HER2-MUTANT NSCLC:
Evolving treatment landscape

Why it matters

2-4% of advanced NSCLC harbour *HER2* mutations

These are associated with poor prognosis and a higher risk of brain metastases

The most common mutation **is exon 20 insertions** (e.g., YVMA)

Early identification and testing

Perform comprehensive genomic profiling with **Next-Generation Sequencing (NGS)** at diagnosis

Tumour tissue preferred but ctDNA and cytological samples suitable

Review results in a multidisciplinary team (MDT) to guide optimal therapy

Targeted therapies are changing outcomes

Antibody–Drug Conjugates (ADCs)

TRASTUZUMAB DERUXTECAN (T-DXd)[1-3]

Key studies: DESTINY-Lung01 and DESTINY-Lung02

- High response rates
- Durable responses in pre-treated patients
- Intracranial activity in patients with brain metastases

Next-Generation HER2 TKIs

ZONGERTINIB [4, 5]

Irreversible HER2-selective TKI (spares WT EGFR)

Key study: Beamion-LUNG1

SEVABERTINIB[6]

Reversible dual HER2/EGFR TKI

Key study: SOHO-01

- High response rates and durable responses in treatment-naïve and previously treated patients
- Responses in patients with stable brain metastases

Proactive toxicity management

Antibody–Drug Conjugates (ADCs)

TRASTUZUMAB DERUXTECAN (T-DXd)

Most common AEs:

- Nausea
- Fatigue
- Anemia & Neutropenia

INTERSTITIAL LUNG DISEASE (ILD) / PNEUMONITIS IS A KEY RISK:

Monitor for: cough, dyspnea

Management: Early detection interrupt treatment initiate corticosteroids promptly

Next-Generation HER2 TKIs

ZONGERTINIB / SEVABERTINIB

Most common AEs:

Diarrhea, Rash

AE Management:

- Early supportive care
- Dose modification if needed
- Typically low-grade and manageable

INTERSTITIAL LUNG DISEASE (ILD)

No clear ILD signal to date; but monitoring remains important

Evolving HER2-targeted treatment strategies (Trial evidence)

	1st Line		2nd Line+	
			No prior HER2-directed Tx	*Prior HER2-directed ADC*
Zongertinib — Oral — Irreversible	Beamion-LUNG1	ONGOING: Beamion-LUNG2	Beamion-LUNG1	Beamion-LUNG1
Sevabertinib — Oral — Reversible	SOHO-01	ONGOING: SOHO-02	SOHO-01	SOHO-01
Trastuzumab deruxtecan (T-DXd) — Infusion	ONGOING: DESTINY-Lung04		*(No prior HER2-antibodies or ADCs)** DESTINY-Lung01	DESTINY-Lung02

**HER2* TKI allowed*

Treatment decisions should be individualised based on patient characteristics, prior therapy, safety profile and other relevant factors

CLINICAL TAKEAWAYS

- **Test early with NGS** to identify *HER2* mutations
- **Targeted therapies improve outcomes,** including in patients with brain metastases
- **Manage toxicities proactively** (ILD for ADCs; diarrhea/rash for TKIs)
- **Sequence therapies thoughtfully** based on efficacy, safety, and CNS disease

*ADC, antibody-drug conjugate; **AEs,** adverse events; **CNS,** central nervous system; **ctDNA,** circulating tumour DNA; **IHC,** immunohistochemistry; **ILD,** interstitial lung disease; **MDT,** multidisciplinary team; **NGS,** next-generation sequencing; **T-DXd,** Trastuzumab deruxtecan; **TKI,** tyrosine kinase inhibitor; **WT,** wild-type.*

Li BT, et al. N Engl J Med. 2022;386:241-51. Jänne PA, et al. J Thorac Oncol. 2025;20(12):1814-1828. Jänne PA, et al. JAMA Network Open. 2025;8(11):e2543107. Heymach JV, et al. N Engl J Med. 2025;392:2321-33. Heymach J, et al. Abstract 6MO, ELCC 2026. Le X, et al. N Engl J Med. 2025;393:1819-32.

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