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Antibody-drug conjugates, immune-checkpoint inhibitors, and their combination in advanced non-small cell lung cancer

Idoko Salifu [a,*], Navneet Singh [b], Maria Berraondo [a], Jordi Remon [c], Stephanie Salifu [d], Eric Severson [a], Angela Quintana [e], Sandra Peiró [e], Shakti Ramkissoon [a,f], Laura Vidal [a], Isagani Chico [a], Kamal S. Saini [a,g]

[a] Labcorp Drug Development Inc., Princeton, NJ, USA
[b] Postgraduate Institute of Medical Education and Research, Chandigarh, India
[c] Paris-Saclay University, department of Cancer Medicine, Gustave Roussy, Villejuif, France
[d] Dix Hills, NY, USA
[e] Vall d'Hebron Institute of Oncology, Barcelona, Spain
[f] Department of Pathology, Wake Forest School of Medicine and Comprehensive Cancer Center, Winston-Salem, NC, USA
[g] Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

A B S T R A C T

Introduction: Advanced non-small cell lung cancer (aNSCLC) is an incurable disease. The effort to develop treatments with more effective systemic agents continues. This has led to the FDA approval of one antibody–drug conjugate (ADC) and eight immune checkpoint inhibitors (ICIs) for patients with aNSCLC.
Areas covered: Due to the demonstrated efficacy of ADCs and ICIs in aNSCLC, treatment combining both agents merits attention. This article, therefore, explores the use of ADCs and ICIs in patients with NSCLC, assesses the scientific rationale for combination treatment, and provides an overview of ongoing trials. It also presents some early efficacy and safety results of such combination use.
Expert opinion: It is not clear whether ADC-immunotherapy has a significant impact on those with a targetable oncogenic driver alteration since targeted therapies are effective. However, in aNSCLC without a targetable oncogenic driver alteration, the combination of ADCs and ICIs has potential and remains an area of active clinical research.

1. Introduction

The treatment of advanced non-small cell lung cancer (aNSCLC) involves an extensive use of systemic anticancer agents. Current therapeutic strategy in the first-line setting for aNSCLC without targetable genomic alterations include the immune checkpoint inhibitors (ICIs) either with PD-(L)1 inhibition monotherapy for selected patients, or combined with platinum-based chemotherapy (CT) with or without CTLA-4 inhibition [1], resulting in up to 30% of patients being alive at 5 years [1–3]. For patients with aNSCLC and targetable genomic alteration, a personalized treatment approach is the standard of care [4].

Drugs with novel mechanisms of action such as antibody drug conjugates (ADC) are being tested in aNSCLC. As a result, more patients with specific genomic alterations can benefit from more precise treatment approaches. One recent example is trastuzumab deruxtecan, an anti-HER2 ADC, which has received an accelerated grant approval by the FDA based on results of the DESTINY-Lung-02 study in pretreated patients with *HER2*-mutant aNSCLC, an orphan disease without effective personalized treatment. Similarly, other ADC are being explored in wild-type aNSCLC with promising results. Indeed, these ADC have reported activity even in previously treated patients, enlarging the potential sequential treatment approaches for this disease [5,6].

Therefore, based on the efficacy of ICIs and ADC in aNSCLC, combination treatment with both agents is of interest in this population. The use of these agents has already shown clinical benefit. [7,8] In the current manuscript, we provide a summary of the recent therapeutic advances in aNSCLC regarding ICIs and ADC, as well as current combination strategies and the challenges they present.

1.1. Antibody-drug conjugates (ADCs)

Antibody drug conjugates (ADCs) are a new class of drugs that can deliver chemotherapeutic compounds selectively into tumor cells with fewer side effects than standard systemic chemotherapy. This is because ADCs combine the best features of monoclonal antibodies and small molecule drugs to enable targeted delivery of highly effective and

* Corresponding author.
E-mail addresses: globalclinicalmonitors@gmail.com (I. Salifu), scm.salifu@gmail.com (S. Salifu).

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cytotoxic payloads to the tumor cell. This allows for bypassing toxicity on non-cancer cells while enhancing the anti-tumor effect of the cytotoxic agent.

An ADC consists of three parts:

i The monoclonal antibody (mAb), which is highly selective for tumor-associated cell surface antigens and ideally has restricted or no expression on normal cells.
ii A small-molecule drug or cytotoxic payload.
iii A linker, which is stable in circulation, releases the cytotoxic agent in target cells.

Because of the highly selective nature of mAb molecules, they typically target receptors that are over-expressed in cancer cells (e.g. TROP2, CEACAM, HER2, CD33, CD30, CD22) [9]. Another important feature of the mAb is that they can only be linked to a limited quantity of payloads. The number of drug molecules attached to the antibody via linkers is represented by the drug to antibody ratio (DAR). For instance, the mean DAR for most common ADC ranges from 3.5 to 7.7 [9]. As a result of this limitation, the payloads are, therefore, highly potent cytotoxic agents (e.g. auristatin, tubulins that target microtubules and calicheamicins or duocarmicins, which bind to the DNA minor groove or topoisomerase inhibitors).

The linker (usually a peptide derivative) could be either cleavable or non-cleavable. For cleavable linkers, the release of the payload could occur prior to or after internalization in the target tumor cell. Factors such as protease, pH, or glutathione sensitivity mediate the release. Non-cleavable linkers rely on the complete lysosomal proteolytic degradation of the antibody, so they have more stability in circulation and lower off-target activity (bystander effect) than cleavable linkers. Trastuzumab deruxtecan is an example of an ADC with a cleavable linker whereas trastuzumab emtansine is an example of an ADC with a non-cleavable linker. In trastuzumab deruxtecan, the humanized monoclonal antibody trastuzumab is covalently linked to the topoisomerase I inhibitor deruxtecan by a cleavable Gly-Gly-Phe-Gly (GGFG) tetrapeptide linker. Trastuzumab emtansine, on the other hand, consists of a covalent linkage of trastuzumab to the cytotoxic agent DM1 by the non-cleavable linker, succinimidyl-trans-4-(N-maleimidylmethyl) cyclohexane-1-carboxylate (SMCC).

In aNSCLC, some ADCs under development and with initial promising clinical data are: datopotamab deruxtecan (Dato-DXd) and sacituzumab govitecan (both anti TROP2), trastuzumab deruxtecan (T-DXd), trastuzumab emtansine, T-DM1, patritumab deruxtecan (antiHER3), telsiotuzumab vedotin (antiMET), and tusamitamab ravtansine (AntiCEACAM5). Of note, datopotamab deruxtecan (Dato-DXd) has been tested as monotherapy and is being tested in combination with ICIs and other immunotherapy approaches, e.g. bispecific antibodies, with or without platinum chemotherapy [6,10,11].

1.1.1. Bystander effect

While most ADCs cause apoptosis by DNA damage or microtubule disruption, some that are sufficiently hydrophobic cross cell membranes to exert a bystander effect [9,12]. This is especially the case of those with cleavable linkers. The free drug is then exported from target tumor cells, across the cell membrane, to kill neighboring tumor cells even if they do not express the relevant antigen on their cell surfaces or are less accessible from the circulatory system. This bystander effect may explain why despite the precise targeting of the ADCs, some may still have potential systemic toxicity, with a narrower therapeutic window for the cleavable linkers than for the non-cleavable linkers.

Despite this indiscriminate mode of action, the bystander effect offers certain potential clinical benefits:

i Possibility of targeting nearby cancer cells with low or absent expression of the target.
ii The degree to which ADCs penetrate tumor tissues is limited due to its binding to cancer cells that are close to tumor vessels and confined to the perivascular space. The bystander effect will, therefore, aid deeper delivery of the payload.
iii While the expectation is that the cytotoxic payload would deplete immune effector cells, the evidence shows, counterintuitively, a possible beneficial effect. This occurs via an increase in tumor-infiltrating lymphocytes (TILs) such as CD4+ and CD8+ lymphocytes with depletion of immunosuppressive cells such as regulatory T cells (Tregs) [9,13].

1.2. Immune checkpoint inhibitors (ICIs)

ICIs are the foundation of current immune-oncology treatment. They reverse tumor-mediated immune cell suppression by binding and blocking receptors present in immune or tumor cells, such as PD-1, PD-L1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4). The enhanced immune function then leads to impressive efficacy in highly immunogenic cancers such as NSCLC, melanomas, and renal cell carcinomas. There are eight ICIs approved by the U.S. Food and Drug Administration (FDA):

- Two CTLA-4 inhibitors: ipilimumab and tremelimumab.
- Three PD-1 inhibitors: pembrolizumab, nivolumab, and cemiplimab.
- Three PD-L1 inhibitors: atezolizumab, durvalumab, and avelumab.

2. Overview of the clinical evidence

2.1. ADCs in non-small cell lung cancer

The following are key clinical trials involving ADCs for which results are available.

2.1.1. Trastuzumab emtansine (T-DM1)

T-DM1 was studied in a phase II trial in 15 heavily pretreated NSCLC patients with HER2 expression (IHC3+, IHC 2+ with HER2/CEP17≥2 by FISH), or with HER2 exon 20 insertion mutations [14]. The overall response rate (ORR) was 7%, median progression-free survival (mPFS) 2.0 months and median overall survival (mOS) 10.9 months. One of the seven patients (14%) with a HER2 exon 20 insertion mutation responded, no patient with HER2 overexpression responded.

In another study evaluating 49 patients with a median of two (2) prior therapies (range 0 to ≥ 3), 20 were IHC 3+ and 29 were IHC 2+, ORR was 20% for IHC 3+ and 0% for IHC 2+, with median duration of response (mDOR) of 7.3 months. However, PFS and OS were not significantly different between groups: mPFS 2.6 and 2.7 months, mOS 12.2 and 12.1 months for IHC 2+ and IHC 3+, respectively [15].

In a phase II study examining T-DM1 in 18 patients with *HER2* mutations (including non-exon 20 mutations) and a median of two (2) prior therapies, ORR was 44%, mPFS 5 months and mOS 11 months. Responses, however, did not correlate with particular *HER2* mutations [16]. T-DM1 was then administered to two (2) additional cohorts. One consisted of four (4) patients with *HER2* mutations and a median of one (1) prior therapy. The ORR in this instance was 50% by positron emission tomography response criteria, with mPFS 6 months. The second cohort had six (6) patients with HER2 amplified tumors (fold change ≥ 2 on MSK-IMPACT or HER2/CEP17≥2) and a median of one (1) prior systemic therapy. ORR was 50%, mDOR 7.5 months, mPFS 6 months and mOS 12 months.

While the sample sizes were small, the response rates ranged from 20- 50%. It is on this basis that the National Comprehensive Cancer Network (NCCN), has T-DM1 listed as an option for NSCLC patients with HER-2 mutations [17]. However, new drugs targeting this alteration have provided more robust clinical data.

2.1.2. Trastuzumab deruxtecan (T-Dxd)

The DESTINY-Lung01 phase II study conducted by Li et al. observed the activity of trastuzumab deruxtecan (6.4 mg/kg) in HER2-overexpressing or *HER2*-mutant NSCLC patients [18]. In the cohort of pre-treated *HER2*-mutant, 91 patients were enrolled. The median duration of follow-up was 13.1 months (range, 0.7 to 29.1). ORR was 55% (95% confidence interval [CI], 44 to 65). The mDOR was 9.3 months (95% CI, 5.7 to 14.7), mPFS 8.2 months (95% CI, 6.0 to 11.9), and mOS 17.8 months (95% CI, 13.8 to 22.1). The safety profile was generally consistent with those from previous solid tumor studies. Importantly, responses were observed across different *HER2* mutation subtypes, as well as in patients with no detectable HER2 expression or HER2 amplification (note that *HER2*-mutant NSCLC may not necessarily express HER2). In the post-hoc subgroup analysis, the ORR was similar in patients with ($N = 33$) and without ($N = 58$) asymptomatic central nervous system (CNS) metastases at baseline (54.5% vs 55.2%), but the duration of response (DoR) was shorter in patients with baseline CNS disease (7.2 months vs. 14.7 months). This data suggests that trastuzumab deruxtecan may cross the blood brain barrier and have central activity, an important issue as some patients with *HER2*-mutant aNSCLC may have brain metastases at baseline [19].

Smith et al. also looked at data from the DESTINY-Lung01 study pertaining to heavily pre-treated HER2 overexpressing NSCLC patients [20]. Two cohorts of patients receiving different doses of T-Dxd were reviewed. 49 patients received T-Dxd 6.4 mg/kg (cohort 1) every 3 weeks while another cohort of 41 patients received 5.4 mg/kg (cohort 1a) every 3 weeks. ORR was 26.5% and 34.1% (table), mPFS was 5.7 mo and 6.7 mo, and mOS was 12.4 mo and 11.2 mo in cohorts 1 and 1a, respectively. The antitumor activity shown across both doses of T-Dxd was encouraging. However, the lower dose of 5.4 mg/kg had a better safety profile with fewer incidences of drug discontinuation, interruptions and dose reductions. Also, cases of interstitial lung disease (ILD) were fewer at the lower dose.

Similarly, the DESTINY-Lung 02, tested two doses of T-Dxd: 5.4 mg/kg or 6.4 mg/kg in 152 patients with *HER2* mutant pretreated aNSCLC. The T-Dxd at the 5.4 mg/kg dose demonstrated clinically meaningful responses (ORR: 57.7% DoR: 8.,7 mo) and the safety profile at both doses was consistent with the established safety profile of T-Dxd; however, a favorable safety profile and a lower incidence of ILD were observed in the T-Dxd 5.4 mg/kg arm [21]. Based on this data FDA approved T-Dxd at 5.4 mg/kg as the first drug for *HER2* mutant. Indeed, there is an ongoing clinical trial testing this agent in a first-line setting compared with standard platinum-based chemotherapy.

2.1.3. Sacituzumab govitecan (IMMU-132)

The structure of this ADC is such that SN 38, an active metabolite of irinotecan, binds to the antibody (anti- TROP2 [a type 1 transmembrane glycoprotein]) by a cleavable linker. Preclinical models have shown that this leads to IMMU-132 delivering 138-fold more irinotecan than is the case with just irinotecan. Cytotoxicity (whether antibody-dependent or complement-dependent) is much reduced [22].

In a study of 54 pretreated patients with aNSCLC, the ORR was 19%, the mDOR 6.0 months (95% CI, 4.8 to 8.3 months); and clinical benefit rate[CBR] (complete response + partial response + stable disease $\geq$ 4 months), 43% [23]. While it did show durable responses in this heavily pretreated patient population and was well tolerated, the level of TROP2expression did not appear to influence response (>90% of 26 assessable archival tumor specimens were highly positive for Trop 2). The primary endpoints of this study were safety and efficacy. ORR was 19% and most patients with high expression of Trop 2 did not respond to treatment.

Despite these encouraging findings, the population size is quite small. Therefore, findings will need to be replicated in a larger population of patients expressing the Trop 2 protein.

2.1.4. Datopotamab deruxtecan (Dato-DXd)

The TROPION PanTumor01 trial is a first-in-human study of datopotamab deruxtecan in solid tumors. This study demonstrated promising antitumor activity with a manageable safety profile in heavily pretreated patients with NSCLC. Updated results from the NSCLC Cohort continue to show the same heartening trend with antitumor activity and durability of responses being observed at the 4 mg/kg, 6 mg/kg and 8 mg/kg doses of Dato-DXd [24,25]. The 6 mg/kg dose was, however, better tolerated with a lower discontinuation rate from adverse events than the 8 mg/kg dose. Patients on the 6 mg/kg dose had an ORR of 28% and a median DOR of 10.5 months (95% CI, 5.6- NE). As a result, the 6 mg/kg dose has been selected for further development. In the subset of patients with actionable genomic alterations (AGA) across the 4 mg/kg, 6 mg/kg and 8 mg/kg doses of Dato-DXd, the ORR was 35% (95% CI, 19.7–53.5) with a median DOR of 9.5 months (95% CI, 3.3 – NE) [26, 27].

2.1.5. Telisotuzumab vedotin (ABBV-399)

In a small phase I/Ib study of 52 patients with advanced NSCLC harboring c-MET dysregulation treated with telisotuzumab vedotin monotherapy, 9 (23%) had objective responses with a median duration of response of 8.7 months; the mPFS was 5.2 months [28].

A subsequent phase II trial (LUMINOSITY) looked at previously treated NSCLC patients with c-MET overexpression determined by immunohistochemistry (IHC) testing [29]. Patients were enrolled into cohorts defined by histopathology (non-squamous [NSQ] or squamous [SQ]) and EGFR mutation status (mutant or wild type [WT]); NSQ cohorts were further divided in groups based on c-MET expression (high or intermediate). Of the 122 patients that were evaluable for ORR, ORR was 36.5% in the NSQ EGFR WT cohort (52.2% in c-Met high group -defined as $\geq$50% cancer cells at 3+ intensity- and 24.1% in c-MET intermediate group) but was modest in the NSQ EGFR mutant and SQ cohorts. The drug, telisotuzumab vedotin, clearly demonstrated promise in the subgroup of patients with c-Met OE NSQ EGFR WT NSCLC (ORR of 52.2%) and is being expanded to the next stage.

These findings are supportive of further studies in larger populations of patients with c-MET dysregulation. An ongoing phase III study looks at disease activity and adverse events in patients receiving intravenous telisotuzumab vedotin versus intravenous docetaxel (see Table 1 below). A key inclusion criterion for this study is that participants must have c-MET overexpressing non-small cell lung cancer (NSCLC).

2.1.6. Patritumab deruxtecan (HER3-DXd)

In a phase I study of 57 patients with locally advanced or metastatic EGFR-mutated NSCLC who had received prior EGFR tyrosine kinase inhibitor (TKI) therapy, HER3- DXd 5.6 mg/kg was administered intravenously once every 3 weeks [31]. The ORR was 39% (95% CI, 26.0–52.4), and mPFS was 8.2 (95% CI, 4.4–8.3) months. Responses were observed in patients regardless of the EGFR tyrosine kinase inhibitor (TKI) resistance mechanisms. In addition, the study observed clinical activity across a broad range of HER3 membrane expression. The safety profile of HER3-Dxd was manageable and had a low rate of discontinuation due to treatment emergent adverse events (9%). These findings support further exploration of the role of HER3-Dxd in aNSCLC patients with EGFR TKI resistance mechanisms.

2.1.7. Anti-CEACAM5

Efficacy analysis of follow-up data from the first-in-human (FIH) study of the ADC tusamitamab ravtansine, an anti-CEACAM5, in patients with nonsquamous non–small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) showed quite impressive results. Patients were stratified into moderate and high expressors of the CEACAM 5 molecule. In the moderate expressor cohort, 2 confirmed partial responses (PR) were observed (ORR 7.1%). In the high expressor cohort, 13 pts had confirmed PRs (ORR 20.3% [95% CI, 12.27%–31.71%]); 27 (42.2%) had stable disease;

Table 1
[30] ADCs for aNSCLC in clinical development.

S/N	Name	Antibody Target	Payload (organelle damage)	Phase	ClinicalTrials.gov Identifier
1	Trastuzumab Deruxtecan	HER2	Exatecan derivative DXd, a highly toxic topoisomerase I inhibitor	III	NCT05048797
2	Telisotuzumab Vedotin	C-MET	Monomethyl auristatin E (microtubule)	III	NCT04928846
3	Tusamitamab Ravtansin	CEACAM5; carcinoembryonic antigen-related cell adhesion molecule 5	Maytansinoid DM4 (Tubulin polymerisation inhibitor)	III	NCT04154956
4	Datopotamab Deruxtecan	TROP2	Topoisomerase I inhibitor Dxd (DNA)	I, II, III	NCT04940325; NCT04484142; NCT04656652; NCT04256691; NCT04612751; NCT04484142; NCT05215340; NCT05555732; NCT05687266; NCT05555732; NCT05215340
5	Mecbotamab Vedotin (CAB-AXL-ADC)	AXL	Monomethyl auristatin E (Microtubule)	II	NCT04681131
6	MRG002	HER2	Monomethyl auristatin E (microtubule)	II	NCT05141786
7	MRG003	EGFR	monomethyl auristatin E (Microtubule)	II	NCT04838548
8	Cofetuzumab Pelidotin	Protein Tyrosine Kinase 7 (PTK7)	Auristatin-0101 (Microtubule inhibitor)	I	NCT04189614
9	Anetumab Ravtansine	Mesothelin	Maytansinoid DM4 (Tubulin polymerisation inhibitor)	I	NCT03455556
10	Patritumab Deruxtecan	HER3	Deruxtecan (topoisomerase I inhibitor)	I	NCT03260491
11	XMT-1522	HER2	Auristatin F- hydroxypropylamide (potent microtubule inhibitor)	I	NCT02952729
12	M1231	MUC1/EGFR	SC209, a hemiasterlin-related microtubule inhibitor	I	NCT04695847

Note that these ongoing clinical trials may not have results. In such instances, these will not have been discussed any further in the relevant sections pertaining to the drugs mentioned in this table.

ORR of 17.8% was observed in 45 patients who had prior anti-PD-1/PD-L1 [32]. Additional and more recent analysis of this data by Ricordel et al. showed that almost half (47%) of these patients who achieved a PR were treated for ≥1 year [33]. This suggests that response to tusamitamab ravtansine in these heavily pretreated patients is not only durable but frequently sustained. This finding forms the basis for the ongoing phase III study of this ADC as monotherapy in previously treated NSQ NSCLC patients with high expression of CEACAM5.

2.1.8. Other ADCs in clinical development

There are several ongoing clinical trials involving the use of ADCs in aNSCLC at various stages of development (see Table 1) [30].

2.2. ICIs in advanced non-small cell lung cancers

The advent of ICIs has revolutionized the treatment landscape for advanced non-small cell lung cancers. This is especially true in instances of tumors with high PD-L1 expression ≥50% where ICIs as monotherapy is a potential strategy, whereas ICIs plus chemotherapy is a potential strategy regardless of PD-L1 status.

2.2.1. Pembrolizumab in aNSCLC

Pembrolizumab plus platinum-based chemotherapy has improved the OS compared with chemotherapy alone in non-squamous aNSCLC (KEYNOTE 189 trial), as well as in squamous aNSCLC (KEYNOTE 407). At 5-year the OS for chemo-immunotherapy strategy versus chemotherapy was 22.0 months (95% CI, 19.5 to 24.5) vs 10.6 months (95% CI, 8.7 to 13.6) in non-squamous and 17.2 months (95% CI, 14.4 to 19.7) versus 11.6 months (95% CI, 10.1 to 13.7) in those with squamous cell histology [34,35]. The value of chemo-immunotherapy was more evident in PD-L1 positive tumors, but PD-L1 negative also benefitted.

Five-year follow-up data from the KEYNOTE-024 study of untreated NSCLC with a PD-L1 TPS (Tumor Proportion Score) of at least 50% and no sensitizing EGFR or ALK alterations continues to show improvement in OS for patients in mono-immunotherapy versus chemotherapy with mOS of 26.3 months (95% CI, 18.3 to 40.4) versus 13.4 months (95% CI, 9.4–18.3) respectively [1].

The KEYNOTE-042 study investigated the use of pembrolizumab versus investigators' choice of a platinum-based therapy as a single agent in previously untreated stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or having metastatic NSCLC all in the absence of EGFR or ALK genomic tumor aberrations [36]. Five-year follow-up data continues to show OS outcomes that favor the pembrolizumab group versus the chemotherapy group regardless of PD-L1 TPS. The mOS by TPS populations were 20.0 versus 12.2 months for pembrolizumab versus chemotherapy in patients with TPS score of ≥50%, 17·7 months versus 13·0 months in patients with TPS score of ≥20%, and 16.4 months versus 12.1 months for those with TPS score of ≥1% [37].

These 5-year follow-up survival data from both the KEYNOTE-024 and KEYNOTE-042 support the continued use of mono-immunotherapy in patients who are not candidates for combination with chemotherapy regardless of the PD-L1 expression level.

KEYNOTE-010, a randomized phase III study in previously treated NSCLC patients regardless of EGFR or ALK mutation, showed clinically significant outcomes in pembrolizumab treated groups. 991 patients were randomized into 3 arms to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg and docetaxel 75 mg/m^2 every 3 weeks. OS was much longer in the pembrolizumab 2 mg/kg than with docetaxel (median 14·9 months vs 8·2 months) and with pembrolizumab 10 mg/kg than with docetaxel (17·3 months vs 8·2 months) [38]. For a summary of findings pertaining to the Keynote 189, 407, 024, and 402 studies, please refer to Table 2.

2.2.2. Second-line use of nivolumab in aNSCLC

The randomized phase III CheckMate-017 looked at the use of nivolumab versus docetaxel in patients with metastatic squamous NSCLC who progressed on or after platinum-based chemotherapy [39].

Table 2
Summary of 3- and 5-year follow-up data on PFS and OS in monotherapy and combined use of ICIs in aNSCLC clinical trials.

Clinical Trial	Phase	Sample population	Histology	Cohorts	Follow-up period (years)	Median PFS, mo (95% CI); HR (95% CI)	Median OS (95% CI), mo; HR (95% CI)	Long term OS benefit by Hazard Ratio, HR (95% CI); OS rate
Keynote-189 [34]	III	616	Non-squamous	Chemo-pembrolizumab versus (vs) chemotherapy	5	9.0 (8.1–10.4) vs 4.9 (4.7–5.5); 0.50 (0.42–0.60)	22.0 (19.5 - 24.5) vs 10.6 (8.7 - 13.6); 0.60 (0.50–0.72)	0.71 (0.59–0.85); 5-y OS rate 18.4% vs 9.7
Keynote-407 [35]	III	559	Squamous	Chemo-pembrolizumab versus chemotherapy	5	8.0 (6.3–8.5) vs 5.1 (4.3–6.0); 0.62 (0.52–0.74)	17.2 (14.4 - 19.7) versus 11.6 (10.1 - 13.7); 0.71 (0.59–0.85)	0.60; (0.50–0.72); 5-y OS rates were 19.4% vs 11.3%
Checkmate-227 [43]	III	2748	Squamous and non-squamous	Nivolumab- Ipilimumab (NIVO+ IPI), NIVO-chemotherapy (chemo), chemo	5	Not Available	Not Available	PD-L1 $\geq$ 1% ($N = 1189$): NIVO + IPI vs chemo (0.77 [0.66–0.91]); 5-y OS rates were 24% (NIVO + IPI), 17% (NIVO), and 14% (chemo) PD-L1 < 1% ($N = 550$) for NIVO + IPI vs chemo (0.65 [0.52–0.81]); 5-y OS rates were 19% (NIVO + IPI), 10% (NIVO + chemo), and 7% (chemo)
Keynote-024 [1]	III	305	Squamous and non-squamous	Pembrollizumab vs chemotherapy (PD-L1 $\geq$ 50%)	5	7.7 (6.1 - 10.2) vs 5.5 months (4.2 - 6.2), (HR, 0.50; 95% CI, 0.39 to 0.65)	26.3 (18.3 to 40.4) vs 13.4 (9.4–18.3)	0.62; (0.48 to 0.81)
Keynote-042 [36,37]	III	1274	Squamous and non-squamous	Pembrollizumab vs chemotherapy	5	TPS $\geq$50%, 6.5 (5.9–8.6) vs 6.5 (6.2–7.6) TPS $\geq$20%, 6.2 (5.4–7.8) vs 6.9 (6.3–8.2) TPS $\geq$1% 5.6 (4.3 –6.2) vs 6.6 (6.4–7.9)	TPS $\geq$50%, 20·0 (15·4–24·2) vs 12·2 (10·4–14·6) TPS $\geq$20%, 17·7 (15·5–21.5) vs 13·0 (11·6–15·3) TPS $\geq$1%16·4 (14–19·6) vs 12·1 (11·3–13·3)	0.68 (0.57 −0.81)
Checkmate 9LA [45]	III	719	Squamous and non-squamous	NIVO + IPI + Chemo vs Chemo	3	-Not Available	Not Available	0.74 (0.62–0.87); 3-y OS rates 27% vs 19%

The mOS was 9.2 months with nivolumab versus 6.0 months with docetaxel.

Another phase III study, the CheckMate-057, looked at patients with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy [40]. This study showed a mOS of 12.2 months among 292 patients in the nivolumab group and 9.4 months among 290 patients in the docetaxel group (HR for death, 0.73; 96% CI, 0.59 to 0.89; $P = 0.002$). It is worth noting that the efficacy of nivolumab was demonstrably greater than docetaxel in subgroups of patients with PD-L1 expression levels of 1% or higher.

These statistically significant variables led to the approval of nivolumab as a single agent in aNSCLC patients having progressed on or after platinum-based chemotherapy [39,40]. A subsequent 2-year follow-up update, continued to validate these findings with OS of 23% for nivolumab, versus 8% for docetaxel in the Checkmate 017 study and 29% for nivolumab, versus 16% for docetaxel respectively in the Checkmate 057 study [41].

2.2.3. Ipilimumab in aNSCLCs

The phase III CheckMate-227 study lead to the FDA approval of a combination of nivolumab and ipilimumab in treatment-naïve patients expressing PD-L1 ($\geq$1%) with no EGFR or ALK genomic tumor aberrations [42]. At 5 years, the OS rates were 24% (nivolumab plus ipilimumab), 17% (nivolumab plus chemotherapy), and 14% (chemotherapy alone) [43]. In patients with PD-L1 < 1%, the 5-year OS rates were 19% (nivolumab plus chemotherapy), 10% (nivolumab plus chemotherapy), and 7% (chemotherapy alone).

The CheckMate-9LA study formed the basis for the FDA approval of nivolumab plus ipilimumab plus 2 cycles of platinum-based chemotherapy [44]. The 3-year OS was 27% in the nivolumab + ipilimumab + chemotherapy group versus 19% in chemotherapy only group [45,46]. Of note is that clinical benefits were still being observed in all randomized subjects and across most subgroups including PD-L1 expression levels and histology. Patients with PD-L1 expression $\leq$ 1% had an overall survival rate of 25% with 1 L nivolumab + ipilimumab + chemotherapy combination versus 15% with chemotherapy alone [45,46]. Among those with squamous histology, the overall survival rate was 24% with the combination regimen versus 11% with chemotherapy alone [46]. For a summary of findings pertaining to the Checkmate 227 and 9LA studies, please refer to Table 2.

2.2.4. Cemiplimab in aNSCLCs

In the phase III EMPOWER-Lung 1 study, 657 patients received either cemiplimab or chemotherapy, and in patients with TPS $\geq$ 50%, mOS was not reached in the patients treated with cemiplimab (95% CI 17·9–not evaluable) at the time of reporting, versus 14.2 months in those treated with chemotherapy [47]. These results led to the FDA approval of cemiplimab in treatment-naïve locally advanced NSCLC not suitable for surgical resection or definitive chemoradiation and in patients with metastatic NSCLCs. At 3 years, mOS of 23.4 (cemiplimab monotherapy)

versus 13.7 months (chemotherapy alone) was observed [48].

The EMPOWER-Lung 3 study examined cemiplimab plus platinum-doublet chemotherapy as first-line treatment for aNSCLC, irrespective of PD-L1 expression or histology [49]. mOS was 21.9 months (95% CI, 15.5–not evaluable) with cemiplimab plus chemotherapy versus 13.0 months (95% CI, 11.9–16.1) with placebo plus chemotherapy. The FDA has approved this strategy.

2.2.5. Atezolizumab in aNSCLCs

The phase III IMpower110 study, enrolled 572 chemotherapy/treatment-naïve patients with metastatic PD-L1 positive NSCLC and no EGFR or ALK genomic tumor aberrations [50]. Among patients with TPS ≥50%, the mOS in those treated with atezolizumab was 20.2 months versus 13.1 months in the chemotherapy treated patients, leading the FDA approval of single agent atezolizumab for treatment of this indication. However, with an additional 17 months of follow-up, there was no statistically significant benefit in 1 L use of atezolizumab versus chemotherapy [51]. mOS was 19. 9 months for atezolizumab versus 16.1 months in the chemotherapy group (HR, 0.87, 95% CI, 0.66–1.14; $p = 0.3091$) [51].

In another study (IMpower150), a total of 1202 treatment-naïve patients with no EGFR or ALK alterations were randomly assigned to receive atezolizumab plus carboplatin plus paclitaxel (ACP group), atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP group), or bevacizumab plus carboplatin plus paclitaxel (BCP group) [52]. There was a significant mOS of 19.2 in the ABCP group versus 14.7 in the BCP group (HR for death, 0.78; 95% CI, 0.64 to 0.96; $P = 0.02$), leading to the FDA approval of atezolizumab for this second indication.

IMpower130 study was a randomized phase III study that examined the use of atezolizumab as first line treatment in patients with metastatic non squamous NSCLC with no EGFR or ALK genomic tumor aberrations [53]. The data showed mOS of 18.6 months in the atezolizumab group and 13.9 months in the chemotherapy group, based on which atezolizumab was approved for the third indication in patients with aNSCLC (Table 3).

2.2.6. Durvalumab in aNSCLCs

In the phase III PACIFIC study 713 patients with unresectable Stage III NSCLC who had completed at least 2 cycles of concurrent platinum-based chemotherapy and received definitive radiation with no disease progression were randomized to receive durvalumab or placebo [54, 55]. The results showed a mPFS of 16.8 months in the durvalumab group versus 5.6 months in the placebo group. The 18-month PFS rate was 44.2% for durvalumab versus 27.0% for placebo, with 72.8% having an ongoing response as opposed to 46.8% for the placebo group. Over a 24-month period, the OS rate was 66.3% (95% CI, 61.7 - 70.4) in the durvalumab group versus 55.6% (95% CI, 48.9 - 61.8) in the placebo group (two-sided $P = 0.005$). These data supported the FDA approval of durvalumab for the above indication. Post-hoc analysis of overall survival data at the 5-year mark showed a mOS of 47.5 months for those treated with durvalumab versus 29.1 months for those on placebo with HR of 0.72 (95% CI, 0.59 - 0.89) [56]. The mPFS was 16.9 months versus 5.9 months with a HR of 0.55 (95% CI, 0.45 - 0.68). While patients enrolled in the PACIFIC study were not randomized on the basis of PD-L1 expression, the primary analysis did look at patients with different PD-L1 expression levels using archived tumor samples obtained before chemoradiotherapy. The data did not show a statistically significant benefit in patients with <1% PD-L1 expression. PD-L1 negative analysis was not a pre-specified endpoint and was not controlled.

The phase III open label POSEIDON trial, looked at a combination of durvalumab (with or without tremelimumab) with chemotherapy versus chemotherapy in first line treatment of patients with metastatic NSCLC [57]. Patients were randomly assigned to tremelimumab plus durvalumab plus chemotherapy ($T + D$+CT), druvalumab plus chemotherapy (D+CT) or chemotherapy (CT). The results showed significant improvement in PFS for the D+CT cohort versus the CT cohort with

Table 3
[82] Key clinical trials in NSCLC that lead to the approval of different immune checkpoint inhibitors.

S. No.	Name	Mechanism	Approved indication (s), per FDA label*	Date of approval by the US FDA
1	Pembrolizumab (Keytruda)	Programmed death 1 (PD-1) inhibitor	As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic mutations, and is: 1) stage III where patients are not candidates for surgical resection or definitive chemoradiation, or 2) metastatic.	April 11, 2019
			In combination with carboplatin and either paclitaxel or nab paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC.	October 30, 2018 August 20, 2018
			In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic mutations. Approval of May 10, 2017 change from Carboplatin to 'platinum chemotherapy': 8/20/2018	October 24, 2016
			As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic mutations should have disease progression on FDA-approved therapy for these aberrations prior to receiving or receiving pembrolizumab.	

(continued on next page)

Table 3 (*continued*)

S. No.	Name	Mechanism	Approved indication (s), per FDA label*	Date of approval by the US FDA
2	Nivolumab (Opdivo)	Programmed death 1 (PD-1) inhibitor	Adult patients with metastatic non-small cell lung cancer expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic mutations, as first-line treatment in combination with ipilimumab.	May 15, 2020
			Adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic mutations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.	May 26, 2020
			Metastatic non-small cell lung cancer in patients with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic mutations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.	October 9, 2015
			Adult patients with resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.	March 4, 2022
3	Ipilimumab (Yervoy)	Cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor	Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic mutations, as first-line treatment in combination with nivolumab.	March 25, 2011
			Treatment of adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic mutations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy.	May 26, 2020
4	Cemiplimab (Libtayo)	Programmed death 1 (PD-1) inhibitor	For the first-line treatment of patients with NSCLC whose tumors have high PD-L1 expression (TPS ≥ 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 mutations, and is: locally advanced, where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.	September 28, 2018
5	Atezolizumab (Tecentriq)	Programmed death Ligand 1 (PD-L1) inhibitor	As adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test	October 15, 2021
			For the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA approved test, with no EGFR or ALK genomic mutations.	May 18, 2020
			In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic mutations.	December 3, 2019
			In combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic mutations.	December 6, 2018
			For the treatment of adult patients with	April 17, 2017

(*continued on next page*)

Table 3 (*continued*)

S. No.	Name	Mechanism	Approved indication (s), per FDA label*	Date of approval by the US FDA
			metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic mutations should have disease progression on FDA-approved therapy for NSCLC harboring these mutations prior to receiving TECENTRIQ.	
6	Durvalumab (Imfinzi)	Programmed death Ligand 1 (PD-L1) inhibitor	For the treatment of adult patients with unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.	May 1, 2017
			In combination with tremelimumab-actl (an anti CTLA-4) and platinum-based chemotherapy, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.	November 10, 2022
7	Avelumab (Bavencio)	Programmed death Ligand 1 (PD-L1) inhibitor	Not approved for lung cancers	March 23, 2017

mPFS of 5.5 versus 4.8 months. While there was a trend towards improvement in OS for D+CT versus CT, this was not statistically significant. The results for the *T* + *D*+CT versus CT, however, did show statistically significant improvements in both PFS and OS. The mPFS was 6.2 months for *T* + *D*+CT versus 4.8 months for CT, while mOS was median OS was 14.0 months with *T* + *D*+CT versus 11.7 months with CT. Of note is that benefits were also seen in those with PD-L1 negative tumors for the *T* + *D*+CT versus CT cohort and for the D+CT versus CT cohort. These results form the basis for the FDA approval of the *T* + *D*+CT combination in this indication.

2.3. Dual therapy with ADC and ICI in aNSCLCs

Having explored the use of ADCs and ICIs in treatment of aNSCLCs and given the efficacy demonstrated in either instance, it is reasonable to explore further a combination of these two agents.

2.3.1. Rationale

The case for combining ADCs and ICIs is supported by several preclinical studies and clinical trials, some of which are summarized below:

a Preclinical evidence:
- i As part of the pro-inflammatory activity that is initiated following injury, disease, infection, or non-physiologic cell death (as occurs with anti-cancer therapy), certain signals, referred to as "damage-associated molecular patterns", (DAMPs) are emitted. DAMPs are endogenous molecules that would have been concealed in normal cells but that are released upon stress, cell injury, or cell death. As a result of this signaling pattern, an interphase is established with the host immune system (particularly with dendritic cells). Following exposure of dendritic cells to cancer cells, they succumb to 'immunogenic cell death' (ICD). This leads to priming of the adaptive arm of the immune system (consisting of various T-cell subsets). These activated T cells in turn target therapy-resistant cancer cells [58–61]. This underpins the theory that chemotherapeutic agents, oncolytic viruses and peptides may induce ICD.
- ii Preclinical studies in mouse models combining T-Dxd in combination with an anti–CTLA-4 antibody showed an increased in TILs [62].
- iii While downregulation of MHC1 expression is a mechanism of tumor escape from the host immune system [63], it has been demonstrated in mouse models that there is an enhancement of anti-tumor activity by upregulation of MHC1 expression using T-Dxd [62,64]. Also an improved anti-tumor activity was seen when this ADC was combined with an anti PD-1 [62].
- iv In a study using melanoma derived patient cell lines and mouse models, a topoisomerase 1 inhibitor, liposomal irinotecan, in combination with ICIs (PD-1 or PD-L1) demonstrated greater tumor control and prolonged survival [65].
- v In a study by Stagg et al. using murine models, they were able to show that monoclonal antibody activity against HER2 receptors is dependent upon the priming of interferon gamma CD8+ T cells [66]. In addition, combining this with ICIs significantly improved the therapeutic activity of this anti HER2 monoclonal antibody [66].
- vi Murine tumor models testing a particular cytotoxic and cytostatic agent (PT 112) have also shown that there is synergy exhibited between ICD and PD- (L)1 blockade [67]. These models showed simultaneous recruitment of immune effectors cells and depletion of tumor suppressor cells in the tumor microenvironment. The possibility of combining this with ICIs, therefore, exists for tumors that are especially resistant to monotherapy with cytotoxic agents.
- vii Other studies have shown that ADC payloads such as maytansine, monomethyl auristatin E (MMAE) and auristatin do induce both ICD and T cell mediated immune responses [68–70].

b Clinical evidence:
- i There are several clinical trials in multiple cancer types, particularly in acute myeloid leukemia (AML) and breast cancers, demonstrating improved OS and increased objective responses following ICD induction with cytotoxic agents such as anthracyclin, cytarabin and doxorubicin [71]. ICD does lead to sensitization of the tumor to immune checkpoint blockade [71].
- ii It has been established that patients responding well to ICIs are typically those demonstrating a high level of CD8+ within the tumor microenvironment prior to treatment. Therefore, combining these drugs with compounds that lead to a higher level of CD8+ T cells could potentially bode well for treatment benefits [72]. Cytotoxic compounds such as chemotherapy not only induce ICD and lead to effector T cell activation, but also do stimulate dendritic cell activation and maturation. With the knowledge that the payloads for ADCs are several cytotoxic agents, the logical next step could possibly be a combination of ICI and ADCs.

In patients with early breast cancer and in a HER2-expressing orthotopic tumor model, combined treatment of trastuzumab emtansine and anti-CTLA-4/PD-1 triggered both innate and adaptive immunity in a breast cancer patient with primary resistance to immunotherapy [73].

2.3.2. Efficacy of combination ADC and ICIs in clinical trials for aNSCLCs

Initial results from the TROPION-Lung02 trial presented by Levy et al. at the 2022 World Conference on Lung Cancer show encouraging efficacy and safety results when combining datopotamab deruxtecan and pembrolizumab with or without platinum chemotherapy. ORR of 37% (median follow-up of 6.5 months) was observed in patients treated with datopotamab deruxtecan and pembrolizumab (doublet therapy) and an ORR of 41% (median follow-up of 4.4 months) in patients receiving datopotamab deruxtecan, pembrolizumab and platinum chemotherapy (triplet therapy) [58,59]. In the subgroup of previously untreated patients, the ORR was 62% (8 of the 13 patients receiving doublet therapy) and 50% (10 of 20 patients receiving triplet therapy). Responses were observed in all PD-L1 expression levels. These results have informed the ongoing phase III TROPION-Lung07 and TROPION-Lung08 clinical trials. The TROPION-Lung07 study evaluates a combination of Dato-DXd and pembrolizumab with or without chemotherapy as first line treatment in aNSCLC patients without actionable genomic alterations and PD-L1 TPS <50% [74]. TROPION-Lung08 trial, on the other hand, looks at Dato-DXd combined with pembrolizumab in treatment-naive patients with advanced/metastatic NSCLCs and PD-L1 TPS >50%. [60].

Another study that is currently recruiting is the TROPION-Lung04 trial which is a phase 1b study investigating the combination of Dato-DXd with durvalumab, AZD2936, or MEDI5752 with or without carboplatin in participants with aNSCLCs [11]. MEDI 5752 is a monovalent bispecific antibody targeting PD-1 and CTLA-4, whereas AZD2936 is an anti-TIGIT/anti-PD-1 bispecific antibody.

The AVANZAR study, a recently initiated phase III clinical trial, looks at the combination of Dato-Dxd with durvalumab and carboplatin in patients with aNSCLCs [10]. Other ongoing trials, such as those listed in Table 4 below, also present a unique opportunity to further explore the efficacy of ADC and ICI combinations in clinical trials specific to aNSCLCs

2.3.3. Toxicity of ADC, ICIs, and their combinations

The advent of ICIs in treatment of cancers has led to a wide array of immune-related adverse events (IrAEs) with manifestations occurring more commonly in the skin, gastrointestinal tract, endocrine, lung, and musculoskeletal systems [75]. While these tend to be delayed and prolonged, toxic deaths from ICIs were less frequent (0.6%) than occurs with chemotherapy [76]. Also, treatment discontinuations were less frequent for PD-(L)1 inhibitors (5.8% vs 13.3%, $P < 0.001$) and CTLA-4 inhibitors (6.2% vs 11.4%, $P = 0.002$) than chemotherapy [76]. However, combination ICIs had higher discontinuation (37.8% vs 11.6%, $P < 0.001$) and higher grade ≥3 AEs (55.3% vs 21.9%, $P < 0.001$) than CI monotherapy [76].

The main toxicities associated with ADCs are hematologic, hepatic, neurologic, and ophthalmic [77]. However, it is important to note that a key pulmonic complication, ILD, does occur and can be fatal [21,78,79]. These are due to the cytotoxic payload and, in some instances, could be the off-target effect of a premature release of the payloads [77].

While certain systemic toxicity may be more common in ADC versus ICIs and vice versa, there are commonalities in systemic affectation. Hence the pervasive concern for possible overlapping toxicity and how to mitigate resultant side effects. In some instances, significant additive toxicity was noted in some of the combination studies involving ICIs and ADCs, while others only showed AEs of Grade 3 or less.

In other tumor types, the combination of ADCs with ICI has also reported activity. In the Kate 2 study, addition of atezolizumab to trastuzumab emtansine was associated with an increased incidence of AEs with serious ones occurring in 43 (33%) of 132 patients who received atezolizumab and 13 (19%) of 68 patients who received placebo [80]. These AEs were mainly thrombocytopenia, anemia, and increased alanine aminotransferase.

Another phase Ib study of pembrolizumab plus trastuzumab emtansine concluded that the combination was safe and tolerable with no Grade 4 AEs [81]. The Grade 3 AEs noted were fatigue, AST increase, ALT increase, pneumonia, pneumonitis, oral mucositis, and vomiting,

Table 4
[30] Clinical trials exploring the combination of ADC and ICI.

S. No.	ADC	ICI	Clinical trial.gov identifier	NSCLC phenotype	Comments
1	CAB-AXL-ADC	PD-1 inhibitor	NCT04681131	Non-specific	Phase II, recruiting, $n = 240$ patients, Prior Disease Progression on a PD(L)1 Inhibitor
2	CAB-ROR2-ADC	PD-1 inhibitor	NCT03504488	Non-specific	Phase II, recruiting, $n = 420$ (includes patients in phase I)
3	CAB-AXL-ADC	PD-1 inhibitor	NCT03425279	Non-specific	Phase I, recruiting, $n = 120$ (includes patients in phase II)
4	XB002	Nivolumab	NCT04925284	Non-specific	Phase I, recruiting, $n = 451$ (includes several patient cohorts of advanced malignancies other than NSCLCs and phase II dose expansion cohorts)
5	Dato-DXd	Pembrolizumab	TROPION-Lung02 NCT04526691	Non- specific	Phase 1b, Multicenter, Open-label Study of Datopotamab Deruxtecan (Dato-DXd) in Combination With Pembrolizumab With or Without Platinum Chemotherapy in Subjects With Advanced or Metastatic Non-Small Cell Lung Cancer
6	Dato-DXd	Durvalumab	TROPION-lung04 NCT04612751	Non-specific	A Phase Ib, Multicenter, 2-Part, Open-Label Study of Datopotamab Deruxtecan (Dato-DXd) in Combination with Immunotherapy With or Without Carboplatin in Participants With Advanced or Metastatic Non-Small Cell Lung Cancer
7	Dato-DXd	Pembrolizumab	TROPION-Lung07 NCT05555732	Non-squamous	A Randomized Phase III Study of Datopotamab Deruxtecan (Dato-DXd) and Pembrolizumab With or Without Platinum Chemotherapy in Subjects With No Prior Therapy for Advanced or Metastatic PD-L1 TPS <50% Non-squamous Non-small Cell Lung Cancer Without Actionable Genomic Alterations
7	Dato-DXd	Pembrolizumab	TROPION-Lung08 NCT05215340	Non-specific	Phase III study to assess the efficacy and safety of datopotamab deruxtecan (Dato-Dxd)) in combination with pembrolizumab versus pembrolizumab alone in participants with advanced or metastatic non-small cell lung cancer (NSCLC) without Actionable Genomic Alterations
9	Dato-DXd	Durvalumab	AVANZAR NCT05687266	Non- specific	A Phase III, randomized, open-label, multicenter, global study to compare the efficacy and safety of Datopotamab Deruxtecan (Dato-DXd) in combination with durvalumab and carboplatin compared with pembrolizumab in combination with histology-specific platinum-based chemotherapy as first-line treatment of adults with stage IIIB, IIIC, or IV NSCLC without actionable genomic alterations (including sensitizing EGFR mutations, and ALK and ROS1 rearrangements)

each in 1 patient.

A combination of T-Dxd with nivolumab in a phase Ib study showed similar safety profiles to data in prior monotherapy studies [78]. Adverse events Grade ≥3 occurred in 43.8% with 18.8% being related to trastuzumab deruxtecan and 18.8% to nivolumab. The most common AEs were anemia (16.7%) and transaminase increase (6.3%). Five (5) patients had treatment-related interstitial lung disease (ILD) with 1 being grade 5 and 4 cases being grade 2 events. There were no other deaths associated with a drug-related AE.

In pooled analysis of data from the DESTINY-Breast01 and Study DS8201 A-J101 (NCT02564900) that looked at 234 patients with unresectable or metastatic HER2 positive breast cancer who received at least one dose of T-Dxd at 5.4 mg/kg, serious adverse reactions occurred in 20% of patients receiving T-Dxd [79]. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%) [79]. These figures are relatively comparable to the 18.8% rate for Grade ≥3 AEs related to T-Dxd in the combination study with nivolumab. Also note that the combination study had one fatal case of ILD versus a fatality rate of 2.6% from ILD documented for the pooled analysis discussed here.

Further studies on the safety and tolerability of these combinations are desirable.

3. Conclusion

Despite advances in treatment of aNSCLCs with ICIs and targeted therapies that have transformed clinical benefit, challenges in treatment of aNSCLCs continue to be widespread and the need for more efficacious therapies still exists across all lines of treatment. Earlier studies in *HER2*-mutated NSCLC have clearly demonstrated the benefits of ADCs, particularly trastuzumab emtansine and trastuzumab deruxtecan as monotherapy in treatment of NSCLC. The potential for benefit, when used in combination with ICIs does exist and should be explored, not just for *HER2*-mutated NSCLCs but also for other forms of NSCLCs. There remains a clear gap in ongoing trials with just a few active early phase combination studies for NSCLCs (Table 3).

The current direction of research into improved management of treatment-naïve aNSCLC focuses on testing for "druggable" oncogenic driver alteration in specific histological subtypes and offering the appropriate targeted therapy if this alteration is detected. In the absence of a targetable oncogenic driver alteration, the mainstay of treatment for aNSCLC is mono-immunotherapy for high PD-L1 (>= 50%) expression and combination of chemotherapy and immunotherapy for absent/low PD-L1 (<50%) expression.

However, there are several knowledge gaps and grey areas – such as which patients would benefit the most from either or both of these classes of drugs, and at what point in their cancer journey, and what would be the optimal combinations and/or sequence of agents, and studies are ongoing to address some of these questions.

It is not clear whether ADC-immunotherapy has a significant role in those with a targetable oncogenic driver alteration since targeted therapies are effective. Additionally, tumor response in those with oncogenic drivers treated with ICIs or ICI combinations with TKIs has been relatively poor and associated with enhanced toxicity [83,84]. In aNSCLC without a targetable oncogenic driver alteration, the combination of ADCs and ICIs has potential and remains an area of active clinical research.

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Idoko Salifu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Navneet Singh:** Writing – review & editing. **Maria Berraondo:** Writing – review & editing. **Jordi Remon:** Writing – review & editing. **Stephanie Salifu:** Writing – review & editing. **Eric Severson:** Writing – review & editing. **Angela Quintana:** Writing – review & editing. **Sandra Peiró:** Writing – review & editing. **Shakti Ramkissoon:** Writing – review & editing. **Laura Vidal:** Writing – review & editing. **Isagani Chico:** Writing – review & editing. **Kamal S. Saini:** Conceptualization, Supervision, Validation, Writing – review & editing.

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Data availability

All data and references mentioned in this manuscript are from publicly available sources. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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