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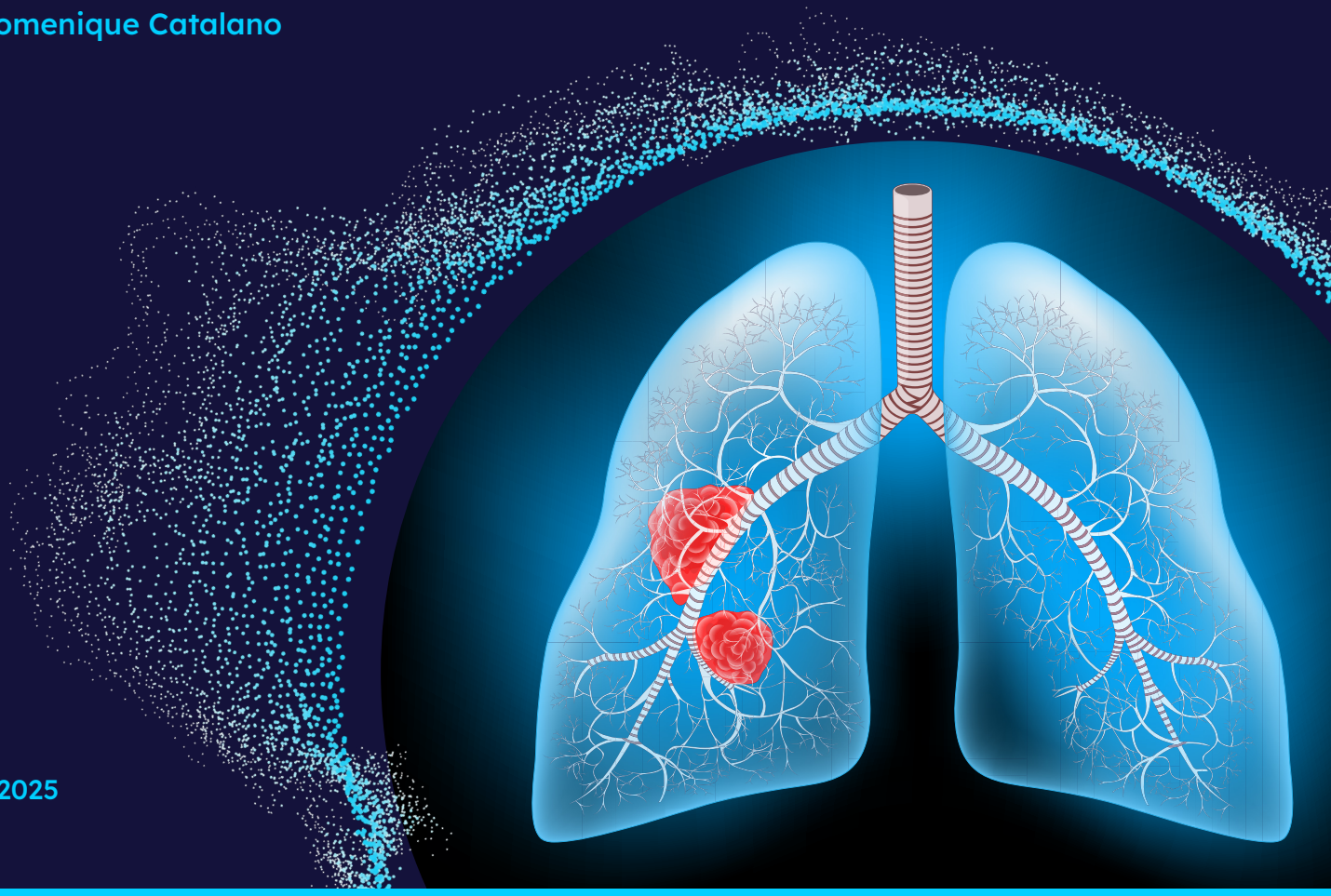
White Paper

Targeting HER3 in EGFR TKI-resistant EGFR-mutated Non-Small Cell Lung Cancer (NSCLC)

By Domenique Catalano



April 2025

The unmet need in EGFR-mutated NSCLC progressing on osimertinib and platinum-based chemotherapy

Effective treatment options are lacking for EGFR-mutated NSCLC patients who have progressed on standard-of-care, first-line osimertinib (marketed as Tagrisso, third-generation EGFR tyrosine kinase inhibitor) and platinum-based chemotherapy. The ability of HER3 to heterodimerize with multiple partners, such as EGFR, HER, MET and PI3K, makes this target a key player in acquired resistance against targeted therapies.[1]

In NSCLC, HER3 overexpression is known to enhance tumor proliferation, impacting resistance to EGFR tyrosine kinase inhibitors (TKIs).[1] Though its weak intracellular tyrosine kinase activity makes HER3 a challenging target for drug development, recent technological advancements like antibody-drug conjugates (ADCs) and bispecific antibodies (bsAbs) have improved HER3's targetability and pharmacological potential. Hence, targeting HER3 may be a valuable tool in this unmet NSCLC patient population.

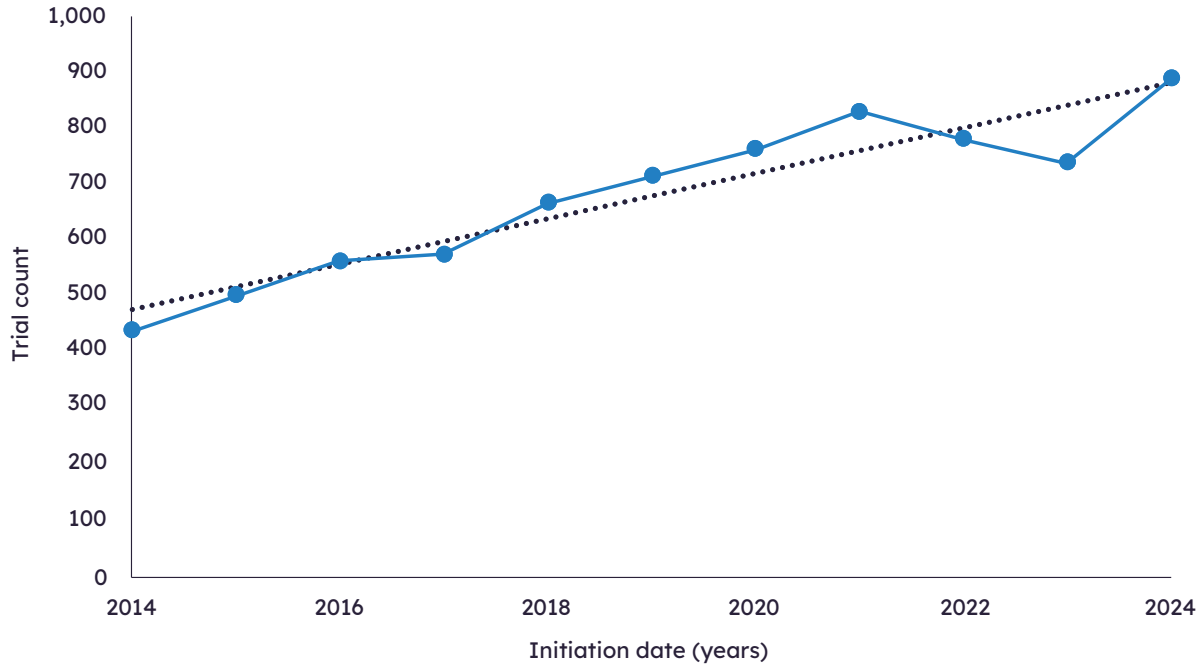
To date, multiple ADC and bsAb HER3-targeted therapies are in clinical development, and as of December 2024, the US FDA approved its first HER3-targeted antibody, zenocutuzumab (marketed as Bizengri, HER2/HER3 bsAb), for adults with NSCLC or pancreatic ductal adenocarcinoma (PDAC) harboring an NRG1 gene fusion with disease progression on or after prior systemic therapy.[2] This approval marks a significant advancement for HER3 as a target and bsAbs as a drug class, making this the 14th bsAb approved by the FDA. As a handful of companies make brisk progression in this field, zenocutuzumab's approval paves the way for more HER3-targeted therapies to support the evolving landscape for HER3 treatments.

This analysis dives into the emerging HER3-targeted drugs and studies for EGFR-mutated NSCLC patients who have progressed on prior treatment with osimertinib/EGFR TKIs and platinum-based chemotherapies.

Prevalence of NSCLC and EGFR mutations in NSCLC

According to the World Health Organization (WHO), lung cancer is the leading cause of global cancer incidence and cancer-related deaths worldwide, accounting for the highest mortality rates in men and women.[3] As depicted in Citeline's Datamonitor Healthcare NSCLC Epidemiology Report, 508,039 newly diagnosed NSCLC cases were estimated across the US, Japan, France, Germany, Italy, Spain, and the UK in 2024, with 183,096 of those cases in the US. By 2042, Citeline forecasts the number of NSCLC diagnosed incident cases will increase by 33% to 244,253 new cases in the US alone and by 22% to 618,618 across the seven major markets, including the US, Japan and 5EU. Despite rapid advancements, many NSCLC patients face poor prognoses, mainly due to lack of effective treatment options for certain genetic mutations or resistance to available therapies. The lack of effective therapies in the second-line NSCLC space is a huge unmet need, as evidenced by the growing number of NSCLC trials across all lines of therapy in the last 10 years, as shown in Figure 1.

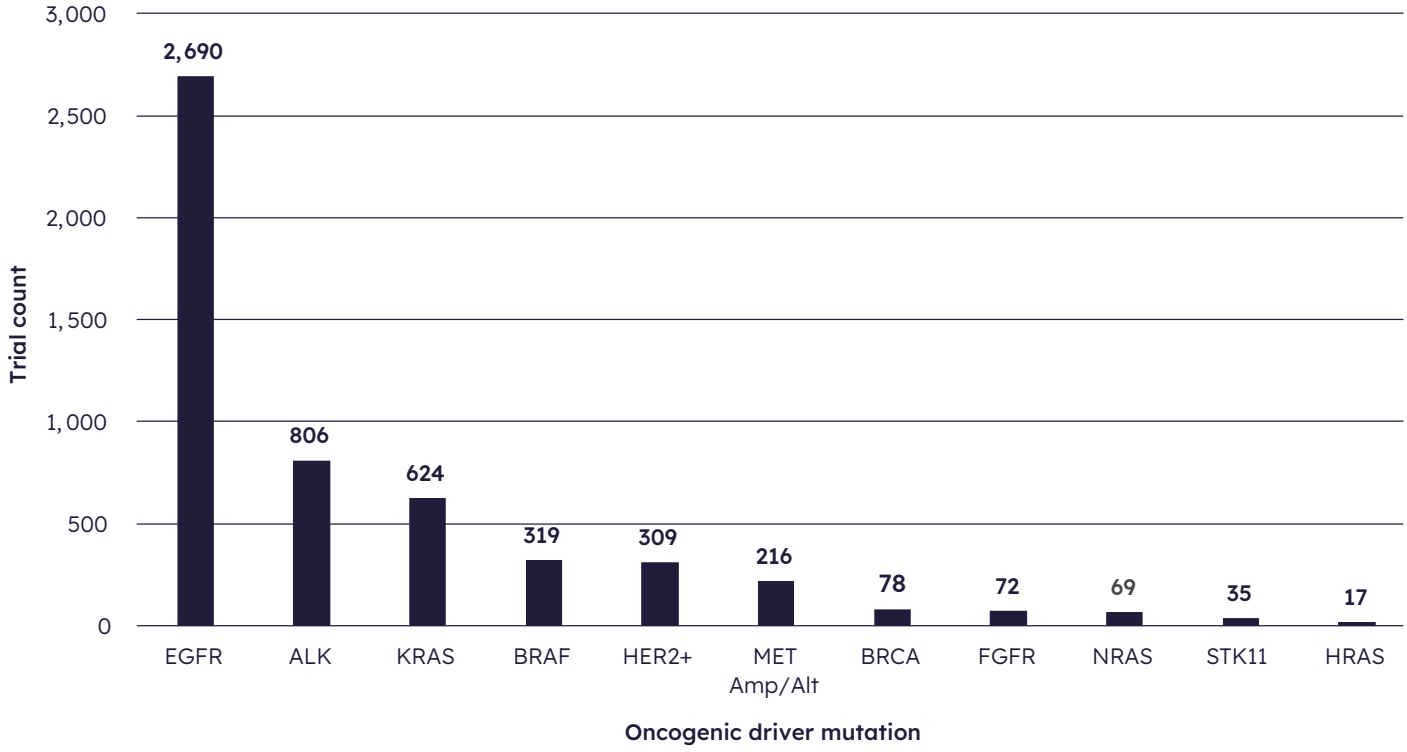
Figure 1. Growth of NSCLC trials by initiation date, 2014–2024



Source: Trialtrove, February 2025

Figure 2 shows that EGFR mutations are the most prevalent oncogenic driver mutation in NSCLC patients, where 14% to 38% of NSCLC patients are diagnosed with EGFR mutations.[4] EGFR mutations are more prevalent in Asian and Caucasian populations, with EGFR exon 19 deletions or exon 21 L858R point mutations comprising approximately 90% of all EGFR mutations.[4] EGFR's prevalence defines it as a significant driver gene in this type of lung cancer.

Figure 2. Trials by NSCLC oncogenic driver mutation



Source: Trialtrove, February 2025

Current standard-of-care in EGFR-mutated NSCLC

EGFR TKIs altered the treatment landscape for advanced EGFR-mutated NSCLC patients. While first- or second-generation EGFR TKIs like afatinib (Gilotrif), erlotinib (Tarceva), and gefitinib (Iressa) are approved as first-line therapy and have been clinically shown to improve median progression-free survival, many patients develop resistance. The two most common resistance mutations are EGFR exon 20 insertion and p.T790M mutations. Third-generation EGFR TKIs were developed to tackle this resistance and have been approved worldwide.

In 2024, amivantamab (marketed as Rybrevant, EGFRxc-MET bsAb) in combination with lazertinib (marketed as Lazcluze, third-generation EGFR TKI) was approved in the US and Europe as first-line treatment for EGFR-mutated (exon 19 deletions or L858R substitution mutations) based on the Phase III MARIPOSA trial, and is now a category 1 recommended treatment per the NCCN Guidelines Version 3.2025, thereby providing stiff competition to Tagrisso.[5] While amivantamab and mobocertinib (marketed as Exkivity, EGFR TKI) received approvals for the treatment of metastatic NSCLC patients whose tumors harbor an EGFR exon 20 insertion mutation, a patient population where there were previously no approved targeted therapies, mobocertinib has since been withdrawn from the market, leaving amivantamab with full ownership of the EGFR exon 20-positive market, a rare market with restricted commercial opportunities.

Due to its superior efficacy as demonstrated in the Phase III FLAURA trial, osimertinib remains the standard-of-care as the preferred treatment for NSCLC patients whose tumors harbor activating EGFR mutations (exon 19 deletion or L858R point mutation). However, resistant mechanisms to osimertinib are quite diverse. Disease progression following treatment with third-generation EGFR TKIs remains inevitable, and managing resistance is a struggle. While amivantamab plus chemotherapy is a category 1 recommended treatment in NSCLC patients with EGFR exon 19 deletions or exon 21 L858R mutations who experienced disease progression after treatment with osimertinib, patients still progress on treatment.[5]

Post-EGFR TKI, platinum-based doublet chemotherapy is the recommended regimen with a median progression-free survival of 5 months, but beyond platinum doublets, subsequent treatment options offer low response rates in the real-world setting, which are around 14% to 15% and progression-free survival of approximately 3 months.[6] For patients with EGFR-mutated locally advanced or metastatic NSCLC whose disease progressed on or after osimertinib and platinum-based chemotherapy, no uniformly accepted standard-of-care exists. Thus, there is a great need for developing effective therapies following osimertinib and chemotherapy in EGFR-mutated NSCLC.

Drug and trial landscape for targeting HER3 in EGFR-mutated NSCLC

The HER family consists of receptors including EGFR, HER2, HER3, and HER4, all of which play a crucial role in cell regulation. Specifically, HER3 signaling acts as a critical regulator to cell growth, proliferation, and survival through interaction with other receptor tyrosine kinases, like EGFR or HER2. HER3's ability to heterodimerize with HER partners and non-HER partners activate a downstream signaling cascade particularly in the PI3K/AKT pathway, leading to significant impacts on cancer cell behavior when overexpressed.[7] Although HER3 exudes weak intracellular tyrosine kinase activity, its ability to heterodimerize with other receptors has gained significant attention.

HER3's role in EGFR TKI resistance has become increasingly evident, as HER3 overexpression is more prevalent in EGFR TKI-resistant patients. Approximately 83% of primary NSCLC tumors and 90% of advanced EGFR-mutated tumors express HER3 after prior EGFR TKI treatment.[8] HER3 is associated with poor treatment outcomes, including reduced survival. Because activation and upregulation of HER3 can lead to resistance to EGFR therapies, HER3 is an attractive therapeutic target, and embracing HER3 as a targeted agent represents a transformative approach to treating EGFR TKI resistance. Table 1 provides a high-level overview of the prominent HER3-targeted therapies in active development for EGFR TKI -resistant, EGFR-mutated NSCLC.

Table 1. Key HER3-targeted agents in active development for EGFR TKI-resistant EGFR-mutated NSCLC

Drug name	Most advanced status in EGFR TKI resistant EGFRm NSCLC	Drug type	Trial location	Company
AMT-562	Phase I	anti-HER3 ADC	Australia	Multitude Therapeutics
YL-202	Phase I	anti-HER3 ADC	USA and China	MediLink Therapeutics (Suzhou) Co., Ltd.
JSKN-016	Phase II	HER3xTROP2 bispecific ADC	China	Alphamab Oncology
DB-1310	Phase I/II	anti-HER3 ADC	USA and China	Duality Biologics
BL-B01D1	Phase III	EGFRxHER3 bispecific ADC	China	Sichuan Biokin Pharmaceutical
Izalontamab	Phase II/III	EGFRxHER3 bsAb	China	Sichuan Biokin Pharmaceutical
SHR-A2009	Phase III	anti-HER3 ADC	China	Jiangsu Hengrui Pharmaceuticals
Patritumab deruxtecan	Pre-registration	anti-HER3 ADC	Global	Daiichi Sankyo in collaboration with Merck & Co.

Source: Pharmaprojects and Trialtrove, February 2025

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A promising therapy is underway with Daiichi Sankyo's patritumab deruxtecan (HER3-DXd) in collaboration with Merck & Co. This innovative HER3-directed ADC was granted US FDA breakthrough therapy designation in December 2021 based on Phase I trial results in patients with EGFR-mutated NSCLC progressing on or after treatment with a third-generation TKI and platinum-based therapies.[9] Following the drug's further evaluation in the pivotal Phase II HERTHENA-Lung01 study, and based on positive data presented at the IASLC 2023 World Conference on Lung Cancer and simultaneously published in the New England Journal of Medicine, the FDA accepted the Biologics License Application (BLA) for patritumab deruxtecan and granted priority review with a PDUFA target date of June 26, 2024.[9] Due to a third-party manufacturing facility issue, the FDA issued a Complete Response Letter (CRL) on the PDUFA date, temporarily denying approval of the drug.[8]

While both companies work closely with the FDA and the third-party manufacturer, patritumab deruxtecan is being evaluated as monotherapy and in combination with other therapies in trials globally. Most notably, the Phase III HERTHENA-Lung02 of patritumab deruxtecan versus platinum-based chemotherapy in EGFR-mutated NSCLC progressing on or after third-generation EGFR TKI met its primary endpoint of improved progression-free survival in September 2024, where results will be presented at a later date and shared with global authorities. Two Phase I trials are ongoing: a study evaluating patritumab deruxtecan plus osimertinib in EGFR-mutated NSCLC in the first- or second-line setting, specifically in patients progressing on prior osimertinib, and a separate study of patritumab deruxtecan in EGFR-mutated NSCLC patients with disease progression during or after EGFR TKI therapy. Both studies aim to better understand the role of HER3-DXd in potential treatment strategies.

In China, Sichuan Baili Pharmaceutical, in collaboration with SystImmune (both subsidiaries of Sichuan Biokin Pharmaceutical), evaluated BL-B01D1 in the first-in-human Phase Ia/Ib BL-B01D1-101 study in solid tumors. The cohort of EGFR-mutated NSCLC patients showed a remarkable efficacy profile and response rates that exceeded current standard-of-care, where approximately 92% of patients received prior TKI treatment. Trial results were presented at ESMO 2023, and the drug received breakthrough therapy designation in September 2024 by China's Center for Drug Evaluation (CDE) for patients with locally advanced or metastatic, non-squamous, EGFR-sensitive NSCLC, who failed prior EGFR TKI treatment.[10] Sichuan Baili-Bio/Baili Pharmaceutical (subsidiaries of Sichuan Biokin Pharmaceutical) are advancing development of this EGFRxHER3 bispecific ADC in the Phase III BL-B01D1-301 study in China. The trial is ongoing and aims to evaluate the efficacy and safety of BL-B01D1 as compared to platinum-based chemotherapy in locally advanced or metastatic non-squamous NSCLC with EGFR-sensitive mutations after EGFR TKI failure.

Sichuan Baili Pharmaceutical is also evaluating izalontamab (SI-B001) in combination with osimertinib in a Phase II/III China trial for NSCLC patients that varies by cohort. Cohort A is evaluating patients with progression on a third-generation EGFR TKI; cohort B is evaluating patients with tumors that are negative for EGFR T790M with progression on any EGFR TKI; cohort C is evaluating patients with EGFR exon 20 insertion mutations.

In Asian countries, including China, Japan, and South Korea, Jiangsu Hengrui Pharmaceuticals is conducting early and late-phase clinical trials evaluating SHR-A2009. Interim results from the first-in-human, Phase I SHR-A2009-I-101 solid tumor trial in China demonstrated promising anti-tumor activity and a tolerable safety profile in EGFR-mutated NSCLC patients progressing on prior EGFR TKI treatment.[11] This drug has now reached Phase III status where study SHR-A2009-301 is actively enrolling patients in China. This is a comparative trial of SHR-A2009 against platinum-based dual-agent chemotherapy in EGFR-mutated NSCLC particularly in patients who failed previous EGFR TKI treatment.

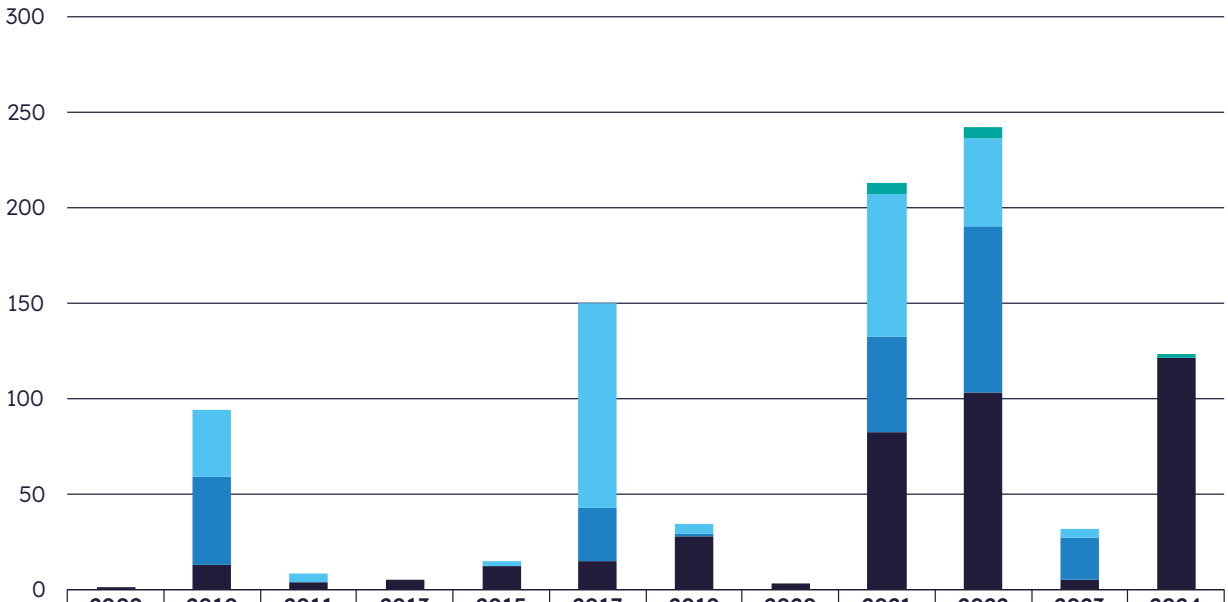
Multiple Phase I and II trials are planned or ongoing, evaluating HER3-targeted therapies in EGFR-mutated NSCLC patients progressing on prior EGFR treatment. Most notable are Duality Biologics' DB-1310 (Phase I/II in the US and China), MediLink Therapeutics (Suzhou)'s YL-202 (Phase I in the US and China), and Alphamab Oncology's JSKN-016 (Phase I and II in China). Multitude Therapeutics' AMT-562 is being evaluated in a Phase I advanced solid tumor trial in Australia that is also enrolling patients with EGFR TKI-resistant NSCLC.

The global distribution of trial sites

Since 2009, 31 clinical trials in second-line or greater NSCLC have evaluated pipeline drugs targeting HER3. The regional distribution of organizations has shifted significantly over this 16-year period.

Figure 3 illustrates that North America had the highest total number of sites for trials that began in the 2010–2019 period with the US being the single nation with the most in that timeframe. In the last five years, Asia has become the region with the highest number of participating sites and China has surpassed the US to take the lead on the global level. European sites held their presence throughout this period, with a growth spurt in 2021-2022, then subsided in the post-pandemic era.

Figure 3. Number of trial sites by region for studies evaluating unapproved HER3 agents in second-line or greater NSCLC



	2009	2010	2011	2013	2015	2017	2019	2020	2021	2022	2023	2024
Oceania	0	0	0	0	0	0	0	0	6	6	0	2
North America	0	35	4	0	3	107	5	0	75	46	5	0
Europe	0	46	0	0	0	28	1	0	50	87	22	0
Asia	1	13	4	5	12	15	28	3	82	103	5	121

Trial years are based on trial initiation start dates. Trials without a disclosed start date are excluded.
Organization (trial site) counts are based on identified sites in Sitetrove.

Source: Sitetrove, March 2025

Table 2 shows the number of organizations per country participating in ongoing clinical trials evaluating unapproved HER3 agents in second-line or greater NSCLC. China alone accounts for 46% of sites followed by the US at 27%. It is likely that more of the future approvals may originate in these countries.

Table 2. Count of ongoing trials per country evaluating unapproved HER3-targeted treatments for second-line or greater EGFR-mutated NSCLC

Organization country	Organization count per country
China	103
United States	61
Spain	21
Japan	12
France	8
Taiwan	6
Republic of Korea	5
Austria	3
Italy	2
Australia	2
Netherlands	1

Source: Sitetrove, March 2025

The future is bright for HER3-targeted agents

Although EGFR TKIs mark a transformative approach in NSCLC treatment, resistance remains a significant challenge. Complex resistance mechanisms involving HER3 and its heterodimers are crucial in developing novel therapeutic strategies. Although advanced R&D of HER3-targeted therapies is ongoing, challenges follow suit. HER3 has structural similarities to other HER receptors, which in turn can create specificity issues. Additionally, HER3-targeted therapies have the potential to inadvertently impact other receptors, ultimately reducing efficacy or creating unexpected complications.

Similar to other mutations, secondary resistance to treatment can also be a hurdle. HER3-targeted therapies in combination with EGFR TKIs are gaining attention for treating EGFR TKI resistance, with ongoing trials evaluating HER3-targeted agents in combination with osimertinib. Another promising approach targets HER3 inhibitors with other treatment modalities, notably immunotherapies, which could enhance the body's immune response to recognize and eliminate cancer cells.

As with any drug, finding the balance between treatment efficacy and patient safety is crucial, and the emphasis on designing next-generation HER3 agents that optimize specificity and efficacy remains the defining pursuit in this research area. Through the process of trials and predictive biomarker analysis, the potential of HER3 targeting in NSCLC fosters a revived hope for overcoming EGFR TKI resistance.

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About the Author

Domenique Catalano is an Oncology Trialtrove Analyst involved in various data enhancements and projects supporting the Ask the Analyst service. She engages in trial landscape analyses and expert subject matter queries in oncology. With extensive primary and secondary research experience in the clinical trial and pharmaceutical industry, Domenique joined Trialtrove in 2023. A graduate of West Chester University in Pennsylvania, Domenique completed a dual major with a BS in both chemistry (pharmaceutical product development) and biology (cell & molecular concentration) and attained her MBA in 2023.

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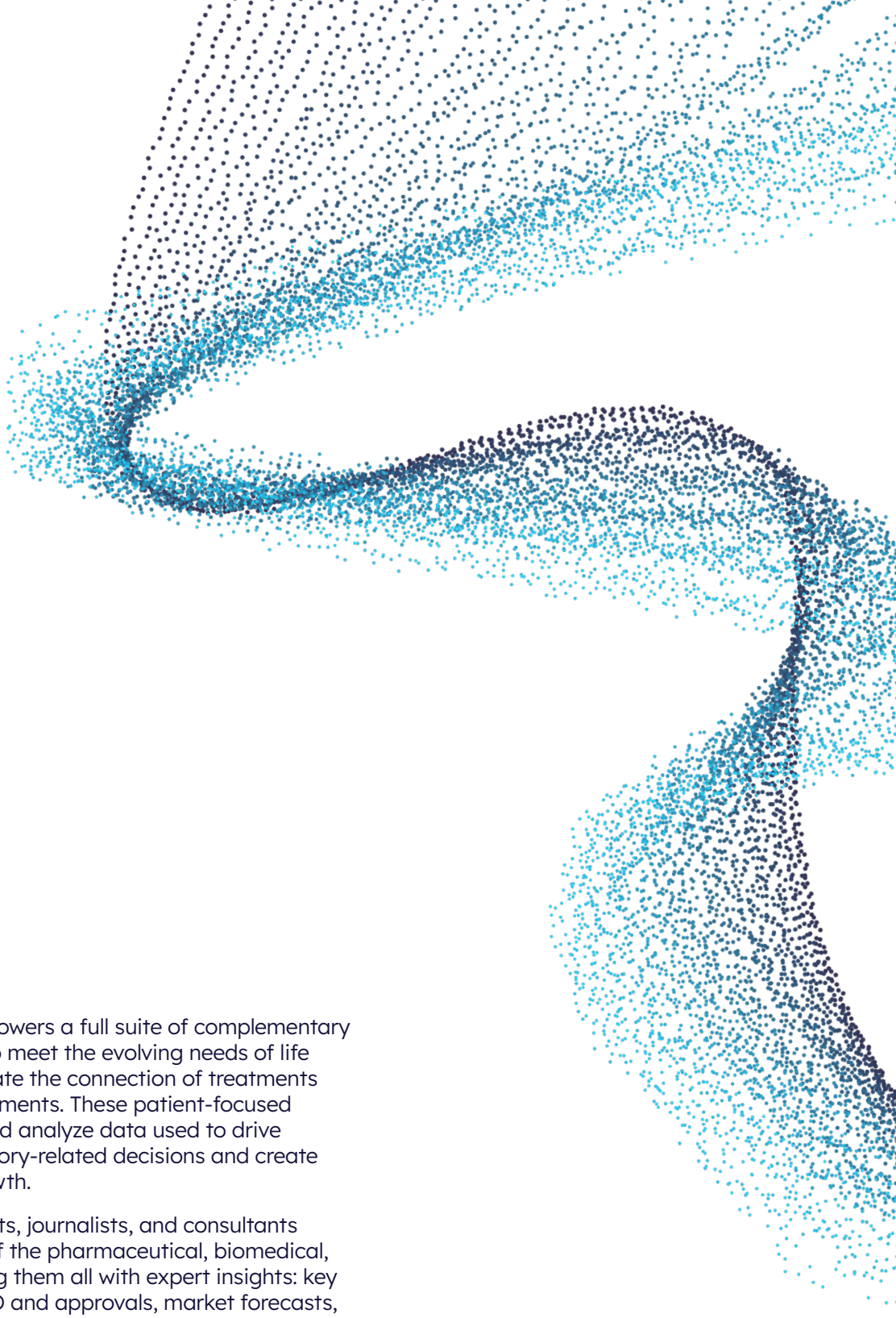

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