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

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by USF Health and touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by USF Health and touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in USF Health and touchIME activities*
- *USF Health and touchIME accept no responsibility for errors or omissions*

touch™ ONCOLOGY

A conversation between:

Prof. Enriqueta Felip

Medical Oncologist,
Vall d'Hebron University Hospital,
Barcelona, Spain

Prof. Keith Kerr

Consultant Pathologist,
Aberdeen University Medical School
and Aberdeen Royal Infirmary,
Aberdeen, UK

touch™ ONCOLOGY

Agenda

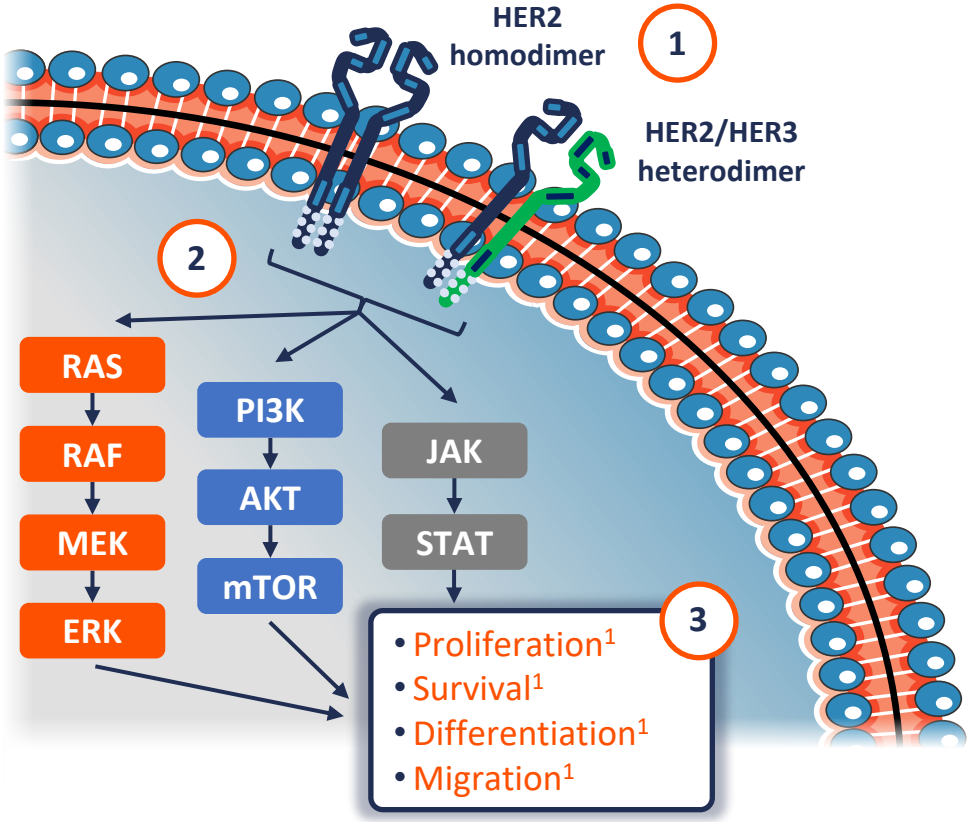
- Activating HER2 alterations in NSCLC
- Testing for HER2 alterations in NSCLC
- Evaluating HER2-targeted treatment in NSCLC

touch™ ONCOLOGY

Activating HER2 alterations in NSCLC

Prof. Enriqueta Felip
Medical Oncologist,
Vall d'Hebron University Hospital,
Barcelona, Spain

HER2 mediates the carcinogenic process in NSCLC



1
- HER2 has no known ligand[1–3]
- Activated via heterodimerization with other HER family receptors or homodimerization[1,2]

2
- Activates downstream signalling pathways[1–3]

3
- Regulates cell processes[1,3]

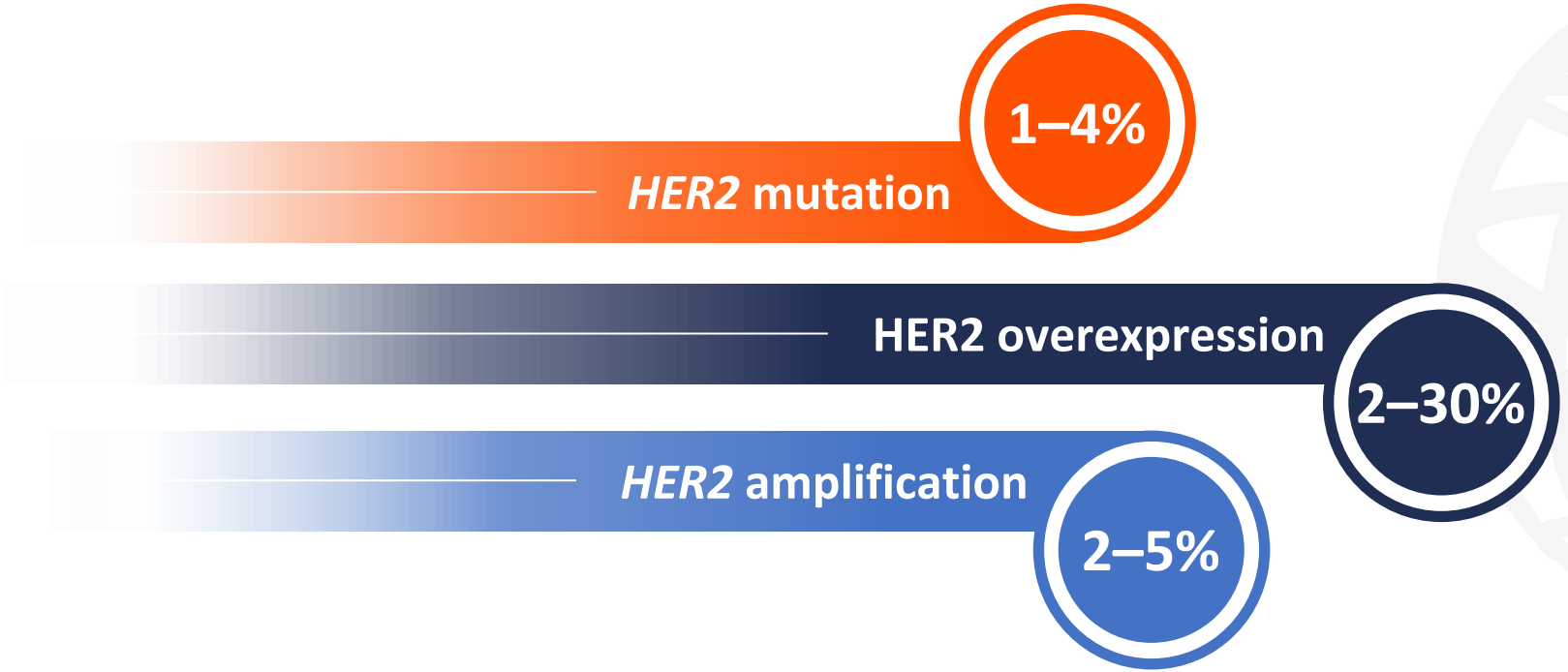
- HER2 alterations that upregulate its activity contribute to carcinogenesis and tumour progression[1]

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.

touch™ ONCOLOGY

Prevalence of HER2 alterations in NSCLC



HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer.
Loeffler E, et al. *Life (Basel)*. 2023;14:64.

touch™ ONCOLOGY

Guidelines for HER2 testing in NSCLC

ESMO[1]

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

ASCO[2]

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

NCCN[3]

- **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).

touch™ ONCOLOGY

Testing for HER2 alterations in NSCLC

Prof. Keith Kerr
Consultant Pathologist,
Aberdeen University Medical School
and Aberdeen Royal Infirmary,
Aberdeen, UK

Techniques for detecting HER2 alterations

Mutation

- NGS (preferred)[1,2]
- Sanger sequencing[1,2]
- ARMS-PCR[1]
- Droplet digital PCR[1]
- Pyrosequencing[2]
- RT-PCR[2]
- qPCR[2]

Amplification

- FISH[1,2]
- NGS[1,2]
- qRT-PCR[1]

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.

touch™ ONCOLOGY

Evaluating HER2-targeted treatments in NSCLC

Prof. Keith Kerr
Consultant Pathologist,
Aberdeen University Medical School
and Aberdeen Royal Infirmary,
Aberdeen, UK

Approved HER2-targeted treatments

Trastuzumab deruxtecan

Advanced NSCLC with **activating *HER2* mutation** and requiring systemic therapy following platinum-based chemotherapy ± immunotherapy[1]

Unresectable or metastatic NSCLC with **activating *HER2* mutations** after prior systemic therapy[2]

Unresectable or metastatic **HER2-positive (IHC 3+)** solid tumours following prior systemic treatment and with no satisfactory treatment options[2]

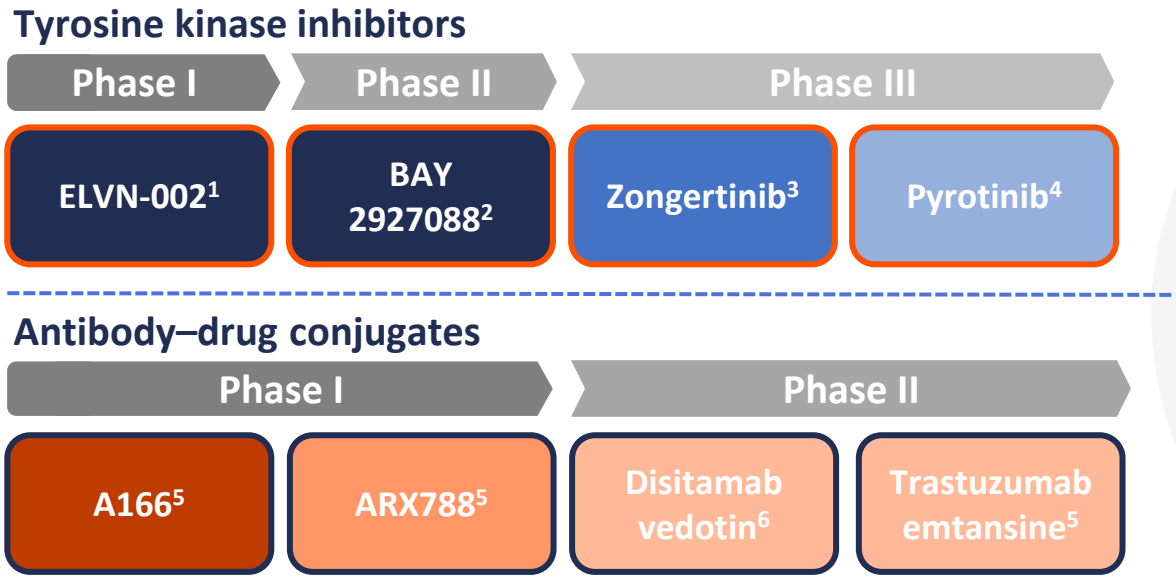
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

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).

touch™ ONCOLOGY

Future directions for HER2-targeted treatments

Examples of HER2-targeted agents in clinical trial



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).

touch™ ONCOLOGY

Trastuzumab deruxtecan in *HER2*-mutated NSCLC

DESTINY-Lung01

Results from *HER2*-mutant cohort[1]

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 2024[2]

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.

touch™ ONCOLOGY

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

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

Smit EF, et al. *Lancet Oncol.* 2024;25:439–54.

touch™ ONCOLOGY

Data for investigational HER2-targeted agents

	Drug	Trial	Patient population	Survival outcomes: 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**
TKI	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**	-
TKI	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.

touch™ ONCOLOGY