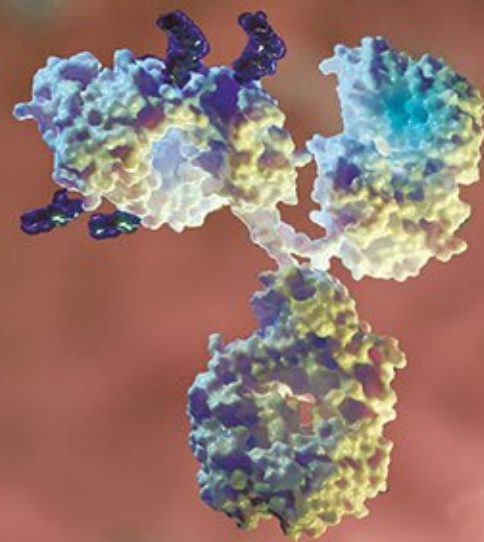
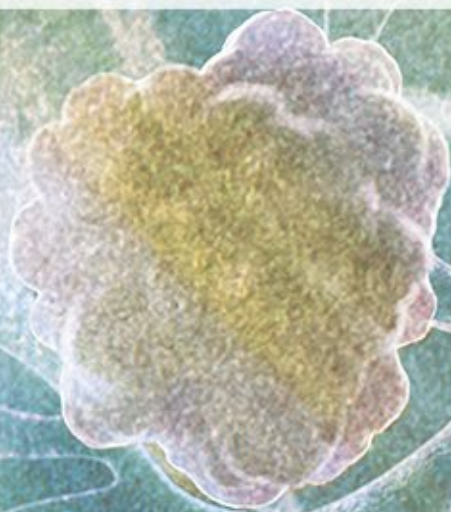


# Precision Payloads:

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



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# Learning Objectives

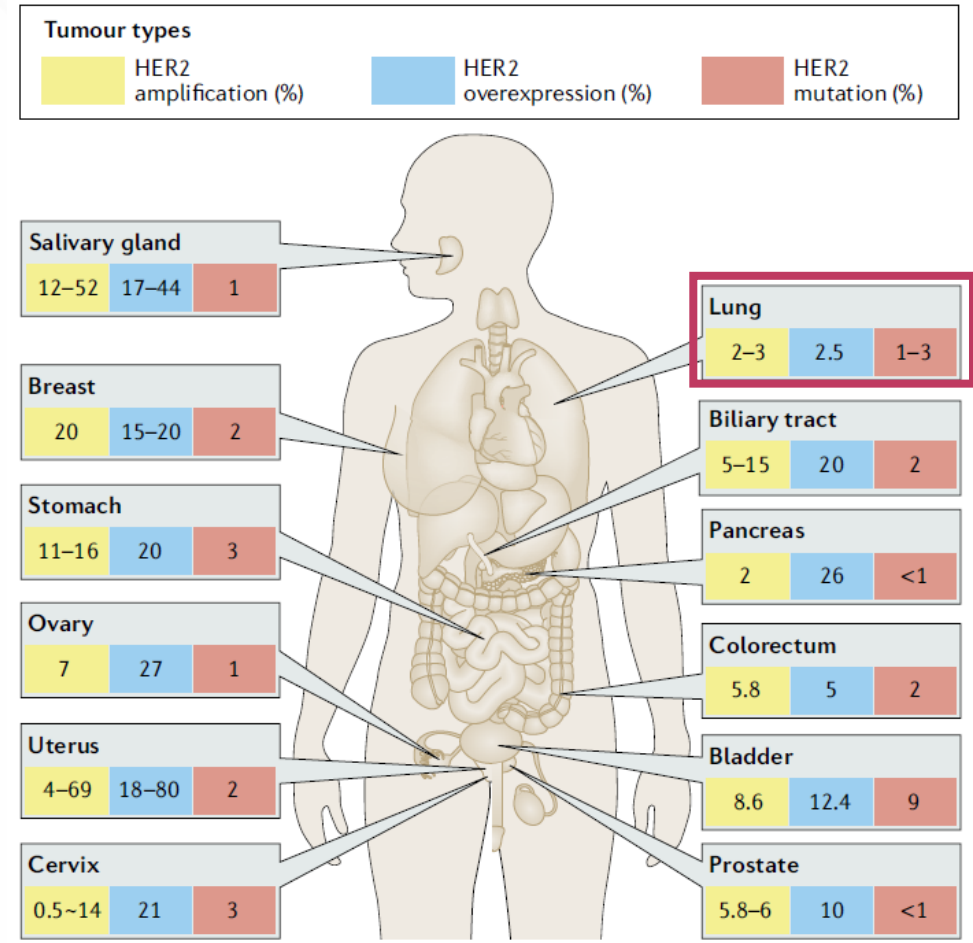
**Upon completion of this activity, participants should be better able to:**

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

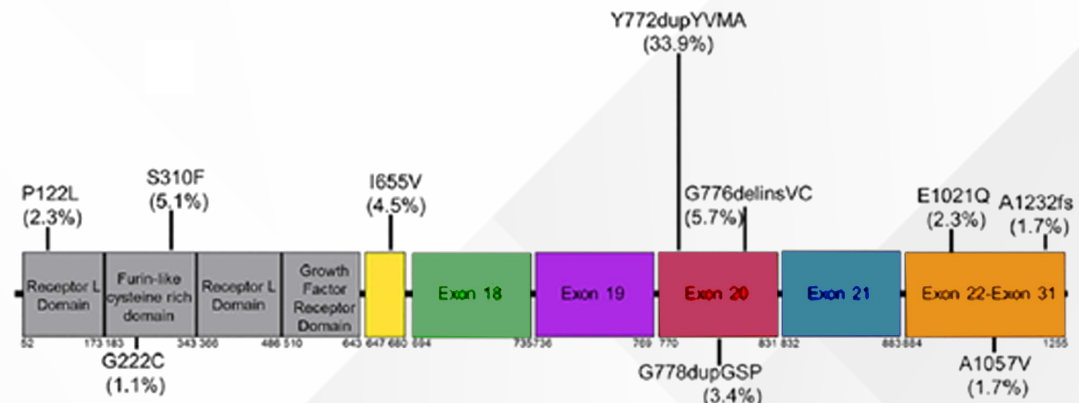
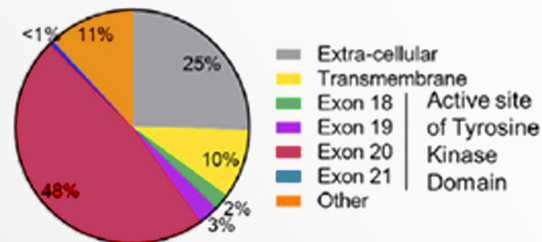
# HER2 as an Oncogenic Driver in Cancer

- 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



# 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!**



# 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  $\geq 2$  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



# 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  $\geq 10\%$  cells
  - IHC3+: strong complete membranous staining in  $\geq 10\%$  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

# 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

# Genomic Testing in NSCLC

NCCN Guidelines version 3.2024  
Non-Small Cell Lung Cancer

## CLINICAL PRESENTATION

## HISTOLOGIC SUBTYPE

## BIOMARKER TESTING

Advanced or metastatic disease

- Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy or plasma testing if appropriate)
- Smoking cessation counseling
- Integrate palliative care

- Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

Squamous cell carcinoma

- Molecular testing, including:
  - *EGFR* mutation (category 1), *ALK* (category 1), *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*ex14 skipping, *RET*, *ERBB2 (HER2)*
  - Testing should be conducted as part of broad molecular profiling
- PD-L1 testing (category 1)

- Consider molecular testing, including:
  - *EGFR* mutation, *ALK*, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*ex14 skipping, *RET*, *ERBB2 (HER2)*
  - Testing should be conducted as part of broad molecular profiling
- PD-L1 testing (category 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**

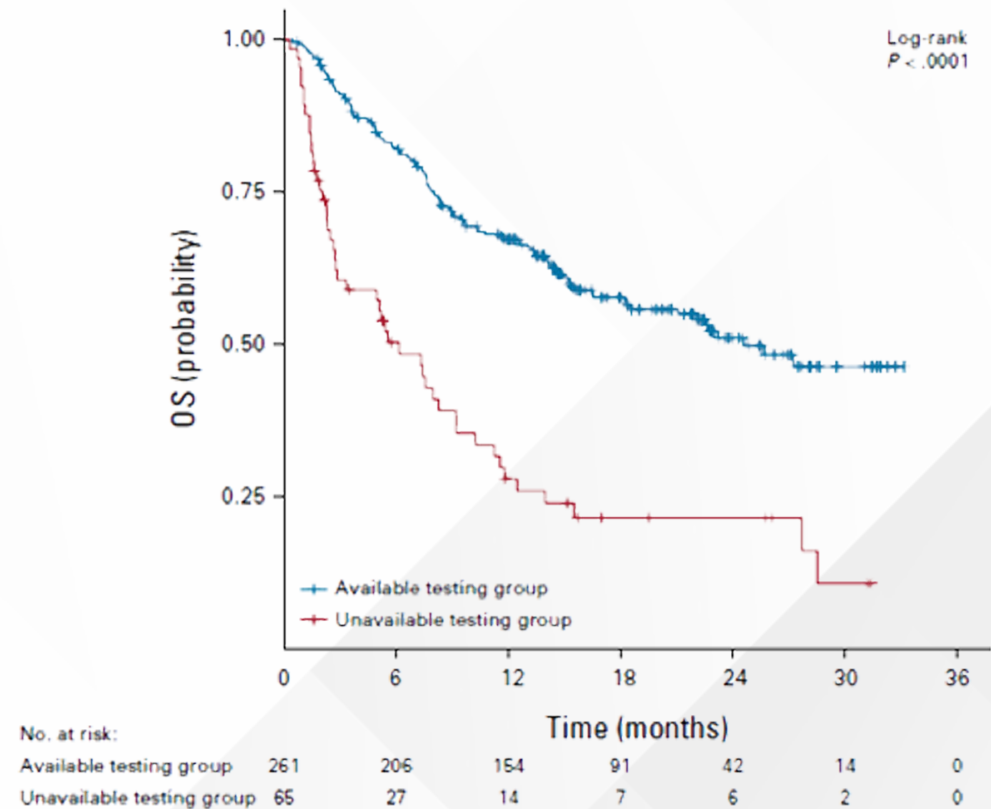
# Biomarker Testing Platforms in NSCLC

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

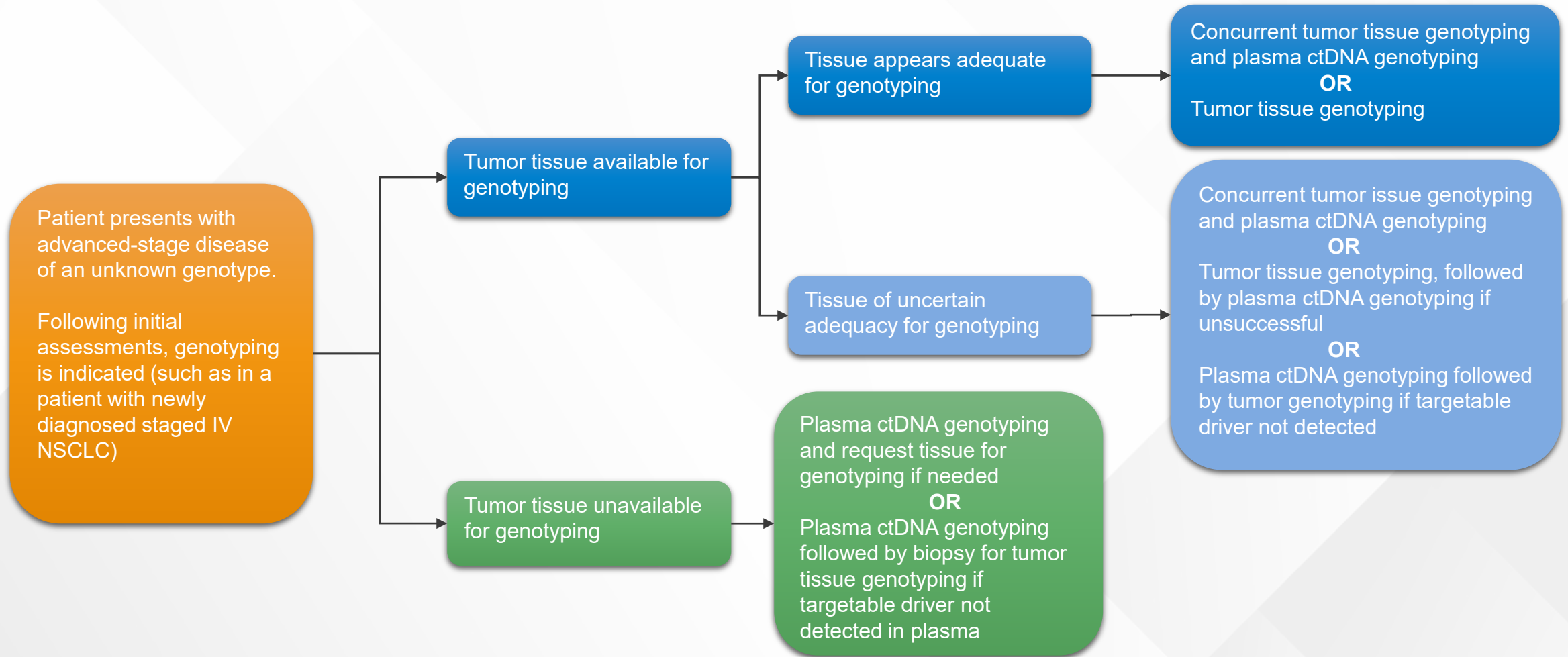
# Availability of Molecular Genotyping Results Impacts Survival in Advanced Non-Squamous NSCLC

- 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



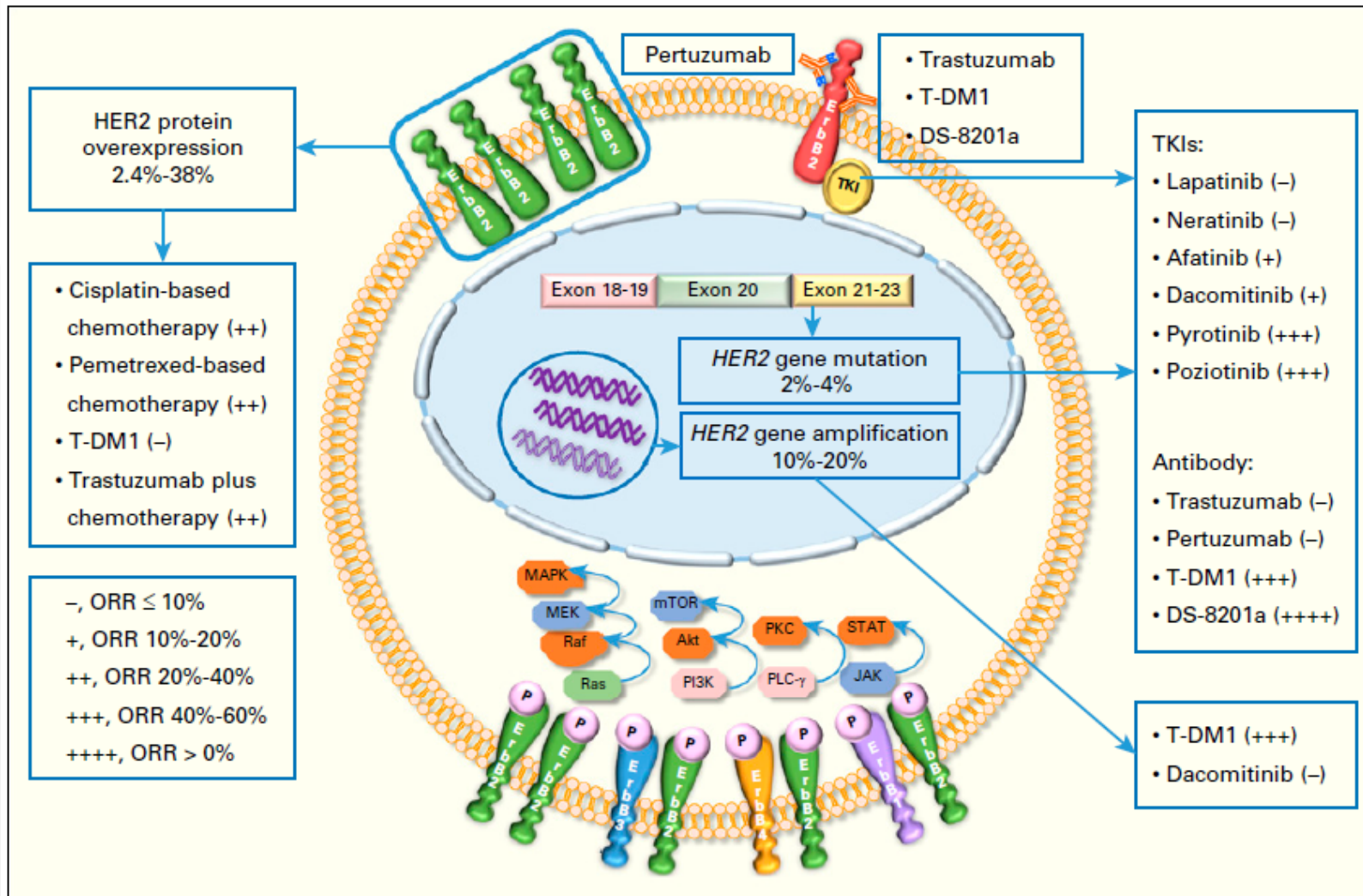
# Algorithm for Incorporation of Liquid Testing Into Initial Work-up of Advanced NSCLC



# 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	<i>HER2</i> Alterations	Sample Size (No.)	Clinical Efficacy
Dacomitinib	No	Phase II study	<i>HER2</i> mutation/amplification	30 (26 with <i>HER2</i> mutation; 4 with <i>HER2</i> amplification)	<i>HER2</i> exon 20 mutation: ORR, 12% (3/26); mPFS, 3 months; mOS, 9 months; 1-year survival, 44% <i>HER2</i> amplification: ORR, 0/4
Neratinib	No	Phase II basket study	<i>HER2</i> mutation	26	ORR, 3.8% (1/26); DCR, 42.3 (11/26); mPFS 5.5 months
Neratinib	Temsirolimus	Phase I study	<i>HER2</i> mutation	14 (6 with <i>HER2</i> mutation)	ORR, 33% (2/6)
Neratinib	Temsirolimus/ no	Randomized phase II study	<i>HER2</i> 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
Pozotinib or afatinib	No	Retrospective study	<i>HER2</i> mutation	7	Pozotinib: ORR, 33% (2/6); DCR, 83% (5/6) Afatinib: ORR, 100% (1/1)
Pozotinib	No	Phase II study	<i>HER2</i> mutation	12	ORR, 50% (6/12); DCR, 83.3% (10/12) at 8 weeks
Pyrotinib	No	Phase II study	<i>HER2</i> mutation	15	ORR, 53.3% (8/15); DCR, 73.3% (11/15); mDOR, 7.2 months; mPFS, 6.4 months

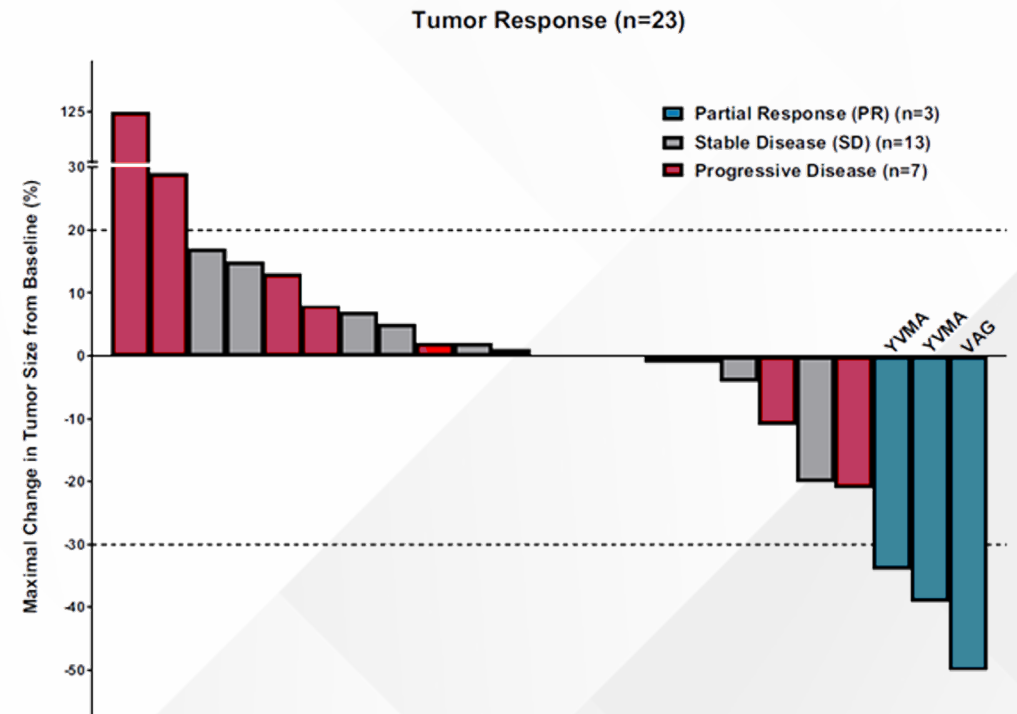
Adapted from Zhao J, Xia Y. *JCO Precis Oncol.* 2020;4:411-425.

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

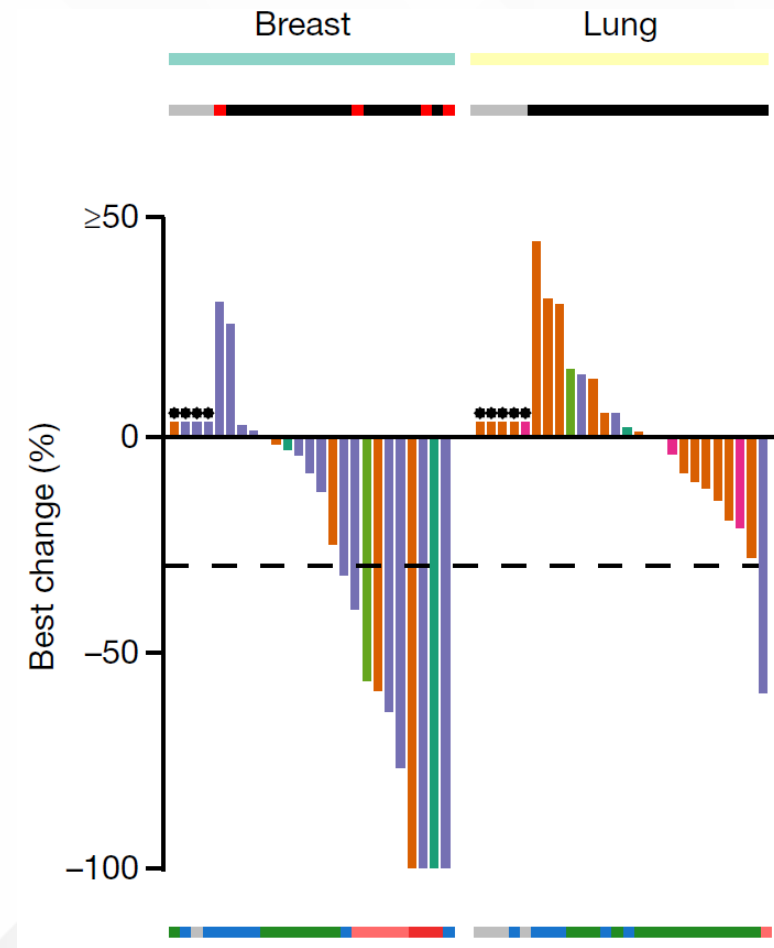
- **Afatinib**: pan-erbB family (*EGFR*, *HER*) irreversible inhibitor that is FDA approved for treatment of advanced *EGFRm* NSCLC
- Bulk of data retrospective, with modest efficacy and limited durability
  - ORR ~10-19%
  - Median time on treatment ~3 months
  - Dosing: 20 mg, 30 mg, or 40 mg daily
- 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



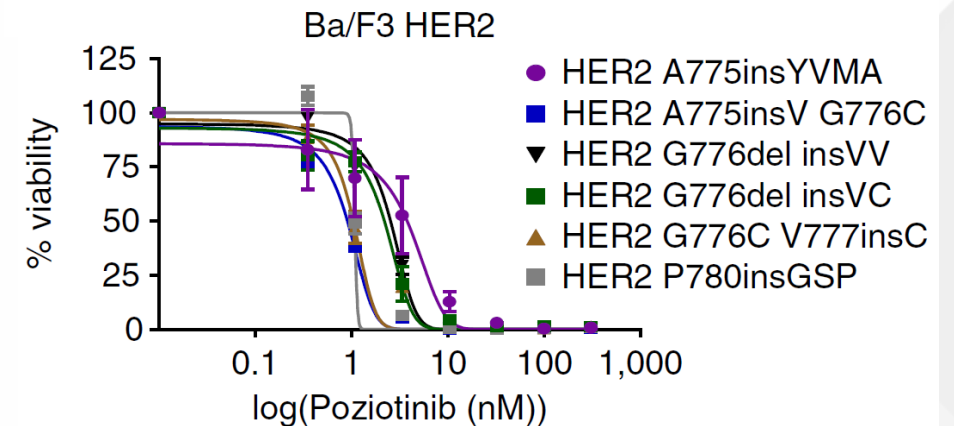
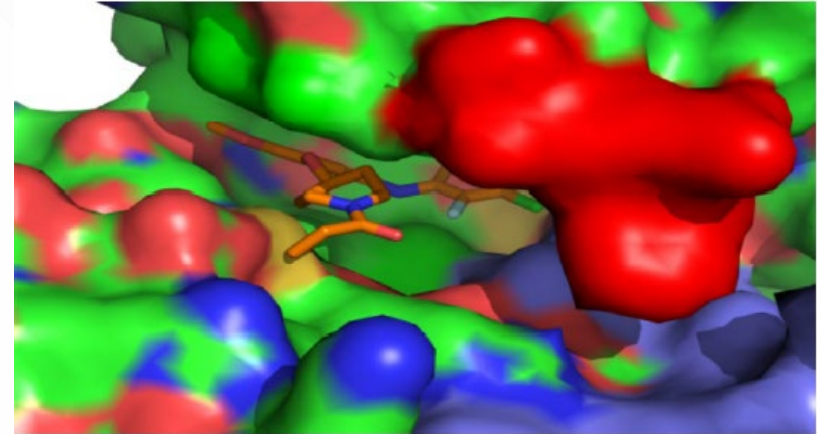
# Neratinib in *HER2*-Mutated NSCLC

- **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



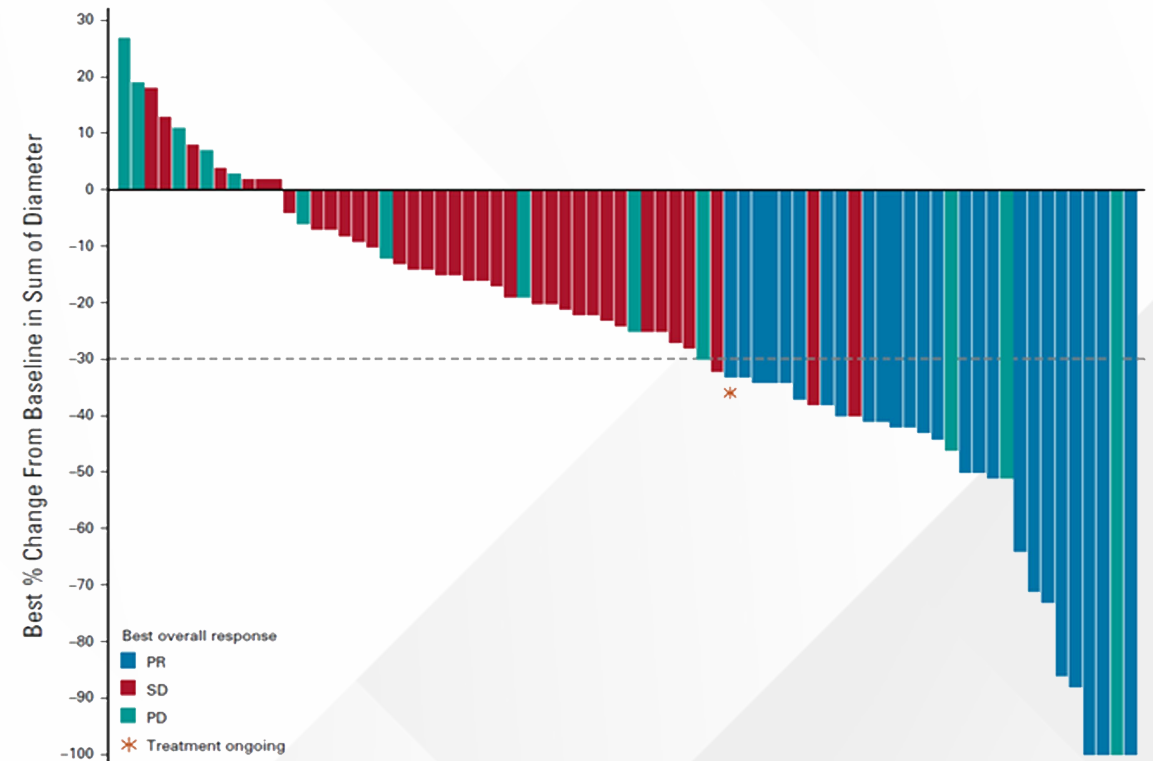
# Poziotinib in *HER2*-Mutated NSCLC

- **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



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

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



# Poziotinib Feasibility Limited by Toxicity

N = 90

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

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)



# 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

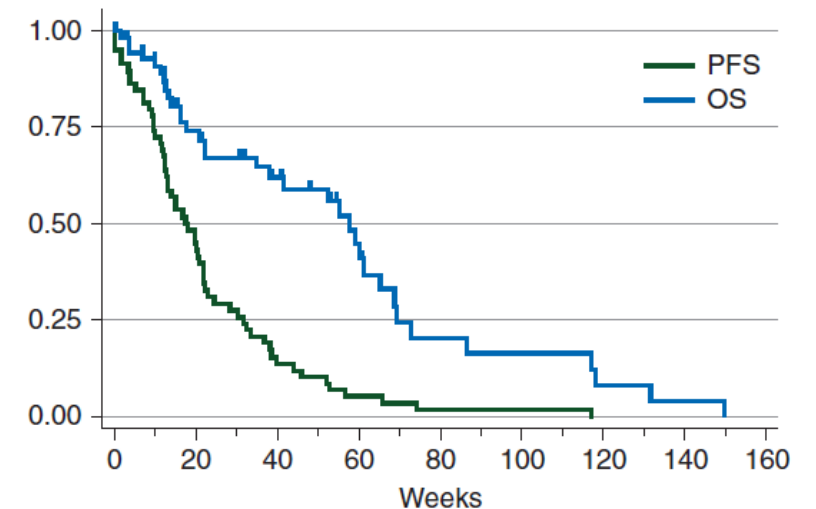
## Trastuzumab + single-agent chemotherapy in *HER2*-mutated NSCLC

- 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 *HER2m* NSCLC



# 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+; <i>HER2</i> gene number copy > 1 (with concurrent <i>EGFR</i> mutation and had progressed on <i>EGFR</i> 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+); <i>HER2</i> amplification (FISH+); serum HER2 ECD positive	101 (only 5 with HER2 IHC3+; 7 with <i>HER2</i> 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; <i>P</i> = .76); median survival, 16 v 14 months; 1-year survival, 57% v 55% ( <i>P</i> = .998)

# 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

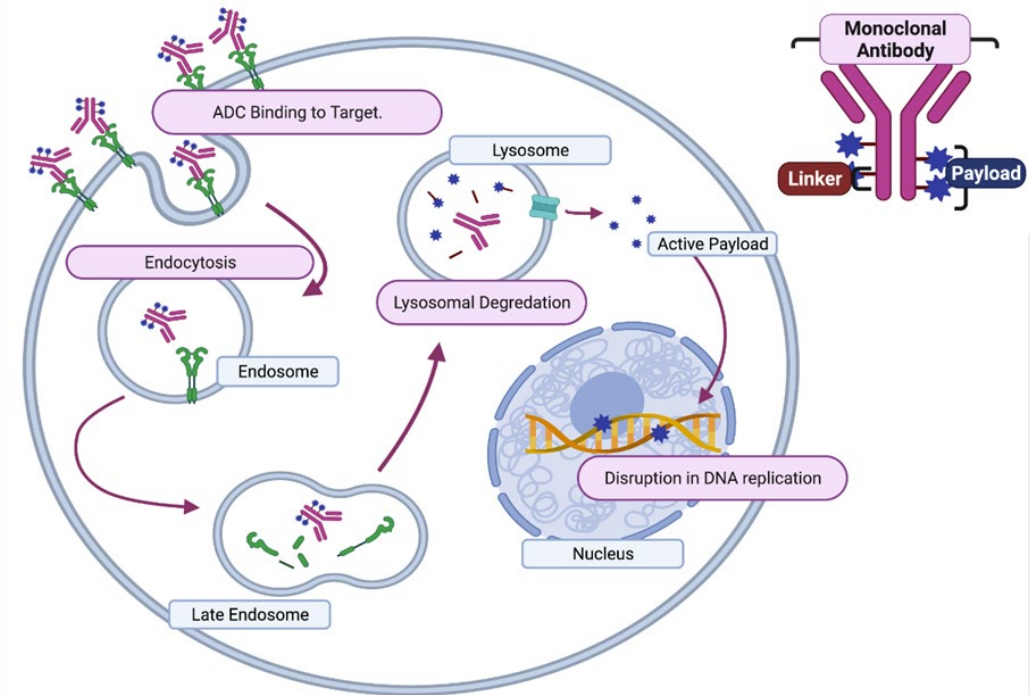
- Non-cleavable
  - Traffic to mature lysosomes for degradation
  - Limited “bystander effect”
- Cleavable
  - Cell physiology (pH, proteases, etc.) key to payload-linker uncoupling
  - Prominent “bystander effect”

## 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

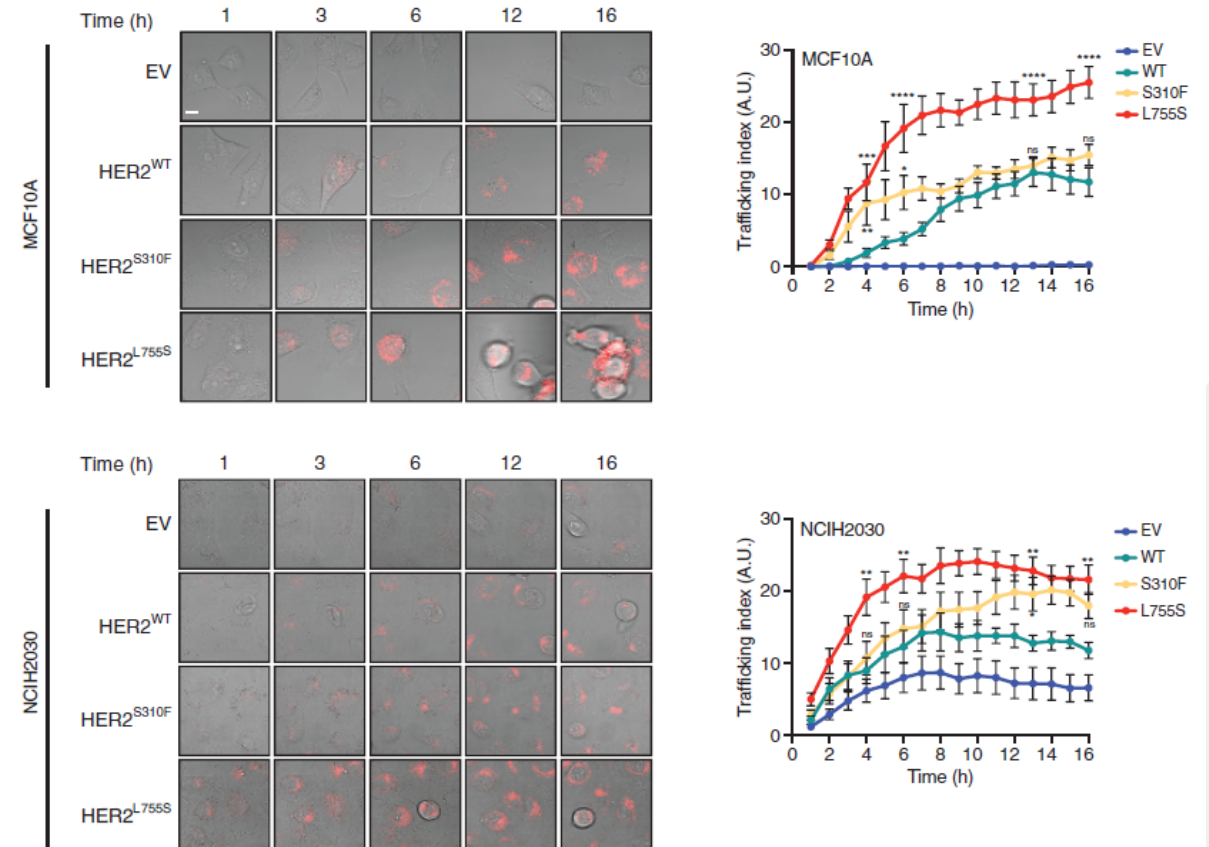
## Mechanism of Action

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

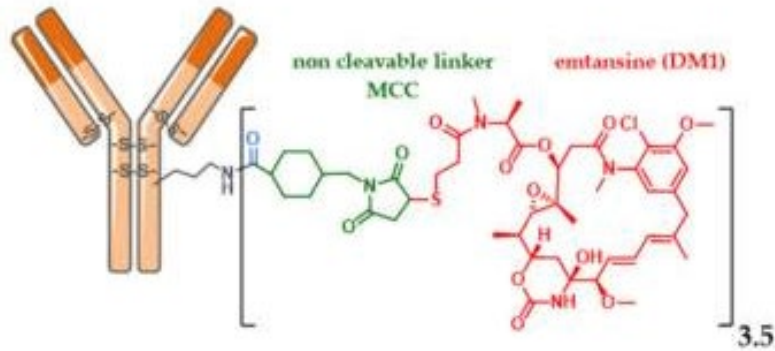


# Rationale for ADCs in HER2-Mutated NSCLC

- 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



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

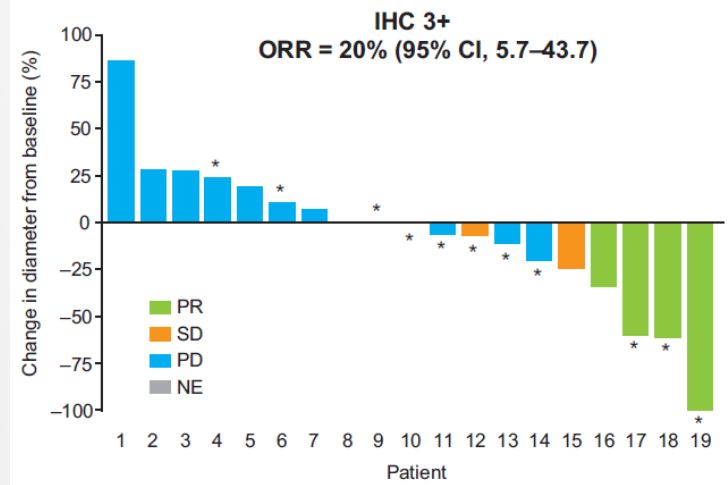
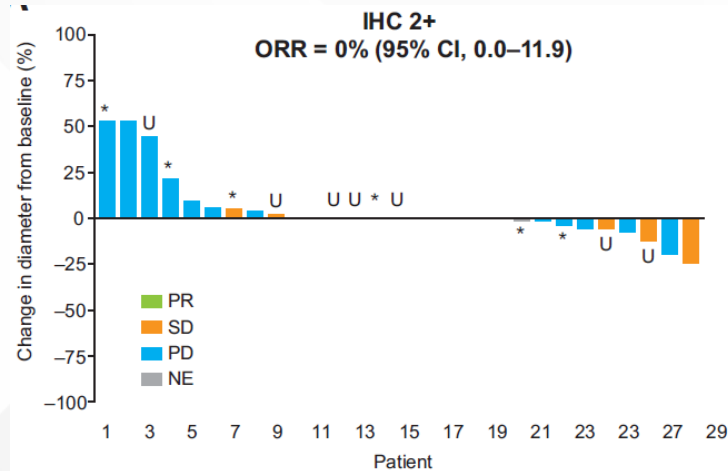


## T-DM1

- 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

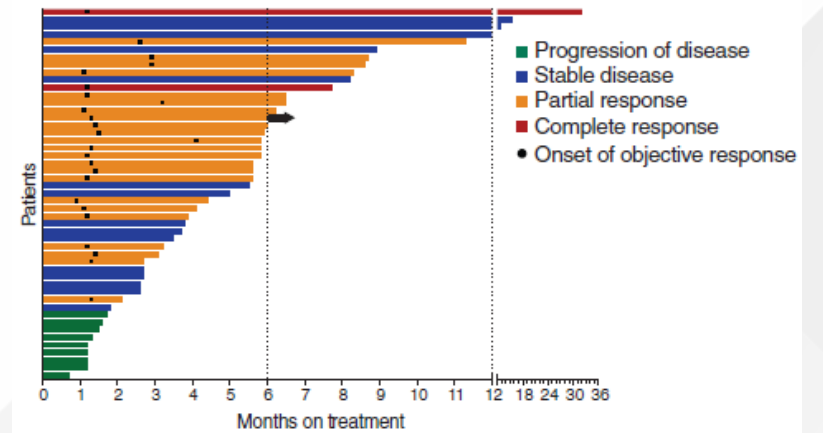
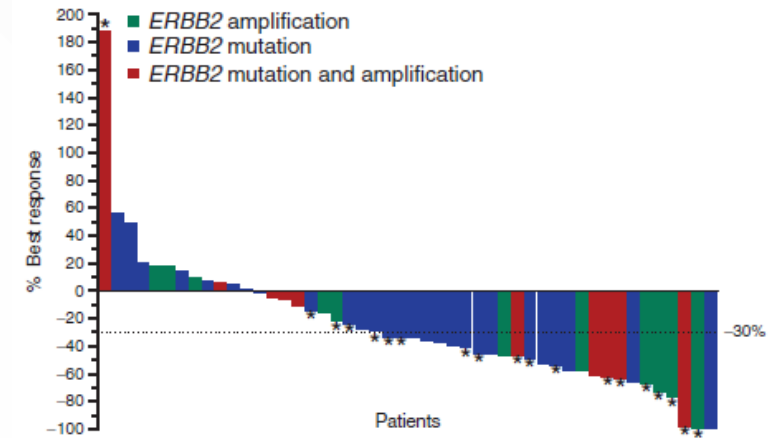
# T-DM1 in *HER2*-Altered NSCLC

## *HER2*-overexpressed NSCLC



\*positive *HER2* amplification

## *HER2*-mutated and/or *HER2*-amplified

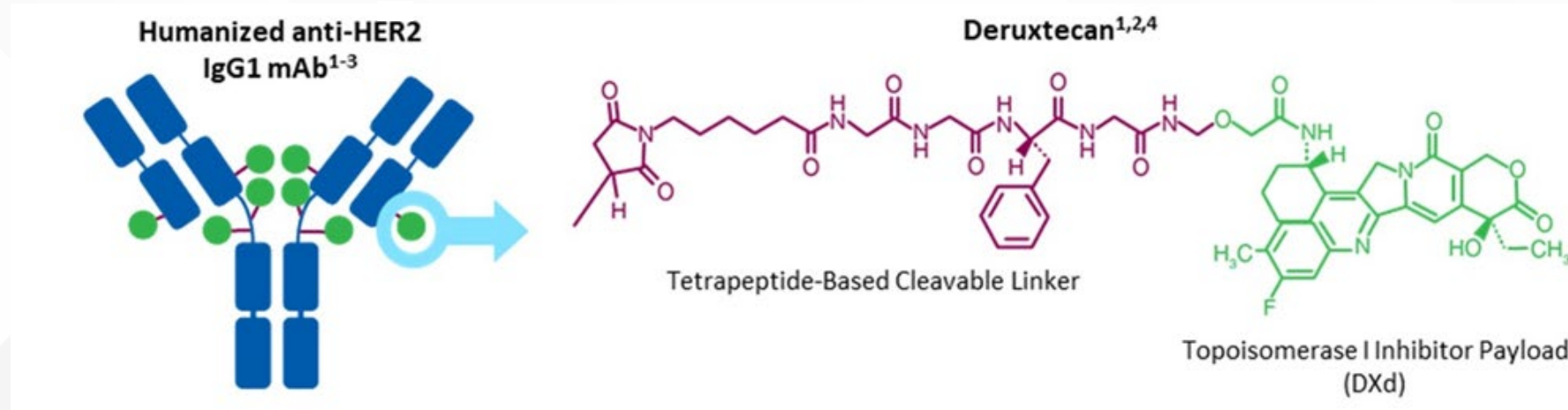


Peters S, et al. *Clin Cancer Res.* 2019;25(1):64-72. Li BT, et al. *Cancer Discov.* 2020;10(5):674-687.

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

# 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<sup>a</sup>
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)<sup>b</sup>



Cohort 1: HER2-overexpressing<sup>c</sup>  
(IHC 3+ or IHC 2+)  
T-DXd 6.4 mg/kg q3w  
N = 49

Cohort 1a: HER2-overexpressing<sup>c</sup>  
(IHC 3+ or IHC 2+)  
T-DXd 5.4 mg/kg q3w  
N = 41

Cohort 2:  
**HER2-mutated**  
T-DXd 6.4 mg/kg q3w  
N = 42

Cohort 2 expansion:  
**HER2-mutated**  
T-DXd 6.4 mg/kg q3w  
N = 49

## Primary end point

- Confirmed ORR by ICR<sup>d</sup>

## Secondary end points

- DOR
- PFS
- OS
- DCR
- Safety

## Exploratory end point

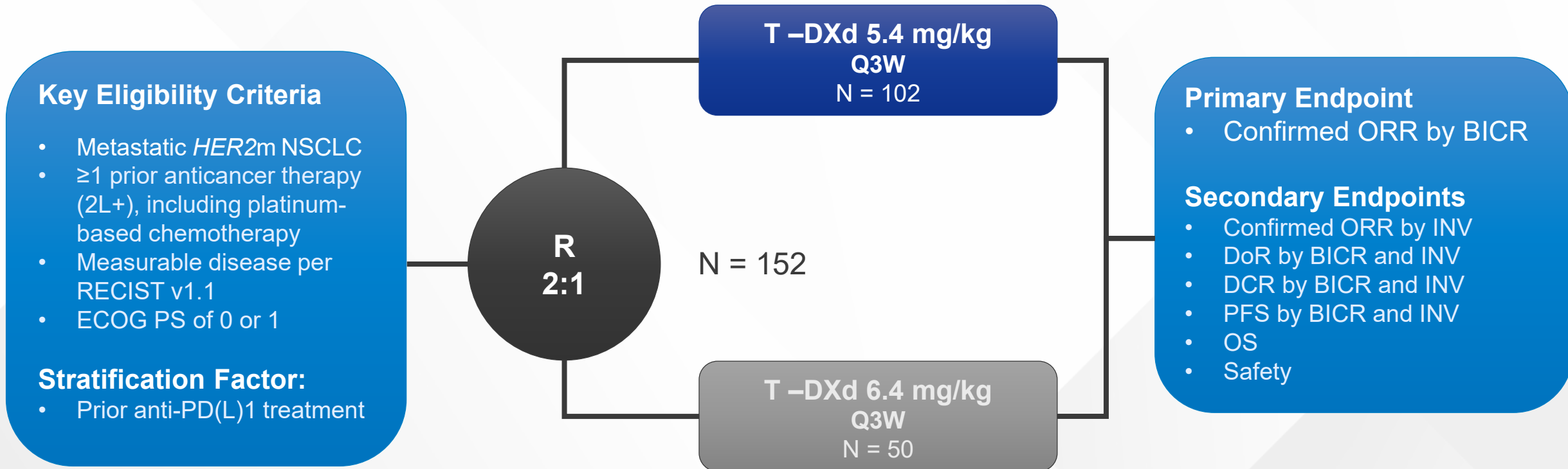
- Biomarkers of response

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



# DESTINY-Lung02 Trial: Study Design

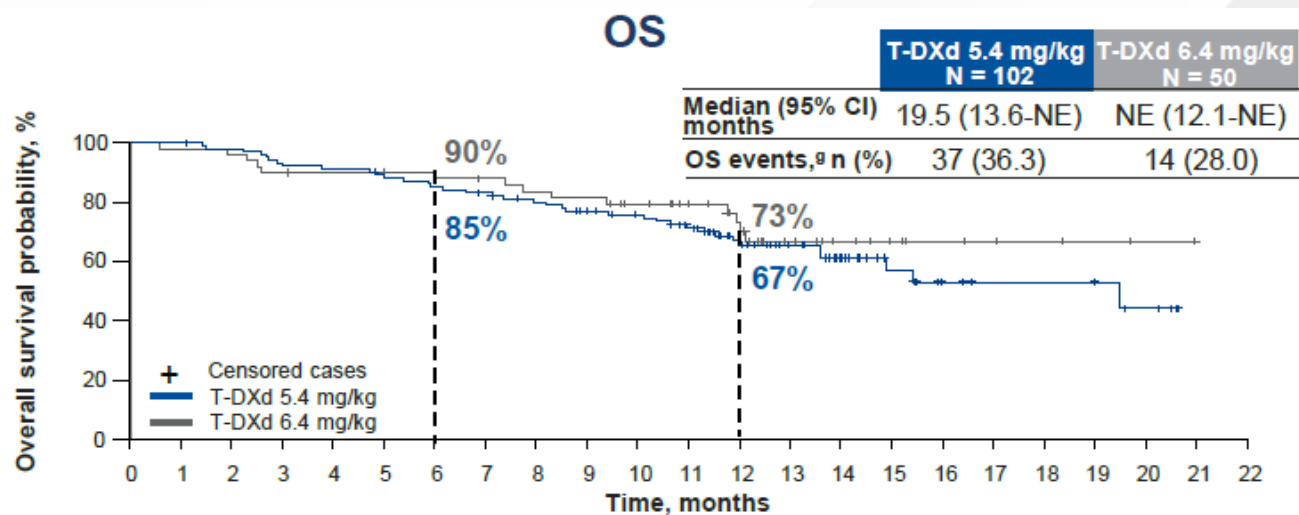
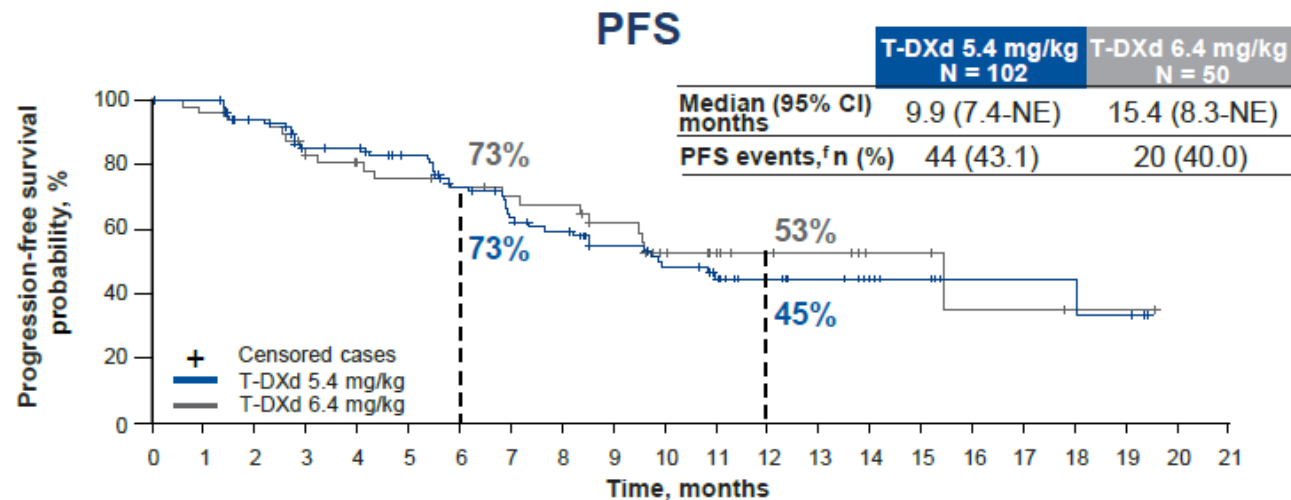
Phase 2 Randomized, Non-Comparative trial



*Patients and investigators were blinded to the dose level*

# Similar Efficacy Observed at Either Dose in DESTINY-Lung02

	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
<b>Response Assessment by BICR</b>		
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
<b>Best confirmed overall response, No. (%)</b>		
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 <sup>a</sup>	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)





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

## Adjudicated Drug-Related ILD

Preferred Term	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101), <sup>a</sup> No. (%)		T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50), <sup>a</sup> No. (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	68 (67.3)	4 (4.0)	41 (82.0)	3 (6.0)
Neutropenia <sup>b</sup>	43 (42.6)	19 (18.8)	28 (56.0)	18 (36.0)
Fatigue <sup>b</sup>	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 <sup>b</sup>	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 <sup>b</sup>	29 (28.7)	5 (5.0)	17 (34.0)	8 (16.0)
Thrombocytopenia <sup>b</sup>	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 <sup>b</sup>	22 (21.8)	3 (3.0)	10 (20.0)	0

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101 <sup>a</sup>	T-DXd 6.4 mg/kg N = 50 <sup>a</sup>
<b>Any grade, n (%)</b>	<b>13 (12.9)</b>	<b>14 (28.0)</b>
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

# 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



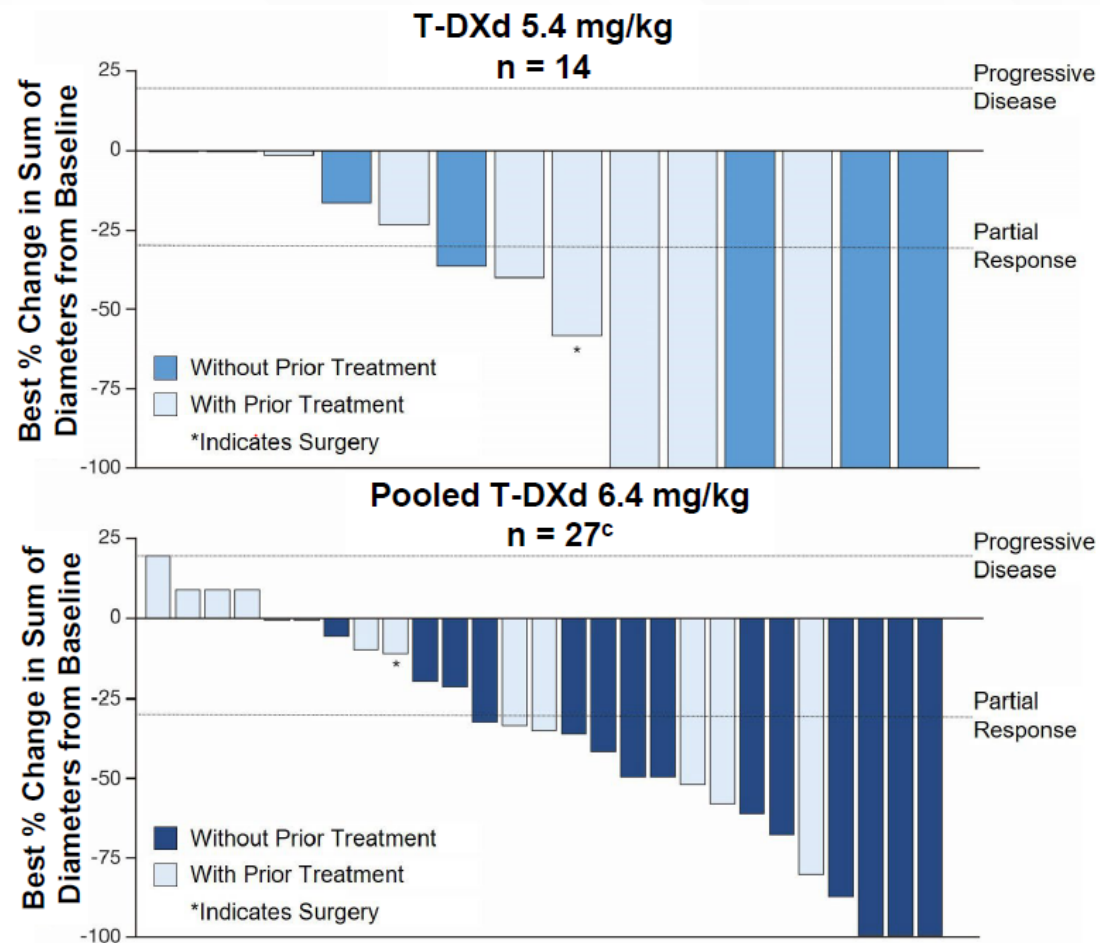
# CNS Efficacy of T-DXd in HER2-Mutated NSCLC

## 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 <i>HER2m</i> /DL-02 BM n = 30
<b>IC-cORR, n (%)<sup>a</sup></b>	<b>7 (50.0)</b>	<b>9 (30.0)</b>
95% CI <sup>b</sup>	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 <sup>c</sup>	0	2 (6.7)
Missing	0	2 (6.7)
<b>IC-DCR, n (%)<sup>a</sup></b>	<b>13 (92.9)</b>	<b>22 (73.3)</b>
95% CI <sup>b</sup>	66.1-99.8	54.1-87.7
<b>IC-DoR, months<sup>d</sup></b>		
Median, (95% CI) <sup>e</sup>	9.5 (3.6-NE)	4.4 (2.9-10.2)

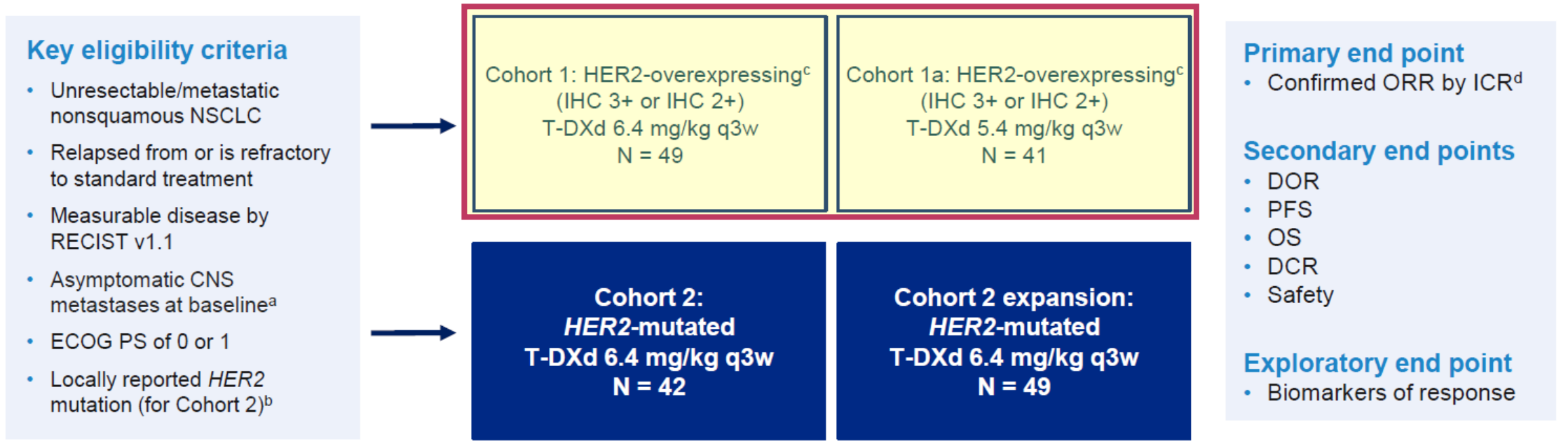
12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response



# T-DXd in Advanced NSCLC With HER2 Overexpression

## DESTINY-Lung01 Study Design

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



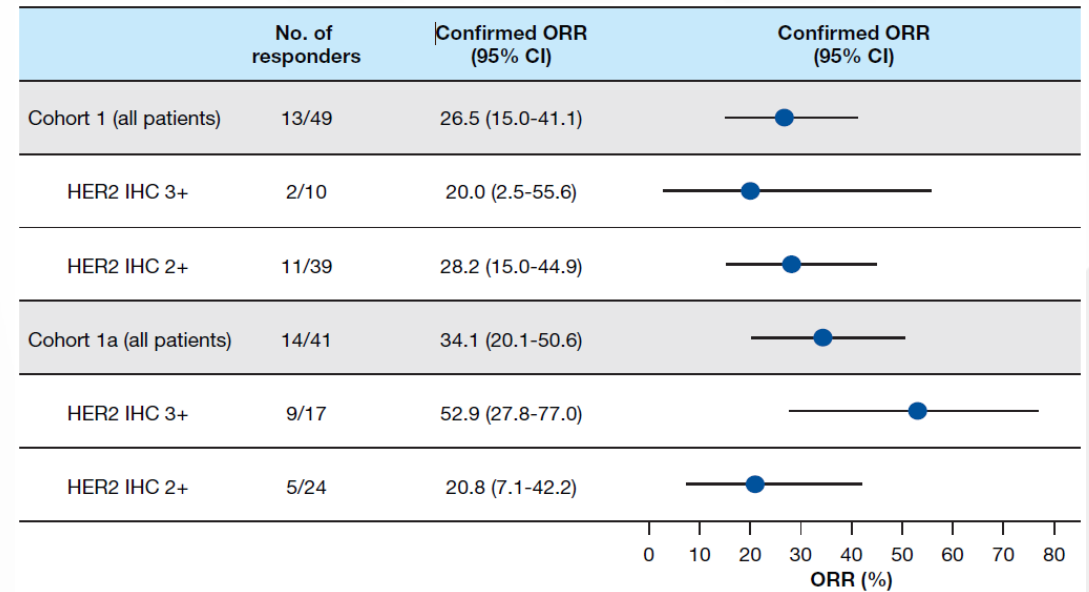
<sup>a</sup>Patients with asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll <sup>b</sup>*HER2* mutation documented solely from a liquid biopsy could not be used for enrollment <sup>c</sup>*HER2* overexpression without known *HER2* mutation was assessed by local assessment of archival tissue and centrally confirmed <sup>d</sup>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 Is More Modest

	Cohort 1 (6.4 mg/kg) N = 49	Cohort 1a (5.4 mg/kg) N = 41
<b>ORR by ICR, % (95% CI)</b>	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
<b>DCR, % (95% CI)</b>	69.4 (54.6-81.8)	78.0 (62.4-89.4)
<b>DoR, median (95% CI), months</b>	5.8 (4.3-NE)	6.2 (4.2-9.8)



**T-DXd is currently NOT approved for patients with advanced NSCLC with HER2 overexpression**

# 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: 52.9%
    - > Median DOR: 6.9 months

# Ongoing T-DXd Clinical Trials

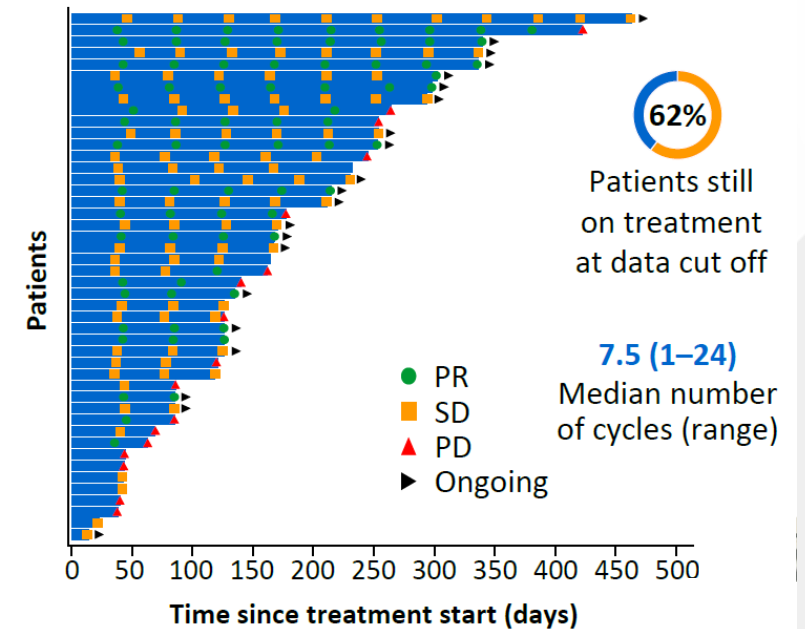
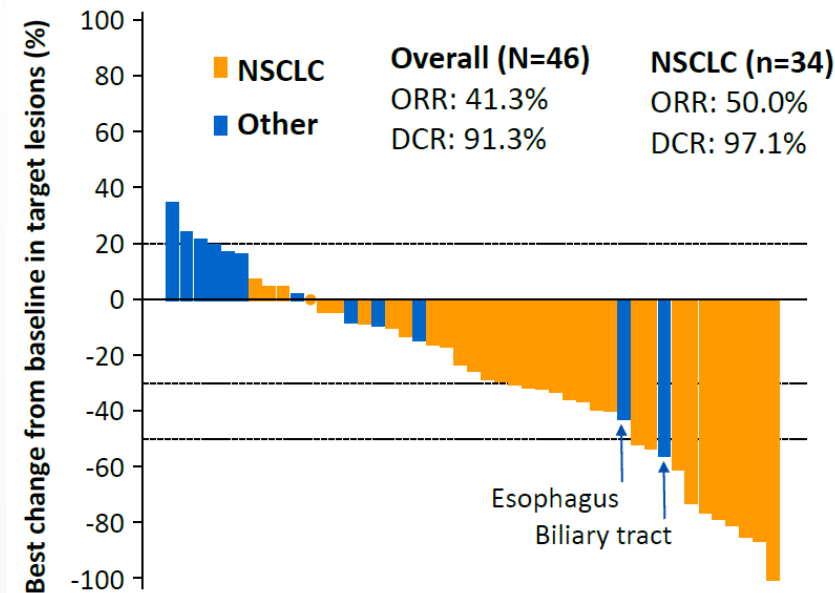
Trial	Phase	Treatment	Setting
<b>DESTINY-Lung03 (NCT04686305)</b>	1b	T-DXd and immunotherapy (durvalumab, MEDI5752) with or without chemotherapy	First-line treatment of patients with advanced or metastatic nonsquamous NSCLC and HER2 overexpression
<b>DESTINY-Lung04 (NCT05048797)</b>	3	T-DXd vs SOC (platinum [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)
<b>DESTINY-Lung05 (NCT05246514)</b>	2	T-DXd	Treatment of patients with HER2 mutant NSCLC who have disease progression on or after at least one line of treatment (2L+)

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

# Are There Novel Targeted Agents That Balance Toxicity and Efficacy?

## Zongertinib

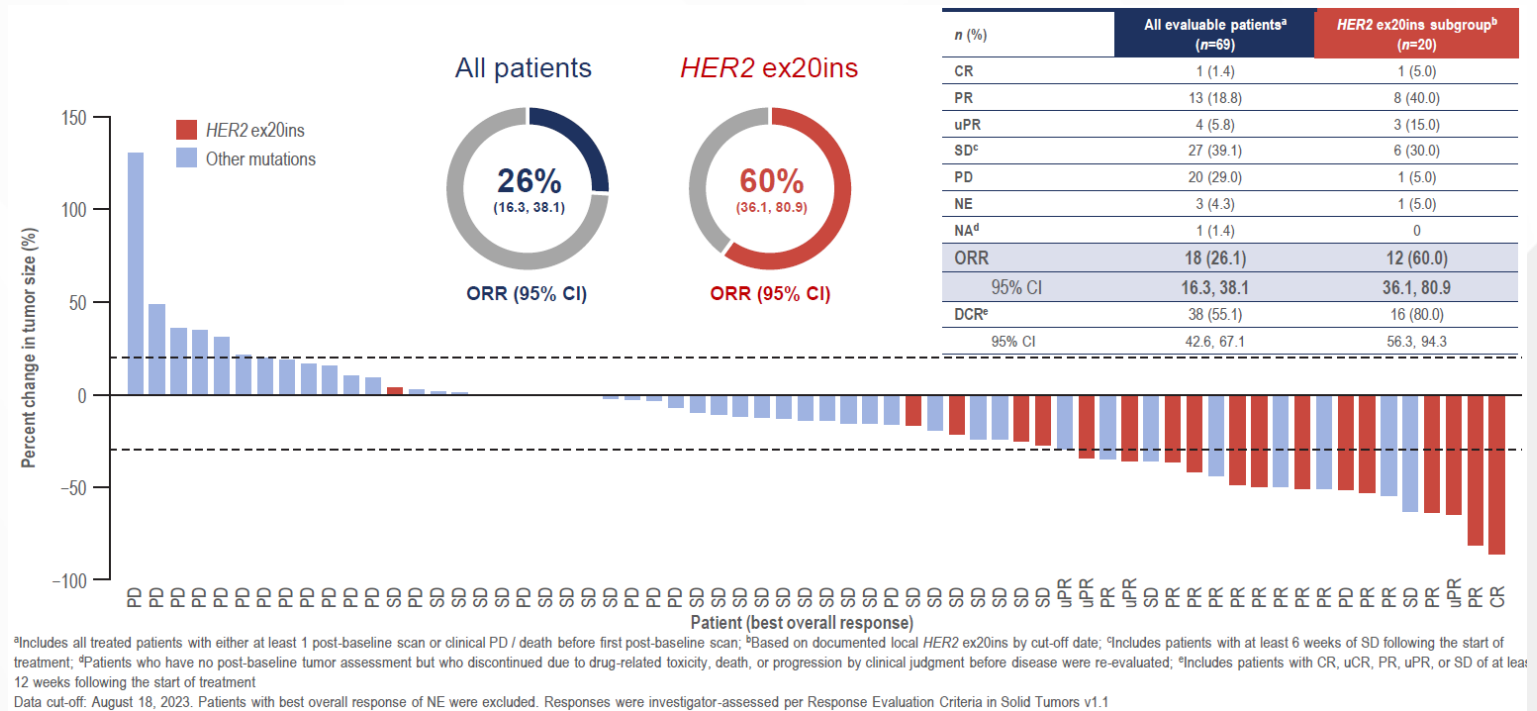
- Next generation HER2-specific TKI
- Early phase data suggests tolerable toxicity profile with promising efficacy



# 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





# 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<sup>a</sup>
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations

<sup>a</sup> *HER2* mutations may be detected in tissue or ctDNA.

<sup>b</sup> Crossover is not permitted.

<sup>c</sup> Investigator's choice of cisplatin or carboplatin.



Randomization  
1:1

Arm 1: T-DXd<sup>b</sup>

Arm 2: Standard of care<sup>b</sup>  
platinum<sup>c</sup> (cisplatin or carboplatin)  
+ pemetrexed  
+ pembrolizumab

Primary Endpoint: PFS

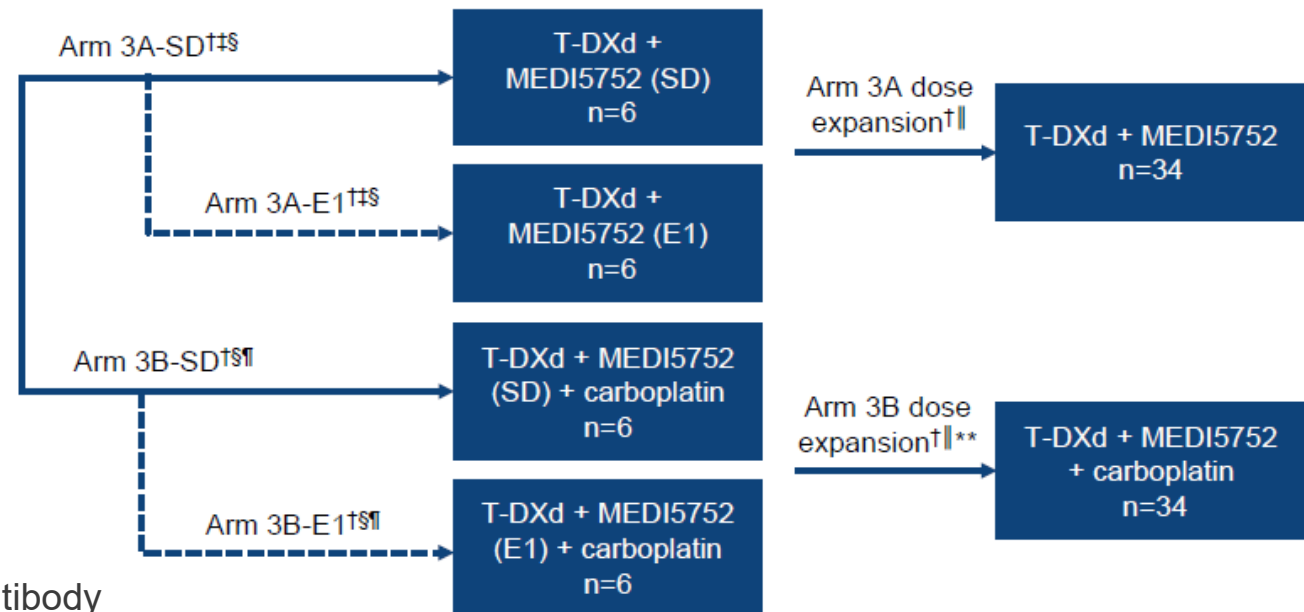
# Can We Bring T-DXd Into the Management of Advanced NSCLC With HER2 Overexpression?

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



# What Role Does Immunotherapy Play in HER2-Mutated NSCLC?

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

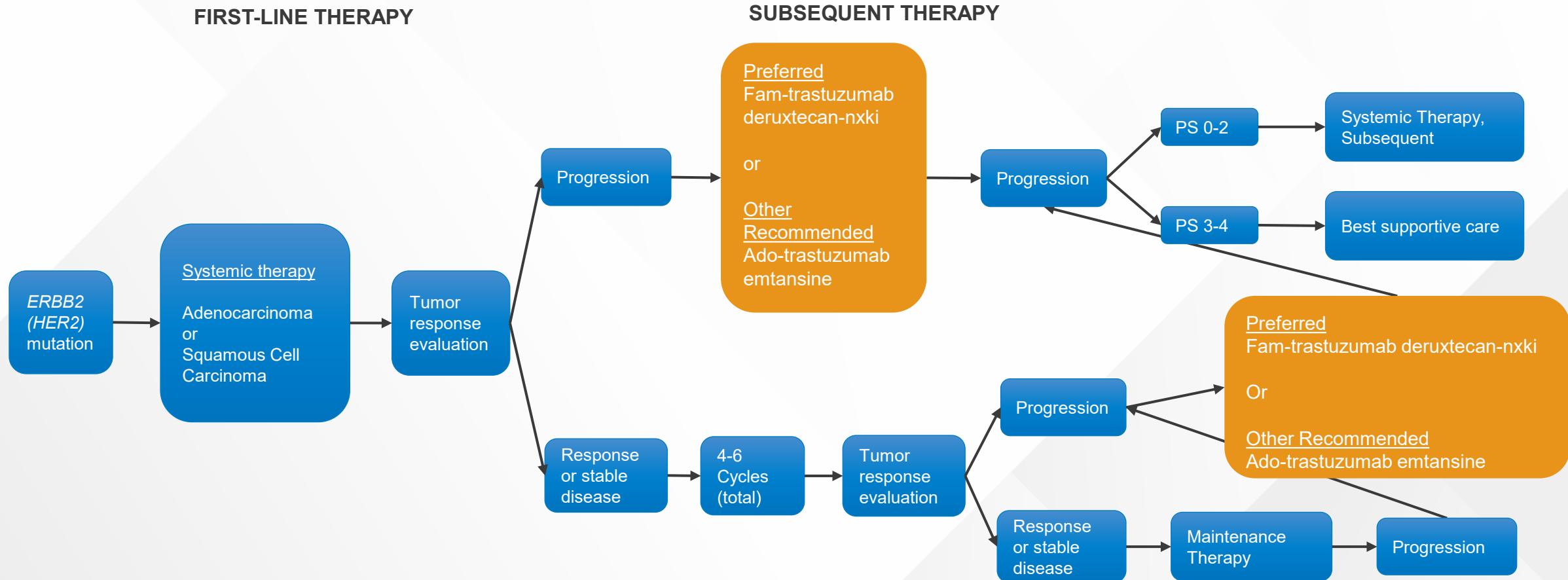
Study	Sample size	ORR	mDoR	mPFS	mOS
Mazieres et al. <sup>1</sup>	29	7%	-	2.5mo	20.3mo
Guisier et al. <sup>2</sup>	23	27%	15.2mo	2.2mo	20.4mo

## 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<sup>3</sup> (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

# Current NCCN Recommendations for Advanced *HER2*-Mutated NSCLC

## *ERBB2* (*HER2*) MUTATION



# 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

# 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+)

# 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



# 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)

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

# 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 <sup>a</sup>	T-DXd 6.4 mg/kg N = 50 <sup>a</sup>
<b>Any grade, n (%)</b>	<b>13 (12.9)</b>	<b>14 (28.0)</b>
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)

# ILD Incidence Across Solid Tumors

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

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) <sup>b</sup>	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) <sup>c</sup>	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.

<sup>a</sup>Patients with multiple ILD/pneumonitis events are listed only once in this table, based on the event with the highest grade.

<sup>b</sup>The HER2-positive breast cancer population (n = 245) is a subset of the entire breast cancer population (n = 510).

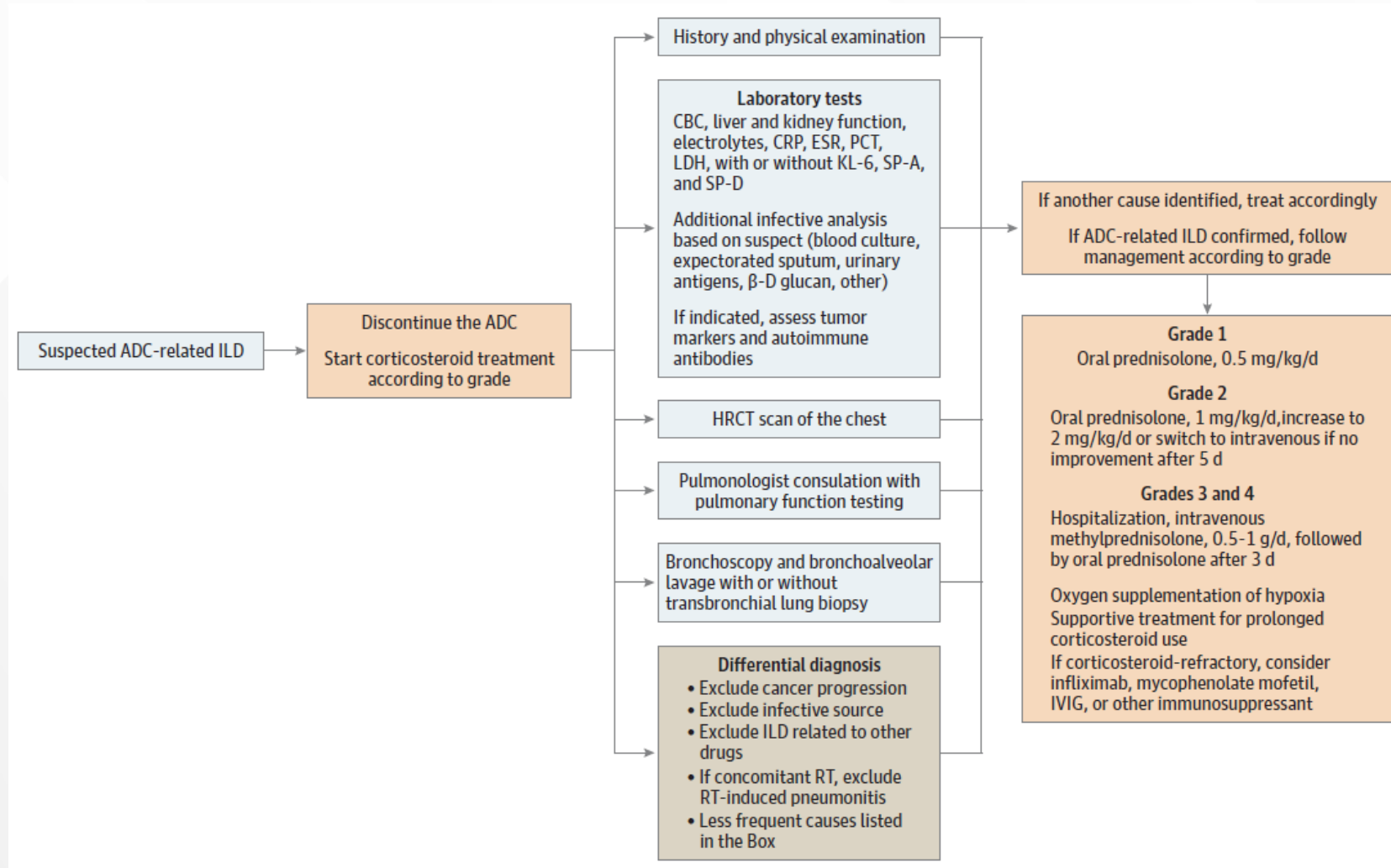
<sup>c</sup>All patients with lung cancer received 6.4 mg/kg q3w of T-DXd.

- 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%

# 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+

# Clinical Management of ILD



# 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

# 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



# 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

# 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

# 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
- Assessment of *HER2* amplification and HER2 overexpression is not routinely performed as part of initial work-up of advanced NSCLC
- Outside of a clinical trial or individual case-based decision, *HER2* amplification and HER2 overexpression do not currently factor into the frontline management of 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 after progression on prior systemic therapy for *HER2*-mutated NSCLC
- 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

# Precision Payloads:

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

