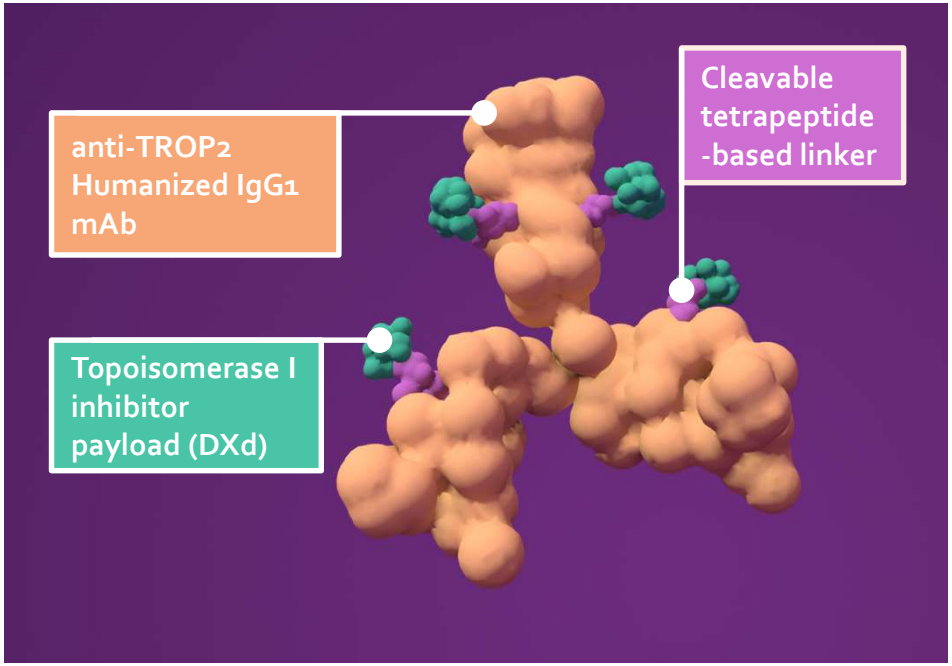
Datopotamab Deruxtecan (Dato-DXd; DS-1062)



- 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

IgG1, immunoglobulin G1; TROP2, 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. Presented at: World Conference on Lung Cancer Singapore; January 2021.

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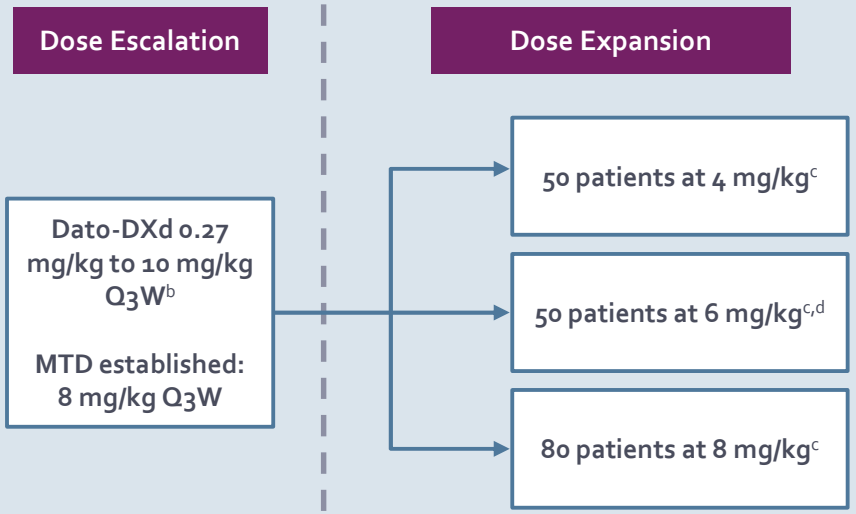
TROPION: First-in-Human Study Design

PATIENTS

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

STUDY DESIGN



ENDPOINTS

1°

- Establish MTD
- Safety
- Tolerability

Select 2°

- C_{max}
- T_{max}
- AUC of DS-1062
- C_{trough}

AUC, area under curve; C_{max}, maximum concentration; MTD, maximum tolerated dose; T_{max}, time to maximum; TNBC, triple-negative breast cancer; US, United States.

[a]Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b]The 4, 6, and 8 mg/kg dose levels are being further evaluated for safety and efficacy. A TNBC cohort is currently open for enrollment at 6 mg/kg, although no TNBC patients are included in this analysis. [c]Inclusive of patients treated in dose escalation and dose expansion. [d]The current analysis includes 45 patients treated at the 6 mg/kg dose (data cutoff: 4 September 2020).

Lisberg AE, et al. Abstract 9619. Presented at: ASCO Annual Meeting; May 29-June 2, 2020; virtual meeting. 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. Presented at: World Conference on Lung Cancer Singapore; January 2021.

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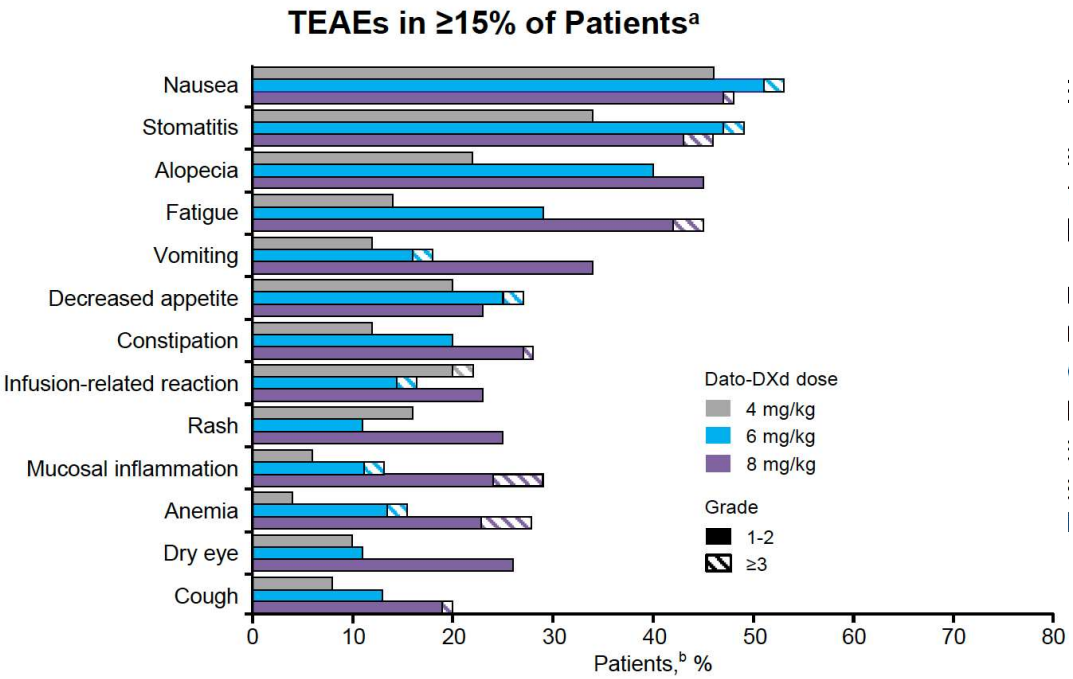
Datopotamab Deruxtecan: Safety Profile



- TEAEs were predominantly nonhematologic
- Rates of grade ≥3 stomatitis and mucosal inflammation were higher with 8 mg/kg vs 4 and 6 mg/kg[c]
- 14 out of 175 patients (8%) had treatment-related ILD as adjudicated by an independent committee[d]
  - 4 mg/kg: 1 patient (grade 3)
  - 6 mg/kg: 1 patient (grade 2)
  - 8 mg/kg: 12 patients (8 patients grade 1-2; 1 patient grade 3; 3 patients grade 5)

Data cutoff: 4 September 2020. Median duration of Dato-DXd exposure (months): 2.09 (0.7-20.0) for 4 mg/kg, 2.07 (0.7-19.7) for 6 mg/kg, 3.33 (0.7-13.5) for 8 mg/kg. [a]Out of 175 patients. [b]Out of 50, 45, and 80 patients treated with 4, 6, or 8 mg/kg, respectively. [c]Grade ≥3 stomatitis: 4 mg/kg, 0%; 6 mg/kg, 2%; 8 mg/kg, 3%. Grade ≥3 mucosal inflammation: 4 mg/kg, 0%; 6 mg/kg, 2%; 8 mg/kg, 5%. [d]Potential ILD occurred on or before data cutoff. Adjudication could have occurred after data cutoff.

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. Presented at: World Conference on Lung Cancer Singapore; January 2021.

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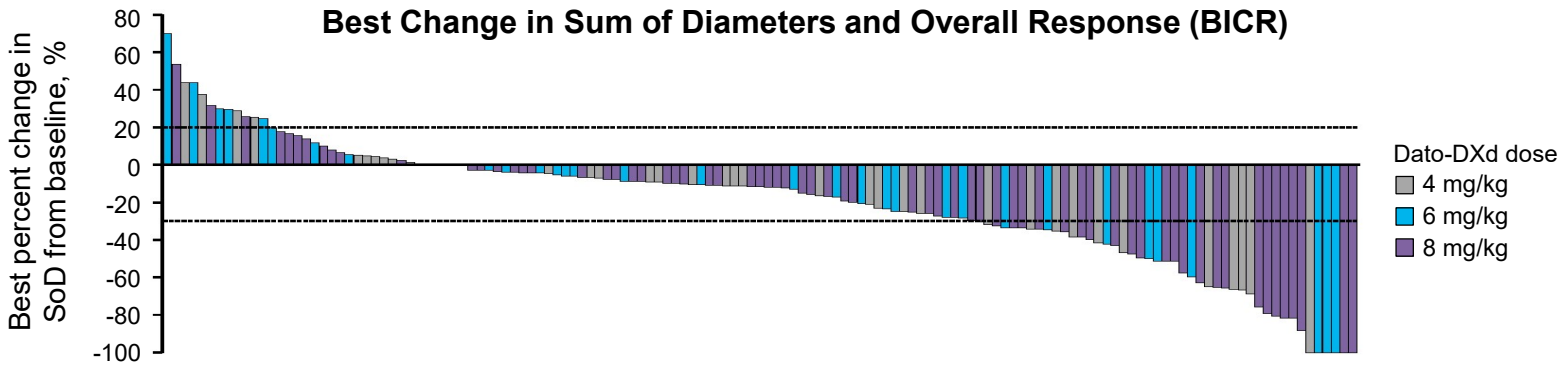
Datopotamab Deruxtecan: Efficacy in NSCLC



Dato-DXd dose	Response-evaluable patients,[a] n	Confirmed CR/PR, [b] n	CR/PR (too early to be confirmed), [b] n	ORR, [b] % (n)	DCR, % (n)	PD, % (n)	Median PFS (95% CI)
4 mg/kg	40	7	2	23 (9)	73 (29)	15 (6)	4.3 months (2.0-NE)
6 mg/kg	39	6	5	51 (8)	67 (26)	21 (8)	8.2 months (1.5-11.8)
8 mg/kg	80	19	1	25 (20)	80 (64)	9 (7)	5.4 months (4.1-7.1)

Preliminary Progression-Free Survival (BICR) [c]

Data cutoff: 4 September 2020.

[a]Includes patients with ≥1 postbaseline scan or who discontinued treatment. [b]Responses are confirmed (CRs/PRs; n = 32) plus those CRs/PRs too early to be confirmed (n = 5). [c]Preliminary PFS limited by earlier censoring by data cutoff due to immature duration of follow-up for 4 and 6 mg/kg dose cohorts.

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. Presented at: World Conference on Lung Cancer Singapore; January 2021.

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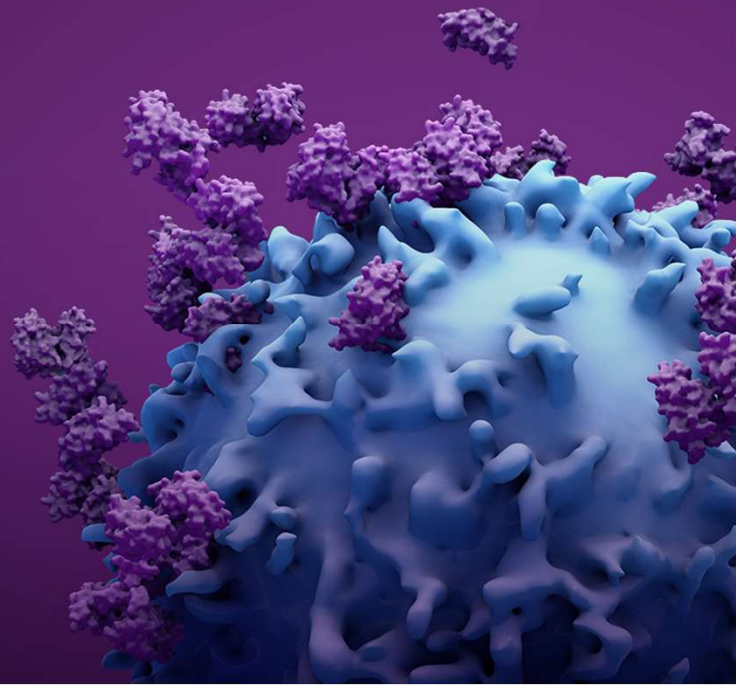
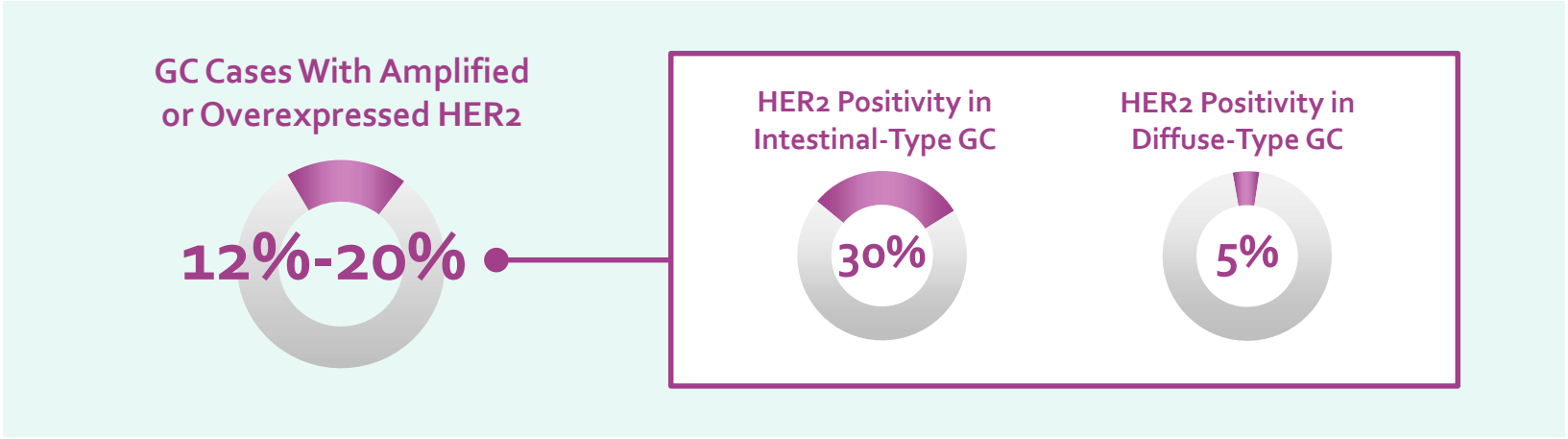
Gastric Cancer



HER2 Is an Important Biomarker and Key Driver of Tumorigenesis in Patients with GC[1,2]

HER2 Is Amplified in 12%-20% of GCs

HER2-positive expression varies by primary tumor localization[3-6]



GC, gastric cancer; GEJ, gastroesophageal junction.

1. Gambardella V, et al. In: Tabernero J, Cervantes A, van Halteren H, eds. Gastrointestinal Tract Tumours: Essentials for Clinicians. Viganello-Lugano, Switzerland: ESMO Press;2016:22-27; 2. Van Cutsem E, et al. *Lancet.* 2016;388:2654-2664; 3. Tanner M, et al. *Ann Oncol.* 2005; 16: 273–278; 4. Gravalos C, et al. *Ann Oncol.* 2008;19(9):1523-29; 5. Van Cutsem E, et al. *Gastric Cancer.* 2015;18(3):476-484; 6. Janjigian YY, et al. *Ann Oncol.* 2012;23(10):2656-2662.

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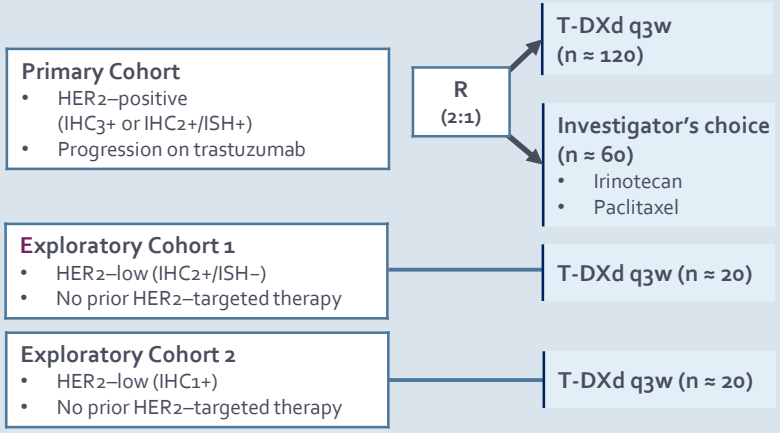
DESTINY-Gastric01: A Phase 2, Multicenter, Open-Label Study of T-DXd In Patients With HER2-Expressing Advanced Gastric or GEJ Adenocarcinoma[1-3]

PATIENTS

Patients with HER2–expressing advanced gastric or GEJ adenocarcinoma

STUDY DESIGN



ENDPOINTS

1°

ORR

Select 2°

- OS
- PFS

1. Shitara K et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: A randomized, phase II, multicenter, open-label study (DESTINY-Gastric01). Presented at: American Society for Clinical Oncology 2020 Virtual Scientific Program; May 29 – 31. Accessed November 6, 2020. URL: https://meetinglibrary.asco.org/record/185492/abstract; 2. U.S. National Library of Medicine CInicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03329690. Accessed: November 8, 2020. Last updated: September 9, 2020; 3. Shitara K et al. *N Engl J Med*. 2020;382(25):2419-2430.

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DESTINY-Gastric01: Trastuzumab Deruxtecan May Be a Safe and Effective Treatment Option for Patients With Advanced, HER2+ Gastric or GEJ Adenocarcinoma[1,2]

ANTITUMOR ACTIVITY

	Median OS (95% CI)
Trastuzumab deruxtecan	12.5 (9.6-14.3)
PC of chemo	8.4 (6.9-10.7)
HR for death, 0.59 (95% CI, 0.39 – 0.88); *P*=0.01	

	Median PFS (95% CI)
Trastuzumab deruxtecan	5.6 (4.3-6.9)
Physician's choice of chemo	3.5 (2.0-4.3)
HR for death, 0.47 (95% CI, 0.31-0.71)	

SAFETY RESULTS

- Most common gr ≥3 AEs were:
  - Decreased neutrophil count (51% in the T-DXd group vs 24% in the PC group)
  - Anemia (38% vs 23%)
  - Decreased white cell count (21% vs 11%)
  - Decreased appetite (17% vs 13%)
- 6 patients in the T-DXd group had febrile neutropenia (all events gr 3 vs 2 in the PC group (1 event each of gr 3 and 4)

HR, hazard ratio; PC, physician's choice.

1. Shitara K et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: A randomized, phase II, multicenter, open-label study (DESTINY-Gastric01). Presented at: American Society for Clinical Oncology 2020 Virtual Scientific Program; May 29 – 31. Accessed November 6, 2020. URL: https://meetinglibrary.asco.org/record/185492/abstract;
2. U.S. National Library of Medicine Clnicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03329690. Accessed: November 8, 2020. Last updated: September 9, 2020; 3. Shitara K et al. *N Engl J Med*. 2020;382(25):2419-2430.

Gastric Cancer | ASCO GI 2021 Update

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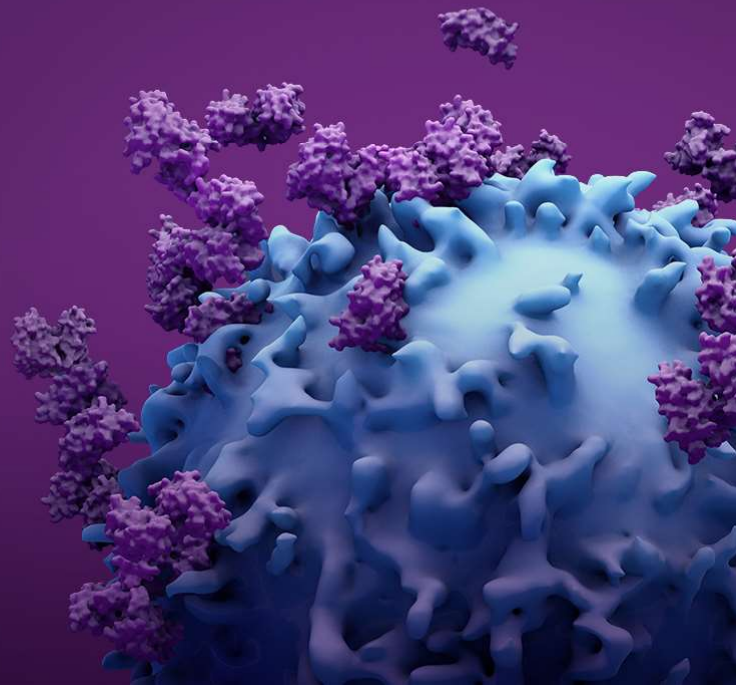
A phase 1b/2, multicenter, open-label, dose-escalation, and dose-expansion study evaluating trastuzumab deruxtecan (T-DXd, DS-8201) monotherapy and combinations in patients with HER2-overexpressing gastric cancer (DESTINY-Gastric03)

Yelena Y. Janjigian, Natasha Viglianti, Feng Liu, Ariadna Mendoza-Naranjo, Liz Croydon



To obtain presentation,
https://meetinglibrary.asco.org/record/193997/abstract

ClinicalTrials.gov Number: NCT04379596

Background and Study Rationale

- Trastuzumab + chemotherapy is a standard 1L option for patients with HER2-overexpressing metastatic gastric cancer or GEJ adenocarcinoma
  - This regimen provides a modest OS benefit vs chemotherapy alone (median OS, 13.8 vs 11.1 months)[1]
- The randomized phase 2 DESTINY-Gastric01 trial showed that T-DXd significantly improved the ORR (51% vs 14%) and OS (12.5 vs 8.4 months) vs chemotherapy alone[2]
- **Based on results of the DESTINY-Gastric01 and DS8201-A-J101 trials, T-DXd was approved by the Japanese Ministry of Health, Labour, and Welfare on September 25, 2020, for the treatment of patients with HER2-positive metastatic gastric cancer that has progressed after chemotherapy**

January 18, 2021:
T-DXd was FDA-approved for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen[3]

GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; OS, overall survival.

1. Bang YJ et al. *Lancet*. 2010;376:687-697; 2. Shitara K et al. *N Engl J Med*. 2020;382:2419-2430; 3. AstraZeneca Press release. January 18, 2021. URL: https://www.astrazeneca.com/media-centre/press-releases/2021/enhertu-approved-in-the-us-for-gastric-cancer.html.

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Inclusion and Exclusion Criteria

PATIENTS

Overall Inclusion Criteria	Part 1 only	Part 2 only
Aged ≥18 years (≥20 years in Japan)	Progression on or after ≥1 prior trastuzumab-containing regimen	Previously untreated for unresectable or metastatic disease
Locally advanced, unresectable or metastatic gastric or GEJ adenocarcinoma		
HER2 IHC 3+ or IHC 2+/ISH+		
Measurable disease per RECIST v1.1		
Adequate organ function, including cardiac, renal, and hepatic function		

Select Exclusion Criteria
History of noninfectious pneumonitis/ILD, current ILD, or suspected ILD that cannot be ruled out by imaging at screening
Uncontrolled intercurrent illness or active infection requiring IV antimicrobials
Lung-specific intercurrent clinically significant severe illness
Spinal cord compression or clinically active CNS metastasis
Pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or cell-free and CART therapy

CART, Chimeric antigen receptor T-cell; CNS, central nervous system; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous.

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DESTINY-Gastric03: T-DXd Monotherapy and Combinations in Patients With HER2-Overexpressing Gastric Cancer

STUDY DESIGN

Dose Escalation

Patient Population

- HER2-overexpressing, metastatic or unresectable gastric or GEJ cancer
- **Progression on/after >1 trastuzumab-containing regimen**

- **Arm 1A: T-DXd + F-FU**
- **Arm 1B: T-DXd + capecitabine**
- **Arm 1C: T-DXd + durvalumab**
- **Arm 1D: T-DXd at lowest RP2D from arm 1A/1B + 5-FU or capecitabine at combination RP2D determined in arm 1A/1B + oxaliplatin**
- **Arm 1E: T-DXd at lowest RP2D from arm 1A/1B/1C + 5-FU or capecitabine at combination RP2D determined in arm 1A/1B + durvalumab**

Dose Expansion

Patient Population

- HER2-overexpressing, metastatic or unresectable gastric or GEJ cancer
- **No prior treatment for metastatic disease**

- **Arm 2A: T-DXd + cisplatin/oxaliplatin + 5-FU/capecitabine**
- **Arm 2B: T-DXd**
- **Arm 2C: T-DXd + 5-FU/capecitabine ± oxaliplatin at RP2D determined in part 1**
- **Arm 2D: T-DXd + F-FU/capecitabine + durvalumab determined in part 1**

ENDPOINTS

Primary

- Part 1: Safety and tolerability, and determination of the RP2D of T-DXd combinations
- Part 2: confirmed ORR

Secondary

- Confirmed ORR (part 1)
- DCR
- DOR
- PFS
- OS
- Safety and tolerability (part 2)

Study started June 3, 2020 and is currently enrolling patients globally

Patient Case - 62 Y/O man, advanced gastric cancer

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- Presented with abdominal discomfort, anorexia and weight loss
- Esophagogastroduodenoscopy (EGD) showed a 3x7 cm ulcerated mass in the distal gastric antrum – confirmed on edocscopic ultrasound (EUS) and staged as uT2N1 based on the presence of gastrohepatic lymphadenopathy of 1.6 cm
- Biopsy revealed poorly differentiated adenocarcinoma with extensive ulceration and signet ring features

Patient Case - 62 Y/O man, advanced gastric cancer

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- Staging CT of the chest, abdomen, and pelvis showed marked soft tissue prominence of the gastric antrum and free fluid lateral to the right hepatic lobe, no intrahepatic lesions were seen, other abdominal organs were unremarkable
- Surgery planned, as disease appeared localized

Patient Case - 62 Y/O man, advanced gastric cancer

- Intraoperatively, the patient was found to have bulky, unresectable lymph node and peritoneal metastases
- A partial gastrectomy was performed, and all visible tumor was resected, margins negative

Patient Case - 62 Y/O man, advanced gastric cancer

Should the surgery have been aborted?

NN1

Slide 80

NN1 Included as a discussion point, as the benefit of palliative gastrectomy +/- metastasectomy is debatable and hasn't been studied prospectively

Norman Nagl, 2/11/2021

Patient Case - 62 Y/O man, advanced gastric cancer

- One month after surgery, CT revealed left supraclavicular bilateral hilar lymphadenopathy and a 3.1 x 1.9 cm liver hypodensity
- PET scan showed diffuse axial skeletal metastases
- Liver biopsy showed the tumor was HER2-positive (IHC 3+)

Patient Case - 62 Y/O man, advanced gastric cancer

Should any additional testing have been performed?

NN1

Slide 82

NN1 Discuss MSI testing

Norman Nagl, 2/11/2021

Patient Case - 62 Y/O man, advanced gastric cancer

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- Patient enrolled in a clinical study of trastuzumab and chemotherapy plus pembrolizumab
- After 3 treatments, PET scan demonstrated near normalization in all previously noted sites of disease
- CT scan showed decreases in the size of liver lesions, lymphadenopathy, and bone metastases

Patient Case - 62 Y/O man, advanced gastric cancer

- After 6 additional cycles, patient returned complaining of cough, fatigue, and shortness of breath
- CT scans show presence of bilateral pulmonary metastases

Patient Case - 62 Y/O man, advanced gastric cancer

Should additional testing for HER2 status be performed?

Patient Case - 62 Y/O man, advanced gastric cancer

What would you recommend for this patient's next course of treatment?

- Trastuzumab + chemo + 5-FU (ToGA)
- Paclitaxel
- Paclitaxel + ramucirumab
- Trastuzumab deruxtecan
- Clinical trial

Patient Case - 62 Y/O man, advanced gastric cancer

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- Patient received trastuzumab deruxtecan at a dose of 6.4 mg/kg q3w
- After 2 cycles, patient experienced a partial response with marked reduction in the size of lung lesions
- Patient experienced mild nausea with treatment, managed with olanzapine and benzodiazepines

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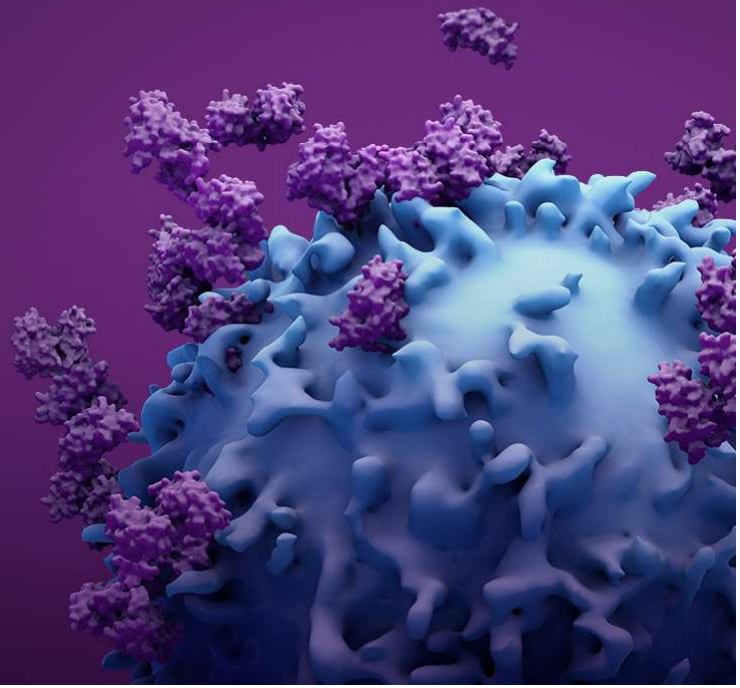
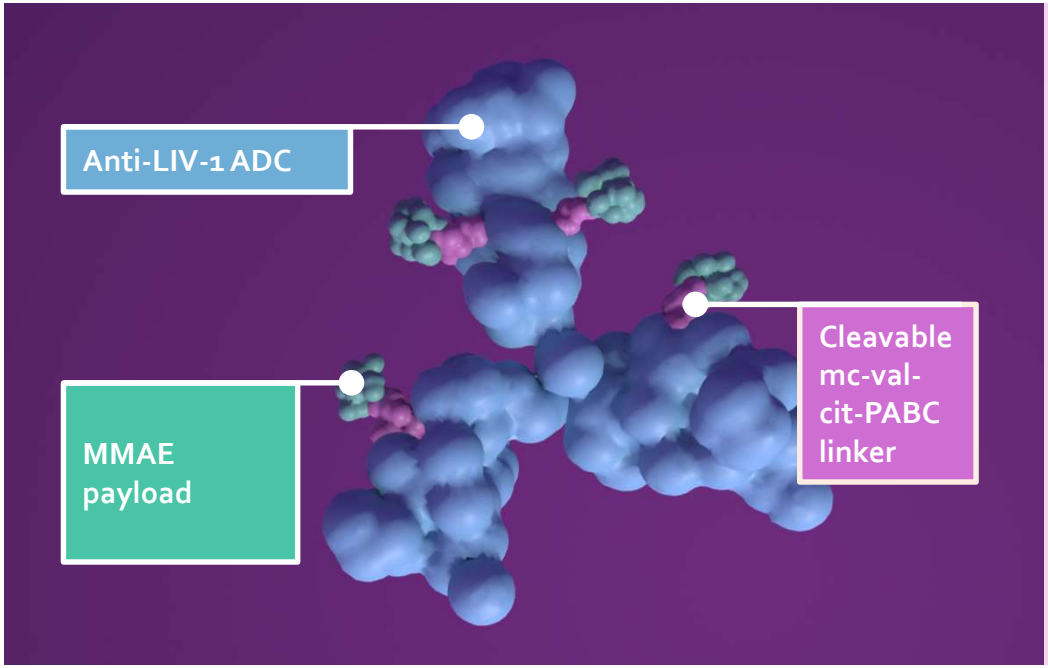
Open-label, phase 2 study of ladiratuzumab vedotin (LV) for advanced gastric and gastroesophageal junction adenocarcinoma (SGNLVA-005, Trial-in-Progress)

Yelena Y. Janjigian, Natasha Viglianti, Feng Liu, Ariadna Mendoza-Naranjo, Liz Croydon



To obtain presentation,
https://meetinglibrary.asco.org/record/194044/abstract

ClinicalTrials.gov Number: NCT04032704



- Ladiratuzumab vedotin delivers a potent microtubule-disrupting agent called MMAE via a protease-cleavable linker, to cancer cells expressing LIV-1[1,2]
- LIV-1 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]

Ladiratuzumab vedotin (SGN-LIV1A; LV)

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.

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LV Monotherapy Was Safe and Showed Antitumor Effects on a 3-Week Cycle in Patients With Metastatic BC

- In a phase 2 study with LV given on a cycle of every 3-weeks, LV was tolerable and active in heavily pretreated patients with metastatic BC at a recommended dose of 2.5 mg/kg
- Maximum tolerated dose was not reached during dose escalation; there were no DLTs
- Main toxicities associated with LV monotherapy were peripheral neuropathy and neutropenia
- The RP2D of 2.5 mg/kg and maximum dose of 200 mg per cycle for LV monotherapy were identified
- Interim results demonstrated clinically meaningful antitumor activity in heavily pretreated patients with metastatic triple-negative BC
- The ORR was 25% (95% CI, 15-38) and the DCR was 58% (N=60 efficacy evaluable patients)

BC, breast cancer; DLT, dose-limiting toxicity.

1. Modi S et al. Phase 1 study of the antibody-drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative metastatic breast cancer, SABCS, 2017, Abstract #PD3-14.

Inclusion and Exclusion Criteria

PATIENTS

Key Inclusion Criteria	Key Exclusion Criteria
Previously treated patients with unresectable locally advanced or metastatic disease	Active concurrent malignancy or previous malignancy within ≤3 years; except malignancies with a negligible risk of metastasis or death
Measurable disease per RECIST v1.1	Any anticancer therapy within 3 weeks of starting study treatment
ECOG 0 or 1 and adequate organ function	Known active CNS lesions that have not been definitively treated
Willing to provide required archival and pretreatment tumor biopsy for assessment of HER3 expression levels by IHC and exploratory biomarkers	Ongoing sensory or motor neuropathy grade ≥2
ECOG PS 0 or 1	
Cohort-specific criteria (gastric and GEJ adenocarcinoma and esophageal SCC cohorts)	
Must have received and progressed during or after ≤ 1 prior line of platinum-based cytotoxic chemotherapy	
May have received prior anti-PD(L)1 therapy, and patients with known HER2 overexpression must have received prior HER2-targeted therapy	

SCC, squamous cell carcinoma.

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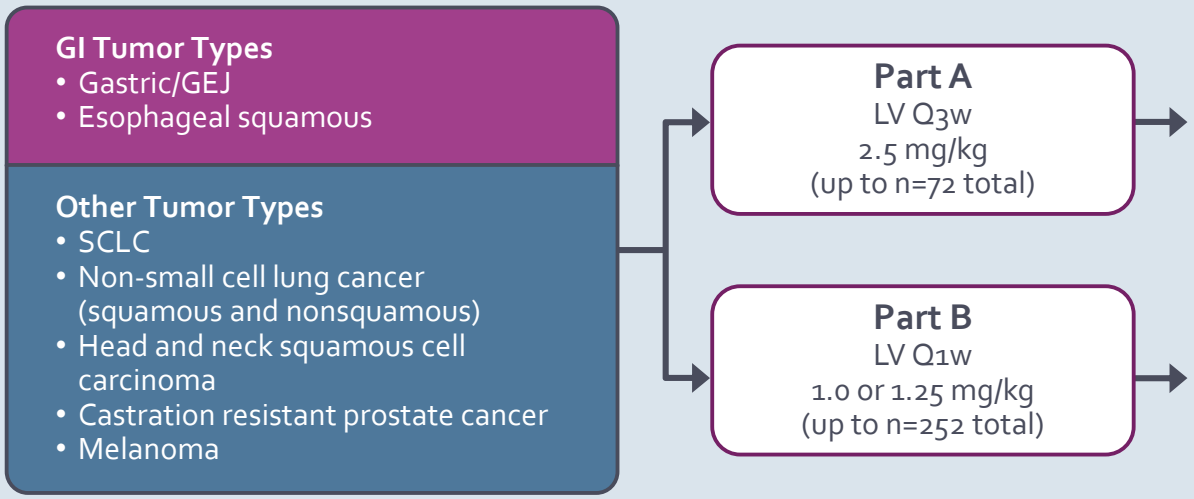
SGNLVA-005 Is an Ongoing, Open-Label, Phase 2 Study Evaluating LV Monotherapy in Patients With Advanced Solid Tumors

STUDY DESIGN



ENDPOINTS

Primary
- ORR (RECIST v1.1)

Secondary
- Safety
- DCR
- DOR
- PFS
- OS

ADCs in GI Cancer Competitive Landscape

Company	Drug Name	Phase	N	Target(s)	Est Study Completion Date
AbGenomics International, Inc.	AbGn-107[1]	**1**	136	AG7 antigen	December 2020
Daiichi Sankyo Cancer Enterprise	Enhertu[2]	**BLA/ Phase 2**	72	HER2/neu or ErbB-2 topoisomerase I inhibitor	August 2021
OBI Pharma, Inc.	OBI-999[3]	**1/2**	185	antigen Globo H (Globo H, SSEA3 and SSEA4)	December 9, 2023
Daiichi Sankyo Cancer Enterprise	DS-6157[4]	**1**	100	GPR20	October 2024
Immunomedics, Inc.	Trodelvy (sacituzumab govitecan-hziy)[5]	**Preclinical**	X	Trop-2	X

Trop-2, tumor-associated calcium signal transducer 2.

1. U.S. National Library of Medicine Clnicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT02908451. Accessed: November 8, 2020. Last updated: July 17, 2020; 2. U.S. National Library of Medicine Clnicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04276415. Accessed: November 8, 2020. Last updated: October 14, 2020; 3. U.S. National Library of Medicine Clnicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04084366. Accessed: November 8, 2020. Last updated: August 4, 2020; 4. U.S. National Library of Medicine Clnicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04014075. Accessed: November 8, 2020. Last updated: October 20, 2020; 5. Cardillo TM. *Bioconjug Chem.* 2015; 26(5):919-931.

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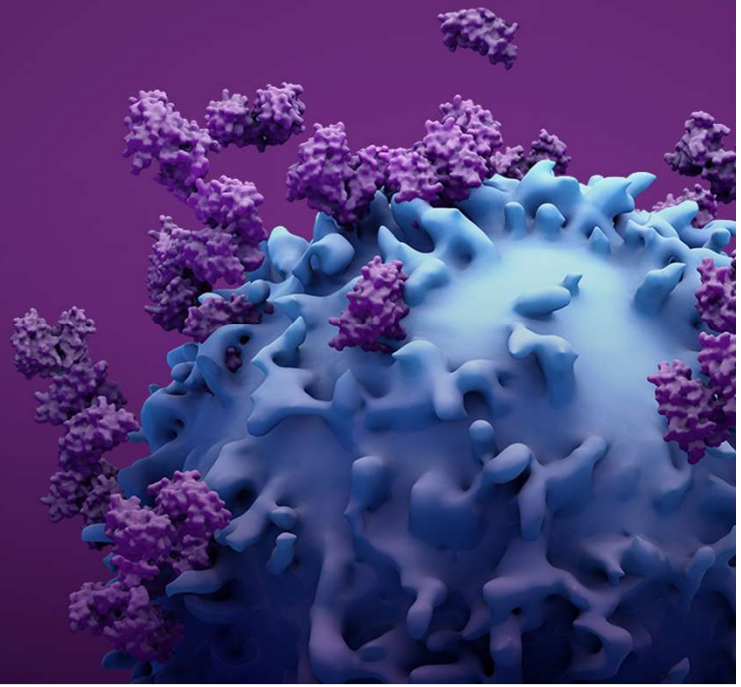

New and Effective Treatment Options for Patients With mCRC Is an Unmet Need

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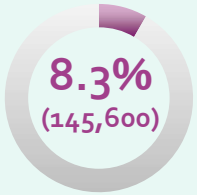
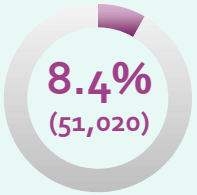
4th MOST COMMON CANCER[1]



of all new cancer cases

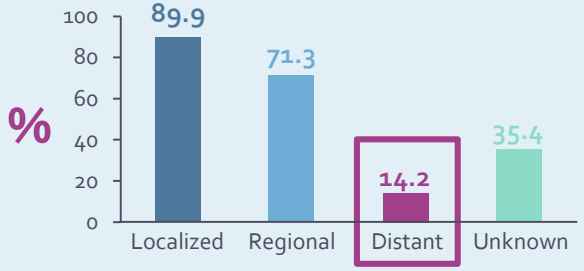


of all cancer deaths

≈50% to 60%

of patients diagnosed with early CRC will develop metastases[2]

5-YEAR SURVIVAL RATE BY STAGE[1]



14.2%

5-year survival rate for patients with mCRC

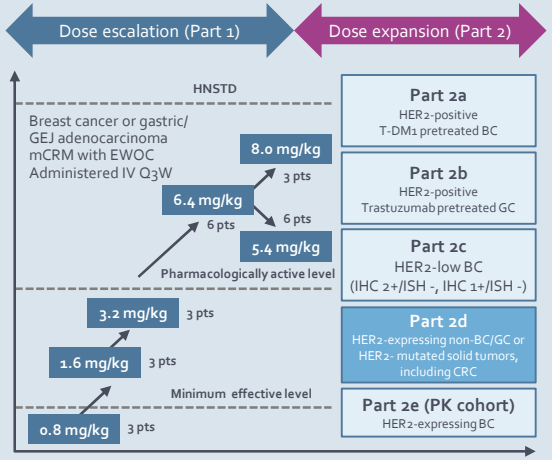
HER2 Overexpression Occurs in ~2% to 5% of all CRCs

mCRC, metastatic colorectal cancer.

1. National Cancer Institute. SEER cancer stat facts: colorectal cancer. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed March 28, 2020; 2. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer Version 2.2020. National Comprehensive Cancer Network. www.nccn.org/professionals/physician_gls/pdf/colon_blocks.pdf. updated March 3, 2020. Accessed March 29, 2020.

J101: Phase 1, Open-Label Study Provided Preliminary Data With T-DXd for Patients With CRC

STUDY DESIGN



ANTITUMOR ACTIVITY

Efficacy measure	CRC (n=20)
Confirmed ORR, n/N (%)	3/19 (15.8)
Confirmed DCR, n/N (%)	16/19 (84.2)
OS, median (range), months	NR (1.0+, 17.9+)
PFS, median (95% CI), months	3.9 (2.1, 8.3)
Duration of follow-up, median (95% CI), months	5.6 (1.6, 12.2)

SAFETY RESULTS

- Among the 259 patients who received ≥1 dose of T-DXd, regardless of tumor type, 99.2% experienced ≥1 TEAE
  - 54.1% had a gr ≥3 TEAE, 22.8% had a serious TEAE, 4.6% had a TEAE leading to death
- Common TEAEs (≥30%):
  - Nausea, decreased appetite, vomiting, anemia, alopecia, fatigue, diarrhea, constipation
- Pts with CRC demonstrated a safety profile similar to the overall population

BC, breast cancer; EWOC, escalation with overdose control; mCRM, modified Continuous Reassessment Method; T-DM1, trastuzumab emtansine.

Yoshino T et al. A multicenter, multicohort, phase 2 study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing metastatic colorectal cancer. Presented at: European Society of Medical Oncology 2018 Scientific Sessions; October 19-23, Munich, Germany.

DESTINY-CRC01: A Phase 2, Multicenter, Open-Label Study of T-DXd in Patients With HER2-Expressing Advanced CRC[1,2]

PATIENTS

- Unresectable and/or metastatic HER2-expressing CRC
- RAS/BRAF wild type
- >2 prior regimens, prior HER2 treatment allowed

STUDY DESIGN

T-DXd 6.4 mg/kg q3w

Cohort A (n=53)
HER2 Positive (IHC 3+ or IHC 2+/ISH+)

A futility monitoring was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C

Cohort B (n=7)
HER2 IHC 2+/ISH−

Cohort C (n=18)
HER2 IHC 1+

ENDPOINTS

1°

- ORR in Cohort A

Select 2°

- PFS
- OS
- DOR

Anticipated Study Completion: 12/2020

1. 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; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03384940. Accessed: November 8, 2020. Last updated: September 9, 2020.

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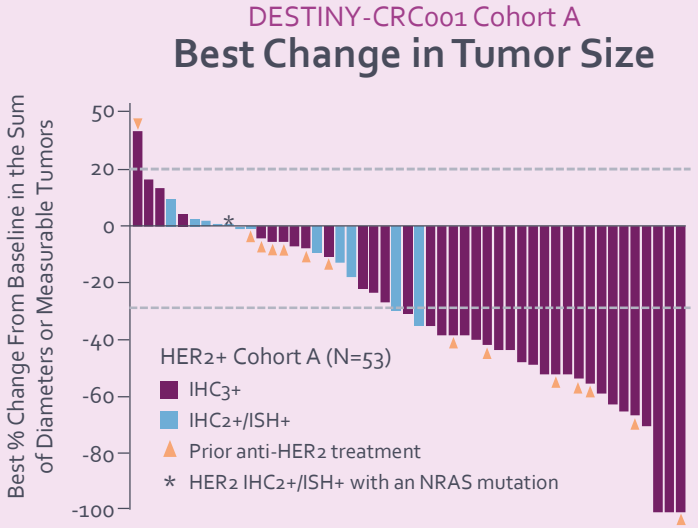
DESTINY-CRC01 Demonstrated Clinically Meaningful Activity With T-DXd in Patients With HER2+ Unresectable/Metastatic CRC[1,2]

ANTITUMOR ACTIVITY

	Total Evaluable in Primary Cohort (n=53)
Confirmed ORR	13 (20.3%) [12.27-31.71]
CR (%)	1.9
PR (%)	43.4
SD (%)	37.7
DCR (%) (95% CI)	83.0 (70.2-91.9)
Median DOR (months) (95% CI)	NE (4.2-NE)
Median PFS (months) (95% CI)	6.9 (4.1-NE)
Months OS (months) (95% CI)	NE (0.74-NE)



SAFETY RESULTS

Type of Adverse Event, n (%)	HER2+ Cohort A (n=53)	All Patients (n=78)
Any TEAE	53 (100)	78 (100)
Drug related	51 (96.2)	73 (93.6)
TEAE grade ≥3	32 (60.4)	48 (61.5)
Drug related	27 (50.9)	38 (48.7)
Serious TEAE	18 (34.0)	26 (33.3)
Drug related	12 (22.6)	14 (17.9)
Dose adjustments		
TEAE associated with discontinuation	5 (9.4)	7 (9.0)
Drug related	2 (3.8)	2 (2.6)
TEAE associated with dose reduction	11 (20.8)	15 (19.2)
Drug related	10 (18.9)	14 (17.9)
TEAE associated with dose interruption	20 (37.7)	27 (34.6)
Drug related	15 (28.3)	19 (24.4)
Death		
TEAE associated with death	5 (9.4)	7 (9.0)
Drug related	2 (3.8)	2 (2.6)

1. 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; 2. AstraZeneca Media Press Release. URL: https://www.astrazeneca.com/media-centre/press-releases/2020/enhertu-achieved-a-tumour-response-rate-of-45p-in-patients-with-her2-positive-metastatic-colorectal-cancer-in-phase-ii-destiny-crc01-trial.html. Accessed: November 8, 2020. Published: May 29, 2020.

CRC

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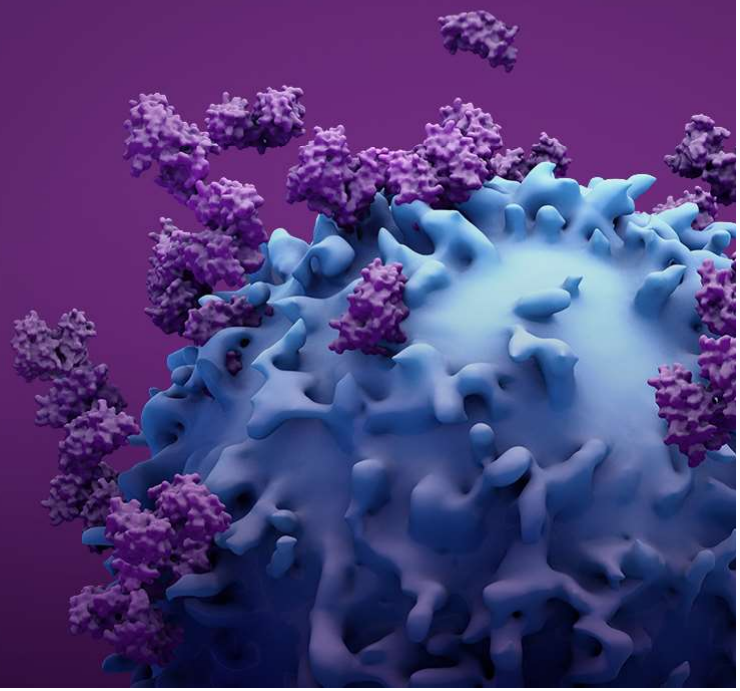
e-Poster Presentation
SABCS 2020

An open-label, phase 2 study of patritumab deruxtecan (HER3-DXd, U3-1402) in patients with previously treated advanced/metastatic colorectal cancer

Kanwal Pratap Singh Raghav, Takayuki Yoshino, Hiroya Taniguchi, Sabine Tejpar, Arndt Vogel, Zev A. Wainberg, Kensei Yamaguchi, Masayuki Kanai, Yali Liu, Sabeen Mekan, Geetha Pudussery, Yang Qiu, Scott Kopetz



To obtain presentation,
https://meetinglibrary.asco.org/record/194139/abstract

ClinicalTrials.gov Number: NCT04479436

Background and Study Rationale

- Current SOC for patients with advanced or metastatic CRC is suboptimal. Few effective targeted therapies exist, and available therapies offer limited therapeutic benefit
- HER3 is overexpressed in most CRC tumors (~50% to 90%) and has been associated with CRC tumor differentiation[1-3]
- In CRC cells, HER3 has been shown to promote cell proliferation and mediate resistance to cytotoxic therapy and chemotherapy

Owing to the high prevalence of HER3 expression in CRC, HER3-DXd is anticipated to be efficacious:[4-7]

- Significant tumor regression was observed with HER3-DXd in several tumor xenograft models of CRC, regardless of *KRAS* mutant status
- Exatecan, the compound from which the topoisomerase 1 inhibitor payload is derived, demonstrated activity in a CRC study in patients resistant to irinotecan, a commonly prescribed therapy for CRC
- Data from clinical trials of metastatic breast cancer and NSCLC have shown promising clinical activity and manageable safety profile in patients treated with HER3-DXd

SOC, standard of care.

1. Baiocchi G et al. *Int J Colorectal Dis*. 2009;24(9):1059-1068; 2. Rajkumar T et al. *J Pathol*. 1993;170(3):271-278; 3. Maurer CA et al. *Hum Pathol*. 1998;29(8):771-777; 4. Koganemaru S et al. *Mol Cancer Ther*. 2019;18:2043-2050; 5. Yonemori K et al. Presented at: ESMO Annual Meeting; September 27-October 1, 2019; Barcelona, Spain; 6. Yu H et al. Presented at: ESMO Annual Meeting; September 19-21, 2020; virtual meeting; 7. Siena S et al. Presented at: ASCO Annual Meeting May 29-June 2, 2020; virtual meeting.

Inclusion and Exclusion Criteria

PATIENTS

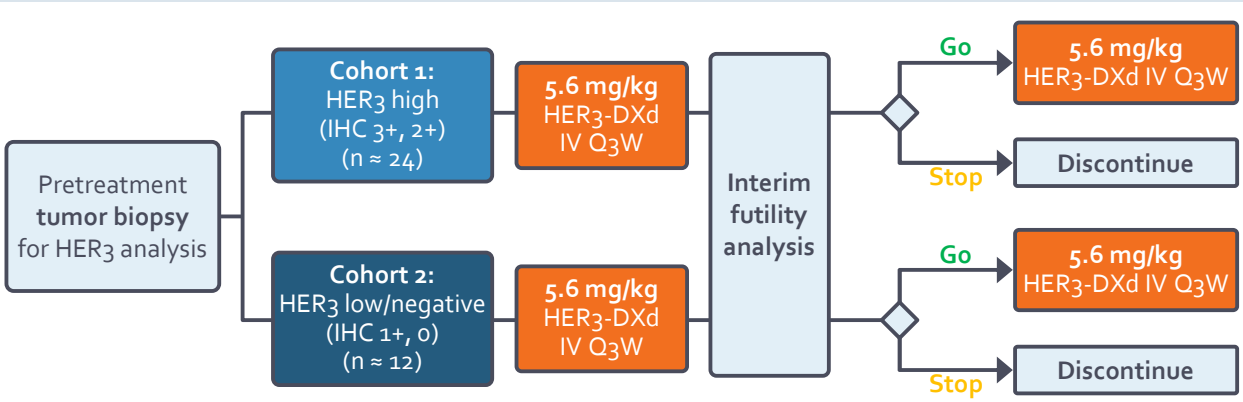
Key Inclusion Criteria	Key Exclusion Criteria
Aged ≥18 years	History of, current, or suspected ILD
Advanced or metastatic CRC	Clinically severe pulmonary compromise resulting from intercurrent pulmonary illness
Disease that is resistant, refractory, or intolerant to ≥2 prior lines of therapy: • Fluoropyrimidine • Irinotecan • Platinum agent • Anti-EGFR agent (if clinically indicated) • Anti-VEGF agent (unless contraindicated) • Immune checkpoint inhibitor with known MSI-H (unless contraindicated)	Receiving chronic systemic corticosteroids dosed at >10 mg prednisone or equivalent or any form of immunosuppressive therapy prior to C1 D1
Willing to provide required archival and pretreatment tumor biopsy for assessment of HER3 expression levels by IHC and exploratory biomarkers	Active CNS disease
ECOG PS 0 or 1	Inadequate washout period for medications/therapies prior to C1 D1
	Unresolved toxicities from previous anticancer therapy (other than alopecia)

U31402-A-U202 Study Design

STUDY DESIGN

Open-label, multicenter, global phase 2 study of HER3-DXd patients with advanced or metastatic colorectal adenocarcinoma

- 2 cohorts based on HER3 expression
- Biopsy samples collected from all patients at screening for HER3 expression measured by IHC



ENDPOINTS

Primary
- ORR (BICR)

Secondary
- DOR
- DCR
- PFS
- ORR (investigator)
- OS
- Safety
- Correlation of HER3 protein expression in tumor tissue with efficacy
- Immunogenicity
- PK

Study started September 2020 and is currently enrolling for part 1

Summary

- There are currently no ADCs approved for use in patients with NSCLC and CRC
- T-Dxd is the first FDA-approved ADC for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen
- Several ADCs, with novel mechanisms of action, are in various stages of development for NSCLC, gastric cancers, and CRCs
- These agents provide promising options for patients

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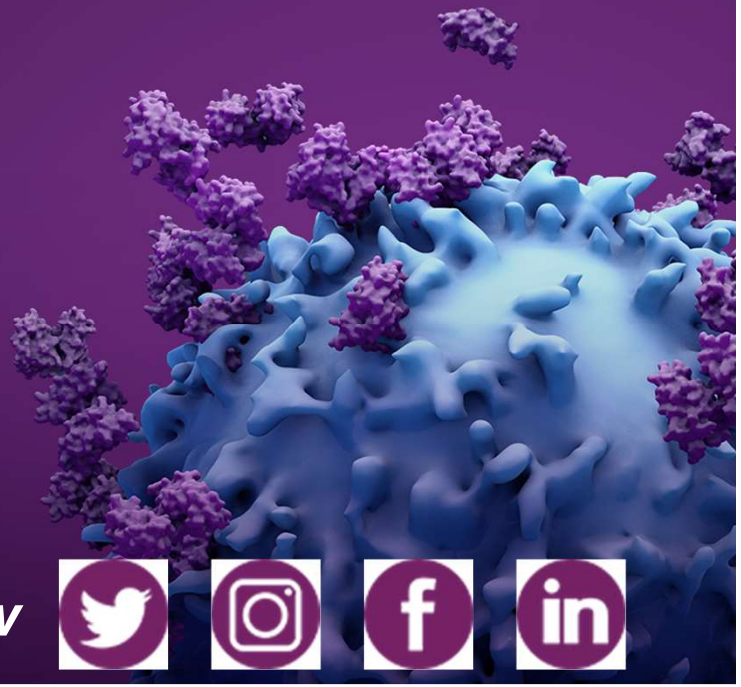
Live Q&A



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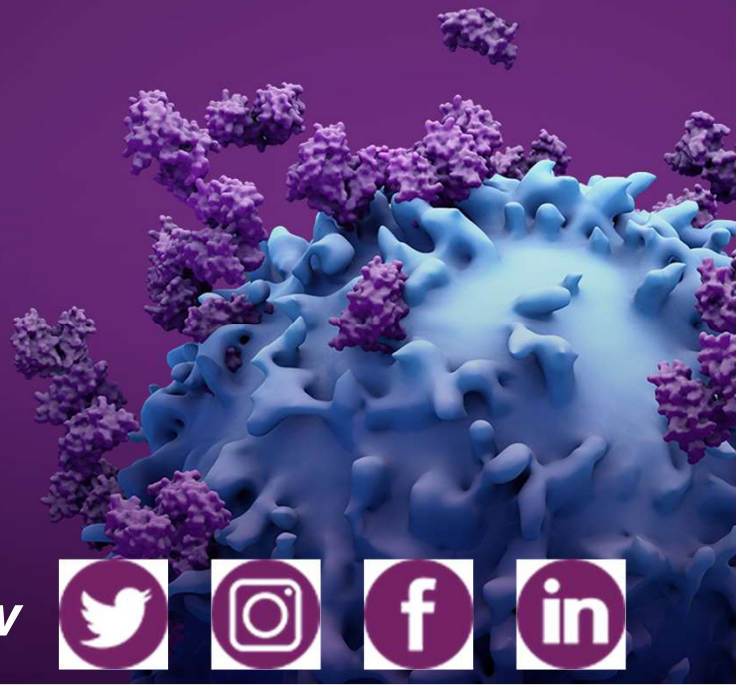
Thank You



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Presentation Breakdown

- Spiro: Slides 1-4
- Sanjiv: Slides 5-8, 37-39, 68, 104-105
- Daver: Slides 9-36
- West: Slides 40-52, 104
- Ram: Slides 53-68, 104
- Shroff: Slides 69-104