Antibody-Drug Conjugates in Advanced Lung Cancer: Is This a New Frontier?

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Abstract: Over the past decade, the lung cancer landscape has been dominated by targeted and immunotherapeutic approaches that have drastically shifted treatment paradigms for patients with advanced non–small cell lung cancer (NSCLC). Despite these scientific and clinical advances, there are still many unmet needs underscoring the importance of novel strategies. Antibody-drug conjugates (ADCs) represent one such strategy that is beginning to alter the therapeutic strategies for patients with advanced NSCLC. The rationale of ADCs is simple: selectively deliver cytotoxic payloads through an antibody-mediated process to target antigens expressed by cancer cells, sparing normal tissue and inflicting damage to tumors. Although this concept has been the leading view, preclinical and clinical observations are demonstrating that only a nascent mechanistic understanding of these agents exists. In this review, we discuss the underlying biology of ADCs and their structure and potential mechanisms of action, examine approved and promising ADC targets in lung cancer, and review emerging ADC targets and combinatorial strategies. Importantly, we address the unanswered questions surrounding ADCs in lung cancer, including biomarker selection, treatment sequencing, and mechanisms of resistance, as well as management of unique ADC-associated toxicities.

Keywords
Antibody-drug conjugate, antigen, drug-to-antibody ratio (DAR), linker, monoclonal antibody, payload

Introduction

Over the past decade, the lung cancer treatment landscape has been dominated by targeted and immunotherapeutic approaches that have drastically shifted treatment paradigms for patients with advanced non–small cell lung cancer (NSCLC). These advances have been predicated on a firmer understanding of the tumor microenvironment and deep sequencing efforts that have unearthed targetable

genomic alterations. Despite these scientific and clinical advances, there are still many unmet needs, underscoring the importance of novel strategies. Antibody-drug conjugates (ADCs) represent one such strategy that is beginning to alter the therapeutic strategies for patients with advanced NSCLC.

The historical roots of ADCs trace back to the early 20th century when scientist Dr Paul Ehrlich, a founder of chemotherapy, conceived of a more targeted delivery of anticancer therapy, termed "the magic bullet."[1] Although early ADCs were limited by pharmacokinetic and pharmacodynamic properties such as poor tumor penetration[2] and insufficient potency of the cytotoxic component,[3] advancements in synthetic biochemistry have culminated in contemporary ADCs that deliver a more selective cytotoxic payload to the tumor. The rationale of ADCs is simple: selectively deliver cytotoxic payloads through an antibody-mediated process to target antigens expressed by cancer cells, sparing normal tissue and inflicting damage to tumors. Although this proposed concept has been the leading view, preclinical and clinical observations are demonstrating that we have only a nascent understanding of the mechanistic actions of these agents. In this review, we discuss the underlying biology of ADCs. We review their structure and potential mechanisms of action, examine approved and promising ADC targets in lung cancer, and review emerging ADC targets and combinatorial strategies. Importantly, we attempt to address the unanswered questions surrounding ADCs in lung cancer, including biomarker selection, treatment sequencing and mechanisms of resistance, and the management of unique ADC-associated toxicities.

Basic Structure and Mechanism of Action

Antibody

An ideal ADC antibody must exhibit a strong binding affinity for its target while maintaining conformational and colloidal stability in circulation, with low cross-reactivity and immunogenicity. The antibody is made up of 2 key components: (1) the antigen-binding fragment, which recognizes and binds the target antigen; and (2) the constant fragment (Fc), which engages immune effector cells and influences serum half-life. The main class of antibody that optimizes these attributes is the humanized immunoglobulin G (IgG) class, of which the IgG1 subtype is the most commonly deployed.[4-6]

There are many candidate antigens for ADC engagement. Ideally, the antigen should be selectively overexpressed on tumors but not normal tissue to limit on- and off-target toxicity. Additionally, the antigen should be consistently accessible to circulating antibodies, reinforcing the importance of high antigen density on the cell surface. Finally, the antigen must exhibit high internalization capacity to facilitate transmembrane trafficking of the ADC construct, enhancing intracellular cytotoxicity.

Linker

The linker is the biochemical compound that connects the antibody to the cytotoxic payload and serves 2 vital roles: (1) maintaining ADC stability in circulation and intact delivery to target tissues; and (2) ensuring appropriate payload uncoupling upon tumor uptake.

Linkers can be divided into 2 categories: noncleavable and cleavable. Noncleavable linkers form nonreducible bonds between amino acid residues with the antibody and payload, which leads to enhanced stability in the bloodstream and limited potential for off-target toxicity.[7] However, ADCs that incorporate noncleavable linkers require trafficking to mature lysosomes for payload uncoupling,[8] resulting in enhanced cellular payload retention, poor payload diffusion across cell membranes, and limiting potential cytotoxic effects on neighboring cells lacking target expression.[9,10]

Conversely, cleavable linkers rely on various components of cell physiology, including pH and the presence of glutathione and proteases, to promote payload uncoupling.[6] Because of this, ADCs with cleavable linkers are generally not reliant on trafficking to mature lysosomes. In addition, payload permeability across cell membranes is typically greater with ADCs that contain cleavable linkers.[11] This results in a greater "bystander effect," which can be particularly important in tumors with heterogeneous target expression and in dense tumors that require significant drug diffusion.

Payload and Drug-to-Antibody Ratio

The payload or "warhead" is the cytotoxic effector of an ADC. A prototypical payload is a cytotoxic compound with effective toxicity at sub-nanomolar and picomolar concentrations. An ideal payload is stable in circulation and does not interfere with ADC target binding and internalization. Modern payloads typically consist of DNA damaging agents, tubulin polymerization inhibitors, or topoisomerase inhibitors. Beyond their direct antitumor effects, the unique physiochemical properties of a specific payload likely affect bystander properties via effects on drug distribution, diffusion, and tumor efflux.[12]

A related attribute of the payload is the number of payload moieties attached to a given antibody, a term referred to as the drug-to-antibody ratio (DAR). The majority of US Food and Drug Administration (FDA)-approved and emerging ADCs in lung cancer have DARs ranging from 2 to 8.[13] Site-specific conjugation techniques have led to improved DAR consistency for modern ADCs. Interestingly, although in vitro data suggest that

higher DAR should equate to greater potency, preclinical studies indicate that increased payload loading may result in more rapid hepatic clearance, exacerbating toxicity and narrowing the therapeutic index.[14]

Mechanism of Action

Although the cytotoxic effect of the payload is believed to be the primary mediator of tumor killing, an effective ADC must engage its target antigen through proper antibody-antigen binding, resulting in prompt internalization, linker degradation, and payload release. Beyond ADC internalization, properties of the payload and linker are important in mediating cytotoxic effects on neighboring cells (ie, the bystander effect). The permeability of a given payload and linker cleavability play critical roles in this process. Finally, although direct cytotoxicity is believed to be the primary mechanism of action for ADCs, antibody-dependent cellular cytotoxicity, antibody-dependent phagocytosis, and complement-mediated cytotoxicity likely play roles as well.[6] For example, the human epidermal growth factor receptor 2 (HER2)-targeting ADC trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), has been shown to induce antibody-dependent cellular cytotoxicity in preclinical models through engagement of the Fc region of trastuzumab with immune effector cells.[15]

Emerging ADC Targets and Therapeutics in Lung Cancer

HER2

Gene mutations in the erb-b2 (ERBB2) receptor tyrosine kinase (RTK) gene, typically occurring as in-frame insertions in exon 20, may be present in 1% to 4% of patients with NSCLC.[16] Additionally, *HER2* gene amplification and protein overexpression have been described in approximately 5% and 10% to 30% of NSCLC cases, respectively,[17-19] although the therapeutic implications of these alterations remain unclear.[20]

Trastuzumab Emtansine. Trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech), was the first ADC targeting the HER2 receptor. It incorporates the HER2-directed antibody trastuzumab and the microtubule-disrupting agent DM-1 via a noncleavable linker. The average DAR is 3.5.[21] Li and colleagues first presented results from a basket trial of 18 patients with *HER2*-mutated NSCLC treated with T-DM1, reporting an overall response rate (ORR) of 44%, with a median progression-free survival (PFS) of 5 months.[22] A more recent phase 2 trial enrolled 22 patients with pretreated NSCLC harboring *HER2* exon 20 insertion mutations and reported an ORR of 38.1%. The median duration of response (DOR), PFS, and overall survival (OS) were 3.5, 2.8, and 8.1 months, respectively.[23] T-DM1 was well-tolerated overall, with the most frequent grade 3/4 adverse events (AEs) being thrombocytopenia (18.2%), appetite loss (4.5%), cardiac dysfunction (4.5%), anemia (4.5%), and hypertension (4.5%).

Trastuzumab Deruxtecan. T-DXd is a novel ADC that utilizes the anti-HER2 monoclonal antibody trastuzumab and a cytotoxic payload of the topoisomerase inhibitor deruxtecan (DXd), conjugated via a tetrapeptide-based cleavable linker.[15] T-DXd has a DAR of 8, with engineered properties to improve stability within the systemic circulation and exert increased bystander effect via a membrane-permeable payload, resulting in enhanced cytotoxic effect in preclinical studies compared with T-DM1.[24,25]

An initial first-in-human, dose-expansion study explored the safety and efficacy of T-DXd in HER2-overexpressing or *HER2*-mutated non-breast, non-gastric solid malignancies. Encouraging efficacy signals were noted, with an ORR of 55.6%, median PFS of 11.3 months, and median DOR of 10.7 months.[26] Despite overall tolerability at the 6.4 mg/kg dose, there were notably 2 treatment-related fatalities secondary to respiratory failure.

The subsequent global phase 2 DESTINY-Lung01 trial evaluated the efficacy of T-DXd at 6.4 mg/kg every 3 weeks in 2 distinct cohorts: HER2-overexpressing (defined by immunohistochemistry [IHC] of 2+ or 3+, cohort 1) and *HER2*-mutated tumors (cohort 2). Updated efficacy analysis from 91 patients treated in cohort 2, published by Li and colleagues, noted an ORR of 55%, disease control rate (DCR) of 92%, median PFS of 8.2 months, and OS of 17.8 months. The safety profile was consistent with prior studies of T-DXd, with a grade 3 or higher treatment-related adverse event (TRAE) rate of 46%. The authors did report a 26% incidence of drug-related interstitial lung disease (ILD), including fatal events in 2 patients.[27]

Following these findings, the phase 2 randomized DESTINY-Lung02 trial was designed to assess the benefit-risk profile of T-DXd at doses of 5.4 or 6.4 mg/kg. Patients with previously-treated *HER2*-mutated NSCLC were randomized in a 2:1 ratio to T-DXd at 5.4 mg/kg or 6.4 mg/kg every 3 weeks. Primary results from this trial, which enrolled a total of 152 patients, noted comparable ORRs of 49% and 56%, respectively. Responses were observed regardless of *HER2* mutation type, amplification status, and the presence of intracranial disease. With a median duration of follow-up of 11.5 months, the median PFS was 9.9 months in the 5.4-mg/kg group and 15.4 months in the 6.4-mg/kg group, numerically favoring the higher dosing at this early efficacy analysis. Safety trends seemed to favor the 5.4 mg/kg dosing schedule, with a lower incidence of grade 3 or higher TEAEs (38.6% vs

58%) compared with the 6.4-mg/kg dose. This included lower rates of adjudicated drug-related ILD (12.9% vs 28%), with the majority being grade 1 to 2. The most common grade 3 or higher TEAEs included cytopenias, fatigue, and nausea.[28] Safety results were consistent with an earlier interim analysis, which ultimately led to the FDA-accelerated approval of T-DXd at 5.4 mg/kg every 3 weeks. Importantly, T-DXd also appears to have encouraging central nervous system efficacy. Among 14 patients with measurable brain metastases treated with T-DXd at 5.4 mg/kg in the DESTINY-Lung02 trial, an intracranial ORR of 50% was seen, with intracranial DOR of 9.5 months. A similar benefit was also observed among patients treated at 6.4 mg/kg.[29] Ongoing studies are now exploring the efficacy of T-DXd in the frontline setting for patients with *HER2*-mutated disease (Table).[30,31]

HER3

HER3, encoded by the *ERBB3* gene, is another member of the HER/ErbB RTK family. HER3 is a partner in HER2/HER3 heterodimerization, leading to downstream intracellular activation of PI3K/AKT signaling pathways.[32] HER3 overexpression and activation have been implicated in mediating resistance to endothelial growth factor receptor (EGFR)-targeted therapies.[33]

Patritumab Deruxtecan. Patritumab deruxtecan (HER3-DXd) is an investigational HER3-targeted ADC consisting of patritumab, a fully humanized anti-HER3 monoclonal antibody, conjugated to the cytotoxic payload DXd via a tetrapeptide-based cleavable linker. The DAR of HER3-DXd is 8.[34] An initial phase 1 trial tested the safety and efficacy of HER3-DXd in patients with *EGFR*-mutated NSCLC that had progressed on an EGFR-directed tyrosine kinase inhibitor (TKI). Results from the 57-patient *EGFR*-mutated cohort revealed HER3-DXd to be well-tolerated, with a recommended phase 2 dose of 5.6 mg/kg every 3 weeks. Most common TRAEs included hematologic toxicities such as thrombocytopenia, neutropenia, and anemia (grade ≥3 rates of 30%, 19%, and 9%, respectively). Four patients (5%) developed ILD on therapy. In terms of efficacy, the ORR was 39%, with a median PFS of 8.2 months. Importantly, responses were observed across a broad spectrum of EGFR/TKI resistance mechanisms.[35]

A separate phase 1 study investigated HER3-DXd at the recommended phase 2 dose in patients without EGFR-sensitizing mutations, including those with (n=17) and without (n=26) identifiable oncogene drivers. ORRs in the 2 cohorts were 35% and 23%, respectively. Again, hematologic toxicities were the most commonly reported grade 3 and higher AEs. The investigators also noted drug-related ILD events in 4 patients, but all were low-grade (grade 1 or 2).[36]

The larger phase 2 HERTHENA-Lung01 trial assessed the efficacy of HER3-DXd in patients with advanced *EGFR*-mutated NSCLC whose disease had progressed on prior EGFR TKI and platinum-based chemotherapy. A total of 225 patients received HER3-DXd at 5.6 mg/kg every 3 weeks, with most patients having received at least 3 lines of prior therapy. After a median study duration of 18.9 months, efficacy results included a confirmed ORR of 29.8%, median DOR of 6.4 months, median PFS of 5.5 months, and median OS of 11.9 months. Early biomarker data from available patients noted responses across a broad range of pretreatment HER3 expression levels and various EGFR/TKI-associated resistance mechanisms. Subgroup analysis from 30 patients with baseline brain metastases noted encouraging intracranial activity, with an intracranial ORR of 33.3%. This included 9 patients (30%) with a complete response and a median DOR of 8.4 months.[37,38] Safety signals were similar to prior phase 1 data. The incidence of adjudicated drug-related ILD was 5.3% (75% grade 1-2), including 1 death.[38]

TROP2

Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein calcium signal transducer encoded by the *Tacstd2* gene,[39,40] with expression present in multiple epithelial cancers, including NSCLC.[41,42] Preclinical studies suggest TROP2 is involved in several cell signaling processes, including proliferation, invasion, and cell migration, with clinical data suggesting that overexpression may confer a poor prognosis in NSCLC.[42]

Sacituzumab Govitecan. Sacituzumab govitecan (SG; Trodelvy, Gilead) is a TROP2-directed ADC comprised of the anti-TROP2 antibody sacituzumab conjugated via a hydrolysable cleavable linker to the topoisomerase inhibitor SN-38. The DAR is 7.6.[43] A phase 1/2 basket trial, IMMU-132-01, evaluated the safety of SG in treatment-refractory epithelial malignancies. The study enrolled 495 patients with SG dosing ranging from 8 to 18 mg/kg, given on days 1 and 8 of a 21-day cycle. Notable TRAEs included diarrhea, neutropenia, anemia, and nausea, with grade 3 or higher AEs reported in 59.6% of patients and 32% of patients requiring dose reductions.[44] A dose of 10 mg/kg was selected for the expansion cohorts. One expansion cohort enrolled 54 patients with previously-treated NSCLC and noted an ORR of 17% and median PFS of 5.2 months.[45] A separate cohort of 62 patients with pretreated SCLC showed an ORR of 17.7%, median PFS of 3.7 months, and median OS of 7.1 months.[44]

Datopotamab Deruxtecan. Datopotamab deruxtecan (Dato-DXd) is an investigational ADC comprised of a recombinant humanized anti-TROP2 IgG1 monoclonal antibody conjugated to the topoisomerase

Table. Ongoing Trials Exploring ADC Combinations in Advanced NSCLC and SCLC

Trial	Phase	Population	ADC target	Treatment arm(s)	Estimated enrollment	Primary endpoint(s)
EVOKE-01	3	Advanced/metastatic NSCLC with progression on or after platinum-based chemotherapy and immunotherapy	TROP2	Sacituzumab govitecan vs docetaxel	520	OS
CARMEN-LC03 (NCT04154956)	3	Previously treated, CEACAM5+ metastatic nonsquamous NSCLC	CEACAM5	Tusamitamab ravtansine vs docetaxel	411	PFS OS
TROPION LUNG-07 (NCT05555732)	3	Untreated advanced/metastatic NSCLC with PD-L1 ≤50%	TROP2	Datopotamab deruxtecan plus pembrolizumab +/- chemotherapy	975	PFS OS
TROPION Lung-08 (NCT05215340)	3	Untreated advanced/metastatic NSCLC with PD-L1 ≥50%	TROP2	Pembrolizumab +/- datopotamab deruxtecan	740	PFS/OS
AVANZAR (NCT05687266)	3	Untreated advanced/metastatic NSCLC	TROP2	Datopotamab deruxtecan with durvalumab and carboplatin	1280	PFS/OS
NCT04928846	3	Previously treated nonsquamous, c-MET+, *EGFR*-wt NSCLC	c-MET	Telisotuzumab vedotin vs docetaxel	698	PFS/OS
HERTHENA-Lung02 (NCT05338970)	3	Previously treated metastatic or locally advanced *EGFR*-mutated NSCLC	HER3	Patritumab deruxtecan	586	PFS
DESTINY Lung04 (NCT05048797)	3	Treatment-naive *HER2*-mutated NSCLC	HER2	Trastuzumab deruxtecan	264	PFS
NCT04042701	1b/2	PD-1–naive *HER2*-mutated or -expressing NSCLC	HER2	Trastuzumab deruxtecan	115	ORR
NCT05280470	2	Pretreated extensive-stage SCLC	B7-H3	Ifinatamab deruxtecan	91	ORR
ARTEMIS-001 (NCT05276609)	1	Pretreated advanced/metastatic solid tumors	B7-H3	HS-20093	177	MTD/ORR

ADC, antibody-drug conjugate; B7-H3, B7 homolog 3 protein; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; EGFR, endothelial growth factor receptor; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; MTD, maximum tolerated dose; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; SCLC, small cell lung cancer; TROP2, trophoblast cell-surface antigen 2; wt, wild type.

I inhibitor deruxtecan via a tetrapeptide-based cleavable linker. This optimized DAR is 4.[46] Dato-DXd was first evaluated in the phase 1 TROPION-PanTumor01 trial, which included a dose-expansion cohort of 180 previously-treated patients with NSCLC who received doses ranging from 4 to 8 mg/kg every 3 weeks. Patients were selected regardless of TROP2 expression. Although the maximum tolerated dose was 8 mg/kg, the recommended dose for further development was 6 mg/kg based on the safety profile. Despite relatively equivalent efficacy between the 6-mg/kg and 8-mg/kg cohorts (ORR, 26% and 23.8%, respectively), drug-related TEAEs were lower in patients treated with 6 mg/kg, with grade 3 and higher events occurring in 26% and 36.3% of patients, respectively. The most frequent TEAEs throughout all dosing cohorts were nausea, stomatitis, and alopecia, the majority being low-grade. Drug-related ILD events were observed in all 3 dosing cohorts (4, 6, and 8 mg/kg), with adjudicated grade 3 and higher cases in 2%, 2% and 5%, respectively. Three of the deaths that were attributed to drug-related ILD were observed in the 8 mg/kg group. Responses to Dato-DXd were durable,

with median DORs of 12.7, 10.5, and 9.6 months across the 4, 6, and 8 mg/kg cohorts, respectively. For patients receiving 6 mg/kg, the median PFS was 6.9 months and the median OS was 11.4 months. TROP2 expression was detected in nearly all cases, with high expression (H-score >100) observed in 73.6% of patients, but there was no discernible relationship between TROP2 expression and efficacy.[47]

The phase 3 TROPION-Lung01 trial enrolled 604 patients with advanced NSCLC with progression on no more than 2 prior lines of therapy. Patients were randomly assigned in a 1:1 ratio to Dato-DXd at 6 mg/kg every 3 weeks or docetaxel 70 mg/m^2 every 3 weeks. At a median follow-up of 13 months, median PFS with Dato-DXd was 4.4 months compared with 3.7 months with docetaxel (hazard ratio [HR], 0.75). The PFS benefit appeared to be more pronounced in nonsquamous (HR, 0.63) compared with squamous (HR, 1.38) histology. The toxicity was consistent with previously reported data. Adjudicated drug-related ILD was observed in 8% of patients treated with Dato-DXd, with 3% experiencing grade 3 or higher ILD and 2% experiencing death secondary to ILD (grade 5).[48]

Updated results from the phase 1b TROPION-Lung02 trial were presented by Goto and colleagues.[49] The trial included several dose-expansion cohorts evaluating the safety and efficacy of Dato-DXd as frontline therapy in either a doublet combination with pembrolizumab or a triplet regimen with platinum chemotherapy. A total of 64 patients were treated with the doublet combination and 72 patients were treated with the triplet regimen; of these, 58% and 75%, respectively, were treated in the frontline setting. Looking at all treated patients, both doublet and triplet combinations showed an encouraging ORR (38% and 49%, respectively) and DCR (84% and 87%, respectively). The median PFS for all patients was 8.3 months in the doublet arm and 7.8 months in the triplet arm. The ORRs were higher for treatment-naive patients, at 50% in the doublet arm and 57% in the triplet arm. Grade 3 and higher drug-related TEAEs occurred in 31% and 58% of the doublet and triplet cohorts, respectively. Common any-grade TEAEs included stomatitis, nausea, anemia, and fatigue. Hematologic TEAEs, particularly high grade (≥3), were more frequently observed with the triplet therapy (anemia 13%, thrombocytopenia 7%, neutropenia 13%) vs the doublet therapy (anemia 2%, thrombocytopenia 0%, neutropenia 0%). Other AEs of special interest for both the doublet and triplet therapies included adjudicated drug-related ILD (all grade: 17% and 22%) and ocular surface toxicities (all grade: 16% and 24%, respectively), with rates of grade 3 and higher ILD being 3% for both treatment groups, and rates of grade and higher 3 ocular toxicity being 2% and 3% for the doublet and triplet arms, respectively.

Dato-DXd has also shown promise in NSCLC with actionable genomic alterations. TROPION-Lung05 is a single-arm phase 2 trial evaluating Dato-DXd as subsequent-line therapy in NSCLC with actionable genomic alterations. Among 137 enrolled patients, ORR was promising at 36%, with a median PFS of 5.4 months, and a median DOR of 7.0 months. Among 78 patients with *EGFR*-mutated NSCLC, an ORR of 44% was observed, with a median PFS of 5.8 months, and a median DOR of 7.0 months.[50]

Other Prominent Therapeutics

Several other ADCs are on the precipice of changing practice in advanced NSCLC. Both tusamitamab ravtansine (Tusa) and telisotuzumab vedotin (Teliso-V) utilize a biomarker-selective approach to guide therapy, and early data suggest that efficacy is related to biomarker expression levels.[51,52] Tusa is composed of an antibody targeting carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5, tusamitamab) conjugated to a DM4 payload with DAR of 3.9.[53] Early studies in subsequent-line setting have shown an ORR of 20% in patients with high (IHC ≥2+ in ≥50% of cells) CEACAM5 expression.[51] Teliso-V incorporates the MET-targeted antibody telisotuzumab conjugated to a vedotin payload with a DAR of 3.1. It has shown particular promise in patients with *EGFR* wild-type NSCLC with high c-MET expression (IHC 3+ in ≥50% cells), with an ORR exceeding 50% in early studies.[52,54] Teliso-V is also showing promise in patients with *EGFR*-mutated disease that has high c-MET expression following progression on osimertinib.[55] Another promising ADC is the B7 homolog 3 protein (B7-H3)-targeted ADC ifinatamab deruxtecan (I-DXd). I-DXd has shown early efficacy in small cell lung cancer, where subgroup data suggest an ORR of greater than 50%, with an encouraging median duration of response of 5.9 months.[56] For additional detail on these and other ADCs, refer to the online supplement at www.hematologyandoncology.net.

New and Emerging ADC Constructs

ADCs as a therapeutic class have evolved considerably. Although many current-generation ADCs are approved or on the verge of approval in lung cancer, the next generation of ADCs looks to build on this success through both novel targeting techniques and payloads.

BL-B01D1 is a first-in-class EGFR/HER3 bispecific ADC attached to a novel topoisomerase payload via a cleavable linker.[57] Early data for this compound suggest promising efficacy, with an ORR of 62% in 34 patients with *EGFR*-mutated NSCLC and 41% among 42 patients

with *EGFR* wild-type NSCLC.

Other novel targeting techniques include the utilization of short protein peptides in place of antibodies to preferentially target tumor tissue. One intriguing class of peptide-toxin conjugates (PTCs) utilizes a 9-20 amino acid peptide structure called a "bicycle peptide," which appears to have slower renal clearance and deeper penetration than other PTCs.[58] BT1718 is an example of a novel first-in-class bicycle-toxin conjugate that selectively binds the surface metalloproteinase MT1-MMP linked to a DM1 payload by a cleavable disulfide linker.[59] This compound is currently being tested in dose escalation as part of a phase 1/2 study in advanced solid tumors (NCT03486730).

Another intriguing class of PTCs are C'Dot-drug conjugates, which utilize ultra-small (<10 nm) nanoparticles. These compounds are expected to have improved therapeutic efficacy owing to a shorter half-life and improved tumor penetration. In addition, their structure enables the conjugation of a high concentration of payload. ELU001 is a novel C'Dot-drug conjugate that targets folate receptor-α and is currently being tested in dose escalation. It consists of 12 folic acid-targeting moieties and 22 exatecan topoisomerase-1 inhibitor payloads.[60]

Conjugates with alternative payloads are also actively under development. A class of compounds called immune-stimulating ADCs uses immunostimulatory molecules such as toll-like receptor (TLR) agonists or stimulator of interferon genes agonists rather than cytotoxic moieties as payloads. Trastuzumab imbotolimod (BDC-1001) consists of a novel TLR 7/8 agonist conjugated to the anti-HER2 antibody trastuzumab via a noncleavable linker. BDC-1001 is being investigated in an ongoing phase 1/2 trial as monotherapy and in combination with nivolumab (Opdivo, Bristol Myers Squibb) in patients with advanced HER2-expressing solid tumors.[61]

Another exciting class of molecules with novel payloads is radioimmunoconjugates, which combine a radionuclide payload with an antibody target. This class of agents is currently approved in solid tumors, including lutetium (^{177}Lu) oxodotreotide (Lutathera, Advanced Accelerator Applications) for neuroendocrine tumors[62] and lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto, Novartis) for metastatic castration-resistant prostate cancer.[63]

Outstanding Issues

With multiple agents on the precipice of approval in advanced NSCLC, several unanswered questions are needed to further optimize treatment strategies, including biomarker selection, toxicity management, therapeutic sequencing, and mechanisms of resistance.

Biomarkers

Which approach will prevail: biomarker-directed or biomarker-agnostic?

Given that ADCs target a unique tumor-associated antigen, it is logical to assume that the expression of this antigen may predict efficacy. However, this has not borne out in all studies. Teliso-V and Tusa appear to have enhanced efficacy in patients with high-level protein expression.[51,52] However, for TROP2-targeted Dato-DXd[64] and HER3-targeted HER3-DXd,[35,38] target protein expression does not appear to influence treatment response. In the absence of clear efficacy differences, an agnostic approach has clear advantages, as patients could begin treatment without the need for additional biomarker testing and/or repeat biopsies. However, if a biomarker can enrich for patients more likely to experience a robust and durable response, this may outweigh the potential delays associated with biomarker testing. That said, biomarker-directed strategies raise additional questions: What is the ideal cut-off for a positive result? How quickly can novel IHC stains be validated and incorporated into clinical practice? Do prior treatments influence the expression of these biomarkers? Are surface protein markers detected by IHC staining the most appropriate biomarker for efficacy, or will other biomarkers (eg, gene amplifications, gene mutations) be more informative?

Toxicity Management

What is the mechanism for the unique toxicities associated with ADCs, and how do providers manage these toxicities?

Many of the AEs associated with ADCs (eg, nausea, vomiting, diarrhea, cytopenias, neuropathy) are commonly encountered with chemotherapeutic agents and are related to the cytotoxic payload used in the ADC. However, the frequency and intensity of AEs are likely dependent on many factors that warrant further investigation, including ADC biochemical properties.

Patient-specific factors likely also influence the AE profile of ADCs. In patients with triple-negative breast cancer receiving SG, the rate of severe neutropenia was doubled in those who were homozygous for the UGT1A1*28 allele.[65] Body weight and its relation to ADC dosing may also play a role. Among patients with breast cancer receiving T-DM1, obesity (body mass index ≥30) was associated with higher rates of all-grade AEs, including cytopenias, hyperbilirubinemia, and peripheral neuropathy.[66] These data suggest further optimization of the therapeutic index may be possible by accounting for both the unique construct of the ADC and patient characteristics.

Although many AEs are common across ADCs and classical chemotherapeutics, several unique ADC-related

AEs have emerged, chief among them being drug-related ILD. Drug-related ILD has been most clearly associated with T-DXd. A pooled analysis of 9 phase 1/2 T-DXd monotherapy studies including 1150 patients across solid tumors identified an overall incidence of drug-related ILD of 15.4%, with a median onset of 5.4 months.[67] Drug-related ILD has also been reported with HER3-DXd and Dato-DXd,[35,38,68] suggesting that this may be a payload-specific toxicity. Drug exposure and dosing likely play a role as well, as the rate of drug-related ILD in the DESTINY-Lung02 trial was 5.9% at the 5.4-mg/kg dose of T-DXd compared with 28.0% at the 6.4-mg/kg dose of T-DXd.[69] Critically, early identification and management appear to be key to preventing significant morbidity. In the aforementioned pooled analysis, the majority of adjudicated ILD events occurred before the implementation of updated management guidelines. Although a detailed discussion of ILD management is beyond the scope of this review, key components of a work-up when ILD is suspected include high-resolution chest computed tomography, a pulmonary consultation with pulmonary function tests, and ruling out alternative causes (eg, infection, malignancy). If no plausible alternative cause is found, prompt initiation of systemic corticosteroids is indicated.[67,70]

Importantly, the mechanism of T-DXd–related ILD remains largely unknown. Several theories have been postulated, including target-dependent uptake (on-target toxicity), target-independent uptake (off-target toxicity), and injury induced by circulating payload.[70] Interestingly, in a preclinical study in which T-DXd or free DXd was injected into monkeys, ILD occurred only in monkeys that received T-DXd, despite the systemic exposure to the DXd payload being higher in those who received free drug.[71] Upon autopsy, T-DXd localization occurred predominantly in alveolar macrophages, although HER2 expression is confined mainly to the bronchial tree in monkeys. Together, this indicates that target-independent ADC uptake may be central to T-DXd–induced lung injury, though additional investigation is warranted.

Treatment Resistance and Sequencing

How do we overcome treatment resistance and properly sequence ADCs?

Given that the use of ADCs for the treatment of lung cancer is still in its infancy, mechanisms of resistance to this therapeutic class are largely unknown and are based primarily on preclinical studies of T-DM1. Various steps in the mechanism of action of ADCs (eg, antibody-target binding, internalization, payload-linker uncoupling, payload retention) have been implicated in mediating drug resistance. These pathways will require further study to identify optimal sequencing strategies.

Conclusion

Technical advancements have led to a renaissance of ADCs as an effective therapeutic class in solid tumors. In lung cancer, we have seen the early success of modern ADCs translate to the first FDA approval in NSCLC, with many additional compounds pending approval. As we enter the clinical era of ADCs in lung cancer, many important unanswered questions remain, including the utility of biomarkers, treatment sequencing, toxicity management, and identification of resistance mechanisms. Addressing these gaps will be critical to providing optimal patient management, and developing novel approaches that maximize survival for our patients.

References

1. Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. *Nat Rev Cancer*. 2008;8(6):473-480.
2. Thurber GM, Schmidt MM, Wittrup KD. Antibody tumor penetration: transport opposed by systemic and antigen-mediated clearance. *Adv Drug Deliv Rev*. 2008;60(12):1421-1434.
3. Lambert JM, Berkenblit A. Antibody-drug conjugates for cancer treatment. *Annu Rev Med*. 2018;69(1):191-207.
4. Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody-drug conjugates for cancer therapy. *Nat Rev Clin Oncol*. 2021;18(6):327-344.
5. Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. *J Hematol Oncol*. 2020;13(1):125.
6. Beck A, Goetsch L, Dumontet C, Corvaïa N. Strategies and challenges for the next generation of antibody-drug conjugates. *Nat Rev Drug Discov*. 2017;16(5):315-337.
7. Oflazoglu E, Stone IJ, Gordon K, et al. Potent anticarcinoma activity of the humanized anti-CD70 antibody h1F6 conjugated to the tubulin inhibitor auristatin via an uncleavable linker. *Clin Cancer Res*. 2008;14(19):6171-6180.
8. Frigerio M, Kyle AF. The chemical design and synthesis of linkers used in antibody drug conjugates. *Curr Top Med Chem*. 2017;17(32):3393-3424.
9. Wada R, Erickson HK, Lewis Phillips GD, et al. Mechanistic pharmacokinetic/pharmacodynamic modeling of in vivo tumor uptake, catabolism, and tumor response of trastuzumab maytansinoid conjugates. *Cancer Chemother Pharmacol*. 2014;74(5):969-980.
10. Li JY, Perry SR, Muniz-Medina V, et al. A biparatopic HER2-targeting antibody-drug conjugate induces tumor regression in primary models refractory to or ineligible for HER2-targeted therapy. *Cancer Cell*. 2016;29(1):117-129.
11. Tang H, Liu Y, Yu Z, et al. The analysis of key factors related to ADCs structural design. *Front Pharmacol*. 2019;10:373.
12. Khera E, Dong S, Huang H, de Bever L, van Delft FL, Thurber GM. Cellular-resolution imaging of bystander payload tissue penetration from antibody-drug conjugates. *Mol Cancer Ther*. 2022;21(2):310-321.
13. Nagayama A, Ellisen LW, Chabner B, Bardia A. Antibody-drug conjugates for the treatment of solid tumors: clinical experience and latest developments. *Target Oncol*. 2017;12(6):719-739.
14. Hamblett KJ, Senter PD, Chace DF, et al. Effects of drug loading on the antitumor activity of a monoclonal antibody drug conjugate. *Clin Cancer Res*. 2004;10(20):7063-7070.
15. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin Cancer Res*. 2016;22(20):5097-5108.
16. Stephens P, Hunter C, Bignell G, et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. *Nature*. 2004;431(7008):525-526.
17. Hirsch FR, Varella-Garcia M, Franklin WA, et al. Evaluation of HER-2/neu gene amplification and protein expression in non-small cell lung carcinomas. *Br J Cancer*. 2002;86(9):1449-1456.
18. Pellegrini C, Falleni M, Marchetti A, et al. HER-2/Neu alterations in non-small cell lung cancer: a comprehensive evaluation by real time reverse transcrip-

tion-PCR, fluorescence in situ hybridization, and immunohistochemistry. *Clin Cancer Res*. 2003;9(10 pt 1):3645-3652.
19. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511(7511):543-550.
20. Liu L, Shao X, Gao W, et al. The role of human epidermal growth factor receptor 2 as a prognostic factor in lung cancer: a meta-analysis of published data. *J Thorac Oncol*. 2010;5(12):1922-1932.
21. Lewis Phillips GD, Li G, Dugger DL, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res*. 2008;68(22):9280-9290.
22. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine for patients with HER2-mutant lung cancers: results from a phase II basket trial. *J Clin Oncol*. 2018;36(24):2532-2537.
23. Iwama E, Zenke Y, Sugawara S, et al. Trastuzumab emtansine for patients with non-small cell lung cancer positive for human epidermal growth factor receptor 2 exon-20 insertion mutations. *Eur J Cancer*. 2022;162:99-106.
24. Ogitani Y, Hagihara K, Oitate M, Naito H, Agatsuma T. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. *Cancer Sci*. 2016;107(7):1039-1046.
25. Nakada T, Sugihara K, Jikoh T, Abe Y, Agatsuma T. The latest research and development into the antibody-drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185.
26. Tsurutani J, Iwata H, Krop I, et al. Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. *Cancer Discov*. 2020;10(5):688-701.
27. Li BT, Smit EF, Goto Y, et al; DESTINY-Lung01 Trial Investigators. Trastuzumab deruxtecan in *HER2*-mutant non-small-cell lung cancer. *N Engl J Med*. 2022;386(3):241-251.
28. Goto K, Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with *HER2*-mutant metastatic non-small-cell lung cancer: primary results from the randomized, phase II DESTINY-Lung02 trial. *J Clin Oncol*. 2023;41(31):4852-4863.
29. Li BT, Planchard D, Goto K, et al. Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2 (ERBB2)-mutant (HER2m) metastatic non–small cell lung cancer (NSCLC) with and without brain metastases (BMs): pooled analyses from DESTINY-Lung01 and DESTINY-Lung02 [ESMO abstract 1321MO]. *Ann Oncol*. 2023;34(1):S762-S763.
30. Li BT, Ahn M-J, Goto K, et al. 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) [ASCO abstract TPS9137]. *J Clin Oncol*. 2022;40(16)(suppl).
31. Borghaei H, Besse B, Bardia A, et al. Trastuzumab deruxtecan plus pembrolizumab in advanced/metastatic breast or non-small cell lung cancer: a phase 1b study [IASLC abstract P01.02]. *J Thorac Oncol*. 2021;16(3)(suppl):S236.
32. Lyu H, Han A, Polsdofer E, Liu S, Liu B. Understanding the biology of HER3 receptor as a therapeutic target in human cancer. *Acta Pharm Sin B*. 2018;8(4):503-510.
33. Gandullo-Sánchez L, Ocaña A, Pandiella A. HER3 in cancer: from the bench to the bedside. *J Exp Clin Cancer Res*. 2022;41(1):310.
34. Hashimoto Y, Koyama K, Kamai Y, et al. A novel HER3-targeting antibody-drug conjugate, U3-1402, exhibits potent therapeutic efficacy through the delivery of cytotoxic payload by efficient internalization. *Clin Cancer Res*. 2019;25(23):7151-7161.
35. Jänne PA, Baik C, Su WC, et al. Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, *EGFR*-mutated non-small cell lung cancer. *Cancer Discov*. 2022;12(1):74-89.
36. Steuer CE, Hayashi H, Su W-C, et al. Efficacy and safety of patritumab deruxtecan (HER3-DXd) in advanced/metastatic non-small cell lung cancer (NSCLC) without EGFR-activating mutations [ASCO abstract 9017]. *J Clin Oncol*. 2022;40(16)(suppl).
37. Johnson ML, Jänne PA, Goto Y, et al. Intracranial efficacy of HER3-DXd in patients with previously treated advanced EGFR-mutated NSCLC: results from HERTHENA-Lung01 [ESMO abstract 1319MO]. *Ann Oncol*. 2023;34(1):S760-S761.
38. Yu HA, Goto Y, Hayashi H, et al. 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. *J Clin Oncol*. 2023;41(35):5363-5375.
39. Ciccarelli FD, Acciarito A, Alberti S. Large and diverse numbers of human diseases with HIKE mutations. *Hum Mol Genet*. 2000;9(6):1001-1007.
40. Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). *Oncotarget*. 2015;6(26):22496-22512.
41. Stepan LP, Trueblood ES, Hale K, Babcook J, Borges L, Sutherland CL. Expression of Trop2 cell surface glycoprotein in normal and tumor tissues: potential implications as a cancer therapeutic target. *J Histochem Cytochem*. 2011;59(7):701-710.
42. Pak MG, Shin DH, Lee CH, Lee MK. Significance of EpCAM and TROP2 expression in non-small cell lung cancer. *World J Surg Oncol*. 2012;10(1):53.
43. Kopp A, Hofsess S, Cardillo TM, Govindan SV, Donnell J, Thurber GM. Antibody-drug conjugate sacituzumab govitecan drives efficient tissue penetration and rapid intracellular drug release. *Mol Cancer Ther*. 2023;22(1):102-111.
44. Bardia A, Messersmith WA, Kio EA, et al. 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. *Ann Oncol*. 2021;32(6):746-756.
45. Heist RS, Guarino MJ, Masters G, et al. Therapy of advanced non-small-cell lung cancer with an SN-38-anti-trop-2 drug conjugate, sacituzumab govitecan. *J Clin Oncol*. 2017;35(24):2790-2797.
46. Okajima D, Yasuda S, Maejima T, et al. Datopotamab deruxtecan, a novel TROP2-directed antibody-drug conjugate, demonstrates potent antitumor activity by efficient drug delivery to tumor cells. *Mol Cancer Ther*. 2021;20(12):2329-2340.
47. Shimizu T, Sands J, Yoh K, et al. First-in-human, phase I dose-escalation and dose-expansion study of trophoblast cell-surface antigen 2-directed antibody-drug conjugate datopotamab deruxtecan in non-small-cell lung cancer: TROPION-PanTumor01. *J Clin Oncol*. 2023;41(29):4678-4687.
48. Ahn MJ, Lisberg A, Paz-Ares L, et al. Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): results of the randomized phase III study TROPION-Lung01 [ESMO abstract LBA12]. *Ann Oncol*. 2023;34(1):S1305-S1306.
49. Goto Y, Su W-C, Levy BP, et al. TROPION-Lung02: datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) in advanced non-small cell lung cancer (aNSCLC) [ASCO abstract 9004]. *J Clin Oncol*. 2023;41(16)(suppl).
50. Paz-Ares L, Ahn MJ, Lisberg AE, et al. TROPION-Lung05: datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer (NSCLC) with actionable genomic alterations (AGAs) [ESMO abstract 1314MO]. *Ann Oncol*. 2023;34(1):S755-S756.
51. Gazzah A, Ricordel C, Cousin S, et al. Efficacy and safety of the antibody-drug conjugate (ADC) SAR408701 in patients (pts) with non-squamous non-small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) [ASCO abstract 9505]. *J Clin Oncol*. 2020;38(15)(suppl).
52. Camidge DR, Bar J, Horinouchi H, et al. Telisotuzumab vedotin (Teliso-V) monotherapy in patients (pts) with previously treated c-Met–overexpressing (OE) advanced non-small cell lung cancer (NSCLC) [ASCO abstract 9016]. *J Clin Oncol*. 2022;40(16)(suppl).
53. Decary S, Berne PF, Nicolazzi C, et al. Preclinical activity of SAR408701: a novel anti-CEACAM5-maytansinoid antibody-drug conjugate for the treatment of CEACAM5-positive epithelial tumors. *Clin Cancer Res*. 2020;26(24):6589-6599.
54. Xie H, Adjei AA. Antibody-drug conjugates for the therapy of thoracic malignancies. *J Thorac Oncol*. 2019;14(3):358-376.
55. Goldman JW, Horinouchi H, Cho BC, et al. Phase 1/1b study of telisotuzumab vedotin (Teliso-V) + osimertinib (Osi), after failure on prior Osi, in patients with advanced, c-Met overexpressing, EGFR-mutated non-small cell lung cancer (NSCLC) [ASCO abstract 9013]. *J Clin Oncol*. 2022;40(16)(suppl).
56. Johnson M, Awad M, Koyama T, et al. Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with refractory SCLC: a subgroup analysis of a phase 1/2 study [IASLC abstract OA05.05]. *J Thorac Oncol*. 2021;16(3)(suppl).
57. Zhang L, Ma Y, Zhao Y, et al. BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic solid tumor: results from a first-in-human phase 1 study [ASCO abstract 3001]. *J Clin Oncol*. 2023;41(16)(suppl).
58. Mudd GE, Brown A, Chen L, et al. Identification and optimization of EphA2-selective bicycles for the delivery of cytotoxic payloads. *J Med Chem*.

2020;63(8):4107-4116.
59. Cook N, Banerji U, Evans J, et al. Pharmacokinetic (PK) assessment of BT1718: a phase I/II a study of BT1718, a first in class bicycle toxin conjugate (BTC), in patients (pts) with advanced solid tumours [ESMO abstract 464P]. *Ann Oncol*. 2019;30(5):174.
60. Ma WW, Tolcher AW, Strauss JF, et al. ELU-FRα-1: a study to evaluate ELU001 in patients with solid tumors that overexpress folate receptor alpha (FRα) [ASCO abstract TPS3158]. *J Clin Oncol*. 2022;40(16)(suppl).
61. Li BT, Pegram MD, Lee K-W, et al. A phase 1/2 study of a first-in-human immune-stimulating antibody conjugate (ISAC) BDC-1001 in patients with advanced HER2-expressing solid tumors [ASCO abstract 2538]. *J Clin Oncol*. 2023;41(16)(suppl).
62. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376(2):125-135.
63. Sartor O, de Bono J, Chi KN, et al; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385(12):1091-1103.
64. Lisberg AE, Sands J, Shimizu T, et al. Dose escalation and expansion from the phase I study of DS-1062, a trophoblast cell-surface antigen 2 (TROP2) antibody drug conjugate (ADC), in patients (pts) with advanced non-small cell lung cancer (NSCLC) [ASCO abstract 9619]. *J Clin Oncol*. 2020;38(15)(suppl).
65. Rugo HS, Tolaney SM, Loirat D, et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. *NPJ Breast Cancer*. 2022;8(1):98.
66. Lee A, Larck C, Moore DC. Impact of obesity on safety outcomes and treatment modifications with ado-trastuzumab emtansine in breast cancer patients. *J Oncol Pharm Pract*. 2022;28(1):49-54.
67. Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. *ESMO Open*. 2022;7(4):100554.
68. Meric-Bernstam F, Spira AI, Lisberg AE, et al. TROPION-PanTumor01: dose analysis of the TROP2-directed antibody-drug conjugate (ADC) datopotamab deruxtecan (Dato-DXd, DS-1062) for the treatment (Tx) of advanced or metastatic non-small cell lung cancer (NSCLC) [ASCO abstract 9058]. *J Clin Oncol*. 2021;39(15)(suppl).
69. Goto K, Sang-We K, Kubo T, et al. 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 [ESMO abstract LBA55]. *Ann Oncol*. 2022;33(7):S1422.
70. Tarantino P, Modi S, Tolaney SM, et al. Interstitial lung disease induced by anti-ERBB2 antibody-drug conjugates: a review. *JAMA Oncol*. 2021;7(12):1873-1881.
71. Kumagai K, Aida T, Tsuchiya Y, Kishino Y, Kai K, Mori K. Interstitial pneumonitis related to trastuzumab deruxtecan, a human epidermal growth factor receptor 2-targeting Ab-drug conjugate, in monkeys. *Cancer Sci*. 2020;111(12):4636-4645.

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Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum. *J Clin Oncol*. 2017;35(10):1103-1111.
46. Shi T, Zhu J, Feng Y, et al. Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(4):439-449.
47. Harter P, Sehouli J, Vergote I, et al; DESKTOP III Investigators. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. *N Engl J Med*. 2021;385(23):2123-2131.
48. Goldberg RM, Kim SR, Fazelzad R, Li X, Brown TJ, May T. Secondary cytoreductive surgery for recurrent low-grade serous ovarian carcinoma: a systematic review and meta-analysis. *Gynecol Oncol*. 2022;164(1):212-220.
49. Grisham RN, Iyer G, Sala E, et al. Bevacizumab shows activity in patients with low-grade serous ovarian and primary peritoneal cancer. *Int J Gynecol Cancer*. 2014;24(6):1010-1014.
50. Manning-Geist BL, Gordhandas SB, Giri DD, et al. Phase II study of enzalutamide in androgen receptor positive, recurrent, high- and low-grade serous ovarian cancer. *Gynecol Oncol*. 2022;164(1):12-17.
51. Gershenson DM, Sun CC, Iyer RB, et al. Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. *Gynecol Oncol*. 2012;125(3):661-666.
52. Hendrikse CSE, van der Ploeg P, van de Kruis NMA, et al. Functional estrogen receptor signal transduction pathway activity and antihormonal therapy response in low-grade ovarian carcinoma. *Cancer*. 2023;129(9):1361-1371.
53. Tang M, O'Connell RL, Amant F, et al. PARAGON: a phase II study of anastrozole in patients with estrogen receptor-positive recurrent/metastatic low-grade ovarian cancers and serous borderline ovarian tumors. *Gynecol Oncol*. 2019;154(3):531-538.
54. Gershenson DM, Miller A, Brady WE, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. *Lancet*. 2022;399(10324):541-553.
55. Monk BJ, Grisham RN, Banerjee S, et al. MILO/ENGOT-ov11: Binimetinib versus physician's choice chemotherapy in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. *J Clin Oncol*. 2020;38(32):3753-3762.
56. Lee BY, Timpson P, Horvath LG, Daly RJ. FAK signaling in human cancer as a target for therapeutics. *Pharmacol Ther*. 2015;146:132-149.
57. Hirata E, Girotti MR, Viros A, et al. Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin β1/FAK signaling. *Cancer Cell*. 2015;27(4):574-588.
58. Fallahi-Sichani M, Becker V, Izar B, et al. Adaptive resistance of melanoma cells to RAF inhibition via reversible induction of a slowly dividing de-differentiated state. *Mol Syst Biol*. 2017;13(1):905.
59. Banerjee S GR, Shinde R, et al. Phase I study of the combination of the dual RAF/of efficacy in low grade serous ovarian cancer MEK inhibitor VS-6766 and the FAK inhibitor defactinib [ESMO abstract 725MO]. *Ann Oncol*. 2021;32(5)(suppl).
60. Banerjee S, Ring KL, Van Nieuwenhuysen E, et al. Initial efficacy and saftey results from ENGOT-ov60/GOG-3052/RAMP 201: a phase 2 study of avutometinib (VS-6766) +/- defactinib in recurrent low-grade serous ovarian cancer [abstract 5515]. *J Clin Oncol*. 2023;41(16)(suppl).
61. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol*. 2018;19(7):904-915.
62. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884.
63. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.
64. Colon-Otero G, Zanfagnin V, Hou X, et al. Phase II trial of ribociclib and letrozole in patients with relapsed oestrogen receptor-positive ovarian or endometrial cancers. *ESMO Open*. 2020;5(5):e000926.
65. Konecny GE, Hendrickson AE, Jatoi A, et al. A multicenter open-label phase II study of the efficacy and safety of palbociclib a cyclin-dependent kinases 4 and 6 inhibitor in patients with recurrent ovarian cancer [ASCO abstract 5557]. *J Clin Oncol*. 2016;34(15)(suppl).
66. Slomovitz B, Deng W, Killion J, et al. A phase II trial of letrozole + ribociclib in women with recurrent low-grade serous carcinoma of the ovary, fallopian tube or peritoneum: a GOG Foundation study [SGO abstract 137]. *Gynecol Oncol*. 2023;176(1)(suppl).

Supporting Online Material

Online-Only Supplement to "Antibody-Drug Conjugates in Advanced Lung Cancer: Is This a New Frontier?"

Additional Antibody-Drug Conjugates in Late Stages of Development in Advanced Lung Cancer

CEACAM5

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a member of a family of cell surface glycoproteins that promote cell proliferation and migration.[1] Different CEACAMs show distinct expression patterns on various cell types, with CEACAM5 being overexpressed in carcinomas of the gastrointestinal tract, genitourinary tract, and respiratory systems, with limited expression in normal tissues.[2]

Tusamitamab Ravtansine. Tusamitamab ravtansine (Tusa) is comprised of the CEACAM5-directed antibody SAR408377, covalently linked to a microtubule destabilizing payload, maytansinoid DM4, via a glutathione cleavable linker. The resulting average DAR is 3.9.[3,4] An initial, first-in-human phase 1 trial of 31 patients with metastatic solid tumors evaluated the safety of Tusa at doses ranging from 5 to 150 mg/m^2 administered every 2 weeks. A maximum tolerated dose of 100 mg/m^2 was ultimately selected for further investigation in dose-expansion cohorts.[5] There were 2 cohorts of patients with nonsquamous non–small cell lung cancer (NSCLC) treated in the dose-expansion phase, stratified by high (immunohistochemistry [IHC] ≥2+ in ≥50% of cells) or moderate (IHC ≥2+ in 1%-49% of cells) CEACAM expression, which included 92 pretreated patients (n=64 for high expression; n=28 for moderate expression).[6] The overall response rate (ORR) was higher in the high-expressor cohort than in the moderate-expressor cohort, at 20.3% vs 7.1%.[7] Safety data of the first-in-human study showed that treatment-emergent adverse events (TEAEs) were reported in 71% of patients, with the majority being low-grade. The most common TEAEs included asthenia, decreased appetite, keratopathy, and nausea.[5]

An updated pooled safety analysis of patients treated with 100 mg/m^2 of Tusa reported an incidence of corneal TEAEs of 30.1% (grade ≥3 rate of 8.6%). The most frequent corneal events were keratitis and keratopathy, at 22% (grade ≥3 rate of 6.5%) and 11.8% (grade ≥3 rate of 2.7%), respectively.[8] Management with primary prophylaxis, including ophthalmic drops, corticosteroid gel, or cold masks, did not show a clear benefit in preventing corneal events. Most corneal events occurred within 4 cycles of treatment (80.4%), with a median recovery time of 20.5 days, and resolution of these TEAEs in 71.4% of patients. The authors noted that corneal events led to a treatment delay in 15.6% of cases and a delay with dose reduction in 7% of cases, without any patients requiring full treatment discontinuation.

The phase 2 CARMEN-LC05 trial is assessing the combination of Tusa and pembrolizumab (cohort T2) with or without platinum (T3) with or without pemetrexed (T4) in patients with advanced treatment-naive nonsquamous NSCLC with any programmed death ligand 1 (PD-L1) level and either moderate or high CEACAM5 expression. Among 25 patients enrolled across the 3 cohorts, initial results noted an ORR of 52% and a disease control rate of 88%. Grade 3 or higher TEAEs occurred in 68% of patients, with any-grade pneumonitis and peripheral neuropathy occurring in 16% and 28% of patients, respectively.[9] Corneal events occurred in 24% of patients and were manageable with dose modification.

More recently, Sanofi, the pharmaceutical producer of Tusa, announced in a press release that the company was suspending the development program for it in light of negative results from the phase 3 CARMEN-LCO3 trial. This trial, which evaluated Tusa monotherapy vs docetaxel in patients with previously treated metastatic CEACAM-expressing NSCLC, reportedly failed to meet its coprimary endpoints of progression-free survival (PFS) or overall survival (OS) improvement after interim assessment by an independent data monitoring committee.[10]

MET

The mesenchymal-to-epithelial transition (*MET*) gene encodes the receptor tyrosine kinase which binds to the ligand hepatocyte growth factor, resulting in receptor homodimerization and intracellular activation of the MAPK and PI3K/AKT signaling pathways.[11] Multiple MET-specific alterations have been identified in NSCLC, including *MET* exon 14 skipping mutation,[12] MET

protein overexpression,[13] and *MET* gene amplification,[14] which can occur de novo or as resistance mechanisms to targeted therapies in oncogene-driven NSCLC.[15,16]

Telisotuzumab Vedotin. Telisotuzumab vedotin (Teliso-V) is a MET-directed ADC composed of an anti–c-MET monoclonal antibody and a microtubule inhibitor (monomethyl auristatin E), conjugated via a cleavable valine-citrulline linker. The DAR is 3.1.[6] A phase 1 dose-escalation trial of Teliso-V, administered at doses from 0.15 to 3.0 mg/kg every 3 weeks, enrolled 16 patients with c-MET–positive (defined by IHC membrane H-score ≥150) NSCLC and reported an ORR of 18.8% with median PFS of 5.7 months.[17] The phase 2 Luminosity trial aimed to identify the c-MET overexpressing NSCLC populations best suited for treatment with Teliso-V. Stage 1 of this study enrolled cohorts that were defined by histology (nonsquamous or squamous) and by epidermal growth factor receptor (*EGFR*) mutation status. The nonsquamous cohort was further divided based on c-MET expression level (high, ≥50% cells with 3+ by IHC; or intermediate, ≥3+ in 25%-50% of cells). A total of 136 patients were treated with 1.9 mg/kg of Teliso-V every 2 weeks. For the response-evaluable population, the ORR was 36.5% in the nonsquamous EGFR wild-type cohort (n=60), with improved response rates stratified by high vs intermediate expression levels (52.2% vs 24.1%, respectively). The response rates were more modest in patients with squamous histology (11.1%) and *EGFR*-mutated disease (11.6%). The most common any-grade AEs were peripheral neuropathy (25%), nausea (22.1%), and hypoalbuminemia (20.6%). There were 2 deaths reported, including 1 patient with pneumonitis.[18] The phase 2 LUNG-MAP S1400K substudy, which enrolled patients with c-MET–positive (H-score ≥150) advanced squamous cell lung cancer, was closed early owing to lack of efficacy (ORR, 9%).[19]

Another distinct population of interest includes patients with *EGFR*-mutated disease who have progressed on prior tyrosine kinase inhibitors (TKIs). An earlier phase 1b study enrolled 42 patients with TKI-resistant EGFR-mutant NSCLC and co-occurring MET alterations, including c-MET overexpression (H-score ≥150 by IHC), MET exon 14 skipping mutation, or MET amplification. Patients were treated with Teliso-V at 2.7 mg/kg every 3 weeks plus erlotinib 150 mg daily. The ORR for the *EGFR*-mutated cohort was 34.5%, with a 6-month PFS rate of 51%. Although 97% of patients had prior EGFR-TKI exposure, only 55% received a third-generation TKI.[20] Improved response rates for patients with higher c-MET expression levels (H-scores ≥225) were seen, with an ORR of 52.6%.[21] A more recent trial explored the combination of Teliso-V plus osimertinib for patients with progression on frontline osimertinib and co-occurring c-MET overexpression (high or intermediate). A total of 25 patients received Teliso-V with concurrent osimertinib (12 patients at 1.9 mg/kg and 7 patients at 1.6 mg/kg). Patients with both high (≥50%, 3+ staining) and intermediate (25%-49%, 3+ staining) c-MET expression had favorable responses, at 50% and 63%, respectively. The combination was well-tolerated, with the most common all-grade AEs being peripheral neuropathy (36%), nausea (20%), and edema (20%).[22]

B7-H3

B7 homolog 3 protein (B7-H3), also known as CD276, is a transmembrane immunoregulatory protein that plays a dual role in T-cell activation. It is a member of the B7 family, which includes several key immune checkpoint receptors, such as PD-L1.[23] B7-H3 is highly expressed in various solid tumor malignancies, including lung, esophageal, and prostate cancers. Expression of B7-H3 has been shown to correlate with poor prognosis in various tumor types, including lung cancer.[24,25]

Infinatamab Deruxtecan. Infinatamab deruxtecan (I-DXd or DS-7300) is a novel B7-H3–targeting ADC. It contains a humanized anti–B7-H3 monoclonal antibody linked to the topoisomerase I warhead deruxtecan via an enzymatically cleavable tetrapeptide link. The DAR is 4.[26] I-DXd is currently being tested in a phase 1/2 first-in-human study for patients with advanced solid tumors. Extended follow-up results of the phase 1 dose-escalation portion of the trial were presented by Doi and colleagues.[27] Patients were enrolled regardless of B7-H3 expression levels. Efficacy and safety results were presented for those patients treated in the 4.8- to 16-mg/kg dose cohorts. Of the 91 response evaluable patients, the ORR was 33%, with responses in 2 of 5 patients with squamous cell carcinoma of the lung and 7 of 9 patients with SCLC. The most common any-grade TEAEs were nausea (61%), infusion reactions (35%), and emesis (31%).

Patients with heavily pretreated SCLC (median of 2 prior lines of therapy) were treated in part 1 of the dose-escalation cohort at doses of 6.4 mg/kg or greater. An updated subgroup analysis of these patients was recently presented by Johnson and colleagues. Of 21 response-evaluable patients who were treated with I-DXd above the minimum effective dose, encouraging results were shown, with an ORR of 52.4% and a median DOR of 5.9 months after a follow-up of 11.7 months. The median PFS and OS were 5.6 months and 12.2 months, respectively. There was no appreciable correlation between B7-H3 level (measured by combined membrane/cytosol H-score) and efficacy; however, this will continue to be explored in future data sets. Overall, the safety profile was consistent with previous reports in the overall phase 1/2 study population, including grade 3 or higher TEAEs in

36.4% of patients. Of note, a total of 3 patients (13.6%) experienced an ILD/pneumonitis event, with all of them being low-grade in severity.[28]

HS-20093. HS-20093 is a B7-H3 targeting ADC that incorporates an immunoglobulin G1 monoclonal antibody conjugated to the payload HS-9265 via a cleavable linker. The reported DAR is 4. The phase 1 ARTEMIS-001 dose-escalation study is evaluating the safety and efficacy of HS-20093[29] for patients with advanced, pretreated solid tumors. The maximum tolerated dose was 12 mg/kg every 3 weeks. A total of 53 patients were included in the analysis, 29 patients with NSCLC and 11 with SCLC. Most common TEAEs were hematologic, including leukopenia, neutropenia, and anemia, followed by nausea, pyrexia, and decreased appetite (all in ≥20% of patients). The ORRs for the 8-mg/kg and 12-mg/kg cohorts were 40.9% and 31.3%, respectively. Among the 11 patients enrolled in the SCLC subgroup, an ORR of 63.6% was observed, with a median PFS of 4.7 months.

References

1. Beauchemin N, Arabzadeh A. Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) in cancer progression and metastasis. *Cancer Metastasis Rev*. 2013;32(3-4):643-671.
2. Hammarström S. The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. *Semin Cancer Biol*. 1999;9(2):67-81.
3. Decary S, Berne PF, Nicolazzi C, et al. Preclinical activity of SAR408701: a novel anti-CEACAM5-maytansinoid antibody-drug conjugate for the treatment of CEACAM5-positive epithelial tumors. *Clin Cancer Res*. 2020;26(24):6589-6599.
4. Kellogg BA, Garrett L, Kovtun Y, et al. Disulfide-linked antibody-maytansinoid conjugates: optimization of in vivo activity by varying the steric hindrance at carbon atoms adjacent to the disulfide linkage. *Bioconjug Chem*. 2011;22(4):717-727.
5. Gazzah A, Bedard PL, Hierro C, et al. Safety, pharmacokinetics, and antitumor activity of the anti-CEACAM5-DM4 antibody-drug conjugate tusamitamab ravtansine (SAR408701) in patients with advanced solid tumors: first-in-human dose-escalation study. *Ann Oncol*. 2022;33(4):416-425.
6. Xie H, Adjei AA. Antibody-drug conjugates for the therapy of thoracic malignancies. *J Thorac Oncol*. 2019;14(3):358-376.
7. Ricordel C, Barlesi F, Cousin S, et al. Safety and efficacy of tusamitamab ravtansine (SAR408701) in long-term treated patients with nonsquamous non–small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) [ASCO abstract 9039]. *J Clin Oncol*. 2022;40(16)(suppl).
8. Gazzah A, Tabernero J, Italiano A, et al. Phase 1/2 study of tusamitamab ravtansine in patients with advanced solid tumors: pooled safety analysis of corneal adverse events [ASCO abstract e15003]. *J Clin Oncol*. 2023;41(16)(suppl).
9. Isambert N, Nagy T, Ravoire M, et al. 13MO Safety and efficacy of tusamitamab ravtansine in combination with pembrolizumab ± chemotherapy in patients with CEACAM5-positive nonsquamous NSCLC (CARMEN-LC05 phase II study). *J Thorac Oncol*. 2023;18(4)(suppl):S46-S47.
10. Sanofi announces end of program evaluating tusamitamab ravtansine after a 2L NSCLC phase 3 trial did not meet a primary endpoint [press release]. https://www.sanofi.com/en/media-room/press-releases/2023/2023-12-21-06-30-00-2799759. Sanofi; December 21, 2023. Accessed March 14, 2024.
11. Sipeki S, Bander E, Buday L, et al. Phosphatidylinositol 3-kinase contributes to Erk1/Erk2 MAP kinase activation associated with hepatocyte growth factor-induced cell scattering. *Cell Signal*. 1999;11(12):885-890.
12. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov*. 2015;5(8):850-859.
13. Tong JH, Yeung SF, Chan AW, et al. MET amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. *Clin Cancer Res*. 2016;22(12):3048-3056.
14. Schildhaus HU, Schultheis AM, Rüschoff J, et al. MET amplification status in therapy-naïve adeno- and squamous cell carcinomas of the lung. *Clin Cancer Res*. 2015;21(4):907-915.
15. Mehlman C, Cadranel J, Rousseau-Bussac G, et al. Resistance mechanisms to osimertinib in EGFR-mutated advanced non-small-cell lung cancer: a multicentric retrospective French study. *Lung Cancer*. 2019;137:149-156.
16. Dagogo-Jack I, Yoda S, Lennerz JK, et al. MET alterations are a recurring and actionable resistance mechanism in ALK-positive lung cancer. *Clin Cancer Res*. 2020;26(11):2535-2545.
17. Strickler JH, Weekes CD, Nemunaitis J, et al. First-in-human phase I, dose-escalation and -expansion study of telisotuzumab vedotin, an antibody-drug conjugate targeting c-Met, in patients with advanced solid tumors. *J Clin Oncol*. 2018;36(33):3298-3306.
18. Camidge DR, Bar J, Horinouchi H, et al. Telisotuzumab vedotin (Teliso-V) monotherapy in patients (pts) with previously treated c-Met–overexpressing (OE) advanced non-small cell lung cancer (NSCLC) [ASCO abstract 9016]. *J Clin Oncol*. 2022;40(16)(suppl).
19. Waqar SN, Redman MW, Arnold SM, et al. 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). *Clin Lung Cancer*. 2021;22(3):170-177.
20. Camidge DR, Barlesi F, Goldman JW, et al. Results of the phase 1b study of ABBV-399 (telisotuzumab vedotin; teliso-v) in combination with erlotinib in patients with c-Met+ non-small cell lung cancer by EGFR mutation status [ASCO abstract 3011]. *J Clin Oncol*. 2019;37(15)(suppl).
21. Camidge DR, Barlesi F, Goldman JW, et al. Phase Ib study of telisotuzumab vedotin in combination with erlotinib in patients with c-met protein-expressing non-small-cell lung cancer. *J Clin Oncol*. 2023;41(5):1105-1115.
22. Goldman JW, Horinouchi H, Cho BC, et al. Phase 1/1b study of telisotuzumab vedotin (Teliso-V) + osimertinib (Osi), after failure on prior Osi, in patients with advanced, c-Met overexpressing, EGFR-mutated non-small cell lung cancer (NSCLC) [ASCO abstract 9013]. *J Clin Oncol*. 2022;40(16)(suppl).
23. Schildberg FA, Klein SR, Freeman GJ, Sharpe AH. Coinhibitory pathways in the B7-CD28 ligand-receptor family. *Immunity*. 2016;44(5):955-972.
24. Inamura K, Yokouchi Y, Kobayashi M, et al. Association of tumor TROP2 expression with prognosis varies among lung cancer subtypes. *Oncotarget*. 2017;8(17):28725-28735.
25. Zhou X, Ouyang S, Li J, et al. The novel non-immunological role and underlying mechanisms of B7-H3 in tumorigenesis. *J Cell Physiol*. 2019;234(12):21785-21795.
26. Yamato M, Hasegawa J, Maejima T, et al. DS-7300a, a DNA topoisomerase I inhibitor, DXd-based antibody-drug conjugate targeting B7-H3, exerts potent antitumor activities in preclinical models. *Mol Cancer Ther*. 2022;21(4):635-646.
27. Doi T, Patel M, Falchook GS, et al. 453O DS-7300 (B7-H3 DXd antibody-drug conjugate [ADC]) shows durable antitumor activity in advanced solid tumors: extended follow-up of a phase I/II study. *Ann Oncol*. 2022;33:S744-S745.
28. Johnson M, Awad M, Koyama T, et al. Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with refractory SCLC: a subgroup analysis of a phase 1/2 study [IASLC abstract OA05]. *J Thorac Oncol*. 2023;18(11)(suppl):S54-S55.
29. Wang J, Duan J, Xing L, et al. ARTEMIS-001: phase 1 study of HS-20093, a B7-H3–targeting antibody-drug conjugate, in patients with advanced solid tumor [ASCO abstract 3017]. *J Clin Oncol*. 2023;41(16)(suppl).