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PROGRESS AND MECHANISMS OF ANTIBODY-DRUG CONJUGATES IN NSCLC THERAPY

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Abstract: Antibody–drug conjugates (ADCs) are emerging as a transformative therapeutic modality for non-small cell lung cancer (NSCLC), bridging the tumor selectivity of monoclonal antibodies with the potent cytotoxicity of chemotherapy payloads. This review summarizes recent clinical progress of ADCs in NSCLC and highlights key design features that shape efficacy and safety, including antigen selection, linker chemistry, payload class, drug–antibody ratio, and the bystander effect. Particular emphasis is placed on clinically advanced targets—HER2, TROP2, HER3, and MET—as well as promising emerging antigens such as B7-H3. Across multiple studies, next-generation ADCs have shown meaningful activity in molecularly defined and treatment-refractory populations, including patients with acquired resistance to EGFR-targeted therapy and those harboring HER2 alterations. However, ADC use is constrained by distinctive toxicities, notably interstitial lung disease/pneumonitis associated with certain topoisomerase I inhibitor payloads, alongside myelosuppression and gastrointestinal adverse events. We further discuss evolving resistance mechanisms (antigen downregulation, impaired internalization, efflux transporters, and microenvironmental barriers) and outline future directions, including biomarker-guided patient selection, rational sequencing, and combination strategies with immune checkpoint inhibitors or targeted agents. Collectively, ADCs are poised to become an integral component of precision therapy for NSCLC, contingent on optimized design and proactive toxicity management.
Keywords: Antibody-drug conjugates; ADCs; NSCLC

1 INTRODUCTION

Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related mortality worldwide. Although recent advances-including molecularly targeted agents such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and anaplastic lymphoma kinase (ALK) inhibitors, as well as immune checkpoint inhibitors (ICIs)-have significantly improved outcomes for some patients with NSCLC, many ultimately develop drug resistance and experience disease progression. Antibody-drug conjugates (ADCs) represent a novel therapeutic strategy that combines the targeting specificity of monoclonal antibodies with highly potent cytotoxic agents. In recent years, ADCs have achieved breakthroughs in solid tumors and are beginning to show promise in NSCLC. The design principle of ADCs is to retain the strong tumor-killing activity of chemotherapy while using antigen-specific antibodies to deliver the drug selectively to tumor cells, thereby improving efficacy and reducing systemic toxicity [1]. The first wave of ADCs achieved success in cancers such as breast cancer; for example, the anti-HER2 ADC trastuzumab emtansine (T-DM1) was effective in breast cancer. However, early attempts to apply T-DM1 in HER2-aberrant NSCLC yielded limited efficacy, temporarily dampening this approach [2]. More recently, next-generation ADCs such as trastuzumab deruxtecan (T-DXd) have demonstrated striking activity in specific NSCLC subtypes, rekindling broad interest. In particular, ADCs offer new therapeutic options for EGFR-mutant disease after acquired resistance to targeted therapy, for HER2-mutant disease with historically limited treatment choices, and for previously challenging tumor antigens (e.g., TROP2 and HER3). This review summarizes the latest clinical progress of ADCs in NSCLC, with a focus on the efficacy and limitations of ADCs against different targets, and further discusses mechanisms of action, toxicity management, resistance mechanisms, and future directions.

2 MECHANISMS OF ACTION AND DESIGN FEATURES OF ADCS

2.1 Structure and Mechanism of Action

ADCs consist of three core components: a monoclonal antibody, a linker, and a cytotoxic payload. The antibody confers high specificity by recognizing target antigens on the tumor-cell surface; the linker conjugates the antibody to a small-molecule drug; and the payload is typically a cytotoxic agent with potency tens of times higher than conventional chemotherapy [1]. After administration, the antibody guides the ADC to tumor cells expressing the corresponding antigen. Following antigen-antibody binding and endocytosis, the ADC is internalized; in the lysosomal environment, the linker is cleaved through enzymatic and/or acid-mediated processes, releasing the active payload and inducing apoptosis of target cells [1]. This “targeted delivery + site-specific release” mechanism enables highly selective tumor killing in vivo while reducing damage to normal tissues.

2.2 Linkers and the "Bystander Effect"

Linker design is critical to both efficacy and safety. Common cleavable linkers include acid-sensitive linkers, protease-cleavable linkers, and disulfide bonds [1]. For example, deruxtecan-based ADCs use a tetrapeptide linker that can be cleaved by intracellular tumor proteases; once cleaved, the released payload has partial membrane permeability and can diffuse into neighboring cells. This “bystander effect” means that even tumor cells with low target-antigen expression may still be killed by drug released from adjacent high-expressing cells, thereby improving overall efficacy [3]. In highly heterogeneous NSCLC, the bystander effect is considered an important contributor to ADC efficacy. For instance, the first-generation anti-HER2 ADC T-DM1 uses a non-cleavable linker and acts predominantly within target cells, with limited bystander activity, which may partly explain its limited efficacy in HER2-heterogeneous lung cancers; in contrast, the next-generation anti-HER2 ADC T-DXd exhibits a bystander effect and can produce substantial antitumor activity even in settings with non-uniform HER2 expression [4]. However, the bystander effect may also broaden the exposure of surrounding normal tissues to payload; for example, injury to alveolar epithelial cells observed in some patients treated with T-DXd has been hypothesized to relate in part to this mechanism, underscoring the need to balance efficacy and toxicity.

2.3 Payload Classes and Immune-related Effects

ADC payloads are ultra-potent small-molecule cytotoxics, most commonly microtubule inhibitors (e.g., MMAE, DM1) and topoisomerase I inhibitors (e.g., deruxtecan, SN-38). Differences in payload mechanism influence both the mode of tumor-cell killing and the toxicity profile. Microtubule inhibitor payloads are typically associated with peripheral neuropathy and myelosuppression, whereas topoisomerase I inhibitor payloads more often cause gastrointestinal adverse events and interstitial pneumonitis/ILD [5,6]. Notably, some payloads can induce immunogenic cell death, promoting tumor-antigen release and immune activation [7]. For example, a study of a novel folate receptor-alpha (FRα)-targeting ADC showed that its topoisomerase inhibitor payload not only killed NSCLC cells but also triggered immunogenic cell death [7]. These immune-related effects provide a mechanistic rationale for combining ADCs with ICIs to enhance antitumor immune responses.

2.4 Target Selection

An ideal ADC target antigen is highly expressed on tumor cells but minimally expressed on normal tissues, is located on the cell membrane, and is readily internalized. The molecular landscape of NSCLC is complex; many driver genes (e.g., EGFR, KRAS) encode intracellular proteins and are not directly targetable by ADCs. However, several surface molecules-such as HER2, TROP2, HER3, MET, and B7-H3-are highly expressed or overexpressed in particular NSCLC subsets, meeting key criteria for ADC targets. Importantly, internalization kinetics influence ADC efficacy. For instance, HER3 is generally a receptor with relatively slow internalization, but in EGFR-mutant NSCLC, HER3 is often overexpressed and ligand-activated, with increased endocytosis, providing a biological basis for anti-HER3 ADC activity [8]. Likewise, TROP2 is broadly expressed in NSCLC, though its physiological function remains incompletely defined, and internalization rates may vary by context. Evidence suggests that EGFR mutations can promote TROP2 internalization, thereby enhancing the cytotoxicity of TROP2 ADCs in EGFR-mutant cells [9]. Therefore, target selection should consider how tumor molecular context shapes antigen expression and internalization. In addition, target heterogeneity and expression level are critical: higher expression generally predicts better ADC responses, whereas marked heterogeneity may require ADCs with a bystander effect to compensate [3].

2.5 New Designs and Optimization Strategies

With continued advances in ADC technology, next-generation designs aim to improve efficacy, widen the therapeutic window, and overcome resistance. Homogeneous conjugation approaches can make ADC structures more uniform, improving pharmacokinetics and controllability. Tumor microenvironment-activatable linkers (e.g., acid-sensitive or matrix metalloproteinase-sensitive) are designed to cleave primarily in the acidic and/or enzyme-rich tumor milieu, reducing premature payload release in normal tissues [1]. A notable example is the B7-H3-targeting ADC YL201, which employs a tumor microenvironment-cleavable linker and a novel topoisomerase I inhibitor payload; in a phase I trial it showed activity across multiple solid tumors while the incidence of ADC-associated ILD was only 1.3%, substantially lower than that seen with some traditional ADCs [1]. Additional optimization directions include increasing the drug-to-antibody ratio (DAR) and developing multifunctional ADCs (e.g., conjugates carrying radioisotopes or immune-stimulatory moieties). Collectively, these innovations may further improve the therapeutic index of ADCs in NSCLC.

3 CLINICAL PROGRESS OF ADC THERAPY IN NSCLC

3.1 HER2-targeting ADCs

3.1.1 Background: HER2 alterations in NSCLC

HER2 is not a high-frequency driver gene in NSCLC, but approximately 2-3% of lung adenocarcinomas harbor activating HER2 mutations, most commonly exon 20 insertions within the intracellular kinase domain [4]. A smaller subset of patients exhibits HER2 gene amplification or high protein expression (IHC 2+ or 3+) without detectable HER2 mutations. These HER2-aberrant NSCLCs are typically insensitive to conventional chemotherapy and to targeted therapies directed at EGFR/ALK and related pathways, and historically there have been limited effective treatment options. Earlier efforts using anti-HER2 monoclonal antibodies and TKIs in lung cancer were largely disappointing, and early trials of ADCs such as T-DM1 achieved objective response rates below 10%. Consequently, HER2-mutant NSCLC has remained an area of substantial unmet need [2].

3.1.2 Trastuzumab deruxtecan (T-DXd)

In recent years, T-DXd has delivered landmark progress in HER2-positive NSCLC. In the DESTINY-PanTumor02 phase II study across multiple solid tumors, Meric-Bernstam and colleagues demonstrated the broad activity of T-DXd in HER2-positive cancers: the overall ORR was 37.1%, and the ORR reached 61.3% among patients with HER2 IHC 3+ disease [5]. In NSCLC-specific trials, teams led by Li and Jänne (e.g., DESTINY-Lung01) reported remarkable efficacy of T-DXd in previously treated advanced HER2-mutant NSCLC, with ORRs of approximately 50-60% and median progression-free survival (PFS) of 8-9 months-highly meaningful outcomes in patients who had failed prior therapies [4,10]. On this basis, the U.S. FDA granted accelerated approval in 2022 for T-DXd in metastatic HER2-mutant NSCLC after prior systemic therapy. A China-developed anti-HER2 ADC, SHR-A1811, also showed activity in a multicenter phase I/II study, achieving an ORR of 41.9% and a median PFS of 8.4 months, suggesting efficacy comparable to T-DXd [10]. Notably, ADC efficacy often correlates with target expression: reports suggest that NSCLC with HER2 IHC 3+ may respond better than tumors with mutation alone but low protein expression; therefore, evaluating HER2 protein expression in HER2-mutant disease may help predict benefit [4,5].

3.1.3 Clinical benefit and safety considerations

The clinical adoption of anti-HER2 ADCs is improving outcomes for this small subgroup of patients with NSCLC. Case series have reported that HER2-mutant NSCLC treated with T-DXd can achieve not only systemic tumor shrinkage but also notable responses in brain metastases [11], suggesting either partial blood-brain barrier penetration or indirect intracranial benefit through systemic disease control. However, anti-HER2 ADCs also present unique toxicity challenges, particularly the risk of interstitial lung disease (ILD). T-DXd-associated ILD occurs in approximately 10-15% of patients, with some events reaching grade 3-5 and occasional treatment-related deaths [5]. In one study of SHR-A1811, 1 of 63 patients died from treatment-related ILD [10]. Accordingly, patients receiving HER2-targeted ADCs require close monitoring for respiratory symptoms and early initiation of corticosteroids when ILD is suspected. Some guidance recommends caution in patients with active interstitial lung abnormalities. Other common adverse events include myelosuppression, gastrointestinal toxicity, and fatigue, which are generally manageable [10]. Overall, anti-HER2 ADCs such as T-DXd have filled a major therapeutic gap in HER2-mutant NSCLC and delivered substantial clinical benefit, but expanding their use must be accompanied by rigorous vigilance for pulmonary toxicity.

3.2 TROP2-targeting ADCs

3.2.1 Rationale for targeting TROP2

TROP2 (also known as TACSTD2) is a transmembrane glycoprotein that is highly expressed in many epithelial tumors, including NSCLC [12]. More than 80% of NSCLC specimens show varying degrees of TROP2 expression, whereas expression in normal lung tissue is limited, making TROP2 an attractive target for ADC therapy. Notably, after acquired resistance to EGFR TKIs in EGFR-mutant NSCLC, tumors often retain high TROP2 expression, creating an opportunity to use TROP2-targeting ADCs to eradicate TKI-resistant clones [13]. The most intensively studied TROP2 ADCs include datopotamab deruxtecan (Dato-DXd) and sacituzumab govitecan, as well as their optimized derivatives.

3.2.2 Datopotamab deruxtecan (Dato-DXd)

Dato-DXd is an ADC comprising a humanized anti-TROP2 IgG1 monoclonal antibody conjugated via a cleavable linker to the topoisomerase I inhibitor deruxtecan. In the first-in-human TROPION-PanTumor01 trial, Dato-DXd produced an objective response rate of approximately 20% in previously treated NSCLC [3]. Although this activity appears somewhat lower than that of some other ADCs, it is important to note that the enrolled population was broad (without stringent selection for TROP2 expression or specific molecular contexts). Moreover, dose-limiting toxicities such as stomatitis were observed at the recommended dose, indicating that subsequent studies must further optimize dose and schedule. A phase III trial (TROPION-Lung01) is evaluating Dato-DXd as second-line therapy for advanced NSCLC versus docetaxel; preliminary reports suggest a PFS benefit, but full details remain pending. In addition, a first-line trial in PD-L1-positive patients (TROPION-Lung08; Dato-DXd plus pembrolizumab) was reportedly stopped after an interim analysis failed to meet expectations, consistent with earlier observations that TROP2-ADC efficacy may be limited in unselected NSCLC populations [12]. These findings suggest that TROP2 ADCs may require more precise patient selection to realize maximal clinical value.

3.2.3 Sacituzumab govitecan and derivatives

Sacituzumab govitecan (IMMU-132) is an ADC in which an anti-TROP2 IgG is conjugated to SN-38 (the active metabolite of irinotecan) through an acid-labile linker. It has been approved in triple-negative breast cancer and has been introduced into lung cancer research. A China-developed related ADC, SKB264 (international generic name: sacituzumab tirumotecan), has shown encouraging activity in NSCLC [9]. In the phase I/II studies reported by Zhao and colleagues (KL264-01 and SKB264-II-08), previously treated EGFR-wild-type and EGFR-mutant NSCLC patients were enrolled. In the overall cohort (n=43), the confirmed ORR was 40% and the median PFS was 6.2 months [9]. Efficacy was higher in the EGFR-mutant subgroup, with an ORR of 55% and a median PFS of 11.1 months [9]. These observations were supported by an additional phase II cohort focused on EGFR-mutant disease, in which 64 patients achieved an ORR of 34% and a median PFS of 9.3 months [9]. Across 107 patients, pooled analyses suggested particularly strong activity of TROP2 ADCs in EGFR-mutant NSCLC, while responses in EGFR-wild-type disease were somewhat lower but still approached an ORR of ~30% [9]. Mechanistically, EGFR mutations may enhance ADC internalization and thereby increase drug sensitivity [9]. Based on these results, phase III trials of SKB264 are underway in EGFR-mutant NSCLC in both first-line and later-line settings.

3.2.4 ADC-immunotherapy combinations

Although single-agent activity is notable, the positioning of TROP2 ADCs across broader NSCLC populations remains under investigation. A particularly compelling example is the OptiTROP-Lung01 phase II study reported by Hong and colleagues, which combined an optimized anti-TROP2 ADC (sacituzumab tirumotecan) with the anti-PD-L1 antibody tagitanlimab as first-line therapy for advanced NSCLC without targetable driver alterations [6]. The ORR was 40.0% in the 3-week dosing cohort and reached 66.7% in the 2-week dosing cohort; the disease control rate exceeded 85%, median PFS had not yet been reached in the more intensive cohort, and 12-month survival was markedly improved [6]. These outcomes are comparable to current first-line standards (e.g., chemoimmunotherapy). Importantly, the safety profile was manageable: the main adverse events were hematologic toxicities such as grade ≥3 neutropenia (~30%) and infrequent grade 1-2 infusion reactions, with no treatment-related deaths [6]. This "chemotherapy-sparing" ADC-immunotherapy regimen provides a new option for patients who are not candidates for, or prefer to avoid, chemotherapy. The results also support potential immune synergy: ADC-mediated tumor killing may release tumor antigens and remodel the tumor microenvironment, thereby augmenting ICI efficacy. In the future, TROP2 ADCs may form complementary combinations with immunotherapy to improve efficacy while reducing conventional chemotherapy toxicity.

3.2.5 Safety profile

The safety profile of TROP2 ADCs depends on payload class. For SN-38-based sacituzumab derivatives, the toxicity spectrum resembles that of irinotecan, with myelosuppression as the most common adverse event (neutropenia incidence ~30%) and gastrointestinal reactions such as mild-to-moderate diarrhea in a subset of patients [6,9]. Reassuringly, although topoisomerase inhibitor-based ADCs can carry ILD risk, the incidence of ILD with sacituzumab derivatives in lung cancer studies has been approximately 1% among 107 patients treated with sacituzumab tirumotecan, only one ILD case was reported [9]. By contrast, because Dato-DXd uses the same deruxtecan payload class as T-DXd, vigilance for ILD is warranted, and sporadic ILD cases have been observed in both breast cancer and lung cancer trials. Accordingly, toxicity monitoring should be tailored to the specific payload and linker features of each TROP2 ADC. In addition, some ADCs employing microtubule toxins (e.g., MMAE) can cause peripheral neuropathy and rash; these adverse events must also be considered in clinical practice.

3.3 HER3-targeting ADCs

3.3.1 Biological rationale

HER3 (ERBB3), a member of the EGFR receptor family, is expressed at limited levels in normal tissues but is often highly expressed in EGFR-mutant lung cancer, where it contributes to survival signaling. After acquired resistance to EGFR TKIs, tumor cells may upregulate HER3 and its ligand heregulin, activating the downstream PI3K-AKT pathway to bypass EGFR inhibition [8]. Thus, HER3 is considered a key alternative pathway in EGFR-mutant NSCLC after TKI resistance. However, because HER3 lacks an active kinase domain, traditional small-molecule targeting strategies have been challenging. ADCs provide a distinct approach for HER3: by using an anti-HER3 antibody to deliver cytotoxic payloads to HER3-expressing tumor cells, ADCs can eliminate resistant clones without requiring direct inhibition of HER3 signaling.

3.3.2 Patritumab deruxtecan (HER3-DXd)

Patritumab deruxtecan (HER3-DXd) is currently the most advanced HER3-targeting ADC. In the HERTHENA-Lung01 phase II study reported by Yu and colleagues, which enrolled metastatic NSCLC after EGFR TKI resistance, HER3-DXd monotherapy demonstrated clear antitumor activity: the confirmed ORR was 27.7% and the median PFS was approximately 5.5 months [8]. Notably, the trial included both EGFR-mutant patients and driver-negative patients; subgroup analyses suggested similar efficacy regardless of the presence of a driver alteration [8]. This implies that HER3 ADCs may have broader utility in HER3-high NSCLC beyond the EGFR-mutant setting. A phase III randomized trial (HERTHENA-Lung02) is ongoing to compare HER3-DXd with standard chemotherapy in EGFR-mutant NSCLC after resistance to third-generation EGFR TKIs such as osimertinib [14]. This study will clarify whether HER3-DXd can become a new standard option after EGFR TKI failure.

3.3.3 Other HER3 ADCs in development

Beyond patritumab deruxtecan, multiple anti-HER3 ADCs are in clinical development. For example, Weng and colleagues reported a novel HER3 ADC (AMT-562) with broad preclinical antitumor activity, including activity in HER3-expressing lung cancer models [15]. Another China-developed HER3 ADC, DB-1310, also demonstrated potent tumor growth inhibition in preclinical studies [16]. Most of these candidates use topoisomerase I inhibitor payloads in an effort to replicate the success of HER3-DXd, though alternative strategies-such as more potent microtubule toxins or dual-target ADCs-are also being explored, without definitive breakthroughs to date. Clinically, some studies are evaluating combinations of HER3 ADCs with EGFR TKIs, with the goal of sustaining EGFR pathway suppression while eradicating HER3-expressing resistant cells to achieve more durable disease control.

3.3.4 Balancing efficacy and safety

Compared with HER2- and TROP2-targeting ADCs, reported ORRs for HER3 ADCs are somewhat lower, which may reflect both the biology of HER3 and the heavily pretreated status of enrolled populations. HER3 expression is often lower and less homogeneous than HER2, potentially limiting ADC potency; additionally, post-EGFR TKI resistance disease is biologically complex, with substantial heterogeneity and diverse resistance mechanisms, which can reduce response rates. Safety is also a key consideration. In the HERTHENA-Lung01 study, 51.1% of patients experienced grade ≥3 adverse events, mainly hematologic toxicities such as neutropenia and anemia [8], highlighting the reduced marrow reserve common in later-line settings and the need for careful dose optimization and supportive care. As with other DXd-based ADCs, a small number of ILD events were observed with HER3-DXd (without reported deaths in this study but requiring close monitoring). Overall, HER3 ADCs open a new therapeutic avenue for EGFR-mutant NSCLC after resistance, but improving efficacy while maintaining safety-potentially through rational combination strategies-will be a major focus of future research.

3.4 MET-targeting ADCs

3.4.1 Role of MET in NSCLC

The MET receptor tyrosine kinase pathway contributes to multiple oncogenic processes in NSCLC. MET amplification or protein overexpression can act as a primary driver or as a mechanism of acquired resistance to EGFR TKIs. Notably, approximately 5-10% of EGFR-mutant NSCLC patients develop MET amplification or bypass activation after TKI resistance, making MET pathway inhibition an important strategy to overcome resistance [13]. Small-molecule MET inhibitors (e.g., capmatinib, tepotinib) are used in NSCLC with MET exon 14 skipping alterations; however, in MET amplification/high-expression settings, small molecules may have limited durability and resistance can emerge readily. ADCs provide an alternative approach for targeting MET-high tumors.

3.4.2 Telisotuzumab vedotin (ABBV-399)

Telisotuzumab vedotin (ABBV-399) is an ADC comprising an anti-c-MET antibody (ABT-700) conjugated to the microtubule toxin MMAE. Early phase I data showed activity in MET-high (IHC 3+) NSCLC but minimal efficacy in MET-low disease [17]. In the subsequent phase II LUMINOSITY single-arm study focusing on MET-high populations, objective response rates were approximately 18-25%; in the EGFR-mutant, MET-high subgroup, the ORR was ~15-20% with a median PFS of about 5.5 months [18]. Although these outcomes are somewhat lower than those reported for contemporaneous TROP2 or HER3 ADCs, they indicate meaningful activity in selected subsets. Evidence also suggests telisotuzumab vedotin can shrink lesions in some EGFR-mutant, MET-amplified resistance cases, potentially delaying progression [19]. Telisotuzumab is being explored in combination with osimertinib to address EGFR-MET-driven resistance. Because its payload is MMAE, its toxicity profile differs: peripheral neuropathy and rash/pruritus have been prominent, alongside common hematologic toxicities [18]. Compared with topoisomerase I inhibitor-based ADCs, a clear ILD safety signal has not been evident for current anti-MET ADCs.

3.4.3 Other anti-MET ADCs

In addition to telisotuzumab, other MET ADCs are under preclinical development. For example, a novel anti-MET ADC employing a higher-affinity antibody and a more stable linker showed greater serum stability and improved pharmacokinetic properties in models compared with telisotuzumab [3]. Although these candidates remain distant from clinical application, technical refinements-such as homogeneous conjugation and linker optimization-may enhance efficacy in MET-aberrant lung cancer. Overall, MET ADCs provide an additional therapeutic intervention for MET-altered NSCLC, particularly in the context of TKI resistance. However, current data suggest their activity may not be sufficient to replace established therapies as monotherapy, and they may be best positioned as part of combination regimens or as a complementary option for carefully selected patients.

3.5 Emerging and Other ADC Targets

In addition to the major targets above, ADCs against several emerging targets are being explored in NSCLC.

3.5.1 B7-H3 (CD276)

B7-H3 is an immune checkpoint molecule that is broadly overexpressed in many solid tumors, including lung cancer, but has limited expression in normal tissues. B7-H3-targeting ADCs have progressed rapidly in recent years. In a phase I/Ib trial reported by Ma and colleagues, the ADC YL201 was evaluated in 312 patients with advanced solid tumors (including NSCLC, small-cell lung cancer, nasopharyngeal carcinoma, and others) [1]. YL201 uses a tumor microenvironment-cleavable linker and a novel topoisomerase I inhibitor payload, and antitumor activity was observed

across cohorts. In the NSCLC subgroup, the ORR was 28.6%, whereas ORRs exceeded 50% in small-cell lung cancer and certain rare types such as lymphoepithelioma-like carcinoma [1]. Importantly, YL201 demonstrated a favorable safety profile at scale: grade ≥3 hematologic toxicities such as neutropenia occurred in ~30%, and ADC-associated ILD was rare (4 cases; 1.3%), with almost no severe infusion reactions [1]. These results suggest that rational ADC design can preserve efficacy while markedly reducing toxicity. B7-H3 ADCs may benefit NSCLC patients who lack actionable driver alterations and require new options, potentially including PD-L1-negative or immunologically "cold" tumors. Given the immunoregulatory role of B7-H3, potential interactions with ICIs should be carefully evaluated in future combination studies.

3.5.2 Folate receptor-alpha (FRα)

Folate receptor-alpha (FRα) is highly expressed in only a subset of lung cancers, but expression can be substantial in certain lung adenocarcinoma patterns (particularly solid-predominant and fetal-like differentiation). An FRα-targeting ADC (mirvetuximab soravtansine) has already been approved in ovarian cancer. Recently, Yuan and colleagues reported that a newer FRα ADC, luveltamab tazevibulin, showed clear antitumor activity in FRα-positive NSCLC preclinical models and induced immunogenic cell death [7]. If clinical trials can be developed with biomarker-based selection, FRα ADCs may offer a precision treatment option for this niche patient subgroup.

3.5.3 CEACAM5 (CEA)

Cs CAR-T-mediated killing depended more strongly on high antigen density [20]. This suggests that even when antigen expression is heterogeneous or moderate, ADCs may still be effective via mechanEACAM5 (carcinoembryonic antigen, CEA) is another surface antigen that can be relatively highly expressed in lung adenocarcinoma, particularly in smoking-associated tumors. Several investigational ADCs (e.g., labetuzumab govitecan) target CEACAM5, though much of the current clinical evidence comes from colorectal cancer. Interestingly, Kim and colleagues compared CEACAM5-targeting ADCs with CAR-T therapy in resistant lung cancer models and found that ADCs were cytotoxic across a range of CEA expression levels, whereaisms such as the bystander effect. Accordingly, CEACAM5 ADCs may become a future option for CEA-positive lung cancer, including selected resistant cases.

3.5.4 Other potential targets

ADC target development for NSCLC continues to expand. Examples include tumor vasculature-associated targets (e.g., DLL3, primarily expressed in neuroendocrine tumors but potentially relevant to some large-cell neuroendocrine lung cancers) and immunosuppressive molecules (e.g., ADCs targeting TGF-β ligand latency-associated proteins). These programs remain in early stages and are not discussed in detail here. Nonetheless, as multi-omics studies reveal additional NSCLC-specific surface antigens, the target landscape for ADCs is expected to broaden further, enabling therapies tailored to distinct histologic and molecular subtypes.

4 SAFETY AND TOXICITY MANAGEMENT

Because ADCs introduce highly potent cytotoxins systemically, their distinct toxicity profiles require close clinical monitoring and proactive management.

4.1 Interstitial Lung Disease (ILD)

Interstitial lung disease (ILD)/pneumonitis is among the most concerning severe adverse events of ADCs, particularly those carrying topoisomerase inhibitor payloads. Patients with NSCLC often have limited pulmonary reserve, and prior radiotherapy or TKI exposure may increase baseline risk of lung injury. Therefore, ADC-associated ILD warrants heightened vigilance in lung cancer treatment. T-DXd-associated ILD occurs at an incidence of approximately 10%, and treatment-related deaths have been reported in both breast cancer and lung cancer cohorts [5,10]. A small number of ILD events have also been observed with HER3-DXd and Dato-DXd. However, ILD risk varies substantially among ADCs: as noted above, a B7-H3 ADC using an innovative linker reported an ILD incidence of only 1% in several hundred patients [1], and ILD with sacituzumab-class TROP2 ADCs has generally been <1-2% [9]. These differences suggest that ILD may be influenced by payload properties, tumor distribution, and underlying patient lung status. In practice, patients receiving higher-risk ADCs (e.g., T-DXd, HER3-DXd) should undergo baseline chest imaging and be followed regularly for respiratory symptoms and imaging changes. New or unexplained cough or dyspnea should prompt strong suspicion for ILD, immediate treatment interruption, and timely corticosteroid intervention. Early recognition and management are critical to reducing severity.

4.2 Myelosuppression

Myelosuppression is a common dose-limiting toxicity of many ADCs, manifesting as neutropenia, anemia, and thrombocytopenia. It may result from off-target payload release into circulation or from ADC binding and internalization by normal progenitor cells that express low levels of the target antigen. For example, neutropenia rates with SN-38-based sacituzumab govitecan can reach 30-50% [6]. T-DXd and HER3-DXd have also reported grade 3-4 neutropenia rates of ~25-50% [8,10]. Hematologic nadirs typically occur 1-2 weeks after dosing and can be managed through dose modification, extending dosing intervals, and prophylactic or therapeutic use of granulocyte colony-stimulating factor (G-CSF). In combination regimens (e.g., ADC plus ICI), clinicians should be attentive to potential additive myelosuppressive effects.

4.3 Hepatotoxicity and Gastrointestinal Adverse Events

Some ADCs cause hepatotoxicity and gastrointestinal adverse events. Payloads in the topoisomerase inhibitor class (DXd or SN-38) can lead to transient elevations of transaminases and signs of biliary injury; although most events are grade 1-2 and reversible, liver function should be monitored regularly [5]. Common gastrointestinal symptoms include nausea and reduced appetite, with occasional diarrhea and mucositis [9]. These toxicities resemble those of small-molecule chemotherapy and can be managed with standard supportive care, such as antiemetics, antidiarrheals, and oral care measures.

4.4 Infusion-related Reactions (IRRs)

Compared with certain naked antibodies or bispecific antibody therapies, severe infusion-related reactions (IRRs) are uncommon with ADCs, likely because ADC antibodies are typically humanized IgG molecules optimized for tolerability. Nonetheless, a small proportion of patients may experience chills, fever, rash, or hypotension during infusion, usually mild to moderate. In a study of intravenous amivantamab (an EGFR-MET bispecific antibody), optimizing infusion procedures and premedication reduced IRR rates from 67% to ~24% [15]. Although IRR rates for ADCs are much lower, preventive measures-such as slower initial infusion rates and premedication with antihistamines and corticosteroids-are reasonable for patients with significant allergy history or those receiving their first ADC infusion. For mild-to-moderate IRRs, infusion should be paused and symptomatic treatment provided; infusion may be resumed at a slower rate once symptoms resolve. Rare severe hypersensitivity reactions necessitate permanent discontinuation.

4.5 Other Toxicities

Other toxicities vary by payload and target. For example, MMAE-containing ADCs can cause peripheral neuropathy, presenting as numbness or sensory loss in the extremities, and warrant periodic neurologic assessment [18]. Skin toxicities such as rash and pruritus have been reported relatively frequently with some ADCs (e.g., telisotuzumab vedotin), potentially due to low-level target expression in skin appendages or payload leakage, and can often be managed with topical agents and antihistamines [18]. Ocular toxicity (e.g., keratopathy) has been reported with certain payload classes (particularly some microtubule inhibitors, such as DM4 derivatives) and may require ophthalmologic monitoring. Overall, ADC toxicity management emphasizes multidisciplinary collaboration and proactive monitoring. Any new symptom should be evaluated for potential treatment-relatedness, with dose adjustment or treatment interruption when necessary to ensure patient safety.

5 RESISTANCE MECHANISMS AND FUTURE PERSPECTIVES

5.1 Mechanisms of Resistance

Although ADCs have shown promise in NSCLC, their efficacy can be constrained by resistance mechanisms. A common mechanism is loss or downregulation of the target antigen. Under selective pressure, tumor cells may undergo phenotypic evolution that reduces target expression. For example, in HER2-mutant NSCLC treated with T-DXd, resistant tumors may exhibit decreased HER2 expression or even emergence of completely HER2-negative clones, thereby losing sensitivity to subsequent anti-HER2 ADCs [4]. Similarly, after TROP2-ADC therapy, evidence suggests that residual cells may show reduced TROP2 internalization and diminished downstream signaling activity, lowering ADC-mediated cytotoxicity [9]. Therefore, repeat biopsies during continued ADC selection pressure to monitor target status can be valuable for understanding and managing resistance.

Drug efflux and metabolism are additional contributors. Once the payload enters the cytosol, overexpression of multidrug resistance transporters (e.g., ABCB1, ABCG2) may pump the payload out of the cell, attenuating toxicity. In addition, because topoisomerase inhibitor payloads act by disrupting DNA topology, tumor cells may partially offset their effects by upregulating DNA damage repair programs.

The tumor microenvironment also plays an important role. Dense stroma and elevated interstitial pressure in solid tumors can impede ADC penetration and distribution, preventing delivery of sufficient drug to deeper tumor regions. Moreover, some resistant clones may adopt dormant or stem-like states that are less sensitive to cytotoxic agents [13]. Baldacci and colleagues reported that drug-tolerant persister cells in EGFR-mutant NSCLC are resistant to conventional TKIs but can be eradicated by TROP2-targeting CAR-T cells indirectly supporting the potential of therapies (including ADCs) that target surface antigens on resistant cells [13]. However, if resistant cells enter dormancy with reduced proliferation, payloads that preferentially kill dividing cells may become less effective. Overall, ADC resistance is typically multifactorial, involving changes at the level of target antigen, tumor-cell intrinsic biology, and the tumor microenvironment.

5.2 Combination and Sequencing Strategies

To delay and overcome ADC resistance, combination strategies merit intensive study. ADC plus ICI combinations are among the most attractive: ADC-mediated cytotoxicity can release tumor antigens and stimulate immune responses,

while ICIs relieve tumor-induced immunosuppression, creating a complementary "two-pronged" effect. In OptiTROP-Lung01, first-line therapy combining a TROP2 ADC with an anti-PD-L1 antibody produced outcomes far superior to historical single-agent data [6]. Future studies should test whether similar benefits extend to other contexts, such as combining HER2-targeting ADCs with immunotherapy to further improve outcomes in HER2-mutant lung cancer.

Combinations of ADCs with small-molecule targeted therapies are also logically compelling. For example, in EGFR-mutant NSCLC with MET amplification at resistance, combining a MET ADC with an EGFR TKI may simultaneously inhibit the primary pathway and the bypass pathway, potentially enhancing efficacy; relevant clinical trials are already underway. Likewise, pairing a HER3 ADC with an EGFR TKI could both suppress signaling and eliminate HER3-expressing resistant cells, potentially prolonging disease control. Nevertheless, combination regimens may introduce additive toxicity, requiring careful optimization of dose and sequencing in trials.

With respect to sequencing, a potential strategy is to administer ADCs after TKIs to eradicate residual resistant clones. For instance, in EGFR-mutant NSCLC at the time of osimertinib resistance, switching directly to a HER3 or TROP2 ADC might limit further expansion of resistant clones and enable chemotherapy-sparing disease control in selected patients. Retrospective series have suggested feasibility; for example, case reports describe patients achieving marked responses when T-DXd was administered promptly after TKI failure [21]. Prospective studies are needed to define the optimal treatment order.

5.3 Next-generation ADC Development

Looking ahead, ADC applications in NSCLC are expected to expand alongside technological advances and improved biological understanding. Priority directions include "smarter" ADC designs-linkers that are more stable in circulation yet selectively activatable in tumors, conjugation technologies that enable higher DARs without compromising antibody properties, and payloads better suited for repeat dosing. Some efforts focus on controllable-release ADCs that liberate payload only in the presence of tumor-enriched enzymes, thereby reducing exposure of normal tissues. Multifunctional ADCs may also emerge, such as radioimmunoconjugates carrying radioisotopes or immunoconjugates delivering immune-stimulatory agents to generate local radiotherapy-like or immunostimulatory effects. In parallel, reducing manufacturing complexity and cost is important: ADCs are often expensive and technically challenging to produce, limiting access. As more companies enter the field and biosimilar development progresses, costs may decrease and enable broader benefit for patients with NSCLC.

5.4 Patient Selection and Biomarkers

Finally, precise patient selection is essential to maximize benefit and avoid overtreatment. Antigen expression remains the foundational selection criterion-for example, using anti-HER2 ADCs in HER2 IHC-high or HER2-mutant disease, and applying anti-MET ADCs in MET IHC 3+ tumors. Beyond antigen levels, additional biomarkers are under exploration. For instance, STK11 mutations are associated with an immunosuppressive microenvironment and reduced benefit from immunotherapy, yet ADCs-which are not fully dependent on T-cell function-may still be effective, offering an opportunity for patients with STK11-mutant tumors and PD-(L)1 resistance [22]. Other candidate biomarkers include post-treatment kinetics of circulating tumor DNA in plasma and levels of circulating tumor cells as potential indicators of response. Future large clinical trials should systematically collect these biomarker data to build more robust decision models for ADC therapy.

6 CONCLUSION

As a "biological missile"-like therapeutic modality, ADCs are increasingly becoming integral to NSCLC treatment. From HER2-mutant disease to EGFR-acquired resistance, from broadly expressed targets such as TROP2 to emerging targets such as B7-H3, ADCs are bringing new hope to patients across NSCLC subtypes. Commentary in leading journals has noted that "the rise of ADCs marks an era of precision oncology centered on antibody-guided drug release" [1]. At the same time, ADCs are not "magic bullets": efficacy can still be improved, safety requires meticulous management, and resistance will inevitably emerge. Nonetheless, with continuing innovation in ADC design, deeper mechanistic insights, and rational combination strategies, the outlook for ADC applications in NSCLC is highly promising. Looking forward, ADCs may work alongside immunotherapy and targeted therapies to shape a new treatment paradigm for lung cancer, enabling more durable and effective control of advanced NSCLC.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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