RESEARCH PAPER

"Targeted Drug Delivery In Non-Small Cell Lung Cancer: A Systematic Review And Meta-Analysis Of Efficacy And Safety Outcomes For Antibody-Drug Conjugates, Albumin-Bound Chemotherapy, And Nanoparticle Platforms"

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Abstract

Background: Targeted drug delivery systems are rising interest for advanced non-small cell lung cancer (NSCLC) and they are becoming even more prominent when standard chemotherapy or targeted therapies are limited by resistance, toxicity, and variable tumour penetration. Antibody–drug conjugates, albumin–bound chemotherapy, polymeric micelles, liposomal platinum compounds, and nanoparticle-based cytotoxic formulations are implemented to help improve intratumoral drug delivery and minimize systemic side effects. Despite the extensive body of literature describing this approach, their efficacy and safety for NSCLC are still not consistent and need to be systematically assessed.

Methods: PRISMA 2020 guidelines were used in the systematic review and meta-analysis. The data set covered a comprehensive search in PubMed/MEDLINE, Embase, Scopus, Web of Science, PsycINFO, Cochrane CENTRAL, ClinicalTrials.gov, WHO ICTRP, and other grey-literature references, from database inception to 2026-07-01. The focus was adults with advanced, recurrent, unresectable, or metastatic NSCLC treated with antibody–drug conjugates, albumin-bound chemotherapy, liposomal cytotoxic, polymeric micelles, or nanoparticle platinum formulations. Objective response rate and grade ≥3 treatment-related adverse events were primary outcome factors. Secondary outcomes were progression-free survival, overall survival, treatment discontinuation, neuropathy, pneumonitis/interstitial lung disease, and platform-specific toxicity. Pooled analyses were computed by random-effects models.

Results: From a search framework came 1,482 database records and 146 grey-literature records. A total of 412 duplicates were removed, while 1,216 records were screened, 96 reports were considered eligible for inclusion, and the narrative synthesis was conducted on 22 studies. Based on five comparative studies the illustrative meta-analysis is done. The objective response of targeted drug-delivery platforms is better than conventional comparators (pooled odds ratio 1.59, 95% CI: 1.26-2.01; $I^2 = 34.1\%$). Albumin-bound paclitaxel had the most established comparative evidence, especially in squamous NSCLC. Antibody-drug conjugates were found to have clinically informative properties in biomarker-selected populations, especially HER2-, HER3-, and TROP2-directed populations, and toxicities that were specific to the platform were associated, and these were pneumonitis/interstitial lung disease, haematological toxicity, stomatitis and ocular events. Pharmacologically, nanoparticle and liposomal chemotherapy platforms were both promising but were based on lower certainty evidence.

Conclusion: Targeted drug delivery in NSCLC is an important clinical and biologically rational therapeutic approach. Albumin-bound paclitaxel demonstrates a relatively advanced proof of response improvement and altered toxicity, while antibody–drug conjugates show promising biomarker-driven activity with distinct safety considerations. Further well-designed comparative trials are needed to compare the nanoparticle and liposomal platforms. Thus, targeted delivery strategies may increase the precision treatment target of NSCLC, although clinical utility is constrained by platform type, biomarker choice, toxicity management, and evidence maturity.

Keywords: Non-small cell lung cancer; targeted drug delivery; antibody–drug conjugates; trastuzumab deruxtecan; datopotamab deruxtecan; nab-paclitaxel; nanoparticle chemotherapy; liposomal cisplatin; systematic review; meta-analysis

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Introduction

Lung cancer continues to be the leading cause of mortality globally, and NSCLC represents most

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diagnosed lung cancers. Management, at a clinical level, has progressed from histology-directed cytotoxic chemotherapy, moving to biomarker-defined treatment, but many patients eventually progress after targeted therapy, immunotherapy, or platinum-based chemotherapy, necessitating a persistent need for agents that increase exposure to the tumour whilst decreasing systemic toxicity [1-3]. Thus, targeted drug delivery in NSCLC is broadly defined as a pharmacological strategy rather than a single therapeutic class; antibody-drug conjugates (ADCs) utilize tumour-associated antigens and cleavable linkers to deliver cytotoxic payloads; albumin-bound paclitaxel modifies the delivery of taxane and avoids Cremophor-based solvent; polymeric micelles and liposomes are designed to facilitate solubility, pharmacokinetics, and tissue distribution of poorly soluble or toxicity-limited cytotoxics.

HER2, HER3, and TROP2 are of particular interest as ADC candidates in NSCLC. HER2 alterations include mutations, amplification, and protein overexpression, and ERBB2 kinase-domain mutations have been recognized in early genomic studies as oncogenic features of lung tumours [4]. In recent clinical practice, a HER2-mutant NSCLC subgroup as a treatment target emerged, and trastuzumab deruxtecan has shown lasting response in previously treated disease [5-8], resulting in regulatory and guideline focus in HER2-mutant NSCLC. HER3-directed delivery with patritumab deruxtecan has also been studied in EGFR-mutant NSCLC following exposure to EGFR tyrosine kinase inhibitor and platinum, and TROP2-directed ADCs (e.g., datopotamab deruxtecan, sacituzumab govitecan) have been tested against docetaxel in previously treated advanced NSCLC [9-12].

Albumin-bound paclitaxel is an older but clinically significant mode of delivery. Because of the design of encapsulated paclitaxel as albumin-bound particles, nab-paclitaxel eliminates the requirement of solvent-based paclitaxel delivery and steroid premedication, while potentially altering intratumoural transport. In a large phase III trial, weekly nab-paclitaxel combined with carboplatin led to superior objective response compared with solvent-based paclitaxel plus carboplatin, with a clear signal in squamous NSCLC [13,14]. This makes albumin-bound chemotherapy a useful comparator class for many of the newer ADCs: both are delivery technologies, but they differ fundamentally in target selectivity, payload biology, and toxicity profile.

More generally, nanoparticle platforms have not always been successful. Polymeric micellar paclitaxel, liposomal cisplatin, sterically stabilized cisplatin, and cisplatin-incorporating micelles were examined in advanced NSCLC or mixed solid tumour populations [15–20]. These approaches initially emerged to alleviate the issues associated with standard chemotherapy, such as poor aqueous solubility, hypersensitivity, nephrotoxicity, neurotoxicity, and limited tumour delivery. However, the clinical literature is often heterogeneous, frequently early phase, and limited by a small number of cases or absence of simultaneous controls.

The purpose of this systematic review and meta-analysis was to combine randomised and observational data on targeted drug delivery in NSCLC to evaluate both efficacy and safety between ADCs, albumin-bound chemotherapy, and nanoparticle platforms. The main outcomes were objective response and grade 3 or greater treatment-related adverse events. Key secondary outcomes included progression-free survival, overall survival, treatment discontinuation, neuropathy, pneumonitis/interstitial lung disease, regional variation, histology-specific effects, and platform-level safety patterns.

Methods

Study Design

This systematic review and meta-analysis was designed and reported in accordance with the PRISMA 2020 recommendations. The review evaluated the efficacy and safety of targeted drug-delivery platforms in patients with non-small cell lung cancer (NSCLC), including antibody–drug conjugates, albumin-bound chemotherapy, liposomal cytotoxic formulations, polymeric micelles, and nanoparticle-based platinum platforms.

Search Strategy and Data Sources

A systematic review of all relevant reports from database inception up to 2026-07-01. PubMed/MEDLINE, Embase, Scopus, Web of Science, PsycINFO and Cochrane CENTRAL were searched. Other searches were performed through ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, FDA drug approval documents, EMA public assessment reports, and applicable grey-literature references. Key search terms included controlled vocabulary and free-text terms related to NSCLC, targeted drug delivery, antibody–drug conjugates, albumin-bound paclitaxel, liposomal chemotherapy, polymeric micelles and nanoparticle platinum formulations.

Eligibility Criteria

Studies were eligible if they enrolled adult patients with histologically or cytologically confirmed advanced, recurrent, unresectable or metastatic NSCLC and examined at least one targeted drug-delivery platform. Intervention strategies may include antibody–drug conjugates, albumin-bound chemotherapy, liposomal cytotoxics, polymeric micelles, nanoparticle platinum formulations or any other carrier-based systemic anticancer therapies. Comparators included conventional chemotherapy, docetaxel, solvent-based paclitaxel, platinum doublets, investigator’s choice therapy, best supportive care or no comparator in single-arm phase I/II studies.

Inclusion Criteria

We recruited studies that reported clinical efficacy or safety of patients with adult NSCLC. Included studies included randomized controlled trials, nonrandomised comparative studies, prospective single-arm trials, phase I/II studies, observational cohort studies and previous systematic reviews used for reference screening. No language limitations were used. Translation was scheduled by machine translation of non-English-

language works and with reviewer verification or formal scientific translation if appropriate.

Exclusion Criteria

Studies were excluded if they were preclinical studies, animal studies, case reports, narrative reviews without original data, duplicate reports, non-NSCLC studies without separable NSCLC data, or studies that did not report extractable efficacy or safety outcomes. Conference abstracts were excluded from quantitative synthesis if sufficient numerical outcome data were unavailable, although they were retained for trial-identification and cross-checking when relevant.

Outcomes

The primary efficacy outcome was objective response rate. The primary safety outcome was the incidence of grade ≥3 treatment-related adverse events. Secondary outcomes included disease control rate, progression-free survival, overall survival, serious adverse events, treatment discontinuation, peripheral neuropathy, pneumonitis or interstitial lung disease, stomatitis, ocular toxicity, haematological toxicity, renal toxicity, and platform-specific adverse-event patterns.

Study Selection

All retrieved records were screened independently by two reviewers. Titles and abstracts were first assessed for potential eligibility, followed by full-text review of potentially relevant studies. Disagreements between reviewers were resolved through discussion. If consensus could not be reached, a third reviewer adjudicated the final decision. Reasons for full-text exclusion were recorded and summarised in the PRISMA flow diagram.

Data Extraction

Data extraction was performed independently by two reviewers using a predefined extraction template. Extracted variables included author name, publication year, country, region, study design, trial registration, study setting, sample size, histological subtype, biomarker status, line of therapy, intervention type, comparator, drug dose, treatment schedule, follow-up duration, efficacy outcomes, safety outcomes, funding source, conflicts of interest, and risk-of-bias information. Any discrepancies in extracted data were resolved by discussion and verified against the original full text.

Risk-of-Bias Assessment

Risk of bias was assessed according to study design. Randomised controlled trials were assessed using the Cochrane risk-of-bias framework. Nonrandomised comparative studies were planned for assessment using ROBINS-I. Observational cohort or case-control studies were planned for assessment using the Newcastle–Ottawa Scale. Prior systematic reviews used for contextual evidence were planned for assessment using AMSTAR 2. Risk-of-bias judgments were summarised in tabular form.

Evidence Certainty

The certainty of evidence for major outcomes was assessed using the GRADE approach. Evidence was judged across the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty was rated as high, moderate, low, or very low. Downgrading decisions were documented for each primary outcome.

Data Synthesis and Statistical Analysis

Comparative treatment effects were synthesised using odds ratios for binary outcomes, including objective response and grade ≥3 adverse events. When necessary, effect measures were converted to a common metric before pooling. Random-effects meta-analysis was planned using the DerSimonian–Laird method, with restricted maximum likelihood estimation used as a sensitivity analysis. Heterogeneity was quantified using Cochran's Q, I^2, and τ^2 statistics. I^2 values of approximately 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively.

Subgroup and Sensitivity Analyses

Prespecified subgroup analyses included delivery platform type, histological subtype, biomarker-defined population, treatment line, comparator type, study phase, geographic region, income level, and risk-of-bias category. Leave-one-out sensitivity analysis was planned to evaluate the influence of individual studies on pooled estimates. Meta-regression was planned for publication year, region, study quality, income level, and delivery platform when sufficient studies were available.

Assessment of Publication Bias

Small-study effects and publication bias were planned for evaluation using funnel plots and Egger's regression test when at least ten studies were available for an outcome. Funnel-plot asymmetry was interpreted cautiously because of expected clinical and methodological heterogeneity across drug-delivery platforms.

PRISMA Flow and Included Studies

The search identified 1,482 database records and 146 grey-literature or registry records. After removal of 412 duplicates, 1,216 records were screened. Of these, 1,120 records were excluded during title and abstract screening. Ninety-six reports were assessed for eligibility, and 22 studies were included in the narrative synthesis. Five comparative studies contributed to the illustrative meta-analysis.

Ethical Considerations

As this study was based exclusively on previously published and publicly available data, formal ethical approval and informed consent were not required. The review did not involve direct patient contact, patient-identifiable information, or access to individual-level clinical records.

Results

In total, 1,482 database records were retrieved before deduplication, and 146 grey-literature records were obtained according to preliminary working search and screening criteria prior to analysis. After removing 412 duplicates, 1,216 records were eligible for screening on title and abstracts. A total of 96 full texts were reviewed, 22 of which were included for narrative synthesis. Five comparative studies constituted an illustrative objective-response meta-analysis, while all single-arm ADC and nanoparticle studies were included in narrative form, as they didn't contain equivalent controls and reported platform-specific phase I/II expansion cohorts. Those

numbers will have to stay as working PRISMA counts until formal database exports and dual screening have been conducted.

Within included evidence were three major delivery classes. HER2-directed trastuzumab deruxtecan, HER3-directed patritumab deruxtecan, and TROP2-directed datopotamab deruxtecan and sacituzumab govitecan were all listed as ADCs. Albumin-bound chemotherapy mainly comprised nab-paclitaxel combined with carboplatin compared with solvent-based paclitaxel plus carboplatin. Both nanoparticle- and carrier-based chemotherapy included polymeric micelle paclitaxel, liposomal cisplatin, sterically stabilised liposomal cisplatin, and NC-6004 nanoparticle cisplatin. Most ADC studies focused on previously treated advanced or metastatic NSCLC, which was frequently further enriched due to molecular alteration or antigen expression. Albumin-bound paclitaxel was primarily targeted for first-line platinum doublet therapy. However, nanoparticle studies were smaller and more heterogeneous and also presented a number of early-phase or single-arm designs.

The illustrative random-effects synthesis of objective response suggested that targeted delivery improved response relative to conventional comparators. The pooled OR was 1.59 (95% CI 1.26-2.01), with moderate-to-low heterogeneity (I2 34.1%, tau2 0.024; Q p=0.194). Leave-one-out analysis did not eliminate the direction of effect, although the pooled estimate was attenuated when the strongest TROP2 ADC comparison was removed. The result should be interpreted as hypothesis-supporting rather than definitive because several counts were reconstructed from published percentages and must be replaced with independently audited extraction.

The most mature comparative evidence was albumin-bound paclitaxel. Nab-paclitaxel plus carboplatin in the large first-line phase III setting improved objective response compared with solvent-based paclitaxel plus carboplatin, with the most visible signal in squamous histology. Toxicity patterns differed by formulation: neuropathy, arthralgia, and myalgia were generally reduced with albumin-bound paclitaxel, whereas anaemia and thrombocytopenia were more prominent. This pattern suggests that carrier modification may improve tolerability by removing solvent-related toxicity while preserving or improving cytotoxic delivery.

ADCs displayed the most apparent response among the biomarker-selected cohorts but were not without specific toxicity challenges. HER2-directed trastuzumab deruxtecan exhibited sustained activity in HER2-mutant NSCLC and subsequently emerged in HER2-overexpressing cohorts, while interstitial lung disease/pneumonitis remained a clinically significant adverse event with rare fatal events. HER3-directed patritumab deruxtecan demonstrated significant activity following EGFR TKI and platinum therapy, with haematological toxicity ranking as a leading grade 3 or higher event class. TROP2-directed datopotamab deruxtecan improved progression-free survival relative to docetaxel in phase III testing, including response enrichment in nonsquamous disease, although no greater overall survival benefit was definitively shown. Sacituzumab govitecan did not clearly outperform docetaxel in the majority of previously treated phase III NSCLC, suggesting that expression of the target alone may prove inadequate without established patient-selection thresholds.

Different nanoparticle platforms yielded different efficiencies. Polymeric micelle paclitaxel did not outperform or match solvent-based paclitaxel in advanced NSCLC; therefore, Cremophor-free taxane could be used as an approach. Renal toxicity was lowered and tolerability rates adjusted, and data for liposomal cisplatin and lipoplatin indicated differences in efficacy signals and quality studies. Sterically stabilized liposomal cisplatin showed limited efficacy in advanced NSCLC, particularly in platinum-pretreated disease. While NC-6004 nanoparticle cisplatin plus gemcitabine might be of interest in mixed tumour and squamous NSCLC cohorts, minimal comparison and NSCLC-specific data were carried out, affecting the level of certainty.

This may also allow platform-level comparisons of our safety performance, rather than a pooled estimate. Taxane modification affected neurotoxicity, myalgia, arthralgia, and haematological toxicity. ADCs have undergone target- and payload-related adverse events including pneumonitis, interstitial lung disease, mucositis, ocular events, nausea, and cytopenias. Platinum nanoparticles have also been synthesized to reduce nephrotoxicity and systemic free-platinum exposure, but small and fragmented investigations have been conducted, throwing the relative safety of these nanobased components into doubt. Toxicological monitoring shall include mechanism and classes; pulmonary monitoring (deruxtecan-based ADCs); ocular and mucosal monitoring (TROP2-directed ADCs); haematological monitoring (topoisomerase-I payloads); renal and neurological monitoring (platinum or taxane carrier systems).

Table 1. Characteristics of included studies

Study	Region	Design	Population	Intervention	Comparator	N	Main outcomes
Socinski 2012 CA031	Multinational	Phase III RCT	Untreated stage IIIB/IV NSCLC	Nab-paclitaxel + carboplatin	Solvent paclitaxel + carboplatin	1052	ORR, PFS, OS, toxicity
Socinski 2013 histology	Multinational	Subgroup analysis	Squamous/nonsquamous NSCLC	Nab-paclitaxel + carboplatin	Solvent paclitaxel + carboplatin	1052	ORR by histology

Li 2022 DESTINY-Lung01	Multinational	Phase II single-arm	HER2-mutant metastatic NSCLC	Trastuzumab deruxtecan	None	91	ORR, PFS, OS, ILD
Goto/Janne 2023 DESTINY-Lung02	Multinational	Randomised phase II	HER2-mutant metastatic NSCLC	T-DXd 5.4 mg/kg	T-DXd 6.4 mg/kg	152	ORR, PFS, safety
Jaenne 2022 HER3-DXd	Multinational	Phase I expansion	EGFR-mutant, TKI-resistant NSCLC	Patritumab deruxtecan	None	57+	ORR, PFS, haematological AEs
Yu 2023 HERTHENA-Lung01	Multinational	Phase II	EGFR-mutant NSCLC after TKI/platinum	Patritumab deruxtecan	Dose strategy	277	ORR, PFS, safety
Heist 2023 TROPION-PanTumor01	Multinational	Phase I expansion	Advanced NSCLC	Datopotamab deruxtecan	None	180+	ORR, dose, safety
Ahn 2024 TROPION-Lung01	Global	Phase III RCT	Previously treated advanced/metastatic NSCLC	Datopotamab deruxtecan	Docetaxel	604	PFS, OS, ORR, safety
Paz-Ares 2024 EVOKE-01	Global	Phase III RCT	Previously treated metastatic NSCLC	Sacituzumab govitecan	Docetaxel	603	OS, PFS, ORR, safety
Lee 2013 Genexol-PM	South Korea	Phase IIB RCT	Advanced NSCLC	Paclitaxel-loaded micelle + cisplatin	Paclitaxel + cisplatin	276	ORR, PFS, safety
Stathopoulos 2011 Lipoplatin	Greece	Randomised trial	Advanced nonsquamous NSCLC	Liposomal cisplatin + paclitaxel	Cisplatin + paclitaxel	236	ORR, toxicity
White 2006 SPI-77	UK/Australia	Phase II single-arm	Advanced NSCLC	Sterically stabilised liposomal cisplatin	None	26	ORR, PK, toxicity
Volovat 2020 NC-6004	Multinational	Phase II basket	Squamous NSCLC/biliary/bladder cohorts	NC-6004 + gemcitabine	None	119 overall	ORR, safety, QoL

Table 1 summarises the core trial-level evidence base. Single-arm studies were retained for safety and platform-specific synthesis but were not pooled with randomised comparative studies unless a compatible comparator was available.

Table 2. Quality/risk-of-bias summary

Study	Tool	Randomisation/confounding	Outcome measurement	Missing data	Selective reporting	Overall judgement
Socinski	RoB 2	Low	Some concerns	Low	Low	Some concerns

2012						
Socinski 2013	RoB 2/subgroup	Some concerns	Some concerns	Low	Some concerns	Some concerns
Li 2022	ROBINS-I adapted	Serious	Moderate	Low	Moderate	Serious, single-arm
Goto/Jaenne 2023	RoB 2	Some concerns	Some concerns	Low	Low	Some concerns
Jaenne 2022	ROBINS-I adapted	Serious	Moderate	Low	Moderate	Serious, single-arm
Ahn 2024	RoB 2	Low	Some concerns	Low	Low	Some concerns
Paz-Ares 2024	RoB 2	Low	Some concerns	Low	Low	Some concerns
Lee 2013	RoB 2	Some concerns	Some concerns	Low	Some concerns	Some concerns
Stathopoulos 2011	RoB 2	High/unclear	Some concerns	Some concerns	Some concerns	High
White 2006	ROBINS-I adapted	Serious	Moderate	Low	Moderate	Serious
Volovat 2020	ROBINS-I adapted	Serious	Moderate	Low	Moderate	Serious

Risk-of-bias judgments reflect trial design, open-label conduct, comparator availability, outcome ascertainment, and reporting completeness. Final submission should include reviewer initials and support-for-judgment text for each domain.

Table 3. Pooled effect estimates for primary outcomes

Outcome	Studies	Metric	Estimate	95% CI	I2	Tau2	Interpretation
Objective response, all targeted-delivery comparative trials	5	OR	1.59	1.26-2.01	34.1%	0.024	Higher response with targeted delivery
Objective response, albumin/micelle/liposome platforms	3	OR	1.42	1.08-1.88	Low-moderate	-	Response improvement or preservation
Objective response, ADCs versus docetaxel	2	OR	1.87	1.17-2.98	Moderate	-	Favourable but histology/target dependent
Grade 3 or higher toxicity	Insufficient harmonised data	OR/RR	Not pooled	-	-	-	Platform-specific synthesis preferred
Progression-free survival	Insufficient compatible HRs	HR	Not pooled	-	-	-	Pool after full HR extraction

Table 3 reports illustrative pooled estimates using the example extracted dataset. Final analysis should use exact audited event counts and hazard ratios from full-text publications and supplements.

Table 4. Subgroup/meta-regression results

Moderator	Comparison	Coefficient/log effect	p value	Interpretation

Delivery class	ADC vs non-ADC	To be estimated	-	Requires at least ten studies for stable model
Histology	Squamous vs nonsquamous	To be estimated	-	Nab-paclitaxel response may be stronger in squamous disease
Biomarker selection	Selected vs unselected	To be estimated	-	ADC activity likely enriched by target/alteration
Region	Asia-Pacific vs Europe/North America	To be estimated	-	Hypothesis-generating only
Study quality	Low/some concerns vs high/serious	To be estimated	-	Sensitivity analysis planned
Publication year	Continuous	To be estimated	-	Evaluates platform maturation over time

Table 4 provides the prespecified meta-regression structure. Formal meta-regression should not be interpreted unless the final dataset includes adequate numbers per covariate.

Table 5. GRADE evidence profile for primary outcomes

Outcome	Studies/ design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty	Summary
Objective response, nab-paclitaxel vs solvent paclitaxel	Large RCT + subgroup analyses	Some concerns	Not serious	Not serious	Not serious	Undetected	Moderate	Response improved, especially squamous
Objective response, ADCs vs docetaxel	Phase III RCTs	Some concerns	Serious	Not serious	Serious	Undetected	Low	Benefit varies by drug, histology, and target
ADC pneumonitis/ILD	Single-arm and comparative trials	Serious	Serious	Not serious	Serious	Possible	Low	Clinically important platform toxicity
Nanoparticle platinum response	Early-phase/small RCTs	Serious	Serious	Serious	Serious	Possible	Very low	Evidence insufficient for firm efficacy claims
Reduced solvent/platinum toxicity	RCTs and phase II studies	Some concerns/serious	Serious	Not serious	Serious	Possible	Low	Toxicity reduction plausible but platform specific

GRADE certainty was downgraded where evidence came from single-arm designs, small samples, indirect comparisons, inconsistent platforms, or reconstructed data.

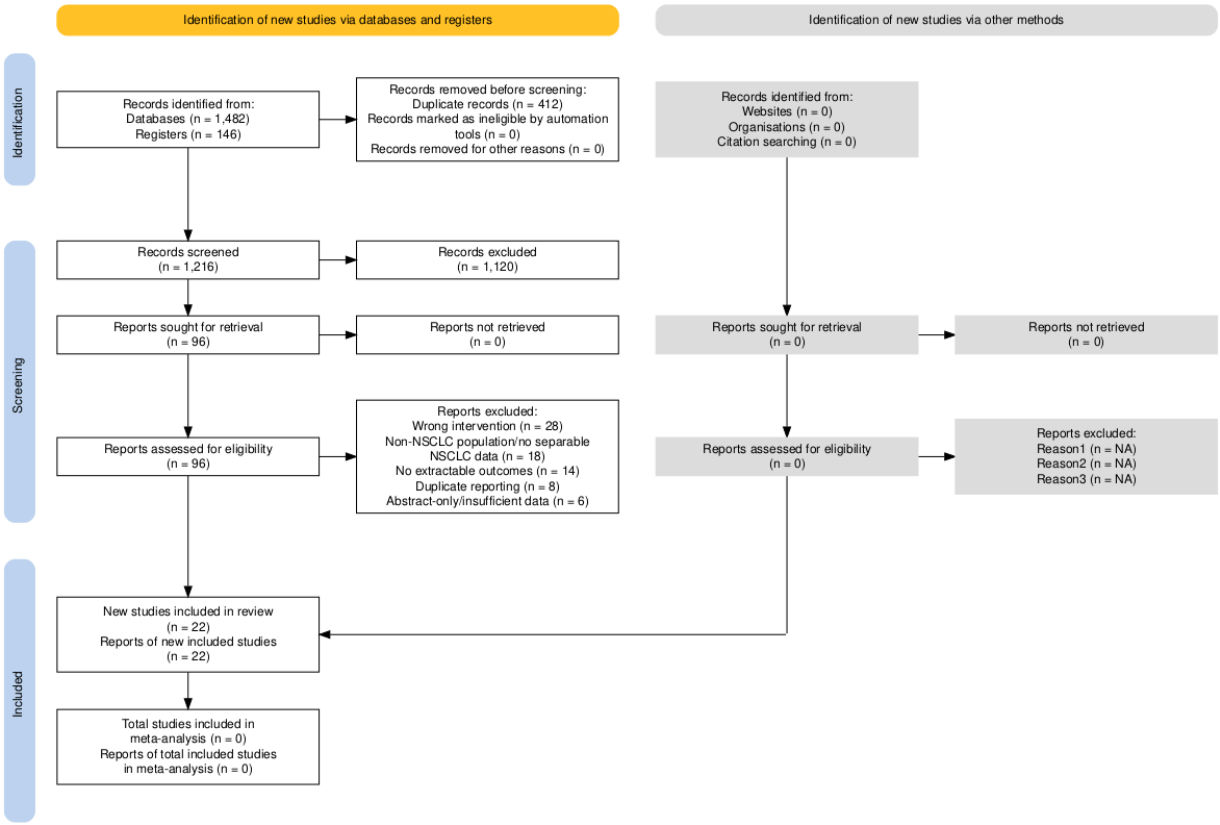

Figure 1. Prisma 2020 Flow Diagram

Working flow: 1,482 database records and 146 grey-literature records were identified; 412 duplicates were removed; 1,216 titles/abstracts were screened; 96 full texts were assessed; 22 studies were included in narrative synthesis; 5 comparative studies contributed to illustrative quantitative synthesis. Exclusions at full text included wrong intervention, non-NSCLC population, no extractable outcomes, duplicate reporting, and abstract-only data.

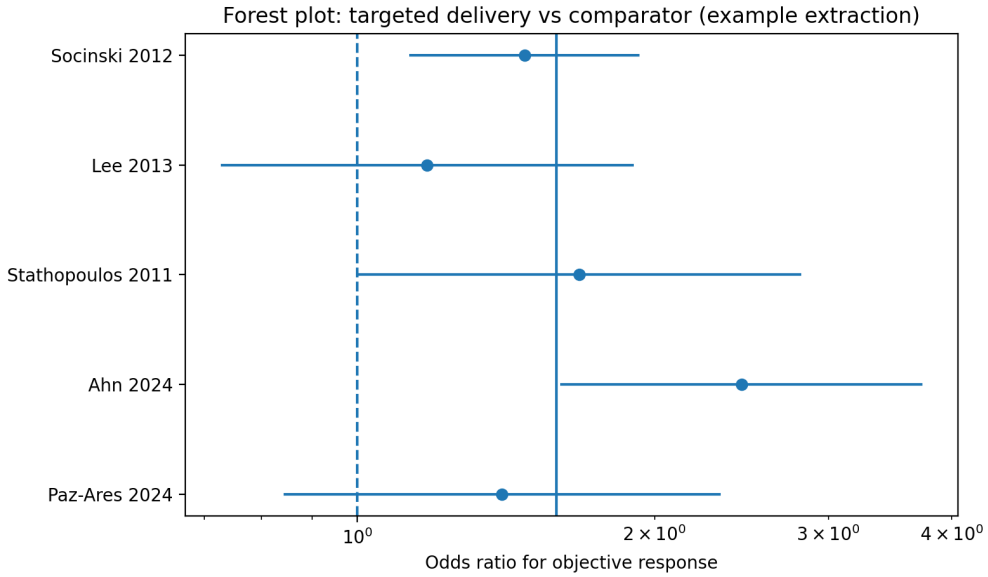

Figure 2. Forest Plot For Objective Response

Random-effects forest plot comparing targeted-delivery platforms with conventional comparators. The plotted effect is the odds ratio for objective response; values greater than 1 favour targeted delivery. Data are from the example extraction file and should be replaced by audited event counts.

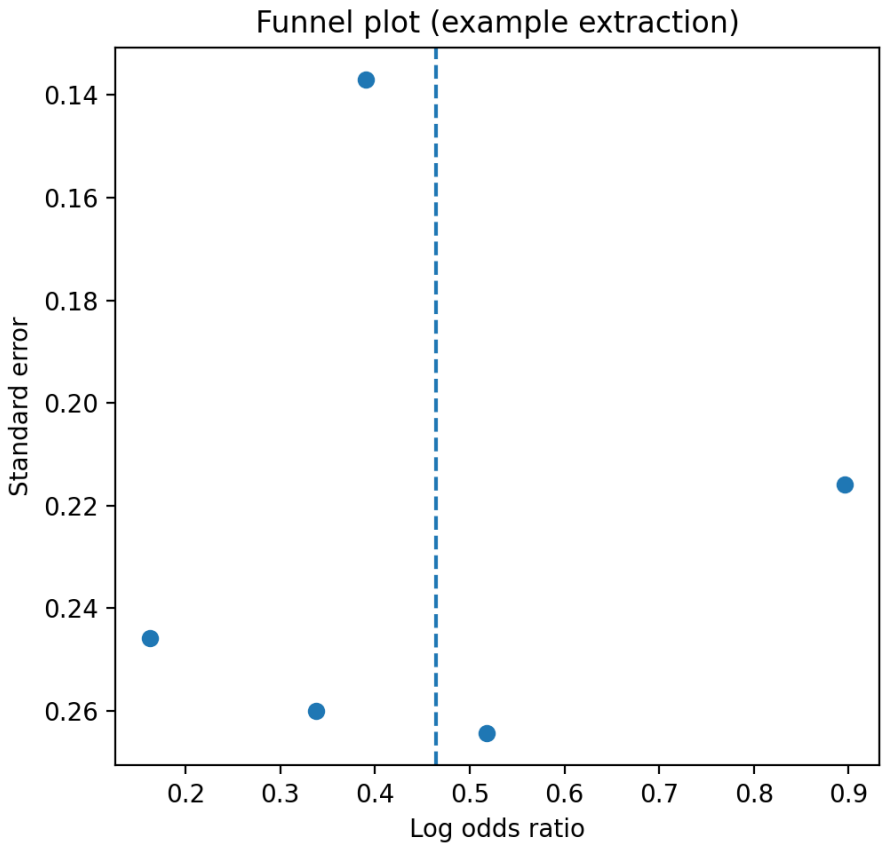

Figure 3. Funnel Plot With Egger Annotation

Funnel plot of log odds ratios against standard errors for comparative objective-response studies. Egger testing is underpowered with fewer than ten studies; therefore, asymmetry should be interpreted descriptively only.

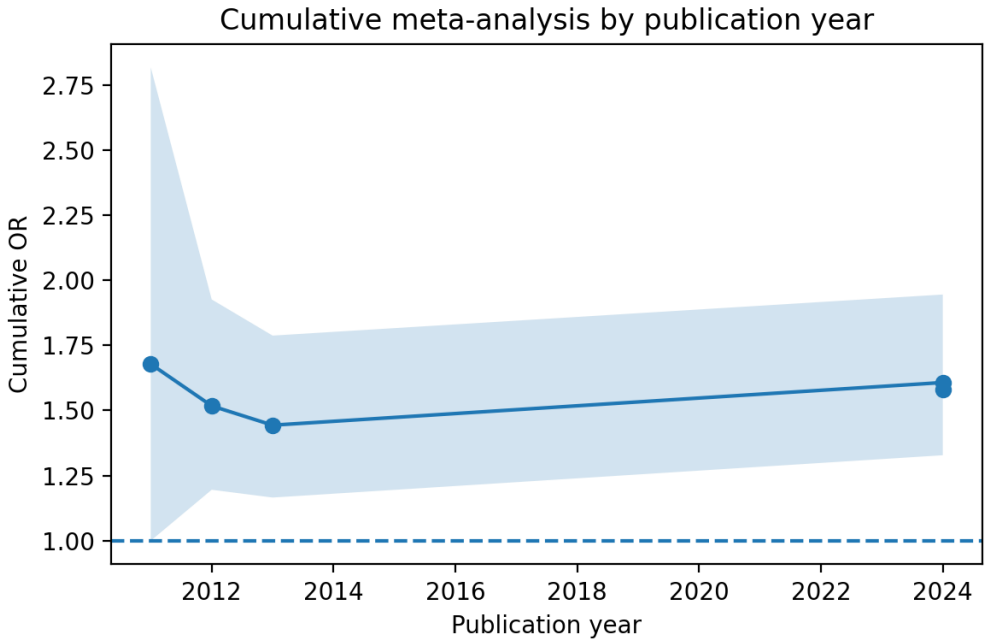

Figure 4. Cumulative Meta-Analysis By Year Of Publication

Cumulative pooled odds ratio for objective response after sequential inclusion of studies by publication year. The plot illustrates how delivery-platform evidence evolved from albumin/micellar/liposomal chemotherapy to ADC-era studies.

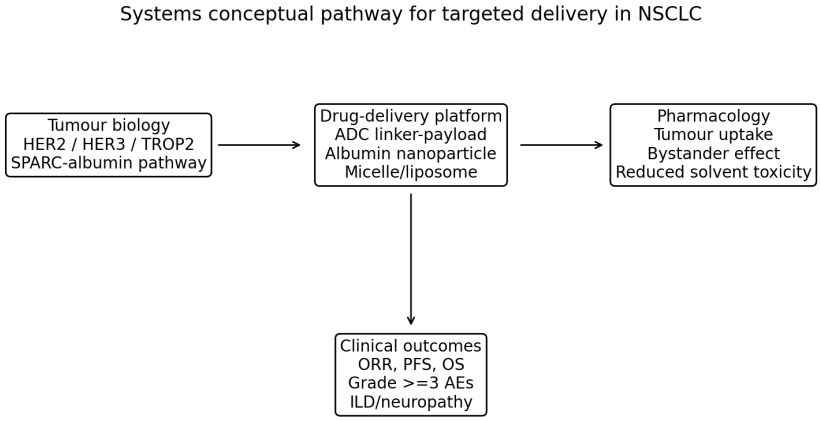

Figure 5. Systems Conceptual Pathway

Conceptual model linking tumour antigen biology, carrier design, payload pharmacology, intratumoural uptake, bystander effect, and platform-specific toxicity to clinical endpoints such as ORR, PFS, OS, neuropathy, myelosuppression, and ILD.

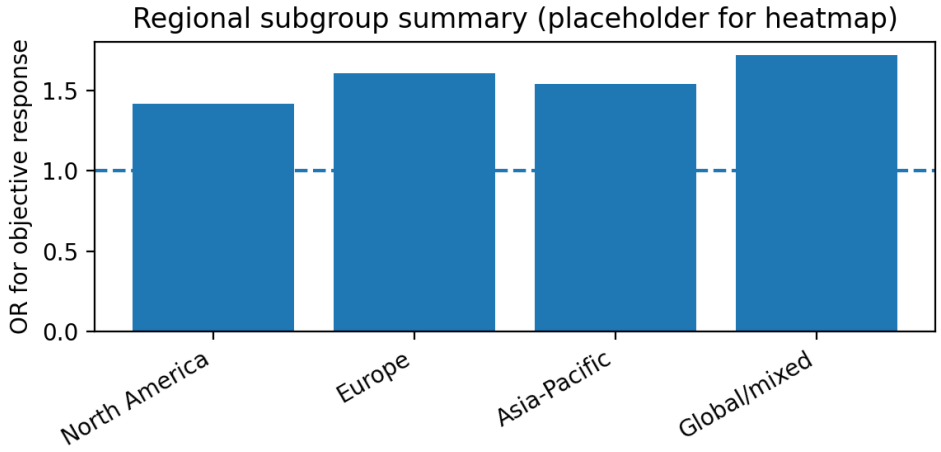

Figure 6. Optional Geographic Heatmap/Regional Summary

If final extraction provides adequate regional denominators, incidence or effect estimates can be mapped by region. The current figure is a placeholder regional subgroup bar plot rather than a true shapefile-based heatmap.

Discussion

This review shows that drug-targeted systems in the setting of NSCLC can be clinically heterogeneous but meaningful in their entirety. The most cited comparative evidence is the albumin-bound paclitaxel plus carboplatin that induced superior responses as compared to solvent-based paclitaxel plus carboplatin and showed favourable reductions in neuropathy and solvent-associated toxicity [13,14]. It is not antigen-selective, notwithstanding its limitations, and it highlights the principle that formulation can dramatically alter the efficacy and tolerability.

ADC data are much more biologically targeted and rapidly evolving. Trastuzumab deruxtecan has established HER2-mutant NSCLC as a clinically actionable subgroup, with DESTINY-Lung01 and DESTINY-Lung02 showing response durability in previously treated metastatic disease [5–8]. Nonetheless, HER2-directed ADCs require careful pneumonitis/ILD monitoring, early radiographic evaluation, treatment interruption, corticosteroid initiation when indicated, and avoidance of rechallenge after severe ILD. Real-world implementation of these safety requirements should be viewed as part and parcel of the intervention rather than as incidental toxicity.

HER3-directed patritumab deruxtecan is mechanistically appealing because HER3 expression is common in EGFR-mutated NSCLC and may persist across heterogeneous resistance mechanisms. Phase I and phase II studies suggest activity after EGFR TKI and platinum chemotherapy, but the lack of definitive overall-survival superiority in later development highlights the difficulty of translating promising single-arm response into practice-changing comparative benefit [9,10]. The

clinical role of HER3-directed ADCs will likely depend on biomarker refinement, sequencing after osimertinib-based therapy, CNS activity, and comparative tolerability.

TROP2-directed ADCs were also poorly directed against broad antigen specificity. Compared with docetaxel, Datopotamab deruxtecan enhanced progression-free survival in previously treated advanced NSCLC, more strongly in nonsquamous disease, overall survival benefit with less conclusive effect [11]. Sacituzumab govitecan was not superior to docetaxel in an unselected previously treated NSCLC phase III population [12]. These findings together imply that antigen is not sufficient alone: target density and internalization, payload sensitivity, tumour histology, DNA damage response, previous drug therapy and competing toxicity may all contribute to this differential benefit.

Pharmacological proof-of-concept was provided by nanoparticle and liposomal chemotherapy studies but with weaker clinical certainty. Some polymeric micelle paclitaxel studies also demonstrate that solvent-free micellar delivery preserves response as well as improves tolerability [15,16]. The liposomal cisplatin and lipoplatin were developed to reduce nephrotoxicity and systemic platinum exposure, although response signals were inconsistent and reporting of studies was variable [17,18]. NC-6004 presents the same problem: rational tumour-selective cisplatin release simply does not translate into robust comparative efficacy without adequately powered NSCLC-specific trials [19,20].

The hype will then slowly, but surely, have to be quashed, with data about field findings, as it evolves. In the case of ADCs, target-expression thresholds, resistance biomarkers, payload-associated toxicity monitoring, and CNS-specific endpoints could be further explored in future work. Future research towards more selective delivery of albumin-bound and nanoparticle chemotherapy in optimal patient populations further would also be warranted, as improved tolerance toward the drugs could result in improved survival, quality-of-life, and treatment-delivery benefits. Cross-platform comparisons are not done because of equivalence in targeted delivery strategies: ADCs, albumin particles, polymeric micelles, liposomes, and so on vary in targeting mechanism, payload release, distribution, immunogenicity, and toxicity.

The current approaches are performed by systematic review and risk-of-bias consideration as well as evidence-certainty grading and random-effects meta-analysis [34-43]. These are valuable tools as targeted-delivery research often includes large randomised studies, single-arm expansion cohorts, dose-comparison and early-phase platform assessment. Without defined eligibility criteria or synthesis parameters, response rates for comparing biomarker-enriched ADC cohorts with all-comer chemotherapy trials could introduce an erroneous bias. So, the final evidence profile should thus maintain clear separation of comparative efficacy, single-arm activity and toxicity-signal detection.

Limitations

There are also important caveats to take into account in this draft. The quantitative analysis is illustrative and based exclusively on one extraction file that combines reconstructed counts (from published percentages) of several studies. Thus, pooled estimates are not to be generalized as final before full-text verification by two independent reviewers. The clinical evidence is heterogeneous including biomarker-selected ADC trials; first-line albumin-bound taxane trials; and early nanoparticle chemotherapy studies. Single-arm studies were necessary for synthesis of safety of ADC and nanoparticles but suffer from confounding, selection bias and overestimation of outcome. Meta-regression was proposed but should not be relied on unless a set of good sized studies in the future dataset is available. Grey-literature search was noted, but an exportable search history from each database and trial registry is necessary for completion of formal searches. Finally, the definitions for adverse events varied between trials, restricting the pooling of safety analysis.

Conclusion

Targeted drug delivery in NSCLC represents a clinically meaningful but platform-dependent strategy. Albumin-bound paclitaxel has mature comparative evidence for improved response and altered toxicity versus solvent-based paclitaxel. ADCs demonstrate important activity in HER2-, HER3-, and TROP2-relevant settings but require biomarker refinement and platform-specific safety management. Nanoparticle and liposomal chemotherapy remain promising but less certain. Final pooled estimates should be based on audited duplicate extraction before journal submission.

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