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Expanding HER2 horizons: Implications for NSCLC and beyond

Practice aid for HER2 alterations in solid tumours with a focus on NSCLC

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HER2 alterations in cancer[1]

HER2 gene mutation

- Alteration of the structure of resultant receptor
- Can lead to constitutive activation of HER2

HER2 gene amplification

- Characterized by increase in number of *HER2* gene copies

HER2 protein overexpression

- Presence of higher number of HER2 receptors at cancer cell membranes
- Causes greater HER2 intracellular signalling activation

Addition of HER2-targeted therapy to FDA-approved tissue-agnostic treatments

Larotrectinib[2] Entrectinib[2] Repotrectinib[3]	Selpercatinib[2]	Trastuzumab deruxtecan[2]
***NTRK* gene fusion**	***RET* gene fusion**	**HER2 positive**
Dabrafenib + trametinib[2]	Pembrolizumab[2]	Dostarlimab[2]
***BRAF V600E* mutation**	**MSI-H/dMMR** **TMB-H (≥10 mut/Mb)**	**dMMR**

Adult patients with unresectable/metastatic HER2-positive (IHC 3+) solid tumours who have received prior systemic treatment and have no satisfactory alternative treatment options[4]

Technique for assessing HER2 overexpression[5,6]

IHC

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ORRs for the approved HER2-targeted therapy trastuzumab deruxtecan in NSCLC*

DESTINY-Lung01[7]

R/R unresectable and/or metastatic nonsquamous NSCLC with activating *HER2* mutation or HER2 overexpression (IHC 2+ or 3+)

***HER2* mutation:**[8]	**HER2 overexpression:**[9]
6.4 mg/kg (n=91) = **55%**	5.4 mg/kg (n=41) = **34.1%** 6.4 mg/kg (n=49) = **26.5%**

DESTINY-Lung02[10]

Metastatic NSCLC with activating *HER2* mutation following disease recurrence or progression during/after ≥1 prior regimen containing a Pt-ChT drug

***HER2* mutation:**[11]

5.4 mg/kg (n=102) = **50%**

6.4 mg/kg (n=50) = **56%**

ORRs for investigational HER2-targeted therapies in NSCLC

Trastuzumab emtansine JapicCTI-194620[12] (n=22)

- Stage III or IV, or postoperative recurrence
- *HER2* exon 20 insertion mutation
- Prior treatment with one or two prior lines of chemotherapy

ORR: 38.1%

Pyrotinib[13] ChiCTR1800020262 (N=78)

- Stage IIIB or IV
- Unresectable
- *HER2* mutations

ORR: 19.2%

BAY 2927088[14] SOHO-01 (N=34)

- Advanced disease
- *HER2* mutation
- Relapsed/refractory to ≥1 systemic therapy

ORR: 70%
(efficacy analysis n=33)

Zongertinib[15] Beamion LUNG-1

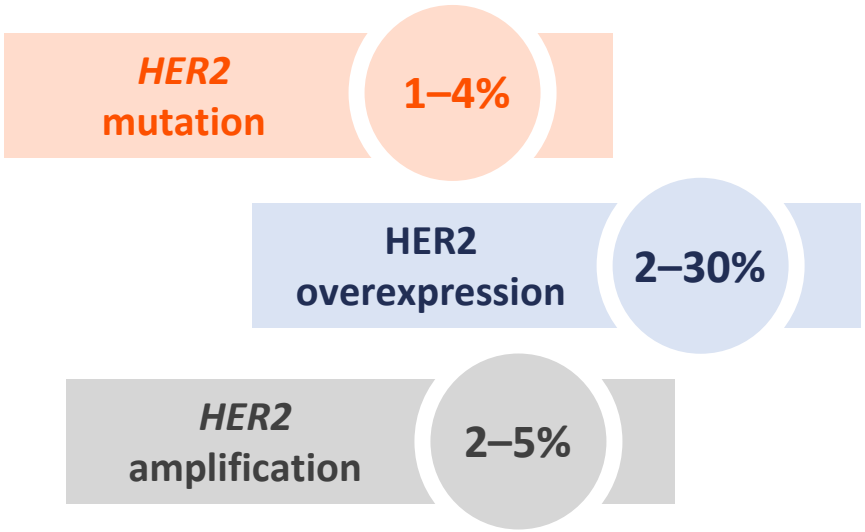
- Advanced, unresectable and/or metastatic
- Phase Ia: *HER2* mutation†; exhausted or not suitable for standard tx options
- Phase Ib: *HER2* mutation; pretreated or tx naïve dependent on cohort

Phase Ia (n=41†)	Phase Ib (n=23)
ORR: 44%	**ORR 74%**

* Trastuzumab deruxtecan is both FDA- and EMA-approved for use in NSCLC with activating *HER2* mutations after prior systemic therapy.[4,16]

† Patients with any solid tumour with a HER2 aberration (overexpression, amplification, somatic mutation or gene rearrangement) could enter phase Ia of the trial; results for patients with *HER2* mutation only presented.[4]

Prevalence of different HER2 alterations in NSCLC[1]



HER2 alteration testing techniques[5,6]

Mutation

NGS (preferred), Sanger sequencing, ARMS-PCR, ddPCR, pyrosequencing, RT-PCR, qPCR

Overexpression

IHC

Amplification

FISH, NGS, qRT-PCR

Guidelines on HER2 molecular testing requirements[17]

NCCN

Molecular testing, including HER2, in patients with advanced or metastatic disease **at clinical presentation**

Complete genotyping including *HER2* in **advanced/metastatic adenocarcinoma, large cell and NSCLC NOS**

Can be **considered in mSCC**

NGS-based approaches preferred

ctDNA testing can be used to **complement tissue testing** to **reduce turnaround time and increase yield of targetable alteration detection**, but **should not be used in lieu of tissue testing**

Current status of HER2-targeted therapies in advanced or metastatic NSCLC[17]

NCCN recommendations

Trastuzumab deruxtecan[17]

- **Preferred subsequent therapy** after first-line treatment in patients with ***HER2*-mutant NSCLC**
- **Option for subsequent therapy** for patients with **HER2 overexpression** (IHC 3+)

Trastuzumab emtansine[17]

- **Alternative subsequent therapy** after first-line treatment in patients with ***HER2*-mutant NSCLC**
- **Switching between agents with a similar MoA at time of progression is not recommended**

FDA approval

- Unresectable or metastatic NSCLC with **activating *HER2* mutations** after prior systemic therapy[4]
- Unresectable or metastatic **HER2-positive (IHC 3+) solid tumours** following prior systemic treatment and with no satisfactory treatment options[4]

Trastuzumab emtansine is **not approved by the FDA** for use in patients with HER2-altered NSCLC[18]

Abbreviations and references

Abbreviations

ARMS, amplification refractory mutation system; ctDNA, circulating tumour DNA; dd, droplet digital; dMMR, mismatch repair deficiency; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; m, metastatic; MoA, mechanism of action; MSI-H, microsatellite instability high; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tropomyosin receptor kinase; ORR, objective response rate; PCR, polymerase chain reaction; Pt-ChT, platinum-based chemotherapy; q, quantitative; R/R, relapsed/refractory; RT-PCR, reverse transcription PCR; SCC, squamous cell carcinoma; TMB-H, tumour mutational burden high; tx, treatment.

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