

Current Status and Future Prospects of TROP-2 ADCs in Lung Cancer Treatment

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Abstract: Lung cancer is the leading cause of mortality worldwide, and non-small cell lung cancer accounts for the majority of lung cancer cases. Chemotherapy and radiotherapy constitute the mainstays of lung cancer treatment; however, their associated side effects involving the kidneys, nervous system, gastrointestinal tract, and liver further add to dismal outcomes. The advent of antibody–drug conjugates (ADCs) could change this situation. Trophoblast surface antigen 2 (TROP-2), a human trophoblast surface antigen, is a tumor-associated antigen that is expressed at low levels in normal tissues and is overexpressed in a variety of malignant tumors. The differential expression of the TROP-2 protein in a variety of tumors makes tumor immunotherapy with ADCs targeting TROP-2 a promising approach. Previous studies have shown that the expression of TROP-2 is related to the prognosis of patients with lung cancer and that TROP-2 expression is different across different histological types; however, research on TROP-2 and TROP-2 ADCs in patients with lung cancer is not comprehensive. The aims of this study were to review the mechanism of action and clinical efficacy of TROP-2 and related drugs in the treatment of lung cancer, to elucidate the prognostic value of TROP-2 in lung cancer, and to discuss the future prospects of TROP-2 ADCs to provide a reference for the precise treatment of lung cancer.

Keywords: TROP-2, antibody–drug conjugates, lung cancer

Introduction

Lung cancer is a significant global health issue and the primary cause of cancer-related deaths worldwide; it is the leading cause of cancer deaths, accounting for an estimated 1.8 million deaths and 18.7% of total cancer deaths worldwide in 2022, according to the latest assessment data from the World Health Organization's International Agency for Research on Cancer (IARC). Lung cancer is classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC).¹ The emergence of targeted therapies and immunotherapy has introduced novel treatment options for patients with advanced NSCLC. EGFR-tyrosine kinase inhibitors (EGFR-TKIs) have better clinical efficacy and lower toxicity compared to chemotherapy, and thus TKIs have been established as the standard first-line treatment regimen for EGFR-mutated advanced NSCLC.² Immunotherapies utilizing immune checkpoint inhibitors (ICIs), particularly programmed death-1 (PD-1) / programmed death ligand-1 (PD-L1) inhibitors have been approved as standard treatment options for advanced NSCLC without driver mutations³ and have significantly improved the outcome of driver mutation-negative NSCLC, with a 5-year overall survival (OS) of 15.5% for second-line treatment with pembrolizumab⁴ and 13.4% for second-line treatment with navilizumab,⁵ leading to a substantial improvement in survival rates.⁶ Nevertheless, only a subset of patients have experienced a positive response to these therapies, and some have even developed drug resistance or severe side effects. One of the primary challenges in modern oncology is to minimize toxic side effects

while enhancing the effectiveness of anticancer drugs. Antibody–drug conjugates (ADCs) constitute a new generation of biopharmaceutical compounds that consist of cytotoxic drugs linked to monoclonal antibodies.⁷ ADCs combine the advantages of highly potent small-molecule cytotoxic drugs with the targeting potential of monoclonal antibodies (mAbs), making them novel antitumor drugs with the potential for precision therapy for lung cancer.

Trophoblast surface antigen 2 (TROP-2) is encoded by the TACSTD2 gene, a member of the TACSTD gene family.⁸ TROP-2 is involved in several intracellular signaling pathways and transduces intracellular calcium signaling, providing critical signals for cell proliferation, survival, self-renewal, and invasion.⁹ TROP-2 also has stem cell-like properties and regulates cell growth, transformation, regeneration, and proliferation; additionally, it plays a role in maintaining tight junction integrity.¹⁰ TROP-2 can increase the concentration of calcium Ca^{2+} in the cytoplasm and induce the release of intracellular calcium reserves in the absence of extracellular calcium ions to promote downstream signaling. The phosphorylation of the S303 site of the TROP-2 protein catalyzed by the PIP2 protein activates IP3 and the downstream calcium signaling pathway, the MAPK signaling pathway, and the PKC signaling pathway, thereby increasing the proliferative capacity of cells.¹¹ TROP-2 and IGF-binding proteins both have thyroglobulin type 1 domains. Both TROP-2 and IGF-binding proteins have thyroglobulin type 1 domains, and studies have shown that TROP-2 can compete for binding to IGF-1R through the thyroglobulin type 1 domain to form a complex, blocking the activation of IGF-1 and its downstream mediators such as β -catenin/slug.¹² Studies have shown that TROP-2 is overexpressed in most human solid epithelial carcinomas and is also considered to be a prognostic marker for most of these tumors. TROP-2 expression can activate the ERK-MAPK signaling pathway by up-regulating the levels of phosphorylated ERK1/2, increasing the expression of Cyclin D1 and Cyclin E and thereby promoting tumor proliferation.⁹ TROP-2 also can promote cell cycle progression through the PI3K/AKT signaling pathway.¹³ TROP-2 is expressed in many normal tissues, including the skin, uterine cervix, esophagus, and tonsil crypts, and it has been found to be up-regulated during accelerated fetal lung growth or expansion.^{10,14,15} In one study, inducing a 75% reduction in TROP-2 expression resulted in a 50% reduction in the percentage of proliferating fibroblasts. Therefore, TROP-2 may play a role in regulating the normal growth of fetal lungs.¹⁶ However, it is also overexpressed in many cancers, and this overexpression is of prognostic significance. Studies have shown that TROP-2 is overexpressed in most human solid epithelial cancers, and it has also been proposed as a prognostic marker for most such tumors.¹⁷

Several ADCs are currently undergoing clinical trials for NSCLC and SCLC and target different receptors. In NSCLC, ADCs include Trastuzumab deruxtecan (T-DXd) targeting HER2,¹⁸ YL202/BNT32610 targeting HER3,¹⁹ Sacituzumab govitecan targeting TROP-2,²⁰ CEACAM5-DM4 (SAR408701) targeting CEACAM5.²¹ And in SCLC, ADCs include Telisotuzumab-vedotin (Teliso-V) targeting c-MET,²² and Rovalpituzumab tesirine (Rova-T) targeting DLL3.²³ TROP-2 is highly expressed in various solid tumors, making it a significant target for the development of ADCs.²⁴ Owing to the complexity of TROP-2 downstream signaling and function, many TROP-2 ADCs are still in the research, development, and clinical trial stages. The clinical efficacy and indications for TROP-2 ADCs in lung cancer are still unclear. In this review, we summarize the clinical data of multiple TROP-2 ADC lung cancer cohorts and discuss the efficacy, safety, and adverse effects of TROP-2 ADCs in NSCLC and SCLC patients; we also identify lung cancer patients suitable for TROP-2 ADCs on the basis of existing studies, establish a more precise treatment plan for patients, and propose that TROP-2 ADCs may improve clinical efficacy and reduce drug resistance. The development of TROP-2 ADCs to improve clinical efficacy and reduce drug resistance is recommended.

Immunobiological Characteristics of Patients with Lung Cancer

Lung cancer is a complex and highly heterogeneous tumor that is influenced by genetic, environmental, microbial, and metabolic factors,²⁵ and tumor cells use various mechanisms to evade the surveillance and clearance of the immune system, resulting in an immunosuppressive tumor microenvironment. The immunobiological characteristics of lung cancer mainly include (1) tumor mutational burden (TMB), (2) PD-L1 expression level, (3) microsatellite instability (MSI), and (4) tumor-infiltrating lymphocytes (TILs). (1) TMB is used to reflect the number of mutations in tumor cells, and when the number of mutations in tumor cells increases, the number of new antigens expressed also increases, thereby enhancing the immune function of the body.²⁶ Therefore, tumors with a high TMB are more likely to elicit an immune response and may be more sensitive to ADCs.²⁷ (2) PD-L1 is a key immunomodulatory molecule, PD-1 is mainly

expressed by activated T lymphocytes and is an important inhibitory checkpoint of the immune response that ensures T-cell tolerance, NK cells in cancer patients may also express PD-1, PD-1/PD-L1 interaction inactivates T cells and NK cells and can inhibit CD8⁺ cytotoxicity immune responses and NK cell-associated innate immunity and the anti-tumor immune response it elicits.²⁸ (3) MSI is a result of functional defects in mismatch repair (MMR) genes that lead to the accumulation of mutations in repeated DNA sequences (microsatellites) in cancer cells. However, the prevalence of MSI in non-small cell lung cancer varies widely across different studies.²⁹ (4) TILs are various types of lymphocytes present in the tumor microenvironment that can reflect the dynamic balance between the tumor and the immune system and can also serve as important indicators for evaluating the effects of immunotherapy and patient prognosis.

Composition, Structure and Mechanism of Action of ADCs

ADCs are an emerging class of antitumor drugs that combine the high specificity of monoclonal antibodies with the high activity of small-molecule cytotoxic drugs. Compared with traditional fully or partially humanized antibodies or antibody fragments, ADCs can release highly active cytotoxins in tumor tissues and thus theoretically have greater efficacy. As ADCs can accurately identify targets without affecting noncancerous cells, they greatly improve the efficacy of drugs and reduce drug toxicity and side effects, which has made ADCs one of the most popular directions of research in the field of precision oncology treatment in recent years. Currently, several ADC drugs have been approved for clinical use worldwide (including for hematological and solid cancers), and more than one hundred ADC drugs are undergoing clinical studies.³⁰

The three key components of ADCs include antibodies, linkers and payloads. Antibodies are usually humanized monoclonal IgG antibodies that are preferentially expressed on tumor cells: humanized immunoglobulins are less prone to inducing adverse immune reactions owing to their low immunogenicity, and IgG isoforms are often used in ADCs owing to their circulatory stability, ease of manufacture and high affinity for the Fc receptor.³¹ The linker connects the antibody to the payload, maintains the stability of the ADC, and ensures that the ADC is delivered intact to the tumor cell target without premature cleavage in the circulation to trigger a normal cytotoxic response. Currently, there are two main types of linkers: cleavable and non-cleavable junctions. As the percentage of injectable antibodies targeted to solid tumors is very small, highly toxic compounds with sub-nanomolar potency are needed, and eligible drugs need to contain suitable functional groups to couple to junctions and remain stable during drug preparation, storage and circulation, as well as have low immunogenicity. Therefore, the cytotoxic drugs that can be used to construct ADCs are currently classified into three main groups: (1) microtubule protein inhibitors, which include auristatin analogs and medeniosine alkaloids; (2) DNA synthesis inhibitors, which include actinomycin, doxorubicin, and pyrrolobenzodiazepines; (3) topoisomerase inhibitors, which include RNA polymerase II and cephalosporin derivatives. The most commonly used drugs are microtubule protein inhibitors, which account for more than half of the clinically developed ADC drugs. Microtubule protein inhibitors destabilize microtubules by binding to microtubule proteins, leading to G2/M phase cell cycle arrest.³²

After the antibody to ADC binds to the specific antigen on the surface of tumor cells, the antigen-ADC complex enters the cytoplasm through receptor-mediated endocytosis and then enters the endosomal/lysosomal pathway to form early endosomes, whereas some of the ADCs are off-target due to reasons such as instability in the coupling between linkers and cytotoxic drugs, and they are released prematurely before they reach their target-targeted tumor cells, causing drug related adverse reactions. Endocytosis causes some of the proton ions to enter the early endosomes, and these proton ions provide an acidic environment for the cytotoxic drug to decouple from the cleavable linkers and thus be released from the early endosomes. Whereas a portion of the ADC returns to the extracellular compartment, this recirculation mechanism serves as a buffer against cell death in case of mis-delivery. Finally, ADCs retained in the early endosome are converted to the late endosome, and the acidic environment causes cytotoxic drugs to decouple from cleavable linkers, whereas non-cleavable linkers and some of the cleavable linkers that remain un-decoupled are decoupled from cytotoxic drugs in the presence of protease-rich lysosomes, allowing free cytotoxic drugs to be released into the cytoplasm. Cytotoxic drugs can cause apoptosis by interfering with microtubule proteins, DNA disruption by insertion into DNA, or affect the synthesis, replication and transcription of DNA in targeted tumor cells via topoisomerase inhibitors or inhibitor of RNA polymerase. The pathway of cell death depends on the cytotoxic drug to which the ADCs are coupled. ADCs can

also release free drug from killed tumor cells into the tumor microenvironment, killing neighboring cancer cells, a process known as the bystander effect (Figure 1).^{33–35}

Current Status of TROP-2 ADC Research

TROP-2 is a promising target for ADC-based therapy because of its differential expression in various tumor types and its association with tumor aggressiveness and poor prognosis; it has been reported to be overexpressed in several solid tumors, such as breast, cervical, esophageal, gastric, colorectal, oral squamous cell, ovarian, prostate, pancreatic, thyroid and bladder cancers.¹⁵ However, the relationship between TROP-2 expression and prognosis in patients with lung cancer varies by subtype. In lung adenocarcinoma, TROP-2 expression was shown to be positively associated with increased lung cancer-specific mortality (univariate risk ratio (HR) = 1.60, 95% CI = 1). A previous study revealed a positive correlation between TROP-2 expression and prognosis in patients with low-grade neuroendocrine tumors (LGNET) (multivariate variable HR = 2.44, 95% CI = 1.16–5.13, $P = 0.022$) and a negative correlation in patients with high-grade neuroendocrine tumors (HGNET) (multivariate variable HR = 0.13, 95% CI = 0.020–0.44, $P = 0.0003$); however, there was no significant correlation found in patients with squamous cell carcinoma (univariate HR = 0.79, 95% CI = 0.35–1.94, $P = 0.79$).³⁶ There is a significant positive correlation between TROP-2 expression and abnormal p53 nuclear accumulation/expression in lung adenocarcinoma.³⁷ Mutant p53 inhibits Smad/p63 signaling by inducing TGF- β production to induce cancer metastasis; whereas inactivation of p63 increases TROP-2 expression. Therefore, it is believed that the ablation of p63 by p53 is associated with TROP-2 overexpression. Additionally, p53 mutations are associated with a poorer clinical prognosis in patients with lung adenocarcinoma, further suggesting that high TROP-2 expression is associated with shorter OS.³⁸ Zheng et al discussed urgent clinical problems related to TROP-2 ADC

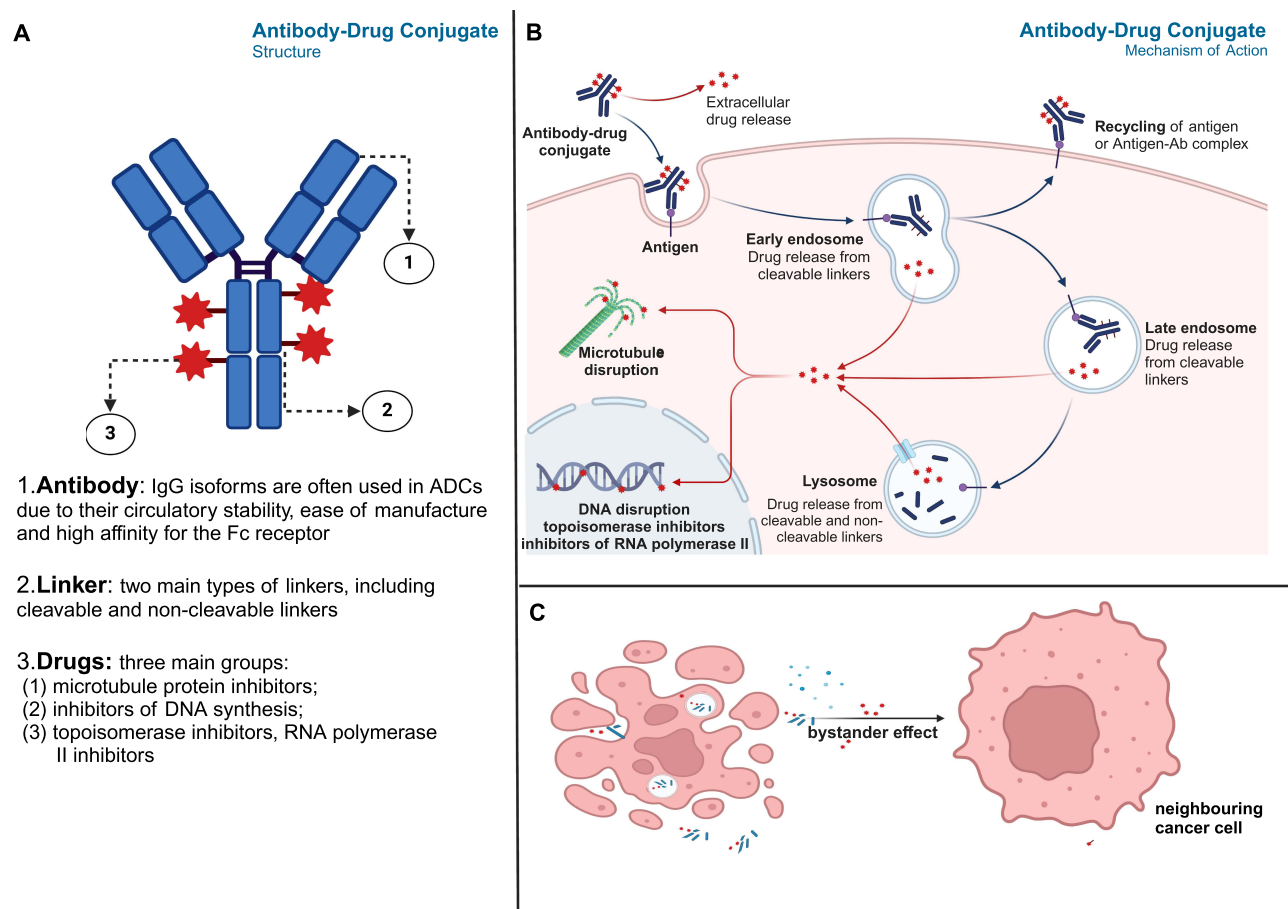


Figure 1 Schematic diagram of the ADC structure and mechanism of action. **(A)** Schematic diagram of the structure of ADC. **(B)** The underlying mechanism of action for ADCs. **(C)** Bystander effect of ADCs on neighbouring cancer cell. (Created with BioRender. L, (M) (2024) BioRender.com/e34m049).

treatment in lung cancer patients, including difficulties in screening patients who can benefit from treatment due to differences in TROP-2 expression in various subtypes of lung cancer and the need to explore advantageous populations and circumvent ADC-associated adverse drug reactions. Notably, high levels of TROP-2 antibodies are correlated with malignancy and metastasis in NSCLC patients. The study concluded that high levels of TROP-2 antibodies can serve as diagnostic biomarkers for NSCLC patients. Additionally, combining TROP-2 antibodies with other tumor markers can further improve detection sensitivity.³⁹

In recent years, research on TROP-2 ADCs has led to many significant advances, among which sacituzumab govitecan-hziy has already been approved for marketing, and a variety of other drugs have entered the preclinical and clinical stages; thus, TROP-2 is emerging as a new star in the field of ADCs. The following is a brief description of the current research status, clinical efficacy and adverse effects of three representative TROP-2 ADCs, providing a reference for the subsequent development of TROP-2 ADCs and screening for indications.

Sacituzumab Govitecan

Sacituzumab govitecan (SG, IMMU-132) is an anti-TROP-2 humanized mAb, hRS7 IgG1, coupled to SN-38, the active metabolite of irinotecan, a topoisomerase I inhibitor.⁴⁰ SG has a high drug-antibody ratio (DAR), ie 7.6, and a unique hydrolysable linker coupling the antibody and SN-38, with the linker permitting the release of therapeutic concentrations of SN-38 within the tumor as well as extracellular release in the tumor microenvironment, producing a bystander effect.⁴¹

Data from multiple study cohorts have demonstrated antitumor efficacy.⁴² The most common SG treatment-related adverse events (TRAEs) reported in the IMMU-132-01 trial were nausea (62.6%), neutropenia (57.8%), diarrhea (56.2%), fatigue (48.3%), alopecia (40.4%) and vomiting (38.6%). Severe AEs were febrile neutropenia, diarrhea and vomiting.⁴³

SKB264

SKB264 is a novel TROP-2 ADC that uses 2-methylsulfonylpyrimidine as a linker coupled to a topoisomerase I inhibitor, the belotecan derivative KL610023, which shares the same monoclonal antibody as SG and has a longer half-life and more potent targeting and antitumor activity than SG does. KL610023 has a bystander effect and can be internalized at the Blocks cell cycle progression at the G2/S phase, leading to cell death. 2-Methylsulfonylpyrimidine is used as a novel coupling group between the junction and the mAb via irreversible nucleophilic aromatic group substitution.

Preclinical studies of SKB264 have demonstrated its ability to inhibit tumor growth in various cell line-derived xenograft (CDX) and patient-derived tumor xenograft (PDX) models, such as lung, breast, gastric and colorectal cancer models. The off-target toxicity of SKB264 observed occurred mainly in TROP-2 high-expressing tissues, including those of the gastrointestinal, hematopoietic and immune systems, but its gastrointestinal adverse effects were milder than those of IMMU-132.⁴⁴

Datopotamab Deruxtecan

Datopotamab deruxtecan (Dato-DXd, DS-1062a) is a novel TROP-2 ADC consisting of the recombinant humanized anti-TROP-2 IgG1 mAb datopotamab coupled with the topoisomerase I inhibitor DXd via a tetrapeptide junction with a DAR of 4. Dato-DXd induces DNA damage and apoptosis through the release of DXd, which is one of the cytotoxic mechanisms of Dato-DXd in cancer cells. Unlike SG, it has a cleavable tetrapeptide junction and a more efficient payload, with high antitumor potency, less systemic toxicity, and better antitumor efficacy in tumors with high TROP-2 expression.^{45,46}

In vitro assays revealed that Dato-DXd inhibited cell growth in vitro and significantly reduced the growth of high-TROP-2-expressing cell lines but had no effect on low-TROP-2-expressing cell lines.⁴⁵ Findings have demonstrated the potential of Dato-DXd in the treatment of lung cancers, and a clinical evaluation of the first human Phase I study of Dato-DXd in patients with advanced solid tumors is underway (ClinicalTrials.gov identifier: NCT03401385). The most common adverse events of any grade included stomatitis (56%) and nausea (62%), and drug-related hematological

toxicity was rare.⁴⁷ This potential advantage of less hematological toxicity may provide an opportunity for the combination of Dato-DXd with other drugs, such as PARP inhibitors.

ADCs in the Therapeutic Algorithm for Lung Cancer (Table I)

TROP-2 ADCs and SCLC

SCLC is a malignant tumor of the lung that originates from the bronchial mucosa or glands and tends to spread early, and 80–85% of patients have extensive metastases at the time of diagnosis. Currently, the main treatment for limited-stage SCLC is chemotherapy combined with chest radiotherapy; only systemic treatment for extensive-stage SCLC can alleviate symptoms and prolong survival. Although chemotherapy is highly effective, it also has a high relapse rate.⁴⁸ Despite many immunotherapies and targeted therapies for SCLC, few improvements in SCLC treatment and survival

Table I Ongoing Clinical Trials of TROP-2 ADCs for the Treatment of Lung Cancer

NCT Number	Study Status	Conditions	Interventions	Primary Outcome Measures
NCT05460273	Active_not_recruiting	Non-small cell lung cancer (NSCLC)	Drug: Datopotamab Deruxtecan	Objective response rate (ORR)
NCT05687266	Recruiting	NSCLC	Drug: Datopotamab Deruxtecan	Progression-free survival (PFS), Overall survival (OS)
NCT04940325	Recruiting	Metastatic lung cancer	Drug: DS-1062a	ORR
NCT05609968	Recruiting	NSCLC	Drug: Sacituzumab Govitecan	PFS
NCT06431633	Not_yet_recruiting	NSCLC	Drug: Sacituzumab Govitecan	Disease free survival (DFS)
NCT04152499	Recruiting	Lung cancer	Drug: SKB264	Phase I: Maximum tolerated dose (MTD) and recommended doses for expansion (RDEs), Phase II: ORR
NCT06074588	Recruiting	NSCLC	Drug: Sacituzumab Tirumotecan	PFS
NCT05941507	Recruiting	Advanced solid tumors	Drug: LCB84	Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
NCT06055465	Recruiting	Lung cancer	Drug: Sacituzumab Govitecan	Pathological complete response (pCR) rate
NCT05633667	Recruiting	Lung cancer	Drug: Sacituzumab Govitecan-hziy	ORR or pCR rate
NCT05186974	Active_not_recruiting	NSCLC	Drug: Sacituzumab Govitecan-hziy	ORR
NCT05089734	Active_not_recruiting	NSCLC	Drug: Sacituzumab Govitecan-hziy	OS
NCT04826341	Suspended	Small cell lung cancer (SCLC)	Drug: Sacituzumab Govitecan	Phase I: MTD, Phase II: ORR
NCT04794699	Recruiting	Solid tumor	Drug: Sacituzumab Govitecan	Dose-limited toxicities (DLTs), MTD, ORR and duration of response (DOR)
NCT06401824	Not_yet_recruiting	NSCLC Stage IV	Drug: Sacituzumab Govitecan	ORR
NCT01631552	Completed	Lung cancer	Drug: Sacituzumab Govitecan-hziy	ORR

(Continued)

Table 1 (Continued).

NCT Number	Study Status	Conditions	Interventions	Primary Outcome Measures
NCT04143711	Recruiting	Solid tumor	Drug: Sacituzumab Govitecan-hziy	DLT, ORR, and treatment emergent adverse event, (TEAE)
NCT03337698	Active_not_recruiting	NSCLC	Drug: Sacituzumab Govitecan	ORR
NCT04644068	Recruiting	NSCLC	Drug: Datopotamab Deruxtecan	AEs, SAEs, and DLT
NCT04526691	Active_not_recruiting	Advanced or metastatic NSCLC	Drug: Datopotamab Deruxtecan	DLTs and TEAE
NCT05215340	Recruiting	Metastatic NSCLC	Drug: Datopotamab Deruxtecan	PFS, OS
NCT06417814	Not_yet_recruiting	Metastatic NSCLC	Drug: Datopotamab Deruxtecan	PFS
NCT05061550	Recruiting	NSCLC	Drug: Datopotamab Deruxtecan	pCR, AEs and SAEs
NCT0555732	Recruiting	Metastatic NSCLC	Drug: Datopotamab Deruxtecan	PFS, OS
NCT04656652	Active_not_recruiting	NSCLC	Drug: DS-1062a	PFS, OS
NCT04484142	Active_not_recruiting	NSCLC	Drug: DS-1062a	ORR
NCT03401385	Recruiting	NSCLC	Drug: Datopotamab Deruxtecan	DLT, AEs
NCT06357533	Recruiting	NSCLC	Drug: Datopotamab Deruxtecan	PFS, OS
NCT06279728	Available	Advanced or Metastatic NSCLC	Drug: Datopotamab Deruxtecan	Unknown
NCT06350097	Recruiting	NSCLC	Drug: Datopotamab Deruxtecan	PFS
NCT04612751	Recruiting	Advanced or metastatic NSCLC	Drug: Datopotamab deruxtecan	DLTs, TEAEs and other safety parameters during the study.

Note: The clinical trials listed in the Table 1 are derived from the <https://clinicaltrials.gov/>.

have been reported. Studies on the use of ADCs in SCLC are still scarce, and CD56, DLL3, DLL4, EpCAM, and TROP-2 have been the main targets for used for the development of ADC drugs (Figure 2).⁴⁹ CD56 is expressed in almost all SCLC.⁵⁰ SCLC express neuroendocrine markers such as synaptophysin, chromogranin-A, and CD56. CD56 is the most sensitive because it stains 90–100% of SCLC, which should serve as an effective target for ADC drugs.⁵¹ In SCLC, DLL3 is overactive on the tumor cell surface and positively correlates with ASCL, a member of the BHLH transcription

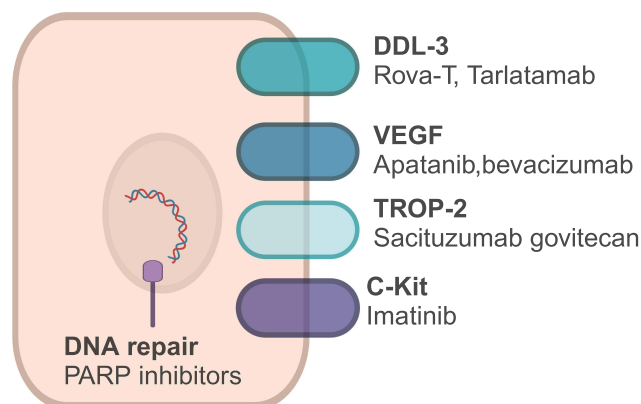


Figure 2 Examples of action sites and emerging therapies for SCLC (created with BioRender. L, (M) (2024) BioRender.com/z11i096).

factors involved in neuroendocrine cell fate determination.⁵² Rovalpituzumab tesirine (Rova-T, SC16LD6.5) is the first cytotoxic cytotoxicity via a protease cleavable junction associated with payload-related DLL3-targeting antibody, and although the first human phase I trial published by Rudin et al showed significant efficacy, with an objective remission rate (ORR) of 18% in extensive-stage SCLC (ES-SCLC) with high DLL3 expression (>50% expression) and an ORR of 38%, in which very little toxicity was reported,⁵³ a follow-up study demonstrated the inefficacy of Rova-T in SCLC.⁵⁴ Therefore the development of DLL3-targeted ADC drugs is still under investigation. The role of DLL4 in lung cancer is controversial. DLL4 expression is accompanied by elevated hypoxia-inducible factor-1 α (HIF1 α), micro vessel density (MVD), and vascular endothelial growth factor (VEGF), which promotes tumor angiogenesis; whereas, DLL4-expressing endothelial cells (ECs) can promote tumor angiogenesis by activating cellular tumor cells by activating Notch1/PTEN signaling and inhibiting the proliferation of neighboring cancer cells, suggesting that endothelial DLL4 has a tumor-suppressive role in lung cancer.^{55,56} EpCAM is heterogeneously expressed in SCLC, with EpCAM-positive cells having greater growth and colony-forming ability. In lung cancer cells, SOX2 induces EpCAM/p21/cell cycle protein A2 by binding to the EpCAM promoter, leading to enhanced cell proliferation. SOX9 inhibits the expression level of SOX2, leading to decreased cell proliferation and a more aggressive phenotype.⁵⁷

Some studies have shown that the IGF-IR pathway plays an important role in the growth of SCLC and that the expression of IGF-IR is increased in SCLC cell lines.^{58,59} TROP-2 can promote tumor proliferation by competing for binding to IGF-IR and blocking the activation of genes such as IGF-1 and its downstream mediator β -catenin/slug, thus suggesting that TROP-2 ADCs are feasible for the treatment of SCLC. Gray et al investigated the TROP-2-targeted ADC IMMU-132 in 50 patients with metastatic and pretreated SCLC (Phase II study). The ORR based on local remission was 17.7%, and the median duration of remission was 5.7 months (range 3.6–19.9 months). In the IMMU-132-01 study, patients with SCLC had an ORR of 17.7%, a median progression-free survival (mPFS) of 3.7 months and a median OS (mOS) of 7.1 months (n = 62).⁴³ Further expansion of the recruitment cohort into the phase II study of IMMU-132-11 is currently underway to assess its activity in patients with ES-SCLC.

Currently, the study of TROP-2 ADCs for the treatment of SCLC is still in the early stages. With the gradual increase in the number of clinical applications of ADCs, explorations of the mechanism of TROP-2 ADC resistance in SCLC to improve the efficacy of drugs, the screening of suitable populations for TROP-2 ADCs and explorations of combination therapy strategies involving ADCs and other drugs in SCLC are urgently needed.

TROP-2 ADCs and NSCLC

Owing to its high TROP-2 expression, because TROP-2 is highly expressed in a variety of NSCLC subtypes, TROP-2 ADCs are considered novel agents with promising development and application for the treatment of NSCLC. Early clinical trial data on the safety and efficacy of the TROP-2 ADCs IMMU-132 and DS-1062 in refractory advanced or metastatic NSCLC have been reported.

Sacituzumab Govitecan-Hziy NSCLC Cohort Study

The development of TROP-2 ADC drugs is booming, and IMMU-132 is one of the products that has received much attention in recent years. IMMU-132 was shown to be efficacious and well tolerated by patients with pretreated metastatic non-small cell lung cancer in a single-arm multicenter trial.⁶⁰ In this trial, the ORR in the evaluable response study population (n = 47) was 19%, the median duration of response (mDOR) was 6.0 months (95% CI, 4.8–8.3 months), and the clinical benefit rate (complete remission + partial remission + stable disease for ≥ 4 months) was 43%. The median PFS and OS in the ITT population were 5.2 months (95% CI, 3.2–7.1 months) and 9.5 months (95% CI, 5.9–16.7 months), respectively. The grade 3 or higher adverse events included neutropenia (28%), diarrhea (7%), nausea (7%), fatigue (6%) and febrile neutropenia (4%). In terms of safety, Trodelvy performed as well as in triple-negative breast cancer, with hematological toxicity remaining unavoidable, with 30% neutropenia observed in the 10 mpk dose group, which somewhat limits its expansion to studies of NSCLC. A separate Phase III registrational clinical trial (NCT05089734) of Trodelvy monotherapy in stage II+ NSCLC patients is ongoing.

The open-label phase I/II IMMU-132-01 basket trial tested the safety, tolerability and efficacy of sacituzumab govitecan-hziy in adult patients (n = 495) with patient-refractory metastatic epithelial cancer. In the phase I/II IMMU-

132-01 trial, patients were enrolled regardless of TROP-2 expression levels, and the cohort of NSCLC patients ($n = 54$) received rigorous pretreatment (median of 3 prior therapies); all patients had received prior platinum-based chemotherapy, and approximately one-third had received prior ICIs (eg, anti-PD-1 or anti-PD-L1) or EGFR inhibitors. The primary endpoints of the study included safety and the ORR, with secondary endpoints of PFS and OS; 54 NSCLC patients included in the study had an ORR of 16.7%, an mPFS of 4.4 months (95% CI: 2.5–5.4), and an mOS of 7.3 months (95% CI: 5.6–14.6).⁴³ However, in this study, more than 90% of the tumor specimens had high levels of TROP-2 IHC expression, making TROP-2 unsuitable as a predictive biomarker.

Datopotamab Deruxtecan NSCLC Cohort Study

Preclinical studies have shown Dato-DXd to be a promising therapeutic option in the treatment of non-small cell lung cancer, with significant antitumor activity in several CDX and PDX models of NSCLC with high expression of TROP-2,⁴⁵ resulting in tumor cell growth inhibition. The apparent antitumor activity and acceptable safety profile of Dato-DXd in preclinical models have led to clinical evaluation advances.

The Phase 1 TROPION-PanTumor01 trial was the first-in-human trial of the safety, tolerability, and antitumor activity of Dato-DXd in the treatment of patients with advanced solid tumors and included a study of Dato-DXd in patients with relapsed/refractory advanced/metastatic NSCLC ($n = 180$).⁴⁷ Among the 180 participants, 61% had received ≥ 3 prior treatment regimens, 84% had received immunotherapy, and 96% had received platinum-based chemotherapy. The primary endpoints of the study were the safety and maximum tolerated dose of Dato-DXd, including the MTD and recommended expansion dose; the secondary endpoints were the antitumor activity, pharmacokinetic properties and antidrug antibody test results. In the study, Dato-DXd was shown to have significant antitumor activity and a manageable safety profile in heavily pretreated patients with advanced NSCLC. In patients treated with 6 mg/kg Dato-DXd, the median PFS was 6.9 months (95% CI, 2.7–8.8 months), and the median OS was 11.4 months (95% CI, 7.1–20.6 months). Monotherapy with 6 mg/kg Dato-DXd led to an ORR of 28% in patients with pretreated NSCLC and a manageable safety profile. The most common treatment emergent adverse events (TEAEs) included nausea, stomatitis and alopecia, and the most common grade ≥ 3 TEAEs were pneumonia, anemia and decreased lymphocyte count. However, overall, the rates of Dato-DXd-related adverse reactions in the treatment of patients with NSCLC were still high, with grade 3 or higher drug-related AEs of 14%, 26%, and 36% in the three trial dose groups, and ILDs were observed in all three dose groups.

In addition, Dato-DXd has also been assessed for efficacy in combination with immune checkpoint inhibitors in the treatment of NSCLC.⁶¹ The results of the phase Ib TROPION-Lung02 study presented at the ASCO Annual Meeting 2023 confirmed the efficacy and safety of Dato-DXd in combination with pembrolizumab $\pm$ platinum-based chemotherapy in patients with advanced NSCLC with no targeted genomic alterations, either primary or treated. As of 7 April 2023, a total of 136 patients were treated. Among these patients, 58% and 75% in the doublet ($n = 64$) and triplet ($n = 72$) groups, respectively, were receiving first-line therapy, with 19% and 25%, respectively, of patients having received prior immunotherapy; the median duration of treatment was 14.8 and 12.9 months in the two groups, respectively. The results of the study revealed that in the first-line treatment population, the ORR was 50% (95% CI: 32–68%) in the doublet group, with 15 confirmed partial remissions (PRs) and 2 unconfirmed PRs, and 57% (95% CI: 42–70%) in the triplet group, with 1 confirmed complete remission (CR) and 29 confirmed PRs. In addition, the disease control rate (DCR) was 91% in both the dual and triple groups, and the mDOR was not reached in either group. In the total population, the ORR was 38% (95% CI: 27–51%) in the dual group and 49% (95% CI: 37–61%) in the triple group. The DCRs were 84% and 87% in the dual and triple groups; the median PFS was 8.3 months (95% CI: 6.8–11.8) and 7.8 months (95% CI: 5.6–11.1), respectively, but data are still being collected. Dato-DXd in the combination regimen also had a manageable safety profile, with the most common adverse events during treatment being stomatitis, nausea, anemia and fatigue, mostly grade 1/2, with no grade 4 or 5 interstitial pneumonitis. The results of the study demonstrate that Dato-DXd + pembrolizumab $\pm$ platinum-based chemotherapy is expected to provide a new effective treatment option for patients with advanced NSCLC.⁶²

SKB264 NSCLC Cohort Study

As SKB264 has more potent antitumor activity than IMMU-132 at the same dose, lower doses of SKB264 can achieve the same efficacy as higher doses of IMMU-132, avoiding more potent adverse effects.⁴⁴ The promising findings of the use of IMMU-132 in a cohort of NSCLC patients have prompted clinical trials of SKB264 for the treatment of NSCLC. The results of a phase I/II clinical trial of SKB264 were presented at ASCO 2023 (Clinical trial information: NCT04152499).⁶³ A total of 43 patients with NSCLC were enrolled in the study, 76% of whom had received more than 2 lines of therapy, including 74% who received chemotherapy, 49% who received immunotherapy, and 30% who received triple-generation EGFR-TKIs. As of February 2023, for the 30 patients with assessable efficacy, the ORR was 43.6%, with an mDOR of 9.3 months, and the mOS had not yet been achieved (median follow-up time 11.5 months); for the 20 patients with EGFR mutations, the ORR was 60%, the mDOR was 9.3 months, and the mPFS was 11.1 months.

Future Outlook for TROP-2 ADCs

Possible Mechanisms of TROP-2 ADC Adverse Reactions

The application of ADCs is a double-edged sword, resulting in significant clinical efficacy while inevitably increasing the risk of drug-related adverse reactions. Only approximately 0.1% of the drug dose is delivered to the targeted diseased cell population after ADC drugs enter the human body, and the vast majority of the drug is distributed in the circulation or to normal cells, leading to unwanted toxicity.⁶⁴ A meta-analysis of adverse reactions in clinical trials of ADC drugs revealed that the incidence of all SG-related adverse events was as high as 97.1% (95% CI, 96.0–98.2%), and the incidence of $\geq$ grade 3 treatment-related adverse events was 61.1% (95% CI, 57.6–64.6%).⁶⁵ To better exploit the therapeutic value of TROP-2 ADC drugs, exploring the mechanism of ADC drug adverse events and thus optimizing the management strategy of adverse events is one of the future research directions for TROP-2 ADC drugs.

Instability of the coupling between the ADC linker and the cytotoxic drug can lead to off-target toxicity due to the premature release of the payload before reaching targeted tumor cells. There are two main types of ADC drug linkers: cleavable and non-cleavable. However, in practice, cleavable linkers can be affected by poor plasma stability in circulation, and peptide-chain structure-based linkers with high sensitivity to proteases in serum or spontaneous decoupling can lead to the premature release of the payload before reaching the target tissues and the bystander effect, causing toxicity to normal cells owing to the increased ability of the drug to permeate cells.⁶⁶ Non-cleavable linkers can maintain high stability in the bloodstream, and internalization, lysosomal delivery and degradation of the ADC complex are necessary to release the active drug. The use of non-cleavable linkers reduces the probability of drug release from the extracellular space, but in contrast to cleavable linkers, they are unable to kill neighboring tumor cells through the bystander effect. In addition, the coupling site of ADC drugs may also modulate the stability and pharmacokinetics of ADCs. A low DAR reduces ADC efficacy, whereas a high DAR increases the chance of aggregation, leading to reduced plasma stability. ADC toxicity due to joint instability is an important factor that causes neutropenia and peripheral neuropathy in patients,⁶⁷ limiting the widespread use of ADC drugs. Therefore, the use of more advanced linker technology to reduce toxicity to normal cells while retaining the beneficial chemical properties that kill cancer cells, improving the coupling site action to create a more homogeneous ADC and increasing the stability of ADC drugs are bottlenecks in ADC drug development.

Receptor-mediated off-target effects are also important factors in ADC-associated adverse reactions. The IgG constant structural domain is highly conserved, allowing for the initiation of effector immune functions through the interaction of the Fc receptor with other components of the immune system, and normal cells can mediate the nondependent internalization of their targets by recognizing and binding the Fc receptor to the antibody component of ADCs. Fc γ R is known to be responsible for antibody-dependent cellular cytotoxicity (ADCC) via the Fc receptor, complement-dependent cytotoxicity (CDC), and cytokines and causes the release of inflammatory mediators. In ADCs, Fc γ R-mediated effector functions may be involved in target-independent uptake and cytotoxicity in normal cells. Alternatively, Fc γ R is an endocytosis cell surface receptor and may mediate ADC internalization, leading to target-independent toxicity in normal cells (Figure 3).⁶⁶

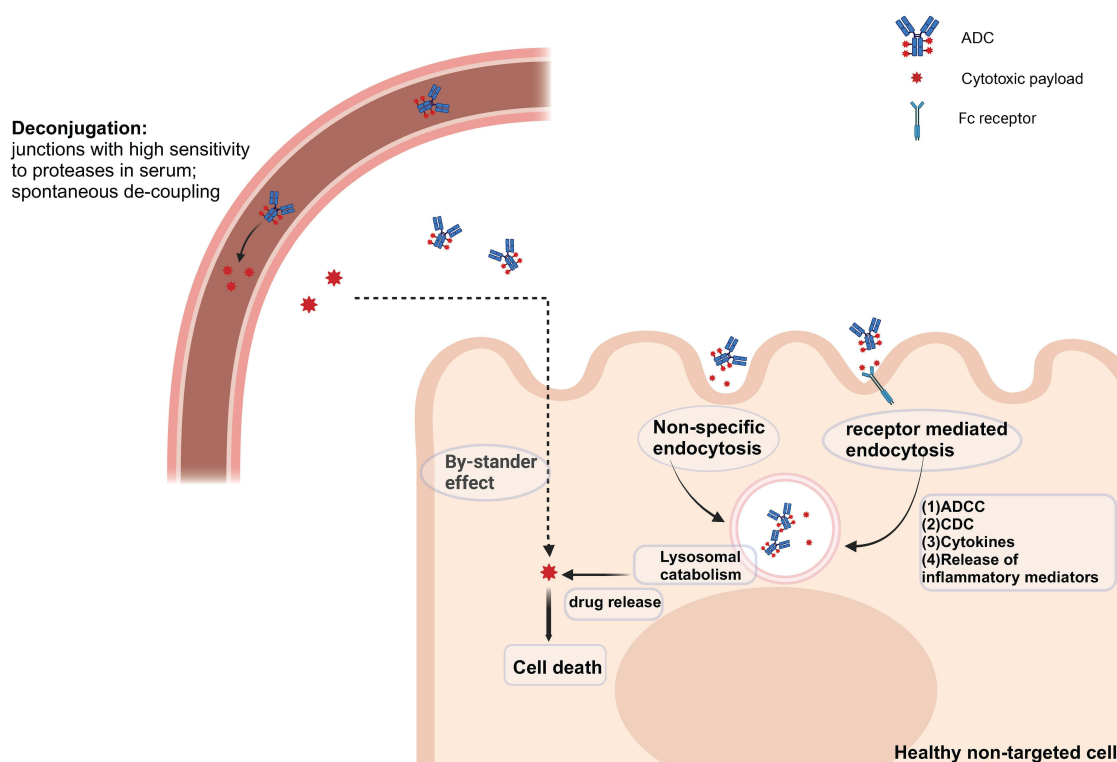


Figure 3 Possible mechanisms of ADC drug toxicity. Intact ADC uptake into normal cells may occur through nonspecific endocytosis or through internalization upon binding to target antigens or Fc/C-type lectin receptors. Payloads released from ADCs or other targeted/nontargeted apoptotic cells in the extracellular fluid may also enter normal cells by passive diffusion of membrane-permeable payloads or by nonspecific endocytosis of membrane-impermeable junction-payload adducts (created with BioRender. L. (M) (2024) BioRender.com/v21f200).

There are still few studies on the mechanism of adverse reactions caused by TROP-2 ADC drugs in lung cancer patients, and understanding the mechanism of adverse reactions will help optimize TROP-2 ADC drugs. It is believed that with the joint efforts of researchers to overcome the shortcomings and challenges of existing ADCs, the next generation of ADC drugs will benefit more oncology patients.

Possible Mechanisms of TROP-2 ADC Resistance

The emergence of ADC drugs has revolutionized the treatment of patients with advanced lung cancer and provided patients with powerful new treatment options, but drug resistance is still a challenge. A review revealed that resistance to ADC drugs is related to antigen expression, the ADC structure and the payload.⁶⁸

Downregulation of Antigen Expression in Tumor Cells

Since ADC drugs are highly dependent on antigen expression for their targeted cytotoxic effects, downregulated antigen expression in cancer cells chronically exposed to the drug is likely to result in acquired resistance to ADC drugs in target cells.⁶⁹ In addition to reduced levels of antigen expression, dimerization of the antigen with another cell surface receptor may also mediate resistance to ADCs.⁶⁸ Given the impact of antigen levels and heterogeneity in mediating ADC resistance, the association between antigen expression and TROP-2 ADC resistance needs to be explored in depth so that resistance can be avoided by adopting, for example, ADCs with bispecific antibodies or used in combination therapies. For example, TROP-2 expression on the surface of lung cancer cells can be upregulated through a feedback mechanism to increase the activity of TROP-2 ADCs, and some studies have shown that there is a significant correlation between TROP-2 expression and p53 mutations and that mutant p53-mediated signaling may affect TROP-2 expression,³⁸ on the basis of these findings, PD-1 inhibitors in combination with TROP-2 ADCs may improve therapeutic efficacy.

Decreased Levels of Internalized ADCs in Tumor Cells

After the ADC antibody binds to the target antigen on the surface of the tumor cell, the antigen-ADC complex enters the cytosol via receptor-mediated endocytosis, initiating the endocytosis mechanism. Sequence changes in the genes encoding the internalization-associated proteins during this process that result in reduced lysosomal acidification and protein hydrolysis activity may alter the intracellular transport of the antigen-ADC complex and reduce the intracellular release of the payload.⁷⁰ ADC drugs that are internalized into cells may alter the tumor cell intracellular environment and thus decrease lysosomal activity. Carla et al reported that a reduction in endosomal/lysosomal activity may be one of the pathways leading to resistance to T-DM1, an ADC drug that targets HER2, with a higher pH in HER2-resistant cells than in wild-type cells, which causes a reduction in lysosomal protein hydrolase activity and reduces T-DM1 internalization.⁷¹ The same mechanism may explain the emergence of resistance to TROP-2 ADCs.

TROP-2 ADC resistance may also occur through the compensatory activation of downstream signaling pathways, such as the PI3K/AKT pathway, the ERK-MAPK pathway, or the JAK-STAT pathway, thereby inhibiting apoptosis and decreasing the inhibitory effect of ADC drugs on tumor cells. These effects can be examined by analyzing the state of several signaling pathways to determine whether proliferation-associated signaling pathways are upregulated or not in drug-resistant lung cancer cell lines.

Upregulation of the Expression of Drug Efflux Pumps

Ample evidence suggests that the expression of ATP-binding cassette (ABC) transporters, especially the multidrug resistance protein 1 (MRP1), which is encoded by ABC subfamily B member 1 (ABCB1), can confer resistance to cytotoxic and targeted chemotherapy.⁷² MRP is often overexpressed in a variety of drug-selected cancer cell lines, and MRP is associated with the resistance of lung cancer cell lines to anticancer drugs.⁷³ Preclinical data also support a role for MRP in other ADC-refractory cancer cell models, as exemplified by T-DM1, where increased expression of MRP1 was observed in a T-DM1-resistant breast cancer cell line, which may be one of the reasons why HER2-positive breast cancer is resistant to T-DM1.⁷⁴ Since many of the ADC many cytotoxic drugs are substrates for drug efflux pump-associated transporter proteins, upregulation of drug efflux pump expression may also contribute to lung cancer cell resistance to ADC.

Optimized Therapeutic Strategies for TROP-2 ADCs

ADC Drug Structure Optimization

In terms of antibody optimization, as the downregulation of TROP-2 antigen expression may lead to the development of drug resistance, the optimization of the TROP-2 mAb and thus the enhancement of the specificity, affinity and pharmacokinetic activity of antibody binding to the antigen is essential for improving the antitumor activity of TROP-2 ADCs. In addition, bispecific or multi-specific antibody-coupled ADCs can be developed to enhance the internalization of TROP-2 ADCs and reduce the occurrence of drug resistance due to the decreased expression of a single TROP-2 antigen. In terms of linker optimization, future studies of TROP-2 ADC linkers should focus on improving the plasma stability, affinity and payload release rate. Current TROP-2 ADCs mainly contain enzyme-cleavable peptide linkers, but the instability of such linkers in plasma and their inherent high hydrophobicity increase the occurrence of ADC drug-related adverse reactions.⁷⁵

The modular structure of ADCs provides the possibility to modify some of their components to develop new compounds that can overcome resistance. Possible mechanisms of resistance to certain payloads (eg, microtubule disruptors) can be referenced and circumvented by altering the cytotoxic payload of drugs with poor efflux substrates. Alternatively, heterogeneous tumor cells surrounding antigen-positive cells could be killed by modifying the cytotoxic drug structure to exploit the bystander effect.³⁴ In addition, the penetration of drugs into tumor cells can be improved by developing smaller TROP-2 ADCs.

Combination Therapy Strategies

Although TROP-2 ADC monotherapy has shown a significant survival benefit in patients with lung cancer, more research is needed. How to maximize the antitumor effect of ADCs, on the one hand, and how to address the resistance problem of ADC monotherapy, on the other hand, make the TROP-2 ADC combination strategy a direction that researchers are constantly exploring. Currently, several clinical trials are exploring the efficacy of TROP-2 ADC combination therapy modalities and have shown encouraging results. In the future, the TROP-2 ADC combination strategy may provide a new option for the first-line treatment of patients with advanced or metastatic NSCLC and SCLC.

A growing body of evidence suggests that ADCs may increase the efficacy of immunotherapeutic agents. The mechanisms involved include the induction of immunogenic cell death, dendritic cell maturation, increased T lymphocyte infiltration, the enhancement of immune memory and the expression of immunomodulatory proteins such as PD-L1 and MHC. In addition, DNA-damaging agents (eg, platinum and topoisomerase inhibitors) that act in the S phase and block the G2/M phase can be appropriately coupled to microtubule-disrupting agents in the ADC cytotoxicity payload to increase their effects in the G2/M phase.⁷⁶ These findings illustrate the great potential of TROP-2 ADCs in combination with immune checkpoint inhibitors, and several trials of ADCs in combination with chemotherapeutic agents or ICIs have been conducted and have demonstrated the enhanced antitumor activity of ADC combination strategies. In a 1b clinical trial (NCT04526691), Dato-DXd in combination with pembrolizumab and platinum-based chemotherapy had a tolerable safety profile and significant activity in patients with first-line and relapsed/refractory NSCLC.⁶¹ As of January 2022, among 46 remission-evaluable patients across cohorts, the ORR was 39% (9 confirmed PRs and 9 PRs to be confirmed), and the DCR was 82.6%. Among the 16 first-line treatment patients with evaluable efficacy, the ORR was 69% (5 confirmed PRs and 6 confirmed PRs), and the DCR was 100%.

TROPION-Lung04 was a multicenter, open, open-label, dose-escalation/confirmation and dose-expansion 1b study that evaluated the safety and efficacy of Dato-DXd and duvarizumab ± carboplatin in 6 cohorts of patients with no targeted genetic alterations in primary or treated advanced/metastatic NSCLC.⁷⁷ Overall, this combination treatment modality had a tolerable and manageable safety profile in patients with advanced/metastatic NSCLC, which is consistent with the known profile of the individual agents, and exhibited significant antitumor activity. In addition, the EVOKE-02 trial evaluated the efficacy and safety of gosatuzumab + pembrolizumab ± platinum in patients with metastatic NSCLC, and the results indicated that the combination was somewhat safe and exhibited some efficacy.⁷⁸ The phase III TROPION-Lung07, TROPION-Lung08, and AVANZAR studies, which are currently underway, are exploring Dato-DXd combination strategies. The results of several studies have reported a manageable safety profile for TROP-2 ADCs in combination with immune checkpoint inhibitors and platinum-based chemotherapy in the treatment of NSCLC, making such combinations with multiple chemotherapeutic agent potential treatment options in the future.

In recent years, preclinical and clinical trials based on the combination of ADCs with other anticancer agents, including chemotherapies, molecularly targeted agents, antiangiogenic agents and immune checkpoint inhibitors, have been actively investigated, and some of the results have led to important advances. A growing body of evidence indicates that TROP-2 ADC combination therapy has significant advantages over monotherapy. However, ADC combination strategies result in potentially increased toxicity overlap, and potential pharmacokinetic interactions need to be considered when designing future combination strategies to reduce cytotoxicity.

Therapeutic Dose and Regimen Optimization

Since most of the adverse effects of ADCs are dose dependent, optimizing the safety of TROP-2 ADCs can start with adjusting the therapeutic dose. Such optimization includes five strategies: setting upper dose limits, upper treatment duration limits, dosing frequency optimization, clinical response-guided dose adjustment, and randomized dose confirmation studies.⁷⁹

The strategy of setting an upper dose limit means that the maximum dose of the TROP-2 ADC needs to be determined according to each patient's body weight and pharmacokinetic properties to avoid unnecessary reactions caused by an overdose. The strategy for determining the upper limit of treatment duration involves controlling the drug dose according to the treatment duration and choosing the appropriate duration of treatment to reduce the risk of chronic and potential adverse reactions. Dosing frequency optimization involves adjusting the peak C_{max} at the same cumulative

dose with reference to the half-life of the drug to mitigate C_{max}-driven adverse events. A patient-response-guided dose adjustment strategy involves the dose being adjusted according to changes in patient symptoms and signs to maximize efficacy and minimize side effects. Randomized dose-confirmation studies are prospective trials in which multiple dose groups of a drug are evaluated to determine the optimal dose to maximize the therapeutic index.

These strategies have been applied in other ADC clinical trials, but there are few studies on TROP-2 ADCs for lung cancer. These five dose exploration strategies are useful for dose development and regimen optimization for future ADCs.

Conclusion

This article provides a comprehensive review of TROP-2 ADCs in lung cancer therapy, including current status, mechanisms of action, and future prospects. Clinical data from multiple TROP-2 ADC lung cancer cohorts are analyzed and provide insights into optimizing treatment regimens, understanding mechanisms of resistance and expanding access to therapies. TROP-2 ADC has emerged as a promising therapeutic approach in the treatment of lung cancer. In clinical trials, TROP-2 ADC has demonstrated efficacy that warrants further investigation. The preliminary results from the IMMU-132 clinical trial indicated efficacy in lung cancer, with the ORR of 17.7% and 19% in SCLC and NSCLC, respectively. The TROP-2 ADC has been demonstrated to markedly diminish tumor size and extend patient survival, while concurrently exhibiting a favorable side effect profile. Consequently, TROP-2 ADC represents a promising avenue for enhancing the quality of life and survival prospects of lung cancer patients, particularly those who are ineligible for or unable to derive benefit from alternative treatments. However, it should be noted that the TROP-2 signaling network may differ significantly between different subtypes of lung cancer. In patients with lung adenocarcinoma and other advanced neuroendocrine tumors, high TROP-2 expression is associated with a poor prognosis. Conversely, in patients with low-grade neuroendocrine tumors, high TROP-2 expression was associated with a more favorable prognosis, whereas no significant correlation was identified in patients with squamous cell carcinoma. Further studies are therefore required in order to determine the upstream regulation of TROP-2 and its downstream effects on tumor growth. This will facilitate the elucidation of the mechanism of resistance to TROP-2-targeted ADCs and the development of effective strategies to counteract it.

It must be acknowledged that this review is not without shortcomings. As TROP-2 ADCs are an emerging therapeutic agent, this review may not encompass the latest research developments or forthcoming clinical trials. Furthermore, it lacks research data on the persistence and late effects of long-term responses in patients following treatment with TROP-2 ADCs. In addition, the cost-effectiveness of TROP-2 ADCs is a crucial factor in evaluating the viability of this emerging therapy for practical clinical application. Additional research is necessary to investigate the potential applications of TROP-2 ADCs in subsequent treatment stages, and combination therapy may prove an effective approach to treating TROP-2 ADCs.

In conclusion, the TROP-2 ADC represents a significant advancement in the field of lung cancer treatment. Further research and innovation will continue to facilitate progress in this field, offering expanded treatment options for lung cancer patients and potentially paving the way for new therapeutic avenues in other cancer types.

Data Sharing Statement

The data presented in this study are available on request from L.Z.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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