

Integrating Advances in HER2-Altered NSCLC in the Community Setting: A Close-Up on Molecular Testing and HER2 Directed Therapies

HER2 Alterations in NSCLC

Resource	Address
Arcila ME, Chaft JE, Nafa K, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. <i>Clin Cancer Res</i> . 2012;18:4910-4918.	https://aacrjournals.org/clincancerres/article/18/18/4910/77504/Prevalence-Clinicopathologic-Associations-and
Burnett H, Emich H, Carroll C, Stapleton N, Mahadevia P, Li T. Epidemiological and clinical burden of <i>EGFR</i> exon 20 insertion in advanced non-small cell lung cancer: A systematic literature review. <i>PLoS One</i> . 2021;16:e0247620.	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0247620
Choudhury NJ, Marra A, Sui JSY, et al. Molecular biomarkers of disease outcomes and mechanisms of acquired resistance to first-line osimertinib in advanced <i>EGFR</i> -mutant lung cancers. <i>J Thorac Oncol</i> . 2023;18:463-475.	https://www.jto.org/article/S1556-0864(22)01932-3/fulltext
Harada G, Yang SR, Cocco E, Drilon A. Rare molecular subtypes of lung cancer. <i>Nat Rev Clin Oncol</i> . 2023;20:229-249.	https://www.nature.com/articles/s41571-023-00733-6
Ji H, Xuan Q, Nanding A, Zhang H, Zhang Q. The clinicopathologic and prognostic value of altered chromosome 17 centromere copy number in HER2 Fish equivocal breast carcinomas. <i>PLoS One</i> . 2015;10:e0132824.	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0132824
Kim EK, Kim KA, Lee CY, Shim HS. The frequency and clinical impact of HER2 alterations in lung adenocarcinoma. <i>PLoS One</i> . 2017;12:e0171280.	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0171280
Le X, Baik CS, Nagasaka M, et al. 1298P Epidemiological and genomic features of patients (pts) with advanced/metastatic (a/m) non-small cell lung cancer (NSCLC) with HER2/ERBB2 mutations within and outside the tyrosine kinase domain (TKD). <i>Ann Oncol</i> . 2024;35(suppl_2):S826.	https://www.annalsofoncology.org/article/S0923-7534(24)02874-6/fulltext
Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. <i>J Clin Oncol</i> . 2013;31:1039-1049.	https://ascopubs.org/doi/pdf/10.1200/JCO.2012.45.3753
LUNGeivity.org. Rare mutations and fusions in NSCLC.	https://rare-mutations.lungevity.org/rare-mutations/about-rare-mutations-and-fusions-nsclc
Nassar AH, Adib E, Kwiatkowski DJ. Distribution of <i>KRAS</i> ^{G12C} somatic mutations across race, sex, and cancer type. <i>N Engl J Med</i> . 2021;384:185-187.	https://www.nejm.org/doi/10.1056/NEJMc2030638
Ninomiya K, Hata T, Yoshioka H, et al. A prospective cohort study to define the clinical features and outcome of lung cancers harboring HER2 aberration in Japan (HER2-CS STUDY). <i>Chest</i> . 2019;156:357-366.	https://www.sciencedirect.com/science/article/abs/pii/S0012369219300315
Nützinger J, Bum Lee J, Li Low J, et al. Management of HER2 alterations in non-small cell lung cancer - The past, present, and future. <i>Lung Cancer</i> . 2023;186:107385.	https://www.sciencedirect.com/science/article/abs/pii/S0169500223009236

Odintsov I, Makarem M, Nishino M, et al. Prevalence and therapeutic targeting of high-level <i>ERBB2</i> amplification in NSCLC. <i>J Thorac Oncol</i> . 2024;19:732-748.	https://www.jto.org/article/S1556-0864(23)02428-0/fulltext
Peters S, Zimmermann S. Targeted therapy in NSCLC driven by HER2 insertions. <i>Transl Lung Cancer Res</i> . 2014;3:84-88.	https://tlcr.amegroups.org/article/view/2263/2886
Ren S, Wang J, Ying J, et al. Consensus for HER2 alterations testing in non-small-cell lung cancer. <i>ESMO Open</i> . 2022;7:100395.	https://www.esmoopen.com/article/S2059-7029(22)00015-1/fulltext
Riudavets M, Sullivan I, Abdayem P, Planchard D. Targeting HER2 in non-small-cell lung cancer (NSCLC): A glimpse of hope? An updated review on therapeutic strategies in NSCLC harbouring HER2 alterations. <i>ESMO Open</i> . 2021;6:100260.	https://www.esmoopen.com/article/S2059-7029(21)00222-2/fulltext
Robichaux JP, Elamin YY, Vijayan RSK, et al. Pan-cancer landscape and analysis of <i>ERBB2</i> mutations identifies pozoitinib as a clinically active inhibitor and enhancer of T-DM1 activity. <i>Cancer Cell</i> . 2019;36:444-457.e7.	https://www.cell.com/cancer-cell/fulltext/S1535-6108(19)30384-8
Shih JY. <i>ERBB2</i> Amplification in NSCLC: How many faces? <i>J Thorac Oncol</i> . 2024;19:668-670.	https://www.jto.org/article/S1556-0864(24)00062-5/fulltext
Tsao AS, Scagliotti GV, Bunn PA Jr, et al. Scientific advances in lung cancer 2015. <i>J Thorac Oncol</i> . 2016;11:613-638.	https://www.jto.org/article/S1556-0864(16)30022-3/fulltext
Zhao J, Xia Y. Targeting HER2 Alterations in non-small-cell lung cancer: A comprehensive review. <i>JCO Precis Oncol</i> . 2020;4:411-425.	https://ascopubs.org/doi/10.1200/PO.19.00333

Molecular Profiling Guidelines and Challenges in NSCLC

Resource	Address
International Association for the Study of Lung Cancer (IASLC). IASLC Global Survey on Biomarker Testing in Lung Cancer – 2024 Update.	https://www.iaslc.org/science-research/scientific-projects/iaslc-global-survey-biomarker-testing-lung-cancer-2024-update
Lung Cancers Today. Community Oncology Insights: Panel Discusses Molecular Testing Approaches, Barriers. <i>Amer Soc Clin Oncol</i> ; 2025.	https://www.youtube.com/watch?v=26W2Cf0YmiA
National Comprehensive Cancer Network® (NCCN). NSCLC. Version 5.2026.	https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
Salgia R, Boehmer LM, Celestin C, Yu H, Spigel DR. Improving care for patients with stage III or IV NSCLC: learnings for multidisciplinary teams from the ACCC National Quality Survey. <i>JCO Oncol Pract</i> . 2021;17:e1120-e1130.	https://ascopubs.org/doi/10.1200/OP.20.00899
Shehata DG, Pan JM, Pan Z, et al. Equity and opportunities in lung cancer care—Addressing disparities, challenges, and pathways forward. <i>Cancers</i> . 2025;17:1347.	https://www.mdpi.com/2072-6694/17/8/1347
Smeltzer MP, King JC, Connolly C, et al. The 2024 International Association for the Study of Lung Cancer Global Survey on Biomarker Testing. <i>J Thorac Oncol</i> . 2025;20:1801-1813.	https://www.jto.org/article/S1556-0864(25)00937-2/pdf

HER2-Targeted Agents in NSCLC

Resource	Address
Armstrong M. ESMO 2025 – Boehringer and Bayer eye the front line. ApexOnco Oncology Pipeline. October 17, 2025	https://www.oncologypipeline.com/apexonco/esmo-2025-boehringer-and-bayer-eye-front-line
Azar I, Alkassis S, Fukui J, et al. Spotlight on trastuzumab deruxtecan (DS-8201,T-DXd) for <i>HER2</i> mutation positive non-small cell lung cancer. <i>Lung Cancer (Auckl)</i> . 2021;12:103-114.	https://www.dovepress.com/spotlight-on-trastuzumab-deruxtecan-ds-8201t-dxd-for-her2-mutation-pos-peer-reviewed-fulltext-article-LCTT
Clancy E. Sevabertinib yields “robust and durable” responses in <i>HER2</i> -mutant NSCLC. <i>Pulmonary Advisor</i> ; November 5, 2025.	https://www.pulmonologyadvisor.com/news/sevabertinib-her2-mutant-nsclc-robust-and-durable-responses/
Doi T, Iwata H, Tsurutani J, et al. Single agent activity of DS-8201a, a <i>HER2</i> -targeting antibody-drug conjugate, in heavily pretreated <i>HER2</i> expressing solid tumors. <i>J Clin Oncol</i> . 2017;35:108-108.	https://ascopubs.org/doi/10.1200/JCO.2017.35.15_suppl.108
Doi T, Shitara K, Naito Y, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a <i>HER2</i> -targeting antibody–drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: A phase 1 dose-escalation study. <i>Lancet Oncol</i> . 2017;18:1512-1522.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30604-6/abstract
Goto K, Brase J, Xu J, et al. EP.12H.08 SOHO-02: Phase III trial of BAY 2927088 in patients with locally advanced or metastatic NSCLC with <i>HER2</i> -activating mutations. <i>J Thorac Oncol</i> . 2024;19:S660.	https://www.jto.org/article/S1556-0864%2824%2902290-1/fulltext
Goto K, Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with <i>HER2</i> -mutant metastatic non-small-cell lung cancer: Primary results from the randomized, phase II DESTINY-Lung02 Trial. <i>J Clin Oncol</i> . 2023;41:4852-4863.	https://ascopubs.org/doi/pdf/10.1200/JCO.23.01361
Heymach J, Yamamoto N, Girard N, et al. 6MO - Zongertinib in treatment-naïve patients with <i>HER2</i> -mutant NSCLC, including those with active brain metastases: Beamion LUNG-1. <i>ESMO Open</i> . 2026;11(suppl 3):106313.	https://www.esmoopen.com/article/S2059-7029(26)00255-3/fulltext
Heymach JV, Ruiter G, Ahn MJ, et al. Zongertinib in previously treated <i>HER2</i> -mutant non-small-cell lung cancer. <i>N Engl J Med</i> . 2025;392:2321-2333.	https://www.nejm.org/doi/10.1056/NEJMoa2503704
Jänne PA, Goto Y, Kubo T, et al. Final analysis results and patient-reported outcomes from DESTINY-Lung02-a dose-blinded, randomized, phase 2 study of trastuzumab deruxtecan in patients with <i>HER2</i> -mutant metastatic NSCLC. <i>J Thorac Oncol</i> . 2025;20:1814-1828.	https://www.sciencedirect.com/science/article/pii/S1556086425009815
Jänne PA, Goto Y, Kubo T, et al. Trastuzumab deruxtecan (T-DXd) in patients with <i>HER2</i> -mutant metastatic non–small cell lung cancer (mNSCLC): Final analysis results of DESTINY-Lung02. <i>J Clin Oncol</i> . 2024;42(suppl_16):8543.	https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.8543

Johnson ML. Beamion LUNG-2: A phase III randomized controlled trial of zongertinib (BI 1810631) versus standard of care (SoC) in patients with locally advanced/metastatic non-squamous non-small cell lung cancer (NSCLC) harboring <i>HER2</i> tyrosine kinase domain (TKD) mutations. <i>J Clin Oncol</i> . 2024;42(suppl 16):TPS8654.	https://www.asco.org/abstracts-presentations/238544
Lai WCV, Feldman DL, Buonocore DJ, et al. PD-L1 expression, tumor mutation burden and response to immune checkpoint blockade in patients with <i>HER2</i> -mutant lung cancers. <i>J Clin Oncol</i> . 2018;36:9060-9060.	https://ascopubs.org/doi/10.1200/JCO.2018.36.15_suppl.9060
Le X, Kim TM, Loong HH, et al. Sevabertinib in advanced <i>HER2</i> -mutant non-small-cell lung cancer. <i>N Engl J Med</i> . 2025;393:1819-1832.	https://www.nejm.org/doi/full/10.1056/NEJMoa2511065
Le X. Sevabertinib (BAY 2927088) in advanced <i>HER2</i> -mutant non-small cell lung cancer (NSCLC): Results from the SOHO-01 study. Presented at ESMO 2025; Abstract LBA75.	https://oncologypro.esmo.org/congress-resources/esmo-congress-2025?presentation=sevabertinib_bay_2927088_in_advanced_her2_mutant
Li BT, Ahn M-J, Goto K, et al. Open-label, randomized, multicenter, phase 3 study evaluating trastuzumab deruxtecan (T-DXd) as first-line treatment in patients with unresectable, locally advanced, or metastatic non-small cell lung cancer (NSCLC) harboring <i>HER2</i> exon 19 or 20 mutations (DESTINY-Lung04). <i>J Clin Oncol</i> . 2022;40(suppl 16):TP9137.	https://ascopubs.org/doi/pdf/10.1200/JCO.2022.40.16_suppl.TPS9137
Li BT, Planchard D, Goto K, et al. 1321MO Trastuzumab deruxtecan (T-DXd) in patients (pts) with <i>HER2</i> (ERBB2)-mutant (<i>HER2m</i>) metastatic non-small cell lung cancer (NSCLC) with and without brain metastases (BMs): Pooled analyses from DESTINY-Lung01 and DESTINY-Lung02. <i>Ann Oncol</i> . 2023;34(suppl 2): S762-S763.	https://www.annalsofoncology.org/article/S0923-7534(23)03191-5/fulltext
Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in <i>HER2</i> -mutant non-small-cell lung cancer. <i>N Engl J Med</i> . 2022;386:241-251.	https://www.nejm.org/doi/10.1056/NEJMoa2112431
Loong HH, Li L, Wu L, et al. SOHO-01: Safety and efficacy of BAY 2927088 in patients with advanced <i>HER2</i> -mutant non-small cell lung cancer (NSCLC) who were pretreated but naïve to <i>HER2</i> -targeted therapy or had not received any treatment for advanced disease. <i>J Clin Oncol</i> . 2025;43:8504.	https://ascopubs.org/doi/10.1200/JCO.2025.43.16_suppl.8504
National Comprehensive Cancer Network® NCCN Clinical Practice Guidelines in Oncology . Non-Small Cell Lung Cancer. Version 5.2026.	https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
Negrao MV, Skoulidis F, Montesio M, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. <i>J Immunother Cancer</i> . 2021;9:e002891.	https://jitc.bmj.com/content/9/8/e002891
Nützinger J, Bum Lee J, Li Low J, et al. Management of <i>HER2</i> alterations in non-small cell lung cancer - The past, present, and future. <i>Lung Cancer</i> . 2023;186:107385.	https://www.lungcancerjournal.info/article/S0169-5002(23)00923-6/abstract

Offin M, Feldman D, Ni A, et al. Frequency and outcomes of brain metastases in patients with HER2-mutant lung cancers. <i>Cancer</i> . 2019;125:4380-4387.	https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.32461
Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, A novel HER2-targeting ADC with a novel DNA topoisomerase i inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. <i>Clin Cancer Res</i> . 2016;22:5097-5108.	https://aacrjournals.org/clincancerres/article/22/20/5097/124857/DS-8201a-A-Novel-HER2-Targeting-ADC-with-a-Novel
Popat S, Yamamoto N, Girard N, et al. LBA74 Zongertinib as first-line treatment in patients with advanced HER2-mutant NSCLC: Beamion LUNG 1. <i>Ann Oncol</i> . 2025;36(suppl 2): S1616.	https://www.annalsofoncology.org/article/S0923-7534(25)04858-6/fulltext
Popat S. Updates in first-line treatment of advanced HER2 (ERBB2)-mutant non-small cell lung cancer: Insights from the European Society for Medical Oncology (ESMO) Congress 2025. <i>Oncol AMJ</i> . 2025;2(suppl_5):2-9.	https://www.emjreviews.com/en-us/amj/oncology/symposium/updates-in-first-line-treatment-of-advanced-her2-erbb2-mutant-non-small-cell-lung-cancer-insights-from-the-european-society-for-medical-oncology-esmo-congress-2025-s33525/
Ruiter G, Smit EF, Soo RA, et al. PT2.12.03 Zongertinib in patients with previously treated HER2-mutant NSCLC and brain metastases at baseline: Beamion LUNG-1. <i>J Thorac Oncol</i> . 2025;20(10_suppl 1):S613-S614.	https://www.jto.org/article/S1556-0864(25)02209-9/abstract
Ruiter G, Tu H-Y, Ahn M-J, et al. PL04.04 Primary phase Ib analysis of Beamion LUNG-1: Zongertinib (BI 1810631) in patients with HER2 mutation-positive NSCLC. <i>J Thorac Surg</i> . 2024;19:S4-S5.	https://www.jto.org/action/showPdf?pii=S1556-0864%2824%2900892-X
Serani S. FDA grants breakthrough status to sevabertinib in 1L HER2+ NSCLC. <i>Targeted Oncology</i> . January 6, 2026.	https://www.targetedonc.com/view/fda-grants-breakthrough-status-to-sevabertinib-in-1l-her2-nsclc
Siegel F, Siegel S, Kotýnková K, et al. Sevabertinib, a reversible HER2 inhibitor with activity in lung cancer. <i>Cancer Discov</i> . 2026;16:81-94.	https://aacrjournals.org/cancerdiscovery/article/16/1/81/771236/Sevabertinib-a-Reversible-HER2-Inhibitor-with
Smit EF, Nakagawa K, Nagasaka M, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung01. <i>J Clin Oncol</i> . 2020;38(suppl 15):9504.	https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.9504
Tan DSW, Goh B-C, Li L, et al. 973MO Phase I/II SOHO-01 study of sevabertinib (BAY 2927088) in HER2-mutant non-small cell lung cancer (NSCLC): Safety and efficacy in Asian patients. <i>Ann Oncol</i> . 2025;36(suppl 4):S2109-S2110.	https://www.annalsofoncology.org/article/S0923-7534(25)05634-0/abstract
U.S. Food & Drug Administration. FDA grants accelerated approval to sevabertinib for non-squamous non-small cell lung cancer. November 19, 2025.	https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sevabertinib-non-squamous-non-small-cell-lung-cancer
U.S. Food & Drug Administration. FDA grants accelerated approval to zongertinib for non-squamous NSCLC with HER2 TKD activating mutations. August 8, 2025.	https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zongertinib-non-squamous-nsclc-her2-tkd-activating-mutations
U.S. Food and Drug Administration. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer. August 11, 2022.	https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-her2-mutant-non-small-cell-lung

U.S. Food and Drug Administration. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors. April 05, 2024.	https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2
U.S. Food and Drug Administration. FDA grants accelerated approval to zongertinib for unresectable or metastatic non-squamous non-small cell lung cancer. February 26, 2026.	https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zongertinib-unresectable-or-metastatic-non-squamous-non-small-cell
Vokes NI, Pan K, Le X. Efficacy of immunotherapy in oncogene-driven non-small-cell lung cancer. <i>Ther Adv Med Oncol</i> . 2023;15:17588359231161409.	https://journals.sagepub.com/doi/10.1177/17588359231161409
Wilding B, Woelflingseder L, Baum A, et al. Zongertinib (BI 1810631), an irreversible HER2 TKI, Spares EGFR signaling and improves therapeutic response in preclinical models and patients with HER2-driven cancers. <i>Cancer Discov</i> . 2025;15:119-138.	https://aacrjournals.org/cancerdiscovery/article/15/1/119/750858/Zongertinib-BI-1810631-an-Irreversible-HER2-TKI
Zongertinib (Hernexeos®). Prescribing information. Boehringer Ingelheim; 2026.	https://pro.boehringer-ingelheim.com/us/products/hernexeos/bipdf/hernexeos-prescribing-information

Emerging HER2-Targeting Agents

Resource	Address
Le X, Piotrowska Z, Spira AI, et al. NVL-330, a selective HER2 tyrosine kinase inhibitor, in patients with advanced or metastatic HER2-altered non-small cell lung cancer: The phase 1 HEROEX-1 study. <i>J Clin Oncol</i> . 2025;43(16_suppl):TPS8665.	https://ascopubs.org/doi/10.1200/JCO.2025.43.16_suppl.TPS8665
Le X. NVL-330, a selective HER2 tyrosine kinase inhibitor, in patients with advanced or metastatic HER2-altered non-small cell lung cancer: The phase 1 HEROEX-1 study. <i>Amer Soc Clin Oncol</i> . 2025; Poster 136A.	https://www.asco.org/abstracts-presentations/252565/poster
Sun Y, Andrews KL, Tangpeerachaikul A, et al. Abstract B057: Preclinical intracranial activity of NVL-330, a selective HER2 tyrosine kinase inhibitor. <i>Mol Cancer Ther</i> . 2025;24(10_suppl): B057.	https://aacrjournals.org/mct/article/24/10_Supplement/B057/766455/Abstract-B057-Preclinical-intracranial-activity-of

All URLs Accessed April 23, 2026