

Decoding HER2 in NSCLC: Advances in biomarker testing and targeted therapies

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Agenda

Activating HER2 alterations in NSCLC

Testing for HER2 alterations in NSCLC

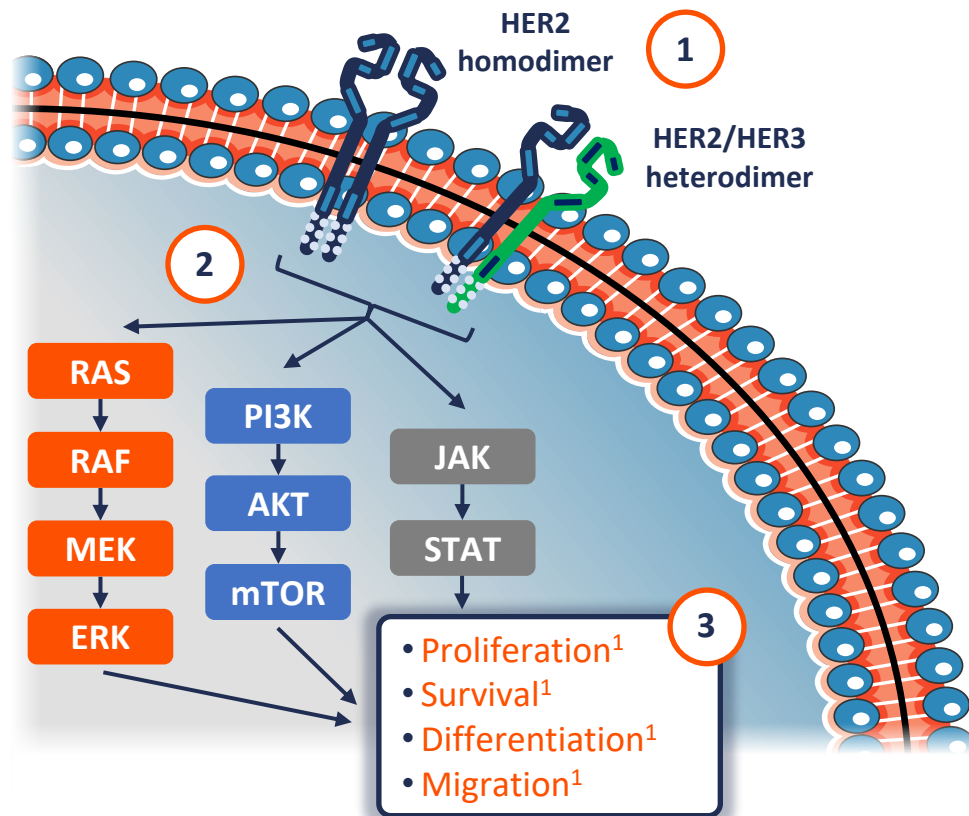
Evaluating HER2-targeted treatment in NSCLC

Activating HER2 alterations in NSCLC

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HER2 mediates the carcinogenic process in NSCLC



- 1
 - HER2 has no known ligand¹⁻³
 - Activated via heterodimerization with other HER family receptors or homodimerization^{1,2}

- 2
 - Activates downstream signalling pathways¹⁻³

- 3
 - Regulates cell processes^{1,3}

- HER2 alterations that upregulate its activity contribute to carcinogenesis and tumour progression¹

HER, human epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

1. Loeffler E, et al. *Life (Basel)*. 2023;14:64; 2. Yu Y, et al. *Cancer Treat Rev*. 2023;114:102520; 3. Bontoux C, et al. *J Pers Med*. 2022;12:1652.

Prevalence of HER2 alterations in NSCLC

HER2 mutation

1–4%

HER2 overexpression

2–30%

HER2 amplification

2–5%

Guidelines for HER2 testing in NSCLC



ESMO¹

- *HER2* mutation testing should be carried out for metastatic non-squamous NSCLC
- Multiplex platforms (NGS) are preferable

ASCO²

- Tissue and/or blood NGS testing for *HER2* alterations

NCCN³

- Complete genotyping including *HER2* in advanced/metastatic adenocarcinoma, large cell and NSCLC NOS
- Can be considered in mSCC
- NGS-based approaches preferred

ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; mSCC, metastatic squamous cell carcinoma; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

1. Hendriks LE, et al. *Ann Oncol.* 2023;34:339–57; 2. Jaiyesimi IA, et al. *J Clin Oncol.* 2024;42:e1–22; 3. NCCN. NSCLC. V6.2024. Available at: www.nccn.org (accessed 25 June 2024).

Testing for HER2 alterations in NSCLC

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Techniques for detecting HER2 alterations

Mutation

- NGS (preferred)^{1,2}
- Sanger sequencing^{1,2}
- ARMS-PCR¹
- Droplet digital PCR¹
- Pyrosequencing²
- RT-PCR²
- qPCR²

Amplification

- FISH^{1,2}
- NGS^{1,2}
- qRT-PCR¹

Overexpression

- IHC^{1,2}

ARMS, amplification refractory mutation system; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction; q, quantitative; qRT-PCR, quantitative real-time PCR; RT-PCR, reverse transcription PCR.

1. Ren S, et al. *ESMO Open*. 2022;7:100482; 2. Bontoux C, et al. *J Pers Med*. 2022;12:1652.

Evaluating HER2-targeted treatments in NSCLC

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Approved HER2-targeted treatments



Trastuzumab deruxtecan



Advanced NSCLC with **activating HER2 mutation** and requiring systemic therapy following platinum-based chemotherapy \pm immunotherapy¹



Unresectable or metastatic NSCLC with **activating HER2 mutations** after prior systemic therapy²



Unresectable or metastatic **HER2-positive (IHC 3+)** solid tumours following prior systemic treatment and with no satisfactory treatment options²

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

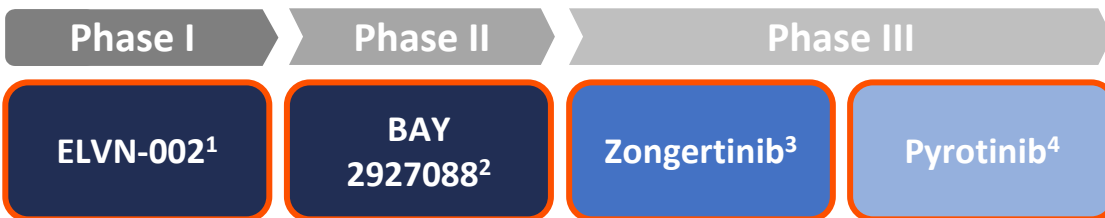
1. EMA. Trastuzumab deruxtecan SmPC. Available at: <https://bit.ly/3VSnhXU> (accessed 28 May 2024);

2. FDA. Trastuzumab deruxtecan PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf (accessed 28 May 2024).

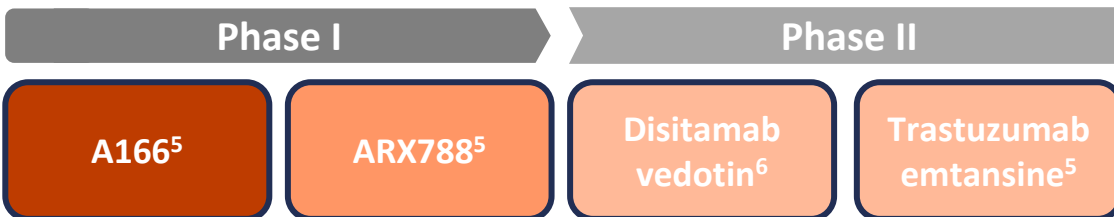
Future directions for HER2-targeted treatments

Examples of HER2-targeted agents in clinical trial

Tyrosine kinase inhibitors



Antibody–drug conjugates



First line

- Trastuzumab deruxtecan in patients with unresectable, la/mNSCLC with *HER2* mutations (DESTINY-Lung04)⁷

HER2, human epidermal growth factor receptor 2; la/mNSCLC, locally advanced or metastatic non-small cell lung cancer.

1. NCT05650879; 2. NCT05099172; 3. NCT06151574; 4. NCT04447118; 5. Vathiotis IA, et al. *Cancers (Basel)*. 2023;15:1286; 6. NCT06185400; 7. NCT05048797.

All clinical trials searchable by NCT number. Available at: <https://clinicaltrials.gov/> (accessed 28 May 2024).

Trastuzumab deruxtecan in *HER2*-mutated NSCLC

DESTINY-Lung01

Results from *HER2*-mutant cohort¹



Patients with *HER2*-mutant metastatic NSCLC refractory to standard treatment

6.4 mg/kg
(n=91)

cORR	55%
mDoR	9.3 months
mPFS	8.2 months
mOS	17.8 months

DESTINY-Lung02

Final analysis presented at ASCO 2024²



Patients with previously treated *HER2*-mutant metastatic NSCLC

5.4 mg/kg
(n=102)

6.4 mg/kg
(n=50)

cORR	50%	56%
mDoR	12.6 months	12.2 months
mPFS	10.0 months	12.9 months
mOS	19.0 months	17.3 months

ASCO, American Society of Clinical Oncology; cORR, confirmed objective response rate; DoR, duration of response; *HER2*, human epidermal growth factor receptor 2; m, median; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

1. Li BT, et al. *N Engl J Med.* 2022;386:241–51; 2. Jänne PA, et al. Presented at: 2024 ASCO Annual Meeting, Chicago, IL, USA. 31 May–4 June 2024. Abstr. 8543.

Trastuzumab deruxtecan in HER2-overexpressing NSCLC

DESTINY-Lung01

Results from HER2-overexpressing cohorts



Patients with HER2-overexpressing (IHC 3+ or 2+ without known *HER2* mutation) unresectable or metastatic NSCLC relapsed/refractory to standard treatment or no standard treatment available

	5.4 mg/kg (n=41)	6.4 mg/kg (n=49)
cORR	34.1%	26.5%
mDoR	6.2 months	5.8 months
mPFS	6.7 months	5.7 months
mOS	11.2 months	12.4 months

Data for investigational HER2-targeted agents

				Survival outcomes				
	Drug	Trial	Patient population	ORR (%)	DCR (%)	mDoR (mos)	mPFS (mos)	mOS (mos)
ADC	Trastuzumab emtansine ¹	JapicCTI-194620 (N=22)	HER2 exon 20 insertion mutation and one or two prior lines of chemotherapy	38.1	52.4	3.5	2.8	8.1
	Pyrotinib ²	ChiCTR1800020262 (N=78)	Stage IIIB–IV NSCLC harbouring HER2 mutations	19.2	74.4	9.9	5.6	10.5
TKI	BAY 2927088 ³	SOHO-01 (N=34) Efficacy analysis n=33	Advanced NSCLC harbouring a HER2-activating mutation and experiencing disease progression after ≥1 systemic therapy, but HER2-targeted therapy naive	70	82	NR	8.1	-
	Zongertinib ⁴	Beamion LUNG-1 (n=41)	HER2 aberration-positive advanced/unresectable/metastatic solid tumours including HER2 mutation-positive NSCLC refractory to/unsuitable for standard treatment	44	93	15.8	BID:13.8 QD: 12.3	-

ADC, antibody–drug conjugate; BID, twice daily; DCR, disease control rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; m, median; mos, months; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; TKI, tyrosine kinase inhibitor.

1. Iwama E, et al. *Eur J Cancer*. 2022;162:99–106; 2. Song Z, et al. *BMC Med*. 2022;20:42; 3. Girard N, et al. Presented at: 2024 ASCO Annual Meeting, Chicago, IL, USA.

30 May–4 June 2024. Abstr. LBA8598; 4. Heymach J, et al. Presented at: 2024 ASCO Annual Meeting, Chicago, IL, USA. 30 May–4 June 2024. Abstr. 8514.