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EDITORIAL

Tomić and Vranić: NSCLC: New FDA approvals in 2025

A remarkable year for NSCLC: Seven new FDA approvals in 2025 across molecular targets

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Non–small cell lung cancer (NSCLC) remains the leading cause of cancer-related morbidity and mortality worldwide. Nevertheless, the past two decades have been marked by a fundamental shift in our understanding of the biology of this aggressive disease. The discovery that NSCLC may harbor an "Achilles heel" in the form of targetable *EGFR* mutations effectively treated with tyrosine kinase inhibitors (TKI) marked the beginning of the era of precision oncology in lung cancer and led to dramatic improvements in clinical outcomes. In 2025, we are witnessing the full impact of this transformation through seven new approvals by the U.S. Food and Drug Administration (FDA) for personalized, biomarker-driven targeted therapies in NSCLC (Figure 1). All these approvals are biomarker-driven and based on specific genomic alterations (Figure 1).

The first approval in May 2025 is related to cMET, a receptor with tyrosine kinase activity that belongs to the MET (Met proto-oncogene) family (1). The approved drug is telisotuzumab vedotin, a MET-directed antibody–drug conjugate (ADC), indicated for patients with stage IV non-squamous NSCLC whose tumors show strong cMET protein overexpression by immunohistochemistry (IHC 3+ in ≥50% of tumor cells) following prior systemic therapy (2). This decision further expands the ADC landscape in NSCLC, reinforcing their role as a viable therapeutic class within biomarker-driven targeted therapy. FDA approval was based on results from the phase II LUMINOSITY study, which demonstrated clinically meaningful objective response rates (ORR) and durable responses (3). This approval underscores the clinical value of the ADC approach, which enables precise delivery of cytotoxic payloads directly to tumor cells, thereby improving efficacy while maintaining an acceptable safety profile. Importantly, telisotuzumab vedotin redefines the diagnostic algorithm for MET-altered NSCLC: in addition to next-generation sequencing (NGS) for *MET* exon 14 skipping mutations and fluorescence in situ hybridization (FISH) for *MET* amplification, IHC assessment of cMET protein overexpression has emerged as a critical biomarker for patient selection.

Further expansion of ADCs in NSCLC targeted therapy is illustrated by the second FDA approval related to the trophoblast cell-surface antigen-2 (TROP-2). TROP-2 expression was initially described in normal tissues (e.g., trophoblasts and fetal tissues), but subsequently, its overexpression has been demonstrated in various cancers (4). The TROP–2–directed datopotamab deruxtecan (Dato-DXd) was

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approved for patients with metastatic EGFR-mutated NSCLC who have previously received EGFR-directed therapy and platinum-based chemotherapy (5). In the TROPION-Lung 05 (phase II)/TROPION-Lung 01 (phase III) studies, Dato-DXd demonstrated clinically meaningful ORR and median duration of response (mDoR) (6,7). However, key questions remain regarding the optimal biomarker (TROP-2 testing by IHC) for Dato-DXd and its ideal placement within the treatment sequence for EGFR-mutant NSCLC. This uncertainty is particularly relevant in light of phase III data showing that first-line combinations of osimertinib plus chemotherapy, or the EGFR-MET bispecific antibody amivantamab combined with the third-generation EGFR inhibitor lazertinib, are superior to osimertinib monotherapy, further complicating therapeutic sequencing decisions. As these combination strategies move earlier in the treatment course, attention has shifted toward optimizing drug delivery without compromising efficacy. In this context, subcutaneous amivantamab, administered in combination with oral lazertinib, a third-generation EGFR TKI, has received FDA approval based on the phase III PALOMA study, which demonstrated non-inferior efficacy and a safety profile comparable to intravenous amivantamab combined with lazertinib (8,9). The subcutaneous formulation was approved across all indications previously granted for the intravenous formulation. In parallel, for the rarer but clinically challenging *EGFR* exon 20 insertion mutations, sunvozertinib has emerged as a newly FDA-approved therapeutic option (10). Based on the phase II WU-KONG1B study, sunvozertinib demonstrated clinically meaningful and durable responses after progression on platinum-based chemotherapy, regardless of prior amivantamab exposure (11).

The remaining three FDA approvals in 2025 involve TKI: one targeting ROS1-rearranged NSCLC and two directed at HER2-altered NSCLC (12–14). Rearrangements of c-ros oncogene 1 (ROS1) are rare and occur in approximately 1–2% of lung adenocarcinomas and are characterized by marked sensitivity to ROS1 inhibitors (15,16). Based on results from the phase II TRUST-I and TRUST-II studies, taletrectinib was approved for both treatment-naïve and previously treated patients (17,18). Given its high ORR, central nervous system activity, prolonged PFS, and activity against acquired resistance mutations, taletrectinib, along with repotrectinib, is currently considered a preferred first-line option over entrectinib or crizotinib (19).

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The choice between taletrectinib and repotrectinib remains a clinical decision in the absence of head-to-head comparative trials.

HER2-targeted therapy has already transformed the management of HER2-positive breast cancer; however, its application in NSCLC has proven more complex due to pronounced biological heterogeneity. In this setting, *HER2 (ERBB2)* amplification, mutation, and HER2 protein overexpression represent distinct and variably prevalent alterations, complicating patient selection and therapeutic positioning. Unlike breast and gastric/gastroesophageal junction cancers, anti-HER2 therapy in metastatic NSCLC is currently approved in the second-line setting. Following progression on prior systemic therapy, the FDA has approved three therapeutic options for HER2-mutant NSCLC: the ADC fam-trastuzumab deruxtecan (T-DXd) based on the phase II DESTINY-Lung01 study, and two TKIs with robust efficacy-zongertinib (Beamion LUNG-1) and sevabertinib (SOHO-1)(20,21). In contrast to zongertinib and sevabertinib, which require molecular confirmation of HER2 mutations, T-DXd occupies a unique position as the first tumor-agnostic HER2-directed therapy for previously treated patients with metastatic HER2 IHC3+ solid tumors, including NSCLC, even in the absence of *HER2 (ERBB2)* mutation status (22,23).

Collectively, these seven FDA approvals in 2025 signal the full maturation of precision oncology in NSCLC, transforming therapeutic decision-making from a one-size-fits-all approach to a strategy defined by molecular biology, molecular profiling (sequencing), and clinical context. The challenge lies in translating these therapeutic advances into treatments that are accessible and implementable globally.

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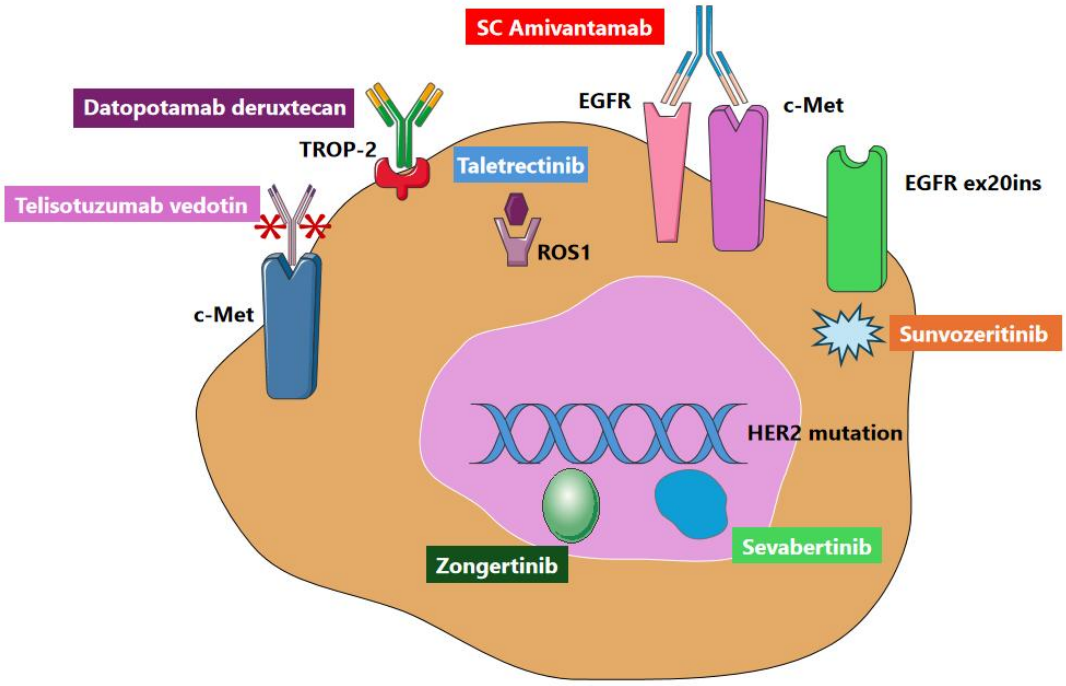

Figure 1. Molecular targets and corresponding FDA-approved targeted therapies in NSCLC. The figure illustrates oncogenic drivers in NSCLC and seven recently FDA-approved agents, including antibody–drug conjugates, bispecific antibodies, and tyrosine kinase inhibitors. Together, the figure highlights the molecular heterogeneity of NSCLC and the expanding landscape of biomarker-driven targeted therapies. Abbreviations: FDA: Food and Drug Administration; NSCLC: Non-small cell lung cancer; SC: Subcutaneous; c-Met: Mesenchymal–epithelial transition factor; TROP-2: Trophoblast cell-surface antigen 2; EGFR: Epidermal growth factor receptor; EGFR ex20ins: EGFR exon 20 insertion mutation; HER2: Human epidermal growth factor receptor 2; ROS: ROS proto-oncogene 1. *Image adapted from Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).*

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