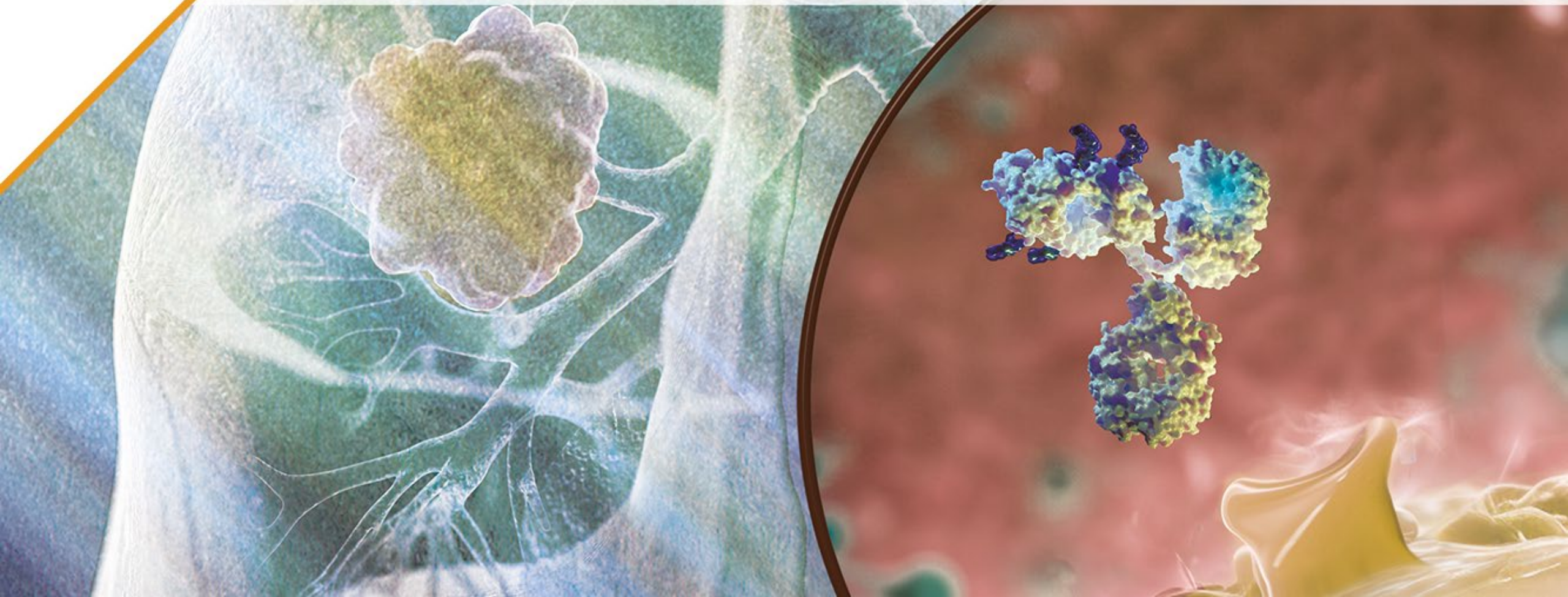
AXIS Medical Education

Precision Payloads:

Exploring ADC-Directed Therapies in HER2-Mutant and Overexpressing Lung Cancer



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Learning Objectives

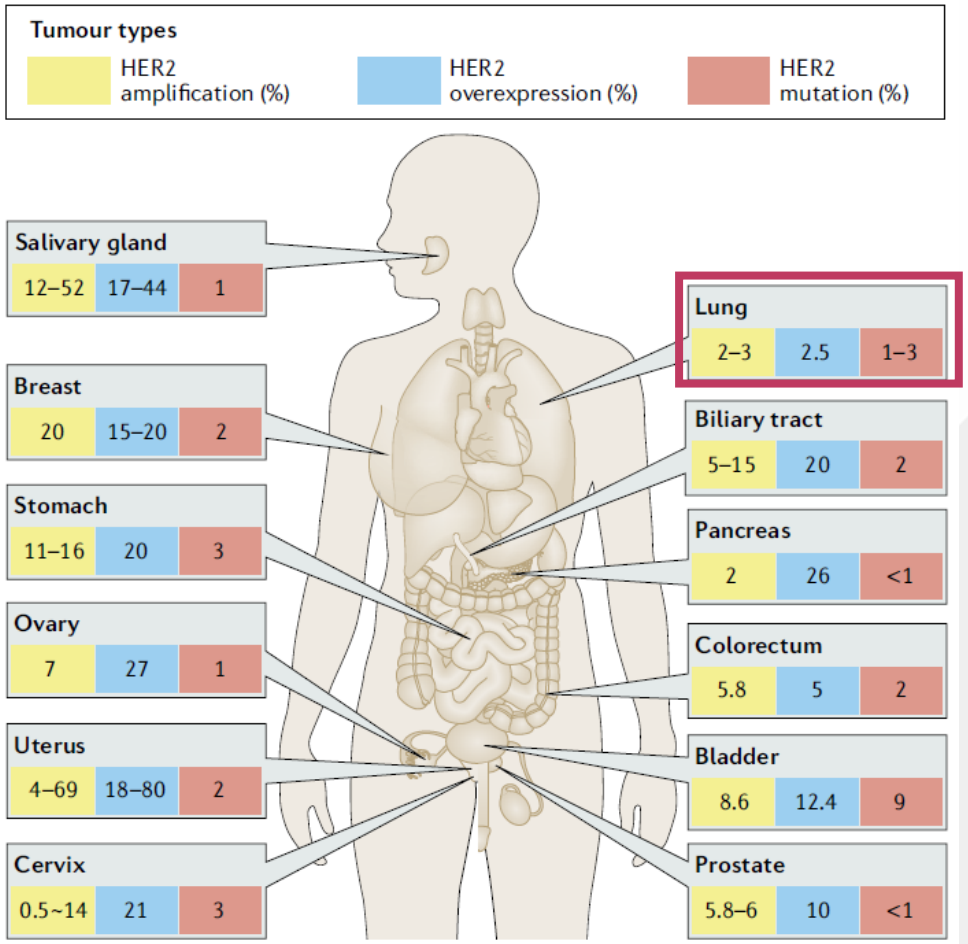
Upon completion of this activity, participants should be better able to:

1. Apply guideline recommendations for patients with NSCLC to detect and identify HER2 alterations to optimize patient outcomes
2. Develop evidence-based approaches to incorporating HER2-directed therapies (eg, ADCs) into the treatment sequence for NSCLC when appropriate
3. Outline strategies to anticipate, mitigate, and manage potential treatment-related AEs in patients with NSCLC receiving HER2-directed treatment

Molecular Testing: Clinical Value and Implications for HER2 Testing

HER2 as an Oncogenic Driver in Cancer

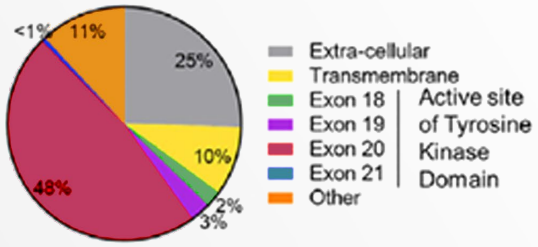
- Receptor tyrosine kinase encoded by erb-b2 receptor tyrosine kinase 2 (*ERBB2*) gene
- Activated via hetero- or homo-dimerization with other erbB family members, with subsequent activation of downstream signaling pathways (PI3K/AKT, MEK/ERK) that promote oncogenesis
- 3 types of alterations observed across solid tumor malignancies:
  - *HER2* gene mutations
  - *HER2* gene amplification
  - *HER2* protein overexpression

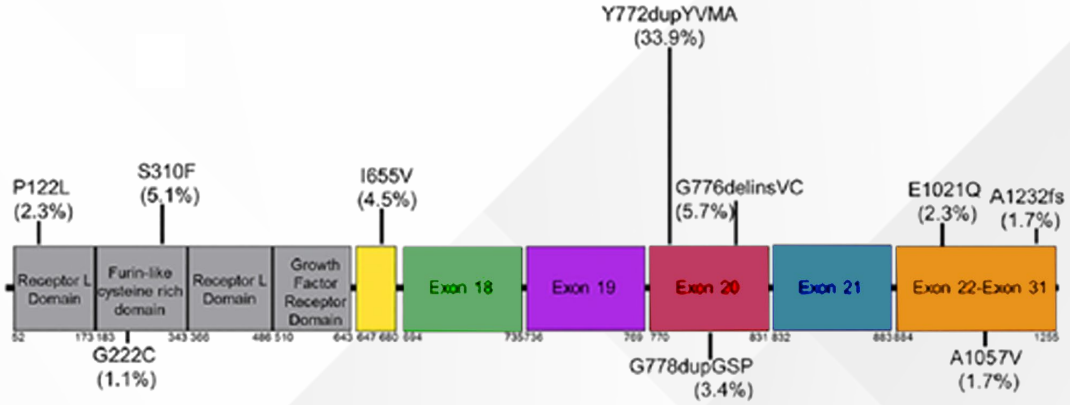


Oh D-Y, Bang Y-J. *Nat Rev Clin Oncol.* 2020;17(1):33-48.
AKT, protein kinase B; ERK, extracellular signal-regulated kinases; HER2, human epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase kinase; PI3K, phosphoinositide 3-kinases.

HER2 Gene Mutations in NSCLC

- Seen in ~1-4% of NSCLC
- More common in younger age (median ~61), female, never-smoker, adenocarcinoma
- Exon 20 insertion mutations are most common
  - YVMA 776-779 insertion most common: ~50-80% of *HER2* mutations
- Other kinase domain mutations (eg, exons 19, 21), juxtamembrane domain mutations, and transmembrane domain mutations also reported
- Primarily mutually exclusive with other drivers (eg, *ALK, EGFR)* but rarely can co-occur
- ***Targetable!***





Zhao J, Xia Y. *JCO Precis Oncol.* 2020;4:411-425. Jebbink M, et al. *Cancer Treat Rev.* 2020:86:101996. Mazières J, et al. *Ann Onc.* 2016;27(2):281-286. Robichaux JP, et al. *Cancer Cell.* 2019;36(4):444-457.e7.
ALK, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer.

HER2 Gene Amplifications in NSCLC

- Seen in ~2-4% of NSCLC as *de novo* alteration
- Can represent acquired mechanism of resistance to targeted therapy
  - ~13% of patients with acquired resistance to EGFR TKI therapy have been shown to harbor *HER2* amp
- No consensus definition, HER2/CEP ≥2 on FISH commonly used as cutoff
- Prognostic significance of *HER2* amplification is unclear
- Does not play major role in upfront treatment decision-making in NSCLC

Zhao J, Xia Y. *JCO Precis Oncol.* 2020;4:411-425. Jebbink M, et al. *Cancer Treat Rev.* 2020:86:101996.
CEP, chromosome enumeration probe; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

HER2 Overexpression in NSCLC

- Highly variable rates depending on cutoff used for positivity, ~3-30% of cases
- Determined by immunohistochemistry (IHC) with various cutoffs used in studies:
  - IHC2+: weak/moderate staining in ≥10% cells
  - IHC3+: strong complete membranous staining in ≥10% cells
  - H-score: semi-quantitative system multiplying staining intensity with % positive cells
- Associated with poor prognosis and shorter OS
- Can be seen in association with *HER2* amplification

Zhao J, Xia Y. *JCO Precis Oncol.* 2020;4:411-425. Jebbink M, et al. *Cancer Treat Rev.* 2020:86:101996.
HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; OS, overall survival.

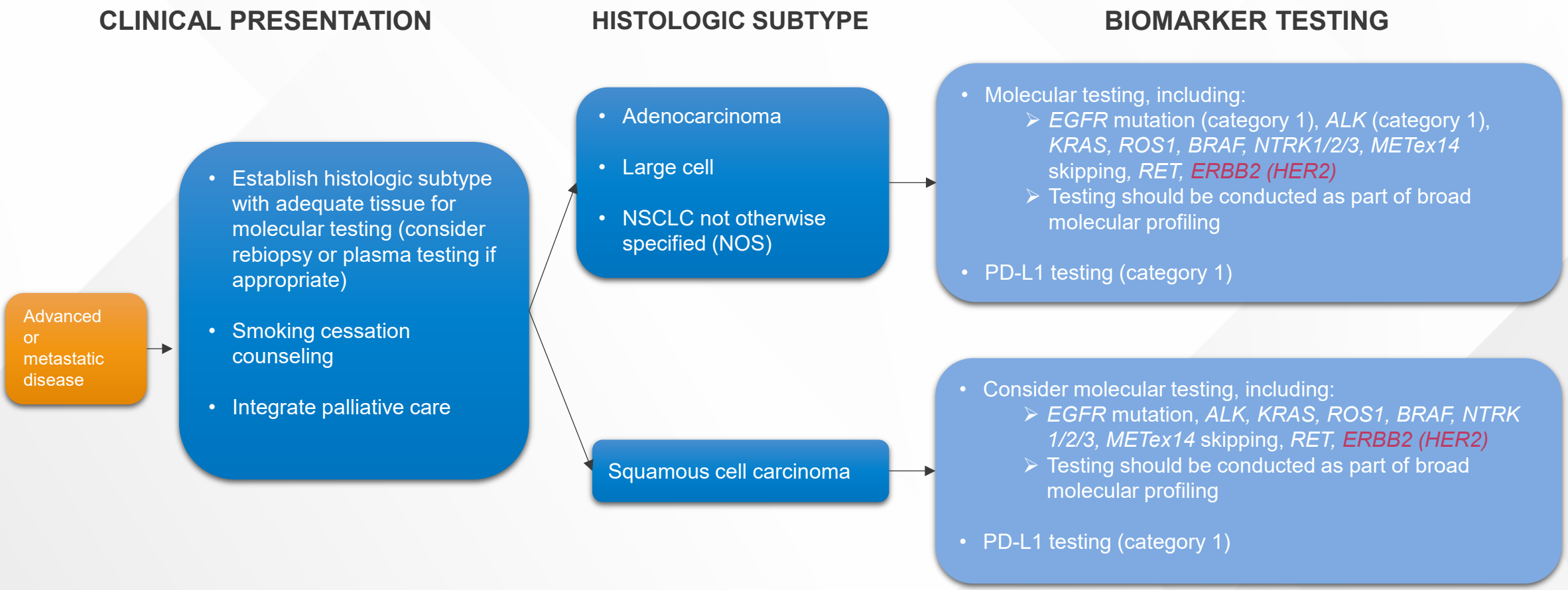
Genomic Testing in NSCLC

- Absolutely critical to clinical frontline decision-making in all stages, including resectable NSCLC and advanced NSCLC
- Comprehensive broad next-generation sequencing (NGS) is the gold standard, utilizing both tissue and blood-based testing platforms
- To assess *HER2* mutations in NSCLC:
  - Comprehensive NGS is preferred
  - Can also be assessed via Sanger sequencing and targeted PCR techniques
- Important to wait for testing results before beginning systemic therapy in advanced NSCLC
  - Availability of genomic testing results has been shown to improve survival in advanced NSCLC
  - If clinical scenario warrants more immediate therapy, begin chemotherapy alone

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (Version 3.2024). © 2024 National Comprehensive Cancer Network.
To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org.
Aggarwal et al. *JCO Precis Oncol.* 2023;7:e2300191.

Genomic Testing in NSCLC

NCCN Guidelines version 3.2024
Non-Small Cell Lung Cancer



Adapted from Ettinger DS, et al. NCCN Guidelines. Non-Small Cell Lung Cancer. Version 3.2024.
HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programed death ligand 1.

Tissue Versus Plasma-Based Testing Considerations

Formalin-fixed Paraffin-embedded Tissue Tumor Testing

- Primary method of tumor testing
- Laboratories accept other specimen types
  - Cytopathology preparations not processed by FFPE methods
- Limitation: insufficient yield for molecular, biomarker, and histologic testing when minimally invasive techniques are used to obtain samples
  - Bronchoscopists and interventional radiologists should procure sufficient tissue to enable all appropriate testing

Circulating Tumor DNA (ctDNA) Testing

- Can be utilized in conjunction with tissue-based testing to achieve genotyping for recommended biomarkers
- Should not be used in lieu of a histologic tissue diagnosis
- High specificity, but significantly compromised sensitivity
  - Up to 30% false-negative rate
- Data support complementary ctDNA and tissue testing to reduce turnaround time and increase yield of targetable alteration detection

Ettinger DS, et al. NCCN Guidelines. Non-Small Cell Lung Cancer. Version 3.2024.
FFPE, formalin-fixed paraffin-embedded; NSCLC, non-small cell lung cancer.

Biomarker Testing Platforms in NSCLC

Molecular Methods	Variant Types				Sensitivity (%)	Turnaround Time
	Point Mutations	Small Deletions, Insertions	Copy Number Alterations	Rearrangements		
Sizing assays	+/-	✓				2 to 3 days
PCR and Sanger sequencing	✓	✓			20-50	3 to 4 days
PCF and pyrosequencing	✓	+/-			20-50	3 to 4 days
PCR and mass spectrometry	✓	+/-			1-10	3 to 4 days
PCR and single-base extension	✓				1-10	3 to 4 days
qPCR and digital PCR	✓	✓		✓	0.00001	2 to 3 days
Allele-specific PCR	✓					1 to 2 days
FISH			+/-	✓	<1	2 to 3 days
NGS: targeted amplicon capture	✓	✓			1-10	7-10 days
NGS: targeted hybridization capture	✓	✓	✓	+/-1	1-5	15-20 days
NGS: whole exome	✓	✓	✓	+/-1	Variable	Weeks
NGS: whole genome	✓	✓	✓	✓	Variable	Weeks

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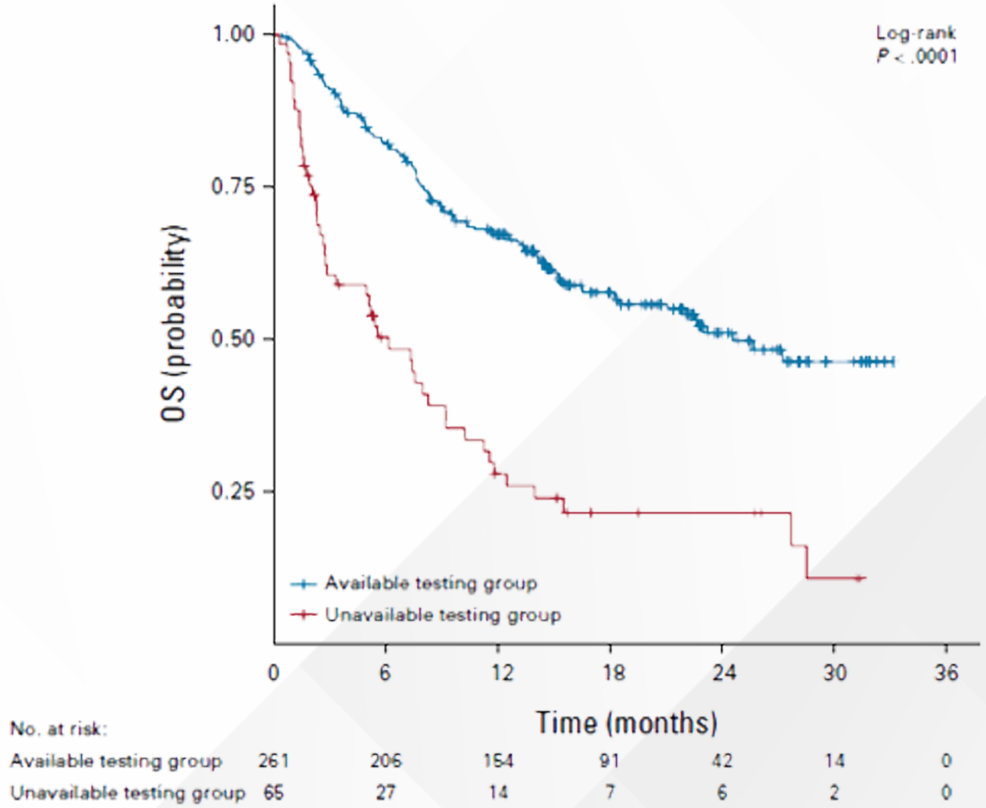
Adapted from Pennell NA, et al. *Am Soc Clin Oncol Educ Book.* 2019:39:531-542.
FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; qPCR, quantitative PCR.

Availability of Molecular Genotyping Results Impacts Survival in Advanced Non-Squamous NSCLC

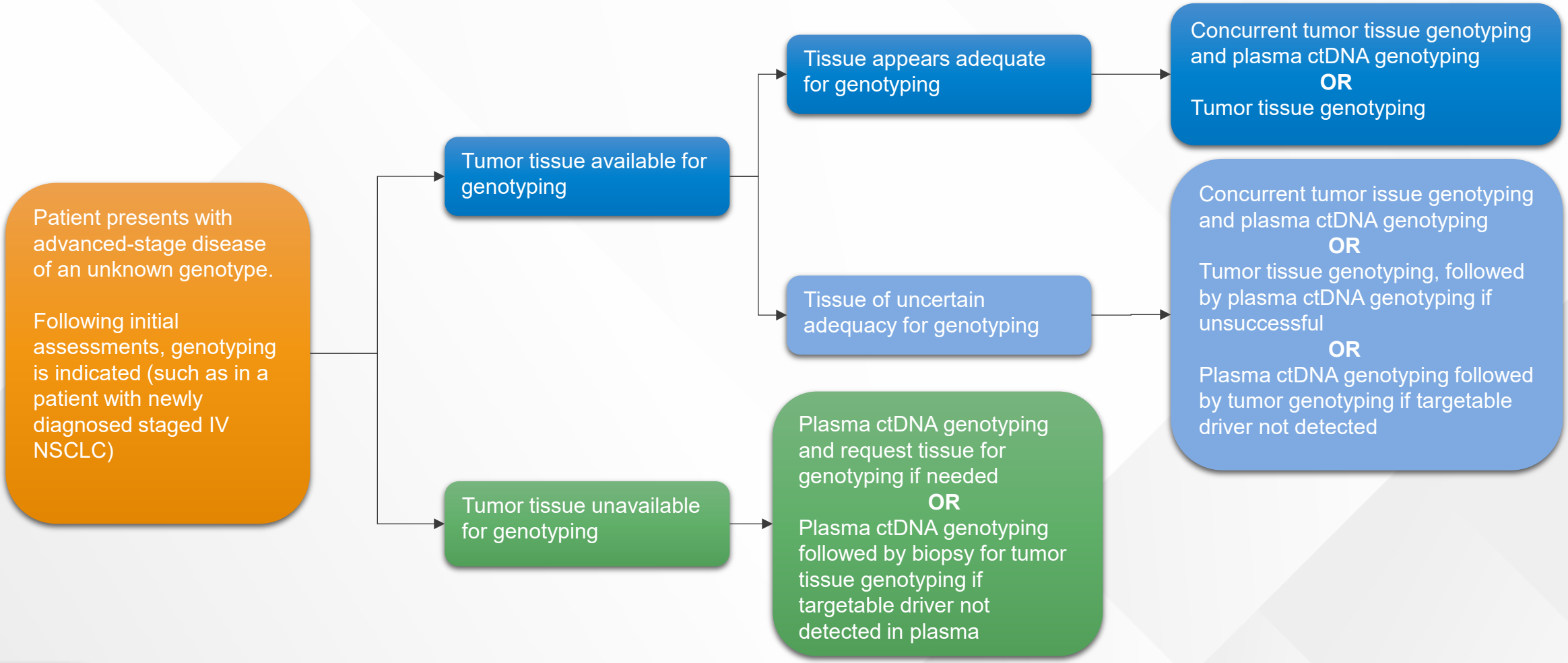
- 360 patient real-world cohort study using electronic health records for patients with newly diagnosed non-squamous NSCLC
- Patients with available molecular results had significantly longer overall survival compared to those without results (HR 0.43, 95% CI 0.30–0.62)
- Adjusted odds ratio higher when concurrent tissue and plasma testing was utilized

Overall Survival



Aggarwal C, et al. *JCO Precis Oncol.* 2023;7:e2300191.
CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer.

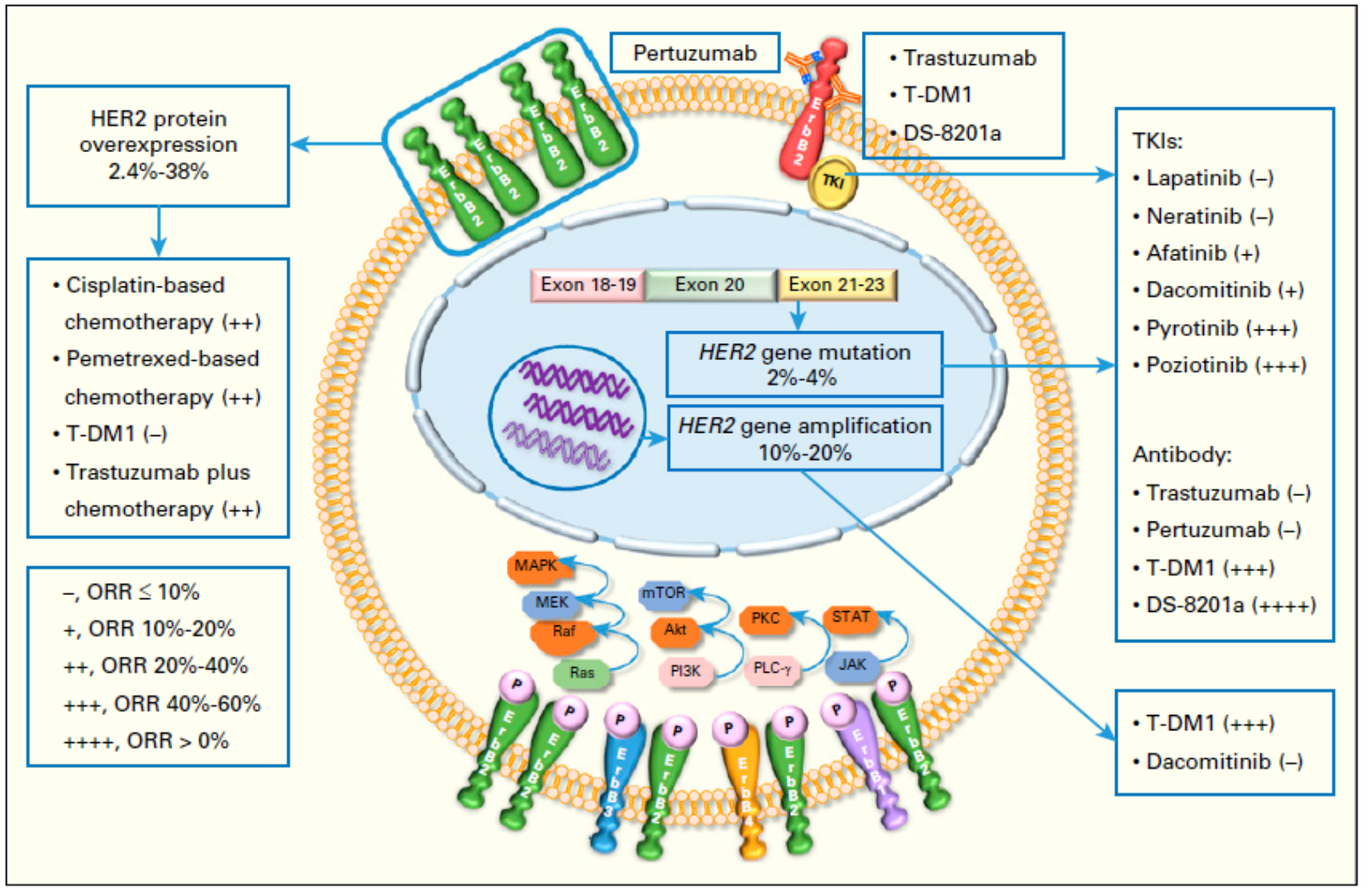
Algorithm for Incorporation of Liquid Testing Into Initial Work-up of Advanced NSCLC



Adapted from Aggarwal C, et al. *Nat Rev Clin Oncol.* 2021;18(1):56-62.
ctDNA, circulating tumor DNA; NSCLC, non-small cell lung cancer.

Treatment Options: Clinical Decision-Making for *HER2*-Mutant/ Overexpressing NSCLC

Treatment Strategies Targeting HER2 in Advanced NSCLC



Zhao J, Xia Y. *JCO Precis Oncol.* 2020;4:411-425.
HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, overall response rate; T-DM1, ado-trastuzumab emtansine; DS-8201a, fam-trastuzumab deruxtecan (T-DXd).

TKI Strategies in *HER2*-Mutated NSCLC

Overview of TKI Strategies in *HER2*-Mutated NSCLC

- No FDA-approved TKI options available for *HER2*-mutated NSCLC
- Both pan-HER and HER2-specific agents have been investigated
- Thus far, strategies have been limited by poor efficacy or unacceptable toxicity

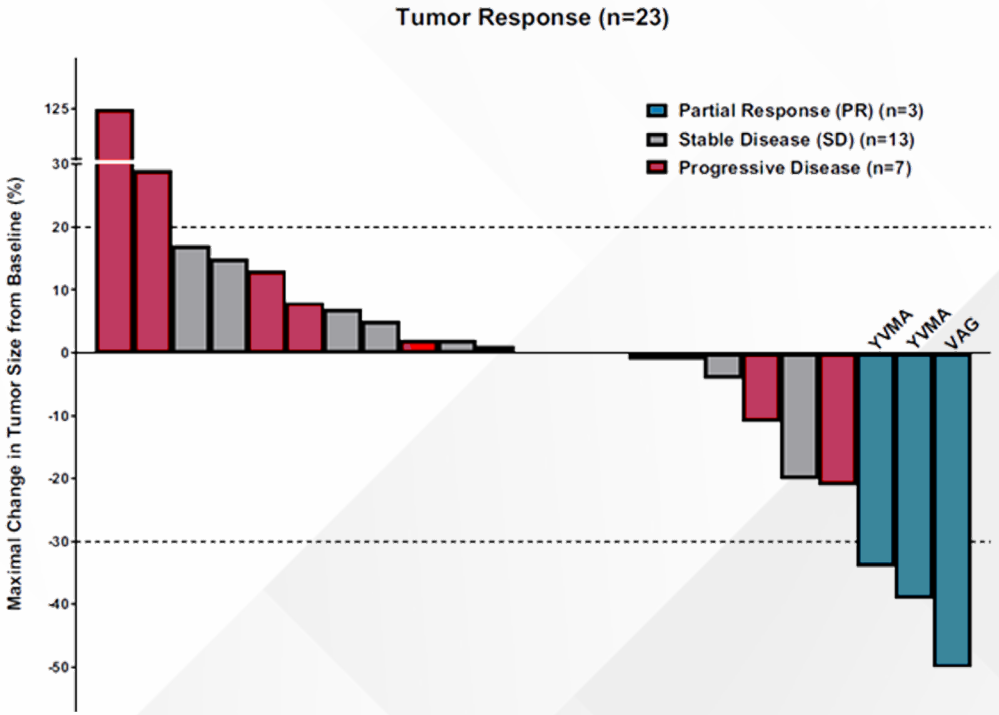
Agent	Combination Therapy	Study	HER2 Alterations	Sample Size (No.)	Clinical Efficacy
Dacomitinib	No	Phase II study	*HER2* mutation/amplification	30 (26 with *HER2* mutation; 4 with *HER2* amplification)	*HER2* exon 20 mutation: ORR, 12% (3/26); mPFS, 3 months; mOS, 9 months; 1-year survival, 44% *HER2* amplification: ORR, 0/4
Neratinib	No	Phase II basket study	*HER2* mutation	26	ORR, 3.8% (1/26); DCR, 42.3 (11/26); mPFS 5.5 months
Neratinib	Temsirolimus	Phase I study	*HER2* mutation	14 (6 with *HER2* mutation)	ORR, 33% (2/6)
Neratinib	Temsirolimus/ no	Randomized phase II study	*HER2* mutation	60	Neratinib: ORR, 0/17; DCR, 35% (6/17); mPFS, 3 months; mOS, 10 months Neratinib + temsirolimus: ORR, 19% (8/43); DCR, 51% (22/43); mPFS, 4.1 months; mOS, 15.8 months
Poziotinib or afatinib	No	Retrospective study	*HER2* mutation	7	Poziotinib: ORR, 33% (2/6); DCR, 83% (5/6) Afatinib: ORR, 100% (1/1)
Poziotinib	No	Phase II study	*HER2* mutation	12	ORR, 50% (6/12); DCR, 83.3% (10/12) at 8 weeks
Pyrotinib	No	Phase II study	*HER2* mutation	15	ORR, 53.3% (8/15); DCR, 73.3% (11/15); mDOR, 7.2 months; mPFS, 6.4 months

Adapted from Zhao J, Xia Y. *JCO Precis Oncol*. 2020;4:411-425.
DCR, disease control rate; HER2, human epidermal growth factor receptor 2; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

Afatinib in *HER2*-Mutated NSCLC

- Afatinib: pan-erbB family (*EGFR, HER)* irreversible inhibitor that is FDA approved for treatment of advanced *EGFR*m NSCLC
- Bulk of data retrospective, with modest efficacy and limited durability
  - ORR ~10-19%
  - Median time on treatment ~3 months
  - Dosing: 20 mg, 30 mg, or 40 mg daily
- Activity may be enriched in patients with YVMA insertion in exon 20
- Toxicity: GI (diarrhea), rash, stomatitis

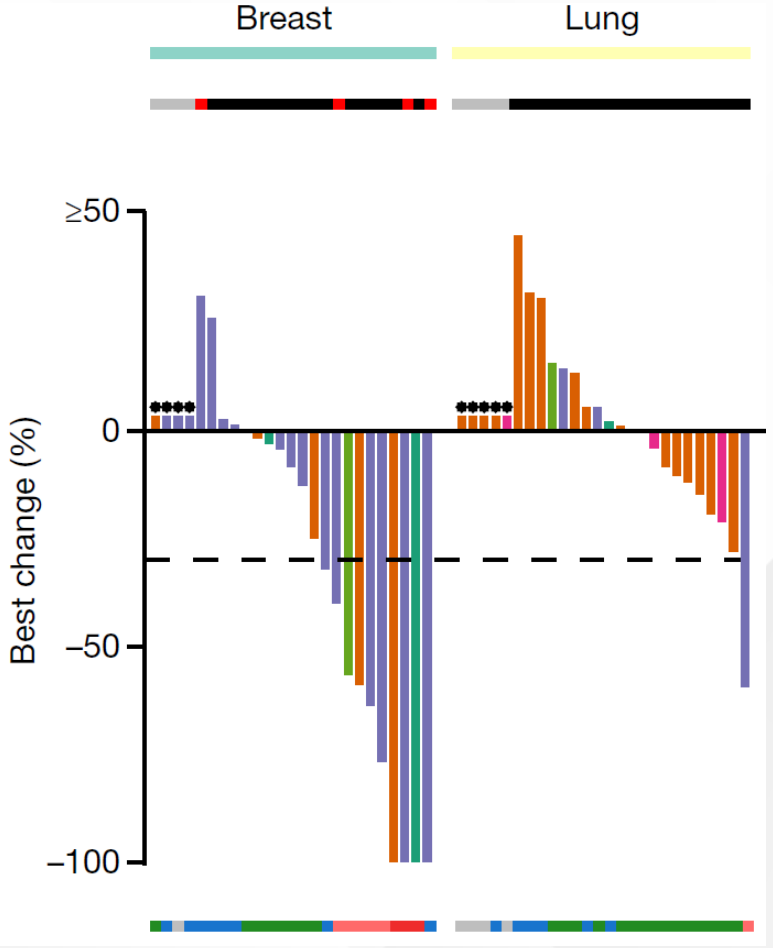
International retrospective multicenter study of afatinib in *HER2*-mutant lung cancers



Lai WV, et al. *Eur J Cancer*. 2019:109:28-35.
EGFR, epidermal growth factor receptor; *EGFR*m, *EGFR* mutated; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, overall response rate.

Neratinib in *HER2*-Mutated NSCLC

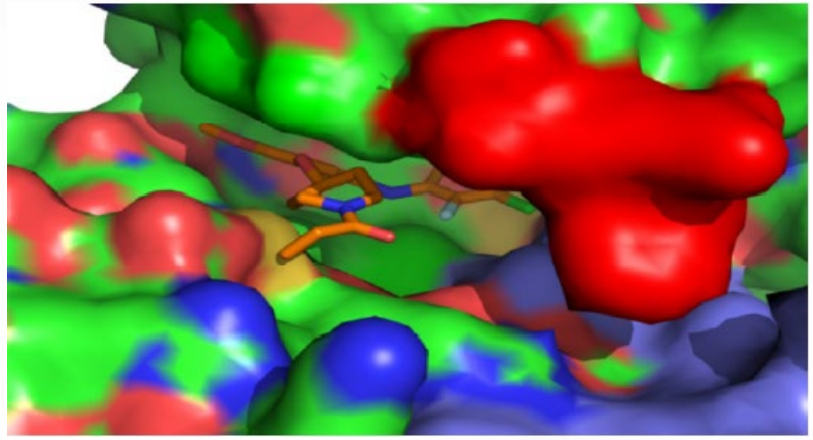
- Neratinib: irreversible pan-HER TKI that binds EGFR, HER2 and HER4
- Limited clinical activity in NSCLC
- In 26 patient NSCLC subgroup from SUMMIT basket trial, only 1 response (ORR 3.8%) observed
  - Dose: 240 mg/day
  - Loperamide prophylaxis

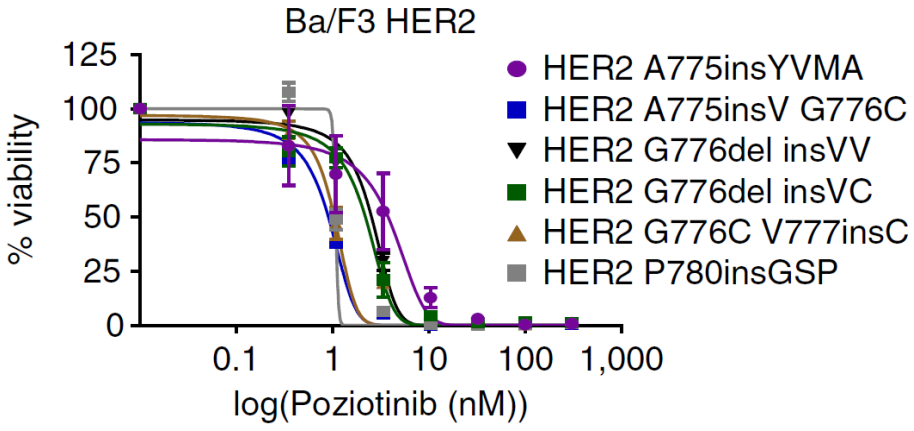


Hyman DM, et al. *Nature*. 2018;554(7691):189-194.
EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

Poziotinib in *HER2*-Mutated NSCLC

- Poziotinib: irreversible pan-erb-b2 TKI
- Unlike earlier generation pan-HER TKIs, conformation of poziotinib allows it to bind to and inhibit HER2 exon 20 insertion mutations
- Investigated in advanced NSCLC with both *HER2* and *EGFR* exon 20 insertion mutations in the phase 2 multi-cohort ZENITH trial
  - Dose: 16 mg/day



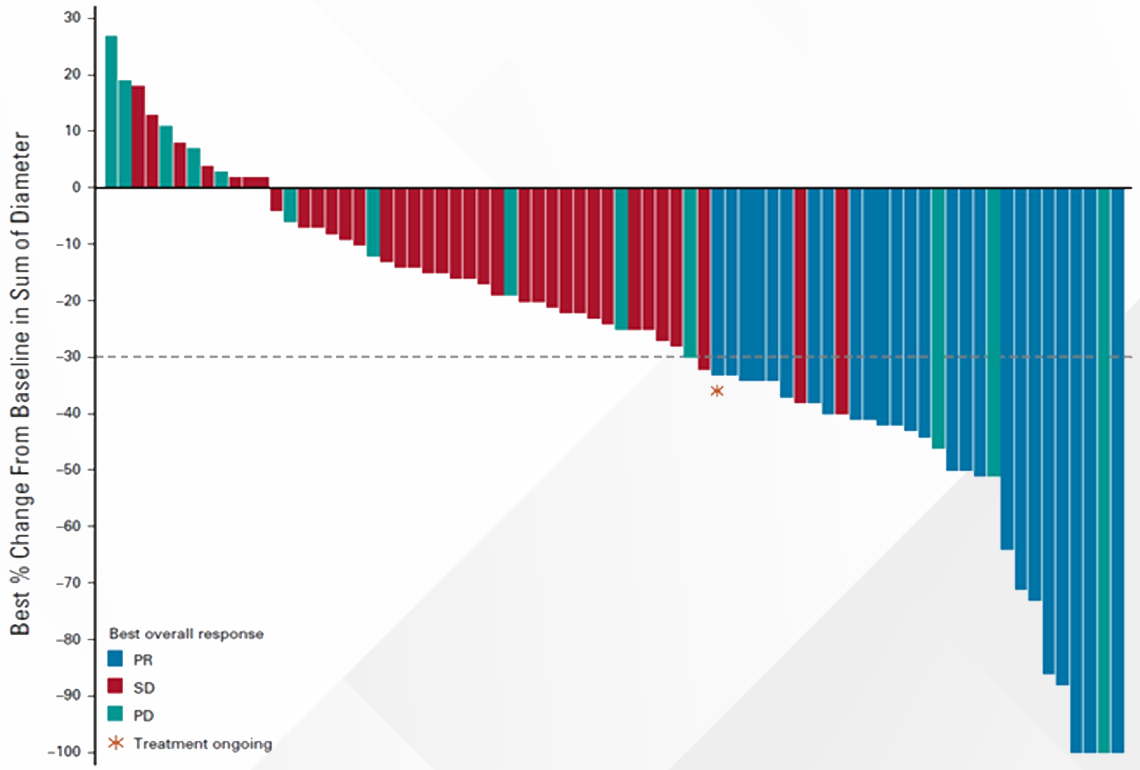


Robichaux JP, et al. *Nat Med.* 2018;24(5):638-646.

EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Poziotinib Demonstrated Promising Efficacy in Previously Treated *HER2*-Mutated NSCLC

Parameter	As-Treated[a] (N = 90)	Evaluable[b] (n = 74)
ORR, No. (%) 95% CI	25 (27.8)[c] 18.9 to 38.2	26 (35.1)[d] 24.4 to 47.1
Best overall response, No. (%)		
CR	0 (0)	0 (0)
PR	25 (27.8)[c]	26 (35.1)[d]
SD	38 (42.2)	35 (47.3)
PD	13 (14.4)	13 (17.6)
NE	14 (15.6)	0 (0)
DCR, No. (%) 95% CI	63 (70.0) 59.4 to 79.2	61 (82.4) 71.8 to 90.3
DoR, months, median (range) 95% CI	5.1 (1-14.1) 4.2 to 5.5	5.1 (0.9-14.1) 4.2 to 5.5
PFS, months, median (range) 95% CI	5.5 (0.0-17.6) 3.9 to 5.8	5.5 (0.6-17.6) 3.9 to 6.2



Le X, et al. *J Clin Oncol*. 2022;40(7):710-718.
CR, complete response; DCR, disease control rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Poziotinib Feasibility Limited by Toxicity

- 78.9% of patients experienced grade ≥3 treatment-related adverse events
- High-grade rash, diarrhea, stomatitis very common
- ~77% of patients required at least one dose reduction

N = 90

AE (preferred term)	Any Grade	Grade 3	Grade 4
Patients with at least one event, No. (%)	88 (97.8)	71 (78.9)	4 (4.4)
Rash (multiple terms)	82 (91.1)	44 (48.9)	0
Diarrhea	74 (82.2)	23 (25.6)	0
Stomatitis (multiple terms)	62 (68.9)	21 (23.3)	1 (1.1)
Paronychia	34 (37.8)	1 (1.1)	0
Dry skin	28 (31.1)	5 (5.6)	0
Decreased appetite	27 (30.0)	2 (2.2)	0
Nausea	26 (28.9)	2 (2.2)	0
Alopecia	25 (27.8)	0	0
Pruritus	24 (26.7)	2 (2.2)	0
Vomiting	21 (23.3)	0	0
Fatigue	20 (22.2)	2 (2.2)	0
Anemia	13 (14.4)	3 (3.3)	0
Weight decreased	13 (14.4)	1 (1.1)	0
Epistaxis	11 (12.2)	0	0
Hypomagnesemia	10 (11.1)	1 (1.1)	1 (1.1)
Asthenia	9 (10.0)	3 (3.3)	0
Hypokalemia	9 (10.0)	3 (3.3)	0
Dry mouth	9 (10.0)	0	0
Dyspnea	3 (3.3)	0	1 (1.1)
Hypocalcemia	3 (3.3)	1 (1.1)	1 (1.1)
Pancreatitis relapsing	1 (1.1)	0	1 (1.1)

Adapted from Le X, et al. *J Clin Oncol.* 2022;40(7):710-718.
AE, adverse event.

Monoclonal Antibody Therapy in *HER2*-Altered NSCLC

HER2-Targeted Monoclonal Antibody Therapy in *HER2*-Mutated NSCLC

Trastuzumab

- Anti-HER2 monoclonal antibody
- Blocks HER2 cleavage, inhibiting downstream signaling

Pertuzumab

- Anti-HER2 monoclonal antibody
- Prevents HER2-partner dimerization

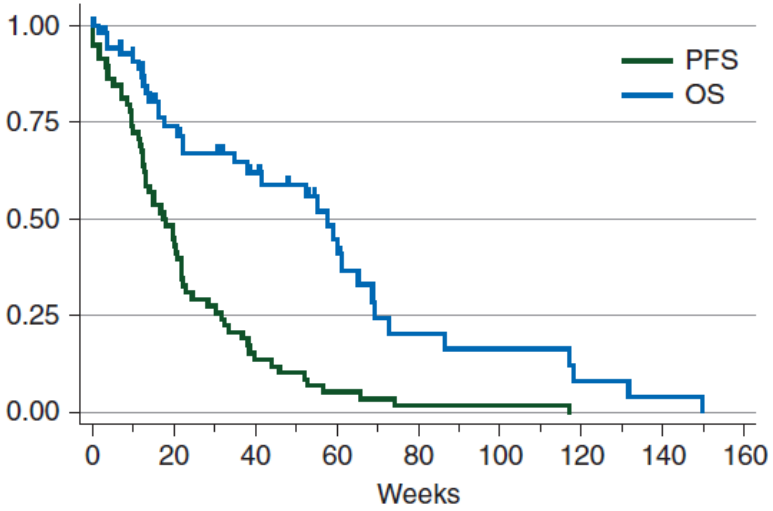
Trastuzumab + single-agent chemotherapy in *HER2*-mutated NSCLC

- Limited retrospective data
- ORR ~50%, PFS 5.1 months
- Unclear whether any advantages over platinum-doublet chemotherapy

Trastuzumab + pertuzumab in *HER2*-mutated solid tumors

- Limited data from phase II basket study
- Among 36 patients (14 NSCLC), ORR 11%

PFS and OS for trastuzumab-chemotherapy in *HER2*m NSCLC



Mazières J, et al. *Ann Onc.* 2016;27(2):281-286. Hainsworth JD, et al. *J Clin Oncol.* 2018;36(6):536-542.
HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Anti-HER2 +/- Chemotherapy in Advanced NSCLC With *HER2* Amplification and HER2 Overexpression

- Interpretation of data difficult in setting of variable cutoffs for HER2 overexpression and *HER2* amplification
- Unclear what additive benefit, if any, trastuzumab brings to platinum-doublet chemotherapy
- Trastuzumab + pertuzumab showed limited efficacy in HER2 amp/overexpressed NSCLC (ORR 13%)

Agent	Combination Therapy	Study	HER2 Alterations	Sample Size (No.)	Clinical Efficacy
Trastuzumab	Paclitaxel	Single-arm phase II study	HER2 IHC 1+ to 3+; *HER2* gene number copy > 1 (with concurrent *EGFR* mutation and had progressed on EGFR TKI monotherapy)	24 (21 with HER2 overexpression)	ORR, 46% (11/24); DCR, 63% (15/24); mDOR, 5.6 months; mPFS 2.3 months
Trastuzumab	Paclitaxel and carboplatin	Phase II study	HER2 IHC 1+ to 3+	56 (31 with HER2 overexpression)	mPFS, 3.3 months; median survival, 10.1 months; 1-year survival rate, 42%; median survival for 1+, 2+ and 3+ HER-2 expression was 14.6, 7.7 and 10.9 months
Trastuzumab	Cisplatin and gemcitabine	Phase II study	HER2 IHC 1+ to 3+ or serum HER2 shed ECD concentrations at least 15 ng/ml by ELISA)	21 (9 with HER2 overexpression)	ORR, 38% (8/21); DCR, 81% (17/21); 1-year survival rate, 62% (13/21); mTTP, 36 weeks
Trastuzumab	Gemcitabine and cisplatin	Randomized phase II study	HER2 overexpression (IHC 2+ to 3+); HER2 amplification (FISH+); serum HER2 ECD positive	101 (only 5 with HER2 IHC3+; 7 with *HER2* FISH+)	Efficacy was similar in the trastuzumab and control arms: ORR, 26% *v* 41%; DCR, 80% *v* 94%; mTTP, 6.3 *v* 7.2 months; mPFS, 6.1 *v* 7 months; 6 trastuzumab-treated patients with HER2 3+ or FISH+ had higher RR (83%) and mPFS (8.5 months)
Trastuzumab	Docetaxel or paclitaxel	Randomized phase II study	Unselected by HER2 status	64 (20 with HER2 overexpression)	Efficacy was similar in the patients treated with docetaxel plus trastuzumab and the patients treated with paclitaxel plus trastuzumab: ORR was 23% (7/30) *v* 32% (11/24; *P* = .76); median survival, 16 *v* 14 months; 1-year survival, 57% *v* 55% (*P* = .998)

Adapted from Zhao J, Xia Y. *JCO Precis Oncol.* 2020;4:411-425. Hainsworth JD, et al. *J Clin Oncol.* 2018;36(6):536-542.
DCR, disease control rate; ECD, extracellular domain; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mDOR, median duration of response; mPFS, progression-free survival; mTTP, median time to progression; NSCLC, non-small cell lung cancer; ORR, overall response rate; RR, response rate; TKI, tyrosine kinase inhibitor.

Antibody-Drug Conjugates in *HER2*-Altered NSCLC

Anatomy of an Antibody-Drug Conjugate (ADC)

Target: Antibody

- Target: selectively expressed or over-expressed on tumor cells
- Antibody: Human/humanized immunoglobulin
- IgG1 most common

Linker

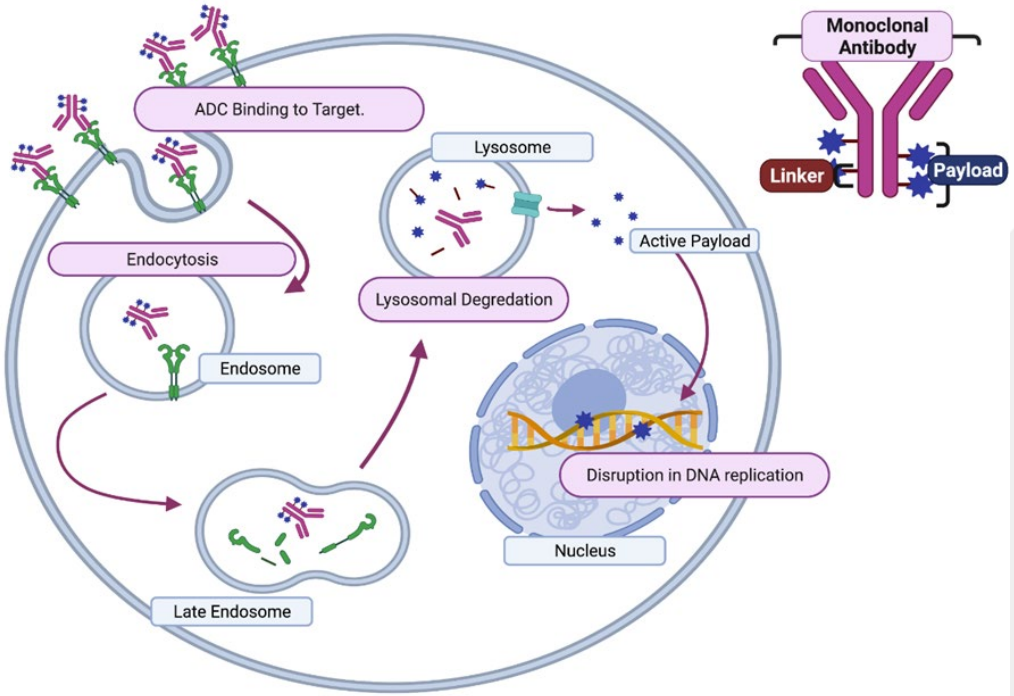
- Non-cleavable
  - Traffic to mature lysosomes for degradation
  - Limited “bystander effect”
- Cleavable
  - Cell physiology (pH, proteases, etc.) key to payload-linker uncoupling
  - Prominent “bystander effect”

Payload

- Highly potent cytotoxin including DNA damaging agents (PBD, calicheamicin), tubulin polymerization inhibitors (MMAE, DM1), and topoisomerase inhibitors (DXd)
- Drug-to-antibody ratio (DAR): number of payload moieties attached to a specific antibody

Mechanism of Action

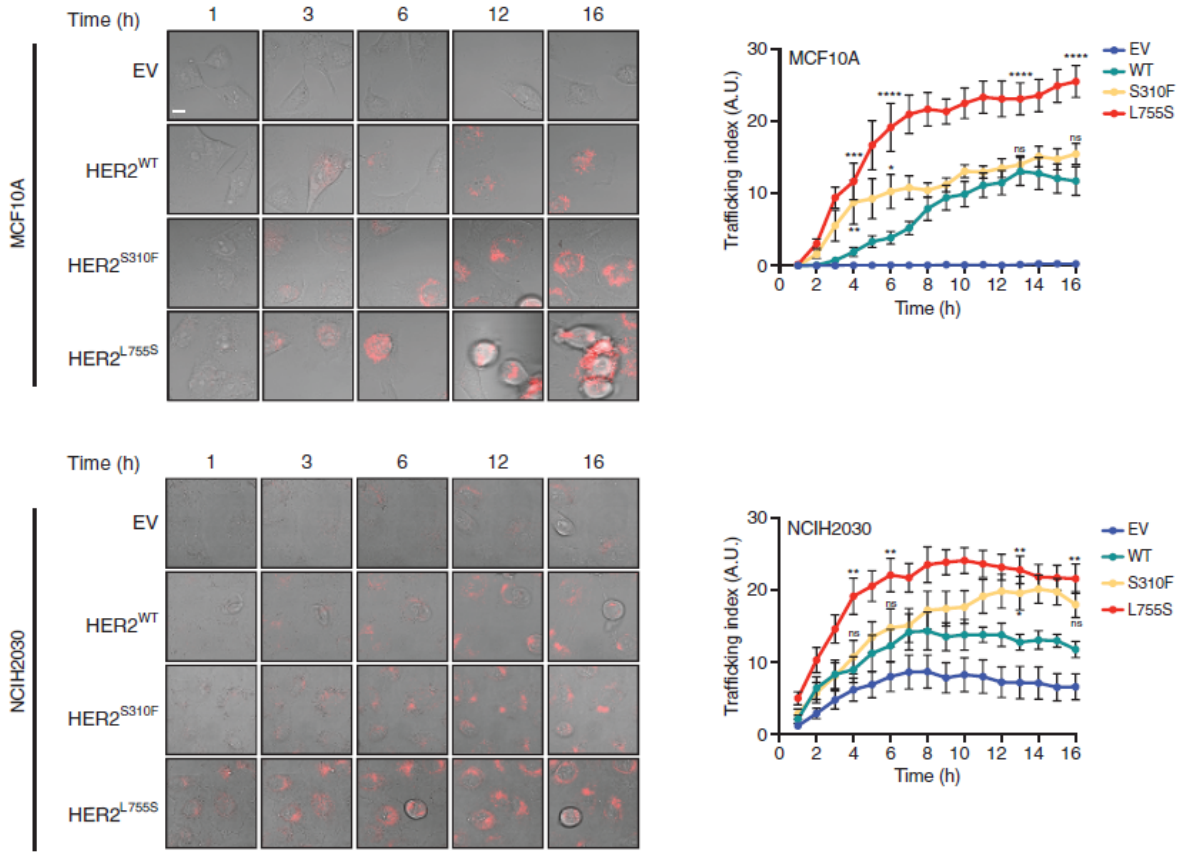
- Payload delivery, ADCC, complement-mediated cytotoxicity, inhibition of oncogenic drivers



Marks JA, et al. *Curr Oncol Rep.* 2022;24(12):1829-1841.
ADCC, antibody-dependent cellular cytotoxicity; DM1, derivative of maytansine 1; DNA, deoxyribonucleic acid; DXd, DX-8951 derivative; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; MMAE, monomethyl auristatin-E; NSCLC, non-small cell lung cancer; PBD, pyrrolobenzodiazepines.

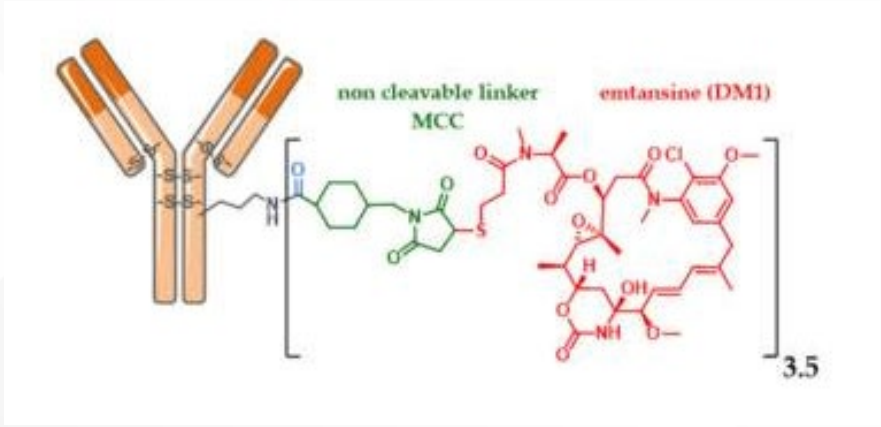
Rationale for ADCs in HER2-Mutated NSCLC

- Receptor internalization upon ADC binding is key to efficacy
- *HER2* mutations increase receptor internalization and ADC cytotoxic activity compared to *HER2*-wild type in preclinical studies



Li BT, et al. *Cancer Discov.* 2020;10(5):674-687.
ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer.

Ado-Trastuzumab Emtansine (T-DM1) in *HER2*-Altered NSCLC



T-DM1

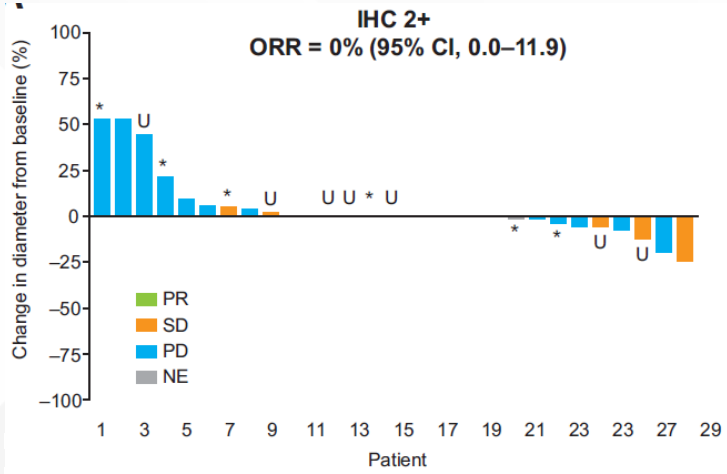
- HER2-targeted ADC of trastuzumab conjugated to the anti-microtubule agent DM1 via a non-cleavable linker
- Approved as subsequent-line therapy in advanced HER2+ breast cancer
- Carries category 2A recommendation for subsequent line therapy in advanced *HER2*-mutated NSCLC

- Efficacy signals observed in *HER2*-mutated and -amplified NSCLC
- Phase II basket study of 49 pts w/ previously treated advanced NSCLC: ORR 51%, mPFS 5 months
  - Dose: 3.6 mg/kg IV over 90 minutes on day 1 of each 21-day cycle until disease progression or unmanageable toxic effects
  - *HER2*-mutated (n=28): ORR 50%
  - *HER2*-amplified (n=11): ORR 50%
  - *co-HER2-mutated/amp* (n=10): ORR 50%
- Multiple phase II trials have demonstrated little benefit for T-DM1 in NSCLC with HER2 overexpression
  - Only observed responses were in patients with either concurrent *HER2* amplification or *HER2* mutations
- Major toxicities: cytopenias, fatigue, elevated LFTs, infusion reactions

Li BT, et al. *Cancer Discov*. 2020;10(5):674-687. Hotta K, et al. *J Thorac Oncol*. 2018;13(2):273-279. Peters S, et al. *Clin Cancer Res*. 2019;25(1):64-72.
ADC, antibody-drug conjugate; DM1, derivative of maytansine 1; HER2, human epidermal growth factor receptor 2; IV, intravenous; LFT, liver function test; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, overall response rate; T-DM1, ado-trastuzumab emtansine.

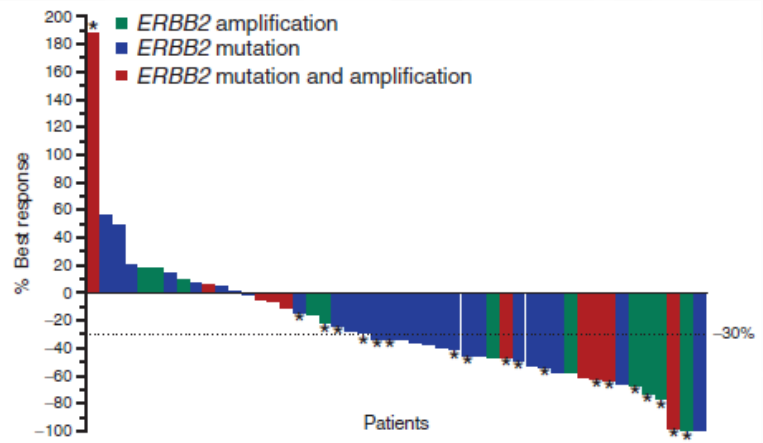
T-DM1 in *HER2*-Altered NSCLC

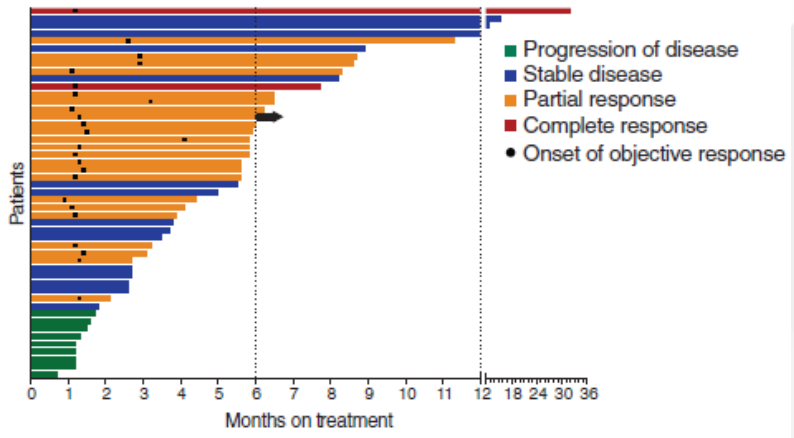
HER2-overexpressed NSCLC



*positive *HER2* amplification

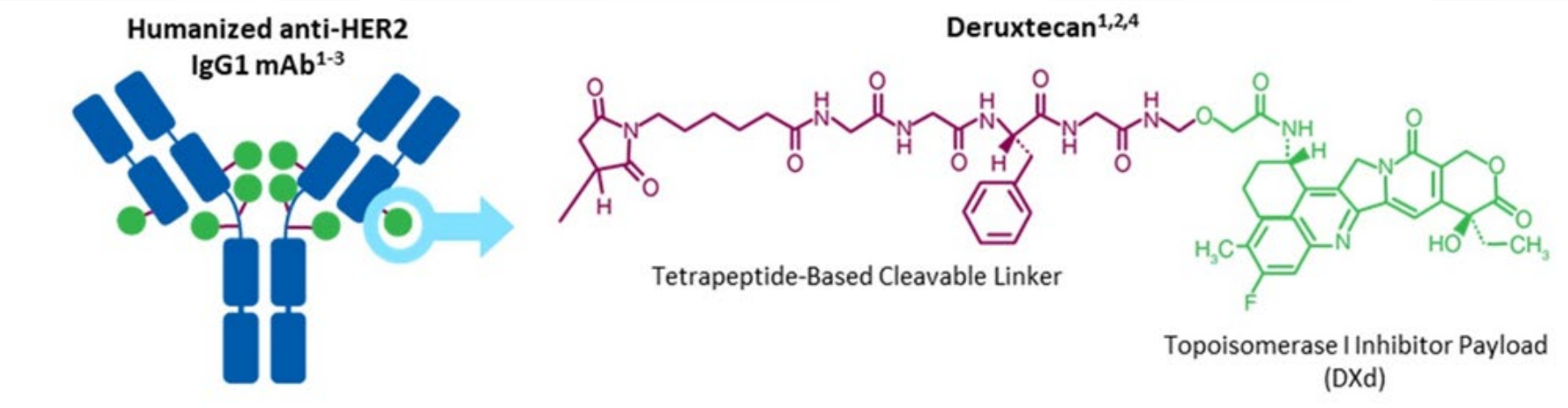
HER2-mutated and/or *HER2*-amplified





Peters S, et al. *Clin Cancer Res.* 2019;25(1):64-72. Li BT, et al. *Cancer Discov.* 2020;10(5):674-687.
ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, ado-trastuzumab emtansine.

Trastuzumab Deruxtecan (T-DXd)



T-DXd

- HER2-targeted ADC of trastuzumab conjugated to deruxtecan (DXd) via cleavable linker with DAR of 8
- Elicits significant bystander effect, supporting use in tumors with heterogeneous HER2-expression
- FDA approvals in advanced HER2-positive and HER2-low breast cancer, HER2-positive gastric or GE junction adenocarcinoma
- Carries category 2A recommendation as the only preferred subsequent line therapy in advanced *HER2*-mutated NSCLC

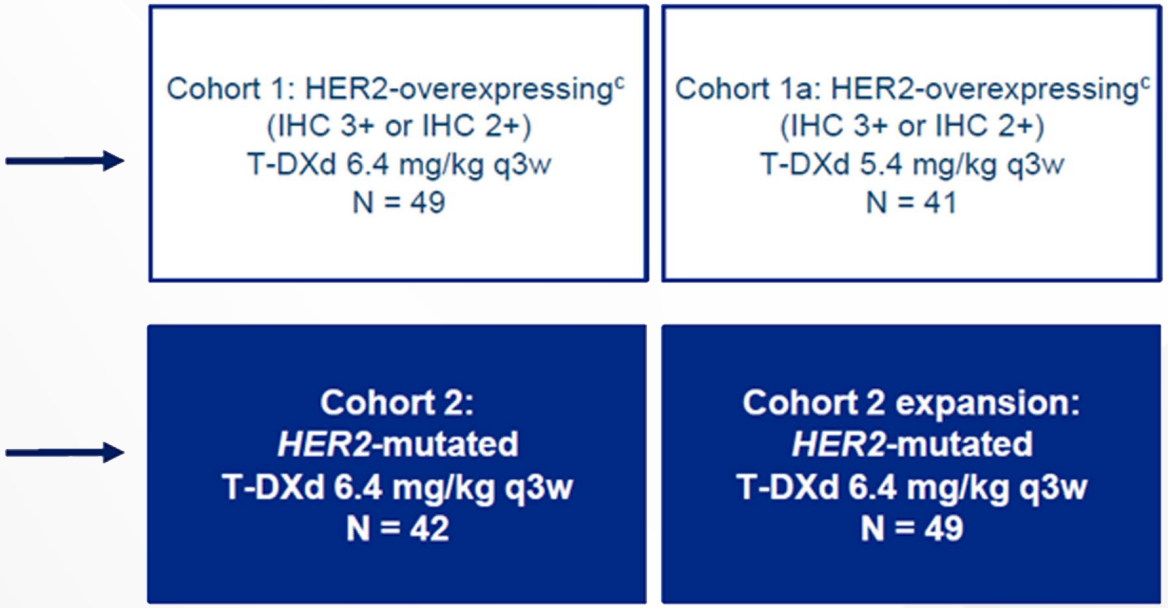
Smit EF, et al. *J Clin Oncol*. 2020;38(15_suppl):9504.
ADC, antibody-drug conjugate; DAR, drug-antibody ratio; GE, gastroesophageal; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; T-DXd, trastuzumab deruxtecan.

DESTINY-Lung01 Trial: Study Design

Multicenter, international, 2-cohort phase 2 trial (NCT03505710)

Key eligibility criteria

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]



Primary end point

- Confirmed ORR by ICR[d]

Secondary end points

- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point

- Biomarkers of response

[a]Patients with asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll [b]*HER2* mutation documented solely from a liquid biopsy could not be used for enrollment [c]HER2 overexpression without known *HER2* mutation was assessed by local assessment of archival tissue and centrally confirmed [d]Per RECIST v1.1

Li BT, et al. ESMO 2021. Abstract LBA45.

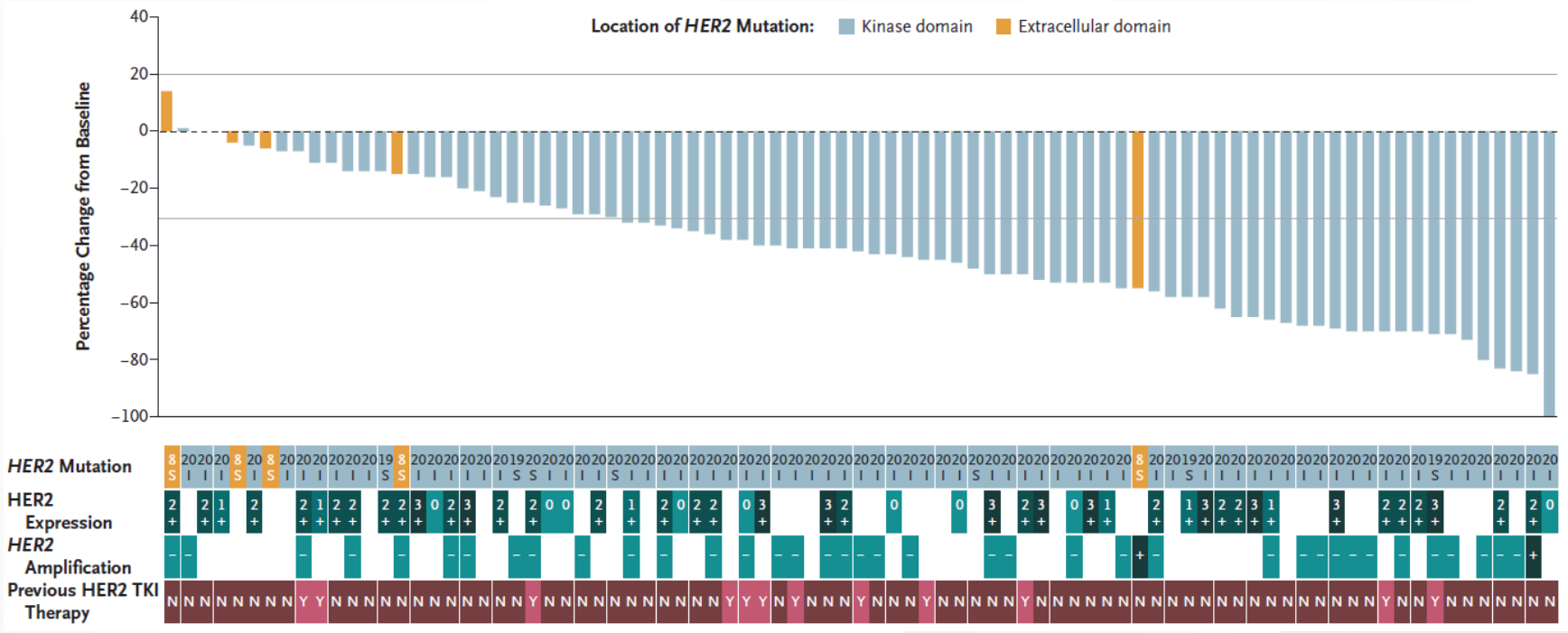
CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

T-DXd Demonstrated Promising Activity in DESTINY-Lung01 in Patients With HER2-Mutated NSCLC

Table 2. Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.

Response Assessment	Patients (N=91)
Confirmed objective response*	
No. of patients	50
Percentage of patients (95% CI)	55 (44–65)
Best response — no. (%)	
Complete response	1 (1)
Partial response	49 (54)
Stable disease	34 (37)
Progressive disease	3 (3)
Response could not be evaluated	4 (4)
Disease control†	
No. of patients	84
Percentage of patients (95% CI)	92 (85–97)
Median time to response (range) — mo‡	1.5 (1.2–9.3)
Median duration of response (95% CI) — mo‡	9.3 (5.7–14.7)

* Confirmed objective response was assessed by independent central review on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Disease control was defined as complete response, partial response, or stable disease at 6 weeks with no progression.
‡ Analyses of time to response and duration of response included only the patients with a confirmed objective response.



Activity observed across *HER2* mutation subtypes and irrespective of *HER2*amp or HER2 expression status

Li BT, et al. ESMO 2021. Abstract LBA45.
HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

DESTINY-Lung02 Trial: Study Design

Phase 2 Randomized, Non-Comparative trial

Key Eligibility Criteria

- Metastatic *HER2*m NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:

- Prior anti-PD(L)1 treatment

R 2:1

N = 152

T –DXd 5.4 mg/kg Q3W
N = 102

T –DXd 6.4 mg/kg Q3W
N = 50

Primary Endpoint

- Confirmed ORR by BICR

Secondary Endpoints

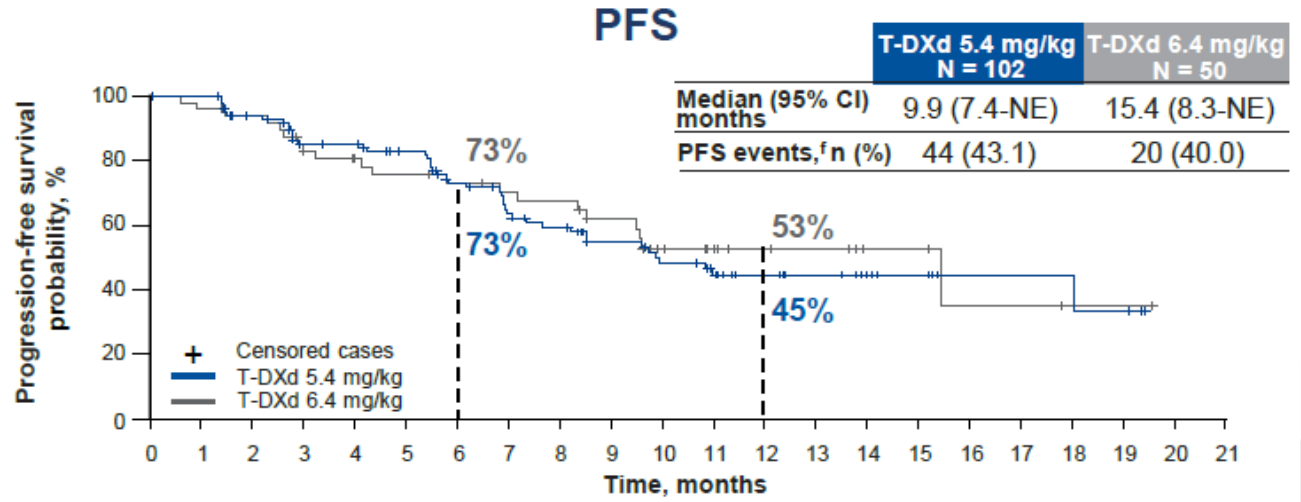
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

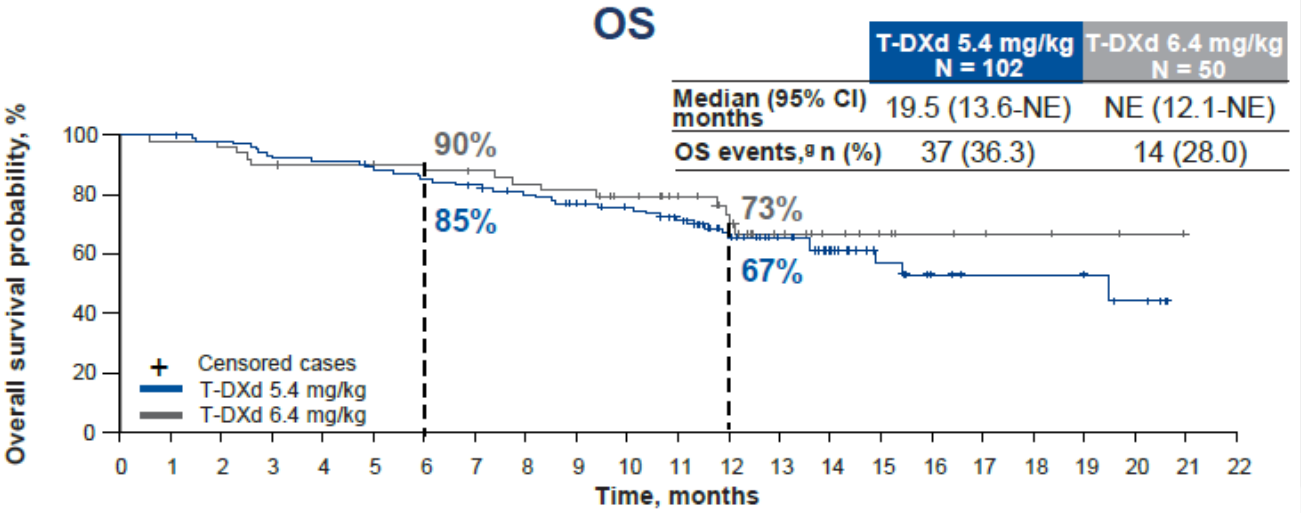
Patients and investigators were blinded to the dose level

Jänne P, et al. WCLC 2023. Abstract MA13.10.
BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; INV, investigators; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan.

Similar Efficacy Observed at Either Dose in DESTINY-Lung02

Response Assessment by BICR	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
Best confirmed overall response, No. (%)		
CR	1 (1.0)	2 (4.0)
PR	49 (48.0)	26 (52.0)
SD	45 (44.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Nonevaluable[a]	3 (2.9)	2 (4.0)
DCR, No. (%)	95 (93.1)	46 (92.0)
95% CI	86.4 to 97.2	80.8 to 97.8
DoR, months, median (95% CI)	16.8 (6.4 to NE)	NE (8.3 to NE)
TTIR, months, median (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Follow-up, months, median (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)





Goto K, et al. *J Clin Oncol.* 2023;41(31):4852-4863. Jänne P, et al. WCLC 2023. Abstract MA13.10.
CR, complete response; DCR, disease control rate; DoR, duration of response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTIR, time to initial response.

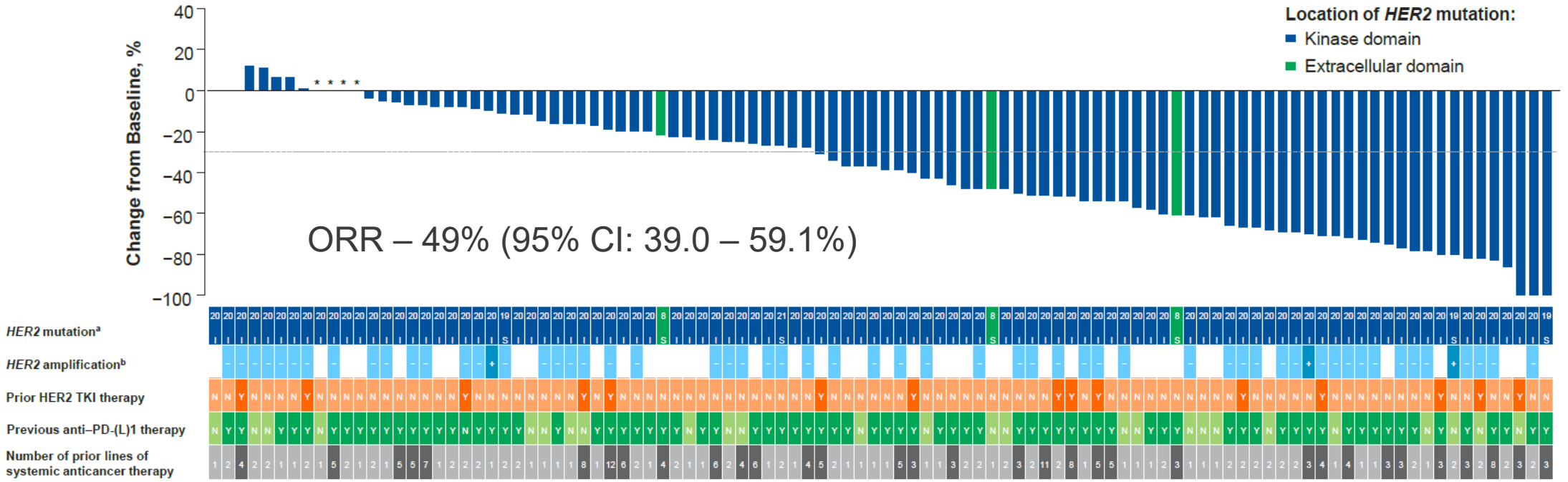
Final Results of DESTINY-Lung02 in Patients with Previously Treated HER2-mutant NSCLC

	T-DXd 5.4 mg/kg N=102	T-DXd 6.4 mg/kg N=50
cORR, %	50.0	56.0
Median DoR, mo	12.6	12.2
Median PFS, mo	10.0	12.9
Median OS, mo	19.0	17.3

Janne PA, et al. *J Clin Oncol.* 2024;42(suppl 16):8543.
cORR, confirmed overall response rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Anti-Tumor Activity of T-DXd 5.4 mg/kg in Advanced HER2-Mutated NSCLC

Best Percentage Change in Tumor Size by BICR With T-DXd 5.4 mg/kg (N=102)



Responses were observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

Goto K, et al. *J Clin Oncol*. 2023;41(31):4852-4863. Jänne P, et al. WCLC 2023. Abstract MA13.10.
BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, overall response rate; T-DXd, trastuzumab deruxtecan.

Safety Profile of T-DXd Is More Favorable at 5.4 mg/kg Compared to 6.4 mg/kg Every 3 Weeks

Preferred Term	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)		T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50),[a] No. (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	68 (67.3)	4 (4.0)	41 (82.0)	3 (6.0)
Neutropenia[b]	43 (42.6)	19 (18.8)	28 (56.0)	18 (36.0)
Fatigue[b]	45 (44.6)	8 (7.9)	25 (50.0)	5 (10.0)
Decreased appetite	40 (39.6)	2 (2.0)	25 (50.0)	2 (4.0)
Anemia[b]	37 (36.6)	11 (10.9)	26 (52.0)	8 (16.0)
Vomiting	32 (31.7)	3 (3.0)	22 (44.0)	1 (2.0)
Constipation	37 (36.6)	1 (1.0)	16 (32.0)	0
Leukopenia[b]	29 (28.7)	5 (5.0)	17 (34.0)	8 (16.0)
Thrombocytopenia[b]	28 (27.7)	6 (5.9)	14 (28.0)	5 (10.0)
Diarrhea	23 (22.8)	1 (1.0)	18 (36.0)	2 (4.0)
Alopecia	22 (21.8)	0	17 (34.0)	0
Transaminases increased[b]	22 (21.8)	3 (3.0)	10 (20.0)	0

Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

Based on these data, T-DXd 5.4 mg/kg IV q3w was granted accelerated FDA approval for the treatment of advanced *HER2*-mutated NSCLC after progression on prior therapy

Goto K, et al. *J Clin Oncol.* 2023;41(31):4852-4863. Jänne P, et al. WCLC 2023. Abstract MA13.10.
HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; IV, intravenous; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

T-DXd FDA Approval in HER2-Mutant NSCLC

- August 2022: FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2/ERBB2* mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy
  - First drug approved for HER2-mutant NSCLC
- FDA also approved the Life Technologies Corporation's Oncomine™ Dx Target Test (tissue) and the Guardant Health, Inc.'s Guardant360® CDx (plasma) as companion diagnostics
  - If no mutation is detected in a plasma specimen, the tumor tissue should be tested
- Recommended dosage for lung cancer:
  - 5.4 mg/kg
  - Intravenous infusion
  - Once every 3 weeks (21-day cycle)
  - Until disease progression or unacceptable toxicity

AXIS Medical Education

FDA.gov. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer. Press release. August 16, 2022.
ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

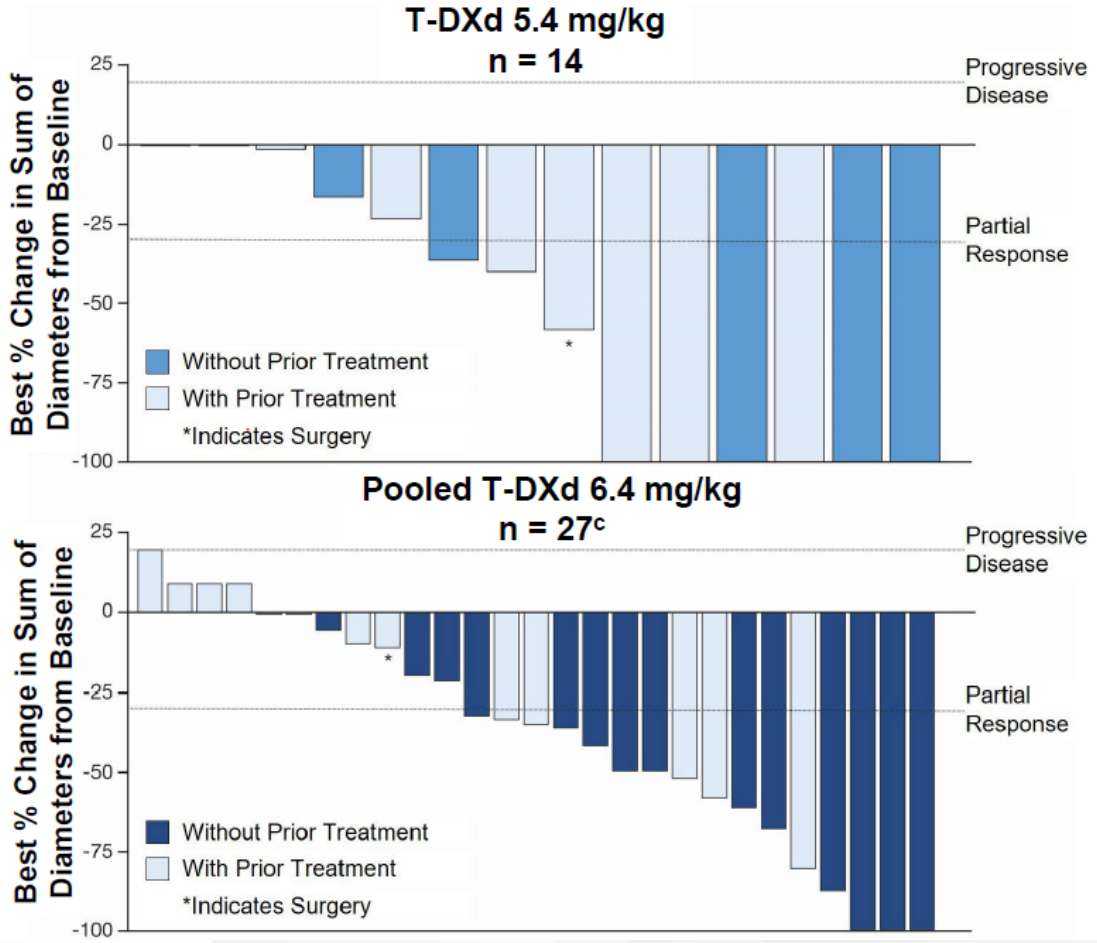
CNS Efficacy of T-DXd in HER2-Mutated NSCLC

Pooled CNS efficacy data from DESTINY-Lung01 and DESTINY-Lung02 Studies

Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM n = 14	Pooled T-DXd 6.4 mg/kg DL-01 *HER2m*/DL-02 BM n = 30
IC-cORR, n (%)[a]	**7 (50.0)**	**9 (30.0)**
95% CI[b]	23.0-77.0	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30.0)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE[c]	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%)[a]	**13 (92.9)**	**22 (73.3)**
95% CI[b]	66.1-99.8	54.1-87.7
IC-DoR, months[d]		
Median, (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response



Li BT, et al. ESMO 2023. Abstract 1321MO.

BM, brain metastases; CNS, central nervous system; CR, complete response; HER2, human epidermal growth factor receptor 2; IC-DCR, intracranial disease control rate; IC-DoR, intracranial duration of response; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

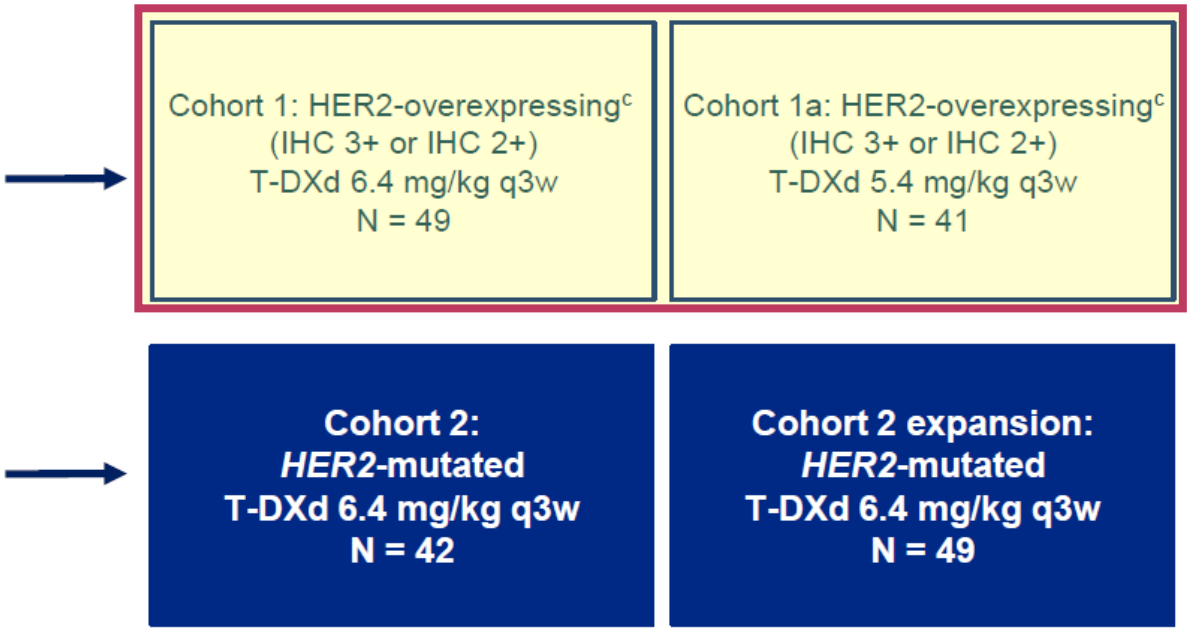
T-DXd in Advanced NSCLC With HER2 Overexpression

DESTINY-Lung01 Study Design

Multicenter, international, 2-cohort phase 2 trial (NCT03505710)

Key eligibility criteria

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]



Primary end point

- Confirmed ORR by ICR[d]

Secondary end points

- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point

- Biomarkers of response

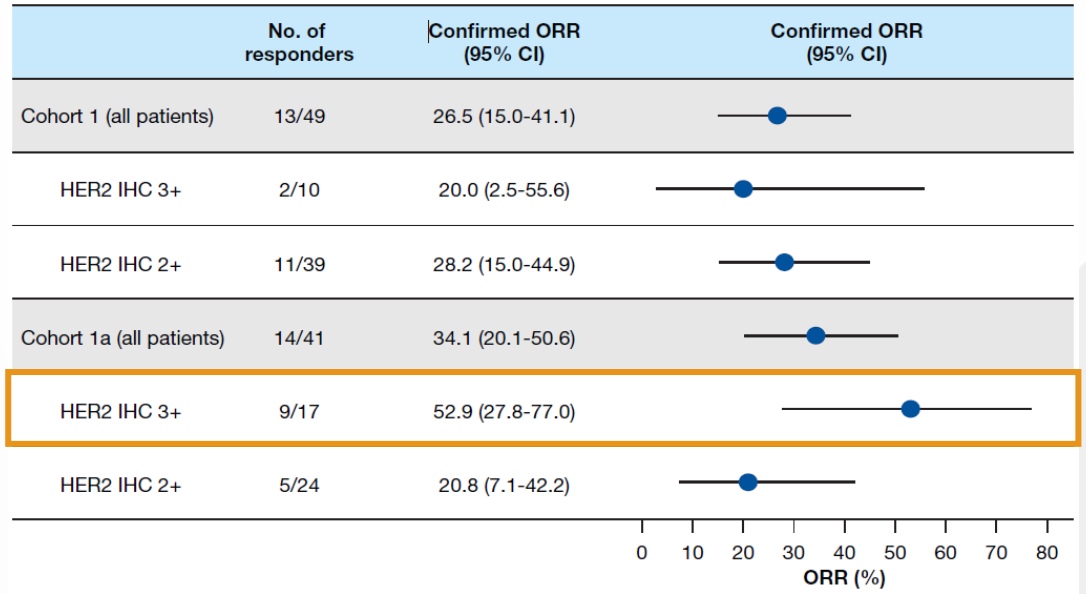
[a]Patients with asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll [b]*HER2* mutation documented solely from a liquid biopsy could not be used for enrollment [c]HER2 overexpression without known *HER2* mutation was assessed by local assessment of archival tissue and centrally confirmed [d]Per RECIST v1.1

Li BT, et al. ESMO 2021. Abstract LBA45.

CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Activity of T-DXd in Advanced NSCLC With HER2 Overexpression

	Cohort 1 (6.4 mg/kg) N = 49	Cohort 1a (5.4 mg/kg) N = 41
ORR by ICR, % (95% CI)	26.5 (15.0-41.1)	34.1 (20.1-50.6)
CR	0	4.9
PR	26.5	29.3
SD	42.9	43.9
PD	22.4	9.8
NE	8.2	12.2
DCR, % (95% CI)	69.4 (54.6-81.8)	78.0 (62.4-89.4)
DoR, median (95% CI), months	5.8 (4.3-NE)	6.2 (4.2-9.8)



Smit EF, et al. ESMO 2022. Abstract 975P; Smit EF, et al. *Lancet Oncol*. 2024;25(4):439-454.
CR, complete response; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

T-DXd FDA Accelerated Approval in Metastatic HER2+ Solid Tumors

- April 2024: T-DXd granted accelerated approval in the U.S. for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options
  - Based on data from DESTINY-PanTumor02 trial and DESTINY-Lung01 trial
  - DESTINY-PanTumor02:
    - ORR: 51.4%
    - Median DOR: 19.4 months
  - DESTINY-Lung01:
    - ORR in HER2 IHC 3+: 52.9%
    - Median DOR: 6.9 months

FDA.gov.
DOR, duration of response; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

Ongoing T-DXd Clinical Trials

Trial	Phase	Treatment	Setting
DESTINY-Lung03 (NCT04686305)	1b	T-DXd and immunotherapy (durvalumab, MEDI5752) with or without chemotherapy	First-line treatment of patients with advanced or metastatic nonsquamous NSCLC and HER2 overexpression
DESTINY-Lung04 (NCT05048797)	3	T-DXd vs SOC (platinum [investigator's choice of cisplatin or carboplatin], pemetrexed, and pembrolizumab)	First-line treatment of patients with unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with HER2 exon 19 or 20 mutations (detected in tissue or circulating tumor DNA)
DESTINY-Lung05 (NCT05246514)	2	T-DXd	Treatment of patients with HER2 mutant NSCLC who have disease progression on or after at least one line of treatment (2L+)

Planchard D, et al. *Ann Oncol.* 2023;34(suppl 2):S848-S849. Li BT, et al. *J Clin Oncol.* 2022;40(16_suppl):TPS9137. ClinicalTrials.gov. NCT05246514.
2L, second line; DNA, deoxyribonucleic acid; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

DESTINY-Lung03 Part 1: T-DXd Monotherapy

- Patients with HER2-OE unresectable, locally advanced or metastatic NSCLC with disease progression on or after one or two prior regimens
  - HER2-OE defined as: ≥25% of tumor cells with IHC 2+ or 3+ by central testing using the DAKO HER2-low IHC assay
- 36 patients received T-DXd 5.4 mg/kg intravenously every 3 weeks
- T-DXd monotherapy (5.4 mg/kg) demonstrated encouraging antitumor activity in patients with pretreated advanced or metastatic HER2-OE NSCLC
  - Consistent with results from DESTINY-Lung01
  - Reinforce HER2 expression as an actionable biomarker in NSCLC
  - Need for HER2 IHC testing in NSCLC

	T-DXd Monotherapy (N=36)	HER2 IHC 3+ (n=16)	HER2 IHC 2+ (n=20)
Confirmed ORR, % (n)	44.4 (16)	56.3 (9)	35.0 (7)
DCR at 12 weeks, %	77.8	81.3	75.0
Median DOR, months	11.0	12.5	6.6
Median PFS, months	8.2	6.9	8.2
Median OS, months	17.1	16.4	17.1

Planchard D, et al. WCLC 2024. OA16.05.

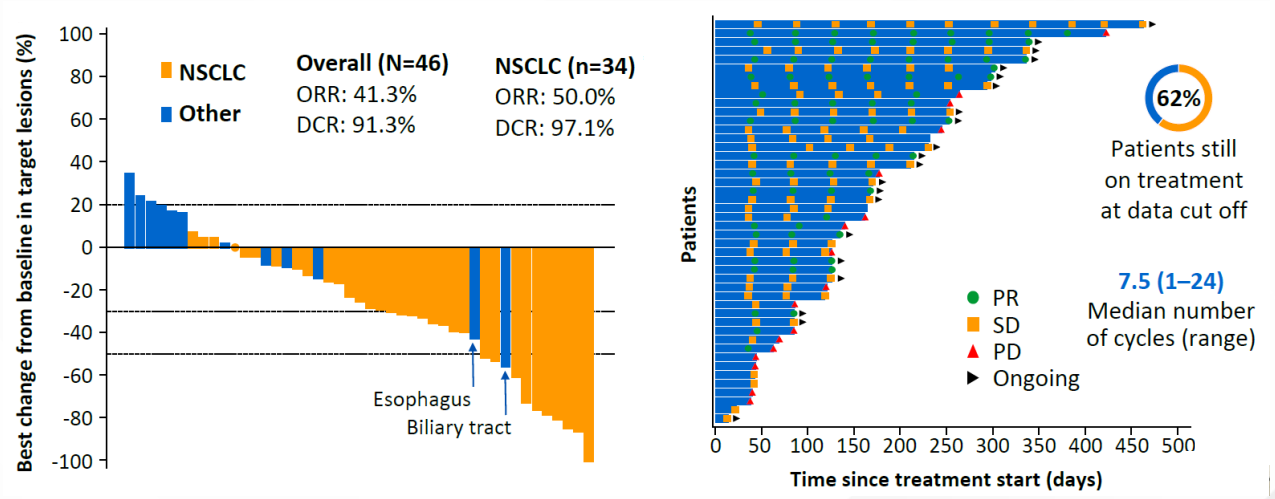
DCR, disease control rate; DOR, duration of response; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; T-DXd, trastuzumab deruxtecan.

Addressing Unmet Needs: Incorporating Treatment Strategies With HER2-Directed Therapies

Are There Novel Targeted Agents That Balance Toxicity and Efficacy?

Zongertinib

- Next generation HER2-specific TKI
- Early phase data suggests tolerable toxicity profile with promising efficacy
- WCLC 2024: Zongertinib was well tolerated and demonstrated promising efficacy in patients with HER2m+ advanced/metastatic NSCLC
  - Primary endpoint of overall response (RECIST version 1.1) by central independent review in the Beamion LUNG-1 Phase Ib Cohort 1 was met (pre-treated NSCLC with a *HER2* TKD mutation)



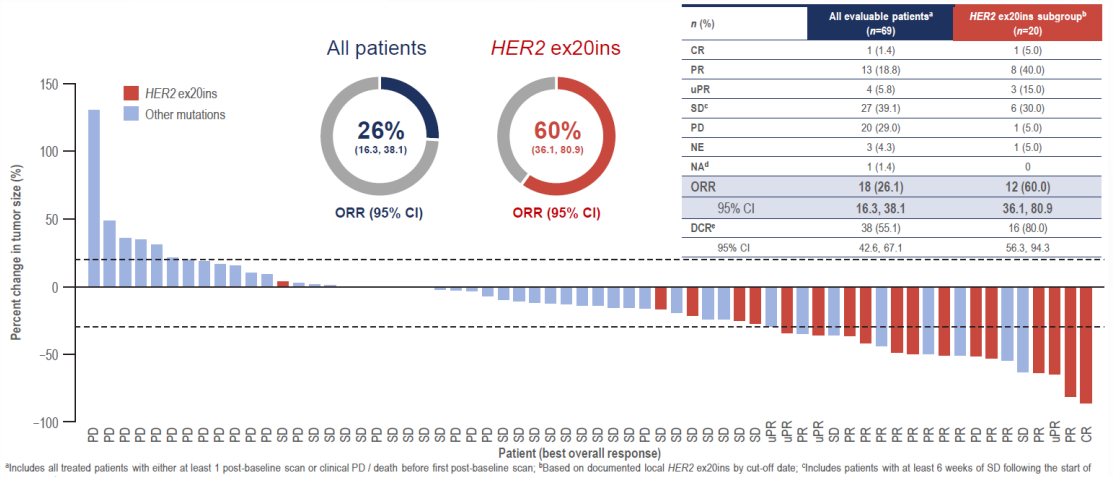
Beamion LUNG-1 Phase Ib Cohort 1	All treated patients at 120 mg (n=75)	After 1:1 randomization implemented	
		120 mg (n=58)	240 mg (n=55)
ORR, %	66.7	72.4	78.2

Yamamoto N, et al. WCLC 2023. Abstract MA13.08. Ruiter G, et al. WCLC 2024. PL-04.04.
DCR, disease control rate; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TKD, tyrosine kinase domain.

Are There Novel Targeted Agents That Balance Toxicity and Efficacy?

BAY 2927088

- Next generation HER2- and EGFR-specific TKI, early phase data suggests promising efficacy in *HER2*-mutated NSCLC
- WCLC 2024: Treatment with BAY 2927088 led to rapid, substantial, and durable responses in patients with pretreated HER2-mutant NSCLC
  - SOHO-01 Cohort D (HER2 activating mutations, HER2 ex20ins, targeted therapy naïve)



n (%)	All evaluable patients[a] (*n*=69)	*HER2* ex20ins subgroup[b] (*n*=20)
CR	1 (1.4)	1 (5.0)
PR	13 (18.8)	8 (40.0)
uPR	4 (5.8)	3 (15.0)
SD[c]	27 (39.1)	6 (30.0)
PD	20 (29.0)	1 (5.0)
NE	3 (4.3)	1 (5.0)
NA[d]	1 (1.4)	0
ORR	18 (26.1)	12 (60.0)
95% CI	16.3, 38.1	36.1, 80.9
DCR[e]	38 (55.1)	16 (80.0)
95% CI	42.6, 67.1	56.3, 94.3

[a]Includes all treated patients with either at least 1 post-baseline scan or clinical PD / death before first post-baseline scan; [b]Based on documented local *HER2* ex20ins by cut-off date; [c]Includes patients with at least 6 weeks of SD following the start of treatment; [d]Patients who have no post-baseline tumor assessment but who discontinued due to drug-related toxicity, death, or progression by clinical judgment before disease were re-evaluated; [e]Includes patients with CR, uCR, PR, uPR, or SD of at lea 12 weeks following the start of treatment

Data cut-off: August 18, 2023. Patients with best overall response of NE were excluded. Responses were investigator-assessed per Response Evaluation Criteria in Solid Tumors v1.1

SOHO-01 Cohort D	20 mg BID (n=43)
ORR, %	72.1
DCR, %	83.7
Median DoR, months	8.7
Median PFS, months	7.5

HHF Loong, et al. ESMO 2023. Abstract 1320MO. Le X, et al. WCLC 2024. Abstract PL-04.03.

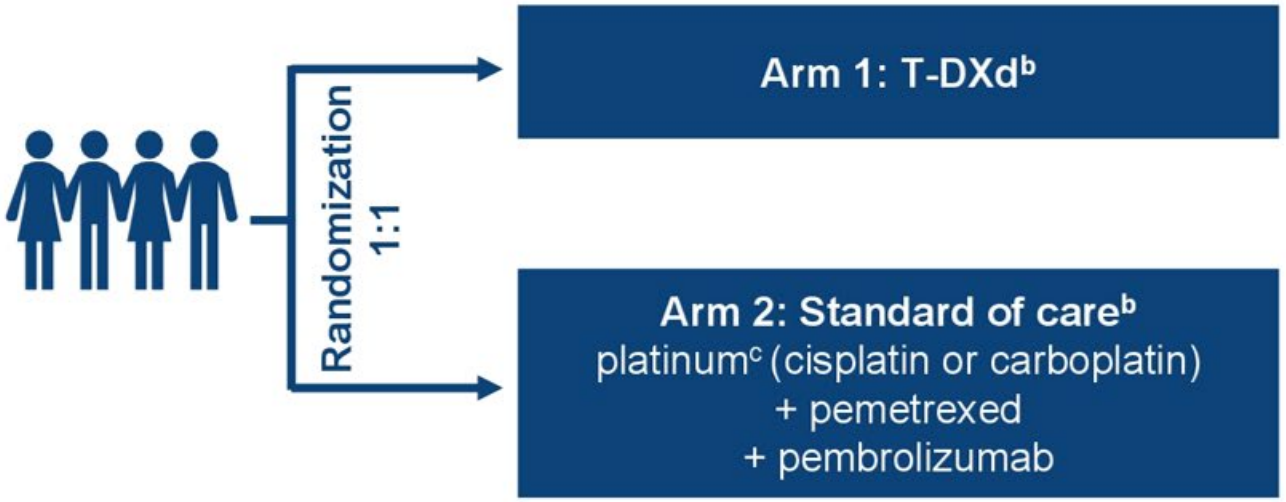
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; HER2, human epidermal growth factor receptor 2; NA, not available; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; uPR, unconfirmed partial response.

Can We Bring T-DXd Into the Frontline Management of Patients With Advanced HER2-Mutated NSCLC?

Phase 3 Randomized DESTINY-Lung04 Trial (NCT05048797)

Patient population (N≈264)

- Unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with *HER2* exon 19 or 20 mutations[a]
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations



[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

Primary Endpoint: PFS

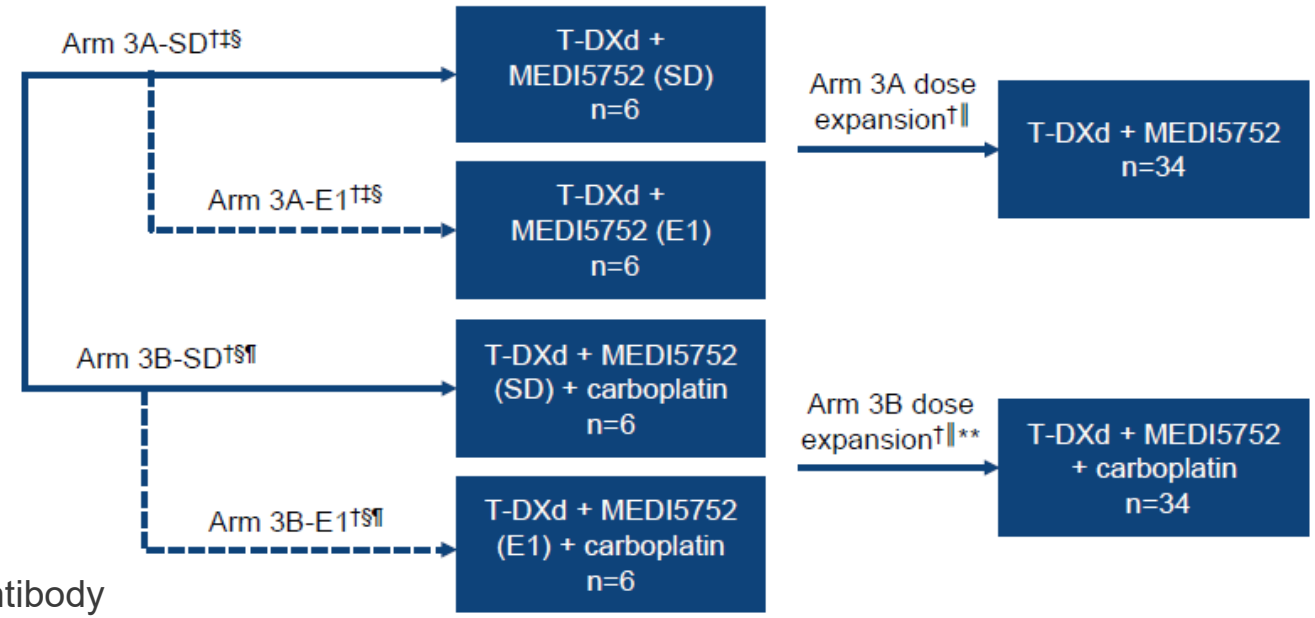
Li BT, et al. ASCO 2022. Abstract TPS9137.
ctDNA, circulating tumor DNA; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Can We Bring T-DXd Into the Management of Advanced NSCLC With HER2 Overexpression?

Phase 1b DESTINY-Lung03 trial of T-DXd combination therapy in NSCLC w/ HER2 overexpression (NCT04686305)

Patient population for Part 3

- Unresectable, locally advanced or metastatic HER2-OE* nonsquamous NSCLC
- Naïve for non-curative treatment for locally advanced or metastatic NSCLC
- No *EGFR* mutations, *EML4-ALK* fusion, or other targetable alterations for which a targeted therapy is available
- WHO/ECOG performance status of 0 or 1



MEDI5752: PD-L1-CTLA-4 bispecific monoclonal antibody

Planchard D, et al. ESMO 2023. Abstract 1507TiP.
ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HER2-OE, HER2 overexpression; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

What Role Does Immunotherapy Play in HER2-Mutated NSCLC?

Anti-PD(L)1 Monotherapy in *HER2*-mutated NSCLC

Study	Sample size	ORR	mDoR	mPFS	mOS
Mazieres et al.[1]	29	7%	-	2.5mo	20.3mo
Guisier et al.[2]	23	27%	15.2mo	2.2mo	20.4mo

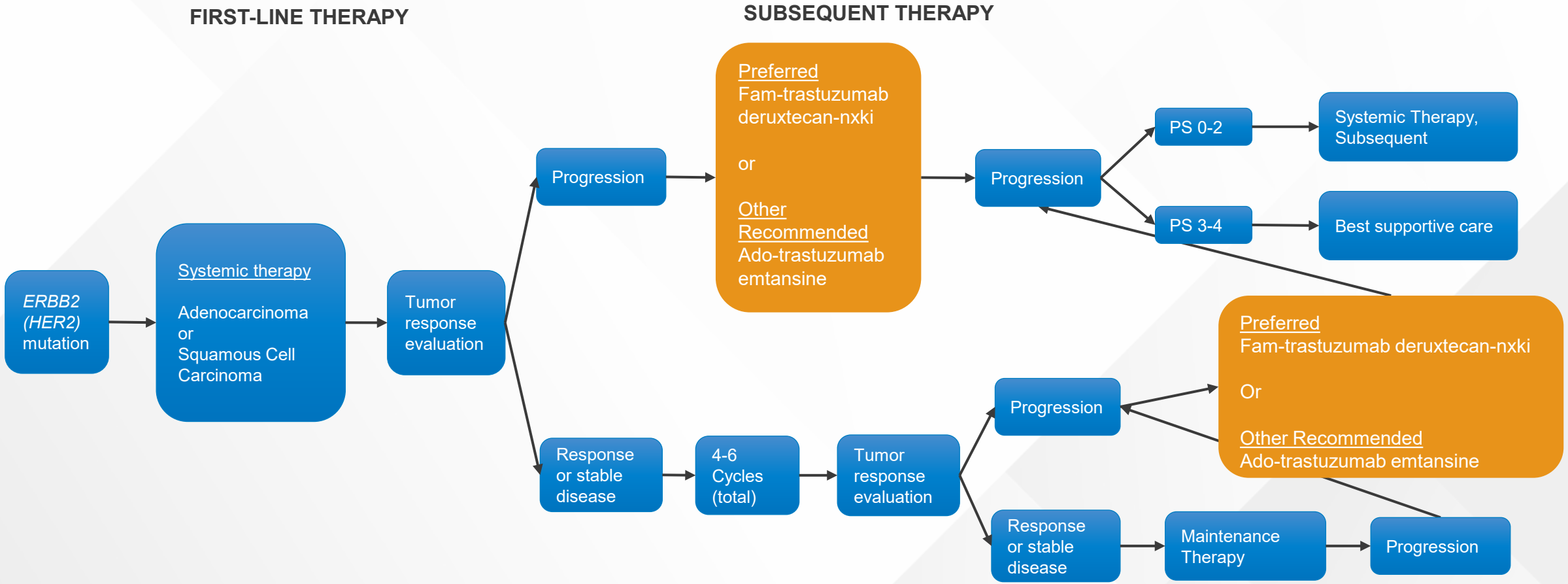
Should anti-PD(L)1 therapy be incorporated into the frontline management of advanced *HER2*-mutated NSCLC?

- Controversial, no prospective randomized data
- NCCN guidelines recommend following approach for advanced NSCLC without driver mutation[3] (see next slide)
- In clinical practice, would not routinely administer frontline anti-PD(L)1 monotherapy
- Decision to add anti-PD(L)1 immunotherapy to platinum-doublet chemotherapy should be patient-specific and incorporate factors such as smoking status, co-mutational profile, patient co-morbidities, etc

1. Mazieres J, et al. *Ann Oncol.* 2019;30(8):1321-1328. 2. Guisier F, et al. *J Thorac Oncol.* 2020;15(4):628-636. 3. Ettinger DS, et al. NCCN Guidelines. Non-Small Cell Lung Cancer. Version 3.2024.
HER2, human epidermal growth factor receptor 2; mDoR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; ORR, overall response rate.

Current NCCN Recommendations for Advanced *HER2*-Mutated NSCLC

***ERBB2 (HER2)* MUTATION**



Adapted from Ettinger DS, et al. NCCN Guidelines. Non-Small Cell Lung Cancer. Version 3.2024.
ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PS, performance status.

Expert Perspective on Management of Advanced HER2-Mutated NSCLC*

HER2-mutated NSCLC

Platinum-doublet chemotherapy +/- anti-PD1 immunotherapy

- Recommend against PD-(L)1 monotherapy
- Patient-specific decision on adding anti-PD-(L)1 ICI
  - Co-mutational profile, smoking status, etc

T-DXd

Subsequent-line chemotherapy

***Should consider enrolling into clinical trial at any line of therapy depending on trial phase and target population**

HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Perspectives on Management of Advanced NSCLC With HER2 Overexpression

- T-DXd now has a tumor agnostic approval for unresectable or metastatic HER2-positive (IHC3+) solid tumors (DESTINY-Lung01 trial)
- NCCN Guidelines now include T-DXd as a systemic therapy option for advanced or metastatic NSCLC (subsequent and progression) for patients with PS 0-2 for adenocarcinoma, large cell, NSCLC NOS, and squamous cell carcinoma, only in patients whose tumors have HER2 overexpression (IHC3+)
- HER2 IHC testing should be incorporated into treatment decision-making in the subsequent line setting

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; NOS, not otherwise specific; PS, performance status.
Smit et al. *Lancet Oncol.* 2024;25:439-454; Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (Version 5.2024).

Surveillance of Potential Treatment-Related Adverse Events

Adverse Events from HER2-Targeted Therapies: TKIs

Skin Reactions

- Most common AEs associated with EGFR TKIs
  - Including alopecia and other hair changes, nail changes, hand/foot reactions, pruritus, and xerosis
- Patients who develop a rash should be advised that this indicates the treatment is working and that the rash usually improves over time
  - Usually presents within 2 weeks of starting treatment
  - If rash does not dissipate sufficiently within 2–4 weeks, interruption of inhibitor therapy is recommended in accordance with PI
- Before starting treatment, patients should be advised/encouraged to:
  - Avoid hot water, soap, over-the-counter acne products, moisturizers, and sunlight
  - Use sunscreens with SPF of at least 15 to minimize skin-related AEs

Diarrhea and Others

- Diarrhea is another common side effect of TKIs
  - Usually appears within the first 4 weeks of treatment
  - May lead to dehydration, electrolyte imbalances, fatigue, malnutrition, and renal insufficiency
  - Some TKIs have mandatory antidiarrheal prophylaxis
- Other reactions observed with TKI use include ocular toxicity and interstitial lung disease

Hirsh V. *Curr Oncol.* 2011;18(3):126-138. Vogel WH, Jennifer P. *J Adv Pract Oncol.* 2016;7(7):723-735.
AE, adverse event; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PI, prescribing information; SPF, sun protection factor; TKI, tyrosine kinase inhibitor.

Adverse Events from HER2-Targeted Therapies: ADCs

T-DM1 in NSCLC (N=49)

Adverse events	Grade 1 *N* (%)	Grade 2 *N* (%)	Grade 3 *N* (%)	Total
Elevated AST or ALT	28 (57)	3 (6)	—	31 (63)
Thrombocytopenia	13 (27)	1 (2)	1 (2)	15 (31)
Fatigue	6 (12)	2 (4)	—	8 (16)
Nausea	14 (29)	—	—	14 (29)
Infusion reaction	2 (4)	5 (10)	—	7 (14)
Anorexia	3 (6)	2 (4)	—	5 (10)
Anemia	1 (1)	3 (6)	1 (2)	5 (10)

NOTE: Treatment-related adverse events with total frequencies of greater than 10%, according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.1 (CTCAE v4.1). There were no grade 4 or 5 adverse events.

T-DXd in NSCLC (N=101)

	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)	
Preferred Term	Any Grade	Grade ≥ 3
Nausea	68 (67.3)	4 (4.0)
Neutropenia[b]	43 (42.6)	19 (18.8)
Fatigue[b]	45 (44.6)	8 (7.9)
Decreased appetite	40 (39.6)	2 (2.0)
Anemia[b]	37 (36.6)	11 (10.9)
Vomiting	32 (31.7)	3 (3.0)
Constipation	37 (36.6)	1 (1.0)
Leukopenia[b]	29 (28.7)	5 (5.0)
Thrombocytopenia[b]	28 (27.7)	6 (5.9)
Diarrhea	23 (22.8)	1 (1.0)
Alopecia	22 (21.8)	0
Transaminases increased[b]	22 (21.8)	3 (3.0)

Common and important observed AEs

- T-DM1: transaminitis, thrombocytopenia, nausea, fatigue
- T-DXd: nausea, neutropenia, fatigue, anemia, thrombocytopenia, GI upset, left ventricular dysfunction, ILD

AXIS Medical Education

Li BT, et al. *Cancer Discov.* 2020;10(5):674-687. Goto K, et al. *J Clin Oncol.* 2023;41(31):4852-4863.
ADC, antibody-drug conjugate; AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

ILD in Advanced NSCLC Treated With T-DXd

- Observed less frequently at 5.4 mg/kg dose (dose that received accelerated FDA approval)

ILD in 5.4 mg/kg arm:

- Median time to onset of 88 days
- 84.6% received steroid treatment
- No patients were retreated
- 61.5% of patients with ILD recovered at time of data cut

Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

Jänne P, et al. WCLC 2023. Abstract MA13.10.
ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

ILD Incidence Across Solid Tumors

Pooled clinical trial data among 1150 patients treated with T-DXd in solid tumor clinical trials

Table 3. Adjudicated drug-related ILD/pneumonitis by tumor type and grade[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All patients ($N = 1150$)	48 (4.2)	89 (7.7)	14 (1.2)	1 (0.1)	25 (2.2)	177 (15.4)
Breast cancer ($n = 510$)	32 (6.3)	51 (10.0)	7 (1.4)	0	15 (2.9)	105 (20.6)
HER2-positive breast cancer treated with T-DXd 5.4 mg/kg q3w ($n = 245$)[b]	9 (3.7)	22 (9.0)	2 (0.8)	0	7 (2.9)	40 (16.3)
Gastric cancer ($n = 294$)	5 (1.7)	15 (5.1)	3 (1.0)	1 (0.3)	1 (0.3)	25 (8.5)
Lung cancer ($n = 203$)[c]	7 (3.4)	16 (7.9)	2 (1.0)	0	6 (3.0)	31 (15.3)
Colorectal cancer ($n = 107$)	0	5 (4.7)	1 (0.9)	0	3 (2.8)	9 (8.4)
Other cancer ($n = 34$)	4 (11.8)	2 (5.9)	1 (2.9)	0	0	7 (20.6)

HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]Patients with multiple ILD/pneumonitis events are listed only once in this table, based on the event with the highest grade.
[b]The HER2-positive breast cancer population ($n = 245$) is a subset of the entire breast cancer population ($n = 510$).
[c]All patients with lung cancer received 6.4 mg/kg q3w of T-DXd.

- Median time to ILD onset: 5.4 months
- Majority received no prior immune checkpoint inhibitors
- Possible risk factors: age <65, enrollment in Japan, lung co-morbidities (asthma, COPD, prior ILD, pulmonary fibrosis, radiation pneumonitis), >6.4 mg/mg dose, baseline SpO2 <95%

AXIS Medical Education

Powell CA, et al. *ESMO Open.* 2022;7(4):100554.
COPD, chronic obstructive pulmonary disease; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

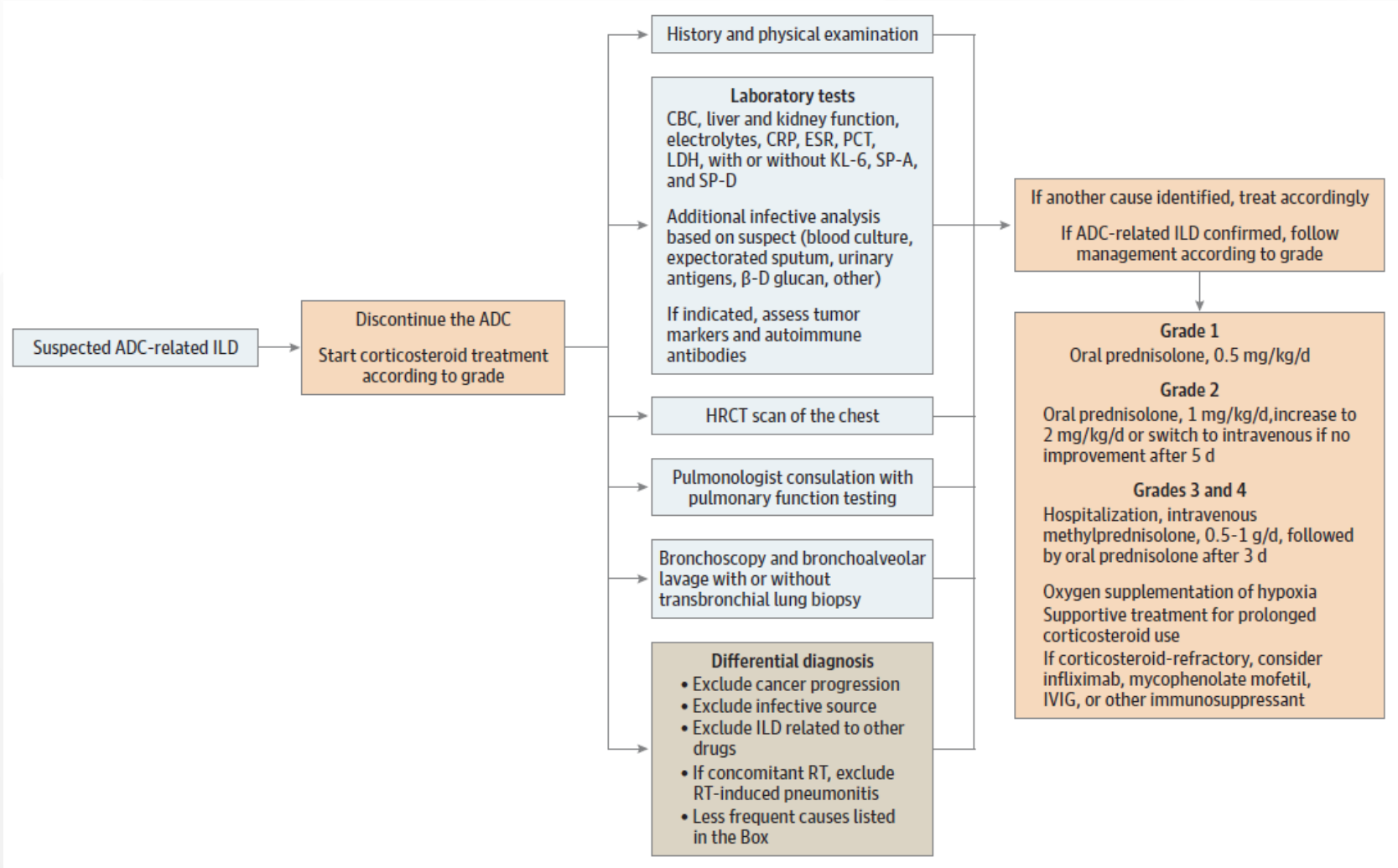
Clinical Management of ILD

- Maintain high index of suspicion, especially in face of new cough, shortness of breath, dyspnea on exertion, fever, etc
- If suspected, **STOP** T-DXd and initiate steroids unless clear alternative cause identified (PE, arrhythmia, etc.)
- Work-up should include:
  - High resolution chest CT, CBC, blood culture, PFTs, pulse oximetry
  - Consult pulmonology to assist with management
  - Consider bronchoscopy to r/o infection, disease progression, etc
  - Consider ID input if infection suspected
- Differential Diagnosis:
  - Infection, cancer progression, RT pneumonitis, ILD – other cause
- Management:
  - Prednisone (typically 1 mg/kg/d)
- Role for re-initiation of T-DXd if ILD resolves?
  - Data for re-initiation is quite limited
  - Per FDA label, can consider in cases of Grade 1 (asymptomatic) ILD
  - Not recommended if ILD is grade 2+

AXIS Medical Education

Powell CA, et al. *ESMO Open.* 2022;7(4):100554. Tarantino P, et al. *JAMA Oncol.* 2021;7(12):1873-1881.
CT, computed tomography; CBC, complete blood count; ID, infectious disease; ILD, interstitial lung disease; PE, pulmonary embolism; PFT, pulmonary function test; RT, radiotherapy; T-DXd, trastuzumab deruxtecan.

Clinical Management of ILD



Tarantino P, et al. *JAMA Oncol.* 2021;7(12):1873-1881.
ADC, antibody-drug conjugate; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; KL-6, Krebs von den Lungen 6; LDH, lactate dehydrogenase; PCT, procalcitonin; RT, radiotherapy; SP-A, surfactant protein-A; SP-D, surfactant protein-D.

ADCs: Real-World Experience

- Use of T-DXd in patients with NSCLC requires meticulous proactive monitoring for potential adverse events such as:
  - ILD/pneumonitis
  - Thrombocytopenia
  - Neutropenia
  - Other gastrointestinal/cardiovascular challenges (left ventricular dysfunction)
- Specific protocols to manage these are available and may involve treatment modification or administration of steroids
- Potential complications with concurrent radiation of the chest and ADC therapy

Considerations

- Balancing treatment benefit with treatment-related toxicities
- Reinforcing recommended dosing regimens for HER2-directed therapies
- Incorporating safety and tolerability data from real-world evidence
- Developing strategies to proactively monitor and treat adverse events for support and adherence

ENHERTU (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo; 2022. Swain SM, et al. *Cancer Treat Rev.* 2022;106:102378. Verma S, et al. *Curr Oncol.* 2023;30(4):4329-4350.
ADC, antibody-drug conjugate; AE, adverse event; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

Practical Application Case

Case Study Patient Presentation and History

Presentation

- A 64 y/o female with newly diagnosed lung adenocarcinoma metastatic to liver and bone presents to your clinic for management
- She is a former ½ PPD smoker for ~10 years, but quit 30 years ago
- She has no other co-morbidities and is fit (ECOG 0)
- Brain MRI is negative for intracranial metastases
- Liver biopsy confirms TTF1+ adenocarcinoma consistent with lung primary
- Additional testing reveals PD-L1 80%

Next Step in Care

- Which of the following is the most appropriate next step in care?
  a) Begin ICI monotherapy +/- platinum-doublet chemotherapy
  b) Begin platinum-doublet chemotherapy
  c) Begin afatinib
  d) Obtain next-generation sequencing (NGS) testing
  e) Unsure

ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; PPD, pack per day; TTF, thyroid transcription factor.

Case Study Clinical Course

- You obtain additional NGS testing that reveals a pathogenic YVMA duplication (*HER2* exon20 insertion mutation)
- You elect to begin systemic therapy with platinum doublet chemotherapy + ICI, with initial treatment response
- After 8 months, imaging reveals growth of new liver and adrenal lesions, with biopsy confirming TTF1+ adenocarcinoma
- Repeat NGS testing confirms HER2 exon20 insertion mutation and shows no other actionable mutations
- She otherwise feels well, apart from mild worsening fatigue

HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; NGS, next-generation sequencing; TTF, thyroid transcription factor.

Case Study Audience Question

- What is your best next step in treatment?
  a) Atezolizumab monotherapy
  b) Docetaxel
  c) Trastuzumab deruxtecan (T-DXd) 5.4 mg/kg
  d) Trastuzumab deruxtecan (T-DXd) 6.4 mg/kg
  e) Poziotinib

Case Study Conclusion and Rationale for Best/Correct Answer

- Given the strong data from the DESTINY-Lung01 trial and subsequent DESTINY-Lung02 trial, T-DXd is the correct answer
- Specifically, T-DXd 5.4 mg/kg is the correct answer, as this dose was found to be effective with less ILD compared to the 6.4 mg/kg dose in the DESTINY-Lung02 trial

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

Key Takeaways

- Alterations in HER2 (mutations, gene amplification, and protein overexpression) are found in NSCLC
- Broad NGS testing to assess for *HER2* mutations and other actionable driver mutations is recommended at time of diagnosis for patients with advanced NSCLC
- Initial management of *HER2*-mutated NSCLC consists of platinum-doublet chemotherapy +/- ICI
- Trastuzumab deruxtecan (T-DXd) is the only HER2-directed therapy with an FDA approval and carries an accelerated approval for *HER2*-mutated NSCLC after progression on prior systemic therapy
- T-DXd is now also FDA-approved for patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment
  - HER2 IHC testing required
- Watch closely for ILD, an important treatment-related adverse event of T-DXd
  - If ILD is suspected, discontinue treatment and promptly initiate steroids, with further work-up and management in coordination with pulmonology and possibly infectious disease specialists

HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer.

AXIS Medical Education

Precision Payloads:

Exploring ADC-Directed Therapies in HER2-Mutant and Overexpressing Lung Cancer