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Review

Next-generation immunotherapy: igniting new hope for lung cancer

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***Abstract*:** Adoption of immunotherapy has completely transformed the treatment landscape of cancer. Patients with advanced cancer treated with immunotherapy may benefit from durable tumor response and long-term survival. The most widely used immunotherapy in solid tumors is anti-programmed-death (ligand) protein (PD-(L)1), which is now an integral part of non-small cell lung cancer (NSCLC) treatment irrespective of histological cell types and tumor stage. However, the vast majority of patients with advanced NSCLC treated with anti-PD-(L)1 still develop therapeutic resistance, and the prognosis after anti-PD-(L)1 resistance is poor. Resistance mechanisms to PD-1 blockade are often complex and encompass a combination of defects within the cancer-immunity cycle. These defects include failure in antigen presentation and T-cell priming, presence of co-inhibitory immune checkpoints, inability of immune cells to infiltrate the tumor, and presence of immunosuppressive tumor microenvironment. Recently, advances in drug design, genomic sequencing, and gene editing technologies have led to development of next-generation immunotherapies that may potentially overcome these resistance mechanisms. In this review, we will discuss the anti-PD-(L)1 resistance mechanism landscape in NSCLC and four novel modalities of immunotherapy in detail, namely novel immune checkpoint inhibitor and targeted therapy combinations, bispecific antibodies, cancer vaccine, and cell therapy. These novel therapeutics have all demonstrated early clinical data in NSCLC treatment and may work synergistically with each other to restore anticancer immunity. In addition, we share our perspectives on the future promises and challenges in the transformation of these novel immunotherapies to standard clinical care.

Plain language summary

Next generation immunotherapy in lung cancer

Immune checkpoint inhibitor with anti-programme-death (ligand) protein (PD-[L]1) is the standard of care for lung cancer treatment however therapeutic resistance is common. Various mechanisms are implicated in immune checkpoint inhibitor resistance. Recently, new generations of immunotherapies including novel immune checkpoint inhibitors, bispecific antibodies, cancer vaccine and cell therapy, have been developed. These novel therapeutics have demonstrated early promising data in lung cancer treatment. In this review, we will discuss these novel immunotherapies in detail and share our perspectives on the future promises and challenges in moving them to standard clinical care.

Keywords: adoptive cell therapy < immunotherapy, bispecific antibodies, cancer vaccines < immunotherapy, checkpoint inhibitors < immunotherapy, lung cancer

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Background

It has long been recognized that the immune system plays a heavy role in surveillance and eradication of cancer cells.[1] The discovery of the immune checkpoint programmed death-ligand protein (PD-L1) and elucidation of its function marked a new milestone in the development of cancer immunotherapy.[2,3] Inhibition of PD-1/PD-L1 interaction leads to reinvigoration of exhausted CD8+ T cells in the tumor microenvironment (TME) and stimulation of antitumor memory.[4] Since the first report of its antitumor activity,[5,6] anti-PD-(L)1 has become a central pillar of cancer treatment, with approval as standard treatment for over 15 cancer types.

Currently, the standard treatment for patients with advanced non-small cell lung cancer (NSCLC) without oncogenic driver alterations is anti-PD-(L)1 with or without chemotherapy.[7,8] PD-L1 expression and driver mutation status are the two established predictive biomarkers for anti-PD-(L)1 treatment. In patients with advanced, *EGFR*/*ALK*-negative NSCLC with high PD-L1 expression, anti-PD-(L)1 monotherapy resulted in superior survival outcomes compared to those treated with platinum-based chemotherapy.[9–11] Similarly, patients with advanced NSCLC treated with PD-1 blockade plus chemotherapy achieved significantly longer overall survival (OS) and progression-free survival (PFS) compared to those treated with chemotherapy alone, regardless of tumor PD-L1 expression.[12–15] Five-year survival rate may reach above 30% in patients treated with anti-PD-(L)1, compared to less than 10% among those without exposure to immune checkpoint inhibitor (ICI) treatment.[16,17]

Recently, PD-(L)1 blockade has been established as a new treatment paradigm for resectable NSCLC. Atezolizumab and pembrolizumab reduced recurrence in patients with resected stage IB ⩾ 4 cm—III (AJCC 7th edition) NSCLC.[18,19] Multiple phase III trials investigating the combination of anti-PD-(L)1 and chemotherapy as neoadjuvant or perioperative treatment in resectable NSCLC reported consistent improvements in pathological complete response rate and event-free survival (EFS).[20–24] Durvalumab was approved for patients with locally advanced, unresectable stage III NSCLC without disease progression after concurrent chemoradiotherapy based on the phase III PACIFIC study.[25,26] In summary, anti-PD-(L)1 is part of the standard treatment for NSCLC at all stages.

Despite the positive clinical promises, most patients develop treatment resistance to anti-PD-(L)1 over time. Up to 90% of patients with advanced NSCLC treated with upfront immunotherapy or immunochemotherapy would develop disease progression in 5 years' time.[27,28] Survival outcomes among patients after disease progression on first-line anti-PD-(L)1 and platinum-based chemotherapy were poor, with a median survival of 9 months.[29]

In addition, NSCLC harboring oncogenic driver alterations such as *EGFR*, *ALK*, *ROS1*, *RET*, and *ERBB2* may not benefit equally from anti-PD-(L)1 treatment.[30] In a multicentre retrospective study, tumors harboring these alterations exhibited response rates below 20% and PFS below 3 months with anti-PD-(L)1.[30] Two randomized phase III studies showed that the addition of anti-PD-(L)1 to chemotherapy did not improve PFS or OS in patients with *EGFR* mutation-positive NSCLC after disease progression on targeted therapy.[31,32]

Extensive research effort has been dedicated to better harness the immune system to overcome anti-PD-(L)1 resistance or enhance anti-PD-(L)1 activity. To design effective therapeutic strategies, it is crucial to understand mechanisms of immune evasion and the complex interaction between immune cells, tumor cells, and TME. In addition to PD-L1 expression and driver mutation status, various biomarkers have been reported as predictors of immunotherapy efficacy. Low tumor mutational burden (TMB), the presence of *STK11* and *KEAP1* mutation, a non-inflammatory gene signature, low tumor infiltrate lymphocyte (TIL) concentration, and human-leukocyte antigen (HLA) homozygosity, have all been reported to be associated with inferior anti-PD-(L)1 treatment outcomes.[33–43] These factors collectively serve as surrogate markers of immune evasion or suppression. Over the past decade, novel immunotherapies have been developed with the objective of overcoming immune evasion and restoring anticancer immunity. In particular, four novel classes of immunotherapies have demonstrated encouraging preclinical and early clinical evidence in treating lung cancer. They include novel combinations of ICI and molecular therapy, bispecific antibodies (BsAb), cancer vaccines, and cell therapy (Figure 1). In this review, we will discuss the mechanisms of immune evasion, followed by the working mechanisms, clinical evidence, and future promises of

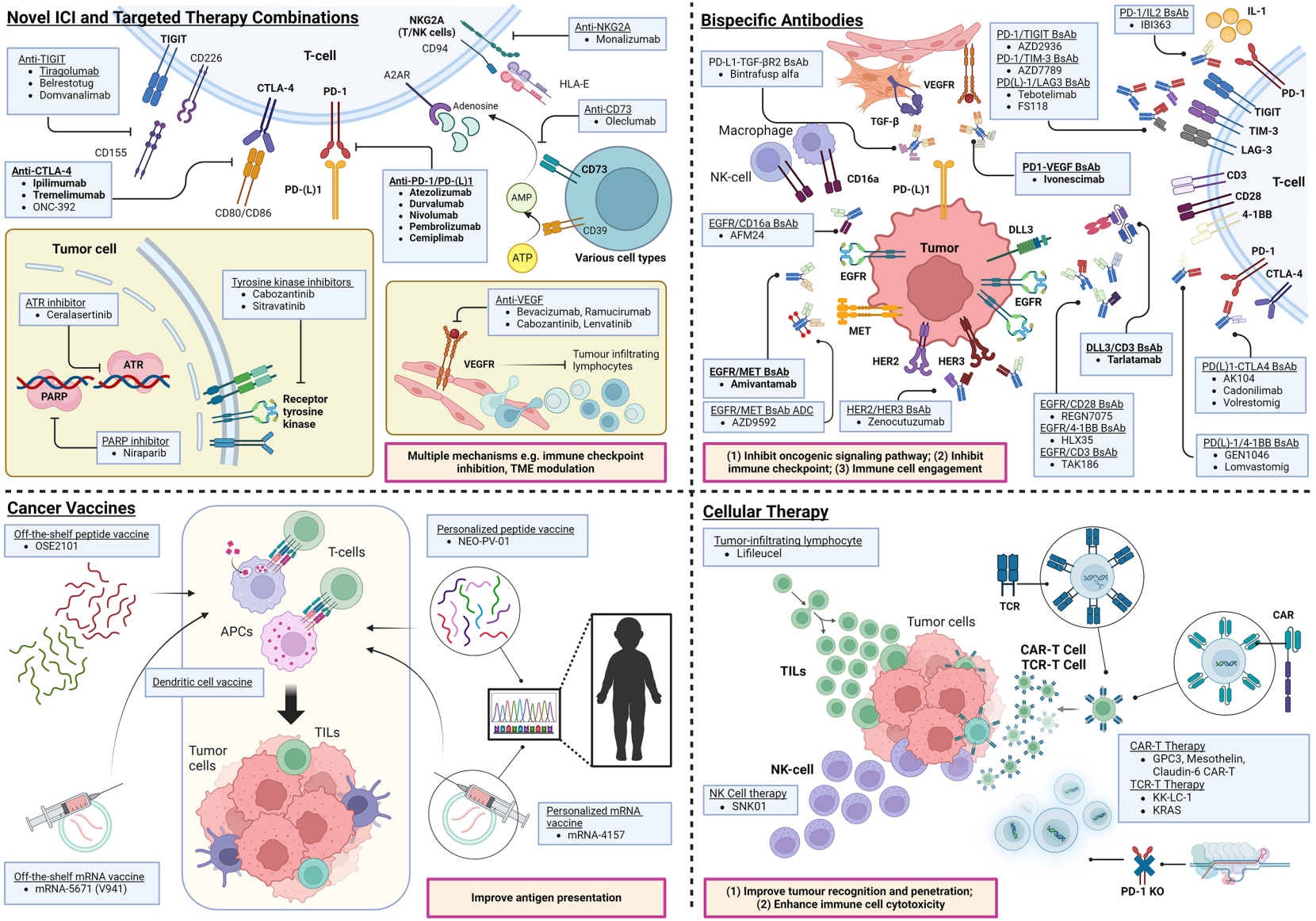

Figure 1. Novel immunotherapy approaches with emerging data in lung cancer. Created with Biorender.

these four novel approaches of immunotherapies. Lastly, we share our perspectives on the future promises and challenges to move these novel immunotherapies to clinic.

Mechanisms of immune evasion

The cancer-immunity cycle, first proposed by Chen and Mellman,[44] highlighted the essential steps required to trigger antitumor immunity. This notion underscored the fact that the PD-1/PD-(L)1 pathway being only one of the many mechanisms why the immune system fails to recognize or eradicate cancer cells. The first step of the cancer-immunity cycle involves engulfment of cancer-specific antigens (also called neoantigens) by antigen presenting cells (APCs) (e.g., dendritic cells). Neoantigens are generated from non-synonymous genetic alterations in the tumor, and thus are cancer-specific and immunogenic. APCs present neoantigens to naïve T cells via major histocompatibility complex (MHC) molecules which trigger T-cell priming and activation in lymph nodes. The activated T cells then traffic to and infiltrate the tumor and exert cytotoxic killing.[44]

Any defect in the cancer-immunity cycle may impair the immune system to recognize and kill cancer cells. Common causes include lack of tumor-specific antigens (TSAs), defect in cancer antigen presentation and T-cell priming, poor infiltration of T cells into tumor, failure in cancer cell recognition by T cells, and presence of co-inhibitory immune checkpoints and immunosuppressive TME.[44] Immune checkpoints can be involved in multiple parts of the cancer-immunity cycle, for instance, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) may act by simultaneously blocking T-cell priming and promoting regulatory T-cell (T-reg) activity.[45]

The presence of certain oncogenic alterations is associated with primary resistance to ICIs. NSCLCs harboring actionable genomic alterations (AGA) such as *EGFR*, *ALK*, *ROS1*, *RET*, and *ERBB2* alterations are associated with lower TMB resulting in inefficient neoantigen presentation and T-cell priming.[46,47] NSCLCs harboring *STK11*, *KEAP1*, and *SMARCA4* alterations are associated with immunosuppressive TMEs that suppress T-cell activity.[48–50] On the contrary, mechanisms leading to acquired resistance to anti-PD-(L)1 are less well understood. Loss-of-function mutations and copy number losses in *β2M* and *JAK1/2*, and reduced HLA expression were observed in a significant proportion of patients with acquired resistance to ICIs, suggesting that defects in antigen presentation and interferon-receptor signaling to be important drivers in ICI resistance.[51,52] Acquired loss-of-function alterations in *STK11*, *KEAP1*, and *SMARCA4* were also detected in ICI-resistant samples, suggesting that they not only cause primary but also acquired ICI resistance.[52]

In the coming section, four novel modalities of immunotherapies, namely novel ICI and molecular therapy combinations, BiAbs, cancer vaccine, and cell therapy, will be discussed in detail. These novel immunotherapies are designed to overcome the different defects in the cancer-immunity cycle (Figure 1) and have demonstrated encouraging clinical data in lung cancer treatment.

Novel combinations of ICIs and molecular targeted therapy

The most mature data in ICI combinations arose from anti-PD-(L)1 and anti-CTLA-4 antibodies. In contrast to anti-PD-(L)1 which functions primarily inside the TME, anti-CTLA-4 promotes T-cell priming in lymph nodes as CTLA-4 competes with the co-stimulatory molecule CD28 on T cells for the B7-ligands expressed on APCs.[53] Three randomized phase III trials, namely CHECKMATE-227, CHECKMATE-9LA, and POSEIDON, demonstrated PFS and OS benefits over chemotherapy alone as first-line treatment for metastatic NSCLC.[54–56] CHECKMATE-227 and CHECKMATE-9LA adopted chemotherapy alone without anti-PD-(L)1 in the control arm, while POSEIDON was a three-arm study, including a control arm of chemotherapy alone, and two study arms including anti-PD-(L)1 plus anti-CTLA-4 plus chemotherapy, and anti-PD-(L)1 plus chemotherapy. As there were no direct comparisons between anti-PD-(L)1 with and without anti-CTLA-4, the additive role of anti-CTLA-4 has not been definitively established. Cross-trial comparisons with other randomized phase III trials such as KEYNOTE-189 and KEYNOTE-407 suggested that patients with PD-L1 negative tumors may benefit more from the addition of anti-CTLA-4. Regarding toxicities, the combination of anti-PD-(L)1 and anti-CTLA-4 is associated with a higher incidence of immune-related adverse events, especially colitis and hypophysitis.[57]

Among the many novel ICI and targeted therapy combinations tested in the clinic currently (Table 1), antibodies against T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), NKG2A, and CD73 showed the most promising early data. TIGIT directly inhibits T/natural killer (NK) cells or interacts with CD155 and CD226 to impede T-cell activation, exhaust effector T cells, and promote T-reg proliferation.[58] Several anti-TIGIT agents are under investigation. CITYSCAPE, a randomized double-blinded phase II study on the combination of tiragolumab or placebo with atezolizumab in chemotherapy-naïve patients with NSCLC, reported improved median PFS (5.4 vs 3.6 months, $p = 0.015$). The benefit was mainly observed among patients with high PD-L1 expression (median PFS 16.6 vs 4.1 months, hazard ratio (HR) = 0.29).[59] ARC-7 was another phase II study that reported PFS benefit with the addition of domvanalimab, an anti-TIGIT antibody, to zimberelimab, an anti-PD-1 antibody, in treatment-naïve NSCLC with high PD-L1 expression (12.0 vs 5.4 months, HR = 0.55).[60] GALAXIES Lung-201, a randomized phase II study, also reported that the addition of belrestotug (an anti-TIGIT) to dostarlimab improved tumor response in patients with advanced PD-L1 high NSCLC.[61] The safety profile of anti-PD-(L)1 plus anti-TIGIT was similar to anti-PD-(L)1 alone. However, two phase III trials, SKYSCRAPER-01 (atezolizumab with and without tiragolumab) and SKYSCRAPER-06 (atezolizumab plus chemotherapy with and without tiragolumab), reported negative PFS outcomes.[62,63] Most recently, sponsor of these studies has halted all late development of tiragolumab in lung cancer. Three other phase III studies, namely ARC-10 (NCT04736173) (zimberelimab plus domvanalimab vs pembrolizumab), STAR-121 (NCT05502237) (zimberelimab plus domvanalimab plus chemotherapy vs pembrolizumab plus chemotherapy), and GALAXIES Lung-301 (NCT06472076) (belrestotug plus dostarlimab vs pembrolizumab), are ongoing, and results are pending.

NKG2A dimerizes with CD94 to recognize HLA-E and acts as an immune checkpoint on both NK and T cells.[64,65] Meanwhile, CD73, along with CD39 and adenosine A2A receptor, are upregulated by the transcription factor hypoxia-inducible factor 1α to coordinate immunosuppressive features in the TME via adenosine signaling. Monalizumab (anti-NKG2A antibody) and oleclumab (CD73 inhibitor) were combined with durvalumab as neoadjuvant therapy for patients with resectable NSCLC in the NeoCOAST study and as consolidation therapy for unresectable stage III NSCLC after concurrent chemoradiation in the COAST study. The former trial demonstrated improved major pathological response rates while the latter demonstrated numerically improved objective response rates (ORR)[66,67] with both durvalumab plus monalizumab and durvalumab plus oleclumab compared to durvalumab monotherapy. These results prompted two actively recruiting trials on these novel agents, the NeoCOAST-2 trial (NCT05061550) in the perioperative setting and the PACIFIC-9 trial (NCT05221840) in the stage III unresectable setting.

Vascular endothelial growth factor (VEGF) inhibition may restore normal vasculature and promote immune cell infiltration into tumors. The combination of PD-1 blockade and VEGF inhibitor has been extensively investigated in both treatment-naïve or ICI-resistant settings, yielding conflicting results. Bevacizumab was approved with atezolizumab and chemotherapy for treatment-naïve metastatic non-squamous NSCLC based on the IMpower150 trial.[68] This combination remains a controversial option for treatment for *EGFR* mutation-positive NSCLC after tyrosine kinase inhibitor (TKI) failure.[69–71] In the ICI-resistant population, pembrolizumab plus ramucirumab improved OS compared to second-line chemotherapy in the phase II Lung Map S1800A trial. Despite previous exposure to anti-PD-(L)1, 22% of patients achieved tumor response to pembrolizumab plus ramucirumab, suggesting that VEGF inhibition resensitized a group of patients to PD-L1 inhibition.[72] This positive signal is being tested in the phase III Pragmatica-Lung study (NCT05633602), which compares ramucirumab plus pembrolizumab with usual care after disease progression on immunochemotherapy. However, other combinations of PD-1 blockade and anti-VEGF inhibitors have been less successful. Addition of lenvatinib to pembrolizumab monotherapy or pembrolizumab/chemotherapy combination in the first-line setting failed to improve OS but led to increased toxicities.[73,74] Other second-line combination studies including sitravatinib and nivolumab in SAPPHIRE, pembrolizumab and lenvatinib in LEAP-008, and cabozantinib and atezolizumab in CONTACT-01, had failed to meet the primary endpoints of OS improvement

Table 1. Ongoing clinical trials testing novel immune checkpoint inhibitors and targeted therapy combinations in lung cancer.

Target	Study agent	Setting	Ph	Status	NCT
CTLA-4	ONC-392	NSCLC failed first-line immunochemotherapy	III	R	NCT05671510
TIGIT	Zimberelimab Domvanalimab Chemotherapy	First-line metastatic NSCLC	III	A, nR	NCT05502237
	Zimberelimab Domvanalimab	First-line metastatic NSCLC with high PD-L1 expression	III	A, nR	NCT04736173
	Vibostolimab Pembrolizumab	First-line metastatic NSCLC	III	R	NCT04738487
	Dostarlimab Belrestotug	First-line metastatic NSCLC with high PD-L1 expression	III	R	NCT06472076
	Durvalumab Domvanalimab	Stage III NSCLC after chemoradiation	III	R	NCT05211895
	Vibostolimab Pembrolizumab Chemotherapy	Treatment-naïve ES-SCLC	III	A, nR	NCT05224141
	Ociperlimab Tislelizumab	Neoadjuvant NSCLC	II	R	NCT05577702
TIGIT, CD73	Zimberelimab ± ± Domvanalimab ± Etrumadenant	First-line metastatic NSCLC	II	A, nR	NCT04262856
TIGIT CD96	Dostarlimab ± Belrestotug ± GSK6097608	First-line metastatic NSCLC	II	R	NCT05565378
LAG-3	Fianlimab Cemiplimab Chemotherapy	First-line metastatic NSCLC	II/III	R	NCT05800015
	Fianlimab Cemiplimab	First-line metastatic NSCLC with high PD-L1 expression	II/III	R	NCT05785767
	Relatlimab Nivolumab ± Chemotherapy	First-line metastatic NSCLC	II	A, nR	NCT04623775
	LBL-007 Tislelizumab	Neoadjuvant NSCLC	II	R	NCT05577702
TIM3	Cobolimab Dostarlimab Docetaxel	NSCLC failed first-line immunochemotherapy	II/III	A, nR	NCT04655976
	S095018 Cemiplimab	First-line metastatic NSCLC	I/II	R	NCT06162572
VISTA	SNS-101 ± Cemiplimab	NSCLC failed standard therapy	I/II	R	NCT05864144

(Continued)

Table 1. (Continued)

Target	Study agent	Setting	Ph	Status	NCT
	HMBD-002 ± Pembrolizumab	NSCLC failed standard therapy	I/II	R	NCT05082610
CD73	Oleclumab Durvalumab	Stage III NSCLC after concurrent chemoradiation	III	R	NCT05221840
	Oleclumab Durvalumab Chemotherapy	Perioperative treatment in resectable NSCLC	II	R	NCT05061550
	Oleclumab Durvalumab	NSCLC failed ICI	II	A, nR	NCT03833440
	PT199 ± Tislelizumab	NSCLC failed standard therapy	I	R	NCT05431270
	S095024 Cemiplimab	First-line metastatic NSCLC	I/II	R	NCT06162572
A2B adenosine receptor	PBF-1129 Nivolumab	NSCLC failed standard treatment	I	R	NCT05234307
NKG2A	S095029 Cemiplimab	First-line metastatic NSCLC	I/II	R	NCT06162572
	Monalizumab Durvalumab	Stage III NSCLC after concurrent chemoradiation	III	R	NCT05221840
	Monalizumab Durvalumab Chemotherapy	Perioperative treatment in resectable NSCLC	II	R	NCT05061550
	Monalizumab Durvalumab	NSCLC failed ICI	II	A, nR	NCT03833440
	Monalizumab Durvalumab Chemotherapy	First-line ES-SCLC	II	R	NCT05903092
IL2 (agonist)	MDNA11 ± Pembrolizumab	NSCLC failed standard therapy	I/II	R	NCT05086692
IL-10, IL-2	DK210 (EGFR)	NSCLC failed standard therapy	I	R	NCT05704985
IL15 (super-agonist)	N-803	NSCLC failed ICI	II	A, nR	NCT03228667
	N-803 Pembrolizumab	NSCLC failed standard therapy	II/ III	A, nR	NCT05096663
	N-803 Pembrolizumab ± chemotherapy	First-line metastatic NSCLC	III	A, nR	NCT03520686
BTLA	Tifcemalimab Toripalimab	LS-SCLC after concurrent chemoradiotherapy	III	R	NCT06095583
CD96	GSK6097608 Dostarlimab Belrestotug	NSCLC failed first-line immunochemotherapy	II	R	NCT03739710

(Continued)

Table 1. (Continued)

Target	Study agent	Setting	Ph	Status	NCT
CD27	Varlilumab Atezolizumab	NSCLC failed first-line immunochemotherapy	I	A, nR	NCT0081688
IKZF2	DKY709 ± PDR001	NSCLC failed standard therapy	I	A, nR	NCT03891953
CCR8	BAY3375968 ± Pembrolizumab	NSCLC failed standard therapy	I	R	NCT0553740
LXR agonist	RGX-104 Durvalumab Chemotherapy	Neoadjuvant NSCLC	I	R	NCT05911308
ICOS	Feladilimab Ipilimumab	NSCLC failed first-line immunochemotherapy	II	R	NCT03739710
	KY1044 ± Atezolizumab	NSCLC failed ICI or ICI naïve	I/II	A, nR	NCT03829501
AXL	SLC-391	NSCLC failed standard therapy	R	R	NCT05860296
	Bemcentinib Pembrolizumab Chemotherapy	First-line metastatic NSCLC	I/II	R	NCT05469178
FAK RAF/MEK	Defactinib (FAK) Avutometinib (RAF/MEK) Nivolumab	NSCLC failed first-line immunochemotherapy and LKB1 mutation	II	R	NCT06495125
MEK	Selumetinib Durvalumab Tremelimumab	NSCLC failed standard therapy	I/II	A, nR	NCT03581487
	Trametinib Pembrolizumab	NSCLC failed standard therapy	I/II	A, nR	NCT03225664
P38 MAPK	ARRY-614 Nivolumab ± Ipilimumab	NSCLC failed ICI	I/II	A, nR	NCT04074967
MET	AL2846 TQB2450	NSCLC failed ICI	III	R	NCT05922345
	Savolitinib Durvalumab	NSCLC failed ICI	II	A, nR	NCT03833440
Epigenetic	Pembrolizumab Guadecitabine Mocetinostat	NSCLC failed ICI	I	A, nR	NCT03220477
PARP	Olaparib Pembrolizumab	Stage III NSCLC after concurrent chemoradiation	III	A, nR	NCT04380636
	Niraparib Pembrolizumab	Maintenance after first-line immunochemotherapy in NSCLC	III	A, nR	NCT04475939

(Continued)

Table 1. (Continued)

Target	Study agent	Setting	Ph	Status	NCT
	Fluzoparib SHR1701	Maintenance after first-line immunotherapy in NSCLC	II	R	NCT04937972
	Niraparib Temozolomide Atezolizumab	Maintenance after first-line immunochemotherapy in ES-SCLC	I	R	NCT03830918
ATR	Ceralasertib Durvalumab	NSCLC failed ICI	II	A, nR	NCT03833440
	Ceralasertib Durvalumab	Maintenance after first-line immunochemotherapy in ES-SCLC	II	R	NCT04699838
	Berzosertib Pembrolizumab Chemotherapy	First-line metastatic NSCLC	I/II	A, nR	NCT04216316
LSD-1	Bomedemstat Atezolizumab	Maintenance after first-line immunochemotherapy in ES-SCLC	I/II	A, nR	NCT05191797
Microtubule binding agent	Plinabulin Nivolumab Ipilimumab	Recurrent ES-SCLC	I/II	A, nR	NCT03575793
	Plinabulin Pembrolizumab Docetaxel	NSCLC failed ICI	II	R	NCT05599789
Ornithine decarboxylase	DFMO Pembrolizumab	STK11 mutant NSCLC	I/II	R	NCT06219174
TGF-β	Livmoniplimab Budigalimab Chemotherapy	First-line metastatic NSCLC	II/III	R	NCT06236438
VEGF	Ramucirumab Pembrolizumab	NSCLC failed first-line immunochemotherapy	III	R	NCT05633602
	Ramucirumab Nivolumab	NSCLC failed first-line chemotherapy or immunotherapy	II	R	NCT03527108
	Camrelizumab Famitinib	First-line metastatic NSCLC	III	R	NCT05042375
E-type prostanoid receptor (EP4)	HTL0039732	NSCLC failed standard therapy	I/II	R	NCT05944237
Telomere	THIO Cemiplimab	NSCLC failed ICI	II	R	NCT05208944

Data cut-off on ClinicalTrials.gov on August 25, 2024. The list is not exhaustive.
A, nR, active, not recruiting; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ES-SCLC, extensive stage-small cell lung cancer; ICI, immune checkpoint inhibitor; LS-SCLC, limited stage-small cell lung cancer; NCT, registration number on ClinicalTrials.gov; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1 protein; Ph, phase; R, recruiting; Status, recruitment status; VEGF, vascular endothelial growth factor.

when compared to docetaxel.[75–77] Several factors may explain the discrepancy in study outcomes. One important factor could be differences in a study population with primary versus acquired ICI resistance. In the Lung Map S1800A and the SAPPHIRE studies, only patients with acquired ICI resistance were enrolled.[72,75] The median durations of prior immunotherapy among patients in the Lung Map S1800A and SAPPHIRE studies were 8.0 and 8.3 months, respectively. In contrast, the LEAP-008 and CONTACT-01 studies did not restrict prior ICI treatment duration.[76,77] Previous studies reported that patients with acquired ICI resistance may benefit more from ICI rechallenge compared to those with primary ICI resistance.[78] In the subgroup analyses of the CONTACT-01 study, patients who received prior ICI treatment for ⩾6 months also benefited more from ICI rechallenge compared to those treated for <6 months (unstratified OS HR 0.78 vs 1.06).[76] Secondly, tumor histology may impact the response to the ICI-VEGF blockade combination. In Lung Map S1800A and CONTACT-01, patients with squamous histology benefited more from ICI-VEGF blockade combination compared to those with non-squamous histology.[72,76] In contrast, the SAPPHIRE study did not enroll patients with squamous histology.[75]

Early clinical data support further research on the combination of PD-1 inhibition and poly ADP-ribose polymerase (PARP) inhibition. Preclinical studies showed that PARP inhibitor upregulated PD-L1 expression in cancer models and resensitized PARP inhibitor-treated cancer cells to T-cell killing.[79] The phase II JASPER trial studied the pembrolizumab–niraparib combination and reported ORR of 56% and 20% in patients with PD-L1 TPS ⩾50% and 1%–49%, respectively.[80] The phase III ZEAL-1L (NCT04475939) study comparing pembrolizumab with or without niraparib maintenance in patients with advanced NSCLC is ongoing.

Despite promising results observed in phase I/II trials, none of the novel ICI combinations beyond anti-PD-(L)1 and anti-CTLA-4 have led to a successful phase III trial thus far. One major reason is the limited understanding of ICI resistance mechanisms and the fact that all randomized trials were conducted in biomarker-unselected populations. These novel ICI and targeted therapy combinations appear to benefit a minor subgroup of patients with anti-PD-(L)1 resistance; however, a biomarker for patient selection is lacking. This has led to novel trial designs specifically searching for immunotherapy biomarkers. HUDSON study was an umbrella trial that was designed to address two questions. First objective was to compare efficacy between four immunotherapy combinations, including durvalumab plus olaparib (PARP inhibitor), durvalumab plus danvatirsen (STAT-3 targeting antisense oligonucleotide), durvalumab plus ceralasertib (D + C, ATR kinase inhibitor), and durvalumab plus oleclumab (anti-CD73), all of which were immunomodulators. Second objective was to investigate whether patients receiving biomarker-guided immunotherapy could achieve better outcomes than those who did not. In summary, 268 patients with disease progression on prior anti-PD-(L)1 therapy received either one of the four drug combinations. The combination of durvalumab and ceralasertib was the only group that had demonstrated favorable efficacy ($n=79$, ORR 14%, median PFS 5.8 months) compared to the other three regimens (pooled $n=189$, ORR 2.6%, median PFS 2.7 months). Intriguingly, ORR appeared better with D + C in the *ATM*-altered biomarker-matched cohort ($n=23$, ORR 26%) than those in the biomarker-nonmatched cohort ($n=46$, ORR 9%), suggesting that *ATM* alterations being a potential predictive biomarker for ATR inhibitor. This combination is now investigated in the phase III LATIFY trial (NCT05450692). In contrast, increased antitumor activity was not observed with durvalumab plus olaparib in patients with homologous repair deficiency or with durvalumab plus oleclumab in patients with high CD73 expression.[81]

Similarly, KEYNOTE-495/KeyImPaCT explored using T-cell inflammatory gene expression profile and TMB as potential predictive biomarkers to guide immunotherapy use. However, both the pembrolizumab plus quavonlimab (anti-CTLA-4) and pembrolizumab plus favezelimab (anti-LAG-3) combinations failed to meet the pre-specified efficacy threshold for further clinical development.[82]

Finally, the potential toxicities of combination therapies should not be overlooked. Even drug combinations involving agents from the same class may result in distinct toxicity profiles. For instance, the combination of anti-PD-(L)1 therapy with sotorasib, a KRAS G12C inhibitor, proved unfeasible in clinical setting due to a high incidence of hepatotoxicity.[83] In contrast, anti-PD-(L)1 can be combined with other KRAS

G12C inhibitors such as adagrasib and olomorasib.[84,85] Each drug combination should be assessed through phase I and/or II clinical trials for toxicity assessment and dose optimization.

Bispecific antibodies

BsAb differs from traditional monoclonal antibody (MoAb) in their ability to simultaneously bind to two different epitopes.[86] In contrast to adoptive cell therapies such as TIL or chimeric antigen receptor-T cell (CAR-T) therapy, BsAb does not require customization and lymphodepletion prior to administration.[87] Current BsAbs used in lung cancer can be broadly categorized according to their mechanisms of action: (1) inhibition of receptor signaling pathways; (2) recruitment of immune effector cells; and/or (3) inhibition of immune checkpoints (Table 2).

Cancer cells frequently depend on the unregulated activation and cross-talk of different receptor signaling pathways, thus synergistic antitumor activity may be achieved through simultaneous inhibition of two oncogenic signaling pathways. Although targeted therapy is efficacious against *EGFR* mutation-positive NSCLC, resistance may emerge via bypass signaling such as *MET* amplification.[88] One of the most successful BsAbs in this category is amivantamab, an EGFR/MET BsAb with an enhanced Fc region which was developed to overcome resistance by *MET* amplification.[89] The combination of amivantamab with lazertinib (a third-generation EGFR TKI) significantly improved PFS over osimertinib monotherapy as first-line treatment for metastatic NSCLC harboring *EGFR* mutation based on the MARIPOSA study.[90] However, the toxicity profile including infusion reaction and venous thromboembolism is a potential challenge for its general adaptation for all patients. Similarly, amivantamab plus chemotherapy improved PFS compared to standard chemotherapy in the TKI-resistant setting in the MARIPOSA-2 study,[91] and in the first-line setting for advanced *EGFR* exon 20 insertion positive tumors in the phase III PAPILLON study.[92] Other EGFR/MET BsAb under active development with phase I/II data include MCLA-129 (NCT04868877) and EMB-01 (NCT03797391).[93,94] AZD9592 is an EGFR/MET bispecific antibody drug conjugate with a topoisomerase I inhibitor payload currently tested in *EGFR* mutation-positive NSCLC patients (NCT05647122).[95]

HER-3 is not a resistance mechanism of EGFR TKI treatment but is commonly expressed in NSCLC especially in *EGFR* mutants, with the ability to dimerize to HER-2 and activate downstream pathways.[96] SI-B001, an EGFR/HER-3 BsAb, in combination with docetaxel, has demonstrated an ORR of 31% in a phase II trial for advanced NSCLC failing prior treatment (NCT05020457).[97] This drug is being studied in *EGFR* mutation-positive patients in combination with osimertinib (NCT05020769) and in combination with SI-B003 (PD-1/CTLA-4 BsAb) in advanced NSCLC without driver mutations (NCT05949606).[98] *NRG-1* fusion is a rare oncogenic driver that produces an oncoprotein that binds preferentially to HER-3.[99] Zenocutuzumab, a HER-2/HER-3 BsAb, reported an ORR of 34% in *NRG-1* fusion cancers including NSCLC in the ongoing eNRGy trial (NCT02912949).[100]

BsAbs can also activate antitumor immunity by directing immune cells to tumors or by inhibiting immune checkpoints. Bispecific T-cell engager (BiTE) comprises two single-chain variable fragments (scFv), with one binding to an epitope and another binding to CD3, thereby directing T cells to tumors.[101] Tarlatamab is a promising DLL3/CD3 BiTE that showed a moderate response rate of 40% with durable clinical benefit in a population of patients with heavily treated small cell lung cancer (NCT05060016).[102] Tarlatamab is being studied in phase III studies as a second-line therapy against standard of care for patients with extensive stage SCLC (NCT05740566) and as maintenance therapy for patients with limited stage SCLC after concurrent chemoradiotherapy (NCT06117774). Other agents in the same class with early clinical data include HPN328 (NCT04471727) and BI-764532 (NCT04429087). BsAb may also contribute to T-cell activation via costimulatory signaling. Examples include REGN7075, an EGFR/CD28 BsAb, and HLX35, an EGFR/41-BB BsAb; both of which are currently evaluated in phase I trials including NSCLC patients (NCT04626635, NCT05360381).

Unrestrained T-cell activation by BiTEs may lead to cytokine-release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In contrast to CAR-T, the incidence and severity of CRS are often lower for BsAb, albeit an earlier onset time was observed.[103] Tarlatamab at 10 mg is associated with mostly low-grade CRS (total incidence at 51%; Grade 3

Table 2. Ongoing clinical trials testing bispecific antibodies in lung cancer.

Target	Study agent	Setting	Ph	Status	NCT
BsAb					
PD-1, CTLA-4	Volrustomig Chemotherapy	First-line metastatic NSCLC	III	R	NCT05984277
	Volrustomig Chemotherapy	Perioperative treatment in resectable NSCLC	II	R	NCT05061550
	Cadonilimab chemotherapy	NSCLC failed first-line immunotherapy	II	R	NCT06467500
	Cadonilimab ± chemotherapy	ES-SCLC failed first-line chemotherapy	II	R	NCT05901584
	Cadonilimab Pemetrexed Anlotinib	NSCLC failed EGFR TKI Chemotherapy and ICI naïve	II	R	NCT06277674
	AK104 Chemotherapy	Perioperative NSCLC	II	R	NCT05377658
	AK104 Chiauranib	ES-SCLC failed immunochemotherapy	I/II	A, nR	NCT05505825
	KN406	First-line metastatic NSCLC	II	R	NCT05420220
	Lorigerlimab	NSCLC failed standard therapy	I	A, nR	NCT03761017
PD-1 TIGIT	AZD2936	First-line metastatic NSCLC or NSCLC failed ICI	I/II	A, nR	NCT04995523
	HLX301	NSCLC failed standard therapy	I/II	R	NCT05102214
PD-1 VEGF	AK112 Chemotherapy	First-line metastatic NSCLC	III	R	NCT05899608
	AK112	NSCLC, multiple cohorts	I/II	R	NCT04900363
	PM8002	ES-SCLC failed chemotherapy	II	R	NCT05879068
PD-1 PD-L1	IBI318 Lenvatinib	NSCLC failed ICI	I	R	NCT04777084
PD-1 TIM-3	AZD7789	NSCLC, ICI pretreated or ICI-naïve	I/II	R	NCT04931654
	Lomvastomig	NSCLC failed standard therapy	I	A, nR	MCT03708328
PD-1 LAG3	RO7247669	NSCLC failed ICI	I/II	R	NCT04140500
PD-L1 4-1BB	GEN1046 ± Pembrolizumab	NSCLC failed ICI	II	A, nR	NCT05117242
PD-L1 CD47	IMM2520	NSCLC failed standard therapy	I	R	NCT05780307
PD-1 ILT4	CDX-585	NSCLC failed standard therapy	I	R	NCT05788484

(Continued)

Table 2. (Continued)

Target	Study agent	Setting	Ph	Status	NCT
EGFR 4-1BB	HLX35	NSCLC failed standard therapy	I	A, nR	NCT05360381
EGFR CD28	REGN7075 Cemiplimab	ICI-naïve advanced NSCLC	I/II	R	NCT04626635
EGFR HER-3	SI-B001 Docetaxel	NSCLC failed first-line immunochemotherapy	III	R	NCT05943795
	SI-B001 Osimertinib	EGFR-mutation-positive NSCLC	II/III	R	NCT05020769
	SI-B001 SI-B003	NSCLC failed standard therapy or untreated	I/II	R	NCT05949606
	SI-B001	NSCLC failed standard therapy	I	R	NCT04603287
EGFR MET	MCLA-129	NSCLC failed standard therapy	I/II	R	NCT04868877
	EMB-01	EGFR-mutant or MET aberrant NSCLC failing standard treatment	I/II	R	NCT03797391
HER-2 HER-3	Zenocutuzumab	Tumor harboring NRG rearrangement	II	R	NCT02912949
HER-2 SIRPα	IMM2902	HER-2 altered	I/II	R	NCT05805956
B7H3 CD28	XmAb808 Pembrolizumab	NSCLC failed standard therapy	I	R	NCT05585034
BiTe					
DLL3 CD3 T cell	BI764532 PD-1 antibody Chemotherapy	First line in ES-SCLC	I	R	NCT06077500
	BI764532	SCLC failed standard therapy	I	R	NCT04429087
	BI764532	SCLC failed standard therapy	II	R	NCT05882058
	Tarlatamab	SCLC failed standard therapy	I	A, nR	NCT03319940
	Tarlatamab	SCLC failed standard therapy	II	A, nR	NCT05060016
	Tarlatamab	SCLC failed chemotherapy	III	A, nR	NCT05740566
	Tarlatamab	LS-SCLC after chemoradiotherapy	III	R	NCT06117774
	Tarlatamab Durvalumab	Maintenance after first-line immunochemotherapy in ES-SCLC	III	R	NCT06211036
	Tarlatamab PD-1 antibody Chemotherapy	First-line in ES-SCLC	I	R	NCT05361395
	HPN328 ± Atezolizumab or Ifinatamab deruxtecan	ES-SCLC failed first-line treatment	I/II	R	NCT04471727

(Continued)

Table 2. (Continued)

Target	Study agent	Setting	Ph	Status	NCT
EGFR CD3 T cell	TAK-186	NSCLC failed standard therapy	I/II	R	NCT04844073
Two HER-2 domains	ZW25	HER-2 expressing cancer	I	A, nR	NCT02892123
ROR1 CD3 T cell	NVG-111	ROR1+ tumor failing standard therapy	I	R	NCT04763083
B7H4 CD3 T cell	GEN1047	NSCLC failed standard therapy	I/II	R	NCT05180474
Bispecific NK cell engager					
EGFR CD16A	AFM24 Atezolizumab	NSCLC failed standard therapy	I/II	R	NCT05109442
Tri-specific NK cell engager					
EGFR NK cell	DF9001	EGFR expressed	I/II	R	NCT05597839
Bispecific antibody linking to radioisotope					
EGFR MET	AC225-FPI_2068	NSCLC failed standard therapy	I	R	NCT06147037

Data cut-off on ClinicalTrials.gov on August 25, 2024. The list is not exhaustive.
A, nR, active, not recruiting; BiTe, Bispecific T-cell engager; BsAb, bispecific antibody; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ES-SCLC, extensive stage-small cell lung cancer; ICI, immune checkpoint inhibitor; LS-SCLC, limited stage-small cell lung cancer; NCT, registration number on ClinicalTrials.gov; NRG, NSCLC, non-small cell lung cancer; Ph, phase; R, recruiting; Status, recruitment status; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

incidence at 1%) and ICANS was relatively uncommon (total incidence at 8%), which occurred primarily during cycle 1. Risk-mitigation strategies such as step-up dosing (starting with 1 mg on cycle 1 day 1 then escalating to the target dose) and prophylactic steroids have significantly improved the drug's safety.[103] Another hurdle is on-target off-tumor toxicity, which may be an issue for targets that are expressed in normal cells such as CEA or EGFR.[104] Strategies to improve specificity include optimizing the relative affinity of target-binding, using multi-specific Ab, or the use of a pro-drug delivery system.[105] TAK-186 is an EGFR/CD3 BsAb that is administered as a pro-drug and is selectively activated in tumor cells due to the higher concentration of proteases within the TME.[106] It is currently evaluated in an ongoing trial for solid tumors including NSCLC (NCT04844073).

Besides the adaptive immune system, there is recent interest in developing BsAb that stimulates the innate immune system. AFM24 is a tetravalent scFV antibody against EGFR and CD16a which recruits NK cells and macrophages.[107] It has demonstrated clinical activity and tolerable safety in ongoing studies involving heavily pretreated NSCLC with an ORR of 26.7% when combined with atezolizumab (NCT05109442) and in *EGFR* mutation-positive NSCLC with a disease control rate of 50% (NCT04259450).[108,109]

Theoretical advantages for using BsAB over MoAb for checkpoint inhibition may include improved specificity, potential sparing of T-reg cells, and ability to overcome MHC downregulation.[110,111] PD-(L)1-CTLA-4 BsAb such as KN-046 (NCT05420220),[112] cadonilimab (AK104) (NCT04172454),[113] and volrustomig

(MEDI5752) (NCT03530397)[114] have all demonstrated clinical activities either as monotherapy or in combination with other agents in NSCLC patients. Confirmatory phase III trials are underway for KN046 plus chemotherapy (NCT04474119) and volrustomig plus chemotherapy (NCT05984277). Cadonilimab plus chemotherapy is being evaluated in phase I/II trials (NCT06467500, NCT06277674).

BsAb targeting other immune checkpoints that are under evaluation for NSCLC include PD-1/TIGIT: AZD2936 (NCT04995523),[115] PD-1/TIM-3: AZD7789[116] (NCT04931654) and lomvastomig (NCT03708328), PDL-1/4-1BB: GEN1046 (NCT05117242),[117] PD-(L)1/LAG3: tebotelimab (NCT03219268)[118] and FS118 (NCT03440437),[119] PD-1/interleukin-2 (IL-2): IBI363.[120] Early preliminary data from these multiple trials suggest modest clinical efficacy with manageable toxicity profiles.

Ivonescimab is a tetravalent BsAb to PD-1 and VEGF. In contrast to conventional BsAb, it forms by attaching two anti-PD-1 ScFv to the c-terminus of the anti-VEGF antibody heavy chain. Preclinical studies have demonstrated ivonescimab to have increased binding avidity to PD-1 in the presence of VEGF inhibition and better potency on PD-1 blockade.[121] A phase I/II study on the combination of chemotherapy and ivonescimab reported ORR of 54% in advanced-stage treatment-naïve *EGFR*/*ALK*-wild type NSCLC, 68% in *EGFR* mutation-positive NSCLC after failing TKI, and 40% in NSCLC after failing both ICI and chemotherapy (NCT04736823).[122] In the phase III HARMONi-A trial (NCT05184712), ivonescimab plus chemotherapy improved median PFS from 4.8 to 7.1 months in patients *EGFR* mutation-positive NSCLC after failing TKI.[123] Recently, HARMONi-2, a phase III clinical trial that compared ivonescimab with pembrolizumab in patients with PD-L1 positive NSCLC, reported that ivonescimab yielded superior PFS. The benefit was observed among patients with both high and low PD-L1 expression.[124]

Bintrafusp alfa is a BsAb composed of an anti-PD-L1 antibody and the extracellular domain of TGF-βRII, trapping TGF-β. TGF-β neutralization may attenuate tumor angiogenesis, epithelial-to-mesenchymal transition, and fibrosis, and TGF-β pathway upregulation has been implicated in resistance to PD-(L)1.[125] While early clinical phase I trial was suggestive of clinical efficacy (NCT02517398), the confirmatory phase III trial comparing bintrafusp alfa with pembrolizumab in PD-L1 high NSCLC was negative and was associated with increased skin toxicities related to TGF-β inhibition (NCT03631706).[126] Similarly, the drug also failed to improve the efficacy of standard chemoradiotherapy in stage III unresectable NSCLC (NCT03840902).[127] SHR-1701 is another PD-L1/TGF-β BsAb with clinical activity in treatment-naïve and chemotherapy-resistant NSCLC (NCT03774979)[128] and potentially as a neoadjuvant treatment with chemotherapy in unresectable stage III patients (NCT04580498).[129]

A number of innovative strategies in BsAb have emerged in recent years. That includes delivery of BsAb by CAR-T cells/oncolytic viruses,[130,131] BsAb drug conjugates,[132] and multi-specific Ab.[133] Undoubtedly, the relative diversity and versatility of BsAb offers numerous opportunities to selectively stimulate antitumor immunity and inhibiting oncogenic signaling pathways. Despite significant advances in BsAb drug development, several challenges remain in its clinical application for solid tumors. One major challenge is the selection of an optimal target antigen. Unlike in hematological malignancies, many targeted antigens are also expressed in normal tissues, which can result in unwanted on-target off-tumor toxicities.[133] Additionally, these antigens may not be constituently expressed on all tumor cells owing to tumor heterogeneity, leading to treatment resistance.[133] Another challenge is the limited drug penetration and immunosuppressive TME in solid tumors.[134] In terms of drug design, beyond antigen selection, considerations in biodistribution, valency, antigen-binding affinity, and kinetics are crucial, as they all impact the drug's efficacy and toxicity profile.[133] An ideal BsAb would demonstrate a long half-life, high specificity, effective tumor permeation, and preferential activation of immune cells within the tumor environment.

Cancer vaccine

Cancer vaccine aims to trigger antitumor immune response by enhancing cancer antigen presentation to T cells, which is similar to an anti-infection vaccine. Cancer antigens can be classified into tumor-associated antigens (TAA) and TSA.[135] The former refers to antigens that are expressed in normal tissues but often overexpressed in cancers,

such as melanoma-associated antigen A3 (MAGE-A3) and mucin 1 (MUC1), while the latter refers to antigens that are exclusively expressed in tumor cells. Although vaccines encoding TAAs can be accessible as an off-the-shelf product, their immunogenicity is often low due to central immune tolerance and heterogeneity in antigen expression. Two phase III studies, namely MAGRIT and START, investigating the role of MAGE-A3 vaccine and MUG1 vaccine, respectively, in the adjuvant setting, failed to improve survival.[136,137]

Vaccines encoding multiple epitopes are more likely to induce immunogenicity. The ATALANTE-1 study compared OSE2101, a vaccine encoding five TAAs commonly expressed in NSCLC (HER-2, CEA, MAGE2, MAGE3, and p53), with standard-of-care chemotherapy (docetaxel or pemetrexed), in patients carrying the HLA-A2 phenotype after previous treatment with ICI and platinum chemotherapy. The study terminated accrual prematurely due to the COVID-19 pandemic. Nonetheless, in the subgroup population who had acquired resistance to ICI ($n=118$), median OS was superior in the OSE2101 arm (11.1 vs 7.5 months, HR = 0.59, $p=0.017$).[138] A phase III study, ARTEMIA, is being planned to validate these findings (NCT06472245).

Advances in tumor molecular sequencing technologies and vaccine design have led to the development of personalized vaccines and novel vaccine platforms (Table 3). Common vaccine platforms include DNA, RNA, peptide-based, cell-based, and viral. DNA and peptide-based vaccines demonstrate limited immunogenicity, but this limitation can be overcome by the addition of immune stimulation adjuvants, such as synthetic Toll-like receptor ligands and granulocyte-macrophage colony stimulating factor.[139] Viral vaccines may trigger immune responses against the vector, eventually lowering the efficacy of the vaccine.[140] Contrarily, mRNA-based vaccines are generally more immunogenic than DNA and peptide vaccines, allow simultaneous encoding of multiple antigens, and may be associated with lower risk of host genome integration.[141] The first step in development of personalized vaccine includes whole exome sequencing, RNA sequencing, and HLA typing on tumor and blood samples from patients. This step allows the identification of all tumor-specific epitopes that are mostly generated from nonsynonymous passenger mutations. The second step is neoantigen selection based on gene expression, clonality, and prediction of epitope-HLA binding using bioinformatic algorithms. Based on the selection, the most immunogenic antigens are identified for subsequent vaccine manufacturing.[142] Significant progress has been made in neoantigen selection with the application of machine learning.[143] One disadvantage of mRNA vaccines is their instability and fast degradation. Adoption of novel delivery systems, such as lipid nanoparticles (LNPs), the addition of poly(A) tail to mRNA, and the use of co-transcriptional capping and nucleoside base modifications, have significantly improved the stability and translation efficiency of mRNA vaccines.[144] Modifications to LNP platforms are actively being developed to enable selective delivery of vaccines to the target organs.[144]

There is a strong rationale for combining cancer vaccine with PD-1 blockade to simultaneously reinvigorate the immune response. In a phase I study, 82 patients with advanced NSCLC, melanoma, or bladder cancer without prior PD-1 inhibitor therapy were enrolled to receive NEO-PV-01, a personalized neoantigen vaccine consisting of up to 20 tumor neoantigens, together with nivolumab.[145] Patients received 3 months of nivolumab while the vaccines were manufactured. Of 82 patients enrolled, 27% were not vaccinated, due to reasons including disease progression ($N=11$), insufficient tumor cellularity, or inadequate neoantigen ($N=4$). The most common adverse events were injection site reactions and flu-like illness which did not lead to NEO-PV-01 dose interruption or discontinuation. ORR was 39% in the NSCLC cohort ($n=18$).[145] This vaccine was also evaluated in combination with pembrolizumab plus chemotherapy in 38 patients with treatment-naïve metastatic non-squamous NSCLC. Similar to previous trials, patients first received 3 months of immunochemotherapy before the vaccine. Seventeen patients did not receive vaccination, including 10 patients who had inadequate tumor cellularity or neoantigens for vaccine production, and 1 patient who had developed disease progression. ORR and median PFS in the vaccinated cohort were 69% and 7.2 months, respectively.[146] While these studies demonstrated the feasibility of combining cancer vaccines with anti-PD-1 and/or chemotherapy in lung cancer, the efficacy of cancer vaccines remains unclear. Importantly, these trials demonstrated two key challenges of personalized vaccines that include a high incidence of

Table 3. Ongoing clinical trials testing cancer vaccines in lung cancer.

Vaccine platform and target	Study agent	Setting	Ph	Status	NCT
Dendritic cell					
Personalized neoantigens	MIDRIXNEO-Lung	Neoadjuvant	I	A, nR	NCT04078269
	PEP-DC vaccine	NSCLC with stable disease or better while on current ICI/chemotherapy/targeted therapy	I	R	NCT05195619
	LK101 Anti-PD-(L)1	NSCLC failed ICI	I	R	NCT05886439
	Neo-DCVac Anti-PD-(L)1	NSCLC failed ICI	I	R	NCT06329908
	DC vaccine	Resected early stage NSCLC	I	R	NCT04147078
	Autologous DC vaccine Atezolizumab	Maintenance therapy after first-line immunochemotherapy in ES-SCLC	I/II	A, nR	NCT04487756
	LG002 Anti-PD-(L)1	Failed ICI	I	R	NCT06329908
CCL21-gene	Intratumoral CCL21-gene modified DC vaccine Pembrolizumab	EGFR/ALK –ve NSCLC failed ICI EGFR/ALK+ve failed TKI	I	A, nR	NCT03546361
NY-ESO-1, MAGE-A3, MAGE-A4, multi-MAGE, Survivin, MUC1, Melan-A	PDC*Lung01 ± Pembrolizumab	Stage II–III NSCLC after resection, OR Stage IV NSCLC on ICI or chemotherapy	I/II	A, nR	NCT03970746
Peptide					
Personalized neoantigens	PNeoVCA Pembrolizumab	NSCLC failed standard therapy	I/II	R	NCT05269381
Telomerase	Pembrolizumab ± UV1	First-line metastatic NSCLC	II	R	NCT05344209
	UCPVAx	NSCLC failed standard treatment	I/II	A, nR	NCT02818426
Survivin	OVM-200	NSCLC failed standard therapy	I	R	NCT05104515
KRAS	KRAS peptide vaccine Nivolumab Ipilimumab	First-line metastatic NSCLC with KRAS mutation	I	R	NCT05254184
	KRAS vaccine (TG-01/QS-21) Nivolumab Daratumumab	NSCLC failed ICI	II	R	NCT06015724

(Continued)

Table 3. (Continued)

Vaccine platform and target	Study agent	Setting	Ph	Status	NCT
Epidermal growth factor	CimaVax-EGF Nivolumab or Pembrolizumab	Failed chemotherapy	I/II	R	NCT02955290
	CIMAvas-EGF	Resected early stage NSCLC	I	R	NCT04298606
ALK	ALK vaccine	ALK-rearranged NSCLC failed TKI	I/II	R	NCT05950139
LRPAP1	TEIPP24	Failed immunochemotherapy HLA-A*0201+	I/II	R	NCT05898763
TERT	UCPVAx Nivolumab	NSCLC failed standard therapy	I/II	A, nR	NCT02818426
mRNA					
Personalized neoantigens	V940 Pembrolizumab	Resected stage II–III NSCLC	III	R	NCT06077760
	Personalized mRNA vaccine	NSCLC failed standard treatment	I	R	NCT03908671
MAGE-A3, CLDN6, KK-LC-1, PRAME, MAGE-A4, MAGE-C1	BNT116 ± Cemiplimab ± Chemotherapy	NSCLC: multiple cohorts	I	R	NCT05142189
	BNT116 Cemiplimab	First-line metastatic NSCLC	II	R	NCT05557591
CEA, HER-2, MAGE2, MAGE3, TP53	OSE2101 Nivolumab or Docetaxel	NSCLC failed first-line immunochemotherapy HLA-A2+	II	R	NCT04884282
DNA					
Personalized neoantigens	DNA vaccine Durvalumab	ES-SCLC on first-line immunochemotherapy	II	R	NCT04397003
CDH3, CD105, YB-1, MDM2, SOX2	Polyepitope plasmid DNA vaccine (STEMVAC)	NSCLC with stable disease or better with immunochemotherapy	II	R	NCT05242965
Virus					
Personalized neoantigens	Gad-PEV or MVA-PEV Pembrolizumab	First-line metastatic NSCLC	I	A, nR	NCT04990479
p53	p53MVA vaccine	NSCLC failed standard therapy	I	A, nR	NCT02432963
Cytotoxic	Intratumoral CAN-2409 Anti-PD-(L)1 ± Chemotherapy	NSCLC with stable disease or progressive disease on first-line anti-PD1	II	A, nR	NCT04495153
Yeast					
Personalized neoantigen	YE-NEO-001	NSCLC failed standard therapy	I	A, nR	NCT03552718

Data cut-off on ClinicalTrials.gov on August 25, 2024. The list is not exhaustive.
A, nR, active, not recruiting; ES-SCLC, extensive stage-small cell lung cancer; HLA, human-leukocyte antigens; ICI, immune checkpoint inhibitor; NCT, registration number on ClinicalTrials.gov; NSCLC, non-small cell lung cancer; Ph, phase; R, recruiting; Status, recruitment status; TKI, tyrosine kinase inhibitor.

manufacturing failure and long manufacturing time. With such a significant proportion of patients may become unfit for vaccination during the period.

Adopting cancer vaccine in the adjuvant setting after tumor resection allows sufficient tumor tissue and time for vaccine production, which was demonstrated in the KEYNOTE-942 study, the first randomized phase II trial to report survival benefit from a cancer vaccine. In this study, 157 patients with resected stage IIIB–IV melanoma were randomized 2:1 to receive adjuvant pembrolizumab with or without mRNA-4157, a personalized, mRNA-based vaccine encoding up to 34 neoantigens. mRNA vaccine was successfully prepared for all except one patient enrolled in the vaccine arm and 91% of patients received mRNA-4157 with 34 neoantigens. There were less disease recurrences in the study arm, with an 18-month recurrence-free survival of 79%, compared to 62% in the control arm (HR = 0.56, $p = 0.05$). Self-limiting injection site reactions and influenza-like symptoms were the major adverse events of mRNA-4157, and the incidence of immune-related adverse events was similar between both arms.[147] Adjuvant mRNA-4157 vaccine is now being studied in resected NSCLC in a phase III trial, where patients were randomized to receive adjuvant pembrolizumab with and without mRNA-4157 (INTerpath-002, NCT06077760).

Recent studies showed that lung cancer harboring oncogenic driver alterations may generate neoantigens as targets for cancer vaccines. mRNA-5671(V941) is a tetravalent cancer vaccine developed by Moderna targeting *KRAS* G12D, G12V, G13D, or G12C mutations. The phase I trial testing mRNA-5671 as monotherapy or in combination with pembrolizumab in patients with *KRAS* mutated solid tumor has completed enrollment and result is pending (NCT03948763). A recent preclinical study reported that immunogenic ALK peptides are found in *ALK*-rearranged tumors, and ALK-based vaccine successfully restored CD8+ T-cell priming and synergized with ICIs in mouse models.[148] Thus, cancer vaccines represent a promising platform for immunity stimulation in oncogene-addicted NSCLCs, a condition that typically responds poorly to ICIs.

Cell therapy

Adoptive cellular therapy (ACT) involves direct delivery of tumor-specific, activated immune cells for tumor killing.[149] Multiple types of cell therapies (NK cell, macrophage, mesenchymal stem cells) are being investigated, while T-cell therapy remains the most well-established. T-cell therapy is classified into three major groups: TIL therapy, CAR-T therapy, and T-cell receptor (TCR)-engineered T-cell therapy (Table 4).

TILs are polyclonal lymphocytes that reside within the tumor. It is believed that TILs represent T cells that can recognize and target TSAs; however, become exhausted or inactivated within the immunosuppressive TME.[150] The presence of abundant TILs has been shown to predict favorable outcomes of ICI.[151,152] TILs are harvested from resected tumors and expanded ex vivo. The objective of ex vivo expansion is to allow rapid proliferation of tumor-specific T cells outside the immunosuppressive TME.[153] Before infusion of expanded TIL product, the patient receives lymphodepletion with chemotherapy, and after TIL infusion, adjuvant IL-2 is administered to stimulate TIL proliferation. Therefore, myelosuppression is a universal side effect due to use of lymphodepleting chemotherapy, while pulmonary edema and capillary leak syndrome are commonly associated with IL-2 use.

Lifileucel is the first FDA-approved TIL therapy for the treatment of advanced melanoma after disease progression on PD-1 blockade, and targeted therapy if *BRAF* V600E mutation is present.[154] The approval was based on a phase III randomized trial that demonstrated superiority with lifileucel over ipilimumab in both PFS and ORR.[155] Following the success in melanoma, emerging data has shown that TIL may be efficacious in patients with lung cancer. The first phase I trial on TIL treatment in lung cancer was reported in 2021.[156] In this trial, TIL was collected from patients prior to PD-1 blockade therapy as anti-PD-(L)1 treatment has been shown to induce terminal differentiation of T cells potentially lowering the efficacy of TIL.[157] Enrolled subjects first received nivolumab monotherapy, and when they developed disease progression, TIL was administered concurrently with nivolumab. Among 13 patients who received TIL and were evaluable for disease response, 3 had confirmed responses (ORR 23%), and out of which 2 patients attained complete responses lasting over 1.5 years.[156]

Recently, a multicentre phase II study reported the preliminary efficacy of lifileucel in patients

Table 4. Ongoing clinical trials testing cell therapy in lung cancer.

Type	Study agent	Setting	Ph	Status	NCT
CAR-T	GPC3/mesothelin-CAR-γδT cells		I	R	NCT06196294
	GPC3/Mesothelin/Claudin/GUCY2C/ B7H3/PSCA/PSMA/MUC1/TGFB/HER-2/ Lewis-Y/AXL/EGFR-CAR-T cells		I	R	NCT03198052
	BOXR1030 (GP3-positive)	GP3+ tumor failed standard therapy	I/II	R	NCT05120271
	Claudin-6 CAR-T cells ± Claudin-6 mRNA lipoplexes vaccine	NSCLC with +ve claudin-6 expression	I	R	NCT04503278
	CEA CAR-T	NSCLC with CEA expression	I/II	R	NCT06006390
CAR-NK	PD-L1 t-haNK cellular therapy + N-803	NSCLC failed ICI	II	A, nR	NCT03228667
TCR-T cells	TCR-T cells	Metastatic NSCLC	I	R	NCT03778814
	KK-LC-1 TCR-T cells	NSCLC failed standard therapy	I	R	NCT05483491
	TCR-T cells	NSCLC failed standard therapy	II	R	NCT03412877
	KRAS TCR-T cells GRT-C903 (adenovirus vaccine) or GRT-R904 (mRNA vaccine)	NSCLC failed standard therapy	I	R	NCT06253520
	KK-LC-1 TCR-T cells	NSCLC failed standard therapy	I	R	NCT05035407
TIL	TIL (from blood) Tislelizumab Docetaxel	NSCLC failed ICI	II	R	NCT05878028
	TIL Pembrolizumab	NSCLC failed standard therapy	I/II	R	NCT06538012
	C-TIL051 Pembrolizumab IL-15	ICI-naïve NSCLC	I	R	NCT05676749
	LN-145	NSCLC failed first-line immunochemotherapy	II	R	NCT04614103
	CD40-augmented TIL	Oncogene driven NSCLC	I/II	R	NCT05681780
	Young TIL	NSCLC failed standard therapy	II	R	NCT02133196
	SOCS1 inactivated TIL	NSCLC failed standard therapy	I/II	R	NCT06237881
	OBX-115 (TIL expressing IL15)	NSCLC failed standard therapy	I/II	R	NCT06060613

(Continued)

Table 4. (Continued)

Type	Study agent	Setting	Ph	Status	NCT
	IOV-4001 (PDCD1 disrupted TIL)	NSCLC failed standard therapy	I/II	R	NCT05361174
Others	Dendritic cells and cytokine-induced killer cells	NSCLC failed chemotherapy	I/II	R	NCT03360630
	COH06 (NK cells expressing PD-L1 and IL-15) Atezolizumab	NSCLC failed ICI	I	A, nR	NCT05334329

Data cut-off on ClinicalTrials.gov on August 25, 2024. The list is not exhaustive.
A, nR, active, not recruiting; CAR, chimeric antigen receptor; ICI, immune checkpoint inhibitor; NCT, registration number on ClinicalTrials.gov; NSCLC, non-small cell lung cancer; Ph, phase; R, recruiting; Status, recruitment status; TCR-T cells, T-cell receptor-T cells; TIL, tumor infiltrating lymphocyte.

with advanced NSCLC resistant to ICI. Of 39 patients enrolled in the study and underwent tumor tissue resection, 28 (72%) received lifileucel infusion and 6 responses (ORR 21%) were observed. Importantly, the TCR repertoire of post-TIL infusion blood samples resembled that of TIL infusion product rather than the tumor or pre-infusion blood samples, indicating that TILs do persist after infusion. Median time from tumor resection to lifileucel infusion took 35 days (range 28–112). Five patients did not receive lifileucel due to patient-related factors and 6 patients had a failure in manufacturing of TIL. Two patients died after lifileucel infusion. While this multicentre study demonstrated that centrally manufactured TIL cell therapy is feasible, it also highlighted several key challenges for widespread clinical application of TIL therapy, which included long manufacturing time, high rate of manufacture failure, toxicity management, modest response rate, and lack of predictive biomarker.[158]

TCR-engineered T-cell therapy and CAR-T-cell therapy involve isolation of autologous T cells from peripheral circulation, followed by ex vivo transduction of a tumor-antigen specific TCR or CAR to improve tumor recognition.[159] TCR-T cells can target both extracellular and intracellular antigens presented via specific HLAs, while CAR-T cells target only extracellular antigens but are not HLA-restricted.[159] CARs generally contain intracellular costimulatory domains to improve T-cell stimulation upon antibody-antigen binding. Despite its success in hematological malignancies, CAR-T therapy in solid tumor treatment is far more challenging due to the lack of TSA, on-target off-tumor toxicities, and impaired tumor infiltration.[160] Active research is ongoing in identifying tumor antigens expressed in solid tumors suitable for CAR-T binding. For example, glypican-3 (GPC3) CAR-T therapy exhibited anticancer activity and a manageable safety profile in a phase 1 trial involving patients with advanced hepatocellular carcinoma.[161] GPC3 CAR-T is now investigated in patients with advanced squamous cell carcinoma of lung (NCT05120271; NCT06196294) as GPC3 is frequently overexpressed in squamous cell carcinoma of lung.[162,163]

Additional approaches have been undertaken to improve safety, efficacy, and persistence of ACT, such as removal of immune checkpoints from T cells with gene editing, and combination with ICIs. In a phase 1 first-in-human study, 12 patients received CRISPR-Cas9 PD-1 edited T-cell therapy without severe toxicities.[164] The incidence of off-target editing, a major concern for CRISPR-Cas9 technology, appeared to be low. After PD-1 editing, significantly more CD8 + IFN-γ + T cells were present in edited T cells compared with unedited T cells, showing the promise of utilizing novel gene editing technologies to improve the quality and persistence of immune cells.[164] PD-1 knockout CAR-T cells are now tested in various types of malignancies, including lung cancer.[165] Similarly, early data suggested that the combination of CAR-T cells and PD-1 blockade or chemotherapy may achieve synergistic activity.[166,167]

Preliminary efficacy of NK cell therapy has also been reported in the literature. NK cell therapy

offers several potential advantages over T-cell therapy. First, NK cells can recognize and kill cells that do not express MHC class I, a common occurrence in cancer as an immune evasion mechanism from T cells. Second, NK cell therapy carries a lower risk of CRS and ICANS. Thirdly, NK cells are hypoimmunogenic, making allogeneic transfer feasible and supporting its use as "off-the-shelf" products.[168] A phase I/IIa clinical trial from Korea reported that the combination of SNK01, an expanded NK cell therapy, with pembrolizumab was safe and improved survival in patients after chemotherapy failure.[169] Another study in China randomized 109 patients with previously treated, ICI naïve, advanced NSCLC to receive pembrolizumab with or without allogeneic NK cells, and reported improved survival in the pembrolizumab plus allogeneic NK cell therapy arm. The addition of allogeneic NK cells to pembrolizumab did not increase toxicities.[170] Recently, CAR-NK cell therapy has been explored, and multiple phase I trials are ongoing in various cancer types.[171]

Future perspective

There is a significant clinical gap to develop better immunotherapy strategies as majority of patients with advanced lung cancer experience resistance to anti-PD-(L)1. In this regard, novel ICI and targeted therapy combinations, BsAb, cancer vaccine, and cell therapy have all exhibited promising efficacies, either as monotherapy or in combination with anti-PD-(L)1. However, the negative results of many phase III novel ICI trials despite favorable results observed in phase I/II trials (e.g. INTR@PID LUNG 037 (bintrafusp alfa vs pembrolizumab), CANOPY-1 (pembrolizumab plus chemotherapy with and without canakinumab), CONTACT-01 (atezolizumab plus cabozantinib vs docetaxel)) serve as important lessons for future clinical trial designs. All these trials were conducted in biomarker-unselected populations based on ORR results from clinical trials of small sample sizes. Biomarker development in immunotherapy is far more challenging than that in targeted therapy, as mechanisms of immune evasion are often multifactorial and may not be accurately captured by current molecular diagnostic tools. Additional translational research should be conducted, incorporating clinical data and novel technologies such as artificial intelligence and multi-omic analysis, for biomarker discovery and rational clinical trial design.

While personalized cancer vaccines represent an excellent platform for antigen presentation, administration in an adjuvant setting may offer most tumor material and adequate time for vaccine production. The identification of immunogenic peptides generated from driver oncogenes offers new hope for patients with oncogene-addicted tumors which are commonly ICI resistant. TIL has demonstrated an ORR of about 20% in the ICI-resistant setting, but long manufacturing time, lack of predictive biomarker, and toxicity remain key challenges for routine clinical application of TIL therapy. Antitumor activity and toxicity profile of cellular therapy will continue to improve with genetic modification in future. Optimal target antigen selection and toxicity mitigation are common challenges with bispecific immune cell engagers and CAR-T-cell therapy. Strategies involving novel immunotherapy combinations, such as combining ICI with cell therapy or vaccines, should be explored to address the multiple facets of immune resistance. When multiple treatment options are available, the optimal treatment sequence becomes a clinically relevant question and requires an individualized approach. Lastly, given the novel mechanisms of these immune therapeutics, their toxicity profiles, especially in long term, remain largely unknown. Continuous effort and vigilance are required to learn about the toxicities and optimize their management.

Conclusion

The development of immunotherapy is moving at a fast pace. Multiple novel immunotherapies have emerged with exciting data and the potential to change clinical practice in the coming decade. It is hopeful that in future, we can precisely harness the immune system to fight lung cancer and bring cure to patients.

Declarations

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Author contributions

Molly S. C. Li: Conceptualization; Data curation; Methodology; Project administration; Visualization; Writing – original draft; Writing – review & editing.

Andrew L. S. Chan: Data curation; Project administration; Visualization; Writing – original draft.

Kevin K. S. Mok: Formal analysis; Project administration; Writing – original draft.

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