INPLASY

INPLASY202610087

doi: 10.37766/inplasy2026.1.0087

Received: 26 January 2026

Published: 26 January 2026

The Landscape of Biomarkers in Antibody-Drug Conjugate (ADC)-Treated Non-Small Cell Lung Cancer (NSCLC): A Scoping Review Protocol

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ADMINISTRATIVE INFORMATION

Support - AstraZeneca.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202610087

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 January 2026 and was last updated on 26 January 2026.

INTRODUCTION

Review question / Objective Review Question "What biomarkers have been identified or explored in non-small cell lung cancer (NSCLC) patients treated with antibody-drug conjugates (ADCs), and how do these biomarkers correlate with treatment response, the development of treatment resistance, safety signal and patient outcomes?"

Objective
This scoping review aims to systematically map the existing evidence on biomarkers in ADC-treated NSCLC populations, including but not limited to predictive, prognostic, safety and pharmacodynamic biomarkers, and to identify gaps in the current clinical practice to guide future research.

Background Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases and remains the leading cause of cancer-related mortality worldwide, posing a significant global health burden. The treatment paradigm for advanced NSCLC has undergone a revolutionary shift over the past two decades, moving from primarily platinum-based chemotherapy to targeted therapies against driver oncogenes (e.g., EGFR, ALK, ROS1) and more recently, to immune checkpoint inhibitors (ICIs). Despite these advances, a substantial proportion of patients either have limited benefit from or eventually develop resistance to these therapies, creating a pressing need for novel and effective treatment strategies.
Antibody-drug conjugates (ADCs) have emerged as a pivotal class of biopharmaceuticals designed to redefine precision oncology. These sophisticated molecules consist of three key components: a monoclonal antibody that specifically targets a tumor-associated surface antigen, a potent cytotoxic payload, and a chemical linker that connects them. This design

allows for the targeted delivery of highly potent chemotherapeutic agents directly to cancer cells, thereby maximizing antitumor efficacy while minimizing systemic exposure and off-target toxicity—a significant limitation of conventional chemotherapy. The clinical activity of ADCs is dependent on the presence of their target antigen on tumor cells, making biomarkers the cornerstone of their development and application.

In NSCLC, several ADCs have demonstrated groundbreaking efficacy, leading to regulatory approvals and changing clinical practice. Trastuzumab deruxtecan (T-DXd), targeting HER2, has demonstrated durable anticancer activity in patients with previously treated HER2-mutant NSCLC. Datopotamab deruxtecan is a TROP2-targeting ADC that has demonstrated superior efficacy in heavily pretreated NSCLC patients in phase 3 TROPION-Lung01 study. In the HERTHENA-Lung01 study, which enrolled patients with advanced-stage EGFR-mutant NSCLC who had disease progression after EGFR TKIs and platinum-based chemotherapy, patritumab deruxtecan (HER3-DXd) demonstrated clinically meaningful and durable efficacy with an ORR and acceptable AEs. More ADCs targeting antigens such as c-MET, CEACAM5, and PTK7 are in various stages of clinical development.

The efficacy of these agents is intrinsically linked to biomarkers. Initially, biomarkers were used primarily for patient selection, exemplified by HER2 protein expression or mutation status for T-DXd. However, the role of biomarkers has rapidly expanded. They are now crucial for understanding complex and heterogeneous response patterns, primary and acquired resistance mechanisms, and the management of unique toxicities such as interstitial lung disease (ILD). Beyond the primary target antigen, biomarkers exist at multiple levels: genomic (e.g., activating mutations, amplifications), proteomic (e.g., protein expression levels by IHC), transcriptomic, and in the circulation (e.g., ctDNA). The relationship between these biomarkers and treatment outcomes is complex, dynamic, and not yet fully elucidated.

This scoping review aims to systematically map the existing evidence on biomarkers in ADC-treated NSCLC populations, including but not limited to predictive, prognostic, safety and pharmacodynamic biomarkers, and to identify gaps in the current clinical practice to guide future research.

Rationale Currently, the evidence on biomarkers for ADCs in NSCLC is fragmented across numerous individual clinical trials, cohort studies, and exploratory analyses. The clinical utility of biomarkers in ADC therapy extends beyond patient selection. For example, HER2 amplification or mutation is a known predictor of response to trastuzumab deruxtecan (T-DXd), emerging data suggest that responses may also occur in patients with lower HER2 expression. Patients with a wide range of TROP2 expression may benefit from datopotamab deruxtecan, but those with a TROP2 H-score higher than 100 had the longest PFS compared to other subgroups. Beyond predictive biomarkers, pharmacodynamic biomarkers—such as changes in circulating tumor DNA (ctDNA) or serum protein levels—may provide early insights into treatment response and emerging resistance mechanisms. Moreover, biomarkers associated with serious toxicities, such as interstitial lung disease (ILD), are critically underexplored yet essential for optimizing patient safety.

This fragmentation obscures a comprehensive understanding of which biomarkers are most clinically relevant, how they should be measured, and for which ADCs they hold predictive value. To date, the reviews on ADCs in NSCLC have typically focused on efficacy and safety outcomes with limited data on biomarker. Others have addressed biomarkers in a broader context of targeted therapy but have not comprehensively synthesized the evidence specific to ADCs.

Based on this situation, a scoping review is needed to systematically map the published ADC data to get a comprehensive picture of the current clinical research status and identify gaps in the field. In this review, we will conduct a scoping review of biomarkers in NSCLC treated with ADC over the past years, including clinical trial data published in article or presented in conferences. This review will allow for the inclusion of diverse study designs and biomarker types without restricting eligibility based on hierarchical evidence levels. Through a systematically analyzing available ADC-treated NSCLC data, covering study population, treatment regimen, clinical outcomes, safety data, and biomarker analysis, this review aim to delineate the research trends, hotspots, challenges, and underexplored areas in ADC biomarker research. It also analysis the current status of various biomarkers in predicting therapeutic efficacy, assessing prognosis, predicting safety issues, and monitoring drug resistance We hope this review can inform clinical trial design, guide biomarker-driven patient management, and identify key research priorities. Furthermore, the findings may reveal inconsistencies in biomarker definitions and assay methodologies, underscoring the need for standardization in future studies.

METHODS

Strategy of data synthesis The literature search will include publications before Nov. 1, 2025, all of which are in English. First, conduct a preliminary search in the PubMed database to identify and supplement the search terms related to the topic to ensure a comprehensive search. Secondly, search databases such as PubMed, EMBASE, Cochrane and Web of Science according to the preset search conditions. Additional searches will also be conducted on the meeting summary as it is not included in the aforementioned database. Third, screen and supplement the reference list of the determined literature. The retrieved references will be imported into the reference management web-based tool, EPPI Reviewer, to integrate references from different electronic databases and delete duplicate records.

The MeSH term used for non-small cell lung cancer is "carcinoma, non-small cell lung". To further screen out the population treated with ADC, we have added the key words of ADC drugs: immunoconjugates, antibody drug conjugate, ADC, immunoconjugate., drug antibody conjugate, conjuagte, T-Dxd, trastuzumab deruxtecan, DS-8201, Enhertu, datopotamab deruxtecan, dato-Dxd, patritumab deruxtecan, her3-dxd, sacituzumab govitecan, trodelvy, telisotuzumab vedotin, ABBV-399, SKB264, MK-2870, sac-TMT, ESG401, FDA018, BL-B01D1, tusamitamab ravtansine, RC48, A116, TDM1, DX126-262, MRG002, FS-1502, ARX788, BB-1701, SHR-A1811, A-264, MK-2870. Peer-reviewed articles published before Nov 1, 2025 were retrieved, and four English databases (PubMed, EMBASE, Cochrane and Web of Science) were searched. Non-human studies and articles on ADC treatment for non-small cell lung cancer that use keywords such as "animal" and "cell" in the title, as well as keywords such as "mouse", "rat", "rat", "rabbit", and "rabbit" in the title/abstract will be excluded.

An example of the search conducted in PubMed is as follows: ("carcinoma, non small cell lung"[MeSH Terms] OR "NSCLC"[Title/Abstract] OR "carcinoma non small cell lung"[Title/Abstract] OR "carcinomas non small cell lung"[Title/Abstract] OR "lung carcinoma non small cell"[Title/Abstract] OR "lung carcinomas non small cell"[Title/Abstract] OR "non small cell lung carcinomas"[Title/Abstract] OR "nonsmall cell lung cancer"[Title/Abstract] OR "non small cell lung carcinoma"[Title/Abstract] OR "non small cell lung carcinoma"[Title/Abstract] OR "carcinoma non small cell lung"[Title/Abstract] OR "non small cell lung cancer"[Title/Abstract]) AND ("immunoconjugates"[MeSH Terms] OR "antibody drug conjugate"[Title/Abstract] OR "ADC"[Title/Abstract] OR "immunoconjugate"[Title/Abstract] OR "drug antibody conjugate"[Title/Abstract] OR ("targed"[All Fields] AND "drug"[All Fields] AND "conjuagte"[Title/Abstract]) OR "T-Dxd"[Title/Abstract] OR "trastuzumab deruxtecan"[Title/Abstract] OR "DS-8201"[Title/Abstract] OR "Enhertu"[Title/Abstract] OR "datopotamab deruxtecan"[Title/Abstract] OR "dato-Dxd"[Title/Abstract] OR "patritumab deruxtecan"[Title/Abstract] OR "her3-dxd"[Title/Abstract] OR "sacituzumab govitecan"[Title/Abstract] OR "trodelvy"[Title/Abstract] OR "telisotuzumab vedotin"[Title/Abstract] OR "ABBV-399"[Title/Abstract] OR "SKB264"[Title/Abstract] OR "MK-2870"[Title/Abstract] OR "sac-TMT"[Title/Abstract] OR "ESG401"[Title/Abstract] OR "FDA018"[Title/Abstract] OR "BL-B01D1"[Title/Abstract] OR "tusamitamab ravtansine"[Title/Abstract] OR "RC48"[Title/Abstract] OR "A116"[Title/Abstract] OR "TDM1"[Title/Abstract] OR "DX126-262"[Title/Abstract] OR "MRG002"[Title/Abstract] OR "FS-1502"[Title/Abstract] OR "ARX788"[Title/Abstract] OR "BB-1701"[Title/Abstract] OR "SHR-A1811"[Title/Abstract] OR "SHR-A1811"[Title/Abstract] OR ("ABT"[All Fields] AND "399"[Title/Abstract]) OR "A-264"[Title/Abstract] OR "MK-2870"[Title/Abstract] OR "T-Dxd"[Title/Abstract]) AND ("biomarkers"[MeSH Terms] OR "biomarker"[Title/Abstract] OR "predictive marker"[Title/Abstract] OR "prognostic marker"[Title/Abstract] OR "molecular marker"[Title/Abstract] OR "response marker"[Title/Abstract] OR "resistance marker"[Title/Abstract] OR "HER2"[Title/Abstract] OR "ERBB2"[Title/Abstract] OR "HER3"[Title/Abstract] OR "ERBB3"[Title/Abstract] OR "TROP2"[Title/Abstract] OR "TACSTD2"[Title/Abstract] OR "CEACAM5"[Title/Abstract] OR "EGFR"[Title/Abstract] OR "MET"[Title/Abstract] OR "c-MET"[Title/Abstract] OR "PD-L1"[Title/Abstract] OR "programmed death ligand 1"[Title/Abstract] OR "FOLR1"[Title/Abstract] OR "MAGEA1"[Title/Abstract] OR "Napi2b"[Title/Abstract] OR "CD276"[Title/Abstract] OR "Nectin-4"[Title/Abstract] OR "AXL"[Title/Abstract] OR "ROR1"[Title/Abstract] OR "PTK7"[Title/Abstract] OR "CLDN6"[Title/Abstract] OR "B7-H4"[Title/Abstract] OR "5T4"[Title/Abstract] OR "MSLN"[Title/Abstract] OR "ADAM9"[Title/Abstract] OR "ITGB6"[Title/Abstract] OR "CDH3"[Title/Abstract] OR "STEAP1"[Title/Abstract] OR "sTn"[Title/Abstract] OR "MUC1"[Title/Abstract] OR "ALPP"[Title/Abstract] OR "LIV-1"[Title/Abstract] OR "IL2RA"[Title/Abstract] OR "SEZ6"[Title/Abstract] OR "CD228"[Title/Abstract] OR "ROR2"[Title/Abstract] OR "CDCP1"[Title/Abstract] OR "CD166"[Title/Abstract] OR "BSG"[Title/Abstract] OR "FGFR2b"[Title/Abstract] OR "CD30"[Title/

Abstract]) AND 0001/01/01:2025/10/31[Date - Publication].

Eligibility criteria The eligibility criteria studies will be based on the Participants, Concept, Context (PCC) framework.
Participants
Patients with non-small cell lung cancer
Inclusion Criteria
1. NSCLC patients receiving ADC treatment or research specimens derived from NSCLC patients receiving ADC treatment
2. Clinical studies or biomarker studies that meet any of the following conditions: 1) Determining enrollment eligibility based on biomarkers; 2) Having an endpoint for biomarker exploration; 3) Prognostic differences/trend of differences in subgroups distinguished by biomarkers; 4) having biomarker-related data
Exclusion Criteria
1. Reviews, systematic reviews (excluding meta-analysis)
2. Case reports, case series, editorials, guideline consensuses or expert opinions, research protocols, etc
3. Basic experimental research
Types of evidence sources
This scoping review will consider published, peer-reviewed primary clinical studies written in English. Clinical studies, such as experimental, descriptive and epidemiological study designs including randomized controlled trials, nonrandomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies, and analytical or descriptive cross-sectional studies will be considered for inclusion. Individual case reports,, review papers including systematic reviews, editorials, comment papers, text, and opinion papers are not eligible.
This proposed scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews, and will be reported according to PRISMA Extension for Scoping Reviews (PRISMA-ScR).

Source of evidence screening and selection
1. After the search is completed, all the citations will be compiled and uploaded into EPPI Reviewer. Duplicate literature records will be eliminated.
2. Two independent reviewers will then pilot test the screening process by reviewing titles and abstracts for adherence to the inclusion criteria.
3. Fifty titles/abstracts are randomly selected for the pilot screening test, and title/abstract screening will only start when 85% or higher conformance is achieved. Two independent reviewers will screen based on title/abstract, and reasons for exclusion will be recorded.
4. Two independent reviewers will thoroughly assess the full text of the selected citations against the inclusion criteria. Reasons for excluding full text records will be documented and included in the final scoping review. The pilot screening test will also be conducted during the evaluation of the full text of the selected citations, following the same process and standards as the title/abstract screening.
In the event of any disagreement between the reviewers at any stage, a third reviewer will be consulted to resolve the issue. A fourth reviewer will act as quality control during the whole evidence screening and selection phase. The complete results of the search and the study inclusion process will be reported in the final scoping review, accompanied by a PRISMA flow diagram.

Data management Data extraction will be completed using a data extraction form. The retrieved information will be cross-checked. Any disagreement will be discussed, and a third reviewer will be involved if necessary. If a study was published more than once, the most informative and complete study will be extracted. If important variables/ information is missing, attempts will be made to contact the authors of the included studies. The extracted data will include information on participants, study methods, concept, context, and key findings related to the outcome measurement relevant to the review question. General information including publication year, study design, and sample size are planned to be extracted. Patient characteristics like gender, age, confirmed diagnosis, disease stages, previous treatment history and other baseline information will be collected. Outcomes including morbidity, treatment regimen, risk factors, biomarkers and other relevant biomarker information will also be extracted. Any necessary adjustments during the data extraction process will be thoroughly explained in the comprehensive scoping review. Efforts will be made to contact authors for clarification on any missing, ambiguous, or incomplete data. Due to the nature of the scoping review, critical appraisal and bias analysis will not be performed.

Reporting results / Analysis of the evidence The PRISMA diagram will be used to illustrate the review process and delineate stages at which studies are excluded along with the relevant reasons. The charted data will be synthesized in a narrative manner, with dimensions plotted

according to the results of thematic grouping when the manuscript is discussed.

Language restriction Only articles published in English will be included in the review.

Country(ies) involved The scoping review is carried out in China.

Keywords Non-small cell lung cancer; NSCLC; antibody-drug conjugate; ADC; biomarker.

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