

Expanding HER2 horizons: ● Implications for NSCLC and beyond

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Agenda

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

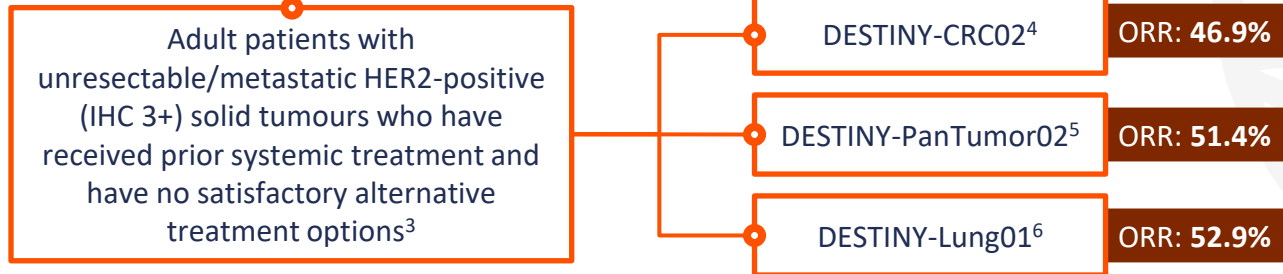
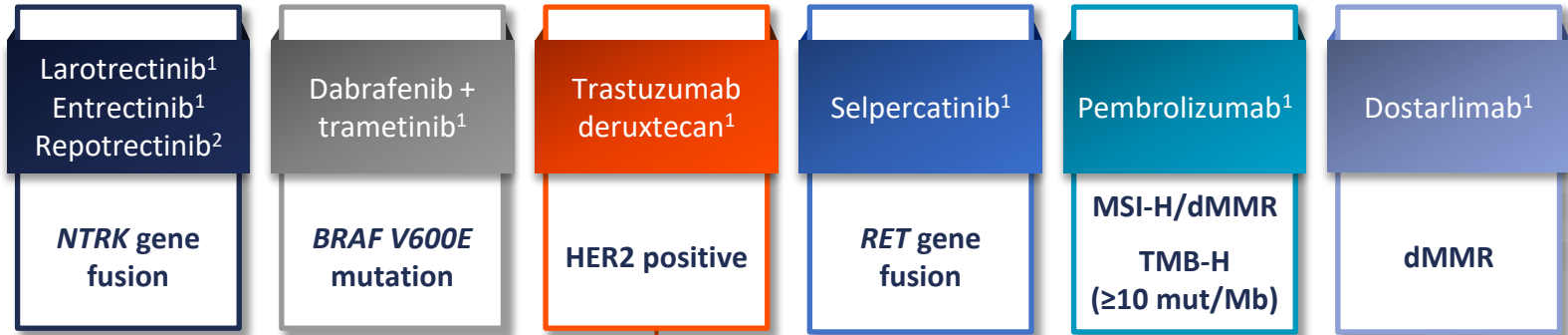
HER2-targeting therapies in NSCLC: Current and future considerations

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



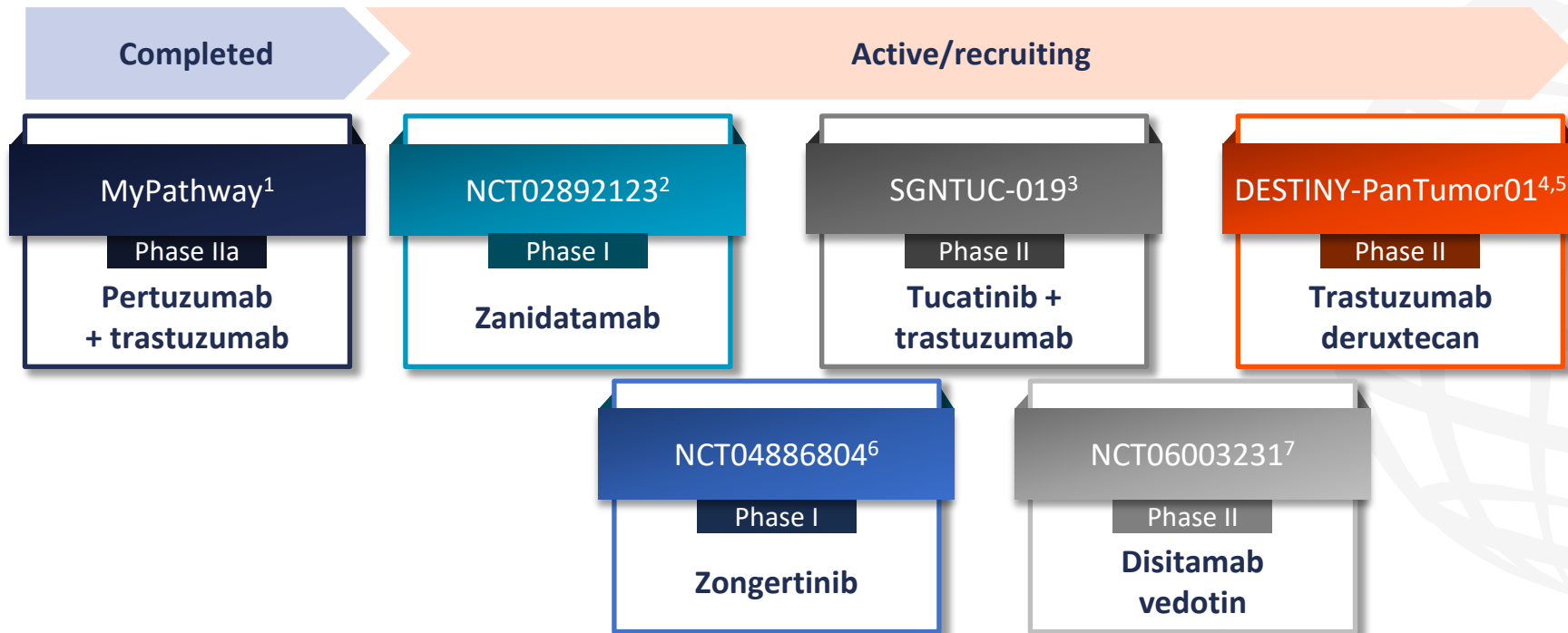
dMMR, mismatch repair deficiency; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MSI-H, microsatellite instability high; NTRK, neurotrophic tropomyosin receptor kinase; ORR, objective response rate; TMB-H, tumour mutational burden high.

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).

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-targeting therapies in NSCLC: Current and future considerations



ORRs for trastuzumab deruxtecan in HER2-altered NSCLC

Destiny-Lung01¹

- 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-Lung02⁴

- 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-194620¹ (n=22)	<ul style="list-style-type: none">• Stage III or IV, or postoperative recurrence• <i>HER2</i> exon 20 insertion mutation• Prior treatment with one or two prior lines of chemotherapy	ORR: 38.1%
Pyrotinib² ChiCTR1800020262 (N=78)	<ul style="list-style-type: none">• Stage IIIB or IV• Unresectable• <i>HER2</i> mutations	ORR: 19.2%
BAY 2927088³ SOHO-01 (N=34)	<ul style="list-style-type: none">• Advanced disease• <i>HER2</i> mutation• Relapsed/refractory to ≥ 1 systemic therapy	ORR: 70% (efficacy analysis n=33)
Zongertinib⁴ Beamion LUNG-1	<ul style="list-style-type: none">• Advanced, unresectable and/or metastatic• Phase Ia: <i>HER2</i> mutation*; exhausted or not suitable for standard tx options• Phase Ib: <i>HER2</i> 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

Mutation

- NGS (preferred)^{1,2}
- Sanger sequencing^{1,2}
- ARMS-PCR¹
- Digital droplet 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; 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.