Exploring the Potential of Antibody-Drug Conjugates in Targeting Non-small Cell Lung Cancer Biomarkers

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ABSTRACT: Antibody-drug conjugates (ADCs), combining the cytotoxicity of the drug payload with the specificity of monoclonal antibodies, are one of the rapidly evolving classes of anti-cancer agents. These agents have been successfully incorporated into the treatment paradigm of many malignancies, including non-small cell lung cancer (NSCLC). The NSCLC is the most prevalent subtype of lung cancer, having a considerable burden on the cancer-related mortality and morbidity rates globally. Several ADC molecules are currently approved by the Food and Drug Administration (FDA) to be used in patients with NSCLC. However, the successful management of NSCLC patients using these agents was met with several challenges, including the development of resistance and toxicities. These shortcomings resulted in the exploration of novel therapeutic targets that can be targeted by the ADCs. This review aims to explore the recently identified ADC targets along with their oncologic mechanisms. The ADC molecules targeting these biomarkers are further discussed along with the evidence from clinical trials.

KEYWORDS: Non-small cell lung cancer, antibody-drug conjugates, novel biomarkers, precision oncology

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Introduction

Cancer diagnosis and treatment options have advanced dramatically over the previous few decades. The discovery of oncogenic drivers and the development of tailored treatment drugs have changed the cancer care concept. Recently, the principles of precision oncology have been of great clinical significance in terms of the identification of cancer biomarkers and the initiation of targeted therapy against them.[1] Non-small cell lung cancer (NSCLC) has been employed as a prototype disease for precision oncology in solid malignancies. The NSCLC is a complex disease with several oncogenic driver mutations. It accounts for roughly 85% of all instances of lung cancer and is further classified as adenocarcinoma (NSCLC-AC), squamous cell carcinoma (NSCLC-SCC), and large cell carcinoma. Approximately 70% of NSCLCs have a non-squamous-origin-such-as-NSCLC-AC-and-NSCLC-large cell carcinoma.[2] More than 50% of NSCLC cases are presented with locally advanced or distant metastasis stage at the time of diagnosis and, unfortunately, carry a poor prognosis with a 5-year survival rate of only 2-20%.[3]

Currently, treatment options in NSCLC patients include surgery, radiation, chemotherapy, immunotherapy, and molecularly targeted therapy, either alone or in combination, depending on the stage, histology, and genetic mutations involved. Surgical removal of the tumor followed by platinum-based adjuvant chemotherapy with or without targeted therapeutic agents is recommended for early-stage NSCLC. Patients suffering from advanced disease receive a combination of chemo-immunotherapy as they are not candidates for surgical interventions. Limitations of these chemotherapeutic agents are the narrow therapeutic index and non-selective nature that causes predictable toxicities even in healthy non-cancerous cells.[4] The NSCLC patients who express various biomarkers and molecular alterations, including epidermal growth factor receptor (EGFR), ALK, ROS1, human epidermal growth factor receptor (HER), BRAF, and many more targeted therapeutic agents are the standard of care.[5-7] The introduction of targeted therapeutic agents markedly improved the prognosis for patients with NSCLC. However, only a limited percentage of patients present with these common genetic mutations and biomarkers.[8] Consequently, only a limited number of patients benefit from these targeted therapies, and a majority of NSCLC patients develop drug resistance within 8 to 16 months of targeted treatment with EGFR-TKIs. A noteworthy resistance mechanism to EGFR-TKIs includes overexpression of AXL, which plays an essential role in intrinsic and adaptive resistance. The overexpression of AXL, even in the absence of other resistance mutations, led to a lack of response of EGFR-TKIs, including Osimertinib. Moreover, the higher generations of TKIs cause more potent inhibition of EGFR, which causes severe skin (pruritus, dry skin, and rash) and gastrointestinal toxicities and consequently necessitates dose reduction. Osimertinib is associated with severe cardiac toxicities, and PI3K inhibitors are associated with hyperglycemia.[9] In addition, on-target treatment resistance is prevalent in ALK and ROS-positive NSCLC patients treated with crizotinib.[10] In essence, higher costs, development of resistance, and toxicities have hampered the widespread use of targeted therapy agents in NSCLC patients. For patients lacking any enforceable oncogenic mutations, immunotherapy with programmed cell death ligand-1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is considered to be the treatment of choice.[4] Nonetheless, most patients receiving immunotherapy or targeted therapy drugs develop resistance

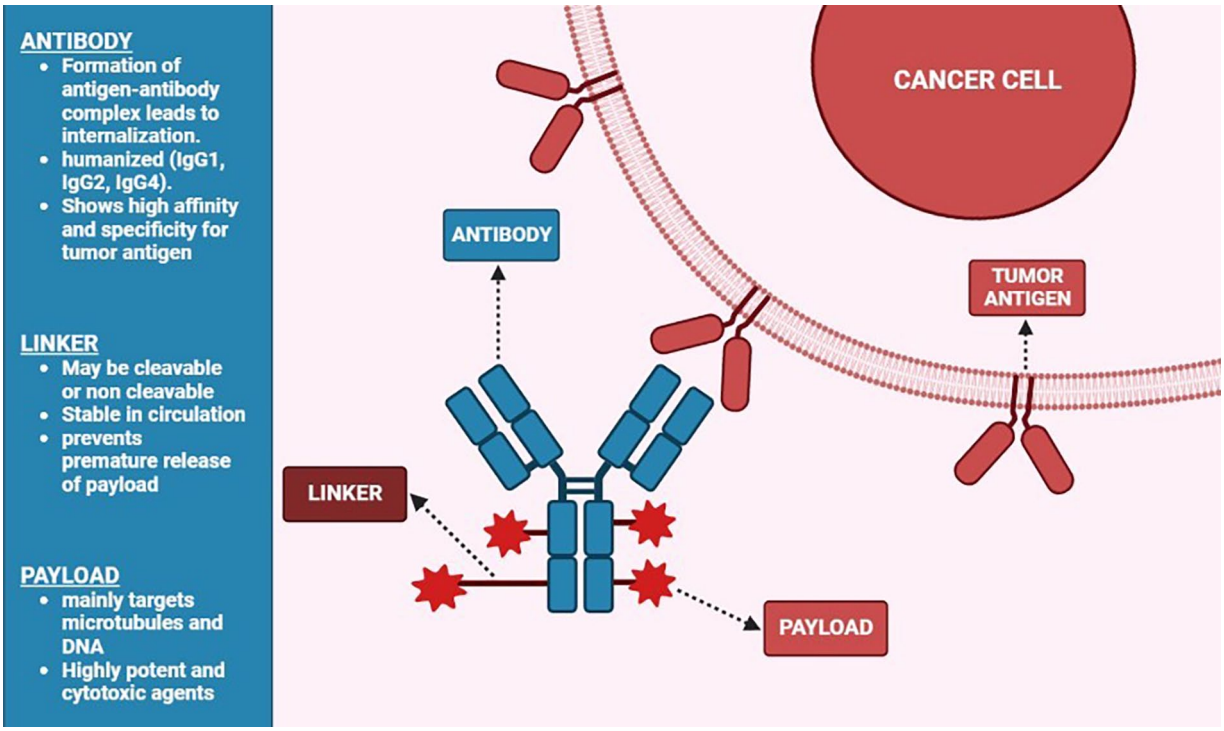

Figure 1. Structural components of antibody-drug conjugates.

within a few years of treatment, prompting the need for novel treatment options.[11]

Antibody-drug conjugates (ADCs) are novel biopharmaceutical drugs that combine the cytotoxic effects of chemotherapeutic agents with the target selectivity of monoclonal antibodies (mAb).[12] Combining these agents is beneficial in overcoming the limitations of both conventional chemotherapy and mAb when used alone. The ADCs, in general, are composed of three components, which are antibodies against the target biomarkers, linker, and the cytotoxic payload.[13] These structural components of ADCs are diagrammatically demonstrated in Figure 1. Earlier, the use of ADCs was limited because of various pharmacokinetic and pharmacodynamic features such as poor tumor penetration and low cytotoxic efficacy. However, these limitations are easily overcome with the advent of newer technology.[14,15] To conquer these challenges, the formulations of ADCs should possess antibodies, the linker moiety, and a cytotoxic payload, which are carefully chosen to create a safe, effective, and pharmacokinetically superior molecule.[16,17] Currently, 13 ADCs are approved by the FDA for various solid and liquid tumors. In the case of NSCLC, Telisotuzumab vedotin (Teliso-V), Sacituzumab govitecan-hziy, Trastuzumab deruxtecan (T-DXd), and Patritumab deruxtecan (HER3-DXd/U3-1402) are currently approved by the FDA. Despite the initially encouraging outcomes in NSCLC patients, several hurdles were encountered in terms of the safety of these novel therapeutic agents. Multiple clinical trials have revealed unanticipated dose-limiting toxicities (DLTs) of the ADCs. Although ADCs are target-based therapies, the payloads may detach and circulate in the circulation or leak out of the target cells, causing adverse effects and systemic toxicities. These toxic effects can be as severe as interstitial lung disease (ILD) and pulmonary fibrosis (datopotamab-deruxtecan), which may ironically produce worse outcomes in patients with NSCLC.[18] Moreover, repetitive use of the existing FDA-approved ADCs in treating NSCLC will eventually lead to the development of resistance and consequently therapeutic failure. Thus, the identification of newer therapeutic targets and biomarkers is necessitated to improve the prognosis of the disease. A variety of novel biomarkers and tumor antigens have been identified and have the potential to be used as target antigens in the treatment of NSCLC. These are, AXL, Transferrin receptor-1 (TfR1), NaPI2b, Tissue factor (TF), Lymphocyte antigen 6 complex, locus E (LY6E), LY6/PLAUR domain-containing protein 3 (LYPD3), Receptor tyrosine kinase (RTK)-like orphan receptor 2 (ROR2), 5T4, B7 homolog 3 protein (B7-H3), Folate receptor α (FRA) and activated leukocyte cell adhesion molecule (ALCAM).

The scope of this review is to provide a detailed discussion regarding various newly identified therapeutic targets and biomarkers along with their oncogenic mechanism in NSCLC. This review focuses on various ADCs that work on those biomarkers in NSCLC, as well as the data from clinical studies.

Novel Antibody-Drug Conjugate Targets for the Treatment of Non–Small Cell Lung Cancer

There are different subtypes of novel ADC targets that can potentially used for the management of NSCLC. In addition, the newer ADCs which are currently under-development stage, have been listed along with their key structural components in Table 1.

Table 1. Structural layout of ADCs currently under development in NSCLC.

MAKER	ADCS TARGETING THAT MARKER	DRUG	ANTIBODY	LINKER
ALCAM	Praluzatamab ravtansine (CX-2009)	DM4	Anti-CD166	Protease-cleavable linker
AXL	Enapotamab vedotin	MMAE	IgG1	Protease cleavable
	ADCT-601/Mipasetamab uzoptirine	Pyrrolobenzodiazepine (PDB) dimer SG3199	IgG1-kappa	Valine-alanine dipeptide/ cathepsine B cleavage
	Mecbotamab vedotin (CAB-Axl-ADC/BA3011)	MMAE (Vedotin)	IgG1-kappa CAB-Axl antibodies	Cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC)
TfR1	CX-2029	Maleimido-caproyl-valine-citrulline-p-aminobenzyloxycarbonyl-monomethyl auristatin E	Anti-CD71	vc
NaPI2b	XMT-1536 (upifitamab rilsodotin)	10 -15 auristatin F-hydroxypropylamide (AF-HPA)	IgG1-kappa	Thioether bond
	XMT-1592	Auristatin Dolalock	Anti-NaPI2b antibody	-
Tissue factor	Tisotumab Vedotin	MMAE	anti-tissue factor (TF) human IgG1-kappa	Protease-cleavable vc linker
	XB-002	MMAE	Human tissue factor-specific antibody (TF-011)	Protease-cleavable vc linker
LY6E	DLYE5953A	MMAE	Anti-LY6E antibody	Maleimidocaproyl-valine-citrulline p-aminobenzyloxycarbonyl
LYPD3	Lupartumab Amadotin (BAY 1129980)	Auristatin W derivative	IgG1-lambda	S-cystine sulfurhydryl
ROR2	Ozuriftamab vedotin (BA3021)	MMAE	IgG1-kappa	A cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl
5T4	ASN004	Auristatin F-hydroxypropylamide	scFvFc antibody	Dolaflexin drug-linker technology
B7-H3	Vobramitamab duocarmazine	seco-DUocarmycin hydroxyBenzamide Azaindole	humanized B7-H3 monoclonal antibody	Cleavable linker
Folate receptor α	MORAb-202 (Farletuzumab ecteribulin)	Eribulin	Farletuzumab	Cathepsin-cleavable linker
	PRO1184	Exatecan	Selective FOLR1,2 mAb	A cleavable, hydrophilic linker

ADC, antibody-drug conjugate; ALCAM, activated leukocyte cell adhesion molecule; MMAE, monomethyl auristatin E; vc, valine citrulline; ROR2, receptor tyrosine kinase (RTK)-like orphan receptor 2; B7-H3, B7 homolog 3 protein; TfR1, transferrin receptor-1; TF, tissue factor; LY6E, lymphocyte antigen 6 complex, locus E; LYPD3, LY6/PLAUR domain-containing protein 3.

Activated Leukocyte Cell Adhesion Molecule

Brain metastasis in NSCLC is associated with poor prognostic incidences, and cell adhesion molecules play a role in mediating this metastatic progression. Activated leukocyte cell adhesion molecule (ALCAM), also known as cluster of differentiation 166 (CD166), resides as both transmembrane and secreted protein and is involved in homotypic and heterotypic cell adhesion process.[19,20] It has a structural resemblance with the Ig superfamily molecules and it was initially identified from the activated leukocytes. The anatomical presence of ALCAM is found in epithelial cells, neurons, myeloid progenitors, vascular endothelial cells, mesenchymal stem cells, bone marrow stromal cells, hematopoietic stem cells, and tumor cells.[21,22] In healthy physiology, ALCAM modulates cell-cell interactions with epithelial cells, leukocytes, and endothelial cells.

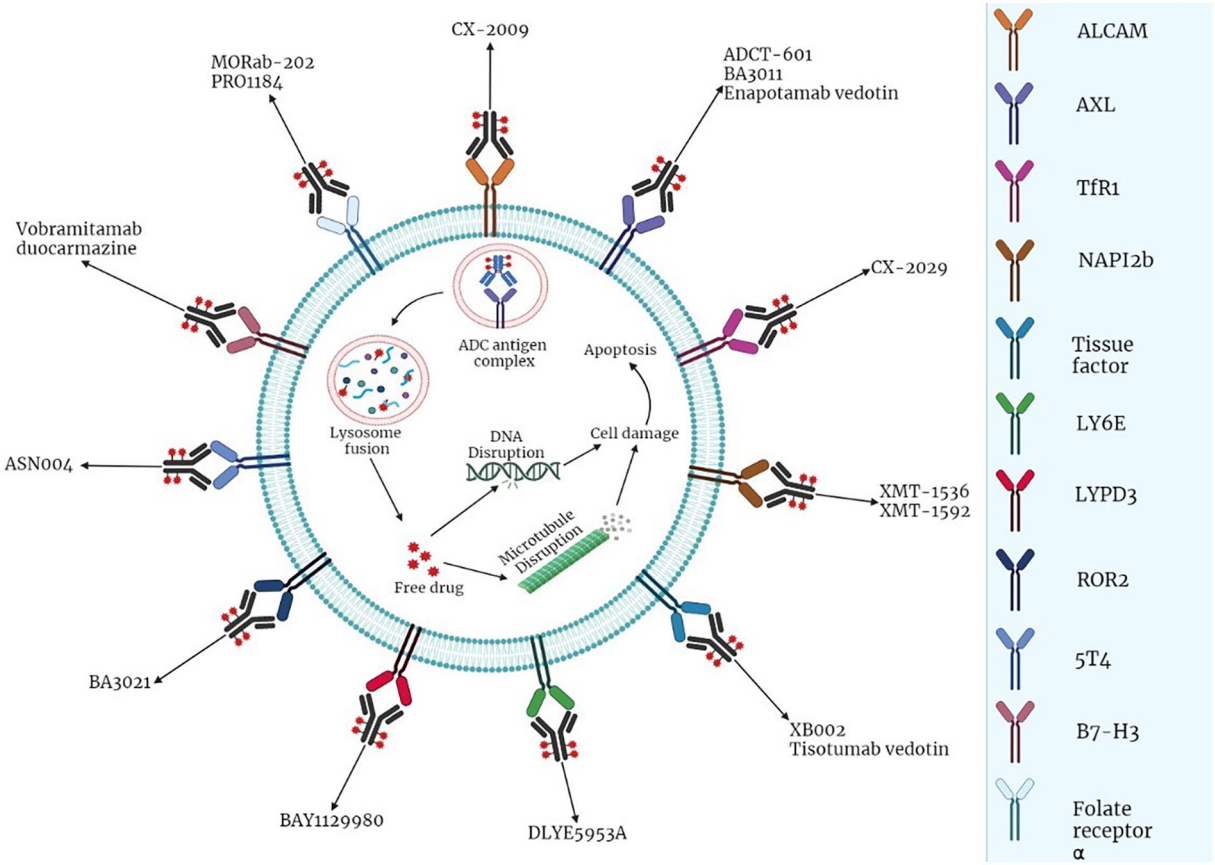

Figure 2. Novel biological targets in NSCLC and the respective ADC molecules along with the mechanism of action of ADCs. ADC, antibody-drug conjugate; ALCAM, activated leukocyte cell adhesion molecule; ROR2, receptor tyrosine kinase (RTK)-like orphan receptor 2; B7-H3, B7 homolog 3 protein; TfR1, transferrin receptor-1; TF, tissue factor; LY6E, lymphocyte antigen 6 complex, LYPD3, locus E; LY6/PLAUR domain-containing protein 3.

The function of ALCAM extends from cell adhesion to involve angiogenesis, monocyte transmigration, T-cell activation, hematopoiesis, neurite extension, leukocyte penetration across the blood-brain barrier, embryonic implantation in the uterus, and osteogenesis.[22] Moreover, this marker has emerged as a cancer progression modulator as it primarily controls cell proliferation, adhesion, migration, and invasion.[23] ALCAM mediates the interaction between NSCLC cancerous cells and brain vascular endothelium.[20] As a result, it is reported to be a promising biomarker to target to achieve anti-cancer efficacy in the NSCLC-TME. For the past few years, TME is thought to be the key parameter for the efficacy of various treatment modalities as it plays a crucial role in cancer progression and survival.[24] Recent studies suggesting stem cell origin of cancer support addressing cancer as a stem cell disease and put forth a "cancer stem cell (CSC) hypothesis." It was hypothesized that tumor development originated from aberrant expression of small populations of cells with two bifurcations: (1) A proportion of cells grew unrestrictedly and favored metastasis, and (2) the other proportion differentiated into phenotypically heterogeneous abnormal subtype designated as CSCs. These CSCs lie in quiescence during the exposure of chemotherapy and radiotherapy and therefore, escape antitumor activity. Survival of these cells leads to tumor growth, recurrence, or metastasis. Various studies have indicated that ALCAM, in conjunction with other molecules such as CD133 and CD44, can be regarded as a viable surface marker to identify such CSCs. The combination of ALCAM-targeting therapy and radiotherapy is an intriguing area to explore as ALCAM targeting may sensitize tumor to the detrimental effects of radiation. It may further enhance tumor cell apoptosis, reduce the risk of metastasis, induce apoptosis of residual CSCs escaping the effect of chemotherapy and radiotherapy, and ameliorate possible radiotherapy-associated resistance.[23,25]

The novel biomarkers and ADCs targeting them are graphically represented in Figure 2.

The course of drug development targeting CD166 yielded a probody drug conjugate (PDC) named praluzatamab ravtansine (CX-2009), whose potency has been evaluated in several solid tumor settings including NSCLC.[26] CX-2009 is a conditionally activated PDC with an anti-CD166 mAb linked with maytansinoid DM4 payload using a protease-cleavable linker and a peptide mask that limits target binding in circulation and healthy tissue.[27,28] After administration and enabling anti-CD166 mAb to selectively bind with ALCAM-expressing tumor cells, DM4 releases due to linker dissolution, which internalizes and binds with tubulin to disrupt the microtubular network and subsequently inhibits cell division and growth.

The masking peptide prevents this bond formation in healthy, unaffected tissues, thus improving the safety portfolio of this drug.[29]

A phase I/II trial (NCT03149549) enrolled 99 patients with advanced solid tumors and evaluated the recommended phase II dose (RP2D) and safety profile of CX-2009 as monotherapy. This dose escalation phase of the trial was designed to determine the RP2D and safety profile along with the preliminary antitumor activity. The drug was found to be safe, and no off-tumor-on-target effects were observed in the form of adverse events (AEs), which supports the concept of high specificity for tumor cells by formulating the PDC. The results demonstrated RP2D of 7 mg/kg every 3 weeks. However, one patient from the NSCLC cohort died due to the occurrence of sepsis, which was drug related. Confirmed partial response (PR) was seen in the patients with breast cancer.[28] Nevertheless, a detailed evaluation of this PDC in patients with NSCLC is awaited from future studies.

AXL

AXL belongs to the TAM family of receptor tyrosine kinases (RTKs), which play an important role in the modulation of cell proliferation, migration, and survival. It exerts its physiological effects by binding with ligand Gas 6 and activating PI3K/AKT, MEK/ERK, and STAT3 pathways. AXL overexpression is seen majorly in NSCLC-AC in locally advanced and metastatic stages with lymph node involvement (stage III–IV) and has been linked with poor clinical outcomes.[30] The AXL expression is observed in nearly 34%-94.5% of NSCLC cases, where it promotes tumor growth and epithelial-mesenchymal transition (EMT). Recent evidence has uncovered the potential role of AXL in the development of resistance to PD-1/PD-L1 immune checkpoint inhibitors. This is thought to be the result of overexpression of AXL, causing enhancement of mitochondrial metabolism, which is responsible for the EMT process and PD-1 resistance. The molecular pathways behind AXL-mediated resistance and oncogenesis remain largely unidentified. However, several recent studies have pointed toward the upregulation of the TMEM14A gene as the culprit behind these consequences.[31] Several therapeutic agents including small molecule inhibitors, mAbs, and ADCs are currently under development to target AXL.[32]

Enapotamab vedotin (HuMax-AXL-ADC) is an AXL-targeted ADC composed by conjugating human anti-AXL specific IgG1 linked to monomethyl auristatin E (MMAE) payload via a protease-cleavable valine-citrulline linker.[33] The first-in-human trial of Enapotamab vedotin (NCT02988817) evaluated the clinical outcomes of the same in pretreated subjects with refractory solid tumors. The dose escalation phase of the study concluded RP2D of 2.2 mg/kg every 3 weeks. Furthermore, the dose expansion phase 2a, included 26 patients with stage III/IV NSCLC who have relapsed on multiple lines of therapies. The results in this population demonstrated overall response rate (ORR) of 19% and disease control rate (DCR) of 50%. Most commonly encountered treatment-related adverse events (TRAEs) were nausea, vomiting, diarrhea, fatigue, weight loss, and decreased appetite.[34]

Another ADC named ADCT-601/mipasetamab uzoptirine is composed of human anti-AXL mAb conjugated to PL1601 using GlycoConnectTM 66 technology, a Val-Ala cleavable linker and potent 68 pyrrolobenzodiazepine dimer cytotoxin SG3199.[35] It is currently being studied as monotherapy and in combination with gemcitabine in a phase 1 trial, in patients with advanced solid tumors including NSCLC. The primary objective of the study is determination of the number of patients with dose-limited toxicity and AEs.[36]

Mecbotamab vedotin (CAB-Axl-ADC/ BA3011), an anti-AXL antibody composed of human anti-AXL IgG1 antibody, a cleavable linker maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-Val-cit-PABC) and MMAE cytotoxic payload which has shown to induce cytotoxicity on AXL-expressing tumors.[37] At present, there are two ongoing studies evaluating the outcomes of this ADC in patients with NSCLC. Both of the studies are evaluating this ADC in patients with advanced diseases as monotherapy and in combination with PD-1 inhibitors.[38,39] The ongoing trials of the novel ADCs are summarized in Table 2.

Transferrin receptor-1

Transferrin receptor-1 (TfR1) also known as cluster of differentiation 71 (CD71) is a membrane glycoprotein involved in cellular iron uptake, which is crucial for cell proliferation and DNA synthesis. To fulfill the iron requirement for tumor growth, TfR1 gene is found to be overexpressed in cancer cells.[40] In addition, it was observed that intracellular iron protects the neoplastic cells from NK cells and the presence of ferritin suppresses the reactive oxygen species accumulation hindering the apoptosis induced by TNF-alpha.[41] The overexpression of TfR1 is generally associated with small cell lung cancer (SCLC) and occasionally with NSCLC. It can be detected by immunohistochemistry (IHC), the Western blot method, immunofluorescence & quantitative real-time polymerase chain reaction (qRT-PCR).[42]

CX-2029 is a PDC composed of a humanized mAb protease-activable anti-TfR1 antibody prodrug, a cytotoxin MMAE payload, and a protease-cleavable dipeptide linker. On administration, the prodrug antibody is cleaved by proteases to release activated CX-2029, which binds to TfR1 on the cell surface, followed by internalization and lysosomal processing. After the release of the cytotoxic payload, it binds to microtubule and arrests the cell cycle (G2-M), resulting in cell death.[43]

A phase I trial PROCLAIM-CX-2029 (NCT03543813) evaluated the safety, maximum tolerated dose (MTD), antitumor activity, and pharmacokinetics of CX-2029 in 45 patients

Table 2. Currently ongoing trials evaluating novel ADC molecules in NSCLC.

ADC NAME	NCT NO.	PHASE	PATIENT CHARACTERISTICS	INTERVENTION	PRIMARY OUTCOME	SECONDARY OUTCOME
Upifitamab rilsodotin [XMT-1536]	NCT03319628	1 & 2	Solid tumors likely to express NaPi2b [includes NSCLC cohort]	XMT-1536 alone	MTD, ORR, Safety, and tolerability, Antineoplastic effects	Antineoplastic effect, DOR, PK parameters, ORR
Enapotamab vedotin	NCT02988817	1 & 2	For phase 1, patients with refractory or relapsed solid tumors who were non-responders or those who are not candidates for standard therapy. In phase II, patients with metastatic/advanced solid tumor or those who are not candidates for standard therapy. [includes NSCLC cohort]	Enapotamab vedotin alone	DLT, TEAEs	PK parameters
Tisotumab vedotin [TF-011-MMAE]	NCT03485209	2	Locally advanced or metastatic solid tumors, which progressed during or after their most recent systemic therapy [includes NSCLC cohort]	Tisotumab vedotin alone and in combination with pembrolizumab with carboplatin or cisplatin	ORR	DCR, DoR, TTR, PFS, OS, AEs
XB-002	NCT04925284	1	Inoperable locally advanced or metastatic solid tumors [includes NSCLC cohort]	XB-002 alone and in combination with nivolumab	MTD, ORR	PFS, DoR, AEs, Safety and tolerability, immunogenicity, OS
Ozuriftamab vedotin [BA3021]	NCT03504488	1 and 2	Advanced solid tumors, Which failed all available standard of care therapy [includes NSCLC]	BA3021 alone and combination PD-1 Inhibitor	Safety profile, ORR	DoR, PFS, OR, DCR, TTR, OS, Immunogenicity
Farletuzumab Ecteribulin [MORAb-202]	NCT05577715	2	Metastatic NSCLC adenocarcinoma, which progressed on prior therapies	Farletuzumab Ecteribulin alone	ORR, TRAEs	Number of participants with AEs and SAEs, PFS, DCR, DoR
	NCT04300556	1 and 2	Platinum-resistant solid tumors [includes NSCLC cohort]	Farletuzumab Ecteribulin alone	ORR, number of participants with SAEs and AEs, and DLT	DoR, DCR, PFS, OS, CBR, PK profiles
AMT-151	NCT05498597	1	Advanced solid tumors [includes NSCLC cohort]	AMT-151 alone	MTD, Incidence of AEs	ORR, DCR, PFS, DoR, OS, PK parameters
PRO1184	NCT05579366	1 & 2	Locally advanced and/or metastatic solid tumors	PRO1184 alone	Incidence of TEAE, DLT	ORR, DCR, PFS, OS, PK parameters
ASN004	NCT04410224	1	Advanced malignant solid tumors, which failed standard therapy or have no standard therapy available	ASN004 alone	MTD	PK parameters, terminal elimination rate, appearance of new tumor lesions
Mecbotamab vedotin [CAB-AXL-ADC/ BA3011]	NCT04681131	2	Metastatic NSCLC, which progressed on a PD-1/L-1 Inhibitor	CAB-AXL-ADC alone and in combination with PD-1 Inhibitor	ORR, Incidence of AEs and SAEs	DoR, DCR, PFS, TTR, OS
Mipasetamab Uzoptirine [ADCT-601]	NCT05389462	1	Advance solid tumors [includes NSCLC]	ADCT-601 alone and in combination with gemcitabine	DLT, number of participants with AEs	ORR, DoR, PFS, OS
Vobramitamab duocarmazine [MGC018]	NCT03729596	1 & 2	Patients with advanced solid tumors [includes NSCLC]	Vobramitamab duocarmazine alone and in combination with Retifanlimab	DLT, number of patients with AEs	ORR, PFS, DoR, OS, and PK parameters

NSCLC, non-small cell lung cancer; DLT, dose-limiting toxicity; ORR, overall response rate; PK, pharmacokinetics; DoR, duration of response; DCR, disease control rate; PFS, progression-free survival; TTR, time in therapeutic range; OS, overall survival; AEs, adverse events; MTD, maximum tolerated dose; TEAEs, treatment-emergent adverse events; SAEs, serious adverse events; PD-L1, programmed cell death ligand; ADC, antibody-drug conjugates; CBR, clinical benefit rate; TRAEs, treatment-related adverse events.

with solid tumors. The MTD was found to be 3 mg/kg, which was also determined to be the RP2D. Out of four patients enrolled with NSCLC, stable disease (SD) was observed in three patients. Infusion-related reactions and hematologic toxicities such as anemia and neutropenia were commonly observed, identical to any MMAE-containing ADCs.[44] The correlation between CD71 expression and therapeutic response was not evaluated in this study, for which further studies are required.

NaPI2b

NaPI2b is a sodium-dependent phosphate transporter which is located on type II pneumocytes of the lung and on the brush border membrane of the small intestine, where it plays an essential role in the maintenance of phosphate homeostasis.[45] NaPi2b overexpression is associated with NSCLC-AC (~75%-90%), female gender, never-smokers, and in cases of KRAS or EGFR mutations.[46] NaPi2b overexpression can be detected by IHC, RT-PCR, droplet digital PCR, and Western blot analysis.[47]

XMT-1536 (upifitamab rilsodotin) is an ADC composed of human antibody conjugated with payload 10-15 auristatin F-hydroxypropyl amide (AF-HPA) via dolaflexin platform. The antibody targets & binds to NaPi2b expressed in tumors, followed by internalization and enzymatic cleavage leading to the release of AF-HPA into cells. AF-HPA binds to tubulin and results in the inhibition of microtubule polymerization, leading to cell cycle arrest and apoptosis.[48] The first-in-human study of this ADC is under phase I/II (NCT03319628) trial, which includes patients with mNSCLC with adenocarcinoma subtype. The study is focused on patients with tumors that are likely to have NaPI2b expression.[49]

XMT-1592 is another investigational ADC targeting NaPI2b, which is under Phase I-II study (NCT04396340) in patients with NSCLC and ovarian cancer.[50] However, the study was later terminated due to the discontinuation of the development program.

Tissue Factor

Tissue factor (TF)/CD-142/factor III/thromboplastin is the key physiologic initiator of the extrinsic coagulation pathway. Under normal physiological conditions, TF is expressed on subendothelial cells, namely pericytes, fibroblasts, and smooth muscle cells.[51] Aberrant expression of TF is observed in NSCLC tumor cells and tumor vasculature, where it is associated with increased metastasis and angiogenesis by vascular endothelial growth factor expression. It elevates the odds of venous thromboembolism in NSCLC patients by triggering blood coagulation. The TF overexpression is mainly observed in patients with NSCLC-AC in locally advanced (stage III–IV) to metastasized T3-T4 tumors.[52] IHC, Western blot analysis, Immunocytochemical staining, qRT-PCR, and enzyme-linked immunosorbent assay (ELISA) are several methods for the detection of TF expression in tumor cells.[53]

Tisotumab Vedotin (TF-011-MMAE) is composed of human TF-specific antibody, a protease-cleavable linker & cytotoxic payload MMAE. ADC targets TF on tumor cells. After binding, it releases MMAE, resulting in cell cycle arrest and apoptosis. The drug also acts on the immune system through an indirect mechanism by activating FcgRIII expressed on natural killer cells, leading to antibody-dependent cellular cytotoxicity and causing immunogenic cell death. It was FDA approved in September 2021 for use in recurrent or metastatic cervical cancer.[54] InnovaTV 207 (NCT03485209) is a phase II trial evaluating Tisotumab vedotin alone or in combination with chemotherapy or immunotherapy in patients with solid tumors including NSCLC.[55]

Lymphocyte Antigen 6 Complex, Locus E

Lymphocyte antigen 6 complex, locus E (LY6E), belongs to the LY6 gene family of proteins located on human chromosomes 6, 8, 11, and 19.[56] Alternatively known as stem cell antigen 2 (SCA2), LY6E is of particular importance in cell-cell adhesion and signal transduction through T-cell receptors.[57] Overexpression of the same in the tumor cells induce modulation of PTEN/P13K/Akt/HIF-1 signaling pathway, which leads to uncontrolled growth, angiogenesis, and metastasis. The LY6E overexpression in tumor cells can be detected by IHC, ELISA, qRT-PCR, and flow cytometry analysis.[58]

DLYE5953A, an anti-LY6E ADC comprised of human mAb (IgG1:MLYE4489A), a protease linker (maleimidocaproyl-valine-citrulline p-aminobenzyloxycarbonyl) & cytotoxic payload MMAE which works as tubulin inhibitor & apoptosis stimulant. A phase I trial (NCT02092792) evaluated these ADCs in 68 patients with solid refractory tumors. The dose escalation phase yielded an RP2D of 2.4 mg/kg. In the dose expansion phase, a total of 5 patients achieved PR out of 25 patients in the NSCLC cohort. Neutropenia was the highest occurring Grade > 3 toxicity in 13% of cases. Other common AEs were peripheral neuropathy, nausea, fatigue, and alopecia. Overall, the preliminary evidence gathered from this trial was encouraging, and further investigation of this ADC in phase II is currently ongoing.[59]

LY6/PLAUR Domain-Containing Protein 3

LY6/PLAUR domain-containing protein 3 (LYPD3), alternatively called C4.4A, is a membrane protein attached to the cell surface by glycosylphosphatidylinositol (GPI) and belongs to LY6/ uPAR (LU) protein family. It is primarily present in skin, placenta, and esophageal endothelial cells and plays an essential role in the cell migration process. The LYPD3 overexpression is commonly observed in patients with NSCLC-SCC and is responsible for the EMT, resulting in metastasis and poor prognosis.[60] IHC, microarray screening, in-situ hybridization,

Northern blotting, and PCR can be utilized for the detection of LYPD3.[61]

Lupartumab Amadotin (BAY 1129980), an anti-LYPD3 ADC, is composed of human IgG1 antibody conjugated to non-cleavable alkyl hydrazide linker via cysteine side chains to a potent microtubule-disrupting auristatin W derivative which works as LYPD3 receptor antagonists.[62] This ADC was under phase I trial (NCT02134197), which was terminated for reasons that are yet to be evaluated.[63]

Receptor Tyrosine Kinase–like Orphan Receptor 2

Receptor tyrosine kinase (RTK)-like orphan receptor 2 (ROR2) is a transmembrane protein moiety that is grouped under the title of conserved ROR2 family of RTKs. The functional cascade of ROR2 runs primarily through Wnt signaling pathway. The Wnt family releases numerous signaling molecules involved in carrying out cell proliferation, differentiation, migration, and apoptosis. From the typical canonical and non-canonical Wnt signaling pathways, Wnt5A is a non-canonical Wnt protein that is upregulated in several carcinomas. ROR2 mediates the Wnt5A signals through complex machinery, and the expression of ROR2 in NSCLC is independent of age, gender, pathological type, lymph node metastasis, cancer cell differentiation, and status of the tumor.[64]

To build up on this approach, Ozuriftamab vedotin (BA3021) was introduced and is currently being evaluated in advanced NSCLC tumors alongside other solid tumors. BA3021 is composed of an anti-ROR2 IgG1-kappa mAb coupled with MMAE through a cleavable (mc-val-cit-PABC) type linker.[65] A phase I/II trial (NCT03504488) is currently under investigation and will be carried out in two parts. Phase I of the study will consist of dose escalation and dose expansion of BA3021 as monotherapy in patients with advanced solid tumors. Phase II of the trial will evaluate the safety and efficacy of BA3021 in combination with PD-1 inhibitors in patients with NSCLC and melanoma.[66]

5T4

Expressed in both NSCLC-SCC and NSCLC-AC subtypes, 5T4 has received attention as a contributing molecular target in the metastasis of this carcinoma. Chromosome 6q14-15 takes responsibility for encoding 5T4 oncofoetal gene, which is typically only expressed during embryonic development with a limited expression in normal human physiology.[67] Significant upregulation of 5T4, otherwise known as trophoblast glycoprotein (TPBG), is detected in several carcinomas including lung, gastric, prostate, pancreas, colon, and ovaries.[68] This overexpression is associated with a poor prognosis due to its contribution in adhesion, cytoskeletal assembling, and motility and EMT playing a crucial role in metastasis of tumor. Moreover, it is also expressed in cancer stem cells (CSCs), which facilitates the emergence of chemoresistance and recurrence of tumorigenesis.[69] Ideally, targeting both CSCs and 5T4 expressing group of tumor entities will produce a more potent and durable response. IHC and Gene expression profiling allow the detection of expressed levels of 5T4 to predict its role in promoting tumorigenesis.[68] In NSCLC, 5T4 is associated with worse clinical outcomes due to its additional co-expression with EMT in undifferentiated cancer cells. Using a 5T4 antibody-tubulin inhibitor ADC conjugate may obstruct the detrimental influence of tumor and based on this deduction, ASN004 was developed and evaluated in several settings of NSCLC including recurrent, metastatic, and adenocarcinoma.

ASN004 incorporates a novel single-chain Fv-Fc antibody conjugated with an auristatin F-hydroxypropylamide payload through a dolaflexin drug-linker technology.[70,71] This novel ADC is currently under phase I clinical trial (NCT04410224) in subjects with advanced solid tumors. At present, the study is in the dose escalation phase involving endpoints such as preliminary antitumor efficacy, safety, and PK parameters.[72]

B7 Homolog 3 Protein

B7 homolog 3 protein (B7-H3), also named CD276, is a type 1 transmembrane protein encoded by chromosome 15 whose imbalanced expression results in a poor prognosis in NSCLC clinical setup.[73] It is housed under an Ig superfamily and is a member of the B7 immunoregulatory molecular family. Despite its broader expression levels in multiple organs including bladder, breast, lymphoid organs, testis, lung, liver, placenta, and prostate, along with osteoblasts and fibroblasts, it is found to have scarce expression, which is rarely reported.[74] Numerous malignancies stem from overtly expressed B7-H3 including NSCLC lines on both messenger ribonucleic acid (mRNA) and protein levels.[75]

The B7-H3 plays both anti-tumoral and pro-tumoral roles, and tumoral B7-H3 overexpression elevates the tumor-infiltrating cytotoxic lymphocytes. It further promotes tumor invasion, facilitates the emergence of chemoresistance, and contributes in tumor metastasis.[76] Such an association with tumor progression, despite its low expression and rare detection, makes B7-H3 one of the potential targets to eradicate cancerous cells. Multiparametric flow cytometry and IHC help in the detection of B7-H3 expression responsible for driving the malignancy of NSCLC.[77,78]

Vobramitamab duocarmazine, also known as MGC018, consists of an anti-B7-H3 mAb attached with a duocarmycin payload through valine-citrulline-seco-duocarmycin hydroxybenzamide azaindole moiety.[79] The payload binds to the minor groove of DNA which leads to an irreversible alkylation of DNA resulting in programmed tumor cell death.[80] A phase I study (NCT03729596) having 29 patients evaluated the preliminary activity, safety, antitumor response, and immunogenicity of MGC018 in patients with advanced solid tumors. The recommended phase II dose (RP2D) of MGC018 was

3 mg/kg. Significant antitumor response, along with a manageable safety profile, was reported in patients with melanoma. Phase II of this study is currently under investigation and includes NSCLC patients.[81] In addition, this agent was being investigated in combination with Retifanlimab (Anti-PD-1 Antibody) in patients with advanced solid tumors including NSCLC in another phase I/II study (NCT03729596).[82] However, the study was terminated in March 2023 due to some organizational decisions.

Folate Receptor α

Folate receptor α (FRA) is a glycosylphosphatidylinositol (GPI)-anchored glycoprotein residing on cellular surface, which mediates the entry of active folate molecules in the cells.[83] Among the four isoforms (alpha, FRA; beta, FRB; gamma, FRG, and delta, FRD), FRA and FRB isoforms are highly homologous. The FRA, also known as FOLR1, has a measurable expression which is largely limited to the apical surfaces of epithelia due to its restricted healthy tissue distribution.[84] This minimal distribution and expression pattern renders inaccessibility problems to the targeting drugs. On the contrary, malignant tumors with an epithelial origin, namely lung cancer, colorectal cancer, ovarian cancer, and breast cancer, show FOLR1 overexpression.

Folate intake is an essential process necessary for cellular metabolism to function, and overexpression of FOLR1 increases influx of folate, which confers a growth benefit to tumors by impacting cell proliferation through alternate cell signaling pathways.[85] Non-smokers and never-smokers show a more significant expression of cytoplasmic FRA than smokers. Moreover, the FRA expression levels are the same for both advanced tumor stages and surgically resected tumors. In addition, the early stages of NSCLC also show the presence of FRA-positive circulating cancer cells.[86] This deduces FRA to be a highly promising marker and target to aim through the antitumor drugs. Immunoblotting and microfiltration assays aid in detection of FRA in which the former has a better positive predictive value than the microfiltration assay. Some other techniques useful for the detection of FRA include electroluminescence and ELISA.[87] Prevalent expression of FRA in NSCLC adenocarcinoma raised a need for development of an approach capable of identifying and targeting this overexpressed biomarker, which led to the introduction of MORAb-202.

Farletuzumab ecteribulin (MORAb-202) is an ADC consisting of farletuzumab antibody and eribulin cytotoxic agent attached through a cathepsin-B cleavable linker. Farletuzumab, prescribed solely as a monoclonal antibody, failed to show statistically significant improvement in progression-free survival (PFS), and payloads used solely triggered antitumor response with a risk of extremely potent toxicity alongside having a limited therapeutic index.[88,89] This embarked on the assembling of both components to form an ADC overcoming these mentioned limitations. After administration of MORAb-202 and its subsequent entry in FRA-positive tumor cells, the linker undergoes enzyme-mediated cleavage, and eribulin initiates antitumor activity to inhibit the cancerous cell proliferation.[90]

A first-in-human study (NCT03386942) of MORAb-202 evaluated the safety and tolerability of the same in patients with FRA-positive advanced solid tumors who failed to respond to standard therapy regimens. Out of 22 enrolled patients, one patient showed a complete response. PR and SD were seen in nine and eight patients, respectively. During the safety analysis, the presence of ILD (grade 1/2) in five patients was correlated with MORAb-202. Moreover, treatment-emergent adverse events (TEAEs) were observed in nearly 95% of patients, with neutropenia, leukopenia, anemia, and rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The levels of FRA were measured pre and post-treatment in the study, and it was found that an increase in the FRA levels was observed following the first cycle of treatment. In addition, higher FRA levels were associated with the highest tumor shrinkage. Another intriguing revelation from this study was a higher bystander effect owing to the greater permeability of eribulin payload despite lower expression of FRA in targeted tumors.[91] This evidence strengthens the claims of targeting even low-expressing tumor cells by ADCs.

CEACAM5

CEACAM5, otherwise termed as carcinoembryogenic antigen-related cell adhesion molecule-5, is a member of the CEACAM group of proteins and is characterized by highly glycosylated proteins with a typical N-terminal variable Ig domain. It is situated on the cell surface, where it exhibits inhibitory effects on p38 activity. Further, it functions as a regulator of various complex biological processes, namely cell proliferation, differentiation, migration, invasion, and death.[92] In the primary early clinical studies (NCT02187848) of the novel ADC Tusamitamab ravtansine or SAR408701, it demonstrated a favorable safety profile and achieved an ORR of 22.7% in patients with heavily treated solid tumors where more than half of tumor cells expressed CEACAM5.[93] On the basis of this success, the ADC was further evaluated in 92 patients with NSCLC showing moderate to high CEACAM5 expression. The results displayed a PR in nearly half of the treated patients. This response lasted even more than a year of treatment. These findings reveal a durable response and long-term benefits, a noteworthy outcome in patients with advanced malignancies who had experienced relapse.

Moreover, other biomarkers such as Claudin 18.2, Claudin 6, SORT1, and SEZ6 are also explored for their involvement in various cellular functions. Development of novel ADCs for these biomarkers have been an active area of investigation. Claudin 18.2 and Claudin 6 are members belonging to the claudin family of proteins forming an integral part of membrane proteins. They play a crucial role in the formation of tight junctions between cells. These biomarkers have been observed in

different cancer types; however, major relation has been found with gastric cancer. TORL-1-23 is an ADC targeting Claudin 6, which has been primarily investigated via first-in-human phase 1 study (NCT05103683).[94,95]

On the other note, CMG901 is a claudin 18.2 targeted ADC which showed good tolerability and an acceptable safety profile in preclinical studies. CMG901 has received FDA approval for undergoing further research in phase 1 clinical trials in patients suffering from gastric cancer (NCT04805307).[96,97]

Sortilin-1, otherwise abbreviated as SORT1, is a transmembrane protein that belongs to the Vps10p domain receptor family, which plays a role in intracellular protein trafficking. Wide expression of SORT1 in various tissues led to the development of a peptide-drug conjugate called Sudocetaxel zendusortide, which was further tested through phase 1, open-label study in patients with advanced solid tumors (NCT04706962).[98,99]

SEZ6, known as seizure-related homolog protein, is a cell surface protein recently found to have high expression, specifically in neuroendocrine tumors and SCLC. ABBC-011, a novel ADC, is being explored to assess anti-SEZ6 activity in a phase 1 trial in patients suffering from Relapsed or Refractory SCLC (NCT03639194).[100,101]

Combination of Antibody-Drug Conjugates with Other Therapies

Combining different chemotherapies with ADCs is a recognized strategy to overcome the limitation of drug resistance and achieve enhanced therapeutic outcomes. As per a few studies, the combination of chemotherapy and ADCs involves a phenomenon of synergism, which influences the expression of tumor cell surface antigens and targets distinct stages of the cell cycle.

Endocrine therapy, which is usually employed in hormone-sensitive cancers, inhibits tumor development either by obstructing hormone synthesis or by interfering with growth-stimulating hormones. ADCs and endocrine therapy, if combined, can collaboratively diminish the chances of tumor cell survival and proliferation. The use of this combination strategy involving unique mechanisms of both entities may also aid in eradicating tumor cells developing resistance.[102]

The combination therapy of ADCs with radiotherapy has two subtypes, including external radiation therapy with ADC and radionuclide antibody conjugates (RACs). RACs are defined as having specific mAbs labeled with radioactive isotopes such as radionuclides and beta emitters linked with payload. On the contrary, the combination of ADCs with external radiation therapy can be concomitant or sequential. Simultaneous administration of ADC and radiotherapy characterizes concomitant radiotherapy. However, the timing of sequential ADC administration varies from study to study, spanning from 77 to 131 days when given before radiotherapy and 420 to 1426 days when given after radiotherapy.[103]

Targeted therapies such as tyrosine kinase inhibitors and anti-angiogenic agents have been administered in clinical settings since several years; however, the effectiveness of combining ADCs with these molecules remains to be unclear. The combined effect of these entities may encompass various mechanisms including enhanced delivery of drug within TME by targeting blood vessels, modulation of tumor surface antigen expression, intratumoral heterogeneity, and induction of synthetic lethality.

Increasing evidence indicates the susceptibility of ADCs to the efficacy of immunotherapeutic agents. The current trend in clinical practice involves combining ADCs with immunotherapy which is supported by numerous preclinical studies and initial results from early-phase trials demonstrating enhanced antitumor effects. The underlying mechanisms are diverse and include Fc-mediated effector functions, improved T-cell infiltration, maturation of dendritic cells, beginning of immunogenic cell death, reinforcement of immunological memory, and expression of immunomodulatory proteins.[104]

Conclusions

The NSCLC is widely known as a prototype disease for precision oncology after decades of intense research and the discovery of numerous oncogenic drivers. The use of targeted therapies and immunotherapies encountered various challenges, the most significant of which were the development of resistance and, consequently, disease progression. The development of various ADC molecules offered an innovative therapeutic approach that resulted in the integration of these agents into the treatment paradigm of NSCLC patients. However, the use of ADCs in patients with oncogenic mutations, including EGFR, HER2, TROP2, and c-MET, was encountered with several challenges. Development of the resistance and toxicities arising from the off-target binding of ADCs were the most prominent issues among many others. This led to exploration of novel biomarkers and development of ADCs to target the same. However, most of these ADCs are currently in phase I/II trials, and it is difficult to derive any strong substantiations regarding the efficacy of these molecules at present. Nevertheless, the results from early-stage trials have been found to be encouraging in advanced solid tumors as well as NSCLC cohorts. Procurement of further data from phase-III trials can provide detailed insights into whether these molecules can broaden the therapeutic armamentarium against NSCLC or not. Designing further studies to evaluate these molecules in combination with other chemotherapeutic or immunotherapeutic agents can aid in further advancements in NSCLC management.

Author Contributions

Conceived and organized the design of the manuscript, performed the literature review and evaluation, and wrote the body of the manuscript: AK, SS, KM, and VBS. Provided administrative, technical, and material support and assisted in editing and reviewing the manuscript: AS, HM, and SB. Performed the literature review, provided material and technical support, and helped to review and edit the manuscript: AK, SS, KM, VBS, and MM.

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