Efficacy and Safety of Antibody-Drug Conjugates for Lung Cancer Therapy: A Systematic Review of Randomized and Non-Randomized Clinical Trials

Abstract Number: 6ER-040

Matteo Gallina[1*], Anna Carollo[2], Anna Gallina[3], Alessio Provenzani[2]

[1]School of Specialization in Hospital Pharmacy, Department of Biological, Chemical and Pharmaceutical Sciences and Technologies (STEBICEF), University of Palermo, Viale delle Scienze, Ed. 16, 90128 Palermo PA, Italy. *e-mail: matteo.gallina01@you.unipa.it

[2]Clinical Pharmacy Service, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (IRCCS ISMETT), Via E. Tricomi 5, 90127 Palermo PA, Italy

[3]Department of Research, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (IRCCS ISMETT), Via E. Tricomi 5, 90127 Palermo PA, Italy

BACKGROUND AND IMPORTANCE

Lung cancer is the leading cause of cancer-related deaths worldwide. Non-Small-Cell Lung Cancer (NSCLC) accounts for 80-90% of all lung cancers. NSCLC treatment is closely aligned with disease stage. Despite advances in immunotherapy and targeted therapies, disease progression often necessitates chemotherapy, which remains limited in efficacy with significant side effects.

Antibody-Drug Conjugates (ADCs) represent an expanding targeted therapy option for the treatment of NSCLC, leveraging monoclonal antibodies to deliver cytotoxic molecules selectively into tumor cells (Figure 1). Trastuzumab Deruxtecan (T-DXd) is currently the only ADC approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating adult patients with advanced NSCLC harboring an activating HER2 (ERBB2) mutation.

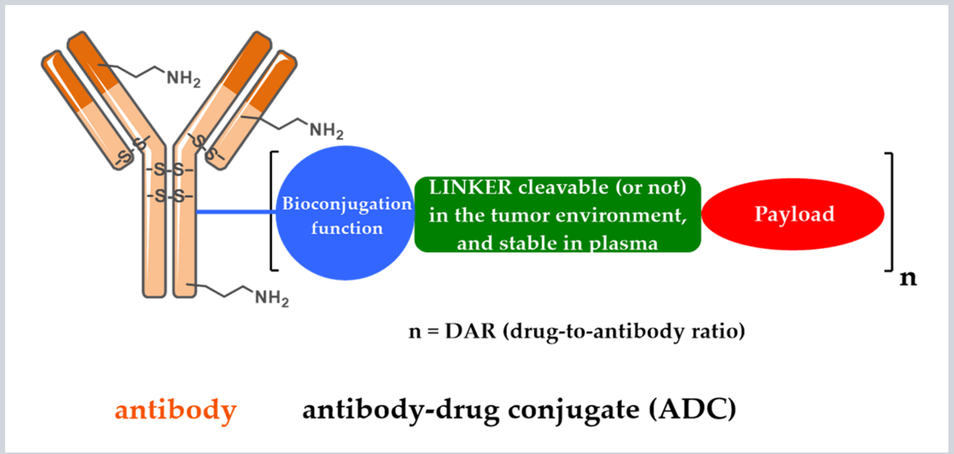

Figure 1. General structure of ADC comprising of antibody, linker and cytotoxic payload.

AIM AND OBJECTIVES

The aim of this study is to conduct a systematic review to evaluate the efficacy and safety profiles of ADCs currently undergoing clinical trials for the treatment of NSCLC. The study focuses on the latest clinical research exploring ADCs targeting specific mutations or overexpressed markers in adult patients affected by NSCLC.

MATERIALS AND METHODS

The study adhered to the PRISMA statement (Figure 2). Literature searches were conducted in PubMed, ClinicalTrial.gov and Web of Science databases, from 2014 to 2024. Only randomized and non-randomized, phase II-IV clinical trials focusing on ADC-based therapies for adult patients affected by NSCLC were selected. The **RoB 2.0** and the **ROBINS-I** were used to evaluate the overall risk of bias of the included studies. While **GRADE** was used to assess the certainty of the evidence. **Efficacy endpoints were categorized based on primary outcomes, while safety was assessed through the frequency and severity of Treatment Emergent Adverse Events (TEAEs)**.

RESULTS

Five ADCs were evaluated, including T-DXd, trastuzumab emtansine (T-DM1), telisotuzumab vedotin, patritumab deruxtecan, and Dato-DXd. T-DXd demonstrated superior efficacy in HER2-overexpressing and HER2-mutant NSCLC. However, HER2-mutant patients exhibited a longer mDOR but a higher incidence of grade ≥3 TEAEs. T-DM1 showed modest efficacy in both HER2-overexpressing and HER2-mutant patients. Dato-DXd demonstrated improved ORR and PFS compared to docetaxel. Patritumab deruxtecan achieved an ORR of 39% in EGFR-mutant NSCLC, while telisotuzumab vedotin exhibited limited activity in c-MET-positive NSCLC. **Frequency and severity of TEAEs varied across ADCs, with ILD being a major concern, highlighting the need for strict patient monitoring and early intervention to mitigate severe adverse events.**

Table 1. Comparative safety and efficacy of ADCs used within the included studies.

ADC included *(study ID, year)*	Key Efficacy Outcomes	Grade ≥3 TEAEs (%)	ILD Incidence (%)	Other common events (incidence %)	Key considerations for safety management
Trastuzumab deruxtecan (T-DXd) *(DESTINY-Lung01/02, 2024)*	ORR: 49.0% - 56.0%. PFS: 9.9 - 15.4 months	38.6% - 58.0%	12.9% - 28.0%	Nausea (67.3-82.0%), neutropenia (42.6-56.0%), fatigue (44.6-50.0%)	Regular ILD monitoring, hematologic checks, antiemetic support
Trastuzumab emtansine *(NCT0228983/UMIN000017709, 2019)*	ORR: 6.7% - 20.0%. PFS: 2.0 - 2.7 months	35% - 40%	6.7%	Thrombocytopenia (40%), hepatotoxicity (20%), fatigue (10%)	Frequent liver function and platelet monitoring
Datopotamab deruxtecan (Dato-DXd) *(TROPION-Lung01, 2024)*	ORR: 26.4%. PFS: 4.4 months	25.6%	8.8%	Stomatitis (47.5%), nausea (34.0%), decreased appetite (22.9%)	Lower toxicity than docetaxel, requires stomatitis prevention
Patritumab deruxtecan *(HERTENA-Lung01, 2024)*	ORR: 39.0%. PFS: 8.2 months	63%	7%	Thrombocytopenia (30%), neutropenia (19%), fatigue (14%)	High hematologic toxicity, close blood count monitoring
Telisotuzumab vedotin *(LUNG-MAP, 2021)*	ORR: 9%. PFS: 3.5 months	17%	-	Fatigue (9%), peripheral neuropathy (4%), nausea (4%)	Lower toxicity, but modest efficacy; requires neuropathy management

DOR: Duration of treatment; ORR: Objective Response Rate; PFS: Progression Free Survival; ILD: Interstitial Lung Disease.

RESULTS

Three RCTs, three non-randomized, and one study without specific allocation, were included, comprising a total of 1,287 patients, with 693 (54%) men, and an average age of 63 years old. Two studies were deemed to have a low risk of bias, while five had a moderate risk or some concerns. **A summary of the main findings is shown in Table 1.**

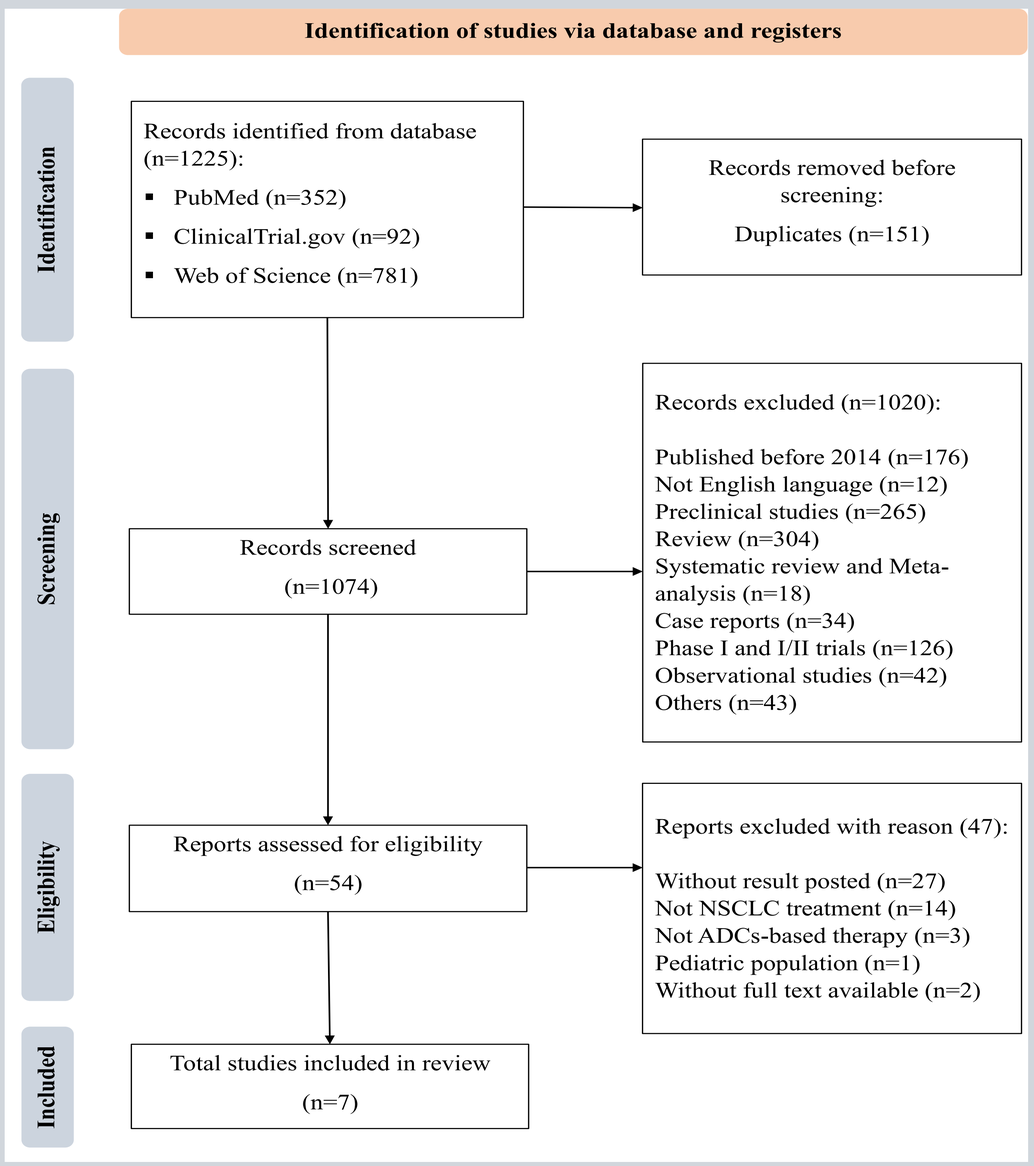

Figure 2. PRISMA flow chart of database search and article screening in the study.

CONCLUSION AND RELEVANCE

ADCs represent a promising advancement in NSCLC treatment. **T-DXd has emerged as the most effective ADC for HER2-mutant NSCLC with manageable safety profile**, whereas Dato-DXd provides a viable alternative for TROP2-expressing tumors. **While ADCs offer significant clinical benefits, careful patient selection and proactive management of adverse events remain crucial**. Ongoing trials will further refine the role of ADCs in personalized NSCLC treatment, potentially expanding their tumor-agnostic use to broader patient populations.

Protocol registration: ***PROSPERO 2025 CRD42025643511***

REFERENCES

- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *The BMJ*. 2021;372. doi:10.1136/bmj.n71.
- Joubert N, Beck A, Dumontet C, Denevault-Sabourin C. Antibody-Drug Conjugates: The Last Decade. *Pharmaceuticals (Basel)*. 2020;13(9):245. doi: 10.3390/ph13090245.
- Remon J, Soria JC, Peters S. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. *Annals of Oncology*. 2021;32(12):1637-1642. doi:10.1016/j.annonc.2021.08.1994