Expanding HER2 horizons: Implications for NSCLC and beyond

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Expert panel

Dr Razelle Kurzrock

Medical Oncologist
Medical College of Wisconsin
Milwaukee, WI, USA

Dr Lyudmila Bazhenova

Medical Oncologist
UC San Diego Moores Cancer Center
San Diego, CA, USA

Dr Ignacio Wistuba

Pathologist
MD Anderson Cancer Center
Houston, TX, USA

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Agenda

HER2-targeted tumour-agnostic therapies in solid tumours: An evolving landscape

HER2-targeting therapies in NSCLC: Current and future considerations

Determining HER2 status in NSCLC: Standardizing testing protocols for quality control

HER2-targeted tumour-agnostic therapies in solid tumours: An evolving landscape

FDA-approved tissue-agnostic therapies

Larotrectinib[1] Entrectinib[1] Repotrectinib[2]	Dabrafenib + trametinib[1]	Trastuzumab deruxtecan[1]	Selpercatinib[1]	Pembrolizumab[1]	Dostarlimab[1]
***NTRK* gene fusion**	***BRAF V600E* mutation**	**HER2 positive**	***RET* gene fusion**	**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[3]

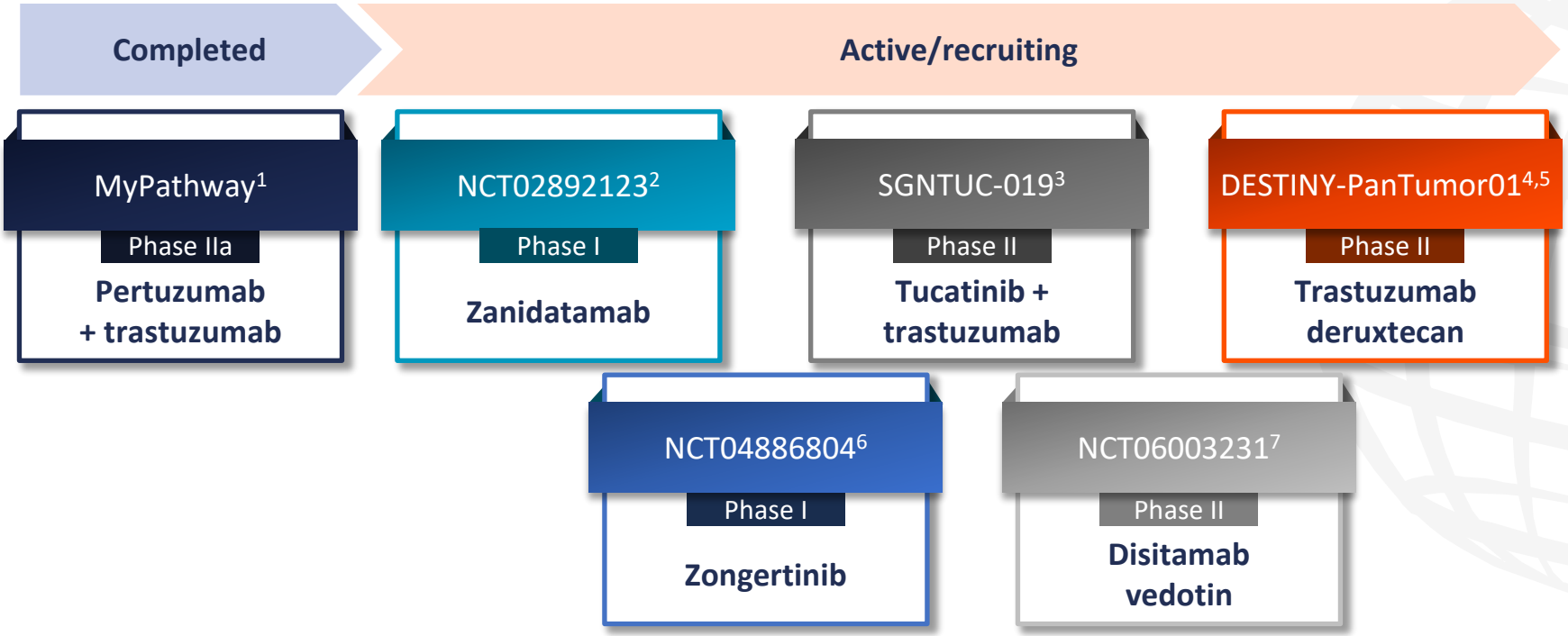
DESTINY-CRC02[4]	ORR: **46.9%**
DESTINY-PanTumor02[5]	ORR: **51.4%**
DESTINY-Lung01[6]	ORR: **52.9%**

dMMR, mismatch repair deficiency; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MSI-H, microsatellite instability high; NTRK, neurotrophic tropomyosin receptor kinase; ORR, objective response rate; TMB-H, tumour mutational burden high.

1. Subbiah V, et al. *CA Cancer J Clin*. 2024;74:433–52; 2. FDA. Repotrectinib PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2024/218213s001lbl.pdf (accessed 2 August 2024); 3. FDA. Trastuzumab deruxtecan PI. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf (accessed 2 August 2024); 4. Raghav KPS, et al. *J Clin Oncol.* 2023;41:3501; 5. FDA. April 2024. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2 (accessed 2 August 2024); 6. Smit EF, et al. *Ann Oncol.* 2022;33(Suppl. 7):S994–5.

Trials of HER2-targeted tumour-agnostic therapies

Selection of completed and ongoing trials



HER2, human epidermal growth factor receptor 2.

1. ClinicalTrials. NCT02091141; 2. ClinicalTrials. NCT02892123; 3. ClinicalTrials. NCT04579380; 4. ClinicalTrials. NCT04639219; 5. Li BT, et al. *Lancet Oncol.* 2024;25:707–19; 6. ClinicalTrials. NCT04886804; 7. ClinicalTrials. NCT06003231.

All clinical trials searchable by NCT number. Available at: https://clinicaltrials.gov/ (accessed 2 August 2024).

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HER2 alterations in cancer

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

HER2, human epidermal growth factor receptor 2.
Loeffler E, et al. *Life (Basel)*. 2023;14:64.

HER2-targeting therapies in NSCLC: Current and future considerations

ORRs for trastuzumab deruxtecan in HER2-altered NSCLC

Destiny-Lung01[1]

- HER2 overexpression (IHC 2+ or 3+) or activating *HER2* mutation
- Nonsquamous
- Unresectable and/or metastatic
- Relapsed/refractory to standard treatment, or no standard treatment available

HER2 mutation:[2]
6.4 mg/kg (n=91) = **55%**

HER2 overexpression:[3]
5.4 mg/kg (n=41) = **34.1%**
6.4 mg/kg (n=49) = **26.5%**

Destiny-Lung02[4]

- Activating *HER2* mutation
- Metastatic
- Disease recurrence or progression during/after at least one prior regimen (second line or later) containing a platinum-based chemotherapy drug

HER2 mutation:[5]
5.4 mg/kg (n=102) = **50%**
6.4 mg/kg (n=50) = **56%**

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

1. ClinicalTrials.gov. NCT03505710. Available at: www.clinicaltrials.gov/study/NCT03505710 (accessed 2 August 2024); 2. Li BT, et al. *N Engl J Med.* 2022;386:241–51; 3. Smit EF, et al. *Lancet Oncol.* 2024;25:439–54; 4. ClinicalTrials.gov. NCT04644237. Available at: www.clinicaltrials.gov/study/NCT04644237 (accessed 2 August 2024); 5. Jänne PA, et al. Presented at: 2024 ASCO Annual Meeting, Chicago, IL, USA. 31 May–4 June 2024. Abstr. 8543.

Investigational HER2-targeted therapies in NSCLC

T-DM1 **JapicCTI-194620**[1] **(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[2] **ChiCTR1800020262** **(N=78)**	• Stage IIIB or IV • Unresectable • *HER2* mutations	**ORR: 19.2%**
BAY 2927088[3] **SOHO-01** **(N=34)**	• Advanced disease • *HER2* mutation • Relapsed/refractory to ≥1 systemic therapy	**ORR: 70%** (efficacy analysis n=33)
Zongertinib[4] **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*) **ORR: 44%** Phase Ib (n=23) **ORR 74%**

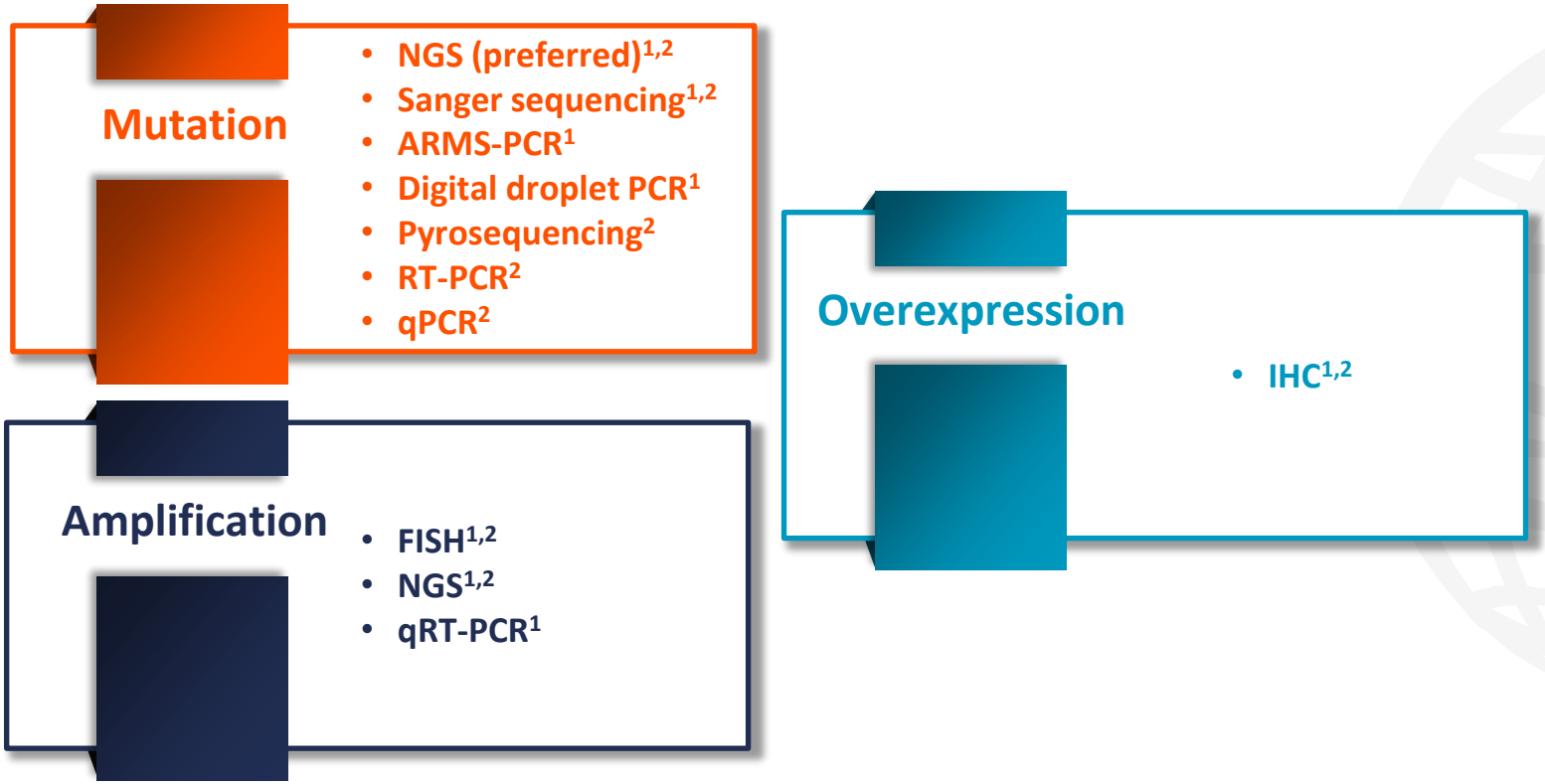
*Patients with any solid tumour with a HER2 aberration (overexpression, amplification, somatic mutation or gene rearrangement) could enter phase Ia of the trial; results for patients with *HER2* mutation only presented.[4]

HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer, ORR, objective response rate; T-DM1, trastuzumab emtansine; tx, treatment.

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.

Determining HER2 status in NSCLC: Standardizing testing protocols for quality control

Techniques for detecting HER2 alterations



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; qPCR, quantitative PCR; qRT-PCR, quantitative real-time PCR; RT-PCR, reverse transcription PCR.

1. Ren S, et al. *ESMO Open.* 2022;7:100395; 2. Bontoux C, et al. *J Pers Med.* 2022;12:1652.