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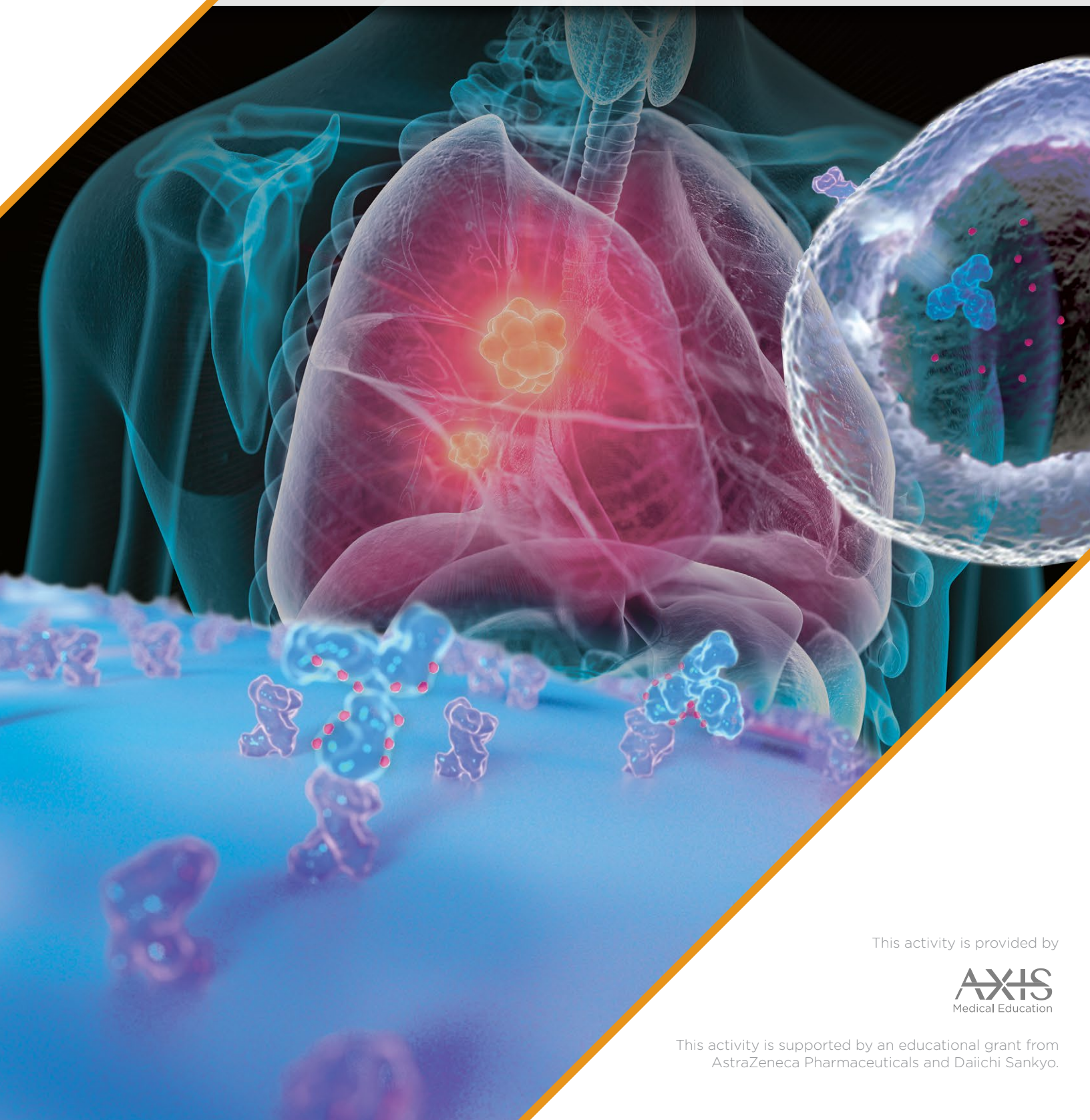
The Clinical Playbook:

Team-based Integration of ADCs in Metastatic NSCLC

This transcript has been edited for style and clarity and includes all slides from the presentation.



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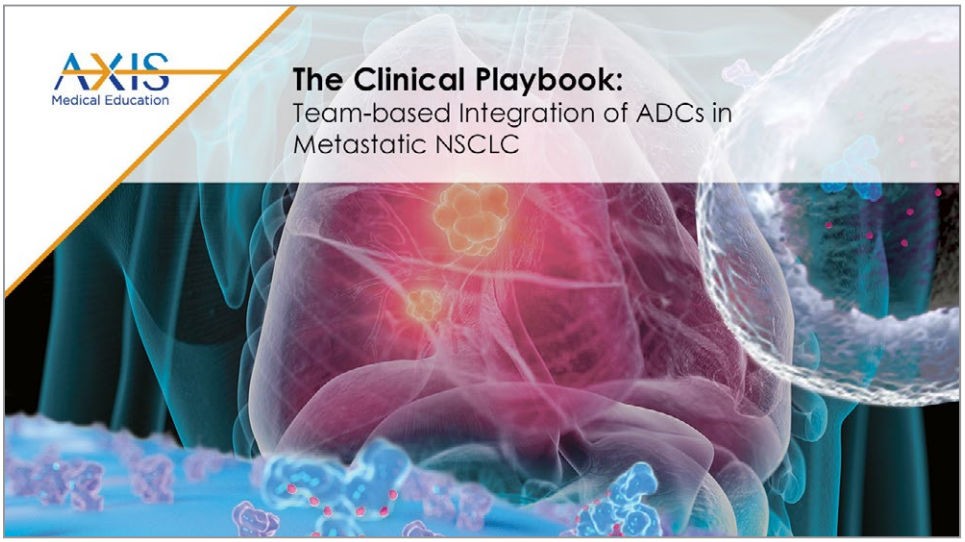
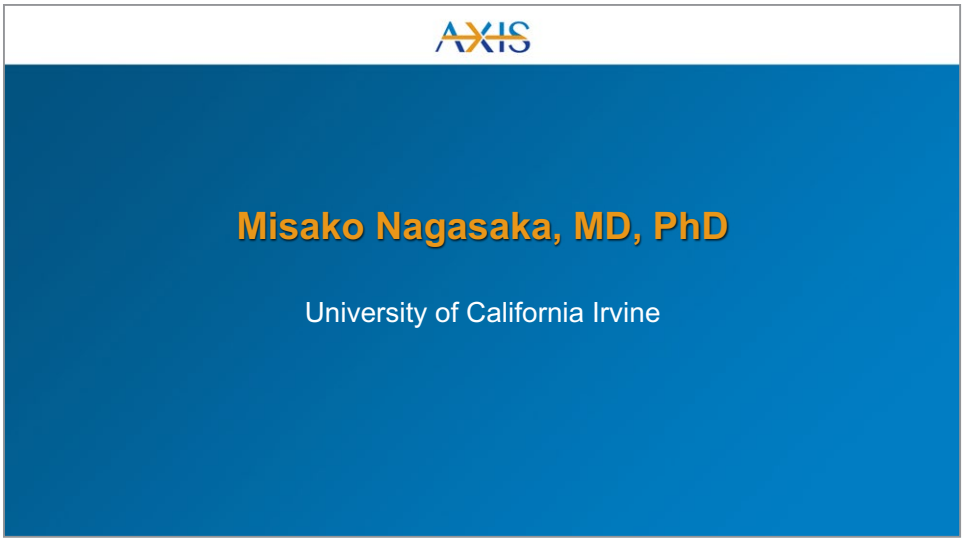
This activity is supported by an educational grant from AstraZeneca Pharmaceuticals and Daiichi Sankyo.

The Clinical Playbook:
Team-based Integration of ADCs in Metastatic NSCLC

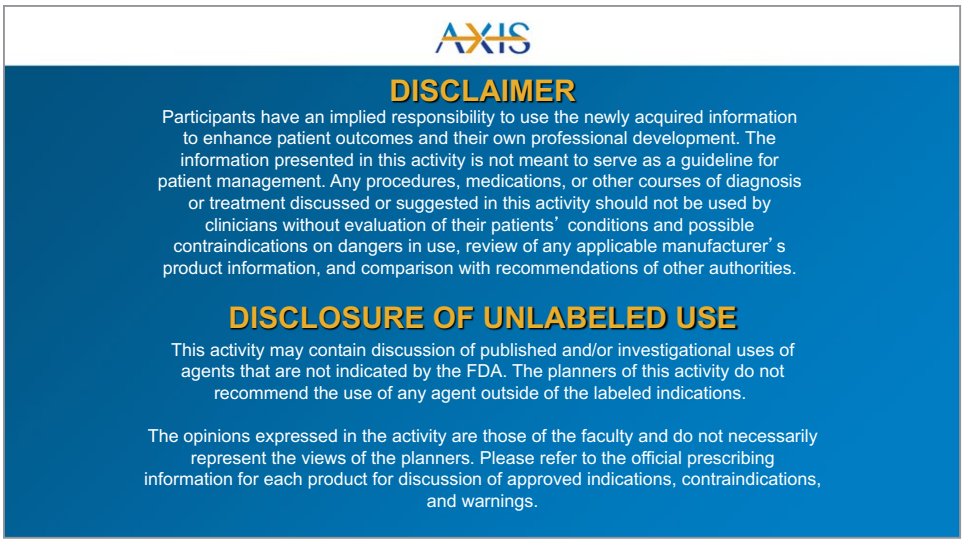
Misako Nagasaka, MD, PhD



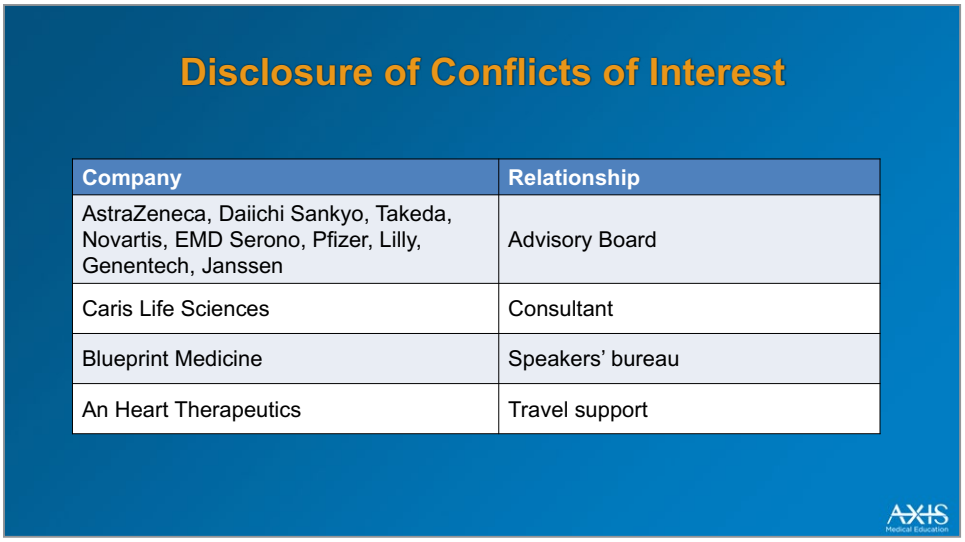
- **Misako Nagasaka, MD, PhD:** Hello, and welcome to this educational activity, *The Clinical Playbook: Team-based Integration of ADCs in Metastatic Non-Small Cell Lung Cancer.*



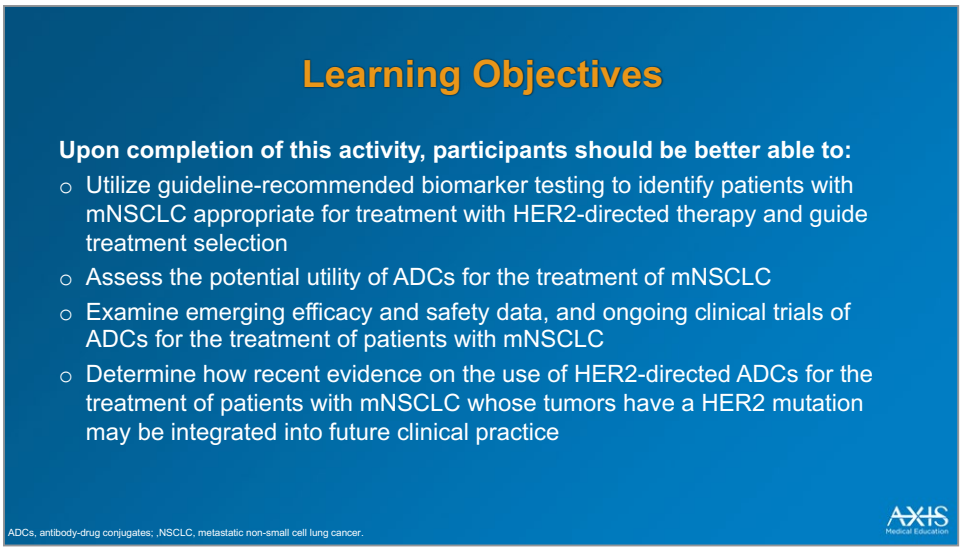
- I am Misako Nagasaka, Associate Clinical Professor from the Division of Hematology and Oncology, Department of Medicine, at the University of California Irvine.



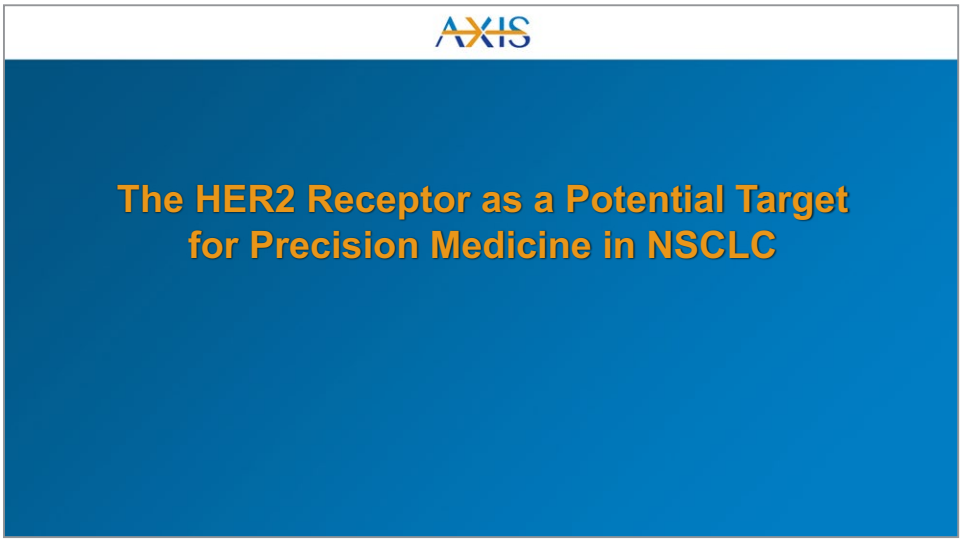
- First, a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development.



- Here is my financial disclosure information.



- Upon completion of this activity, participants should be better able to: Utilize guideline-recommended biomarker testing to identify patients with metastatic non-small cell lung cancer appropriate for treatment with HER2-directed therapy and guide treatment selection. Assess the potential utility of ADCs for the treatment of metastatic non-small cell lung cancer. Examine the emerging efficacy and safety data, and ongoing clinical trials of ADCs for the treatment of patients with metastatic non-small cell lung cancer. Determine how recent evidence on the use of HER2-directed ADCs for the treatment of patients with metastatic non-small cell lung cancer whose tumors have a HER2 mutation may be integrated into future clinical practice.



- The HER2 receptor is a potential target for precision medicine in non–small cell lung cancer (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.

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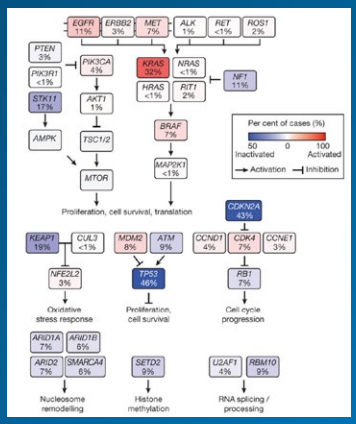
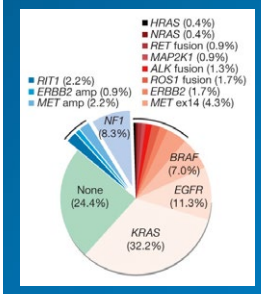
- HER2 is a tyrosine kinase receptor, growth promoting protein expressed on the surface of many types of tumors, including gastric, breast, and lung cancers. In some tumors, HER2 overexpression is associated with a specific HER2 gene alteration known as amplification and is often associated with aggressive disease and poorer prognosis. Other HER2 gene alterations (called HER2 mutations) have been identified in NSCLC, specifically adenocarcinomas, as distinct molecular targets. Approximately 2% to 4% of patients with NSCLC have HER2 mutations, which have been independently associated with cancer cell growth and poor prognosis.

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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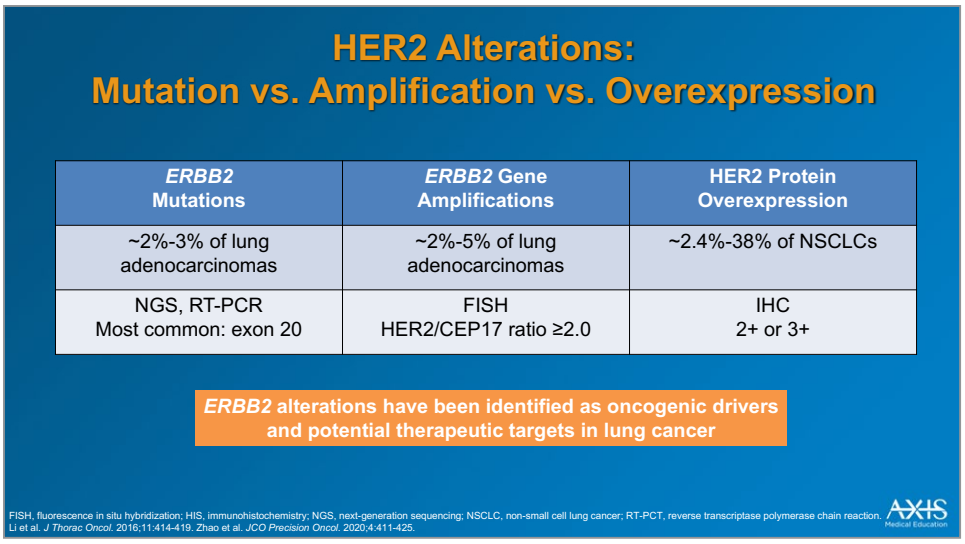
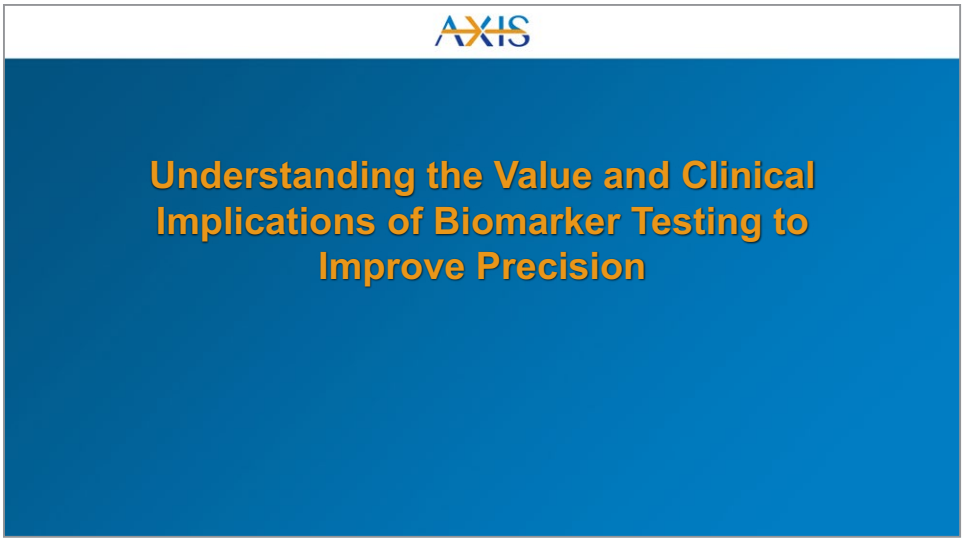
- HER2-activating mutations occur in 2% of lung cancers. These mutations are transforming in lung cancer models and result in kinase activation.

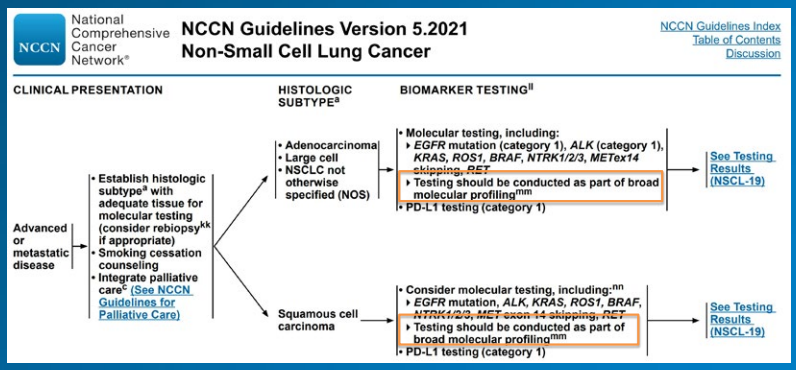


- The HER2 alteration is an *ERBB2* alteration and has been identified as an oncogenic driver and potential therapeutic target in lung cancers. *ERBB2* mutations occur in about 2% to 3% of lung adenocarcinomas. These mutations are most common in exon 20 and are detected typically with with next-generation sequencing or reverse transcriptase polymerase chain reaction. *ERBB2* amplification occurs in about 2% to 5% of lung adenocarcinomas and is picked up with fluorescence in situ hybridization. HER2 protein overexpression occurs in 2.4% to 38% of NSCLCs and is commonly found with immunohistochemistry.



- Understanding the value and clinical implications of biomarker testing to improve precision medicine.

Best Practice Recommendations for Biomarker Testing in NSCLC

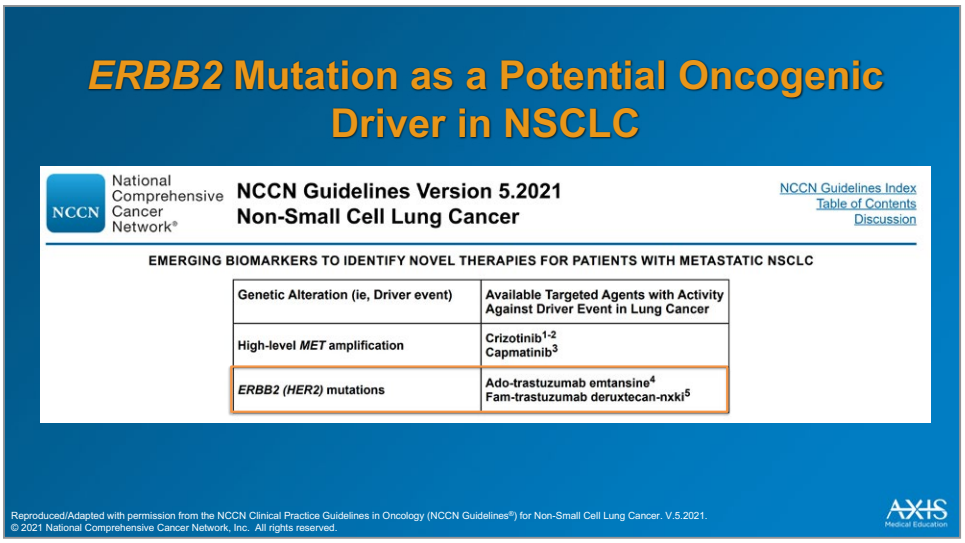


- Biomarker testing for genetic variants is recommend in the NCCN Guidelines based on the outcomes associated with use of targeted therapy in eligible patients with metastatic NSCLC.

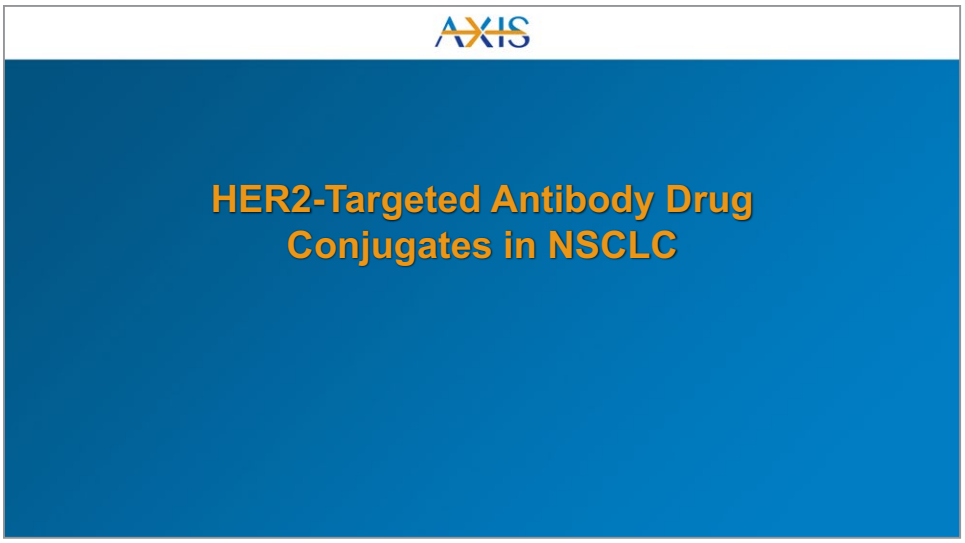
Importance of Broad Molecular Profiling

"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."

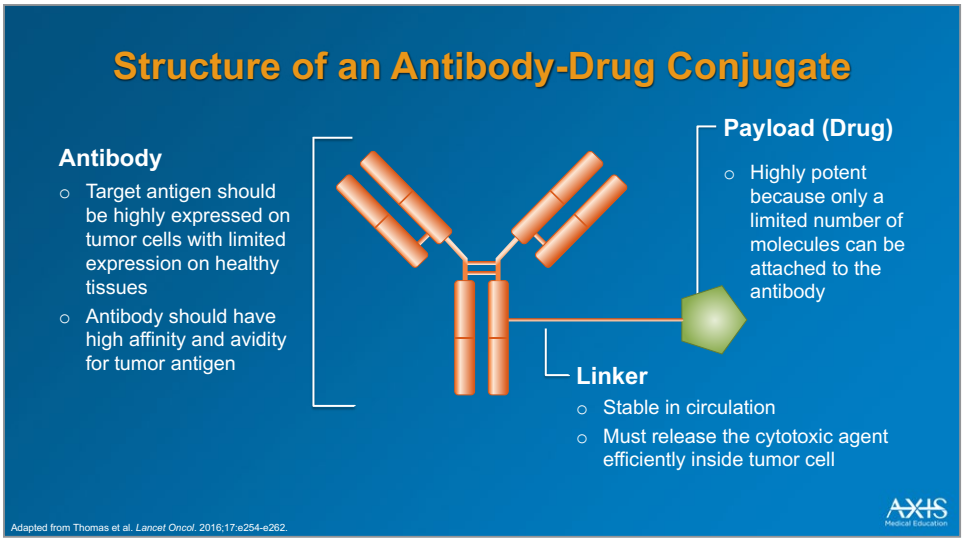
- The NCCN non-small cell lung cancer guidelines panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC.



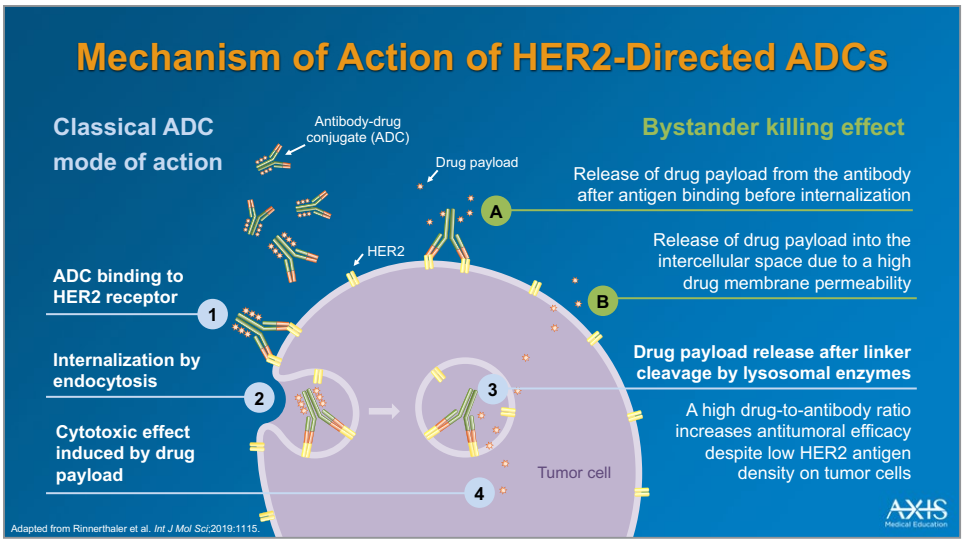
- Current NCCN Guidelines have identified emerging biomarkers to identify novel therapies for patients with metastatic NSCLC, including HER2 or *ERBB2* mutations. Current guidelines list the antibody-drug conjugates of ado-trastuzumab emtansine (T-DM1) and fam-trastuzumab deruxtecan as available targeted agents with activity against HER2 mutations.



- HER2 targeted antibody drug conjugates (ADCs) in NSCLC.

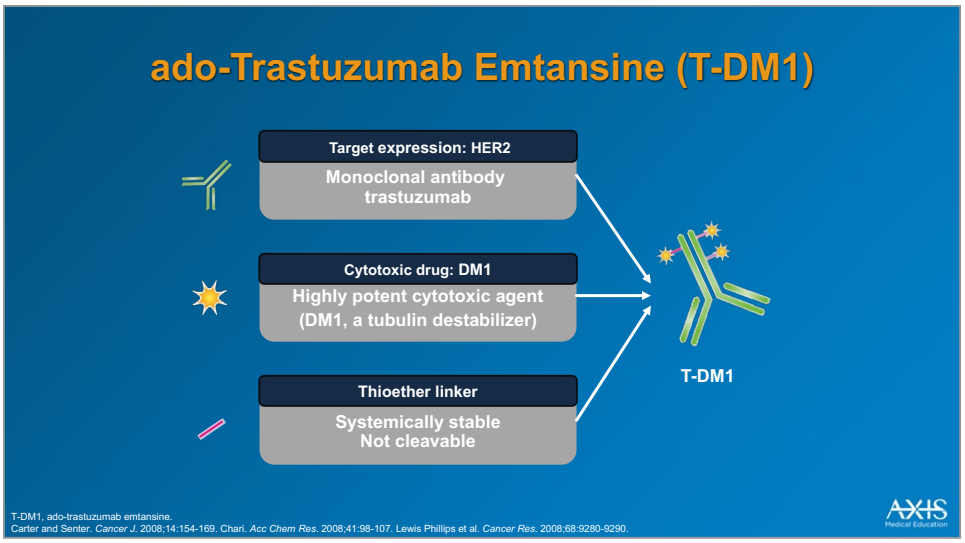


- An ADC consists of a monoclonal antibody conjugated to a cytotoxic agent via a linker. The antibody is specific to tumor cell surface proteins, thereby providing the specificity and potency not achievable with traditional drugs. The linker is the short chemical spacer that binds the drug to the antibody, which must be stable in circulation. In the cell, most linkers are labile; however, some are stable, requiring degradation of the antibody and linker to release the cytotoxic agent. The cytotoxic drug used in ADCs is usually highly potent, with IC-50 values in the subnanomolar range in cell culture.

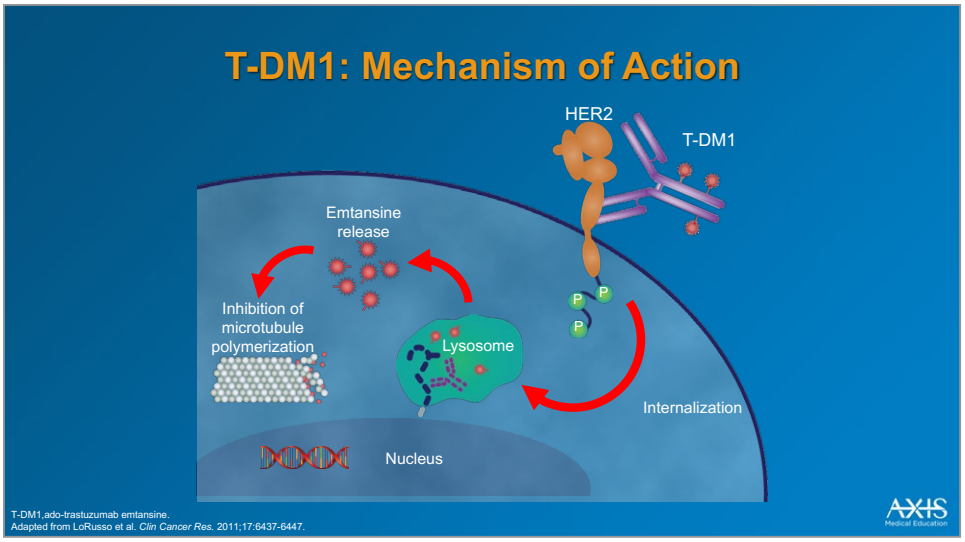


- Classical mode of action of ADCs with cleavable linkers include the following steps. ADC binds to the HER2 receptor. After binding of the monoclonal anti-HER antibody component of the ADC, the HER2 expressed on the cell surface of tumor cells, the ADC HER2 complex is internalized by endocytosis. After linker cleavage by lysosomal proteases, the drug payload is released and can induce a cytotoxic effect leading to tumor cell death.

  A high drug-to-antibody ratio can increase antitumoral efficacy despite a low HER2 antigen density on tumor cells. Bystander killing effect is also an important mode of action to know about. Using cleavable linkers, ADCs can be designed to promote drug release from the target cell to the extracellular space. Thereby, surrounding and bystander cells, which may or may not express the ADC target antigen, can be killed by taking up the cytotoxic drug. This bystander killing can occur if the cytotoxic drug is released from the antibody after antigen binding before internalization. Additionally, the drug payload can be released from the tumor cell into the intracellular space due to a high membrane permeability of the ADC drug payload.



- Of note, T-DM1 is an agent that combines DM1, a cytotoxic maytansinoid and the stable MCC linker. T-DM1 is consisted of DM1 attached via stable non-cleavable linker to trastuzumab. The linker is not cleavable and so there is no bystander affect.



- Let's now go over the mechanism of action of T-DM1. HER2 binding occurs by T-DM1 selectively binding to the HER2 receptor at subdomain IV. HER2 antitumor activities include disruption of ligand-independent HER2 signaling, antiproliferative and apoptotic effects, mediation of antibody-dependent cellular cytotoxicity, and inhibition of HER2 shedding. DM1 cytotoxic activity occurs through internalization and DM1 release. Once bound to the HER2 receptor, the T-DM1/HER2 receptor complex is internalized via endocytosis. DM1 release occurs by T-DM1 undergoing proteolytic degradation inside the target cell. This releases the active chemotherapy, DM1. DM1 binds to microtubules and inhibits their polymerization, causing cell-cycle arrest and cell death.

Ado-Trastuzumab Emtansine: Phase 2 Trials in Pretreated NSCLC

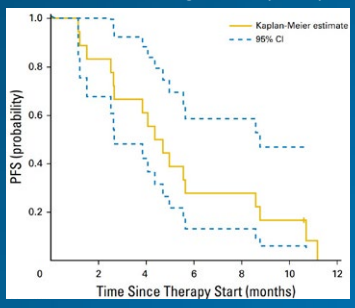
	Phase 2	Phase 2	Phase 2 Basket		
HER2 Alteration	HER2-overexpressing or HER2-mutant	HER2-overexpressing	HER2-mutant	HER2 amplified	HER2-amplified/mutant
N	15	49	18	6	25/49
Overall Response Rate	6.7%	20%	44%	50%	51%

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.

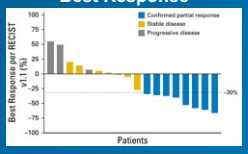
- There are a few phase 2 studies that evaluated T-DM1 in NSCLC. Modest activity of response rates between 6.7% to 51% were seen, although the small number of patients, ranging from 6 to 49, makes it difficult to assess these studies.

Ado-Trastuzumab Emtansine: Phase 2 Basket Trial

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

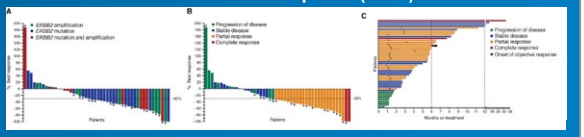


Best Response



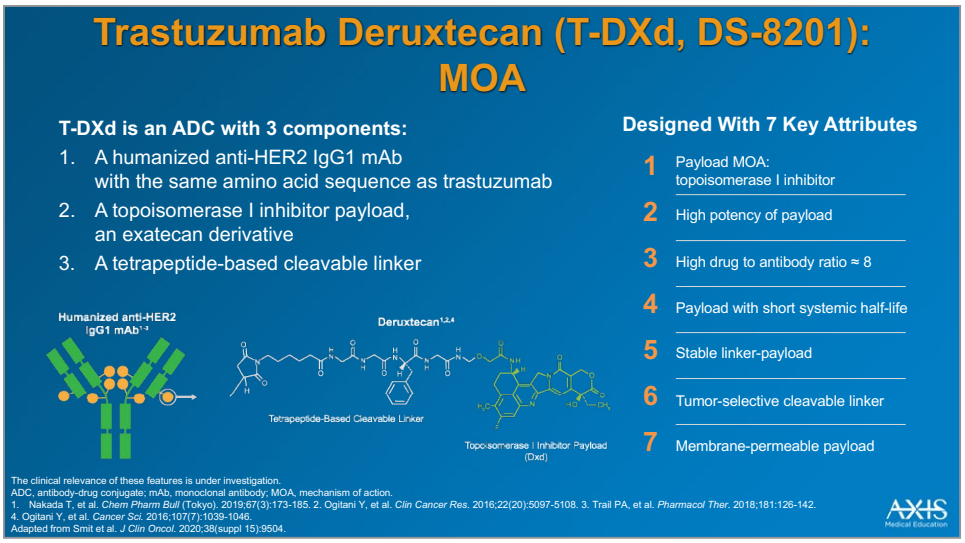
ORR	44%
Best ORR by either RECIST or modified PERCIST for *ERBB2*-amplified/mutant patients	51%
mPFS	5.0 months
mDOR	4.4 months

Best Overall Response (N=48)

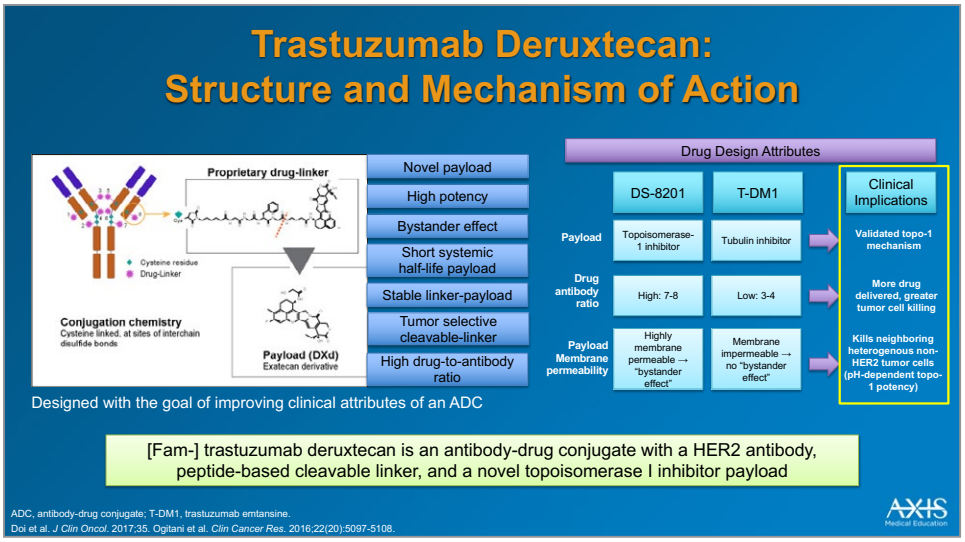


ORR, overall response rate; mPFS, median progression-free survival; mDOR, median duration of response; RECIST, Response Evaluation Criteria in Solid Tumors.
Li et al, *J Clin Oncol.* 2018;36:2532; *Cancer Discov.* 2020;10:674.

- In the phase 2 basket trial of ado-trastuzumab emtansine, the best overall response rate by either RECIST or modified PERCIST for *ERBB2*-amplified/mutant patients was 51%, with a median progression-free survival of 5 months. Based on these data, the NCCN Guidelines list T-DM1 as an available targeted agent with activity against HER2 mutations.

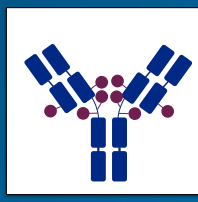
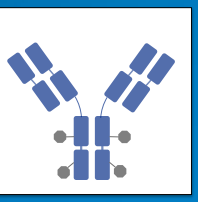


- Trastuzumab deruxtecan (T-DXd) is being clinically evaluated across a number of HER2-expressing or mutated cancers, including breast cancer, colorectal cancer, NSCLC, and others. It is already FDA approved for breast and gastric/GE junctional tumors. The HER2-directed ADC T-DXd received Breakthrough Therapy designation from the FDA, in May 2020, for the treatment of patients with metastatic NSCLC whose tumors have a HER2 mutation and with disease progression on or after platinum-based therapy, based on results of the phase 2 DESTINY-Lung01 trial, which we will look at in details in the following portion of my talk.



- T-DXd is an ADC with a HER2 antibody, peptide-based cleavable linker, and a novel topoisomerase I inhibitor payload. This HER2-directed ADC is characterized by a high drug-to-antibody ratio, and these ADCs promote a bystander killing effect, which explain the antitumor activity even in HER2 low expressing tumors. A higher drug-to-antibody ratio increases the amount of internalized cytotoxic drug molecules despite a low HER2 antigen density on the tumor cell surface.

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.

- There are some differences between T-DXd and T-DM1. As mentioned earlier, T-DM1 uses a stable uncleavable linker. For this reason, there is no bystander anti-tumor effect with T-DM1, whereas with T-DXd, since the linker is cleavable this leads to bystander anti-tumor effect. Additionally, T-DXd is characterized by a high drug-to-antibody ratio at 8:1, whereas this was only 3.5:1 for T-DM1. A higher drug-to-antibody ratio increases the amount of internalized cytotoxic drug molecules and could have efficacy despite a low HER2 antigen density on the tumor cell surface.

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

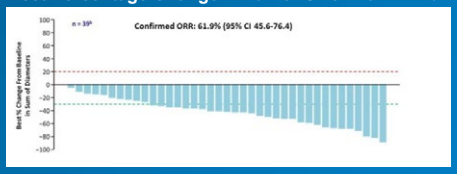
NSCLC, non-small cell lung cancer; ORR, objective response rate; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.
Adapted from Smit et al. *J Clin Oncol*. 2020;38(suppl 15):9504.

- The study design of DESTINY-Lung01 is important to go over. In this open-label multicenter phase 2 study, patients were eligible if they had HER2 mutated or expressing nonsquamous NSCLC relapsed or refractory to standard therapy, no prior HER2 targeted therapy except for pan-HER tyrosine kinase inhibitors (TKIs) were allowed. Cohort 1 enrolled those with HER2 expressing and cohort 2 enrolled those with HER2 mutated tumors. The primary endpoint was confirmed overall response rate by independent central review.

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.

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- Presented at the 2020 ASCO Virtual Scientific Program, results of the DESTINY-Lung01 trial initially showed a confirmed objective response rate of 61.9%, including a 2.4% complete response rate, a 59.5% partial response rate, and a 28.6% stable disease rate in 42 patients with unresectable/metastatic non-squamous HER2-mutant NSCLC treated with T-DXd monotherapy at 6.4 mg/kg. Median progression-free survival was 14 months, median overall survival was not reached, and the disease control rate was 90.5%.

  In terms of toxicity, the most common grade 3 or higher treatment emergent adverse events were decreased neutrophil count at 26.2%, anemia at 16.7%, and there were 5 cases or 11.9% of confirmed treatment-related grade 2 interstitial lung disease or ILD and pneumonitis. Based on these data, the NCCN Guidelines list T-DXd as an available targeted agent with activity against HER2 mutations, and T-DXd was granted Breakthrough Therapy designation in the United States for HER2 mutant metastatic NSCLC in May 2020.

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.

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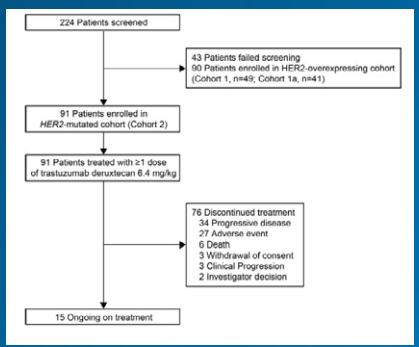
- The updated primary analysis results from the HER2 mutant cohort of the DESTINY-Lung01 phase 2 trial, investigating T-DXd in patients with HER2-mutated metastatic NSCLC was reported as a late break in presentation at ESMO and published in *The New England Journal of Medicine* in September 2021. The total number of patients reported was 91. Again, these were patients who had progressed following one or more systemic therapies. The confirmed overall response rate by ICR was 54.9%. Disease control rate was 92.3% with a median duration of response of 9.3 months, median progression-free survival of 8.2 months, and a median overall survival of 17.8 months.

  Any treatment-related adverse event (TRAE) was seen in 96.7% of patients with grade 3 or TRAEs at 46.2%. Importantly, the adjudicated drug-related ILD was seen in 26%. Of the 26%, approximately 19.8% were grade 1 and 2, and approximately 6.6% were grade 3 and higher.

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.

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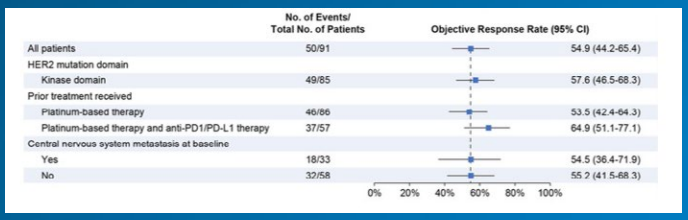
- This is the trial profile and baseline characteristics of the HER2 mutated cohort. Between May 2018 and July 2020, a total of 91 patients with HER2 mutant NSCLC were enrolled and treated with T-DXd. The median number of previous cancer therapies among the enrolled patients was 2 with a range of 0 to 7. A total of 95% of the patients had received previous platinum-based therapy and 66% had received anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death protein ligand 1 (PD-L1) treatment; 76% of 91 patients discontinued study treatment with the most common cause being disease progression.

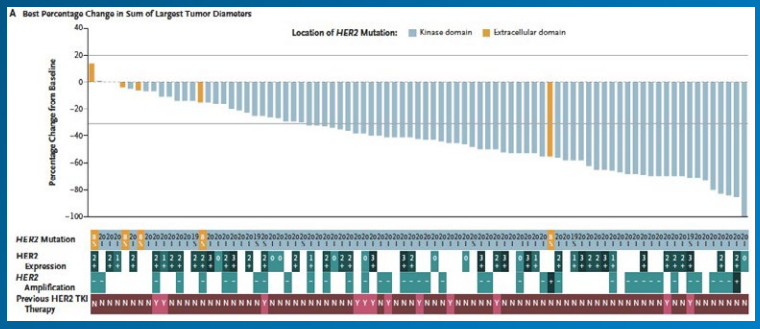
DESTINY-Lung01: HER2-Mutated mNSCLC Response to Trastuzumab Deruxtecan



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.

- Efficacy was consistently observed across different subgroups, including those who had previously been treated with a HER2 tyrosine kinase inhibitor and those with CNS metastasis, which is particularly prevalent in this population.

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.

- Responses to treatment were observed in patients with different HER2 mutation subtypes across three exon locations, exon 19, 20, and 8, as well as in patients who had no detectable HER2 expression or tested negative for HER2 amplification. Responses were also seen in those who were previously treated with HER2 TKIs.

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.

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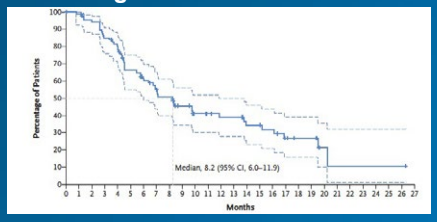
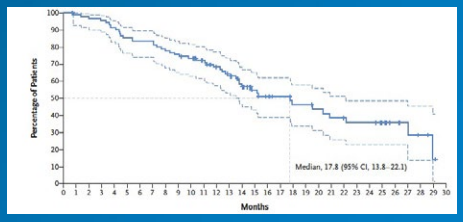
- The biomarker analysis from the study showed that of the 91 patients enrolled, 86% had exon 20 insertions. Any HER2 protein expression was detected in 44 of 53 patients. Nine patients had no detectable HER2 expression. HER2 amplification was found in 2 of 45 patients. Responses to treatment were observed 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.

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.

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- The Kaplan-Meier analysis of progression-free survival and overall survival was presented in *The New England Journal of Medicine*. Median progression-free survival was 8.2 months. The median overall survival was 17.8 months.

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.

- Overall, the safety profile of T-DXd in patients with HER2 metastatic NSCLC was generally consistent with that in previously reported studies. In total 49% of patients had drug-related grade 3 or higher adverse events, which were generally hematologic or gastrointestinal in nature. However, 26% of patients had adjudicated drug-related interstitial lung disease, 75% of these events were of grade 1 or 2, but four patients had grade 3 pulmonary toxic events, and two patients died.

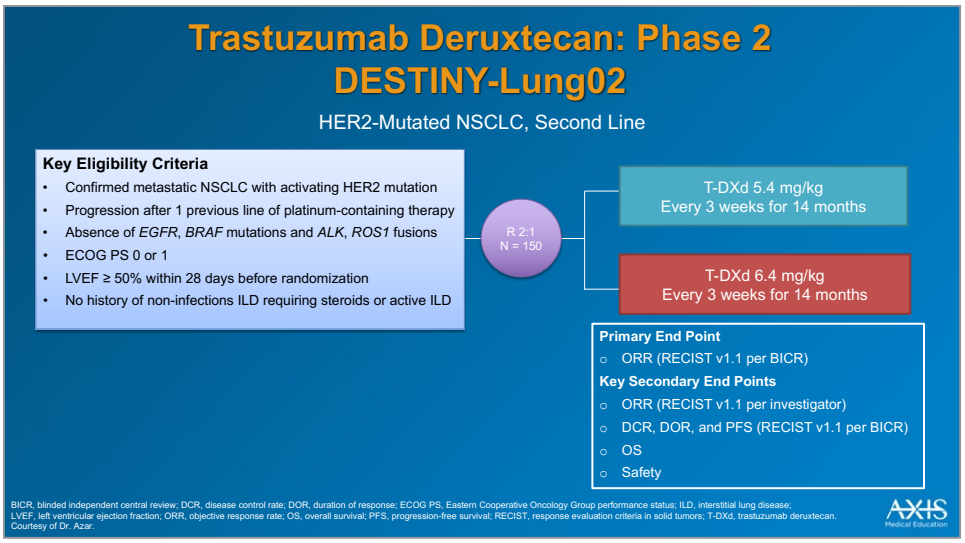
  However, the development of this toxic effect was not predictable, and as a consequence patients must be carefully monitored. Adverse events of ILD in the present study were actively managed on the basis of the protocol-defined management guidelines for ILD, including prompt initiation of steroids. This resulted in 13 of the patients, more than 50%, having recovered from ILD at the time of data cutoff. Further research is needed to determine which patients are at greatest risk and how to most effectively manage this potentially fatal adverse event.

DESTINY-Lung01: HER2-Overexpressing NSCLC

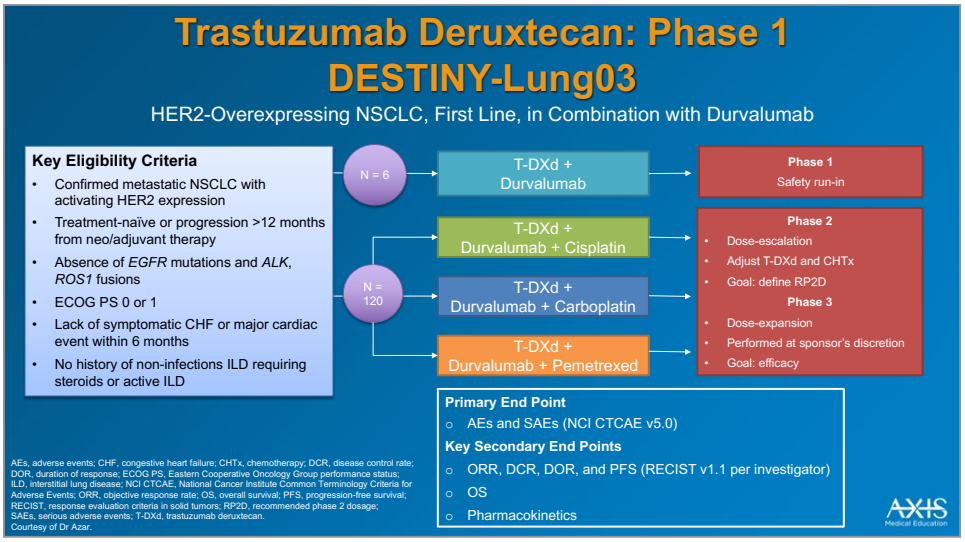
Results	IHC 3+ (N = 10)	IHC 2+ (N = 39)	Overall (N = 49)
Confirmed ORR, n (%)	2 (20.0)	10 (25.6)	12 (**24.5**)
CR	0	(2.6)	(2.0)
PR	2 (20.0)	(23.1)	(22.4)
SD	6 (60.0)	(41.0)	(44.9)
PD	1 (10.0)	(25.6)	(22.4)
DCR, n (%)	8 (80.0)	26 (66.7)	34 (69.4)
Median DoR, mo	6.0	5.8	6.0
Median PFS, mo	-	-	5.4
Median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

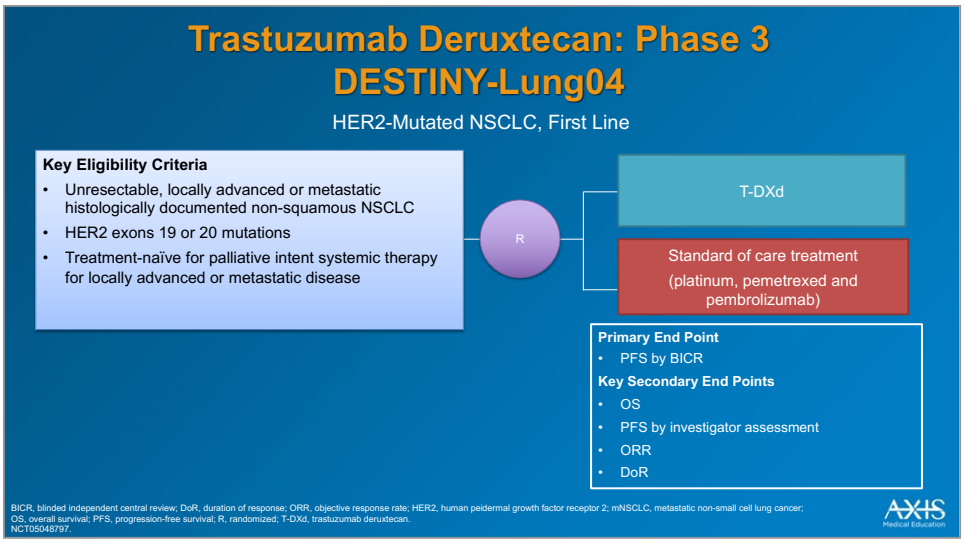
- In an interim analysis of the HER2 overexpressing metastatic NSCLC cohort of the DESTINY-Lung01 trial, T-DXd demonstrated preliminary evidence of antitumor activity, with a confirmed objective response rate by ICR of 24.5%, including 1 complete response and 11 partial responses. The median duration of response was 6 months, and the estimated median progression-free survival was 5.4 months.



- The phase 2 DESTINY-Lung02 trial has just started recruitment and is evaluating the safety and efficacy of T-DXd in patients with HER2-mutated metastatic non-small cell lung cancer with disease recurrence or progression during or after at least one prior platinum-containing treatment regimen, and this trial is comparing two starting doses, 5.4 mg/kg versus 6.4 mg/kg.



- In Destiny Lung03, T-DXd and immunotherapy with various combinations of chemotherapy will be studied, ultimately to bring the treatment forward to the first-line setting in those with metastatic NSCLC with HER2 expression.



- DESTINY-Lung04 is for HER2 mutated NSCLC, randomizing patients to T-DXd versus standard of care chemoimmunotherapy in the first-line setting.

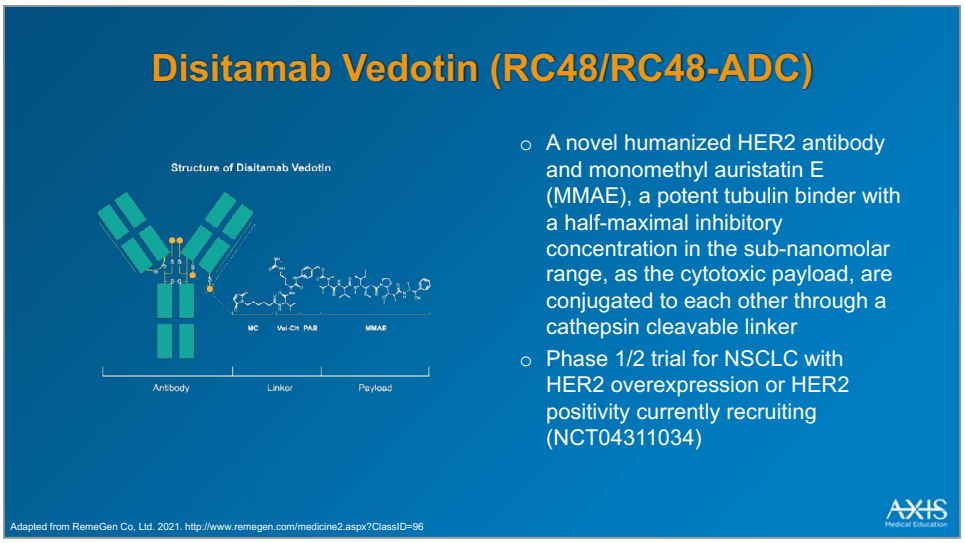
Trastuzumab Deruxtecan: Summary of Clinical Trials in NSCLC

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.

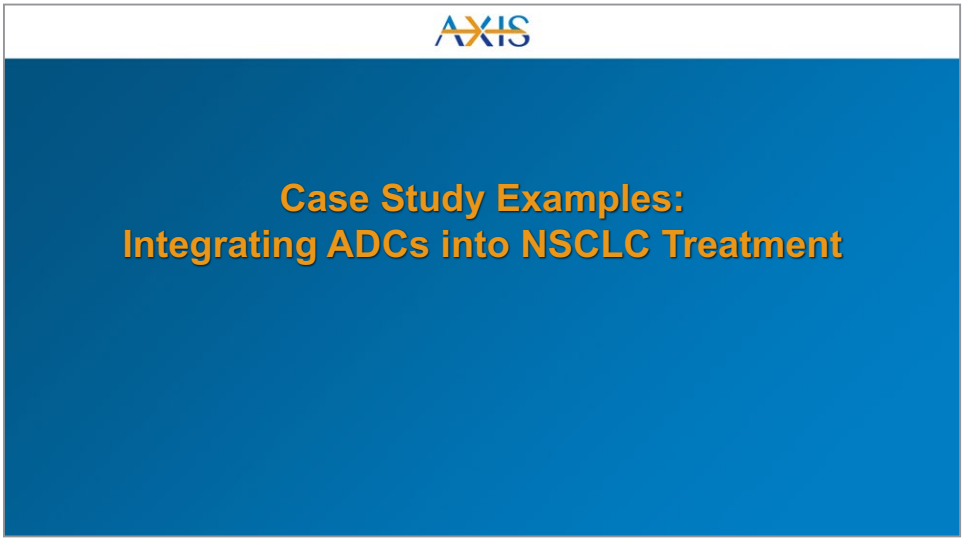
- Many studies utilizing T-DXd in NSCLC are ongoing in different settings.

  For DESTINY-Lung01, we should hear more about the updates in the HER2 overexpression cohort in the near future as data matures. As mentioned earlier, DESTINY-Lung02 is looking at two different doses, 6.4 versus 5.4 mg/kg in the second line setting. DESTINY-Lung03 is for HER2 overexpressed NSCLC, and the idea is to move the drug to the treatment naïve setting in combination with chemotherapy and immunotherapy. DESTINY-Lung04 is for HER2 mutated NSCLC, randomizing patients to T-DXd versus standard of care chemoimmunotherapy in the first-line setting. Other studies such as NCT04042701 and HUDSON, are evaluating the combination of T-DXd with immunotherapy in the immunotherapy naïve setting and refractory settings.

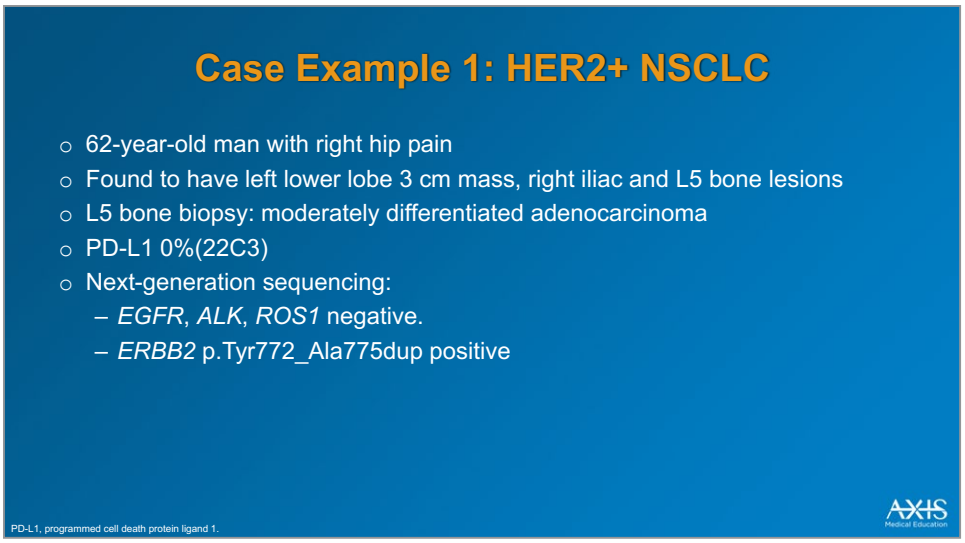


- Disitamab vedotin selectively delivers anti-cancer agent monomethyl auristatin E (MMAE) into HER2-positive tumor cells and is a novel ADC. In disitamab vedotin, a novel humanized HER2 antibody and MMAE, a potent tubulin binder with a half maximal inhibitory concentration in the subnanomolar range, as the cytotoxic payload, are conjugated to each other through a cathepsin cleavable linker with optimized drug-antibody ratio. The anti-HER2 antibody allows disitamab vedotin to selectively deliver the anti-cancer agent MMAE to HER2-expressing tumor cells.

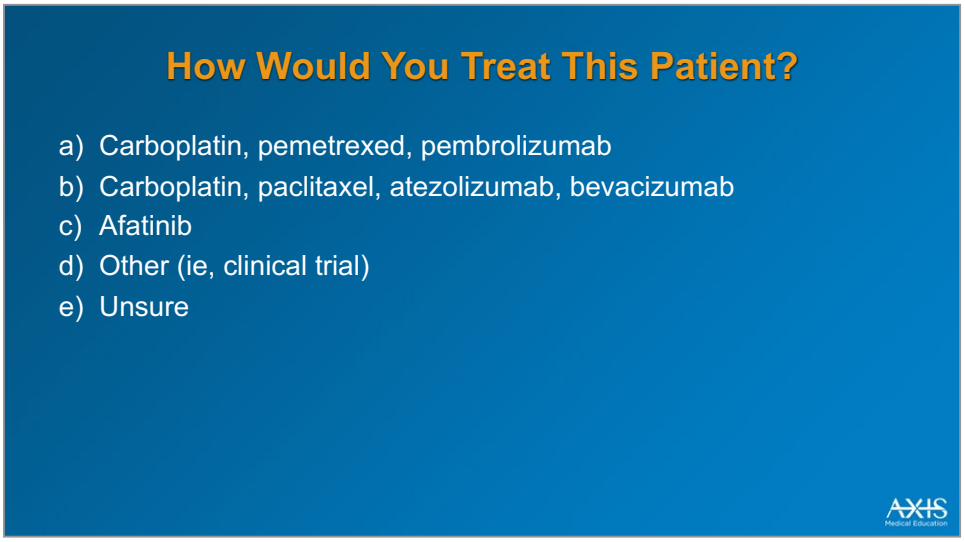
  In China, disitamab vedotin is being developed across five indications, including gastric cancer, urothelial cancer, late-stage breast cancer, NSCLC, and bile duct cancer. A phase 1/2 trial of this agent in patients with advanced NSCLC with HER2 overexpression or HER2 mutation is currently recruiting patients.



- Now, let me share with you two cases.



- The first case is of a patient with HER2 mutated NSCLC. This is a 62-year-old gentleman who presented with right hip pain. He was found to have a 3-cm left lower lobe mass and right iliac and L5 bone lesions. The L5 bone biopsy specimen showed moderately differentiated adenocarcinoma. PD-L1 was 0% by 22C3. Next-generation sequencing reported *EGFR, ALK*, and *ROS1* to be negative; however, *ERBB2* was positive.



- How would you treat this patient?
  a) Carboplatin, pemetrexed, pembrolizumab
  b) Carboplatin, paclitaxel, atezolizumab, bevacizumab
  c) Afatinib
  d) Other, such as clinical trials
  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

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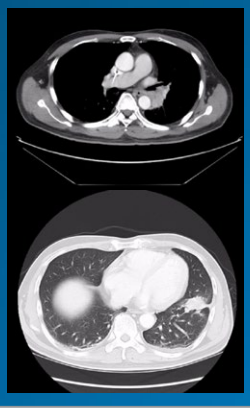
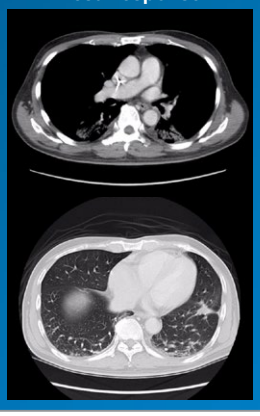
- This patient ended up getting carboplatin, pemetrexed, pembrolizumab for his first-line treatment. He was on this treatment from May to December 2017 when he unfortunately experienced disease progression. At the time of progression, he appeared at an outside institute and enrolled onto a clinical trial utilizing poziotinib. He was treated from January to September 2018.

Third Line: Trastuzumab Deruxtecan

Baseline



~7 Months Post Start of Therapy
Best Response



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- And then he came to me. For his third-line treatment, he received trastuzumab deruxtecan. The patient derived benefit with shrinkage of his primary lesion in the left-sided lung mass, as well as lymph nodes. Maximum reduction of disease was seen at 7 months after the start of therapy. This patient received T-DXd for his third-line therapy and still had a response, but based on DESTINY-Lung01 results I would suggest considering the use of this agent in the second-line setting post-platinum therapy.

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.

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- Here is another case. This is a case of HER2 amplified NSCLC. A 66-year-old woman who presented with a cough. She was treated with antibiotics for pneumonia, but there was no improvement. This led to a CT chest, which revealed left-sided pleural effusion and multiple pleural-based lesions. The biopsy specimen of the pleural lesion was positive for adenocarcinoma. PD-L1 was 0% by 22C3. Next-generation sequencing revealed *ALK* and *ROS1* to be negative; however, she was positive for *EGFR* exon 21 L858R.

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

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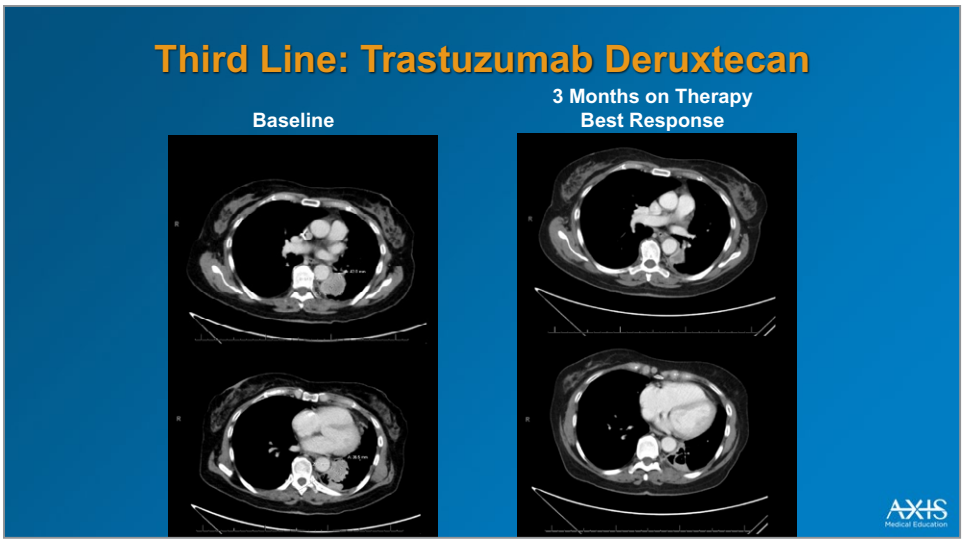
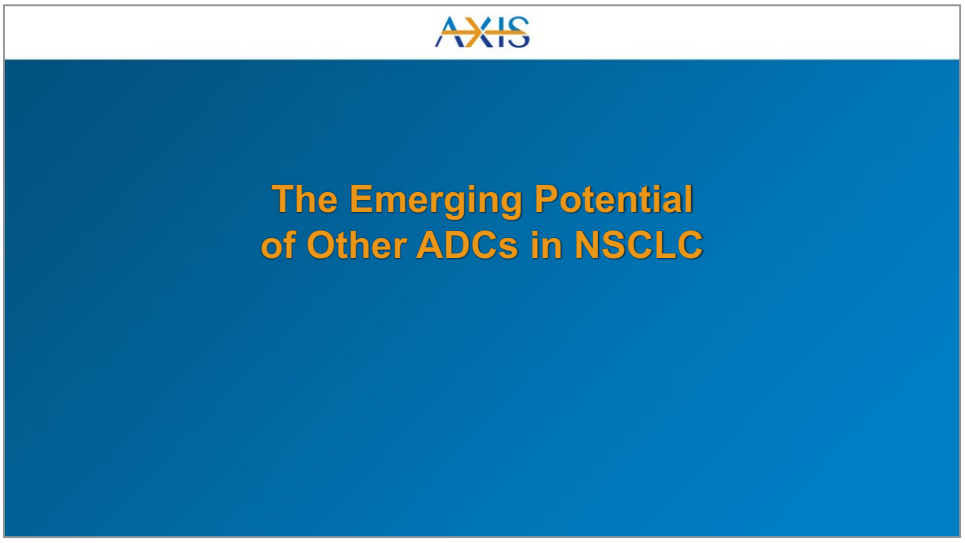
- She was treated with osimertinib for first-line therapy from July 2017 to January 2018. Unfortunately, she experienced disease progression in multiple areas, and for her second-line of therapy she received carboplatin, pemetrexed, and pembrolizumab from February 2018 to February 2019. Disease eventually progressed, and upon progression, she was found to have HER2 overexpression 2+ by IHC.



- This patient also received T-DXd for third-line therapy. She also had a response to therapy, as shown by the reduction in size of her left-sided lung mass. It is important to note that HER2 overexpression is one of the known mechanisms of EGFR TKI resistance, although in this particular patient I am not entirely sure when HER2 overexpression developed, because she received osimertinib first, followed by chemoimmunotherapy.



- The emerging potential of other ADCs in NSCLC.

ADCs With Other Targets in NSCLC

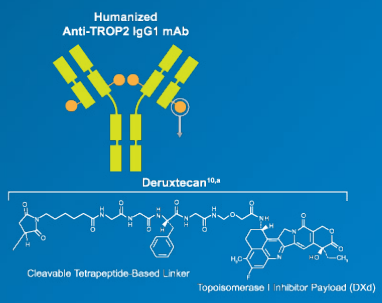
ADC Target	ADC
TROP2	Datopotamab deruxtecan (DS-1062; Dato-DXd)
	Sacituzumab govitecan (IMMU-132)
HER3	Patritumab deruxtecan (U3-1402; HER3-DXd)

ADC, antibody-drug conjugate.

- Other ADCs in development include datopotamab deruxtecan and sacituzumab govitecan, which are TROP2 ADCs, and patritumab deruxtecan which is an HER3 ADC.

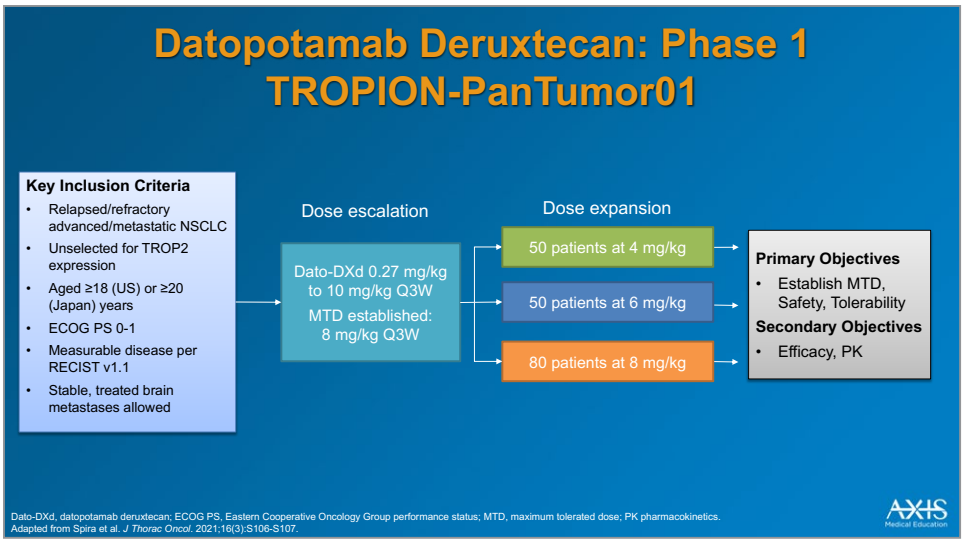
Datopotamab Deruxtecan

- 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.

- TROP2 is a transmembrane glycoprotein, which is highly expressed in NSCLC and other solid tumors. Datopotamab deruxtecan is a TROP2-directed ADC composed of a humanized anti-TROP2 IgG1 monoclonal antibody, a topoisomerase 1 inhibitor payload, and a tetrapeptide-based cleavable linker.



- TROPION-PanTumor01 is an ongoing, multicenter, open-label, first-in-human, dose-escalation and dose-expansion phase 1 study of datopotamab deruxtecan (Dato-DXd) in patients with advanced solid tumors, including advanced metastatic relapsed/refractory NSCLC. The study is currently ongoing in the United States and Japan. Enrollment in the NSCLC cohort has been completed.

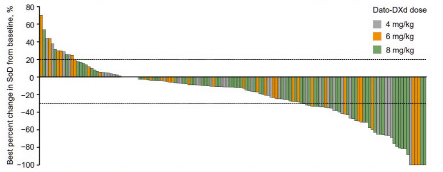
  The study consists of a dose-escalation portion and a dose-expansion portion. The primary objective of the dose-escalation portion was to identify the maximum tolerated dose and the recommended dose for expansion. Patients were planned for enrollment into 8 dosing cohorts to receive an intravenous infusion of Dato-DXd in 3-week cycles different doses.

  In the dose-expansion portion, the primary objectives are to confirm the safety and tolerability of Dato-DXd at the recommended dose for expansion determined in the dose-escalation portion. These analyses include 175 patients treated at 4 mg/kg, 6 mg/kg, and 8 mg/kg doses of Dato-DXd in both the dose escalation and expansion cohorts. The NSCLC cohort, as previously mentioned, are now fully enrolled.

Datopotamab Deruxtecan: Phase 1 TROPION-PanTumor01

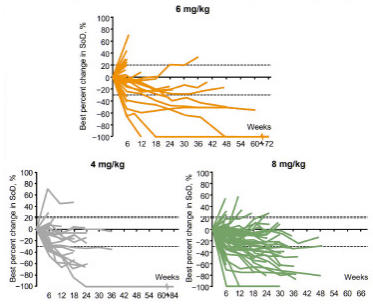
Antitumor Activity of Dato-DXd

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.

AXIS Medical Education

- The enrollment was completed for the NSCLC cohort, and updated results from the NSCLC dose expansion cohort was presented by Dr. Spira and colleagues at World Lung in January 2021. Dato-DXd demonstrated early antitumor activity in patients with advanced metastatic NSCLC that progressed on standard treatment.

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%

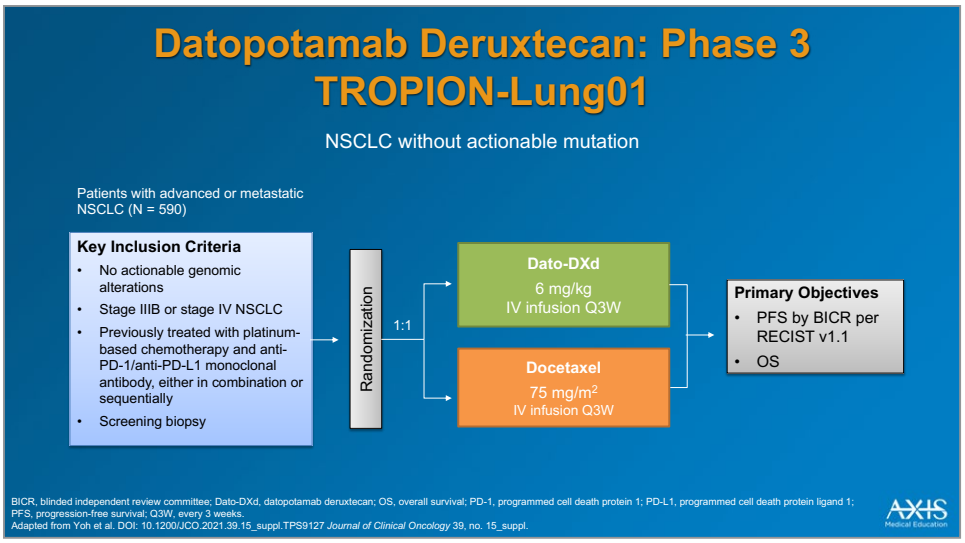
Conclusions:

- 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

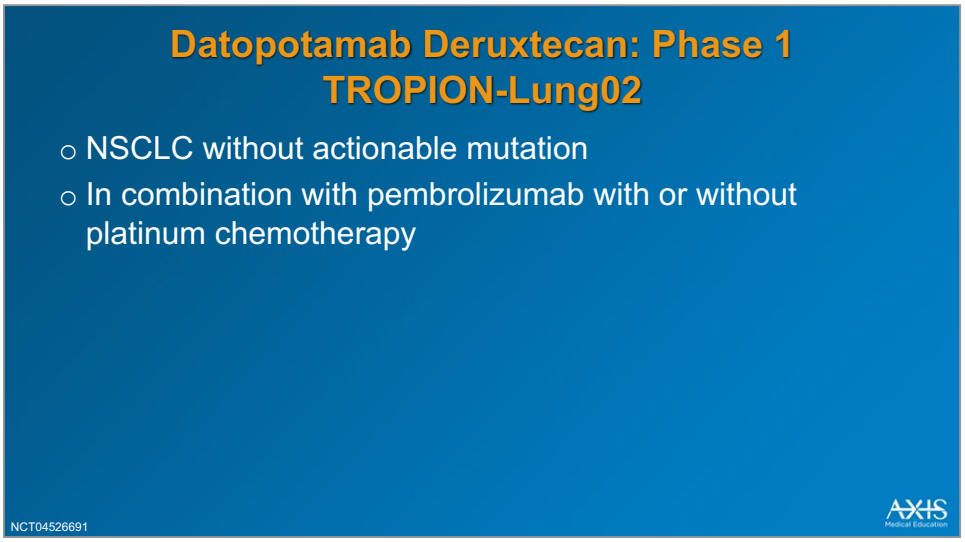
AEs, adverse events; AGA, actionable genomic alterations; BICR, blinded independent central review; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate.
Garon et al. Presented at 2021 ESMO Congress; September 16-21, 2021; Virtual. Abstract LBA49.

AXIS Medical Education

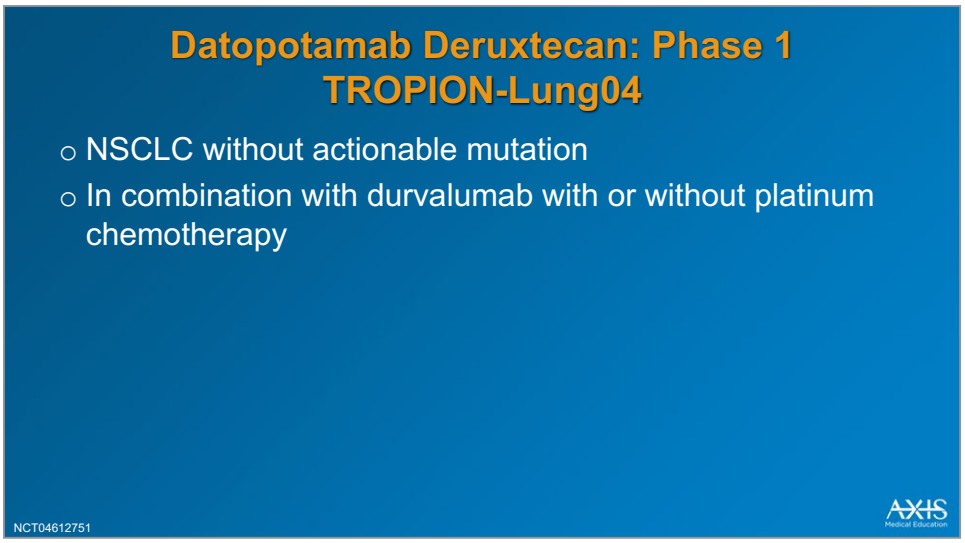
- Preliminary results from the patients with actionable genomic alterations in the phase 1 TROPION-PanTumor01 trial were presented at ESMO September 2021. There were 29 patients with tumors harboring *EGFR*, three with *ALK*, one with *ROS1*, and one with *RET*, and they received 4, 6, or 8 mg/kg of Dato-DXd. Confirmed overall response rate by blinded independent review committee (BICR) was 35% across different doses. The median duration of response was 9.5 months, and common adverse events included nausea and stomatitis.



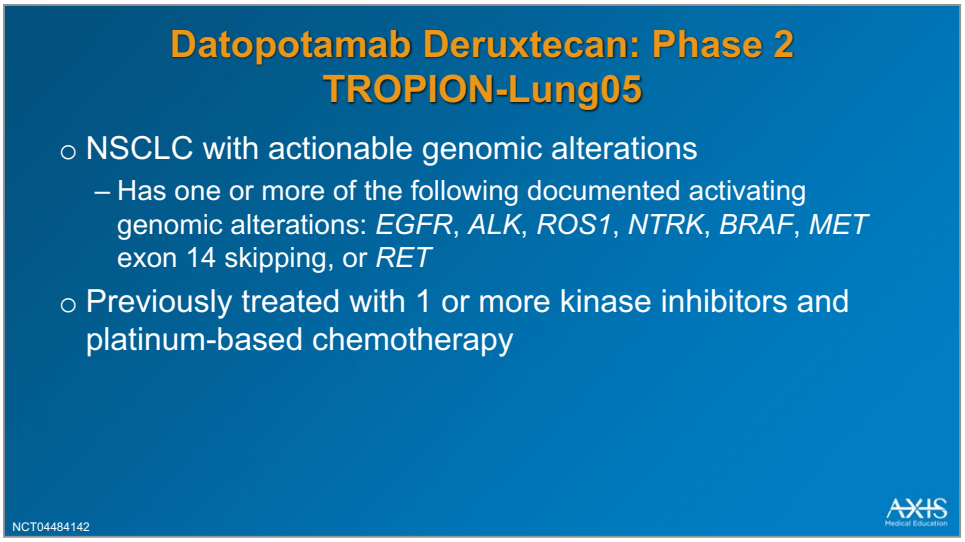
- TROPION-Lung01 is the randomized, phase 3 study of Dato-DXd versus docetaxel in previously treated advanced or metastatic NSCLC without actionable genomic alterations. Patients will be stratified by histology, squamous vs nonsquamous, most immediate prior therapy, and geographic region. The primary endpoints of this study include progression-free survival by BICR and overall survival.



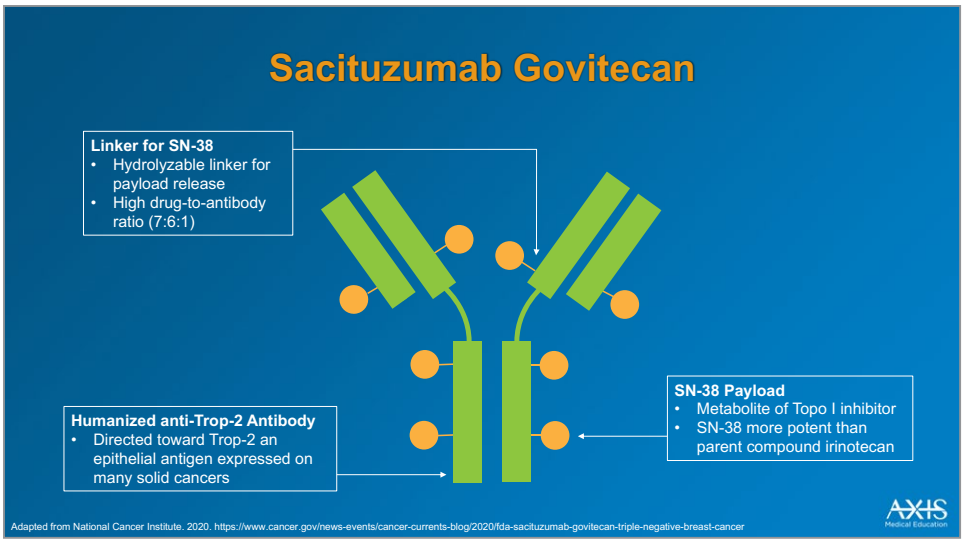
- The TROPION-Lung02 study is a phase 1 study where Dato-DXd will be evaluated with pembrolizumab with or without platinum chemotherapy in patients with advanced or metastatic NSCLC.



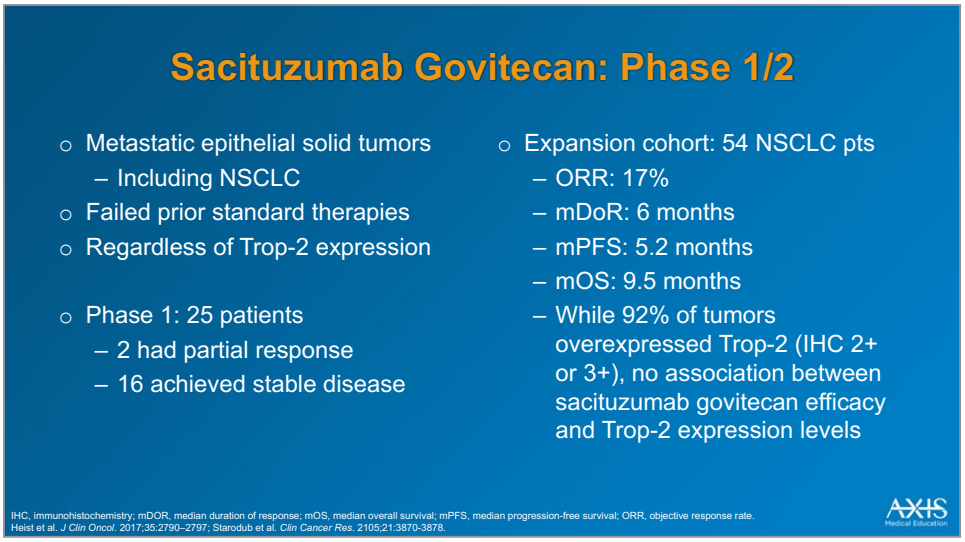
- The TROPION-Lung04 study is a phase 1, looking at the combination of Dato-DXd with durvalumab with or without platinum chemotherapy in patients with advanced or metastatic NSCLC without actionable mutations.



- And the TROPION-Lung05 study is a phase 2 study evaluating Dato-DXd in previously treated patients with activating genomic mutations including *EGFR*, *ALK, ROS1, NTRK, BRAF, MET* exon 14 skipping, or *RET*.



- Sacituzumab govitecan is another TROP2 ADC. In April 2020, FDA gave accelerated approval to sacituzumab govitecan for metastatic triple-negative breast cancer. In April 2021, FDA gave accelerated approval of sacituzumab to those with metastatic urothelial cancer who previously received platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor.



- The expansion cohort of 54 NSCLC patients who had disease progression on prior standard therapies demonstrated an objective response rate of 17% regardless of TROP-2 expression. Median duration of response was 6 months, median progression-free survival was 5.2 months, and median overall survival was 9.5 months.

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

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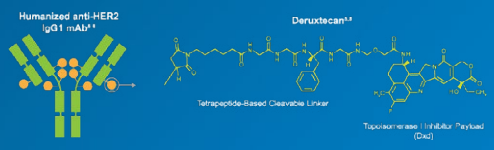
- TROPiCS-03 is an ongoing phase 2 study, enrolling metastatic solid tumors of NSCLC, head and neck squamous cell cancer, or endometrial cancer. The NSCLC cohort is enrolling those with disease progression after prior platinum-based chemotherapy and PD-1/PD-L1 or those who had recurrence or relapse or lack of response within 6 months of completion of chemotherapy for those with locally advanced disease.

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.

AXIS Medical Education

- Patritumab deruxtecan is a novel HER3-directed ADC, composed of 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. It is being developed as a salvage therapy after disease progression on EGFR TKIs in NSCLC patients with tumors harboring activating *EGFR* mutations.

Patritumab Deruxtecan: Phase 1

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

Dose Escalation

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

HER3-DXd 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**

HER3-DXd 5.6 mg/kg Q3W **n = 45**

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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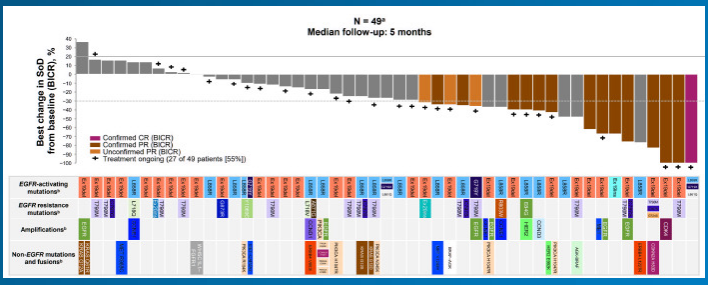
- In the phase 1 study, patients who had disease progression on previous EGFR TKIs were enrolled. In the dose escalation portion of the study the recommended dose was determined to be 5.6 mg/kg IV every 3 weeks, safety was manageable, and the dose expansion portion of the study enrolled those who were pretreated with at least one EGFR TKI and at least one prior platinum-based chemotherapy.

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.

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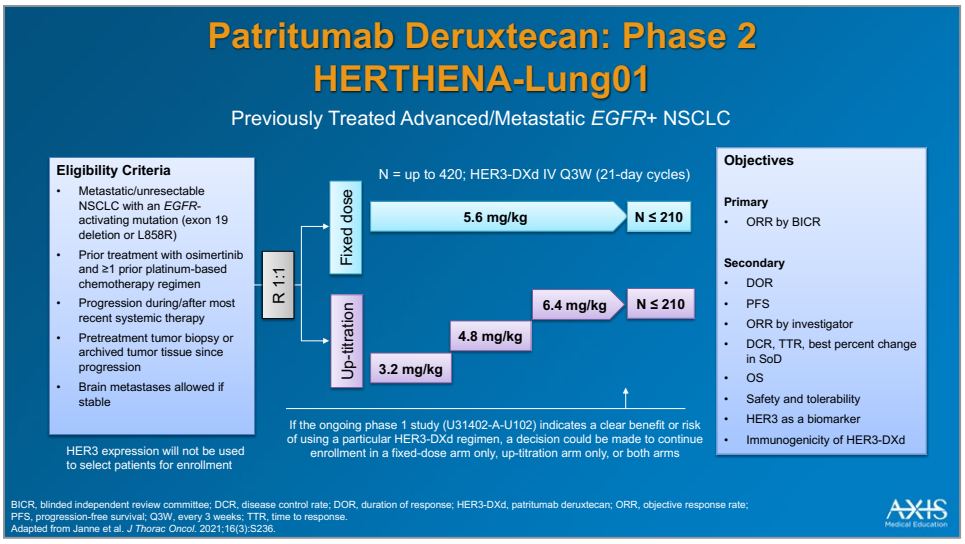
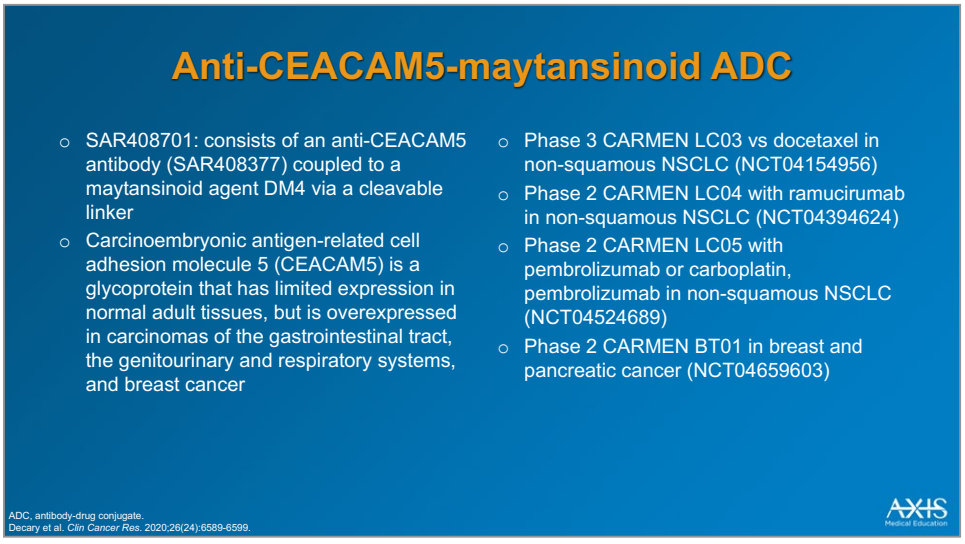
- Preliminary antitumor activity and safety was demonstrated in heavily pretreated patients with a confirmed objective response rate of 25% in 56 patients with *EGFR*-mutated NSCLC with prior EGFR TKI and platinum-based chemotherapy. Almost all evaluable tumors expressed high levels of HER3 at baseline. Activity was observed in patients with and without diverse mechanisms of TKI resistance, including *EGFR* C797S mutation, *MET* amplification, HER2 mutation, *BRAF* fusion, and *PIK3CA* mutation. These data support further clinical investigation of this HER3-directed ADC in a patient population with no available targeted therapy treatments.



- HERTHENA-Lung01 is a phase 2 study of single-agent patritumab deruxtecan or HER3-DXd in patients after failure of EGFR TKIs and platinum-based chemotherapy and is currently enrolling patients. Patients will be randomized 1:1 to receive one of two HER3-DXd every-3-week dose regimens that will be independently evaluated. A 5.6 mg/kg fixed-dose regimen, Arm 1, or an up-titration dose regimen, Arm 2. After review of data from an ongoing phase 1 study with similar patients treated with either of these regimens, a decision could be made to continue enrollment into one or both arms. The primary objective is to evaluate the efficacy of HER3-DXd as measured by objective response rate by BICR. The plan is to enroll 420 patients globally at approximately 135 study sites.



- An additional ADC is SAR408701, which is an anti-CEACAM5 ADC.

  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 in breast tissue. SAR408701 consists of an anti-CEACAM5 antibody coupled to a maytansinoid agent DM4 via a cleavable linker. Multiple studies are ongoing in NSCLC and other tumor types.

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.

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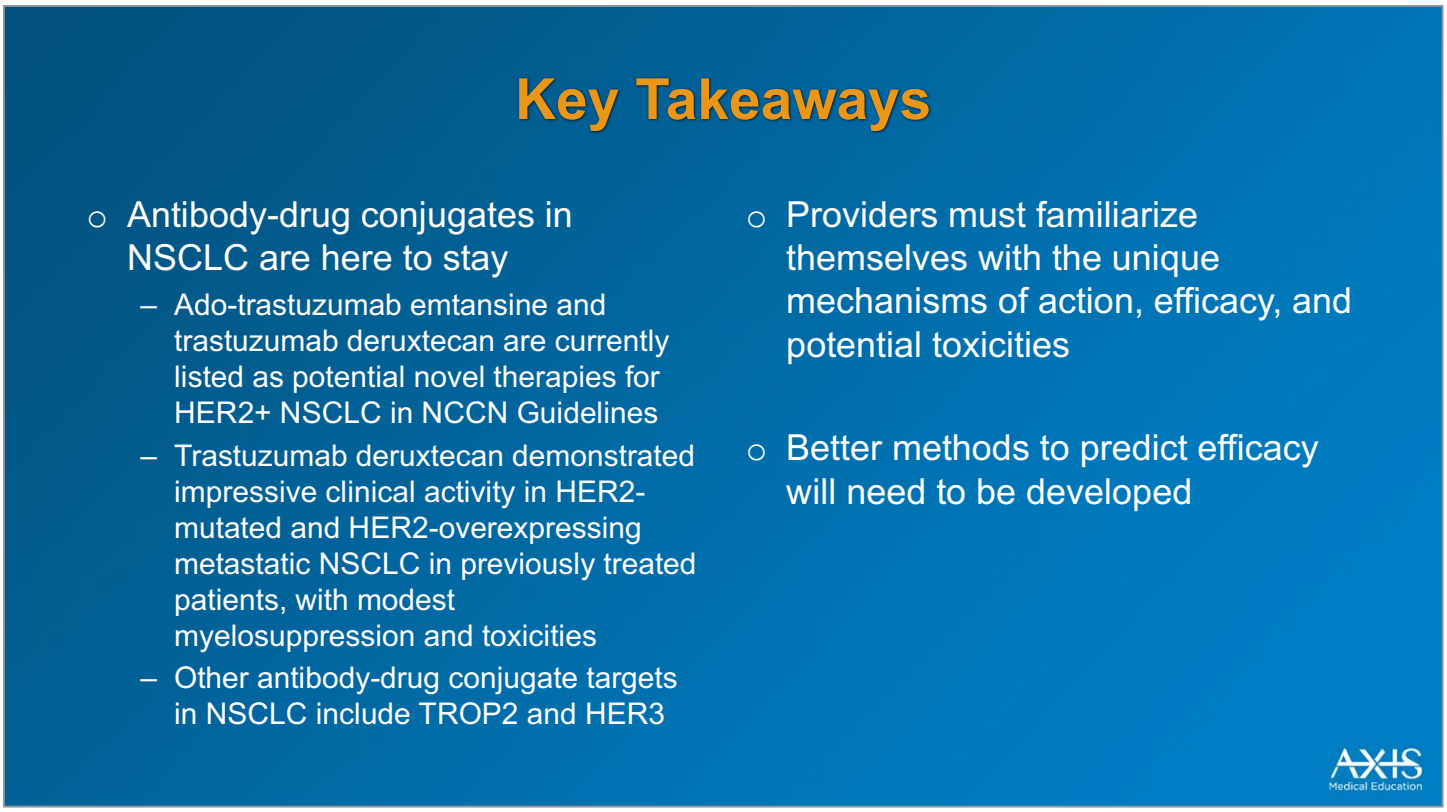
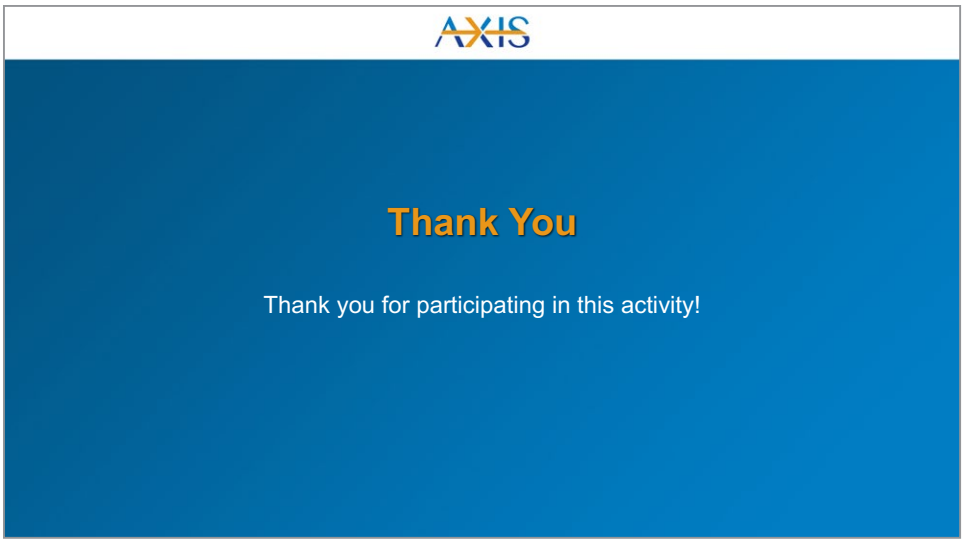
- To summarize the other ADC targets of TROP2 and HER3, for TROP2 there are two agents datopotamab deruxtecan or Dato-DXd and sacituzumab govitecan. Preliminary results from the TROPION-PanTumor01 showed promising results for NSCLC patients. Thus datopotamab deruxtecan is being evaluated in NSCLC in different settings, and the main studies include TROPION-Lung01, 02, and 04. Sacituzumab govitecan is already approved in triple-negative breast cancer and urothelial cancer. This phase 1/2 study showed encouraging results in NSCLC patients, and the TROPiCS-03 study is ongoing. Patritumab deruxtecan or HER3-DXd is a HER3 ADC. This agent showed promising activity in patients with NSCLC harboring *EGFR* who are heavily pretreated. HERTHENA-Lung01 is ongoing, and another study NCT04676477 is evaluating the combination of patritumab deruxtecan with osimertinib.

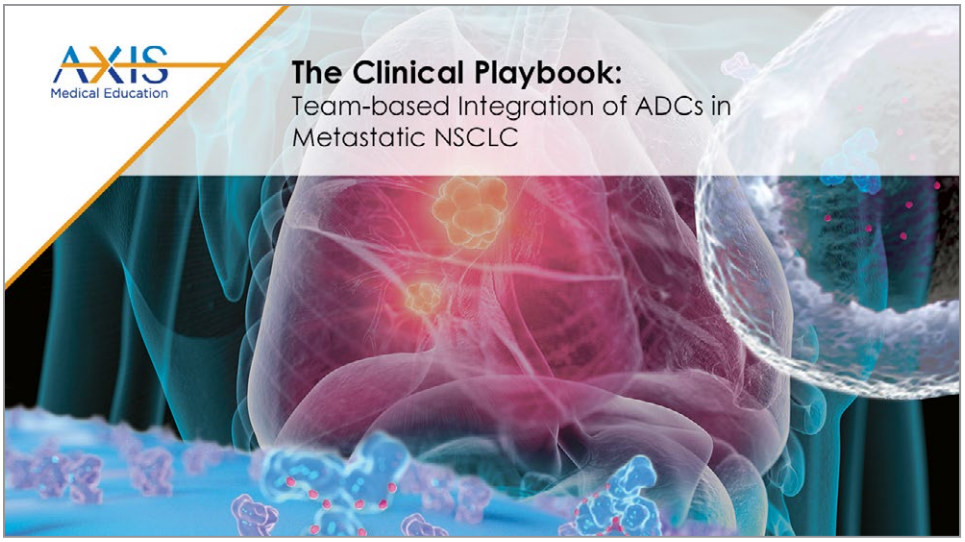


ADCs in NSCLC are here to stay. T-DM1 and T-DXd are currently listed as potential novel therapies for HER2-positive NSCLC in NCCN Guidelines. Trastuzumab deruxtecan or T-DXd demonstrated impressive clinical activity in previously treated HER2-mutated and HER2-overexpressing metastatic NSCLC, with modest myelosuppression and toxicities. Other ADC 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, as well as methods to detect potential patients who are at high risk for developing toxicities would also need to be studied. In particular, I would like to highlight the ILD or pneumonitis rates that were demonstrated from DESTINY-Lung01 study. Any grade adjudicated drug-related ILD from this study of the HER2 mutated cohort was high at 26%, although most are low grades. Of the 26%, approximately 19.8% were grade 1 and 2 and approximately 6.6% were grade 3 and higher. It would be important to determine in future studies those patients who are at a higher risk of developing drug-related ILD or pneumonitis and determine ways to detect this early to prevent potential fatal events. Other than the ILD pneumonitis, T-DXd, as mentioned earlier, appears to be well-tolerated with toxicities related to cytotoxic therapy, such as neutropenia NGI-related events, given the efficacy of T-DXd with a confirmed objective response rate of 54.9% in HER2-mutated metastatic NSCLC, for which there are no approved targeted therapies. I think this is a promising agent and hope that this therapy will benefit future patients.



- Thank you for participating in this activity.



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