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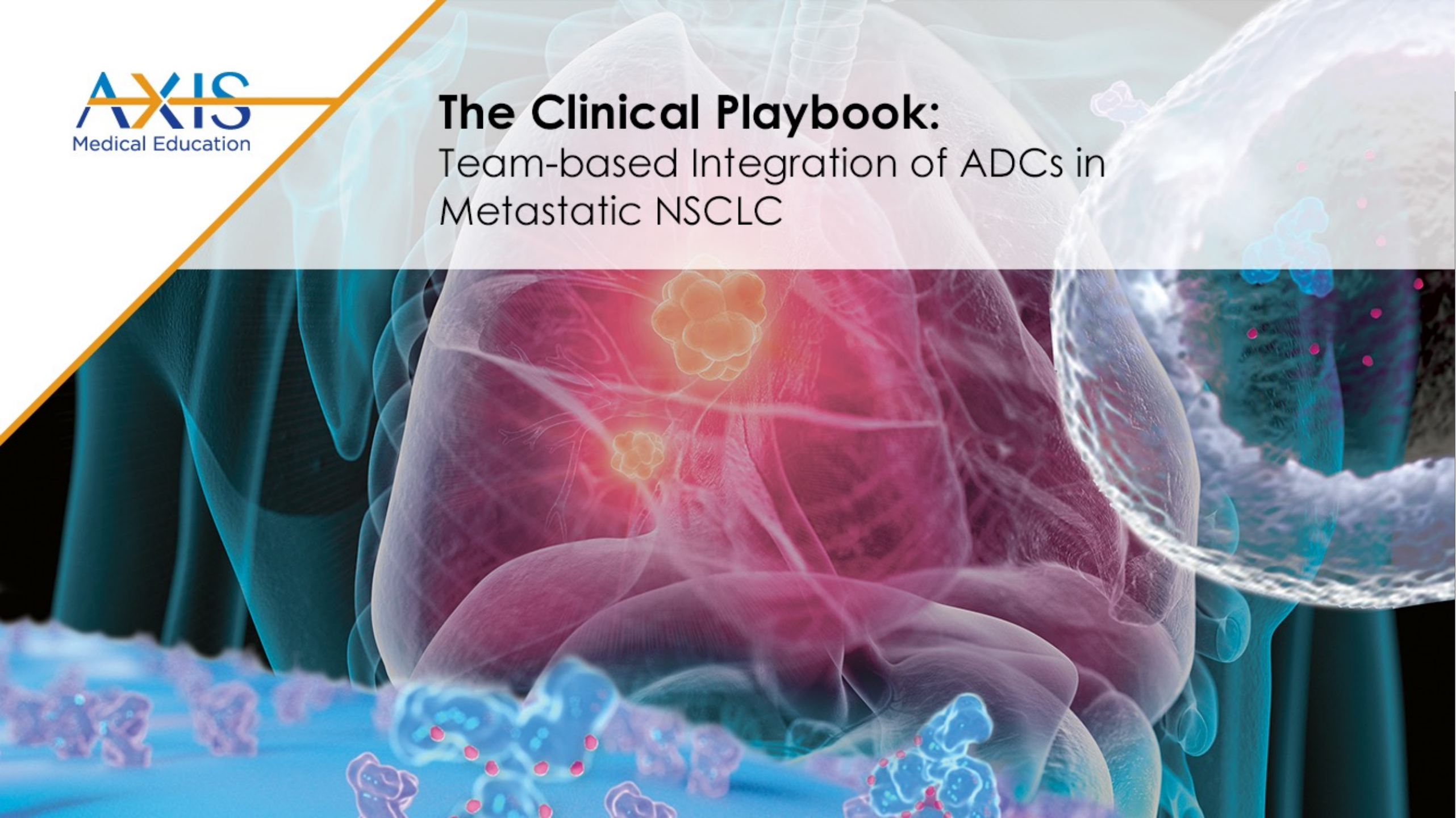
The Clinical Playbook:

Team-based Integration of ADCs in Metastatic NSCLC



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Disclosure of Conflicts of Interest

Misako Nagasaka, MD, PhD

Company	Relationship
AstraZeneca, Daiichi Sankyo, Takeda, Novartis, EMD Serono, Pfizer, Lilly, Genentech, Janssen	Advisory Board
Caris Life Sciences	Consultant
Blueprint Medicine	Speakers' bureau
An Heart Therapeutics	Travel support

Learning Objectives

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

- Utilize guideline-recommended biomarker testing to identify patients with mNSCLC appropriate for treatment with HER2-directed therapy and guide treatment selection
- Assess the potential utility of ADCs for the treatment of mNSCLC
- Examine emerging efficacy and safety data, and ongoing clinical trials of ADCs for the treatment of patients with mNSCLC
- Determine how recent evidence on the use of HER2-directed ADCs for the treatment of patients with mNSCLC whose tumors have a HER2 mutation may be integrated into future clinical practice

ADCs, antibody-drug conjugates; NSCLC, metastatic non-small cell lung cancer.

The HER2 Receptor as a Potential Target for Precision Medicine in NSCLC

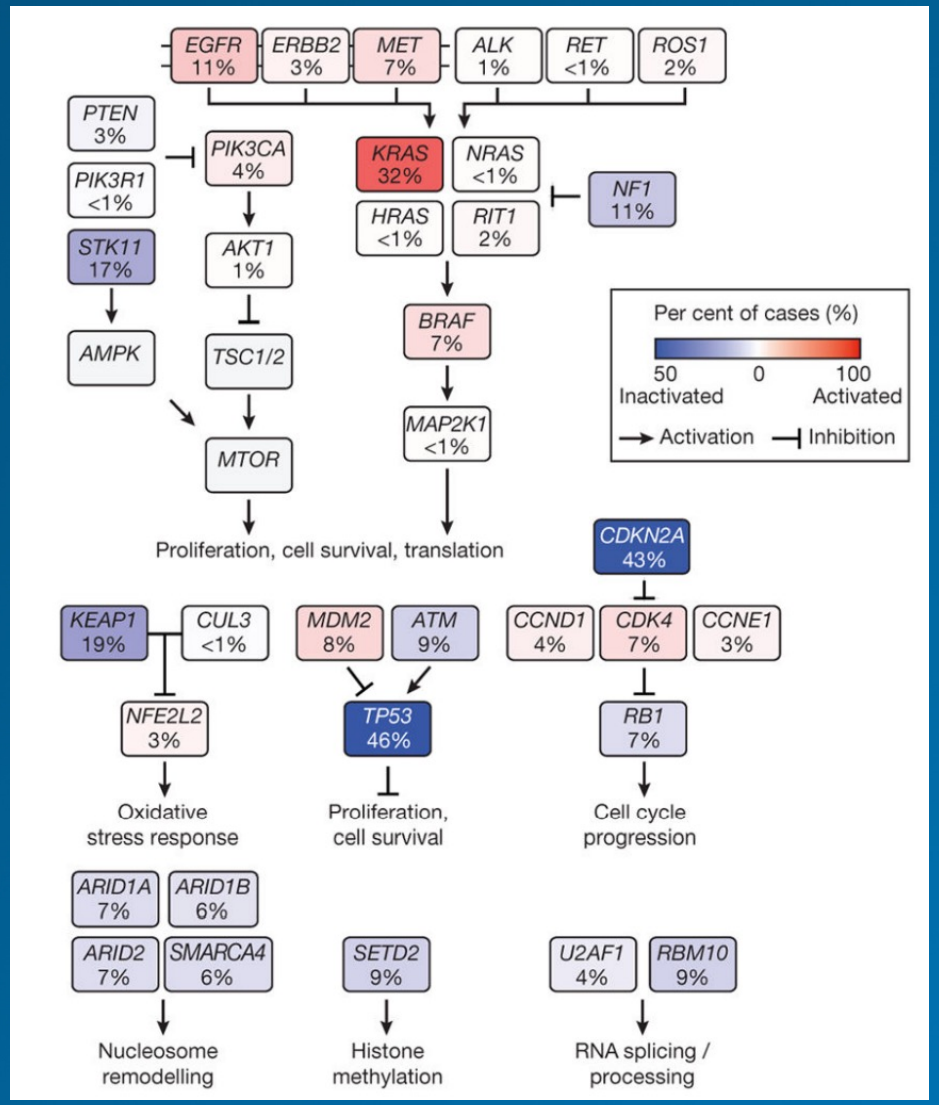
HER2 as a Target In Cancer

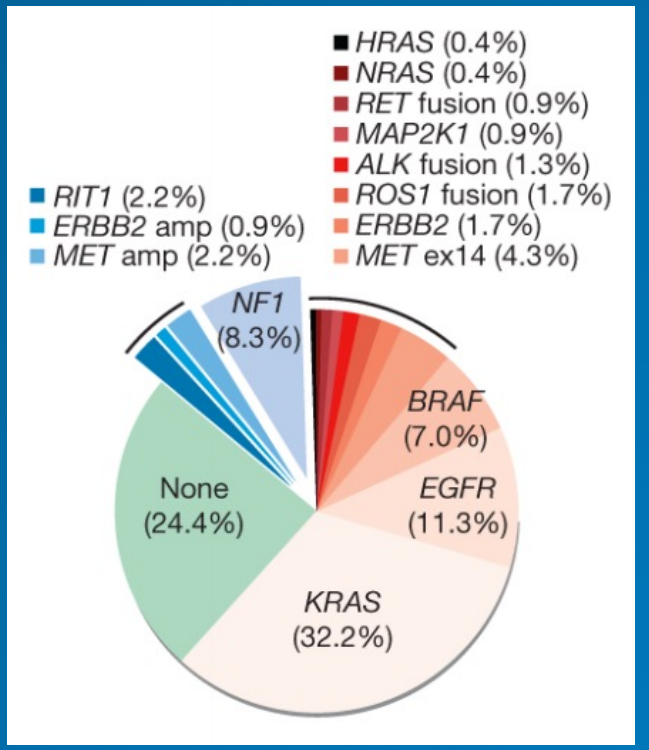
- HER2 is an actionable target in both breast and gastric cancers
  - HER2 testing with IHC or ISH is recommended
- FDA-approved anti-HER2 therapies:
  - Ado-trastuzumab emtansine (T-DM1)
  - Fam-trastuzumab deruxtecan-nxki
  - Lapatinib
  - Margetuximab
  - Neratinib
  - Pertuzumab
  - Trastuzumab
  - Tucatinib

FDA, US Food & Drug Administration; IHC, immunohistochemistry; ISH, in situ hybridization.

NCCN Guidelines. Breast Cancer version 5.2021. Gastric Cancer version 4.2021; Zhao et al. *JCO Precision Oncol.* 2020;4:411-425.

HER2 Mutations in NSCLC





- *ERBB2*–activating mutations occur in 2% of lung cancers
- These mutations are transforming in lung cancer models and result in kinase activation

The Cancer Genome Atlas Research Network. *Nature* 2014;511:543-550.

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HER2 Alterations: Mutation vs. Amplification vs. Overexpression

ERBB2 Mutations	*ERBB2* Gene Amplifications	HER2 Protein Overexpression
~2%-3% of lung adenocarcinomas	~2%-5% of lung adenocarcinomas	~2.4%-38% of NSCLCs
NGS, RT-PCR Most common: exon 20	FISH HER2/CEP17 ratio ≥2.0	IHC 2+ or 3+

***ERBB2* alterations have been identified as oncogenic drivers and potential therapeutic targets in lung cancer**

FISH, fluorescence in situ hybridization; HIS, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; RT-PCT, reverse transcriptase polymerase chain reaction.

Li et al. *J Thorac Oncol*. 2016;11:414-419. Zhao et al. *JCO Precision Oncol.* 2020;4:411-425.

Understanding the Value and Clinical Implications of Biomarker Testing to Improve Precision

Best Practice Recommendations for Biomarker Testing in NSCLC

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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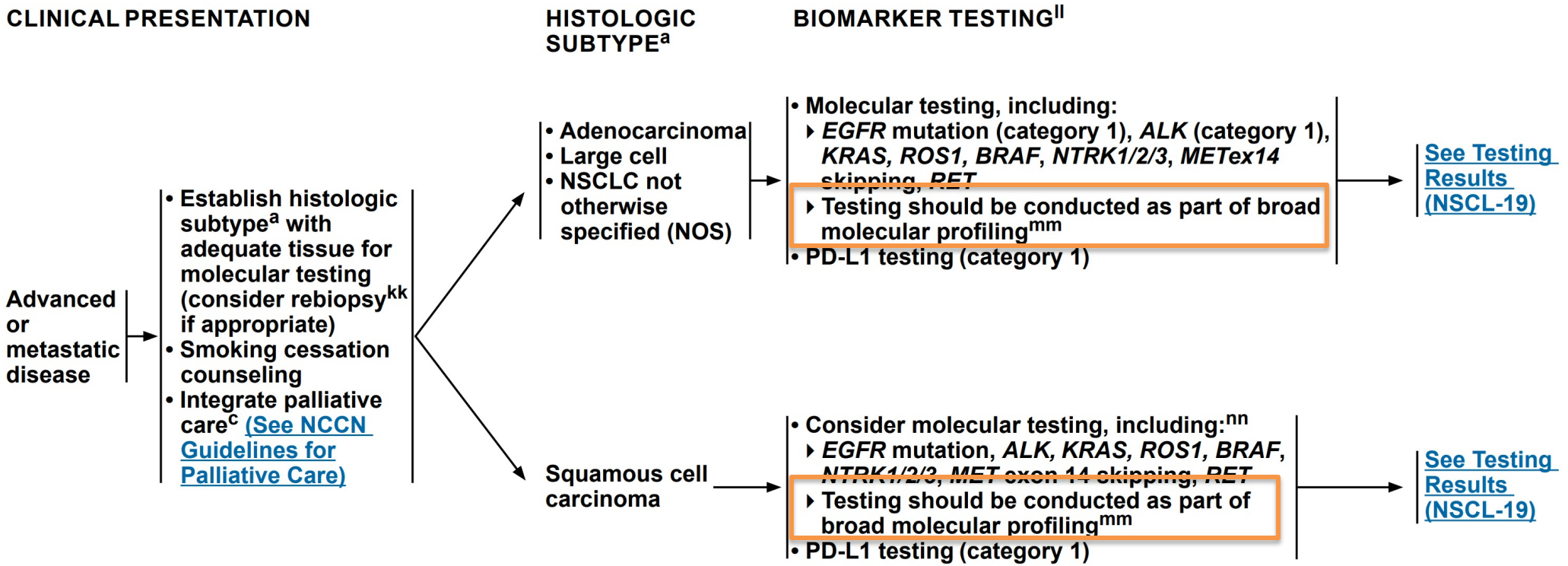

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Importance of Broad Molecular Profiling

"The NCCN NSCLC Guidelines Panel strongly advises **broader molecular profiling** with the goal of **identifying rare driver mutations** for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC."

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ERBB2 Mutation as a Potential Oncogenic Driver in NSCLC

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification	Crizotinib[1-2] Capmatinib[3]
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine[4] Fam-trastuzumab deruxtecan-nxki[5]

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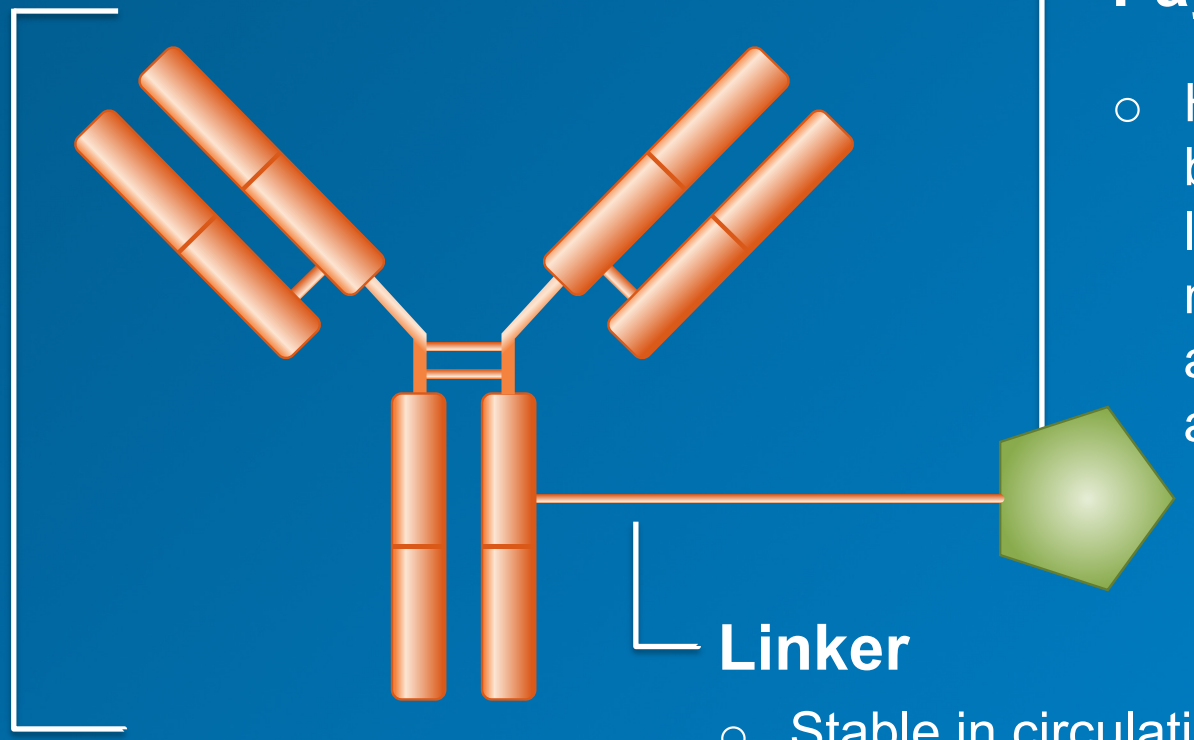
HER2-Targeted Antibody Drug Conjugates in NSCLC

Structure of an Antibody-Drug Conjugate

Antibody

- Target antigen should be highly expressed on tumor cells with limited expression on healthy tissues
- Antibody should have high affinity and avidity for tumor antigen



Payload (Drug)

- Highly potent because only a limited number of molecules can be attached to the antibody

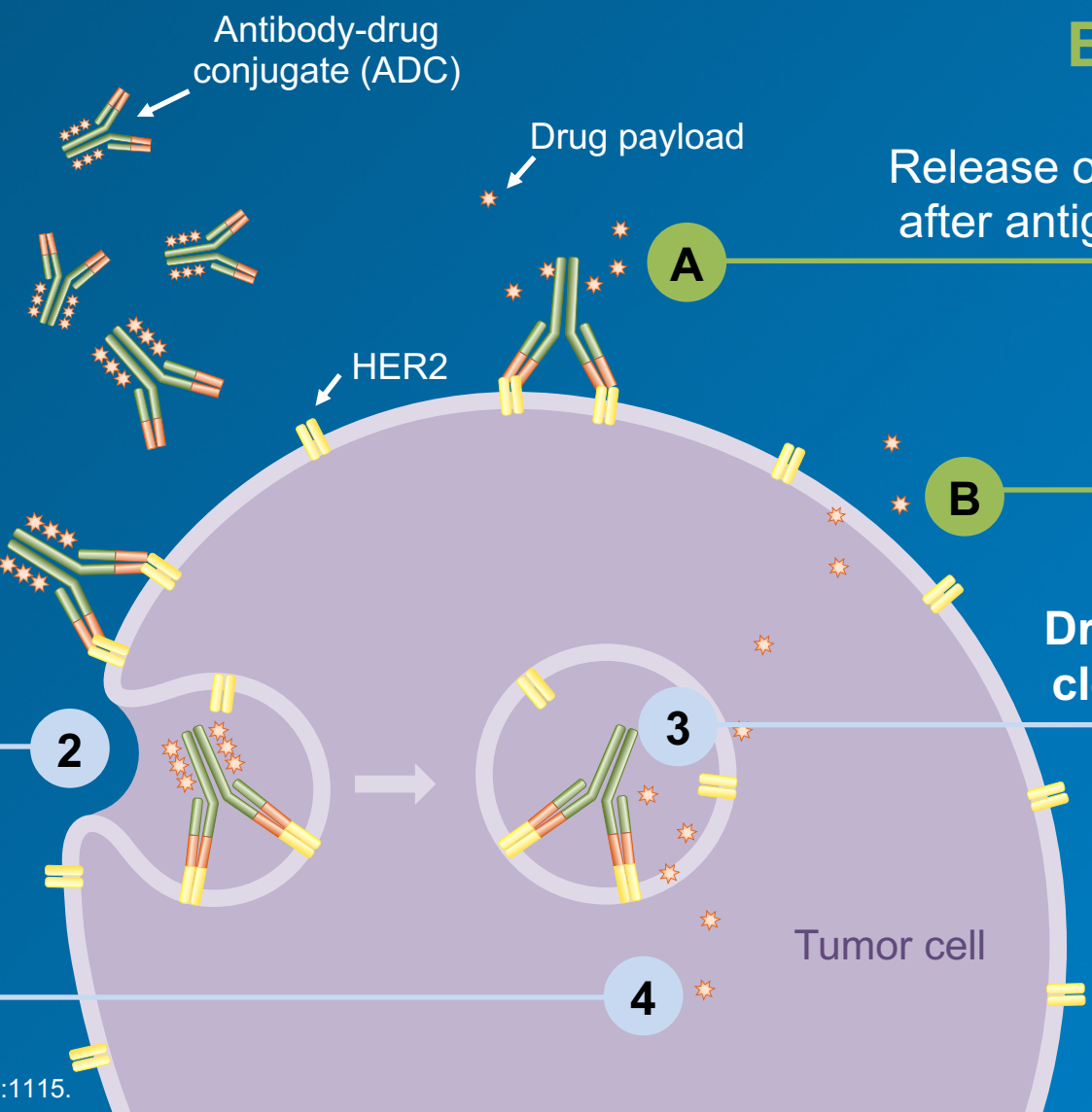
Linker

- Stable in circulation
- Must release the cytotoxic agent efficiently inside tumor cell

Adapted from Thomas et al. *Lancet Oncol*. 2016;17:e254-e262.

Mechanism of Action of HER2-Directed ADCs

Classical ADC mode of action



ADC binding to HER2 receptor — 1

Internalization by endocytosis — 2

Cytotoxic effect induced by drug payload — 4

Bystander killing effect

A — Release of drug payload from the antibody after antigen binding before internalization

B — Release of drug payload into the intercellular space due to a high drug membrane permeability

Drug payload release after linker cleavage by lysosomal enzymes — 3

A high drug-to-antibody ratio increases antitumoral efficacy despite low HER2 antigen density on tumor cells

Adapted from Rinnerthaler et al. *Int J Mol Sci*;2019:1115.

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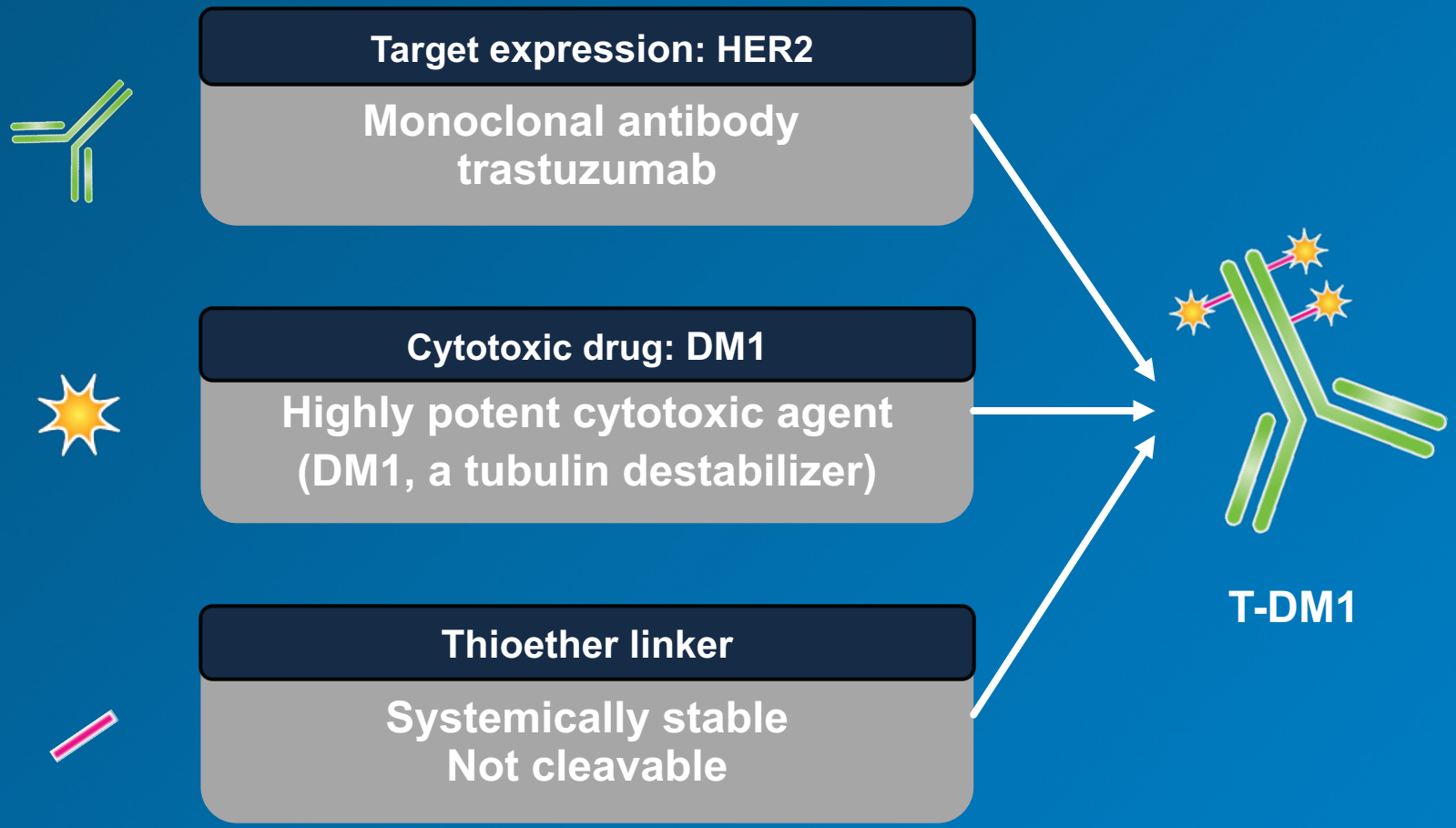
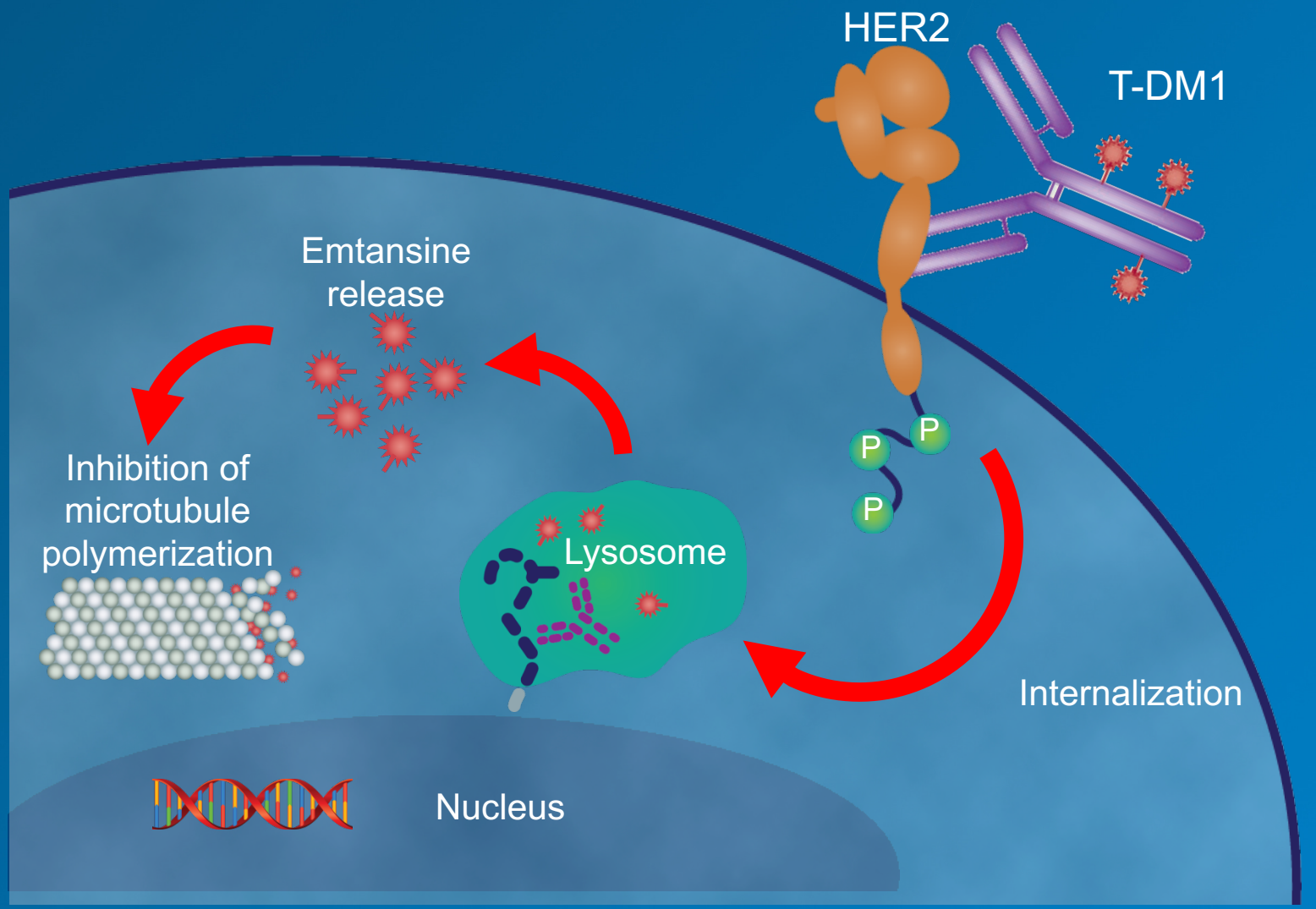
ado-Trastuzumab Emtansine (T-DM1)



T-DM1, ado-trastuzumab emtansine.

Carter and Senter. *Cancer J*. 2008;14:154-169. Chari. *Acc Chem Res*. 2008;41:98-107. Lewis Phillips et al. *Cancer Res*. 2008;68:9280-9290.

T-DM1: Mechanism of Action



T-DM1,ado-trastuzumab emtansine.
Adapted from LoRusso et al. *Clin Cancer Res.* 2011;17:6437-6447.

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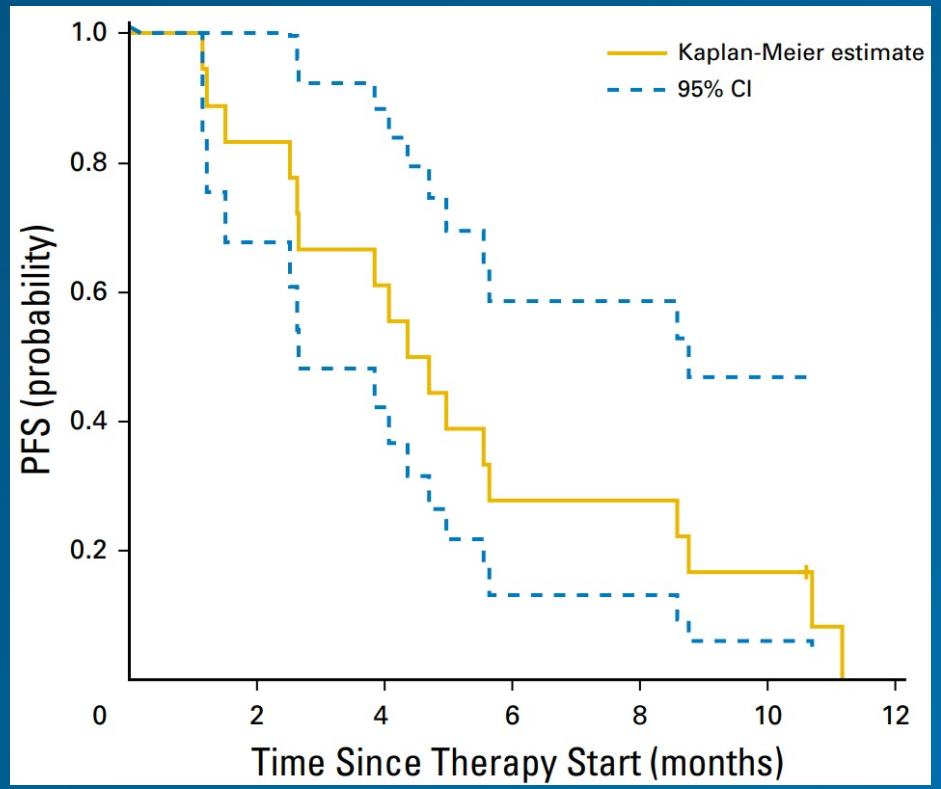
Ado-Trastuzumab Emtansine: Phase 2 Trials in Pretreated NSCLC

	Phase 2	Phase 2	Phase 2 Basket		
HER2 Alteration	HER2-overexpressing or HER2-mutant	HER2-overexpressing	HER2-mutant	HER2 amplified	HER2-amplified/mutant
N	15	49	18	6	25/49
Overall Response Rate	6.7%	20%	44%	50%	51%

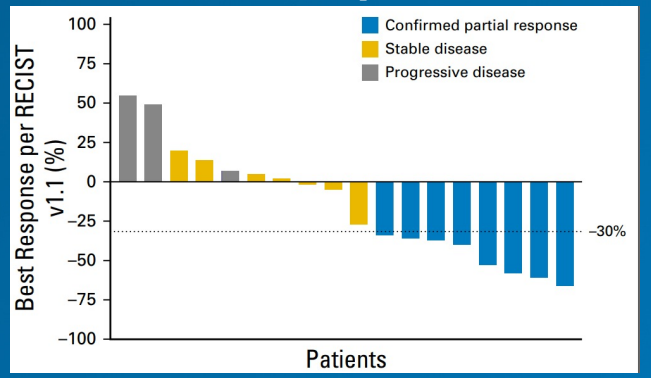
Ricciuti et al, *Semin Cancer Biol*. 2021;69:268-278. Hotta et al, *J Thorac Oncol.* 2018;13:273-279.
Peters et al, *Clin Cancer Res.* 2019;25:64–72. Li et al, *J Clin Oncol.* 2018;36:2532-2537; *Cancer Discov*. 2020;10:674.

Ado-Trastuzumab Emtansine: Phase 2 Basket Trial

Progression-free Survival
In *HER2*-mutant Lung Cancers (N = 18)

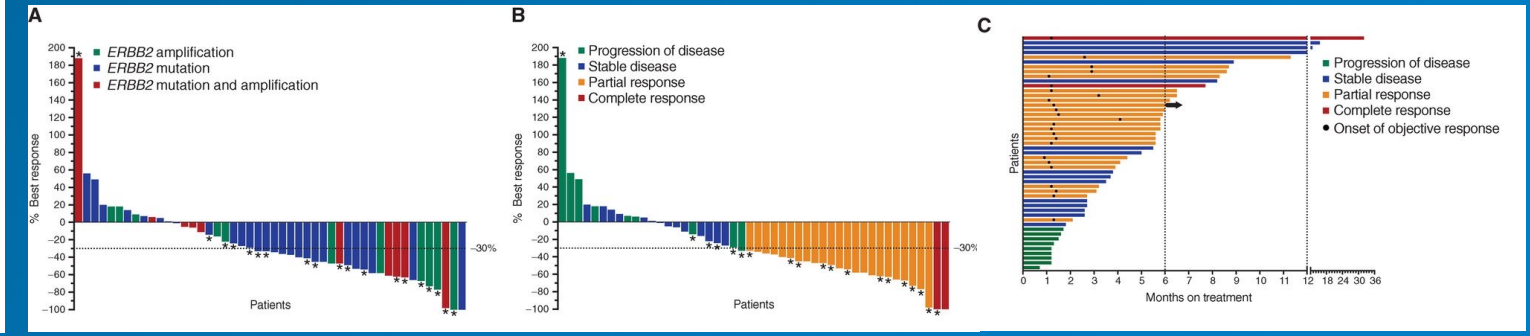


Best Response



ORR	44%
Best ORR by either RECIST or modified PERCIST for *ERBB2*-amplified/mutant patients	51%
mPFS	5.0 months
mDOR	4.4 months

Best Overall Response (N=48)



***ERBB2* Alteration Status** | **Best Response** | **Duration of Treatment**

ORR, overall response rate; mPFS, median progression-free survival; mDOR, median duration of response; RECIST, Response Evaluation Criteria in Solid Tumors.

Li et al, *J Clin Oncol*. 2018;36:2532; *Cancer Discov*. 2020;10:674.

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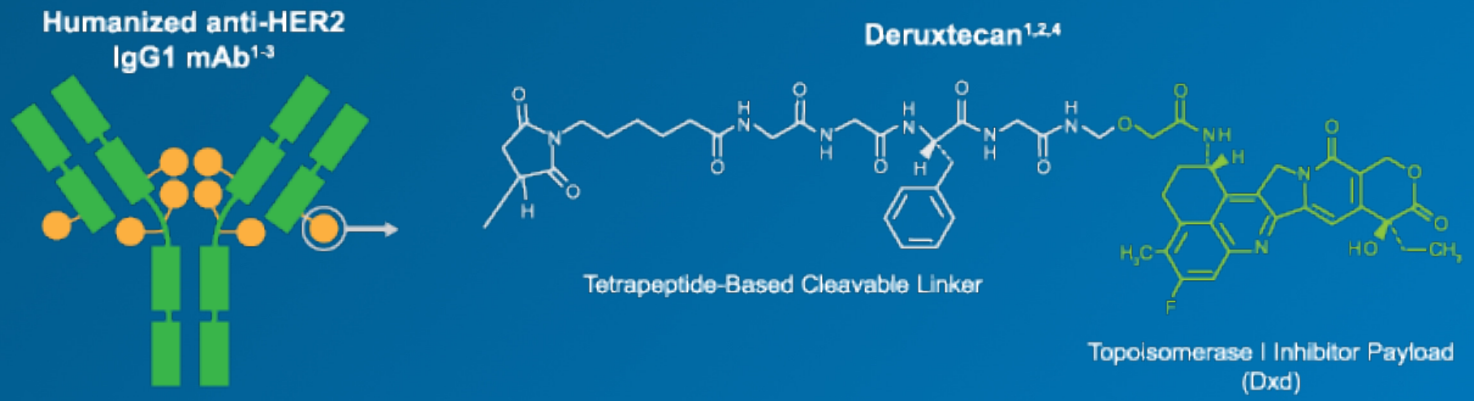
Trastuzumab Deruxtecan (T-DXd, DS-8201): MOA

T-DXd is an ADC with 3 components:

1. A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
2. A topoisomerase I inhibitor payload, an exatecan derivative
3. A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio = 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate; mAb, monoclonal antibody; MOA, mechanism of action.
1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142.
4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.
Adapted from Smit et al. *J Clin Oncol*. 2020;38(suppl 15):9504.

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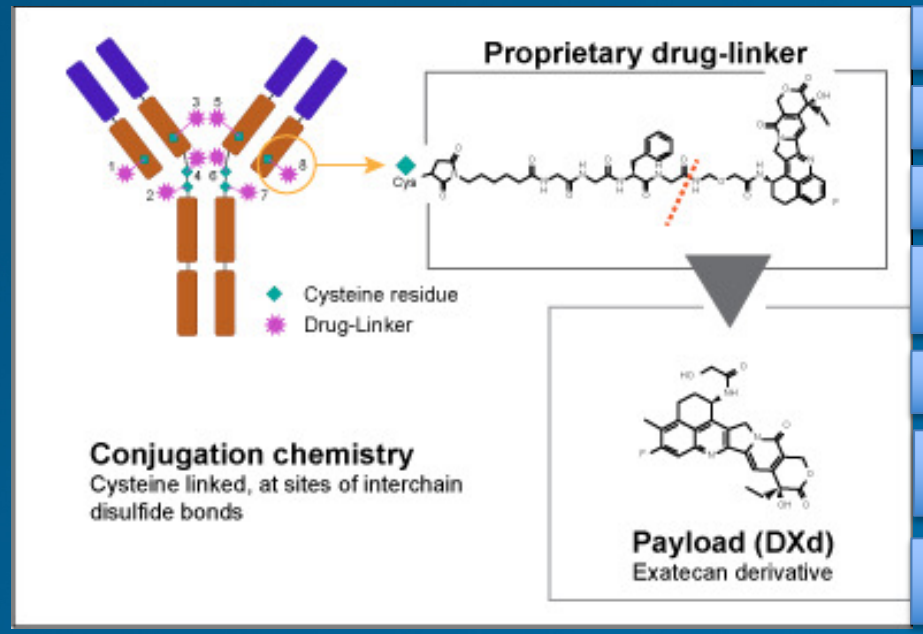
Trastuzumab Deruxtecan: Structure and Mechanism of Action



- Novel payload
- High potency
- Bystander effect
- Short systemic half-life payload
- Stable linker-payload
- Tumor selective cleavable-linker
- High drug-to-antibody ratio

Designed with the goal of improving clinical attributes of an ADC

Drug Design Attributes

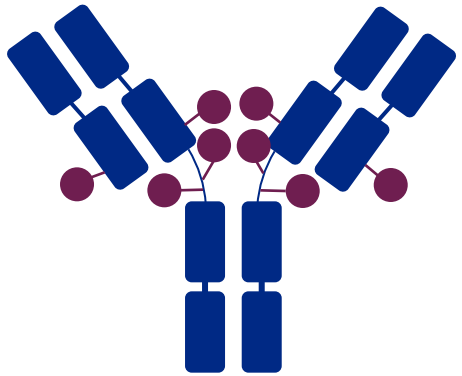
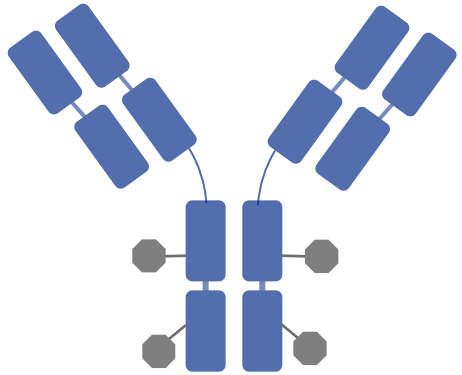
	DS-8201	T-DM1	Clinical Implications
Payload	Topoisomerase-1 inhibitor	Tubulin inhibitor	**Validated topo-1 mechanism**
Drug antibody ratio	High: 7-8	Low: 3-4	**More drug delivered, greater tumor cell killing**
Payload Membrane permeability	Highly membrane permeable → "bystander effect"	Membrane impermeable → no "bystander effect"	**Kills neighboring heterogenous non-HER2 tumor cells (pH-dependent topo-1 potency)**

[Fam-] trastuzumab deruxtecan is an antibody-drug conjugate with a HER2 antibody, peptide-based cleavable linker, and a novel topoisomerase I inhibitor payload

ADC, antibody-drug conjugate; T-DM1, trastuzumab emtansine.

Doi et al. *J Clin Oncol*. 2017;35. Ogitani et al. *Clin Cancer Res*. 2016;22(20):5097-5108.

ADC Characteristic Differences Between T-DXd and T-DM1

T-DXd[1]	T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]	T-DM1[5]
	Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule	
	~8:1	**Drug-to-antibody ratio**	~3.5:1	
	Yes	**Tumor-selective cleavable linker?**	No	
	Yes	**Evidence of bystander anti-tumor effect?**	No	

ADC, antibody-drug conjugate; MoA, mechanism of action; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]The clinical relevance of these features is under investigation.
1. Nakada et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-185. 2. Ogitani et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Trail et al. *Pharmacol Ther.* 2018;181:126-142.
4. Ogitani et al. *Cancer Sci.* 2016;107:1039-1046. 5. LoRusso et al. *Clin Cancer Res.* 2011;17:6437-6447.

Trastuzumab Deruxtecan: DESTINY-Lung01

An open-label, multicenter, phase 2 study (NCT03505710)

Patients

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- HER2-expressing or HER2-activating mutation
- No prior HER2-targeted therapy, except pan-HER TKIs

Cohort 1

HER2-expressing (IHC 3+ or IHC 2+)

T-DXd 6.4 mg/kg q3w

Cohort 2

HER2 mutated

T-DXd 6.4 mg/kg q3w

Primary Endpoint

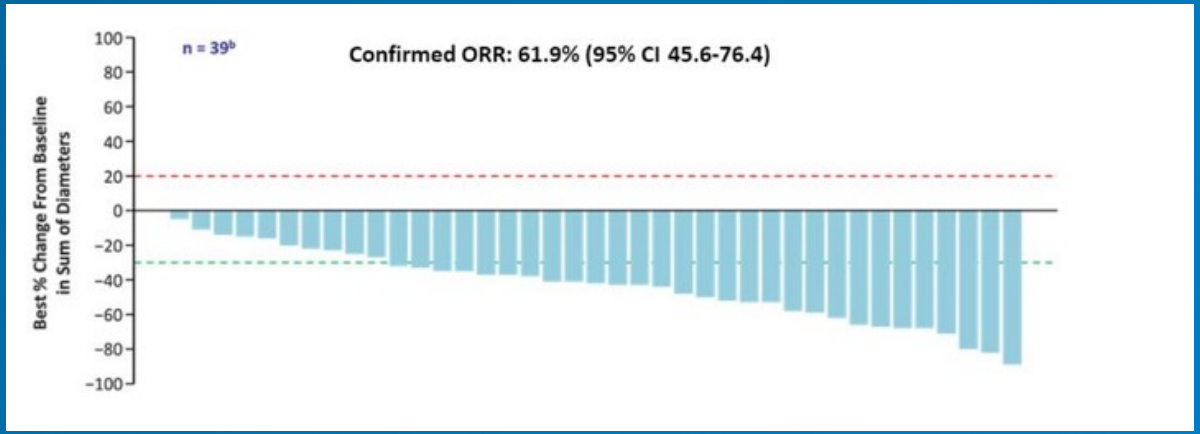
- Confirmed ORR by independent central review

NSCLC, non-small cell lung cancer; ORR, objective response rate; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.
Adapted from Smit et al. *J Clin Oncol*. 2020;38(suppl 15):9504.

Trastuzumab Deruxtecan: DESTINY-Lung01 HER2-Mutated NSCLC

	Patients (N = 42)
Confirmed ORR, n (%)	26 (**61.9**)
CR	1 (2.4)
PR	25 (59.5)
SD	12 (28.6)
PD	2 (4.8)
DCR, %	90.5
Median DoR, mo	NR
Median PFS, mo	14.0
Median OS, mo	NR

Best Percentage Change in Tumor Size With T-DXd



May 2020: FDA granted Breakthrough Therapy designation for the treatment of patients with mNSCLC whose tumors are HER2+ and with disease progression on or after platinum-based therapy

CR, complete response; DCR, disease control rate; DoR, duration of response; mNSCLC, metastatic non-small cell lung cancer; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

Smit et al. *J Clin Oncol*. 2020;38(suppl 15):9504; *J Thorac Oncol*. 2021;16(3):S173.

ESMO 2021: Phase 2 DESTINY-Lung01 Trial T-DXd in HER2-Mutated mNSCLC

Efficacy	N = 91
Confirmed ORR by ICR	**54.9%**
CR	1.1%
PR	53.8%
SD	37.4%
PD	3.3%
DCR	92.3%
mDOR	9.3 mo
mPFS	8.2 mo
mOS	17.8 mo

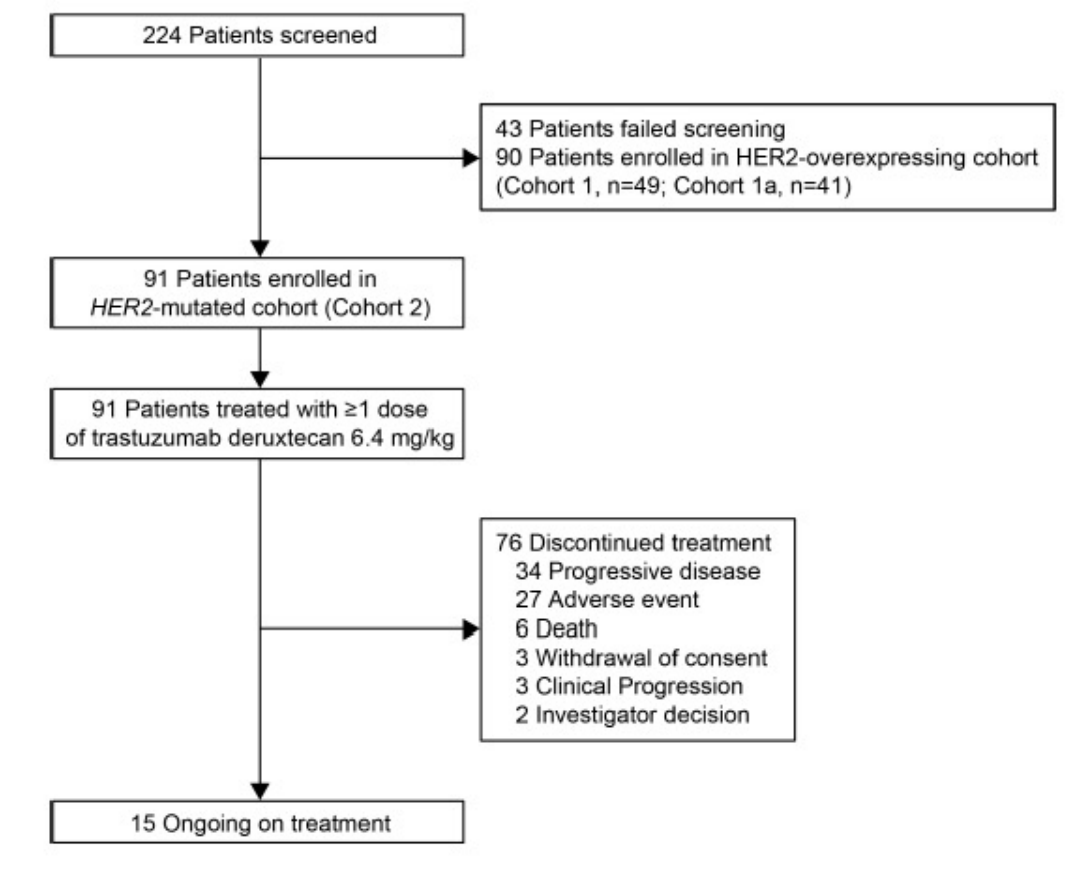
Safety	N = 91
Any TRAE	96.7%
Grade ≥3 TRAE	46.2%
Neutropenia	19%
Any grade adjudicated drug-related ILD	26%

CR, complete response; DCR, disease-control rate; HER2, human epidermal growth factor receptor 2; ICR, independent central review; ILD, interstitial lung disease; mDOR, median duration of response; mNSCLC, metastatic non-small cell lung cancer; mPFS, median progression-free survival; mOS, median overall survival; ORR, objective response rate; PD, progressive disease; PR, partial response; SD stable disease; TRAE, treatment-related adverse event.

Li et al. *Ann Oncol*. 2021;32(suppl 5):S1283-S1346; *N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2112431.

DESTINY-Lung01: HER2-Mutated mNSCLC Patients

Trial Profile



Baseline Characteristics

Characteristic	N = 91
Median age	60 years
Location of HER2 mutation	
Kinase domain	93%
Extracellular domain	7%
Median # of lines of previous cancer therapy	2
Previous cancer therapy	99% (n = 1)
Platinum-based therapy	95%
Docetaxel	20%
Anti-PD-1 or anti-PD-L1 treatment	66%
HER2 TKI	14%
CNS metastases at baseline	36%
Previous lung resection	22%

CNS, central nervous system; HER2 human epidermal growth factor receptor 2; PD-1 programmed cell death protein 1; PD-L1 programmed cell death protein ligand 1; TKI, tyrosine kinase inhibitor.

Smit et al. *J Clin Oncol*. 2020;38(15):9504. Li et al. *N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2112431.

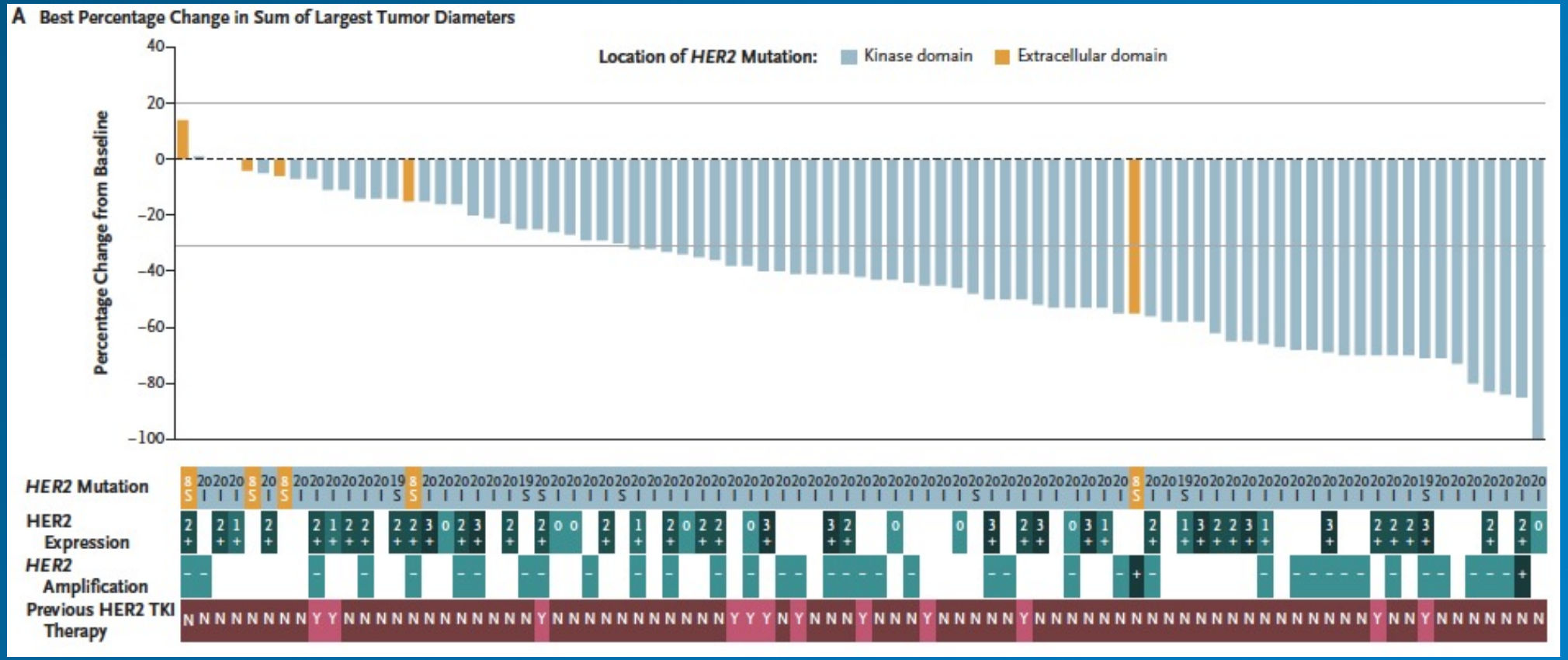
DESTINY-Lung01: HER2-Mutated mNSCLC Response to Trastuzumab Deruxtecan

	No. of Events/ Total No. of Patients	Objective Response Rate (95% CI)
All patients	50/91	54.9 (44.2-65.4)
HER2 mutation domain		
Kinase domain	49/85	57.6 (46.5-68.3)
Prior treatment received		
Platinum-based therapy	46/86	53.5 (42.4-64.3)
Platinum-based therapy and anti-PD1/PD-L1 therapy	37/57	64.9 (51.1-77.1)
Central nervous system metastasis at baseline		
Yes	18/33	54.5 (36.4-71.9)
No	32/58	55.2 (41.5-68.3)

HER2, human epidermal growth factor receptor 2; mNSCLC, metastatic non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

Smit et al. *J Clin Oncol*. 2020;38(15):9504. Li et al. *N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2112431.

DESTINY-Lung01: HER2-Mutated mNSCLC Antitumor Activity



HER2, human epidermal growth factor receptor 2; mNSCLC, metastatic non-small cell lung cancer.

Smit et al. *J Clin Oncol*. 2020;38(15):9504. Li et al. *N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2112431.

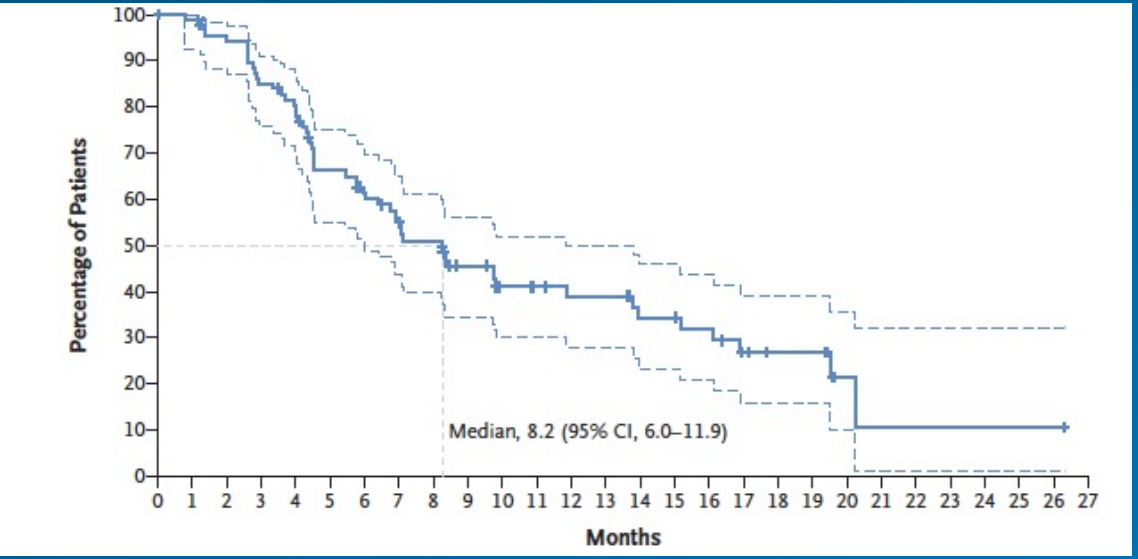
DESTINY-Lung01: HER2-Mutated mNSCLC Biomarker Analyses

- All 91 enrolled patients had a tumor with a locally reported HER2 mutation
  - Most (86%) were exon 20 insertions
  - Other, less common were single-nucleotide variants in exon 19 or 20 of the kinase domain or in exon 8 of the extracellular domain
- Tumor tissue available to evaluate HER2 protein expression (n = 53) and gene-amplification status (n = 45)
  - Any HER2 protein expression (ie, an immunohistochemical score of 1+ to 3+) detected in 44 of 53 patients
  - 9 patients had no detectable HER2 expression
  - HER2 amplification found in 2 of 45 patients
- Responses to treatment were observed in patients with different HER2 mutation subtypes across three exon locations, as well as in patients who had no detectable HER2 expression or tested negative for HER2 amplification

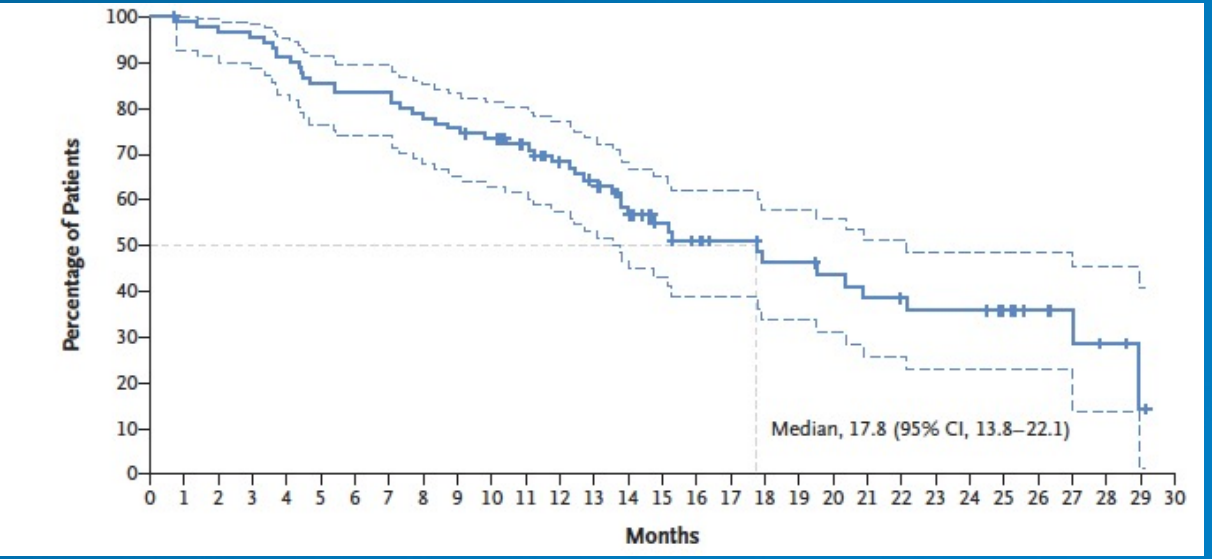
HER2, human epidermal growth factor receptor 2; mNSCLC, metastatic non-small cell lung cancer.
Smit et al. *J Clin Oncol*. 2020;38(15):9504. Li et al. *N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2112431.

DESTINY-Lung01: HER2-Mutated mNSCLC PFS and OS

Progression-free Survival



Overall Survival



HER2, human epidermal growth factor receptor 2; mNSCLC, metastatic non-small cell lung cancer; OS overall survival; PFS, progression-free survival.

Smit et al. *J Clin Oncol*. 2020;38(15):9504. Li et al. *N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2112431.

DESTINY-Lung01: HER2-Mutated mNSCLC Safety

Table 3. Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).

Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
	number of patients (percent)				
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)*	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue†	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia§	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

* One patient had grade 5 (i.e., fatal) pneumonitis that was assessed as drug-related by the investigator (subsequently adjudicated as interstitial lung disease). Another patient had grade 3 interstitial lung disease, as reported by the investigator, and died; the reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee. All adjudicated events of drug-related interstitial lung disease are reported in Table S5.
† This category includes the preferred terms fatigue, asthenia, and malaise.
‡ This category includes the preferred terms neutrophil count decreased and neutropenia.
§ This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased.
¶ This category includes the preferred terms white-cell count decreased and leukopenia.

HER2, human epidermal growth factor receptor 2; mNSCLC, metastatic non-small cell lung cancer.
Smit et al. *J Clin Oncol*. 2020;38(15):9504. Li et al. *N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2112431.

Trastuzumab Deruxtecan: DESTINY-Lung01 HER2-Overexpressing NSCLC

Results	IHC 3+ (N = 10)	IHC 2+ (N = 39)	Overall (N = 49)
Confirmed ORR, n (%)	2 (20.0)	10 (25.6)	12 (**24.5**)
CR	0	(2.6)	(2.0)
PR	2 (20.0)	(23.1)	(22.4)
SD	6 (60.0)	(41.0)	(44.9)
PD	1 (10.0)	(25.6)	(22.4)
DCR, n (%)	8 (80.0)	26 (66.7)	34 (69.4)
Median DoR, mo	6.0	5.8	6.0
Median PFS, mo	-	-	5.4
Median OS, mo	-	-	11.3

CR, complete response; DCR, disease control rate; DoR, duration of response; IHC, immunohistochemistry; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Nakagawa et al. *J Thorac Oncol*. 2021;16(3):S109-S110.

Trastuzumab Deruxtecan: Phase 2 DESTINY-Lung02

HER2+ NSCLC, Second Line

Key Eligibility Criteria

- Confirmed metastatic NSCLC with activating HER2 mutation
- Progression after 1 previous line of platinum-containing therapy
- Absence of *EGFR*, *BRAF* mutations and *ALK*, *ROS1* fusions
- ECOG PS 0 or 1
- LVEF ≥ 50% within 28 days before randomization
- No history of non-infections ILD requiring steroids or active ILD

Primary End Point

- ORR (RECIST v1.1 per BICR)

Key Secondary End Points

- ORR (RECIST v1.1 per investigator)
- DCR, DOR, and PFS (RECIST v1.1 per BICR)
- OS
- Safety

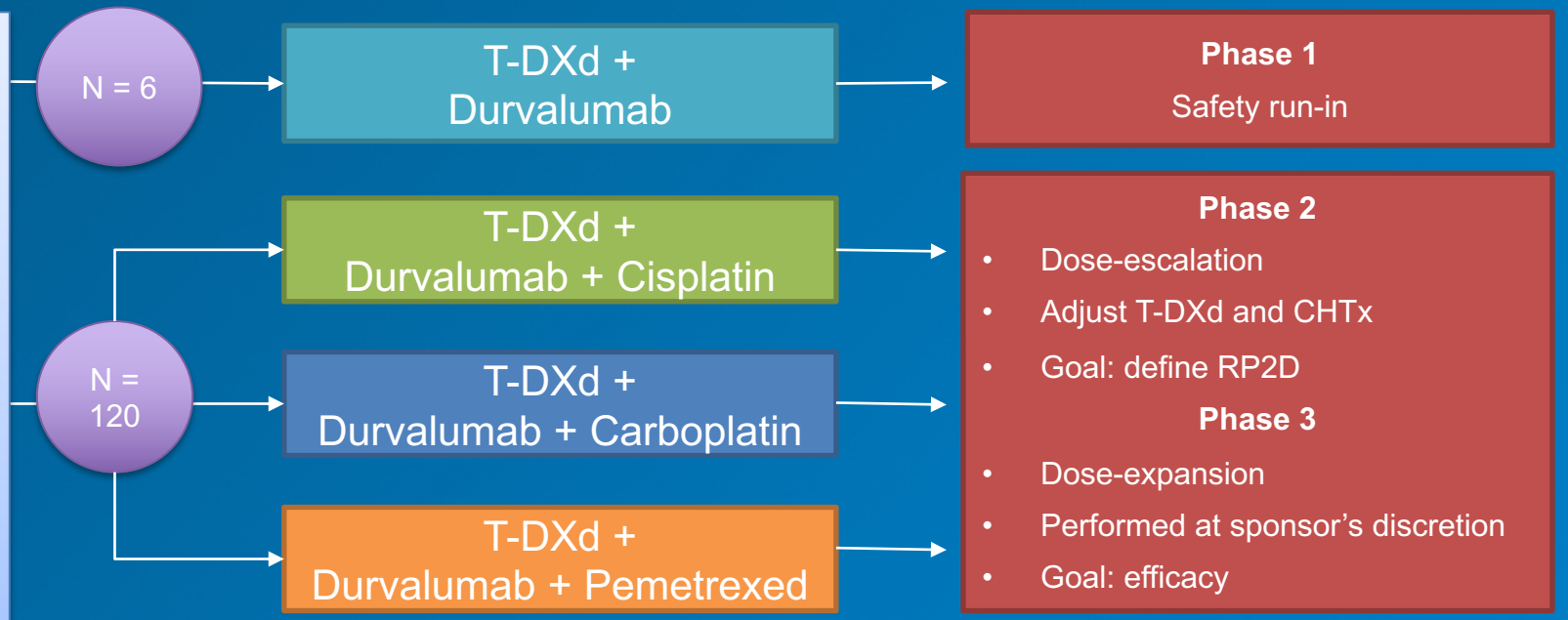
BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; T-DXd, trastuzumab deruxtecan.
Courtesy of Dr. Azar.

Trastuzumab Deruxtecan: Phase 1 DESTINY-Lung03

HER2+ NSCLC, First Line, In Combination with Durvalumab

Key Eligibility Criteria

- Confirmed metastatic NSCLC with activating HER2 expression
- Treatment-naïve or progression >12 months from neo/adjuvant therapy
- Absence of *EGFR* mutations and *ALK*, *ROS1* fusions
- ECOG PS 0 or 1
- Lack of symptomatic CHF or major cardiac event within 6 months
- No history of non-infections ILD requiring steroids or active ILD



Primary End Point

- AEs and SAEs (NCI CTCAE v5.0)

Key Secondary End Points

- ORR, DCR, DOR, and PFS (RECIST v1.1 per investigator)
- OS
- Pharmacokinetics

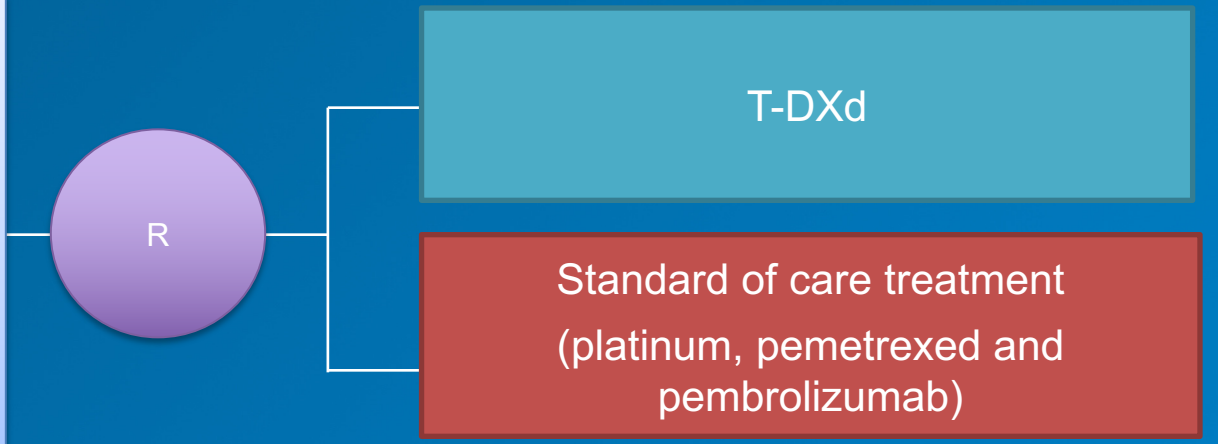
AEs, adverse events; CHF, congestive heart failure; CHTx, chemotherapy; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; RP2D, recommended phase 2 dosage; SAEs, serious adverse events; T-DXd, trastuzumab deruxtecan.
Courtesy of Dr Azar.

Trastuzumab Deruxtecan: Phase 3 DESTINY-Lung04

HER2-Mutated NSCLC, First Line

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic histologically documented non-squamous NSCLC
- HER2 exons 19 or 20 mutations
- Treatment-naïve for palliative intent systemic therapy for locally advanced or metastatic disease



Primary End Point

- PFS by BICR

Key Secondary End Points

- OS
- PFS by investigator assessment
- ORR
- DoR

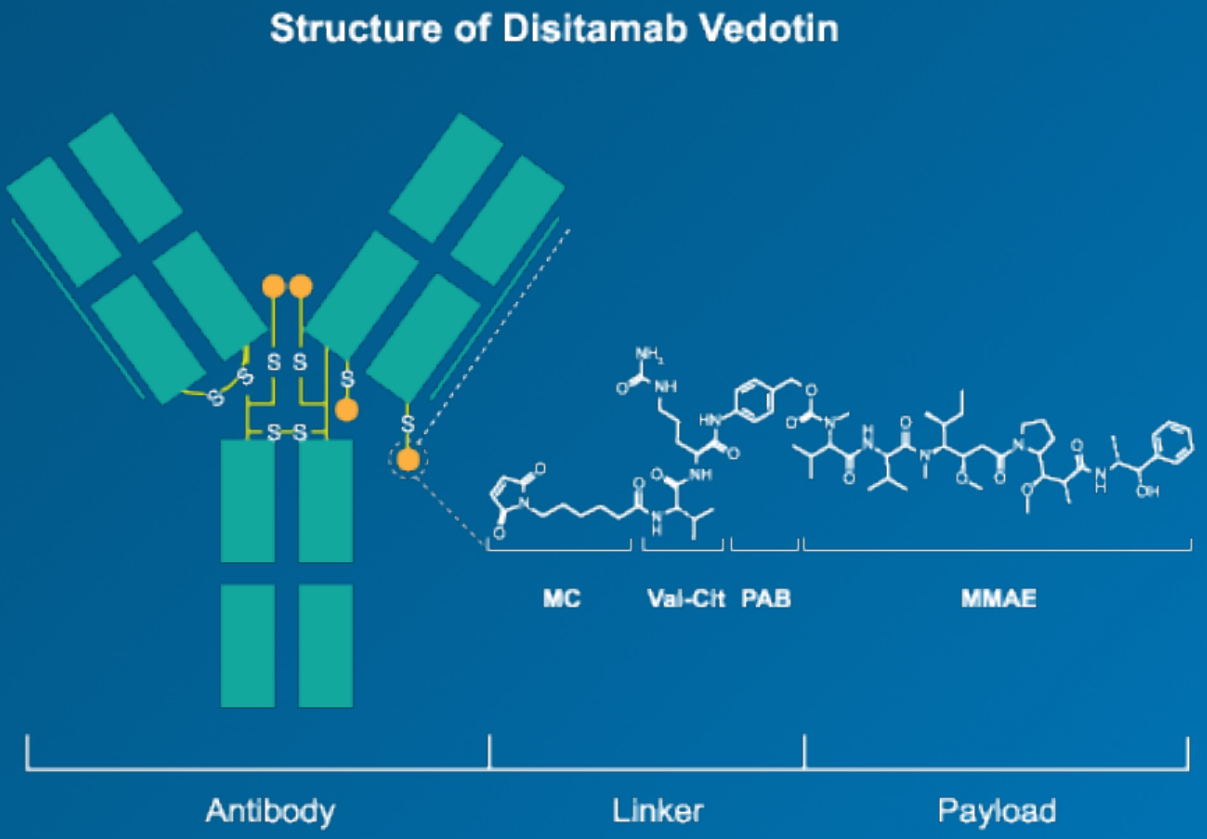
BICR, blinded independent central review; DoR, duration of response; ORR, objective response rate; HER2, human peidermal growth factor receptor 2; mNSCLC, metastatic non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; R, randomized; T-DXd, trastuzumab deruxtecan.
NCT05048797.

Trastuzumab Deruxtecan: Summary of Clinical Trials in NSCLC

Trial	HER2 Alteration	NSCLC Setting	Treatment
DESTINY-Lung01 NCT03505710 Phase 2, single-arm	HER2-overexpressing HER2-mutant	Second line	T-DXd
DESTINY-Lung02 NCT04644237 Phase 2, randomized	HER2-mutant	Second line, disease recurrence or progression during or after ≥1 prior platinum-containing treatment regimen	T-DXd 6.4 mg/kg q3w T-DXd 5.4 mg/kg q3w
DESTINY-Lung03 NCT04686305 Phase 1b	HER2-overexpressing	First line, treatment-naive	T-DXd + durvalumab +/- chemotherapy (cisplatin, carboplatin, or pemetrexed)
DESTINY-Lung04 NCT05048797 Phase 3	HER2-mutant	First line	T-DXd vs. Standard of care treatment (platinum, pemetrexed, and pembrolizumab)
NCT04042701 Phase 1	HER2-overexpressing HER2-mutant	No prior treatment with anti-PD-1, anti-PD-L1, or HER2 agents	T-DXd + pembrolizumab
HUDSON NCT03334617 Phase 2 umbrella	-	Second line, progressed on prior anti-PD1/PD-L1 therapy	T-DXd + durvalumab vs other novel anti-cancer agents + durvalumab

NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Disitamab Vedotin (RC48/RC48-ADC)



- A novel humanized HER2 antibody and monomethyl auristatin E (MMAE), a potent tubulin binder with a half-maximal inhibitory concentration in the sub-nanomolar range, as the cytotoxic payload, are conjugated to each other through a cathepsin cleavable linker
- Phase 1/2 trial for NSCLC with HER2 overexpression or HER2 positivity currently recruiting (NCT04311034)

Adapted from RemeGen Co, Ltd. 2021. http://www.remegen.com/medicine2.aspx?ClassID=96

Case Study Examples:
Integrating ADCs into NSCLC Treatment

Case Example 1: HER2+ NSCLC

- 62-year-old man with right hip pain
- Found to have left lower lobe 3 cm mass, right iliac and L5 bone lesions
- L5 bone biopsy: moderately differentiated adenocarcinoma
- PD-L1 0%(22C3)
- Next-generation sequencing:
  - *EGFR*, *ALK*, *ROS1* negative.
  - *ERBB2* p.Tyr772_Ala775dup positive

PD-L1, programmed cell death protein ligand 1.

How Would You Treat This Patient?

a) Carboplatin, pemetrexed, pembrolizumab
b) Carboplatin, paclitaxel, atezolizumab, bevacizumab
c) Afatinib
d) Other (ie, clinical trial)
e) Unsure

Case 1: Treatment

First-line

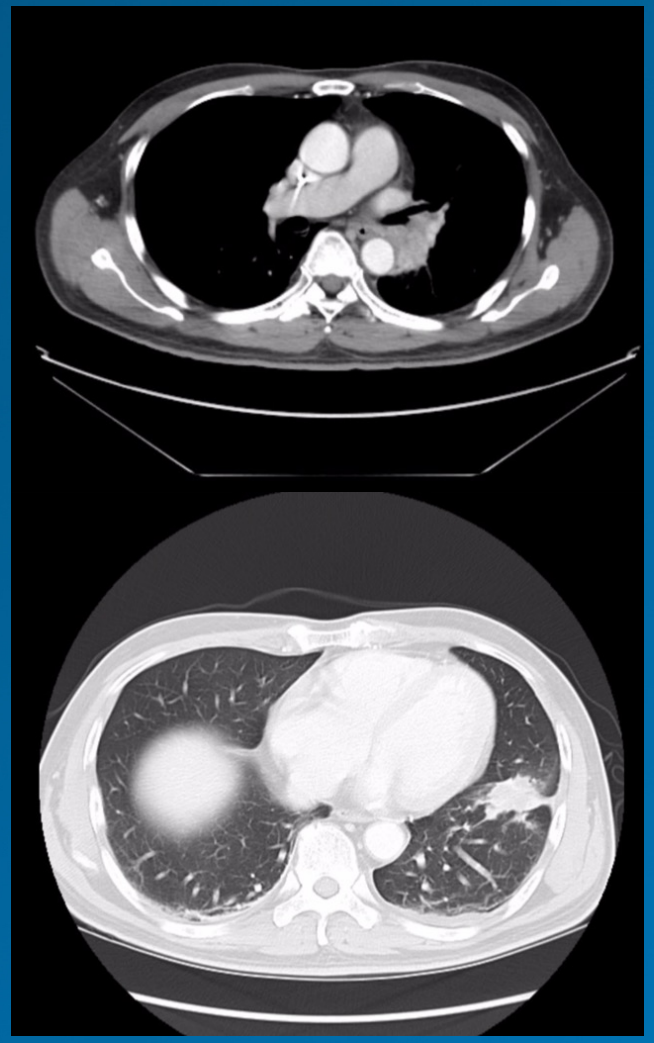
- Carboplatin, pemetrexed, pembrolizumab
- 5/2017-12/2017

Second-line

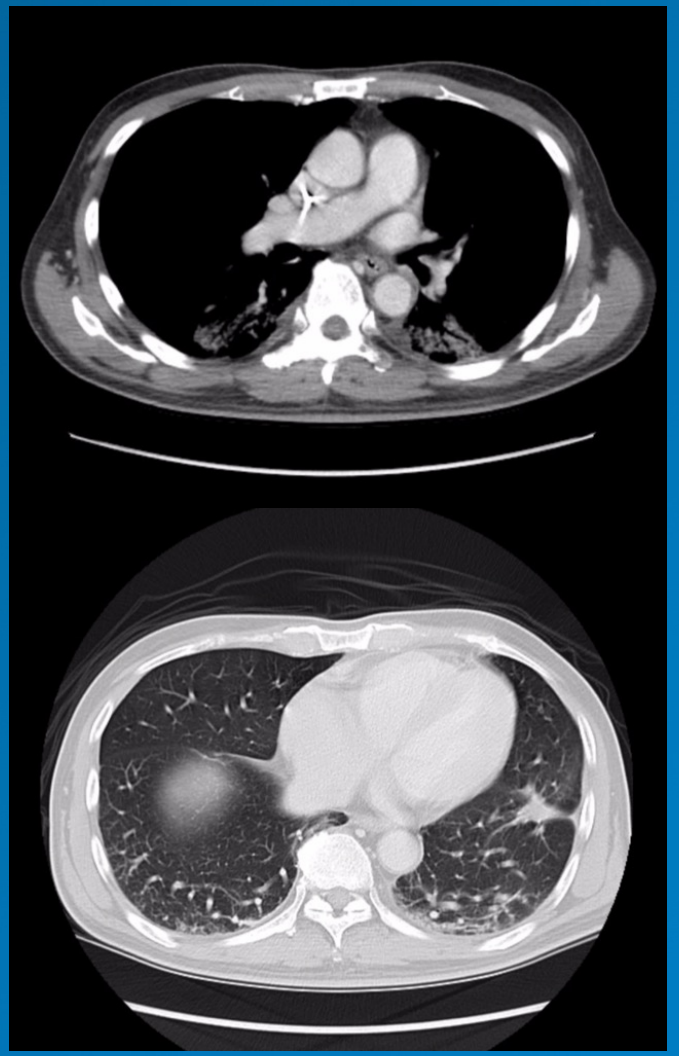
- Clinical trial (poziotinib at MD Anderson Cancer Center)
- 1/2018-9/2018

Third Line: Trastuzumab Deruxtecan

Baseline



~7 Months Post Start of Therapy
Best Response



Case Example 2: HER2 Amplified NSCLC

- 66-year-old woman presents with cough, treated with antibiotics for “pneumonia” without improvement
- CT chest scan revealed left-sided pleural effusion and multiple pleural-based lesions
- Biopsy of the pleural lesion positive for adenocarcinoma
- PD-L1 0%(22C3)
- Next-generation sequencing:
  - *ALK*, *ROS1* negative
  - *EGFR* exon 21 p.L858R positive

CT, computed tomography; PD-L1, programmed cell death protein ligand 1.

Case 2: Treatment

First-line

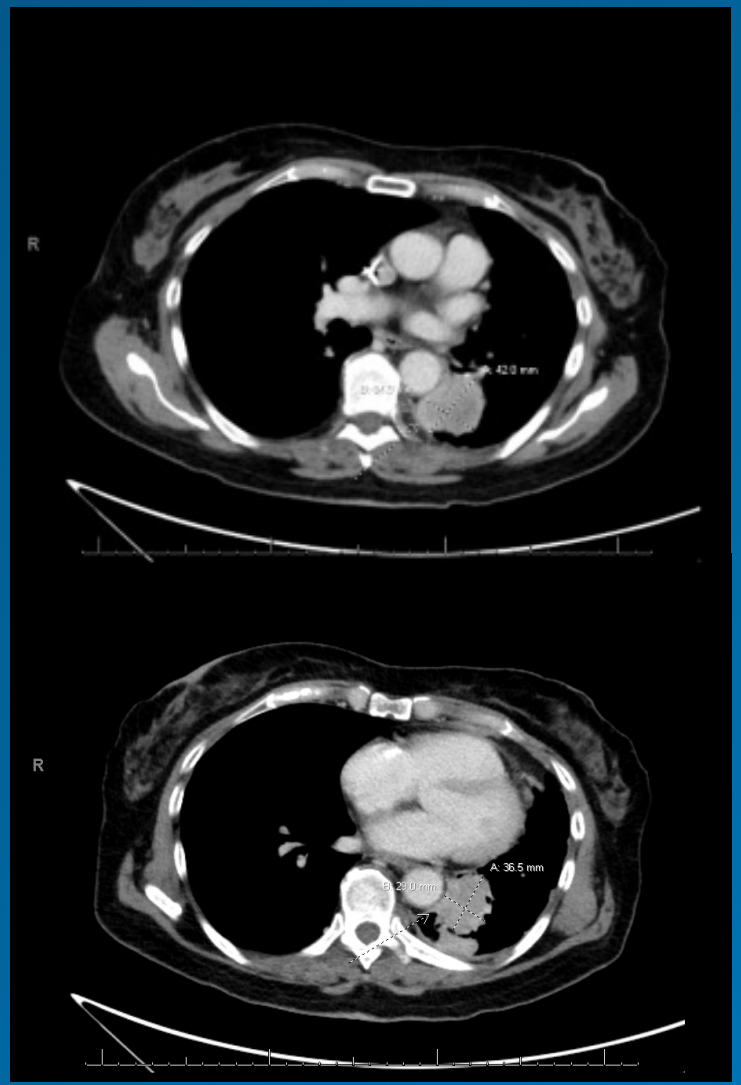
- Osimertinib 80 mg daily
- 7/2017-1/2018

Second-line

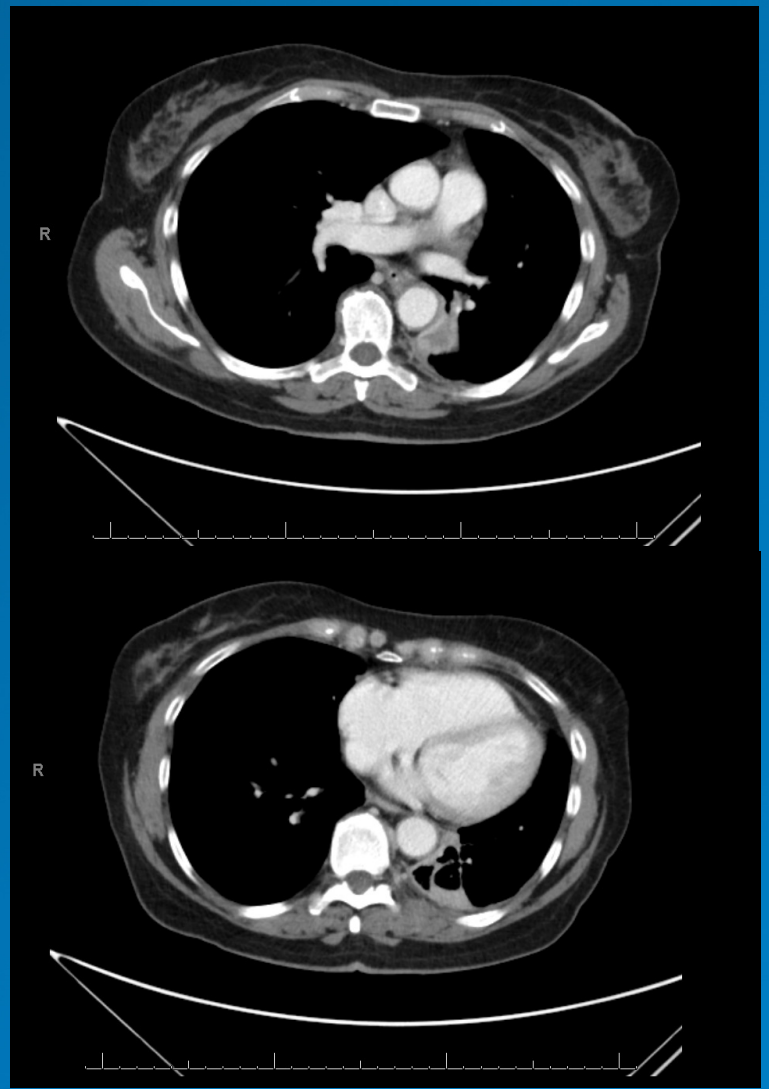
- Carboplatin, pemetrexed, pembrolizumab
- 2/2018-2/2019
- Eventually progressed: Was found to have HER2 2+ overexpression

Third Line: Trastuzumab Deruxtecan

Baseline



3 Months on Therapy
Best Response



AXIS Medical Education

The Emerging Potential of Other ADCs in NSCLC

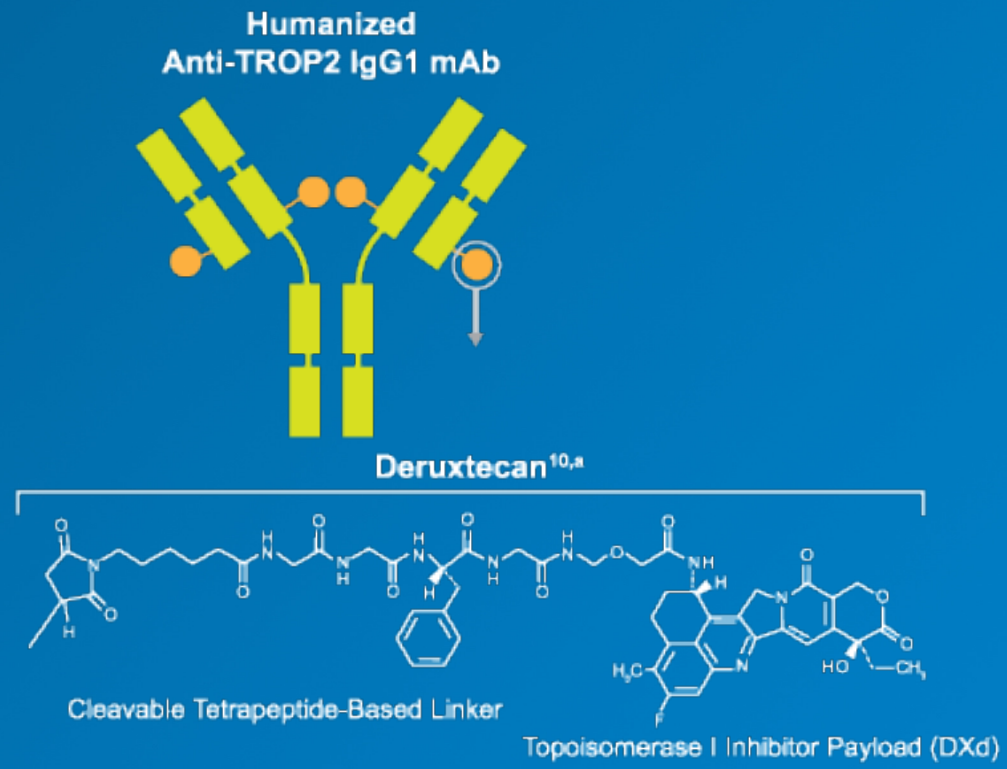
ADCs With Other Targets in NSCLC

ADC Target	ADC
TROP2	Datopotamab deruxtecan (DS-1062; Dato-DXd)
	Sacituzumab govitecan (IMMU-132)
HER3	Patritumab deruxtecan (U3-1402; HER3-DXd)

ADC, antibody-drug conjugate.

Datopotamab Deruxtecan

- TROP2
  - A transmembrane glycoprotein
  - Highly expressed in NSCLC and other solid tumors
  - High TROP2 expression associated with poor prognosis, making it a promising therapeutic target
- Datopotamab deruxtecan
  - TROP2-directed ADC composed of 3 components:
    1. A humanized anti-TROP2 IgG1 mAb
    2. A topoisomerase 1 inhibitor payload (exatecan derivative, DXd)
    3. A tetrapeptide-based cleavable linker

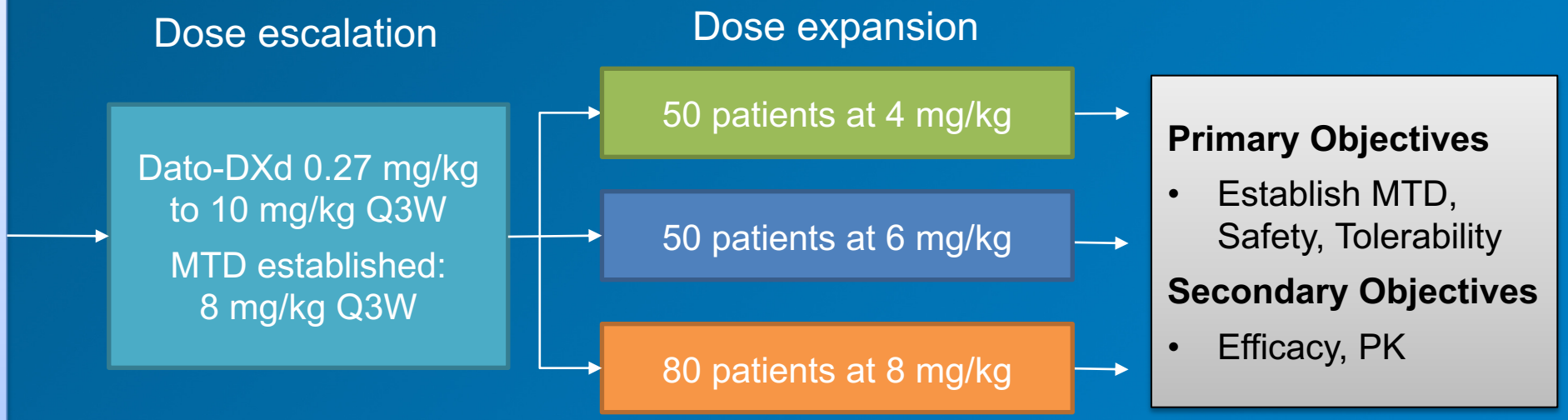


ADC, antibody-drug conjugate; mAb, monoclonal antibody
Adapted from Spira et al. *J Thorac Oncol*. 2021;16(3):S106-S107.

Datopotamab Deruxtecan: Phase 1 TROPION-PanTumor01

Key Inclusion Criteria

- Relapsed/refractory advanced/metastatic NSCLC
- 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



Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose; PK pharmacokinetics.
Adapted from Spira et al. *J Thorac Oncol*. 2021;16(3):S106-S107.

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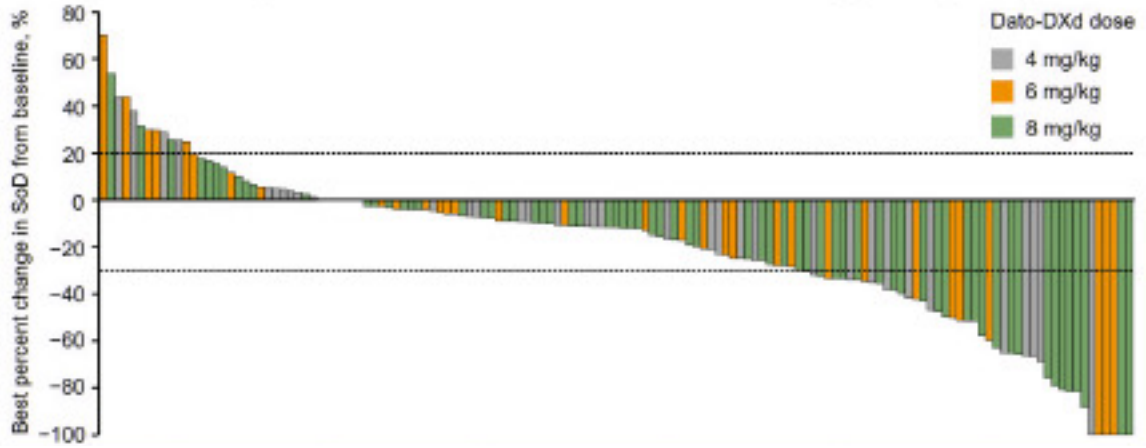
Datopotamab Deruxtecan: Phase 1 TROPION-PanTumor01

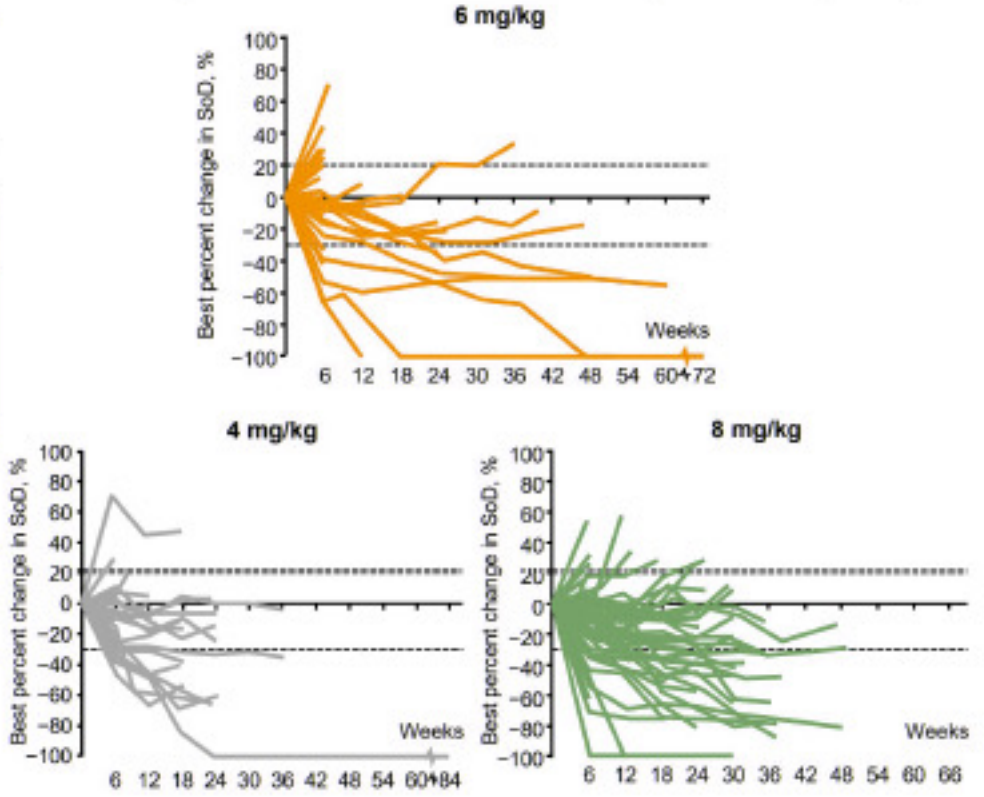
Antitumor Activity of Dato-DXd

Best Change in Sum of Diameters and Overall Response (BICR)



Dato-DXd dose	Response-evaluable patients, n	Confirmed CR/PR, n	CR/PR (too early to be confirmed), n	ORR, % (n)	DCR, % (n)	PD, % (n)
4 mg/kg	40	7	2	23 (0)	73 (20)	15 (6)
6mg/kg	39	6	2	21 (8)	67 (26)	21 (8)
8 mg/kg	80	19	1	25 (20)	80 (64)	9 (7)

Change in Sum of Diameters for Target Lesions (BICR)



Preliminary Progression-free Survival (BICR)

- Median PFS (95% CI)
  - 4 mf/kg: 4.3 months (2.0-NE), 6 mg/kg: 8.2 months (1.5-11.8), 8 mg/kg: 5.4 months (4.1-7.1)

BICR, blinded independent review committee; CR/PR, complete response/partial response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival.

Spira et al. *J Thorac Oncol*. 2021;16(3):S106-S107.

ESMO 2021: Phase 1 TROPION-PanTumor01 Trial Dato-DXd in mNSCLC With Actionable Genomic Alterations

- 34 patients with advanced/metastatic NSCLC with AGAs
  - 4 mg/kg (n = 8)
  - 6 mg/kg (n = 10)
  - 8 mg/kg (n = 16)
- Investigator-reported AGAs:
  - *EGFR* (n = 29)
  - *ALK* (n = 3)
  - *ROS1* (n = 1)
  - *RET* (n = 1)
- Median duration on study: 13 mo

Efficacy Results	
Confirmed ORR by BICR across doses	35%
Median DOR	9.5 mo
Most common any-grade AEs	
Nausea	62%
Stomatitis	56%

Conclusions:

- Antitumor activity and safety in advanced/metastatic NSCLC patients with AGAs are encouraging
- Ongoing phase 2 TROPION-Lung05 trial (NCT04484142) is assessing Dato-DXd at 6 mg/kg in advanced/metastatic NSCLC with AGAs after targeted therapies and platinum chemotherapy

AEs, adverse events; AGA, actionable genomic alterations; BICR, blinded independent central review; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate.

Garon et al. Presented at 2021 ESMO Congress; September 16-21, 2021; Virtual. Abstract LBA49.

Datopotamab Deruxtecan: Phase 3 TROPION-Lung01

NSCLC without actionable mutation

Patients with advanced or metastatic NSCLC (N = 590)

Key Inclusion Criteria

- No actionable genomic alterations
- Stage IIIB or stage IV NSCLC
- Previously treated with platinum-based chemotherapy and anti-PD-1/anti-PD-L1 monoclonal antibody, either in combination or sequentially
- Screening biopsy

Randomization 1:1

Dato-DXd
6 mg/kg
IV infusion Q3W

Docetaxel
75 mg/m^2
IV infusion Q3W

Primary Objectives

- PFS by BICR per RECIST v1.1
- OS

BICR, blinded independent review committee; Dato-DXd, datopotamab deruxtecan; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; Q3W, every 3 weeks.

Adapted from Yoh et al. DOI: 10.1200/JCO.2021.39.15_suppl.TPS9127 *Journal of Clinical Oncology* 39, no. 15_suppl.

Datopotamab Deruxtecan: Phase 1 TROPION-Lung02

- NSCLC without actionable mutation
- In combination with pembrolizumab with or without platinum chemotherapy

NCT04526691

Datopotamab Deruxtecan: Phase 1 TROPION-Lung04

- NSCLC without actionable mutation
- In combination with durvalumab with or without platinum chemotherapy

NCT04612751

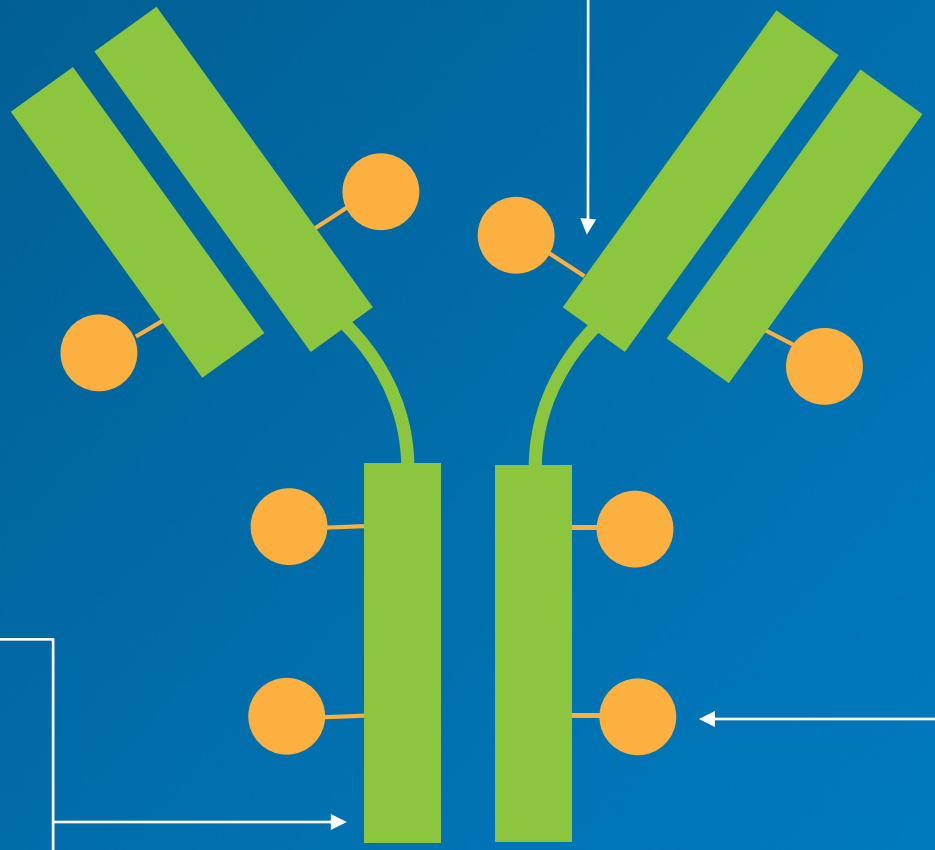
Datopotamab Deruxtecan: Phase 2 TROPION-Lung05

- NSCLC with actionable genomic alterations
  - Has one or more of the following documented activating genomic alterations: *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*
- Previously treated with 1 or more kinase inhibitors and platinum-based chemotherapy

NCT04484142

Sacituzumab Govitecan

Linker for SN-38
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7:6:1)



Humanized anti-Trop-2 Antibody
- Directed toward Trop-2 an epithelial antigen expressed on many solid cancers

SN-38 Payload
- Metabolite of Topo I inhibitor
- SN-38 more potent than parent compound irinotecan

Adapted from National Cancer Institute. 2020. https://www.cancer.gov/news-events/cancer-currents-blog/2020/fda-sacituzumab-govitecan-triple-negative-breast-cancer

Sacituzumab Govitecan: Phase 1/2

- Metastatic epithelial solid tumors
  - Including NSCLC
- Failed prior standard therapies
- Regardless of Trop-2 expression

- Phase 1: 25 patients
  - 2 had partial response
  - 16 achieved stable disease

- Expansion cohort: 54 NSCLC pts
  - ORR: 17%
  - mDoR: 6 months
  - mPFS: 5.2 months
  - mOS: 9.5 months
  - While 92% of tumors overexpressed Trop-2 (IHC 2+ or 3+), no association between sacituzumab govitecan efficacy and Trop-2 expression levels

IHC, immunohistochemistry; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate.

Heist et al. *J Clin Oncol*. 2017;35:2790–2797; Starodub et al. *Clin Cancer Res*. 2105;21:3870-3878.

Sacituzumab Govitecan: Phase 2 TROPiCS-03

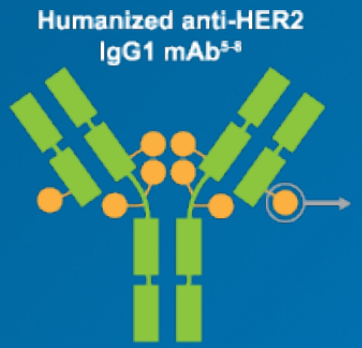
- Patients with metastatic solid tumors
  - NSCLC, head and neck squamous cell carcinoma, or endometrial cancer

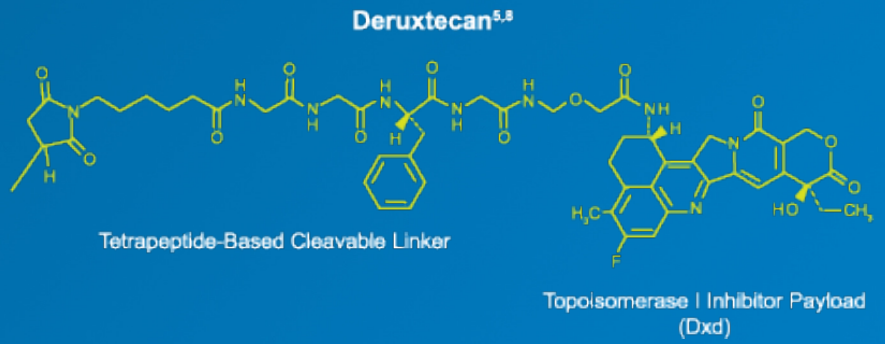
- NSCLC: progressed after prior platinum-based chemotherapy and PD-L1/PD-1 directed therapy; recurrence/relapse or lack of response within 6 months of completion of chemotherapy for locally advanced disease

PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.
ClinicalTrials.gov. NCT03964727

Patritumab Deruxtecan

- Novel, investigational HER3-directed ADC
- Comprising a fully human anti-HER3 IgG1 mAb (patritumab) covalently linked to a topoisomerase I inhibitor payload, an exatecan derivative, via a tetrapeptide-based cleavable linker

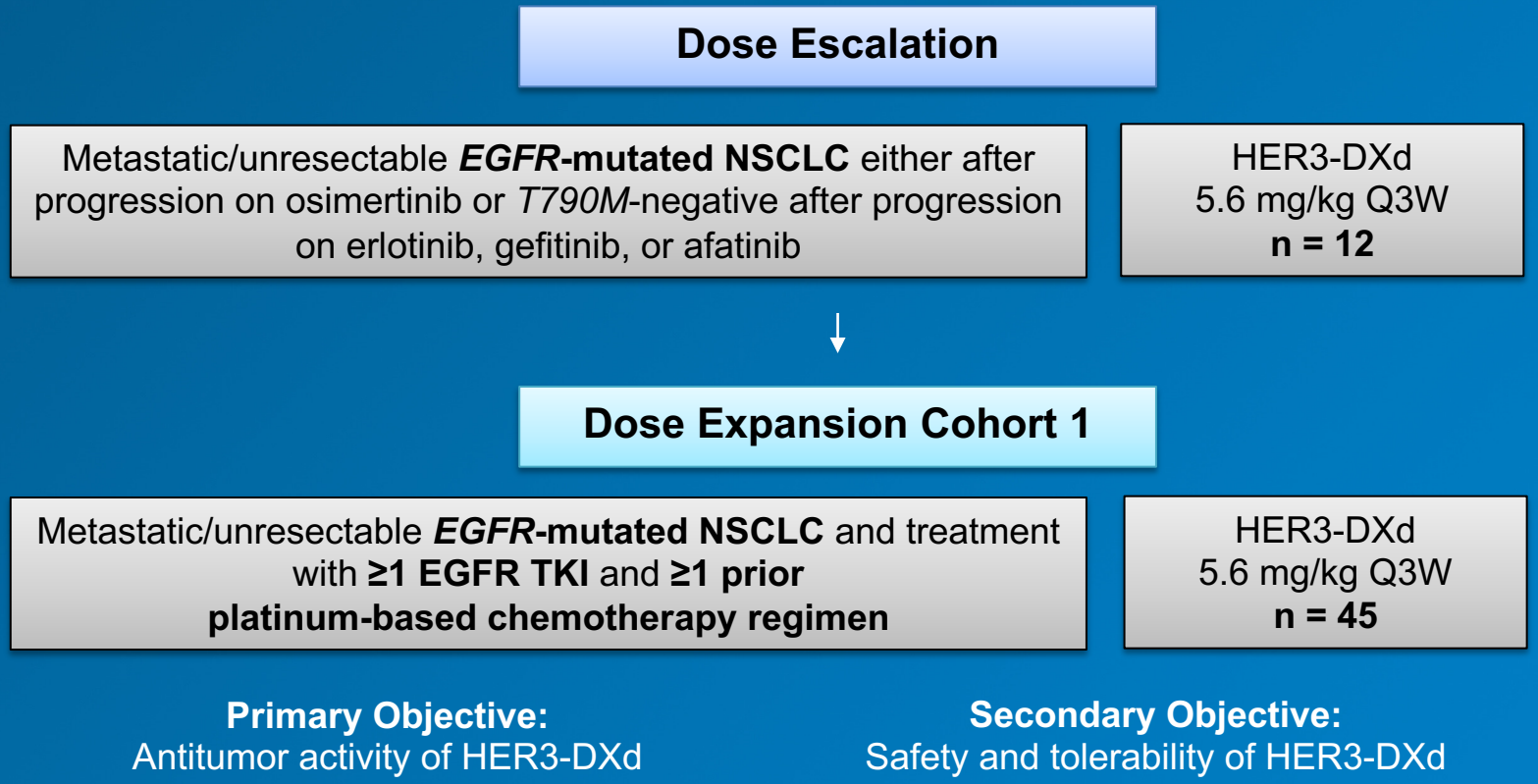




ADC, antibody-drug conjugate; mAb, monoclonal antibody.
Adapted from Yu et al. *J Thorac Oncol*. 2021;16(3):S107.

Patritumab Deruxtecan: Phase 1

- Global, multicenter, open-label phase 1 study
- Patients with metastatic/unresectable NSCLC, including patients harboring an *EGFR*-activating mutation



Primary Objective:
Antitumor activity of HER3-DXd

Secondary Objective:
Safety and tolerability of HER3-DXd

- Stable brain metastases were allowed
- Pretreatment tumor tissue (after progression on TKIs) required for retrospective analysis of HER3 expression

HER3-DXd, patritumab deruxtecan; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitor.
Adapted from Yu et al. *J Thorac Oncol*. 2021;16(3):S107.

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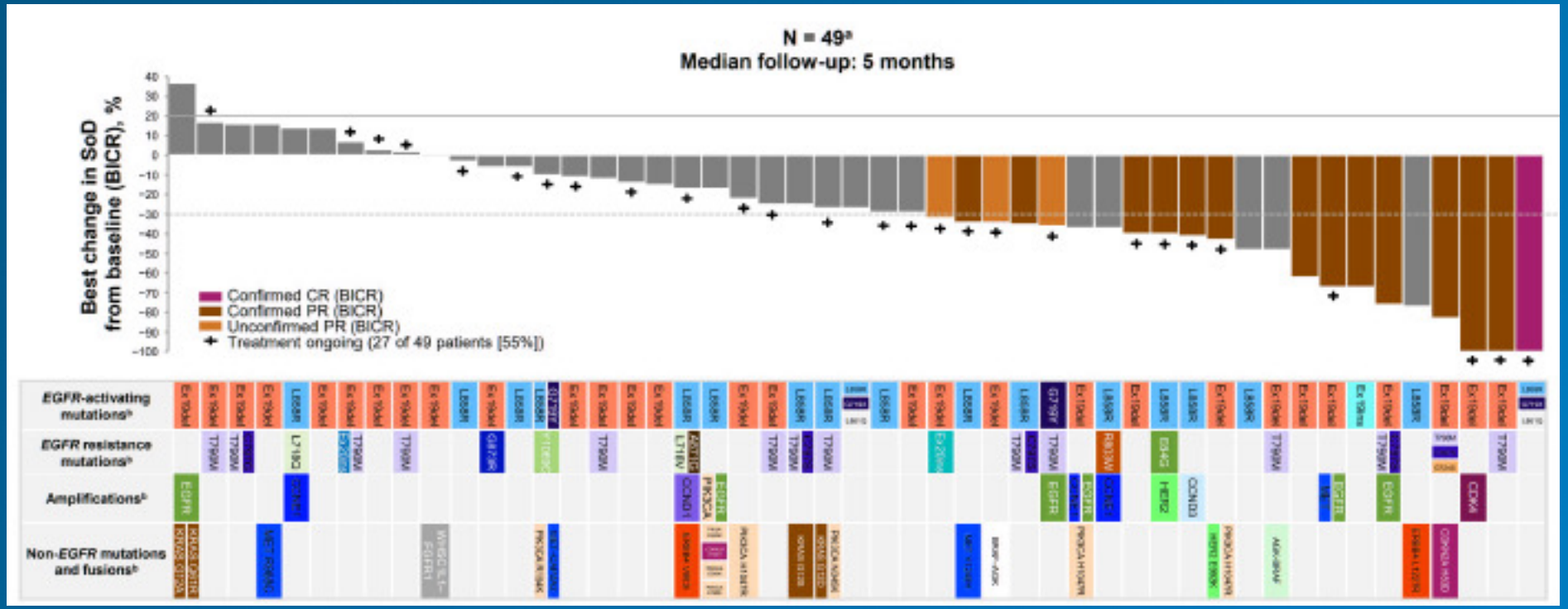
Patritumab Deruxtecan: Phase 1



- HER3-DXd 5.6 mg/kg demonstrated antitumor activity in *EGFR*+ NSCLC with diverse TKI resistance mechanisms
- Confirmed ORR by BICR: 25% (14/56; 14.4-38.4)

BICR, blinded independent review committee; HER3-DXd, patritumab deruxtecan; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
Yu et al. *J Thorac Oncol*. 2021;16(3):S107; Janne et al. *J Thorac Oncol*. 2021;16 (3):S237.

AXIS Medical Education

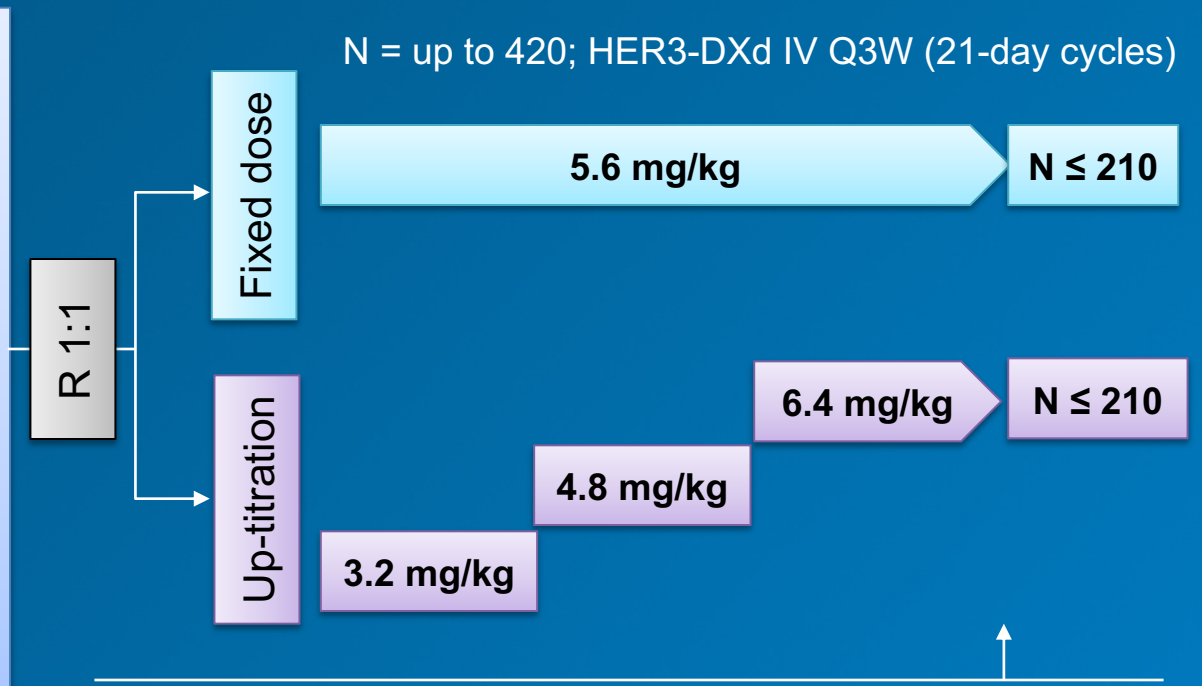
Patritumab Deruxtecan: Phase 2 HERTHENA-Lung01

Previously Treated Advanced/Metastatic *EGFR*+ NSCLC

Eligibility Criteria

- Metastatic/unresectable NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)
- Prior treatment with osimertinib and ≥1 prior platinum-based chemotherapy regimen
- Progression during/after most recent systemic therapy
- Pretreatment tumor biopsy or archived tumor tissue since progression
- Brain metastases allowed if stable

HER3 expression will not be used to select patients for enrollment



If the ongoing phase 1 study (U31402-A-U102) indicates a clear benefit or risk of using a particular HER3-DXd regimen, a decision could be made to continue enrollment in a fixed-dose arm only, up-titration arm only, or both arms

Objectives

Primary

- ORR by BICR

Secondary

- DOR
- PFS
- ORR by investigator
- DCR, TTR, best percent change in SoD
- OS
- Safety and tolerability
- HER3 as a biomarker
- Immunogenicity of HER3-DXd

BICR, blinded independent review committee; DCR, disease control rate; DOR, duration of response; HER3-DXd, patritumab deruxtecan; ORR, objective response rate; PFS, progression-free survival; Q3W, every 3 weeks; TTR, time to response.

Adapted from Janne et al. *J Thorac Oncol*. 2021;16(3):S236.

Anti-CEACAM5-maytansinoid ADC

- SAR408701: consists of an anti-CEACAM5 antibody (SAR408377) coupled to a maytansinoid agent DM4 via a cleavable linker
- Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a glycoprotein that has limited expression in normal adult tissues, but is overexpressed in carcinomas of the gastrointestinal tract, the genitourinary and respiratory systems, and breast cancer

- Phase 3 CARMEN LC03 vs docetaxel in non-squamous NSCLC (NCT04154956)
- Phase 2 CARMEN LC04 with ramucirumab in non-squamous NSCLC (NCT04394624)
- Phase 2 CARMEN LC05 with pembrolizumab or carboplatin, pembrolizumab in non-squamous NSCLC (NCT04524689)
- Phase 2 CARMEN BT01 in breast and pancreatic cancer (NCT04659603)

ADC, antibody-drug conjugate.

Decary et al. *Clin Cancer Res*. 2020;26(24):6589-6599.

Other ADC Targets: Trop-2 and HER3

ADC	Target	Phase	Trial	Population/Results
datopotamab deruxtecan (DS-1062)	Trop-2	1	TROPION-PanTumor01 (NCT03401385)	demonstrated early antitumour activity in patients with advanced/metastatic NSCLC who had progressed on standard treatment
		3	TROPION-Lung01 (NCT04656652)	versus docetaxel in patients with advanced or metastatic NSCLC without actionable genomic alterations previously treated with platinum-based chemotherapy and PD-1/PD-L1 monoclonal antibody, either in combination or sequentially
		1	TROPION-Lung02 (NCT04526691)	with pembrolizumab with or without platinum chemotherapy in patients with advanced or metastatic NSCLC
		1	TROPION-Lung04 (NCT04612751)	with durvalumab with or without platinum chemotherapy in patients with advanced or metastatic NSCLC
sacituzumab govitecan (IMMU-132)		1/2	NCT01631552	patients NSCLC who had failed prior standard therapies, regardless of Trop-2 expression; ORR 17%
		2	TROPICS-03 (NCT03964727)	metastatic solid tumors, including NCSLC
patritumab deruxtecan (U3-1402)	HER3	1	NCT03260491	patients with previously treated metastatic or locally advanced *EGFR*+ NSCLC; preliminary antitumor activity and safety in heavily pretreated patients, with a confirmed ORR of 25% in 56 patients with *EGFR*+ NSCLC with prior EGFR TKI and platinum-based chemotherapy; almost all evaluable tumors expressed high levels of HER3 at baseline
		2	HERTHENA-Lung01 (NCT04619004)	patients with previously treated metastatic or locally advanced *EGFR*+ NSCLC
patritumab deruxtecan + osimertinib		1	NCT04676477	patients with locally advanced or metastatic *EGFR*+ NSCLC

ADC, antibody-drug conjugate; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TKI, tyrosine kinase inhibitor.

Key Takeaways

- Antibody-drug conjugates in NSCLC are here to stay
  - Ado-trastuzumab emtansine and trastuzumab deruxtecan are currently listed as potential novel therapies for HER2+ NSCLC in NCCN Guidelines
  - Trastuzumab deruxtecan demonstrated impressive clinical activity in HER2-mutated and HER2-overexpressing metastatic NSCLC in previously treated patients, with modest myelosuppression and toxicities
  - Other antibody-drug conjugate targets in NSCLC include TROP2 and HER3
- Providers must familiarize themselves with the unique mechanisms of action, efficacy, and potential toxicities
- Better methods to predict efficacy will need to be developed

AXIS Medical Education

The Clinical Playbook:

Team-based Integration of ADCs in Metastatic NSCLC