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Telisotuzumab vedotin: The first-in-class c-Met-targeted antibody-drug conjugate granted FDA accelerated approval for treatment of non-squamous non-small cell lung cancer (NSCLC)

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SUMMARY: Telisotuzumab vedotin represents a clinically important antibody-drug conjugate (ADC) that received accelerated approval from the US Food and Drug Administration in May 2025, establishing it as the first-in-class targeted therapy for adult patients with immunohistochemistry (IHC)-confirmed high-c-Met, EGFR wild-type, locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC). Its mechanism of action relies on precise targeting of the c-Met protein receptor, followed by internalization and release of the potent cytotoxic payload monomethyl auristatin E (MMAE) to eradicate tumor cells. The pivotal phase II LUMINOSITY trial demonstrated that the high c-Met overexpressing group had an overall response rate (ORR) of 34.6%. This therapeutic agent addresses a critical unmet need within a molecularly defined NSCLC subpopulation, marking a substantial advancement in c-Met-targeted oncology. The regulatory authorization and clinical use of telisotuzumab vedotin may significantly advance precision medicine for NSCLC, though an ongoing phase III trial will further confirm its efficacy and safety and determine its eligibility for full regulatory approval in the future.

Keywords: MET, lung cancer, NSCLC, Teliso-V

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and represents one of the leading causes of cancer-related mortality worldwide (*1*). Based on its histopathological characteristics, NSCLC is primarily classified into three major subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma constitutes the most prevalent subtype, representing approximately 40% of NSCLC cases, followed by squamous cell carcinoma (25-30%), and large cell carcinoma (10-15%) (*2*). The development of targeted therapies for NSCLC stands as a paradigm of precision oncology in solid tumors. From epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors to breakthrough agents against emerging targets such as human epidermal growth factor receptor 2 (HER2) and Kirsten rat sarcoma viral oncogene homologue (KRAS), NSCLC treatment has entered an era of molecularly guided precision therapy (*3,4*). While significant advances have been made in targeted therapies for NSCLC, acquired resistance to targeted agents remains a critical challenge in clinical practice, substantially hampering further improvements in therapeutic efficacy. The development of novel-targeting agents holds promise for enhancing patient outcomes.

On May 14, 2025, the US Food and Drug Administration (FDA) granted accelerated approval to telisotuzumab vedotin (Emrelis) for the treatment of patients with locally advanced or metastatic non-squamous NSCLC exhibiting high c-Met protein expression (defined as strong staining in ≥ 50% of tumor cells) who have experienced disease progression following a prior systemic therapy (*5*). Concurrently, the FDA approved the VENTANA MET (SP44) RxDx assay as a companion diagnostic tool to identify patients with high c-Met tumors eligible for this therapy. Telisotuzumab vedotin is a tripartite antibody-drug conjugate consisting of: (*i*) A humanized immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that specifically binds to the c-Met receptor on tumor cell surfaces; (*ii*) A protease-cleavable valine-citrulline linker tethering the antibody to the cytotoxic payload; and (*iii*) The microtubule-inhibiting agent monomethyl auristatin E (MMAE), which induces tumor cell apoptosis through inhibition of microtubule polymerization (*6*). Following binding to c-Met-overexpressing tumor cells and subsequent internalization, telisotuzumab vedotin releases MMAE,

enabling targeted cytotoxicity against actively dividing cancer cells while minimizing toxicity to normal tissues. As the first and currently only FDA-approved antibody-drug conjugate specifically indicated for high c-Met NSCLC, this agent addresses a significant therapeutic gap in this molecularly defined patient population.

The accelerated approval of telisotuzumab vedotin was based on findings from the LUMINOSITY trial (NCT03539536) (*7*). This multicenter, open-label, multi-cohort phase 2 clinical trial evaluated the therapeutic efficacy of telisotuzumab vedotin in the treatment of non-squamous EGFR wild-type NSCLC with c-Met overexpression (≥ 25% of tumor cells with 3+ staining, with high expression defined as ≥ 50% of tumor cells with 3+ staining and moderate expression defined as 25-50% of tumor cells with 3+ staining). Participants received telisotuzumab vedotin at a dose of 1.9 mg/kg *via* intravenous infusion every two weeks until disease progression or unacceptable toxicity. A total of 78 patients in the high c-Met expressing group were included in the efficacy analysis. The primary endpoint, the overall response rate (ORR), was 34.6%, and the secondary endpoints were as follows: the disease control rate (DCR) was 60.3%, the median duration of response (DOR) was 9.0 months, median progression-free survival (PFS) was 5.5 months, and median overall survival (OS) was 14.6 months (*7*). In the moderate c-Met expression group, 83 patients were included in the efficacy analysis. The primary endpoint, the ORR, was 22.9%, and the secondary clinical endpoints were as follows: the DCR was 57.8%, median DOR was 7.2 months, median PFS was 6.0 months, and median OS was 14.2 months (*7*). In terms of treatment-related adverse events (AEs), the most common all-grade AEs were peripheral sensory neuropathy (30%), peripheral edema (16%), and fatigue (14%); the most common grade ≥ 3 AE was peripheral sensory neuropathy (7%) (*7*).

Previously, small-molecule inhibitors targeting c-Met, such as capmatinib, tepotinib, and savolitinib, have been approved for the treatment of advanced NSCLC patients with tumors harboring *MET* exon 14 (METex14) skipping mutations. Telisotuzumab vedotin represents a first-in-class antibody-drug conjugate directed against the biomarker of c-Met protein overexpression. This agent provides a critical second-line and beyond treatment option for EGFR wild-type, high c-Met non-squamous NSCLC patients who previously lacked effective targeted therapies. As an agent with accelerated approval, its confirmatory phase III trial (TeliMET NSCLC-01, NCT04928846) is currently underway, directly comparing telisotuzumab vedotin versus docetaxel in the treatment of non-squamous, c-Met-overexpression, EGFR wild-type advanced/metastatic NSCLC, with OS and PFS as primary endpoints (*8*). The trial outcomes will determine its eligibility for full regulatory approval in the future.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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