Scientific Research Publishing

Journal of Biosciences and Medicines, 2025, 13(1), 145-162
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Application and Research Advancement of Antibody-Conjugated Drugs in Non-Small Cell Lung Cancer

Binting Huang, Kaifang Li, Xiangsheng Wu, Fuyi Zhang, Yepeng Li*

Department of Oncology and Radiotherapy, Youjiang Medical College for Nationalities Affiliated Hospital, Baise, China
Email: *1035813513@qq.com

How to cite this paper: Huang, B.T., Li, K.F., Wu, X.S., Zhang, F.Y. and Li, Y.P. (2025) Application and Research Advancement of Antibody-Conjugated Drugs in Non-Small Cell Lung Cancer. *Journal of Biosciences and Medicines*, **13**, 145-162.
https://doi.org/10.4236/jbm.2025.131012

Received: December 6, 2024
Accepted: January 13, 2025
Published: January 16, 2025

Abstract

Lung cancer is one of the malignant tumor diseases with high morbidity and high mortality in the world. Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer. Currently, chemotherapy, targeted therapy, immunotherapy or combination therapy is the main treatment for NSCLC, but it is still inevitably faced with the challenges of acquired drug resistance and tumor progression. The birth of antibody conjugator provides a new choice for its treatment. Antibody conjugator is a new type of biotherapeutic drug which is connected by monoclonal antibody via linker and cytotoxic drug. It has the characteristics of precision, high efficiency and low toxicity, etc. In recent years, its research and development and clinical trials have been endless. It shows that this new type of drug has great potential in the field of tumor therapy. In this paper, the structural characteristics, mechanism of action, current application, research achievements, challenges, countermeasures and development of ADC in NSCLC treatment are reviewed.

Keywords

Non-Small Cell Lung Cancer, Antibody Coupling Drugs, Combination Therapy, Adverse Reaction

1. Introduction

Based on the analysis of a number of statistical reports, the incidence and mortality of lung cancer are at the forefront worldwide [1], and in China, lung cancer has become the first cause of death of malignant tumors [2]. Lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and the common pathological type is non-small cell lung cancer, account-

ing for about 85% [1]. Most patients with NSCLC lack obvious specific symptoms in the early stage, and the opportunity for surgery is often lost when the diagnosis has reached the advanced stage [3]. Therefore, the treatment mode of NSCLC is mainly surgical treatment combined with postoperative platinum adjuvant therapy for early patients. Patients with advanced NSCLC who have lost their adaptation to surgical treatment are mainly treated with targeted therapy, radiotherapy, chemotherapy or combination therapy. However, due to the staging requirements of surgical treatment and the easy recurrence after radiotherapy, chemotherapy is faced with the challenge of acquired drug resistance, and the 5-year survival rate corresponding to each treatment is still low in patients with advanced NSCLC. Therefore, it is urgent to seek an efficient, stable and low-toxicity treatment strategy.

The original concept of antibody-drug conjugate (ADC) originated from the "magic bullet" proposed by Paul Ehrlich 100 years ago. Since the 1980s, antibody-drug conjugate has been rapidly developed along with the development of monoclonal antibodies [4]. In recent years, many ADC drugs have been approved by the FDA, which has subsequently become a hot spot in the field of tumor therapy. Some ADC drugs have shown good efficacy in the treatment of advanced NSCLC patients, bringing survival hope to patients. This article will review the current research progress and related applications of ADC in NSCLC, and further discuss its clinical efficacy, adverse reactions and limitations.

2. Structure, Characteristics and Mechanism of ADC

ADC is a new type of targeted anti-tumor biologics that connects monoclonal antibodies to cytotoxic drugs through ligands [5] [6]. By specifically binding to the target antigen on the cell surface, it targets and transmits small cytotoxic molecules to tumor cells, and then transmits them to the cell through endocytosis to form lysosomes, in which small cytotoxic molecules coupled with monoclonal antibodies can be released through proteases to specifically kill tumor cells [5] [7]. Each component plays a different role.

Target antigen is an important starting point for ADC design and a driving factor for successful delivery of cytotoxic drugs to target cells [8]. An ideal target antigen should have the following action characteristics: 1) High expression on the surface of target cells, low expression or no expression on the surface of normal cells [8] [9]; 2) Low accessibility, which can prevent antigen from dissociating and then binding with antibodies in the blood circulation system [10]; 3) With internalization properties, it can not only deliver cytotoxic drugs in ADC to the target cells completely to play a killing role, but also prevent unendocytotic toxic drugs from mistakenly playing a role in normal cells [8] [11]; 4) Target antigens with non-secretory and secretory properties can cause ADC targeting to bind to normal structures outside tumor cells, reducing ADC targeting specificity and drug safety [12]. At present, many targets have been clinically studied as antigens in ADC, which are mainly divided into blood system tumor target antigens and

solid tumor target antigens. The blood system tumor target antigens mainly include CD19, CD22, CD30, CD33, etc., while the solid tumor target antigens mainly include HER-2, EGFR, Trop-2, etc. [9] [13]. Among known ADCs developed and applied, HER-2 is an ideal target for many applications [14].

As an important part of ADC drug design, Monoclonal antibody (mAb) can be called the backbone of ADC, featuring target specificity, low immunogenicity, low cross-reactivity, and long cycle half-life [15]. It can specifically recognize the target antigen on the surface of tumor cells and bind to it, thus mediating the process of ADC internalization and entering the cell to play a killing role. The immune effect of ADC is mainly derived from monoclonal antibodies. Due to its strong immune and drug resistance side effects, the murine antibodies originally used have been replaced by humanized antibodies or fully humanized antibodies, which further reduces the immunogenic side effects of antibodies, that is, low immunogenicity [16]. Nowadays, IgG1 is commonly used to construct ADC antibodies, because compared with IgA, IgM, IgG2 and other subtypes, IgG1 has a longer half-life and higher permeability [17], which can improve the antibody dependent cell-mediated cytotoxicity and complement dependent cell-mediated cytotoxicity, etc., thus further improving drug efficacy [18].

As a bridge connecting monoclonal antibodies with cytotoxic drugs, linkers play an important role in the design of ADC, determining the pharmacokinetics, stability, therapeutic efficacy and toxicity of ADC [15] [19]. The linker should be able to bind closely to antibodies and cytotoxic drugs, maintain high stability in the blood circulatory system and normal tissue cells, avoid the drug to free before reaching the target, thus reducing off-target toxicity, and effectively release cytotoxic drugs after the antibody binds to the target antigen, so as to play the precise killing effect of ADC on tumor cells. Linkers can be divided into lysable linkers and non-lysable linkers [18]. Lyable linkers take advantage of the specificity of the target cell's internal environment to dissociate and release cytotoxic drugs in the cell [20]. Non-lytic linkers are cleaved through intracellular lysosomes after the internalization of cytotoxic drugs to release cytotoxic drugs. Compared with the two, each has its advantages and disadvantages. The metabolites produced by lytic linkers can produce a bystander killing effect, but it is more likely to produce off-target toxicity [21]. Non-lytic linkers have higher specificity, stability and safety, and can release cytotoxic drugs more accurately and efficiently, thus increasing the therapeutic window.

Cytotoxic drug is the key factor to determine the killing effect of ADC, and should have high toxicity and high stability. At present, the common cytotoxic drugs are mainly divided into three categories: 1) Microtubule inhibitors, the representative drugs are Auristatin derivatives (such as MMAE, MMAF, etc.), and medenin derivatives (such as DM1, DM4, etc.); 2) DNA damage agents, representative drugs are: kazimycin, Dukakamycin, etc.; 3) Other small molecule poisons, such as: alpha-amanita carinic, etc.

Since the listing of Getuzumab as the world's first ADC in 2000, 15 ADCs have

been approved for listing worldwide, among which 13 ADCs have been approved by FDA, and more than 140 ADCs are still in the clinical research stage [22].

3. Application of ADC in NSCLC

At present, the common target antigens are human epidermal growth factor receptor-2, trophoblast surface antigen-2, human epidermal growth factor receptor-3, tyrosine protein kinase 7 and mesenchymal epithelial transformation antigen.

3.1. Human Epidermal Growth Factor Receptor-2

Human epidermal growth factor receptor 2 (HER2), a member of the ERBB tyrosine kinase family, activates the downstream program through the PI3K-AKT and MEK-ERK pathways, thereby driving the proliferation of tumor cells [23]. In NSCLC, HER-2 protein is mainly manifested in three forms: HER-2 mutation, HER-2 amplification, and HER-2 overexpression, and the incidence rates are about 2% - 4% [24], 2% - 3% [12], and 4.3% - 27.9% [25], respectively.

3.1.1. T-DM1

T-DM1 (Trastuzumab Emtasine), also known as emettrazumab, is an ADC conjugated from trastuzumab via a thioether linker to the cell microtubule inhibitor metametacin DM1. T-DM1 was the first ADC to be used in HER-2 receptor-positive NSCLC trials. Its payload, Metansine, mainly kills tumor cells by inhibiting cell tubulin polymerization [26]. Through *in vitro* experiments, Cretella *et al.* found that T-DM1 could not only inhibit the proliferation of NSCLC cells with high expression of HER-2, thereby inducing apoptosis, but also effectively overcome the resistance of gefitinib [27]. The Phase II basket trial conducted by Li *et al.* recruited 18 patients with advanced lung adenocarcinoma who had received previous treatment and had HER-2 gene mutation. After T-DM1 treatment, their ORR reached 44% and mPFS reached 5 months [28]. At the same time, Li *et al.* conducted a phase II clinical trial named NCT02675829, which used T-DM1 to treat patients with HER-2 mutation and/or amplification of NSCLC. The results showed that: After 5 months of mPFS, the response rates of HER-2 amplification, mutation and coamplification/mutation were 55%, 50% and 50%, respectively. Patients treated with T-DM1 showed good efficacy and tolerance, with relatively few adverse reactions, mostly manifested as anemia or thrombocytopenia [29]. Therefore, T-DM1 is recommended by NCCN as a Class 2A drug for the treatment of advanced NSCLC with HER-2 mutation. In summary, the above studies found that in the treatment of NSCLC, the expression level of HER-2 has a certain impact on the efficacy of T-DM1, which also means that future studies on the expression pathway of HER-2 signal and gene modification can help to accurately target NSCLC patients who can benefit from T-DM1 treatment.

3.1.2. T-DXd (Trastuzumab Deruxtecan)

T-DXd (trastuzumab deruxtecan), also known as Trastuzumab, is an ADC that is conjured from Trastuzumab via a cleavable maleimide tetrapeptide-like linker to

a topoisomerase I inhibitor called DXd. T-DXd has a higher drug-to-antibody ratio (DAR) than T-DM1, with a DAR of 3.5 for T-DM1 and 8 for T-DXd [30]. Its payload DXd induces DNA double strand break and apoptosis by binding to topoisomerase DNA complex [31].

Patients with advanced NSCLC with HER-2 mutation or HER-2 overexpression who had received standard treatment were included in DESTINY-Lung01 to receive a 3-week regimen of T-DXd at a dose of 6.4 mg/kg, and the efficacy and adverse drug events were observed. The study results showed that, The ORR and mPFS of the HER-2 overexpression group were 24.5% and 5.4 months respectively. Compared with the overexpression group, the results of the HER-2 mutant group were more ideal, and the ORR of the HER-2 mutant group was 55%, mPFS was 8.2 months, mDOR was 9.3 months and mOS was 17.8 months. The proportion of patients with grade 3 or higher adverse drug events was 46%, and the most common adverse reaction was neutropenia (19%), but 23 patients developed drug-induced lung disease (DILD), and 2 patients died from it [32]. In conclusion, it can be confirmed that patients with HER-2 mutant NSCLC are highly likely to benefit from T-DXd treatment, but it is still necessary to be vigilant against the occurrence of DILD and other adverse events. The changes in patients' condition should be closely monitored in the early stage of treatment, and the overall medication regimen should be adjusted in a timely and reasonable manner. Based on the conclusion of DESTINY-Lung01, 152 patients with metastatic NSCLC were enrolled in DESTINY-Lung02 and randomly treated with two different doses of T-DXd (6.4 mg/kg, 5.4 mg/kg). In the low-dose group, the ORR was 53.8% and the incidence of related adverse drug events was 31.7%, while in the high-dose group, the ORR was 42.9% and the incidence of related adverse drug events was 58.0% [33]. In conclusion, T-DXd has a certain degree of anti-tumor activity and drug safety, and DESTINY Lung02 has proved that 5.4 mg/kg group has more tumor destruction and safety than 6.4 mg/kg group. Based on the results obtained in this trial, T-DXd was granted accelerated approval by FDA in August 2022. It can be used to treat patients with HER-2 mutations, unresectable or metastatic NSCLC.

At present, DESTINY Lung03 and DESTINY Lung04 are still in the experimental stage; DESTINY-Lung03 aims to study the efficacy, adverse reactions and prognosis of T-DXd, anti-PD-L1 monoclonal antibody Valiumab and chemotherapy drugs alone or in combination [34]. DESTINY-Lung04 aims to study the comparison of efficacy of T-DXd and platinum-Pemetrexed Pembrolizumab combination therapy [35]. It is believed that through a number of studies on T-DXd and NSCLC, it is expected to further enhance clinical efficacy, and improve patient prognosis and quality of life in the future.

3.1.3. Other HER-2 Targeting ADC Drugs

Vedicetumab is a kind of ADC which is formed by conjugated human anti-HER-2 extracellular domain monoclonal antibody with valine-citrulline linker and methyloritatin, and is also the first ADC in China [36]. Other ADCs such as A166

and SYD985 are still in the research stage.

3.2. Trophoblastic Surface Antigen 2

Trophoblast cell surface antigen 2 (Trop2) is a transmembrane glycoprotein that can mediate proliferation, invasion, metastasis and apoptosis of tumor cells [37] and is also a protein product of TACSTD2 gene. It can be achieved through its mediated signaling pathways, mainly through regulating the expression of cell cycle-related proteins, calcium ion signaling pathways, and reducing fibronectin adhesion [38]. Trop-2 is highly expressed on the surface of NSCLC, SCLC, breast cancer, rectal cancer and other tumor cells [39]. Therefore, ADC drugs developed with Trop-2 as the target antigen provide many new options for human to overcome malignant tumor diseases. Trop-2 is highly expressed in 64% of lung adenocarcinoma and 75% of lung squamous cell carcinoma [40], which is closely related to poor prognosis of the disease [41].

3.2.1. Dato-DXd

Dato-DXd (Datopotamab deruxtecan) is an ADC that is synthesized from a human anti-TROP2 monoclonal antibody coupled with a tetrapeptidase linker and topoisomerase I inhibitor DXd. Dato-DXd is characterized by high anti-tumor activity, high safety, and low toxicity. It can induce DNA double strand break and apoptosis through DXd, resulting in the death of tumor cells, and at the same time, play a bystander effect, thereby eliminating target tumor cells and surrounding heterogeneous tumor cells [42].

TROPION Lung01 mainly uses Dato-DXd and docetaxel in the treatment of locally advanced or metastatic NSCLC patients who have received at least one previous treatment to compare the efficacy and safety of the two in such patients. The results showed that the mPFS of Dato-DXd group and docetaxel group were 4.4 months and 3.7 months, mDOR was 7.0 months and 5.6 months, and ORR was 26.4% and 12.8%, respectively. In patients with non-squamous NSCLC, mPFS in Dato-DXd group and Docetaxel group were 5.6 months and 3.7 months, respectively. The most common adverse reactions in Dato-DXd group during treatment were stomatitis (mostly grade 1/2) and nausea [43]. In summary, it is clear that in the current study stage, Dato-DXd shows more ideal anti-tumor activity and more reliable drug safety, which will bring more treatment options and survival hopes for patients with non-squamous NSCLC locally advanced or metastatic NSCLC.

TROPION Lung02 was mainly used to treat patients with advanced NSCLC (including some patients who had not been treated before) with Dato-DXd and palizumab in combination treatment group, and Dato-DXd with palizumab and platinum chemotherapy in combination treatment group, so as to compare the efficacy and safety of the two groups in these patients. The results showed that mPFS in the two-group and three-group were 10.8 months and 7.8 months, and ORR were 38% and 47%, respectively. For first-line treatment patients, ORR in the two-group and three-group were 60% and 55%, respectively. No new therapeutic adverse reactions were reported [44]. In conclusion, both of the two

combined regiments can produce good efficacy and relatively mild adverse reactions in newly treated or treated NSCLC patients. This research result also lays a solid foundation for further discussion and development of ADC-drug combination therapy such as Dato-DXd.

TROPION Lung04 mainly used the Dato-DXd combined with duvaliumab (PD-L1 inhibitor) group and the Dato-DXd combined with duvaliumab and carboplatin group in 6 cohorts to treat patients without AGA and advanced/metastatic NSCLC (some of whom had not received prior treatment) To compare the safety and tumor efficacy of the two combination regimens in these patients; Up to now, the study data of Cohort 2 and Cohort 4 have been disclosed at the WCLC held in 2023. According to the study data, among the first-line treatment population, the ORR of the two-therapy group and the triple-therapy group in cohort 2 are 50.0% and 76.9%, respectively, and the ORR of the two groups in cohort 4 are 47.4% and 71.4%, respectively [45]. In conclusion, regardless of the expression level of PD-L1, the above combined treatment regimen showed significant therapeutic effects and controllable safety tolerance, and the triple therapy group showed better clinical efficacy compared with the double therapy group. For patients without AGA NSCLC, both groups showed good research prospects.

TROPION Lung05 was designed to evaluate the efficacy and safety of Dato-DXd in the treatment of NSCLC. It included 137 patients with NSCLC who had received at least one targeted therapy and one platinum-containing chemotherapy in the past, and were divided into stage IIB, IIC or IV. In the overall patient population, the ORR was 35.8%, mPFS was 5.4 months, mDOR was 7.0 months, and DCR was 78.8%. Among patients with EGFR mutations, Dato-DXd had better outcomes, with an ORR of 43.6%, mPFS of 5.8 months, mDOR of 7.0 months, and DCR of 82.1%. Among 68 EGFR-sensitive mutants or T790M-positive patients who had previously received ocitinib treatment, the ORR was 49.1%. At ESMO ASIA in 2023, data from the Asian population of the TROPION-Lung05 study was presented, and the Asian cohort had an ORR of 42.4%, mPFS of 5.4 months, mDOR of 4.4 months, and DCR of 80.3%. Higher disease response rates were observed, with ORR of 48.9%, mDOR of 4.4 months, DCR of 87.2%, and median PFS of 5.7 months. Dato-DXd has shown good safety in both the general population and the Asian population [46]. In conclusion, this study not only revealed the relatively comprehensive and effective treatment coverage and drug safety of Dato-DXd in NSCLCL, but also demonstrated its therapeutic advantages in the treatment of NSCLC patients with EGFR mutation.

At present, three Phase III studies (TROPION Lung07, TROPION Lung08, AVANZAR) are still in progress.

3.2.2. IMMU-132

IMMU-132 (Sacituzumab govitecan, SG) is an ADC formed from human monoclonal antibody HRS7 coupled to the active irinotecan metabolite SN-38 via cleavable linker CL2A. SN-38 inhibits topoisomerase I to cause DNA damage and exerts anti-tumor activity [47]. In addition, IMMU-132 can further kill cells by

blocking signal transduction, and exert antibody-dependent cell-mediated cytotoxicity and bystander effect [48]. NCT01631552 included 54 patients with metastatic NSCLC and treated them with IMMU-132 to evaluate efficacy and safety. The trial results showed that ORR was 19.0%, DO was 6.0 months, mPFS was 5.2 months, mOS was 9.5 months, and CBR was 43%. Grade ≥3 adverse events were mainly neutropenia, nausea and diarrhea [49]. This study proved that IMMU-132 has good clinical efficacy and tolerance in the treatment of metastatic NSCLC, and such patients can obtain relatively prolonged survival after IMMU-132 treatment. Reix-02 mainly evaluated the efficacy of IMMU-132 combined with pembrolizumab or platinum-based chemotherapeutics in advanced NSCLC [50], WCLC published preliminary data in 2023, and the ORR in cohort A (PD-L1 tumor ratio score ≥50%) was 75%. ORR in cohort B (PD-L1 tumor ratio score <50%) was 44%; The incidence of adverse events was 96%, and the most common adverse events were diarrhea, anemia, fatigue, etc. This data demonstrates the efficacy and controllable safety of IMMU-132 combined with palizumab in the treatment of advanced NSCLC, and also indicates that IMMU-132 combined therapy is expected to overcome the difficulty of strong resistance to immunotherapy, providing hope for patients with advanced NSCLC who have failed immunotherapy.

3.2.3. SKB264

SKB264 is an ADC that is conjugated by the 2-(methylsulfonyl) pyrimidine linker of human monoclonal antibody HRS7 and T030, a derivative of the novel topoisomerase I inhibitor Belotexan. After internalization, T030 can block cell cycle arrest, causing it to stay in the G2/S phase, resulting in cell death. Compared with IMMU-132, it has stronger anti-tumor activity and more accurate targeting [51]. In the ASCO Annual Meeting in 2023, data from the Phase II study of SKB264 in the treatment of advanced treatable NSCLC were updated, which showed that ORR of wild-type patients and EGFR mutant patients were 26.3% and 60%, mPFS were 5.3 months and 11.1 months, respectively, and 1-year OS rates were 60.6% and 80.7%, respectively. The toxic and side effects of SKB264 are mainly manifested as hematological toxicity [52]. In conclusion, based on SKB264 treatment, the survival length of EGFR mutant patients was better than that of wild-type patients. The remaining clinical studies on SKB264 are ongoing.

3.3. Human Epidermal Growth Factor Receptor-3

Human epidermal growth factor receptor 3 (HER3) is a member of the tyrosine kinase family, but it does not have the ability to regulate tyrosine kinase activity. It mainly forms dimers by binding with other members of the family. It promotes the transphosphorylation of tyrosine residues, continuously activates downstream signaling pathways such as PI3K/AKT, and thus makes tumor cells develop drug resistance [53]. HER3 is widely expressed in NSCLC, colorectal cancer, breast cancer and other tumor cells [54]. Research data show that 19% of NSCLC has HER3 overexpression [55]. While HER3 is expressed in a variety of malignant tumors, it is also accurately overexpressed in NSCLC, and it mediates an important

mechanism of tumor drug resistance. This makes HER3 a promising therapeutic target in the field of NSCLC treatment.

U3-1402 (Patritumab deruxtecan/HER3-DXd) is a tetrapeptide-based lytic ligon conjugated by monoclonal antibody Patritumab and DXd, a topoisomerase I inhibitor. It also induces DNA double strand break and apoptosis through DXd, in which the bystander effect produced by lytic linkers also plays a role. Clinical trials of HERTHENA-Lung01 and HERTHENA-Lung02 have been carried out.

HERTHENA-Lung01 studied the efficacy of U2-1402 in patients with metastatic/advanced NSCLC who had previously been treated with EGFR-Tkis and carried EGFR mutations. The results showed that the ORR of 5.6 mg/kg group was the highest in the dose-increasing cohort. Based on these results, 57 patients were enrolled in the dose-expansion cohort to receive U2-1402 (5.6 mg/kg), with ORR of 39%, DCR of 72%, mOR of 2.6 months, and mPFS of 8.2 months. Among them, 53% of patients had tumor diameter reduced by ≥30% compared with the previous imaging examination after treatment. Patients treated by the results and with the recommended dose have a higher ORR than traditional chemotherapy regiments [56]. In summary, the efficacy of U2-1402 is relatively significant, and it is expected to replace traditional chemotherapy drugs in the future and become the first-line treatment for this type of NSCLC patient group.

In the HERTHENA-Lung01II study, two U2-1402 protocols were used to treat patients with advanced EGFR-mutated NSCLC who had received platinum-based chemotherapy and EGFR-TKI [5.6 mg/kg; 3.2, 4.8, 6.4 mg/kg dose increasing ladder], WCLC published the test data in 2022, and the ORR of 5.6mg/kg group was 28.4%, DOR 6.0 months, mOS 11.9 months, and mPFS 5.5 months [57]. In summary, U2-1402 has a significant therapeutic efficacy in patients with EGFR-mutated NSCLC who have previously received EGFR-TKI and/or platinum-based chemotherapy regimen.

HERTHENA-Lung02 mainly studied the effect of U2-1402 on advanced NSCLC patients with EGFR mutation and previously treated with EGFR-Tkis. The study data showed that the ORR of U2-1402 was 29.8%, the mDOR was 6.4 months, and the mPFS was 5.5 months, among which 210 patients were treated with EGFR-Tkis. After re-examination, imaging examination can observe the tumor shrinkage of different degrees [58].

Grade ≥3 adverse drug events in the above two clinical trials were mainly hematological toxic reactions such as thrombocytopenia and neutropenia [56]-[58]. The results indicated that U2-1402 is highly likely to be well tolerated, but a larger number of trials and data are needed to support the degree of bone marrow suppression after treatment to fully ensure drug safety.

3.4. Tyrosine Protein Kinase 7

Protein tyrosine kinase 7 (PTK7) is a transmembrane protein, which mainly mediates the regulation of Wnt signaling pathway and leads to the occurrence and development of tumors [59].

PF-06647020 is an ADC derived from a humanized monoclonal antibody coupled to a microtubule inhibitor Au0101 via a valine-citrulline lytic linker. NCT02222922 mainly studies the efficacy of PF-06647020 on patients with advanced solid tumors who have been resistant to standard anti-tumor therapy in the past. The solid tumor module mainly selects NSCLC, advanced ovarian cancer and triple-negative breast cancer. The research results show that: Among the 25 patients with NSCLC, the ORR was 16%, mDOR was 5.7 months, DCR was 56%, and mPFS was 2.9 months [60], and its efficacy deserves continuous attention.

3.5. Mesenchymal Epithelial Transforming Antigen

Mesenchymal-epithelial transition factor (MET) is a tyrosine kinase hepatocyte growth factor receptor. When it binds to tyrosine kinase hepatocyte growth factor, Activation of MET signaling pathway leads to homologous polymerization and phosphorylation of intracellular tyrosine residues, thereby activating downstream signaling pathways such as PI3K/AKT and MAPK, and ultimately promoting the development of tumor cells [61].

ABBV-399 (Telisotuzumab vedotin, Teliso-V) is an ADC derived from the monoclonal antibody ABT-700 coupled to the microtubule inhibitor MMAE via a valine-citrulline lytic linker. It restricts the mechanism of drug resistance related to intracellular signaling through the payload MMAE, and ultimately achieves the purpose of effectively killing tumor cells [62]. A Phase I/Ib clinical study was set to study ABBV-399 monotherapy to evaluate the efficacy and safety of this regimen in patients with treated NSCLC. The results showed that 23% of MET-positive NSCLC patients achieved objective response, with a DOR of 8.7 months and an mPFS of 5.2 months. In the overall evaluation of drug-related adverse events, fatigue was the most common adverse event (54%), followed by peripheral neuropathy (42%), nausea (38%), etc. [63]. It is proved that ABBV-399 single drug regimen has accurate targeting, good efficacy and controllable safety. Today, there is a problem of EGFR resistance in the treatment of NSCLC. A Phase Ib clinical study focused on patients with MET-positive advanced NSCLC treated with ABBV-399 monotherapy or combined with erotinib showed that the ORR of EGFR-MET (+) patients was 32.1%, of which, The ORR of patients with high MET expression was 52.6%. The common grade ≥3 drug-related adverse events were peripheral neuropathy (7%) and hypophosphatemia (7%) [64]. Thus, the effectiveness of ABBV-399 in the treatment of NSCLC was again verified, and it also brought hope for the treatment of NSCLC patients who had previously received standardized targeted therapy and with EGFR mutation.

3.6. Other ADCs

At present, many ADCs are still in the active research stage, such as XMT-1536, Sacituzumab govitecan, CX-2009, etc. According to the results of existing clinical trials, a series of ADC combination therapy studies are in hot progress, and the subsequent research results are worth looking forward to.

4. Analysis of Challenges and Countermeasures Faced by ADC

4.1 Insufficient Anti-Tumor Activity

4.1.1. Unsatisfactory DAR

As an innovative drug driven by the trend of "precision medicine", ADC is characterized by accuracy, effectiveness and low toxicity. Although it has achieved gratifying results at the current stage, it still faces the challenge that its efficacy has not reached the ideal effect. Small molecule toxic drugs in ADCs are the key to their tumor lethality. The failure to select suitable linkers and toxic drugs in the setting of drug components is the main factor, resulting in the failure of DAR to reach the ideal range. Therefore, ADC with low DAR may have the evaluation outcome of insufficient anti-tumor activity in the evaluation of efficacy. However, excessive DAR may increase off-target toxicity of drugs, thereby affecting efficacy and increasing safety risks [65]. In summary, one of the ways to obtain ideal DAR values is to carefully select linkers and payloads, increase ADC single-component studies, and set stable coupling sites.

4.1.2. Potential Drug Resistance Risk

Due to the heterogeneity and high development of tumor cells, combined with the special action links of ADC (intact extracellular ADC, antibodies about to bind to antigens, cytotoxic drugs released within the cell), tumor cells have a great potential risk of drug resistance. The mechanism of drug resistance in tumor cells may be related to target antigen, antibody binding, internalization, lysosome, release and function of payload, signaling pathway mediating it, and internal environment.

1) Changes in target antigen

Mutated target antigens can change the ability of ADC antibodies to recognize them. Relevant studies have shown that heterodimerization of HER2, HER3, and HER4 family members can reduce the efficacy of trastuzumab [66]. Another study showed that reduced expression level of target antigen could lead to insufficient internalization of trastuzumab to lysosomes, resulting in decreased sensitivity of HER-2 targeted cellular drugs [67]. It is worth noting that tumor cells also evade ADC recognition and binding by changing the type of target antigen or regulating the number of target antigen expression, resulting in immune escape. Therefore, double-specific and double-para-antibodies, which are also in the hot research spot today, can be used to increase the recognition, binding and internalization of ADC target cells to minimize the risk of drug resistance.

2) Changes in the lysozyme's internal environment

Non-lytic linkers and partially lytic linkers are cleaved mainly through intracellular lysosomes to release payloads. Studies have found that the reduction of lysosomal transporters can inhibit the toxic effects of various ADCs' payloads [68]. Some lysable linkers tend to break at low PH, while lysosomal environments with elevated PH also prevent the release of payloads by inhibiting their proteolytic enzymes [69]. Therefore, the use of new techniques to stabilize lysosomal PH and

maintain the stability of its internal environment may restore the anti-tumor properties of ADC against drug-resistant tumor cells.

3) Activation of the bypass channel

Tumor cells may evade ADC-mediated signaling pathways by activating bypass pathways [70]. To this end, it is still necessary to further explore the new ways and internal mechanisms of tumor cell development and a comprehensive understanding of the "enemy" in order to better optimize the existing ADC research and development technology, so as to improve the efficacy.

In addition, in-depth study of ADC combination therapy (combination chemotherapy, immunotherapy, targeted therapy, etc.) can also improve the adverse situation of tumor drug resistance, and provide important ideas for the treatment difficulties of advanced/recurrent patients.

4.2. Drug-Related Adverse Reactions

Based on the above clinical trials of ADC drugs for NSCLC, the main treatment-related adverse reactions were hematological toxicity (neutrophil or platelet decline, etc.). The most serious adverse event was the development of DILD in DESTINY-Lung01, in which two patients died. Fundamentally, we still need to attach great importance to ADC action links, patient drug safety assessment, clinical drug regimen, patient life education, etc. For example, to further stabilize the ADC structure, reduce or even avoid the possibility of ADC off-target, comprehensively evaluate the patient's condition and drug indications, rationally select the ADC dose, improve the functional detoxification drug regimen, and provide individualized dietary nutrition guidance, emotional comfort and other optimization measures, thereby improving the safety of ADC and reducing the occurrence of drug-related adverse reactions.

5. Summary and Prospect

At present, most of the developed ADCs are quite effective in the field of NSCLC clinical research, especially in advanced patients who have received standardized anti-tumor therapy. They not only have good efficacy and controllable safety, but also have achieved certain results in the field of combination therapy, which also indicates that ADC is expected to become a new choice for drug resistance/progression after first-line therapy. However, it is still necessary to return to the central points of ADC drugs—high efficiency, accuracy, stability, low toxicity, and can not ignore the shortcomings of other failed trials, such as: Adverse drug events that may be caused by off-target toxicity (especially pulmonary toxicity events led by DILD), insufficient anti-tumor activity, drug resistance caused by immune escape, etc. With the progress of modern medical technology, ADC drug design, action links, tumor cell internal environment, combination therapy and other component events should be started. To discover and select appropriate target antigens and antibodies, improve linker stability, enhance payload toxicity and connectivity, capture link vulnerabilities, improve the internal environment of tumor

cells to make ADC more easily inhibit its development, and explore combined therapeutic strategies of various types of ADCs, so as to develop new ADCs, activate therapeutic potential, and bring more survival hopes to NSCLC patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Liu, Z.C., Li, Z.X., Zhang, Y., *et al.* (2019) Interpretation of 2020 Global Cancer Statistics Report. *Journal of Integrated Cancer Therapy Electronic*, **7**, 1-14.

[3] Zhang, X. (2019) Application of Gefitinib Targeted Therapy Combined with Concurrent Chemoradiotherapy in Patients with Non-Small Cell Lung Cancer. *Chinese Journal of Medical Sciences*, **35**, 29-31+38.

[4] Gauzy-Lazo, L., Sassoon, I. and Brun, M. (2020) Advances in Antibody-Drug Conjugate Design: Current Clinical Landscape and Future Innovations. *SLAS Discovery*, **25**, 843-868. https://doi.org/10.1177/2472555220912955

[5] Drago, J.Z., Modi, S. and Chandarlapaty, S. (2021) Unlocking the Potential of Antibody-Drug Conjugates for Cancer Therapy. *Nature Reviews Clinical Oncology*, **18**, 327-344. https://doi.org/10.1038/s41571-021-00470-8

[6] Zheng, H., Zheng, Y.Q., Shi, Y.C., *et al.* (2019) Research Progress of HER-2 Targeting Antibody Coupling Drugs. *Chinese Journal of Immunology*, **39**, 640-645+652. (In Chinese)

[7] Yao, X.J. (2019) Research Progress of Antibody Drug Conjugations. *Journal of Chinese and Foreign Medical Research*, **18**, 185-188. (In Chinese)

[8] Li, B.L., Feng, H.L., Wei, F., *et al.* (2019) Research Progress and Challenges of Drug Conjugations for Tumor Antibodies. *Chinese Oncology Clinic*, **49**, 850-857. (In Chinese)

[9] Li, J., Wu, Y.L., Ma, C.C., *et al.* (2019) Research Progress of Antibody Conjugation Drugs. *West China Pharmaceutical Journal*, **38**, 586-592. (In Chinese)

[10] Diamantis, N. and Banerji, U. (2016) Antibody-Drug Conjugates—An Emerging Class of Cancer Treatment. *British Journal of Cancer*, **114**, 362-367. https://doi.org/10.1038/bjc.2015.435

[11] Feng, T., Zhang, H.L. and Tong, H. (2022) Research Progress of Antibody-Drug Conjugate for Tumor Targeting Drugs. *Hebei Medicine*, **44**, 447-452. (In Chinese)

[12] Oh, D. and Bang, Y. (2019) Her2-targeted Therapies—A Role Beyond Breast Cancer. *Nature Reviews Clinical Oncology*, **17**, 33-48. https://doi.org/10.1038/s41571-019-0268-3

[13] Lambert, J.M. and Berkenblit, A. (2018) Antibody-Drug Conjugates for Cancer Treatment. *Annual Review of Medicine*, **69**, 191-207. https://doi.org/10.1146/annurev-med-061516-121357

[14] Liao, S., Wang, B., Zeng, R., Bao, H., Chen, X., Dixit, R., *et al.* (2021) Recent Advances in Trophoblast Cell-Surface Antigen 2 Targeted Therapy for Solid Tumors. *Drug Development Research*, **82**, 1096-1110. https://doi.org/10.1002/ddr.21870

[15] Hafeez, U., Parakh, S., Gan, H.K. and Scott, A.M. (2020) Antibody-Drug Conjugates for Cancer Therapy. *Molecules*, **25**, Article No. 4764. https://doi.org/10.3390/molecules25204764

[16] Waldmann, H. (2018) Human Monoclonal Antibodies: The Benefits of Humanization. In: Steinitz, M., Ed., *Human Monoclonal Antibodies*, Springer New York, 1-10. https://doi.org/10.1007/978-1-4939-8958-4_1

[17] Jin, Y., Schladetsch, M.A., Huang, X., Balunas, M.J. and Wiemer, A.J. (2022) Stepping Forward in Antibody-Drug Conjugate Development. *Pharmacology & Therapeutics*, **229**, Article ID: 107917. https://doi.org/10.1016/j.pharmthera.2021.107917

[18] Liu, W.C., Li, H.F. and Hu, C.H. (2023) Current Situation and Prospect of Anti-Body Coupling Drugs. *Progress in Biochemistry and Biophysics*, **50**, 1167-1189.

[19] Shi, F., Liu, Y., Zhou, X., Shen, P., Xue, R. and Zhang, M. (2022) Disitamab Vedotin: A Novel Antibody-Drug Conjugates for Cancer Therapy. *Drug Delivery*, **29**, 1335-1344. https://doi.org/10.1080/10717544.2022.2069883

[20] Ji, S.M., Wang, Y.Z. and Yang, J.B. (2021) Study on the Molecular Characteristics and Pharmacokinetics of Antibody-Coupled Drugs. *Chinese Journal of Clinical Pharmacology*, **37**, 777-782. (In Chinese)

[21] Tang, H., Liu, Y., Yu, Z., Sun, M., Lin, L., Liu, W., *et al.* (2019) The Analysis of Key Factors Related to ADCs Structural Design. *Frontiers in Pharmacology*, **10**, Article No. 373. https://doi.org/10.3389/fphar.2019.00373

[22] Dumontet, C., Reichert, J.M., Senter, P.D., Lambert, J.M. and Beck, A. (2023) Antibody-Drug Conjugates Come of Age in Oncology. *Nature Reviews Drug Discovery*, **22**, 641-661. https://doi.org/10.1038/s41573-023-00709-2

[23] Yang, Y., Meng, Y., Fan, X.S., *et al.* (2015) Expression of HER2 and COX-2 in Non-Small Cell Lung Cancer. *Cancer Progress*, **13**, 533-537.

[24] Xu, F., Yang, G., Xu, H., Yang, L., Qiu, W. and Wang, Y. (2020) Treatment Outcome and Clinical Characteristics of HER2 Mutated Advanced Non-Small Cell Lung Cancer Patients in China. *Thoracic Cancer*, **11**, 679-685. https://doi.org/10.1111/1759-7714.13317

[25] Wang, X.G. (2016) Clinical Significance of HER-2 Protein Overexpression and Gene Abnormality in Non-Small Cell Lung Cancer. Shanxi Medical University.

[26] Wolska-Washer, A. and Robak, T. (2019) Safety and Tolerability of Antibody-Drug Conjugates in Cancer. *Drug Safety*, **42**, 295-314. https://doi.org/10.1007/s40264-018-0775-7

[27] Cretella, D., Saccani, F., Quaini, F., Frati, C., Lagrasta, C., Bonelli, M., *et al.* (2014) Trastuzumab Emtansine Is Active on HER-2 Overexpressing NSCLC Cell Lines and Overcomes Gefitinib Resistance. *Molecular Cancer*, **13**, Article No. 143. https://doi.org/10.1186/1476-4598-13-143

[28] Li, B.T., Shen, R., Buonocore, D., Olah, Z.T., Ni, A., Ginsberg, M.S., *et al.* (2018) Ado-trastuzumab Emtansine for Patients with HER2-Mutant Lung Cancers: Results from a Phase II Basket Trial. *Journal of Clinical Oncology*, **36**, 2532-2537. https://doi.org/10.1200/jco.2018.77.9777

[29] Li, B.T., Michelini, F., Misale, S., Cocco, E., Baldino, L., Cai, Y., *et al.* (2020) HER2-Mediated Internalization of Cytotoxic Agents in ERBB2 Amplified or Mutant Lung Cancers. *Cancer Discovery*, **10**, 674-687. https://doi.org/10.1158/2159-8290.cd-20-0215

[30] Linehan, A.S., Fitzpatrick, O.M. and Morris, P.G. (2021) Profile of Trastuzumab Deruxtecan in the Management of Patients with HER2-Positive Unresectable or

Metastatic Breast Cancer: An Evidence-Based Review. *Breast Cancer*: *Targets and Therapy*, **13**, 151-159. https://doi.org/10.2147/bctt.s245024

[31] Pommier, Y. (2006) Topoisomerase I Inhibitors: Camptothecins and beyond. *Nature Reviews Cancer*, **6**, 789-802. https://doi.org/10.1038/nrc1977

[32] Li, B.T., Smit, E.F., Goto, Y., Nakagawa, K., Udagawa, H., Mazières, J., *et al.* (2022) Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **386**, 241-251. https://doi.org/10.1056/nejmoa2112431

[33] Goto, K., Sang-We, K., Kubo, T., Goto, Y., Ahn, M., Planchard, D., *et al.* (2022) LBA55 Trastuzumab Deruxtecan (T-DXd) in Patients (Pts) with HER2-Mutant Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results from the Phase 2 DESTINY-Lung02 Trial. *Annals of Oncology*, **33**, S1422. https://doi.org/10.1016/j.annonc.2022.08.057

[34] Planchard, D., Brahmer, J.R., Yang, J.C., Chen, Y., Lee, K., Suksomboon charoen, T., *et al.* (2022) Abstract CT572: Phase 1b Dose-Escalation and Dose-Expansion Study Evaluating Trastuzumab Deruxtecan (T-DXd) in Combination with Durvalumab and Cisplatin, Carboplatin, or Pemetrexed in Advanced or Metastatic, HER2-Overexpressing, Nonsquamous Non-Small Cell Lung Cancer (NSCLC): Destiny-Lung03. *Cancer Research*, **82**, CT572. https://doi.org/10.1158/1538-7445.am2022-ct572

[35] Li, B.T., Ahn, M., Goto, K., Mazieres, J., Padda, S.K., William, W.N., *et al.* (2022) Open-Label, Randomized, Multicenter, Phase 3 Study Evaluating Trastuzumab Deruxtecan (T-DXd) as First-Line Treatment in Patients with Unresectable, Locally Advanced, or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring HER2 Exon 19 or 20 Mutations (DESTINY-Lung04). *Journal of Clinical Oncology*, **40**, TPS9137. https://doi.org/10.1200/jco.2022.40.16_suppl.tps9137

[36] Jin, Y.B., Cai, Q., Ji, J., *et al.* (2019) Inhibitory Effect of Antibody-Coupled Drug Vedicetuzumab on Gastric Cancer Cells with Different Expression Levels of HER-2 *in Vitro*. *Journal of Clinical Oncology*, **28**, 1-7.

[37] Lenárt, S., Lenárt, P., Šmarda, J., Remšík, J., Souček, K. and Beneš, P. (2020) Trop2: Jack of All Trades, Master of None. *Cancers*, **12**, Article No. 3328. https://doi.org/10.3390/cancers12113328

[38] Goldenberg, D.M., Stein, R. and Sharkey, R.M. (2018) The Emergence of Trophoblast Cell-Surface Antigen 2 (TROP-2) as a Novel Cancer Target. *Oncotarget*, **9**, 28989-29006. https://doi.org/10.18632/oncotarget.25615

[39] Long, Y., Xie, F. and Zhou, X.F. (2019) Datopotamab Deruxtecan, an Antibody-Coupled Drug Targeting Trophoblast Cell Surface antigen 2. *Journal of Clinical Pharmacotherapy*, **22**, 18-22.

[40] Mito, R., Matsubara, E., Komohara, Y., Shinchi, Y., Sato, K., Yoshii, D., *et al.* (2020) Clinical Impact of TROP2 in Non-small Lung Cancers and Its Correlation with Abnormal P53 Nuclear Accumulation. *Pathology International*, **70**, 287-294. https://doi.org/10.1111/pin.12911

[41] Liu, X., Deng, J., Yuan, Y., Chen, W., Sun, W., Wang, Y., *et al.* (2022) Advances in Trop2-Targeted Therapy: Novel Agents and Opportunities Beyond Breast Cancer. *Pharmacology & Therapeutics*, **239**, Article ID: 108296. https://doi.org/10.1016/j.pharmthera.2022.108296

[42] Chen, L.L. and Song, Q.B. (2019) New Progress of Dato-DXd in the Treatment of Advanced Non-Small Cell Lung Cancer. *Cancer Prevention Research*, **51**, 535-541. (In Chinese)

[43] Girard, N., Okamoto, I., Lisberg, A.E., Pons-Tostivint, E., Cornelissen, R., Hong, M.H., *et al.* (2024) 59P Datopotamab Deruxtecan (Dato-Dxd) in Patients with

Previously Treated Advanced Non-Small Cell Lung Cancer (NSCLC): Nonsquamous (NSQ) Histology in the Phase III TROPION-Lung01 Trial. *ESMO Open*, **9**, Article ID: 102638. https://doi.org/10.1016/j.esmoop.2024.102638

[44] Goto, Y., Su, W., Levy, B.P., Rixe, O., Yang, T., Tolcher, A.W., *et al.* (2023) TROPION-Lung02: Datopotamab Deruxtecan (Dato-Dxd) Plus Pembrolizumab (Pembro) with or without Platinum Chemotherapy (pt-Ct) in Advanced Non-Small Cell Lung Cancer (aNSCLC). *Journal of Clinical Oncology*, **41**, 9004-9004. https://doi.org/10.1200/jco.2023.41.16_suppl.9004

[45] Borghaei, H., Waqar, S.N., Bruno, D.S., Kitazono, S., Wakuda, K., Spira, A.I., *et al.* (2023) TROPION-Lung04: Phase 1b, Multicenter Study of Datopotamab Deruxtecan (Dato-DXd) in Combination with Immunotherapy ± Carboplatin in Advanced/Metastatic Non-Small Cell Lung Cancer (mNSCLC). *Journal of Clinical Oncology*, **41**, TPS3158. https://doi.org/10.1200/jco.2023.41.16_suppl.tps3158

[46] Ahn, M., Cho, B.C., Goto, Y., Yoh, K., Su, W., Shimizu, J., *et al.* (2023) 552P TROPION-Lung05: Datopotamab Deruxtecan (Dato-DXd) in Asian Patients (Pts) with Previously Treated Non-Small Cell Lung Cancer (NSCLC) with Actionable Genomic Alterations (AGAs). *Annals of Oncology*, **34**, S1684-S1685. https://doi.org/10.1016/j.annonc.2023.10.630

[47] Sun, L.P. and Miao, Q.-F. (2023) Research Progress of Antibody Coupling Drugs Targeting TROP2. *Chinese Journal of Pharmaceutical Biotechnology*, **18**, 428-434. (In Chinese)

[48] Ocean, A.J., Starodub, A.N., Bardia, A., Vahdat, L.T., Isakoff, S.J., Guarino, M., *et al.* (2017) Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate for the Treatment of Diverse Epithelial Cancers: Safety and Pharmacokinetics. *Cancer*, **123**, 3843-3854. https://doi.org/10.1002/cncr.30789

[49] Bardia, A., Messersmith, W.A., Kio, E.A., Berlin, J.D., Vahdat, L., Masters, G.A., *et al.* (2021) Sacituzumab Govitecan, a Trop-2-Directed Antibody-Drug Conjugate, for Patients with Epithelial Cancer: Final Safety and Efficacy Results from the Phase I/II IMMU-132-01 Basket Trial. *Annals of Oncology*, **32**, 746-756. https://doi.org/10.1016/j.annonc.2021.03.005

[50] Reck, M., Liu, S.V., Owen, S.P., Garon, E.B., Neal, J.W., Vicente, D., *et al.* (2022) EP08.02-098 Phase 2 EVOKE-02 Study of Sacituzumab Govitecan and Pembrolizumab ± Platinum in First-Line Metastatic NSCLC. *Journal of Thoracic Oncology*, **17**, S448. https://doi.org/10.1016/j.jtho.2022.07.781

[51] Cheng, Y., Yuan, X., Tian, Q., Huang, X., Chen, Y., Pu, Y., *et al.* (2022) Preclinical Profiles of SKB264, a Novel Anti-TROP2 Antibody Conjugated to Topoisomerase Inhibitor, Demonstrated Promising Antitumor Efficacy Compared to IMMU-132. *Frontiers in Oncology*, **12**, Article ID: 951589. https://doi.org/10.3389/fonc.2022.951589

[52] Fang, W., Cheng, Y., Chen, Z., Wang, W., Yin, Y., Li, Y., *et al.* (2023) SKB264 (TROP2-ADC) for the Treatment of Patients with Advanced NSCLC: Efficacy and Safety Data from a Phase 2 Study. *Journal of Clinical Oncology*, **41**, 9114-9114. https://doi.org/10.1200/jco.2023.41.16_suppl.9114

[53] Liu, L.-Q., Pan, X.-Q., Su, Z., *et al.* (2019) U3-1402, an Antibody-Coupling Drug Targeting HER3. *Journal of Clinical Pharmacotherapy*, **17**, 1-4.

[54] Waqar, S.N., Redman, M.W., Arnold, S.M., Hirsch, F.R., Mack, P.C., Schwartz, L.H., *et al.* (2021) A Phase II Study of Telisotuzumab Vedotin in Patients with c-MET-Positive Stage IV or Recurrent Squamous Cell Lung Cancer (LUNG-MAP Sub-Study S1400K, NCT03574753). *Clinical Lung Cancer*, **22**, 170-177.

https://doi.org/10.1016/j.cllc.2020.09.013

[55] Lyu, H., Han, A., Polsdofer, E., Liu, S. and Liu, B. (2018) Understanding the Biology of HER3 Receptor as a Therapeutic Target in Human Cancer. *Acta Pharmaceutica Sinica B*, **8**, 503-510. https://doi.org/10.1016/j.apsb.2018.05.010

[56] Jänne, P.A., Baik, C., Su, W., Johnson, M.L., Hayashi, H., Nishio, M., *et al.* (2021) Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, EGFR-Mutated Non-Small Cell Lung Cancer. *Cancer Discovery*, **12**, 74-89. https://doi.org/10.1158/2159-8290.cd-21-0715

[57] Yu, H.A., Goto, Y., Hayashi, H., Felip, E., Chih-Hsin Yang, J., Reck, M., *et al.* (2023) HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor-Mutated Non-Small-Cell Lung Cancer after Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy. *Journal of Clinical Oncology*, **41**, 5363-5375. https://doi.org/10.1200/jco.23.01476

[58] Janne, P.A., Johnson, M.L., Goto, Y., Yang, J.C., Vigliotti, M., Dong, Q., *et al.* (2021) HERTHENA-Lung01: A Randomized Phase 2 Study of Patritumab Deruxtecan (HER3-DXd) in Previously Treated Metastatic EGFR-Mutated NSCLC. *Journal of Clinical Oncology*, **39**, TPS9139. https://doi.org/10.1200/jco.2021.39.15_suppl.tps9139

[59] Puppo, F., Thomé, V., Lhoumeau, A., Cibois, M., Gangar, A., Lembo, F., *et al.* (2010) Protein Tyrosine Kinase 7 Has a Conserved Role in Wnt/β-Catenin Canonical Signalling. *EMBO Reports*, **12**, 43-49. https://doi.org/10.1038/embor.2010.185

[60] Maitland, M.L., Sachdev, J.C., Sharma, M.R., Moreno, V., Boni, V., Kummar, S., *et al.* (2021) First-in-Human Study of PF-06647020 (Cofetuzumab Pelidotin), an Antibody-Drug Conjugate Targeting Protein Tyrosine Kinase 7, in Advanced Solid Tumors. *Clinical Cancer Research*, **27**, 4511-4520. https://doi.org/10.1158/1078-0432.ccr-20-3757

[61] Ko, B., He, T., Gadgeel, S. and Halmos, B. (2017) MET/HGF Pathway Activation as a Paradigm of Resistance to Targeted Therapies. *Annals of Translational Medicine*, **5**, Article No. 4. https://doi.org/10.21037/atm.2016.12.09

[62] Wang, J., Anderson, M.G., Oleksijew, A., Vaidya, K.S., Boghaert, E.R., Tucker, L., *et al.* (2017) ABBV-399, a c-Met Antibody-Drug Conjugate That Targets both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence. *Clinical Cancer Research*, **23**, 992-1000. https://doi.org/10.1158/1078-0432.ccr-16-1568

[63] Camidge, D.R., Morgensztern, D., Heist, R.S., Barve, M., Vokes, E., Goldman, J.W., *et al.* (2021) Phase I Study of 2- or 3-Week Dosing of Telisotuzumab Vedotin, an Antibody-Drug Conjugate Targeting C-Met, Monotherapy in Patients with Advanced Non-Small Cell Lung Carcinoma. *Clinical Cancer Research*, **27**, 5781-5792. https://doi.org/10.1158/1078-0432.ccr-21-0765

[64] Camidge, D.R., Barlesi, F., Goldman, J.W., Morgensztern, D., Heist, R., Vokes, E., *et al.* (2023) Phase Ib Study of Telisotuzumab Vedotin in Combination with Erlotinib in Patients with C-Met Protein-Expressing Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **41**, 1105-1115. https://doi.org/10.1200/jco.22.00739

[65] Abuhelwa, Z., Alloghbi, A. and Nagasaka, M. (2022) A Comprehensive Review on Antibody-Drug Conjugates (ADCs) in the Treatment Landscape of Non-Small Cell Lung Cancer (NSCLC). *Cancer Treatment Reviews*, **106**, Article ID: 102393. https://doi.org/10.1016/j.ctrv.2022.102393

[66] Phillips, G.D.L., Fields, C.T., Li, G., Dowbenko, D., Schaefer, G., Miller, K., *et al.*

(2014) Dual Targeting of HER2-Positive Cancer with Trastuzumab Emtansine and Pertuzumab: Critical Role for Neuregulin Blockade in Antitumor Response to Combination Therapy. *Clinical Cancer Research*, **20**, 456-468. https://doi.org/10.1158/1078-0432.ccr-13-0358

[67] Ritchie, M., Tchistiakova, L. and Scott, N. (2013) Implications of Receptor-Mediated Endocytosis and Intracellular Trafficking Dynamics in the Development of Antibody Drug Conjugates. *mAbs*, **5**, 13-21. https://doi.org/10.4161/mabs.22854

[68] Hamblett, K.J., Jacob, A.P., Gurgel, J.L., Tometsko, M.E., Rock, B.M., Patel, S.K., *et al.* (2015) SLC46A3 Is Required to Transport Catabolites of Noncleavable Antibody Maytansine Conjugates from the Lysosome to the Cytoplasm. *Cancer Research*, **75**, 5329-5340. https://doi.org/10.1158/0008-5472.can-15-1610

[69] Dean, A.Q., Luo, S., Twomey, J.D. and Zhang, B. (2021) Targeting Cancer with Antibody-Drug Conjugates: Promises and Challenges. *MABs*, **13**, Article ID: 1951427. https://doi.org/10.1080/19420862.2021.1951427

[70] Khoury, R., Saleh, K., Khalife, N., Saleh, M., Chahine, C., Ibrahim, R., *et al.* (2023) Mechanisms of Resistance to Antibody-Drug Conjugates. *International Journal of Molecular Sciences*, **24**, Article No. 9674. https://doi.org/10.3390/ijms24119674