Novel targeted therapies for NSCLC: Exploring *HER2* dysregulation

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Agenda

How is *HER2* dysregulated and what is its clinical relevance in patients with NSCLC?

What are the current challenges in treating patients with *HER2*-mutant NSCLC?

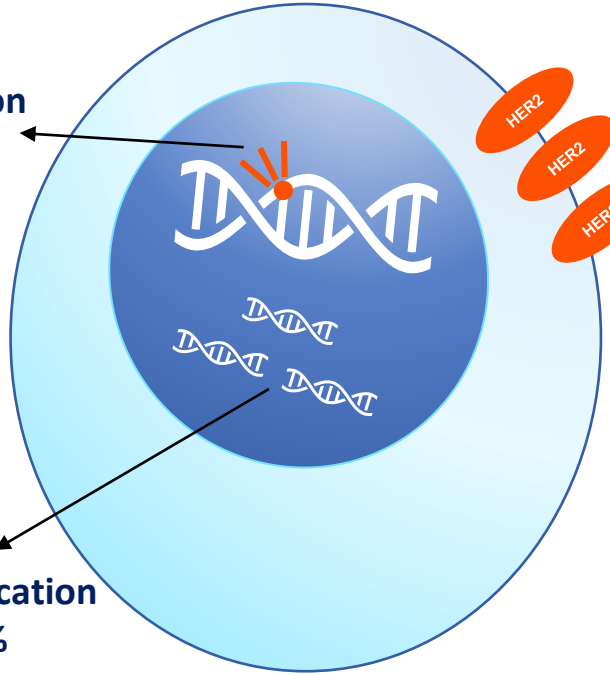
What are the latest data on HER2-targeted therapies for patients with *HER2*-mutant NSCLC?

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

Dysregulation of *HER2* in patients with NSCLC[1–3]

- Majority of mutations occur in exon 20 (80–90%) and less frequently in exons 18–19 and 21–23
- Most common in females, Asians, never-smokers, and patients with adenocarcinoma

***HER2* mutation 2–4%**



HER2 overexpression 2–38%

- High expression (IHC score of 3+) observed in 2–6% of patients with NSCLC

- Acquired *HER2* amplification has been shown to be higher in patients resistant to EGFR-TKIs vs de novo *HER2* amplification
- Independent of *HER2* mutation

***HER2* amplification 10–20%**

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

1. Zhao J, Xia Y. *JCO Precis Oncol*. 2020;4:411–25; 2. Garrido-Castro AC, Felip E. *Transl Lung Cancer Res*. 2013;2:122–7;
3. Peters S, Zimmerman S. *Transl Lung Cancer Res*. 2014;3:84–8.

HER2 dysregulation and clinical outcomes in NSCLC

Mutation

- Prognostic impact of exon 20 mutation is unknown[1]
- Insertion mutations can be resistant to HER2-targeting TKIs[2]

Overexpression

- Overexpression is an indicator of poor prognosis[3]
- Possible association with intrinsic chemoresistance[1]

Amplification

- Prognostic value of *HER2* amplification is ambiguous and based on anecdotal reports[4]

- While HER2 overexpression is reported as an indicator of poor prognosis in NSCLC, further research is needed to understand how *HER2* dysregulation affects outcomes in advanced NSCLC

ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

1. Zhao J, Xia Y. *JCO Precis Oncol*. 2020;4:411–25; 2. ESMO. Metastatic NSCLC Clinical Practice Guidelines. 2020. Available at: www.esmo.org/content/download/347819/6934778/1/ESMO-CPG-mNSCLC-15SEPT2020.pdf (accessed 1 September 2021); 3. Liu L, et al. *J Thorac Oncol*. 2010;5:1922–32; 4. Kim EK, et al. *PLoS One*. 2017;12:e0171280.

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Genetic testing in NSCLC: Guideline recommendations

Genetic alteration	ESMO[1]	NCCN[2]
EGFR mutation	I, A	Yes
ALK rearrangement	I, A	Yes
ROS1 rearrangement	II, A	Yes
BRAF mutation	II, A	Yes
NTRK rearrangement	II, A	No
NTRK1/2/3 fusions	No	Yes
KRAS mutation	No	Yes
MET mutation	No	Yes
RET rearrangement	No	Yes
HER2 mutation	No	No

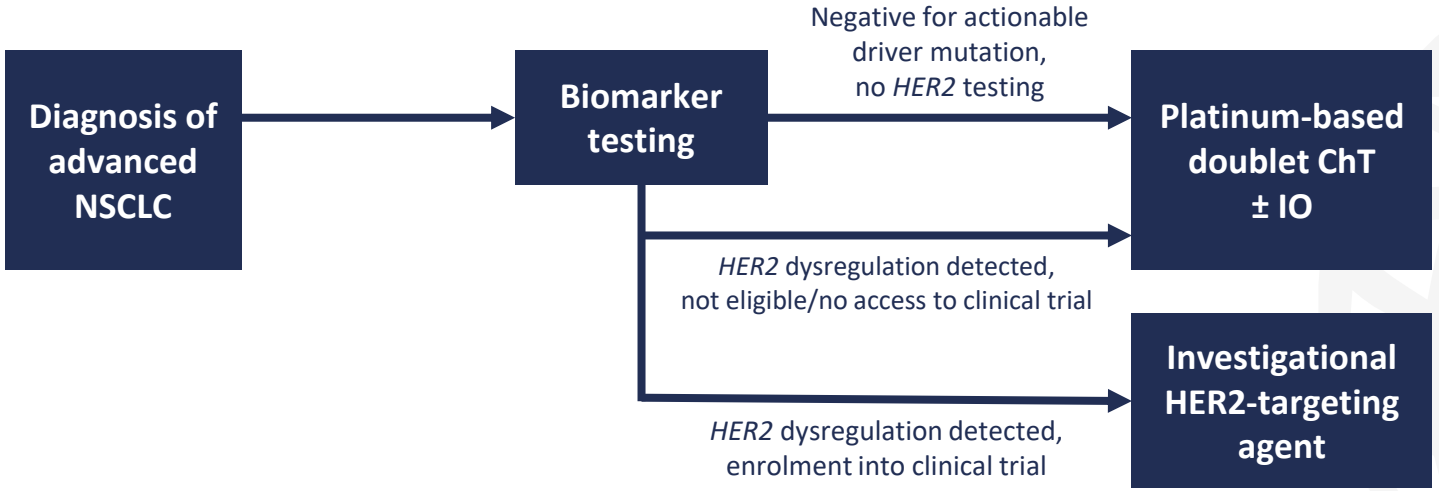
- Guidelines recommend broad genetic profiling prior to initiation of therapy for advanced NSCLC[1,2]
- *HER2* testing is not currently recommended due to limited data, but recruitment into clinical trials is encouraged[1,2]
- A retrospective observational chart review study (MYLUNG; 2018–2020) of 3,474 patients with advanced NSCLC in the US assessed testing rates for five biomarkers: *ALK*, *BRAF*, *EGFR*, *ROS1* and PD-L1[3]

Fewer than half of patients (46%) received all five biomarker tests[3]

ESMO, European Society for Medial Oncology; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.

1. ESMO. Metastatic NSCLC Clinical Practice Guidelines. 2020. Available at: www.esmo.org/content/download/347819/6934778/1/ESMO-CPG-mNSCLC-15SEPT2020.pdf (accessed 1 September 2021); 2. NCCN. NSCLC Guidelines Version 5.2021. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 1 September 2021).
3. Robert NJ, et al. *J Clin Oncol*. 2021;39(15 Suppl.):9004.

HER2-dysregulation and current treatment guidelines[1,2]



- There is currently no standard of care for patients with NSCLC and *HER2*-dysregulation, however, guidelines encourage recruitment into clinical trials with HER2-targeting agents

ChT, chemotherapy; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; IO, immunotherapy; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.

1. ESMO. Metastatic NSCLC Clinical Practice Guidelines. 2020. Available at: www.esmo.org/content/download/347819/6934778/1/ESMO-CPG-mNSCLC-15SEPT2020.pdf (accessed 1 September 2021); 2. NCCN. NSCLC Guidelines Version 5.2021. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 1 September 2021).

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HER2-targeting ADCs: Latest efficacy and safety data

HER2-targeting ADC	Study details	Efficacy results	Safety results
Ado-trastuzumab emtansine (T-DM1)	Phase II basket trial including patients with metastatic lung adenocarcinoma with *HER2* amplification or mutation[1,2]	N=18 • ORR: 44% (95% CI, 22–69) • mPFS: 5 months (95% CI, 3–9)	AEs included low grade infusion reactions, thrombocytopenia and elevated hepatic transaminases
Trastuzumab deruxtecan (T-DXd)	Phase II DESTINY-Lung01 trial in patients with metastatic NSCLC refractory to standard treatment and with HER2 overexpression or a *HER2*-activating mutation[3–5]	N=91 • ORR: 54.9% (95% CI, 44.2–65.4) • mPFS: 8.2 months (95% CI, 6.0–11.9) • mOS: 17.8 months (95% CI, 13.8–22.1) • mDOR: 9.3 months (95% CI, 5.7–14.7)	• TRAEs occurred in 97% of patients • 46% of TRAEs were grade ≥3 including neutropenia • Drug-related ILD occurred in 26% of patients and resulted in 2 deaths
	Phase II DESTINY-Lung02 trial is currently recruiting patients with *HER2*-mutated metastatic NSCLC who have recurrence or progression during/after at ≥1 regimen of prior anticancer therapy (≥2L), which must have included a Pt-based ChT[6]		

2L, second-line; ADC, antibody-drug conjugate; AE, adverse event; ChT, chemotherapy; CI, confidence interval; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; Pt, platinum; TRAE, treatment-related adverse event.

1. NCT02675829; 2. Li BT, et al. *J Clin Oncol*. 2018;36:2532–7; 3. NCT03505710; 4. Li BT, et al. *N Engl J Med*. 2021. doi:10.1056/NEJMoa2112431; 5. Li BT, et al. Presented at: ESMO Virtual Congress 2021, 16–21 September 2021. Abstr. LBA45; 6. NCT04644237.

Trial information by NCT number available at: www.clinicaltrials.gov (accessed 1 September 2021).

HER2-targeting TKIs: Latest efficacy and safety data

HER2-targeting TKI	Study details	Efficacy results	Safety results
Poziotinib	Phase II ZENITH20 trial[1] including patients with treatment-naive metastatic NSCLC and *EGFR* or *HER2* exon 20 mutation. Preliminary data on efficacy and safety have been recently reported from the ZENITH20-4 cohort[2]	N=48 • ORR: 44% (95% CI, 29.5–58.8) • mPFS: 5.6 months (range, 0–20.2+) • mDoR: 5.4 months (range, 2.8–19.1+) • DCR: 75%	• 12% discontinued due to AEs • AEs included grade ≥3 dermal and GI toxicities
Pyrotinib	Phase II single-arm study in chemotherapy-treated patients with advanced NSCLC and *HER2* exon 20 mutations[3,4]	N=60 • ORR: 30% (95% CI, 18.8–43.2) • mPFS: 6.9 months (95% CI, 5.5–8.3) • mOS: 14.4 months (95% CI, 12.3–21.3) • mDoR: 6.9 months (95% CI, 4.9–11.1)	• TEAEs grade ≥3 in 28% of patients • Most common TEAE was diarrhoea (20%)
	Phase III trial (PYRAMID-1) is recruiting patients with advanced NSCLC and *HER2* exon 20 mutations, and will compare pryotinib and docetaxel in the 2L setting[5]		
Tarloxotinib	Phase II study (RAIN-701)[6] in advanced NSCLC including patients with *HER2* exon 20 mutation, evaluating the clinical activity of tarloxotinib in the 2L setting[7]	First analysis showed 44% (n=9) patients exhibited tumour reduction	First analysis showed low rates of severe EGFR-related AEs such as rash and diarrhoea

2L, second-line; CI, confidence interval; DCR, disease control rate; EGFR, epidermal growth factor receptor; GI, gastrointestinal; 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, objective response rate; TEAE, emergent-related adverse event; TKI, tyrosine kinase inhibitor. 1. NCT03318939; 2. Cornelissen R, et al. Presented at: ESMO Virtual Congress 2021, 16–21 September 2021. Abstr. LBA46; 3. NCT02834936; 4. Zhou C, et al. *J Clin Oncol*. 2020;38:2753–61; 5. NCT04447118; 6. NCT03805841; 7. Liu S. *Ann Oncol*. 2020;31(Suppl. 4):S1142–215.
Trial information by NCT number available at: www.clinicaltrials.gov (accessed 1 September 2021).

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HER2-targeting combinations

HER2-targeting combination	Study details	Efficacy results
Pertuzumab + trastuzumab (HER2 mAb + HER2 mAb)	Phase IIa basket trial (My Pathway) including 30 patients with *HER2*-mutant or HER2-positive refractory NSCLC[1]	• *HER2*-mutant: ORR 21% • HER2-positive: ORR 13%
Trastuzumab deruxtecan + pembrolizumab (HER2 ADC + ICI)	Phase Ib, open-label, two-part, multicentre, non-randomized, multiple-dose study including two cohorts of patients with NSCLC with HER2-expression or *HER2* mutation[2]	• Ongoing • Estimated primary completion: August 2022
Trastuzumab + tucatinib (HER2 mAb + TKI)	Phase IIb basket trial of trastuzumab and tucatinib, evaluating the clinical activity in solid tumours with *HER2* alterations, including a cohort for NSCLC[3]	• Ongoing • Estimated primary completion: January 2023

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

1. Hainsworth JD, et al. *J Clin Oncol*. 2018;36:536–42; 2. NCT04042701; 3. NCT04579380.

Trial information by NCT number available at: www.clinicaltrials.gov (accessed 1 September 2021).

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